Ismail Jatoi
Manfred Kaufmann
Editors

Management of Breast Diseases

Springer

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ISBN: 978-3-540-69742-8 e-ISBN: 978-3-540-69743-5

DOI: 10.1007/978-3-540-69743-5

Springer Heidelberg Dordrecht London New York

Library of Congress Control Number: 2009934509

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Cover design: eStudio Calamar, Figueres/Berlin

Printed on acid-free paper

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Preface

In 2002, Lippincott published the *Manual of Breast Diseases*, edited by Professor Ismail Jatoi. The current book, *Management of Breast Diseases*, is an adaptation of that manual, with Professor Manfred Kaufmann of the Goethe-University of Frankfurt serving as co-editor. Most of the chapters from the original manual have been either extensively revised or discarded, and several new chapters added. This text contains more material than the original manual, but it is still intended as a basic guide for the wide spectrum of clinicians (surgeons, gynecologists, oncologists, radiation oncologists, internists, general practitioners) who treat breast diseases, both benign and malignant.

To compile this text, we assembled experts from throughout the world. Thus, this text provides not only a broad overview of breast diseases, but also highlights different perspectives from different parts of the world. Yet, it is worth noting that the management of breast cancer is now largely predicated on evidence-based medicine. Several large, randomized prospective trials have demonstrated the efficacy of breast cancer screening and chemoprevention. Other large trials have addressed the impact of systemic therapy, radiotherapy, and variations in local therapy on breast cancer mortality. Many of these landmark trials are discussed in this text, and they clearly have had a beneficial effect. Indeed, since about 1990, breast cancer mortality rates have declined substantially in most industrialized countries, and this trend is expected to continue in the years ahead.

We are deeply indebted to all the investigators who contributed chapters to this text. They have diverse interests, but all share the common goal of reducing the burden of breast diseases. Additionally, we thank Ms. Stephanie Benko, Ms. Gabriele Schroeder, and the editorial staff of Springer for their valuable assistance. We hope that clinicians will find this text to be an informative guide for the management of breast diseases.

Bethesda, MD, USA — Ismail Jatoi
Frankfurt, Germany — Manfred Kaufmann

Acknowledgements

I. Jatoi

I wish to thank my wife, Fiza Jatoi, and my children for their understanding and support while I pursued a career in the military and academia. Also, I am deeply indebted to my mentors, who, over the years, have been a source of inspiration: Rene Wegria, George E. Block, Victor Richards, and Michael Baum.

M. Kaufmann

This book is dedicated to my mentor Fred Kubli, Heidelberg.
I want to thank my wife Brigitte and our daughters Diana and Linda, whose patience, understanding and tolerance makes my work possible.

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Anatomy and Physiology of the Breast

1

Martha C. Johnson

List of Abbreviations

BCL-2	B-cell CLL/Lymphoma 2
BRCA1	Breast Cancer 1
BM	Basement Membrane
BrdU	Bromodeoxyuridine
CD	Cluster of Differentiation
CSF	Colony Stimulating Factor
CTGF	Connective Tissue Growth Factor
DES	Diethylstilbestrol
ECM	Extracellular Matrix
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
ER	Estrogen Receptor
FGF	Fibroblast Growth Factor
FSH	Follicle Stimulating Hormone
GH	Growth Hormone
GnRH	Gonadotropin-Releasing Hormone
hCG	Human Chorionic Gonadotropin
HGF	Hepatocyte Growth Factor
HIF	Hypoxia Inducible Factor
HPG	Hypothalamic-Pituitary-Gonadal
hPL	Human Placental Lactogen
ICC	Interstitial Cell of Cajal
IgA	Immunoglobulin A
IGF	Insulin-like Growth Factor
IGFBP	IGF Binding Protein
IgM	Immunoglobulin M
IR	Insulin Receptor
Jak	Janus Kinase
Ki67	A Nuclear Antigen in Cycling Cells
LH	Luteinizing Hormone
MMPs	Matrix Metalloproteinases
OXT	Oxytocin
PR	Progesterone Receptor
PRL	Prolactin
PRLR	Prolactin Receptor
PTH	Parathyroid Hormone
PTHrP	Parathyroid Hormone Related Peptide
Sca	Stem Cell Antigen
SP	Side Population
Stat	Signal Transducer and Activator of Transcription
TDLU	Terminal Ductal Lobular Unit
TEB	Terminal End Bud

This chapter is a review of the development, structure and function of the normal human breast. It is meant to serve as a backdrop and reference for the chapters that follow on pathologies and treatment. It presents an overview of normal gross anatomy, histology, and hormonal regulation of the breast followed by a discussion of its structural and functional changes from embryonic development through postmenopausal involution. This section includes recent data on some of the hormones, receptors, growth factors, transcription factors and genes that regulate this amazing nutritive organ.

From the outset, it is important to keep in mind that information in any discussion of human structure and function is hampered by the limited methods of study available. Observations can be made, but experimental studies are limited. Therefore, much of what is discussed in terms of the regulation of function has, of necessity, been based on animal studies, primarily the mouse, and/or studies of cells in culture. Significant differences between human and mouse mammary glands are summarized at the end of the chapter.

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_1, © Springer-Verlag Berlin Heidelberg 2010

The number of genes and molecules that have been investigated as to their role in the breast is immense. In discussing each stage of breast physiology, I have included a summary of the important hormones and factors involved. Some of the additional factors that have received less attention in the literature are included in Table 1.1 in the appendix. Table 1.2 in the appendix is a list of important mouse gene knockouts and their effects on the mammary gland.

1.1 Gross Anatomy of the Breast

Milk secreting glands for nourishing offspring are present only in mammals and are a defining feature of the class Mammalia [1]. In humans, mammary glands are present in both females and males, but typically are functional only in the postpartum female. In rare circumstances, men have been reported to lactate [2]. In humans, the breasts are rounded eminences that contain the mammary glands as well as an abundance of adipose tissue (the main determinant of size) and dense connective tissue. The glands are located in the subcutaneous layer of the anterior and a portion of the lateral thoracic wall. Each breast contains 15–20 lobes(Fig. 1.1) that each consist of many lobules. At the apex of the breast is a pigmented area, the areola, surrounding a central elevation, the nipple. The course of the nerves and vessels to the nipple runs along a suspensory apparatus consisting of a horizontal fibrous septum that originates at the pectoral fascia along the fifth rib, and two vertical septa, one along the sternum and the other at the lateral border of the pectoralis minor muscle [3].

1.1.1 Relationships and Quadrants

The breast is anterior to the deep pectoral fascia and is normally separated from it by the retromammary (submammary) space (Fig. 1.1). The presence of this space allows for breast mobility relative to the underlying musculature: portions of the pectoralis major, serratus anterior and external oblique muscles. The breast extends laterally from the lateral edge of the sternum to the mid-axillary line and from the second rib superiorly to the sixth rib inferiorly. An axillary tail (of Spence) extends toward the axilla, or armpit.

For clinical convenience, the breast is divided into quadrants by a vertical line and a horizontal line intersecting at the nipple. The highest concentration of glandular tissue is found in its upper outer quadrant. A separate central portion includes the nipple and areola (Fig. 1.2). Positions on the breast are indicated by numbers based on a clock face [4, 5].

1.1.2 Nerve Supply

Innervation of the breast is classically described as being derived from anterior and lateral cutaneous branches of intercostal nerves four through six, with the fourth nerve being the primary supply to the nipple [6]. The lateral and anterior cutaneous branches of the second, third and sixth intercostal nerves, as well as the supraclavicular nerves (from C3 and C4), can also contribute to breast innervation [6]. Most of the cutaneous nerves extend into a plexus deep upto the areola. The extent to which each intercostal nerve supplies the breast varies among individuals and even between breasts in the same individual. In many women, branches of the first and/or the seventh intercostal nerves also supply the breast. Fibers from the third (most women [7]) and fifth intercostal nerves may augment the fourth in supplying the nipple [8].

Sensory fibers from the breast relay tactile and thermal information to the central nervous system. Cutaneous sensitivity over the breast varies among women, but is consistently greater above the nipple than below it. The areola and nipple are the most sensitive and are important for sexual arousal in many women [9]. This likely reflects the high density of nerve endings in the nipples [10]. Small breasts are more sensitive than large breasts [11], and women with macromastia report relatively little sensation in the nipple-areola complex [12].

While the apical surface of the nipple has abundant sensory nerve endings, including free nerve endings and Meissner's corpuscles, the sides of the nipple and the areola are less highly innervated. The dermis of the nipple is supplied by branched free nerve endings sensitive to multiple types of input. Nipple innervation is critical since normal lactation requires stimulation from infant suckling [13]. The peripheral skin receptors are specialized for stretch and pressure.

Efferent nerve fibers supplying the breast are primarily postganglionic sympathetic fibers that innervate smooth muscle in the blood vessels of the skin and subcutaneous tissues. Neuropeptides regulate mammary

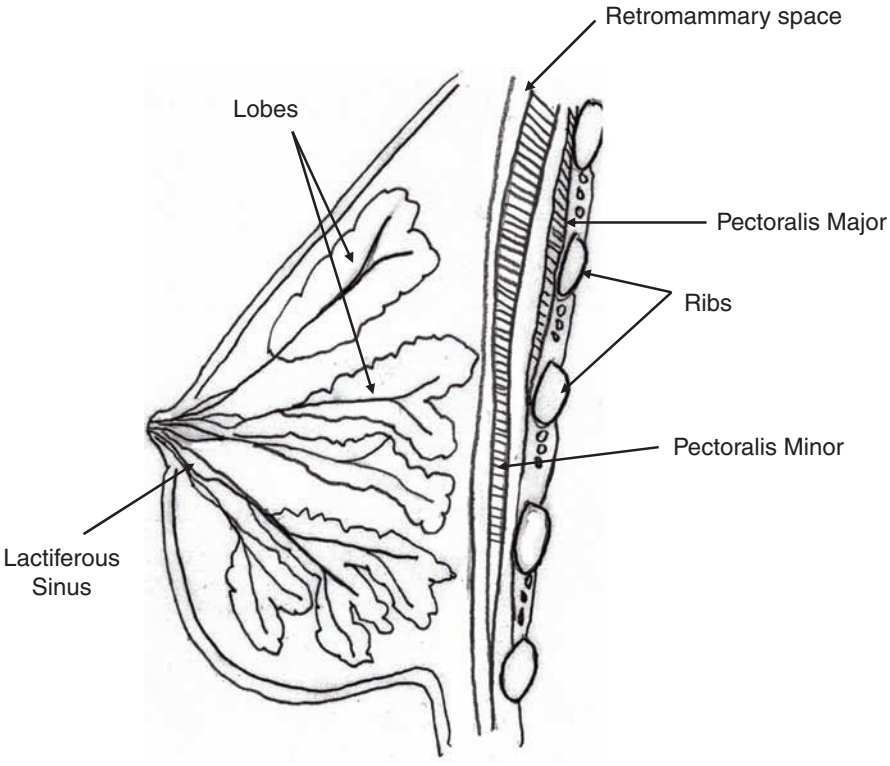

Fig. 1.1 Sagittal section through the lactating breast

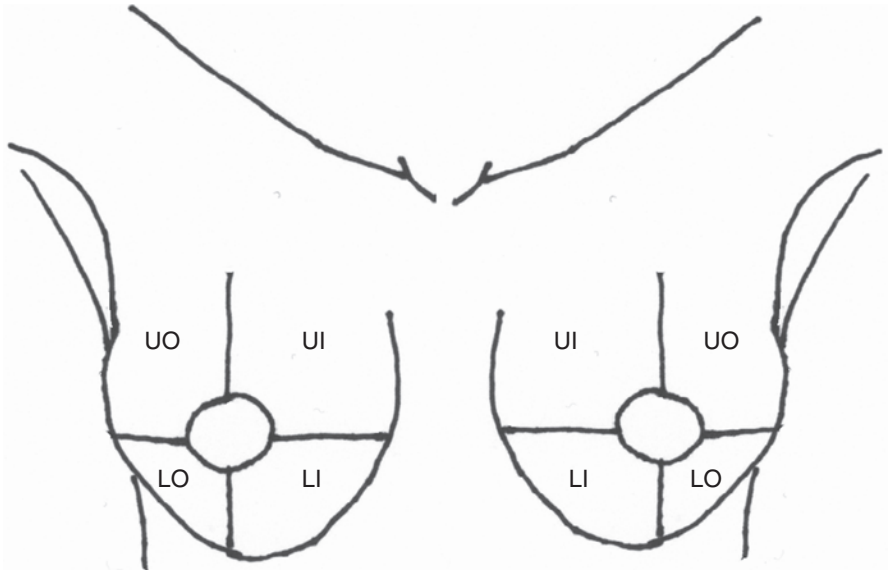

Fig. 1.2 Breast quadrants: *UO* upper outer, *UI* upper inner, *LO* lower outer, and *LI* lower inner

gland secretion indirectly by regulating vascular diameter. Sympathetic fibers also innervate the circular smooth muscle of the nipple (causing nipple erection), smooth muscle surrounding the lactiferous ducts and the arrector pili muscles [14]. The abundance of sympathetic innervation in the breast is evident following mammoplasty, when postsurgical complex regional pain syndrome (an abnormal sympathetic reflex) is relieved by sympathetic blockade of the stellate ganglion [15].

When milk is ejected by myoepithelial cell contraction, the normally collapsed large milk ducts that end

on the nipple surface must open to allow the milk to exit. The opening of these ducts is likely to be mediated by neurotransmitters that are released antidromically from axon collaterals in response to stimulation of nerve endings in the nipple. This local reflex may also promote further myoepithelial contraction. In stressful situations, neuropeptide Y released from sympathetic fibers may counteract this local reflex, resulting in a diminished volume of milk available to the infant [16].

1.1.3 Vascular Supply

Arteries contributing to the blood supply of the breast include branches of the axillary artery, the internal thoracic artery (via anterior intercostal branches) and certain posterior intercostal arteries (Fig. 1.3). Of the anterior intercostal arteries, the second is usually the largest and, along with numbers three through five, supplies the upper breast, nipple and areola. The branches of the axillary artery supplying the breast include the highest thoracic, lateral thoracic and subscapular and the pectoral branches of the thoracoacromial trunk [4]. Venous drainage of the breast begins in a plexus around the areola and continues from there and from the parenchyma into veins that accompany the arteries listed above, but includes an additional superficial venous plexus [17]. The arterial supply and venous drainage of the breast are both variable. Microvasculature within lobules differs from that found in the denser interlobular tissue, with vascular density (but not total vascular area) being higher in the interlobular region than within the lobules [18]. Vascularity of the breast, as measured by ultrasound Doppler, changes during the menstrual cycle and is greatest close to the time of ovulation [19].

1.1.4 Lymphatic Drainage

Lymphatics of the breast drain primarily to the axillary nodes, but also to nonaxillary nodes, especially internal mammary (aka parasternal) nodes located along the internal mammary artery and vein. Some lymphatics travel around the lateral edge of pectoralis major to reach the pectoral group of axillary nodes, some travel through or between pectoral muscles directly to the

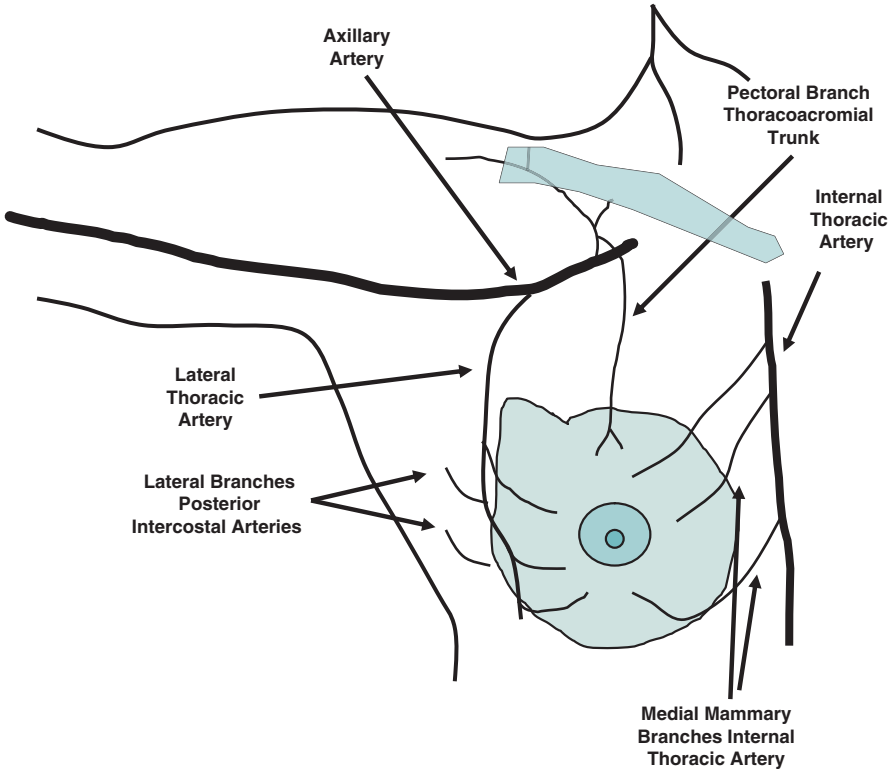

Fig. 1.3 Vascular supply of the breast. Arterial blood is supplied by branches of the axillary artery (lateral thoracic and pectoral branch of the thoracoacromial trunk). Additional blood supply is from medial mammary branches of the internal thoracic (internal mammary) artery and from lateral branches of the posterior intercostal arteries. Venous drainage is via veins that parallel the arteries with the addition of a superficial plexus (not shown)

apical axillary nodes, and others follow blood vessels through pectoralis major to the internal mammary nodes. Internal mammary nodes are located anterior to the parietal pleura in the intercostal spaces. Connections between lymphatic vessels can cross the median plane to the contralateral breast [20].

There are 20–40 axillary nodes that are classified into groups based on their location relative to the pectoralis minor. From inferior to superior, (a) the nodes below and lateral to pectoralis minor comprise the low (Level I) nodes, (b) those behind the pectoralis minor make up the middle (Level II) nodes and (c) those above the upper border of pectoralis minor constitute the upper (Level III) nodes (Fig. 1.4). Lymphatic plexuses are found in the subareolar region of the breast, the interlobular connective tissue and the walls of lactiferous ducts. Vessels from the subareolar lymphatic plexus drain to the contralateral breast, the internal mammary lymph nodes and the axillary nodes [4]. Both dermal and parenchymal lymphatics drain to the same axillary lymph nodes regardless of quadrant, with lymph from the entire breast often draining through a small number of lymphatic trunks to one or two axillary nodes [21].

Sentinel lymph nodes are those that are the first along the route of lymphatic drainage from a primary tumor [22]. Much of the information about normal breast lymphatic drainage has been implied from clinical studies aimed at identifying sentinel nodes. These studies often use the injection of radioactive tracer into a lesion, but techniques vary as do the results. It is generally accepted that most breast tumors metastasize via lymphatics to axillary lymph nodes. The degree to which metastasis involves internal mammary nodes is debated. One study [23] states that the rate of metastasis to internal mammary nodes is less than 5%, while another claims that over 20% of tumors drain, at least in part, into internal mammary nodes [24].

In women volunteers with normal breast tissue, isotope injected into parenchyma or into subareolar tissue drained, at least in part, into internal mammary nodes in

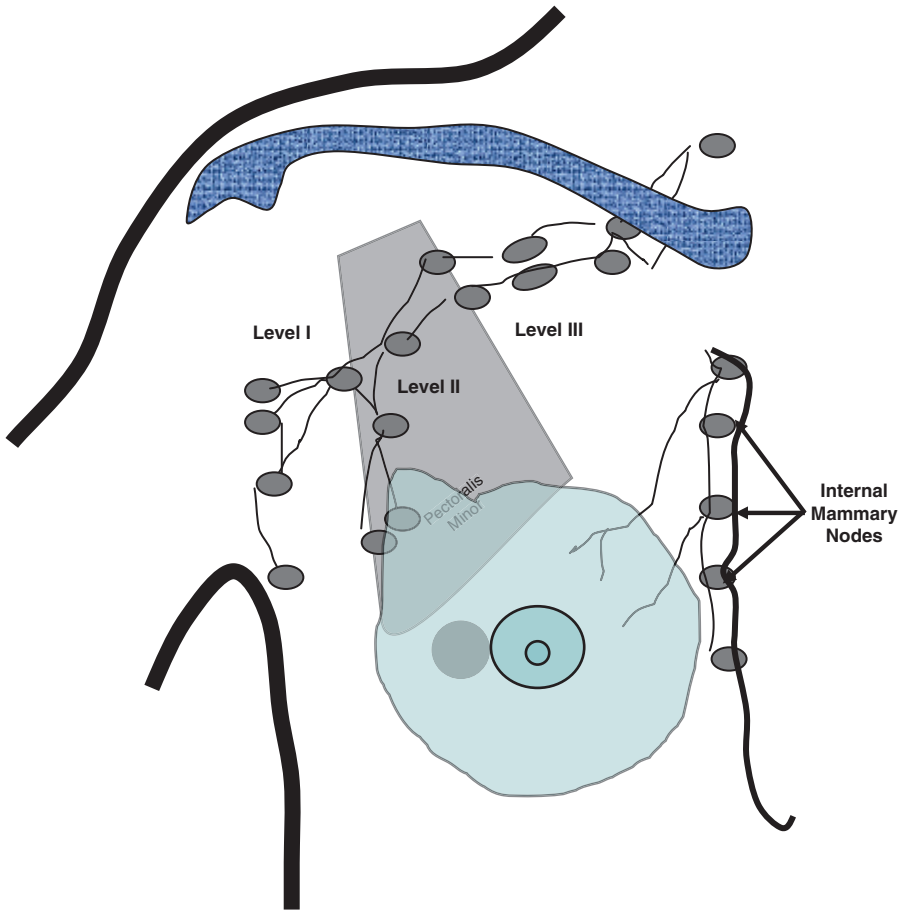

Fig. 1.4 Lymphatic drainage of the breast. Most drainage is into the axillary nodes indicated as Level I, Level II, and Level III, based on their relationship to the pectoralis minor muscle. Level I nodes are lateral to the muscle, Level II are behind it, and Level III are medial to it. Also, note the internal mammary nodes located just lateral to the edge of the sternum and deep to the thoracic wall musculature

20–86% of cases [25]. Microinjection of dye directly into lymph vessels of normal cadavers revealed that all superficial lymph vessels, including those in the nipple and areolar region, enter a lymph node in the axilla close to the lateral edge of the pectoralis minor (group I). Superficial vessels run between the dermis and the parenchyma and some run through the breast tissue itself to deeper nodes and into the internal mammary system [26]. Drainage to internal mammary nodes from small breasts (especially in thin and/or young women) is more likely to pass into internal mammary nodes than is drainage from large breasts [27].

1.1.5 Gross Anatomical Changes Throughout the Lifespan

The breast of a newborn human is a transient slight elevation that may exude small amounts of colostrum-like fluid known colloquially as "witch's milk." Human female and male breasts are indistinguishable until puberty [28]. Puberty begins with thelarche, the beginning of adult breast development. The age of thelarche is getting younger. Among whites in 1970, the mean age was 11.5 years, but in 1997, it had declined to10 years. Among blacks, thelarche occurs about 1 year earlier than in whites [29]. The first indication of thelarche is the appearance of a firm palpable lump deep to the nipple, the breast bud. It corresponds to stage II of the Tanner [30] staging system. (Stage I is prepubertal; stage III exhibits obvious enlargement and elevation of the entire breast; stage IV, very transient, is the phase of areolar mounding and contains periareolar fibroglandular tissue; stage V exhibits a mature contour and increased subcutaneous adipose tissue). The human breast achieves its final external appearance 3–4 years after the beginning of puberty [31].

Following puberty, the breast undergoes less dramatic changes during each menstrual cycle (discussed in detail later). The texture of the breast is least nodular just before ovulation; therefore, clinical breast exams are best done at this time. In addition, the breast appears less dense on mammograms during the follicular phase. The volume of each breast varies 30–100 mL over the course of the menstrual cycle. It is greatest just prior to menses, and minimal on day 11 [32]. The breast enlarges during pregnancy and lactation and the post-lactational breast may exhibit stria (stretch marks) and sag. The postmenopausal breast is often pendulous.

1.2 Histology

1.2.1 Overview

The adult human breast is an area of skin and underlying connective tissue containing a group of 15–20 large modified sweat glands (referred to as lobes (Fig. 1.1)) that collectively make up the mammary gland. The most striking thing about breast morphology is its remarkable heterogeneity among normal breasts, both within a single breast and between breasts [33]. The glands that collectively make up the breast are embedded in extensive amounts of adipose tissue and are separated by bands of dense connective tissue (Fig. 1.5) (suspensory, or Cooper's ligaments [6]) that divide it into lobes [34] and extend from the dermis to the deep fascia.

The lobules within each lobe drain into a series of intralobular ducts that, in turn, drain into a single lactiferous duct (Fig. 1.6) that opens onto the surface of the nipple. The part of each lactiferous duct closest to the surface of the nipple is lined by squamous epithelium [35] that becomes more stratified as it nears its orifice. In a nonlactating breast, the opening of the lactiferous duct is often plugged with keratin [4, 36]. Deep to the areola, each lactiferous duct expands slightly into a sinus that acts as a small reservoir (Fig. 1.1).

The mammary gland is classified as branched tubuloalveolar, although true alveoli do not typically develop until pregnancy. Individual lobules are embedded in

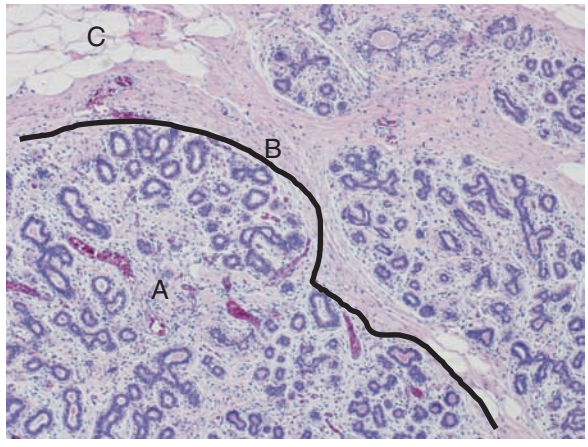

Fig. 1.5 Low power micrograph (50×) of an active (but not lactating) human breast. The dark line outlines a portion of a lobule. Note (a) the areolar connective tissue within the lobule and between the ductules, (b), the dense connective tissue between lobules and (c) adipose tissue. Some secretory product has accumulated within the ductules of the lobule

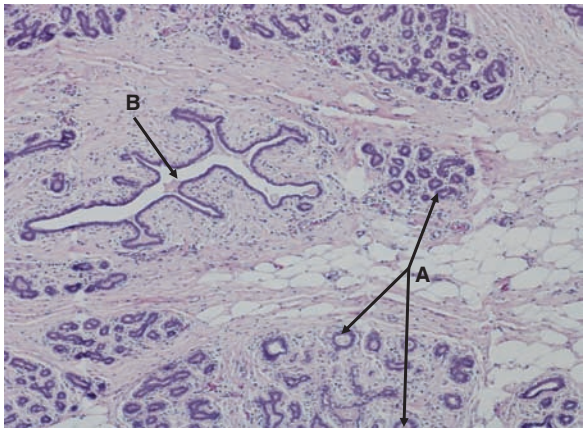

Fig. 1.6 Low power micrograph (50×) of an active (but not lactating) human breast. Arrows at (a) indicate intralobular ducts (ductules) within lobules. True acini are not present at this stage. The arrow at (b) indicates the lumen of a lactiferous (interlobular) duct

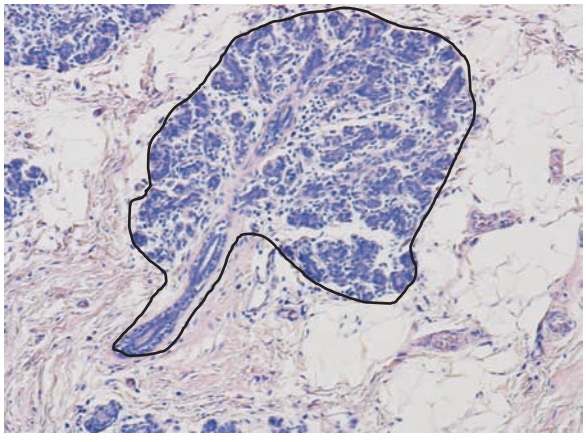

Fig. 1.7 Intermediate power micrograph (100×) of an active (but not lactating) human breast. A terminal ductal lobular unit (TDLU) and its duct are outlined. Note the abundant adipose tissue and dense irregular connective tissue surrounding the TDLU

loose connective tissue stroma that is highly cellular and responds to several hormones [35]. Terminal ductal lobular units (TDLUs) are considered to be the functional units of the human mammary gland. Each TDLU consists of an intralobular duct and its associated saccules (also called ductules). These saccules differentiate into the secretory units referred to as acini or alveoli [37]. The alveoli are outpocketings along the length of the duct and at its terminus. A TDLU resembles a bunch of grapes [38] (Fig. 1.7).

3-D reconstruction of the parenchyma from serial sections of human breast tissue [39] reveals no overlap

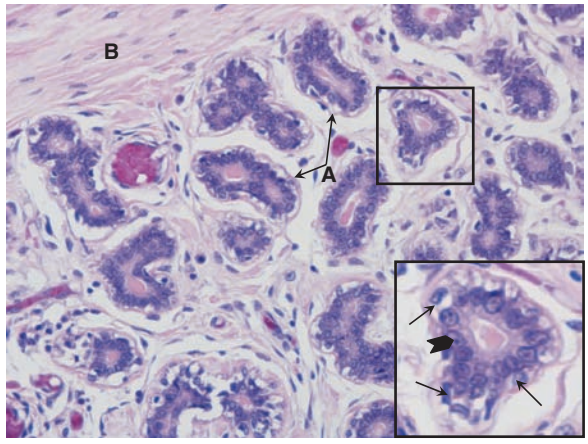

Fig. 1.8 Intermediate power micrograph (200×) of an active (but not lactating) human breast. The *arrows* labeled A indicate basement membranes (BM) surrounding individual ductules. The letter B is in the dense irregular connective tissue surrounding this lobule. Note the pale elongated nuclei of fibroblasts and the collagen fibers surrounding the letter B. The inset indicated by the *rectangle* is enlarged in the lower right corner. *Arrows* in the inset indicate myoepithelial cells and the chevron indicates a luminal epithelial cell

in territories drained by adjacent ducts. However, a recent computer generated 3-D model based on a single human breast found that anastomoses do exist between the branching trees of adjacent ducts [40].

The ductwork of the breast has progressively thicker epithelium as its tributaries converge toward the nipple. The smallest ducts are lined with simple cuboidal epithelium, while the largest are lined with stratified columnar epithelium [41]. The epithelial cells have little cytoplasm and oval central nuclei with one or more nucleoli and scattered or peripheral chromatin [36].

The entire tubuloalveolar system, including each saccule, is surrounded by a basement membrane (BM) (Fig. 1.8). Between the luminal epithelial cells and the BM is interposed an incomplete layer of stellate myoepithelial cells. The myoepithelial layer is attenuated in the smaller branches of the ductwork and in the alveoli. Macrophages and lymphocytes are found migrating through the epithelium toward the lumen [42].

1.2.2 Nipple and Areola

The nipple and the areola are hairless [36]. Nipple epidermis is very thin and sensitive to estrogen. Sweat glands and small sebaceous glands (of Montgomery) are

found in the areola and produce small elevations on its surface. The skin of the adult nipple and areola is wrinkled due to the presence of abundant elastic fibers [4] and contains long dermal papillae. Lactiferous ducts open on the surface of the nipple and parenchymal tissue radiates into the underlying connective tissue. The stroma of the nipple is a dense irregular connective tissue that contains both radial and circumferential smooth muscle fibers. Contraction of the smooth muscle fibers results in erection of the nipple and further wrinkling of the areola [4]. Nipple erection can occur in response to cold, touch or psychic stimuli. Smaller bundles of smooth muscle fibers are located along the lactiferous ducts [43].

1.2.3 Parenchyma

1.2.3.1 Luminal Epithelial Cells

Luminal epithelial cells carry out the main function of the breast: milk production. The secretory prowess of the luminal epithelial cells is impressive. They can produce three times their own volume each day. Luminal epithelial cells have scant cytoplasm and a central, oval nucleus with marginal heterochromatin. They are cuboidal to columnar and each cell has a complete lateral belt of occluding (tight) junctions near its apex and E-cadherin (a transmembrane protein found in epithelial adherens junctions) on its lateral surfaces [44]. During lactation, luminal cells contain the organelles typical of cells secreting protein, as well as many lipid droplets for release into milk [36].

1.2.3.2 Myoepithelial Cells

Myoepithelial cells surround the luminal cell layer (Insert, Fig. 1.8) and are located between it and the BM, which they secrete [45]. In the ducts and ductules, myoepithelial cells are so numerous that they form a relatively complete layer [4, 46]. In alveoli, the myoepithelial cells form a network of slender processes that collectively look like an open-weave basket [35]. Myoepithelial cell processes indent the basal surface of nearly every secretory cell [36] and contain parallel arrays of myofilaments and dense bodies, features commonly found in smooth muscle cells. They also contain smooth muscle-specific proteins and form gap junctions with each other [47].

While myoepithelial cells have many features common to smooth muscle cells, they are still true epithelial cells. They contain cytokeratins 5 and 14, exhibit desmosomes and hemidesmosomes [48, 49], and are separated from connective tissue by a BM. Compared to luminal cells, they contain higher concentrations of β integrins (receptors that attach to extracellular matrix (ECM) elements and mediate intracellular signals) [50].

Myoepithelial cells utilize the adhesion molecule P-cadherin [44] (a transmembrane protein), the knockout of which results in precocious and hyperplastic mammary gland development in mice [51]. They also express growth factor receptors, and produce matrix metalloproteinases (MMPs) and MMP inhibitors that modify ECM composition. Cell–cell contacts between the myoepithelial cells and their luminal cell neighbors allow for direct signaling [52] between the two cell types, and their basal location puts them in a good position to mediate interactions between the luminal cells and the ECM.

In addition to contracting to express milk toward the nipple, myoepithelial cells establish epithelial cell polarity by synthesizing the BM. Specifically, they deposit fibronectin (a large glycoprotein that mediates adhesion), laminin (a BM component that has many biological activities) collagen IV and nidogen (a glycoprotein that binds laminin to type IV collagen). Human luminal cells cultured in a type I collagen matrix form cell clusters with reversed polarity and no BM [49]. Introducing myoepithelial cells corrects the polarity and leads to the formation of double-layered acini with central lumina. Laminin [53] is unique in its ability to substitute for the myoepithelial cells in reestablishing normal polarity [49].

Other roles of mammary myoepithelial cells include lineage segregation during development and promoting luminal cell growth and differentiation [46, 54]. They also play an active role in branching morphogenesis [55] and even exhibit a few secretory droplets during pregnancy and lactation [31]. The myoepithelial cell rarely gives rise to tumors itself [56] and is thought to act as a natural tumor suppressor [46].

1.2.3.3 Stem Cells

Definitions and Terms

The idea of a population of mammary gland stem cells [57] has existed since the 1950s. These cells would either give rise to two daughter stem cells or to one

stem cell and one lineage specific progenitor cell that would, in turn, give rise to either luminal cells or myoepithelial cells [58].

A rigorous definition of a tissue-specific stem cell requires that it meet five criteria [59]. It must: (1) be multipotential, (2) self renew, (3) lack mature cell lineage markers, (4) be relatively quiescent, and (5) effect the long-term regeneration of its "home" tissue in its entirety. Much of the mammary cell literature takes liberty with these criteria, often applying the term "stem cell" to cells that can give rise to either (but not both) of the two parenchymal cell types. Others argue [60] that the existence of true human mammary epithelial stem cells in adults has not been unequivocally demonstrated.

Structure and Function of Mammary Stem Cells

A cell that stains poorly with osmium [61] in mouse mammary epithelium has been equated to the mammary gland stem cell. These cells are present at all stages of differentiation and undergo cell division shortly after being placed in culture, even in the presence of DNA synthesis inhibitors. They do not synthesize DNA, but do incorporate the nucleotide precursors needed for RNA synthesis. In mice, stem cell daughter cells differentiate in explant cultures in the presence of lactogenic hormones [62].

Stem cells are distinguishable phenotypically from mammary epithelial progenitor cells. The progenitor cells produce adherent colonies in vitro, are a rapidly cycling population in the normal adult and have molecular features indicating a basal position. Stem cells have none of those properties, and in serial culture studies, murine stem cells disappear when growth stops [63]. Murine mammary cells transplanted into host tissue will reconstitute a functional mammary ductal tree that is morphologically indistinguishable from the normal gland [64]. Furthermore, a fully differentiated mammary gland can be derived from a single murine stem cell clone [65, 66].

Examples of Cells Referred to as Mammary Stem Cells

- Human mammary epithelial cells with neither luminal cell nor myoepithelial cell markers.
- Subpopulations of mammary gland cells separated by flow cytometry that produce colonies containing both luminal and myoepithelial cells [67].
- Human mammary stem cells that are capable of forming TDLU-like structures in 3-D gel cultures. They can give rise to K19/K14 +/–, –/– (both are luminal) and –/+ (myoepithelial) cells, each of which are lineage restricted progenitors [68].
- Mammary cells that pump out loaded Hoechst 33342 dye and separate by flow cytometry into a "side population" (SP). However, in the mammary gland, the evidence that the SP is enriched for stem cells is only correlative.
- Mammary cells that are quiescent, based on their retention of BrdU that was incorporated during a prior period of proliferation, that also lack both luminal and myoepithelial cell markers. By this method, 5% of mouse mammary epithelial cells are quiescent stem cells. They also express Sca-1 (a stem cell marker), are progesterone receptor (PR) negative and are located within the luminal cell layer [69].

Clearly, the criteria for labeling a cell a mammary stem cell vary.

Location of Mammary Stem Cells

The concentration of stem cells in the human breast is highest in ducts [68]. They tend to be quiescent and surrounded by patches of proliferating cells and differentiated progeny [70]. Stem cells are believed to be the pale cells intermediate in position between the basal and luminal compartments of the mammary epithelium. However, a cell line has been isolated from the luminal compartment in humans that can generate itself, secretory cells and myoepithelial cells [55].

Classifications of Mammary Stem Cells

Human stem cells and progenitors are classified several ways. One classification system is based on steroid hormone receptors: Estrogen receptor (ER)α/PR – negative stem cells function during early development and ERα/PR – positive stem cells are required for homeostasis during menstrual cycling [70]. In another scheme, stem cells in nulliparous women are classified as type one while stem cells found in parous women are classified as type two. The parity-induced murine

mammary epithelial cells are able to form mammospheres in culture and, when transplanted, establish a fully functional mammary gland [71]. The nulliparous type is more vulnerable to carcinogenesis [72]. A third scheme [73] classifies mammary progenitors into three types: (1) a luminal-restricted progenitor that produces only daughter cells with luminal cell markers, (2) a bipotent progenitor (the "stem cell" described by other investigators?) that produces colonies with a core of luminal cells surrounded by cells with the morphology and markers of myoepithelial cells, and (3) a progenitor that generates only myoepithelial cells.

A special stem cell (like) type has been identified in multiparous human females. It is pregnancy induced, does not undergo apoptosis following lactation and is capable of both self renewal and production of progeny with diverse cellular fates [74]. This cell type constitutes as much as 60% of the epithelial cell population in multiparous women and may be related to the parity-related resistance to breast cancer [72].

Factors Regulating Stem Cells

The development of suspension cultures in which human stem cells form "mammospheres" [75] has facilitated the study of various pathways regulating the self-renewal and differentiation of normal mammary stem and progenitor cells [76]. A specific cell's "stemness" decreases as that cell becomes more differentiated. Stem cells can self-renew and proliferate within their niche, where they are maintained in their undifferentiated state by cell–ECM and cell–cell interactions. These interactions involve integrins and cadherins, respectively. However, very little is known about the regulation of stem cell proliferation and interaction in vivo.

1.2.4 Basement Membrane

The luminal cells of the mammary gland rest on a BM (except where myoepithelial cell processes intervene). Components of the mammary gland BM include collagen type IV, laminin, nidogens 1 and 2, perlecan and fibronectin [77–79]. All of these components are found within the BMs of ducts, lobules and alveoli in both humans and mice.

Many mammary epithelial cell functions require a BM including: milk production [80], suppression of programmed cell death [81], interaction with prolactin (PRL) [82] and the expression of ERα needed to respond to estrogen. Reconstituted BM (or collagen type IV or laminin) and lactogenic hormones can substitute for the BM requirement for ER expression [83]. Precise contact between epithelial cells and their underlying BM is critical for the maintenance of tissue architecture and function. For example, cultured mammary epithelial cells unable to anchor normally to the laminin in their BM have disrupted polarity and are unable to secrete β-casein, the most abundant milk protein [84]. Laminin activates expression of the β-casein gene [85]. In tissue culture, mammary epithelial cells require laminin and specific β1 integrins for survival [78, 86]. Nidogen-1 connects laminin and collagen networks to each other, is essential for BM structural integrity [78] and promotes lactational differentiation [87]. Integrins are essential for cell-BM interactions that are required for lactogenic cellular differentiation [88]. β1 integrin is required for alveolar organization and optimal luminal cell proliferation [89], and along with laminin, is required for end bud growth during puberty [90]. The fibronectin-specific integrin is localized to myoepithelial cells and is thought to be required for hormone-dependent cell proliferation [79].

The ability to culture cells in 3-D using synthetic BM culture systems such as Matrigel™, has opened the door to investigations of normal, as well as cancerous breast physiology [91]. Normal mammary epithelial cells seeded into Matrigel™ form small cell masses, develop apico-basal polarity, secrete ECM components basally and develop apical Golgi and junctional complexes. The cell masses form a lumen by cavitation involving the removal of central cells by programmed cell death [92], and in the process of becoming differentiated, form tight junctions prior to secreting milk [93].

1.2.5 Stroma

There are three types of connective tissue in the breast: loose connective tissue within lobules (intralobular), dense irregular connective tissue between lobules (interlobular) and adipose tissue (also interlobular) (Fig. 1.5). The dense connective tissue contains thick bundles of collagen and elastic fibers that surround the individual lobular units. Breast stroma is not a passive structural support; epithelial-stromal interactions play key roles in development and differentiation. The

intralobular loose connective tissue is in close relationship to the ductules and alveoli of the mammary gland, and is responsive to hormones.

1.2.5.1 Cells in Breast Stroma

While cells found in the interlobular connective tissue are primarily fibroblasts or adipocytes, the intralobular connective tissue also contains macrophages, eosinophils, lymphocytes, plasma cells and mast cells.

Fibroblasts form a basket-like layer around the human TDLU external to its BM [94] (Fig. 1.9). In the intralobular connective tissue, fibroblasts have attenuated cytoplasmic processes that form a network via cell-cell connections [33]. The connections serve to link the fibroblasts adjacent to the BM with those found within the lobular stroma. Mammary gland fibroblasts have ultrastructural features typical of synthetically active cells. Other cells in the intralobular connective tissue are interspersed within the fibroblast network such that cell-cell interaction is facilitated. Intralobular fibroblasts are CD34 (a marker for early stem-like cells) positive [35].

Two populations of human mammary gland fibroblasts can be distinguished based on staining for the cell surface enzyme dipeptidyl peptidase IV, an enzyme implicated in breast cancer metastasis. Intralobular fibroblasts are negative for this enzyme, but interlobular fibroblasts are positive [95]. Human breast fibroblasts have the ability to inhibit the growth of epithelial cells. If the ratio of fibroblasts to epithelial cells is high, however, the fibroblasts enhance epithelial cell proliferation [96, 97].

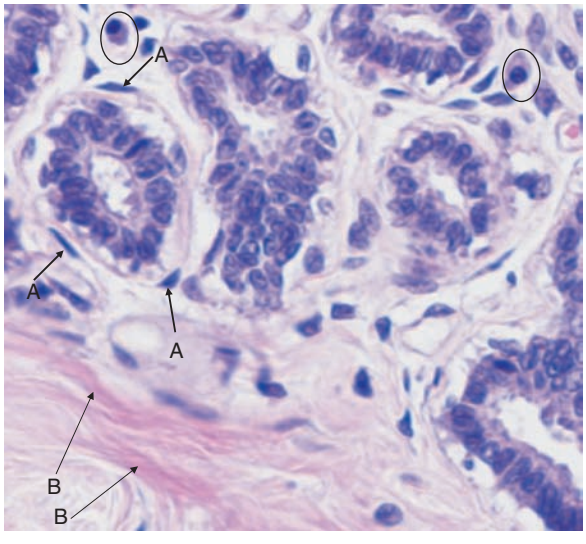

Fig. 1.9 High power micrograph (400×) of an active (but not lactating) human breast. *Arrows* labeled A indicate nuclei of fibroblasts surrounding a ductule. *Arrow*s labeled B indicate collagen fiber bundles and the ovals surround plasma cells

Adipocytes (Fig. 1.5) are common in the breast. High breast density on mammogram (negatively correlated with fat) is a risk factor for breast cancer [98]. In pregnant women, the adipocytes are closer to the epithelium and the number of fat-filled cells is markedly reduced throughout pregnancy and lactation. Adding adipocytes to murine epithelial cells in vitro, enhances mammary cell growth and seems to be required for the synthesis of casein.

Macrophages are localized near the epithelium during certain stages of breast development and have been shown to be critical for proper duct elongation. The macrophage growth factor, CSF1, promotes murine mammary gland development from branching morphogenesis to lactation [99]. Macrophages may also play a role in both angiogenesis and the ECM remodeling required during morphogenesis [100]. They are localized in close proximity to developing alveoli during pregnancy, and are present during involution where they likely help clear out milk lipid droplets and/or apoptotic debris [101]. Eosinophils are present during postnatal development where they are believed to interact with macrophages to induce proper branching morphogenesis [102].

Lymphocytes migrate into the mammary gland during lactation facilitated by specific adhesion molecules expressed on local endothelial cells. Lymphocytes themselves can be found in milk. Plasma cells derived from B-lymphocytes are abundant in the stroma before and during lactation when they secrete antibodies that are taken up by the epithelial cells and released into milk [103].

Mast cells contain several potent mediators of inflammation, including histamine, proteinases and several cytokines. Nevertheless, the precise functions of mast cells are still unknown [104]. Since mast cells are associated with bundles of collagen in human breast stroma, they may play a role in collagen deposition [105].

Recently, two additional stromal cell types have been identified: the interstitial cell of Cajal (ICC) and the ICC-like cell. These cells have two or three long, thin

monoliform processes [106] and establish close contacts with various immunoreactive cells, including lymphocytes, plasma cells, macrophages and mast cells [107]. ICCs from the breast form "intercellular bridges" in vitro [108]. They have caveolae, overlapping processes, stromal synapses (close contacts) and gap junctions. They also exhibit dichotomous branching. Collectively, the ICCs make up a labyrinthine system that may play a pivotal role in integrating stromal cells into a functional assembly with a defined 3-D structure [109].

1.2.5.2 Extracellular Matrix

The 3-D organization of the ECM affects many aspects of cell behavior: shape, proliferation, survival, migration, differentiation, polarity, organization, branching, and lumen formation [102]. Two principle ways that the ECM can affect cell behavior are to: (1) harbor various factors and/or their binding proteins to be released when needed, and (2) directly regulate cell behavior via cell-ECM interactions [82].

Stromal fibronectin and its receptor, $\alpha_5\beta_1$ integrin, play an important role in ovarian hormone-dependent regulation of murine epithelial cell proliferation. The fibronectin receptor is more closely correlated with proliferation and more rapidly regulated by estrogen and progesterone than is fibronectin itself. Thus, it is likely that the receptor, rather than fibronectin, is hormonally regulated. Mouse fibronectin levels increase threefold between puberty and sexual maturity and remain high during pregnancy and lactation [110].

Integrins, the major ECM receptors, link the ECM to the actin cytoskeleton and to signal transduction pathways [111] involved in directing cell survival, proliferation, differentiation and migration. They mediate interactions between stroma and parenchyma. Specific integrin functions in the human mammary gland have been reviewed elsewhere [112].

Proteoglycans, large heavily glycosylated glycoproteins, are abundant in breast ECM and correlate with increased mammographic density, a risk factor for breast cancer [113]. They are also important in coordinating stromal and epithelial development and mediating cell–cell and cell–matrix interactions. Several regulatory proteins in the mammary gland bind to proteoglycan glycosaminoglycans, including fibroblast growth factors (FGFs), epidermal growth factors (EGFs) and hepatocyte growth factor (HGF) [114].

1.3 Synopsis of Hormones and Other Factors that Regulate Breast Structure and Function

1.3.1 Hormones

This segment is a brief overview of reproductive hormonal events in the female, particularly as they affect the breast. Details of endocrine involvement in each phase of breast development and function are discussed in Sect. 1.4.

The hormonal control of human reproduction involves a hierarchy consisting of the hypothalamus, the anterior pituitary gland and the gonads: the hypothalamo–pituitary–gonadal (HPG) axis. In the female, the main hormones involved are: (1) gonadotropin-releasing hormone (GnRH) from the hypothalamus, (2) luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary, and (3) estrogen and progesterone, steroid hormones derived from cholesterol and made in the ovary (Fig. 1.10). The levels of these hormones vary dramatically throughout each menstrual cycle (Fig. 1.11), as well as during the various stages of a woman's lifetime.

GnRH causes the anterior pituitary gland to secrete LH and FSH. The hypothalamus releases GnRH in a pulsatile manner from axon terminals of neurons in the medial basal hypothalamus [115]. Pulsatile release of GnRH into the hypothalamo–hypophyseal portal system, which carries it directly to the pituitary gland, is essential for its function.

LH and FSH promote new ovarian follicle growth during the first 11–12 days of the menstrual cycle. The follicle, in turn, secretes both steroid hormones, estrogen and progesterone. Estrogen and progesterone are transported in the blood bound to proteins, primarily albumin and specific hormone binding globulins [116]. Just before ovulation, there is a sudden marked increase in both LH and FSH, a surge that leads to ovulation and the subsequent formation of a corpus luteum from the follicle.

Between ovulation and the beginning of menstruation, the corpus luteum secretes large amounts of estrogen and progesterone. These hormones have a negative feedback effect on secretion of LH and FSH in the pituitary gland, as well as GnRH secretion in the hypothalamus (Fig. 1.10). Estrogen primarily promotes the development of female secondary sex characteristics, including the breast. Progesterone mainly prepares the

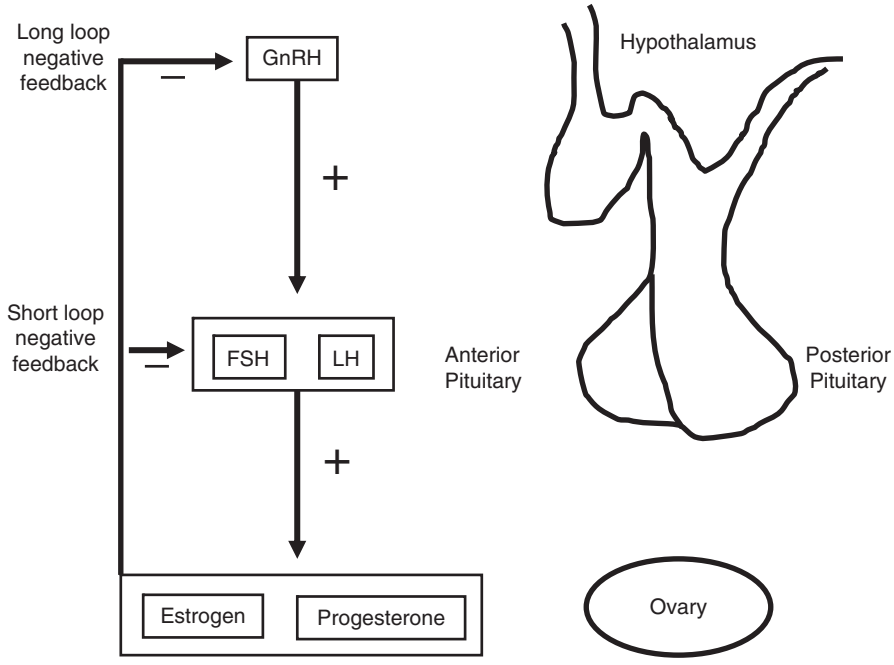

Fig. 1.10 Endocrine feedback loops in the hypothalamo-hypophyseal-gonadal axis

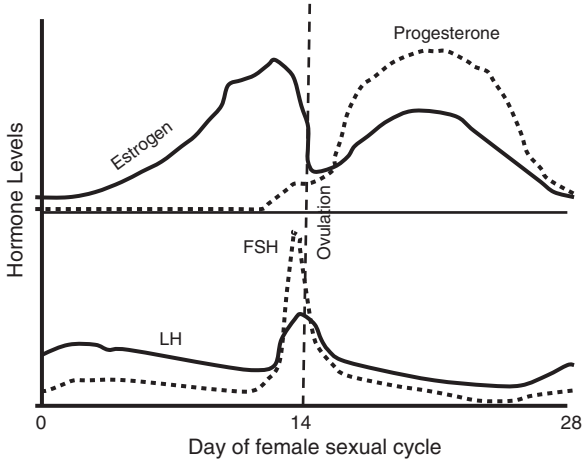

Fig. 1.11 Graph of hormonal levels in the menstrual cycle. The *upper panel* of the graph indicates levels of ovarian steroid hormones. The *lower panel* indicates levels of pituitary gonadotropins

uterus for the receipt and nurture of the embryo and fetus, and prepares the breast for lactation. During pregnancy, estrogen and progesterone are secreted primarily by the placenta. The main effects of estrogen on the breast are: (1) stromal tissue development, (2) growth of breast ductwork and (3) fat deposition [116]. Progesterone is required for lobuloalveolar differentiation of the breast [117].

These steroid hormones bind to receptors that belong to a superfamily of related receptors. The ER is an intracellular receptor that functions as a DNA binding transcription factor [118, 119]. There are two forms of ER: ERα and ERβ that are coded on different genes [120]. Estrogen binding affinity is high at both receptors and both are expressed in the breast. In the normal human breast, ERα is expressed in approximately 15–30% of luminal epithelial cells [121], whereas ERβ is found in myoepithelial cells and stromal cells [118]. Estrogen binds to the ER and the ER-estrogen complex translocates to the nucleus of the cell, where it binds to DNA and effects transcriptional changes leading to alterations in cell function. ER signaling can also act in a nonclassical pathway by interacting with other transcription factors bound to promoters of responsive genes [122]. ERα-estrogen complexes activate gene transcription, while ERβ-estrogen complexes can either activate or inhibit transcription [118, 123]. In mice, binding of estrogen to ERα stimulates mammary cell proliferation in nearby cells, but ERα positive cells themselves do not seem to proliferate and stem cells are ERα negative [124–126]. However, in humans, some quiescent ERα and PR positive cells are believed to be stem cells that act as steroid sensors and stimulate proliferation in neighboring ERα and PR negative cells [127]. It is also possible, however, that estrogen down-regulates ERα in mammary epithelial cells, and that ERα positive cells

divide later, when they are no longer identifiable as ERα positive [128, 129]. The dissociation of ER positive cells and proliferating cells implies that paracrine factors mediate the mitogenic activity of estrogen [121, 130]. ERβ is important in alveolar differentiation, specifically for the development of adhesion molecules and zonulae occludentes required for lactation [131].

The PR (see review by Seagroves and Rosen [132]) comes in two isoforms, PRA and PRB that arise from a single gene. PR knockout mice have demonstrated the critical role of progesterone in both pregnancy associated ductal branching and lobuloalveolar development [133]. Estrogen induces the expression of PRs [127], and 96–100% of cells expressing steroid receptors express both ER and PR [121, 127]. Progesterone bound to its receptor enters the nucleus where the PR-progesterone complex binds to DNA [134]. In mice, PRA expression is associated with progesterone induced lateral branching, whereas PRB is associated with alveogenesis [135]. PRA expression is found in cells adjacent to the ones that respond to progesterone by increased proliferation and/or differentiation. Thus, the actions of progesterone are also likely to be mediated by paracrine factors [136–138]. Neuregulin, a member of the EGF family of proteins and known for its role in neural development, promotes lobuloalveolar development and may be one such paracrine factor [139]. Both luminal and myoepithelial cells express PRB, and PRB positive cells may be directly stimulated to proliferate [140] by progesterone. When human postmenopausal breast tissue is treated with estrogen, progesterone, or both, epithelial cells proliferate, apoptosis declines and expression of ERα, ERβ and PR decreases [141].

Hormones not made in the ovary are also important to breast function, especially the neuroendocrine hormones PRL and oxytocin (OXT). PRL, named for its ability to promote lactation, is a polypeptide secreted in the anterior pituitary gland. The hypothalamus-derived PRL inhibitory hormone (dopamine) inhibits PRL secretion. PRL's actions are diverse and it is an absolute requirement for normal lactation. It promotes mammary gland growth and development, as well as synthesis and secretion of milk [142, 143]. PRL signal transduction involves the PRL receptor (PRLR, a transmembrane cytokine receptor induced by estrogen [144]), and PRLR requires Jak2 and the transcription factor Stat5 for developmental activity.

OXT is a peptide synthesized by neurons in the supraoptic and paraventricular nuclei of the hypothalamus [145]. It travels along the axons of these neurons to be stored in the posterior pituitary, where it is released into the bloodstream. OXT stimulates uterine contraction during labor and parturition and acts on myoepithelial cells in the breast to eject milk from alveoli into lactiferous ducts. Both PRL and OXT release are stimulated by the suckling reflex. The OXT receptor is a G-protein-coupled receptor and has been localized to human myoepithelial cells, even in nonlactating glands [146]. Mammary gland OXT receptors increase near parturition [10]. OXT has also been implicated in breast development, mating and maternal behavior. However, OXT-deficient female rodents are fertile, mate normally, conceive and deliver offspring and appear to show normal maternal behavior. Nevertheless, the pups die within 24 h because their mothers are unable to nurse them [147].

Many other hormones are important to breast development and function, but their roles are less well understood, including growth hormone (GH) [148]; androgens [149]; and thyroid hormone.

1.3.2 Other Regulators of Breast Development

Amphiregulin, HGF, EGF, TGFα, IGF and FGF3 have all been proposed as paracrine mediator(s) of estrogen effects [150, 151]. For example, amphiregulin is upregulated during ductal elongation [152] and amphiregulin and HGF promote ductal branching [139, 153–156]. EGF, a potent mitogen, is expressed on human breast stromal fibroblasts and EGF receptors (EGFRs[1]) are found on epithelial cells [158]. EGF is essential for mammary ductal growth and branching {Kamalati, 1999 #374}. Both EGF and HGF work with transforming growth factor alpha (TGFα), another mitogen [159], to promote lobuloalveolar development [160].

IGF-I is important in pubertal ductal morphogenesis in rodents, where it is believed to mediate the actions of

[1]EGFRs belong to the ErbB family of receptors, a group of receptors that are interdependent from the binding of their ligands to the activation of downstream pathways. Some ErbB-targeted therapies are aimed at inhibiting multiple ErbB receptors and interfering with the cooperation that exist between receptors. Members of the ErbB family accept cues from multiple ligands, including EGF, TGFα, amphiregulin, and several neuregulins [157]

GH [161] and estrogen [162]. IGF-I and IGF-II can bind to several different receptors, including IGF-IR, the insulin receptor (IR) and EGFR. In fact, the mitogenic action of IGF-I may require EGFR [163]. Both IFG-I and IGF-II bind to IGF binding proteins (IGFBPs) that modulate their actions. The binding proteins bind the IGFs to matrix proteins and to cell membranes, providing a local pool that enhances their availability. Within the breast, IGFs are believed to function both as endocrine and autocrine/paracrine factors [162].

A recent addition to the list of growth factors important in breast development is connective tissue growth factor (CTGF). CTGF promotes lactational differentiation and its expression can be induced by glucocorticoids in the murine breast cell line HC11, a cell line established from a mid-pregnant mouse mammary gland. Neither estrogen nor progesterone regulates CTGF expression, but it is expressed in the mouse mammary gland during pregnancy and lactation [164]. CTGF is also present in normal human breast epithelial cells and stromal cells [165].

1.4 Mammary Gland Structure and Function Throughout Life

1.4.1 Prenatal Development of the Breast

1.4.1.1 Events of Prenatal Breast Development

It is especially important to understand the prenatal development of the breast, since initial carcinogenic events may occur in this period [166–168]. Studies of prenatal human breast development have, of necessity, been observational and not experimental. They involve postmortem analyses of difficult to obtain human specimens. Mechanisms of differentiation have largely been inferred from studies on animals, primarily the mouse. Very early development of the mouse mammary gland and the factors that regulate it (including Wnt, FGF, TBX3 and parathyroid hormone related protein (PTHrP)) have recently been reviewed [169], but the initial cues that induce the formation of the human breast remain unknown [58].

Complicating matters in the study of human breast development is the heterogeneity of staging systems. Some are based on physical measurements and others on the date of last known menses. This heterogeneity makes inter-study comparisons difficult, at best. In addition, there is dramatic intra-breast variability at any given time with respect to developmental progress [170]. Stages of human breast development include (dates are approximate, overlapping and highly variable): Ridge, 4 weeks – proliferation of epithelial cells [97]; Disk, 6 weeks – globular thickening; Cone, 7 weeks; Bud, 8 weeks; Branching, 10–12 weeks; Canalization, 16 weeks; Vesicle, 20–32 weeks and Newborn [171, 172].

Typically, the first indications of human mammary glands are two parallel band-like thickenings of ectodermally derived epidermis: the mammary line or ridge, that in the [35] 5–7 week old [173] embryo, extend from axilla to groin. The most convincing evidence that this ridge is actually the precursor to the human breast is the fact that supernumerary nipples and breasts locate along that line [33]. Only part of the thoracic region of each ridge normally persists and forms a nodule [33]. This epithelial nodule penetrates the underlying mesenchyme and gives off 15–24 sprouts, each of which, in turn, gives rise to small side branches [173]. Epithelial-mesenchymal tissue interaction involves extensive cross-talk between parenchyma and stroma and is requisite for normal breast development [174]. The epithelial ingrowth is made up of solid cords of primitive glycogen-rich cells surrounded by a basal lamina. Each sprout will later canalize to form a lactiferous duct. The primary bud is initially about the size of a hair follicle and contains two distinct epithelial cell populations, central and peripheral. Concentric layers of supporting mesenchyme surround the bud. Hair follicles do not form in the area near the breast bud, possibly due to lateral inhibition [33].

As secondary outgrowths vertically penetrate the mesenchyme [33], each projection has a slender stalk with a bulbous end and is covered by a continuous BM [159]. The papillary layer of the dermis encases the growing cords and gives rise to the vascularized fibrous tissue around ducts and within the lobules. The deeper reticular layer becomes interlobular connective tissue and suspensory ligaments [35].

The cellular constituents of the secondary outgrowths are morphologically similar, but immunologically diverse. Immunohistochemical staining for luminal and myoepithelial cell markers reveals a gradual progression to the adult phenotypes [170]. At 28 weeks, the primordial breast cells still stain positively for both luminal and myoepithelial markers [175]. Between 20

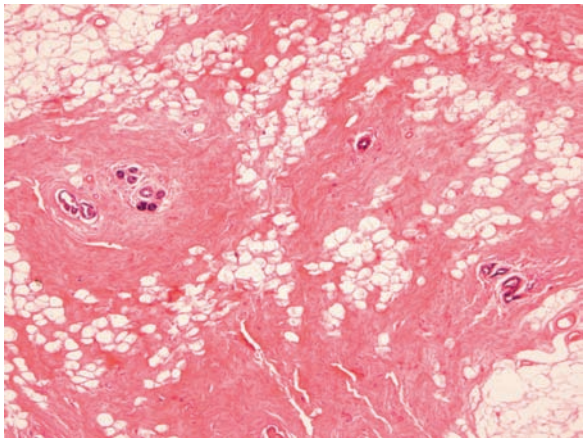

Fig. 1.12 Low power micrograph (50×) of a fetal human breast. A few ducts are present, but adipose and dense irregular connective tissues predominate

and 32 weeks, differentiation of mesenchyme into fat within the dense connective tissue stroma occurs.

Prenatal branching morphogenesis is accompanied by canalization via apoptosis of centrally located cells [176]. By the end of the fetal period, the secondary outgrowths are canalized and distinct luminal and myoepithelial cell populations are present (Fig. 1.12).

Late in the fetal period, the original invagination site of the primary bud evaginates to form the nipple [35]. Prior to parturition, the lumens of the mammary gland ductal tree are distended with secretory products of the epithelial cells, but the extent of this activity varies greatly from individual to individual as well as from lobule to lobule within a single breast. Typically, luminal cells already contain fat droplets, rough endoplasmic reticulum and apical membranes with blebs and pits characteristic of secretory cells. Underlying myoepithelial cells are structurally mature with numerous hemidesmosomes anchored to a tortuous BM. Their orientation, in contrast to the luminal cells, is parallel to the BM [177]. Myoepithelial cells late in gestation contain typical smooth muscle markers and are positive for Ki-67, a nuclear marker that indicates proliferation [170].

1.4.1.2 Hormonal Regulation of Prenatal Breast Development

Human female and male mammary glands develop similarly *in utero* (not so in some animals [178, 179]) and this phase of breast development is thought to be autonomous, in the sense that it does not require hormonal input [174]. This statement is based partly on the observation that fetal mice lacking receptors for estrogen, progesterone, GH or PRL exhibit normal prenatal mammary gland development [102, 180].

However, several observations point to an endocrine input in prenatal breast development. Toward the end of gestation, the alveolar epithelium becomes active and it makes the "witch's milk" seen in newborn infants. This event is attributed to the release of fetal pituitary PRL from maternal and placental steroid inhibition. Also, human fetal serum PRL rises in late gestation and peaks at term [181] and the PRLR is present in fetal breast tissue [176]. ERα is present in human mammary epithelial cells beginning in the 30th week of gestation [182], a time of high mammary epithelial cell proliferative activity. PR expression is also present in the fetus, but both ER and PR expression are highly variable during this period [183]. ERα and PR are both up-regulated shortly before birth [182]. In addition, some claim that after week 15, human breast development is influenced by testosterone [35]. Near term, the breast can respond to maternal and placental steroids and to PRL.

1.4.1.3 Genes, Transcription Factors and Growth Factors During Prenatal Breast Development

BCL-2, an inhibitor of apoptosis, is expressed maximally in fetal breast and absent in the epithelium of the normal adult breast. At week 18 of gestation, BCL-2 is highly expressed in the basal epithelial cell layer and surrounding mesenchyme and is thought to play a role in preventing apoptosis and allowing for cell population expansion [184]. *BRCA1*, a tumor suppressor gene is expressed at a high level in human fetal breasts between week 21 and 26 of gestation and is closely associated with differentiation [185].

TGF-α is expressed in the developing breast where it promotes both proliferation and differentiation [159]. It is localized to the developing stroma and the epithelial bud. TGF-β is seen in the ECM throughout prenatal development where it modulates cell-ECM interaction [35], inhibiting cell proliferation [102, 159, 186, 187]. BM inhibits the expression of TGF-β [188]. Tenascin-C, which regulates rodent mammary cell differentiation in culture [189], and promotes growth in fetal tissues, is present around the neck of the human breast bud

(a highly proliferative region) [35]. During the prenatal period, as in other life stages, EGF and its receptor may mediate estrogen effects. PTHrP is required for formation of mammary-specific mesenchyme [102] and appears to modulate stromal function during fetal branching morphogenesis [190].

1.4.2 Breast Development from Birth to Puberty

1.4.2.1 Events in Breast Development from Birth to Puberty

Studies of newborn infants and young children [191, 192] indicate that the mammary gland remains active after birth and even produces casein during the first 2 months. Lobules are well formed and some contain secretions. Ducts end in short ductules lined with two cellular layers; an inner epithelial and an outer myoepithelial. Specialized intra- and interlobular connective tissues are similar to those in the adult breast [33].

During the first 2 years of life, branching and terminal lobule development continues. By 2 years of age, however, the lobules have completely involuted (although myoepithelial cells remain) [175]. Between 2 years and puberty, breast development essentially just keeps pace with body growth [172] and, during this time, epithelial proliferation is consistently low [183].

There are four stages of lobule development in the human mammary gland [193]. Type 1 lobules consist of clusters of 6–11 ductules and are present prior to puberty; Type 2 lobules have more ductules, develop during puberty and are characteristic of the inactive breasts of nulliparous women; Type 3 lobules have still more ductules (up to 80) and develop during pregnancy; and Type 4 lobules are characteristic of lactating breasts and are never found in nulliparous women. Women at various life stages have different percentages of each lobule type and each type is thought to give rise to specific kinds of pathologies [194].

1.4.2.2 Hormones in Breast Development from Birth to Puberty

During fetal life, although the breast may not require hormones to develop, it is exposed to placental hormones, especially estrogen and progesterone. These hormones promote growth, but inhibit PRL, which is required for the mammary gland to become functional. At birth, the release of infant PRL from the inhibitory maternal and placental hormones frees PRL to promote milk secretion. As a result, 80–90% of infants (female and male) secrete "witch's milk."

Breast size in infants is related to circulating PRL levels [195]. Preterm infants have higher PRL levels between weeks 2 and 6 after birth than during the first week [195]. Between eight and 16 weeks of age, children of both genders have a surge of reproductive hormones, including estrogen. By 3 months, girls have higher estrogen levels than boys and the amount of breast tissue is positively correlated with estrogen levels [196]. PRs are expressed in 5–60% of mammary epithelial cells for up to 3 months postpartum [182]. Collectively, these observations seem to indicate that the child's own gonadal secretions may be active in the breast in early postnatal life.

1.4.2.3 Other Regulatory Factors in Breast Development from Birth to Puberty

TGF-α continues to be present after birth in both the luminal epithelium and interlobular stroma. It is concentrated in epithelia of terminal buds and lobular buds. TGF-α disappears from the breasts of male newborn infants after 4 days, but persists in females for up to 25 days postpartum [159]. The proliferation marker, Ki-67, is present in infant breast bud epithelium, predominantly in the neck region of terminal buds, but not in infants older than 25 days (coinciding with the disappearance of TGF-α). TGF-β (the growth inhibitor) [197] localizes to the stromal tissue near the epithelium in neonates. It declines after 3 months of age [159]. BCL-2 is found in luminal cells, but is no longer found in myoepithelial cells or fibroblasts, from 28 weeks of gestation through puberty [183].

1.4.3 Puberty

1.4.3.1 Events in the Breast During Puberty

The mammary gland is unique among glands in that it undergoes most of its branching during adolescent rather than fetal development. Branching in puberty, as in the fetus, involves cross-talk between epithelium and stroma during which patterns of side-branching are determined

by stromal cues [102]. The mammary gland duct system develops into its mature lobuloalveolar arrangement in a sequential manner. Ducts elongate, their epithelia thicken and the adjacent connective tissue increases in volume. In mice, club shaped structures called terminal end buds (TEBs) form at the ends of ducts. They are formed by stem cells and have the greatest proliferation rates [198]. Each TEB is the leading edge of a growing duct, as it advances, branches and then forms alveolar buds.

The TEB is made up of a single outer layer of undifferentiated cap cells and multiple inner layers of "body" cells. Cells in the trailing edge of the cap cell layer differentiate into myoepithelial cells. Lumen formation in the segment trailing the TEB involves apoptosis [199], with as much as 14% of internally located cells undergoing apoptosis concurrently. Subsequent branching is both via TEB bifurcation and more proximal lateral branching [200].

Branching during puberty is highly variable. The previously blunt-ended ductal termini undergo dichotomous branching, while lateral buds form more proximally. The primary ducts extend into underlying tissue from the nipple, giving rise to segmental ducts, subsegmental ducts and terminal ducts in order. The terminal ducts give rise to acini. The acini arising from one human terminal duct and surrounded by intralobular connective tissue collectively make up a TDLU [33]. During puberty, stem cell numbers increase [201]. By age 15, human breast structure is established centrally, but continues to expand peripherally. By age 18, parenchymal architecture is typical of the nulliparous adult [33].

Within the stroma, undifferentiated mesenchymal cells attach to the under surface of the basal lamina in the mid section of each end bud and form a monolayer outside of the myoepithelial cell layer. The mesenchymal cells will eventually become fibroblasts synthesizing collagen and other ECM molecules [202]. Large quantities of adipose tissue are deposited within inter- and intralobular connective tissue during this time, although dense irregular connective tissue remains the predominant tissue type at the end of puberty.

While significant glandular differentiation occurs during puberty, the process continues for at least another 10 years [35], and the most dramatic phases of breast development don't occur until pregnancy. Between puberty and the first pregnancy, the mammary gland is resting or inactive (Fig. 1.13). There is some debate as to whether any true secretory units develop prior to pregnancy. There is, however, agreement that the lobules of the resting breast consist essentially of ducts and that a few alveoli may be present during the late luteal (postovulatory) phase of menstrual cycles. It is an issue that is moot, since ducts, as well as alveoli, are capable of secretion**.** Over the next few years, clusters of 8–11 alveolar buds are found within each TDLU. Later cyclic hormonal variations result in smaller, but more numerous alveolar buds.

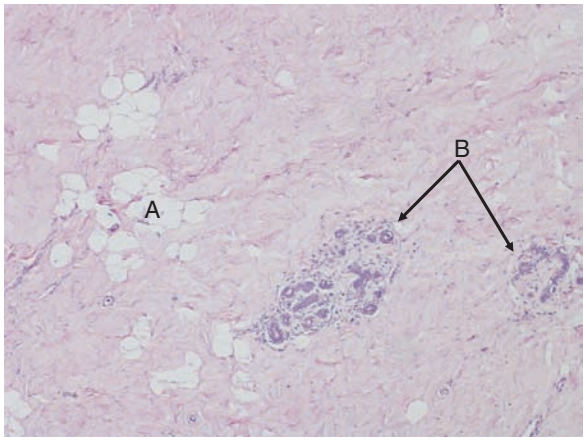

Fig. 1.13 Low power micrograph (50×) of an inactive human breast. The letter A indicates adipose tissue. The *arrows* at B indicate lobules. Note the low number of ductules in each lobule, as compared to the lobules in the active breast at the same magnification in Fig. 5., and the lobules of the pregnant breast, also at the same magnification in Fig. 15

1.4.3.2 Hormonal Regulation of the Breast During Puberty

Puberty is initiated by the maturation of the HPG axis and results in the hormonally driven outgrowth of the mammary epithelial tree [200]. A gradual increase in GnRH secretion by the hypothalamus, which does not occur in significant amounts during childhood [116], promotes ovarian steroid production by way of LH and FSH. Changes during puberty result from the surges of both pituitary and ovarian hormonal activity.

During the first 1–2 years following menarche, when cycles are often anovulatory, the breast is exposed to the unopposed actions of estrogen. This period is a window during which ductal growth occurs [203]. Estrogen responsiveness and control is essential for normal pubertal breast development [204] and serum estrogen levels parallel breast development during this period [176]. Duct epithelial thickening, elongation and branching are all promoted by estrogen. So are the expansion and differentiation of stromal and adipose

tissue [102, 203]. Not surprisingly, ERs are found in both epithelium and stroma. Estrogen is so potent that women with the gonadal dysgenesis of Turner's syndrome, who normally do not develop breasts, will do so if treated with estrogen [205].

During puberty (as in all life stages), the lobules with the greatest degree of proliferation consistently have the highest numbers of both ER and PR positive cells and the highest proliferation rates. There is a progressive decrease in both proliferation and steroid receptor expression as lobules (and their cells) become more differentiated [206]. GH and its receptor are essential for mammary gland development during puberty in the rodent [148, 207]. In fact, GH may be the pituitary hormone most central to mammary development at this time and probably acts by way of stromal IGF–I [207]. Two other hormones participating in pubertal breast development are glucocorticoids and vitamin D3.

1.4.3.3 Other Regulatory Factors in Breast Development During Puberty

Factors important to breast development during puberty include transcriptional target genes and locally produced molecules that mediate the effects of the major mammogens. IGFs are important to the survival of mammary gland cells during puberty and are known to suppress apoptosis [208]. Other factors include immune mediators, such as CSF-1 and eotaxin (important in the recruitment or production of macrophages and eosinophils, respectively), cell adhesion and axonal guidance proteins, ECM remodeling enzymes (e.g., MMPs and their inhibitors) and TGF-βs (inhibitors of duct development) [209].

1.4.4 The Adult Premenopausal Breast

1.4.4.1 Cyclic Events in the Premenopausal Adult Breast

Early in each menstrual cycle, ducts are cordlike with little or no lumen. The midcycle increase of estrogen causes luminal cells to get taller, lumens to form and secretions to accumulate in ducts and alveoli. Ductule cells undergo secretory differentiation during the luteal phase [36], while the stroma becomes more vascular [13] and accumulates fluid. Premenstrual enlargement and discomfort are attributed to this hyperemia and edema.

Mammary proliferative rates are higher in the luteal phase as measured by thymidine labeling [210], number of mitotic figures [211] and the percentage of cells that stain for Ki-67. When samples are controlled for both menstrual dates and progesterone levels, the proliferative index is found to be more than twice as high in the luteal phase than in the follicular phase. The apoptosis index does not differ significantly between phases of the cycle [212].

Morphological changes [211] divide the menstrual cycle into four phases. In stage 1 (days 0–5), it is difficult to distinguish between the luminal and myoepithelial layers. Both cell types have round nuclei and minimal amounts of pale cytoplasm. Sharp luminal borders with eosinophilic intraluminal secretions are common, but apoptosis and mitosis are mostly absent. The stroma is slightly edematous. In stage 2 (days 6–15), it is easier to distinguish epithelial and myoepithelial layers and many lobules show myoepithelial cell vacuolation. There are no mitoses or apoptotic bodies and there is no stromal edema or infiltrate. In stage 3 (days 16–24), lobules are larger and each lobule contains more ductular units. Two distinct layers of epithelial cells are easily distinguished. Myoepithelial cells are more vacuolated and luminal cells are more oval and basophilic. Mitotic and apoptotic cells are both detected and edema and infiltrate are again found in the interlobular stroma. In the last stage (days 25–28), vacuolization is extensive and luminal cells have cytoplasmic basophilia and prominent nuclei with large nucleoli. The most characteristic features of this final stage are frequent mitotic figures and increased apoptotic activity. While this phase of the cycle demonstrates more apoptosis, there are still only a small number of scattered cells undergoing the process [213]. Stromal edema is extensive and there are more inflammatory cells.

During the preovulatory period (days 0–14; stages 1 and 2), epithelial cells exhibit few microvilli and sparse secretory organelles. In the postovulatory phase (days 15–28; stages 3 and 4), luminal cells have prominent microvilli and more rough endoplasmic reticulum, secretory vacuoles and glycogen [214]. Several BM components vary in amount during the menstrual cycle, including laminin, fibronectin, collagen types IV and V and proteoglycans, all of which are lowest in mid-cycle. Collagens type I, III, VI and VII do not exhibit cyclic variation [215]. Immunoglobulin secretion within the human mammary gland exhibits cyclic fluctuations [216]; specifically, levels of IgA and the secretory

component are both highest in the preovulatory phase of the menstrual cycle. However, there is conflicting evidence indicating that immunoglobulin levels may be constant throughout the cycle [210].

Mammary gland development in each cycle never fully regresses to the starting point of the preceding cycle. Each cycle results in slightly more development and new budding until about age 35. The progressive increase in the number of lobules is accompanied by an increase in the size of each lobule and a reduction in the size of individual ductules and alveoli within the lobules.

1.4.4.2 Hormones Regulating the Adult Premenopausal Breast

The part of the menstrual cycle exhibiting the highest rate of epithelial proliferation in the breast is the luteal phase. The luteal phase is also the period during which both estrogen and progesterone levels are highest [127, 176] (Fig. 1.11). When breast tissue from nonpregnant women is xenografted into mice, treatment with estrogen (at high, i.e., luteal, levels) is the best inducer of epithelial proliferation [127]. Estrogen stimulates both DNA synthesis and bud formation [172].

In that proliferation is highest during the luteal phase, the hormonal milieu at this time must favor proliferation in the breast. The ERs and PRs in the human breast vary with the stage of the menstrual cycle, but there is disagreement as to when in the cycle, levels for each receptor are high and low [217]. One study states that ER positive cells are most abundant during days 3 through seven and PR positive cells are most abundant during the following week (days 8–14) [218], while another study found both ER and PR positive cells most abundant in the second week (days 8–14) of the cycle [219].

Estrogen at low (i.e., follicular) concentrations induces PR expression and cells expressing ERα are also PR positive. ERα/PR positive cells may act as steroid sensors, secreting paracrine factors that, in turn, regulate the proliferative activity of adjacent ERα/PR negative cells [127]. Local levels of estradiol in the normal human breast are highest during the luteal phase when plasma progesterone levels are also high. Progesterone may promote the local conversion of estrogen precursors into potent estradiol in normal breast tissue [220]. EGFR is also maximally expressed in the luteal phase and is found primarily in stromal and myoepithelial cells [221].

1.4.4.3 Stat5 in the Adult Premenopausal Breast

Stat5 is activated at a basal level in nonpregnant human breast epithelial cells and is specific to luminal cells and absent in myoepithelial cells. It regulates PRLR expression and may prevent apoptosis in differentiated epithelial cells. It is maintained in a state of activation by PRL [222].

1.4.5 Pregnancy

1.4.5.1 Events in the Breast During Pregnancy

In pregnancy, as in other phases of breast structure and function, there is remarkable heterogeneity among lobules; some are quiescent, while others proliferate. During early pregnancy, distal ducts branch and create both more lobules and more alveoli within each lobule [217]. During the first trimester, there can be as much as a tenfold increase in the number of alveoli/lobule number. Breast enlargement in this phase of pregnancy is due to both cellular hypertrophy and hyperplasia [223] (Fig 1.14). Luminal epithelial cells differentiate into cells with typical secretory cell morphology. At the same time, the epithelial and adipose compartments of the mammary gland shift their lipid metabolism in a concerted way, such that fatty acid availability to the epithelial cell is increased [224]. Some

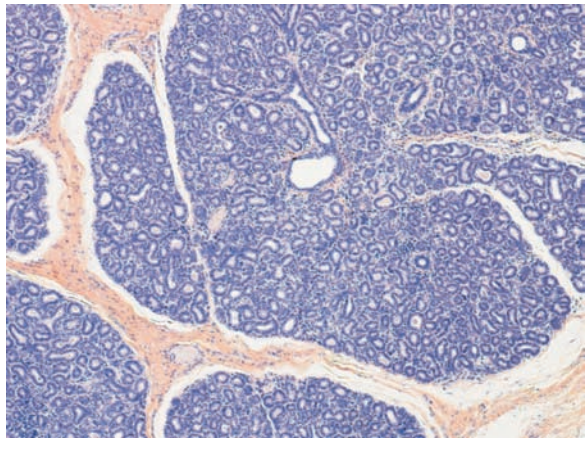

Fig. 1.14 Low power micrograph (50×) of a pregnant human breast. Note the huge number of ductules in each lobule and the dense irregular connective tissue separating the lobules. There is little adipose tissue

adipocytes may actually trans-differentiate into epithelial cells [225].

By mid-pregnancy, lobuloalveolar structure is established and ductules differentiate into alveoli. Each lobule contains a mixture of alveolar and tubular end-pieces that have budded off from the terminal portion of the duct system and many of these end-pieces are still solid knots of cells [226]. The lobules now include some that can be classified as Type 3 (described earlier) [193].

In the last trimester, epithelial cells are full of lipid droplets and adipophilin (lipid droplet associated protein) expression is increased. Luminal cells also have prominent endoplasmic reticulum, hypertrophied Golgi and swollen mitochondria. Enzymes characteristic of lactation are present [223]. Although luminal cell differentiation into secretory cells is advanced, it is not yet maximal. The secretory product (colostrum) filling the lumens has a high antibody content and is more similar in composition to blood plasma than to milk [36]. Breast enlargement in the third trimester is due both to this distention of acini by colostrum and an increase in stromal vascularity. Fat and connective tissue at this stage have now largely been replaced by parenchyma [217]. The remaining fibrous connective tissue has been infiltrated with plasma cells, lymphocytes and eosinophils [43].

Nulliparous women have lobules that are less differentiated than those of parous women. Among parous women, those who were pregnant before the age of 20, have a greater persistence of the more differentiated lobule type [172]. Changes in the breast that occur during pregnancy, specifically the complete differentiation of Type 3 lobules, are permanent and each subsequent pregnancy results in the accumulation of additional differentiated lobules [193]. In animal models, exposures to the high levels of estrogen and progesterone typical of pregnancy induce long-term alterations in gene expression in mammary epithelial cells. These alterations may induce a decrease in growth factors and an increase in apoptosis [227], and may contribute to the widespread phenomenon of pregnancy-induced protection against cancer. Breast tissues of postmenopausal parous women express numerous genes in both parenchyma and stroma that differ from those expressed in postmenopausal nulliparous women [228].

1.4.5.2 Hormones in the Breast During Pregnancy (Fig. 1.15)

The placenta secretes estrogens and progesterone and takes over this function from the corpus luteum as pregnancy continues into the second and third trimesters. Near the end of pregnancy, maternal estrogen levels are as much as 30-fold greater than before conception. Progesterone levels increase about tenfold during pregnancy [116]. Estrogen, with the help of progesterone, prepares the mother's breasts for lactation by promoting breast enlargement and growth of the duct system. Progesterone also promotes lobuloalveolar differentiation at this time [136]. However, estrogen and progesterone both inhibit the actual secretion of milk by the breast during pregnancy.

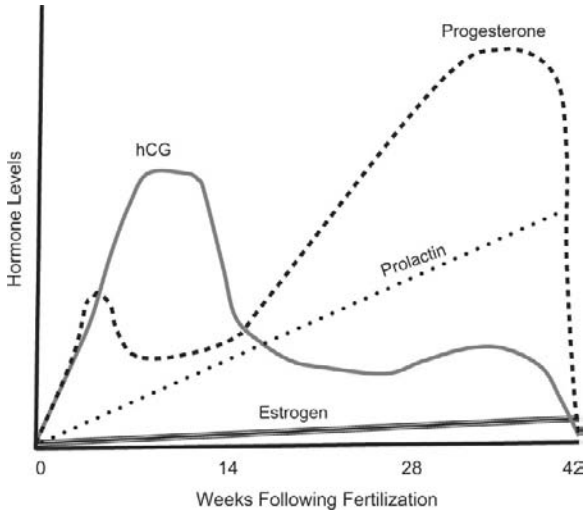

Fig. 1.15 Graph of hormonal levels during pregnancy

The xenograft model in which human mammary epithelial cells are seeded into collagen gels containing fibroblasts, and then placed under the renal capsule of athymic nude mice, has been a fruitful tool for examining hormonal regulation of human mammary gland development [97]. Normal human ductal structure develops in the graft. Treatment of host mice with diethylstilbestrol (DES), a synthetic estrogen, increases the number of ducts per unit area. Continuous treatment with DES induces expression of PR in luminal cells and down-regulates epithelial ERα. Estrogen plus progesterone treatment induces epithelial PR and then progesterone down-regulates its own receptor.

When the host mice become pregnant, mammary epithelial cells proliferate, the human ducts become distended with secretions and the apical cytoplasm of luminal cells is vacuolated. Both β casein and fat globule protein are increased [97]. PR knockout mice have shown that pregnancy-associated ductal side-branching and lobuloalveolar development require PRB expression [133].

During pregnancy, the trophoblast also secretes human chorionic gonadotropin (hCG). Levels of this hormone rise dramatically in early pregnancy, peak in the eighth to tenth week after fertilization and then fall to a constant level that is maintained until parturition (Fig. 1.15). hCG causes the corpus luteum to secrete massive quantities of estrogen and progesterone that are required to maintain the endometrium. Peak levels of hCG coincide with the highest levels of proliferation in the mother's breast. Human breast tissue implanted into nude mice that were then impregnated shows the same concurrence of proliferation and high hCG levels. Implants in nonpregnant mice can be stimulated to proliferate in a dose-dependent manner by exogenous hCG, but only if ovaries are intact, implying that hCG acts indirectly by increasing ovarian steroid production [229].

Even a single pregnancy carried to term (especially by a young mother) can protect against breast cancer. Pregnancy exposes the breast to a unique hormone profile, including prolonged progesterone elevation, human placental lactogen (hPL, aka human chorionic somatomammotropin), altered glucocorticoid secretion and increased levels of estrogen and PRL [230]. There are multiple pregnancy-induced permanent changes in the breasts of parous women, including: lower levels of PRL [231], a more differentiated gland with greater complexity of secretory lobules and less proliferative activity [193], an altered gene expression profile involving over 70 genes (in rodents) [232], and increased innate immune response proteins and DNA repair proteins [228]. In rats, it has been shown that hCG can substitute for pregnancy in its protective benefit. Furthermore, both pregnancy and treatment with hCG create the same (protective) genomic signature [233]. Some believe that this transformation occurs in the stem cell population, changing stem cells from a less differentiated "Stem cell 1" to a more differentiated, less vulnerable "Stem cell 2" [234]. hPL is a general metabolic hormone that is made by the placenta in quantities several times greater than the other placental hormones combined. Secretion of hPL begins about 3 weeks after fertilization and continues to rise throughout the rest of pregnancy. It enhances the effect of estrogen [97].

As is true in other life stages, several additional hormones are important to breast development in pregnancy. PRL from the mother's anterior pituitary rises from the fifth week of pregnancy until birth, at which time the levels of PRL are 10–20-fold higher than before conception. Estrogen, progesterone, PRL, GH and thyroid hormones are all essential to duct elongation and branching, as well as to alveolar budding [176].

1.4.5.3 Other Regulatory Factors in Breast Development during Pregnancy

FGFs [235] promote growth and alveolar differentiation during pregnancy, and CTGF is expressed during this time, possibly promoting lactational differentiation just as it does epithelial cells in culture. BRCA1 protects genomic stability and is expressed in rapidly proliferating tissues such as the mammary epithelium during pregnancy [236], where it favors differentiation at the expense of proliferation [237].

1.4.6 Lactation

1.4.6.1 Events in the Lactating Breast

During lactation, mammary lobules enlarge further and acinar lumens dilate, filled with a granular material and fat globules. Lobule size still varies significantly within the gland, at this time probably reflecting variations in milk secretory activity. The lactating breast is very similar to the breast of a pregnant woman, except that secretory products have markedly distended the ducts and acini [43] (Fig. 1.16). Myoepithelial cells increase

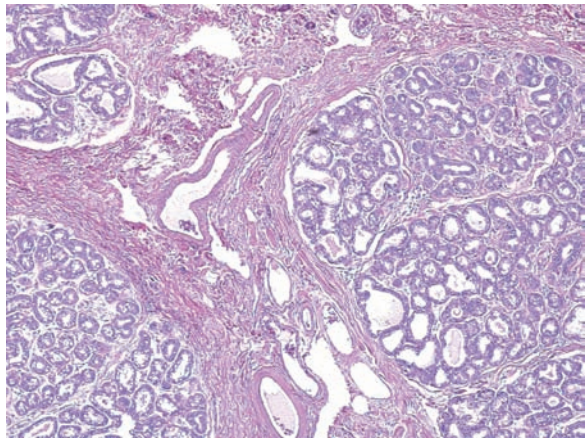

Fig. 1.16 Low power micrograph (50×) of a lactating human breast. Note the dilated ductules (now acini), many of which are filled with milk. The vasculature is abundant in the interlobular connective tissue

in number during pregnancy, but their differentiation is not complete until the onset of lactation when the number of myofilaments increases dramatically and contractile activity begins [10].

The luminal epithelium in the lactating breast has the expected secretory machinery: rough endoplasmic reticulum, a moderate number of rod-shaped mitochondria and Golgi complexes lateral and apical to the nucleus [36]. The membrane-bounded secretory vesicles contain extremely electron-dense protein granules (casein) suspended in a less dense fluid, presumably containing lactose [238] and noncasein whey proteins [36]. Endocytic vesicles seen throughout the luminal cell are thought to be involved in transcellular transport of immunoglobulins and other substances. Abundant lipid droplets are not membrane bounded, occur in a variety of sizes and contain fatty acids from the blood as well as some synthesized within mammary cells [36].

The lactating breast has increased density on MRI, consistent with increased glandular volume. There is diffuse high signal intensity on T2-weighted images, reflecting the high water fraction within milk [239].

1.4.6.2 The Process of Lactation

Placental hormones hPL, estrogen and progesterone are withdrawn at parturition, and maternal PRL, like fetal PRL, is freed from their inhibitory effects allowing the functional differentiation of the mammary gland to proceed. A 2–3 week period of secretion ensues before the appearance of fully mature milk.

In humans, transplacental transport of immunoglobulins provides humoral immunity to the newborn for the first weeks of life. This protection is complemented by IgA and lactoferrin, a protein with antimicrobial properties, in the colostrum. These proteins are able to cross the epithelium lining the infant digestive tract intact [240].

Beginning about 36 h after parturition, milk volume increases more than tenfold [241]. Tight junctions in the breast are tightly closed during lactation [93] and this decrease in permeability is accompanied by an increase in milk secretion. In the transition to mature milk, concentrations of sodium and chloride fall and lactose concentration increases. These changes are dependent on the closure of mammary epithelial tight junctions [242].

Milk composition varies during lactation and even between suckling episodes. Usually, milk is about 88% water, 7% carbohydrate (mainly lactose), 3.5% lipid (mainly triglycerides) and 1.5% protein (mainly lactalbumin and casein). Milk also contains important ions (sodium, potassium, chloride, calcium and phosphate), vitamins and IgA antibodies [243], as well as other antimicrobial substances such as cytokines and complement [244]. Human milk has several components not found in cow's milk, including lactoferrin, growth factors, long chain polyunsaturated fatty acids and glycoconjugates. The advantages of breast milk over formula feeding are many, including immune benefits and better mental development [245]. Formula fed infants have a different growth pattern and a greater risk of obesity than do breast fed infants [246]. However, the touted advantages of lower cancer risk and lower blood pressure later in life, as well as the claim that over half of infant deaths in North America are due to a failure to fully breast feed, may be exaggerated [247–249].

The lactating breast can be viewed as a lipid synthesizing machine. In mice, lipid secretion over a 20 day period is equal in weight to the entire lactating mouse [250]. In humans, maternal body fat and milk fat concentration are positively related. Low milk fat is correlated with increased milk volume, perhaps because infant demand is higher [251].

Secretory processes in the mammary gland involve five mechanisms: merocrine secretion, apocrine secretion, transport across the apical membrane, transcytosis of interstitial molecules and paracellular transit [241]. The two main mechanisms utilized by the luminal epithelial cells during lactation are merocrine and apocrine secretion.

Proteinaceous material is secreted by the merocrine method. Proteins destined for release into the lumen are synthesized in the rough endoplasmic reticulum, shuttled through the Golgi apparatus and carried by secretory vesicles to the surface membrane with which they fuse, emptying only their contents into the lumen. Protein secretion in the breast is primarily constitutive [241]. Most of the calcium in milk is also likely released via exocytosis of Golgi-derived secretory vesicles. Additional calcium transport from the cytoplasm to the surface is mediated by a calcium ATPase [252].

Lipid droplets are released from the cell by apocrine secretion, even though the loss of cytoplasm is slight [43]. The total amount of membrane lost over time, however, is extensive [36] and must be replaced by the endoplasmic reticulum – Golgi system [253]. The membrane released into the milk has two functions: it is the main source of phospholipids and cholesterol for

the infant, and it prevents released fat globules from coalescing into larger globules that might be difficult to secrete [241].

Specific transport mechanisms for sodium, potassium, chloride, calcium and phosphate ions are all present in the breast. Sodium, potassium, chloride and water directly permeate the cell membrane [254]. There is a glucose pathway across the apical membrane [255] and apical pathways also provide a means for the direct transfer of therapeutic drugs into milk [256]. Lactose secretion is primarily responsible for the osmotic movement of water into milk.

Transcytosis of interstitial molecules is one means whereby intact proteins can cross the mammary epithelium. Immunoglobulins enter milk via this mechanism [257]. IgA is synthesized by plasma cells and binds to receptors on the basal surface of the mammary alveolar cell. The IgA-receptor complex is endocytosed and transported to the apical surface where the receptor is cleaved and the cleaved portion is secreted along with the IgA. Other proteins, hormones and growth factors are thought to be secreted by similar mechanisms [241]. Once the IgA enters the newborn gut, it is also transcytosed across that epithelium [257].

The paracellular pathway allows passage of substances between epithelial cells. During lactation, however, the passage of even small molecular weight substances between epithelial cells is blocked by the very tight tight junctions mentioned earlier. Neutrophils, however, can apparently diapedese between epithelial cells to reach the milk after which the tight junctions reform behind them. It is important that the tight junctions are leaky both during pregnancy and following involution. This allows secretory products to leave the gland (presumably preventing distention) and protective molecules to enter the milk space in the former case, and products of mammary cell dissolution to be cleared from the breast in the latter [241].

1.4.6.3 Hormones During Lactation and Nursing

As mentioned earlier, progesterone promotes the functional differentiation of the breasts: budding of alveoli and transition of luminal epithelial cells into cells capable of milk secretion. PRL is essential for the functional differentiation of the breast following parturition, and pulsatile release of PRL is essential for successful lactation [58]. During labor, the levels of β-endorphins increase and stimulate the release of PRL [258]. PRL enhances development of tight junctions [242] and is one of several hormones important for lactation that is secreted in the breast itself [259] (GH is another [260]). After birth, maternal PRL levels fall, but a surge of PRL secretion occurs during each nursing episode. Unlike OXT release, which can occur in response to a baby's cry, the burst in PRL secretion requires the suckling stimulus [261]. Women with low levels of PRL during pregnancy have difficulty lactating [262]. GH, parathyroid hormone and insulin also promote lactation.

Each time the baby nurses, neural impulses transmitted to the hypothalamus result in the release of OXT. OXT, in turn, causes myoepithelial cells to contract and express milk from the alveoli into the lactiferous ducts, a process known as milk "let-down." However, psychogenic factors can inhibit the "let down" reflex [116, 261] since the hypothalamic neurons that synthesize OXT receive inputs from higher brain centers as well as the somatic afferent signals from the breast.

The short-term regulation of milk synthesis is related to the degree to which the breast is emptied during each feeding and perhaps to the frequency of feeding; thus, it is coupled closely to infant appetite [263]. After several months of breast feeding, especially if the infant is also being fed solid foods, FSH and LH levels will rise and reestablish the menstrual cycle. However, prior to that time, PRL inhibits LH and FSH secretion, preventing ovulation and mediating the contraceptive effect of breast feeding [116]. Even if nursing remains the sole source of infant nutrition, the secretory capacity of the breast eventually diminishes. Theories abound as to why this occurs, including secretory cell aging or a programmed developmental response related to maternal endocrine changes and/or target cell adaptations [264].

1.4.6.4 Other Regulatory Factors During Lactation

Clusterin, a glycoprotein involved in epithelial differentiation and morphogenesis, is up-regulated at the end of pregnancy. Blocking clusterin production in mice results in a decrease in the levels of milk production [265]. Alcohol consumption, often recommended to mothers with lactational difficulty, has been shown to increase PRL, but it decreases OXT, with the net effect of reducing milk yield [266].

1.4.6.5 Effects of Lactation on the Nursing Mother

While the breast and its hormonal milieu are important in the production of milk, lactation, in turn, has effects on the mother's body. These effects are highly variable. Most reports indicate that postpartum weight loss does not differ between lactating and nonlactating women, nor does regional weight distribution. Pregnancy promotes fat deposition in a gynoid subcutaneous distribution (buttocks and thighs), and postpartum weight loss is from the same regions, returning proportions to prepregnancy ratios [267].

PRL inhibits GnRH secretion and it also inhibits the action of GnRH on the pituitary and antagonizes the action of gonadotropins on the ovaries. As a result of these interactions, ovulation is inhibited. Thus, ovaries are inactive and estrogen and progesterone outputs fall. Nearly half of the menstrual cycles after menses resume are anovulatory. Nevertheless, 5–10% of women who are breastfeeding become pregnant [268].

New mothers are often anxious to lose the weight gained during pregnancy. Slow weight loss (about 1 lb/week) does not have an adverse effect on milk volume or composition if proper nutrition is maintained and nursing is on demand. Maternal plasma PRL concentration generally increases under conditions of negative energy balance and may protect lactation [269].

1.4.6.6 Calcium Metabolism During Lactation

Since milk is rich in calcium, the mammary gland needs a steady supply of calcium and mechanisms to secrete and concentrate it in milk. Mothers are in negative calcium balance during lactation. In spite of the fact that calcium is toxic to cells, mammary epithelial cells must transport large amounts of it from extracellular fluid through their cytoplasm into milk. The huge amount of calcium leaving the mother results in mobilization of skeletal calcium and a reduction in her bone mass. The increased bone resorption has been attributed to falling estrogen levels and increased PTHrP levels during lactation. Mammary epithelial cells secrete PTHrP into the circulation, directly participating in the dissolution of bones [270]. Amazingly, the calcium lost during breastfeeding is fully restored within a few months of weaning and women who breastfeed do not have long-term deficits in bone calcium [271].

1.4.7 Postlactational Involution

There are three overlapping stages to postlactational involution [101]. The first phase is reversible (by suckling [272]) and includes secretion cessation and loss of alveolar cell phenotype. The second involves alveolar cell apoptosis and phagocytosis and the third is characterized by regrowth of stromal adipose tissue.

While the size and secretory activity of the human mammary gland decline slowly as the infant begins to eat other foods, scientific understanding of postlactational involution is based primarily on laboratory animal studies where weaning is artificially abrupt and early (however, apoptosis also occurs in gradual weaning [272]). In these animals, secretion continues for a day or so and glands become so distended with milk that cells and alveolar walls rupture. Milk accumulation in the lumens of ducts and alveoli, as well as within the luminal epithelium itself, inhibits milk synthesis. A reduction in the volume of secretory cells and further inhibition of secretion ensues [172]. Immediately before postweaning apoptosis, the conformation of β1 integrin changes to a nonbinding state [78], disrupting the cell-ECM interaction and leading to a loss of the differentiated lactational phenotype [273]. Lactation-associated genes are inactivated (e.g., for β-casein) and involution-associated genes (e.g., for stromelysin) are activated [274]. This phase ultimately involves hundreds of genes [275].

Dedifferentiation and apoptosis will occur even if the animal becomes pregnant, suggesting that tissue remodeling is necessary for subsequent lactation [272]. Apoptosis, the actual death process, involves a loss of cell junctions and microvilli, nuclear chromatin condensation and margination, nucleolar dispersion, folding of nuclear membrane and nuclear fragmentation [276]. As much as 80% of mammary epithelial cells undergo apoptosis [277].

Autophagy, a mechanism whereby a cell destroys its own organelles [278], is intense in the luminal epithelium during involution. Lysosomal enzymes increase and remain high while other enzymes decline. Vacuoles contain organelles in various stages of degradation [36]. Cell autolysis, collapse of acini and narrowing of tubules, as well as macrophage infiltration, occur in parallel with regeneration of connective tissue [172]. Degenerating cells and debris are likely removed by the macrophages [279], although viable alveolar epithelial cells also phagocytose their apoptotic neighbors

[280]. The large number of apoptotic cells are cleared quickly and efficiently [277]. Myoepithelial cells generally persist [36].

During postlactational involution, inflammatory processes are suppressed and ECM degrading MMPs increase, as does the ratio of metalloproteinases to their inhibitors [101, 273, 281]. Both the BM and the stromal matrices are degraded [282, 283] in rodents, but BMs remain intact in cows and goats [272].

Although breast vascularity increases throughout life in nulliparous women, it is reset at a level below baseline subsequent to lactation [284] in women who have given birth. However, from the end of lactation to the onset of menopause, breasts of parous women contain more glandular tissue than those of nulliparous women [172].

IGFBP may initiate apoptosis by sequestering IGF-I, an important cell survival factor in the mammary gland [208, 285, 286], TGF-β_3 also may be an apoptosis initiator for alveolar cells [155] and is up-regulated by milk stasis at the beginning of weaning [277].

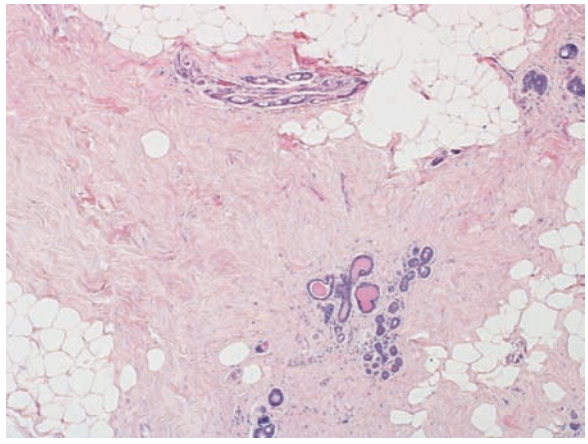

Fig. 1.17 Low power micrograph (50×) of a postmenopausal involuting human breast. As in the fetal breast (Fig. 12.) there are few ductules, abundant adipose tissue and dense irregular connective tissue

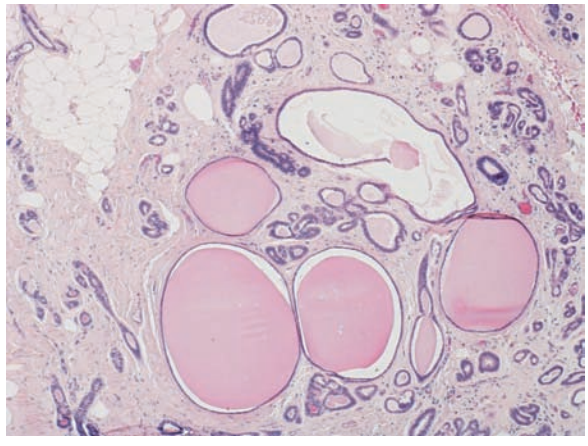

Fig. 1.18 Low power micrograph (50×) of a postmentopausal involuting human breast. Note the large cysts common in involuted breasts

1.4.8 Postmenopausal Involution

The permanent cessation of the menstrual cycle, menopause, occurs naturally with the decline of hormonal production between the ages of 35 and 60. Ovarian steroid production ceases almost completely. Following menopause, the breast regresses, with a decline in the number of more highly differentiated lobules and an increase in the number of less differentiated lobules (Figs. 1.17 and 1.18). Since parous women begin menopause with a higher number and percentage of the more differentiated lobule type, the postmenopausal events in the two groups differ in extent [33].

In postmenopausal involution, in contrast to postlactational involution, lobules and ducts are both reduced in number. Intralobular stroma (loose connective tissue) is replaced by collagen, while glandular epithelium and interlobular connective tissue regress and are replaced by fat. Periductal macrophages containing lipofuscin are often seen in the postmenopausal breast. Eventually, all that remains are a few acini and ducts embedded in a fatty stroma containing scattered wisps of collagen. Fibroblasts and elastic fibers decline in number [43]. A positive side-effect of the replacement of dense stroma with fat is the more effective use of mammographic screening in postmenopausal women, since the dense tumors contrast the fat [33]. The epithelium of some ducts may proliferate, and that of others may secrete and convert interrupted ducts into cysts [223] (Fig. 1.18).

1.4.9 Concluding Comments

The breast is studied by clinicians primarily due to its pathologies, especially cancer, and these will be addressed in the remainder of this text. In this chapter, I have attempted to provide a synopsis of current understanding of its normal structure and function. It is a unique and fascinating organ. The only gland that

completes the majority of its development after birth, it undergoes dramatic, complex, hormonally regulated changes during puberty. It varies moderately during each menstrual cycle, prepares for its primary function during pregnancy, and reaches its most differentiated status only following parturition. Involution ensues following each cycle of pregnancy, parturition and lactation, though permanent changes occur after the birth of even a single child that can be protective against cancer. The breast regresses after lactation to a much less differentiated state and may repeat this cycle over several more pregnancies and births. Once the ovary ceases to produce adequate estrogen and progesterone, the breast involutes, reverting to a structure not unlike that of a prepubertal child. I hope that this rather cursory review of normal breast biology serves as adequate foundation for the subsequent chapters and a reminder that the normal human breast is truly a fascinating and wonderful organ.

Acknowledgements I am extremely grateful to the following colleagues for their critical reading of the manuscript and their remarkable insights and their willingness to share them:

Juanita Anders, Ph.D., Diane Borst, Ph.D., Mathina Calliope, M.Ed., MFA Mary Lou Cutler, Ph.D., David Johnson, J.D., Walter Johnson, M.D., Stephen Rothwell, Ph.D., Richard Siarey, Ph.D. and John Wu, Ph.D. Also, thanks to Richard Conran, M.D. Ph.D., J.D. and Stephen Rothwell, Ph.D. for providing specimens for the micrographs included herein.

1.5 Appendix

1.5.1 A Brief Comparison of Murine and Human Breast

Differences between human and murine breasts include: (1) The mouse has a well-defined "fat pad" stroma into

Table 1.1 Additional factors that have been studied in the breast

Factor	Experimental model	Function	Reference
Jak/Stat	Various	Signaling pathway used by PRL and other hormones	Review [287]
Leptin	Cell culture	Promotes mammary epithelial cell proliferation	[288]
Hypoxia-inducible factor (HIF) 1	Mice null for HIF 1	Required for secretory differentiation and activation and production and secretion of milk of normal volume and composition	[117]
Notch signaling pathway	Human epithelial cell mammospheres in culture	Promotes proliferation of progenitor cells and promotes myoepithelial cell fate commitment and branching morphogenesis	[289]
Wnt signaling pathway	Human epithelial cell mammospheres in culture	(May) play role in human mammary stem cell self-renewal, differentiation and survival	[290]
Wnt signaling pathway	Rodents	Mammary rudiment development, ductal branching and alveolar morphogenesis	[291]
Gata-3	Genetically altered mice	Promotes stem cell differentiation into luminal cells, maintains the luminal cell type and is required for lactational sufficiency	[125, 292]
Hedghog signaling pathway	Mice	Involved in every stage of mammary gland development	[293]
Hedghog signaling pathway	Genetically altered mice	Repression is required for mammary bud formation	[294]
Stat5	Humans and genetically altered mice	Present in luminal cells and not myoepithelial cells. Regulates PRLR expression. Promotes growth and alveolar differentiation during pregnancy and cell survival during lactation	[222, 295]
Elf5	Mice	Required for growth and differentiation of alveolar epithelial cells in pregnancy and lactation	[296]
HEX, a homeobox gene	Normal human breast and normal and tumor cells lines	Amount in nucleus much higher during lactation. May play role in lactational differentiation	[297]

Table 1.2 Selected mammary gland-related mouse gene knockouts

Gene knocked out	Stage	Effect of knockout	Reference
LEF-1	Embryo	Fails to form first mammary buds	[298]
Tb×3	Embryo	Fails to form first mammary buds	[299]
Ms×2	Embryo	Arrests at mammary sprout stage	[300]
PTHrP	Embryo	Failure of branching morphogenesis	[301]
c-Src	Puberty	Fewer TEBs and decreased ductal outgrowth	[302]
ERα	Puberty	Failed expansion of ductal tree	[180]
PR	Puberty	Failed lobuloalveolar development	[303]
PRL	Virgin adult	No lobular decorations	[304]
CSF 1	Pregnancy	Incomplete ducts with precocious lobuloalveolar development	[305]
Cyclin D1	Pregnancy	Reduced acinar development and failure to lactate	[306]
α-lactalbumin	Lactation	Viscous milk	[307]
Whey acidic protein	Lactation	Pups die	[308]
OXT	Lactation	Inability to eject milk	[309]

which its ductwork grows. Human explants will not grow into the murine fat pad. Human stroma is much more fibrous. (2) The functional unit of the human is the terminal ductal lobular unit (TDLU), which has the appearance of a bunch of grapes arising from a stem (duct) and is embedded in loose connective tissue. The comparable mouse structure is the lobuloalveolar unit. It also contains alveoli and ductwork. However, during murine development the terminal end bud (TEB), a solid bulbous structure, is most often referred to in the literature. (3) Male mouse mammary glands regress prenatally under the influence of androgens, but infant human breasts are indistinguishable by gender. (4) Estrogen receptor alpha (ERα) is found in epithelia and stroma in the mouse, but, while expressed in human breast epithelial cells, it has not been documented in human breast stroma. (5) The mouse has five pairs of mammary glands, each pair regulated by slightly different factors, while the human has just one pair.

References

1. Romer AS (1970) The vertebrate body., 4th edn. WB Saunders, Philadelphia
2. Swaminathan N. Strange but true: males can lactate. ScientificAmerican.com. 2007
3. Wuringer E et al (1998) Nerve and vessel supplying ligamentous suspension of the mammary gland. Plast Reconstr Surg. 101(6):1486–93
4. Stranding S (ed). Gray's anatomy: the anatomical basis of clinical practice. 39th ed. Edinburgh: Elsevier, Churchill, Livingstone; 2005. p. 7
5. Moore KL. Clinically oriented anatomy. 5th ed. Baltimore: Lipincott Williams and Wilkins; 2006
6. Sarhadi NS, Shaw-Dunn J, Soutar DS (1997) Nerve supply of the breast with special reference to the nipple and areola: Sir Astley Cooper revisited. Clin Anat. 10(4):283–8
7. Schlenz I et al (2000) The sensitivity of the nipple-areola complex: an anatomic study. Plast Reconstr Surg. 105(3):905–9
8. Jaspars JJ et al (1997) The cutaneous innervation of the female breast and nipple-areola complex: implications for surgery. Br J Plast Surg. 50(4):249–59
9. Schlenz I, et al Alteration of nipple and areola sensitivity by reduction mammaplasty: a prospective comparison of five techniques. Plast Reconstr Surg. 2005;115(3):743–51; discussion 752–4
10. Wakerley JB. Milk ejection and its control. In: Neill JD, editor. Knobil and Neill's physiology. San Diego: Elsevier; 2006. p. 3129–3190
11. DelVecchyo C et al (2004) Evaluation of breast sensibility using dermatomal somatosensory evoked potentials. Plast Reconstr Surg. 113(7):1975–83
12. Godwin Y et al (2004) Investigation into the possible cause of subjective decreased sensory perception in the nipple-areola complex of women with macromastia. Plast Reconstr Surg. 113(6):1598–606
13. Bloom W, Don Fawcett W. A textbook of histology. 10th ed. Philadelphia: WB Saunders; 1975
14. Franke-Radowiecka A, Wasowicz K (2002) Adrenergic and cholinergic innervation of the mammary gland in the pig. Anat Histol Embryol. 31(1):3–7

15. Papay FA et al (1997) Complex regional pain syndrome of the breast in a patient after breast reduction. Ann Plast Surg. 39(4):347–52
16. Eriksson M et al (1996) Distribution and origin of peptide-containing nerve fibres in the rat and human mammary gland. Neuroscience. 70(1):227–45
17. Ricbourg B (1992) Applied anatomy of the breast: blood supply and innervation. Ann Chir Plast Esthet. 37(6):603–20
18. Naccarato AG et al (2003) Definition of the microvascular pattern of the normal human adult mammary gland. J Anat. 203(6):599–603
19. Weinstein SP, et al Hormonal variations in the vascularity of breast tissue. J Ultrasound Med. 2005;24(1):67–72; quiz 74
20. O'Rahilly M. Carpenter and Swenson, vessels, lymphatic drainage and the breast. 2004
21. Nathanson SD et al (2001) Pathways of lymphatic drainage from the breast. Ann Surg Oncol. 8(10):837–43
22. Braithwaite LR (1923) The flow of lymph from the ileocaecal angel, and its possible bearing on the cause of duodenal and gastric ulcer. Br J Surg. 11:7–26
23. Krag D et al (1998) The sentinel node in breast cancer–a multicenter validation study. N Engl J Med. 339(14):941–6
24. Estourgie SH et al (2004) Lymphatic drainage patterns from the breast. Ann Surg. 239(2):232–7
25. Vendrell-Torne E, Setoain-Quinquer J, Domenech-Torne FM (1971) Study of normal mammary lymphatic drainage using radioactive isotopes. J Nuclear Med. 13(11):801–5
26. Suami H et al (2008) The lymphatic anatomy of the breast and its implications for sentinel lymph node biopsy: a human cadaver study. Ann Surg Oncol. 15(3):863–71
27. Krynyckyi BR, Shim J, Kim CK. Internal mammary chain drainage of breast cancer. Ann Surg. 2004;240(3):557; author reply 558
28. Kellokumpu-Lehtinen P, Johansson RM, Pelliniemi LJ (1987) Ultrastructure of human fetal mammary gland. Anat Rec. 218(1):66–72
29. Herman-Giddens ME et al (1997) Secondary sexual characteristics and menses in young girls seen in office practice: a study from the pediatric research in office settings network. Pediatrics. 99(4):505–12
30. Tanner J (1962) Growth at adolescence., 2nd edn. Blackwell Scientific, Oxford
31. Tavassoli FA (1999) Pathology of the breast., 2nd edn. Appleton and Lange, Stamford, CT
32. Hussain Z et al (1999) Estimation of breast volume and its variation during the menstrual cycle using MRI and stereology. Br J Radiol. 72(855):236–45
33. Howard BA, Gusterson BA (2000) Human breast development. J Mammary Gland Biol Neoplasia. 5(2):119–37
34. Nelson CM, Bissell MJ (2005) Modeling dynamic reciprocity: engineering three-dimensional culture models of breast architecture, function, and neoplastic transformation. Semin Cancer Biol. 15(5):342–52
35. Rosen PR. Rosen's breast pathoogy. 2nd ed. Philadelphia, PA: Lippincott williams and Wilkins; 2001
36. Pitelka DR (1988) The mammary gland. In: Weiss L (ed) Cell and tissue biology: a textbook of histology. Elsevier Biomedical, New York, pp 880–98
37. Pathology, U.o.V.D.o. I. Gross Anatomy and Histology. 1998-2007 [cited; Available from: www.med-ed.virginia.edu/courses/path/gyn/breast1.cfm
38. Cardiff RD (1998) Are the TDLU of the human the same as the LA of mice? J Mammary Gland Biol Neoplasia. 3(1): 3–5
39. Moffat DF, Going JJ (1996) Three-dimensional anatomy of complete duct systems in human breast: pathological and developmental implications. J Clin Pathol. 49(1):48–52
40. Ohtake T et al (2001) Computer-assisted complete three-dimensional reconstruction of the mammary ductal/lobular systems: implications of ductal anastomoses for breast-conserving surgery. Cancer. 91(12):2263–72
41. Junqueira L, Carneiro J. Basic histology text and atlas. 10th ed. New York: Lange Medical Books McGraw-Hill; 2003
42. Ferguson DJ (1985) Intraepithelial lymphocytes and macrophages in the normal breast. Virchows Arch A Pathol Anat Histopathol. 407(4):369–78
43. Ross M, Pawlina W. Histology, a text and atlas. 5th ed. Baltimore: Lippincott Williams and Wilkins; 2006
44. Daniel CW, Strickland P, Friedmann Y (1995) Expression and functional role of E- and P-cadherins in mouse mammary ductal morphogenesis and growth. Dev Biol. 169(2): 511–9
45. Woodward WA et al (2005) On mammary stem cells. J Cell Sci. 118(Pt 16):3585–94
46. Deugnier MA et al (2002) The importance of being a myoepithelial cell. Breast Cancer Res. 4(6):224–30
47. Monaghan P, Moss D (1996) Connexin expression and gap junctions in the mammary gland. Cell Biol Int. 20(2):121–5
48. Glukhova M et al (1995) Adhesion systems in normal breast and in invasive breast carcinoma. Am J Pathol. 146 (3):706–16
49. Gudjonsson T et al (2002) Normal and tumor-derived myoepithelial cells differ in their ability to interact with luminal breast epithelial cells for polarity and basement membrane deposition. J Cell Sci. 115(Pt 1):39–50
50. Schmeichel KL, Weaver VM, Bissell MJ (1998) Structural cues from the tissue microenvironment are essential determinants of the human mammary epithelial cell phenotype. J Mammary Gland Biol Neoplasia. 3(2):201–13
51. Radice GL et al (1997) Precocious mammary gland development in P-cadherin-deficient mice. J Cell Biol. 139(4): 1025–32
52. Faraldo MM et al (2005) Myoepithelial cells in the control of mammary development and tumorigenesis: data from genetically modified mice. J Mammary Gland Biol Neoplasia. 10(3):211–9
53. Adriance MC et al (2005) Myoepithelial cells: good fences make good neighbors. Breast Cancer Res. 7(5):190–7
54. El-Sabban ME, Abi-Mosleh LF, Talhouk RS (2003) Developmental regulation of gap junctions and their role in mammary epithelial cell differentiation. J Mammary Gland Biol Neoplasia. 8(4):463–73
55. Gudjonsson T et al (2005) Myoepithelial cells: their origin and function in breast morphogenesis and neoplasia. J Mammary Gland Biol Neoplasia. 10(3):261–72
56. Lakhani SR, O'Hare MJ (2001) The mammary myoepithelial cell–Cinderella or ugly sister? Breast Cancer Res. 3(1):1–4
57. Liu S et al (2006) Hedgehog signaling and Bmi-1 regulate self-renewal of normal and malignant human mammary stem cells. Cancer Res. 66(12):6063–71
58. Hennighausen L, Robinson GW (2005) Information networks in the mammary gland. Nat Rev Mol Cell Biol. 6(9):715–25

59. Savarese TM et al (2006) Normal breast stem cells, malignant breast stem cells, and the perinatal origin of breast cancer. Stem Cell Rev. 2(2):103–10
60. Smalley M, Ashworth A (2003) Stem cells and breast cancer: a field in transit. Nat Rev Cancer. 3(11):832–44
61. Chepko G, Smith GH (1997) Three division-competent, structurally-distinct cell populations contribute to murine mammary epithelial renewal. Tissue Cell. 29(2):239–53
62. Smith GH, Medina D (1988) A morphologically distinct candidate for an epithelial stem cell in mouse mammary gland. J Cell Sci. 90(Pt 1):173–83
63. Smith GH, Strickland P, Daniel CW (2002) Putative epithelial stem cell loss corresponds with mammary growth senescence. Cell Tissue Res. 310(3):313–20
64. Daniel CW et al (1968) The in vivo life span of normal and preneoplastic mouse mammary glands: a serial transplantation study. Proc Natl Acad Sci USA. 61(1):53–60
65. Kordon EC, Smith GH (1998) An entire functional mammary gland may comprise the progeny from a single cell. Development. 125(10):1921–30
66. Shackleton M et al (2006) Generation of a functional mammary gland from a single stem cell. Nature. 439(7072): 84–8
67. Stingl J et al (1998) Phenotypic and functional characterization in vitro of a multipotent epithelial cell present in the normal adult human breast. Differentiation. 63(4):201–13
68. Villadsen R et al (2007) Evidence for a stem cell hierarchy in the adult human breast. J Cell Biol. 177(1):87–101
69. Welm BE et al (2002) Sca-1(pos) cells in the mouse mammary gland represent an enriched progenitor cell population. Dev Biol. 245(1):42–56
70. Clarke RB (2005) Isolation and characterization of human mammary stem cells. Cell Prolif. 38(6):375–86
71. Matulka LA, Triplett AA, Wagner KU (2007) Parity-induced mammary epithelial cells are multipotent and express cell surface markers associated with stem cells. Dev Biol. 303(1):29–44
72. Russo J et al (2006) The concept of stem cell in the mammary gland and its implication in morphogenesis, cancer and prevention. Front Biosci. 11:151–72
73. Stingl J et al (2005) Epithelial progenitors in the normal human mammary gland. J Mammary Gland Biol Neoplasia. 10(1):49–59
74. Wagner KU, Smith GH (2005) Pregnancy and stem cell behavior. J Mammary Gland Biol Neoplasia. 10(1):25–36
75. Dontu G et al (2003) In vitro propagation and transcriptional profiling of human mammary stem/progenitor cells. Genes Dev. 17(10):1253–70
76. Liu S, Dontu G, Wicha MS (2005) Mammary stem cells, self-renewal pathways, and carcinogenesis. Breast Cancer Res. 7(3):86–95
77. Guelstein VI et al (1993) Myoepithelial and basement membrane antigens in benign and malignant human breast tumors. Int J Cancer. 53(2):269–77
78. Prince JM et al (2002) Cell-matrix interactions during development and apoptosis of the mouse mammary gland in vivo. Dev Dyn. 223(4):497–516
79. Woodward TL et al (2001) Fibronectin and the alpha(5) beta(1) integrin are under developmental and ovarian steroid regulation in the normal mouse mammary gland. Endocrinology. 142(7):3214–22
80. Streuli CH, Bissell MJ (1990) Expression of extracellular matrix components is regulated by substratum. J Cell Biol. 110(4):1405–15
81. Pullan S et al (1996) Requirement of basement membrane for the suppression of programmed cell death in mammary epithelium. J Cell Sci. 109(Pt 3):631–42
82. Streuli C (1999) Extracellular matrix remodelling and cellular differentiation. Curr Opin Cell Biol. 11(5):634–40
83. Novaro V, Roskelley CD, Bissell MJ (2003) Collagen-IV and laminin-1 regulate estrogen receptor alpha expression and function in mouse mammary epithelial cells. J Cell Sci. 116(Pt 14):2975–86
84. Weir ML et al (2006) Dystroglycan loss disrupts polarity and beta-casein induction in mammary epithelial cells by perturbing laminin anchoring. J Cell Sci. 119(Pt 19):4047–58
85. Streuli CH et al (1995) Laminin mediates tissue-specific gene expression in mammary epithelia. J Cell Biol. 129(3):591–603
86. Farrelly N et al (1999) Extracellular matrix regulates apoptosis in mammary epithelium through a control on insulin signaling. J Cell Biol. 144(6):1337–48
87. Pujuguet P et al (2000) Nidogen-1 regulates laminin-1-dependent mammary-specific gene expression. J Cell Sci. 113(Pt 5):849–58
88. Streuli CH, Edwards GM (1998) Control of normal mammary epithelial phenotype by integrins. J Mammary Gland Biol Neoplasia. 3(2):151–63
89. Li N et al (2005) Beta1 integrins regulate mammary gland proliferation and maintain the integrity of mammary alveoli. Embo J. 24(11):1942–53
90. Klinowska TC et al (1999) Laminin and beta1 integrins are crucial for normal mammary gland development in the mouse. Dev Biol. 215(1):13–32
91. Barcellos-Hoff MH et al (1989) Functional differentiation and alveolar morphogenesis of primary mammary cultures on reconstituted basement membrane. Development. 105(2): 223–35
92. Blatchford DR et al (1999) Influence of microenvironment on mammary epithelial cell survival in primary culture. J Cell Physiol. 181(2):304–11
93. Neville MC (2006) Lactation and its hormonal control. In: Neill JD (ed.) Knobil and Neill's Physiology of Reproduction. San Diego: Elsevier. p. 2993–3054
94. Eyden BP et al (1986) Intralobular stromal fibroblasts in the resting human mammary gland: ultrastructural properties and intercellular relationships. J Submicrosc Cytol. 18(2):397–408
95. Atherton AJ et al (1992) Dipeptidyl peptidase IV expression identifies a functional sub-population of breast fibroblasts. Int J Cancer. 50(1):15–9
96. Sadlonova A et al (2005) Breast fibroblasts modulate epithelial cell proliferation in three-dimensional in vitro coculture. Breast Cancer Res. 7(1):R46–59
97. Parmar H, Cunha GR (2004) Epithelial-stromal interactions in the mouse and human mammary gland in vivo. Endocr Relat Cancer. 11(3):437–58
98. Boyd NF et al (2006) Mammographic density: a hormonally responsive risk factor for breast cancer. J Br Menopause Soc. 12(4):186–93
99. Gouon-Evans V, Lin EY, Pollard JW (2002) Requirement of macrophages and eosinophils and their cytokines/chemokines

for mammary gland development. Breast Cancer Res. 4(4):155–64
100. Schwertfeger KL, Rosen JM, Cohen DA (2006) Mammary gland macrophages: pleiotropic functions in mammary development. J Mammary Gland Biol Neoplasia. 11(3–4):229–38
101. Monks J et al (2002) Do inflammatory cells participate in mammary gland involution? J Mammary Gland Biol Neoplasia. 7(2):163–76
102. Sternlicht MD (2006) Key stages in mammary gland development: the cues that regulate ductal branching morphogenesis. Breast Cancer Res. 8(1):201
103. Nishimura T (2003) Expression of potential lymphocyte trafficking mediator molecules in the mammary gland. Vet Res. 34(1):3–10
104. Dabiri S et al (2004) The presence of stromal mast cells identifies a subset of invasive breast cancers with a favorable prognosis. Mod Pathol. 17(6):690–5
105. Hartveit F (1993) Mast cell association with collagen fibres in human breast stroma. Eur J Morphol 31(3):209–18
106. Popescu LM, Andrei F, Hinescu ME (2005) Snapshots of mammary gland interstitial cells: methylene-blue vital staining and c-kit immunopositivity. J Cell Mol Med. 9(2):476–7
107. Popescu LM et al (2005) The connective connection: interstitial cells of Cajal (ICC) and ICC-like cells establish synapses with immunoreactive cells. Electron microscope study in situ. J Cell Mol Med. 9(3):714–30
108. Radu E et al (2005) Cajal-type cells from human mammary gland stroma: phenotype characteristics in cell culture. J Cell Mol Med. 9(3):748–52
109. Gherghiceanu M, Popescu LM (2005) Interstitial Cajal-like cells (ICLC) in human resting mammary gland stroma. Transmission electron microscope (TEM) identification. J Cell Mol Med. 9(4):893–910
110. Haslam SZ, Woodward TL (2003) Host microenvironment in breast cancer development: epithelial-cell-stromal-cell interactions and steroid hormone action in normal and cancerous mammary gland. Breast Cancer Res. 5(4):208–15
111. Hynes RO (2002) Integrins: bidirectional, allosteric signaling machines. Cell. 110(6):673–87
112. Schatzmann F, Marlow R, Streuli CH (2003) Integrin signaling and mammary cell function. J Mammary Gland Biol Neoplasia. 8(4):395–408
113. Alowami S et al (2003) Mammographic density is related to stroma and stromal proteoglycan expression. Breast Cancer Res. 5(5):R129–35
114. Delehedde M et al (2001) Proteoglycans: pericellular and cell surface multireceptors that integrate external stimuli in the mammary gland. J Mammary Gland Biol Neoplasia. 6(3):253–73
115. Silverman AJ, Livne I, Witkin JW (1994) The gonadotropin-releasing hormone (GnRH), neuronal systems: immunocytochemistry and in situ hybridization. In: Knobil E, Neill JD (eds) The Physiology of Reproduction. Raven, New York, pp. 1683–709
116. Arthur Guyton C, John Hall E. Textbook of medical physiology. 11th ed. Elsevier Saunders. p. 1018
117. Seagroves TN et al (2003) HIF1alpha is a critical regulator of secretory differentiation and activation, but not vascular expansion, in the mouse mammary gland. Development. 130(8):1713–24
118. Speirs V et al (2002) Distinct expression patterns of ER alpha and ER beta in normal human mammary gland. J Clin Pathol. 55(5):371–4
119. Levin ER (2005) Integration of the extranuclear and nuclear actions of estrogen. Mol Endocrinol 19(8):1951–9
120. Li X et al (2004) Single-chain estrogen receptors (ERs) reveal that the ERalpha/beta heterodimer emulates functions of the ERalpha dimer in genomic estrogen signaling pathways. Mol Cell Biol. 24(17):7681–94
121. Clarke RB et al (1997) Dissociation between steroid receptor expression and cell proliferation in the human breast. Cancer Res. 57(22):4987–91
122. Howell A (2006) Pure oestrogen antagonists for the treatment of advanced breast cancer. Endocr Relat Cancer 13(3):689–706
123. Hall JM, McDonnell DP (1999) The estrogen receptor beta-isoform (ERbeta) of the human estrogen receptor modulates ERalpha transcriptional activity and is a key regulator of the cellular response to estrogens and antiestrogens. Endocrinology. 140(12):5566–78
124. Asselin-Labat ML et al (2006) Steroid hormone receptor status of mouse mammary stem cells. J Natl Cancer Inst. 98(14):1011–4
125. Asselin-Labat ML et al (2007) Gata-3 is an essential regulator of mammary-gland morphogenesis and luminal-cell differentiation. Nat Cell Biol. 9(2):201–9
126. Sleeman KE et al (2007) Dissociation of estrogen receptor expression and in vivo stem cell activity in the mammary gland. J Cell Biol. 176(1):19–26
127. Clarke RB (2006) Ovarian steroids and the human breast: regulation of stem cells and cell proliferation. Maturitas. 54(4):327–34
128. Cheng G et al (2004) Estrogen receptors ER alpha and ER beta in proliferation in the rodent mammary gland. Proc Natl Acad Sci USA. 101(11):3739–46
129. Khan SA, Bhandare D, Chatterton RT Jr (2005) The local hormonal environment and related biomarkers in the normal breast. Endocr Relat Cancer. 12(3):497–510
130. Mallepell S et al (2006) Paracrine signaling through the epithelial estrogen receptor alpha is required for proliferation and morphogenesis in the mammary gland. Proc Natl Acad Sci USA. 103(7):2196–201
131. Forster C et al (2002) Involvement of estrogen receptor beta in terminal differentiation of mammary gland epithelium. Proc Natl Acad Sci USA. 99(24):15578–83
132. Seagroves TN, Rosen JM. Control of mammary epithelial cell proliferation: the unique role of the progesterone receptor. In: Burnstein K, editor. Sex hormones and cell cycle regulation. Kluwer; 2002. p. 33–55
133. Conneely OM, Jericevic BM, Lydon JP (2003) Progesterone receptors in mammary gland development and tumorigenesis. J Mammary Gland Biol Neoplasia. 8(2):205–14
134. Leonhardt SA, Boonyaratanakornkit V, Edwards DP (2003) Progesterone receptor transcription and non-transcription signaling mechanisms. Steroids. 68(10–13): 761–70
135. Aupperlee MD, Haslam SZ (2007) Differential hormonal regulation and function of progesterone receptor isoforms in normal adult mouse mammary gland. Endocrinology. 148(5):2290–300

136. Lydon JP, Sivaraman L, Conneely OM (2000) A reappraisal of progesterone action in the mammary gland. J Mammary Gland Biol Neoplasia. 5(3):325–38
137. Cunha GR et al (1997) Elucidation of a role for stromal steroid hormone receptors in mammary gland growth and development using tissue recombinants. J Mammary Gland Biol Neoplasia. 2(4):393–402
138. Brisken C, Rajaram RD (2006) Alveolar and lactogenic differentiation. J Mammary Gland Biol Neoplasia. 11(3–4): 239–48
139. Yang Y et al (1995) Sequential requirement of hepatocyte growth factor and neuregulin in the morphogenesis and differentiation of the mammary gland. J Cell Biol. 131(1): 215–26
140. Kariagina A, Aupperlee MD, Haslam SZ (2007) Progesterone receptor isoforms and proliferation in the rat mammary gland during development. Endocrinology. 148(6):2723–36
141. Eigeliene N, Harkonen P, Erkkola R (2006) Effects of estradiol and medroxyprogesterone acetate on morphology, proliferation and apoptosis of human breast tissue in organ cultures. BMC Cancer. 6:246
142. Freeman ME et al (2000) Prolactin: structure, function and regulation of secretion. Physiol Rev. 80(4):1523–631
143. Horseman ND (1999) Prolactin and mammary gland development. J Mammary Gland Biol Neoplasia. 4(1):79–88
144. Dong J, Tsai-Morris CH, Dufau ML (2006) A novel estradiol/estrogen receptor alpha-dependent transcriptional mechanism controls expression of the human prolactin receptor. J Biol Chem. 281(27):18825–36
145. Honda K et al (2004) Prolactin releasing peptides modulate background firing rate and milk-ejection related burst of oxytocin cells in the supraoptic nucleus. Brain Res Bull. 63:315–9
146. Bussolati G et al (1996) Immunolocalization and gene expression of oxytocin receptors in carcinomas and non-neoplastic tissues of the breast. Am J Pathol. 148(6):1895–903
147. Reversi A, Cassoni P, Chini B (2005) Oxytocin receptor signaling in myoepithelial and cancer cells. J Mammary Gland Biol Neoplasia. 10(3):221–9
148. Kleinberg DL, Feldman M, Ruan W (2000) IGF-I: an essential factor in terminal end bud formation and ductal morphogenesis. J Mammary Gland Biol Neoplasia. 5(1):7–17
149. Labrie F (2006) Dehydroepiandrosterone, androgens and the mammary gland. Gynecol Endocrinol. 22(3):118–30
150. Wilson CL et al (2006) Effects of oestrogen on gene expression in epithelium and stroma of normal human breast tissue. Endocr Relat Cancer. 13(2):617–28
151. Woodward TL, Xie JW, Haslam SZ (1998) The role of mammary stroma in modulating the proliferative response to ovarian hormones in the normal mammary gland. J Mammary Gland Biol Neoplasia. 3(2):117–31
152. Lamarca HL, Rosen JM (2007) Estrogen regulation of mammary gland development and breast cancer: amphiregulin takes center stage. Breast Cancer Res. 9(4):304
153. Zhang HZ et al (2002) Estrogen mediates mammary epithelial cell proliferation in serum-free culture indirectly via mammary stroma-derived hepatocyte growth factor. Endocrinology. 143(9):3427–34
154. Soriano JV et al (1998) Roles of hepatocyte growth factor/scatter factor and transforming growth factor-beta1 in mammary gland ductal morphogenesis. J Mammary Gland Biol Neoplasia. 3(2):133–50
155. Pollard JW (2001) Tumour-stromal interactions. Transforming growth factor-beta isoforms and hepatocyte growth factor/scatter factor in mammary gland ductal morphogenesis. Breast Cancer Res. 3(4):230–7
156. Kamalati T et al (1999) HGF/SF in mammary epithelial growth and morphogenesis: in vitro and in vivo models. J Mammary Gland Biol Neoplasia. 4(1):69–77
157. Britten CD (2004) Targeting ErbB receptor signaling: a pan-ErbB approach to cancer. Mol Cancer Ther. 3(10):1335–42
158. Wiesen JF et al (1999) Signaling through the stromal epidermal growth factor receptor is necessary for mammary ductal development. Development. 126(2):335–44
159. Osin PP et al (1998) Breast development gives insights into breast disease. Histopathology. 33(3):275–83
160. Normanno N, Ciardiello F (1997) EGF-related peptides in the pathophysiology of the mammary gland. J Mammary Gland Biol Neoplasia. 2(2):143–51
161. Ruan W, Kleinberg DL (1999) Insulin-like growth factor I is essential for terminal end bud formation and ductal morphogenesis during mammary development. Endocrinology. 140(11):5075–81
162. Wood TL, Yee D (2000) Introduction: IGFs and IGFBPs in the normal mammary gland and in breast cancer. J Mammary Gland Biol Neoplasia. 5(1):1–5
163. Ahmad T et al (2004) The mitogenic action of insulin-like growth factor I in normal human mammary epithelial cells requires the epidermal growth factor receptor tyrosine kinase. J Biol Chem. 279(3):1713–9
164. Wang W et al (2008) Glucocorticoid induced expression of connective tissue growth factor contributes to lactogenic differentiation of mouse mammary epithelial cells. J Cell Physiol. 214(1):38–46
165. Jiang WG et al (2004) Differential expression of the CCN family members Cyr61. CTGF and Nov in human breast cancer. Endocr Relat Cancer. 11(4):781–91
166. Anbazhagan R, Gusterson BA (1994) Prenatal factors may influence predisposition to breast cancer. Eur J Cancer. 30A(1):1–3
167. Hilakivi-Clarke L, de Assis S (2006) Fetal origins of breast cancer. Trends Endocrinol Metab. 17(9):340–8
168. Trichopoulos D, Lagiou P, Adami HO (2005) Towards an integrated model for breast cancer etiology: the crucial role of the number of mammary tissue-specific stem cells. Breast Cancer Res. 7(1):13–7
169. Hens JR, Wysolmerski JJ (2005) Key stages of mammary gland development: molecular mechanisms involved in the formation of the embryonic mammary gland. Breast Cancer Res. 7(5):220–4
170. Jolicoeur F (2005) Intrauterine breast development and the mammary myoepithelial lineage. J Mammary Gland Biol Neoplasia. 10(3):199–210
171. Arey L (1974) Developmental anatomy: a textbook and laboratory manual of embryology. Revised 7th ed. WB Saunders, Philadelphia
172. Russo J, Russo IH (1999) Mammary gland development. In: Knobil E, Neill, JD, (eds) Encyclopedia of reproduction San Diego: Academic Press.
173. Sadler TW (2003) Langman's medical embryolgy., 9th edn. Lippincott Williams and Wilkins, Baltimore
174. Robinson GW, Karpf AB, Kratochwil K (1999) Regulation of mammary gland development by tissue interaction. J Mammary Gland Biol Neoplasia. 4(1):9–19

175. Anbazhagan R et al (1998) The development of epithelial phenotypes in the human fetal and infant breast. J Pathol. 184(2):197–206
176. Hovey RC, Trott JF, Vonderhaar BK (2002) Establishing a framework for the functional mammary gland: from endocrinology to morphology. J Mammary Gland Biol Neoplasia. 7(1):17–38
177. Tobon H, Slazar H (1974) Ultrastructure of the human mammary gland. I. Development of the fetal gland throughout gestation. J Clin Endocrinol Metab. 39(3):443–56
178. Kratochwil K, Schwartz P (1976) Tissue interaction in androgen response of embryonic mammary rudiment of mouse: identification of target tissue for testosterone. Proc Natl Acad Sci USA. 73(11):4041–4
179. Turner CW (1930) The anatomy of the mammary gland in cattle. II. Fetal development. Missouri Agric Exp Sta Res Bull. 160:5–39
180. Bocchinfuso WP et al (2000) Induction of mammary gland development in estrogen receptor-alpha knockout mice. Endocrinology. 141(8):2982–94
181. Aubert MJ, Grumbach MM, Kaplan SL (1975) The ontogenesis of human fetal hormones. III. Prolactin. J Clin Invest. 56(1):155–64
182. Keeling JW et al (2000) Oestrogen receptor alpha in female fetal, infant, and child mammary tissue. J Pathol. 191(4):449–51
183. Naccarato AG et al (2000) Bio-morphological events in the development of the human female mammary gland from fetal age to puberty. Virchows Arch. 436(5):431–8
184. Nathan B, Anbazhagan R, Clarkson P, Bartkova J (1994) Expression of BCL-2 in thedeveloping human fetal and infant breast. Histopathology. 24:73–6
185. Magdinier F et al (1999) BRCA1 expression during prenatal development of the human mammary gland. Oncogene. 18(27):4039–43
186. Casey TM et al (2007) Mammary epithelial cells treated concurrently with TGF-alpha and TGF-beta exhibit enhanced proliferation and death. Exp Biol Med (Maywood). 232(8):1027–40
187. Stull MA et al (2004) Growth factor regulation of cell cycle progression in mammary epithelial cells. J Mammary Gland Biol Neoplasia. 9(1):15–26
188. Streuli CH et al (1993) Extracellular matrix regulates expression of the TGF-beta 1 gene. J Cell Biol. 120(1):253–60
189. Chammas R et al (1994) Laminin and tenascin assembly and expression regulate HC11 mouse mammary cell differentiation. J Cell Sci. 107(Pt 4):1031–40
190. Dunbar ME, Wysolmerski JJ. The role of parathyroid hormone-related protein (PTHrP) in mammary development, lactation, and breast cancer. 1996 [cited; Available from: http://mammary.nih.gov/reviews/development/Wyso1001/slides/introduction.html
191. McKiernan J, Coyne J, Cahalane S (1988) Histology of breast development in early life. Arch Dis Child. 63(2): 136–9
192. McKiernan JF, Hull D (1981) Breast development in the newborn. Arch Dis Childhood. 56:525–9
193. Russo J, Russo IH (1994) Toward a physiological approach to breast cancer prevention. Cancer Epidemiol Biomark Prev. 3(4):353–64
194. Russo J, Russ IH (1987) Development of the human mammary gland. In: Neville MD, Daniel C (eds) The mammary gland: development, regulation and function. Plenum, New York
195. McKiernan JF, Hull D (1981) Prolactin, maternal oestrogens, and breast development in the newborn. Arch Dis Child. 56(10):770–4
196. Schmidt IM et al (2002) Gender difference in breast tissue size in infancy: correlation with serum estradiol. Pediatr Res. 52(5):682–6
197. Pierce DF Jr et al (1993) Inhibition of mammary duct development but not alveolar outgrowth during pregnancy in transgenic mice expressing active TGF-beta 1. Genes Dev. 7(12A):2308–17
198. Russo I, Medado J, Russo J (1989) Endocrine influences on the mammary gland. In: Jones T, Mohr U, Hunt E (eds) Integument and mammary glands. Springer, Berlin
199. Humphreys RC (1999) Programmed cell death in the terminal end bud. J Mammary Gland Biol Neoplasia. 4(2): 213–20
200. Humphreys RC et al (1996) Apoptosis in the terminal end bud of the murine mammary gland: a mechanism of ductal morphogenesis. Development. 122(12):4013–22
201. Britt K, Ashworth A, Smalley M (2007) Pregnancy and the risk of breast cancer. Endocr Relat Cancer. 14(4):907–33
202. Williams JM, Daniel CW (1983) Mammary ductal elongation: differentiation of myoepithelium and basal lamina during branching morphogenesis. Dev Biol. 97(2):274–90
203. Topper YJ, Freeman CS (1980) Multiple hormone interactions in the developmental biology of the mammary gland. Physiol Rev. 60(4):1049–106
204. Anderson E, Clarke RB, Howell A (1998) Estrogen responsiveness and control of normal human breast proliferation. J Mammary Gland Biol Neoplasia. 3(1):23–35
205. Laurence DJ, Monaghan P, Gusterson BA (1991) The development of the normal human breast. Oxf Rev Reprod Biol. 13:149–74
206. Russo J et al (2001) Cancer risk related to mammary gland structure and development. Microsc Res Tech. 52(2):204–23
207. Feldman M et al (1993) Evidence that the growth hormone receptor mediates differentiation and development of the mammary gland. Endocrinology. 133(4):1602–8
208. Marshman E, Streuli CH (2002) Insulin-like growth factors and insulin-like growth factor binding proteins in mammary gland function. Breast Cancer Res. 4(6):231–9
209. Howlin J, McBryan J, Martin F (2006) Pubertal mammary gland development: insights from mouse models. J Mammary Gland Biol Neoplasia. 11(3–4):283–97
210. Going JJ et al (1988) Proliferative and secretory activity in human breast during natural and artificial menstrual cycles. Am J Pathol. 130(1):193–204
211. Ramakrishnan R, Khan SA, Badve S (2002) Morphological changes in breast tissue with menstrual cycle. Mod Pathol. 15(12):1348–56
212. Navarrete MA et al (2005) Assessment of the proliferative, apoptotic and cellular renovation indices of the human mammary epithelium during the follicular and luteal phases of the menstrual cycle. Breast Cancer Res. 7(3):R306–13
213. Andres AC, Strange R (1999) Apoptosis in the estrous and menstrual cycles. J Mammary Gland Biol Neoplasia. 4(2):221–8
214. Fanager H, Ree HJ (1974) Cyclic changes of human mammary gland epithelium in relation to the menstrual cycle–an ultrastructural study. Cancer. 34:574–85

215. Ferguson JE et al (1992) Changes in the extracellular matrix of the normal human breast during the menstrual cycle. Cell Tissue Res. 268(1):167–77
216. McCarty KS Jr et al (1982) Immunoglobulin localization in the normal human mammary gland: variation with the menstrual cycle. Am J Pathol. 107(3):322–6
217. Kass R, Mancino AT, Rosenbloom AL, Klimberg VS, Bland KI (2004) Breast physiology: normal and abnormal development and function. In: Bland KI, Copeland EM III (eds) The breast: comprehensive management of benign and malignant disorders. Saunders, St. Louis, Missouri
218. Silva JS et al (1983) Menstrual cycle-dependent variations of breast cyst fluid proteins and sex steroid receptors in the normal human breast. Cancer. 51(7):1297–302
219. Fabris G et al (1987) Pathophysiology of estrogen receptors in mammary tissue by monoclonal antibodies. J Steroid Biochem. 27:171–6
220. Dabrosin C (2005) Increased extracellular local levels of estradiol in normal breast in vivo during the luteal phase of the menstrual cycle. J Endocrinol. 187(1):103–8
221. Gompel A et al (1996) Epidermal growth factor receptor and c-erbB-2 expression in normal breast tissue during the menstrual cycle. Breast Cancer Res Treat. 38(2):227–35
222. Nevalainen MT et al (2002) Basal activation of transcription factor signal transducer and activator of transcription (Stat5) in nonpregnant mouse and human breast epithelium. Mol Endocrinol. 16(5):1108–24
223. Ham AW (1969) Histology., 6th edn. JB Lippincott, Philadelphia
224. Russell TD et al (2007) Cytoplasmic lipid droplet accumulation in developing mammary epithelial cells: roles of adipophilin and lipid metabolism. J Lipid Res. 48(7):1463–75
225. Morroni M et al (2004) Reversible transdifferentiation of secretory epithelial cells into adipocytes in the mammary gland. Proc Natl Acad Sci USA. 101(48):16801–6
226. Piliero SJ, Jacobs MS, Wischnitzer S (1965) Atlas of histology. JB Lippincott, Philadelphia
227. Medina D (2005) Mammary developmental fate and breast cancer risk. Endocr Relat Cancer. 12(3):483–95
228. Balogh GA et al (2006) Genomic signature induced by pregnancy in the human breast. Int J Oncol. 28(2):399–410
229. Popnikolov N et al (2001) Reconstituted normal human breast in nude mice: effect of host pregnancy environment and human chorionic gonadotropin on proliferation. J Endocrinol. 168(3):487–96
230. Numan M (1994) Maternal behavior. In: Knobil E, Neill JD (eds) The physiology of reproduction. Raven, New York, pp. 221–302
231. Eliassen AH, Tworoger SS, Hankinson SE (2007) Reproductive factors and family history of breast cancer in relation to plasma prolactin levels in premenopausal and postmenopausal women. Int J Cancer. 120(7):1536–41
232. Blakely CM et al (2006) Hormone-induced protection against mammary tumorigenesis is conserved in multiple rat strains and identifies a core gene expression signature induced by pregnancy. Cancer Res. 66(12):6421–31
233. Russo J et al (2005) Breast differentiation and its implication in cancer prevention. Clin Cancer Res. 11(2 Pt 2): 931s–6s
234. Russo J et al (2005) The protective role of pregnancy in breast cancer. Breast Cancer Res. 7(3):131–42
235. Jackson D, Bresnick J, Dickson C (1997) A role for fibroblast growth factor signaling in the lobuloalveolar development of the mammary gland. J Mammary Gland Biol Neoplasia. 2(4):385–92
236. Laud K et al (2001) Expression of BRCA1 gene in ewe mammary epithelial cells during pregnancy: regulation by growth hormone and steroid hormones. Eur J Endocrinol. 145(6):763–70
237. Furuta S et al (2005) Depletion of BRCA1 impairs differentiation but enhances proliferation of mammary epithelial cells. Proc Natl Acad Sci USA. 102(26):9176–81
238. Burkitt HG, Young B, Heathe JW (1993) Wheater's functional histology, a text and colour atlas., 3rd edn. Churchill Livingstone, Edinburgh
239. Espinosa LA et al (2005) The lactating breast: contrast-enhanced MR imaging of normal tissue and cancer. Radiology. 237(2):429–36
240. Forsyth I. Mammary gland, overview. In: Knobil E, Neill JD, editors. Encyclopedia of reproduction. Academic; 1999. p. 81–88
241. Neville MC. Milk secretion: an overview. 1998 [cited 07/31/2007]; Available from: http://mammary.nih.gov/Reviews/lactation/Neville001/index.html
242. Itoh M, Bissell MJ (2003) The organization of tight junctions in epithelia: implications for mammary gland biology and breast tumorigenesis. J Mammary Gland Biol Neoplasia. 8(4):449–62
243. Young B, Wheater PR (2006) Wheater's functional histology: a text and colour atlas., 5th edn. Churchill Livingstone Elsevier, Oxford, p. 437
244. Kolb AF (2002) Engineering immunity in the mammary gland. J Mammary Gland Biol Neoplasia. 7(2):123–34
245. Uauy R, De Andraca I (1995) Human milk and breast feeding for optimal mental development. J Nutr. 125(8 Suppl):2278S–80S
246. Lawson M (2007) Contemporary aspects of infant feeding. Paediatr Nurs. 19(2):39–46
247. Owen CG et al (2003) Effect of breast feeding in infancy on blood pressure in later life: systematic review and meta-analysis. BMJ. 327(7425):1189–95
248. Martin RM et al (2005) Breast-feeding and cancer: the Boyd Orr cohort and a systematic review with meta-analysis. J Natl Cancer Inst. 97(19):1446–57
249. Frank JW, Newman J (1993) Breast-feeding in a polluted world: uncertain risks, clear benefits. CMAJ. 149(1):33–7
250. Rudolph MC et al (2007) Metabolic regulation in the lactating mammary gland: a lipid synthesizing machine. Physiol Genomics. 28(3):323–36
251. Villalpando S, del Prado M (1999) Interrelation among dietary energy and fat intakes, maternal body fatness, and milk total lipid in humans. J Mammary Gland Biol Neoplasia. 4(3):285–95
252. Neville MC (2005) Calcium secretion into milk. J Mammary Gland Biol Neoplasia. 10(2):119–28
253. Keenan TS, Franke WW, Mather IH, Morre DJ (1978) Endomembrane composition and function in milk formation. In: Larson BL (ed) Lactation. Academic, New York, p 105
254. Linzell JL, Peaker M (1971) Mechanism of milk secretion. Physiol Rev. 51(3):564–97
255. Neville MC (1990) The physiological basis of milk secretion. Ann N Y Acad Sci. 586:1–11

256. Fleishaker JC, McNamara PJ (1988) In vivo evaluation in the lactating rabbit of a model for xenobiotic distribution into breast milk. J Pharmacol Exp Ther. 244(3): 919–24
257. Hunziker W, Kraehenbuhl JP (1998) Epithelial transcytosis of immunoglobulins. J Mammary Gland Biol Neoplasia. 3(3):287–302
258. Csontos K et al (1979) Elevated plasma beta-endorphin levels in pregnant women and their neonates. Life Sci. 25(10):835–44
259. Clevenger CV, Plank TL (1997) Prolactin as an autocrine/paracrine factor in breast tissue. J Mammary Gland Biol Neoplasia. 2(1):59–68
260. Mol JA et al (2000) Progestin-induced mammary growth hormone (GH) production. Adv Exp Med Biol. 480:71–6
261. McNeilly AS et al (1983) Release of oxytocin and prolactin in response to suckling. Br Med J (Clin Res Ed). 286(6361):257–9
262. Martin RH, Oakey RE (1982) The role of antenatal oestrogen in postpartum human lactogenesis: evidence from oestrogen-deficient pregnancies. Clin Endocrinol (Oxford England). 17(4):403–8
263. Daly SE et al (1996) Frequency and degree of milk removal and the short-term control of human milk synthesis. Exp Physiol. 81(5):861–75
264. Hadsell D, George J, Torres D (2007) The declining phase of lactation: peripheral or central, programmed or pathological? J Mammary Gland Biol Neoplasia. 12(1):59–70
265. Itahana Y et al (2007) Regulation of clusterin expression in mammary epithelial cells. Exp Cell Res. 313(5):943–51
266. Mennella JA, Pepino MY, Teff KL (2005) Acute alcohol consumption disrupts the hormonal milieu of lactating women. J Clin Endocrinol Metab. 90(4):1979–85
267. Butte NF, Hopkinson JM (1998) Body composition changes during lactation are highly variable among women. J Nutr. 128(2 Suppl):381S–5S
268. Ganong's Review of Medical Physiology. 23rd ed. Lange. 2009. p. 452
269. Dewey KG (1998) Effects of maternal caloric restriction and exercise during lactation. J Nutr. 128(2 Suppl):386S–9S
270. Wysolmerski J (2005) Calcium handling by the lactating breast and its relationship to calcium-related complications of breast cancer. J Mammary Gland Biol Neoplasia. 10(2):101–3
271. Kovacs CS (2005) Calcium and bone metabolism during pregnancy and lactation. J Mammary Gland Biol Neoplasia. 10(2):105–18
272. Wilde CJ, Knight CH, Flint DJ (1999) Control of milk secretion and apoptosis during mammary involution. J Mammary Gland Biol Neoplasia. 4(2):129–36
273. Talhouk RS, Bissell MJ, Werb Z (1992) Coordinated expression of extracellular matrix-degrading proteinases and their inhibitors regulates mammary epithelial function during involution. J Cell Biol. 118(5):1271–82
274. Marti A et al (1999) Transcription factor activities and gene expression during mouse mammary gland involution. J Mammary Gland Biol Neoplasia. 4(2):145–52
275. Stein T, Salomonis N, Gusterson BA (2007) Mammary gland involution as a multi-step process. J Mammary Gland Biol Neoplasia. 12(1):25–35
276. Jaggi R. Morphological changes during programmed cell death (PCD) in the involuting mouse mammary gland. 1996 [cited; Available from: http://mammary.nih.gov/reviews/development/Jaggi001/index.html
277. Baxter FO, Neoh K, Tevendale MC (2007) The beginning of the end: death signaling in early involution. J Mammary Gland Biol Neoplasia. 12(1):3–13
278. Thorburn A (2007) Apoptosis and autophagy: regulatory connections between two supposedly different processes. Apoptosis. 13(1):1–9
279. Atabai K, Sheppard D, Werb Z (2007) Roles of the innate immune system in mammary gland remodeling during involution. J Mammary Gland Biol Neoplasia. 12(1):37–45
280. Fadok VA (1999) Clearance: the last and often forgotten stage of apoptosis. J Mammary Gland Biol Neoplasia. 4(2):203–11
281. Watson CJ (2006) Involution: apoptosis and tissue remodelling that convert the mammary gland from milk factory to a quiescent organ. Breast Cancer Res. 8(2):203
282. Streuli CH, Gilmore AP (1999) Adhesion-mediated signaling in the regulation of mammary epithelial cell survival. J Mammary Gland Biol Neoplasia. 4(2):183–91
283. Martinez-Hernandez A, Fink LM, Pierce GB (1976) Removal of basement membrane in the involuting breast. Lab Invest. 34(5):455–62
284. Simpson HW et al (2002) Pregnancy postponement and childlessness leads to chronic hypervascularity of the breasts and cancer risk. Br J Cancer. 87(11):1246–52
285. Flint DJ, Tonner E, Allan GJ (2000) Insulin-like growth factor binding proteins: IGF-dependent and -independent effects in the mammary gland. J Mammary Gland Biol Neoplasia. 5(1):65–73
286. Lochrie JD et al (2006) Insulin-like growth factor binding protein (IGFBP)-5 is up-regulated during both differentiation and apoptosis in primary cultures of mouse mammary epithelial cells. J Cell Physiol. 207(2):471–9
287. Watson CJ, Burdon TG (1996) Prolactin signal transduction mechanisms in the mammary gland: the role of the Jak/Stat pathway. Rev Reprod. 1(1):1–5
288. Hu X et al (2002) Leptin–a growth factor in normal and malignant breast cells and for normal mammary gland development. J Natl Cancer Inst. 94(22):1704–11
289. Dontu G et al (2004) Role of Notch signaling in cell-fate determination of human mammary stem/progenitor cells. Breast Cancer Res. 6(6):R605–15
290. Dontu G, Wicha MS (2005) Survival of mammary stem cells in suspension culture: implications for stem cell biology and neoplasia. J Mammary Gland Biol Neoplasia. 10(1):75–86
291. Rowley M, Grothey E, Couch FJ (2004) The role of Tbx2 and Tbx3 in mammary development and tumorigenesis. J Mammary Gland Biol Neoplasia. 9(2):109–18
292. Kouros-Mehr H et al (2006) GATA-3 maintains the differentiation of the luminal cell fate in the mammary gland. Cell. 127(5):1041–55
293. Lewis MT, Veltmaat JM (2004) Next stop, the twilight zone: hedgehog network regulation of mammary gland development. J Mammary Gland Biol Neoplasia. 9(2):165–81
294. Hatsell S, Frost AR (2007) Hedgehog signaling in mammary gland development and breast cancer. J Mammary Gland Biol Neoplasia. 12(2–3):163–73
295. Groner B (2002) Transcription factor regulation in mammary epithelial cells. Domest Anim Endocrinol. 23(1–2): 25–32

296. Zhou J et al (2005) Elf5 is essential for early embryogenesis and mammary gland development during pregnancy and lactation. Embo J. 24(3):635–44
297. Puppin C et al (2006) HEX expression and localization in normal mammary gland and breast carcinoma. BMC Cancer. 6:192
298. van Genderen C et al (1994) Development of several organs that require inductive epithelial-mesenchymal interactions is impaired in LEF-1-deficient mice. Genes Dev. 8(22): 2691–703
299. Davenport TG, Jerome-Majewska LA, Papaioannou VE (2003) Mammary gland, limb and yolk sac defects in mice lacking Tbx3, the gene mutated in human ulnar mammary syndrome. Development. 130(10):2263–73
300. Satokata I et al (2000) Msx2 deficiency in mice causes pleiotropic defects in bone growth and ectodermal organ formation. Nat Genet. 24(4):391–5
301. Dunbar ME et al (1999) Parathyroid hormone-related protein signaling is necessary for sexual dimorphism during embryonic mammary development. Development. 126(16):3485–93
302. Kim H, Laing M, Muller W (2005) c-Src-null mice exhibit defects in normal mammary gland development and ERalpha signaling. Oncogene. 24(36):5629–36
303. Lydon JP et al (1995) Mice lacking progesterone receptor exhibit pleiotropic reproductive abnormalities. Genes Dev. 9(18):2266–78
304. Horseman ND et al (1997) Defective mammopoiesis, but normal hematopoiesis, in mice with a targeted disruption of the prolactin gene. Embo J. 16(23):6926–35
305. Pollard JW, Hennighausen L (1994) Colony stimulating factor 1 is required for mammary gland development during pregnancy. Proc Natl Acad Sci USA. 91(20):9312–6
306. Fantl V et al (1995) Mice lacking cyclin D1 are small and show defects in eye and mammary gland development. Genes Dev. 9(19):2364–72
307. Stinnakre MG et al (1994) Creation and phenotypic analysis of alpha-lactalbumin-deficient mice. Proc Natl Acad Sci USA. 91(14):6544–8
308. Triplett AA et al (2005) Expression of the whey acidic protein (Wap) is necessary for adequate nourishment of the offspring but not functional differentiation of mammary epithelial cells. Genesis. 43(1):1–11
309. Wagner KU et al (1997) Oxytocin and milk removal are required for postpartum mammary gland development. Genes Funct. 1(4):233–44

Congenital and Developmental Abnormalities of the Breast

2

Michele A. Shermak

Development of the mammary glands begins in the male and female embryo in identical fashion. During the fourth to fifth week of fetal development, primitive milk streaks, also known as galactic bands, form [1–4]. These are single, thickened ridges of ectoderm that extend bilaterally from the axillary to the inguinal region. Each band consolidates to form a mammary ridge on the thorax, and the remaining band regresses. At 6–8 weeks, a primary bud forms, with thickening of the mammary anlage, which penetrates into the chest wall mesenchyme. The primary mammary bud gives rise to secondary buds that extend into the surrounding connective tissue and become the lactiferous ducts and their branches. The mesenchyme surrounding the duct systems becomes the fibrous stroma and fat of the breast. Between 12 and 16 weeks of development, mesenchymal cells differentiate into the smooth muscle of the nipple-areolar complex (NAC), and branches link to future secretory alveoli. The secondary mammary anlage then develops with differentiation of hair follicles and sweat glands. Between 20 and 30 weeks, placental sex hormones induce canalization of the branched epithelial tissues. By 32–40 weeks, the parenchyma differentiates into alveolar and lobular structures. The epidermis at the origin of the mammary gland becomes depressed, forming a shallow mammary pit onto which the lactiferous ducts open, becoming the NAC. The breast bud becomes palpable at 34 weeks, measuring approximately 3 mm at 36 weeks of age and 4–10 mm by 40 weeks (Fig. 2.1). Soon after birth, the nipple rises because of proliferation of the mesenchyme underneath, and the areola becomes pigmented. Under the influence of maternal hormones that pass into the placenta, male and female neonates may secrete colostral milk, also known as witch's milk, up to 4–7 days postpartum. Neonates also may demonstrate hyperplasia of the breast, which typically regresses within a few weeks or months of life.

Intrauterine development progresses autonomously and is governed by epithelial-mesenchymal signaling, unlike development in puberty and pregnancy, which depends primarily on hormonal stimulation [4]. Various growth factors regulate mesenchymal-epithelial interactions to guide development [5, 6]. There is good evidence to support that formation of the mammary mesenchyme is directed by signals from the epithelial bud. Transforming growth factor alpha (TGF-α) stimulates ductal and lobulo-alveolar development. TGF-β affects canalization of ductal structures and suppression of lactation. Inhibin and activin are members of the TGF-β family that lead to mammary duct elongation and alveolar development [6]. IGF-1 impacts ductal growth and is expressed in mammary stroma [6, 7]. Laminin-5 aids in hemidesmosome attachment and signaling. Hepatocyte growth factor/scatter factor enhances ductal end bud size, numbers and branching. It is mitogenic for luminal cells and morphogenic to myoepithelial cells [6, 8]. Estrogen is critical for epithelial cell proliferation and ductal morphogenesis [9]. The presence of matrix metalloproteinase (MMP) and the absence of tissue inhibitor of metalloproteinases (TIMP's) allow necessary disruption of basement membrane and the involution process after weaning. BCL-2 and parathyroid hormone-related protein are other factors that signal the growth and development of the mammary gland [10].

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_2, © Springer-Verlag Berlin Heidelberg 2010

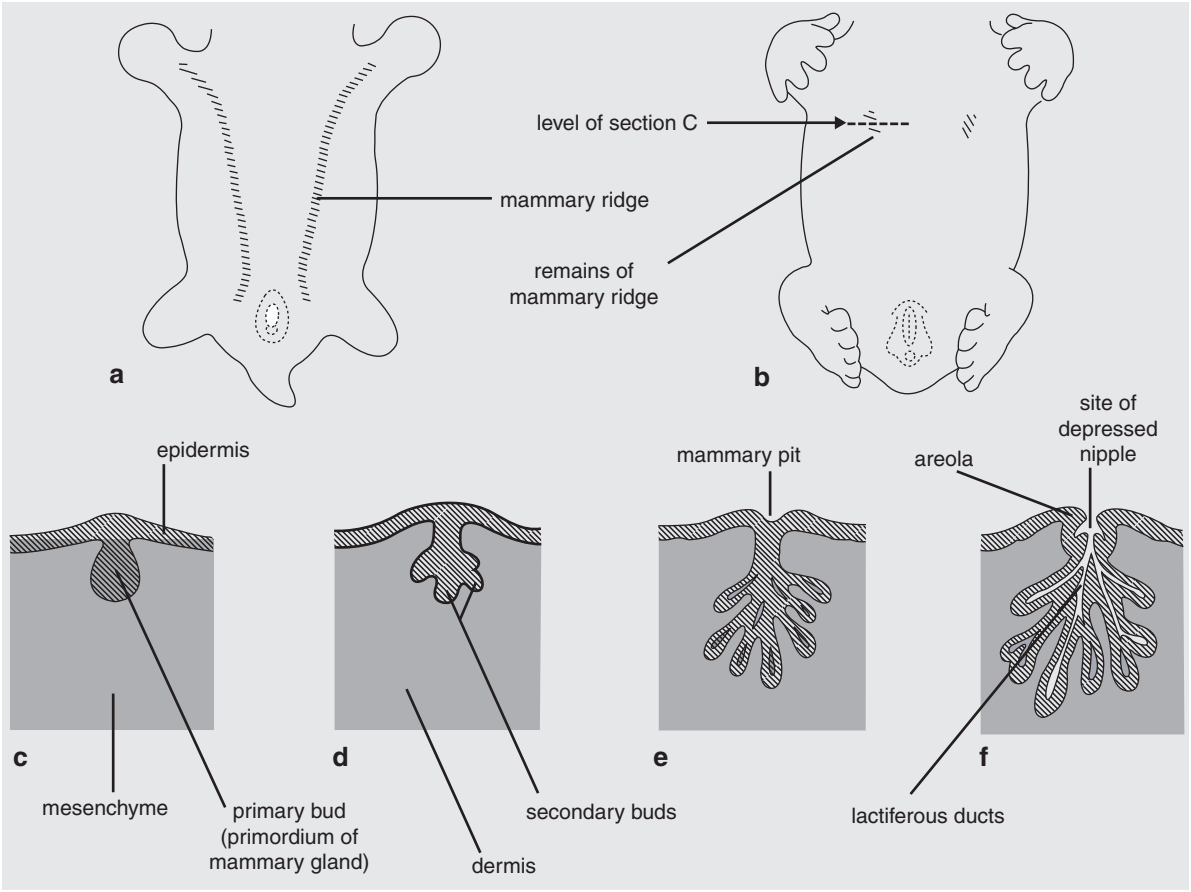

Fig. 2.1 Embryonic development of the mammary glands. (**a**) Ventral view of a 28-day embryo, with regression of the mammary ridge by 6 weeks, as represented in (**b**). (**c–f**) Cross sections of the developing breast bud from 6 weeks to birth. (From [2], with permission)

From birth until puberty, the breast remains largely unchanged. Breasts are identical in boys and girls until puberty. Breast development (thelarche) in girls is usually the first sign of sexual maturation. The mammary glands in males normally undergo no postnatal development. Puberty typically occurs at 9 to 13 years of age [11]. At puberty, the breasts rapidly grow and mature under the influence of elevated estrogen, progesterone, and prolactin levels and growth hormones, including luteinizing and follicular-stimulating hormone (LH and FSH), which stimulate estrogen secretion as well as hypothalamic gonadotropin-releasing hormone [6]. Elevated estrogen levels stimulate ductal growth and branching, whereas progesterone influences lobular and alveolar development. Testosterone and dihydrotestosterone, which are androgens, limit breast development [12]. Prolactin stimulates the alveolar buds. Thyroxine also plays a regulatory role. The volume and elasticity of the connective tissues increase, as does the vascularity and fat deposition. Progressive enlargement of the breasts occurs. Other signs of puberty typically follow the onset of thelarche.

Three major periods of the breast life cycle occur after puberty. The first is breast development from adolescence until approximately 25 years. Both stromal and lobular units develop during this period. Pregnancy increases breast weight, with involution postpartum. The female breast further remodels after lactation. After age 35 years, involution occurs with fat replacing breast tissue [9]. With significant decreases in estrogen levels at menopause, ninety percent of the epithelium undergoes apoptosis and fat cells replace breast tissue [12, 13].

2.1 Anatomy of the Breast

The breasts are situated superficial to the pectoralis major muscle and are hemispheric in shape with an elliptical base in the average young woman. Although breasts vary markedly in size, they normally extend between the second and sixth ribs, vertically, and horizontally between the lateral edge of the sternum and the midaxillary line (Fig. 2.2).

The three major components of the breast include skin, subcutaneous tissue and breast tissue, including parenchyma and supporting stroma. The breast gland is firmly adherent to the skin by suspensory ligaments of Cooper. These fibrous bands, which traverse and support the breast, connect the skin and the deep fascia overlying the pectoralis major muscle.

Lactiferous ducts open on the nipple, and each drains a lobe. The lobes are arranged radially around the breast. Each lobe consists of 20–40 lobules, separated by connective tissue and fat. Each lobule contains 10–100 alveoli. Under the areola, each lactiferous duct has a dilated portion called the lactiferous sinus in which milk accumulates during lactation.

The arterial supply of the breast includes the internal mammary and lateral thoracic arteries, as well as lateral and anterior cutaneous branches of the intercostal arteries from interspaces three, four, and five, and subdermal vessels. Venous drainage flows primarily into the axilla, with further drainage into the internal thoracic, lateral thoracic and intercostal veins. Most of the lymph drains into superficial and axillary nodes. The second to sixth intercostal nerves, chiefly the fourth lateral intercostal nerve, innervate the breast gland and overlying skin.

2.2 Premature Thelarche

Premature thelarche is a benign condition describing premature breast development before the age of 8 years. Premature thelarche is especially prevalent during the first 2 years of life and often resolves during childhood. This condition is typically isolated and rarely progresses to precocious puberty, which is maturation of the hypothalamic-pituitary-gonadal axis with development of two or more sexual characteristics [12, 14]. Volta et al studied 119 girls with premature thelarche, and found that 80% presented prior to 2 years of age, and 60% regressed completely [15].

Some studies report differences of the hormonal milieu of girls affected by premature thelarche. Bioassays have found higher levels of estrogen in girls with premature thelarche. An activating mutation in the GNAS gene, which codifies for the alpha subunit of G stimulating protein, has also been reported [14, 16]. Increased FSH-driven follicular development and mutations in the FSH receptor with higher than normal response levels have also been hypothesized [17–19]. These finding suggest premature thelarche may be an incomplete form of precocious puberty. Phenotypically, girls may also demonstrate accelerated growth and bone age, but are otherwise medically and sexually normal.

Premature thelarche may result from gonadotropin-dependent or gonadotropin-independent estrogen formation, as well as increased sensitivity of estrogen receptors and increased aromatization of adrenal precursors. Exogenous estrogen exposure such as that from cosmetics and hair products, and hormones used in stockbreeding, may serve as an endocrine disruptor [17–19]. Serum levels and metabolic clearance rates of estrogen may be low in children leading to significant effects with exposure that might not be as significant for adults [20]. The possibility of endocrine disorders resulting from hypothalamic lesions, ovarian granulosa cell tumors, follicular cysts, adrenocortical tumors, syndromic and medicinal etiologies must be excluded, and demand a thorough history and physical examination [21].

Premature thelarche must be distinguished from precocious puberty. Characteristics of precocious puberty include estrogenization of vaginal mucosa and labia minora, body odor, pubic and axillary hair, acceleration of growth and rapid bone maturation [12]. No more than 18% of girls with premature thelarche go on to develop precocious puberty [19]. If precocious puberty is suspected, the child should be monitored clinically and referred to a pediatric endocrinologist.

2.3 Breast Masses

Before puberty, it is not unusual to have nodular growth of one or both breasts in either sex. Up to 90% of neonates of both sexes may have palpable breast tissue that may increase in size after birth, but this typically resolves within the first few months after birth [12]. Nodules are typically soft, mobile, and uniform, and

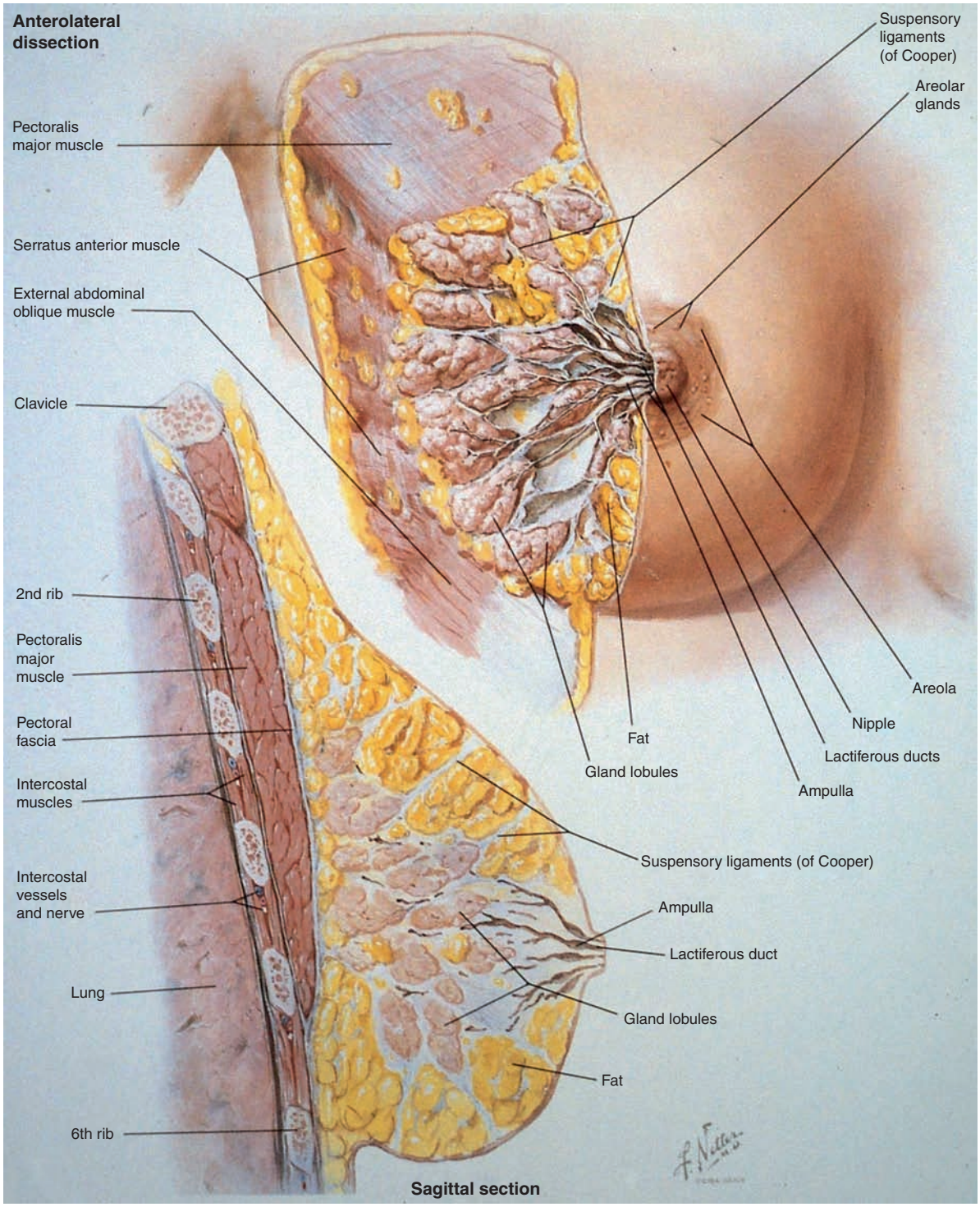

Fig. 2.2 Anatomy of the female breast. (From Netter, FH. Atlas of human anatomy. Summit, NJ: CIBA-GEIGY Corporation, 1989: Plate 167, with permission)

they tend to disappear spontaneously after a few weeks or months; so observation is recommended. Tumors of the pediatric breast are generally benign and rarely may be malignant [22].

Possible causes of breast masses in children include fibroadenoma, hemangioma, lymphangioma, lipoma, abscess and fat necrosis after trauma [23, 24]. Fibroadenoma is the most common breast tumor in pubertal females [12]. Four types of fibroadenomas exist: common fibroadenoma, giant fibroadenoma, juvenile fibroadenoma and phylloides tumors. Common fibroadenomas are most prevalent and present between 14 and 16 years of age. Fibroadenomas usually have a firm, rubbery feel on examination, are mobile, non-tender, and have well-demarcated borders. Cystosarcoma phylloides tumors, which only represent 0.4% of all adolescent breast masses, may reach 20 cm in size [25].

Biopsy of the prepubertal breast may irreversibly hinder later development and is rarely required for diagnosis [24]. Careful physical examination is recommended. Imaging studies like ultrasound may follow, and if there is concern, fine needle aspirate is suggested. Excisional biopsy should be performed in cases of persistently painful or rapidly enlarging lesions, and in children who have a history of malignancy [24, 26] (Fig. 2.3).

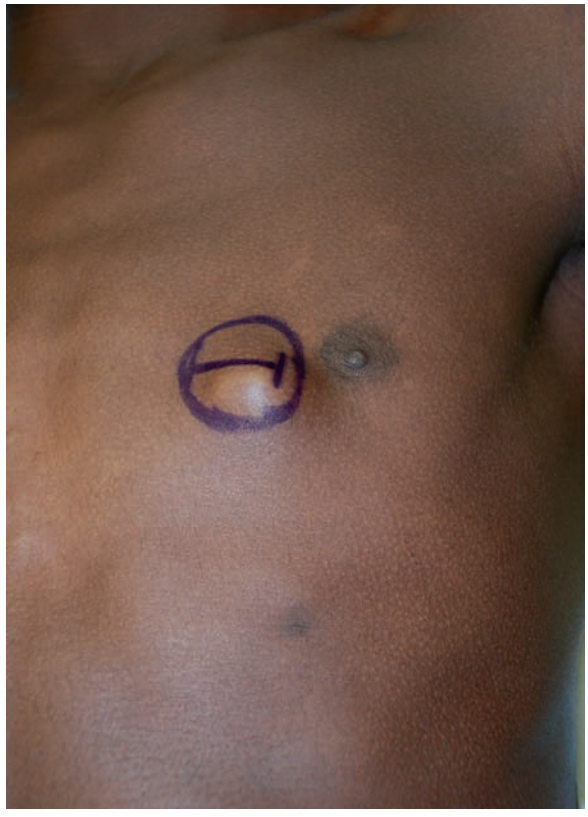

Fig. 2.3 Teenaged male with a *left* breast mass that grew over the course of 3 months. This mass proved to be a spindle cell embryonal rhabdomyosarcoma

2.3.1 Gynecomastia

Gynecomastia is the most common form of breast hyperplasia, appearing in 30–57% of healthy men [27]. The term gynecomastia stems from the Greek words gyne (woman) and mastos (breast), and describes female-like enlargement of the male breast leading to glandular proliferation [12] (Fig. 2.4). Gynecomastia presentation may be unilateral or bilateral, and may or may not be associated with pain.

Gynecomastia occurs at 3 time intervals: the neonatal period, adolescence, and old age. Up to 60% of males may develop gynecomastia during adolescence, with peak incidence at mid-puberty. About 75% resolve within 2 years of onset with the rest persisting into adulthood [12, 28].

Gynecomastia may be classified according to the amount of glandular tissue, such as glandular, true gynecomastia; fatty glandular; and simple fatty

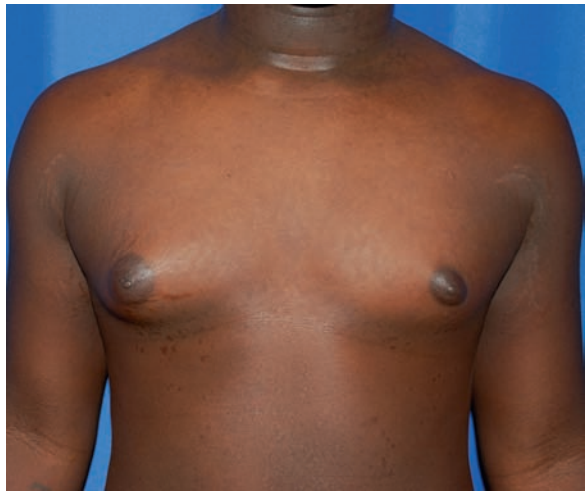

Fig. 2.4 A young man with idiopathic true gynecomastia. The patient was treated with ultrasound-assisted liposuction

gynecomastia, known as pseudogynecomastia. With true gynecomastia, a firm, rubbery mass may be palpated just below the NAC. The Simon classification of gynecomastia is as follows: Grade 1 is characterized by moderate breast enlargement without skin redundancy; Grad 2a by moderate breast enlargement without skin redundancy; 2b by moderate breast enlargement with marked skin redundancy; and Grade 3 with both marked breast enlargement and skin redundancy [29].

Gynecomastia is most often physiologic, but may manifest a pathologic condition. Gynecomastia is thought to result from serum imbalance in, or production of, estrogens and androgens [27]. There may be a lag in testosterone secretion leading to greater estrogen effect [12]. In adolescents, pediatricians and/or endocrinologists should assess the possibility of hormonal etiology of gynecomastia to reveal possible pathologic conditions, such as hyperthyroidism, congenital adrenal hyperplasia, testicular tumors and hypogonadotopic hypogonadism [12]. A unilateral, firm, fixed mass with overlying skin changes is suspicious for cancer, and should be explored as a possible etiology through mammography or diagnostic fine needle biopsy.

Medical and surgical treatments are available for gynecomastia. Indications for treatment include psychosocial stress and pain, as well as concern for malignancy. While medical treatment is less invasive, it is often ineffective. The basis of medical treatment is hormonal manipulation, which may result in undesirable side-effects. Testosterone and danazol increase androgen level; clomiphene citrate and tamoxifen are antiestrogens, and testolactone is an aromatase inhibitor [30, 31]. Surgical treatments provided by plastic surgeons include liposuction, breast tissue resection and skin reduction [32–35].

2.3.2 Accessory Breast Tissue: Polymastia/Polythelia

Occurrence of accessory breast tissue is most often sporadic, but is familial in 10% of the affected population. Occurrence averages between 0.22 and 6% of the general population. Women have a higher rate than men [36].

The most common type of accessory breast tissue is polythelia. *Polythelia*, the presence of supernumerary nipples or nipple areolar complexes, is the most common anomaly of the pediatric breast and is found in both boys and girls (Fig. 2.5). Polythelia may occur at any point along the embryonic milk line, from axilla to groin. The condition is both sporadic and familial. Sporadic cases may be associated with nephrourologic abnormalities, and polythelia should therefore heighten suspicion of possible renal abnormalities [22, 36]. Cardiovascular problems associated with polythelia include high blood pressure and conductive or rhythm disturbances [37]. Surgery is requested for esthetic reasons or due to discomfort.

Polymastia is the presence of supernumerary breasts. When a mass is located along the milk line from axilla to groin, the possibility of breast tissue should be considered. Aberrant breast tissue may be found off this axis including the face, neck, torso, vulva, and lower extremities [36]. A common site of ectopic breast tissue is the axilla [37] (Fig. 2.6). Resection should occur prior to puberty to avoid possible glandular development, with elliptical excision sufficing for surgical treatment [22]. The accessory breast tissue often

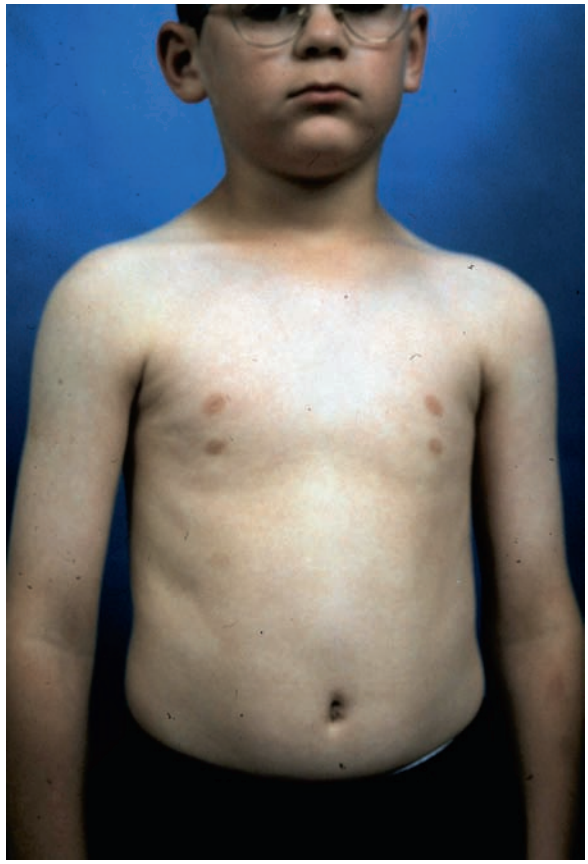

Fig. 2.5 Adolescent male presenting with bilateral polythelia

Fig. 2.6 Young woman with polymastia with accessory axillary breast tissue

manifests itself symptomatically during menstrual periods or pregnancy when the breast tissue becomes tender, enlarged, or lactates. Fine needle aspiration confirms diagnosis [38]. Surgery may be performed when the breast mass causes discomfort due to tenderness or when secreting milk [37].

2.4 Congenital Breast Hypoplasia/ Aplasia

2.4.1 *Poland Syndrome*

Poland Syndrome is the most frequent cause of congenital breast aplasia or hypoplasia. It presents as a spectrum of congenital deformities of the chest wall, breast and upper extremity in a unilateral fashion (Fig. 2.7). Defined by unilateral absence of the sternocostal head of the pectoralis major muscle, this syndrome was named by Clarkson for Alfred Poland who published his findings in 1841 [39, 40]. The syndrome occurs sporadically in 1 of every 20,000–30,000 live births [22, 41]. Men are affected more frequently than women (3:1), and the right side is more often affected than the left (3:1) [42]. No cases of bilateral involvement have been reported. Renal hypoplasia, certain leukemias and Mobius syndrome have also been associated with the chest wall defects [43]. A great spectrum of clinical presentations exist, ranging from mild, with hypomastia and pectoral hypoplasia, to severe, with lack of pectoral major and minor muscles, high insertion of rectus abdominis muscle, paucity of subcutaneous tissue, alopecia of the axilla, rib deformities

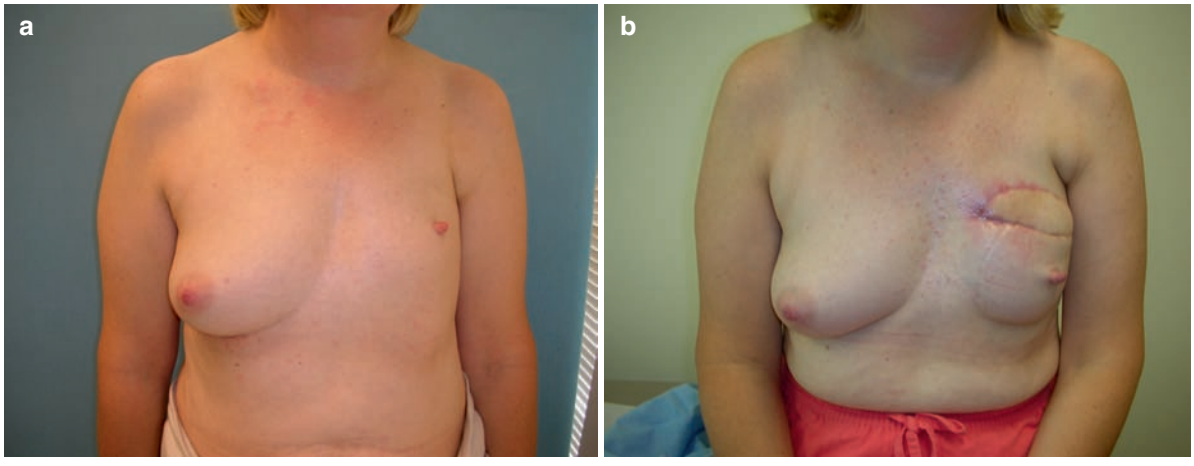

Fig. 2.7 (**a**) Poland's deformity with aplastic breast and absent anterior axillary fold as a result of absent pectoralis major muscle. (**b**) A latissimus musculocutaneous flap was performed to reconstruct the involved breast. This woman will need further tissue to better approximate her contralateral breast

(II to IV or III to V), sternal rotation, amastia, superior disposition of the NAC and anomalies of the upper extremity including brachysyndactyly [41, 42, 44].

Most cases are sporadic and not familial. It is hypothesized that the etiology of Poland Syndrome is related to an intrauterine accident. One theory is vascular: that the subclavian blood supply is interrupted during limb bud development in the sixth week of gestation, known as *subclavian artery supply disruption sequence,* disrupting normal development of the chest wall and upper limb [41, 45, 46]. Another theory is related to abnormal migration of embryonic tissues. In a 9-mm embryo, the limb bud that forms the pectoralis muscle develops; by the time it becomes a 15-mm embryo, the bud splits into clavicular, pectoral and sternal components. Faulty attachment or failure of attachment of this primitive limb bud to the upper rib cage and sternum would explain Poland deformity [44, 47].

Patients may desire reconstruction by a plastic surgeon to improve abnormal contours of the chest, anterior axillary fold and breast. Whereas men desire treatment for asymmetry and lack of soft tissue fill on the upper chest, women desire the provision of a symmetrical breast mound, a natural appearing NAC, infraclavicular fullness and a normal anterior axillary fold [43, 46]. While implants have been the mainstay of breast reconstruction in Poland syndrome [48], autologous options include latissimus myocutaneous flap reconstruction possibly with an expander or implant [49], microvascular free flaps including perforator flaps [46, 50] and fat grafting [51]. Latissimus muscle has been traditionally used to simulate the pectoralis major head and anterior axillary fold, and to fill the upper chest, while also providing skin [49, 52]. Endoscopic techniques with minimal scar may be applied to implant placement or latissimus flap transposition [41]. Autologous rib grafting, costal cartilage resection and/or sternal osteotomy may be required [43, 44]. Contralateral, symmetry procedures such as mastopexy might also be necessary.

2.4.2 Tubular/Tuberous Breast

Tuberous breast is a term first coined by Rees and Aston [53]. The breast has normal function but abnormal morphology. Tuberous breast deformity describes a hypoplastic breast with constricting ring around the base of the breast, breast tissue herniation into the areola, deficient skin envelope and inframammary fold malposition (Fig. 2.8). With the narrowed transverse breast diameter and base constriction, the breast appears to herniate into an oversized and protuberant areola [53, 54]. As a result of the breast's appearance, another name for tubular breast deformity is the *Snoopy-nose deformity* [55]. The condition may be unilateral or bilateral, and exact incidence is unknown.

Patients consult with plastic surgeons to correct their deformity. Treatment objectives include expanding the base circumference and the skin of the lower hemisphere, releasing constricting skin tightness at the areolar junction, lowering the inframammary fold, increasing breast volume and height and decreasing areolar diameter [54, 56]. A periareolar approach

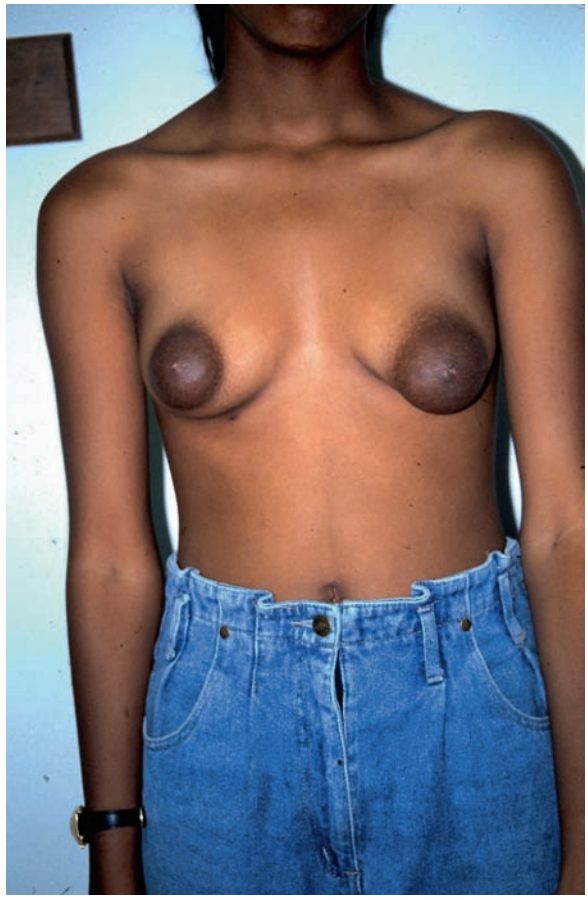

Fig. 2.8 Tubular breast deformity with narrowed base diameter and pseudo-herniated breast tissue through an enlarged nipple-areolar complex (NAC)

allows alteration of the areolar diameter and division and widening of breast tissue to increase breast base diameter. A tissue expander or implant under the divided breast tissue assists in improving deficient breast volume [57–60].

2.4.3 Idiopathic Asymmetry

The initiation of thelarche may occur on one side and proceed at a faster rate for unknown reasons. In most cases, both breasts become relatively equal in volume by the end of puberty. A small degree of breast asymmetry is not uncommon or abnormal; however, a marked inequality of breast volume can be noticeable (Fig. 2.9). Hueston noted that patients experience difficulty in concealing asymmetry greater than 33%, with everyday attire [61].

Idiopathic breast asymmetry is classifiable into six categories: unilateral hypoplasia, asymmetrical hypoplasia, unilateral hyperplasia, asymmetric hyperplasia, hyperplasia/hypoplasia and hypoplasia associated with chest wall deformities. Unilateral hypoplasia is most common and may vary from the minimal idiopathic form to severe Poland syndrome. Associated with breast hypoplasia is a small and cephalad-displaced NAC, and in rare instances, the NAC is absent. Etiologies of breast asymmetry have been described, including differential end organ response to hormonal stimulation during development, tumors, medications and iatrogenic causes, including operations, radiation and trauma [62, 63].

Breast asymmetry may cause physical discomfort as well as psychiatric embarrassment. Early surgical correction may be warranted. Postponing corrective surgery for adolescents with significant asymmetry may be psychologically detrimental and unnecessary.

Plastic surgeons use reconstructive techniques to create improved symmetry. Hypoplastic breasts are augmented and may require tissue expansion as a first stage. Tissue expansion preceding placement of a permanent implant allows descent and expansion of the hypoplastic breast and NAC, as well as expansion of the deficient soft-tissue envelope [62]. Particularly in young patients, the expansion process may take place over years until the opposite, unaffected breast reaches maturity [62]. In more severe cases of hypoplasia, the latissimus may be transposed over top of the implant to improve contour and decrease risk of contracture. Correction or camouflage of underlying chest wall deformities may be necessary. The unaffected breast may have ptosis requiring a mastopexy to achieve improved symmetry.

2.4.4 Amastia/Athelia

Total absence of the breast is called amastia, and absence of the nipple is athelia. Amastia and athelia result when the mammary ridges fail to develop or completely disappear [25]. The first recorded reference to amastia was in "The Song of Solomon" in the Bible: "We have a little sister, and she hath no breast: What

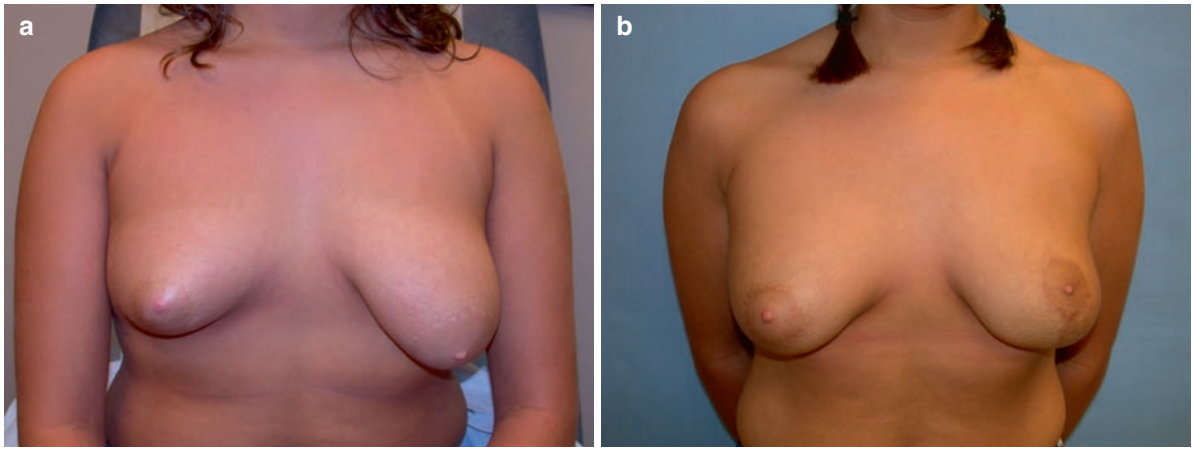

Fig. 2.9 (**a**) Idiopathic breast asymmetry with *left*-sided ptosis and contralateral hypomastia. (**b**) Postoperative result with *left* mastopexy and *right* breast augmentation

shall we do for our sister in the day that she shall be spoken for [1]?" The fictional Amazonian nation was comprised of independent women who removed one of their breasts to gain a competitive advantage in archery. In 1939, Froriep first reported a case of amastia [64].

Amastia has been reported as an isolated finding and a syndromic component. Trier reviewed the literature extensively in 1965 and noted three presentations after reviewing 43 patients: bilateral amastia with congenital ectodermal defects, unilateral amastia and bilateral amastia with variable associated anomalies. Associated abnormalities include cleft palate, hypertelorism, anomalous pectoral muscles, upper limb deformities and abnormalities of the genitourinary tract [64]. Amastia is often associated with anomalous chest wall development, such as in Poland Syndrome (Fig. 2.7). Syndromes with amastia include ectodermal dysplasia, an autosomal dominant hereditary disease, and Mayer-Rokitansky-Kuster-Hauser syndrome with vaginal-uterine agenesis [65–67]. Familial cases have been reported, and inheritance is believed to be autosomal dominant in those cases [1, 64, 68].

Athelia is an extremely rare condition. Absence of the nipples, like amastia, has been reported as a dominant trait in some families and as a finding in various syndromes, including the family of ectodermal dysplasias [69, 70]. Athelia is a component of Al Awadi/Raas-Rothschild syndrome, a lethal autosomal recessive facio-skeletal-genital syndrome [71]. Athelia has also been described as part of the scalp-ear-nipple (SEN) syndrome, an autosomal dominant condition with aplasia cutis congenital, posterior scalp nodules and malformed ears. A case was reported in which the patient had choanal atresia and athelia that was likely induced by methimazole treatment for hyperthyroidism in the pregnant mother [72].

Surgical correction is performed in stages with initial tissue expansion followed by definitive implant. Breast reconstruction may also be performed with autogenous tissue, in particular, free flaps from the abdomen or gluteal region.

2.5 Inverted Nipples

Sir Ashley Cooper first described this entity in 1840. Inverted nipples occur when the tight, shortened deep tissues retract the nipple. Developmentally, this entity originates from a lack of proper elevation of the nipple from proliferation of the mesenchyme underlying the future NAC [73].

Inverted nipples are found in about 2% of the female population and are most frequently bilateral [73, 74]. Although most cases are congenital, acquired causes occur as the result of scarring mastitis, partial mastectomy and prior drainage procedures. Syndromes such as Robinow syndrome and carbohydrate-deficient glycoprotein syndrome include inverted nipples in their constellation of findings [75, 76].

Concerns related to inverted nipples range from esthetic to functional to psychological. Women with this condition may have difficulty breast-feeding. Numerous plastic surgical techniques have been introduced for correction of the inverted nipple [73, 77, 78]. Nipple sensory change, scarring, vascular compromise, obliteration of the ductal system with faulty lactation, and incomplete correction, as well as a high rate of recurrence, may complicate correction.

2.6 Gigantomastia

2.6.1 *Juvenile Hypertrophy*

Prepubertal hypertrophy is usually bilateral, and virginal hypertrophy developing after puberty may be unilateral or bilateral [22]. Juvenile gigantomastia may be associated with rapid growth to massive proportions in the period surrounding puberty [79]. The breasts are firm and may be nodular. Serum hormone levels are normal, and pregnancy test should be checked to rule this out as a cause. Imaging should be considered to rule out an enlarging mass, and MRI is the preferred modality. Malignancy is rare in prepubertal and pubertal breast at 1.3% [79]. Symptoms associated with significant breast hypertrophy include bra grooving, shoulder, neck and back pain, postural problems, difficulty breathing while supine, and skin necrosis [79]. The physical discomfort coupled with the negative attention and accompanying psycholosocial issues result in a very difficult, sensitive situation, which may merit surgical treatment [80, 81].

Goals of surgery are volume reduction with symmetrical breast size and anatomically correct nipple areolar position. Treatment includes breast reduction

techniques. Surgery is best delayed until the end of puberty when breast growth is complete. The risk of recurrence of hypertrophy exists after breast reduction, leading to consideration of hormone therapy or even mastectomy and implant reconstruction [79].

2.6.2 Gravid-Induced Gigantomastia

This entity, though more rare, is similar to virginal hypertrophy, except that rapidly progressive gigantomastia occurs during pregnancy [82–84]. Macromastia may be evident prior to pregnancy, but is exacerbated by pregnancy. Gravid gigantomastia may occur after normal, unaffected pregnancies, but subsequent pregnancies will more likely result in similar gigantomastia. Like virginal hypertrophy, gravid gigantomastia is related to end-organ hypersensitivity to elevated circulating hormone levels, including estrogen and prolactin. A serum factor, like an autoimmune antibody that interferes with the normal hormone-receptor complex, has been proposed [85].

Because of extreme growth, patients experience severe pain, skin ulceration and imminent infection from the wounds. Breasts are tense, firm, and may demonstrate large superficial veins and peau d'orange skin changes. Erosion of veins under excoriated skin threatens hemorrhage.

Either breast reduction or mastectomy is recommended for these patients. Breast surgery performed at the time of pregnancy may threaten viability or developmentally affect the fetus. Some opt for therapeutic abortion, a radical but curative choice [83].

Bromocriptine has been prescribed after delivery to induce involution and , in some cases, during gestation to delay surgical therapy. It lowers secretion of prolactin or may act directly on the breast [85]. Bromocriptine may have teratogenic effects on the fetus [86].

2.6.3 Drug-Induced Gigantomastia

Some cases of gigantomastia are induced by medications. Hormonal therapy, corticosteroids, marijuana, D-penicillamine, cimetidine and the antiepileptic sulpiride may lead to unilateral or bilateral gigantomastia

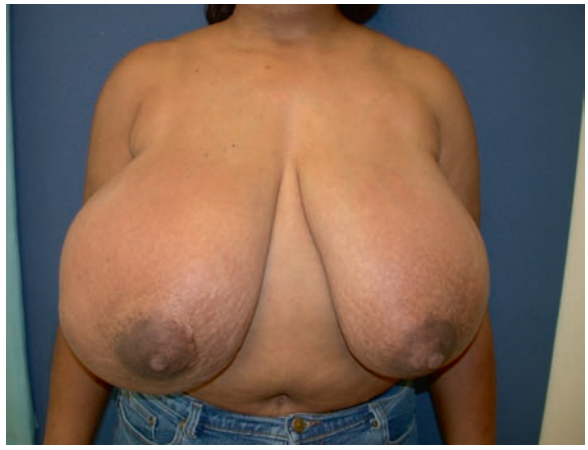

Fig. 2.10 Female with autoimmune disease on multiple anti-inflammatory medications, including prednisone with gigantomastia of acute onset

(Fig. 2.10). D-penicillamine, an anti-inflammatory medication prescribed for rheumatologic disorders such as scleroderma, has been frequently reported as a cause for gigantomastia [87–89]. Reversal of gigantomastia occurs with danazol treatment or with stopping D-penicillamine therapy [88]. Medications either stimulate hormones or act locally. Cessation of the potentially offending medication should first be attempted to reverse gigantomastia.

2.7 Deformational Breast Abnormalities: Iatrogenic, Traumatic

Traumas, incisions, infection or radiation to the young female breast may lead to subsequent scarring restricting breast growth. Seatbelt injuries cause compression to skin and underlying fat and may result in breast atrophy and asymmetry [90] (Fig. 2.11). Radiation therapy to the chest wall to treat childhood malignancies ultimately impair breast development [91]. The injured breast nearly always results in hypoplastic deformity, with a combination of deficiencies in skin, nipple areola and/or glandular tissue. Scar tissue at the site of trauma tethers breast tissue to the chest wall, or the injury may result in violation of the breast bud, impeding normal development.

Burn injury may compromise the breast bud or restrict breast growth through constrictive scar

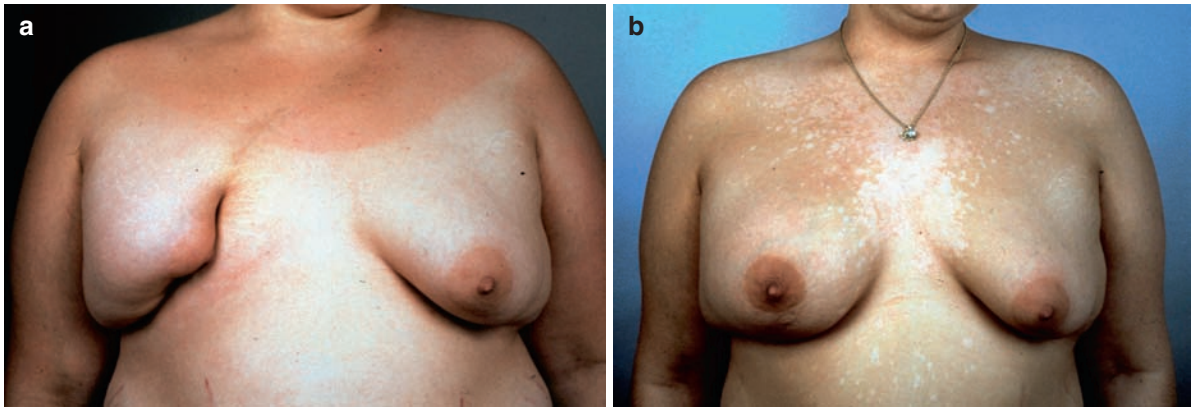

Fig. 2.11 (**a**) Patient after traumatic seatbelt injury leading to ischemia of right medial breast. (**b**) Same patient after complex reconstruction with implant (Photos courtesy of Dr. Joseph P. Delozier, with permission)

contracture (Fig. 2.12). Excision and grafting at the initial injury must be performed judiciously to avoid long-term injury and ultimately allow normal growth as burn scar will restrict breast growth and development [92].

Breast and pectoral muscle maldevelopment have been reported in children who have undergone anterolateral and posterolateral surgical incisions though the fourth intercostal space, an approach used for congenital heart surgery [93]. Anterolateral thoracostomies resulted in 60% of the patients subsequently having a greater than 20% discrepancy in volume of the breast and pectoral muscles on the ipsilateral and unaffected sides as reported in a retrospective study from the Children's Hospital of Pittsburgh. Tube thoracostomy is one of the more common pediatric injuries, and results in scar and fibrous tissue tethering the breast to the chest wall [22].

Great caution must be exercised when creating incisions around the prepubertal breast. Because breast malignancies are so rare in prepubertal patients, biopsy of a suspicious mass is warranted only after a reasonable observation period. Nodular deformities in the breast have been reported after core needle biopsy and diagnosed as reactive spindle cell nodules. These are benign masses resulting from an exuberant reparative response and myofibroblast influx after needle trauma [94].

2.8 Conclusion

Because our culture places importance on breasts and fuels a pervasive fear of breast cancer, individuals with breast and chest wall deformities and breast masses spark strong concerns. Many of these deformities are congenital and based on faulty developmental processes. The breast deformity may be a marker for other

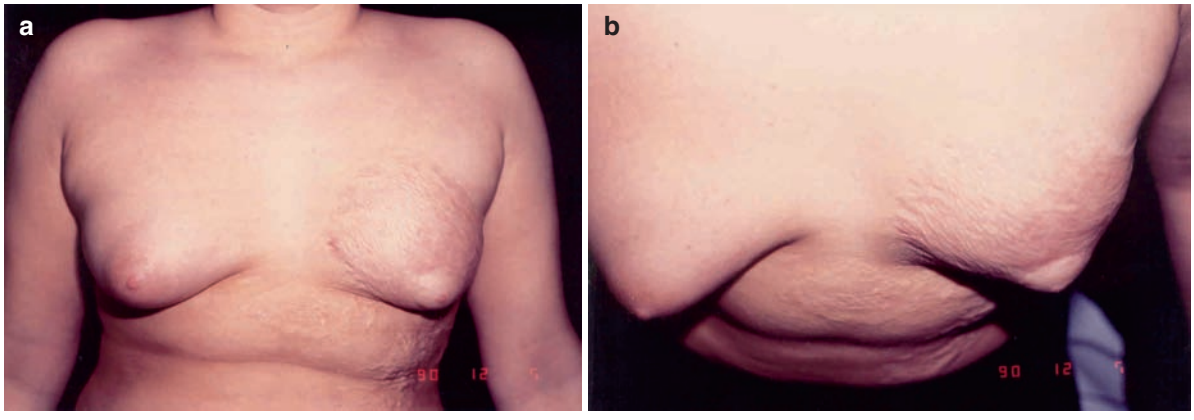

Fig. 2.12 Frontal and bird's eye views of patient with *left* breast burn and constricting scar leading to asymmetry. (Photos courtesy of Dr. Robert J. Spence, with permission)

underlying systemic disorders, principally involving the genitourinary and cardiac systems due to parallel development in the embryo. Some breast deformities are iatrogenic, and the potential for damage to the developing breast bud must be considered when considering surgery on the chest of a prepubertal patient.

Although rarely of functional importance, obvious breast deformities may generate devastating psychological stress, causing isolation and withdrawal from social situations. These patients benefit from early consultation with physicians to address their concerns and direct them to treatment to reconstruct their deformity. The reconstructive breast surgeon aims to preserve breast structures and blood supply while achieving improved symmetry and a more normal appearance. Self-esteem is often much improved after surgery even if exact symmetry is not achieved.

References

1. Bland KI, Romrell LJ (1998) Congenital and acquired disturbances of breast development and growth. In: Bland KI, Copeland EM III (eds) The breast: comprehensive management of benign and malignant diseases. WB Saunders, Philadelphia, pp. 214–32
2. Moore KL (1988) The developing human. WB Saunders, Philadelphia, pp. 426–8
3. Osborne MP (1996) Breast development and anatomy. In: Harris JR, Lippman ME, Morrow M et al (eds) Diseases of the breast. Lippincott-Raven, Philadelphia, pp. 1–14
4. Robinson GW, Karpf AB, Kratochwil K (1999) Regulation of mammary gland development by tissue interaction. J Mammary Gland Biol Neoplasia. 4:9–19
5. Cunha GR, Hom YK (1996) Role of mesenchymal-epithelial interactions in mammary gland development. J Mammary Gland Biol Neoplasia. 1:21–35
6. Imagawa W, Pedchenko VK, Helber J, Zhang H (2002) Hormone/growth factor interactions mediating epithelial/stromal communication in mammary gland development and carcinogenesis. J Steroid Biochem Molec Biol. 80: 213–30
7. Loladze AV, Stull MA, Rowzee AM et al (2006) Epithelial-specific and stage-specific functions of insulin-like growth factor-I during postnatal mammary development. Endocrinology. 147:5412–23
8. Sasaki M, Enami J (1999) Mammary fibroblast-derived hepatocyte growth factor and mammogenic hormones stimulate the growth of mouse mammary epithelial cells in primary culture. Endocr J. 46:359–66
9. Zhang H-Z, Bennett JM, Smith KT et al (2002) Estrogen mediates mammary epithelial cell proliferation in serum-free culture indirectly via mammary stroma-derived hepatocyte growth factor. Endocrinology. 143:3427–34
10. Dunbar ME, Young P, Zhang J-P et al (1998) Stromal cells are critical targets in the regulation of mammary ductal morphogenesis by parathyroid hormone-related protein. Dev Biol. 203:75–89
11. Neinstein LS (1999) Breast disease in adolescents and young women. Pediatr Clin North Am. 46:607–29
12. Diamantopoulos S, Bao Y (2007) Gynecomastia and premature thelarche: a guide for practitioners. Pediatr Rev. 28: e57–68
13. Roman R, Johnson MC, Codner E et al (2004) Activating *GNAS1* gene mutations in patients with premature thelarche. J Pediatr. 145:218–22
14. Wiseman BS, Werb Z (2002) Stromal effects on mammary gland development and breast cancer. Science. 296:1046–9
15. Volta C, Bernasconi S, Cisternino M et al (1998) Isolated premature thelarche and thelarche variant: clinical and auxological follow-up of 119 girls. J Endocrinol Invest. 21: 180–3
16. Codner E, Roman R (2008) Premature thelarche from phenotype to genotype. Pediatr Endocrinol Rev. 5:760–5
17. Crofton PM, Evans NEM, Wardhaugh B et al (2005) Evidence for increased ovarian follicular activity in girls with premature thelarche. Clin Endocrinol. 62:205–9
18. Hannon TS, King DW, Brinkman AD et al (2002) Premature thelarche and granlosa cell tumors: a search for FSH receptor and G5alpha activating mutations. J Pediatr Endocrinol Metab. 15(Suppl 3):891–5
19. Verrotti A, Ferrari M, Morgese G, Chiarelli F (1996) Premature thelarche: a long-term follow-up. Gynecol Endocrinol. 10: 241–7
20. Chiabotto P, Costante L, de Sanctis C (2006) Premature thelarche and environmental pollutants. Minerva Med. 97: 277–85
21. Arisaka O, Arisaka M, Kitamure Y et al (1985) Precocious breast development: a case of unilateral hyperplasia of the adrenal cortex. Eur J Pediatr. 143:308–10
22. Sadove AM, van Aalst JA (2005) Congenital and acquired pediatric breast anomalies: a review of 20 years' experience. Plast Reconstr Surg. 115(4):1039–50
23. Chang DS, McGrath MH (2007) Management of benign tumors of the adolescent breast. Plast Reconstr Surg. 120: 13e–19
24. West KW, Rescoria FJ, Scherer LR, Grosfeld JL (1995) Diagnosis and treatment of symptomatic breast masses in the pediatric population. J Pediatr Surg. 30:182–7
25. Arca MJ, Caniano DA (2004) Breast disorders in the adolescent patient. Adolesc Med. 15:473–85
26. Bode MK, Rissanen T, Apaja-Sarkkinen M (2007) Ultrasonography and core needle biopsy in the differential diagnosis of fibroadenoma and tumor phyllodes. Acta Radiol. 48:708–13
27. Lanitis S, Starren E, Read J (2008) Surgical management of gynaecomastia: outcomes from our experience. The Breast 17(6):596–603
28. Handschin AE, Bietry D, Husler R et al (2008) Surgical management of gynecomastia – a 10-year analysis. World J Surg. 32:38–44
29. Simon BE, Hoffman S, Kahn S (1973) Classification and surgical correction of gynecomastia. Plast Reconstr Surg. 51:48–56
30. Braunstein GD (1993) Current concepts: gynecomastia. N Engl J Med. 328:490–5
31. Carlson HE (1980) Current concepts: gynecomastia. N Engl J Med. 303:795–9

32. Botta SA (1998) Alternatives for the surgical correction of severe gynecomastia. Aesthetic Plast Surg. 22:65–70
33. Colombo-Benkmann M, Buse B, Stern J, Herfarth C (1999) Indications for and results of surgical therapy for male gynecomastia. Am J Surg. 178:60–3
34. Tashkandi M, Al-Qattan MM, Hassanain JM et al (2004) The surgical management of high-grade gynecomastia. Ann Plast Surg. 53:17–20
35. Teimourian B, Pearlman R (1983) Surgery for gynecomastia. Aesthetic Plast Surg. 7:155–7
36. Loukas M, Clarke P, Tubbs RS (2007) Accessory breasts: a historical and current perspective. Am Surg. 73:525–8
37. Grossl NA (2000) Supernumerary breast tissue: historical perspectives and clinical features. Southern Med J. 93: 29–32
38. Velanovich V (1995) Ectopic breast tissue, supernumerary breasts, and supernumerary nipples. South Med J. 88:903–6
39. Marks MW, Argenta LC, Izenberg PH et al (1991) Management of the chest wall deformity in male patients with Poland's syndrome. Plast Reconstr Surg. 87:674–81
40. Poland A (1841) Deficiency of the pectoral muscles. Guys Hosp Rep. 6:191
41. Borschel GH, Costantin DA, Cederna PS (2007) Individualized implant-based reconstruction of Poland syndrome breast and soft tissue deformities. Ann Plast Surg. 59: 507–14
42. da Silva Freitas R, Tolazzi ARD, Martins VDM et al (2007) Poland's syndrome: different clinical presentations and surgical reconstructions in 18 cases. Aesth Plast Surg. 31: 140–6
43. Bouvet JP, Leveque D, Bernetieres F et al (1978) Vascular origin of Poland syndrome? A comparative rheographic study of the vascularization of the arms in eight patients. Eur J Pediatr. 128:17
44. Urschel HC, Byrd S, Sethi SM et al (1984) Poland's syndrome: improved surgical management. Ann Thorac Surg. 37:204–11
45. Hochberg J, Ardenghy M, Graeber GM, Murray GF (1994) Complex reconstruction of the chest wall and breast utilizing a customized silicone implant. Ann Plast Surg. 32:524–8
46. Hester TR, Bostwick J (1982) Poland's syndrome: correction with latissimus muscle transposition. Plast Reconstr Surg. 69:226–33
47. Pinsolle V, Chichery A, Grolleau J-L, Chavoin JP (2008) Autologous fat injection in Poland's syndrome. J Plast Reconstr Aesthetic Surg. 61:784–91
48. Gautam AK, Allen RJ, LoTemio MM et al (2007) Congenital breast deformity reconstruction using perforator flaps. Ann Plast Surg. 58:353–8
49. Shamberger RC, Welch KJ, Upton J (1989) Surgical treatment of thoracic deformity in Poland's syndrome. J Pediatr Surg. 24:760–5
50. Longaker MT, Glat PM, Colen LB, Siebert JW (1997) Reconstruction of breast asymmetry in Poland's chest wall deformity using microvascular free flaps. Plast Reconstr Surg. 99:429–36
51. Seyfer AE, Icochea R, Graeber GM (1988) Poland's anomaly: natural history and long-term results of chest wall reconstruction in 33 patients. Ann Surg. 208:776–82
52. Ohmori K, Takada H (1980) Correction of Poland's pectoralis major muscle anomaly with latissimus dorsi musculocutaneous flaps. Plast Reconstr Surg. 65:400–4
53. Rees TD, Aston S (1976) The tuberous breast. Clin Plast Surg. 49:339–47
54. Dinner MI, Dowden RV (1987) The tubular/tuberous breast syndrome. Ann Plast Surg. 19:414–20
55. Teimourian B, Adham MN (1983) Surgical correction of the tuberous breast. Ann Plast Surg. 10:190–3
56. Elliott MP (1988) A musculocutaneous transposition flap mammaplasty for correction of the tuberous breast. Ann Plast Surg. 201:53–7
57. Foustanos A, Zavrides H (2006) Surgical reconstruction of tuberous breasts. Aesthetic Plast Surg. 30:294–300
58. Mandrekas AD, Zambacos GJ, Anastasopoulos A et al (2003) Aesthetic reconstruction of the tuberous breast deformity. Plast Reconstr Surg. 112:1099–108
59. Toranto IR (1981) Two-stage correction of tuberous breasts. Plast Reconstr Surg. 67:642–6
60. von Heimburg D, Exner K, Kruft S, Lemperle G (1996) The tuberous breast deformity: classification and treatment. Br J Plast Surg. 49:339–45
61. Hueston JT (1976) Unilateral agenesis and hypoplasia: difficulties and suggestions. In: Goldwyn RM (ed) Plastic and reconstructive surgery of the breast. Little Brown, Boston, pp. 361–73
62. Argenta LC, VanderKolk C, Friedman RJ et al (1985) Refinements in reconstruction of congenital breast deformities. Plast Reconstr Surg. 76:73–80
63. Smith KJ, Palin WE, Katch V et al (1986) Surgical treatment of congenital breast asymmetry. Ann Plast Surg. 17:92–101
64. Trier WC (1965) Complete breast absence. Plast Reconstr Surg. 36:431–9
65. Amesse L, Yen FF, Weisskopf B, Hertweck SP (1999) Vaginal uterine agenesis associated with amastia in a phenotypic female with a de novo 46,XX,t(8;13)(q22.1;q32.1) translocation. Clin Genet. 55:493–5
66. Breslau-Siderius EJ, Toonstra J, Baart JA, Koppeschaar HP, Maassen JA, Beemer FA (1992) Ectodermal dysplasia, lipoatrophy, diabetes mellitus, and amastia: a second case of the AREDYLD syndrome. Am J Med Genet. 44:374–7
67. Taylor GA (1979) Reconstruction of congenital amastia with complication. Ann Plast Surg. 2:531–4
68. Rich MA, Heimler A, Waber L, Brock WA (1987) Autosomal dominant transmission of ureteral triplication and bilateral amastia. J Urol. 137:102–5
69. Burck U, Held KR (1981) Athelia in a female infant – heterozygous for anhidrotic ectodermal dysplasia. Clin Genet. 19:117–21
70. Tsakalakos N, Jordaan FH, Taljaard JJ, Hough SF (1986) A previously undescribed ectodermal dysplasia of the trichoodonto-onychial subgroup in a family. Arch Dermatol. 122: 1047–53
71. Mollica F, Mazzone D, Cimino G, Opitz JM (1995) Severe case of Al Awadi/Raas-Rothschild syndrome or new, possibly autosomal recessive facio-skeleto-genital syndrome. Am J Med Genet. 56:168–72
72. Barbero P, Valdez R, Rodríguez H, Tiscornia C, Mansilla E, Allons A, Coll S, Liascovich R (2008) Choanal atresia associated with maternal hyperthyroidism treated with methimazole: a case-control study. Am J Med Genet A. 146A: 2390–5
73. Lee H-B, Roh T-S, Chung Y-K et al (1998) Correction of inverted nipple using strut reinforcement with deepithelialized triangular flaps. Plast Reconstr Surg. 102:1253–8
74. Park HS, Yoon CH, Kim HJ (1999) The prevalence of congenital inverted nipple. Aesthet Plast Surg. 23:144–6

75. Lorenzetti MH, Fryns JP (1996) Inverted nipples in Robinow syndrome. Genet Couns. 7:67–9
76. Young G, Driscoll MC (1999) Coagulation abnormalities in the carbohydrate-deficient glycoprotein syndrome: case report and review of the literature. Am J Hematol. 60:66–9
77. Kurihara K, Maezawa N, Yanagawa H et al (1990) Surgical correction of the inverted nipple with a tendon graft: hammock procedure. Plast Reconstr Surg. 86:999–1003
78. Teimourian B, Adham MN (1980) Simple technique for correction of inverted nipple. Plast Reconstr Surg. 65:504–6
79. Baker SB, Burkey BA, Thronton P, LaRossa D (2001) Juvenile gigantomastia: presentation of four cases and review of the literature. Ann Plast Surg. 46:517–25
80. Lee MC, Lehman JA, Tantri DP et al (2003) Bilateral reduction mammoplasty in an adolescent population: adolescent bilateral reduction mammoplasty. J Craniofac Surg. 14: 691–5
81. Piza-Katzer H (2005) Reduction mammaplasty in teenagers. Aesth Plast Surg. 29:385–90
82. Kullander S (1976) Effect of 2 br-alpha-ergocryptin (CB 154) on serum prolactin and the clinical picture in a case of progressive gigantomastia in pregnancy. Ann Chir Gynaecol. 65:227–33
83. Swelstad MR, Swelstad BB, Rao VK, Gutowski KA (2006) Management of gestational gigantomastia. Plast Reconstr Surg. 118:840–8
84. Wølner-Hanssen P, Palmer B, Sjöberg NO, Astedt B (1981) Gigantomastia. Acta Obstet Gynecol Scand. 60:525–7
85. Gargan TJ, Goldwyn RM (1987) Gigantomastia complicating pregnancy. Plast Reconstr Surg. 80:121–4
86. Hedberg K, Karlsson K, Lindstedt G (1979) Gigantomastia during pregnancy: effect of a dopamine agonist. Am J Obstet Gynecol. 133:928–31
87. Craig HR (1988) Penicillamine-induced mammary hyperplasia: report of a case and review of the literature. J Rheumatol. 15:1294–7
88. Taylor PJ, Cumming DC, Corenblum B (1981) Successful treatment of D-penicillamine-induced breast gigantism with danazol. Br Med J (Clin Res Ed). 282:362–3
89. Tchebiner JZ (2002) Breast enlargement induced by D-penicillamine. Ann Pharmacother. 36:444–5
90. Matthews RN, Khan FT (1998) A seat belt injury to the female breast. Br J Plast Surg. 51:653
91. Rosenfield NS, Haller JO, Berdon WE (1989) Failure of development of the growing breast after radiation therapy. Pediatr Radiol. 19:124–7
92. Kunert P, Schneider W, Flory J (1988) Principles and procedures in female breast reconstruction in the young child's burn injury. Aesth Plast Surg. 12:101–6
93. Cherup LL, Siewers RD, Futrell JW (1986) Breast and pectoral muscle maldevelopment after anterolateral and posterolateral thoracotomies in children. Ann Thorac Surg. 41:492–7
94. Gobbi H, Tse G, Page DL et al (2000) Reactive spindle cell nodules of the breast after core biopsy or fine-needle aspiration. Am J Clin Pathol. 113:288–94

Nipple Discharge

Jill R. Dietz

3

3.1 Introduction

Nipple discharge is a presenting complaint of between 3–7.4% of women seeking medical care for breast problems [1, 2]. While the majority of these patients will have a benign process, nipple discharge can be the sole sign of cancer in 1% of patients [3]. The evaluation and treatment of nipple discharge varies greatly in practice and in the literature, causing confusion for both patients and physicians. Differentiating between physiologic and pathologic nipple discharge is critical in order to identify patients in need of a diagnostic work-up and treatment plan.

3.2 Anatomy and Physiology

A review of the anatomy and physiology of the human mammary ductal system is helpful in understanding the etiology of nipple discharge. The female breast has approximately 15–20 lobes that radiate from the nipple. Each lobe is comprised of glands (lobules) and branching milk ducts. The breast milk is produced in the terminal ductal lobular units (TDLU), which empty into a branching ductal network that leads to the proximal duct. The proximal ducts converge toward the areola and empty into the nipple. The mammary ducts are lined by actively dividing epithelial cells that slough on a regular basis. The nipple orifices of nonlactating women are usually blocked by a keratin plug that prevents the leakage of normal ductal secretions.

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During pregnancy, the ductal system proliferates and secretions are produced in response to large increases in estrogen, progesterone and prolactin (which is released by the anterior pituitary gland). After parturition, lactation is promoted by persistently elevated levels of prolactin, and rapidly declining levels of estrogen and progesterone. The nursing infant causes further release of prolactin via the suckling reflex, thus stimulating milk production. These same hormones that promote and sustain breast feeding can also contribute to physiologic nipple discharge in nonlactating women. Pathologic discharge is caused by a growth or proliferation of the mammary ductal epithelial lining.

3.3 Definition

Nipple discharge is fluid that flows or is expressed from the mammary ducts and is present in a small percentage of women. Nipple secretions are found within the ductal system and are by-products of the epithelial cells that are undergoing cellular turnover. These physiologic secretions are generally not evident to most women because they are blocked by the keratin plug and eventually reabsorbed. Goodson and King found secretions, or nipple aspirate fluid (NAF), in up to 81.2% of asymptomatic women by using a suction aspirating device [4]. Studies have confirmed that the ability to aspirate nipple secretions is influenced by age, race, parity and hormonal status but is successful in the majority of patients [5, 6]. Although nipple secretions are considered normal, the mammary ducts are the origin of most breast cancers, making the fluid secreted by the ducts a point of interest for researchers.

Many studies have been done on aspirated nipple secretions examining cellular changes and biochemical

I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_3, © Springer-Verlag Berlin Heidelberg 2010

composition [5, 7–9]. NAF contains cholesterol and other steroids, estrogens and other hormones, immunoglobulin, lactose, fatty acids, and alpha-lactalbumin. Exogenous compounds such as caffeine, nicotine, pesticides and other drugs are also found in nipple secretions. Lang and Kuerer have compiled an extensive list of compounds found intraductally by various studies [10]. The color of NAF, which can vary from white to dark green, is related to the cholesterol, lipid peroxide and estrogen content [11]. The normal cellular make up of NAF consists of foam cells, a few epithelial cells, and other cells of hematogenous origin [12].

When secretions become abundant or persistent enough that they discharge spontaneously from the duct orifice, they are known as nipple discharge. Nipple discharge is generally categorized as "physiologic" or "pathologic" discharge. Physiologic discharge can be caused by exogenous or endogenous hormones, medications, direct stimulation, stress or endocrine abnormalities. Although the cause of the hormonal influence may be pathologic, as is the case with prolactinoma, the ductal system itself has no abnormality, so the resultant discharge is classified as physiologic. Most physiologic discharge is bilateral, nonspontaneous, and involves multiple ducts. These characteristics result from the central effect of an outside influence on the breast. The color of the discharge can vary from milky to yellow, gray, brown, or dark green depending on the composition and cause of the physiologic discharge. As with NAF, darker colored discharges are associated with higher levels of estrogens and cholesterol [13] (Fig. 3.1). Because there is rarely an intraductal pathologic abnormality involved with this type of discharge, localization procedures or breast biopsies are not necessary.

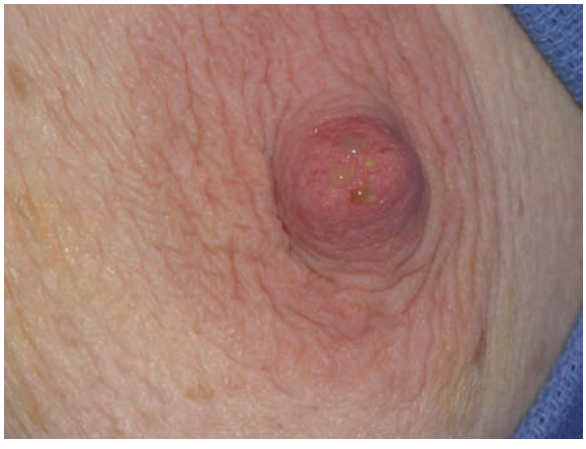


Fig. 3.1 Classic presentation of physiologic nipple discharge

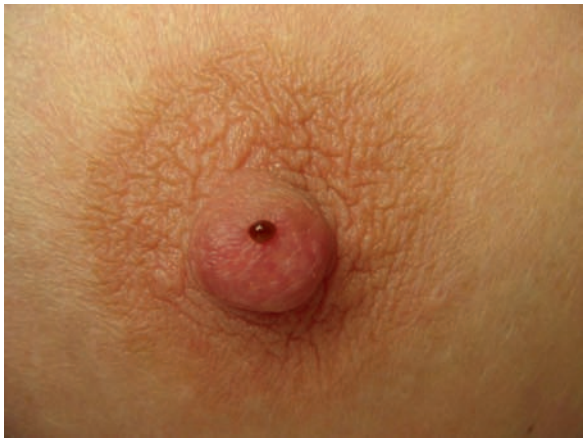


Fig. 3.2 Classic presentation of pathologic nipple discharge

Pathologic nipple discharge is caused by an abnormality of the duct epithelium. It is typically unilateral and from a single duct. The discharge is spontaneous or at least easily expressible. The patient often notices the discharge after a warm shower that likely removes the keratin plug. The pathologic lesion often causes ductal obstruction and dilatation so that the fluid which collects in the duct is subsequently released when the plug is removed or the duct is expressed. The color of the discharge is usually clear, serous or bloody, although pathologic nipple discharge can present as other colors (Fig. 3.2). This type of discharge tends not to be affected by the menstrual cycle or hormonal status. While some women seek care when they first notice the discharge, many will delay until the discharge becomes socially embarrassing or bloody. Although the majority of these women will have a benign etiology for their nipple discharge, all patients with pathologic nipple discharge need a thorough evaluation to rule out cancer.

3.4 Incidence

Approximately 5% of women presenting for breast care have a complaint of nipple discharge [14, 15]. The incidence is likely underreported since many women do not seek medical care for this symptom. Women

who have physiologic discharge, an otherwise normal exam and normal imaging, have a very low chance of having a malignancy [16, 17].

Patients with nipple discharge have a higher relative risk for cancer than the asymptomatic population. While the vast majority of patients with pathologic nipple discharge have benign proliferative lesions as the etiology, breast cancer is found to be the cause of the nipple discharge in 4–21% of cases [1, 3, 18–24]. Those patients with nipple discharge associated with a mass or skin change have an even higher relative risk of cancer. One study showed that the incidence of carcinoma for patients with discharge and a mass was 61.5% as compared to 6.1% for patients with discharge alone [2].

While most patients with pathologic nipple discharge have normal mammograms, many studies have shown that an abnormal mammogram in patients with pathologic nipple discharge is associated with an increased risk for cancer [18, 24–27]. As should palpable masses,suspicious radiologic findings should be evaluated by stereotactic or core needle biopsy prior to duct excision.. This will diagnose a malignancy in some patients, allowing for definitive surgical treatment. If minimally invasive biopsy is not available, then the mammographic abnormality will need to be evaluated at the time of duct excision.

Bloody or guaiac positive discharge also increases a person's risk of cancer, although most cases of bloody nipple discharge are benign, and cancer has been found to be the cause of discharge of milky and serous fluid [3]. Advanced age or postmenopausal status has also been shown to increase the risk of breast cancer being the cause of the pathologic discharge [22].

The number of breast cancer cases presenting as nipple discharge has dropped over the last few decades. Copeland's series of patients in the 1950s reported that 25 out of 67 (37%) patients with nipple discharge had breast cancer [28]. Whereas, more recent studies of patients undergoing duct excision for pathologic nipple discharge tend to have cancer rates between 5 and 10% [16, 22, 23]. The decrease in the incidence of cancer presenting in this way is likely due to the earlier detection of breast cancer with improved imaging techniques and increased screening, which shifts diagnosis to earlier stage disease. Another possibility is that minimally invasive biopsy of imaging and clinical abnormalities are being performed to establish a preoperative cancer diagnosis, thus moving these patients out of the category of women undergoing surgical biopsy for the diagnosis of nipple discharge.

Even though the most significant cause of nipple discharge is cancer, most cases have a benign etiology. Many studies do not differentiate the exact histology of benign lesions, although it is clear that papillomas or papillomatosis are responsible for a large percentage of pathologic nipple discharge. Other reported causes are duct ectasia, epithelial hyperplasia and fibrocystic changes [3, 18, 25]. As duct excision techniques become more sophisticated, the percentage of proliferative lesions identified goes up and fewer cases of duct ectasia and fibrocystic changes are found. This suggests that there is a proliferative ductal process accounting for most, if not all, cases of pathologic nipple discharge [22, 23, 26].

3.5 Characteristics and Etiology

Discharge from the nipple can present as a spectrum of signs, from a tiny opaque drop during breast examination to alarming bloody discharge that stains the patients clothing. The presentation and history is important in categorizing the discharge as either "physiologic" or "pathologic." Even though some causes of bilateral multiduct discharge are from a pathologic source, such as a pituitary adenoma, the effect is central and not the result of a ductal abnormality. These discharges are better categorized as physiologic or "nonpathologic" discharge. This grouping system is helpful in determining both the evaluation and treatment necessary for that patient. Table 3.1 shows the classic presentation of each type of nipple discharge.

Table 3.1 Characteristics of pathologic and physiologic nipple discharge

Characteristic	Physiologic	Pathologic
Laterality	Bilateral	Unilateral
#Ducts	Multiple	One
Spontaneity	Expressed	Spontaneous
Color	Multicolored, milky, gray, green, brown, yellow	Bloody, serous, clear
Consistency	Sticky, thick	Watery, copius

Table 3.2 Causes of nonpathologic nipple discharge

Hormonal variation
Pregnancy/postlactational
Mechanical stimulation
Galactorrhea
Duct ectasia
Bloody discharge of pregnancy
Infection (zuska's disease)
Montgomery gland discharge
Fibrocystic change

Physiologic nipple discharge has various presentations and etiologies. Table 3.2 reviews the most common causes of nonpathologic nipple discharge. Over 75% of nipple discharges are physiologic in nature and do not require surgical intervention [1]. The evaluation and treatment of physiologic nipple discharge should be focused on identifying the external factor that is stimulating the breasts.

Galactorrhea is physiologic discharge from the nipple that resembles breast milk but occurs in a patient who is not lactating. The discharge is a thin, watery milk-like substance that usually arises from both breasts. The most common scenario is a postpartum woman who continues to discharge from one or both breasts long after she has stopped breastfeeding. She may have some concern regarding the discharge and may attempt to repeatedly express the fluid. The continued stimulation of the nipple causes further discharge, perpetuating the cycle. Other sources of nipple stimulation such as the friction of clothing, or nipple involvement during intimacy, can also aggravate the symptom. Again, explaining to the patient the likely etiology of the discharge and reassurance is usually sufficient.

Thin, milky discharge can occur around menarche and menopause when the breasts are exposed to extreme hormonal variation. The discharge is self-limited and simply requires reassuring the patient. Nipple discharge can also be seen in newborns as a result of maternal hormones that cross the placental barrier prior to parturition. After delivery, the precipitous drop in estrogen and progesterone levels associated with the high neonatal prolactin levels cause stimulation of the infant's breast tissue. This discharge, commonly referred to as "witches milk," lasts only a few weeks [29].

Galactorrhea can result from an increase in prolactin levels. Most often, the levels are elevated due to medication, although the most significant cause is a pituitary adenoma that secretes prolactin. Prolactinoma should be expected if the patient has the classic triad of symptoms: amenorhea, galactorrhea and infertility. The tumor arises from the anterior pituitary gland and can become quite large causing symptoms of diplopia from compression of the optic chiasm. If a prolactinoma is suspected, a prolactin level should be drawn, which will be abnormal (>30 ng/mL). Screening nipple discharge patients with prolactin levels is not cost effective considering fewer than one in one thousand cases are due to a pituitary adenoma [30]. If a tumor is found, it can be successfully treated with a dopamine agonist, which will also eliminate the discharge. Occasionally, surgical excision of the tumor may be necessary.

Other rare causes of galactorrhea are listed in Table 3.3 along with the categories of medications that have been known to cause nipple discharge. Thoracic surgery or chest trauma has been reported to cause nipple discharge. The injury stimulates the afferent thoracic nerves and the hypothalamic-pituitary axis resulting in increased prolactin release, which in turn stimulates nipple discharge [31].

Opalescent physiologic discharges, which are multicolored and nonserous, emanate from one or both breasts and usually from multiple ducts. The discharge may only be evident with vigorous expression by the patient, or may be very easily expressed and copious. Creamy white, tan or yellow discharge may present next to a duct producing a brown, dark green or blackish discharge. Although this type of discharge is often alarming to the patient because the dark color is assumed to be blood, it is quite unlikely for it to be associated with an intraductal lesion. A tissue test, where the discharge is placed on a thin white tissue, often results in absorption of the drop, which then proves the discharge is green. It can be difficult to differentiate green discharge from guaiac positive discharge on hemoccult testing. When duct excision is done for this type of discharge, histology often shows normal breast tissue, duct ectasia or fibrocystic changes. Most patients with physiologic discharge are willing to be followed after being reassured of its benign nature. On a rare occasion, the patient may request surgery to eliminate copious discharge. If the discharge is associated with pain and fibrocystic changes, the patient should be informed that it is not

Table 3.3 Causes of galactorrhea (hyperprolactinemia)

Postlactational
Mechanical stimulation
Stress
Chest trauma or surgery
Pituitary and hypothalamic tumors
Ectopic prolactin (bronchogenic carcinoma)
Chronic renal failure
Hypothyroidism
Acromegaly
Cushing's disease
Lactogenic drugs
Estrogens
Progestins
Androgens (testosterone)
Long-term opiate use (e.g., morphine, cocaine)
Anesthetics
Phenothiazines (e.g., Compazine®,Thorazine®)
Antidepressants (e.g., Elavil®, Prozac®, Paxil®)
Monoamine oxidase inhibitors (e.g.,Nardil®, Parmate®)
Antipsychotics (e.g.,Clozaril®)
Antihypertensives (e.g., Aldomet®, Calan®)
Butyrophenones (e.g., Haldol®)
Thioxanthenes (e.g., Navane®)
Benzodiazepines (e.g.,Valium®)
Other prescribed drugs (e.g., Tagamet®, INH, Danocrine, Reglan®)

likely that the surgery will decrease her pain. It may also result in decreased nipple sensation and the inability to breastfeed, particularly if bilateral excisions are performed. If an underlying cause for the nipple discharge can be identified, then it can be addressed, such as a medication change or cessation of hormones.

Communication of cysts with ductal structures appears to be responsible for nipple discharge in some instances. In these situations, the cyst, often presenting as a mass, may disappear with the onset of discharge. Whenever a patient presents with nipple discharge and an associated mass, the mass must be evaluated. In this case, aspirated cyst fluid characteristics will likely correlate to the nipple discharge, and no further evaluation is necessary. A ductogram may show communication with the cyst. Although this is an interesting finding, a ductogram is not necessary if there is clinical evidence that the cyst is related to the discharge. If the problem persists, many patients prefer excision to control the discharge.

Some breast infections present with purulent and malodorous nipple discharge. This condition is treated like other breast infections. Large abscess cavities may be apparent and should be drained. Cellulitis in association with nipple discharge may be indicative of a deep abscess cavity. If it is unclear whether an abscess has formed, an ultrasound may be useful. Otherwise, conservative treatment with an antibiotic that has adequate gram positive coverage is appropriate initial therapy. The discharge itself may be a useful source to test for microbiology and sensitivities. Zuska's disease is a condition of chronic periareolar abscess with sinus formation and can result in intermittent nipple discharge and infection. Excision of the entire ductal system on the effected side, including the sinus tract is often associated with the fewest recurrences [32]. Because this problem occurs almost exclusively in smokers, major duct excision in this setting is also associated with a higher incidence of ischemic necrosis and other complications. A smoking cessation program may reverse this cycle of chronic infection or at least decrease the complications if duct excision is performed.

Duct ectasia is a condition, which results in poor emptying of ductal secretions, stagnation and inflammationof the ducts. The associated nipple discharge can present spontaneously or require vigorous expression to elicit a thick, white discharge. Bilateral, multiduct involvment varying in color is the most common presentation. The drainage is thought to be secondary to increased glandular secretions due to chronic inflammation [33].

Fibrocystic disease: Several series report that fibrocystic disease is a common histologic finding in many duct excision specimens from patients with pathologic nipple discharge. Series using localization techniques have very high proliferative lesion retrieval rates, which suggest that most cases of pathologic discharge are caused by intraductal abnormalities and not fibrocystic change [22, 26, 34]. In cases where fibrocystic change or normal breast tissue is reported, it is important to ensure that all the excised tissue is analyzed or

that the correct tissue was excised. Some papillomas are only 1–2 mm in size and could easily be missed with the sampling error of serial sectioning. A high suspicion for a missed proliferative lesion should remain when the histologic diagnosis of fibrocystic change is reported for duct excision specimens.

Occasionally, women who are in their third trimester of pregnancy or who are postpartum will experience bloody nipple discharge. While it is common to have a milky discharge at this time, bloody discharge is rare, often unilateral and may be expressible from multiple ducts. The bloody discharge is often noted after an abrupt increase in breast size associated with the pregnancy. In women, who have asymmetrical breast growth during pregnancy, bloody nipple discharge is more often associated with the larger breast [35]. The bloody discharge can accompany normal lactation and is often found during pumping. She may be concerned about breast cancer or the blood harming her nursing infant. The bleeding is usually minimal and self-limited and is unlikely to cause a problem for the nursing infant. The majority of case reports describe resolution of bleeding by the third month after delivery. Cytologic evaluation of nipple discharge in pregnant or postpartum patients often reveals abnormal appearing cells that are the result of normal epithelial changes during lactation. These cells may be falsely interpreted as arising from cancer and therefore cytologic examination of this discharge must be interpreted with caution. This bloody discharge during pregnancy and lactation is an unusual circumstance in which it may be reasonable to postpone or at least delay further evaluation. It must be appreciated that if the discharge is associated with a mass or persists as a unilateral, single duct discharge, then further evaluation is needed.

Montgomery gland discharge presents from the large areolar sebaceous glands known as Montgomery's tubercles, and is not truly the nipple discharge. This type of discharge usually occurs at times of extreme changes in hormonal status such as menarche or menopause. The discharge has characteristics of physiologic discharge as it is commonly found coming from many glands and is either serous or opaque in nature. This type of discharge requires reassurance unless infection occurs. In this case, antibiotic therapy and occasionally, excision of the infected gland is indicated. There are rare reports of duct communication to the Montgomery glands causing nipple discharge. This presents as pathologic discharge from the tubercle of the areola [36].

Nipple discharge in the male patient is treated similarly to that in females. Puberty in adolescents, and the same drugs and medical conditions that stimulate gynecomastia in men can cause nipple discharge. The evaluation should include mammography in addition to careful history and physical examination. Any suspicious mass or mammographic abnormality should be biopsied. In Leis's series of 6,200 patients, 5 out of 24 (20.8%) men diagnosed with cancer had nipple discharge as the presenting symptom. Evaluation is mandatory for male patients with pathologic nipple discharge, especially when associated with a mass, because of the increased risk of cancer and decreased survival rate of male patients with invasive breast cancer [18].

Pathologic nipple discharge is caused by an intraductal abnormality and is therefore typically a unilateral finding. Although it is possible for the pathology to involve more than one ductal system, the typical presentation is consistent discharge from a single duct orifice. The discharge can be watery clear, serosanguinous, dark brown old blood, or bright blood. Occasionally, reports of carcinoma with other types of discharge, such as milky, have been reported, but this is distinctly unusual [17, 37]. Table 3.4 reviews the common etiologies of pathologic nipple discharge.

Papilloma: (Fig. 3.3) A large percentage of pathologic nipple discharge is attributed to papillomas or papillomatosis. Papillomas are often found centrally in the subareolar region. Solitary papillomas arise from the larger ducts compared to the smaller, often multiple papillomas, which are more peripherally located and arise from the TDLU. Peripheral papillomas can occur bilaterally and have a higher recurrence rate after excision than the solitary central variety. Multiple, peripheral papillomas present with pathologic nipple discharge less frequently than central papillomas [31, 38].

Table 3.4 Causes of pathologic nipple discharge

Papilloma
Papillomatosis
Papillary cancer
Ductal carcinoma in situ
Invasive ductal carcinoma
Ductal epithelial hyperplasia
(?) Cysts/fibrocystic disease/duct ectasia

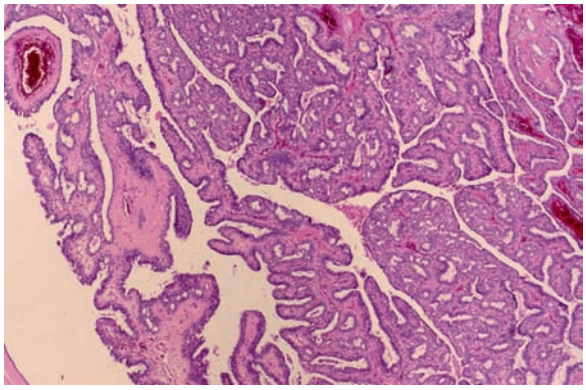


Fig. 3.3 Histologic section through an intraductal papilloma showing the vascular stroma with epithelial lining

In the past, there has been much controversy over whether papillomas are premalignant. It is generally accepted that central, solitary papillomas have little malignant potential although they should be completely excised to avoid recurrence [39]. In contrast, papillomas arising in small, more peripheral ducts can be associated with cancer. Ohuchi reconstructed ductal excision specimens from patients with pathologic nipple discharge and found that cancer was associated with 37.5% of peripheral papillomas but not with central papillomas [40]. Hou et al. showed that 70% of malignancies found on duct excision for nipple discharge were located over 2 cm from the nipple [41]. Patients with nipple discharge, who are found to have peripheral lesions on ductography, should be considered for a preoperative localizing procedure to guide the surgeon during surgical biopsy. These patients should also have careful follow up since the risk of recurrence or development of cancer is higher than that for central lesions [39].

Carcinoma: (Fig. 3.4) One percent of all breast cancers present with nipple discharge as the only symptom [3]. Approximately one in ten cases of pathologic nipple discharge will have cancer as the etiology and the incidence increases if the discharge is bloody. The rationale for investigation in patients with pathologic nipple discharge is to rule out cancer as the source. While there are a number of diagnostic tests available that correlate with the malignant potential of a lesion, no single test can rule out carcinoma, so duct excision is recommended. Imaging abnormalities or suspicious clinical findings should be worked up and biopsied to assist in establishing a diagnosis.

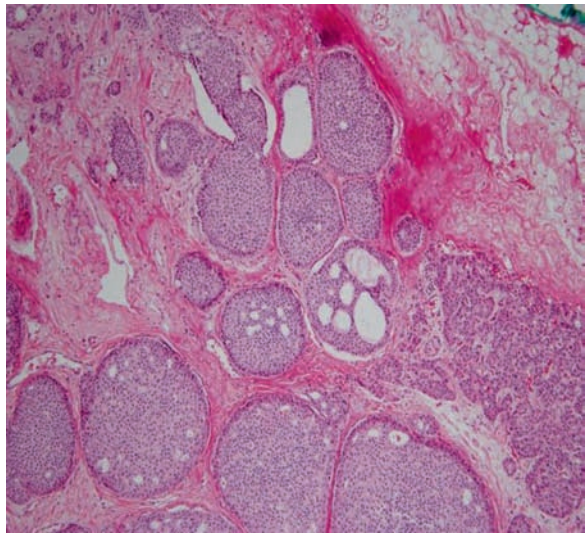


Fig. 3.4 Histologic representation of ductal carcinoma in situ

3.6 Diagnostic Evaluation

Many diagnostic tests are available to evaluate patients with nipple discharge. Before embarking on any of these, a full history must first be taken, including the patient's age, gynecologic and sexual history, and use of medication and hormones. Pertinent medical history such as previous endocrine problems or chest trauma should also be ascertained. The characteristics of the discharge must be noted, including laterality, spontaneity, number of ducts involved, color and consistency. Physical exam should include a breast exam, assessing for palpable masses, lymphadenopathy, skin changes and nipple inversion or lesions. The information obtained from a careful history and a confirming physical exam will frequently lead to a diagnosis and limit the tests needed prior to duct excision.

3.7 Mammography

If it is determined that the patient has physiologic nipple discharge, no additional procedures are needed. Mammography is reserved for patients in the appropriate age group and risk categories if physiologic discharge is the presenting symptom. All patients with pathologic nipple discharge should undergo mammographic evaluation regardless of age. Still, mammography is often normal in

cases of discharge associated with cancer. Fung found that only 2 out of 15 patients with cancer causing nipple discharge had mammograms suggestive of malignancy [42]. Mammography might identify a separate or associated lesion that may alter the course of management. Mammographic abnormalities associated with nipple discharge increase the likelihood of a malignancy [25]. If a mammographic abnormality is visualized, this finding takes precedence and a stereotactic or ultrasound guided core biopsy should be performed. If a minimally invasive biopsy is not done, then a needle localization excisional biopsy should be performed.

3.8 Ultrasound

Ultrasound has been used for patients with pathologic nipple discharge to view dilated ducts. This technique has also been used with saline lavage of the discharging duct to dilate and obtain cytology from the duct under echographic guidance [43, 44]. Chung compared ultrasound to ductography and found that ultrasound is superior for defining small 0.5 cm lesions and to evaluate multiple ductal systems. Ultrasound-guided localization of the lesion is particularly helpful in cases of failed cannulation during ductography [45]. Ductography remains superior to ultrasound for visualizing the extent of abnormality within a ductal system and for detection of microcalcifications [46]. High-resolution ultrasound is performed at 13–15 MHz and has a higher sensitivity for the diagnosis of intraductal pathology than conventional ultrasound (75 vs. 30%). Although it has a lower specificity than conventional ultrasound performed at 7.5 MHz, high-resolution ultrasound appears to be better for evaluating proximal ducts [47, 48] (Fig 3.5). If an identified peripheral lesion can be visualized by ultrasound, needle localization or ultrasound-guided fine needle aspiration (FNA) may be performed. The sensitivity of cytologic examination of ultrasound-guided FNA is only 50% however, and duct excision is warranted to remove the lesion [49]. Two recently published studies looked at patients with nipple discharge who underwent ultrasound-guided percutaneous Mammotome excision of their intraductal abnormalities. Both of these studies report that 95% of patients were discharge free after the procedure. Thorough prebiopsy work-up and patient selection is critical for this procedure to be successful [50, 51].

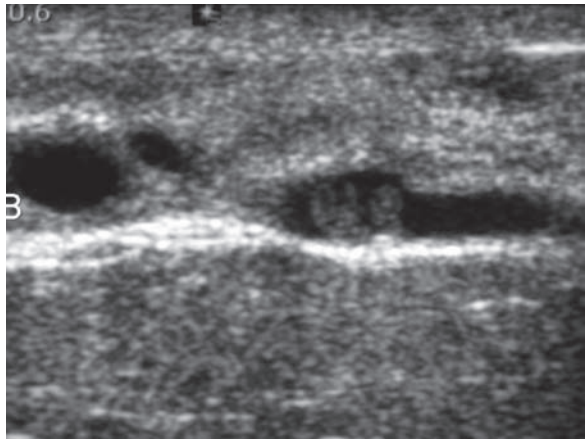


Fig. 3.5 Ultra sound of a dialated duct showing an intraductal lesion

3.9 MRI

Magnetic Resonance Imaging is being used more often as an additional diagnostic tool for breast diseases. It is particularly useful in young women with dense breast tissue where more conventional tests such as mammography and ultrasound have a lower sensitivity. MRI has a higher sensitivity than standard ductography but still cannot differentiate benign from malignant disease [52–54]. MR-ductography has been developed as an additional tool for patients with pathologic nipple discharge and can be useful for identifying the extent of the disease. While expense is an issue, it is not as invasive as conventional ductography and does not have the problem of failed cannulation. Fusion imaging of MR ductography and MR mammography can provide useful information on the extent of disease, and size and shape of the lesion. This is helpful for resection planning and in suspected cancer cases where breast conservation will be attempted [55, 56].

3.10 Occult Blood

Testing nipple discharge for occult blood has been evaluated in many studies. Bloody or heme-positive discharge has been associated with an increased incidence of cancer. In one large series, discharge was tested for occult blood using a Bililabstix reagent strip. All patients with the eventual diagnosis of cancer tested positive even though less than half were grossly

bloody [3]. Since there are reports of cancers identified in non-bloody discharge, if the discharge is characteristically pathologic, it should be evaluated even if it is heme-occult negative.

3.11 Cytology

Many physicians will send nipple discharge for cytologic evaluation. In a large screening study where cytology was performed on over 20,000 patients with nipple discharge, only 0.2% patients were either positive or suspicious for malignancy. In this same series, 61 of 404 detected cancers had nipple discharge. In these 61 cases, cytology findings were: 24 negative, 18 positive, 7 suspicious, and 12 atypical for a sensitivity of 60.7% [57]. The ability to detect malignancy by cytologic examination of nipple discharge ranges from 45 to 82% [17, 18, 58–60]. Nipple discharge cytology has a 0.9–2.6% false positive rate [18, 60] (Fig. 3.6).

Cytology alone should not be used to determine if surgical excision is necessary because of the high false negative and false positive rates. In cases of positive nipple cytology and mammographic changes suggestive of malignancy, a diagnostic surgical procedure may be justified [61]. If the mammographic abnormality is biopsied preoperatively and a cancer diagnosis is established, then a thorough workup and definitive diagnosis can be performed. For patients with pathologic nipple discharge and no mass or mammographic abnormality, a biopsy should be done regardless of cytologic findings.

Cytology examination is not recommended for pregnant patients due to the difficulty in differentiating normal from abnormal proliferative changes. Positive cytology in cases of pathologic nipple discharge or nipple lesions can be helpful, but in cases in which the clinical evaluation is suspicious without positive cytology or if cytology is positive without a corresponding high level of clinical suspicion, tissue biopsy is required. A negative cytology report in the setting of clinical nipple discharge could erroneously reassure the patient who still needs further evaluation.

3.12 Biochemical Markers

Several researchers have addressed the role of biochemical markers in nipple discharge in an attempt to diagnose breast cancer. Certain LDH isoenzyme levels have been found to be elevated in the nipple discharge of patients with breast cancer. The test is relatively simple and inexpensive but is associated with a false negative rate in cases where a cancer is in another area of the breast and not associated with the discharge [62]. Immunoassays for CEA have been done using small nitrocellulose-backed disks placed on the nipples of cancer patients. Nipple secretions from 94% of the patients with cancer

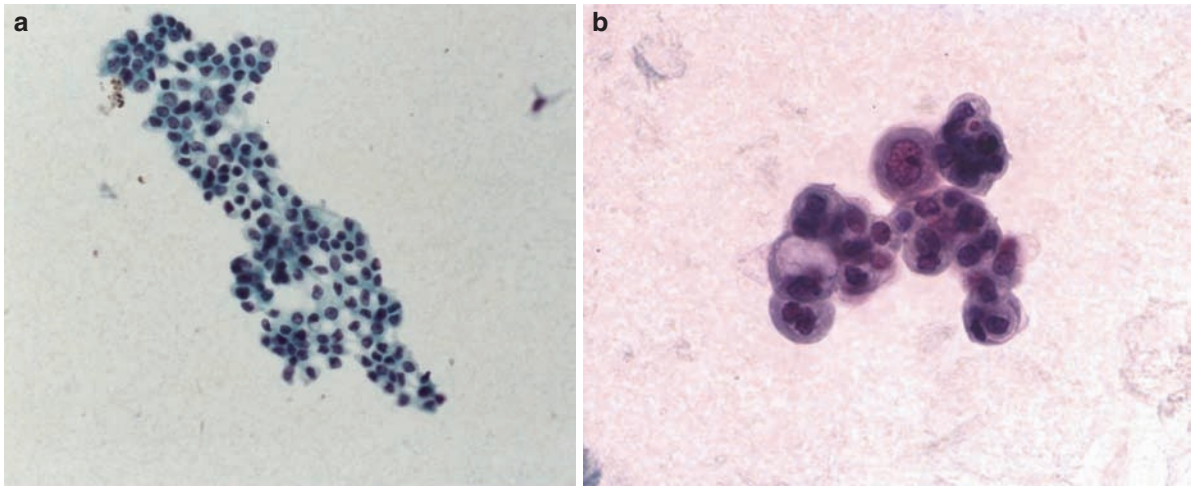


Fig. 3.6 (**a**) Nipple discharge cytology showing benign ductal cells and proteinaceous material. (**b**) Nipple discharge cytology showing malignant cells

had significantly higher levels of CEA than from those without cancer. This difference was not apparent in healthy controls [63]. Several studies of NAF and abnormal discharge using immunoassays for CEA show similar trends whereas others show no difference [64–66]. Using a modified breast pump to obtain NAF, Sauter found that decreased levels of prostatic specific antigen (PSA) were associated with an increased breast cancer risk [6]. In a recent study, Liu found that basic fibroblast growth factor (bFGF) from nipple fluid was significantly increased in breast cancer patients over controls [67]. Sauters group has also looked at proteonomic analysis of ductal fluids using SELDI-TOF-mass spectrometry showing differential expression between women with and without breast cancer [68]. These tests using nipple discharge or secretions may aid in the diagnosis of breast cancer and are promising for future screening and diagnosis, but are currently not accurate enough to rule out carcinoma or negate the need for biopsy in patients with nipple discharge.

3.13 Ductal Imaging

Ductography, or galactography has proven useful for preoperative localization of intraductal lesions [69, 70] (Fig. 3.7). Due to the significant false negative rate, however, the decision to operate should not be based solely on the ductogram results [20]. The ability of ductography to distinguish between benign and malignant disease remains limited [46, 71]. A recent study reported an increase in the duct excision yield of neoplastic growths from 67 to 100% by using preoperative ductography [70]. This procedure is easily performed by inserting a 30-gauge blunt tip needle into the discharging duct orifice and instilling 0.1–1.5 mL of water-soluble contrast. Mammograms are taken in two views and will show a filling defect or duct cut-off in most circumstances [19]. In cases where the ductal lesion is far from the nipple, ductography can be combined with preoperative needle localization to assist the surgeon with the excision [70, 72]. Other techniques combine preoperative ductography with methylene blue dye injection to assist the surgeon in removing the lesion [70, 73].

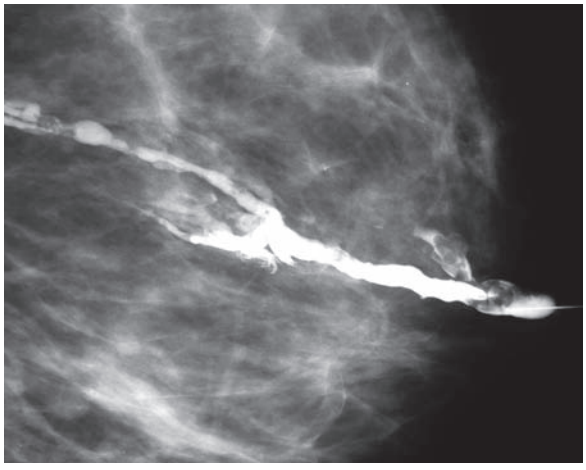


Fig. 3.7 Ductogram showing the typical lobulated appearance of a benign intraductal papilloma

Standard ductography via the nipple is not possible in many patients who have had previous duct surgery with retained or new duct lesions or for patients who have dilated ducts that cannot be accessed through the nipple. In these cases, percutaneous ductography has been described using ultrasound guidance. This procedure allows for identification and localization of the lesion to assist with surgical excision [74].

Despite the advances in diagnostic and radiologic techniques, patients with pathologic nipple discharge frequently come to surgical excision. Because there are no tests that can adequately differentiate benign from malignant intraductal lesions, removal of the lesion is necessary [2].

3.14 Surgical Evaluation and Treatment

Surgery for pathologic nipple discharge can be a less than satisfying procedure. Duct excision is typically performed blindly because the intraluminal pathology cannot be visualized directly during surgery. Duct excision can cause decreased sensation to the nipple and prevent the ability to breast feed depending on the extent of dissection. The surgeon must judge the amount of tissue to be excised so as to assure adequate removal of the lesion without unnecessary destruction of normal breast tissue. Benign or normal pathology findings could result from not excising the lesion, from the pathologist not identifying the lesion within the specimen or possibly from a truly negative pathology.

Various techniques for surgical removal of the mammary ducts have been described. A major duct excision removes all or most of the subareolar ductal tissue through either a circumareolar or radial incision

[18, 75]. Traditionally, this approach was used for pathologic nipple discharge prior to the availability of localizing procedures. It is still useful in cases of copious physiologic discharge for which the patient requests surgery or for cases where localizing attempts are unsuccessful or show multiple duct involvement. After the incision is made, the ducts are encircled and tied off as they enter the nipple. The subareolar tissue is coned out for several centimeters to remove all apparent ductal tissue. The recurrence rate of nipple discharge after this procedure is very low, although the proliferative lesion retrieval rate is less than for more directed techniques [16]. The circumareolar incision and more extensive subareolar tissue resection necessary to perform a major duct excision may disrupt the nerve supply to the nipple and leave the patient with numbness, nipple retraction and the inability to nurse on that side. Care must be taken to avoid cautery burn to the undersurface of the nipple to limit the possibility of nipple necrosis [76].

A more limited or segmental duct resection can be performed by cannulating the discharging duct with a probe. The tissue is removed from around the probe deep within the breast. The goal is to remove an entire ductal system from the nipple to the terminal duct lobular unit. This is useful in cases where localizing attempts have failed and the location of the lesion is unknown or for deep lesions. A circumareolar incision is commonly made in the quadrant of the discharging duct [77]. A flap is created undermining to the nipple and the dilated or blue duct is encircled. It is important to dissect into the nipple to remove the proximal duct tissue to prevent recurrent discharge [76]. A useful adjunct to this procedure is preoperative ductography combined, if necessary, with needle localization for a deep abnormality. The proximal duct is removed with the assistance of a probe or blue dye while the deep lesion is identified by excising the tissue around the localizing wire [72]. Duct excision using a lacrimal probe guide has the advantage of identifying the proximal portion of the discharging duct. The probe may, however enter the wrong duct at a bifurcation or be unable to be advanced to the level of pathology.

Microdochectomy is a procedure, which removes the abnormal duct while preserving surrounding normal breast tissue [22, 78]. The technique involves identifying and cannulating the discharging duct preoperatively by ductography. Blue dye is then injected into the abnormal ductal system through the cannula placed during the preoperative ductogram. The duct is dissected from the nipple toward the deeper ducts removing only the blue-stained duct tissue. This technique is described with a transareolar incision, which is a radial incision through the nipple, or a small curvilinear incision within the areola or at the areolar edge can be used as well [22, 79]. This technique has the benefit of removing the discharging duct while preserving the normal ducts in an effort to limit sensation loss and retain the ability to breastfeed.

3.15 Mammary Ductoscopy

Mammary ductoscopy allows for direct visualization of the intraductal lesion by passing a small endoscope through the nipple into the ductal system after the duct orifice is dilated. This technique is becoming more widely used, especially in cases of pathologic nipple discharge and reports the highest proliferative lesion rates of all localizing techniques [26, 80–83]. The visual component alone of ductoscopy cannot adequately differentiate benign from malignant lesions [84]. Other studies show excellent sensitivity (98 and 96%) with ductoscopy and cytology or intraductal biopsy, which can help with planning resection [34, 85].

The ability to enter the ductal system and directly visualize ductal abnormalities has distinct advantages. The intraductal pathology can be visualized during the time of surgical excision and the scope itself can direct the surgeon to the lesion (Fig. 3.8). Intraoperative visualization of the lesion enables adequate removal of the abnormality while preserving surrounding normal tissue. Ductoscopy enables the surgeon to identify the abnormality within the specimen and assists the pathologist in locating the lesion [86]. Mammary ductoscopy may limit the extent of surgery necessary to excise intraductal pathology, as well as help in identifying the lesions to be removed including lesions within the nipple itself, which can be left behind, and multiple deeper lesions, which occur in 25% of cases, more accurately[26]. Intraductal biopsy tools are becoming available, which will provide histology samples of intraductal pathology [87]. As technical advances are made, the possibility of diagnosis and treatment of intraductal pathology is on the horizon.

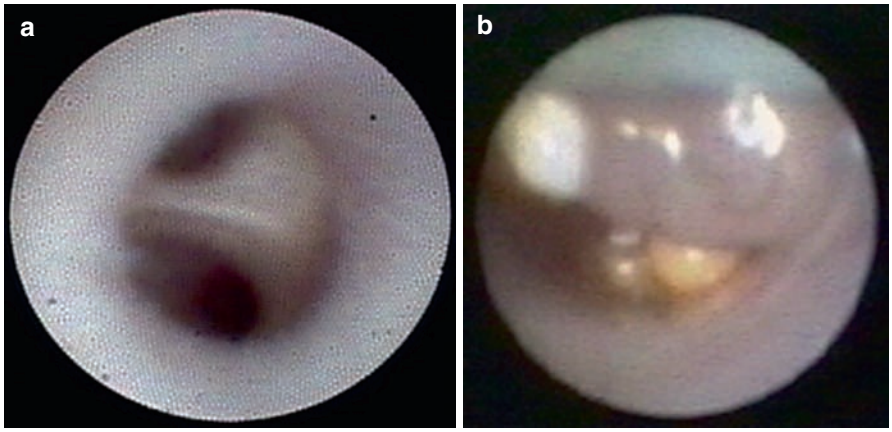


Fig. 3.8 Intraductal images through the mammary ductoscope. (**a**) Normal duct bifurcation. (**b**) Intraductal papilloma

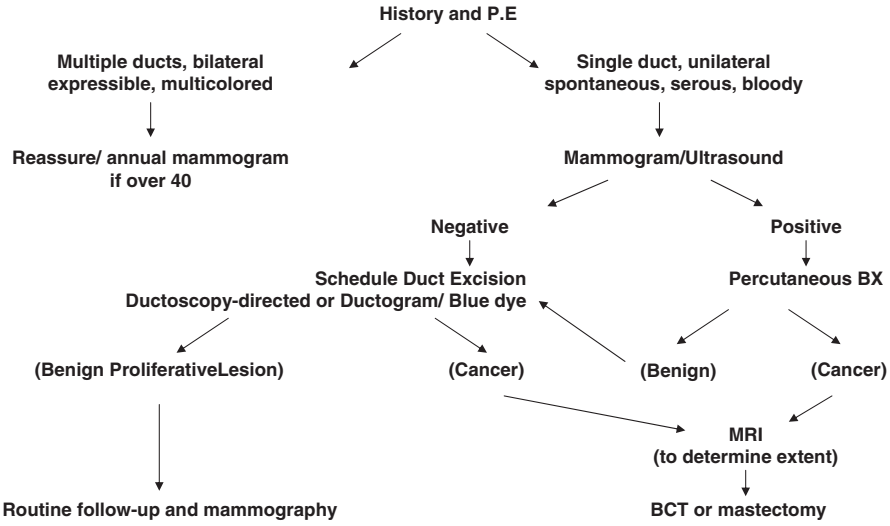
3.16 Follow Up

Anywhere from 5 to 20% of duct excision cases will turn out to be malignant. The treatment of breast cancer presenting as nipple discharge has traditionally been mastectomy. Many series suggest that intraductal cancer presenting as nipple discharge is more extensive and has a higher recurrence rate than DCIS in other areas of the breast [37, 88–90]. Ito found that in 26 patients with nonpalpable breast cancer associated with nipple discharge that were treated with duct-lobular segmentectomy, only one patient had microscopic residual disease found in the follow up mastectomy specimen. These findings suggest that segmental duct resection is an adequate surgery for nonpalpable cancers presenting with nipple discharge [91]. If cancer is found at the time of duct excision for pathologic nipple discharge, then MRI may be useful for determining the extent of disease. Reexcision, which is often needed to obtain clear margins, will also help determine residual disease.

Carcinoma of the ipsilateral breast following duct excision has been reported in a number of series [3, 25, 37]. Many of these patients were found to have benign disease or no pathologic diagnosis at the original surgery. In these cases, it is likely that the lesion causing the discharge was not removed during the first procedure. These cancers typically present as masses rather than recurrent nipple discharge because of the interruption of the ductal system at the time of the original duct excision. Close follow-up is essential for patients with nipple discharge in which no proliferative lesion was seen on analysis of the specimen, and for patients with peripheral papillomas. Patients undergoing breast conservation who have in-situ carcinomas as the cause of their nipple discharge should also have post-operative radiation therapy and close mammographic and clinical follow-up [37].

Nipple discharge, in the majority of patients with this symptom, is physiologic discharge that usually does not require further evaluation. Spontaneous, clear or bloody, single duct discharge should be worked up with imaging modalities and most of these patients need excision to rule out carcinoma. While technology is rapidly advancing and we have many options available for ductal evaluation, none of these can satisfactorily rule out malignancy as the cause of the discharge. Therefore, at this time, excision of the affected duct is still considered standard of care. The preoperative and excisional techniques you will utilize in this patient population will depend somewhat on the availability of equipment and expertise at your institution. It is clear, however, that the more guided and localized the excision, the greater the chance of identifying the proliferative cause of the discharge. Figure 3.9 illustrates the algorithm used at the Cleveland Clinic Foundation for the evaluation of nipple discharge. As imaging and biopsy techniques become more advanced, it is conceivable that in the near future, many nipple discharge patients will be able to forgo surgical excision altogether without compromising their diagnosis.

Fig. 3.9 Algorithm



References

1. Devitt JE (1985) Management of nipple discharge by clinical findings. Am J Surg. 149:789
2. Gulay H, Bora S, Kilicturgay S, Hamaloglu E, Goskel HA (1994) Management of nipple discharge. J Am Coll Surg. 178:471–4
3. Chaudary M, Millis R, Davies G et al (1982) Nipple discharge: the diagnostic value of testing for occult blood. Ann Surg. 196:651
4. Goodson WH, King EB (1998) Discharges and secretions of the nipple. In: Bland KI, Copeland EM (eds) The breast: comprehensive management of benign and malignant diseases., 2nd edn. WB Saunders, Philadelphia, pp 51–74
5. Sartorius OW, Smith HS, Morris P et al (1977) Cytological evaluation of breast fluid in the detection of breast diseases. J Natl Cancer Inst. 59:1073–80
6. Sauter ER, Daly M, Linahan K et al (1996) Prostate-specific antigen levels in nipple aspirate fluid correlate with breast cancer risk. Cancer Epidemiol Biomark Prev. 5(120): 967–70
7. Petrakis NL, Mason L, Lee R (1975) Association of race, age, menopausal status, and cerumen type with breast fluid secretion in nonlactating women as determined by nipple aspiration. J Natl Cancer Inst. 54:829–34
8. Sauter E, Wagner-Mann C, Ehya H et al (2007) Biologic markers of breast cancer in nipple aspirate fluid and nipple discharge are associated with clinical findings. Cancer Detect Prev. 31(1):50–8
9. Wrensch MR, Petrakis NL, Gruenke LD et al (1990) Factors associated with obtaining nipple aspirate fluid: analysis of 1,428 women and literature review. Breast Cancer Res Treat. 15(1):39–51
10. Lang J, Kuerer H (2007) Breast ductal secretions: clinical features, potential uses, and possible applications. Cancer Control. 14(4):350–9
11. Petrakis NL (1986) Physiologic, biochemical, and cytologic aspects of nipple aspirate fluid. Breast Cancer Res Treat. 8:7–19
12. Papanicolaou GN, Bader GM, Holmquist DG (1958) Exfoliative cytology of the human mammary gland and its value in the diagnosis of cancer and other diseases of the breast. Cancer. 11:337–409
13. Petrakis NL, Lee RE, Miike R et al (1988) Coloration of breast fluid related to concentration of cholesterol, cholesterol epoxides, estrogens and lipid peroxides. Am J Clin Pathol. 89:117–20
14. Santen RJ, Mansel R (2005) Benign Breast disorders. N Engl J Med. 353(3):275–85
15. Seltzer MH (2004) Breast complaints, biopsies, and cancer correlated with age in 10,000 consecutive new surgical referrals. Breast J. 10:111–7
16. Dillon M, NaMohd Nazri S, Nasir S et al (2006) The role of major duct excision and microdochectomy in the detection of breast carcinoma. BMC Cancer. 6:164
17. Ciatto S, Bravetti P, Cariaggi P (1986) Significance of nipple discharge clinical patterns in selection of cases for cytologic examination. Acta Cytologica. 30(1):17–20
18. Leis HP Jr (1989) Management of nipple discharge. World J of Surg. 13(6):736–42
19. Tabar L, Dean PB, Pentek Z (1983) Galactography: the diagnostic procedure of choice for nipple discharge. Radiology. 149:31–8
20. Dawes LG, Bowen C, Luz VA, Morrow M (1998) Ductography for nipple discharge: no replacement for ductal excision. Surgery. 124(4):685–91
21. Paterok EM, Rosenthal H, Sabel M (1993) Nipple discharge and abnormal galactogram. Results of a long-term study (1964–1990). Eur J Obstet Gynecol Reprod Biol. 50: 227–34
22. Lau S, Kuchenmeister I, Stachs A et al (2005) Pathologic nipple discharge: surgery is imperative in postmenopausal women. Ann Surg Oncol. 12(7):246–51

23. Vargas H, Perla Vargas M, Eldrageely K et al (2006) Outcomes of clinical and surgical assessment of women with pathological nipple discharge. Am Surg. 72:124–8
24. Cabioglu N, Hunt KK, Singletary SE et al (2003) Surgical decision-making and factors determining a diagnosis of breast carcinoma in women presenting with nipple discharge. Am Coll Surg. 196(3):354–64
25. Carty NJ, Mudan SS, Ravichandran D, Royle GT, Taylor I (1994) Prospective study of outcome in women presenting with nipple discharge. Ann R Coll Surg Engl. 76:387–9
26. Dietz JR, Crowe JP, Grundfest S et al (2002) Directed duct excision by using mammary ductoscopy in patients with pathologic nipple discharge. Surgery. 132:582–7
27. Johnson TL, Kini SR (1991) Cytologic and Clinicopathologic features of abnormal nipple secretions: 225 cases. Diagn Cytopathol. 7:17–22
28. Copeland M, Higgins T (1960) Significance of discharge from the nipple in nonpuerperal mammary conditions. Ann Surg. 151(5):638–48
29. Arnold G, Neiheisel M (1997) A comprehensive approach to evaluating nipple discharge. Nurse Pract. 22(7):96–111
30. Newman HF, Klein M, Northrup JD et al (1983) Nipple discharge: frequency and pathogenesis in an ambulatory population. NY St J Med. 83:928
31. Haagensen DD (1971) Diseases of the breast., 2nd edn. WB. Saunders, Philadelphia
32. Zuska JJ, Crile G Jr, Ayres NW (1951) Fistulas of lactiferous ducts. Am J Surg. 81:312–7
33. Fiorica JV (1994) Nipple discharge. Obstet Gynecol Clin North Am. 21:453–60
34. Liu GY, Lu JS, Shen KW, Wu J, Chen CM et al (2008) Fiberoptic ductoscopy combined with cytology testing in the patients of spontaneous nipple discharge. Breast Cancer Res Treat. 108:271–7
35. Lafreniere R (1990) Bloody nipple discharge during pregnancy and/or lactation: a rational for conservative treatment. J Surg Oncol. 43:228–30
36. Sakai T, Makita M, Akiyama F, Uehara K et al (2006) Intraductal papilloma with bloody discharge from Montgomery's areolar tubercle examined by ductoscopy from the areola. Breast Cancer. 13(1):104–6
37. Bauer RL, Eckhert KH Jr, Nemoto T (1998) Ductal carcinoma in situ-associated nipple discharge: a clinical marker for locally extensive disease. Ann Surg Oncol. 5(5):452–5
38. Cardenosa G, Eklund GW (1991) Benign papillary neoplasms of the breast: mammographic findings. Radiology. 181:751–5
39. Carter D (1977) Intraductal papillary tumors of the breast. Cancer. 39:1689–92
40. Ohuchi N, Abe R, Kasai M (1984) Possible cancerous change of intraductal papilloma of the breast. Cancer. 54:605–11
41. Hou MF, Huang TJ, Liu GC (2001) The diagnostic value of galactography in patients with nipple discharge. Clin Imaging. 25:75–81
42. Fung A, Rayter Z, Fisher C et al (1990) Preoperative cytology and mammography in patients with single-duct nipple discharge treated by surgery. Br J Surg. 77(11):1211–2
43. Teboul M (1988) A new concept in breast investigation: echo-histological acino-ductal analysis or analytic echography. Biomed Pharmacoth. 42:289–96
44. Feige C (1988) Dynamic morpho-cyto-echography and the echographic galactoscopy endoductal sample; intrinsic and extrinsic markers in the detection of breast cancers. Ultrasound Med and Biol. 14(1):97–108
45. Rissanen T, Reinikainen H, Apaja-Sarkkinen M (2007) Breast sonography in localizing the cause of nipple discharge. J Ultrasound Med. 26:1031–9
46. Chung SY, Lee K, Park KS, Lee Y, Bae SH (1995) Breast tumors associated with nipple discharge: correlation of findings on galactography and sonography. Clin Imaging. 9(3):165–71
47. Cilotti A, Campassi C, Bagnlesi P et al (1996) Pathologic nipple discharge. High resolution versus conventional ultrasound in the evaluation of ductal disease. Breast Dis. 9:1–13
48. Ballesio L, Maggi C, Savelli S et al (2007) Adjunctive diagnostic value of ultrasonography evaluation in patients with suspected ductal breast disease. Radiol Med. 112:354–65
49. Sardanelli F, Imperiale A, Zandrino F et al (1997) Breast intraductal masses. Ultrasound-guided fine needle aspiration after galactography. Radiology. 204:143–8
50. Govindarajulu S, Narreddy SR, Shere MH et al (2006) Sonographically guided mammotome excision of ducts in the diagnosis and management of single duct nipple discharge. EJSO. 32:725–8
51. Torres-Tabanera M, Alonso-Bartolome P, Vega-Bolivar A, Sanchez-Gomez SM et al (2008) Percutaneous microductectomy with directional vacuum-assisted system guided by ultrasonography for the treatment of breast discharge: experience in 63 cases. Acta Radiol. 49(3):271–6
52. Yoshimoto M, Kasumi F, Iwase T, Takahashi K, Tada T, Uchida Y (1997) Magnetic resonance galactography for a patient with nipple discharge. Breast Cancer Res Treat. 42:87–90
53. Ballesio L, Maggi C, Savelli S et al (2008) Role of breast magnetic resonance imaging (MRI) in patients with unilateral nipple discharge: preliminary study. Radiol med. 113: 249–64
54. Morrogh M, Morris E, Liberman L et al (2007) The predictive value of ductography and magnetic resonance imaging in the management of nipple discharge. Ann Surg Oncol. 14(12):3369–77
55. Hirose M, Nobusawa H, Gokan T (2007) MR ductography: comparison with conventional ductography as a diagnostic method in patients with nipple discharge. Radiographics. 27:S183–96
56. Hirose M, Otsuki N, Hayano D, Shinjo H, Gokan T et al (2006) Multi-volume fusion imaging of MR ductography and MR mammography for patients with nipple discharge. Magn Reson Med Sci. 5(2):105–12
57. Takeda T, Matsui A, Sato Y et al (1990) Nipple discharge cytology in mass screening for breast cancer. Acta Cytologica. 34(2):161–4
58. Dunn JM, Lucarotti E, Wood SJ et al (1995) Exfoliative cytology in the diagnosis of breast disease. Br J Surg. 82:789–91
59. Florio M, Manganaro T, Pollicino A et al (1999) Surgical approach to nipple discharge: a ten-year experience. J Surg Oncol. 71:235–8
60. Knight DC, Lowell D, Heimann A, Dunn E (1986) Aspiration of the breast and nipple discharge cytology. Surg Gynecol Obstet. 163:415–20

61. Ranieri E, Virno F, D'Andrea M et al (1955) The role of cytology in differentiation of breast lesions. Anticancer Res. 15:607–12
62. Kawamoto M (1994) Breast cancer diagnosis by lactate dehydrogenase isoenzymes in nipple discharge. Cancer. 73:1836–41
63. Imayama IS, Mori M, Ueo H et al (1996) Presence of elevated carcinoembryonic antigen on absorbent disks applied to nipple area of breast cancer patients. Cancer. 78(6):12229–34
64. Inaji H, Yayoi E, Maeura Y, Matsuura N, Tominaga S, Koyama H et al (1987) Carcinoembryonic antigen estimation in nipple discharge an adjunctive tool in the diagnosis of early breast cancer. Cancer. 60:3008–13
65. Nishiguchi T, Hishimoto T, Funahashi S et al (1992) Clinical usefulness of carcinoembryonic antigen measurement in nipple discharge as an adjunctive tool for diagnosis of breast cancer. Jpn J of Clin Path. 40(1):67–72
66. Fortova L, Garber JE, Sadowsky NL et al (1998) Carcinoembryonic antigen in breast nipple aspirate fluid. Cancer Epidemiol Biomark Prev. 7(3):195–8
67. Liu Y, Wang JL, Chang H et al (2000) Breast-cancer diagnosis with nipple fluid bFGF (letter). Lancet. 356(9229):567
68. Sauter E, Shan S, Hewett J et al (2005) Proteomic analysis of nipple aspirate fluid using SELDI-TOF-MS. Int J Cancer. 114:791–6
69. Baker KS, Davey DD, Stelling CB (1994) Ductal abnormalities detected with galactography: frequency of adequate excisional biopsy. Am J Roentgenol. 162:821–4
70. Van Zee KJ, Perez GO, Minnard E, Cohen M (1998) Preoperative ductography increases the diagnostic yield of major duct excision for nipple discharge. Cancer. 82(10):1874–80
71. Rongione AJ, Evans BD, Kling KM, McFadden DW (1996) Ductography is a useful technique in evaluation of abnormal nipple discharge. Am Surg. 62:785–8
72. Cardenosa G, Doudna C, Eklund GW (1994) Ductography of the breast: techniques and findings. Am J of Roentgenol. 162:1081–7
73. Saarela AO, Kiviniemi HO, Rissanen TJ (1997) Preoperative methylene blue staining of galactographically suspicious breast lesions. Int Surg. 82(4):403–5
74. Hussain S, Lui DM (1997) Ultrasound-guided percutaneous galactography. Eur J Radiol. 24:163–5
75. Urban JA (1963) Excision of the major duct system of the breast. Cancer. 16:516–20
76. Srivastava A, Griwan MS, Samaiyar SS et al (1995) A safe technique of major mammary duct excision. JR Coll Edinb. 40:35–7
77. Jardines L (1996) Management of nipple discharge. Am Surg. 62:119–22
78. Tan W, Lim TC (1992) Transareolar dye-injection microdochectomy. Am Surg. 58(7):404–8
79. Sharma N, Huston T, Simmons R (2006) Intraoperative intraductal injection of methylene blue dye to assist in major duct excision. Am J Surg. 191:553–4
80. Matsunaga T, Ohta D, Misaka T et al (2001) Mammary ductoscopy for diagnosis and treatment of intraductal lesions of the breast. Breast Cancer. 8:213–21
81. Shen KW, Wu J, Lu J, Han Q, Shen Z, Nguyen M et al (2000) Fiberoptic ductoscopy for patients with nipple discharge. Cancer. 89:1512–9
82. Escobar PF, Crowe JP, Matsunaga T, Mokbel K (2006) The clinical applications of mammary ductoscopy. Am J Surg. 191(2):211–5
83. Al Sarakbi W, Salhab M, Mokbel K (2006) Does mammary ductoscopy have a role in clinical practice? Int Semin Surg Oncol. 3:16
84. Louie LD, Crowe JP, Dawson AE, Lee KB et al (2006) Identification of breast cancer in patients with pathologic nipple discharge: does ductoscopy predict malignancy? Am J Surg. 192:530–3
85. Hunerbein M, Dubowy A, Raubach M, Gebauer B, Topalidis T, Schlag P (2007) Gradient index ductoscopy and intraductal biopsy of intraductal breast lesions. Am J Surg. 194:511–4
86. Pereira B, Mokbel K (2005) Mammary ductoscopy: past, present, and future. Int J Clin Oncol. 10:112–6
87. Hunerbein M, Raubach M, Gebauer B, Wolfgang S, Schlag P (2006) Ductoscopy and intraductal vacuum-assisted biopsy in women with pathologic nipple discharge. Breast Cancer Res Treat. 99:301
88. Solin LJ, Recht A, Fourquet A et al (1991) Ten-year results of breast-conserving surgery and definitive irradiation for intraductal carcinoma of the breast. Cancer. 68: 2337–44
89. Fowable BL, Solin LJ, Goodman RL (1987) Results of conservative surgery and radiation for intraductal noninvasive breast cancer. Am J Clin oncol. 10:110–1
90. Recht A, Danoff B, Solin LJ et al (1985) Intraductal carcinoma of the breast: results of treatment with excisional biopsy and radiation. J Clin Oncol. 3:1339–43
91. Ito Y, Tamaki Y, Nakano Y et al (1997) Nonpalpable breast cancer with nipple discharge: how should it be treated? Anticancer Res. 17(1B):791–4

Mastalgia

4

Amit Goyal and Robert E. Mansel

Mastalgia is a common breast symptom that may affect up to 70% of women in their lifetime [1]. It is most common in women aged 30–50 years. Breast pain may be bilateral, unilateral or in part of one breast. Whilst most patients experience mastalgia of mild or moderate severity and accept this as part of the normal changes that occur in relation to the menstrual cycle, a proportion (10–20%) experience severe pain that causes distress, affects their daily lives and leads them to seek treatment [2]. The severity of pain associated with cyclical mastalgia can be substantial, similar in magnitude to chronic cancer pain and slightly less than that associated with rheumatoid arthritis [3].

In a study of 1,171 premenopausal women attending a gynecology clinic, 69% reported regular premenstrual discomfort, 11% had moderate-to-severe cyclic mastalgia and 36% had consulted a doctor about the symptoms. Breast pain interfered with usual sexual activity (48%), physical activities (37%), social activities (12%) and school activities (8%) [4].

4.1 Etiology

The etiology of cyclical mastalgia has not been established. Some evidence has implicated elevated estrogen levels, low progesterone levels, or an abnormal estrogen/progesterone ratio [5]. The cyclical nature of pain, swelling, tenderness and nodularity together with postmenopausal cessation suggest a relationship between the symptoms and estrogen effects [6, 7]. However, measurement of estrogen, progesterone and prolactin levels have not shown consistent abnormalities. There is no correlation of water retention, psychological factors or caffeine intake with mastalgia. The role of iodine deficiency, alterations in levels of fatty acid in the breast, fat intake in the diet remains unclear.

4.2 Classification

Mastalgia can be separated into four main groups, cyclical mastalgia, noncyclical mastalgia, chest wall pain and non-chest wall pain [8] (Table 4.1). History will often reveal the temporal association of cyclical mastalgia with the menstrual cycle but the best way to assess whether pain is cyclical is to ask the patient to complete a breast pain chart (Fig. 4.1). This is especially useful in patients who have had a hysterectomy. A pain chart quantifies patient's symptoms and has the added advantage of assessing effectiveness of therapy. Two-thirds of women have cyclical pain, and the remaining third have noncyclical pain.

4.3 Cyclical Mastalgia

Cyclical breast pain usually occurs during the late luteal phase of the menstrual cycle and resolves at the onset of menses (Table 4.1). Patients with cyclical pain are by definition premenopausal, and most often in their thirties. Many women normally experience premenstrual discomfort, fullness, tenderness or heaviness of the breast 3 to 7 days before each period in relation to the menstrual cycle. Tender lumpiness in

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_4, © Springer-Verlag Berlin Heidelberg 2010

Table 4.1 Classification of mastalgia[a]

Breast pain	Cause
Cyclical pain	Hormonal stimulation of normal breast lobules before menses
Noncyclical pain	Stretching of Cooper's ligaments Pressure from brassiere Fat necrosis from trauma Hidradenitis suppurativa Focal mastitis Periductal mastitis Cyst Mondor's disease (sclerosing periphlebitis of breast veins)
Non-breast pain	
Chest wall pain	Tietze's syndrome (costochondritis) Localized lateral chest wall pain Diffuse lateral chest wall pain Radicular pain from cervical arthritis
Non-chest wall pain	Gallbladder disease Ischemic heart disease

[a]Reproduced with permission from Santen and Mansel 2005 [8]

breasts and increased breast size at this time, which regresses postmenstrually, is equally normal. Patients with cyclical mastalgia typically suffer increasing severity of pain from mid-cycle onwards, with the pain improving at menstruation. The pain is usually bilateral, described as heaviness with the breast being tender to touch, and it commonly affects the upper outer quadrant of the breast. The pain may radiate to the axilla and down the medial aspect of the upper arm. The pain varies in severity from cycle to cycle but can persist for many years. Cyclical mastalgia is relieved by menopause. Physical activity can increase the pain; this is particularly relevant for women whose occupations include lifting and prolonged use of the arms. The impact of mastalgia on quality of life is often underestimated. Cyclical mastalgia is distinct from premenstrual syndrome (PMS), which is characterized by physical, psychological and emotional symptoms associated with the menstrual cycle. The two may occur together or independently. Although mastalgia is a well-documented symptom in PMS, PMS is not necessarily present in women with cyclical mastalgia [9].

4.4 Noncyclical Mastalgia

Noncyclical breast pain is unrelated to the menstrual cycle and occurs in both pre- and postmenopausal women. Patients are usually in their forties. Pain may be continuous but is usually described as having a random time pattern. The pain is often localized and described as "burning" or "drawing." The pain may be due to a tender cyst, periductal mastitis, stretching of Cooper's ligaments, trauma (including breast biopsy or surgery), sclerosing adenosis, Mondor's disease and cancer [8]. The majority of patients, however, are found to have no cause to explain their mastalgia despite thorough investigations.

4.5 Chest Wall Pain

Musculoskeletal pain is almost always unilateral, brought on by activity and can be reproduced by pressure on specific area of the chest wall. Women known to have spondylosis or osteoarthritis are more likely to have musculoskeletal pain rather than true breast pain. Pain arising from the chest wall may be mistakenly attributed to the breast. Pain that is limited to a particular area and characterized as burning or knifelike in nature may arise from the chest wall. Several distinct

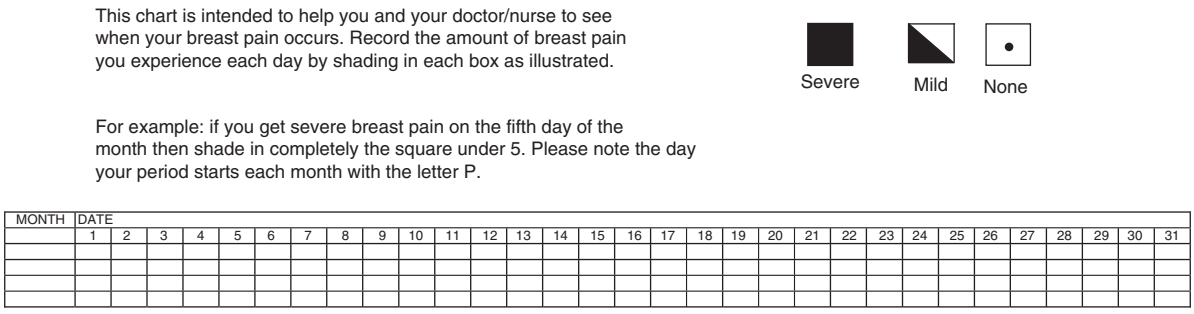

Fig. 4.1 Cardiff breast pain chart

types of pain can be distinguished, including localized or diffuse lateral chest wall pain, radicular pain from cervical arthritis and pain from Tietze's syndrome (costochondritis). In Tietze syndrome, the pain is often felt in the medial quadrants of the breast overlying the costal cartilages, which are the source of the pain. It has a chronic time course and on examination, one or several costal cartilages are tender and feel enlarged.

4.6 Non-chest Wall Pain

This group consists of patients who have pain due to a non-breast cause, such as gall-stones and angina.

4.7 Mastalgia and Breast Cancer

Cancer is an uncommon cause of breast pain. Breast pain associated with cancer is noncyclical, unilateral and well localized. Breast cancer is found in 2–7% of patients presenting with pain as the primary symptom [10–14]. It is not clear if breast pain increases the risk of subsequent breast cancer. Two case-control studies and one cohort study [15–17] have shown a significant increase in breast cancer risk in women with cyclical mastalgia. Plu-Bureau et al. [17] studied 210 premenopausal women diagnosed to have breast cancer who were matched with 210 controls from the same geographic area on age, education level and age at first full-term pregnancy. A previous history of cyclical mastalgia was found to be associated with an increased risk of breast cancer (Relative Risk adjusted for family history of breast cancer, prior benign breast disease, age at menarche, oral contraceptive use>2.12). Similar findings were reported by the authors in a cohort study of 247 premenopausal women diagnosed to have benign breast disease [15]. They showed that the breast cancer risk increased with increasing duration of cyclical mastalgia. Goodwin et al. [16] studied 192 premenopausal women with a node-negative breast cancer and 192 age-matched premenopausal controls. Breast tenderness scores were significantly higher premenstrually in patients with breast cancer. The odds ratio of breast cancer for severe tenderness was 3.32. However, it is documented that women presenting to physicians with symptoms have higher mammographic and biopsy interventions, which may lead to a diagnosis bias in these studies.

In contrast, Khan et al. [18] found that women who experienced breast pain were less likely to have breast cancer. They analyzed data of 5,463 women attending a breast care center in New York. Eight hundred and sixty one of thousand five hundred and thirty two women who reported breast pain at their initial visit were diagnosed with breast cancer. Odds ratio after adjustment for age and additional risk factors was 0.63.

Further evidence is needed to define the association between mastalgia and breast cancer. Clinical examination of the breasts and assessment of the patient's individual risk for breast cancer should be the main determinants of offering diagnostic breast imaging to patients with mastalgia.

4.8 Psychosocial Factors

Traditional surgical view that pain in the breast is largely an expression of psychoneurosis was challenged by Preece et al., [19] who found that women with mastalgia had similar anxiety, depression and phobia to women with varicose veins. The psychological morbidity in varicose vein and mastalgia patients was significantly lower than that of psychiatric patients, except for few patients with breast pain who failed to respond to treatment.

Other studies have found that women with mastalgia have increased anxiety and depression compared with asymptomatic women [20]. It is not clear if psychological distress contributes to or is a consequence of mastalgia. The emotional symptoms are significantly higher in women with severe mastalgia. The anxiety and depression in women with severe mastalgia are comparable with those of women with newly diagnosed breast cancer on the morning of their surgery [21]. Those who respond to treatment have a significant improvement in psychosocial function, but patients refractory to treatment continue to have high levels of distress [21].

More recently, Colegrave et al., [22] found that women with breast pain had increased anxiety, depression, somatization and history of emotional abuse compared to women with breast lumps alone, suggesting psychosocial factors contribute to mastalgia. Relaxation therapy by listening to relaxation audio tape can improve symptoms of mastalgia [23].

4.9 Clinical Assessment and Investigations

A careful history is necessary to exclude non-breast conditions. Clinical examination must be performed to exclude a mass lesion in the breast and define breast tenderness and chest wall tenderness. Breast lump should be evaluated by "triple assessment", which includes palpation, imaging and percutaneous core needle biopsy or fine-needle aspiration cytology. Chest wall should be examined by lifting the breast with one hand while palpating the underlying muscles and ribs with the other hand (Fig. 4.2). Lateral and medial chest wall tenderness can be elicited by rolling the patient to her side, allowing the breast to fall away from the chest wall (Fig. 4.2). If no mass is identified, further investigation is not indicated and the patient should be reassured that there is no sinister cause for her symptoms. The impact of the pain on the patient's quality of life should then be determined. Severe mastalgia tends to interfere with work, hugging children and sexual relationships. If treatment is being considered, patients should be asked to complete a pain chart (Fig. 4.1) for at least 2 months to allow identification of the pattern of pain and to assess the number of days of pain in each menstrual cycle.

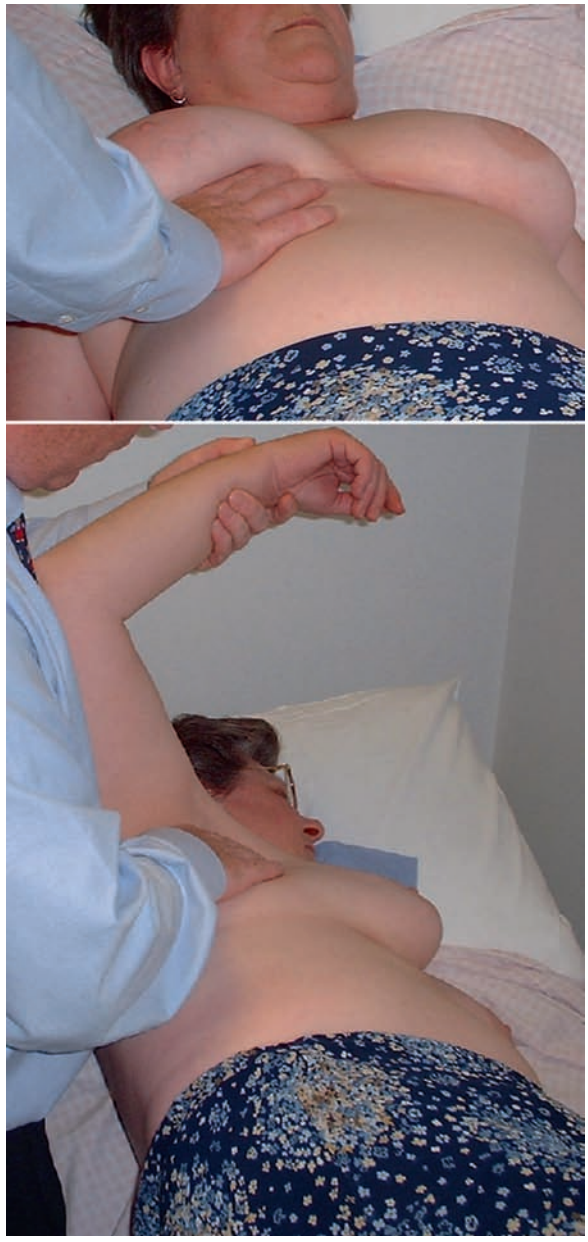

Fig. 4.2 Examination techniques to elicit chest wall tenderness

4.10 Treatment

4.10.1 Cyclical Mastalgia

The primary indication for treatment is pain, which interferes with everyday activities. Many women who present to hospital do so because they are worried that mastalgia may indicate breast cancer. Reassurance that cancer is not responsible for their symptoms is the only treatment necessary in up to 85% of women with cyclical mastalgia [24]. The key to effective management of patients with mastalgia is a 'listening physician' who can express empathy and understanding for the impact that breast pain has on women's lifestyle. Some women can improve their pain with simple measures such as wearing a well-fitting bra to support the pendulous breasts. Antibiotics are ineffective for mastalgia and should be used only when a specific diagnosis of periductal mastitis or lactational infection has been made. Diuretics, vitamin E, vitamin B6, caffeine reduction and progestogens (oral or topical) have not been shown to be of value in cyclical mastalgia [25–31]. Women who start oral contraceptive or hormone replacement therapy may report breast pain, which usually settles with continued therapy. Some patients who are taking an oral contraceptive find that their breast pain improves after stopping the pill and changing to mechanical contraception, but no individual oral contraceptive has been shown to specifically cause mastalgia. The use of oral contraceptives and hormone

replacement therapy has not been systematically studied, but for persistent symptoms, use of alternative preparations, preparations that contain low-dose estrogen or stopping medication may produce relief.

Evening primrose oil has been used, at oral doses of 1–3 g daily, however two recent randomized trials have found that its efficacy does not differ from that of placebo [31, 32]. Evening primrose oil's prescription license in the United Kingdom was revoked in October 2002 due to lack of efficacy over placebo. One small randomized trial found improvement in premenstrual breast swelling and tenderness with low fat (15% of total calories) and high carbohydrate diet [33]. This diet may be difficult to sustain and further research is needed before low-fat diet can be recommended to reduce breast pain. There has been a growing interest in phytoestrogens, herbal agents and nutritional supplements for treatment of breast pain. Isoflavones were found to be effective in cyclical mastalgia in a small randomized trial [34]. *Agnus castus* was well tolerated and was effective in controlling the symptoms of cyclical mastalgia in a placebo-controlled, randomized trial of 97 women suffering from cyclical mastalgia [35]. These studies need to be repeated in larger numbers to clarify the therapeutic value of these alternative approaches in breast pain.

Topical non-steroidal anti-inflammatory drugs (NSAIDs) are well tolerated and effective in treating breast pain and should be considered for pain control in those who prefer topical therapy. In a randomized controlled trial, diclofenac gel was found to be superior to placebo in premenopausal women with cyclical or noncyclical mastalgia [36].

The efficacy of Bromocriptine (dopamine agonist) has been confirmed in randomized trials and in a recent meta-analysis [37], but it is not used these days because of frequent and intolerable side effects (nausea, dizziness, headache and postural hypotension).

Goserelin (Zoladex®), a potent synthetic analog of luteinizing hormone-releasing hormone (LHRH), induces reversible ovarian suppression with castrate levels of ovarian hormones being attained within 72 h [38–40]. In a randomized controlled trial, we found that goserelin injection was superior to sham injection in treating severe mastalgia [41]. However, side effects (vaginal dryness, hot flushes, decreased libido, oily skin or hair and decrease in breast size) are common and thus goserelin should be kept in reserve for patients who are refractory to other forms of treatment. Goserelin can be used to induce a rapid relief of symptoms in patients with severe mastalgia and the response can be maintained with alternative therapies.

Danazol is a synthetic androgen that has antigonadotrophic effects on the pituitary. It prevents luteinizing hormone surge, and inhibits ovarian steroid formation. Danazol relieves breast pain and tenderness and the response is usually seen within 3 months [42, 43]. However, side effects occur in 30% of patients and result in discontinuation of treatment in a significant number of patients [44]. Danazol has superior efficacy compared with bromocriptine [45]. The side effects of danazol treatment (weight gain, deepening of the voice, menstrual irregularity or amenorrhea, hot flashes, depression, headaches and muscle cramps) can be limited by reducing the dose once response has been achieved. The response can be maintained with doses as low as 100 mg daily, given on days 14–28 of the menstrual cycle [42].

Tamoxifen has proven to be effective in the treatment of both cyclical and noncyclical mastalgia in randomized controlled trials [46, 47]. Tamoxifen 10 mg daily has equal efficacy but fewer adverse effects compared with 20 mg daily [48]. Its use is limited to no more than 6 months under specialist supervision as tamoxifen is not licensed for mastalgia in the United States or the United Kingdom. Common side-effects with 10 mg daily regimen are menstrual irregularities, hot flashes, weight gain, vaginal dryness and bloating. The incidence of thromboembolic events, endometrial cancer and cataracts with short-term treatment for mastalgia is unknown. Tamoxifen is cheaper, has higher response rates and less side-effects compared with danazol [49].

4-hydroxytamoxifen (4-OHT) is a potent antiestrogenic metabolite of tamoxifen with much higher affinity for estrogen receptors than tamoxifen. Recently, a percutaneous gel formulation of 4-hydroxytamoxifen (Afimoxifene®) has been found to be superior to placebo in the treatment of cyclical mastalgia in a phase II randomized trial [50]. Topical application avoids high systemic exposure to 4-OHT compared with oral tamoxifen, thus potentially reducing the risk of systemic side-effects. Further studies are needed before Afimoxifene® can be recommended for mastalgia.

There is insufficient evidence on the role of surgery in treatment of mastalgia and surgical intervention-should be approached with great caution. Retrospective data from Cardiff found that mastectomy in contrast to localized excision needs to be performed for symptom relief [51]. Surgery should be reserved for a minority of women who suffer from intractable symptoms and

in whom non-breast causes of pain have been excluded. A multidisciplinary team approach involving the surgeon, psychologist and breast care nurse is required when offering surgery to these women. The women should be counseled to inform them of the potential complications and the risk of persistence of symptoms.

4.10.2 Noncyclical Mastalgia

When pain is truly arising from the breast, the approach outlined for cyclical pain is used. Musculoskeletal pain often responds to oral or topical NSAIDs. Patients with persistent localized chest wall symptoms can be effectively treated by injection of a combination of local anesthetic and steroid into the tender site. Injection of local anesthetic confirms the correct identification of the painful area by producing complete disappearance of the pain.

4.11 Management Algorithm

The protocol followed in Cardiff Breast Unit is outlined in Fig. 4.3. Most patients can be reassured and discharged from the clinic if breast examination is normal. Imaging (mammogram/ultrasonography) is only done based on the patient's breast cancer risk and examination findings. Patients requesting treatment are given lifestyle advise (e.g. wear well fitted bra), asked to record their pain in the Cardiff Breast Pain Chart and return to the clinic in 3 months. First-line treatment includes the use of topical or oral mild analgesic agents such as paracetamol and NSAIDs. Patients with persistent symptoms after 3 months of treatment are started on tamoxifen, at a dose of 10 mg daily for three to 6 months. Treatment failures are started on danazol, at a dose of 200 mg daily (reduced to 100 mg a day after relief of symptoms) or only during the luteal phase of the menstrual cycle. Non-responders with severe pain are started on goserelin depot injection, 3.6 mg/month for 6 months. If the outlined treatment plan is followed, about 70–80% of patients should experience substantial relief of symptoms. Non-hormonal contraception is essential with tamoxifen and danazol because both have deleterious effects on the fetus.

References

1. Ader DN, South-Paul J, Adera T, Deuster PA (2001) Cyclical mastalgia: prevalence and associated health and behavioral factors. J Psychosom Obstet Gynaecol. 22:71–6

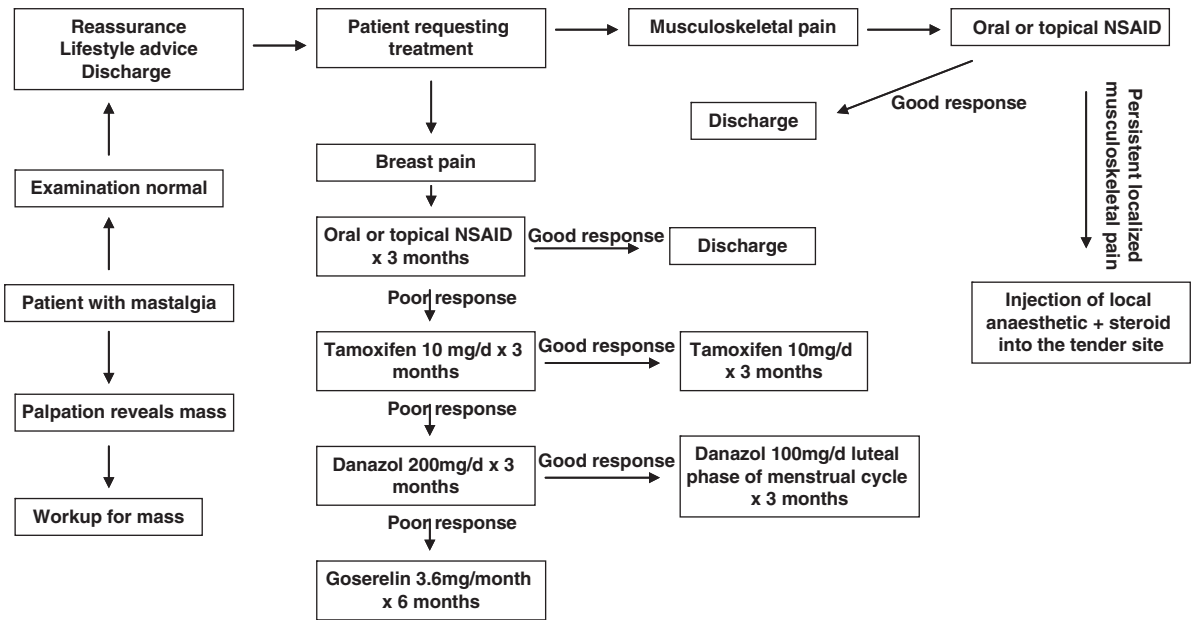

Fig. 4.3 Algorithm for the management of mastalgia

2. Cyclical breast pain–what works and what doesn't. Drug Ther Bull. 1992;30:1–3
3. Khan SA, Apkarian AV (2002) The characteristics of cyclical and non-cyclical mastalgia: a prospective study using a modified McGill Pain Questionnaire. Breast Cancer Res Treat. 75:147–57
4. Ader DN, Shriver CD (1997) Cyclical mastalgia: prevalence and impact in an outpatient breast clinic sample. J Am Coll Surg. 185:466–70
5. Rose DP, Boyar AP, Cohen C, Strong LE (1987) Effect of a low-fat diet on hormone levels in women with cystic breast disease. I. Serum steroids and gonadotropins. J Natl Cancer Inst. 78:623–6
6. Wang DY, Fentiman IS (1985) Epidemiology and endocrinology of benign breast disease. Breast Cancer Res Treat. 6:5–36
7. Wisbey JR, Kumar S, Mansel RE, Peece PE, Pye JK, Hughes LE (1983) Natural history of breast pain. Lancet. 2:672–4
8. Santen RJ, Mansel R (2005) Benign breast disorders. N Engl J Med. 353:275–85
9. Ader DN, Shriver CD, Browne MW (1999) Cyclical mastalgia: premenstrual syndrome or recurrent pain disorder? J Psychosom Obstet Gynaecol. 20:198–202
10. Barton MB, Elmore JG, Fletcher SW (1999) Breast symptoms among women enrolled in a health maintenance organization: frequency, evaluation, and outcome. Ann Intern Med. 130:651–7
11. Lumachi F, Ermani M, Brandes AA, Boccagni P, Polistina F, Basso SM, Favia G, D'Amico DF (2002) Breast complaints and risk of breast cancer. Population-based study of 2,879 self-selected women and long-term follow-up. Biomed Pharmacother. 56:88–92
12. Fariselli G, Lepera P, Viganotti G, Martelli G, Bandieramonte G, Di Pietro S (1988) Localized mastalgia as presenting symptom in breast cancer. Eur J Surg Oncol. 14:213–5
13. Smallwood JA, Kye DA, Taylor I (1986) Mastalgia; is this commonly associated with operable breast cancer? Ann R Coll Surg Engl. 68:262–3
14. Preece PE, Baum M, Mansel RE, Webster DJ, Fortt RW, Gravelle IH, Hughes LE (1982) Importance of mastalgia in operable breast cancer. Br Med J (Clin Res Ed). 284:1299–300
15. Plu-Bureau G, Le MG, Sitruk-Ware R, Thalabard JC (2006) Cyclical mastalgia and breast cancer risk: results of a French cohort study. Cancer Epidemiol Biomarkers Prev. 15: 1229–31
16. Goodwin PJ, DeBoer G, Clark RM, Catton P, Redwood S, Hood N, Boyd NF (1995) Cyclical mastopathy and premenopausal breast cancer risk. Results of a case-control study. Breast Cancer Res Treat. 33:63–73
17. Plu-Bureau TJC, Sitruk-Ware R, Asselain B, Mauvais-Jarvis P (1992) Cyclical mastalgia as a marker of breast cancer susceptibility: results of a case-control study among French women. Br J Cancer. 65:945–9
18. Khan SA, Apkarian AV (2002) Mastalgia and breast cancer: a protective association? Cancer Detect Prev. 26:192–6
19. Preece PE, Mansel RE, Hughes LE (1978) Mastalgia: psychoneurosis or organic disease? Br Med J. 1:29–30
20. Jenkins PL, Jamil N, Gateley C, Mansel RE (1993) Psychiatric illness in patients with severe treatment-resistant mastalgia. Gen Hosp Psychiatry. 15:55–7
21. Ramirez AJ, Jarrett SR, Hamed H, Smith P, Fentiman IS (1995) Psychosocial adjustment of women with mastalgia. Breast. 4:48–51
22. Colegrave S, Holcombe C, Salmon P (2001) Psychological characteristics of women presenting with breast pain. J Psychosom Res. 50:303–7
23. Fox H, Walker LG, Heys SD, Ah-See AK, Eremin O (2009) Are patients with mastalgia anxious, or does relaxation therapy help? Breast. 6:138–42
24. Barros AC, Mottola J, Ruiz CA, Borges MN, Pinotti JA (1999) Reassurance in the treatment of mastalgia. Breast J. 5:162–5
25. Smallwood J, Ah-Kye D, Taylor I (1986) Vitamin B6 in the treatment of pre-menstrual mastalgia. Br J Clin Pract. 40:532–3
26. Ernster VL, Goodson WH III, Hunt TK, Petrakis NL, Sickles EA, Miike R (1985) Vitamin E and benign breast "disease": a double-blind, randomized clinical trial. Surgery. 97:490–4
27. Parazzini F, La Vecchia C, Riundi R, Pampallona S, Regallo M, Scanni A (1986) Methylxanthine, alcohol-free diet and fibrocystic breast disease: a factorial clinical trial. Surgery. 99:576–81
28. Allen SS, Froberg DG (1987) The effect of decreased caffeine consumption on benign proliferative breast disease: a randomized clinical trial. Surgery. 101:720–30
29. McFadyen IJ, Raab GM, Macintyre CC, Forrest AP (1989) Progesterone cream for cyclic breast pain. BMJ. 298:931
30. Maddox PR, Harrison BJ, Horobin JM, Walker K, Mansel RE, Preece PE, Nicholson RI (1990) A randomised controlled trial of medroxyprogesterone acetate in mastalgia. Ann R Coll Surg Engl. 72:71–6
31. Goyal A, Mansel RE (2005) A randomized multicenter study of gamolenic acid (Efamast) with and without antioxidant vitamins and minerals in the management of mastalgia. Breast J. 11:41–7
32. Blommers J, de Lange-De Klerk ES, Kuik DJ, Bezemer PD, Meijer S (2002) Evening primrose oil and fish oil for severe chronic mastalgia: a randomized, double-blind, controlled trial. Am J Obstet Gynecol. 187:1389–94
33. Boyd NF, McGuire V, Shannon P, Cousins M, Kriukov V, Mahoney L, Fish E, Lickley L, Lockwood G, Tritchler D (1988) Effect of a low-fat, high-carbohydrate diet on symptoms of cyclical mastopathy. Lancet. 2:128–32
34. Ingram DM, Hickling C, West L, Mahe LJ, Dunbar PM (2002) A double-blind, randomized controlled trial of isoflavones in the treatment of cyclical mastalgia. Breast. 11:170–4
35. Halaska M, Beles P, Gorkow C, Sieder C (1999) Treatment of cyclical mastalgia with a solution containing a Vitex agnus castus extract: results of a placebo-controlled double-blind study. Breast. 8:175–81
36. Colak T, Ipek T, Kanik A, Ogetman Z, Aydin S (2003) Efficacy of topical nonsteroidal anti-inflammatory drugs in mastalgia treatment. J Am Coll Surg. 196:525–30
37. Srivastava A, Mansel RE, Arvind N, Prasad K, Dhar A, Chabra A (2007) Evidence-based management of mastalgia: a meta-analysis of randomised trials. Breast. 16:503–12
38. Thomas EJ, Jenkins J, Lenton EA, Cooke ID (1986) Endocrine effects of goserelin, a new depot luteinising hormone releasing hormone agonist. Br Med J (Clin Res Ed). 293:1407–8

39. Shaw RW (1992) An open randomized, comparative study of the effect of goserelin depot and danazol in the treatment of endometriosis. Zoladex endometriosis study team. Fertil Steril. 58:265–72
40. Fraser HM, Sandow J (1985) Suppression of follicular maturation by infusion of a luteinizing hormone-releasing hormone agonist starting during the late luteal phase in the stumptailed macaque monkey. J Clin Endocrinol Metab. 60:579–84
41. Mansel RE, Goyal A, Preece P, Leinster S, Maddox PR, Gateley C, Kubista E, von Fournier D (2004) European randomized, multicenter study of goserelin (Zoladex) in the management of mastalgia. Am J Obstet Gynecol. 191:1942–9
42. O'Brien PM, Abukhalil IE (1999) Randomized controlled trial of the management of premenstrual syndrome and premenstrual mastalgia using luteal phase-only danazol. Am J Obstet Gynecol. 180:18–23
43. Mansel RE, Wisbey JR, Hughes LE (1982) Controlled trial of the antigonadotropin danazol in painful nodular benign breast disease. Lancet. 1:928–30
44. Gateley CA, Miers M, Mansel RE, Hughes LE (1992) Drug treatments for mastalgia: 17 years experience in the Cardiff mastalgia clinic. J R Soc Med. 85:12–5
45. Hinton CP, Bishop HM, Holliday HW, Doyle PJ, Blamey RW (1986) A double-blind controlled trial of danazol and bromocriptine in the management of severe cyclical breast pain. Br J Clin Pract. 40:326–30
46. Fentiman IS, Caleffi M, Brame K, Chaudary MA, Hayward JL (1986) Double-blind controlled trial of tamoxifen therapy for mastalgia. Lancet. 1:287–8
47. Messinis IE, Lolis D (1988) Treatment of premenstrual mastalgia with tamoxifen. Acta Obstet Gynecol Scand. 67:307–9
48. Fentiman IS, Caleffi M, Hamed H, Chaudary MA (1988) Dosage and duration of tamoxifen treatment for mastalgia: a controlled trial. Br J Surg. 75:845–6
49. Kontostolis E, Stefanidis K, Navrozoglou I, Lolis D (1997) Comparison of tamoxifen with danazol for treatment of cyclical mastalgia. Gynecol Endocrinol. 11:393–7
50. Mansel R, Goyal A, Nestour EL, Masini-Eteve V, O'Connell K (2007) A phase II trial of Afimoxifene (4-hydroxytamoxifen gel) for cyclical mastalgia in premenopausal women. Breast Cancer Res Treat. 106:389–97
51. Davies EL, Cochrane RA, Stansfield K, Sweetland HM, Mansel RE (1999) Is there a role for surgery in the treatment of mastalgia? Breast. 8:285–8

Management of Common Lactation and Breastfeeding Problems

5

Lisa H. Amir and Verity H. Livingstone

Lactation is a physiologic process under neuroendocrine control; breastfeeding is a technical process by which milk is transferred from the maternal breast to the infant. Success depends on maternal health, adequate mammogenesis, unimpeded lactogenesis, successful galactopoiesis, effective milk transfer and appropriate quality and quantity of daily milk intake. Each phase of lactation and breastfeeding is influenced by multiple predisposing, facilitating, or impeding biopsychosocial factors: puberty, pregnancy, childbirth, breast stimulation and drainage, maternal milk ejection reflex, maternal and infant breastfeeding technique, frequency and duration of suckling and the pattern of breast use. All these factors are influenced by other factors such as maternal knowledge, attitude, motivation, mood and health; infant health and behavior; and support from family, friends and healthcare professionals.

The concept of breastfeeding kinetics as developed by Livingstone conveys the idea that there is a dynamic interaction between a breastfeeding mother and her infant over time [1]. Most disorders of lactation are iatrogenic due to impeded establishment of lactation or inadequate ongoing stimulation and drainage of the breast. Most breastfeeding difficulties are due to the lack of knowledge, poor technical skills or lack of support. Almost all problems are reversible. Prevention, early detection and management should become a routine part of the maternal and child health care.

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5.1 Prenatal Period

Prenatal breastfeeding goals are to assist families to make an informed choice about infant feeding, prepare women cognitively and emotionally for breastfeeding, identify and modify risk factors to lactation and breastfeeding and offer anticipatory guidance. These goals can be achieved by providing prenatal breastfeeding education and by performing a prenatal lactation assessment [2, 3].

5.1.1 Informed Choice

Health professionals must assist families in making an informed decision by discussing the recommended infant feeding guidelines, including benefits of breastfeeding and the risks of breast milk substitutes [4–6]. The World Health Organization recommends exclusive breastfeeding for the first 6 months, with the introduction of complementary foods and continued breastfeeding for up to 2 years or beyond [7, 8]. Dettwyler has examined the relationships between age at weaning and life history variables, such as length of gestation, body weight and eruption of molars, among nonhuman primates [9]. She estimates that if humans followed primate patterns rather than cultural customs, children would continued to be breastfed for somewhere between 2.5 and 7 years [9].

5.1.1.1 Benefits of Breastfeeding

To the Infant

- Human milk is species specific; it is the ideal nutrition because the protein and fat content are uniquely suited to the needs of the infant. It also provides protection against iron and vitamin deficiencies [10].

I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_5, © Springer-Verlag Berlin Heidelberg 2010

- Breast milk contains more than 100 biologically active ingredients. It offers immunologic protection to an otherwise immunodeficient neonate [11]. The enteromammary immune cycle provides specific maternal antibodies to infant antigens [12]. It protects against otitis media, gastroenteritis, respiratory tract infections, urinary tract infections, other bacterial and viral diseases and necrotizing enterocolitis [13–20].
- Breastfeeding provides a close interaction between mother and infant and helps the two develop a strong, positive, emotional bond, which has long-term psychological advantages [21].
- The action of breastfeeding facilitates correct jaw and dental development [22].
- Breastfeeding may prevent overweight and obesity in children and adults [19, 23, 24] and is associated with lower blood pressure [25].

To the Mother

- Breastfeeding provides psychological satisfaction and close maternal bonding between mother and infant [26]. It offers a regular opportunity to sit and relax during the often exhausting early parenting period [27].
- Women who do not breastfeed are at increased risk of developing premenopausal breast cancer [28] and possibly ovarian cancer [29].
- Using breastfeeding as the sole nourishment activity causes lactation amenorrhea, which is an effective and reliable method of contraception and child spacing [30].
- It reduces postpartum anemia.

To Society

- Breast milk is a natural resource that is replenished and does not leave waste.
- The future of a society depends on the health of its children.
- Breastfeeding is the most health-promoting, disease-preventing and cost-effective activity mothers can do.

5.1.1.2 The Hazards of Infant Formula

Inadequate nutrition: Infant formula may contain inadequate or excessive micronutrients. They lack essential fatty acids known to be vital for myelination and proper brain and retinal development. Some brands of formula contain excess vitamin D [31].

Bacterial contaminants: Powdered infant formula is not a sterile product [32, 33]. The most serious bacterial contaminant, *Enterobacter sakazakii,* can cause rare, but life-threatening neonatal meningitis, bacteremia and necrotizing enterocolitis [32, 34].

Contaminants: A variety of other contaminants – including excessive aluminum, lead and iodine – have been identified, and many brands of formula have been withdrawn due to these discoveries [35–37].

Impaired cognitive development: Several well-controlled studies have reported significantly lower intelligence quotient scores and poorer development in children who lack breast milk in their diet [38–41].

Allergies: More formula-fed infants develop atopic dermatitis [42].

Morbidity and mortality: The added risk of bottle-feeding can account for 7% of infants hospitalized for respiratory infections and, in the United States, formula fed infants have a tenfold risk of being hospitalized for any bacterial infection. They have more than double the risk of contracting lower respiratory tract infections, and otitis media is up to 3–4 times more prevalent [43, 44]. Formula-fed infants have a higher incidence of childhood cancers and inflammatory bowel diseases in adulthood [45–47]. Formula feeding accounts for 2–26% of insulin-dependent diabetes mellitus in children [48, 49].

Costs: It costs approximately $1,000–$2,300 to formula feed an infant for 12 months (depending on the type of formula used) [50]; therefore, many infants in low-income families are at risk for receiving low-cost and inappropriate alternative fluids and the early introduction of table foods. It is also time consuming to purchase and prepare formula. Lack of breastfeeding results in increased healthcare costs [51, 52].

5.1.2 Prenatal Education

Breastfeeding is a learned skill that should be taught prenatally; physicians can use models in their offices to help reinforce the learning process [53]. Industry-developed literature on infant feeding should not be distributed because it gives mixed messages to breastfeeding families [54].

5.1.3 Prenatal Lactation Assessment

Lactation is essential for the survival of most mammalian species and can be considered the final stage of the reproductive cycle. Mammogenesis begins in the embryo and continues throughout life, with active growth phases during puberty and pregnancy. It is controlled by a complex hormonal milieu. Clinical signs of successful mammogenesis are breast growth, increased breast sensitivity and the excretion of a colostrum-like fluid by the end of pregnancy (lactogenesis I [55]). Failure of mammogenesis presents clinically as a lack of or an abnormality in breast growth and development during puberty or pregnancy.

5.1.3.1 Screening for Risk Factors

During the prenatal period, physicians have an opportunity to screen women for certain biological, psychological and social risk factors that might interfere with mammogenesis, successful lactation or breastfeeding. A formal *prenatal lactation assessment* should be performed in the third trimester as a routine component of antenatal care for all women.

Maternal Biological Risk Factors for Successful Lactation

- Anatomically abnormal breasts, including hypoplastic or conical breasts, may never lactate adequately because of insufficient glandular development associated with failure of mammogenesis [56, 57].
- Breast surgery, in particular reduction mammoplasty, may interfere with glandular or lactiferous duct function [58, 59].
- Certain endocrinopathies, including thyroid, pituitary and ovarian dysfunction and relative infertility, may interfere with lactation [60, 61].
- Chronic maternal illnesses, such as diabetes mellitus, systemic lupus erythematosus and hypertension, may cause maternal fatigue but usually do not affect lactation.
- Women with physical disabilities usually can breastfeed, but they may have to be given guidance and assistance with regard to safe, alternative nursing positions.
- Complications of pregnancy such as gestational diabetes, pregnancy-induced hypertension and preterm labor may result in early maternal infant separation, which can interfere with the initiation of lactation. Antenatal expression of colostrum may be useful when potential neonatal hypoglycemia is anticipated [62].
- Maternal infections such as hepatitis B and C, human immunodeficiency virus (HIV) or cytomegalovirus may be transmitted to the infant in *utero,* but the added viral load through breast milk is probably clinically insignificant [63]. In industrial countries, it would seem prudent to advise HIV-positive women not to breastfeed [64].
- Women who use illicit drugs, such as amphetamines, cocaine or heroin should be informed about the risks and counseled about abstinence [65]. If the use continues, the women should be advised not to breastfeed. Maternal smoking is not advisable; however, the risks of smoking and artificial feeding are greater than the risks of smoking and breastfeeding [66, 67]. Breastfeeding should therefore be recommended in spite of smoking. Moderate use of alcohol should not be a contraindication to breastfeeding [65].
- A previous unsuccessful breastfeeding experience may herald future problems.
- Previous or chronic psychiatric disorders, including depression, may recur in the postpartum period and interfere with maternal parenting abilities. These mothers need extra help during the early postpartum period.

Infant Biological Risk Factors for Successful Lactation

Several infant factors interfere with the establishment of lactation and breastfeeding. These include neonatal illness, which necessitates early maternal/infant separation, and sucking, swallowing or breathing disorders. Some factors can be identified or predicted prenatally.

Psychological Risk Factors

There is interplay between the many forces that influence a woman's choice of feeding methods [68–70].

Beliefs: Many women have preconceived ideas about feeding their infants. They may have anxieties and concerns over their ability to breastfeed, they may believe their breasts are too small or their nipples too large, or they may fear the consequences of altered breast appearance. They may have had previous unsuccessful breastfeeding experiences or family members who offer negative advice. It is important to clarify beliefs surrounding breastfeeding.

Attitudes: The physician should explore the woman's attitudes toward breastfeeding, returning to work and breastfeeding in public. Prenatal exploration of these areas helps families start addressing their own attitudes.

Knowledge and skills: The physician should explore the woman's knowledge by asking what she knows about infant feeding and how she is planning to feed her infant.

Social Risk Factors

Women are more likely to succeed in breastfeeding if they have support from their family and friends. In the prenatal phase, the goal is to help to foster a positive emotional environment among family, friends and community.

Family support: Throughout history, women have been supported in their decision to breastfeed by grandmothers, sisters, close friends or doulas. Nowadays, with the disintegration of the traditional family, lack of support often culminates in abandonment of breastfeeding [71, 72].

Peer support: Single teenaged mothers experience considerable peer pressure to continue the carefree life of youth, and they may opt for the perceived freedom of bottle-feeding rather than the commitment to breastfeeding. Peer support programs have been shown to be an effective way of helping to increase the duration of breastfeeding [73].

Community support: Many women are embarrassed about breastfeeding in public. A prenatal discussion around the issue of breastfeeding in public may help. Employment outside the home need not be a reason for stopping breastfeeding; planning, flexibility and good child care can support a mother to maintain lactation during prolonged hours of separation.

5.1.3.2 Prenatal Breast Examination

After reviewing the woman's history, a careful breast examination should be performed.

Size and Symmetry

It is not until pregnancy that the full maturation of the mammary glands occurs. Lactogenic hormones, including estrogen, progesterone, prolactin, insulin, thyroid and growth hormones, trigger the development of the mammary epithelial cells, acinar glands and lactiferous ducts. By 16 weeks of gestation, lactation can occur. The breasts usually enlarge by at least one bra cup size or about 200 mL during pregnancy or in the first month postpartum [74, 75]. Variations in breast appearance or asymmetry may indicate lactation insufficiency and therefore should be noted; future milk synthesis should be closely monitored. Scars give clues to potential glandular, ductal or nerve disruption.

Nipple Graspability

For infants to latch and suckle effectively, they should be able to grasp the nipple and areola tissue and form a teat. The areola can be gently pinched to assess its elasticity and graspability. Nipples may protrude, pseudoprotrude, remain flat, pseudoinvert or truly invert. They may be large or small. There is no evidence to support nipple preparation such as nipple stretching exercises or the use of nipple shells because the anatomy of the nipple and areola is not altered by prenatal exercises [76]. The action of sucking by the infant helps to thaw out the nipple and form a teat during the process of breastfeeding. It is only true inverted nipples that may impede correct latching and suckling. The Nipplette (Avent, Suffolk, England) was designed to help correct inverted nipples prenatally [77]. Cutting off the needle end of a 20-mL syringe and reversing the plunger can make a simplified version [78]. The flange end of the syringe can be placed over the nipple and gentle suction applied to draw out the nipple slowly. There are no data to confirm that the syringe works, but clinical experience suggests that it may be useful in helping to make the nipple area more

graspable [78]. There is no need to apply lotions or oils to the breasts to soften the skin, and normal daily bathing with soap is recommended.

5.1.3.3 Anticipatory Guidance

After completing a careful history and physical examination, the following anticipatory guidance should be offered.

- Avoid medicated or interventional labor. Soon after natural childbirth, infants exhibit an instinctive rooting behavior to locate and latch onto the breast. Medications and complications of childbirth may interfere with this neurodevelopmental behavior [79, 80].
- Initiate breastfeeding or breast pumping as soon as possible following complete delivery of the placenta because it is thought that early breast stimulation initiates lactation [27, 81], although evidence is conflicting [75].
- Breastfeed or pump on demand, every 2–3 h because regular breast drainage and stimulation facilitates lactogenesis [82, 83].
- Practice rooming and bedding in for 24 h per day. Maternal-infant separation impedes regular breast drainage and stimulation [84–86].
- Combined mother and infant nursing care facilitates patient-centered teaching [87].
- Relieve engorgement early to prevent involutional atrophy of lactocytes [88].
- Avoid routine supplementation because it causes "breast confusion" by removing an infant's hunger drive, thereby decreasing breast stimulation and drainage [89, 90].
- Avoid rubber nipples and pacifiers. If infants are demonstrating hunger cues by sucking, they are hungry. Offering a pacifier is not an appropriate maternal response to these infants' cues. The infant should suckle on the breast frequently to establish successful lactation [81, 91].
- Exclusive breastfeeding ensures that the infant receives adequate colostrum, including secretary immunoglobulin A (IgA) and other unique hormonal factors that contribute to the infant's health, growth and development [12].
- Avoid formula because it predisposes the neonate to potential allergies and other risk factors associated with artificial foods. The immature gut is not designed to digest cow milk or soya milk [92].
- Review the availability of community resources postpartum; close follow-up in the postpartum period is crucial for successful breastfeeding [4].

5.2 Intrapartum Period

5.2.1 Establishing Lactation

Breastfeeding should be considered the fourth stage of labor; childbirth is not complete until the infant is latched on to the breast and suckling, thus triggering lactogenesis. Soon after delivery, neonates exhibit a natural locating reflex and can find the nipple themselves, if permitted. Once the nipple is located, they root, latch onto it, and suckle instinctively. Studies have shown that this process may take 60–120 min and that the locating and suckling instinct can be impaired if foreign objects are inserted into neonate's mouths soon after birth or if the infant is sedated secondarily to maternal medication [93, 94].

Early suckling is crucial for four reasons. Firstly, it allows an imprinting to occur as the neonate learns to grasp and shape a teat and suckle effectively while the nipple and areola are still soft and easily grasped. Secondly, the neonate ingests a small amount of colostrum, which has a high content of maternal secretary IgA, which acts as the first immunization to the immuno-immature neonate. Thirdly, following parturition and the delivery of an intact placenta, the inhibitory effects of the hormones of pregnancy are removed, and the prolactin receptors in the mammary gland become responsive. Lastly, early suckling stimulates the release of lactotrophs, including prolactins, which trigger the onset of milk synthesis. Frequent episodes of breast stimulation cause surges of prolactin, which maintain lactogenesis. Clinical signs of successful lactogenesis are fullness of the breasts postpartum with the production of colostrum initially and then a gradual change to transitional milk and mature milk within about 36–48 h [95].

Galactopoiesis is the process of ongoing milk synthesis. It follows successful mammogenesis and unimpeded lactogenesis. The rate of milk synthesis varies

Fig. 5.1 Ten steps to Successful Breastfeeding

Every facility providing maternity services and care for newborn infants should:

1. Have a written breastfeeding policy that is routinely communicated to all health care staff
2. Train all health care staff in skills necessary to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.
4. Help mothers initiate breastfeeding within a half hour of birth.
5. Show mothers how to breastfeed and how to maintain lactation even if they should be separated from their infants.
6. Give newborn infants no food or drink other than breast milk, unless medically indicated.
7. Practice rooming in - allow mothers and infants to remain together 24 hours a day.
8. Encourage breastfeeding on demand.
9. Give no artificial teats or pacifiers (also called dummies or soothers) to breastfeeding infants.
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.

throughout the day and between mothers. It is controlled by regular and complete drainage and is primarily an autocrine (i.e., local) action. Recent studies suggest that ongoing milk synthesis is inhibited by the buildup of local suppressor peptide called feedback inhibitor of lactation (FIL) [96]; regular suckling removes this inhibition [97, 98]. Prolactin surges stimulate the breast alveoli to actively secrete milk, and oxytocin causes the myoepithelial cells surrounding the glands and the ductules to contract and eject milk down the ducts to the nipples. These contractions effectively squeeze the fat globules across the cell membrane into the ducts. As a feed progresses, the quality and quantity of milk produced change. The fore milk, at the beginning of the feed, is composed mainly of milk that has collected between feeds, and it has lower fat and higher whey content than hind milk. The fat content increases as the "degree of breast fullness" decreases [99]. Serum prolactin levels should increase several-fold following suckling; lack of a prolactin response may be significant. Prolactin levels fall over the first 4–6 weeks, and the suckling-induced prolactin surges are markedly reduced by 3 months, virtually disappearing by 6 months, and yet lactation can continue [100, 101]. Current understanding is that the requirement of blood prolactin for lactation is permissive rather than regulatory [102].

5.2.2 Factors that Help to Establish Lactation

Following childbirth, mothers and neonates should remain together, skin to skin, to allow the process of breastfeeding to begin. Neonates instinctively know how to locate the breast and suckle, but mothers must be taught.

The World Health Organization and the United Nations Children's Fund recognized the importance of successful establishment of breastfeeding in the hospital, and they launched the global Baby Friendly Hospital Initiative in 1992. This is an educational quality assurance program for hospitals based on the joint statement "Protecting, Supporting and Promoting Breastfeeding – The Special Role of Maternity Services," which outlines ten simple steps designed to protect these delicate physiologic processes [103] (Fig. 5.1).

5.2.3 Factors that Interfere with Lactation

Insufficient maternal milk is the most common reason given for stopping breastfeeding in the early weeks. The cause is often iatrogenic resulting from mismanagement during the critical early phase. Many maternal and infant factors contribute to lactation failure, including premammary gland, mammary gland, and postmammary gland causes.

5.2.3.1 Failure of Mammogenesis

In the normal course of events, mammogenesis begins in the embryo and continues throughout life with active growth phases during puberty and pregnancy. Mammogenesis is controlled by a complex hormonal milieu that cannot be covered in depth in this chapter.

The hormones involved include the pituitary hormones: prolactin, adrenocorticotropic hormone, growth hormone, thyrotropin, follicle-stimulating hormone and luteinizing hormone. In addition, steroid hormones from the ovary, adrenal glands and placenta, plus thyroid hormones and insulin, contribute to mammary growth and function either directly or indirectly [75].

Failure of mammogenesis presents clinically as a lack of, or an abnormality in, breast growth and development during puberty, adulthood or pregnancy and may be due to any or a combination of the following factors:

Preglandular Failure

The most common cause of premammary glandular failure is a deficiency of mammary growth stimulating hormones, but other possibilities include the presence of biologically inactive hormones or antibodies to the hormones preventing their normal action [104]. Pathological conditions associated with disrupted production can be hypothalamic or pituitary in origin. Destruction of the hypothalamus can occur as a result of encephalitis, infiltration of tumor following lymphocytic hypophysitis, or idiopathic causes [105]. Pituitary causes include space-occupying lesions, hyperplasia, empty sella syndrome, acromegaly, pituitary stalk section, and Sheehan syndrome [106]. A pregnancy-specific mammary nuclear factor (PMF) has been identified, which is stimulated by progesterone. PMF may suppress genes involved in mammary gland development [107].

Glandular Failure

Glandular failure is defined as lack of mammary gland response to normal lactogens during pregnancy. A PMF imbalance or end-organ receptor failure, such as estrogen or prolactin mammary gland receptor deficits, may occur. The regulatory factors involved in the development of the myoepithelial cells prior to lactation are not well understood.

5.2.3.2 Failure of Lactogenesis

Lactogenesis II, or the onset of copious milk secretion, occurs close to parturition. It is under endocrine control of the pituitary gland via prolactin and other lactogenic hormones. The decline of placental hormones, particularly progesterone, following delivery of an intact placenta, associated with early and frequent suckling, are the major triggers to establishing milk synthesis. Clinical evidence of lactogenesis II is an increase in breast size, which occurs about 60 h postpartum, but can range between 24 and 102 h after birth [108]. Failure of lactogenesis presents clinically as lack of breast engorgement and lack of colostrum production.

Preglandular

Preglandular causes of failure of lactogenesis include an intrinsic lack of lactogenic hormones, biologically inactive lactogens or lactogenic antibodies [109]. In addition to the pituitary and hypothalamic pathologies, factors predisposing to a reduction in pituitary hormone production in the postpartum period, in particular prolactin, include drugs such as bromocriptine and retained placental fragments [110]. The latter demonstrates the inhibitory effect of estrogen and progesterone on the initiation of lactogenesis.

Glandular

Glandular causes include a lack of mammary gland responsiveness to lactogenic hormones, including plasma membrane receptor deficits or faulty gene transcription [111].

Postglandular

Postglandular causes relate to a delay in the initiation of breastfeeding. The length of delay that becomes significant has not been clarified, but it undoubtedly plays a role. Unlimited access to the breast increases milk intake and infant growth in the first 2 weeks [112]. The use of supplementary feeding with formula, which is routine in some hospitals, may have a detrimental effect on milk synthesis in a mother who planned exclusively to breastfeed after hospital discharge [113]. Unrelieved engorgement is also recognized as having a negative feedback effect on milk synthesis. This condition may be due to the buildup of inhibitor factors in the milk or to pressure effects by the milk volume.

5.2.3.3 Failure of Galactopoiesis

The action of many hormones is involved in the maintenance of lactation. Failure of galactopoiesis presents clinically as lack of copious milk production. Causes of failure of galactopoiesis include the following:

Preglandular

An intrinsic lack of lactogenic hormones is one cause. Contributing factors to reduced milk synthesis include certain drugs (e.g., estrogen-containing contraceptives, pseudoephedrine [114]), heavy smoking or superimposed pregnancy.

Glandular

Glandular causes include unresponsiveness to lactogenic hormones or secondary to failure of mammogenesis or lactogenesis.

Postglandular

The most common cause of lactation failure is a delay in early and frequent breast simulation and inadequate drainage, which commonly occurs when mothers and infants are separated because of existing or anticipated health problems. Newborns usually suckle effectively when they are positioned appropriately at the breast; however, the maternal physiological ability to lactate rapidly declines if both breasts are not stimulated quickly following parturition and drained every 2 or 3 h. There is a window for the initiation of lactation, and studies have shown that the duration of lactation correlates inversely with the time of the first breast stimulation. The extrinsic lack of prolactin surges fail to trigger and maintain lactation [115].

Inadequate drainage as a result of infrequent suckling or ineffective breastfeeding techniques leads to the lack of removal of the milk and a buildup of local inhibitor factors in the retained milk, which shuts down ongoing milk synthesis. Involution of the glands commences, leading to premature weaning. After delivery, there is considerable vascular and lymphatic congestion in the breast tissue, leading to a rise in interductal pressure. If unrelieved, the engorgement impedes the intraductal flow of milk and reduces circulation, rapidly causing pressure atrophy at the alveoli and inhibiting the establishment of a good milk supply. Impairment to milk drainage as a result of lactiferous duct outlet obstruction also may occur following mammoplasty or surgical reconstruction of the breast, although newer surgical techniques attempt to maintain the integrity of the lactiferous ducts [59, 116, 117]. Neifert et al. found a threefold increase in the risk of lactation insufficiency in women who had undergone breast surgery compared to women without surgery [58]. Where there was a periareolar incision, the risk was 5 times greater than when there was no history of breast surgery [58].

Breast fullness or engorgement may prevent infants from latching effectively. This leads to sore nipples, caused by tongue trauma, inadequate breast stimulation, drainage and insufficient milk intake by the infant. If the breast milk intake is low, the infant remains hungry and may receive formula supplement and become satiated. The net result is milk retention, impeded lactogenesis and maternal unhappiness. Hot compresses and manual expression of milk before latching helps to improve the attachment, and cold compresses reduce swelling after feeds [118, 119].

The fluid requirements of healthy newborn infants are minimal for the first few days. Neonates drink 7–20 mL of colostrum per feed initially, and they do not require extra fluids. Prelacteal and complementary feeds may upset the process of lactogenesis by removing the neonate's hunger drive and decreasing the frequency of breast stimulation and drainage [90, 120]. Night sedation may offer a temporary respite, but the lack of breastfeeding at night can impede lactogenesis because of irregular breast stimulation and drainage.

If frequent efficient breastfeeding is not possible, for example, if a mother is separated from her sick infant, she should be shown how to express her milk regularly, either by hand or by using a breast pump, to ensure complete breast drainage and prevent milk stasis. Contrary to popular belief, this does not lead to an excessive milk synthesis but prevents early and irreversible involution. Mothers should pump at least 6 times daily [121].

5.2.4 Milk Transfer

Milk is transferred from the breast by the infant during breastfeeding, in combination with the maternal milk

ejection reflex. The rate of transfer of milk from the breast to the infant depends on various factors, including milk synthesis and the volume of pooled milk, the strength and frequency of the milk ejection reflex, and the technical process of breastfeeding [122]. The milk ejection reflex, or letdown, is stimulated by oxytocin released from the posterior pituitary following direct nipple stimulation and via hypothalamic triggering. It causes smooth-muscle contractions and propels milk through the ducts and out of the nipple pores. The character of the reflex varies between women and over time; some mothers have a well-developed letdown, whereas others have a slow, irregular reflex. With conditioning, oxytocin release occurs in response to infant crying or as the mother prepares to feed [100]. Confidence facilitates the ejection reflex and anxiety may impede it [123, 124].

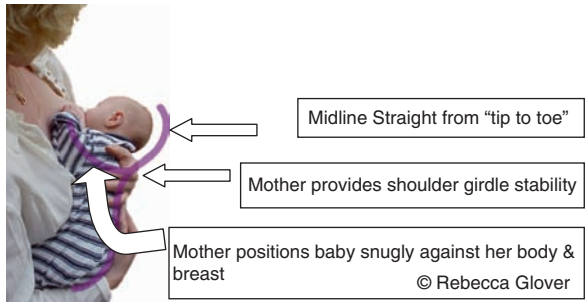

Fig. 5.2 A positionally stable baby (from [126], used with permission)

5.2.4.1 Factors that Help Milk Transfer

Basic Breastfeeding Skills

Breastfeeding is a technical process of transferring milk from the breast. It depends on careful positioning and attachment of the infant to the breast and on an intact suckling ability of the infant. Parenting starts at birth; therefore, hospital staff should encourage mothers to assume this role as soon as possible. Mothers should be shown how to breastfeed [87, 125].

Positioning. The mother should be sitting comfortably with her arms and back supported and her feet raised on a small stool. The infant should be placed on her lap, facing the uncovered breast; a pillow may help raise up the baby. The infant's body should be well supported and straight, with the infant snug against her body [126] (Fig. 5.2). Breastfeeding is easier if two hands are used to start with. The breast should be cupped with one hand underneath using the thumb and fingers to shape the breast to form an oval that matches the shape of the mouth, lifting the breast up slightly while directing the nipple toward the infant's mouth. The other hand is used to support the infant's back and shoulders. The infant's arms should be free to embrace the breast and the body held very close to the mother, stomach to stomach.

Attachment. The latching technique involves brushing the nipple against the infant's upper lip and waiting until the infant roots, lifting his or her head and opening the mouth wide. This often requires "teasing the baby" and encouraging the mouth to open wider than before. When the mother can see the gaping mouth, she should quickly draw the baby forward over the nipple and onto areola tissue. The baby's bottom lip, jaw and chin sink into the breast first, so that he takes a good mouthful of breast [126]. The amount of areola available to the mouth depends on the size of the areola and on the neonate's gape. It is incorrect to assume that all the areola tissue should be covered. The lips should be everted or flanged and placed well behind the nipple base. The chin is extended into the breast and the nose is adjacent to it. Young infants do not have the ability to maintain their position at the breast alone, and so the mother must continue to sandwich her breast and support the infant's back and shoulders throughout the duration of the feed. Older infants are able to latch and maintain themselves more easily and suckle comfortably in an elbow crook.

Suckling. An infant who is correctly latched and has a mouthful of soft breast tissue will draw the nipple and the areola tissue to the junction of the hard and soft palate to form a teat and then will initiate suckling. The more elastic and extensible the breast tissue, the easier it is for the young infant. A fixed, retracted or engorged nipple and areola tissue make it harder for this to occur. The jaw is raised and the gums compress the breast tissue; the tongue protrudes over the lower gums, grooves and undulates in a coordinated manner. The cheeks and tongue help to form a bolus of milk. The jaw lowers, and the soft palate elevates to close the nasopharynx; a slight negative pressure is created, and the milk is effectively transferred and swallowed in a coordinated manner [127, 128] (Fig. 5.3).

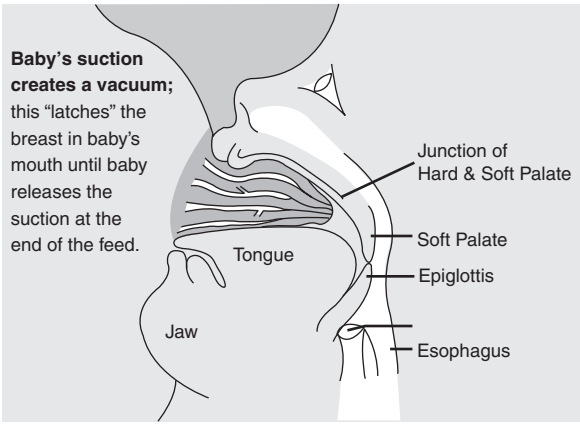

Fig. 5.3 The essential mouthful (from [126], used with permission)

5.2.4.2 Factors Impeding Milk Transfer

The milk ejection reflex is a primitive one and is not easily blocked. The effects of adrenaline can reduce it temporarily if the mother is subjected to sudden unpleasant or extremely painful physical or psychological stimuli. This could include embarrassment or fear, inducing a stress reaction with the release of adrenaline, which can cause vasoconstriction and impede the action of oxytocin. Over time, however, this inhibition seems to be overcome. The strength and frequency of the ejection reflex depend on hypophysial stimulation of the posterior pituitary and suckling pressure on the lactiferous ducts, causing oxytocin release. The more milk that has pooled between feeds, the more is ejected with the initial let down [100, 123].

Inefficient milk transfer may be the result of poor maternal breastfeeding technique in positioning the infant at the breast or in facilitating his or her attachment because of a lack of knowledge or maternal or infant physical disabilities. In addition, improper positioning and attachment lead to decreased breast stimulation and inadequate drainage, which result in decreased milk production and decreased milk intake. Simple correction of the position and latch is often the only remedy needed to improve the quality of the feed.

Inefficient milk transfer also may result from poor neonate suckling technique either because of an inability to grasp the nipple correctly or because of a suck, swallow or breath disorder. Large, well-defined nipples may entice the neonate to suckle directly on the nipple, resulting in sore nipples and ineffective milk transfer. Retrognathia, cleft lip or palate, an uncoordinated, weak, flutter, or a bunched-up tongue may interfere with effective sucking dynamics, often because the jaw fails to compress the breast or the tongue and cheeks are unable to create the necessary negative pressure to draw in the milk [129]. These infants may benefit from suck training, but clinical experience suggests that as the mandible elongates and facial muscles strengthen, the dynamics of sucking improve naturally [130]. *Ankyloglossia* (tongue-tie) is an important cause of suckling difficulties. The tethered tongue is unable to protrude over the gum and cannot move upward; the teat is not stripped correctly, and less milk is transferred. The nipple often becomes traumatized and sore. The infant may not thrive, and milk production decreases because of inadequate drainage. A simple surgical release of the frenulum is required and should be done as soon as possible when clinically indicated; after a few weeks, it is often difficult to alter the way these infants suckle [131–133]. Recently, a posterior tongue-tie has been recognized as a cause of nipple pain [134]. In addition to restricted tongue movement and elevation, palpation of resistance at the base of the tongue indicates a posterior tongue-tie [135].

5.2.5 Milk Intake

Over the first few days, the infant drinks small volumes of colostrum of 7–20 mL per feed. This rapidly increases to approximately 760–840 mL/day, with approximately seven or eight feeding episodes. The milk intake per feed is about 80–120 mL. Breasts have a great capacity to yield milk and can produce double this amount. If necessary, a woman can feed from one breast exclusively [136].

5.2.5.1 Frequency

Infants are able to recognize hunger and should be fed according to their cues. Most newborns breastfeed every 2–3 h, causing frequent surges of prolactin, which help to ensure full lactation. Mothers who have a low milk supply should be encouraged to breastfeed frequently to ensure good drainage and stimulation.

5.2.5.2 Duration

Studies show that the duration of a breastfeed varies between mother-infant pairs [137]. The rate of milk transfer is not uniform. Some breastfeeding pairs have a rapid milk transfer and, hence, a very short feed. This is because of the large amount of milk that has collected in the breasts since the previous feed and the well-established milk ejection reflex. Others have long feeds because milk ejection is poor, the breastfeeding technique is relatively ineffective, or milk production is slow and the pooled milk volume is low, which consequently leads to a slowed milk transfer. Previously held beliefs that most of the feed is taken in the first few minutes or that both breasts should be used at each feed fail to recognize the uniqueness of each nursing pair.

5.2.5.3 Pattern of Breast Use

The quality and quantity of milk intake depend on the pattern of breast use. Between feeds, milk is synthesized and collects in the lactiferous ducts. This low-fat milk is readily available at the start of each feed. As the feed progresses, the volume of milk the infant drinks will decrease, but the quality increases as more fat is passed into the milk. The infant should remain at the first breast until the rate of flow of milk is no longer sufficient to satisfy the infant. The second breast should then be offered.

5.2.5.4 Factors that Help Milk Intake

To establish lactation, both breasts should be offered at each feed. The removal of colostrum facilitates ongoing lactogenesis. When lactation is well established, the first breast should be comfortably drained before switching to the second. This will prevent milk stasis and results in a balanced milk production and optimum infant growth. Mothers with a high milk yield may feed unilaterally, whereas mothers with a slow rate of milk synthesis should feed bilaterally. When the rate of milk transfer is rapid, the infant may gag, choke and pull away from the breast; frequent burping is recommended in this situation, as is manual expression of some milk before attaching the infant.

5.2.5.5 Factors that Impair Milk Intake

A "happy to starve" infant that sleeps for long periods may fail to thrive because of inadequate daily milk intake. A pause in feeding after a few minutes of sucking may be interpreted incorrectly as the infant having had enough, leading to early termination of the feed. A crying, discontented infant may be given a pacifier to prolong the time between feeds. A mother also may be under the impression that only one breast should be used at each feed and choose not to feed off the second side even though the neonate is still hungry. Newborns frequently pause while feeding, and these episodes may last several minutes. Problems arise when a mother terminates a feed or switches to the other side prematurely because this alters the quality and quantity of the milk consumed.

5.2.6 Maternal Psychosocial Health

The psychological and social health of the mother is crucial throughout all stages of breastfeeding. A mother who is ambivalent about breastfeeding and who lacks support may allow her infant fewer chances to suckle, thereby inhibiting lactogenesis and galactopoiesis. A mother who lacks confidence or knowledge may interpret any breastfeeding infant problem as being due to insufficient milk; a consequent move to bottle-feeding compounds the problem. Lack of support from family and friends can negatively influence her endeavors [72, 138].

5.2.7 In-hospital Risk Assessment

Some mothers and infants are at high risk for lactation and breastfeeding difficulties. As discussed previously, several biopsychosocial risk factors can be identified prenatally, and this information should be readily available in hospitals. A routine in-hospital breastfeeding risk assessment should be performed [139] (Fig. 5.4).

Newborns often lose weight within the first few days as the result of normal physiologic fluid losses [140]. If breastfeeding is successfully established, this weight loss should be no greater than about 7%. Excessive weight loss may imply inadequate food intake and deserves a detailed clinical breastfeeding assessment. The underlying cause is usually easy to

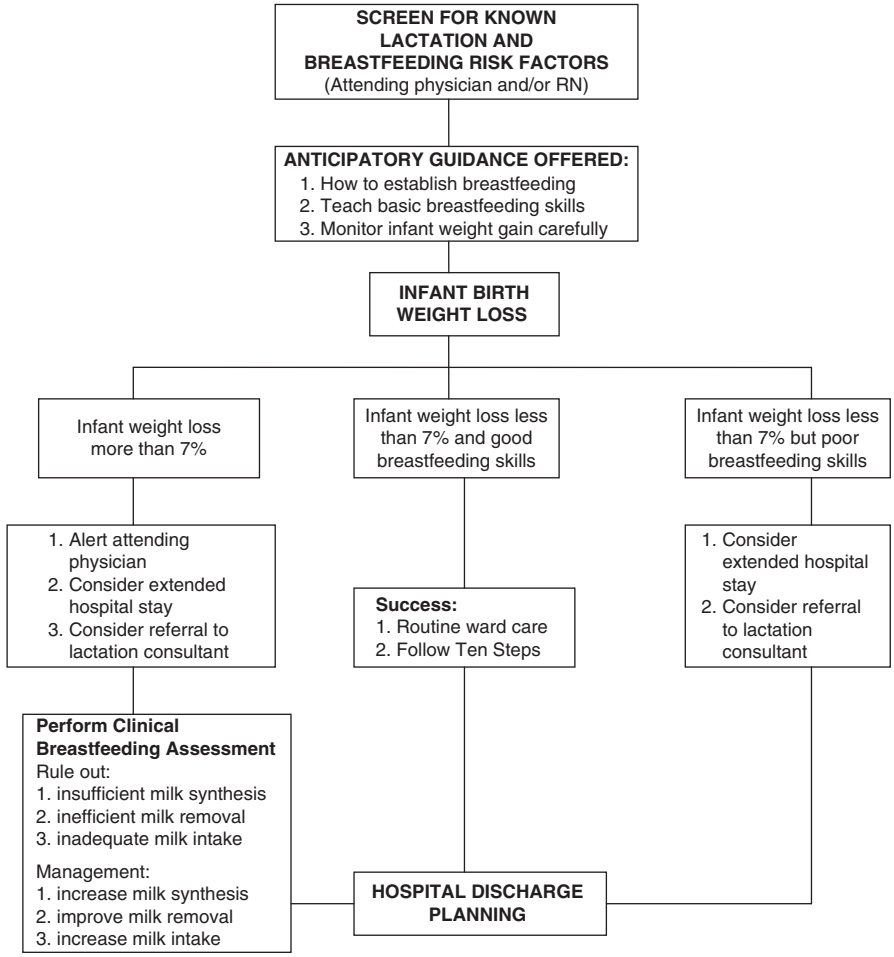

Fig. 5.4 In-hospital breastfeeding assessment

elucidate and management can be directed toward either increasing the rate of maternal milk synthesis, improving milk transfer or increasing the daily quantity or quality of milk intake [1, 141].

If the neonate's weight continues to fall, additional calories must be provided either as the mother's own breast milk, pasteurized donor breast milk or formula. Some neonates have preexisting difficulties grasping and suckling at the breast. In these situations, wide-based rubber nipples and thin silicone nipple shields are useful suck training devices that encourage normal biomechanical jaw excursions.

5.2.8 Hospital Discharge Planning

Hospital stays are short. Discharge planning enables a physician to review the stages of lactation and breastfeeding and allows early identification of potential or actual problems. All mothers should be taught the signs that their baby is breastfeeding well and instructed to call for advice if they have concerns (Fig. 5.5). If an infant has lost more than 7% of his or her birth weight at the scheduled hospital discharge, or if the mother-infant pair has known risk factors for breastfeeding difficulties, a delayed discharge or early community follow-up for breastfeeding assistance would be appropriate. All other mothers and infants should be reassessed within 1 week of birth [142].

5.3 Postpartum Period

5.3.1 Clinical Breastfeeding Assessment

Lactation and breastfeeding difficulties manifest in many ways, including infant problems such as failure to thrive, colic, fussiness, early introduction of supplements or

Fig. 5.5 Signs your baby is breastfeeding well

By three or four days of age, your baby:

- has wet diapers: at least 4-5 noticeable times (looks or feels wet) in twenty-four hours (pale and odorless urine)
- has at least 2-3 bowel movements in twenty-four hours (color progressing from brownish to seedy mustard yellow).
- breastfeeds at least 8 times in twenty-four hours.
- is content after most feedings.

Other signs that suggest your baby is breastfeeding well are:

- You can hear your baby swallowing during feeding.
- Your breasts are full before feedings and soft after feedings.
- Your baby is only drinking breast milk.

If any one of these signs is not present after your baby is 3 or 4 days old or if you are having problems, please call for help.

Physician/Midwife:_____ Community Health Nurse:

If your baby is breastfeeding well, make an appointment within the first week for you and your baby to see either your Family Physician, Midwife, or Community Health Nurse.

Birth Weight:_____Discharge Weight:_____

Weight at One Week:_____

maternal concerns such as breast discomfort, sore cracked nipples, engorgement mastitis or postpartum depression. Different clinical complexes of symptoms and signs or syndromes reflect the normal variations in maternal lactation ability and infant breastfeeding ability. These symptoms and signs are not diagnostic. Diagnosis and problem solving starts with a detailed history and physical examination of both mother and infant, including breastfeeding history and observation. Once the etiology and pathophysiology have been elucidated, successful management depends on sound knowledge of the anatomy of the breast, the physiology of lactation and the mechanics of infant suckle combined with a clear understanding of breastfeeding kinetics [126, 143].

The rate of breast milk synthesis varies throughout the day and between mothers. It depends on a variety of central and local factors, including direct breast stimulation and breast drainage [95, 144]. In clinical practice, approximately 15% of mothers have a high rate of milk synthesis of 60 mL/h or more (hyperlactation), and about 15% of mothers have a low rate of synthesis of 10 mL/h or less (hypolactation) (Fig. 5.6).

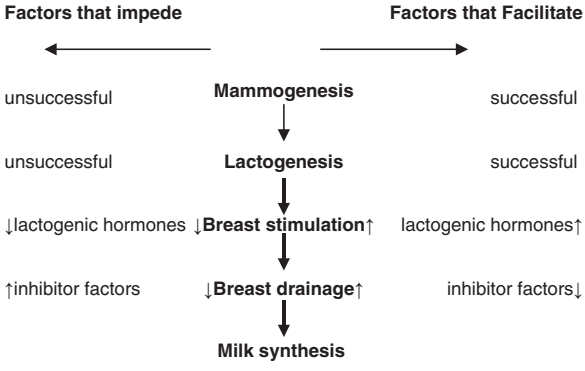

Fig. 5.6 Maternal milk synthesis

5.3.2 Insufficient Milk Syndrome

The most common reason given for abandoning breastfeeding in the early postpartum period is insufficient milk. The etiology is multifactorial, but most causes are reversible if the mother receives accurate breastfeeding management advice early in the postpartum period. A small percentage is irreversible (Fig. 5.7).

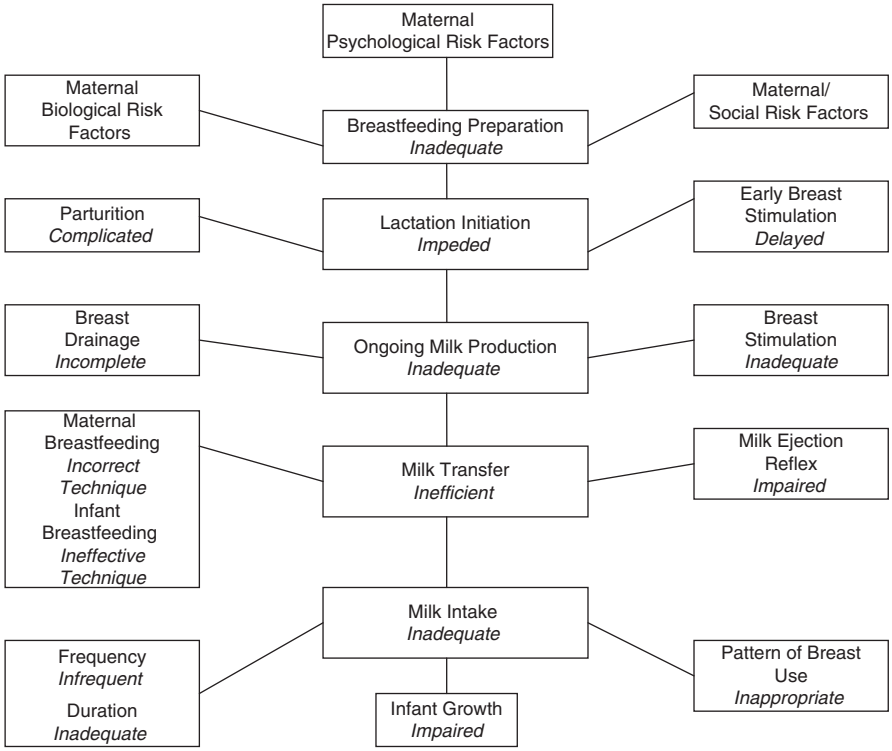

Fig. 5.7 Neonatal insufficient milk syndrome

If the mother is having difficulties breastfeeding or if the infant's weight is continuing to fall or is more than 7% below birth weight, a careful evaluation is required. This involves a detailed clinical breastfeeding assessment incorporating maternal and infant history and breastfeeding history, and includes a careful maternal and infant examination. Observation of breastfeeding is required to assess positioning, latching, suckling and swallowing. An accurate test feed followed by estimating residual milk in the breasts by pumping are helpful measurements when assessing maternal milk yield and infant milk intake. Caution must be taken when using standard office scales due to their unreliability in measuring small volume changes [145]. Other causes of infant failure to thrive, such as cardiac or respiratory problems, should always be considered.

In broad terms, management includes avoiding the precipitating factors, improving maternal milk synthesis by increasing breast stimulation and drainage, improving milk removal by correcting the breastfeeding technique and increasing the infant's daily milk intake by increasing the frequency and duration of breastfeeding. A small percentage of neonates will require complementary feeds. Metoclopramide (10 mg 3 times a day) and domperidone (20 mg 3 times a day) are effective galactogogues when increased prolactin stimulation is required [146, 147]. Mothers may need support and reassurance that partial breastfeeding or mixed feeding is still beneficial.

5.3.3 Maternal Hyperlactation Syndrome

Hyperlactation may result in a characteristic clustering of maternal and infant symptoms and signs. Milk stasis, blocked ducts, deep radiating breast pain, lactiferous ductal colic, inflammatory mastitis, infectious mastitis and breast abscess are common problems. Clinical experience has shown that most mothers experiencing any or all these symptoms have a high rate of milk synthesis and have large, thriving infants, or else they have started to wean and are not draining their breasts regularly. These symptoms and signs are all consequences of a rapid rate of milk synthesis combined with milk retention resulting from incomplete breast drainage. They represent the clinical spectrum of the maternal hyperlactation syndrome [148, 149] (Fig. 5.8). The pathophysiology is analogous to the renal system; retention of urine, due to incomplete

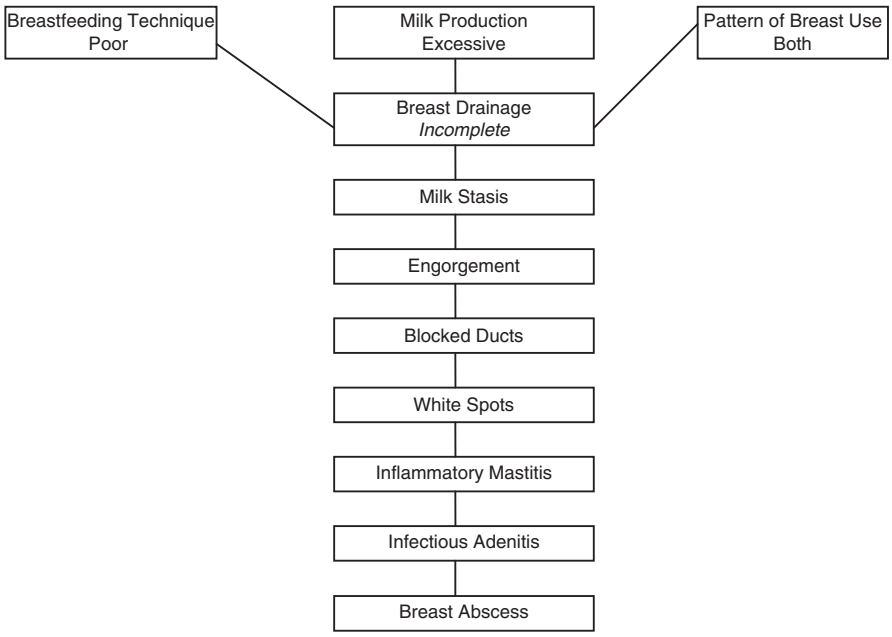

Fig. 5.8 Maternal hyperlactation

bladder emptying, may result in lower and upper urinary tract disease, including bladder distension, spasms, ureteric colic and hydronephrosis. This problem may become complicated with ascending urinary tract infections, including trigonitis, urethritis, cystitis, pyelonephritis and renal abscess.

Lactation problems occur when a mother with a high milk output switches her infant from one breast to the other before the first side has been adequately drained. A strong milk-ejection reflex causes a rapid letdown of a large volume of pooled milk, and the infant quickly becomes satiated before all the lactiferous ducts are drained. Incomplete drainage may be aggravated by poor position and latch or by impaired infant suckling [150]. When this occurs repeatedly, some of the ducts and lobules constantly remain full.

5.3.3.1 White Spot

A small white spot may be visible on the nipple; such a spot represents edematous epithelium blocking the nipple pore and milk flow. In some situations, duct obstruction is due to a small granule of casein milk precipitate [151]. Lactiferous duct outlet obstruction can cause increased retrograde pressure. Mothers may complain of sharp, "knife-like" cramps or shooting pains deep in the breast, often between feeds, because of ductal cramping or colic because of myoepithelial smooth-muscle contractions.

5.3.3.2 Milk Stasis

A firm, lumpy, slightly tender quadrant in the breast may be felt because of milk stasis. Over time, if this area is not drained, cytokines from the milk may seep into the interstitial tissue, causing it to become inflamed and erythematous, signifying an inflammatory mastitis [152, 153].

5.3.3.3 Acute Mastitis

It was recognized in 1940 that when a breach occurs in the mucous membrane, such as a cracked nipple, superficial skin infections could lead to a deeper cellulitis, adenitis and mastitis [154]. Livingstone et al. found that 50–60% of sore, cracked nipples were contaminated with *Staphylococcus aureus* or other microorganisms [155]. Subsequent study showed that 25% of mothers with infected, sore nipples developed mastitis if they were not treated aggressively with systemic antibiotic [156]. A high rate of milk synthesis combined with continuous poor drainage of a segment of the breast may result in the stagnant milk becoming

secondarily infected with common skin pathogens via an ascending lactiferous duct infection and leads to acute mastitis. Infectious mastitis also may be caused by a blood-borne infection; however, that is uncommon and more likely in non-puerperal mastitis [157]. Puerperal mastitis has been found to affect 17% of breastfeeding women who present with breast pain, redness, lumps, general malaise, chills or sweats and fever [158].

5.3.3.4 Chronic Mastitis

Chronic mastitis, as in chronic urinary tract infections, may be due to reinfection or a relapsed infection. Reinfection occurs sporadically because of exposure to a new pathogen, commonly transmitted from the infant. A relapsed infection occurs shortly after completion of therapy; it signifies inadequate primary treatment and failed eradication of the pathogen. An underlying cause, such as a nidus of infection deep in the breast tissue, should be considered. It is hypothesized that lactiferous duct infections may lead to stricture formation, duct dilation and impaired drainage. The residual milk remains infected.

5.3.3.5 Breast Abscess

Inadequately treated mastitis and ongoing milk retention can develop into a breast abscess. A high fever with chills and general malaise, associated with a firm, well-demarcated, tender, fluctuating mass, usually with erythema of the skin, indicates abscess formation, although, in some instances, systemic symptoms may be absent. Ultrasonography of the breast and needle aspiration under local anesthesia are useful diagnostic techniques for identifying collections of fluid or pus and distinguishing mastitis from a galactocele or inflammatory breast cancer [159–161].

5.3.3.6 Management Goals

Maternal hyperlactation syndrome can be prevented by decreasing the rate of milk synthesis and preventing milk retention by improving milk removal and breast drainage.

Decreased Rate of Milk Synthesis

Reducing breast stimulation and drainage can decrease the rate of milk synthesis. Decreasing the frequency and duration of breastfeeding reduces prolactin surges, and milk synthesis remains blocked via central inhibitory factors. Decreasing the frequency of breast drainage results in milk retention in the lactiferous ducts, and inhibitor peptides collect and block ongoing milk production via a local negative feedback mechanism. In practical terms, the infant should remain at one breast per feed until he or she is full and spontaneously releases the breast. In this way, the volume of milk ingested is less, but the fat content and calorific value increases as the feed progresses [162]. A higher fat intake often satiates the infant for a longer period and decreases the hunger drive. The interval between feeds is lengthened and milk synthesis declines, whereas the second breast remains full longer, and local inhibitor further reduces milk synthesis in that breast. In a small number of mothers, unilateral breastfeeding may result in over-drainage and can contribute to the ongoing high rate of milk synthesis. In these cases, bilateral breastfeeding and incomplete drainage may result in a decline in overall milk synthesis (e.g., 2–3 min on the first side followed by a good burp, and then 3–5 min on the second side). If milk supply does not become manageable with one-sided feeding, the mother can completely express both breasts on one occasion and then feed from one breast for a block of time (e.g., 4–6 h) before switching breasts [163].

Decreased Milk Retention

Regular breastfeeding facilitates milk removal and breast drainage. When positioned and latched correctly, the infant is usually effective at removing milk and draining each segment. The modified cradle position allows the mother to cup the breast with her hand and apply firm pressure over the outer quadrant and compress retained milk toward the nipple while the infant suckles. If the milk is flowing rapidly, the mother should stop compressing the breast. Switching breastfeeding positions and using the under-the-arm hold allows thorough drainage of all segments and prevents milk stasis. Breastfeeding should start on the fullest breast and the infant should remain on this breast until all areas feel soft. As the pressure in the duct is relieved, breast pain and discomfort lessen.

Removal of Obstruction

If a small white dot on the nipple becomes visible, indicating a blocked nipple pore and outlet obstruction, gentle abrasion or a sterile needle can be used to remove the epithelial skin and relieve the obstruction. Occasionally, a small calculus or granule will pop out suddenly, relieving the obstruction. On firm compression, a thick stream of milk will often gush out, indicating patency. Occasionally, breastfeeding is ineffective at removing the thickened inspissated milk, and manual or mechanical expression may therefore be necessary. The mother should be shown how to compress her breast firmly using a cupped hand, squeezing gently toward the nipple while pumping to dislodge the milk or calculus. It may be helpful to try massaging in front of the lump toward the nipple, as if "trying to clear a pathway" (Smillie CM cited by [164]). If the breast expression fails to relieve the obstructed segment, a technique known as *manual stripping can* be used [165]. This involves cupping the breast between the finger and thumb and applying firm, steady pressure over the tender section, starting from the periphery over the rib cage and drawing the fingers and thumb slowly together toward the nipple, stripping out thickened milk or pus. This procedure should be repeated several times. The skin must be well lubricated before attempting to do this. Analgesia may be necessary, but even with mastitis, the discomfort lessens as the procedure continues. The intraductal pressure is relieved as milk or pus is slowly extruded. Mothers must be taught this technique and instructed to repeat the procedure every few hours, standing in the shower, using soapy fingers, until the breast feels softer and milk is flowing freely.

If a breast abscess has formed, needle aspiration is preferred to incision and drainage under local or general anesthesia [160, 161]. Repeat needle aspiration may be required [166]. In very large or loculated abscesses, incision may be necessary. The incision should be radial, not circumferential, to minimize duct severance. A large drain should be inserted and daily irrigations continued until the cavity closes. It is important that the dressings be applied in a manner such that the infant can continue to breastfeed or the mother should use an efficient breast pump. Regular drainage prevents further milk stasis and maintains lactation.

Treating Infection

Correct breastfeeding techniques and improved drainage of milk are the *sine qua non* of treatment, but antibiotic therapy may be necessary. Inflammatory mastitis occurs within 12–24 h of milk blockage, leading to an infectious mastitis within 24–48 h. Under normal conditions, the milk leukocyte count is less than 10^6 mL of milk, and the bacterial count is less than 10^3 bacteria per milliliter. Within 48 h of breast symptoms, the leukocyte count increases to more than 10^6 mL of milk, but the bacterial count remains low. This is considered noninfectious inflammation of the breast, and improved milk drainage will resolve the situation quickly [152]. Infectious mastitis is defined as having a bacterial count of more than 10^6 mL of milk. In clinical practice, treatment is empirical. Breast pain and erythema associated with flu-like systemic symptoms and a fever are highly suggestive of infectious mastitis and require antibiotic therapy if not resolving within 24 h [167]. Common bacterial pathogens include *Staphylococcus aureus, Escherichia coli, group A β-haemolytic Streptococcus* with occasional *Streptococcus faecalis* and *Klebsiella pneumonia.* In contrast, nonpuerperal breast infections are mixed infections with a major anaerobic component. Antibiotics of choice include penicillinase-resistant penicillins such as dicloxacillin or flucloxacillin, cephalosporins, sulfonamides and clindamycin. A 10–14 day course may be required. The breast milk excretion of these antibiotics is minimal, and continuation of breastfeeding is considered safe. Clinical improvement is usually seen within 24–48 h, the erythema subsides, the fever decreases and breast pain improves [167]. A persistent fluctuant mass may indicate abscess formation.

Prevention of Recurrence

Excessive milk retention can be prevented by correct breastfeeding techniques, ensuring a proper latch, regular drainage and not skipping feeds. Mothers should avoid pressure on the breast (e.g., from their finger on the breast, or a seat belt, or tight clothing) as the milk ducts are easily compressed [168]. Sleeping through the night, returning to work, the introduction of breast milk substitutes such as bottles of formula, the introduction of table foods and weaning are all typical periods when breastfeeds may be missed. The resultant

"breast confusion" can lead to inadequate drainage and milk retention. Mothers with a high milk output should become skilled at palpating their breasts for lumps, and the bra should be removed before feeding if it is practical to do so. Areas of breast lumpiness or caking that persist after breastfeeding may indicate milk stasis or a blocked duct. Thorough expression of this residual milk should relieve the situation and prevent secondary complications.

Supportive Measures

Mastitis is an inflammatory process that can be complicated by infection and produce systemic symptoms in an already exhausted mother. Home help and bed rest is advisable, and analgesia such as ibuprofen or acetaminophen may be necessary. Hot compresses applied to the breast, before breastfeeding or milk expression, encourage blood flow and smooth muscle relaxation, which in turn helps milk transfer. Cold compresses after feeds may decrease inflammation and edema.

Anecdotal cases of maternal toxic shock syndrome have been reported, and in rare circumstances, *Staphylococcus* toxins can be ingested by the infant [169]. Continuation of breastfeeding is always recommended. Weaning may lead to increased milk stasis and abscess formation. If a mother chooses to wean abruptly or if clinically indicated, a lactation suppressant such as cabergoline may be used (0.25 mg twice daily for 2 days) [114, 170].

5.3.4 Sore Nipples

Sore nipples, particularly during the first few days of breastfeeding, are a common symptom experienced by an estimated 80% of breastfeeding mothers. It is generally accepted that transient nipple soreness is within normal limits. Factors such as frequency and duration of breastfeeding, skin or hair color and nipple preparation do not seem to make a difference in preventing tenderness. Increasing or persistent discomfort is pathological and requires careful evaluation. Detailed studies of infant suckling at the breast have illustrated how tongue friction or gum compression, resulting from inappropriate latch, can cause trauma and result in superficial skin abrasions and painful nipples [171, 172]. In many cases, repositioning can have a dramatic effect and instantaneously remove the pain and discomfort [173, 174]. However, recent research suggests that some infants exert higher than normal intraoral vacuums causing pain to their mothers [175].

A small percentage of women have naturally sensitive nipples, which remain uncomfortable throughout the duration of breastfeeding, despite careful technique. They experience sensitive nipples, even in their nonlactating state. When nipple pain, excoriations, dermatitis or ulceration continue despite careful maternal breastfeeding technique, a detailed history and physical examination are required to elucidate secondary causes of sore nipples.

5.3.4.1 Nipple Trauma

To suckle correctly, an infant must grasp sufficient breast tissue to form a teat, draw it to the back of the pharynx, and initiate suckling in a coordinated manner using rhythmic jaw compressions and a grooved, undulating tongue. Many maternal nipple and infant oral anatomic anomalies can interfere with effective latch and suckle, resulting in nipple trauma and pain. Clinical findings such as maternal inelastic, flat, pseudoinverted or inverted nipples and infant cleft lip and palate are easily identified. More subtle findings may include infant retrognathia, which refers to a small or posterior positioned mandible, or the Pierre-Robin malformation, which combines severe micrognathia, or a posterior tongue with a relative ineffective activity of the muscles that protract the tongue and ankyloglossia [129, 176].

Management includes using a semi-upright breastfeeding position, which allows gravity to aid in jaw extension and minimizes the degree of overbite and friction. Continuous support and shaping of the breast throughout the feed with hand support of the infant's head and shoulders stabilize the neck and jaw muscles. Heat and gentle manipulation of the nipple may elongate it sufficiently to enable a correct latch. If clinically indicated, frenotomy can release a tethered tongue [177]. Over a period of a few weeks, a hypoplastic mandible rapidly elongates, the facial muscles strengthen, the nipple tissue becomes more distensible, the latch improves, and nipple trauma and pain resolve.

5.3.4.2 Chapped Nipples

Dry, cracked nipples may be chapped due to loss of moisture barrier in the stratum corneum because of constant wet and dry exposure combined with nipple friction. Management goals include avoiding further trauma by modifying breastfeeding technique, avoiding excessive drying and restoring the moisture barrier. Moist wound healing allows the epithelial cells to migrate inward and heal the cracks and ulcers [178]. Moisturizers and emollients such as USP modified anhydrous lanolin applied to the nipples and areolae after each feed are cheap and effective. In most situations, breastfeeding should continue during therapy; if repositioning fails to modify or relieve the pain and discomfort, it may be advisable to stop breastfeeding for 48–72 h to allow healing to occur. The breasts should be emptied every 3–4 h, and an alternative feeding method should be used. It is inappropriate to try to mask the pain by numbing with ice or using strong analgesia or nipple shields because this will fail to correct the underlying cause and may lead to further nipple trauma.

5.3.4.3 Bacterial Infection of the Nipple

Staphylococcus aureus is frequently found distributed over the skin. Natural barriers, such as the stratum corneum, skin dryness, rapid cell turnover and acid pH of 5–6, of the infant's skin usually prevent infection. For disease to result, preexisting tissue injury or inflammation is of major importance in pathogenesis. As in other clinical situations, when there is a break in the integument of the skin surface, there is a predisposition to a secondary infection because of bacterial or fungal contamination, which may lead to a delay in wound healing. Sore nipples associated with skin breakage, including cracks, fissures and ulceration, have a high chance of being contaminated with microorganisms. The clinical findings on the nipple and areola of local erythema, excoriations, purulent exudates and tenderness are suggestive of colonization with coagulase-positive *S. aureus*. Livingstone et al. showed that mothers with young infants who complained of moderate to severe nipple pain and who had cracks, fissures, ulcers or exudates had a 54% chance of isolation of *S. aureus* [155]. In some clinical situations, a blocked nipple pore appears white and on culturing is found to be contaminated with *S. aureus*. Most cases of cellulitis, mastitis and breast abscess involve an ascending lactiferous duct infection with *S. aureus* or β-hemolytic streptococcus. Management includes careful washing with soap and water of the nipples to remove crusting and the use of appropriate antibiotics. Topical antibiotic ointments such as fusidic acid (Fuccidin) or mupirocin (Bactroban) may be effective in conjunction with systemic penicillinase-resistant antibiotics, such as dicloxacillin, cephalosporin or erythromycin in penicillin-allergic patients [156]. Treatment should continue for 7–10 days until the skin is fully healed. The source of the infection is often from the infant's oropharyngeal or ophthalmic flora. In persistent or recurrent infections, it may be necessary to treat the infant as well [179].

5.3.4.4 Candidiasis

Candidiasis is commonly caused by *Candida albicans* and less frequently by other Candida species. It may be a primary or secondary skin infection. *C. albicans* is endogenous to the gastrointestinal tract and mucocutaneous areas. Normal skin does not harbor *C. albicans*; however, almost any skin damage caused by trauma or environmental changes may lead to rapid colonization by *C. albicans*. Isolation of the organism from a diseased skin may not be the cause of the disease but may be coincidental. *C. albicans* can be a secondary invader in preexisting pathological conditions and may give rise to further pathology. Candidiasis should be suspected when persistent nipple symptoms, such as a burning sensation on light touch and severe nipple pain during feeds, are combined with minimal objective findings on the nipple [180]. Typical signs include a shiny or flaky appearance of the nipple and areola associated with nipple and breast pain [181]; the breast appears normal without the inflammation and fullness associated with mastitis. A high incidence of oral mucocutaneous candidiasis has been noted in the newborn following vaginal delivery in the presence of maternal candidal vulvovaginitis. Typical symptoms of nipple/breast candidiasis often develop following maternal antibiotic use [182, 183]. Clinical examination of the infant is mandatory because *C. albicans* is passed from the infant's oral pharynx to the mother's nipple, which, being a warm, moist, frequently macerated epidermis, is easily colonized and possibly infected when the integument is broken. Diagnosis is based on clinical signs and symptoms [184, 185].

The treatment of cutaneous candidiasis includes careful hygiene, removal of excessive moisture and topical therapy with broad-spectrum antifungal agents such as nystatin, clotrimazole, miconazole or 2% ketoconazole. The creams should be applied to the nipple and areola after each breastfeed for 10–14 days. In addition, other sites of candidiasis in both mother and infant, including maternal vulvovaginitis, intertrigo or infant diaper dermatitis, should be treated simultaneously with a topical antifungal cream. Oral thrush in the infant should be treated aggressively with an oral antifungal solution such as nystatin suspension 100,000 U/g. After each feed, the oral cavity should be carefully painted and then 0.5 mL of nystatin suspension inserted into the mouth by dropper for 14 days. In countries where oral miconazole gel is available, this is used in the infant's mouth and on the mother's nipples [186]. Oral fluconazole 3 mg/kg daily for 14 days or oral ketoconazole 5 mg/kg daily for 7 days may be used for the treatment of oropharyngeal candidiasis in newborns. Gentian violet 0.5–1% aqueous solution is cheap and effective if used sparingly under medical supervision. Daily painting of the infant's mouth and mother's nipples for about 5–7 days is usually sufficient. Excessive use may cause oral ulceration [187]. Failure to eradicate fungal infections is usually due to user, not medication failure. Occasionally, more serious underlying medical conditions such as diabetes or immunodeficiencies may exist. Systemic antifungal agents may be required; regimes vary from fluconazole 150 mg every second day for three dose [186] to 200 mg loading dose , followed by 100 mg daily for 14 days [143] (p. 282). In addition, topical corticosteroids may reduce nipple pruritus and erythema [188]. Foreign objects contaminated with yeast, including soothers and rubber nipples, should be avoided or sterilized, if possible, to prevent reinfection. Lay literature is full of nonpharmacologic treatments for candidiasis with little evidence to support them. The healthcare provider is cautioned against recommending regimens that are complicated. In an otherwise healthy person, the immune defense mechanism can control the growth of candida, assuming the skin integument is intact and remains dry.

5.3.4.5 Dermatitis

Dermatitis of the nipple may be endogenous atopic eczema, irritant contact or allergic contact dermatitis [189, 190]. Contact dermatitis in the nipple is an eczematous reaction to an external material applied, worn or inadvertently transferred to the skin. It may be an allergic or an irritant response. Patients may complain of dry, pruritic or burning nipples with signs of inflammation, erythema and edema or excoriations, desquamation or chronic plaque formation. The typical description is of an itching, spreading rash. Management includes careful avoidance of all irritants such as creams, preservatives, detergents, and fragrances. Irritation from frequent expressing can be reduced by using a lubricant, such as purified lanolin, on the nipples and areolae prior to pumping. A potent topical corticosteroid such as mometasone furoate can be applied thinly to the nipple and areola after a feed once a day for up to 10 days [189, 190]. Regular use of emollients may prevent recurrence. Chronic dermatitis is often colonized with *S. aureus,* which may require topical or oral antibiotic therapy.

5.3.4.6 Paget's Disease

Paget's disease is an intraepidermal carcinoma for which the most common site is the nipple and areola. It usually presents as unilateral erythema and scaling of the nipple and areola and looks eczematous [191]. Unfortunately, the condition is usually part of an intraductal carcinoma, and treatment necessitates cessation of breastfeeding.

5.3.4.7 Vasospasm or Raynaud's Phenomenon

Vasospasm, or Raynaud's phenomenon, of the nipple manifests as a blanching of the nipple tip with pain and discomfort radiating through the breast after and between feeds [192]. It may be associated with excoriated and infected nipples. There may be a history of cold-induced vasospasm of the fingers (Raynaud's phenomenon). Repetitive trauma to the nipple from incorrect latch or retrognathia, combined with local inflammation or infection and air cooling, can trigger a characteristic painful vasospastic response. Correcting the latch and alternating breastfeeding positions throughout the feed will prevent ongoing nipple trauma. Avoiding air exposure and applying warm dry heat to the nipples after feeds may help. Standard pharmacologic therapy for Raynaud's phenomenon can be effective in reducing the vasospasms; oral magnesium

supplements and nifedipine are usually helpful [193, 194]. Local infections should be treated aggressively and breastfeeding stopped for several days if necessary to allow healing to occur.

5.3.4.8 Psoriasis

Psoriasis may present as a pink, flaky plaque over the areola as a result of skin trauma. There is usually an existing psoriatic history. Standard treatment includes fluorinated steroid ointments and keratolytic agents, which should be applied after feeds and then washed off carefully before feedings.

For many years, the medical and nursing literature has recommended a variety of management approaches for sore nipples, ranging from topical application of cold tea bags, carrots and vitamin E, to lanolin, masse cream, antiseptics, alcohol preparations and air drying [195]. The efficacy of each of these modalities has not been proven, however; in fact, the latter is now thought to be detrimental by abstracting water from the skin and precipitating protein, which leaves the skin less pliable and more prone to fissuring. Healthcare professionals are cautioned against using nontraditional adjunct management modalities for sore nipples because of the risk of iatrogenic disease.

5.3.5 Induced Lactation and Relactation

Given the growing understanding of the value of breastfeeding in terms of nutrition and nurturing, women are seeking information about breastfeeding and adoption [26]. Induced lactation in the non-pregnant woman has been described for many years in both scientific and lay publications and includes the first reports by Hippocrates [196]. Auerbach and Avery reported on 240 women who attempted to breastfeed adopted children [197]. There are several anecdotally described methods of inducing lactation and preparing for breastfeeding, some of which can be started before the arrival of the infant. Direct nipple stimulation has been described as the most important component of inducing lactation and preparing to breastfeed [197]. Nipple stimulation can be performed by hand or by such mechanical means as an electric breast pump. Hand stimulation has the advantage of being easy and portable, but mechanical pumping stimulates greater milk production in lactating women [198].

A variety of pharmacological lactotrophs and galactogogues have been used to induce lactation [199, 200]. Estrogen and progesterone are used to promote mammogenesis by stimulating alveoli and lactiferous duct proliferation. They inhibit milk synthesis by blocking the action of prolactin on the mammary glands and therefore are used in preparation for breastfeeding. Galactogogues such as phenothiazine, sulpiride, and domperidone also have been described [114]. They are dopamine antagonists and block the inhibition of prolactin, which is a potent lactotroph. Metoclopramide and chlorpromazine are commonly used galactogogues but have many potential side effects, including sedation, extrapyramidal symptoms and tardive dyskinesia [201]. Domperidone has little effect on the central nervous system and has fewer side effects [146]. Drug excretion in breast milk is very limited and in combination with low milk production probably does not pose a risk to the infant. Relactation is often more successful than induced lactation [202].

5.3.6 Medicines and Breastfeeding

Most drugs transfer into breast milk, but generally at low, subclinical doses [203]. In general, if the medication is safe to use in infants, it will be safe for the breastfeeding mother [204]. Only a small number of medications are contraindicated during breastfeeding: these include antineoplastic agents, ergotamine, methotrexate, cyclosporine, radiopharmaceuticals [205]. Physicians and mothers need to consider the risks and benefits of any medicine. General advice is to use topical/local medicines where possible, choose drugs with shorter half-lives, and use drugs where there is previous experience in lactating women. Information is available about safe use of medicines while breastfeeding; see Fig. 5.9 for list of resources.

5.4 Conclusion

As the prevalence of breastfeeding continues to increase, health professionals will be expected to take a leadership role in the promotion, protection and support of

Fig. 5.9 Sources of information on medicines for breastfeeding women [206]

Reference books

- Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation*. 7th Ed, Philadelphia: Lippincott Williams & Wilkins, 2005.
- Hale T. *Medication and Mother's Milk*. 11th ed. Texas: Pharmasoft Medical Publishing, 2004 (available from http://neonatal.ttuhsc.edu/lact/)

Websites

- A new searchable website (LactMed) has been set up by the US National Library of Medicine http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT
- World Health Organization. Breastfeeding and maternal medication http://www.who.int/child-adolescent-health/New_Publications/NUTRITION/BF_Maternal_Medication.pdf

Telephone advice

- Pharmacy departments of tertiary maternity hospitals

breastfeeding by providing appropriate guidance, diagnosis and breastfeeding management throughout the full course of lactation.

References

1. Livingstone V (1995) Breastfeeding kinetics: a problem-solving approach to breastfeeding difficulties. World Rev Nutr Diet. 78:28–54
2. Livingstone V (1994) Prenatal lactation assessment. J SOGC. 16:2351–9
3. O'Campo P, Faden RR, Gielen AC et al (1992) Prenatal factors associated with breastfeeding duration: recommendations for prenatal interventions. Birth. 19:195–201
4. Britton C, McCormick FM, Renfrew MJ, et al. Support for breastfeeding mothers. The Cochrane Collaboration: CD001141; 2007
5. Miracle DJ, Fredland V (2007) Provider encouragement of breastfeeding: efficacy and ethics. J Midwifery Womens Health. 52:545–8
6. Berry NJ, Gribble KD (2008) Breast is no longer best: promoting normal infant feeding. Matern Child Health. 4:74–9
7. World Health Organization. Expert consultation on the optimal duration of exclusive breastfeeding. Conclusions and recommendations. 2001 [cited; Available from: http://www.who.int/inf-pr-2001/en/note2001-07.html
8. World Health Organization. Global strategy for infant and young child feeding. 2003 [cited; Available from: http://www.who.int/child-adolescent-health/NUTRITION/global_strategy.html
9. Dettwyler KA (2004) When to wean: biological versus cultural perspectives. Clin Obstet Gynecol. 47:712–23
10. Pisacane A, De Vizia B, Valiante A et al (1995) Iron status in breast-fed infants. J Pediatr. 127:429–31
11. Newburg DS (2005) Innate immunity and human milk. J Nutr. 135:1308–12
12. Hanson LA (2007) Session 1: feeding and infant development breast-feeding and immune function. Proc Nutr Soc. 66:384–96
13. Kramer MS, Chalmers B, Hodnett ED et al (2001) Promotion of breastfeeding intervention trial (PROBIT): a randomized trial in the republic of Belarus. JAMA. 285:413–20
14. Kramer MS, Guo T, Platt RW et al (2003) Infant growth and health outcomes associated with 3 compared with 6 mo of exclusive breastfeeding. Am J Clin Nutr. 78:291–5
15. Quigley MA, Cumberland P, Cowden JM et al (2006) How protective is breast feeding against diarrhoeal disease in infants in 1990s England? A case-control study. Arch Dis Child. 91:245–50
16. Dewey KG, Heinig MJ, Nommsen-Rivers LA (1995) Differences in morbidity between breast-fed and formula-fed infants. J Pediatr. 126:696–702
17. Oddy WH, Sly PD, de Klerk NH et al (2003) Breast feeding and respiratory morbidity in infancy: a birth cohort study. Arch Dis Child. 88:224–8
18. Marild S, Hansson S, Jodal U et al (2004) Protective effect of breastfeeding against urinary tract infection. Acta Pediatr. 93:164–8
19. Horta BL, Bahl R, Martines JC et al (2007) Evidence on the long-term effects of breastfeeding: systematic reviews and meta-analyses. World Health Organization, Geneva
20. McGuire W, Anthony MY (2003) Donor human milk versus formula for preventing necrotising enterocolitis in preterm infants: systematic review. Arch Dis Child Fetal Neonatal Ed. 21:249–54
21. Baumgartner C (1984) Psychomotor and social development of breast-fed and bottle-fed babies during their first year of life. Acta Paediatr Hung. 25:409–17
22. Davis DW, Bell PA (1991) Infant feeding practices and occlusal outcomes: a longitudinal study. J Can Dent Assoc. 57:593–4
23. Owen CG, Martin RM, Whincup PH et al (2005) Effect of infant feeding on the risk of obesity across the life course: a quantitative review of published evidence. Pediatrics. 115:1367–77
24. Harder T, Bergmann R, Kallischnigg G et al (2005) Duration of breastfeeding and risk of overweight: a meta-analysis. Am J Epidemiol. 162:397–403
25. Martin RM, Gunnell D, Davey Smith G (2005) Breastfeeding in infancy and blood pressure in later life: systematic review and meta-analysis. Am J Epidemiol. 161:15–26
26. Gribble KD (2006) Mental health, attachment and breastfeeding: implications for adopted children and their mothers. Int Breastfeed J. 1:5
27. Widstrom AM, Wahlberg V, Matthiesen AS et al (1990) Short-term effects of suckling and touch of the nipple on maternal behavior. Early Hum Dev. 21:153–63

28. Collaborative Group on Hormonal Factors in Breast Cancer (2002) Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50, 302 women with breast cancer and 96, 973 women without the disease. Lancet. 360:187–95
29. Ip S, Chung M, Raman G, et al. Breastfeeding and maternal and infant health outcomes in developed countries, in evidence report/technology assessment No. 153 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center, under Contract No. 290-02-0022). AHRQ Publication No. 07-E007. Rockville, MD: Agency for Healthcare Research and Quality; 2007
30. Kennedy KI, Visness CM (1992) Contraceptive efficacy of lactational amenorrhoea. Lancet. 339:227–30
31. Walker M (1993) A fresh look at the risks of artificial infant feeding. J Hum Lact. 9:97–107
32. Forsythe SJ (2005) *Enterobacter sakazakii* and other bacteria in powdered infant milk formula. Matern Child Nutr. 1:44–50
33. Morais TB, Sigulem DM, Maranhao HS et al (2005) Bacterial contamination and nutrient content of home-prepared milk feeding bottles of infants attending a public outpatient clinic. J Trop Pediatr. 51:87–92
34. FAO/WHO Expert meeting, *Enterobacter sakazakii* and other microorganisms in powdered infant formula: Meeting report, in Microbiological Risk Assessment Series 10. 2006
35. Frank JW, Newman J (1993) Breast-feeding in a polluted world: uncertain risks, clear benefits. Can Med Assoc J. 149:33–7
36. Walker M. Summary of the hazards of infant formula: part 2. 1998, International Lactation Consultant Association
37. Walker M. Summary of the hazards of infant formula: monograph 3. 2004, International Lactation Consultant Association
38. Lucas A, Morley R, Cole T et al (1992) Breast milk and subsequent intelligence quotient in children born preterm. Lancet. 339:261–4
39. Pollock JI (1994) Long-term associations with infant feeding in a clinically advantaged population of babies. Develop Med Child Neurol. 36:429–40
40. Lanting CI, Fidler V, Huisman M et al (1994) Neurological differences between 9-year-old children fed breast-milk or formula-milk as babies. Lancet. 344:1319–22
41. Elwood PC, Pickering J, Gallacher JE et al (2005) Long term effect of breast feeding: cognitive function in the Caerphilly cohort. J Epidemiol Community Health. 59:130–3
42. Gdalevich M, Mimouni D, David M et al (2001) Breastfeeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. J Am Acad Dermatol. 45:520–7
43. Howie PW, Forsyth JS, Ogston SA et al (1990) Protective effect of breast feeding against infection. Br Med J. 300: 11–6
44. Quigley MA, Kelly YJ, Sacker A (2007) Breastfeeding and hospitalization for diarrheal and respiratory infection in the United Kingdom millennium cohort study. Pediatrics. 119:e837–42
45. Martin RM, Gunnell D, Owen CG et al (2005) Breastfeeding and childhood cancer: a systematic review with metaanalysis. Int J Cancer. 117:1020–31
46. Klement E, Cohen RV, Boxman J et al (2004) Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis. Am J Clin Nutr. 80:1342–52
47. Akobeng AK, Ramanan AV, Buchan I et al (2006) Effect of breastfeeding on risk of coeliac disease: a systematic review and meta-analysis of observational studies. Arch Dis Child. 91:39–43
48. Taylor JS, Kacmar JE, Nothnagle M et al (2005) A systematic review of the literature associating breastfeeding with type 2 diabetes and gestational diabetes. J Am Coll Nutr. 24:320–6
49. Owen CG, Martin RM, Whincup PH et al (2006) Does breastfeeding influence risk of type 2 diabetes in later life? A quantitative analysis of published evidence. Am J Clin Nutr. 85:1043–54
50. Costs of Having a Baby. [cited 2 June 2008]; Available from: http://www.surebaby.com/costs.php
51. Cattaneo A, Ronfani L, Burmaz T et al (2006) Infant feeding and cost of health care: a cohort study. Acta Paediatr. 95:540–6
52. Smith JP, Thompson JF, Ellwood DA (2002) Hospital system costs of artificial infant feeding: estimates for the Australian capital territory. Aust N Z J Public Health. 26:543–51
53. Su LL, Chong YS, Chan YH et al (2007) Antenatal education and postnatal support strategies for improving rates of exclusive breastfeeding: randomised controlled trial. Br Med J. 335:596
54. Minchin MK (1998) Who is responsible for breastfeeding failure? In breastfeeding matters: what we need to know about infant feeding. Alma, Melbourne, pp 45–79
55. Kulski JK, Hartmann PE (1981) Changes in human milk composition during the initiation of lactation. Aust J Exp Biol Med Sci. 59:101–14
56. Neifert M, Seacat J, Jobe WE (1985) Lactation failure due to insufficient glandular development of the breast. Pediatrics. 76:823–8
57. Huggins KE, Petok ES, Mireles O (2000) Markers of lactation insufficiency: a study of 34 mothers. In: Auerbach K (ed) Current issues in clinical lactation. Jones and Bartlett, MA, pp 25–35
58. Neifert M, DeMarzo S, Seacat J et al (1990) The influence of breast surgery, breast appearance and pregnancy-induced breast changes on lactation sufficiency as measured by infant weight gain. Birth. 17:31–8
59. Johansson AS, Wennborg H, Blomquist L et al (2003) Breastfeeding after mammaplasty and augmentation mammaplasty. Epidemiology. 14:127–9
60. Marasco L, Marmet C, Shell E (2000) Polycystic ovary syndrome: a connection to insufficient milk supply? J Hum Lact. 16:143–8
61. Buhimschi CS (2004) Endocrinology of lactation. Obstet Gynecol Clin N Am. 31:963–79
62. Cox SG (2006) Expressing and storing colostrum antenatally for use in the newborn period. Breastfeed Rev. 14:11–6
63. ACOG committee opinion (1999) Breastfeeding and the risk of hepatitis C virus transmission. Int J Gynecol Obstet. 66:307–8
64. WHO HIV and Infant Feeding Technical Consultation. Held on behalf of the Inter-agency Task Team (IATT) on Prevention of HIV Infections in Pregnant Women, Mothers and their Infants, Geneva, October 25-27, Consensus statement. 2006

65. Howard C, Lawrence RA (1998) Breast-feeding and drug exposure. Obstet Gynecol Clin North Am. 25:195–216
66. Woodward A, Douglas RM, Graham NMH et al (1990) Acute respiratory illness in Adelaide children: breastfeeding modifies the effect of passive smoking. J Epidemiol Community Health. 44:224–30
67. Nafstad P, Jaakola JJK, Hagen JA et al (1996) Breastfeeding, maternal smoking and lower respiratory tract infections. Eur Respir J. 9:2623–9
68. Bottorff JL, Morse JM (1990) Mothers' perceptions of breast milk. J Obstet Gynecol Neonatal Nurs. 19:518–27
69. Sheehan A, Schmied V, Cooke M (2003) Australian women's stories of their baby-feeding decisions in pregnancy. Midwifery. 19:259–66
70. Wells KJ, Thompson NJ, Kloeben-Tarver AS (2002) Intrinsic and extrinsic motivation and intention to breastfeed. Am J Health Behav. 26:111–20
71. Bryant CA (1982) The impact of kin, friend and neighbor networks on infant feeding practices. Cuban, Puerto Rican and Anglo families in Florida. Soc Sci Med. 16(20): 1757–65
72. Baranowski T, Bee D, Rassin DK et al (1983) Social support, social influence, ethnicity and the breastfeeding decision. Soc Sci Med. 17:1599–611
73. Rossman B (2007) Breastfeeding peer counselors in the United States: helping to build a culture and tradition of breastfeeding. J Midwifery Womens Health. 52:631–7
74. Kent JC, Mitoulas L, Cox DB et al (1999) Breast volume and milk production during extended lactation in women. Exp Physiol. 84:435–47
75. Czank C, Henderson JJ et al (2007) Hormonal control of the lactation cycle. In: Hale TW, Hartmann P (eds) Textbook of human lactation. Hale, L. P, Amarillo, Texas, pp 89–111
76. Alexander JM, Grant AM, Campbell MJ (1992) Randomised controlled trial of breast shells and Hoffman's exercises for inverted and non-protractile nipples. Br Med J. 304:1030–2
77. McGeorge DD (1994) The "Niplette": an instrument for the non-surgical correction of inverted nipples. Br J Plast Surg. 47:46–9
78. Kesaree N, Banapurmath CR, Banapurmath S et al (1993) Treatment of inverted nipples using a disposable syringe. J Hum Lact. 9:27–9
79. Righard L, Alade MO (1990) Effect of delivery room routines on success of first breast-feed. Lancet. 336:1105–7
80. Smith LJ (2007) Impact of birthing practices on the breastfeeding dyad. J Midwifery Womens Health. 52:621–30
81. Murray EK, Ricketts S, Dellaport J (2007) Hospital practices that increase breastfeeding duration: results from a population-based study. Birth. 34:202–11
82. Klaus MH (1987) The frequency of suckling. Obstet Gynecol Clin North Am. 14:623–33
83. Yamauchi Y, Yamanouchi I (1990) Breastfeeding frequency during the first 24 hours after birth in full-term neonates. Pediatrics. 86:171–5
84. Yamauchi Y, Yamanouchi I (1990) The relationship between rooming-in/not rooming-in and breastfeeding variables. Acta Paediatr Scand. 79:1017–22
85. Elander G, Lindberg T (1984) Short mother-infant separation during first week of life influences the duration of breastfeeding. Acta Paediatr Scand. 73:237–40
86. Ball HL, Ward-Platt MP, Heslop E et al (2006) Randomised trial of infant sleep location on the postnatal ward. Arch Dis Child. 91:1005–10
87. Royal College of Midwives (1991) Successful breastfeeding. Churchill Livingstone, New York, pp 25–33
88. Moon JL, Humenick SS (1989) Breast engorgement: contributing variables and variables amenable to nursing intervention. J Obstet Gynecol Neonatal Nurs. 18:309–15
89. Newman J (1990) Breastfeeding problems associated with the early introduction of bottle and pacifiers. J Hum Lact. 6:59–63
90. Shrago L (1987) Glucose water supplementation of the breastfed infant during the first three days of life. J Hum Lact. 3:82–6
91. Woolridge MW (1995) Baby-controlled breastfeeding: biocultural implications in breastfeeding. In: Stuart-Macadam P, Dettwyler KA (eds) Breastfeeding: biocultural perspectives. Aldine de Gruyter, New York, pp 217–42
92. Newburg DS, Walker WA (2007) Protection of the neonate by the innate immune system of developing gut and of human milk. Pediatr Res. 61:2–8
93. Widström AM, Ransjö-Arvidson AB, Christensson K et al (1987) Gastric suction in healthy newborn infants. Effects on circulation and developing feeding behaviour. Acta Paediatr Scand. 76:566–72
94. Nissen E, Lilja G, Matthiesen AS et al (1995) Effects of maternal pethidine on infants' developing breastfeeding behaviour. Acta Paediatr. 84(2):140–5
95. Hartmann PE, Prosser CG (1984) Physiological basis of longitudinal changes in human milk yield and composition. Federation Proc. 43:2448–53
96. Wilde CJ, Addey CV, Boddy LM et al (1995) Autocrine regulation of milk secretion by a protein in milk. Biochem J. 305:51–8
97. Prentice A, Addey CVP, Wilde CJ (1989) Evidence for local feedback control of human milk secretion. Biochem Soc Trans. 17:122–4
98. Wilde CJ, Addey CV, Bryson JM et al (1998) Autocrine regulation of milk secretion. Biochem Soc Symp. 63:81–90
99. Czank C, Mitoulas LR, Hartmann PE (2007) Human milk composition – fat. In: Hale TW, Hartmann P (eds) Textbook of human lactation. Hale, L. P, Amarillo, Texas, pp 49–67
100. McNeilly AS, Robinson IC, Houston MJ et al (1983) Release of oxytocin and prolactin in response to suckling. Br Med J. 286:257–9
101. Cox DB, Owens RA, Hartmann PE (1996) Blood and milk prolactin and the rate of milk synthesis in women. Exp Physiol. 81:1007–20
102. Cregan MD, Hartmann PE (1999) Computerized breast measurement from conception to weaning: clinical implications. J Hum Lact. 15:89–96
103. WHO/UNICEF (1989) Protecting, promoting and supporting breastfeeding: the special role of maternity services. World Health Organization, Geneva
104. Djiane J, Houdebine LM, Kelly P (1981) Prolactin-like activity of anti-prolactin receptor antibodies on casein and DNA synthesis in the mammary gland. Proc Natl Acad Sci. 78:7445–8
105. Pestell RG, Best JD, Alford F (1990) Lymphocytic hypophysitis: the clinical spectrum of the disorder and evidence for an autoimmune pathogenesis. Clin Endocrinol. 33:457–66

106. Imura H (1994) The pituitary gland. Raven, New York, pp 1–28
107. Rillema JA (1994) Development of the mammary gland and lactation. Trends Endocrinol Metab. 5:1469–540
108. Kent JC (2007) How breastfeeding works. J Midwifery Womens Health. 52:564–70
109. Livingstone VH, Gout PW, Crickmer SD et al (1994) Serum lactogens possessed normal bioactivity in patients with lactation insufficiency. Clin Endocrinol. 41:193–8
110. Neifert MR, McDonough SL, Neville MC (1981) Failure of lactogenesis associated with placental retention. Am J Obstet Gynecol. 140:477–8
111. Kelly PA, Djiane J, Pastel-Vinay MC et al (1991) The prolactin/growth hormone receptor family. Endocr Rev. 12: 235–51
112. De Carvalho M, Robertson S, Friedman A et al (1983) Effect of frequent breastfeeding on early milk production and infant weight gain. Pediatrics. 72:307–11
113. Forster D, McLachlan H, Lumley J (2006) Factors associated with continuing to feed any breast milk at six months postpartum in a group of Australian women. Int Breastfeed J. 1:18
114. Hale TW (2007) Medications that alter milk production. In: Hale TW, Hartmann P (eds) Textbook of human lactation. Hale, L. P, Amarillo, Texas, pp 479–89
115. Aono T, Shioji T, Shoda T et al (1977) The initiation of human lactation and prolactin response to suckling. J Clin Endocrinol Metab. 44:1101–6
116. Widdice L (1993) The effects of breast reduction and breast augmentation surgery on lactation: an annotated bibliography. J Hum Lact. 9:161–7
117. Ramsay DT (2007) The anatomy of the lactating breast: latest research and clinical implications. Infant 3:59–63
118. Newton M, Newton NR (1951) Postpartum engorgement of the breast. Am J Obstet Gynecol. 61:664–7
119. Shrago LC (1991) Engorgement reconsidered. Breastfeed Abstr. 11:1–2
120. Lennon I, Lewis BR (1987) Effect of early complementary feeds on lactation failure. Breastfeed Rev. 11:24–6
121. Hill PD, Aldag JC, Chatterton RT (1999) Effects of pumping style on milk production in mothers of non-nursing preterm infants. J Hum Lact. 15:209–16
122. Drewett RF, Woolridge MW (1981) Milk taken by human babies from the first and second breast. Physiol Behav. 26:327–9
123. Newton M, Newton NR (1948) The let-down reflex in human lactation. J Pediatr. 33:698–704
124. Prime DK, Geddes DT, Hartmann PE (2007) Oxytocin: milk ejection and maternal-infant well-being. In: Hale TW, Hartmann P (eds) Textbook of human lactation. Hale, L. P, Amarillo, Texas, pp 141–55
125. Neifert MR (2004) Breastmilk transfer: positioning, latch-on, and screening for problems in milk transfer. Clin Obstet Gynecol 47:656–75
126. Glover R, Wiessinger D (2008) The infant-maternal breastfeeding conversation: helping when they lose the thread. In: Watson Genna C (ed) Supporting sucking skills in breastfeeding infants. Jones and Bartlett, Sudbury, Massachusetts, pp 97–129
127. Woolridge MW (1986) The 'anatomy' of infant sucking. Midwifery. 2:164–71
128. Righard L, Alade MO (1992) Sucking technique and its effect on success of breastfeeding. Birth. 19:185–9
129. Watson Genna C (2008) The influence of anatomical and structural issues on sucking skills. In: Watson Genna C (ed) Supporting sucking skills in breastfeeding infants. Jones and Bartlett, Sudbury, Massachusetts, pp 181–226
130. McBride MC, Danner SC (1987) Sucking disorders in neurologically impaired infants: Assessment and facilitation of breastfeeding. Clin Perinatol. 14:109–31
131. Hogan M, Westcott C, Griffiths M (2005) Randomized, controlled trial of division of tongue-tie in infants with feeding problems. J Paediatr Child Health. 41:246–50
132. Amir LH, James JP, Beatty J (2005) Review of tongue-tie release at a tertiary maternity hospital. J Paediatr Child Health. 41:243–5
133. Dollberg S, Botzer E, Grunis E et al (2006) Immediate nipple pain relief after frenotomy in breast-fed infants with ankyloglossia: a randomized, prospective study. J Pediatr Surg. 41:1598–600
134. Coryllos E, Genna CW (2004) Congenital tongue-tie and its impact on breastfeeding. American Academy of Pediatrics: Section on Breastfeeding. 1–6
135. Coryllos EV, Watson Genna C, Fram JLV (2008) Minimally invasive treatment for posterior tongue-tie (the hidden tongue-tie). In: Watson Genna C (ed) Supporting sucking skills in breastfeeding infants. Jones and Bartlett, Sudbury, Massachusetts, pp 227–34
136. Daly SEJ, Di Rosso A, Owens RA et al (1993) Degree of breast emptying explains changes in the fat content, but not fatty acid composition, of human milk. Exp Physiol. 78: 741–55
137. Woolridge MW, Baum JD, Drewett RF (1982) Individual patterns of milk intake during breastfeeding. Early Hum Dev. 7:265–72
138. Anderson AK, Damio G, Himmelgreen DA et al (2004) Social capital, acculturation, and breastfeeding initiation among Puerto Rican women in the United States. J Hum Lact. 20:39–45
139. Livingstone V (1996) In-hospital lactation assessment. J SOGC. 18:19–28
140. Dewey KG, Heinig MJ, Nommsen LA et al (1992) Growth of breast-fed and formula-fed infants from 0 to 18 months: the DARLING study. Pediatrics. 89:1035–41
141. Livingstone VH (1990) Problem-solving formula for failure to thrive in breast-fed infants. Can Fam Physician. 36:1541–5
142. The Academy of Breastfeeding Medicine Protocol Committee (2007) ABM Clinical Protocol #2 (2007 Revision): Guidelines for hospital discharge of the breastfeeding term newborn and mother: "the going home protocol". Breastfeed Med. 2:158–65
143. Lawrence RA, Lawrence RM. Breastfeeding: a guide for the medical profession. Vol 6th. Mosby, St Louis; 2005
144. Daly SE, Owens RA, Hartmann PE (1993) The short-term synthesis and infant-regulated removal of milk in lactating women. Exp Physiol. 78:209–20
145. Meier PP (1990) The accuracy of test weighing for preterm infants. J Pediatr Gastroenterol Nutr. 10:62–5
146. Da Silva OP, Knoppert DC, Angelini MM et al (2001) Effect of domperidone on milk production in mothers of

premature newborns: a randomized, double-blind, placebo-controlled trial. CMAJ. 164:17–21
147. Academy of Breastfeeding Medicine. Protocol #9: Use of galactogogues in initiating or augmenting maternal milk supply. 2004. http://www.bfmed.org/ace-files/protocol/galactogogues.pdf
148. Livingstone V (1996) Too much of a good thing: maternal and infant hyperlactation syndromes. Can Fam Physician. 42:89–99
149. Daly S (1986) The short-term synthesis and infant regulated removal of milk in lactating women. Exp Physiol. 78:208–20
150. Fetherston C (1998) Risk factors for lactation mastitis. J Hum Lact. 14:101–9
151. Inch S (2006) Breastfeeding problems: prevention and management. Community Pract. 79:165–7
152. Thomsen AC, Espersen T, Maigaard S (1984) Course and treatment of milk stasis, noninfectious inflammation of the breast, and infectious mastitis in nursing women. Am J Obstet Gynecol. 149:492–5
153. Fetherston C (2001) Mastitis in lactating women: physiology or pathology? Breastfeed Rev. 9:5–12
154. Walsh A. Acute mastitis. Lancet. 1949;(2):635–9
155. Livingstone VH, Willis CE, Berkowitz J (1996) *Staphylococcus aureus* and sore nipples. Can Fam Physician. 42:654–9
156. Livingstone V, Stringer LJ (1999) The treatment of *Staphylococcus aureus* infected sore nipples: a randomized comparative study. J Hum Lact. 15:241–6
157. Hughes LE, Mansel RE, Webster DJT (1989) Infection of the breast. In: Hughes LE, Mansel RE, Webster DJT (eds) Benign disorders and diseases of the breast: concepts and clinical management. Bailliere Tindall, London, pp 143–50
158. Amir LH, Forster DA, Lumley J et al (2007) A descriptive study of mastitis in Australian breastfeeding women: incidence and determinants. BMC Public Health. 7:62
159. Hayes R, Michell M, Nunnerley HB (1991) Acute inflammation of the breast – the role of breast ultrasound in diagnosis and management. Clin Radiol. 44:253–6
160. Christensen AF, Al-Suliman N, Nielson KR et al (2005) Ultrasound-guided drainage of breast abscesses: results in 151 patients. Br J Radiol. 78:186–8
161. Ulitzsch D, Nyman MKG, Carlson RA (2004) Breast abscess in lactating women: US-guided treatment. Radiology. 232:904–9
162. Woolridge MW, Ingram JC, Baum JD (1990) Do changes in pattern of breast usage alter the baby's nutrient intake? Lancet. 336:395–7
163. van Veldhuizen CGA (2007) Overabundant milk supply: an alternative way to intervene by full drainage and block feeding. Int Breastfeed J. 2:11
164. Campbell SH (2006) Recurrent plugged ducts. J Hum Lact. 22:340–3
165. Bertrand H, Rosenblood LK (1991) Stripping out pus in lactational mastitis: a means of preventing breast abscess. Can Med Assoc J. 145:299–306
166. Dixon JM (1988) Repeated aspiration of breast abscesses in lactating women. Br Med J. 297:1517–8
167. World Health Organization. Mastitis: Causes and Management: WHO/FCH/ CAH/00.13, Geneva; 2000
168. Ramsay DT, Kent JC, Owens RA et al (2004) Ultrasound imaging of milk ejection in the breast of lactating women. Pediatrics. 113:361–7
169. Arsenault G. Toxic shock syndrome associated with mastitis. Can Fam Physician. 1992;38:399, 401, 456
170. Ferrari C, Piscitelli G, Crosignani PG (1995) Cabergoline: a new drug for the treatment of hyperprolactinaemia. Hum Reprod. 10:1647–52
171. Langton D, Ramsay D, Jacobs S, et al. Efficacy of frenulotomy for ankyloglossia in breast-fed infants. Perinatal Society of Australia and New Zealand 8th Annual Congress. Sydney, Australia; 2004. p. 44
172. Watson Genna C, Sandora L (2008) Normal sucking and swallowing. In: Watson Genna C (ed) Supporting sucking skills in breastfeeding infants. Jones and Bartlett, Sudbury, Massachusetts, pp 1–41
173. Woolridge MW (1986) Aetiology of sore nipples. Midwifery. 2:172–6
174. Gunther M (1945) Sore nipples: causes and prevention. Lancet. 2:590–3
175. McClellan H, Geddes D, Kent J et al (2008) Infants of mothers with persistent nipple pain exert strong sucking vacuums. Acta Paediatr. 97(9):1205–9
176. Danner SC (1992) Breastfeeding the infant with a cleft defect. NAACOGS Clin Issu Perinat Womens Health Nurs. 3:634–9
177. Lalakea ML, Messner AH (2003) Ankyloglossia: does it matter? Pediatr Clin N Am. 50:381–97
178. Sharp DA (1992) Moist wound healing for sore or cracked nipples. Breastfeed Abstr. 12:1
179. Amir L (2002) Breastfeeding and *Staphylococcus aureus*: three case reports. Breastfeed Rev. 10:15–8
180. Amir LH, Pakula S (1991) Nipple pain, mastalgia and candidiasis in the lactating breast. Aust N Z J Obstet Gynaecol. 31:378–80
181. Francis-Morrill J, Heinig MJ, Pappagianis D et al (2004) Diagnostic value of signs and symptoms of mammary candidosis among lactating women. J Hum Lact. 20: 288–95
182. Morrill JF, Heinig MJ, Pappagianis D et al (2005) Risk factors for mammary Candidosis among lactating women. JOGNN. 34:37–45
183. Dinsmoor MJ, Viloria R, Lief L et al (2005) Use of intrapartum antibiotics and the incidence of postnatal maternal and neonatal yeast infections. Obstet Gynecol. 106:19–22
184. Amir LH, Garland SM, Dennerstein L et al (1996) *Candida albicans*: is it associated with nipple pain in lactating women? Gynecol Obstet Invest. 41:30–4
185. Brent NB (2001) Thrush in the breastfeeding dyad: results of a survey on diagnosis and treatment. Clin Pediatr (Phila). 40:503–6
186. The Royal Women's Hospital. Clinical Practice Guideline: Thrush in lactation. 2005 [cited; Available from: http://www.thewomens.org.au/ThrushinLactation
187. Utter AR (1990) Gentian violet treatment for thrush: can its use cause breastfeeding problems. J Hum Lact. 6:178–80
188. Huggins KE, Billon SF (1993) Twenty cases of persistent sore nipples: collaboration between lactation consultant and dermatologist. J Hum Lact. 9:155–60
189. Amir LH (1993) Eczema of the nipple and breast: a case report. J Hum Lact. 9:173–5

190. Whitaker-Worth DL, Carlone V, Susser WS et al (2000) Dermatologic diseases of the breast and nipple. J Am Acad Dermatol. 43:733–51
191. Webster DJT (2000) Disorders of the nipple and areola. In: Hughes LE, Mansel RE, Webster DJT (eds) Benign disorders and diseases of the breast. Concepts and clinical management. WB Saunders, London, pp 199–208
192. Lawlor-Smith L, Lawlor-Smith C (1996) Raynaud's phenomenon of the nipple: a preventable cause of breastfeeding failure? Med J Aust. 166:448
193. Anderson JE, Held N, Wright K (2004) Raynaud's phenomenon of the nipple: a treatable cause of painful breastfeeding. Pediatrics. 113:e360–4
194. Garrison CP (2002) Nipple vasospasms, Raynaud's syndrome, and nifedipine. J Hum Lact. 18:382–5
195. Riordan J, Auerbach KG (1999) Breastfeeding and human lactation., 2nd edn. Jones and Bartlett, Boston
196. Jelliffe DB, Jelliffe EFP (1972) Non-puerperal induced lactation (Letter). Pediatrics. 50:170–1
197. Auerbach KG, Avery JL (1981) Inducted lactation: a study of adoptive nursing by 240 women. Am J Dis Child. 135: 340–3
198. Walker M, Auerbach KG (1999) Breast pumps and other technologies. In: Riordan J, Auerbach KG (eds) Breastfeeding and human lactation. Jones and Bartlett, Boston, pp 279–332
199. Goldfarb L. Inducing lactation www.asklenore.com. 2007 [cited; Available from: www.asklenore.com
200. Newman J, Goldfarb L. Newman-Goldfarb protocols for induced lactation: decision tool (Poster). International Society for Research in Human Milk and Lactation. Perth, Australia; 2008
201. Jiménez-Jiménez JR, García-Ruiz PJ, Molina JA (1997) Drug-induced movement disorders. Drug Saf. 16:180–204
202. Phillips V (1993) Relactation in mothers of children over 12 months. J Trop Pediatr. 39:45–8
203. Hale TW, Kristensen JH, Ilett KF (2007) The transfer of medications into human milk. In: Hale TW, Hartmann P (eds) Textbook of human lactation. Hale, L. P, Amarillo, Texas, pp 465–77
204. Spencer JP, Gonzalez LSI, Barnhart DJ (2001) Medications in the breast-feeding mother. Am Fam Physician. 64: 119–26
205. American Academy of Pediatrics Committee on Drugs (2001) Transfer of drugs and other chemicals into human milk. Pediatrics. 108:776–89
206. Amir L (2007) Medicines and breastfeeding: information is available on safe use (Letter). Med J Aust. 186:485

Evaluation of a Breast Mass

6

Alastair M. Thompson, Alan M. Cook, Jean McCulloch, Gillian Little, and Denis McLean

6.1 Introduction

Breast lumps are common in women of all ages and may present to the medical profession through a range of routes including:

- A symptomatic breast lump detected by the patient or her partner.
- A breast lump detected on incidental examination by a clinical practitioner or through breast screening.

A breast mass in a man, gynaecomastia, is usually secondary to systemic disturbance or medication or, more rarely, male breast cancer [1].

The breast is an adapted sweat gland subject, in the adult female, to cyclical changes under the influence of oestrogen, progesterone and other hormones; thus, the breast not only changes on a monthly basis during the reproductive years but also over a woman's lifetime. The internal architecture of the breast comprises glandular, stromal and adipose tissues based on the anterior chest wall. The arterial blood supply is from the axillary vessels, the internal mammary artery and intercostal perforating vessels with lymphatic drainage primarily to the axillary lymph nodes.

The diagnosis of a breast mass should be on the basis of *triple assessment*, namely clinical (history and examination), imaging (usually mammography and/or ultrasound) and cytopathological diagnosis (cytology or histology). Applying the use of triple assessment aims to minimise the impact of any one method of diagnosis being less than 100% sensitive and 100% specific to diagnose or exclude breast cancer; combining the three modalities means that only 1 in 500 cancers may be missed.

This chapter focuses on the evaluation of a breast mass in women from the viewpoint that a woman with a breast lump will usually consider the lump to be a cancer until proven otherwise. In well-organised health care settings, full assessment and confident diagnosis can be achieved as a single "one stop" service. The approach presented therefore aims to establish or exclude the presence of breast cancer and thereafter define the nature of and treat, where required, any benign lesion identified. This model of assessment of a breast mass requires multi-disciplinary input from breast clinicians, nursing, imaging, pathology and technical and administrative staff working as a team.

6.2 Routes of Presentation

6.2.1 Symptomatic Breast Mass

Most commonly, a female patient or her partner finds a new lump in one or both breasts. Due to the high level of publicity about breast lumps, the patient will often be concerned that she has breast cancer and therefore seek rapid review: in some healthcare settings, this will be to a qualified doctor and in others, a qualified nurse. However, whatever the route of self-presentation, timely review in order to minimise the duration of anxiety is desirable. In some countries, there are official targets, which stipulate that women should be seen at a specialist breast clinic, for example, within 2 weeks of presenting to a healthcare professional. The efficacy of

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_6, © Springer-Verlag Berlin Heidelberg 2010

this approach is unproven and indeed may skew the service provision. Similarly, encouraging regular breast self-examination may not improve early detection of breast cancers, but continues to be promoted in much of the Western media. Instead, many organisations promote breast awareness among women, with the hope that breast cancer will be detected as a change in the breast at an early stage.

6.2.2 Screening

Building on three decades of experience in the Scandinavian countries and in North America, a number of countries currently have screening for breast cancer, usually in the form of mammographic screening. National screening programmes may be based on both efficacy and financial considerations, for example in the UK, the target group for the national breast screening programme are women of 50–70 years and screening comprises two-view mammography every 3 years.

In young women with a family history or inherited pre-disposition to cancer, MRI is increasingly being used and now has an evidence base for detecting breast cancers at an early stage.

6.2.3 Incidental Detection of the Breast Mass on Clinical Examination

This is more frequently a route of presentation in the elderly population. Thus, it may be considered good practise that women over the age of 50 undergoing general physical examination should have a routine breast examination. Certainly, on admission to hospital, all women should have breast examination, and this may detect either an incidental breast cancer or the cause of symptoms elsewhere in the body.

6.3 History of Presentation

The single best predictor of the probable underlying pathology of a breast mass or breast lump is the age of the patient (Table 6.1). Benign causes of a breast mass are most common at a young age, and breast cancer is increasingly common with age, particularly over the age of 65 years.

The presenting features of a lump (Table 6.2), as noted by the woman or her medical examiner, should include a number of key features, which may give some hints as to the underlying pathology. These include whether the lump is single or multiple and any changes in the lump since first noticed (for example with the menses).

While associated features are sought (Table 6.3), if present, they often reflect a more advanced breast cancer. Bleeding from the nipple (Fig. 6.1), indrawing of the nipple (Fig. 6.2), eczema of the nipple or areolar (which may be eczema or intraepithelial malignancy – Paget's disease of the nipple) changes in the skin (erythema, peau d'orange – the appearance of the breast skin like that of an orange due to skin oedema), skin nodules (Fig. 6.3) and enlarged axillary lymph nodes (Fig. 6.3) may be less common than they once were, but it is important that these features are sought.

Other relevant findings include an endocrine history, including hormone replacement therapy or contraceptive usage, gynaecological history, family history and other medical/surgical history. The relevant features of the patient's history may be best recorded using a set proforma in the clinic (for example Fig. 6.4),

Table 6.1 Patient age and likely diagnosis of a breast mass

Age (years)	Features	Diagnosis	Treatment
15–70	Poorly defined lumpiness; may change with menses	Benign changes "fibrocystic"	Reassurance
15–30	Smooth mobile lump: usually single	Fibroadenoma	Excision if patient requests
35–55	Well circumscribed lump(s), usually multiple	Cyst(s)	Aspiration
20–55	Painful, red, hot lump	Abscess	Drainage
40–90	Ill-defined craggy lump	Cancer	Dependent on staging

Table 6.2 Presenting features of a breast lump – questions to ask

One lump or more than one lump?
Where is the lump?
How big is the lump?
Is it sore/tender/painful?
Is the lump hard or soft?
Does the lump change with the menses?
Are there any other features of the lump Skin changes Nipple indrawing Nipple discharge One or multiple ducts Blood stained or not Is it mobile in the breast? Is the lump fixed to the skin or chest wall?
Are there problems in the other breast?
Have you had a breast lump before?
Are there lumps elsewhere in the body?

Table 6.3 Associated features of a breast lump

Skin changes Erythema Peau d'orange Skin tethering/puckering Eczematous appearance Ulceration
Nipple discharge
Nipple retraction/flattening
Pain (on palpation, all the time)
Palpable axillary lymph nodes

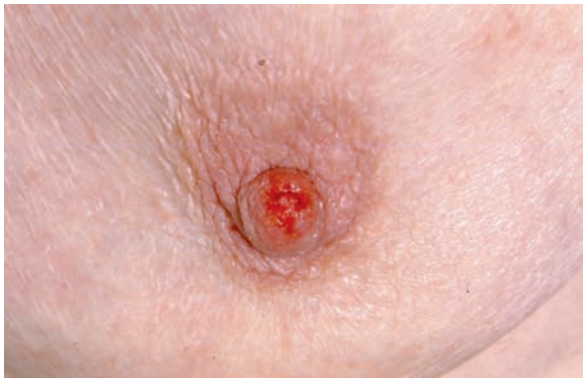


Fig. 6.1 Bleeding nipple discharge. The discharge should be examined for the number of ducts from which it emanates, and the discharge assessed for cytology or the presence of blood as appropriate

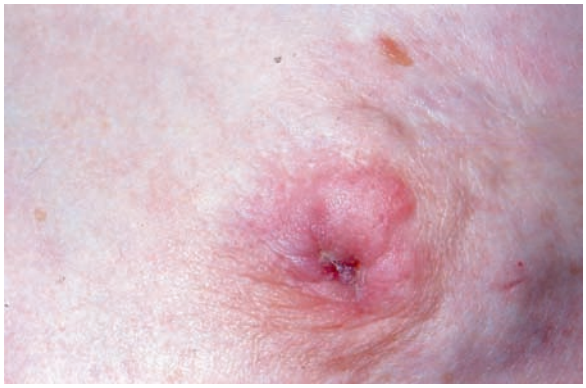


Fig. 6.2 Nipple retraction due to cancer; note the small core needle biopsy scar to the right of the areolar

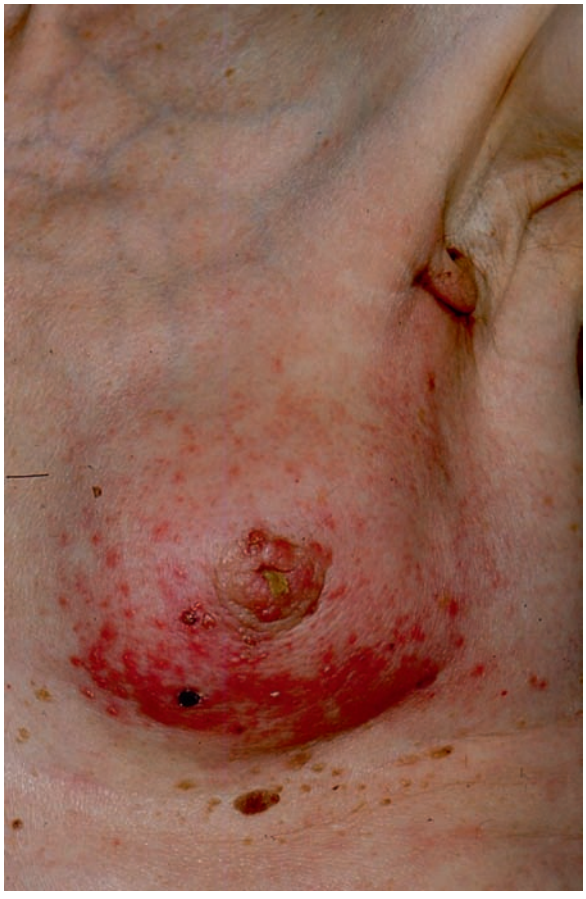
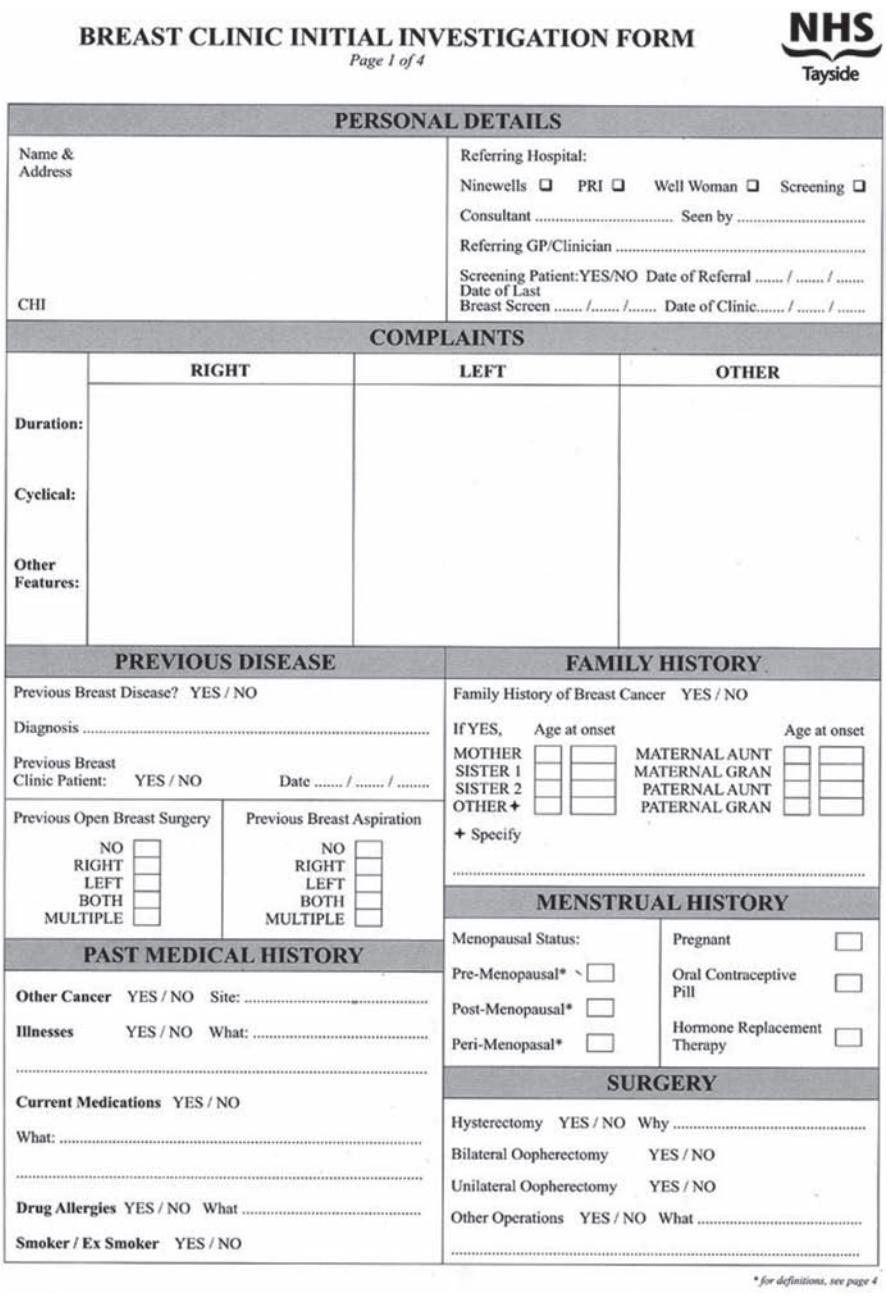


Fig. 6.3 Skin nodules from advanced breast cancer overlying a breast mass; a nodal mass is also visible in the axilla



BREAST CLINIC INITIAL INVESTIGATION FORM

Page 1 of 4

NHS Tayside

PERSONAL DETAILS

Name & Address

CHI

Referring Hospital:

Ninewells ☐ PRI ☐ Well Woman ☐ Screening ☐

Consultant ..... Seen by .....

Referring GP/Clinician .....

Screening Patient:YES/NO Date of Referral ..... / ..... / .....

Date of Last Breast Screen ..... /..... /..... Date of Clinic..... / ..... / .....

COMPLAINTS

	RIGHT	LEFT	OTHER
Duration:			
Cyclical:			
Other Features:			

PREVIOUS DISEASE

Previous Breast Disease? YES / NO

Diagnosis .....

Previous Breast Clinic Patient: YES / NO Date ..... / ..... / .....

Previous Open Breast Surgery

NO ☐
RIGHT ☐
LEFT ☐
BOTH ☐
MULTIPLE ☐

Previous Breast Aspiration

NO ☐
RIGHT ☐
LEFT ☐
BOTH ☐
MULTIPLE ☐

PAST MEDICAL HISTORY

Other Cancer YES / NO Site: .....

Illnesses YES / NO What: .....

.....

Current Medications YES / NO

What: .....

.....

Drug Allergies YES / NO What .....

Smoker / Ex Smoker YES / NO

FAMILY HISTORY

Family History of Breast Cancer YES / NO

If YES, Age at onset

MOTHER ☐ ☐
SISTER 1 ☐ ☐
SISTER 2 ☐ ☐
OTHER + ☐ ☐

Age at onset

MATERNAL AUNT ☐ ☐
MATERNAL GRAN ☐ ☐
PATERNAL AUNT ☐ ☐
PATERNAL GRAN ☐ ☐

+ Specify

.....

MENSTRUAL HISTORY

Menopausal Status:

Pre-Menopausal* ☐
Post-Menopausal* ☐
Peri-Menopasal* ☐

Pregnant ☐

Oral Contraceptive Pill ☐

Hormone Replacement Therapy ☐

SURGERY

Hysterectomy YES / NO Why .....

Bilateral Oopherectomy YES / NO

Unilateral Oopherectomy YES / NO

Other Operations YES / NO What .....

.....

** for definitions, see page 4*

Fig. 6.4 Proforma for recording the relevant clinical history used in everyday practise. Note the CHI (community health index) is the unique patient identifier from which the patient's age can be deduced

where the key features of the patient's presenting history and past medical history can be readily reviewed.

6.4 Clinical Examination

Clinical examination should aim to discern how many lumps there are, the nature of the mass and any associated features. It is important for the practitioner to seek permission from the woman to conduct a bilateral breast examination and, particularly for male practitioners, to have a female chaperone available. Breast examination is considered by many authorities to be an intimate physical examination and each woman should be accorded due respect. The manner in which the breast examination is conducted is important in optimising the detection of abnormalities in the breast [2].

The patient should be naked to the waist in a warm, private, room. Breast examination should be conducted in a logical and sequential fashion so that both the patient and the practitioner are comfortable and any abnormalities will be detected. Care must be taken to examine both breasts in succession, noting differences in symmetry between the two. Usually, the normal breast is best examined first as the appearance and texture of each individual woman's breast can be quite different from other women but is quite likely to be the same as on the contra-lateral side. Initial inspection to look for skin dimpling or changes in the shape of the breast may detect benign lesions such as a fibroadenoma, a cyst or a breast cancer. If no immediately apparent abnormality is detected, it may be appropriate to ask the woman where the mass she feels is located.

Initial inspection may be with the patient sitting in an upright position, hands by her sides (Fig. 6.5). By asking her to raise her hands, clinical abnormalities such as indrawing of skin tethered to a cancer or nipple indrawing may be accentuated (Fig. 6.6). Next, asking the woman to place her hands on her hips and press in (contracting the pectoralis muscles) may accentuate a deeply tethered cancer and hence draw the eye to a tumour.

While obvious abnormalities (Figs. 6.2, 6.3, and 6.5) merit further inspection and palpation with the patient in the upright position, more detailed palpation may be best carried out with the patient lying flat, with one pillow for comfort, on an examination couch. The patient should be asked to raise her arm behind her head to fix the breast in a relatively static position. By palpation using a gentle rotating movement with the flat of the fingers, even small lumps may be detected, using varying degrees of pressure to detect lumps that are lying at different depths in the breast tissue [3]. Using the flattened fingers of one hand and a gentle rotating movement, the whole breast on the normal side (including the retroarolar tissues) may be palpated before moving to the side with a clinical abnormality. Care should be taken to record the position, shape and calliper measurement of the size of the lesion(s) together with any other features (tender, red, single or multiple etc). Clinical examination has a 54% sensitivity to detect (rule out) breast cancer and a 94% specificity to rule in breast cancer [3].

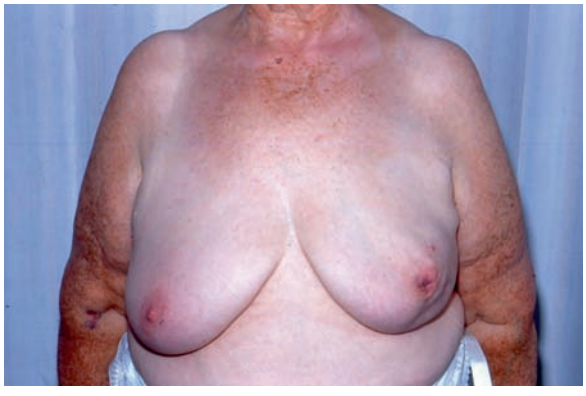


Fig. 6.5 *Left* breast cancer: nipple retraction and skin tethering

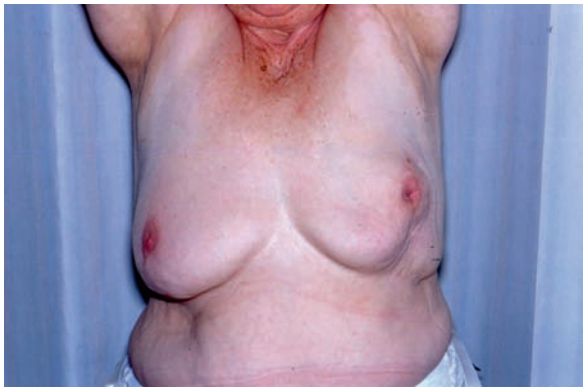
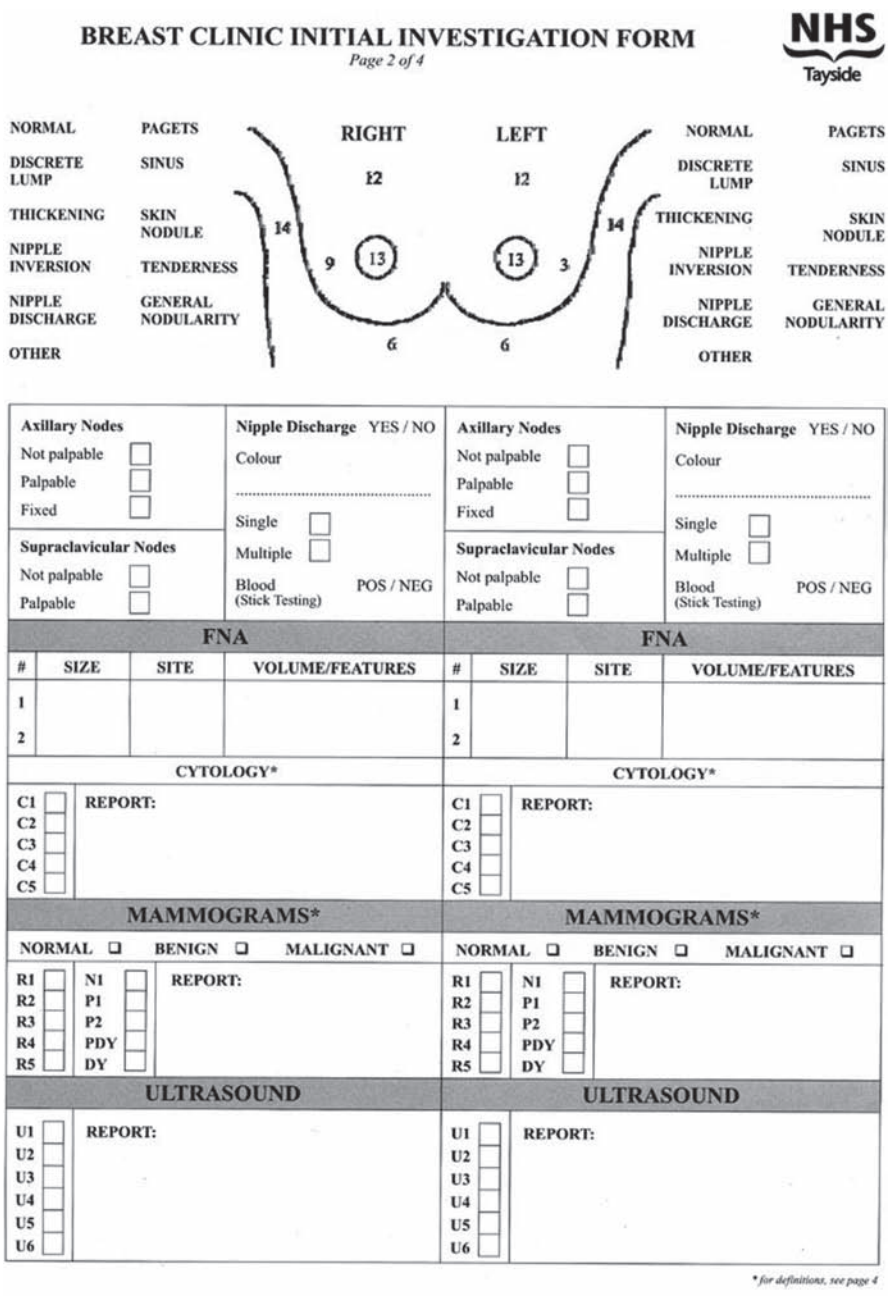


Fig. 6.6 *Left* breast cancer: skin effects seen in Fig. 6.5 are more prominent as the arms are raised

In patients with a history of nipple discharge, the patient may be asked to elicit the discharge by pressing on the nipple or areolar, thus avoiding the practitioner hurting the patient. The number of ducts producing a discharge (single or multiple?), the colour of the discharge (is it milky?, is it obviously blood stained? Fig. 6.1) and testing for blood using urinary dip sticks may all be noted.

Following breast examination, bilateral axillary examination should be performed on each side in turn. This may be most readily accomplished by asking the patient to sit up, and for the examination of the right axilla, the practitioner takes the patient's right forearm, supporting the weight of the forearm to relax the axilla. Using the fingers of the practitioner's left hand, the walls of the axilla and the apex of the axilla can be gently palpated and any lumps and their consistency noted. A similar arrangement can be used for the left axilla (the practitioner taking the patients left forearm in his or her left hand and examining the axilla with the fingers of the right hand). Thereafter, the infraclavicular, supraclavicular and cervical lymph nodes should be examined for lymphadenopathy and



BREAST CLINIC INITIAL INVESTIGATION FORM

Page 2 of 4

NHS Tayside

NORMAL · PAGETS · DISCRETE LUMP · SINUS · THICKENING · SKIN NODULE · NIPPLE INVERSION · TENDERNESS · NIPPLE DISCHARGE · GENERAL NODULARITY · OTHER

RIGHT LEFT

12 12 14 14 9 13 13 3 6 6

Axillary Nodes	Nipple Discharge YES / NO	Axillary Nodes	Nipple Discharge YES / NO
Not palpable ☐	Colour	Not palpable ☐	Colour .....
Palpable ☐	Single ☐	Palpable ☐	Single ☐
Fixed ☐	Multiple ☐	Fixed ☐	Multiple ☐
Supraclavicular Nodes	Blood (Stick Testing) POS / NEG	**Supraclavicular Nodes**	Blood (Stick Testing) POS / NEG
Not palpable ☐		Not palpable ☐	
Palpable ☐		Palpable ☐	

FNA

#	SIZE	SITE	VOLUME/FEATURES
1			
2			

CYTOLOGY*

C1 ☐ C2 ☐ C3 ☐ C4 ☐ C5 ☐ REPORT:

MAMMOGRAMS*

NORMAL ☐ BENIGN ☐ MALIGNANT ☐

R1 ☐ R2 ☐ R3 ☐ R4 ☐ R5 ☐ N1 ☐ P1 ☐ P2 ☐ PDY ☐ DY ☐ REPORT:

ULTRASOUND

U1 ☐ U2 ☐ U3 ☐ U4 ☐ U5 ☐ U6 ☐ REPORT:

** for definitions, see page 4*

Fig. 6.7 Proforma for recording the relevant examination findings and investigations (continuation of the proforma shown in Fig. 6.4)

any findings recorded on the clinic examination sheet (Fig. 6.7).

6.5 Investigation

Investigation of a breast mass may be conducted and recorded (Fig. 6.7) following clinical history and examination using imaging and, ideally, before fine needle aspiration cytology or core biopsy as these latter interventions may cause bruising, which, in turn, makes it more difficult to interpret the imaging appearances.

6.6 Imaging

Standard initial imaging is to use bilateral two-view mammography (craniocaudal (Fig. 6.8) and mediolateral oblique (Fig. 6.9) views), with additional coned

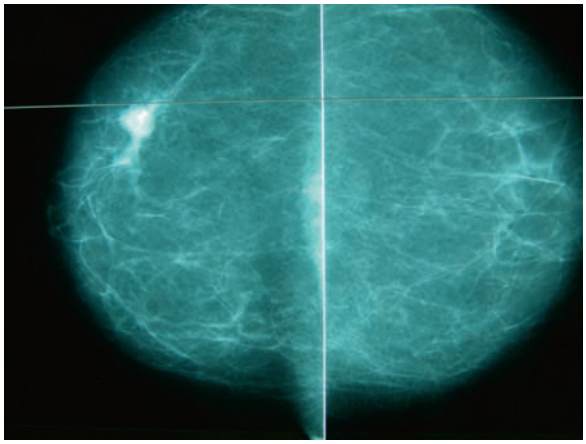


Fig. 6.8 Craniocaudal mammograms showing a *right* breast cancer as a stellate lesion, which was clinically palpable. The horizontal guide line allows ready comparison between the two breasts

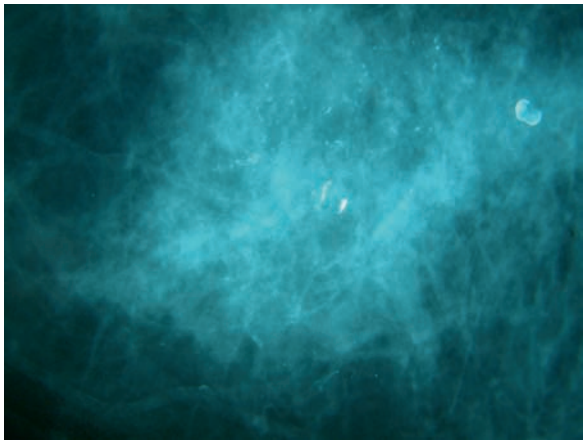


Fig. 6.10 Magnification views of a breast mass showing the microcalcifications associated with ductal carcinoma in situ

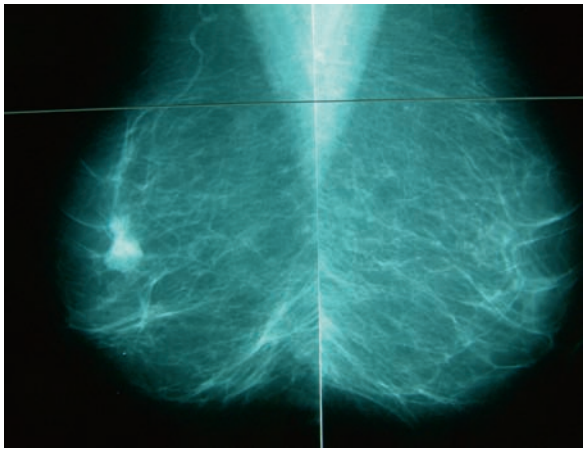


Fig. 6.9 Medio-lateral oblique views of the same patient as in Fig. 6.8

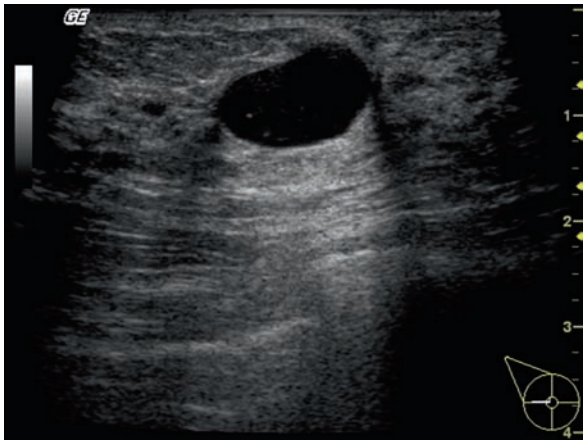


Fig. 6.11 Ultrasound of a breast cyst: note the smooth outline, fluid filled lesion

or magnified views (Fig. 6.10) of any abnormality as appropriate for women aged 35 years and older, and ultrasound as the primary imaging modality for women younger than 35 years. This somewhat arbitrary cut off is based on the higher breast density in younger women, which may make it difficult to detect even quite a large cancer; with increasing age, the breast parenchyma is replaced by fatty tissue and breast cancer becomes easier to detect in the older breast. Pre-menopausal women should confirm they are not pregnant before undergoing mammography, although the likelihood of causing harm to a foetus is low. Ultrasound may be used to supplement mammography in the older age group and, similarly, if ultrasound detects what appears to be a malignant lesion in a younger women, or clinical suspicion persists, then mammography should be performed.

6.7 Breast Ultrasound

Ultrasound is performed using warmed gel as a contact between the probe and the patient's breast. It will detect one or more lesions and may accurately measure a breast mass in multiple dimensions. Ultrasound can identify whether a breast mass is cystic (Fig. 6.11) or solid (Fig. 6.12), may identify multiple pathologies

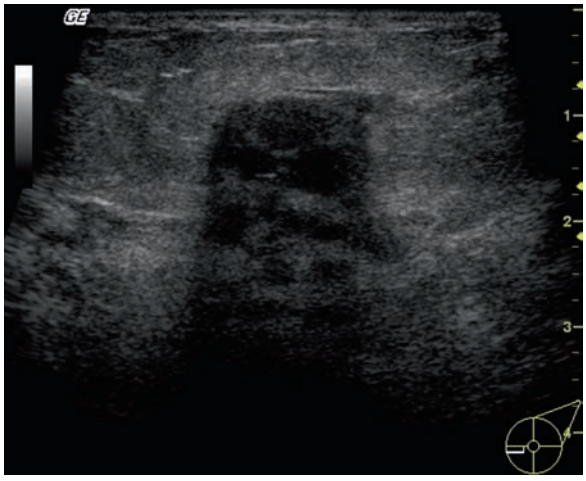


Fig. 6.12 Ultrasound of a breast cancer: note the irregular margin and dense acoustic shadow in contrast to Figs. 6.11 and 6.15

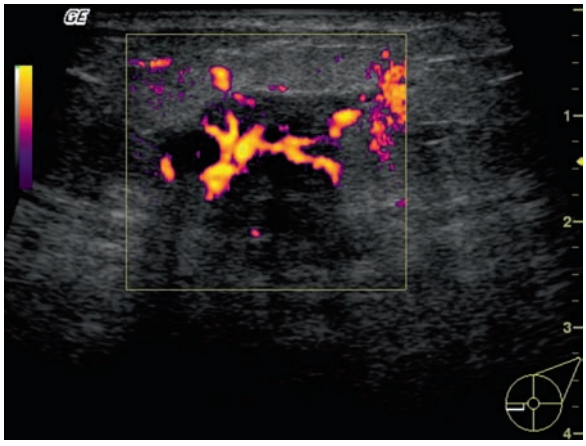


Fig. 6.14 Ultrasound of a breast cancer demonstrating the vascularity of the cancer

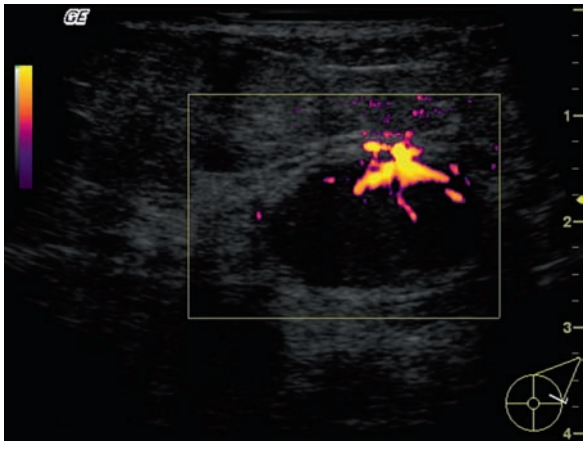


Fig. 6.13 Ultrasound of a breast cyst within which there is an intracystic tumour (vascularity demonstrated using Doppler as white branched signal within the cyst; using false colour Doppler will demonstrate the vascularity even more prominently)

Table 6.4 Ultrasound classification for breast masses

Code	Description
U1	Normal diffuse benign
U2	Single cyst
U3	Solid benign
U4	Suspicious of malignancy
U5	Malignant
U6	Multiple cysts

(e.g. an intracystic cancer Fig. 6.13) and can also be used to demonstrate blood flow and vascularity in a breast mass (Fig. 6.14). The ultrasound appearances can be categorised for reporting (Table 6.4).

Ultrasound is particularly useful to delineate cysts (Fig. 6.11) and subsequently direct and confirm the drainage of the cyst. It can also be extremely useful to delineate a fibroadenoma (Fig. 6.15). The typical picture of a carcinoma with an irregular border and casting an acoustic shadow (Fig. 6.12) is usually quite different to a fibroadenoma (Fig. 6.15) and cysts (Fig. 6.11), and makes ultrasound useful in the clinic to indicate the likely pathology of a lump. However, high grade carcinoma and an older or cellular fibroadenoma can appear quite similar, emphasising the need for needle sampling of such lesions.

Ultrasound can also be used to examine the axilla for lymph node involvement with metastasis (Fig. 6.16), and in combination with fine needle aspiration cytology or core biopsy (see below), it can be quite sensitive at detecting malignant lymphandenopathy.

6.8 Mammography

Mammography may suggest the nature of a breast mass as benign (e.g. breast cysts: smooth outlines with multiple masses visible; Fig. 6.17) or malignant (stellate mass with irregular outline; Figs. 6.8 and 6.9). Mammography is increasingly sensitive with the increasing age of a woman.

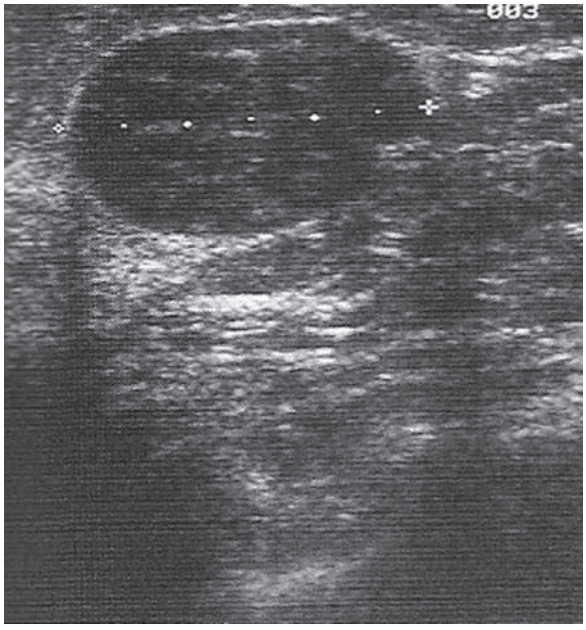


Fig. 6.15 Ultrasound of a fibroadenoma; note the ovoid appearance with the long axis (being measured here) parallel to the skin surface and the well-defined acoustic shadow from the edges of the lesion. Contrast the appearances to those of Fig. 6.12

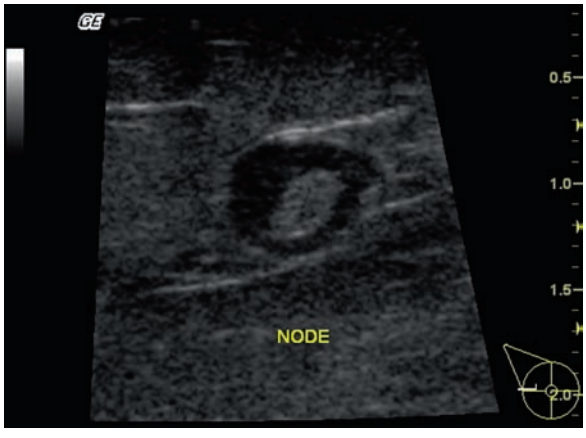


Fig. 6.16 Ultrasound of a malignant axillary lymph node

An abnormality on the mammograms should be visible in two dimensions (Figs. 6.8 and 6.9), but finer details such as microcalcification may require magnification views (Fig. 6.10) and may or may not correspond to a palpable abnormality. While such fine details may indicate a benign or malignant (Fig. 6.10) pathology, further localisation and investigation will be required. Whatever the findings, they can be annotated for future reference and reporting (Table 6.5).

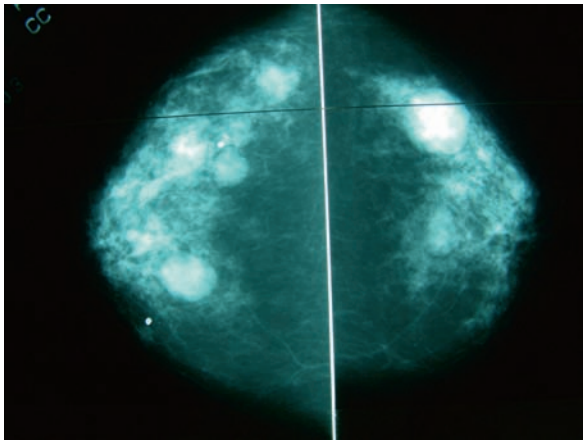


Fig. 6.17 Bilateral cysts on craniocaudal mammograms

Table 6.5 Mammographic appearances of the breast

Code	Description
R1	Normal
R2	Benign
R3	Indeterminate
R4	Probably malignant
R5	Malignant

Breast ultrasound and mammography are the mainstays of radiological evaluation of a breast mass and may be conducted at the time of clinical history and examination to allow progress to needle biopsy of a lesion as part of a one-stop diagnostic breast clinic.

6.9 Magnetic Resonance Imaging (MRI)

Recently, magnetic resonance imaging (MRI) has been increasingly adopted [4], particularly where mammography and ultrasound are inconclusive or to image the breast in the presence of silicone implants and in screening women with a genetically high risk of breast cancer. MRI can also be used to distinguish single from multi-focal lesions for women with breast cancer looking towards breast conservation, although not usually available at the time of initial consultation. In addition to pre-operative assessment, MRI may provide useful information (Figs. 6.18–6.20) on the extent, size, multi-focality, invasion into adjacent structures

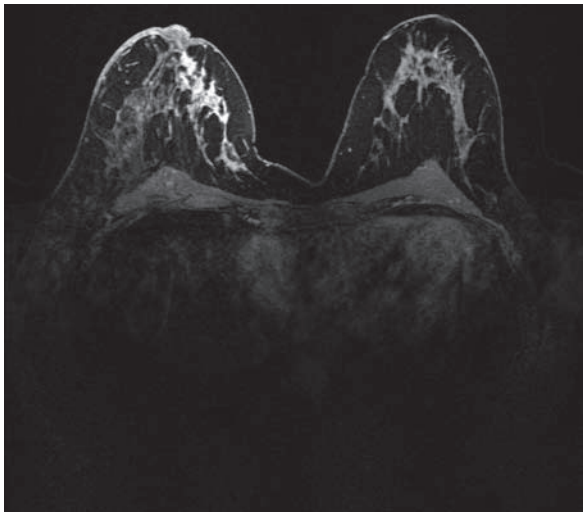


Fig. 6.18 MRI demonstrating mass secondary to DCIS (*left* half of figure)

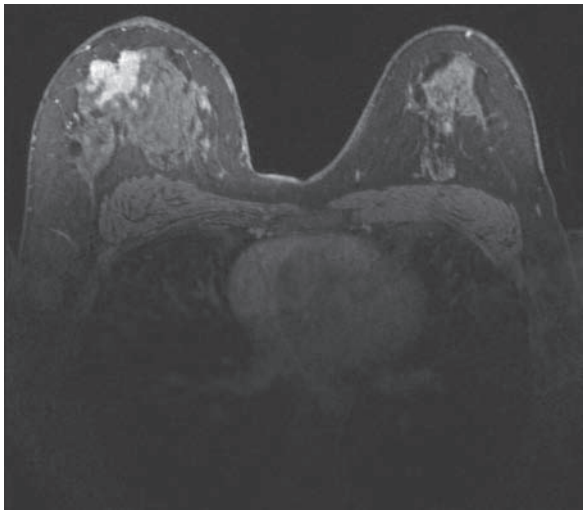


Fig. 6.19 MRI of invasive breast cancer (*left* half of figure)

and presence of more extensive DCIS than mammographically evident.

6.10 Other Imaging Techniques

Positron emission tomography combined with computerised tomography (PET/CT) may be performed as an investigation for breast cancer either to obtain

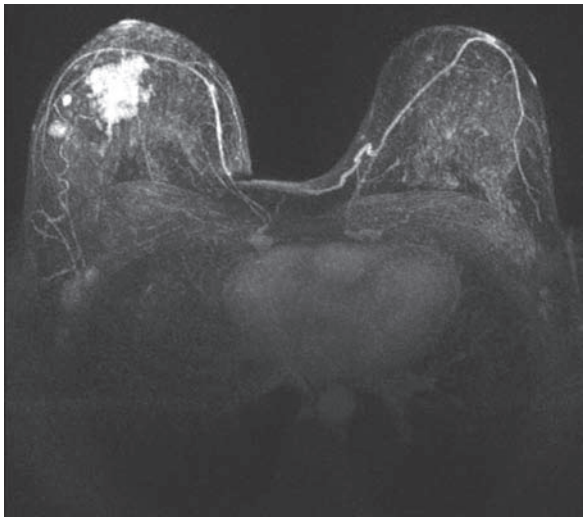


Fig. 6.20 Early enhancement of MRI of patient in Fig. 6.19 demonstrating multi-focality

functional imaging as a baseline for subsequent therapy or as part of whole body imaging for metastatic disease. Although the radiation dosages and access to such facilities at present limit their use, they may well play a role in future in the evaluation of a breast mass or in the evaluation of axillary lymph nodes for metastatic disease.

6.11 Pathology Diagnosis

The third component of triple assessment after clinical history/examination and imaging is cytological or histopathological diagnosis.

Fine needle aspiration cytology is useful to determine the nature of a breast mass (and indeed may also be therapeutic for a cyst) and has an overall sensitivity and specificity to detect 93% of cancers [5]. However, rare false positives (1/500) do occur usually with fibroadenoma or pregnant/lactating breast samples. Fine needle aspiration cytology is conducted by using a blue (23 gauge) needle and 5–10 mL syringe flushed with heparin placed into the breast mass. Either through localising a palpable mass with the fingers of one hand and directing the needle into the lump using clinical experience (Fig. 6.21) or, for impalpable lesions, using guidance with ultrasound or stereotactic localisation, the needle is introduced into the lesion.

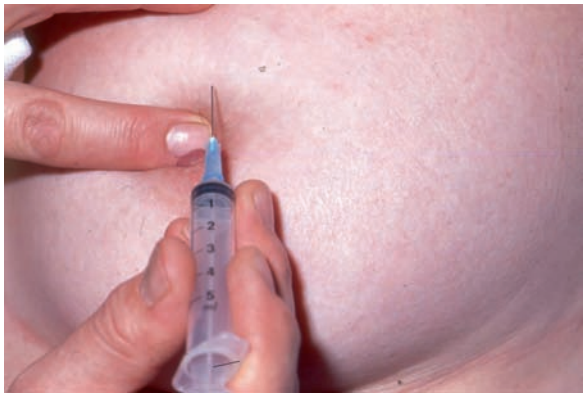


Fig. 6.21 Approach to fine needle aspiration cytology: lesion stabilised between the operator's fingers and the 21 g needle introduced through alcohol swabbed skin parallel to the chest wall (to minimise the chance of pneumothorax)

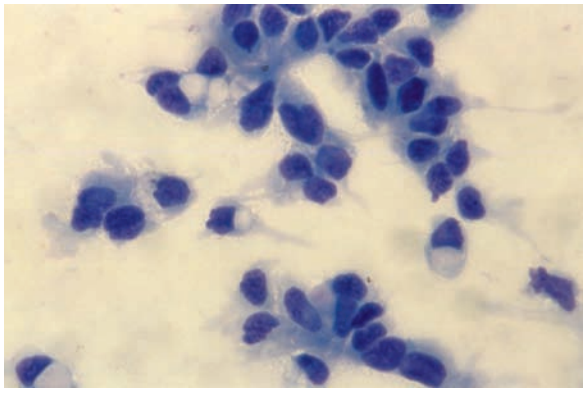


Fig. 6.22 Example of malignant (C5) cytology; note the pleomorphism, densely stained nuclei and dyscohesive cells

Care should be taken when conducting the fine needle aspiration under ultrasound guidance as the ultrasound contact gel can distort appearances of the cellular aspirate. With slight suction and 12–20 passages through the breast mass, a small amount of material can be aspirated into the hollow needle and subsequently spread onto a slide. Following staining, a skilled cytologist can, within a 10–15 min turn-around time, determine whether or not there are malignant cells present in the aspirate (Fig. 6.22). The cytology can be reported on a scale of one (insufficient material or acellular aspirate) to five (malignant) (Table 6.6). If necessary, the fine needle aspirate can be repeated to establish the diagnosis using a fresh needle/syringe combination; however, if the first needle aspirate is unsatisfactory, most practitioners will proceed to core biopsy.

Table 6.6 Cytology scoring for breast cytology

Code	Description
C1	Insufficient material for diagnosis
C2	Benign
C3	Atypia, probably benign
C4	Suspicious of malignancy
C5	Malignant

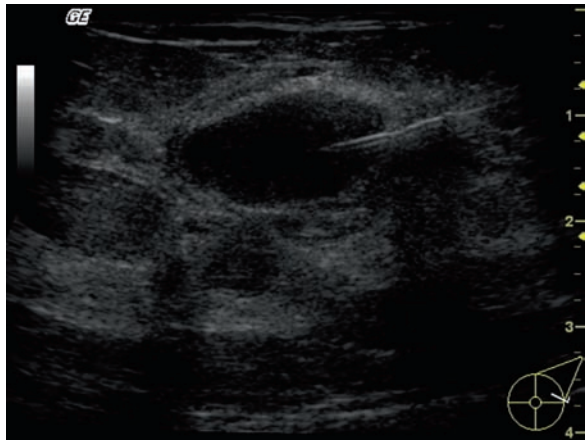


Fig. 6.23 Core needle inserted under ultrasound guidance into a fibroadenoma for histological confirmation of the diagnosis

Ultrasound guidance is particularly useful for core biopsy using a 14 gauge needle, which should be undertaken under local anaesthetic to confirm the diagnosis of a benign lesion such as a fibroadenoma (Fig. 6.23) and thus prevent the need for excisional biopsy. Stereotactically guided core biopsies can take an extremely accurate core sample from lesions with radiological features such as microcalcification and subsequent specimen X-rays can confirm that the microcalcification has been sampled (Fig. 6.24). Core biopsy (95% sensitivity) may be more sensitive than fine needle aspiration cytology (sensitivity 91%) for clinically suspicious masses more than 2 cm in size [6]. More recent vacuum devices usually deployed under radiological guidance (and local anaesthesia) have the advantage of taking multiple relatively large cores of tissue from the same small area and may, under some circumstances, actually be able to excise a lesion completely.

Rarely, it is impossible to establish a diagnosis even with repeated fine needle aspiration cytology or from core biopsy – core biopsy being a pre-requisite before

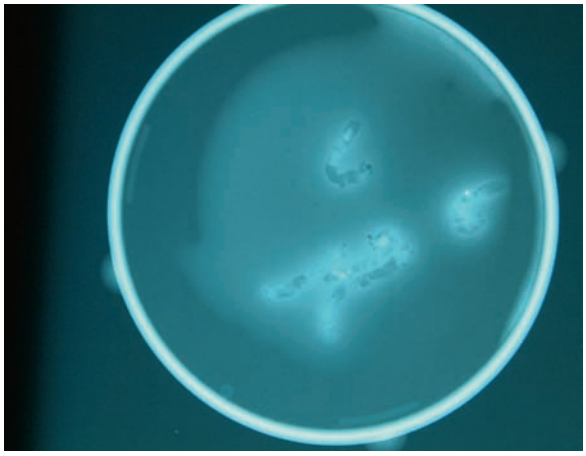


Fig. 6.24 X-ray image of cores from a core biopsy confirming the calcification present in the targeted mass is represented in the cores

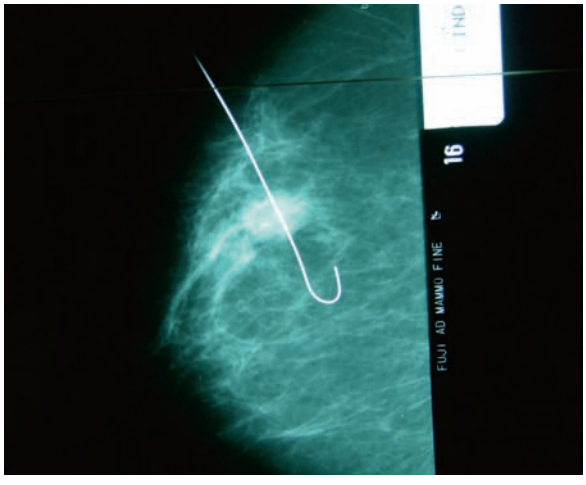


Fig. 6.25 Needle localisation of a breast mass to ensure the correct mass is excised at the time of surgery

mastectomy or axillary clearance is performed. In such circumstances, a diagnostic excisional biopsy of the lump may be considered and may require wire-guided localisation, particularly on the background of a lumpy breast, to ensure that the correct breast mass is excised (Fig. 6.25) so that the diagnosis can be established.

6.12 Patient Plan

Following triple assessment, it is thereafter important to discuss with the patient whether any lump can be left alone, should be excised or whether – if a diagnosis of cancer has been made – staging tests should be performed prior to definitive treatment. These decisions should be formally recorded.

6.13 Benign Breast Masses

The focus of this chapter on malignant breast masses reflects the concerns of patients to exclude cancer and that of clinicians not to miss a cancer. However, benign breast changes and lumps are more common than breast cancer. Approximately only one in ten women attending a symptomatic breast clinic will have a mass that turns out to be malignant, and the management of benign breast masses is also an important component in clinical practise.

The same principles of triple assessment apply to all benign breast masses as to a lump which turns out to be malignant. The features of a benign breast lump can also be described in a similar fashion with associated features noted (Tables 6.1–6.3). Following the diagnosis of a benign breast mass, if no further intervention is required, a written information booklet describing the benign features that can occur in the breast may be helpful to reinforce verbal reassurance. Women should still be encouraged to represent to the service if any new mass appears in future – it is not unknown for a woman to have sought and obtained appropriate reassurance for benign breast changes then at a later date to find a new mass which turns out to be malignant.

6.13.1 Benign Nodularity

Many women notice changes in their breasts on a monthly cycle, but may become worried if lumpiness or a breast mass persists beyond two menstrual cycles (6–8 weeks), particularly if associated with asymmetry between the two sides, even if there is some cyclical change. The history and clinical examination will often point to this variation of normal breast, which is in keeping with the expected responses to endocrine fluctuations on a monthly basis in pre-menopausal women. Pre-menstrual discomfort or pain may also highlight the "normality" of this change. However, even with a low clinical concern on history and

examination, imaging (ultrasound or mammography as first line, dependent on the age of the patient) if necessary supplemented by fine needle aspiration cytology or even core biopsy may be required for reassurance of the patient and clinician. This may be particularly useful if there is a family history of breast cancer or if the patient is anxious about the changes she has noted.

6.13.2 Changes Associated with Pregnancy and Lactation

The breasts undergo enormous physiological and morphological changes during the early stages of pregnancy and these evolve during the postpartum period into the lactating breast. Benign lumpiness is a common feature of the breasts in pregnant women and when breast feeding. However, pathological changes can occur and breast cancer may present as inflammatory breast cancer mimicking an abscess (see below) which, while rare, should be considered. New, focal breast lumps should be investigated by triple assessment (using ultrasound rather than mammography in pregnancy). Lactational cysts are not uncommon and as part of triple assessment, aspiration may lead to resolution of the problem.

6.13.3 Fibroadenoma

An aberration of normal development and involution (ANDI), this smooth, non-tender mobile lump may be single, lobulated or occasionally multiple. Ultrasound as part of triple assessment may identify a typical appearance (Fig. 6.15), although fine needle aspiration cytology can show cytological atypia requiring biopsy. Excision may be considered if the patient wishes.

6.13.4 Phyllodes Tumour

Phyllodes tumour (a biphasic stromal and epithelial lesion) may appear on clinical and imaging evidence to be very similar to a fibroadenoma. However, histology (core biopsy) will demonstrate features ranging from benign, through borderline histology to frankly sarcomatous (hence the former term cystosarcoma phyllodes) or alternatively classed as high or low grade variants. Excision with a margin of normal tissue and follow up for local recurrence for 5 years thereafter is required.

6.13.5 Cysts

One in twelve women develop a symptomatic cyst in their lifetime. A cyst may be single or multiple and both mammography (Fig. 6.17) and ultrasound (Fig. 6.11) are useful in the diagnosis. Aspiration (Fig. 6.26) both establishes the diagnosis and treats the cyst. However, blood in the cyst aspirate or a residual mass may be due to an intracystic cancer (Fig. 6.13), so the remaining lesion will require biopsy; cytology of the cyst aspirate is otherwise unrewarding. Cysts may refill, particularly if not completely aspirated and require repeated aspiration or, occasionally, excision.

6.13.6 Breast Sepsis

A breast abscess presents as a painful red mass, warm to the touch, which may occupy the whole breast. An abscess occurs in two groups of women. In young, breast feeding mothers, Staphlococcus aureus is the usual organism; the abscess usually sits adjacent to the areolar and early intervention with amoxycillin (or erythromycin if penicillin allergic) at the cellulitic stage may prevent formation of an abscess. The differential

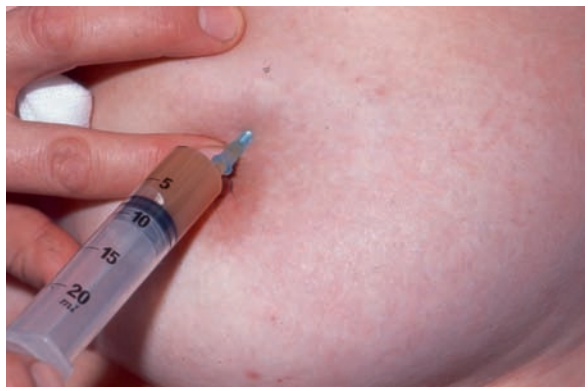


Fig. 6.26 Needle aspiration of a breast cyst yielding typical breast cyst fluid

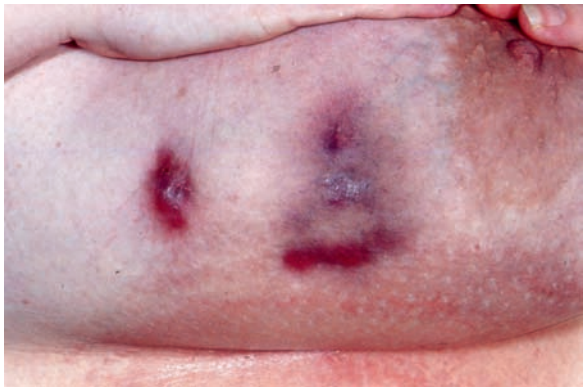


Fig. 6.27 Multiple abscesses and scars in a 50 year old smoker with periductal mastitis for 5 years

diagnosis includes inflammatory breast cancer and so ultrasound evaluation is useful to identify focal pus. Once formed, an abscess may be drained under topical local anaesthesia using aspiration through a wide bore needle (which may need to be repeated) and anti-biotic cover or by formal incision and drainage, particularly if loculated. A subsequent mammary duct fistula may form and require surgical excision. If possible, the mother should be encouraged to continue breast feeding to reduce breast engorgement.

In women aged 35–55, often smokers, multiple abscess formation may occur throughout both breasts (Fig. 6.27) and may not be confined to the nipple areolar area. The process of duct ectasia with enlarged ectatic ducts surrounded by an inflammatory infiltrate may lead to a slit-like nipple retraction (in contrast to the retraction seen with a cancer) and creamy nipple discharge, which may be blood stained. Subsequent inflammatory episodes with periductal mastitis may progress to abscess formation. While the anaerobic bacteria may respond to amoxycillin (or erythromycin and metronidazole) if treatment is commenced early, the repeated development of abscesses, which may require formal drainage, leaves a scarred, often discoloured breast (Fig. 6.27).

6.13.7 Intraduct Papilloma

This may imitate breast cancer by presenting as a blood stained nipple discharge from a single duct (Fig. 6.1). Triple assessment should determine if there is any other pathology and the papilloma may be visible on ultrasound. Cytology of the nipple discharge may reveal papillary clusters of epithelial cells and although ductoscopy has some advocates, excision of the relevant duct under general anaesthesia is advocated to establish the diagnosis and exclude any evidence of malignancy, which may be focal within a papilloma.

6.13.8 Skin Lesions

Skin lesions may occur on the breast as elsewhere in the body. An epidermoid cyst (formerly referred to as sebaceous cyst) may give the impression of a small (usually <1 cm) breast mass; it is usually possible to demonstrate that it is intradermal and there may be a punctum visible that can produce creamy material. Epidermoid cysts are usually located adjacent to the sternum or in the inframammary fold. In contrast, a lipoma is usually 1–4 cm in size, deep to the skin and may require triple assessment to distinguish it from other breast masses. Additional breast tissue in the form of an accessory breast tissue can present as a mass in the axilla or subcutaneous mass just inferior to the breast in the mid clavicular line. Assessment with ultrasound and fine needle aspiration cytology may establish the diagnosis. Accesssory breast tissue rarely requires intervention unless symptomatic.

6.13.9 Fat Necrosis

A woman presenting with a breast mass secondary to fat necrosis is usually suggested by a history of trauma and bruising post injury with a palpable lump, which takes several weeks to resolve. On mammography, fat necrosis may have similar features to a breast cancer with a stellate appearance, but fine needle aspiration cytology will identify foamy macrophages (macrophages filled with fat globules) and, if required, core biopsy will also support the diagnosis.

6.13.10 Other Lesions

Other breast lesions, usually detected by breast screening, such as sclerosing adenosis or a radial scar may

mimic small breast cancers on imaging but rarely present as a palpable breast mass.

In general, surgical excision of benign lumps, if required, should try to use approaches which minimise scarring to the breast, whether conducted under local anaesthetic or general anaesthesia. This includes using a circumareolar incision (with tunnelling to the lesion if required), submammary or axillary approaches. In a larger breast, it may be necessary to cut directly into the breast skin overlying a breast mass and then the skin tension lines of the breast should be used to ensure scars heal with minimal cosmetic deficit.

6.14 Summary

A range of underlying breast pathology can lead to the presentation of a woman with a breast mass. Triple assessment: the history and clinical examination complemented by imaging and cytopathological diagnosis can usually establish the diagnosis and point to appropriate management.

References

1. Niewoehner CB, Schorer AE (2008) Gynaecomastia and breast cancer in men. Brit Med J. 336:709–13
2. Saslow D, Hannan J, Osuch J et al (2004) Clinical breast examination: practical recommendations for optimising performance and reporting. CA Cancer J Clin 54:327–44
3. Barton MB, Harris R, Fletcher SW (1999) Does this patient have breast cancer? The screening clinical examination: should it be done? How? JAMA. 282:1270–80
4. Bluemke DA, Gatsonis CA, Chen MH et al (2004) Magnetic resonance imaging of the breast prior to biopsy. JAMA. 292:2735–42
5. Vetrani A, Fulciniti F, Di Benedetto G et al (1992) Fine – needle aspiration biopsies of breast masses. An additional experience of 1153 cases (1985 to 1988) and a meta analysis. Cancer. 69:736–40
6. Dennison G, Anand R, Makar SH, Pain JA (2003) A prospective study of the use of fine-needle aspiration cytology and core biopsy in the diagnosis of breast cancer. Breast J 9:491–3

Breast Cancer Epidemiology

7

Nikolaus Becker

7.1 Descriptive Epidemiology

Breast cancer is by far the most common cancer among females. It is estimated that 1.15 million new cases occurred in 2002 worldwide, contributing approximately 23% of all female cancers. Considering both sexes combined, it is still the second most frequent cancer site overall [1].

Geographically, its frequency is very unevenly distributed in the world, with the highest incidence in the industrialised regions of Europe and North America. About 316,000 new cases were estimated in Europe in 2002 and about 230,000 in North America with the highest age-standardised incidence rate in the United States (99.4 per 100,000). Moderate incidence rates are reported from Eastern Europe, South America, Southern Africa and Western Asia, while the incidence is low in most parts of Africa and Asia, with the lowest incidence rate of 16.5 per 100,000 in Central Africa (Fig. 7.1). It is noteworthy that the incidence rates may be affected by the implementation of early detection/screening programmes, which lead to advancement of diagnosis to earlier ages and may even lead to diagnosis of otherwise never emerging cancers.

Compared to other cancer sites, survival is relatively good for breast cancer, reaching 5-year survival rates of up to 81%. Survival is also rather unevenly distributed in the world, with the highest figures in the United States (81%) and lowest in the developing areas (Table 7.1).

Five-year survival may also be affected by early detection programmes, since advancement of diagnosis at an earlier stage of disease leads to prolonged survival, partially artificially and partially due to a real benefit in terms of better treatment and decreased fatality [2].

The high incidence together with good survival makes breast cancer to the cancer site with the highest prevalence in the world. It is estimated that about 4.4 million women are alive with a breast cancer diagnosis within the last 5 years, again relatively more in the industrialised countries with high incidence and especially good prognosis and less in the developing countries with lower incidence and worse prognosis.

Breast cancer is also the most frequent cause of cancer death among females, with estimated 411,000 annual deaths worldwide (190,000 in developed and 221,000 in developing countries) or 14% of all female cancer deaths. However, considering both sexes and all cancer sites together, an implication of the good survival is that it ranks at the fifth position in cancer mortality overall, after cancers of the lung (1.18 million deaths annually), stomach (700,000), liver (598,000) and colon and rectum (529,000). Breast cancer mortality also shows remarkable geographical variation, but it is less pronounced than it is for incidence, again due to the overall relatively favourable prognosis (see Fig. 7.1).

Breast cancer incidence is increasing in most countries, with higher slopes of increase in those countries with previously lower incidence. Only recently, some countries report indications for a levelling-off of incidence rates ([3] including detailed references). Breast cancer mortality is also increasing in many countries, though many of the developed countries report decreasing mortality rates since the late 1980s/early 1990s.

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_7, © Springer-Verlag Berlin Heidelberg 2010

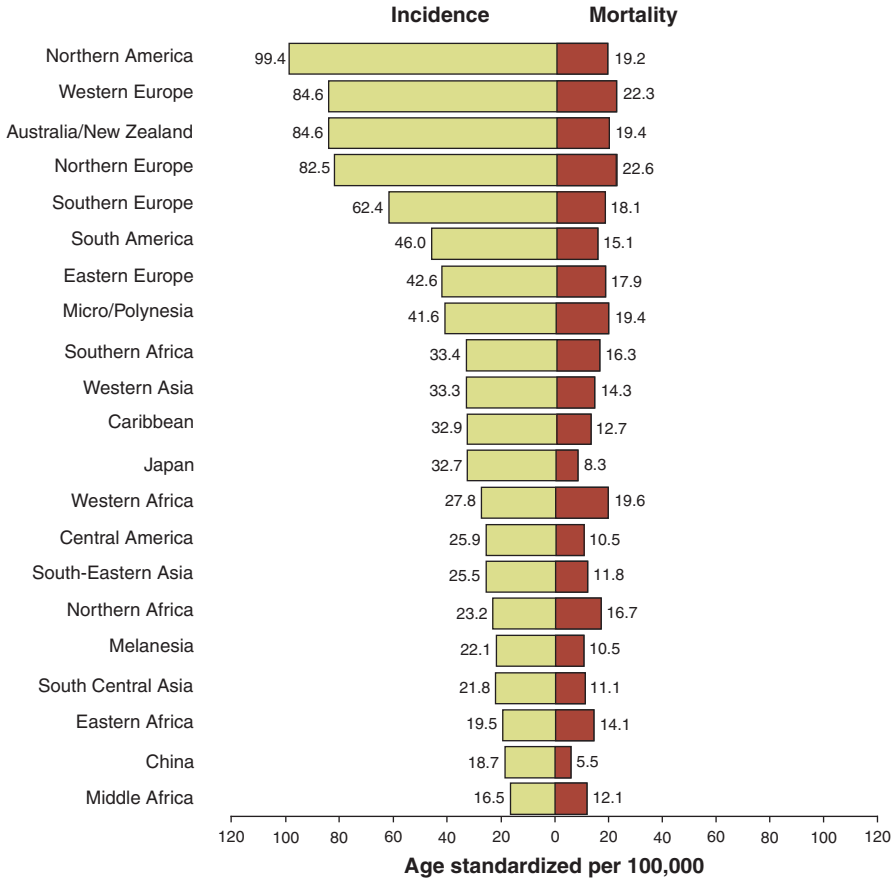

Fig. 7.1 Incidence and mortality rates for breast cancer. Rates are age-standardised with world standard as reference and given per 100,000 (source: [1])

Table 7.1 Estimated 5-year survival from breast cancer in the world

Area country	Estimated 5-year survival
Developed areas	
United States	81
Eastern Europe	58
Western Europe	74
Japan	75
All developed areas	73
Developing areas	
South America	67
India	46
Thailand	62
Sub-Saharan Africa	32
All developing areas	57

Rates are age-standardised using the world population as standard and given in percent (source: [1])

7.2 Aetiology

The uneven geographical distribution of breast cancer gave early rise to the question whether it might be determined by genetic or ethnic factors. This issue could be resolved by the elegant epidemiological approach of "migrant studies," in which cancer incidence among emigrants/immigrants was observed and compared to the respective incidence in the country of origin and the country of immigration. The first reports already (cited, e.g. in Ref. [4]) clearly demonstrated that incidence of most cancer sites including breast varied with a changing environment and moved away from the rates prevalent in the place of origin towards the rates prevalent at the place of immigration, underpinning the relevance of environmental factors, including life style habits and socioeconomic conditions in (breast) cancer aetiology.

On the other hand, the migrant studies did not completely rule out genetics or ethnicity in breast cancer

aetiology, and the observation of familial aggregation of breast cancer indicated clearly to the relevance of a genetic component.

The currently known environmental and societal risk factors include reproductive behaviour, age at menarche and menopause, oestrogen intake, body mass index (post-menopausal), alcohol consumption and exposure to ionising radiation [5]. Major risk factors for other cancer sites or cancer overall, such as tobacco consumption or dietary habits, seem to play, if at all, a minor role (see Table 7.2).

7.2.1 Inheritance

A family history of breast cancer is an established risk factor [6, 7]. The relative risk is elevated by about 1.5–3.0 when first degree relatives (mother or sisters) have the disease. A family history does not necessarily imply inheritance, since environmental factors or personal habits may also be clustered in families. However, involvement of high-penetrance germline mutations is considered related to about 5–10% of all breast cancers.

Two genes, "breast cancer gene 1" (BrCa1) and "breast cancer gene 2" (BrCa2) have so far been identified. They do, however, not explain the entire association pattern of inheritance so that further genes are expected to be involved and are thus searched for.

7.2.2 Tobacco

In most of the studies, which investigated the potential association of tobacco with breast cancer, no risk increase has been found. Though some few reports about a moderately elevated risk exist, female breast cancer is not considered related to tobacco smoke [8].

7.2.3 Diet

Dietary factors have been suggested for a long time as being of major relevance for breast cancer, especially a high fat intake for elevated risk [9, 10] and high fruits and vegetable consumption for reduced risk [11].

Table 7.2 Overview on established and presumed risk factors for breast cancer (source: [5])

Risk factor	Direction of effect[a]
Well-confirmed risk factors	
Family history in first-degree relative	↑↑
Height	↑
Benign breast disease	↑↑
Mammographically dense breasts	↑↑
Age at first birth >30 years vs., <20	↑↑
Menopause at >54 years vs., <45	↑↑
High endogenous oestrogen levels	↑↑
Post-menopausal hormone use	↑
Ionising radiation exposure	↑↑
Menarche at <12 years vs. >14	↑
Alcohol use (≥1 drink/day)	↑
High body mass index (post-menopausal)	↑
High body mass index (pre-menopausal)	↓
Tamoxifen	↓
Probable relationship exists, based on substantial data	
High endogenous androgen levels	↑↑
Current oral contraceptive use	↑
Physical activity	↓
Lactation (longer durations)	↓
Folate	↓
Carotenoids	↓
Weak, if any, relationship exists, based on substantial data	
Total dietary fat intake during adulthood	–
Induced or spontaneous abortion	–
Cigarette smoking	–
Past oral contraceptive use	–
Exposure to electromagnetic fields	–
Inconsistent findings or limited study to date	
High endogenous prolactin levels	↑↑
High plasma insulin-like growth factor levels	↑↑
I level	
High endogenous progesterone levels	↑
High endogenous vitamin D levels	↓
Childhood bodyfatness	↓
In utero exposures	↑
Non-steroidal anti-inflammatory drug use	↓
Organochlorine exposure	–
Adult-onset diabetes	↑
Thyroid disease	↑

↑ slight to moderate increase in risk; ↑↑ moderate to large increase in risk; ↓ slight to moderate decrease in risk; ↓↓ moderate to large decrease in risk

– no association.

[a]Arrows indicate the approximate magnitude of the relationship

Note: The magnitude of the risk can vary substantially, depending on the exact comparison being made. For example, having a family history of breast cancer in a first-degree relative is a consistent breast cancer risk factor. However, the magnitude of the association increases substantially the earlier the age at diagnosis in the relative(s) and with the number of relatives affected

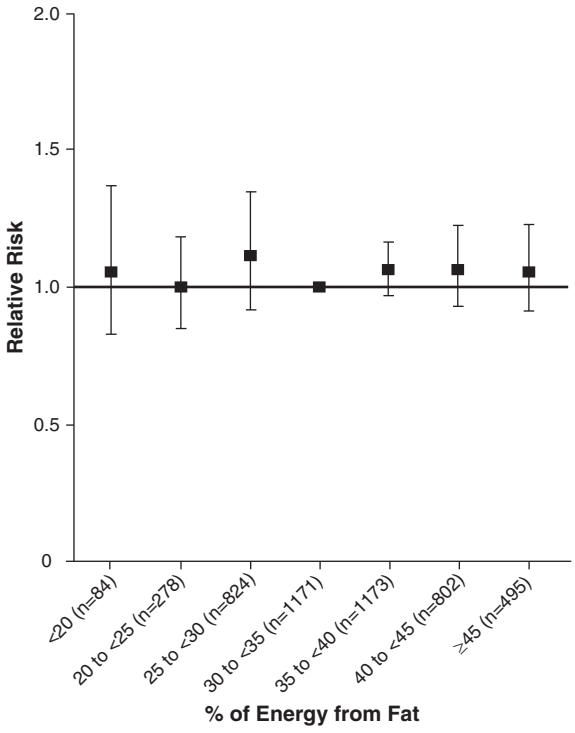

Fig. 7.2 Results of a pooled analysis of seven cohort studies to fat intake and breast cancer risk. Presented are relative risks in dependence upon seven categories of fat intake (source: [40])

Recent studies and meta-analyses question this view [12]. At least, fat consumption during adulthood does apparently not affect breast cancer risk (Fig. 7.2).

Further investigations focus now to a potential role during childhood and adolescence, eventually mediated through modulating age at menarche and body height [13].

Correspondingly, a pooled analysis of eight cohort studies provided a null result for the presumed association between fruits and vegetable consumption and breast cancer risk [14], which was supported by the analysis of the largest currently running cohort study on cancer and nutrition, EPIC [15] (Fig. 7.3).

Also, fibre intake, presumed to be related to breast cancer by counteracting to circulating oestrogen levels, could not be found associated to breast cancer risk in the pooled analysis of cohort studies [16].

Open research questions address intake of phytooestrogens or more general specific dietary products, such as soy products and their compounds (which include phytooestrogens) for which indications for a decreased breast cancer risk have been reported [17].

7.2.4 Alcohol

Alcohol consumption is an established risk factor for breast cancer. A large pooled analysis of 53 cohort studies, including 58,515 breast cancer cases confirmed the relationship and a clear dose-response relationship [19], which was confirmed by a recent analysis from EPIC [20]. The relative risk increases to RR > 1.3 for an average daily alcohol consumption of 35–44 g compared to no alcohol consumption and to RR > 1.4 for an average daily consumption of 45 g or more (Fig. 7.4).

These findings resulted in a recommendation to limit alcohol consumption to one drink per day, which must be seen in the context of also-reported *beneficial* effects of alcohol consumption in relation to cardiovascular diseases.

7.2.5 Reproductive Factors

Reproductive factors are established risk factors for breast cancer. Having born, at least one child decreases

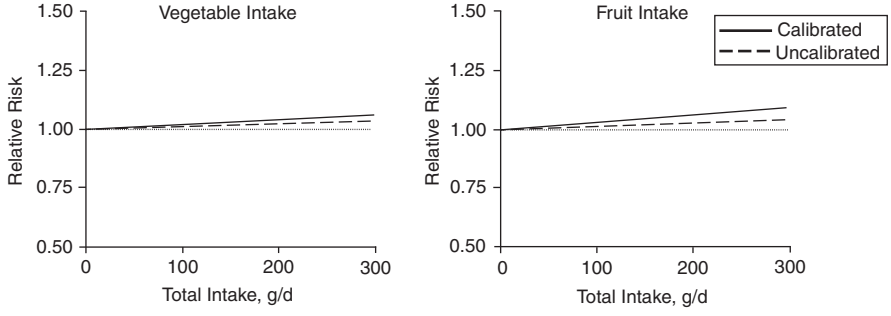

Fig. 7.3 Relative risk for breast cancer according to total vegetable and fruit intake (source: [15])

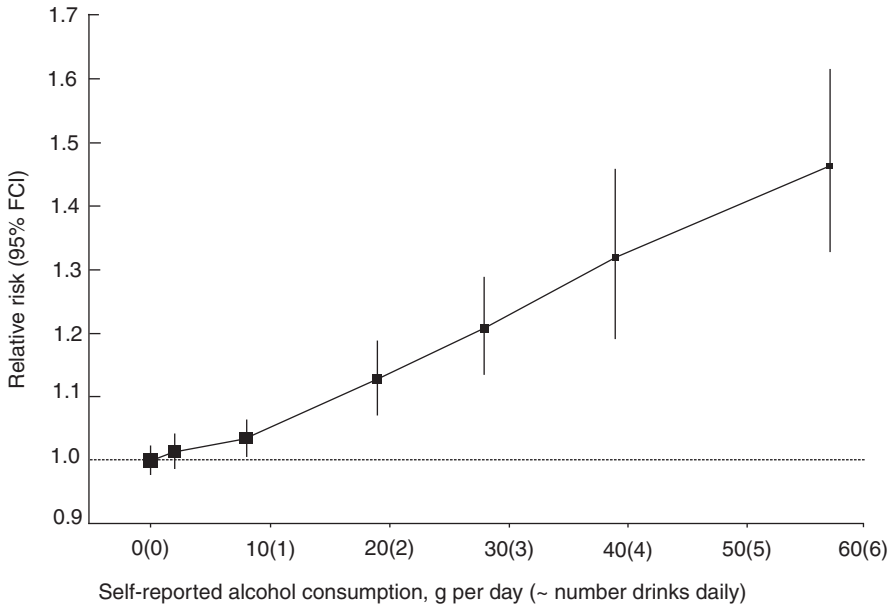

Fig. 7.4 Relative risk of breast cancer in relation to reported daily intake of alcohol. Relative risks are stratified by study, age parity, age at first birth and smoking (source: [18])

the risk on the average by about 25% compared to nulliparous women. In detail, however, reduction of relative risk is strongest if age at first birth is below 20 years (RR > 0.5), gets weaker with increasing age at first birth, and is even increased by about 20% with an age at first birth of 35 years or above [21]. This implies that the relative risk more than doubles if age at first birth is 35 years or more compared to an age of 20 years or less. Furthermore, the risk declines with an increasing number of pregnancies. A pooled analysis of 20 studies quantified the risk reduction to 3% per child for breast cancers, which were diagnosed before menopause and 12% for post-menopausal breast cancers [22]. Late age at menarche reduces the risk of breast cancer by 9 or 4% per year, respectively [22]. Breast feeding most likely reduces breast cancer risk additional to childbearing [18].

7.2.6 Endogenous Sex Hormones and Hormone Intake

7.2.6.1 Endogenous Sex Hormones

The observation that early menarche and late menopause increase the risk of breast cancer provided an early indication to a crucial role of the endogenous exposure to sex hormones in breast carcinogenesis. But, only recently, the pooled analyses of large prospective studies on the basis of hormone levels for oestrogens and androgens measured in blood samples were able to demonstrate and quantify clearly the elevation of breast cancer risk with increasing endogenous sex hormone exposure among post-menopausal women (Table 7.3, [23]).

These results have been confirmed by large subsequent studies (e.g. [24] with further references).

For pre-menopausal women, the data base is limited and reported findings about increased breast cancer risk with high estradiol levels inconsistent [25].

7.2.6.2 Exogenous Sex Hormones

The use of combined oral oestrogen-progestogen contraceptives is considered an established risk factor for breast cancer [26]. The assessment was carried out on the basis of dozens of epidemiological studies having included about 60,000 women with breast cancer. The relative risk is increased among current and recent users by about RR > 1.24 [27] and is higher among women with a breast cancer diagnosis in young ages (under 35 years) and an early start of contraceptive intake (under 20 years). It is less increased among women with a breast cancer diagnosis in older age, and the excess risk tends to zero when cessation of oral contraceptive intake dates back 10 years or more (Fig. 7.5). It is noteworthy

Table 7.3 Risk of breast cancer associated with a doubling of hormone concentration, with and without adjustment for another hormone[a]

Hormones in the model	RR (95% CI) associated with a doubling in hormone concentration	
	Unadjusted	Adjusted for other hormone
Estradiol and androstenedione†		
Estradiol	1.25 (1.08–1.44)	1.15 (0.99–1.35)
Androstenedione	1.35 (1.14–1.60)	1.27 (1.06–1.53)
Estradiol and DHEA‡		
Estradiol	1.24 (1.02–1.49)	1.19 (0.98–1.44)
DHEA	1.24 (1.03–1.50)	1.19 (0.98–1.45)
Estradiol and DHEAS§		
Estradiol	1.25 (1.11–1.41)	1.19 (1.05–1.35)
DHEAS	1.20 (1.08–1.32)	1.15 (1.04–1.27)
Estradiol and testosterone#		
Estradiol	1.31 (1.17–1.48)	1.18 (1.04–1.34)
Testosterone	1.42 (1.25–1.61)	1.32 (1.15–1.51)
Estradiol and SHBG¶		
Estradiol	1.21 (1.05–1.40)	1.20 (1.04–1.38)
SHBG	0.88 (0.76–1.02)	0.91 (0.80–1.06)

[a]*CI* confidence interval; *DHEA* dehydroepiandrosterone; *DHEAS* dehydroepiandrosterone sulphate; *NYU WHS* New York University women's health study; *ORDET* study of hormones and diet in the aetiology of breast tumours; *RERF* radiation effects research foundation; *SHBG* sex hormone-binding globulin; *SOF* study of osteoporatic fractures; *RR* relative risk

†374 case patients, 986 control subjects from Columbia, MO, United States; Nurses' Health Study, United States; Rancho Bernardo, United States; SOF, United States; and Washington County, United States

‡231 case patients, 423 control subjects from Columbia, MO, United States; Nurses' Health Study, United States; Washington Country, United States

§577 case patients, 1,483 control subjects from Columbia, MO, United States; Nurses' Health Study; NYU WHS, United States; ORDET, Italy; Rancho Bernardo, United States; RERF, Japan; SOF, United States; Washington County, United States

¶371 case patients, 1,137 control subjects from Columbia, MO, United States; Guernsey, U.K.; ORDET, Italy; Rancho Bernardo, United States; RERF, Japan; SOF, United States; Washington County, United States

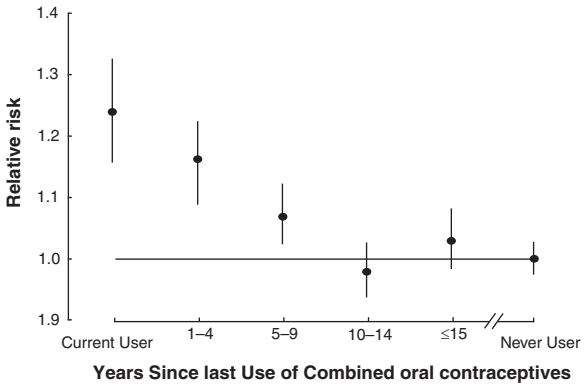

Fig. 7.5 Relative risk of breast cancer (given with 95% confidence intervals) by time since last use of combined oral contraceptives in comparison to non-users (source: [27])

that there is, on the other hand, evidence also for a protective effect of these contraceptives against cancers of the endometrium and the ovary [26].

Correspondingly, also post-menopausal combined oestrogen-progestogen hormone replacement therapy (HRT) is considered an established risk factor for breast cancer [26]. Data bases were again a multitude of epidemiological studies and two randomised trials. The risk elevation was higher for the combined HRT than for HRT with oestrogen alone. It became stronger with duration of administration, with an average increase of risk per year of administration by 2.3% [28] (Fig. 7.6).

Risk elevation was largely confined to current and recent users. Five years after cessation of treatment, the excess risk approached zero. Risk increase by duration of use was higher among women with lower weight or BMI and vice versa, and breast cancers were less advanced at time of diagnosis than among non-users [28].

The analysis failed to provide more detailed quantitative data in terms of effects of dose level or timing of progestogen addition [26].

7.2.7 Body Mass Index

Overweight (Body mass index BMI between 25 and less than 30) and obesity (BMI ≥30) are established risk

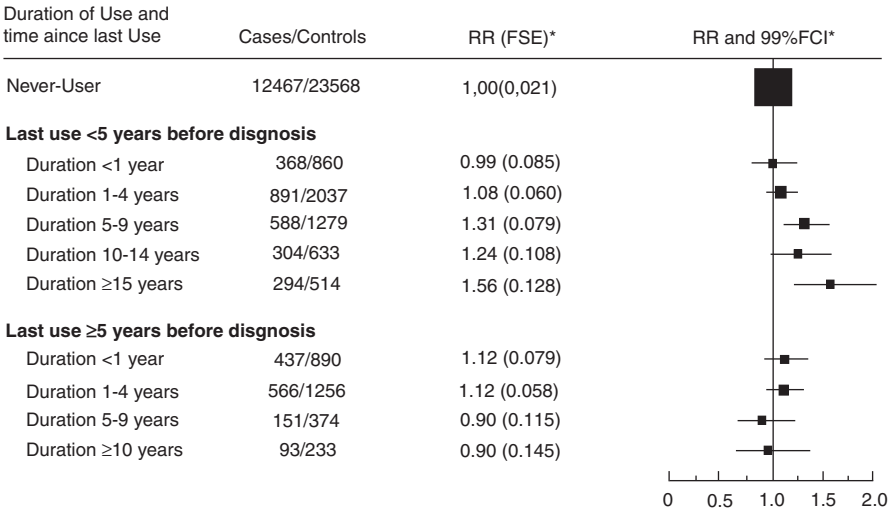

Fig. 7.6 Relative risk (RR) of breast cancer for duration of use within categories of time since last use of hormone replacement therapy (HRT) (source: [28])

factors for breast cancer [29] . Importantly, a high BMI increases the risk only among post-menopausal women, while in pre-menopausal women, a moderately elevated BMI decreases the risk (Table 7.4, [31]). About 8.6% of all breast cancers in the European Union are attributed to overweight (4.1%) and obesity (4.5%), i.e. about 12,800 cases annually [32]. In a pooled analysis, a relative risk increase of RR > 1.19 was found per 5 kg/m^2 of BMI [33]. The relationship was weakened, however, by controlling for endogenous sex hormones to RR > 1.02 (not significant) indicating to a hormone-related underlying mechanism [41].

Controlling body weight is thus currently one of the major recommendations for breast cancer prevention and assumed having the strongest impact for reducing incidence and mortality of the disease.

7.2.8 Height

Body size is also an established risk factor for breast cancer [31]. In a large cohort, the relative risk increase was estimated to RR > 1.11 per 5 cm additional body size. Reference height was 1.60 m or less [34]. Meta-analyses provided relative risks of 1.03–1.09 per 5 cm additional height [35]. Body size is of course unlikely to be a direct course of breast cancer, but it must be conceived as an indicator of early life factors (e.g. childrens' nutrition in affluent societies), which may also affect, e.g. age at menarche.

7.2.9 Physical Activity

Physical activity is considered an established protective factor for breast cancer [29, 30], though inconsistencies in the available studies appear having not yet been ruled out sufficiently [5]. They may be based on inconsistent definitions of physical activity and make quantification and subsequent translation of the observed effects into practical recommendations difficult. The indications for a true effect appear stronger for post-menopausal breast cancers than for pre-menopausal [35]. Due to the mentioned problems, current recommendations are confined to the rather general advice of regular physical activity either during daily life or as leisure time activity.

7.2.10 Ionising Radiation

Ionising radiation, including X-rays and gamma radiation, is an established risk factor for breast cancer [36]. After a latency time of 5–10 years, the risk increases with radiation dose and decreases with age at onset of exposure [37]. Thus, e.g. mammography is basically an exposure, which implies some additional risk for breast cancer and raises the question on the magnitude of practically relevant added risk taking latency into account.

Most of the empirical data on radiation effects come from the long-term observational studies among the

Table 7.4 Pooled multivariate relative risks and 95% confidence intervals for breast cancer according to categories of height, weight, and body mass index, the pooling project of diet and cancer

Anthropometric	Pre-menopausal†			Post-menopausal			Total		
Variable	No. of cases	RR‡	95% CI§	No. of cases	RR‡	95% CI	No. of cases	RR¶	95% CI
Height (m)	149	1.0	Reference	724	1.0	Reference	970	1.0	Reference
<1.60	202	1.21	0.94, 1.55	921	1.09	0.98, 1.21	1,261	1.10	1.00, 1.20
1.60–≤1.65	196	1.06	0.82, 1.36	916	1.23	1.11, 1.37	1,253	1.20	1.09, 1.32
1.65–≤1.70	117	1.14	0.86, 1.52	491	1.24	1.09, 1.41	688	1.24	1.11, 1.38
1.70–≤1.75	39	1.42	0.95, 2.12	156	1.28	0.94, 1,76	213	1.22[a]	0.90, 1.65
≥1.75									
p value, test for trend		0.41			<0.001			0.001	
BMI (kg/m)	158	1.0	Reference	363	1.0	Reference			
<21	223	1.24	0.97, 1.57	632	1.14	0.99, 1.33			
21–≤23	131	1.03	0.78, 1.35	699	1.15	1.00, 1.34			
23–≤25	82	1.08	0.79, 1.48	564	1.26	1.09, 1.47			
25–≤27	47	0.97	0.66, 1.44	401	1.43	1.21, 1.67			
27–≤29	32	0.96	0.60, 1.52	224	1.21	1.01, 1.46			
29–≤31	10	0.55	0.26, 1.15	140	1.29	1.03, 1.60			
31–≤33	20	0.58	0.34, 1.00	185	1.27	1.03, 1.55			
≥33									
p value, test for trend		0.007			0.001				

[a]Test for heterogeneity between studies, $p < 0.05$

†The Adventist Health Study was not included in analyses of pre-menopausal women

‡Multivariate relative risks (RR) were adjusted for age at menarche (≥11, 12, 13, 14, ≥15 years), parity (0, 1–2, ≥3), age at birth of first child (≤20, 21–25, 26–30, >30 years), post-menopausal hormone use (ever, never), oral contraceptive use (ever, never), history of benign breast disease (no, yes), maternal history of breast cancer (no, yes), history of breast cancer in a sister (no, yes, no sisters), smoking status (ever, never), education (less than high-school graduation, high-school graduation, more than high-school graduation), fat intake (quintiles), fibre intake (quintiles), energy intake (continuous), and alcohol intake (0, >0≤1.5, 1.5≤5, 5≤15, 15≤30, ≥30 g/day)

§CI, confidence interval

¶The model included all of the above terms, and menopausal status at diagnosis (pre-menopausal, post-menopausal, uncertain)

atomic bomb survivors in Hiroshima and Nagasaki whose exposure was however largely different in terms of intensity and duration from medical exposures to be considered nowadays. Other sources are data from treatment for tuberculosis or Hodgkin lymphoma and benign breast disease. Several projections have been carried out on the basis of these data estimating the breast cancer risk induced by mammography, which are summarised in IARC [30]. The quintessence is that regular mammography screening (MS) starting with the age of 50 years might induce 10–50 breast cancers deaths among one million participating women within the rest of their lifespan, and 100–200 breast cancer deaths when MS started with the age of 40 years. These additional cases are to be compared with the ten of thousands "usually" occurring breast cancer deaths within this life span, or the assumed benefit of a high-quality screening programme.

7.3 Primary Prevention

Derived from the known etiologic factors and their accessibility to deliberate modulation, primary prevention can act via weight control in post-menopausal life, maintenance of physical activity throughout life and no or low-level alcohol consumption. Previously propagated interventions as low fat and high fruits and vegetables consumption in adulthood are unlikely to benefit specifically in the prevention of breast cancer though they may nevertheless have their role in the prevention of other cancers or other life-threatening diseases.

Due to the hormone-dependency of breast cancer, chemoprevention based on hormonal active agents might have or even already have a place in the prevention of the disease. The agents that have been investigated or are currently under investigation are tamoxifen,

raloxifen or other selective oestrogen receptor modulators (SERM). The effects of these agents do not seem to be beneficial only in terms of a reduced breast cancer risk, but extend also to reduced risks for e.g. osteoporosis, but are counterbalanced to some extent by increased risks for other diseases so that an individual benefit/risk balance appears required.

7.4 Secondary Prevention/Screening

Due to its easy accessibility from outside, the breast is the target for established or formerly presumed early detection interventions. They include breast-self examination (BSE), physical examination (PE) by a trained doctor or MS. Up to now, only MS could be approved to be effective in terms of reducing breast cancer mortality [30]. Randomised studies could not confirm any mortality reduction by regular BSE [30]. For PE, there is no sufficient evidence available in favour or against a benefit of this type of intervention. For MS, overall ten randomised studies demonstrated a mortality reduction of breast cancer, however, limited to the age range 50–69 years, which led to the recommendation of biannually two-view screening of the breast.

Generally, screening has side effects such as false-positive mammographies, unnecessary biopsies or even surgery and overdiagnosis, which cannot be avoided and counterbalance, therefore the benefit of screening [2]. The overall benefit/harm balance is thus fragile and has to be controlled by continuous quality-assurance of screening, which appears most effectively to be done by organised programmes. Quality indicators have been derived from the randomised trials and target ranges determined for their optimal working points, which are basis for most of the European breast screening programmes [38, 39].

References

1. Parkin M, Bray F, Ferlay J, Pisani P (2005) Global Cancer Statistics, 2002. CA Cancer J Clin. 55:74–108
2. Morrison AS (1992) Screening in chronic disease. Monographs in epidemiology and biostatistics. Vol 19. Oxford University, New York Oxford
3. Kumle M (2008) Declining breast cancer incidence and decreased HRT use. Lancet. 372:608–9
4. Doll R, Peto R (1981) The Causes of Cancer. J Natl Cancer Inst. 66:1191–308
5. Adami H-O, Hunter D, Trichopoulos D (eds) (2008) Textbook of cancer epidemiology. 2nd ed. Oxford University
6. Collaborative Group on Hormonal Factors in Breast Cancer (2001) Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies, including 58 209 women with breast cancer and 101 986 women without the disease. Lancet. 358:1389–99
7. Lynch TL, Silva E, Snyder C, Lynch JF (2008) Hereditary breast cancer: part I. Diagnosing hereditary breast cancer syndromes. Breast J. 14:3–13
8. IARC (2004) IARC monographs on the evaluation of carcinogenic risks to humans. Tobacco Smoke and involuntary smoking. Vol 83. International Agency for Research on Cancer, World Health Organization. IARC, Lyon
9. Carroll KK, Braden LM, Bell JA, Kalamegham R (1986) Fat and cancer. Cancer. 58:1818–25
10. Prentice RL, Sheppard L (1990) Dietary fat and cancer: consistency of the epidemiologic data, and disease prevention that may follow from a practical reduction in fat consumption. Cancer Causes Control. 1:81–97
11. World Cancer Research Fund (1997) Food, nutrition and the prevention of cancer: a global perspective. World Cancer Research Fund/American Institute for Cancer Research, Washington
12. Willett WC (1998) Dietary fat intake and cancer risk: a controversial and instructive story. Cancer Biol. 8:245–53
13. Trichopoulos D, Adami H-O, Ekbom A, Hsieh CC, Lagiou P (2008) Early life events and conditions and breast cancer risk: from epidemiology to etiology. Int J Cancer. 122:481–5
14. Smith-Warner SA, Spiegelman D, Yaun S-S, Adami H-O, Beeson W, Kusih LH, Van den Brandt PA, Folsom AR, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S, Miller AB, Potter JD, Rohan TE, Speizer FE, Toniolo P, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Hunter D (2001) Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. JAMA. 285:769–76
15. Van Gils CH, Peeters PHM, Bas Bueno-de-Mesquita H, Boshuizen HC, Lahmann PH, Clavel-Chapelon F, Thiébaut A, Kesse E, Sieri S, Palli D, Tumino T, Panico S, Vineis P, Gonzalez CA, Ardanaz E, Sánchez M-J, Amiano P, Navarro C, Quirós JR, Key TJ, Allen N, Khaw K-T, Bingham SA, Psaltopoulou T, Koliva M, Trichopoulou A, Nagel G, Lisneisen J, Boeing H, Berglund G, Wirfält E, Hallmans G, Lenner P, Overvad K, Tjonneland A, Olsen A, Lund E, Engeset D, Alsaker E, Norat T, Kaaks R, Slimani N, Riboli E (2005) Consumption of vegetables and fruits and risk of breast cancer. JAMA. 293:183–93
16. Willett WC (2001) Diet and breast cancer. J Intern Med. 249:395–411
17. Lof M, Weiderpass E (2006) Epidemiologic evidence suggests that dietary phytoestrogen intake is associated with reduced risk of breast, endometrial, and prostate cancers. Nutr Res. 26:609–19
18. Collaborative Group on Hormonal Factors in Breast Cancer (2002) Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50 302 women with breast cancer and 96 973 women without the disease. Lancet. 360: 187–95

19. Collaborative Group on Hormonal Factors in Breast Cancer (2002) Alcohol, tobacco and breast cancer – collaborative reanalysis of individual data from 53 epidemiological studies, including 58 515 women with breast cancer and 95 067 women without the disease. Br J Cancer. 87:1234–45
20. Tjonneland A, Christensen J, Olsen A, Stripp C, Thomsen BL, Overvad K, Peeters PHM, Van Gils CH, Bas Bueno-de-Mesquita H, Ocké MC, Thiébaut A, Fournier A, Clavel-Chapelon F, Berrino F, Palli D, Tumino R, Panico S, Vineis P, Agudo A, Ardanaz E, Martinez-Garcia C, Amiano P, Navarro C, Quirós JR, Key TJ, Reeves G, Khaw K-T, Bindham S, Trichopoulou A, Trichopoulos D, Naska A, Nagel G, Chang-Claude J, Boeing H, Lahmann PH, Manjer J, Wirfält E, Hallmans G, Johansson E, Lund E, Skeie G, Hjartaker A, Ferrari P, Slimani N, Kaaks R, Riboli E (2007) Alcohol intake and breast cancer risk: the European prospective investigation into cancer and nutrition (EPIC). Cancer Causes Control. 18:361–73
21. MacMahon B, Cole P, Lin TM, Lowe CR, Mirra AP, Ravnihar B, Salber EJ, Valaoras VG, Yuasa S (1970) Age at first birth and breast cancer risk. Bull Org Mond Santé/Bull World Health Organ. 43:209–21
22. Clave-Chapelon F, Gerber M (2002) Reproductive factors and breast cancer risk. Do they differ according to age at diagnosis? Breast Cancer Res Treat. 72:107–15
23. Endogenous Hormones and Breast Cancer Collaborative Group (2002) Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst. 94:606–16
24. Kaaks R, Rinaldi S, Key TJ, Berrino F, Peeters PH, Biessy C et al (2005) Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. Endocr Relat Cancer. 12:1071–82
25. Kaaks R, Berrino F, Key T, Rinaldi S, Dossus L, Biessy C et al (2005) Serum sex steroids in premenopausal women and breast cancer risk within the European prospective investigation into cancer and nutrition (EPIC). J Natl Cancer Inst. 97:755–65
26. IARC. IARC monographs on the evaluation of carcinogenic risks to humans. Combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy. Vol 91. International Agency for Research on Cancer, World Health Organization. IARC, Lyon; 2007
27. Collaborative Group on Hormonal Factors in Breast Cancer (1996) Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet. 347:1713–27
28. Collaborative Group on Hormonal Factors in Breast Cancer (1997) Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. Lancet. 350:1047–59
29. IARC. Weight control and physical activity. IARC handbooks of cancer prevention. Vol 6. International Agency for Research on Cancer, World Health Organization. IARC, Lyon; 2002
30. IARC. Breast cancer screening. IARC handbooks of cancer prevention. Vol 7. International Agency for Research on Cancer. World Health Organization. IARC, Lyon; 2002
31. Van den Brandt PA, Spiegelman D, Yaun S-S, Adami H-O, Beeson L, Folsom AR, Fraser G, Goldbohm RA, Graham S, Kushi L, Marshall JR, Miller AB, Rohan T, Smith-Warner SA, Speizer FE, Willett WC, Wolk A, Hunter DJ (2000) Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol. 152:514–27
32. Bergström A, Pisani P, Tenet V, Wolk A, Adami H-O (2001) Overweight as an avoidable cause of cancer in Europe. Int J Cancer. 91:421–30
33. Endogenous Hormones and Breast Cancer Collaborative Group (2003) Body mass index, serum sex hormones and breast cancer risk in postmenopausal women. J Natl Cancer Inst. 95:1218–26
34. Baer HJ, Rich-Edwards JW, Colditz GA, Hunter DJ, Willett WC, Michels KB (2006) Adult height, age at attained height and incidence of breast cancer in premenopausal women. Int J Cancer. 119:2231–5
35. World Cancer Research Fund/American Institute of Cancer Research (2007) Food, nutrition, physical activity, and the prevention of cancer: a global perspective. AICR, Washington DC
36. IARC (2000) IARC monographs on the evaluation of carcinogenic risk to humans. ionizing radiation, part 11: X- and Gamma (γ)-Radiation, And Neutrons. Vol 75. International Agency for Research on Cancer, World Health Organization. Lyon: IARC
37. Jung H (2001) Is there a real risk of radiation-induced breast cancer for postmenopausal women? Radiat Environ Biophys. 40:169–74
38. Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L, Puthaar E (eds) (2006) European guidelines for quality assurance in breast cancer screening and diagnosis, 4th edn. Office for Official Publications of the European Communities, Luxembourg
39. Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L, Puthaar E (eds) (2008). European guidelines for quality assurance in breast cancer screening and diagnosis. 4th ed. Summary Document. Ann Oncol. 19:614–22
40. Hunter DJ, Spiegelman D, Adami H-O, Beeson L, Van den Brandt PA, Folsom AR, Fraser GE, Goldbohm RA, Graham S, Howe GR, Kusih LH, Marshall JR, McDermott A, Miller AB, Speizer FE, Wolk A, Yaun S-S, Willett W (2000) Cohort studies of fat intake and the risk of breast cancer – a pooled analysis. N Engl J Med. 334:356–61
41. The Endogenous Hormones and Breast Cancer Collaborative group (2002) Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst. 94:606–16

Breast Cancer Screening

8

Ismail Jatoi

In our society, there is a deeply rooted belief that the early detection of cancer is invariably beneficial, and evidence to the contrary is often viewed with skepticism. Today, several breast cancer screening methods are available, and it is important that we evaluate these critically and base screening recommendations on good evidence rather than assumptions. To realize how assumptions about cancer screening can be misleading, consider the history of lung cancer screening. For many years, it was assumed that screening for lung cancer with sputum cytology or chest radiographs would be beneficial. Eventually, four randomized prospective trials showed that this assumption was wrong [1]. Thus, we do not routinely recommend lung cancer screening today, although additional trials examining its efficacy are ongoing. The example of lung cancer screening serves to illustrate why it is necessary to first obtain evidence concerning the efficacy of cancer screening, before implementing it into clinical practice.

Over the years, a few investigators have steadfastly maintained that breast cancer is systemic at inception and that screening would have little impact on reducing mortality [2, 3]. Proponents of this paradigm argued that the early detection and timely extirpation of the primary breast tumor would not alter the natural history of the disease. Indeed, a prominent physician once argued that we were missing the forest (the systemic problem) because our efforts were primarily directed at the tree (the breast tumor) [4]. However, most clinicians never accepted this view. For many years, the prevailing view has been that breast cancer begins as a cell or clone of cells that multiply and grow in size [5]. At some point during the growth of this breast mass, metastasis occurs, and the resulting metastatic deposits lead to the death of the patient. This paradigm led to the belief that the early detection and treatment of breast cancer (before the onset of symptoms) could significantly reduce mortality. Therefore, there is considerable interest that is focused on screening as a means of reducing breast cancer mortality.

Today, there are five breast cancer screening methods that are commonly utilized: mammography, clinical breast examination (CBE), breast self-examination (BSE), magnetic resonance imaging (MRI) and ultrasound [6]. Various studies have examined the efficacy of screening in reducing breast cancer mortality, and this chapter reviews these studies (Table 8.1). It is also important to note that breast-screening programs target large, healthy (asymptomatic) populations, and very few women who undergo screening will actually be diagnosed with breast cancer. Thus, the potential risks of breast cancer screening must be weighed against its potential for benefit. The risks and benefits of breast cancer screening are emphasized in this chapter.

8.1 Cancer Screening Principles

Cancer therapy is generally directed toward patients who have symptoms. However, proponents of screening have long argued that the asymptomatic period in the natural history of cancer represents a “window of opportunity” for treatment [7]. The total preclinical phase (TPCP) refers to the period from the initiation of cancer to the onset of symptoms [8]. Generally, the beginning of the TPCP is not known. However, the

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_8, © Springer-Verlag Berlin Heidelberg 2010

Table 8.1 Evidence of benefit for the breast cancer screening modalities

Screening modality	Randomized controlled trials to assess mortality benefit		Significant reduction in breast cancer mortality
Mammography	HIP Malmo Two country Stockholm	Gothenburg Edinburg CNBSS I CNBSS II UK Age Trial	25% in women aged 50 year and older (7–9 year follow-up) 18% in women aged 40–49 year (>12 year of follow-up)
Breast self-examination (BSE)	St. Petersburg, Russia, Shanghai, China		No proven benefit
Clinical breast examination (CBE)	India		Results not yet available
Ultrasound	Japan		Results not yet available
Magnetic resonance imaging (MRI)			No randomized controlled trials to assess mortality benefit

HIP health insurance plan; *CNBSS* Canada national breast screening study

detectable preclinical phase (DPCP) is a component of the TPCP and refers to the period when the cancer is detectable with a screening test. The starting point of the DPCP depends on the screening test used. A screening test that detects cancer very early in its natural history will be associated with a longer DPCP when compared with a test that detects it later. The sensitivity of a screening test refers to the proportion of patients with a disease who have a positive result (true positive rate); the specificity of a test refers to the proportion of patients without the disease who have a negative result (true negative rate) [9]. A longer DPCP is associated with a more sensitive screening test. Prevalence refers to the total number of persons who have a disease at a particular time; incidence refers to the number of persons who develop a disease over a period [10]. In any screening program, the first screening round is referred to as the prevalent screen, and the cancers detected are known as the prevalent cancers. The number of cancers detected during the prevalent screen depends on the DPCP (i.e., a longer DPCP is associated with a greater number of prevalent cases). Following the prevalent screen, the subsequent screening rounds are known as the incident screens, and the cancers detected are referred to as the incident cancers. Cancers diagnosed between screening sessions generally present as symptomatic cases and are referred to as interval cancers [11]. Anderson et al. showed that, as a group, the prevalent cancers generally have a more favorable tumor biology and better prognosis than cancers detected at the incident screens [10]. The interval cancers generally have the worst prognosis [11].

Cole and Morrison argued that before the screening of any cancer was initiated, three conditions had to be met [8]. First, there must be effective treatment for the cancer, and the treatment must be more effective in screen-detected cases than in clinically detected cases. Obviously, if there is no available treatment for the cancer, then screening will provide no survival advantage. Additionally, if treatment is equally effective in screen-detected and clinically detected cases, then, again, screening will provide no survival advantage. Second, there should be a high prevalence among persons who undergo screening. A high prevalence is necessary to justify the expense of a screening program. Lastly, the cancer should have serious consequences (i.e., a high mortality rate or significant morbidity).

Many investigators believe that breast cancer meets the three conditions outlined by Cole and Morrison. Numerous studies have been undertaken to determine the efficacy of breast cancer screening in reducing mortality. However, before discussing these breast cancer screening studies, we must first consider the biases inherent in those studies. Three biases merit particular attention: lead time, length, and selection.

8.1.1 Lead-Time Bias

Screening detects cancers "early," but this alone cannot justify screening. Screening can only be justified if it prevents or delays the time of death from cancer. Survival refers to the period from diagnosis of cancer to

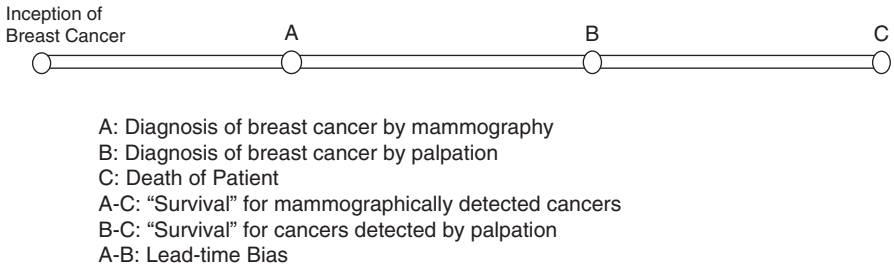

Fig. 8.1 Breast Cancer Timeline

death. "Lead-time bias" refers to the interval between the diagnosis of cancer by screening and by usual clinical detection [12]. As screening advances the time of breast cancer diagnosis, patients with screen-detected cancers will appear to have better survival rates than those with clinically detected cancers, even if screening does nothing to delay death. As a result of lead-time bias, screening may appear to prolong life, when it simply extends the period over which the cancer is observed. The effect of lead-time bias is illustrated in Fig. 8.1.

8.1.2 Length Bias

Slower growing cancers exist for a longer period in the preclinical phase and are more likely to be detected by screening. In contrast, faster growing tumors exist for a shorter period in the preclinical phase and are more likely to be detected in the intervals between screening sessions. This phenomenon is termed length bias [13]. Indeed, we now know that there are differences in the biologic properties of the mammographically detected (screen-detected) breast cancers and those detected clinically. When histologic differentiation, tumor necrosis, mitotic counts, estrogen and progesterone receptors, histological type, DNA ploidy, and S-phase fraction are compared, the mammographically detected cancers are generally found to have a more favorable tumor biology [14].

8.1.3 Selection Bias

Women who are health conscious are more likely to volunteer for periodic breast cancer screening. In general, these women are more likely to eat nutritional foods, exercise regularly, and maintain a healthy lifestyle. As a result, volunteers have a lower mortality rate from all causes than women who do not volunteer for breast cancer screening. This is sometimes referred to as the healthy-screenee effect [15]. Thus, studies that compare volunteers for breast cancer screening with nonvolunteer controls are subject to a selection bias. The lower mortality of women who undergo screening might not necessarily be due to screening but due to other factors associated with healthy volunteers. The effect of selection bias was suggested in a case-control study from the United Kingdom. Moss et al. compared volunteers and nonvolunteers for breast cancer screening [16]. Women from two separate communities were compared. In one community, women had the opportunity to undergo periodic screening (screening district), whereas in the other community, no screening program was available (comparison district). These authors found that breast cancer mortality was higher among the nonvolunteers of the screening district compared with women in the comparison district. This difference in mortality was attributed to selection bias.

Various studies examined the efficacy of breast cancer screening: case-control, retrospective, and prospective; however, the best way to exclude the biases discussed here is to conduct randomized prospective clinical trials with all-cause mortality as the endpoint. Unfortunately, clinical trials that use all-cause mortality as the endpoint require huge numbers of subjects and are therefore not practical. Thus, the breast cancer screening trials have used cause-specific (breast cancer) mortality as a surrogate endpoint. These randomized prospective trials are discussed in the following sections.

8.2 Mammography Screening

The distinction between diagnostic mammography and screening mammography should be emphasized [17]. Diagnostic mammography is used to evaluate patients

with breast symptoms (such as a breast lump). In contrast, mammography screening targets asymptomatic women. In this chapter, we consider the merits of mammography screening, and diagnostic mammography is discussed elsewhere in this book.

The concept of mammography screening for asymptomatic women has evolved over many years. Salomon, a surgeon, is credited with initiating mammography in 1913, using gross mastectomy specimens [18]. Subsequently, in 1930, Warren reported on the use of mammography in patients [19]. The concept of mammography screening for asymptomatic women was proposed by Gershon-Cohen et al. in the 1950s [20]. In the 1950s and 1960s, Gershon-Cohen et al. and Egan published reports indicating that mammography could detect impalpable cancers in asymptomatic women [21, 22]. Soon after, randomized prospective trials were initiated to determine the efficacy of mammography screening in reducing mortality from breast cancer.

Nine randomized prospective trials have examined the efficacy of mammography screening [23]. These are the health insurance plan (HIP) trial of New York, Swedish Two County, Gothenburg, Stockholm, Malmo, Edinburgh, Canadian National Breast Screening Study I (CNBSS I), CNBSS II, and the United Kingdom Age Trial. A total of about 661,000 women have been enrolled in these nine trials, and approximately 331,000 were below the age of 50 at the start of these trials.

The design of these trials differs considerably (Table 8.2). Some of the trials evaluated the efficacy of screening with mammography and CBE, whereas others evaluated the efficacy of screening with mammography alone. In some, mammography screening was undertaken with one view per breast, while other trials included two views per breast. The screening interval in these trials ranged from 12 to 33 months, and the ages of the women enrolled ranged from 39 to 74 years. Additionally, the randomization method varied (i.e., cluster or individual).

8.2.1 Health Insurance Plan Trial

The HIP trial was initiated in New York in 1963 and involved 60,696 women between the ages of 40 and 64 at entry [24]. Women were randomized either to undergo periodic screening or to receive usual medical care. Screening consisted of mammography and CBE. Analysis of the cancers detected by screening in the HIP trial revealed the following: 45% were detected by CBE alone, 33% by mammography alone, and 22% by mammography and CBE. Thus, any reduction in breast cancer mortality in the screened group cannot be attributed to

Table 8.2 Characteristics of the randomized controlled trials of mammography screening

Trial	Entry years	Age at entry	Screening method	Randomization	Screening Frequency	No. of women
HIP	1963–1969	40–64	2-view MM and PE	Individual	Annually, 4 rounds	60, 696
Malmo	1976–1986	45–69	1-or 2-view MM	Cluster: birth cohort	18–20 mo, 5 rounds	41, 478
Two-country	1977–1985	40–74	1-view MM	Cluster: geographic	24–33 mo, 4 rounds	133, 065
Stockholm	1981–1985	40–64	1-view MM	Cluster: birth cohort	28 mo, 2 rounds	59, 176
Gothenburg	1982–1988	40–59	2-view MM	Individual (age <50 year) Cluster (age >50 year)	18 mo, 4 rounds	49, 553
Edinburg	1978–1985	45–64	1-or 2-view MM and PE	Cluster: physician	24 mo, 4 rounds	54, 671
CNBSS I	1980–1987	40–49	2-view MM and PE	Individual: volunteer	Annually, 5 rounds	50, 430
CNBSS II	1980–1987	50–59	2-view MM and PE vs. PE	Individual: volunteer	Annually 5 rounds	39, 405
UK age trial	1991–1997	40–41	2-view MM at first year; 1-view MM subsequently	Individual	Annually	160, 921

HIP health insurance plan; *CNBSS* Canada national breast screening study; *PE* physical exam; *MM* mammography

mammography alone. Indeed, any mortality reduction in the study group may also mean that CBE is an effective screening modality.

At 10-year follow-up, the HIP trial demonstrated a 29% reduction in breast cancer mortality in the screened group [24]. This result also can be described in terms of a relative risk (RR) reduction (RR of 1.0 indicates no difference between the screened and control groups). Thus, after 10 years of follow-up, the RR of death from breast cancer in the study group was 0.71 (95% confidence interval (CI), 0.55–0.93). The CI does not cross 1.0, indicating that the result is statistically significant.

There has been considerable interest in comparing the effect of screening in women who were below and above age 50 years at the start of the trials [25]. If these two subsets are examined separately, differences emerge. In the HIP trial, at 10 years follow-up, the RR of death from breast cancer for women below the age of 50 in the screened group was 0.77 (95% CI, 0.50–1.16) whereas for those above age 50, it was 0.68 (95% CI, 0.49–0.96). Thus, there was no significant benefit to screening women below age 50, but for those over age 50, periodic screening significantly reduced breast cancer mortality. With further follow-up to 18 years, however, the benefit of screening younger women in the HIP trial begins to approach statistical significance, with RR of death from breast cancer of 0.77 (95% CI, 0.53–1.11) compared with controls [26]. This trend is seen in other trials as well and is further discussed below.

8.2.2 Swedish Trials

Four randomized prospective trials on breast cancer screening were conducted in Sweden: the two-county (Kopparberg and Ostergotland), Malmo, Stockholm, and Gothenburg trials [27]. These trials were initiated between the years 1976 and 1982 and enrolled approximately 283,000 women between the ages of 40 and 74. In these trials, women were randomized either to undergo periodic screening with mammography alone or to receive usual care. CBE was used as a screening modality in the HIP, Edinburgh, and Canadian trials, but not in any of the Swedish trials.

In 1993, Nystrom et al. published an overview of the four Swedish trials based on 5–13 years of follow-up [27]. For women of all ages, a significant reduction in breast cancer mortality was seen in the screened group, with RR of 0.76 (95% CI, 0.66–0.87). For women aged 40–49 at the start of the trials, however, there was an insignificant reduction in breast cancer mortality in the study group, with RR 0.87 (95% CI, 0.63–1.20). In 1996, another overview was conducted, with an additional 4 years of follow-up [28]. In that overview, the benefit of screening for women aged 40–49 at the start of the Swedish trials approached statistical significance, with RR 0.77 (95% CI, 0.59–1.01). A further follow-up overview of the Swedish trials was reported in 1997 by Hendrick et al. [29]. In that study, the RR of breast cancer death in the screened group was 0.71 (95% CI, 0.57–0.89) for women aged 40–49 years at the start of the trials. Thus, with long-term follow-up, a statistically significant benefit to screening younger women finally emerges in the Swedish trials.

8.2.3 Edinburgh Trial

The Edinburgh randomized trial of breast cancer screening recruited 44,288 women between the ages of 45 and 64 from 1978 and 1981 [30]. This initial recruitment included 11,391 women between the ages of 45 and 49 at entry (cohort one). Subsequently, an additional 10,383 women were recruited in two cohorts during the periods 1982–1983 (cohort two) and 1984–1985 (cohort three) [31]. Thus, the Edinburgh trial included a total of 54,671 women who were between the ages of 45 and 64 at the start of the study.

The design of the trial was similar to that of the HIP trial. Women were randomized either to undergo periodic screening with mammography and CBE or to receive usual care. For women of all ages, after 10 years of follow-up, the RR of death from breast cancer in the screened group was 0.82 (95% CI, 0.61–1.11). For women below age 50 at entry, the RR was 0.78 (95% CI, 0.46–1.31). Alexander et al. reported the results of 14 years of follow-up for all women enrolled in the Edinburgh trial [32]. The RR of death in the screened group, when compared with the control group, was 0.87 (95% CI, 0.70–1.06). After adjusting for the socioeconomic status of the general medical practices from which the participants in the study were recruited, the rate ratio was 0.79 (95% CI, 0.60–1.02).

8.2.4 Canadian Trials

The CNBSS consisted of two separate randomized prospective trials (CNBSS I and CNBSS II), both initiated in 1980 [33, 34]. The CNBSS I was specifically designed to assess the efficacy of screening women below age 50 and included 50,430 women between the ages of 40 and 49 at the start of this study. Women were randomized either to undergo periodic screening or to receive usual care. Screening consisted of annual mammography and CBE. After an average follow-up of 7 years, there was an insignificant excess in breast cancer mortality in the screened group, with RR 1.36 (95% CI, 0.84–2.21). This insignificant excess in mortality persisted even after 10.5 years of follow-up, with RR 1.14 (95% CI, 0.83–1.56).

The CNBSS II examined the efficacy of screening women who were between the ages of 50 and 59 at the start of the trial. The design of the CNBSS II study was different from that of the CNBSS I. Women were randomized to undergo either screening with annual mammography and CBE (study group) or CBE alone (control group). Surprisingly, after 7 years of follow-up, breast cancer mortality in the two groups was nearly identical, with the RR of death in the study group 0.97 (95% CI, 0.62–1.52). Similar results were reported after 13 years' follow-up; the number of breast cancer deaths in the study and control groups was 107 and 105, respectively, and the cumulative rate ratio was 1.02 (95% CI, 078–1.33) [35]. These results might be interpreted to mean that mammography screening does nothing to reduce breast cancer mortality beyond that which can be achieved by screening with CBE alone. The potential use of CBE as a screening method is discussed later in this chapter.

8.2.5 United Kingdom Age Trial

To further assess the efficacy of mammography screening for women aged 40–49, a randomized prospective trial was undertaken in the United Kingdom [36]. This trial involved 160,921 women, of whom, a third received annual screening invitations and two-thirds received usual care. Women were aged 40 or 41 at the start of the trial to ensure that all results were based solely on mammography screening in women before age 50. At a mean follow-up of 10.7 years, there was no significant reduction in breast cancer mortality in the screened group, with the RR of death being 0.83 (95% CI, 0.66–1.04). Thus, the results of this study are consistent with those of previous trials showing no significant benefit to mammography screening in younger women.

8.3 Overview (Meta-Analyses) of the Mammographic Screening Trials

Several overviews (meta-analyses) of the mammography screening trials have been published. Many have focused on the results for women who were between the ages of 40 and 49 years at the start of the trials, but have not included the results of the recent United Kingdom Age Trial, which is unlikely to substantively change the conclusions of earlier meta-analyses. In 1995, Kerlikowske et al. published a meta-analysis of the eight randomized controlled trials and four case-control studies on mammography screening that had been undertaken up to that point in time [37]. This meta-analysis showed that, for women between the ages of 50 and 74 at the start of the studies, a significant reduction in breast cancer mortality was evident in the screened group after 7–9 years' follow-up, with RR 0.74 (95% CI, 0.66–0.83). Longer follow-up did not alter the magnitude of this benefit. In contrast, for women between the ages of 40 and 49 at the start of these studies, the duration of follow-up did affect the risk of death from breast cancer. For these younger women, the RR of death from breast cancer in the screened group was 1.02 (95% CI, 0.73–1.27) after 7–9 years' follow-up and 0.83 (95% CI, 0.65–1.06) after 10–12 years of follow-up. That same year, Smart et al. reported a meta-analysis of all published and presented data on the eight mammographic screening trials [38]. For women in the screened group between the ages of 40 and 49 at the start of the trials, the RR of death from breast cancer was 0.84 (95% CI, 0.69–1.02).

In 1996, an updated meta-analysis of the eight mammographic screening trials reported in Falun, Sweden [28]. In that study, the RR of death from breast cancer in the screened group for women aged 40–49 years at entry was 0.85 (95% CI, 0.71–1.01) compared with controls. The following year, Hendrick et al. published a meta-analysis of the eight mammographic screening trials, with average follow-up time of

12.7 years [29]. For women aged 40–49 at the start of the screening trials, a significant reduction in breast cancer mortality was seen in the screened group, the RR being 0.82 (95% CI, 0.71–0.95). A more recent meta-analysis demonstrated that screening mammography every 1–2 years in women 40–49 years of age results in a 15% decrease in breast cancer mortality after 14 years of follow-up (RR, 0.85 [95% CI, 0.73–0.99]) [39]. Thus, the various overviews indicate that a statistically significant benefit of screening younger women emerges with longer follow-up.

Clearly, these results indicate that the impact of mammography screening differs between younger and older women. For women who are over age 50 at the start of the screening trials, a significant reduction in breast cancer mortality is apparent after 7–9 years of follow-up, and longer follow-up does not change the magnitude of that benefit. In contrast, for women below age 50 at the start of the screening trials, the benefit of screening emerges gradually, with a significant reduction in breast cancer mortality appearing after 12 or more years of follow-up.

Gotzsche and Olsen scrutinized data from eight randomized controlled trials on mammography screening and argued that most of these trials were flawed (with the exception of the Canadian trials and the Malmo trial in Sweden) [40]. These authors reported discrepancies in the number of women randomized to the screened and control arms of the studies and also differences in the mean ages of women in the two arms of the studies. In their meta-analysis, the authors only included trials that they believed were adequately randomized, and concluded that mammography screening had no effect on breast cancer mortality (pooled RR 1.04, 95% CI, 0.84–1.27). This review was widely criticized [41, 42]. In 2006, Gotzsche and Nielsen updated this controversial overview, and included six trials in their meta-analysis (two trials that they considered adequately randomized and four that were considered as having suboptimal randomization) [43]. In their updated overview, the authors concluded that mammography screening reduces breast cancer mortality by about 20% (RR > 0.80, 95% CI, 0.73–0.88). However, the authors pointed out that the risks of mammography screening were considerable. False-positive results were far more common than true positives, and many women who underwent mammography screening were likely "over-diagnosed" as having breast cancer ("over-diagnosis" is discussed later in this chapter).

8.4 Effect of Age on Mammographic Screening

The effectiveness of mammography screening for women aged 40–49 has been a topic of intense controversy for many years. Several medical organizations have further fueled this controversy by issuing guidelines on mammography screening that were at odds with one another [44]. Despite opposition from a few medical groups, mammography screening for younger women has been widely recommended in the United States. This is not necessarily the case in Europe, however. Indeed, for many years, the United States has stood alone among the major industrialized countries in encouraging mammography screening for women between the ages of 40 and 49. There are several possible reasons for the difference between the American and European positions on this issue [45]. For instance, the "fee for service" health care system in the United States may encourage the use of mammography screening for younger women. Additionally, the medico-legal climate in the United States may contribute to the greater willingness of American physicians to recommend mammography screening for women below age 50. Yet despite the widespread use of mammography screening for younger women in the United-States, the U.S. breast cancer mortality rates continue to mirror those of many industrialized countries that do not recommend screening for this age group [46].

Why does it take longer to see a benefit for women who are below age 50 at the start of the mammography screening trials? There are several possible explanations [47]. One possibility is that screening may detect very slow-growing (indolent) tumors in younger women. Thus, a reduction in breast cancer mortality may take longer to appear. Kerlikowske has argued, however, that if this is the case, then detecting these slow-growing tumors after age *50* perhaps could provide the same reduction in risk of breast cancer deaths [48]. Alternatively, screening might not be very effective in younger women. Indeed, the delayed benefit of screening younger women actually might be attributed to screening these women after the age of 50. This possibility was studied by de Koning et al. using a computer simulation model known as MISCAN (microsimulation screening analysis) [49]. Their study suggested that most of the reduction in breast cancer mortality for women who were between the

ages of 40 and 49 at the start of the screening trials was, in fact, the result of screening these women beyond the age of 50.

Another important question is why the effect of mammography screening is different for women below and above age 50. Some investigators have argued that there is no rational basis for the abrupt change in the effectiveness of mammographic screening at age 50 [50]. Yet age 50 corresponds approximately to the age of the menopause, and the biology and epidemiology of breast cancer differ in premenopausal and postmenopausal women [51]. There is a steep rise in breast cancer incidence until about age *50,* followed by a less rapid increase after that age [52]. Recently, we pointed out that there are important qualitative age-interactions with respect to the etiology, prognosis, and treatment of breast cancer, and these interactions may suggest that breast cancers in younger and older women are different diseases, derived from different pathways [53]. A qualitative age-interaction is defined as the reversal of RRs or rates according to age at diagnosis. Once thought rare, qualitative age-interactions are commonly reported in studies that examine the etiology, prognosis, and treatment of breast cancer [54]. For instance, nulliparity, obesity, and oral contraceptives decrease breast cancer risk in younger women but increase risk in older women [50]. Additionally, high-risk tumors are common in younger women, whereas low-risk tumors are more common in the elderly, with bimodal peak frequencies at ages 50 and 70, respectively. By this we mean that premenopausal women have a higher proportion of larger tumors (>2 cm), node-positive tumors, and estrogen receptor-negative tumors than do postmenopausal women [53, 55]. Therefore, the results of the mammography screening trials are consistent with the results of other studies showing differences in the biology and epidemiology of breast cancers in younger and older women. Baines has drawn attention to the "mortality paradox" associated with mammography screening in younger women [56]. Baines points out that, during the initial years of follow-up, many of the screening trials actually show an increased number of deaths associated with mammography screening in younger women, with a decrease in the number of deaths evident after longer follow-up. In contrast, mammography screening in older women is associated with an immediate reduction in mortality.

Why might mammography screening be less effective in premenopausal women than in postmenopausal women? This question cannot be answered with any degree of certainty at the present time, but several possibilities should be considered. As screening advances the time of breast cancer diagnosis and allows for the early initiation of therapy, one might speculate that postmenopausal women benefit more from early therapy than do premenopausal women. Another possibility is that the sensitivity of mammography might be lower in premenopausal women, making it less effective as a screening test. Finally, Tabar et al. suggested that tumors of premenopausal women grow more rapidly than those of postmenopausal women [57]. In fact, the incidence of interval cancers (diagnosed between screening sessions) appears to be greater in premenopausal than in postmenopausal women. Thus, Tabar et al. suggest that reducing the interval between screening sessions (from 2 to 1 year) may improve the efficacy of mammographic screening for younger women.

Much interest centers on the optimal age for initiation of mammography screening (40 vs. 50), while the upper age limit for screening has received less attention. Although organizations in the United States generally recommend mammography screening for women aged 70 and older, little data support these recommendations [58]. Analysis of data from the Swedish trials might be interpreted to mean that mammography screening for women over age 70 is not effective [59]; however, meaningful conclusions cannot be drawn because few women over age 70 were included in these trials. Because a woman's risk of developing breast cancer increases with age, the efficacy of mammography screening for older women remains an important issue. Using a mathematical model (the Markov model), Kerlikowske et al. studied the effect of mammography screening in older women [60]. Their analysis suggests that mammography screening after age 69 is moderately cost-effective and results in a small gain in life expectancy for women with high bone mineral density (BMD) but is more costly in those with low BMD. These investigators calculated that, to prevent one death, either 1,064 women with high BMD or 7,143 women with low BMI, would need to be screened routinely from ages 69 to 79 years. Clearly, the risks and benefits of mammography screening should be weighed carefully before recommending it for older women. The risks of screening are discussed later in this chapter.

8.5 Screening Breast Ultrasound

Breast ultrasound (sonography) is primarily used to evaluate specific abnormalities discovered either on CBE or mammography. However, in recent years, there has been growing interest in the use of screening ultrasound as a supplement to mammography screening for women at increased risk for breast cancer and for those with dense breasts [61]. It has been suggested that ultrasound screening might be indicated for women with dense fibroglandular breast tissue, where the sensitivity of mammography is diminished. Recently, the American college of radiology imaging network (ACRIN) conducted a large prospective evaluation of mammography screening and ultrasound in approximately 2,809 women who were at increased risk for breast cancer and had heterogeneously dense or extremely dense breast parenchyma in at least one breast quadrant [62]. In this study, screening with mammography and ultrasound was associated with a 55% increased breast cancer detection rate when compared to screening with mammography alone. However, the addition of screening ultrasound was associated with a substantial increase in the number of false-positive results. To date, the impact of screening ultrasound on breast cancer mortality is not known. A large-scale randomized controlled trial is now underway in Japan to assess the impact of screening with both mammography and ultrasound on breast cancer mortality [63]

8.6 Screening Breast MRI

There have been at least six nonrandomized prospective studies that have evaluated annual MRI screening (in conjunction with mammography screening) for women at increased risk for developing breast cancer [64]. These studies were conducted in the United States, the Netherlands, Canada, the United Kingdom, Germany and Italy. Women who participated in these studies were BRCA 1 and BRCA 2 mutation carriers and others with a strong family history of breast cancer. In several of these studies, women were also screened with breast ultrasound and/or CBE. These studies showed that the sensitivity of MRI ranged from 77 to 100%, while the sensitivity of mammography or ultrasound ranged from 16 to 40%. Although the sensitivity of MRI is greater than that of mammography, its specificity is lower. Kriege et al reported that the specificity of MRI was 88% compared to 95% for mammography [65]. Furthermore, there is no data indicating whether or not the improved sensitivity of MRI screening translates to a greater reduction in breast cancer mortality. In April 2007, the American cancer society (ACS) issued guidelines for the use of MRI as an adjunct to mammography in breast cancer screening [66]. The ACS panel recommended breast MRI screening for BRCA mutation carriers, first-degree relatives of known BRCA mutation carriers who have not undergone genetic testing, women who have received radiation treatment to the chest, such as for Hodgkin's disease, and women with an approximately 20–25% or greater lifetime risk of breast cancer.

8.7 Screening by Clinical Breast Examination

CBE can be used either for screening (detecting cancers in asymptomatic women) or diagnosis (evaluating breast complaints). Screening by CBE differs from screening by BSE in that it requires the use of trained personnel. Since the advent of mammography screening, the role of CBE as a screening modality has diminished. Indeed, there is evidence to suggest that the increased use of mammography screening in the United States generally has been accompanied by a decline in the use of CBE as a screening modality [67]. Yet several influential medical organizations, such as the American College of Radiology, the ACS, and the American Medical Association continue to recommend screening with CBE in addition to mammography [68]. It is also important to note that about 5–10% of all breast cancers are detectable by CBE but not by mammography [68]. Although the impact of screening by CBE on breast cancer mortality has not been fully elucidated, it seems premature to abandon screening by CBE. Furthermore, screening programs should train their personnel to perform proper CBE.

CBE readily detects cancers larger than 1 cm [69]. Additionally, in the U.S. breast cancer detection and demonstration project (BCDDP), 39% of mammographically detected cancers smaller than 1 cm also were detectable by CBE [70]. Mittra et al. suggested

that careful screening by CBE would fail to detect in situ cancers and 22% of the mammographically detected invasive cancers smaller than 1 cm [69]. They argued that this advantage of mammography over CBE is not likely to be clinically significant.

A large randomized prospective trial was initiated in the Philippines in the late 1990s to assess the impact of screening by CBE on breast cancer mortality [71]. Women were randomized to receive either a combination of screening by CBE and instructions on the technique of breast-self examination or usual care. Women were aged 35–64 years at entry, and a total of 404,947 women were randomized (216,884 of these to the intervention arm and 188,063 to the control arm). Five rounds of screening were planned at intervals of 1–2 years, and the primary endpoint of the study was mortality. However, the study was terminated in December, 1997 (after the first screening round) because of poor compliance among the screen-positive women (many women with abnormalities detected on CBE declined further investigations or treatment).

It should be noted that four of the mammography screening trials have also included CBE as a screening modality: HIP, Edinburgh, and the Canadian NBSS I and II [25, 30, 33, 34]. The results of these four trials suggest that screening with CBE can effectively detect breast cancers. Barton et al. calculated that screening by CBE has a sensitivity of approximately 54% and a specificity of about 94% [72].

In the HIP trial, women were randomized to screening with mammography and CBE or no screening [26]. This study was conducted during the early years of the development of mammography, and a disproportionately large number of cancers were detected by CBE. Overall, in the HIP trial, 67% of the cancers in the screened population were detected by CBE. Of these, *45%* were detected by CBE alone and 22% by CBE and mammography. Only 33% of the cancers were detected by mammography alone. In the HIP trial, age seemed to influence the effectiveness of CBE in detecting breast cancer. For women aged 50–59 years, 40% of the cancers were detected by CBE alone and 42% by mammography alone; however, for women aged 40–49, CBE was much more effective in detecting tumors than mammography, with 61% of cancers detected by CBE alone and 19% by mammography alone. Thus, CBE might have contributed much to the reduction in breast cancer mortality observed in the screened group of the HIP trial.

In the Edinburgh trial, women were randomized to screening with mammography and CBE or no screening [30]. In that study, 74% of the cancers in the screened group were detected by CBE, with 3% detected by CBE alone and 71% by mammography and CBE. Mammography alone detected 26% of the cancers in the screened population. Thus, the Edinburgh trial also suggests that screening by CBE is effective in detecting cancers.

In the CNBSS I, women aged 40–49 were randomized to either screening with mammography and CBE or no screening [33]. The results of the CNBSS I trial are consistent with those of other trials, showing no benefit to screening younger women during the first 7–9 years of follow-up. In the CNBSS II, women aged 50–59 at entry were randomized to either screening with CBE alone or CBE and mammography [34]. While other trials showed a benefit to mammography screening for this age group, the CNBSS II found that it provided no survival advantage. This result might be interpreted to mean that mammography screening contributes nothing to breast cancer mortality reduction beyond that achievable with screening with CBE alone. In the CNBSS, CBE detected *59%* of the cancers in women aged 40–49. Of these, 32% were detected by CBE alone and 27% by CBE and mammography. For women aged 50–59, 44% of the cancers were detected by CBE, with 18% detected by CBE alone and 26% detected by CBE and mammography. The results of the CNBSS are therefore consistent with those of the HIP trial, indicating that screening by CBE is more effective in detecting cancers of younger women.

Although screening by CBE is effective in detecting breast cancer, its impact on breast cancer mortality is not known. If screening by CBE could reduce breast cancer mortality, it might be particularly useful in developing countries, where mammography screening is not affordable and breast cancer mortality rates are rising. As mentioned previously, a large trial to assess the efficacy of screening CBE on breast cancer mortality was initiated in the Philippines in the late 1990s, but terminated because of poor compliance [71]. However, another large trial was initiated in India in 1998 under the direction of Dr. Indraneel Mittra [73]. In the Indian trial, 120,000 women between the ages of 30–60 years are randomized to either an intervention arm (consisting of screening CBE, teaching of screening BSE, and visual inspection of the cervix by trained female health workers), or usual care. The women randomized to the

intervention arm will receive screening every 18 months for 6 years. The total follow-up period planned for this trial is 10 years.

Mittra et al. have argued that there is also a need for a clinical trial whereby women are randomized to either receive screening with mammography or CBE [69]. They have argued that there is compelling evidence to indicate that screening with CBE is a potentially effective screening modality, and that a direct comparison with screening mammography is therefore warranted.

8.8 Screening by Breast Self-Examination

Screening by BSE has been advocated since the early part of the twentieth century [74]. Today, it is widely promoted by various medical societies, breast cancer advocacy groups, and the media as an effective screening tool (generally in conjunction with mammography screening). Many hospitals and clinics throughout the United States sponsor classes where women are taught BSE techniques. BSE is a very appealing screening method because it is inexpensive, self-generated, and nonintrusive. Yet its efficacy in reducing breast cancer mortality has never been demonstrated.

Two randomized controlled trials have examined the efficacy of screening by BSE on breast cancer mortality. The first of these was the World Health Organization trial of BSE undertaken in St. Petersburg, Russia [75]. Women in this study were recruited from 1985 to 1989. There were 57,712 women from 14 randomly selected outpatient hospitals who were taught BSE. Another 64,759 women from another 14 outpatient hospitals served as controls. Semiglazov et al. reported the preliminary results of this trial in 1992 [75]. The number of breast cancers detected in the two arms of the study was nearly identical (190 cases in the BSE group and 192 in the control group), and there was no significant difference in mortality between the two groups. Additionally, no significant differences were found between the two groups with respect to the size of the primary tumor or incidence of nodal metastasis. Of note, the BSE-trained group had a higher number of excisional biopsies for benign lesions, the RR being *1.5* in the BSE group compared with controls (95% CI, 1.1–1.9). Semiglazov et al. reported a further update of this study in 1999 and again found no significant difference in the death rates between the BSE and control groups [76].

Another BSE trial was initiated in Shanghai, China, between 1989 and 1991 [77]. In that trial, 267,040 women were randomly assigned on the basis of work sites (520 textile factories) to receive either intensive BSE instruction (study group) or sessions on the prevention of low back pain (control group). After *5* years' follow- up, the number of breast cancer cases and the rate of breast cancer mortality were nearly identical in the two groups. Yet there was more than a twofold increase in the number of breast biopsies in the BSE group compared with the control group.

An updated meta-analysis of the Russian and Shanghai trials was reported by Kosters and Gotzsche from the Nordic Cochrane Center [73]. There was no statistically significant difference in breast cancer mortality between the BSE screening and control groups, RR 1.05 (95% CI, 0.90–1.24). However, almost twice as many breast biopsies with benign results were performed in the BSE groups when compared to the controls groups, RR 1.88 (95% CI, 1.77–1.99). Thus, screening by BSE is not without risk. There is evidence that it can generate considerable anxiety among women. Furthermore, false-positive and false-negative results may incur considerable costs and risks.

8.9 Potential Hazards of Screening

Clearly, breast cancer screening has advantages. The randomized controlled trials discussed in this chapter indicate that mammography screening can reduce breast cancer mortality by about 25% in postmenopausal women. Additionally, screen-detected cancers are generally smaller than those detected clinically and are therefore more amenable to treatment with conservative surgery (i.e., lumpectomy, quadrantectomy, or segmental resection) than cancers detected clinically. Furthermore, breast MRI might be a particularly useful screening tool for women at high risk for breast cancer (such as mutation carriers), because its sensitivity is greater than that of mammography.

Yet there are certain hazards associated with breast cancer screening. Five potentially harmful consequences of screening merit consideration: lead time, false positives, radiation exposure, overdiagnosis, and cost (Table 8.3).

Table 8.3 Potential hazards of screening

Lead time	Advanced notice of a cancer diagnosis without tangible gain
Radiation exposure (mammography)	Possible increased risk of breast cancer in patients susceptible to the effects of low-dose radiation
False-positives	Results in unnecessary breast biopsies
Over-diagnosis	Adverse financial/emotional consequences of being falsely labeled as a cancer patient
Cost	Costs of breast cancer screening may divert resources away from more mundane health care needs

8.9.1 Lead Time

Screening advances the time of breast cancer diagnosis, but this does not benefit all women. The randomized controlled trials indicate that mammography screening in postmenopausal women reduces breast cancer mortality by about *25%*. Thus, for most women, advancing the time of breast cancer diagnosis by mammography screening does not change the outcome. As a result of screening, many women are simply given advanced notice of a cancer diagnosis with no tangible gain. This "lead time" effect of screening (in the absence of any tangible benefit) may have an adverse impact on quality of life.

8.9.2 False Positives

False positives are cases that are reported as suspicious or malignant on screening that, on further evaluation (such as a breast biopsy), prove benign. False positives have an adverse effect on quality of life and result in additional health care expenditures. For mammography screening, the false-positive rate is much greater in the United States than in Europe, perhaps because of the fear of litigation in the United States, resulting in a greater unwillingness of American radiologists to commit themselves to a benign diagnosis [78].

Elmore et al. calculated that, after ten mammograms, a woman in the United States has about a 49% cumulative risk of a false-positive result [79]. Overall, approximately 10.7% of all screening mammograms in the United States lead to a false-positive result. For woumen between the ages of 40-49, the cumulative risk is about 56%, whereas for those aged 50–79, the cumulative risk of a false-positive result after ten mammograms is about 47%. In contrast, the cumulative 10-year risk of a false-positive mammogram in the Norwegian Breast Cancer Screening program is about 21% [80].

Evidence from the CNBSS II suggests that there are fewer false-positives associated with screening by CBE [69]. In that study, women aged 50–59 were randomized to either screening with CBE or screening with mammography and CBE. No significant difference was found in the mortality between the two arms of the study. The rate of biopsy of benign breast lumps was 3 times higher with combined screening, however, compared with screening with CBE alone.

One study found that women are generally aware that mammography screening can produce false-positive results [82]. The study also indicated that most women consider false positives an acceptable consequence of mammography screening and are willing to tolerate such results. Indeed, the survey found that 63% of all women thought that 500 or more false positives per life saved was reasonable, and 37% were willing to tolerate as many as 10,000 false positives per life saved. Yet analyses of data from the U.S. national health interview survey (NHIS) indicate that false-positive mammograms have an adverse effect on the quality of life [82]. In this random sampling of the U.S. population, women who had previously experienced false-positive mammograms were more likely to report symptoms of anxiety and depression.

8.9.3 Radiation Exposure

Bailar was one of the first to suggest that low-dose radiation exposure from mammography screening might induce breast cancer [83]. Subsequently, Beemsterboer et al. developed a computer simulation model to estimate breast cancer deaths caused from exposure to low-dose radiation and the number of lives saved as a result of mammography screening [84]. These estimates were based on data from the Swedish mammography screening trials and the Netherlands breast cancer screening program. In their model, the ratio between the number of breast cancer deaths prevented with those induced as a result of mammography

screening for women aged 50–69 was 242:1, assuming a 2-year screening interval and a mean glandular dose of 4 mGy to each breast from a two-view mammogram. When mammography screening was expanded to include women aged 40–49, the ratio was 97:1. Thus, according to this model, the potential hazards of low-dose radiation are greatly increased if mammography screening is initiated below age 50.

Swift et al. called attention to the potential hazards of mammography screening in carriers of the gene for ataxia-telangiectasia (AT) [85]. These carriers are at increased risk for developing breast cancer after exposure to relatively low doses of radiation. Approximately 1.4% of all individuals are heterozygote carriers of the gene for AT, so the population potentially at risk from the harmful effects of low-dose radiation is large. Identifying these persons before mammography screening would be a huge, expensive undertaking and is probably not feasible. The amount of radiation required to induce breast cancer in a heterozygote carrier of the gene for AT is not clear. Some investigators speculate that a total dose of 20 mGy would be required [85, 86]. If so, a carrier of the AT gene who undergoes mammography screening every 2 years might accumulate a hazardous dose of ionizing radiation over a 10-year period, assuming a mean glandular dose of 4 mGy to each breast from a two-view mammogram.

Women who carry mutations in the *BRCA1* and *BRCA2* genes have an increased risk of developing breast cancer. Over the years, several medical organizations have recommended that BRCA 1 and BRCA 2 mutation carriers begin annual mammography screening at age 25–30 years [68, 87]. These recommendations did not consider, however, the potential hazards of low-dose radiation associated with mammography screening. The *BRCA 1* and *BRCA2* genes are required for DNA repair, and it has been suggested that women who carry mutations in these genes might be very sensitive to the effects of low doses of radiation [88]. The cumulative lifetime risk of radiation-induced breast cancer mortality is higher in younger women, and a recent study suggests that there is no net benefit for mammography screening in BRCA mutation carriers who are younger than age 35 [89]. These concerns make breast MRI a particularly attractive screening option for young women who carry the BRCA 1 or BRCA 2 mutation. In contrast to mammography, there is no radiation exposure associated with MRI screening.

8.9.4 Over-Diagnosis

During the last 30 years, breast cancer incidence in the United States has increased dramatically, partly because of the impact of "over-diagnosis" attributable to mammography screening. Peeters and colleagues defined over-diagnosis as "a histologically established diagnosis of intraductal or invasive cancer that would never have developed into a clinically manifest tumor during the patient's normal life expectancy if no screening examination had been carried out" [90]. Long-term follow-up of the Malmo screening trial suggests that about a quarter of the breast cancers detected with mammography screening represent over-diagnosis [91].

To understand how screening might over-diagnose invasive breast cancer, consider the following hypothetical situation. A 65-year-old woman with severe coronary artery disease undergoes routine mammography screening. As a result of that screening, an occult (nonpalpable) invasive breast cancer is discovered. This cancer is treated with surgery, radiotherapy, and tamoxifen. One year later, this patient dies of a myocardial infarction (MI). As mammography screening advances the time of breast cancer diagnosis by about 2–4 years, this patient's breast cancer probably would not have been discovered without screening. She probably would have died of a MI, never knowing that she had breast cancer and would have been spared the treatments resulting from her cancer diagnosis. This example illustrates how screening might unmask invasive cancers that would not have become clinically symptomatic or pose a threat to a woman's normal life expectancy. Recently, Zahl et al. suggested that some of the occult invasive breast cancers detected by mammography screening might ultimately have undergone spontaneous regression [92].

However, an even greater problem associated with mammography screening is the over-diagnosis of non-invasive (in situ) cancers [93]. Since the advent of mammography screening, the incidence of ductal carcinoma in situ (DCIS) has increased dramatically [94]. DCIS is rarely palpable and therefore seldom detected by clinical examination. Most cases of DCIS are diagnosed by mammography screening. Indeed, before the advent of mammography screening, DCIS accounted for only 1–2% of all breast cancer cases in the United States [95]. In more recent years, DCIS has accounted for more than 12% of all breast cancer cases and about 30% of those discovered mammographically [96].

Many clinicians have long assumed that DCIS is a preinvasive cancer that, if left untreated, invariably progresses to invasive breast cancer. This assumption was based on two observations. First, after simple excision of DCIS, recurrences often occur, many of which are invasive breast cancers. Second, DCIS often is adjacent to invasive breast cancer, suggesting that DCIS was the precursor to the invasive tumor. Evidence now suggests, however, that most cases of DCIS would not progress to manifest breast cancers clinically during a woman's lifetime. Nielsen et al. reported the results of 110 medico-legal autopsies performed at the Fredericksburg Hospital in Copenhagen, Denmark [97]. These autopsies were performed on women who had died of accidents. DCIS was found incidentally in 15% of these women, a prevalence 4–5 times greater than the number of overt cancers expected to develop over a 20-year period. Additionally, in two separate studies, Rosen et al. and Page et al. retrospectively reviewed benign breast biopsies and found numerous instances where the initial pathologist overlooked DCIS [98, 99]. In both studies, only about 25% developed clinically manifest invasive breast cancers after 15–18 years follow-up. Finally, in women with a previous diagnosis of breast cancer, Alpers and Wellings found DCIS in about 48% of contralateral breasts at autopsy, but only about 12.5% of these women would be expected to develop contralateral breast cancer over a 20-year period [100]. Together, these studies suggest that perhaps only one of every four or five cases of DCIS detected mammographically would progress to a clinically manifest breast cancer during a woman's lifetime.

8.9.5 Cost

Health care resources are often limited, particularly in developing countries. Ideally, these resources should be distributed equitably across a wide range of health care programs to obtain the maximum benefit. Again, it is important to emphasize that women who are invited to participate in breast cancer screening programs are not "patients" and most do not become patients. Yet breast cancer screening programs often use expensive technology. Resources directed toward maintaining breast cancer screening programs could lower resources available for more pressing and mundane health care programs, adversely affecting the health of an entire community. To put this matter into perspective, Kattlove et al. estimated, in 1995, the cost of potentially saving one life over a 10-year period with mammography screening [101]. For women aged 40–49, the estimated cost of screening was considerably higher when compared to the cost of screening for women aged 50–59, which in turn was higher than the cost for women aged 60–69. If health care resources are limited, then age should be considered when deciding how best to appropriate scarce resources. Additionally, it is important to consider that the cost-effectiveness of CBE screening for breast cancer in developing countries such as India may compare favorably with that of mammography screening in the developed countries [102].

8.10 Conclusion

More is known about screening for breast cancer than for any other type of cancer. In this chapter, the commonly used breast cancer screening methods were discussed. These are mammography, CBE using trained personnel, BSE, ultrasound, and MRI. Randomized controlled trials indicate that mammography screening in postmenopausal women can reduce breast cancer mortality by about 25%; however, its effect in premenopausal women is disputed. To date, no data are available from randomized prospective trials comparing the effect of screening by CBE with no screening on breast cancer mortality. However, several mammography screening trials incorporated CBE as a screening modality, and the results of these trials suggest that CBE might be an effective screening tool. A large, randomized, prospective study has been initiated in India to study this possibility further. Thus far, data from two large, randomized, prospective trials indicate that screening with BSE has no effect in reducing breast cancer mortality.

In the lay media, considerable emphasis is placed on the potential benefits of breast cancer screening, and little attention paid to its potential risks. Women who volunteer for breast cancer screening are generally healthy, and the vast majority will derive no tangible gain from screening. Many women seem to be poorly informed about the impact of screening on their risk of dying of breast cancer. Black et al. surveyed 200 women between the ages of 40 and 50 with no

history of breast cancer and found that these women overestimated their probability of dying of breast cancer by more than 20-fold and the effectiveness of screening in reducing mortality by sixfold [103]. Thus, a more balanced presentation about breast cancer risk and the effectiveness of screening is warranted. Not only should the potential for benefit be discussed with each woman prior to screening, but the potential risks outlined as well.

Yet it is also important to note that several recent studies have suggested that breast cancer screening has contributed to declines in population-based breast cancer mortality rates [104, 105]. Inequalities in the use of screening (as well as differences in the effectiveness of screening) might also partly account for the widening racial disparity in breast cancer mortality rates in the United States [106]. Clearly, a closer scrutiny of population-based statistics is needed to better discern the overall impact of breast cancer screening.

Acknowledgment The opinions or assertions contained herein are the private views of the authors and should not be construed as reflecting the views of the Departments of the Army, Navy, or Defense.

References

1. Eddy DM (1989) Screening for lung cancer. Ann Intern Med. 111:232–7
2. MacDonald I (1951) Biological predeterminism in human cancer. Surg Gynecol Obstet. 92:443–52
3. Black MM, Speer FD (1953) Biological variability of breast carcinoma in relation to diagnosis and therapy. NY State J Med. 53:1560–3
4. Devitt JE (1994) Breast cancer: have we missed the forest because of the tree? Lancet. 344:734–5
5. Haagensen CD (1956) Diseases of the breast. WB Saunders, Philadelphia
6. Jatoi I (1999) Breast cancer screening. Am J Surg. 177:518–24
7. Jatoi I (1997) Breast cancer: a systemic or local disease? Am J Clin Oncol. 20:536–9
8. Cole P, Morrison AS (1980) Basic issues in population screening for cancer. J Natl Cancer Inst. 64:1263–72
9. Nielsen C, Lang RS (1999) Principles of screening. Med Clin North Am. 83:1323–37
10. Anderson TJ, Lamb J, Alexander F et al (1986) Comparative pathology of prevalent and incident cancers detected by breast cancer screening: Edinburgh breast screening project. Lancet. 1:519–23
11. Gilliland FD, Joste N, Stauber PM et al (2000) Biologic characteristics of interval and screen-detected breast cancer. J Natl Cancer Inst. 92:743–9
12. Xu IL, Prorok PC (1995) Non-parametric estimation of the post-lead-time survival distribution of screen- detected cancer cases. Stat Med. 14:2715–25
13. Black WC, Welch HG (1993) Advances in diagnostic imaging and overestimation of disease prevalence and the benefits of therapy. N Engl J Med. 328:1237–43
14. Kiemi PJ, Joensuu H, Toikkanen S et al (1992) Aggressiveness of breast cancers found with and without screening. Br Med J. 304:467–9
15. Schmidt JG (1990) The epidemiology of mass breast cancer screening – a plea for a valid measure of benefit. J Clin Epidemiol. 43:215–22
16. Monsees BS, Destouet JM (1992) A screening mammography program: staying alive and making it work. Radiol Clin North Am. 30:211–9
17. Hurley SF, Kaldor JM (1992) The benefits and risks of mammographic screening for breast cancer. Epidemiol Rev. 14:101–30
18. Salomon A (1913) Beitrage zur pathologie und klinik der maminacrcinome. Arch f klin Chir. 101:573–668
19. Warren SL (1930) A roentgenologic study of the breast. Am J Roentgenol. 24:113–24
20. Gershon-Cohen I, Ingleby H, Moore L (1956) Can mass X-ray surveys be used in detection of early cancer of the breast? JAMA. 161:1069–71
21. Gershon-Cohen I, Hermel MB, Berger SM (1961) Detection of breast cancer by periodic X-ray examinations. JAMA. 176:1114–6
22. Egan RL (1962) Mammography, an aid to diagnosis of breast carcinoma. JAMA. 182:839–43
23. Fletcher SW, Black W, Harris R et al (1993) Report of the international workshop on screening for breast cancer. J Natl Cancer Inst. 85:1644–56
24. Shapiro S, Venet W, Strax P et al (1982) Ten- to fourteen-year effect of screening on breast cancer mortality. J Natl Cancer Inst. 69:349–55
25. Eddy DM, Hasselblad V, McGivney W et al (1988) The value of mammography screening in women under age 50 years. JAMA. 259:1512–9
26. Shapiro S, Venet W, Strax P et al (1988) Periodic screening for breast cancer: the Health Insurance Plan Project and Its Sequelae, 1963–1986. Johns Hopkins University, Baltimore
27. Nystrom L, Rutqvist LE, Wall S et al (1993) Breast cancer screening with mammography: overview of Swedish randomized trials. Lancet. 341:973–8
28. Organizing Committee and Collaborators (1996) Breast cancer screening with mammography in women aged 40–49 years: report of the Organizing Committee and Collaborators, Falun Meeting, Falun, Sweden (21 and 22 March 1996). Int J Cancer. 68:693–9
29. Hendrick RE, Smith RA, Rutlege JH et al (1997) Benefit of screening mammography in women aged 40–49: a new meta-analysis of randomized controlled trials. Monogr Natl Cancer Inst. 22:87–92
30. Alexander FE, Anderson TI, Brown H et al (1994) The Edinburgh randomised trial of breast cancer screening: results after 10 years of follow-up. Br J Cancer. 70:542–8
31. Alexander FE (1997) The Edinburgh randomized trial of breast cancer screening. Monogr Natl Cancer Inst. 22:31–5

32. Alexander FE, Anderson TI, Brown HK et al (1999) 14 years of follow-up from the Edinburgh randamised trial of breast cancer screening. Lancet. 353:1903–8
33. Miller AB, Baines CI, To T et al (1992) Canadian national breast screening study I. Breast cancer detection and death rates among women aged 40 to 49 years. Can Med Assoc J. 147:1459–76
34. Miller AB, Baines CJ, To T et al (1992) Canadian national breast screening study II. Breast cancer detection and death rates among women aged 50 to 59 years. Can Med Assoc J. 147:1477–88
35. Miller AB, To T, Baines CI, Wall C (2000) Canadian national breast screening study-2: 13-year results of a randomized trial in women aged 50–59 years. J Natl Cancer Inst. 92:1490–9
36. Mosss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L (2006) Trial management group. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomized controlled trial. Lancet. 368(9552):2053–60
37. Kerlikowske K, Grady D, Rubin SM et al (1995) Efficacy of screening mammography. A meta-analysis. JAMA. 273: 149–54
38. Smart CR, Hendrick RE, Rutledge JH III et al (1995) Benefit of mammography screening in women ages40 to 49 years: current evidence from randomized controlled trials. Cancer. 75:1619–25
39. Humphrey LL, Helfand M, Chan BK, Woolf SH (2002) Breast cancer screening: a summary of the evidence for the U.S. preventive services task force. Ann Intern Med. 137: 347–60
40. Gotzsche PC, Olsen O (2000) Is screening for breast cancer with mammography justifiable? Lancet. 355:129–34
41. Duffy SW, Tabar L (2000) Screening mammography re-evaluated. Lancet. 355:747–8
42. Dean PB (2000) Final comment. The articles by Gotzsche and Olsen are not Official Cochrane reviews and lack scientific merit. Lakartidningen. 97:3106
43. Gotzsche PC, Nielsen M. Screening for breast cancer with mammography. Cochrane Database Syst Rev. 2006;(4): CD001877
44. Jatoi I (1997) The case against mammographic screening for women in their forties. In: Jatoi I (ed) Breast cancer screening. Landes Biosciences, Austin, TX, pp 35–49
45. Jatoi I, Baum M (1993) American and European recommendations for screening mammography in younger women: a cultural divide? RMJ. 307:1481–3
46. Davis DL, Love SM (1994) Manmographic screening. JAMA. 271:152–3
47. Fletcher SW (1997) Breast cancer screening among women in their forties: an overview of the issues. Monogr Natl Cancer Inst. 22:5–9
48. Kerlikowske K (1997) Efficacy of screening mammography among women aged 40 to 49 years and 40 to 69 years: comparison of relative and absolute benefit. Monogr Natl Cancer Inst. 22:79–86
49. de Koning HJ, Boer R, Warmerdam PG et al (1995) Quantitative interpretations of age-specific mortality reductions from the Swedish breast cancer screening trials. J Nati Cancer Inst. 87:1217–23
50. Kopans DB (1997) The case in favor of mammographic screening for women in their forties. In: Jatoi I (ed) Breast cancer screening. Landes Biosciences, Austin, TX, pp 9–34
51. Elwood JM, Cox B, Richardson AK. The effectiveness of breast cancer screening by mammography in younger women. Online J Curr Clin Trials. 1993 (Doc No. 32)
52. Clemmensen J (1948) Carcinoma of the breast: results from statistical research. Br J Radiol. 21:583
53. Jatoi I, Anderson WF, Rosenberg PS (2008) Qualitative age-interactions in breast cancer: a tale of two diseases? Am J Clin Oncol. 31:504–6
54. Willett W (1990) Nutritional epidemiology. Oxford University, New York
55. Henderson IC (1992) Biologic variations of tumors. Cancer. 69:1888–95
56. Baines CJ (2003) Mammography screening: are women really giving informed consent? J Natl Cancer Inst. 95(20): 1512–3
57. Tabar L, Fagerberg G, Day NE et al (1987) What is the optimum interval between mammographic screening examinations? An analysis based on the latest results of the Swedish two-county breast cancer screening trial. Br J Cancer. 55:547–51
58. Leitch AM, Dodd GD, Constanza M et al (1997) American cancer society guidelines for the early detection of breast cancer: update 1997. CA Cancer J Clin. 47:150–3
59. Larsson LG, Nystrom L, Wall S et al (1996) The Swedish randomized mammography screening trials. J Med Screen. 3:129–32
60. Kerlikowske K, Salzmann P, Phillips KA et al (1999) Continuing screening mammography in women aged 70 to 79 years: impact on life expectancy and cost-effectiveness. JAMA. 282:2156–63
61. Kuhl CK (2008) The "coming of age" of nonmammographic screening for breast cancer. JAMA. 299(18):2203–5
62. Berg WA, Blume JD, Cormack JB (2008) Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA. 299(18):2151–63
63. Tohno E, Ueno E, Watanabe H (2009) Ultrasound screening of breast cancer. Breast Cancer. 16(1):18–22
64. Jatoi I, Anderson WF (2008) Management of women who have a genetic predisposition for breast cancer. Surg Clin North Am. 88(4):845–61
65. Kriege M, Brekelmans CT, Boetes C et al (2004) Efficacy of MRI and mammography for breast cancer screening in women with a familial or genetic predisposition. N Engl J Med. 351(5):427–37
66. Saslow D, Boetes C, Burke W et al (2007) American cancer society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 57(2):75–89
67. Bums RB, Freund KM, Ash AS et al (1996) As mammography use increases, are some providers omitting clinical breast examination? Arch Intern Med. 156:741–4
68. Saslow D, Hannan J, Osuch J et al (2004) Clinical breast examination: practical recommendations for optimizing performance and reporting. CA Cancer J Clin. 54: 327–44
69. Mittra I, Baum M, Thornton H et al (2000) Is clinical breast examination an acceptable alternative to mammographic screening? BMJ. 321:1071–3

70. Report of the Working Group to review the National Cancer Institute-American Cancer Society breast cancer detection demonstration projects. J Nati Cancer Inst. 1979;62: 639–709
71. Pisani P, Parkin DM, Ngelangel C, Esteban D et al (2006) Outcome of screening by clinical examination of the breast in a trial in the Philippines. Int J Cancer. 118(1):149–54
72. Barton MB, Harris R, Fletcher SW (1999) Does this patient have breast cancer? The screening clinical breast examination: should it be done? How? JAMA. 282:1270–80
73. Kosters JP, Gotzsche PC. Regular self-examination or clinical examination for early detection of breast cancer. Cochrane Database of Systematic Reviews 2003, issue 2. Art. No. CD003373. DOI: 10.1002/14651858.CD003373
74. Adair FE (1933) Clinical manifestations of early cancer of the breast – with a discussion on the subject of biopsy. N Engl J Med. 208:1250–5
75. Semiglazov VF, Moiseyenko VM, Bavli JL, Migmanova N et al (1992) The role of breast self-examination in early breast cancer detection (results of the 5-year USSR/WHO randomized study in Leningrad). Eur J Epidemiol. 8(4):498–502
76. Semiglazov VF, Moiseyenko VM, Manikhas AG, Protsenko SA, Kharikova RS, Ivanow VG et al (1999) Role of breast self-examination in early detection of breast cancer: Russia/WHO prospective randomized trial in St.Petersburg. Cancer Strategy. 1:145–51
77. Thomas DB, Gao DL, Ray RM, Wang WW, Allison CJ, Chen FL et al (2002) Randomized trial of breast self-examination: final results. J Natl Cancer Inst. 94(19):1445–57
78. Fletcher SW, Elmore JG (2005) False-positive mammograms – can the USA learn from Europe? Lancet. 365:7–8
79. Elmore JG, Barton MB, Moceri VM et al (1998) Ten-year risk of false-positive screening mammograms and clinical breast examinations. N Engl J Med. 338:1089–96
80. Hofvind S, Thorsen S, Tretli S (2004) The cumulative risk of a false-positive recall in the Norwegian breast cancer screening program. Cancer. 101:1501–7
81. Schwartz LM, Woloshin S, Sox HC et al (2000) U.S. women's attitudes to false-positive mammography results and detection of ductal carcinoma in situ: cross sectional survey. BMJ. 320:1635–40
82. Jatoi I, Zhu K, Shah M, Lawrence W (2006) Psychological distress in U.S. women who have experienced false-positive mammograms. Breast Cancer Res Treat. 101:191–200
83. Bailar JC (1976) Mammography: a contrary view. Ann Intern Med. 84:77–84
84. Beemsterboer PM, Warmerdam PG, Boer R et al (1998) Radiation risk of mammography related to benefit in screening programmes: a favourable balance? J Med Screen. 5:81–7
85. Swift M, Morrell D, Massey RB et al (1991) Incidence of cancer in 161 families affected by ataxia-telangiectasia. N Engl J Med. 325:1831–6
86. Werneke U (1997) Ataxia telangiectasia and risk of breast cancer. Lancet. 350:739–40
87. Robson M, Offit K (2007) Clinical practice. Management of an inherited predisposition to breast cancer. N Engl J Med. 357(2):154–62
88. Vaidya JS, Baum M (1997) Benefits and risks of screening mammography in women with BRCA1 and BRCA2 mutations. JAMA. 278:290
89. de Gonzalez AM, Berg CD, Visvanathan K, Robson M (2009) Estimated risk of radiation-induced breast cancer from mammographic screening for young BRCA mutation carriers. J Natl Cancer Inst. 101:205–9
90. Peeters PH, Verbeek AL, Straatman H et al (1989) Evaluation of over-diagnosis of breast cancer in screening with mammography: results of the Nijmegen programme. Int J Epidemiol. 18:295–9
91. Zackrisson S, Andersson I, Janzon L, Manjer J, Garne JP (2006) Rate of over-diagnosis of breast cancer 15 years after end of Malmo mammographic screening trial: follow-up study. Br Med J. 332(7543):689–92
92. Zahl P, Maehlen J, Welch HG (2008) The natural history of invasive breast cancers detected by screening mammography. Arch Intern Med. 168(21):2311–6
93. Jatoi I, Baum M (1995) Mammographically detected ductal carcinoma in situ: are we overdiagnosing breast cancer? Surgery. 118:118–20
94. Welch HG, Woloshin S, Schwartz LM (2008) The sea of uncertainty surrounding ductal carcinoma in situ – the price of screening mammography. J Natl Cancer Inst. 100(4): 228–9
95. Moore MM (1991) Treatment of ductal carcinoma in situ of the breast. Semin Surg Oncol. 7:267–70
96. Emster VL, Barclay J, Kerlikowske K et al (1996) Incidence of and treatment for ductal carcinoma in situ of the breast. JAMA. 275:913–8
97. Nielsen M, Thomsen JL, Primdahl S et al (1987) Breast cancer and atypia among young and middle aged women: a study of 110 medicolegal autopsies. Br J Cancer. 56: 814–9
98. Rosen PR, Braun DW Jr, Kinne DE (1980) The clinical significance of pre-invasive breast carcinoma. Cancer. 46:919–25
99. Page DL, Dupont WD, Rogers LW et al (1982) Intraductal carcinoma of the breast: follow-up after biopsy only. Cancer. 49:751–8
100. Alpers CE, Wellings SR (1985) The prevalence of carcinoma in situ in normal and cancer-associated breasts. Hum Pathol. 16:796–807
101. Kattlove H, Liberati A, Keeler B et al (1995) Benefits and costs of screening and treatment for early breast cancer: development of a basic benefit package. JAMA. 273: 142–8
102. Okonkwo QL, Draisma G, der Kinderen A, Brown ML, de Koning HJ (2008) Breast cancer screening policies in developing countries: a cost-effectiveness analysis for India. J Natl Cancer Inst. 100:1290–300
103. Black WC, Nease RF, Tosteson AN (1995) Perceptions of breast cancer risk and screening effectiveness in women younger than 50 years of age. J Natl Cancer Inst. 87:720–31
104. Berry DA, Cronin KA, Plevritis SK et al (2005) Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med. 353(17):1784–92
105. Jatoi I, Chen BE, Anderson WF, Rosenberg PS (2007) Breast cancer mortality trends in the United States according to estrogen receptor status and age at diagnosis. J Clin Oncol. 25(13):1683–90
106. Jatoi I, Anderson WF, Rao SR, Devesa SS (2006) Breast cancer trends among black and white women in the United States. J Clin Oncol. 23(31):7836–41

Breast Imaging

9

Lawrence W. Bassett, Anne C. Hoyt,
Cheryce Poon, and Lien Tran

9.1 Introduction

Mammography continues to be the primary imaging modality for breast cancer screening and diagnosis. In the last decade, the introduction of digital mammography ranks as the most important technologic improvement in breast imaging. Advances in the overall quality of mammography performance are related to the efforts of programs established both by professional societies and government agencies. Introduction of the American College of Radiology (ACR) Mammography Accreditation Program in 1987 [1] and the Mammography Quality Standards Act in 1994 [2] is among the most significant of these efforts. In addition, the ACR breast imaging reporting and data system (BI-RADS) continues to improve the communication of mammography results, monitoring and tracking of patients and quality assurance activities, such as the medical audit [3]. Owing to its importance and now widespread international use, the BI-RADS-standardized lexicon should be understood by referring physicians and will be used throughout this chapter. The latest edition of BI-RADS includes ultrasound and breast magnetic resonance imaging (MRI).

Ultrasonography is the most important adjunctive imaging modality for mammography. Like mammography, ultrasonography also has undergone significant technical improvements that have extended its contributions to breast imaging. Other imaging modalities include MRI (Breast MRI) and radiolonuclide imaging. Advances in imaging-guided breast biopsy techniques led to the widespread use of stereotactic- and ultrasound-guided breast core needle biopsy (CNB) as the primary method for breast biopsy.

9.2 Mammography

Mammography exams can be divided into two basic types: Screening and Diagnostic. *Screening mammography* is an examination of an asymptomatic woman to detect clinically occult breast cancer [4]. The standard screening examination includes two views of the breast: a mediolateral oblique (MLO) and a craniocaudal (CC) (Fig. 9.1) [5]. The effectiveness of screening mammography for mortality reduction from breast cancer has been confirmed by evaluations of randomized clinical trials [6]. While there is general agreement that screening mammography reduces mortality from breast cancer in women over 50 years of age, there has been considerable debate over the effectiveness of screening mammography for women aged 40–49 [7]. Based on evidence of benefit from meta-analysis of randomized controlled studies [8], the American Cancer Society (ACS) and most major professional medical societies continue to recommend mammography screening for women aged 40–49. An important follow-up to the screening studies in Sweden, published in 2002, strongly supports the value of mammography screening in women aged 40–49 [9]. This study also proved that the reductions in breast cancer mortality were due to mammography screening rather than advancements in treatment. In this national clinical trial, seven Swedish counties were offered screening mammography and their breast cancer mortality rates were compared to counties without mammography screening.

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_9, © Springer-Verlag Berlin Heidelberg 2010

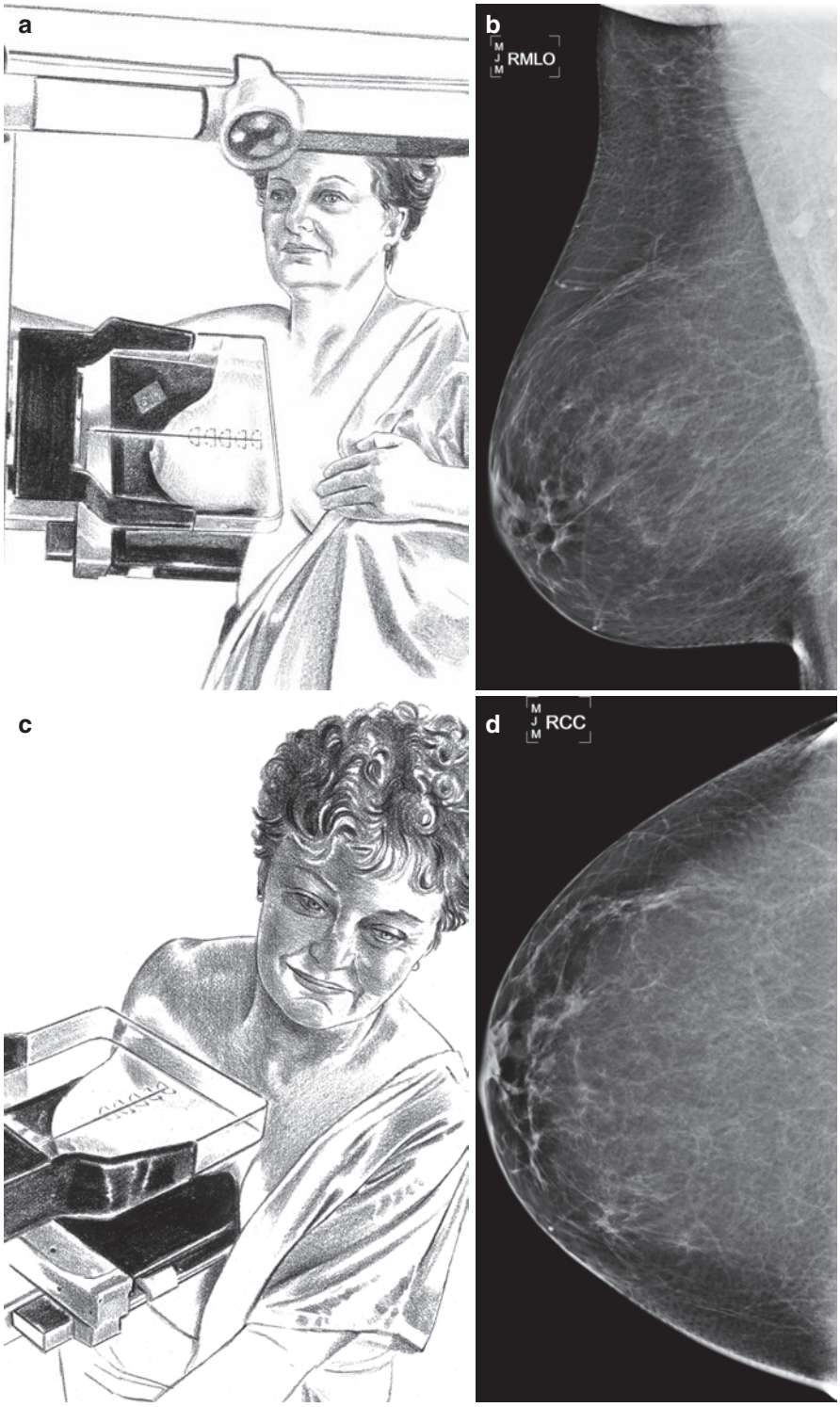

Fig. 9.1 Screening mammograms. (**a**) Positioning for the right mediolateral oblique (MLO) projection. (**b**) Right full-field digital mammography MLO image. (**c**) Positioning for the Right craniocaudal (CC) view. (**d**) Right full-field digital mammography CC image

Mortality reduction was 30% for women in counties that offered screening without mammogram and 45% in women who actually had mammograms in the screening trial. Advancements in treatment were the same in the screened and not screened counties. Therefore, the mortality reduction in screened counties could only be attributed to the availability of mammography screening.

After the widespread use of mammography in the United States, the majority of breast cancers detected were detected earlier. In 2002, this motivated a revision of the American Joint Committee on Cancer (AJCC) staging system for breast cancer [10]. Since most cancers were being detected at Stage 1 (invasive tumors ≤2 cm), the AJCC subdivided Stage 1 into these subcategories: (1) Tis > carcinoma-in-situ (preinvasive), (2) T1mic > microinvasion ≤1 mm, (3) T1a > 1–5 mm, (4) T1b > 5 mm–1 cm, and (5) T1c > 1–2 cm. The Chair of the Committee made this statement: "The need for substantial changes in the staging system for breast cancer stemmed from continuing developments in breast cancer diagnosis and management. First, with the widespread use of screening mammography, most breast tumors are now first detected when they are very small…"

Diagnostic Mammography, sometimes called *problem-solving mammography*, is indicated when there are clinical findings such as a palpable lump, localized pain, nipple discharge, or an abnormal screening mammogram that requires additional workup [11]. The diagnostic examination involves a complete workup tailored to a symptomatic patient or one with abnormal findings on a screening examination.

Diagnostic mammograms should always be performed when a biopsy is being considered for a palpable lump in a woman over 30 years of age. The purpose of mammography prior to the biopsy is to define better the nature of the clinical abnormality and to find unexpected lesions, including multifocal carcinoma or intraductal component of an invasive carcinoma. The diagnostic mammogram could also reveal that the finding is benign and does not require a biopsy. An example of the latter would be a typical fibroadenoma or an area of fat necrosis due to previous surgery [4]. To correlate the clinical and imaging findings, a marker (e.g., radiopaque "BB" or other) is often placed over the area of clinical concern prior to performing the mammograms (Fig. 9.2a); the diagnostic workup may include additional views of the breast using spot compression and magnification techniques, correlative clinical breast examination and ultrasonography (Fig. 9.2b). With some exceptions, a radiologist should be on site and supervise the performance of a diagnostic mammography and should convey the results directly to the patient.

9.2.1 The Mammography Report

Prior to 1990, many radiologists and training programs had developed their own terminology and methods for reporting mammograms. Referring physicians often complained that the terminology was confusing, conclusions were equivocal, and recommendations were unclear. The American College of Radiology Breast Imaging and Reporting System (BI-RADS®) was a response to complaints from referring physicians about these problems [3]. The BI-RADS reporting system uses standardized descriptors and final assessment categories that are linked directly to recommended management protocols. In its development, there was input from the American College of Surgeons, College of American Pathologists, American Medical Association, National Cancer Institute, Centers for Disease Control and Prevention, Food and Drug Administration and American Cancer Society. The BI-RADS standardized report includes four components: (1) the reason for the examination, (2) the overall breast tissue composition, (3) the description of the findings using standardized BI-RADS terminology, and (4) the final assessment category, which is linked by a numeric category to the recommendation for management.

9.2.1.1 Reason for the Examination

Examples include "Screening," "Palpable mass," "Additional workup of a screening detected abnormality" and "6-month follow-up of a probably benign finding."

9.2.1.2 Breast Tissue Composition

Since the sensitivity of mammography is directly related to the relative amounts of fat and fibroglandular tissue in the patient's breast, it is important for the referring physician to be aware of the overall breast tissue composition. The overall breast tissue composition can

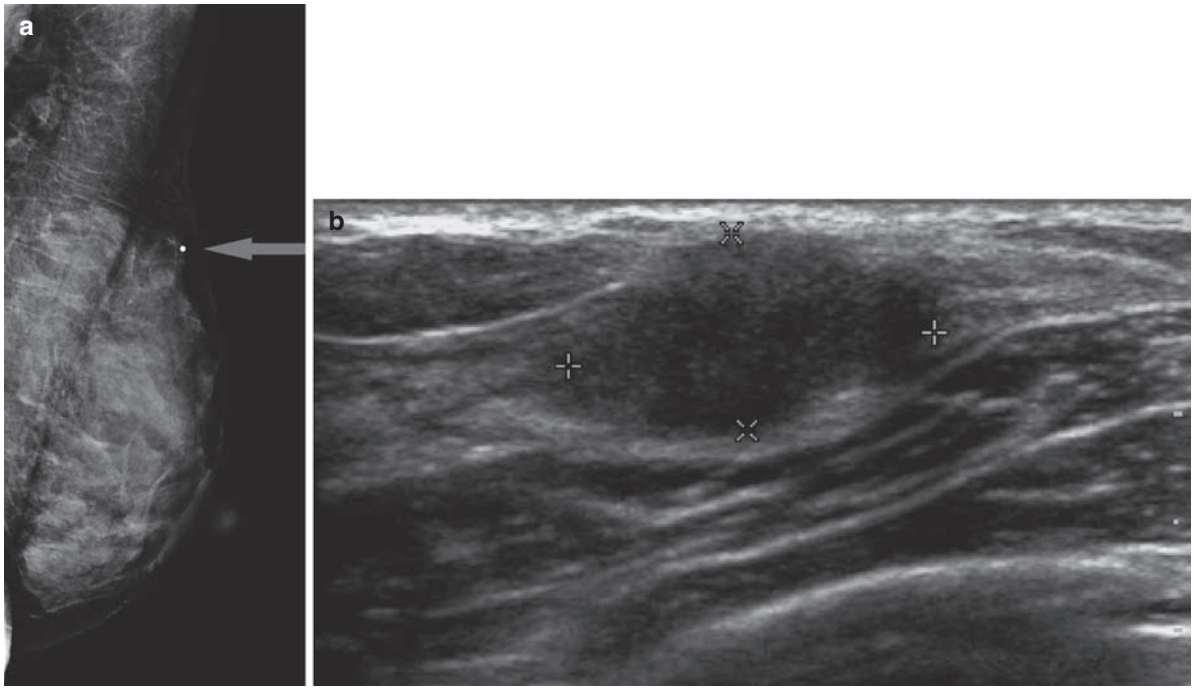

Fig. 9.2 Palpable mass. (**a**) Digital Left MLO view. A metallic "BB" marker (*arrow*) was placed over the palpable mass prior to performing the image. Due to the extremely dense breast tissue, a mass could not be seen or ruled out. (**b**) Ultrasound over the palpable mass revealed a lobular solid mass, parallel to the surface of the breast ("wider-than-tall"), with circumscribed margins, consistent with a fibroadenoma

range from almost all fatty tissue (dark gray to black on the mammogram) to extremely dense tissue (white on the mammogram). Breast cancers are white (radiodense) on mammograms. As a result, fatty tissue provides an excellent background in which to detect small cancers. On the other hand, dense tissue (white on mammograms) can obscure breast cancers. The four categories of breast tissue composition are: (1) almost entirely fatty, (2) scattered islands of fibroglandular tissue, (3) heterogeneously dense (which may lower the sensitivity of mammography) and (4) extremely dense (which lowers the sensitivity of mammography) (Fig. 9.3).

9.2.1.3 Description of Findings

Normal, benign and suspicious findings are described using a standard lexicon. The descriptors reflect the probability of malignancy. Masses and calcifications are the most common abnormalities found on mammograms, and the BI-RADS descriptors of these abnormalities are found later in this chapter.

9.2.1.4 Final Assessment Categories

The BI-RADS report ends with a Final Assessment (Impression or Conclusion), which is associated with a specific recommendation for management. If the report includes both a mammography exam and an ultrasound exam, there should be an Overall Assessment that summarizes the overall BI-RADS category for the two exams. In other words, if the mammogram was "Negative" (BI-RADS 1) but the ultrasound exam showed a "Suspicious" mass; the Overall Assessment would be "Category 4 – Suspicious." The BI-RADS Final Assessment is currently placed into one of seven categories, each of which indicates a recommended management protocol (Table 9.1):

BI-RADS Category 0 – "*incomplete, need additional imaging evaluation"* is reserved for screening exams that require additional workup before a final assessment can be made. Additional workup usually involves tailored additional mammography views or breast ultrasound. Once the workup is completed, the examination is placed into one of the Final Assessment Categories, each of which has a specific management recommendation (Table 1):

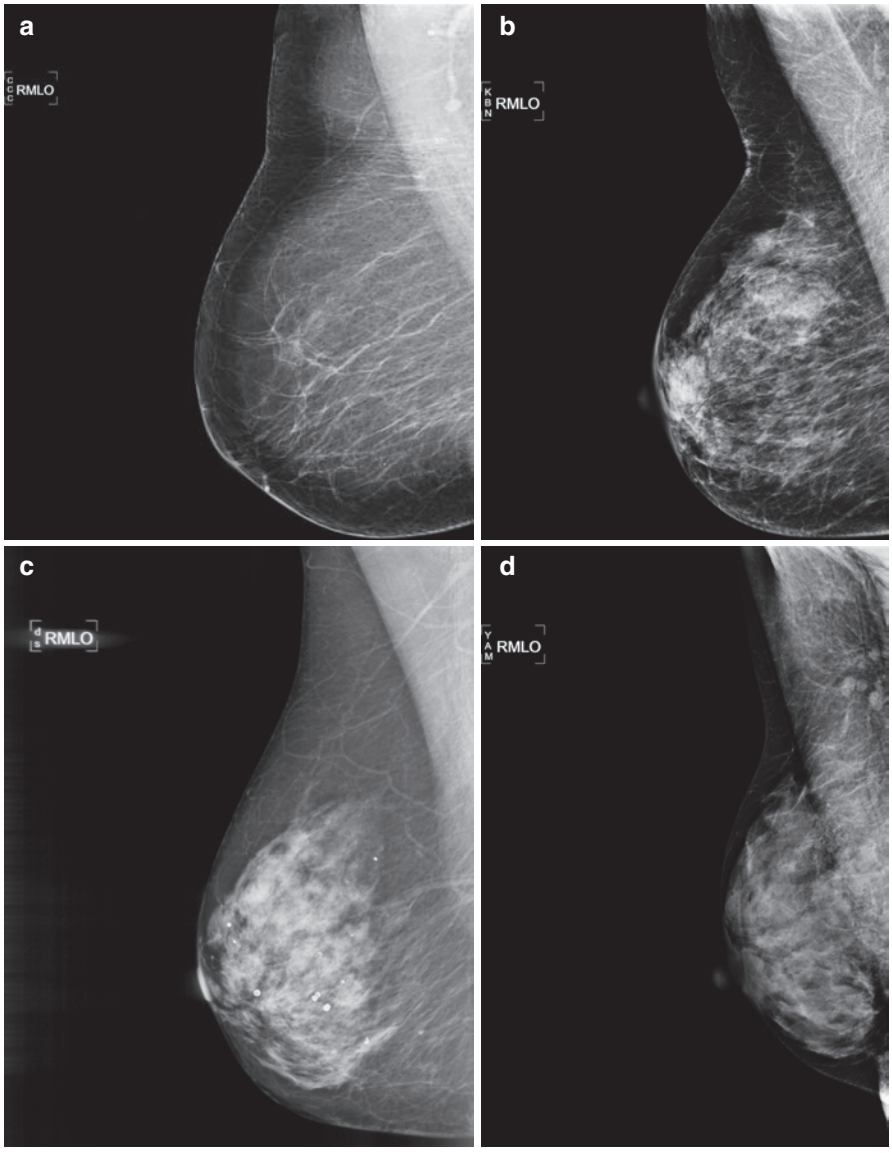

Fig. 9.3 The four BI-RADS descriptors for breast density (presented in right MLO digital mammograms). (**a**) Type 1 – almost entirely fatty. (**b**) Type 2 – scattered islands of fibroglandular tissue. (**c**) Type 3 – heterogeneously dense. (**d**) Type 4 – extremely dense

BI-RADS Category 1 – *Negative*: There is nothing to comment on.

BI-RADS Category 2 – *Benign.* This means the examination is negative except for some typically benign finding(s).

BI-RADS Category 3 – *Probably benign.* This is used for findings that have a high probability of being benign (≥98%).

BI-RADS Category 4 – *Suspicious*. This includes abnormalities that do not have definite morphology of cancer but have enough concern to urge a biopsy. The most recent BI-RADS places these into three subcategories: 4A (low suspicion), 4B (intermediate suspicion), and 4C (high suspicion) [3].

BI-RADS Category 5 – *Highly suggestive of malignancy*. These cases show classic findings of breast cancer (≥95% likelihood of malignancy).

Assigning a BI-RADS assessment category (0–6), to each mammography report provides a user-friendly mechanism for tracking and monitoring mammography patients, that does not require an understanding of medical terminology. Thus, office staff supervised by a healthcare provider can verify that the breast imaging recommendations are carried out.

The assignment of a final assessment to each examination also facilitates outcome analyses, such as the medical audit of a mammography practice or a community screening project. The medical audit is a quality assurance

Table 9.1 BI-RADS report final assessment categories

Category	Definition	Recommendation
0	Incomplete assessment	Additional imaging workup
1	Negative	Routine screening
2	Benign finding(s)	Routine screening
3	Probably benign	Short-term follow-up (6 months)
4	Suspicious abnormality	Biopsy
5	Highly suggestive of malignancy	Appropriate action should be taken
6	Known (biopsy-proven) cancer	Appropriate action

activity to determine the effectiveness of mammography by comparing the mammography interpretation to the outcome of a biopsy or 2-year follow-up [12]. For this purpose, the mammography examination must be categorized as *positive or negative* for cancer, and the outcome is based on the result of biopsies or clinical follow-up that verifies whether or not cancer was present.

Furthermore, the use of the BI-RADS system eliminates uncertainty concerning the mammography interpretations: If the final assessment is Negative (category 1), Benign (category 2) or Probably Benign (category 3), the interpretation is categorized as *Negative* for the medical audit. If the final assessment is Suspicious (category 4) or Highly Suggestive of Malignancy (category 5), the interpretation is considered *Positive* for the medical audit. A clinical follow-up or a biopsy will determine whether or not the imaging interpretation was correct.

9.2.2 Describing the Location of an Abnormality

When there is a palpable finding in the breast that is referred for imaging evaluation, it is very important that the referring Health Care Provider provides the exact location of the palpable finding identified on the clinical exam (Fig. 9.4). Often the patient does not know the location of the finding you are concerned about when she arrives for her imaging examination.

These are current recommendations for indicating the area of concern based on your clinical examination (your responsibility) and on the breast imaging reports (the radiologist's responsibility):

1. Right vs. Left breast.
2. Quadrant location: right upper outer (RUO), right upper inner (RUI); etc.
3. Clock-face location RUO 10:00; LUO 2:00; etc.
4. In addition, it is really helpful if you provide the distance from the nipple (FN) of the area of concern. A palpable finding you are concerned about in the Left Upper Outer breast at 2:00 could be anywhere from 1 to 10 cm from the nipple depending on the breast size.

9.2.3 Masses

A *mass* is defined as a space-occupying lesion that is seen on at least two mammographic projections [3]. If a density is seen on only one view, it is described as an "asymmetry." In BI-RADS, masses are described by their shape and margins (Fig. 9.5). The *shape* can be round, oval, lobular or irregular. Oval and round masses are usually benign. An irregular shape suggests a greater likelihood of malignancy. The *margins* of masses are the most important indicator of the likelihood of malignancy [13]. The margins can be described as circumscribed, microlobulated, obscured (partially hidden by adjacent tissue), indistinct (ill-defined) or spiculated. *Circumscribed* margins favor a benign etiology, and the likelihood of malignancy for a circumscribed mass is very low, probably less than 2% [14–16]. Additional workup may be necessary to verify that the margins are completely circumscribed. This workup usually involves additional projections of the mass and magnification spot-compression views. Ultrasound is often necessary to determine whether a round or oval circumscribed mass is cystic or solid. If the mass is a simple cyst, no further workup is needed. If it is solid, the shape and margins, and clinical findings should be further evaluated. A solitary, nonpalpable, completely circumscribed solid mass is often managed with a 6-month follow-up to establish that it is stable (not growing). If available, previous exams should be compared. If stable, continued mammography surveillance is recommended for at least 2 years [17]. The presence of multiple circumscribed masses is even stronger evidence of benignity, indicating multiple cysts, fibroadenomas or benign intrammamary lymph nodes [18], and follow-up in 1 year is often sufficient. If one of the masses is "dominant", biopsy is indicated. Dominant masses would include those that are significantly larger, not as well

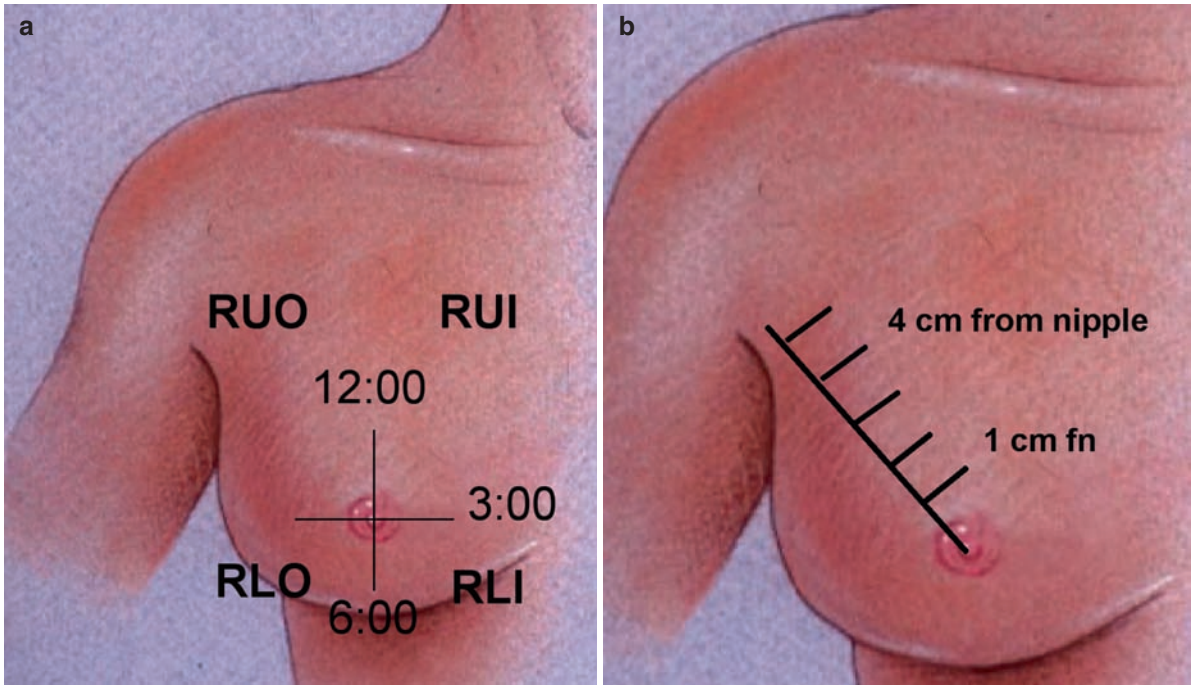

Fig. 9.4 Describing the exact location of a clinical or imaging finding. (**a**) Laterality, quadrant and clock face location. (**b**) Distance from the nipple

circumscribed, growing or palpable. *Microlobulated* margins increase the likelihood of malignancy. If the mass is directly adjacent to fibroglandular tissue of similar density, the margin may be *obscured*, and additional imaging should be done in an attempt to show the margins as completely as possible. The finding of *Indistinct* margins is suspicious for malignancy. A mass with *spiculated* margins has lines radiating from its border, and this finding is Highly Suggestive of Malignancy. An area of spicules without any associated mass is called an *architectural distortion*.

The *density* of a mass compared with normal fibroglandular tissue provides another clue as to its etiology. In general, benign masses tend to be lower in density than carcinomas; however, the density of a mass is not always a reliable sign as to whether it is benign or malignant [19].

9.2.4 Calcifications

Calcifications are described on mammograms by their morphology and distribution (Fig. 9.6). The calcifications can be placed into three general categories: (1) *Typically benign* calcifications can usually can be identified by their mammographic features and include skin, vascular, coarse, large rod-like, round, egg-shell and milk-of-calcium types; (2) *Intermediate concern* calcifications are described as amorphous or indistinct (these are tiny or flake-shaped calcifications that are small or hazy in appearance so that a more specific morphologic classification cannot be made; and (3) *Higher probability of malignancy* calcifications can be described as *plemorphic or heterogenous* or *fine, linear and branching*.

Calcifications are also characterized in mammography reports by their distribution: (1) *grouped* or *clustered* calcifications include more than five in a small area (<2 cm) and can be benign or malignant [20]. *Linear* calcifications are in a line and may have small branch points. When *linear* calcifications are in a line and branching, their distribution is duct-like and suspicious for malignancy. *Segmental* calcifications are distributed in a duct and its branches, with the possibility of multifocal carcinoma in a lobe (or segment) of the breast. A segmental distribution tends to be "triangular" with the apex toward the nipple. *Regional* calcifications are in a larger volume of breast tissue, and usually do

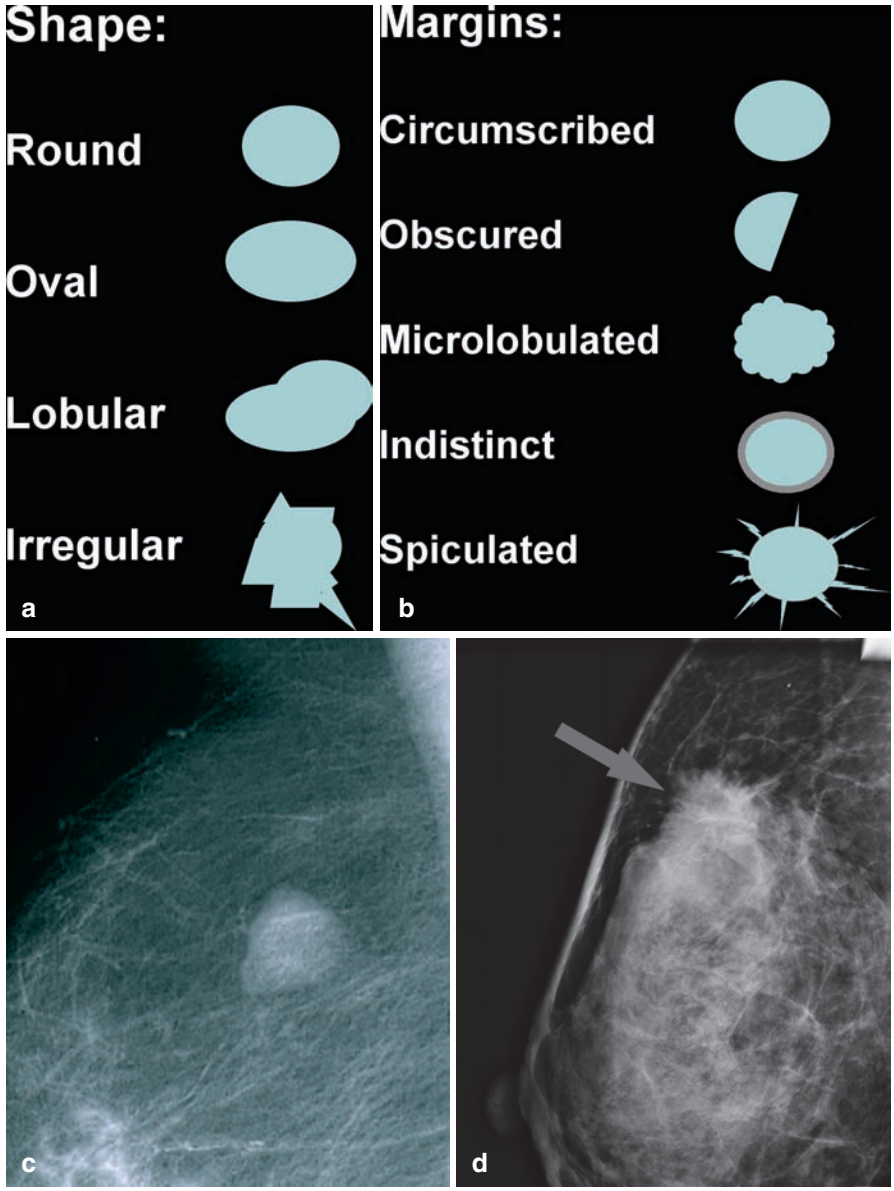

Fig. 9.5 BI-RADS standardized description of masses. (**a**) Shape varies from round (most likely benign) to irregular (most likely malignant). (**b**) Margins vary from circumscribed (most likely benign) to spiculated (most likely malignant). (**c**) Lobular, circumscribed mass (*arrow*). Biopsy revealed fibroadenoma. (**d**) Irregular mass with spiculated and partially obscured margins (*arrow*). Biopsy revealed invasive ductal carcinoma

not indicate suspicious calcifications. *Diffuse or scattered* calcifications are distributed randomly through both breasts and are almost always benign.

9.2.5 Indirect and Secondary Signs of Malignancy

Other important findings that can be described in the BI-RADS report include indirect or subtle signs of malignancy, such as a new or evolving asymmetry or an architectural distortion [21, 22]. Other secondary signs of malignancy include skin thickening, nipple retraction and axillary node enlargement.

A new or evolving asymmetry is identified by comparison with prior examinations and requires additional workup, which may include additional mammography views, ultrasound and biopsy. Asymmetrically distributed fibroglandular tissue may be a normal variant, but could be subtle sign of underlying malignancy (Fig. 9.7).

An "architectural distortion" is described as radiating spicules without a central mass and may

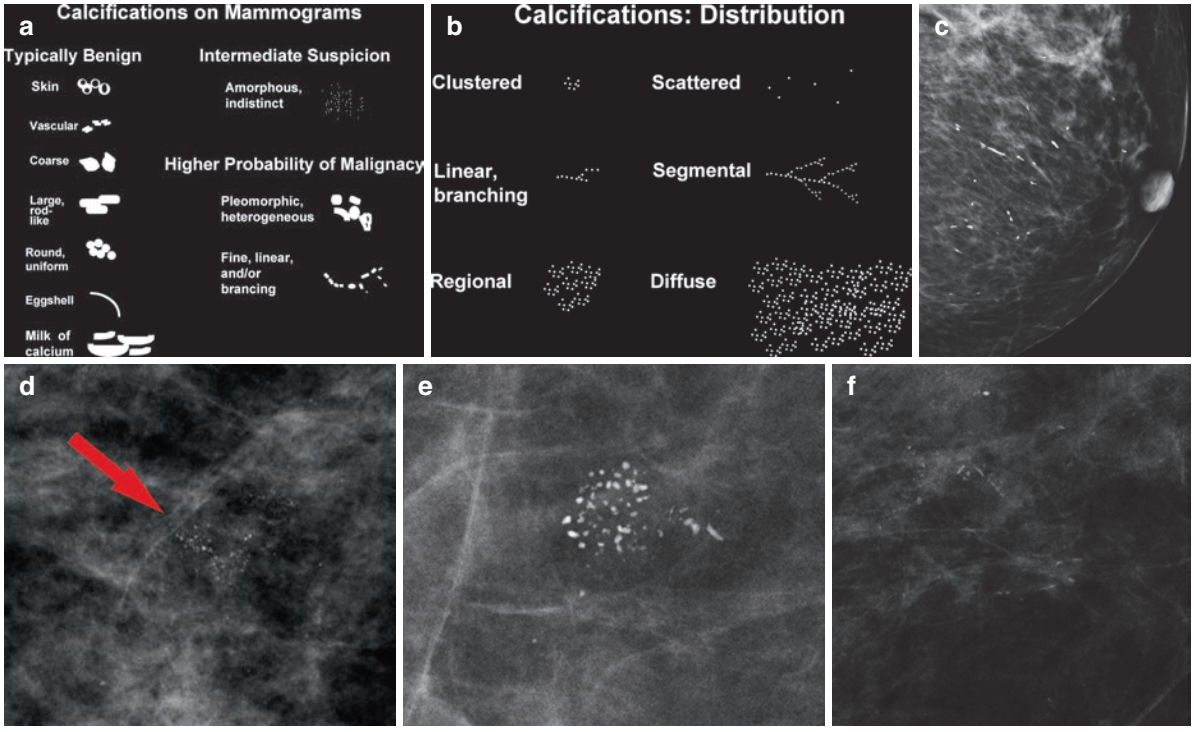

Fig. 9.6 BI-RADS standardized description of calcifications. (**a**) Morphology of calcifications. Based on their morphology, calcifications are categorized as typically benign, intermediate suspicion, and higher probability of malignancy. (**b**) Distribution of calcifications. Based on their distribution, calcifications are described as clustered (suspicious), linear, branching (high suspicion), regional (low suspicion), scattered (not suspicious, segmental (high suspicion), or diffuse (not suspicious). (**c**) Typically benign, rod-like and solid calcifications of ductal ectasia (secretory calcifications) in a regional distribution that occur in perimenopausal and postmenopausal women due to secretions trapped in the ducts. (**d**) Intermediate concern calcifications. Faint, amorphous calcifications in a clustered distribution. Biopsy revealed benign, columnar cell lesion. (**e**) Higher probability of malignancy calcifications. Heterogeneous (pleomorphic) calcifications in a clustered distribution. Biopsy revealed ductal carcinoma in situ. (**f**) Higher probability of malignancy calcifications. Linear, branching calcifications in a linear distribution. Biopsy revealed ductal carcinoma in situ

be difficult to perceive (Fig. 9.8). Both benign and malignant entities, including surgical scar, radial scar and invasive carcinoma, may present as an architectural distortion on mammograms.

Skin thickening also can be seen with benign conditions, including postradiation change, mastitis, inflammatory breast carcinoma, lymphatic obstruction and fluid-overload states, such as congestive heart failure and renal failure.

New skin or nipple retraction is often a sign of an underlying malignancy. In addition, unilateral axillary lymph node enlargement can result from a breast primary cancer, metastases from other cancers or inflammatory conditions.

9.2.6 Potential Adverse Consequences of Screening

Referring healthcare providers should be aware of the possible adverse consequences of mammography screening, the likelihood of each and strategies to lower their likelihood. Potential adverse consequences of mammography include excessive biopsies, inadequate communication of results, anxiety associated with a return visit for more views, pain and discomfort, false reassurance and delay in diagnosis [4].

In the process of detecting as many early breast cancers as possible, a certain number of biopsies will

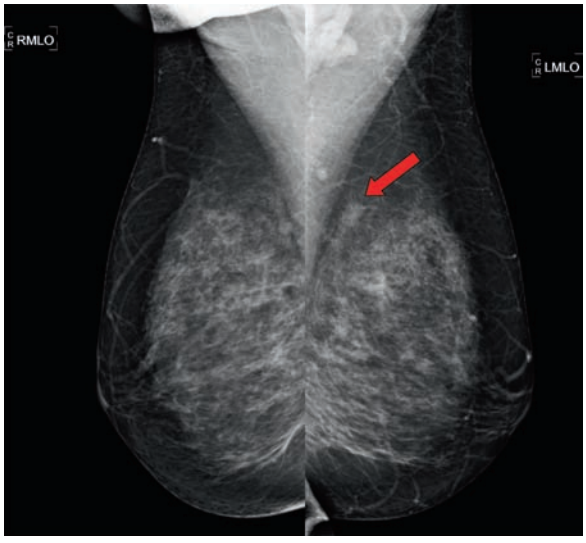

Fig. 9.7 Right MLO and Left MLO digital mammograms show an asymmetry (*arrow*) in the left upper breast. Additional workup confirmed the asymmetry as a real finding, and a biopsy revealed invasive ductal carcinoma

be done for benign mammographic abnormalities. The positive predictive value of biopsies done for mammographic abnormalities (number of cancers detected/number of biopsies) can vary significantly from one facility to another. The recommended positive biopsy rate for experienced interpreting physicians is 25–40% [12]. The average in U.S. facilities is close to 20% [23]. Failing to communicate mammography results has been a relatively a common problem in the past [24]. The failure to communicate results can lead to delay in diagnosis and treatment of breast cancer. The failure to communicate results in a *timely fashion* can lead to unnecessary anxiety in women. In addition to the formal report to the referring healthcare provider, women are notified of their results by the mammography facility. The Mammography Quality Standards Act requires that this notification is direct (no intermediary), in writing and in lay language for patients [2].

Substantial anxiety can be generated when a woman has to return for additional or repeat mammographic views. These extra views should be done as soon as feasible to reduce anxiety. Staff should be supportive and available to answer any questions.

When properly performed, mammography may be uncomfortable and rarely painful. If women have unnecessary pain and sever discomfort, they may not return for future screening examinations. Therefore, mammography should be performed using proper breast compression, so that women would feel as little pain and discomfort as possible. Routine mammography should not be done when the breast is tender or in

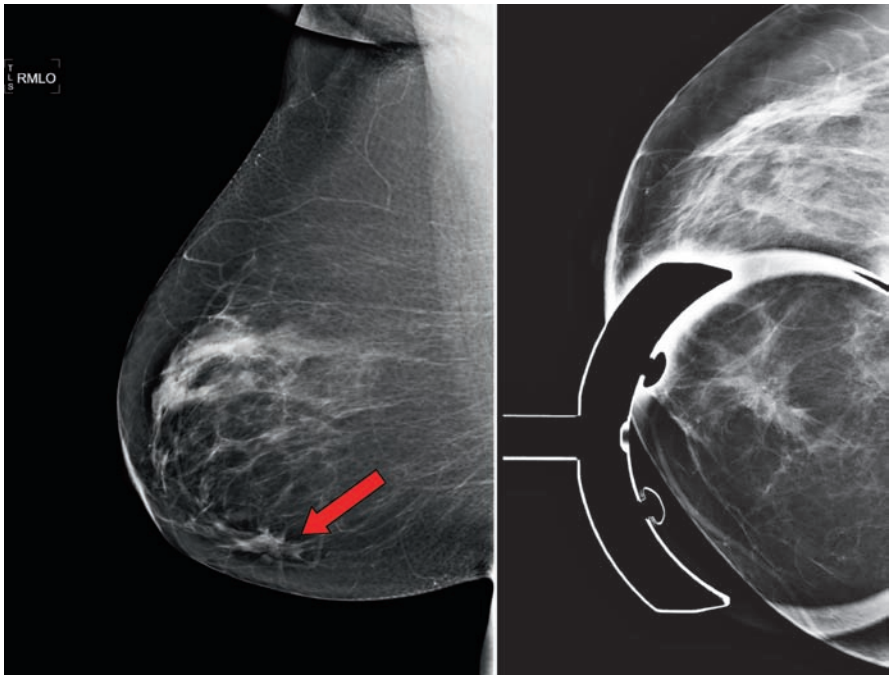

Fig. 9.8 Architectural distortion. (**a**) Right MLO digital mammogram shows an area of architectural distortion (*arrow*) in the inferior breast. (**b**) Spot compression views confirmed the persistence of the architectural distortion. Biopsy revealed invasive breast carcinoma

the week before menstruation for women who have breast pain associated with menses [25–27].

False reassurance occurs when a woman ignores a palpable abnormality because of a previous negative screening mammogram. Delay in diagnosis occurs when a clinical finding is not acted on because mammograms turn out to be negative. Referring healthcare providers should inform women that a negative mammogram should not delay the evaluation of a clinically suspicious breast lump or other suspicious clinical finding. A lump or other abnormal clinical finding that develops after a negative screening examination should be evaluated as soon as possible and not delayed until the next screening examination.

9.2.7 False-negative Mammograms

A false-negative mammogram is one that is interpreted as negative, but cancer is diagnosed within a predetermined time, usually defined as 1–2 years. A 1995 Physician Insurers Association of America (PIAA) study disclosed that failure to diagnose breast cancer had become the leading cause for malpractice cases lost by physicians [28]. Causes of false-negative mammograms include dense breast tissue, suboptimal technical quality, errors in interpretation and failure of communication [29]. The most common cause of a false-negative mammogram is dense fibroglandular tissue [30]. The sensitivity of mammography decreases with increasing tissue density (Fig. 9.3).

The use of proper technical factors is particularly crucial in detecting breast cancer, especially in evaluating a woman with dense breast tissue. Suboptimal positioning and underexposure increase the risk of a false-negative mammogram. Using dedicated equipment, adequate compression and proper exposure can optimize the mamographic examination. Furthermore, digital mammography has been shown to improve cancer detection in women with dense breasts [31].

9.3 Breast Ultrasound

Breast ultrasound is an essential adjunct to mammography for the workup and diagnosis of palpable and mammographically detected abnormalities. Historically, breast ultrasound was used to differentiate solid and cystic masses. In the past decade and a half, advances in ultrasound technology have led to high-resolution ultrasound equipment and to the identification of sonographic features to help differentiate benign and malignant solid masses [32–34]. In addition to lesion characterization, breast ultrasound is used to guide interventional breast procedures, including cyst aspiration, CNB, fine needle aspiration and ultrasound-guided preoperative needle localization.

9.3.1 Technical Advances

Current ultrasound technology has made enormous strides in the last 15 years. State-of-the-art breast ultrasound equipment systems utilize linear array, high-resolution probes with optional supplemental processing technologies resulting in superior image quality when compared to conventional sonography. Supplemental processing techniques include spatial compounding and tissue harmonic imaging. Spatial compounding obtains multiple simultaneous images at different angles, which are then superimposed into a single compound image, resulting in reduced artifacts. Clinically, this results in clearer visualization of cystic contents, improved contrast resolution and tissue differentiation, enhanced delineation of anatomic margins and improved depiction of internal architecture of solid lesions [34, 35]. Tissue harmonic imaging is another ultrasound technique that minimizes artifacts leading to better lesion conspicuity and margin depiction when compared to conventional sonographic imaging [36, 37]. Power Doppler technology allows for visualization of vascular structures, including tiny, low-flow vessels, which may surround or penetrate breast tissue and masses. Knowledge of lesion vascularity is important in planning interventional procedures and is helpful in characterizing certain types of breast lesions.

9.3.2 Normal Anatomy

Breast ultrasound reveals the breast anatomic structures from the skin surface to the chest wall (Fig. 9.9). Normal skin measures less than 3 mm and is composed of two parallel echogenic (white) lines separated by a thin, hypoechoic (dark) band. Just deep to the skin lies the

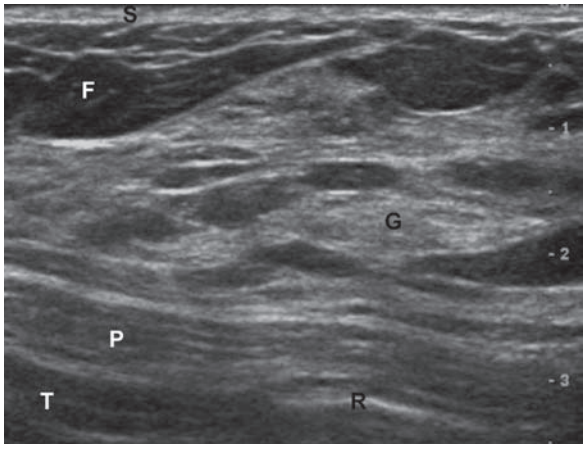

Fig. 9.9 Normal breast anatomy on ultrasound. The skin (*S*) is represented by horizontal echogenic lines. Below this there is a layer of hypoechoic subcutaneous fat (*F*). This is followed by alternating bands of fibroglandular tissue (*G*). The retromammary fat lies on the chest wall. The pectoral muscle (*P*), ribs (*R*) and thoracic cavity (*T*) are deep to the retromammary fat

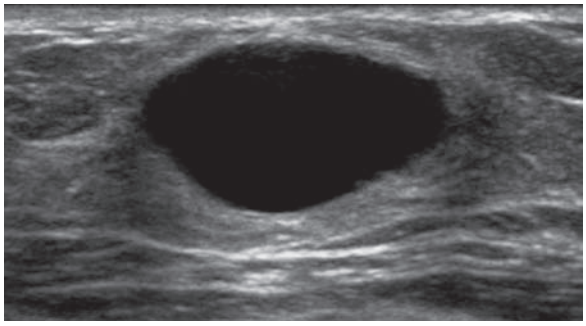

Fig. 9.10 Simple cyst. Ultrasound features are a round or oval, anechoic (black with no internal echoes) mass with smooth margins, an imperceptible wall, and increased posterior acoustic echoes

subcutaneous fat followed by the interwoven bands of fibroglandular tissue and breast fat. Both subcutaneous and breast fat are mildly hypoechoic (gray), whereas the fibroglandular tissue is hyperechoic (light gray to white). Deep to the fibroglandular tissue is the retroglandular fat, which lies against the chest wall. The chest wall is composed of the more superficial band of the pectoralis muscle, the ribs laying deep to the pectoralis muscle and the parietal pleura. The pectoralis muscle, ribs and pleura have characteristic sonographic features that are easily and reliably identified. The lung parenchyma is not sonographically visible as the ultrasound beam does not propagate well through air.

9.3.3 Cystic Masses

Breast ultrasound can reliably identify cystic masses. The BI-RADS descriptors for the three types of cystic masses are: (1) a *simple cyst,* (2) *a complicated cyst* and (3) a *complex mass*.

The sonographic features of a *simple* cyst are a round or oval shaped, anechoic (black with no internal echoes) mass with smooth margins, an imperceptible wall and increased posterior acoustic echoes (Fig. 9.10). The latter feature (increased posterior echoes) means it appears as if a flashlight is shining through the back of the cyst. Because cysts develop within the terminal duct lobular unit of the breast, it is not uncommon to see clusters of cysts or coalescing cysts. Simple cysts need no further workup unless a cyst aspiration is indicated. Indications for cyst aspiration include a painful cyst, a large cyst that compromises mammographic imaging, patient anxiety or a debris-filled complicated cyst that needs to be aspirated to rule out a solid mass.

It is not uncommon to identify a "cyst" with fine internal echoes, such as a debris-filled cyst. The result is a cyst with echogenic interior. These cystic masses do not fulfill the criteria for a simple cyst and are called *complicated* cysts. When a complicated cyst is suspected, further evaluation may be needed. Ultrasound-guided aspiration can be performed to verify its cystic nature, to exclude a solid mass and to confirm complete resolution of the mass after aspiration.

A *complex* mass is defined as a mass with both cystic and solid components. Usually, the solid component is described as a mural nodule or an intracystic mass. A complex mass can also be composed of thick walls and anechoic center. A cyst with a solid component is suspicious for a malignancy, such as a papillary carcinoma or a necrotic infiltrating carcinoma. Benign papillomas can also present as a complex mass. The diagnostic evaluation of a complex mass is ultrasound-guided CNB of the solid component or surgical excision.

9.3.4 Solid Masses

Criteria differentiating benign and malignant solid masses have evolved. Several studies have defined criteria to aid in the distinction of benign and malignant solid

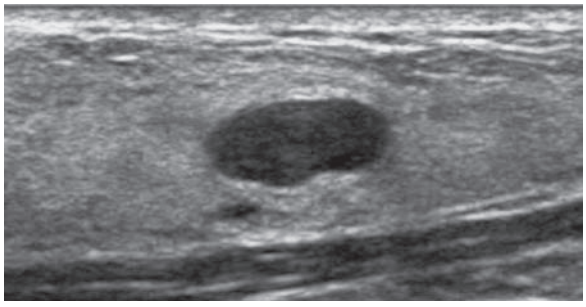

Fig. 9.11 Typical sonographic features of a benign solid mass. This mass is oriented "parallel" to the skin ("wider-than-tall"), oval with circumscribed margins and <3 gentle lobulations. Findings are typical for a fibroadenoma

breast masses [32, 33]. Although no single or combination of sonographic features is 100% diagnostic for a benign mass, careful use of established criteria can help differentiate benign and malignant solid masses and avoid biopsy of certain solid masses. Mass shape, margins, orientation relative to the skin surface, echogenicity and posterior echoes are the minimum preliminary characteristics that should be assessed in solid masses.

Typically benign sonographic features of solid masses include an ellipsoid or oval shape, width greater than anteroposterior diameter (orientation parallel to the skin surface), three or fewer gentle lobulations, circumscribed margins, a pseudocapsule, echogenicity hyperechoic to fat (whiter than fat) and *absence* of any malignant features (Fig. 9.11).

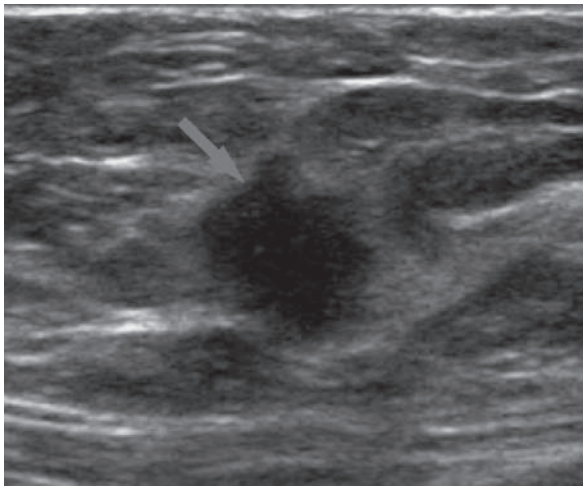

Fig. 9.12 Typical sonographic features of a malignant solid mass. The hypoechoic mass (*arrow*) manifests an irregular shape with angular margins, is orientated "not parallel" to the skin ("taller-than-wide"), and is surrounded by a thick, echogenic (*white*) halo. Biopsy revealed invasive ductal carcinoma

Malignant sonographic features of solid masses include an irregular or angular shape; more than three lobulations; ill-defined, spiculated or microlobulated margins; width greater than anteroposterior diameter (orientation not parallel to the skin surface or "taller than wide"); markedly hypoechoic (dark) echogenicity; a surrounding thick, echogenic (white) halo; posterior shadowing (black shadows posterior to the mass), duct extension; and associated calcifications (Fig. 9.12).

In conclusion, the results of benign vs. malignant ultrasound features of solid masses are helpful. These features have potential for decreasing the number of biopsies performed for benign solid masses. Studies have also shown interobserver variability from one ultrasound interpreter to another in the evaluation for these features and in making a final diagnosis [38]. Furthermore, there appears to be overlap in these features, and some malignant masses may have features suggesting they are benign, which could lead to false-negative interpretations of malignant solid masses. Therefore, these sonographic diagnostic criteria should not be generally applied as the sole criteria in determining whether to perform a biopsy of a solid mass. Additional investigations are needed to explore issues of reproducibility of specific criteria in a variety of practices and among different interpreters.

Solid masses with any suspicious mammographic or sonographic feature should undergo biopsy. Any palpable or growing benign-appearing solid mass warrants at least a needle biopsy. However, an incidentally identified, nonpalpable solid mass that demonstrates benign mammographic and sonographic features may be managed with a 6-month follow-up.

9.3.5 Screening Ultrasound

Screening ultrasound is defined as bilateral whole breast ultrasound of an asymptomatic woman with normal mammograms. The sensitivity of screening mammography is decreased in women with dense breasts as the dense tissue may obscure underlying lesions. Several studies have shown that small, clinically and mammographically occult breast cancers may be detected with screening ultrasound in women with dense breast tissue [39–43]. This can be attributed to the ability of ultrasound to "look through" dense breast tissue and identify otherwise occult benign and malignant masses.

Despite the encouraging results from these studies, many potential drawbacks are associated with screening ultrasound. Of particular concern is the high number incidental benign masses encountered during screening ultrasound for which either biopsy, aspiration, or short-interval follow-up ultrasound is recommended. Furthermore, there is lack of proven short-interval follow-up ultrasound criteria for probably benign incidentally identified masses.

Several studies of screening ultrasound (37,085 total exams) detected 127 additional cancers resulting in a prevalence of 0.34% (3.4 additional cancers per 1,000) [39–41, 43–45]. However, 2–6% of women undergoing screening ultrasound will receive a recommendation for biopsy with an approximate positive predictive value of only 5–16%. An additional 3–10% of patients will receive a recommendation for short-interval follow-up ultrasound [39–45]. Additional problems include an extremely limited ability to detect ductal carcinoma in situ (DCIS), patient anxiety and morbidity associated with additional biopsy procedures, added cost, lengthy exam times and highly variable ultrasound performance skill levels among practicing technologists and radiologists.

Results of a recent study of screening breast ultrasound in high risk women conducted by the American College of Radiology Imaging Network (ACRIN 6666) and the Avon Foundation are due in 2008. This large, prospective trial of whole breast ultrasound in high risk women with dense breasts will be the first study to independently evaluate screening ultrasound compared to screening mammography. The primary goal of the study is to assess the diagnostic yield of whole breast bilateral screening ultrasound combined with mammography compared to mammography alone for the detection of breast cancer. Two of the secondary goals include determining the sensitivity and specificity of screening whole-breast ultrasound and mammography independently, and validating probably benign ultrasound imaging criteria [45, 46].

9.4 Core Needle Biopsy

Several breast biopsy alternatives are available to the patient with a suspicious finding. Prior to 1990, the biopsy of imaging-detected breast lesions was limited to excisional biopsy. Introduced in 1990, CNB has become a desirable alternative to excisional biopsy because it is less costly, results in less morbidity and leaves minimal to no scar. CNB of the breast overcomes the limitations of FNAC because insufficient samples are less frequent, the interpretation can be performed by a pathologist without special training in cytopathology, and CNB can differentiate invasive from in-situ breast cancer [47, 48].

CNB are performed with a large-bore (8-–14-gauge needle) in combination with imaging guidance to sample a clinical or imaging identified abnormality. Imaging guidance can be provided by ultrasound or mammography (stereotactic). Stereotactically guided CNB uses two views acquired at different angles to determine the location of a lesion in the breast. Choice of ultrasound vs. stereotactically guided CNB is based on which modality best demonstrates the abnormality and the location of the abnormality in the breast. However, ultrasound is usually preferred because it is faster and more comfortable for the patient.

9.4.1 *Indications, Relative Contraindications and Complications*

Imaging-guided CNB is indicated for most nonpalpable, mammographically suspicious abnormalities [49]. Abnormalities categorized as “probably benign” (BI-RADS 3), “suspicious” (BI-RADS 4) and “highly suggestive of malignancy” (BI-RADS 5) can undergo biopsy. Overuse of the technique for sampling of “probably benign” (BI-RADS 3) abnormalities that would otherwise be managed with a 6-month follow-up can increase the cost of screening with little to no benefit [50]. CNB of “highly suggestive of malignancy” (BI-RADS 5) lesions can expedite surgical planning by avoiding the need to perform intraoperative frozen-section analysis to verify malignancy prior to definitive surgical treatment.

Stereotactic CNB is contraindicated in patients who exceed the weight limit of the biopsy table or have extremely thin breasts that preclude safely firing the biopsy device. Abnormalities located just under the skin or areola or deep against the chest wall may be inaccessible. Microcalcifications that are widely separated and not clustered or too faint to resolve with the stereotactic unit may be inappropriate for stereotactic

CNB. Patients, who are unable to cooperate, lie prone or still; who have bleeding disorders; or who are on anticoagulation therapy may not be suitable candidates. The location of the abnormality in the breast of a woman with breast implants dictates whether biopsy is feasible.

CNB of the breast has proven to have few complications. Unusual, but potential complications include neck, back, arm, and shoulder pain related to patient positioning; bleeding; infection; and vasovagal reactions. In patients with normal coagulation profiles and no predisposition to infection, the risk of serious bleeding or infection is minimal.

9.4.2 Appropriate Postcore Biopsy Follow-Up

CNB is a sampling technique; hence, appropriate post CNB follow-up to ensure lesion stability is critical in all patients with a benign biopsy result. The rate of false-negative CNB results is not known with certainty, but it is believed to be approximately 2% [51]. This percentage is likely to be lower at centers performing a large number of biopsies, and those that correlate their radiological and pathological results on a regular basis. Several steps can be followed to minimize false-negative biopsy results. An adequate number of core samples should be obtained at biopsy to avoid sampling error, and specimen radiography should be performed in all cases where calcifications are sampled to verify that the calcifications are contained within the biopsy core samples. Once the biopsy result is reported, radiologic-pathologic concordance or discordance should be assessed. In our practice, any patient with radiologic-pathologic discordance undergoes excisional biopsy of the abnormality. In addition, a number of problem CNB histologic diagnoses may require excisional biopsy. There is consensus that a CNB diagnosis of atypical ductal hyperplasia mandates excisional biopsy. There is still some controversy about the need for excisional biopsy after CNB diagnosis of radial scar, papilloma, lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH) [52–57]. More recent studies of LCIS and ALH cases diagnosed at CNB have shown upgrade rates to malignancy at excisional biopsy to be approximately 17–19%. This approaches the upgrade rate in patients with ADH [58, 59]. For this reason, in our practice, we now recommend surgical excision when LCIS or ALH is identified at CNB.

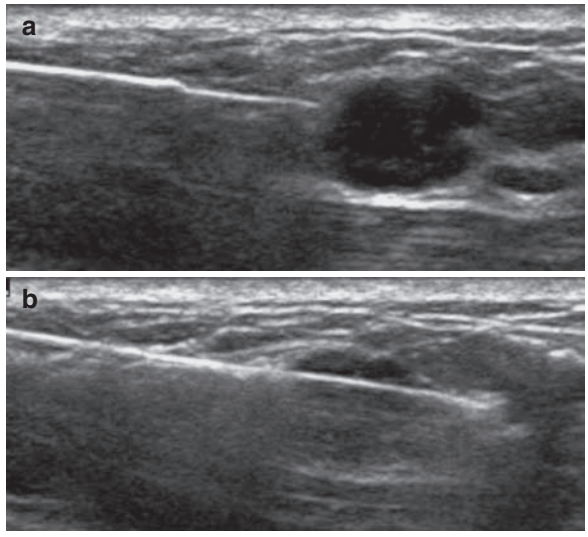

Fig. 9.13 Ultrasound-guided core needle biopsy. (**a**) Pre-fire image shows the biopsy needle tip at the edge of the mass undergoing biopsy. (**b**) Post-fire image confirms that the biopsy needle is within the mass

Finally, appropriate post CNB imaging follow-up of benign diagnoses is essential unless the findings are "definite benign" (e.g., imaging fibroadenoma and pathology fibroadenoma). This post benign CNB follow-up begins with a 6-month follow-up using the imaging modality that best demonstrated the abnormality prior to biopsy (mammography or ultrasound). If the imaging remains stable 6 months after biopsy, then the patient can return to her annual screening schedule. Any interval growth or suspicious change on imaging or clinical grounds warrants surgical excision.

9.5 Magnetic Resonance Imaging of the Breast

MRI has been applied successfully for the evaluation of silicone breast implants for intracapsular and extracapsular rupture [60]. The initial studies to determine the potential value of MRI for detecting breast cancer were performed in the 1980s. In these studies, MRI was not found to be reliable for the detection or diagnosis of breast cancer [61]. Later investigations using intravenous MR contrast agents showed a high sensitivity for the detection of breast cancer as cancers

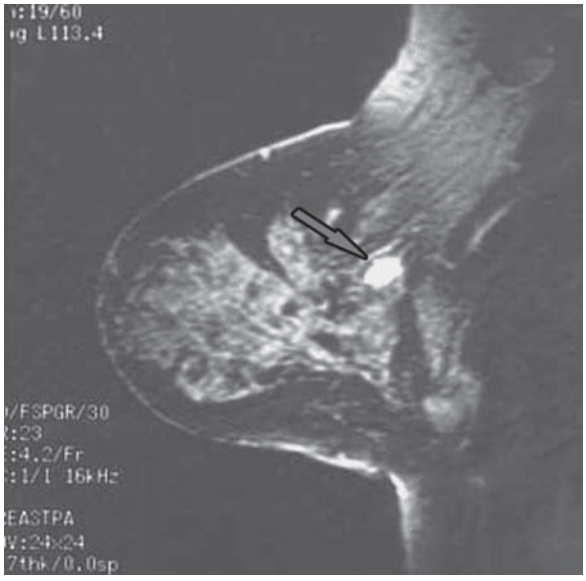

Fig. 9.14 A 50-year-old woman with enlarged axillary lymph nodes that proved on fine needle aspiration to be consistent with breast cancer metastases. Mammograms and ultrasound were negative. The contrast-enhanced MRI sagittal (from the side) image shows contrast uptake in an irregular mass (*arrow*) near the chest wall. Biopsy revealed an invasive ductal carcinoma

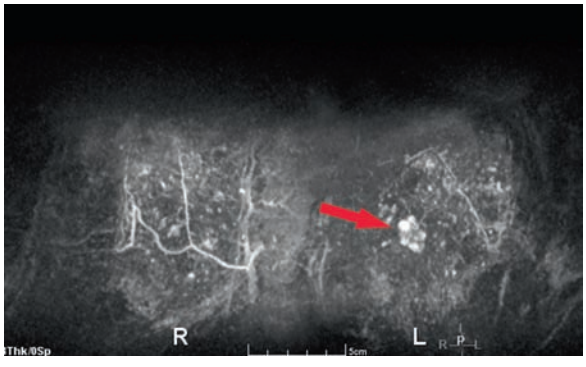

Fig. 9.15 A 35-year-old woman referred for high risk (BRCA2) screening MRI. The contrast-enhanced MRI coronal (looking at the patient from the front, anterior to posterior) image shows contrast uptake in a lobular mass with dark internal septations (*arrow*) typical for fibroadenoma. A biopsy as requested by the patient and confirmed a fibroadenoma

showed rapid contrast enhancement (Fig. 9.14) [62–66]. However, specificity varies as numerous benign entities can also show rapid contrast enhancement (Fig. 9.15).

There are now several established indications for contrast-enhanced breast MRI: (1) determining the size and extent of invasive cancers; (2) identifying multifocal and multicentric lesions; (3) evaluating the ipsilateral breast of a woman with unilateral axillary metastases, (4) identifying recurrent carcinoma in the conservatively treated breast.

9.5.1 Contrast-Enhanced Breast MRI for Breast Cancer Screening

A recent multiinstitutional study conducted by Lehman, et al. [67] concluded that women at high risk for breast cancer would benefit from screening MRI. In that study, high risk included women 25 years of age or older who were genetically at high risk, defined as BRCA1/BRCA2 carriers or with at least a 20% probability of carrying such a mutation. The study found that screening MR imaging had a higher biopsy rate with the PPV of biopsies performed as a result of MR being 43%, and helped detect more cancers than either mammography or ultrasound. The cancer yields for each test were 3.5% for MR, 1.2% for mammography and 0.6% for US. The use of MR in addition to mammography in screening women at high risk for breast cancer is becoming more evident in practice and in the literature.

Recently, the ACS recommended breast MRI screening for women at high risk for breast cancer (BRCA1/BRCA2 mutation or first degree relative with this mutation, a 20–25% or greater lifetime risk for breast cancer, radiation to the chest between ages 10–30, history of Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome or first-degree relative with such syndromes) [68].

9.6 Radionuclide Imaging

Another area of active investigation involves radionuclide scanning of the breast after the injection of the radionuclide-labeled substances that concentrate in breast tumors. Technetium-99 m (Tc99M) methoxyisobutyl isonitrile (MIBI) breast scintigraphy (*scintimammography*) has been under investigation for several years now. Early reports indicated high sensitivity (>90%) and specificity (slightly <90%) [69]. Later reports, however, indicate a relatively low sensitivity for small cancers, those found only by mammography

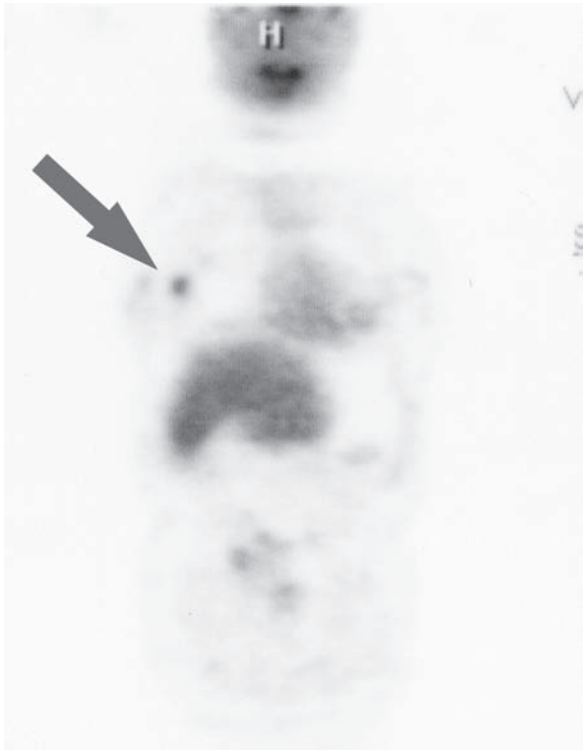

Fig. 9.16 Positron emission tomography (PET) image shows an area of radionuclide enhancement (*arrow*) at the site of an invasive cancer in the right breast

(56%), and 1 cm or smaller (39%) [70, 71]. However, a new technology (breast-specific gamma imaging) using this radionuclide agent image specially designed for the breast is undergoing clinical trials [72, 73]. In these early trials, it proved to be useful in avoiding biopsies of palpable breast masses with indeterminate mammographic and ultrasonographic features that will not be removed if the scintigraphic study is negative. Thus, the role of Tc99M scintimammography is yet to be determined.

Tumor uptake also has been identified on positron emission tomography (PET) after the injection of fluorine-18 2-deoxy-2-fluoro-D-glucose (Fig. 9.16) [74]. The agent also accumulates in axillary nodes, providing information about nodal status. These methods will require additional studies to determine sensitivity, specificity and cost-effectiveness.

In addition, Tc99m sulfur colloid has been proven useful and is now widely used for the identification of sentinel nodes [75, 76]. Prior to surgery, the isotope is injected into the breast in the vicinity of a biopsy proven breast cancer. The injected isotope should drain through the same lymphatic chain as the tumor. At surgery, the sentinel nodes draining the site of the cancer are identified using a radioisotope probe. The sentinel nodes are removed and evaluated histologically. If the sentinel nodes are negative for tumor, axillary node dissection and its associated complications can be avoided.

References

1. McLelland R, Hendrick RE, Zinninger MD et al (1991) The American college of radiology mammography accreditation program. Am J Roentgenol. 157:497
2. Mammography Quality Standards Act of 1992. Public Law 102539
3. American College of Radiology (ACR) (2003) Breast imaging reporting and data system (BI-RADS). 3rd ed. Reston, VA: ACR
4. Bassett LW, Hendrick RE, Bassford TL, et al (1994) Quality determinants of mammography; clinical practice guideline. No 13. AHCPR Publication 95-0632. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services, October 1994
5. American College of Radiology. Standards for the performance of screening mammography. [Adopted by the ACR Council 1990, Revised 1994]. In: ACR Digest of Official Actions. Reston, VA: ACR, 199
6. Tabar L, Fagerberg CJ, Gad A et al (1985) Reduction in mortality from breast cancer after mass screening with mammography: randomized trial from the breast cancer screening working group of the Swedish National Board of Health and Welfare. Lancet. 1:829–32
7. National Institutes of Health Consensus Development Panel (1997) National Institutes of Health Consensus Development Panel: breast cancer screening for women 40–49, January 21–23 1997. J Natl Cancer inst. 39:1015–26
8. Smart CR, Hendrick RE, Rutledge JH III et al (1995) Benefit of mammography screening in women ages 40 to 49 years. Current evidence from randomized controlled trials. Cancer. 75:1619–26
9. Duffy SW, Tabar L, Chen HH et al (2002) Impact of organized mammography screening service on breast carcinoma mortality in Swedish counties. Cancer. 95:458–69
10. Singletary SE, Allred C, Ashley P et al (2003) Staging system for breast cancer: revisions for the 6th edition of the AJCC cancer staging manual. Surg Clin North Am. 83(4): 803–19
11. American College of Radiology (ACR) (1994) Clinical Practice Guideline for the performance of diagnostic mammography and problem-solving breast evaluation [Adopted by the ACR Council 1994]. In: ACR Digest of Official Actions. Reston, VA: ACR
12. Linver MN, Osuch JR, Brenner RJ et al (1995) Mammography medical audit: primer for the mammography quality standards act (MQSA). AJR Am J Roentgenol. 165:19–25

13. Gold RH, Montgomery CK, Rambo ON (1973) Significance of margination of benign and malignant infiltrative mammary lesions: roentgenologic-pathologic correlation. Am J Roentgenol. 118:881–94
14. Hall FM, Storella JM, Silverstone DZ et al (1988) Nonpalpable breast lesions: recommendations for biopsy based on suspicion of carcinoma at mammography. Radiology. 167:353–8
15. Moskowitz M (1983) The predictive value of certain mammographic signs in screening for breast cancer. Cancer. 51: 1007–11
16. Sickels EA (1994) Nonpalpable, circumscribed, noncalcified solid breast masses: likelihood of malignancy based on lesion size and age of patient. Radiology. 192:439–42
17. Brenner RJ, Sickles EA (1989) Acceptability of periodic follow-up as an alternative to biopsy for mammographically detected lesions interpreted as probably benign. Radiology. 171:645–6
18. Feig SA (1992) Breast masses: mammographic and sonographic evaluation. Radiol Clin North Am. 30:67–92
19. Jackson VP, Dines KA, Bassett LW et al (1991) Diagnostic importance of radiographic density of noncalcified breast masses: analysis of 91 lesions. AJR Am J Roentgenol. 157:25–8
20. Bassett LW (1992) Mammographic analysis of calcifications. Radiol Clin North Am. 30:93–105
21. Sickles EA (1986) Mammographic features of 300 Consecutive nonpalpable breast cancers. Am J Roentgenol. 146:661–3
22. Sickles EA (1984) Mammographic features of "early": breast cancer. Am J Roentgenol. 143:461–4
23. Brown ML, Houn F, Sickles EA et al (1995) Screening mammography in community practice: positive predictive value of abnormal finding and yield of follow-up diagnostic procedures. Am J Roentgenol. 165:1373–7
24. Robertson CL, Kopans DB (1989) Communication problems after mammographic screening. Radiology. 172:443–4
25. Brew MD, Billings JD, Chisholm RJ (1989) Mammography and breast pain. Australas Radiol. 33:335–6
26. Jackson VP, Loex AM, Smith DJ (1998) Patient discomfort during screen-film mammography. Radiology. 168:421–3
27. Stomper PC, Kopans DB, Sadowsky NL et al (1988) Is mammography painful? A multicenter patient study. Arch Intern Med. 148:521–4
28. Physician Insurer's Association of America (1995) Breast cancer study 1995. Physician Insurers Association of America, Washington, DC
29. Feig SA, Shaber GS, Patchefsky A et al (1977) Analysis of clinically occult and mammographically occult breast tumors. Am J Roentenol. 128:403–8
30. Mann BD, Giuliano AE, Bassett LW et al (1983) Delayed diagnosis of breast cancer as a result of normal mammograms. Arch Surg. 118:23–4
31. Pisano ED, Gatsonis CA, Hendrick E et al (2005) Diagnostic performance of digital versus film mammography for breast cancer screening. N Engl J Med. 343:1773–83
32. Fornage BD, Lorigan JG, Andry E (1989) Fibroadenoma of the breast: sonographic appearance. Radiology. 172: 671–5
33. Stavros AT, Thickman D, Rapp CL et al (1995) Solid breast nodules: use of sonography to distinguish between benign and malignant lesions. Radiology. 196:123–34
34. Entrekin R, Jackson P, Jago JR, Porter BA (1999) Compound Imaging in breast ultrasound: technology and early clinical experience. Medicamundi. 43(3):35–43
35. Entrekin RR, Porter BA, Sillesen HH et al (2001) Real-time spatial compound imaging: application to breast, vascular, and musculoskeletal ultrasound. Semin Ultrasound CT MR. 22(1):50–64
36. Rosen EL, Soo MS (2001) Tissue harmonic imaging sonography of breast lesions: improved margin analysis, conspicuity and image quality compared to conventional ultrasound. Clin Imaging. 25(6):379–84
37. Mesurolle B, Helou T, El-Khoury M et al (2007) Tissue harmonic imaging, frequency compound imaging and conventional imaging: use and benefit in breast sonography. J Ultrasound Med. 26(8):1041–51
38. Rahbar G, Sie AC, Hansen GC et al (1999) Benign versus malignant solid breast masses: US differentiation. Radiology. 213:889–94
39. Gordon PB, Goldenberg SL (1995) Malignant breast masses detected only by ultrasound: a retrospective review. Cancer. 76:626–60
40. Buchberger W, Niehoff A, Obrist P et al (2002) Clinically and mammographically occult breast lesions: detection and classification with high resolution sonography. Semin Ultrasound CT MR. 21:325–36
41. Kaplan SS (2001) Clinical utility of bilateral whole-breast US in the evaluation of women with dense breast tissue. Radiology. 221:641–9
42. Crystal P, Strano SD, Shcharynski S et al (2003) Using sonography to screen women with mammographically dense breasts. Am J Roentgenol. 181:177–82
43. Kolb TM, Lichy J, Newhouse JH (1998) Occult cancer in women with dense breasts: detection with screening US – diagnostic yield and tumor characteristics. Radiology. 207:191–9
44. Kolb TM, Lichy J, Newhouse JH (2002) Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27, 825 patient evaluations. Radiology. 225:165–75
45. Berg WA (2003) Rationale for a trial of screening breast ultrasound: American college of radiology imaging network (ACRIN) 6666. Am J Roentgenol. 180:1225–8
46. ACRIN Current Protocols page (last updated 11/9/07). ACRIN Web site. Available at www.acrin.org. Accessed 12 Jan 2008
47. Parker SH, Lovin JD, Jobe WE et al (1990) Stereotactic breast biopsy with a biopsy gun. Radiology. 176:741–7
48. Jackson VP, Bassett LW (1990) Stereotactic fine-needle aspiration biopsy for nonpalpable breast lesions. Am J Roentgenol. 154:1196–7
49. Bassett LW, Winchester DP, Caplan RB et al (1997) Stereotactic core-needle biopsy of the breast. CA Cancer J Clin. 47:171–90
50. Sickles EA, Parker SH (1993) Appropriate role of core breast biopsy in the management of probably benign lesions. Radiology. 199:315
51. Lee CH, Philpotts LE, Horvath LJ et al (1999) Follow-up of breast lesions diagnosed as benign with stereotactic core-needle biopsy: frequency of mammographic change and false negative rate. Radiology. 212:189–94

52. Brem RF, Behrndt VS, Sanow L et al (1999) Atypical ductal hyperplasia: histologic underestimation of carcinoma in tissue harvested from impalpable breast lesions using 11-G stereotactically guided directional vacuum-assisted biopsy. Am J Roentgenol. 172:1405–7
53. Jackman RJ, Nowels W, Rodriguez-Soto J et al (1999) Stereotactic, automated, large-core needle biopsy of nonpalpable breast lesions: false-negative rates and histologic underestimation rates after long-term follow-up. Radiology. 210:799–805
54. Liberman L, Bracero N, Vuolo MA et al (1999) Percutaneous large-core biopsy of papillary breast lesions. Am J Roentgenol. 172:331–7
55. Liberman L, Sama M, Susnik B et al (1999) Lobular carcinoma in situ at percutaneous breast biopsy: surgical biopsy findings. Am J Roentgenol. 173:291–9
56. Philpotts LE, Shaheen NA, Carter D et al (1999) Comparison of rebiopsy rates after stereotactic core-needle biopsy of the breast with 11-G vacuum suction probe vs. 14-G automatic gun. Am J Roentgenol. 172:683–7
57. Brenner RJ, Jackman RJ, Parker SH et al (2002) Percutaneous core needle biopsy of radial scars of the breast: when is excision necessary? Am J Roentgenol. 179:1179–84
58. Foster MC, Helvie MA, Gregory NE et al (2004) Lobular carcinoma in situ or atypical lobular hyperplasia at core-needle biopsy: is excisional biopsy necessary? Radiology. 231:813–9
59. Mahoney MC, Robinson-Smith TM, Shaughnessy EA (2006) Lobular neoplasia at 11-gauge vacuum-assisted stereotactic biopsy: correlation with surgical excisional biopsy and mammographic follow-up. Am J Roentgenol. 187:949–54
60. Gorczyca DP, Sinha S, Ahn CY et al (1992) Silicone breast implants in vivo: MR imaging. Radiology. 185:407–10
61. El Yousef SJ, O'Connell DM, Duchesneau RH et al (1985) Benign and malignant breast disease: magnetic resonance and radiofrequency pulse sequences. Am J Roentgenol. 145:1–8
62. Heywang SH, Hahn D, Schmidt H et al (1986) MR imaging of the breast using gadolinium-DTPA. J Comput Asst Tomogr. 10:199–204
63. Kaiser WA (1992) MRM promises earlier breast cancer diagnosis. Diagn Imaging Int. 11:44–50
64. Heywang-Kobrunner SH (1993) Contrast-enhanced MRI of the breast-overview after 1250 patient examinations. Electromedica. 2:43–52
65. Harms SE, Flamig DP, Hesley KL et al (1993) MRI of the breast with rotating delivery of excitation off resonance: Clinical experience with pathologic correlation. Radiology. 186:493–501
66. Gilles R, Guinebretiere JM, Lucidarme O et al (1994) Nonpalpable breast tumors: diagnosis with contrast-enhanced subtraction dynamic MRI. Radiology. 191:625–31
67. Lehman CD, Isaacs C, Schnall MD et al (2007) Cancer yield of mammography, MR, and US in high-risk women: prospective multi-institution breast cancer screening study. Radiology. 244(2):381–8
68. Saslow D, Boetes C, Burke W et al (2007) American cancer society guidelines for breast screening with MRI as an adjunct to mammography. Cancer J Clin. 57(2):75–89
69. Khalkhali I, Mena I, Jouanne E et al (1994) Prone scintimammography in patients with suspicion of carcinoma of the breast. J Am Coll Surg. 178:491–7
70. Tolmos J, Cutrone JA, Wang B et al (1998) Scintimammographic analysis of non palpable breast lesions previously identified by conventional mammography. J Natl Cancer inst. 90:846–9
71. Prats E, Carril J, Herranz R et al (1998) Spanish multicenter scintigraphic study of the breast using Tc99m MIBI: report of results. Rev Esp Med Nucl. 17:338–50
72. Brem RF, Petrovitch I, Rapelyea JA, Young H, Teal C, Kelly T (2007) Breast-specific gamma imaging with 99mTc-Sestamibi and magnetic resonance imaging in the diagnosis of breast cancer–a comparative study. Breast J. 13:465–9
73. Brem RF, Floerke AC, Rapelyea JA, Teal C, Kelly T, Mathur V (2008) Breast-specific gamma imaging as an adjunct imaging modality for the diagnosis of breast cancer. Radiology. 247:651–7
74. Adler LP, Crowe JP, Al-Kasisi NK et al (1993) Evaluation of breast masses and axillary lymph nodes with (F-18) 2-Deoxy-2-fluro-D-glucose PET. Radiology. 187:743–50
75. Winchester DJ, Sener SF, Winchester DP et al (1999) Sentinel lymphadencotomy for breast cancer: experience what 180 consecutive patients: efficacy of filtered technetium 99m sulphur colloid with overnight migration time. J Am Coll Surg. 188:597–603
76. Schwartz GF, Guiliano AE, Veronesi U (2002) Consensus Conference Committee. Proceeding of the consensus conference of the role of sentinel lymph node biopsy in carcinoma or the breast April 19-22, 2001, Philadelphia, PA, USA. Breast J. 8:124–38

Premalignant and Malignant Breast Pathology

10

Young Kyung Bae and Edward W. Gabrielson

Breast cancer is the most common type of cancer among women in developed countries, and significant advances have been made in recent decades to improve the detection and diagnosis of this disease. These advances have also resulted in increasing recognition of noninvasive breast disease, including lesions that are thought to be preinvasive precursors to breast cancer. In addition, advances have been made in breast cancer therapy and in the recognition of markers that can help predict both the natural history of disease and, in many cases, responses to particular therapies. Thus, the role of the pathologist in the management of breast cancer is evolving beyond simple diagnosis to include providing predictive information that can enhance individualized care.

Rather than providing a comprehensive treatise on the pathology of breast cancer, this chapter is intended to provide an overview of the framework that pathologists use to diagnose and classify breast cancers. Unusual forms of breast cancer are only briefly discussed, and the chapter emphasizes characteristics of common forms of invasive breast cancer and preinvasive breast lesions. In addition to summarizing the morphological characteristics of these common cancers and preinvasive lesions, the chapter discusses molecular features and markers that are currently available to help stratify breast cancers according to aggressive potential and to predict how specific tumors are likely to respond to specific therapies.

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10.1 Morphologic Variants of Invasive Breast Cancer

10.1.1 Ductal Carcinoma

While the term "ductal carcinoma" implies that the cancer arises from the epithelial cells lining breast ducts, this term is used in practice to include most cancers of the breast that are not clearly lobular in nature. Thus, the morphological characteristics of ductal cancers are highly variable, although some reasonably distinctive types of ductal breast cancer can be recognized (see below). In general, though, most ductal breast cancers cannot be subclassified and thus are considered as "not-otherwise-specified" (NOS).

This NOS category includes tumors with highly variable architectural growth patterns, cytological features, and stromal reaction. In some cases, well-defined ductal or glandular structures are formed by the neoplastic cells, while in others, sheets of highly undifferentiated cells are present. Cytologic features of the cancers vary from cells that closely resemble normal breast epithelial cells to cells that are undifferentiated or differentiated into a heterologous pattern. Stromal reaction can vary from loose fibrous tissue to hard gritty scar tissue, formerly known as a "scirrhous reaction." Importantly, some invasive ductal breast cancers have well-circumscribed borders, whereas others have trabeculae of tumor extending into adjacent stroma. Several variants of growth for ductal carcinoma are shown in Fig. 10.1.

In light of the difficulties faced in subclassification of ductal breast cancers according to morphological features, grading scales have been developed to stratify these cancers according to morphological features associated

I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_10, © Springer-Verlag Berlin Heidelberg 2010

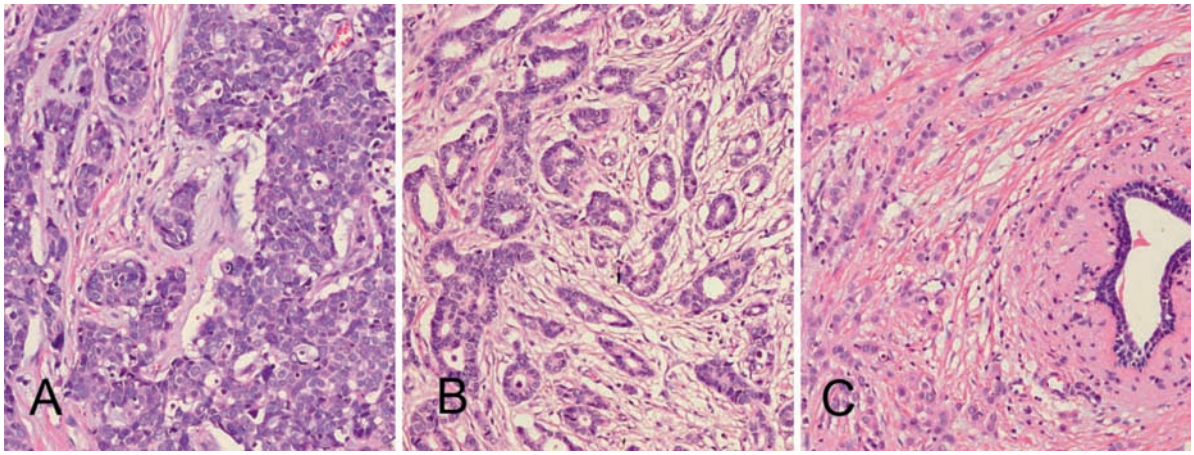

Fig. 10.1 Common variants of invasive breast cancer. Panel A shows a poorly differentiated (grade 3) ductal breast cancer with large, atypical cells, minimal formation of tubular structures, and frequent mitoses. Panel B shows a well-differentiated (grade 1) ductal breast cancer, with minimal atypia and tendency of tumor to grow with tubular structures. Panel C shows an infiltrating lobular carcinoma, with cancer cells arranged in single-file chords. Note uninvolved duct to *right* of panel

with aggressive behavior. The most commonly used is the Nottingham system developed originally by Bloom and Richardson (SBR) and subsequently modified by Elston and Ellis [1–3]. In general, nuclear grade, tubule formation, and mitotic rate are each scored on a scale from 1 to 3 (one being the best and three the worst), and the score of all three components are added together to give the "grade." Thus, the lowest possible score (1+1+1=3) is given to well-differentiated tumors that all form tubules and have a low mitotic rate (<10/10 HPF), and the highest possible score is 9 (3+3+3=9). The Elston-Ellis modification of this system increases the objectivity of criteria for the three component elements of grading, specifically approaching quantifying mitoses in a more rigorous fashion. These modifications have enhanced reproducibility of grading among pathologists and, more importantly, have led to acceptance by clinicians as prognostically significant.

Tubular Carcinoma of the breast is an unusual variant of invasive ductal carcinoma that is well differentiated and characterized by an orderly tubular formation. These cancers average only 1 cm in size, and the microscopic appearance can be mistaken for benign disease because of the well-differentiated appearance of the cells and associated glandular structures and the rare mitoses. However, the glands do typically have angulated contours (in contrast to benign disease) and reactive stroma, as well as invasion into fat at the periphery of many lesions. Furthermore, immunohistochemical stains (such as p63, calponin or smooth muscle actin) can confirm the lack of myoepithelial cells. These cancers most commonly occur in perimenopausal or postmenopausal women and have an excellent prognosis.

Molecular studies have shown that tubular cancers have fewer genomic changes at the chromosomal level than conventional ductal cancers [4], indicating that this morphological variant is a distinct disease process. Although it is not uncommon for ductal breast cancers to have a tubular pattern in association with other patterns of ductal carcinoma (mixed pattern), the prognosis of these cancers is highly variable, and thus the term "tubular carcinoma" should only be used for cancers without other elements.

Cribriform Carcinoma is another uncommon variant of breast cancer with an excellent prognosis. As implied by the name, this type of breast cancer has an appearance similar to the more common cribriform variant of *in situ* cancer. This distinction is important, obviously, because invasive cribriform carcinoma does have the potential to metastasize.

Mucinous Carcinoma, also known as colloid carcinoma, is a somewhat more common variant of well-differentiated ductal breast cancer. This is a variant that usually occurs in postmenopausal women, and has a distinctive gross appearance of a gelatinous mass. Microscopically, these cancers have small clusters of well-differentiated cells that float in lakes of mucin. It is uncommon for these cancers to metastasize, particularly if they are less than 3 cm in size. As seen with

tubular carcinoma, molecular studies have shown these cancers to have relatively few genomic changes [5]. However, it is also quite common to find areas of mucinous differentiation in conventional ductal carcinoma, and it is therefore important to restrict the use of the term "mucinous carcinoma" to those cancers with a mucinous pattern throughout ("pure mucinous").

Medullary Carcinoma of the breast is a variant that is characterized by large, atypical cells and poorly differentiated growth pattern, but ironically has a better prognosis than ductal carcinoma, NOS. Grossly, these cancers are generally well circumscribed, which correlates with microscopic findings of pushing, rather than infiltrative, borders. The neoplastic cells are large and pleomorphic, with large nuclei, prominent nucleoli, and frequent mitoses. These cells characteristically have indistinct borders, growing in a syncytial pattern that is similar to that seen in embryonal carcinoma. Another distinctive microscopic feature is the presence of a lymphocytic infiltrate, which is prominent at the periphery of the tumor and also extends into nests of tumor cells. Medullary cancers, as strictly defined, have a significantly better prognosis than ductal carcinoma, NOS, and the prognosis is particularly good for tumors less than 3 cm in size [6]. Medullary cancers are relatively more common in women with germline mutations of the BRCA1 gene [7].

*Metaplastic Carcinoma i*s a term that does not refer to a distinct form of breast cancer, but rather to ductal breast cancers with a predominant differentiation pattern that is not typical of ductal or glandular differentiation. The most common pattern seen in these cancers is a spindle-cell pattern, which often shows squamous differentiation in some areas. In such cases, the epithelial origin is evident, but in other, less differentiated spindle-cell tumors, immunohistochemical stains are needed to confirm that the tumor is a carcinoma, rather than a sarcoma.

Other patterns of differentiation that mimic osteosarcoma, chondrosarcoma, rhabdomyosarcoma, or fibrous histiocytoma can also be seen in metaplastic breast cancers. When evaluating tumors with such appearances, it is always important to remember that true sarcomas of the breast are less common than metaplastic carcinomas, and thus rigorous immunohistochemical evaluation is always needed to resolve any uncertainties.

Other uncommon variants of ductal carcinoma can also occur, including apocrine carcinoma [8], defined by the predominance of apocrine-like tumor cells. Another variant of ductal carcinoma is secretory carcinoma [9], which occurs principally in children and has a good prognosis. Yet another uncommon variant of ductal carcinoma is carcinoma with neuroendocrine features, which includes tumors diagnosed as carcinoid tumors [10]. Pathologists continue to debate the significance of neuroendocrine differentiation in breast cancer, and there does not appear to be any prognostic significance attached to this diagnosis as opposed to ductal carcinoma, NOS.

10.1.2 Lobular Carcinoma

Lobular carcinoma is a distinctive form of breast cancer that is typically characterized by small, poorly cohesive cells. In the classic form of the disease, these cells infiltrate as single cells or single-file strands, and do not form glands or tubular structures. Although these cancers are accompanied by a dense stromal reaction, they often have a gross consistency that is less distinctive than ductal carcinoma.

The major differential diagnosis of infiltrating lobular carcinoma is that of ductal carcinoma and in most cases, this distinction can be made by histologic appearance. The distinguishing molecular characteristic of lobular carcinoma, useful for differential diagnosis in questionable situations, is the lack of E-cadherin expression [11]. This loss of E-cadherin is due to mutation of the gene in many cases [12], and this molecular alteration is likely responsible for the poor cohesiveness of lobular cancer tumor cells.

There are several variants of lobular carcinoma. Pleomorphic lobular carcinoma has a greater degree of nuclear pleomorphism and larger cytoplasm than classic lobular cancer, and a histiocytoid variant has a granular, foamy cytoplasm. Many lobular cancers have cells with signet ring cell features, and tumors with a predominance of these cells are sometimes termed "signet ring cell carcinoma." This variant appears to be the result of defects (including mutations) in α-catenin, a gene that is in the same pathway as E-cadherin.

Perhaps the most commonly overlooked variant of lobular carcinoma is the tubulolobular variant, which can readily be confused with infiltrating ductal carcinoma or tubular carcinoma. In tubulolobular carcinoma, the carcinoma cells cluster to form small tubular formations that have a minute or indistinguishable lumen. This type of cancer has a behavior like that of

classic lobular carcinoma, rather than that of tubular carcinoma.

Compared to ductal cancers, lobular carcinomas have a tendency to be multifocal in the breast and to metastasize to a variety of different sites, including the gastrointestinal system and ovaries [13]. Interestingly, metastases of lobular cancer often remain occult, resulting in relatively little morbidity, and the survival rate for lobular cancer is similar to that of ductal carcinoma [13]. It is not infrequent to find breast cancers with mixtures of lobular and ductal morphological features, and thus it appears likely that these variants are closely related.

10.1.3 Malignant Tumors of Stroma Origin

Phyllodes Tumors are mixed epithelial and stromal proliferations of the breast with increased stromal cellularity and characteristic cleft-like spaces with broad "leaf-like" papillae. These tumors are usually well circumscribed and grossly resemble fibroadenomas, although they tend to be somewhat larger in size. Phyllodes tumors most commonly occur between the ages of 40 and 50 (prior to menopause), which is about 15 years older than the typical age of patients with fibroadenoma.

Microscopically, phyllodes tumors are composed of a hypercellular stroma and benign glandular elements. The clinical behavior of these tumors correlates to a large extent with the appearance of the stroma, although a sharp distinction between benign and malignant phyllodes tumor is often not possible. Tumors that microscopically resemble fibroadenomas with a cellular stroma (without atypia) are associated with a benign clinical course. The increased cellularity in these tumors tends to be concentrated in the periductal areas and has a fibroblastic appearance with occasional admixture of adipose tissue. By contrast, malignant phyllodes tumors have overgrowth of glands by stroma with malignant features, including nuclear atypia and numerous mitoses, and infiltrating, rather than pushing, borders [14]. The increased cellularity in these malignant tumors is no longer concentrated around ducts, and frequently large areas of tumor show only stroma without glandular elements. Malignant phyllodes tumors may also have pleomorphic stromal elements, such as cartilage or bone.

The major concern for treatment of phyllodes tumors is that of local recurrence, and local excision is usually adequate for patient management [15]. Cytologically malignant phyllodes tumors do have the potential to metastasize to lungs and bone, however. These metastases show only the stomal elements of the original tumors.

Angiosarcoma of the breast is a malignant tumor that typically occurs in young women and presents as a soft, noncalcified mass [16]. This tumor is characterized by anastomosing networks of irregular vascular channels lined by atypical endothelial cells. The prognosis of this lesion is generally poor, with a correlation between microscopic grade and outcome. There is now concern that angiosarcoma is being reported with increasing frequency in the irradiated breast after breast-conserving therapy [17]. This cancer commonly spreads via hematogenous metastases, in contrast to carcinoma of the breast. Pathologists must take care to exclude benign vascular proliferations when making the diagnosis of angiosarcoma.

10.2 Pathology of Invasion and Metastases

Breast cancer spreads by direct invasion into adjacent normal tissues (breast and chest wall), by lymphatics to lymph nodes and secondary sites, and by blood vessels. While rigorous measures are now used to assess extent of disease at the time of diagnosis, it is not uncommon for breast cancer metastases to be occult for extended periods of time, manifesting as distant disease years or even decades after initial diagnosis [18].

Local invasion can involve the skin and nipple as well as breast parenchyma, and this extension tends to be more extensive in lobular cancers than ductal cancers. It is important to understand that invasion frequently extends beyond the grossly defined tumor mass, as demonstrated by Rosen and coworkers (PMID: 163139). In this study, radical mastectomy specimens were carefully evaluated microscopically in areas beyond the confines of a 2 cm "local excision" performed on the specimens, and even for cancers less than 1 cm, residual invasive carcinoma was found in 11% of the cases. Similarly, nipple invasion can be found in approximately 20–30% of clinically detected breast cancers, especially in cases with the tumor masses located less than 2.5 cm from the

nipple [19, 20]. These studies underscore the importance of a thorough pathological evaluation of margins for cases with conservative surgical management. Interestingly, however, evaluation of local invasion does not have great implications regarding distant disease, since metastases appear to represent independent events that are not temporally related to local recurrences [21].

Metastases to lymph nodes usually involve axillary lymph nodes, with less frequent involvement of internal mammary nodes and supraclavicular nodes. It is very uncommon to find metastases to supraclavicular nodes without axillary node metastases [22], consistent with these nodes representing a more distal region of the same drainage system. Metastases to internal mammary nodes are also far more common in cases with axillary metastases than those without [23], and this pattern of lymph node metastases is uncommon in cancer arising in the outer half of the breast.

Since a major reason for axillary node sampling in breast cancer is to improve staging, full axillary lymph node dissection has largely been replaced by *sentinel lymph node biopsy*. Clinical studies have shown that if the sentinel node is negative, other nodes of the axilla will be negative in almost all cases. By contrast, if the sentinel node is positive, other nodes in the axilla will be positive in about one-third to one-half of cases. For patients with a positive sentinel node, completion axillary dissection provides additional prognostic information, maintains local control, and may have a survival benefit [24].

One hotly debated issue in breast cancer pathology has been the significance of micrometastases in sentinel nodes. For a number of years, many pathology laboratories have gone to great lengths to rigorously evaluate sentinel nodes for possible minute foci of breast cancer, using approaches that include serial sectioning, immunohistochemical stains to highlight epithelial cells, and RT-PCR to detect epithelial-specific markers. However, based on available data, the value of such rigorous evaluation is uncertain.

Several clinical studies have addressed the issue of importance of micrometastases [25–27]. In general, findings of micrometastases by immunohistochemical methods do not appear to predict recurrence, although one case-control retrospective study found a significantly higher rate of recurrence for patients with micrometastases larger than 0.2 cm, but not for patients with isolated tumor cells [25]. One possible explanation for the lack of significance of isolated tumor cells is that some of these patients may have had those cells dislodged during surgery; thus, these cells might not represent true metastases [28].

Inflammatory breast carcinoma (IBC) is a rare but highly aggressive form of breast cancer that is usually diagnosed based on the presence of typical clinical symptoms, including redness, swelling, and warmth. These clinical findings are frequently, but not always, associated with pathologic findings of dermal lymphatic invasion. The presence of dermal lymphatic invasion on microscopic examination in the absence of clinical signs (occult inflammatory cancer) is an indicator of poor prognosis, though perhaps not as ominous as the disease with clinical symptoms [29, 30]. IBC is not associated with a specific histologic tumor type [31], but epidemiologic and molecular evidence suggest that IBC is a distinct disease entity rather than a subtype of locally advanced breast cancer [32].

Paget's disease of the breast is a name given to a crusted lesion of the nipple caused by intraepithelial infiltration of breast cancer cells [33]. Pathologically, this condition can occasionally resemble in situ squamous cell carcinoma of malignant melanoma, but the rarity of these diseases in the nipple should alert pathologists to consider Paget's disease as the primary consideration in the differential of intraepithelial carcinoma of the nipple. Most associated breast cancers are of the ductal type, and only occasionally are the associated cancers more than 2 cm from the involved nipple [34].

10.3 Proliferative and Preinvasive Breast Disease

Increasingly, breast disease evaluated and diagnosed at early, preinvasive stages of the neoplastic process. This section discusses our understanding of various morphological forms of preinvasive breast disease from both biological and clinical perspectives, beginning with lesions that are considered to be in situ carcinoma.

Ductal carcinoma in situ (DCIS), the most common form of in situ breast cancer is characterized by large, cohesive cells with distinctive cell borders that frequently form lumens. DCIS is often classified by pathologists according to nuclear grade. High-grade DCIS is diagnosed based on cytologically malignant nuclear features, and this is often associated with zonal "comedo"

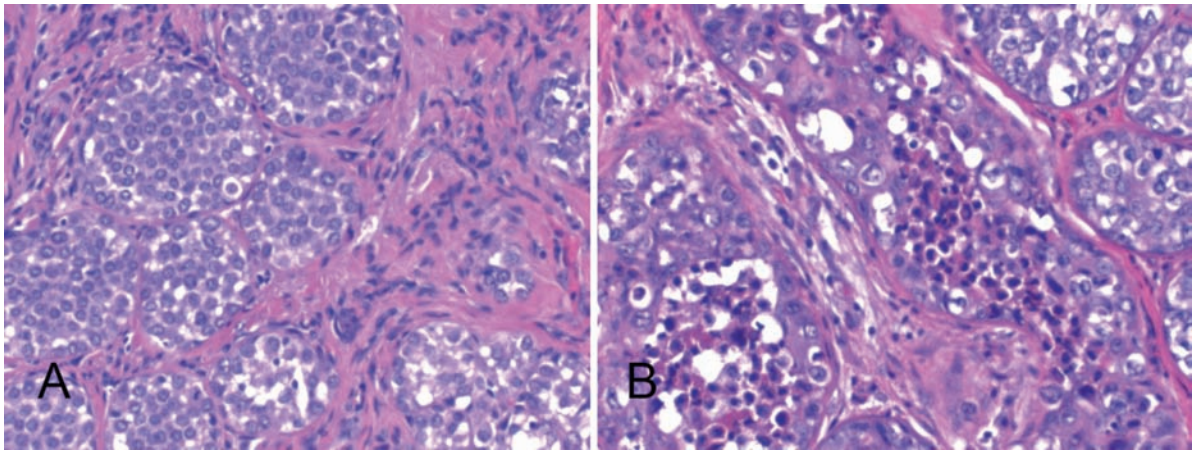

Fig. 10.2 Common patters of in situ breast carcinoma. Panel A shows lobular carcinoma in situ (LCIS), which is characterized by distension of terminal duct lobular units with small, round, poorly cohesive cells. There is generally a lack of atypia and necrosis. Panel B shows high-grade ductal carcinoma in situ (DCIS), which is characterized by atypical cells filling ductal structures. Note cellular atypia and central "comedo" necrosis within these ducts

necrosis within large ducts (see Fig. 10.2). By contrast, low-grade DCIS is characterized by growth of relatively uniform and cytologically bland cells without significant necrosis. Architecturally, low-grade DCIS presents in solid, cribriform or micropapillary forms, or combinations of these patterns. Micropapillary DCIS is distinguished clinically from other forms of low-grade DCIS by its greater tendency toward multifocality [35].

There is important clinical and pathological data providing evidence that DCIS represents a direct precursor to invasive breast cancer, including observations that women with DCIS have a high risk for synchronous or subsequent ipsilateral invasive breast cancer. For example, Page and colleagues demonstrated that all invasive carcinomas occurring in patients with previously biopsied low-grade DCIS developed in the same quadrant of the same breast in which the DCIS was found previously [35]. Pathological evidence to support the *in situ* to invasive progression model includes observations that the cells of *in situ* breast cancers cytologically resemble those of invasive breast cancers, and occasionally the invasive cancer appears to "burst out" of ducts that have *in situ* cancer. Molecular data have confirmed the clonal link between synchronous DCIS and invasive breast cancer [36, 37].

Given that the nuclear atypia and molecular profile of high-grade DCIS is one that is associated with poor prognosis in invasive duct carcinoma, one might suspect that high-grade DCIS would be associated with the greater risk of recurrence and progression to invasive mammary carcinoma. While the short-term risk of recurrence is greater for high-grade DCIS, long-term follow-up suggests that low-grade DCIS more frequently recurs later (10–20 years) and that the overall risk of recurrence is similar among each of these groups [35, 38]. One explanation of this observation would be that high-grade DCIS is a more advanced form of *in situ* neoplasia and thus temporally closer to the invasive phase of breast cancer. Alternatively, high-grade DCIS could represent a different disease process that grows at a more rapid rate than low-grade DCIS. This second possibility is supported by observations that invasive cancers associated with high-grade DCIS are usually also high grade, and invasive cancers associated with low-grade DCIS are usually low grade.

The major variables that are predictive of local recurrence (as either *in situ* or invasive breast cancer) are close (less than 1 mm) or positive surgical margins and high-grade DCIS [38, 39]. Interestingly, high-grade DCIS tends to form as a continuous neoplasm, whereas low-grade DCIS often has discontinuous intraductal growth [40, 41]. While these findings would seem to contradict the higher risk for recurrence of high-grade DCIS, it is quite possible that the natural history of low-grade DICS is simply that many of these lesions do not progress to more aggressive forms of neoplasia.

Atypical ductal hyperplasia is a type of preinvasive breast neoplasia that merges morphologically with low-grade DCIS. It is important for clinicians to

understand that there is often not a sharp distinction between DCIS and ADH, and interobserver pathologist concordance in differentiating these lesions has been shown less than perfect, even when standardized criteria are used by expert breast cancer pathologists [42]. Quantitative criteria based upon size (2 mm) [43] or numbers of ducts involved (two ducts) [44] have been proposed to make this distinction for clinical management, but it seems doubtful that such quantitative breakpoints reflect true biologic distinctions.

Atypical ductal hyperplasia diagnosed on core needle biopsy has been found to be frequently associated with coexisting DCIS or invasive carcinoma [45], and therefore the management of this lesion generally includes complete excisional biopsy with negative margins.

Lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH), unlike DCIS, virtually never form grossly detectable lesions. Rather, these diseases are usually identified incidentally, often when coexisting with a mass-forming lesion such as a fibroadenoma or sclerosing adenosis. Calcifications are not particularly indicative of LCIS, and when calcifications are associated with LCIS, they more typically involve the surrounding normal breast tissue adjacent to the LCIS than the neoplasm itself [46]. The peak incidence of LCIS (40–50 years) is approximately a decade earlier than that for DCIS [47].

LCIS and ALH appear to represent a continuum of a disease process that is characterized by discohesive, small, uniform cells that fill the terminal duct lobular unit (Fig. 10.2). The major criteria used to diagnose LCIS, as opposed to ALH, is distension of these terminal duct lobular units. Cellular atypia, mitoses, and necrosis are usually absent in these lesions. Frequently, "signet ring cells" – formed by intracytoplasmic mucin – provide a useful diagnostic finding. While the bulk of the lesion is classically centered within the lobules, LCIS frequently extends up into the ducts where it undermines the native duct epithelium to yield a "cloverleaf" pattern. However, LCIS virtually never extends into the major ducts and overlying skin of the nipple (as does Paget's disease). A very important difference between LCIS and DCIS is that LCIS more frequently occurs as bilateral (35 vs. 10%) and multifocal (70 vs. 33%) disease [48, 49].

On the basis of this multifocal nature of the disease, the diagnosis of LCIS/ALH is significant as an indicator that both breasts are at risk for subsequent invasive mammary carcinoma, with the magnitude of that risk corresponding to the degree of proliferative change. Interestingly, most invasive cancers occurring in association with LCIS are ductal, although the percentage of lobular cancers in patients with LCIS is somewhat higher than that in the general female population [50]. Thus, LCIS and ALH are probably best considered to be markers of generally increased risk for breast cancer, rather than an indicator of local disease [51, 52]. However, several studies have shown that LCIS diagnosed on core needle biopsy is frequently associated with adjacent DCIS or invasive cancer [51, 52], and follow-up surgical excision is frequently recommended for this diagnosis on core biopsy. By contrast, when diagnosed on excisional biopsy, ALH and LCIS generally do not require further intervention, even when present at a surgical margin [51, 52]. Conversely, for some patients with genetic predisposition, bilateral prophylactic mastectomy may be considered.

10.4 Molecular Markers in Breast Cancer Management

Estrogen receptor (ER) and progestin receptor have been measured routinely as a part of breast cancer assessment for almost three decades. These measurements have significance for prognosis and even greater significance for predicting whether a particular breast cancer will respond to anti-estrogen therapy. Originally, these receptors were measured with binding assays on tissue homogenates, but almost all laboratories now measure these receptors by immunohistochemistry. IHC-based assays have a number of advantages, including the ability of the pathologist to visualize receptor expression, specifically in tumor cells. While ER is the actual target for specific pharmacological agents (such as tamoxifen), progestin receptor is also commonly measured as an indicator of ER activity.

While clinicians often give little thought to how the laboratory measures ER/PR, it is worth noting that there are several potential pitfalls in these analyzes, and oncologists should work closely with pathology laboratories to assure optimal testing practices. One important issue is that of specimen type and fixation. Sensitive immunohistochemical measurements of ER/PR require breast cancer tissues to be adequately fixed in formalin, and this requires at least 6–8 h in most situations [53]. Interestingly, needle core biopsies are less likely to be

inadequately fixed (compared to resection specimens). When testing results for adequately fixed resection specimens are compared to adequately fixed biopsy specimens, nearly 100% concordance in results can be seen. Thus, in general, it is not necessary to retest breast cancer resection specimens if there is confidence in test results from biopsy samples.

A second issue in ER/PR testing is the threshold for calling a positive result. In the landmark study that established the superiority of IHC testing for ER, staining on a nine-point semiquantitative scale was compared to the response to adjuvant anti-estrogen therapy [53]. Although there was a strong correlation between score and response, it was also noted that even patients with as few as 1% of cells staining weakly for ER might benefit from hormonal therapy. More recent studies have found that weak staining of as few as 1% of cells for PR is also an indicator of potential response to hormonal therapy [54]. Given the relatively low toxicity of anti-estrogen therapy, it is important to consider using low cutoffs for calling breast cancers ER/PR positive.

Yet another issue in ER/PR testing is the value of measuring these receptors in DCIS. Intuitively, it would seem that testing DCIS for ER/PR is probably warranted if anti-estrogen therapy is being considered. However, there is relatively little published data supporting the use of ER/PR testing of DCIS to predict whether anti-estrogen chemoprevention will be beneficial. One study has shown that patients with ER/PR positive DCIS have a significant reduction in risk of subsequent recurrence as invasive disease when treated with anti-estrogen therapy, whereas such benefit was not seen in patients with ER-negative DCIS. Additional data is probably needed to guide clinical practice in this area.

HER2 is an oncogene protein that is a member of the epidermal growth factor receptor family and overexpressed in approximately 10–20% of breast cancers that have amplification of the corresponding gene. HER2 status is an important prognostic marker [55] as well as a marker predictive of response to trastuzumab, a humanized monoclonal antibody to the receptor protein.

It is now recommended that HER2 testing be conducted using an algorithm that defines positive, equivocal, and negative values for both HER2 protein expression and gene amplification [56]. A positive HER2 result by IHC is staining of 3+ (uniform, intense membrane staining of >30% of invasive tumor cells), and this is typically used as evidence for gene amplification and potential for response to trastuzumab. An equivocal IHC (2+) result should trigger fluorescent in situ hybridization (FISH), where a result of more than six HER2 gene copies per nucleus, or a FISH ratio (HER2 gene signals to chromosome 17 signals) of more than 2.2 is interpreted as positive. A negative result is an IHC staining of 0 or 1+, a FISH result of less than 4.0 HER2 gene copies per nucleus, or a FISH ratio of less than 1.8. Accuracy of HER2 testing by IHC is dependent on the experience of the testing laboratory, as well as the reagents used for testing. Currently, only the HerceptTest, based on the Dako A0485 antibody, and the CB11 antibody used on the Ventana autostainer are approved by the FDA for IHC assessment of HER2 [57].

Interestingly, HER2/Neu appears to be even more commonly amplified (and overexpressed) in high-grade DCIS than in invasive breast cancer [58]. There is still no satisfactory biological explanation for this phenomenon, and more importantly, amplification of HER2/neu in DCIS does not have any clinical implications regarding patient treatment.

Other individual prognostic and predictive molecular markers have also been shown over the years to have prognostic significance for breast cancer. A comprehensive review of this topic is well beyond the scope of this chapter, and it is notable that measuring multiple markers in parallel, using high-throughput technologies such as microarrays, shows greater promise for prognostication than individual markers. This topic is discussed below in the section on molecular classification of breast cancer.

One general class of markers that has unequivocal importance in breast cancer prognosis is that of proliferation. Proliferation can be assessed by counting mitoses, and the mitotic score is a component of the grading system commonly used for breast cancer. Alternatively, or in addition, proliferation can be assessed by flow cytometry, or more commonly, by measuring Ki67 by immunohistochemistry [59].

Molecular profiling has emerged as an extension of panels of prognostic and predictive markers, and two commercially market platforms are currently available. MammaPrint is a microarray based assay marketed by Agendia that measures mRNA levels of 70 genes in the "Amsterdam breast cancer gene signature". Several follow-up studies have validated the use of this profile

[60, 61], and the FDA has cleared this test to predict recurrence for lymph node-negative breast cancer patients under 61 years of age with tumors of less than 5 cm. The other available profile, Oncotype DX, is marketed by Genomic Health and is also appropriate for women with early stage invasive breast cancer. This test uses RT-PCR to determine the mRNA levels of genes in a 21-gene panel and reports a "recurrence score" that can be used along with other patient data to determine whether chemotherapy is warranted. Several clinical studies have also validated the use of this profile in clinical management of early stage breast cancer [62, 63]. Neither test is appropriate for use in patients with carcinoma *in situ* or metastatic breast cancer.

There is still some uncertainty regarding the appropriate use of these molecular profiling panels for breast cancer management. In many cases, conventional pathological diagnostic information (such as sub-type of cancer and grade of cancer) are sufficient for the oncologist to make a reasonable decision regarding the use of chemotherapy for a breast cancer patient. The tests can be particularly useful for situations where the pathological features generally indicate a favorable prognosis, but additional objective data is desired before making the decision to withhold chemotherapy. Both tests are expensive (approximately $4,000), but there can be an overall cost savings when an informed decision to not use chemotherapy can be made.

The selection of a particular test is one that has implications regarding specimen collection. For the Oncotype DX, the pathologist selects an appropriate tissue block and sends several thin sections of formalin-fixed, paraffin-embedded tissue sample to Genomic Health. Thus, this test may be performed on routinely processed specimens, and does not require any advanced planning or alteration of the surgical protocol. By contrast, the MammaPrint assay works on fresh tissue, which arguably uses RNA that has less degradation than fixed tissue. However, for this test, a sample must be collected from an unfixed tumor specimen within an hour of surgery and placed in a company-provided container, which is then shipped to Agendia. This process can alter the surgical technique and obviously must be coordinated with the pathology laboratory.

Molecular classification is yet a further extension of molecular profiling. Molecular classification is based on the general concept that breast cancer is intrinsically a heterogeneous disease, and that stratifying breast cancers along a single prognostic spectrum is insufficient to fully characterize this disease. One approach to molecular classification is based on analysis of gene expression microarray data, and this has led to the proposition that there are five subtypes of invasive breast carcinoma (luminal A, luminal B, normal breast-like, HER2-overexpressing, and basal-like), and these classes appear to be associated with different clinical outcomes [64]. Other studies [65] have also recognized large-scale gene differences between estrogen receptor-positive and ER-negative breast cancers, as well as suggestions of additional molecular subsets within, or in addition to, these broad categories.

The case for classification of breast cancer by microarray data may be significantly overstated, however. As noted by Andre and Pusztai [66], statistical methods to actually determine the number of robust clusters in hierarchical clustering algorithms have not been applied in these breast cancer microarray publications. These authors illustrate the inherently unstable nature of hierarchical clustering results by using five different statistical methods for assessing the optimal number of clusters in the data and showing that each method finds the number of robust clusters to be no more than two to three. The instability is further illustrated by slightly modifying the gene sets used for clustering or adding new cases to an existing data set. In either situation, many cases, which previously clustered together using one gene set, become dispersed into other clusters or a completely new dendrogram is generated.

Recognizing that microarray analysis has limitations in breast cancer classification, the concept of a *basal-like phenotype* has become one of the prominent themes in contemporary breast cancer pathology. These tumors are largely triple negative and express genes characteristic of basal epithelial cells and normal breast myoepithelial cells, including basal cytokeratins. Although several immunohistochemical surrogates have been proposed for basal-like carcinomas [67, 68], including triple-negative status and ER-HER2 negative (double negative) status, there is no internationally accepted definition or consensus for basal-like carcinomas. Therefore, basal-like carcinomas are still a poorly characterized subgroup of breast cancers and there is a possibility that basal-like carcinomas defined by other groups consisted of quite heterogeneous population of breast cancers.

References

1. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. C. W. Elston and I. O. Ellis. Histopathology. 1991;19:403–10. Histopathology. 2002;41(3A):151–2, discussion 2–3
2. Simpson JF, Gray R, Dressler LG et al (2000) Prognostic value of histologic grade and proliferative activity in axillary node-positive breast cancer: results from the Eastern cooperative oncology group companion study, EST 4189. J Clin Oncol. 18(10):2059–69
3. Rakha EA, El-Sayed ME, Lee AH et al (2008) Prognostic significance of Nottingham histologic grade in invasive breast carcinoma. J Clin Oncol. 26(19):3153–8
4. Waldman FM, Hwang ES, Etzell J et al (2001) Genomic alterations in tubular breast carcinomas. Hum Pathol. 32(2):222–6
5. Fujii H, Anbazhagan R, Bornman DM, Garrett ES, Perlman E, Gabrielson E (2002) Mucinous cancers have fewer genomic alterations than more common classes of breast cancer. Breast Cancer Res Treat. 76(3):255–60
6. Eichhorn JH (2004) Medullary carcinoma, provocative now as then. Semin Diagn Pathol. 21(1):65–73
7. Lakhani SR (1999) The pathology of hereditary breast cancer. Dis Markers. 15(1–3):113–4
8. O'Malley FP, Bane A (2008) An update on apocrine lesions of the breast. Histopathology. 52(1):3–10
9. Rosen PP, Cranor ML (1991) Secretory carcinoma of the breast. Arch Pathol Lab Med. 115(2):141–4
10. Maluf HM, Koerner FC (1994) Carcinomas of the breast with endocrine differentiation: a review. Virchows Arch. 425(5):449–57
11. Acs G, Lawton TJ, Rebbeck TR, LiVolsi VA, Zhang PJ (2001) Differential expression of E-cadherin in lobular and ductal neoplasms of the breast and its biologic and diagnostic implications. Am J Clin Pathol. 115(1):85–98
12. Berx G, Cleton-Jansen AM, Strumane K et al (1996) E-cadherin is inactivated in a majority of invasive human lobular breast cancers by truncation mutations throughout its extracellular domain. Oncogene. 13(9):1919–25
13. Arpino G, Bardou VJ, Clark GM, Elledge RM (2004) Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res. 6(3):R149–56
14. Petrek J (2004) Phyllodes tumors. In: Harris J, Lippman ME, Morrow M, Osborne CK (eds) Diseases of the breast. Lippincott-Raven, Philadelphia, pp 669–75
15. Browder W, McQuitty JT Jr, McDonald JC (1978) Malignant cystosarcoma phylloides. Treatment and prognosis. Am J Surg. 136(2):239–41
16. Donegan WL (1979) Sarcoma of the breast. Major Probl Clin Surg. 5:504–42
17. Monroe AT, Feigenberg SJ, Mendenhall NP (2003) Angiosarcoma after breast-conserving therapy. Cancer. 97(8): 1832–40
18. Brinkley D, Haybrittle JL (1975) The curability of breast cancer. Lancet. 2(7925):95–7
19. Morimoto T, Komaki K, Inui K et al (1985) Involvement of nipple and areola in early breast cancer. Cancer. 55(10): 2459–63
20. Rosen PP, Fracchia AA, Urban JA, Schottenfeld D, Robbins GF (1975) "Residual" mammary carcinoma following simulated partial mastectomy. Cancer. 35(3):739–47
21. Veronesi U, Marubini E, Del Vecchio M et al (1995) Local recurrences and distant metastases after conservative breast cancer treatments: partly independent events. J Natl Cancer Inst. 87(1):19–27
22. Veronesi U, Cascinelli N, Bufalino R et al (1983) Risk of internal mammary lymph node metastases and its relevance on prognosis of breast cancer patients. Ann Surg. 198(6):681–4
23. Donegan WL (1977) The influence of untreated internal mammary metastases upon the course of mammary cancer. Cancer. 39(2):533–8
24. Morrow M (2001) Is axillary dissection necessary after positive sentinel node biopsy? Yes!. Ann Surg Oncol. 8(9 Suppl):74S–6S
25. Susnik B, Frkovic-Grazio S, Bracko M (2004) Occult micrometastases in axillary lymph nodes predict subsequent distant metastases in stage I breast cancer: a case-control study with 15-year follow-up. Ann Surg Oncol. 11(6):568–72
26. Kahn HJ, Hanna WM, Chapman JA et al (2006) Biological significance of occult micrometastases in histologically negative axillary lymph nodes in breast cancer patients using the recent American joint committee on cancer breast cancer staging system. Breast J. 12(4):294–301
27. Chagpar A, Middleton LP, Sahin AA et al (2005) Clinical outcome of patients with lymph node-negative breast carcinoma who have sentinel lymph node micrometastases detected by immunohistochemistry. Cancer. 103(8):1581–6
28. Page DL, Anderson TJ, Carter BA (1999) Minimal solid tumor involvement of regional and distant sites: when is a metastasis not a metastasis? Cancer. 86(12):2589–92
29. Gruber G, Ciriolo M, Altermatt HJ, Aebi S, Berclaz G, Greiner RH (2004) Prognosis of dermal lymphatic invasion with or without clinical signs of inflammatory breast cancer. Int J Cancer. 109(1):144–8
30. Amparo RS, Angel CD, Ana LH et al (2000) Inflammatory breast carcinoma: pathological or clinical entity? Breast Cancer Res Treat. 64(3):269–73
31. Resetkova E (2008) Pathologic aspects of inflammatory breast carcinoma: part 1. Histomorphology and differential diagnosis. Semin Oncol. 35(1):25–32
32. Wu M, Merajver SD (2005) Molecular biology of inflammatory breast cancer: applications to diagnosis, prognosis and therapy. Breast Dis. 22:25–34
33. Sakorafas GH, Blanchard K, Sarr MG, Farley DR (2001) Paget's disease of the breast. Cancer Treat Rev. 27(1):9–18
34. Paone JF, Baker RR (1981) Pathogenesis and treatment of Paget's disease of the breast. Cancer. 48(3):825–9
35. Bellamy CO, McDonald C, Salter DM, Chetty U, Anderson TJ (1993) Noninvasive ductal carcinoma of the breast: the relevance of histologic categorization. Hum Pathol. 24(1):16–23
36. Zhuang Z, Merino MJ, Chuaqui R, Liotta LA, Emmert-Buck MR (1995) Identical allelic loss on chromosome 11q13 in microdissected in situ and invasive human breast cancer. Cancer Res. 55(3):467–71
37. Fujii H, Marsh C, Cairns P, Sidransky D, Gabrielson E (1996) Genetic divergence in the clonal evolution of breast cancer. Cancer Res. 56(7):1493–7
38. Hetelekidis S, Collins L, Silver B et al (1999) Predictors of local recurrence following excision alone for ductal carcinoma in situ. Cancer. 85(2):427–31

39. Solin LJ, Yeh IT, Kurtz J et al (1993) Ductal carcinoma in situ (intraductal carcinoma) of the breast treated with breast-conserving surgery and definitive irradiation. Correlation of pathologic parameters with outcome of treatment. Cancer. 71(8):2532–42
40. Holland R, Hendriks JH, Vebeek AL, Mravunac M, Schuurmans Stekhoven JH (1990) Extent, distribution and mammographic/histological correlations of breast ductal carcinoma in situ. Lancet. 335(8688):519–22
41. Faverly DR, Burgers L, Bult P, Holland R (1994) Three-dimensional imaging of mammary ductal carcinoma in situ: clinical implications. Semin Diagn Pathol. 11(3):193–8
42. Schnitt SJ, Connolly JL, Tavassoli FA et al (1992) Interobserver reproducibility in the diagnosis of ductal proliferative breast lesions using standardized criteria. Am J Surg Pathol. 16(12):1133–43
43. Tavassoli FA (1998) Ductal carcinoma in situ: introduction of the concept of ductal intraepithelial neoplasia. Mod Pathol. 11(2):140–54
44. Page DL, Rogers LW (1992) Combined histologic and cytologic criteria for the diagnosis of mammary atypical ductal hyperplasia. Hum Pathol. 23(10):1095–7
45. Renshaw AA, Cartagena N, Schenkman RH, Derhagopian RP, Gould EW (2001) Atypical ductal hyperplasia in breast core needle biopsies. Correlation of size of the lesion, complete removal of the lesion, and the incidence of carcinoma in follow-up biopsies. Am J Clin Pathol. 116(1):92–6
46. Hutter RV, Snyder RE, Lucas JC, Foote FW Jr, Farrow JH (1969) Clinical and pathologic correlation with mammographic findings in lobular carcinoma in situ. Cancer. 23(4):826–39
47. Schnitt SJ, Morrow M (1999) Lobular carcinoma in situ: current concepts and controversies. Semin Diagn Pathol. 16(3):209–23
48. Warner NE (1969) Lobular carcinoma of the breast. Cancer. 23(4):840–6
49. Urban JA (1970) Bilaterality of breast cancer: biopsy of the contralateral breast. Cancer. 23(6):315–8
50. Wheeler JE, Enterline HT, Roseman JM et al (1974) Lobular carcinoma in situ of the breast. Long-term follow-up. Cancer. 34(3):554–63
51. Elsheikh TM, Silverman JF (2005) Follow-up surgical excision is indicated when breast core needle biopsies show atypical lobular hyperplasia or lobular carcinoma in situ: a correlative study of 33 patients with review of the literature. Am J Surg Pathol. 29(4):534–43
52. Foster MC, Helvie MA, Gregory NE, Rebner M, Nees AV, Paramagul C (2004) Lobular carcinoma in situ or atypical lobular hyperplasia at core needle biopsy: is excisional biopsy necessary? Radiology. 231(3):813–9
53. Harvey JM, Clark GM, Osborne CK, Allred DC (1999) Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol. 17(5):1474–81
54. Mohsin SK, Weiss H, Havighurst T et al (2004) Progesterone receptor by immunohistochemistry and clinical outcome in breast cancer: a validation study. Mod Pathol. 17(12): 1545–54
55. Paik S, Hazan R, Fisher ER et al (1990) Pathologic findings from the National surgical adjuvant breast and bowel project: prognostic significance of erbB-2 protein overexpression in primary breast cancer. J Clin Oncol. 8(1): 103–12
56. Wolff AC, Hammond ME, Schwartz JN et al (2007) American society of clinical oncology/college of American pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Arch Pathol Lab Med. 131(1):18
57. Gown AM (2008) Current issues in ER and HER2 testing by IHC in breast cancer. Mod Pathol. 21(Suppl 2):S8–15
58. Allred DC, Clark GM, Molina R et al (1992) Overexpression of HER-2/neu and its relationship with other prognostic factors change during the progression of in situ to invasive breast cancer. Hum Pathol. 23(9):974–9
59. van Diest PJ, van der Wall E, Baak JP (2004) Prognostic value of proliferation in invasive breast cancer: a review. J Clin Pathol. 57(7):675–81
60. van de Vijver MJ, He YD, van't Veer LJ, et al A gene expression signature as a predictor of survival in breast cancer. N Engl J Med. 2002;347(25):1999–2009
61. Buyse M, Loi S, van't Veer L, et al Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. J Natl Cancer Inst. 2006;98(17): 1183–92
62. Paik S, Shak S, Tang G et al (2004) A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. 351(27):2817–26
63. Paik S, Tang G, Shak S et al (2006) Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 24(23): 3726–34
64. Perou CM, Sorlie T, Eisen MB et al (2000) Molecular portraits of human breast tumours. Nature. 406(6797):747–52
65. Sotiriou C, Neo SY, McShane LM et al (2003) Breast cancer classification and prognosis based on gene expression profiles from a population-based study. Proc Natl Acad Sci USA. 100(18):10393–8
66. Andre F, Pusztai L (2006) Molecular classification of breast cancer: implications for selection of adjuvant chemotherapy. Nat Clin Pract Oncol. 3(11):621–32
67. Cheang MC, Voduc D, Bajdik C et al (2008) Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. Clin Cancer Res. 14(5):1368–76
68. Rakha EA, Reis-Filho JS, Ellis IO (2008) Basal-like breast cancer: a critical review. J Clin Oncol. 26(15):2568–81

Lobular Carcinoma in Situ

11

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Abbreviations

ADH	Atypical ductal hyperplasia
ALH	Atypical lobular hyperplasia
CGH	Comparative genomic hybridisation
CNB	Core-needle biopsy
DCIS	Ductal carcinoma in situ
ER	Oestrogen receptor
FGFR1	Fibroblast growth factor receptor 1
IDC	Invasive ductal carcinoma
ILC	Invasive lobular carcinoma
LCIS	Lobular carcinoma in situ
LN	Lobular neoplasia
LIN	Lobular intraepithelial neoplasia
LOH	Loss of heterozygosity
MRI	Magnetic resonance imaging
PLCIS	Pleomorphic lobular carcinoma in situ
PLC	Pleomorphic lobular carcinoma
PgR	Progesterone receptor

11.1 Introduction

The reduced mortality from breast cancer seen in recent years is probably related to an accumulation of factors, including the use of aggressive multi-disciplinary treatment regimes, advances in our understanding of the cell biology of breast tumours and hence the development of targeted therapies, knowledge of the associated risk factors for developing invasive disease, and of course the introduction of the mammographic screening programme. The breast screening programmes however have also contributed to the increasing incidence of benign and pre-invasive lesions identified in needle biopsies, and hence has raised issues regarding the significance and management of such lesions (e.g. columnar cell lesions, usual and atypical hyperplasias and in situ carcinomas).

This chapter is dedicated to the fascinating morphological entity that is lobular carcinoma in situ (LCIS). LCIS is the pre-invasive counterpart of invasive lobular carcinoma (ILC), which is the most commonly diagnosed "special" type of invasive carcinoma, comprising 5–15% of all breast cancer cases [1, 2]. The management of patients diagnosed with LCIS is difficult because of the conflicting ideas in the literature regarding the biological and clinical significance of this lesion. Some of the important issues with LCIS relate to the most appropriate nomenclature, the lack of specific mammographic abnormalities, its role as a risk indicator or as a non-obligate precursor for the development of invasive carcinoma and, with this in mind, the best clinical approach for the management of patients diagnosed with LCIS in core-needle biopsy (CNB). Herein we review our evolving understanding of this entity.

11.2 Historical Perspective

LCIS has been extensively characterised since its first description as an "atypical proliferation of acinar cells" by Ewing, back in 1919 [3]. The first clear clinical–pathological description using the term *LCIS* was by Foote and Stewart in 1941 [4]. Foote and Stewart used this name in order to describe the morphologic

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases*,
DOI: 10.1007/978-3-540-69743-5_11, © Springer-Verlag Berlin Heidelberg 2010

similarities between the cells of LCIS and those of an otherwise overt ILC, an entity that had already been described. They derived equivalences from ductal carcinoma in situ (DCIS) in a way that foci of neoplastic cells were surrounded and contained within a basement membrane in both entities. Foote and Stewart inferred that LCIS, in a way analogous to DCIS, could be an established precursor step towards the development of invasive cancer given that they also observed LCIS occurring side by side with ILC. Thus, they suggested mastectomy as the standard form of treatment, a management plan that was accepted by several clinical groups for many years [4]. In 1967, McDivitt et al. reported on the long-term clinical outcome of 50 patients diagnosed with LCIS and demonstrated that such patients were indeed at an increased risk for developing invasive carcinoma. Importantly this risk affected both breast and was cumulative, in that the risk of future breast cancer in the ipsilateral breast rose from 15% at 10 years to 35% at 20 years and the risk in the contraleral breast rose from 15% at 10 years to 25% at 20 years [5]. The bilateral and cumulative risk of subsequent carcinoma following LCIS was supported by other studies with long-term clinical follow up data [6, 7–9], but the recommendations for the management of patients varied as the role of LCIS being a risk indicator or actual precursor lesion became a matter for debate. Several studies have established that this risk of developing invasive cancer does not equal that conferred by a diagnosis of DCIS and that LCIS is not an obligate precursor of invasive cancer in the same way as is high-grade DCIS of comedo type [10, 11]. As a consequence, radical surgical treatment such as mastectomy and wide local excision fell out of favour with the adoption of clinical management options involving close clinical follow-up with regular mammography, chemoprevention with tamoxifen, follow-up only, or simply "no action" [6, 9, 12–17].

More recently, several lines of evidence now suggest that LCIS is indeed a non-obligate precursor as well as a risk indicator for the development of invasive carcinoma [18]. The data are discussed in more detail below, but for example, epidemiological data suggest LCIS is more likely to be associated with a concurrent or subsequent diagnosis of ILC than invasive ductal carcinoma (IDC) [19, 20]. Li et al. [20] analysed 37,692 DCIS and 4490 LCIS patients and found that LCIS patients were 5.3-fold more likely than DCIS patients to develop ILC. Molecular genetic analysis has demonstrated that LCIS and ILC harbour the same genetic alterations [18, 21–28]. These data have been as precise as LCIS harbouring the same gene mutation in E-cadherin [28] or the same mitochondrial DNA sequence variations [21, 24] to that found in concurrent or subsequent ILC. Such data strongly implicate a clonal evolution from LCIS to ILC and hence LCIS being a non-obligate precursor lesion in the development of ILC. This idea is again changing the face of LCIS from a biological and clinical management point of view.

11.3 Epidemiology of LCIS

The majority of breast carcinomas fall into the category of IDC, no special type. These comprise approximately 70–80% of all breast cancers. Not surprisingly, the rest are classified as "special type" and a few examples include lobular, tubular and mucinous carcinomas [29]. LCIS is a rare lesion, found less frequently than DCIS [30]. The actual incidence of LCIS in the general population has proved difficult to estimate since LCIS has few specific clinical or radiological abnormalities: LCIS is not a palpable lesion and tends not to be associated with microcalcifications [31–33], although mammorgraphic density has been associated with a higher risk of LCIS [31]. Furthermore, when examining a surgical specimen, there are no definitive macroscopic features of LCIS to guide the pathologist when sampling surgical tissue specimens. The diagnosis of LCIS is therefore generally made as an incidental, microscopic finding in breast biopsy carried out for other reasons and thus the early and preventive diagnosis of LCIS poses a challenge for oncologists. Owing to this clinical scenario, the real incidence of LCIS in the general population is unknown, and many asymptomatic women presumably will remain undiagnosed.

LCIS is an uncommon finding in autopsy series [34–36] and the incidence of LCIS in otherwise benign breast biopsy is between 0.5 and 4.3% [6–9, 37–40]. In a compilation of data of more than 10,000 cases from 19 series of breast biopsy performed for non-palpable but mammographically detected abnormalities, LCIS was found in 1.1% of all biopsies and 5.7% of all breast malignancies [30]. The incidence of LCIS has risen by 300% between the years 1978 and 1998 [38, 41]. This may be largely due to the increased use

of mammographic screening and as a consequence the increased frequency of finding LCIS associated with other abnormalities, since, as mentioned above LCIS is not typically associated with mammographic abnormalities. The findings may be more complicated than this with age-related changes in the frequency of LCIS and associations with the use of combined oestrogen and progestin hormone therapy [38, 41, 42]. The use of hormone replacement therapy was shown to correlate with an increased risk of developing breast cancer with a lobular phenotype [42, 43].

Women diagnosed with LCIS are usually between 40 and 50 years old, with less than 10% of patients with LCIS being post-menopausal [7, 9, 30, 31, 37, 44]. This is a decade earlier than the age of those diagnosed with DCIS and almost 2 decades of those with ILC, which is a post-menopausal disease with mean age of presentation around 60 years [45, 46]. This may reflect a reportedly slow timeframe for LCIS to develop into invasive disease [7, 8, 47].

11.4 Natural History of LCIS

LCIS is a risk factor and a precursor for cancer progression but it is associated with low mortality rates. Women diagnosed with LCIS are at risk of developing subsequent invasive carcinoma that ranges up to 12 times higher than the risk of the general population [30]. It has been demonstrated that the rate of development of invasive carcinoma is about 1–2% per year, with a lifetime risk of 30–40% following a diagnosis of LCIS [6, 48]. It is difficult to predict which patients diagnosed with LCIS will go on to develop invasive disease and which will remain benign. The ability to do so would be invaluable information to have at diagnosis. Some data suggest that the extent of disease and size of nuclei might be predictive for the subsequent development of breast cancer [7, 49–52]. Page et al. [39] highlighted the importance of classifying atypical lobular hyperplasia (ALH) and LCIS separately since the relative risk for subsequently developing breast cancer was different in women diagnosed with ALH compared with LCIS. Patients diagnosed with ALH have a four to fivefold higher risk than the general population (women of a comparable age who have had a breast biopsy performed for no atypical proliferative disease). This relative risk is doubled to 8–10 times for LCIS.

LCIS is characteristically multi-focal and bilateral and the risk of subsequent malignancy can affect both breasts [6–8, 31, 53–55]. This makes for difficult management strategies in patients with this disease and was a reason for advocating bilateral mastectomy or mastectomy with contralateral biopsy. However the indolent nature of LCIS suggests such aggressive surgical treatment is not necessary in most cases. Around 50% of patients diagnosed with LCIS show multiple foci in the ipsilateral breast, with Beute and colleagues observing as many as 70% of cases having multi-focal disease [31]. In addition, approximately 30% of patients have further LCIS in the contralateral breast [6–8, 46, 56–58]. Haagensen et al. [59] analysed 267 cases where lobular neoplasia (LN) coexisted with one of the usual forms of breast carcinoma and determined that the subsequent development of contralateral breast cancer was 3 times more likely in patients diagnosed with LCIS than in those without LCIS. Others have also shown that the development of a contralateral breast tumour is more common in patients diagnosed with LCIS than those patients without LCIS [60–62]. Ringberg et al. studied a series of women who underwent bilateral mastectomy for clinical and mammographically unilateral invasive disease or for unilateral in situ disease. In both sets of patients the frequency of LCIS in the contraleral breast was significantly higher than for DCIS or invasive carcinoma and the frequency of bilateral LCIS (60%) was higher than for bilateral DCIS (19%) [63]. Interestingly, multi-focal LCIS or DCIS was seen in the clinically and mammographically normal contralateral breast in approximately 20 and 30% of patients respectively [63].

The risk for subsequent development of breast cancer is thus considered to be bilateral [58]. Some data suggested that the risk was equal for both breasts [9, 37, 53] whereas other studies indicate that the breast in which the index LCIS was diagnosed is more at risk than the contralateral breast [8, 20, 39, 40, 51, 52, 64]. Andersen et al. identified LCIS in 52/3299 benign breast cases, and over the follow-up period 11 patients developed invasive breast cancer, being nine ipsilateral and four contralateral tumours. This was considered 12 times the frequency expected and the risk for breast cancer assumed as bilateral [37]. As part of the Nashville Breast Studies, Page et al. analysed a cohort of 252 patients who underwent benign surgical biopsies and a diagnosis of ALH between 1950 and 1985 [39, 40]. They determined that the development of invasive carcinoma after ALH was about 3 times more likely to arise in the ipsilateral compared to

the contralateral breast. On the otherhand, Chuba et al. [53] analysed the follow up data from a large series of LCIS of the Surveillance, Epidemiology and End Results (SEER) database and found no difference in the frequency of secondary breast tumour development between the ipsilateral or contralateral breast.

There is typically an extended time frame required for the development of invasive carcinoma and this has significant implications for the long-term management of patients. Page et al. [7] demonstrated that the majority of women who developed invasive cancer did so within 15 years of LCIS diagnosis. In a separate study, Rosen et al. demonstrated that for those patients who subsequently developed breast cancer, half did so between 15 and 30 years after biopsy, with an average interval of 20.4 years [8].

The type of invasive carcinoma that arises following a diagnosis of LCIS may be either a lobular or a ductal carcinoma [6–8, 53]. This has raised the question as to whether LCIS is actually a risk indicator for the development of breast cancer rather than a true precursor lesion. The co-existence of LCIS with DCIS is likely to explain the development of IDC with the DCIS being the precursor lesion for the ductal carcinoma [65, 66]. There is also considerable evidence to suggest that LCIS is indeed a non-obligate precursor lesion for ILC. For example, the incidence of ILC occurring with LCIS is significantly greater than that without LCIS [7, 9, 17, 19, 67]. LCIS was identified in 91% of ILC cases in one study [19]. Page et al. reported that 70% of invasive carcinomas were lobular type following the original diagnosis of LCIS [7]. In addition, Fisher et al. reported, in their observations of the National Surgical Adjuvant Breast Project (NASBP), that following surgical excision for LCIS, 14 and 8% of patients had ipsilateral or contraletral breast tumour recurrence, respectively. Of the recurrences that were invasive carcinomas, 90% of ipsilateral and 75% of contraletral recurrences were of lobular type [50]. Also of note was their observation that the invasive recurrence in the ipsilateral breast was more commonly at the same site as the index LCIS lesion, which contributes to the theory that LCIS is a precursor lesion [50].

In addition to the epidemiological data described above, the morphologic similarity between cells of LCIS and ILC and an increasing amount of molecular evidence (see below) supports the role of LCIS as a direct non-obligate precursor lesion for ILC [18, 21, 23–25, 27, 28, 68–71].

11.5 Histopathological Characteristics of LCIS

The term *LCIS* incorporates a spectrum of disease and so Page introduced the term *atypical lobular hyperplasia* (ALH) [39] to describe a less well-developed form of the same disease (Fig. 11.1). There is some justification for this stratification into ALH and LCIS since the risk of developing invasive carcinoma following a diagnosis of ALH or LCIS was shown to differ (relative risk of four to fivefold for ALH and eight to tenfold for LCIS) [39]. However, the distinction between ALH and LCIS can be subjective and open to intra- and inter-observer variability. The umbrella terminology of LN was proposed by Haagensen et al. in 1978 [6] to cover the morphological spectrum of proliferations encompassing both ALH and LCIS, thereby removing this subjectivity but also removing the term *carcinoma* from the diagnosis of a lesion that did not warrant the same management as DCIS (surgery, clear margins, etc.). LN is preferred by some, particularly in situations like core-needle biopsies where little tissue is available and so making a distinction between ALH and LCIS is a difficult prospect [72]. More recently, the lobular intra-epithelial neoplasia (LIN) classification system was also introduced [73], which is a three-tiered classification covering the spectrum of disease (ALH, LCIS and PLCIS (see below)). There is a divided opinion in clinical practise as to the most appropriate classification scheme.

LCIS and ALH have striking histological features [27] (Fig. 11.1). Classical LCIS is the most common subtype among several morphological variants and is comprised of a monotonous population of small neoplastic cells that are round, polygonal or cuboidal in shape. The nuclei are uniform and the chromatin is fine and evenly dispersed. These cells fill the breast acini that become largely distended. The cells have a high nuclear/cytoplasm ratio and scant cytoplasm. Another finding is the presence of cells containing clear vacuoles, known as intra-cytoplasmic lumina. Glandular formation, mitoses, calcification, and necrosis are uncommon features. The cells within the acini are loosely cohesive and regularly spaced. Pagetoid spread (Fig. 11.2), characterised by neoplastic cells spreading along adjacent ducts underneath intact overlying epithelium, is a common finding. In such occasions, the lobular architecture is maintained. In addition to these cytological features of classic LCIS,

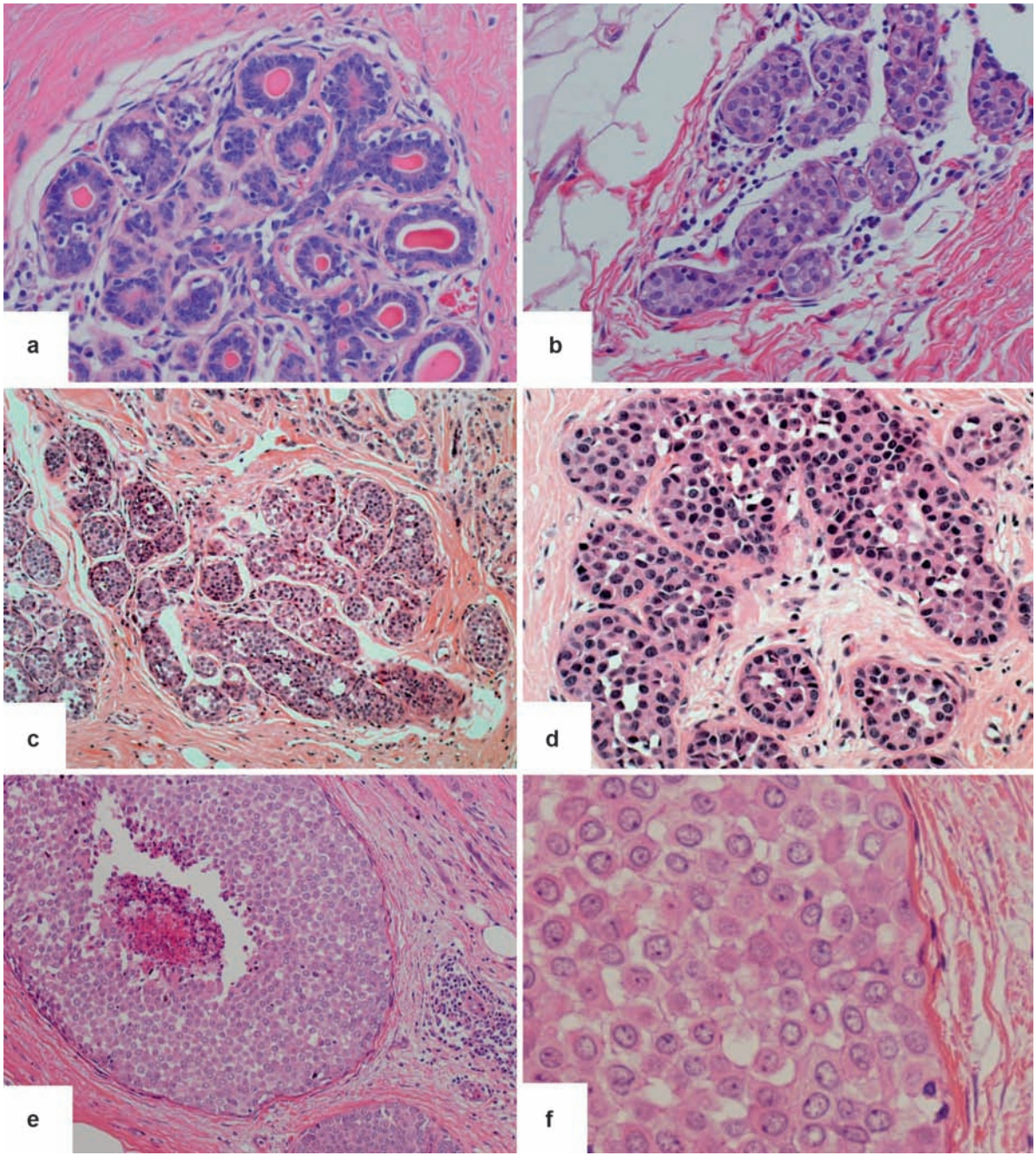

Fig. 11.1 (**a**) Normal terminal duct-lobular unit with a double epithelial-myoepithelial cell layer and open lumen with eosinophilic secretion; (**b**) lobular unit distended by atypical lobular hyperplasia; (**c**) low power view of lobular unit distended by lobular carcinoma in situ (LCIS); (**d**) high power view of LCIS showing the monomorphic population of cells, discohesion and low-grade nuclei; (**e**) pleomorphic lobular carcinoma in situ (PLCIS) with central necrosis; (**f**) high power view of PLCIS showing vesicular nuclei, prominent nucleoli, apocrine cytoplasm and discohesive cells

which account for a group of cells which can also be referred to as type A cells, there is also a subtype of classical LCIS with similar architecture but containing type B cells which have mild to moderately large and clear nuclei, some increase in pleomorphism, and more abundant cytoplasm [74].

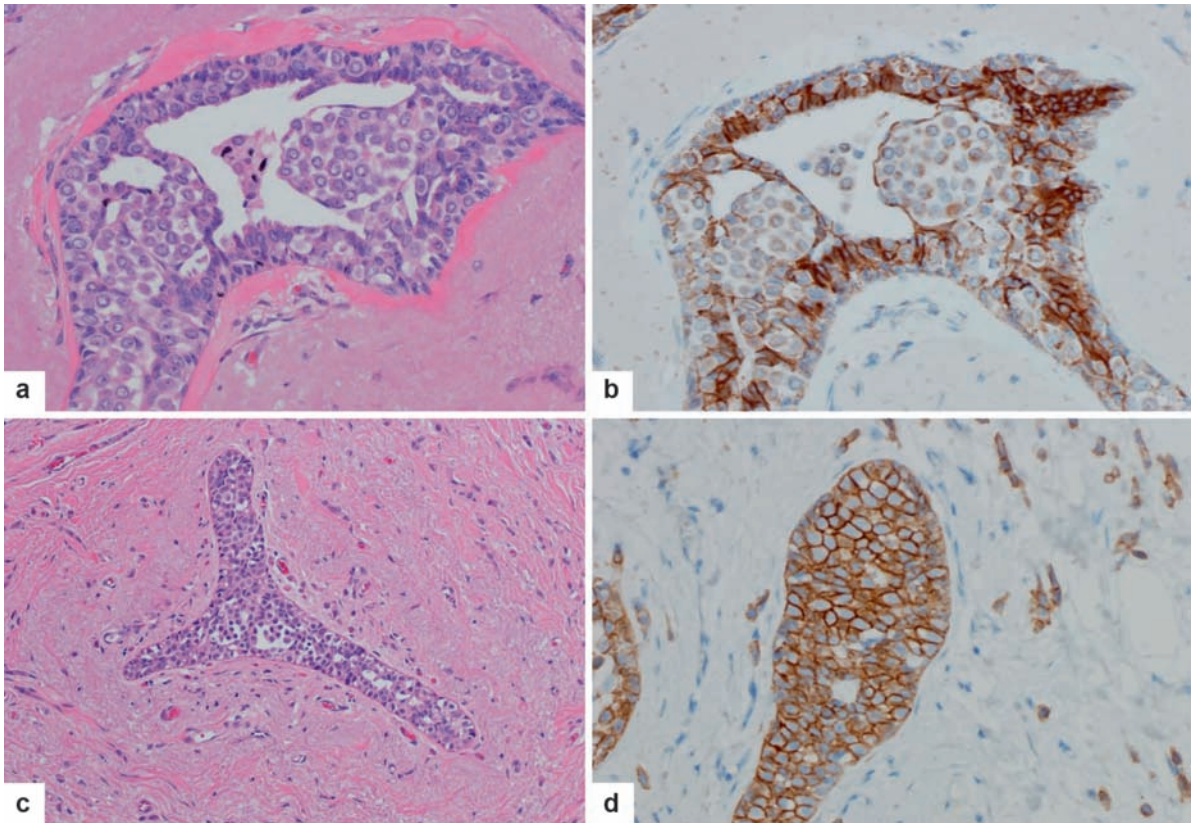

Fig. 11.2 (**a**) Pagetoid distribution of LCIS in large duct. LCIS cells are seen beneath the luminal epithelium of the duct which is displaced; (**b**) E-cadherin immunohistochemistry staining of the same duct as in *a*, showing Pagetoid distribution of LCIS cells filling the lumen. Neoplastic cells are uniformly negative for E-cadherin whereas the remaining luminal and myoepithelial cells show strong E-cadherin expression; (**c**) LCIS in large duct; (**d**) E-cadherin immunohistochemistry staining of the same duct as in *c*. In this instance the neoplastic cells of both LCIS and the invasive lobular carcinoma (ILC), which surrounds the LCIS lesion, are positive for E-cadherin expression. This finding highlights the difficulty with using immunohistochemistry to aid diagnosis and the possibility of misdiagnosing the lesion as a ductal carcinoma in situ (DCIS). This can lead, in some instances, to mismanagement of patients

According to Page et al. [75] a diagnosis of LCIS can be rendered when more than half the acini in an involved lobular unit is filled and distended by the characteristic cells, leaving no central lumina. In practical terms, it means a distention of the acini, which can be translated as eight or more cells present in the transversal diameter of an acinus. ALH on the other hand represents a lesion composed of the same cytological features as described above, yet where cells only partly fill the acini, with only minimal or no distention of the lobule. Lumina and myoepithelial cells can still be identified, and the number of acini compromised is less than half according to the criteria of Page. Myoepithelial cells can be seen within the neoplastic population. Therefore the distinction between ALH and LCIS is based on the extent of disease.

Recently a high-grade variant of LCIS was described and termed *pleomorphic lobular carcinoma in situ* (PLCIS) (Fig. 11.1) [76]. The neoplastic cells of PLCIS show marked pleomorphic and large nuclei, which is pushed to one side of the plasma membrane. Nucleoli are prominent and cytoplasm is eosinophilic. In addition, signet ring cells can be identified [77]. There is cellular discohesion, as described in classic LCIS; however, central necrosis and calcification are features much more commonly associated with PLCIS when compared to the classical type. Sneige et al. have described PLCIS nuclei as being typically 4 times larger than the size of a lymphocyte whereas nuclei of type A cells are 1–1.5 times larger and nuclei of type B cells are up to twice the size of a lymphocyte. Apocrine differentiation at the morphologic and immunohistochemical levels is a

common finding in the pleomorphic variant in contrast to the classic variant. The presence of higher-grade cellular features, necrosis, and calcification can make the distinction from DCIS difficult emphasising the importance of recognising this lesion. PLCIS is frequently associated with the cytologicaly similar invasive pleomorphic lobular carcinoma (PLC) [75, 78, 79].

11.6 Differential Diagnoses of LCIS

Although the histological features of ILC and LCIS are well described, there are situations where the differentiation between a lobular carcinoma and a ductal carcinoma is challenging. One of the most important, and also the most difficult differential diagnosis of classic LCIS is with DCIS, in particular DCIS of the solid, low nuclear grade type, also referred as intermediate type due to the overlapping features between ductal and lobular lesions [65, 80–82]. Similarly, differentiating PLCIS from moderate-high-grade DCIS may prove difficult. The exercise of distinguishing LCIS from low-grade solid DCIS can be difficult since morphologically they may be remarkably similar, in particular when DCIS involves the acini (termed *cancerisation of lobules*) with minimal or no lobular distortion. Morphological clues are nuclear size and pleomorphism, which may be greater in DCIS (although this is less useful when dealing with PLCIS), and the presence of secondary lumen formation and cellular cohesion that also point to a ductal lesion rather than LCIS. A diagnosis of DCIS can render completely different management implications for a patient. For instance, patients diagnosed with LCIS can be managed by chemoprevention with tamoxifen, clinical follow up with mammography, offered clinical follow-up alone or simply no action [6, 9, 12, 17, 83, 84]. The treatment of DCIS aims to eradicate the lesion from the breast with wide local excision, excision and radiation therapy, or mastectomy and, in addition, assessment of margin status is clinically important, warranting further re-excision in DCIS but not LCIS [85–87]. The literature on the use of radiotherapy for LCIS is limited and currently, there is little data to recommend its role in clinical management. Precise diagnosis is therefore essential.

Furthermore, LCIS can often be found to coexist with low-grade solid DCIS or PLCIS within the same duct–lobular unit. On such occasions, one should make both diagnoses and the patient should be managed as for DCIS. Other situations of potential difficulty with diagnosing LCIS include a small set of alterations like foci of lactational change with intra-cytoplasmic lipid droplets, or clear cell change. These can bear a resemblance to ALH/LCIS if not recognised. One should also be aware about the possibility of colonisation of sclerosing adenosis and radial scar by cells of LCIS. The quality of the preservation of the tissue is another issue that should be taken into account when analysing a breast biopsy or surgical specimen of such examples. When the pathologist faces a situation like this it becomes imperative to utilise ancillary techniques like immunohistochemistry to demonstrate the myoepithelial cell layer or basement membrane in order to make the distinction.

11.7 Molecular Pathology of LCIS

Recent years have seen the emergence of a wealth of biomarkers of disease pathogenesis and the application of innovative and sophisticated techniques for molecular genetic analyses of breast cancer. This has generated vast amounts of new data on the molecular features of small pre-invasive lesions and invasive carcinomas of the breast and has contributed to our current understanding of the pathways involved in the evolution of disease [98], as well as providing biomarkers (ER, PgR, Her2, E-cadherin, EGFR) that form a crucial part of diagnostic practise and therapeutic options. Molecular analyses of ALH and LCIS has helped clarify some of the important issues regarding these lesions, in particular whether ALH and LCIS are simply risk indicators or non-obligate precursors for the development of invasive cancer. These studies have also identified some of the earliest genetic alterations that define the lobular phenotype. Continued molecular pathological analyses will further tease out precise mechanisms and molecules that have roles in the pathogenesis of specific breast cancer types. For example, lobular and low-grade ductal proliferations show remarkably similar immunohistochemical and molecular features yet they differ with respect to clinical presentation (LCIS being more frequently multi-focal and bilateral), the risk of progression to invasive carcinoma and the metastatic propensity to certain sites [88–90]. The molecular basis for these features is currently unclear.

11.7.1 Immunophenotype of LCIS

Table 11.1 highlights the expression pattern of a series of diagnostic and molecular markers in LCIS and other pre-invasive lesions. The majority (over 90%) of LCIS exhibit high levels of expression of the hormone receptors, oestrogen (ER) and progesterone (PgR) receptor in nearly all (>70%) neoplastic cells. It has recently been shown that ER-alpha and ER-beta are both overexpressed in LCIS [91]. Most LCIS are negative for classic biomarkers of aggressiveness: HER2 overexpression and gene amplification, and p53 and show a low Ki67 (proliferation) index [27, 91–98]. This immunohistochemical profile does not vary markedly as to whether the LCIS is associated with invasive carcinoma or not [94]. This is also consistent with the immunophenotype of the invasive counterpart, ILC and closely overlaps with that seen in atypical ductal hyperplasia (ADH) and low-grade DCIS/IDC and is at variance to that seen in high-grade DCIS/IDC. Despite their high grade, PLCIS/PLC are also likely to be ER positive; however they also harbour an immunohistochemical profile to match their more aggressive phenotype, including overexpression and gene amplification of HER2, occasional positivity for p53 and a higher proliferative (Ki67) index [71, 76, 93, 99]. The pleomorphic variants, PLCIS and PLC, also express GCDFP-15 (gross cystic disease fluid protein-15), correlating with the high frequency with which these lesions show apocrine differentiation [76, 78].

11.7.2 Role of E-Cadherin in LCIS

The neoplastic cells of all types of lobular proliferation (in situ and invasive lesions of both classic and pleomorphic types) characteristically lack the expression of E-cadherin in the vast majority of cases (Fig. 11.2) whereas normal breast epithelial cells and the majority of "ductal" lesions (ADH, DCIS and most invasive ductal carcinomas (IDCs) have been shown to exhibit positive staining by immunohistochemistry [25, 28, 71, 76, 80, 82, 99–111]. E-cadherin is a transmembrane protein with a crucial role in calcium-dependent cell–cell adhesion and cell cycle regulation through the β-catenin/Wnt pathway. The loss or down regulation of this molecule has been implicated in the characteristic discohesive nature of lobular neoplastic cells, the single cell/single file infiltrative growth pattern and possibly also the peculiar metastatic progression of ILC to unusual distant sites [88–90].

E-cadherin inactivation or down regulation occurs via a combination of genetic, epigenetic and transcriptional mechanisms. Loss of chromosome 16q is a frequent event in lobular carcinomas, as detected by comparative genomic hybridisation (CGH) or loss of heterozygosity (LOH) analysis specifically around the locus (16q22.1) of the E-cadherin gene (CDH1) (see below). This is usually accompanied by truncating mutations or gene promoter methylation leading to biallelic inactivation of the gene and negative staining by immunohistochemistry [22, 23, 25, 28, 69, 70, 102, 103, 110–114]. The down-regulation

Table 11.1 Comparison of immunohistochemical marker expression between LCIS and other preinvasive lesions

	ALH	LCIS	Pleomorphic LCIS	DCIS (low grade)	DCIS (high grade)
ER	+	+	+/−	+	−/+
PgR	+	+	+/−	+	−/+
HER2	−	−	−/+	−	+/−
p53	−/+	−/+	+/−	−/+	+/−
Ki-67	Low	Low	Mod-High	Low	High
E-cadherin	−	−	−	+(memb)	+(memb)
β-catenin	−	−	−	+(memb)	+(memb)
p120(ctn)	−(cyto)	−(cyto)	−(cyto))	+(memb)	+(memb)
GCDFP-15	−/+	−/+	+/−	−/+	−/+

ER oestrogen receptor; *PgR* progesterone receptor; *GCDFP*-15 gross cystic disease fluid protein-15; −/+ lesions are typically negative although some can be positive; +/− lesions are typically positive although some can be negative; *memb* membranous; *cyto* cytoplasmic; *Mod* moderate

of E-cadherin in ILC was recently demonstrated to occur via activation and expression of the E-cadherin transcriptional repressors SLUG, SNAIL and ZEB1 [115, 116]. Gene mutation analysis consistently identified protein-truncating mutations in ILCs but failed to find any pathogenic mutation in low- and high-grade IDCs of NST or medullary carcinomas [110, 112, 113] though a report of 83 IDC found mutations in four cases [117]. E-cadherin mutations have also been identified in PLC [108] supporting the close association of these tumour types. In addition, Vos et al. [28] have demonstrated the same truncating mutation in the E-cadherin gene in LCIS and the adjacent ILC. This important data provides strong evidence for the role of E-cadherin gene inactivation early in the pathogenesis of lobular lesions and supports the hypothesis for a precursor role for LCIS in the development of ILC. Evidence for E-cadherin inactivation being directly related to the lobular phenotype arose from the development of a mouse tumour model based on conditional E-cadherin mutations and epithelial-specific knockout of p53. Mammary tumours and metastases developed that had a strong morphological resemblance to human lobular carcinoma [118]. However, the tumours lacked expression of ER and PR, were positive for basal keratins and required *Trp53* gene mutations for initiation, which are features not typically associated with LCIS and ILC.

Despite E-cadherin down regulation occurring as early as ALH, mutational analysis of pure (no evidence of associated invasive carcinoma) ALH and LCIS demonstrated that CDH1 mutations were frequent in LCIS but rare in ALH [106]. The authors speculated, therefore, that the inactivating mutations of E-cadherin are not responsible for the down regulation of the protein seen in ALH and that mutation occurs post "loss" of expression. It is unclear whether this scenario is peculiar to pure ALH or also occurs in ALH associated with invasive carcinoma or whether there are technical reasons for this finding owing to the very small nature of ALH. Further analyses are required to confirm this hypothesis.

11.7.3 E-Cadherin Immunohistochemistry as a Diagnostic Tool

As the management of patients differ with regards to DCIS or LCIS at the margins, correct classification is important and so the use of auxillary techniques may help in this regard. Immunohistochemical analyses have shown that E-cadherin expression is down regulated in >80% of lobular proliferations (in situ, invasive and pleomorphic types) (Fig. 11.2) but is strongly expressed in normal luminal epithelial cells and the majority of ductal proliferations (ADH, DCIS and IDC) [25, 27, 71, 98, 99, 102–104, 109, 110, 112–114, 119]. As such some authors have advocated the use of E-cadherin as an adjunct antibody to differentiate lobular and ductal lesions [80–82, 100, 105, 120], this may be particularly useful in challenging situations such as solid in situ proliferations with indeterminate features, where, as the authors suggested the following: (1) lesions positive for E-cadherin should be classified as DCIS, (2) cases that are negative for E-cadherin should be classified as LCIS and (3) cases of in situ carcinoma with indeterminate features where E-cadherin also shows a mixed positive and negative expression pattern should be classified as a mixed lesion [80]. Interestingly, Goldstein et al. found that patients with LCIS showing patchy immunoreactivity were more likely to develop a subsequent ipsilateral carcinoma of ductal type compared to those patients with an E-cadherin negative LCIS [14, 121].

There are some issues with the practise of using auxillary techniques such as E-cadherin immunohistochemistry to aid diagnosis if it is applied in the wrong context due to a lack of understanding of the biology behind E-cadherin or lack of detailed inspection of the staining. It is clear that not all lobular carcinomas are negative for E-cadherin (Fig. 11.2) and so misinterpretation of "aberrant" positive staining may lead some pathologists to exclude a diagnosis of lobular carcinoma in favour of a ductal carcinoma, despite the morphology suggesting otherwise. It was recently demonstrated [116] that ILC positive for E-cadherin also had neoplastic cells exhibiting aberrant E-cadherin and β-catenin staining, which appeared as incomplete membrane, golgi or cytoplasmic staining. The presence of E-cadherin gene mutations in some of these tumours suggested that, despite being expressed, E-cadherin is probably dysfunctional. Thus, the immunohistochemical staining should only be used as a guide to help confirm a diagnosis rather than to change a diagnosis made on morphology.

Down-regulation of E-cadherin mediates the loss of expression or aberrant localisation of a series of molecules (β-catenin, α-catenin and p120(ctn)) comprising the cytoplasmic complex of adherens junctions. Like E-cadherin, these molecules show membranous

localisation by immunohistochemistry in normal luminal epithelial cells and in most IDCs. However, in ALH/LCIS, β-catenin and α-catenin typically show complete loss of expression, although aberrant staining in the cytoplasm or golgi has been noted and p120 typically shows displacement to the cytoplasm [25, 71, 101,102,106,111,116,122,123].Immunohistochemical staining for β-catenin and p120 are therefore useful techniques for discriminating between lobular and ductal proliferations, though as described above, not all tumours conform to this "rule".

11.7.4 E-Cadherin as a Predisposition Gene for LCIS?

E-cadherin gene mutations are also important in the pathogenesis of diffuse gastric carcinoma, leading to similar growth features to those seen for ILC. Diffuse gastric cancer has a familial pre-disposition and germline mutations in the E-cadherin gene have been demonstrated in up to one third of the families [124, 125]. The clinical presentation of LCIS (multi-focal and bilateral) and data from epidiemiological studies suggest that LCIS/ILC also has a familial aspect [126–129]. Despite the clear pathogenetic role of E-cadherin mutations in these lesions, germline mutations in E-cadherin are rarely identified in familial LCIS and ILC [130–134]. Several lines of evidence strongly suggest that *BRCA1*, *BRCA2*, *MLH1* and *MSH2* [129, 135, 136] germline mutations are also not significantly involved in the pathogenesis of familial lobular neoplasms. An association has been found between the familial disposition of ILC and the *CHK2* U157T mutation [137]. Other culprit genes for the familial cases of LCIS and ILC remain elusive and the biology behind the multi-focal and bilateral nature of LCIS is currently unknown.

11.7.5 Molecular Genetic Analysis of LCIS

The techniques of laser capture microdissection in combination with DNA sequencing, CGH and LOH have contributed enormously to our understanding of the molecular genetics of breast cancer, including small pre-invasive lesions, such as ALH and LCIS [69, 70, 98].

DNA sequencing of mitochondrial DNA [138] has been applied to assess the clonality of LCIS and both synchronous and metachronous ILC [21, 24]. Common sequence variations were identified between lesions from the same patient. Like E-cadherin gene mutation analysis, this was a highly specific mechanism of demonstrating that some cases of LCIS are clonally related to ILC, thereby confirming the non-obligate precursor nature of this disease.

CGH [70, 139, 140] is a technique that provides an overview of changes in DNA copy number across the whole genome and has been instrumental in defining the multi-step model of breast cancer development [98] and the genomic loci harbouring genes with critical roles in tumour development, for example, the amplification of oncogenes or losses of tumour suppressor genes. The method is restricted to detecting non-reciprocal or unbalanced structural changes in DNA where there is a physical change in copy number of a region of the genome. Structural rearrangements such as balanced translocations and altered ploidy cannot be identified. Test (tumour) and reference (normal genomic) DNA are differentially labelled with green and red fluorescent dyes, mixed in a 1:1 ratio in the presence of human cot-1 DNA (to block repetitive sequences), and co-hybridised to a representation of the human genome. Traditionally this was from metaphase chromosomes prepared from cultured normal lymphocytes, but now, with recent advances in technology, bacterial artificial chromosome (BAC) or oligo microarray-based CGH platforms are available. The higher resolution of the microarray-based technology enables for the identification and fine mapping of small genetic aberrations and high-level amplifications. Specialised capture and analysis softwares convert hybridisation intensity data to a linear red–green ratio profile to determine regions exhibiting significant changes in DNA copy number.

There are only a handful studies that have analysed ALH/LCIS using chromosomal [22, 141, 142] or microarray-based CGH [26, 143, 144] and most highlight the recurrent nature of loss of 16q as an important and early genetic event in the pathogenesis of lobular neoplasms. By chromosomal CGH, the most frequent chromosomal changes in LCIS involve loss of 8p, 16p, 16q, 17p, 17q, and 22q, and gain of 1q and 6q. In all studies, losses were more prevalent than gains [22,

141, 142]. Lu et al. compared the whole genome CGH profiles between ALH and LCIS and found no statistically significant qualitative and quantitative alterations (ALH: range of 0–9, mean of 2.9; LCIS: range of 0–8, mean of 2.9) [142] indicating that ALH and LCIS are closely related lesions at both the morphological and molecular levels. The alterations identified overlap with those seen in low-grade DCIS giving support to close evolutionary development of lobular and low-grade ductal pathways [70, 98].

Array CGH of microdissected synchronous LCIS and ILC demonstrated concordant molecular genetic profiles [26, 144] giving strong support to the common clonality of these lesions and the concept that LCIS is indeed a direct precursor to the development of ILC. Cases of pure ALH and LCIS (not associated with invasive carcinoma) were also studied using aCGH [143]. The surprising finding from this study was that ALH harboured a greater genomic instability to that found in LCIS in the same study or other lobular lesions reported in the literature. This was unexpected for several reasons, for example, the close relatedness of ALH and LCIS (in terms of the frequency in which they co-exist and their overlapping morphological and molecular features), the assumed transition of ALH to LCIS and the hypothesis that as lesions develop and progress they acquire more not fewer genetic alterations. It was proposed that pure ALH may be amenable to significant genetic change, which causes lethality to the neoplastic clone rather than progression to LCIS [143]. This is an interesting concept that might explain why progression of ALH to invasive disease is quite rare [143]. However, again the issue with ALH is the very small nature of the lesion and hence the amount of DNA available for analysis is always going to be limited making analysis and validation of the arising molecular data difficult.

There is clearly heterogeneity in the expression of some biomarkers in ILC/PLC, such as the amplification and overexpression of fibroblast growth factor receptor 1 (FGFR1) and cyclin D1. This variability may go some way to explain the variable clinical nature of these tumours. FGFR1 is a transmembrane receptor tyrosine kinase that undergoes overexpression due the complex amplification of the gene region at 8p11.2 in ~10% of breast tumours [114, 145]. FGFR1 may represent a useful therapeutic target in a manner akin to the targeting of HER2 in invasive breast cancers. Cyclin D1 is a cell cycle check point molecule that is over expressed and amplified in almost 70% and 15% of breast cancers, respectively [146]. The gene for cyclin D1, *CCND1*, is located at 11q13.3 and like FGFR1 is the target for a complex region of DNA amplification. These molecules presumably have a profound influence on driving the proliferative capacity of the neoplastic cells. FGFR1 and cyclin D1 have not been definitively characterised in ALH/LCIS but there is evidence of gene amplification of both these regions in LCIS [26] suggesting they are probably key, early events in the pathogenesis of a proportion of lobular lesions.

PLCIS and PLC exhibit a close molecular genetic association with the LCIS and ILC, as demonstrated by microarray CGH data, with frequent gain of 1q and 16p and loss of 11q and 16q. This work also highlighted that PLCIS is a genetically advanced lesion and a direct precursor to PLC [71, 99]. Genetic alterations were also identified in PLCIS/PLC that overlapped with those detected in high-grade DCIS/IDC (e.g. *HER2* and *MYC* amplification) [71, 76, 93, 99] and it is these alterations that probably account for the high grade and aggressive nature of pleomorphic lobular variant [78, 79].

LOH assesses allelic imbalance at specific candidate tumour suppressor gene loci in tumour cells relative to matched normal tissue. LOH data in LCIS are limited but do demonstrate a similarity between LCIS and ILC, with a frequent finding being losses on 16q around the CDH1 gene locus [23, 25, 68, 94, 106]. Clearly the loss of 16q is an important and an early genetic alteration in the pathogenesis of lobular and low-grade ductal neoplasia. As described above this contributes to the loss of E-cadherin, but it is unclear whether the loss of other tumour suppressor genes located in this genomic region also contributes to the lobular phenotype. The genes from this region involved in the development of low-grade IDCs are also unknown and much work has been attempted to address this [147–150]. A recent development has demonstrated that the expression of two genes located closely to E-cadherin (CDH1) on 16q, Dipeptidase 1 (DPEP1) and CCCTC-binding factor (CTCF), are down-regulated in LCIS relative to normal cells [151]. Both molecules are candidate tumour suppressor genes from other studies [148, 152–154] though it is unclear whether these play a functional role in LCIS development.

11.8 Detection and Clinical Managemenet of LCIS

11.8.1 Radiology

The radiological assessment of LCIS is considered a difficult task. Mammography analysis is generally of restricted importance and value in such a role. Even fully developed ILCs may pose challenging scenarios for most radiologists due to its infiltrative pattern of spread as diffuse or single cells and with minimal stromal reaction. Thus, magnetic resonance imaging (MRI) has been considered an alternative imaging technique for evaluating lobular lesions. For example, Weinstein et al. [155] demonstrated that MRI had shown more extensive tumour than conventional imaging and affected the clinical management in 16 (50%) of 32 patients with ILC. However there have been few large studies on this matter. Mann et al. reviewed the literature using meta-analysis and concluded that MRI has a valuable role in the investigation of ILC, providing extra lesion characterisation that cannot be achieved by conventional imaging studies such as mammography and so can be useful in patient management. Noteworthy, the authors established that in 32% of patients, additional ipsilateral lesions were detected and in 7% contralateral lesions are only detected by MRI. As a result, MRI was shown to have the capabilities of altering surgical management [156].

Few studies assessed the importance of MRI in the diagnosis of LCIS. Port et al. [157] studied 378 patients (126 ALH and 252 LCIS) using MRI and concluded that MRI screening generated more biopsies for a large proportion of patients and facilitated detection of cancer in only a small highly selected group of patients that were typically PLCIS, where in general there is higher presence of calcification. Again, this finding stresses the difficulty in assessing LCIS by imaging.

11.8.2 LCIS at Margins

The presence of LCIS at the margins of a surgical specimen is another matter of debate, though most accept it is not necessary to obtain clear margins. Stolier et al. [158] described a cohort of 40 patients undergoing breast-conserving therapy for ILC and investigated the presence of LCIS in the surgical specimen and its relationship to the surgical margins. Within a mean follow-up time of 67 months, there were no local recurrences regardless of the fact that 38% of patients had close or involved margins. These findings lead the authors to conclude that LCIS in the surgical margin does not impact the risk of local recurrence and therefore may not require re-excision for close or involved surgical margins.

11.8.3 Chemoprevention Therapy for LCIS Patients

The multi-focal/bilateral nature of LCIS combined with its low rate of progression to invasive carcinoma lends it to chemopreventative therapy as a source of treatment. Hormonal therapy has been shown to play a role in preventing progression of DCIS into invasive cancer when combined with lumpectomy and radiation therapy [159]. The role of chemoprevention with tamoxifen in reducing the risk of women developing invasive cancer following a diagnosis of LCIS was evaluated using data obtained from the National Surgical Adjuvant Breast and Bowel Project (NASBP) P-1 Prevention Trial [12]. This was a large prospective clinical trial that demonstrated a tamoxifen-related reduction in the incidence of invasive cancer of 49% overall. Specifically related to high-risk patients previously diagnosed with LCIS, the reduction in risk was 56%: 18/411 and 8/415 participants on the placebo vs. tamoxifen arms of the study developed invasive cancer, respectively [12]. Another NASBP chemoprevention trial of high-risk women was initiated on the back of this data, the Study of Tamoxifen and Raloxifene (STAR) trial [160, 161]. Raloxifene was equally as effective as tamoxifen in preventing the development of invasive carcinoma in LCIS patients [162].

11.8.4 Management of Patients Diagnosed with LCIS in Core-Needle Biopsy

CNB is one of the most commonly used techniques for evaluating breast masses and abnormal mammographic

findings. The rate in which LCIS is the sole diagnostic finding in core biopsy is quite rare, ranging from 0.5 to 2.9% of CNB specimens taken for mammographically abnormalities [30, 72, 83, 163–174]. The rate at which classic LCIS or ALH is reported to be associated with calcification in CNB is extremely variable, ranging from 8 to 53% [72, 83, 163, 165, 166, 169, 175]. However, it is important to note that in the majority of these cases the calcification was mostly associated with fibrocystic change, including columnar cell change [72]. Since ALH and LCIS do not commonly present as clinically or radiologically abnormalities, the finding of these lesions in CNB should therefore warrant further radiological–clinical–pathological assessment to determine the possibility of sampling error or the risk of missing co-existing DCIS or invasive cancer.

In recent years, there has been a surge in the number of studies assessing the significance of finding ALH/LCIS in CNB and whether further surgical sampling should be the recommended management for these patients. It is known that a core biopsy diagnosis of ADH correlates with presence of in situ or invasive carcinoma in ~25% cases in the following excised specimens and so surgical excision was recommended following the diagnosis of ADH in CNB [176, 177]. The data in the literature regarding the risk in which pure ALH/LCIS found on CNB is upgraded to DCIS or invasive carcinoma on further surgical excision are quite variable. Some report low rates of upgrading the disease [83, 173, 178]. Both Jacobs et al. and Frykberg et al. [30, 169] have stated that an incidental finding of ALH or LCIS should not warrant a wide local excision of the lesion, in the same way that clear margins are not necessary for LCIS. Middleton et al. also reported that calcifications on its own should not be a criterion for excision. Based on their findings, excisional biopsy of LCIS should be warranted only when it is associated with a synchronous mass lesion [83]. Many studies have found that LCIS was upstaged at subsequent excision to DCIS or invasive carcinoma at a rate similar to or higher than that reported for ADH [72, 83, 163, 166, 168, 170, 171, 174, 179–183]. Many of these studies therefore advocated further excision in these cases because the completely benign cases cannot be reliably predicted, although CNB showing histologic features of extensive classic LCIS or pleomorphic LCIS were shown to have a higher rate of cancer underestimation [180, 184].

The data available regarding PLCIS are rather limited [32, 72, 83, 166, 169, 185]; however, the morphological and molecular features of PLCIS is circumstantial evidence alone to suggest that PLCIS has an aggressive clinical behaviour more akin to high-grade DCIS than classic LCIS. It seems prudent, therefore, to manage all such patients as though they have DCIS with further excision and margin assessment.

Most of these data were obtained from retrospective studies consisting of small numbers of cases and so the subsequent management recommendations are therefore based more on pragmatism than scientific evaluation. To formally define the risk of ALH/LCIS on CNB, there is a need for unbiased prospective series where surgical excision is performed on all cases, although this may be problematic in clinical practise. Elsheikh and Silverman studied a cohort of 33 patients with a diagnosis of ALH and LCIS in CNB, including the prospective analysis of 18 patients managed with further excision that was given in an unselected manner. An important finding from these 18 patients was that an underestimation of cancer was seen in 20% of ALH and 38% of LCIS [180]. Further studies of this nature would be of benefit to support these findings. Nevertheless, there is some degree of consensus in that a multi-disciplinary approach is essential and that further excision should be performed on all cases of ALH/LCIS diagnosed on CNB when [72, 169, 170, 186, 187]:

1. Another lesion, which would itself be an indication for surgical excision, is present on the core biopsy (e.g. ADH or a radial scar).
2. There is discordance between the clinical or radiological findings with pathological assessment.
3. There is an associated mass lesion or an area of architectural distortion.
4. If the LCIS showed mixed histological features with difficulty in distinguishing the lesion from DCIS, or showed a mixed E-cadherin staining pattern or necrosis.
5. The morphology was consistent with that of the pleomorphic variant of LCIS.

11.9 Summary

LCIS is a fascinating lesion that has undergone an interesting and evolving history. Our current understanding of LCIS includes:

- LCIS is an uncommon pathological entity in the general population.
- The current understanding is that LCIS is both a risk indicator and a non-obligate precursor for the development of invasive cancer.
- The risk is cumulative, approaching 1% per year, and is bilateral. Although there are mixed reports as to whether this bilateral risk is equivalent or preferential to the breast in which the index lesion was diagnosed.
- There is considerable data to support LCIS being a non-obligate precusor lesion: overlapping cytological features of LCIS and ILC; high frequency in which LCIS and ILC are associated either concurrently or subsequently; identical molecular genetic alterations found between LCIS and ILC (concurrent or subsequent), including gene mutations in E-cadherin, mitochondrial DNA sequence variations and DNA copy number changes.
- Chemoprevention with tamoxifen or raloxifene is effective at reducing the risk of subsequent invasive carcinoma.
- LCIS rarely exhibits clinical or mammographic abnormalities and so it is often detected in core biopsy as an incidental finding. The presence of pure LCIS on CNB should therefore warrant investigation as to the reason for performing the initial biopsy and the possibility for missing the mass lesion. Pure LCIS in CNB is frequently upgraded to DCIS or invasive carcinoma in subsequent surgical excision suggesting further excision is recommended.
- Pleomorphic LCIS is a variant of classic LCIS with morphological and molecular features similar to the more aggressive high-grade DCIS. Although there is limited data in the literature, PLCIS currently warrants the same management as for DCIS.

Acknowledgements Leonard Da Silva is a recipient of a fellowship from the Ludwig Institute for Cancer Research.

References

1. Arpino G, Bardou VJ, Clark GM, et al Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res. 2004;6:R149–56
2. Martinez V, Azzopardi JG. Invasive lobular carcinoma of the breast: incidence and variants. Histopathology. 1979; 3:467–88
3. Ewing J. Neoplastic diseases. Philadelphia: WB Saunders; 1919
4. Foote FW, Stewart FW. Lobular carcinoma in situ: a rare form of mammary cancer. Am J Pathol. 1941;17:491–6
5. McDivitt RW, Hutter RV, Foote FW Jr, et al In situ lobular carcinoma. A prospective follow-up study indicating cumulative patient risks. JAMA. 1967;201:82–6
6. Haagensen CD, Lane N, Lattes R, et al Lobular neoplasia (so-called lobular carcinoma in situ) of the breast. Cancer. 1978;42:737–69
7. Page DL, Kidd TE Jr, Dupont WD, et al Lobular neoplasia of the breast: higher risk for subsequent invasive cancer predicted by more extensive disease. Hum Pathol. 1991;22: 1232–9
8. Rosen PP, Kosloff C, Lieberman PH, et al Lobular carcinoma in situ of the breast. Detailed analysis of 99 patients with average follow-up of 24 years. Am J Surg Pathol. 1978;2:225–51
9. Wheeler JE, Enterline HT, Roseman JM, et al Lobular carcinoma in situ of the breast. Long-term followup. Cancer. 1974;34:554–63
10. Goldstein NS, Vicini FA, Kestin LL, et al Differences in the pathologic features of ductal carcinoma in situ of the breast based on patient age. Cancer. 2000;88:2553–60
11. Skinner KA, Silverstein MJ. The management of ductal carcinoma in situ of the breast. Endocr Relat Cancer. 2001; 8:33–45
12. Fisher B, Costantino JP, Wickerham DL, et al Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90:1371–88
13. Frykberg ER, Bland KI. In situ breast carcinoma. Adv Surg. 1993;26:29–72
14. Goldstein NS, Kestin LL, Vicini FA. Clinicopathologic implications of E-cadherin reactivity in patients with lobular carcinoma in situ of the breast. Cancer. 2001;92: 738–47
15. Grooff PN, Pamies RJ, Hunyadi S. Lobular carcinoma in situ: what clinicians need to know. Hosp Pract (Off Ed). 1993;28:122, 125, 129–30
16. Haagensen CD. Lobular carcinoma of the breast. A precancerous lesion? Clin Obstet Gynecol. 1962;5:1093–101
17. Wheeler JE, Enterline HT. Lobular carcinoma of the breast in situ and infiltrating. Pathol Annu. 1976;11:161–88
18. Lakhani SR. In-situ lobular neoplasia: time for an awakening. Lancet. 2003;361:96
19. Abdel-Fatah TM, Powe DG, Hodi Z, et al High frequency of coexistence of columnar cell lesions, lobular neoplasia, and low grade ductal carcinoma in situ with invasive tubular carcinoma and invasive lobular carcinoma. Am J Surg Pathol. 2007;31:417–26
20. Li CI, Malone KE, Saltzman BS, et al Risk of invasive breast carcinoma among women diagnosed with ductal carcinoma in situ and lobular carcinoma in situ, 1988–2001. Cancer. 2006;106:2104–12
21. Aulmann S, Penzel R, Longerich T, et al Clonality of lobular carcinoma in situ (LCIS) and metachronous invasive breast cancer. Breast Cancer Res Treat. 2008;107(3):331–5
22. Etzell JE, Devries S, Chew K, et al Loss of chromosome 16q in lobular carcinoma in situ. Hum Pathol. 2001;32:292–6
23. Lakhani SR, Collins N, Sloane JP, et al Loss of heterozygosity in lobular carcinoma in situ of the breast. Clin Mol Pathol. 1995;48:M74–8

24. Morandi L, Marucci G, Foschini MP, et al Genetic similarities and differences between lobular in situ neoplasia (LN) and invasive lobular carcinoma of the breast. Virchows Arch. 2006;449:14–23
25. Sarrio D, Moreno-Bueno G, Hardisson D, et al Epigenetic and genetic alterations of APC and CDH1 genes in lobular breast cancer: relationships with abnormal E-cadherin and catenin expression and microsatellite instability. Int J Cancer. 2003;106:208–15
26. Shelley Hwang E, Nyante SJ, Yi Chen Y, et al Clonality of lobular carcinoma in situ and synchronous invasive lobular carcinoma. Cancer. 2004;100:2562–72
27. Simpson PT, Gale T, Fulford LG, et al The diagnosis and management of pre-invasive breast disease: pathology of atypical lobular hyperplasia and lobular carcinoma in situ. Breast Cancer Res. 2003;5:258–62
28. Vos CB, Cleton-Jansen AM, Berx G, et al E-cadherin inactivation in lobular carcinoma in situ of the breast: an early event in tumorigenesis. Br J Cancer. 1997;76:1131–3
29. Ellis IO, Schnitt SJ, Sastre-Garau X, et al Invasive breast carcinomas. In: Tavassoli FA, Devilee P, editors. Pathology and genetics of tumours of the breast and female genital organs. Lyon: IARC; 2003. p. 13–59
30. Frykberg ER. Lobular carcinoma in situ of the breast. Breast J. 1999;5:296–303
31. Beute BJ, Kalisher L, Hutter RV. Lobular carcinoma in situ of the breast: clinical, pathologic, and mammographic features. AJR Am J Roentgenol. 1991;157:257–65
32. Georgian-Smith D, Lawton TJ. Calcifications of lobular carcinoma in situ of the breast: radiologic-pathologic correlation. AJR Am J Roentgenol. 2001;176:1255–9
33. Sonnenfeld MR, Frenna TH, Weidner N, et al Lobular carcinoma in situ: mammographic-pathologic correlation of results of needle-directed biopsy. Radiology. 1991;181:363–7
34. Alpers CE, Wellings SR. The prevalence of carcinoma in situ in normal and cancer-associated breasts. Hum Pathol. 1985;16:796–807
35. Bartow SA, Pathak DR, Black WC, et al Prevalence of benign, atypical, and malignant breast lesions in populations at different risk for breast cancer. A forensic autopsy study. Cancer. 1987;60:2751–60
36. Nielsen M, Thomsen JL, Primdahl S, et al Breast cancer and atypia among young and middle-aged women: a study of 110 medicolegal autopsies. Br J Cancer. 1987;56:814–9
37. Andersen JA. Lobular carcinoma in situ of the breast. An approach to rational treatment. Cancer. 1977;39:2597–602
38. Li CI, Anderson BO, Daling JR, et al Changing incidence of lobular carcinoma in situ of the breast. Breast Cancer Res Treat. 2002;75:259–68
39. Page DL, Dupont WD, Rogers LW, et al Atypical hyperplastic lesions of the female breast. A long-term follow-up study. Cancer. 1985;55:2698–708
40. Page DL, Schuyler PA, Dupont WD, et al Atypical lobular hyperplasia as a unilateral predictor of breast cancer risk: a retrospective cohort study. Lancet. 2003;361:125–9
41. Li CI, Daling JR, Malone KE. Age-specific incidence rates of in situ breast carcinomas by histologic type, 1980 to 2001. Cancer Epidemiol Biomark Prev. 2005;14:1008–11
42. Li CI, Weiss NS, Stanford JL, et al Hormone replacement therapy in relation to risk of lobular and ductal breast carcinoma in middle-aged women. Cancer. 2000;88:2570–7
43. Li CI, Malone KE, Porter PL, et al Relationship between menopausal hormone therapy and risk of ductal, lobular, and ductal-lobular breast carcinomas. Cancer Epidemiol Biomark Prev. 2008;17:43–50
44. Akashi-Tanaka S, Fukutomi T, Nanasawa T, et al Treatment of noninvasive carcinoma: fifteen-year results at the National Cancer Center Hospital in Tokyo. Breast Cancer. 2000;7:341–4
45. Ringberg A, Andersson I, Aspegren K, et al Breast carcinoma in situ in 167 women–incidence, mode of presentation, therapy and follow-up. Eur J Surg Oncol. 1991;17:466–76
46. Rosen PP, Senie RT, Farr GH, et al Epidemiology of breast carcinoma: Age, menstrual status, and exogenous hormone usage in patients with lobular carcinoma in situ. Surgery. 1979;85:219–24
47. Rosen PP. Lobular carcinoma in situ and intraductal carcinoma of the breast. Monogr Pathol. 1984;(25):59–105
48. Andersen JA. Lobular carcinoma in situ. A long-term follow-up in 52 cases. Acta Pathol Microbiol Scand [A]. 1974;82:519–33
49. Fisher ER, Costantino J, Fisher B, et al Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) Protocol B-17. Five-year observations concerning lobular carcinoma in situ. Cancer. 1996;78:1403–16
50. Fisher ER, Land SR, Fisher B, et al Pathologic findings from the National Surgical Adjuvant Breast and Bowel Project: twelve-year observations concerning lobular carcinoma in situ. Cancer. 2004;100:238–44
51. Ottesen GL, Graversen HP, Blichert-Toft M, et al Carcinoma in situ of the female breast. 10 year follow-up results of a prospective nationwide study. Breast Cancer Res Treat. 2000;62:197–210
52. Ottesen GL, Graversen HP, Blichert-Toft M, et al Lobular carcinoma in situ of the female breast. Short-term results of a prospective nationwide study. The Danish Breast Cancer Cooperative Group. Am J Surg Pathol. 1993;17:14–21
53. Chuba PJ, Hamre MR, Yap J, et al Bilateral risk for subsequent breast cancer after lobular carcinoma-in-situ: analysis of surveillance, epidemiology, and end results data. J Clin Oncol. 2005;23:5534–41
54. Fisher ER, Fisher B. Lobular carcinoma of the breast: an overview. Ann Surg. 1977;185:377–85
55. Salvadori B, Bartoli C, Zurrida S, et al Risk of invasive cancer in women with lobular carcinoma in situ of the breast. Eur J Cancer. 1991;27:35–7
56. Bodian CA, Perzin KH, Lattes R. Lobular neoplasia. Long term risk of breast cancer and relation to other factors. Cancer. 1996;78:1024–34
57. Rosen PP, Braun DW Jr, Lyngholm B, et al Lobular carcinoma in situ of the breast: preliminary results of treatment by ipsilateral mastectomy and contralateral breast biopsy. Cancer. 1981;47:813–9
58. Urban JA. Bilaterality of cancer of the breast. Biopsy of the opposite breast. Cancer. 1967;20:1867–70
59. Haagensen CD, Lane N, Bodian C. Coexisting lobular neoplasia and carcinoma of the breast. Cancer. 1983;51:1468–82
60. Claus EB, Stowe M, Carter D, et al The risk of a contralateral breast cancer among women diagnosed with ductal and lobular breast carcinoma in situ: data from the Connecticut Tumor Registry. Breast. 2003;12:451–6

61. Habel LA, Moe RE, Daling JR, et al Risk of contralateral breast cancer among women with carcinoma in situ of the breast. Ann Surg. 1997;225:69–75
62. Webber BL, Heise H, Neifeld JP, et al Risk of subsequent contralateral breast carcinoma in a population of patients with in-situ breast carcinoma. Cancer. 1981;47:2928–32
63. Ringberg A, Palmer B, Linell F, et al Bilateral and multifocal breast carcinoma. A clinical and autopsy study with special emphasis on carcinoma in situ. Eur J Surg Oncol. 1991;17:20–9
64. Marshall LM, Hunter DJ, Connolly JL, et al Risk of breast cancer associated with atypical hyperplasia of lobular and ductal types. Cancer Epidemiol Biomarkers Prev. 1997;6:297–301
65. Maluf H, Koerner F. Lobular carcinoma in situ and infiltrating ductal carcinoma: frequent presence of DCIS as a precursor lesion. Int J Surg Pathol. 2001;9:127–31
66. Rosen PP. Coexistent lobular carcinoma in situ and intraductal carcinoma in a single lobular-duct unit. Am J Surg Pathol. 1980;4:241–6
67. Sasson AR, Fowble B, Hanlon AL, et al Lobular carcinoma in situ increases the risk of local recurrence in selected patients with stages I and II breast carcinoma treated with conservative surgery and radiation. Cancer. 2001;91:1862–9
68. Nayar R, Zhuang Z, Merino MJ, et al Loss of heterozygosity on chromosome 11q13 in lobular lesions of the breast using tissue microdissection and polymerase chain reaction. Hum Pathol. 1997;28:277–82
69. Reis-Filho JS, Lakhani SR. The diagnosis and management of pre-invasive breast disease: genetic alterations in pre-invasive lesions. Breast Cancer Res. 2003;5:313–9
70. Reis-Filho JS, Simpson PT, Gale T, et al The molecular genetics of breast cancer: the contribution of comparative genomic hybridization. Pathol Res Pract. 2005;201:713–25
71. Reis-Filho JS, Simpson PT, Jones C, et al Pleomorphic lobular carcinoma of the breast: role of comprehensive molecular pathology in characterization of an entity. J Pathol. 2005;207:1–13
72. Menon S, Porter GJ, Evans AJ, et al The significance of lobular neoplasia on needle core biopsy of the breast. Virchows Arch. 2008;452:473–9
73. Bratthauer GL, Tavassoli FA. Lobular intraepithelial neoplasia: previously unexplored aspects assessed in 775 cases and their clinical implications. Virchows Arch. 2002;440:134–8
74. Schnitt SJ, Morrow M. Lobular carcinoma in situ: current concepts and controversies. Semin Diagn Pathol. 1999;16:209–23
75. Page DL, Anderson TJ, Rogers LW. Carcinoma in situ (CIS). In: Page DL, Anderson TJ, editors. Diagnostic histopathology of the breast. New York: Churchill Livingston; 1987. p. 157–92
76. Sneige N, Wang J, Baker BA, et al Clinical, histopathologic, and biologic features of pleomorphic lobular (ductal-lobular) carcinoma in situ of the breast: a report of 24 cases. Mod Pathol. 2002;15:1044–50
77. Fadare O. Pleomorphic lobular carcinoma in situ of the breast composed almost entirely of signet ring cells. Pathol Int. 2006;56:683–7
78. Eusebi V, Magalhaes F, Azzopardi JG. Pleomorphic lobular carcinoma of the breast: an aggressive tumor showing apocrine differentiation. Hum Pathol. 1992;23:655–62
79. Weidner N, Semple JP. Pleomorphic variant of invasive lobular carcinoma of the breast. Hum Pathol. 1992;23:1167–71
80. Jacobs TW, Pliss N, Kouria G, et al Carcinomas in situ of the breast with indeterminate features: role of E-cadherin staining in categorization. Am J Surg Pathol. 2001;25:229–36
81. Maluf HM. Differential diagnosis of solid carcinoma in situ. Semin Diagn Pathol. 2004;21:25–31
82. Maluf HM, Swanson PE, Koerner FC. Solid low-grade in situ carcinoma of the breast: role of associated lesions and E-cadherin in differential diagnosis. Am J Surg Pathol. 2001;25:237–44
83. Middleton LP, Grant S, Stephens T, et al Lobular carcinoma in situ diagnosed by core needle biopsy: when should it be excised? Mod Pathol. 2003;16:120–9
84. Wolmark N, Dunn BK. The role of tamoxifen in breast cancer prevention: issues sparked by the NSABP Breast Cancer Prevention Trial (P-1). Ann N Y Acad Sci. 2001;949:99–108
85. Burstein HJ, Polyak K, Wong JS, et al Ductal carcinoma in situ of the breast. N Engl J Med. 2004;350:1430–41
86. Morrow M, Strom EA, Bassett LW, et al Standard for the management of ductal carcinoma in situ of the breast (DCIS). CA Cancer J Clin. 2002;52:256–76
87. Schwartz GF. The role of radiotherapy in ductal carcinoma in situ of the breast. Breast J. 2000;6:315–6
88. Borst MJ, Ingold JA. Metastatic patterns of invasive lobular versus invasive ductal carcinoma of the breast. Surgery. 1993;114:637–41; discussion 641–2
89. Harris M, Howell A, Chrissohou M, et al A comparison of the metastatic pattern of infiltrating lobular carcinoma and infiltrating duct carcinoma of the breast. Br J Cancer. 1984;50:23–30
90. Lamovec J, Bracko M. Metastatic pattern of infiltrating lobular carcinoma of the breast: an autopsy study. J Surg Oncol. 1991;48:28–33
91. Middleton LP, Perkins GH, Tucker SL, et al Expression of ERalpha and ERbeta in lobular carcinoma in situ. Histopathology. 2007;50:875–80
92. Baqai T, Shousha S. Oestrogen receptor negativity as a marker for high-grade ductal carcinoma in situ of the breast. Histopathology. 2003;42:440–7
93. Middleton LP, Palacios DM, Bryant BR, et al Pleomorphic lobular carcinoma: morphology, immunohistochemistry, and molecular analysis. Am J Surg Pathol. 2000;24:1650–6
94. Mohsin SK, O'Connell P, Allred DC, et al Biomarker profile and genetic abnormalities in lobular carcinoma in situ. Breast Cancer Res Treat. 2005;90:249–56
95. Porter PL, Garcia R, Moe R, et al C-erbB-2 oncogene protein in in situ and invasive lobular breast neoplasia. Cancer. 1991;68:331–4
96. Ramachandra S, Machin L, Ashley S, et al Immunohistochemical distribution of c-erbB-2 in in situ breast carcinoma–a detailed morphological analysis. J Pathol. 1990;161:7–14
97. Rudas M, Neumayer R, Gnant MF, et al p53 protein expression, cell proliferation and steroid hormone receptors in ductal and lobular in situ carcinomas of the breast. Eur J Cancer. 1997;33:39–44
98. Simpson PT, Reis-Filho JS, Gale T, et al Molecular evolution of breast cancer. J Pathol. 2005;205:248–54
99. Simpson PT, Reis-Filho JS, Lambros MB, et al Molecular profiling pleomorphic lobular carcinomas of the breast:

evidence for a common molecular genetic pathway with classic lobular carcinomas. J Pathol. 2008;215:231–44
100. Bratthauer GL, Moinfar F, Stamatakos MD, et al Combined E-cadherin and high molecular weight cytokeratin immunoprofile differentiates lobular, ductal, and hybrid mammary intraepithelial neoplasias. Hum Pathol. 2002;33: 620–7
101. Dabbs DJ, Kaplai M, Chivukula M, et al The spectrum of morphomolecular abnormalities of the E-cadherin/catenin complex in pleomorphic lobular carcinoma of the breast. Appl Immunohistochem Mol Morphol. 2007;15:260–6
102. De Leeuw WJ, Berx G, Vos CB, et al Simultaneous loss of E-cadherin and catenins in invasive lobular breast cancer and lobular carcinoma in situ. J Pathol. 1997;183:404–11
103. Droufakou S, Deshmane V, Roylance R, et al Multiple ways of silencing E-cadherin gene expression in lobular carcinoma of the breast. Int J Cancer. 2001;92:404–8
104. Gamallo C, Palacios J, Suarez A, et al Correlation of E-cadherin expression with differentiation grade and histological type in breast carcinoma. Am J Pathol. 1993;142:987–93
105. Goldstein NS, Bassi D, Watts JC, et al E-cadherin reactivity of 95 noninvasive ductal and lobular lesions of the breast. Implications for the interpretation of problematic lesions. Am J Clin Pathol. 2001;115:534–42
106. Mastracci TL, Tjan S, Bane AL, et al E-cadherin alterations in atypical lobular hyperplasia and lobular carcinoma in situ of the breast. Mod Pathol. 2005;18:741–51
107. Palacios J, Benito N, Pizarro A, et al Relationship between ERBB2 and E-cadherin expression in human breast cancer. Virchows Arch. 1995;427:259–63
108. Palacios J, Sarrio D, Garcia-Macias MC, et al Frequent E-cadherin gene inactivation by loss of heterozygosity in pleomorphic lobular carcinoma of the breast. Mod Pathol. 2003;16:674–8
109. Rasbridge SA, Gillett CE, Sampson SA, et al Epithelial (E-) and placental (P-) cadherin cell adhesion molecule expression in breast carcinoma. J Pathol. 1993;169:245–50
110. Roylance R, Droufakou S, Gorman P, et al The role of E-cadherin in low-grade ductal breast tumourigenesis. J Pathol. 2003;200:53–8
111. Sarrio D, Perez-Mies B, Hardisson D, et al Cytoplasmic localization of p120ctn and E-cadherin loss characterize lobular breast carcinoma from preinvasive to metastatic lesions. Oncogene. 2004;23:3272–83
112. Berx G, Cleton-Jansen AM, Nollet F, et al E-cadherin is a tumour/invasion suppressor gene mutated in human lobular breast cancers. Embo J. 1995;14:6107–15
113. Berx G, Cleton-Jansen AM, Strumane K, et al E-cadherin is inactivated in a majority of invasive human lobular breast cancers by truncation mutations throughout its extracellular domain. Oncogene. 1996;13:1919–25
114. Reis-Filho JS, Simpson PT, Turner NC, et al FGFR1 emerges as a potential therapeutic target for lobular breast carcinomas. Clin Cancer Res. 2006;12:6652–62
115. Aigner K, Dampier B, Descovich L, et al The transcription factor ZEB1 (deltaEF1) promotes tumour cell dedifferentiation by repressing master regulators of epithelial polarity. Oncogene. 2007;26:6979–88
116. Da Silva L, Parry S, Reid L, et al Aberrant expression of E-cadherin in lobular carcinomas of the breast. Am J Surg Pathol. 2008;32:773–83
117. Lei H, Sjoberg-Margolin S, Salahshor S, et al CDH1 mutations are present in both ductal and lobular breast cancer, but promoter allelic variants show no detectable breast cancer risk. Int J Cancer. 2002;98:199–204
118. Derksen PW, Liu X, Saridin F, et al Somatic inactivation of E-cadherin and p53 in mice leads to metastatic lobular mammary carcinoma through induction of anoikis resistance and angiogenesis. Cancer Cell. 2006;10:437–49
119. Moll R, Mitze M, Frixen UH, et al Differential loss of E-cadherin expression in infiltrating ductal and lobular breast carcinomas. Am J Pathol. 1993;143:1731–42
120. Lehr HA, Folpe A, Yaziji H, et al Cytokeratin 8 immunostaining pattern and E-cadherin expression distinguish lobular from ductal breast carcinoma. Am J Clin Pathol. 2000; 114:190–6
121. Reis-Filho JS, Cancela Paredes J, Milanezi F, et al Clinicopathologic implications of E-cadherin reactivity in patients with lobular carcinoma in situ of the breast. Cancer. 2002;94:2114–5; author reply 2115–6
122. Dabbs DJ, Bhargava R, Chivukula M. Lobular versus ductal breast neoplasms: the diagnostic utility of p120 catenin. Am J Surg Pathol. 2007;31:427–37
123. Rieger-Christ KM, Pezza JA, Dugan JM, et al Disparate E-cadherin mutations in LCIS and associated invasive breast carcinomas. Mol Pathol. 2001;54:91–7
124. Guilford P, Hopkins J, Harraway J, et al E-cadherin germline mutations in familial gastric cancer. Nature. 1998; 392:402–5
125. Kaurah P, MacMillan A, Boyd N, et al Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. JAMA. 2007;297:2360–72
126. Allen-Brady K, Camp NJ, Ward JH, et al Lobular breast cancer: excess familiality observed in the Utah Population Database. Int J Cancer. 2005;117:655–61
127. Claus EB, Risch N, Thompson WD, et al Relationship between breast histopathology and family history of breast cancer. Cancer. 1993;71:147–53
128. Claus EB, Stowe M, Carter D. Family history of breast and ovarian cancer and the risk of breast carcinoma in situ. Breast Cancer Res Treat. 2003;78:7–15
129. Lakhani SR, Gusterson BA, Jacquemier J, et al The pathology of familial breast cancer: histological features of cancers in families not attributable to mutations in BRCA1 or BRCA2. Clin Cancer Res. 2000;6:782–9
130. Keller G, Vogelsang H, Becker I, et al Diffuse type gastric and lobular breast carcinoma in a familial gastric cancer patient with an E-cadherin germline mutation. Am J Pathol. 1999;155:337–42
131. Masciari S, Larsson N, Senz J, et al Germline E-cadherin mutations in familial lobular breast cancer. J Med Genet. 2007;44:726–31
132. Rahman N, Stone JG, Coleman G, et al Lobular carcinoma in situ of the breast is not caused by constitutional mutations in the E-cadherin gene. Br J Cancer. 2000;82: 568–70
133. Salahshor S, Haixin L, Huo H, et al Low frequency of E-cadherin alterations in familial breast cancer. Breast Cancer Res. 2001;3:199–207
134. Schrader KA, Masciari S, Boyd N, et al Hereditary diffuse gastric cancer: association with lobular breast cancer. Fam Cancer. 2007;7(1):73–82

135. Anon. Pathology of familial breast cancer: differences between breast cancers in carriers of BRCA1 or BRCA2 mutations and sporadic cases. Breast Cancer Linkage Consortium. Lancet. 1997;349:1505–10
136. Stone JG, Coleman G, Gusterson B, et al Contribution of germline MLH1 and MSH2 mutations to lobular carcinoma in situ of the breast. Cancer Lett. 2001;167:171–4
137. Huzarski T, Cybulski C, Domagala W, et al Pathology of breast cancer in women with constitutional CHEK2 mutations. Breast Cancer Res Treat. 2005;90:187–9
138. Greaves LC, Taylor RW. Mitochondrial DNA mutations in human disease. IUBMB Life. 2006;58:143–51
139. Albertson DG. Profiling breast cancer by array CGH. Breast Cancer Res Treat. 2003;78:289–98
140. Kallioniemi A, Kallioniemi OP, Sudar D, et al Comparative genomic hybridization for molecular cytogenetic analysis of solid tumors. Science. 1992;258:818–21
141. Buerger H, Simon R, Schafer KL, et al Genetic relation of lobular carcinoma in situ, ductal carcinoma in situ, and associated invasive carcinoma of the breast. Mol Pathol. 2000;53:118–21
142. Lu YJ, Osin P, Lakhani SR, et al Comparative genomic hybridization analysis of lobular carcinoma in situ and atypical lobular hyperplasia and potential roles for gains and losses of genetic material in breast neoplasia. Cancer Res. 1998;58:4721–7
143.Mastracci TL, Shadeo A, Colby SM, et al Genomic alterations in lobular neoplasia: a microarray comparative genomic hybridization signature for early neoplastic proliferationin the breast. Genes Chromosomes Cancer. 2006;45:1007–17
144. Nyante SJ, Devries S, Chen YY, et al Array-based comparative genomic hybridization of ductal carcinoma in situ and synchronous invasive lobular cancer. Hum Pathol. 2004;35:759–63
145. Elbauomy Elsheikh S, Green AR, Lambros MB, et al FGFR1 amplification in breast carcinomas: a chromogenic in situ hybridisation analysis. Breast Cancer Res. 2007; 9:R23
146. Reis-Filho JS, Savage K, Lambros MB, et al Cyclin D1 protein overexpression and CCND1 amplification in breast carcinomas: an immunohistochemical and chromogenic in situ hybridisation analysis. Mod Pathol. 2006;19:999–1009
147. Powell JA, Gardner AE, Bais AJ, et al Sequencing, transcript identification, and quantitative gene expression profiling in the breast cancer loss of heterozygosity region 16q24.3 reveal three potential tumor-suppressor genes. Genomics. 2002;80:303–10
148.Rakha EA, Armour JA, Pinder SE, et al High-resolution analysis of 16q22.1 in breast carcinoma using DNA amplifiable probes (multiplex amplifiable probe hybridization technique) and immunohistochemistry. Int J Cancer. 2005;114:720–9
149. Rakha EA, Green AR, Powe DG, et al Chromosome 16 tumor-suppressor genes in breast cancer. Genes Chromosomes Cancer. 2006;45:527–35
150. van Wezel T, Lombaerts M, van Roon EH, et al Expression analysis of candidate breast tumour suppressor genes on chromosome 16q. Breast Cancer Res. 2005;7:R998–1004
151. Green AR, Krivinskas S, Young P, et al Loss of expression of chromosome 16q genes DPEP1 and CTCF in lobular carcinoma in situ of the breast. Breast Cancer Res Treat. 2008;107:41–5
152. Aulmann S, Blaker H, Penzel R, et al CTCF gene mutations in invasive ductal breast cancer. Breast Cancer Res Treat. 2003;80:347–52
153. Austruy E, Jeanpierre C, Antignac C, et al Physical and genetic mapping of the dipeptidase gene DPEP1 to 16q24.3. Genomics. 1993;15:684–7
154. McIver CM, Lloyd JM, Hewett PJ, et al Dipeptidase 1: a candidate tumor-specific molecular marker in colorectal carcinoma. Cancer Lett. 2004;209:67–74
155. Weinstein SP, Orel SG, Heller R, et al MR imaging of the breast in patients with invasive lobular carcinoma. AJR Am J Roentgenol. 2001;176:399–406
156. Mann RM, Hoogeveen YL, Blickman JG, et al MRI compared to conventional diagnostic work-up in the detection and evaluation of invasive lobular carcinoma of the breast: a review of existing literature. Breast Cancer Res Treat. 2008;107:1–14
157. Port ER, Park A, Borgen PI, et al Results of MRI screening for breast cancer in high-risk patients with LCIS and atypical hyperplasia. Ann Surg Oncol. 2007;14:1051–7
158. Stolier AJ, Barre G, Bolton JS, et al Breast conservation therapy for invasive lobular carcinoma: the impact of lobular carcinoma in situ in the surgical specimen on local recurrence and axillary node status. Am Surg. 2004;70: 818–21
159. Fisher B, Dignam J, Wolmark N, et al Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet. 1999;353:1993–2000
160. Vogel VG. Follow-up of the breast cancer prevention trial and the future of breast cancer prevention efforts. Clin Cancer Res. 2001;7:4413s–8s; discussion 4411s–2s
161. Vogel VG, Costantino JP, Wickerham DL, et al The study of tamoxifen and raloxifene: preliminary enrollment data from a randomized breast cancer risk reduction trial. Clin Breast Cancer. 2002;3:153–9
162. Vogel VG, Costantino JP, Wickerham DL, et al Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA. 2006;295:2727–41
163. Arpino G, Allred DC, Mohsin SK, et al Lobular neoplasia on core-needle biopsy–clinical significance. Cancer. 2004; 101:242–50
164. Bauer VP, Ditkoff BA, Schnabel F, et al The management of lobular neoplasia identified on percutaneous core breast biopsy. Breast J. 2003;9:4–9
165. Berg WA, Mrose HE, Ioffe OB. Atypical lobular hyperplasia or lobular carcinoma in situ at core-needle breast biopsy. Radiology. 2001;218:503–9
166. Crisi GM, Mandavilli S, Cronin E, et al Invasive mammary carcinoma after immediate and short-term follow-up for lobular neoplasia on core biopsy. Am J Surg Pathol. 2003; 27:325–33
167. Dmytrasz K, Tartter PI, Mizrachy H, et al The significance of atypical lobular hyperplasia at percutaneous breast biopsy. Breast J. 2003;9:10–2
168. Foster MC, Helvie MA, Gregory NE, et al Lobular carcinoma in situ or atypical lobular hyperplasia at core-needle biopsy: is excisional biopsy necessary? Radiology. 2004; 231:813–9

169. Jacobs TW, Connolly JL, Schnitt SJ. Nonmalignant lesions in breast core needle biopsies: to excise or not to excise? Am J Surg Pathol. 2002;26:1095–110
170. Liberman L, Sama M, Susnik B, et al Lobular carcinoma in situ at percutaneous breast biopsy: surgical biopsy findings. AJR Am J Roentgenol. 1999;173:291–9
171. Mahoney MC, Robinson-Smith TM, Shaughnessy EA. Lobular neoplasia at 11-gauge vacuum-assisted stereotactic biopsy: correlation with surgical excisional biopsy and mammographic follow-up. AJR Am J Roentgenol. 2006; 187:949–54
172. Renshaw AA, Cartagena N, Derhagopian RP, et al Lobular neoplasia in breast core needle biopsy specimens is not associated with an increased risk of ductal carcinoma in situ or invasive carcinoma. Am J Clin Pathol. 2002;117: 797–9
173. Renshaw AA, Derhagopian RP, Martinez P, et al Lobular neoplasia in breast core needle biopsy specimens is associated with a low risk of ductal carcinoma in situ or invasive carcinoma on subsequent excision. Am J Clin Pathol. 2006; 126:310–3
174. Shin SJ, Rosen PP. Excisional biopsy should be performed if lobular carcinoma in situ is seen on needle core biopsy. Arch Pathol Lab Med. 2002;126:697–701
175. Elsheikh TM, Silverman JF. Follow-up surgical excision is indicated when breast core needle biopsies show atypical lobular hyperplasia or lobular carcinoma in situ: a correlative study of 33 patients with review of the literature. Am J Surg Pathol. 2005;29:534–43
176. Liberman L, Cohen MA, Dershaw DD, et al Atypical ductal hyperplasia diagnosed at stereotaxic core biopsy of breast lesions: an indication for surgical biopsy. AJR Am J Roentgenol. 1995;164:1111–3
177. Moore MM, Hargett CW 3rd, Hanks JB, et al Association of breast cancer with the finding of atypical ductal hyperplasia at core breast biopsy. Ann Surg. 1997;225:726–31; discussion 731–3
178. Nagi CS, O'Donnell JE, Tismenetsky M, et al Lobular neoplasia on core needle biopsy does not require excision. Cancer. 2008;112:2152–8
179. Cangiarella J, Guth A, Axelrod D, et al Is surgical excision necessary for the management of atypical lobular hyperplasia and lobular carcinoma in situ diagnosed on core needle biopsy?: a report of 38 cases and review of the literature. Arch Pathol Lab Med. 2008;132:979–83
180. Elsheikh TM, Silverman JF. Wider excision following core biopsies of lobular neoplasia. Breast J. 2007;13:631–2; author response 633
181. Karabakhtsian RG, Johnson R, Sumkin J, et al The clinical significance of lobular neoplasia on breast core biopsy. Am J Surg Pathol. 2007;31:717–23
182. Londero V, Zuiani C, Linda A, et al Lobular neoplasia: core needle breast biopsy underestimation of malignancy in relation to radiologic and pathologic features. Breast. 2008;17(6):623–30
183. Margenthaler JA, Duke D, Monsees BS, et al Correlation between core biopsy and excisional biopsy in breast high-risk lesions. Am J Surg. 2006;192:534–7
184. Esserman LE, Lamea L, Tanev S, et al Should the extent of lobular neoplasia on core biopsy influence the decision for excision? Breast J. 2007;13:55–61
185. Sapino A, Frigerio A, Peterse JL, et al Mammographically detected in situ lobular carcinomas of the breast. Virchows Arch. 2000;436:421–30
186. Lee AH, Denley HE, Pinder SE, et al Excision biopsy findings of patients with breast needle core biopsies reported as suspicious of malignancy (B4) or lesion of uncertain malignant potential (B3). Histopathology. 2003;42:331–6
187. Reis-Filho JS, Pinder SE. Non-operative breast pathology: lobular neoplasia. J Clin Pathol. 2007;60:1321–7

Ductal Carcinoma in Situ

12

Robin M. Ciocca and Monica Morrow

12.1 Introduction

Ductal carcinoma in situ (DCIS), also known as intraductal cancer, is characterized by the proliferation of malignant mammary ductal epithelial cells without evidence of invasion beyond the basement membrane. In the past, DCIS was an uncommon lesion, and was considered a favorable type of carcinoma, which was readily cured by mastectomy. The use of screening mammography has resulted in a remarkable increase in the incidence (or detection rate) of DCIS. Between 1973 and 1992, age adjusted incidence rates of DCIS rose from 2.3 to 15.8 per 100,000 women, a 58% increase. In comparison, the incidence of invasive breast cancer increased by 34.3% in the same period [1]. This increase was observed for both White and African-American women and in those over and under 50 years of age. However, it appears that DCIS accounts for a higher proportion of screen-detected cancers in women aged 40–49 years than in their older counterparts. Ernster et al. analyzed the data on 653,833 screening mammograms and found that 28.2% (95% confidence interval (CI) 23.9–32.5%) of screen-detected cancers in women aged 40–49 were DCIS compared with 16% in women aged 70–84 years (95% CI 13.3–18.7%) [2]. In more recent years, the increase in the incidence rate of DCIS has slowed, with a 1.8-fold increase seen between 1992 and 2001, and a 1.1-fold increase in the latter part of this time interval (1997–2001) [3]. The increasing frequency of the diagnosis of DCIS has led some to suggest that screening results in the detection of biologically indolent DCIS and leads to unnecessary treatment. While it is clear that DCIS is a significant risk factor for the development of invasive breast carcinoma, many women diagnosed with DCIS will not develop invasive carcinoma during their lifetime [4]. The management of DCIS has become a major clinical dilemma due to our inability to predict which DCIS will progress to invasive carcinoma or the time interval in which recurrent DCIS or invasive carcinoma will occur after simple excision. In addition, the presence of invasive carcinoma cannot reliably be excluded without the complete excision of the DCIS lesion, which in some cases will necessitate mastectomy. In this chapter, we will review the data on the natural history of DCIS and the outcome of various therapies with an emphasis on the data from randomized clinical trials.

12.2 Presentation

Prior to the advent of routine screening mammography, DCIS made up less than 2% of all breast cancer diagnoses [5]. Clinical presentations of DCIS include a palpable mass, nipple discharge or Paget's disease of the nipple. DCIS may also be an incidental finding in a breast biopsy performed for another indication. The previously discussed widespread use of screening mammography has significantly increased the number of patients diagnosed with DCIS. A study by Ernster et al. found that approximately 1 in every 1,300 screening mammograms leads to a diagnosis of DCIS and approximately 20% of all breast cancers are now diagnosed before invasion occurs [2].

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_12, © Springer-Verlag Berlin Heidelberg 2010

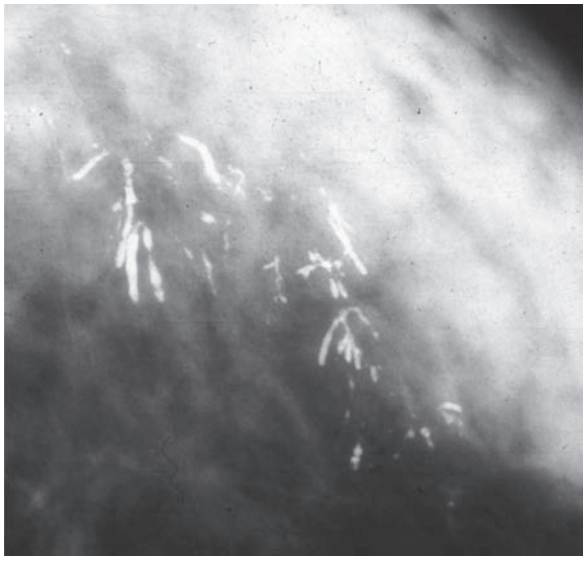


Fig. 12.1 Calcifications due to high-grade ductal carcinoma in situ (DCIS). The branching linear pattern of these coarse calcifications is highly predictive of malignancy

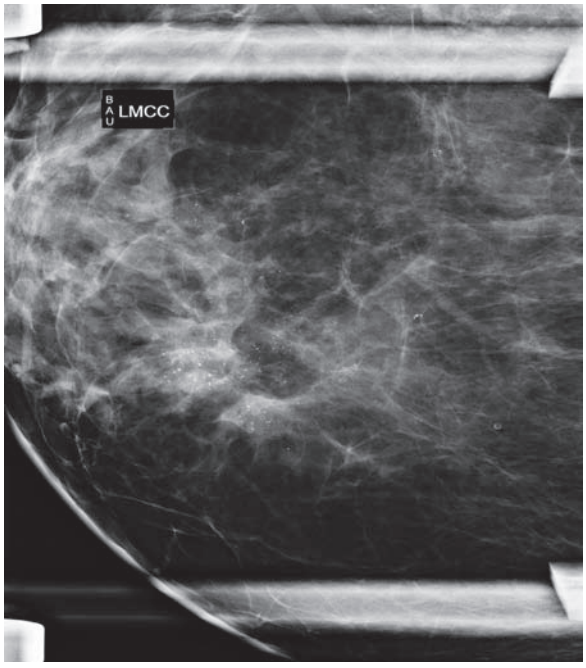


Fig. 12.2 Fine, granular calcifications associated with well-differentiated low-grade DCIS

The most common mammographic manifestation of DCIS is microcalcifications [6]. A retrospective review of 190 consecutive cases of DCIS found that 62% presented as microcalcifications, 22% had soft tissue changes, and 16% had no pertinent findings on their mammogram [7]. Microcalcifications associated with DCIS are frequently clustered and may be focal or diffuse; they tend to be variable in size and shape [6]. High-grade comedo-type DCIS often presents as linear, branching, coarse calcifications (Fig. 12.1), while the calcifications associated with well-differentiated noncomedo DCIS tend to be fine and granular (Fig. 12.2) [8]. Although magnification views can help better characterize the pleomorphism of microcalcifications, the comedo and noncomedo subtypes of DCIS cannot reliably be distinguished by mammography alone [9].

The size and extent of a DCIS lesion is a very important factor in determining optimal surgical management. Standard two-view mammography may underestimate the extent of disease, particularly in well-diffferentiated DCIS [8, 9]. Holland et al. examined the mastectomy specimens of 82 patients treated for DCIS, comparing the final histologic size of the DCIS lesion to the size measured by the preoperative mammogram. A size discrepancy of more than 2 cm was present in 44% of well-differentiated DCIS lesions. The mammographic and histologic sizes were better correlated for pure comedo tumors where a difference of more than 2 cm was only present in 12% of cases [10]. The use of magnification views, in addition to standard two-view mammography resolves much of this size discrepancy. In a follow-up study where size was estimated from magnification views, a size discrepancy greater than 2 cm was present in only 14% of cases regardless of the histology of the DCIS [8]. Based on these findings, diagnostic views should be performed of all calcifications, even if the need for biopsy is evident from the initial two-view mammogram.

Although mammography is still considered the mainstay for the diagnosis of DCIS, difficulties in determining the extent of DCIS even with magnification mammography have led to studies of other imaging modalities. To date, breast ultrasound, scintimammography, and positron emission tomography (PET) have not been shown to be reliable tools for either the diagnosis of DCIS or for determining its extent [11]. Great interest exists in the utility of magnetic resonance imaging (MRI). While multiple studies have demonstrated that MRI is more sensitive than mammography for the detection of invasive carcinoma [12–14], its ability to

detect DCIS is less clear. Older studies have reported sensitivities ranging from 16–73% for the detection of DCIS with MRI [13–17]. Bluemke et al. conducted a multicenter trial in which they performed MRIs prior to breast biopsy in 821 patients referred for biopsy due to suspicious findings on mammographic assessment, clinical exam, or ultrasound. MRI results were interpreted at each site without knowledge of the pathologic results. In this study, 63 cases of DCIS were diagnosed, only 46 of which were detected by prebiopsy MRI, a sensitivity of 73% [16]. Another study by Kriege et al. evaluating the efficacy of MRI and mammography for breast cancer screening in women with a familial or genetic predisposition to breast cancer found that MRI failed to detect five of the six cases of DCIS occurring in the 1,909 women they screened with both modalities. MRI performed well for the detection of invasive cancer with an overall sensitivity of 79.5%, but the sensitivity was only 16% for the detection of DCIS [17]. However, a recent study by Kuhl et al. of 7,319 women examined with both MRI and mammography for diagnostic assessment and screening found MRI to be more sensitive than mammography in detecting DCIS. Of the 7,319 patients in the study, 193 had a final pathologic diagnosis of pure DCIS. Of those cases, 93 (56%) were diagnosed by mammography and 153 (92%) by MRI; of the 89 high-grade DCIS lesions, 43 (48%) were missed by mammography, but diagnosed by MRI. Age, menopausal status, personal or family history of breast cancer or of benign breast disease, and breast density of women with MRI-only diagnosed DCIS did not differ significantly from those of women with mammographically diagnosed DCIS [18]. These results differ dramatically from the other published reports and must be reproduced outside a single institution before concluding that there is a role for MRI in screening for DCIS. The high incidence of cancer diagnosed in this population (6% of patients screened) indicates that this was not purely a screening study. In addition, for a test to be considered a good screening tool, it must also be cost effective. In this study, over 7,000 MRI exams were performed to detect 60 cases of DCIS that were not detected by standard mammographic screening and 574 women underwent a biopsy for an ultimately benign diagnosis.

In addition to evaluating its role in screening, the utility of MRI in determining the extent of DCIS has also been examined. One study of 34 patients, which compared the predicted size of DCIS by preoperative MRI with final pathologic size, found that MRI overestimated the size of the lesion by about 50% in 34 patients studied [19]. It appears that MRI overestimates the size of both large and small DCIS lesions. In a study of 18 patients with lesions estimated to be greater than 5 cm by MRI, size was overestimated in 30% of patients [20]. Schouten van der Velden et al. examined 21 patients with lesions <10 mm and found that MRI accurately assessed tumor size in only 38% of patients [21]. In another study of 45 patients with DCIS, a wide variety of MRI appearances of the DCIS lesions were noted. The authors suggested that these imaging features may be a reflection of biologic differences among DCIS lesions, but this remains to be proven. However, they did note that overestimation of the size of DCIS by MRI was most likely to occur for diffuse, less dense DCIS lesions [22]. At present, the role of MRI in the patient with DCIS is uncertain. The documented overestimation of size of the DCIS lesion has the potential to result in unnecessary mastectomies, and a recent study comparing local recurrence rates and contralateral cancer incidence in women selected for breast conserving therapy with and without MRI fails to document a decrease in ipsilateral breast tumor recurrence (IBTR) rates or contralateral cancers at 8 years for patients selected with MRI [23].

12.3 Diagnosis

Most cases of DCIS diagnosed today are nonpalpable lesions identified by screening mammography, and image-guided biopsy techniques are the standard of care for diagnosis. Calcifications without an associated mass are not routinely visible using ultrasound, so in the majority of cases the diagnostic procedure is a stereotactic core needle biopsy (SCNB) using mammographic localization. MRI-guided biopsies are reserved for cases where MRI is the only imaging modality, which detects the area of concern. When compared to open surgical biopsy, SCNB has been shown to be highly accurate, cost-effective, and spares the patient an operative procedure should the abnormality prove to be of a benign histology [24–26]. Initial concerns regarding the delay in diagnosis of cancer due to false-negative results with the use of SCNB have been addressed as experience with the technique has become widespread and standard indications for open surgical biopsy developed. In a study by Pfarl et al., 318 patients

underwent SNCB with subsequent surgical excision. The false-negative rate of SCNB was 3.3% and decreased to 0.6% when SCNB was performed by radiologists with experience of more than ten cases. All of the false-negative cases were identified immediately because of failure to sample calcifications or imaging-histologic discordance [27]. The use of SCNB decreases the number of surgical procedures patients need to undergo to complete local therapy and decreases the cost of local therapy whether the treatment is mastectomy or breast conserving therapy [28]. SCNB procedures should be performed by physicians properly trained in the technique. Multiple cores should be obtained and radiographed to ensure adequate sampling of the area of concern, and a marker should be placed at the biopsy site as a guide for future excision if a diagnosis of DCIS or invasive cancer is made [29]. Failure to identify calcifications in the specimen radiographs or discordance between the pathologic diagnosis and the mammographic findings are indications for a repeat SCNB if a targeting problem is identified, or needle localization and surgical excision.

Open surgical biopsy is indicated in patients who are not considered candidates for SCNB due to the weight restrictions of the stereotactic table, the inability to lay prone for the duration of the procedure (20–40 min), small breast size not permitting the full throw of the automated biopsy device, or superficial lesions, which may pose technical problems in obtaining an adequate biopsy. Certain characteristics of biopsy targets may also pose difficulties in the use of SCNB for diagnosis. These include widely separated calcifications for which useful coordinates may not be able to be generated and faint calcification or vague asymmetric densities that cannot be well-visualized by the stereotactic imaging system [30]. Anticoagulation has also been described as contraindication to SCNB. However, Melotti et al. found that the rate of complications such as hematoma formation was no higher in patients who could not stop their anticoagulation for SCNB when compared to a control group who was not anticoagulated [31]. Continued refinement of biopsy devices and experience with the procedure has decreased the number of patients who are not candidates for diagnosis by SCNB. When open biopsy is performed, preoperative needle localization is used to guide surgical excision. Incisions should be long enough to allow for removal of the specimen in one piece. Fragmentation should be avoided as it makes margin assessment and size determination difficult [32]. Specimens should be oriented so that the involved margins can be reliably identified for reexcision. Frozen section is not indicated as it may destroy tissue needed for a final diagnosis and cannot reliably distinguish between atypical hyperplasia and DCIS.

A diagnosis of DCIS by SCNB does not reliably exclude the presence of invasive carcinoma. The frequency of invasive carcinoma as the final diagnosis in cases initially diagnosed as DCIS by SCNB ranges from 15–27% [33–36]. Multiple studies have sought to determine if the presence of invasion can be predicted based on the characteristics of the DCIS in the core specimen [33, 35, 36]. Reproducible clinical, mammographic, and histologic predictors of invasion have not been identified.

12.4 Pathology

The World Health Organization (WHO) defines DCIS as "a neoplastic intraductal lesion characterized by increased epithelial proliferation, subtle to marked epithelial atypia and an inherent, but not necessarily obligate tendency for progression to invasive breast cancer" [37]. DCIS arises from the epithelium in the terminal duct lobular unit. It is a heterogeneous disease and likely represents a stage in a continuum from usual ductal hyperplasia to atypical ductal hyperplasia to carcinoma in situ to invasive carcinoma.

A universally accepted classification system of DCIS does not exist. Traditionally, classification of DCIS emphasized architecture, cytologic features, and necrosis, alone or in combination. Based solely on architecture, DCIS can be divided into five major types: comedo, cribiform, micropapillary, papillary, and solid [38]. The trend, however, has been a move away from a solely architectural classification since many DCIS lesions contain more than one architectural type. In 1997, a consensus committee recommended that architectural patterns, nuclear grade, and necrosis be included in the pathology report. In this consensus statement, nuclear grade was divided into low (Grade 1), intermediate (Grade 2), and high (Grade 3). Grade 1 DCIS is characterized by a monomorphic appearance and nuclei 1.5– 2 times the size of a normal red blood cell (Fig. 12.3). The chromatin pattern is finely dispersed

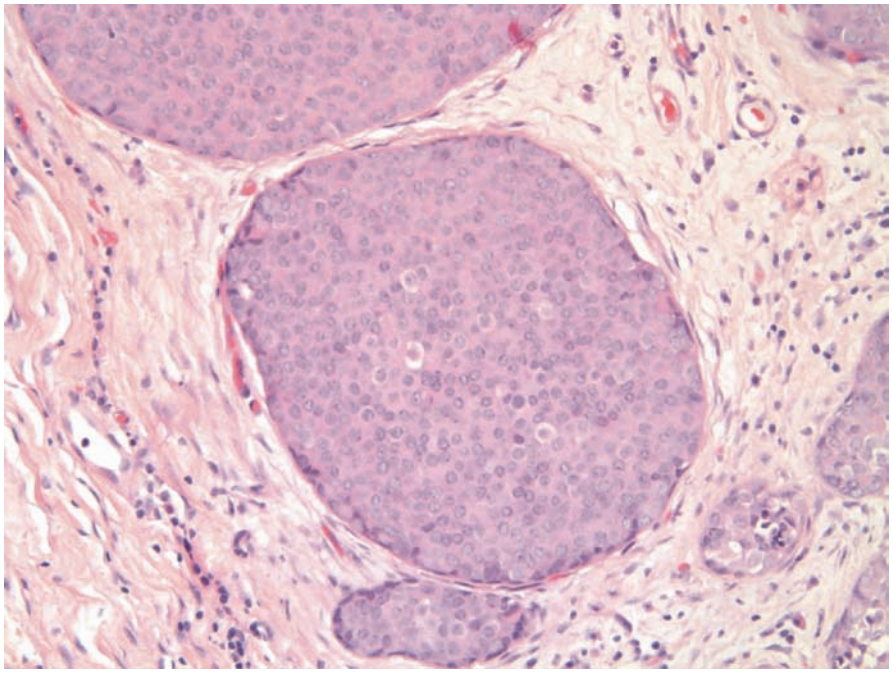


Fig. 12.3 Grade I DCIS. The cells are polarized with a monomorphic appearance. Nuclei are 1.5–2 times the size of a normal red blood cell with finely dispersed chromatin

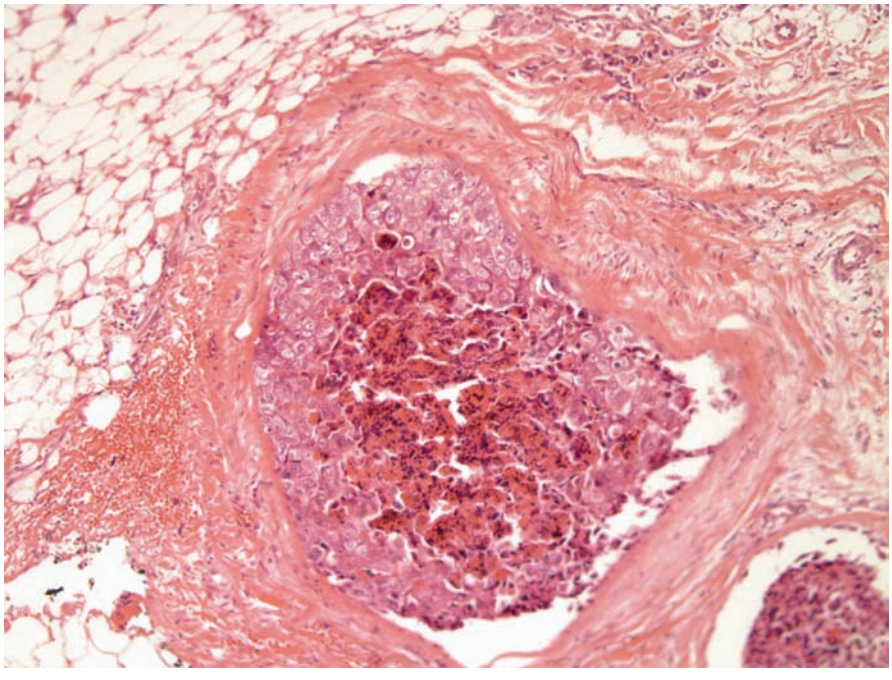


Fig. 12.4 Grade 3 DCIS. Cells are markedly pleomorphic and enlarged. Nuclei have irregular membranes and course, clumped chromatin with prominent nucleoli

with occasional nucleoli. Mitosis can occasionally be seen. The cells are usually polarized. In Grade 3 DCIS, the cells are markedly pleomorphic and enlarged usually more than 2.5 times the normal duct epithelium nucleus. The nucleus shows irregular membranes and course clumped chromatin with prominent nucleoli. Mitosis may be conspicuous (Fig. 12.4). Grade 2 DCIS is defined by nuclei that are neither Grade 1 nor Grade 3. Comedo necrosis is defined as central zone necrosis within a duct, usually in a linear pattern within ducts if

sectioned longitudinally. The term "punctuate" necrosis is applied to necrosis that is present, but does not encompass a central zone. Different grades of DCIS can be seen within the same duct profile. Furthermore, the three-tiered grading system does not imply progression from Grade 1 to Grade 3 [39].

Silverstein et al. proposed a classification for DCIS based on nuclear grade and necrosis [40]. This system stratified DCIS into three groups: nonhigh nuclear grade without necrosis, nonhigh nuclear grade with necrosis, and high nuclear grade with or without necrosis. As with the other proposed classification systems, this system has not been prospectively validated as a predictor of outcome in DCIS. Gene-expression profiling has shown that high-grade DCIS exhibits greater overall genetic change when compared to low-grade DCIS [41–43]. A specific genetic profile associated with progression to invasive carcinoma has not been identified, and many of the genetic alterations seen in invasive carcinoma are also present in DCIS, suggesting that the events critical for transformation to invasive carcinoma may occur before the clinical development of DCIS. Low-grade DCIS lesions are usually estrogen receptor (ER) positive, and less than 20% express HER-2 *neu* and p53. High-grade DCIS shows HER-2 *neu* overexpression and p53 mutations in approximately two-thirds of cases, and less than 25% of high-grade DCIS lesions express ER positivity [44].

The differing pathologic, molecular and clinical features of DCIS make it a biologically heterogeneous disease. Unfortunately, none of the classification systems proposed to date are useful in identifying which DCIS lesions will recur as invasive carcinoma or even which DCIS lesions will recur at all. The ability to develop molecular prognostic signatures in DCIS has been limited by the small size of many lesions, the need to submit the entire specimen for diagnostic pathology to exclude the presence of invasive carcinoma and the long natural history of DCIS.

12.5 Natural History of DCIS

The risk of progression to invasive carcinoma is the major reason for treating DCIS. Unfortunately, the past era of treatment of DCIS by mastectomy means that limited information on the natural history of this lesion is available. Indirect evidence from autopsy studies, epidemiologic studies comparing risk factors for DCIS and invasive carcinoma, comparisons of the characteristics of screen-detected and clinically evident DCIS, and most recently, molecular markers have all been used to address this question.

The most direct evidence of the risk of progression to invasive carcinoma comes from several small studies of women initially thought to have benign breast disease, who on later review of their pathology specimens, were reclassified as having DCIS. This population is heavily weighted toward small, low-grade DCIS lesions (those most likely to be called benign). In addition, no effort was made to assess margin status and completeness of excision in these cases. In a review of 11,760 breast biopsies, Page et al. identified 25 DCIS lesions, which were originally categorized as benign. Invasive carcinoma developed in seven women (28%) at a mean of 6.1 years after biopsy (range 3–10 years) [45]. The elevated risk of invasive carcinoma was constant over 24 years of follow-up and represents a relative risk of 11 compared with age-matched controls [46]. In a similar study, Rosen et al. identified 30 women with untreated DCIS with complete follow-up available for 15. Invasive carcinoma occurred in seven women at a mean of 9.7 years after biopsy, an incidence of 27% if all cases are included or 53% if only those with complete follow-up are counted [47]. In this report, as well as the report of Page et al. [46], all of the subsequent invasive carcinomas were in the index breast, and the majority occurred in the vicinity of the initial biopsy, suggesting that they did arise from the DCIS lesion. Eusebi et al. reported 80 cases of DCIS, only two of which were high grade, which were followed for a median of 16.7 years. Eleven invasive carcinomas and five recurrent DCIS lesions were observed, a total recurrence rate of 20% [48].

These studies clearly document an elevated risk for the development of invasive carcinoma after a diagnosis of DCIS, even when the lesions are small and low grade. Autopsy studies support the idea that DCIS is a risk factor for breast cancer development rather than a common finding in the breasts of asymptomatic women. Bartow et al. performed subgross sampling of the breasts of 519 women aged 14 and older who died of causes unrelated to breast carcinoma and identified only one case of DCIS, although five occult invasive carcinomas were found [49]. In a similar study, Alpers and Wellings examined 185 breasts from 101 women and identified DCIS in 11 cases (6%). DCIS was present in 5% of the

56 women aged 49 or younger, 10% of the women between ages 50 and 69, and only 1 of 59 women older than 70 years [50]. Other studies have reported DCIS in 0.2–18% of autopsy specimens [51–53]. Studies of prophylactic mastectomy specimens from women at increased risk of breast cancer development, usually on the basis of BRCA 1 or 2 mutations, have identified incidental DCIS in 13–15% of patients [54, 55]. Together, the autopsy studies and the prophylactic mastectomy studies indicate that DCIS is an uncommon finding in the breast, unlike the situation with prostate cancer in older men. The incidence of asymptomatic DCIS increases as the level of risk increases, further supporting its role as a precursor of invasive carcinoma.

Risk factors for DCIS and invasive carcinoma have also been examined as evidence of a link between these two entities. Gapstur et al. used prospectively collected risk factor data from 37,105 women in the Iowa Women's Health Study to examine the concordance between risk factors for DCIS and invasive carcinoma. After 11 years of follow-up, 1,520 breast cancers, including 175 cases of DCIS had developed in the cohort. The risk factor profiles for invasive carcinoma and DCIS did not differ, and the magnitude of risk conveyed by each of the risk factors was similar as well [56]. Kerlikowske et al., in a study of 39,542 women undergoing screening mammography [57], and Claus et al., in a case control study [58], have reported a similar concordance in risk factors.

More recently, molecular alterations in DCIS and coexisting invasive carcinoma have been compared to provide support for the concept that DCIS is a precursor lesion. In one study of 305 tumors with both an in situ and an invasive component, the expression of tumor markers such as ER, the progesterone receptor (PR), c-erbB-2, Ki-67, bcl-2, and p53 was almost identical between the two components [59]. In a study of 21 tumors, Zhuang et al. demonstrated that when loss of heterozygosity of chromosome 11q13 was present in the DCIS component, the same alteration was present in the invasive component [60]. Warnberg et al. also found that the gene expression profile of low-grade DCIS was very similar to that of low-grade invasive cancer, but different from that of high-grade DCIS and high-grade invasive cancer [59], suggesting that low-grade DCIS progresses to low-grade invasive carcinoma rather than high-grade DCIS. To date, specific genetic profiles associated with progression to invasive cancer have not been identified.

12.6 Treatment of the Breast

The uncertainty regarding the natural history of DCIS has resulted in treatments ranging from total mastectomy or excision and radiation therapy (RT) to simple excision alone. Treatment with mastectomy or excision and RT reflects the belief that DCIS is a cancer, albeit a favorable one, which should be treated aggressively. Management of DCIS with excision and observation reflects the viewpoint that DCIS is a precursor lesion, although not an obligate one, and that many women with DCIS will not develop invasive breast cancer during their lifetimes and should be spared the morbidity of aggressive treatments such as mastectomy or RT. Until relatively recently, attempts to compare the outcomes of these treatments were confounded by their use in different populations of women with DCIS, the small size of many single-institution studies, and the lack of standardization in the measurement of the size of the DCIS lesion, the method of histologic grading used, and the technique of margin evaluation. The results of a number of prospective, randomized trials with well-defined patient populations have provided valuable information on treatment outcomes obtained on large numbers of women with DCIS treated in a variety of settings. These studies are discussed in detail in the sections on excision and irradiation and excision alone. Randomized trials comparing mastectomy to other forms of therapy in DCIS have not been carried out, but because mastectomy was the only treatment used for DCIS for many years, retrospective studies provide outcome data, which can be extrapolated to the population of women with DCIS as a whole.

12.6.1 Mastectomy

Mastectomy results in cure rates of approximately 98% for patients who undergo this procedure for DCIS. This is true regardless of the method of detection, histologic grade or subtype of the DCIS [61]. Recurrence of carcinoma after mastectomy for DCIS may occur in two ways. The first is due to the presence of undetected invasive carcinoma in the original specimen. The frequency of this scenario has lessened as a more uniform and extensive pathologic processing of mastectomy specimens has become common. In addition,

Table 12.1 Rate of local recurrence and distant metastasis after mastectomy for DCIS

–	No. of patients	Median follow-up (months)	Patients with local recurrence	Patients with distant metastasis
Kinne [63]	101	131	11	1
Jha [64]	176	88	0	0
Ward [65]	123	120	1	Not reported
Silverstein [66]	167	78	2	2
Arnesson [67]	28	77	0	One contralateral breast cancer
Warneke [68]	75	43 (mean)	1	0

the outcomes of older studies of DCIS were often confounded by the lack of a standard definition of DCIS, which excluded all patients with invasive carcinoma. For example, in a report by Haagenson in 1971, patients were considered to have DCIS if less than half the lesion consisted of invasive element [62]. With strict adherence to the modern definition of DCIS as the complete absence of invasive carcinoma, unrecognized invasive disease should be present in less than 5% of mastectomy specimens [63]. Another reason for recurrence after mastectomy is the development of de novo invasive carcinoma in residual breast tissue that is manifest as a local recurrence or distant metastases [32]. The failure of recurrence rates to increase with longer follow-up periods suggests that most recurrences are due to undetected invasive disease at the time of initial diagnosis rather than residual breast tissue. Studies of the treatment of DCIS by mastectomy are summarized in Table 12.1 [63–68]. Currently, the indications for mastectomy for DCIS include patient preference, multicentric disease, diffuse malignant-appearing calcifications on mammography, large lesions relative to the size of the breast, failure to achieve negative margins despite adequate surgical attempts and the presence of contraindications to radiotherapy [69].

12.6.2 Breast-Conserving Surgery and Radiation Therapy

Mastectomy is clearly effective for the treatment of DCIS, but overtreats a large percentage of patients. As breast-conserving therapy (BCT) became accepted for the treatment of invasive breast cancer; it seemed logical to expand its use to women with DCIS, a more favorable lesion. There have been no prospective, randomized trials comparing mastectomy and BCT for the treatment of DCIS. However, the results of many studies have shown that BCT can achieve low recurrence rates and acceptable overall and disease-free survival for appropriately selected patients. However, it is important to recognize that unlike the situation in invasive carcinoma where the risk of metastatic disease is present at the time of diagnosis, in the patient with DCIS, the risk of metastatic disease at presentation is negligible. The appropriateness of breast conserving approaches in DCIS is determined by the risk of local failure and the ability to salvage patients with local recurrence.

The four randomized studies assessing the benefits of RT in conjunction with conservative surgery are summarized in Table 12.2 [70–73]. These studies randomized over 3,800 patients to excision alone and excision combined with postoperative RT. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 [70], European Organization for Research and Treatment of Cancer 10853 (EORTC) [71], and United Kingdom, Australia and New Zealand (UK/ANZ) [72] trials, 50 Gy of radiation was administered to the whole breast in 25 fractions. A boost to the tumor bed was employed in 9% of patients in the NSABP B-17 trial and 5% in the EORTC 10853 trial. In the Swedish Breast Cancer Group (SweDCIS) [73] trial, the majority of patients received 50 Gy over 25 fractions, but a small subset received 54 Gy given in 2-week treatment intervals with a gap of 2 weeks.

The NSABP B-17 study randomized 813 patients, 403 treated with excision alone and 410 who received RT after excision. Approximately one-third of the patients were 49 years of age or less, and only 29% of participants had clinically evident DCIS. Palpable tumors were reported in 17% of these patients; the remaining 83% were detected by mammography alone

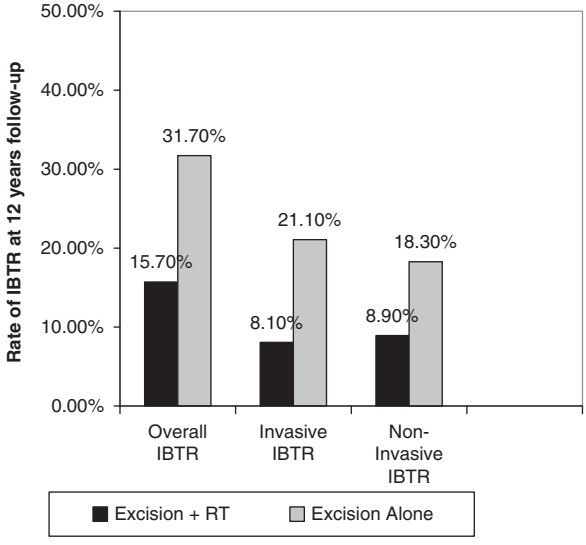
Table 12.2 Studies assessing the benefits of radiation therapy (RT) in conjuction with conservative surgery in the treatment of DCIS

–	Total patients	Excision alone	Excision with RT	IBTR with excision alone (%)	IBTR with excision and RT (%)	Risk reduction (%)
NSABP B-17 [70]	813	413	410	31.7	15	57
EORTC [71]	1,010	503	507	26	15	47
UK/ANZ [72]	1,701	508	522	16	7	62
Swe-DCIS [73]	1,046	520	526	22	7	37

*NSABP N*ational Surgical Adjuvant Breast and Bowel Project
EORTC European Organization for Research and Treatment of Cancer
UK/ANZ United Kingdom/Australia and New Zealand
Swe-DCIS Swedish Breast Cancer Group
IBTR ipsilateral breast tumor recurrence

[74]. The definition of a negative margin used in this trial was tumor filled ducts not touching an inked surface, and less than 1% of the participants in either arm of the study had an unknown margin status. At 12 years of follow-up, the cumulative incidence of IBTR for the excision alone group was 31.7% compared to 15.7% for those women treated with excision followed by RT, a 57% reduction of IBTR ($p><0.000005$) as a consequence of RT. This reduction was seen for both invasive and noninvasive IBTR, although the magnitude of benefit of RT in reducing invasive recurrences (21.1% after lumpectomy alone, 8.1% with RT) was slightly greater than that seen for noninvasive recurrences (18.3% lumpectomy alone, 8.9% with RT) [70]. The 12-year overall survival rates were equivalent for both groups with only 17 patients developing regional or distant metastases. With such a low rate of metastases, no survival difference between groups would be anticipated. These results are summarized in Fig. 12.5 [70].

The EORTC 10853 trial randomized 1,010 patients with DCIS less than 5 cm in size and without evidence of Paget's disease. The DCIS was detected by mammography alone in 71% of cases, 21% had palpable masses, and the remainder nipple discharge. The mean diameter of the mammographic abnormality in both groups was 20 mm. Positive margins were present in 218 participants. Five hundred three patients were treated with excision alone and 507 had RT after excision. At 10 years follow-up, the incidence of IBTR was 26% for the excision alone group and 15% for the postoperative RT cohort, a 47% cumulative reduction of IBTR. The benefit of RT was observed in patients both older and younger than 40 years of age, for those with clinical and mammographic DCIS, and for all the histologic grades



IBTR- Ipsilateral Breast Tumor Recurrence
RT- Radiation Therapy
NSABP- National Surgical Adjuvant Breast and Bowel Project

Fig. 12.5 Rates of overall ipsilateral breast tumor recurrence (IBTR), invasive IBTR and noninvasive IBTR for excision + RT vs. excision alone for patients in national surgical adjuvant breast and bowel project (NSABP) B-17

and architectural types of DCIS. The 10-year overall survival rate was 95% in both arms [71].

The UK/ANZ trial was a randomized study whose goal was to assess the benefits of both RT and tamoxifen in the treatment of DCIS. Seventeen hundred and one patients were randomized in 2 × 2 factorial design into four subgroups: excision alone, excision and RT, excision and tamoxifen, and excision with both RT and tamoxifen. Participating centers were allowed to select which randomizations to participate in, making

interpretation of the data more difficult than in the other three studies. Patients were required to have negative margins to be entered into the study, but unlike the NSABP B-17 trial and the EORTC 10853 study, this study allowed patients with microinvasion to be randomized (3% total). The IBTR for the 522 patients who received RT was 7% compared to 16% for the 508 patients who did not, a risk reduction of 62% at a follow-up of 5 years [72].

The SweDCIS trial randomized 1,046 patients with DCIS confined to one quadrant or less of the breast to excision alone or RT after surgery. Approximately 20% of patients in both groups had positive or unknown margins. At a follow-up of 5.5 years, the IBTR was 7% for the patients randomized to postoperative RT and 22% for the surgery alone group, a hazard ratio of 0.33 [73].

In all four of the trials discussed, the proportion of recurrences, which were invasive cancers did not differ between the excision alone and the excision and RT groups. A recent meta-analysis of these four studies by Viani et al. concluded that the addition of RT to lumpectomy resulted in a 60% reduction in the risk for developing an IBTR [75]. This consistent benefit was observed in spite of differences in study design, patient populations, and surgical techniques. The use of RT did not increase the likelihood of an invasive recurrence, and a subset of patients receiving no benefit from RT could not be identified in these studies, although the magnitude of absolute benefit from RT varied with the risk of recurrence. No survival benefit was seen for RT in any of the studies, which is not surprising based on the very low death rate. A larger number of patients and much longer follow-up times would be needed to determine if any survival benefit exists. This is analogous to the situation in invasive carcinoma where individual studies demonstrated a significant reduction in the risk of IBTR when RT was added to surgery, but no survival benefit. However, the 15-year results of the Oxford Overview analysis show a statistically significant improvement in both breast cancer-specific survival and overall survival with the addition of RT to lumpectomy [76].

Many efforts have been made to define characteristics of DCIS that put patients at increased risk for IBTR, particularly invasive IBTR. Failure to obtain a negative margin has been associated with a higher rate of IBTR in most studies. Tumor touching ink is universally accepted as a positive margin, and many surgeons and radiation oncologists prefer margins greater than 2 mm. The idea of a 2 mm cutoff for a negative margin is supported by the work of Faverly et al. who found that gaps between islands of DCIS growing along the length of a duct are usually less than 1 mm [77]. Neuschatz and colleagues also found that patients with margins less than 2 mm were found to have residual DCIS about 36% of the time in subsequent reexcision specimens; those with margins greater than 2 mm infrequently had residual disease at reexcision [78]. Other studies have not confirmed the benefit of a 2 mm margin. Rodrigues et al. found the same IBTR rate for patients with negative margins, defined as greater than 2 mm, as in those with positive/close margins in 230 patients followed a mean of 8 years [79]. Nakamura et al. found a strong correlation between margin status and IBTR. They retrospectively reviewed 260 patients treated for DCIS with RT. They observed a 30% crude incidence of IBTR for margins less than 1 mm; IBTR dropped to 17% for 1–9 mm margins and to 2% when margins were greater than 10 mm [80]. Dunne et al. performed a meta-analysis of reports from both randomized trials and retrospective studies of margin width in patients with DCIS treated with RT [81]. The combined data for 5,500 patients demonstrated a lower risk of IBTR for margins 2 mm or greater, than for those less than 2 mm (hazard ratio 0.67, 95%CI 0.51–0.89; $p > 0.01$). No difference in the rate of IBTR was noted when 2 mm margins were compared to those 5 mm or greater [81]. One explanation for the difference in importance of margin width among studies is the great variability among institutions in the method of determining margin status. Direct conversation between the surgeon and pathologist is helpful in the decision process regarding the adequacy of an excision.

Patient age at the time of diagnosis is another factor that has correlated with IBTR. Younger patients consistently have higher rates of IBTR when compared to their older counterparts. In NSABP B-24, a study that looked at the efficacy of tamoxifen in addition to excision and RT for DCIS, patients in the placebo group who were less than 49 years of age had a twofold increase in IBTR compared to patients over age 50 years [70]. In the EORTC trial of RT vs. none, age less than 40 years was associated with a hazard ratio for IBTR of 1.89 [71]. Solin et al. found a local failure rate of 31% at 10 years for patients ≤39 years old; this rate decreased to 6% for patients ≥60 years [82]. The association of young age and an increased risk of IBTR is one that has

been consistently observed in both randomized and nonrandomized trials, in contrast to the variable results seen with some of the other factors discussed below.

Multiple studies have examined the histologic characteristics of DCIS to determine if any pathologic subtypes lead to an increased risk of IBTR. In the pathologic subset analysis of NSASP B-17, nine features were examined, including comedonecrosis, histologic type, margins, lymphoid infiltrate, nuclear grade, multifocality, cancerization of lobules, stroma, and tumor size. At 8 years of follow-up, only comedonecrosis had an impact on IBTR with a hazard ratio of 2.1 ($p > 0.002$). The IBTR rate was 11% for low-grade lesions without necrosis, 15% for low-grade lesions with necrosis, and 15% for high-grade lesions with necrosis in this study [83]. A similar impact of comedonecrosis on IBTR was observed in the NSABP B-24 study [84]. However, length of follow-up may have an impact on the extent to which comedonecrosis increases IBTR. In a study by Solin et al., with 5 years follow-up, patients with high-grade DCIS with comedonecrosis had an IBTR rate of 11% vs. 2% for patients who lacked both of these findings. At 10 years, however, no difference between groups was seen with a 17% incidence of IBTR for the comedonecrosis group and 15% for the noncomedonecrosis group ($p > 0.2$) [82].

Many studies have evaluated the impact of the size of the DCIS lesion on IBTR, but the findings are not consistent. DCIS presenting as a mass is associated with higher IBTR rates, a higher incidence of occult invasion and a greater likelihood of multicentricity than DCIS diagnosed on screening mammography. However, accurate determination of the size of DCIS is difficult. Macroscopic examination of the surgical specimen rarely identifies a gross tumor that can be measured, so size must be determined from the histologic sections. DCIS is often present as multiple discontinuous foci on multiple slides, so the size "measurement" is often the pathologist's best estimate. Mammography tends to underestimate the size of DCIS, so this method is not reliable either [8, 9]. More in-depth sequential specimen examination to allow a more accurate size determination has been described by Silverstein et al., but this method is not feasible in most laboratory settings [85]. Given this variability, it is not surprising that the EORTC trial found no relationship between size and IBTR [71], while the NSABP B-17 study observed significant differences in IBTR for lesions less than 5 mm in size and those between 5 mm and 1 cm in size [70].

A few studies have looked at the relationship between IBTR and common biologic markers found in DCIS. One study found an increased rate of IBTR in primary DCIS lesions lacking ER, PR, and bcl-2 expression [86]. However, a report by Cornfield et al. found no significant correlation between disease recurrence and expression of ER, PR, p53, HER-2/*neu*, Ki-67, p21, or bcl-2. Patients in this study were treated with wide local excision alone and received no postoperative RT or hormonal therapy, providing a better sense of the true prognostic significance of these markers free of potentially confounding treatment-related influences [87]. At present, validated markers predicting the behavior of DCIS remain to be identified.

12.6.3 Wide Local Excision Alone

Although RT has been shown to decrease IBTR in the four randomized studies discussed earlier, no survival benefit has been attributed to its use. RT is also expensive, time consuming, and virtually mandates mastectomy for the treatment of recurrences. Lagios was among the first to suggest that excision alone with an adequately wide margin could be sufficient treatment for small DCIS lesions, based on his work with serial sectioning of mastectomy specimens. In 1989, he reported 79 patients treated with wide local excision alone for DCIS lesions less than 25 mm. At an average follow-up of 135 months, the IBTR rate was 22% ($n > 17$); 58% ($n > 10$) of these recurrences were invasive. Despite this, there were no breast cancer-specific deaths or distant metastases in the 79 patients studied. The most significant variable associated with IBTR was margin width. In the 15 patients with margins ≥1 cm, there were only two recurrences, but in the three patients with margins ≤1 mm, all experienced recurrence [88]. Silverstein et al. reported 346 patients treated with excision alone with a 20% rate of IBTR at an average of 5 years follow-up. Again, 58% of the recurrences were invasive [89]. In a subsequent retrospective study examining the impact of margin width on IBTR, no benefit was seen for postoperative RT in 133 patients whose lesions were excised with margin widths ≥1 cm in all directions [90]. However, in this 20-year retrospective study, patients in the excision alone group were treated in a more recent time period than those receiving RT. IBTR rates in DCIS patients

treated in a more recent time period have decreased over time, even without changes in therapy. Hiramatsu et al. reported a decrease in LR rates from 12 to 2% with 6.5 years of follow-up when patients treated between 1976–1985 were compared to those treated from 1985–1995 [91]. Attempts to reproduce the findings that wide excision alone is associated with a low risk of LR based on margin width alone or the size and grade of DCIS using other retrospective data sets have been unsuccessful [92]. Studies on the treatment of DCIS with local excision alone are summarized in Table 12.3 [48, 67, 88, 89, 93–97]. In general, these studies are small, have limited follow-up, and include a highly selected patient population. Patients in most of these studies had small mammographically detected tumors of low histologic grade, making it difficult to compare these outcomes to those observed in the randomized trials of excision with and without radiation.

Although the randomized trials of RT vs. none clearly indicate a reduction in IBTR with RT [71–74], critics of these studies point to the fact that the size of the negative margin was not mandated (or measured) in these studies, postexcision mammography to document complete removal of calcifications was not employed, and the extent of pathologic tissue sampling was also not specified. Many of these concerns have been addressed by two prospective studies of the treatment of DCIS with wide excision alone. To test the hypothesis that wide excision alone with a margin of ≥1 cm was an adequate treatment regimen for small grade I/II DCIS lesions, a prospective, single-arm trial was initiated at the Dana-Farber/Harvard Cancer Center. This study initially planned to enroll 200 patients, but was stopped at 158 patients after the IBTR rate met the rules for termination of accrual. The median age of the patient population was 51 years and 94% had DCIS detected by mammography alone. The median mammographic tumor size was 0.9 cm (range, 0.1–2.5 cm). The median follow-up was 3.6 years (range, 0–6.9 years). There were 13 recurrences reported as the first site of failure between 0.6 and 5.2 years after entry into the study; nine (69%) were recurrent DCIS and four (31%) were invasive. The rate of IBTR was 2.4% per patient-year (95% CI, 1.3–4.1%) corresponding to a 5-year rate of 12%. All but one of the 13 recurrences were detected by mammography. In the four patients that developed invasive disease, none had evidence of axillary metastasis and all had tumors less than 1 cm without lymphovascular invasion. Three of the patients in this group were treated with excision/RT and one underwent mastectomy; all remain free of recurrence at a mean follow-up of 33 months (range 13–62 months). Of the nine patients who had recurrent DCIS, six were treated with excision/RT and three had mastectomy. All are free of recurrence at a mean follow-up of 30.4 months (range 10–65 months). Eight patients developed contralateral breast cancer during the follow-up period. The association of certain covariates (age, nuclear grade, necrosis, etc.) with the risk of IBTR was not formally analyzed because the study was stopped short of its accrual goal.

Table 12.3 Studies investigating the treatment of DCIS with wide excision alone

–	Year	No. of Patients	Follow-up (years)	IBTR (%) (*n*)	Recurrences invasive (%)
Carpenter [93]	1989	28	3.1[a]	18 (5)	20
Arnesson [67]	1989	38	5[b]	13 (5)	40
Lagios [88]	1990	79	11.2[a]	22 (17)	58
Schwartz [94]	1992	70	4[a]	15 (11)	27
Eusebi [48]	1994	80	17.5[a]	20 (16)	69
Kestin [95]	2000	31	7.0[b]	6 (2)	50
Silverstein [89]	2002	346	5.8[a]	18 (61)	41
Sanders [96]	2005	28	31[b]	43 (12)	92
Wong [97]	2006	158	3.6[b]	8 (13)	31

IBTR ipsilateral breast tumor recurrence
DCIS ductal carcinoma in situ
[a]Mean
[b]Median

Table 12.4 Patient characteristics in E5194: prospective trial of treatment by excision alone [98]

–	Low/intermediate-grade DCIS	High-grade DCIS
Number of patients	579	101
Median size	6 mm	7 mm
Margin ≥1 cm	46%	48%
Margin ≥5 mm	67%	75%
Tamoxifen planned	31%	31%

DCIS ductal carcinoma in situ

Based on their findings, the study authors concluded that excision with a margin of ≥1 cm without RT was not a sufficient treatment even for small, favorable DCIS lesions [97]. The first results of the multiinstitutional Intergroup E5194 trial examining wide local excision alone have also been presented. This study was open to patients with DCIS at least 3 mm in size excised to a margin of 3 mm or more. Patients with low or intermediate-grade lesions up to 2.5 cm in size were eligible while for those with high-grade lesions, defined as nuclear grade 3 with necrosis, the upper size limit was 1 cm. The protocol specified that the lumpectomy specimen be completely embedded and sequentially sectioned for the determination of tumor size and margin status. Postexcision mammography to document the complete removal of calcifications was also mandated. The characteristics of the 711 study patients with a median age of 60 years are summarized in Table 12.4 [98]. After a median follow-up of 5 years, the IBTR rate in the low/intermediate grade group was 6.8% (95% CI 4.4–9.1%), and 50% of the recurrences were invasive. In the high-grade group, the rate of IBTR was 13.7% (95% CI 6.2–21.1%), and 47% of the recurrences were invasive. The incidence of contralateral breast cancer in the low- and high-grade groups was 3.5 and 4.2%, respectively. These results confirm the findings of other studies that the treatment of high-grade DCIS with excision alone is associated with a high rate of local failure even with relatively short periods of follow-up. Although the results for the low to intermediate-grade group are more promising, as previously noted, there is a persistent risk of recurrence in this group in years 5–10 after radiation treatment, so further follow-up is needed before concluding that the risk of IBTR after excision alone is acceptable [98].

12.7 Treatment of the Axilla

DCIS is a noninvasive malignancy and by definition does not possess the ability to metastasize to regional nodes. In a National Cancer Database review of 10,946 patients with DCIS who had an axillary dissection, only 3.6% were found to have metastases [99]. These patients presumably had invasive carcinoma, which was not sampled. In mammographically detected DCIS, axillary metastases are even less frequent, and found in fewer than 2% of cases [100, 101]. By the mid-1990s, it was recognized that the morbidity of axillary dissection clearly outweighed the potential benefit of the procedure in the patient with DCIS and it was largely abandoned.

The availability of sentinel node biopsy as a lower morbidity staging technique, coupled with the observation that immunohistochemistry (IHC) allows the detection of tumor cells in lymph nodes originally classified as tumor free, has reopened the debate on axillary staging in DCIS. Klauber-Demore et al. reported that 2 of 76 patients with DCIS had axillary nodal metastases detected by hematoxylin and eosin (H & E) staining, and an additional seven had metastases detected only by IHC. Two of these patients retrospectively had invasive carcinoma identified in the DCIS lesion, and one third had a contralateral invasive breast cancer [102]. In a similar study, Pendas et al. found metastases by H & E staining in 2 of 87 women with DCIS, and an additional three had IHC detected disease [103]. These represent highly selected subsets of patients with DCIS. In contrast, Lara et al. performed a retrospective study of 102 patients with DCIS whose initial treatment included an axillary dissection. The axillary lymph nodes that were originally interpreted as negative by H & E stains were retrieved and resectioned. Micrometastases were identified in 13% ($n > 13$) of the patients by IHC. Of the 13 patients with positive lymph nodes, seven had high-grade DCIS, five had intermediate-grade DCIS, and one had low-grade DCIS. With a mean follow-up of 19 years, 85% of the patients were alive without evidence of disease, and 12% had developed disease recurrence 2–12 years after the initial diagnosis. However, none of the patients with recurrence had micrometastasis detected by IHC when the nodes were reexamined, casting doubt upon the prognostic significance of IHC-detected micrometastases in the patient with DCIS [104]. These findings do not support the routine use of IHC for the examination of lymph nodes in DCIS,

Table 12.5 Risk of axillary recurrence in DCIS

Treatment	Study	Rate/1,000 patient years
Lumpectomy	NSABP B-17	0.76
Lumpectomy + RT	NSABP B-17	0.86
Lumpectomy + RT	NSABP B-24	0.49
Lumpectomy + RT + Tamoxifen	NSABP B-24	0.46

RT radiotherapy
NSABP National Surgical Adjuvant Breast and Bowel Project
Data from Ref. [105]

Data from the NSABP B-17 and B-24 trials provides important information on the risk of axillary recurrence in an unselected patient population treated in the modern era. In the NSABP B-17 trial, 7 of 623 patients experienced axillary recurrence after 15 years of follow-up. One of these occurred in a patient who underwent an axillary dissection at presentation, and two occurred after an invasive IBTR, leaving only three failures in 620 patients with DCIS alone [105]. Axillary failures in NSABP B-24 were even less frequent, occurring in 6 of 1,799 patients, including one who was found to have undiagnosed microinvasion after 11.6 years of follow-up [105]. The rates of axillary recurrences by treatment in these studies are summarized in Table 12.5 [105] . Regardless of treatment, axillary recurrence is observed in less than 1 per 1,000 patient years of follow-up, a low rate of recurrence, which does not justify the routine performance of sentinel node biopsy in the patient with DCIS.

The selective use of sentinel node biopsy in DCIS patients at significant risk for having coexistent invasive carcinoma is appropriate. Even with the use of large gauge vacuum-assisted core biopsy, as many as 20% of those initially diagnosed as DCIS will be found to have invasive carcinoma. There is general consensus that if a mastectomy, usually performed for large areas of DCIS where the risk of sampling error is high, is undertaken, then sentinel node biopsy should be performed [29]. Gross or clinically evident DCIS and a biopsy, which is "suspicious" for microinvasion are circumstances where invasion is frequently found and sentinel node biopsy should be considered, although not all studies have identified this as a risk factor [100]. The routine use of sentinel lymph node biopsy in patients being treated with a breast conserving approach is not supported by the available data. Although sentinel node biopsy is clearly a less morbid procedure than axillary dissection, it is associated with morbidity, which is significantly more frequent than the likelihood of identifying axillary metastases. In the American College of Surgeons Oncology Group Z10 trial, 5,327 patients had sentinel node biopsy alone. Six months after surgery, 7% had lymphedema, 4% had a decreased range of motion of the involved extremity and 9% reported axillary parasthesias. A variety of minor wound complications were also noted [107].

12.8 Endocrine Therapy

The benefit of tamoxifen in reducing the risk of IBTR and new contralateral breast cancers in women with ER positive invasive carcinoma, coupled with its ability to reduce breast cancer incidence in high risk women [108, 109] suggested that it might have a beneficial role in DCIS. Two randomized prospective trials have examined the use of tamoxifen in DCIS patients, and the results of these studies are summarized in Table 12.6 [70, 72].

NSABP B-24 was a double-blind, randomized trial involving 1,804 patients treated with lumpectomy and postoperative RT and then randomly assigned to tamoxifen 20 mg daily for 5 years ($n>902$) or placebo ($n>902$). Approximately 25% of patients in both groups had positive or unknown margins of resection; 33% of patients were ≤49 years old. Tumor size, method of detection and presence of comedonecrosis was equivalent for both groups. At 7 years follow-up, the cumulative incidence of any (invasive or noninvasive) IBTR was 11.1% for patients treated with lumpectomy, radiation, and placebo; for women treated with lumpectomy, radiation, and tamoxifen, the cumulative incidence was 7.7% ($p>0.02$). The primary benefit of tamoxifen treatment was a reduction in the incidence of invasive carcinoma from 5.3 to 2.6%. No difference in the incidence of noninvasive carcinoma was seen between groups. The cumulative incidence of all contralateral breast cancers was reduced by 53% for the tamoxifen group at 7 years. The cumulative incidence of all ipsilateral and contralateral cancers was 16.9% in the placebo group and 10% in the tamoxifen group. Age at diagnosis was significantly associated with a higher incidence of IBTR and a greater absolute benefit from tamoxifen therapy. The annual rate of IBTR for women ≤49 years was 29.2 per 1,000, and for

Table 12.6 Studies examining the use of tamoxifen in the treatment of DCIS

–	Follow-up (median)	Tamoxifen	Placebo	Invasive events		Noninvasive events		All events	
–	–	–	–	TAM	Placebo	TAM	Placebo	TAM	Placebo
NSABP B-24 [70]	84 months	902 points	902 points	2.6%	5.3%	5.0%	5.8%	7.7%	11.1%
UK/ANZ [72]	52.6 months	794 points	782 points	6%	4%	7%	10%	13%	15%

NSABP National Surgical Adjuvant Breast and Bowel Project
UK/ANZ United Kingdom/Australia and New Zealand
TAM tamoxifen
DCIS ductal carcinoma in situ

women ≥50 years it was 13.3 per 1,000. The use of tamoxifen resulted in a 32.7% reduction of IBTR for women less than 50-years old; for those older than 50 years, tamoxifen reduced IBTR by 30.1%. Tamoxifen was found to reduce the risk of recurrence in patients with both positive and negative margins. However, rates were lower in the negative margin cohort (14.5/1,000/year) receiving placebo than in the positive margin cohort (16.9/1,000/year) treated with tamoxifen, indicating that tamoxifen therapy is not a substitute for a negative margin of resection. At 7 years, an overall survival of 95% was observed for both groups; of the patients who died, approximately 75% in both groups died before any breast cancer event was observed [70].

The United Kingdom, Australia and New Zealand (UK/ANZ) trial enrolled 1,701 patients in a 2×2 design. The outcome of the randomization to RT vs. no RT has been discussed in a previous section. Fifteen hundred seventy-six patients were randomly allocated to the groups for the tamoxifen comparison. Negative margins were required for inclusion into the trial and greater than 90% of patients were ≥50 years of age. With a median follow-up of 52.6 months, tamoxifen did not significantly reduce the overall event rate, nor the rate of invasive events, but reduced the rate of ipsilateral DCIS by 26% ($p > 0.08$) [72].

NSABP B-24 clearly showed a reduction in recurrence when tamoxifen was administered, but the UK/ANZ study did not concur with this finding. It is possible that the difference in age and margin status between participants in the two studies contributed to this disparity. Younger age at diagnosis is known to be a risk factor for IBTR, and less than 10% of the patients in the UK/ANZ trial were ≤50 years of age. The 2×2 factorial design of the UK/ANZ study could also have contributed to the discrepant results; only 33% of patients in the tamoxifen group received postoperative RT. Although a subgroup analysis of both groups (RT vs. no RT) showed the same pattern of results for tamoxifen [72], studies in invasive cancer examining the benefit of tamoxifen with and without RT support a synergistic effect between the treatments [110].

In both of these studies, ER status was not examined. Subsequently, Allred and colleagues reported on the effects of tamoxifen by ER status in a subset of 628 of the 1,804 patients (327 placebo and 301 tamoxifen patients) participating in the trial. ER status was determined both centrally using IHC or by reports from accruing sites. Overall, 482 patients (77%) were found to be ER-positive, and in these patients, a benefit from tamoxifen was clearly seen ($RR > 0.41$; $p > 0.0002$). Significant reductions in the incidence of both the ipsilateral and contralateral cancers were observed. In women with ER-negative DCIS, little benefit was seen from tamoxifen ($RR > 0.80$; $p > 0.51$). These findings are consistent with a large body of literature indicating that the benefits of tamoxifen are confined to women with ER-positive invasive breast cancer and indicate that ER expression is an important predictor of response to tamoxifen in DCIS [111]. However, serious side effects have been reported from the use of tamoxifen, with an increased risk of endometrial cancer, stroke, deep venous thrombosis and pulmonary embolism reported in postmenopausal patients [70, 112]. A careful selection of patients who are most likely to have a favorable risk/benefit ratio is important when making treatment recommendations for DCIS patients, particularly because no survival benefit has been attributed to the use of tamoxifen in this setting.

Studies comparing the use of aromatase inhibitors (AI) to tamoxifen in postmenopausal women with invasive breast cancer demonstrated superiority of the AIs in lowering recurrence rates and reducing the

incidence of contralateral breast cancers when compared to tamoxifen [113–115]. Two studies are currently underway to investigate the use of AIs in DCIS. The first of these is NSABP B-35, a clinical trial comparing anastrozole with tamoxifen in postmenopausal patients with ER-positive DCIS treated with lumpectomy and RT. This trial opened in January 2003 and completed accrual of 3,000 patients in June 2006 [116]. The second trial is the International Breast Cancer Intervention Study (IBIS-II), a randomized, double-blind study to determine whether tamoxifen or anastrozole is more effective in preventing local recurrences and contralateral breast cancers in patients with DCIS. Patients are randomized to 20 mg of tamoxifen or 1 mg of anastrozole daily for 5 years. This study opened in May 2003 and hopes to accrue 4,000 patients through multiple European sites [117]. Preliminary results are not yet available from either of these studies.

12.9 Treatment Selection

The initial step in treatment selection is to determine, on the basis of history and physical examination, imaging, and pathologic findings, whether the patient is a candidate for a breast-conserving approach. If so, the risks and benefits and what is entailed in breast conservation with or without radiation, as well as mastectomy (including reconstruction), should be described in detail. The risk of local recurrence, particularly an invasive recurrence, is a major focus of this discussion because regardless of the type of local therapy selected, the risk of breast cancer-specific mortality is extremely low. Guidelines for the selection of local therapy in DCIS have been developed by a joint committee of the American College of Surgeons, American College of Radiology, and the College of American Pathologists [29]. Absolute indications for mastectomy include multicentric DCIS or diffuse, malignant-appearing microcalcifications covering an area too large to encompass with a cosmetic resection [69]. The persistence of tumor at resection margins after a reasonable number of surgical attempts is also an indication for mastectomy. Although DCIS lesions are not clinically detectable, they may be quite large. Morrow et al. found that contraindications to breast-conserving surgery were present in 33% of patients with DCIS compared with only 10% of patients with stage I invasive carcinoma. Extensive disease that could not be encompassed with a cosmetic resection was the major contraindication to BCT in those with DCIS [118]. Most patients who require mastectomy can be identified before surgery with a careful imaging evaluation with diagnostic mammography. As discussed in the section on Presentation, at present, MRI cannot be considered part of the routine preoperative evaluation of the woman with DCIS. In patients who appear to have localized DCIS suitable for treatment with a breast-conserving approach, mammographically occult DCIS extensive enough to require mastectomy is uncommon. Some studies have suggested that micropapillary DCIS and DCIS presenting as pathologic nipple discharge are more likely to be extensive in the breast than other histologic subtypes or presentations [119, 120]. Although these findings do not represent a contraindication to breast conservation in patients who are otherwise suitable candidates, they should be considered when discussing the possibility of additional surgery if lumpectomy is attempted.

For the woman who appears to have mammographically localized DCIS and is a candidate for breast conservation, a decision regarding the magnitude of benefit that will be obtained from RT cannot be made until the lesion has been excised and a pathology report is available. To facilitate decision making, a detailed pathologic evaluation is necessary. The evaluation should include inking of the specimen and measurement of both specimen and tumor size before sectioning. Because accurate measurement of microscopic DCIS is often difficult, reporting the number of blocks in which DCIS is present, as well as its largest single extent in any one slide, is often useful. The correlation of microcalcifications with DCIS (i.e., whether DCIS is present only in areas of calcifications or in calcifications and adjacent breast tissue) as well as the margin status should be noted. If margins are involved, the extent of involvement should be stated; when margins are negative, proximity of the lesion to the margin should be noted. As discussed previously, four prospective, randomized trials have demonstrated that in women with DCIS, the use of postoperative RT reduces the risk of recurrence compared with treatment by excision alone, by 50–60% [71–74]. These trials have identified young patient age (≤40 years) and, to a lesser extent, clinical presentations of DCIS, and the presence of comedonecrosis as factors predictive of higher rates of IBTR that are useful for identifying patient

groups likely to achieve that greatest absolute benefit from RT. Evidence from the NSABP B-24 trail indicates that tamoxifen is beneficial in women with ER-positive DCIS [106, 111]. This is consistent with a large body of data on the effect of tamoxifen in invasive cancer. We routinely determine ER status by IHC for all DCIS and the use of tamoxifen is limited to women with ER expression. The most favorable risk-benefit ratio for tamoxifen use is in premenopausal women with two breasts at risk, and the combination of tamoxifen and RT maximally reduces the risk of ipsilateral IBTR [110]. Tamoxifen is an option, but not a necessity, for the treatment of DCIS, which should be discussed with women with ER-positive disease who do not have contraindications to the drug. For patients with ER-positive DCIS, the combined effects of tamoxifen and breast RT reduced the risk of invasive recurrence by approximately 81% [110]. In spite of this, an examination of tamoxifen usage among 1,622 patients treated for unilateral DCIS at eight National Comprehensive Cancer Network Centers between 1997 and 2003 demonstrated that only 41% received tamoxifen. Factors significantly associated with receipt of tamoxifen included diagnosis after July 1999, BCT in patients under age 70 years, receipt of RT, prior hysterectomy and no history of vascular disease. The use of tamoxifen in patients undergoing BCT varied from 34 to 74% between centers [121].

In light of these findings, we approach patients before surgery with the assumption that breast irradiation will be a part of their treatment if they choose BCT. Contraindications to RT, as for invasive cancer, include prior therapeutic irradiation to the ipsilateral breast, diagnosis early in pregnancy and active scleroderma or systemic lupus erthyematosus. Large areas of DCIS that cannot be excised to clearly negative margins with an acceptable cosmetic outcome should prompt a discussion of mastectomy. An adequate excision is of particular concern in patients younger than 40 years of age with high-grade ER-negative DCIS because of their higher baseline risk of recurrence and lack of benefit from tamoxifen. In patients who are candidates for breast irradiation, the final decision about the risks and benefits of RT and tamoxifen in an individual case is made when the final pathology report is available. Although it is clear that there are some patients who receive a small absolute benefit from either irradiation or tamoxifen, the final decision regarding the use of RT and tamoxifen is heavily influenced by the patient's perception of what level of benefit is meaningful to her. The ability to treat IBTR with further breast preservation using reexcision and RT is one of the potential benefits of initial treatment with excision alone. However, IBTR is psychologically traumatic, and only 44% of patients who had a recurrence after initial treatment by excision alone in the NSABP B-17 trial chose breast-conserving surgery again [74]. Furthermore, approximately 50% of recurrences are invasive and carry a risk of distant metastasis.

What constitutes an adequate negative margin for breast-conserving surgery has been the source of much debate. As previously discussed, convincing data to support a reduction in the rate of IBTR when negative margins of more than 1–2 mm are obtained is lacking. In light of this, we do not believe that a single margin width is appropriate for all patients. Factors to consider when making a decision regarding the need for reexcision include the amount of DCIS close to the margin, which margin is close or involved, and the findings on postoperative mammography. Extensive DCIS is clearly of more concern than a single duct that is separate from the main area of DCIS. "Close" margins on the anterior and posterior specimen surfaces are of no concern if there is no residual breast tissue in these areas. Those within the parenchyma (i.e., medial, lateral, superior, inferior) have the potential for more disease to be present. The presence of residual calcifications and close margins mandate reexcision. Other factors, such as patient age, that influence the risk of recurrence should also be considered. In general, margins 1 mm or less warrant reexcision, although if this would necessitate mastectomy or sacrifice of the nipple-areolar complex, the decision is made on case-by-case basis. There is uncertainty regarding the number of reexcisions, which should be performed in an effort to obtain negative margins for BCT. In a study of 2,770 patients, 13% with DCIS, treated between 1981 and 2006, the risk of IBTR based on the number of surgical excisions required to obtain negative margins was examined. At a median follow-up of 73 months, the actuarial rates of IBTR at 5 and 10 years were 2.5 and 5.0% in patients undergoing a single excision and 4.9 and 5.6% for those having two or more reexcisions ($p > 0.02$). In multivariate analysis, the number of reexcisions was not a significant predictor of IBTR. However, patients with a histologic diagnosis of DCIS were more likely to require reexcision than those with a diagnosis of invasive carcinoma [122].

The use of sentinel node biopsy is reserved for patients undergoing mastectomy. If a presurgical diagnosis of DCIS is made by percutaneous core needle biopsy, invasive carcinoma is found in approximately 20% of cases at the time of surgical excision [33–36]. As discussed previously, invasion is more frequent in large areas of DCIS, and the performance of a mastectomy precludes subsequent sentinel node biopsy. In patients undergoing breast conservation, sentinel node biopsy can be selectively applied to the subset of women found to have invasive carcinoma after surgical excision.

The available data suggest that patient knowledge of the risks and benefits of local therapy options is low, and patient participation in the decision-making process is limited. Katz et al. performed a population-based survey of 1,884 women diagnosed with DCIS or invasive carcinoma in 2002. The mastectomy rate was 30% and did not vary between women diagnosed with invasive carcinoma or DCIS. Greater patient involvement in the decision-making process was significantly correlated with the receipt of mastectomy; only 5% of White women who stated that their surgeon made the surgical decision received mastectomy compared to 17% of women who shared the decision with their surgeon and 27% of women who stated that they made the treatment decision ($p<0.001$) [123]. In a study limited to the 659 women with DCIS, those with high-grade lesions greater than 2 cm in size were most likely to undergo mastectomy (53%), although mastectomy was recommended in only 28% of this group. Patient concerns about the receipt of radiation and about recurrence were strongly correlated with mastectomy [124].

12.10 Follow-Up

Follow-up care for patients treated for DCIS should be performed at regular intervals by physicians experienced in the management of DCIS. The goals of follow-up are the prompt detection of IBTR or new cancers and the identification of sequale, which may be attributed to the treatment of the original DCIS lesion, with intervention provided as needed. There is no role for routine imaging studies or laboratory testing to screen for metastatic disease in the asymptomatic patient with an initial diagnosis of DCIS.

As discussed in the section on treatment, approximately 50% of recurrences after breast conservation with or without RT are invasive and 50% are recurrent DCIS. Prognosis is better for subclinical recurrences, which are more likely to be DCIS [125]. Follow-up is accomplished through routine history and physical exam, and mammography. History and physical exam is usually performed every 6 months for years 1–5 and then yearly thereafter; follow-up visits may be rotated among different members of the treatment team. Patients need to be evaluated with a complete breast exam at each visit to assess for new masses, retractions or other changes that can be suggestive of IBTR. Cosmetic outcome of BCT as well as changes related to the use of RT should also be evaluated. In some cases, physical exam can be the first indicator of IBTR even before mammographic changes are evident [126]. In patients treated by mastectomy, the chest wall and/or skin flaps if a reconstruction was performed or need to be examined. Routine mammography of the reconstructed breast is not indicated, so physical exam is the primary method of detecting recurrence.

Annual mammography is a critical part of the follow-up of the DCIS patient. In some cases, a posttreatment baseline mammogram of the affected breast performed within the first year after treatment is useful to document the changes from surgery and radiation at a time when concerns about IBTR are low. Scar formation, seroma, hematoma, and contour deformity are often found after treatment [127]. Although scar tissue at the surgical site is a common finding, one series found an identifiable scar present in only 25% of patients undergoing mammography after BCT [128]. Skin thickening is another common finding, particularly in patients treated with RT. This thickening is best appreciated by comparison to the contralateral breast and often subsides with time. Postsurgical and radiation-induced changes are most pronounced 6–12 months after treatment and often resolve within 1–3 years [129]. Calcifications due to fat necrosis are also common in the irradiated breast. These calcifications usually appear 2–5 years after initial treatment and tend to be coarse and round with radiolucent centers. Additional magnification and spot compression views can be used to better visualize the surgical site and any other areas of concern [127].

The mammographic findings of a recurrence have the typical appearance of a malignant tumor superimposed upon the postsurgical changes of the treated breast. Dershaw et al. examined 29 recurrences after BCT detected by mammography and found that 19 were

detected because of calcification, nine due to a mass without calcifications, and one patient had both a mass and calcifications. However, a palpable mass or new mammographic finding is not invariably associated with a recurrence [130]. Benign processes such as fat necrosis, fibrosis, and inflammation secondary to RT can cause these findings. Stereotactic biopsy techniques are useful in differentiating these benign entities from recurrent tumor and are the preferred method of diagnosing mammographic abnormalities as in the untreated breast.

Mammography should be performed yearly after the first baseline mammogram as a bilateral exam (in the patient with two breasts) according to the guidelines of the American Cancer Society and the American College of Radiology. The current American Cancer Society guidelines for screening with MRI state that there is insufficient evidence to recommend follow-up MRIs in women with a diagnosis of DCIS unless they have other risk factors such as known or suspected BRCA mutation [131].

Follow-up is also directed at screening for any sequale of treatment. In patients taking tamoxifen, a history of spotting or bleeding should be sought and an annual pelvic exam performed. Because the risk of breast cancer mortality after an initial diagnosis of DCIS is extremely low, patients should be encouraged to attend to other preventative health measures, such as screening colonoscopy, smoking cessation, and cholesterol maintenance.

12.11 Treatment of Recurrence

The goal of follow-up in patients treated for DCIS is to detect and treat locoregional recurrences as early as possible. In patients treated with a breast conserving approach with or without RT, approximately half of all recurrences are invasive, even in those who adhere to recommended guidelines for follow-up. In 1–4% of patients who recur postmastectomy, recurrences are almost always invasive [66, 68, 132, 133].

The outcome of salvage treatment for recurrence after BCT is a major determinant of the appropriateness of this treatment approach in the patient with DCIS. Solin et al. reported 90 patients initially treated with BCT with RT who experienced an IBTR. Five of these patients presented with local-regional disease. The histology at the time of IBTR was invasive carcinoma in 53 patients (59%), DCIS in 34 patients (38%), angiosarcoma in one patient (1%) and unknown for two patients (2%). The median interval from initial treatment to local or local-regional failure was 4.7 years. Mastectomy was used as salvage treatment in 76 (84%) of patients; nine patients (10%) were treated with repeat wide local excision. Axillary nodes were evaluated at the time of salvage surgery in 45 patients (50%), and five of the 45 patients had one or more positive nodes. Adjuvant systemic therapy (chemotherapy, hormones, or both) was given to 27 patients (30%). With a mean follow-up of 5.8 years, the 10-year rates of overall survival, cause-specific survival, and freedom from distant metastases after salvage treatment were 83, 95, and 91%, respectively. Adverse prognostic factors for the development of subsequent distant metastases after salvage treatment were invasive histology of the IBTR and positive axillary lymph nodes [134]. Graham and colleagues reported 14 patients who developed IBTR after initially being treated with wide local excision alone; 50% of these recurrences were invasive. Salvage treatment consisted of mastectomy for 4 (29%) patients, reexcision plus RT for 6 (43%) patients, reexcision alone for 2 (14%) patients, and RT alone for the remaining 2 (14%) patients. Of the 14 patients included in this report, only 1 (7%) developed distant metastases after salvage treatment [135]. These reports suggest that recurrences in patients initially treated for DCIS can be salvaged with continued high rates of overall survival as well as freedom from distant metastases.

Although mastectomy is considered the standard of care for salvage treatment when recurrences occur after initial BCT with RT, outcomes of further BCT, usually in patients not initially receiving RT, have been reported. The largest experience comes from the NSABP B-17 trial. One hundred four patients whose primary DCIS was treated by lumpectomy alone subsequently developed an IBTR. Fifty-four (51.9%) were treated with a second lumpectomy. Of these, 14 (26%) received postoperative RT. The proportion of patients with an invasive and a DCIS IBTR receiving a second lumpectomy was approximately equal. Three of the 54 patients who underwent a second lumpectomy developed a second IBTR; all were in the group of patients whose first IBTR was DCIS. One of these patients developed distant disease and was still alive at the time of the report. It was not reported whether or not these three patients were in the group of patients who

received RT after their second lumpectomy. Eighteen of 47 IBTRs that occurred in patients treated initially with lumpectomy and RT were treated by a second lumpectomy; 50% of patients whose IBTR was DCIS (15 of 30) in this group received a second lumpectomy; second lumpectomy was used for only 3 of 17 patients with an invasive recurrence. Four patients (27%) with a noninvasive IBTR developed a second IBTR after second lumpectomy; none of the three patients with invasive recurrences developed a second IBTR [74].

The outcomes of reirradiation after a repeat lumpectomy for IBTR are derived from the limited use of this technique in invasive disease. Deutsch et al. reported 39 patients treated with excision of the IBTR and postoperative RT after a previous lumpectomy and whole breast RT. Eight of these women were initially treated for DCIS. With a median follow-up of 51.5 months, eight patients (20.5%) developed a second IBTR and four of these women also developed distant metastases. An additional four women also developed distant metastases without evidence of a second IBTR. The repeat course of RT to the operative area was well tolerated in all patients, and no late sequelae occurred other than skin pigmentation changes [136]. Although further recurrences appear to be more common when further BCT is employed for salvage therapy, the rates are low enough to consider this as an acceptable treatment for selected patients who did not receive RT as part of their initial treatment. In patients who received prior RT, mastectomy remains the standard treatment for invasive recurrence while excision alone may be considered for highly selected DCIS recurrences, which are low grade, small in size, and occur in older women.

Although mastectomy is a highly effective treatment for DCIS, it does not completely eliminate the risk of chest wall recurrence, with recurrence rates of 1–4% [66, 68, 132, 133] seen in most series. Recurrence may be due to de novo DCIS or invasive cancer arising from residual breast tissue, incomplete surgical excision of DCIS, or occult invasive disease. The largest reported series on the management of chest wall recurrences after mastectomy for DCIS reviewed the presentation and treatment of ten patients who experienced a chest wall recurrence after initial treatment for DCIS. The average time to recurrence was 5.4 years. Six patients presented with pure DCIS, three with DCIS and microinvasion and one patient with possible microinvasion as the histology of the IBTR. All patients were treated with RT following local excision of the LR. With an average of 5 years follow-up after IBTR, nine of these patients were alive with no evidence of disease; one patient died with metastatic disease 2 years after the IBTR. This report found that young patient age, multiquadrant disease, and the presence of residual normal breast tissue were common features among these chest wall recurrences [137].

Although recurrence is more common in patients treated with BCT for DCIS than those initially treated with mastectomy, salvage therapy is highly effective. Lee et al. examined a group of 150 DCIS patients with IBTR; 87 of the recurrences were DCIS and 63 were invasive. These recurrences occurred in a group of 1,236 patients treated for DCIS; 430 patients with mastectomy, 310 with excision and RT and 496 with excision alone. With a median follow-up of 72 months, the probability of developing distant disease or the rate of breast cancer-specific mortality was not significantly higher for the group of patients with an IBTR compared to those without [138]. While this is reassuring, it is clear from the Oxford Overview Analysis that failure to maintain local control is associated with an increased risk of breast cancer death [76]. The demonstration of a mortality effect for IBTR in DCIS will require a metaanalysis of a large number of patients with a prolonged period of follow-up as was the case for studies of lumpectomy with and without RT in invasive cancer.

Management of the axilla after IBTR should parallel management strategies in the primary treatment setting (discussed in detail in the section on Treatment of the Axilla). If the recurrence is DCIS, sentinel node biopsy is indicated if a mastectomy is performed. If a prior sentinel node biopsy was done, repeat lymphatic mapping can be attempted, but axillary dissection is not indicated in the absence of histologic documentation of invasive carcinoma. In the patient with an invasive recurrence, axillary staging is necessary and sentinel node biopsy is the preferred technique if not performed at the time of initial diagnosis. Several studies have reported successful repeat lymphatic mapping and sentinel node biopsy, although with a lower sentinel node identification rate than when the procedure is performed for the first time [139–142]. The likelihood of success decreases significantly as the number of lymph nodes removed in the initial procedure increases [139, 143]. However, these studies did not perform completion axillary dissection to determine the accuracy of re-do sentinel node biopsy and lack sufficient numbers of patients and duration of follow-up to

clearly establish the safety of this approach. In the patient with an invasive recurrence where the axillary nodal status will be the major determinant of the need for systemic therapy, axillary dissection remains standard management.

12.12 Conclusion

DCIS is a heterogenous lesion of the breast whose natural history is not entirely understood. Treatment decisions should be based on information obtained through clinical evaluation, mammography, and pathologic sampling. Current data suggest that breast-conserving surgery and RT is appropriate for the majority of women with DCIS. A better understanding of the molecular profile of DCIS may help to refine indications for RT and to identify women at high risk of local recurrence after RT who might benefit from initial treatment with mastectomy. At present, mastectomy is reserved for cases where the disease cannot be encompassed by a cosmetic resection or it is preferred by the patient. Patients who undergo mastectomy for DCIS should be offered evaluation by a plastic surgeon preoperatively to discuss reconstructive options. Local excision without RT may be used with caution in selected patients, although reproducible characteristics of patients who are good candidates for this option remain to be defined.

References

1. Ernster VL, Barclay J, Kerlikowske K et al (1996) Incidence of and treatment for ductal carcinoma in situ of the breast. JAMA. 275:913–8
2. Ernster VL, Ballard-Barbash R, Barlow WE et al (2002) Detection of ductal carcinoma in situ in women undergoing screening mammography. J Natl Cancer Inst. 94:1546–54
3. Li CI, Daling JR, Malone KE (2005) Age-specific incidence rates of in situ breast carcinomas by histologic type, 1980 to 2001. Cancer Epidemiol Biomark Prev. 14:1008–11
4. Li CI, Malone KE, Saltzman BS et al (2006) Risk of invasive breast carcinoma among women diagnosed with ductal carcinoma in situ and lobular carcinoma in situ, 1988–2001. Cancer. 106:2104–12
5. Rosner D, Bedwani RN, Vana J et al (1980) Noninvasive breast carcinoma: results of a National Survey by the American College of Surgeons. Ann Surg. 192:139–47
6. Goedde TA, Frykberg ER, Crump JM et al (1992) The impact of mammography on breast biopsy. Am Surg. 58: 661–6
7. Ikeda DM, Andersson I (1989) Ductal carcinoma in situ: atypical mammographic appearances. Radiology. 172:661–6
8. Holland R, Hendriks JH (1994) Microcalcifications associated with ductal carcinoma in situ: mammographic-pathologic correlation. Semin Diagn Pathol. 11:181–92
9. Stomper PC, Connolly JL (1992) Ductal carcinoma in situ of the breast: correlation between mammographic calcification and tumor subtype. AJR Am J Roentgenol. 159:483–5
10. Holland R, Hendriks JH, Vebeek AL et al (1990) Extent, distribution and mammographic/histological correlations of breast ductal carcinoma in situ. Lancet. 335:519–22
11. Evans A (2003) The diagnosis and management of pre-invasive breast disease: radiological diagnosis. Breast Cancer Res. 5:250–3
12. Gilles R, Guinebretiere JM, Lucidarme O et al (1994) Nonpalpable breast tumors: diagnosis with contrast-enhanced subtraction dynamic MR imaging. Radiology. 191:625–31
13. Orel SG, Schnall MD, Powell CM et al (1995) Staging of suspected breast cancer: effect of mr imaging and MR-guided biopsy. Radiology. 196:115–22
14. Boetes C, Mus RD, Holland R et al (1995) Breast tumors: comparative accuracy of MR imaging relative to mammography and US for demonstrating extent. Radiology. 197:743–7
15. Fobben ES, Rubin CZ, Kalisher L et al (1995) Breast MR imaging with commercially available techniques: radiologic-pathologic correlation. Radiology. 196:143–52
16. Bluemke DA, Gatsonis CA, Chen MH et al (2004) Magnetic resonance imaging of the breast prior to biopsy. JAMA. 292:2735–42
17. Kriege M, Brekelmans CT, Boetes C et al (2004) Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med. 351:427–37
18. Kuhl CK, Schrading S, Bieling HB et al (2007) MRI for diagnosis of pure ductal carcinoma in situ: a prospective observational study. Lancet. 370:485–92
19. Menell JH, Morris EA, Dershaw DD et al (2005) Determination of the presence and extent of pure ductal carcinoma in situ by mammography and magnetic resonance imaging. Breast J. 11:382–90
20. Gilles R, Zafrani B, Guinebretiere JM et al (1995) Ductal carcinoma in situ: MR imaging-histopathologic correlation. Radiology. 196:415–9
21. Schouten van der Velden AP, Boetes C, Bult P et al (2006) The value of magnetic resonance imaging in diagnosis and size assessment of in situ and small invasive breast carcinoma. Am J Surg. 192:172–8
22. Esserman LJ, Kumar AS, Herrera AF et al (2006) Magnetic resonance imaging captures the biology of ductal carcinoma in situ. J Clin Oncol. 24:4603–10
23. Solin LJ, Orel SG, Hwang WT et al (2008) Relationship of breast magnetic resonance imaging to outcome after breast-conservation treatment with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ. J Clin Oncol. 26:386–91
24. Jackman RJ, Nowels KW, Rodriguez-Soto J et al (1999) Stereotactic, automated, large-core needle biopsy of nonpalpable breast lesions: false-negative and histologic underestimation rates after long-term follow-up. Radiology. 210: 799–805

25. Groenewoud JH, Pijnappel RM, van den Akker-Van Marle ME et al (2004) Cost-effectiveness of stereotactic large-core needle biopsy for nonpalpable breast lesions compared to open-breast biopsy. Br J Cancer. 90:383–92
26. Gundry KR, Berg WA (1998) Treatment issues and core needle breast biopsy: clinical context. AJR Am J Roentgenol. 171:41–9
27. Pfarl G, Helbich TH, Riedl CC et al (2002) Stereotactic 11-gauge vacuum-assisted breast biopsy: a validation study. AJR Am J Roentgenol. 179:1503–7
28. Golub RM, Bennett CL, Stinson T et al (2004) Cost minimization study of image-guided core biopsy versus surgical excisional biopsy for women with abnormal mammograms. J Clin Oncol. 22:2430–7
29. Morrow M, Harris JR (2007) Practice guideline for the management of ductal carcinoma in-situ of the breast (dcis). J Am Coll Surg. 205:145–61
30. Bassett L, Winchester DP, Caplan RB et al (1997) Stereotactic core-needle biopsy of the breast: a report of the joint task force of the American college of radiology, American college of surgeons and college of American pathologists. CA Cancer J Clin. 47:171–90
31. Melotti MK, Berg WA (2000) Core needle breast biopsy in patients undergoing anticoagulation therapy: preliminary results. AJR Am J Roentgenol. 174:245–9
32. Sakorafas GH, Tsiotou AG (2000) Ductal carcinoma in situ (dcis) of the breast: evolving perspectives. Cancer Treat Rev. 26:103–25
33. Burbank F (1997) Stereotactic breast biopsy of atypical ductal hyperplasia and ductal carcinoma in situ lesions: improved accuracy with directional, vacuum-assisted biopsy. Radiology. 202:843–7
34. Mendez I, Andreu FJ, Saez E et al (2001) Ductal carcinoma in situ and atypical ductal hyperplasia of the breast diagnosed at stereotactic core biopsy. Breast J. 7:14–8
35. Lee CH, Carter D, Philpotts LE et al (2000) Ductal carcinoma in situ diagnosed with stereotactic core needle biopsy: can invasion be predicted? Radiology. 217:466–70
36. Liberman L, Dershaw DD, Rosen PP et al (1995) Stereotaxic core biopsy of breast carcinoma: accuracy at predicting invasion. Radiology. 194:379–81
37. Tavassoli F, Devilee P (2003) World health organization: tumors of the breast and female genital organs. IARC, Lyon, France, p 67
38. Rosen PP (1997) Intraductal carcinoma; breast pathology. Lippincott-Raven, Philadelphia, pp 227–73
39. Schwartz GF, Lagios MD, Carter D et al (1997) Consensus conference on the classification of ductal carcinoma in situ. Hum Pathol. 28:1221–5
40. Silverstein MJ, Poller DN, Waisman JR et al (1995) Prognostic classification of breast ductal carcinoma-in-situ. Lancet. 345:1154–7
41. Porter DA, Krop IE, Nasser S et al (2001) A sage (serial analysis of gene expression) view of breast tumor progression. Cancer Res. 61:5697–702
42. Porter D, Lahti-Domenici J, Keshaviah A et al (2003) Molecular markers in ductal carcinoma in situ of the breast. Mol Cancer Res. 1:362–75
43. Ma XJ, Salunga R, Tuggle JT et al (2003) Gene expression profiles of human breast cancer progression. Proc Natl Acad Sci USA. 100:5974–9
44. Burstein HJ, Polyak K, Wong JS et al (2004) Ductal carcinoma in situ of the breast. N Engl J Med. 350:1430–41
45. Page DL, Dupont WD, Rogers LW et al (1982) Intraductal carcinoma of the breast: follow-up after biopsy only. Cancer. 49:751–8
46. Page DL, Dupont WD, Rogers LW et al (1995) Continued local recurrence of carcinoma 15–25 years after a diagnosis of low-grade ductal carcinoma in situ of the breast treated only by biopsy. Cancer. 76:1197–200
47. Rosen PP, Braun DW Jr, Kinne DE (1980) The clinical significance of pre-invasive breast carcinoma. Cancer. 46:919–25
48. Eusebi V, Feudale E, Foschini MP et al (1994) Long-term follow-up of in situ carcinoma of the breast. Semin Diagn Pathol. 11:223–35
49. Bartow SA, Pathak DR, Black WC et al (1987) Prevalence of benign, atypical and malignant breast lesions in populations at different risk for breast cancer. A forensic autopsy study. Cancer. 60:2751–60
50. Alpers CE, Wellings SR (1985) The prevalence of carcinoma in situ in normal and cancer-associated breasts. Hum Pathol. 16:796–807
51. Bhathal PS, Brown RW, Lesueur GC et al (1985) Frequency of benign and malignant breast lesions in 207 consecutive autopsies in Australian women. Br J Cancer. 51:271–8
52. Kramer WM, Rush BF Jr (1973) Mammary duct proliferation in the elderly. A histopathologic study. Cancer. 31: 130–7
53. Nielsen M, Thomsen JL, Primdahl S et al (1987) Breast cancer and atypia among young and middle-aged women: a study of 110 medicolegal autopsies. Br J Cancer. 56:814–9
54. Kauff ND, Brogi E, Scheuer L et al (2003) Epithelial lesions in prophylactic mastectomy specimens from women with BRCA mutations. Cancer. 97:1601–8
55. Hoogerbrugge N, Bult P, de Widt-Levert LM et al (2003) High prevalence of premalignant lesions in prophylactically removed breasts from women at hereditary risk for breast cancer. J Clin Oncol. 21:41–5
56. Gapstur SM, Morrow M, Sellers TA (1999) Hormone replacement therapy and risk of breast cancer with a favorable histology: results of the Iowa women's health study. JAMA. 281:2091–7
57. Kerlikowske K, Barclay J, Grady D et al (1997) Comparison of risk factors for ductal carcinoma in situ and invasive breast cancer. J Natl Cancer Inst. 89:76–82
58. Claus EB, Stowe M, Carter D (2001) Breast carcinoma in situ: risk factors and screening patterns. J Natl Cancer Inst. 93:1811–7
59. Warnberg F, Nordgren H, Bergkvist L et al (2001) Tumor markers in breast carcinoma correlate with grade rather than with invasiveness. Br J Cancer. 85:869–74
60. Zhuang Z, Merino MJ, Chuaqui R et al (1995) Identical allelic loss on chromosome 11q13 in microdissected in situ and invasive human breast cancer. Cancer Res. 55:467–71
61. O'Sullivan MJ, Morrow M (2007) Ductal carcinoma in situ–current management. Surg Clin North Am. 2007;87:333–51, viii
62. Haagensen C (1971) Diseases of the breast., 2nd edn. WB Saunders, Philadelphia
63. Kinne DW, Petrek JA, Osborne MP et al (1989) Breast carcinoma in situ. Arch Surg. 124:33–6

64. Jha MK, Avlonitis VS, Griffith CD et al (2001) Aggressive local treatment for screen-detected DCIS results in very low rates of recurrence. Eur J Surg Oncol. 27:454–8
65. Ward BA, McKhann CF, Ravikumar TS (1992) Ten-year follow-up of breast carcinoma in situ in Connecticut. Arch Surg. 127:1392–5
66. Silverstein MJ, Barth A, Poller DN et al (1995) Ten-year results comparing mastectomy to excision and radiation therapy for ductal carcinoma in situ of the breast. Eur J Cancer. 31A:1425–7
67. Arnesson LG, Smeds S, Fagerberg G et al (1989) Follow-up of two treatment modalities for ductal cancer in situ of the breast. Br J Surg. 76:672–5
68. Warneke J, Grossklaus D, Davis J et al (1995) Influence of local treatment on the recurrence rate of ductal carcinoma in situ. J Am Coll Surg. 180:683–8
69. Morrow M, Strom EA, Bassett LW et al (2002) Standard for the management of ductal carcinoma in situ of the breast (DCIS). CA Cancer J Clin. 52:256–76
70. Fisher B, Land S, Mamounas E et al (2001) Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the national surgical adjuvant breast and bowel project experience. Semin Oncol. 28:400–18
71. Bijker N, Meijnen P, Peterse JL et al (2006) Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European organization for research and treatment of cancer randomized phase iii trial 10853–a study by the EORTC breast cancer cooperative group and EORTC radiotherapy group. J Clin Oncol. 24:3381–7
72. Houghton J, George WD, Cuzick J et al (2003) Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomized controlled trial. Lancet. 362:95–102
73. Emdin SO, Granstrand B, Ringberg A et al (2006) Swedcis: radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomized trial in a population offered mammography screening. Acta Oncol. 45: 536–43
74. Fisher B, Dignam J, Wolmark N et al (1998) Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from national surgical adjuvant breast and bowel project b-17. J Clin Oncol. 16:441–52
75. Viani GA, Stefano EJ, Afonso SL et al (2007) Breast-conserving surgery with or without radiotherapy in women with ductal carcinoma in situ: a meta-analysis of randomized trials. Radiat Oncol. 2:28
76. Clarke M, Collins R, Darby S et al (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Lancet. 366:2087–106
77. Faverly DR, Burgers L, Bult P et al (1994) Three-dimensional imaging of mammary ductal carcinoma in situ: clinical implications. Semin Diagn Pathol. 11:193–8
78. Neuschatz AC, DiPetrillo T, Steinhoff M et al (2002) The value of breast lumpectomy margin assessment as a predictor of residual tumor burden in ductal carcinoma in situ of the breast. Cancer. 94:1917–24
79. Rodrigues N, Carter D, Dillon D et al (2002) Correlation of clinical and pathologic features with outcome in patients with ductal carcinoma in situ of the breast treated with breast-conserving surgery and radiotherapy. Int J Radiat Oncol Biol Phys. 54:1331–5
80. Nakamura S, Woo C, Silberman H et al (2002) Breast-conserving therapy for ductal carcinoma in situ: a 20-year experience with excision plus radiation therapy. Am J Surg. 184:403–9
81. Dunne C, Burke JP, Morrow M (2009) et al The effect of margin status on the local recurrence following breast conservation and radiation therapy for DCIS. J Clin Oncol. 27:1615–20
82. Solin LJ, Fourquet A, Vicini FA et al (2001) Mammographically detected ductal carcinoma in situ of the breast treated with breast-conserving surgery and definitive breast irradiation: long-term outcome and prognostic significance of patient age and margin status. Int J Radiat Oncol Biol Phys. 50:991–1002
83. Fisher ER, Dignam J, Tan-Chiu E et al (1999) Pathologic findings from the national surgical adjuvant breast project (nsabp) eight-year update of protocol b-17: intraductal carcinoma. Cancer. 86:429–38
84. Fisher ER, Land SR, Saad RS et al (2007) Pathologic variables predictive of breast events in patients with ductal carcinoma in situ. Am J Clin Pathol. 128:86–91
85. Silverstein MJ, Lagios MD, Craig PH et al (1996) A prognostic index for ductal carcinoma in situ of the breast. Cancer. 77:2267–74
86. Provenzano E, Hopper JL, Giles GG et al (2003) Biological markers that predict clinical recurrence in ductal carcinoma in situ of the breast. Eur J Cancer. 39:622–30
87. Cornfield DB, Palazzo JP, Schwartz GF et al (2004) The prognostic significance of multiple morphologic features and biologic markers in ductal carcinoma in situ of the breast: a study of a large cohort of patients treated with surgery alone. Cancer. 100:2317–27
88. Lagios MD, Margolin FR, Westdahl PR et al (1989) Mammographically detected duct carcinoma in situ. Frequency of local recurrence following tylectomy and prognostic effect of nuclear grade on local recurrence. Cancer. 63:618–24
89. Silverstein MJ (2002) The Van Nuys/university of Southern California experience by treatment; ductal carcinoma in situ of the breast. Lippincott Williams and Wilkins, Philadelphia, pp 337–42
90. Silverstein MJ, Lagios MD, Groshen S et al (1999) The influence of margin width on local control of ductal carcinoma in situ of the breast. N Engl J Med. 340:1455–61
91. Hiramatsu H, Bornstein BA, Recht A et al (1995) Local recurrence after conservative surgery and radiation therapy for ductal carcinoma in situ: possible importance of family history. Cancer J Sci Am. 1:55–61
92. Macausland SG, Hepel JT, Chong FK et al (2007) An attempt to independently verify the utility of the Van Nuys prognostic index for ductal carcinoma in situ. Cancer. 110: 2648–53
93. Carpenter R, Boulter PS, Cooke T et al (1989) Management of screen detected ductal carcinoma in situ of the female breast. Br J Surg. 76:564–7
94. Schwartz GF, Finkel GC, Garcia JC et al (1992) Subclinical ductal carcinoma in situ of the breast. Treatment by local excision and surveillance alone. Cancer. 70:2468–74

95. Kestin LL, Goldstein NS, Martinez AA et al (2000) Mammographically detected ductal carcinoma in situ treated with conservative surgery with or without radiation therapy: patterns of failure and 10-year results. Ann Surg. 231:235–45
96. Sanders ME, Schuyler PA, Dupont WD et al (2005) The natural history of low-grade ductal carcinoma in situ of the breast in women treated by biopsy only revealed over 30 years of long-term follow-up. Cancer. 103:2481–4
97. Wong JS, Kaelin CM, Troyan SL et al (2006) Prospective study of wide excision alone for ductal carcinoma in situ of the breast. J Clin Oncol. 24:1031–6
98. Hughes L, Wang M, Page DL et al Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of Eastern Cooperative Oncology Group. J Clin Oncol. (in press)
99. Winchester DP, Menck HR, Osteen RT et al (1995) Treatment trends for ductal carcinoma in situ of the breast. Ann Surg Oncol. 2:207–13
100. Silverstein MJ, Rosser RJ, Gierson ED et al (1987) Axillary lymph node dissection for intraductal breast carcinoma–is it indicated? Cancer. 59:1819–24
101. Solin LJ, Kurtz J, Fourquet A et al (1996) Fifteen-year results of breast-conserving surgery and definitive breast irradiation for the treatment of ductal carcinoma in situ of the breast. J Clin Oncol. 14:754–63
102. Klauber-DeMore N, Tan LK, Liberman L et al (2000) Sentinel lymph node biopsy: is it indicated in patients with high-risk ductal carcinoma-in-situ and ductal carcinoma-in-situ with microinvasion? Ann Surg Oncol. 7:636–42
103. Pendas S, Dauway E, Giuliano R et al (2000) Sentinel node biopsy in ductal carcinoma in situ patients. Ann Surg Oncol. 7:15–20
104. Lara JF, Young SM, Velilla RE et al (2003) The relevance of occult axillary micrometastasis in ductal carcinoma in situ: a clinicopathologic study with long-term follow-up. Cancer. 98:2105–13
105. Julian TB, Land SR, Fourchotte V et al (2007) Is sentinel node biopsy necessary in conservatively treated DCIS? Ann Surg Oncol. 14:2202–8
106. Fisher B, Dignam J, Wolmark N et al (1999) Tamoxifen in treatment of intraductal breast cancer: national surgical adjuvant breast and bowel project b-24 randomized controlled trial. Lancet. 353:1993–2000
107. Wilke LG, McCall LM, Posther KE et al (2006) Surgical complications associated with sentinel lymph node biopsy: results from a prospective international cooperative group trial. Ann Surg Oncol. 13:491–500
108. Dunn BK, Wickerham DL, Ford LG (2005) Prevention of hormone-related cancers: breast cancer. J Clin Oncol. 23:357–67
109. Anon (1998) Tamoxifen for early breast cancer: an overview of the randomised trials. Early breast cancer trialists' collaborative group. Lancet. 351:1451–67
110. Fisher B, Bryant J, Dignam JJ et al (2002) Tamoxifen, radiation therapy or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. J Clin Oncol. 20:4141–9
111. Allred D, Bryant J, Land S et al (2002) Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: findings from NSABP b-24. Breast Cancer Res Treat. 76:S36
112. Dignam JJ, Fisher B (2000) Occurrence of stroke with tamoxifen in NSABP b-24. Lancet. 355:848–9
113. Baum M, Buzdar A, Cuzick J et al (2003) Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (arimidex, tamoxifen alone or in combination) trial efficacy and safety update analyses. Cancer. 98:1802–10
114. Coates AS, Keshaviah A, Thurlimann B et al (2007) Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study big 1–98. J Clin Oncol. 25:486–92
115. Goss PE (2003) Emerging role of aromatase inhibitors in the adjuvant setting. Am J Clin Oncol. 26:S27–33
116. NSABP. Clinical trials overview web site. Pittsburgh, PA; 2007
117. International breast cancer intervention study-ii web site: IBIS Trials; 2007
118. Morrow M, Bucci C, Rademaker A (1998) Medical contraindications are not a major factor in the underutilization of breast conserving therapy. J Am Coll Surg. 186:269–74
119. Patchefsky AS, Schwartz GF, Finkelstein SD et al (1989) Heterogeneity of intraductal carcinoma of the breast. Cancer. 63:731–41
120. Bauer RL, Eckhert KH Jr, Nemoto T (1998) Ductal carcinoma in situ-associated nipple discharge: a clinical marker for locally extensive disease. Ann Surg Oncol. 5:452–5
121. Yen TW, Kuerer HM, Ottesen RA et al (2007) Impact of randomized clinical trial results in the national comprehensive cancer network on the use of tamoxifen after breast surgery for ductal carcinoma in situ. J Clin Oncol. 25:3251–8
122. O'Sullivan MJ, Li T, Freedman G et al (2007) The effect of multiple reexcisions on the risk of local recurrence after breast conserving surgery. Ann Surg Oncol. 14:3133–40
123. Katz SJ, Lantz PM, Janz NK et al (2005) Patient involvement in surgery treatment decisions for breast cancer. J Clin Oncol. 23:5526–33
124. Katz SJ, Lantz PM, Janz NK et al (2005) Patterns and correlates of local therapy for women with ductal carcinoma-in-situ. J Clin Oncol. 23:3001–7
125. Fowble B, Hanlon AL, Fein DA et al (1997) Results of conservative surgery and radiation for mammographically detected ductal carcinoma in situ (DCIS). Int J Radiat Oncol Biol Phys. 38:949–57
126. Ashkanani F, Sarkar T, Needham G et al (2001) What is achieved by mammographic surveillance after breast conservation treatment for breast cancer? Am J Surg. 182:207–10
127. Dershaw DD (1995) Mammography in patients with breast cancer treated by breast conservation (lumpectomy with or without radiation). AJR Am J Roentgenol. 164:309–16
128. Dershaw DD, Shank B, Reisinger S (1987) Mammographic findings after breast cancer treatment with local excision and definitive irradiation. Radiology. 164:455–61
129. Mendelson EB (1992) Evaluation of the postoperative breast. Radiol Clin North Am. 30:107–38
130. Dershaw DD, McCormick B, Osborne MP (1992) Detection of local recurrence after conservative therapy for breast carcinoma. Cancer. 70:493–6

131. Saslow D, Boetes C, Burke W et al (2007) American cancer society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 57:75–89
132. Lagios MD (1990) Duct carcinoma in situ. Pathology and treatment. Surg Clin North Am. 70:853–71
133. Cutuli B, Teissier E, Piat JM et al (1992) Radical surgery and conservative treatment of ductal carcinoma in situ of the breast. Eur J Cancer. 28:649–54
134. Solin LJ, Fourquet A, Vicini FA et al (2005) Salvage treatment for local or local-regional recurrence after initial breast conservation treatment with radiation for ductal carcinoma in situ. Eur J Cancer. 41:1715–23
135. Graham MD, Lakhani S, Gazet JC (1991) Breast conserving surgery in the management of in situ breast carcinoma. Eur J Surg Oncol. 17:258–64
136. Deutsch M (2002) Repeat high-dose external beam irradiation for in-breast tumor recurrence after previous lumpectomy and whole breast irradiation. Int J Radiat Oncol Biol Phys. 53:687–91
137. Kim JH, Tavassoli F, Haffty BG (2006) Chest wall relapse after mastectomy for ductal carcinoma in situ: a report of 10 cases with a review of the literature. Cancer J. 12:92–101
138. Lee LA, Silverstein MJ, Chung CT et al (2006) Breast cancer-specific mortality after invasive local recurrence in patients with ductal carcinoma-in-situ of the breast. Am J Surg. 192:416–9
139. Port ER, Garcia-Etienne CA, Park J et al (2007) Reoperative sentinel lymph node biopsy: a new frontier in the management of ipsilateral breast tumor recurrence. Ann Surg Oncol. 14:2209–14
140. Intra M, Trifiro G, Viale G et al (2005) Second biopsy of axillary sentinel lymph node for reappearing breast cancer after previous sentinel lymph node biopsy. Ann Surg Oncol. 12:895–9
141. Barone JL, Feldman SM, Estabrook A et al (2007) Reoperative sentinel lymph node biopsy in patients with locally recurrent breast cancer. Am J Surg. 194:491–3
142. Roumen RM, Kuijt GP, Liem IH (2006) Lymphatic mapping and sentinel node harvesting in patients with recurrent breast cancer. Eur J Surg Oncol. 32:1076–81
143. Port ER, Fey J, Gemignani ML et al (2002) Reoperative sentinel lymph node biopsy: a new option for patients with primary or locally recurrent breast carcinoma. J Am Coll Surg. 195:167–72

13 Surgical Considerations in the Management of Primary Invasive Breast Cancer

Ismail Jatoi

In the nineteenth century, German pathologist Rudolf Virchow (Fig. 13.1) studied the morbid anatomy of breast cancer. He undertook a series of postmortem dissections and postulated that breast cancer spreads along fascial planes and lymphatic channels [1]. Little importance was given to the hematogenous spread of cancer. Virchow's hypothesis influenced the work of the American surgeon, William Halsted (Fig. 13.2). In the late nineteenth century, Halsted described radical mastectomy (MT), which is performed for the treatment of breast cancer [2]. This operation removed the breast, the underlying pectoralis muscles, and the ipsilateral axillary lymph nodes. Thus, in keeping with the postulates of Virchow' s hypothesis, the lymphatic channels connecting the breast and axillary lymph nodes were extirpated *en bloc*. Halsted argued that resection of a node-negative breast cancer was curative, believing that such tumors were extirpated before they spread through the lymphatics. Halsted also maintained that the extent of both the MT and axillary dissection were important determinants of outcome. Therefore, breast cancer recurrence and distant metastases were often attributed to inadequate surgery.

By the early twentieth century, the radical MT had become widely accepted as the standard treatment for breast cancer. The risk of local recurrence was far less with the radical MT than with other contemporary procedures. The radical MT was also credited with improving survival from breast cancer during the early years of the twentieth century [3]. This improvement in survival was probably largely attributable to the effect of lead time bias, rather than to any advancement in surgical technique. Indeed, by the turn of the century, patients were seeking medical attention sooner (with smaller tumors).

Fig. 13.1 Dr. Rudolph Virchow (courtesy of the national library of medicine archives)

One important observation was inconsistent with the Halsted paradigm. About 30% of node-negative breast cancer patients die of metastatic disease within 10 years after surgery [4]. This finding suggested that the lymphatics are not the only source for the distant spread of cancer. Yet, most surgeons in the early twentieth century were not willing to discard the Halstedian concept

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_13, © Springer-Verlag Berlin Heidelberg 2010

Fig. 13.2 Dr. William Halsted (courtesy of the national library of medicine archives)

that the distant spread of breast cancer occurs solely through the lymphatics. Some proposed that metastatic spread through the internal mammary and supraclavicular lymph node chains might account for distant relapse in women whose axilla were free of nodal involvement [5, 6]. Extirpation of these additional nodal chains failed to improve outcome, however, and these more extensive lymphadenectomies were soon abandoned [7, 8].

The radical MT remained the cornerstone for the treatment of breast cancer for about the first three quarters of the twentieth century. Thereafter, the operation lost favor. By the latter half of the twentieth century, many surgeons regarded the radical MT as too debilitating, and several centers reported good outcome with less extensive surgery [9, 10]. These lesser procedures included the modified radical MT (which spares the pectoralis muscles) and simple excision of the primary breast tumor. The trend toward less radical surgery was attributable to two important factors [11]. Firstly, surgeons during the latter half of the twentieth century were seeing patients with smaller tumors, and these were often amenable to local excision. Secondly, there were improvements in radiotherapy (RT) techniques, enabling tumoricidal doses to be delivered effectively without significant damage to surrounding tissues. Thus, many surgeons developed an interest in breast conserving surgery (BCS), undertaken in conjunction with breast RT.

Skepticism concerning the merits of the Halsted radical MT surfaced in 1962, when Bloom et al. reported about the survival of 250 patients with primary breast cancer who received no treatment [12]. These patients were diagnosed clinically between the years 1805 and 1933 at the Middlesex Hospital in London, England, and the tissue diagnosis was established at autopsy. The survival rate of these untreated patients was almost identical to Halsted's patients who were treated with the radical MT. This seemed to suggest that surgery contributes little to reducing the risk of death from breast cancer but the impact of surgery 100 years ago might have been quite different from what it is today. Patients in the late nineteenth century generally presented with cancers at an advanced stage. In many instances, distant metastases were perhaps already present, and therefore surgery might have had little impact on the natural history of the disease. In contrast, patients seen today generally present with early disease. Thus, in the absence of metastases, local therapy alone could cure some patients.

During the last 25 years, the tenets of the Halsted paradigm were put to test in several large, randomized prospective trials. These trials examined the effect of various surgical options in the treatment of breast cancer. None of these trials compared surgical treatment with any treatment, and so the true effect of surgery on breast cancer mortality was never established. The results of these trials suggested, however, that breast conserving therapy (BCT) (partial removal of the breast in conjunction with RT) was a viable option for most women with breast cancer.

The National Surgical Adjuvant Breast Project-04 (NSABP-04) and King's/Cambridge trials randomized patients with clinically node-negative breast cancer to either early or delayed treatment of the axilla [13, 14]. In the NSABP-04 trial, 1,665 clinically node-negative women received either no initial treatment to the axilla or initial treatment with either axillary lymph node dissection (ALND) or RT [13]. About 18% of patients who received no initial axillary treatment developed axillary adenopathy and subsequently were treated with ALND. Yet, there was no significant difference in breast cancer mortality between patients in the three arms of the trial. In the King's/Cambridge trial, 2,243 women with clinically node-negative breast cancer were randomly assigned

to either total MT and immediate RT to the axilla or total MT and careful observation of the axilla [14]. In the group assigned to observation, RT was delayed until there was progression or recurrence of the disease in the axilla. No significant difference in breast cancer mortality was found between the two groups, however. The NSABP-04 and King's/Cambridge trials indicated that the delayed treatment of the axilla does not adversely affect breast cancer mortality. This finding suggests that the axillary lymph nodes are not a nidus for the further spread of cancer, a finding that is inconsistent with the Halsted hypothesis.

Halsted also proposed that breast cancer is a locally progressive disease. He argued that metastases occurred by the contiguous and centrifugal spread of cancer from the primary tumor in the breast. If this were true, then the extent of the MT should influence survival. During the last 30 years, this hypothesis was tested in six large, randomized prospective trials. These were the Milan I, Institute of Gustave-Roussy (GR), NSABP-06, U.S. National Cancer Institute, European Organization for the Research and Treatment of Cancer (EORTC), and Danish Group trials [15–20] (Figs. 13.3a, b). These trials compared either the radical MT or the modified radical MT with less extensive procedures (variously labeled as segmentectomy, lumpectomy, tylectomy, quadrantectomy or wide local excision), undertaken in conjunction with an ALND. All these trials showed that the extent of the MT has no impact on breast cancer mortality.

The NSABP-06 was the largest of these six trials [17]. There were 1,843 patients randomized to one of three groups: total MT and axillary dissection (modified radical MT), lumpectomy and axillary dissection, or lumpectomy and axillary dissection followed by breast RT. The NSABP-06 found no difference in survival between patients in the three arms of the study; however, the incidence of local breast tumor recurrence in the lumpectomy plus breast radiation group was significantly lower than in the lumpectomy group who received no radiation. Thus, RT is generally used today in conjunction with BCS in the treatment of primary breast cancer.

13.1 Local Recurrences

Local recurrences following total MT may occur on the chest wall; the skin overlying the chest wall; or the axillary, internal mammary, supraclavicular and infraclavicular lymph nodes [21]. However, women treated with BCS are also at risk for recurrences in the ipsilateral breast [22]. Thus, breast cancer patients treated with BCS have, overall, a greater risk of local recurrence than those treated with total MT. For many years, Fisher argued that ipsilateral breast tumor recurrences following BCS are indicators of distant disease that is already present [23]. He argued that such recurrences were markers for poor prognosis but not the cause of the poor prognosis. Studies have shown that, following BCS, women who develop ipsilateral breast tumor recurrences have greater than a threefold increased risk of developing distant metastases when compared to those who do not develop such recurrences [24]. Also, patients who develop recurrences in the ipsilateral breast within 3–5 years following BCS seem to have a worse prognosis than those who develop such recurrences later [25].

Radiation therapy can reduce the risk of ipsilateral breast tumor recurrences. In the NSABP-06 study, the risk of ipsilateral breast tumor recurrences was about 40% following lumpectomy and about 10% following lumpectomy and RT [17]. For patients treated with total

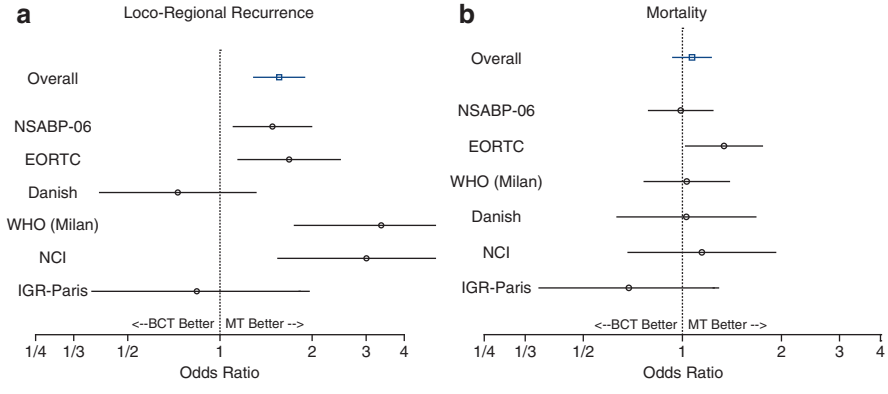

Fig. 13.3 Petograms showing locoregional recurrence (**a**) and mortality (**b**) results with odds ratios and confidence intervals for the six randomized trials comparing breast conserving therapy (BCT) and mastectomy (MT) for early breast cancer (From Ref. [28])

MT, the risk of ipsilateral breast tumor recurrences was essentially nil. Ipsilateral breast tumor recurrences are generally treated with salvage MT (total MT), and the 10-year actuarial survival for these patients is about 58% [21]. In contrast, local recurrences in the chest wall, ipsilateral axilla or supraclavicular and infraclavicular fossa carry a worse prognosis. More than 90% of these patients will develop distant metastases, and most will die of their disease within 10 years after recurrence [26].

What factors influence the risk of ipsilateral breast tumor recurrence following BCS? Several investigators have addressed this question. Borger et al. studied 1,026 patients treated at the Netherlands Cancer Institute with BCS and RT [27]. Univariate analysis showed that seven factors were associated with an increased risk of ipsilateral breast tumor recurrence: age, residual tumor at re-excision, histologic tumor type, presence of any components of carcinoma in situ component, vascular invasion, microscopic margin involvement and whole-breast radiation dose. Only two factors remained independently significant after proportional hazard regression analysis: age and the presence of vascular invasion. Thus, ipsilateral breast tumor recurrence rates were 6% for patients less than 40 years of age and 8% for patients with tumors showing vascular invasion at 5 years. In the absence of these factors, the risk of ipsilateral breast tumor recurrence after BCS was only about 1% at 5 years.

A recent overview of the six major randomized trials comparing MT vs. BCT (BCS + RT) confirmed that there was a substantial increase in the risk of loco-regional recurrence associated with BCT, pooled odds ratio 1.561, 95% CI, 1.289–1.890; $p < 0.001$ [28] (Fig. 13.3a). Yet, in this analysis, there was no significant difference in mortality between the two groups, odds ratio 1.070, 95% CI, 0.935–1.224; $p > 0.33$ (Fig. 13.3b). However, this meta-analysis may have lacked the statistical power to discern a small but significant effect of local recurrence on breast cancer mortality. Alternatively, competing causes of mortality (heart disease, stroke, etc) may have obscured a potentially small effect of local recurrence on mortality in this meta-analysis. It should be noted that, in these trials, women were followed closely, and those who developed ipsilateral breast tumor recurrences following BCT were immediately treated with MT (salvage MT).

In recent years, there has been mounting evidence to indicate that local recurrences are indeed associated with an increase in breast cancer mortality. A pooled analysis of 15 trials comparing RT vs. no RT after BCS showed that the omission of RT was associated with a threefold increase in ipsilateral breast tumor recurrences and a small (8.6%) but statistically significant increase in mortality [29]. Also, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported the results of a collaborative meta-analysis of randomized trials of RT and various types of surgery for early breast cancer [30]. Comparisons were made between RT vs. no RT, more surgery vs. less surgery (with or without RT), and more surgery without RT vs. less surgery with RT, etc. These investigators found that the avoidance of local recurrence, either in the conserved breast or elsewhere (chest wall, regional lymph nodes, etc) was important in reducing breast cancer mortality. Over a 15-year period, one breast cancer death could be prevented for every four local recurrences avoided.

Turner et al. reported that women who carry a *BRCA* mutation *(BRCA1* or *BRCA2)* are more likely to develop ipsilateral breast tumor recurrences following BCS and RT [31]. However, the median time to ipsilateral breast tumor recurrence was 7.8 years for patients with *BRCA1* or *BRCA2* mutations, compared with 4.7 years for patients without such mutations. The longer time to recurrence in the carriers of these mutations suggests that these were second de novo primary tumors. The *BRCA* genes play an important role in DNA repair, and some studies seem to suggest that persons who carry mutations in these genes are extremely sensitive to the effects of RT [32]. Thus, one might speculate that RT administered following BCS may play a role in the development of de novo ipsilateral breast cancers in the carriers of *BRCA* mutations. Pierce and colleagues followed 160 BRCA carriers and 445 matched controls who underwent BCS following a diagnosis of breast cancer. These authors reported that mutation carriers who had not undergone oophorectomy were at increased risk for ipsilateral breast tumor recurrences, while those who had undergone oophorectomy were not [33]. Yet, BRCA mutation carriers also face a high risk of developing breast cancer in the contralateral breast, and many are now opting for contralateral prophylactic MT at the time of initial breast cancer diagnosis. A recent study found that BRCA mutation carriers in North America were more willing to accept contralateral prophylactic mastectomy following a breast cancer diagnosis than were their counterparts in Europe [34]. Large variations in the acceptance of contralateral prophylactic MT were reported, ranging from 0% in Norway to 49.3% in the United States.

13.2 Surgical Options

Today, a patient with primary breast cancer might consider three surgical options: modified radical MT, modified radical MT with contralateral prophylactic MT or BCS (Table 13.1). A modified radical MT refers to the removal of the breast and the ipsilateral lymph nodes (the sentinel lymph node is first removed, and if metastatic cancer is evident, then the patient generally undergoes an ALND). If the patient chooses this option, she can often avoid RT (although postmastectomy RT is recommended for patients with large tumors (>5 cm) and/or extensive lymph node involvement [35]. Patients treated with the modified radical MT should generally be offered breast reconstructive surgery, which is discussed later. Also, some women with unilateral breast cancer might opt for a modified radical MT and a contralateral prophylactic MT (i.e., bilateral MT), particularly if they carry the BRCA 1 or BRCA 2 gene mutations or have anxiety over the possibility of developing a new cancer in the opposite breast. Finally, a patient with unilateral breast cancer may choose to undergo a breast-conserving procedure along with removal of axillary lymph nodes. This is often the preferred option because it results in the best cosmetic and tactile outcome. If a patient elects this option, she will generally require RT to reduce the risk of ipsilateral breast tumor recurrence. However, lumpectomy plus adjuvant endocrine therapy alone (without RT) might be a suitable option for women 70 years of age or older with early estrogen-receptor-positive breast cancer [36].

Table 13.1 Surgical options for primary invasive breast cancer

Modified radical MT	Resection of entire breast Sentinel lymph node biopsy (SLNB)/axillary dissection Breast reconstruction Radiotherapy (RT) sometimes required
Modified radical MT and contralateral prophylactic MT	Resection of both breasts SLNB/axillary dissection on side containing the cancer Bilateral breast reconstruction RT sometimes required
Breast conserving surgery	Resection of tumor and margin of normal tissue SLNB/axillary dissection RT generally required

Various terms are used to describe breast-conserving procedures, including segmental MT, lumpectomy, tylectomy, wide local excision and quadrantectomy. Essentially, these terms refer to the extirpation of the breast tumor with various margins of normal breast tissue. The terms *segmental MT* and *lumpectomy are* used interchangeably. These terms refer to the resection of the breast tumor with enough surrounding normal tissue to result in microscopically tumor-free surgical margins. By definition, tumor cells may approach to within one cell's breadth of the surgical margin. The term *extended tylectomy* was used at the Guy's Hospital in London to describe resection of the breast tumor plus surrounding breast tissue within 3 cm of the tumor mass [37]. The microscopic status of the surgical margins was not defined. In the *quadrantectomy,* described by Veronesi et al. at the Tumor Institute of Milan, Italy, the entire quadrant of the breast containing the tumor is removed [15]. In the six randomized trials comparing BCT and MT, there was considerable heterogeneity with respect to the risk of ipsilateral breast tumor recurrence, and this was most likely attributable to variations in surgical procedures [28]. For example, in the Milan trial, patients treated with BCT underwent quadrantectomy (excision of the tumor with 2–3-cm margin of normal tissue around it), whereas in the Danish and US National Cancer Institute trials, a simple excision of the tumor (with no gross involvement of the margins) was performed.

After any breast-conserving procedure, RT is generally administered to eliminate occult tumor foci remaining in the ipsilateral breast. RT to the breast can be initiated 10–14 days after surgery. If chemotherapy is also planned, RT is postponed until one or more doses of chemotherapy are administered. RT is discussed in a separate chapter in this book.

Most patients with primary breast cancer are suitable candidates for BCS, but there are a few contraindications [31] (Table 13.2). These are only

Table 13.2 Factors that may influence surgical option for primary breast cancer (breast-conserving surgery (BCS) vs. MT)

Patient preference
Pregnancy
Previous RT
Collagen vascular disease
Tumor size in relation to breast size
Multicentric disease

relative contraindications, however, and each patient's circumstances should be examined closely [38]. For example, pregnant patients are generally advised not to undergo BCS because RT carries substantial risk to the fetus. Yet, it is important to remember that several months of chemotherapy are generally given before RT. Thus, if RT is to be administered after delivery, BCS is an acceptable option. Patients who have had previous RT to the breasts are also often advised not to undergo BCS. However, radiation oncologists may wish to consider the previous dose of radiation adminstered, and some of these patients might be successfully treated with BCS and RT. Additionally, certain coexisting medical problems, such as collagen vascular diseases, may adversely affect the cosmetic results after RT and thereby increase the risk of complications. Collagen vascular disease is an issue only when there is active disease.

Patients with large tumors often are advised to undergo a modified radical MT rather than a breast-conserving procedure [39]. The appropriate tumor size for BCS is poorly defined, however. The various clinical trials used different criteria to recruit patients for BCS. In the Milan trial, BCS was an option only for patients with tumors smaller than 2.5 cm, and those patients underwent excision of the entire quadrant of the breast (quadrantectomy) containing the tumor [15]. In the NSABP-06 trial, patients with tumors smaller than 4 cm were eligible for BCS (lumpectomy), whereas the subsequent NSABP trials accepted patients with tumors as large as 5 cm [17]. An important consideration is the size of the tumor in relation to the size of the breast. Today, in some centers, preoperative chemotherapy is used to decrease the size of large tumors, making BCS feasible for more women [40]. Thus, a patient with a large tumor and a small breast might be a suitable candidate for BCS if she is prepared to receive preoperative chemotherapy.

Some surgeons argue that BCS should be contraindicated if the tumor is close to or involves the nipple-areola complex. Yet, the nipple-areola complex can be easily excised along with the tumor. Although sacrifice of the nipple-areola complex may result in a cosmetic deformity, many women prefer this to losing the entire breast. Thus, the patient's wishes should be considered.

A patient with multicentric cancer (involving more than one quadrant of the breast) is generally not a suitable candidate for BCS. Careful physical examination of the breasts and a preoperative mammogram are helpful in determining the presence of multicentric disease. A patient with a suspicious breast mass should have a mammogram prior to any diagnostic biopsy. Mammograms obtained immediately after a breast biopsy are often difficult to interpret due to postbiopsy changes. Thus, if cancer is confirmed with a biopsy, a postbiopsy mammogram might make it difficult to determine whether a patient is a suitable candidate for a breast-conserving operation.

In recent years, breast magnetic resonance imaging (MRI) has been widely utilized in women with newly diagnosed breast cancers to help determine eligibility for BCT. MRI will occasionally identify additional cancer foci in either the ipsilateral or contralateral breast that are not evident on either clinical examination or mammography [41]. On the basis of MRI findings, MT (and even bilateral MT) might be recommended for patients who otherwise might have been considered suitable candidates for BCT. The use of breast MRI in the initial evaluation of women with primary breast cancer has therefore generated considerable controversy. Many investigators argue that the additional cancer foci detected on MRI might be adequately treated with RT and systemic therapy, and that the use of breast MRI needlessly increases MT rates. A retrospective study from the University of Pennsylvania compared women with early stage breast cancer who underwent preoperative evaluation with or without breast MRI [42]. In this study, all women underwent BCT, but in some cases the eligibility for BCT was determined by MRI and conventional mammography, while in others it was determined by conventional mammography alone. The authors found that breast MRI at the time of initial diagnosis was not associated with improvements in outcome.

BCS is a more complex treatment than the modified radical MT. The procedure generally requires two separate incisions, one to remove the primary breast tumor and the other to remove the axillary lymph nodes. In addition, patients treated with BCS require postoperative RT. Nattinger et al. analyzed the U.S. National Surveillance, Epidemiology, and End-Results Tumor Registry and found that, with the increased use of BCS, a greater number of patients were receiving inappropriate surgical treatment for primary breast cancer [43]. *Appropriate* surgical therapy was defined as either total MT with ALND (modified radical MT) or BCS with ALND and RT. During the period from 1983 through 1995, the proportion of women undergoing an inappropriate form of modified radical MT remained stable at 2.7%. During this period, however, the proportion receiving an inappropriate form of BCS

(omission of RT or ALND or both) increased from 10% in 1989 to 19% at the end of 1995.

Since publication of the results of the NSABP-06 trial, there has been a gradual increase in the use of BCS in the United States. There has also been considerable geographic variation in the acceptance of this procedure, however. Several years ago, Nattinger et al. reported that the frequency of BCS in the various states ranged from 3.5 to 21.2% [44]. The highest frequency was reported in the mid-Atlantic (20%) and New England states (17%), and the lowest in the eastern (5.9%) and western South-Central states (73%). A similar geographic variation in the use of BCS was reported in an analysis of patients treated within the U.S. Department of Defense (DoD) Healthcare System [45]. In the DoD system, physicians rotate through various hospitals in the United States and abroad. Yet, geographic variation in the use of BCS persists. Thus, patient preferences in various parts of the United States might differ, resulting in variation in the acceptance of one procedure over another.

In the United States, the use of unilateral MT for women with primary breast cancer declined from about 76.5% in 1988 to 38% in 2004, while use of BCS dramatically increased during this same period [46]. But this study also found that radiation is frequently omitted after BCS, particularly among racial/ethnic minorities and younger and older women. Paradoxically, in the United States, the use of bilateral mastectomies for early stage unilateral breast cancer has more than doubled between the years 1998 and 2004 [47]. This may not only reflect the wider use of genetic testing and identification of women with BRCA 1 and BRCA 2 mutations who are at greater risk for the development of contralateral breast cancers, but also a greater involvement of women in the decision-making process. Thus, in recent years, the surgical treatment of breast cancer in the United States seems to be polarizing, with more and more women opting for either BCS or more aggressive surgery (bilateral MT), while use of unilateral MT diminishes.

The impact of contralateral prophylactic MT on breast cancer mortality has never been studied in a randomized prospective trial. However, a large retrospective study suggested that contralateral prophylactic MT reduced breast cancer mortality by about 43% [48]. At least part of this benefit might have been due to a selection bias (women who opted for contralateral prophylactic MT might have been healthier, with lower all-cause mortality) [49]. Nonetheless, this study also showed that contralateral prophylactic MT reduces breast cancer risk in the opposite breast by about 90%, and its wider acceptance throughout the United States may partly reflect a desire to reduce anxiety about developing a new cancer in the opposite breast.

By 1990, 18 states had passed legislation requiring physicians to disclose options for the treatment of breast cancer. Nattinger et al. studied the effect of this legislation on the use of BCS [50]. They found that such legislation has only a small, transient effect on the rate of use of BCS. Dolan et al. reported that medically indigent women treated in public hospitals are less likely to receive BCS when compared with more affluent patients treated in private hospitals [51]. A recent study suggests that, when fully informed of the two available options for the treatment of primary breast cancer (BCS or MT), many women will choose MT [52]. Women may choose MT for peace of mind or to avoid RT. Thus, several complex factors, and not insurance coverage alone, appear to be influencing trends in the surgical treatment of primary breast cancer.

13.2.1 Breast Reconstructive Surgery

For some patients with primary breast cancer, BCS is not a suitable option. As mentioned previously, for some pregnant patients, those with large or multicentric cancers, patients who have been previously treated with RT to the breast, and those with active collagen vascular disease, BCS might not be suitable. These patients are often advised to undergo modified radical MT (total breast removal and ALND). Most of these patients are good candidates for breast reconstructive surgery, which may be performed either at the time of surgery for primary breast cancer (immediate reconstruction) or later (delayed reconstruction). For several years, there were concerns that immediate reconstructive surgery might mask locoregional recurrences and thereby contribute to a worse outcome [53]. Thus, many investigators recommended delayed reconstruction; however, studies suggest that immediate reconstruction does not adversely affect outcome [54, 55]. Furthermore, immediate reconstruction allows two procedures (the cancer operation and reconstruction) to be performed with the use of one anesthetic and might even be associated with less psychosocial morbidity [56].

Several options are available for breast reconstruction, including the placement of implants or the

creation of latissimus dorsi myocutaneous, transverse rectus abdominis myocutaneous (TRAM) and free flaps. Additionally, the deep inferior epigastric artery perforator (DIEP) flap has been gaining popularity in recent years [57]. A detailed review of breast reconstruction is found in a separate chapter in this text and in surgical atlases [58].

Reconstruction with breast implants is used widely [59]. Several methods are now available, including permanent implants, permanent expandable implants and serial expansion of tissue with an expandable implant followed by implant exchange. Tissue expanders are placed beneath the pectoral muscles and then gradually inflated over several weeks by injecting saline through a subcutaneous port. Once a skin mound is produced that is slightly larger than required, a permanent implant is inserted. Tissue expanders are feasible only for women with small or medium-sized breasts who have not had prior skin radiation. Both silicone gel and saline implants have been used. There have been concerns that silicone gel implants may result in an increased risk of connective tissue disorders. Indeed, this concern has resulted in considerable litigation and debate [60]. Several studies, however, failed to demonstrate any association between silicone implants and connective tissue disorders [61, 62].

A breast mound can be refashioned using a myocutaneous flap, where skin and muscle from one anatomic region are transferred to the chest wall, with the vascular pedicle remaining attached. The latissimus dorsi myocutaneous flap is quite popular and is suitable for patients with large breasts or who have been previously treated with RT [63]. Thus, it is often used in women who have had RT as part of BCS and who subsequently develop a recurrence requiring salvage MT. Unfortunately, it does not contain sufficient tissue bulk, and so an implant is generally required beneath the flap.

The TRAM has a greater risk of potential complications than does the latissimus dorsi flap [58]. It has several advantages as well, however, and is now the most commonly used flap in the United States. The TRAM flap provides sufficient bulk of tissue so that an implant beneath the flap is not necessary. The TRAM flap is useful for patients with a moderate or excessive amount of lower abdominal fat who require additional soft tissue on the chest wall. Thus, it provides not only sufficient tissue for breast reconstruction but also results in an abdominoplasty.

Finally, a breast mound can be refashioned using free flaps; the free TRAM flap is the most popular [64]. In a free flap, the skin and underlying muscle are detached from their vascular pedicle, and microvascular techniques are used to reestablish the blood supply once the flap is placed on the chest wall. The free TRAM flap has several advantages over the standard TRAM flap. Less rectus abdominus muscle is required, and the medial contour of the breast generally looks better because a tunnel for the vascular pedicle is not required. Surgeons must have special expertise in performing microvascular procedures.

Among women treated with MT, less than 20% will undergo breast reconstruction [65]. In 1999, the Women's Health and Cancer Rights Act (WHCRA) was implemented, mandating insurance coverage for breast reconstruction after MT, and additional legislation was passed in 2001, imposing penalties on noncompliant insurers [66]. However, this legislation has not significantly increased the overall use of breast reconstruction in the United States or reduced variations across geographic regions and patient subgroups.

13.3 Management of the Axilla

Since the late nineteenth century, breast cancer surgery has been closely linked to surgery of the axilla. Today, axillary surgery remains an integral part of BCS and the modified radical MT. Nonetheless, surgical management of the axilla is a topic of intense controversy. Axillary lymph node metastases are no longer considered a prerequisite for distant metastases. Thus, the impact of axillary surgery on survival, local control and staging is frequently debated.

ALND refers to the extirpation of lymph nodes in the axilla. The lymph nodes in the axilla are divided into three compartments based on their anatomic relationship to the pectoralis minor muscle [67]. Lymph nodes lateral to the pectoralis minor muscle are classified as level I nodes, those posterior to its lateral and medial borders are classified as level II nodes, and those medial to the muscle are classified as level III nodes. A *complete* ALND refers to the extirpation of lymph nodes from all three compartments. In contrast, a *partial* ALND refers to the extirpation of lymph nodes only from levels I and II, and axillary sampling indicates only resection of the level I nodes.

Metastases to the axillary lymph nodes generally occur in an orderly fashion. Thus, lymph nodes in level

I are generally involved first, followed by involvement of nodes in level II and then level III. *Skip metastases* indicate the involvement of lymph nodes at levels II or III but not level I; these occur rarely. Veronesi et al. studied the distribution of nodal metastases in 539 patients who underwent complete ALND [68]. Level I nodes were involved in 58% of patients, levels I and II in 22%, and all three levels in 16%. In their series, skip metastases were present in only 4% of cases. Today, most authorities recommend extirpation of lymph nodes from levels I and II (a partial ALND); ten or more nodes are usually removed [69]. A partial ALND correctly stages 96% of patients with primary breast cancer as either node-positive or node-negative and rarely gives rise to significant lymphedema of the upper extremity. The 4% false-negative rate associated with a partial ALND is attributable to skip metastases. This false-negative rate can be further reduced with resection of nodes from levels I-III (complete ALND), but this may increase the risk of upper-extremity lymphedema.

The technique of partial ALND is discussed in surgical atlases [58]. Essentially, the procedure involves resection of lymph nodes superiorly to the level of the axillary vein, laterally to the latissimus dorsi muscle and medially to the medial border of the pectoralis minor muscle. Particular attention should be paid to identifying the long thoracic and thoracodorsal nerves. The long thoracic nerve (nerve of Bell) runs along the lateral aspect of the chest wall and supplies the serratus anterior muscle. Injury to this nerve results in a *winged scapula.* The thoracodorsal nerve accompanies the subscapular artery along the posterior aspect of the axilla and supplies the latissimus dorsi muscle.

What impact does ALND have on survival, local control and staging in patients with primary breast cancer? In recent years, several clinical trials have shed some light on this question. The impact of ALND on the management of patients with primary breast cancer remains a contentious issue.

13.3.1 Survival

For many years, the ALND was considered an important determinant of survival for patients with primary breast cancer. Halsted and his disciples fostered this notion more than 100 years ago, arguing that breast cancer spreads first to the regional lymph nodes and then to distant sites. Subsequently, some investigators provided retrospective data suggesting that the extent of the ALND does influence survival for patients with primary breast cancer. Such data are misleading, however, because there is no accounting for a *stage migration effect.* Consider, as an example, a patient with a 1.5-cm tumor and one metastatic lymph node to the axilla. Surgeon A may perform an extensive lymph node dissection and remove that node. On the other hand, surgeon B may perform a less extensive lymph node dissection and fail to uncover the metastatic node. Thus, if treated by surgeon A, this patient would be diagnosed as having stage II breast cancer. If treated by surgeon B, the same patient would be diagnosed as having stage I disease. When survival rates are compared for any given stage, it may seem that patients treated by surgeon A do better, but this may be attributable to the stage migration effect rather than any therapeutic benefit of the more extensive lymph node dissection.

The best way to determine whether the ALND has any effect on mortality is to compare treatment with ALND and without ALND in a randomized prospective trial. Such a study has never been conducted, although the results of the NSABP-04 and the King's/Cambridge trials, discussed already, indicate that the delayed treatment of the axilla has no effect on breast cancer mortality [13, 14]. The results of these trials might be interpreted to mean that the axillary lymph nodes are not a nidus for the further spread of cancer. Nonetheless, some investigators argue that the NSABP-04 and King's/Cambridge trials did not include sufficient numbers of patients to detect small differences in survival between those randomized to either early or delayed treatment of the axilla [70]. Additionally, meta-analyses of randomized trials seem to suggest that there is a survival benefit associated with ALND, but this benefit might diminish in women who receive adjuvant systemic therapy [30, 71].

13.3.2 Axillary Relapse

Axillary lymph node metastasis is found in 35–40% of patients with palpable breast cancers [72]. In many instances, nodal involvement is not clinically evident when the patient first presents with primary breast cancer. Indeed, up to 30% of clinically node-negative patients are shown to have nodal involvement

following ALND [73]. In the absence of ALND, many of these patients eventually would develop clinical evidence of nodal involvement. The NSABP-04 and King's/Cambridge trials provide important information on the effect of axillary treatment in clinically node-negative patients. These trials indicate that RT and ALND are equally effective in achieving local control of the axilla. In the NSABP-04 trial, clinically node-negative patients with primary breast cancer either received no treatment to the axilla or treatment with ALND or RT [13]. About 18% of the patients who received no initial axillary treatment went on to develop axillary adenopathy within 5 years. In contrast, axillary adenopathy developed in only 2% of patients whose axilla had been treated. Similar results were reported in the King's/Cambridge trial, where clinically node-negative patients were randomized to receive total MT; and RT to the axilla or total MT and observation of the axilla [14]. Taken together, these studies suggest that treatment of the axilla (with either ALND or RT) will reduce the 5-year risk of axillary relapse by about 90%.

The importance of axillary treatment on local control is also reported in retrospective studies. Baxter et al. reviewed the records of 112 breast cancer patients who underwent lumpectomy without ALND [74]. When these patients first presented with breast cancer, they had no evidence of axillary lymph node involvement on clinical examination. During the subsequent 10-year period, about 28% of these patients developed axillary adenopathy. Axillary adenopathy developed in 10% of patients who presented with tumors 1 cm or less in diameter, in 26% of those who presented with tumors 1.1–2.0 cm, and in 33% of those with primary tumors greater than 2.1 cm in diameter.

The extent of the ALND seems to influence the risk of axillary relapse. Graverson et al. reviewed the records of 3,128 patients with primary breast cancer who were clinically node negative at initial presentation [75]. The 5-year risk of axillary relapse ranged from 19% when no nodes were removed to 3% when more than five nodes were removed. In the NSABP-04 study, no patient who had more than six nodes removed developed a relapse in the axilla. Thus, an adequate ALND is essential in reducing the risk of relapse in the axilla.

Axillary relapse is generally considered a marker of tumor biology, indicating an increased risk of distant metastasis and death. These relapses are not considered the cause of poor prognosis. Yet, many women are emotionally devastated following axillary relapse. Additionally, axillary relapses can cause significant morbidity. Major vessels and nerves of the axilla sometimes are invaded by the tumor, causing lymphedema or pain. In such instances, the axilla is difficult to manage. Surgical clearance of such axilla often is associated with increased morbidity. Thus, adequate treatment of the axilla at the time of initial diagnosis of primary breast cancer is important.

13.3.3 Staging

For patients with primary breast cancer, clinical assessment of the axilla is notoriously inaccurate. About 30% of patients with palpable axillary nodes prove to be node negative following ALND, and about 30% of clinically node-negative patients prove to have nodal involvement [73]. Thus, the ALND traditionally played a vital role in staging patients with primary breast cancer (as either node negative or node positive).

The prognostic significance of nodal metastasis is poorly understood. For many years, physicians assumed that nodal status was simply a chronological variable. Thus, it was argued that node-positive patients fare worse than node-negative patients because their cancers are discovered later in their natural history. However, a study using the San Antonio Tumor registry seemed to suggest that nodal status is also a marker of tumor biology, because nodal status at initial diagnosis was found to also predict outcome after relapse [76]. In that study, patients with four or more involved nodes at initial diagnosis were found to have a significantly worse outcome after relapse compared with node-negative cases. Additionally, node-positive, high-risk tumors (>2 cm, ER-negative, high grade, node-positive) are more common in younger patients (with a peak age of onset at 50 years), while node-negative, low-risk tumors (<2 cm, ER-positive, low grade, node-negative) tend to occur later in life (with a peak age of onset at 70 years) [77].This observation is also consistent with the notion that nodal status is a predictor of tumor biology and not simply tumor chronology.

The importance of ALND as a staging procedure was underscored in a study from the Institute Curie in Paris, France [78]. In that study, 658 breast cancer patients treated with lumpectomy and breast RT were

randomly assigned to either ALND or axillary RT. Adjuvant chemotherapy was administered to a few of these patients, and the decision to administer adjuvant therapy was based on nodal status. However, nodal status was not assessed in patients whose axillae were treated with RT, and so none of those patients received adjuvant chemotherapy. There was a small but significantly greater overall 5-year survival rate ($p > 0.014$) in the group treated with ALND (96.6%) compared with the group treated with axillary RT (92.6%). Many investigators attribute this small benefit to adjuvant chemotherapy. Therefore, if nodal status will influence the decision to administer adjuvant systemic therapy, the axilla should be managed with ALND and not with RT.

Node-positive patients have a worse prognosis than node-negative patients. Nodal status, however, does not predict response to therapy. Indeed, for both node-negative and node-positive patients, adjuvant systemic therapy reduces the annual odds of relapse and death by approximately 30 and 25%, respectively [79], although the absolute benefit of adjuvant systemic therapy is greater in node-positive patients because their risk of relapse and death is greater. As an example, consider two groups of breast cancer patients: a node-positive group with a 60% risk of death from breast cancer over the next 10 years and a node-negative group with a 20% risk of death. For both groups, the appropriate systemic therapy would reduce the risk of death from breast cancer by about 25%. For this node-positive group, however, the absolute benefit would be 15% (25% of 60% is 15%), whereas for this node-negative group, the absolute benefit would be only 5% (25% of 20% is 5%). Thus, nodal status provides important information not only about prognosis but also about the impact of adjuvant systemic therapy. An older woman with a good prognosis, node-negative tumor might be less willing to accept the toxicity of systemic therapy compared with a younger woman with a poor prognosis, node-positive tumor. However, in more recent years, the adjuvant treatment of breast cancer has been increasingly based on tumor predictive factors (ER status, HER2 status), which determine the responsiveness of a particular tumor to a specific treatment [80]. Thus, endocrine therapy (either tamoxifen or aromatase inhibitors) is administered to patients with ER-positive tumors, and herceptin is administered to patients with HER2-positive tumors.

13.4 Sentinel Lymph Node Biopsy

The ALND is not without risks. The procedure is associated with wound infections and morbidity of the upper extremity. Wound infection rates between 8% and 19% have been reported, but the reasons for this are poorly understood [81–83]. Some investigators speculate that the high rate of axillary wound infection might be due to the dead space beneath devascularized skin flaps or to an altered local immune response from disruption of local lymphatics. The ALND is also associated with significant morbidity of the upper extremity. In one series, the following upper extremity complications were reported: Paresthesia in 70% of patients, pain in 33%, weakness in 25%, arm lymphedema in 10%, and stiffness in 10% [84]. Today, more than half the patients with primary breast cancer are node negative. If identified appropriately, these patients could be spared the potential morbidity associated with ALND. In recent years, attention has turned to sentinel lymph node biopsy (SLNB) as a means of achieving this goal.

The sentinel lymph node is the first node to receive lymphatic drainage from a tumor. For any nodal basin, one might assume that, if the sentinel lymph node is free of metastatic tumor, then all other nodes in the basin should be free of tumor as well. Alternatively, involvement of the sentinel lymph node may mean that other nodes in the basin are involved. Thus, the SLNB is a diagnostic test that is useful in determining the status of the regional lymph nodes. This technique allows the surgeon to determine the status of the regional lymph nodes and avoid the morbidity associated with a more extensive lymph node dissection. For patients with primary breast cancer, the contraindications to SLNB include the presence of palpable axillary lymph node metastasis and prior breast or axillary surgery that might interfere with lymphatic drainage [85].

The SLNB technique was first described by Cabanas in 1977 as a means of assessing patients with penile carcinoma who might benefit from inguinofemoroiliac dissection [86]. Subsequently, Morton et al. demonstrated the feasibility and accuracy of SLNB for nodal staging in melanoma. [87]. More recently, SLNB has been widely used to stage patients with primary breast cancer, with the goal of reducing the morbidity of ALND [88]. Once identified, the sentinel node is excised and sent for histopathologic evaluation. Several studies have shown that the SLNB is quite accurate in predicting the status of the axillary lymph nodes

[89, 90]. Surgeons can identify the first draining (sentinel) lymph node by injecting blue dye or radioactive colloid intradermally around the primary tumor. Subareolar injection appears to be as accurate as peritumoral injection [91]. In fact, for nonpalpable, mammographically detected cancers, subareolar injection might be preferable. There has also been debate as to whether injection with radioactive colloid and blue dye is more accurate than injection with blue dye alone as a means of identifying the sentinel node. Morrow et al. compared the two methods in a randomized trial and found that they were equally effective [92]. Thus, the preferences of the surgeon determine which method is used.

Giuliano et al. compared 134 patients with primary breast cancer who received standard ALND with 164 patients who underwent SLNB followed by completion ALND [93]. The reported incidence of nodal metastasis was 29 and 42%, respectively. Thus, the reported incidence of node-positive cases is greater with SLNB than with standard ALND. Following ALND, one or two sections of each nonsentinel lymph node are generally examined with routine hematoxylin and eosin (H and E) staining; however, pathologists pay more attention to the sentinel lymph node. These nodes often are evaluated with multiple sectioning, H and E staining and immunohistochemical staining for cytokeratin. Thus, the SLNB results in a focused histopathologic evaluation of a single lymph node, and the probability of identifying micrometastases is thereby increased. The clinical relevance of these extra cases of micrometastases is poorly understood.

The long-term effects of SLNB alone (omitting axillary clearance) are poorly understood, however. The false-negative rate of SLNB might be as high as 10%, compared with 4% following a level I and II ALND [94]. The false-negative rate refers to the percentage of patients with nodal metastases who are incorrectly designated as node negative. False-negatives may lead to incorrect decisions concerning adjuvant therapy, thereby affecting outcome. These and other concerns about SLNB will be addressed in ongoing trials comparing long-term outcome following SLNB or ALND. However, randomized trials have now shown that SLNB can significantly reduce the morbidity associated with ALND [95–97]. SLNB has therefore been widely accepted now in the management of early breast cancer.

The sentinel node biopsy concept is discussed in more detail in a separate chapter in this book.

13.5 Conclusion

The modern surgical treatment of primary breast cancer dates back to the late nineteenth century, with Halsted's description of the radical MT. However, the radical MT is now rarely utilized in breast cancer management. Today, BCS with RT is the preferred option for most women with primary breast cancer. For those who are not suitable candidates for BCS, the modified radical MT is an acceptable alternative, and in recent years, greater numbers of women have been opting for modified radical MT and a contralateral prophylactic MT (i.e., bilateral MT). Patients treated with the modified radical MT or bilateral MT will generally seek breast reconstructive surgery. It should also be noted that recent studies indicate that local recurrences may increase the risk of death from breast cancer, with four local recurrences resulting in one additional breast cancer death over a 15-year period. Thus, RT should be considered for most women who opt for BCS. Over the years, the management of the axilla has been a topic of considerable interest. Today, SLNB is considered the preferred alternative to the standard ALND. There are several ongoing trials comparing long-term outcomes following SLNB vs. ALND.

Acknowledgment The opinions or assertions contained herein are the private views of the authors and should not be construed as reflecting the views of the Departments of the Army, Navy, or Defence.

References

1. Virchow R (1863) Cellular pathology. JB Lippincott, Philadelphia
2. Halsted WS (1894) The results of operations for the cure of cancer of the breast performed at the Johns Hopkins hospital from June 1889 to January 1894. Ann Surg. 20:497–55
3. Margolese RG (1999) Surgical considerations for invasive breast cancer. Surg Clin North Am. 79:1031–46
4. Bonnadonna G, Valagussa P (1988) The contribution of medicine to the primary treatment of breast cancer. Cancer Res. 48:2314–24
5. Urban JA, Marjoni MA (1971) Significance of internal mammary lymph node metastases in breast cancer. AJR Am J Roentgenol. 111:130–6
6. Wagensteen OH (1957) Another look at supraradical operation for breast cancer. Surgery. 41:857–61
7. Andreassen M, Dahl-Iversen E, Sorensen B (1954) Extended exeresis of regional lymph nodes at operation for carcinoma

of breast and the result of a 5-year follow-up of the first 98 cases with removal of the axillary as well as the supraclavicular glands. Acta Chir Scan. 107:206–13
8. Lacour J, Bucalossi P, Cacers E et al (1976) Radical mastectomy versus radical mastectomy plus internal mammary dissection. Cancer. 37:206–14
9. McWhirter R (1955) Simple mastectomy and radiotherapy in treatment of breast cancer. Br J Radiol. 28:128–39
10. Mustakalio S (1972) Conservative treatment of breast carcinoma–review of 25-year follow-up. Clin Radiol. 23:110–6
11. Margolese R (1992) Surgical considerations in selecting local therapy. J Natl Cancer Inst Monogr. 11:41–8
12. Bloom HJG, Richardson WW, Harries EJ (1962) Natural history of untreated breast cancer (1805–1933). BMJ. 2: 213–21
13. Fisher B, Redmond C, Fisher ER et al (1985) Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Eng J Med. 312:674–81
14. Cancer Research Campaign Working Party (1980) Cancer research campaign (King's/Cambridge) trial for early breast cancer. Lancet. 2:55–60
15. Veronesi U, Cascinelli N, Mariani L et al (2002) Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 347:1227–32
16. Arriagada R, Le MG, Rochard F et al (1996) Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. J Clin Oncol. 14: 1558–64
17. Fisher B, Anderson S, Bryant J et al (2002) Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 347:1233–41
18. Poggi MM, Danforth DN, Sciuto LC et al (2003) Eighteen-year results in the treatment of early breast carcinoma with mastectomy versus breast-conservation therapy. Cancer. 98:696–702
19. van Dongen JA, Voogd AC, Fentiman IS et al (2000) Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European organization for research and treatment of cancer 10801 trial. J Natl Cancer Inst. 92:1143–50
20. Bilchert-Toft M, Rose C, Anderson JA et al (1992) Danish randomized trial comparing breast-conservation therapy with mastectomy. J Natl Cancer Inst Monogr. 11:19–25
21. Lonning PE (1991) Treatment of early breast cancer with conservation of the breast: a review. Acta Oncol. 30:779–92
22. Fowble B (1999) Ipsilateral breast tumor recurrence following breast-conserving surgery for early stage invasive breast cancer. Acta Oncol. 13(Suppl):9–17
23. Fisher B (1996) Personal contributions to progress in breast cancer research and treatment. Semin Oncol. 23:414–27
24. Fisher B, Anderson S, Fisher ER et al (1991) Significance of ipsilateral breast tumor recurrence after lumpectomy. Lancet. 338:327–31
25. Kurtz JM, Spitalier JM, Amalric R et al (1990) The prognostic significance of late local recurrence after breast-conserving therapy. Int J Radiat Oncol Biol Phys. 18:87–93
26. Donegan WL, Perez-Mesa CM, Watson FR (1966) A biostatistical study of locally recurrent breast carcinoma. Surg Gynecol Obstet. 122:529–40
27. Borger J, Kemperman H, Hart A et al (1994) Risk factors in breast-conservation therapy. J Clin Oncol. 12:653–60
28. Jatoi I, Proschan MA (2005) Randomized trials of breast-conserving therapy versus mastectomy for primary breast cancer: a pooled analysis of updated results. Am J Clin Oncol. 28(3):289–94
29. Ving-Hung V, Verschraegen C (2004) Breast-conserving surgery with or without radiotherapy: pooled analysis for risks of ipsilateral breast tumor recurrence and mortality. J Natl Cancer Inst. 96:114–21
30. Early Breast Cancer Trialists' Collaborative Group (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Lancet. 366: 2087–106
31. Turner BC, Harrold E, Matloff E et al (1999) BRCA1/BRCA2 germline mutations in locally recurrent breast cancer patients after lumpectomy and radiation therapy: implications for breast-conserving management in patients with BRCA1/BRCA2 mutations. J Clin Oncol. 17:3017–24
32. Kinzler KW, Vogelstein B (1997) Gatekeepers and caretakers. Nature. 386:761–3
33. Pierce LJ, Strawderman M, Narod SA et al (2000) Effect of radiotherapy after breast-conservig treatment in women with breast cancer and germline BRCA ½ mutations. J Clin Oncol. 18(19):3360–9
34. Metcalfe KA, Lubinski J, Ghadirian P et al (2008) Prediction of contralateral prophylactic mastectomy in women with a BRCA 1 or BRCA 2 mutation: the hereditary breast cancer clinical study group. J Clin Oncol. 26(7):1093–7
35. Benson J, Jatoi I (2009) Management options breast cancer: case histories, best practice, and clinical decision-making. Informa Healthcare, London
36. Hughes KS, Schnaper LA, Berry D et al (2004) Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med. 351(10):971–7
37. Atkins H, Hayward JL, Klugman OJ et al (1972) Treatment of early breast cancer: a report after ten years of a clinical trial. BMJ. 2(5811):423–9
38. Winchester O, Cox J (1992) Standards for breast-conservation treatment. CA Cancer J Clin. 42:134–62
39. Foster RS, Wood WC (1998) Alternative strategies in the management of primary breast cancer. Arch Surg. 133: 1182–6
40. Veronesi D, Bonadonna G, Zurrida S et al (1995) Conservation surgery after primary chemotherapy in large carcinomas of the breast. Ann Surg. 222:609–11
41. Lehman CD, Gatsonis C, Kuhl CK et al (2007) MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer. N Engl J Med. 356: 1295–303
42. Solin LJ, Orel SG, Hwang SG et al (2008) Relationship of breast magnetic resonance imaging to outcome after breast-conservation treatment with radiation for women with early stage invasive breast carcinoma or ductal carcinoma in situ. J Clin Oncol. 26:386–91
43. Nattinger AB, Hoffmann RG, Kneusel RT et al (2000) Relation between appropriateness of primary therapy for early stage breast carcinoma and increased use of breast-conserving surgery. Lancet. 356:1148–53

44. Nattinger AB, Gottlieb MS, Veum J et al (1992) Geographic variation in the use of breast-conserving treatment for breast cancer. N Engl J Med. 326:1147–9
45. Kelemen JJ, Poulton T, Swartz MT et al (2001) Surgical treatment of early stage breast cancer in the department of defense healthcare system. J Am Coll Surg. 192:293–7
46. Freedman RA, He Y, Winer EP, Keating NL (2009) Trends in racial and age disparities in definitive local therapy of early stage breast cancer. J Clin Oncol. 27(5):713–9
47. Tuttle TM, Haberman EB, Grund EH et al (2007) Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. J Clin Oncol. 25(33):5203–309
48. Herrinton LJ, Barlow WE, Yu O et al (2005) Efficacy of prophylactic mastectomy in women with unilateral breast cancer: a cancer research network project. J Clin Oncol. 23(19): 4275–86
49. Helzlsouer KJ (2005) Contralateral prophylactic mastectomy: quantifying benefits and weighing the harms. J Clin Oncol. 23(19):4251–3
50. Nattinger AB, Hoffmann RG, Shapiro R et al (1996) The effect of legislative requirements on the use of breast-conserving surgery. N Engl J Med. 335:1035–40
51. Dolan J, Granchi TS, Miller CC et al (1999) Low use of breast-conservation surgery in medically indigent populations. Am J Surg. 178:470–4
52. Collins ED, Moore CP, Clay KF et al (2009) Can women with early stage breast cancer make an informed decision for mastectomy? J Clin Oncol. 27(4):519–25
53. Dowden RV, Rosato FE, McGraw JB (1979) Reconstruction of the breast after mastectomy for cancer. Surg Gynecol Obstet. 149:109–15
54. Johnson CH, van Heerden JA, Donohue JH et al (1989) Oncological aspects of immediate breast reconstruction following mastectomy for malignancy. Arch Surg. 124:819–23
55. Vinton AL, Traverso W, Zehring RD (1990) Immediate breast reconstruction following mastectomy is as safe as mastectomy alone. Arch Surg. 125:1303–8
56. Dean C, Chetty D, Forrest APM (1983) Effects of immediate breast reconstruction on psychosocial morbidity after mastectomy. Lancet. 1:459–62
57. Damen TH, Mureau MA, Timman R et al (2009) The pleasing end result after DIEP flap breast reconstruction: a review of additional operations. J Plast Reconstr Aesthet Surg. 62(1):71–6
58. Jatoi I, Kaufmann M, Petit JY (2006) Atlas of breast surgery. Springer, Heidelberg
59. Corral CJ, Mustoe TA (1996) Special problems in breast cancer therapy: controversy in breast reconstruction. Surg Clin North Am. 76:309–26
60. Hulka BS, Kerkvliet NL, Tugwell P (2000) Experience of a scientific panel formed to advise the federal judiciary on silicone breast implants. N Engl J Med. 342:812–5
61. Nyren O, Yin L, Josefsson S et al (1998) Risk of connective tissue disease and related disorders among women with breast implants: a nation-wide retrospective cohort study in Sweden. BMJ. 316:417–22
62. Janowsky EC, Kupper LL, Hulka BS (2000) Meta-analyses of the relation between silicone breast implants and the risk of connective tissue diseases. N Engl J Med. 342:781–90
63. Schneider WJ, Hill HL Jr, Brown RG (1977) Latissimus dorsi myocutaneous flap for breast reconstruction. Br J Plast Surg. 30:277–81
64. Amez Z, Smith R, Eder R (1988) Breast reconstruction by the free lower transverse rectus abdominis muscular cutaneous flap. Br J Plast Surg. 41:500–7
65. Alderman AK, McMahon L, Wilkins EG (2003) The national utilization of immediate and early delayed breast reconstruction and the impact of sociodemographic factors. Plast Reconstr Surg. 111:695–703
66. Alderman AK, Wei Y, Birkmeyer JD (2006) Use of breast reconstruction after mastectomy following the Women's Health and Cancer Rights Act. JAMA. 295(4):387–8
67. Jatoi I (1999) Management of the axilla in primary breast cancer. Surg Clin North Am. 79:1061–73
68. Veronesi U, Rilke R, Luini A et al (1987) Distribution of axillary node metastases by level of invasion. Cancer. 59:682–7
69. Morrow M (1996) Axillary dissection: when and how radical? Semin Surg Oncol. 12:321–7
70. Harris JR, Osteen RT (1985) Patients with early breast cancer benefit from effective axillary treatment. Breast Cancer Res Treat. 5:17–21
71. Samphao S, Eremin JM, El-Sheemy M, Eremin O (2009) Management of the axilla in women with breast cancer: current clinical practice and a new selective targeted approach. Ann Surg Oncol. 15(5):1282–96
72. Epstein RI (1995) Routine or delayed axillary dissection for primary breast cancer? Eur J Cancer. 31A:1570–3
73. Sacks NPM, Baum M (1993) Primary management of carcinoma of the breast. Lancet. 342:1402–8
74. Baxter N, McCready DR, Chapman JA et al (1996) Clinical behavior of untreated axillary nodes after local treatment for primary breast cancer. Ann Surg Oncol. 3:235–40
75. Graverson HP, Bilchert-Toft M, Andersen J et al (1988) Danish breast cancer cooperative group. Breast cancer: risk of axillary recurrence in node-negative patients following partial dissection of the axilla. Eur J Surg Oncol. 14: 407–12
76. Jatoi I, Hilsenbeck SG, Clark GM et al (1999) The significance of axillary lymph node metastasis in primary breast cancer. J Clin Oncol. 17:2334–40
77. Jatoi I, Anderson WF, Rosenberg PS (2008) Qualitative age interactions in breast cancer: a tale of two diseases? Am J Clin Oncol. 31:504–6
78. Cabanes PA, Salmon RI, Vilcoq JP et al (1992) Value of axillary dissection in addition to lumpectomy and radiotherapy in early breast cancer. Lancet. 339:1245–8
79. Gelber RD, Goldhirsch A, Coates AS (1993) Adjuvant therapy for breast cancer: understanding the overview. J Clin Oncol. 11:580–5
80. Lonning PE (2007) Breast cancer prognostication and prediction: are we making progress? Ann Oncol. 18(Suppl 8): viii 3–7
81. Bold RI, Mansfield PF, Berger DH et al (1998) Prospective, randomized, double-blind study of prophylactic antibiotics in axillary lymph node dissection. Am J Surg. 176:239–43
82. Coit DG, Peters M, Brennan MF (1991) A prospective randomized trial of perioperative cefazolin treatment in axillary and groin dissection. Arch Surg. 126:1366–72
83. Rotstein C, Ferguson R, Cummings KM et al (1992) Determinants of clean surgical wound infections for breast procedures at an oncology center. Infect Control Hosp Epidemiol. 13:207–14

84. Ivens D, Hoe AL, Podd TJ et al (1992) Assessment of morbidity from complete axillary dissection. Br J Cancer. 66:136–8
85. Lyman GH, Giuliano AE, Somerfield MR et al (2005) American society of clinical oncology guideline recommendations for sentinel lymph node biopsy in early stage breast cancer. J Clin Oncol. 23:7703–20
86. Cabanas RM (1977) An approach for the treatment of penile carcinoma. Cancer. 39:456–66
87. Morton DL, Wen DR, Wong JR et al (1992) Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg. 127:392–9
88. Chen AY, Halpern MT, Schrag MM et al (2008) Disparities and trends in sentinel lymph node biopsy among early stage breast cancer patients (1998–2005). J Natl Cancer Inst. 100(7):462–74
89. Giuliano AE, Jones RC, Brennan M (1997) Sentinel lymphadenectomy in breast cancer. J Clin Oncol. 15:2345–50
90. Veronesi D, Paganelli G, Galimberti V (1997) Sentinel node biopsy to avoid dissection in breast cancer with clinically negative lymph nodes. Lancet. 349:1864–7
91. Smith LF, Cross MJ, Klimberg VS (2000) Subareolar injection is a better technique for sentinel node biopsy. Am J Surg. 180:434–7
92. Morrow M, Rademaker AW, Bethke KP et al (1999) Learning sentinel node biopsy: results of a prospective trial of two techniques. Surgery. 126:714–20
93. Giuliano AE, Dale PS, Turner RR et al (1995) Improved axillary staging of breast cancer with sentinel node lymphadectomy. Ann Surg. 222:394–9
94. McMasters KM, Giuliano AE, Ross MI et al (1998) Sentinel lymph node biopsy for breast cancer – not yet standard of care. N Engl J Med. 339:990–5
95. Veronesi U, Paganelli G, Viale G et al (2003) A randomized comparison of sentinel node biopsy with routine axillary dissection in breast cancer. N Engl J Med. 349(6): 546–53
96. Lucci A, McCall LM, Beitsch PD et al (2007) Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American college of surgeons oncology group trial Z0011. J Clin Oncol. 25: 3657–63
97. Mansel RE, Fallowfield L, Kissin M et al (2006) Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC trial. J Natl Cancer Inst. 98(9): 599–609

Sentinel Node Concept

14

John R. Benson and Vassilis Pitsinis

14.1 Introduction

Some form of axillary surgery is an integral component in the locoregional management of early breast cancer. Surgical techniques have become progressively less extensive over the past 30 years in terms of both parenchymal and nodal resection of breast and axillary tissues, respectively. Despite the widespread introduction of breast conservation surgery (BCS), a formal axillary lymph node dissection (ALND) was, until recently, the standard procedure of choice for the management of the axilla in the majority of patients irrespective of primary tumour characteristics. Breast screening programmes and heightened public awareness have led to smaller tumour size at presentation and a lower proportion of patients with nodal involvement. Approximately 25–30% of patients now have nodal disease at the time of diagnosis compared with 50% two decades ago [1]. For those patients with positive nodes, removal of axillary nodes containing tumour foci minimises the chance of locoregional relapse and can provide crucial information for guiding systemic adjuvant treatments. Moreover, axillary nodal status remains the single most important prognostic factor in breast cancer and has yet to be superceded by newer molecular indices [1, 2]. Nonetheless, for node-negative patients with favourable primary tumour parameters, ALND represents over-treatment and can be associated with significant morbidity [3, 4]. Increased rates of node negativity have spurred the investigation of non-invasive methods for imaging the axillary nodes. However, these alone are questionable as a staging modality because of the limitations of resolution at the microscopic tumour level. Axillary ultrasound in combination with percutaneous node biopsy for tissue acquisition is yielding useful pre-operative staging information on regional nodes [5]. The optimum method for managing the axilla in breast cancer patients remains controversial, but there is compulsion to apply surgical methods for purposes of staging in all patients with invasive cancer. The aforementioned stage shift coupled with failure of ALND dissection to confer any clear survival benefit [6, 7] have prompted exploration of less intrusive methods for surgical staging of the axilla. These alternative methods involve either a blind or targeted form of sampling in which a variable, though restricted, number of nodes are removed (usually <4–5 nodes). Non-targeted sampling of the axillary nodes has been championed by a surgical minority for several years, but this technique has now evolved into a targeted form of sampling using blue dye alone, the so-called blue dye-assisted node sampling (BDANS) [8]. Sentinel lymph node biopsy (SLNB) has been embraced around the world as a standard of care for breast cancer patients and ideally incorporates dual localization techniques using both blue dye and radioisotopic localization. Though SLNB is now the dominant method for staging the axilla in clinically node-negative patients, technical aspects mandate standardisation and confirmation that long-term survival is not impaired as a consequence of either withholding systemic therapies or failing to remove non-sentinel nodes in the context of false negativity is awaited.

Breast cancer is a heterogeneous disease in terms of its pathobiology and this renders any blanket approach to the management of the axilla inappropriate. A selective policy based on thresholds of probability for nodal involvement could include not only ALND, but also SLNB, BDANS and observation alone. It should be noted that it is not the absolute incidence of nodal

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_14, © Springer-Verlag Berlin Heidelberg 2010

involvement per se which is important, but rather the proportion of these metastases which develop into clinically relevant disease. The latter might manifest either as locoregional relapse or as distant metastases, which have arisen from axillary deposits acting as a source for tertiary spread.

This chapter will address nodal anatomy and patterns of lymphatic dissemination in breast cancer together with underlying biological paradigms. Some basic clinical issues will be discussed, including the indications for ALND, the optimum method for staging the axilla in patients who do not require ALND and whether a group of patients for whom axillary surgery can be safely omitted exist.

14.2 Anatomy of the Axillary Lymph Nodes

An understanding of nodal anatomy is important in the surgical management of breast cancer. There is often confusion in the designation of nodal groupings with classification based on clinical, anatomical or surgical criteria.

1. Clinical groupings – medial, lateral, anterior, posterior, apical
2. Anatomical groupings – lateral, anterior (pectoral), posterior (subscapular), central, subclavicular, interpectoral (Rotter's)
3. Surgical – the axillary lymph nodes can be divided into three compartments, which are defined in terms of their relationship to the pectoralis minor muscle [9].

LEVEL I – nodes below and lateral to the pectoralis minor muscle

LEVEL II – nodes deep to the muscle and lying posterior to the medial and lateral borders of the pectoralis minor muscle

LEVEL III – nodes above and medial to pectoralis minor

A complete ALND refers to removal of axillary nodes at levels I, II and III, whilst a partial ALND implies a more limited clearance of nodes at levels I and II only. The term sampling describes a blind or targeted resection of a variable number of nodes, usually at level I; the number of nodes removed is generally inversely related to the degree of targeting (Fig. 14.1).

14.3 Lymphatic System of the Breast

Metastases to regional lymph nodes is a common pattern of dissemination for solid epithelial tumours, which commonly invade local structures and spread in a progressive and sequential manner from a primary tumour focus. The locoregional pathways of spread lie in anatomical continuity with lymphatic vessels, which act as a link between the index tumour and regional nodes. Metastatic dissemination of breast cancer occurs predominantly via the lymphatic system in accordance with the Halstedian paradigm, though it is acknowledged that a significant proportion of breast cancers are systemic at the outset as a result of tumour cells entering the bloodstream at an early stage of neoplastic development. Furthermore, such haematogenous dissemination is not conditional upon nodal involvement and access to the circulation can occur through both lymphatico-venous communications in regional nodes and the "leaky" endothelium of the tumour neovasculature.

The lymphatics of the breast form an extensive and complex network of periductal and perilobular vessels, which drain principally to the axillary nodes. The mammary gland is derived from ectoderm and develops from anterior thoracic wall structures. As noted by Haagensen [10], the lymphatics of the breast skin and parenchymal tissue are interconnected, and this accounts for preferential drainage of cutaneous malignancies to axillary nodes. Moreover, current practises in SLNB, whereby tracer agents are injected intradermally, are dependent upon the lymphatic system of the breast functioning as a single biological unit. Flow within this network of valveless vessels is passive, and this results in a degree of plasticity, which is relevant to malignant infiltration; the unidirectional flow of lymph may be diverted due to blockage at proximal sites by tumour emboli. The subepithelial lymphatics of the skin of the breast represent part of the superficial system of the neck, thorax and abdomen. These vessels are confluent over the surface of the body, and the subepithelial plexus of lymphatics communicates directly with subdermal vessels to form a cutaneous plexus. Within the region of the nipple-areolar complex, this cutaneous plexus is linked to the Sappey subareolar plexus, which receives lymphatics from the glandular tissue of the breast and has a key role in accommodating the dramatic surges of lymph flow occurring during

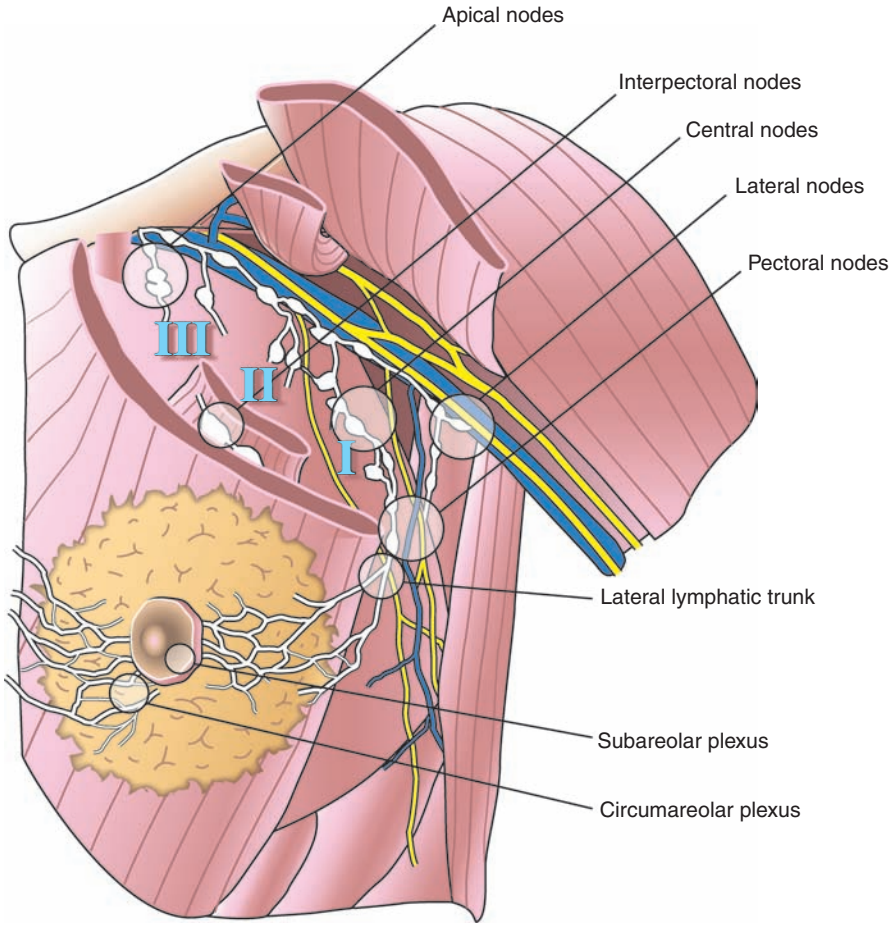

Fig. 14.1 The axillary lymph nodes are located at levels I, II and III; this is a surgical classification and indicating nodes, which lie below/lateral, deep/posterior and above/medial to the pectoralis minor muscle, respectively. The lymphatic system of the breast is a complex network of arborising vessels. A cutaneous plexus is linked to a subareolar plexus, which receives lymphatics from the glandular tissue of the breast. From this subareolar and a related circumareolar plexus, lymph flows principally to the axillary nodes via a lateral lymphatic trunk

lactation [11, 12]. From this subareolar and a related circumareolar plexus, lymph flows principally to the axillary nodes via a lateral lymphatic trunk. This, together with minor inferior and medial lymphatic trunks, drain along the surface of the breast to penetrate the cribriform fascia and reach the various groups of axillary nodes (Fig. 14.1).

Although the internal mammary nodes were recognised by Handley as a primary route for lymphatic drainage from medial and central zones of the breast [13], the majority of breast cancers metastasise to the axillary nodes irrespective of the index quadrant [14]. Fewer than 10% of node-positive tumours exclusively affect the internal mammary nodes, and clinical manifestations of such metastases are rare. Furthermore, the biological significance of internal mammary node involvement is uncertain [15] and substantial morbidity can ensue from surgical extirpation of these nodes, with no gains in overall survival from these more aggressive resections [16]. The internal mammary chain (IMC) represents one of the accessory drainage pathways of the breast and is considered to receive up to one-quarter of lymphatic flow. However, former estimates based on post-partum injection of colloidal gold suggested that as little as 3% of the breast lymph flows to the IMC. The IMC is identified on routine lymphoscintigraphy during sentinel node localization in about 15% of cases [14]. Accessory pathways of lymphatic drainage assume greater importance in more advanced states of disease when the main axillary drainage route has become obstructed [14, 17]. In addition to the IMC, these accessory pathways include the following routes:-

1. Substernal, crossover (contralateral IMC) [12, 18]
2. Pre-sternal crossover (contralateral breast) [19]
3. Mediastinal [19]
4. Rectus abdominus muscle sheath to subdiaphragmatic and subperitoneal plexus (liver and peritoneal nodes)

Interestingly, with the advent of lymphoscintigraphy as part of sentinel lymph node mapping, drainage to the IMC is more likely when isotope is injected deep within the breast (close to the pectoral fascia) and uncommon when peri-areolar injections are employed [20].

The original definition of the sentinel lymph node was *"the first draining lymph node on the direct pathway from the primary tumour site"* [21]. In its purist form, this definition implied that there was a single node to which cancer cells drain first before proceeding on to higher echelon nodes. The sentinel node hypothesis is "Halstedian" and presupposes a sequential and orderly spread of cancer cells from the primary tumour to the first draining or sentinel node (usually level I), from whence passage to level II and in turn level III nodes occurs. This hypothesis has proved to be slightly imperfect and does not accord with the current understanding of lymphatic drainage patterns from anatomical studies nor the pathophysiology of disordered lymphatic flow [22]. The networks of lymphatic vessels arborise extensively in multiple directions [23] and converge towards a group of three to five lymph nodes at level I of the axilla [24] (Fig. 14.2). Detailed anatomical studies undertaken in the 1950s revealed no evidence of a single first or "sentinel" lymph node at the "gates of the axilla" towards which all lymphatic channels converge before passing to more distal nodes. As experience with SLNB has accrued using several different methodologies, the average number of nodes removed is between two and three with false-negative rates being minimised when multiple sentinel nodes are harvested [25]. Indeed, when palpably suspicious nodes are also removed at operation and classified as "sentinel", many studies report an average of almost four nodes [22, 26]. This group of sentinel nodes may therefore correspond to the group of three to five nodes at level I from which there is a predictable passage of lymph towards level II and level III nodes. The "plasticity" of the lymphatic system potentially allows skip metastases to occur in which nodes at levels II and III become involved in the absence of disease affecting level I nodes. In a study of the distribution of nodal metastases in more than 500 patients, Veronesi and colleagues reported skip metastases in only 4% of cases [27]. In this study, level I nodes alone were found to be involved in 58%, levels I and II nodes in 22% and all three levels in 16% of patients. Despite the occurrence of skip lesions, there is generally an orderly passage of lymph from nodes at level I through levels II and III. When nodes at levels I and II are tumour free, the chance of skip metastases at level III is only 2–3%. For this reason, a standard ALND involves clearance of nodes at levels I and II (partial ALND) only. When at least ten nodes have been removed during a partial ALND, the axilla should be correctly staged in 96% of patients with primary breast cancer. When fewer than ten negative nodes are resected, there is less confidence that the axillary basin is truly negative and involved nodes may have been left behind in a non-targeted dissection. Conversely, when overtly malignant nodes are present at levels I and II, it is customary to undertake a complete ALND, which includes level III nodes. The ipsilateral supraclavicular nodes can subsequently be irradiated when extensive nodal involvement is confirmed histologically. More radical resection of axillary nodes is associated with greater upper limb morbidity, including lymphoedema, shoulder stiffness, pain and parasthesia [3, 4]. The benefits of ALND in terms of regional disease control, staging information and prognostication must be balanced against these potential sequelae of which lymphoedema is the most serious concern. The overall incidence of lymphoedema is cited between 10–30% [4, 28–30]. Rates are generally lower for a level II ALND (10–15%) compared with a level III ALND (25%). The combination of a complete ALND with irradiation of the axilla can lead to rates of lymphoedema as high as 40%. There is rarely any justification for combined axillary dissection and irradiation nowadays. Furthermore, surgeons often loosely refer to level II/III ALND in the literature and this confounds interpretation of data on rates of lymphoedema formation. It has been commented that removal of an additional three to four nodes maximum at level III is unlikely to significantly impact on documented rates of lymphoedema [31]. The latter remains a common complication, which can lead to major physical and psychological morbidity [32], and in the long term to the rare complication of lymphangiosarcoma (Stewart–Treves Syndrome) [33]. Though it is often the non-dominant upper limb which is affected (most breast cancers occur on the left side), lymphoedema causes symptoms of heaviness and discomfort with associated functional impairment and an unsightly appearance. The accumulation of protein-rich fluid within the extracellular compartment renders the limb prone to recurrent superficial infection, which contributes to more chronic inflammatory changes with fibrosis. Disruption and blockage of the lymphatics raises hydrostatic

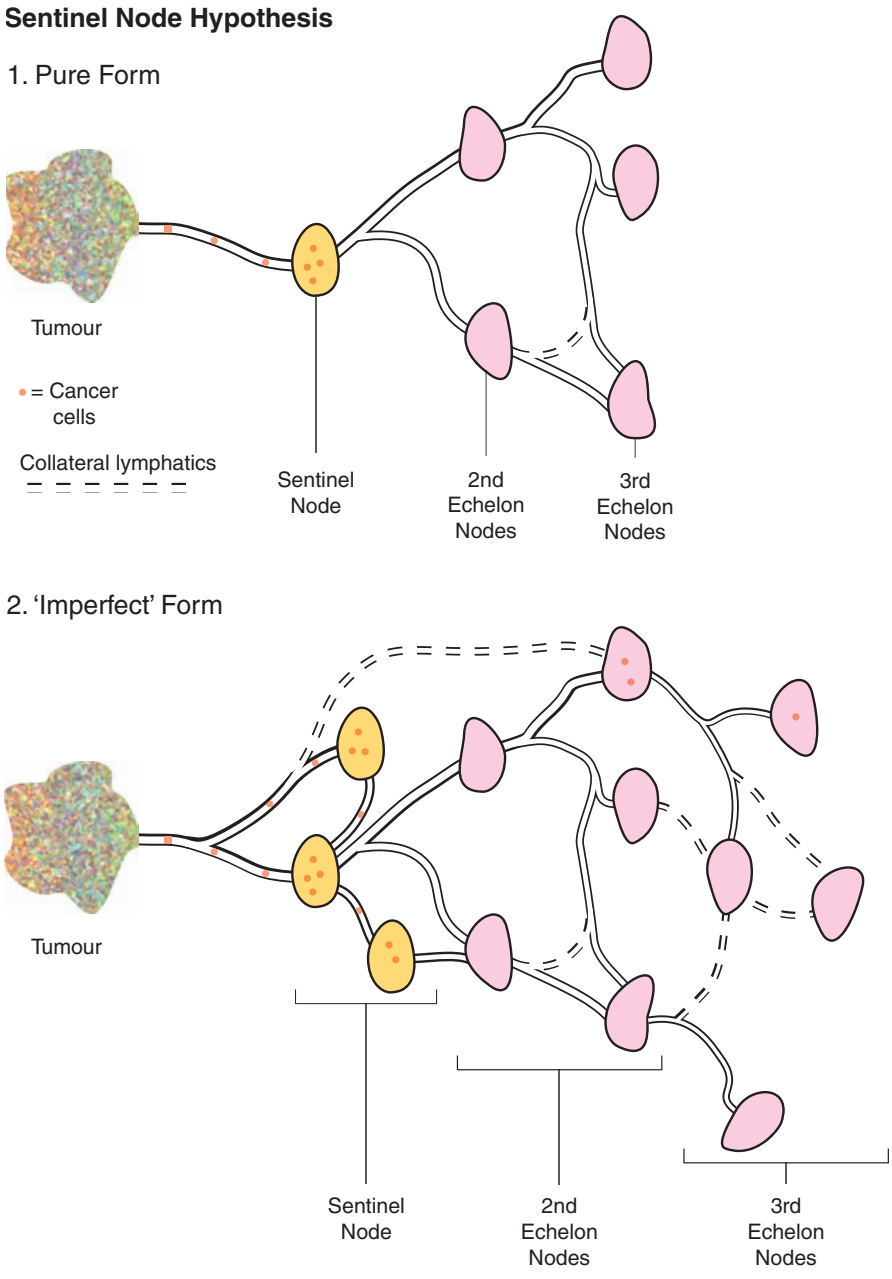

Fig. 14.2 (**1**) According to the sentinel node hypothesis in its "*pure*" form, cancer cells pass from a primary tumour focus to a first draining or sentinel node, from where sequential passage to second and third echelon nodes occurs. (**2**) In reality, cancer cells drain initially to a group of three to five nodes, which are all "sentinel" nodes if they are blue, hot, blue and hot or palpably suspicious. The plasticity of the lymphatic system permits cancer cells to travel via collaterals to non-sentinel nodes. This accounts for the finite false-negative rate of sentinel node biopsy

pressure within other parts of the lymphatic system and promotes further tissue oedema by hampering absorption of excess fluid back into the lymphatic vessels. The precise aetiology of lymphoedema remains unclear, but it is related to the extent of extirpation of axillary nodes. The latter disrupts lymphatic drainage pathways and thus compromised function is more likely when surgical dissection is more extensive [32].

14.4 Axillary Lymph Node Dissection

14.4.1 Surgical Aspects

The axilla is a pyramidal space with an apex directed into the route of the neck and a base bounded infront by the anterior axillary fold (lower border of pectoralis

major), behind by the posterior axillary fold (tendons of latissimus dorsi and teres major muscles) and medially by the chest wall [17]. The axillary tissue is composed of adipose and nodal elements. A partial (level II) ALND involves resection of all tissue inferior to the level of the axillary vein with no attempt to skeletonise the latter. All nodal/fatty tissue is cleared from the lateral edge of the latissimus dorsi muscle and to the medial border of pectoralis minor muscle. Wrapping of the arm during surgery permits flexion and adduction of the upper arm with relaxation of the pectoralis major muscle, which facilitates dissection towards the apex of the axilla. The pectoralis minor muscle was previously either removed or divided to gain access to higher echelon nodes (namely at level III). The nerves to serratus anterior (long thoracic) and latissimus dorsi (thoracodorsal nerve) muscles are closely applied to the medial and posterior walls of the axilla, respectively. These are important motor nerves and should be preserved during axillary surgery unless encased by tumour. Damage to the long thoracic nerve results in a winged scapula and care should be taken not to inadvertently draw this structure laterally away from the chest wall during dissection of the axillary contents. By contrast, the intercostobrachial nerve (ICBN) is purely sensory and crosses the axilla towards its base. It tends to be embedded in fatty/nodal tissue and its anatomical course renders it vulnerable during extirpative surgery. The ICBN has historically been considered a minor sensory nerve whose sacrifice during axillary surgery results in transient sensory loss and parasthesiae with minimal symptoms. In recent years, increasing attention has focused on chronic residual morbidity consequent to nerve division and pathophysiology of the ICBN. Provided the nerve is not encased by infiltrative tissue, oncological clearance is adequate and some surgeons advocate preservation of the ICBN, particularly when there is no macroscopic evidence of nodal involvement. Temple and colleagues found that more than one-third of patients in whom the ICBN was sacrificed reported symptoms of dysthaesthesia/parasthesia and concluded that nerve preservation reduces long-term morbidity [34]. However, the main nerve trunk often divides distally into smaller branches, which can preclude preservation. Inadvertent division is not uncommon and the potential benefits of nerve preservation are dubious and poorly documented; nerve preservation does not eliminate potential sensory disturbances. Furthermore, randomised trials investigating preservation of the ICBN reveal no significant reduction in incidence of pain and parasthesia with long-term follow up. Nerve division can be associated with relatively normal sensation due to neural anastomoses in the vicinity of the shoulder and upper arm. Conversely, the majority of pain symptoms associated with nerve section are controlled with simple analgesia and resolve after a few months [35, 36]. It has been suggested that maintenance of an intact nerve can increase the chance of subsequent entrapment by scar tissue, which can lead to troublesome and persistent symptoms.

A formal ALND is indicated for all patients with early stage breast cancer who are clinically node positive (i.e. considered to have clinically malignant nodes). In addition, clinically node-negative tumours measuring >5 cm in maximum diameter or those patients with inflammatory cancers should undergo ALND at the outset. The chance of nodal involvement is related to tumour size and it is difficult to justify SLNB for larger tumours when there is a high probability of node positivity. Furthermore, there is no clinical trial data on the efficacy of SLNB as a staging procedure for tumours exceeding 5 cm for which false-negative rates are likely to be unacceptably high. Clinical examination of the axilla is notoriously inaccurate with a 30% error rate either way i.e. 30% of clinically node-negative patients will prove to have pathological nodal involvement whilst 30% of clinically node-positive patients will have no evidence of axillary metastases. Pre-operative axillary ultrasound and percutaneous node biopsy is increasingly being used to identify node-positive patients who can then proceed to ALND as either primary surgical treatment or following induction chemotherapy. Percutaneous needle biopsy of lymph nodes will confirm positivity in more than 90% of women with ≥4 positive nodes and select 40–50% of node-positive cases overall [5, 37]. Those patients with non-inflammatory tumours ≤5 cm in size are eligible for some form of node sampling as a staging procedure (SLNB, BDANS or blind sampling) [38]. Notwithstanding previous comments, it remains unclear whether patients with a negative axillary ultrasound and core biopsy are candidates for SLNB when tumour size exceeds 5 cm.

14.4.2 Overall Survival

Axillary metastases are viewed as indicators of risk for distant relapse and do not determine clinical outcome

[39]. The majority of studies have not demonstrated any gains in survival from ALND, though the NSABP-B04 trial was confounded by salvage dissection for local recurrence and not powered to detect any benefit smaller in magnitude than 7% [40]. Others have suggested that some benefit may be derived from more thorough node dissection [41–43]. A large meta-analysis of 3,000 cases has claimed a survival benefit of 5.4% from ALND [44]. Nonetheless, though meta-analyses can partly overcome the problem of underpowering, they cannot readily distinguish between the effects of removing nodal tissue per se and the effect of adjuvant systemic treatments on overall survival.

The issue of whether locoregional treatment can directly impact on long-term survival was clarified by a milestone publication by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) in 2006 [45]. This showed an overall survival benefit at 15 years from local radiation to either the breast following BCS or the chest wall after mastectomy. For those treatment comparisons where the difference in local recurrence at 5 years was less than 10%, survival was unaffected. Where differences in local relapse were substantial (>10%), there were moderate reductions in breast cancer-specific and overall mortality. The absolute reductions were 19% for local recurrence at 5 years and 5% for breast cancer mortality at 15 years. This represents one life saved for every four locoregional recurrences prevented by radiotherapy at 5 years. It is unclear precisely what the proportional contribution of local vs. regional reductions in relapse were as absolute nodal recurrence rates were very low [45].

If ALND conferred a clear survival advantage, then this should be the standard of care for all patients with breast cancer. These data from the EBCTCG on long-term follow up suggest that locoregional recurrence may act as a determinant of distant disease in a subgroup of women. Locoregional treatments are potentially curative in the absence of micrometastases when disease is confined to the breast and lymph nodes. Under these circumstances, when locoregional management is incomplete, cancer cells or even "oligometastases" may persist within the regional nodes and develop into distant metastases at a later date. For the majority of patients, local recurrence reflects the innate biological features of a tumour and is a marker of risk for distant relapse [46].

14.4.3 Axillary Relapse

Local control of disease is therefore important and can impact on long-term survival of breast cancer patients. The role of ALND in achieving locoregional control is well established. The NSABP B-04 and King's/Cambridge trials provide key observations on the effect of axillary treatment in clinically node-negative patients and reveal that rates of recurrence are up to sixfold higher for untreated axillae [40, 47]. In the NSABP B-04 study, rates of axillary recurrence at 10 years follow up were 17.8% for patients without axillary treatment (i.e. simple mastectomy only) vs. less than 3% for patients who underwent dissection (1.4%) or irradiation of the axilla (3.1%) [40]. Similar results were reported by the Kings/Cambridge trial in which clinically node-negative patients were randomised to the following treatment arms (a) total mastectomy and radiotherapy to the axilla or (b) total mastectomy and observation of the axilla [47]. Thus, treatment of the axilla with either surgery or irradiation will reduce the 5-year risk of relapse by almost 90%. However, it is the avoidance of uncontrolled axillary relapse which is pertinent; this can cause significant morbidity with invasion of major nerves and blood vessels causing pain and lymphoedema. In the pre-screening era of radical and modified radical mastectomy, axillary recurrence often reflected intrinsically aggressive disease with chest wall infiltration, which precluded satisfactory attempts at surgical or radioablation [48]. Most cases of axillary relapse after BCS for smaller tumours have a more "benign" phenotype and are salvageable with either surgery or radiotherapy in 70–90% of cases [49].

Though adequate management of the axilla at the time of initial diagnosis of breast cancer is essential, partial or complete ALND nowadays represents overtreatment for most patients in terms of locoregional control. The axilla can be accurately staged with more restrictive methods of targeted sampling, which identify those clinically node-negative patients who can safely avoid formal ALND. Overall rates of local recurrence following ALND typically vary from 0.8–2.5% at 10 years. It is essential that rates of axillary relapse after sampling techniques, which deselect patients for ALND remain below those for this "gold standard" procedure [50–53]. Though previous studies showed that the risk of axillary relapse was inversely related to the extent of ALND and the number of nodes removed [54], targeted approaches to node sampling should

minimise false-negative rates and ensure that any residual disease within axillary nodes is low volume.

14.5 Methods for Axillary Node Sampling

The recognition that axillary dissection was principally a staging procedure with concomitant morbidity led to investigation of alternative methods for surgical staging of the axilla. These included axillary sample and more recently SLNB. Both of these methods aim to remove between three to five biologically relevant nodes compared with 10–20 nodes for a partial ALND [37]. SLNB is a sophisticated form of targeted axillary node sampling, and methods of blind axillary sampling have evolved into blue-dye node assisted sampling (BDNAS). There is generally an inverse relationship between the average number of nodes sampled and the degree of targeting i.e. blue dye alone, isotope alone or a combined method. Accurate targeting of nodes reduces the chance of a false-negative result.

14.5.1 Four Node Axillary Sampling

All methods of sampling are reliant on the sequential involvement of axillary node metastases from level I to level III with a low incidence of skip metastases [27]. Rosen noted that more than 50% of node-positive T1 tumours involve only one or two nodes and these are usually within level I territory [55]. Axillary sampling was introduced more than two decades ago by Sir Patrick Forrest in Edinburgh and has been widely practised in Scotland but more selectively elsewhere [56]. Initial studies showed that the original technique of a blind four-node sample from level I could stage the axilla with an estimated accuracy of 97% [57]. Four-node sampling has been compared with axillary clearance in randomised studies [58, 59], and harvesting of further nodes as part of a completion axillary dissection does not increase rates of node positivity [58]. Blind four-node sampling is not associated with impaired locoregional control [57], and there is no evidence to date of any detriment in overall survival [60]. For those patients found to be positive on node sampling, the axilla can either be irradiated (one to two nodes positive) or surgically cleared (three to four nodes positive) [37]. Rates of local control are excellent for both approaches and regional recurrence rates are 5% at 10 years for patients with negative nodes who have been sampled [57].

14.5.2 Blue Dye-assisted Node Sampling (BDANS)

A potential problem with standard or blind forms of sampling is lack of certainty that four nodes have been retrieved. It can be difficult to identify nodes amongst the fibro-fatty tissue of the axilla (even when the axillary tail has been mobilised). Blind sampling of axillary nodes requires skill and has been criticised for being too random and unreliable [61]. Standard four-node axillary sampling has evolved into a blue-dye assisted variant, which permits a more targeted sampling and better standardisation of technique [8, 37]. Interestingly, the pre-existence of a minimalist staging procedure in the UK has led some to question the additional benefits of SLNB using dual localization procedures (dye and isotope), which have cost implications. A survey undertaken in 1999 revealed that 47% of British surgeons used axillary sampling (either blind or dye-guided) and this figure increased to 64% in 2001 [62]. In the absence of nuclear medicine facilities, the standard four-node sample has been adapted as a "BDNAS". This is a practical option for identification of three to four relevant nodes and avoids use of isotope, which may present financial and logistical problems for some breast units. Some surgeons have opted to use BDNAS despite availability of radioisotope and with increasing experience of SLNB, removal of three to four nodes seems optimal after all! Bleiweiss refers to a "sentinel node plus" technique in which surgeons remove a similar number of nodes during an otherwise conventional SLNB as for a BDNAS [22].

14.6 Sentinel Lymph Node Biopsy

The essence of the sentinel node hypothesis has been discussed above and presupposes a sequential spread of cancer cells to the "sentinel node" from whence passage

to higher echelon nodes occurs. If the sentinel node does not contain metastases, then the remaining non-sentinel lymph nodes (NSLN) are likewise presumed to be tumour free. Conversely, if tumour deposits are found in the sentinel node, then it is implicit that there is NSLN involvement and completion ALND is indicated. A crucial parameter is the false-negative rate, which is the proportion of patients incorrectly diagnosed as node negative. The denominator for this calculation should be the number of node-positive patients and not the total number of patients, which has been erroneously used in some reports. False-negative rates for SLNB are between 5–10%, which are slightly higher than for ALND and considered acceptable. However, it should be noted that in conventional ALND, much of the axillary nodal tissue is excised and false negativity in this context is less consequential. By contrast, inappropriate management decisions may ensue from understaging with SLNB and undetected tumour deposits in NSLN may lead to regional relapse and become a source of distant metastases. It is unclear whether the detection of more than one sentinel node is attributable to limitations or variations in technique, rather than recognition that the lymphatic system of the breast does not drain to a single node but to a group of nodes (Fig. 14.2).

In practise, it appears that the axilla can be adequately staged by removal of three to four relevant nodes – as in sampling. McCarter found that 15% of patients had four or more nodes removed at the time of SLNB and claimed that at least three nodes were required to identify 99% of node-positive patients. False-negative rates are significantly higher when only one SLN is removed (16.5%), but much lower when multiple nodes are harvested or "sampled" [63]. Goyal and colleagues reported that amongst node-positive tumours, 99.6% of metastases were contained within the first four nodes, suggesting that removal of more than four nodes is unnecessary [25]. It therefore appears that between two and four nodes should be removed for optimum staging. The sentinel lymph node is subjected to more detailed pathological scrutiny with multiple step-sections and immunohistochemical staining than is the case for routine nodal tissue. This more intense pathological examination of the sentinel lymph node potentially upstages disease and increases rates of node positivity to levels above those expected for standard ALND. Perhaps of more concern is the finding of macrometastases in NSLN when only micrometastases are present in the sentinel lymph node. This suggests that the latter has lower biological priority and that patterns of lymphatic flow exist which preferentially direct tumour cells to these non-sentinel nodes [64]. It has been suggested that when more than three "sentinel" nodes are removed, routine pathological processing may be sufficient and compatible with low false-negative rates [65].

14.6.1 Technical Aspects

The technique of SLNB was initially assessed in peer-reviewed pilot studies using blue dye only (patent blue, isosulphan blue and methylene blue). These early studies identified the sentinel node in only two-thirds of cases and a learning curve for the technique was evident as further experience was accrued. Krag and colleagues introduced radioactive tracers (Technetium-99m colloid) as an alternative method for identification of the sentinel lymph node [66], whilst others have used a dual localization method with detection of "blue" and "hot" nodes. Morrow and colleagues randomised patients to SLNB using either blue dye alone or blue dye combined with isotope and showed these to be of similar performance [67]. There is international consensus that dual localization methods are preferable and associated with a short learning curve and optimal performance indicators such as rates of identification and false negativity. In a review by the American Society of Clinical Oncology Expert Panel (ASCO), the overall false-negative rate for the SLNB technique was 8.4% with a range of 0–29% [68]. This analysis involved more than 10,000 patients who underwent SLNB followed by completion ALND for validation. Patients were distributed between 69 single and multi-institutional studies and yielded sensitivity rates varying from 71–100%. The average false-negative rate in these non-randomised studies was comparable to that reported for the NSABP B-32 study (9.7%) [69, 70]. The latter is one of four large randomised trials of SLNB; the NSABP B32 [69], SNAC [71] and EIO [72] trials compared SLNB with SLNB followed by ALND (A vs. A+B), whilst the UK ALMANAC study randomised patients to SLNB vs. ALND or node sampling (A vs. B) [73] (Table 14.1). Within all trials, SLNB positive patients underwent completion ALND. Therefore, dual localization with dye and isotope maximise identification rates (>90%) and are associated with high negative

Table 14.1 Randomised trials of sentinel lymph node biopsy (SLNB)

Trial	Study population	Study groups
ALMANAC (UK) [73]	Any invasive tumour, clinical N0; ($n>1,260$)	Axillary lymph node dissection (ALND) or ANS vs. SLNB (if positive SLN, proceeded to ALND or RT to axilla; if negative SLN, observed)
NSABP-B32 (USA) [69, 70]	Clinical T1 – 3, N0; ($n>4,000$)	SLNB + ALND vs. SLNB (if positive SLN, proceeded to ALND; if negative SLN, observed)
SNAC (Australia/ New Zealand) [71]	≤30 mm invasive tumour, clinical N0; ($n>1,060$)	SLNB + ALND vs. SLNB (if positive SLN, proceeded to ALND; if negative SLN, observed)
European institute of oncology (Milan) [72]	T1, N0; ($n>516$) to ALND; if negative SLN, observed)	SLNB + ALND vs. SLNB (if positive SLN, proceeded

ANS axillary node sampling; *RT* radiotherapy; *ALMANAC* axillary lymphatic mapping against nodal axillary clearance; *SNAC* sentinel node vs. axillary clearance

predictive values (>95%). Furthermore, this method is recommended for "beginners" and use of lymphoscintigraphy has also been advocated as an adjunct during the learning phase, particularly when isotope only is used for localization [74, 75]. However, lymphoscintigraphy does not generally yield additional staging information, which influences management and ablative therapy is not routinely directed at extra-axillary nodal sites at the present time. A positive lymphoscintigram can be helpful, especially in the context of an IMC sentinel lymph node [76]. However, a negative lymphoscintigram does not preclude identification of axillary sentinel lymph nodes with standard intra-operative methods. There is probably no advantage in the use of lymphoscintigraphy for most patients with tumours in the outer quadrants of the breast and a low likelihood of extra-axillary node involvement [77, 78].

Though intra-tumoral injection of dye/isotope is no longer used, peritumoral, subcutaneous, intradermal and subareolar sites are practised (Fig. 14.3). Based on evidence that the skin envelop shares a common pattern of lymphatic drainage with the parenchyma of the breast and these converge upon the same sentinel node (s) [10], there is a trend towards subareolar injection, which gives less "shine through" but requires more prolonged massage. The latter may encourage migration of tumour cells to the sentinel node (so-called traumatic metastases or "traumets") [79]. Benign epithelial cells may be similarly displaced and be interpreted as a false-positive result on immunohistochemistry [80]. Peri-areolar injections give poorer visualisation of the IMC and when lymphoscintigraphy is employed, it is advisable to inject isotope deeper within the breast parenchyma (closer to the deep fascia) [81]. Technetium [99] – labelled nanocolloid or an equivalent radioisotope (20MBq) is injected at least 2 h before surgery but can be administered on the preceding day if more convenient. A special licence and training is required for handling of radioisotope and injection is best undertaken by nuclear medicine personnel. It is sensible to use a slightly larger carrier molecule (e.g. sulphur colloid) in these circumstances in order to ensure retention within the lymphatic system up until the time of surgery. The dye of choice is injected by the surgeon at the time of surgery and the breast is massaged for between 2 and 5 min. Some surgeons use 1–2 mL of undiluted dye, whilst others dilute 2 mL of dye with saline up to a final volume of 5 mL. However, larger volumes of injectate cause troublesome staining both of the breast tissues intra-operatively and of the skin post-operatively. Reduced volumes of dye may be appropriate in smaller breasted women and avoids more prolonged staining of the breast skin (of up to 12 months).

There is general consensus that SLNB should aim to remove all nodes which are blue, hot, blue and hot or palpably suspicious. Some nodes are blue, but not hot and others are non-blue and hot. Sometimes, it can be helpful to trace a blue lymphatic towards a node, which may not necessarily be blue (but may be hot and should be removed). The decision when to stop sampling during surgery can be difficult; some surgeons consider any radioactive node to be hot, but use of count ratios can limit the number of nodes excised when activity levels are diffuse and high among three or more nodes. It is conventional to designate a node as being hot in terms of either the sentinel node: background count (3:1) or the sentinel node: ex-vivo count (10:1) [82].

No formal health economic evaluation of SLNB has yet been undertaken and it may prove to be cost neutral

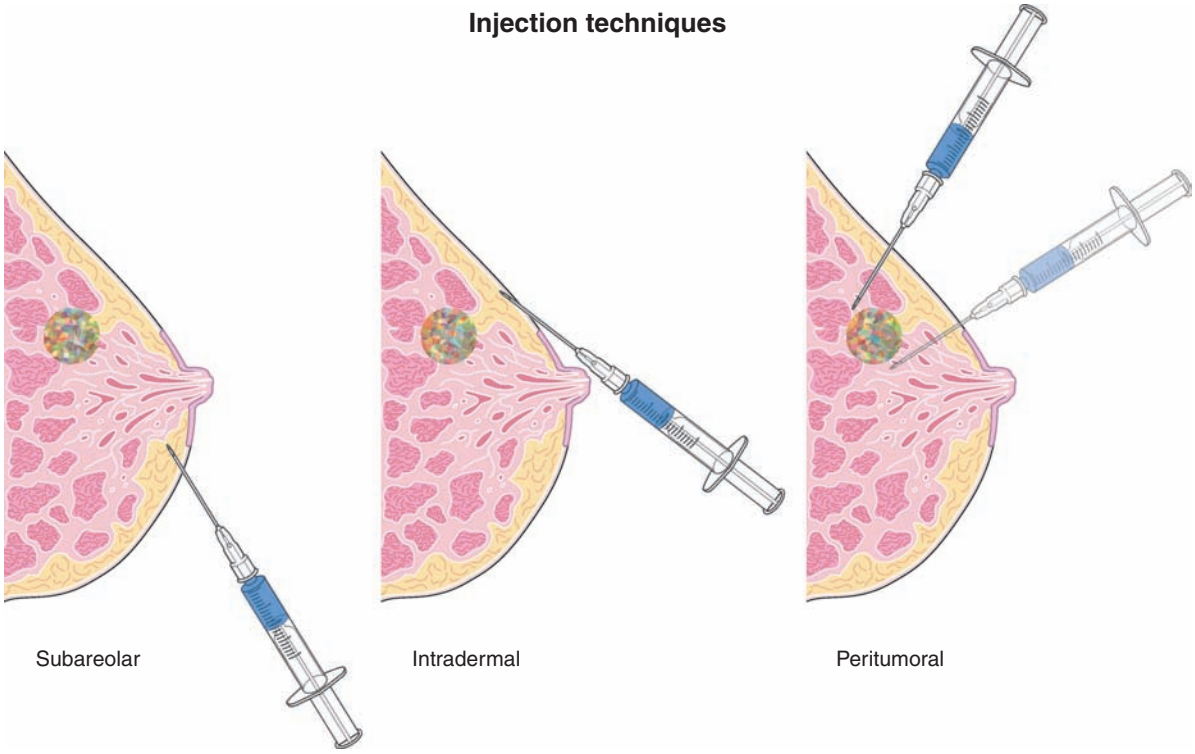

Fig. 14.3 Sites of injection of tracer agents (*blue dye* and radiocolloid)

compared with ALND due to additional costs of equipment, isotope, personnel, etc. Moreover, in some units, patients are now discharged early with drains in situ following ALND and this will reduce the relative cost of the latter procedure [83]. Methods for intra-operative assessment of sentinel lymph nodes obviate the need for a delayed ALND, but detection of micrometastases using either touch imprint cytology (TIMC) or frozen section remains problematic [84, 85]. Newer reverse transcriptase polymerase chain reaction (RT-PCR) based techniques can potentially overcome difficulties of limited pathological sampling of nodes and operating parameters set at a threshold for detection of metastases >0.2 mm in size (i.e. macro- and micrometastases) but not isolated tumour cells (≤0.2 mm) [86]. Real-time PCR may permit quantitation of tumour load and differentiation between macro- and micrometastases. It should be appreciated that the definition of nodal micrometastases (>0.2 mm; ≤2 mm) is arbitrary and there is no sudden transition from low risk to high risk. The term staging implies a discontinuous concept, yet in reality, there is a continuum in the extent of nodal involvement. Nodal status is the single most important prognostic factor in breast cancer and determines the propensity to form distant metastases. Nonetheless, for women with node-positive disease, a single node is affected in up to 60% of cases, amongst whom almost half contain micrometastases only. These observations are related to the more intensive pathological examination of the sentinel lymph node and were the NSLNs to be assessed as thoroughly, some would probably be deemed positive, which would otherwise be negative on routine pathological processing without step-sectioning nor immunohistochemistry. Interestingly, an exhaustive study by Weaver and colleagues suggests that upstaging of NSLNs from more detailed pathological examination is an infrequent event [87].

14.6.2 Completion Axillary Lymph Node Dissection

This relatively high incidence of isolated sentinel node positivity with low-volume disease has created management dilemmas in terms of both further (completion) axillary surgery and systemic treatment. The chance of NSLN involvement is related to the volume

of disease in the sentinel node. Cserni found on meta-analysis that when macrometastases (>2 mm) were present in the sentinel node, the incidence of NSLN involvement was 50%, but only 15% for micrometastases (>0.2 mm ≤2 mm) and 9% for isolated tumour cells (≤2 mm) [88]. However, there is much heterogeneity in terminology and definition of isolated tumour cells and micrometastases with lack of reproducibility between categories. The risk of residual NSLN disease for an individual patient can be estimated from a multivariate nomogram, which incorporates several factors such as primary tumour size and grade [89]. However, nomograms devised for estimation of NSLN involvement are difficult to reliably apply in practise and in particular may not be transferable to data sets generated from other institutions. Furthermore, these are less accurate when the predicted incidence of NSLN positivity is low [90]. Current US guidelines recommend completion ALND for all patients with macro- or micrometastastic deposits in the sentinel lymph node, but not for isolated tumour cells. This includes micrometastases detected either by routine H&E staining or immunohistochemistry alone [68]. Some pathologists have recently suggested that *any* intra-parenchymal deposit measuring ≤0.2 mm constitutes a micrometastasis and consider these intra-parenchymal foci to be more biologically important than subcapsular deposits (Sarah Pinder – personal communication).

A delayed ALND can be technically challenging, especially in the context of immediate breast reconstruction. Furthermore, there may be increased morbidity with higher rates of lymphoedema for those patients undergoing delayed ALND following a positive SLNB compared with ALND ab initio. Within the ALMANAC study, there was evidence of clinically significant morbidity from SLNB when analysed on an intention-to-treat basis [73]. This morbidity most likely relates to delayed ALND in sentinel lymph node positive patients. For some patients, the risk: benefit ratio for detection of NSLN positive cases may not justify completion ALND. The decision for further axillary surgery should be guided by variables such as primary tumour characteristics and nodal metastatic load together with patient preference. The proportion of retrieved nodes, which contain (micro-) metastases may be a critical factor in determining NSLN involvement [26]. It may be appropriate to omit further surgery when micrometastases are present in one out of four nodes as opposed to a single node or even one out of two nodes. In a group of 200 sentinel lymph node positive (micro- or macrometastases) patients from Memorial Sloan Kettering Cancer Centre who did not undergo further axillary surgery, rates of local recurrence at 3 years follow up was 2% [50]. Low rates of axillary relapse are unlikely to translate into any meaningful reduction in long-term survival amongst an older group of patients with smaller, non-high grade tumours and micrometastases only in the sentinel lymph node [91]. Ongoing studies addressing this issue of NSLN involvement stratify patients on the basis of metastatic load in the sentinel lymph node [92–95] (Table 14.2).

14.7 Indications for Sentinel Lymph Node Biopsy

Most of the validatory studies on SLNB were confined to tumours measuring 2 cm or less. With increasing tumour size, there is a greater probability of nodal involvement and gross metastatic disease within a lymph node may prevent uptake of dye and isotope. Lymph flow is passive and will be readily diverted to "non-sentinel" nodes yielding a false-negative result [22]. A heavily infiltrated node, which is non-blue and cold may once have constituted the "true" sentinel node but subsequently been demoted due to diversion of lymph flow within a complex lymphatic network. Patients with clinically positive nodes are more likely to have extensive pathological involvement and should not be offered SLNB. Some of these clinically node-

Table 14.2 Trials investigating management of sentinel node positive patients

Trial	Sentinel node status	Randomisation
ACOSOG – Z0011 [92]	Macro-/Micrometastases	ALND[a] vs. no further surgery
IBCSG 23-01 [93, 94]	Micrometastases	ALND vs. no further surgery
AMAROS [95]	Macro-/Micrometastases	ALND vs. axillary radiotherapy

[a]Axillary lymph node dissection

positive patients will be found to have innocent nodes on axillary ultrasound and core biopsy/FNAC of a node may be negative. Provided the primary tumour is non-inflammatory and not locally advanced, these patients could be considered for SLNB.

SLNB is usually contraindicated for tumours exceeding 5 cm in size and some younger patients (<40 years) with T2 tumours of higher grade may be more appropriately managed with ALND at the outset due to a relatively high probability of nodal involvement. Guiliano's group have reported the successful application of SLNB to tumours in excess of 5 cm [96]. Nonetheless, false-negative rates are higher when there is a greater chance of node positivity and current trials are evaluating the accuracy of SLNB for tumours measuring between 3–5 cm [71]. The Australian SNAC II trial is examining SLNB in tumours exceeding 3 cm in size and includes both multifocal and multicentric tumours.

14.7.1 Ductal Carcinoma in Situ

The indications for SLNB have broadened in recent years to include patients with widespread DCIS undergoing mastectomy and even some localized forms of DCIS associated with a clinical or radiological mass lesion [97–99]. There is consensus that extensive high nuclear grade (HNG) DCIS on imaging, which mandates mastectomy or DCIS presenting as a palpable lesion are indications for SLN biopsy. Typical cases of screen-detected localized areas of DCIS do not qualify for routine SLNB. An incidental invasive component is found in up to 20% of cases of DCIS in which mastectomy is the choice of operation and extensive DCIS is a risk factor for invasive malignancy from historical studies. A significant proportion of those patients with microinvasion (≤1 mm) diagnosed on core biopsy will have further invasive foci on definitive histology. SLNB is advisable for all patients with microinvasion, up to 10% of whom will be sentinel lymph node positive [97]. Nonetheless, despite reports of node positivity rates approaching 15% in high risk DCIS and DCIS with micro-invasion [100], many cases involve isolated tumour cells or micrometastases only, which may not be clinically relevant [98]. When the target of biopsy is not microcalcification, many of these patients will have further invasive foci on definitive histology, which mandates some form of axillary staging. Moreover, between 10 and 15% of lesions diagnosed as DCIS using large bore vacuum devices will show invasion on complete excision [101].

14.7.2 Multifocal and Multicentric Tumours

Multifocal and multicentric tumours were initially found to be associated with high false-negative rates and were considered a contraindication to SLNB [102]. This was consonant with the misguided assumption that tumours located in different quadrants of the breast drain through mutually exclusive lymphatic pathways and therefore SLNB would lead to inaccurate axillary lymph node staging [102]. More recent publications refute this viewpoint and SLNB is no longer precluded by the presence of multiple tumour foci either within the same (multifocality) or different (multcentricity) quadrants of the ipsilateral breast [102–104]. Furthermore, evidence from lymphoscintigraphy supports the notion that the various quadrants of the breast share common lymphatic drainage channels, which converge upon the subareolar region [105].

14.7.3 Neoadjuvant Chemotherapy

The incorporation of SLNB into neoadjuvant schedules for early stage breast cancer is evolving at the time of writing. Initial reports suggested that SLNB was contraindicated in the context of primary chemotherapy (PC) due to high false-negative rates [106].

Current practise is dominated by results from the NSABP B27 trial, which investigated SLNB after PC [107]. Early analyses revealed high false-negative values with variable identification rates (72–100%) and highlighted the issue of differential downstaging of primary tumour and axillary nodes. More recent reports have shown overall false-negative rates of 10–11% with a pooled estimate of 12% for SLNB following PC [108]. These figures are comparable to conventional SLNB for primary surgical treatment [68]. Identification rates are more than 85% when dual localization methods are used and appear independent of tumour size or nodal status, though extensive nodal disease at presentation can be associated with higher false-negative rates [108].

There is potential loss of staging information when SLNB is performed after PC, and the clinical relevance of a negative result in this setting is uncertain; the presence of ITCs may indicate downstaging of micro- or macrometastatic disease and are assumed to have different biological significance from the finding of ITC's pre-treatment. It has been suggested that completion ALND can be omitted in patients with micrometastases in the SLN post-PC [109]. By contrast, a negative SLNB prior to PC can provide useful staging information and completion ALND can be withheld with a greater degree of confidence. Those patients with a positive SLNB before starting PC will be committed to an ALND. SLNB undertaken prior to chemotherapy will minimise the risk of a false-negative result and may allow more accurate initial staging [110, 111]. Furthermore, upfront SLNB provides important information on prognostication and can guide decisions about radiotherapy and other adjuvant treatments. However, there is no quantification of regional metastatic load and some advocate SLNB after PC to take advantage of potential nodal downstaging and avoidance of axillary dissection in up to 40% of patients [112, 113]

14.7.4 Pregnancy

The development of breast cancer during pregnancy presents unique management problems with a prominent emotional dimension. Though termination may be advocated in the first trimester, surgical treatments can be safely undertaken in any trimester of pregnancy [114]. Adjuvant therapies, including radiotherapy and chemohormonal therapies are usually deferred until after delivery, though chemotherapy (but *not* tamoxifen) can be safely administered in the second trimester when organogenesis is complete and teratogenic effects are minimal [115, 116]. Radiotherapy is absolutely contraindicated in the gravid state, but interestingly, the dose of radiation from exposure to technetium radiocolloid in SLNB is only 20MBq. This is well below the safe upper limit for pregnant women and therefore SLNB using isotopic localization only could be employed; note that blue dye can stain placental and foetal tissue and should be avoided. If there are concerns about use of radioisotope during pregnancy, then axillary staging could be carried out as a delayed procedure (if ALND at the outset is deemed inappropriate).

14.8 Omission of Surgical Axillary Staging

It is conceded that a selected group of sentinel lymph node positive patients might safely avoid completion ALND. What about omission of SLNB in the first place for certain patients? The SLNB procedure is associated with minimal morbidity and can be undertaken as a day case [117]. Against this background, it is perhaps difficult to propose omission of SLNB for any form of invasive breast cancer. Many clinicians feel intuitively that with the advent of SLNB, all patients with invasive disease should at least undergo this procedure. It is a matter of judgement as to what constitutes an acceptable rate of axillary recurrence and cost of identifying the few node-positive cases in low risk groups of patients. The cost efficacy of SLNB decreases with a low risk of regional relapse.

There are concerns about the consequences of omission of SLNB in the small number of patients, with favourable prognostic indices, who are found to be node positive and have a resultant change in their treatment plan [38]. Many advocate SLNB for all patients with clinically node-negative invasive breast cancer, including microinvasion (≤1 mm), up to 10% of whom will be node positive [97]. By contrast, Cady has emphasised the marked stage shift, which has occurred following introduction of widespread screening mammography during the past 25 years [118]. We have entered an era in breast cancer management when disease is "small" and the incidence of nodal involvement low – and many patients have micrometastastic disease only. Cady maintains that defined groups of patients now exist with such a low probability of nodal disease that even SLNB can be eliminated. These include patients with screen-detected T1a and T1b tumours (≤1 cm) of non-high grade together with small papillary, colloid and other special types of cancer. Any invasive tumour with lymphovascular invasion should be staged with SLNB [38, 119]. In a study involving 400 clinically node-negative patients with T1 and T2 tumours, Greco and colleagues reported unexpectedly low rates of axillary relapse at 5 years when initial surgery was omitted due to patient refusal. Overall rates of relapse were 6.7% and all cases of axillary recurrence were managed successfully with salvage surgery, and with careful follow up, it was concluded that regional disease does not become unresectable or untreatable [120].

14.9 Conclusion

With the advent of SLNB and other minimalist sampling techniques, approaches to the management of the axilla have become more complex in recent years and at times present challenges to both the clinician and patient. Axillary surgery encompasses both staging and therapeutic procedures and it is important to select patients appropriately to avoid under- and over-treatment of patients, respectively. SLNB is now the dominant and preferred method for staging the axilla, but several questions remain unanswered. These relate to several aspects, including methodology, interpretation and clinical significance of nodal metastases together with long-term outcome in terms of locoregional control and overall survival. False-negative rates must be kept to a minimum by routine use of dual localization techniques and intra-operative digital examination with removal of all nodes, which are not only hot/blue but also palpably suspicious. Radionucleotide facilities are not universally available and SLNB has been adapted into a more pragmatic technique of BDANS with harvesting of about four axillary lymph nodes. It is essential that ALND is undertaken at the outset when indicated, particularly with respect to larger, locally advanced and/or multifocal tumours and in the setting of neoadjuvant chemotherapy. Conversely, discretion must be exercised when managing older patients with small, non-high grade tumours. For some patients, completion ALND may not be justified, whilst for others, any form of surgical axillary staging might be safely omitted [121]. Individualised recommendations based on the risk of relapse, which includes formal analysis of the risks, benefits and cost of treatment is the ideal approach to management of the axilla. This strategy should incorporate a spectrum of options, including ALND, targeted sampling and observation alone.

References

1. Carter CL, Allen C, Henderson DE (1989) Relation of tumour size, lymph node status and survival in 24, 740 breast cancer cases. Cancer. 73:505–8
2. Rosen PP, Groshen S, Saigo PE et al (1989) Pathologic prognostic factors in stage I (T1N0M0) and stage II (T1N1M0) breast carcinoma: a study of 644 patients with median follow up of 18 years. J Clin Oncol. 7:1239–51
3. Kissin MW, Querci della Rovere G, Easton D, et al Risk of lymphoedema following the treatment of breast cancer. Br J Surg. 1986;73:580–4
4. Ivens D, Hoe AL, Podd TJ et al (1992) Assessment of morbidity from complete axillary dissection. Br J Cancer. 66: 136–8
5. Britton PD, Goud A, Godward S, et al (2008) Use of ultrasound-guided axillary node core biopsy in staging of early breast cancer. Eur Radiol. DO1 10.1007/s00330-008-1177–5
6. Fisher B, Montague F, Redmond C et al (1985) Ten-year results of a randomized trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med. 312:674–81
7. Baum M, Coyle PJ (1977) Simple mastectomy for early breast cancer and the behaviour of the untreated nodes. Bull Cancer. 64:603–10
8. Purushotham AD, MacMillan RD, Wishart G (2005) Advances in axillary surgery for breast cancer – time for a tailored approach. Eur J Surg Oncol. 31:929–31
9. Jatoi I (1999) Management of the axilla in primary breast cancer. Surg Clin North Am. 79:1061–73
10. Haagensen CD (1986) Anatomy of the mammary glands. In: Haagensen CD (ed) Diseases of the breast., 3rd edn. WB Saunders, Philadelphia
11. Sappey M. Traite d'Anatomie Descriptive. 2nd ed. Paris; 1888
12. Rouviere H (1932) Anatomie des lymphatiques de l'homme. Masson, Paris
13. Handley RS, Thackray AC (1949) The internal mammary lymph chain in carcinoma of the breast. Lancet. 2:276
14. Borgstein PJ, Meijer S, Pijpers RJ et al (2000) Functional lymphatic anatomy for sentinel node biopsy in breast cancer: echoes from the past and the periareolar blue dye method. Ann Surg. 232:81–9
15. Mansel RE, Goyal A, Newcombe RG (2004) Internal mammary node drainage and its role in sentinel node biopsy: the initial ALMANAC experience. Clin Breast Cancer. 5:279–84
16. Veronesi U, Cascinella N, Greco M et al (1985) Prognosis of breast cancer patients after mastectomy and dissection of internal mammary nodes. Ann Surg. 202:702–7
17. McMinn RMH (1990) Last's anatomy (regional and applied). 18th ed. Churchill Livingstone
18. Osborne MP, Jeyasingh K, Jewkes RF et al (1979) The preoperative detection of internal mammary node metastases in breast cancer. Br J Surg. 66:813
19. Thomas JM, Redding WH, Sloane JP (1979) The spread of breast cancer: importance of the intrathoracic lymphatic route and its relevance to treatment. Br J Caner. 40:540
20. Tanis PJ, Neiweg OE, Valdes Olmos RA et al (2001) Anatomy and physiology of lymphatic drainage of the breast from the perspective of sentinel node biopsy. J Am Coll Surg. 192:399–409
21. Morton DL, Wen DR, Wong JH et al (1992) Technical details of intra-operative lymphatic mapping for early stage melanoma. Arch Surg. 127:392–9
22. Bleiweiss I (2006) Sentinel lymph nodes in breast cancer after 10 years: rethinking basic principles. Lancet Oncol. 7:686–92
23. Romrell LJ, Bland KI. Anatomy of the breast, axilla, chest wall and related metastatic sites. Chapter 2. In: Bland KI, Copeland EM (eds) The breast, Vol I. 3rd ed. Saunders; 2004 ISBN 0-7216-9490-X

24. Turner-Warwick RT (1959) The lymphatics of the breast. Br J Surg. 46:574–82
25. Goyal A, Newcombe RG, Mansell RE (2005) Clinical relevance of multiple sentinel nodes in patients with breast cancer. Br J Surg. 92:438–42
26. Rescigno J, Taylor LA, Aziz MS et al (2005) Predicting negative axillary lymph node dissection in patients with positive sentinel lymph node biopsy: can a subset of patients be spared axillary dissection? Breast Cancer Res Treat. 94:S35
27. Veronesi U, Rilke R, Luini A et al (1987) Distribution of axillary node metastases by level of invasion. Cancer. 59:682–7
28. Jacobsson S (1967) Studies of the blood circulation in lymphoedematous limbs. Scan J Plast Recon Surg. 3:1–81
29. Schuneman J, Willich N (1998) Lympheodema of the arm after primary treatment of breast cancer. Anticancer Res. 18:2235–6
30. Mortimer PS, Bates DO, Brassington HD et al (1996) The prevalence of arm oedema following treatment for breast cancer. Q J Med. 89:377–80
31. Morrow M (2008) Miami breast cancer conference. Orlando, Florida, USA
32. Pain SJ, Purushotham AD (2000) Lymphoedema following surgery for breast cancer. Br J Surg. 87:1128–41
33. Stewart FW, Treves N (1948) Lymphangiosarcoma in postmastectomy oedema. Cancer. 1:64–81
34. Temple WJ, Ketcham AS (1985) Preservation of the intercostobrachial nerve during axillary dissection for breast cancer. Am J Surg. 150:406–13
35. Abdullah TI, Iddon J, Barr L, Baildam AD, Bundred NJ (1998) Prospective randomized controlled trial of preservation of the intercostobrachial nerve. Br J Surg. 85:1443–5
36. Salmon RJ, Ansquer Y, Asselain B (1998) Preservation versus section of the intercostobrachial nerve (ICBN) in axillary dissection for breast cancer – a prospective randomized trial. Eur J Surg Oncol. 24:158–61
37. MacMillan RD, Blamey RW (2004) The case for axillary sampling. Adv Breast Cancer. 1:9–10
38. Benson JR, Querci della Rovere G, Axilla Management Consensus Group. Management of the axilla in women with breast cancer. Lancet Oncol. 2007;8:331–48
39. Fisher B (1992) The evolution of paradigms for the management of breast cancer: a personal perspective. Cancer Res. 52:2371–83
40. Fisher B, Montague F, Redmond C et al (1985) Ten-year results of a randomized trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med. 312:674–81
41. Harris JR, Osteen RT (1985) Patients with early breast cancer benefit from effective axillary treatment. Breast Cancer Res Treat. 5:17–21
42. Gardner B, Feldman J (1993) Are positive axillary nodes in breast cancer markers for incurable disease? Ann Surg. 218:270–8
43. Moffat FL, Sewofsky GM, Davis K et al (1992) Axillary node dissection for early breast cancer: some is good but all is better. J Surg Oncol. 51:8
44. Orr RK (1999) The impact of prophylactic axillary node dissection on breast cancer survival: a Bayesian meta-analysis. Ann Surg Oncol. 6:109–16
45. Early Breast Cancer Trialists Collaborative Group (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Lancet. 366:2087–106
46. Benson JR, Querci della Rovere G (2002) The biological significance of ipsilateral local recurrence of breast cancer: determinant or indicator of poor prognosis. Lancet Oncol. 3:45–9
47. Cancer Research Campaign Working Party (1980) Cancer research campaign (King's/Cambridge) trial for early breast cancer. Lancet. 2:55–60
48. Epstein RJ (1995) Routine or delayed axillary dissection for primary breast cancer? Eu J Cancer. 31A:1570–3
49. Fowble B, Solin L, Schultz D, Goodman R (1989) Frequency, sites of relapse and outcome of regional node failures following conservative surgery and radiation for early breast cancer. Int J Oncol Biol Phys. 17:703–10
50. Naik AM, Fey J, Gemignani M, Heerdt A et al (2004) The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection. Ann Surg. 240:462–71
51. Chung MA, Steinhoff MM, Cady B (2002) Clinical axillary recurrence in breast cancer patients after a negative sentinel node biopsy. Am J Surg. 184:310–4
52. Blanchard DK, Donohue JH, Reynolds C (2003) Relapse and morbidity in patients undergoing sentinel lymph node biopsy alone or with axillary dissection for breast cancer. Arch Surg. 138:482–8
53. Benson JR, Wishart GC, Forouhi P, Jones B, Provenzano E, Pinder SE (2007) Axillary recurrence in breast cancer patients after a negative sentinel lymph node biopsy. Eur J Cancer. 6(7):153
54. Graverson HP, Blichert-Toft M, Andersen J et al (1988) Danish breast cancer cooperative group. Breast cancer: risk of axillary recurrence in node negative patients following partial dissection of the axilla. Eur J Surg Oncol. 14: 407–12
55. Rosen PP, Siago PE, Braun DW et al (1993) Axillary micro- and macrometastases in breast cancer: prognostic significance of tumour size. Ann Surg. 194:585–91
56. Forrest APM, Everington D, McDonald C, Steele RJC, Chetty U, Stewart HJ (1995) The Edinburgh randomised trial of axillary sampling or clearance after mastectomy. Br J Surg. 82:1504–8
57. Lambah A, Dixon JM, Prescott RJ, Jack W, Forrest APM, Rodger A et al (2001) Randomised study of axillary clearance versus four-node sampling. Eur J Cancer. 37(Suppl 5):2
58. Steel RJ, Forrest APM, Chetty U (1985) The efficacy of lower axillary sampling in obtaining lymph node status in breast cancer: a controlled randomised trial. Br J Surg. 72: 368–9
59. Chetty U (2001) Axillary node sampling to evaluate the axilla. World J Surg. 25:773–9
60. Rampaul RS, Pinder SE, Morgan DAL et al (2003) Long-term regional recurrence and survival after axillary node sampling for breast cancer. Eur J Cancer. 39(Suppl 1):23
61. Kissin M (2005) Debate entitled management of the axilla in women with breast cancer: Which is the best way of staging the axilla?. The Royal Society of Medicine, London

62. Gaston MS, Dixon JM (2004) A survey of surgical management of the axilla in UK breast cancer patients. Eur J Cancer. 40:1738–42
63. McCarter MD, Yeung H, Fey J et al (2001) The breast cancer patients with multiple sentinel nodes: when to stop? J Am Coll Surg. 192:692–7
64. Cserni G (2005) Evaluation of sentinel nodes in breast cancer. Histopathology. 46:697–702
65. Dabbs DJ, Johnson R (2004) The optimal number of sentinel lymph nodes for focused pathological examination. Breast J. 10:101–5
66. Krag D, Weaver D, Ashikaga T et al (1998) The sentinel node in breast cancer. A multicentre validation study. N Eng J Med. 339:941–6
67. Morrow M, Rademaker AW, Bethke KP et al (1999) Learning sentinel node biopsy: results of a prospective randomised trial of two techniques. Surgery. 126:714–22
68. Lyman GH, Guiliano AE, Somerfield MR et al (2005) The American society of clinical oncology guideline recommendations for sentinel lymph node biopsy in early stage breast cancer. J Clin Oncol. 23:7703–20
69. Julian TB, Krag D, Brown A et al (2004) Preliminary technical results of NSABP B-32, a randomised phase III clinical trial to compare sentinel node resection to conventional axillary dissection in clinically node-negative breast cancer patients. Breast Cancer Res Treat. 88:S11
70. Krag DN, Anderson SJ, Julian TB et al (2007) Technical outcomes of sentinel-lymph node resection and conventional axillary lymph node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. Lancet Oncol. 8:881–8
71. Gill PG (2004) Sentinel lymph node biopsy versus axillary clearance in operable breast cancer. The RACS SNAC trial, a multicenter randomised trial of the royal Australian college of surgeons (RACS) section of breast surgery, in collaboration with the National Health and Medical Research Council Clinical Trials Center. Ann Surg Oncol. 11: 216S–21S
72. Veronesi U, Paganelli G, Viale G et al (2003) A randomised comparison of sentinel node biopsy with routine axillary dissection in breast cancer. NEJM. 349:546–53
73. Mansel RE, Goyal A, Fallowfield L et al (2006) Sentinel node biopsy versus standard axillary treatment: results of the randomised multicentre UK ALMANAC trial. J Natl Cancer Inst. 98:599–609
74. Veronesi U (1997) Sentinel node biopsy in breast cancer. Lancet. 350:809
75. O'Hea BJ, Hill ADK, El-Shirbiny AM et al (1998) Sentinel lymph node biopsy in breast cancer: initial experience at memorial sloan-kettering cancer center. J Am Coll Surg. 186:423–7
76. Benamor M, Nos C, Freneaux P, Clough K (2003) Impact of internal mammary sentinel node imaging in breast cancer. Clin Nucl Med. 28:375–8
77. McMasters KM, Wong SL, Tuttle TM et al (2000) Preoperative lymphoscintigraphy for breast cancer does not improve the ability to identify axillary sentinel nodes. Ann Surg. 231:724–31
78. Upponi SS, McIntosh SA, Wishart GC et al (2002) Sentinel lymph node biopsy in breast cancer – is lymphoscintigraphy really necessary. Eur J Surg Oncol. 28(5):479–80
79. Rosser RJ (2001) Safety of sentinel lymph node dissection and significance of cytokeratin micrometastases. J Clin Oncol. 19:1882–3
80. Bleiweiss IJ, Legmann MD, Nagi CS, Jaffer S (2006) Sentinel lymph nodes can be falsely positive due to iatrogenic displacement and transport of benign epithelial cells. J Clin Oncol. 24:2013–8
81. Tanis PJ, Neiweg OE, Valdes Olmos RA et al (2001) Anatomy and physiology of lymphatic drainage of the breast from the perspective of sentinel node biopsy. J Am Coll Surg. 192:399–409
82. Kuehn T, Bembenek A, Decker T et al (2004) A concept for the clinical implementation of sentinel lymph node biopsy in patients with breast carcinoma with special regard to quality assurance. Cancer. 103:451–61
83. Chapman D, Purushotham A (2001) Acceptability of early discharge with drains in situ after breast surgery. Br J Nurs. 10:1447–50
84. Lambah PA, McIntrye MA, Chetty U, Dixon JM (2003) Imprint cytology of axillary lymph nodes as an intra-operative diagnostic tool. Eur J Surg Oncol. 29:224–8
85. Salem AA, Douglas-Jones AG, Sweetland HM, Mansel RE (2006) Intra-operative evaluation of axillary sentinel lymph nodes using touch imprint cytology and immunohistochemistry. Eur J Surg Oncol. 32:484–7
86. Julian TB, Blumencranz P, Deck K et al (2008) Novel intraoperative molecular test for sentinel lymph node metastases in patients with early stage breast cancer. J Clin Oncol. 26:3338–45
87. Weaver DL, Krag DN, Ashikaga T et al (2000) Pathologic analysis of sentinel and nonsentinel lymph nodes in breast carcinoma. Cancer. 88:1099–107
88. Cserni G, Gregori D, Merletti F et al (2004) Non-sentinel node metastases associated with micrometastatic sentinel nodes in breast cancer: metaanalysis of 25 studies. Br J Surg. 91:1245–52
89. Van Zee KJ, Manasseh DM, Bevilacqua JL et al (2002) A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. Ann Surg Oncol. 10:1140–51
90. Pal A, Provenzano E, Duffy SW et al (2008) A model for predicting non-sentinel lymph node metastatic disease when the sentinel lymph node is positive. Br J Surg. 95:302–9
91. Park J, Fey JV, Naik AM, et al (2005) A declining rate of completion axillary dissection in sentinel lymph node positive breast cancer patients is associated with the use of a multivariate nomogram. Breast Cancer Res Treat. 100:S80 (abstr 2001)
92. American College of Surgeons Oncology Group – ACSOG – Z0011. A randomised study of axillary node dissection in women with clinical T1-2, N0, M0 breast cancer who have a positive sentinel node. www.acosog.org/studies/organ
93. Glimberti V (2006) International breast cancer study group trial of sentinel node biopsy. J Clin Oncol. 24:210–1
94. IBCSG 23-01 protocol. Available at www.ibcsg.org
95. Meijnen P, Rutgers EJT, van de Velde CHJ et al (2004) AMAROS: after mapping of the axilla; radiotherapy or surgery? Trial update. Eur J Surg. 2(Suppl 3):79
96. Chung MH, Ye W, Guiliano AE (2001) Role for sentinel lymph node dissection in the management of large (≥ 5cm) invasive breast cancer. Ann Surg Oncol. 8(9):668–92

97. Intra M, Zurrida S, Maffini F et al (2003) Sentinel lymph node metastasis in microinvasive breast cancer. Ann Surg Oncol. 10:1160–5
98. Klauber-DeMore N, Tan LK, Liberman L et al (2000) Sentinel lymph node biopsy: is it indicated in patients with high-risk ductal carcinoma in situ and ductal carcinoma in situ with microinvasion? Ann Surg Oncol. 7:636–42
99. Benson JR, Wishart GC, Forouhi P, Hill-Cawthorne G, Pinder SE (2007) The role of sentinel node biopsy in patients with a pre-operative diagnosis of carcinoma in situ. Eur J Cancer. 6(7):131
100. Zavotsky J, Hansen N, Brennan MB et al (1999) Lymph node metastasis from ductal carcinoma in situ with microinvasion. Cancer. 85:2439–43
101. Jackman RJ, Nowels KW, Rodriguez-Soto J et al (1999) Stereotactic, automated, large core needle biopsy of nonpalpable breast lesions: false-negative and histologic underestimation rates after long-term follow up. Radiology. 210:799–805
102. Veronesi U, Paganelli G, Galimberti V et al (1997) Sentinel node biopsy to avoid axillary dissection in breast cancer with clinically negative nodes. Lancet. 349:1864–7
103. Goyal A, Newcombe RG, Mansell RE et al (2004) ALMANAC Trialist Group. Sentinel lymph node biopsy in patients with multifocal breast cancer. Eur J Surg Oncol. 30:475–9
104. Toumisis E, Zee KJV, Fey JV et al (2003) The accuracy of sentinel lymph node biopsy in multicentric and multifocal invasive breast cancers. J Am Coll Surg. 197:529–34
105. Holwitt DM, Gillanders WE, Aft RL et al (2008) Sentinel lymph node biopsy in patients with multicentric/multifocal breast cancer: low false-negative rate and lack of axillary recurrence. Am J Surg. 196:562–5
106. Gentilini O, Trifiro G, Soleldo J et al (2006) Sentinel lymph node biopsy in patients with multicentric breast cancer. The experience of the European institute of oncology. Eur J Surg Oncol. 32:507–10
107. Nason KS, Anderson BO, Dunwald LK et al (2000) Increased false negative sentinel node biopsy rates after pre-operative chemotherapy for invasive breast cancer. Cancer. 89:2187–94
108. Mamounas E, Brown A, Anderson S et al (2005) Sentinel node biopsy after neoadjuvant chemotherapy: results of the national surgical adjuvant breast and bowel project B-27. J Clin Oncol. 23:2694–702
109. Mamounas E (2008) Miami breast cancer conference. Orlando, Florida, USA
110. Schrenk P, Tausch C, Wolfl S, et al (2008) Sentinel node mapping performed before preoperative chemotherapy may avoid axillary dissection in breast cancer patients with negative or micrometastatic sentinel nodes. Am J Surg. doi: 10.1016/j.amjsurg.2007.08.068
111. Schrenk P, Hochreiner G, Fridrik M et al (2003) Sentinel node biopsy performed before preoperative chemotherapy for axillary node staging in breast cancer. Breast J. 9:282–7
112. Sabel MS, Schott AF, Kleer CG et al (2003) Sentinel node biopsy prior to neoadjuvant chemotherapy. Am J Surg. 186:102–5
113. Fisher B, Brown A, Mamounas E et al (1997) Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from the national surgical adjuvant breast and bowel project B-18. J Clin Oncol. 15:2483–93
114. Gianni L, Baselga J, Eiermann W, et al (2002) First report of the European cooperative trial in operable breast cancer (ECTO): effects of primary systemic therapy (PST) in local-regional disease. Proc Am Soc Clin Oncol. 21:34a (abstr 132)
115. Theriault RL (2000) Breast cancer during pregnancy. In: Singletary SE, Robb GL (eds) Advanced therapy of breast disease. BC Decker, Ontario, pp 167–73
116. Berry DL, Theriault RL, Holmes FA et al (1999) Management of breast cancer during pregnancy using a standardised protocol. J Clin Oncol. 17:855–61
117. Doll DC, Ringenberg QS, Yarbro JW (1989) Antineoplastic agents and pregnancy. Semin Oncol. 16:337–46
118. Purushotham AD, Upponi S, Klevesath MB, Bobrow L, Millar K, Myles JP et al (2005) Morbidity following sentinel lymph node biopsy in primary breast cancer – a randomised controlled trial. J Clin Oncol. 23:4312–21
119. Cady B, Stone MD, Schuler J et al (1996) The new era in breast cancer: invasion, size and nodal involvement dramatically decreasing as a result of mammographic screening. Arch Surg. 131:301–8
120. Greco M, Agresti R, Cascinella N, Casalini P et al (2000) Breast cancer patients treated without axillary surgery. Ann Surg. 232(1):1–7
121. Dabbs DJ, Fung M, Landsittel D et al (2004) Sentinel lymph node micrometastases as a predictor of axillary tumour burden. Breast J. 10:101–5

Breast Reconstructive Surgery

15

A. Tahernia, D. Erdmann, and M. R. Zenn

15.1 Introduction

Breast reconstruction following mastectomy can be achieved by a variety of techniques using alloplastic implants, autogenous tissues, or both. In the last 30 years, breast reconstruction has progressed from a rarely requested procedure to one that has become an integral part of patient management. The modern era of breast reconstruction began in 1963 with the introduction of the silicone gel prosthesis. In 1972, Radovon described the use of tissue expansion for breast reconstruction. This technique allowed patients with more significant skin deficits to benefit from reconstruction. In the early 1980s, the use of autologous tissue for breast reconstruction was revolutionized by Hartrampf with introduction of the transverse rectus abdominis muscle (TRAM) flap. These developments have resulted in more natural and esthetically acceptable outcomes. Experience over time has also shown breast reconstruction to be an oncologically safe component of the overall treatment plan. Perhaps most importantly, breast reconstruction yields psychological benefits for women, offering a sense of normalcy, a "return to wholeness" and a way to leave the cancer experience behind them. Women gain the freedom to wear a variety of clothing, without the need for external prosthesis, which may be cumbersome and embarrassing.

Historically, almost all breast reconstructions were delayed for months or years after mastectomy. It was feared that immediate breast reconstruction would compromise adjuvant treatments and that it would increase postoperative complications. There were concerns of masking locoregional recurrences and rendering treatment of such disease as difficult. However, studies have shown that this is not the case. Today, in the right clinical scenario, patients can undergo immediate breast reconstruction with a minimum compromise to their overall cancer management and a maximum benefit.

Breast reconstruction has become an integral part of the multidisciplinary approach to breast cancer. In order to optimize results, patient selection is critical. Factors that need consideration prior to embarking upon a reconstruction include: stage of the cancer, patient comorbidities, possible adjuvant radiotherapy, availability of autologous tissue, and most importantly, the patient's own desires.

In this chapter we will review the indications, timing, principles and techniques of breast reconstruction following mastectomy. We will also review the role of radiation in breast reconstruction and how it impacts surgical decision-making.

15.2 Indications for Reconstruction

Patients who are candidates for breast reconstruction are those who have undergone mastectomy for cancer extirpation. However, with advances in the understanding of the genetic basis of breast cancer and identification of BRCA1 and BRCA2 genes, more patients with familial history of breast cancer are undergoing prophylactic mastectomies. Therefore, breast reconstruction is not only limited to patients with a diagnosis of breast cancer. Regarding indications for prophylactic mastectomy, the Society of Surgical Oncology has developed the following guidelines (Fig. 15.1).

Patients with metastatic disease are not candidates for reconstruction, and in those who have significant

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_15, © Springer-Verlag Berlin Heidelberg 2010

Suggested Indications for Prophylactic Mastectomy by the Society of Surgical Oncology

Women with no prior history of breast cancer
Atypical hyperplasia
Family history of premenopausal bilateral breast cancer
Dense breats associated with atypical hyperplasia or family history of premenopausal bilateral breast cancer or both
Women with unilateral breast cancer
Diffuse microcalcifications
Labular carcinoma in situ
Large breast,difficult to evaluate
History of lobular carcinoma in situ followed by unilateral breast cancer
History of atypical hyperplasia,primary family history, age at diagnosis < 40 y

Fig. 15.1 Table Indications for Prophylactic Mastecomy

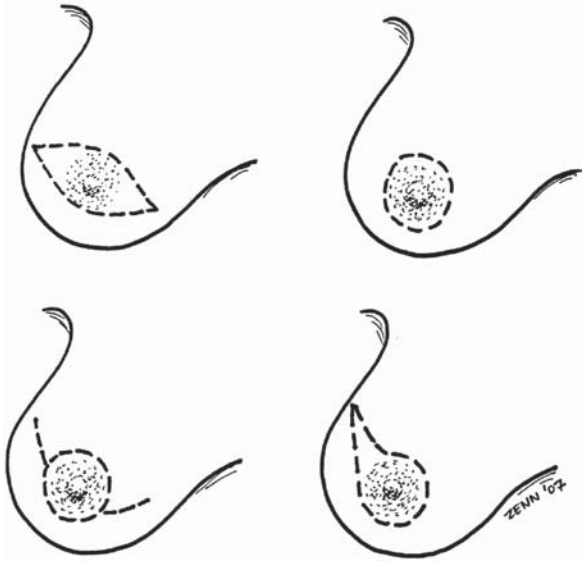

Fig. 15.2 Skin sparing mastectomy incisions: varying incisions used in skin sparing mastectomy. The incision is in part determined by areas of previous biopsy. The goal is to minimize area of scar on the skin envelope by incorporating biopsy incisions

medical comorbidities, mastectomy may be the only reasonable surgical intervention, as the stress of reconstructive surgery may be prohibitive.

15.3 Skin Sparing Mastectomy

The technique of skin sparing mastectomy has greatly improved the esthetic outcomes of autologous breast reconstruction. It is an oncologically safe procedure in patients with Stage I and II cancers. It allows the mastectomy to be performed with preservation of most of the natural breast skin envelope and infra-mammary fold.

The skin-sparing mastectomy technique involves a periareolar incision with or without some type of lateral extension for exposure and removal of breast tissue (Fig. 15.2). Prior biopsy site is ideally included within the planned surgical incision. Although more time consuming than traditional cancer ablative methods, this technique permits maximal preservation of skin and provides excellent cosmetic results. Several studies have validated its oncologic safety and no studies have shown any statistically increased risk of tumor recurrence or compromised local control of the disease following skin-sparing mastectomies.

The use of complete skin-sparing mastectomy successfully reduces scar burden and skin color discrepancies, allows for optimal preservation of the preoperative breast shape, and may minimize the need for a contralateral procedure to achieve breast symmetry. The success of this procedure is dependent upon proper patient selection and ability of the oncologic surgeon to safely perform extensive skin flap mobilization in a precise plane through limited exposure and adequately remove all breast parenchyma. Patients with previous radiation, cupsize larger than C, or surgeons unfamiliar with the technique should not have skin sparing mastectomy.

The reconstruction of lumpectomy defects remains controversial. These patients have received irradiation, which complicates revisional surgery. In most cases, if cosmesis is unacceptable, patients require completion mastectomy and reconstruction from scratch, removing the problematic irradiated tissues.

15.4 Timing of Breast Reconstruction

Breast reconstruction can begin at the time of mastectomy (immediate) or anytime following adjuvant treatment (delayed). During the early development of breast reconstruction techniques, reconstruction was performed in a delayed fashion, meaning months or years after the mastectomy. Combining a reconstructive procedure with the mastectomy presented several concerns with the possibility of increased complications and possible delays in postoperative delivery of

adjuvant treatment. These concerns however have been shown to be unwarranted.

Immediate reconstruction is usually reserved for Stage I and some Stage II breast cancer patients. Immediate reconstruction is more convenient for patients as it limits the number of exposures to anesthesia and has psychological benefits. With immediate reconstruction, esthetics is improved, since incisions tend to be shorter and there is less skin removal. Immediate reconstruction is not an alternative for the patient not psychologically prepared for a reconstructive procedure. Some patients are simply overwhelmed by their new diagnosis and cannot make decisions beyond cancer treatment. Also, patients in whom radiation therapy is planned should not have immediate reconstruction. Sufficient studies have shown the negative impact of radiation on complications and the final results, that reconstruction should be delayed.

Delayed reconstruction may be the only option in some patients for various reasons. Some may not have access to a reconstructive surgeon at the time of the mastectomy. Others may feel that they need to deal individually with each step of the cancer treatment protocol. This will allow them to weigh all their options with regard to type of reconstructive method and selection of a reconstructive surgeon. As mentioned previously, delayed reconstruction is recommended for patients with advanced disease who will require postmastectomy radiotherapy (PMRT). Some of the problems radiotherapy may produce include fat necrosis, shrinkage of autogenous tissue flaps, thinning of overlying chest skin, and periprosthetic capsular contracture. These patients should be reassured that a delayed reconstruction is in their best long term interest and that esthetic results can be equal to immediate reconstruction. Most delayed reconstructions can be initiated 4 months after completion of chemotherapy and 6 months after radiation therapy.

15.5 Alloplastic vs. Autogenous Reconstruction

15.5.1 Alloplastic Reconstruction

Today, most mastectomy patients are candidates for tissue expander/implant reconstruction. In general, the best results are seen in patients with moderate breast size and minimal ptosis (inferior displacement of the nipple–areolar complex). This is the reconstruction of choice for small breasted women considering contralateral augmentation as part of their reconstruction. Patients who will be receiving radiation however are not good candidates for prosthetic reconstruction as radiotherapy can lead to capsular contracture, infection, implant extrusion, and rarely rib fractures. In these situations, autologous reconstruction or a combination of implant with autologous tissue should be considered.

All breast reconstructions require more than one operation and the process may extend over many months. Alloplastic reconstruction with use of tissue expanders/implants is the simplest technique and the one chosen by over 75% of patients who undergo breast reconstruction. Potential advantages of expander/implant reconstruction over other techniques include: (1) relative simplicity of the surgical procedure, (2) use of adjacent tissue of similar color, texture, and sensation, (3) elimination of distant donor-site morbidity, (4) minimal incisional scarring, and (5) reduced operative time and postoperative recovery compared to tissue reconstruction. Implant reconstruction yields the best results in patients with moderate breast volumes (500 g or less), no or minimal ptosis, and presence of sufficient healthy soft-tissue coverage. Patients with large or markedly ptotic breasts, matching surgery on the contralateral breast may be necessary in order to achieve symmetry. This would mean the patient would need breast reshaping either by a breast reduction or breast lift (mastopexy). Prosthetic reconstruction can occur in one of three ways: (1) single-stage reconstruction with use of primary implants, (2) two-staged reconstruction with use of initial tissue expanders followed by exchange for permanent implants, and (3) single-stage reconstruction with placement of adjustable expanders-implants that remain in place and need not be exchanged once the desired volume has been achieved.

Before looking at each of these modalities, a brief review of the technique of implant placement will allow for a better understanding of the anatomic considerations which are essential to optimal outcomes. Breast implants or tissue expanders must be placed in the submuscular position (Fig. 15.3). This is due to the fact that after a mastectomy no gland remains and so healthy vascularized soft tissue coverage is lacking. All implants induce a foreign body reaction and formation of a discrete fibrous shell or capsule. Under the influence of a variety of factors, this capsule may undergo the process of capsular contracture which can distort breast shape.

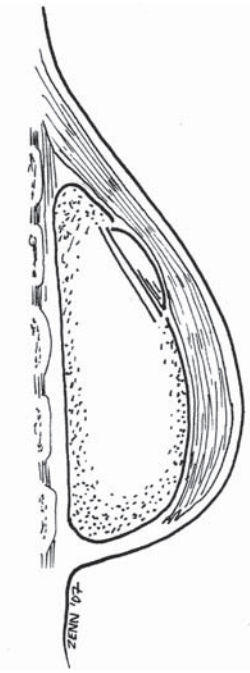

Fig. 15.3 Implant/expander placement: tissue expanders can be placed in a subpectoral or submuscular position. This figure demonstrates a subpectoral prosthesis with most of the implant covered with pectoralis major muscle. In a true submuscular position, the rectus abdominis and serratus anterior muscles would be covering the inferomedial and inferolateral aspects of the prosthesis, respectively

Submuscular placement helps cover the implant with healthy tissue which hides capsular distortion and may help prevent it. Many variables can influence the development of capsular contracture and they include type of implant surface, implant placement, infection, and use of radiation. We will revisit the issue of capsular contracture later in the complications section.

The key landmark for any breast reconstruction is the inframammary fold (IMF). Every effort is made to recreate a natural fold that matches the contralateral fold in position and symmetry. The critical measurement to consider when selecting an implant is the base diameter of the breast. Other factors to be considered are the height and projection of the breast. These factors are all accounted for preoperatively with the appropriate marks made on the patient's chest before creation of the submuscular pocket. After completion of the mastectomy, the viability of the mastectomy flaps is assessed. Poorly perfused tissue is excised and if there is any doubt as to the adequacy of soft-tissue coverage, the reconstruction should be delayed. If all looks well, an area under the pectoralis muscle is dissected forming a submuscular pocket for the implant. This dissection involves identification and elevation of the lateral border of the pectoralis major muscle, and release of the muscles from its origin on the 5th rib. Dissection is also carried laterally, elevating the serratus anterior muscle. The location of the pocket will ultimately determine the level of the IMF.

15.5.2 Implant Types

The silicone gel-filled breast implant was first developed in 1963 for women with small breasts who desired augmentation. This was later applied to breast reconstruction to restore shape and contour in women following mastectomies. In 1992, the US Food and Drug Administration established a moratorium on the use of silicone gel-filled implants until 2005 in the United States. These implants were only available under protocol for reconstructive purposes. The concern with the silicone implants was a presumed association with connective tissue disorders as well as metachronous development of breast cancer. Multiple retrospective studies over the past 20 years have shown this to be invalid, and as such these implants have been re-approved for use in the United States use by the FDA in 2005.

Following the 1992 FDA moratorium on silicone gel implants, there was an expected surge in the use of saline filled implants. An advantage with these implants is that, a desired volume can be achieved with intraoperative instillation of saline into an empty implant. Several problems have been associated with saline implant use such as firmness, wrinkling of the implant, and complete deflation of the mound upon rupture. In comparison, silicone implants are softer, have a more natural appearance and are filled with cohesive gel which maintains its shape upon outer shell failure.

Implants also come in different shapes and can have different surface characteristics. All implants regardless of whether they are saline or silicone filled, have a silicone outer shell. With respect to shape, the most commonly available types are the round and anatomical or teardrop-shaped implants. Both shapes are commonly used and achieve excellent results. Choice is largely physician driven. Placement and fixation of an anatomic implant is more critical as it can be noticeable if the implant is turned, not upright. Round implants are more forgiving. Textured surface implants have been shown to be less associated with capsular contracture, whereas smooth implants are less likely to cause rippling of the overlying skin. There are several variables needing consideration before choosing the ideal implant for a patient with no perfect solution. To make the best

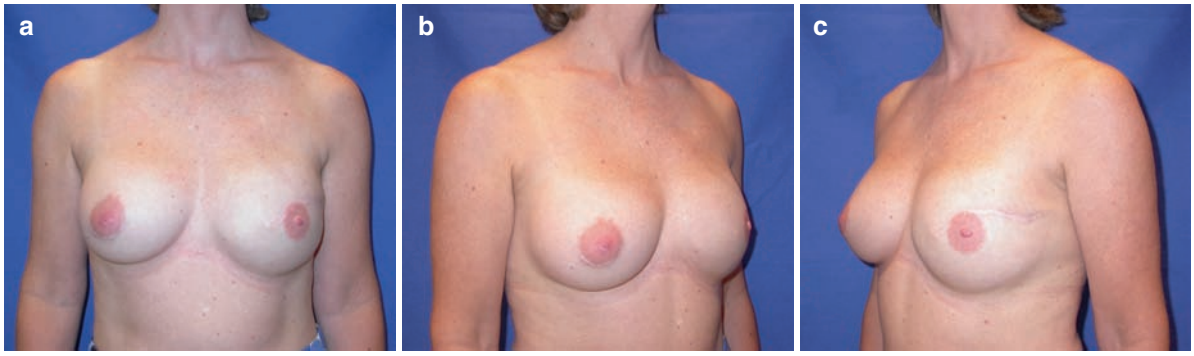

Fig. 15.4 Tissue expansion/exchange: this is a 45-year-old patient who underwent immediate placement of a tissue expander on the left, subsequent expansion, and exchange for an implant. At the implant exchange, she had a contralateral breast augmentation for better symmetry. These photos represent her 9 month postoperative visi

decision, the patient should be educated on these issues and be an integral part of the decision making process.

15.5.3 Two Stage Expander/Implant Reconstruction

Two stage reconstruction using an initial expander followed by secondary permanent implant placement is the gold standard for implant reconstruction. It is especially desirable when there is insufficient tissue after mastectomy or when the desired size and shape of the breast cannot be safely and consistently achieved with a single-stage procedure. With expansion, adjustments to the implant pocket at the time of the second procedure, allows a more consistent reconstruction of the moderately sized breast with mild ptosis. Prosthetic reconstruction in patients with large breasts and significant ptosis requires a contralateral reduction or mastopexy to achieve symmetry, a symmetry that will only occur in clothes.

The procedure for expander placement creates a submuscular pocket of pectoralis and serratus muscles. Expander selection is based on the height and width of the desired breast. Most plastic surgeons favor textured expanders with integrated valves. They allow direct instillation of fluid through insensate mastectomy skin which is not painful to the patient. Following skin closure, a magnet is used to identify the port and an initial volume of saline is instilled, from zero to 300 mL or more. Additional expansion continues postoperatively 2 weeks after expander placement. The patient is seen in clinic and 50–100 cc are instilled every 2–3 weeks. Usually, this is carried out over a 2 month period until the desired amount of expansion has occurred. Most surgeons overexpand by 10–25% as there is some retraction of the soft tissue once the expander is replaced with the permanent implant. If the patient is receiving chemotherapy, the exchange procedure is delayed up to 4 weeks after completion of treatment to avoid issues with wound healing that may result. Following completion of expansion, the exchange of the expander for a permanent implant involves recreation of the incision, removal of the expanders, adjustments of the pocket and IMF, and permanent implant placement (Fig. 15.4). Suction drains are placed and patient is placed in support bra for 10–14 days to keep the implant properly oriented. If postoperative radiation of empty is planned, the expander is irradiated at final volume and exchange is delayed from 4 to 6 months depending on radiation induced edema and induration.

15.5.4 Single Stage Reconstruction with Implants

With skin sparing mastectomy of a small breast, placement of an implant can be done immediately. The goal is to maintain the breast envelope and fill it with volume. Since the skin after mastectomy is thin and relatively ischemic, healthy vascularized muscle is required to ensure implant longevity. In the one stage approach, tissue expansion of the pectoralis does not occur and so muscle coverage must be obtained in another way. This is accomplished with latissimus dorsi muscle transfer. At the time of mastectomy, the latissimus is harvested via an open or endoscopic approach and rotated to the

anterior chest where it drapes over the final breast implant. Although the shortened reconstructive process is attractive to patients, this approach is technically more difficult than a two stage approach to obtain optimal results. Immediate single-stage reconstruction is best suited for patients with small, round breasts with a resection weight of about 300 g. The implant should be placed in a subpectoral pocket .When there is concern about inferior mastectomy skin flap viability, the implant may be placed in a "total" submuscular pocket that includes the pectoralis major, serratus anterior laterally, and the superior fascia of the rectus abdominis muscle. Should skin necrosis occur, then the lower portion of the implant will not be exposed. Some experimental work is now being performed to see if a skin substitute (like Alloderm) can replace the latissimus muscle and lower patient morbidity.

15.5.5 Permanent Tissue Expander/ Implant Reconstruction

One stage breast reconstruction with permanent expander implants was introduced in 1984 with expandable double lumen silicone gel/saline filled prosthesis. The implant can be partially filled at the time of reconstruction and gradually inflated postoperatively over a 3–6-month period, until symmetry is achieved. The device is placed in a similar manner as previously described. The major drawback of breast reconstruction with anatomic expander implants is that it is hard to get the skin to expand in a breast shape. This is the advantage of having a second stage – better shape. Disadvantages of this approach include superficial infection and discomfort often associated with the port. In addition, a second procedure is needed to remove the port.

15.5.6 Complications of Implant Reconstruction

As would be expected with any foreign body, there are certain risks associated with the use of implants. Infection, extrusion, malposition, and capsular contracture are among the most common. The incidence of infection of breast implants is generally around 2%, but studies have shown an increased risk in the setting of chemotherapy, radiation, and previous axillary node dissection. As a result, the incidence implant infection in the setting of breast reconstruction is higher, with some studies reporting infection in up to 10% of patients. Treatment of implant infection or extrusion require removal of the implant followed by antibiotic therapy. A period of 4–6 months should pass before embarking on a secondary reconstruction. Extrusion of implants can be secondary to infection or poor soft tissue coverage. For this reason, many surgeons prefer "total muscle" coverage of the implant at the time of surgery. It is thought that covering the entire implant with muscle will still protect the implant in the setting of a skin dehiscence, which would otherwise potentially expose an implant that has less soft tissue coverage.

All implants induce a foreign body reaction and formation of a discrete fibrous shell or capsule. Many variables influence the occurrence of significant capsular contracture, such as implant type, textured surface, filler substance, submuscular placement, and subclinical infection. Capsular contracture is classified based on severity. The Baker Classification categorizes this as follows:

Grade 1: The breast is soft and natural appearing
Grade 2: The breast is less soft with palpable distortion but still appears natural
Grade 3: The breast is firm with visible distortion
Grade 4: The breast is firm, painful, and visibly distorted

Using this classification as a guide and evaluating each patient individually, severe cases of contracture (grades 3 and 4) may require surgery for removal of the capsule and replacement of the prosthesis (Fig. 15.5). Factors that have been shown to reduce the incidence of this complication include submuscular placement of the implant and use of a textured surface implant.

15.6 Autogenous Reconstruction

Advances in breast reconstruction during the past 20 years offer women the option of undergoing breast reconstruction with their own tissue and without the need for breast implants or expanders. The first application of autogenous transfer for breast reconstruction occurred in 1977 with the use of the latissimus dorsi muscle flap. Myocutaneous flaps permit the

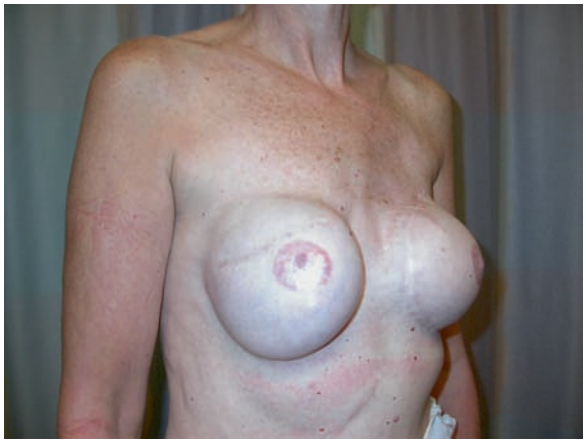

Fig. 15.5 Capsular contracture: this is a 57-year-old patient 5 years after right implant reconstruction and left implant reconstruction with a latissimus flap due to radiation. Note the distorted shapes of the breasts and thinning skin envelope

transposition of additional skin, underlying fat, and muscle for reconstruction of the breast. The most common donor sites for autogenous tissue are the lower abdomen, back, and gluteal regions. These areas are considered to have tissue excess and can be contoured to produce a more esthetic appearance. Flap reconstructions are particularly useful when there is a significant skin deficiency following mastectomy. With immediate breast reconstruction, the use of a flap can permit the creation of a breast that is relatively symmetrical with the contralateral breast with similar tissue characteristics.

The transfer of myocutaneous flaps is possible due to the blood supply to the overlying skin and subcutaneous tissue from the underlying muscle via musculocutaneous perforators. The transfer of myocutaneous flaps can be accomplished as pedicled flaps or free flaps. Pedicled flaps refer to tissue blocks that are transferred from the lower abdomen or back to the mastectomy site following elevation of the myocutaneous unit from its bed. The pedicle, consisting of an artery and a vein(s) may be skeletonized, but is left intact and serves as the axis of rotation of the flap. Free tissue transfer relies on the technique of microsurgery and in breast reconstruction applies to the transfer of tissue from the lower abdomen or gluteal regions to the chest wall. This involves elevating the tissue needed, identifying its major vascular pedicle and dividing it. This is followed by relocation of the tissue to the chest along with microvascular anastomosis of the donor vessels to the recipient vessels. In breast reconstruction, the most common recipient vessels are the internal mammary vessels and the thoracodorsal vessels.

Autogenous reconstruction can be performed in both the immediate and delayed setting. Today, when patients are felt to be at very high risk for radiotherapy, autogenous reconstruction is performed in a delayed fashion. Immediate reconstruction would occur if sentinel node sampling reveals no evidence of lymph node metastasis and tumor size is small. Overall, autogenous breast reconstruction yields the most durable and natural appearing results with the greatest applicability. It has several advantages over implant reconstruction:

1. A large volume of the patient's tissue is available.
2. Prosthesis is not required, obviating problems such as implant infection, prosthesis, contracture, and extrusion.
3. It offers versatility in shaping the new breast with creation of natural ptosis and fill of the infraclavicular hollow and anterior axillary fold.
4. It can withstand postoperative radiotherapy much better than implant reconstruction.
5. The excellent vascularity of the tissues allows for improved wound healing, especially in an irradiated chest wall.

The autogenous tissues available in decreasing order of frequency of use are the TRAM flap, the latissimus dorsi flap, superior and inferior gluteal flaps, upper thigh flap, lateral tranverse thigh flap, and deep circumflex iliac artery (DCIA) flap. Each of these flaps, described as a myocutaneous flap, can also be harvested as a new generation perforator flap which relies on free tissue transfer without sacrifice of the underlying muscle. We will review these flaps and adjunctive methods available for optimal reconstructive outcomes.

15.6.1 Pedicled TRAM Flap/Unipedicled Flap

The pedicled TRAM flap was first described in 1982 by Hartrampf. Since then, the procedure has gained popularity and it remains the most commonly performed method of autologous breast reconstruction. A lower abdominal transverse skin island is designed overlying the rectus abdominis muscles. This is the same tissue removed during an abdominoplasty, hence its appeal. The overlying skin and subcutaneous tissue

receive their blood supply from perforating vessels from the underlying rectus muscle.

The rectus abdominis muscle receives a dual blood supply from the superior and inferior epigastric vessels. The pedicled flap is based on the superior epigastric vessels due to a better point of rotation to reach the chest. The vessels are the continuation of the internal mammary vessels and are distant from the lower abdomen. This means the degree of perfusion of the overlying skin and fat is limited and care must be exercised in deciding how much tissue to carry. It does not require microsurgical skills and is therefore more applicable to most plastic surgeons. The muscle with its overlying adipose tissue and skin are simply tunneled through the upper abdomen to the chest wall into the contralateral or ipsilateral mastectomy defect (Fig. 15.6).

The concept of perfusion becomes relevant when looking at flap survival and partial flap loss called fat necrosis. Fat necrosis manifests as a subcutaneous firmness, which often compromises the esthetic outcomes of the reconstruction. In addition, it causes anxiety in patients and surgeons in view of its differential diagnosis as a cancer recurrence. A simple way of thinking about this is that the risk of fat necrosis increases as the distance from the muscle perforators increases. The concept of angiosomes was first introduced by Taylor over 20 years ago. An angiosome represents a three-dimensional tissue unit supplied by a source artery. Each source artery directly supplies perforators to the muscle and skin of a discrete area called the primary angiosome. A neighboring area may still be supplied by this source artery through secondary, less reliable "choke vessels," and these areas are secondary angiosomes. The primary blood supply territory of the superior epigastric artery is the upper abdomen. The lower abdomen is supplied in a pedicled TRAM flap by connections between the superior epigastric system (secondary) and the inferior epigastric system (primary to the lower abdomen). Intuitively, the best supplied tissues are present over the rectus muscles in direct continuity with the muscular perforators. This is referred to as Zone 1 of the TRAM flap (Fig. 15.7). As seen in the figure, there are a total of 4 zones of a TRAM flap. Zone 2 represents the area medial to the elevated rectus across the midline, zone 3 represents the area lateral to elevated rectus. Zone 4 is the furthest from the elevated rectus,

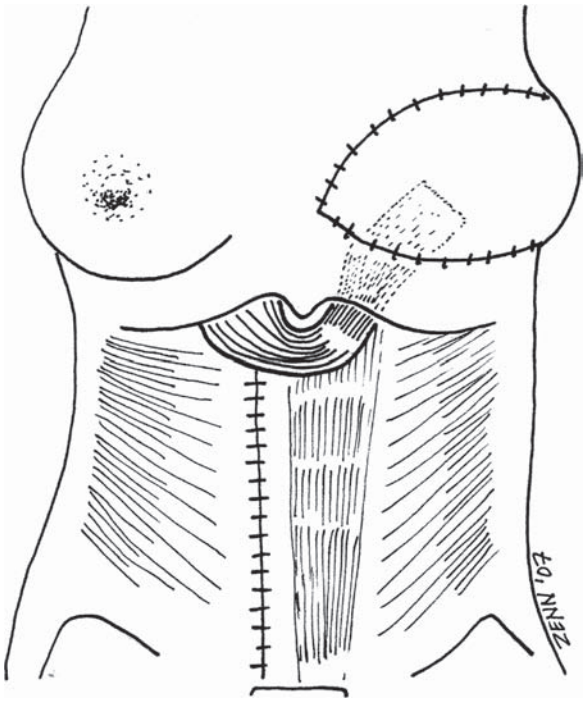

Fig. 15.6 Unipedicled TRAM flap: this picture demonstrates the unipedicled TRAM flap. This flap has been transposed to the contralateral chest. The pedicled TRAM flap can also be transferred onto the ipsilateral chest

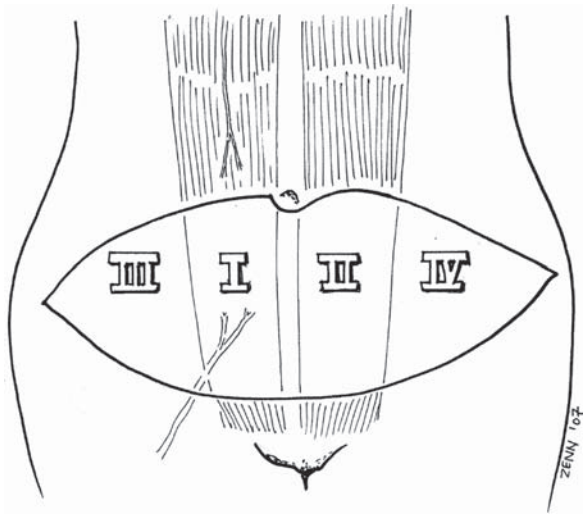

Fig. 15.7 TRAM vascular zones: the lower abdominal tissue that is transferred in a TRAM flap is divided into 4 zones based on degree of perfusion. Zone 1 has the best perfusion as it is the area directly over the deep inferior epigastric artery. Zone 2 is the area directly medial and has the second best perfusion. Zone 3 is the area lateral to zone 1 with a less robust blood supply than zone 2. Zone 4 is the area farthest from the pedicle and thus has the most tenuous blood supply. Because of its relatively poor perfusion, zone 4 is the first area discarded in flap transfer if debulking of the tissue block is necessary prior to inset

representing the area with the most tenuous blood supply present in the TRAM flap. The risk of fat necrosis is higher in patients with history of COPD, diabetes mellitus, hypertension, obesity, and smoking history. In these patients, the pedicled TRAM may not be the best choice for reconstruction. Free TRAM transfer, bipedicled TRAM, and pedicled TRAM after delay may be more appropriate in these settings.

Following harvest and transposition of the flap to the mastectomy defect, the TRAM flap is inset or positioned in place. Attention is turned to recreating a symmetrical breast, with IMF at same level and breast volume and projections also being similar. Often the volume of TRAM is in excess of what is needed, and in this setting, the zones furthest from the pedicle, demonstrating the poorest perfusion, can be partially resected down to the volume desired. The skin of the flap can also be de-epithelialized to leave behind enough epidermis to only bridge the mastectomy skin defect (Fig. 15.8).

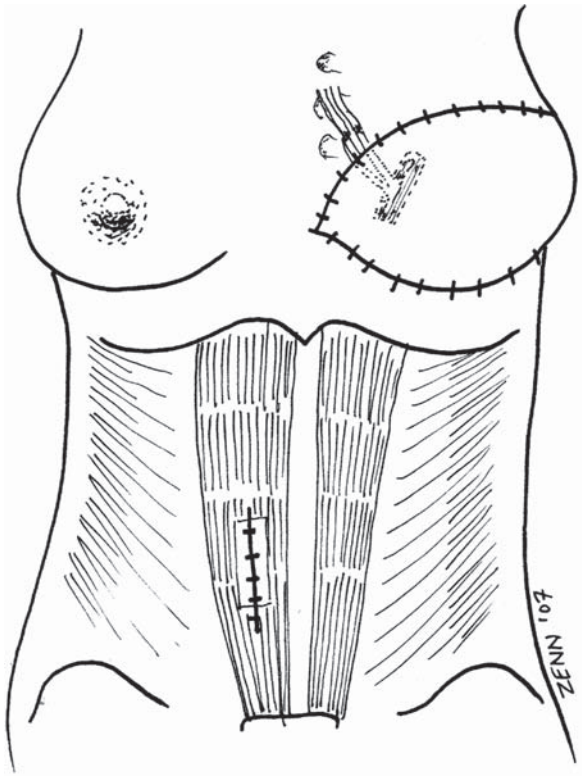

Fig. 15.8 Free TRAM flap: this figure demonstrates a muscle-sparing-free TRAM flap where only a small portion of the rectus muscle and fascia surrounding the deep inferior epigastric pedicle is included. The pedicle can be coapted to either the thoracodorsal or internal mammary system. Here the anastomosis is to the internal mammary vessels

The donor site also needs careful attention to avoid hernias and bulges. With the rectus muscle harvested on one side, the chance of hernia is about 5%. For this reason, mesh reconstruction of the muscle defect should be considered when primary closure is not possible or is tenuous. Despite these adjunctive procedures, up to 30% of patients still experience a bulge or hernia in the lower abdomen with full muscle harvest. The clinical significance of this is debated.

15.6.2 Bipedicled TRAM Flap

The use of the two rectus muscle pedicles increases the blood flow to the overlying skin and fat, thereby increasing the reliability and size of the flap. However, indications are limited because of the morbidity associated with abdominal wall damage from loss of both rectus muscles. It is used primarily to augment circulation in obese patients, smokers, and diabetics. It is also used in patients with limited abdominal tissue; hence all zones are required for reconstruction, and in patients who are unwilling to undergo reduction of the contralateral breast. It has been shown that patients who undergo unipedicled reconstruction have a 40% decrease in abdominal muscle strength compared to a 64% decrease in bipedicled flaps. With previous abdominal midline scars, some surgeons have reported acceptable results in these patients using the bipedicled TRAM. In larger centers, free flap reconstruction has largely supplanted the use of the bipedicled TRAM.

15.6.3 Midabdominal TRAM Flap

In the morbidly obese patients who would be considered high risk for the standard lower abdominal TRAM flap, the midabdominal TRAM represents an acceptable alternative. In this variant, the horizontal location of the abdominal ellipse is moved upwards toward the midabdomen in order to increase the blood flow to the overlying skin and fat. The supplying superior epigastric vessels are not so distant and perfusion of the tissue, now a primary angiosome, is improved. It is ironic that the obese patient with a significant abdominal pannus is a poor candidate for a standard TRAM. This is because the tissues, though significant, are

poorly vascularized and edematous. Use of the ample mid or upper abdomen avoids the use of these poorer tissues in the reconstruction, avoiding complications. Abdominal closure is facilitated by the large pannus. The main disadvantage, the highly visible scar in the mid or upper abdominal area, is less of a concern for the morbidly obese patients, who benefit somewhat from reduction of abdominal redundancy.

15.6.4 Free TRAM Flaps

The free TRAM flap utilizes the primary blood supply of the lower abdomen, the deep inferior epigastric vessels. It thus has better vascularity and less risk of ischemia in the peripheral zones (abdominal zones 2, 3 and 4). Because of this improved tissue perfusion, there is a lower incidence of fat necrosis when compared to the pedicled TRAM flap. Additionally, this flap reliably carries a larger amount of skin and adipose tissue than the pedicled TRAM. Since it is not possible to pedicle a flap based on the inferior epigastrics to the chest, these vessels must be divided and microscopically reconnected.

These vessels are connected with either the thoracodorsal or internal mammary vessels (Fig. 15.9). In immediate breast reconstruction, the thoracodorsal vessels are usually targeted since they are usually fully exposed by the oncologic surgeon during axillary node dissection. In the delayed setting, the internal mammary vessels are more often chosen for the microvascular anastomosis. This recipient site has the advantage of being free of previous scarring around vessels, being centrally located facilitating microsurgery, and allowing a more medial positioning of the flap. Studies from numerous cancer centers show distinct advantages of the free TRAM over its pedicled counterpart. There is a less than 10% chance of fat necrosis with free flap reconstruction compared to 30% with the pedicled TRAM. As in the pedicled TRAM, the free TRAM flap is also associated with abdominal wall bulges and hernias, but less so. One study quoted the incidence of hernia to be 12% in the pedicled TRAM and 3–6% in the free TRAM flap. The free TRAM also avoids the bulge in the epigastrium and the disruption of the IMF that is required by the tunneling of the pedicled flap from the lower abdomen. Free flaps do not require tunnel formation, and a sharply demarcated IMF is possible during the first operation.

Among the recent advances in free flap reconstruction, muscle-sparing and perforator flaps have been introduced. In the muscle sparing TRAM variant (Fig. 15.10), only the central portion of muscle surrounding the deep inferior epigastric pedicle is taken with the flap leading to less disruption of the rectus fibers as compared to the conventional free TRAM, where the complete transverse width of the muscle is removed. In the muscle sparing TRAM, muscle

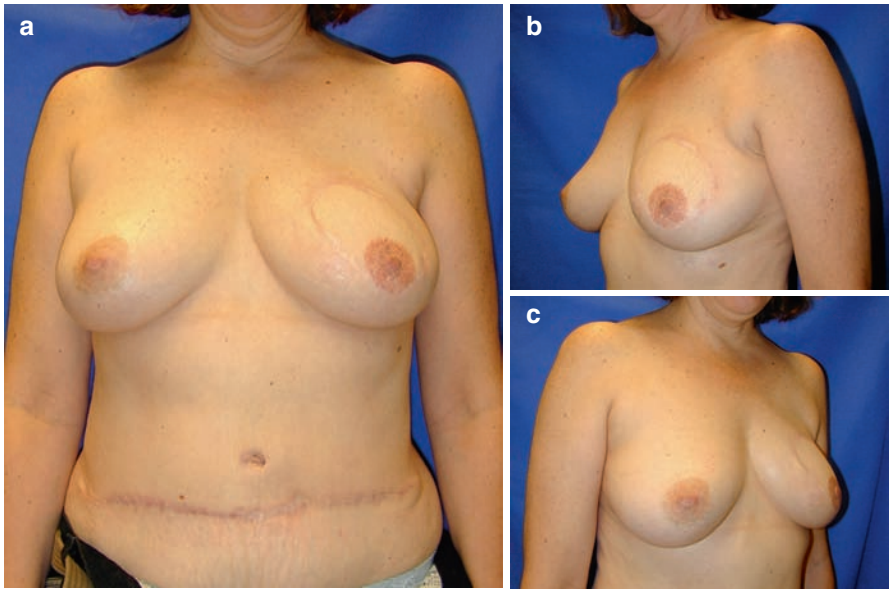

Fig. 15.9 Pedicled TRAM: this is a 43-year-old patient who underwent immediate breast reconstruction with a pedicled TRAM. These are 1 year postoperative photos. The areola was reconstructed with tattoos and the nipple by nipple sharing from the contralateral nipple

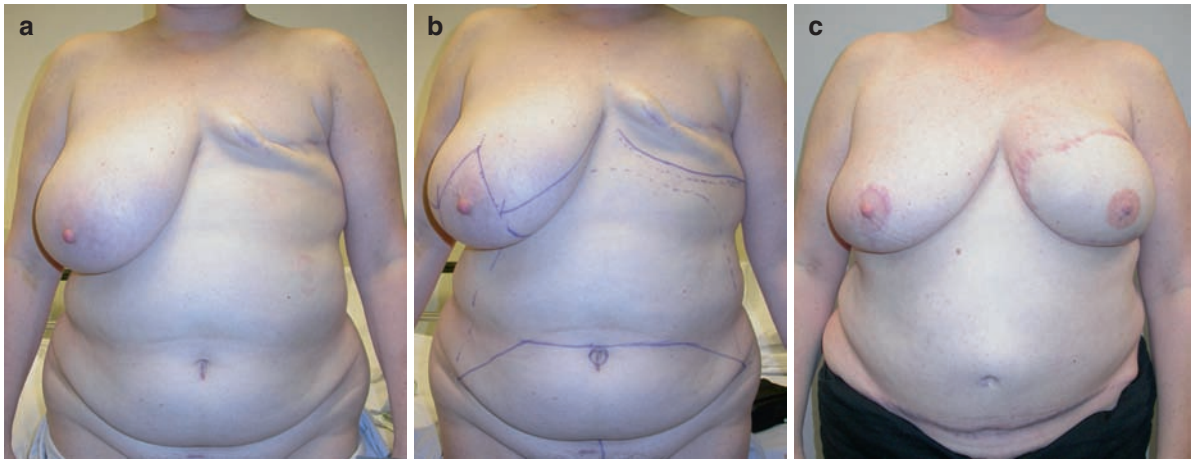

Fig. 15.10 Breast-reduction with free TRAM: this is a 40-year-old patient who underwent delayed reconstruction. (**a**, **b**) Preoperative defect and markings. Her right breast was too large to match so she had a reduction on the right and a muscle sparing free TRAM flap on the left (**c**, **d**). These photos are at 1 year follow-up

continuity is maintained as is a significant portion of the muscle innervation, so the rates of hernia and bulge are less. In contradistinction, pedicled flap reconstruction mandates elevation of the entire rectus muscle leaving behind a large area of the lower abdomen often requiring mesh reinforcement.

Perforator flaps represent the newest generation of free flap reconstruction. The concept of a perforator flap emphasizes the blood vessels, not the muscles. The skin island and accompanying fat are isolated on perforating vessels that come through muscle from the source artery, leaving intact innervated muscle. In breast reconstruction, the dominant perforator flap used is the deep inferior epigastric perforator (DIEP) flap. The superficial inferior epigastric artery (SIEA) perforator flap has also been used; however, it less available due to the anatomic variability seen in patients.

The DIEP flap preserves the whole rectus muscle and its sheath. It can be based on a single large perforator or as many as 4 or 5 perforators. When skeletonizing the perforators, the rectus sheath above and below the perforator is incised for a short distance to identify the vessel connection with the deep inferior epigastric system. The advantages of the DIEP flap include avoidance of muscle sacrifice and decreased abdominal wall morbidity, decreased postoperative pain, and decreased hospital stay. It usually also avoids the problems of a tight fascial closure and can preclude the need for synthetic mesh. Although the DIEP, based on a few perforators, has less perfusion than a free TRAM flap which is based on all perforators, the incidence of fat necrosis is similar and perfusion is still superior to a pedicled TRAM. One of the disadvantages of the DIEP flap is the technically more challenging dissection.

The free SIEA flap provides the same abdominal skin and fat for reconstruction as the DIEP flap. Of the two flaps, the SIEA causes less donor site morbidity. Since the superficial epigastric vessles are superficial rectus fascia, no incision must be made in the abdominal fascia and no vessel dissection is performed through the rectus abdominus muscle. The flap however is limited by the variability in its vascular anatomy. The SIEA and vein are only inconsistently present in sufficient caliber to reliably support sufficient tissue for breast reconstruction. Disadvantages of the SIEA flap are a smaller pedicle diameter and shorter pedicle length than TRAM or DIEP flaps. When performed successfully, esthetic results of SIEA flap breast reconstruction is indistinguishable from a TRAM or DIEP flap.

15.6.5 Latissimus Dorsi Musculocutaneous Flap

As previously alluded to, the latissimus dorsi muscle can be used for autogenous breast reconstruction. It is often combined with implant reconstruction in patients

with moderate sized breasts, and in those with smaller breasts it can be used alone. With this operation, skin and muscle from the back are transferred to the mastectomy defect. It is safe with a reliable blood supply. The blood supply to the pedicled latissmus flap is the thoracodorsal vessels. In the event that these vessels are injured during surgery, the latissimus can still be raised based on the serratus branch of the thoracodorsal vessel. In this situation, retrograde flow from the intercostals system, through the serratus branch maintains tissue perfusion

The indications for use of the latissimus dorsi muscle in breast reconstruction include: (1) primary reconstruction with or without implant/tissue expander; (2) patients with inadequate abdominal tissue, or patients who are unwilling to have an abdominal scar; (3) secondary reconstruction with implant after radiation therapy; and (4) as a salvage procedure for implant or tissue reconstruction when failure of reconstruction has occurred.

The skin paddle on the back over the muscle is quite healthy and is well perfused when placed directly over the latissimus muscle (primary angiosome). A patient who has undergone a skin sparing mastectomy may require mainly muscle and only a small circle of skin to replace the nipple–areolar complex. The latissimus muscle flap is usually used in combination with implant/expanders to achieve a desired breast volume to match the contralateral breast. In some patients who need added volume but do not want implants, the extended latissimus dorsi flap can be used. With this method, a more aggressive fat and skin harvest increases the bulk of flap and forms a larger breast. Disadvantages of this technique include the high incidence of seroma at the donor site and a large scar deformity on the back.

15.6.6 Gluteal Musculocutaneous and Perforator Flaps

Gluteal tissues are a distant second or third choice for total autogenous breast reconstruction. They are a distant choice due to the popularity of the abdominal tissue donor site and the difficulty of the gluteal vessel dissection. The gluteus maximus myocutaneous free flap was first described in 1983. The superior gluteal free flap is based on the superior gluteal vessels and the inferior gluteal flap is based on the inferior gluteal vessels. For any flap, the width of the skin island may be up to 13 cm and allow a primary donor closure, while the length varies from 10 to 30 cm. While there is ample adipose tissue to allow for reconstruction in the gluteal region, gluteal fat is more fibrous than abdominal wall fat. This can make shaping of the tissue more difficult during insetting of the flap and limit the final appearance of the reconstruction. Important anatomic differences exist between the superior and inferior gluteal flaps (Fig. 15.11). The superior gluteal artery is shorter and must be connected to the internal mammary system for the tissues to be placed properly on the chest. The inferior gluteal artery is longer and can reach the thoracodorsal vessels if needed. Dissection of the inferior gluteal artery can put the inferior gluteal and posterior femoral cutaneous nerves at risk, not an issue with the superior gluteal artery dissection. While harvest of the gluteal tissue can leave a deformity of the buttock, the superior flap mimics more a buttock "lift" and is better tolerated. Ultimately, the choice of superior vs. inferior will

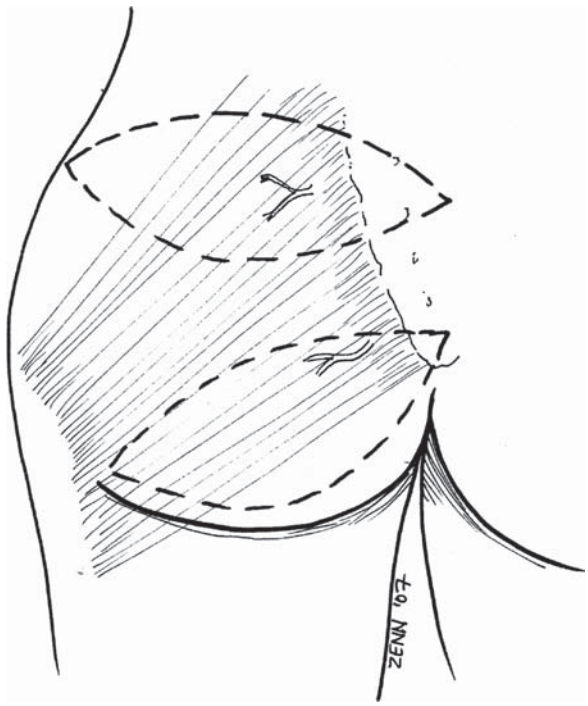

Fig. 15.11 Gluteal artery flaps: This figure demonstrates the zones of the superior and inferior gluteal artery flaps. These flaps can be harvested as musculocutaneous or perforator flaps

depend on the distribution of the gluteal fat. For both gluteal flaps, dissection of the pedicles is more tedious when compared to dissection of vessels in a free TRAM flap.

Keeping in line with the concept of perforator flaps like the DIEP, the superior and inferior gluteal artery flaps have also been described as perforator flaps (SGAP and IGAP). The muscle is spared in this technique and therefore one is also able to obtain a longer vascular pedicle. The main disadvantage of these operations is the time it takes to perform them. They are more technically demanding than other flaps and often require position changes for harvest and/or inset.

15.7 Nipple-Areola Reconstruction

Creating a nipple-areolar complex is an integral part of the breast reconstruction. It enhances the final cosmetic result and creates a more natural looking reconstructed breast. It is typically performed 3 months after the mound reconstruction. It is delayed in the setting of a reconstruction that is to be radiated. It is the last step in the process of postmastectomy surgical rehabilitation.

The nipple can be reconstructed with local tissue of the reconstructed breast or as a nipple graft from the contralateral breast. When utilizing local tissue, flaps can be designed to wrap skin and fat into conical shapes to recreate a projecting nipple. Examples of such flaps include the skate, C-V, Bell, and Tab flaps among others. All local flaps suffer from shrinkage during the healing phase and may not match the contralateral nipple. Large nipples can best be matched with "nipple sharing" when the contralateral nipple is bisected, half used as a free nipple graft for reconstruction. This reduces the large nipple and creates an opposite twin from like tissue.

The areola is reconstructed so that it is symmetrical and similar in color and diameter to the areola of the opposite breast. Methods used for reconstruction include skin grafts, areolar sharing from the other breast, and tattooing. Tattooing is the most common method as it is simple and avoids the need for a skin graft. If skin grafting is performed, further intradermal tattooing may be required to achieve symmetry to the opposite nipple-areolar complex.

15.8 Contralateral Breast

While breast reconstruction can nicely replace a breast lost to mastectomy, it rarely produces a breast that is symmetrical with the unaffected contralateral breast. As a result, the patient may require alteration of the opposite breast to achieve symmetry. The options available for the contralateral breast include mastopexy, breast reduction, implant augmentation, and prophylactic mastectomy with reconstruction.

Mastopexy, or a breast lift procedure, is performed to correct a ptotic breast. The procedure involves lifting of the nipple–areolar complex and reshaping of the breast cone to match the reconstructed breast in size and position. Breast reduction can effect similar changes but also reduces the volume of the contralateral breast (Fig. 15.10). In patients who have a reconstructed breast that is larger than their native breast, augmentation mammoplasty of the opposite breast can be performed. Lastly, patients who request contralateral mastectomy must understand that a reconstruction can achieve a reasonable breast form but is not an equal substitute for a natural breast.

15.9 Radiation and Breast Reconstruction

Irradiation is known to cause permanent damage to cells involved in wound healing and as such can negatively impact healing of a flap or graft. Following the milestone publications in 1997 in the *New England Journal of Medicine* of randomized clinical trials performed in Denmark and British Columbia which demonstrated a survival benefit in patients with postmastectomy radiation (PMRT), the use of radiotherapy in the appropriate setting has become standard of care. Current indications for PMRT include: (1) tumors with positive margins, (2) tumors that are T3 or greater (>5 cm), and (3) presence of 4 or more positive axillary nodes. Although the role of PMRT in breast cancer patients has been well-defined and is propitious, its effects on breast reconstruction are not as well accepted. A number of studies have looked at the long-term outcomes of radiation therapy on both implant and autologous reconstruction.

A review by Spear et al. of 40 patients who underwent implant reconstruction followed by PMRT showed

that over 45% of patients required revisional surgery with either implant replacement or autogenous tissue as compared to 10% in patients who did not receive radiation. They showed a 33% rate of capsular contracture in the irradiated group compared to 0% in the control group. Cosmetic outcomes are also considered inferior in the irradiated reconstructed breast. The risk of implant exposure and infection are higher following PMRT. Autogenous reconstruction is also negatively impacted by irradiation. A recent study from MD Anderson compared irradiation of immediate TRAM flaps to irradiation of delayed TRAM flaps. The study demonstrated a similar incidence of early complications. These included vessel thrombosis, partial flap loss, and mastectomy flap necrosis. However, the immediate TRAM flap group had a higher incidence of late complications (fat necrosis, volume loss, and contracture) with 28% of patients requiring revisional surgery. With PMRT in the setting of implant reconstruction, another consideration is the delivery of the radiation. The implant/expander can cause technical problems with the design of the radiation fields, particularly as it pertains to the internal mammary nodes. Therefore the presence of an implant may result in exclusion of the internal mammary chain with increasing doses delivered to the lung and heart.

Due to the high incidence of complications, most reconstructive surgeons will not pursue implant reconstruction in the patient who will need radiation. Most will perform a delayed reconstruction after completion of radiation. It is however often difficult to predict preoperatively who will be a candidate for immediate breast reconstruction and who will need radiation. In patients who are undergoing prophylactic mastectomies immediate reconstruction can be pursued. In breast cancer patients, if the tumor is greater than 5 cm then the patient will need PMRT and immediate reconstruction should be avoided. In patients without clear indications for PMRT, the ultimate need for radiation is unknown. In this situation, when immediate reconstruction is required, a separate sentinel lymph node sampling procedure can be performed. If the sentinel lymph node is negative, most reconstructive surgeons will pursue immediate reconstruction assuming that it is the wish of the patient.

As indications for postmastectomy radiation and other treatment modalities continue to change, the approach to breast reconstruction needs to adapt to maintain an appropriate balance between minimizing the risk of recurrence and providing the most durable and best esthetic reconstructive outcome. Delayed reconstruction is typically performed 6 months after the cessation of PMRT to allow full healing of the chest to limit healing difficulties.

15.10 Chemotherapy

As part of the postmastectomy regimen, patients with breast cancer may need chemotherapy. It is well-known that certain chemotherapeutic agents can hinder wound healing and this can impact the breast reconstruction in the immediate postoperative period. Once the wound is healed (typically 3–4 weeks), chemotherapy can be initiated. In the long term, the effect of chemotherapy on breast reconstruction is negligible, and a history of previous chemotherapy has virtually no adverse effects. However, development of a chronic, nonhealing wound after an immediate reconstruction can delay the administration of chemotherapy until the wound has healed. For this reason, in patients undergoing breast reconstruction who are scheduled to undergo chemotherapy, secondary procedures such as exchange of tissue expanders for implants or tissue flap revision are delayed 2–3 months after the cessation of adjuvant chemotherapy.

15.11 Conclusion

Modern breast reconstruction techniques provide a reliable source of rehabilitation and return to normalcy for patients following treatment for breast cancer. It has become an integral aspect of breast cancer management. As a member of the multidisciplinary breast cancer team, the reconstructive surgeon provides valuable input on the appropriate timing and techniques for reconstruction. Breast reconstruction can be done safely and effectively at the time of mastectomy or as a delayed procedure.

Irrespective of the timing of reconstruction, a spectrum of techniques is available from which the patient and surgeon can choose. These can involve breast implants, autologous tissue or both. Implant reconstruction is a relatively simple and effective method of breast reconstruction, but may not be suitable for all patients,

particularly those who need or have had radiation therapy. Autologous methods in contrast are more surgically demanding, but they consistently yield better esthetic results than implant reconstruction, particularly when combined with skin sparing mastectomy.

The goal of breast reconstruction is to restore the size, shape and appearance of the breast as closely as possible after mastectomy. This aids in the restoration of body image and makes it possible for patients to wear virtually all types of clothing with confidence. As we see further refinements in microsurgical techniques, it becomes possible to reconstruct a breast with a minimum morbidity and a lifetime benefit.

References

1. Chevray P. Breast reconstruction with superficial inferior epigastric artery flaps: a prospective comparison with TRAM and DIEP flaps. Plastic Reconstr Surg. 2004;114(5):1077–83
2. Tachi M, Atsushi Y. Choice of flaps for breast reconstruction. Int J Clin Oncol. 2005;(10):289–297
3. Granzow J, Levine J, Chiu E, LoTempio M, Allen R. Breast reconstruction with perforator flaps. Plastic Reconstr Surg. 2007;120(1):1–12
4. Ascherman J, Hanasono M, Hughes D. Implant reconstruction in breast cancer patients treated with radiation therapy. Plastic Reconstr Surg. 2006;117(2):358–65
5. Wang H, Olbrich K, Erdmann D, Georgiade G. Delay of TRAM flap reconstruction improves flap reliability in the obese patient. Plastic Reconstr Surg. 2005;116(2):613–8
6. Kronowitz S, Robb G. Breast reconstruction with postmastectomy radiation therapy: current issues. Plastic Reconstr Surg. 2004;114(4):950–60
7. Kronowitz S, Hunt K, Bucholz T, Robb G. Delayed-immediate breast reconstruction. Plastic Reconstr Surg. 2004;113(6):1617–28
8. Lipa J, Youssef A, Robb G, Chang D. Breast reconstruction in older women: advantages of autogenous tissue. Plastic Reconstr Surg. 2003;111(3):1110–22
9. Jabor M, Shayani P, Collins D, Karas T, Cohen B. Nipple-areola reconstruction: satisfaction and clinical determinants. Plastic Reconstr Surg. 2002;110(2):458–64
10. Alderman A, Wilkins E, Kim H, Lowery J. Complications in postmastectomy breast reconstruction: two-year results of the michigan breast reconstruction outcome study. Plastic Reconstr Surg. 2002;109(7):2266–75
11. Malata C, Mc Intosh A, Purushotham A. Immediate breast reconstruction after mastectomy for cancer. Br J Surg. 2000; 87:1455–1472
12. Shons A, Mosiello G. Postmastectomy breast reconstruction: current techniques. Cancer Control. 2001;8(5):419–4226
13. Agha-Mohammadi S, De La Cruz C, Hurwitz D. Breast reconstruction with alloplastic implants. J Surg Oncol. 2006; 94:471–478
14. Spear S, Spittlet C. Breast reconstruction with implants and expanders. Plastic Reconstr Surg. 2001;107(1): 177–87
15. Zenn MR, Millard JA. Free inferior gluteal harvest with sparing of the posterior femoral cutaneous nerve. J Reconstr Microsurg. 2006;22(7):509–12
16. Zenn MR. Insetting of the superficial inferior epigastric artery flap in breast reconstruction. Plastic Reconstr Surg. 2006;117(5):1407–11
17. Bostwick J. Breast reconstruction following mastectomy. CA Cancer J Clin. 1995;45:289–304
18. Spear S, Carter M, Schwarz K. Prophylactic mastectomy: indications, options, and reconstructive alternatives. Plastic Reconstr Surg. 2005;115(3):892–910
19. Kronowitz S, Kuerer H. Advances and surgical decision-making for breast reconstruction. Cancer. 2006;107(5):893–907
20. Ahmed S, Snelling A, Whitworth H. Breast reconstruction. BMJ 2005;330:943–948
21. Pomahac B, May J, Slavin S. New trends in breast cancer management: is the era of immediate breast reconstruction changing? Ann Surg. 2006;244(2):282–8
22. Hidalgo D, Borgen P, Petrek J, Cody H, Disa J. Immediate reconstruction after complete skin-sparing mastectomy with autologous tissue. J Am Coll Sur. 1998;187(1):17–21
23. Kenkel J, Hoover S. Breast cancer, cancer prevention and breast reconstruction. Selected Readings in Plastic Surg. 2002;30(9):1–41
24. Chiu E, Ahn C. Breast reconstruction. In: McCarthy J, editor. Current therapy in plastic surgery. Philadelphia: Saunders; 2006. p. 352–361
25. Elliot F. Breast reconstruction- free flap techniques. In: Thorne C, editor. Grabb & Smith Plastic Surgery. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 648–656
26. Zenn M, Garofalo J. Unilateral nipple reconstruction with nipple sharing: time for a second look. Plastic Reconstr Surg. 2009;123(6):1640–53

The Role of Radiotherapy in Breast Cancer Management

16

Ruth Heimann

16.1 Introduction to Radiation Oncology

At the end of nineteenth century (1895), Wilhelm Roentgen announced the discovery of "a new kind of ray" that allows the "photography of the invisible." The biological and therapeutic effects of the newly discovered X-rays were soon recognized, particularly because of the dermatitis and epilation they caused. In the early 1896, a few weeks after the public announcement of Roentgen's discovery, among the first therapeutic uses, Emil Grubbe in Chicago irradiated a patient with recurrent carcinoma of the breast and Herman Gocht in Hamburg Germany, irradiated a patient with locally advanced inoperable breast cancer and another patient with recurrent breast cancer in the axilla [1]. Despite the technical limitations of the early equipment, tumor shrinkage and at times complete elimination of the tumor were noticed. However, the full potential of radiation therapy could not be achieved in those early days because of the limited knowledge regarding fractionation, treatment techniques and uncertainties in how to calculate the tissue dose so as to deliver safe and effective doses of radiation.

16.1.1 Physics of Radiation Therapy

The X-rays and gamma rays are part of the spectrum of electromagnetic radiation that also includes radio waves, infrared, visible and ultra violet light. They are thought of as small packets of energy called photons. The X-rays reaching the tissue deposit their energy and because the energy is quite high, it causes ejection of orbital electrons from the atoms, resulting in ionization; hence the term ionizing radiation. Once the energy is deposited, many interactions occur, resulting in the generation of more free electrons and free radicals. Because the human body is made mostly of water, the energy absorption leads to a chain reaction, resulting in the formation of multiple, reactive free radical intermediates. Any of the cell constituents such as proteins, lipids, RNA, DNA can be damaged. Apoptosis, signal transduction, lipid peroxidation are all altered as a result of direct or indirect effects of radiation, however DNA double-strand breaks seem to be the most critical damage that if unrepaired or incorrectly repaired will result in cell death.

The radiation dose is measured in terms of the amount of energy absorbed per unit mass. Presently, the measurement unit is Gray (1 Gy is equal to 1 J/kg). The past measurement unit was the Rad, and 100 Rads > 1 Gy. The beam energy determines its medical usefulness. The clinically useful energy ranges of the electromagnetic radiation are: superficial radiation 10–125 keV, orthovoltage 125–400 keV, and supervoltage, over 1,000 keV (>1 MeV). As the beam energy increases, it can penetrate deeper and more uniformly into tissue, and the skin sparing increases. The reason for skin sparing is that the electrons that are created from the interaction between photons and the tissue travel some time before they interact with tissue molecule and deposit the maximum dose. In the superficial and orthovoltage ranges, because of the lower energies, most of the dose is deposited at or very close to the skin (i.e., with significant skin dose), a significant dose is absorbed in bones, and useful beam energy cannot reach tissues at more than a couple of centimeters deep,

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_16, © Springer-Verlag Berlin Heidelberg 2010

resulting in marked dose inhomogeneity in the tissue. The great advantage of the supervoltage/megavoltage photons is that as the energy increases, the penetration of the X-ray increases, absorption into bone is not higher than the surrounding tissue and skin sparing increases. Therefore, maximum dose does not occur on the skin but at depth in the tissue, and more homogeneity can be achieved in the targeted volume.

The era of modern radiation therapy started approximately 50–60 years ago when supervoltage machines became widely available because of advances in technology resulting from atomic energy research, the development of the radar, and advances in computing. The availability of high-energy beam revolutionized the field of radiation oncology. Initially, the Cobalt machine, a byproduct of atomic research and subsequently the linear accelerator (LINAC) generating beams with the energy ranging from 4 to 24 MeV became available; currently, LINACs are mostly in use. A photograph of a LINAC is shown in Fig. 16.1. In the LINAC, electrons are accelerated to very high speeds using electromagnetic waves in the frequency of the microwave range. The high-speed electrons are guided to strike a tungsten target to produce the X-rays.

For certain clinical circumstances, the electron beam is preferred. Electrons differ in the way they deposit energy in the tissue. With electrons, the maximum dose is reached close to the skin surface with minimum skin sparing; however, there is a marked fall in radiation dose at certain depth in the tissue. This depth can be carefully chosen depending on the energy of the electron beam. Electron beams are mostly used for therapy of superficial tumors or to supplement (boost) photon therapy.

Fig. 16.1 A linear accelerator (LINAC) used for radiation therapy treatments (photograph courtesy of Elekta)

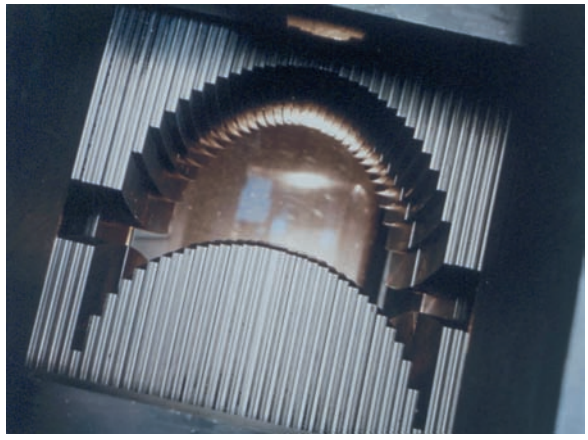

Fig. 16.2 The multileaf collimator (MLC) used to shape the treatment beam (photograph courtesy of Elekta)

To conform to the tumor shape and anatomy, the radiotherapy beam is tailored to each individual patient by using beam modifiers placed in the path of the beam. They may include such devices as collimator, tissue compensators, individually constructed blocks, or more recently, the multileaf collimator (MLC). An image of a MLC is shown in Fig. 16.2. From the early days of manual computing when dose was calculated in a single point in the treated volume, recent computing advances led us to calculate dose in 3D in the tumor and surrounding tissue and account for differences in tissue density (i.e., lung, bone) as well as modify the dose inside the target area by "dose painting" or intensity-modulated radiation therapy (IMRT). We are now able to deliver more accurate radiation treatments and tailor treatments to individual patient anatomy with increased efficacy and less morbidity. When dose can be delivered more accurately to the tumor and more normal surrounding tissue can be spared, dose intensification can be attempted to achieve higher cure rates without increased complications. Uniform dose distribution and reduced dose in the surrounding tissue result in decreased acute and long-term side effects. Exclusion of as much normal tissue as possible from the path of the radiation beam is always of great importance, since many patients are also receiving chemotherapy that may result in higher probability of late complications.

16.1.2 Radiation, Surgery and Chemotherapy

Radiation therapy is a local-regional curative modality that can be used either alone or in combination with surgery and chemotherapy. The rationale for combining surgery and radiation is because their patterns of failure are different. Radiation is less effective and failures occur more at the center of the tumor where there is the largest volume of tumor cells, some necrotic and in hypoxic conditions. Radiation is most effective at the margins where the tissue is well vascularized and the volume of tumor cells is the lowest. The extent of the surgery on the other hand is usually limited by the normal structures in the proximity of the tumor. The bulk of the tumor can be usually excised, but to remove all microscopic disease, at times, the surgery may need to be too extensive. Hence, the failures of surgery are usually at the margins of excision, and that is where radiation is the most effective. To increase its therapeutic effectiveness, the radiation can also be combined with chemotherapeutic agents. Because these two modalities have different mechanisms of cell kill and can interfere with different phases of the cell cycle, the combined effects may be additive, synergistic, or chemotherapy may act as sensitizer to the effects of radiation, however it also increases the probability of side effects.

16.1.3 Technical Aspects of Radiation Planning and Delivery

Radiation therapy is an integral part of the management of all stages of breast cancer. Prior to embarking on radiation treatments, careful treatment planning is necessary. This includes decisions regarding patient positioning and immobilization. Both are essential for accuracy of therapy to ensure day to day reproducibility, and patient comfort. The treatment planning is done with the aid of a simulator, which is a machine with identical geometrical characteristics as the treatment machine, however instead of high-energy treatment rays it generates diagnostic X-rays to image the target (i.e., the irradiated volume). More recently, computer tomography (CT), an ultrasound (US) have been incorporated into the simulator, allowing even more accurate target identification in the actual treatment position. In the future, other imaging modalities such as magnetic resonance imaging (MRI) and positron emission tomography (PET) may also be incorporated. After the target and normal structures have been delineated in 3D, alternative treatment plans are generated and optimized. The plan that gives the best coverage of the target with minimal dose to the surrounding tissue and minimal inhomogeneities is chosen. The dose and homogeneity in the target are of great importance. Cold and hot spots have to be minimized because cold spots in the target will leave cancer undertreated, thus a source of disease recurrence, while hot spots may increase the risk of complications. The treatment planning is a team effort between the physician, physicist, dosimetrist and technologist. It is an interactive process that usually goes through multiple iterations until the optimal plan is reached.

In the treatment of nonmetastatic breast cancer, the radiation is aimed at the breast/chest wall, and depending on the clinical situation, also at the regional lymphatics such as the supraclavicular, axillary, and internal mammary lymph nodes. The treatment goal is eradication of tumor with minimal side effects. The CT scanner can be used to delineate the targeted area and the critical structures to which dose should be limited. The beam arrangement that traverses the least amount of normal critical organs is chosen. In the treatment of the intact breast or chest wall, medial and lateral tangential beams are used (Fig. 16.3). Tangential beams allow the encompassing of the breast tissue while including limited amounts of lung or heart. Using 3D or IMRT treatment planning software, the dose distribution is calculated for the entire breast volume. Beam modifiers are incorporated to minimize the volume of tissue receiving higher or lower than the prescribed dose, and minimize the dose to the skin surface while ensuring that the glandular tissue several millimeters under the skin is not undertreated. IMRT allows the generation of a more homogenous plan, thus resulting in less acute side effects such as moist desquamation, pain, and breast lymphedema [2, 3]. Figure 16.4 demonstrates the more homogeneous dose achieved with IMRT, eliminating the "hot spots."

In many situations, IMRT also affords better conforming of the dose around the breast tissue, thus decreasing the dose to heart, lung, contralateral breast and axilla, as well as less scatter dose [4]. To treat the supraclavicular or axillary nodes and limit the dose to the spinal cord, a field shown in Fig. 16.5 is used. This field is usually an

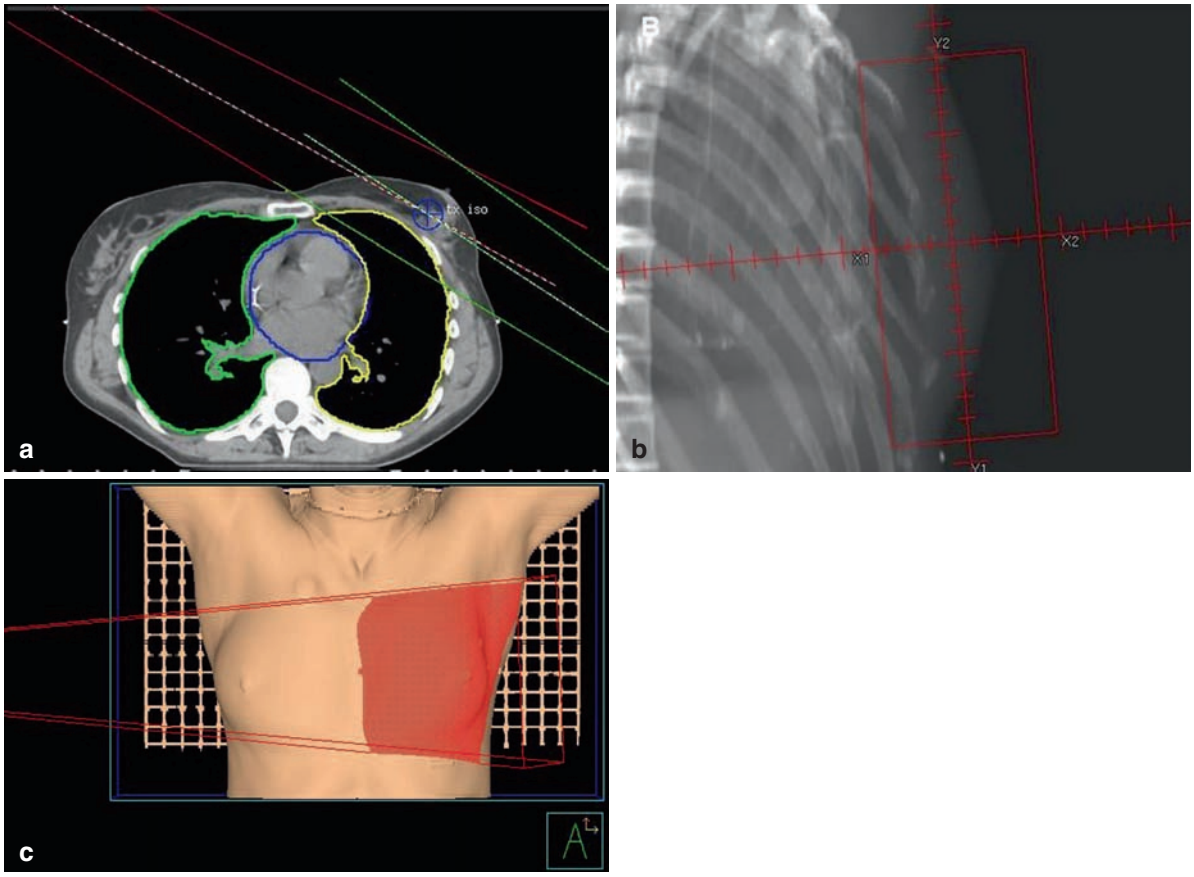

Fig. 16.3 Tangential beam arrangement for the treatment of the intact breast or chest wall. (**a**) An axial view showing the medial and lateral tangential beams covering the breast tissue. (**b**) The view from the beam direction, "beams eye view." Note the small amount of lung or heart in the treated volume. (**c**) The projection of the tangential beams on the patient's skin. These views were obtained from computer tomography (CT)-based simulation workstation

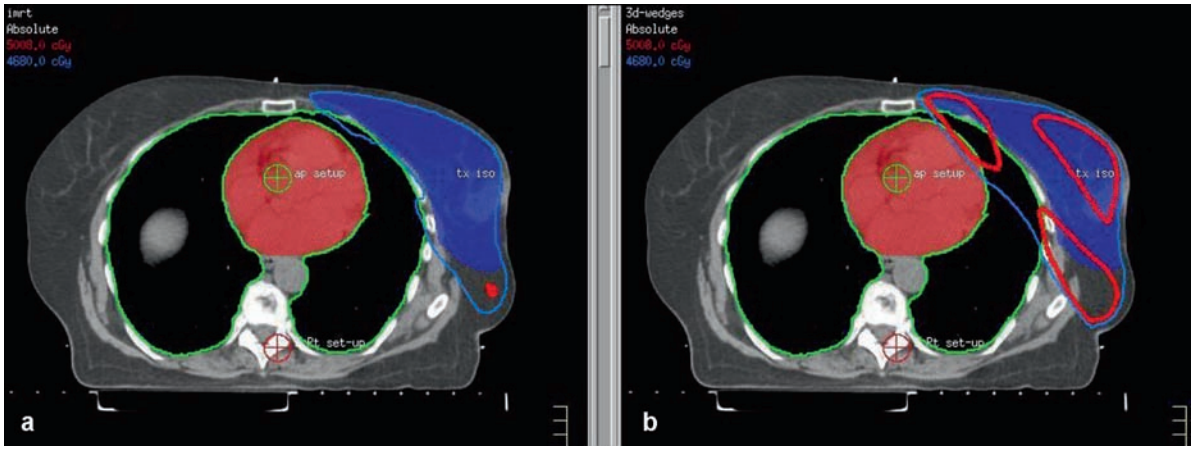

Fig. 16.4 Dose distribution in the breast using intensity-modulated radiation therapy planning-IMRT (**a**) and 3D treatment planning (**b**). Note the elimination of "hot spots" in the IMRT plan

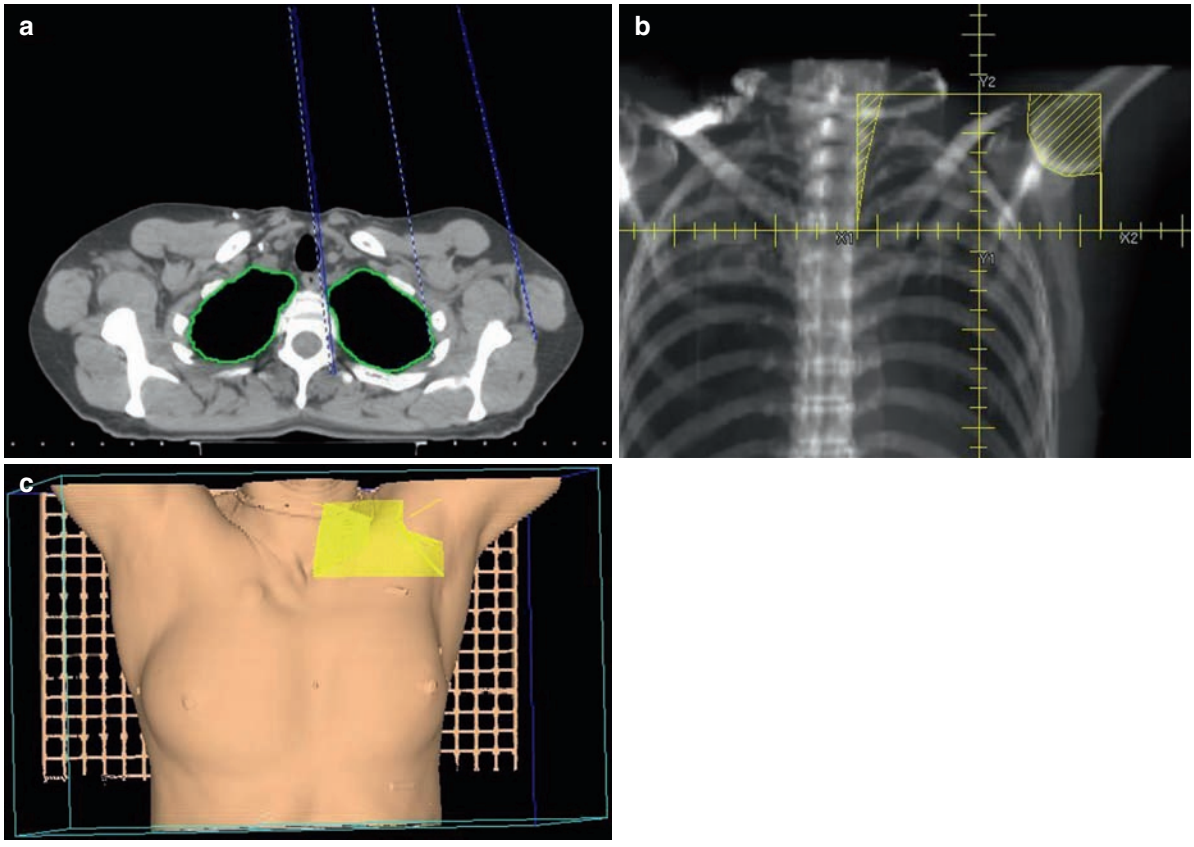

Fig. 16.5 The beam arrangement for the supraclavicular and axillary apex area. (**a**) An axial view. Note how the beam is directed to avoid the spinal cord. (**b**) The view from the beam angle also showing the blocking of the spinal cord and humeral head. (**c**) The beam as it projects on the patient skin

anterior/posterior field slightly angled to exclude the upper thoracic and lower cervical spinal cord. Various techniques are used to perfectly match all the fields so as to prevent an overlap or a gap between them. Depending on the clinical situation, radiation treatments are given daily for 5 1/2–6 1/2 weeks. Most commonly in the United States, 1.8 or 2.0 Gy fractions are being used. Fractionation is necessary to keep the normal tissue complications to a minimum while still achieving maximum tumor control. Several hypofractionated schedules using 15 fractions of 2.66–3.20 Gy in 3–5 weeks have been tested in randomized trial [5, 6]. The early results show equivalence for local control and cosmesis to the schedule of 2.0 Gy in 5 weeks. It is not clear how the local control with shorter schedules compares with the schedules that use 1.8 and 2.0 Gy and boost. Sufficient long-term follow-up is not yet available for the hypofractionated schedules, thus the effects of the larger fraction sizes on lung and heart are yet unknown.

16.1.4 Adverse Effects of Radiation to the Breast

Treatments are usually well tolerated. Acute side effects may include fatigue, breast edema, skin erythema, hyperpigmentation, and at times desquamation mostly limited to the inframammary fold and axilla. Acute skin changes usually should resolve 1–2 weeks post-treatment. Higher treatment fraction sizes may result in more moist desquamation during therapy, more breast edema and fibrosis, thus jeopardizing the cosmetic outcome. The cosmesis post treatment is usually good to excellent in a large majority of patients. However, there are no good objective quantitative criteria to evaluate the cosmetic outcome. Posttherapy, there is a gradual improvement in the appearance of the breast, hyperpigmentation resolves, skin color returns to normal, and breast edema resolves. The return to normal color and

texture happens in a large majority of patients [7] but in some, it may take 2 or even up to 3 years.

With modern megavoltage therapy and treatment planning, the long-term side effects are limited. They depend on the radiation dose, fraction size, the energy of the beam and the volume of radiated tissue. Most of the side effects can be limited with appropriate treatment planning.

Symptomatic pneumonitis is exceedingly rare, occurring in less than 1% of patients, particularly in those treated only with tangential fields and not receiving chemotherapy. The risk is 3–5% if chemotherapy is given and if the supraclavicular nodes need to be treated. It has been noted that if chemotherapy and radiation are given sequentially instead of concomitantly, the risk is lower. A study by Lingos et al showed that the risk of radiation pneumonitis was 1% if chemotherapy and radiation were given sequentially and could be as high as 9% if the treatments were concurrent. [8]. The risk also depends on the type, dose and scheduling of the chemotherapeutic agents. The risk is further reduced by using 3D or IMRT treatment planning techniques. Those patients in whom symptomatic pneumonitis develops, it is usually mild, and reversible either spontaneously or after a short course of steroids. Damage to the brachial plexus may develop in less than 1% of the women treated with the currently used doses and fraction sizes. Larger fraction size may result in an increased risk of brachial plexopathy. There is a small risk of rib fractures, and soft tissue necrosis is exceedingly rare. In more than 2,000 patients treated at the University of Chicago Center [7], no rib fractures or soft tissue necrosis were noted. Radiation may cause damage to the heart. The effects are dependent on the radiation technique used. The early trials of postmastectomy radiation have shown an increase in cardiac deaths in the long-term survivors [9]. However, in those days, an anteroposterior photon beam was used to treat the internal mammary nodes (IMN), resulting in full-dose radiation to a large segment of the heart [10]. More recent reports show less effect on cardiac disease [11, 12]. With the currently used 3D and IMRT treatment planning techniques, excessive doses to large part of the heart can be avoided. The effects on the heart may include pericarditis [13] and acceleration of coronary artery disease. Many of the active and currently used chemotherapeutic agents (Adriamycin, Taxol) may also have deleterious effects on the heart. Except in rare occasions, the radiation and these chemotherapeutic agents are not given concurrently. No significantly increased risk of heart-related complication has been noted using sequential chemotherapy and radiation treatments. However, the long-term combined effects of cardiotoxic chemotherapeutic agents and radiation are not yet completely known because the newer drugs have not been used that long. Cardiac disease may become evident 10 to even 20 years post therapy. Thus, longer follow-up will be needed before firm conclusions are reached. There has been substantial increase in the use of Trastuzumab in the treatment of breast cancer. There are no data showing increased cardiac toxicity when combining radiation and Trastuzumab, but longer follow-up will be necessary for more definitive data. In the interim, particular attention should be given to the treatment planning of left sided breast cancer after cardiotoxic chemotherapy, even more so if IMN need to be treated. New treatment planning techniques using IMRT are being studied to decrease the volume of heart and lung treated.

Lymphedema may develop following axillary dissection and can be exacerbated with radiation. Although not life-threatening, it can significantly impact on quality of life. The risk of lymphedema depends on the extent of axillary node dissection and the extent of the radiation to the axilla. With a complete axillary dissection, including all three levels of axillary nodes and radiation therapy, the risk of lymphedema may be more than 40%. However, if the surgery is only limited to level I and II dissection and the axilla is not radiated, some lymphedema may develop in up to 30% of women but the risk of significant lymphedema is only 3–5%. The risk can be reduced by preventing trauma or infections to the arm on the dissected side. The condition can be chronic. It can be stabilized with physical therapy and manual lymphatic decompression but at times is difficult to eliminate. Early physical therapy and manual lymphatic decompression are very important and may reverse early stages of lymphedema.

There is a small risk of second malignancies in long-term breast cancer survivors treated with radiation [14]. In general, for a woman with breast cancer, the risk of contralateral breast cancer is approximately 0.5–1% per year, of which 3% or less could be attributed to previous radiation [15, 16]. In the study by Boice et al., most of the risk was seen among women radiated before age 45. After age 45, there was little, if any, risk of radiation-induced secondary breast cancers. This has been further confirmed in a case control study in a cohort of more than 56,000 mostly perimenopausal and postmenopausal

women. The dose to the contralateral breast was calculated to be 2.51 Gy, and the overall risk of contralateral breast cancer was not increased in patients receiving radiation therapy. The secondary tumors were evenly distributed in various quadrants of the breast, also arguing against radiation-related contralateral breast cancer [17]. In patients, treated at the University of Chicago, with mastectomy between 1927 and 1987, there was no increase in contralateral breast cancer in women who also received chest wall radiation [18].

Other treatment-related malignancies include lung cancer, sarcoma, and leukemia. The risk of treatment-related lung cancer is small. Studies from the Connecticut Tumor registry of patients treated between 1945 and 1981 show that in 10-year survivors, approximately nine cases of radiotherapy induced lung cancer per year would be expected to occur among 10,000 treated women [19]. The risk is significantly increased with smoking [20]. The reported cumulative risk of sarcoma in the radiation field is 0.2% at 10 years [21]. The risk of leukemia is minimal with radiation only, however in combination with alkylating agents, the risk may be higher [22]. There are conflicting reports regarding the risk of esophageal cancer [23, 24]. Possibly, the increased risk in some studies is related to radiation techniques that used an anterior-posterior field to treat the IMN. In general, in most contemporary plans, the esophagus is excluded from the path of the beam. Many published studies tend to report the risk of second malignancies as the relative risks. It is important to realize when reading and evaluating the clinical literature that from the patients' and physicians' perspective, the concept of relative risk is not very informative because the relative risk of an event with radiation may be very high compared to no radiation, but if the absolute risk is very low, it has no management or practical clinical value. Thus, absolute numbers or percentages of the risk are much more relevant and informative.

16.2 Radiation Therapy in the Early Stage Breast Cancer

16.2.1 Ductal Carcinoma in Situ

Ductal carcinoma in situ (DCIS), noninvasive ductal carcinoma, or intraductal carcinoma refers to proliferation of malignant cells confined within the basement membrane. DCIS, a premalignant condition, if untreated, is likely to progress to invasive breast cancer [25, 26]. Management of DCIS remains one the most controversial aspects of breast cancer treatment. It is a disease of the mammographic era with a significant increase in the incidence rate in the last decade. The nonpalpable DCIS, which comprises the majority of currently diagnosed disease, was almost unknown 25–30 years ago. In 2006, more than 61,000 women were diagnosed with DCIS [27]. The natural history is long, and although the incidence has been increasing in recent years, there are few studies of the alternative treatment options that have sufficient power and length of follow-up to have definite answers. The treatment options include simple mastectomy, or local excision, with or without radiation. Several factors are important in the management decision of a patient with DCIS. Any evidence that the disease is or could be extensive such as diffuse, suspicious, or indeterminate micro calcifications or multicentricity, as well as a mammogram, which is difficult to follow, or if there is uncertainty that the patient can comply with a program of routine mammograms for follow-up are contraindications for breast conserving surgery. Status of the margin following local excision and the histologic subtype are important when making treatment decisions, and as always, patient wishes and comorbidities need be considered. If negative margins of excision cannot be obtained, breast conservation attempts have to be abandoned. Among histologic subtypes, high-grade nuclei and comedo necrosis appear to be more aggressive variants and seem to have a higher risk of recurrence or progression to invasive breast cancer. However, it is not clear if the risk of recurrence is higher with comedo DCIS, or just that the recurrences appear sooner and if the follow-up were long enough, the recurrence rate would be the same in patients with comedo or non-comedo histology.

Mastectomy was traditionally the standard of therapy for DCIS. The recurrence rates following mastectomy were 1% or less and the cancer related mortality 2% [28]. However, after the documented success with breast-conserving therapy in infiltrating ductal carcinoma, it became increasingly difficult in the daily practice to recommend mastectomy to women with DCIS. Paradoxically, women who were adhering to a strict regimen of screening and were detected as having DCIS could be "rewarded" with mastectomy, while if they just would have waited a few years for the disease to

progress to invasion, they could have breast-sparing surgery. There are no randomized trials that compare mastectomy to breast-conserving therapy, however a decision analysis of trade-offs shows that there may only be a 1–2% difference in the actuarial survival rates at 10 and 20 years if the initial therapy is breast-conserving surgery and radiation compared to mastectomy [29]. The small difference is most likely because at least half of recurrences after breast conservation are DCIS and among the other half that are invasive, most are detected at an early stage. As in many other clinical dilemmas in breast cancer management, the National Surgical Adjuvant Breast and Bowel Project (NSABP) investigators significantly contributed to the changes in practice and redefined the standard of care in DCIS. NSABP-17 is a large, prospective randomized trial of 818 women that shows, with a median follow-up of 8 years, that radiation therapy following breast-conserving surgery reduces both the invasive and non invasive ipsilateral breast cancer recurrences and the particular impact was on the reduction of invasive breast cancer recurrences. The incidence of noninvasive cancer was reduced from 13 to 9%, and invasive breast cancer from 13 to 4% [30]. Mortality due to breast cancer after 8 years was 1.6%. All patients benefited from radiation irrespective of tumor size or pathologic characteristics. No features could be identified that would allow selection of patients in whom radiation could be eliminated [31, 32]. A separate analysis of the effects of radiation on DCIS in the earlier NSABP-06 trial also showed a reduction in local failure with radiation [33]. A randomized trial performed by the European Organization for Research and Treatment of Cancer (EORTC) breast cancer cooperative group confirmed the NSABP-17 finding [34]. With radiation, the local recurrences at 10 years decreased from 26 to 15%. In multivariate analysis, the addition of radiation, the architecture, grade of DCIS and margins status were independent predictors of recurrence. It is clear that negative margins are important for local control; however controversy exists regarding the definition of adequate negative margins. Both the width of margins and the radiation dose influence local control. Boost radiotherapy has been shown to significantly decrease the risk of relapse in young women [35]. Excellent local control was also achieved when boost was given even when margins were defined as DCIS not touching the ink [36]. Although with longer follow-up and more information from the combined prospective and retrospective studies, the data may change, with the current information available in patients who are candidates for breast conservation, the local recurrence after excision alone is 20–30% and this can be reduced with radiation to approximately 10–15%. To further improve the outcome, NSABP performed a study in which all patients who were candidates for breast conservation were treated with local excision followed by radiation and randomized to Tamoxifen or placebo. This study, NSABP-24, enrolled more than 1,800 women [37]. Tamoxifen therapy resulted in 50% decrease in recurrences compared to radiation only without Tamoxifen.

In several retrospective studies, attempts were also made to determine the patients in whom radiation can be eliminated. Silverstein et al. devised a scoring system combining the size of the DCIS, margins, grade, and necrosis [38]. This scoring was subsequently modified showing that margins alone are predictive of local recurrence [39]. Using the information regarding pathologic margins, the authors attempted to develop criteria when DCIS can be satisfactorily treated by local excision, when radiation therapy should be added, and when mastectomy is required. However, because the number of events in relation to the number of patients was low, the differences were not statistically significant and firm conclusions could not be reached [40]. In a recent update, they showed that in the low-risk patients when margins of excision are more than 1 cm, the 12-year local recurrence rate is 13.9% compared to 2.5% if postexcision radiation is given [41]. The widths of the margins can significantly compromise cosmesis. In breast-conservation surgery, the surgical margins' width is in close inverse correlation with cosmesis. When performing the surgical excision, the surgeon is carefully balancing an oncologic surgery to achieve adequate margins and cosmesis because wide margins and removal of large amount of tissue may significantly impact on cosmesis. It is also important to recognize that because of the pathologic characteristics of DCIS, it is frequently difficult to determine the exact size of the DCIS and many pathologists are reluctant to do so. Thus, since many times the pathologic size is unavailable or cannot be accurately ascertained, some studies report DCIS size in millimeters, others in number of slides with DCIS, while others by using its mammographic size. This heterogeneity makes the comparison of local recurrence rates between studies difficult. A prospective study reported by Wong et al. attempted to select patients with DCIS in whom radiation following conservative surgery can be eliminated [42]. They

included grade 1 and 2 DCIS, ≤2.5 cm, excised with more than 1 cm margins. The rate of local recurrence was 2.4% per year, corresponding to a 5-year recurrence rate of 12%. The study closed early because the number of recurrences met the predetermined stopping rules. This study demonstrated that it is very difficult to select patients in whom radiation can be omitted. Some small, incidental DCIS and small, low-grade DCIS excised with wide margins (>1 cm) can be followed after the local excision without radiation. DCIS size, margins, histology, mammographic presentation, age, comorbidities, life expectancy and patient preference are all factors in decision making regarding the optimal management of each individual patient.

Table 16.1 Overall survival (%) in six randomized trials of breast-conserving treatment compared to mastectomy

Stage I and II breast cancer		
Treatment (references)	Mastectomy (%)	BCT(%)
NSABP B-06[47]	47	46
NCI[48]	58	54
Milan[44]	59	58
IGR(Paris)[49]	65	73
EORTC[45]	73	71
DBCCG[46]	82	79

Follow- up of 6 to 20 years

BCT breast conservation therapy; *DBCCG* Danish breast cancer cooperative group; *EORTC* European Organization for Research and Treatment of Cancer; *IGR* Institute Goustave Roussy; *NCI* National Cancer Institute; *NSABP* National Surgical Adjuvant Breast and Bowel Project

16.2.2 Invasive Breast Cancer

16.2.2.1 Breast Conservation

In 1990, the National Institutes of Health (NIH) convened a Consensus Conference to address the issue of breast-conserving therapy in stage I and II breast cancer [43]. The participants concluded that breast-conserving therapy is equivalent and possibly better than mastectomy. The summary statement is presented in Fig. 16.6. The conclusions were based on six randomized trials that all showed equal survival in patients treated with breast-conserving therapy compared to those undergoing mastectomies. With additional follow-up and update, the results have been further confirmed and they are holding [44–49] (Table 16.1). Breast-conserving therapy means local excision of the bulk of the tumor followed by moderate doses of radiation to eradicate residual foci of tumor cells in the remaining breast. Despite the NIH Consensus Conference conclusions, it seems that the acceptance of breast-conserving therapy is far from uniform and greatly varies by geographical areas [50–52]. Overall, breast conservation rates vary from 60 to 70 %. There are significant barriers for utilization of breast-conserving therapy [53–56]. Medical contraindications and patient choice do not seem to be the major factors in the under utilization of breast-conserving surgery [57]. More than 80% of the women, independent of age or race, if given the option, will opt for breast conservation.

NIH Consensus Conference (1990)
Early-Stage Breast Cancer (38)

Breast conservation therapy is an appropriate method of primary therapy for the majority of women with stage I and II breast cancer and is *preferable* because it provides *survival equivalent* to the total mastectomy and axillary dissection while preserving the breast.

Fig. 16.6 The National Institutes of Health (NIH) consensus conference statement

The role of the radiation is to decrease the risk of local failure in the breast but it also contributes to survival [23, 58–60]. It accomplishes what mastectomy would have done i.e., treatment to the entire breast. Treatments are usually delivered to the whole breast and are followed with an additional radiation, "boost" to the lumpectomy site. Careful pathologic studies of mastectomy specimens have shown that microscopic residual disease is present away from the primary (index) tumor, however the highest burden is in the same quadrant less than 4 cm from the primary tumor [61]. Extrapolation from early radiation therapy studies established the appropriate dose to eradicate microscopic foci of disease in the range of 45–50 Gy. This is the dose usually given to the entire breast. The higher burden of microscopic disease around the primary site is encompassed in the "boost" volume. Reported local control rates in the randomized trials and retrospective studies vary from 70 to 97% [7, 47, 62]. Many factors

have been suggested as having an impact on local control rates. Some have been confirmed in multiple studies while some were shown not to be of importance when longer follow-up and more data became available. Higher radiation doses to the lumpectomy site that are achieved by using a "boost" have been shown to improve the local control rates [63]. Most local recurrences following mastectomy occur in the first 3–5 years postsurgery, however post breast conserving therapy recurrences have been documented to occur up to 20 years. Up to 5–8 years from diagnosis, most of the recurrences are in the same quadrant as the primary. Subsequently, the proportion changes in favor of tumor "elsewhere" in the breast [64]. These are most likely second primaries.

The determination whether a patient is candidate for breast-conserving surgery and radiation is a multidisciplinary effort in which close communication between the surgeon, the mammographer, the pathologist, the medical oncologist, and the radiation oncologist is necessary. Contraindications for breast-conserving surgery [65, 66] include:

1. Multicentric disease, i.e., disease in separate quadrants of the breast.
2. Diffuse malignant appearing, or indeterminate microcalcifications.
3. Prior radiation treatments to doses that combined with the planned dose will exceed tissue tolerance. This may happen in women who have received radiation at younger age for lymphoma, particularly Hodgkin's disease.
4. Inability to obtain negative surgical margins following attempts for breast-conserving surgery. Negative excision margins appear to be the most important factor impacting on local control. If the margins are positive, the risk of local recurrence is increased [7, 67]. Focally positive margins can be controlled with radiation but more extensively involved margins are usually an indication for reexcision. However, data are also emerging, demonstrating that by increasing the boost dose, the local recurrences are similar to the local recurrences in women with negative margins of excision [7, 68].
5. Pregnancy is a contraindication for breast-conserving therapy because of the concerns on the effects of radiation on the fetus. Sometimes, surgery can be done during the third trimester and followed with radiation after delivery. This latter is to be done only after careful consideration because chances for cure ought not to be compromised for cosmetic reasons.

Relative contraindications for breast conservation include:

1. Tumor size: size of the tumor as compared to the breast size may pose some challenge from the cosmetic outcome perspective. Majority of the randomized trials of breast-conserving therapy included women whose tumors were ≤4 cm. But, the tumor size is mainly a consideration as it relates to the cosmetic outcome. Breast conservation should only be attempted if an acceptable cosmetic outcome can be achieved. If the tissue deficit because of the size of the tumor is large in relation to the breast size, than it is preferable to perform a mastectomy followed by breast reconstruction. The ratio between tumor size and patient's breast size determines the advisability of breast-conserving therapy.
2. Tumor location: tumor location in the vicinity of the nipple may require excision of the nipple-areola complex. This may result in less than optimal cosmesis but does not impact on outcome. Many women will opt for breast preservation even if the nipple is removed because it still leaves behind most of the breast tissue and native skin.
3. Breast size: there are some technical difficulties in the radiation treatment of women with large breasts, but if adequate immobilization can be devised and adequate dose homogeneity can be achieved, breast conservation is preferable to a mastectomy that would result in major asymmetry.
4. History of collagen vascular disease: individuals with history of collagen vascular disease, particularly lupus or scleroderma are reported to be at significantly increased risk of complications, particularly soft tissue and bone necrosis, most likely because of compromised microvasculature. Other criteria like patient age, family history, positive axillary lymph nodes are not contraindications for breast-conserving therapy.

Although breast cancer appears to be more aggressive in very young women, there is no clear evidence that if the currently used criteria for breast-conserving therapy are followed, breast conservation should be denied to young women. Very young women aged 35 or less may have more aggressive disease and they are at higher risk of both distant and local recurrences. Some have been

advocating mastectomy for these women, however to date, there has been no documented benefit in survival to mastectomy. At the other end of the age spectrum, although the perception may be that cancer is less aggressive and that older women are not as interested in breast preservation, the studies do not support this contention. Several reports have in fact shown that survival and disease-free survival from breast cancer are lower in older women [69–71]. There are also no indications that elderly women have significantly more problems tolerating radiation compared to younger women.

A challenging question is whether mutations in the two genes that predispose to breast cancer, BRCA-1 and BRCA-2, are a contraindication for radiation and thus breast-conserving treatment. Hypothesis yet to be proven is whether radiation to the remaining breast tissue, or scatter radiation to the contralateral breast increase the risk of a second breast cancer, or conversely, radiation is more effective in patients with known mutations because the normal function of the genes is DNA repair and the mutations could prevent the tumor cells escape from the effects of radiation. If unable to repair the damaged DNA, the effects of controlling the tumor with radiation may be enhanced. In a case control study of women treated with breast-conserving surgery and radiation, early results showed that following radiation, there is no increased risk of events in the ipsilateral breast in patients with known BRCA mutations compared to those with no mutations [72]. A subsequent update with additional follow-up shows that BRCA1/2 mutations are independent predictors of local recurrence. However, in women with BRCA1/2 mutations who also underwent oophorectomy, the local recurrence rate following breast-conserving surgery and radiation was 8% compared to 10% in women with sporadic breast cancer [73]. Interestingly, the 10-year risk of contralateral breast cancer in the BRCA1/2 carriers was 16% despite the oophorectomy. In a different study, when patients with local recurrence following radiation were matched with a group without local recurrence, mutations were found to be more common in patients with recurrences and they occurred primarily in younger women, in different quadrants than the index tumor, and occurred late, most likely representing new primaries [74]. There is currently no evidence that women with mutations in BRCA-1 or BRCA-2 or with a family history of breast cancer have worst survival rates if offered breast-conserving therapy, including radiation [75], particularly if they also undergo oophorectomy and receive adjuvant systemic therapy [73].

Table 16.2 Local recurrence (%) following local excision compared with local excision and radiation in stage I breast cancer

	Excision	Excision andradiation	Follow-up (years)
Liljergen et al.[77]	24	8	10
Clark et al.[76]	35	11	8
Lim et al[79]	23	N/A	7

N/A not applicable

Several studies have attempted to define a subpopulation of patients who may not need radiation (Table 16.2). They vary in length of follow-up, inclusion criteria and details of therapy. In studies from Sweden and from Canada, the investigators tried to determine if in patients with small tumors, radiation could be omitted. Thus, they limited their studies to patients with ≤2 cm node-negative tumors [76, 77]. These trials showed a significant decrease in local failures when radiation was given but no significant difference in survival. Nevertheless, there was a trend toward overall survival benefit in the group receiving radiation [76, 78]. None of the trials were powered with sufficient number of patients to detect <10% benefits in survival. In a prospective single institution study, attempts were made to select the most favorable patients with lowest risk of recurrence and enroll them in a study of only breast-conserving surgery without radiation [79]. The criteria for inclusion were tumor size ≤2 cm, negative axillary nodes, absence of lymphatic invasion, absence of extensive intraductal component, at least 1 cm margin of normal breast tissue around the tumor, and the breast easy to follow mammographically. The median tumor size was 6 mm. Even in this very favorable group, the failure rate was 24% at 7 years. The trial was closed prematurely because the observed failure rate exceeded the expected rate predetermined by the trial stopping rules. This study highlights the difficulty in selecting the patients in whom radiation treatments can be eliminated.

Chemotherapy or Tamoxifen may contribute to local control but by themselves are not sufficient. For example, in the NSABP-06 trial, the local failure in patients undergoing only local excision without radiation was approximately 32%. In those who underwent local excision and also received chemotherapy, it was close to 40%, demonstrating that chemotherapy did not decrease the local failure rates. However, in the comparable group who after local excision were receiving

both chemotherapy and radiation, the cumulative risk at 12 years was only 5% [78], while in those receiving radiation only, the local failure rates were 12%. This demonstrates that radiation decreases the local recurrence rates and is further decreased when also combined with chemotherapy. Other studies have also confirmed better local control rates with the addition of chemotherapy to radiation [80, 81]. Even the very high doses of chemotherapy alone that were given as part of bone marrow transplant programs were not sufficient for local control [82].

To increase the feasibility of breast-conserving therapy, neoadjuvant chemotherapy has been attempted with satisfactory results. Some women who would not be candidates for breast conservation because of tumor size may become candidates for breast conservation if they first receive chemotherapy and the tumor shrinks, without impacting on their survival [83].

Many women who undergo breast-conserving therapy are also receiving adjuvant chemotherapy, and in these women, the sequencing of chemotherapy and radiation need to be decided. One prospective randomized trial and several retrospective studies had somewhat conflicting results. Some studies show that giving chemotherapy first before radiation increases the risk of local failure, while others show that giving chemotherapy first does not significantly increase local failure rates and it may result in better distant disease-free survival and overall survival [84–86]. If local excision with negative margins is achieved and the patient is a candidate for breast conservation, it is unlikely that her survival will be impacted by delay in radiation because of initial chemotherapy, particularly with the shorter dose dense chemotherapy regimens. Thus, in general, women complete their chemotherapy before proceeding with the radiation treatments. In some instances, concomitant chemotherapy and radiation therapy have been given. However, this may increase the risk of side effects and jeopardize the cosmetic outcome without demonstrated benefit in outcome.

Depending on the clinical situation, radiation is delivered to the draining lymphatics that include axilla, supraclavicular nodes and IMN. Axillary radiation is indicated if the axilla has not been dissected, if a limited dissection was done and it includes positive nodes, or if gross disease was found, particularly in the apex of the axilla close to the axillary vein. Communication between the surgeon and the radiation oncologist regarding the findings at surgery is of great importance. The undissected axillary apex nodes and supraclavicular nodal areas are treated if the axilla has been dissected and positive nodes were found. Attempts should be made in this situation to eliminate the dissected portion of the axilla from the path of the beam. With the advent of CT-based 3D treatment planning and IMRT, the treatment to the draining lymphatics can be individually tailored to the anatomy and the extent of the disease. Treatment to the IMN is given at times if the primary lesion is medially or centrally located and the axillary lymph nodes are positive with metastatic breast cancer. CT-based 3D treatment planning and in selected patients, IMRT planning are of advantage, particularly for left-sided lesions where further care needs to be undertaken to minimize the amount of treated heart. Treatment of the regional lymphatics in addition to the tangential fields adds technical complexity to the treatments and particular attention is paid in matching the fields so as not to under- or overtreat. Use of IMRT in these situations may eliminate the need to match fields.

Good disease control in the axilla with minimum morbidity can be obtained from radiation to axilla without dissection [87] when the axilla is clinically negative. Thus, axillary dissection is indicated if the results would change the planned therapy. In patients who undergo sentinel node biopsy if the sentinel node has no disease, radiation to the axilla is omitted. If the node is positive, complete dissection or radiation to the axilla are likely to be of equivalent efficacy [87].

Close follow-up after breast conservation is essential to detect local recurrences, new primaries and contralateral disease. In general, true local recurrences occur earlier while disease in other quadrants develops later, i.e., 5 years or longer after therapy. Although institutional policies for mammographic follow-up vary, a reasonable policy would be mammograms of the index breast at 6 months after completion of therapy, followed by yearly bilateral mammograms.

Postmastectomy Radiation

Postmastectomy, the risk of local recurrence varies depending on the number of positive nodes in the axilla, size of the tumor, length of follow-up, and how the local recurrences are being scored. As number of nodes with metastatic disease in the axilla increases, the risk of chest wall recurrences increases. In fact, the number of positive axillary lymph nodes has more impact on the rate of chest wall recurrence than the size of the tumor. The length of follow-up and how the

recurrences are being scored are also important. Frequently, if a patient develops metastatic disease, there is a tendency to overlook a local recurrence. Most local-regional recurrences occur in the first 3–5 years following mastectomy, but disease may recur even 10–15 years postmastectomy [88, 89]. Thus long-term follow-up is important in evaluating the risk of recurrences [90]. Local recurrences impact on survival and also have a significant impact on the quality of life. Chest wall recurrences may ulcerate, and become malodorous and painful. Radiation can significantly decrease the risk of local recurrences postmastectomy. The benefit is proportional to the risk. Once clinically manifested, the likelihood of controlling a recurrence is only 50–60%. There is some disagreement regarding who should be receiving postmastectomy irradiation. Most are in agreement when it comes to patients with four or more positive nodes in the axilla or a tumor more than 5 cm in size. But, the dilemma starts with a woman for example with 3.5–4 cm tumor and three positive nodes, particularly if she is young? Do we have sufficient information to counsel these younger women when the potential life expectancy is 20–30 years? Data on sufficient cohorts of women with the various combinations of tumor size, number of positive axillary lymph nodes, and long enough follow-up are difficult to come by, particularly for those who also receive chemotherapy. Recht et al. reviewed the local failure rates in patients treated with mastectomy and chemotherapy without radiation in the various Eastern Cooperative Group trials [91]. Their results are shown in Table 16.3. Arriagada et al. reported the cumulative rates of chest wall failure in patients not receiving chemotherapy to be up to 30–35% in women with four or more positive nodes, and 25–30% if one to three nodes are positive [92].

Table 16.3 Percent cumulative incidence of LRF (10 years) following mastectomy and chemotherapy

Size						
Node Positive	≤1	1–2	1–3	1–4	1–5	≥5
1	3	11	12	10	6	27
2	8	14	12	20	14	31
3	20	18	11	8	14	36
4	19	17	22	26	37	33
5–6	22	23	27	25	22	47
7–9	12	33	30	32	32	41
≥10	39	30	31	36	35	31

LRF local regional failure. Data from Recht et al. [91], with permission

The impact of chest wall radiation on survival had been controversial because the natural history of breast cancer is long, the techniques of radiation are continuously improving, allowing better coverage of the target with less morbidity, and because currently in majority of the women, chemotherapy is also given. Older meta-analyses and reports from pre 3D treatment era showed that radiation decreases breast cancer deaths, but in some studies, an increase in the risk of cardiovascular disease was noted [9, 93, 94]. Very few of the studies included in these meta-analyses used 3D radiation therapy planning or gave chemotherapy. The capability currently exists to design CT-guided plans tailored to individual's anatomy. When treatments are designed with CT-guided planning, the exact target location can be determined and the volume of lung and heart in the treatment field minimized, thus decreasing the risk of long-term side effects. Image-guided radiation techniques and respiratory gating have the potential to further decrease the long-term sequelae or radiation.

Two contemporary randomized studies from Denmark and Canada in which women were treated with chemotherapy show better disease-free and overall survival in patients who also received radiation therapy to the chest wall and draining nodes in addition to systemic therapy (Table 16.4) [90, 95–97]. The benefit from radiation therapy on survival was in fact equivalent to the known benefit women achieve from chemotherapy [98]. To date, these are the most relevant trials to our current clinical practice. These studies reignited the discussions regarding the benefits of postmastectomy radiation. Particularly, some questioned the benefits in women with one to three positive nodes. The question posed was could the finding be extrapolated to the practice in the United States, since in some women in the Danish Breast Cancer Cooperative Group trial, the median number of lymph nodes dissected

Table 16.4 Impact of postmastectomy radiation therapy on overall survival in patients also receiving systemic therapy

Overall survival (%)				
	Follow-up (year)	CMF and radiation	CMF	*p*value
Overgaard et al.[95]	18	39	29	0.015
Ragaz et al. [90)]	20	52 TAM and radiation	43 TAM	0.02
Overgaard et al. [96)]	10	45	36	0.03

CMF cytoxan, methotrexate, 5 fluorouracil; *TAM* tamoxifen

was only seven. Some argued that usually in the United States, the axillary node dissections are more extensive. The investigators reanalyzed their data separately for women with one to three positive nodes and also in those with ten or more nodes dissected. They confirmed the significant benefit in survival in women with one to three positive nodes and also in those who had the more extensive axillary dissection [97]. A second criticism of the Danish and Canadian trials was that the chemotherapy used was cyclophosphamide, methotrexate and 5-fluorouracil (CMF). This regimen is less frequently used. Contemporary regimens are more dose intense and the question has been raised whether the benefits of radiation therapy are maintained with more intense regimens. There are no randomized trials to answer this question. However, an elegant analysis done by Ragaz et al. shows that at all chemotherapy dose intensity level, radiation therapy significantly decreases the risk of recurrence [90]. Radiation therapy to decrease the local recurrences was needed even following the very high doses of chemotherapy used in bone marrow transplant studies [82]. This has also been confirmed in the most recent update of the Early Breast Cancer Trialists Collaborative Group [23]. A trial in the United States was initiated to answer specifically the question of the benefit of postmastectomy radiation in women with one to three positive nodes. However, the trial had to be closed due to low accrual rates. Since in both the Canadian and Danish trials, women were also treated to their IMN; this question also has received renewed interest. Radiation therapy to the IMN may benefit the women with medial or central lesion in whom multiple axillary nodes are positive. Inclusion of the IMN, particularly on the left side, will undoubtedly increase the volume of heart treated, and depending on the technique used may possibly increase the dose to the esophagus. Thus, if the IMNs are to be included, treatments should be done with CT-based planning so that the IMN can be localized and the volume of lung, heart and esophagus minimized. Two randomized trials, one in Canada and the second in Europe, are in progress, addressing the extent of radiation needed to the draining lymphatics,

The management of locoregional breast cancer recurrences depends on the prior therapy. Disease that recurs after breast-conserving surgery and radiation therapy is usually treated with mastectomy. There have been attempts in patients in whom a very early recurrence is found to only perform an excision with satisfactory results. However, the number of patients treated in this manner is low and the follow-up too short to realize the full impact of this management strategy [99]. A full course of radiation for the second time is difficult to deliver because of the risk of long-term complications. The breast may become fibrotic and cosmetically unappealing. However, recently some data have been emerging regarding the feasibility of retreatment, particularly if there has been a long interval since prior therapy and if only partial breast treatment is done. If feasible, a recurrence that occurs postmastectomy should be excised with negative margins. Radiation, particularly if not previously given will decrease the risk of further recurrences. The radiation fields need to encompass the chest wall and regional lymphatics, not only the area of recurrence, because it seems that if only a small radiation field is used, recurrences may appear just outside the irradiated area [100]

Radiation and Breast Reconstruction

Many women who undergo mastectomy also opt for breast reconstruction. The techniques of reconstructive surgery have been changing. There is a significant decrease in the use of silicone or saline implants in favor of autologous tissue with pedicle or microanastomosis. The reconstructed, vascularized tissue is of great advantage in minimizing the risk of complications from radiation. The reported risk of complications in patients undergoing reconstruction and radiation varies anywhere from 18 to 51%. In the more recent publications, the risk of complications is at the lower end of range, probably because of improvement in the techniques of both surgery and radiation. The optimal sequencing of radiation and reconstructive surgery is not well established, thus multiple factors need to be considered and because a general consensus is lacking, good communication between all the members of the oncologic team is essential. The issue under consideration is the operation in a previously irradiated field if the reconstruction is being done following radiation. However, the concerns are less with the techniques that are using autologous vascularized tissues. On the other hand, if the reconstruction is done immediately after mastectomy and this is followed with the radiation, there are concerns regarding the cosmesis, firming and fat necrosis after radiating the reconstruction, and the possible obscuring of a recurrence. However, there are data showing that the great majority of the recurrences are not obscured by the myocutaneous

flap [101]. In general, good to excellent cosmesis is being achieved in the majority of the women who have radiation to the reconstructed breast. If there are no other contraindications, breast cancer occurring in an augmented breast can be treated with breast conservation. There may be some complications such as scaring or fat necrosis but the risk seems to be low [102] and the cosmetic outcome very good, thus the augmentation does not need to be removed prior to radiation. In the minority of patients in whom complications will later develop, the reconstruction may have to be revised or removed. This treatment strategy would leave the majority of women with the breast augmentation spared.

16.3 Locally Advanced Breast Cancer

Locally advanced and inflammatory breast cancers, stage III disease, pose a major management challenge. Because of the very high risk of local and distant failure, no single modality is satisfactory in controlling the disease, thus all three treatment modalities i.e., chemotherapy, radiation therapy and surgery need to be incorporated in a management plan. Since this disease presentation is not very common and because its definition encompasses a spectrum of diseases from large primary tumors with some skin edema, or small, limited skin ulceration to huge necrotic masses or global inflammatory changes, large randomized trials to define the standard of care are lacking. If the patient is a candidate for mastectomy, surgery may be performed upfront followed by adjuvant systemic therapy and radiation. Radiation alone as the local treatment modality in patients with large tumors is suboptimal. Control of the disease can only be obtained, at most in 50% of the patients and large doses are needed, which may result in long-term sequelae, including fibrosis and tissue necrosis [103]. However, postmastectomy radiation is very effective in reducing the local failure rates. The microscopic residual disease can be well controlled with 50–60 Gy and failure rates would decrease from 30–40 to 10–15%. Because the risk of metastatic disease is very high, there is general consensus for the need for systemic therapy despite the fact that several small randomized trials failed to demonstrate benefit for chemotherapy, probably because the patient numbers were low and the disease is very heterogeneous. However, retrospective studies show significant benefits compared to historical controls [104, 105].

Despite the general consensus that there is need for aggressive control of both local and distant disease, there are some controversies regarding the sequencing of the various therapies and the need for both radiation and surgery for local control. In most situations, even if the patients are technically operable, neoadjuvant chemotherapy is given first. Response rates to neoadjuvant chemotherapy are usually good and complete clinical response can be achieved in up to 30% of the patients. Patients with the best response have also the best chances for survival. If a good response to chemotherapy is obtained, then mastectomy is undertaken followed with additional chemotherapy and radiation. Comprehensive radiation fields are used to include the chest wall and draining lymphatics tailored to the anatomy and clinical situation. If there is no response to initial chemotherapy, a switch to radiation or different chemotherapy regimen is needed. Although not clearly established, retrospective reviews indicate that the local control is better if both surgery and radiation are given than with either modality alone [106].

Inflammatory breast cancer has a very high risk of metastatic disease and also very high risk of local failure if surgery alone is performed. Because of the involvement of dermal lymphatics, the disease is much more extensive than can be clinically appreciated; therefore, even if negative margins can be obtained, the disease soon recurs. Historically, because of its systemic nature, the 5-year survival rates were at most 10%. However, with the combination of chemotherapy, surgery, and radiation, the 5-year survival rates are approaching 30–50% [105]. More recently, only minimal, if any, additional improvements in outcome have been noted [107, 108] The sequencing of treatments depends on response to therapy. Neoadjuvant chemotherapy is initiated as soon as possible and response assessed after each cycle. If good response is obtained, surgery is being performed followed with additional chemotherapy and radiation to the chest wall and draining lymphatics. If however, response to chemotherapy is poor, radiation is added in order to bring the patient to a stage of operability. Because of the competing risks of both local and distant disease, concomitant chemotherapy and radiation protocols have been attempted with promising preliminary results [109–111]. The challenge is to concomitantly give sufficient chemotherapy to be therapeutically effective for metastatic disease as well as sufficient dose of radiation to control local disease, all this without severe complications.

16.4 Radiation as Palliation

Radiation treatments are frequently an integral component of the palliative management plan for advanced and metastatic disease. Painful, weeping, malodorous chest wall recurrences can be controlled with radiation, thus significantly contributing to quality of life and the ability to resume normal life style. The symptomatic effects of brain, bone, spinal cord, brachial plexus, choroidal, and liver metastases can be palliated with radiation and the effects can be durable for the lifetime of the patient. Single brain metastases or few metastases in the same proximity can be boosted with stereotactic radiosurgery or stereotactic radiotherapy, significantly improving the outcome, particularly if the disease at the primary site is controlled, or there is no evidence of disease elsewhere. (Stereotactic radiosurgery refers to a single large fraction, while stereotactic radiotherapy refers to fractionated stereotactic therapy using a relocatable frame). When the goal is palliation, decisions regarding dose, fractionation and length of therapy are determined based on the life expectancy and quality of life considerations. It is important to always keep in mind that the goals are palliation, thus the side effects should be kept to a minimum and the treatment course kept as short as possible.

16.5 Summary

Radiation therapy is an integral part of the management of breast cancer in all stages of breast cancer from DCIS to metastatic disease. Treatments should be tailored to each patient's clinical situation and anatomy to obtain the best disease control with minimum side effects. The new and developing technologies such as 3D treatment planning, IMRT, and image-guided techniques provide us with the tools to accomplish this goal.

References

1. de Moulin D (1983) A short history of breast cancer. Martinus Nijhoff, Boston
2. Harsolia A, Kestin L, Grills I et al (2007) Intensity-modulated radiotherapy results in significant decrease in clinical toxicities compared with conventional wedge-based breast radiotherapy. Int J Radiat Oncol Biol Phys. 68:1375–80
3. Pignol J, Olovotto I, Rakovitch E, et al Phase III randomized study of intensity-modulated radiation therapy versus standard wedging technique for adjuvant breast radiotherapy. Int J Radiat Oncol Biol Phys. 2006;66:S1(abstr)
4. Woo TC, Pignol JP, Rakovitch E et al (2006) Body radiation exposure in breast cancer radiotherapy: impact of breast IMRT and virtual wedge compensation techniques. Int J Radiat Oncol Biol Phys. 65:52–8
5. Whelan T, MacKenzie R, Julian J et al (2002) Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst. 94:1143–50
6. Yarnold J, Ashton A, Bliss J et al (2005) Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomized trial. Radiother Oncol. 75:9–17
7. Heimann R, Powers C, Halpem HJ et al (1996) Breast preservation in stage I and II carcinoma of the breast. The University of Chicago experience. Cancer. 78:1722–30
8. Lingos TI, Recht A, Vicini F et al (1991) Radiation pneumonitis in breast cancer patients treated with conservative surgery and radiation therapy. Int J Radiat Oncol Biol Phys. 21:355–60
9. Cuzick J, Stewart H, Rutqvist L et al (1994) Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy [scientific misconduct-data to be reanalyzed] [see comments]. J Clin Oncol. 12: 447–53
10. Rutqvist LE, Lax I, Fornander T et al (1992) Cardiovascular mortality in a randomized trial of adjuvant radiation therapy versus surgery alone in primary breast cancer [see comments]. Int J Radiat Oncol Biol Phys. 22:887–96
11. Vallis KA, Pintilie M, Chong N et al (2002) Assessment of coronary heart disease morbidity and mortality after radiation therapy for early breast cancer. J Clin Oncol. 20: 1036–42
12. Giordano SH, Kuo YF, Freeman JL et al (2005) Risk of cardiac death after adjuvant radiotherapy for breast cancer. J Natl Cancer Inst. 97:419–24
13. Pierce SM, Recht A, Lingos TI et al (1992) Long-term radiation complications following conservative surgery (CS) and radiation therapy (RT) in patients with early stage breast cancer [see comments]. Int J Radiat Oncol Biol Phys. 23:915–23
14. Neugut AI, Weinberg MD, Ahsan H, et al Carcinogenic effects of radiotherapy for breast cancer. Oncology (Huntingt). 1999;13:1245–56; discussion 1257, 1261–45
15. Boice JD Jr, Harvey EB, Blettner M et al (1992) Cancer in the contralateral breast after radiotherapy for breast cancer [see comments]. N Engl J Med. 326:781–5
16. Gao X, Fisher SG, Emami B (2003) Risk of second primary cancer in the contralateral breast in women treated for early stage breast cancer: a population-based study. Int J Radiat Oncol Biol Phys. 56:1038–45
17. Storm HH, Andersson M, Boice JD Jr et al (1992) Adjuvant radiotherapy and risk of contralateral breast cancer. J Natl Cancer Inst. 84:1245–50
18. Abdalla I, Thisted RA, Heimann R (2000) The impact of contralateral breast cancer on the outcome of breast cancer patients treated by mastectomy. Cancer J. 6:266–72

19. Inskip PD, Stovall M, Flannery JT (1994) Lung cancer risk and radiation dose among women treated for breast cancer [see comments]. J Natl Cancer Inst. 86:983–8
20. Neugut AI, Murray T, Santos J et al (1994) Increased risk of lung cancer after breast cancer radiation therapy in cigarette smokers [see comments]. Cancer. 73:1615–20
21. Taghian A, de Vathaire F, Terrier P et al (1991) Long-term risk of sarcoma following radiation treatment for breast cancer. Int J Radiat Oncol Biol Phys. 21:361–7
22. Curtis RE, Boice J Jr, Stovall M et al (1992) Risk of leukemia after chemotherapy and radiation treatment for breast cancer [see comments]. N Engl J Med. 326:1745–51
23. Clarke M, Collins R, Darby S et al (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Lancet. 366: 2087–106
24. Kirova YM, Asselain B, Fourquet A (2007) Oesophageal carcinoma as second malignancy after irradiation for breast cancer. From meta-analysis and large epidemiologic studies to patients' records and dosimetric questions: where is the truth? Large-scale institutional experience. Breast Cancer Res Treat. 106:S199
25. Page DL, Dupont WD, Rogers LW et al (1995) Continued local recurrence of carcinoma 15–25 years after a diagnosis of low-grade ductal carcinoma in situ of the breast treated only by biopsy. Cancer. 76:1197–200
26. Betsill WL Jr, Rosen PP, Lieberman PH et al (1978) Intraductal carcinoma. Long-term follow-up after treatment by biopsy alone. JAMA. 239:1863–7
27. Smigal C, Jemal A, Ward E et al (2006) Trends in breast cancer by race and ethnicity: update 2006. CA Cancer J Clin. 56:168–83
28. Frykberg ER, Bland KI (1994) Overview of the biology and management of ductal carcinoma in situ of the breast. Cancer. 74:350–61
29. Hillner BE, Desch CE, Carlson RW et al (1996) Trade-offs between survival and breast preservation for three initial treatments of ductal carcinoma-in-situ of the breast. J Clin Oncol. 14:70–7
30. Fisher B, Dignam J, Wolmark N et al (1998) Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from national surgical adjuvant breast and bowel project B-17. J Clin Oncol. 16:441–52
31. Fisher ER, Costantino J, Fisher B et al (1995) Pathologic findings from the national surgical adjuvant breast project (NSABP) Protocol B-17. Intraductal carcinoma (ductal carcinoma in situ). The National Surgical Adjuvant Breast and Bowel Project Collaborating Investigators [see comments]. Cancer. 75:1310–9
32. Fisher ER, Dignam J, Tan-Chiu E et al (1999) Pathologic findings from the national surgical adjuvant breast project (NSABP) eight-year update of Protocol B-17: intraductal carcinoma [see comments]. Cancer. 86:429–38
33. Fisher ER, Leeming R, Anderson S et al (1991) Conservative management of intraductal carcinoma (DCIS) of the breast. Collaborating NSABP investigators. J Surg Oncol. 47: 139–47
34. Bijker N, Meijnen P, Peterse JL et al (2006) Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European organization for research and treatment of cancer randomized phase III trial 10853–a study by the EORTC breast cancer cooperative group and EORTC radiotherapy group. J Clin Oncol. 24:3381–7
35. Omlin A, Amichetti M, Azria D et al (2006) Boost radiotherapy in young women with ductal carcinoma in situ: a multicentre, retrospective study of the rare cancer network. Lancet Oncol. 7:652–6
36. Sahoo S, Recant WM, Jaskowiak N et al (2005) Defining negative margins in DCIS patients treated with breast-conservation therapy: the university of Chicago experience. Breast J. 11:242–47
37. Fisher B, Dignam J, Wolmark N et al (1999) Tamoxifen in treatment of intraductal breast cancer: national surgical adjuvant breast and bowel project B-24 randomized controlled trial [see comments]. Lancet. 353:1993–2000
38. Silverstein MJ, Lagios MD, Craig PH et al (1996) A prognostic index for ductal carcinoma in situ of the breast [see comments]. Cancer. 77:2267–74
39. Silverstein MJ, Lagios MD, Groshen S et al (1999) The influence of margin width on local control of ductal carcinoma in situ of the breast [see comments]. N Engl J Med. 340:1455–61
40. Heimann R, Karrison T, Hellman S (1999) Treatment of ductal carcinoma in situ [letter]. N Engl J Med. 341:999–1000
41. Macdonald HR, Silverstein MJ, Lee LA et al (2006) Margin width as the sole determinant of local recurrence after breast conservation in patients with ductal carcinoma in situ of the breast. Am J Surg. 192:420–2
42. Wong JS, Kaelin CM, Troyan SL et al (2006) Prospective study of wide excision alone for ductal carcinoma in situ of the breast. J Clin Oncol. 24:1031–6
43. NIH consensus development conference (1991) Treatment of early stage breast cancer. J Am Med Assoc. 265:391–5
44. Veronesi U, Cascinelli N, Mariani L et al (2002) Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 347:1227–32
45. van Dongen JA, Bartelink H, Fentiman IS et al (1992) Randomized clinical trial to assess the value of breast-conserving therapy in stage I and II breast cancer, EORTC 10801 trial. Monogr Natl Cancer Inst. 11:15–8
46. Blichert-Toft M, Rose C, Andersen JA et al (1992) Danish randomized trial comparing breast-conservation therapy with mastectomy: six years of life-table analysis. Danish breast cancer cooperative group. Monogr Natl Cancer Inst. 11:19–25
47. Fisher B, Anderson S, Bryant J et al (2002) Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 347:1233–41
48. Poggi MM, Danforth DN, Sciuto LC et al (2003) Eighteen-year results in the treatment of early breast carcinoma with mastectomy versus breast-conservation therapy: the national cancer institute randomized trial. Cancer. 98:697–702
49. Arriagada R, Le MG, Rochard F et al (1996) Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institute Gustave- Roussy breast cancer group. J Clin Oncol. 14:1558–64
50. Farrow DC, Hunt WC, Samet JM (1992) Geographic variation in the treatment of localized breast cancer [see comments]. N Engl J Med. 326:1097–101

51. Nattinger AB, Goodwin JS (1994) Geographic and hospital variation in the management of older women with breast cancer. Cancer Control. 1:334–8
52. Joslyn SA (1999) Geographic differences in the treatment of early stage breast cancer. Breast J. 5:29–35
53. Lazovich DA, White E, Thomas DB et al (1991) Underutilization of breast-conserving surgery and radiation therapy among women with stage I or II breast cancer [see comments]. JAMA. 266:3433–8
54. Lazovich D, Solomon CC, Thomas DB et al (1999) Breast-conservation therapy in the United States following the 1990 national institutes of health consensus development conference on the treatment of patients with early stage invasive breast carcinoma. Cancer. 86:628–37
55. Hiotis K, Ye W, Sposto R et al (2005) The importance of location in determining breast conservation rates. Am J Surg. 190:18–22
56. Hiotis K, Ye W, Sposto R et al (2005) Predictors of breast-conservation therapy: size is not all that matters. Cancer. 103:892–9
57. Morrow M, Bucci C, Rademaker A (1998) Medical contraindications are not a major factor in the underutilization of breast conserving therapy. J Am Coll Surg. 186:269–74
58. Joslyn SA (1999) Radiation therapy and patient age in the survival from early stage breast cancer. Int J Radiat Oncol Biol Phys. 44:821–6
59. Whelan TJ, Julian J, Wright J et al (2000) Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. J Clin Oncol. 18:1220–9
60. Punglia RS, Morrow M, Winer EP et al (2007) Local therapy and survival in breast cancer. N Engl J Med. 356:2399–405
61. Holland R, Veling SH, Mravunac M et al (1985) Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. Cancer. 56:979–90
62. Kurtz JM, Amalric R, Brandone H et al (1989) Local recurrence after breast-conserving surgery and radiotherapy. Frequency, time course, and prognosis. Cancer. 63: 1912–7
63. Bartelink H, Horiot JC, Poortmans PM et al (2007) Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881–10882 trial. J Clin Oncol. 25:3259–65
64. Recht A, Silen W, Schnitt SJ et al (1988) Time-course of local recurrence following conservative surgery and radiotherapy for early stage breast cancer. Int J Radiat Oncol Biol Phys. 15:255–61
65. Winchester DP, Cox JD (1992) Standards for breast-conservation treatment. CA Cancer J Clin. 42:134–62
66. Winchester DP, Cox JD (1998) Standards for diagnosis and management of invasive breast carcinoma. American College of Radiology. American College of Surgeons. College of American Pathologists. Society of Surgical Oncology. CA Cancer J Clin. 48:83–107
67. Park CC, Mitsumori M, Nixon A et al (2000) Outcome at 8 years after breast-conserving surgery and radiation therapy for invasive breast cancer: influence of margin status and systemic therapy on local recurrence. J Clin Oncol. 18: 1668–75
68. Jones H, Antonini N, Collette L et al (2007) The impact of boost dose and margins on the local recurrence rate in breast-conserving therapy: results from the EORTC boost-no boost trial. Int J Radiat Oncol Biol Phys. 69:S2
69. Mueller CB, Ames F, Anderson GD (1978) Breast cancer in 3, 558 women: age as a significant determinant in the rate of dying and causes of death. Surgery. 83:123–32
70. Yancik R, Ries LG, Yates JW (1989) Breast cancer in aging women. A population-based study of contrasts in stage, surgery, and survival. Cancer. 63:976–81
71. Singh R, Hellman S, Heimann R (2004) The natural history of breast carcinoma in the elderly: implications for screening and treatment. Cancer. 100:1807–13
72. Pierce LJ, Strawderman M, Narod SA et al (2000) Effect of radiotherapy after breast-conserving treatment in women with breast cancer and germline BRCA1/2 mutations. J Clin Oncol. 18:3360–9
73. Pierce LJ, Levin AM, Rebbeck TR et al (2006) Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. J Clin Oncol. 24:2437–43
74. Turner BC, Harrold E, Matloff E et al (1999) BRCA1/BRCA2 germline mutations in locally recurrent breast cancer patients after lumpectomy and radiation therapy: implications for breast-conserving management in patients with BRCA1/BRCA2 mutations [see comments]. J Clin Oncol. 17:3017–24
75. Hellman S (1999) The key and the lamppost. J Clin Oncol. 17:3007–8
76. Clark RM, Whelan T, Levine M et al (1996) Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario clinical oncology group. J Natl Cancer Inst. 88:1659–64
77. Liljegren G, Holmberg L, Bergh J et al (1999) 10-year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. J Clin Oncol. 17:2326–33
78. Fisher B, Stewart A, Redmond C et al (1995) Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med. 333:1456–61
79. Lim M, Bellon JR, Gelman R et al (2006) A prospective study of conservative surgery without radiation therapy in select patients with Stage I breast cancer. Int J Radiat Oncol Biol Phys. 65:1149–54
80. Fisher B, Dignam J, Bryant J et al (1996) Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors [see comments]. J Natl Cancer Inst. 88: 1529–42
81. Fisher B, Dignam J, Mamounas EP et al (1996) Sequential methotrexate and fluorouracil for the treatment of node-negative breast cancer patients with estrogen receptor-negative tumors: eight-year results from National Surgical Adjuvant Breast and Bowel Project (NSABP) B-13 and first report of findings from NSABP B-19 comparing methotrexate and fluorouracil with conventional cyclophosphamide, methotrexate, and fluorouracil [see comments]. J Clin Oncol. 14:1982–92

82. Carter DL, Marks LB, Bean JM et al (1999) Impact of consolidation radiotherapy in patients with advanced breast cancer treated with high-dose chemotherapy and autologous bone marrow rescue. J Clin Oncol. 17:887–93
83. Fisher B, Bryant J, Wolmark N et al (1998) Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol. 16:2672–85
84. McCormick B, Begg CB, Norton L et al (1993) Timing of radiotherapy in the treatment of early stage breast cancer [letter; comment]. J Clin Oncol. 11:191–3
85. Heimann R, Powers C, Fleming G et al (1994) Does the sequencing of radiotherapy and chemotherapy affect the outcome in early stage breast cancer: a continuing question. Int J Radiat Oncol Biol Phys. 30(Suppl 1):241
86. Recht A, Come SE, Henderson IC et al (1996) The sequencing of chemotherapy and radiation therapy after conservative surgery for early stage breast cancer. N Engl J Med. 334:1356–61
87. Fisher B, Redmond C, Fisher ER et al (1985) Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med. 312:674–81
88. Heimann R, Hellman S (2000) Clinical progression of breast cancer malignant behavior: what to expect and when to expect it. J Clin Oncol. 18:591–9
89. Sugg SL, Ferguson DJ, Posner MC et al (2000) Should internal mammary nodes be sampled in the sentinel lymph node era? Ann Surg Oncol. 7:188–92
90. Ragaz J, Olivotto IA, Spinelli JJ et al (2005) Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst. 97:116–26
91. Recht A, Gray R, Davidson NE et al (1999) Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: experience of the Eastern cooperative oncology group. J Clin Oncol. 17:1689–700
92. Arriagada R, Rutqvist LE, Mattsson A et al (1995) Adequate locoregional treatment for early breast cancer may prevent secondary dissemination. J Clin Oncol. 13:2869–78
93. Anon. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group [see comments] [published erratum appears in N Engl J Med 1996 Apr 11;334(15):1003]. N Engl J Med. 1995;333:1444–55
94. Correa CR, Litt HI, Hwang WT et al (2007) Coronary artery findings after left-sided compared with right-sided radiation treatment for early stage breast cancer. J Clin Oncol. 25:3031–7
95. Nielsen HM, Overgaard M, Grau C et al (2006) Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish breast cancer cooperative group DBCG 82 b and c randomized studies. J Clin Oncol. 24:2268–75
96. Overgaard M, Jensen MB, Overgaard J et al (1999) Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen: Danish breast cancer cooperative group DBCG 82c randomized trial [see comments]. Lancet. 353:1641–8
97. Overgaard M, Nielsen HM, Overgaard J (2007) Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b and c randomized trials. Radiother Oncol. 82:247–53
98. Hellman S (1997) Stopping metastases at their source (editorial). N Engl J Med. 337:996–7
99. Salvadori B, Marubini E, Miceli R et al (1999) Reoperation for locally recurrent breast cancer in patients previously treated with conservative surgery. Br J Surg. 86:84–7
100. Halverson KJ, Perez CA, Kuske RR et al (1990) Isolated local-regional recurrence of breast cancer following mastectomy: radiotherapeutic management [see comments]. Int J Radiat Oncol Biol Phys. 19:851–8
101. Slavin SA, Love SM, Goldwyn RM. Recurrent breast cancer following immediate reconstruction with myocutaneous flaps. Plast Reconstr Surg. 1994;93:1191–204; discussion 1205–197
102. Ryu J, Yahalom J, Shank B et al (1990) Radiation therapy after breast augmentation or reconstruction in early or recurrent breast cancer. Cancer. 66:844–7
103. Spanos WJ Jr, Montague ED, Fletcher GH (1980) Late complications of radiation only for advanced breast cancer. Int J Radiat Oncol Biol Phys. 6:1473–6
104. Touboul E, Lefranc JP, Blondon J et al (1992) Multidisciplinary treatment approach to locally advanced non-inflammatory breast cancer using chemotherapy and radiotherapy with or without surgery. Radiother Oncol. 25:167–75
105. Hortobagyi GN (1994) Multidisciplinary management of advanced primary and metastatic breast cancer. Cancer. 74:416–23
106. Perez CA, Graham ML, Taylor ME et al (1994) Management of locally advanced carcinoma of the breast. I. Non-inflammatory. Cancer. 74:453–65
107. Gonzalez-Angulo AM, Hennessy BT, Broglio K et al (2007) Trends for inflammatory breast cancer: is survival improving? Oncologist. 12:904–12
108. Hance KW, Anderson WF, Devesa SS et al (2005) Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the national cancer institute. J Natl Cancer Inst. 97:966–75
109. Masters G, Heimann R, Skoog L et al (1997) Concomitant chemoradiotherapy with vinorelbine and paclitaxel with filgrastim(G-CSF) support in patients with unresectable breast cancer. Breast Cancer Res Treat. 46:75
110. Formenti SC, Symmans WF, Volm M et al (1999) Concurrent paclitaxel and radiation therapy for breast cancer. Semin Radiat Oncol. 9:34–42
111. Kao J, Conzen SD, Jaskowiak NT et al (2005) Concomitant radiation therapy and paclitaxel for unresectable locally advanced breast cancer: results from two consecutive phase I/II trials. Int J Radiat Oncol Biol Phys. 61:1045–53

Adjuvant Systemic Therapy for Breast Cancer: An Overview

17

Virginia G. Kaklamani and William J. Gradishar

A recommendation for adjuvant systemic therapy is commonly made to women with a diagnosis of early stage breast cancer. The standard adjuvant therapies include chemotherapy, endocrine therapy, and antibody therapy (i.e., trastuzumab). Data from the Surveillance, Epidemiology and End Results (SEER) registries in the United States report a reduction in breast cancer-related mortality of *7.5%* since 1973, whereas during the same period, the incidence of invasive breast cancer increased by *25%* [1–4]. The improvement in survival for patients with early stage breast cancer coincides with the widespread use of screening mammography and the administration of systemic adjuvant therapy [5–7].

The decision to offer adjuvant therapy is made after providing the patient with a thorough discussion of her prognosis based on clinical and biologic characteristics of the primary tumor. Once an estimate of the risk of recurrence and mortality secondary to breast cancer is established for a population of breast cancer patients with similar characteristics, the medical oncologist can provide the patient with an estimate of potential benefit derived from the addition of adjuvant systemic therapy. Benefit from adjuvant systemic therapy is described in terms of reducing the risk of recurrence and death from breast cancer. An equally important issue that must figure in the discussion of adjuvant systemic therapy is the associated toxicity, both acute and chronic. Only after considering both the potential benefit and toxicity related to adjuvant systemic therapy can either the medical oncologist or the patient make a rational decision regarding its use. Hundreds of individual clinical trials involving thousands of patients have been conducted to assess the efficacy of various adjuvant chemotherapy or endocrine programs in women with early stage breast cancer. The fundamental message that is gleaned from this experience is that adjuvant systemic therapy does reduce the risk of recurrence and improve survival in women with early stage breast cancer [5, 8]. This chapter provides an overview of this experience and suggests guidelines to use when evaluating patients who are potential candidates for adjuvant systemic therapy.

The three meta-analyzes (overview analyzes) of randomized clinical trials of chemotherapy and endocrine therapy in early stage breast cancer patients provide the largest data set showing that systemic adjuvant therapy does reduce the risk of recurrence and death related to breast cancer [5, 8]. Because the overview analyses include thousands of patients and events (e.g., recurrences and deaths), greater validity is assigned to estimates of benefit derived from adjuvant therapy. On the other hand, the overview analyses also have the potential weakness of obscuring important differences in the design of individual trials (i.e., drug dose, duration of therapy and variation of schedule). Critical to understanding the overview analyses is an appreciation of how efficacy of adjuvant therapy is reported. Two concepts are worth reviewing: proportional risk reduction and absolute risk reduction. *Proportional risk reduction* can be viewed as the percentage of negative outcomes that were avoided (recurrences or deaths) because adjuvant systemic therapy was administered. The overview analyses actually reported the *annual* proportional risk reduction for the risk of an event (e.g., recurrence or death) occurring. The annual risk *compounds* to give the risk of an adverse event at some future time. *Absolute risk reduction* of an adverse event simply states what percentage of patients, at a specific time, have avoided an adverse event (recurrence or death) by having received adjuvant therapy compared with a group of similar

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases*,
DOI: 10.1007/978-3-540-69743-5_17, © Springer-Verlag Berlin Heidelberg 2010

patients who did not receive that therapy. Absolute risk reduction is a smaller number than proportional risk reduction. Unfortunately, a misunderstanding of the terms frequently leads patients and physicians to erroneous conclusions regarding the benefits of adjuvant systemic therapy. Finally, it is important to appreciate that estimate of benefits, as reported by the overview analyzes, apply to populations of patients with similar characteristics rather than an individual patient.

17.1 Role of Adjuvant Polychemotherapy

17.1.1 EBCTCG Systematic Review on Polychemotherapy (Oxford Overview)

Since the initiation of the first randomized trials of adjuvant therapy, several prospective randomized clinical trials comparing adjuvant chemotherapy with placebo have been conducted and reported. Most trials compare local therapy with or without the addition of systemic chemotherapy. The trials vary by type of agent investigated, treatment duration and number of agents. Because individual trials may yield different results as a result of statistical and other biases, attempts have been made to perform systematic reviews of multiple studies that examined similar questions. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has met every 5 years since the mid-1980s to perform a systematic review of all randomized clinical trials that have been performed in early stage breast cancer. Early meta-analyzes have focused on CMF- and anthracycline-like regimens showing the superiority of receiving adjuvant therapy vs. no treatment. Currently, the most recent publication on the systematic review of polychemotherapy for early breast cancer is from the 2005 Overview [8]. This review includes 194 randomized trials in early breast cancer of almost 150,000 women. With a 15-year follow-up, chemotherapy offered a significant benefit in both recurrence-free survival (RFS) and breast cancer mortality in women under the age of 50 (12.3% 15-year benefit in RFS; SE > 1.6; $P<0.00001$; 10.0% benefit in mortality; SE > 1.6; $P<0.00001$). For women over the age of 50, the benefit although significant, was not as high (4.1% 15-year benefit in RFS; SE > 1.2; $P<0.00001$; 30% relative benefit in mortality; SE > 1.3; $P<0.00001$). This benefit remained significant regardless of the axillary lymph node status. The benefit from adjuvant chemotherapy was higher in ER-poor disease compared with ER-positive disease but remained significant in both subgroups of patients. In women under the age of 50 with ER-poor disease, the 5-year benefit from chemotherapy was 13.2% (SE 2.4; $P<0.00001$), whereas the benefit in the same population with ER-positive disease was 7.6% (SE 1.7; $P<0.00001$). Similarly, in women 50–69 years old with ER-poor disease, the 5-year benefit from chemotherapy was 9.6% (SE 1.8; $P<0.00001$), whereas the benefit in the same population with ER-positive disease was 4.9% (SE 0.9; $P<0.00001$).

Recently, results from the EBCTCG were published focusing on the role of chemotherapy in ER-poor breast cancer [9]. The meta-analysis included 96 trials and about 20,000 women with ER-poor breast cancer. The meta-analysis showed that adjuvant chemotherapy significantly reduced the risk of recurrence, breast cancer mortality as well as overall mortality in women. More specifically, in women under the age of 50, there was a 15% absolute benefit (HR: 0.73, $P>0.0002$) in RFS and an 8% absolute benefit (HR 0.75, $P>0.0003$) in mortality. In women between the ages of 50 and 69, the absolute benefit in RFS with the use of chemotherapy was 10% (HR:0.82, $P<0.00001$) and in mortality 6% (HR:0.87, $P>0.0009$).

Abundant data exists demonstrating the activity of the taxanes in metastatic breast cancer. When the taxanes were evaluated in metastatic breast cancer, they proved to be a very effective option for anthracycline-resistant patients [10–12]. As a first-line therapeutic approach in advanced breast cancer, the combination of taxanes with anthracyclines produced high response rates that ranged from 46 to 94% [13–15]. Based on the activity of paclitaxel and docetaxel in metastatic breast cancer, both taxanes are considered first-line options for patients with metastatic disease. The contribution of taxanes to adjuvant chemotherapy programs for early breast cancer has been evaluated in at least ten large randomized trials.

17.1.1.1 Intergroup 9344

The addition of paclitaxel to AC was evaluated in the Cancer and Leukemia Group B (CALGB) 9344 trial. In this trial, 3,170 patients with axillary node-positive

breast cancer were randomized to the standard AC regimen or to AC followed by 4 cycles of paclitaxel (175 mg/m^2 every 3 weeks) [16]. An initial randomization compared three different doses of doxorubicin (60, 75, and 90 mg/m^2), but there was no difference in outcome based on the different AC regimens. Tamoxifen was offered to patients with ER-positive tumors ($n \sim 2{,}000$). Both treatment arms were balanced with regards to patient and tumor characteristics: 62% premenopausal; 58% ER+; 46% 1–3 positive axillary nodes; and 42% 4–9 positive axillary nodes. At the first pre-planned interim analysis with a median follow-up of 22 months, the addition of paclitaxel resulted in a 22% reduction in the annual odds of recurrence and a 26% reduction in the annual odds of death. These findings translated into a 4% absolute improvement in disease-free survival (DFS) ($P > 0.0077$) and a 2% absolute improvement in OS ($P > 0.039$) for patients treated with paclitaxel. The initial data was published in 2003. With a median follow-up of 69 months, the number of recurrences ($n > 1{,}054$) and deaths ($n > 742$) had increased by more than two-fold compared to the previous analysis. There was a significant improvement both in RFS (HR: 0.83, $P > 0.0023$) and in OS (HR: 0.82, $P > 0.0064$) with the addition of paclitaxel. The subset of patients who received tamoxifen (e.g., ER+ tumors) did not appear to derive significant benefit from the addition of paclitaxel. In contrast, the patients with ER-negative tumors had a statistically significant improvement in DFS. One of the criticisms of the study design was that the two treatment arms differed in the total number of chemotherapy cycles administered (4 vs. 8).

17.1.1.2 NSABP-28

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-28 randomized 3,060 patients with axillary node-positive breast cancer to AC (60/600 mg/m^2)×4 or AC×4 followed by paclitaxel (225 mg/m^2)×4 [17]. The primary objective of the trial was to evaluate DFS and OS. Patients aged 50 years or older, as well as patients with tumors expressing positive hormone receptors, were offered tamoxifen for a total of 5 years. The groups were stratified according to the number of positive axillary lymph nodes, tamoxifen administration and type of surgery performed. With a median follow-up of 65 months, the DFS was 76% in the paclitaxel arm vs. 72% in the control arm (HR:0.83, $P > 0.006$), and OS was 85% in both arms (HR:0.93, $P > 0.46$). Toxicity in this trial included neurotoxicity in the paclitaxel arm and a small incidence of febrile neutropenia (3%). This trial also did not control the total number of cycles of chemotherapy administered (4 vs. 8). Also, concurrent use of tamoxifen was allowed, which may have limited the effectiveness of the paclitaxel in this trial.

17.1.1.3 ECOG 2197

This trial included a total of 2,952 patients with either axillary node-positive or high-risk node-negative breast cancer [18]. Patients were randomized to 1 of 2 arms: Doxorubicin (60 mg/m^2 every 3 weeks) and docetaxel (60 mg/m^2 every three weeks) (AT) for 4 cycles or AC for 4 cycles. The study was powered to detect a 25% improvement in DFS with AT. After a median of 53 months, both DFS (87%; HR: 1.08, $P > 0.43$) and OS (not reached; HR:1.09, $P > 0.48$) were similar in the 2 arms. AT was slightly superior in ER- patients (82 vs. 79%), but that difference did not reach statistical significance. Febrile neutropenia occurred in 19% of patients in the AT arm compared with 6% of patients in the AC arm. This study showed that there was no improvement in outcome with the use of AT compared with AC in early stage breast cancer. Furthermore, AT appeared to be more toxic.

17.1.1.4 PACS 01

This trial randomized 1,999 women with lymph node-positive breast cancer to receive 6 cycles of FEC100 (5-FU:500 mg/m², epirubicin: 100 mg/m², cyclophosphamide: 500 mg/m²) or 3 cycles of FEC100 followed by 3 cycles of docetaxel 100 mg/m^2 [19]. With follow-up of 60 months, DFS was 78% in the taxanes- containing arm compared to 73% in the FEC100 arm (HR > 0.82; $P > 0.012$). The OS also significantly favored the taxane-containing arm (91 vs. 87%, respectively; HR > 0.73; $P > 0.017$). Subgroup analyzes showed that the significance in the DFS was observed in the >50 year old population and in the population with 1–3 positive lymph nodes, whereas the other groups did not seem to benefit from the addition of docetaxel.

17.1.1.5 GEICAM 9906

This trial included a total of 1,248 patients with axillary node-positive early stage breast cancer [20]. Patients were randomized into two treatment arms: (1) FEC90 (5-FU 600 mg/m^2, epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2) every 3 weeks for a total of 6 cycles; (2) FEC90 every 3 weeks for 4 cycles followed by paclitaxel 100 mg/m^2 every week for 8 cycles. After a median of 46 months, there was a significant difference in DFS (85 vs. 79%; HR:0.63, $P>0.0008$) in favor of the taxane arm. However, there was no significant difference in OS (95 vs. 92%; HR: 0.74, $P>0.137$). The benefit of taxane in DFS was independent of hormone receptor, menopausal or HER2 status. Both regimens were well tolerated, with increased incidence of peripheral neuropathy and myalgias in the paclitaxel arm and higher incidence of febrile neutropenia and mucositis in the anthracycline alone arm.

17.1.1.6 ECOG E1199

This 4-arm trial attempted to answer two questions: (1) which is a better taxane, docetaxel or paclitaxel [21] and (2), which is a better administration schedule, weekly or every 3 weeks. AC was administered initially for 4 cycles every 3 weeks. Subsequently, patients were randomized to 1 of 4 arms: (1) Paclitaxel 175 mg/m^2 every 3 weeks for 4 cycles (P3); (2) Paclitaxel 80 mg/m^2 every week for 12 doses (P1); (3) Docetaxel 100 mg/m^2 every 3 weeks for 4 cycles (D3); (4) Docetaxel 35 mg/m^2 every week for 12 doses (D1). Patients eligible for the study had either axillary lymph node-positive disease or high-risk axillary node-negative disease. A total of 4,988 patients were randomized to the 4 arms. The 4-year DFS was similar between the 4 arms (P3>80.6%, P1>83.5%, D3>83.1%, D1>80.5%). Similarly, there was no difference in the 4-year OS (P3>88.7%, P1>91.7%, D3>89.3%, D1>88.9%). When comparing P3 with P1, there was a trend toward improvement in DFS and 15% fewer relapses in the P1 arm.

17.1.1.7 US Oncology 9735

The US Oncology performed an adjuvant trial in women with stage I, II or III breast cancer [22]. The 2 arms were: doxorubicin at 60 mg/m^2 and cyclophosphamide at 600 mg/m^2 given every 3 weeks for 4 cycles (AC), and docetaxel at 75 mg/m^2 and cyclophosphamide at 600 mg/m^2 given every 3 weeks for 4 cycles (TC). The most recent presentation of the trial included data on 7 years of follow-up. A total of 1,016 patients were randomized between the two treatment arms. The DFS significantly favored the TC arm (81 vs. 75%; HR>0.74; $P>0.033$). Furthermore, when evaluating patients over the age of 65, TC was again found to be superior to AC, although both groups did worse than the group of patients under 65 years old. This difference may be due to the fact that older women were more likely to have higher risk disease. The superiority of TC was independent of HER2 status or HR status. The OS was significantly better in women receiving TC compared with AC (87 vs. 82%, respectively; HR>0.69; $P>0.032$). Both regimens were well tolerated, with TC having a higher incidence of febrile neutropenia (12 patients in TC vs. six patients in AC) and AC having three long-term fatal toxicities (one patient with CHF, another with myelodysplastic syndrome and one with myelofibrosis). From the results of this trial, TC emerges as a valuable regimen in the adjuvant treatment of breast cancer, and may replace AC as the new "standard of care" for women who are not considered for a combination of an anthracycline and taxane.

17.1.1.8 BIG 02-98

The BIG 02-98 trial randomized 2,887 patients with axillary lymph node-positive early stage breast cancer to one of four treatment arms [23]: (1) doxorubicin 75 mg/m^2 every 3 weeks for 4 cycles (A) followed by cyclophosphamide 100 mg/m^2 p.o. days 1–14, methotrexate 40 mg/m^2 days 1 and 8, 5-fluorouracil 600 mg/m^2 days 1 and 8 (CMF) for 3 cycles; (2) AC for 4 cycles followed by CMF for 3 cycles; (3) A/AC followed by docetaxel 100 mg/m^2 every 3 weeks for 4 cycles (T) followed by CMF for 3 cycles; (4) Doxocubicin 50 mg/m^2 and docetaxel 75 mg/m^2 every 3 weeks for 4 cycles followed by CMF for 3 cycles. The first 2 arms were considered the control arms and arm 3 and 4 were considered experimental. The primary endpoint of the trial was DFS with secondary endpoints, including OS and toxicity. After a median follow-up of 5 years [23], docetaxel treatment resulted in a borderline improvement of DFS (HR: 0.86; 95%CI 0.74–1.00; $P>0.05$). The DFS in the sequential docetaxel arm was better than the concurrent docetaxel arm (HR: 0.83; 95%CI 0.69–1.00; $P>0.05$) and in the sequential control arm (HR: 0.79; 95%CI

0.64–0.98; $P>0.035$). All treatment regiments were well tolerated, with the concurrent docetaxel arm resulting in higher incidence of febrile neutropenia and the sequential docetaxel arm resulting in higher incidence of stomatitis and sensory neuropathy. This trial highlights the benefit from the addition of a taxane to an anthracycline regimen, and also provides an insight into the different schedules of administrations of chemotherapy, showing that a sequential approach may provide better benefit compared with a concurrent approach.

17.1.1.9 TAXIT 216

This adjuvant trial included 972 women with lymph node-positive early stage breast cancer and randomized them into two treatment arms [24]: (1) Epirubicin 120 mg/m^2 every 3 weeks for 4 cycles (E) followed by CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, 5-FU 600 mg/m^2) days 1 and 8 of a 28 day cycle for 4 cycles; (2) E followed by docetaxel 100 mg/m^2 every 3 weeks for 4 cycles followed by CMF. With a median follow-up of 53.6 months, there was a nonsignificant improvement in DFS in the docetaxel arm (HR: 0.79; 95%CI 0.61–1.00; $P>0.06$) as well as a similar improvement in OS (HR>0.72; 95%CI 0.5–1.04; $P>0.08$). Although there is a trend to benefit in the taxane arm, this benefit does not reach statistical significance.

17.1.1.10 MA21

This trial randomized 2,104 axillary node-positive or high-risk node-negative women into three treatment arms [25]: (1) CEF (cyclophosphamide 75 mg/m^2 p.o. days 1–14, epirubicin 60 mg/m^2 and 5FU 500 mg/m^2 both i.v. Days 1 and 8 plus antibiotics (cotrimoxazole or cipro) for 6 cycles), (2) Dose dense EC (epirubicin 120 mg/m^2 and cyclophosphamide 830 mg/m^2 both iv, plus filgrastim and epoetin alfa for 6 cycles every 2 weeks followed by 4 cycles of paclitaxel 175 mg/m^2 every 3 weeks), (3) AC/T (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 both i.v. every 3 weeks for 4 cycles followed by paclitaxel 175 mg/m^2 every 3 weeks for 4 cycles). The primary endpoint of the study was RFS with secondary endpoints, including OS, toxicity and quality of life (QOL). At a median follow-up of 30.4 months, the 3-year RFS was 90.1% in the CEF arm, 89.5% in the EC/T arm and 85% in the AC/T arm. There was a significant difference when comparing AC/T to CEF in favor of CEF (HR: 1.49, 95% CI 1.12–1.99; $P>0.005$). AC/T was also significantly inferior to EC/T (HR: 1.68, 95% CI 1.25–2.27; $P>0.0006$). All regimens were well tolerated but the AC/T arm had a lower incidence of febrile neutropenia (4.8%) compared with CEF (22.9%) and EC/T (16.7%). Sensory neuropathy was worse in the taxane-containing arms (Grade 1/2 CEF: 25.7%, EC/T: 65.8%, AC/T: 64.1%). The results of this trial point toward a benefit of dose-dense regimens. Furthermore, it suggests that the role of taxanes in a sequential nondose-dense fashion may be limited. It is unclear how the results of this study can be compared with the results of the CALGB 9741 trial in which dose-dense ACT was found to be superior compared with the same regimen given in a nondose-dense fashion.

17.1.1.11 HeCOG 10/97

This trial included 604 patients with axillary node-positive or high-risk node-negative early stage breast cancer [26]. Patients were randomized into the following arms: (1) 3 cycles of epirubicin 110 mg/m^2 followed by 3 cycles of paclitaxel 250 mg/m^2 followed by 3 cycles of "intensified" CMF (cyclophosphamide 840 mg/m^2, methotrexate 47 mg/m^2 and fluorouracil 840 mg/m^2); (2) 4 cycles of epirubicin followed by 4 cycles of CMF. All cycles were given every 2 weeks with granulocyte colony-stimulating factor (G-CSF) support. After a median follow-up of 62 months, there was a nonsignificant improvement in DFS (HR: 1.16; 95%CI 0.87–1.55; $P>0.31$) as well as OS ($P>0.38$) favoring the taxane arm. The lack of a statistically significant benefit in the taxane arm may be due to the relatively small number of patients included in the trial.

17.1.2 European Cooperative Trial in Operable Breast Cancer (ECTO)

This trial included 1,355 axillary lymph node-positive or high-risk node-negative patients [27] and randomized them into one of three treatment arms: (1) Doxocuribin 60 mg/m^2 every 3 weeks for 4 cycles followed by CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, 5-FU 600 mg/m^2 days 1,8 every 28 days) for 4 cycles; (2) doxorubicin 60 mg/m^2 with paclitaxel 200 mg/m^2 every 3 weeks for 4 cycles followed by CMF for 4 cycles

(3) neoadjuvant doxorubicin 60 mg/m^2 with paclitaxel 200 mg/m^2 every 3 weeks for 4 cycles followed by CMF for 4 cycles followed by surgery. With a 43-month median follow-up, there was a significant difference in progression-free survival (PFS) between arms 1 and 2 in favor of the taxane arm (HR: 0.65; 95%CI 0.47–0.90; $P>0.01$). When comparing arms 2 and 3, there was no significant difference in PFS. OS was also not significantly different between the three treatment arms.

17.1.2.1 MD Anderson 94-002

The MD Anderson trial compared 8 cycles of FAC chemotherapy to 4 cycles of paclitaxel (250 mg/m^2 over 24 h) followed by 4 cycles of FAC [28].Between 1994 and 1998, 524 patients with operable (T1-3, N0-1, M0) breast cancer were randomized to the two treatment arms. In 174 (33%) patients, the first 4 cycles were received preoperatively, and after surgery, an additional 4 cycles of chemotherapy (FAC) were administered. More than half the patients had N1 disease, and two-thirds had T2 lesions. Overall, 259 patients were treated on the FAC arm, and 265 were treated on the docetaxel arm. With a median follow-up of 43.5 months, DFS was 83% in the FAC group and 86% in the docetaxel arm ($P>0.09$). A subset analysis according to estrogen receptor status showed a trend toward improvement in DFS in patients receiving docetaxel regardless of the hormone receptor status of the tumor. As expected, the docetaxel arm was associated with more febrile neutropenia, but no toxic deaths were reported. The investigators concluded that although statistical significance was not reached, there was a trend toward improvement in outcome for patients receiving docetaxel. Although this trial is much smaller in size compared to Intergroup 9344 or NSABP-B-28, the trial design did control for the total number of chemotherapy cycles administered (n>8).

17.1.2.2 BCIRG 001

The Breast Cancer International Research Group (BCIRG) 001 trial is a randomized clinical trial that compared a simultaneous taxane–anthracycline regimen to an anthracycline-based regimen [29]. Patients were randomized to receive one of two chemotherapeutic regimens, FAC or TAC, for 6 cycles. Patients were stratified according to the number of positive axillary lymph nodes (1–3 or 4+). At the completion of the 6 cycles of chemotherapy, patients on both treatment arms were offered adjuvant tamoxifen and radiation according to each center's guidelines. Major eligibility criteria included a good performance status, age <70 years and positive axillary lymph nodes. The primary endpoint of the study was DFS, and two secondary endpoints were overall survival and toxicity.

A total of 1,491 patients with axillary node-positive breast cancer were enrolled. More than 50% of the patients in both arms had a T2 tumor, and 62% had 1–3 lymph nodes positive for breast cancer. After a median follow-up of 33 months, the DFS for the TAC arm was 82% compared to 74% for the FAC arm ($P>0.0011$), a difference representing a 36% relative risk reduction (Cox-multivariate model). There were 170 events in the FAC arm vs. 119 events in the TAC arm. Furthermore, OS was 92% in the TAC arm and 87% in the FAC arm, a difference representing a 29% relative risk reduction by the Cox model ($P>0.049$).

In contrast to many previous clinical trials, the greatest absolute benefit derived from TAC for both reducing risk of recurrence and death was in the lower risk, better prognosis group of patients. The greatest benefit for TAC chemotherapy appears in the patients with 1–3 positive lymph nodes (DFS 90 vs. 79%; $P>0.002$) compared to no significant difference between the two regimens in patients with four or more positive axillary lymph nodes (69 vs. 67%; $P>0.33$). Similarly, OS was higher in the TAC-treated patients with 1–3 positive axillary lymph nodes (96 vs. 89%; $P>0.006$), whereas it did not differ within groups in the patients with four or more positive lymph nodes (86 vs. 84%; $P>0.75$). Furthermore, hormone receptor-positive and hormone receptor-negative patients benefited from TAC chemotherapy compared to FAC, with a similar relative risk reduction (38% in HR- vs. 32% in HR+ patients). These results contradict the notion that taxanes benefit primarily the patients with hormone receptor- negative breast cancer (Intergroup 9344, NSABP B-28).

The toxicity profile of the two regimens favored FAC, since patients receiving TAC were more likely to experience febrile neutropenia (23.9 vs. 2.4%) and anemia. At the same time, there were no deaths related to toxicity reported in either treatment arm. Other toxicities seen more frequently in the TAC arm were diarrhea, stomatitis, and weakness, while nausea and vomiting were seen more frequently in patients treated with FAC. Interestingly, a significantly higher percentage of premenopausal women became amenorrheic following TAC chemotherapy compared to FAC (51.4 vs. 32.8%).

After reviewing the preliminary data from these clinical trials, it is apparent that the precise role of the taxanes in the adjuvant treatment of breast cancer remains to be defined. There is some evidence from retrospective analyzes that the benefit of taxanes in HR-positive patients is limited. Hayes et al. performed a retrospective analysis for a subgroup of patients who participated in the Intergroup 9344 trial. Their results showed that patients with HER2-positive tumors benefited from paclitaxel regardless of their HR status. However, in HER2-negative patients, paclitaxel only benefited the HR-negative patients [30]. Furthermore, data from the CALGB analyzed retrospectively showed that chemotherapy was of little or no benefit in LN-positive and HR-positive patients [31]. These data are retrospective and therefore should be interpreted with caution. The evidence available thus far suggests that the taxanes will likely provide an incremental improvement in outcome for patients with early stage breast cancer. The optimal regimen and the patient characteristics that are best suited for a taxane-containing regimen requires further study.

17.1.3 Intergroup Trial C9741/CALGB Trial 9741

The concept of dose-dense chemotherapy, administering the drugs with a shortened inter-treatment interval, is based on the observation that a given dose of chemotherapy always kills a certain fraction of exponentially growing cancer cells [32]. Because human cancer cells grow by nonexponential Gompertzian kinetics, more frequent administration of cytotoxic agents would be more effective in minimizing residual tumor burden compared to dose-escalating chemotherapy [33]. To test this hypothesis, the CALGB performed a study on women with axillary node-positive breast cancer [34] using a 2×2 factorial design. A total of 2,005 patients were randomly assigned to receive one of the following regimens: (1) sequential A (60 mg/m^2)×4 →T (175 mg/m^2)×4→C×4 with doses administered every 3 weeks, (2) sequential A×4 →T×4 →C×4 with doses administered every 2 weeks with filgrastim, (3) AC×4 →T×4 with doses administered every 3 weeks, or (4) A C×4 →T×4 with doses administered every 2 weeks with filgrastim.

The patients randomized had a median age of 50 years, 65% had ER-positive tumors, and the median number of axillary lymph nodes involved was three. At a median follow-up of 36 months, there was a statistically significant improvement on DFS for the dose-dense regimen (every 2 weeks) compared with the every 3-week regimen (4-year DFS 82 vs. 75%, respectively; RR > 0.74; $P > 0.01$). Overall survival was also improved in the dose-dense arm, but did not reach statistical significance (3-year OS 92 vs. 90%, respectively; RR > 0.69; $P > 0.013$).

The toxicity profile of the three regimens did not differ significantly. The number of cycles delayed ranged from 6–8%, whereas overall, only 3% of patients were hospitalized with febrile neutropenia, and grade 4 granulocytopenia was more frequent in the every 3-week regimen compared to the dose-dense, every 2-week regimens (33 vs. 6%; $P<0.0001$). The percent of patients requiring RBC transfusions was higher in the concurrent dose-dense arm, with 13% of patients requiring at least one RBC transfusion. The use of dose-dense chemotherapy with the concurrent use of filgrastim has raised the concern that the incidence of MDS/AML would increase. However, the 3-year incidence of AML/MDS was 0.18% and was similar within the four treatment arms and comparable to other adjuvant therapy programs with long follow-up.

The results of this trial are very encouraging for the incorporation of dose-dense chemotherapy with this regimen in every day practice for women with axillary node-positive breast cancer. The regimen offers a survival advantage compared with the standard every-3-week regimen and is not associated with increased side effects. It may still be early to definitively conclude that the dose-dense regimen is not associated with increased risk of AML/MDS since the follow-up period was 3 years.

17.1.4 Metaanalysis of Taxane-Based Combination Trials

A recent meta-analysis was performed to quantify the benefit from adjuvant taxane therapy as well as to perform subset analyzes in patient populations [35]. Of thirteen trials and 22,903 patients identified for the meta-analysis, it was determined that the addition of a taxane to an anthracycline-containing regimen significantly improved DFS (HR: 0.83; 95%CI 0.79–0.87; $P<0.00001$) and OS (HR: 0.85; 95%CI 0.79–0.91;

$P<0.00001$), with an absolute improvement of 5% in DFS and 3% in OS. The investigators also found that the benefit from taxanes was significant for both ER+ and ER-patients, and was independent of whether paclitaxel or docetaxel was used. Finally, the number of positive axillary lymph nodes did not influence the benefit from taxanes since the benefit was similar in patients with one to three positive lymph nodes and for patients with four or more positive lymph nodes.

17.1.5 New Chemotherapy Combinations in Early Stage Breast Cancer

The success of gemcitabine (G) in combination with taxanes in the treatment of metastatic breast cancer has led to its incorporation in clinical trials for early stage breast cancer [36]. The NSABP B38 trial, which compares TAC and AC→T with AC→TG has already completed enrollment. Most recently, the results of the TANGO (Pacli*t*axel, *An*thracycline, *G*emcitabine and Cycl*o*phosphamide) trial were presented. This was a randomized phase III trial comparing EC→T (Epirubicin 90 mg/m^2, Cyclophosphamide 600 mg/m^2 every 21 days for 4 cycles followed by Paclitaxel 175 mg/m^2 every 21 days for 4 cycles) with EC→TG (G > Gemcitabine 1,250 mg/m^2 day 1 and 8 of 21 days for 4 cycles). With a total of 3,152 patients enrolled and median follow-up of 34.9 months, there was no significant difference in DFS (HR > 1.0 (95% CI 0.8–1.2), which was the primary endpoint of the trial, or OS (HR > 1.1 (95% CI 0.9–1.4). Toxicity was acceptable in both arms with a higher incidence of neutropenia in the investigational arm (34 vs. 27%; $P<0.0001$). Although the results of the NSABP B38 trial are still not available, the enthusiasm for the use of gemcitabine in early stage breast cancer is limited.

17.1.6 Preoperative Chemotherapy

Preoperative (also primary or neoadjuvant) chemotherapy was initially used for locally advanced disease. However, in recent years, the use of preoperative chemotherapy has become widely used for operable disease, especially in tumors that are considered to be larger than 2 cm in diameter [37]. Initial randomized trials evaluated the efficacy of neoadjuvant chemotherapy in relation to adjuvant chemotherapy. These trials showed that there is no difference in benefit between preoperative and adjuvant chemotherapy in terms of clinical outcomes. The first large randomized trial to compare preoperative with adjuvant chemotherapy in patients with operable breast cancer was the NSABP B-18 trial [38]. This trial assigned 751 patients to receive preoperative AC and 742 patients to receive postoperative AC. In its most recent update and a follow-up of 16 years, there was no difference in DFS (HR: 0.93; 95%CI 0.81–1.06; $P>0.27$) or OS (HR: 0.99; 95%CI 0.85–1.16; $P>0.90$) between the two treatment arms [39]. The objective clinical response in the preoperative AC group was 79%. A pathologic complete response (pCR) was documented in 13% of patients. Individuals who achieved pCR had a superior DFS and OS compared with patients who did not achieve pCR (DFS HR: 0.47, $P<0.0001$; OS HR: 0.32, $P<0.0001$). Since then, several other trials have been reported on the use of preoperative chemotherapy in operable breast cancer.

17.1.6.1 NSABP B-27

Several of the most recent studies investigated the potential contribution of taxanes administered in primary chemotherapy regimens. The NSABP B-27 trial randomized patients with early stage, operable breast cancer to one of three treatment arms: (1) preoperative AC × 4, followed by surgery and no additional adjuvant chemotherapy; (2) preoperative AC × 4, followed by docetaxel × 4, followed by surgery and no additional chemotherapy; or (3) AC × 4, followed by surgery, followed by adjuvant docetaxel × 4 [39]. Tamoxifen for 5 years was offered to patients with hormone receptor-positive breast cancers. The trial enrolled patients with operable breast cancers (T1c-T3, N0/N1, M0). Patients were stratified according to age, tumor size and clinical nodal status. A total of 2,411 patients were randomized to the three treatment arms. In its most recent update [39] and a median of 8 years of follow-up, there was no difference in DFS according to treatment arms (group 2 vs. group 1: HR:0.92; 95%CI 0.78–1.08, $P>0.29$; group 3 vs. group 1: HR:0.92, 95%CI 0.78–1.08, $P>0.29$). Similarly, there was no difference in OS between the treatment arms. However, when comparing response rates, AC produced a RR of 86%, whereas the addition of docetaxel significantly

increased the response rate to 91% ($P<0.001$). The rate of pCR was also increased with the addition of the taxane from 13% with AC to 26% in group 2 ($P<0.001$). As seen in NSABP B18, pCR was a predictor of improved DFS (HR: 0.49, $P<0.0001$) and OS (HR:0.36, $P<0.0001$).

17.1.6.2 GEPAR-DUO Study

Von Minckwitz et al. [40] reported the results of a randomized clinical trial evaluating preoperative, dose-dense doxorubicin/docetaxel vs. sequential doxorubicin/docetaxel as preoperative chemotherapy in operable breast cancer. A total of 913 patients with primary operable breast cancer (T2-3, N0-2, M0) were randomized between dose-dense doxorubicin/docetaxel × 4 (50/75 mg/m^2 every 14 days, with G-CSF support) or AC × 4 (60/600 mg/m^2) every 21 days, followed by docetaxel (100 mg/m^2) × 4, every 21 days. The pCR was 14.3% in the sequential treatment arm vs. 7.0% in the dose-dense arm (HR: 2.22; 90% CI, 1.52–3.24; $P<0.0001$). The response by imaging methods was 78.6% in the sequential arm and 68.6% in the dose-dense arm (HR: 1.68, 95% CI 1.24–2.29, $P<0.001$). The breast conservation rate was also superior for the sequential treatment arm compared to the dose dense treatment arm (75.1 vs. 65.3%; $P<0.005$). Both regimens were well tolerated, but the rate of neutropenia was higher in the sequential arm compared to the dose-dense arm (66.4 vs. 44.7%). One issue that is not addressed by the design of the study is whether the difference in efficacy between treatment arms can be explained by difference in the number of chemotherapy cycles administered (4 vs. 8).

17.1.6.3 Aberdeen Study

The Aberdeen study [41] was designed to evaluate the efficacy of preoperative docetaxel compared to anthracycline-based treatment. Additionally the study was designed to evaluate the efficacy of neoadjuvant docetaxel in patients initially failing to respond to neoadjuvant anthracycline-based chemotherapy. Patients with a large primary tumors (≥3 cm) or locally advanced tumors were eligible. A total of 162 patients initially received 4 cycles of neoadjuvant chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisolone (CVAP). Patients who did *not* achieve an objective response to 4 cycles of CVAP received four additional cycles of docetaxel (100 mg/m^2). Patients who achieved a clinical response to CVAP were randomized to either four additional cycles of CVAP or 4 cycles of docetaxel. At the end of treatment (8 cycles), patients underwent surgery. After 4 cycles of CVAP, the overall clinical response rate (complete response and partial response) was 66%. In the responding patients, 4 additional cycles of docetaxel resulted in a significantly enhanced clinical response rate compared with those receiving 4 additional cycles of CVAP (94 vs. 66%; $P>0.001$). Furthermore the administration of docetaxel to patients with tumors initially responsive to CVAP resulted in significantly increased pCR (30.8 vs. 15.4%). The incidence of hematologic toxicities, especially leukopenia and granulocytopenia was higher in patients receiving 8 cycles of CVAP. In patients who failed to respond to the initial CVAP therapy, treatment with 4 cycles of CVAP resulted in an objective response rate of 55% and a pCR rate of 2%.

17.1.6.4 MD Anderson Study

Green and colleagues presented the initial results of a study in which patients with stage I-IIIa breast cancer were randomized to receive either weekly paclitaxel for 12 doses or paclitaxel every 3 weeks for 4 cycles, followed by standard FAC chemotherapy for 4 cycles [42]. The weekly dose of paclitaxel was based on the axillary nodal status of the patient: axillary node-negative patients received 80 mg/m^2/week × 12 and axillary node-positive patients received 150 mg/m^2/week, 3 weeks out of 4. The every-3-week schedule of paclitaxel was administered at 250 mg/m^2 as a 24-h infusion. Surgery was not undertaken until all systemic chemotherapy had been administered. Results from the 258 patients enrolled in the study showed a statistically significant improvement in the pCR rate with weekly paclitaxel treatment, regardless of nodal status (pCR rate > 28% for node-positive patients and 29.4% for node-negative patients), followed by FAC compared to the standard 3-weekly schedule of paclitaxel followed by FAC (pCR rate > 13.7% for node-positive patients and 13.4% for node-negative patients). These findings support the notion of schedule dependency of paclitaxel and also reaffirm that the incorporation of taxanes into primary chemotherapy regimens may improve pCR rates. If a pCR is a surrogate marker for

improved survival, regimens with highest pCR rate should be considered the optimal preoperative and/or adjuvant chemotherapy program.

17.1.6.5 AngloCeltic Trial

In this trial, 363 patients with large primary tumors (3 cm or more) were eligible to receive preoperative chemotherapy with either AC (doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2) every 3 weeks for 6 cycles or AT (doxorubicin 60 mg/m^2, docetaxel 75 mg/m^2) every 3 weeks for 6 cycles [43]. The complete pathologic response rates (pCR) were similar in the two groups (17% with AC and 20% with AT; $P>0.42$), and there was a trend to improvement in overall clinical response rate favoring the AT arm (70 vs. 61%; $P>0.06$).

The preoperative chemotherapy approach provides a useful model to investigate the antitumor activity of novel therapeutic approaches and to address biologic questions through the availability of sequential tissue sampling. Although it is still too early to come to any conclusion about a survival advantage with the use of taxanes in the neoadjuvant setting, these trials point to interesting observations. The use of taxanes preoperatively appears to increase clinical response as well as pCR rate. It has been shown in some trials that pCR is associated with increased DFS and subsequently OS. It seems plausible that the use of taxanes preoperatively may confer a survival advantage to patients with early stage breast cancer, but only the completion and maturation of large data sets will definitely address this issue. More importantly, the use of preoperative chemotherapy may identify patients with tumors resistant to anthracyclines and who might benefit more from non-cross resistant, adjuvant therapy. In the future, it may be possible to identify molecular markers that predetermine sensitivity and resistance to certain therapeutic approaches. The opportunity to obtain tissue samples, before and after systemic treatment is administered, provides a "laboratory" for evaluating molecular markers. In the meantime, women who are offered preoperative chemotherapy should ideally enter a clinical trial.

17.1.6.6 High Dose Chemotherapy

The rationale behind the use of high-dose chemotherapy (HDC) necessitating stem cell support comes from the work of Skipper, Schabel and Frei [44–46]. Skipper's rules summarize the scientific rationale for using HDC and stem cell support [47].

Rule 1- "The total tumor-cell-kill hypothesis": In order to achieve cure, it is necessary to eradicate all sensitive and resistant cancer cells.

Rule 2- "The dose response and first kinetics hypothesis": This rule states that a single dose of a specific chemotherapeutic regimen will kill a certain fraction of tumor cells. Therefore, administering a chemotherapy agent with a steep dose-response curve provides an advantage in achieving maximal cancer cell death.

Role 3- "The inverse rule": This rule states that there is an inverse correlation between the total cancer cell burden and the curability by chemotherapy.

These three rules helped investigators design an optimal setting for the use of HDC. Using a combination of chemotherapeutic agents, performing the procedure at the lowest possible tumor burden and using high doses of the chemotherapeutic agents provide the ideal scenario.

The relationship of HDC and breast cancer has been a turbulent one. In the early to mid 1990s, a large number of women diagnosed with breast cancer were offered HDC followed by autologous stem cell transplantation for their breast cancer. In 1994 and 1995 alone, 4,503 transplants were performed, whereas in 1996 and 1997, the number reached 5,695 [48]. There was also a trend toward offering transplant to individuals with earlier stage disease. While in 1989, only 7% of patients undergoing transplantation had localized disease, this number increased to 49% in 1995 [49]. However, only a small number of patients receiving transplantation for breast cancer did so in the context of a clinical trial. However, the enthusiasm for HDC/ASCT in breast cancer came to an end due to results of clinical trials presented at the 1999 American Society of Clinical Oncology (ASCO) meeting, showing the HDC approach offered no better outcomes for patients compared to those receiving standard dose adjuvant chemotherapy. In addition, the highly publicized discrepancies, found after an audit in the trials presented by Bezwoda and his colleagues, fueled the skepticism regarding the benefit associated with HDC. Media coverage portrayed the available results in the most negative way. Subsequently, trials that were ongoing at that time were unable to accrue patients and had to close prematurely.

There are still several unanswered questions regarding the role of transplantation. To achieve adequate statistical power to answer these questions, large randomized multicenter trials would be required, so it seems unlikely at the present time that these questions will ever get answered.

Patients were eligible if they had >10+axillary lymph nodes or 4–9+axillary lymph nodes with poor prognostic features. Adjuvant chemotherapy with either single agent doxorubicin (75 mg/m^2 every 3 weeks for 4 cycles) or CAF (described previously) for 4–6 cycles was administered. All 132 patients received HDC with Stamp V (cyclophosphamide 1,500 mg/m^2 CI + thiotepa 125 mg/m^2 CI + carboplatin 200 mg/m^2 CI × 96 h). There were no treatment-related deaths and with median follow-up of 51 months, the DFS and OS were 72 and 81%, respectively.

17.1.7 Phase III Trials in Early Stage Breast Cancer

Several Phase III trials incorporating HDC have been completed to date. Although several of the trials did not reach their accrual goal, it has become apparent that HDC does not provide an advantage in early stage breast cancer. Furthermore, the toxic nature of the regimens used provides another reason for not incorporating HDC in the treatment of early stage breast cancer.

17.1.7.1 ECOG

A phase III trial conducted by the Eastern Cooperative Oncology Group (ECOG) was published after a median follow-up of 6.1 years [50]. In this study, women with ten or more positive axillary lymph nodes were eligible to be randomized to conventional chemotherapy vs. HDC/SCT. Patients in the conventional therapy arm received cyclophosphamide 100 mg/m^2 p.o. per day given at days 1–14, doxorubicin 30 mg/m^2 i.v. given on days 1 and 8 and 5-FU 500 mg/m^2 i.v. given on days 1 and 8 (CAF) every 28 days for 6 cycles. Patients in the HDC/SCT arm received CAF followed by a continuous infusion of cyclophosphamide 6 g/m^2 and thiotepa 800 mg/m^2 over a 4-day period. The HDC was given on days 6, 5, 4 and 3 before the infusion of the stem cells. Both groups received breast irradiation and tamoxifen as indicated. Of the 540 patients enrolled, 511 were included in the analysis (the analysis was not an intention-to treat analysis). An additional 94 patients had minor protocol violations and the investigators performed two analyzes according to the inclusion, or not, of these patients. Nine patients (4%) died between day 2 and 55 of the transplant and another nine developed myelodysplastic syndrome or acute leukemia in the transplant arm. There was no statistical difference between standard chemotherapy and the HDC treatment arms with respect to DFS (47 vs. 49%), OS (62 vs. 58%) and TTR (48 vs. 55%). However, when analyzing only the 417 patients who did not have any protocol violations, TTR was improved by 10% in the HDC/SCT arm (45 vs. 55% respectively) ($P > 0.045$) [50]. This large phase III trial did not show any benefit in performing stem cell transplant as part of the adjuvant treatment of women with high-risk breast cancer. The high incidence of treatment-related mortality and occurrence of secondary MDS/acute leukemia may be one of the reasons for the lack of effect observed in this study. Therefore, the development of less toxic preparative regimens could potentially show a benefit for HDC followed by stem cell rescue in resectable breast cancer. This study may also have been underpowered to detect a small difference between the two treatment arms. It will be up to the treating physicians and especially the patients to decide what a meaningful improvement in survival is, given the increased toxicity with the addition of HDC/SCT in breast cancer.

17.1.8 Trials with Allo-Transplants in Breast Cancer

Until recently, there has been little interest in pursuing allogeneic transplants as therapies for breast cancer. This lack of interest was based on the negative trials utilizing HDC/SCT in metastatic and resectable breast cancer. However, the most important reason was the toxicities associated with allogeneic transplantation. There is some evidence clinically for a graft-vs.-tumor (GVT) effect in breast cancer. A patient with inflammatory breast cancer who developed graft-vs.-host disease (GVHD) after a HLA-matched allogeneic

transplant, was noted to have complete resolution of her liver metastases [51]. Another small trial performed at MD Anderson Cancer Center examined the use of allogeneic peripheral blood stem cell transplantation in ten patients with poor-risk metastatic breast cancer. Patients received a conditioning regimen with cyclophosphamide, carmustine and thiotepa (CBT), and GVHD prophylaxis with either cyclosporine- or tacrolimus-based regimens [52]. Three patients developed acute GVHD, and four developed chronic GVHD. One patient had a CR, five had PRs, and four had stable disease. In two patients, metastatic liver lesions regressed in association with GVHD, upon withdrawal of immunosuppressive therapies [52]. Median PFS was 238 days. These results suggest that there may be a GVT effect in breast cancer, and support the evaluation of less toxic nonmyeloablative techniques.

Curently, there is little interest in allogeneic bone marrow transplant and breast cancer. However, with improvement in the toxicity profile of the myeloablative regimens, there may still be a role for studying this approach.

17.1.9 Conclusions

Several trials have so far been reported on the use of HDC/SCT in women with high-risk and metastatic breast cancer. These trials, as a whole, have not shown a convincing benefit for the role of this treatment modality. Potential explanations for negative results include inadequate number of patients enrolled in the trials, the high toxicity rate associated with HDC in the studies or flaws in study design. It seems plausible that HDC may be the treatment of choice for certain subpopulations of patients with breast cancer. Longer follow-up of these studies may provide us with a clearer picture of the role of HDC in the treatment of breast cancer. In the meantime, the emergence of new chemotherapeutic agents, such as the taxanes, and the use targeted therapy with monoclonal antibodies and small molecule tyrosine kinase inhibitors show more promising results for future study design. Future studies in the area of HDC/SCT in breast cancer will have to overcome the negative history associated with this treatment modality. However, available research suggests a possible role for nonmyeloablative allogeneic transplants in breast cancer. Nevertheless, HDC/ASCT should not be recommended to women with breast cancer outside the context of a clinical trial.

17.1.10 The Use of Genomics in Breast Cancer

The use of DNA microarrays in breast cancer has provided us with useful information about different breast cancer subtypes [53]. Perou and colleagues used a method of hierarchical clustering. This technique is used to group genes on the basis of similarity in the pattern with which their expression varies over the tumor samples, which are used. By performing hierarchical clustering, investigators were able to classify the breast tumors into subtypes distinguished by their different gene expression profile. This way, investigators were able to identify at least four groups of tumors that had different molecular features. Those four groups were: (1) luminal-type, (2) basal-type, (3) ERBB2+ and (4) normal breast. The luminal subtype is the most common subgroup and makes up the hormone receptor-expressing breast cancers, whereas the basal and ERBB2 subtypes are characterized by lack of expression of the hormone receptor genes.

The need for a clinically useful genomic test, which includes a small number of genes and can predict both prognosis and treatment response, led investigators to the development of several platforms, which are currently used in practice. These platforms include an assay based on 70 genes (MammaPrint®), a 76- gene assay, Onco*type* Dx, an assay based on wound response, the two-gene assay and an assay based on intrinsic subtypes. All these assays incorporate a unique gene set and have been validated. Recently, investigators compared the predictions derived from these gene sets [54] and although the gene set for each of these assays was different, all, but the two-gene assays, were able to identify significant outcome differences within a dataset. Furthermore, when comparing MammaPrint® to Onco*type* DX, the two tests currently used more in clinical practice, there was a 77–81% concordance.

17.1.11 70-Gene Assay (MammaPrint®)

Researchers from the Netherlands developed an inkjet-synthesized oligonucleotide microarray based on 70 genes with which they were able to classify breast cancer patients into a good-signature and poor-signature group [55]. Furthermore, using samples from 295

patients with breast cancer, the same researchers were able to validate their assay [56]. This assay is based on young (≤52 years of age) patients with a <5 cm primary breast cancer independent of axillary lymph node status. Individuals with a poor signature were found to have a 4.6 higher risk of developing distant metastases compared to the good-signature group in a multivariable model. Furthermore, this model was found to be predictive of distant metastases both in lymph node-positive and –negative patients. The value of this model also lies in the fact that both hormone receptor-positive and –negative patients were included. However, a disadvantage of this test is the fact that it can only be performed on fresh frozen tissue and therefore, planning at the time of surgery is needed. This test is being used in a prospective clinical trial in Europe called MINDACT (*M*icroarray for *N*ode negative *D*isease may *A*void *C*hemo*T*herapy).

17.1.11.1 76-Gene Assay

Wang et al. [57] used 115 node-negative cancers to develop a 76-gene assay and then validated it in an independent sample of 171 breast cancers. This signature had a hazard ratio of 5.55 (95% CI, 2.3–9.2) and outperformed all univariate tests. The same investigators validated this assay in a more diverse population of lymph node-negative patients obtained from multiple institutions [58]. More specifically, tissue was obtained from 180 lymph node-negative patients who had not received adjuvant systemic treatment and from 55 ER+ lymph node-negative patients who had received tamoxifen. In the sample of the 180 patients, the 76-gene signature gave a hazards ration of 7.41, with a sensitivity for distant metastasis-free survival (DMFS) of 90% and a specificity of 50%. In the 55 ER+, tamoxifen-treated dataset, the hazard ratio was 6.15, with a sensitivity of 80% and a specificity of 40% for DMFS. Interestingly, when looking at the 70-gene assay and the 76-gene assay, only three genes appear in both datasets.

Recently, the concordance among different gene-expression predictors was evaluated [54]. Five gene-expression-based models were compared in a dataset of 295 samples. The models tested were the recurrence score (RS) [59], the 70-gene profile [55], the intrinsic subtypes [53], as well as the wound response [60] and the two-gene ratio [61]. The investigators found that most of the models had high rates of concordance in their outcome predictions. The 70-gene profile and the RS had a high degree of agreement (77–81%). The above findings confirm that there probably is no "standard" predictive gene profile in breast cancer and that several gene sets can provide useful clinical information.

Onco*type* DX is based on measurement of gene expression from frozen, paraffin-embedded (FPE) tissue [62]. After RNA extraction from FPE, primers and probes for the specific genes are used to quantitate RNA expression by RT-PCR. The expression of each gene is measured in triplicate and then normalized relative to a set of five reference genes (ACT [the gene encoding β-actin], GAPDH, GUS, RPLPO, and TFRC). The assay uses 21 genes and calculates a RS. These genes came from the final analysis of three independent studies involving 447 patients and 250 candidate genes [63–65]. The study by Cobleigh et al. [65] included 79 patients with invasive breast cancer and ten or more positive axillary lymph nodes. RNA expression of seven reference genes and 185 cancer-related genes was performed. In a second study by Esteban and his colleagues [63], 146 lymph node-positive and –negative patients with invasive breast cancer were selected. The same genes were selected as in the previous study. In both of these studies, there were several genes that had a significant association with DFS. In the third study, conducted by Paik et al. [64], the results of the previous two studies were taken into account and 234 patient blocks from the NSABP B-14 and B20 studies were evaluated. Paik and his colleagues were able to identify the final 21 genes, which included 16 cancer-related genes and five reference genes. The RS ranges from zero to 100 and patients are divided into three different risk categories: (1) Low-risk group (RS 0-17); (2) Intermediate-risk group (RS 18–30); (3) High-risk group (RS 31–100).

17.1.12 *Clinical Data*

17.1.12.1 Initial Studies

The 21-gene assay was validated using samples from patients participating in the NSABP B-14 trial [59, 66]. This trial included patients with ER, lymph node-negative breast cancer. This trial was performed on 668 patient samples available from the original trial. The overall group had a distant recurrence-free survival of 85%. Fifty one percent of patients were classified as low-risk, 22%

as intermediate-risk and 27% as high-risk. Subsequently, Kaplan-Meier estimates for the proportion of patients who were free of a distant recurrence at 10 years were calculated. The resulting estimate for rate of distant recurrence for the low-risk group (6.8%) was significantly lower than the rate in the high-risk group (30.5%) ($P<0.001$), validating this risk assessment tool [59]. Furthermore, a multivariate model, including known risk factors such as age at surgery, tumor size and grade, ER and HER2 amplification, showed that the RS was the strongest predictor of risk of distant recurrence (HR 2.81; 95% CI 1.70–4.64) compared with the other risk factors, and all other factors did not have a significant association with risk of recurrence. However, two subgroups of patients were underrepresented in this study; only 59 patients were under the age of 40 and only 34 patients had tumors over 4 cm in largest diameter. Furthermore, only 109 patients had tumors under 1 cm. Therefore, the results of this study should be interpreted with caution in these two patient subgroups. However, in the rest of the population, these results clearly show the emergence of a new predictive model for women with ER-positive, axillary lymph node-negative breast cancer.

Another validation study used patient samples from the Northern California Kaiser Permanente tumor registry [67]. Breast cancer patients were eligible if they had axillary lymph node-negative disease, were under the age of 75 and had not received adjuvant chemotherapy for their disease. Cases were patients ($n>220$) who died of breast cancer. Controls ($n>570$) were individually matched to the cases by age, race, year of diagnosis, place of origin and adjuvant tamoxifen therapy, and were individuals who were alive at the date of death of their matched case. The relative risk of death in ER-positive patients on tamoxifen was 2.8% in the low-risk patients, 10.7% in intermediate-risk patients and 15.5% in high-risk patients, whereas in tamoxifen-untreated patients, the risk of death was 6.2, 17.8 and 19.9%, respectively.

However, a third study [68], including 149 samples from patients with breast cancer failed to confirm the above correlations. More specifically, 149 patients with stage I or IIA breast cancer, who had undergone definitive surgery between 1978 and 1995 at the University of Texas MD Anderson Cancer Center, were included in this study. Selection criteria included no prior adjuvant chemotherapy or tamoxifen therapy, follow-up of at least 5 years and availability of tumor tissue. The patient database included both ER- positive and ER- negative patients, and the majority of the patients (84.6%) were Caucasian. There was no significant correlation between RS and 10-year RFS. However, other parameters that are traditionally associated with RFS, such as tumor grade, tumor size and age also did not correlate with it. Potential explanations for the above findings include: data was generated from a single institution, potentially leading to selection bias and the inclusion of ER-negative patients. Furthermore, when examining the association of tumor grade with recurrence, there was a correlation between high nuclear grade tumors and improved outcome, which is contrary to other studies.

17.1.12.2 Response to Endocrine Therapy

Another question that the same group of researchers attempted to answer was whether there was a benefit from adjuvant tamoxifen in the different risk groups [69]. The NSABP B-14 trial, in which patients with ER - positive tumors were randomized to receive tamoxifen or placebo, was used as the dataset for this analysis. Of the 2,817 patients who were randomized to the trial, 645 were evaluable for this study. Patient characteristics and clinical outcomes were similar to the overall population. In the low RS group, the addition of tamoxifen significantly improved DRFS (85.9% DRFS in the placebo arm vs. 93.1% DRFS in the tamoxifen arm; $P>0.04$). In the intermediate RS group, tamoxifen again was found to be beneficial (62.2% DRFS in the placebo arm vs. 79.5% DRFS in the tamoxifen arm; $P>0.02$). However, in the high RS group, there appeared to be a smaller benefit from the addition of tamoxifen (68.7% DRFS in the placebo arm vs. 70.3% DRFS in the tamoxifen arm; $P>0.82$). Although these results are intriguing, clinicians may be hard pressed to deny tamoxifen therapy to their patients based on these results.

17.1.12.3 Response to Chemotherapy

In a follow-up study, investigators assessed the ability of the assay to predict the response to adjuvant chemotherapy [70]. To validate whether the RS would predict chemotherapy benefit, tumor samples were selected from the NSABP B-20 protocol. According to this protocol, patients with node-negative, ER-positive breast cancer were randomized into three groups: In the first group, patients received adjuvant chemotherapy with CMF followed by tamoxifen; in the second group, patients received adjuvant MF chemotherapy (methotrexate, 5-FU) followed by tamoxifen; in the third group, patients

received adjuvant tamoxifen without any chemotherapy. Out of 2,299 patients participating in the NSABP B-20 trial, paraffin-embedded blocks were available in 651 patients. The subset of patients for which paraffin-embedded blocks were available had similar clinical characteristics and outcome to the overall population. The primary endpoint of the study was DRFS, whereas secondary endpoints of the study were RFS and OS. Onco*type* DX was performed on 651 patient samples, with 54.2% being in the low-risk, 20.6% in the intermediate-risk and 25.2% in the high-risk group. When patients were divided into the three risk groups (high-, intermediate- and low-risk groups), patients in the low-risk group had little, if any, benefit from the addition of chemotherapy (95.6% DRFS in the chemotherapy arm vs. 96.8% DRFS in the tamoxifen-alone arm; $P>0.61$). Additionally, in the intermediate-risk group, the addition of chemotherapy did not show any significant benefit (89.1% DRFS in the chemotherapy arm vs. 90.9% DRFS in the tamoxifen alone arm; $P>0.39$). However, in the high-risk group, the addition of chemotherapy significantly improved DRFS (88.1% DRFS in the chemotherapy arm vs. 60.5% DRFS in the tamoxifen alone arm; $P<0.0001$). Furthermore, when analyzing the two chemotherapy groups separately, the benefit was similar regardless of the chemotherapy administered. This finding changed our clinical practice. Several patients to whom we offer adjuvant chemotherapy may actually not benefit from it. However, when looking at the relative benefit from chemotherapy in the three groups, the data on the intermediate group do not exclude a potential benefit from chemotherapy. More specifically, the mean relative benefit from chemotherapy in the low-risk group was 1.31 (95% CI 0.46–3.78) (Values over one point toward no benefit from chemotherapy, whereas values below one suggest a benefit from chemotherapy), showing a clear lack of benefit with the addition of chemotherapy; in the high-risk group, the benefit was 0.26 (95% CI 0.13–0.53), showing a clear benefit of chemotherapy; however in the intermediate-risk, group the benefit was 0.61 (95% CI 0.24–1.59). Although the result for patients in the intermediate-risk group was not statistically significant, the mean value was below one, pointing toward the possibility of a benefit in that subgroup of patients. Finally, when assessing individual genes, there was a trend toward increased benefit from chemotherapy with higher expression of proliferation genes and lower expression of the ER group genes.

Most recently, data were presented using genomic assays in women with axillary node-positive disease. The SWOG 8814 trial consisted of 3 arms: Arm A received tamoxifen 20 mg/day for 5 years; Arm B received CAF for 6 cycles with concurrent tamoxifen, which continued for a total of 5 years; Arm C received CAF chemotherapy for 6 cycles, followed by tamoxifen for a total of 5 years. Arms A and C were included in the current analysis. In an analysis of the SWOG 8814 trial, a subset of 367 samples was included in the genomic analysis. A total of 148 samples from arm A and 219 samples from arm C were available, and although they represented a subset (40%) of the total samples from the trial, they were found to be representative of the main trial. When assessing prognosis of the groups, women with low RS had a significantly better prognosis compared with women with intermediate or high RS (10-year DFS: low RS: 60%, intermediate RS: 49%, high RS: 43%). In relation to benefit from chemotherapy, there was no significant difference between the tamoxifen and tamoxifen plus chemotherapy arm in individuals with low (10-year DFS 60 vs. 64%, respectively $P>0.97$) or intermediate RS (10-year DFS 49 vs. 63%, respectively $P>0.48$). However, women with high RS in the tamoxifen-treated arm did significantly worse compared with the tamoxifen + chemotherapy arm (10-year DFS 43 vs. 55%, respectively $P>0.033$). These results were very similar to the results from the NSABP B-20 study. In this study, 40% of the patients had a low RS, whereas 28% had intermediate and 32% had high RS. Although it is still premature to speculate on the cutoff of the chemotherapy benefit in axillary node-positive patients, it is reasonably safe to assume that women with low RS receive either no or a small benefit from adjuvant chemotherapy, whereas in women with high RS, there is a clear benefit from chemotherapy. More studies are needed to evaluate the effectiveness of chemotherapy in patients with intermediate RS. (see MINDACT and TAILORx below)

Although the above results are very exciting, there are some caveats: (1) CMF or MF is rarely used as adjuvant chemotherapy today (The use of anthracyclines and more recently taxanes, is increasing in the adjuvant setting, leading to difficulty in interpreting results where CMF was used as the standard regimen), (2) the aromatase inhibitors are now commonly used in the adjuvant setting, rather than tamoxifen alone.

To address the concern about the use of CMF chemotherapy, a recent study evaluated the significance of the RS in patients receiving neoadjuvant docetaxel [71]. A total of 72 patients were included in the study. Of the 12 patients who had CR, nine had high RS, three had an

intermediate RS, whereas no responses were observed in patients with a low RS. These results, although preliminary, confirm previous results. Another neoadjuvant trial incorporated the use of Onco*type* DX. In this trial, 89 patients received chemotherapy with an anthracycline and a taxane, and 12% achieved pCR. The likelihood of pCR was found to be significantly related to the RS. More specifically, the higher the RS, the higher the likelihood of achieving pCR [72].

17.1.13 Analysis from the TransATAC Trial

In this analysis, patients who were enrolled in the ATAC trial and were randomized to receive either tamoxifne or anastrozole were included. Patients had to be HR positive and could not have received adjuvant chemotherapy. The total number of patient blocks that were processed for this analysis was 1,308. The RS was found to be significantly correlated with disease recurrence in node-negative patients, with the low RS patients having a 96% distant recurrence-free survival (DRFS) compared with 88% and 75% in the intermediate and low RS, respectively. Similarly, the RS was predictive of DRFS in the node-positive patients (83, 72, 51%, respectively). In a subsequent analysis and when comparing patients who received tamoxifen with patients receiving anastrozole, there was a trend to a higher benefit from anastrozole in the high RS patients compared with tamoxifen. This was true in the node-negative population, whereas in the node-positive population, there did not seem to be a difference between the treatment arms. These results confirm that the RS can be used not only in women who will receive tamoxifen for adjuvant endocrine therapy but also for women who will receive an aromatase inhibitor.

17.1.13.1 Future Directions

The Intergroup has initiated a phase III clinical trial (TAILORx) based on the Onco*type* DX assay. Patients with node-negative, ER-positive breast cancer will be divided into three treatment arms depending on their RS. Patients with a low RS will be given endocrine therapy, patients with a high RS will be given chemotherapy followed by endocrine therapy, and patients in the mid-range RS category will be randomized to receive or not chemotherapy followed by endocrine therapy. The choice of chemotherapy and endocrine therapy will be left up to the treating physician. Exclusion criteria include HER2-positive tumors, and patients who are eligible for the trial have to be able to receive adjuvant chemotherapy. This is a very intriguing trial since this is one of the first attempts to prospectively incorporate genetic markers in the adjuvant therapy of breast cancer. Results from this trial will shed some light into the benefit from chemotherapy in individuals with mid-range RS. For the purpose of this trial, the cutoffs for low- (RS 0–10) intermediate- (RS 11–25) and high- RS (RS 26–100) have been more conservative. The trial design makes the assumption that there is sufficient data to conclude that there is no added benefit from chemotherapy in the low RS patients, whereas the benefit from chemotherapy is clear in the high RS patients.

In Europe, the MINDACT trial is currently open to accrual. This trial will be assessing patients on a clinical-pathological risk model as well as the 70-gene signature model. Patients found to be in the low risk category on both assessments will receive endocrine therapy. Patients found to be in the high risk category on both assessments will receive chemotherapy followed by endocrine therapy. Patients with discordant results will be randomized either taking into account the clinicopathologic features or taking into account the risk based on gene expression to receive or not chemotherapy followed by endocrine therapy.

17.2 Role of Adjuvant Endocrine Therapy

Until very recently, tamoxifen has been viewed as the optimal and only choice for adjuvant endocrine therapy. Data from the EBCTCG overview analysis reported a 50% relative reduction in the risk of relapse and a 28% relative reduction in the risk of death in ER-positive patients treated with 5 years of tamoxifen [5]. This benefit was observed regardless of menopausal or lymph node status and in those women receiving and not receiving chemotherapy. There was no such benefit documented in ER-negative cancers receiving tamoxifen. Tamoxifen has also been associated with a 47% reduction in the risk of developing contralateral breast cancer{1998 65 /id}.

Because the risk for breast cancer recurrence continues for an indefinite period following treatment, there has been great interest in defining the optimal duration

and composition of endocrine therapy. Multiple trials have established that 5 years of treatment is superior to 1 or 2 years{1998 65 /id}. Data from clinical trials has also shown that more than 5 years of tamoxifen appears to convey no additional benefit over 5 years of treatment.{1998 65 /id;Fisher, 1996 75 /id} The NSABP B-14 trial evaluated the role of adjuvant tamoxifen in axillary node-negative patients. Patients receiving 5 years of tamoxifen were re-randomized to continued tamoxifen or placebo. After 7 years of follow-up, DFS in the placebo arm (82%) was better than in the continued tamoxifen arm (78%) ($P>0.03$). Overall survival was 94% for women who received 5 years of tamoxifen therapy and 91% for women who received tamoxifen for greater than 5 years ($P>0.07$). There is also concern about increasing toxicity with longer durations of tamoxifen therapy and the development of tamoxifen resistance. Both the ATLAS (Adjuvant Tamoxifen-Longer Against Shorter) and ATTOM (Adjuvant Tamoxifen- Treatment Offer More?) trials are evaluating the issue of whether durations of tamoxifen longer than 5 years will result in additional clinical benefit.

While 5 years of tamoxifen appears to be the optimal treatment duration, there is data suggesting the benefit of tamoxifen persists well beyond the 5 years of therapy. Furthermore, two ongoing trials, the ATLAS and the ATTOM, will evaluate the optimal duration of adjuvant tamoxifen therapy. In the most recent overview analysis, there is a persistent decrease in the risk of recurrence and death extending through the 15th year [73]. The absolute reduction in the risk of recurrence was greatest in the first 5 years, whereas the improvement in OS grew larger over the first 10 years. While this data suggests a significant benefit to tamoxifen in many women, a not insignificant percentage of relapses and deaths will occur in the decade following the completion of 5 years of tamoxifen.

In the last 3 years, the third-generation aromatase inhibitors have been widely evaluated in postmenopausal patients with early stage breast cancer. The preliminary results from these trials have challenged the predominant position of tamoxifen in the adjuvant setting.

17.2.1 Aromatase Inhibitors

The use of aromatase inhibitors has dramatically increased in the past few years with the introduction of new, more selective aromatase inhibitors, such as anastrozole, exemestane and letrozole. This class of agents effectively blocks the extra-ovarian sites of estradiol synthesis, decreasing its serum concentration by more than 90% in postmenopausal woman [74, 75]. The currently available selective aromatase inhibitors (anastrozole, letrozole and exemestane) are better tolerated by patients compared to the older nonselective, aminoglutethimide. In contrast to tamoxifen, the newer aromatase inhibitors lack partial agonist activity and thus appear to avoid a concerning toxicity associated with tamoxifen, endometrial cancer [76]. There also appears to be a reduced risk of thromboembolic disease associated with the use of the aromatase inhibitors. Because of this lack of estrogen agonist activity, aromatase inhibitors can potentially result in the loss of bone density. Unlike tamoxifen, the aromatase inhibitors do not appear to be beneficial in premenopausal women. Even the newer aromatase inhibitors are unable to inhibit ovarian aromatase activity and as a result are unable to suppress estrogen synthesis in premenopausal women.

With the clinical development of the more specific third-generation aromatase inhibitors in the 1990s, we now have alternatives to tamoxifen in the metastatic and adjuvant setting. Over the last several years, large randomized clinical trials have demonstrated the superiority of aromatase inhibitors compared to megestrol acetate as second-line therapy of advanced disease following prior treatment with tamoxifen [77–79]. In addition, the aromatase inhibitors have been shown to be as effective, if not superior to tamoxifen as first-line therapy of advanced disease [80, 81].

Data is now available from several randomized clinical trials in the adjuvant setting that suggest a superior clinical outcome for postmenopausal patients who receive an aromatase inhibitor as a component of their adjuvant therapy program.

17.2.2 Arimidex, Tamoxifen and Combination (ATAC) Trial

The results from the ATAC trial were initially presented with a median follow-up of 33 months in 2001 [82]. The ATAC trial enrolled 9,366 postmenopausal patients, with HR- positive or unknown disease, who were randomized to 5 years of anastrozole, tamoxifen or the combination of both agents. Only 20% of enrolled patients received adjuvant chemotherapy. The combination arm was

closed to accrual after the first analysis of the data when it was shown that there would not be any efficacy or tolerability benefit compared with tamoxifen. The trial was most recently updated after a median of 100 months of follow-up. The trial's primary endpoint was DFS with secondary endpoints, including OS, TTR and contralateral breast cancer. With a total of 1,704 events, DFS was significantly better in the anastrozole arm (HR: 0.90, 95% CI 0.82–0.99; $P>0.025$). When evaluating HR+ patients, only DFS was 15% improved in the anastrozole arm (HR: 0.85, 95% CI 0.76–0.94; $P>0.003$). The absolute difference in recurrence in the HR+ population at 9 years was 4.8%. However, OS did not show significant improvement in either group (HR: 1.00, 95% CI 0.89–1.12, $P>0.99$ for all patients; HR: 0.97, 95%CI 0.86–1.11, $P>0.7$ in HR+ patients). Interestingly, the incidence of contralateral breast cancer was significantly lower in the anastrozole group (HR: 0.68, 95%CI 0.49–0.94; $P>0.02$). Time to distant recurrence was also significantly improved in the anastrozole arm (HR: 0.86, 95% CI 0.75–0.98; $P>0.022$). The benefit from anastrozole persisted beyond the 5 years of therapy and the risk for fractures at 9 years was similar in the two treatment arms. Other side effects included hot flashes (35.6% in the anatrozole arm compared with 40.8% in the tamoxifen arm), vaginal discharge (3.6% in the anatrozole arm compared with 13.2% in the tamoxifen arm) and musculo-skeletal disorders (35.7% in the anatrozole arm compared with 29.6% in the tamoxifen arm). This trial established aromatase inhibitors as a first-line adjuvant treatment in postmenopausal women with HR+ breast cancer. The lack of OS benefit may be due to the inclusion of patients with unknown HR status, although longer follow-up may be necessary given the long natural course of HR+ breast tumors.

17.2.2.1 BIG 1-98 Trial

This large randomized trial randomized patients into four treatment arms: (1) tamoxifen for a total of 5 years; (2) letrozole for a total of 5 years; (3) tamoxifen for 2 years followed by letrozole for 3 years; (4) letrozole for 2 years followed by tamoxifen for 3 years [83]. To date, analysis has been performed on 4,922 patients randomly assigned to the first two arms and a median follow-up of 76 months [80]. The primary endpoint of the trial was DFS, with secondary endpoints including OS, and toxicity. All women were postmenopausal and HR positive. The updated results showed that DFS was significantly improved in the letrozole group by 12% (HR > 0.88, 95%CI 0.78–0.99; $P>0.03$). The OS was not significantly different between groups (HR > 0.87, 95%CI 0.75–1.02; $P>0.08$), however time to distant recurrence was significantly better in the letrozole group (HR > 0.85, 95%CI 0.71–1.00; $P>0.05$). All subgroups of patients seemed to benefit equally from the use of letrozole. Adverse events were not common in either group and both medications were well tolerated. However, more patients on the letrozole arm reported at least one adverse event of any grade (2,292 patients on letrozole vs. 2,165 patients on tamoxifen), and at least one life-threatening or fatal adverse event (4.6% in letrozole group vs. 3.8% in tamoxifen group). As expected, women on letrozole had a higher incidence of bone fractures (8.6 vs. 5.8% respectively; $P<0.001$) and arthralgias (20.0 vs. 13.5%, respectively; $P<0.001$). On the other hand, women on tamoxfen had a higher incidence of hot flashes (37.4 vs. 32.8%; $P<0.001$), thromboembolic events (3.8 vs. 2.0%; $P<0.001$) and vaginal bleeding (8.3 vs. 3.8%; $P<0.001$). Overall, BIG 1-98 confirmed the results of the ATAC trial, showing a superiority of AIs in upfront use in postmenopausal women with early stage breast cancer. However, to date, none of the trials have found any significant difference in OS. Longer follow-up may be needed to confirm a superior OS in this patient population.

The ASCO Technology Assessment Working Group recently updated their recommendations on the use of aromatase inhibitors in early breast cancer [84]. Taking into account the update of the ATAC trial, the Committee considers anastrozole a reasonable treatment option for a postmenopausal woman with HR-positive breast cancer, who has an absolute or relative contraindication (i.e., history of blood clots, intolerance of tamoxifen, prior use of a SERM, etc) to the use of tamoxifen.

17.2.2.2 ABCSG-8/ARNO 95 Trial

Based on efficacy data and lack of documented cross-resistance between these two drug classes, a next logical step was to explore the clinical efficacy related to the sequential use of tamoxifen and aromatase inhibitors. A small study reported in 2001 evaluated the strategy of switching patients from tamoxifen to the

older aromatase inhibitor, aminoglutethimide [85]. A total of 380 postmenopausal women who had received tamoxifen for approximately 3 years were randomized to continuing tamoxifen for 2 more years or to discontinuing tamoxifen and switching to aminoglutethimide to complete 5 years of therapy. At a median follow-up of 61 months, there was no difference between the two groups in terms of DFS, but there did appear to be a benefit in terms of OS and breast cancer-specific survival in the patients treated with aminoglutethimide.

A subsequent trial led by the same group of investigators evaluated the same question, but used anastrozole, rather than aminoglutethimide [86]. In this trial, 448 patients who had received tamoxifen for over 2 years were randomized to continue tamoxifen for a total of 5 years or to switch to anastrozole for the same time period. At a median follow-up of 36 months, there was a statistically significant improvement in event-free survival and PFS for the patients who received the seoSquence of tamoxifen followed by anastrozole. There was a trend toward an improved overall survival that was not statistically significant. An update of these data did not show any improvement in OS [87]. This data is not sufficiently mature to justify switching the majority of tamoxifen-treated patients to the nonsteroidal aromatase inhibitor, anastrozole prior to completing 5 years of tamoxifen.

The ABCSG 8 trial was recently updated. Investigators performed two analyzes. The first was the analysis on "sequential" therapy. This analysis included the 2,922 patients who were initially randomized to either tamoxifen for 5 years or tamoxifen for 2 years followed by anastrozole for 3 years. This analysis did not include patients in the tamoxifen arm who elected to switch to anastrozole. The second analysis was the "switch" analysis in which patients who had a breast cancer event prior to the switch from tamoxifen to anastrozole were not included. In the sequential analysis, RFS was higher in the anastrozole arm (HR:0.79, 95% CI: 0.65–0.95) In this analysis, OS was significantly higher in the anastrozole group (HR:0.77; 95%CI:0.61–0.97). In the switch analysis, there was a significant difference in the RFS favoring the anastrozole arm (HR:0.73 95%CI:0.61–0.88). Although both analyzes suffer from bias, this study confirms the superiority of using an aromatase inhibitor at some point during therapy in women with early stage HR-positive breast cancer.

17.2.3 International Exemestane Study Group 031 (IES) Trial

An additional trial recently published evaluated switching patients from tamoxifen to the steroidal aromatase inhibitor exemestane [88]. In this trial, 2,362 post-menopausal women receiving tamoxifen as adjuvant therapy were randomly assigned to switching to exemestane after 2 or 3 years of tamoxifen or continuing tamoxifen to complete 5 years of therapy. The most recent update included 55.7 months of follow-up [89]. DFS in the intention-to-treat population was significantly better in the exemestane group (HR: 0.76, 95% CI: 0.66–0.88; $P>0.0001$). There was no statistically significant difference in OS between the groups (HR: 0.85, 95% CI: 0.71–1.02; $P>0.08$). However, in the ER+ and ER-unknown group, there was a significant difference in OS in favor of the exemestane group (HR: 0.83, 95% CI: 0.69–1.00; $P>0.05$). Cardiovascular adverse events were similar in the two treatment arms (22.1% in the exemestane arm compared with 20.9% in the tamoxifen arm), whereas fractures favored the tamoxifen treatment arm (7.0% in the exemestane arm compared with 4.9% in the tamoxifen arm; $P>0.003$). The incidence of osteoporosis was also higher in the exemestane arm (9.2% in the exemestane arm compared with 7.2% in the tamoxifen arm; $P>0.01$). On the other hand, serious gynecologic events occurred more frequently in the tamoxifen arm (6.4% in the exemestane arm compared with 9.8% in the tamoxifen arm, $P<0.001$).

17.2.4 National Cancer Institute of Canada (NCIC) MA17 Trial

While more than 5 years of tamoxifen therapy has not conferred an improvement in clinical outcome compared to 5 years of therapy, the addition of an aromatase inhibitor following 5 years of tamoxifen therapy has been proposed as a way of exploiting the benefits of both agents. The NCIC MA17 trial investigated the effectiveness of adding 5 years of letrozole in postmenopausal women who had completed 5 years of tamoxifen compared to 5 years of tamoxifen alone [90]. The primary end point of the study was DFS. A total of 5,187 patients who had discontinued tamoxifen less than 3 months before enrollment were randomized. At the

first analysis, with a median follow-up of 2.4 years, the 4-year DFS was 93% in the letrozole group and 87% in the placebo group. This difference was statistically significant ($P<0.001$), and the study was terminated according to stopping rules that had been incorporated into the study. An analysis of adverse events revealed that arthralgias were more common in the letrozole group and there was a trend toward increased osteoporosis. The letrozole-treated patients had a decreased risk of vaginal bleeding as well as a significant decrease in contralateral breast cancers. In an unplanned subset analysis, there appeared to be benefit in both node-negative and node-positive women, with a hazard ratio for recurrence of 0.47 in the node-negative group and 0.60 in the node-positive group. An update of this study, including survival results was presented at the 2004 ASCO [91], showing that individuals with lymph node-positive disease had a significantly improved overall survival with the use of letrozole (HR > 0.61; $P>0.04$), whereas in the node-negative population, there was no significant difference in the OS (HR > 1.52; $P>0.24$).

An update on the MA-17 trial showed that DFS significantly improved with time on letrozole ($P<0.0001$ for hazard ratio trends based on time-dependent Cox model), whereas OS was not significantly different ($P>0.33$ for hazard ratio trends based on time-dependent Cox model) [92]. However, OS was significantly better with the use of letrozole in LN-positive patients ($P>0.038$ for hazard ratio trends based on time-dependent Cox model). The above data show that longer the therapy with an AI continues, the larger the incremental benefit.

The MA17 is the first trial that has shown improvement in OS with the use of an AI in the adjuvant setting. Concerns about the prolonged use of AIs have to do with long-term toxicity, with particular concern regarding loss of bone density and implications about future risk of fractures. Because of these uncertainties, longer follow-up of this data set will be necessary before we can fully appreciate the benefits and risks of sequential therapy.

Patients enrolled in the MA-17 trial will be rerandomized to receive letrozole for an additional 5 years compared to placebo. This strategy will provide an opportunity to study extended treatment duration with aromatase inhibitors

17.2.4.1 NSABP B33

This trial randomized women who had completed 5 years of adjuvant tamoxifen therapy to either placebo or exemestane for a total of 5 years [93]. The primary endpoint of the trial was DFS. However, with the publication of NCIC MA17, accrual was stopped a little after 2 years of the study initiation. By that time, accrual was at 53.3% of planned with 1,598 patients enrolled. Subsequently, the trial was unblended and women on the placebo arm were offered exemestane. Women on the exemestane arm were offered continuation of their exemestane therapy for a total of 5 years. Upon unblinding, 72% of patients on the exemestane arm elected to continue exemestane and 44% on the placebo arm elected to switch to exemestane. With a median follow-up of 30 months and in intent-to-treat analysis, there was a trend toward improvement in DFS in the exemestane group (HR: 0.68; $P>0.07$). However, there was a significant benefit in RFS favoring the exemestane group (HR: 0.44; $P>0.004$). The OS was similar in the 2 arms (HR: 1.20, $P>0.63$). Although this study did not reach its accrual goal and a substantial number of patients either discontinued treatment with exemestane or switched from placebo to exemestane, there still was a benefit seen with the use of exemestane after 5 years of tamoxifen. These findings confirm the findings from the NCIC MA17 trial.

With the completion of the four trials incorporating AIs in the adjuvant treatment of breast cancer, there are several questions that remain unanswered: (1) What is the optimal endocrine therapy; (2) What is the optimal duration of therapy; (3) What is the optimal sequencing of endocrine agents. What has become obvious from these trials is that 5 years of tamoxifen therapy is not an adequate treatment. The addition of an AI at some point during the course of therapy should be recommended. However, whether the AI should be given as initial treatment or sequenced with tamoxifen remains to be determined.

17.2.5 Tamoxifen Exemestane Adjuvant Multinational (TEAM) Trial

Recently, data from the TEAM trial with 2.75 years of follow-up were presented. This trial randomized postmenopausal women with early stage breast cancer to receive exemestane for 5 years or tamoxifen for 5 years. However, after the results of the IES trial, the trial was amended for ethical reasons to evaluate sequential therapy with 2.5-3 years of tamoxifen followed by exemestane for a total of 5 years compared with upfront

exemestane for 5 years. The primary endpoint of the trial was DFS at 5 years with secondary endpoints, including OS and long-term tolerability and safety. A total of 9,775 women were randomized between the two treatment arms. Toxicity profile between the 2 arms showed that tamoxifen in general had worse gynecologic toxicities with 3.1% vaginal hemorrhage compared with 1.6% in the exemestane arm ($P<0.0001$) and 6.8% vaginal discharge compared with exemestane's 2.3% ($P<0.0001$). Hot flashes were also worse with tamoxifen (33.3 vs. 28.5%, respectively; $P\leq0.001$). However, arthralgia was worse with exemastane at 17.9% compared with 9.2% in the tamoxifen arm ($P<0.001$), and reported osteoporosis was 4.7% in exemestane compared with 2.1% with tamoxifen ($P\leq0.001$). DFS at 2.75 years favored exemestane (HR > 0.89 (95% CI 0.77–1.03)), although the result did not reach statistical significance. RFS was also superior, with exemestane HR > 0.85 (0.72–1.00; $P>0.05$) as was time to distant metastasis HR > 0.81 (CI 0.67–0.98; $P<0.03$). The results of this trial are similar to the previous adjuvant trials comparing tamoxifen with an AI, providing further evidence that AIs should be considered as a first-line option in postmenopausal women with early stage HR-positive breast cancer.

17.2.6 Ovarian Ablation

Castration was first reported as an effective therapy for metastatic breast cancer over 100 years ago, at a time when hormones had not been characterized [94]. Several different means of causing ovarian ablation have been studied in the interim: surgical oophorectomy, radiation-induced ablation of the ovaries, and more recently, medical therapy with LH-releasing hormone (LHRH) agonists.

LHRH is produced by the hypothalamus and stimulates the release of LH and FSH from the anterior pituitary, which in turn stimulates the ovaries to synthesize estrogen and progesterone. Under normal conditions, LHRH is released in a pulsatile manner and results in pulsatile release of LH and FSH. Continuous administration of an LHRH agonist overstimulates the LHRH receptors and causes an initial rise in LH and FSH. However, after 1 to 2 weeks, desensitization of the LHRH receptors leads to decreased release of FSH and LH [95]. The ovaries respond by decreasing the synthesis of estrogen, and within 4 weeks of starting therapy with an LHRH agonist, circulating estrogen levels are at a postmenopausal level [150]. Unlike other ways of causing castration, serum estradiol levels return to normal within 4 weeks of discontinuing the use of the LHRH agonist [95].

In 1992, the EBCTCG performed a meta-analysis, which showed that adjuvant oophorectomy resulted in a sustained favorable impact on DFS and OS. Since then, several trials have addressed whether ovarian ablation adds to the effects of chemotherapy or if it can be used in lieu of adjuvant chemotherapy with equal or better results. Among the most recent clinical trials that have attempted to address the role of ovarian ablation as a component of adjuvant therapy are those discussed below.

One of the first studies addressing this issue was presented by Roche et al. [96] in which 162 premenopausal women with axillary node-positive, hormone receptor-positive early stage breast cancer were randomized to receive either 6 cycles of FAC (FU 500 mg/m^2, adriamycin 50 mg/m^2, cyclophosphamide 500 mg/m^2 every 3 weeks) or ovarian ablation (surgical or radiotherapeutic) plus tamoxifen 30 mg for 2 years (HT arm). The median age of enrolled patients was 45 years. After a median follow-up of 84 months, DFS was significantly better in the HT arm (82.8%) compared to those receiving chemotherapy (55%). OS however was not significantly different in the 2 arms (84 vs. 74%). Although the study did not include a CAF+ tamoxifen arm, these findings are intriguing, suggesting endocrine therapy as an alternative to adjuvant chemotherapy

17.2.6.1 FASG 06

The FASG 06 trial also attempted to assess the impact of hormonal blockade in women with axillary node-positive breast cancer [97]. The investigators randomized 333 premenopausal women with operable breast cancer to receive tamoxifen 30 mg/day plus IM triptorelin 3.75 mg every month for 3 years (arm A, $n>164$) or 6 cycles of FEC 50 (5-FU 500 mg/m^2, epirubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2 every 21 days) (arm B, $n>169$). After a median follow-up of 54 months, the DFS was similar between arm A and B (91.7 vs. 80.9%, respectively; $P>0.12$). Overall survival was also similar (97 vs. 92.9%, respectively; $P>0.18$).

Arriagada et al. [98]reported on 926 patients receiving adjuvant chemotherapy for breast cancer randomized

to receive no further treatment following chemotherapy (465 patients) or ovarian suppression in the form of ovarian radiation or use of an LHRH analog for 3 years (461 patients). Baseline characteristics were well balanced between the two groups. Mean age of patients was 43 years, 90% of the patients had positive lymph nodes and 76% had hormone receptor-positive disease. At a median follow-up of 9.8 years, the OS was similar between the two groups (68% in the no treatment arm vs. 66% in the ovarian suppression arm; $P>0.19$), as was the DFS (49 vs. 48%, respectively; $P>0.52$). When analyzing the data according the hormone receptor status or amenorrhea status, the results remained unchanged between the two groups.

17.2.6.2 ECOG 5188/INT-0101

An update of the ECOG 5188/INT-0101 was also presented in 2003 [99]. A total of 1,504 women with axillary node-positive, hormone receptor-positive breast cancer were randomized to 1 of 3 treatment arms: (1) CAF (cyclophosphamide 100 mg/m^2 p.o. qd×14 days; doxorubicin 30 mg/m^2 i.v. days 1 and 8; 5-FU 500 mg/m^2 i.v. day 1 and 8 for 6 28-day cycles); (2) CAF + goserelin×5 years (CAF+Z); or (3) CAF+goserelin×5 years + tamoxifen×5 years (CAF+Z+T). At 9.6 years of median follow-up, the addition of Z to CAF did not reduce the rate of recurrence (HR 0.93, 1- sided $P>0.25$) or improve overall survival (HR>0.88; 1-sided $P>0.14$). However, there was an improvement in recurrence rate in the CAF+Z+T arm compared to CAF (HR 0.73; 1-sided $P<0.01$), which has so far not translated to an improved OS (HR 0.91; 1-sided $P>0.21$). The criticisms of this study are the absence of a CAF+T arm and the fact that it was a 1-sided analysis. There also seemed to be a benefit for the addition of goserelin to CAF in women under the age of 40 with a 9-year DFS of 55 vs. 48% in the CAF arm. This is probably explained by the fact that only 66% of those women achieved menopause after CAF chemotherapy and there was an improvement in DFS in women achieving menopause (59% 9-year DFS vs. 40%).

17.2.6.3 INT0142

This trial was designed to compare DFS, OS, TTR and QOL in patients receiving adjuvant tamoxifen (T) or T with ovarian ablation for 5 years (OA) [100]. The trial was designed to accrue 1,684 patients but enrolled only 345 women before closing due to poor accrual rate. The survival analysis was underpowered and failed to show a difference between the two treatment arms (DFS: 87.8% in T vs. 90.3% in T+OA; OS: 95% in T vs. 97.5% in T+ OA). However, the QOL analysis was not underpowered and showed that women in the T+OA group suffered from more menopausal symptoms compared with the T arm.

The results of these studies raise several issues: (1) Does ovarian suppression offer additional benefit in premenopausal women with hormone receptor-positive breast cancer who receive adjuvant chemotherapy, if they remain premenopausal after the completion of chemotherapy? (2) Can chemotherapy be replaced with ovarian suppression with similar clinical benefit? (3) Is there a benefit to adding ovarian suppression to tamoxifen. Several ongoing international trials described below are attempting to critically address these issues. Three ongoing trials, the SOFT, TEXT and PERCHE are evaluating the role of tamoxifen and aromatase inhibitors in combination with ovarian ablation in premenopausal women.

17.2.7 LHRH-Agonists in Early Breast Cancer Overview Group

In a recent meta-analysis of 16 randomized trials, including 11,906 premenopausal women, researchers evaluated the role of LHRH agonists [101]. When used as the only therapy for HR-positive breast cancer, LHRH agonists did not significantly decrease the risk of recurrence (HR: 0.72, 95% CI 0.49–1.04; $P>0.08$) or death after recurrence (HR: 0.82, 95% CI 0.47–1.43; $P>0.49$) compared to no systemic therapy. LHRH agonists also did not produce an added benefit to tamoxifen since recurrence (HR: 0.85, 95% CI 0.67–1.09; $P>0.20$), and deaths after recurrence (HR: 0.84, 95% CI 0.59–1.19; $P>0.33$) were similar in the tamoxifen and the LHRH+ tamoxifen arms. The addition of an LHRH agonist to chemotherapy with or without tamoxifen, however, showed an improvement in recurrence (HR: 0.88, 95% CI 0.77–0.99; $P>0.04$) and death after recurrence (HR: 0.85, 95% CI 0.73–0.99; $P>0.04$). When comparing chemotherapy with an LHRH agonist in women with hormone receptor-positive disease,

there was no significant difference in the 2 arms in regard to recurrence (HR: 1.04, 95% CI 0.92–1.17; $P>0.52$) or death after recurrence (HR: 0.93, 95% CI 0.79–1.10; $P>0.40$). Finally, studies comparing an LHRH agonist + tamoxifen with chemotherapy did not show any significant benefit between the 2 arms in relation to recurrence (HR: 0.90, 95% CI 0.75–1.08; $P>0.25$) or death after recurrence (HR: 0.89, 95% CI 0.69–1.15; $P>0.37$).

From the above data, it seems that in premenopausal women with HR+ breast cancer, the use of an LHRH agonist produces similar benefit to adjuvant anthracycline-based chemotherapy or CMF. However, none of the studies included in this meta-analysis had incorporated a taxane in their adjuvant chemotherapy regimen. There also seems to be a benefit to the addition of an LHRH agonist to chemotherapy with or without tamoxifen. A limitation of the studies included in the meta-analysis is the fact women were not randomized based on their menopausal status after receiving adjuvant chemotherapy.

17.3 Treatment of HER2-positive Tumors in the Adjuvant Setting

Trastuzumab (Herceptin®, Genetech, San Francisco, California, USA), is a humanized murine monoclonal antibody. It binds HER2, a transmembrane receptor, which is overexpressed in 20–30% of all breast cancers. Previously, overexpression of HER2 was a negative prognostic and predictive risk factor for survival; however, with the introduction of trastuzumab, the prognosis of patients with HER2+ disease is improving in all treatment settings. However, much controversy remains in the use of trastuzumab, including: the optimal integration of adjuvant trastuzumab (concurrent with chemotherapy or sequential following chemotherapy); the optimal treatment duration (less than 1 year, 1 year or 2 years); and finally, the treatment choice upon disease progression (whether to continue trastuzumab, or not with an alternative cytotoxic agent). Current trials are ongoing to help answer these questions. Novel therapeutics, such as Lapatinib (Tykerb®, GlaxoSmithKline; Research Triangle Park, NC), an oral tyrosine kinase inhibitor, which blocks both the epithelial growth factor receptor (EGFR) and HER2, and Pertuzumab (Omnitarg ™, Genentech, San Francisco, CA, USA), a humanized monoclonal antibody, directed against heterodimerization of HER2 and HER3 have entered phase II and III clinical trials and may ultimately prove useful in the adjuvant setting.

17.3.1 NSABP B31 and NCCTG 9831 Joint Analysis

Since trastuzumab was effective in improving RR, duration of response, and OS in MBC, large randomized adjuvant trials were initiated [102, 103]. The results from these trials were recently published. The NSABP and the North Central Cancer Treatment Group (NCCTG) published a joint analysis based on the B-31 and N9831 [102]. These trials were closed due to the superiority of the trastuzumab arm. The B31 protocol enrolled 2,043 node-positive, HER2-positive (IHC 3+ or FISH+) patients with early stage breast cancer and randomized them to 4 cycles of doxorubicin (A) and cyclophosphamide (C) ($A>60$ mg/m^2 and $C>600$ mg/m^2, q 21 days), followed by paclitaxel ($T>175$ mg/m^2) given every 3 weeks for 4 cycles (Group 1) or the same chemotherapy with weekly trastuzumab ($H>4$ mg/kg loading dose, than 2 mg/kg weekly) for 52 weeks starting with the paclitaxel (Group 2) . The protocol was later amended to allow weekly paclitaxel similar to the N9831 trial. The N9831 randomized 3,505 HER2-positive (IHC 3+ intensity or HER2 overamplified by fluorescent in situ hybridization (FISH)), node-positive (the protocol was amended at a later point to include high-risk, node-negative [greater than 2 cm ER+ or >1 cm if ER-]) patients into three groups: The control group, Group A, received 4 cycles of AC followed by weekly T (80 mg/m^2) for 12 weeks; Group B received 4 cycles of AC, followed by 12 weekly doses of T, followed by sequential weekly trastuzumab for 52 weeks; and Group C received 4 cycles of AC, followed by 12 weekly doses of T concomitantly with weekly trastuzumab, which would be continued for 40 more weeks after completion of paclitaxel. The combined analysis grouped the control groups (Group 1 and Group A from B31 and N9831, respectively) and compared them to Group 2 and Group C from B31 and N9831, respectively. Since there was no group in the B31 trial that evaluated sequential trastuzumab, N9831's Group B was not included in the combined analysis.

Patients in both studies were excluded if they had any history of coronary disease, arrhythmias, cardiomegaly, congestive heart failure or cardiomyopathy, or required medications for angina pectoris or valvular heart disease. Further, to ascertain any compromise in left ventricular ejection fraction (LVEF), either multiple gated acquisition scanning (MUGA) and/or echocardiography were obtained (B31 used MUGA scanning only). Prior to receiving trastuzumab, patients had to have an LVEF ≥ lower limit of normal (LLN) for the institution and not have a decrease of less than 16% points from their previous baseline (prior to starting AC). Further, if any patient developed symptoms of congestive heart failure at any time of therapy (during AC or during trastuzumab), therapy was terminated. Patients were required to have either MUGA or echocardiography (ECHO) prior to and after completing AC, and at 6, 9, and 18 months of therapy. If the LVEF declined 16 or more percentage points from baseline or 10–15% points from their baseline to below the LLN, trastuzumab was held for 1 month. Upon reevaluation, if the LVEF remained below the set limits, trastuzumab was discontinued.

Both trials were terminated early by the independent data-monitoring committee (IDMC) based on the significant benefits trastuzumab had in the adjuvant setting compared to the control arm. The primary end point, DFS, was reached, and at a median follow-up of 2 years, there was a statistically significant reduction in recurrence of 52% (Hazard Ratio [HR] 0.48, 95% confidence interval [CI]: 0.30 to 0.59; $P<0.0001$) for patients receiving trastuzumab with a distant recurrence-free survival in the trastuzumab and nontrastuzumab arm at 4 years of 89.7 and 73.7%, respectively. Further, OS was improved by a third; (HR, 0.67, 95% CI: 0.48–0.93; $P>0.015$). The absolute survival difference in the two treatment arms was 2.5% (94.3 vs. 91.7%) at 3 years, and 48% at 4 years (91.4 vs. 86.6%). The two trials combined in this analysis had very similar results as to the benefit of trastuzumab in early stage breast cancer. Interestingly, brain metastases were more commonly seen as a first site of recurrence in the trastuzumab-treated group than the control group. Possible theories include delayed failures at local sites compared to distant sites and the limitation that trastuzumab has in crossing the blood-brain barrier [104, 105].

The incidence of symptomatic congestive heart failure (New York Heart Association [NYHA] class III or IV) or other cardiac-related deaths at 3 years in the B31 study was 0.8% in the control group compared to 4.1% in the trastuzumab-treated group. In addition, 14% of trastuzumab-treated patients had to discontinue therapy secondary to asymptomatic decreases in LVEF, whereas 4% stopped secondary to symptomatic cardiotoxicity [106]. In the N9831 trial, the 3-year cumulative incidence of NYHA class III or class IV CHF was 2.9% in the trastuzumab-treated group compared to 0% in the control group. Interestingly, interstitial pneumonitis, albeit rare, occurred more commonly in the trastuzumab-treated group compared with the control group. Patients with stage I-IIA breast cancer who required radiation therapy did not have any increased incidence of radiation adverse events when radiation was given concurrently with trastuzumab [107]. The combined analysis revealed the significant benefit in the reduction of recurrence and death. However, the benefit of trastuzumab in the 191 node-negative patients still needs to be evaluated. As subsequently reported, an unplanned interim analysis revealed that concurrent use of trastuzumab with paclitaxel was more effective than sequential use in both DFS and OS; however, the results from the planned analysis are still pending [108].

17.3.2 HERceptin Adjuvant (HERA) Trial

Another large, phase III international, multi-center trial, the HERA trial, conducted by the Breast International Group (BIG) 1-01, sequenced trastuzumab after primary surgery and after a minimum of 4 cycles of adjuvant or neoadjuvant chemotherapy [109]. Over 5,000 HER2-positive patients with early stage breast cancer were randomized to receive trastuzumab or observation. If randomized to receive trastuzumab, patients received an initial dose of 8 mg/kg followed by maintenance doses of 6 mg/kg every 3 weeks for 1 or 2 years. Additionally, patients were required to have node-positive disease or if node -negative, a tumor greater than 1 cm and normal cardiac function with LVEF ≥55%. Cardiac monitoring via MUGA or ECHO was done at baseline and 3, 6, 12, 18, 24, 30, 36 and 60 months after randomization. Trastuzumab was stopped in any patient with LVEF ≤45% or who developed a 10% absolute decrease in their baseline LVEF and

below 50%. Trastuzumab was permanently discontinued if the LVEF did not return to above LLN per protocol within 3 weeks.

At a median follow-up of 1 year, an interim analysis of 3,387 patients (1,694 with trastuzumab and 1,693 with placebo) revealed 127 new events in the trastuzumab-treated group compared to 220 in the control group, with a risk reduction of 46% (HR: 0.54; 95% CI: 0.43–0.67; $P<0.0001$) and absolute improvement in 2-year DFS of 8.4% (95% CI: 2.1–14.8). The 2-year OS was not statistically significant, HR: 0.76 (95% CI: 0.47–1.24; $P>0.26$). As seen in the NSABP/NCCTG joint analysis, brain metastases occurred more frequently in the trastuzumab-treated group compared with the placebo. The incidence of symptomatic heart failure in the trastuzumab-treated group (1.7%) was lower than that seen in the concurrent arms of combined analysis. Unlike the NSABP/NCCTG joint analysis, in which 191 patients were node negative [102], one third (550 patients) of the HERA patients had node-negative disease and only 26% of the patients in the study received a taxane with an anthracycline compared to 100% in the joint analysis. However, the same gains were seen in the node-negative population and the anthracyline-naïve patients, as was seen in the NSABP/NCCTG joint analysis [102]. After the interim analysis, patients in the placebo arm were able to cross-over and receive trastuzumab therapy. Of the 1,698 placebo-treated patients, 861 were elected to take trastuzumab. Now, after 2 years since the first analysis was initially presented, benefit in DFS has been maintained [110] (HR > 0.64; 95% CI 0.54, 0.76). Furthermore, the OS was also significantly improved (HR > 0.66; 95% CI 0.47, 0.91).

The HERA trial evaluated the use of sequential trastuzumab in order to circumvent added cardiotoxicity of combining an anthracycline with trastuzumab, as well as to determine the optimal duration of trastuzumab therapy. Sequential therapy appears to improve DFS by nearly 50%. Cardiotoxicity was lower than seen in the joint analysis. There are multiple reasons for the lower incidence of cardiotoxicity, including: more frequent cardiac monitoring, different modalities of monitoring, sequential therapy, as well as fewer patients exposed to anthracycline therapy. The third arm, in which patients received 2 years of sequential trastuzumab, will help determine the optimal treatment duration.

17.3.3 Breast Cancer International Research Group (BCIRG) 006

The BCIRG initiated a phase III, multicenter trial to evaluate the adjuvant use of trastuzumab concurrently with a nonanthracycline after multiple phase II trials confirmed the feasibility of this approach [103, 111]. The BCIRG 006 randomized 3,222 HER2 -positive patients (FISH only) with axillary lymph node-positive or high-risk lymph node- negative (tumor size greater than 2 cm, estrogen and progesterone receptor status negative, histologic and/or nuclear grade 2–3, or age <35) breast cancer to 2 arms containing adjuvant AC followed by docetaxel (T, 100 mg/m^2 q 21 days for 4 cycles) with or without trastuzumab (weekly during chemotherapy then every 21 days), while the third arm included docetaxel and carboplatin (TCarbo) (T, 75 mg/m^2; Carbo, AUC of 6 every 3 weeks × 6) with H for 1 year) [112]. The interim analysis after 36 months of treatment revealed statistically significant risk reduction of DFS of 39% (HR: 0.61, 95% CI 0.48–0.76; $P<0.0001$) with AC-TH (arm 2) compared to control and a risk reduction of 33% (HR, 0.67, 95% CI 0.54–0.83; $P>0.0003$) with TCarboH (arm 3) compared to the control arm. OS, a secondary endpoint, was also significantly improved in both trastuzumab arms compared with the control nontrastuzumab arm (AC-TH: HR > 0.59, 95% CI 0.42–0.85, $P>0.004$; TCH: HR > 0.66, 95% CI 0.47–0.93, $P>0.017$). All regimens were well tolerated with a lower incidence of grade 3/4 neutropenia (TCH: 66.2%, AC-T: 63.3%, AC-TH: 71.3%) and higher incidence of thrombocytopenia in the TCH arm (TCH: 5.4%, AC-T: 1.0%, AC-TH: 1.2%). Four patients developed leukemia in the two anthracycline arms, whereas there was no incidence of leukemia in the TCH arm. Cardiac toxicity was similar in the AC-T and TCH arms with four cases each of grade 3/4 CHF compared with 20 in the AC-TH arm.

The BCIRG 006 results were similar to the combined analysis in highlighting the benefit from adjuvant trastuzumab [102]. Further, the BCIRG trial showed that nonanthracycline therapy concurrently with trastuzumab was effective.

The BCIRG 006 trial also evaluated the role of *TOPO II*, a gene which is in a nearby region to the HER2/*neu* gene [112]. The protein product of this gene is a target for anthracyclines, and therefore the rationale was that individuals who co-amplify HER2/*neu*

and *TOPO II* would benefit from the use of an anthracycline. In an analysis performed on a total of 2,990 patients, co-amplification of the two genes was found in 35% of cases. Furthermore, co-amplified patients had a higher DFS compared with the non co-amplified (HR > 1.44; 95% CI 1.16–1.78; $P<0.001$). However, there did not appear to be a difference among the three treatment arms based on co-amplification, whereas in the non-coamplified group, the use of trastuzumab, regardless of the chemotherapeutic regimen with which it was administered, proved to benefit DFS significantly ($P<0.001$). Although these results are interesting, it is still premature to use them in clinical practice. Therefore to date, clinical testing for TOPO2A is not recommended.

17.3.3.1 FINher Trial

The last adjuvant trastuzumab trial, the FINher (Finland Herceptin), tested whether an abbreviated course of trastuzumab was effective [113]. The FINher trial included patients with early stage breast cancer (axillary node positive or tumor >2 cm with negative axillary nodes and negative PR). The trial included two randomizations: the first was a randomization between docetaxel (100 mg/m^2 q 21 days for 3 cycles) and vinorelbine (25 mg/m^2); the second included only HER2-positive patients (HER2 overamplified [2+ or 3+] detected by chromogenic in situ hybridization [CISH]) and randomized to weekly trastuzumab, or not, for a total of 9 weeks. A total of 232 HER2-positive patients were randomized to receive either adjuvant docetaxel every 3 weeks for 3 cycles or vinorelbine on days 1, 8, 15 of 21-day cycle for 3 cycles with or without concurrent weekly trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly). All patients then received FEC every 21 days for 6 cycles. RFS was the primary endpoint, while the secondary end points evaluated LVEF, adverse events and OS. The docetaxel dose was amended to 80 mg/m^2 because of high incidence of neutropenic fevers.

After a median follow-up of 3 years, HER2-positive patients treated with trastuzumab had a significantly improved RFS (HR, 0.42; 95% CI: 0.21–0.83; $P>0.01$) and decreased distant recurrence (HR, 0.29; 95% CI: 0.13–0.64; $P>0.002$) compared to HER2- positive patients treated without tras- treated arm (HR, 0.41; 95% CI: 0.16–1.08, $P>0.07$). The hazard ratio for recurrence in HER2 overamplified, trastuzumab-treated patients did not significantly change with the type of chemotherapy, number of lymph nodes involved or center providing therapy. Further, HER2- positive patients treated with trastuzumab had a distant DFS at 3 years compared with HER2- negative patients (HR, 1.09; 95% CI 0.52–2.29; $P>0.82$); however, as expected, HER2 -positive patients treated without trastuzumab did worse than HER2- negative patients. Regarding toxicities, there was no decline in LVEF in HER2-positive patients treated with trastuzumab, but surprisingly, they had a greater stabilization of their LVEF compared to other therapies. The short course of trastuzumab therapy was effective in this small sample size; moreover, the abbreviated course appears to have less cardiotoxicity compared to a more prolonged course evaluated in other adjuvant trials. Future trials such as the HERA trial will be able to address the question on duration of therapy with trastuzumab in early stage breast cancer. In the meantime, 1 year of therapy should be considered optimal.

17.3.4 Ongoing and Future Trials

Trials assessing the efficacy of different chemotherapeutic regimens are focusing on the addition of newer agents such as capecitabine and gemcitabine, as well as the optimal schedule and duration of treatment. To date, the role of capecitabine has been evaluated in elderly patients in CALGB 49907 and found to be inferior in RFS (HR: 2.09; 95%CI 1.4–3.2) and OS (HR:1.85; 95%CI 1.1–3.1) compared to either AC or CMF. The CALGB 40101 trial compares AC with paclitaxel for a total of four or 6 cycles. The NSABP B36 trial is comparing AC to FEC in women with lymph node-negative breast cancer. The NSABP B38 is incorporating gemcitabine in the adjuvant treatment. More specifically, it compares TAC, AC followed by paclitaxel or AC followed by the combination of paclitaxel and gemcitabine. However, given the recent results from the TANGO trial, which did not show any improvement in DFS or OS with the addition of gemcitabine to EC followed by T, the enthusiasm is small. Several trials are incorporating bevacizumab, a monoclonal antibody against the vascular endothelial growth factor (VEGF) in their regimens. The NSABP B40 is a neoadjuvant and adjuvant protocol in which patients

are randomized into one of six treatment arms. This protocol evaluates the addition of bevacizumab as well as capecitabine in the neoadjuvant/adjuvant setting. ECOG E5103 is a 3-arm trial in which patients receive either AC followed by paclitaxel (AC→T) or AC→T with bevacizumab, either only during chemotherapy or adding a maintenance arm as well.

Finally, several trials are evaluating the optimal treatment plan for women with HER2-positive breast cancer. The NSABP B41 trial is a neoadjuvant/adjuvant trial in which patients are randomized to receive chemotherapy with AC→T with trastuzumab, lapatinib or the combination. Similarly, the BIG 2-06 trial compares trastuzumab with lapatinib or their combination. The NSABP B44 trial is taking one step further to assess the additive effect of traztuzumab and bevacizumab. Patients are randomized to chemotherapy with trastuzumab or the combination of traztuzumab and bevacizumab.

The completion of these ongoing trials will establish new "standards of care" in the treatment of early stage breast cancer.

Reference

1. Del Turco MR (1999) Breast cancer update: encouraging trends.... many new questions. CA Cancer J Clin. 49(3):135–7
2. Hankey BF, Ries LA, Edwards BK (1999) The surveillance, epidemiology, and end results program: a national resource. Cancer Epidemiol Biomarkers Prev. 8(12):1117–21
3. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. CA Cancer J Clin. 1999;49(1):8–31, 1
4. Mettlin C (1999) Global breast cancer mortality statistics. CA Cancer J Clin. 49(3):138–44
5. Anon. Polychemotherapy for early breast cancer: an overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 1998;352(9132):930–42
6. Olivotto IA, Bajdik CD, Plenderleith IH et al (1994) Adjuvant systemic therapy and survival after breast cancer. N Engl J Med. 330(12):805–10
7. Quinn M, Allen E (1995) Changes in incidence of and mortality from breast cancer in England and Wales since introduction of screening. United Kingdom Association of Cancer Registries. BMJ. 311(7017):1391–5
8. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. Lancet. 365(9472):1687–717
9. Early Breast Cancer Trialists' Collaborative Group, Clarke M, Coates AS, et al Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomized trials. Lancet. 2008;371(9606):29–40
10. Ravdin PM, Burris HA III, Cook G et al (1995) Phase II trial of docetaxel in advanced anthracycline-resistant or anthracenedione-resistant breast cancer. J Clin Oncol. 13(12):2879–85
11. Seidman AD, Tiersten A, Hudis C et al (1995) Phase II trial of paclitaxel by 3-hour infusion as initial and salvage chemotherapy for metastatic breast cancer. J Clin Oncol. 13(10):2575–81
12. Valero V, Holmes FA, Walters RS et al (1995) Phase II trial of docetaxel: a new, highly effective antineoplastic agent in the management of patients with anthracycline-resistant metastatic breast cancer. J Clin Oncol. 13(12):2886–94
13. Gianni L, Munzone E, Capri G et al (1995) Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. J Clin Oncol. 13(11):2688–99
14. Nabholtz JM, Mackey JR, Smylie M et al (2001) Phase II study of docetaxel, doxorubicin, and cyclophosphamide as first-line chemotherapy for metastatic breast cancer. J Clin Oncol 19(2):314–21
15. Sledge GW, Neuberg D, Bernardo P et al (2003) Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol. 21(4):588–92
16. Henderson IC, Berry DA, Demetri GD et al (2003) Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol. 21(6):976–83
17. Mamounas EP, Bryant J, Lembersky B et al (2005) Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. J Clin Oncol. 23(16):3686–96
18. Goldstein LJ, O'Neill A, Sparano JA, et al E2197: Phase III AT (doxorubicin/docetaxel) vs. AC (doxorubicin/cyclophosphamide) in the adjuvant treatment of node-positive and high-risk node-negative breast cancer. 2005 ASCO Annual Meeting Proceedings; American Society of Clinical Oncology. 2005. p. 16S (#512)
19. Roche H, Fumoleau P, Spielmann M et al (2006) Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 trial. J Clin Oncol. 24(36):5664–71
20. Martin M, Rodriguez-Lescure A, Ruiz A, et al Multicenter, randomized phase III study of adjuvant chemotherapy for node-positive breast cancer comparing 6 cycles of FE90C versus 4 cycles of FE90C followed by 8 weekly paclitaxel administrations: interim efficacy analysis of GEICAM 9906 trial. Breast Cancer Res Treat. 2005;94(Suppl 1):S20 (#39)
21. Sparano JA, Wang M, Martino S et al (2008) Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med. 358(16):1663–71
22. Jones S, Holmes FA, O'Shaughnessy J, et al Extended follow-up and analysis by age of the US Oncology Adjuvant trial 9735: docetaxel/cyclophosphamide is associated with an overall survival benefit compared to doxorubicin/

cyclophosphamide and is well tolerated in women 65 or older. Breast Cancer Res Treat. 2007;106(Suppl 1):#12. Ref Type: Generic
23. Francis P, Crown J, Di LA et al (2008) Adjuvant chemotherapy with sequential or concurrent anthracycline and docetaxel: Breast International Group 02–98 randomized trial. J Natl Cancer Inst. 100(2):121–33
24. Bianco AR, De Matteis A, Manzione L, et al Sequential Epirubicin-Docetaxel-CMF as adjuvant therapy of early breast cancer: results of the Taxit216 multicenter phase III trial: American Society of Clinical Oncology. 2008. p. 18S (#520)
25. Burnell M, Levine M, Chapman JA, et al A randomized trial of CEF versus dose-dense EC followed by paclitaxel versus AC followed by paclitaxel in women with node-positive or high-risk node-negative breast cancer, NCIC CTG MA.21: results of an interim analysis. 2006
26. Fountzilas G, Skarlos D, Dafni U et al (2005) Postoperative dose-dense sequential chemotherapy with epirubicin, followed by CMF with or without paclitaxel, in patients with high-risk operable breast cancer: a randomized phase III study conducted by the Hellenic Cooperative Oncology Group. Ann Oncol. 16(11):1762–71
27. Gianni L, Baselga J, Eiermann W, et al European Cooperative Trial in Operable Breast Cancer (ECTO): improved freedom from progression (FFP) from adding paclitaxel (T) to doxorubicin (A) followed by cyclophosphamide methotrexate and fluorouracil (CMF). Proceedings of the American Society of Clinical Oncology; ASCO. 2005. p. 513
28. Buzdar AU, Singletary SE, Valero V et al (2002) Evaluation of paclitaxel in adjuvant chemotherapy for patients with operable breast cancer: preliminary data of a prospective randomized trial. Clin Cancer Res. 8(5):1073–9
29. Martin M, Pienkowski T, Mackey J et al (2005) Adjuvant docetaxel for node-positive breast cancer. N Engl J Med. 352(22):2302–13
30. Hayes DF, Thor AD, Dressler LG et al (2007) HER2 and response to paclitaxel in node-positive breast cancer. N Engl J Med. 357(15):1496–506
31. Berry DA, Cirrincione C, Henderson IC et al (2006) Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA. 295(14):1658–67
32. Skipper HE. Laboratory models: some historical perspectives. Cancer Treat Rep. 1986;70:3–7. Ref Type: abstr
33. Norton L. Theoretical concepts and the emerging role of taxanes in adjuvant therapy. Oncologist. 2001;3(Suppl):30–5. Ref Type: abstr
34. Citron ML, Berry DA, Cirrincione C et al (2003) Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol. 21(8):1431–9
35. De Laurentiis M, Cancello G, D'Agostino D et al (2008) Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. J Clin Oncol. 26(1):44–53
36. Albain KS, Nag SM, Calderillo-Ruiz G et al (2008) Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. J Clin Oncol. 26(24):3950–7
37. NCCN Clinical Practice Guidelines in Oncology. NCCN 2008; www.nccn.org
38. Fisher B, Bryant J, Wolmark N et al (1998) Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol. 16(8):2672–85
39. Rastogi P, Anderson SJ, Bear HD et al (2008) Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol. 26(5):778–85
40. von MG, Raab G, Caputo A et al (2005) Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO study of the German Breast Group. J Clin Oncol. 23(12):2676–85
41. Smith IC, Heys SD, Hutcheon AW et al (2002) Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol. 20(6):1456–66
42. Green MC, Buzdar AU, Smith T et al (2005) Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. J Clin Oncol. 23(25):5983–92
43. Evans TR, Yellowlees A, Foster E et al (2005) Phase III randomized trial of doxorubicin and docetaxel versus doxorubicin and cyclophosphamide as primary medical therapy in women with breast cancer: an anglo-celtic cooperative oncology group study. J Clin Oncol. 23(13):2988–95
44. Schabel FM Jr (1975) Animal models as predictive systems. Cancer chemotherapy: fundamental and recent advances. Year Book Medical, Chicago, pp 322–55
45. Skipper HE, Schabel FM Jr, Wilcox WS (1964) Experimental evaluation of potential anticancer agents. XIII. On the criteria and kinetics associated with "curability" of experimental leukemia. Cancer Chemother Rep. 35:1–111
46. Frei E III, Canellos GP (1980) Dose: a critical factor in cancer chemotherapy. Am J Med. 69(4):585–94
47. Peters WP, Dansey R (1997) New concepts in the treatment of breast cancer using high-dose chemotherapy. Cancer Chemother Pharmacol. 40(Suppl):S88–93
48. McCarthy P, Hurd D, Rowlings P et al (1999) Autotransplants in men with breast cancer. ABMTR Breast Cancer Working Committee. Autologous Blood and Marrow Transplant Registry. Bone Marrow Transplant. 24(4):365–8
49. National Hospital Discharge Survey for 1990 and 1991. US Department of Health and Human Services. Public Health Service, Center for Disease Control, National Center for Health Statistics. Hospital Care Statistics Branch, Hyattsville, MD. 1991
50. Tallman MS, Gray R, Robert NJ et al (2003) Conventional adjuvant chemotherapy with or without high-dose chemotherapy and autologous stem-cell transplantation in high-risk breast cancer. N Engl J Med. 349(1):17–26
51. Eibl B, Schwaighofer H, Nachbaur D et al (1996) Evidence for a graft-versus-tumor effect in a patient treated with marrow ablative chemotherapy and allogeneic bone marrow transplantation for breast cancer. Blood. 88(4):1501–8
52. Ueno NT, Rondon G, Mirza NQ et al (1998) Allogeneic peripheral-blood progenitor-cell transplantation for poor-risk

patients with metastatic breast cancer. J Clin Oncol. 16(3): 986–93
53. Perou CM, Sorlie T, Eisen MB et al (2000) Molecular portraits of human breast tumors. Nature. 406(6797):747–52
54. Fan C, Oh DS, Wessels L et al (2006) Concordance among gene-expression-based predictors for breast cancer. N Engl J Med. 355(6):560–9
55. Van't Veer LJ, Dai H, van der Kooy K, et al Gene-expression profiling predicts clinical outcome of breast cancer. Nature. 2002;415(6871):530–6
56. van de Vijver MJ, He YD, van't Veer LJ, et al A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med. 2002;347(25):1999–2009
57. Wang Y, Klijn JG, Zhang Y et al (2005) Gene-expression profiles to predict distant metastasis of lymph node-negative primary breast cancer. Lancet. 365(9460):671–9
58. Foekens JA, Atkins D, Zhang Y et al (2006) Multicenter validation of a gene-expression-based prognostic signature in lymph node-negative primary breast cancer. J Clin Oncol. 24(11):1665–71
59. Paik S, Shak S, Tang G et al (2004) A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. 351(27):2817–26
60. Chang HY, Nuyten DS, Sneddon JB et al (2005) Robustness, scalability, and integration of a wound-response gene-expression signature in predicting breast cancer survival. Proc Natl Acad Sci USA. 102(10):3738–43
61. Ma XJ, Wang Z, Ryan PD et al (2004) A two-gene expression ratio predicts clinical outcome in breast cancer patients treated with tamoxifen. Cancer Cell. 5(6):607–16
62. Cronin M, Pho M, Dutta D et al (2004) Measurement of gene expression in archival paraffin-embedded tissues: development and performance of a 92-gene reverse transcriptase-polymerase chain reaction assay. Am J Pathol. 164(1):35–42
63. Esteban JM, Baker JB, Cronin M et al (2003) Tumor gene expression and prognosis in breast cancer: multi-gene RT-PCR assay of paraffin-embedded tissue. Proc Am Soc Clin Oncol. 22:850
64. Paik S, Shak S, Tang G et al (2003) Multi-gene RT-PCR assay for predicting recurrence in node-negative breast cancer patients – NSABP studies B-20 and B-14. Breast Cancer Res Treat. 82:A16
65. Cobleigh MA, Bitterman P, Baker J et al (2003) Tumor gene expression predicts distant disease-free survival (DDFS) in breast cancer patients with 10 or more positive nodes: high throughout RT-PCR assay of paraffin-embedded tumor tissues. Proc Am Soc Clin Oncol. 22:A3415
66. Fisher B, Costantino J, Redmond C et al (1989) A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen receptor-positive tumors. N Engl J Med. 320(8): 479–84
67. Habel LA, Shak S, Jacobs MK et al (2006) A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients. Breast Cancer Res. 8(3):R25
68. Esteva FJ, Sahin AA, Cristofanilli M et al (2005) Prognostic role of a multigene reverse transcriptase-PCR assay in patients with node-negative breast cancer not receiving adjuvant systemic therapy. Clin Cancer Res. 11(9):3315–9
69. Paik S, Shak S, Tang G, et al Expression of the 21 genes in the Recurrence Score assay and prediction of clinical benefit from tamoxifen in NSABP study B-14 and chemotherapy in NSABP study B-20. Breast Cancer Res Treat. 2004;88(Suppl 1):S15 #24
70. Paik S, Tang G, Shak S et al (2006) Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 24(23):3726–34
71. Chang JC, Hilsenbeck SG, Yee D, et al Gene-expression profiles as predictors of response to neoadjuvant taxotere and adriamycin/cytoxan: a prospective, randomized multicenter trial in breast cancer. Breast Cancer Res Treat. 2005;94 (Suppl 1):S31 (#304)
72. Gianni L, Zambetti M, Clark K, et al Gene-expression profiles of paraffin-embedded core biopsy tissue predict response to chemotherapy in patients with locally advanced breast cancer. ASCO. 2004:3S (#501)
73. Bryant J, Fisher B, Dignam J. Duration of adjuvant tamoxifen therapy. J Natl Cancer Inst Monogr. 2001;(30):56–61
74. Goss P, Grynpas M, Qi S, Hu H (2001) The effects of exemestane on bone and lipids in the ovariectemized rat. Breast Cancer Res Treat. 69(3):224
75. Goss PE, Strasser K (2001) Aromatase inhibitors in the treatment and prevention of breast cancer. J Clin Oncol. 19(3):881–94
76. Group AT (2001) The ATAC (Arimidex, Tamoxifen, alone or in combination) adjuvant breast cancer trial in postmenopausal women. Breast Cancer Res Treat. 69(3):210
77. Buzdar A, Jonat W, Howell A et al (1996) Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. Arimidex Study Group. J Clin Oncol. 14(7):2000–11
78. Buzdar A, Douma J, Davidson N et al (2001) Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. J Clin Oncol. 19(14):3357–66
79. Kaufmann M, Bajetta E, Dirix LY et al (2000) Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized, double-blind trial. The Exemestane Study Group. J Clin Oncol. 18(7):1399–411
80. Mouridsen H, Gershanovich M, Sun Y et al (2001) Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol. 19(10):2596–606
81. Nabholtz JM, Buzdar A, Pollak M et al (2000) Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. J Clin Oncol. 18(22):3758–67
82. Baum M, Budzar AU, Cuzick J, Forbes J, Houghton JH, Klijn JG, Sahmoud T; ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomized trial. Lancet. 2002;359(9324):2131–9
83. Coates AS, Keshaviah A, Thurlimann B et al (2007) Five years of letrozole compared with tamoxifen as initial adjuvant

therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1–98. J Clin Oncol. 25(5):486–92
84. Winer EP, Hudis C, Burstein HJ et al (2003) American Society of Clinical Oncology technology assessment working group update: use of aromatase inhibitors in the adjuvant setting. J Clin Oncol. 21(13):2597–9
85. Boccardo F, Rubagotti A, Amoroso D et al (2001) Sequential tamoxifen and aminoglutethimide versus tamoxifen alone in the adjuvant treatment of postmenopausal breast cancer patients: results of an Italian cooperative study. J Clin Oncol. 19(22):4209–15
86. Boccardo F, Rubagotti A, Amoroso D, et al Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment. Breast Cancer Res Treat. 2003;82(Suppl 1):S6. Ref Type: abstr
87. Jakesz R, Kaufmann M, Gnant M, et al Benefits of switching postmenopausal women with hormone-sensitive early breast cancer to anastrazole after 2 years adjuvant tamoxifen: combined results from 3,123 women enrolled in the ABCSG Trial 8 and the ARNO 95 Trial. Breast Cancer Res Treat. 2004;88(Supp 1):S7. Ref Type: abstr
88. Coombes RC, Hall E, Gibson LJ et al (2004) A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med. 350(11):1081–92
89. Coombes K, Paridaens R, Jassem J, et al First mature analysis of the Intergroup Exemestane Study (IES): a randomized trial in postmenopausal patients with early breast cancer who remain disease-free after two to three years of tamoxifen. Proceedings of the American Society of Clinical Oncology: ASCO. 2006. p. 9s (#LBA527)
90. Goss PE, Ingle JN, Martino S et al (2003) A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early stage breast cancer. N Engl J Med. 349(19):1793–802
91. Goss P, Ingle JN, Martino S, et al Updated analysis of the NCIC CTG MA.17 randomized, placebo (P) controlled trial of letrozole (L) after five years of tamoxifen in postmenopausal women with early stage breast cancer. Proc Am Soc Clin Oncol. 2004;22(14S). Ref Type: abstr
92. Ingle JN, Goss P, Tu D, Shepard HM, Pater JL. Analysis of duration of letrozole extended adjuvant therapy as measured by hazard ratios of recurrence over time for patients on NCIC CTG MA17. San Antonio; 2005
93. Mamounas EP, Jeong JH, Wickerham DL et al (2008) Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat. Analysis of the National Surgical Adjuvant Breast and Bowel Project B-33 Trial. J Clin Oncol. 26(12):1965–71
94. Beatson GT (1896) On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. Lancer. 2:104–7
95. Nicholson RI, Walker KJ, Walker RF et al (1989) Review of the endocrine actions of luteinising hormone-releasing hormone analogues in premenopausal women with breast cancer. Horm Res. 32(Suppl 1):198–201
96. Roche H, Mihura J, de Lafontan B, et al Castration and tamoxifen vs chemotherapy (FAC) for premenopausal, node- and receptors-positive breast cancer patients: a randomized trial with a 7 years follow-up. Proc Am Soc Clin Oncol. 1996;15:134. Ref Type: abstr
97. French Adjuvant Study Group. Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 randomized trial. J Clin Oncol. 2001;19(3):602–11
98. Arriagada R, Le GM, Spielmann M, et al Randomized trial of adjuvant ovarian suppression in 926 premenopausal patients with early breast cancer treated with adjuvant chemotherapy. Proc Am Soc Clin Oncol. 2003;22:14. Ref Type: abstr
99. Davidson NE, O'Neill AM, Vukov AM et al (2005) Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). J Clin Oncol. 23(25):5973–82
100. Robert NJ, Wang M, Cella D, et al Phase III comparison of tamoxifen versus tamoxifen with ovarian ablation in premenopausal women with axillary node-negative receptor-positive breast cancer? 3 cm. Proc Am Soc Clin Oncol. 2003;22:16. Ref Type: abstr
101. Cuzick J, Ambroisine L, Davidson N et al (2007) Use of luteinizing-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomized adjuvant trials. Lancet. 369(9574):1711–23
102. Romond EH, Perez EA, Bryant J et al (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 353(16):1673–84
103. Slamon D, Pegram M (2001) Rationale for trastuzumab (Herceptin) in adjuvant breast cancer trials. Semin Oncol. 28(1 Suppl 3):13–9
104. Bendell JC, Domchek SM, Burstein HJ et al (2003) Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer. 97(12):2972–7
105. Burstein HJ, Lieberman G, Slamon DJ, Winer EP, Klein P (2005) Isolated central nervous system metastases in patients with HER2-overexpressing advanced breast cancer treated with first-line trastuzumab-based therapy. Ann Oncol. 16(11):1772–7
106. Tan-Chiu E, Yothers G, Romond E et al (2005) Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol. 23(31):7811–9
107. Halard MY, Pisansky TM, Solin LJ, et al Adjuvant radiotherapy (RT) and trastuzumab in stage I-IIa breast cancer: Toxicity data from North Cancer Treatment Group Phase III N9831. 2006 Proceedings of American Society of Clinical Oncology; American Society of Clinical Oncology. 2008
108. Perez EA, Suman VJ, Davidson NE et al (2008) Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol. 26(8):1231–8
109. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 353(16):1659–72

110. The HERA study Team. Trastuzumab (H: Herceptin) following adjuvant chemotherapy (CT) significantly improves disease-free survival (DFS) in early breast cancer (BC) with HER2 overexpression: the HERA Trial. Breast Cancer Res Treat. 2005;94(Suppl 1):S9 (#11). Ref Type: Generic
111. Pegram MD, Pienkowski T, Northfelt DW et al (2004) Results of two open-label, multicenter phase II studies of docetaxel, platinum salts, and trastuzumab in HER2-positive advanced breast cancer. J Natl Cancer Inst. 96(10):759–69
112. Slamon D, Eiermann W, Robert N, et al Phase III randomized trial comparing doxorubicin and cyclophosphamide, followed by docetaxel with doxorubicin and cyclophosphamide, followed by docetaxel and trastuzumab with docetaxel, carboplatin and trastuzumab in HER2-positive early breast cancer patients: BCIRG 006 study. Breast Cancer Res Treat. 2006;100(Suppl 1):#52. Ref Type: Generic
113. Joensuu H, Kellokumpu-Lehtinen PL, Bono P et al (2006) Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 354(8):809–20

Endocrine Therapy

18

Sacha J. Howell and Anthony Howell

18.1 Introduction

The link between ovarian hormones and breast cancer began to be formed as early as 1882 when TW Nunn observed the "spontaneous" regression of breast cancer in a woman 6 months after her menstruation ceased [1]. Oophorectomy was first proposed by the German clinician, Schinzinger, on the basis of his observation that younger women had more aggressive breast cancer [2]. However, it was not until 1896 that Beatson reported the first results of therapeutic oophorectomy in women with recurrent and locally advanced breast cancer, demonstrating regressions in three cases [3]. This paved the way for several other surgeons to replicate his work and demonstrate response rates in the order of 20–30% in terms of pain control and objective regression [4–6]. Oestrogen itself wasn't isolated and identified until 1923, and the first man-made oestrogen was synthesised in 1933 [7, 8]. In the mid 1940s, such synthetic oestrogens became some of the first additive systemic therapies for breast cancer and it wasn't until the early 1970s that the first systemic anti-oestrogen, tamoxifen, came into clinical practice (Table 18.1). Tamoxifen, largely overtook additive oestrogen therapy, not due to increased efficacy, but rather its better tolerability. The majority of subsequent developments in breast cancer endocrine pharmacotherapy have centred around the generation of alternative strategies to abrogate the effects of oestrogen on breast cancer cells, including inhibition of the aromatase enzyme, oestrogen receptor (ER) downregulation and pharmacological suppression of ovarian oestrogen production (Table 18.1). In the following chapter, we review the available data on such endocrine agents. As with the drug development paradigm in all fields of oncology, we start with advanced breast cancer and then describe how such therapies have been translated to the adjuvant and neoadjuvant settings.

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18.2 Endocrine Therapy in Advanced Breast Cancer

18.2.1 Ovarian Ablation

Following the observations by Beatson and his peers on surgical oophorectomy, ovarian irradiation was also shown to be effective [9]. No formal comparison of the two types of ovarian ablation (OA) has been performed but they were considered equivalent in the Oxford Overview [10]. It is possible that irradiation may be less effective, since oestrogen secretion may continue for some time after treatment, and in a small number of cases, menses may resume [11]. More modern series of patients treated by oophorectomy are shown in Table 18.2. Objective response rates (ORRs) vary between 22.5 and 51.0%, with a median duration of remission of about 16 months [12–14]. When tamoxifen was shown to be active in pre-menopausal women, the question of how it compared with OA was asked. A meta-analysis of four studies showed no significant difference in response rate, time to progression (TTP) and survival between the two approaches, although there was a non-significant trend in favour of tamoxifen [15–18]. However, 6/25 (24%) of patients initially treated by tamoxifen responded to subsequent oophorectomy

I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases*,
DOI: 10.1007/978-3-540-69743-5_18, © Springer-Verlag Berlin Heidelberg 2010

Table 18.1 Timeline of the introduction of endocrine therapies in use today[a]

Therapy	Author[b] (reference)	Date
Ovarian ablation (OA)	Beatson [3]	1896
Ovarian irradiation	DeCourmelles [9]	1922
Androgens	Ulrich [97]	1938
Oestrogens	Haddow [84]	1944
Progestins	Escher [160]	1951
Hypophysectomy	Perrault [161]	1952
Adrenalectomy	Huggins [69]	1953
Tamoxifen	Cole [32]	1971
Aminoglutethamide	Griffiths [71]	1973
LHRHanalogues	Klijn [19]	1982
Raloxifene	Buzdar [42]	1988
Letrozole	Iveson [162]	1993
Exemestane	Zilembo [163]	1995
Pureanti-oestrogens	Howell [55]	1995
Anastrazole	Jonat [164]	1996

[a]Includes the important conceptual advances of hypophysectomy and adrenalectomy
[b]first author of first paper

whereas 4/47 (8.5%) responded to tamoxifen after oophorectomy, suggesting to the authors that tamoxifen should be used first in the sequence.

Luteinising hormone releasing hormone (LHRH) analogues were first used to treat advanced pre-menopausal breast cancer in 1982 [19–21]. Ovarian oestrogen production is controlled by the hypothalamic pituitary ovarian axis, the hypothalamus releases LHRH in a pulsatile fashion under normal physiological conditions. LHRH regulates the pituitary release of gonadotrophins which, in turn, stimulates ovarian oestrogen production. LHRH analogues (buserelin, goserelin, leuporelin, triptorelin) have higher binding affinities to pituitary gonadotrophin-releasing hormone (GnRH) receptors and greater resistance to degradation than endogenous LHRH. Chronic administration of LHRH analogues causes internalisation of pituitary GnRH receptors, thus rendering the gonadotrophic cells refractory to endogenous LHRH. LHRH analogue administration causes an initial rise in serum oestrogen concentrations, which may lead to a tumour flare before a decline in oestrogen concentrations to post-menopausal levels after 2–3 weeks [20]. Although several LHRH analogues are available, over 90% of reported patients have been treated with goserelin [21, 22]. Goserelin is administered as a subcutaneous

Table 18.2 OA alone and comparative trials with other approaches in pre-menopausal women with advanced breast cancer

Reference	Treatment	*n*	ORR (%)	ORR ER+(%)	ORR ER –(%)	MDR (months)
[14]	Oophorectomy	639	29.5	–	–	16
[12]	Oophorectomy	105	51.0	71	21	16
[13]	Oophorectomy	71	50.7	67	17	–
[16]	Ovarian abl^	111	22.5	–	–	4[a]
	v Tamoxifen	109	22.9	–	–	6[a]
[23]	Goserelin	228	36.4	44	31	11
[25]	Goserelin	69	31			4[a]
	vOophorectomy	67	27			6[a]
[26]	Buserelin	54	34			6.3[a]
	v Tamoxifen	54	28			5.6[a]
	v Both	53	48			9.7[a]
[27]	LHRH+T	250	39	42		602 days
	v Tamoxifen	256	30	33		350 days

ORR objective response rate; *MDR* median duration of response
^Some oophorectomy and other irradiation
[a]progression-free survival

injection in a depot formulation once every 28 days. In an overview of all studies, 36.4% of patients had an objective response with a median duration of response of 11 months [23, 24]. Response rates to the other less commonly used LHRH analogues have also been reported (buserelin 14–41%, leuporelin 34–44% and triptorelin 30–70%; [21]) (Table 18.2). The only randomised trial of oophorectomy vs. an LHRH agonist (goserelin) showed no statistically significant difference between the two treatments for response, failure-free or overall survival, although the study was underpowered ([25], Table 18.2). The question of whether the combination of an LHRH agonist with tamoxifen is superior to either drug used alone was investigated by the EORTC [26]. The combination of buserelin with tamoxifen was associated with a greater response rate, median progression-free survival (9.7 months for the combination, 6.3 months buserelin alone, 5.6 months tamoxifen alone, $P > 0.03$) and overall survival (Table 18.2). In an overview analysis of four trials, the combination of LHRH agonist + tamoxifen vs. an LHRH agonist alone, the combination was associated with a greater response rate, progression free and overall survival [27]. Finally, the question arises whether aromatase inhibitors (AIs) should be used before or after tamoxifen in goserelin-treated patients. Responses have been reported to the combination of goserelin and anastrozole [28] and goserelin and 4-hydroxyandrostenedione [29] after failure of goserelin and tamoxifen but data are not available for the reverse treatment (i.e. AI followed by tamoxifen). Thus, the combination of an LHRH agonist with tamoxifen is superior to using either alone, and since there is a survival advantage in these studies, combination ovarian suppression, by surgical or pharmacological means, plus tamoxifen is considered the first-line treatment of choice in pre-menopausal women with advanced breast cancer.

18.2.2 Selective Oestrogen Receptor Modulators

18.2.2.1 Tamoxifen

Tamoxifen is a trichlorophenylethylene and was initially developed as a contraceptive, but was shown to induce ovulation [30, 31]. The trans isomer of tamoxifen was shown to be pre-dominantly anti-oestrogenic whereas the cis isomer was oestrogenic [30]. In the immature rat uterus assay, tamoxifen inhibited the action of oestrogen, whereas it was a partial agonist on the uterus in the absence of oestrogen. The first clinical study with tamoxifen in breast cancer began in 1969 [32]. Forty six post-menopausal patients were treated with 10–20 mg of tamoxifen daily for 3 months. An objective remission rate of 22% was seen, comparable with stilboestrol, but with reduced toxicity. Subsequent studies using the 20 mg dose have confirmed an overall objective response rate (ORR) (CR + PR) of 34%. If patients with disease stabilisation for ≥6 months are included, the clinical benefit of tamoxifen increases to 53% [33]. Fossati et al reviewed all comparative trials of tamoxifen with other agents up until that time. This overview of 35 randomised trials involving 5,160 patients produced 38 comparisons with other endocrine therapies [34]. Overall, the ORR for tamoxifen was 29% and for other therapies combined, 30%. In addition, survival data were available from 24 of these studies ($n > 4{,}126$) and showed no significant differences between therapies. It is important to note that these analyses did not include modern AIs. These tend to show higher response rates, and the modern AIs confer survival advantages over tamoxifen [35].

A number of studies have investigated whether a combination of tamoxifen with other endocrine therapies is superior to tamoxifen alone. A higher ORR was seen for combinations of tamoxifen with aminoglutethimide, fluoxymesterone and corticosteroids but not with bromocriptine, oestrogen, nandrolone and progestins (22 randomised studies, 2,949 patients). Overall, the hazard ratio for combination vs. single-agent therapy was 1.34, but monotherapy was better tolerated and there was no significant survival advantage for combinations (12 studies with 1,819 patients).

18.2.2.2 Other Selective Oestrogen Receptor Modulators (SORMs)

The term "selective ER modulator" implies compounds have alternative agonist or antagonist effects on different target organs. Several approaches have been used to improve on tamoxifen by attempting to increase antitumour activity, maintaining a positive effect on bone and lipids and reducing gynaecologic toxicity, particularly endometrial cancer. Two basic approaches have been taken in chemical modifications of tamoxifen: by altering its side chains to produce toremifene, idoxifene

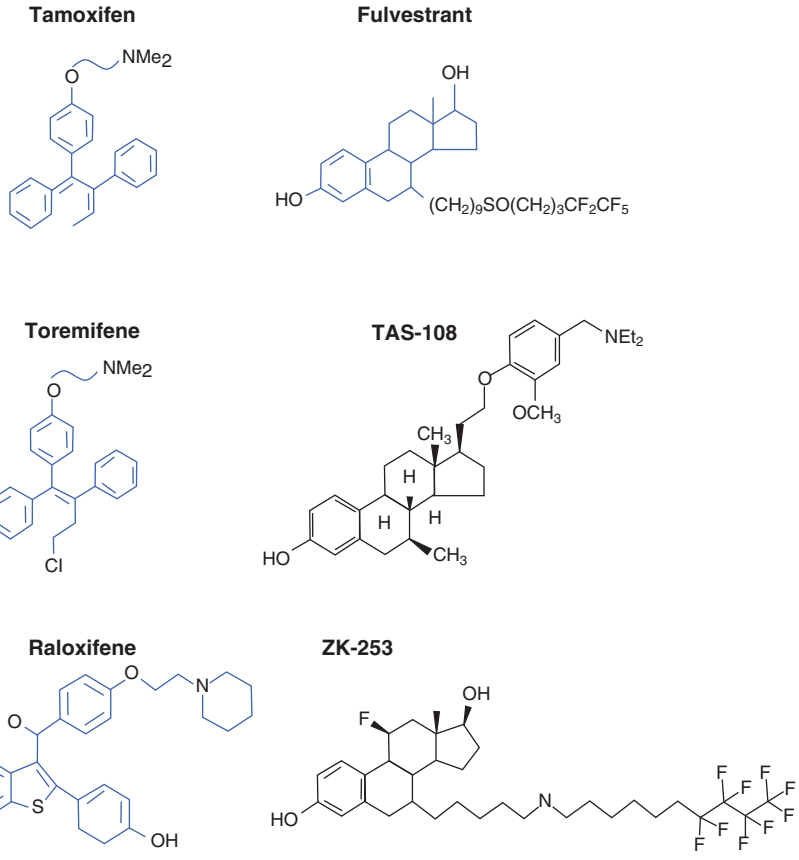

Fig. 18.1 Chemical structure of triphenylethylene selective oestrogen receptor (ER) modulators tamoxifen and toremifene and the benzopyrene derivative "fixed ring" compound raloxifene (*left panel*). Also shown are the selective ER downregulator fulvestrant and ER destabilisers TAS-108 and ZK-253. Adapted from [65, 66, 159]

and droloxifene or by altering the triphenylethylene ring structure of tamoxifen to produce non-steroidal "fixed ring" compounds such as the benzothiophene derivatives, raloxifene and arzoxifene and benzopyran derivatives such as acolbifene and its prodrug EM800 ([36–38]; Fig. 18.1).

18.2.2.3 "Tamoxifen-like" Triphenylethylene SERMs

For each of the triphenylethylene SERMs, pre-clinical data suggested improved activity over tamoxifen, which led to their clinical development. Examples of differential activity compared with tamoxifen include the reduction of liver DNA adducts with toremifene and the higher binding activity and reduced oestrogenicity in the rat uterus of droloxifene and idoxifene [38]. However, in five, phase III trials, toremifene had exactly the same activity as tamoxifen, and the potential reduction in carcinogeneity was not investigated [39]. Despite the potential favourable activity of droloxifene, it was shown to be inferior to tamoxifen in a phase III trial and its development was stopped [40]. Idoxifene was compared with tamoxifen in two phase III trials, which showed almost no difference in efficacy between the two agents, but because of potentially increased gynaecological toxicity, idoxifene development was also stopped [38, 41]

18.2.2.4 "Fixed-Ring" SERMs

Interest in these agents was founded on their lack of agonist activity on the endometrium whilst maintaining agonist activity on bone. Although raloxifene binds to the ER with similar affinity to tamoxifen, its activity is not superior to tamoxifen in advanced breast cancer. In a study of 14 patients failing tamoxifen, there was only one minor response to raloxifene 200 mg/day [42]. As first-line therapy in 21 patients with ER +ve metastatic disease, raloxifene 150 mg b.i.d. resulted in 4 (19%) partial responses with an additional 3 (14%) showing stable disease [43]. Given these data, raloxifene has not

been developed for advanced breast cancer. Arzoxifene, another benzothiophene analogue related to raloxifene, showed good efficacy in phase II trials in tamoxifen-pretreated patients. However, in a recently reported phase III trial vs. tamoxifen, enrollment was stopped after an interim analysis of the first 200 patients, suggesting arzoxifene was significantly inferior to tamoxifen [44].

Acolbifene (EM-652) is a benzopyrene derivative of an orally active pro-drug EM-800 (SCH-57050). It has significantly higher ER binding and was more effective than fulvestrant (see below) at inhibiting estradiol-induced breast cancer cell proliferation in-vitro and in the MCF-7 nude mouse model. Again, phase II studies showed promising activity in tamoxifen-pretreated patients, but acolbifene appeared to have lower activity than anastrozole in a phase III randomised trial, and development was attenuated although further development is planned [45].

18.2.3 Fulvestrant (Faslodex; ICI 182,780)

The data outlined above indicate that neither the many analogues of the triphenylethylene tamoxifen nor the "fixed ring" compounds have shown superior efficacy to tamoxifen. The search for novel agents that would completely block ER signalling led to the synthesis of a series of steroidal 7α alkylamide analogues of estradiol. Of these, ICI 164,384 was the first "pure" anti-oestrogen to be described, completely blocking the uterotrophic action of both estradiol and tamoxifen in rats [46]. Following this, a far more potent "pure" oestrogen antagonist, fulvestrant, was developed and entered clinical evaluation [47]. Fulvestrant is a 7α alkylsulphonic analogue of estradiol that is structurally distinct from the non-steroidal oestrogen antagonists (Fig. 18.1). The side chain is responsible for the inhibitory action through its effect on the ER. Fulvestrant inhibits dimerisation and nucleo-cytoplasmic shutting of the ER and reduces its half life secondary to an increase in ubiquitination. In-vitro fulvestrant showed no evidence of the low-dose stimulation of MCF-7 cell proliferation that is secondary to the partial agonist activity of tamoxifen. Fulvestrant also inhibited colony formation in semi-solid media of pleural effusion cells taken from patients resistant to tamoxifen. In this assay, tamoxifen was shown to stimulate growth and this could also be inhibited by additional fulvestrant [48]. In-vivo, the doses of fulvestrant used clinically, inhibited growth of MCF-7 cells in the nude mouse model to the same extent as tamoxifen but acted for twice as long [47, 49]

The first human study in cancer patients was a pre-surgical trial in 56 women with breast cancer who were randomised to receive no pre-operative treatment ($n>16$) or daily intra-muscular (i.m.) fulvestrant (6 mg, $n>21$; 18 mg, $n>16$) for 7 days prior to surgery [48]. There was no evidence of agonist activity of fulvestrant; it inhibited ER and PR expression almost completely and reduced proliferation by approximately two thirds. In a more recent study, fulvestrant at 50, 125 or 250 mg doses given as single i.m. injections 14–21 days prior to surgery reduced ER and Ki67 expression in a dose-dependent manner to a greater extent than tamoxifen (at 20 mg/day). Whereas the agonist effect of tamoxifen increased PR, fulvestrant significantly reduced PR, demonstrating pure antagonist effects on the ER [50]. The fulvestrant-induced reduction of ER expression in primary breast cancers is dose dependent. A single intramuscular dose of 250 mg gives mean plasma concentrations of 5 ng/mL and reduces ER expression by approximately 70% [50], whereas the 18 mg/day dosage produced a plasma concentration of 23 ng/mL and near-complete suppression of ER [48]. Although the steady-state plasma concentration is similar with the approved dose (AD; 250 mg q4 weeks) and loading dose (LD; 500 mg on Day 0, 250 mg on Day 14, 250 mg on Day 28 and q4 weeks thereafter), steady state is achieved in 1 month with the LD compared to 4–6 months with the AD [51]. Preliminary data also suggest that a high-dose regimen (HD; 500 mg on Day 0, 500 mg on Day 14, 500 mg on Day 28 and q4 weeks thereafter) has greater efficacy in the reduction of primary breast cancer mean Ki67 % at 4 and 16 weeks ($P<0.001$ for both) compared with the AD [52]. Thus, higher dosing may translate into greater anti-tumour effects than the standard dose schedule in MBC [53].

Pre-clinical data suggesting that fulvestrant may be beneficial in the treatment of tamoxifen-resistant tumours was supported by the first phase II clinical study of fulvestrant. Over two thirds (13/19, 69%) of post-menopausal women with tamoxifen-resistant disease treated with fulvestrant experienced clinical benefit [54, 55]. Moreover, a long duration of response was observed in these women (median duration 25

months), supporting pre-clinical evidence that fulvestrant suppressed tumour growth for longer than tamoxifen [49]. Thus, fulvestrant was shown not to be cross-resistant with tamoxifen in the clinical setting.

Fulvestrant at the AD was tested in two phase III trials, against the then standard second-line agent, anastrozole, in post-menopausal women with advanced breast cancer whose cancers had progressed after receiving anti-oestrogen treatment [56, 57]. Both studies had a similar design in which fulvestrant (250 mg/month i.m., $n>428$) was compared with the aromatase inhibitor (AI), anastrozole (1 mg/day orally, $n>423$). In one study, fulvestrant was administered as a single 5 mL injection in an open-label comparison (international), whereas in the other study, fulvestrant was administered as two separate 2.5 mL injections in a double-blind comparison (North American). At median follow-up (FU) of 15.1 months, the median TTP was comparable in both groups (5.5 vs. 4.1 months for fulvestrant and anastrozole, respectively and the OR rate was not significantly different between the two groups, being 19.2% in the fulvestrant group compared with 16.5% in the anastrozole group ($P>0.31$). In addition, there were no differences in OR rates between fulvestrant and anastrozole in the subgroup of patients who had any visceral metastases (15.7 vs. 13.2%, respectively; $P>0.49$) or those with visceral metastases only (18.8 vs. 14.0%, respectively; $P>0.43$) [58].

In patients who had an OR, further FU was performed at a median of 22.1 months [21]. The median DoR was 16.7 and 13.7 months in patients who responded to fulvestrant ($n>84$) and anastrozole ($n>73$), respectively; mean duration of response was significantly greater for fulvestrant than anastrozole (HR 1.30; 95% CI 1.13, 1.50; $P<0.01$). A similar proportion of patients experienced clinical benefit (43.5% patients receiving fulvestrant and 40.9% patients receiving anastrozole) and the median duration of CB was also similar between the groups (11.8 vs. 11.2 months, respectively). A survival analysis conducted at a median FU of 27 months showed that overall survival was very similar with fulvestrant and anastrozole (median 27.4 vs. 27.7 months, respectively; HR 0.98; 95% CI 0.84, 1.15; $P>0.809$), and that three quarters of patients had died in each group (74.5 vs. 76.1%, respectively) [59].

The efficacy of first-line fulvestrant vs. tamoxifen has been investigated in post-menopausal women with metastatic or locally advanced breast cancer. In a phase III study, endocrine-naïve patients, or patients who had completed endocrine therapy ≥1 year previously, were treated with either fulvestrant (250 mg/month i.m. injection with placebo tamoxifen, $n>313$) or tamoxifen (20 mg/day orally with placebo fulvestrant, $n>274$) [37]. Approximately 20–25% of patients had received prior adjuvant treatment therapy for their primary breast cancer. In the intent-to-treat (ITT) population, fulvestrant did not meet the criteria for non-inferiority to tamoxifen (upper 95% CI <1.25) for the TTP endpoint (median 6.8 vs. 8.3 months, respectively; HR 1.18; 95% CI 0.98, 1.44; $P>0.088$). OR rates were similar between the two arms (31.6% for fulvestrant vs. 33.9% for tamoxifen). However, CB rates were significantly higher in the tamoxifen group (54.3% for fulvestrant vs. 62.0% for tamoxifen; $P>0.026$). In patients experiencing an OR, the median duration of response was similar (17.3 vs. 19.8 months with fulvestrant and tamoxifen, respectively). In a post-hoc analysis of patients with breast tumours that were positive for both ER and PgR (42% of patients), the findings for median TTP were again shown to be comparable in the two groups (11.4 vs. 8.5 months for fulvestrant and tamoxifen, respectively; HR 0.85%; 95% CI 0.63, 1.15; $P>0.31$).

In the combined analysis of the two phase III trials of patients undergoing second-line treatment with fulvestrant and anastrozole, the safety population comprised 423 patients in each group [60]. Adverse events (AEs) were generally mild to moderate in intensity. The most commonly reported AEs with fulvestrant and anastrozole respectively, were nausea (26.0 vs. 25.3%), asthenia (22.7 vs. 27.0%), pain (18.9 vs. 20.3%), vasodilation (17.7 vs. 17.3%) and headache (15.4 vs. 16.8%). Joint disorders was the only AE that was significantly different between the groups, experienced by fewer patients receiving fulvestrant vs. anastrazole (5.4 vs. 10.6%, respectively; $P>0.0036$). Local injection site reactions occurred in 1.1% of courses in patients given a single 5 mL injection and in 4.6 and 4.4% of courses in patients given two 2.5 mL fulvestrant or placebo injections, respectively

In the study comparing fulvestrant and tamoxifen, the safety population comprised 310 and 271 patients respectively and the median FU was 14.5 months [37]. The most commonly reported AEs in the fulvestrant and tamoxifen groupsrespectively were nausea (20.3 vs. 22.5%), asthenia (19.4 vs. 20.3%), vasodilation (14.8 vs. 21.4%), pain (13.9 vs. 19.2%) and bone pain (13.9 vs. 17.0%). There were fewer patients treated

with fulvestrant and who experienced hot flashes (17.7 vs. 24.7%) compared with tamoxifen; ($P > 0.05$).

Data were collected on 338 patients with advanced breast cancer treated in ten specialist centres in order to determine the effectiveness of fulvestrant after previous endocrine therapy and chemotherapy, and in tumours with various ER and PR expression patterns. The clinical benefit rate (CBR) was approximately 40% whether fulvestrant was used first, second or third line; however, in common with other endocrine therapies, the response rate declined when used fourth line and beyond. Fulvestrant also gives a CB rate of approximately 40% after first- or second-line chemotherapy and gives similar CB rates in the ER/PR subtypes and whether tumours were HER2 positive or not. These results were similar to the data from the clinical trials outlined above [61]. Pre-clinical data have suggested that following failure of long-term oestrogen deprivation or aromatase inhibition, fulvestrant is most effective if the low oestrogen environment is maintained [62–64]. This has important implications for sequencing and combinations of endocrine agents and is the subject of at least three clinical trials yet to report efficacy data (SOFEA, SWOG S0226 and FACT).

18.2.3.1 Other Pure Oestrogen Antagonists in Development

Although fulvestrant is the first pure oestrogen antagonist, several other pure oestrogen antagonists are undergoing pre-clinical development. ZK-703 and ZK-253, which destabilise the ER, have been investigated using the MCF-7 xenograft model, and both were more effective than tamoxifen or fulvestrant at inhibiting the growth of ER-positive xenografts and they also showed highly potent activity in tamoxifen-resistant xenografts [65]. These agents are now entering clinical development. Another compound with pure anti-oestrogenic activity (TAS-108 (SR 16234) has completed phase I and II trials and is now being evaluated in a multi-centre phase III study [66–68].

18.2.3.2 Aromatase Inhibitors

The observations that adrenal hyperplasia occurred after oophorectomy in rodents and that oestrogen and estradiol could still be detected in oophorectomised women, suggesting an extra-ovarian source of oestrogens, led to the introduction of adrenalectomy by Huggins and Dao to treat women with breast cancer (Table 18.1; [69, 70]). This approach produced responses in post-menopausal women as frequently and with similar durations as oophorectomy in pre-menopausal women. Although corticosteroids showed some adrenal suppressive effects, the era of systemic inhibitors of oestrogen biosynthesis was initiated with the use of the anti-epileptic drug aminoglutethimide. This was later shown to be as effective as adrenalectomy with respect to tumour response and duration of response [71, 72]. The demonstration by Santen and his colleagues that aminoglutethimide inhibited the peripheral conversion of adrenal androgens to oestrogens by the enzyme aromatase [73] led to the search for and development of specific and progressively more potent inhibitors of the aromatase enzyme (for reviews see [74–76]).

Aromatase is an enzyme of the cytochrome p450 super-family and is highly expressed in the granulosa cells of the ovary, where its expression depends on cyclical gonadotrophin stimulation. Aromatase is found at low levels in subcutaneous fat, liver, muscle, brain, normal breast and breast cancer tissue, including the epithelial cells in some but not all cancers [77, 78]. The AIs were developed in the 1980s and 1990s and have been termed first-, second- and third-generation inhibitors in chronological order of their development (Fig. 18.2). They are further classified as type 1 or type 2 inhibitors according to their mechanisms of action (Fig. 18.2). Type 1 inhibitors such as exemestane are steroidal analogues of androstenedione. These compounds are metabolised by aromatase to produce metabolites, which destroy the enzyme, hence the term "suicide inhibitors". In contrast, type II inhibitors such as anastrazole and letrozole bind reversibly to the haem group of the enzyme via the nitrogen atom.

Studies have demonstrated that the third-generation AIs (anastrozole, letrozole and exemestane) inhibit total body and tumour aromatisation by over 95% and consequently reduce concentrations of post-menopausal estradiol by over 95% (Table 18.3). Crossover studies have demonstrated that letrozole is slightly more active than anastrozole as an inhibitor of whole body aromatase, but whether this is clinically significant is not clear [79]. In a study comparing the effectiveness of letrozole with anastrozole in

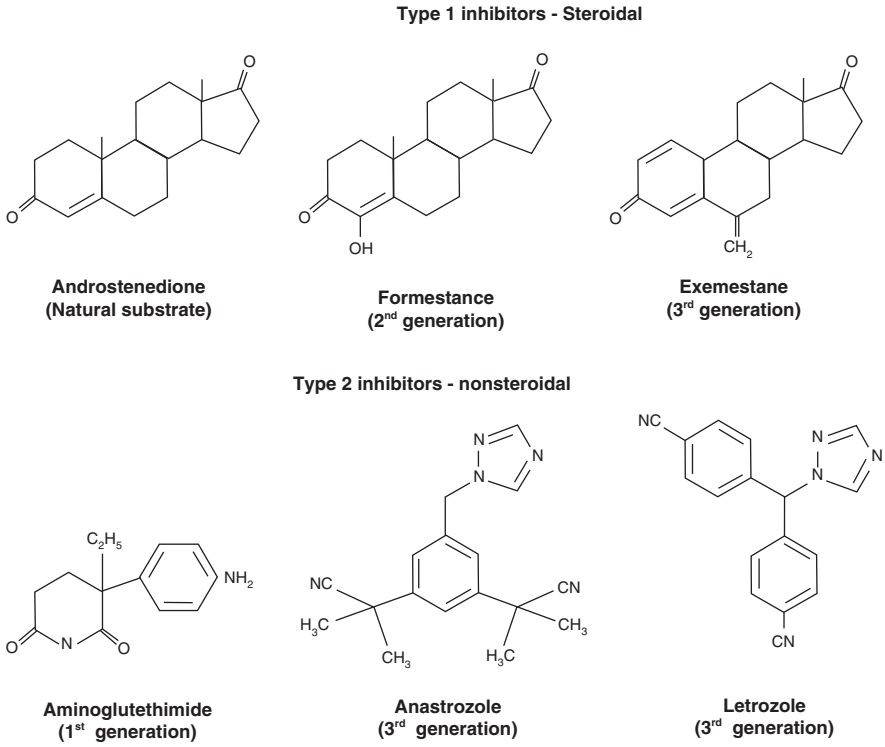

Fig. 18.2 Chemical structure of the substrate of the aromatase enzyme, androstenedione, and first-, second- and third-generation inhibitors of type 1 and type2

advanced breast cancer, no significant differences were seen in response rate, TTP or survival in the ER + population, suggesting the two AIs are clinically equivalent. However, more data are required, particularly from ongoing studies comparing the efficacy of the third-generation AIs head to head in the adjuvant setting [80]. Studies also demonstrate that the third-generation AIs have no appreciable effect on adrenal cortisol or aldosterone biosynthesis, whereas aminoglutethimide suppressed the synthesis of both steroids and fadrozole suppressed aldosterone biosynthesis [74].

The third-generation AIs were first assessed as second-line agents against the then standard treatment, megestrol acetate (MA). Thereafter, in a series of important large phase III randomised trials, they were compared with tamoxifen in the first-line setting (Tables 18.3 and 18.4). These studies first established that third-generation AIs were superior to MA and then that they were superior to tamoxifen. These results differed from previous studies with first- and second-generation compounds where, in general, no advantage in efficacy was established [34, 81]. An overview demonstrated a survival advantage in trials of third-, but not first- and second- generation AIs [35].

18.3 Oestrogens, Androgens and Progestins

Several other approaches to treat advanced breast cancer with endocrine therapy have proved successful, but generally to a lesser degree than those agents described above. Of these agents, oestrogens, androgens and progestins will be discussed briefly below. High doses of synthetic oestrogens such as triphenylethylene and stilbestrol were shown to inhibit growth of the mammary gland [82] and tumours [83] in rodents. These considerations led Haddow et al to assess the effect of high doses of the synthetic oestrogens, trichlorophenylethylene and diethylstilboestrol in women with advanced breast cancer, and demonstrated that they could induce tumour regressions [84]. Treatment with oestrogens such as diethylstilboestrol and ethinyloestradiol proved to be the most efficacious and demonstrated equivalent efficacy but increased toxicity when compared with tamoxifen in randomised phase II studies [85–90]. It was also demonstrated that additive oestrogens had relatively shallow dose response curves [91, 92]. Indeed, a study of 523 post-menopausal women reported response rates of 10, 15, 17 and 21% to 1.5, 15, 150 or

Table 18.3 Trials of aromatase inhibitors (AIs) compared with megestrol acetate as second-line therapy for advanced disease

Reference	AIs	*n*	ORR (%)	CBR	Median TTP	Median OS
[165]	Anastrozole	263	10	35	4.8	Not given
	MA 160 mg	253	8	34	4.8	Not given
[166]	Letrozole	174	24+	35	5.6	25
	MA 160 mg	189	16	32	5.5	22
[167]	Letrozole	199	16	27	3	29
	MA 160 mg	201	15	24	3	26
[168]	Exemestane	366	15	37	4.7+	NR+
	MA 160 mg	403	12	35	3.8	28

AI aromatase inhibitor; *ORR* objective response rate; *CBR* clinical benefit rate; *TTP* time to progression; *MA* megestrol acetate; *OS* overall survival; *NR* not reached
+Significant difference from the result with MA

Table 18.4 Trials of AIs compared with tamoxifen as first-line therapy for advanced disease

Reference	AI studied	*n*	ORR (%)	CBR (%)	Median TTP (months)
[169]	Letrozole	453	30[a]	49[a]	9.4[a]
	Tamoxifen	454	20	38	6.0
[170]	Anastrozole	171	21	59[a]	11.1[a]
	Tamoxifen	182	17	46	5.6
[171]	Anastrozole	340	33	56	8.2
	Tamoxifen	328	33	56	8.3
[172]	Exemestane	61	41	57	Not given
	Tamoxifen	59	17	42	Not given

AI aromatase inhibitor; *ORR* objective response rate; *CBR* clinical benefit rate; *TTP* time to progression
[a]Significant difference from the result with tamoxifen

1,500 mg/day of diethylstilbestrol respectively, with a concomitant increase in toxicity but very similar response durations [91]. Furthermore, Stoll demonstrated that the greater the time between menopause and oestrogen treatment, the greater chance of obtaining a tumour response [92]. This suggests that tumours developing or growing in a low-oestrogen environment have increased sensitivity to growth inhibition by oestrogen, akin to the supersensitivity of breast cancer cell lines cultured in low-oestrogen conditions in the laboratory [93, 94]. These more recent data have reignited the enthusiasm for further research into estradiol therapy, in particular at lower, better tolerated doses following the failure of third-generation AIs [95, 96].

Androgens were the first systemic therapy to be used to treat metastatic breast cancer [97]. With high-dose oestrogens, they were the treatment of choice until the development of the anti-oestrogens in the 1970s. Understandably, their use waned, primarily because of the associated toxicities, particularly virilisation, but also because, in general, they were found to be less effective than oestrogens and anti-oestrogens. The androgens testosterone, fluoxymesterone, testolactose danazol and calusterone are associated with ORRs of approximately 20%, which is lower than other available additive endocrine therapies [98]. Anti-androgens such as flutamide have received only limited evaluation. In one trial, a single partial response was seen in 29 evaluable patients given flutamide 750 mg daily [99]. However, the recent demonstration, using RNA microarrays, of a group of ER – ve but AR +ve apocrine tumours has led to renewed interest in the assessment of anti-androgen therapy in this restricted group of tumours [100].

Progesterone was synthesised in the 1930s and shown to inhibit oestrogen-stimulated tumour growth

in rats [101]. After the first clinical use [102], a large number of progesterone analogues were tested, most of which had clinical activity, although the precise mechanism of anti-tumour action is unclear [103–105]. Similar to high-dose oestrogens, the highest response rates to progestins are more likely to be seen in patients with ER and PR +ve tumours, treated more than 10 years after the menopause, with a long disease-free interval (>2 years) and soft tissue disease, although acceptable response rates have been reported for visceral disease [106]. At standard doses, trials suggest that progestins give equivalent responses to tamoxifen but with considerably greater toxicity, including weight gain, hypertension and oedema [34]. In a large randomised trial, including 341 patients comparing 160, 800 and 1,600 mg of MA/day, there were no significant differences in response rates [107]. Importantly, MA has been shown in large randomised studies to be inferior to treatment with third-generation AIs as second-line therapy, and its use is generally confined to at least fourth-line therapy and often in end stage disease (Table 18.4).

In principle, pure progesterone receptor antagonists (PAs) and progesterone receptor modulators (PRMs, mixed agonist/antagonists) form a new category of hormonal agents for breast cancer but their development has been delayed because of efficacy and toxicity problems [108]. Two phase II studies of mifepristone (second and third line) showed 4PRs in 33 patients [108, 109], and in a second-line study of onapristone, there were ten objective remissions in 101 evaluable patients [110]. As first-line agents, mifepristone showed 11% objective remissions (3/28, [111]) and onapristone 56% PR (10/18, [112]), with a median duration of remission of 70 weeks. Onapristone is well tolerated symptomatically, but the majority of patients treated developed liver function test abnormalities and a phase III study vs. MA was stopped. A new PA without liver toxicity is now in phase II clinical trial (Lonaprisan, ZK230211), and PAs may well prove to be an important new endocrine therapy.

18.3.1 Adjuvant Therapy

18.3.1.1 Tamoxifen

The use of adjuvant systemic endocrine therapy in early breast cancer began in earnest in the 1970s due to the improved tolerability of tamoxifen compared with the existing treatments described above. Although a small study, in women with node-positive early breast cancer, demonstrated an improvement in event-free survival with 2 years of aminoglutethamide vs. placebo, the benefit was lost with longer FU [113]. Notably, 19% of women discontinued treatment due to toxicity and the trial was stopped early due to the incidence of fatal agranulocytosis in the treatment arm. The tolerability and efficacy of tamoxifen in advanced breast cancer led to a profusion of clinical studies, in varied patient populations. To facilitate rigorous examination of these centrally collected data from every women in all randomised breast cancer adjuvant trials, the Early Breast Cancer Trials Collaborative Group (EBCTCG) was formed to co-ordinate quinquennial world-wide meta-analyses. In the first such overview published in 1988, 28 trials of tamoxifen adjuvant therapy were analysed, including 16,513 patients of whom nearly 4,000 had died. This study found that mortality was significantly reduced when comparing any tamoxifen with no tamoxifen ($P<0.0001$) in women 50 or older, for whom assignment to tamoxifen reduced the annual odds of death during the first 5 years by about one fifth [114]. In the second overview, data from 30,000 women randomised in tamoxifen trials demonstrated a highly significant reduction in the annual rates of both recurrence and death in favour of tamoxifen (25 ± 2 and $17 \pm 2\%$, respectively: $2p < 0.00001$ for both), an effect size comparable to the effects of OA seen in trials, including 3,000 women below age 50 (26 ± 6 and $25 \pm 7\%$, respectively: $2p > 0.0004$) [115]. Tamoxifen was also shown to reduce the risk of developing contralateral breast cancer (CLBC) by $39 \pm 9\%$: $P<0.00001$). Of particular interest from this overview was the observation that the avoidance of recurrence with tamoxifen was predominantly during years 0–4, but the avoidance of mortality was highly significant both during and after years 0–4. Thus, the cumulative differences in survival produced by relatively brief tamoxifen treatment (median 2 years) were larger at 10 than at 5 years. Further analysis revealed that longer-term tamoxifen (for 2 or 5 years) was significantly more effective than shorter tamoxifen regimens.

The third overview gave strong evidence from the 55 trials analysed which indicated that there was no survival benefit in any tested duration of tamoxifen in women with ER-poor tumours (8,000 of 38,000 women) [116]. In contrast, in the remaining 30,000 women (18,000 ER positive and nearly 12,000 with

ER unknown), the proportional mortality reductions were 12 ± 3, 17 ± 3 and 26 ± 4% for tamoxifen durations of approximately 1, 2 and 5 years. Again, the improvement in survival grew steadily larger throughout the first 10 years of FU. The proportional mortality reductions were similar for women with node-positive and node-negative disease, but the absolute mortality reductions were greater in node-positive women. In the trials of about 5 years of adjuvant tamoxifen, the absolute improvements in 10-year survival were 10.9 ± 2.5% for node-positive breast cancer (61.4 vs. 50.5%, 2p<0.00001) and 5.6 ± 1.3% for node-negative breast cancer (78.9 vs. 73.3%, 2p<0.00001), benefits which were largely irrespective of age and menopausal status. Furthermore, the proportional reductions in CLBC were 13 ± 13, 26 ± 9 and 47 ± 9% in trials of 1, 2 or 5 years of tamoxifen.

The data were strengthened further in the fourth overview with publication of data from 66,000 women in 71 trials and included 15-year survival data for the first time [117]. For ER-positive disease, allocation to about 5 years of adjuvant tamoxifen reduced the annual breast cancer death rate by 31 ± 3% (SE), largely irrespective of the use of chemotherapy and of age (<50, 50–69, ≥70 years), progesterone receptor status, or other tumour characteristics. As seen previously, the magnitude of effect in reduction in the risk of death grew after discontinuation of tamoxifen and was more than twice as big at 15 years as at 5 years after diagnosis (Fig. 18.3).

In the absence of consistent data or long FU in studies of longer durations of tamoxifen, 5 years of tamoxifen became the "gold standard" adjuvant endocrine therapy. The data on increased durations of tamoxifen beyond 5 years are not conclusive. In the recently presented ATLAS study of approximately 11,500 women, continuation of tamoxifen to 10 years significantly reduced recurrence rate but not breast cancer-specific or ovarian suppression (OS) compared to stopping tamoxifen therapy at 5 years [118]. Whether intermediate durations between 5 and 10 years are superior to 5 years is not known and it is unlikely that such studies will be performed in view of the incorporation of the third-generation AIs into more contemporary treatment algorithms. Such treatment algorithms and the relative toxicities of tamoxifen and the AIs are discussed below.

18.4 Ovarian Ablation (OA) and Ovarian Suppression (OS)

As with tamoxifen, the EBCTCG overviews have used meta-analysis to demonstrate improved outcome with OA/OS in women with ER-positive or unknown early breast cancer [10, 119]. However, in contrast to the effects of tamoxifen, which show little confounding by the administration of cytotoxic chemotherapy, the situation with OA/OS is more complex. Cytotoxic chemotherapy regimens, those that include alkylating agents in particular, can induce premature menopause. Indeed, individual randomised studies in pre-menopausal women with ER-positive breast cancers have shown that women who enter the menopause due to chemotherapy fair better than those who do not [120, 121]. In the most recent overview to include OA, the available randomised trials produced data on 4,317 women younger than 50 years of age treated with OA by surgery or radiotherapy [117]. As these studies were generally performed earlier than studies of OS, most patients (63%) had not had the tumour ER status assessed. In such a young population, it can be assumed that as many as 30–40% of these women would have

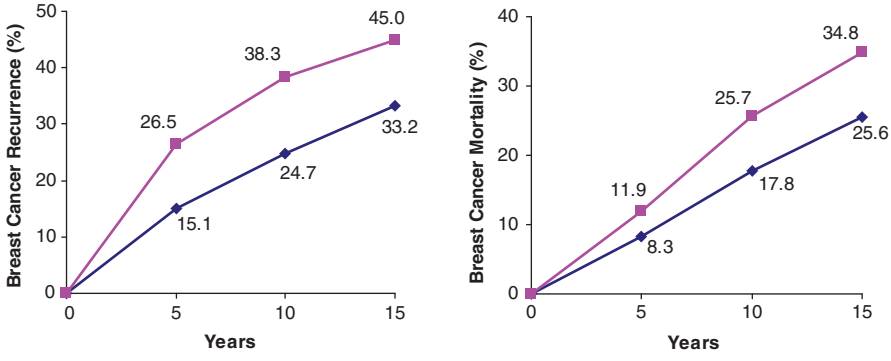

Fig. 18.3 15-year probabilities of recurrence (*left panel*) and breast cancer-related mortality (*right panel*) with 5 years of tamoxifen vs. not in ER-positive (or ER-unknown) disease demonstrating divergence of the curves beyond the treatment period for mortality only (adapted from [117]

had ER-negative breast cancers. Despite this, OA significantly reduced the risk of breast cancer recurrence (HR0.83 2p>0.0005) and death (HR0.86, 2p>0.01), although to a lesser degree compared to the earlier overviews. This relatively weak effect was probably due to an increase in more effective systemic therapies, including combination chemotherapy. When subgroups of women were analysed for the effect of OA dependent on co-treatment with chemotherapy, both those aged <40 and 40–49 demonstrated numerical improvements in the annual hazard ratios for breast cancer mortality only in the absence of chemotherapy (HR 0.71 vs. 1.04 and 0.68 vs. 0.98, respectively). However, the absolute numbers of women in such studies were too small for formal statistical significance to be reached.

More recently, the EBCTCG has published a report on 9,022 hormone receptor-positive women with a median FU of 6.8 years randomised in 16 studies of OS [119]. In an attempt to reduce the confounding by additional systemic therapies, the trials were divided into those that assessed OS as the only adjuvant treatment, those that combined OS with tamoxifen, chemotherapy, or both, and those that directly compared OS (with or without tamoxifen) with a chemotherapy regimen. Only 338 women were randomised into four trials comparing LHRH agonists to no other systemic therapy. Treatment did not have a significant effect on recurrence (28.4% relative reduction in HR (95%CI, −3.5–50.3%; $P>0.08$) or on death after recurrence (17.8%, −52.8–42.9%; $P>0.49$). However, the apparent effect size was large and consistent with that described above for OA, suggesting that larger trials may produce a statistically significant outcome.

However, in view of the emergence of tamoxifen as a highly effective therapy it is highly unlikely that such trials will be conducted. Indeed, analysis of data from 407 women randomised to no systemic therapy vs. OS plus tamoxifen demonstrated significant reductions in BC recurrence (58.4%, 95%CI 36.0–72.9, $P<0.0001$) and death after recurrence (46.6%, 3.4–70.5, $P>0.04$) with active treatment. Some of the efficacy of this combination is clearly due to tamoxifen, and analysis of a further five trials ($n>1{,}013$) demonstrated no significant benefit to the addition of OS to tamoxifen alone in terms of BC recurrence or survival after recurrence (HR 0.85, 95% CI 0.67–1.09, $P>0.20$ and HR 0.84, 95% CI 0.59–1.19, $P>0.33$, respectively). The percentage change in HR /was far superior for both outcomes in the <40 compared to 40–49 year age group, suggesting that younger women may be more likely to derive benefit from OS in addition to tamoxifen, however, neither analysis reached statistical significance ($P>0.22$ for <40 years vs. $P>0.99$ for 40–49 years).

This question of the need for OS in addition to tamoxifen, but after the use of cytotoxic chemotherapy was also addressed in the overview but without a definite conclusion. As mentioned above, a non-significant improvement in the percentage change in HR for recurrence was seen for the <40 years age group with the addition of OS to chemotherapy and tamoxifen (−31.2%, 95%CI −67.5–46.0, $P>0.33$) but not for the 40–49 year group (5.3%,−33.3–66.3, $P>0.82$). However, there was little difference between the two groups in terms of death after recurrence, and the decision to suppress ovarian function in addition to treating with tamoxifen in women who remain pre-menopausal, post-chemotherapy remains the subject of clinical trials. The IBCSG-2402 (SOFT) trial will attempt to answer this question by randomising 3,000 pre-menopausal women to tamoxifen alone, tamoxifen plus OA/OS or the steroidal AI exemestane plus OA/OS [122]. The duration of OS in this study will be for 5 years and results should hopefully inform clinical practise on this issue if sufficient women who have received chemotherapy are randomised.

The issue as to whether OS (±tamoxifen) is as efficacious as cytotoxic chemotherapy in pre-menopaulsal women was also analysed by the EBCTCG[119]. There were no significant differences in BC recurrence or death between chemotherapy and endocrine therapy in either age group alone, or when combined. Some have argued that this implies equivalent efficacy between the two approaches, and that younger women can be spared the toxicity of chemotherapy. However, the benefits of tamoxifen are not confounded by the use of chemotherapy (see above) and a major research goal is to identify which patients will benefit from either therapy alone or both in combination. Appropriate predictive and prognostic approaches are discussed elsewhere in this publication.

18.5 Aromatase Inhibitors

The superiority of the third-generation AIs over tamoxifen in advanced BC made them attractive options for

post-menopausal women in the adjuvant setting. Three basic trial designs were adopted to test AI adjuvant efficacy (Fig. 18.5):

1. Monotherapy AI for 5 years vs. tamoxifen
2. Switching or sequencing from tamoxifen to AI (or the reverse) halfway through 5 years of treatment
3. Extended adjuvant therapy, randomising to AI or placebo/no further therapy after the completion of about 5 years of tamoxifen.

These approaches will be discussed separately where possible, although switches following data release and multi-arm studies make this impractical at times. The major results are summarised in Tables 18.5–18.7. The relative toxicity profiles between tamoxifen and the AIs are discussed at the end of this section (Table 18.8).

18.5.1 Monotherapy Comparisons Between Tamoxifen and AI

The first large randomised study to examine the efficacy of the AI anastrazole against tamoxifen was the ATAC study. In its original form, this was a three-arm study, testing anastrazole 1 mg daily vs. tamoxifen 20 mg daily vs. the combination. At the initial analysis, the combination arm was discontinued because it showed no efficacy or tolerability benefits over tamoxifen alone [123]. The results of the two remaining monotherapy arms at a median FU of 100 months demonstrated a significant advantage with anastrazole in terms of relapse-free survival, distant metastasis-free survival and the incidence of CLBC ([124]; Table 18.5). Similarly, in the monotherapy arms of the

Table 18.5 Studies comparing 5 years of tamoxifen vs. 5 years of AI in post-menopausal early breast cancer

Study	Reference	Rx	*n*	FU	Mean age	G3	LN+	T>2	DFS	TTDR	OS	CLBC
ATAC†	[124]	Tam	2,618	100	64.1	23.3	33.5	37.1				
		anastrazole	2,598		64.1	23.7	34.9	36.1	0.85(0.76–.94)[a]	0.84(0.72–.97)[b]	0.97(0.86–1.11)	0.6(0.42–0.85)[a]
BIG 1-98‡	[126]	Tam	2,459	76	61	NR	41.2	37.7				
		Letrozole	2,463		61	NR	41.5	36.5	0.88(0.78–0.99)[b]	0.85(0.72–1.0)	0.87(0.75–1.01)	NR

NR not reported
†Hormone receptor-positive tumours only; ‡intent-to-treat analysis
[a]P<0.01
[b]P<0.05

Table 18.6 Studies comparing switching/sequencing strategies of tamoxifen and AI in post-menopausal early breast cancer

Study	Reference	Therapy	*n*	FU	age	G3	LN+	T>2	DFS	TTDR	OS	CLBC
IES†	[130]	Tam	2,372	56	64.2	18.8	43.8	51.4				
		Tam-Exe	2,352		64.3	20.3	44.6	49.0	0.75(0.65–0.77)[a]	0.83(0.70–0.98)[b]	0.83(0.69–1.0)[b]	0.56(0.33–98)[b]
ARNO95	[131]	Tam	490	30.1	60.5	19.2	26.9	37.3		6.7% DR		1.0%
		Tam-Ana	489		60.9	15.5	25.9	35.7	0.66(0.44–1.0)[b]	5.5% DR	0.53(0.28–0.99)[b]	1.4% NS
ITA	[129]	Tam	225	63	63	19	100	51			*n*>21	0.9%
		Tam-Ana	223		63	24	100	49	0.35(0.18–0.68)[a]	0.49(0.22–1.05)	*n*>12 NS	0.4% NS
ABCSG8	[132]	Tam	1,454	~75	NR	0	26	26				
		Tam-Ana	1,472		NR	0	26	26	0.79(0.65–0.95)[b]	NR	0.77(0.61–0.97)[b]	NR
Meta	[173]	Tam	1,997	30	63	7	34	NR				22(1%)
		Tam-Ana	2,009		63	6	34	NR	0.59(0.48–0.74)[a]	0.61(0.45–0.83)[a]	0.71(0.52–0.98)[b]	14(1%) NS
BIG 1-98	[126]	Letrozole	1,546	71	NR	NR	42	NR				
		Tam-Let‡	1,548		NR	NR	42	NR	1.05(0.84–1.32)	1.22(0.88–1.69)	1.13(0.83–1.53)	NR
		Let-Tam‡	1,540		NR	NR	42	NR	0.96(0.76–1.21)	1.05(0.75–1.47)	0.90(0.65–1.24)	NR
TEAM	[128]	Exe	~5,000	33	NK	27	48	NR	0.89(0.72–1.03)	0.81(0.67–0.94)[b]	NR	NR
		Tam-Exe	~5,000		NK	27	48	NR				

FU follow up (median); *NR* not reported; *DFS* disease-free survival; *TTDR* time to distant recurrence; *OS* overall survival; *CLBC* contralateral breast cancer†Hormone receptor-positive/unknown tumours only; ‡compared to letrozole alone
[a]P<0.01
[b]P<0.05

Table 18.7 Extended adjuvant studies of AIs post 5 years tamoxifen

Study	Reference	Therapy	*n*	FU	Mean age	G3	LN+	T>2	DFS	TTDR	OS	CLBC
MA 17	[134]	Placebo	2,587	30	62	NR	46	NR				
		Letrozole 5 year	2,583		62	NR	45	NR	0.58(0.45–0.76)[a]	0.60(0.43–0.84)[a]	0.82(0.57–1.19)	0.63(0.18–2.21)
ABCSG6a	[136]	Placebo	466	62	69	20	31	37				
		Anastrazole 3 year	386		68	20	34	38	0.62(0.40–0.96)[b]	0.53(0.29–0.96)[b]	0.89(0.59–1.34)	0.67(0.25–1.80)
NSABP -B33‡	[135]	Placebo	799	30	60	NR	48	~33			*n*>13	*n*>8
		Exemstane 5 year	799		60	NR	48	~33	0.68 (NR)	0.69(NR)	*n*>16	*n*>2

FU follow up (median); *NR* not reported; *DFS* disease-free survival; *TTDR* time to distant recurrence; *OS* overall survival; *CLBC* contralateral breast cancer

‡Intent-to-treat analysis

[b]P<0.05; [a]P<0.01

Table 18.8 Relative toxicity profiles of AIs and tamoxifen in adjuvant and extended adjuvant studies

	AI vs. tamoxifen 5 years[124, 125]	AI vs. tamoxifen 3 years after tam 2 years [130, 172]	AI vs. placebo/no treatment [134, 136]
Hot flushes	↓	→	↑
Alopecia	→	→	↑
Vaginal bleeding	↓	↓ or →	↓
Endometrial cancer	↓	→ (↓[a])	→ or ↓
Ischaemic cerebrovascular events	↓ or →	→	→
Ischaemic cardiac events	→ (↑[b])	→	→
Venous thromboembolic events	↓	↓	→
Arthralgia	↑	↑	↑
Osteoporosis	↑	↑	↑
Fractures	↑	↑ or →	↑ or →

↑ significant increase; → no significant difference; ↓ significant reduction

[a]Significant increase in serious gynaecological events, including endometrial hyperplasia and hysterectomy for tamoxifen over exemestane in IES study

[b]significant increase in serious (grade 3–5) ischaemic cardiac events with letrozole in BIG 1-98 study

BIG 1-98 study, letrozole demonstrated increased efficacy over tamoxifen at a median FU of 51 months [125]. The patient populations differed somewhat between these two studies, hence the inclusion of these details in Table 18.5. Definitions of trial endpoints also differed, including the inclusion of non-breast cancer second malignancies in disease-free survival (DFS) in BIG 1-98 but not ATAC, and the inclusion of ductal carcinoma in situ (DCIS) in DFS in ATAC but not BIG 1-98. Full details of the trial endpoints can be found in the quoted references. Despite these differences, the outcome of the monotherapy arms of the two trials is very similar (Table 18.5). In the most recent presentation of the BIG 1-98 study, which included all 4 arms for the first time, letrozole monotherapy was reported to show a borderline significant improvement in overall survival with a HR compared to tamoxifen of 0.81 (95%CI 0.69–0.94, $P>0.05$) at 76 months FU [126]. However, following the prior release of studies demonstrating a benefit from switching to an AI from tamoxifen after 2–3 years, the monotherapy tamoxifen arm was un-blinded and patients were offered letrozole. Such patients (approximately 25%) were censored from the final analysis, "concentrating" the effect of

those that had relapsed on tamoxifen and potentially biasing the results in favour of letrozole. In the uncensored population, the HR in favour of letrozole was 0.87 (95%CI 0.75–1.02, $P>0.08$) and the true HR probably lies somewhere in between 0.81 and 0.87 but is highly unlikely to be statistically significant [126].

A third large monotherapy study, including 5,000 ER-positive patients, was also initiated to compare 5 years of tamoxifen vs. the same duration of the steroidal AI exemestane (the TEAM study). However, following the release of results from the IES study (see below), the study design was changed to include 9,775 patients and to compare the efficacy of 5 years of exemestane with a switching strategy from tamoxifen to exemestane after approximately 2–3 years [127]. No published efficacy data are available from this study, however results have been presented and will be discussed below [128].

18.5.2 Switching/Sequencing Strategies

It is worth considering the temporal relapse patterns for tamoxifen and AI in the monotherapy studies before considering the switching strategies. Kaplan-Meier curves for DFS and time to distant recurrence (TTDR) in both the ATAC and BIG 1-98 studies separated early, during the first 2 years of therapy [123, 126]. This early divergence is best seen by examining smoothened hazard ratio curves for the treatment arms, which demonstrate significant divergence by year 1, which increases to year 2 (Fig. 18.5). Thus, the superiority of AIs in reducing recurrence is manifest early on in treatment, and a strategy of randomisation after 2–3 years of tamoxifen will exclude women with the most endocrine-resistant tumours. All, but oneof the two-arm studies in this category has adopted a "switching" strategy i.e. randomising patients after all have been treated with tamoxifen for 2–3 years, thus pre-selecting for endocrine sensitivity (Fig. 18.4) [126, 128–131]. The exception is the ABCSG 8 study in which a planned "sequencing" strategy was adopted, in which all patients were randomised immediately post-surgery [132]. However, the inclusion criteria for this particular study also ensured a degree of pre-selection of a more endocrine-sensitive phenotype, by excluding women who required chemotherapy and those with grade 3 tumours. Indeed, the relatively good prognostic features of the tumours in ABCSG 8 were exemplified by the lowest mastectomy rate (19%) of any of the AI adjuvant studies. The sequencing strategy has also been examined in

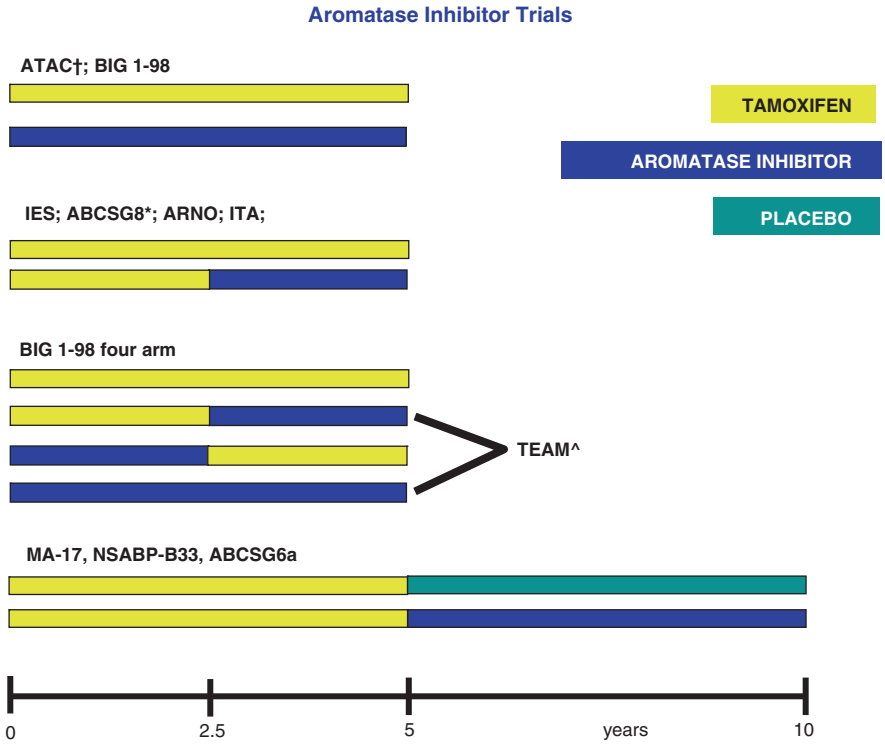

Fig. 18.4 Schematic representation of trials designs for adjuvant aromatase inhibitor (AI) studies. *†ATAC* combination arm closed at first interim analysis **ABCSG8* randomisation before any endocrine therapy, all other switching studies randomised after 2–3 years of tamoxifen, *^TEAM* study initially planned to compare tamoxifen vs. exemestane for 5 years but changed to switch strategy after IES results, ♥ 3years AI vs. no treatment in ABCSG6a after tamoxifen 5 years ± 2 years aminoglutethamide

the BIG 1-8 four arm study (Fig. 18.4), with randomisation before any treatment, and this study is also the only study so far to examine the reverse switch, i.e. AI (letrozole) for 2–3 years followed by tamoxifen. The TEAM study is also included in this section, as discussed above, and the major results from these studies, including a meta-analysis of the three studies using anastrazole, are presented in Table 18.7.

The most striking observation from Table 18.7 is that, compared to 5 years of tamoxifen, a switch from tamoxifen to AI after 2–3 years significantly improved DFS in all studies. This translated to significant improvements in overall survival in the larger IES, ARNO95 and ABCSG8 studies, and meta-analysis of the three anastrazole studies demonstrated a 29% reduction in the risk of death compared to tamoxifen alone. Such data are not available from the BIG 1-98 study due to the reported switch of 1/3rd of patients from tamoxifen to letrozole after unblinding of the monotherapy tamoxifen arm. The release of the data discussed so far and those from the extended adjuvant studies (see below) led an American Society of Clinical Oncology (ASCO) technology assessment report to conclude that "optimal adjuvant hormonal therapy for a post-menopausal woman with receptor-positive breast cancer should include an AI" [133]. The optimal strategy could not be determined, however, and further data from trials was awaited.

Most recently, the BIG 1-98 and TEAM studies have shed further light on the optimal strategy [126, 128]. Although there were no significant differences in any endpoint comparing either switch strategy with letrozole monotherapy in BIG 1-98 (Table 18.6, Fig. 18.4), the HRs with the letrozole to tamoxifen sequence appeared more favourable than those with the reverse strategy [126]. This was corroborated by data from the TEAM study demonstrating a significant improvement in time to distant metastasis with exemestane compared with the tamoxifen to exemestane sequence [128]. As with many of the studies, which reported more recently, TEAM suffered from a change in its design (see above), crossover of a relatively large proportion of patients and, of most concern, discontinuation of trial therapy in 29.5% of those taking tamoxifen and 18.9% of those on exemestane by 2.75 years FU. Thus, the results are far from "clean" but suggest a detrimental outcome in patients who start therapy with tamoxifen rather than exemestane, akin to the early separation of Kaplan-Meier curves discussed above. Thus, the data so far suggest that initiation of adjuvant endocrine therapy in post-menopausal women should be with an AI and that continuing to 5 years with the same therapy or switching to tamoxifen after 2–3 years appear equally efficacious.

18.5.3 Extended Adjuvant Therapy

Three studies have examined the efficacy of switching to an AI following completion of approximately 5 years of tamoxifen ([134–136] Fig. 18.5; Table 18.7). MA17 was the first to report and the results led to the study being unblinded after only 2.4 years median FU [137]. Patients randomised to letrozole had significantly improved DFS and TTDR, although in the whole group, no improvement in OS was seen (Table 18.7). However, in a subsequent update of these data, subgroup analysis did show an improvement in OS in the 45% of women with involved axillary lymph nodes at primary surgery (HR 0.61, 95% CI>0.38–0.98; $P>0.04$) [134]. Furthermore, the women who had initially been randomised to placebo were subsequently offered letrozole and 1,579 women accepted with a median time from tamoxifen of 2.8 years [138]. Eight hundred and four women chose to have no further therapy. Notably, this was not a randomisation and patients in the letrozole group were younger; had better performance status and were more likely to have had node-positive disease and adjuvant chemotherapy than those in the no treatment group. At a median follow-up of 5.3 years, disease-free

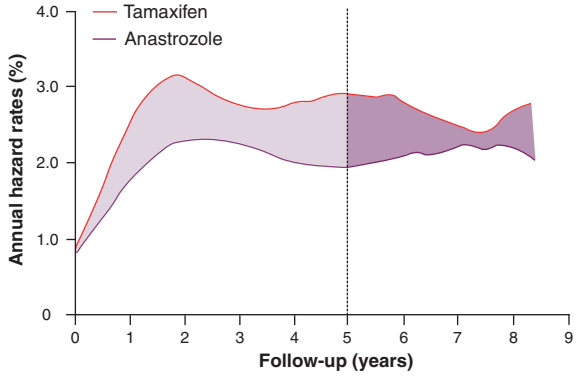

Fig. 18.5 Smoothed hazard rate curves for time to recurrence in the ATAC study (taken from [124]) demonstrating the increasingly disparate risk of relapse over time occurring during the first 2 years of therapy

survival (HR 0.37; 95% CI, 0.23–0.61; $P<0.0001$) and distant DFS (HR, 0.39; 0.20–0.74; $P>0.004$) were superior in the treated group [138].

By comparison, the other two studies of extended adjuvant therapy are relatively small but show reductions in DFS and TTDR of a similar magnitude to the MA17 study ([135, 136]; Table 18.7). Interpretation of ABCSG6a is complicated by its design as a follow -up on study of ABCSG6, which randomised women to 5 years of tamoxifen ± 2 years of aminoglutethamide, and also by its use of 3 years of AI. Interpretation of NSABP-33 is also complicated by the closure to recruitment and unblinding of the study after only 2.5 years of accrual and following the release of the MA17 data. Subsequently, women on placebo were offered exemestane and 44% accepted. However, rather surprisingly, only 72% in the exemestane group continued on treatment. With 30 months of median follow-up, original exemestane assignment resulted in a borderline statistically significant improvement in 4-year DFS (91 vs. 89%; RR > 0.68; $P>0.07$) and a significant increase in 4-year relapse-free survival (RFS; 96 vs. 94%; RR > 0.44; $P>0.004$) despite the high cross-over rate.

Thus, extending adjuvant therapy with an AI after 5 years of tamoxifen reduces the risk of relapse and in those with node-positive disease may improve overall survival. However, important questions still remain:

1. As 5 years of tamoxifen is no longer the "gold standard" of therapy, does extending AI therapy following a tam-AI sequence still provide added benefit?
2. Does switching back to an AI after an AI-tam sequence add benefit, and if so, what is the optimal duration of therapy?
3. Which subgroups of patients should be treated with extended adjuvant therapy?
4. What are the long-term toxicities of the AIs?
5. What are the economic implications for continued/continuous adjuvant therapy.

Further studies are underway to provide additional information on some of these questions.

18.5.4 Neoadjuvant Endocrine Therapy

Primary systemic treatment with chemotherapy, endocrine therapy or biological therapy has the capacity to downstage the primary tumour to facilitate breast-conserving surgery. In addition, the presence of an accessible primary tumour allows for serial biopsies and biomarker studies during therapy. However, neoadjuvant therapy does not provide a survival advantage over the same regimen delivered in the adjuvant setting. Two randomised phase III neoadjuvant studies have been performed to evaluate third-generation AIs against tamoxifen, with randomisations according to the three arms of the ATAC study [139] and the monotherapy arms of the BIG 1-98 study [140]. In IMPACT, no significant differences were seen between the three arms in terms of the primary endpoint, overall response (anastrozole, 37%; tamoxifen, 36%; and the combination, 39%). There were non-significant trends in favour of anastrazole over tamoxifen in inducing response in larger tumours thought initially to require mastectomy and in tumours over-expressing HER2 [139]. In contrast, the P024 study randomised women to four, rather than 3 months of letrozole vs. tamoxifen and the AI demonstrated a significant improvement in the rates of response (60 vs. 41%; $P>0.004$) and successful breast-conserving surgery (48 vs. 36%, $P>0.036$). Differences in response rates between letrozole and tamoxifen were most marked for tumours that were positive for HER1 and/or HER2 and ER (88 vs. 21%, $P>0.0004$) [141].

Thus, neoadjuvant biomarker substudies appeared to have identified a subgroup of women in whom an AI would be of particular benefit over tamoxifen, compared with the overall population. However, in the translational sub-studies of ATAC and BIG 1-98, central analysis of tumour blocks from 2,006 of 5,880 (34%) and 3,650 of 4,922 (74%) patients in the monotherapy arms only, could not substantiate a differential benefit with AI over tamoxifen with regard to quantitative ER, PR or HER-2 expression [142, 143]. Central analysis of Ki-67 (BIG 1-98) and Oncotype DX assay (ATAC) in these trials have also failed to formally identify subgroups that particularly benefit from an AI over tamoxifen, although the magnitude of treatment benefit for letrozole vs. tamoxifen was numerically greater among patients with high tumour Ki-67 (HR > 0.53; 95% CI, 0.39–0.72) than among patients with low tumour Ki-67 (HR > 0.81; 95% CI, 0.57–1.15) with a borderline significant p value for interaction of 0.09 [141, 144].

In view of the randomised data with letrozole and anastrazole, the AIs are considered the treatment of choice for neoadjuvant endocrine therapy in post-menopausal women. Indeed, in a randomised phase II study

of anastrazole or exemestane vs. combination chemotherapy with doxorubicin and paclitaxel in 239 women with T2-4N1-2M0 ER and/or PR-positive breast cancers, no significant differences were seen in response rates, time to response or pathological complete response rates between the two groups [145]. Thus, neoadjuvant endocrine therapy offers the chance to test endocrine sensitivity in the primary tumour prior to surgery, and may hold utility in identifying a population of patients who do not require adjuvant chemotherapy thereafter. To this end, the investigators of the IMPACT and P024 studies have devised a pre-operative endocrine prognostic index (PEPI) according to the residual tumour characteristics after 3–4 months of neoadjuvant AI to determine which patients remain at high risk of relapse and should be considered for other therapies, including cytotoxic chemotherapy and novel agents [146]. The four factors included in the PEPI algorithm are tumour and lymph node stages, Ki67 and ER status. Patients with the lowest PEPI (group1) had 5-year relapse-free survival of 90–95% in both P024 and IMPACT studies despite only 10% of such women receiving chemotherapy. In contrast, those with the worst PEPI (group 3) had only 50–60% 5-year RFS despite ~40% having received adjuvant chemotherapy. Although longer FU and further validation of this approach is required, neoadjuvant endocrine therapy may demonstrate utility in "screening" tumours for endocrine sensitivity prior to surgery, thus rationalising the use of cytotoxic chemotherapy to women with endocrine-insensitive tumours.

18.5.5 Toxicity of AIs and Tamoxifen

Although the use of the third-generation AIs has increased significantly over the last 5–10 years, following publication of the efficacy results described above, some issues remain regarding the tolerability of these drugs. Tamoxifen toxicity is well described and related to both its anti-oestrogenic and oestrogenic effects in various tissues of the body. Compared to no therapy, tamoxifen induces menopausal symptoms such as hot flushes and night sweats as an anti-oestrogen, however gynaecological events such as endometrial hyperplasia and malignancy result from its oestrogenic effects on the uterus [117]. Tamoxifen also behaves as an oestrogen in the bone in post-menopausal women and also promotes thromboembolism. As almost all women with ER-positive early breast cancer in the developed world will receive endocrine therapy consisting of tamoxifen, an AI or both, it is perhaps best to consider the relative incidences of the more important toxicities between the two drug classes (Table 18.8).

In the two largest randomised studies to include monotherapy arms comparing tamoxifen with an AI, the toxicity results were comparable [123, 125]. Compared with tamoxifen, both anastrazole and letrozole therapy resulted in significantly reduced incidence of hot flushes, uterine carcinoma and venous thromboembolism, the latter two reflecting the absence of oestrogenic effects with aromatase inhibition. Indeed, in the extended adjuvant MA17 study, letrozole significantly reduced the incidence of vaginal bleeding and uterine carcinoma over placebo, whilst increasing new diagnoses of osteoporosis, again confirming its purely anti-oestrogenic properties [134]. The absence of a significant increase in fractures in the MA17 study is likely due to the neutral comparator i.e. placebo control, compared with the bone sparing comparator i.e. tamoxifen in ATAC and BIG 1–98 and a possible carry over effect on bone of previous adjuvant treatment with tamoxifen. The risk of osteoporosis with AIs is now of little concern as several studies have demonstrated the efficacy of bisphosphonates in completely ameliorating the negative impact of the AIs on bone, and guidelines for the management of AI-induced bone loss have been published [147–150]. It is likely that these guidelines will need to be restructured following the release of data from at least two large studies demonstrating improvements in DFS with the addition of bisphosphonates to adjuvant therapy protocols, irrespective of bone density, and the suggestion of a positive outcome with a switch from AI to tamoxifen rather than the more commonly used reverse scenario [126, 151, 152].

Perhaps the most troublesome symptom observed with AIs is arthralgia. The mechanism is poorly understood, but thought to be mediated by the profound suppression of oestrogen, and can result in significant tenosynovial changes and increased intra-articular fluid [153]. Factors associated with the development of arthralgia include prior HRT use, adjuvant chemotherapy and obesity, and there is anecdotal evidence that switching from one class of AI to the other, or even switching drugs within the same class, can alleviate such symptoms in a proportion of women, however prospective studies are required to confirm this [154]. Of particular concern are two recent observations:

1. 25–50% of women, who were prescribed a 5-year course of endocrine therapy, will have discontinued all treatment by the fourth year of therapy, with higher rates in non-trial practise [155–157].
2. Women who have side effects early on in their treatment have an improved outcome with reduced recurrence rates compared to those wisth minimal or absent symptoms.

These observations indicate the pressing need for improvements in the management of the toxicities of these highly effective drugs. Furthermore, in women whose symptoms cannot be alleviated completely, communication of the potential benefits may provide reassurance, improving adherence and ultimately, outcome [158].

18.5.6 Concluding Remarks

The substantial benefits of developments in endocrine therapy since Beatson's initial observation of its effectiveness are outlined above. These include the groundbreaking demonstration of the survival advantage of 5 years of adjuvant therapy with tamoxifen as a result of the Oxford Overview process and the more recent demonstration of a survival advantage of AIs in advanced breast cancer and the distant disease-free advantage in adjuvant trials compared with tamoxifen. However, these positive results lead to further questions concerning, for example, the optimum duration of adjuvant AIs, whether we might consider intermittent therapy and how to incorporate AIs into the treatment of women who develop breast cancer pre-menopausally. Most of the effectiveness of endocrine therapy is related to modulating the effects of oestrogen on the ER. Recent studies have demonstrated that changes in oestrogen levels can induce further responses using low dose E after an AI, which gives an indication that there are more potential benefits to be discovered by prolonging the period of endocrine responsiveness. Although it is beyond the scope of this article, recent studies have begun to indicate how tamoxifen and AI resistance may be circumvented by combinations of endocrine therapy with growth factor and signal transduction inhibitors. These new areas remain to be explored by further laboratory and clinical research and will almost certainly add to our knowledge of how we might further enhance the effectiveness of endocrine therapy

References

1. Nunn T. On cancer of the breast. J. and A. Churchill: London (UK); 1882. p. 71
2. Schinzinger A (1889) Ueber carcinoma mammae. 18th Congress of the German society for surgery. Beilage zum Centralblatt fur Chirurgie. 16:55–6
3. Beatson G (1896) On the treatment of inoperable cases of carcinoma of the mamma. Suggestions for a new method for treatment with illustrative cases. Lancet. 2:162–5
4. Boyd S (1900) On oophorectomy in cancer of the breast. Br Med J. 2:1161–7
5. Thomson A (1902) Analysis of cases for which oophorectomy was performed for inoperable carcinoma of the breast. Br Med J. 2:1538
6. Lett H (1905) An analysis of 99 cases of inoperable carcinoma of the breast treated by oophorectomy. Lancet. 1:227
7. Allen E, Doisy E (1923) An ovarian hormone. Preliminary report on its localisation, extraction and partial purification, and action in test animals. JAMA. 81:819–21
8. Cook J, Dodds E, Hewett C (1933) A synthetic oestrus-exciting compound. Nature. 131:56–7
9. DeCourmelles F (1922) La radiotherapie indirecte, ou dirigee par les correlations organiques. Arch Elect Med. 32:264
10. EBCTCG. Ovarian ablation for early breast cancer. Cochrane Database Syst Rev. 2000;(3):CD000485
11. Block G, Vial A, Pullen F (1958) Estrogen secretion following operative and irradiation castration in cases of mammary cancer. Surgery. 43:415
12. Conte CC et al (1989) Therapeutic oophorectomy in metastatic breast cancer. Cancer. 64(1):150–3
13. Oriana S et al (1989) Clinical response and survival according to estrogen receptor levels after bilateral ovariectomy in advanced breast cancer. Eur J Surg Oncol. 15(1):39–42
14. Veronesi U, Pizzocaro G, Rossi A (1975) Oophorectomy for advanced carcinoma of the breast. Surg Gynecol Obstet. 141(4):569–70
15. Buchanan RB et al (1986) A randomized comparison of tamoxifen with surgical oophorectomy in premenopausal patients with advanced breast cancer. J Clin Oncol. 4(9):1326–30
16. Crump M et al (1997) An individual patient-based meta-analysis of tamoxifen versus ovarian ablation as first-line endocrine therapy for premenopausal women with metastatic breast cancer. Breast Cancer Res Treat. 44(3):201–10
17. Ingle JN et al (1986) Randomized trial of bilateral oophorectomy versus tamoxifen in premenopausal women with metastatic breast cancer. J Clin Oncol. 4(2):178–85
18. Sawka CA et al (1997) A randomized crossover trial of tamoxifen versus ovarian ablation for metastatic breast cancer in premenopausal women: a report of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trial MA.1. Breast Cancer Res Treat. 44(3):211–5
19. Klijn JG, de Jong FH (1982) Treatment with a luteinising hormone-releasing hormone analogue (buserelin) in premenopausal patients with metastatic breast cancer. Lancet. 1(8283):1213–6
20. Prowell TM, Davidson NE (2004) What is the role of ovarian ablation in the management of primary and metastatic breast cancer today? Oncologist. 9(5):507–17

21. Robertson JF, Blamey RW (2003) The use of gonadotrophin-releasing hormone (GnRH) agonists in early and advanced breast cancer in pre- and perimenopausal women. Eur J Cancer. 39(7):861–9
22. Williams MR et al (1986) The use of an LH-RH agonist (ICI 118630, Zoladex) in advanced premenopausal breast cancer. Br J Cancer. 53(5):629–36
23. Blamey RW et al (1992) Goserelin depot in the treatment of premenopausal advanced breast cancer. Eur J Cancer. 28A (4–5):810–4
24. Blamey RW et al (1993) Survival data relating to the use of goserelin depot in the treatment of premenopausal advanced breast cancer. Eur J Cancer. 29A(10):1498
25. Taylor CW et al (1998) Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. J Clin Oncol. 16(3): 994–9
26. Klijn JG et al (2000) Combined treatment with buserelin and tamoxifen in premenopausal metastatic breast cancer: a randomized study. J Natl Cancer Inst. 92(11):903–11
27. Klijn JG et al (2001) Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol. 19(2):343–53
28. Forward DP et al (2004) Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer. Br J Cancer. 90(3):590–4
29. Stein RC et al (1990) The clinical and endocrine effects of 4-hydroxyandrostenedione alone and in combination with goserelin in premenopausal women with advanced breast cancer. Br J Cancer. 62(4):679–83
30. Harper MJ, Walpole AL (1966) Contrasting endocrine activities of cis and trans isomers in a series of substituted triphenylethylenes. Nature. 212(5057):87
31. Harper MJ, Walpole AL (1967) A new derivative of triphenylethylene: effect on implantation and mode of action in rats. J Reprod Fertil. 13(1):101–19
32. Cole MP, Jones CT, Todd ID (1971) A new anti-oestrogenic agent in late breast cancer. An early clinical appraisal of ICI46474. Br J Cancer. 25(2):270–5
33. Litherland S, Jackson IM (1988) Antioestrogens in the management of hormone-dependent cancer. Cancer Treat Rev. 15(3):183–94
34. Fossati R et al (1998) Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31, 510 women. J Clin Oncol. 16(10):3439–60
35. Mauri D et al (2006) Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. J Natl Cancer Inst. 98(18):1285–91
36. Baumann CK, Castiglione-Gertsch M (2007) Estrogen receptor modulators and down regulators: optimal use in postmenopausal women with breast cancer. Drugs. 67(16): 2335–53
37. Howell A et al (2004) Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial. J Clin Oncol. 22(9):1605–13
38. Johnston SR (2005) Endocrinology and hormone therapy in breast cancer: selective oestrogen receptor modulators and downregulators for breast cancer – have they lost their way? Breast Cancer Res. 7(3):119–30
39. Pyrhonen S et al (1999) Meta-analysis of trials comparing toremifene with tamoxifen, and factors predicting outcome of antiestrogen therapy in postmenopausal women with breast cancer. Breast Cancer Res Treat. 56(2):133–43
40. Buzdar A et al (2002) Phase III randomized trial of droloxifene and tamoxifen as first-line endocrine treatment of ER/PgR-positive advanced breast cancer. Breast Cancer Res Treat. 73(2):161–75
41. Arpino G et al (2003) Idoxifene versus tamoxifen: a randomized comparison in postmenopausal patients with metastatic breast cancer. Ann Oncol. 14(2):233–41
42. Buzdar AU et al (1988) Phase II evaluation of Ly156758 in metastatic breast cancer. Oncology. 45(5):344–5
43. Gradishar W et al (2000) Effects of high-dose raloxifene in selected patients with advanced breast carcinoma. Cancer. 88(9):2047–53
44. Deshmane V et al (2007) Phase III double-blind trial of arzoxifene compared with tamoxifen for locally advanced or metastatic breast cancer. J Clin Oncol. 25(31):4967–73
45. Labrie F (2006) Future perspectives of selective estrogen receptor modulators used alone and in combination with DHEA. Endocr Relat Cancer. 13(2):335–55
46. Wakeling AE, Bowler J (1987) Steroidal pure antioestrogens. J Endocrinol. 112(3):R7–10
47. Wakeling AE, Dukes M, Bowler J (1991) A potent specific pure antiestrogen with clinical potential. Cancer Res. 51(15):3867–73
48. DeFriend DJ et al (1994) Investigation of a new pure antiestrogen (ICI 182780) in women with primary breast cancer. Cancer Res. 54(2):408–14
49. Osborne CK et al (1995) Comparison of the effects of a pure steroidal antiestrogen with those of tamoxifen in a model of human breast cancer. J Natl Cancer Inst. 87(10): 746–50
50. Robertson JF et al (2001) Comparison of the short-term biological effects of 7alpha-[9-(4, 4, 5, 5, 5-pentafluoropentylsulfinyl)-nonyl]estra-1, 3, 5, (10)-triene-3, 17beta-diol (Faslodex) versus tamoxifen in postmenopausal women with primary breast cancer. Cancer Res. 61(18): 6739–46
51. McCormack P, Sapunar F (2007) Pharmacokinetic profile of the fulvestrant (Fasolodex) loading-dose regimen in postmenopausal women with hormone receptor-positive advanced breast cancer. Breast Cancer Res Treat. 106(Suppl 1):S116
52. Kuter I, Hegg R, Singer CF, Badwe R, Lowe E. On behalf of the NEWEST Investigators. Fulvestrant 500 mg vs 250 mg: first results from NEWEST, a randomised, phase II neoadjuvant trial in postmenopausal women with locally advanced, estrogen receptor-positive breast cancer. Breast Cancer Res Treat. 2007;106(Suppl)
53. Robertson JF (2007) Fulvestrant (Faslodex) – how to make a good drug better. Oncologist. 12(7):774–84
54. Howell A et al (1996) Pharmacokinetics, pharmacological and anti-tumour effects of the specific anti-oestrogen ICI

182780 in women with advanced breast cancer. Br J Cancer. 74(2):300–8
55. Howell A, Robertson J (1995) Response to a specific antioestrogen (ICI 182780) in tamoxifen-resistant breast cancer. Lancet. 345(8955):989–90
56. Osborne CK et al (2002) Double-blind, randomised trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol. 20(16): 3386–95
57. Howell A et al (2002) Fulvestrant, formerly ICI 182, 780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol. 20(16):3396–403
58. Mauriac L et al (2003) Fulvestrant (Faslodex) versus anastrozole for the second-line treatment of advanced breast cancer in subgroups of postmenopausal women with visceral and non-visceral metastases: combined results from two multicentre trials. Eur J Cancer. 39(9):1228–33
59. Howell A et al (2005) Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma: a prospectively planned combined survival analysis of two multicenter trials. Cancer. 104(2):236–9
60. Robertson JF et al (2003) Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials. Cancer. 98(2):229–38
61. Howell A, Abram P (2005) Clinical development of fulvestrant ("Faslodex"). Cancer Treat Rev. 31(Suppl 2):S3–9
62. Ariazi EA et al (2006) Emerging principles for the development of resistance to antihormonal therapy: implications for the clinical utility of fulvestrant. J Steroid Biochem Mol Biol. 102(1–5):128–38
63. Macedo LF et al (2008) Combination of anastrozole with fulvestrant in the intratumoral aromatase xenograft model. Cancer Res. 68(9):3516–22
64. Martin LA et al (2005) The anti-oestrogen ICI 182, 780, but not tamoxifen, inhibits the growth of MCF-7 breast cancer cells refractory to long-term oestrogen deprivation through down-regulation of oestrogen receptor and IGF signalling. Endocr Relat Cancer. 12(4):1017–36
65. Hoffmann J et al (2004) Characterization of new estrogen receptor destabilizing compounds: effects on estrogen-sensitive and tamoxifen-resistant breast cancer. J Natl Cancer Inst. 96(3):210–8
66. Yamaya H et al (2005) Safety, tolerability, and pharmacokinetics of TAS-108 in normal healthy post-menopausal female subjects: a phase I study on single oral dose. J Clin Pharm Ther. 30(5):459–70
67. Blakely LJ et al (2004) A phase I and pharmacokinetic study of TAS-108 in postmenopausal female patients with locally advanced, locally recurrent inoperable, or progressive metastatic breast cancer. Clin Cancer Res. 10(16): 5425–31
68. Buzdar AU (2005) TAS-108: a novel steroidal antiestrogen. Clin Cancer Res. 11(2 Pt 2):906s–8s
69. Huggins C, Dao TL (1953) Adrenalectomy and oophorectomy in treatment of advanced carcinoma of the breast. J Am Med Assoc. 151(16):1388–94
70. Nathanson I, Towne L (1939) The urinary excretion of estrogen and androgen and FSH following administration of testosterone to human female castrates. Endocrinology. 25:754
71. Griffiths CT et al (1973) Preliminary trial of aminoglutethimide in breast cancer. Cancer. 32(1):31–7
72. Wells SA Jr et al (1982) Comparison of surgical adrenalectomy to medical adrenalectomy in patients with metastatic carcinoma of the breast. Cancer Res. 42(8 Suppl):3454s–7s
73. Santen RJ et al (1978) Aminoglutethimide inhibits extraglandular estrogen production in postmenopausal women with breast carcinoma. J Clin Endocrinol Metab. 47(6): 1257–65
74. Geisler J (2008) Aromatase inhibitors: from bench to bedside and back. Breast Cancer. 15(1):17–26
75. Geisler J, Lonning PE (2005) Aromatase inhibition: translation into a successful therapeutic approach. Clin Cancer Res. 11(8):2809–21
76. Smith IE, Dowsett M (2003) Aromatase inhibitors in breast cancer. N Engl J Med. 348(24):2431–42
77. Miller WR, Forrest AP (1974) Oestradiol synthesis by a human breast carcinoma. Lancet. 2(7885):866–8
78. Miki Y, Suzuki T, Sasano H (2007) Controversies of aromatase localization in human breast cancer–stromal versus parenchymal cells. J Steroid Biochem Mol Biol. 106(1–5): 97–101
79. Geisler J et al (2002) Influence of letrozole and anastrozole on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomised, cross-over study. J Clin Oncol. 20(3):751–7
80. Rose C et al (2003) An open randomised trial of second-line endocrine therapy in advanced breast cancer. Comparison of the aromatase inhibitors letrozole and anastrozole. Eur J Cancer. 39(16):2318–27
81. Gibson LJ, et al Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Database Syst Rev. 2007;(1):CD003370
82. Gardner W, Smith G, Strong L (1935) Inhibition of normal gland. Proc Soc Exper Biol Med. 33:138
83. Lacassagne A. Apparition d'adenocarcinomes mammaires chez des souris males traits pare une substance oestrogene synthetique. CR Soc Biol, Paris. 1938;129:64
84. Haddow A, Watkinson J, Paterson E (1944) Influence of synthetic oestrogens upon advanced malignant diseases. BMJ. 2(4368):393–8
85. Beex L et al (1981) Tamoxifen versus ethinyl estradiol in the treatment of postmenopausal women with advanced breast cancer. Cancer Treat Rep. 65(3–4):179–85
86. Gockerman JP et al (1986) Randomised comparison of tamoxifen versus diethylstilbestrol in estrogen receptor-positive or -unknown metastatic breast cancer: a Southeastern Cancer Study Group trial. Cancer Treat Rep. 70(10):1199–203
87. Heuson JC et al (1975) Comparative trial of nafoxidine and ethinyloestradiol in advanced breast cancer: an E.O.R.T.C. study. Br Med J. 2(5973):711–3
88. Ingle JN et al (1981) Randomised clinical trial of diethylstilbestrol versus tamoxifen in postmenopausal women with advanced breast cancer. N Engl J Med. 304(1):16–21
89. Matelski H et al (1985) Randomised trial of estrogen vs. tamoxifen therapy for advanced breast cancer. Am J Clin Oncol. 8(2):128–33
90. Stewart HJ, et al The tamoxifen trial – a double-blind comparison with stilboestrol in postmenopausal women with advanced breast cancer. Eur J Cancer. 1980;Suppl 1:83–8

91. Carter AC et al (1977) Diethylstilbestrol: recommended dosages for different categories of breast cancer patients. Report of the Cooperative Breast Cancer Group. JAMA. 237(19):2079–8
92. Stoll BA (1967) Effect of Lyndiol, an oral contraceptive, on breast cancer. Br Med J. 1(5533):150–3
93. Martin LA et al (2005) Elevated ERK1/ERK2/estrogen receptor cross-talk enhances estrogen-mediated signalling during long-term estrogen deprivation. Endocr Relat Cancer. 12(Suppl 1):S75–84
94. Masamura S et al (1995) Estrogen deprivation causes estradiol hypersensitivity in human breast cancer cells. J Clin Endocrinol Metab. 80(10):2918–25
95. Ellis M, et al (2008) A randomised phase 2 trial of low dose (6 mg daily) versus high dose (30 mg daily) estradiol for patients with estrogen receptor-positive aromatase inhibitor-resistant advanced breast cancer, in SABCS. San Antonio, Texas, USA
96. Lewis JS et al (2005) Intrinsic mechanism of estradiol-induced apoptosis in breast cancer cells resistant to estrogen deprivation. J Natl Cancer Inst. 97(23):1746–59
97. Ulrich P. Testosterone et son role possible dans le traitment de certains cancers du sein. Int Union Against Cancer. 1939;4:377
98. Muss HB (1992) Endocrine therapy for advanced breast cancer: a review. Breast Cancer Res Treat. 21(1):15–26
99. Perrault DJ et al (1988) Phase II study of flutamide in patients with metastatic breast cancer. A National Cancer Institute of Canada Clinical Trials Group study. Invest N Drugs. 6(3):207–10
100. Farmer P et al (2005) Identification of molecular apocrine breast tumours by microarray analysis. Oncogene. 24(29): 4660–71
101. Noble R, Collip J (1941) Regression of estrogen-induced mammary tumours in female rats following removal of the stimulus. Can Med Assoc J. 44:1–5
102. Escher G. Clinical improvement of inoperable breast carcinoma under steroid treatment. Proceedings of the 1st Conference on Steroid Hormones and Mammary Carcinoma, Chicago. The Therapeutic Trials Committee of the council on Pharmacy and Chemistry of the American Medical Association. 1949:92–9
103. Lundgren S et al (1990) Influence of progestins on serum hormone levels in postmenopausal women with advanced breast cancer–I. General findings. J Steroid Biochem. 36(1–2):99–104
104. Segaloff A, Ochsner A. Progress report: results of studies by the Cooperative Breast Cancer Group. 1960:109–41
105. Stoll BA (1967) Progestin therapy of breast cancer: comparison of agents. Br Med J. 3(5561):338–41
106. Haller DG, Glick JH (1986) Progestational agents in advanced breast cancer: an overview. Semin Oncol. 13(4 Suppl 4):2–8
107. Abrams J et al (1999) Dose-response trial of megestrol acetate in advanced breast cancer: cancer and leukemia group B phase III study 8741. J Clin Oncol. 17(1):64–73
108. Klijn JG, Setyono-Han B, Foekens JA (2000) Progesterone antagonists and progesterone receptor modulators in the treatment of breast cancer. Steroids. 65(10–11):825–30
109. Romieu G et al (1987) The antiprogestin RU486 in advanced breast cancer: preliminary clinical trial. Bull Cancer. 74(4):455–61
110. Jonat W, Giurescu M, Robertson J (2002) The clinical efficacy of progesterone antagonists in breast cancer. In: Robertson J, Nicholson R, Hayes D (eds) Endocrine therapy of breast cancer. Martin Dunitz, London, pp 118–124
111. Perrault D et al (1996) Phase II study of the progesterone antagonist mifepristone in patients with untreated metastatic breast carcinoma: a National Cancer Institute of Canada Clinical Trials Group study. J Clin Oncol. 14(10): 2709–12
112. Robertson JF et al (1999) Onapristone, a progesterone receptor antagonist, as first-line therapy in primary breast cancer. Eur J Cancer. 35(2):214–8
113. Jones AL et al (1992) Adjuvant aminoglutethimide for postmenopausal patients with primary breast cancer: analysis at 8 years. J Clin Oncol. 10(10):1547–52
114. Anon. EBCTCG, Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer. An overview of 61 randomised trials among 28,896 women. Early Breast Cancer Trialists' Collaborative Group. N Engl J Med. 1988;319(26):1681–92
115. Anon. EBCTCG, Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. Lancet. 1992;339(8784):1–15
116. Anon. EBCTCG, Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 1998;351(9114): 1451–67
117. EBCTCG (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 365(9472):1687–717
118. Peto R, Davies C (2007) ATLAS (Adjuvant Tamoxifen, Longer Against Shorter): international randomised trial of 10 versus 5 years of adjuvant tamoxifen among 11 500 women preliminary results, in SABCS. San Antonio, Texas, USA
119. Cuzick J et al (2007) Use of luteinising hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone- receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. Lancet. 369(9574):1711–23
120. Boccardo F et al (2000) Cyclophosphamide, methotrexate, and fluorouracil versus tamoxifen plus ovarian suppression as adjuvant treatment of estrogen receptor-positive pre-/perimenopausal breast cancer patients: results of the Italian Breast Cancer Adjuvant Study Group 02 randomised trial. boccardo@hp380.ist.unige.it. J Clin Oncol. 18(14):2718–27
121. Jonat W et al (2002) Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: the Zoladex Early Breast Cancer Research Association Study. J Clin Oncol. 20(24):4628–35
122. Regan MM et al (2008) Premenopausal endocrine-responsive early breast cancer: who receives chemotherapy? Ann Oncol. 19(7):1231–41
123. Baum M et al (2002) Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet. 359 (9324):2131–9

124. Forbes JF et al (2008) Effect of anastrozole and tamoxifen as adjuvant treatment for early stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol. 9(1):45–53
125. Coates AS et al (2007) Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1–98. J Clin Oncol. 25(5):486–92
126. Mouridsen H, et al (2008) BIG 1-98: A randomised, double-blind phase III study evaluating letrozole and tamoxifen given in sequence as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer, in SABCS. San Antonio, Texas, USA
127. Jones, S.E., *Exemestane as adjuvant treatment of early breast cancer: intergroup exemestane study/tamoxifen exemestane adjuvant multicenter trials*. Clin Breast Cancer, 2006. 6 Suppl 2: p.S41-4
128. Jones S, et al (2008) Results of the first planned analysis of the TEAM (tamoxifen exemestane adjuvant multinational) prospective randomised phase III trial in hormone-sensitive postmenopausal early breast cancer, in SABCS. San Antonio, Texas, USA
129. Boccardo F et al (2006) Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian tamoxifen anastrozole (ITA) trial. Ann Oncol. 17(Suppl 7):vii10–4
130. Coombes RC et al (2007) Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet. 369(9561):559–70
131. Kaufmann M et al (2007) Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: the ARNO 95 Study. J Clin Oncol. 25(19):2664–70
132. Jakesz R, et al (2008) Tamoxifen and anastrozole as a sequencing strategy in postmenopausal women with hormone-responsive early breast cancer: updated data from the Austrian breast and colorectal cancer study group trial 8, in SABCS. San Antonio, Texas, USA
133. Winer EP et al (2005) American society of clinical oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. J Clin Oncol. 23(3):619–29
134. Goss PE et al (2005) Randomised trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst. 97(17):1262–71
135. Mamounas EP et al (2008) Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. J Clin Oncol. 26(12):1965–71
136. Jakesz R et al (2007) Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomised Austrian Breast and Colorectal Cancer Study Group Trial 6a. J Natl Cancer Inst. 99(24):1845–53
137. Goss PE et al (2003) A randomised trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early stage breast cancer. N Engl J Med. 349(19): 1793–802
138. Goss PE et al (2008) Late extended adjuvant treatment with letrozole improves outcome in women with early stage breast cancer who complete 5 years of tamoxifen. J Clin Oncol. 26(12):1948–55
139. Smith IE et al (2005) Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomised trial. J Clin Oncol. 23(22):5108–16
140. Ellis MJ et al (2001) Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomised trial. J Clin Oncol. 19(18):3808–16
141. Viale G et al (2008) Prognostic and predictive value of centrally reviewed Ki-67 labelling index in postmenopausal women with endocrine-responsive breast cancer: results from Breast International Group Trial 1–98 comparing adjuvant tamoxifen with letrozole. J Clin Oncol. 26(34): 5569–75
142. Dowsett M et al (2008) Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER-2) status with recurrence in the arimidex, tamoxifen. Alone or in combination trial. J Clin Oncol. 26(7):1059–65
143. Rasmussen BB et al (2008) Adjuvant letrozole versus tamoxifen according to centrally-assessed ERBB2 status for postmenopausal women with endocrine-responsive early breast cancer: supplementary results from the BIG 1–98 randomised trial. Lancet Oncol. 9(1):23–8
144. Dowsett M, et al (2008) Risk of distant recurrence using oncotype DX in postmenopausal primary breast cancer patients treated with anastrozole or tamoxifen: a TransATAC study, in SABCS. San Antonio, Texas, USA
145. Semiglazov VF et al (2007) Phase 2 randomised trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer. 110(2):244–54
146. Ellis MJ et al (2008) Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumour characteristics. J Natl Cancer Inst. 100(19):1380–8
147. Aapro M et al (2008) Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol. 19(3):420–32
148. Gnant M et al (2008) Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. Lancet Oncol. 9(9):840–9
149. Brufsky A et al (2007) Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. J Clin Oncol. 25(7):829–36
150. Reid DM et al (2008) Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group. Cancer Treat Rev. 34(Suppl 1):S3–18
151. Eidtmann H, et al (2008) The effect of zoledronic acid on aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36 months follow-up of ZO-FAST, in SABCS. San Antonio, Texas, USA

152. Gnant M, et al (2008) Adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in premenopausal women with hormone-responsive, stage I and II breast cancer: First efficacy results from ABCSG-12, in ASCO. Chicago, USA
153. Morales L et al (2008) Prospective study to assess short-term intra-articular and tenosynovial changes in the aromatase inhibitor-associated arthralgia syndrome. J Clin Oncol. 26(19):3147–52
154. Sestak I et al (2008) Risk factors for joint symptoms in patients enrolled in the ATAC trial: a retrospective, exploratory analysis. Lancet Oncol. 9(9):866–72
155. McCowan C et al (2008) Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. Br J Cancer. 99(11):1763–8
156. Chlebowski RT, Geller ML (2006) Adherence to endocrine therapy for breast cancer. Oncology. 71(1–2):1–9
157. Partridge AH et al (2008) Adherence to initial adjuvant anastrozole therapy among women with early stage breast cancer. J Clin Oncol. 26(4):556–62
158. Cuzick J et al (2008) Treatment-emergent endocrine symptoms and the risk of breast cancer recurrence: a retrospective analysis of the ATAC trial. Lancet Oncol. 9(12):1143–8
159. Howell SJ, Johnston SR, Howell A (2004) The use of selective estrogen receptor modulators and selective estrogen receptor down-regulators in breast cancer. Best Pract Res Clin Endocrinol Metab. 18(1):47–66
160. Escher G, White A et al (1951) Newer steroids in the treatment of advanced mammary carcinoma. In: Symposium on steroids in experimental and clinical practice. Philadelphia: Blackiston
161. Perrault M et al (1952) Total hypophysectomy in the treatment of breast cancer; first French case; future of the method. Therapie. 7(4):290–300
162. Iveson TJ et al (1993) Phase I study of the oral nonsteroidal aromatase inhibitor CGS 20267 in postmenopausal patients with advanced breast cancer. Cancer Res. 53(2):266–70
163. Zilembo N et al (1995) Endocrinological and clinical evaluation of exemestane, a new steroidal aromatase inhibitor. Br J Cancer. 72(4):1007–12
164. Jonat W et al (1996) A randomised trial comparing two doses of the new selective aromatase inhibitor anastrozole (Arimidex) with megestrol acetate in postmenopausal patients with advanced breast cancer. Eur J Cancer. 32A(3): 404–12
165. Buzdar A et al (1996) Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. Arimidex Study Group. J Clin Oncol. 14(7):2000–11
166. Dombernowsky P et al (1998) Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomised trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. J Clin Oncol. 16(2):453–61
167. Buzdar A et al (2001) Phase III, multicenter, double-blind, randomised study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. J Clin Oncol. 19(14):3357–66
168. Kaufmann M et al (2000) Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomised, double-blind trial. The Exemestane study group. J Clin Oncol. 18(7):1399–411
169. Mouridsen H et al (2001) Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol. 19(10):2596–606
170. Nabholtz JM et al (2000) Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomised trial. Arimidex study group. J Clin Oncol. 18(22):3758–67
171. Bonneterre J et al (2001) Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor-positive advanced breast carcinoma. Cancer. 92(9):2247–58
172. Paridaens R et al (2003) Mature results of a randomised phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer. Ann Oncol. 14(9): 1391–8
173. Jonat W et al (2006) Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early stage breast cancer: a meta-analysis. Lancet Oncol. 7(12):991–6

Chemotherapeutic Agents

19

Mattea Linder and Gunter von Minckwitz

19.1 Cytotoxic Agents

Cytotoxic agents still have to be considered as the backbone of treatment for many patients, especially those who are not considered highly hormone-sensitive. The following overview addresses drugs that are registered and currently most frequently used in breast cancer.

19.1.1 Topoisomerase II Inhibitors: Anthracyclines

The exact mechanism of action of topoisomerase inhibitors is complex. It is thought to interact with DNA by intercalation and inhibition of macromolecular biosynthesis. This inhibits the progression of the enzyme topoisomerase II, which unwinds DNA for transcription. Anthracyclines stabilize the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being resealed and thereby stopping the process of replication. Anthracyclines are important agents in the treatment of breast cancer, optimizing adjuvant and neoadjuvant chemotherapy regimes, being indicated for nodal positive, breast cancer regardless the hormone receptor status or HER2neu status. The most commonly used anthracyclines are epirubicin and doxorubicin (Table 19.1). In Europe, the treatment of breast cancer with anthracyclines started already in 1980, whereas in the U.S. it started in 1990 due to the late approval from the Food and Drug Administration (FDA).

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The dose in which anthracyclines should be used is still not fully established; however, there is agreement that the therapeutic window is between 20 and 25 mg/m²/week for doxorubicin and 30–40 mg/m²/week for epirubicin. Schedules using lower doses have shown significantly lower efficacy and schedules using higher doses, especially of doxorubicin, have shown no increase in efficacy but higher toxicity.

Anthracyclines are used nowadays as single agents, only in rare occasions, in metastatic disease. In the adjuvant setting, they are either used in combination with cyclophosphamide or taxanes or as three drug combinations with 5-fluorouracil and cyclophosphamide or docetaxel and cyclophosphamide. The FE120C regime seems to have become the gold standard [1]. The 5-year event-free survival was 63% for patients treated with FEC in comparison to 53% treated with CMF ($P > 0.009$), the corresponding survival rates were 70 and 77%, respectively ($P > 0.03$). Alternative to that, the FE100C regime has been quite popular in Europe. But it has only proven superiority to the FE50C regime, which is nowadays considered to be underdosed [2]. Other studies supported the superiority to an anthracycline-containing regime to other schemes. The NEAT trial for example is a combined analysis from two phase III studies from England and Scotland, where the benefit of 4 cycles of EC (100 mg/m^2) followed by 4 cycles of CMF vs. 6 or 8 cycles of CMF was investigated. The study population consisted of 2,391 patients with early breast cancer [3]. The superiority in this application scheme occurred only when an anthracycline was given in a triple or quadruple combination as in FEC or EC→ P or E → CMF and the dose intensity exceeded >30 mg/m^2 BSA [4].

Other studies investigating the optimal regime again presented different results. The National Surgical Adjuvant breast and Bowel Project (NSABP) studies

I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases*,
DOI: 10.1007/978-3-540-69743-5_19, © Springer-Verlag Berlin Heidelberg 2010

Table 19.1 A summary of topoisomerase II inhibitors

Medication	Trade name® (selection)	Dosing (mg/m² BSA)	Precautions	Interactions	Side effects
Epirubicin	Farmorubicin	90–120 q3w	Save i.v. application, cardiotoxicity, dose reduction when liver impairment	Interferone, H2-antihistaminics	Cardiomyopathy, chronic heart failure, myelosuppression AML/MDS, mucositis, tissue damage, vomiting, alopecia
Doxorubicin	Adriamycin, Adriblastin	60–75 q3w	Save i.v. application, cardiotoxicity, dose reduction when liver impairment	Interferone, H2-antihistaminics	Cardiomyopathy, chronic heart failure, myelosuppression AML/MDS, mucositis, tissue damage, vomiting, alopecia
Caelyx/Doxil		40–50 q4w	Infusion time 60 min	Premedication	Myelosuppression, mucositis, vomiting, cardiomyopathy and chronic heart failure (risk reduced due to formulation), tissue toxicity, acneform skin changes, alopecia, hypersensitivity reaction

B-15 and B-23 showed that 4 cycles of doxorubicin and cyclophosphamide were equivalent to 6 cycles CMF in regard of OS and DFS. AC is not only better tolerable with fewer side effects but has the advantage of shorter application course [5, 6]. Similar results were also shown by the Spanish Breast Cancer Research Group (GEICAM), where 6 cycles of CMF vs. 6 cycles of FAC were investigated [7]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) publicated results from a 15-year meta-analysis comparing the benefit of CMF-containing regimes to anthracycline-containing ones [8]. Fourteen thousand breast cancer patients were included who participated in different studies between 1995 and 2000. The study demonstrated that anthracycline-containing regime vs. CMF regimes were significantly more effective in preventing recurrence ($P>0.001$, HR 0.89) and increasing survival ($P<0.00001$) regardless of age, hormone receptor status, or lymph node status.

One of the clinically most relevant side effects of anthracyclines is the cardiotoxicity, which can finally result in cardiomyopathy and chronic heart failure. The probability of incurring doxorubicin-induced congestive heart failure was related to the total dose of doxorubicin administered. An increase in drug-related congestive heart failure was more often seen in a 3-weekly regime than in a weekly regime when doxorubicin was given. Another risk factor was the patient's age, whereas the performance status, sex, race, and tumor type were no isolated risk factors [9, 10]. The likelihood depends directly on the lifetime cumulative dose given, as well as on other risk factors (e.g., radiation to the mediastinal lymph nodes like the Mantel field irradiation for Hodgkin's disease or preexisting cardiac comorbidities). More than 600 mg/m² doxorubicin and 900 mg/m² epirubicin should not be given during the course of chemotherapy. The NCCT trail showed that in a population of 1,576 patients receiving 4 cycles of AC, the incidence of a LVEF reduction was 23.4%, observed during or within 1 year after 4 cycles of AC treatment; however the majority had only grade 1 and 2, and a reduction below 15% of the initial value only occurred in about 2.5% [11]. In a 7-year follow-up period of the FASG trials, the risk of developing a left ventricular dysfunction was 1.36% in comparison

to the control group without an anthracycline-containing regime the reduction of the LVEF was only 0.2% [12], the cumulative doses given here ranged from 300 to 600 mg/m^2.

The most frequent acute toxicity is neutropenia with a risk of febrile neutropenia that is usually below the threshold of 20%, where growth factors are recommended for prevention. Only the three-drug combination TAC has a febrile neutropenia rate of around 20% and requires primary G-CSF (and potentially antibiotics) prophylaxis. Another side effect, which is rare but should be mentioned, is the risk of inducing an acute leukemia (especially acute myeloid leukemia (AML)) or myelodysplastic syndrome (MDS).

AC regimens employing intensified doses of cyclophosphamide requiring G-CSF support were characterized by increased rates of subsequent AML/MDS. Because most of the breast cancer patients who received anthracyclines also received cyclophosphamide, an alkylating agent linked independently to secondary leukemia, it is difficult to determine the precise contribution of the anthracyclines component to the development of hematologic cancer in these patients [13].

In a meta-analysis of the NSABP with 8,563 adjuvant breast cancer patients receiving cumulative doxorubicin doses of 240 mg/m^2 in combination with cyclophosphamide (mean cumulative dose of cyclophosphamide, 4,500 mg/m^2), it was shown that 0.5% developed either AML or MDS [13]. Additional studies of adjuvant treatment with AC regimens suggest that rates of secondary leukemia range from 0.31 to 0.8% [14–16]. But all in all, the risk of suffering from this kind of secondary malignancy was small relative to that of breast cancer relapse.

A liposome-encapsulated form of doxorubicin has been marketed as Doxil/Caelyx or Myocet. Through this process, the liposome is protected from the monocyte-macrophage system and therefore remains longer in the body's circulation. They are most commonly used to treat ovarian cancer, AIDS-related Kaposi's sarcoma and multiple myeloma, but it is also used to treat advanced and metastasized breast cancer. Equal efficacy to nonencapsulated doxorubicin has been shown in several phase III studies. Liposomal encapsulation of doxorubicin results in a different pharmacokinetic profile, by which cardiotoxicity is significantly reduced even at higher cumulative doses. However, other toxicities like mucositis and hand-foot syndrome become more prominent and are dose- and schedule-dependent.

19.2 Taxanes (Tubulin Inhibitors)

The mode of action of taxane-based chemotherapeutic agents is the inhibition of the mitotic progress (M-phase) and the stabilization of microtubuli in the cell, which results in an arrest of the G2 phase, and therefore no further cell proliferation or maturation occurs [17]. The substances were first educed from the bark (paclitaxel) and the needles of the pacific yew tree (docetaxel). Meanwhile, ways are found to produce these agents semi-synthetic. Due to the hydrophobic behavior of both substances, lipid-based solvents are needed (Cremophor EL, Triton), as well as special i.v. infusion tubes. This can induce hypersensitivity reactions, which are manageable when corticoids and antihistamins are given as premedication before and after the start of taxane-based chemotherapy. Nab-paclitaxel/ABI007 is a polyethoxylated castor oil-free albumin-bound paclitaxel and does not require this premedication. Paclitaxel and docetaxel are approved for the treatment of patients with primary node-positive and metastatic breast cancer (MBC), nab-paclitaxel only for MBC.

19.2.1 Docetaxel and Paclitaxel

Docetaxel and paclitaxel are used as single agents, predominantly in the metastatic setting. While docetaxel and nab-paclitaxel are more frequently used as infusions every 3 weeks, paclitaxel appears to be more effective when used in weekly intervals. Paclitaxel- and docetaxel-containing regimes are considered as (neo-) adjuvant standard treatments for patients, especially with nodal positive and hormone receptor-negative primary breast cancer. They are either used as single agents in sequence to anthracyclines, e.g., (F)EC-D, A(E)C-P or as simultaneous combinations with anthracyclines and/or cyclophosphamide (AD, AP, DC, DAC). Dose-dense schedules mainly use paclitaxel based on a better tolerability.

Studies to underline this are the PACS-02 study [18] and the BCIRG-001 study [19], which have the highest level of evidence. The overall survival after 5 years was 87% in the TAC-arm and 81% in the FAC-arm ($P > 0.008$) for the BCIRG-001 study. The PACS-01 study, where 3 cycles FE100C followed by 3 cycles docetaxel was given in comparison to 6 cycles FE100C, showed a significant overall survival for the FE100C

D arm ($P>0.0013$) as well as for the event-free survival ($P>0.0012$). There are inconsistent results if hormone receptor-positive patients also take advantage of this class of drugs. The analysis of subgroups of the CALGB-9344 study [20] was not able to show a significant survival for estrogen receptor-positive patients, whereas the BCIRG-001 and the PACS-01 studies were able to demonstrate this advantage.

The side effects of taxanes are shown in Table 19.2. They range from myelosuppression, mucositis/stomatitis, arthralgia, elevated liver enzymes, diarrhea and obstipation. One of the most compromising side effect is the peripheral polyneuropathy, which occurs in more than 10% but from grade 3 and 4 suffer only in 0.8% [21]. In most cases, the polyneuropathy resolves after ending with the taxane-based chemotherapy, but unfortunately, it can take from a few months up to a few years.

A phase III trial compared nab-paclitaxel with conventional paclitaxel in patients with MBC. In this trial, 454 patients were randomly assigned to 3-week cycles of either nab-paclitaxel 260 mg/m^2 intravenously without premedication ($n=229$) or standard paclitaxel 175 mg/m^2 intravenously with premedication ($n=225$). Results showed that in the nab-paclitaxel group, the response rate was significantly higher (33 vs. 19%, $P>0.001$) and time to progression was significantly longer (23.0 vs. 16.9 weeks; hazard ratio>0.75, $P>0.006$) compared with standard paclitaxel group. Although the dosage of nab-paclitaxel was 49% higher than standard paclitaxel, the incidence of grade 4 neutropenia was significantly lower under nab-paclitaxel treatment (9 vs. 22%, $P<0.001$). Grade 3 sensory neuropathy was more common in the nab-paclitaxel arm than in the standard paclitaxel arm (10 vs. 2%, $P<0.001$), but improved rapidly (median, 22 days). No hypersensitivity reactions occurred with nab-paclitaxel despite the absence of premedication and shorter administration time [22]. The U.S. FDA approved nab-paclitaxel in January 2005 for the U.S. market as monotherapy for women with advanced breast cancer, after the failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. In Europe, the EMEA (European Medicines Agency) has approved nab-paclitaxel in January 2008 as monotherapy, after the failure of first-line chemotherapy and with contraindication for an anthracycline-containing regime.

19.2.2 Ixabepilone

Another new agent of this class is ixabepilone. It belongs to the epothilones and is expected to block the ability of cells to modify the internal skeleton that they need to divide and multiply as the taxanes do. Ixabepilone is also expected to affect non-cancer cells such as nerve cells, which could cause side effects like the peripheral neuropathy as a very common side effect of taxanes. Treatment with ixabepilone caused new or worsening peripheral neuropathy in approximately 65% of patients treated. Other commonly observed toxicities were anemia, leucopenia, thrombocytopenia, fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, and musculoskeletal pain [23–25]. Ixabepilone is indicated in combination with capecitabine or as monotherapy for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated. In October 2007, the FDA approved ixabepilone for the treatment of aggressive metastatic or locally advanced breast cancer no longer responding to currently available chemotherapy regimes. In November 2008, the EMEA has refused a marketing authorization for ixabepilone [26].

19.2.3 Vinorelbine

Vinorelbine is a semisynthetic vinca alkaloid with efficacy against breast cancer and another variety of solid tumors as non-small cell lung cancer, head and neck cancer, and Hodgkin's lymphoma. It blocks the cell growth also by interfering with microtubules and therefore stopping mitosis. It is mostly used in second- or third-line therapy in patients with anthracyclines or taxanes pretreated advanced breast cancer or in combination therapy with cisplatin, carboplatin, or gemcitabin. The combination with capecitabine showed good efficacy, as well as the combination with trastuzumab, in cases of Her2neu positive breast cancer [27–29].

The substance was approved in the 90s in the U.S. and in Europe for lung cancer and achieved further approvals for breast cancer in the following years.

Table 19.2 A summary of tubulin inhibitors

Medication	Trade name® (selection)	Dosing (mg/m² BSA)	Precautions	Interactions	Side effect (samples)
Paclitaxel	Taxol	135–250 q3w; 80 weekly	Premedication	Interaction with inhibitors and inducer of CYP3A4	Polyneuropathy, myelosuppression, stomatitis/mucositis, palmar-plantar erythrodysesthesia, fatigue, arthralgia, nausea, vomiting, diarrhea, musculoskeletal pain, hypersensitivity reaction, skin and nail changes, alopecia
Docetaxel	Taxotere	75–100 q3w	Premedication	Interaction with inhibitors and inducer of CYP3A4	Polyneuropathy, myelosuppression, stomatitis/mucositis, palmar-plantar erythrodysesthesia, fatigue, arthralgia, nausea, vomiting, diarrhea, musculoskeletal pain, hypersensitivity reaction, skin and nail changes, alopecia
Nab- Paclitaxel	Abraxane	260 q3w	None	Interaction with inhibitors and inducer of CYP3A4 and CYP2C8	Polyneuropathy, myelosuppression, stomatitis/mucositis, hand foot syndrome, fatigue, arthralgia, nausea, vomiting, diarrhea, musculoskeletal pain, hypersensitivity reaction, skin and nail changes, alopecia
Ixapepilone	Imprexa	40 q3w	Premedicaion, BSA greater than 2.2 m² should be calculated based on 2.2 m²	Interaction with inhibitors and inducer of CYP3A4	Peripheral neuropathy, myelosuppression, stomatitis/mucositis, hand foot syndrome fatigue/asthenia, myalgia, alopecia, nausea, vomiting, diarrhea, musculoskeletal pain, anorexia, abdominal pain, nail disorder
Vinorelbine	Navelbine	30 weekly	Save i.v. application, dose reduction when live function is impaired	Interaction with inhibitors and inducer of CYP3A4	Neutropenia, neurotoxicity, vomiting, constipation, elevated liver enzymes

Since 2004, an oral formulation has been marketed and registered in Europe for the same settings. It has shown a similar efficacy and safety profile between both intravenous and per o.s. (p.o.) formulations, avoiding local toxicity induced by the intravenous vinorelbine.

19.2.4 Alkylating Agents

19.2.4.1 Cyclophosphamide

Cyclophosphamide is a widely used anticancer prodrug that needs to be activated by the cytochrome P450 in the liver. The resulting metabolite is called 4-hydroxycyclophosphamide (4-OH-CPA). It has to undergo β-elimination to yield phosphoramide mustard and acrolein, which alkylates DNA and protein, respectively. This leads to a connection of guanine nucleobases in DNA and therefore disrupting the cell cycle and the cell growth [30, 31].

It is one of the best known agents of this class and has a long history in the treatment of all kind of cancers. Even today, 50 years after its introduction, it is one of the most widely used chemotherapeutic agents [32]. Cyclophosphamide is nowadays part of the majority of chemotherapeutic regimes in the treatment of breast cancer in the adjuvant and neoadjuvant setting as well as in the palliative setting. It is also used in the treatment of other types of carcinomas such as leukemia, multiple myeloma, or the retinoblastoma. When used as a single agent in the treatment of breast cancer, a response rate between 10 and 50% was reached. In general, it is part of the combination therapy regimes, especially with anthracyclines as doxorubicin (AC) or epirubicin (EC) but also with methotrexate and 5-fluorouracil (CMF) [33, 34]. Alkylating agents are stated to have a procarcinogenetic effect. So, above the dose of 1,000 mg/m^2 BSA, mesna needs to be added because of the risk of hemorrhagic cystitis, which can lead to an increase risk of developing urinary bladder malignancies. Cyclophosphamide can also induce myeloproliferative or lymphoproliferative malignancies. But, as it is mostly given in combination with anthracyclines, it is hard to differentiate the contribution to the hematological malignancies of these two agents. The risk of developing it occurs independently of the cumulative dose.

19.2.4.2 Bendamustin

Another substance of this group is bendamustin (Table 19.3). It is a drug with a hybrid compound. On one side, it has an alkylating agent, and on the other side, it has a structure similar to a nucleoside analog, although nucleoside activity has not been demonstrable. Its function is not yet clear, but there is evidence that it might be a purine analog. Additionally, clinical activity has been demonstrated in patients with alkylating agent resistant disease [35].

It is a long known cytotoxic agent, which was once widely used in the former German Democratic Republic for a variety of cancers types. The main indication is in hematological malignancies like Hodgkin's, non-Hodgkin's disease, multiple myeloma, chronic lymphocytaemia, but there are promising results for bendamustin in breast cancer patients in the second- or third-line chemotherapy [36, 37]. In a phase III trial, bendamustin/cyclophosphamide/5-fluorouracil was compared with conventional CMF as first-line treatment for MBC and achieved a longer progression-free survival [38]. Current ongoing studies are evaluating new schedules, doses, and the management of toxicities and combinations with other cytotoxic agents (e.g., NCT00661739, NCT00705250) to optimize the cancer therapy with bendamustine. Bendamustin seems to have a favorable range of side effects, especially for heavily pretreated patients with metastasized breast cancer. In a phase II study, the main

Table 19.3 An overview of alkylating agents

Medication	Trade name® (selection)	Dosing (mg/m^{2}BSA)	Precautions	Interactions	Side effect (samples)
Cyclophosphamide		600–1,000 (in combination therapy, short infusion)	>1,000 mg/m^2: uro protection with mesna, sufficient hydration	Barbiturates, cimetidin	Myelosuppression, nausea, vomiting, cystitis, secondary malignancies (AML/MDS)
Bendamustin	Ribomustin	120–150 mg/m^{2}day 1.2 q4w	None, no standardregime available	None	Myelosurppression, mucositis, stomatistis, nausea, vomiting, alopecia

side effects reported were myelosuppression, infection, mucositis, and diarrhea. Those events mostly occurred within grade 1–2 and were well manageable [39].

19.2.5 Antimetabolites

19.2.5.1 Methotrexate

Methotrexate, 5-FU, capecitabine are the agents, which are frequently used in the treatment of the metastatic disease (Table 19.4). It is a widely used antimetabolite. The range of indication goes from the oncological indication for the treatment of all sorts of cancer (e.g., breast cancer, ovarial cancer, and acute lymphatic leukemia) to abort induction (in combination with misoprostol), and it also shows efficacy for the prevention and therapy of meningeosis carcinomatosa or primary cerebral CNS lymphomas when given as an intrathecal injection. In breast cancer, it is mostly used in combination with cyclophosphamide and 5-fluorouracil (CMF). The EBCTCG showed in a meta-analysis that there are no significant differences between the proportional risk reductions (in recurrence or in breast cancer mortality) between CMF-containing regimes vs. anthracycline-containing regimes. But, looking closer at subgroup analysis e.g., hormone receptor-positive disease, there might still be a significant advantage for anthracycline-based regimes [4].

19.2.5.2 Capecitabine

Capecitabine is an antimetabolite belonging to the fluoropyrimidine carbamate class and causes cell injury via RNA- and DNA-related mechanisms. It is an orally administered precursor of 5-fluorouracil (5-FU). It is converted to 5-FU by carboxyesterase, cytidine deaminase, and thymidine phosphorylase (present in the liver and in tumors).

Capecitabine is indicated for the treatment of patients with MBC resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated, e.g., patients who have received cumulative doses of 400 mg/m^2 of doxorubicin or doxorubicin equivalents. It was approved in the U.S. in second- to third-line MBC in 1998 as monotherapy (response rate of 25.6%), and in 2001 in combination with docetaxel, as this combination used as first-line treatment for anthracycline-pretreated MBC revealed a survival benefit compared to docetaxel alone [40, 41]. One of the most frequent and compromising side effect is hand-foot syndrome with an incidence of up to 20%, and diarrhea. The mechanism behind the

Table 19.4 Selection of antimetabolites used in breast cancer

Medication	Trade name®(selection)	Dosing (mg/m^{2}BSA)	Precautions	Interactions	Side effect (samples)
Methotrexate		40–60 i.v. (gyn. oncology)	Dose reduction when renal impairment, leucovorin-rescue possible	Warfarin, 5-FU	Myelosuppression, mucositis, stomatitis, diarrhea
5-Fluorouracil		600–750 twice weekly i.v. q4w	None	Methotrexate, Leucovorin	Myelosuppression, palmar-plantar erythrodysesthesia, alopecia, nail changes, mucositis, stomatitis, diarrhea, nausea, vomiting
Capecitabine	Xeloda	2,000–2,500 daily p.o. d1-14 q22	None	Methotrexate, Leucovorin	Myelosuppression, palmar-plantar erythrodysesthesia, cardiovascular, diarrhea
Gemcitabine	Gemcar	800–1,250 daily i.v. d1,8, q29	None	Cisplatin, radiosensitizer	Myelosuppression, edema, abdominal cramping

hand-foot syndrome remains unclear but a relation between the peak and the cumulative dose has been shown. In colon cancer, a correlation of occurrence of hand-foot syndrome and efficacy was observed [42]. In general, the side effects are manageable with a dose interruption or reduction, and a complete stop of the therapy is usually not necessary. As diarrhea can be debilitating and potentially life-threatening on rare occasions, guidelines were developed by an ASCO panel for treating chemotherapy-induced diarrhea [43]. No prophylactic treatment for diarrhea is recommended. In case of CTCAE grade 2–4 diarrhea, the following cautions and pharmacological approaches should be taken: first, does reduction or even discontinuation of the medication; second, loperamide administered as an initial 4-mg dose followed by 2-mg doses every 4 h until diarrhea is improved. This dosage and regimen is moderately effective. In severe cases, octreotide, a synthetic octapeptide, can be administered at doses ranging from 100μg twice daily p.o. to 500 μg 3 times daily, with a maximum tolerated dose of 2,000 μg 3 times daily in a 5-day-regime.

The palmar-plantar erythrodysesthesia can become very painful and impair significantly the patients quality of life. A dose reduction should be done when CTCAE grade 2 palmar-plantar erythrodysesthesia occurs. Use of vitamin B6 pyridoxine (50–150 mg b.i.d.) has been reported to be of possible benefit [44] and is permitted for symptomatic or secondary prophylactic treatment.

19.2.5.3 Gemcitabine

Another agent of the group of antimetabolites is gemcitabine, a nucleoside analog, interfering with the DNA replication, leading to an arrest in cell growth, and therefore to apoptosis. It is not only used in a variety of solid tumors such as breast cancer but also in ovarian cancer, non–small cell lung cancer, pancreatic cancer, and bladder cancer. It is indicated in combination with paclitaxel for patients with locally advanced or metastasized disease, who have already been treated with an anthracycline-containing poly-chemotherapy, if not contraindicated. Taxanes are a class of drugs that do not have overlapping side effects with gemcitabine, and hence combinations of these agents with gemcitabine are feasible [45, 46]. Moreover, the addition of gemcitabine to taxanes in MBC patients have led to improved response rate, and with paclitaxel, demonstrated significant improvements in overall survival and time to progression over paclitaxel alone in the first- [47, 48], second-, or third-line therapy [49]. Gemcitabine in combination with docetaxel is associated with less side effects than the combination of capecitabine with docetaxel [50]. Due to increased radio-sensitivity induced by gemcitabine, radiotherapy should not take place within less than 7 days after the last dose.

19.2.6 Platinum-containing Chemotherapy Agents

Cisplatin or carboplatin are widely used drugs to treat various types of cancers, including sarcomas, solid carcinomas (e.g., small cell lung cancer, and ovarian cancer), lymphomas and germ cell tumors as well as breast cancer (Table 19.5). Platinum complexes are formed in cells, which bind and cause cross-linking of DNA, which leads to induction of apoptosis, ultimately.

The largest benefit of using carboplatin over cisplatin is the reduction of side effects, particularly the elimination of the renal toxicity of cisplatin. This is due to the added stability of carboplatin in the bloodstream, which prevents proteins from binding to it. This in turn reduces the amount of the protein–carboplatin complexes to be excreted. The lower excretion rate of carboplatin leads to a longer retention half-life of 30 h for carboplatin, compared to 1.5–3.6 h in the case of cisplatin.

Nausea and vomiting are less severe and more easier controlled, compared to the incessant vomiting and diarrhea that some patients may experience during cisplatin treatment. The main drawback of carboplatin is its severe myelosuppression.

Platinum compounds are not frequently used as single agents for breast cancer therapy. The combination with paclitaxel and carboplatin for patients with advanced or MBC provides an anthracycline-free treatment option [51–53]. These recent studies showed a good response in combination with paclitaxel and trastuzumab for HER2-positive breast cancer patients, especially when an anthracycline-containing regime is not preferred to avoid late cardiotoxicity. However, the addition of carboplatin to a combination of docetaxel and trastuzumab did not lead to a higher efficacy. Experimental data suggest that triple-negative breast cancer or BRCA I or II gene mutated breast cancer may

Table 19.5 Overview of platinum-containing chemotherapy agents

Medication	Trade name® (selection)	Dosing	Precautions	Interactions	Side effect (samples)
Cisplatin		Total dose (mg) = (target AUC) × (GFR + 25)	Dose reduction according to GFR	None	Myelosuppression, renal toxicity, alopecia, nausea, vomiting, neurotoxicity, ototoxicity, electrolyte disturbances
Carboplatin		Total dose (mg) = (target AUC) × (GFR + 25)	Dose reduction according to GFR	None	Myelosuppression, renal toxicity, alopecia, nausea, vomiting, neurotoxicity, ototoxicity, electrolyte disturbances

have increased sensitivity to platinum-based chemotherapy [54].

19.2.7 Targeted Agents

19.2.7.1 Agents Directed Against Human Epidermal Growth Factor Receptor (HER)2

Trastuzumab

Trastuzumab is the most common and widely used agent for HER2- positive breast cancer. It is a humanized monoclonal antibody that binds on human epidermal growth factor receptor type 2 (HER2, also referred to as HER2/neu or ErbB-2) on the breast cancer tissue. It was first described more than two decades ago [55]. This receptor occurs in 20–30% of invasive breast carcinomas. High levels of HER2 in tumors are associated with a more aggressive biological behavior and those patients have decreased overall survival [56].

In the U.S., trastuzumab received first approval in 1998 for first-line MBC in combination with paclitaxel as well as for the second- and third-line as monotherapy [48]. In 2006, the FDA granted approval to trastuzumab as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel for the adjuvant treatment of women with node-positive, HER2-overexpressing breast cancer [57]. In Europe, it received approval in 2000 for advanced and (metastatic) HER2-positive breast cancer, and in 2006 for early HER2-positive breast cancer. In the advanced setting, trastuzumab is now approved for use as a first-line therapy in combination with paclitaxel where anthracyclines are unsuitable, as first-line therapy in combination with docetaxel, and as a single agent in third-line therapy. In May 2007, trastuzumab received European approval for use in combination with anastrozole for the treatment of women with advanced HER2-positive breast cancer that is also estrogen and progesterone-receptor positive. The main side effect of trastuzumab is cardio-dysfunction due to HER2 receptor also being expressed on myocyte. As opposed to anthracycline-associated cardiotoxicity, this cardiodysfunction appears within 6 months of treatment: first as an asymptomatic decrease of the left ejection fraction, which can lead to a chronic heart failure over time. If the agent is discontinued on time, the decrease is frequently fully reversible. No sufficient data is available on cardiotoxicity after long-term treatment with trastuzumab. Apart from infrequent hypersensitivity reactions, trastuzumab is well tolerated, and especially, hematological toxicities are negligible.

Several studies analyzed the benefit gained from (neo-) adjuvant trastuzumab usage. One was the HERA trial, which started in 2001 as an international multicenter, randomized trial that compared 1 or 2 years of trastuzumab treatment with observation alone after standard neoadjuvant or adjuvant chemotherapy in women with HER2-positive, node-positive, or high-risk node-negative breast cancer (NCT00045032). Primary objective was the overall survival (OS), DFS and the relapse-free survival (RFS), the safety and tolerability of trastuzumab, and the incidence of cardiac dysfunction. Other studies, all investigating the effect of trastuzumab to standard chemotherapy in Her2neu-positive breast cancer patients were the NSABP B-31 trial, the North

Central Cancer Treatment Group (NCCTG) N9831 trial, and the Breast Cancer International Research Group (BCIRG) 006 trial, and finally, also a subgroup of the FinHer Study [58–61]. In a meta-analysis by Baselga et al. [62], of these studies, which included over 13,000 patients, the clear benefit was shown for all patients receiving trastuzumab after the standard chemotherapy with about one third lower mortality and with a trend toward an improvement of the overall survival. Further follow-up will clarify the final survival benefit as well as the optimal treatment duration (1 or 2 years).

Lapatinib

Lapatinib inhibits the tyrosine kinase activity associated with two oncogenes, EGFR (epidermal growth factor receptor) and HER2. Lapatinib inhibits receptor signal processes by binding to the ATP-binding pocket of the EGFR/HER2 protein kinase domain, preventing self-phosphorylation and subsequent activation of the signal mechanism. In 2006, lapatinib was approved in combination with capecitabine for the treatment of patients with advanced or MBC, whose tumors overexpress HER2 and who have received prior therapies, including anthracyclines, taxanes, and trastuzumab (second or third line) [63]. The drug is marketed under the propriety names Tykerb (mostly U.S.) and Tyverb (mostly Europe). In a phase III study, lapatinib combined with capecitabine produced a 51% reduction in the risk of disease progression compared with capecitabine monotherapy without an increase in serious toxic effects or symptomatic cardiac events in patients with normal left ventricular ejection fraction at baseline [64]. The most common side effect, which leads to a discontinuation of the drug intake, is diarrhea [65–67]. Skin rash and elevation of liver enzymes are further common side effects of this compound. Although rarely life-threatening, the physical and psychosocial distress associated with these dermatologic reactions may reduce compliance with EGFR inhibitors. There are data suggesting that the occurrence and severity of rash appeared to correlate with plasma concentrations and clinical response [68], but the final assessment of this correlation is still pending.

Because of the associated cardiac toxicity observed with trastuzumab, Perez et al. analyzed cardiac function in patients treated with lapatinib in 18 phase I–III lapatinib clinical trials [69]. In the cardiac safety evaluation, the LVEF was similarly affected by lapatinib in both breast cancer and non-breast cancer patients. The 1.3% incidence of symptomatic and asymptomatic decreases in LVEF in patients treated with lapatinib was less than that expected within a matched cohort of the general population (3–6% incidence of asymptomatic LVEF decrease) and less than that of trastuzumab-treated breast cancer patients. Thus, there is currently no firm evidence that lapatinib causes cardiac toxicity at all. These cardiac safety results support the rationale for studying lapatinib in the adjuvant setting.

Pertuzumab

Pertuzumab (Omnitarg) is a fully humanized monoclonal antibody, which acts by blocking the association of HER2 with other HER family members, including the EGFR, HER3, and HER4 [70]. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two major signal pathways: mitogen-activated protein kinase and phosphatidylinositol-3-kinase. Inhibition of these signaling pathways can result in cell growth arrest and apoptosis [71]. Clinical trials are currently ongoing for all sorts of solid tumors like breast, prostate, lung, and ovarian cancer (Table 19.6).

19.2.7.2 Targeted Agents Affecting Tumor Angiogenesis and Other Targets

Bevacizumab

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to VEGF (vascular endothelial growth factor) and inhibits the biologic activity in vitro and in vivo assay systems [72]. Bevacizumab prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in vitro models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in mice caused reduction of microvascular growth and inhibition of metastatic disease progression. Therapies that inhibit VEGF may have multiple effects on angiogenesis and tumor growth, most importantly, reducing the tumor's blood supply,

Table 19.6 Anti Her2 agents

Anti-Her2 Agent	Trade name® (selection)	Mode of action	Dosing	Interactions	Side effects (samples)
Trastuzumab	Herceptin	Humanized monoclonal antibody targets the extracellular domain of the HER2 protein	2 mg/kg body weight,	Interaction with inhibitors and inducer of CYP3A4	Cardiotoxicity, increasing of liver enzymes, skin rash, flu-like symptoms, headache, diarrhea, nausea, vomiting, fatigue, abdominal pain, increased cough, dyspnea, rash, neutropenia, anemia, myalgia
Lapatinib	Tykerb (USA), Tyverb (EU)	HER-1 and-2-neu-receptor-tyrosinkinase antibody	Lapatinib 1250 mg dialy p.o.	Interaction with inhibitors and inducer of CYP3A4	Diarrhea, nausea, vomiting, skin rash, fatigue, arthralgia, cardiotoxicity, headache, abdominal pain, loss of weight, increasing of liver enzymes
Pertuzumab	Omnitarg	A humanized monoclonal antibody, a first-in-class HER heterodimer inhibitor that binds to HER2 dimerization domain, inhibits the interaction of HER2 with other HER family members. Ligand-activated signaling from HER2:HER1 and HER2:HER3 heterodimers is thereby inhibited	420 mg pertuzumab following a loading dose of 840 mg	Interaction with inhibitors and inducer of CYP3A4, currently used in phase III studies	Diarrhea, nausea, vomiting, fatigue, cardiotoxicity, skin rash, loss of weight, increasing of liver enzymes

preventing the development of new blood vessels in the tumor and facilitating the delivery of chemotherapy to the tumor cells [73, 74].

Based on preclinical findings that have shown the activity of bevacizumab in breast cancer, bevacizumab monotherapy was tested in MBC. Cobleigh et al. evaluated the safety and efficacy in a phase I / II dose escalation trial in patients with previously treated MBC [75]. The overall response rate was 9.3% (confirmed response rate, 6.7%), the median duration of confirmed response was 5.5 months (range 2.3–13.7 months) and the overall survival was 10.2 months. Bevacizumab was well tolerated; side effects were mainly headache, nausea and vomiting, hypertension, minor bleeding (epistaxis), venous thrombo-embolic events and proteinuria.

Aflibercept

Aflibercept (VEGF Trap) is a fully human soluble VEGF receptor fusion protein with a unique mechanism of action. It is a potent angiogenesis inhibitor, which binds VEGF-A more tightly than monoclonal antibodies. It blocks all VEGF-A and -B isoforms plus placental growth factor (PIGF), another angiogenic growth factor that appears to play a role in tumor angiogenesis. VEGF Trap has a relatively long half-life of approximately 2 weeks.

A number of phase III studies of aflibercept in combination with other chemotherapeutic agents currently are enrolling patients in the U.S., Europe, and other countries around the world, investigating aflibercept

not only in breast cancer but also in other types of malignancies (ovarian and fallopian tubes, lung cancer, colorectal, leukemia, lymphoma, pancreas, prostate, etc.). So far, the agent seems feasible regarding the range of side effects.

Sorafenib

Sorafenib is an oral multikinase inhibitor targeting both tumor cells and the tumor vasculature [76, 77]. An inhibitor of signal transduction, sorafenib, prevents tumor cell proliferation and angiogenesis via its effects on the Raf/MEK/ERK [78] pathway at the level of Raf kinase [79] and tyrosine kinases vascular endothelial growth factor receptor-2 (VEGFR-2) and platelet-derived growth factor receptor β (PDGFR-β). Sorafenib demonstrated broad-spectrum antitumor activity in nonclinical studies, in which tumor growth arrest was achieved in colon and non–small cell lung cancer xenograft models [80–83]. Furthermore, significant inhibition of angiogenesis was observed as decreased microvessel density and microvessel area [84].

Sorafenib demonstrated single-agent activity in multiple phase I/II studies, and tolerated and inhibited tumor growth in patients with refractory solid tumors, including breast cancer. In several fixed combinations of chemotherapy, sorafenib-treated patients showed a partial response, with most of the patients reaching stable disease. Concurrent treatment of sorafenib with doxorubicin or irinotecan yielded in an increase of AUC of 21% up to 42%, respectively. The most common side effects associated with sorafenib therapy were dermatologic (including hand-foot syndrome reaction, rash, erythema, alopecia, and pruritus), gastrointestinal (including diarrhea and nausea), and fatigue. Other toxicities associated with sorafenib include hypertension, mainly in the first weeks of treatment, which is generally manageable with standard antihypertensive therapy, mild lymphopenia, and hypophosphatemia.

Sunitinib

Another not yet approved agent for the therapy of advanced breast cancer is sunitinib. Sunitinib is also an oral, multitargeted tyrosine kinase inhibitor that inhibits vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor, stem cell factor receptor (KIT), and colony-stimulating factor-1 receptor. Burstein et al. showed in a phase II study similar side effects as sorafenib, with a good clinical efficacy in monotherapy in metastasized breast cancer patients [85]. Final phase III trials need to further evaluate the overall efficacy.

RAD001 (Everolimus)

RAD001, a signal transduction inhibitor, is an orally bioavailable rapamycin ester analog that demonstrates potent antiproliferative effects against a variety of mammalian cell types. It acts by selectively inhibiting mTOR (mammalian target of rapamycin), an intracellular protein kinase implicated in the control of cellular proliferation of activated T-lymphocytes (immunsuppressive indication) and neoplastic cells (cancer indication). MTOR is a serine/threonine kinase, which is part of the PI3K/AKT/mTOR pathway (phosphoinositide-3-kinase/RAC-alpha serine/threonine-protein kinase/mTOR pathway) and belongs to the family of phosphatidylinositol kinases. These kinases are involved in the regulation of a wide range of growth-related cellular functions, including transcription, translation, membrane protein degradation, and reorganization of the actin cytoskeleton. RAD001 was clinically developed as an immunosuppressant for the prevention of allograft rejection in 1996 and therefore gained its approval [86, 87]. In addition, an indirect tumor effect of RAD001 results from the drug inhibiting neovascular endothelial cell proliferation in the tumor [88, 89]. The activity of RAD001 is the sum of its direct effects on tumor cells and its indirect effects on the vascular component of the supporting peritumoral stroma.

Preclinical and early clinical evaluations showed an impressive growth inhibitory effect of RAD001 against breast cancer cells [90]. Further phase II trials will consolidate its potency in breast cancer therapy (Table 19.7).

19.2.7.3 Selective Estrogen Receptor Modulators (SERMS)

Tamoxifen

The most commonly used drug for the treatment of breast cancer in this class is tamoxifen (Table 19.8). It binds to and blocks the estrogen receptor on all body cells, which leads to a decrease in the DNA synthesis

Table 19.7 Agents directed against tumor angiogenesis

Agent	Trade name	Mode of action	Dosing	Interactions	Side effects (samples)
Bevacizumab	Avastin	VEGF-monoclonal antibody with antiangiogenetic effects	7.5–15 mg/kg body weight q3w i.v.		Proteinuria, hypertension (hypertensive crisis), fatigue, nausea, vomiting, mucositis, stomatitis, fatigue, would healing disturbances
RAD 001, Everolimus	Certican	mTOR protein inhibitor, with antiproleferative and immune suppressive effects	5 mg daily	Interaction with inhibitors and inducer of CYP3A4	Fatigue, headache, nausea, vomiting, loss of appetite, vertigo, stomatitis, mucositis, myelosuppression, hyperglycemia, changes in triglycerides values
Sorafenib	Nexavar	Multikinase-inhibitor with antiproliferative (Raf-Kinase) and antiangiogenetic (tyrosine kinase) effect	800 mg (twice 400 mg) daily p.o.	Interaction with inhibitors and inducer of CYP3A4	Palmar-plantar erythrodysesthesia, skin rash, hypertension (hypertensive crisis), nausea, vomiting, diarrhea, myelosuppression, electrolyte disturbances, cataract, thrombosis
Aflibercept		Fusion protein targeting vascular endothelial growth factor (VEGF)	6.0 mg/kg body weight q3w i.v.	Currently used in phase II studies	Proteinuria, hypertension (hypertensive crisis), fatigue, nausea, vomiting, mucositis, stomatitis, epistaxis, wound healing disturbances

of this cell and to an inhibition of cell growth on hormone receptor-positive breast cancer tissue. The cell remains in the G_0 and G_1 phases of the cell cycle.

Tamoxifen is currently used for the treatment of estrogen receptor-positive breast cancer regardless the stage in pre- and postmenopausal women. Additionally, it is the most common hormone treatment for male breast cancer. It was first approved in 1977 by the FDA for the treatment of women with MBC and in ensuing years, for adjuvant treatment of breast cancer. It is also approved by the FDA for the prevention of breast cancer in women at high risk of developing the disease and further for the reduction of contralateral cancer. Tamoxifen is a pro-drug with little affinity to the estrogen receptor. It needs to be metabolized into its active form eloxifen (4-hydroxytamoxifen and *N*-desmethyl-4-hydroxytamoxifen) by the cytochrome P450 2D6 in the liver. Reduced cytochrome P450 2D6 activity (so-called "poor metabolizer") leads to therapeutic failure of tamoxifen in the prevention and treatment of breast cancer, and those patients will not fully benefit from a therapy.

Tamoxifen is a well-tolerated and accepted drug; however, there are a few side effects, which may interfere with the compliance. Adverse events, which were seen relative frequently, were hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, light-headedness, headache, hair thinning and/or partial hair loss, vaginal dryness, and in some cases, an elevation of the triglyceride level in the blood. Those side effects usually also occur with natural menopause, in which the women is put into by the drug. There is also evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism.

The American Cancer Society has stated tamoxifen as a carcinogen because the incidence of endometrial cancer is increased in women taking tamoxifen. One explanation for this is the partial agonistic effect on other tissues than the breast tissue [91, 92]. These cancers occur almost exclusively in postmenopausal women and become manifest early by postmenopausal bleeding. Serial ultrasound scans for the

detection of endometrial thickening is not helpful, as many patients develop subendometrial edema, induced by tamoxifen, which cannot be discriminated from malignant growth.

Fulvestrant

A further development of tamoxifen is the pure antiestrogen fulvestrant, an irreversible estrogen receptor antagonist without estrogenic activity. It leads to down-regulation and degrading of estrogen receptors. Fulvestrant is indicated for metastatic disease with progression following antihormonal therapy.

In a meta-analysis of four trials ($n=2,125$) by Valachis et al. [93], the efficacy in terms of OS, TTP, CB, and ORR of fulvestrant was investigated. They showed that there was no statistical difference in the primary objectives against tamoxifen or aromatase inhibitor. The side effects are within the range of all antihormonal therapy agents, with a significant reduction of joint disorders [94, 95].

Aromatase Inhibitors

The role of tamoxifen in the treatment of breast cancer has been challenged following the implementation of the third generation of aromatase inhibitors (anastrozole, letrozole, and exemestane). Aromatase inhibitors block the enzyme called aromatase and thus prevent the conversion from androgens into estrogens. In premenopausal women, estrogen is mostly produced by the ovaries, and the inhibition of the aromatase does not significantly decrease the production and the amount of circulating estrogen. The opposite happens: the slight decrease in estrogen activates the hypothalamus and pituitary axis to increase gonadotropin secretion, which in turn increases the FSH and LH levels.

The range of side effects is similar to tamoxifen, except a clinically relevant increase in osteopenia and osteoporosis due to the complete estrogen depletion induced by these compounds. Many patients are complaining about arthralgias and myalgias, which impairs compliance for drug intake. In contrast to tamoxifen, the incidences of endometrial cancer and thrombo-embolic events are not elevated by aromatase inhibitors. All different substances of aromatase inhibitors are approved for the treatment of breast cancer in postmenopausal women regardless of the stage.

19.2.7.4 Gonadotropin-Releasing Hormone (GnRH) Analogs

GnRH or luteinizing hormone (LHRH) analogs have a high affinity to the GnRH/LHRH receptor pituitary surface. Once LHRH is blocked with the natural messenger, a sequence of biochemical events is triggered that leads to the release of LH. LHRH agonists initially stimulate the release of LH, resulting in a transient elevation in serum estradiol in women. However, chronic administration causes down-regulation of the GnRH receptors, thus inhibiting the secretion of LH and ultimately the production of estradiol. Due to the permanent stimulation, it finally leads to a stop of the release of LH and FSH and an ovarian suppression. Side effects include electrolyte disorder, decreased bone mineral density, depression, breast pain, memory loss, dizziness, dyspareunie, edema, musculoskeletal disorders, anxiety, arthralgia, amenorrhea, headache, hot flashes, loss of libido, vaginal bleeding, weight gain, and tiredness. It is approved for the treatment of hormone-sensitive cancers of the breast (only in pre-/perimenopausal women), and it is also used for several gynaecologic diseases as well as in assisted reproduction [96, 97] (Table 19.8).

19.2.8 Bone-Targeted Agents

19.2.8.1 Bisphosphonates

There are two classes of bisphosphonates: the N-containing and non-N-containing bisphosphonates. The two types of bisphosphonates work differently in inhibiting osteoclasts (Table 19.9).

Non-nitrogenous Bisphosphonates

The non-nitrogenous bisphosphonates (disphosphonates) are metabolized in the cell to compounds that replace the terminal pyrophosphate moiety of adenosine triphosphate (ATP), forming a nonfunctional molecule that competes with ATP in the cellular energy metabolism. The osteoclast initiates apoptosis and

Table 19.8 Antihormonal agents

Agent	Trade name® (selection)	Mode of action	Dosing	Interactions	Side effects (samples)
Tamoxifen	Nolvadex	Selective estrogen receptor modulator	20–40 mg dialy p.o.	Cyp 2D6 interaction metabolization into active form endoxifen	Fatigue, thromboembolic events, increasing triglyceride blood count, vaginal dryness, vaginal bleeding, endometrium cancer, headache, hot flushes, menopausal symptoms
Exemestan Anastrozol Letrozol	Aromasin Arimidex Femara	Aromatase inhibitors	25 mg dialy p.o. 1 mg dialy p.o. 2.5 mg dialy p.o.	None	Fatigue, increasing triglyceride blood count, osteoporosis, vaginal dryness, vaginal bleeding, headache, hot flushes, arthralgia, headache, nausea, vomiting, menopausal symptoms
Goserelin	Zoladex	GnRH (gonadotropin-releasing hormone)- agonist	3.6 mg q4w s.c. or 10.8 mg q12w s.c.	None	Fatigue, hot flushes, osteoporosis, hypertension, hypotension, headache, arthalgia, menopausal symptoms
Fulvestrant	Faslodex	Hormone receptor antagonist and modulator	250 mg q4w i.m.	None	Nausea, vomiting, constipation, diarrhea, abdominal pain, headache, backpain, hot flushes, sore throat, vaginal bleeding, thromboembolic events

dies, leading to an overall decrease in the breakdown of bone.

Non-N-containing bisphosphonates have different potencies related to that of etidronate:

Etidronate	1
Clodronate	10
Tiludronate	10

Nitrogenous Bisphosphonates

Nitrogenous bisphosphonates act on bone metabolism by binding and blocking the enzyme farnesyl diphosphate synthase (FPPS) in the HMG-CoA reductase pathway (also known as the mevalonate pathway).

N-containing bisphosphonates have a much higher potency compared to Non-nitrogenous bisphosphonates:

Pamidronate	100
Neridronate	100
Olpadronate	500
Alendronate	500
Ibandronate	1,000
Risedronate	2,000
Zoledronate	10,000

Table 19.9 Bone-targeted agents

Agent	Trade name® (selection)	Mode of action	Dosing	Interactions	Side effects (samples)
Zoledronic acid	Zometa	Inhibition of osteoclasts	4 mg q4w i.v.	With calcium, Mg, Fe containing substances and with antacida when taken together	Stomach pain, and inflammation and erosions of the esophagus,flu-like symptoms, osteonecrosis of the jaw, electrolyte disturbances, renal failure, osteonecrosis of the jaw, musculoskeletal pain zoledronic acid, ibandronate, clodronate, pamidronate and alendronate Precaution sufficient hydration! Substitution of vitamin D and calcium p.o.
Ibandronate	Bondronate		6 mg q4w i.v. or 50 mg daily p.o.		
Clodronate	Bonefos		1,600 mg dialy p.o.		
Pamidronate	Aredia		90 mg q4w i.v.		
Alendronate	Fosamax		10 mg p.o.		
Denosumab	AMG 162	IgG2-anti-RANKL-antibody	0.01 b.i.s. 3 mg/kg body weight q4w, i.v. or s.c.	Currently used in phase III studies	

Bisphosphonates are used clinically for the treatment of osteoporosis, osteitis deformans (Paget's disease of the bone), bone metastases (with or without hypercalcemia), multiple myeloma, and other conditions that feature bone fragility.

High-potency intravenous bisphosphonates have shown to modify progression of skeletal metastasis in several forms of cancer, especially breast cancer. In a randomized control trial, women with breast cancer who received zoledronic acid had a 36% reduction of risk for a recurrence of their breast cancer, a new cancer in the opposite breast, or metastasis to bone compared to women who did not receive that therapy.

Zoledronate, clodronate, ibandronate, and pamidronate are approved for the therapy of (bone-) metastasized breast cancer. Zoledronic acid is the most potent commercially available nitrogen-containing bisphosphonate to date, characterized by an imidazole side ring containing two nitrogen atoms [98]. Some recent (pre)-studies showed also an effect of the angiogenesis, invasion and adhesion of tumor cells, and overall tumor progression, and therefore, there might be an additional therapeutic effect [99]. Alendronate is only approved for osteoporosis in postmenopausal women.

The osteonecrosis of the jaw (ONJ) is a rare but significant side effect of bisphosphonates, especially caused by nitrogen-containing derivatives. The risk for developing ONJ is much higher during intravenous bisphosphonate therapy than for patients on oral bisphosphonates. This is most likely because bisphosphonates administered intravenously are taken up much more readily by bone than those administered orally. Current evidence also shows that 60% of osteonecrosis cases occurred after dental surgical procedures, such as tooth extraction [100]. Other risk factors are corticosteroid use, diabetes mellitus, clinically and radiographically apparent periodontitis, tooth extractions, and smoking, as well as the route of administration, the potency of the bisphosphonate, and the duration of use [101]. The risk for developing ONJ remains unknown but attempts to quantify it showed a great range from 0.00038% (three cases in 780,000 patients) [102, 103] to 0.04% [104].

19.2.8.2 Rank Ligand Inhibitors

Denosumab

Denosumab is a fully human monoclonal antibody that specifically targets a ligand known as RANKL (that binds to a receptor known as RANK), which is a key mediator of osteoclast formation, function, and survival. Denosumab is designed to target RANKL (receptor activator of nuclear factor-kappa-B ligand), a protein that acts as the primary signal to promote bone removal. In many bone loss conditions, RANKL overwhelms the body's natural defense against bone destruction. Denosumab therefore mimics the endogenous effects of osteoprotegerin. Denosumab is currently under investigation in clinical trials (phase III) as a treatment tool in patients with (metastatic) breast cancer, prostate cancer, multiple myeloma, giant cell cancer, as well as prevention metastasis of the named tumor, osteoporosis, tumor-associated bone loss, and therapy-associated loss of bone density. In a phase III study, denosumab showed good efficacy in reducing urinary N-telopeptide, a marker for excessive bone resorption in cancer patients with bone metastasis [105]. Another study by Ellis et al. compared the efficacy and tolerability of denosumab vs. placebo in non-metastazised breast cancer patients receiving an aromatase inhibitor. They showed that denosumab had good efficacy in reducing the risk of bone loss induced by aromatase inhibitor. The bone mineral density within the 24 months study period was significantly increased when given to women with a low mineral bone density at study entry. The adverse events were similar to the placebo group [106] .

References

1. Levine MN et al (1998) Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 16(8):2651–8
2. French Adjuvant Study Group (2001) Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 Randomized Trial. J Clin Oncol. 19:602–11
3. Poole CJ et al (2006) Epirubicin and cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy for early breast cancer. N Engl J Med. 355(18):1851–62
4. Meta Analysis of the EBCTCG (1998) Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 352(9132):930–42
5. Fisher B et al (2004) Treatment of axillary lymph node–negative, estrogen receptor–negative breast cancer: updated findings, from national surgical adjuvant breast and bowel project clinical trials. J Natl Cancer Inst. 96(24):1823–31
6. Fisher B et al (1990) Two months of doxorubicin/cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol. 8:1483–96
7. Marin M et al (2003) Doxorubicin in combination with fluorouracil and cyclophosphamide(i.v. FAC regime, day 1,21) versus methotrexate in combination with fluorouracil and cyclophosphamide (i.v. CMF regime 1,21) as adjuvant chemotherapy for operable breast cancer. A study by the GEICAM group. Ann Oncol. 14:833–42
8. Early breast cancer trialists' Collaborative Group (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. Lancet. 365:1687–717
9. Von Hoff DD et al (1979) Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 91(5): 710–7
10. Kesavan S et al (1996) Anthracycline-induced cardiotoxicity. Ann Intern Med. 125:47–58
11. Perez EA et al (2004) Effect of doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 intergroup adjuvant trial. J Clin Oncol. 22: 3700–4
12. Fumoleau P et al (2003) Long-term benefit/risk ratio of epirubicin (EPI)-based adjuvant chemotherapy (CT) in operable breast cancer (BC) patients (pts): 7-year analysis in 3577 pts of French Adjuvant Study Group (FASG) trials. Proc Am Soc Clin Oncol. 22:23
13. Smith RE et al (2003) Acute myeloid leukemia and myelodysplastic syndrome after doxorubicin-cyclophosphamide adjuvant therapy for operable breast cancer: the National Surgical Adjuvant Breast and Bowel Project Experience. J Clin Oncol. 21:1195–204
14. Diamandidou E et al (1996) Treatment-related leukemia in breast cancer patients treated with fluorouracil-doxorubicin-cyclophosphamide combination adjuvant chemotherapy: the University of Texas M.D. Anderson Cancer Center experience. J Clin Oncol. 14:2722–30
15. Albain K et al (2001) Overall survival after cyclophosphamide, adriamycin, 5-FU, and tamoxifen (CAFT) is superior to T alone in postmenopausal, receptor(+), node(+) breast cancer: new findings from phase III Southwest Oncology Group Intergroup Trial S8814 (INT-0100). Proc Am Soc Clin Oncol. 20:94a

16. Praga C, Bergh J, Bliss J et al (2005) Risk of myeloid leukemia and myelodysplastic syndrome in trials of adjuvant epirubicin for early breast cancer: correlation with doses of epirubicin and cyclophosphamide. J Clin Oncol. 23: 4179–91
17. Rowinsky EK. Clinical pharmacology of taxol. J Natl Cancer Inst Monogr. 1993;(15):25–37
18. Roché H et al (2006) Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. J Clin Oncol. 24(36):5664–71
19. Martin M et al (2005) Adjuvant docetaxel for node-positive breast cancer. N Engl J Med. 352(22):2302–13
20. Henderson IC et al (2003) Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol. 21(6):976–83
21. Fachinfo für Paclitaxel, Version November 2007
22. Gradishar WJ et al (2005) Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol. 23(31):7794–803
23. Perez EA, et al Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. J Clin Oncol. 2007;25(23):3407–14. Epub 2007 Jul 2
24. Thomas E, et al Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in patients with taxane-resistant metastatic breast cancer. J Clin Oncol. 2007;25(23):3399–406. Epub 2007 Jul 2
25. Baselga J et al (2009) Phase II genomics study of ixabepilone as neoadjuvant treatment for breast cancer. J Clin Oncol. 27(4):526–34
26. www.emea.europa.eu/humandocs/PDFs/EPARZ ixempra/17705609en.pdf
27. Finek J et al (2009) A phase II trial of oral vinorelbine and capecitabine in anthracycline-pretreated patients with metastatic breast cancer. Anticancer Res. 29(2):667–70
28. Nolè F et al (2009) Phase II study of an all-oral combination of vinorelbine with capecitabine in patients with metastatic breast cancer. Cancer Chemother Pharmacol. 64(4):673–80
29. Bartsch R et al (2007) Capecitabine and trastuzumab in heavily pretreated metastatic breast cancer. J Clin Oncol. 25(25):3853–8
30. Chen L et al (2002) Cytochrome P450 gene-directed enzyme prodrug therapy (GDEPT) for cancer. Curr Pharmaceut Des. 8:1405–16
31. Schwartz PS et al (2003) Sustained P450 expression and prodrug activation in bolus cyclophosphamide-treated cultured tumor cells. Impact of prodrug schedule on P450 gene-directed enzyme prodrug therapy. Cancer Gene Ther. 10:571–82
32. Brock N (1989) Oxazaphosphorine cytostatics: Past-Present-Future, Seventh Cain Memorial Award Lecture1. Cancer Res. 49:1–7
33. Bonadonna G et al (1995) Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. N Engl J Med. 332(14):901–6
34. Piccart MJ (2001) Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. J Clin Oncol. 19(12):3103–10
35. Cheson BD et al (2009) Bendamustine: rebirth of an old drug. J Clin Oncol. 27(9):1492–501
36. Pirvulescu C et al (2008) Bendamustin in metastatic breast cancer: an old drug in new design. Breast Care. 3:333–9
37. Jamitzky T (1996) Third-line chemotherapy with bendamustin for metastatic breast cancer. A prospective pilot study. 7th EORTC Breast Cancer Working Conference. Eur J cancer. 32A(Suppl 2):47
38. von Minckwitz G et al (2005) Bendamustine prolongs progression-free survival in metastatic breast cancer (MBC): a phase III prospective, randomized, multicenter trial of bendamustine hydrochloride, methotrexate and 5-fluorouracil (BMF) versus cyclophosphamide, methotrexate and 5-fluorouracil (CMF) as first-line treatment of MBC. Anticancer Drugs. 16(8):871–7
39. Reichmann U et al (2007) Salvage chemotherapy for metastatic breast cancer: results of a phase II study with bendamustine. Ann Oncol. 18:1981–4
40. O'Shaughnessy J et al (2002) Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol. 20(12):2812–23
41. www.fda.gov/ohrms/dockets/AC/07/slides/2007-4332s1-01-FDA-Cortazar.ppt
42. Fachinfo 10.2008
43. Wadler S, Benson AB 3rd, Engelking C et al (1998) Recommended guidelines for the treatment of chemotherapy-induced diarrhea. J Clin Oncol. 16:3169
44. Bauer P, Köhne K (1994) Evaluation of experiments with adaptive interim analyses. Biometrics. 50:1029–41
45. Albain KS et al (2008) Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. J Clin Oncol. 26(24):3950–7
46. Gudena V et al (2008) Gemcitabine and taxanes in metastatic breast cancer: a systematic review. Ther Clin Risk Manag. 4(6):1157–64
47. O'Shaughnessy J, Miles D, Vukelja S et al (2002) Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol. 20: 2812–23
48. Beslija S, Obralic N, Basic H, et al Randomized trial of sequence vs combination of capecitabine (X) and docetaxel (T): XT vs T followed by X after progression as first-line therapy for patients (pts) with metastatic breast cancer (MBC). J Clin Oncol (Meeting Abstracts). 2006;24:571
49. Martin M, Ruiz A, Munoz M et al (2007) Gemcitabine plus vinorelbine versus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. Lancet Oncol. 8:219–25
50. Chan S, et al Phase III study of gemcitabine plus docetaxel compared with capecitabine plus docetaxel for anthracycline-pretreated patients with metastatic breast cancer. J Clin Oncol. 2009;27(11):1753–60. Epub 2009 Mar 9

51. Perez EA et al (2004) Carboplatin in combination therapy for metastatic breast cancer. Oncologist. 9:518–27
52. Perez EA et al (2000) A phase II study of paclitaxel plus carboplatin as first-line chemotherapy for women with metastatic breast carcinoma. Cancer. 88:124–31
53. Loesch D et al (2002) Phase II multicenter trial of a weekly paclitaxel and carboplatin regimen in patients with advanced breast cancer. J Clin Oncol. 20:3857–64
54. Sirohi B. Platinum-based chemotherapy in triple-negative breast cancer. Ann Oncol. 2008;19(11):1847–52. Epub 2008 Jun 20
55. Abella JV (2009) Breakdown of endocytosis in the oncogenic activation of receptor tyrosine kinases. Am J Physiol Endocrinol Metab. 296:E973–84
56. Clifford AH (2007) (2007) Trastuzumab – mechanism of action and use in clinical practice. N Engl J Med. 357: 39–51
57. www.cancer.gov/cancertopics/druginfo/fda-trastuzumab
58. Romond EH, Perez EA, Bryant J et al (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 353:1673–84
59. Piccart-Gebhart MJ et al (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 353:1659–72
60. Slamon D et al (2005) Phase III randomized trial comparing doxorubicin and cyclophosphamide, followed by docetaxel (AC-T) with doxorubicin and cyclophosphamide, followed by docetaxel and trastuzumab (AC TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2-positive early breast cancer patients: BCIRG 006 study. Breast Cancer Res Treat. 94(Suppl 1):S5
61. Joensuu H et al (2006) Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 354:809–20
62. Baselga J et al (2006) Adjuvant trastuzumab: a milestone in the treatment of HER2-positive early breast cancer. Oncologist. 11(Suppl 1):4–12
63. www.cancer.gov/cancertopics/druginfo/fda-lapatinib
64. Geyer CE, Forster J, Lindquist D et al (2006) Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 355:2733–43
65. Dhillon S, et al Lapatinib. Drugs. 2007;67:2101–8; discussion 2109–10
66. Mukherjee A, Dhadda AS, Shehata M et al (2007) Lapatinib: a tyrosine kinase inhibitor with a clinical role in breast cancer. Expert Opin Pharmacother. 8:2189–204
67. Montemurro F, Valabrega G, Aglietta M (2007) Lapatinib: a dual inhibitor of EGFR and HER2 tyrosine kinase activity. Expert Opin Biol Ther. 7:257–68
68. Burris HA, Hurwitz HI, Dees EC et al (2005) Phase I safety, pharmacokinetics, and clinical activity study of lapatinib(GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas. J Clin Oncol. 23:5305–13
69. Perez EA, Byrne JA, Hammond IW et al (2006) Results of an analysis of cardiac function in 2, 812 patients treated with lapatinib. J Clin Oncol. 24:S18
70. Adams CW et al (2006) Humanization of a recombinant monoclonal antibody to produce a therapeutic HER dimerization inhibitor, pertuzumab. Cancer Immunol Immunother. 55(6):717–27
71. Attard G, et al A phase Ib study of pertuzumab, a recombinant humanised antibody to HER2, and docetaxel in patients with advanced solid tumours. Br J Cancer. 2007;97: 1338–43
72. Presta LG, Chen H, O'Connor SJ et al (1997) Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res. 57:4593–9
73. Kerbel R, Folkman J (2002) Clinical translation of angiogenesis inhibitors. Nat Rev Cancer. 2:727–39
74. Jain RK (2001) Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med. 7:987–9
75. Cobleigh MA, Langmuir VK, Sledge GW et al (2003) A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. Semin Oncol. 30: 117–24
76. Adnane L, Trail PA, Taylor I et al (2005) Sorafenib (BAY 43-9006, Nexavar®, a dual-action inhibitor that targets RAF/MEK/ERK pathway in tumor cells and tyrosine kinases VEGFR/PDGFR in tumor vasculature. Methods Enzymol. 407:597–612
77. Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, Chen C, Zhang X, Vincent P, McHugh M, Cao Y, Shujath J, Gawlak S, Eveleigh D, Rowley B, Liu L, Adnane L, Lynch M, Auclair D, Taylor I, Gedrich R, Voznesensky A, Riedl B, Post LE, Bollag G, Trail PA. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res. 2004;64(19):7099–109. PMID: 15466206
78. Thompson N, Lyons J (2005) Recent progress in targeting the Raf/MEK/ERK pathway with inhibitors in cancer drug discovery. Curr Opin Pharmacol. 5(4):350–6. Review. PMID: 15955734
79. Caraglia M, Tassone P, Marra M, Budillon A, Venuta S, Tagliaferri P. Targeting Raf-kinase: molecular rationales and translational issues. Ann Oncol. 2006;17(Suppl 7): vii124–7. PMID: 16760274
80. Carter CA, Chen C, Brink C, Vincent P, Maxuitenko YY, Gilbert KS, Waud WR, Zhang X. Sorafenib is efficacious and tolerated in combination with cytotoxic or cytostatic agents in preclinical models of human non-small cell lung carcinoma. Cancer Chemother Pharmacol. 2007 Feb;59(2): 183–95. Epub 2006 May 25
81. Lee D, Heymach JV. Emerging antiangiogenic agents in lung cancer. Clin Lung Cancer. 2006;7(5):304–8. Review
82. Kumar A, Wakelee H. Second- and third-line treatments in non-small cell lung cancer. Curr Treat Options Oncol. 2006;7(1):37–49. Review. PMID: 16343367
83. Herbst RS, Onn A, Sandler A. Angiogenesis and lung cancer: prognostic and therapeutic implications. J Clin Oncol. 2005;23(14):3243–56. Review. PMID: 15886312
84. Wilhelm S, Chien DS (2002) BAY 43-9006: preclinical data. Curr Pharm Des. 8(25):2255–7. Review. PMID: 12369853
85. Burstein HJ et al (2008) Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 26(11):1810–6
86. Huang S, Houghton PJ (2002) Inhibitors of mammalian target of rapamycin as novel antitumor agents: from bench to clinic. Curr Opin Investig Drugs. 3:295–304

87. Lane H, Tanka C, Kovaril T et al (2003) Preclinical and clinical pharmacokinetic/pharmacodynamic modeling to help to define an optimal biological dose for the oral mTOR inhibitor, RAD 001, in oncology. Proc Am Soc Clin Oncol. 22:237
88. Francesc V, Chambard JC, Pouyssegur J (1999) p70s6 Kinase-mediated protein synthesis is a critical step for vascular endothelial cell proliferation. J Biol Chem. 274:26776–82
89. Guba M, von Breitenbuch P, Steinbauer M et al (2002) Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth. Nat Med. 8:128–35
90. Lane H et al (2003) Preclinical and clinical pharmacokinetic/pharmacodynamic modeling to help to define an optimal biological dose for the oral mTOR inhibitor, RAD 001, in oncology. Proc Am Soc Clin Oncol. 22:237
91. Osborne CK (1998) Tamoxifen in the treatment of breast cancer. N Engl J Med. 339(22):1609–18
92. Desta Z et al (2004) Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system in vitro: prominent roles for CYP3A and CYP2D6. J Pharmacol Exp Ther. 310(3):1062–75
93. Valachis A, Mauri D, Polyzos NP, Mavroudis D, Georgoulias V, Casazza G Fulvestrant in the treatment of advanced breast cancer: A systematic review and meta-analysis of randomized controlled trials. Crit Rev Oncol Hematol. 2009 Apr 13
94. McKeage K et al (2004) Fulvestrant: a review of its use in hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. Drugs. 64(6):633–48
95. Jones SE et al (2005) Effectiveness and tolerability of fulvestrant in postmenopausal women with hormone receptor-positive breast cancer. Clin Breast Cancer. 6(Suppl 1):S9–14
96. Engel JB et al (2007) Drug insight: clinical use of agonists and antagonists of luteinizing-hormone-releasing hormone. Nat Clin Pract Endocrinol Metab. 3(2):157–67
97. www.fda.gov
98. Russell RG, Rogers MJ (2005) Bisphosphonates: from the laboratory to the clinic and back again. Bone 1999;25:97–106, Clezardin P. Anti-tumour activity of zoledronic acid. Cancer Treat Rev. 31(Suppl 3):1–8
99. Lipton A (2008) Emerging role of bisphosphonates in the clinic – antitumor activity and prevention of metastasis to bone. Cancer Treat Rev. 34:S25–30
100. Woo SB, Hellstein JW, Kalmar JR (2006) Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med. 144(10):753–61. Review
101. Sawatari Y, Marx RE. Bisphosphonates and bisphosphonate-induced osteonecrosis. Oral Maxillofac Surg Clin North Am. 2007;19(4):487–98, v–vi
102. Felsenberg D, Hoffmeister B, Amling M, Mundlos S, Seibel MJ, Fratzl P (2006) Onkologie: Kiefernekrosen nach hoch dosierter Bisphosphonattherapie. Deutsches Ärzteblatt. 103(46):3078–81
103. Sambrook P, Olver I, Goss A (2006) Bisphosphonates and osteonecrosis of the jaw. Aust Fam Physician. 35(10): 801–3
104. Mavrokokki T, Cheng A, Stein B, Goss A (2007) Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. J Oral Maxillofac Surg. 65(3):415–23
105. Fizazi K et al (2009) Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. J Clin Oncol. 27(10):1564–71
106. Ellis GK et al (2008) Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for non-metastatic breast cancer. J Clin Oncol. 26(30):4875–82

HER2-Targeted Therapy

20

Phuong Dinh, Gianluca Tomasello, and Martine J. Piccart

20.1 Introduction

Up to 25% of women with breast cancer have tumors, which are human epidermal growth factor receptor-2 (HER2) positive, associated with an aggressive phenotype, higher recurrence rate and reduced survival [1, 2]. In these patients with poorer prognosis, combination chemotherapy (±endocrine therapy), up until recently, was the only treatment modality available.

Trastuzumab (Herceptin®), a monoclonal antibody directed against the extracellular domain of HER2, has been investigated extensively in the clinical setting of advanced breast cancer, both as monotherapy and in combination with standard chemotherapeutic drugs. More recently, it has been tested in HER2-positive patients with early breast cancer in five adjuvant trials.

Despite impressive results in both clinical arenas, many controversies remain regarding its use. For patients with early breast cancer, controversy still exists regarding the optimum timing, duration, and schedule of trastuzumab. For those with metastatic disease, the controversy of whether to cease altogether or continue with trastuzumab beyond progression still needs answering.

This chapter discusses the evolution of HER2-targeted therapy, beginning with the initial success of trastuzumab to the controversies that remain, and from there, to the discussion of newer anti-HER2 approaches currently under investigation.

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20.2 Targeting the HER2 Receptor

HER2 belongs to the human epidermal growth factor receptor (EGFR) family of tyrosine kinases consisting of EGFR (HER1; erbB1), HER2 (erbB2, HER2/*neu*), HER3 (erbB3), and HER4 (erbB4). All these receptors have an extracellular ligand-binding region, a single membrane-spanning region, and a cytoplasmic tyrosine-kinase-containing domain, the last being absent in HER3. Ligand binding to the extracellular region results in homo- and heterodimer activation of the cytoplasmic kinase domain and phosphorylation of a specific tyrosine [3], leading to the activation of various intracellular signaling pathways involved in cell proliferation and survival.

HER2 was first identified as an oncogene activated by a point mutation in chemically-induced rat neuroblastomas [4], and soon after, found to be amplified in breast cancer cell lines [5]. In the clinic, patients with HER2 gene-amplified tumors were shown to represent approximately 25–30% of the human breast population, having poorer disease-free survival (DFS) [6–8], and also displaying resistance to certain chemotherapeutic agents [9–11].

With the accumulating body of evidence supporting the HER2 oncogene hypothesis, the HER2 receptor represented an ideal target for anticancer therapy. By targeting HER2 receptors, either intracellularly or extracellularly, downstream pathways could be indirectly inhibited to induce cell cycle arrest, apoptosis, as well as inhibition of tumor cell invasion and metastases [12].

Two main therapeutic strategies have been developed so far to target the HER2 receptor; monoclonal antibodies, and small molecule kinase inhibitors. Trastuzumab (Herceptin; Genentech, South San Francisco) is a recombinant, humanized anti-HER2 monoclonal antibody and was the first clinically active anti-HER2 therapy to be characterized. Trastuzumab exerts its action

I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_20, © Springer-Verlag Berlin Heidelberg 2010

through several mechanisms including (1) induction of receptor downregulation/degradation [13], (2) prevention of HER2 ectodomain cleavage [14], (3) inhibition of HER2 kinase signal transduction [15] via ADCC, and (4) inhibition of angiogenesis [16].

On the other hand, small molecule HER2 kinase inhibitors are cheaper to produce but are often less specific, since they can simultaneously inhibit multiple targets. Unlike trastuzumab, most of them are still in a relatively early phase of clinical development.

20.2.1 Importance of Accurately Identifying HER2

A HER2 positive status is not only an adverse prognostic marker in breast cancer but also a positive predictive marker of response to anti-HER2 therapies. Tailored treatment requires proper identification of these patients who are most likely to derive benefit, and least likely to experience unnecessary toxicity. The guidelines from the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) for HER2 testing have recently been published, endeavoring to improve laboratory standardization and test reproducibility.

HER2 status is thus reported as an algorithm of positive, equivocal, and negative results defined as (a) HER2 positive – immunohistochemistry (IHC) staining of 3+ (uniform, intense membrane staining of >30% of invasive tumor cells, a fluorescence in situ hybridization (FISH) result of more than 6.0 HER2 gene copies per nucleus, or a FISH ratio (HER2 gene signals to chromosome 17 signals) of more than 2.2; (b) HER2 negative – IHC staining of 0 or 1+ FISH result of less than 4.0 HER2 gene copies per nucleus, or FISH ratio of less than 1.8; and (c) HER2 equivocal – IHC 3+ staining of 30% or less of invasive tumor cells or 2+ staining, a FISH result of 4–6 HER2 gene copies per nucleus, or FISH ratio between 1.8 and 2.2.

20.3 Trastuzumab in the Metastatic Setting

Since the first reports of trastuzumab's activity in HER2+ MBC, many studies have been conducted to investigate the optimum schedule in this patient group, both as single-agent therapy and in combination.

20.3.1 Single-agent Therapy in Heavily Pretreated Patients

In an early trial evaluating weekly trastuzumab efficacy in 222 women with HER2+ MBC that had progressed after one or two chemotherapy regimens [17], the response rate (RR) was 15% in the intent-to-treat population and was significantly higher in strong HER2+ overexpressors (18 vs. 6% for those with 3+ and 2+ IHC, respectively). The median response duration was 9.1 months. Cardiac dysfunction was the most common adverse event, occurring in 5% of treated patients, many of whom had received prior doxorubicin.

The alternative 3-weekly schedule of trastuzumab was investigated in a phase II study [18] of 105 patients where comparable results were achieved (overall RR of 19% and clinical benefit rate of 33%). Median time to progression (TTP) was 3.4 months (range 0.6–23.6 months).

20.3.2 First-Line Single-Agent Therapy

The benefit of first-line trastuzumab monotherapy was studied in 114 women with HER2+ MBC [19], randomized to receive first-line treatment with trastuzumab 4 mg/kg loading dose, followed by 2 mg/kg weekly, or a higher 8 mg/kg loading dose, followed by 4 mg/kg weekly. RRs in 111 assessable patients with 3+ and 2+ HER2 overexpression by IHC were 35% (95% CI 24.4–4s4.7%) and none (95% CI, 0–15.5%), respectively. The RRs in 108 assessable patients with and without HER2 gene amplification by FISH analysis were 34% (95% CI 23.9–45.7%) and 7% (95% CI 0.8–22.8%), respectively. Interestingly, overall RR was nearly double that reported for previously treated patients. There was no clear evidence of a dose-response relationship for response, survival, or adverse events.

20.3.3 Trastuzumab in Combination with Chemotherapy

20.3.3.1 Trastuzumab and Taxanes

Preclinical studies have shown additive or synergistic interactions between trastuzumab and multiple cytotoxic agents, including platinum analogs, taxanes,

anthracyclines, vinorelbine, gemcitabine, capecitabine and cyclophosphamide [20]. The pivotal randomized combination trials of trastuzumab [21, 22] demonstrated that trastuzumab plus a taxane is associated with a clinical benefit that is superior to that of a taxane alone.

The first trial enrolled 469 HER2+ MBC patients who had not received prior treatment for advanced disease. For those patients who had previously received anthracyclines in the adjuvant setting or who were not suitable to receive anthracyclines ($n>188$), randomization took place between paclitaxel with or without trastuzumab. All other patients ($n>281$) were randomized to receive an anthracycline plus cyclophosphamide with or without trastuzumab. The addition of trastuzumab to chemotherapy was associated with a longer TTP (median 7.4 vs. 4.6 months; $P<0.001$), a higher rate of objective RR (50 vs. 32%, $P<0.001$), a longer duration of response (median 9.1 vs. 6.1 months; $P<0.001$), a lower rate of death at 1 year (22 vs. 33%, $P>0.008$), and longer survival (median survival 25.1 vs. 20.3 months; $P>0.01$ and 20% relative reduction in the risk of death overall) [4]. However, cardiotoxicity was more common with combined treatment, especially with AC plus trastuzumab (27%), leading to the recommendation that anthracyclines and trastuzumab should not be combined.

In a phase II study of 95 HER2-normal and HER2+ MBC patients evaluating weekly trastuzumab and paclitaxel therapy [23], the overall RR was 56.8% (95%CI 47–67%). In those with HER2+ tumors, the overall RR was higher than those with HER2-normal tumors (Range of 67–81% compared with range of 41–46%). Treatment was associated with grade 3/4 neutropenia in 6%, and three patients had severe cardiac complications.

In the M77001 trial, which investigated the combination of weekly trastuzumab plus weekly or 3-weekly docetaxel in 188 MBC patients, the median overall survival (OS) was 22.7 months with docetaxel alone and 31.2 months with trastuzumab plus docetaxel ($P>0.0062$), after 24 months of follow-up. All investigated clinical outcomes including median TTP (10.6 vs. 5.7 months) were superior for trastuzumab plus docetaxel vs. docetaxel alone.

More recently, a randomized multicenter phase II study of 98 HER2+ MBC patients investigated the combination of trastuzumab/docetaxel against sequential trastuzumab followed by docetaxel at progression. Preliminary results have shown a significantly longer median progression-free survival (PFS) with the combination arm (9.1 vs. 4 months, $P>0.0004$), although there were more serious adverse events, namely with neutropenic fevers. No statistical difference in cardiac toxicity was observed [24].

Despite the fact that no mature data are currently available to compare trastuzumab plus a taxane vs. trastuzumab alone, many consider the combination of a taxane and trastuzumab to represent the best current first-line option for women with HER2+ MBC.

20.3.3.2 Trastuzumab and Platinum Salts

In addition to a possible synergistic interaction [20], in vitro data suggests that trastuzumab may also reverse primary platinum resistance by modulating HER2 activity [25]. The benefit of adding platinum salts to trastuzumab-based combination therapy was shown in a phase III trial comparing trastuzumab and paclitaxel with and without carboplatin in 194 women with HER2+ MBC [26]. The addition of carboplatin to paclitaxel and trastuzumab significantly improved RR (52 vs. 36%) and median PFS (10.7 vs. 7.1 months). Although the triple therapy was associated with higher rates of grade 3/4 hematologic toxicity, there was no difference in the rates of neurologic, cardiopulmonary, or febrile complications.

In contrast, a lack of benefit for adding carboplatin to trastuzumab plus a taxane was shown in the BCIRG 007 trial [27], in which 263 previously untreated patients with HER2 FISH+ MBC were randomly assigned to trastuzumab plus eight courses of either docetaxel alone (TH) (100 mg/m^2 every 3 weeks) or docetaxel (75 mg/m^2 every 3 weeks) plus carboplatin (TCH) (AUC of 6). A first analysis, performed at 39 months of median follow-up, showed no difference in median OS between the two groups (36.5 months in both arms). Triple combination therapy was associated with more episodes of thrombocytopenia, nausea and emesis, but fewer episodes of sensory neuropathy, myalgias, skin/nail changes and neutropenic infection.

20.3.3.3 Trastuzumab Plus Vinorelbine

Trastuzumab and vinorelbine constitute effective and well-tolerated first-line treatment for HER2+ MBC. In a multicentre phase II study evaluating this combination in 54 women [28], the RR was 68% (95%CI 54–80%). Two patients experienced cardiotoxicity in excess of grade 1; one patient experienced symptomatic heart failure.

This combination was also shown to be effective in patients who had progressed while receiving anthracyclines and taxanes [29–31]. The combination of trastuzumab with vinorelbine was well tolerated in all of these trials. There was no evidence that this combination resulted in more cardiac events compared with trastuzumab alone.

20.3.3.4 Trastuzumab with Capecitabine

Several studies have demonstrated that trastuzumab and the 5-fluorouracil prodrug, capecitabine, have at least additive antitumor activity in human breast cancer models [32], and this has been supported by recent studies in the clinical setting.

In a phase II trial of 27 MBC patients refractory to anthracyclines and taxanes who received capecitabine (1,250 mg/m^2 twice daily for 14 of every 21 days) plus weekly trastuzumab, there were 12 objective responses (45%) with four complete responses [33]. Nine additional patients (33%) had disease stabilization for at least 9 weeks, and the median PFS was 6.7 months. There was a low incidence of grade 3 or 4 adverse events.

This high RR was mirrored in a phase II study of first-line trastuzumab–capecitabine therapy, in which an objective RR of 76% (5 CR, 14 PR) was recorded [34]. In both phase II studies, the combination of trastuzumab plus capecitabine was generally well tolerated. There was no evidence of greater cardiotoxicity with this combination.

20.3.3.5 Trastuzumab Plus Gemcitabine

Trastuzumab plus gemcitabine was evaluated in a phase II study [35] with 64 patients, where the majority (95%) had been treated with prior anthracyclines and taxanes. Gemcitabine (1,200 mg/m^2 weekly Day 1, 8 in a 21-day cycle) plus weekly doses of trastuzumab was administered until disease progression. The objective RR was 38% in the intent-to-treat population (23 of 61) and 44% among the 39 patients with HER2 3+ expression. The median response duration was 5.8 months, median OS was 14.7 months, and median TTP was 5.8 months. Trastuzumab plus gemcitabine was well tolerated with no cases of clinical congestive heart failure.

20.3.3.6 Trastuzumab with Poly-Chemotherapy

Trastuzumab has also been added to combination chemotherapy for MBC. Several studies have shown that triple combinations are effective and produce high RRs [36–41], although overlapping toxicities must be carefully considered.

20.3.4 Trastuzumab in Combination with Hormonal Therapy

In the estrogen receptor (ER)-positive patient populations, the rate of HER2 positivity is between 11 and 35% [42–44]. Resistance to hormonal therapy, particularly tamoxifen, appears to be a characteristic of ER+, HER2+ tumors [45], and it has been hypothesized that the addition of trastuzumab to hormonal therapy may overcome this relative resistance. In preclinical studies, the combination of tamoxifen with anti-HER2 antibodies can produce a greater inhibitory effect on cell growth than either agent alone [46, 47]. Some evidence also indicates that compared with tamoxifen, aromatase inhibitors may elicit a greater response in HER2+ tumors [48]. Taken together, these findings provide a clear rationale for combining trastuzumab with hormonal agents in patients with HER2+/ER+ MBC.

In a multicenter, open-label, phase II trial assessing the combination of letrozole and trastuzumab in 31 evaluable patients with HER2+/ER+ MBC [49], a RR of 26%, including 1 CR, was reported. An additional eight patients had stable disease. Two patients withdrew from the study due to toxicity (one patient had grade 3 arthralgia and one patient developed congestive heart failure).

The international, multicenter, randomized, phase III TAnDEM trial evaluated anastrozole with or without trastuzumab in the first- and second-line treatment of postmenopausal women with HER2+/ER+ MBC [47], and allowed for cross-over at the time of progression. A total of 208 patients were randomized. The results showed that the addition of trastuzumab to anastrozole significantly improved clinical outcomes for HER2+ and ER+ MBC patients, with a doubling of PFS (4.8 months vs. 2.4 months; $P > 0.0016$), a tripling of the overall RR (20.3 vs. 6.8%; $P > 0.018$), and long-term benefit for 15% of patients on the combination arm who did not progress for at least

2 years, allowing for a significant delay in receiving chemotherapy.

20.3.5 Trastuzumab after Disease Progression

An important clinical question is whether trastuzumab should be continued after progression on a first-line trastuzumab-containing regimen. Preclinical data and retrospective analysis of clinical trials support the hypothesis that continuing treatment with trastuzumab after disease progression may provide patient benefit [50–52].

An extension study of the pivotal phase III trial of trastuzumab combined with chemotherapy as first-line treatment evaluated the safety of continuing the biological agent monotherapy beyond disease progression. Although not designed to evaluate efficacy, the RR to second-line trastuzumab was similar for patients who initially received chemotherapy alone and for those who initially received chemotherapy plus trastuzumab (14 and 11%, respectively), as was median response duration (about 7 months).

In another retrospective analysis, trastuzumab alone or combined with a different chemotherapy was continued beyond disease progression in 80 patients with HER2+ MBC. Continued trastuzumab appeared safe, and 32 responses were noted (four complete responses).

In a study of 105 patients with HER2+ MBC who had received two or more trastuzumab-containing regimens, RRs were, in fact, similar for second-line as compared to first-line therapy, with some first-line nonresponders eventually achieving a response in second-line treatment. Nonfatal cardiac events were reported in 22 patients and most patients were able to continue trastuzumab.

Apart from these retrospective studies, there is no convincing prospective evidence to support the use of extended trastuzumab therapy after progression. Recently, two prospective trials looking at this issue have closed. The first was the US Intergroup study randomizing patients who had progressed on taxanes plus trastuzumab to vinorelbine vs. vinorelbine plus trastuzumab. This trial closed early due to low accrual. The other was the BIG 3–05 study [53], which randomized 152 patients who had progressed on trastuzumab, to either capecitabine or capecitabine plus trastuzumab. This trial also closed early due to slow accrual but the preplanned interim analysis of 119 patients showed a longer TTP favoring the combination arm (33 vs. 24 weeks, $P > 0.178$), and no difference in serious adverse events.

In the absence of convincing prospective results, a central registry program that collects information longitudinally from a large number of patients with HER2+ breast cancer during the course of their disease was initiated (RegistHER, www.registher.com) to learn about the long-term side effects and benefits of prolonged trastuzumab therapy [54].

20.4 Trastuzumab in the Adjuvant Setting

Encouraged by the highly reproducible antitumor activity of trastuzumab in the metastatic setting, four major international studies, with enrollment of over 13,000 women, were launched in 2000–2001 to investigate the role of trastuzumab in the adjuvant setting ; HERA [55, 56], the combined North American trials NSABP-B31 and NCCTG/N9831 [57, 58], and BCIRG 006 [59, 60]. In 2005, the initial results of these four trials, alongside a smaller Finnish trial, FinHer [61] were released, which showed significant benefit in reducing recurrence and mortality. Updated analyzes for most of these trials have recently been presented, including that of another trial PACS-04 [62], which, in contrast, had negative results (Table 20.1).

Tables 20.2 and 20.3 provide an overview of the study characteristics as well as the clinical benefit of each of the adjuvant trials.

20.4.1 The Adjuvant Trials

20.4.1.1 HERA Trial

HERA, the largest study, was an international, multicenter, randomized controlled trial comparing 1-year or 2 years of 3-weekly trastuzumab with observation (no trastuzumab) in patients with HER2-positive early breast cancer. Both node-positive (68%) and node-negative diseases (only if >1 cm tumor size) (32%) were included.

Table 20.1 Trial designs and patient characteristics in adjuvant trastuzumab studies

	HERA [55, 56]	B31/N9831 [57, 58]	BCIRG 006 [59, 60]	FinHer [61]
Planned/patients included	5,102/3,401	2,043/1,736 /2,766/1,615	3,222/3,222	232/232
Median follow-up (months)	23.5	2.9 years	36	36
Treatment regimens	1-year H vs. Obs *after any* CT regimen completed(2-years H not included in analysis)	AC×4→P×4 AC×4→P×4+HP given 3-weekly AC×4→P×12 AC×4→P×12+H P given weekly Starting *concurrently* with P (AC×4→P×12+H starting *after* P not included in analysis)	AC×4→D×4 AC×4→D×4+H starting *concurrently* with DDCb×6+H D given 3 weekly	V weekly×8 *or* D 3 weekly×3 *With or without* H weekly×9 *concurrently* then FEC 3 weekly×3
Trastuzumab schedule	Every 3 weeks	Weekly/weekly	Weekly with CT, then every 3 weeks	Weekly
Primary endpoints	DFS	OS/DFS (DFS for combined analyzes)	DFS	RFS
HER2 testing	Centralized IHC±FISH	IHC a/o FISH in "approved" laboratories	Centralized FISH	Centralized CISH
Age<50 years (%)	51	51	52	NA
Node-negative disease (%)	32[a]	5.7	29[b]	16[c]
Grade 3 tumors (%)	60	69	NA	65
Taxane-based chemotherapy (%)	26	100	100	50
Planned endocrine therapy (%)	46	52	54	NA
Normal cardiac function	At completion of loco-regional therapy and chemotherapy	At completion of AC×4	After surgery	After surgery
Particip. countries (*n*)	39	1	40	1

A adriamycin; *CISH* chromogenic in situ hybridization; *C* cyclophosphamide; *Cb* carboplatin; *CT* chemotherapy; *D* docetaxel; *DFS* disease-free survival; *E* epiadriamycin; *F* 5-fluorouracil; *FISH* fluorescence in situ hybridization; *H* Herceptin®(trastuzumab); *HR* hazard ratio; *IHC* immunohistochemistry; *NA* not available; *OS* overall survival; *P* paclitaxel; *RFS* relapse-free survival; *T* trastuzumab; *V* vinorelbine

[a]Only if tumor size >1 cm. [b]Only if other concomitant risk factors (grade >1, hormone receptors negative). [c]Only if size >20 mm and PgR negative

The design of the trial was pragmatic in that it wanted to explore the potential benefit of trastuzumab given after and independently of the type of chemotherapy in order for the results to be applicable in many countries with varying clinical practices. Most patients received anthracycline-based regimens while only 26% of patients were also given taxanes.

The recent update at 23.5 months median follow-up demonstrated an unadjusted hazard ratio (HR) for the risk of death with trastuzumab as 0.66 (95%CI 0.47–0.91; $P>0.0115$), corresponding to an absolute OS benefit of 2.7%. The unadjusted HR for the risk of an event with trastuzumab was 0.64 (0.54–0.76; $P<0.0001$), corresponding to an absolute DFS benefit of 6.3%.

Table 20.2 Efficacy results of adjuvant trastuzumab studies

	HERA [55, 56???]		B31 + N9831 [57, 58???]		BCIRG006 [59, 60???]			FinHer [61???]	
	Control (n > 1,698)	*1-year H (n > 1,703)*	*Control (n > 1,679)*	*1-year H (n > 1,672)*	*AC-D*	*AC-DH*	*DCbH*	*Control (n > 115)*	*H 9-week (n > 116)*
Events for DFS									
Patients with events	321	218	261	133	192	128	142	27	12
Distant events	233	152	193	96	143	93	98	26	8
Events for OS	90	59	92	62	80	49	56	14	6
HR for DFS	0.64		0.48			0.61	0.67	0.42	
95% CI	0.54–0.76		0.39–0.59			0.48–0.76	0.54–0.83	0.21–0.83	
P-value	<0.0001		<0.00001			<0.0001	0.0003	0.0078	
HR for OS	0.66		0.65			0.59	0.66	0.41	
95% CI	0.47–0.91		0.51–0.84			0.42–0.85	0.47–0.93	0.47–1.08	
P-value	0.0115		0.0007			0.004	0.0017	0.07	
Median follow-up	23.5 months		34.8 months		36 months			36 months	

A doxorubicin; *C* cyclophosphamide; *H* Herceptin®(trastuzumab); *NA* not available; *T* docetaxel. Defined in all trials as breast cancer relapses, second malignancies, deaths; the Finnish trial uses recurrence-free survival instead

Table 20.3 Molecularly-targeted agents in HER2-positive breast cancer

Name	Class	Mechanism of action	Phase of development
Trastuzumab	Monoclonal antibody	Block HER-2	Phase III
Lapatinib	Small molecule – TKI	Reversible inhibition of EGFR and HER-2	Phase III
HKI-272	Small molecule	Irreversible inhibition of EGFR and HER-2	Phase II
Pertuzumab	Monoclonal antibody	Block HER-2	Phase III
17-AAG	Derivate of geldanamycin	Hsp90 inhibitor	Phase II
Bevacizumab	Monoclonal antibody	Block VEGF	Phase III
Pazopanib	Small molecule Multitargeted TK inhibitor	Inhibition of VEGFR/PDGFR and c-kit	Phase II
Trastuzumab-DM1	Monoclonal antibody-drug-conjugate	Selective delivery of a chemo-therapeutic drug to HER2-positive breast cancer cells	Phase II

TK tyrosine kinase; *TKI* tyrosine kinase inhibitor; *EGFR* epidermal growth factor receptor; *VEGF* vascular endothelial growth factor; *VEGFR* vascular endothelial growth factor receptor; *PDGFR* platelet-derived growth factor receptor

20.4.1.2 The Combined American NSABP-B31 and NCCTG-N9831 Trials

The NSABP-B31 trial compared 4 cycles of doxorubicin and cyclophosphamide followed by 4 cycles of 3-weekly paclitaxel (arm 1) with the same regimen plus 52 weeks of trastuzumab beginning with the first cycle of paclitaxel (arm 2). The NCCTG-N9831 trial randomized patients in 1 of 3 regimens: 4 cycles of doxorubicin and cyclophosphamide followed by 12 cycles of weekly paclitaxel (arm A), the same regimen followed by 52 weekly doses of trastuzumab (arm B), or the same regimen plus 52 weekly doses of trastuzumab initiated concomitantly with paclitaxel (arm C).

Because arms 1 and 2 of NSABP-B31 and arms A and C of NCCTG-N9831 were similar, the National Cancer Institute (NCI) and Food and Drug Administration (FDA) approved a joint analysis with exclusion of arm B. Only 5.7% of patients were node negative.

In the recent update at 2.9 years median follow-up, the trastuzumab-treated group had a longer DFS (HR 0.49; 95%CI 0.41–0.58; $P<0.0001$) and OS (HR 0.63; 95%CI 0.49–0.81; $P>0.0004$), similar to the results of the first interim analysis, despite some degree of cross-over.

20.4.1.3 BCIRG 006 Trial

The BCIRG 006 trial evaluated the benefit of adding trastuzumab to two chemotherapy regimens, one with and one without anthracyclines, with the intention of maximizing efficacy and minimizing cardiotoxicity, in both node-negative (29%, with one other concomitant risk factor) and node-positive (71%) patients. The regimens were either with 4 cycles of doxorubicin and cyclophosphamide followed by 4 cycles of 3-weekly docetaxel (AC-D) as the control arm, or with 4 cycles of AC-D combined with 1 year of trastuzumab (AC-DH) or 6 cycles of docetaxel and carboplatin with 1 year of trastuzumab (DCbH).

The most recent second interim efficacy analysis was reported after a median follow-up of 36 months. For DFS, the HR was 0.61 (95%CI 0.48–0.76; $P<0.0001$) for the AC-DH arm and 0.67 (95%CI 0.54–0.83; $P>0.00003$) for the DCbH arm, compared with the AC-D. This translated to absolute benefits (from years 2 to 4) of 6 and 5%, respectively. The HR for OS was 0.59 (95%CI 0.42–0.85; $P>0.004$) for AC-DH and 0.66 (95%CI 0.47–0.93; $P>0.017$) for DCbH, over AC-D.

20.4.1.4 FinHer Trial

In the FinHer trial, patients with node-positive (84%) or high-risk node- negative disease (defined as tumors >2 cm and PgR negative) (16%), were randomized to 3 cycles of 3-weekly docetaxel or 8-weekly cycles of vinorelbine followed by 3 cycles of fluorouracil, epirubicin and cyclophosphamide (FEC), with the primary aim of the trial comparing treatment using docetaxel or vinorelbine. The subset of HER2+ patients ($n>232$) were further randomized to either receive ($n>116$) or not receive ($n>116$) 9 weeks of trastuzumab given concurrently with docetaxel or vinorelbine.

With 3-year median follow-up, there was a significant reduction in distant recurrence (HR 0.29; 95%CI 0.13–0.64; $P>0.002$), an improved 3-year DFS (HR 0.42; 95%CI 0.21–0.83; $P>0.01$), and a nonstatistically significant trend toward improved OS (HR 0.41; 95%CI 0.16–1.08; $P>0.07$) favoring the patients treated with trastuzumab.

20.4.1.5 PACS-04 Trial

PACS-04 was a 4-arm trial involving 3,010 node-positive early breast cancer patients with two randomizations; the first for all patients between docetaxel plus epirubicin vs. FEC; and the second for a subset of 528 HER2+ patients to sequential trastuzumab or observation.

With a median follow-up of 48 months, the HR for DFS with trastuzumab was 0.86 (95%CI 0.61–1.22), which was not statistically significant. An exploratory analysis of time to first event suggested that trastuzumab was more effective at reducing the risk of a first event during the first 18 months of therapy, but not thereafter. The incidence of cardiotoxicity was 1.7%, and of asymptomatic LVEF decrease was 4.2%.

20.4.2 Trastuzumab Efficacy in the Adjuvant Trials

Despite differences in patient population and trial design, including chemotherapy regimen, the timing of trastuzumab initiation, and the schedule and duration

of trastuzumab administration, highly reproducible and impressive results have been produced across most of the trials except PACS-04; 33–58% reduction in the recurrence rate and a 30% reduction in mortality. This degree of benefit in early breast cancer is the largest reported since the introduction of tamoxifen in ER+ disease. Although these results are impressive, the median follow-up times ranged from 23.5 to 48 months, and thus, much longer follow-up will be needed to evaluate whether this trastuzumab effect will weaken over time.

20.4.3 Trastuzumab Safety in the Adjuvant Trials

Hypersensitivity was the most common adverse effect of trastuzumab, and occurred mainly with the first infusion. Unexpected short-term side effects did not emerge in any of the trials, with the exception of nine cases of interstitial pneumonitis in B-31 and N9831, though the relationship to trastuzumab is still not clearly defined.

Cardiotoxicity remains the most important adverse effect of trastuzumab. Across the adjuvant trials, the definitions for cardiac events, the schedules for cardiac monitoring, the analyses of cardiac endpoints and follow-up times, all differed.

Nonetheless, it appears that the incidence of cardiac events with trastuzumab was not high, ranging from 0.4% in the BCIRG 006 trial to 4.1% in the B-31 trial. Within the control arms of all studies, the incidence of cardiac events ranged from 0 to 0.8%.

In the cardiac safety analysis of the NSABP B-31 trial [63], the 3-year cumulative incidence of cardiac events was 4.1% (95%CI 2.9–5.8%), which corresponded to a difference of 3.3% (95%CI 1.7–4.9%) from the control arm. Asymptomatic drops in LVEF occurred in 11.3% and over 60% of these showed a significant improvement in cardiac function over time. Women with hypertension, borderline LVEF (50–54%) or greater age at entry appeared at higher risk for CHF, but no apparent increase occurred among patients with left-sided lesions receiving radiotherapy. In HERA, risk factors associated with cardiac side effects of trastuzumab included a higher mean cumulative dose of doxorubicin or epirubicin; a lower screening LVEF and a higher body mass index [64].

20.4.4 The Remaining Controversies with Adjuvant Trastuzumab

Although generally accepted as standard of care in HER2+ breast cancer patients, some controversies remain regarding trastuzumab timing, duration and optimum schedule with other adjuvant therapies.

In the five adjuvant trials, the timing of trastuzumab initiation varied considerably. In HERA, trastuzumab was delayed for a median time of 8 months after surgery; for 4 months in the combined B-31 and N9831 group, and for 1 month in FinHer and the platinum-taxane arm of BCIRG 006. The rationale for the early administration of trastuzumab concurrent with chemotherapy lies in the hypothesis that synergism is possible between certain chemotherapy agents and trastuzumab [65, 66]. In preclinical models, enhanced antitumor activity has been observed when trastuzumab was combined with cyclophosphamide, doxorubicin, paclitaxel, methotrexate, etoposide and vinblastine.

This combination strategy, however, has the potential for enhancing serious toxicities, with the most troublesome being that of cardiotoxicity. When given concomitant with taxanes, a higher rate of asymptomatic decrease in LVEF (HR 2.1, 95%CI 1.7–2.6; $P<0.0001$) was observed between arms 1 and 2 in NSABP-B31. Also, a higher rate of trastuzumab discontinuation was seen, with 14% in NSABP-B31, 10.8% in NCCTG-N9831, and 4.3% in HERA [67].

Whether trastuzumab should be avoided during radiotherapy is still unclear. Preclinical studies suggest that human breast cancer cells damaged by radiation may be especially vulnerable to injury if they are also deprived of essential signal transduction mechanisms by disruption of the HER-2 growth factor receptor pathway [68]. The toxicity data available so far for concomitant trastuzumab and radiotherapy has not been worrisome. In NCCTG-N9831 after a median follow-up of 1.5 years, Halyard et al. [69] reported no significant differences in skin reaction, pneumonitis, dyspnoea, cough, esophageal dysphagia, or neutropenia among the treatment arms, and no increase in the frequency of cardiac events. Nevertheless, only long-term follow-up data will provide an answer regarding any potential cardiac damage.

The optimal duration of trastuzumab therapy is also controversial and has obvious financial implications. In opting to give trastuzumab for 9 weeks only

as opposed to the empirical standard of 52 weeks, FinHer was particularly provocative in evaluating whether a shorter duration of treatment could be equally efficacious.

The shorter trastuzumab treatment in FinHer produced comparable HRs for DFS (0.42) and OS (0.41), although, the confidence intervals were wide for both (95%CI 0.21–0.83, $P>001$ and 95%CI 0.16–1.08, $P>0.07$, respectively). This may, in part, be explained by the upfront use of trastuzumab within a synergistic chemotherapy combination with vinorelbine or docetaxel, or the efficacious administration of FEC itself. Furthermore, synergism between FEC and trastuzumab may have occurred due to the long half-life of trastuzumab exerting its action several weeks after the last administration [70]. This group of investigators is now launching a 3,000-patient trial directly, comparing the 9 weeks of trastuzumab therapy to 52-weeks.

Not to be considered as standard treatment at present, FinHer, nonetheless, generates interesting hypotheses for the design of other studies as well, including PHARE (Protocol of Herceptin Adjuvant with Reduced Exposure) and Persephone, both comparing 6-months vs. 1-year of trastuzumab treatment. Conversely, the results of the 2-year vs. 1-year treatment in HERA will determine whether longer therapy can improve upon efficacy, at minimal toxicity cost.

Other controversies relate to how best to schedule taxane therapy, and whether anthracyclines could be avoided in trastuzumab-containing regimens.

In an unplanned, premature analysis directly comparing arms B (sequential) and C (concurrent) of NCCTG-N9831 [71], with 1,682 patients, the HR for DFS was 0.64 (95%CI 0.46–0.91; stratified logrank 2P>0.00114) and HR for OS was 0.74 (95%CI 0.43–1.26; stratified logrank 2P>0.2696), favoring concurrent over sequential taxane treatment. However, the incidence of cardiac events was also greater with the concurrent treatment [70], and no final conclusion can be drawn before seeing the mature results of this comparison.

BCIRG 006 was interesting in its suggestion that a nonanthracycline regimen, combined with trastuzumab, may be adequate to treat HER2+ early breast cancer patients. Both the HRs for DFS (0.67; 95%CI 0.54–0.83; $P>0.00003$) and OS (0.66; 95%CI 0.47–0.93; $P>0.017$), for DCbH over AC-D were impressive after 36 months of follow-up. In addition, cardiotoxicity was very low in the DCbH arm.

20.5 Beyond Trastuzumab: Other Anti-HER-2 Targeted Therapies

What are the future directions for the treatment of HER2+ patients? Will trastuzumab become the ultimate wonder-drug, after all is reconciled with the various controversies for both adjuvant and metastatic patients? Are we simply at a point of treatment-refinement?

Trastuzumab has, indeed, produced impressive results, but the reality is that a significant proportion of patients will still eventually fail trastuzumab therapy. Whether this is from recurrence after adjuvant trastuzumab, or from the development of resistance while on metastatic treatment, the clinical dilemma arises in the choice of what best to use next. Indeed, it has been well documented that among metastatic patients who initially respond, many will develop resistance within 1 year of trastuzumab initiation [72, 73].

Many of the molecular mechanisms underlying resistance to trastuzumab are still not well characterized, but there are several hypotheses for this: (1) altered receptor-antibody interaction with masking of HER2 by MUC4 (a membrane-associated glycoprotein mucin-4 [74]; (2) increased signaling from other HER receptors; (3) PTEN (phosphatase and tensin homolog) inactivation or loss resulting in increased Akt activity [75]; (4) reduced p27kip1 [76] and (5) increased IGF-R signaling [77, 78].

Many novel drugs are being developed in parallel with the gradual unraveling of these resistance pathways. These drugs have variable but interesting properties including: (1) dual inhibition against EGFR and HER2, such as lapatinib, pertuzumab and HKI-272; (2) antiangiogenesis such as bevacizumab or pazopanib; (3) anti-mTOR action such as temsirolimus; and (4) anti-Hsp90 action such as 17-AAG.

20.5.1 Trastuzumab Combined with EGFR Inhibitors

Some studies have shown that the combination of trastuzumab with other molecularly targeted therapies may be an interesting strategy to overcome resistance. In the preclinical setting, it has been shown that HER-2 overexpression can activate and potentiate EGFR

signaling and therefore, the combined inhibition of EGFR and HER-2 should result in greater tumor growth inhibition [79]. This dual inhibition has resulted in higher levels of the cyclin-dependent kinase inhibitor $p27^{kip1}$ than the blockade of either receptor alone.

However, the clinical results for dual-inhibition with two-drug combinations have been less impressive. In a phase I-II trial of trastuzumab and gefitinib, a small molecule against EGFR, conducted in 36 patients with HER2+ MBC without prior trastuzumab therapy, efficacy was low with only one complete response (CR), one partial response (PR), and a time to progression (TTP) of 2.9 months, which is shorter than what had been previously observed for trastuzumab monotherapy. The authors hypothesized that this low efficacy was the result of induced phosphorylation of HER3 (ErbB3), and therefore, the switch to an alternative survival pathway [80]. Additional clinical trials using gefitinib for the treatment of breast cancer are still ongoing.

20.5.2 Lapatinib

Lapatinib is a small molecule tyrosine kinase inhibitor, which is capable of dual receptor inhibition of both EGFR and HER2. It is an ATP mimetic that competitively binds to the ATP-binding cleft at the activation loop of target kinases, thereby inhibiting both kinase activities. Lapatinib also has the advantage of being able to bind and inhibit $p95^{HER2}$, which is the truncated form of HER2 lacking an extracellular domain but possessing greater kinase activity than wild-type HER2. Because trastuzumab is unable to neither bind nor inhibit $p95^{HER2}$, its resistance may be mediated at least, in part, through the expression of $p95^{HER2}$ in disease progression [81].

In single-agent phase I/II studies, lapatinib has resulted in objective responses between 4.3 and 7.8% in HER2+ patients who had progressed on multiple trastuzumab-containing regimens [82], with a substantial number having stable disease at 4 months (34–41%) and 6 months (18–21%).

In the combination study EGF10151 [83] using capecitabine with or without lapatinib, in 321 patients with HER2+, locally advanced or MBC refractory to trastuzumab, the benefit in TTP (27 weeks vs. 19 weeks; HR 0.57; 95%CI 0.43–0.77; $P>0.00013$) was impressive. Furthermore, there appeared to be also a benefit in CNS progression (2 vs. 11%; $P>0.0445$). This has been hypothesized to be due to the small molecule of lapatinib to penetrate the intact blood-brain-barrier, rather than the result of a decreased HER2 expression in the cancer cells present in the CNS. This was also recently investigated by Lin et al. who was able to demonstrate modest partial responses (6%) using lapatinib in heavily pretreated and trastuzumab-exposed patients with radiotherapy-resistant brain metastases. These investigators demonstrated that almost one-fifth of the patients were able to achieve 20% or greater reduction in CNS tumor volume. All the above studies were not only pivotal in showing the CNS benefit of using lapatinib, but also in demonstrating that the HER2 receptor remains a viable target even after initial trastuzumab failure [84].

Lapatinib is currently being evaluated in two adjuvant trials, following positive results in the metastatic setting. The ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) trial is a four-arm randomized adjuvant study comparing 1-year therapy of either lapatinib, trastuzumab, its combination, or an interesting sequence of 12 weeks of trastuzumab followed by a 6-week wash-out period and then, 34 weeks of lapatinib. The ALTTO study opened in June 2007 and will accrue 8,000 patients with HER2+ early breast cancer world-wide. The other trial, TEACH (Tykerb® Evaluation After Chemotherapy) evaluates the effectiveness of 12 months of lapatinib vs. placebo, given as either immediate or delayed therapy, in HER2+ early breast cancer, and will complete enrolment of 3,000 patients in early 2008.

20.5.3 HKI-272

HKI-272 is a small molecule kinase inhibitor highly active against HER2+ human breast cancer cell lines in vitro. It also inhibits EGFR and the proliferation of EGFR-dependent cells. HKI-272 reduces HER2 receptor autophosphorylation in cells at doses consistent with inhibition of cell proliferation and functions as an irreversible binding inhibitor, most likely by targeting a cysteine residue in the ATP-binding pocket of the receptor [85].

The phase I trial testing HKI-272 as a single agent in 73 patients with solid tumors overexpressing HER2 or EGFR has reported preliminary data for 51 patients. In 23 evaluable MBC patients, seven confirmed PR

and two unconfirmed PR, with an overall RR of 17%, were reported. The maximal dose tolerated (MTD) was 320 mg/day given once daily, for a dose limiting toxicity (DLT) of grade 3 diarrhea [86]. A phase II trial with HKI-272 with trastuzumab combination is currently being conducted [87].

20.5.4 Pertuzumab

Pertuzumab is a fully recombinant humanized monoclonal antibody (mAb) against HER2. While trastuzumab binds to domain IV of HER-2, which is not involved in receptor dimerization, pertuzumab binds to a domain II, which is a different dimerization epitope on the HER2 receptor, and thereby blocks heterodimerization of HER2 with EGFR and HER3 and hence, intracellular signaling [88, 89]. This ability to prevent the ligand-induced formation of HER2-containing heterodimers makes pertuzumab an attractive therapeutic option for patients who have failed trastuzumab.

In a phase II trial conducted in 79 MBC patients with low HER2 expression, pertuzumab has shown modest activity at either low doses (six patients showed PR and 18 SD) or high doses (14 patients experienced SD) with acceptable toxicity [90].

In another phase II trial testing the efficacy of the pertuzumab-trastuzumab combination in 33 HER2+ MBC patients who had received prior trastuzumab, there was one reported complete response (3%), five confirmed partial responses (15%), and seven reports of stable disease for 6 months (21%), producing a clinical benefit rate of 39%. The treatment was well tolerated, with most adverse events being mild to moderate [91]. A phase III randomized placebo-controlled registration study in MBC is currently planned, and it will test the docetaxel/trastuzumab combination with or without pertuzumab [92].

20.5.5 Bevacizumab

In HER2+ breast cancer, preclinical models have demonstrated that HER2 amplification is associated with an increase in VEGF gene expression [93]. The vascular endothelial growth factor (VEGF) receptor family plays an essential role in angiogenesis, and therefore in cancer metastases dissemination [94]. The principal agent targeting VEGF is bevacizumab, a humanized monoclonal antibody directed against VEGF, which can reduce tumor angiogenesis [95] and the tumor interstitial fluid pressure, leading to a better delivery of large therapeutic molecules into solid tumors.

In a first ever trial testing the combination of multiple monoclonal antibodies in humans, Pegram et al. [96] tested bevacizumab and trastuzumab in 9 HER2+, chemotherapy-naïve MBC patients. Grade 1 and 2 adverse events included diarrhea, fatigue and nausea, with no higher grade events. Preliminary efficacy results showed one complete response, four partial responses and two patients with stable disease.

A phase II extension study [97] indicated an overall RR of 54% in 34 patients, with one complete response for this combination. However, 13 patients experienced grade 1 or 2 cardiac events and therefore, this combination still warrants further cautious evaluation. Currently, a randomized phase III trial of first-line chemotherapy and trastuzumab with or without bevacizumab for HER2 + MBC patients is being planned [98].

20.5.6 Pazopanib

Pazopanib is a multitargeted antiangiogenic tyrosine kinase inhibitor directed against vascular endothelial growth factor receptor (VEGFR1, 2, 3), platelet-derived growth factor receptor (PDGFR- α/β) and c-Kit. A phase I trial combining lapatinib and pazopanib in 33 patients with solid tumors demonstrated an acceptable safety profile, with three patients developing grade 3 diarrhea and one patient grade four fatigue. Preliminary efficacy was also encouraging, with ten patients demonstrating prolonged disease stabilization of >16 weeks (median 21.5 weeks) and three patients achieving tumor shrinkage of <30% [99]. Currently, a randomized, open label multicentre phase II trial is being conducted; looking at first line lapatinib vs. lapatinib and pazopanib in HER2+ MBC patients [100].

20.5.7 17-AAG (Anti-HSP-90)

Hsp90 is a molecular chaperone protein required for the stress-survival response, for protein refolding, and

for the conformational maturation of a variety of client signaling proteins. Some of these client molecules include estrogen and progesterone receptors, and certain transmembrane receptors such as HER2, EGFR, and PDGFR [101].

In in vivo studies, Hsp90 inhibition induces rapid degradation of HER2, loss of pAkt and tumor growth inhibition. A phase I trial of KOS-953 (17-AAG in cremophor; tanespimycin) combined with trastuzumab conducted in 25 patients with advanced solid tumors, with 17 patients with HER2+ MBC showed a clinical benefit of more than 50% (1 PR, 3 MR and 5 SD lasting at least 4 months) in MBC patients [102]. A phase II trial combining trastuzumab and KOS-953 resulted in two confirmed PR, one unconfirmed PR and 2 SD in 13 evaluable HER2+ MBC patients previously treated with chemotherapy and trastuzumab. Grade 1 or 2 toxicities included fatigue (50%), diarrhea (38%), dizziness (31%), headache (25%), and dyspnea (19%). Three cases of grade 3 toxicities were reported (headache/fatigue; elevated LFTs; unsteady gait/euphoria) [103]. Single-agent and first-line window studies are currently being planned.

20.5.8 Trastuzumab DM1

This new drug is a first-in-class HER2 antibody-drug conjugate (ADC), comprising the maytansinoid DM1 (inhibitor of tubulin polymerization) chemically linked to a monoclonal antibody that targets the HER2 protein (trastuzumab).

A phase I study evaluating the safety and pharmacokinetics of T-DM1 given every 3 weeks to 18 patients with HER2+ MBC, who had progressed on trastuzumab-containing regimens, reported a MTD of 3.6 mg/kg (no neuropathy, G1 noncumulative and rapidly reversible thrombocytopenia). Promising antitumor activity (four ongoing partial responses) was also observed [104]. A phase II trial in HER2+ MBC has been initiated [105].

20.6 Conclusions

Trastuzumab has had resounding success in demonstrating efficacy in both metastatic and adjuvant HER2+ breast cancer patients. However, despite the vast number of trials with varying designs, there are still some unanswered questions relating to its optimum use. In the adjuvant setting, questions of when to use trastuzumab, for how long, in what combinations, and for whom, warrant further evaluation. In the metastatic setting, the issue of whether trastuzumab should be discontinued or continued at the point of progression remains unresolved. If, indeed, trastuzumab was to continue, would a change in the companion chemotherapeutic agent be sufficient or must another molecularly targeted agent be added?

With the increasing use of trastuzumab in the adjuvant setting, the speculation is that trastuzumab resistance will be encountered more frequently. Research efforts must continue to find strategies to overcome such resistance, either with rational combinations of different drugs with trastuzumab, or innovative discovery of other anti-HER2 therapies.

Thus, the journey for HER2-targeted therapy remains evolutionary. With the experience with trastuzumab, many hurdles have been encountered, and with that, many important lessons have been learnt. But this journey needs to continue in the search of even better strategies that can optimize clinical benefit and minimize treatment toxicity for the HER2-positive breast cancer subpopulation.

References

1. Slamon DJ, Clark GM, Wong SG et al (1987) Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 235:177–82
2. Slamon DJ, Godolphin W, Jones LA et al (1989) Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science. 244:707–12
3. Yarden Y (2001) The EGFR family and its ligands in human cancer: signaling mechanisms and therapeutic opportunities. Eur J Cancer. 37(Suppl 4):S3–8
4. Schechter AL, Stern DF, Vaidyanathan L et al (1984) The neu oncogene: an erb-B-related gene encoding a 185, 000-M, tumor antigen. Nature. 312:513–6
5. King CR, Kraus MH, Aaronsen SA (1985) Amplification of a novel v-erb-related gene in a human mammary carcinoma. Science. 229:974–6
6. Depowski P, Mulford D, Minot P et al (2002) Comparative analysis of HER-2/neu protein overexpression in breast cancer using paraffin-embedded tissue and cytologic specimens. Mod Pathol. 15:70A
7. Joensuu H, Isola J, Lundin M et al (2003) Amplification of erbB2 and erbB2 expression are superior to estrogen receptor status as risk factors for distant recurrence in pT1N0Mo

breast cancer: a nationwide population-based study. Clin Cancer Res. 9:923–30
8. Press MF, Bernstein PA, Thomas LF et al (1997) HER-2/neu gene amplification characterized by fluorescence in situ hybridization: poor prognosis in node-negative breast carcinomas. J Clin Oncol. 15:2894–904
9. Muss HB, Thor AD, Berry DA et al (1994) c-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. N Engl J Med. 330:1260–6
10. Paik S, Bryant J, Park C et al (1998) erbB-2 and response to doxorubicin in patients with axillary lymph node-positive, hormone receptor-negative breast cancer. J Natl Cancer Inst. 90:1361–70
11. Thor AD, Berry DA, Budman DR et al (1998) erbB-2, p53, and efficacy of adjuvant therapy in lymph node-positive breast cancer. J Natl Cancer Inst. 90:1346–60
12. Mendelsohn J, Baselga J (2003) Status of epidermal growth factor receptor antagonists in the biology and treatment of cancer. J Clin Oncol. 21:2787–99
13. Klapper L, Waterman H, Sela M et al (2000) Tumor-inhibitory antibodies to HER-2/ErbB-2 may act by recruiting c-Cbl and enhancing ubiquitination of HER-2. Cancer Res. 60:3384–88
14. Molina MA, Codony-Servat J, Albanell J et al (2001) Trastuzumab (Herceptin), a humanized anti-HER2 receptor monoclonal antibody, inhibits basal and activated HER2 ectodomain cleavage in breast cancer cells. Cancer Res. 61:4744–9
15. Clynes RA, Towers TL, Presta LG et al (2000) Inhibitory Fc receptors modulate in vivo cytotoxicity against tumor targets. Nat Med. 6:443–6
16. Izumi Y, Xu L, di Tomaso E et al (2002) Tumour biology: herceptin acts as an anti-angiogenesis cocktail. Nature. 416:279–80
17. Cobleigh MA, Vogel CL, Tripathy D et al (1999) Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol. 17(9):2639–48
18. Baselga J, Carbonell X, Castaneda-Soto NJ et al (2005) Phase II study of efficacy, safety, and pharmacokinetics of trastuzumab monotherapy administered on a 3-weekly schedule. J Clin Oncol. 23(10):2162–71
19. Vogel CL, Cobleigh MA, Tripathy D et al (2002) Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol. 20(3):719–26
20. Pegram MD, Konecny GE, O'Callaghan C et al (2004) Rational combinations of trastuzumab with chemotherapeutic drugs used in the treatment of breast cancer. J Natl Cancer Inst. 96(10):739–49
21. Slamon DJ, Leyland-Jones B, Shak S et al (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 344(11):783–92
22. Marty M, Cognetti F, Maraninchi D et al (2005) Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol. 23(19):4265–74
23. Seidman AD, Fornier MN, Esteva FJ et al (2001) Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. J Clin Oncol. 19(10):2587–95
24. Hamberg P, Bontenbal M, Vernhout RM, et al Combined trastuzumab/docetaxel versus sequential trastuzumab followed by docetaxel at progression as first-line chemotherapy for HER2-positive metastatic breast cancer: preliminary results (multicenter BOOG-study; 2002-02). San Antonio Breast Cancer Symposium, San Antonio, 13th–16th Dec 2007; abstr 1077
25. Pegram MD, Finn RS, Arzoo K et al (1997) The effect of HER-2/neu overexpression on chemotherapeutic drug sensitivity in human breast and ovarian cancer cells. Oncogene. 15(5):537–47
26. Robert N, Leyland-Jones B, Asmar L et al (2006) Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. J Clin Oncol. 24(18):2786–92
27. Pegram M, Forbes JF, Pienkowski T, et al BCIRG 007: first overall survival analysis of randomized phase III trial of trastuzumab plus docetaxel with or without carboplatin as first-line therapy in HER2 amplified metastatic breast cancer. J Clin Oncol. 2007;25:34s; abstr
28. Burstein HJ, Harris LN, Marcom PK et al (2003) Trastuzumab and vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer: multicenter phase II trial with clinical outcomes, analysis of serum tumor markers as predictive factors, and cardiac surveillance algorithm. J Clin Oncol. 21(15):2889–95
29. Jahanzeb M, Mor JE, Yunus F et al (2002) Phase II trial of weekly vinorelbine and trastuzumab as first-line therapy in patients with HER2(+) metastatic breast cancer. Oncologist. 7(5):410–7
30. Burstein HJ, Kuter I, Campos SM et al (2001) Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. J Clin Oncol. 19(10):2722–30
31. Chan A, Martin M, Untch M et al (2006) Vinorelbine plus trastuzumab combination as first-line therapy for HER 2-positive metastatic breast cancer patients: an international phase II trial. Br J Cancer. 95(7):788–93
32. Fujimoto-Ouchi K, Sekiguchi F, Tanaka Y (2002) Antitumor activity of combinations of anti-HER-2 antibody trastuzumab and oral fluoropyrimidines capecitabine/5´-dFUrd in human breast cancer models. Cancer Chemother Pharmacol. 49:211–6
33. Schaller G, Fuchs I, Gonsch T et al (2007) Phase II study of capecitabine plus trastuzumab in human epidermal growth factor receptor 2 overexpressing metastatic breast cancer pretreated with anthracyclines or taxanes. J Clin Oncol. 25(22):3246–50
34. Xu L, Song S, Zhu J et al (2004) Results of a phase II trial of Herceptin® plus Xeloda® in patients with previously untreated HER2-positive metastatic breast cancer. Breast Cancer Res Treat. 88(Suppl 1):S128
35. O'Shaughnessy JA, Vukelja S, Marsland T et al (2004) Phase II study of trastuzumab plus gemcitabine in chemo-

therapy-pretreated patients with metastatic breast cancer. Clin Breast Cancer. 5(2):142–7
36. Wardley A, Antón-Torres A, Pivot X, et al Trastuzumab plus docetaxel with or without capecitabine in patients with HER2-positive advanced/metastatic breast cancer: first efficacy results from the phase II MO16419 (CHAT) study. Breast Cancer Res Treat. 2006;100: abstr 2063
37. Perez EA, Suman VJ, Rowland KM et al (2005) Two concurrent phase II trials of paclitaxel/carboplatin/trastuzumab (weekly or every-3-week schedule) as first-line therapy in women with HER2-overexpressing metastatic breast cancer: NCCTG study 983252. Clin Breast Cancer. 6(5):425–32
38. Polyzos A, Mavroudis D, Boukovinas J, et al A multicenter phase II study of docetaxel, gemcitabine and trastuzumab administration as first-line treatment in patients with advanced breast cancer (ABC) overexpressing HER-2. J Clin Oncol 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). 2004;22(Suppl 14S):728
39. Fountzilas G, Christodoulou C, Tsavdaridis D et al (2004) Paclitaxel and gemcitabine, as first-line chemotherapy, combined with trastuzumab in patients with advanced breast cancer: a phase II study conducted by the Hellenic Cooperative Oncology Group (HeCOG). Cancer Invest. 22(5):655–62
40. Venturini M, Bighin C, Monfardini S et al (2006) Multicenter phase II study of trastuzumab in combination with epirubicin and docetaxel as first-line treatment for HER2-overexpressing metastatic breast cancer. Breast Cancer Res Treat. 95(1):45–53
41. Yardley DA, Greco FA, Porter LL, et al First-line treatment with weekly docetaxel, vinorelbine, and trastuzumab in HER2-overexpressing metastatic breast cancer (HER2+ MBC): A Minnie Pearl Cancer Research Network phase II trial. J Clin Oncol 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). 2004;22(Suppl 14S):643
42. Arpino G, Green SJ, Allred DC et al (2004) HER-2 amplification, HER-1 expression, and tamoxifen response in estrogen receptor-positive metastatic breast cancer: a Southwest Oncology Group Study. Clin Cancer Res. 10(17):5670–6
43. Fornier MN, Seidman AD, Panageas KS et al (2002) Correlation of ER/PR [immunohistochemistry (IHC)] status to HER2 status by IHC and gene amplification (GA) [fluorescent in-situ hybridization (FISH)], and response rate (RR) for weekly (W) trastuzumab (H) and paclitaxel (T) in metastatic breast cancer (MBC) patients (pts). Proc Am Soc Clin Oncol. 21:56a
44. Pinto AE, Andre S, Pereira T et al (2001) C-erbB-2 oncoprotein overexpression identifies a subgroup of estrogen receptor positive (ER+) breast cancer patients with poor prognosis. Ann Oncol. 12:525–33
45. Lipton A, Ali SM, Leitzel K et al (2002) Elevated serum Her-2/neu level predicts decreased response to hormone therapy in metastatic breast cancer. J Clin Oncol. 20:1467–72
46. Benz CC, Scott GK, Sarup JC et al (1993) Estrogen-dependent, tamoxifen-resistant tumorigenic growth of MCF-7 cells transfected with HER2/neu. Breast Cancer Res Treat. 24:85–95
47. Mackey JR, Kaufman B, Clemens M, et al Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer. Breast Cancer Res Treat. 2006;100:abstr 3
48. Ellis MJ, Coop A, Singh B et al (2001) Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1– and/or ErbB-2–positive, estrogen receptor–positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol. 19:3808–16
49. Marcom PK, Isaacs C, Harris L et al (2007) The combination of letrozole and trastuzumab as first- or second-line biological therapy produces durable responses in a subset of HER2-positive and ER-positive advanced breast cancers. Breast Cancer Res Treat. 102(1):43–9
50. Tripathy D, Slamon DJ, Cobleigh M (2004) Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. J Clin Oncol. 22(6):1063–70
51. Fountzilas G, Razis E, Tsavdaridis D et al (2003) Continuation of trastuzumab beyond disease progression is feasible and safe in patients with metastatic breast cancer: a retrospective analysis of 80 cases by the Hellenic Cooperative Oncology Group. Clin Breast Cancer. 4(2):120–5
52. Gelmon KA, Mackey J, Verma S. Use of trastuzumab beyond disease progression: observations from a retrospective review of case histories. Clin Breast Cancer. 2004;5:52–8; discussion 59–62
53. Von Minckwitz G, Vogel P, Schmidt M, et al Trastuzumab treatment beyond progression in patients with HER2-positive metastatic breast cancer – the TBP study (GBG 26/BIG 3-05). San Antonio Breast Cancer Symposium, San Antonio, 13th–16th Dec 2007; abstr 4056
54. Pusztai L, Esteva FJ (2006) Continued use of trastuzumab (herceptin) after progression on prior trastuzumab therapy in HER2-positive metastatic breast cancer. Cancer Invest. 24(2):187–91
55. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al (2005) Trastuzumab after adjuvant chemotherapy HER2-positive breast cancer. N Engl J Med. 353:1659–72
56. Smith I, Procter M, Gelber RD et al (2007) 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomized controlled trial. Lancet. 369:29–36
57. Romond EH, Perez EA, Bryant J et al (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 353:1673–84
58. Perez EA, Romond H, Suman VJ, et al Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer. J Clin Oncol, 2007 ASCO Annual Meeting Proceedings. 2007;25(18s):LBA512
59. Slamon D, Eiermann W, Robert N, et al Phase III randomized trial comparing doxorubicin and cyclophosphamide, followed by docetaxel (AC T) with doxorubicin and cyclophosphamide, followed by docetaxel and trastuzumab (AC TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2-positive early breast cancer patients: BCIRG 006 study. Breast Cancer Res Treat. 2005;94 (Suppl 1):S5; abstr 1
60. Slamon D, Eiermann W, Robert N, et al BCIRG 006: 2nd interim analysis phase III randomized trial Phase III comparing doxorubicin and cyclophosphamide, followed by docetaxel (AC-T) with doxorubicin and cyclophosphamide, followed by docetaxel and trastuzumab (AC- TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2-positive early breast cancer patients: Breast Cancer Res Treat. 2006;100, General Session 2; abstr S2

61. Joensuu H, Kellokumpu-Lehtinen PL, Bono P et al (2006) Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 354:809–20
62. Spielmann M, Roche H, Humblet Y, et al 3-year follow-up of trastuzumab following adjuvant chemotherapy in node-positive HER2-positive breast cancer patients: results of the PACS-04 trial. San Antonio Breast Cancer Symposium, San Antonio, 13th–16th Dec; abstr 72
63. Tan-Chiu E, Yothers G, Romond E et al (2005) Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol. 23(31):7811–9
64. Suter TM, Procter M, van Veldhuisen DJ et al (2007) Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. J Clin Oncol. 25:1–8
65. Balsega J, Norton L, Albanell J et al (1998) Recombinant humanized anti-HER2 antibody (Herceptin) enhances the antitumor activity of paclitaxel and doxorubicin against HER2/neu overexpressing human breast cancer xenografts. Cancer Res. 58:2825–31
66. Pegram M, Hsu S, Lewis G et al (1999) Inhibitory effects of combinations of HER-2/neu antibody and chemotherapeutic agents used for treatment of human breast cancers. Oncogene. 18:2241–51
67. Rastogi P, Jeong J, Geyer CE, et al Five-year update of cardiac dysfunction on NSABP B-31, a randomized trial of sequential doxorubicin/cyclophosphamide (AC)->paclitaxel (T) vs AC->T with trastuzumab (H). J Clin Oncol, 2007 ASCO Annual Meeting Proceedings. 2007;25(18s): LBA512
68. Pietras RJ, Joseph CP, Gallardo D et al (1999) Monoclonal antibody to HER-2/neu receptor modulates repair of radiation-induced DNA damage and enhances radiosensitivity of human breast cancer cells overexpressing this oncogene. Cancer Res. 59:1347–55
69. Halyard MY, Pisansky TM, Solin LJ, et al Adjuvant radiotherapy and trastuzumab in stage I-IIA breast cancer: toxicity data from North Central Cancer Treatment Group Phase III trial N9831. J Clin Oncol, 2006 ASCO Annual Meeting Proceedings. 2006;24(18s):LBA523
70. Leyland-Jones B, Gelmon K, Ayoub JP et al (2003) Pharmacokinetics, safety, and efficacy of trastuzumab administered every three weeks in combination with paclitaxel. J Clin Oncol. 21:3965–71
71. Perez EA, Suman VJ, Davidson N, et al NCCTG-N9831. May 2005 Update. Slide presentation at the 41st American Society of Clinical Oncology Annual Meeting, Orlando, Florida, May 13-17, 2005. Available at http://www.asco.org/ac/1,10003,_12-002511-00_18-0034-00_19-005815-00_21-001,00.asp
72. Esteva FJ, Valero V, Booser D et al (2002) Phase II study of weekly docetaxel and trastuzumab for patients with HER2-overexpressing metastatic breast cancer. J Clin Oncol. 20(7):1800–8
73. Albanell J, Baselga J (2001) Unraveling resistance to trastuzumab (Herceptin): insulin-like growth factor-I receptor, a new suspect. J Natl. Cancer Inst. 93:1830–2
74. Nagy P, Friedlander E, Tanner M et al (2005) Decreased accessibility and lack of activation or ErbB2 in JIMT-1, a herceptin-resistant, MUC4-expressing breast cancer cell line. Cancer Res. 65:473–82
75. Nagata Y, Lan KH, Zhou X et al (2004) PTEN activation contributes to tumor inhibition by trastuzumab and loss of PTEN predicts trastuzumab resistance in patients. Cancer Cell. 6:117–27
76. Nahta R, Takahashi T, Ueno NT et al (2004) p27(kip1) downregulation is associated with trastuzumab resistance in breast cancer cells. Cancer Res. 64(11):3981–6
77. Lu YH, Zi XL, Zhao DJ et al (2001) Insulin-like growth factor-I receptor signaling and resistance to trastuzumab (Herceptin). J Nat Cancer Inst. 93:1852–7
78. Nahta R, Yuan LX, Zhang B et al (2005) Insulin-like growth factor-I receptor/human epidermal growth factor receptor 2 heterodimerization contributes to trastuzumab resistance of breast cancer cells. Cancer Res. 65(23):11118–28
79. Normanno N, De LA CM et al (2002) Cooperative inhibitory effect of ZD1839 (Iressa) in combination with trastuzumab (Herceptin) on human breast cancer cell growth. Ann Oncol. 13(1):65–72
80. Arteaga, CL, O'Neil A, Moulder SL, et al ECOG1100: a phase I-II study of combined blockade of the erbB receptor network with trastuzumab and gefitinib "Iressa" in patients with Her2-overexpressing metastatic breast cancer. Breast Cancer Res Treat. 2004;88:abstr 25
81. Xia W, Liu LH, Ho P et al (2004) Truncated ErbB2 receptor (p95ErbB2) is regulated by heregulin through heterodimer formation with ErbB3 yet remains sensitive to the dual EGFR/ErbB2 kinase inhibitor GW572016. Oncogene. 23:646–53
82. Howard A, Burris HA III (2004) Dual kinase inhibition in the treatment of breast cancer: initial experience with the EGFR/ErbB-2 inhibitor Lapatinib. Oncologist. 9(Suppl 3):10–5
83. Geyer CE, Forster JM, Lindquist D et al (2006) Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 355:2733–43
84. Lin NU, Dieras V, Paul D, et al EGF105084, a phase II study of lapatinib for brain metastases in patients with HER2+ breast cancer following trastuzumab-based systemic therapy and cranial radiotherapy. J Clin Oncol 2007 ASCO Annual Meeting Proceedings Part I. 2007;25(Suppl 18S):1012
85. Rabindran SK, Discafani CM, Rosfjord EC et al (2004) Antitumor activity of HKI-272, an orally active, irreversible inhibitor of the HER-2 tyrosine kinase. Cancer Res. 64:3958
86. Wong KK, Fracasso PM, Bukowski RM, et al HKI-272: an irreversible pan-erbB receptor tyrosine kinase inhibitor: preliminary phase 1 results in patients with solid tumors. J Clin Oncol. 2006;24(Suppl 18):abstr 3018
87. NCT00398567. A Phase 1/2 Study of HKI-272 In Combination With Herceptin In Subjects With Advanced Breast Cancer, available at www.clinicaltrials.gov
88. Franklin MC, Carey KD, Vajdos FF et al (2004) Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. Cancer Cell. 5:317–28
89. Jackson JG, St Clair P, Sliwkowski MX et al (2004) Blockade of epidermal growth factor- or heregulin-dependent ErbB2 activation with the anti-ErbB2 monoclonal antibody 2C4 has divergent downstream signaling and growth effects. Cancer Res. 64:2601–9

90. Cortes J, Baselga J, Kellokumpu-Lehtinen J, et al Open label, randomized, phase II study of pertuzumab in patients with metastatic breast cancer with low expression of HER2. J Clin Oncol 2005 ASCO Annual Meeting Proceedings. 2005;23(16S), Part I of II (Suppl):3068
91. Baselga J, Cameron D, Miles D, et al Objective response rate in a phase II multicenter trial of pertuzumab (P), a HER2 dimerization inhibiting monoclonal antibody, in combination with trastuzumab (T) in patients (pts) with HER2-positive metastatic breast cancer (MBC), which has progressed during treatment with T. Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. 2007;25(Suppl 18S):1004
92. Available at www.gene.com/gene/pipeline/status/index.jsp
93. Petit AM, Rak J, Hung MC et al (1997) Neutralizing antibodies against epidermal growth factor and ErbB-2/neu receptor tyrosine kinases down-regulate vascular endothelial growth factor production by tumor cells in vitro and in vivo: angiogenic implications for signal transduction therapy of solid tumors. Am J Pathol. 151:1523–30
94. Folkman J (1995) Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med. 1:27–31
95. Kim KJ, Li B, Winer J et al (1993) Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. Nature. 362:841–4
96. Pegram M, Yeon C, Ku NC. Phase 1 combined biological therapy of breast cancer using two humanized monoclonal antibodies directed against HER2 prot-oncogene and vascular endothelial growth factor. Breast Cancer Res Treat. 2004;88(Suppl):S124; abstr 3039
97. Pegram M, Chan D, Dichmann RA, et al Phase II combined biological therapy targeting the HER2 proto-oncogene and the vascular endothelial growth factor using trastuzumab and bevacizumab as first-line treatment of HER2-amplified breast cancer. Breast Cancer Res Treat. 2006;100(Suppl 1):S28; abstr 301
98. Study NCT00520975: First-line chemotherapy and trastuzumab with or without bevacizumab in treating patients with metastatic breast cancer that overexpresses HER-2/Neu. Available at www.clinicaltrials.gov
99. Dejonge M, Savage S, Verweij J, et al A phase I, open-label study of the safety and pharmacokinetics of pazopanib and lapatinib administered concurrently. J Clin Oncol 2006 ASCO Annual Meeting Proceedings Part I. 2006;24(Suppl 18S):3088
100. Study NCT00347919: A Phase II, Open-Label, Randomized, Multicenter Trial of GW786034 (Pazopanib) in Combination With Lapatinib (GW572016) Compared to Lapatinib Alone as First-line Therapy in Subjects With Advanced or Metastatic Breast Cancer With ErbB2 Fluorescence In Situ Hybridization (FISH) Positive Tumors. Available at www.clinicaltrials.gov
101. Grem JL, Morrison G, Guo XD et al (2005) Phase I and pharmacologic study of 17-(allylamino)-17-demethoxygeldanamycin in adult patients with solid tumors. J Clin Oncol. 23:1885–93
102. Modi S, Stopeck A, Gordon MS, et al Phase I trial of KOS-953, a heat shock protein 90 inhibitor, and trastuzumab. J Clin Oncol 2006 ASCO Annual Meeting Proceedings Part I. 2006;24(Suppl 18S):501
103. Modi S, Stopeck A, Kinden H, et al Tanespimycin (an Hsp90 inhibitor) and trastuzumab is an active combination in patients with HER2-positive trastuzumab-refractory metastatic breast cancer: phase 2 trial. San Antonio Breast Cancer Symposium, San Antonio; 13th–16th Dec 2007: abstr 6066
104. Modi S, Beeram M, Krop IE, et al A phase I study of trastuzumab-DM1 (T-DM1), a first-in-class HER2-antibody drug conjugate (ADC), in patients (pts) with HER2+ metastatic breast cancer (BC). ASCO 2007 Breast Cancer Symposium; abstr 168
105. NCT00509769. A phase II, single-arm, open-label study of trastuzumab-MCC-DM1 administered intravenously to patients with HER2-positive metastatic breast cancer who have progressed while receiving HER2-directed therapy, available at www.clinicaltrials.gov

Inflammatory and Locally Advanced Breast Cancer

21

Ana Maria Gonzalez-Angulo and Gabriel N. Hortobagyi

The term locally advanced breast cancer (LABC) includes a variety of breast tumors with different prognoses, ranging from neglected slow growing tumors to the aggressive inflammatory breast cancer (IBC). These tumors continue to be challenging because of their high rate of relapse and subsequent death. However, with the multidisciplinary approach that includes preoperative systemic therapy, surgery, and radiotherapy, the prognosis for these patients has improved. In general, patients with tumors larger than 5.0 cm in diameter, patient with tumors that involve the skin or the chest wall, or patients with fixed axillary, or any supraclavicular, infraclavicular, or internal mammary lymph node metastasis are considered to have LABC. A distinct subtype of LABC, IBC, is a rapidly progressive disease characterized by the presence of edema and erythema of the skin.

This chapter reviews the epidemiology, staging, diagnosis, prognostic factors, molecular markers, and treatment approaches for these malignancies. IBC, although included in the definition of LABC, will have separate annotations due to its distinct clinical presentation and aggressive behavior.

21.1 Epidemiology

Since the establishment of screening programs with mammography, the rate of patients diagnosed with LABC has significantly declined. Among women who participate in regular mammographic screening programs, less than 5% have stage III disease [1]. However, national and worldwide rates remain higher, perhaps because many women from underserved populations in the United States and other countries do not have access to screening programs; in consequence, 50–80% of newly found malignant breast neoplasms in countries with limited resources represent LABC [1–3]. The age distribution at diagnosis of patients with stage III breast cancer in the United States is similar to the age distribution at other stages: 1% of patients are 29 years or younger, 9% are 30–39 years, 22% are 40–40 years, 20% are 50–59 years, 19 are 60–69 years, 18% are 70–79 years and 12% are 80 years or older according to the American College of Surgeons National Cancer Data Base statistics [4]. The same source indicates that patients with stage III breast cancer have a 5-year relative survival rate of 54% and a 10-year relative survival rate of 36% [4]. However, LABC includes different tumors with important variations in outcome that not only depend on the tumor-node-metastases (TNM) stage but on the biology of the tumor itself.

IBC is a rare, distinct epidemiologic form of LABC. A recent analysis by Hance et al. of the Surveillance, Epidemiology, and End Results (SEER) database [5] looked at 180, 224 histologically confirmed invasive breast cancer patients diagnosed between the years 1988 and 2000. IBC comprised approximately 2% of all breast cancer cases in the database. The mean age at diagnosis of IBC was 58.8 years, and these patients were younger than patients with non-IBC LABC, who tended to present at a mean age of 66.2 years ($P<0.001$). Interestingly, among women with IBC, the median age at diagnosis was younger for African American women than for white women. During this time period, the analysis also showed the incidence rate of IBC

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_21, © Springer-Verlag Berlin Heidelberg 2010

increasing by approximately 25% for white women (2.0–2.5 cases per 100,000 women-years) and 19% for black women (2.6–3.1 cases per 100,000 women-years) [6]. Differences in IBC incidence rates have also been observed within different states in the U.S., and also across different countries, accounting for approximately 10% of cases in Pakistan [7] and 20% in Tunisia [8]. Due to the rarity of IBC, epidemiological studies that have addressed the etiology of IBC are sparse and mostly retrospective. Factors such as age of menarche, menopausal status, smoking, and alcohol consumption have not been consistently associated with IBC [6, 9]. In a small retrospective study by Chang et al. [9], high body mass index (BMI >26.65 kg/m^2) was associated with an increased risk for IBC when compared to non-IBC patients (odds ratio > 2.40, 95% CI 1.05–5.73). Clinical and epidemiological studies that have investigated the clinical outcome of patients with IBC have consistently demonstrated a worse outcome when compared to both LABC and non T4 breast cancer. In the SEER study by Hance et al. [5], IBC accounted for 7% of all breast cancer-specific deaths and had a median survival of 2.9 years compared to 6.4 years for patients with LABC. Anderson et al. [10] showed that the 5-year actuarial survivals for all breast cancer patients who had either estrogen receptor (ER)-positive or ER-negative tumors were 91% (95% CI, 90.8–91.2%) and 77% (95% CI, 76.6–77.5%), respectively, when compared to IBC patients whose corresponding survivals were 48.5% (95% CI, 45.2–52.1%) and 25.3% (95% CI, 22.1–28.5%) for ER-positive and ER-negative tumors, respectively.

21.2 Diagnosis and Staging

Like any breast cancer, LABC can be detected by mammography, but most of the cases are easily palpable and even visible since some of them represent neglected tumors present for a long time before diagnosis. However, some LABC can present without a dominant mass, requiring diagnostic mammographic and sonographic assessment and, on occasions, magnetic resonance imaging (MRI). Core needle biopsy is the preferred method for histologic diagnosis. Incisional biopsies are seldom required. Diagnosis can also be established by fine needle aspirate (FNA). Although this modality cannot differentiate invasive from noninvasive tumors, it provides information about tumor grade, estrogen, progesterone and HER2/*neu* receptor status, as well as other markers, such as p53 and Ki67. FNA may also be used to confirm the presence of lymph node metastasis when guided by ultrasound. Once the diagnosis of invasive cancer is made, the patient should undergo a full staging evaluation to determine the extent of the disease. A complete physical examination is complemented with baseline biochemical profile and tumor markers. Bilateral mammograms are essential to rule out clinically occult lesions in the same or the contralateral breast. Ultrasonography is useful to measure tumor size but is even more important to assess whether axillary, supraclavicular or infraclavicular lymph nodes are involved. MRI is used mainly to define the extent of local disease in patients for whom neither mammography nor sonography provide clear bidimensional measurements. Once the extent of local involvement is established, patients should have evaluation for systemic disease. Chest radiograph, radionuclide bone scan, and computed tomography (CT) of the abdomen are usually obtained to rule out distant metastases. Other tests, such as CT scan of the chest, pelvis or brain, and body MRI are performed if physical examination or symptoms indicate the need for these examinations. Increasingly, positron emission tomography (PET) is being employed for initial staging and to determine the potential malignant nature of solitary masses in other organs.

The diagnosis of IBC is clinical. Unlike other forms of invasive breast cancer that usually present with a painless mass, IBC has a variety of clinical presentations, making the diagnosis somewhat difficult. In 1956, Haagensen [11] recognized this problem and established a set of clinical diagnostic criteria that are still in use. Clinical characteristics of IBC include a painful, tender, rapidly enlarging breast, and edema and erythema of the skin of the breast. More often than not, a breast mass is not palpable. Other changes associated with IBC include “peau d’orange” (skin of an orange) appearance of the overlying skin of the breast [12] that represents the exaggerated appearance of hair follicle pits that occurs secondary to skin edema. Flattening, crusting, and retraction of the nipple can also occurs as the disease progresses [13] Unfortunately, most of the clinical characteristics associated with IBC are nonspecific, resulting in a significant number of cases being initially diagnosed as mastitis or breast abscesses. This results in delays in appropriate investigation, and

together with the rapid rate of disease progression that is pathognomonic of IBC, a significant proportion of patients present with advanced disease. Multiple reports have shown the high frequency of ipsilateral axillary and supraclavicular lymph node involvement, with up to one third of patients also presenting with distant metastases at the time of diagnosis [5, 13–15]. Figure 21.1 shows different clinical presentations of IBC. The pathological characteristic of IBC is the presence of dermal lymphatic invasion, and although this frequently correlates with the clinical findings, it is not always the case and therefore it is not considered pathognomonic of IBC or required to confirm the clinical diagnosis. The TNM system from the American Joint Committee on Cancer (AJCC) designates IBC as a T4d tumor that is staged as either IIIB IIIC or IV, depending on the staging work-up [16]. The Institute Gustave-Roussy uses the *Poussee Evolutive* (PEV) breast cancer classification based on the rate of development and extent of involvement of the breast [17]. Four categories are recognized within this system: PEV 0, defined as a tumor with no recent increase in size or presence of inflammatory signs; PEV 1, defined as a tumor with an increase in size over the last 2 months with no inflammatory signs; PEV 2, defined as a tumor with inflammatory signs of edema, erythema and warmth, involving less than half of the breast skin surface; and PEV 3, defined as a tumor with inflammatory signs involving more than half of the breast skin surface. Under this system, PEV 2 and 3 would be consistent with the diagnosis of IBC.

As with LABC, histologic diagnosis can be made by core biopsy or FNA, although some recommend a full-thickness skin biopsy. Baseline assessment is the same recommended for any LABC; unfortunately, IBC grows to advanced stages without necessarily forming a palpable mass, and this pattern of growth, which infiltrates in sheaths, as opposed to forming masses explains why many IBCs are difficult to image with conventional mammography. However, new imaging techniques are being studied for the diagnosis and follow-up of this disease. In an 80-patient study at the M. D. Anderson Cancer Center, MRI was the most accurate imaging technique in detecting a primary breast parenchymal lesion in IBC patients. Sonography was useful in diagnosing regional nodal disease. PET/CT provided additional information on distant metastasis [18]. Figure 21.2 shows a case of IBC imaged by MRI and PET scan.

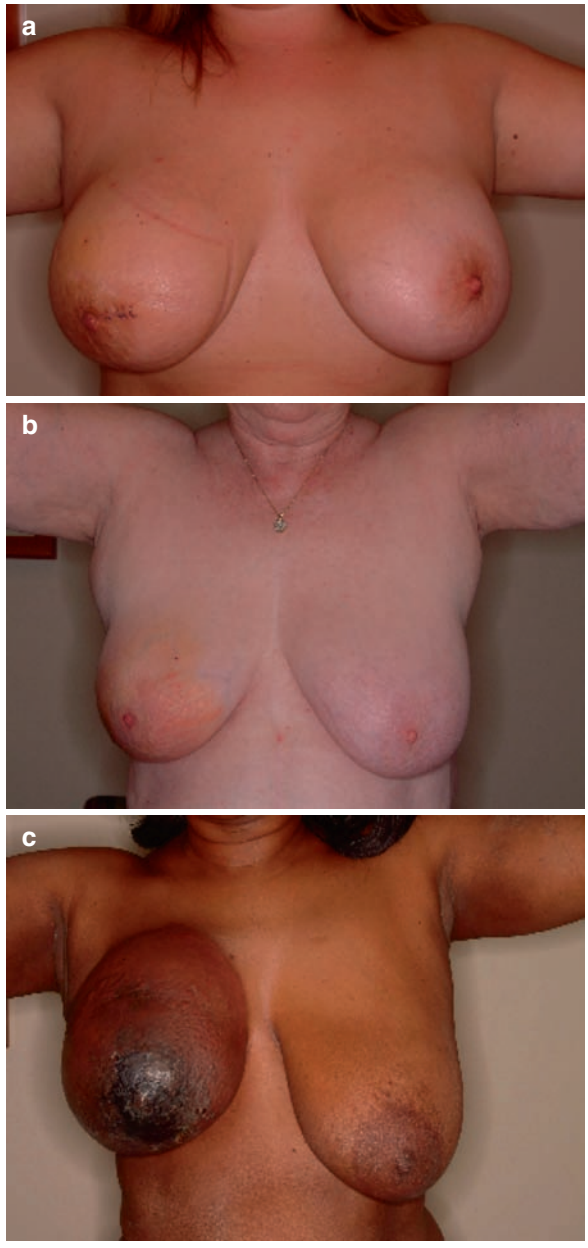

Fig. 21.1 Different presentations of inflammatory breast cancer: mild erythema and edema (**a**), skin discoloration (**b**), classic "*peau d'orange*" (skin of an *orange*), flattening, crusting and retraction of the nipple can also occur as the disease progresses (**c**)

21.3 Management

LABC and IBC should be treated by a multidisciplinary team, where all interested specialists (radiologists, pathologists, medical oncologists, surgeons and radiation oncologists) examine the patient, review the

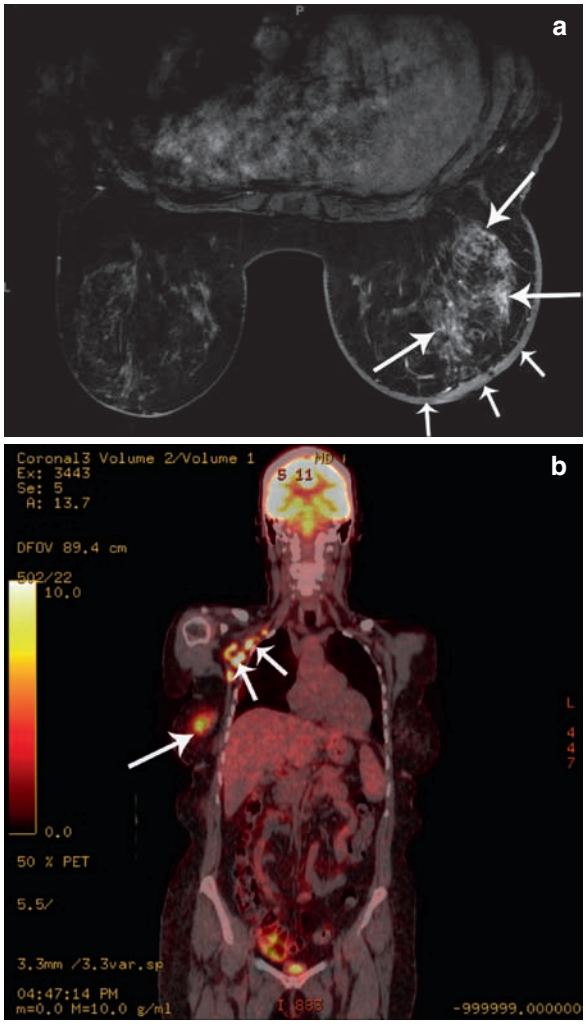

Fig. 21.2 Contrast enhanced T1-weighted fat-saturated axial image shows asymmetric non mass-like enhancement in the right breast (*long arrows*), with marked global skin thickening (*short arrows*) (**a**). Coronal PET/CT in a different plane shows hypermetabolic *right* breast mass (*long arrows*), and *right* subpectoral adenopathy (*short arrows*) (**b**)

diagnostic tests and together determine the best type and sequence of treatments before they are implemented.

21.4 Systemic Therapy

Neoadjuvant Chemotherapy: Several randomized trials evaluated the addition of chemotherapy to local therapies to determine the role of systemic therapy in the survival of patients with LABC [19–23]. Grohn et al. [20] published a randomized trial in which 120 patients with operable stage III breast cancer were randomized to receive postoperative radiation therapy (RT) alone, postoperative chemotherapy alone, or radiotherapy and chemotherapy. The 3-year recurrence rates were 68, 57 and 13%, for patients who received chemotherapy alone, RT alone, and both treatments, respectively, ($P<0.001$). The investigators also found an overall survival (OS) benefit for patients who received both chemotherapy and RT, ($P<0.01$). Thus, for patients with operable LABC, combined chemotherapy and RT offered the greatest benefit. Other randomized trials that have evaluated the role of adjuvant chemotherapy in patients with stage III breast cancer have shown only a trend toward improved survival. A study evaluated 231 patients with stage III disease who received local-regional therapy (either mastectomy plus radiation or radiation alone) and then were randomized to receive chemotherapy or observation. Chemotherapy prolonged the disease-free interval to 55 months, compared with only 23 months in patients who did not receive systemic treatment, but the difference was not statistically significant [21]. The European Organization for Research and Treatment of Cancer (EORTC) completed a trial of 363 patients who were randomized to RT alone, RT plus hormonal therapy, RT plus chemotherapy, or RT plus hormonal therapy plus chemotherapy. The time to progression was longer in the group treated with RT plus chemotherapy plus hormonal therapy. The study also showed a trend for improved survival with any systemic therapy, but this difference was not statistically significant [22, 23]. In retrospect, all these studies were largely underpowered due to their modest sample size (Table 21.1).

Primary systemic therapy (neoadjuvant chemotherapy or hormonal therapy) is advantageous since it has the potential of in-vivo assessment of tumor response and of reducing the extent of the primary tumor and regional lymphatic disease to make breast conservation an option. The first clinical trials with neoadjuvant chemotherapy were reported in the 1970s [24, 25]; since then, multiple reports of using systemic therapy in this setting have documented its benefit. In a study of 110 patients with inoperable breast cancer who were treated with an induction chemotherapeutic regimen consisting of doxorubicin and vincristine, investigators found that 89% of patients had a response: 16% had a complete response and 55% had a partial response. All patients were treated with RT after completing chemotherapy. From the patients who had responded to

Table 21.1 Response and survival for stage III breast carcinoma after combined modality treatment

Authors	Year	Regimen	No. of patients	Pathological complete response (%)	Clinical complete response (%)	Medial survival (month)	3-year OS (month)	5-year OS (%)
De Lena et al. [24]	1978	CT+RT±S	110	NA	NA	36	50	NA
Bedwinek et al. [148]	1892	CT+RT+CT	22	NA	5	28	40	NA
Pawlicki et al. [42]	1983	CT CT+RT+CT CT+S+RT+CT	40 34 13	NA	1	NA NA NA	13 32 62	NA NA NA
Valagussa et al. [38]	1983	CT+RT CT+RT+CT CT+S+CT	72 126 79	NA	NA	30 42 58	43 60 64	20 36 49
Balawajder et al. [43]	1983	CT+RT CT+RT+S	23 30	NA NA	NA NA	NA NA	NA NA	46 38
Hery et al. [91]	1986	CT+RT+CT	25	NA	14	NA	67	56
Conte et al. [149]	1987	CT+S+CT	39	8	15	NA	60	NA
Swain et al. [28]	1987	CT±S+RT+CT	76	30	49	56	NA	NA
Hobar et al. [150]	1988	CT+S±RT+CT	36	11	8	NA	NA	46
Jacquillat et al. [41]	1988	CT+RT+CT	98	NA	30	NA	77	NA
Hortobagyi et al. [145]	1988	CT±S+RT	174	8	17	66	65	55
Piccart et al. [147]	1988	RT/CT+S+CT	59	10	5	42	NA	NA
Perloff et al. [146]	1988	CT±S±RT+CT	113	NA	22	39	NA	NA
Touboul et al. [93]	1992	CT+RT+CT±S+CT	82	NA	10	NA	85	81
von Minckwitz [45]	2005	CT+S+RT	913	11	43	NA	NA	NA

CT chemotherapy; *NA* not available; *RT* radiation therapy; *S* surgery

chemotherapy, 87% achieved a complete response with a 3-year OS of 53%, compared with 41% for historical controls. The results of the above study led to further trials using neoadjuvant therapy, for patients with inoperable disease [26–29]. In a 1983 report from the University of Texas M.D. Anderson Cancer Center of a series of 52 patients with LABC, treatment with three cycles of neoadjuvant anthracycline-containing chemotherapy, followed by local therapy, and then adjuvant chemotherapy for 2 years rendered 94% of patients free of disease. At a median follow-up of 60 months, 40% of patients remained free of disease [29]. Figure 21.3 illustrates a LABC before and after neoadjuvant chemotherapy. The National Cancer Institute (NCI) studied 76 patients with LABC treated with induction chemotherapy until maximum clinical response. Patients with complete response were then treated with irradiation and other patients underwent surgery and irradiation. All patients received adjuvant chemotherapy for at least 6 months. The objective response rate was 93%: 49% had complete response, 44% had partial response, and 7% had stable disease. The median

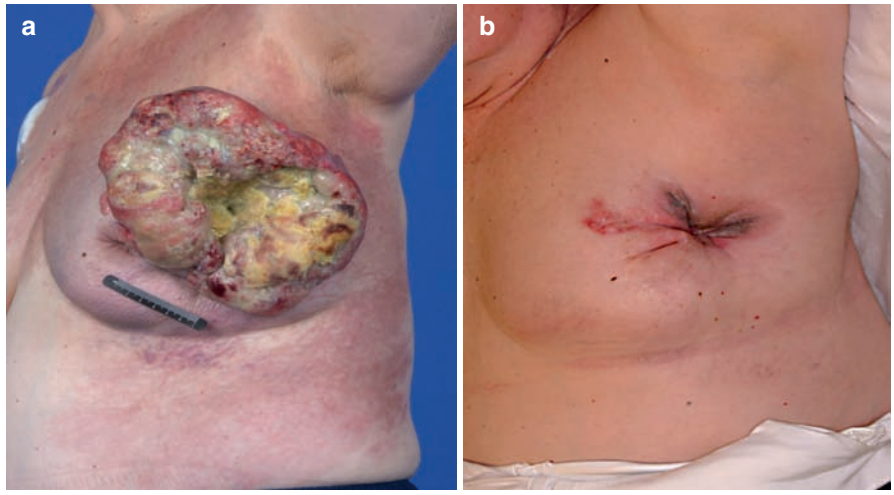

Fig. 21.3 Locally advanced breast cancer that presented with an exofitic mass (**a**), and follow-up after 4 cycles of 5-FU, doxorubicin and cyclophosphamide (**b**)

survival for all patients was 39 months [28]. Although, there was a high rate of complete remission in this study, it might have been an artifact of the evaluation method, since this high remission rate has not correlated with longer survival and has not been confirmed by other studies.

Neoadjuvant chemotherapy has been compared with adjuvant chemotherapy in multiple randomized trials that included patients with LABC [30–35]. In a randomized trial of 272 patients with operable breast tumors greater than 3 cm in diameter by Mauriac et al., patients received either mastectomy followed by adjuvant chemotherapy or neoadjuvant chemotherapy followed by local-regional treatment. Patients who received neoadjuvant chemotherapy had longer OS, at a median follow-up of 34 months ($P>0.04$). However, there was a higher percentage of patients in the neoadjuvant arm who received chemotherapy, and the improved survival may reflect the benefit of chemotherapy in general rather than neoadjuvant chemotherapy in particular. Nevertheless, this trial showed that the outcome of patients who had neoadjuvant chemotherapy was not worse than the outcome for patients who received adjuvant chemotherapy [30, 36]. The Institut Curie published a randomized trial of 414 premenopausal patients with stage T2-3, N0-1, M0 disease who were treated with either 4 cycles of neoadjuvant chemotherapy followed by local-regional treatment or primary irradiation with or without surgery followed by adjuvant chemotherapy. The 5-year OS was 86% for the neoadjuvant group and 78% for the adjuvant group ($P>0.04$). However, as in the previous trial, the neoadjuvant group could have received more aggressive chemotherapy [31]. In 1994, Semiglazov et al., reported their randomized trial of 271 women with stage IIB-IIIA breast cancer who received preoperative chemotherapy plus RT or preoperative RT alone. After initial treatment, all patients underwent mastectomy and adjuvant chemotherapy. The disease-free survival rates at 5 years were 81% in the primary chemotherapy arm and 72% in the arm that received adjuvant chemotherapy only ($P>0.04$). The group that received neoadjuvant chemotherapy showed a trend toward improved survival (86 vs. 78%) [32]. Powles et al. from the Royal Marsden Hospital completed a randomized trial of 212 women with stage T0-4, N0-1, M0 operable breast cancer were divided into two treatment groups. One group received four cycles of primary chemoendocrine therapy followed by surgery and four cycles of adjuvant chemotherapy; the second group received surgery and eight cycles of adjuvant chemoendocrine therapy. There were no differences in local relapse, disease-free survival, or OS rates. However, the rate of breast-conserving therapy was higher for the patients who received primary chemoendocrine therapy [33]. The largest trial of neoadjuvant chemotherapy reported to date is National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18, which involved 1,523 patients with T1-3, N1-0, M0 operable breast cancer [34, 35]. In this randomized trial, patients received four cycles of doxorubicin plus cyclophosphamide, given either preoperatively or as postoperative adjuvant therapy. Overall, a clinical complete response was seen in 35% of patients, but only 17% of patients who had locally advanced disease with a primary tumor greater than 5 cm in diameter had a clinical complete response. Rates of response to

primary chemotherapy were 75% for all patients with LABC compared with 81% for patients with tumors measuring 2–5 cm in diameter, and 79% for patients with tumors less than 2 cm. In this trial, comparison of the adjuvant and neoadjuvant groups revealed no differences in the 5-year rates of disease-free survival (66.3 vs. 66.7%), or OS (80.0 vs. 79.6%). No survival differences were seen in the subgroup of patients with T3 tumors. However, in a recent update of the trial results presented at the National Cancer Institute State of the Sciences Meeting, there was significantly higher recurrence-free survival rate for patients treated with neoadjuvant chemotherapy, although this benefit appeared to be restricted to the premenopausal group. Similar findings were reported by the EORTC in another large randomized trial of 698 patients with stage T1c-4b, N0-1, M0 operable breast cancer [36]. Patients received four cycles of neoadjuvant chemotherapy with fluorouracil, epirubicin, and cyclophosphamide (FEC) either before or after surgery. At a median follow-up of 56 months, there were no significant differences between the two arms in OS rates, progression-free survival rates, or time to locoregional recurrence. Of the 101 patients in the neoadjuvant chemotherapy arm who initially had stage T3 or T4, tumors, 41% had tumors downstaged to pT2, 17% to pT1, and 5% to pathologic complete response (pCR), demonstrating that neoadjuvant chemotherapy can result in significant downstaging of primary tumors in patients with LABC. Although these larger studies have been conducted in patients with early stage disease, they have included some patients with locally advanced malignancy and have demonstrated that neoadjuvant and adjuvant chemotherapy produce equivalent outcomes. The findings of trials that included exclusively patients with LABC are similar, but the smaller numbers of patients limited their statistical power [28, 38–43]. Some of these studies have suggested that neoadjuvant therapy offers a survival benefit for patients with more advanced cancers [30, 31]. Nonetheless, the studies that showed improved survival among patients receiving neoadjuvant chemotherapy were confounded by the fact that these groups received more aggressive treatment and their results must be interpreted with caution. The benefit of taxane addition to neoadjuvant chemotherapy for LABC was suggested in a trial that studied 167 patients treated with four cycles of induction cyclophosphamide, vincristine, doxorubicin, and prednisolone (CVAP) chemotherapy. Responders received either four additional cycles of CVAP or four cycles of docetaxel; nonresponders were all treated with four cycles of docetaxel. Patients who received docetaxel showed significantly higher clinical and pathologic response rates and significantly better 3-year survival rates (97 vs. 84%; $P>0.02$) [44]. These results suggested that the addition of a taxane may provide a survival benefit for patients with LABC. The role concurrent vs. sequential taxanes and dose-dense chemotherapy was evaluated in the "Geparduo" study by the German Gynecologic Oncology Group (AGO) [45]. This phase III study investigated 913 women with untreated operable breast cancer (T2-3, N0-2, M0) randomly assigned to receive either doxorubicin plus docetaxel (concurrent) every 14 days for four cycles with filgrastim support, or doxorubicin plus cyclophosphamide every 21 days followed by docetaxel every 21 days for four cycles each (sequential). The primary end point was the incidence of pathologic complete (invasive and noninvasive) response (pCR) in the breast and axillary nodes. A pCR was achieved in 94 patients (10.6%), but the likelihood was significantly greater with sequential docetaxel (14.3%; $n>63$) than with concurrent (7.0%; $n>31$) (odds ratio, 2.22; 90% CI, 1.52–3.24; $P<0.001$). They concluded that sequential docetaxel was more effective at inducing pCR than dose-dense concurrent docetaxel in combination with doxorubicin as preoperative treatment for patients with operable breast cancer. Another study from the AGO tested the role of noncross-resistant chemotherapy after no clinical response to two cycles of docetaxel, doxorubicin and cyclophosphamide (TAC) [46]. Patients with histologically confirmed invasive, unilateral or bilateral breast cancer were included in the "Gepartrio" study. LABC were eligible and randomized to a different stratum. Six-hundred and twenty nonresponding patients were randomized to continue TAC or to receive a combination of vinorelbine and capecitabine for four cycles. The pCR rates were similar and quite low in both arms of the study (5.3 vs. 5.9%, $P>0.7$). This study, as well as the Aberdeen neoadjuvant trial, [44] show the low probabilities of pCR in clinical nonresponders to initial chemotherapy. The AGO recently presented the part of the results of a trial of 1,510 patients, including 453 patients with HER2-positive disease [47]. Patients with either large operable (T3) and locally advanced (T4), or negative estrogen (ER) and progesterone (PR)-receptor status, or ER/PR positive tumors but clinically node-positive disease, were recruited in 115 German centers to receive 4 cycles of epirubicin and cyclophosphamide

(EC) and to be then randomized to either 4 cycles of docetaxel or 4 cycles of docetaxel and capecitabine, or 4 cycles of docetaxel followed by 4 cycles of capecitabine (sequential administration). Patients with HER2-positive tumors received concomitant trastuzumab. The pCR rates were 22.1, 19.3, and 21.7% for the three groups, respectively, but there appeared to be a favorable effect in T4 tumors that needs to be further investigated.

Neoadjuvant Endocrine Therapy: The role of neoadjuvant hormonal therapy for patients with LABC has been assessed in several small studies. Veronesi et al. [48] treated 46 postmenopausal women with LABC with no inflammatory signs with tamoxifen. At 6 weeks, 17% of patients had an objective response; with further therapy, 30% of all patients achieved responses. Although these response rates are somewhat lower than those typically reported for chemotherapy, this study demonstrated that hormonal therapy is a safe and effective alternative in postmenopausal women for whom chemotherapy may not be an option. In a British randomized trial, [49] 80 patients with LABC received either neoadjuvant chemotherapy or endocrine therapy with a luteinizing hormone-releasing hormone (LHRH) analog, goserelin, for premenopausal women and 4-hydroxyandrostenedione for postmenopausal women. In the chemotherapy arm, 27% of patients had a complete response and 27% had a partial response. In contrast, no patients in the endocrine therapy arm had a complete response and only 10% had a partial response, indicating that induction hormonal therapy is less effective than chemotherapy. However, for patients who cannot tolerate or decline chemotherapy, hormonal treatment is a viable alternative. The M.D. Anderson Cancer Center experience with neoadjuvant tamoxifen includes a single-arm trial of 47 patients with LABC who either were older than 75 years or who had severe comorbid conditions that precluded the use of chemotherapy. After 6 months of therapy, 47% of patients had achieved an objective response and 6% of patients had a complete response. At a median follow-up of 40 months, 49% of all patients remained disease-free [50].

The use of neoadjuvant aromatase inhibitors was studied by Ellis et al. [51] who reported a randomized trial of tamoxifen vs. letrozole in postmenopausal patients with hormone receptor-positive tumors that were not candidates for breast-conserving therapy. Overall, 60% of patients treated with letrozole responded, and 48% underwent successful breast-conserving therapy, compared with 41 and 36%, respectively, with tamoxifen. These studies established the benefit of neoadjuvant hormonal therapy in a subset of patients not treated with chemotherapy. However, for patients who can tolerate chemotherapy, this remains the recommended treatment.

Neoadjuvant Trastuzumab: Several prospective studies of LABC have addressed the role of trastuzumab in combination with primary systemic chemotherapy. The first study reported, used a combination docetaxel and cisplatin every 3 weeks with weekly trastuzumab for four cycles in 48 patients (including some IBC cases). The pCR rate was 17% in breast and axilla and the regimen was well tolerated [52]. A second single-arm study used a combination of docetaxel and trastuzumab in 22 patients. They reported a clinical complete response rate of 40%, including nine patients with IBC [53]. The NOAH (NeOAdjuvant Herceptin) trial [54] is the largest international phase III randomized trial of neoadjuvant trastuzumab in combination with chemotherapy in patients with HER2-positive LABC. All patients received neoadjuvant chemotherapy with three cycles of doxorubicin-paclitaxel, 4 cycles of paclitaxel and 3 cycles of cyclophosphamide/methotrexate/5-fluorouracil. Patients with HER2-positive tumors ($n>288$) were randomized to receive concomitant trastuzumab or chemotherapy alone. Primary end point was event-free survival; secondary end points included objective response rate, in-breast pCR. Addition of trastuzumab significantly improved the pCR rate (43 vs. 23%, $P>0.002$). The authors concluded that neoadjuvant trastuzumab in combination with chemotherapy is feasible and highly active in patients with HER2-positive LABC, in addition to that, cardiac safety data for patients receiving trastuzumab were similar to data for patients not receiving trastuzumab.

Inflammatory Breast Cancer: IBC is a challenging clinical entity characterized by rapid progression and early dissemination. Before the introduction of combination chemotherapy in the treatment paradigm, IBC was a uniformly fatal disease with fewer than 5% of patients, treated with either surgery and/or radiotherapy, surviving past 5 years, with an expected median survival of less than 15 months [55]. Its management in the last 40 years has evolved, [13] with current treatment guidelines emphasizing the use of a multi-disciplinary approach [56] using neoadjuvant systemic therapy followed by locoregional treatment, including surgery and RT.

Historically, the use of surgery [14], RT [57] or a combination of the two [58] improved locoregional control rates but had minimal effect on survival, and most patients died of distant disease. One of the earliest studies that showed the benefit of neoadjuvant chemotherapy in the treatment of IBC was a retrospective analysis of 179 patients with stage III IBC, in which patients who received chemotherapy followed by surgery and RT had a superior 5-year disease-free survival of 40% compared to 24% for patients who received surgery and RT, and with 6% for patients who received radiation alone [59]. Several other studies have confirmed the survival advantage conferred by the addition of neoadjuvant chemotherapy to locoregional therapy, as well as the higher survival outcomes for patients who achieve a clinical complete response or a pCR [60, 61].

The use of anthracycline-based chemotherapy is known to improve both disease-free survival and OS in breast cancer patients [62]. The M. D. Anderson group compared four anthracycline-containing regimens in combination with locoregional therapy in a total of 242 patients with IBC [60, 63–65]. All four regimens had equal efficacy, with an overall response rate of 72% and a pCR rate of 12% after neoadjuvant chemotherapy. Patients who achieved either a complete or a partial response had a 15-year OS rate of 51 and 31%, respectively, compared to 7% for those who achieved minimal response. The addition of taxanes to anthracycline neoadjuvant chemotherapy in the treatment of IBC has also shown benefit. A study from M. D. Anderson compared FAC (fluorouracil/doxorubicin/cyclophosphamide) alone with FAC followed by paclitaxel, in patients with IBC, and showed higher pCR rates (25 vs. 10%) and higher median OS and progression-free survival in the group receiving the additional taxane, although the survival differences were limited to the patients with ER-negative tumors [66].

A high incidence of HER2 over expression has been observed in patients with IBC, suggesting the appropriate setting for the use of trastuzumab. Several prospective studies mentioned above that included patients with IBC, have addressed the issue of trastuzumab in combination with neoadjuvant chemotherapy. The first trial, from the University of Miami, used a combination docetaxel and cisplatin every 3 weeks with weekly trastuzumab for four cycles in 33 patients with LABC and IBC, achieving pCR rate of 22% [52]. A second study, from Baylor College of Medicine in Houston, combined docetaxel with trastuzumab in 22 patients, nine of which had IBC: 40% of all patients had a complete clinical response [53]. The NOAH trial focused on LABC, and included patients with IBC; 62 of them had HER2-positive disease and were randomized to either chemotherapy, or chemotherapy plus concomitant trastuzumab. pCR rates were 48% in the group that received additional trastuzumab and 13% in the group that received chemotherapy alone. These results, in combination with the recent survival advantage seen with the addition of adjuvant trastuzumab [67, 68] in early stage breast cancer patients, indicate an important role for trastuzumab in the treatment of patients with HER2 over expressed/amplified IBC. Furthermore, lapatinib, a potent dual (ErbB1 and ErB2) reversible, tyrosine kinase inhibitor, is also being currently studied in patients with HER2-overexpressed IBC. A phase II trial to confirm the sensitivity of IBC to lapatinib and to determine whether response is HER2 or EGFR dependent was completed by Johnston et al. [69] in 45 patients with recurrent or anthracycline-refractory IBC. There was a 50% response rate to lapatinib in patients that had HER2-positive tumors; time to progression was not reported. The authors concluded that lapatinib was well tolerated with clinical activity in heavily pretreated HER2-positive, but not EGFR-positive/HER2-negative IBC. In this study, coexpression of pHER2 and pHER3 in tumors seems to predict for a favorable response to lapatinib. Later on, a phase II trial of 42 patients with newly diagnosed HER2-positive IBC was reported by Cristofanilli et al. [70]. Patients went to receive lapatinib monotherapy (days 1–14) followed by an additional 12 weeks in combination with weekly paclitaxel. The primary objective was pCR in breast and lymph nodes at the time of definitive surgical resection upon completing 14 weeks of therapy. Of the evaluable patients, 95% had a clinical response and 17% had a pCR.

Other agents that are currently being studied for the treatment of IBC include antiangiogenic agents and Ras pathway inhibitors. IBC tumors are known to be highly vascular tumors that express a number of angiogenic factors such as vascular endothelial growth factor (VEGF) [71]. This has prompted a number of studies looking at the role of anti-VEGF agents such as bevacizumab [72] and sunitinib [73], in combination with chemotherapy, in the treatment of IBC, with promising results. A neoadjuvant trial studied 21 patients with IBC and LABC who were treated with bevacizumab for cycle 1, followed by six cycles of

bevacizumab with doxorubicin and docetaxel every 3 weeks. After locoregional therapy, patients received eight cycles of bevacizumab alone, and hormonal therapy when indicated. Tumor biopsies and dynamic contrast-enhanced MRI (DCE-MRI) were obtained at baseline, and after cycles 1, 4, and 7. A median decrease of 66.7% in phosphorylated VEGFR2 in tumor cells ($P>0.004$) and median increase of 128.9% in tumor apoptosis ($P>0.0008$) were seen after bevacizumab alone. These changes persisted with the addition of chemotherapy. There were no significant changes in microvessel density or VEGF-A expression. On DCE-MRI, parameters reflecting reduced angiogenesis, a median decrease of 34.4% in the inflow transfer rate constant ($P>0.003$), 15.0% in the backflow extravascular- extracellular rate constant ($P>0.0007$) and 14.3% in extravascular-extracellular volume fraction ($P>0.002$) were seen after bevacizumab alone. The authors concluded that bevacizumab had inhibitory effects on VEGF receptor activation and vascular permeability, and induced apoptosis in tumor cells. Based on preclinical and phase I studies, farnesyl transferase inhibitors that block the farnesylation of prenylated proteins (including the Rho subfamily of GTPases highly expressed in IBC) are currently being studied in combination with chemotherapy [74, 75]. No clinical results are available from these studies.

The role of high-dose chemotherapy with autologous bone marrow transplant has been explored in patients with IBC, but no definitive data have demonstrated improved survival. Arun et al. described a series of 24 patients with IBC who underwent high-dose chemotherapy with autologous stem cell transplantation in addition to standard multidisciplinary treatment. The 2-year OS rate was 73% [76]. Investigators from Washington University reported the 4-year OS rate of 47 patients treated with high-dose chemotherapy and stem cell transplantation to be at 52% [77]. Another trial of bone marrow transplantation for IBC from Germany involved 56 patients who had a 3-year survival rate of 72% [78]. The largest report of this intervention included 120 patients who received conventional dose chemotherapy, surgery, and were treated sequentially with single- or tandem-cycle dose-intense chemotherapy regimens. At a median follow-up of 61 months (range, 21–161 months), the estimated 5-year relapse-free survival (RFS) and OS rates were 44% (95% CI, 34–53%) and 64% (95% CI, 55–73%), respectively [79]. Although the survival data from these trials seems encouraging, the patient populations were highly selected, and further research is clearly needed before high-dose chemotherapy with stem cell transplantation is recommended outside the context of a clinical trial.

21.5 Local Therapy

Historically, patients with locally advanced disease have been treated with radical mastectomy if technically possible. In 1943, Haagensen and Stout, two surgeons at Memorial Hospital in New York, published the results of surgical treatment in patients with breast cancer. They reviewed 1,040 women, 61.5% of them treated with radical mastectomy; of these, 36% were free of disease at 5 years. Reviewing the cases of the patients whose disease recurred, the authors identified eight factors that were associated with recurrence: distant metastases, inflammatory carcinoma, supraclavicular lymph node involvement, edema of the arm, satellite breast skin nodules, intercostal or parasternal nodules, extensive edema of skin over the breast, and carcinoma that developed during pregnancy or lactation. They concluded that any of these signs of advanced disease made a tumor "categorically inoperable." The authors also defined five "grave signs": skin ulceration, edema of limited extent, fixation of tumor to the chest wall, axillary lymph nodes greater than 2.5 cm in diameter, and fixed axillary lymph nodes. Any patient who had two or more "grave signs" was also considered to have inoperable disease since only one of such patients was without disease recurrence at 5 years. Finally, the authors recommended that surgery not be performed in patients with locally advanced disease who had the worst prognoses [80]. After this publication, fewer patients with LABC were treated with mastectomy, although surgical treatment did not produce high survival rates even in those patients considered to have operable disease under the referenced criteria.

Failure of mastectomy alone to produce good survival rates prompted the use of primary RT for locally advanced tumors, especially those that were considered inoperable. In 1965, Baclesse [81] reported a series of 431 patients that received primary RT. The 5-year survival was 41% for the 95 patients who were classified as having Columbia Clinical Classification stage C disease, and 13% for the 200 patients who

had stage D. In a retrospective series of 454 patients with T3, or T4, nonmetastatic breast cancer who underwent primary RT and 133 of whom also underwent mastectomy, the median survival was 2.5 years, and relapse occurred in 45% of patients within 18 months. The authors concluded that RT alone was inadequate for patients with LABC [82]. For patients who are treated with primary RT, a high dose of radiation is necessary to optimize local control. This was initially described in a retrospective review of 137 patients, by Harris et al. [83], who found that treatment with a total radiation dose greater than 6,000 rads was associated with improved local control and improved freedom from distant metastatic relapse. Likewise, Sheldon et al. [84] found that among 192 patients with LABC treated with RT alone, the patients that received total doses greater than 6,000 cGy had improved rates of local control (83 vs. 70%, $P > 0.06$). However, such higher doses were associated with long-term complications, including chest wall fibrosis, brachial plexopathy, lymphedema, skin ulceration, and rib necrosis [85–87].

Recent evidence has shown the importance of local control with adequate surgery and RT for LABC. A series of 542 patients treated at M. D. Anderson Cancer Center with neoadjuvant chemotherapy, mastectomy, and radiation were compared to 134 patients who received similar treatment but without radiation. Irradiated patients had a lower rate of local-regional recurrence (10-year rates: 11 vs. 22%, $P > 0.0001$), and radiation reduced local-regional recurrence for patients with clinical T3 or T4 tumors, pathological tumor size greater than 2 cm, or four or more positive nodes ($P < 0.002$ for all comparisons). Radiation improved cause-specific survival in patients with stage equal or greater than IIIB, clinical T4 tumors, and four or more positive nodes ($P < 0.007$ for all comparisons). On multivariate analyzes of cause-specific survival, the hazard ratio (HR) for lack of radiation was 2.0 (95% CI, 1.4–2.9; $P < 0.0001$). The authors concluded that after neoadjuvant chemotherapy and mastectomy, comprehensive radiation was found to benefit both local control and survival for patients presenting with clinical T3 tumors or stage III disease and for patients with four or more positive nodes [88].

One of the benefits of neoadjuvant chemotherapy for patients with LABC is that it can result in downstaging sufficient enough to allow for breast conservation in patients who otherwise would not be candidates for limited surgery. In a review of 143 patients with stage IIB to IIIC, who had complete or partial response to induction chemotherapy and underwent mastectomy and axillary lymph node dissection at the M. D. Anderson Cancer Center, the authors applied strict criteria to determine which of these patients might have been candidates for breast conservation. Thirty-three patients (32%) had complete resolution of skin edema, residual tumor diameter less than 5 cm, and absence of known multicentric disease or extensive lymphatic invasion and would have been eligible for breast-conservation surgery [89]. At the time of surgery, 42% of these patients had a pCR of the primary tumor and 45% were node negative; no eligible patients had multicentric disease, and none developed recurrence in the chest wall after mastectomy. At a median follow-up of 34 months, three patients had developed metastatic disease, suggesting that breast-conserving surgery is a reasonable option for carefully selected patients with LABC. More recently, Kuerer et al. [90] reviewed the M. D. Anderson experience of breast-conserving therapy following neoadjuvant chemotherapy in 109 patients with stage II or III breast cancer. Fifty-five percent of patients had a clinical complete response and half of them had a pCR. Chemotherapy decreased the median tumor diameter from 4–1 cm, and due to the high response rate, the authors recommended that metallic tumor markers be placed in patients if the primary tumor shrinks to 2 cm or less in diameter. Calais et al. [91] treated patients with neoadjuvant chemotherapy followed by mastectomy for tumors at least 3 cm in diameter or lumpectomy for tumors smaller than 3 cm. They reported that 49% of patients could be treated with breast-conserving therapy and that rates of local failure did not differ for the patients treated with mastectomy vs. breast conservation. In 1978, De Lena et al. [24] demonstrated that LABC could be managed effectively with neoadjuvant chemotherapy, RT, and then adjuvant chemotherapy. With this approach, most patients had breast preservation, with a local recurrence rate of 24%. Other investigators have similarly reported that regimens of induction chemotherapy followed by irradiation permit breast preservation and have associated rates of local relapse rates of 19–24% [40, 92]. Some authors have recommended that breast conservation via either lumpectomy or irradiation be used only in those patients who respond to induction chemotherapy, reserving mastectomy for patients who do not adequately respond to chemotherapy [27, 93].

Table 21.2 M. D. Anderson cancer center selection criteria and contraindications for breast-conserving surgery after primary systemic therapy

Selection criteria
Patient desires breast-conserving therapy
Adequate response to neoadjuvant systemic therapy
Ability to completely excise residual disease with acceptable cosmesis
Availability of RT
Contraindications
Skin edema
Residual tumors≥5 cm
Skin or chest wall fixation
Extensive lymphovascular invasion
Extensive suspicious microcalcifications
Multicentricity
Medical contraindications to radiation

Table 21.2 summarizes the M. D. Anderson Selection Criteria and Contraindications for Breast conservation in patients with LABC. Other investigators have confirmed that with careful patient selection, breast conservation after induction chemotherapy is as effective as mastectomy in 34–81% of patients with locally advanced disease [94, 95]. In NSABP B-18, patients who were treated with four cycles of neoadjuvant regimen of doxorubicin and cyclophosphamide (AC) had a higher rate of breast conservation than did women treated with adjuvant AC (67 vs. 60%; $P>0.002$). However, of the 69 women who were initially recommended for mastectomy but whose tumors were downstaged and treated with lumpectomy after AC therapy, 14.5% had recurrence in the ipsilateral breast, compared with only 6.9% of those women who were initially candidates for lumpectomy ($P>0.04$) [33]. Findings of the EORTC Trial 10902 were similar; 23% of the patients in the neoadjuvant chemotherapy arm, who were initially candidates only for mastectomy, were able to be treated with lumpectomy instead [36].

The radiation dose and treatment fields used to treat breast cancer do not change with the use of neoadjuvant systemic therapy. However, neoadjuvant systemic therapy may affect the treatment of the regional lymph nodes. The main determinant of whether the axillary apex and the supraclavicular fossa need therapy is the number of positive lymph nodes. Primary systemic therapy may affect this by downstaging the axillary lymph nodes, and there are limited data to ascertain whether the threshold of axillary involvement should be different for this group of patients than for patients who have surgery up-front. The American Society of Therapeutic Radiation Oncology recommends adjuvant RT for postmastectomy patients who had locally advanced disease or four or more positive axillary lymph nodes [96]. Because neoadjuvant systemic therapy changes the extent of residual disease, there are no well-defined selection criteria for radiotherapy use after mastectomy [97]. Buchholz et al. [98] investigated local recurrent rates in patients treated with neoadjuvant chemotherapy followed by mastectomy without adjuvant radiation. They found that the risk of local recurrence was a function of both the extent of pathological residual disease and the initial clinical stage [98, 99]. For this reason, in our institution, the current recommendation is postmastectomy irradiation for all patients with clinical LABC (any T3, or any N2-3 disease) [100].

IBC is inoperable by definition. The standard management of this entity is multidisciplinary, including neoadjuvant chemotherapy, mastectomy, local-regional radiotherapy, and hormonal therapy for hormone receptor-positive disease. Because IBC tends to be diffusely distributed throughout the breast tissue, breast-conserving therapy seems inadequate. In a small report of 26 patients with IBC, who were treated with neoadjuvant chemotherapy, RT, surgery and adjuvant chemotherapy, the authors noted local recurrences in two of ten patients treated with mastectomy and in 7 of 13 patients treated with breast conservation [101]. Although the number of patients was small, this evidence suggests that breast conservation may not be adequate regional therapy.

Even with optimal local therapy, the rates of local-regional relapse from IBC remain high. In a report of 95 patients from Washington University, the local-regional failure rates were 73% for patients treated with radiation alone, 27% for those treated with radiation and surgery, 65% for patients treated with chemotherapy plus radiation, and 16% for those treated with chemotherapy, surgery and radiation [102]. Even with combined modality, most reports show that 14–34% of patients will experience a local recurrence [64, 102–107]. Some studies have suggested an improvement in local control by using twice-daily fractionated RT [104, 108, 109]. Chu et al. reported that such therapy reduced the rates of local relapse from 69 to 33% [108]. A second report by Barker et al. showed a reduction from 46 to 27% [104]. Additional ways of reducing the rates of local-regional failure in IBC using newer techniques of RT are under investigation.

21.6 Prognostic Factors of Locally Advanced Breast cancer

Prognostic factors for LABC are, in general, similar to those for breast cancer at other stages. For patients with locally advanced disease, axillary lymph node involvement is probably the most important prognostic factor and is usually present. However, a subset of patients has primary tumors larger than 5 cm in diameter but no evidence of lymph node metastases (T3-4, N0). One group reported that the 5-year survival rate for patients in this subset to be 82%, compared with 46% for patients with lymph node involvement [105]. Similarly, other investigators have reported 5-year survival rates of 72–75% for patients with T3, N0 disease [106, 107]. For patients with nodal involvement, survival rates depend, in part, on the number of involved nodes and nodal stage. One study reported a 5-year survival of 73% for patients with metastases in one to three lymph nodes, compared with 46% for patients with metastases in four or more nodes [105], although most of these patients did not receive chemotherapy. In a series of 277 patients with LABC treated with combined modality therapy, Valagussa et al. showed a decline in survival rates with increasing nodal stage. The 5-year OS was 49% for patients with N0 disease, 40% for patients with N1 disease, and 17% for patients with N2 disease ($P > 0.0008$) [38]. The size of the primary tumor also has prognostic significance for patients with breast cancer, including tumors larger than 5 cm in diameter. A report from the San Antonio Data Base indicated that patients with tumors measuring 5–6 cm in diameter had a 5-year disease-free survival rate of 72%, compared with 57% for patients with tumors larger than 6 cm [109]. Valagussa et al. similarly reported 5-year OS rates of 65% for patients with malignant breast tumors less than 5 cm in diameter, 36% for patients with tumors 5–10 cm, and 16% for patients with tumors greater than 10 cm. In addition, the size of the primary tumor predicted for axillary lymph node involvement, with larger tumors having higher rates of axillary metastasis [38].

The prognostic significance of hormone receptor status in patients with LABC is unclear. In an evaluation of 124 patients with stage III breast cancer in which ER assays were performed, Stewart et al. found that, in patients with operable tumors, ER positivity was associated with a significantly longer disease-free survival and a higher OS rate. However, in patients with inoperable tumors, ER status had no effect on prognosis. These findings may have been an artifact because of the small sample size [110]. The significance of other prognostic factors such as histologic subtype, nuclear grade, and measures of proliferation for locally advanced disease is most likely similar to that for earlier stage breast cancers. Several studies have evaluated the role of thymidine labeling index in LABC with conflicting results. One study found that a high labeling index was associated with higher rates of response to chemotherapy [111], whereas another found that a high labeling index predicted shorter survival [112]. No other markers have been studied specifically to assess prognosis in locally advanced disease.

21.7 Molecular Biology of IBC

The designation of "inflammatory" in IBC derives from the breast skin changes that resemble an acute inflammatory process. However, a true state of inflammation is not present in IBC. These skin changes are due to invasion of the dermal lymphatic vessels by tumor emboli rather than infiltration of inflammatory cells [13, 113], and it is believed that these invasive tumor emboli create the reservoir for cancer cells that then further disseminate through the body to form distant metastases [114]. When compared to noninflammatory LABC, IBC tumors tend to be of high grade, have a negative hormone receptor status [115, 116] and over express HER2 [117]; all factors that predict for a poorer outcome [5]. Other biological features of IBC include mutation at the p53 suppressor gene, overexpression of E-cadherin and increased expression of pro-angiogenic factors.

The function of the p53 gene product is to inhibit tumor growth through cell-cycle arrest or induction of apoptosis. Mutation or absence of the p53 gene is associated with tumor progression, and decreased response to chemotherapy occurs in at least 50% of sporadic breast cancers [118]; in addition, a high level of p53 protein in the nucleus is associated with poor clinical outcome [119]. In an analysis of 24 patients with IBC, Riou et al. [120] showed that patients with tumors that exhibited a combination of a p53 gene mutation and nuclear expression of the p53 protein had an 8.6-fold higher risk of death when compared to the patients

with tumors with wild type p53. An analysis of 48 patients with IBC at the M. D. Anderson Cancer Center [121] confirmed these results, showing a lower estimated 5-year progression-free survival and OS for patients with nuclear p53 positive (35 and 55%, respectively) compared to p53 negative tumors (44 and 54%, respectively).

E-cadherin, a calcium-regulated, transmembrane glycoprotein expressed in normal breast epithelium, is essential to maintain cell-cell adhesion contact and is considered to be a tumor suppressor. Loss of E-cadherin contributes to increased proliferation, and promotes invasion and metastases [122]. Both animal and human IBC tumor models have shown an increased expression of E-cadherin compared to non IBC breast tumors. Tomlinson et al. [123] observed that in the MARY-X xenograft model, E-cadherin was over expressed 10- to 20-fold, and was required for IBC tumor emboli formation in the dermal lymphatics of nude and SCID mice. In addition, the same IBC xenograft model has also been shown to express the sialyl-lewis x/a-deficient MUCI, a glycoprotein that acts as ligand for the cell adhesion receptor E-selectin and that promotes lymphovascular invasion [124]. Kleer et al. [122] confirmed these pre clinical findings in patient samples by comparing 20 IBC samples to 22 stage-matched, non-IBC tumor samples. Thus, it appears that the over expression of E-cadherin and expression of sialyl-lewis x/a-deficient MUCI is unique to IBC and appears to contribute to the integrity of the tumor emboli as they invade dermal lymphatics.

IBC tumors are known to be highly vascular with associated features of angiolymphatic invasion consisting of increased microvessel density, high endothelial cell proliferation and expression of angiogenic factors (basic fibroblast growth factor [bFGF], VEGF, interleukin 6 and interleukin 8) [125–127]. The WIBC-9 animal xenograft IBC model overexpresses other angiogenic factors such as Ang -1, Tie-1 and Tie-2, when compared to a noninflammatory breast cancer xenograft (SK-BR3) [128]. Lymphangiogenic factors, including VEGF-C, VEGF-D, VEGFR-3, Prox-1 and lymphatic vessel endothelial receptor 1 have also been shown to be strongly expressed in IBC [129].

The role of p27kip1, a cyclin-dependent kinase inhibitor that is thought to be involved in induction of apoptosis, cell adhesion, promotion of cell differentiation and regulation of drug resistance [130–132], was studied in IBC by M. D Anderson investigators who evaluated the role of p27kip1 in 38 IBC patients that had received primary systemic chemotherapy [133]. In this study, p27kip1 was down regulated in the majority of patients (84.2%) and predicted for poor outcome.

Despite the multitude of studies that have looked at the role of various molecular markers described above, in IBC, a more thorough understanding of the biology of IBC is required. The markers described above are not specific for IBC and their prognostic and predictive roles have been studied in small groups of patients. Therefore, they cannot be considered validated and further studies will be important to distinguish LABC from IBC at the molecular level.

A preclinical study directed to identify genetic determinants of IBC was completed by van Golen et al. [134]. The authors found 17 transcripts to be differentially expressed between the IBC cell line SUM149 and human mammary epithelial cells (HME), nine of which were expressed solely in the tumor cell line. Using *in situ* hybridization technique, expression patterns of all seventeen transcripts were further confirmed in 20 archival IBC and 30 non IBC LABC tissue samples. Two genes were found that were uniquely altered in the IBC specimens compared to the non-IBC samples: Rho C GTPase was found over expressed in more than 90% of IBC tumors compared to 38% of non-IBC specimens. WNT-1-induced secreted protein 3 (Wisp 3) was found lost in more than 80% of IBC specimens vs. only 21% of non-IBC tumors. The role of both genes in IBC has since been extensively studied [134]. Rho C GTPase, a member of the Ras superfamily of small GTP-binding proteins [135] is thought to contribute to the metastatic characteristic of IBC by promoting cell motility and invasion, disruption of cell-cell junctions and up regulation of angiogenic factors (VEGF, bFGF) [136, 137]. WISP3, a gene coding for insulin-like growth factor-binding related protein (IGFBP-rP9) has been shown to be a tumor suppressor gene [138], regulating tumor cell growth, invasion, and angiogenesis. Loss of Wisp 3 protein expression is thought to contribute to the aggressive phenotypic feature of IBC. In vitro evidence also shows that Wisp 3 shares an inverse relationship with Rho C GTPase expression [139].

High-throughput methods using cDNA microarrays have been used to study the phenotypic features of IBC. Van Laere et al. [140], performed genome-wide expression profiling of 16 IBC and 18 nonstage-matched non-IBC pretreatment samples. Using unsupervised

hierarchical clustering, they identified a set of 50 genes that segregated IBC samples from non-IBC samples with an accuracy of 88%. They observed a high number of nuclear factor kappa B (NF-kB)-related genes in the IBC samples compared to the non-IBC samples. NF-kB is an important mediator of cell migration, invasion, and metastasis that may contribute to the aggressive nature of IBC. Bertucci et al. [141] identified a set of 109 genes (from 81 patients, 31 of which had IBC) that correctly predicted 79% of IBC specimens and 89% of non IBC specimens, and a set of 85 genes that had an 85% accuracy of predicting for pCR. In an extension of the same study [142], the authors showed that the subtypes (luminal A and B, basal, ERBB2-over expressing and normal breast-like) used to classify non IBC tumors [143] were also present in their IBC cohort, suggesting that despite the aggressive phenotype of IBC, it may not be distinguishable from other breast cancers. In contrast, Van Laere et al. [144] were able to segregate IBC tumors into basal-like and ErbB2 overexpressing groups that could be distinguished from non-IBC tumors. The discrepancy between the two studies may be explained by the different definitions of IBC used to include patients in both studies and at the same time, illustrates how this may affect the results and interpretation of any molecular study.

21.8 Survival

Patients with LABC cancer are at high risk of relapse and death as a result of metastatic disease. Table 21.3 shows the median survival rates and OS rates at 3 and 5 years from the date of trial registration in patients with stage III breast cancer. The reported median survival rates of patients with stage III cancer range from 28 to 66 months [24, 28, 38, 145–148]. OS rates were 13–77% at 3 years and 20–56% at 5 years [24, 28, 38, 41–43, 93, 145, 146, 148–150]. Buzdar et al. [64] reported the experience of 374 patients with noninflammatory LABC at M. D. Anderson treated in two different clinical trials from 1974 to 1989. In the first trial, 174 patients were treated with FAC for three cycles, followed by local therapy with mastectomy and axillary lymph node dissection, RT or both. Patients then received adjuvant chemotherapy with FAC, with or without maintenance chemotherapy with CMF. After induction chemotherapy, 17% of patients had a complete response and 71% had a partial response. The 10-year disease-free survival rates were 55% for patients with stage IIIA and 30% for patients with stage IIIB. The 10-year OS rates were 62% for patients with stage IIIA and 31% for patients with stage IIIB. In the second study, 200 patients received three cycles of vinblastine, doxorubicin, cyclophosphamide, and prednisone (VACP), followed by surgery, RT, or both, and then received adjuvant chemotherapy for a total of eight cycles. The response to induction therapy was similar to the previous trial, with 18% of patients having a complete response, and 66% having a partial response. Combined data from both studies showed that the locoregional recurrence rates were 7% for patients with stage IIIA disease and 26% for patients with stage IIIB disease.

Despite the clear stepwise advances that are being made in the adjuvant treatment of breast cancer, a favorable effect of new therapies on the survival of patients with IBC has not been established. Improvement in survival over time would suggest that, in aggregate, new treatments are helping women with IBC live longer [66]. Based on this precedent, investigators at the M. D. Anderson Cancer Center completed an analysis of 498 patients treated in their institution to evaluate whether the survival of women with IBC has improved over the past 30 years. At a median follow-up of 5.8 years, there were 238 recurrences and 236 deaths. The median recurrence-free survival duration was 2.3 years and the median OS time was 4.2 years. A multivariate model for recurrence-free survival and OS after adjustment for patient and disease characteristics showed that increasing year of diagnosis was not associated with a decrease in the risk for recurrence (hazard ratio, [HR], 1.00; 95% confidence interval [CI], 0.97–1.04) or death (HR, 0.97; 95% CI, 0.94–1.01). The investigators concluded that there has not been an important change in the prognosis of patients with IBC in the last 30 years and that clinical trials focusing on the management of this aggressive urgently needed [151]. Another report from Panades et al. [152] also failed to show breast cancer-specific survival differences when comparing IBC patients treated between 1980 and 1990 with patients treated between 1991 and 2000. The 10-year breast cancer-specific survival rates were 27.4% (95% confidence interval [CI], 18.8–36.7%) and 28.6% (95% CI, 20.3–37.5%), respectively ($P > 0.37$).

A retrospective analysis from the M. D. Anderson Cancer Center studied patients categorized into 2 groups

Table 21.3 Responses and median and 5-year survival for patients with inflammatory breast cancer treated with combined modality treatment

Authors	Year	Regimen	No. of patients	Complete and partial response (%)	5-year OS (%)	Mean survival (month)
De Lena et al. [24]	1978	CT + RT ± CT	36	24 (66)	NA	25
Krutchik et al. [154]	1979	CT + RT + CT	32	NA	NA	24
Chu et al. [108]	1980	RT + CT	16	NA	NA	>26
Pouillart et al. [154]	1981	CT + RT + CT	77	NA	NA	34
Zyberberg et al. [156]	1982	CT + S + CT ± RT	15	14 (93)	70	>56
Pawlicki et al. [42]	1983	CT + S ± RT	72	NA	28 (3 year)	NA
Loprinzi et al. [157]	1984	S + CT + RT + CT	9	NA	55	>25
Fastenberg et al. [158]	1985	CT ± RT ± S	63	NA	NA	43
Keilling et al. [159]	1985	CT + S + CT	41	NA	NA	63
Ferriere et al. [160]	1986	CT + RT ± S + CT	75	NA	NA	54
Israel et al. [161]	1986	CT + S + CT	25	NA	NA	62
Pourny et al. [162]	1986	CT + S ± RT + CT	33	NA	60	70
Alberto et al. [163]	1986	CT + S ± CT + RT	22	NA	10	26
Perez et al. [103]	1987	CT + RT CT + S + RT	23 32	NA	NA	2546
Jacquillat et al. [164]	1987	CT + RT + CT + H	66	NA	66	NA
Brun et al. [101]	1988	CT + RT + S + CT	26	8 (33)	NA	31
Thoms et al. [165]	1989	CT + S + CT + RT	61	37 (60)	35	61
Swain and Lippmann [166]	1989	CT + RT + S + CT + H	45	43 (98)	NA	36
Fields et al. [102]	1989	CT + S + RT + CT	37	NA	44	49
Rouesse et al. [167]	1989	CT + RT + CT + H	91	34	40	36
Maloisel et al. [168]	1990	CT + S + CT + RT + H	43	38 (88)	75	46
Koh et al. [169]	1990	CT + RT + CT CT + S + CT + RT CT + S + CT + RT	40 23 43	NA	37 30 40	39 38 31
Arriagada et al. [170]	1990	CT + RT + CT	99	NA	55 (4 year)	NA
Attia-Sobol et al. [105]	1993	CT ± S + RT + CT	109	12 (20)	55	70
Mourali et al. [171]	1993	CT + RT + CT CT + S + CT	34 34	12 (19)	18 18	27 27
Chevallier et al. [172]	1993	CT + RT ± CT ± S	196	140 (71)	32	37
Fein et al. [173]	1994	CT + S + RT RT ± S ± CT	33 17	NA	39 39	NA
Thomas et al. [106]	1995	CT + RT + CT ± H	125	94 (75)	50	NA
Ueno et al. [174]	1995	CT ± RT ± S + CT ± RT	178	127 (71)	30	40
Curcio et al. [175]	1999	CT + S ± RT	33	NA	30	NA
Arthur et al. [176]	1999	CT + RT ± S + CT	38	27 (71)	33	NA
De Boer et al. [177]	2000	CT + RTCT + S + RT	34 19	NA	38 15	35 35

CT chemotherapy; *H* hormonal therapy; *NA* not available; *RT* radiation therapy; *S* surgery

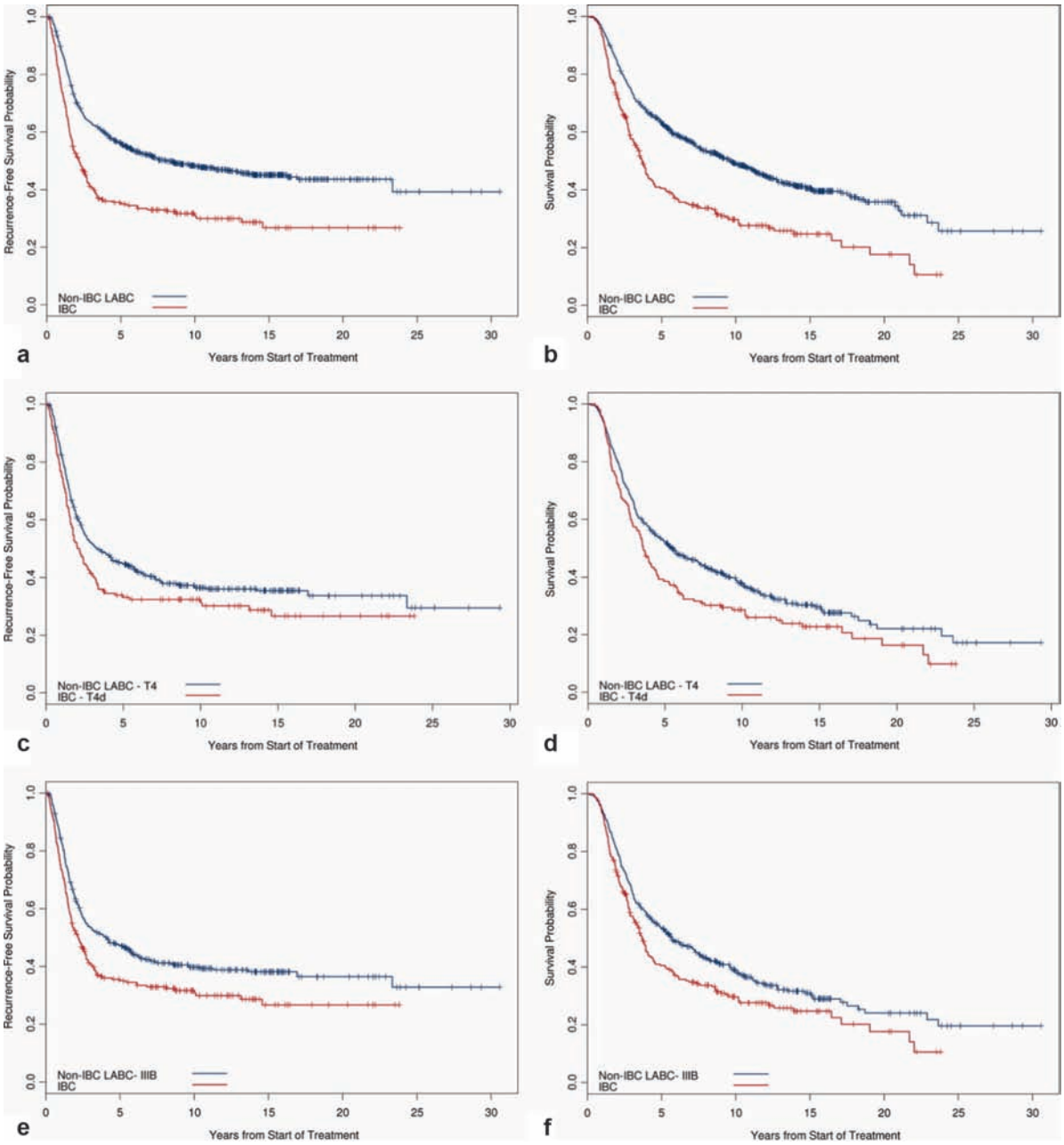

Fig. 21.4 Kaplan-Meier representation of relapse-free survival (RFS) rates by patient group: (**a**) IBC (*red line*) vs. LABC (*blue line*); (**b**) Kaplan-Meier representation of overall survival (OS) rates are shown in the same two patient groups. Kaplan-Meier representation of RFS is shown in two patients' groups: (**c**) IBC vs. non-IBC LABC (T4 *only*); and (**d**) is the Kaplan-Meier representation of OS rates in the same groups. Kaplan-Meier representation of RFS in two patients' groups is shown for (**e**) IBC vs. non-IBC LABC (stage IIIB) and (**f**) Kaplan-Meier representation of OS rates in the same groups. From Cristofanilli et al. [155]

on the basis of their clinical diagnosis of IBC or non-IBC LABC. LABC was defined as stage IIB, IIIA, IIIB, or IIIC breast cancer (AJCC system) [16]. A clinical diagnosis of IBC required the presence of diffuse erythema, heat, ridging, or peau d'orange (corresponding to T4d in the AJCC classification system) [16]. The clinical diagnosis was confirmed for all patients by assessment of a multidisciplinary team, and all

patients were treated in separate but parallel protocols with similar multidisciplinary approaches consisting of induction chemotherapy, locoregional treatment (surgery and radiotherapy), adjuvant chemotherapy, and hormonal therapy (for ER-positive disease). The median follow-up period was 69 months and pCR rates were 13.9 and 11.7% in the IBC and non-IBC LABC groups, respectively ($P>0.42$). The 5-year estimates of cumulative incidence of recurrence were 64.8% for IBC and 43.4% for non-IBC LABC ($P<0.0001$). Patients with IBC had significantly higher cumulative incidence of local-regional recurrence and distant soft-tissue and bone disease. The 5-year OS rates were 40.5% for the IBC group (95% CI, 34.5–47.4%) and 63.2% for the non-IBC LABC group (95% CI, 60.0–66.6%; $P<0.0001$) (see Fig. 21.4). The authors concluded that IBC was associated with a worse prognosis and a distinctive pattern of early recurrence compared with LABC [153]. This evidence demonstrates that IBC should be treated separately from non-IBC LABC and that the use of standard combinations of cytotoxic agents alone will not substantially modify the prognosis of patients with this disease. More sensitive diagnostic interventions and novel therapeutic strategies should be developed to increase the efficacy of systemic treatments.

Lastly, LABC and IBC although molecularly heterogeneous, currently are approached based on the hormone receptor-positive, HER2-positive, and triple-negative groupings. Treatments for these three groups are partially overlapping, the "major" therapeutic intervention is different in the groups: endocrine therapy, HER2-directed therapy and chemotherapy, respectively and should be complemented with adequate local-regional therapy and reconstructive surgery (Fig. 21.5).

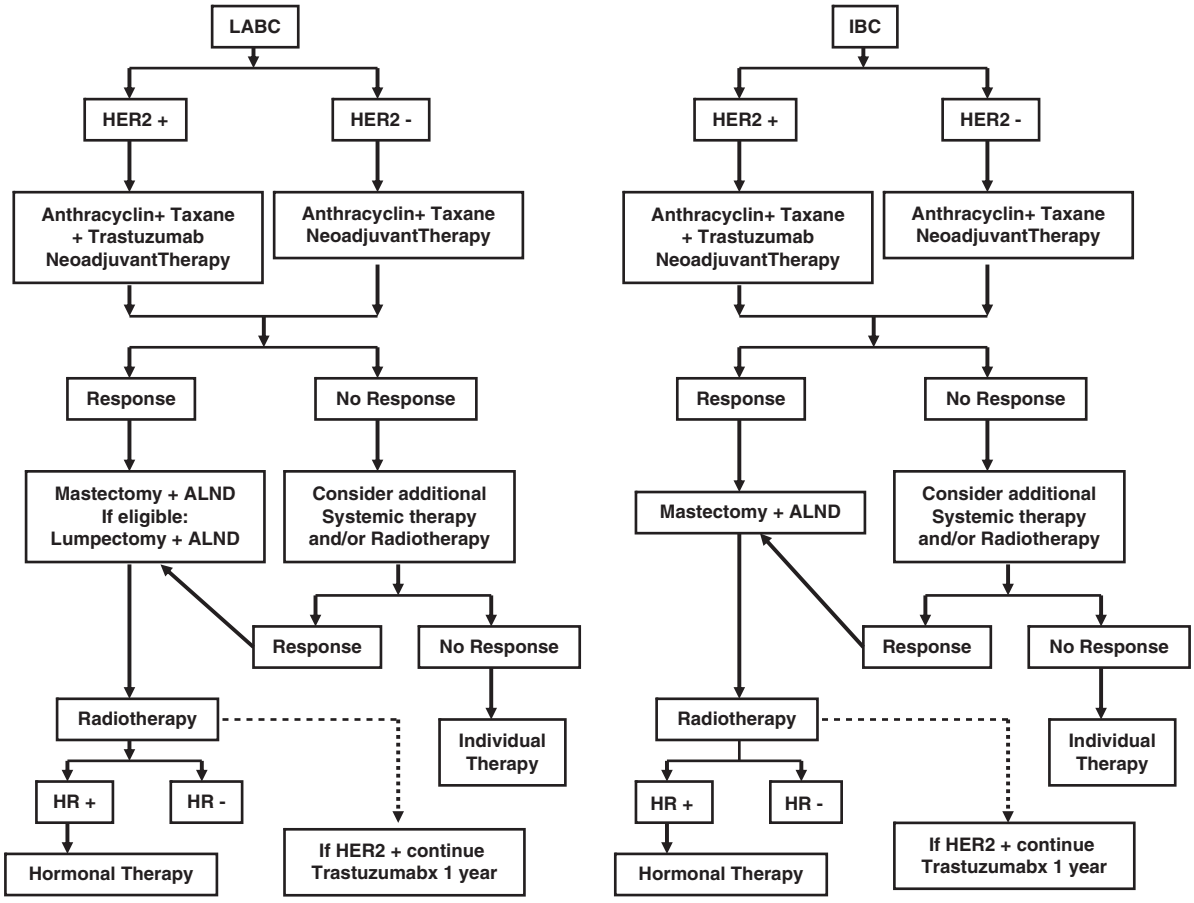

Fig. 21.5 Flow diagram describing the management of LABC and IBC

References

1. Seidman H (1987) Survival experience in the breast cancer detection demonstration project. CA Cancer J Clin. 37:528–90
2. Zeicner GI, Mohar BA, Ramirez UMT (1993) Epidemiologia del cancer de mama en el instituto nacional de cancerologia (1989–1990). Cancerologia. 35:810–4
3. Eniu A, Carlson RW, Aziz Z, Bines J, Hortobágyi GN, Bese NS, Love RR, Vikram B, Kurkure A, Anderson BO; Global Summit Treatment and Allocation of Resources Panel (2006) Breast cancer in limited-resource countries: treatment and allocation of resources. Breast J. 12(Suppl 1): S38–53
4. American College of Surgeons National Cancer Data Base (2002) http://www.facs.org/cancer/publicncdb.html. Accessed 5 Jan 2008
5. Hance KW, Anderson WF, Devesa SS, Young HA, Levine PH (2005) Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results (SEER) program at the National Cancer Institute. J Natl Cancer Inst. 97:966–75
6. Anderson WF, Schairer C, Chen BE, Hance KW, Levine PH (2006) Epidemiology of inflammatory breast cancer (IBC). Breast Dis. 22:9–23
7. Aziz SA, Pervez S, Khan S, Kayani N, Azam SI, Rahbar MH (2003) Case control study of prognostic markers and disease outcome in inflammatory carcinoma breast: a unique clinical experience. Breast J. 7:398–404
8. Mourali N, Muenz LR, Tabbane F, Belhassen S, Bahi J, Levine PH (1980) Epidemiologic features of rapidly progressing breast cancer in Tunisia. Cancer. 46:2741–6
9. Chang S, Buzdar AU, Hursting SD (1998) Inflammatory breast cancer and body mass index. J Clin Oncol. 16: 3731–5
10. Anderson WF, Chu KC, Chang S (2003) Inflammatory breast cancer and non-inflammatory locally advanced breast carcinoma: distinct clinicopathologic entities? J Clin Oncol. 21:2254–9
11. Haagensen CD. Inflammatory carcinoma, diseases of the breast. Philadelphia, PA: W.B. Saunders; 1956. p. 488–98
12. Leitch A. Peau d'orange in acute mammary carcinoma: its cause and diagnostic value. Lancet. 1:861–3
13. Jaiyesimi IA, Buzdar AU, Hortobagyi G (1992) Inflammatory breast cancer: a review. J Clin Oncol. 10: 1014–24
14. Lee BJ, Tannenbaum EN (1924) Inflammatory carcinoma of the breast. Surg Gynecol Obstet. 39:580–95
15. Merajver SD, Weber BL, Cody R, Zhang D, Strawderman M, Calzone KA, LeClaire V, Levin A, Irani J, Halvie M, August D, Wicha M, Lichter A, Pierce LJ (1997) Breast conservation and prolonged chemotherapy for locally advanced breast cancer: the University of Michigan experience. J Clin Oncol. 15:2873–81
16. Singletary SE, Allred C, Ashley P, Bassett LW, Berry D, Bland KI, Borgen PI, Clark G, Edge SB, Hayes DF, Hughes LL, Hutter RV, Morrow M, Page DL, Recht A, Theriault RL, Thor A, Weaver DL, Wieand HS, Greene FL (2002) Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol. 20:3628–36
17. Denoix P (1970) The institute's contribution to the definition of factors guiding the choice of treatment: phase I development. In: Denoix P (ed) Treatment of malignant breast tumors. Vol. 32. Springer, Berlin
18. Yang WT, Le-Petross HT, Macapinlac H, Carkaci S, Gonzalez-Angulo AM, Dawood S, Resetkova E, Hortobagyi GN, Cristofanilli M (2008) Inflammatory breast cancer: PET/CT, MRI, mammography, and sonography findings. Breast Cancer Res Treat. 109(3):417–26
19. Klefström P, Gröhn P, Heinonen E, Holsti L, Holsti P (1987) Adjuvant postoperative radiotherapy, chemotherapy, and immunotherapy in stage III breast cancer. II. 5-year results and influence of levamisole. Cancer. 60:936–42
20. Gröhn P, Heinonen E, Klefström P, Tarkkanen J (1984) Adjuvant postoperative radiotherapy, chemotherapy, and immunotherapy in stage III breast cancer. Cancer. 54:670–4
21. Derman DP, Browde S, Kessel IL, De Moor NG, Lange M, Dansey R, Seymour L, Bezwoda WR (1989) Adjuvant chemotherapy (CMF) for stage III breast cancer: a randomized trial. Int J Radiat Oncol Biol Phys. 17:257–61
22. Schaake-Koning C, van der Linden EH, Hart G, Engelsman E (1985) Adjuvant chemo- and hormonal therapy in locally advanced breast cancer: a randomized clinical study. Int J Radiat Oncol Biol Phys. 11:1759–63
23. Rubens RD, Bartelink H, Engelsman E, Hayward JL, Rotmensz N, Sylvester R, van der Schueren E, Papadiamantis J, Vassilaros SD, Wildiers J et al (1989) Locally advanced breast cancer: the contribution of cytotoxic and endocrine treatment to radiotherapy. An EORTC Breast Cancer Co-operative Group Trial (10792). Eur J Cancer Clin Oncol. 25:667–78
24. De Lena M, Zucali R, Viganotti G, Valagussa P, Bonadonna G (1978) Combined chemotherapy-radiotherapy approach in locally advanced (T3b–T4) breast cancer. Cancer Chemother Pharmacol. 1:53–9
25. Hortobagyi GN, Blumenschein GR, Tashima CK. Multidisciplinary treatment of locally advanced (stage III) breast cancer. Proc Am Soc Clin Oncol. 1978;19:361; abstr c-219
26. Schick P, Goodstein J, Moor J, Butler J, Senter KL (1983) Preoperative chemotherapy followed by mastectomy for locally advanced breast cancer. J Surg Oncol. 22:278–82
27. Perloff M, Lesnick GJ (1982) Chemotherapy before and after mastectomy in stage III breast cancer. Arch Surg. 117: 879–81
28. Swain SM, Sorace RA, Bagley CS, Danforth DN Jr, Bader J, Wesley MN, Steinberg SM, Lippman ME (1987) Neoadjuvant chemotherapy in the combined modality approach of locally advanced nonmetastatic breast cancer. Cancer Res. 47:3889–94
29. Hortobagyi GN, Blumenschein GR, Spanos W, Montague ED, Buzdar AU, Yap HY, Schell F (1983) Multimodal treatment of locoregionally advanced breast cancer. Cancer. 51(5):763–8
30. Mauriac L, Durand M, Avril A, Dilhuydy JM (1991) Effects of primary chemotherapy in conservative treatment of breast cancer patients with operable tumors larger than 3 cm. Results of a randomized trial in a single center. Ann Oncol. 2:347–54
31. Scholl SM, Fourquet A, Asselain B, Pierga JY, Vilcoq JR, Durand JC, Dorval T, Palangié T, Jouve M, Beuzeboc P

(1994) Neoadjuvant versus adjuvant chemotherapy in premenopausal patients with tumors considered too large for breast-conserving surgery: preliminary results of a randomized trial. Eur J Cancer. 30A:645–52
32. Semiglazov VF, Topuzov EE, Bavli JL, Moiseyenko VM, Ivanova OA, Seleznev IK, Orlov AA, Barash NY, Golubeva OM, Chepic OF (1994) Primary (neoadjuvant) chemotherapy and radiotherapy compared with primary radiotherapy alone in stage IIb-IIIa breast cancer. Ann Oncol. 5:591–5
33. Powles TJ, Hickish TF, Makris A, Ashley SE, O'Brien ME, Tidy VA, Casey S, Nash AG, Sacks N, Cosgrove D (1995) Randomized trial of chemoendocrine therapy started before or after surgery for treatment of primary breast cancer. J Clin Oncol. 13:547–52
34. Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, Cruz AB Jr, Fisher ER, Wickerham DL, Wolmark N, DeCillis A, Hoehn JL, Lees AW, Dimitrov NV (1997) Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol. 15:2483–93
35. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, Wickerham DL, Begovic M, DeCillis A, Robidoux A, Margolese RG, Cruz AB Jr, Hoehn JL, Lees AW, Dimitrov NV, Bear HD (1998) Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol. 16:2672–85
36. Mauriac L, MacGrogan G, Avril A, Durand M, Floquet A, Debled M, Dilhuydy JM, Bonichon F (1999) Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: a unicenter randomized trial with a 124-month median follow-up. Institut Bergonié Bordeaux Groupe Sein (IBBGS). Ann Oncol. 10:47–52
37. van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L (2001) Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol. 19:4224–37
38. Valagussa P, Zambetti M, Bignami P, de Lena M, Varini M, Zucali R, Rovini D, Bonadonna G (1983) T3b–T4 breast cancer: factors affecting results in combined modality treatments. Clin Exp Metastasis. 1:191–202
39. Rubens RD, Sexton S, Tong D, Winter PJ, Knight RK, Hayward JL (1980) Combined chemotherapy and radiotherapy for locally advanced breast cancer. Eur J Cancer. 16:351–6
40. Conte PF, Alama A, Bertelli G, Canavese G, Carnino F, Catturich A, Di Marco E, Gardin G, Jacomuzzi A, Monzeglio C (1987) Chemotherapy with estrogenic recruitment and surgery in locally advanced breast cancer: clinical and cytokinetic results. Int J Cancer. 40:490–4
41. Jacquillat C, Baillet F, Weil M, Auclerc G, Housset M, Auclerc M, Sellami M, Jindani A, Thill L, Soubrane C (1988) Results of a conservative treatment combining induction (neoadjuvant) and consolidation chemotherapy, hormonotherapy, and external and interstitial irradiation in 98 patients with locally advanced breast cancer (IIIA-IIIB). Cancer. 61:1977–82
42. Pawlicki M, Skolyszewski J, Brandys A (1983) Results of combined treatment of patients with locally advanced breast cancer. Tumori. 69:249–53
43. Balawajder I, Antich PP, Boland J (1983) An analysis of the role of radiotherapy alone and in combination with chemotherapy and surgery in the management of advanced breast carcinoma. Cancer. 51:574–80
44. Heys SD, Hutcheon AW, Sarkar TK, Ogston KN, Miller ID, Payne S, Smith I, Walker LG, Eremin O; Aberdeen Breast Group (2002) Neoadjuvant docetaxel in breast cancer: 3-year survival results from the Aberdeen trial. Clin Breast Cancer. 3(Suppl 2):S69–74
45. von Minckwitz G, Raab G, Caputo A, Schütte M, Hilfrich J, Blohmer JU, Gerber B, Costa SD, Merkle E, Eidtmann H, Lampe D, Jackisch C, du Bois A, Kaufmann M (2005) Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO study of the German Breast Group. J Clin Oncol. 23:2676–85
46. von Minckwitz G, Blohmer JU, Loehr A, Raab G, Eidtmann H, Hilfrich J, Gerber B, Huober J, Costa SD, Jackisch C, Loibl S, Schickling O, Zuna I, Kaufmann M. Comparison of docetaxel/doxorubicin/cyclophosphamide (TAC) versus vinorelbine/capecitabine (NX) in patients non-responding to 2 cycles of neoadjuvant TAC chemotherapy. First results of the phase III GEPARTRIO-Study by the German Breast Group. Breast Cancer Res Treat. 2005;94(Suppl 1):S19; abstr 38
47. von Minckwitz G, Rezai M, Loibl S, Fasching P, Huober J, Tesch H, Bauerfeind I, Hilfrich J, Mehta K, Untch M. Evaluating the efficacy of capecitabine given concomitantly or in sequence to epirubicin/cyclophosphamide followed by docetaxel as neoadjuvant treatment for primary breast cancer. First efficacy analysis of the GBG/AGO intergroup-study "GeparQuattro". Breast Cancer Res Treat. 2007;106(Suppl 1):S21; abstr 79
48. Veronesi A, Frustaci S, Tirelli U, Galligioni E, Trovò MG, Crivellari D, Magri MD, Tumolo S, Grigoletto E (1981) Tamoxifen therapy in postmenopausal advanced breast cancer: efficacy at the primary tumor site in 46 evaluable patients. Tumori. 67:235–8
49. Gazet JC, Ford HT, Coombes RC (1991) Randomized trial of chemotherapy versus endocrine therapy in patients presenting with locally advanced breast cancer (a pilot study). Br J Cancer. 63:279–82
50. Hoff PM, Valero V, Buzdar AU, Singletary SE, Theriault RL, Booser D, Asmar L, Frye D, McNeese MD, Hortobagyi GN (2000) Combined modality treatment of locally advanced breast carcinoma in elderly patients or patients with severe comorbid conditions using tamoxifen as the primary therapy. Cancer. 88:2054–60
51. Ellis MJ, Coop A, Singh B, Mauriac L, Llombert-Cussac A, Jänicke F, Miller WR, Evans DB, Dugan M, Brady C, Quebe-Fehling E, Borgs M (2001) Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol. 19:3808–16
52. Hurley J, Doliny P, Reis I, Silva O, Gomez-Fernandez C, Velez P, Pauletti G, Powell JE, Pegram MD, Slamon DJ (2006) Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer. J Clin Oncol. 24:1831–8

53. Van Pelt AE, Mohsin S, Elledge RM, Hilsenbeck SG, Gutierrez MC, Lucci A Jr, Kalidas M, Granchi T, Scott BG, Allred DC, Chang JC (2003) Neoadjuvant trastuzumab and docetaxel in breast cancer: preliminary results. Clin Breast Cancer. 4:348–53
54. Gianni L, Semiglazov V, Manikhas GM, Eiermann W, Lluch A, Tjulandin S, Feyereislova A, Vanhauwere B, Valagussa P, Baselga J. Neoadjuvant trastuzumab plus doxorubicin, paclitaxel and CMF in locally advanced breast cancer (NOAH trial): Feasibility, safety and antitumor effects. Proc Breast Cancer Symp. 2007;1:131; abstr 144
55. Bozzetti F, Saccozzi R, De Lena M, Salvadori B (1981) Inflammatory cancer of the breast: analysis of 114 cases. J Surg Oncol. 18:355–61
56. Shenkier T, Weir L, Levine M, Olivotto I, Whelan T, Reyno L; Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 15. Treatment for women with stage III or locally advanced breast cancer. CMAJ. 2004;170:983–94
57. Atkins HL, Horrigan WD (1961) Treatment of locally advanced carcinoma of the breast with roentgen therapy and simple mastectomy. Am J Roentgenol Radium Ther Nucl Med. 85:860–4
58. Toonkel LM, Fix I, Jacobson LH, Bamberg N, Wallach CB (1986) Locally advanced breast carcinoma: results with combined regional therapy. Int J Radiat Oncol Biol Phys. 12:1583–7
59. Perez CA, Fields JN, Fracasso PM, Philpott G, Soares RL Jr, Taylor ME, Lockett MA, Rush C (1994) Management of locally advanced carcinoma of the breast. II. Inflammatory carcinoma. Cancer. 74:466–76
60. Ueno NT, Buzdar AU, Singletary SE, Ames FC, McNeese MD, Holmes FA, Theriault RL, Strom EA, Wasaff BJ, Asmar L, Frye D, Hortobagyi GN (1997) Combined modality treatment of inflammatory breast carcinoma: twenty years of experience at M.D. Anderson Center. Cancer Chemother Pharmacol. 40:321–9
61. Bauer RL, Busch E, Levine E, Edge SB (1995) Therapy for inflammatory breast cancer: impact of doxorubicin-based therapy. Ann Surg Oncol. 2:288–94
62. Early Breast Cancer Trialists' Collaborative Group (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. Lancet. 365:1687–717
63. Singletary SE, Ames FC, Buzdar AU (1994) Management of inflammatory breast cancer. World J Surg. 18:87–92
64. Buzdar AU, Singletary SE, Booser DJ, Frye DK, Wasaff B, Hortobagyi GN (1995) Combined modality treatment of stage III and inflammatory breast cancer. M.D. Anderson Cancer Center experience. Surg Oncol Clin N Am. 4:715–34
65. Cristofanilli M, Buzdar AU, Sneige N, Smith T, Wasaff B, Ibrahim N, Booser D, Rivera E, Murray JL, Valero V, Ueno N, Singletary ES, Hunt K, Strom E, McNeese M, Stelling C, Hortobagyi GN (2001) Paclitaxel in the multimodality treatment for inflammatory breast carcinoma. Cancer. 92:1775–82
66. Cristofanilli M, Gonzalez-Angulo AM, Buzdar AU, Kau SW, Frye DK, Hortobagyi GN (2004) Paclitaxel improves the prognosis in estrogen receptor-negative inflammatory breast cancer: the M.D. Anderson Cancer Center experience. Clin Breast Cancer. 4:415–9
67. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N (2005) Trastuzumab plus adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 353:1673–84
68. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Láng I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Rüschoff J, Suto T, Greatorex V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD (2005) Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 353:1659–84
69. Johnston S, Trudeau M, Kaufman B, Boussen H, Blackwell K, Lorusso P, Lombardi DP, Ben Ahmed S, Citrin DL, Desilvio ML, Harris J, Westlund RE, Salazar V, Zaks TZ, Spector NL (2008) Phase II study of predictive biomarker profiles for response targeting human epidermal growth factor receptor 2 (HER-2) in advanced inflammatory breast cancer with lapatinib monotherapy. J Clin Oncol. 26(7): 1066–72
70. Cristofanilli M, Boussen H, Baselga J, Lluch A, Ben Ayed F, Friaha M, Ben Ahmed S, Hurley J, Johnston S, Kaufman B, Findlay M, Olopade O, Shannon C, Harris J, Stein S, Spector N. A phase II combination study of lapatinib and paclitaxel as a neoadjuvant therapy in patients with newly diagnosed inflammatory breast cancer (IBC). Breast Cancer Res Treat. 2006;100(Suppl 1):S5; abstr 1
71. Van der Auwera I, Van Laere SJ, Van den Eynden GG, Benoy I, van Dam P, Colpaert CG, Fox SB, Turley H, Harris AL, Van Marck EA, Vermeulen PB, Dirix LY. Increased angiogenesis and lymphangiogenesis in inflammatory versus noninflammatory breast cancer by real-time reverse transcriptase-PCR gene expression quantification 92004. Clin Cancer Res. 10:7965–71
72. Wedam SB, Low JA, Yang SX, Chow CK, Choyke P, Danforth D, Hewitt SM, Berman A, Steinberg SM, Liewehr DJ, Plehn J, Doshi A, Thomasson D, McCarthy N, Koeppen H, Sherman M, Zujewski J, Camphausen K, Chen H, Swain SM (2006) Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer. J Clin Oncol. 24:769–77
73. Overmoyer B, Fu P, Hoppel C, Radivoyevitch T, Shenk R, Persons M, Silverman P, Robertson K, Ziats NP, Wasman JK, Abdul-Karim FW, Jesberger JA, Duerk J, Hartman P, Hanks S, Lewin J, Dowlati A, McCrae K, Ivy P, Remick SC (2007) Inflammatory breast cancer as a model disease to study tumor angiogenesis: results of a phase IB trial of combination SU5416 and doxorubicin. Clin Cancer Res. 13:5862–8
74. Johnston SR, Hickish T, Ellis P, Houston S, Kelland L, Dowsett M, Salter J, Michiels B, Perez-Ruixo JJ, Palmer P, Howes A (2003) Phase II study of the efficacy and tolerability of two dosing regimens of the farnesyl transferase

inhibitor, R115777, in advanced breast cancer. J Clin Oncol. 21:2492–9
75. http://www.clinicaltrials.gov/ct2/results?term=breast+cancer+AND+FTI+inhibitors. Accessed 02 Aug 2008
76. Arun B, Slack R, Gehan E, Spitzer T, Meehan KR (1999) Survival after autologous hematopoietic stem cell transplantation for patients with inflammatory breast carcinoma. Cancer. 85:93–9
77. Adkins D, Brown R, Trinkaus K, Maziarz R, Luedke S, Freytes C, Needles B, Wienski D, Fracasso P, Pluard T, Moriconi W, Ryan T, Hoelzer K, Safdar S, Rearden T, Rodriguez G, Khoury H, Vij R, DiPersio J (1999) Outcomes of high-dose chemotherapy and autologous stem-cell transplantation in stage IIIB inflammatory breast cancer. J Clin Oncol. 17:2006–14
78. Schwartzberg L, Weaver C, Lewkow L, McAneny B, Zhen B, Birch R, West W, Tauer K, Buckner C (1999) High-dose chemotherapy with peripheral blood stem cell support for stage IIIB inflammatory carcinoma of the breast. Bone Marrow Transplant. 24:981–7
79. Somlo G, Frankel P, Chow W, Leong L, Margolin K, Morgan R Jr, Shibata S, Chu P, Forman S, Lim D, Twardowski P, Weitzel J, Alvarnas J, Kogut N, Schriber J, Fermin E, Yen Y, Damon L, Doroshow JH (2004) Prognostic indicators and survival in patients with stage IIIB inflammatory breast carcinoma after dose-intense chemotherapy. J Clin Oncol. 22:1839–48
80. Haagensen CD, Stout AP (1943) Carcinoma of the breast: II. Criteria of operability. Ann Surg. 118:859–70
81. Baclesse F (1965) Five-year results in 431 breast cancers treated solely by roentgen rays. Ann Surg. 161:103–4
82. Zucali R, Uslenghi C, Kenda R, Bonadonna G (1976) Natural history and survival of inoperable breast cancer treated with radiotherapy and radiotherapy followed by radical mastectomy. Cancer. 37:1422–31
83. Harris JR, Sawicka J, Gelman R, Hellman S (1983) Management of locally advanced carcinoma of the breast by primary radiation therapy. Int J Radiat Oncol Biol Phys. 9:345–9
84. Sheldon T, Hayes DF, Cady B, Parker L, Osteen R, Silver B, Recht A, Come S, Henderson IC, Harris JR (1987) Primary radiation therapy for locally advanced breast cancer. Cancer. 60:1219–25
85. Fletcher GH, Montague ED (1965) Radical irradiation of advanced breast cancer. Am J Roentgenol Radium Ther Nucl Med. 93:573–84
86. Baclesse F. Roentgen therapy as the sole method of treatment of cancer of the breast. Am J Roentgenol Radium Ther Nucl Med. 1949;62(3):311–9; discussion 349–54
87. Spanos WJ Jr, Montague ED, Fletcher GH (1980) Late complications of radiation only for advanced breast cancer. Int J Radiat Oncol Biol Phys. 6:1473–6
88. Huang EH, Tucker SL, Strom EA, McNeese MD, Kuerer HM, Buzdar AU, Valero V, Perkins GH, Schechter NR, Hunt KK, Sahin AA, Hortobagyi GN, Buchholz TA (2004) Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. J Clin Oncol. 22:4691–9
89. Singletary SE, McNeese MD, Hortobagyi GN (1992) Feasibility of breast-conservation surgery after induction chemotherapy for locally advanced breast carcinoma. Cancer. 69:2849–52
90. Kuerer HM, Singletary SE, Buzdar AU, Ames FC, Valero V, Buchholz TA, Ross MI, Pusztai L, Hortobagyi GN, Hunt KK (2001) Surgical conservation planning after neoadjuvant chemotherapy for stage II and operable stage III breast carcinoma. Am J Surg. 182:601–8
91. Calais G, Descamps P, Chapet S, Turgeon V, Reynaud-Bougnoux A, Lemarié E, Fignon A, Body G, Bougnoux P, Lansac J et al (1993) Primary chemotherapy and radiosurgical breast-conserving treatment for patients with locally advanced operable breast cancers. Int J Radiat Oncol Biol Phys. 26:37–42
92. Héry M, Namer M, Moro M, Boublil JL, LaLanne CM (1986) Conservative treatment (chemotherapy/radiotherapy) of locally advanced breast cancer. Cancer. 57: 1744–9
93. Touboul E, Lefranc JP, Blondon J, Ozsahin M, Mauban S, Schwartz LH, Schlienger M, Laugier A, Guerin RA (1992) Multidisciplinary treatment approach to locally advanced non-inflammatory breast cancer using chemotherapy and radiotherapy with or without surgery. Radiother Oncol. 25:167–75
94. Bonadonna G, Veronesi U, Brambilla C, Ferrari L, Luini A, Greco M, Bartoli C, Coopmans de Yoldi G, Zucali R, Rilke F et al (1990) Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. J Natl Cancer Inst. 82:1539–45
95. Schwartz GF, Birchansky CA, Komarnicky LT, Mansfield CM, Cantor RI, Biermann WA, Fellin FM, McFarlane J (1994) Induction chemotherapy followed by breast conservation for locally advanced carcinoma of the breast. Cancer. 73:362–9
96. Harris JR, Halpin-Murphy P, McNeese M, Mendenhall NP, Morrow M, Robert NJ (1999) Consensus statement on postmastectomy radiation therapy. Int J Radiat Oncol Biol Phys. 44:989–90
97. Taylor ME, Haffty BG, Shank BM, Halberg FE, Martinez AA, McCormick B, McNeese MD, Mendenhall NP, Mitchell SE, Rabinovitch RA, Solin LJ, Singletary SE, Leibel S, Recht A (2000) Postmastectomy radiotherapy. American college of radiology. ACR appropriateness criteria. Radiology. 215(Suppl):1153–70
98. Buchholz TA, Tucker SL, Masullo L, Kuerer HM, Erwin J, Salas J, Frye D, Strom EA, McNeese MD, Perkins G, Katz A, Singletary SE, Hunt KK, Buzdar AU, Hortobagyi GN (2002) Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. J Clin Oncol. 20:17–23
99. Buchholz TA, Strom EA, Perkins GH, McNeese MD (2002) Controversies regarding the use of radiation after mastectomy in breast cancer. Oncologist. 7:539–46
100. Buchholz TA, Hunt KK, Whitman GJ, Sahin AA (2003) Hortobagyi GN (2003) Neoadjuvant chemotherapy for breast carcinoma: multidisciplinary considerations of benefits and risks. Cancer. 98:1150–60
101. Brun B, Otmezguine Y, Feuilhade F, Julien M, Lebourgeois JP, Calitchi E, Roucayrol AM, Ganem G, Huart J, Pierquin B (1988) Treatment of inflammatory breast cancer with combination chemotherapy and mastectomy versus breast conservation. Cancer. 61:1096–103

102. Fields JN, Perez CA, Kuske RR, Fineberg BB, Bartlett N (1989) Inflammatory carcinoma of the breast: treatment results on 107 patients. Int J Radiat Oncol Biol Phys. 17:249–55
103. Perez CA, Fields JN (1987) Role of radiation therapy for locally advanced and inflammatory carcinoma of the breast. Oncology (Williston Park). 1:81–94
104. Barker JL, Montague ED, Peters LJ (1980) Clinical experience with irradiation of inflammatory carcinoma of the breast with and without elective chemotherapy. Cancer. 45:625–9
105. Attia-Sobol J, Ferrière JP, Curé H, Kwiatkowski F, Achard JL, Verrelle P, Feillel V, De Latour M, Lafaye C, Deloche C et al (1993) Treatment results, survival and prognostic factors in 109 inflammatory breast cancers: univariate and multivariate analysis. Eur J Cancer. 29A:1081–8
106. Thomas F, Arriagada R, Spielmann M, Mouriesse H, Le Chevalier T, Fontaine F, Tursz T (1995) Pattern of failure in patients with inflammatory breast cancer treated by alternating radiotherapy and chemotherapy. Cancer. 76: 2286–90
107. Moore MP, Ihde JK, Crowe JP Jr, Hakes TP, Kinne DW (1991) Inflammatory breast cancer. Arch Surg. 126:304–6
108. Chu AM, Wood WC, Doucette JA (1980) Inflammatory breast carcinoma treated by radical radiotherapy. Cancer. 45:2730–7
109. Clark GM (2000) Prognostic and predictive factors. In: Harris JR (ed) Diseases of the Breast., 2nd edn. Lippincott Williams and Wilkins, Philadelphia
110. Stewart JF, King RJ, Winter PJ, Tong D, Hayward JL, Rubens RD (1982) Oestrogen receptors, clinical features and prognosis in stage III breast cancer. Eur J Cancer Clin Oncol. 18:1315–20
111. Gardin G, Rosso R, Campora E, Repetto L, Naso C, Canavese G, Catturich A, Corvò R, Guenzi M, Pronzato P et al (1995) Locally advanced non-metastatic breast cancer: analysis of prognostic factors in 125 patients homogeneously treated with a combined modality approach. Eur J Cancer. 31A:1428–33
112. Silvestrini R, Daidone MG, Valagussa P, Salvadori B, Rovini D, Bonadonna G (1987) Cell kinetics as a prognostic marker in locally advanced breast cancer. Cancer Treat Rep. 71:375–9
113. Gruber G, Ciriolo M, Altermatt HJ, Aebi S, Berclaz G, Greiner RH (2004) Prognosis of dermal lymphatic invasion with or without clinical signs of inflammatory breast cancer. Int J Cancer. 109:144–8
114. Jardines L, Haffty BG, Theriautl RL (1999) Locally advanced, locally recurrent and metastatic breast cancer. In: Pazdur R, Coia LR, Hoskins WJ, Wagman Ld (eds) Cancer management. a multidisciplinary approach., 3rd edn. PRR, Melville, NY, pp 73–88
115. Paradiso A, Tommasi S, Brandi M, Marzullo F, Simone G, Lorusso V, Mangia A, De Lena M (1989) Cell kinetics and hormonal receptor status in inflammatory breast carcinoma: comparison with locally advanced disease. Cancer. 64:1922–7
116. Kleer CG, van Golen KL, Merajver SD (2000) Molecular biology of breast cancer metastasis inflammatory breast cancer: clinical syndrome and molecular determinants. Breast Cancer Res. 2:423–9
117. Turpin E, Bièche I, Bertheau P, Plassa LF, Lerebours F, de Roquancourt A, Olivi M, Espié M, Marty M, Lidereau R, Vidaud M, de Thé H (2002) The increased incidence of ERBB2 over expression and TP53 mutation in inflammatory breast cancer. Oncogene. 21:7593–7
118. Davidoff AM, Humphrey PA, Iglehart JD, Marks JR (1991) Genetic basis for p53 over expression in human breast cancer. Proc Natl Acad Sci USA. 88:5006–10
119. Faille A, De Cremoux P, Extra JM, Linares G, Espie M, Bourstyn E, De Rocquancourt A, Giacchetti S, Marty M, Calvo F (2005) P53 mutations and overexpression in locally advanced breast cancers. Br J Cancer. 69:145–50
120. Riou G, Lê MG, Travagli JP, Levine AJ, Moll UM (1993) Poor prognosis of p53 gene mutation and nuclear overexpression of p53 protein in inflammatory breast carcinoma. J. Natl. Cancer Inst. 85:1765–7
121. Gonzalez-Angulo AM, Sneige N, Buzdar AU, Valero V, Kau SW, Broglio K, Yamamura Y, Hortobagyi GN, Cristofanilli M (2004) p53 expression as a prognostic marker in inflammatory breast cancer. Clin Cancer Res. 10:6215–21
122. Kleer CG, van Golen KL, Braun T, Merajver SD (2002) Persistent E-cadherin expression in inflammatory breast cancer. Mod Pathol. 14:458–64
123. Tomlinson JS, Aplaugh ML, Barsky SH (2001) An intact overexpressed E-cadherin/alpha, beta-catenin axis characterizes the lymphovascular emboli of inflammatory breast carcinoma. Cancer Res. 61:5231–41
124. Alpaugh ML, Tomlinson JS, Kasraeian S, Barsky SH (2002) Cooperative role of E-cadherin and sialyl-lewis X/A-deficient MUC1 in the passive dissemination of tumor emboli in inflammatory breast carcinoma. Oncogene. 21:3631–43
125. Van der Auwera I, Van Laere SJ, Van den Eynden GG, Benoy I, van Dam P, Colpaert CG, Fox SB, Turley H, Harris AL, Van Marck EA, Vermeulen PB, Dirix LY (2003) Inflammatory breast cancer shows angiogenesis with high endothelial proliferation rate and strong E-cadherin expression. Br J Cancer. 88:718–25
126. Van der Auwera I, Van Laere SJ, Van den Eynden GG, Benoy I, van Dam P, Colpaert CG, Fox SB, Turley H, Harris AL, Van Marck EA, Vermeulen PB, Dirix LY (2004) Increased angiogenesis and lymphangiogenesis in inflammatory versus noninflammatory breast cancer by real-time reverse transcriptase-PCR gene expression quantification. Clin Cancer Res. 10:7965–71
127. Kleer CG, Van Golen KL, Merajver SD (2002) Molecular biology of breast cancer metastasis Inflammatory breast cancer:clinical syndrome and molecular determinants. Breast Cancer Res. 2:423–9
128. Shirakawa K, Tsuda H, Heike Y, Kato K, Asada R, Inomata M, Sasaki H, Kasumi F, Yoshimoto M, Iwanaga T, Konishi F, Terada M, Wakasugi H (2001) Absence of endothelial cells, central necrosis and fibrosis are associated with aggressive inflammatory breast cancer. Cancer Res. 61:445–51
129. Van der Auwera I, Van den Eynden GG, Colpaert CG, Van Laere SJ, van Dam P, Van Marck EA, Dirix LY, Vermeulen PB (2005) Tumor lymphangiogenesis in inflammatory breast carcinoma: a histomorphometric study. Clin Cancer Res. 11:7637–42
130. Katayose Y, Kim M, Rakkar AN, Li Z, Cowan KH, Seth P (1997) Promoting apoptosis: a novel activity associated

with the cylin-dependent kinase inhibitor p27. Cancer Res. 57:5441–5
131. Durand B, Gao FB, Raff M (1997) Accumulation of the cycline-dependent kinase inhibitor p27/kip1 and the timing of oligodendrocyte differentiation. EMBO J. 16:306–17
132. St Croix B, Florenes VA, Rak JW, Flanagan M, Bhattacharya N, Slingerland JM, Kerbel RS (1996) Impact of the cylin-dependent kinase inhibitor p27kip1 on resistance of tumor cells to anti cancer agents. Nat Med. 2:1204–10
133. Gonzalez-Angulo AM, Guarneri V, Gong Y, Cristofanilli M, Morales-Vasquez F, Sneige N, Hortobagyi GN, Esteva FJ (2006) Downregulation of the cyclin-dependent kinase inhibitor p27kip1 might correlate with poor disease-free and overall survival in inflammatory breast cancer. Clin Breast Cancer. 7:326–30
134. van Golen KL, Davies S, Wu ZF, Wang Y, Bucana CD, Root H, Chandrasekharappa S, Strawderman M, Ethier SP, Merajver SD (1995) A novel putative low-affinity insulin-like growth factor-binding protein LIBC (lost in inflammatory breast cancer), and RhoC GTPase correlate with the inflammatory breast cancer phenotype. Clin Cancer Res. 5:2511–9
135. Ridley AJ (1997) The GTP-binding protein Rho. Int J Biochem Cell Biol. 29:1225–9
136. van Golen KL, Wu ZF, Qiao XT, Bao LW, Merajver SD (2000) RhoC GTPase, a novel transforming oncogene for human mammary epithelial cells that partially recapitulates the inflammatory breast cancer phenotype. Cancer Res. 60: 5832–8
137. van Golen KL, Wu ZF, Qiao XT, Bao L, Merajver SD (2000) RhoC GTPase overexpression modulates induction of angiogenic factors in breast cells. Neoplasia. 2:418–25
138. Kleer CG, Zhang Y, Pan Q, van Golen KL, Wu ZF, Livant D, Merajver SD (2002) WISP3 is a novel tumor suppressor gene of inflammatory breast cancer. Oncogene. 21:3172–80
139. Kleer CG, Zhang Y, Pan Q, Gallagher G, Wu M, Wu ZF, Merajver SD (2004) WISP3 and RhoC guanosine triphosphatase cooperate in the development of inflammatory breast cancer. Breast Cancer Res Treat. 6:110–5
140. Van Laere SJ, Van den Eynden GG, Van der Auwera I, Vandenberghe M, van Dam P, Van Marck EA, van Golen KL, Vermeulen PB, Dirix LY (2006) Identification of cell-of-origin breast tumor subtypes in inflammatory breast cancer by gene expression profiling. Breast Cancer Res Treat. 95:243–55
141. Bertucci F, Finetti P, Rougemont J, Charafe-Jauffret E, Nasser V, Loriod B, Camerlo J, Tagett R, Tarpin C, Houvenaeghel G, Nguyen C, Maraninchi D, Jacquemier J, Houlgatte R, Birnbaum D, Viens P (2004) Gene expression profiling for molecular characterization of inflammatory breast cancer and prediction of response to chemotherapy. Cancer Res. 64:8558–65
142. Bertucci F, Finetti P, Rougemont J, Charafe-Jauffret E, Nasser V, Loriod B, Camerlo J, Tagett R, Tarpin C, Houvenaeghel G, Nguyen C, Maraninchi D, Jacquemier J, Houlgatte R, Birnbaum D, Viens P (2005) Gene expression profiling identifies molecular subtypes of inflammatory breast cancer. Cancer Res. 65:2170–8
143. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS, Thorsen T, Quist H, Matese JC, Brown PO, Botstein D, Eystein Lønning P, Børresen-Dale AL (2001) Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA. 98: 10869–74
144. Van Laere S, Van der Auwera I, Van den Eynden G, Van Hummelen P, van Dam P, Van Marck E, Vermeulen PB, Dirix L (2005) Identification of cell-of-origin breast tumor cell subtypes in inflammatory breast cancer by gene expression profiling. Br J Cancer. 97:1165–74
145. Hortobagyi GN, Ames FC, Buzdar AU, Kau SW, McNeese MD, Paulus D, Hug V, Holmes FA, Romsdahl MM, Fraschini G et al (1988) Management of stage III primary breast cancer with primary chemotherapy, surgery, and radiation therapy. Cancer. 62:2507–16
146. Perloff M, Lesnick GJ, Korzun A, Chu F, Holland JF, Thirlwell MP, Ellison RR, Carey RW, Leone L, Weinberg V et al (1988) Combination chemotherapy with mastectomy or radiotherapy for stage III breast carcinoma: a Cancer and Leukemia Group B study. J Clin Oncol. 6:261–9
147. Piccart MJ, de Valeriola D, Paridaens R, Balikdjian D, Mattheiem WH, Loriaux C, Arrigo C, Cantraine F, Heuson JC (1988) Six-year results of a multimodality treatment strategy for locally advanced breast cancer. Cancer. 62:2501–6
148. Bedwinek J, Rao DV, Perez C, Lee J, Fineberg B (1982) Stage III and localized stage IV breast cancer: irradiation alone vs irradiation plus surgery. Int J Radiat Oncol Biol Phys. 8:31–6
149. Conte PF, Alama A, Bertelli G, Canavese G, Carnino F, Catturich A, Di Marco E, Gardin G, Jacomuzzi A, Monzeglio C et al (1987) Chemotherapy with estrogenic recruitment and surgery in locally advanced breast cancer: clinical and cytokinetic results. Int J Cancer. 40:490–4
150. Hobar PC, Jones RC, Schouten J, Leitch AM, Hendler F (1988) Multimodality treatment of locally advanced breast carcinoma. Arch Surg. 123:951–5
151. Gonzalez-Angulo AM, Hennessy BT, Broglio K, Meric-Bernstam F, Cristofanilli M, Giordano SH, Buchholz TA, Sahin A, Singletary SE, Buzdar AU, Hortobágyi GN (2007) Trends for inflammatory breast cancer: is survival improving? Oncologist. 12:904–12
152. Panades M, Olivotto IA, Speers CH, Shenkier T, Olivotto TA, Weir L, Allan SJ, Truong PT (2006) Evolving treatment strategies for inflammatory breast cancer: a population-based survival analysis. J Clin Oncol. 20:1941–50
153. Cristofanilli M, Valero V, Buzdar AU, Kau SW, Broglio KR, Gonzalez-Angulo AM, Sneige N, Islam R, Ueno NT, Buchholz TA, Singletary SE, Hortobagyi GN (2007) Inflammatory breast cancer (IBC) and patterns of recurrence: understanding the biology of a unique disease. Cancer. 110:1436–44
154. Pouillart P, Palangie T, Jouve M, Garcia-Giralt E, Vilcoq JR, Bataini JP, Calle R, Fenton J, Mathieu G, Rousseau J, Asselain B (1981) Inflammatory breast carcinoma treated with a combination of chemotherapy and radiation therapy. Results of a randomized trial studying the therapeutic role of an immunotherapy with BCG. Bull Cancer. 68:171–86
155. Krutchik AN, Buzdar AU, Blumenschein GR, Hortobagyi GN, Tashima CK, Gutterman JU, Yap HY, Hersh EM (1979) Combined chemoimmunotherapy and radiation therapy of inflammatory breast carcinoma. J Surg Oncol. 11:325–32

156. Zylberberg B, Salat-Baroux J, Ravina JH, Dormont D, Amiel JP, Diebold P, Izrael V (1982) Initial chemoimmunotherapy in inflammatory carcinoma of the breast. Cancer. 49:1537–43
157. Loprinzi CL, Carbone PP, Tormey DC, Rosenbaum PR, Caldwell W, Kline JC, Steeves RA, Ramirez G (1984) Aggressive combined modality therapy for advanced local-regional breast carcinoma. J Clin Oncol. 2:157–63
158. Fastenberg NA, Martin RG, Buzdar AU, Hortobagyi GN, Montague ED, Blumenschein GR, Jessup JM (1985) Management of inflammatory carcinoma of the breast. A combined modality approach. Am J Clin Oncol. 8:134–41
159. Keiling R, Guiochet N, Calderoli H, Hurteloup P, Krzisch C (1985) Preoperative chemotherapy in the treatment of inflammatory breast cancer. Prog Clin Biol Res. 201:95–104
160. Ferreire JP (1986) Resusltats du traitement des cancers inflammatoires du sein par une association therapeutique comportant une chimiotherapie initiale. In: Jacquillat C, Weil M, Khayat D (eds) Neo-adjuvant chemotherapy. John Libbey, London
161. Israel L, Breau JL, Morere JF (1988) Neo-adjuvant chemotherapy without radiation therapy in inflammatory breast cancer carcinoma. In: Jacquillat C, Weil M, Khayat D (eds) Neo-adjuvant chemotherapy. John Libbey, Paris
162. Pourny C (1986) Traitements par chimiotherapie premiere de cancers du sein MO, localement advances (T3T4) ou s'accompagnant de signes inflammatoires locaux. In: Jaquillat C, Weil M, Khayat D (eds) Neo-adjuvant chemotherapy. John Libbey, London
163. Alberto P, Schafer P, Mermillod B (1986) Traitement combine descancers inflammatoires du sein par chimotherapie suivie de chirurgie et de radiotherapie. In: Jaquillat C, Weil M, Khayat D (eds) Neo-adjuvant chemotherapy. John Libbey, London
164. Jaquillat C, Weil M, Auclerc G (1986) Neo-adjuvant chemotherapy in the conservative management of breast cancers: study on 205 patients. In: Jaquillat C, Weil M, Khayat D (eds) Neo-adjuvant chemotherapy. John Libbey, London
165. Thoms WW Jr, McNeese MD, Fletcher GH, Buzdar AU, Singletary SE, Oswald MJ (1989) Multimodal treatment for inflammatory breast cancer. Int J Radiat Oncol Biol Phys. 17:739–45
166. Swain SM, Lippman ME. Treatment of patients with inflammatory breast cancer. Important Adv Oncol. 1989:129–50
167. Rouëssé J, Sarrazin D, Spielmann M, Le Chevalier T, Oudinot P, Guasch Jordan I, Mouriesse H, Levin FM (1989) Treatment of inflammatory cancer of the breast. Combined chemotherapy and radiotherapy. Apropos of 270 women treated at the Institut Gustave-Roussy. Bull Cancer. 76:87–92
168. Maloisel F, Dufour P, Bergerat JP, Herbrecht R, Duclos B, Boilletot A, Giron C, Jaeck D, Haennel P, Jung G et al (1990) Results of initial doxorubicin, 5-fluorouracil, and cyclophosphamide combination chemotherapy for inflammatory carcinoma of the breast. Cancer. 65:851–5
169. Koh EH, Buzdar AU, Ames FC, Singletary SE, McNeese MD, Frye D, Holmes FA, Fraschini G, Hug V, Theriault RL et al (1990) Inflammatory carcinoma of the breast: results of a combined-modality approach–M.D. Anderson Cancer Center experience. Cancer Chemother Pharmacol. 27: 94–100
170. Arriagada R, Mouriesse H, Spielmann M, Mezlini A, Oudinot P, le Chevalier T, Cuvier C, Fontaine F, Travagli JP, May-Levin F et al (1990) Alternating radiotherapy and chemotherapy in non-metastatic inflammatory breast cancer. Int J Radiat Oncol Biol Phys. 19:1207–10
171. Mourali N, Tabbane F, Muenz LR, Behi J, Ben Moussa F, Jaziri M, Levine PH (1990) Ten-year results utilizing chemotherapy as primary treatment in nonmetastatic, rapidly progressing breast cancer. Cancer Invest. 11:363–70
172. Chevallier B, Roche H, Olivier JP, Chollet P, Hurteloup P (1993) Inflammatory breast cancer. Pilot study of intensive induction chemotherapy (FEC-HD) results in a high histologic response rate. Am J Clin Oncol. 16:223–8
173. Fein DA, Mendenhall NP, Marsh RD, Bland KI, Copeland EM 3rd, Million RR (1994) Results of multimodality therapy for inflammatory breast cancer: an analysis of clinical and treatment factors affecting outcome. Am Surg. 60: 220–5
174. Ueno NT, Buzdar AU, Singletary SE, Ames FC, McNeese MD, Holmes FA, Theriault RL, Strom EA, Wasaff BJ, Asmar L, Frye D, Hortobagyi GN (1997) Combined-modality treatment of inflammatory breast carcinoma: twenty years of experience at M.D. Anderson Cancer Center. Cancer Chemother Pharmacol. 40:321–9
175. Curcio LD, Rupp E, Williams WL, Chu DZ, Clarke K, Odom-Maryon T, Ellenhorn JD, Somlo G, Wagman LD (1999) Beyond palliative mastectomy in inflammatory breast cancer–a reassessment of margin status. Ann Surg Oncol. 6:249–54
176. Arthur DW, Schmidt-Ullrich RK, Friedman RB, Wazer DE, Kachnic LA, Amir C, Bear HD, Hackney MH, Smith TJ, Lawrence W Jr (1999) Accelerated superfractionated radiotherapy for inflammatory breast carcinoma: complete response predicts outcome and allows for breast conservation. Int J Radiat Oncol Biol Phys. 44:289–96
177. De Boer RH, Allum WH, Ebbs SR, Gui GP, Johnston SR, Sacks NP, Walsh G, Ashley S, Smith IE (2000) Multimodality therapy in inflammatory breast cancer: is there a place for surgery? Ann Oncol. 11:1147–53

Preoperative (Neoadjuvant) Systemic Therapy

22

Kathrin Schwedler and Manfred Kaufmann

22.1 Introduction

Neoadjuvant systemic therapy today has become a widely accepted standard therapeutical approach for early breast cancer [1–3].

The concept was first used to treat patients with locally advanced or inoperable breast cancer, to induce tumor response to decrease tumor mass and improve surgical conditions.

Showing promising results, the concept was extended to patients with less advanced tumors with the aim to increase the number of breast-conserving surgery (BCS) by further reducing tumor mass and treating occult systemic disease prior to the locoregional component.

Chemotherapy regimens should be similar to those established in the postoperative adjuvant setting.

Today, the neoadjuvant approach is used for four major reasons:

- Increasing rates of BCS by reduction of tumor size
- Elimination of possible distant micro-metastases
- Receipt of early information on response or resistance to chemotherapy by "in vivo assay"
- Reduction of mortality from breast cancer with reduced toxicity

22.2 Neoadjuvant Systemic Chemotherapy (NST)

Meanwhile, large phase-III randomized clinical trials have compared the pre- and postoperative use of well-established chemotherapy regimens (Table 22.1).

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In the NSABP B-18 trial, more than 1,500 patients with primary breast cancer were randomized to 4 cycles of adriamycine/cyclophosphamide either before or after surgery.

In the neoadjuvant setting, the clinical response rate (cRR) was 80%, complete clinical response (cCR) occurred in 36% of the patients and complete pathological response (cPR) in 13%, respectively.

Four percent of patients with cPR had residual ductal carcinoma in situ (DCIS), what emphasizes the necessity of surgery even after complete decline in medical imaging.

The rate of BCS was 67% in the group of neoadjuvant treated patients which was significantly higher than the control group (60%).

At present, follow-up of the patients still shows no difference between the neoadjuvant or adjuvant setting in terms of overall survival (OS).

Merely locoregional recurrence rates were higher in the subgroup of those patients, who had an initial indication for mastectomy, but underwent BCS after good clinical response (15 vs. 7%) [4–6].

Anthracycline-based regimens showed improved survival rates compared to local treatment for advanced or inflammatory breast cancer.

Consecutively, results for the adriamycine/cyclophosphamide combination in the NSABP B-18 trial were confirmed for other anthracycline-containing regimens [7–9].

A cPR during neoadjuvant chemotherapy is an important predictive marker for a significant improvement of DFS [10, 11].

Well-established prognostic factors like tumor size, nodal status or patient´s age also apply for the neoadjuvant strategy.

Recent meta-analyses affirmed the results of neoadjuvant settings and showed equivalent data for death, disease progression and distant recurrence [12].

I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases*,
DOI: 10.1007/978-3-540-69743-5_22, © Springer-Verlag Berlin Heidelberg 2010

Table 22.1 BCS rates after adjuvant and neoadjuvant systemic chemotherapy (NST)

Trial	N patients	Regimen	BCS rate (%) adjuvant setting	BCS rate (%) neoadjuvant setting
NSABP B-18 [4]	1,523	AC	60	67
ECTO [8, 9]	1,355	AP-CMF	34	65
EORTC [7]	448	FEC	21	37
Scholl [46]	414	FAC	77	82
NSABP B-27[47]	2,411	AC/AC-Doc	–	61/63
Untch AGO [48]	631	EP/E-P	–	50/61
GeparDuo [49]	913	ddADoc/AC-Doc	–	66/75
GeparTrio [50]	2,090	DAC/TAC-NX	–	73
Smith [51]	104	CVAP/CVAP-P	–	48/67
Penault-Llorca [52]	200	AC/AT	–	45/56
Buzdar [53]	174	FAC/P	–	46/48

AC adriamycin, cyclophosphamide; *P* paclitacel; *MF* methotrexate, fluorouracil; *E* epirubicin; *Doc* docetacel; *dd* dose-dense; *D* docetacel; *T* taxotere; *Nx* capecitabine; *V* vincristine

Merely locoregional recurrences occurred more frequently in the neoadjuvant chemotherapy arms with a hazard ratio of approximately 1.2.

For the most part, this greater risk was attributed to those trials that did not demand surgery after a cCR but used radiotherapy alone, which means that surgery is also necessary for pCR patients.

22.3 Taxane-based Neoadjuvant Chemotherapy Regimens

The superiority of taxane-based adjuvant therapies, especially in patients with positive nodal status was proven by a large number of randomized clinical trials [13]. Furthermore, there is already good evidence for the weekly vs. three-weekly application of docetaxel or paclitaxel [14].

The largest study evaluating the addition of docetaxel to a neoadjuvant anthracycline-based chemotherapy (NSABP-27 trial: AC-Doc –OP vs. AC-OP vs. AC-OP-Doc) was able to show a significant increase of response rates in the taxane-containing setting (cRR 91 vs. 85%; pCR 26 vs. 14%).

Nevertheless, the addition of a taxane after neoadjuvant chemotherapy and surgery did not lead to an improvement of either BCS-rate, DFS or OS.

There is analog data for a variety of taxane-based regimens like CVAP or TAC.

Most notably, clinical response after the first two cycles seems to correlate significantly with a good overall response and a high cPR rate.

No further benefit was shown for patients who were switched to a noncross-resistant regimen after minor response on the anthracycline-taxane-based standard (GeparTrio-trial) [15].

The addition of a secondary postoperative chemotherapy after minor response in the neoadjuvant setting does not lead to a better individual outcome.

Basically, data seem to support the use of both an anthracycline and a taxane to accomplish a maximum reduction of tumor size.

Combined or sequential use of the two substance groups are both acceptable.

The sequential application of the taxane after the anthracycline was associated with better response rates in the neoadjuvant setting (pCR 22 vs. 11% GeparDuo-trial). Furthermore, sequential therapy regimens seem to provide better BCS rates than combination therapy (75 vs. 66% GeparDuo-trial). Combination therapy is associated with increased myelosuppression.

At least, the question remains unanswered, whether the observed benefit is a result of the sequential use or because of the differences in total delivered doses of

cytostatics, which are usually higher in the sequential setting, and the longer treatment duration.

Dose-dense regimens in the neoadjuvant setting may lead to improved clinical outcomes in patients with high-risk primary breast cancer although the treatment is less well tolerated [16].

Analogous to the results of adjuvant taxane-based trials, docetaxel should be administered in three-weekly intervals and paclitaxel in weekly intervals, respectively.

22.4 Neoadjuvant Targeted Therapy

The Her2-receptor belongs to a group of human epidermal growth factors. It is overexpressed in circa 25–30% of primary breast cancers.

Trastuzumab is a humanized receptor antibody directed against Her2, which has been proven to lead to an improved OS and DFS both in the metastasized situation and the adjuvant setting [17].

There are only a few evidences for the neoadjuvant use of trastuzumab. In some small phase II trials, the addition of the antibody leads to significantly higher pCR rates [18, 19].

A randomized phase three trial to assess the primary systemic use of the antibody was closed early because of the superiority of the trastuzumab-chemotherapy-combination in an early interims analysis. cPR rates in this treatment-group were significantly higher (65 vs. 26%) despite no differences in the observed BCS rates (57 vs. 53%) [20, 21].

The concomitant application of trastuzumab and an anthracycline seems to be safe as already demonstrated in several trials [22]. Nevertheless, this combination should still be reserved to study treatment until more follow-up data is available.

At present, the combination of trastuzumab with an anthracycline-based regimen should contain anthracyclines with a lower cardiac toxicity (e.g., epirubicin, pegylated doxorubicin).

The toxicity of concomitant vs. sequential administration of trastuzumab with an anthracycline is currently under evaluation in the ACOSOG 1041 trial.

It remains still unknown whether neoadjuvant trastuzumab has an impact on DFS and OS or whether its preoperative use is superior to the adjuvant setting.

Ongoing studies will answer these questions in the near future.

22.5 Influence of Histologic Subtypes on the Response of Neoadjuvant Systemic Treatment

Negative hormone receptor status is one of the strongest predictors for a good chemo-sensitivity. pCR rates in this group exceed 40% [23].

In contrast, high ER/PR levels appeared to correlate with a lower pCR rate.

Tumors with a high nuclear grading were found to be more sensitive to neoadjuvant chemotherapy compared to highly differentiated breast cancer.

The invasive lobular carcinoma (ILC) subtype is characterized by a more diffuse imaging in ultrasound and mammography. As a result, invasive lobular breast cancer tends to be diagnosed in an advanced stage – basically a primary systemic treatment would be a good offer for those patients [24, 25].

On an average, patients with ILC are older, the tumor is highly endocrine-responsive, Her2-negative and has a low nuclear grade.

Multicentric or bilateral disease is common.

Despite the less aggressive biological phenotype, DFS and OS were found to be similar to the invasive ductal carcinoma [26].

In the neoadjuvant setting, ILC are connected with significant lower cPR rates.

Therefore, patients with ILC should be given an adequate advise prior to a neoadjuvant systemic therapy with the intention to provide BCS.

22.6 Evaluation of Tumor Response after Neoadjuvant Systemic Treatment

An accurate monitoring of tumor extent by means of ultrasound and mammography as well as an accurate photodocumentation of the tumor localization on the patient´s skin [1] at baseline is inevitable in the neoadjuvant setting. Other options are tattoos on the skin or titanium clips into the center of the tumor [27] (Fig. 22.1).

Ultrasound correlates largely with the histological extent of the invasive tumor component whereas mammography focuses the in situ component if microcalcifications are present [28].

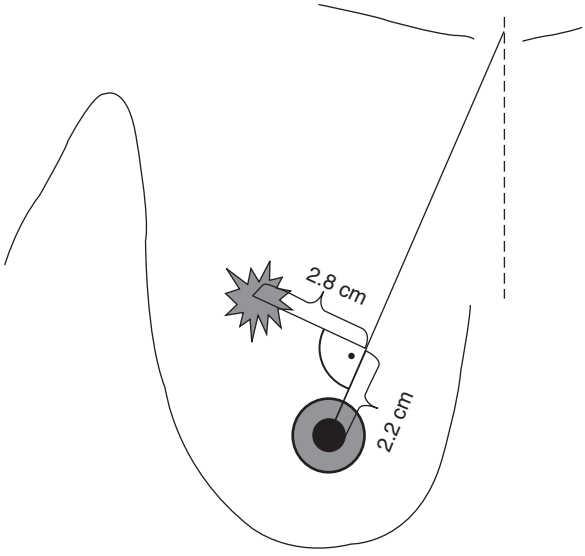

Fig. 22.1 Photodocumentation of tumor localization prior to neoadjuvant systemic therapy (acc.1)

In case of multicentricity, imprecise presentability in above-named imaging or invasive lobular disease, additionally performed magnetic resonance imaging (MRI) might be helpful to observe the tumor decline.

Early response evaluation, usually done by palpation and ultrasound imaging, should be performed after 6–9 weeks to recognize a cCR as soon as possible.

Nomograms were developed to predict pathologic response and metastasis-free survival, and can serve as a basis to integrate future biological markers into clinical models [29].

Tumor response can differ in the neoadjuvant systemic therapy – irrespective of the histologic subtype. A concentric diminution of the tumorous area or a more lumpy decomposition is possible.

It is not possible to make any predictions concerning the development of an individual tumor during a neoadjuvant treatment with present experience.

About 3% of all breast cancers are chemoresistant and increase during primary systemic therapy.

In those patients, a switch of treatment should be considered – either to a non cross-resistant regimen or to immediate surgical treatment.

After the completion of neoadjuvant chemotherapy, any initially performed diagnostic imaging should be repeated prior to surgery.

In case of missing presentation in mammography and ultrasound, ambiguous results or multicentricity, preoperative MRI, and if necessary, MRI-guided marking of the tumor residuals should be performed [30].

22.7 Breast Conserving Surgery (BCS)

The biggest advantage of neoadjuvant systemic therapy certainly is the reduction of tumor size – in many cases, a precondition for a BCS.

Twenty-five to thirty percent of patients who are initially considered candidates for mastectomy are able to undergo BCS after completion of neoadjuvant chemotherapy [4, 5, 7].

The BCS rate is higher in patients with complete or partial clinical response and who were treated at a competence center [31].

It is important that especially the surgeon sees the patient before, during and after the courses of neoadjuvant systemic treatment.

Surgery can be accomplished in new tumor margins. Nevertheless, the remission characteristics of the tumor do not always lead to conditions, which allow BCS.

In contrast to the invasive component of the breast cancer, which usually takes good remission during the systemic therapy, the intraductal part seems to be less influenceable. Margins defined as R0 are consistent with the primary operative setting.

The decision for BCS can be made irrespective of the histologic subtype of breast cancer. Inflammatory breast cancer and so far more than two multicentric disease or extensive micro-calcifications are indications for mastectomy [28].

Basically, any surgery within new tumor margins includes the risk of false-negative resection margins, for example in case of discontinuous remission. For this reason, any indication for mastectomy cannot be standardized but has to be made individually by the surgeon and not least, has to accommodate patient´s wishes.

22.8 Evaluation of the Axilla in the Neoadjuvant Treatment Setting

In the primary operative therapy, sentinel-node-biopsy (SLNB) is the method of choice for nodal staging in patients with no clinically and ultrasonographically conspicuous axillary lymph nodes (stage T1-3, N0, M0).

SLNB in the primary operative setting has an identification rate of 86–93%. The false-negative rate is 7–13% [32].

There is only few clinical data available for the neoadjuvant setting. Chemotherapy might influence first the SLN and later subsequent lymph nodes with occult tumorous affection. This may lead to an increased false-negative rate in the following surgery.

Available data for SLNB after neoadjuvant chemotherapy showed variable detection rates (84–95%). False-negative rates had a range of 0–33% [33–35].

Patients with clinically affected lymph nodes at beginning of any preoperative chemotherapy should require an axillary lymph node dissection with a sampling of at least ten lymph nodes. However, primary systemic treatment sterilizes approximately 25% of initially positive lymph nodes.

These patients may be over-treated by a complete axillary dissection (ALND). Several trials showed a very high false-negative rate in this group. For this reason, ALND seems to be the method of choice. Those patients who demand SLNB after preoperative systemic treatment should be informed about the lack of data for this approach.

SLNB before preoperative chemotherapy may be an appropriate alternative. The proportion of patients with T1-stage and clinically negative, but histologically involved lymph nodes is up to 30% [36].

The main disadvantage of this approach is the additional surgery with the risk of infection or wound healing disorders, and a subsequent delay of therapy.

Furthermore, this approach will probably not have any influence on the therapeutic decision for systemic treatment. An initially positive nodal status may be an indication for postmastectomy radiotherapy.

Further investigation on this question in larger trials is required.

22.9 Radiation Therapy after Neoadjuvant Systemic Therapy

Radiotherapy and systemic treatment are independent factors with a significant value concerning the outcome of patients with operable breast cancer.

Analog to the primary operative setting, radiotherapy after BCS is obligatory to prevent locoregional recurrences [28, 37, 38].

Postmastectomy radiation therapy is beneficial in patients with an initial T3 or T4 tumor, even in those who subsequently achieved a good remission, because the locoregional recurrence rate remains high in this group.

Even in case of a cCR, radiotherapy alone cannot substitute surgery as histologically detected tumor residuals can be found in up to 30% of patients [39].

Radiotherapy of lymphatic vessels commonly conforms to postoperative nodal status and should be indicated in case of four or more positive axillary lymph nodes.

In this subgroup of patients, 10-year locoregional recurrence rates add up to 30% [40].

Radiation of lymphatic vessels should also be considered in patients who present initially with clinically positive lymph nodes, even after decrease of altered lymph nodes during neoadjuvant systemic therapy.

22.10 Neoadjuvant Systemic Endocrine Therapy

As an alternative to neoadjuvant chemotherapy, neoadjuvant endocrine therapy is an option mainly for postmenopausal women with highly endocrine responsive breast cancer.

Tumor characteristics should include e.g., high ER/PR sensitivity, low nuclear grade or low Ki67 [23].

Semiglazov et al compared 3 month of preoperative hormonal treatment (anastrozole and exemestane) to a neoadjuvant taxane-based chemotherapy (4 × AT). Results were similar in terms of cRR (79 vs. 76%) [41].

Data to evaluate the efficacy of neoadjuvant tamoxifen vs. different aromatase inhibitors is also available.

Neoadjuvant endocrine therapy with aromatase inhibitors seems to be more effective than tamoxifen treatment in terms of cRR and BCS rate [42, 43] (Table 22.2).

Basically, the pCR rates in the neoadjuvant endocrine setting are very low. After 3-month of tamoxifene therapy, cPR rates range at about 2%, even treatment with aromatase inhibitors is not associated with a significant higher benefit (5% cPR rate).

There are data suggesting that a prolonged (4–6 months) administration of preoperative hormonal therapy is associated with higher response rates up to 10% [44].

Table 22.2 BCS rates after neoadjuvant endocrine therapy

Trial	N patients	Regimen	BCTrate (%)
Eiermann [42]	337	Letrozole/Tamoxifen	45/35
Smith [54]	330	Anastrozole/Tamoxifen/ Anastrozol + Tamoxifen	46/22/26
Gil [55]	55	Exemestane	42
Paepke [56]	33	Letrozole 4 monthsLetrozole 8 months	67
Semiglazov [41]	121	Chemotherapy/Anastrozole/Exemestane	24/32/34

In summary, the neoadjuvant endocrine treatment seems to be an option for those patients who are not candidates for neoadjuvant or adjuvant chemotherapy or have contraindications for surgery because of comorbidities, a poor general condition or advanced age.

22.11 Conclusions

Neoadjuvant systemic therapy should be considered if postoperative adjuvant chemotherapy is also indicated.

The same regimens can be used in the neoadjuvant and adjuvant therapeutical setting – this was recently affirmed at the St Gallen 2009 Expert Consensus Conference [45].

Main objective of the neoadjuvant approach is to increase the rate [45] of BCS and to ameliorate operative options, respectively.

Neoadjuvant chemotherapy is less effective in patients with a low proliferating, highly differentiated and endocrine responsive breast cancer. ILCs, a low Ki-67 value tend to lead to minor response as well.

In these cases, one should discuss whether chemotherapy is indicated and useful.

The treatment duration should envelop a period of at least 18 weeks. After completion of a neoadjuvant setting, no postoperative chemotherapy is indicated. The surgery should take place 2–4 weeks after the last cycle and can be performed within new tumor margins.

Neoadjuvant endocrine therapy is particularly an option for patients with highly endocrine-sensitive tumors who have contraindications for any surgical approach.

The duration of therapy should be at least 4–8 months.

Neoadjuvant systemic therapies offer new treatment options and provide the opportunity to investigate new prognostic and predictive markers as well as to study breast cancer biology, and to develop new effective anticancer drugs.

References

1. Kaufmann M, Goldhirsch A, Hortobagyi GH et al (2006) International expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: an update. J Clinc Oncol. 23:2600–8
2. Kaufmann M, von Minckwitz G, Bear HD et al (2007) Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new per spectives 2006. Ann Oncol. 18(2):1927–34
3. Gralow JR, Burstein HJ, Wood W et al (2008) Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease. J Clinc Oncol. 26:814–9
4. Fisher B, Brown A, Mamounas E et al (1997) Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from national surgical adjuvant breast and bowel project B-18. J Clin Oncol. 15:2483–3
5. Fisher B, Bryant J, Wolmark N et al (1998) Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol. 16:2672–85
6. Wolmark N, Wang J, Mamounas E, et al Preoperative chemotherapy in patients with operable breast cancer: nine-year results from national surgical adjuvant breast and bowel project B-18. J Natl Cancer Inst Monogr. 2001;(30):96–102
7. van der Hage JA, van de Velde CJ, Julien JP et al (2001) Preoperative chemotherapy in primary operable breast cancer: results from the European organization for research and treatment of cancer trial 10902. J Clin Oncol. 19:4224–37
8. Gianni L, Baselga L, Eiermann W et al (2005) Feasibility and tolerability of sequential doxorubicin/paclitaxel followed by cyclophosphamide/methotrexate and fluorouracil and its effects on tumor response as preoperative chemotherapy. Clin Cancer Res. 11:8715–21

9. Gianni L, Baselga L, Eiermann W, et al European Cooperative Trial in Operable Breast Cancer (ECTO): improved freedom from progression (FFP) from adding paclitaxel (T) to doxorubicin (A) followed by cyclophosphamide methotrexate and fluorouracil (CMF). Proc Am Soc Clin Oncol. 2005;37a
10. Bear HD, Anderson S, Smith RE, et al A randomized trial comparing preoperative doxorubicin/cyclophosphamide (AC) to preoperative AC followed by preoperative docetaxel (T) and to preoperative AC followed by postoperative T in patients with operable carcinoma of the breast: results of NSABP B-27. San Antonio Breast Cancer Symposium 2004, San Antonio Texas, December 8–11, 2004
11. Bear HD, Anderson S, Smith RE et al (2006) Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: national surgical adjuvant breast and bowel project protokol B-27. J Clin Oncol. 24:2019–27
12. Mauri D, Pavlidis N, Ioannidis JP (2005) Neoadjuvant versus adjuvant systemic treatment for breast cancer: a meta-analysis. J Natl Cancer Inst. 97:188–94
13. Evans TR, Yellowlees A, Foster E et al (2005) Phase III randomized trial of doxorubicin and docetaxel versus doxorubicin and cyclophosphamide primary medical therapy in women with breast cancer: an anglo-celtic cooperative oncology group study. J Clin Oncol. 23:2988–95
14. Green MC, Buzdar AU, Smith T et al (2005) Weekly paclitaxel improves pathologic complete remission inoperable breast cancer when comparend with paclitaxel once every three weeks. J Clin Oncol. 23:5983–92
15. von Minckwitz G, Blohmer JU, Loehr A, et al Comparison of docetaxel/doxorubicin/cyclophosphamide (TAC) versus vinorelbine/capecitabine (NX) in patients non-responding to 2 cycles of neoadjuvant TAC chemotherapy – first results of the phase III GEPARTRIO-Study by the German breast group
16. Untch M, Möbus V, Kuhn W, et al Intensive dose-dense compared with conventionally scheduled preoperative chemotherapy for high-risk primary breast cancer. J Clin Oncol 2009; Apr 13. San Antonio Breast Cancer Symposium 2005, San Antonio, Texas, December 8–12, 2005
17. Seidman AD, Bery D, Cirrinicione C et al (2004) CALGB 9840: phase III study of weekly paclitaxel via 1-hour infusion versus standard 3h infusion every third week in treatment of metastatic breast cancer, with trastuzumab for Her2-positiveMBC and randomized for T in Her2 normal MBC. Proc Am Soc Clin Oncol. 23:512a
18. Gralow JR, Burstein HJ, Wood W et al (2008) Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease. J Clin Oncol. 26:814–9
19. Gianni L, Semiglazov V, Manikhas GM, et al Neoadjuvant trastuzumab plus doxorubicin, paclitaxel, and CMF in locally advanced breast cancer (NOAH-trial): Feasibility, safety, and anti-tumor effects. Proc Am Soc Clin Oncol Breast Cancer Symposium. 2007;10s (abstr 532)
20. Buzdar AU, Ibrahim NK, Francis D et al (2005) Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol. 23:3676–85
21. von Minckwitz G, Kaufmann M, Kümmel S, et al Integrated meta-analysis on 6402 patients with early breast cancer receiving neoadjuvant anthracycline-taxane +/- trastuzumab containing chemotherapy. San Antonio Breast Cancer Symposium 2008; (abstr 79)
22. Buzdar AU, Valero V, Ibrahim NK et al (2007) Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. Clin Cancer Res. 13:228–33
23. Colleoni M, Viale G, Zahrieh D et al (2008) Expression of ER, PgR, Her1, Her2, and response: a study of preoperative chemotherapy. Ann Oncol. 19:465–72
24. Cristofanilli M, Gonzalez-Angulo A, Sneige N et al (2005) Invasive lobular carcinoma classic type: response to primary chemotherapy and survival outcomes. J Clin Oncol. 23:41–8
25. Wenzel C, Bartsch R, Hussian D et al (2007) Invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) of breast differ in response following neoadjuvant therapy with epidoxorubicinn and docetaxel+G-CSF. Breast Cancer Res Treat. 104:109–14
26. Arpino G, Bardou VJ, Clark GM et al (2004) Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res. 6:R149–56
27. von Minckwitz G, Raab G, Caputo A et al (2005) Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO study of the German breast group. J Clin Oncol. 23:2676–85
28. Kaufmann M, Morrow M, von Minckwitz G, R. Harris Loco-regional treatment of primary breast cancer: consensus recommendations from an international expert panel. Cancer. 2009 (in press)
29. Rouzier R, Pusztai L, Delaloge S et al (2005) Nomograms to predict pathologic complete response and metastasis-free survival after preoperative chemotherapy for breast cancer. J Clin Oncol. 23:8331–9
30. Manton DJ, Chaturvedi A, Hubbard A et al (2006) Neoadjuvant chemotherapy in breast cancer: early response prediction with quantitative MR imaging and spectroscpoy. Br J Cancer. 94:427–35
31. Loibl S, von Minckwitz G, Raab G et al (2006) Surgical procedures after neoadjuvant chemotherapy in operable breast cancer – results of the GEPARDUO trial. Ann Surg Oncol. 13:1434–42
32. McMasters KM, Tuttle TM, Carlson DJ et al (2000) Sentinel lymph node biopsy for breast cancer: a suitable alternative to routine axillary dissection in multi-institutional practice when optimal technique is used. J Clin Oncol. 18:2560–6
33. Breslin TM, Cohen L, Sahin A et al (2000) Sentinel lymph node biopsy is accurate after neoadjuvant chemotherapy for breast cancer. J Clin Oncol. 18:3480–6
34. Julian TB, Patel N, Dusi D et al (2001) Sentinel lymph node biopsy after neoadjuvant chemotherapy for breast cancer. Am J Surg. 182:407–10
35. Mamounas EP, Brown A, Anderson S et al (2005) Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer. Results from national surgical adjuvant breast and bowel project protocol B-27. J Clin Oncol. 23:2694–702

36. Pockaj BA, Gray RJ (2004) Surgical management of locally advanced breast cancer. J Clin Oncol. 22:85–91
37. Clarke M, Collins R, Darby S et al (2005) Early breast cancer trialists´collaborative group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Lancet. 366:2087–106
38. Recht A, Edge SB, Solin LJ et al (2001) Postmastectomy radiotherapy: clinical practice guidelines of the American society of clinical oncology. J Clin Oncol. 19:1539–69
39. Ring A, Webb A, Ashley S et al (2003) Is surgery necessary after complete clinical remission following neoadjuvant chemotherapy for early breast cancer? J Clin Oncol. 21:4540–5
40. Recht A, Gray R, Davidson NE et al (1999) Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: experience of the Eastern cooperative oncology group. J Clin Oncol. 17:1689–700
41. Semiglazov VF, Semiglazov V, Ivanov V et al (2004) The relative efficacy of neoadjuvant endocrine therapy versus chemotherapy in postmenopausal women with ER-positive breast cancer. J Clin Oncol. 23:7s
42. Eiermann W, Paepke S, Apfelstaedt J et al (2001) Preooperative treatment of postmenopausal breast cancer patients with letrozole: a randomized double-blind multicenter study. Ann Oncol. 12:1527–32
43. Ellis MJ, Coop A, Singh B et al (2001) Letrozole is more effective neoadjuvant endocrine chemotherapy than tamoxifen for erbB-1-and/or erbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol. 19:3808–16
44. Mustacchi G, Ceccherini R, Milani S et al (2003) Tamoxifen alone versus adjuvant tamoxifen for operable breast cancer of the elderly: long-term results of the phase III randomized controlled multicenter GRETA trial. Ann Oncol. 14:414–20
45. Goldhirsch A, Ingle JN, Gelber RD, et al (2009) Thresholds for therapies: highlights of the International Consensus on the primary therapy of early breast cancer 2009. Ann Oncol. 20:1319–29
46. Scholl SM, Fourquet A, Asselain B et al (1994) Neoadjuvant versus adjuvant chemotherapy in premenopausal patients with tumors considered too large for breast conserving surgery: preliminary results of a randomized trial: S6. Eur J Cancer. 30A:645–52
47. NSABP (2001) The effect on primary tumor response of adding sequential taxotere to adriamycin and cyclophosphamide: preliminary results of the NSABP protocol B-27. Breast Cancer Res Treat. 69:210
48. Untch M, Konency G, Ditsch N et al (2002) Dose-dense sequential epirubicine-paclitaxel as preoperative treatment of breast cancer: results of a randomized AGO study. Proc Am Soc Clin Oncol. 21:133a
49. von Minckwitz G, Raab G, Schütte M, et al Dose-dense versus sequential Adriamycin/docetaxel combination as preoperative chemotherapy (pCHT) in operbale breast cancer (T2-3, N0-2, M0): primary endpoint analysis of the GEPARDUO study. Proc Am Soc Clin Oncol. 2003;21:43a (abstr 168)
50. von Minckwitz G, Blohmer JU, Raab G, et al Comparison of docetaxel/doxorubicin/cyclophosphamide (TAC) versus vinorelbine/capecitabine (NX) in patients non-responding to 2 cycles of neoadjuvant TAC chemotherapy – first results of the phase III GEPARTRIO-study by the German breast group. San Antonio Breast Cancer Symposium 2005
51. Smith IC, Heys SD, Hutcheon AW et al (2002) Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol. 20:1456–66
52. Penault-Llorca F, Sastre X, Fiche M et al (1999) Pathological response to neoadjuvant chemotherapy (CT): final results of a prospective randomized trial of 4AT vs. 4AC as induction therapy in patients with operable breast cancer using Sataloff classification. Breast Canc Res Treat. 57:67
53. Buzdar AU, Singletary SE, Theriault RL et al (1999) Prospective evaluation of paclitaxel versus combination chemotherapy with fluorouracil, doxorubicin and cyclophosphamide as neoadjuvant chemotherapy in patients with operable breast cancer. J Clin Oncol. 17:3412–7
54. Smith I, Dowsett M, Ebbs SR et al (2005) Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen or both in combination: the immediate preoperative Anastrozole, Tamoxifen or combined with tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol. 23:5108–16
55. Gil Gil A, Barnadas A, Cirera L, et al Primary hormonal therapy with exemestane in patients with breast tumors >3cm in diameter: results of a Spanish multicenter phase II trial. J Clin Oncol. 2004;23:28s (Suppl; abstr 603)
56. Paepke S, Tulusan A, Kiesel L et al (2003) A multicenter study of pre-operative treatment with letrozole for optimal duration of treatment in postmenopausal women with ER and/or PgR positive breast cancer. Proc Am Soc Clin Oncol. 22:80

Metastatic Breast Cancer

23

Tejal A. Patel and Edith A Perez

Metastatic breast cancer is a leading cause of morbidity and mortality that needs to be understood and conquered. Although fewer than 10% of patients with breast cancer initially present with the metastatic disease, it will eventually develop in a substantial proportion of them [1]. Therapy for metastatic breast cancer remains palliative. The average survival time after the diagnosis of metastatic breast cancer is 24 months, although it varies widely according to the metastatic site, biological characteristics, patient condition and treatment [1]. The median survival time traditionally has been lower for patients with visceral disease (6–13 months) compared with those with bone-only disease (18–30 months). There has been recent epidemiological data to suggest improvement in breast cancer mortality in the past 15 years in the United Kingdom and the United States [2]. One of the reports demonstrated that after adjustment of several factors, similar cohort of women diagnosed with metastatic breast cancer in late 1990s compared with early 1990s, had better survival by 30%. This was seen even though a greater proportion of women diagnosed in late 1990s had already been better treated and exposed to prior chemotherapy and biological treatments as part of adjuvant care.

Although definitive curative therapy for metastatic breast cancer is lacking for most patients, various therapies are used in an attempt to retard progression of disease, to ameliorate symptoms, and to improve the quality and duration of survival time. Therapeutic goals are directed at improving symptoms related to the cancer, response rates and prolongation of progression-free survival and overall survival times. Although Quality of life (QOL) measurements have been more recognized as important, no consensus exists with regard to the best way or questionnaire or instrument to accurately measure it. Retrospective reports of increasing number of women being treated systemically over the years and corresponding increasing survival suggest that systemic therapy for metastatic breast cancer is associated with improved survival.

The three biological parameters currently used for treatment decisions include estrogen receptor (ER), progesterone receptor (PR), and HER2. However, other specific factors are critical to the decision-making process, which are highlighted in Fig. 23.1. In general, hormonal approaches have classically included antiestrogens as well as aromatase inhibitors for the treatment of patients with ER-positive tumors who do not have rapidly progressive visceral or even nonvisceral disease. Although there is no rigid standard for the sequencing of therapy for the management of metastatic breast cancer, chemotherapy has a role in the treatment program for nearly all patients with this disease, as tumor progression to hormonal therapies eventually occurs in most patients. Chemotherapy-based treatments have been the initial choice for patients with negative estrogen (ER) status, with visceral disease, or with ER-positive disease who have tumor progression after endocrine therapy [3]. Multiple chemotherapeutic agents with different mechanisms of action and toxicity profiles are active in breast cancer. Improved objective response rates and improved duration of response compared with older therapies have been reported in studies, evaluating optimal dosing and sequencing of these newer agents, alone or in combination with other drugs.

Optimism has been renewed with the emergence of novel biologically-based treatment strategies. In addition to the well-defined improvements in the supportive care of patients with metastatic breast cancer, a

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_23, © Springer-Verlag Berlin Heidelberg 2010

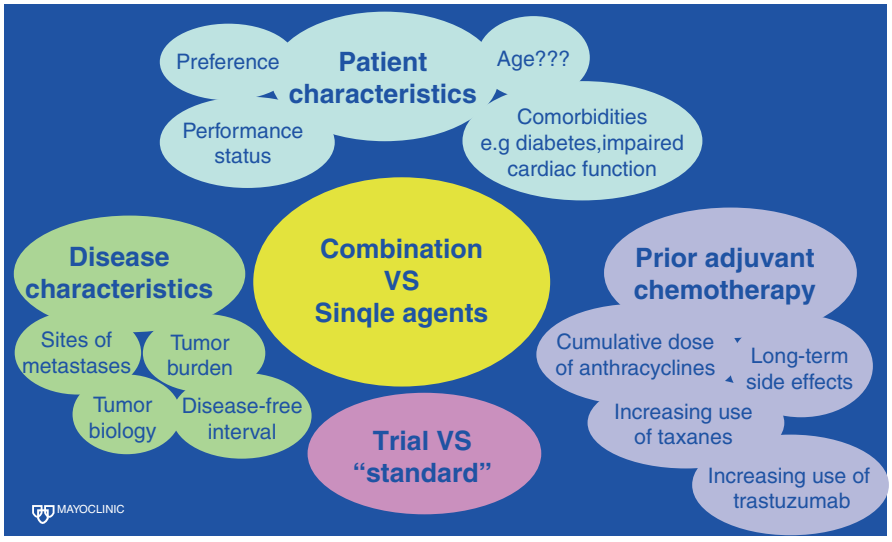

Fig. 23.1 Metastatic breast cancer: patient and disease influence treatment decisions

variety of new therapeutic agents with favorable therapeutic ratios became available recently. These agents include hormonal, chemotherapeutic and biological targeted therapies. How best to incorporate these new strategies into the current management of patients continue to be the focus of intensive and promising preclinical and clinical research. A humanized version of a murine antibody directed against the extracellular domain of HER2, and a small molecule inhibitor of tyrosine kinases HER1 and HER2 have been developed for the treatment of patients with breast cancer whose tumor over express HER2. A monoclonal antibody targeting the vascular endothelial growth factor (VEGF) has also been recently approved by regulatory agencies.

Current research focuses on investigation of biologic targets for primary or secondary prevention along with treatment options for patients who develop metastatic disease. Standard oncology outcomes of response, survival, and time to progression (TTP) remain important, along with recognition of the importance of evaluating surrogate markers of clinical efficacy, as well as QOL and time without symptoms or toxicity. New agents that are cytostatic or that inhibit tumor angiogenesis, metastasis, or invasion represent a challenge in the design of clinical trials in breast cancer. Because the predominant effect of these agents may be stabilization of tumor size or prevention of metastases, traditional radiographic response rates may be suboptimal to evaluate efficacy. Valid intermediate endpoints, including biologic correlates, will be important in dosage and scheduling of these agents and in determination of the clinical situation in which they should be evaluated. Data collected from surrogate studies involving methodologies such as positron emission tomography (PET), tumor biopsies before and after therapy may be relevant in this regard.

The material that follows addresses therapeutic options for patients with metastatic breast cancer, based on biological characteristics. They include hormonal therapy, chemotherapy and current available biological therapies. The chapter also covers supportive therapies, alternative therapies and mechanisms of drug resistance, as well as selected areas of ongoing research.

23.1 Hormonal Therapy

Stimulation for growth of breast carcinomas by estrogen is well established, and the aim of hormonal therapy is to interfere with this phenomenon. Several strategies have been used to inhibit estrogen-stimulated breast cancer growth; these act by one of two mechanisms: inhibition of estrogen action or inhibition of estrogen production.

Estrogen action can be systemically blocked using antiestrogens, such as selective estrogen receptor modulators (SERMs) or downregulators (SERDs) or aromatase inhibitors [4]. In premenopausal women, estrogen production can be blocked by ovarian ablation using surgery, irradiation, or by the use of luteinizing hormone-releasing hormone (LHRH) agonists [1, 4].

In postmenopausal women, estrogen production can be blocked using inhibitors of aromatase enzyme, which is responsible for extra-ovarian estrogen production after menopause [1]. Because hormonal therapy is generally well tolerated, it is an attractive treatment option for patients with metastatic breast cancer [1]. Approximately 40–50% of women with ER-positive metastatic breast cancer will respond to hormonal therapy (based on objective reduction of tumor size or stabilization of disease); predictive factors that are associated with response include degree of ER or PR expression, long disease-free interval, and nonvisceral disease, although many other biological factors appear to also play a role [1, 4].

23.1.1 Premenopausal

Historically, the first line of endocrine manipulation in metastatic premenopausal women was ovarian ablation by surgery or radiation [5]. In the late 1970s and early 1980s, studies demonstrated that tamoxifen, already known to be effective in postmenopausal breast cancer, was also active in premenopausal women with widespread disease [6].

Tamoxifen inhibits the growth of breast cancer cell by being competitive inhibitor of estrogen at its receptor but also has demonstrated other tissue-specific partial estrogen agonist activity. The agonist effects result in advantage (prevention of bone demineralization) or disadvantage (increased risk of uterine cancer and thromboembolic events). Due to its selective target depending agonists/antagonist profile, tamoxifen is designated as selective estrogen receptor modulator (SERM) [6].

Tamoxifen was also found to be of similar efficacy when compared with ovarian ablation in several small studies as well as a meta-analysis (Table 23.1) [7, 8]. Thus, by the late 1980s and early 1990s, tamoxifen became the standard approach for the treatment of premenopausal women with metastatic disease.

After failure of antiestrogens, second-line treatment involves estrogen deprivation. For premenopausal women, estrogen deprivation is achieved by ovarian ablation using surgery or irradiation, which removes the major source of estrogen production, or LHRH agonists (goserelin, buserelin), which inhibit ovarian estrogen production by blocking pituitary production of the gonadotrophins luteinizing hormone and follicle-stimulating hormone [1]. LHRH agonists have shown to be effective in reducing estrogen levels to below postmenopausal levels within 21–28 days in >90%, but not 100% of premenopausal women [9]. A multicenter randomized trial comparing goserelin and ovariectomy demonstrated similar efficacy, with response rates of 31 and 27% (P>0.05) and overall survival of 37 and 33

Table 23.1 Results of randomized trials assessing the role of tamoxifen vs. aromatase inhibitors in metastatic breast cancer

Trial	RR (P value)	PFS or TTP (P value)	OS (P value)
TARGET (n>668) [19] phase III			
Tamoxifen 20 mg daily	32.6%	8.3 months	–
Anastrozole 1 mg daily	33% (P 0.787)	8.2 months (P > 0.05)	
North American (n>353) [24] phase III			
Tamoxifen 20 mg daily	17%	5.6 months	–
Anastrozole 1 mg daily	21% (P > 0.05)	11.1 months (P 0.005)	–
Mouridsen et al. (n>916) [23] phase III			
Tamoxifen 20 mg	21%	6 months	30 months
Letrozole 2.5 mg daily	32% (P 0.0002)	9.4 months (P < 0.0001)	34 months (P >0.05)
EORTC (n>371) [25] phase III			
Tamoxifen 20 mg daily	31%	5.5 months	82% 1 year
Exemestane 25 mg daily	46% (P 0.005)	9.9 months (P 0.028)	86% 1 year (P 0.821)

TARGET the tamoxifen or arimidex randomized group efficacy and tolerability study; *RR* response rate; *CB* clinical benefit; *SD* stable disease; *TTP* time to progression; *EORTC* European Organization for Research and Treatment of Cancer

months (P>0.05), respectively [10]. LHRH agonists may be preferable because their action is reversible. The major side effects experienced with LHRH agonists are hot flashes and tumor flares [10]. Tumor flare is a transient reaction characterized by a dramatic increase in bone pain, skin erythema, and /or increase in the size and/or number of metastatic skin nodules, and occurs in about 3–13 patients treated with tamoxifen or LHRH agonists [11]. This reaction almost never occurs with treatment with aromatase inhibitors.

Combination treatments with LHRH agonists plus tamoxifen have also been examined. Several small clinical trials have shown that there may be an increase in objective RR, progression-free survival, and an improved survival (P 0.02) in women who received the combination in comparison with LHRH agonists alone [12]; further study would be required before routinely recommending this approach as standard of care, as three of the four studies included in the meta-analysis, did not have formal crossover of patients who received the LHRH agonist alone to tamoxifen as second-line therapy [12]. Additionally, there was no systematic toxicity or large QOL data collected.

The use of aromatase inhibitor in premenopausal women is not recommended as it leads to an increase in gonadotropin secretion and ovarian stimulation due to reduced feedback of estrogen to the hypothalamus and pituitary in some animal models [13, 14]. This principle is demonstrated further in application of letrozole, a third-generation aromatase inhibitor, for the induction of ovulation [15]. About 20% of women, who are amenorrheic after chemotherapy, are still premenopausal and therefore, these women should be tested prior to initiation of aromatase inhibitors [16]. However, even these levels may be transiently modified by the chemotherapy, and it is generally advisable to use other agents for the initial six or so months.

23.1.2 Postmenopausal

After loss of ovarian function in postmenopausal women, extraovarian aromatase is responsible for estrogen production, catalyzing the formation of estrone and estradiol from androgen precursors in the adrenal gland [17]. In the past few years, direct comparative studies between aromatase inhibitors and tamoxifen have demonstrated aromatase inhibitors to be at least equivalent to tamoxifen and possibly more effective for first-line treatment of postmenopausal metastatic breast cancer [18–20].

Aromatase inhibitors are generally divided into two types. Type I aromatase inhibitors, such as formestane (Lentaron depot®) and exemestane (Aromasin®), are highly specific steroidal agents that irreversibly inhibit aromatase by binding its substrate-binding site. Because the inhibition is irreversible, renewed estrogen production requires synthesis of new aromatase molecules. Therefore, type I aromatase inhibitors are perhaps more appropriately called *aromatase inactivators*. Type II aromatase inhibitors such as aminoglutethimide, anastrozole (Arimidex®) and letrozole (Femara®) are nonsteroidal agents that act by reversibly binding the cytochrome P-450 moiety of the aromatase enzyme. Because blockade is reversible, ongoing estrogen deprivation requires the continued presence of the drug [21]. First-generation (testolactone, aminoglutethimide) and second-generation (formestane, fadrozole) compounds of both classes are characterized by lower selectivity and potency when compared with newer aromatase inhibitors (exemestane, anastrozole, and letrozole) [21]. There is evidence suggesting a lack of cross-resistance between type I and II aromatase inhibitors [21].

Several trials comparing aromatase inhibitors and tamoxifen in the first-line metatastatic setting consistently demonstrated prolonged TTP and improved toxicity profile (see Table 23.1) [22–26].

Another agent in use currently, includes fulvestrant (Faslodex®), a "pure" estrogen antagonist that binds to and downregulates the ER in a mechanism distinct from that of the AI or tamoxifen [27]. Phase III clinical trials in postmenopausal women with metastatic breast cancer have found fulvestrant to be at least as effective and well tolerated as anastrozole after disease progression or recurrence on tamoxifen, and as effective as exemestane following disease progression or recurrence on nonsteroidal aromatase inhibitors [28, 29]. Fulvestrant has also showed some activity in patients with visceral and HER2+ disease, generally regarded as being less responsive to hormonal treatment [30]. A retrospective review of two phase III trials (0020 and 0021) compared the efficacy and tolerability of fulvestrant 250 mg given by intramuscular injection once monthly (one 5 mL (trial 0020) or two 2.5 mg (trial 0021) injections) compared with anastrozole 1 mg demonstrated noninferiority of fulvestrant relative to anastrozole [28]. The Evaluation

of Faslodex and Exemestane Clinical Trial (EFECT) comparing fulvestrant loading-dose (LD) regimen with 500 mg intramuscularly on day 0, 250 mg on days 14, 28, and 250 mg every 28 days with exemestane 25 mg demonstrated no significant differences in median duration of benefit or adverse events [29]. This last study was somewhat disappointing, as the hope had been that fulvestrant given with loading doses would have been more effective than exemestane in this setting. So, either agent is viewed as appropriate after disease progression to a nonsteroidal aromatase inhibitor. The role of loading dose of fulvestrant is still a matter of debate, as the regulatory agency-approved dose does not include a loading approach.

Progestins or androgens also have been used as hormonal therapy and appear to inhibit breast cancer growth by several mechanisms [1]. Progestins, however, are associated with the side effects of weight gain and fluid retention; androgens are associated with virilization [1]. Typically, these hormones are now considered third-line therapy after failure of estrogen deprivation.

More recently, interest has been directed toward the use of estradiol for patients with ER-positive aromatase inhibitor-resistant advanced breast cancer. A small randomized phase II trial, discussed at 2008 San Antonio Breast Cancer Symposium, treated 34 patients with low dose estradiol (2 mg oral 3 times a day), and 32 patients received high-dose (10 mg oral 3 times a day) estradiol [31]. Major exclusions included history of venous thrombosis, heart disease, uncontrolled hypercalcemia and fulvestrant in the last 21 months. PET scan was conducted at baseline and after 24 h as a predictor of response (predefined as ≥12% increase in FDG uptake). Clinical benefit rates (CBRs) (stable disease plus response) were 25% (one partial response (PR) and seven stable diseases (SD) out of 32) on the 30 mg arm and 29% (3PR, 7SD out of 34) on the 6 mg arm. PET-flare was seen in all responders, 9 out of 13 patients with SD and only 3 out of 30 patients with progressive disease (PD). The protocol review and monitoring committee closed the 30 mg arm early, as 6 mg arm was as effective as the 30 mg arm with greater safety, and can be considered for palliative treatment of advanced ER+ breast cancer [31]. Further studies of this lower-dose regimen are warranted.

23.2 Chemotherapy

Patients with hormone-refractory metastatic breast cancer, ER-negative disease, or symptomatic progressive or visceral disease are candidates for systemic chemotherapy with or without other biological treatments. For patients with HER2+ disease, either trastuzumab or lapatinib are typically used with chemotherapy. Many active agents are available for the management of metastatic breast cancer. Anthracyclines and taxanes are the most active agents, followed by alkylating agents, antimetabolites and vinca alkaloids. Used as a single agent, they produce objective response rates of 20–50% [32]. There has also been the influx of targeted agents and many others are under evaluation (see Fig. 23.2). An area that is receiving increasing attention in terms of chemotherapy is the best approach for patients with so-called "triple negative disease" (ER, PR and HER2 negative).

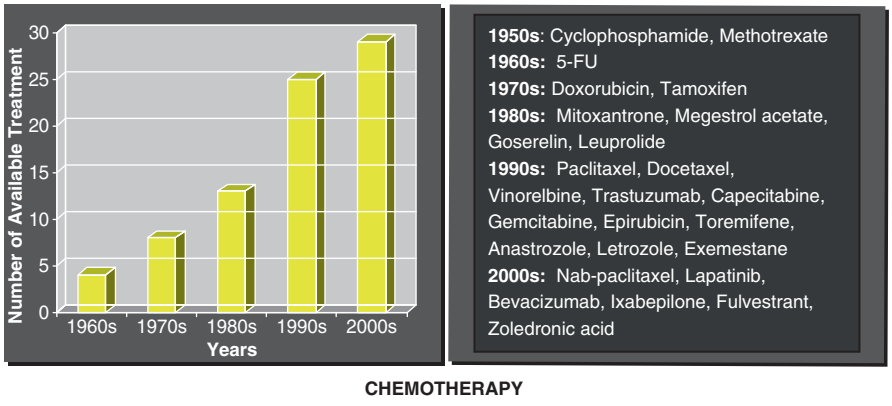

Fig. 23.2 Timeline: growing number of breast cancer therapies

23.3 Single: Agent Activity

23.3.1 Paclitaxel

Taxanes are considered evidence-based essential components in the therapy of metastatic breast cancer. Paclitaxel, isolated from the bark of the pacific yew tree (*taxus brevifolia*), was discovered in National Cancer Institute (NCI) program created to screen natural compounds [33]. Paclitaxel binds to tubulin, promotes stabilization of microtubules, causing G_2 mitotic phase cell cycle arrest and inhibiting cell replication [34]. Paclitaxel may also suppress cell proliferation and modulate immune response [34]. Paclitaxel has been extensively studied in both treatment-naïve (response rates 32–62%; CR 4–17%) and previously treated (response rates up to 55%; CR up to 14%) patients with metastatic breast cancer [35].

Several phase III clinical trials have been conducted to optimize the dose and schedule of paclitaxel. Paclitaxel infusion of 175 mg/m^2 over 3 h every 3 weeks became a reasonable standard approach after the comparison of three different doses of paclitaxel in treatment of MBC in CALGB 9342. Paclitaxel (175, 210 or 250 mg/m^2 every 3 weeks), did not show significant dose effect for response, TTP (3.9 months, vs. 4.1 months, vs. 4.9 months; $P>0.12$), or overall survival (11 months, vs. 12 months, vs. 14 months; $P>0.30$) [36]. However, it did demonstrate significant dose-dependent toxicity, especially neuropathy (7 vs. 19. vs. 32%, respectively; $P>0.0001$).

Further optimization of the schedule was evaluated with a study (CALGB 9840) that compared weekly administration of paclitaxel at 80 mg/m^2 (1 h infusion) with every 3-week infusion of paclitaxel at 175 mg/m^2 (3 h infusion) in 735 women with metastatic breast cancer [37]. Weekly therapy was associated with significantly higher response rates (40 vs. 28%; $P>0.0017$), median TTP (9 months vs. 5 months; $P>0.0008$) and median overall survival (24 vs. 12 months; $P>0.0092$). The toxicity profile also differed in that more myelosuppression (5% vs. 15%) was seen with the every 3 week therapy as compared with weekly therapy; more grade 3 neurotoxicity (24% vs. 12%) seen with weekly regimen as compared with Q 3wkly regimen. The same schedule was evaluated in the Anglo-Celtic IV trial in 560 randomized patients [38]. Patients received weekly paclitaxel at 90 mg/m^2 for 12 weeks or every 3-week paclitaxel 175 mg/m^2 for 6 cycles. This trial confirmed that weekly paclitaxel produced a higher response rate (42 vs. 27%, $P>0.002$) but TTP not significantly different (23.9 vs. 22 weeks). The treatment duration limitation was felt to be the explanation for non significant TTP. Not only the treatment schedule, but also the total dose of paclitaxel appeared to be important for efficacy. Thus, the decision to utilize paclitaxel weekly or every 3 weeks should be made depending on the expected activity, toxicity and patient convenience.

Paclitaxel is relatively insoluble in water, and therefore to aid intravenous administration, it is combined with polyoxyethylated castor oil or cremophor. Cremophor is utilized to formulate other water insoluble drugs, but large quantity is required to make paclitaxel more soluble. This can alter its distribution as well as distribution of other drugs when given in combination, as well as contribute to its toxicity profile. Toxicities of paclitaxel include alopecia, myalgias and arthralgias, with severity ranging from mild to incapacitating pain, normally starting 24–72 h post chemotherapy and lasting for 2–4 days. Anaphylactic reactions are also a possibility necessitating premedications with corticosteroids and antihistamines. The typical dexamethasone dose currently used is 10 mg intravenously before each treatment, although other regimens are also used.

23.3.2 Docetaxel

Docetaxel is synthesized from extracts of the needles of European yew tree (*Taxus baccata*) [33]. It has similar chemical structure as Paclitaxel, and also causes G_2 Mitotic cycle arrest. However, compared with paclitaxel, docetaxel demonstrated greater affinity for the tubulin binding site [39], a different polymerization pattern [39] and overall more potent antitumor activity in vitro and in vivo models [33, 40].

Docetaxel, an alternative taxane, has exhibited single agent antitumor activity in both previously untreated patients (overall response rates (ORRs) of 50–68%) as well as heavily pretreated patients (response rates between 12 and 57%) [41, 42]. Single-agent docetaxel compared favorably to doxorubicin, vinblastine/mitomycin, 5-FU/vinorelbine, and methotrexate/5-FU in randomized trials [43–45].

The recommended single-agent dose for docetaxel range from 60–100 mg/m^2 (over 1 h infusion) every 21 days. The above doses are derived from a phase III trial in which 527 women who had tumor progression on one

prior regimen for metastatic disease (or within 6 months of adjuvant therapy) were randomized to increasing doses of docetaxel (60, 75 and 100 mg/m^2) administered every 21 days [46]. There was significant dose dependency seen with increase in response rate (22.1 vs. 23.3 vs. 36.1%; $P>0.007$) but no significant difference seen in TTP (13.9 vs. 13.7 vs. 18.6 weeks) or overall survival. An increase in both hematologic and nonhematologic toxicities was seen with increasing dose, including grade 3 or 4 neutropenia (76, 84, and 93% with 60, 75 and 100 mg/m^2 , respectively), febrile neutropenia (5, 7, and 14%, respectively) [46]. Primary prophylaxis with hematopoietic colony-stimulating factors was not administered. Depending on the goals of therapy, any of the studied doses can be utilized in treatment of metastatic breast cancer although the majority of patients are treated with the 100 or 75 mg/m^2 dose, and many times with prophylactic growth factor support to ameliorate febrile Neutropenia.

Studies of weekly infusions of docetaxel have not demonstrated any improvement in activity or toxicity as compared to the once every 3-week treatments. A phase III clinical trial was conducted to determine the optimal schedule of docetaxel dosing in terms of safety and efficacy [47]. A total of 118 patients were randomized to a starting infusion of 35 mg/m^2 weekly for 3 consecutive weeks followed by 1 week of rest or 75 mg/m^2 every 3 weeks. Docetaxel every-3-weeks infusion resulted in statistically significant increase in response rate (35.6 vs. 20.3%) as compared to weekly infusion, and similar progression-free survival (PFS) and OS [47]. There was a higher overall toxicity rate (grade 3 and 4) in the every-3-week treatment arm vs. the weekly treatment arm (88.1 vs. 55.9%, respectively; $P>0.0001$). However, weekly therapy is associated with more hyperlacrimation (lacrimal gland stenosis), fatigue, skin and nail toxicity [48]. Other toxicity of therapy in general includes neutropenia, mucositis, incomplete alopecia and fluid retention syndrome [49]. Docetaxel-induced adverse events occur more frequently in patients with impaired liver function, and a reduction in dosage in these patients is recommended [49].

23.3.3 Nab-Paclitaxel

Nab-paclitaxel (Nanoparticle albumin bound paclitaxel, Abraxane®) is a noncremophor formulation of paclitaxel in which albumin replaces cremophor, and a nanoparticle measuring 120–150 nm is formed. Preclinical data have shown increased intratumoral drug levels of nab-paclitaxel [50]. Two possible mechanisms have been suggested for this increased delivery of paclitaxel to the tumor tissue, one based on the size of nab-paclitaxel nanoparticle and the other arising from possible transcytosis of albumin and paclitaxel across blood vessels [50, 51].

Multiple phase I-III studies have evaluated the safety and efficacy of nab-paclitaxel. In a pivotal multicenter phase III study that ultimately led to the approval of nab-paclitaxel, 454 evaluable patients with metastatic breast cancer were randomized to receive either every-3-week dosing of nab-paclitaxel at 260 mg/m^2 without premedications or paclitaxel 175 mg/m^2 with premedications [52]. Nab-paclitaxel demonstrated higher response rates compared with standard paclitaxel (33 vs. 19%, $P>0.001$) and longer TTP (23 vs. 16.9 weeks, respectively; hazard ratio>0.75; $P>0.006$). The incidence of grade 4 neutropenia was significantly lower for nab-paclitaxel compared with conventional paclitaxel (9 vs. 22%, respectively; $P<0.001$) despite a 49% higher paclitaxel dose. Grade 3 sensory neuropathy was more common in then nab-paclitaxel arm than in the standard paclitaxel arm (10 vs. 2%, respectively, $P<0.001$). No hypersensitivity reactions occurred in the nab-paclitaxel group despite the absence of premedication and shorter administration time [52].

23.3.4 Which Taxane?

A best taxane can be defined after consideration of toxicity, response rate as well as expense, but many variables complicate the interpretation of available head-to-head trials of these agents in metastatic setting (see Table 23.2). As a result, overall drug-specific advantage is dependent on dose and schedule. The only trial directly comparing the two taxanes included 449 anthracycline refractory women randomized to every-3-week treatment with either docetaxel at 100 mg/m^2 or paclitaxel at 175 mg/m^2 [53]. The docetaxel group had nonsignificant higher response rate (32 vs. 25%), statistically significant higher median TTP (5.7 vs. 3.6 months) and median overall survival (15.4 vs. 12.7 months) [53]. However, both hematologic and nonhematologic toxicities were worse with docetaxel. Nevertheless, the higher incidence of toxicity in the docetaxel treatment arm did not influence

Table 23.2 Results of randomized trials assessing the role of taxanes in metastatic breast cancer

Study	RR	DFS/TTP	OS
CALGB 9342 (*n*>474) [36]			
Paclitaxel 175 mg/m²Q3wk	23%	3.9 months	11 months
Paclitaxel 210 mg/m²Q3wk	26% (*P* >0.05)	4.1 months	12 months
Paclitaxel 250 mg/m²Q3wk	21% (*P* >0.05)	4.9 months (*P* 0.12)	14 months (*P* 0.3)
CALGB 9840 (*n*>735) [37]			
Paclitaxel 80 mg/m²wkly	40%	9 months	24 months
Paclitaxel 175 mg/m²Q3wk	28% (*P* 0.0017)	5 months (*P* 0.0008)	12 months (*P* 0.009)
Anglo-Celtic IV (*n*>560) [38]			
Paclitaxel 90 mg/m²wkly X 12	47%	23.9 weeks	Not available
Paclitaxel 175 mg/m²Q3wk X 6	27% (*P* 0.002)	22 weeks (*P* 0.06)	
Harvey et al 527 [46] phase III			
Docetaxel 60 mg/m²Q3wk	22.1%	13.9 weeks	Not available
Docetaxel 75 mg/m²Q3wk	23.3%	13.7 weeks	
Docetaxel 100 mg/m²Q3wk	36.1% (*P* 0.007)	18.6 weeks (*P* 0.014)	
Rivera et al (*n*>118) [47] phase III			
Docetaxel 35 mg/m²wkly ¾ wks	20.3%	5.5 months	18.6 month
Docetaxel 75 mg/m²Q3wk	35.6% (*P* NR)	5.7 months (*P* 0.46)	18.3 month (*P* 0.34)
Gradishar et al [52] (*n*>454) phase III			
Nab paclitaxel 260 mg/m²Q3wk	33%	23 weeks	–
Paclitaxel 175 mg/m²Q3wk	19% (*P* 0.001)	16.9 weeks (*P* 0.006)	
Jones et al [53] (*n*>449) phase III			
Docetaxel 100 mg/m²Q3wk	32%	5.7 months	15.4 month
Paclitaxel 175 mg/m²Q3wk	25% (*P* 0.10)	3.6 months (*P* <0.0001)	12.7 month (*P* 0.03)
Gradishar et al [54] (*n*>302) randomized phase II			
Nab paclitaxel 100 mg/m²wkly	58%		
Nab paclitaxel 150 mg/m²wkly	62%	Immature	Immature
Nab paclitaxel 300 mg/m²Q3wk	33%		
Docetaxel 100 mg/m²Q3wk	36% (*P* <0.05)		

RR response rate; *DFS* disease-free survival; *TTP* time to progression; *OS* overall survival; *n* number; *wkly* weekly

QOL measurements. The major criticism for this study is that the dose and schedule chosen for paclitaxel is not considered optimal because weekly dosing is associated with increased response rate and TTP.

Taking all the studies in context, the decision for a particular taxane should be based on toxicity profile and dosing schedule that best meets the therapeutic needs and convenience. Weekly paclitaxel appears to be consistently more active with different toxicity; although every-3-week docetaxel is also considered appropriate [37]. For docetaxel, weekly does not offer the same advantage.

Nab paclitaxel has also been compared with docetaxel in a relatively small trial. Gradishar and colleagues presented the third interim analysis of a randomized phase II trial that compared nab-paclitaxel given weekly at two different doses (100 and 150 mg/m²), nab-paclitaxel given every 3 weeks at a high dose (300 mg/m²), and the standard dose of docetaxel (100 mg/m²) given

every 3 weeks [54]. Results showed patients receiving both weekly doses of nab-paclitaxel had significantly higher response rates (58 and 62% for 100 and 150 mg/m^2, respectively) than those receiving docetaxel (36%) as well as those receiving nab-paclitaxel every 3 weeks (33%). Preliminary analysis of PFS showed all three nab-paclitaxel arms to be superior to docetaxel. Toxicity analysis showed that neutropenia was more statistically increased in the docetaxel treatment group compared with all three doses of nab-paclitaxel. Neutropenia was also seen more frequently in the high-dose 3-weekly and 150 mg/m^2 dose weekly nab paclitaxel. There was no significant difference in rates of peripheral neuropathy between the nab-paclitaxel and docetaxel arms. The authors of the report concluded that nab-paclitaxel at 100 mg/m^2 administered weekly was superior to docetaxel as well as nab-paclitaxel every 3 weeks [54]. Unfortunately, plans for a formal phase III study of these two agents were abandoned in 2009.

23.3.5 Anthracyclines

Anthracyclines agents such as doxorubicin, epirubicin and pegylated liposomal doxorubicin (PLD) are one the most active regimens in breast cancer and are used in treatment of both early stage and metastatic disease. The precise mechanism of action of anthracyclines in breast cancer in vivo remains unknown. In experimental system, anthracyclines have a variety of mechanism of action, including (but not exclusive) intercalation of DNA, and thus inhibiting the activity of topo-isomerase II, which normally cleaves DNA and aids in maintaining its tertiary structure [55]. Anthracyclines are powerful iron chelator creating complexes that can bind DNA and cell membranes and produce free radicals that immediately cleave the DNA and cell membranes [55].

Doxorubicin when compared with paclitaxel in the first-line metastatic setting had better overall response rate (ORR) (41 vs. 25%) as well as longer PFS (7.5 vs. 3.9 months, $P \leq 0.001$). Median survival was not significantly different (18.3 vs. 15.6 months), with crossover response rates of 30% (to doxorubicin) and 16% (to paclitaxel) [56]. Main toxicities included grade 4 neutropenia (85 vs. 40% with paclitaxel; $P \leq 0.001$), febrile neutropenia (20 vs. 7%, $P \leq 0.001$), sensory neuropathy (0 vs. 9%; $P \leq 0.01$) and congestive heart failure (4 vs. 0%; P 0.015) [56].

Epirubicin, an anthracycline analog, is less cardiotoxic and myelotoxic than doxorubicin at equimolar doses, thereby allowing the safe administration of cumulative doses between 950 and 1,000 mg/m^2. In multiple randomized clinical trials, epirubicin and doxorubicin dosages administered both weekly and every 3 weeks yield equivalent response rates and TTP among patients with metastatic breast cancer [57–59].

Combination therapy of epirubicin and paclitaxel was evaluated in first-line metastatic setting in a phase III clinical trial, where patients were randomly assigned to either EP (epirubicin 75 mg/m^2 and paclitaxel 200 mg/m^2) or EC (epirubicin 75 mg/m^2 and cyclophosphamide 600 mg/m^2) administered intravenously every 3 weeks for maximum of six cycles [60]. The primary outcome of PFS (7 vs. 7.1 months) and secondary outcome measures of overall survival (13 vs. 14 months) and response rates (65 vs. 55%) were not significantly different. There was increased toxicity seen in the EP arm compared with EC (grade 3 and 4 mucositis (6% EP vs. 2% EC, P 0.0006); grade 3 and 4 neurotoxicity (5% EP vs. 1% EC; P 0.0001) [60]. Combinations of epirubicin and docetaxel have also been evaluated in multiple small phase II randomized studies. One study compared single-agent docetaxel 100 mg/m^2 (D) with the combination of docetaxel 80 mg/m^2 and epirubicin 75 mg/m^2 (ED) [61]. The response rate (72 vs. 79%), PFS (median 9 vs. 11 months) and overall survival (median 18 vs. 21 months) were not significantly different with increased toxicity in the combination arm [61].

Another step toward attempting to reduce anthracycline-associated cardiotoxicity was by encapsulating the water-soluble drug within a phospholipid membrane (liposome) that acts as a carrier of drug [62]. PLD is enclosed in liposomes coated with polyethylene glycol that function as a barrier to prevent destruction by reticuloendothelial system and prevent the rapid degradation of the encapsulated drug [63]. Clinical studies demonstrate the prolonged circulation time (plasma half life of 45 h compared with about 10 h for PLD and doxorubicin, respectively) [64]. This extended circulation time enables accumulation of the drug at sites of neoplasia due to increased permeability of tumor vasculature [63].

A phase III trial comparing doxorubicin 60 mg/m^2 dosed every 3 weeks with PLD 50 mg/m^2 dosed every 4 weeks found similar PFS (6.9 vs. 7.8 months) and OS (21 vs. 22 months), with an improved toxicity

profile, including decrease in cardiotoxicity [65]. Including prior anthracycline exposure, median cumulative anthracycline dose in PLD arm was 398 mg/m^2 and conventional doxorubicin arm was 421 mg/m^2. The risk of developing cardiotoxicity was significantly higher for patients receiving doxorubicin than for those receiving PLD (48 patients on doxorubicin, ten patients on PLD; P<0.001, HR 3.16 for cumulative anthracycline dose at the first, protocol-specified, cardiac event) [65]. Toxicities more often associated with the doxorubicin treatment group included alopecia (66 vs. 20%), nausea (53 vs. 37%), and neutropenia (10 vs. 4%). Palmar-planter erythrodyesthesia (48 vs. 2%), stomatitis (22 vs. 15%) and mucositis (23 and 13%) were more often seen with PLD than doxorubicin [65].

23.3.6 Ixabepilone

Ixabepilone is a novel epothilone, binds to tubulin in a distinct site compared to the taxanes, and leads to microtubule stabilization. Preclinical studies demonstrate that ixabepilone activity is not substantially affected by over-expression of P-glycoprotein or mutations in β tubulin, both of which have been linked to resistance to taxanes [66, 67].

A phase II study was conducted to evaluate ixabepilone as a first-line metastatic chemotherapy in patients previously treated with adjuvant anthracycline. A total of 65 patients were enrolled and treated with ixabepilone 40 mg/m^2 intravenously every 3 weeks [68]. ORR was 41.5% (95% confidence interval (CI), 29.4–54.4%), median duration of response was 8.2 months (95% CI, 5.7–10.2 months), and median survival was 22 months (95% CI, 15.6–27 months) [68]. Treatment-related adverse events were manageable and mostly grade 1 and 2.

Even in heavily pretreated patients, ixabepilone has demonstrated durable and notable responses. A phase II study enrolled 126 patients with measurable disease who had tumor progression while receiving prior anthracycline, taxane, and capecitabine [69]. Patients were heavily pretreated (88% had received at least two lines of prior chemotherapy in the metastatic setting). Ixabepilone was given intravenously at 40 mg/m^2 every 3 weeks. ORR by independent radiology facility was 11.5% (95% confidence interval (CI), 6.3–18.9%), median duration of response and PFS was 5.7 and 3.1 months, respectively as well as median overall survival of 8.6 months [70]. Grade 3 and 4 treatment-related toxicity included peripheral sensory neuropathy (14%), fatigue/asthenia (13%), myalgia (8%) and stomatitis/mucositis (6%) [69]. Based on the above data, ixabepilone is the only single agent approved in the setting of metastatic breast cancer refractory to anthracyclines, taxanes and capecitabine.

In summary, results of phase II trials demonstrate response rates up to 42% in patients with metastatic breast cancer previously untreated with taxanes, and 11.5% in patients with anthracycline-, taxane- and capecitabine-resistant disease, using a dose of 40 mg/m^2 every 3 weeks; without need for corticosteroid premedications [68, 70]. Ixabepilone has also demonstrated clinical activity and is acceptable in combination with capecitabine in patients with metastatic breast cancer, including those with disease resistant to anthracycline, taxanes and capecitabine [66, 70].

23.3.7 Capecitabine

Capecitabine is a rationally designed oral fluoropyrimidine carbamate that is enzymatically activated to 5-FU, preferentially in tumor cells and also in the liver [35]. This method of administration is similar to the effect of continuous administration of 5-FU, as well as it may spare normal tissue from chemotherapy-related toxicities. Capecitabine is commonly dosed orally twice a day, 14 days out of a 21-day cycle, and has demonstrated response rates of 30–37% in the first-line metastatic setting. A randomized trial of capecitabine compared with intravenous CMV (cyclophosphamide, methotrexate, 5-fluorouracil) showed improved response rates and similar median overall survival with improved toxicity profile [71]. In patients that are heavily pretreated, including previous anthracycline and taxane, capecitabine has demonstrated ORRs of 26% with median survival of 12.2 months and median duration of response of 8.3 months. Most common treatment-related adverse events were hand and foot syndrome (62%), diarrhea (58%), nausea (55%), and stomatitis (34%) [72]. Although the US Food and Drug Administration approved dosage daily dose is 2,500 mg/m^2, many trials have reported the need to reduce the dosage in patients because of toxicity, and this reduction appears to have minimal impact on efficacy [73].

23.4 Other Active Agents

23.4.1 Gemcitabine

Gemcitabine, intravenous antimetabolite chemotherapy, has a modest toxicity profile and well-demonstrated antitumor activity of 0–37% as first-line therapy in a series of phase II studies [68, 74]. Combination therapy with gemcitabine and paclitaxel was associated with significantly improved median OS (18.6 vs. 15.8 months; $P>0.0489$), median TTP (6.1 vs. 4 months; $P>0.0187$) and ORR (41.4 vs. 26.2%; $P>0.0002$) compared with paclitaxel alone [75]. There was more grade 3/4 neutropenia (47.9 vs. 11.5%) as well as fatigue on the combination arm as compared to paclitaxel [75]. Only 15.6% of patients in single-agent arm received gemcitabine off-study after disease progression.

23.4.2 Vinorelbine

Vinorelbine, a vinca alkaloid and microtubule-stabilizing agent, has clinically significant single-agent activity both in untreated (21–44% responses) and previously treated patients (11 vs. 64% responses) with advanced disease [76]. Vinorelbine is generally well tolerated, although dose may be limited by hematologic toxicity, constipation or neuropathy [76].

23.4.3 Irinotecan

Irinotecan is a semi-synthetic derivative of camptothecan, an alkaloid extract from plant *camptotheca acuminate*, and inhibits topoisomerase I, which is responsible for modifying DNA during replication [77]. SN-38, the active metabolite of irinotecan, binds to topoisomerase I-DNA complex and causes damage to the double-strand DNA, leading to apoptosis [77]. Irinotecan has demonstrated activity in phase I/II studies in patients with metastatic breast cancer, prompting further evaluation in a randomized phase II setting. A total of 103 patients with metastatic breast cancer who experienced disease progression after one to three chemotherapy regimens (at least one anthracycline- or taxane-based regimen), were randomly assigned to irinotecan in 6-week cycles comprising 100 mg/m^2 weekly for 4 weeks, then a 2-week rest or 240 mg/m^2 every 3 weeks [69]. In the weekly arm, the objective response rate was 23%, median response duration was 4.9 months (range, 1.9–15.9 months), and median overall survival was 9.7 months (95% CI, 8–14.2 months). In every-3-week treatment group, the objective response rate was 14%, median response duration was 4.2 months (range, 3.1–13.9 months), and median overall survival was 8.6 months (95% CI, 7–12.3 months). Grade 3–4 adverse events with ≥10% incidence included neutropenia (29%) and diarrhea (17%) in the weekly arm and neutropenia (36%), vomiting (20%), dyspnea (18%), nausea (16%), and diarrhea (12%) in the every-3-weekly arm [69]. Although not yet approved for treatment of metastatic breast cancer, irinotecan is an active drug with good tolerability. A pegylated formulation of this agent is currently under evaluation for this disease.

23.5 Combination Therapy

Whether combination chemotherapy is superior to single-agent chemotherapy as treatment for metastatic breast cancer continues to be debated. For patients with rapidly PD, treatment regimens with the most response rate are highly advantageous. At this point, it is unclear if combination chemotherapy offers any survival advantage compared with optimal use of single agents in sequence, which will be essentially impossible to prove due to the inability to conduct a trial in which there is 100% compliance with using either combination or two particular agents in sequence. Coexisting medical conditions and the patient's ability to tolerate the treatment are also considered when making the decision.

23.6 Taxane-based Combinations

23.6.1 Taxane and Doxorubicin

The combination of taxane and anthracyclines is attractive because of incomplete cross-resistance. Several phase III trials have compared anthracycline-taxane combinations to standard anthracycline-based combinations

[78–82]. In summary, response rates favored the arms with taxanes, and none favored the arm without a taxane but no significant improvement in complete response rate. TTP favored the taxane arm in some of the studies.

The combination of paclitaxel and anthracyclines has produced unexpected cardiac toxicity in some studies. Sequencing paclitaxel after doxorubicin as well as reducing the duration of infusion of both drugs reduces toxicity without reducing efficacy; however the regimen is still associated with high incidence of cardiotoxicity. Strategies to reduce the cardiotoxicity associated with the combination included substituting epirubicin or liposomal doxorubicin, limiting the doxorubicin per cycle to 50 mg/m^2 and limiting the cumulative dose of doxorubicin to 360 mg/m^2 [82].

There are conflicting data in regards to the advantage of combination treatment of paclitaxel and anthracyclines compared with non taxane-containing anthracycline regimen [79, 83]. The only trial showing advantage of the combination over traditional anthracycline-containing regimen compared the safety and efficacy of doxorubicin and paclitaxel (AT) to FAC as first-line therapy for metastatic breast cancer. A total of 267 women were randomized to either AT (doxorubicin 50 mg/m^2, followed 24 h later by paclitaxel 220 mg/m^2 or FAC (5-fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2), each administered every 3 weeks for up to eight cycles. ORR (68 vs. 55%; $P>0.032$), TTP (8.3 vs. 6.2 months, $P>0.34$) and overall survival (23.3 months vs. 18.3 months, $P>0.013$) favored AT compared with FAC [83]. The incidence of cardiotoxicity was low in both arms.

The Eastern Cooperative Oncology Group 1193 addresses the issue of sequential use of the two. A total of 739 patients were randomized to receive paclitaxel (T at 175 mg/m^2 over 24 h), doxorubicin (A at 60 mg/m^2), or paclitaxel/doxorubicin (AT; 50 and 150 mg/m^2/24 h) as first-line treatment. The AT combination produced a response rate of 46% compared with response rates of 34 and 33% for A and T, respectively [84]. Nevertheless, median overall survival was not significantly prolonged with AT, with rates of 20.1, 22.2 and 22.4 months for A, T and AT, respectively. A survival benefit may not have occurred because patients who failed with single agents were crossed over to the other agent, with a response rate of 20% for those crossing from A to T and 14% for those crossing from T to A. Therefore, A and T given sequentially or in combination may have similar impact on overall outcome.

There are arguably better data available for the docetaxel-anthracycline combination in comparison to older anthracycline-based regimens. In a randomized phase II-III study, 216 women were randomized to either AT (doxorubicin 50 mg/m^2 and docetaxel 75 mg/m^2) or FAC (fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2) every 3 weeks [85]. Median TTP (8 vs. 6.6 months, respectively; $P>0.004$) and overall survival (22.6 vs. 16.2 months, respectively; $P>0.019$) were longer for patients on AT compared with FAC. The ORR was also significantly higher in patients with AT compared with FAC (58 vs. 37%, respectively; $P>0.003$). There was no differences in grade 3–5 neutropenia and infections (AT 89% and FAC 84%, AT 12% vs. FAC 9%), but neutropenic fever was more common in AT treatment arm (33 vs. 9%, $P<0.001$). Congestive heart failure was observed in 3 and 6% of patients on AT and FAC [85].

The combination of PLD plus docetaxel was compared with docetaxel monotherapy in 751 patients with advanced breast cancer previously treated with adjuvant anthracycline [86]. Patients were randomized to receive docetaxel (D) at 75 mg/m^2 or PLD 30 mg/m^2 followed by docetaxel 60 mg/m^2 every 21 days. The primary endpoint of TTP was increased from 7 months for D, to 9.8 months for PLD+D (HR 0.65; 95% CI 1.41, 2.35; $P>0.000001$). The secondary endpoint of ORR was also significantly improved for the PLD+D (26 vs. 35%, P 0.0085). The overall survival was similar between the two arms at short-term follow-up. There was no difference in grade 3/4 neutropenia (65 vs. 66%), febrile neutropenia (6 vs. 7%) and overall incidence of grade 3/4 drug-related adverse events (66 vs. 74%) for D and PLD+D, respectively. There was no increase in cardiac toxicity as demonstrated by congestive heart failure reported as 1% in both arms. Additional follow-up is needed to determine the impact of the combination on overall survival [86]

The combination of doxorubicin with either taxane was evaluated in the ERASME 3 trial, which compared the combination of doxorubicin and paclitaxel with the combination of doxorubicin and docetaxel in 200 chemotherapy-naïve women with metastatic breast cancer [81]. Patients were treated with either paclitaxel-doxorubicin (doxorubicin 50 mg/m^2 followed 1 h later by paclitaxel 175 mg/m^2 (arm P)) or docetaxel-doxorubicin (doxorubicin 50 mg/m^2 followed 1 h later by docetaxel 75 mg/m^2 (arm D)) every 3 weeks for a maximum of four cycles, followed by four cycles of

single-agent paclitaxel (arm P) or docetaxel (arm D). The primary end point of the study was QOL measurement. Secondary end points were toxicity, OS and PFS. The PFS (8.7 vs. 8 month) and overall survival (21.4 vs. 27.3 months) as well as QOL scores were not significantly different, but both had different toxicity profile [81].

A pooled analysis of individual patient data, reported in 2008 comparing anthracycline and taxane combinations with anthracycline and non taxane combination included eight trials and 3,034 patients [87]. In single-agent trials, response rates were similar in the taxanes (38%) and in the anthracyclines (33%) treatment groups ($P>0.08$). The hazard ratios for taxanes compared with anthracyclines were 1.19 (95% CI, 1.04–1.36; $P>0.011$) for PFS and 1.01 (95% CI, 0.88–1.16; $P>0.90$) for survival. In combination trials, response rates were 57% (10% complete) in taxane-based combinations and 46% (6% complete) in control arms ($P<0.01$). The hazard ratios for taxane-based combinations compared with control arms were 0.92 (95% CI, 0.85–0.99; $P>0.31$) for PFS and 0.95 (95% CI, 0.88–1.03; $P>0.24$) for overall survival. The authors concluded that taxanes were significantly worse than single-agent anthracyclines in terms of PFS, but not in terms of response rates or survival. Taxane-based combinations were significantly better than anthracycline-based combinations in terms of response rates and PFS, but not in terms of survival [87].

23.6.2 Taxane and Nonanthracycline Combination

23.6.2.1 Carboplatin/Paclitaxel

Three hundred twenty seven patients with advanced breast cancer were randomized to receive either paclitaxel 175 mg/m^2 followed by epirubicin 80 mg/m^2 (group A) or paclitaxel 175 mg/m^2 and carboplatin at an AUC of 6 mg/mL per minute(Group B) every 3 weeks for 6 cycles [88]. Median survival was not significantly different between the two groups (22.4 vs. 27.8 months, $P>0.25$), whereas mean time to treatment failure was significantly longer in patients treated with paclitaxel/carboplatin (8.1 vs. 10.8 months, $P>0.04$). Both regimens were well tolerated and QOL assessment or cost analysis did not reveal any significant differences between the two regimens. A Phase II study evaluated the combination in first-line metastatic setting. A total of 53 patients were treated with paclitaxel 200 mg/m^2 and carboplatin at an AUC of 6 mg/mL per minute administered every 3 weeks. The ORR was found to be 62% (95% CI, 48–75%), with complete responses in 16%, and partial responses in 46% [89]. Therapy was generally well tolerated. Grade 3–4 neutropenia was observed in 82% of patients but there were no episodes of febrile neutropenia or sepsis. Grade 3 peripheral neuropathy occurred in 16% of patients. The 12-month survival rate was 72% [89]. In a recent phase III trial, 416 patients with metastatic breast cancer were randomized to be treated with paclitaxel 175 mg/m^2 and carboplatin at an AUC of 6 mg/mL per minute (PCb) every 3 weeks for 6 cycles or gemcitabine 1,000 mg/m^2 (days 1 and 8) plus docetaxel 75 mg/m^2 on day 8 only) (GDoc) every 3 weeks for 6 cycles or weekly paclitaxel 80 mg/m^2 Q weekly X 12 weeks (Pw) [90]. Trastuzumab was given to patients with HER2 over-expressing tumors. The primary endpoint of the study was survival and preferred the single-agent paclitaxel arm (29.9 months for PCb, 26.9 for GDoc, and 41 months for Pw; $P>0.037$). There was no significant difference in TTP. Severe myelotoxicity and mucosites were more frequent with GDoc, while severe neuropathy with PCb and Pw. QOL did not differ significantly between the three treatment groups, while cost analysis favored weekly paclitaxel [90].

23.6.2.2 Gemcitabine/Paclitaxel

A 2008 phase III clinical trial evaluated the combination therapy with gemcitabine and paclitaxel in the first-line metastatic setting. Five hundred and twenty nine patients with measurable metastatic breast cancer and prior adjuvant anthracycline were randomly assigned to receive either paclitaxel (175 mg/m^2 over 3 h every 21 days) and gemcitabine (1,250 mg/m^2 over 30 min, on days 1 and 8 every 21 days) or paclitaxel alone (175 mg/m^2 over 3 h on day 1 every 21 days), and was associated with significantly improved median OS (18.6 months vs. 15.8 months; $P>0.0489$), median TTP (6.1 vs. 4 months; $P>0.0187$) and ORR (41.4 vs. 26.2%; $P>0.0002$) compared with paclitaxel alone [75]. There was more grade 3/4 neutropenia (47.9 vs. 11.5%) as well as fatigue on the combination arm as compared to paclitaxel [75]. Only 15.6% of patients in single-agent arm received gemcitabine off-study after disease progression. Gemcitabine and paclitaxel is a reasonable

combination for women who require cytoreduction with manageable toxicities.

23.6.2.3 Capecitabine/Docetaxel

Capecitabine and docetaxel combination has been evaluated in a phase III clinical trial, which randomized 511 women with measurable metastatic breast cancer as well as prior treatment with anthracycline to receive either intravenous docetaxel (75 mg/m^2 intravenously (IV) on day 1 every 3 weeks) and oral capecitabine (1,250 mg/m^2 bid on days 1–14 every 3 weeks), or intravenous docetaxel (100 mg/m^2 IV on day 1 every 3 weeks) [91]. Despite using a lower dose of docetaxel, the combination demonstrated higher response rate (42 vs. 30%, *P* 0.006), superior TTP (6.1 vs. 4.2 months, *P* 0.0001), and longer overall survival (14.5 vs. 11.5 months, $P > 0.0126$) [91]. More grade 3 adverse events occurred with combination therapy (71 vs. 49%, respectively). The main criticism of the design of this study is the lack of crossover from docetaxel to capecitabine in the single-agent arm. Only 27% of patients who received single-agent docetaxel received capecitabine off-study after disease progression [91].

23.6.2.4 Gemcitabine/Docetaxel

The combination of gemcitabine and docetaxel was tested in a phase III trial. Patients with metastatic breast cancer who had received prior anthracyclines (either adjuvant or metastatic setting) were randomized to receive either gemcitabine 1,000 mg/m^2 (days 1 and 8) plus docetaxel 75 mg/m^2 (day 1) (GD) or capecitabine 1,250 mg/m^2 twice daily (days 1–14) plus docetaxel 75 mg/m^2 (day 1) every 3 weeks (CD) [92]. The primary objective was PFS. No difference was observed between the two groups in terms of PFS (8.05 vs. 7.98 months), RR (32%), or OS (*P* 0.983). Time to treatment failure (defined as discontinuation, PD, death as a result of any cause, or the start of a new anticancer therapy) was superior in GD arm ($P > 0.059$). Toxicity profile differed in that grade 3/4 leukopenia (GD 78% vs. CD 66%, *P* 0.025) and transfusion (GD 17%, CD 7%, $P > 0.0051$) were more seen in GD, and grade 3/4 diarrhea, mucositis and hand-and-foot syndrome were higher in the CD arm.

23.6.2.5 Ixabepilone and Capecitabine

The combination of ixabepilone and capecitabine in treatment of metastatic breast cancer has been evaluated in two large phase III metastatic breast cancer trials comparing efficacy and toxicity of the combination regimen vs. capecitabine alone. The first trial published in 2007 included 752 patients with tumor progression on anthracycline and taxane-based therapy. Patients were randomly assigned to ixabepilone 40 mg/m^2 intravenously on day 1 of a 21-day cycle plus capecitabine 2,000 mg/m^2 orally on days 1 through 14 of a 21-day cycle, or capecitabine alone 2,500 mg/m^2 on the same schedule. The combination of ixabepilone and capecitabine increased median PFS compared to capecitabine monotherapy (5.8 vs. 4.2 months), with a 25% decrease in estimated risk of disease progression (hazard ratio, 0.75; 95% confidence interval (CI), 0.64–0.88; $P > 0.0003$) [93]. Grade 3 and 4 treatment-related sensory neuropathy (21 vs. 0%), fatigue (9 vs. 3%), neutropenia (68 vs. 11%) as well as rate of death as a result of toxicity (3 vs. 1%, with patients with liver dysfunction ≥grade 2 at greater risk) were more frequent with combination therapy than monotherapy [93]. This is the only regimen currently approved by regulatory agencies for patients with tumor refractory to anthracyclines and taxanes.

The second phase III study evaluated similar population of patients with anthracycline- and taxane-resistant metastatic breast cancer but also prospectively analyzed the ER/PR/HER2 negative ("triple negative") patient subgroup and compared to the group as a whole [94]. A total of 752 patients were randomized to either ixabepilone 40 mg/m^2 intravenously q3 weeks plus capecitabine 2,000 mg/m^2 orally on days 1 through 14 of a 3-week cycle, or capecitabine alone 2,500 mg/m^2 on the same schedule. Ninety one patients in the combination arm and 96 patients in capecitabine monotherapy arm had triple negative disease. The combination demonstrated superior ORR (35 vs. 14%) /and PFS (5.8 months vs. 4.2 months) in all patients as well as the triple negative subgroup. The objective response rate was (27 vs. 9%) and PFS was (4.1 vs. 2.1 months; HR 0.75) in the triple negative subgroup, favoring the combination arm compared with the capecitabine monotherapy arm [94]. Grade 3 and 4 treatment-related adverse events in the combination arm were sensory neuropathy (21%), fatigue (9%) and neutropenia (68%). The combination of ixabepilone and capecitabine may offer a specific advantage in subset of breast cancer patients

with triple negative disease and should be explored further.

23.7 Biologic Agents

23.7.1 Trastuzumab

The HER-2/neu(c-erbB2) protooncogene product, a transmembrane growth factor receptor involved in mitogeneic signaling, is overexpressed in approximately 18–25% of patients with breast cancer [95]. Trastuzumab, a recombinant humanized anti-HER-2/neu monoclonal antibody, has been developed and has been shown to inhibit the growth of breast cancer cells overexpressing HER2.

An important factor in identifying patients who benefit from trastuzumab is the evaluation of the overexpression of the HER2 receptor. Expression of the receptor is assessed by immunohistochemistry (IHC) and is scored on a 4-point scale of 0, 1+, 2+ or 3+. Recommendations for HER2 testing that are published endorse 3+ expression by standard IHC or gene amplification by fluorescent in situ hybridization (FISH) prior to treatment with trastuzumab. Moreover, there are also data for 7% discordance between HER2 positivity in the primary tumor and in metastasis, and retesting of new metastatic disease is generally recommended [96].

Trastuzumab is administered as an outpatient loading dose of 4 mg/kg by intravenous infusion over 90 min with subsequent weekly dose of 2 mg/kg over 30 min. In previously treated patients with HER2-positive advanced breast cancer, trastuzumab therapy produced ORRs of 12–15%, with median response durations of 5.1–8.4 months [97].

Combination of trastuzumab and anastrozole has been evaluated in a phase III trial TAnDEM presented in 2006. Patients were randomized to receive treatment with anastrozole 1 mg daily or anastrozole plus trastuzumab (4 mg/kg intravenous on day 1, then 2 mg/kg intravenously once a week) until disease progression [98]. The primary endpoint was median PFS. The study demonstrated statistically significant increased response rate (20.3 vs. 6.8%; $P>0.018$), and PFS (4.8 vs. 2.4 months; $P>0.0007$) in patients with combination arm compared to anastrozole alone. Median overall survival was not statistically significant (28.5 vs. 23.9 months; $P>0.325$), although 70% of patients with anastrozole crossed over to the trastuzumab treatment. An additional exploratory analysis showed that among 145 patients with liver metastases, the combination arm had significantly longer OS (41.3 vs. 32.1 months; $P>0.04$) and PFS (7.7 vs. 3.8 months; $P>0.006$) compared to anastrozole alone [98]. Subsequent, exploratory, *post hoc* analysis showed that median overall survival was now statistically significant for the combination therapy at randomization by 11.3 months (28.5 vs. 17.2 months; P 0.0479), as well as for the combination therapy after PD on anastrozole (25.1 vs. 17.2 months; P 0.0404) [99].

Preclinical data demonstrate that trastuzumab may potentiate the efficacy of chemotherapy by facilitating the induction of apoptosis [100]. In general, patients receive combination of chemotherapy plus trastuzumab for 6 months and if disease is stable, continuation of trastuzumab alone until progression or toxicity. In order to define the benefits of addition of trastuzumab to chemotherapy, a pivotal trial randomized 469 patients with HER2-positive metastatic breast cancer to first-line chemotherapy ± trastuzumab. Chemotherapy consisted of doxorubicin (or epirubicin) and cyclophosphamide or paclitaxel [101]. The addition of trastuzumab to chemotherapy demonstrated statistically significant increase in time to disease progression (7.4 vs. 4.6 months), response rate (50 vs. 32%), duration of response (9.1 vs. 6.1 months), median survival (25.1 vs. 20.3 months), and a statistically significant decrease in risk of death [101]. Cardiac dysfunction in the concurrent anthracycline – trastuzumab treatment group was 27% (and mainly affecting patients who received ≥300 mg/m^2 of doxorubicin or ≥450 mg/m^2 of epirubicin) compared with 13% in paclitaxel – trastuzumab group and 8% in anthracycline and cyclophosphamide alone [101]. Due to this, trastuzumab was originally only approved in combination with paclitaxel. There also has been a randomized phase II trial with docetaxel – trastuzumab combination compared with docetaxel monotherapy, showing significant advantage and no increase in toxicity [102].

Two concurrent phase II trials evaluated two different schedules of triplet chemotherapy with combination of carboplatin, paclitaxel and trastuzumab. Patients received every-3-week therapy ($n>43$) consisting of a 200 mg/m^2 dose of paclitaxel/carboplatin AUC of 6 mg/mL per minute and trastuzumab (an initial 8 mg/kg dose and subsequent 6 mg/kg doses) administered every 21 days for 8 cycles or weekly therapy ($n>48$) consisting of a

80 mg/m^2 dose of paclitaxel/carboplatin AUC of 2 mg/mL per minute for 3 out of 4 weeks, with weekly trastuzumab (an initial 4 mg/kg dose and subsequent 2 mg/kg weekly) administered every 4 weeks for 6 cycles [103]. Trastuzumab was continued until disease progression or unacceptable toxicity. The ORR with every-3-week therapy was 65% (90% confidence interval (CI), 51–77%), with a median time to disease progression of 9.9 months and median overall survival time of 2.3 years. The ORR with weekly therapy was 81% (90% CI, 70–90%), with median time to disease progression of 13.8 months and a median OS of 3.2 years. Hematologic and nonhematologic toxicities occurred significantly less frequently with weekly therapy vs. every-3-week therapy [103]. Newer ongoing trails are evaluating the role of carboplatin as part of phase III studies.

Trastuzumab has also been evaluated with other combination chemotherapy, including vinorelbine, capecitabine, gemcitabine, cisplatin and liposomal doxorubicin, and has shown significant advantage compared with chemotherapy alone [104]. Unfortunately, disease progression inevitably occurs during or after completion of therapy with trastuzumab. In the pivotal phase III trial of trastuzumab plus chemotherapy, patients were given the opportunity to enroll in a nonrandomized extension trial upon disease progression, providing an opportunity to continue trastuzumab-based treated beyond progression [105]. A total of 247 patients with documented disease progression received weekly intravenous trastuzumab in the extension study, with concurrent therapies at the discretion of the treating physician. The group of patients who had not received trastuzumab in the original trial had a response rate of 14% in the extension study, and the group who had received trastuzumab for the second time had a similar response rate of 11%, suggesting that trastuzumab might retain activity after disease progression [105]. Longer duration of therapy did not increase the risk of cardiac dysfunction [105].

There are many other separate studies that have reported that patients who had received trastuzumab after progression lived significantly longer than patients who had only received one trastuzumab-containing regimen [106, 107]. One of the studies included 54 patients through multiple lines of trastuzumab and analyzed for time to tumor progression for first-, second- and beyond second-line treatment, response rates and overall survival. Stable disease and objective response combined, CBRs were 85.2% in first line, 68.5% in second line and 58.3% in beyond second line (three to seven lines) [106, 107]. These data suggest that some patients benefit from continued trastuzumab treatment. However, caution should be utilized when interpreting these results as there may be a selection bias due to several reasons. Firstly, patients whose disease progresses rapidly and who are to receive further therapy would be excluded, enriching the patient population for trastuzumab responders. Secondly, due to nonrandomized nature of these trials, there exists the possibility of selection bias based on differences in patient characteristics and investigator bias in evaluating response and toxicity. There are ongoing randomized phase III trials to evaluate second-line therapy with trastuzumab in combination with a variety of cytotoxic regimens.

23.7.2 Lapatinib

Lapatinib, an orally bioavailable, reversible, dual epidermal growth factor receptor (EGFR)/HER2 tyrosine kinase inhibitor is an alternative noncross-resistant approach for patients that progress on trastuzumab-based therapy [107]. Lapatinib mimics ATP and binds to the ATP binding site at the tyrosine kinase domain, and as a result, inhibits the receptor phosphorylation and activation of HER1 and HER2 homodimers and heterodimers, thereby blocking the downstream signaling pathway involved in proliferation, and survival [108].

In previously treated patients, lapatinib has single-agent activity of about 24% and as high as 50% seen in inflammatory breast cancer [104]. In a phase III study, patients with advanced HER2-positive breast cancer patients that had progressed on initial chemotherapy plus trastuzumab were randomly assigned to either combination therapy (lapatinib at a dose of 1,250 mg/day continuously plus capecitabine at a dose of 2,000 mg/m^2 on days 1–14 of a 21-day cycle) or monotherapy (capecitabine alone at a dose of 2,500 mg/m^2 on days 1–14 of a 21-day cycle) [109]. The median TTP was improved to 8.4 months in combination therapy compared with 4.4 months in the monotherapy group. There was no increase in serious toxic effects or symptomatic cardiac events [109]. Lapatinib is now approved by the FDA in combination with capecitabine for the treatment of patients with metastatic breast cancer after progression on trastuzumab.

Lapatinib has also been evaluated in combination with paclitaxel in HER2-negative as well as

HER2-uncharacterized metastatic breast cancer [110]. Five hundred seventy nine women with metastatic breast cancer were randomly assigned to first-line therapy with paclitaxel 175 mg/m^2 every 3 weeks plus lapatinib 1,500 mg/day or paclitaxel 175 mg/m^2 every 3 weeks plus placebo (PL). In 86 HER2-positive patients (15%), treatment with paclitaxel-lapatinib resulted in statistically significant improvements in TTP, EFS, ORR, and clinical benefit rate (CBR) compared with paclitaxel-placebo. No differences between treatment groups were observed for any end point in HER2-negative patients [110].

A randomized, double-blind, placebo-controlled study included 1,286 patients with HER2-positive breast cancer who were treated with lapatinib 1,500 mg/day plus letrozole 2.5 mg/day or letrozole 2.5 mg alone [111]. HER2 status of patients was not required for randomization into the study; however PFS was the primary endpoint in HER2-positive patients in post-study analysis. Two hundred nineteen patients were deemed HER 2 positive, and patients who received the combination treatment had significantly increased PFS (8.2 vs. 3 months, $P>0.019$), ORR (28 vs. 15%; $P>0.021$) compared with treatment with letrozole alone [111].

One study has assessed the efficacy and tolerability of two lapatinib administration schedules as first-line monotherapy in patients with HER2-positive locally advanced or metastatic breast cancer [112]. A total 138 patients were randomly assigned to one of two lapatinib dose cohorts and received either 1,500 mg once daily or 500 mg twice daily for a median of 17.6 weeks. The ORR was 24% in intent-to-treat population and 31% patients derived clinical benefit (CR, PR or stable disease for ≥24 weeks). The median time to response was 7.9 weeks, and the progression-free survival rates at 4 and 6 months were 63 and 43%, respectively. The most common lapatinib-related adverse events were diarrhea, rash, pruritis and nausea, and all of these were grade 1 or 2. There were no significant differences in clinical activity or adverse event profile between the dosing schedules [112].

23.7.3 CNS Metastases in HER2-positive Breast Cancer

A higher proportion of patients with HER2-positive metastatic breast cancer treated with trastuzumab develop symptomatic brain metastases [113]. Three hypotheses have been proposed to explain this phenomenon (1) Greater propensity of HER-2 phenotype for the central nervous system (2) trastuzumab prolongs survival of patients and CNS metastasis is a late manifestation (3) trastuzumab may not cross the blood brain barrier. Lapatinib was associated with regression of CNS lesions in a small phase II trial. A multicenter phase II trial was conducted for further evaluation of the CNS activity of lapatinib and/or lapatinib and capecitabine. CNS objective responses to lapatinib were observed in 6% of patients (≥50% volumetric reduction of CNS lesions in the absence of steroid use, progressive extra-CNS disease, progressive neurologic symptoms). Twenty-one percent of patients experienced ≥20% volumetric reduction in their CNS disease. CNS objective response with lapatinib plus capecitabine was 20% with 40%, experiencing ≥20% volumetric reduction in CNS lesions [114].

23.7.4 Bevacizumab

Angiogenesis has been implicated in the pathogenesis of malignancy and metastasis. Bevacizumab (BV) is a recombinant humanized mouse monoclonal antibody (93% human), targeting vascular endothelial growth factor (VEGF) that is composed of mouse VEGF-binding site jointed to a human IgG framework [115]. BV recognizes all isoforms of VEGF-A, prevents receptor binding, leading to inhibition of angiogenesis. BV in vitro assays demonstrate dose-dependent inhibition of VEGF-induced proliferation, migration and survival of vascular endothelial cells, as well as increased permeability of these cells by preventing the binding of soluble VEGF to its receptors on the surface of endothelial cells [115]. There are studies suggesting a synergistic interaction between chemotherapy and BV. One hypothesis that anti-VEGF agents can cause transient vasoconstriction of the large aberrant blood vessels supplying the tumor, which in turn improves blood flow, decreases hypoxia and allows for better delivery of chemotherapeutic agents [116].

Initial phase III trial published in 2005, randomized 462 previously treated metastatic breast cancer patients to treatment with combination of capecitabine (2,500 mg/m^2/day in two divided doses day 1 through 14 every 3 weeks) plus BV 15 mg/kg compared with capecitabine (2,500 mg/m^2/day in two divided doses

day 1 through 14 every 3 weeks) alone [117]. Combination therapy significantly increased the response rate (19.8 vs. 9.1%) but did not result in a longer PFS (4.86 vs. 4.17 months). Overall survival (15.1 vs. 14.5 months) was also comparable in both treatment groups [117]. Another phase III trial conducted by the North American Breast Intergroup (E2100) compared paclitaxel with the combination paclitaxel and BV as initial treatment in 722 women with locally recurrent or metastatic breast cancer and no prior treatment for metastatic disease [118]. Patients were randomized to paclitaxel (90 mg/m^2 days 1, 8, and 15 every 28 days) with or without BV (10 mg/kg on days 1 and 15). The addition of BV to paclitaxel demonstrated significantly prolonged PFS compared with paclitaxel alone (11.8 vs. 5.9 months), and increased the response rate (36.9 vs. 21.2%), but overall survival was not different (26.7 vs. 25.2 months) [118]. Statistically significant toxicities, including grade 3 or 4 hypertension (14.8 vs. 0%), proteinuria (3.6 vs. 0%), headache (2.2 vs. 0%), cerebrovascular ischemia (1.9 vs. 0%), infection (9.3 vs. 2.9%) seen more frequently with the combination therapy. Treatment with combination of capecitabine and BV improved response rates but not PFS or OS as compared with combination of paclitaxel and BV. This can be explained by the substantial difference between the two patient populations; all patients on the capecitabine study had received previous anthracycline and taxane therapy, and most (>85%) had received chemotherapy for metastatic setting, whereas only 35.2% of patients on paclitaxel study had received any previous chemotherapy and only 13.2% had received both anthracycline and taxane as adjuvant therapy [118]. There is a possibility that paclitaxel is uniquely synergistic with BV [119]. BV may also have more effect early on in the disease when angiogenesis pathways are less redundant [118]. BV was FDA approved in 2008 as first-line treatment in combination with paclitaxel.

More recently, a phase III randomized, double-blind study evaluated the combination of docetaxel and BV in first-line therapy for patients with locally recurrent or metastatic breast cancer [120]. A total of 736 patients were randomized to docetaxel (D) 100 mg/m^2 PL or docetaxel plus either BV 7.5 mg/kg or BV 15 mg/kg. Docetaxel was administered every 3 weeks for up to nine cycles, while BV and placebo were administered until disease progression or unacceptable toxicity. After a median follow-up of 11 months, PFS (8.7 vs. 8.8 months for the low- and high-dose BV, respectively) as well as ORR was significantly superior for both BV-containing treatment groups compared with D alone (8 months). Overall survival results were not different at the time of the report (short follow-up).

The addition of BV to any of the two taxanes (weekly paclitaxel or docetaxel every 3 weeks) significantly increases the response rate and prolonged the time to disease progression as part of first-line therapy for patients with HER2 normal MBC. Longer follow-up is needed for the determination of benefits to the overall survival. The efficacy of BV with chemotherapy for patients with refractory disease to chemotherapy remains to be determined, although the first study reported in combination with capecitabine did not demonstrate benefit compared to chemotherapy alone [117].

23.8 Mechanisms of Drug Resistance

Resistance to chemotherapeutic agents account for over 90% of failure of treatment in patients with metastatic breast cancer [121]. A number of mechanism by which human breast cancer cells become resistant to chemotherapy have been described (Table 23.3). Overcoming mechanisms of drug resistance is important for the effective management of breast cancer.

23.9 High-dose Chemotherapy with Stem Cell Rescue

The delivery of very high doses of chemotherapy, requiring hematopoietic stem cell support, does not add a significant survival benefit above that achieved with standard dose conventional chemotherapy [122]. A meta-analysis of 740 women enrolled in six randomized controlled trials did not demonstrate any statistically significant difference in overall survival, but toxicity was more severe in the high-dose group. The authors concluded that high-dose chemotherapy with bone marrow or stem cell transplantation should not be given to women with metastatic breast cancer outside of clinical trials. We agree with this recommendation.

Table 23.3 Mechanisms of chemotherapy resistance

Mechanism of resistance	Examples
Decreased drug influx– decreased expression and inactivating mutations of the carrier	Antifolates Nucleoside analogs
Increased drug efflux– Transporter proteins such as MDR (multidrug resistance) and ABC (ATP binding cassette) actively transport drug out of the cells. Target hydrophobic drugs	Anthracyclines Taxanes Platinum Vinca alkaloids Topoisomerase I/II inhibitors
Drug inactivation– resulting in diminished amount of free drug available. By either over-expression (DPD (dihydropyrimidine dehydrogenase) that catabolyzes 5FU) or activation of detoxifying enzymes (glutathione)	Antifolates Nucleoside analogs Anthracyclines Vinca alkaloids
Drug target– alterations of expression levels or mutation in chemotherapy target	Antifolate Taxanes Topoisomerase inhibitors Vinca alkaloid
DNA damage repair– capacity of cancer cell to repair the damage caused by chemotherapy	Platinum Antifolates
Drug induced cell cycle arrest vs. apoptosis– Inactivation in tumor suppressor genes causing inabilitygo/toundergo apoptosis. Cell cycle arrest promotes DNA repair and survival)	PlatinumTaxanes Anthracyclines

23.10 Supportive Therpy

23.10.1 Bisphosphonates

Bone metastasis occurs in up to 70% of patients with advanced breast cancer, and is the site of first recurrence in up to 40% of women with relapsing breast cancer [123]. Breast cancer cells secrete parathyroid hormone-related protein, interleukin-6, prostaglandin E_2, tumor necrosis factor, and macrophage colony-stimulating factor, which increase the expression of RANKL and consequently stimulate osteoclastic activity [124]. Bisphosphonates, potent inhibitor of osteolytic activity, have been the primary treatment for managing skeletal conditions characterized by increased osteoclast-mediated conditions, including metastatic breast cancer to the bones [125]. Potential uses in breast cancer treatment, including prevention or delay in skeletal complications, palliation of bone pain in patients with documented bone metastases as well as prevention of bone loss due to systemic therapy [125]. Oral therapy clodronate 1,600 mg/day had been evaluated in a placebo-controlled trial in 173 patients with breast cancer metastasis [126]. The study demonstrated that clodronate resulted in statistically significant improvement in hypercalcemia episodes (28 vs. 52, $P<0.01$), reduction in number of vertebral fractures (84 vs. 124/100 patient years, $P>0.025$), as well as a trend toward improvement in nonvertebral fractures and radiation requirement for pain [126].

A prospective, randomized, placebo-controlled trial evaluated the intravenous bisphosphonate pamidronate. A total of 382 patients with metastatic breast cancer and had at least one lytic lesion were given pamidronate 90 mg as a 2-h intravenous infusion, monthly for 12 cycles, or placebo. Pamidronate resulted in an improved median interval to occurrence of the first skeletal complications (13.1 vs. 7 months, $P>0.005$), as well as lower number of skeletal complications (43 vs. 56%; $P>0.008$) [127]. Increase in bone pain as well as decline in performance status occurred at a lower rate in the pamidronate-treated group [127]. There is data to suggest benefit of pamidronate 45 mg as a 1 h intravenous infusion, resulting in improvement of median TTP by 48% when given along with chemotherapy [128].

Zoledronic acid (Zol) was compared with a dose of 90 mg of pamidronate (Pam) in patients with metastatic breast carcinoma with at least one osteolytic lesion. A total of 1,130 patients with either 4 mg of Zol or 8 mg of Zol as a 15-min infusion or 90 mg of Pam as a 2-h infusion every 3–4 weeks for 12 months.

Results demonstrated no difference in primary end point of skeletal-related event (SRE) between treatment groups (43% in Zol 4 mg, 45% in Pam). Among the subset of patients with metastatic breast carcinoma to the bone ($n>528$ patients), the 4 mg Zol group had a trend toward lower SRE (48 vs. 58%, $P>0.058$). The time to first SRE was significantly longer in the 4 mg Zol group compared with Pam group (310 vs. 174 days, $P>0.013$) [129]. Intravenous pamidronate 90 mg as a 2-h infusion or zoledronic acid 4 mg as a 15-min infusion every 3–4 weeks are recommended for women with imaging evidence of bone metastases to be continued until evidence of substantial decline in patient's general performance status [130].

23.11 Alternative Approaches

National Center for Complementary and Alternative Medicine (NCCAM) defines Complementary and alternative medicine (CAM) as group of diverse medical and health care systems, practices, and products that are not presently considered to be part of traditional, conventional medicine [131]. NCI and NCCAM are currently sponsoring various clinical trials to study complementary and alternative treatments for cancer alone or in combination with conventional treatments.

23.12 Surgery or Radiofrequency Ablation for Metastatic Disease- Oligometastases

In the absence of curative treatment for the majority of patients, the goal of therapy is focused on symptom control, improved QOL and prolongation of survival. However, there exists a subset of women with metastatic breast cancer who have limited systemic tumor burden and biologically indolent disease. These long-term survivors tend to be young, with an excellent performance status, and limited metastatic disease [132]. For such patients, combined modality approaches, often including surgery or radiation, appear to provide a better chance for long-term progression-free survival than chemotherapy alone.

Interest has also been directed toward locoregional treatment (LRT) of patients with breast cancer who present with synchronous metastasis. A recent study evaluated 581 patients, of whom 320 received LRT and 261 received no LRT [133]. LRT consisted of exclusive locoregional radiotherapy in 249 patients (78%), surgery of the primary tumor with adjuvant locoregional radiotherapy in 41 patients (13%), and surgery alone in 30 patients (9%). The 3-year overall survival rates were 43.4% and 26.7% in LRT and no LRT, respectively ($P>0.00002$). The association between LRT and improved survival was most impressive in women with visceral metastases (median survival time of 25 months vs. 13 months and 3-year overall survival rate of 34.2 vs. 17.8% in patients treated with LRT vs. no LRT, respectively; P 0.0005) [133]. The study demonstrates the impact of LRT, specifically locoregional radiation, on survival in patients with metastatic breast cancer. Although currently there are no randomized prospective trials showing that resection of any metastatic site prolongs survival compared with systemic therapy alone, ongoing discussions may allow such trials to be conducted.

23.13 Summary

An extensive array of basic and clinical research has been performed throughout the last decade in an attempt to improve the outcome of patients with metastatic breast cancer. Despite significant advances, cure after a diagnosis of metastatic breast cancer for the majority of patients remains an elusive goal utilizing current therapeutic options. At this time, many therapeutic options are available, and no single method has been clearly demonstrated as being optimal. Given the novel mechanisms of action of new antitumor compounds coupled with their favorable toxicity profiles, continued improvement in survival and QOL may be achieved in patients with advanced disease. Participation in clinical trials remains a major priority.

Future advances in breast cancer treatment will depend on tailoring therapy to individual patients, developing new cytotoxic agents and novel combinations, and improving dose-scheduling strategies to achieve increased antitumor activity with improved tolerability. Beyond the traditional antineoplastic approach, new types of agents such as inhibitors of tumor migration and invasiveness, and compounds that inhibit the signal transduction pathways involved in malignant transformation and growth

may lead to significant improvement in the treatment of all patients with breast cancer.

The choice of specific agents in the management of metastatic breast cancer will be made increasingly in the context of the biology of the disease and the prior treatment received. Studies to evaluate the different alterations in the expression of genes that control the cell cycle will be of critical importance in understanding and optimizing the different treatment modalities for metastatic breast cancer. The importance of clinical trials and obtaining biopsies of the metastatic tumor to evaluate biology also should be emphasized. Participation in clinical trials is necessary for the continued investigation of novel agents and treatment approaches, and is recommended for the management of metastatic breast cancer. The pace at which these new therapies are evaluated depends on patient accrual, and can be enhanced by education of patients on the clinical trial process and their eligibility for open trials.

References

1. Ellis MJ, Hegg D, Lippman ME (2000) Treatment of metastatic breast cancer, in diseases of the breast. Lippincott Williams and Wilkins, Philadelphia, pp 749–97
2. Chia SK et al (2007) The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. Cancer. 110(5):973–9
3. Amar S, Roy V, Perez EA (2009) Treatment of metastatic breast cancer: looking toward the future. Breast Cancer Res Treat. 114(3):413–22
4. Olin JJ, Muss HB. New strategies for managing metastatic breast cancer. Oncology (Williston Park). 2000;14(5):629–41; discussion 642–4, 647–8
5. Pritchard KI (2003) Endocrine therapy of advanced disease: analysis and implications of the existing data. Clin Cancer Res. 9(1 Pt 2):460S–7S
6. Pritchard KI et al (1980) Tamoxifen therapy in premenopausal patients with metastatic breast cancer. Cancer Treat Rep. 64(6–7):787–96
7. Crump M et al (1997) An individual patient-based meta-analysis of tamoxifen versus ovarian ablation as first-line endocrine therapy for premenopausal women with metastatic breast cancer. Breast Cancer Res Treat. 44(3): 201–10
8. Sawka CA et al (1997) A randomized crossover trial of tamoxifen versus ovarian ablation for metastatic breast cancer in premenopausal women: a report of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trial MA.1. Breast Cancer Res Treat. 44(3):211–5
9. Burger CW, Prinssen HM, Kenemans P (1996) LHRH agonist treatment of breast cancer and gynecological malignancies: a review. Eur J Obstet Gynecol Reprod Biol. 67(1): 27–33
10. Taylor CW et al (1998) Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. J Clin Oncol. 16(3):994–9
11. Plotkin D et al (1978) Tamoxifen flare in advanced breast cancer. JAMA. 240(24):2644–6
12. Klijn JG et al (2001) Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol. 19(2):343–53
13. Sinha S et al (1998) Effect of CGS 20267 on ovarian aromatase and gonadotropin levels in the rat. Breast Cancer Res Treat. 48(1):45–51
14. Smith IE, Dowsett M (2003) Aromatase inhibitors in breast cancer. N Engl J Med. 348(24):2431–42
15. Higgins MJ, Davidson NE (2009) What is the current status of ovarian suppression/ablation in women with premenopausal early stage breast cancer? Curr Oncol Rep. 11(1):45–50
16. Smith IE et al (2006) Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol. 24(16):2444–7
17. Grodin JM, Siiteri PK, MacDonald PC (1973) Source of estrogen production in postmenopausal women. J Clin Endocrinol Metab. 36(2):207–14
18. Mouridsen H et al (2001) Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol. 19(10):2596–606
19. Bonneterre J et al (2001) Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor-positive advanced breast carcinoma. Cancer. 92(9):2247–58
20. Nabholtz JM et al (2003) Anastrozole (Arimidex) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results. Eur J Cancer. 39(12):1684–9
21. Briest S, Davidson NE (2007) Aromatase inhibitors for breast cancer. Rev Endocr Metab Disord. 8(3):215–28
22. Bonneterre J et al (2000) Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the tamoxifen or arimidex randomized group efficacy and tolerability study. J Clin Oncol. 18(22):3748–57
23. Mouridsen H et al (2003) Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol. 21(11):2101–9
24. Nabholtz JM et al (2000) Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. J Clin Oncol. 18(22):3758–67
25. Paridaens RJ et al (2008) Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organization for Research and Treatment of Cancer Breast Cancer Cooperative Group. J Clin Oncol. 26(30):4883–90

26. Vergote I et al (2000) Randomized study of anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women. Eur J Cancer. 36(Suppl 4):S84–5
27. Chia S, Gradishar W (2008) Fulvestrant: expanding the endocrine treatment options for patients with hormone receptor-positive advanced breast cancer. Breast. 17(Suppl 3):S16–21
28. Mauriac L et al (2003) Fulvestrant (Faslodex) versus anastrozole for the second-line treatment of advanced breast cancer in subgroups of postmenopausal women with visceral and non-visceral metastases: combined results from two multicentre trials. Eur J Cancer. 39(9):1228–33
29. Chia S et al (2008) Double-blind, randomized placebo-controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol. 26(10):1664–70
30. Buzdar AU (2008) Fulvestrant–a novel estrogen receptor antagonist for the treatment of advanced breast cancer. Drugs Today (Barc). 44(9):679–92
31. Ellis MJ, Dehdahti F, Kommareddy A, Jamalabadi-Majidi S, Crowder R, Jeffe DB, Gao F, Fleming G, Silverman P, Dickler M, Carey L, Marcom PK Siteman Cancer Center, St Louis; University of Chicago, Chicago; Case Western Reserve University, Cleveland; MSKCC, New York; UNC, Chapel Hill; Duke University, Durham. A randomized phase 2 trial of low dose (6 mg daily) versus high dose (30 mg daily) estradiol for patients with estrogen receptor-positive aromatase inhibitor resistant advanced breast cancer. In San Antonio Breast Cancer Symposium. San Antonio; 2008
32. Bernard-Marty C, Cardoso F, Piccart MJ (2004) Facts and controversies in systemic treatment of metastatic breast cancer. Oncologist. 9(6):617–32
33. Saloustros E, Mavroudis D, Georgoulias V (2008) Paclitaxel and docetaxel in the treatment of breast cancer. Expert Opin Pharmacother. 9(15):2603–16
34. Rowinsky EK, Donehower RC (1995) Paclitaxel (taxol). N Engl J Med. 332(15):1004–14
35. Jatoi I. Manual of breast diseases. In: Jatoi I, editor. Philadelphia: Lippincott Williams and Wilkins; 2002
36. Winer EP et al (2004) Failure of higher-dose paclitaxel to improve outcome in patients with metastatic breast cancer: cancer and leukemia group B trial 9342. J Clin Oncol. 22(11):2061–8
37. Seidman AD et al (2008) Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol. 26(10):1642–9
38. Verrill M. Anglo-Ceptic IV: first results of a UK National Cancer Research Network randomized phase III (pharmacogenetic trial of weekly compared to 3-weekly paclitaxel in patients with locally advanced or metastatic breast cancer. In Proceedings ASCO annual meeting. Chicago, Illinois; 2007
39. Diaz JF, Andreu JM (1993) Assembly of purified GDP-tubulin into microtubules induced by taxol and taxotere: reversibility, ligand stoichiometry, and competition. Biochemistry. 32(11):2747–55
40. Hanauske AR et al (1992) Effects of Taxotere and taxol on in vitro colony formation of freshly explanted human tumor cells. Anticancer Drugs. 3(2):121–4
41. Baur M et al (2008) A phase II trial of docetaxel (Taxotere) as second-line chemotherapy in patients with metastatic breast cancer. J Cancer Res Clin Oncol. 134(2):125–35
42. Dieras V et al (1996) A multicentre phase II study of docetaxel 75 mg m-2 as first-line chemotherapy for patients with advanced breast cancer: report of the Clinical Screening Group of the EORTC. Br J Cancer. 74(4):650–6
43. Chan S et al (1999) Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. J Clin Oncol. 17(8):2341–54
44. Nabholtz JM et al (1999) Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. 304 Study Group. J Clin Oncol. 17(5):1413–24
45. Sjostrom J et al (1999) Docetaxel compared with sequential methotrexate and 5-fluorouracil in patients with advanced breast cancer after anthracycline failure: a randomized phase III study with crossover on progression by the Scandinavian Breast Group. Eur J Cancer. 35(8):1194–201
46. Harvey V et al (2006) Phase III trial comparing three doses of docetaxel for second-line treatment of advanced breast cancer. J Clin Oncol. 24(31):4963–70
47. Rivera E et al (2008) Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. Cancer. 112(7):1455–61
48. Burstein HJ et al (2000) Docetaxel administered on a weekly basis for metastatic breast cancer. J Clin Oncol. 18(6): 1212–9
49. Cortes JE, Pazdur R (1995) Docetaxel. J Clin Oncol. 13(10):2643–55
50. Desai N et al (2006) Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. Clin Cancer Res. 12(4):1317–24
51. Henderson IC, Bhatia V (2007) Nab-paclitaxel for breast cancer: a new formulation with an improved safety profile and greater efficacy. Expert Rev Anticancer Ther. 7(7):919–43
52. Gradishar WJ et al (2005) Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol. 23(31):7794–803
53. Jones SE et al (2005) Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol. 23(24):5542–51
54. Gradishar W. A randomized phase II trial of Qw or Q3w of ABI 007 (ABX) vs. Q3w solvent-based docetaxel (TXT) as first-line therapy in metastatic breast cancer (MBC). In 29th Annual Breast Cancer Symposium. San Antonio, Texas; 2006
55. Lowenthal EA, Carpenter JT Jr (1995) The use of anthracyclines in the adjuvant treatment of breast cancer. Cancer Treat Rev. 21(3):199–214
56. Paridaens R et al (2000) Paclitaxel versus doxorubicin as first-line single-agent chemotherapy for metastatic breast cancer: a European Organization for Research and treatment of cancer randomized study with cross-over. J Clin Oncol. 18(4):724–33

57. Bontenbal M et al (1998) Doxorubicin vs epirubicin, report of a second-line randomized phase II/III study in advanced breast cancer. EORTC Breast Cancer Cooperative Group. Br J Cancer. 77(12):2257–63
58. Brambilla C et al (1986) Phase II study of doxorubicin versus epirubicin in advanced breast cancer. Cancer Treat Rep. 70(2):261–6
59. Jain KK et al (1985) A prospective randomized comparison of epirubicin and doxorubicin in patients with advanced breast cancer. J Clin Oncol. 3(6):818–26
60. Langley RE et al (2005) Phase III trial of epirubicin plus paclitaxel compared with epirubicin plus cyclophosphamide as first-line chemotherapy for metastatic breast cancer: United Kingdom National Cancer Research Institute trial AB01. J Clin Oncol. 23(33):8322–30
61. Pacilio C et al (2006) Is epirubicin effective in first-line chemotherapy of metastatic breast cancer (MBC) after an epirubicin-containing adjuvant treatment? A single centre phase III trial. Br J Cancer. 94(9):1233–6
62. Lorusso V, Manzione L, Silvestris N (2007) Role of liposomal anthracyclines in breast cancer. Ann Oncol. 18(Suppl 6):vi70–3
63. Brown JM, Giaccia AJ (1998) The unique physiology of solid tumors: opportunities (and problems) for cancer therapy. Cancer Res. 58(7):1408–16
64. Gabizon A et al (1994) Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polyethylene-glycol coated liposomes. Cancer Res. 54(4):987–92
65. O'Brien ME et al (2004) Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol. 15(3):440–9
66. Dumontet C, Jordan MA, Lee FF (2009) Ixabepilone: targeting betaIII-tubulin expression in taxane-resistant malignancies. Mol Cancer Ther. 8(1):17–25
67. Lee FY et al (2001) BMS-247550: a novel epothilone analog with a mode of action similar to paclitaxel but possessing superior antitumor efficacy. Clin Cancer Res. 7(5):1429–37
68. Roche H et al (2007) Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, as first-line therapy in patients with metastatic breast cancer previously treated with anthracycline chemotherapy. J Clin Oncol. 25(23): 3415–20
69. Perez EA et al (2004) Randomized phase II study of two irinotecan schedules for patients with metastatic breast cancer refractory to an anthracycline, a taxane, or both. J Clin Oncol. 22(14):2849–55
70. Perez EA et al (2007) Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. J Clin Oncol. 25(23):3407–14
71. Oshaughnessy JA et al (2001) Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. Ann Oncol. 12(9):1247–54
72. Blum JL et al (2001) Multicenter. Phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients. Cancer. 92(7):1759–68
73. Ershler WB (2006) Capecitabine monotherapy: safe and effective treatment for metastatic breast cancer. Oncologist. 11(4):325–35
74. Wirk B, Perez E (2006) Role of gemcitabine in breast cancer management: an update. Semin Oncol. 33(1 Suppl 2): S6–14
75. Albain KS et al (2008) Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. J Clin Oncol. 26(24):3950–7
76. Zelek L et al (2001) Weekly vinorelbine is an effective palliative regimen after failure with anthracyclines and taxanes in metastatic breast carcinoma. Cancer. 92(9):2267–72
77. Potmesil M (1994) Camptothecins: from bench research to hospital wards. Cancer Res. 54(6):1431–9
78. Baltali E et al (2002) Paclitaxel and doxorubicin combination in the first-line treatment of metastatic breast cancer. Tumori. 88(3):200–3
79. Biganzoli L et al (2002) Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: the European Organization for Research and treatment of cancer 10961 multicenter phase III trial. J Clin Oncol. 20(14):3114–21
80. Biganzoli L et al (2003) Doxorubicin-paclitaxel: a safe regimen in terms of cardiac toxicity in metastatic breast carcinoma patients. Results from a European Organization for research and treatment of cancer multicenter trial. Cancer. 97(1):40–5
81. Cassier PA et al (2008) A phase-III trial of doxorubicin and docetaxel versus doxorubicin and paclitaxel in metastatic breast cancer: results of the ERASME 3 study. Breast Cancer Res Treat. 109(2):343–50
82. Valero V, Hortobagyi GN (2003) Are anthracycline-taxane regimens the new standard of care in the treatment of metastatic breast cancer? J Clin Oncol. 21(6):959–62
83. Jassem J et al (2001) Doxorubicin and paclitaxel versus fluorouracil, doxorubicin, and cyclophosphamide as first-line therapy for women with metastatic breast cancer: final results of a randomized phase III multicenter trial. J Clin Oncol. 19(6):1707–15
84. Sledge GW et al (2003) Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol. 21(4):588–92
85. Bontenbal M et al (2005) Phase II to III study comparing doxorubicin and docetaxel with fluorouracil, doxorubicin, and cyclophosphamide as first-line chemotherapy in patients with metastatic breast cancer: results of a Dutch community setting trial for the clinical trial group of the comprehensive cancer centre. J Clin Oncol. 23(28):7081–8
86. Sparano J, Makhson-Anatoly N, Semiglazov V, Tjulandin S, Balashova O, Bondarenko I, Bogdanova N, Chatikhine V, Zhuang S, Xiu L, Yuan Z, Rackoff W Albert Einstein Coll of Med, New York; City Onc Hosp #62, Moscow, Russian Federation; NN Petrov Res Inst of Onc, St-Petersburg, Russian Federation; NN Blokhin Can Res Cntr, Moscow, Russian Federation; Regional Onc Dispensary, Dnepropetrovsk, Ukraine; State Med Acad, Dnepropetrovsk, Ukraine; PA Herzen Onc Res Inst, Moscow, Russian Federation; OrthoBiotech Onc R and D, J and JPRD, Raritan. Pegylated liposomal doxorubicin (PLD) plus docetaxel

significantly improves time to progression (TTP) compared with docetaxel (D) monotherapy in patients with advanced breast cancer (ABC) treated with adjuvant anthracycline: results from a randomized phase 3 study. In San Antonio Breast Cancer Symposium. San Antonio; 2008
87. Piccart-Gebhart MJ et al (2008) Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. J Clin Oncol. 26(12):1980–6
88. Fountzilas G et al (2004) Paclitaxel and epirubicin versus paclitaxel and carboplatin as first-line chemotherapy in patients with advanced breast cancer: a phase III study conducted by the Hellenic Cooperative Oncology Group. Ann Oncol. 15(10):1517–26
89. Perez EA et al (2000) A phase II study of paclitaxel plus carboplatin as first-line chemotherapy for women with metastatic breast carcinoma. Cancer. 88(1):124–31
90. Fountzilas G et al (2008) A randomized phase III study comparing three anthracycline-free taxane-based regimens as first-line chemotherapy in metastatic breast cancer: A Hellenic Cooperative Oncology Group study. Breast Cancer Res Treat. 115(1):87–99
91. O'Shaughnessy J et al (2002) Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol. 20(12):2812–23
92. Chan S et al (2009) Phase III study of gemcitabine plus docetaxel compared with capecitabine plus docetaxel for anthracycline-pretreated patients with metastatic breast cancer. J Clin Oncol. 27(11):1753–60
93. Thomas ES et al (2007) Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol. 25(33):5210–7
94. Rugo HS, Thomas ES, Lee RK, Fein LE, Peck R, Verrill M. UCSF Comprehensive Cancer Center, San Francisco, CA; Kaiser Permanente, Oakland, CA; The St. Lukes Medical Center, Quezon City, Philippines; The Centro de Oncologia Rosario, Sante Fe, Argentina; Bristol-Myers Squibb, Wallingford, CT; Northern Institute for Canacer Research, Newcastle upon Tyne, United Kingdom. Combination therapy with the novel epothilone B analog, ixabepilone, plus capecitabine has efficacy in ER/PR/HER2-negative breast cancer resistant to anthracyclines and taxanes. In San Antonio Breast Cancer Symposium. San Antonio; 2007
95. Perez EA (1999) HER-2 as a prognostic, predictive, and therapeutic target in breast cancer. Cancer Control. 6(3):233–40
96. Nielsen DL, Andersson M, Kamby C (2009) HER2-targeted therapy in breast cancer. Monoclonal antibodies and tyrosine kinase inhibitors. Cancer Treat Rev. 35(2):121–36
97. Orman JS, Perry CM (2007) Trastuzumab: in HER2 and hormone receptor co-positive metastatic breast cancer. Drugs. 67(18):2781–9
98. Mackey JR, Kaufman B, Clemens M, Bapsy PP, Vaid A, Wardley A, Tjulandin S, Jahn M, Lehle M, Jones A. Cross Cancer Institute, Edmonton, Canada; Chaim Sheba Medical Center, Tel Hashomer, Israel; Krankenanstalt Mutterhaus der Borromaerinnen, Trier, Germany; Kidwai Memorial Institute of Oncology, Bangalore, India; Rajiv Gandhi Cancer Institute, New Delhi, India; Christie Hospital NHS Trust, Manchester, United Kingdom; Russian Cancer Research Center, Moscow, Russian Federation; F Hoffmann-La Roche, Basel, Switzerland; Royal Free Hospital, London, United Kingdom. Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer. In San Antonio Breast Cancer Symposium. San Antonio; 2006
99. Clemens M, B.K, Mackey JR, Bapsy P, Vaid A, Wardley A, Tjulandin S, Révil C, Lehle M, Jones A. Trastuzumab plus anastrozole may prolong overall survival in postmenopausal women with HER2-positive, hormone-dependent metastatic breast cancer: Results of a post-hoc analysis from the TAnDEM study. In 2007 Breast Cancer Symposium; 2007
100. Pegram MD et al (2004) Rational combinations of trastuzumab with chemotherapeutic drugs used in the treatment of breast cancer. J Natl Cancer Inst. 96(10):739–49
101. Slamon DJ et al (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 344(11):783–92
102. Marty M et al (2005) Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol. 23(19):4265–74
103. Perez EA et al (2005) Two concurrent phase II trials of paclitaxel/carboplatin/trastuzumab (weekly or every-3-week schedule) as first-line therapy in women with HER2-overexpressing metastatic breast cancer: NCCTG study 983252. Clin Breast Cancer. 6(5):425–32
104. Metro G, Mottolese M, Fabi A (2008) HER2-positive metastatic breast cancer: trastuzumab and beyond. Expert Opin Pharmacother. 9(15):2583–601
105. Tripathy D et al (2004) Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. J Clin Oncol. 22(6):1063–70
106. Bartsch R et al (2006) Analysis of trastuzumab and chemotherapy in advanced breast cancer after the failure of at least one earlier combination: an observational study. BMC Cancer. 6:63
107. Spector N (2008) Treatment of metastatic ErbB2-positive breast cancer: options after progression on trastuzumab. Clin Breast Cancer. 8(Suppl 3):S94–9
108. Nelson MH, Dolder CR (2006) Lapatinib: a novel dual tyrosine kinase inhibitor with activity in solid tumors. Ann Pharmacother. 40(2):261–9
109. Geyer CE et al (2006) Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 355(26): 2733–43
110. Di Leo A et al (2008) Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. J Clin Oncol. 26(34):5544–52
111. Johnston S, O'Rourke L, Wang W, Pegram M, Press MF, Maltzman J. Correlation of tumor burden, liver and bone metastasis with serum extracellular domain HER2 expression in front-line metastatic breast cancer. In San Antonio Breast Cancer Symposium. San Antonio; 2008
112. Gomez HL et al (2008) Efficacy and safety of lapatinib as first-line therapy for ErbB2-amplified locally advanced or metastatic breast cancer. J Clin Oncol. 26(18):2999–3005
113. Clayton AJ et al (2004) Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. Br J Cancer. 91(4):639–43
114. Lin NU et al (2009) Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. Clin Cancer Res. 15(4):1452–9

115. Fox SB, Generali DG, Harris AL (2007) Breast tumor angiogenesis. Breast Cancer Res. 9(6):216
116. Jain RK (2005) Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science. 307 (5706):58–62
117. Miller KD et al (2005) Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol. 23(4):792–9
118. Miller K et al (2007) Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 357(26):2666–76
119. Miller KD, Sweeney CJ, Sledge GW Jr (2001) Redefining the target: chemotherapeutics as antiangiogenics. J Clin Oncol. 19(4):1195–206
120. Miles D, Chan A, ROmieu G, et al. Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer: AVADO, in ASCO. Chicago, Illinois; 2008
121. Longley DB, Johnston PG (2005) Molecular mechanisms of drug resistance. J Pathol. 205(2):275–92
122. Farquhar C, et al. High-dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with metastatic breast cancer. Cochrane Database Syst Rev. 2005(3): CD003142
123. Mehrotra B (2009) Bisphosphonates–role in cancer therapies. J Oral Maxillofac Surg. 67(5 Suppl):19–26
124. Roodman GD (2001) Biology of osteoclast activation in cancer. J Clin Oncol. 19(15):3562–71
125. Drake MT, Clarke BL, Khosla S (2008) Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc. 83(9):1032–45
126. Paterson AH et al (1993) Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. J Clin Oncol. 11(1):59–65
127. Hortobagyi GN et al (1996) Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. N Engl J Med. 335(24):1785–91
128. Conte PF et al (1996) Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. The Aredia Multinational Cooperative Group. J Clin Oncol. 14(9):2552–9
129. Rosen LS et al (2004) Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer. 100(1):36–43
130. Hillner BE et al (2000) American Society of Clinical Oncology guideline on the role of bisphosphonates in breast cancer. American Society of Clinical Oncology Bisphosphonates Expert Panel. J Clin Oncol. 18(6): 1378–91
131. JD W (2008) Cancer: principles and practice of oncology. 8th ed. Hellman S, DeVita VT Jr, Rosenberg SA, editors. Philadelphia, PA: Lippincott Williams and Wilkins
132. Hortobagyi GN (2002) Can we cure limited metastatic breast cancer? J Clin Oncol. 20(3):620–3
133. Le Scodan R et al (2009) Breast cancer with synchronous metastases: survival impact of exclusive locoregional radiotherapy. J Clin Oncol. 27(9):1375–81

Hormone Replacement Therapy: A Critical Review

24

Joseph Ragaz and Joshua Budlovsky

24.1 Introduction

The aim of this chapter is to review the most recent aspects of hormone replacement therapy (HRT), and to clarify its impact on associated health conditions amidst growing uncertainties. Special emphasis has been placed on its effect on cardiovascular conditions and breast cancer, the two most important outcomes affected by HRT, and on identifying ideal candidates for HRT as well as defining the optimum new HRT regimens.

Until the publication in 2002 of the first Women's Health Initiative (WHI) randomized trial [1], HRT was increasingly used to treat the variety of symptoms attributed to menopause, as well as to prevent most menopause-associated medical conditions. These policies were based largely on observational and case–control studies, providing evidence that HRT, besides providing control of menopausal symptoms, is also associated with cardiovascular, colon cancer, and bone fracture benefits. Most intriguing were data associating HRT with a significant all-cause mortality reduction [2–5], and paradoxically, despite increased breast cancer incidence rates, with improved rates of breast cancer mortality [5].

In 2002, the first WHI controlled randomized trial of HRT using estrogen plus progestin reported increased hazard rates from HRT for coronary heart disease (CHD) and strokes, as well as adverse effects on breast cancer and thromboembolism. While the previously seen HRT benefits for bones and against colon cancer were confirmed, the WHI group concluded that increased hazards outweighed the HRT benefits.

The first goal of this review is to identify the strengths and weaknesses of the published HRT data and especially to put into perspective all WHI HRT analyses. Special emphasis is placed on HRT indications for women who become menopausal as a result of a natural or iatrogenically-induced ovarian suppression, and who suffer with postmenopausal symptoms. These are mostly women aged 50–59 and/or <10 years from menopause.

The second objective of this review is to define the new generation of HRT regimens – agents of the lowest active dose that will palliate vasomotor and other menopausal symptoms effectively. This issue is important as the "classical" estrogen, the Premarin 0.625 tablets and Provera 2.5 mg used in most observational and in the WHI HRT trials, are considered more toxic, and thus likely associated with substantially more hazards.

24.2 The Women's Health Initiative (WHI) Hormone Replacement (HRT) Trials

The Women's Health Initiative (WHI) is perhaps the most extensive population research investigation undertaken in recent decades [6].

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_24, © Springer-Verlag Berlin Heidelberg 2010

The WHI program included four randomized controlled clinical trials to evaluate the health benefits and risks among 68,132 postmenopausal women in the age range 50–79 at randomization. Enrollment into the WHI began in 1993 and concluded in 1998.

1. *TRIAL ONE* involved HRT testing in healthy women and with uterus intact the impact of conjugated equine estrogens (CEE, Premarin, 0.625 mg/day) plus progestin (medroxyprogesterone acetate 2.5 mg/day vs. placebo). The primary objective was to determine the HRT impact on CHD prevention, with breast cancer as an anticipated adverse effect. Additional HRT-related conditions constituted secondary objectives. Overall, 16,608 women were randomized to this trial.
2. *TRIAL TWO* was designed for women without uterus and randomized to conjugated equine estrogens (CEE, Premarin) *alone* vs. placebo, with the same objectives as TRIAL ONE. Altogether, 10,739 women were recruited to this trial.
3. *TRIAL THREE* tested low fat against conventional diet for breast and colorectal cancer prevention, with 48,835 women randomized.
4. *TRIAL FOUR* tested the impact of calcium and vitamin D supplementation. Hip fractures were the designated primary outcome, with other fractures and colorectal cancer as secondary outcomes. In total, 36,282 women were randomized to this trial.

The WHI program also includes an observational study (ObSt) that comprised 93,676 postmenopausal women recruited from the same population base as the randomized trials. The ObSt is intended to provide additional knowledge about risk factors for a range of diseases, including cancer, cardiovascular disease, and fractures. It has an emphasis on biological markers of disease risk and on risk-factor changes as risk modifiers.

Table 24.1 provides information on enrollment by age-group in the various WHI components.

The estrogen plus progestin trial ended early on July 8, 2002, when evidence had accumulated that the health risks exceeded the benefits for this study population, according to predefined WHI planning committee criteria. The second HRT trial in the estrogen-alone component was also halted early, on February 29, 2004, because of increased risks of stroke. The Dietary and Ca-D-Vitamin trials ended as planned on March 31, 2005. The follow-up of participating women is planned through 2010, which will give an average follow-up duration of 13 years in the four randomized trials and 12 years in the observational study.

Table 24.1 Age at trial start, and frequency of the vasomotor (postmenopausal) symptoms in women participating in the first Women's Health Initiative (WHI) Hormone Replacement Therapy (HRT) trial with estrogen plus progestin vs. placebo

Age categories	Estrogen ± progestin (*N*: 8,506)	Placebo (*N*: 8,102)
Mean age at trial start	63.2	63.3
Age 50–59	33.3%	33.1%
Age 60–69	45.3%	45.1%
Age 70–79	21.8%	21.7%
Years since menopause		
<10	32.7%	33.5%
10–19	21.7%	22.3%
>20	21.7%	22.3%
Vasomotor symptoms		
None	60.7%	60.8%
Mild	25.8%	26.1%
Moderate/severe	12.6%	12.0%

Trial participants, *N*: 16,608

According to Rossouw et al. [104]

With both WHI HRT trials ending prematurely, women already enrolled in the trials were asked to stop the allocated therapy. Soon afterwards, women worldwide were told to discontinue or to never start the HRT.

24.3 The WHI HRT Trials: Background

The WHI HRT trials were planned because of rising concerns that past HRT observational and case–controlled studies were based on small patient sample size or on study results with preselected participants who were in a better state of health than women who were not eligible for HRT. Thus, the objectives of the WHI studies were to determine, from large randomized trials, the individual HRT-related outcomes, in order to influence the clinical practice, whereby HRT was increasingly prescribed not only for the palliation of postmenopausal symptoms, but also for reduction of heart disease morbidity, cardiac mortality, and in general, to slow down the chronic degenerative conditions related to aging.

24.3.1 The First WHI Trial

The July 17, 02 JAMA article reported the results of the first of the two trials – the Estrogen plus Progestin (E2+Prog) vs. placebo. Between 1993–1998, the WHI enrolled 16,608 women aged 50–79 with an intact uterus into the first HRT study, and randomized them into:

1. *ARM ONE,* 8,506 women receiving Premarin 0.625 mg/day (estrogen)+Provera 2.5 mg/day (progestin) vs.
2. *ARM TWO* with placebo pills.

The primary outcome measures were events related to *incident* cases of:

1. *Coronary heart disease – CHD* (EVENT 1)
2. *Invasive breast cancer* (EVENT 2)

Secondary outcomes included EVENT 3: Stroke; EVENT 4: thromboembolism defined as deep vein thrombosis or pulmonary embolism; EVENT 5: colon cancer; EVENT 6: endometrial cancer; and EVENT 7: skeletal fractures (hip, vertebral, or other osteoporotic).

Information on death was provided for cardiovascular causes, breast cancer, other cancers, and other known causes.

A "Global index" summarized the balance of the seven incidence events, as well as the "death due to other causes" and was defined as the definitive marker of benefit or hazard.

Each event as well as the Global index were expressed as absolute numbers/10,000 person-years, and as Hazard rates (with increased hazards defined as HR = 1.0; and benefits as HR = 1.0), with appropriate 95% confidence intervals (CI). Over 25% of cases were past or current HRT users, with over 30% of those having had HRT use of >5 years duration prior to randomization. Median age was 63.1 years, with only one third (33%) of the participants being less than 60 years of age.

Results

The first WHI HRT trial with Premarin + Provera versus Placebo was terminated on the advice of the independent Data and Safety Monitoring Board after a mean 5.2 years of follow-up because of an increased risk of breast cancer and an overall assessment of harms exceeding benefits for chronic disease prevention.

A summary of the most *complete trial results* published (Table 24.2–24.3) ending July 7, 2002 (mean follow-up 5.6 years), confirmed the interim findings. Specifically reported were a 26% increase in breast

Table 24.2 Clinical outcome by the randomization assignment. The first WHI HRT trial. Annaul event %, and hazards (HR) with appropriate 95% confidence limits (C.I.)

	HRT (*N:* 8506) (%)	Placebo (*N:* 8102) (%)	HR	95% confidence intervals
CHD – any event	0.37	0.30	1.29	0.85–1.97
CHD deaths	0.07	0.06	1.18	0.47–2.98
Nonfatal MI	0.30	0.23	1.32	0.82–2.13
Stroke – any	0.29	0.21	1.41	0.86–2.31
Fatal	0.04	0.03	1.20	0.32–4.49
Nonfatal	0.21	0.14	1.50	0.83–2.70
Thromboembolism	0.34	0.16	2.11	**1.26–3.55**
Pulmonary embolism	0.16	0.08	2.13	0.99–4.56
Cancer				
Invasive breast cancer	0.38	0.30	1.26	0.83–1.92
Endometrial cancer	0.05	0.06	0.83	0. 29–2.32
Colorectal cancer	0.10	0.16	0.63	0.32–1.24
Fractures	1.47	1.91	0.76	**0.63–0.92**
Total deaths	0.52	0.53	0.98	0.95–1.39

95% Confidence intervals in bold and underline indicate statistical significance, "*P*"<0.05
According to Rossouw et al. [104]

Table 24.3 WHI HRT first and second trials: impact on HRT on total mortality, coronary heart disease, and strokes

Age	HRT %	Placebo %	RR	95% CI
Total mortality				
50–59 (*N:* 8,832)	0.24	0.31	**0.70**	**0.51–0.96**
60–69 (*N:* 12,362)	0.76	0.74	1.05	0.87–1.26
70–79 (*N:* 6,153)	1.52	1.36	1.14	0.94–1.37
CHD – incidence				
50–59 (*N:* 8,832)	**0.26**	**0.28**	**0.93**	**0.65–1.33**
60–69 (*N:* 12,362)	0.56	0.58	0.98	0.79–1.21
70–79 (*N:* 6,153)	1.05	0.86	1.26	**1.00–1.59**
Strokes – incidence				
Years since menopause				
50–59 (*N:* 8,832)	**0.20**	**0.17**	**1.13**	**0.73–1.76**
60–69 (*N:* 12,362)	0.50	0.33	1.50	1.17–1.92
70–79 (*N:* 6,153)	0.82	0.66	1.21	0.93–1.58

Annual event %, analysis according to age (50–59 vs. 60–69 vs. 70–79)Based on WHI first HRT trial, Rossouw et al. [104], p. 1471, Table 4

cancer incidence, 29% increase of CHD, 41% increase in risk of stroke, and a doubling of the rates of thromboembolism. None of these hazards, with the exception of thromboembolism, were increased with statistical significance. There was also a significant 25% *reduction* of skeletal fracture rates, a 37% reduction of colorectal cancer, a 17% reduction of endometrial cancer, and a 2% reduction of deaths from any cause.

However, despite these benefits, the Global index was increased (HR = 1.15, 95%CI: 0.95–1.39).

In absolute terms, the results of the first WHI HRT trial confirmed in the estrogen plus progestin arm *excess* of CHD (excess of 0.07%); breast cancer (excess of 0.08%), stroke (excess of 0.08%), pulmonary embolism (excess of 0.08%); but *reduced events* of skeletal fractures (reduction by 0.44%); colorectal cancer (reduction by 0.06%); endometrial cancer (reduction by 0.01%); and of *total deaths* (reduced by 0.01%/year). Blood lipid levels showed favorable profile, with reductions in low-density lipoprotein cholesterol (−12.7%) and increases in high-density lipoprotein cholesterol (+7.3%) and triglycerides (+6.9%).

Thus, authors concluded that for an average 5.2 years follow time:

1. Overall health risks of combined estrogen plus progestin exceeded benefits among healthy postmenopausal U.S. women.
2. All-cause mortality was not different between the two groups.
3. The risk-benefit profile is not consistent with the requirements for an intervention for primary prevention of chronic diseases such as CHD.

The Data and Safety Monitoring Board *(DSMB)* reviewing the interim May 31, 2002 analyses found adverse effects in cardiovascular disease within the monitoring boundaries (i.e., not requiring the stopping of the trial). However, the increased risks for invasive *breast cancer* necessitated a premature termination of the trial. All investigators, trial participants, and public at large were informed about these results and their interpretation, and trial participants randomized to the HRT were asked to stop their allocated hormones.

24.3.2 The Second WHI HRT Trial

Despite the early termination of the first WHI estrogen plus progestin trial in 2002, the second WHI estrogen-alone trial was continued. In this trial, women after hysterectomy were randomized into *ARM ONE*, of HRT with estrogen alone (conjugated estrogen, [CEE, Premarin 0.625 mg/day continuously]) without the progestin (5,310 women), vs. *ARM TWO* of placebo (5,429 women).

Of all participants, only less than one third (30.8%) were <60 years of age; and over 47% were past or current HRT users before enrollment. Approximately, 40% of all participants had oophorectomy with hysterectomy (39.5 vs. 42% in arm of CEE vs. Placebo, respectively). Forty eight percent of women in the trial had been treated for hypertension and 15% had therapy for elevated cholesterol. Overall, 86% of all patients had no first-degree relative with breast cancer, and 74.5% had no benign breast disease in the past.

Estimated hazard ratios (with adjusted 95% confidence intervals) for CEE vs. placebo for the major clinical outcomes available through February 29, 2004 are shown in Table 24.5. Overall, there was a 9% reduction of CHD, a 33% (nonsignificant) increase in thromboembolism, a 39% increase in strokes, and an 8% increase in colorectal cancer; reduced were rates of breast cancer, by 23%; overall skeletal fractures by a significant 30%, and significant 39% reduction of hip fractures. Total death rate was increased nonsignificantly, by 4%; and so was the global index, by 1%.

For the outcomes significantly affected by CEE, there was an absolute excess risk of 12 additional strokes per 10,000 person-years and an absolute risk reduction of six fewer hip fractures per 10,000 person-years. The estimated risk for all monitored events in the global index was a nonsignificant excess of two events per 10,000 person-years.

On account of these results, the second WHI trial on CEE alone vs. placebo concluded that the use of CEE, in women after hysterectomy, after follow-up of 6.8 years:

a. Increases the risk of strokes.
b. Decreases the risk of hip fracture.
c. Does not affect the CHD incidence.
d. With a possible reduction in breast cancer risk requiring further investigation.
e. The sum of combined events was equivalent in the CEE and placebo groups, indicating no overall benefit and no hazards.
f. Thus, CEE should not be recommended for chronic disease prevention in postmenopausal women.

As a result of these data, after reviewing data through November 30, 2003, the National Institutes of Health (NIH) decided in February 2004 to end the intervention phase of the second WHI HRT trial early, with results published in the April 14, 2004 issue of the *Journal of American Medical Association* [89].

Consequences of the WHI reports. The recommendations to stop HRT resulted, in subsequent years, in millions of women in the Western world discontinuing HRT, even if they were in the age-group of 50–59, and suffering with vasomotor symptoms. By then, approximately 38% of postmenopausal women in the United States used HRT. In the year 2000 alone, just prior to the WHI HRT trial publication, 46 million prescriptions were written for Premarin (conjugated estrogens), making it the second most frequently prescribed medication in the United States and accounting for more than $1 billion U.S. in sales [90].

By the end of 2002, the use of hormone-replacement therapy had decreased by 38% in the United States, with approximately 20 million fewer prescriptions written in 2003 than in 2002. By the year 2005, the decrease was by 71%, and the drop continues [16].

This move represents one of the most dramatic health policy shifts registered in the recent medical history. HRT benefits from most past case–control and observational studies were in question, and most publications of the WHI trials and editorials universally agreed on more harm than benefits of HRT.

Thus, at the start of the critique, we ask several questions, specifically about the age of participants as over 2/3rd were >age 60; also questioned is the possible adverse impact of HRT using progestins, as estrogen alone had more beneficial breast cancer profile. Lastly, questioned is appropriateness of HRT agents – in the era when high-dose Premarin and Provera both used in WHI HRT trials are agents considered more toxic than the newer regimens based on lower hormone dose or nonoral use.

24.4 Overview of the WHI HRT Trial

24.4.1 Analyses According to Age (Table 24.3)

Overall, when all women are analyzed, the WHI first HRT trials showed more CHD, strokes, and thromboembolism. Also, higher breast cancer incidence rates were seen in the first WHI HRT trial but not in the second trial. These hazards were highlighted in most WHI publications since 2002. However, if one takes the results for younger women – those aged 50–60 or those

<10 years since menopause – the results look different (Table 24.3).

Table 24.3 shows that relative risks for *total mortality* of women aged 50–59 at the time of enrollment to the first WHI HRT trial is substantially reduced, with a statistically significant 30% reduction of all-cause mortality (HR = *0.70*; 95% CI: 0.51–0.96).

Similarly, CHD for women aged 50–59 was not adversely affected (HR = 0.93, 95% CI: 0.65–1.33), and for women <10 years since menopause, the CHD showed a nonsignificant reduction, by 24% (HR = *0.76*, 95% CI: 0.50–1.16).

Importantly, incidence rates of strokes were also not affected in the younger women, with hazards moderately elevated but without statistical significance (HR = 1.13, 95% CI: 0.73–1.76). It was only in the older age-groups, age 60+, that stroke hazards were increased more substantially (Table 24.3). However, even in the elderly age-group, the absolute rates of strokes in association with HRT are considerably lower than the risks due to potentially avoidable life style factors such as smoking, lack of exercise, overweight, and/or alcohol consumption.

Specifically, the actual rates of strokes taking women of all ages from the first WHI trial – figures which do matter when individual decisions are made for a given woman suffering with menopausal symptoms – were 0.19% in the HRT group vs. 0.11% for women in the placebo group, for an absolute increase of +0.08% of stroke incidence. The corresponding increase in women in 50–59 age-group is +0.02%.

24.4.2 Breast Cancers: Analyses According to Past Hormone Use

Taking all participants in the first WHI HRT trial, breast cancer incidence rates were increased nonsignificantly (when *HR = 1.26*, 95% adjusted CI: 0.83–1.92). However, Table 24.4 shows that 74.1% of all women who were without the past HRT use prior to the study enrolment had no increase of invasive breast cancer (HR = 1.06). It was only in women with past hormone intake and in particular for those with >5 years that the HRT was associated with a significant increase in breast cancer rate (Table 24.4).

24.4.3 Impact of HRT and Duration of Follow-Up

With the follow-up duration of patients enrolled in the first WHI HRT trials, further interesting observations were noted for CHD [91]. While in the first years of the trial there was a fluctuation of cardiac hazards (ranges 0.99–1.78), in the subsequent follow-up (years of 6–8+), the hazard rates were reduced, with CHD reduced by 22% (HR = 0.78). Similarly, for strokes, in years 1–3, the hazard rates fluctuated between 0.99–1.79; however in years 6–8+, the stoke rates were reduced by 34% (HR = 0.66) [1, 73, 76].

Table 24.4 Breast cancer rates, according to prior use of progestin

Panel A: WHI first HRT trial with estrogen + progestin, vs. placebo (according to JAMA, 2002, pp. 328–329)				
Prior use of HRT (*N*)	Estrogen + progestin (*N*: 8,506)	Placebo (*N*: 8,102)	HR	95% CI
All (*N*:16,604)	166 (0.38%)	124 (0.30%)	**1.26**	0.83–1.92
No prior use of menopausal hormones (*N*: 12,304)	114 (0.34%)	102 (0.33%)	**1.06**	0.7–1.97
Prior use <5 years (3,005)	32 (1.4%)	15 (0.8%)	**2.13**	1.15–3.94
Prior use 5–10 years (783)	11 (0.59%)	2 (0.1%)	**4.61**	1.01–21.02
Prior use >10 years (515)	9 (0.66%)	5 (0.38%)	**1.81**	0.60–5.43
Panel B: WHI second trial estrogen (CEE) alone vs. placebo (according to JAMA, 2006, Vol. 295, N 14, Table 2, p. 1650; and Fig. 3, p. 1653)				
Prior use of HRT (N)	Estrogen (*N*: 5,310)	Placebo (*N*: 5,429)	**HR**	**95% CI**
All	104 (0.28%)	124 (0.30%)	**0.80**	0.62–1.04
No prior use of menopausal hormones (7,802)	52 (0.27%)	79 (0.40%)	**0.65**	0.46–0.92
Yes prior use of menopausal hormones (2,937)	52 (0.29%)	54 (0.28%)	**1.02**	0.70–1.50

Noted are higher hazards of breast cancer seen in the first WHI HRT trial (progestin added to estrogen) compared to the second HRT trial (estrogen alone)

24.5 Overview of the Second WHI HRT Trial

24.5.1 Analyses According to Age (24.5)

The second WHI trial was halted in 2004, due to the perceived excess of overall hazards over benefits. However, the analysis restricted to the age-group 50–69 (Table 24.5) showed a 44% reduction of CHD events approaching statistical significance (*HR = 0.56,* 0.30–1.03). This compares, also in this trial, to much less CHD protection of HRT for women aged 60–69 (HR = 0.92) and basically no effect among women aged 70–79 (HR = 1.04).

A nonsignificant increase of thromboembolism was seen, with HR = 1.22, 1.31 and 1.44, respectively, for ages 50–59, 60–69, and 70–79.

As with the first WHI trial, strokes were also not increased among *young women aged 50–69* (HR = 1.08, 95% CI: 0.57–2.04), although the rates were increased nonsignificantly among participants aged 60–69 and 70–79 (HR = 1.65 and 1.25, respectively, Table 24.5).

Surprisingly, and in contrast to the first WHI trial, breast cancer rates after CEE alone were not increased, and (Table 24.6 a-c) outlines that most subsets of the second WHI trial actually experienced a substantial reduction of invasive breast cancers in association with CEE. That reduction reached statistical significance in the sizable subset of women *without* underlying breast cancer risk factors (see below).

Also confirmed in this trial were reductions of colorectal cancer, with the rates reduced more so in younger women aged 50–59 (HR = 0.59), with less CRC benefit with increasing age (HR = 0.88 and 2.09, respectively for age-groups 60–69 and 70–79, respectively).

Bone fractures, among all participants (except the women <age 60 with very few events) were reduced consistently, with trends for more protection among younger women (*HR = 0.33*, for the ages 60–69 vs. *HR = 0.62*, for ages 70–79).

Total death rates were reduced nonsignificantly by 27% among young women aged 50–69 – more so when compared to women aged 60–69 and 70–70 (HRs = 1.01, and 1.20 respectively).

Table 24.5 Impact of HRT on estrogen-related outcomes, in the second WHI HRT trial (estrogen alone vs. placebo), according to age groups

	CEE (%)	Placebo (%)	HR	95% CI
Coronary heart disease				
Age 50–69	0.14	0.24	**0.56**	0.30–1.03
Age 60–69	0.54	0.59	0.98	0.69–1.23
Age 70–79	0.88	0.84	1.04	0.75–1.44
Stroke				
Age 50–69	0.16	0.16	**1.08**	0.57–2.04
Age 60–69	0.49	0.30	1.65	**1.16–2.36**
Age 70–79	0.71	0.57	1.25	0.85–1.82
Venous thromboembolism				
Age 50–69	0.15	0.13	**1.22**	0.62–2.42
Age 60–69	0.31	0.23	1.31	0.86–2.00
Age 70–79	0.40	0.28	1.44	0.86–2.44
Invasive breast cancer				
Age 50–69	0.21	0.29	**0.72**	0.43–1.21
Age 60–69	0.26	0.36	0.72	0.49–1.07
Age 70–79	0.32	0.34	0.94	0.56–1.60
Colorectal cancer				
Age 50–69	0.07	0.12	**0.59**	0.25–1.41
Age 60–69	0.16	0.19	0.88	0.52–1.48
Age 70–79	0.32	0.15	2.09	**1.08–4.04**
Total deaths				
Age 50–69	0.29	0.39	**0.73**	0.47–1.13
Age 60–69	0.79	0.79	1.01	0.79–1.29
Age 70–79	1.54	1.30	1.20	0.93–1.54

According to Anderson et al. [105], modified from Fig. 5, p. 1709

24.5.2 Analysis of Invasive Breast Cancer

The unexpected yet potentially most important aspect of the WHI second HRT trial involved invasive breast cancer analyses. Taking all trial participants, the hazard rates of invasive breast cancer were reduced by 20% – a reduction approaching statistical significance (*HR = 0.80,* 95% CI: 0.62–1.04).

As seen in Table 24.6, women with no past history of breast disease (79.6% of the participants) had a significant 43% reduction of invasive breast cancer by HRT (*HR = 0.57*, 95% CI: 0.41–0.78). Similarly, women without a history of first-degree relative with breast cancer (86% of the trial population) had a statistically significant 32% reduction of invasive breast cancer with estrogen alone (Table 24.6, *HR = 0.68,* 95% CI: 0.50–0.92).

Table 24.6 **a-c** Rates of invasive breast cancer, second WHI HRT trial, CEE vs. placebo, in women with hysterectomy: impact of prior risk factors (conditions)

Past benign breast disease (*N*)	CEE (5,310) (% event)	Placebo (429) (% event)	HR	95% CI
Panel A: Risk of invasive breast cancer, as determined by history of benign breast disease				
All patients (10,739)	0.28	0.34	**0.80**	0.62–1.04
No (7,681)	**0.23**	**0.39**	**0.57**	**0.41–0.78**
Yes, 1 biopsy (1,439)	0.45	0.29	1.60	0.82–3.14
Yes, >1 biopsy (545)	0.41	0.19	2.54	0.73–8.86
Panel B: Prior risk for breast cancer determined by first-degree relative with breast cancer				
First-degree relative with breast cancer	**CEE (%)**	**Placebo (%)**	**HR**	**95% CI**
None (8,554)	**0.23**	**0.34**	**0.68**	0.50–0.92
>1 (1,382)	0.41	0.19	2.54	0.73–8.86
Panel C: Rates of invasive breast cancer prior risk for breast cancer as determined by Gail score				
5-year Gail risk score	**CEE (%)**	**Placebo (%)**	**HR**	**95% CI**
<1.25 (4,278)	**0.24**	**0.32**	**0.76**	0.54–1.17
1.25–1.74 (3,308)	**0.18**	**0.39**	**0.45**	**0.26–0.76**
>1.75 (3,153)	0.43	0.34	1.28	0.83–1.97

95% confidence intervals in bold and underline indicate statistical significance, "*P*"<0.05

According to JAMA, 2006, vol 295, N 14, Table 2, p. 1650, Fig. 3 on p. 1653

Related to these data are the results according to the Gail score at the time of randomization (Table 24.6c), showing similar trends: a substantial 24-55% reduction of breast cancer in low/medium risk subsets, with a nonsignificant increase in those with a high Gail risk score. Also, women with no prior estrogen or progestin use (i.e., no "prior menopausal hormone use," Table 24.7) had a statistically significant 35% reduction of the rates of new invasive breast cancer (*HR = 0.65*, 95% CI: 0.46–0.92).

24.6 HRT and Breast Cancer Incidence: Changing Trends after WHI Trial Reports?

The data from the WHI HRT trials as published in the year 2002 had a strong impact on the previous HRT use, worldwide. Within months, the medical community and population at large were alerted about the HRT hazards. By the year 2003 – within 1 year of the first WHI HRT trial publication – only 65% of the previous year's HRT prescriptions were filled in North America, with the HRT use reduction representing one of the most substantial shifts of medical policies ever recorded.

In 2007, Ravdin et al. published data indicating a *reduction of breast* cancer incidence in 2003 in USA – associating these trends with the HRT policy shifts [16]. Specifically, data from SEER showed that the age-adjusted incident rates of women's breast cancer in the USA fell between the years 2002 and 2003 by 6.7%. However, the rates in 2004 subsequently showed a leveling relative to the 2003 rates, with little additional decrease. The decrease of new breast cancer rates was evident only in women 50 years of age or older and was more evident in cancers that were estrogen-receptor positive than in those that were estrogen-receptor negative. According to the authors, the decrease in breast cancer incidence seems to be related to the first WHI trial report – and to the ensuing HRT use reduction among the postmenopausal women in the United States.

These data were subsequently updated, and reinforced by Chlebowski et al. [17], showing from the WHI update of the first HRT trial, a firm association between discontinuation of estrogen plus progestin combination, and decrease, with 1–2 years, of new breast cancers. No data regarding breast cancer rate dynamics are available from the second HRT trial.

Table 24.7 Invasive breast cancer in the second WHI HRT trial: impact of HRT with CEE alone, according to prior estrogen or progesterone (hormone) exposure

	CEE (*N*: 5,310) (%)	Placebo (*N*: 5,429) (%)	HR	95% CI
All women (*N*: 10,739)	0.28	0.34	0.80	0.62–1.04
Prior estrogen use: no (5,763 women)	0.27	0.40	**0.68**	**0.48–0.96**
Prior estrogen use: yes (any length, (4,976 women))	0.29	0.30	**0.98**	0.67–1.44
Prior estrogen + progestin use: yes (468 women)	0.44	0.16	**2.35**	0.60–9.14

According to JAMA Apr. 2006, Vol. 295, Table 2, p. 1650, Fig. 3, p. 1653

24.7 Comments Regarding HRT Policy Shift and Reduced Breast Cancer Incidence Rates

The data linking the primarily estrogen receptor-positive breast cancer incidence rate reduction with HRT discontinuation are of great interest. However, it has also been identified that the downward trends of breast cancer incidence rates started before the year 2002, already evident from the mid- to late 1990s.

After the implementation of screening mammography, there was an increase of Breast cancers among postmenopausal women. Screening mammography reached maximum in the late 1990s, with 70.1% of women having biennial mammograms [92]. In parallel, postmenopausal breast cancer rates according to SEER's data declined, and began to shift from older into younger ages at onset, probably because prevalent older screened breast cancer patients were removed from the general population [92]. Recent declines in HRT usage after the July 2002 WHI announcement have likely accelerated this decreasing incidence trend among older women.

Other data such as lifestyle factor including increased exercise, better diet, and DCIS (ductal carcinoma in-situ) management provide factors. Of interest, is the DCIS guideline changes in the late 1980s and throughout the 1990s – with the more aggressive management leading to more frequent excisions of the DCIS lesions, which could have also been an additional factor contributing to the subsequent reduction in invasive breast cancer, independent of the HRT [93].

Also, data from Europe have shown that, between the years 2002 and 2005, breast cancer incidence rates were stable in Norway and Sweden despite the sharp decline in the use of HRT, contrasting the results reported by Ravdin's et al. [94, 95].

These opinions do indicate that while there may have been an accelerated rate of breast cancer reduction observed related to the year 2002 WHI HRT publication, the reductions when projected over long time, are continuous since the 1990s – and thus not restricted to the recent times since the year 2002.

Thus, while a continuous drop in breast cancer incidence is evident over the last 10–15 years, Ravdin and Chlebowski data are nevertheless compatible with the changing HRT use policies contributing after the year 2002 toward other largely multifactorial epidemiology factors, cumulatively resulting in an ongoing breast cancer incidence reduction in the Western world.

Correlations of the fluctuating incidence trends with the breast cancer mortality trends will be very important. Breast cancer mortality reduction has been noted in most Western countries from the early 1990s – and in some pockets of the Western world already in the early 1980s [96], a time era with well established and/or *increasing* HRT intake. Thus, the long-term follow-up of HRT impact on breast cancer mortality will be needed to clarify the complex issue of hormonal impact on human carcinogenesis.

24.8 Estrogen Breast Cancer Protective and Progestin A Breast Cancer Carcinogen? Identification of a New Paradigm

The analyses of the WHI HRT trials showing invasive breast cancer reduction with CEE alone implicate differentiating estrogen effect as possible protective chemopreventive activity for breast cancer.

However, review of the first WHI HRT randomized trial has shown estrogen *plus* progestin combination a substantial breast cancer rate increase, significant statistically in some subgroups. While the magnitude of invasive breast cancer rate increase after combined estrogen *plus* progestin vary among subsets such as those with differing duration of prior hormone use, the rates of the estrogen–progestin combinations were almost never decreased.

Table 24.4 show these results. Table 24.4 shows breast cancer rates from the first HRT trial, all increased, with rates for all participants increased by 26% (HR = 1.26, 95% CI: 0.83–1.92); of particular increases are rates in subgroups with prior hormone use, with HR ranges 2.13–4.61. Noted is that even in those with no prior hormone use, the incidence was increased by 6% (HR = 1.06, 95% CI: 0.7–1.97).

As seen in Table 24.7, the breast cancer incidence rates from the second HRT trial are reduced by 20% in all participants (HR = 0.80, 95% CI: 0.62–1.04), with rates statistically significantly lower among women with prior use of hormones (HR = 0.65, 95% C: 0.46–0.92); furthermore, Table 24.7 shows breast cancer rates according to prior estrogen or progestin, with no rate increase in women taking prior estrogen (HR = 0.98, 95% CI: 0.67–1.44); however a more substantial (although not statistically significant) increase when progestin is also added (HR = 2.35, 95% CI: 0.60–9.14).

The emerging concepts of progestin contributing to the carcinogenic effect of breast cancer, and estrogen *alone* being potentially breast cancer protective, are new and require urgent confirmation in both epidemiology and molecular biology studies. However, in the absence of new HRT trials, there is evidence that estrogen, in women with hysterectomy used alone without progestin, as randomized in the second WHI HRT trial is not only safe with regard to breast cancer carcinogenesis, but in appropriately selected subsets, may be protective.

24.9 Summary

Overall, three main observations from the WHI randomized HRT trials are contributory and new:

First, that the CHD and overall mortality endpoints of chronic disorders will not be positively affected by HRT in the trial participants who were >60-years old, many over the age of 70. These more elderly women are therefore poor candidates to initiate HRT.

Second, that women without a history of significant risk factors for breast cancer may have a significant protection for subsequent incidence of invasive breast cancer using estrogen alone, without progestin.

Third, this review based on the WHI HRT trials shows that in *younger women* the decision-generating algorithm for HRT use will be substantially different than in more elderly postmenopausal women, not only as the intensity of menopausal symptoms is typically more severe, but also as most HRT-associated hazards are substantially lower, and benefits higher.

Thus, as identified in this chapter, the WHI trial data when applied to *appropriate candidates*, do confirm some of the conclusions generated in the past decades of large observational studies with long follow-up: that HRT will improve the quality of life in most women entering menopause, and in addition may have all-cause mortality benefits most evident among younger women aged 50–69. After estrogen alone, HRT may be associated with reduced breast cancer rates. Thus, in well selected candidates, HRT-associated hazards are small, and have to be viewed in perspective with quality of life benefits of HRT due to reduction of menopausal symptoms for women suffering these symptoms, and in view of other avoidable risk factors.

24.10 Concluding Remarks

There is no doubt that HRT issues remain complex, even after a thorough research as demonstrated in this chapter. Our knowledge of hormones and their impact on benefit and hazard in humans continues to evolve.

It would be fair to conclude that the WHI trials, as did the prior observational studies, contributed greatly by generating large amounts of essential data. These indicate that no single answer with regard to HRT recommendations do exist for *all* women.

When considering HRT, individual heterogeneity based on age and the known risk factors for each condition affected by HRT will need to be taken into consideration. To add to the complexity and thus challenges of clinicians and women dealing with HRT, these factors are influenced by an array of largely unknown genetic predispositions affecting most HRT-associated conditions.

It is very likely, as with most therapies of human conditions, that some women will derive a great deal of benefit from HRT with few hazards; some will have some benefit, and some none. Some even in the younger age category, if genetically predisposed, may suffer more hazards than benefits – the inevitable outcome of most classes of medications for some individuals.

It remains without saying that all HRT benefits and hazards will have be to monitored on an on-going basis, with women and their practitioners kept fully informed at all times about the complex HRT therapy as its research continues to evolve. This issue is important, primarily in view of the fact that the WHI trial reanalyses as illustrated in our review confirm that the perception of the HRT facts and the recommendations of today may not necessarily apply to tomorrow.

Accepting an HRT program is ultimately the decision of each individual woman, who should make the final decision, at times accepting small hazards for a substantial improvement in the quality of her life. The important condition in this decision process, however, is a full knowledge of all facts – those fully emphasized as well as those in small print. This is the goal of this review.

24.11 Appendix I

24.11.1 Observational and Case–Control HRT Studies Prior to the Publications of the 2002 WHI HRT Trials. Breast Cancer

The collaborative Group on Hormonal Factors in Breast Cancer collected and reanalyzed individual data on over 50,000 breast cancer cases and over 100,000 healthy women, as seen from 51 different epidemiological studies OG HRT [7]. It thus represented, until the year 2002, the most comprehensive overview of HRT ever published.

The results of this meta-analysis were that for current or recent HRT users, when compared to nonusers, the relative risk for breast cancer was increased, with Hazards rates (HR) = 1.023/year, translating into a 2.3% increase of annual incidence of breast cancer. The overall risk increased with the duration of HRT use, so that in users of over 15 years, cumulative Hazard rates (HR) of 1.3 for incidence was observed.

A 2002 review on the subject [8], summarized these results and indicated that while a breast cancer risk increase has been observed, it should be assessed in relation to other epidemiological causes for breast cancer risk increase [9].

For instance, much higher rates in the range of 40–60% (HR = 1.4–1.6) have been reported due to other conditions such as moderate alcohol consumption [10], absence of exercise [11, 12], nulliparity, or high caloric intake [13].

The past HRT policies are also to be viewed in conjunction with data showing that in the population of women at large, up to 45% mortality is from cardiovascular disease and less than 5% from breast cancer. Thus, the moderate increase of breast cancer rates related to HRT will result in lesser absolute added risk than the cardiovascular mortality – considered in the years before 2002 to benefit from HRT. Thus, the breast cancer hazards were acceptable for those women who suffer with severe menopausal symptoms, as in absolute terms, a small increase in the risk of breast cancer would be tolerable because the overall risk benefit ratio would favor HRT. Indeed, all-cause mortality was improved by HRT, shifting the HRT equation in favor of overall benefits [3, 14].

24.11.1.1 HRT and Carcinogenesis vs. Promotional Effect

The surprisingly short time period of recorded breast cancer events in relation to HRT – i.e., fluctuations of breast cancer rates are seen within 1–2 years of HRT start or discontinuation – negate the HRT effect on *carcinogenesi*s and shift the emphasis to tumor *promotion*. These data are obtained not only from the past observational trials [15], but also from the recent WHI HRT analyses [1] and related epidemiology reports [16, 17].

The promotional rather than carcinogenic mechanisms would implicate the HRT effect primarily on the preformed malignant lesions, with resulting increased cell division of hormone sensitive clones. The accelerated formation of microcalcifications, and subsequently, earlier diagnosis through mammogram or physical examination would follow. In those women, however, the carcinogenic events presumably had occurred earlier and most likely with no connection with HRT. Thus, the *promotional* effect of HRT should be distinguished from any causative role.

These data also indicate a possibility that in the absence of HRT, the same tumor could develop later in time, but would present with a biologically more aggressive disease, and at a more advanced stage clinically. The data from the old literature described in either bacteria [18] or in cancer clones [19] indicate that with time, as a result of random ongoing mutations during cellular divisions in either bacteria or malignant tumor clones, there will be an exponential increase of mutants with aggressive, therapy-resistant phenotypes. Thus, tumors diagnosed later in their history would be more aggressive and less sensitive to hormonal, chemotherapy, or radiation treatments [19].

Several large observational studies indeed confirmed lower tumor aggressiveness in HRT users [5, 20–26], which may explain the observations of reduced breast cancer mortality in HRT users compared to nonusers, despite increased incidence [5, 21, 22, 24]. For instance, Grodstein et al. reported in the update of Nurse's health study [5] a significant reduction of breast cancer mortality (adjusted RR > 0.76) in women taking HRT for less than 10 years, despite the moderately increased breast cancer incidence rates (RR > 1.09–1.4). In addition, the HRT users in this study had a significant reduction of overall all-cause mortality (adjusted RR > 0.63), with a similar survival improvement in cases with a strong family history of breast cancer (RR > 0.65) or in cases who had HRT after oophorectomy (RR > 0.71).

Chlebowski et al. however were unable to confirm these observations from the recent WHI trial [27]. Estrogen plus progestin increased the rates of total and invasive breast cancers compared with placebo (199 vs. 150 cases; HR, 1.24, $P > 0.003$). The invasive breast cancers diagnosed in the estrogen plus progestin group were similar in histology and grade but were larger (mean 1.7 cm vs. 1.5 cm, respectively; $P > 0.04$) and were at more advanced stage (regional/metastatic 25.4 vs. 16.0%, respectively; $P > 0.04$) compared with those diagnosed in the placebo group.

In favor of Nurse's health study results, however, are data from the second WHI trial showing overall, reduced breast cancer incidence rates, after the use of HRT with estrogen alone (Tables 24.2–24.4). In this trial, women were randomized to estrogen (conjugated equine estrogen, CEE) without progestin, vs. placebo. In women with CEE, the incidence rates of invasive breast cancer were significantly reduced in the majority of participants (80%) *without* the past history of benign breast disease or without a first-degree relative with breast cancer, or similarly, significantly reduced were the breast cancer rates in participants without the past use of estrogens or progestins [28].

In view of these new data, the HRT association with breast carcinogenesis and biology is becoming more complex. The long-term follow-up outcomes of the WHI HRT trials with emphasis for a possible protective role of estrogen-alone on the rates of both breast cancer incidence and mortality.

Ravdin et al. recently reported a possible link between decreasing breast cancer incidence rates – as documented in U.S. – and *reduced HRT use* after the year 2002 – the year when the first results of the WHI HRT were published indicating excess of hazards over benefits. While comments regarding this association have been raised [29], a careful evaluation of not only incidence but also of mortality rates will be required, in order to clarify the important interactions of HRT use and breast cancer outcome.

24.11.2 Nononcological Aspects of HRT: Cardiac and Cardiovascular Events. Data Evaluation Before the 2002–2004 WHI HRT Trials

24.11.2.1 Estrogens and Lipids

Several longitudinal studies of postmenopausal women have shown a strong effect of estrogen on lipid metabolism [30], resulting in reduction of the plasma low density lipoproteins (LDL) and an increase in the high density lipoproteins (HDL). As the HDL/LDL ratio is one of the best predictors of future cardiovascular outcomes [31], it is plausible that in the long-term there could be significant benefit of estrogen use due to reduced atherogenesis. This mechanism may explain the long-term HRT benefits in the primary prevention of cardiac events [32–34], which exceeds its short-term hazards attributed, in all likelihood, to the HRT-associated increase in the rates of thromboembolism.

The most convincing evidence for the beneficial effects of HRT on lipid metabolism comes from the Postmenopausal Estrogen/Progestin Interventions, the PEPI trial [15], showing a significant reduction, at 3 years follow-up, of LDL-cholesterol (LDL-C) in HRT users, with HDL-cholesterol (HDL-C) levels increased compared to pretreatment levels. The PEPI trial is the

first placebo controlled *randomized* study to document that estrogen either alone or in combination with progestin significantly improves the serum lipid profile, thus confirming number of reports from *nonrandomized* studies. The results of the study also suggest that the effect on lipids may be comparable between estrogen alone and estrogen/progestin combination, particularly, using the newly available micronized progestin. The significance of these data for prevention of cardiac mortality is yet to be determined. The *long-term* follow-up of the ongoing randomized WHI trial [35] will provide a definitive answer to this issue. The PEPI trial is particularly important in view of other studies in which a modest incremental HDL-C increase (4–5 mg/dL) was associated with a 20–25% reduction of CHD. These findings are in line with the long-term follow-up of the observational HRT studies.

More recently, Darling et al. studied HRT and simvastatin in comparative lipid analyses [36] documenting that while the effect of simvastatin was greater than that of hormone therapy with regard to LDL-C reduction, the plasma concentration of Lp(a) lipoprotein – a known risk factor for CHD – *decreased* with hormone therapy (mean decrease, 27%; 95% confidence interval, 20–34%), but not with simvastatin [36].

24.11.2.2 Estrogen Effects on Vessels: Biochemical Effects

Other mechanisms indicate possible favorable vascular effect of estrogen. Thus, uptake of LDL is reduced by coronary arteries of monkeys fed with atherogenic diets randomized to estrogens [37, 38]. Also, estrogens are known to modulate the prostacycline-mediated vasodilating effect [39] and interact with calcium channel blockers [40] and Lp(a) [30, 41–44]. Furthermore, estrogen therapy significantly increased the catabolism of LDL [45]; estrogens also lowered the tissue concentration of adhesion molecules such as E-selectin, ICAM-1, and VCAM-1, yet another mechanism that may be known to reduce atherogenesis [46].

24.11.2.3 Direct Estrogen Effect on Vessel Wall

Another line of evidence suggestive of a protective effect of estrogens involves studies of direct effects of HRT on vessel walls. Estrogen receptors (ER) are present in the muscularis layer of arteries, and improved blood flow through the coronaries, documented upon estrogen exposure, is probably ER mediated [47, 48]. Consistent with these observations is the finding that in ovariectomized female monkeys, estrogen protected vessels from vasoconstriction after exposure to acetylcholine [49]. In other trials estrogen exposure led to a reduction of systemic vascular resistance [47, 49, 50]. Similar observations were also subsequently made in postmenopausal women [51, 52], where in one study estrogen reduced arterial impedance and vascular tone after 6 weeks of treatment [53].

Other investigators confirmed increased hyperemic response and vasodilatation after estrogen administration [54]. Pines et al. found improved flow velocity and improvement of the mean cardiac ejection fraction in estrogen users, as measured by aortic sonograms [55]. Finally, estrogen was found, in a placebo-controlled trial [55], to improve performance of women on a treadmill and to decrease symptoms of coronary artery disease [56] – effects which may be explained by the above-outlined estrogen effects on vessel vasculature.

24.11.2.4 Epidemiological Data on Estrogen and Heart Disease: HRT and Primary Prevention of Cardiovascular Disease

Most population-based studies examining HRT in the primary prevention of cardiac events have shown a strong risk reduction in users with cardiac mortality rates reduced between 20–60% [52, 57–62]. The magnitude of the HRT effect is similar between case–control and cross sectional studies [50]. While several hypotheses were offered to explain these observations, the most favored concern the favorable effects of estrogen on lipid metabolism [32, 38, 56, 63–65] and endothelial function [40, 47, 51, 53, 66, 67]. There is a possible bias due to the participation in the HRT cohort of healthier women, who may also undergo cardiac screening more effectively [60] as none of these studies were randomized. While these biases may exist, they do not fully account for the strong association of HRT with improved lipid profile and estrogen favorable vessel effect, both emerging as long-term surrogates for improved cardiac outcomes [32, 57, 62, 68].

24.11.2.5 Epidemiological Data on Estrogen and Heart Disease: Secondary Prevention

Once the atherosclerotic plaques and/or coronary occlusions produce clinical symptoms, therapy is usually not curative. Indeed, most interventions for the secondary prevention are expected to relieve symptoms, slow down progression, but not to completely reverse the lesions. Although the favorable lipid changes are seen early, the effects of HRT on the cardiovascular outcomes may take decades. It has also been predicted that, compared to its effect in primary prevention, hormonal therapy will have lower impact once the process of atherosclerosis has already advanced.

Indeed, the only randomized trial of secondary prevention, the HERs study, showed little cardiovascular protection. HERS trial was first published in the late 1990s [69] and updated recently [70]. A total of 2,763 women, 65 years or older (mean age: 66.7 years), with a history of myocardial infarction, were randomized in a double-blind placebo-controlled design, to be treated with either HRT (conjugated equine estrogen, CEE, 0.635 mg, plus daily medroxyprogesterone acetate, MPA, 2.5 mg/day) or placebo. At 4 years of follow-up, the authors reported no significant differences in deaths from CHD or myocardial infarction between the two arms (RR > 0.99, 95% CI: 0.80–1.22). The lack of an overall effect was seen despite a reduction of LDL levels and increase of HDL levels. More women in the HRT group had thromboembolic events (TEs) (RR > 2.89, 95% CI 1.50–5.58) and gallbladder disease (RR > 1.38, CI 1.00–1.92). There was no difference in cancer rates or overall mortality. For the latter two parameters, however, the power of the study was greatly limited. The authors' conclusion was that HRT does not reduce the overall rate of CHD in postmenopausal women with established coronary disease, and that the risk of thromboembolism and of gall stones is increased.

Examining the interaction of relative risk over time, interesting trends were observed. In the first year of the study, more cardiac events were seen in the users (RR > 1.52). In the second year, however, that increase was not seen any more, with the incidence of cardiac mortality or of the nonfatal infarctions among users vs. nonusers being equal (RR > 1.0). Subsequently, in years three and four, the risk of these events in HRT users was actually reduced (RR of 0.87 and 0.67, respectively), consistent with the degree of risk reduction seen in long-term follow-up observational primary prevention studies. The updated 2002 study showed, after the follow-up ranging 4–8 years, overall, no effect (RR > 0.99–1.0). However, the proportions of patients with at least 80% adherence to HRT declined from 81% in the first years, to only 45% in the year 6 [70].

Overall, these data indicate that in women with advanced atherosclerosis, the HRT may temporarily increase the morbidity, or even mortality, but in long-term, HRT plays no role in improving cardiac outcome once arterial occlusions occur. However, even in this population, HRT showed favorable effects on serum lipids, similar to the results of the primary prevention trials.

The increased event rate in the first years in the cohort of elderly women with established atherosclerosis exposed to HRT could be due to initial precipitating events such as thromboembolism or minor blood pressure fluctuations, not uncommon in the population of patients with advanced vessel disease. These complications would be, however, of lesser consequence in younger women without coronary disease. In these women, not only substantial improvements in the quality of life, but in long-term follow-up, also beneficial effect on lipid metabolism, and thus cardiac disease prevention, can be anticipated.

The analyses of the WHI HRT trials mirror these observations. Manson et al. [71] reported in the WHI ancillary substudy of 1,064 women aged *50–59* years at randomization of the second HRT trial (women with hysterectomy) results of estrogen (0.625 mg/day) impact on coronary-artery calcium scores as measured by computed tomography. The CT scans were carried out at 8.7 years after randomization, with the coronary-artery calcium scores measured at a central reading center without knowledge of randomization status.

The results showed the mean coronary-artery calcium score after trial completion to be significantly lower among the women aged 50–59 receiving estrogen than among those receiving placebo ($P > 0.02$ by rank test). After adjustment for coronary risk factors, the multivariate odds ratios for coronary-artery calcium scores in the group with at least 80% adherence to the study (estrogen or placebo) were reduced by 36% (HR = 0.64, $P > 0.01$).

Authors concluded that among women 50–59 years old at enrollment, the calcified-plaque burden in the

coronary arteries after trial completion was lower in women assigned to estrogen than in those assigned to placebo.

Our review of the WHI data [72] in women below age 60 shows early trends toward reduced CHD hazards (Table 24.3), with a significant all-cause mortality reduction in women aged 50–59. It is only among women over 60 and in particular in those over 70 that a nonsignificant trend is seen for increased CHD events. These data mirror the HERs trial: HRT has no impact on cardiac events in elderly women and failure of HRT in secondary prevention – yet they attest to the HRT potential benefit in primary prevention in women <60.

24.11.2.6 HRT and the "Timing" Hypothesis

Clarkson et al. published a series of analyses where they tested in primates the impact of immediate vs. delayed administration of estrogen in conjunction with atherosclerogenic diet [33]. Compared to controls, HRT showed a substantial reduction of the atherosclerotic plaques at the time of autopsy – but only if administered at the same time as atherogenic diet. Delayed HRT administration, late into starting the high-fat diet, had outcomes similar to animals who never received HRT.

More recently, Grodstein et al. [74] have prospectively examined the relation of HRT to CHD, according to the timing of hormone initiation, relative to age and time since menopause. Participants were postmenopausal women in the Nurses' Health Study, with follow-up extending from 1976 to 2000. The study showed that women beginning HRT near menopause had a significantly reduced risk of CHD – by 36% for estrogen alone (RR > 0.66, 95% CI: 0.54–0.80), and 28% for estrogen with progestin (RR > 0.72, 95% CI: 0.56–0.92). On the other hand, in the elderly women, at least 10 years after menopause – a subgroup demographically similar to those in the WHI – they found no significant relation between HRT and CHD among women who initiated therapy (HR = 0.87, 95% CI: 0.69–1.10 for estrogen alone; RR > 0.90, 95% CI: 0.62–1.29 for estrogen with progestin).

These data, same as the HERs trial [70, 75] confirm that no cardio-protective HRT effects are demonstrated when HRT is delivered after a more prolonged exposure of estrogen deficit state, and after the atherosclerotic plaques have formed.

Willet and Colditz, the principal authors of the Nurse's Health Study (NHS) – which showed substantial and significant cardioprotection by HRT – summarized the differences between the two trials recently [76]. In the WHI trial, women were eligible up to the age of 79 years, whereas in the NHS – and most observational studies showing cardiac benefits – more than 80% of the women initiated HRT use within 10 years of menopause.

Second, the NHS included women with much longer follow-up who had already been using hormone therapy for years. Thus, the effect mediated by improved lipid profile could have emerged in the NHS, but less likely in the WHI trial, with much shorter time of both HRT exposure, and follow-up duration.

Third, as in the HERS trial [69] where a transient risk elevation soon after HRT start is followed by risk reduction, the increased CHD risk is limited to the short interval soon after the initiation of HRT even in the WHI trials: For estrogen plus progestin, the relative risks for CHD were 1.68 for <2 years, 1.25 for 2–5 years, and 0.66 for 5 or more years [1, 76]. Prentice et al in the commentary on the WHI HRT trial [77] confirmed that when stratified by year from initiation of hormone therapy, the findings for CHD from the Nurses' Health and the WHI trials did not differ appreciably.

Hence the reanalysis of the WHI data according to age of participants – reflecting the "timing" of HRT start – and length of follow-up, may after all support the decades-long HRT research, which confirms both biochemical and lipid surrogate protection, but also a reduction of cardiac events in association with HRT.

24.11.3 Nononcological Aspects of HRT: Thrombo-Embolism (TE)

Estrogens are known to increase blood clotting, due to their effects on several clotting factors including fibrinogen, factors VII, X, and antithrombin III [78]. As a result, HRT is known to moderately increase the incidence of thromboembolism with HR ranging from 1.1–4.00 [3, 58, 69, 79–81]. However, despite these trends, no increase in mortality with HRT has been reported [82].

Abnormalities of clotting factors, however, may contribute to the HRT-associated complications [83–87]. It has been shown that a genetic variant of Factor V Leiden (especially the Factor V G1691A variant) is

responsible for the majority of TEs in users of birth control pills [84]. In women with established coronary disease, as reported in two clinical trials, the Leiden mutation was present in 8 (16.7%) of 48 cases with TEs compared with only 7 (6.3%) of 112 without TEs. In women with the factor V Leiden mutation who were treated with HRT, the estimated absolute incidence of TEs was 15.4 in 1,000 per year compared with 2.0 in 1,000 per year in women without the mutation who were taking a placebo (HR = 7.7) [87]. Van de Water [85] confirmed that in patients with myocardial infarction, the frequency of factor V Leiden mutation was 14.6% in patients <50 years old in the study group compared with 3.6% in patients in the control group [83].

With regard to strokes, a meta-analysis of 3,399 patients with stroke [86] showed a statistically significant association with factor VG 1691A variant (Leiden) [86].

The problem of thrombembolism in HRT users may be further complicated by other confounding factors, especially smoking. In a group with high Factor V or high Factor VII levels, smoking or high blood pressure increased the relative risk for myocardial infarction up to 50-fold [88].

Thus thromboembolism in the first years of HRT exposure could be responsible for vascular events leading to strokes and CHD, with genetic factors affecting coagulation in the first time exposure raising the risk. The first exposure to hormones will thus select the individuals prone on genetic grounds to thromboembolism, increased by other risk factors such as age, smoking, or hypertension. Subsequently, women continuing on HRT would experience fewer TEs, and may benefit, in long-term, from HRT. The "timing" hypothesis (see below) suggests that more adverse CVS events are related to thromboembolism in the first years of HRT exposure, followed by reduced hazard rates. This is confirmed in most observational trials by the dynamics of the HERs study, which is now also emerging in the WHI reports [1, 73, 76].

These data indicate that preventative measures in individuals prone to TE selected for HRT have to be considered. These should include interventions ranging from life style changes (i.e., emphasis on regular exercise, less sedentary activities, smoking cessation, reduced alcohol intake), to more targeted anti-TE interventions such as regular dose ASA (aspirin) – or in extreme cases where HRT is clearly required due to severity of menopausal symptoms, low doses of warfarin.

24.12 Appendix II

24.12.1 New HRT Agents

24.12.1.1 Clinical Equivalence of Intranasal and Oral 17β-Estradiol for Symptoms of Menopause [97]

This study confirmed that intranasal administration of 300 μg/day estradiol was at least as effective as oral administration of 2 mg/day estradiol in alleviating postmenopausal symptoms, with less frequent mastalgia and uterine bleeding and without the metabolic consequences of the first-pass effect.

24.12.1.2 A Prospective Randomized Comparative Study of the Effects of Intranasal and Transdermal 17β-Estradiol on Postmenopausal Symptoms and Vaginal Cytology [98]

Intranasal and transdermal 17β-estradiol combined with vaginal progesterone gel as a continuous HRT caused a similar decrease in vasomotor symptoms and did not have any significant effect on vaginal maturation index after 12 weeks of treatment in this study population.

Results of this study have shown that intranasal administration of 17β -estradiol (E2) is at least as effective as oral administration of 2 mg/day E2 in alleviating postmenopausal symptoms, with less frequent mastalgia and uterine bleeding and without the metabolic consequences of the first-pass effect.

Also, it is well-tolerated and provides a reproducible, easily adjustable dosing mechanism. Sustained-release vaginal progesterone gel ensures high endometrial protection and avoids the side-effects and possible risks linked to oral progesterones.

24.12.1.3 Efficacy and Acceptability of Intranasal 17β-Oestradiol for Menopausal Symptoms: Randomized Dose-Response Study. Aerodiol Study Group [99]

A third study documenting that intranasally administered 17β-oestradiol is significantly better than placebo

in reducing menopausal symptoms, and is similar to that of oral oestradiol. It was well-tolerated. Intranasal administration avoids first-pass metabolism and provides a reproducible, easily adjustable dosing mechanism that represents a new option for HRT.

24.12.1.4 Efficacy and Tolerability of Pulsed Estrogen Therapy: A 12-Week Double-Blind Placebo-Controlled Study in Highly Symptomatic Postmenopausal Women [100]

Pulsed estrogen therapy, achieved by intranasal estradiol 150 µg/day and 300 µg/day, significantly reduced the incidence of moderate to severe vasomotor symptoms, compared with placebo. *The 300-µg/day dose* demonstrated a greater and more rapid therapeutic effect, with no clinically significant difference in tolerability, compared with the 150-µg/day dose, and therefore offers the best efficacy/safety ratio when initiating treatment with intranasal estradiol.

24.12.1.5 Twice-Weekly Transdermal Estradiol and Vaginal Progesterone as Continuous Combined HRT in Postmenopausal Women: A 1-Year Prospective Study [101]

Transdermal estradiol and a twice-weekly administration of the vaginal progesterone gel Crinone constitutes a new, viable HRT regimen. It represents a practical option for a no-bleed treatment, ensuring both high endometrial protection and the inherent safety linked to administrating physiologic hormones nonorally.

24.12.1.6 Vaginal Progesterone in Menopause: Crinone 4% in Cyclical and Constant Combined Regimens [102]

This study also shows that vaginal progesterone can be used to maintain normal uterine morphology with a decrease in systemic side effects and when used in combination with estrogen without bleeding.

24.12.1.7 Relationship Between Long Durations and Different Regimens of Hormone Therapy and Risk of Breast Cancer [103]

Women using unopposed estrogen replacement therapy (ERT) (exclusive ERT use), even for 25 years or longer, had no appreciable increase in risk of breast cancer. Ever users of HRT (includes HRT users who also had used ERT) had a 1.7-fold increased risk of breast cancer, including a 2.7-fold increased risk of invasive lobular carcinoma.

References

1. Rossouw JE, Anderson GL, Prentice RL, et al Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3): 321–33
2. Bush TL, Cowan LD, Barrett-Connor E, et al Estrogen use and all-cause mortality. Preliminary results from the Lipid Research Clinics Program Follow-Up Study. JAMA. 1983; 249(7):903–6
3. Grady D, Rubin SM, Petitti DB, et al Hormone therapy to prevent disease and prolong life in postmenopausal women [see comments]. Ann Intern Med. 1992;117(12):1016–37
4. Ragaz J, Coldman AJ. Age-matched all-cause mortality impact of hormone replacement therapy: applicability to breast cancer survivors. Breast Ca Res Treat. 1999;57:30
5. Grodstein F, Stampfer MJ, Colditz GA, et al Postmenopausal hormone therapy and mortality [see comments]. N Engl J Med. 1997;336(25):1769–75
6. Prentice RL, Anderson GL. The Women's Health Initiative: lessons learned. Annu Rev Public Health. 2007;29:131–50
7. Anon. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer [see comments] [published erratum appears in Lancet 1997 Nov 15;350(9089): 1484]. Lancet. 1997;350(9084):1047–59
8. Ragaz J. Hormone replacement therapy in patients with a prior breast cancer history: a critical review. In: Jatoi I, editor. Manual of breast disease. Lippincott Williams and Wilkins; 2002
9. Singletary SE. Rating the risk factors for breaat cancer. Ann Surg. 2003;4:474–82
10. Longnecker MP, Berlin JA, Orza MJ, Chalmers TC. A meta-analysis of alcohol consumption in relation to risk of breast cancer. JAMA. 1988;260(5):652–6
11. Bernstein L, Henderson BE, Hanisch R, Sullivan-Halley J, Ross RK. Physical exercise and reduced risk of breast cancer in young women [see comments]. J Natl Cancer Inst. 1994;86(18):1403–8

12. Rockhill B, Willett WC, Hunter DJ, Manson JE, Hankinson SE, Colditz GA. A prospective study of recreational physical activity and breast cancer risk. Arch Intern Med. 1999;159(19):2290–6
13. Henderson B, Pike M, Bernestein L, Ross R. Breast cancer. 1996:1022–40
14. Grodstein F, Manson JE. Relationship between hormone replacement therapy, socioeconomic status, and coronary heart disease. JAMA. 2003;289(1):44
15. Anon. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial [see comments] [published erratum appears in JAMA 1995 Dec 6;274(21): 1676]. JAMA. 1995;273(3):199–208
16. Ravdin PM, Cronin KA, Howlader N, et al The decrease in breast-cancer incidence in 2003 in the United States.[see comment]. N Engl J Med. 2007;356(16):1670–4
17. Chlebowski RT, Kuller LH, Prentice RL, et al Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med. 2009;360(6):573–87
18. Luria SE, Delbruck M. Mutations of bacteria from virus sensitivity to virus resistance. Genetics. 1943;28:491–511
19. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep. 1979;63(11–12):1727–33
20. Magnusson C, Holmberg L, Norden T, Lindgren A, Persson I. Prognostic characteristics in breast cancers after hormone replacement therapy. Breast Cancer Res Treat. 1996;38(3): 325–34
21. Willis DB, Calle EE, Miracle-McMahill HL, Heath CW Jr. Estrogen replacement therapy and risk of fatal breast cancer in a prospective cohort of postmenopausal women in the United States [see comments]. Cancer Causes Control. 1996;7(4):449–57
22. Jernstrom H, Frenander J, Ferno M, Olsson H. Hormone replacement therapy before breast cancer diagnosis significantly reduces the overall death rate compared with never-use among 984 breast cancer patients. Br J Cancer. 1999; 80(9):1453–8
23. Holli K, Isola J, Cuzick J. Low biologic aggressiveness in breast cancer in women using hormone replacement therapy. J Clin Oncol. 1998;16(9):3115–20
24. Schairer C, Gail M, Byrne C, et al Estrogen replacement therapy and breast cancer survival in a large screening study. J Natl Cancer Inst. 1999;91(3):264–70
25. Fowble B, Hanlon A, Freedman G, et al Postmenopausal hormone replacement therapy: effect on diagnosis and outcome in early-stage invasive breast cancer treated with conservative surgery and radiation. J Clin Oncol. 1999;17(6): 1680–8
26. Gapstur SM, Morrow M, Sellers TA. Hormone replacement therapy and risk of breast cancer with a favorable histology: results of the Iowa Women's Health Study [see comments]. JAMA. 1999;281(22):2091–7
27. Chlebowski RT, Hendrix SL, Langer RD, et al Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA. 2003;289(24):3243–53
28. Stefanick ML, Anderson GL, Margolis KL, et al Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA. 2006;295(14):1647–57
29. Bluming AZ. A decline in breast-cancer incidence. N Engl J Med. 2007;357(5):509; author reply 513
30. Mosca L, Jahnige K, Giacherio D, et al Beneficial effects of hormone replacement on lipoprotein(a) levels in postmenopausal women. Prev Cardiol. 1999;2:51–8
31. Crouse JR 3rd, Furberg CD. Treatment of dyslipidemia: room for improvement? [In Process Citation]. Arterioscler Thromb Vasc Biol. 2000;20(11):2333–5
32. Bush TL, Barrett-Connor E, Cowan LD, et al Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. Circulation. 1987;75(6):1102–9
33. Clarkson TB, Williams TB, Adams MR, Wagner JD, Klein KP. Experimental effects of estrogens and progestins on the coronary artery wall. 1993:169–74
34. Wagner JD. Rationale for hormone replacement therapy in atherosclerosis prevention. J Reprod Med. 2000;45(3 Suppl): 245–58
35. McGowan JA, Pottern L. Commentary on the Women's Health Initiative. Maturitas. 2000;34(2):109–12
36. Darling GM, Johns JA, McCloud PI, Davis SR. Estrogen and progestin compared with simvastatin for hypercholesterolemia in postmenopausal women. N Engl J Med. 1997; 337(9):595–601
37. Adams J, Carder PJ, Downey S, et al Vascular endothelial growth factor (VEGF) in breast cancer: comparison of plasma, serum, and tissue VEGF and microvessel density and effects of tamoxifen. Cancer Res. 2000;60(11):2898–905
38. Wagner JD, Clarkson TB, St. Clair RW, Schwenke DC, Shively CA, Adams MR. Estrogen and progesterone replacement therapy reduces low density lipoprotein accumulation in the coronary arteries of surgically postmenopausal cynomolgus monkeys. J Clin Invest. 1991;88(6):1995–2002
39. Steinleitner A, Stanczyk FZ, Levin JH, et al Decreased in vitro production of 6-keto-prostaglandin F1 alpha by uterine arteries from postmenopausal women. Am J Obstet Gynecol. 1989;161(6 Pt 1):1677–81
40. Collins P, Rosano GM, Jiang C, Lindsay D, Sarrel PM, Poole-Wilson PA. Cardiovascular protection by oestrogen–a calcium antagonist effect? Lancet. 1993;341(8855):1264–5
41. Mijatovic V, Kenemans P, Netelenbos JC, et al Oral 17b-estradiol continuously combined with dydrogeterone lowers serum lipoprotein(a) concentrations in healthy postmenopausal women. J Clin Endocrinol Metab. 1997; 82:3543–7
42. Mijatovic V, van der Mooren MJ, Stehouwer CD, Netelenbos JC, Kenemans P. Postmenopausal hormone replacement, risk estimators for coronary artery disease and cardiovascular protection. Gynecol Endocrinol. 1999; 13(2):130–44
43. Mosca L, Grundy SM, Judelson D, et al Guide to preventive cardiology for women. AHA/ACC Scientific Statement Consensus panel statement. Circulation. 1999;99(18): 2480–4
44. Shlipak MG, Simon JA, Vittinghoff E, et al Estrogen and progestin, lipoprotein(a), and the risk of recurrent coronary heart disease events after menopause. JAMA. 2000;283(14): 1845–52
45. Tikkanen MJ, Nikkila EA, Kuusi T. High-density lipoprotein-2 and hepatic lipase:reciprocal changes produced by estrogens and norgestrel. J Clin Endocrinol Metab. 1982; 54:1113–7

46. Gaulin-Glasser T, Farrel WJ, Pfau SE. Modulation of circulating cellular adhesion molecules in postmenopausal women with coronary artery disease. J Am Coll Cardiol. 1998;31: 1555–60
47. McGill HC Jr. Sex steroid hormone receptors in the cardiovascular system. Postgrad Med. 1989;Spec No:64–8; discussion 89–90. No abstract available
48. Losordo DW, Kearney M, Kim EA. Variable expression of the estrogen receptor in normal and atherosclerotic coronary arteries of premenopausal women. Circulation. 1996;89:1501–10
49. Williams JK, Adams MR, Klopfenstein HS. Estrogen modulates responses of atherosclerotic coronary arteries. Circulation. 1990;81(5):1680–7
50. Grodstein F, Stampfer M. The epidemiology of coronary heart disease and estrogen replacement in postmenopausal women. Prog Cardiovasc Dis. 1995;38(3):199–210
51. Gilligan DM, Quyyumi AA, Cannon RO 3rd. Effects of physiological levels of estrogen on coronary vasomotor function in postmenopausal women. Circulation. 1994;89(6): 2545–51
52. Reis SE, Holubkov R, Young JB, White BG, Cohn JN, Feldman AM. Estrogen is associated with improved survival in aging women with congestive heart failure: analysis of the vesnarinone studies. J Am Coll Cardiol. 2000; 36(2):529–33
53. Bourne T, Hillard TC, Whitehead MI, Crook D, Campbell S. Oestrogens, arterial status, and postmenopausal women [letter] [see comments]. Lancet. 1990;335(8703):1470–1
54. Sarrel PM, Lindsay D, Rosano GM, Poole-Wilson PA. Angina and normal coronary arteries in women: gynecologic findings. Am J Obstet Gynecol. 1992;167(2):467–71
55. Pines A, Fisman EZ, Levo Y, et al The effects of hormone replacement therapy in normal postmenopausal women: measurements of Doppler-derived parameters of aortic flow. Am J Obstet Gynecol. 1991;164(3):806–12
56. Rosano GM, Panina G. Oestrogens and the heart. Therapie. 1999;54(3):381–5
57. Stampfer MJ, Colditz GA, Willett WC, et al Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study [see comments]. N Engl J Med. 1991;325(11):756–62
58. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease in women [see comments]. JAMA. 1991;265(14):1861–7
59. Nabulsi AA, Folsom AR, White A, et al Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. The Atherosclerosis Risk in Communities Study Investigators [see comments]. N Engl J Med. 1993;328(15):1069–75
60. Grodstein F, Stampfer MJ, Manson JE, et al Postmenopausal estrogen and progestin use and the risk of cardiovascular disease [see comments] [published erratum appears in N Engl J Med 1996 Oct 31;335(18):1406]. N Engl J Med. 1996;335 (7):453–61
61. Hu FB, Stampfer MJ, Manson JE, et al Trends in the incidence of coronary heart disease and changes in diet and lifestyle in women [see comments]. N Engl J Med. 2000; 343(8):530–7
62. Mosca L. The role of hormone replacement therapy in the prevention of postmenopausal heart disease. Arch Intern Med. 2000;160(15):2263–72
63. Miller VT, Muesing RA, LaRosa JC, Stoy DB, Phillips EA, Stillman RJ. Effects of conjugated equine estrogen with and without three different progestogens on lipoproteins, high-density lipoprotein subfractions, and apolipoprotein A-I. Obstet Gynecol. 1991;77(2):235–40
64. Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnikar V, Sacks FM. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins [see comments]. N Engl J Med. 1991;325(17): 1196–204
65. Rosano GM, Panina G. Cardiovascular pharmacology of hormone replacement therapy. Drugs Aging. 1999;15(3): 219–34
66. Harder DR, Coulson PB. Estrogen receptors and effects of estrogen on membrane electrical properties of coronary vascular smooth muscle. J Cell Physiol. 1979;100(2):375–82
67. Rosano GM, Sarrel PM, Poole-Wilson PA, Collins P. Beneficial effect of oestrogen on exercise-induced myocardial ischaemia in women with coronary artery disease [see comments]. Lancet. 1993;342(8864):133–6
68. Stampfer MJ, Colditz GA, Willett WC. Menopause and heart disease. A review. Ann N Y Acad Sci. 1990;592:193–203; discussion 257–62
69. Hulley S, Grady D, Bush T, et al Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group [see comments]. JAMA. 1998;280(7):605–13
70. Grady D, Herrington D, Bittner V, et al Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA. 2002;288(1):49–57
71. Manson JE, Allison MA, Rossouw JE, et al Estrogen therapy and coronary-artery calcification. N Engl J Med. 2007;356 (25):2591–602
72. Rossouw JE, Prentice RL, Manson JE, et al Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007;297(13):1465–77
73. Harman SM. Estrogen replacement in menopausal women: recent and current prospective studies, the WHI and the KEEPS. Gend Med. 2006;3(4):254–69
74. Grodstein F, Manson JE, Stampfer MJ. Hormone therapy and coronary heart disease: the role of time since menopause and age at hormone initiation. J Womens Health (Larchmt). 2006;15(1):35–44
75. Hulley S. Estrogens should not be initiated for the secondary prevention of coronary artery disease: a debate. Can J Cardiol. 2000;16(Suppl E):10E–2E
76. Willett WC, Manson JE, Grodstein F, Stampfer MJ, Colditz GA. Re: combined postmenopausal hormone therapy and cardiovascular disease: toward resolving the discrepancy between observational studies and the Women's Health Initiative clinical trial. Am J Epidemiol. 2006;163(11):1067–8; author reply 1068–9
77. Prentice RL, Langer RD, Stefanick ML, et al Combined analysis of Women's Health Initiative observational and clinical trial data on postmenopausal hormone treatment and cardiovascular disease. Am J Epidemiol. 2006;163(7): 589–99
78. Meade TW. Haemostatic function and ischaemic heart disease. Adv Exp Med Biol. 1984;164:3–9
79. Petitti DB, Wingerd J, Pellegrin F, Ramcharan S. Oral contraceptives, smoking, and other factors in relation to risk of

venous thromboembolic disease. Am J Epidemiol. 1978; 108(6):480–5
80. Barrett-Connor E. Hormone replacement and cancer. Br Med Bull. 1992;48(2):345–55
81. Grady D, Wenger NK, Herrington D, et al Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. Ann Intern Med. 2000;132(9):689–96
82. Devor M, Barrett-Connor E, Renvall M, Feigal D Jr, Ramsdell J. Estrogen replacement therapy and the risk of venous thrombosis [see comments]. Am J Med. 1992; 92(3):275–82
83. Danby W. HT and WHI: The Baby and The Bathwater. Personal communications. 2002
84. Rosing J, Tangs G. Effects of oral contraceptives on hemostasis and thrombosis. Am J Obstet Gynecol. 1999;180:375–82
85. Van de Water NS, French JK, Lund MB, Hyde TA, White HD, Browett PJ. Prevalence of factor V Leiden and prothrombin variant G20210A in patients age <50 years with no significant stenosi at angiography three ot four weeks after myocardial infarction. J Am Coll Cardiol. 2000; 36:717–22
86. Wu AH, Tsongalis GJ. Correlation of polymorphisms to coagulation and biochemical risk factors for cardiovascular diseases. Am J Cardiol. 2001;87:1361–6
87. Herrington DM, Vittinghoff E, Howard TD, et al Factor V Leiden, hormone replacement therapy, and risk of venous thromboembolic events in women with coronary disease. Arterioscler Thromb Vasc Biol. 2002;22(6):1012–7
88. Redondo M, Watzke HH, Stucki B, Sulzer I, Biasiutti FD, Binder BR, et al Coagulations factors I, V, VII, and X, prothrombin gene 20210G-A transition, and factor V Leiden in coronary artery disease: high factor V clotting activity is an independent risk factor for myocardial infarction. Arteriosclr Thromb Vasc Biol. 1999;78:1020–5
89. Anderson GL, Limacher M, Assaf AR, et al Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 2004;291(14):1701–12
90. Fletcher SW, Colditz GA. Failure of estrogen plus progestin therapy for prevention. JAMA. 2002;288(3):366–8
91. Investigators WGftWsHI; Rossouw JE, Anderson GL, et al Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321–33
92. Anderson WF, Reiner AS, Matsuno RK, et al Shifting breast cancer trends in the United States. J Clin Oncol. 2007;25(25):3923–9
93. Cady B, Chung MA, Michaelson JS. A decline in breast cancer incidence. N Eng J Med. 2007;357(5):509–13
94. Zahl PH, Maehlen J. A decline in breast-cancer incidence. N Engl J Med. 2007;357(5):510–1; author reply 513
95. Zahl PH, Strand BH, Maehlen J. Incidence of breast cancer in Norway and Sweden during introduction of nationwide screening: prospective cohort study. BMJ. 2004;328(7445): 921–4
96. Ragaz J, Spinelli JJ, Hryniuk W, Budlovsky J, Franco E. Breast cancer (BrCa) mortality reduction in the western world: therapeutic versus diagnostic interventions. Implications for cancer care organization processes. Cancer Res. 2009;69(Suppl 2):383–4
97. Mattsson LA, Christiansen C, Colau JC, et al Clinical equivalence of intranasal and oral 17beta-estradiol for postmenopausal symptoms. Am J Obstet Gynecol. 2000;182(3): 545–52
98. Odabasi AR, Yuksel H, Demircan SS, Kacar DF, Culhaci N, Ozkara EE. A prospective randomized comparative study of the effects of intranasal and transdermal 17 beta-estradiol on postmenopausal symptoms and vaginal cytology. J Postgrad Med. 2007;53(4):221–7
99. Studd J, Pornel B, Marton I, et al Efficacy and acceptability of intranasal 17 beta-oestradiol for menopausal symptoms: randomised dose-response study. Aerodiol Study Group. Lancet. 1999;353(9164):1574–8
100. Rozenbaum H, Chevallier O, Moyal M, Durand G, Perineau M, This P. Efficacy and tolerability of pulsed estrogen therapy: a 12-week double-blind placebo-controlled study in highly symptomatic postmenopausal women. Climacteric. 2002;5(3):249–58
101. Cicinelli E, de Ziegler D, Galantino P, et al Twice-weekly transdermal estradiol and vaginal progesterone as continuous combined hormone replacement therapy in postmenopausal women: a 1-year prospective study. Am J Obstet Gynecol. 2002;187(3):556–60
102. de Ziegler D, Ferriani R, Moraes LA, Bulletti C. Vaginal progesterone in menopause: Crinone 4% in cyclical and constant combined regimens. Hum Reprod. 2000;15(Suppl 1):149–58
103. Li CI, Malone KE, Porter PL, et al Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. JAMA. 2003;289(24):3254–63
104. Rossouw et al JAMA. 2007
105. Anderson et al JAMA. 2004
106. Calle EE, Miracle-McMahill HL, Thun MJ, Heath CW Jr. Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. J Natl Cancer Inst. 1995;87(7):517–23
107. Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20–69 years [letter] [see comments]. Lancet. 2000;355(9217):1822
108. Jatoi I, Chen BE, Anderson WF, Rosenberg PS. Breast cancer mortality trends in the United States according to estrogen receptor status and age at diagnosis. J Clin Oncol. 2007; 25(13):1683–90
109. Kerlikowske K, Miglioretti DL, Buist DS, Walker R, Carney PA. Declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. J Natl Cancer Inst. 2007;99(17):1335–9
110. Genant HK, Lucas J, Weiss SE, et al Low-dose esterified estrogen therapy: effects on bone, plasma estradiol concentrations, endometrium, and lipid levels. Arch Intern Med. 1997;157:2609–15
111. Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH. Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. JAMA. 2002;287: 2668–76
112. Grodstein F, Manson JE, Colditz GA, et al A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med. 2000;133:933–41
113. Harman SM, Brinton EA, Cedars M, et al KEEPS: The Kronos Early Estrogen Prevention Study. Climacteric. 2005; 8(1):3–12

Breast Diseases in Males

25

John T. Vetto

25.1 The Male Breast

The male breast is normally a rudimentary structure composed of small ducts and fibrous tissue with variable amounts of periductal fat, identical histologically to the breast of prepubertal females [1]. In the absence of estrogenic stimulation, lobules are not seen. The incidences in males of absent breasts or nipples and of supernumerary nipples are identical to the incidences in females [2]. In the absence of enlargement, breast tissue in the male is confined to the area directly behind the areola; therefore, clinical breast examination (CBE) is very easy in males and usually can be performed with just one or two examining fingers.

25.2 Gynecomastia

Gynecomastia, the most common clinical and pathologic benign condition of the male breast [3], is defined as an enlargement of the ductal and fibrous stromal components and is clinically and histologically distinct from pseudogynecomastia, in which clinical breast enlargement is due to swelling of the surrounding subcutaneous fat [2]. True gynecomastia may range in size from a small retroareolar disc to enlargement that approximates that of an adult female breast [4]. Primary (idiopathic, physiologic) gynecomastia occurs in 30–70% of male children and is thought to occur during developmental periods of relative estrogen excess or androgen deficiency [1]. Typically, it resolves spontaneously, and, in the presence of an otherwise normal history and physical examination (PE), it requires no specific workup or treatment unless it persists or is severe, in which case psychological counseling and/or surgery may be needed in selected cases [5–7]

Secondary (pathologic) gynecomastia can be due to a myriad of underlying conditions (Table 25.1) and medications (Table 25.2) [1–3, 6, 8–12]. Careful history and PE often disclose the underlying cause without the need for additional testing or sex-steroid chemistry panels, and treatment consists of correction of the underlying condition or discontinuation of the causative medication. Suspected cases of pathologic gynecomastia in pediatric patients should be referred to a pediatric endocrinologist [5]. Treatment of secondary gynecomastia, however, may not be necessary or even possible in situations in which the underlying condition is not correctable or the patient is asymptomatic, or the causative medication should not be discontinued.

In symptomatic patients, a variety of hormonal options are available (testosterone, clomiphene, tamoxifen, danazol), none of which have been studied in a systematic manner and some of which can be associated with significant side effects [5, 6]. Published indications for surgery include: failure of medical therapy; persistence despite 1 year of observation; progressive size, symptoms, or psychosocial issues; and persistence after puberty [13]. In our hands, surgical excision (by subcutaneous mastectomy, sparing the nipple) is often the treatment of choice because it is definitive (provided care is taken to remove all the enlarged tissue) and, in some cases, can be accomplished with the patient under local anesthesia and/or in an outpatient setting. A recent series found that surgery for gynecomastia is associated with low rates of atypical findings on final pathology (3%) and need for revision (7%).

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_25, © Springer-Verlag Berlin Heidelberg 2010

Table 25.1 Conditions associated with gyneocmastia

Endocrine	Adrenal insufficiency Thyrotoxicosis Testicular failure
Genetic	Kleinfelter's syndrome
Liver	Chronic liver failure
Pulmonary	Bronchiectasis Chronic bronchitis Tuberculosis
Renal	Chronic renal failure
Neurologic	Transverse myelitis
Tumors	CNS, especially hypothalamus, pituitary Lung Testicular, especially seminomas, teratomas Prostate (related to therapy)
Others	Malnutrition Trauma

Table 25.2 Drugs associated with gynecomastia

Class	Drug
Antiandrogens	Cypoterone Flutamide
Antibiotics/antifungals	Griseofulvin Isoniazid Ketoconazole Metronidazole
Cardiovascular agents	Amiodorone Captopril Digitoxin Enalapril Methyldopa Nifedipine Reserpine Verapamil
Chemotherapeutics	(Especially) Cylophosphamide
Diuretics	Thiazides Spinolactone
Hormones	Androgens and anabolic steroids Chorionic gonadotropin Estrogens and estrogen agonists
Illicit drugs/drugs of abuse	Alcohol Amphetamines Heroin LSD Marijuana Methadone
Psychoactive agents	Diazepine Haloperidol Phenothiazine Tricyclic antidepressants
Ulcer medications	Cimetadine Omperazole Ranitadine
Others	Phenytoin, Penicillamine

Higher complication rates were associated with higher patient BMI and specimen weights [14].

Because secondary gynecomastia may be unilateral and painless in many cases [7, 13], the major clinical concern regarding this lesion is distinguishing it from breast cancer [6–9]. This topic is discussed in detail subsequently (see "Differential Diagnosis of Breast Masses in Males" and "FNA-based Evaluation of Breast Masses in Males").

25.3 Other Benign Breast Conditions

A variety of benign conditions common to the female breast are also seen in males and, with the exception of gynecomastia, are similar in both genders in terms of presentation, histology, diagnosis, and treatment [3]. These are listed in Table 25.3 [15–39].

Another occasional exception is nipple discharge; benign milky discharge can occur in males (especially the colostrum-like "witch's milk" of male neonates (1)), and benign nonmilky discharge is occasionally seen in males, but bloody discharge in a male is more commonly associated with malignancy than it is in females [40–42]. For example, in a review of Treves et al. of 42 cases of nipple discharge in males, more than half (57%) were associated with a clinical breast cancer. Of the discharges associated with benign conditions, all nonbloody discharges were due to gynecomastia (and had often been present for years), whereas bloody but benign discharges were due to papilloma [43]. Accordingly, males presenting with bloody nipple discharge have carcinoma until proven otherwise; those in whom a cancer is not found can be evaluated and treated in a fashion similar to females (i.e., ductography and papilloma excision) [42]. Nipple discharge in males is also discussed throughout the sections that follow.

Table 25.3 Benign breast conditions in males

		Ref[a]
Benign solid tumors of the breast and connective tissue		
	Fibroadenoma	[15, 16]
	Fibromatosis	[17–19]
	Leiomyoma	[20, 21]
	Mesenchymoma	[3, 178]
	Myofibroblastoma	[22, 23, 177, 297]
	Papilloma, intracystic papilloma	[24, 25]
	Phyloides tumor (benign)	[3]
	Juvenile papillomatosis	[179]
	Benign hemangiopericytoma	[180]
Benign solid tumors of the dermis/subcutis		
	Granular cell tumor	[26]
	Lipoma, lipoblastoma	[27]
	Pilomatrixoma	[28]
Infections/infestations	Sparganosis	[29]
	Tuberculosis	[30–32]
Inflammatory and autoimuune conditions		
	Granulomatous mastitis	[33]
	Lupus mastitis	[34]
	Nodular fasciitis	[35]
Vascular lesions	Cavernous hemangioma	[36, 37]
	Hemangioma	[38, 39]

[a]*Ref* reference number-see table of contents

25.4 Breast Cancer in Males

Breast cancer in males (BCM) is one of the oldest diseases in recorded history. First reported in the Smith Papyrus, European reports date back to a 1307 case report by an English surgeon, John of Aderne. Subsequent case reports by Ambroise Pare and Fabrius Hildanus in the 16th and 17th century, respectively, followed [8]. Periodic reporting continued in the latter half of the 20th century, when large series began to appear [8, 44–54], leading to our current understanding of the disease.

Although only about than 1% of breast cancer occurs in men, this disease accounts for 0.16% of all cancer deaths in males (approximately 450 cancer deaths in the United States per years) [55–57]. The widely held notion of BCM as a late-presenting disease with a dismal prognosis is largely a result of earlier [44–49, 58–61] and even some more recent [53, 62, 63] series consisting mostly of patients presenting with advanced stage disease. Much of the previous data are flawed by single-institution experience, repeated reports from the same institutional series, small sample size, and failure to control for stage and patient age. The well-known tendency for this disease to present late in older males (who already may possess comorbid conditions leading to subsequent death from noncancer causes) and to be associated with second cancers may explain in part the previously reported low crude survival for BCM.

As discussed later, newer series [50, 51, 54, 64–66], including our own [11], refute this notion and indicate that breast cancer in men carries the same prognostic factors as the disease in women and that the stage-for-stage outcomes are also the same. A 2006 series from Japan noted that survival from BCM had improved in that country since 1980–1984, while it had been stable in females [67]. One recent U.S. study has actually shown that men with breast cancer had significantly better disease-specific survival than their female counterparts [68]. This newer information leads to the question of whether breast cancer is the same or a different disease in men and women. This issue is also discussed in this chapter, including a detailing of how breast cancer in men is similar to, and how it differs from, breast cancer in females (BCF).

A grammatical note: Tumors do not possess gender; therefore, the term "male breast cancer" is not as correct as BCM or even "cancer of the male breast" [8]. Thus, throughout this chapter, the disease is referred to as BCM, as opposed to BCF.

25.4.1 Global Distribution

In a meta-analysis, Sasco and colleagues determined that the BCM accounts for about 1% of all breast cancer worldwide [69]. The global distribution of BCM is similar to that of BCF (i.e., BCM is very rare in areas with a low incidence of breast cancer in general), with a few exceptions. For example, BCM is common in Egypt, an area of relatively low BCF incidence, probably because of high rates of schistosomiasis-related liver failure [70]. In contrast, BCM rates are low and fairly even in European countries (1.5–3 per million) and reflect variances in the rates for BCF, with higher rates found in France, Hungary, Austria, and Scotland [71].

25.4.2 U.S. Incidence

The number of cases of BCM and the percentage of breast cancer occurring in males both appear to be rising in the U.S.; in 2007 there were 2,030 cases of BCM (up from 1,300 cases in 1999), which represented 1.27% of all breast cancers (up from 0.74% in 1999). Some recent U.S. reports also suggest that the incidence of BCM may be rising [72–74]. This rise in the percentage of breast cancers that occur in males may be related in part to a recent decline in breast cancer incidence in females [74].

There were 44,910 deaths (out of a total of 178,480 cases) from BCF and 450 deaths from BCM in 2007. Thus, the current likelihood of dying from BCF and from BCM are similar (25.3 and 22.3%, respectively) [57]. These numbers support the previously mentioned recent reports of a prognosis for BCM which is at least the same at BCF. As previously noted, these figures pertain to disease specific survival; crude survival in BCM is lowered by co-morbidities, especially in older men, and by higher risks of second malignancies in men with breast cancer, especially younger men, and especially second breast primaries [75, 76].

25.4.3 Associated Factors and Conditions

Factors associated with the development of BCM (Table 25.4) include the following:

1. *Advanced age*. The annual incidence of BCM increases steadily (lacking the premenopausal peak seen in females) [57] between 35 years of age (0.1 case per 100,000 men) and 85 years of age (11.1 cases per 100,000) [70]. The mean age of diagnosis was 64.5 years in our series [11] and 61.8 years in the series by Borgen et al., compared with 55.5 years for matched female breast cancer controls in that same study [50]. The greatest incidence occurs 5–10 years later in males than in females; in a recent VA cooperative study, the mean age at diagnosis was 67 years for BCM and 57 years for BCF [77]. It is rarely found before the age of 26, although it has been reported in a 5-year-old boy [78].
2. *Black race*. Several studies have shown a disproportionate number of cases of BCM in Blacks [77, 79, 80]. A large study of BCM in California revealed an age-adjusted incidence rate/100,000 men of 1.65 for Blacks vs. 1.31 for Whites; BCM rates were lowest for Hispanics and Asians/Pacific Islanders (0.68 and 0.66, respectively). Age and stage at diagnosis in that study also differed by race, with Blacks more likely to be diagnosed at a younger age and more advanced stage ($P>0.001$)[79]. At least one study has shown racial disparities in BCM treatment and outcome, with Black men less likely to undergo Medical Oncology consultation and chemotherapy,

Table 25.4 Factors associated with the development of BCM[a]

Age[b]
Black race
Prolonged heat exposure
Previous chest wall radiation
Positive family history for breast cancer (in male or female relatives) BRCA mutations (especially BRCA2)
Conditions of relative hyperestrogeny Testicular abnormalities Exogenous estrogens Obesity Liver disease Klinefelter's syndrome[c]

[a]Direct causation has not been established for some factors

[b]Incidence of BCM is directly related to age

[c]Increases BCM risk by 50-fold

and experiencing a breast-cancer specific mortality ratio more than triple that of White men [81].

3. *Prolonged heat exposure*, which may have a suppressive effect on testicular function [58, 82–85]. The role of electromagnetic field exposure remains controversial [8, 82, 84–86].
4. *Previous chest wall radiation*, especially radiation given for the treatment of childhood malignancies [87, 88]. Children treated for lymphoma are at particular risk, felt to be due to both chest wall radiation and altered gonadal function [89] The risk for breast cancer after radiation appears to be similar for men and women, as is the indirect relationship between age of exposure and risk and the lag time between exposure and disease (12–36 years) [86, 90–93]. Accordingly, it is generally recommended that males with such exposure history should be carefully observed [69]. A statistically significant increase in BCM risk among Japanese atom bomb survivors has also recently been reported [94].
5. *Conditions of relative hyperestrogeny*. These conditions include testicular abnormalities, such as the sequelae of mumps infections and infectious orchitis [8, 85], undescended testes [69, 85], orchiectomy, late puberty, infertility and male potential hypogonadism [58, 85, 95, 96], disorders that cause gynecomastia (gynecomastia itself is associated with up to 43% of BCM cases, but there are no data for direct causation) [3, 44], exogenous estrogen, obesity, liver disease (due to cirrhosis, bilharziasis, schistosomiasis, and chronic malnutrition) [69, 85, 87, 88], and Klinefelter's syndrome, which (despite its rarity) accounts for 3% of BCM cases [97] and is associated with a 50-fold increased risk of BCM [98].

   In fact, the risk of breast cancer in men with Klinefelter's syndrome approaches that of females, probably due in part to the fact that these men actually develop hypertrophied breasts that contain both acini and lobules (the normal male breast does not contain lobules) [97]. This histological event explains the fact that lobular carcinoma in men is rare and usually only associated with Klinefelter-related cases (see "Histologies" section to follow). Men with Kleinfelter's syndrome are also at higher risk for non-Hodgkin's lymphoma and lung cancer, and their mortality for BCM is particularly high if they have XXY mosaicism [99].

   Both prostate cancer and prostate cancer treatment have been linked to BCM [85, 100, 101], presumably due to both medical and surgical castration. However, this association is controversial; breast cancer is rarely reported among men receiving estrogens for prostate cancer, and malignant breast masses in these patients are more often metastatic deposits than BCM [102].

   The preceding associations would lead one to the conclusion that BCM is caused by relative estrogen excess. Although breast cancer can be easily promoted in a number of animal species by hormone administration, clear data indicating causation in humans are lacking, probably because of the relative rarity of BCM and the corresponding small sample sizes in most studies. For example, reports of BCM and fibroadenomas among males taking estrogen for transsexual male-to-female surgery have been anecdotal only [103–105]. Data from blood chemistry studies attempting to demonstrate hormonal differences among BCM patients compared with control subjects have been sparse and conflicting. Taken together, most studies show no difference in testosterone, estradiol, and luteinizing hormone levels [106, 107], whereas one study showed increased prolactin and follicle stimulating hormone levels in BCM patients compared with matched controls [108].
6. *Alcohol* taken in excess has been linked to MBC risk in some series [84, 85], but this may be linked to the previously mentioned risks of liver disease and relative hyperestrogeny. One European Case-Control Study found an odds ratio of 5.89 for alcohol intake >90 g/day, compared to light consumers (<15 g/day) [109]. The effect of dietary factors (meat, fruit, and vegetable consumption) is unproven [85, 110].
7. *Suspected* genetic factors include BRCA mutations (discussed below), androgen receptor (AR) gene mutations, CYP17 polymorphisms, Cowden's syndrome, and CHEK2 mutations [85], although data for this later factor is conflicting [110].
8. *Environmental factors*: Isolated reports also suggest links between BCM and occupational exposure to gasoline and combustion products [85, 111] and employment in blast furnaces, steel works, and rolling mills [112].

25.4.4 Family History and Genetics

A family history of BCM or females is present in about 30% of cases of BCM [69], with 14% reporting breast cancer in a first-degree relative in one series [113].

Whereas multiple cases of BCM within families has been reported [60, 114], it is rare; more typically (as one would expect from the rarity of BCM), the risk for BCM is associated with a history of BCF. Similarly, a family history of BCM imparts increased breast cancer risk to the female relatives [115, 116].

Taken together, this information suggests that (a) similar to the situation in BCF, most cases of BCM are "sporadic" (i.e., a specific gene mutation is not identified) and (b) a familial form of breast cancer exists in which both males and females show an increased risk for developing breast cancer [70]. Similar to BCF, studies reveal the association of BCM with a multitude of chromosomal and gene abnormalities [55, 98, 117], especially on the 13q chromosome [117]. The best characterized of these mutations are in the *BRCA2* gene; these mutations may be associated with up to 20% of BCM cases (particularly in Jews, in whom up to 19% carry BRCA2 germline mutations, compared to only 4% of non-Jewish men) [118, 119] . However, they have a low penetrance; only one in seven *BRCA2* carriers have a family history of breast cancer [120, 121]. The usefulness of *BRCA2* testing for relatives of BCM patients is discussed later (see "Testing of Family Members").

Data regarding the association between BCM and *BRCA1* mutations is conflicting [120–122]. While BRCA1 mutations are typically point mutations and BRCA 2 are more typically genomic rearrangements, the importance of BRCA2 genomic rearrangements in BCM is controversial and may be population dependent; one study from France recommended screening for BRCA 2 genomic rearrangements [123], while studies from the U.S., Italy, and Finland found low rates and did not recommend such screening [124–126]. Specific mutations in BRCA 2 leading to BCM have been identified, including founder mutations such as 8765delAG, 185delAG, and 6174delAT [119, 127, 128]. Again, however, their penetrance is relatively low – 6.8% in one recent series [120, 129].

A hereditary nonpolyposis colon cancer (HNPCC) kindred has been identified in which a male member had both an *MLH1* mutation and breast cancer, suggesting that BCM may be part of the HNPCC syndrome [130]. Loss of the Y chromosome and another 13q chromosomal abnormality, del [16] q13, have been recurrent findings in BCM patients. [131]. An AR gene mutation has been found in BCM associated with Reifenstein syndrome (inherited androgen resistance) [132], but at least one report suggests no correlation between AR expression and either the clinicopathologic features or outcome for BCM [133]. Although *p53* mutation rates are similar for BCM and BCF (43%) [134], BCM is rarely seen in Li-Fraumeni syndrome [134], probably because of the relative rarity of both BCM and this syndrome.

25.4.5 Histologies

Because the male breast contains only ductal tissue, most cases of BCM are ductal type, predominantly ductal invasive (85–90% of most series [8], 79% in our series [11]), with the remainder usually "pure" ductal carcinoma in situ (DCIS) or ductal variants [40, 87, 135–139]. ADH has also recently been described in men undergoing biopsy for presumed gynecomastia [140, 141]. All histologies of breast cancer have been encountered in males, including Paget disease (unilateral and bilateral, both alone and associated with either DCIS or invasive tumors) [135, 142–144], inflammatory carcinoma [145], cribiform carcinoma [146], mucinous cancers [147], and papillary cancers (both solid and cystic) [147–151]. "Pure" DCIS accounts for 5–15% of BCM [8, 136, 137] and is less common among BCM compared with BCF cases, probably because of the higher detection rate of ductal neoplasms at the DCIS stage in females by screening mammography [45]. Interestingly, DCIS rates in males have been rising over the last 3 decades, suggesting earlier detection despite the fact that BCM is not a screened-for disease [137].

As expected, lobular cancers are extremely rare in men (who lack lobular tissue) and usually are not found at all in many series [50, 63, 147], including our own [11], but have been described in case reports [87, 152, 153] and in large data sets [51]. As mentioned previously, this event probably occurs in diseases associated with the formation of lobules in the male breast, notably Klinefelter's syndrome [97]. BCM is bilateral at diagnosis in about 2% of cases, similar to the incidence for BCF [139, 144].

Secretory carcinoma, a rare variant of breast cancer that is the most common type seen in children, has been reported in boys [154–156] and in a 51-year-old man [157]. Because of its rarity, neither the natural history of this tumor nor the optimal management is well established, although the tumor generally behaves in an indolent fashion and the prognosis appears to be good [155].

25.4.6 Tumor Biology

Most cases of BCM are estrogen receptor (ER) positive (65–94% in recent studies [50, 63, 87, 158, 159] and 85% in our series [11]); therefore, a greater percentage of male patients will be treated with tamoxifen or will respond to hormonal manipulation than will female patients [158, 160, 161]. Similarly, BCM is more commonly progesterone receptor positive (PR) (93% of cases in two series) [159, 162]. Unlike the situation for BCF, hormone receptor expression in BCM does not seem to correlate with patient age or with histologic grade of the lesion, tumor stage, or lymph node status [70], a finding that further suggests that BCM in general is associated with relative estrogen excess. Further, because the majority of BCM cases are hormone receptor positive and because of the rarity of this disease, it is still uncertain if hormone receptor positive tumors carry the same positive prognostic implication as BCF [163]. As opposed to ER expression in BCF, BCM seems to express high levels of both ER-αand ER-β, whereas ER-β expression on BCF tends to be reduced [159].

AR expression has been reported in 39–87% of BCMs and seems more common on tumors from older patients [159, 162], but a clinical importance for AR expression in BCM has not been clearly demonstrated [132, 133]. The incidence of high-grade histology among BCM varies widely among series (20–73%) [11, 63] but is probably overall similar to the incidence in BCF [50]. One study, however, reported proportionately more high-grade histology among a cohort of low stage BCM patients [164]. Whereas most (but not all) [68] breast cancer tends to present at later stages in males than in females (due, in part to the low index of suspicion and lack of screening in males), the discrepancy in stage distribution, and thus the difference in overall prognosis between BCM and BCF is shrinking as more and more recent series are examined (discussed in more detail in the section on "Prognosis").

25.4.7 Staging

BCM is staged using the same TNM (tumor, nodes, metastases) staging system of the American Joint Committee on Cancer (AJCC) as for BCF [165].

25.4.8 Physical Findings

Because BCM is not a screened-for disease, it presents primarily (up to 79–85% of cases) as a unilateral firm, painless or minimally tender, subareolar mass [51, 66, 160] found on either self-examination or CBE. Seventy percent of the men in our own series presented in this fashion [11]. Because the skin of the nipple is frequently involved, up to 25–30% of cases are technically stage T4 [66]. The mass is often eccentric (i.e., not directly behind the nipple, especially when there is coexisting gynecomastia or other conditions of ductal hypertrophy), slightly irregular, and firm [70]. Whereas nipple discharge in females is usually nonbloody and associated with benign conditions, discharge in men is more often bloody and a sign of malignancy, including DCIS [40, 41, 43, 137]. Discharge cytology may be diagnostic, and a bloody discharge in a male has an 80% likelihood of indicating an underlying tumor [43].

25.4.9 Imaging

Mammography has a limited role in the diagnosis of BCM for a variety of reasons. First, it is a rare disease for which general population screening is unlikely to be cost-effective. Second, the breast is not significantly enlarged in most cases and is therefore difficult to image [8]. Finally, the utility of mammography for detecting BCM is questionable; although there are indeed characteristic mammographic features of BCM (especially eccentricity, nipple and skin retraction, skin ulceration and thickening, and axillary adenopathy [166]) these features are not always present, or there is substantial overlap between these features and the mammographic appearance of benign lesions [167].

For example, suspicious microcalcifications were found in only four of 50 cases of BCM evaluated by mammography by Borgen and colleagues [113], and Cooper et al. found no malignant findings among 263 mammograms in males obtained for abnormal findings on CBE, even among those cases found to be cancer on biopsy [168]. In our diagnostic test study of breast masses in males (See "Fine-Needle Aspiration-Based Evaluation of Breast Masses in Males), mammography was found to add no additional diagnostic information to the combination of PE and fine-needle aspiration (FNA) [169].

Accordingly, despite the reported high sensitivity and negative predictive value (NPV) for BCM detection [170], recent studies have concluded that mammography adds little information to initial patient evaluation [171, 172]; in one recent study of men undergoing mammography to evaluate a dominant suspicious mass, only four cancers were found, and all were suspected on clinical exam [172].

High resolution Doppler ultrasound can be useful in men for differentiating benign from malignant lesions, guiding biopsy, and staging known cancers [166, 170, 173] Although ductography is helpful in evaluating discharge in females, it has a limited role in men [8]. The role of technetium-99 sestamibi scanning for the detection of BCM is limited by false-positive results caused by gynecomastia, lymphoma, and other benign and malignant conditions; compounds other than methoxyisobutyl (MIBI) may provide more accurate results [174–176]. More recent nuclear medicine techniques, such as breast specific gamma imaging, have not yet been evaluated in males to any significant extent.

25.5 Differential Diagnosis of Breast Masses in Males

The differential diagnosis of a breast lump in a male includes both BCM and a variety of benign conditions and benign tumors (Table 25.3) [1–3], including myofibroblastomas [22, 23, 78, 177] and mesenchymomas (also known as *hamartomas* or *angiolipomas*) [3, 178]. Juvenile papillomatosis ("Swiss cheese disease"), which presents as a localized palpable mass, was recently reported in the breasts of male infants. This lesion often is associated with a family history of breast cancer and coexists with malignancy in almost half of cases [179]. Hemangiopericytomas have also been described in the male breast [87, 180]; these connective tissue tumors can range from benign to highly malignant. Similarly, both benign [3] and malignant [87, 181] phylloides tumors have been described in males.

The differential diagnosis of a mass in the male breast includes other malignancies besides BCM (Table 25.5), most often primary lymphomas (especially non-Hodgkin's B cell lymphomas, occasionally linked to HIV infection) [182–185], angiosarcomas [186, 187], and metastases from other primaries. This latter group is the perhaps the most common malignancy in the male breast besides BCM, similar to the situation in females. These come from a variety of primary sites, which in men include prostate cancer [102], eccrine carcinomas [188], lung cancer [189], and especially melanomas, the most common source of metastases to the male breast (58% in one series) [147]. Other malignant tumors described in the male breast in case reports include Merkle cell carcinoma [190], invasive squamous cell cancer. [191], and adenoid cystic carcinoma [192].

The major point on the differential for BCM is gynecomastia, which (unlike BCM) has a bimodal age distribution. At presentation, however, older patients with

Table 25.5 Malignant breast conditions in males

	Ref[a]
Breast Cancer in Males	
Invasive ductal	(Many)
Invasive lobular	[51, 87, 152, 153]
Ductal carcinoma in situ (DCIS)	[136–139]
Paget's disease	[135, 142–144]
Inflammatory carcinoma	[145]
Cribiform carcinoma	[146]
Mucinous cancers	[147]
Papillary carcinoma (both solid and cystic)	[147–151]
Secretory	[154–157]
Primary lymphomas	[182–185]
Sarcomas	
Angiosarcomas	[186, 187]
Phylloides tumors (malignant)	[87, 181]
Hemingiopericytoma	[87, 180]
Other malignant primary tumors	
Merkle cell carcinoma	[190]
Invasive squamous cell cancer	[191]
Adenoid cystic carcinoma	[192]
Metastases from other primaries	
Prostate cancer	[102]
Eccrine carcinoma	[188]
Lung cancer	[189]
Melanoma	[147]

[a]*Ref* reference number-see table of contents

gynecomastia have a similar mean age as BCM patients, and as many as 80% (63% in our study) [11] do not have pain or tenderness [9]. Although gynecomastia is typically rubbery and less firm than BCM, this distinction is not always clear on PE, and (as noted earlier), mammograms that are negative or show gynecomastia do not necessarily rule out malignancy. Thus, in the older male patient who presents to a surgeon or breast clinic with a unilateral palpable breast mass, the main diagnostic task is to rule out BCM (rare, but often treatable for cure) while avoiding open biopsy if possible (unnecessary in asymptomatic benign lesions, which will constitute the majority of masses seen) [10, 12].

Patient history does not reliably distinguish between gynecomastia and BCM, for two important reasons. First, the incidence of use of medications known to be associated with gynecomastia (Table 25.2) has been found to be similar between patients with benign breast conditions and BCM [10]. Second, comparing Tables 25.1 and 25.4, it is evident that some conditions (especially chronic liver diseases and Klinefelter's syndrome) are associated with the development of both gynecomastia and BCM [11]. Indeed, gynecomastia is associated with BCM [138–140], but studies are divided as to whether it is causative [84, 85].

25.5.1 Fine-Needle Aspiration-Based Evaluation of Breast Masses in Males

Thus, a frequent diagnostic challenge is to distinguish between gynecomastia and malignancy, both of which can be either unilateral or bilateral [193]. In experienced hands, FNA can distinguish between gynecomastia and BCM with good reliability (Fig. 25.1) [194–197]. Sensitivity, specificity, and accuracy rates were 100% in a study by Joshi and colleagues [198], although there is a small tendency in many reported series toward false-positive results, likely secondary to the high cellularity and epithelial hyperplasia commonly found in aspirates of gynecomastia [197]. Whereas some researchers believe that this "diagnostic dilemma" can be addressed only by routine open biopsy [10, 199], in our breast clinics we favor a multidisciplinary nonsurgical approach that combines PE with needle biopsy.

Because of our experience and success with FNA-based "triple testing" of palpable breast masses in female patients [200–202], we studied the accuracy and cost-effectiveness of the elements of the triple test (PE, FNA, and mammography) for the evaluation of breast masses in males. As noted previously, although some investigators advocate mammography for the evaluation of these lesions [9], experience is limited [10], sensitivity is at best 88% (i.e., no better than PE alone in ours and other studies) [169, 203], no benefit has been demonstrated for patients younger than 50 years of age [168], false-positive results are the rule with certain benign lesions such as gynecomastia [48] and epidermal cysts [12], published information on the relationship between calcifications and malignancy is conflicting [9, 87, 204], and its use for breast cancer detection is currently felt to be limited [166–168, 171–173] Accordingly, we chose to study a diagnostic approach to palpable breast masses in males that used the combination of PE and FNA (PE + FNA) without mammography since we believed mammography would add only increased patient charges.

Indeed, in the 13 cases in our study where the referring provider had already ordered a mammogram, the

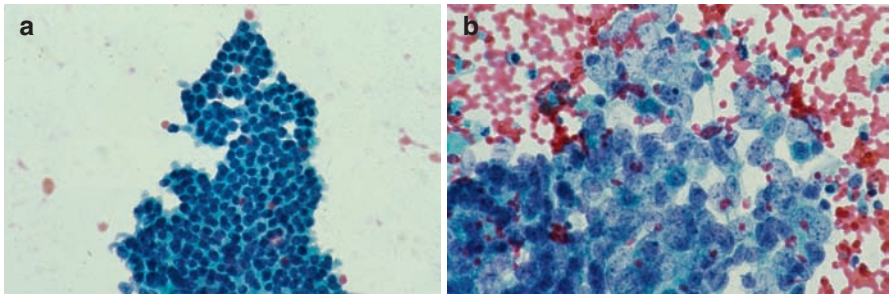

Fig. 25.1 Fine-needle aspiration can distinguish between gynecomastia and malignancy in the male breast. (**a**) Gynecomastia, demonstrating cohesive groups of ductal epithelial cells with small oval nuclei, scant cytoplasm with little variability in size and shape, and smooth nuclear contours; (**b**) Invasive ductal carcinoma, demonstrating a mitotic figure, hyperchromatic and pleomorphic nuclei. Diff-Quik staining, 40×

test added no additional diagnostic information to that already provided by PE+FNA, nor did it change the clinical management of any case [169]. We do recommend bilateral mammography as a preoperative test in cases where PE+FNA indicate the presence of a malignancy.

In our study, when both PE and FNA were benign, no cancers developed at the index sites during follow-up of these lesions (NPV and specificity 100%). Open biopsy confirmed malignancy in all cases for which both tests were suspicious (positive predictive value [PPV] and sensitivity 100%). In all seven cases where the tests were not in agreement, open biopsy was benign. In these cases, FNA (two false-positives) proved more accurate than PE (five false-positives). Overall the combination of PE+FNA avoided open biopsy in over half the cases, resulting in an average decrease in patient charges of $510 per case. We concluded that the combination of PE and FNA for the evaluation of breast masses in males is diagnostically accurate and results in a reduction in patient charges compared with routine open biopsy [169].

The nonoperative evaluation of breast masses in males can employ either cytology (FNA) or core biopsy, depending on with which modality a given institution has more experience. Whereas core needle biopsy is advocated by many, we [169, 202, 204], like others [205–209], favor an FNA-based diagnostic scheme for the evaluation of breast masses in males because it is rapid and offers in-clinic results using Diff-Quik staining.

This approach, however, is associated with two caveats. First, lesions with concordant negative evaluations are followed clinically, resulting in a "true-negative" rate that is not based on pathology results. Although this method introduces potential error compared with routine open biopsy, in our study, no cancers were detected after up to 60 months of follow-up (which included eight subsequent open biopsies, all benign) [169], consistent with the findings of a study by Somers et al., which showed no tumors developing in female patients with concordant negative triple tests (TTs) after up to 74 months of follow-up [210]. Secondly, concern may be expressed over the fate of lesions left unbiopsied and the potential effect this could have on patient care and potential charge reductions. The calculated reductions in our study took into account the "failure" rate for observation of benign concordant lesions that went on to undergo open biopsy anyway (21%,) during the mean follow-up period [169]. This number is similar to the percentage of older male patients with benign breast conditions who present with pain or other symptoms prompting excision (20–34%) as reported in ours and other series [9, 11]; in fact, we have not had any more "failures" with additional follow-up. Further, given the potential charge reduction of $510 per case with the use of PE+FNA, it would have taken the removal of all remaining observed lesion, plus one, to negate the observed cost-effectiveness of this diagnostic approach [169].

Other authors have looked at diagnostic test combinations for breast lesions in men. In a retrospective review from Italy of various combinations of PE, FNA, ultrasonography, and mammography, Ambrogetti et al. found a sensitivity rate of 100% for the combination of PE and mammography [203]. We found the same sensitivity for PE+FNA and favor cytologic over mammographic information for the purposes of confidently reassuring patients that they do not need open biopsy and for avoiding disaster in centers where patients diagnosed clinically as having gynecomastia are treated by liposuction [14, 211]. Further, the information provided by FNA can be used to distinguish benign from malignant breast masses [212], primary breast cancers from metastases to the breast [213–215], and to determine grade and other tumor features prior to neoadjuvant therapy (especially by adding DNA image cytometry to cytologic evaluation of the material) [216]. The combination of history, PE, and mammography has also recently been advocated as being highly accurate for the evaluation of unilateral breast masses in males, but this conclusion was reached retrospectively, and without considering FNA in the analysis [217].

In summary, although open biopsy remains the gold standard for the evaluation of breast masses in men [3, 218], it is the most expensive choice and often unnecessary, and the use of FNA-based diagnosis can safely avoid it in most cases.

25.6 Breast Cancer in Males: Treatment and Outcomes

25.6.1 Surgery

Surgical excision is the mainstay for resectable BCM. For example, most (50 of 54, or 93%) of patients in our review had some type of primary surgical therapy (all three patients who presented with stage IV and one

patient with stage IIIB disease did not) [11]. Although radical mastectomy (RM) was traditionally the treatment of choice because of the paucity of male breast tissue and the resultant proximity of these lesions to the chest wall, surgical therapy has evolved in both the United States and Europe toward more limited procedures. For example, a 30-year review of 170 cases treated at the National Cancer Institute of Italy in Milan noted a trend from RM to modified radical mastectomy (MRM) and, finally, total mastectomy (TM; for smaller and DCIS lesions) in the later period of the study [46]. A similar surgical trend was noted during approximately the same time period in the United States [113, 219], and more recent series report that RM is now used infrequently, [11, 40, 50] probably because of the reported equivalent survival after MRM compared with RM [220] and the fact that most of these tumors do not invade beyond the pectoralis fascia and can be resected with limited in-continuity muscle excision when they do.

The National Cancer Data Base (NCDB) has reported on a large BCM treatment study in which the treatments received by 3,627 matched pairs of BCM and BCF patients were compared. In this study, men were more likely to be treated with mastectomy than women (MRM, 65% of men vs. 55.15% of women; RM 2.5% of men vs. 0.9% of women; TM, 7.6% of men vs. 3.4% of women; $P<0.001$) [221]. Although some more recent studies also advocate MRM or TM for men [66, 84, 222], others note the feasibility of breast conserving operations [223, 224] and even nipple sparing [225] if the lesions is eccentric. Using intraoperative sonography to augment breast conservation in men found to have occult cancers on work-up of symptoms has recently been reported [226].

Although two-level axillary dissection was the gold standard for pathologic staging of the clinically negative axilla in BCM , several reports and series have shown the utility and accuracy of sentinel lymph node biopsy (SLNB) in avoiding the need for routine axillary dissection for clinically node negative cases [66, 84, 227–231], since at least half of BCM cases are node negative in large series [65], and this number is increasing to 55–80% in more recent series with more T1 lesions [229–231]. Similar to the experience in BCF, SLNB for BCM has been shown to be feasible and accurate; one difference is a higher rate of tumor in additional (nonsentinel) nodes in men compared to women [229].

These surgical trends have lead to a decrease in the magnitude and morbidity of breast operations in males.

Recommendations already exist for the treatment of DCIS in males with TM rather than MRM [232], and theoretically, one could extend current surgical recommendations for DCIS in females, such as the Van Nuys Prognostic Index (VNPI), [233] to males. Indeed, in our series of recently treated BCMs, five patients with stage T0 or small T1 disease ("minimal breast cancer") were treated with lumpectomy alone, with no local recurrences during the 4.5-year follow-up period [11]. Others have advocated this limited approach [136], although some reports indicate that men with DCIS have high local failure rates and may still come to bilateral TM [138, 139].

Similar to the management of BCF, potentially curative operative therapy for BCM must be postponed or modified in the event of a concurrent immediately life-threatening condition. This judgment consideration is of particular importance in older men with frequent comorbid conditions. For example, a report from Japan documents a "two-stage" approach to BCM in a 61-year-old man suffering acutely from an aortic dissection. After successfully addressing the dissection, the surgeons removed the tumor with the patient under local anesthetic, completing a definitive breast procedure 1 month later [234].

25.6.2 Radiation

Radiation therapy (RT) has been applied inconsistently for the treatment of BCM in the past. For example, in large retrospective reviews such as the previously mentioned 1999 NCDB study, men were more likely to receive RT postmastectomy than their matched female controls (men, 29%; women, 11%; $P<0.041$) but were less likely to receive RT after lumpectomy (men, 54%; women 68%; $P<0.001$) [221]. RT clearly reduces the reported 4–31% postoperative loco-regional recurrence rate [8, 122, 235], especially when the pectoralis muscle and chest wall are found to be involved at operation. As one would expect, adjuvant use of RT in this setting improves local control, but not disease-related survival [66, 235, 236].

RT is often recommended after mastectomy for BCM [223, 235], where it has been noted to be used more

frequently postmastectomy than in females [236]. In fact, male gender was found to be an independent predictive factor for the use of postmastectomy RT in a BC Cancer Agency review [237]. More recently, as noted in the prior section, RT has been used for breast preservation, especially in cases of DCIS [223–226]. In fact, a review of BCM treated at Guys Hospital concluded that the indications for RT for BCM were similar to those for BCF [84]. Similarly, the BC Cancer Agency review concluded that men having mastectomy for breast cancer should receive adjuvant RT along guidelines similar to those for women, with the caveat that common indications for postmastectomy RT (T4 lesions and extensive nodal involvement) may be more common in men [237].

25.6.3 Adjuvant Chemotherapy

Because of the rarity of BCM, the perceived role of tamoxifen as the cornerstone of adjuvant therapy, and the higher mean age of BCM patients (with attendant lower overall performance status), chemotherapy is less used for BCM, and therefore information on the use of adjuvant cytotoxic chemotherapy for BCM is sparse and mostly retrospective. In the NCDB study, men were less likely to receive chemotherapy than their matched female controls (men, 26.7%; women, 40.6%; $P<0.001$) after any form of surgical therapy. [221].

Nonetheless, most series of BCM patients treated with chemotherapy report benefit [65, 84, 223], particularly for groups at higher risk of disease-related death, such as younger patients with receptor negative and node positive disease [66, 81, 222]. In a combined experience from Memorial Sloan-Kettering Cancer Center and the Oschsner Clinic, Borgen et al. found a reduction in distant relapse from adjuvant chemotherapy of 11% (from 57 to 46%) for node-positive patients [113]. Similarly, an improved 5-year survival rate (80%) compared with stage-matched historical controls has been reported for a cohort of 24 node-positive patients treated with cytoxan-methotrexate-fluorouracil (CMF) [238].

In fact, CMF is the only chemotherapy regimen to be prospectively studied in BCM to date; the NCI MB-82 study prospectively treated 31 node positive BCM patients with 12 cycles of CMF. Survival rates at 10, 15, and 20 years were 65, 52, and 42%, respectively. The study was uncontrolled but the authors concluded that chemotherapy may produce a survival benefit [239]. Similar to the situation in BCF, some data in BCM also suggest a benefit of adjuvant chemotherapy for node-negative disease [240]. In the MD Anderson review adriamycin-based regimens were more commonly used (81%) than CMF (16%), and a decreased risk of death among patients receiving chemotherapy was also noted [65]. To date, use of trastuzamab in HER-2 positive BCM is limited to a single case report [241].

Interestingly, another prospective study of chemotherapy in BCM involved the use of high-dose chemotherapy and autotransplantation in 13 BCM patients; six had stage II disease, four were stage III, and three had metastatic disease. Of the 12 tumors tested for hormone receptors, all were positive. The median age at transplantation was 50 years. Five patients received cyclophosphamide, thiotepa, and carboplatin; the other eight patients received other alkylator-based regimens. There were no cases of nonengraftment and no treatment-related deaths. Three of the ten patients receiving autotransplantation for adjuvant therapy relapsed 3, 5, and 50 months posttransplant and died of disease; the remaining patients were alive with no evidence of disease at the median follow-up time of 23 months (range, 6–30 months). Of the three men treated for metastatic disease, one progressed and the other two relapsed at 7 and 16 months posttransplant [298]. However, at the present time autotransplantation for BCM is an unlikely option due to the negative results of prospective trials in BCF.

The use of primary systemic (“neoadjuvant”) chemotherapy to “downsize” tumors and subsequently treat them with salvage mastectomy and/or chest wall radiation has used for the treatment of locally advanced BCM with reported success [8, 65, 113]; 6% of patients in the MD Anderson series were treated n this fashion. Unlike the situation in BCF, the goal of neoadjuvant therapy for BCM is to improve local control, rather than increase the use of breast conservation.

25.6.4 Hormone Therapy

Because up to 90% of BCM cases are hormone receptor positive [84], hormone therapy is standard adjuvant therapy in men [65, 66, 84, 163, 222], and used more often than in women [77]. Tamoxifen is commonly accepted as a first-line therapy for BCM [160, 161] and is often used alone, due in part to the older mean

age and higher comorbidities of BCM patients. An early report of 1–2 years of adjuvant tamoxifen therapy in BCM patients revealed a 15% improvement in overall 5 year survival (from 44 to 61%) and a 28% improvement in 5 year disease-free survival (from 28 to 56%) [242]. The current recommendation is to use a standard 5 year tamoxifen course, although noncompliance with this regimen is higher in males than females (25 vs. 4% in one series) [56]. This higher noncompliance with tamoxifen in BCM is associated with a greater frequency and severity of side effects in men, including (in descending order of frequency) decreased libido, weight gain, hot flashes, altered mood, and depression.

Another antiestrogen, the pure ER antagonist fulvestrant, has been used for advanced BCM with reported success [243]; the role of gonadotropin-releasing hormones in the management of male metastatic breast cancer is uncertain [244]. Aromatase inhibitors (AIs) have been found to produce effective suppression of estradiol levels in males and some reports have demonstrated objective responses in advanced BCM [245, 246]. A recent report noted that AIs are now being used for BCM in clinical practice [163], probably in part due to the above-mentioned severity of tamoxifen side effects in males. Intratumoral aromatase has been found to be expressed in 27% of breast tumors in males and to correlate with a more favorable histology and clinical outcome [247].

25.6.5 Palliative Therapy

As one would expect from the high rate of ER and PR expression in BCM, hormonal manipulation has been the cornerstone of the treatment of distant disease since its first description in 1942 by Farrow and Adair, who noted regression after orchiectomy [248]. Tamoxifen is the current mainstay of palliative hormonal therapy, with overall response rates of 70% for receptor positive tumors [160]. As indicated above, recent case reports suggest that patients with metastatic disease who relapse on tamoxifen probably should be treated with second-line hormonal therapy (similar to the situation for postmenopausal BCF patients) [243, 245, 246], with palliative chemotherapy reserved for nonresponders and receptor-negative tumors. Particularly advanced cases of BCM may metastasize to unusual locations, notably the eye [249–251], skin [252, 253], and mandibular region [254, 255], each demanding a tailored approach to palliation.

25.6.6 Prognostic Factors

Similar to BCF, the most significant prognostic factors for BCM are AJCC stage and its elements: tumor size and lymph node status [11, 40, 50, 65, 87, 256, 257]. Lymph node status seems to be particularly important [81, 256, 257]. This major similarity between BCF and BCM was first established in 1987, when Hultborn and colleagues demonstrated that age, tumor size, and lymph node status were the most important prognosticators by multivariate analysis among a group of 166 BCM patients [256]. In 1993, Guinee et al. reported that tumor size greater than 3 cm significantly impaired prognosis and that 5-year survival was directly related to the number of nodes involved: 55% when four or more nodes were positive, 73% for one to three positive nodes, and 90% for node-negative patients (84% at 10 years). Skin involvement, chest wall fixation, and tumor ulceration (all of which are more common in BCM than BCF) were not independently prognostic in their study [257].

Our group subsequently reported on a multivariate analysis relating a number of factors to disease-free survival. We examined the impact of several patient and tumor factors, including the elements of TNM stage, tumor grade (low to intermediate vs. high), receptor status (positive vs. negative), personal or family history of breast cancer (positive vs. negative), age (younger or older than 60), and presentation (asymptomatic vs. pain and nipple discharge vs. painless mass) for prognostic impact in multivariate analysis using the Cox proportional hazards model [258]. Only AJCC stage and its components (tumor size, nodal status, and presence of metastases) correlated with survival [11].

We hypothesized that by controlling for the effect of age (by relating to disease-free rather than crude survival), age "dropped out" as significant, unlike earlier studies that used crude survival (see next section) [256]. Other recent multivariate analyzes have come to similar conclusions [50, 66, 97, 259, 260]. As mentioned previously, a recent study by El-Tamer and colleagues actually found a better disease-specific survival for BCM compared to BCF because men were 4 times more likely than females to die of diseases other than their

breast cancer. [68]. Many of these disease are second cancers – a recent study found that 12.5% of men with breast cancer develop a second primary malignancy, particularly of the small intestine, rectum, pancreas, skin (nonmelanomas), prostate, and lymphohemopoietic system [261]. BRCA2 (and to a lesser extent, BRCA1) mutations may explain the higher incidence of pancreatic and prostate cancers.

A recent study of FACS analysis and IHC staining of BCM specimens found that both ER and HER2/neu expression were higher in BCM compared to BCF; 55% of BCM specimens were found to have HER2/neu overexpression in this series. Although, as previously mentioned, the prognostic significance of hormone receptor positivity and HER2/neu overexpression in BCM is not entirely clear [70, 163], this study found that tumor expression of p53, ER, and cathepsin B correlated with better clinical outcome [262].

25.6.7 Prognosis: Are BCM and BCF "Different" Diseases? A Critical Appraisal of the Literature

In terms of prognosis, the essential question in BCM is whether or not the disease is biologically distinct from BCF. As mentioned previously, in part because BCM is a disease of older men (with, by definition, frequent comorbid conditions) who tend to present late (at a mean of 10.2 months in one series) [51], older series, which examined only crude (overall) survival (which does not control for age, stage , or comorbidity), reached the inevitable conclusion that it carries a worse prognosis than BCF [44–48, 58–60]. This concept also has been fostered by the occasional case report emphasizing widespread and unusual metastases in BCM patients [62, 249–255, 263–265], as well as more recent studies reporting only overall survival [66, 77]. By the early 1990s, however, some studies were reporting a worse prognosis only for men with positive nodes [44, 113]. These investigators hypothesized that because most cases of BCM were centrally located, node positivity was a worse sign than in cancers in women.

Subsequent series found similar survival between males and females afflicted with breast cancer when the cases in men were controlled for age and stage [50, 51, 266]. For example, Borgen et al., reviewing a 16-year, two-institution database, found similar AJCC stage-related survivals between 58 cases of BCM and matched BCF controls [50]. Donnegan et al., in an 18-institution review of 217 patients with BCM, also showed similar stage-related survival to cases of BCF, but they also found late presentation and advanced stage to be a common theme, resulting in a low 10-year survival as a result of censored events (25% of the patients in his series died during follow-up due to non-cancer causes) [51]. As already mentioned, this phenomenon actually lead to better disease- specific survival in men compared to women in the study by El-Tamer, et al. [68].

Accordingly, at our institution, we chose to study a more "recent" cohort of patients who presented mostly to multidisciplinary breast clinics for evaluation of their masses [11]. These factors may explain why (1) the mean tumor size in our series (2.7 cm) was smaller than that in even fairly recent reports [44–49, 66, 267], (2) more than half (57%) of our cases were early stage (AJCC stage groupings 0-IIA; half of tumors were stages T0 or T1 at presentation), and (3) 62% were node negative (118 of 604 total lymph nodes removed [19.5%] were pathologically positive for tumor). Whereas these figures are still higher than those for BCF, taken together with the literature as a whole, especially studies of BCM seen at different time frames [49], they do suggest a much called-for trend of increased awareness and earlier diagnosis [160, 266]. Some of the lower stages seen in our series may be attributable to our previously published standardized approach to breast masses in males, which involves a high index of suspicion combined with rapid and accurate evaluation of the mass in question by aspiration cytology (see "FNA-based diagnosis," above) [95, 169]. This approach has been used for the past 16 years at the institutions that contribute data to our studies.

We calculated disease specific survival by the method of Kaplan and Meier, counting deaths from other causes as censored events [268] and comparing survival curves by log-rank analysis [269]. The overall 5-year disease-free survival for our entire patient group was 87%–better than that reported by series that included "older "data [65, 66]. As demonstrated in Fig. 25.2, Five- and 10-year disease-related survival rates were AJCC stage-related; 100 and 71%, respectively, for early stage (stage groupings 0-IIA) disease, and 71 and 20% respectively for advanced stage (stage groupings IIB-IV) disease. This difference in survival was highly statistically significant by log-rank test ($P>0.0051$).

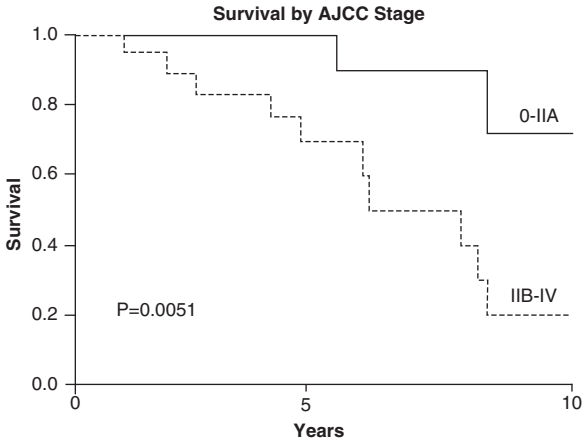

Fig. 25.2 Disease free survival of males with breast cancer, by American Joint Committee on Cancer (AJCC) stages, for early (stage groupings I-IIA) and later (stage groups IIB-IV) disease, by the method of Kaplan and Meier. The curves are significantly different by the log-rank test. Reprinted from reference [11], with permission

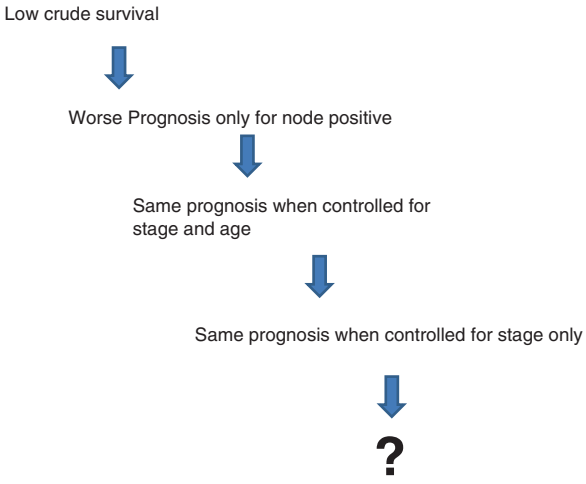

Fig. 25.3 Trends in the outcomes for breast cancer in males (BCM) compared to females, as reported in the literature. See text for details

Table 25.6 Five-year disease-free survival for breast cancer by surveillance, epidemiology, and end results (SEER) stages

SEER stage	Males[a] (%)	Females[b] (%)
Localized	100	97
Regional	81	78
Metastatic	33	22

[a]Data from reference 11

[b]SEER data from Fritz A. A SEER cancer statistics review 1973–1995. Bethesda, MD: NCI Cancer Statistics Branch, 1998

Further, Table 25.6 lists the 5-year survivals of the patients in our study by the Surveillance, Epidemiology, and End Results (SEER) database staging system (localized, regionally metastatic, and distant disease), compared with published survival numbers by SEER stages for BCF during approximately the same time as our study [270]. As can be seen in the Table, the stage-related 5-year survivals for BCM and BCF were similar [11]. To reach this finding in our study, we needed only to control only for stage, not age. As alluded to above under "Prognostic Factors," however, it should be noted that the Kaplan-Meier method does control for age in a BCM series somewhat by censoring deaths from other causes.

The series from M.D Anderson also compared localized and regional disease in men and women and also found 5 and 10 year outcomes in men (localized: 86 and 75% survivals, respectively; regional: 70 and 43% survivals, respectively) to be similar to those reported in women [65].

All existing data on BCM are marred by its retrospective, historical, and "patchy" nature. We applaud the Commission on Cancer for their efforts in performing a Patient Care Evaluation Study in BCM [160, 221] and also Memorial Sloan-Kettering Cancer Center's ongoing a National Male Breast Cancer Registry (see section entitled "Tumor Registries" to follow).

Based on the trend we have seen in the literature (Fig. 25.3), including our own study [11], one wonders whether future data will show a further decrease in the presenting size and stage of BCM, with survival rates approaching those of BCF, without the necessity for even a stage correction. At present, this seems doubtful. Although the mean size of tumors in BCF cases is expected to decrease to below 1.0 cm in the next 10 years, such a trend for BCM is unlikely because this is an uncommon disease that is not screened for and therefore will continue to present in a most cases as a palpable mass. Nonetheless, a high index of suspicion [160, 266] combined with a uniform approach to diagnosis [169] and education and screening of high-risk populations [87] may bring about continued decreases in stage at presentation and attendant mortality.

For the present, one of the most important implications of the recent information suggesting that BCM is not a biologically more aggressive disease than the same condition in females is to emphasize to providers

that BCM should be treated for cure in most cases. Similar to the situation in females, such treatment should include optimal (but not overly aggressive) local control [49, 223–225], adjuvant hormonal therapy for receptor-positive tumors (most breast tumors in men) [52, 65, 66, 84, 163, 164, 222], and consideration of adjuvant chemotherapy for high-risk patients [65, 84, 87, 223, 271].

More recently, investigators have attempted to answer the question of whether or not BCM is a different disease from BCF by using biologic rather than descriptive data. On a cellular level, a recent report has cataloged 4 cases of CD34 positive BCM, suggesting the possible existence of a CD34 positive breast cancer stem cell, similar to the cancer stem cell postulated for BCF [272]. On a chromosomal level, Rudlowski et al. have recently reported a shared pattern of chromosomal imbalances between BCM and BCF, including +1q, −8p, +8q, −13q, +16p, −16q, +17q, and +20q, suggesting that similar genetic events may underlie the development and progression of breast cancer in both males and females [273]. Conversely, on a genetic level, a recent study found significant dissimilarities in DNA ploidy, p21, and p53 between clinically homogenous groups of BCM and BCF, suggesting somewhat distinct tumor oncogenesis [274].

Table 25.7 Comparison of BCM and females

Similarities	Differences
Associated factors Age Exposure to estrogens Chest wall radiation	Incidence, ability for early detection
Association with BRCA2 mutations	Association with BRCA1, other syndromes
Mostly ductal histologies	Incidence of lobular histology, pure DCIS
Usually solitary tumors	Most common location within the breast
Importance of physical examination (PE)	Role of mammography
Staging system	
Usefulness of FNA-based diagnosis	Differential diagnosis
Stage-for-stage treatment Central role of resection and sentinel node biopsy Importance of adjuvant hormonal therapy	
Main prognostic factors	Incidence of ER, PR expression
Stage-for-stage prognosis[a]	

FNA fine-needle aspiration
[a]When controlled for stage and co-morbidities; see Fig. 25.2, Table 25.6, and text

25.6.8 *Similarities and Differences Between BCM and BCF: A Summary* (Table 25.7)

Like BCF, BCM is most commonly of ductal histology [8, 11, 40, 87, 135], is associated with relative estrogen excess [8, 44, 47, 58, 69, 85, 88, 95, 96, 98], is staged by the TNM system [165], and is best treated by multimodality therapy (most often surgery followed by adjuvant therapy). Cases not resectable for cure can be treated by a combination of palliative therapies (surgery, chemotherapy, RT, or hormonal therapy). BCM and BCF appear to have similar prognostic factors [11, 40, 50, 65, 87, 256, 257] and similar stage-for-stage survival [11, 50, 51, 65, 266], especially if one controls for age and comorbid conditions. Like BCF, BCM appears to be mostly a singular event, with synchronous and metachronous tumors less common [275–278], although men do have a higher incidence of second nonbreast primary tumors [261].

There are also several clear clinical differences between BCM and BCF. Besides the previously noted older mean age for BCM patients, this disease is by definition usually centrally located and often involves the nipple [87]. Accordingly, whereas nipple discharge in BCF is usually nonbloody and associated with benign conditions, discharge in BCM is more often bloody and a sign of malignancy, including DCIS, and discharge cytology may be diagnostic [40, 41]. The vast majority of cases of BCM are hormone-receptor positive (65–93% in recent studies [50, 63, 65, 87] and 85% in our series [11]). Thus, tamoxifen has become the mainstay of therapy for many patients [65, 66, 77, 84, 160, 161, 163, 222], although it may be associated with a greater frequency and severity of dose-limiting side effects in men than in women [56].

25.7 Breast Cancer Survivorship Issues in Males

25.7.1 Follow-Up

There are no recommendations for follow-up that are specific to BCM; rather, the same follow-up schedule used for BCF is generally recommended for BCM. For patients with invasive tumors, such schedules usually involve a history and PE (especially CBE) every 3 months for the first 2 years, then every 6 months for the next 2 years, and then yearly. This follow-up is based on the theory that 75% of recurrences of breast cancer occur in the first 2 years and 10% in the next 2-year period, with the recurrence rate leveling-off to approximately 1% per year thereafter [279].

While PE is particularly important in male patients, the value of follow-up mammography for BCM has not been studied and would be expected to be lower than for BCF (see preceding discussion in section entitled "Diagnosis"). An American Society of Clinical Oncology consensus panel on breast cancer follow-up has not found clear efficacy of other tests, such as liver function tests, alkaline phosphatase level, and chest radiographs [280], although such tests are commonly ordered [279]. Both randomized and nonrandomized studies have demonstrated that more intensive tests for detecting recurrence, such as bone scans, computed tomography scans, and tumor markers, do not confer survival benefit and are best reserved for the detection of metastases in symptomatic patients [279, 281].

25.7.2 Testing of Family Members

There is a known association between BCM development and mutations in the BRCA genes; any BCM patient has a greater than 10% risk of carrying a BRCA, (especially BRCA2) mutation, even in the absence of other first degree relatives affected with breast, ovarian, or prostate cancer. Accordingly, current NCCN guidelines recommend testing men with BCM ("index relatives") for a BRCA mutation [282]. Nonetheless, it is important to remember that most cases of BCM are "sporadic" (i.e., not associated with known gene mutations) [283] and that BRCA2 gene mutations in men appear to have low penetrance in terms of actually causing the disease [121]; only 4–7% of patients with BCM report having a first degree relative of either sex with breast cancer. Penetrance does vary geographically; overall the risk of BCM among BRCA2 mutation carriers is only 6%, while one series of BCM in Iceland found a rate of 40% [282]. Also, it should be noted that a 6% risk of BCM represents a 100-fold increase over population risk [282].

Because BCM is not usually a screened-for disease, the finding that a male individual in a BCM family is a mutation carrier gives little useful preventative information beyond emphasizing that PE and a low threshold for biopsy of any masses or areas of discharge should be a routine part of that person's regular medical care. Such increased awareness and measures may be instituted for these individuals even without genetic testing if the family history is concerning.

For female patients, however, the implications of discovering a BRCA mutation in a male index relative are much greater because such mutations confer on these persons a 56–87% BCF risk by age 70 [284], a 2–12% risk of contralateral BCF within 5 years of a diagnosis of BCF [285], and a 27% ovarian cancer risk by age 70 [286]. In a study in Denmark, Storm and Olsen found female, but not male, offspring of BCM patients to have an increased relative risk (16.4) of breast cancer compared with the general population [287].

Accordingly, we would agree with the NCCN guidelines and with Diez and colleagues that "all new male cases of breast cancer should be regarded as being possibly inherited and should be fully investigated," especially if potential transmissions of BRCA2 mutations to female offspring are involved [282, 288].

Rarer but higher penetrance genetic events which have been associated with an increased risk of BCM include mutations in the PTEN tumor suppressor gene (Cowden's syndrome), AR gene, CHEK2 gene, and CYP17 (especially CYP17A1) polymorphisms [282]. As mentioned earlier, data for AR and CHEK2 is conflicting [85, 110, 133].

25.7.3 Tumor Registry

As mentioned previously, Memorial Sloan-Kettering Cancer Center has started a national registry of BCM cases (www.mskcc.org)

25.7.4 Psychological Issues/Resources/Support Groups

The often neglected psychological aspects of men having a "cancer of women" have only recently been recognized in the literature [289], all of which at present comes from groups in the UK. In a phenomenological study from Liverpool investigators noted four key issues for BCM patients: living with the disease, concealment as a coping strategy, contested masculinity (which is worsened by the diminished libido effects and erectile dysfunction of tamoxifen), and interacting with health services geared toward treating breast cancer as a feminized illness [290]. Not surprisingly, investigators at Cardiff University found that a quarter of men with BCM experienced traumatic stress symptoms specific to their diagnosis and heightened by embarrassment, stigma, altered body image, and unmet informational needs in 56% of patients surveyed, particularly for gender-specific information [291–293].

That said, at present gender-specific information on BCM is limited. However, because BCM is similar to BCF in terms of histology, prognostic factors, state-for-stage prognosis, and treatment recommendations, information regarding breast cancer in general is useful to male patients. The educational Web pages of national breast cancer awareness and support organizations such as the American Cancer Society (www.cancer.org), the National Cancer Institute (www.cancer.gov), the Susan G. Komen for the Cure Foundation (www.komen.org), as well as the internet resource www.breastcancer.org do contain fairly good sections on BCM.

Similarly, support groups for BCM are few. The Bridging the Gap Male Breast Cancer Awareness Group, a group formed in the Portland, Oregon area by BCM patients and their families, seeks to raise awareness of BCM to promote earlier diagnosis and treatment. The author has had the privilege of serving as a medical advisor for this group. The founders of this group wished to avoid the term *support*; hence, the members chose the term *awareness* instead. Information on this group can be obtained at www.breastfriends.com or by email to lagere@earthlink.net.

The John W. Nick Foundation is a not-for-profit private foundation headquartered in Vero Beach, Florida, founded in 1995 by Nancy Nick, with the help of her mother Patricia and son Adam, in memory of her father John Nick who died from breast cancer at the age of 58 in 1991. The mission of the foundation is to foster education regarding breast cancer in men, including risk, prevention, and treatment. The group has designed an awareness ribbon that is pink throughout (like the well-known ribbon) except for the right tip, which is blue, symbolizing the fact that breast cancer on occasion affects males as well. The foundation can be reached through its Web page at www.johnwnickfoundation.org.

There are very few books or articles available regarding BCM. Sadly, the book "The Warriors Way" by John Cope (Lake Oswego [OR]: Hearts that Care Publishing, 2000) has gone out of print since the author, a BCM patient, succumbed to a recurrence of his disease. Available references in print include:

1. Allen T [294]. This is a BCM awareness article that focuses on the various awareness and support efforts, especially on the part of a particular survivor, Dave Lyons, who is known to the author.
2. Parker JN and Parker PM [295]. A remarkably complete source book providing basic information on BCM and its treatment, medications and nutritional issues, resources and books, and legal and insurance information for patients.
3. Landay D [296]. A valuable resource for all cancer survivors, regardless of diagnosis, gender, or age.

Acknowledgments I gratefully acknowledge the assistance of Si-Youl Jun, MD, Darius Paduch, MD, Heidi Eppich, and Richard Shih for their assistance in collection of the Oregon data on BCM; Waldemar Schmidt, MD, PhD, Rodney Pommier, MD, John DiTomasso, MD, Heidi Eppich, William Wood, MD, and Dane Moseson, MD, for their contribution to the diagnostic test data for the evaluation of breast masses in males; and Elsevier for granting permission to reprint parts of the resulting publications [11, 200]. The assistance of Irene Perez Vetto, RN, MN, ANP, AOCN, in reviewing and editing the manuscript is also gratefully acknowledged.

References

1. Ellis H (1992) Anatomy of the breast. In: Isaacs JH (ed) Textbook of breast disease. Mosby Year Book, St. Louis, p 2
2. Hughes LE, Mansel RE, Webster DJT (1989) Benign disorders and diseases of the breast: concepts and clinical management. Bailliere Tindall, London, p 167
3. Rosen PP, Oberman HS (1993) Tumors of the mammary gland (atlas of tumor pathology, series 3, fascicle 7). Armed Forces Institute of Pathology, Washington, DC, p 282
4. Hall R, Anderson J, Smart GA et al (1980) Fundamentals of clinical endocrinology. Pitman Medical, London, p 198

5. Cakan N, Kamat D (2007) Gynecomastia: evaluation and treatment recommendations for primary care providers. Clin Pediatr. 46:487–90
6. Narula HS, Carlson HE (2007) Gynecomastia. Endocrinol Metab Clin North Am. 36:497–519
7. Li RZ, Xia Z, Lin HH, et al (2007) Childhood gynecomastia: a clinical analysis of 240 cases. Zhongguo Dang Dai Er Ke Za Zhi. 9:404–6
8. Wilhelm MC, Langenburg SE, Wanebo HJ (1998) Cancer of the male breast. In: Bland KI, Copeland EM (eds) The breast: comprehensive management of benign and malignant disease. WB Saunders, Philadelphia, pp 1416–20
9. Chantra PK, So JS, Wollman JS et al (1995) Mammography of the male breast. AJR Am J Roentgenol. 164:853–8
10. O'Hanlon DM, Kent P, Kerri MJ et al (1995) Unilateral breast masses in men over 40: a diagnostic dilemma. Am J Surg. 170:24–6
11. Vetto J, Jun S–Y, Paduch D et al (1999) Stages at presentation, prognostic factors, and outcomes of breast cancer in males. Am J Surg. 177:379–83
12. Braunstein GD (1993) Gynecomastia. N Engl J Med. 328:490–5
13. Abaci A, Buyukgebiz A (2007) Gynecomastia: review. Pediatr Endocrinol Rev. 5:489–99
14. Handschin AE, Bietry D, Husler R et al (2008) Surgical management of gynecomastia– a 10-year analysis. World J Surg. 32:38–44
15. Shin SJ, Rosen PP (2007) Bilateral presentation of fibroadenoma with digital fibroma-like inclusions in the male breast. Arch Pathol Lab Med. 131:1126–9
16. Sklair-Levy M, Sella T, Alweiss T et al (2008) Incidence and management of complex fibroadenoma. AJR Am J Roentgenol. 190:214–8
17. Meshikhes AW, Butt S, Al-Jaroof A, Al-Saeed J (2005) Fibromatosis of the male breast. Breast J. 11:294
18. Macchetti AH, Arana HR, Riberio-Silva A et al (2006) Fibromatosis of the male breast: a case report with immunohistochemistry study and review of the literature. Clinics. 61:351–4
19. Li A, Lui CY, Ying M et al (2007) Case of fibromatosis of the male breast. Australas Radiol. 51:B34–6
20. Khachemoune A, Rodriquez C, Lyle S, Jiang SB (2005) Genital leiomyoma: a surgical excision for both diagnosis and treatment of a unilateral leiomyoma of the male nipple. Dermatol Online J. 11:20
21. Aronovich D, Kaminsky O, Schindel A (2005) Retroareolar leiomyoma of the male breast. Isr Med Assoc J. 7:121–2
22. Desrosiers L, Rezak S, Larkin A et al (2007) Myofibroblastoma of the male breast: a rare entity of increasing frequency that can be diagnosed on needle core biopsy. Histopathology. 51:568–72
23. Sharma A, Sen AK, Chaturvedi NK, Yadav R (2007) Myofibroblastoma of the male breast: a case report. Indian J Pathol Microbiol. 50:326–8
24. Georgountzos V, Ioannidou-Mouzaka L, Tsouroulas M et al (2005) Benign intracystic papilloma in the male breast. Breast J. 11:361–2
25. Yamamoto H, Okada Y, Taniguchi H et al (2006) Intracystic papilloma in the breast of a male given long-term phenothiazine therapy: a case report. Breast Cancer. 13:84–8
26. Adeniran A, Al-Ahmadie H, Mahoney MC et al (2004) Granular cell tumor of the breast: a series of 17 cases and review of the literature. Breast J. 10:528–31
27. Zani A, Cozzi DA, Uccini S, Cozzi F (2007) Unusual breast enlargement in an infant: a case of breast lipoblastoma. Pediatr Surg Int. 23:361–3
28. Ali MZ, Ali FZ (2005) Pilomatrixoma breast mimicking carcinoma. J Coll Physicians Pak. 15:248–9
29. Tung CC, Lin JW, Chou FF (2005) Sparganosis in male breast. J Formos Med Assoc. 104:127–8
30. Winzer KJ, Menenakos C, Braumann C et al (2005) Breast mass due to pectoral muscle tuberculosis mimicking breast cancer in a male patient. Int J Infect Dis. 9:176–7
31. Marie I, Herve F, Robaday S, Levesque H (2007) Tuberculosis myositis mimicking breast cancer. QJM. 100:59
32. Ursavas A, Ege E, Bilgen OF et al (2007) Breast and osteoarticular tuberculosis in a male patient. Diagn Microbiol Infect Dis. 58:477–9
33. Reddy KM, Meyer CE, Nakdjevani A, Shrotria S (2005) Idiopathic granulomatous mastitis in the male breast. Breast J. 11:73
34. Fernandez-Flores A, Crespo LG, Alonso S, Montero MG (2006) Lupus mastitis in the male breast mimicking inflammatory carcinoma. Breast J. 12:272–3
35. Squillaci S, Tallarigo F, Patarino R, Bisceglia M (2007) Nodular fasciitis of the male breast: a case report. Int J Surg Pathol. 15:69–72
36. Franco RL, deMoraes Schenka NG, Schenka AA, Alvarenga M (2005) Cavernous hemangioma of the male breast. Breast J. 11:511–2
37. Kinoshita S, Kyoda S, Tsuboi K et al (2005) Huge cavernous hemangioma arising in the male breast. Breast Cancer. 12:231–3
38. Kondi-Pafitis A, Kairi-Vassilatou E, Grapsa D et al (2005) a large benign vascular neoplasm of the male breast. A case report and review of the literature. Eur J Gynaecol Oncol. 26:454–6
39. Vourtsi A, Zervoudis S, Pafiti A, Athanasiadis S (2006) Male breast hemangioma-a rare entity: a case report and review of the literature. Breast J. 12:260–2
40. Cutuli B, Dilhuydy JM, DeLafontan B et al (1997) Ductal carcinoma in situ of the male breast: analysis of 31 cases. Eur J Cancer. 33:35–8
41. Lopex-Rios F, Vargas-Castrillon J, Gonzalez-Palacios F et al (1998) Breast carcinoma in situ in a male: report of a case diagnosed by nipple discharge cytology. Acta Cytol. 42:724–44
42. Detraux P, Benmussa M, Tristant H et al (1985) Breast disease in the male: galactographic evaluation. Radiology. 154:605–6
43. Treves N, Robbins GF, Amoroso WL (1956) Serous and serosanguinous discharge from the male nipple. Arch Surg. 90:319–29
44. Heller KS, Rosen PP, Shattenfeld DD et al (1978) Male breast cancer: a clinicopathologic study of 97 cases. Ann Surg. 188:60–5
45. Adami HO, Holmberg L, Malker B et al (1985) Long-term survival in -1–06 males with breast cancer. Br J Cancer. 52:99–103
46. Salvadori B, Saccozzi R, Manzari A et al (1994) Prognosis of breast cancer in males: an analysis of 170 cases. Eur J Cancer. 30A:930–5

47. Cutuli B, Lacroze M, Dilhuydy JM, et al (1995) Male breast cancer: results of the treatment and prognostic factors in 397 cases. Eur J Cancer. 31A:160–4
48. Stierer M, Rosen H, Weitensfelder W et al (1995) Male breast cancer: Australian experience. World J Surg. 19: 687–93
49. Gough DB, Donohue JH, Evans MM (1993) A 50-year experience of male breast cancer: is outcome changing? Surg Oncol. 2:325–33
50. Borgen PI, Senie RT, McKinnon WMP et al (1997) Carcinoma of the male breast: analysis of prognosis compared to matched female patients. Ann Surg Oncol. 4:385–8
51. Donegan WL, Redlich PN, Lang PJ et al (1998) Carcinoma of the breast in males: a multiinstitutional survey. Cancer. 83:498–509
52. Ribeiro G (1985) Male breast carcinoma-a review of 30 I cases from the Christie Hospital and Holt Radium Institution, Manchester. Br J Cancer. 51:115–9
53. Goss PE, Reid C, Pintilie M et al (1999) Male breast carcinoma: review of 229 patients who presented to the Princess Margaret Hospital during 40 years: 1955–1996. Cancer. 85:629–39
54. Vaizey C, Burke M, Lange M (1999) Carcinoma of the male breast-a review of91 patients from Johannesburg Hospital breast clinics. S Afr J Surg. 37:6–8
55. Teixeira MR, Pandis N, Dietrich CU et al (1998) Chromosome banding analysis of gynecomastia and breast carcinomas in men. Genes Chromosomes Cancer. 23:16–20
56. Anelli TF, Anelli A, Tran KN et al (1994) Tamoxifen administration is associated with a high rate of treatment-limiting symptoms in male breast cancer patients. Cancer. 74(1):74–7
57. American Cancer Society (2007) Cancer Facts and Figures 2007. American Cancer Society, Atlanta
58. Thomas DB, Jimenez LM, McTiernan A et al (1992) Breast cancer in men: risk factors with hormonal implications. Am J Epidemiol. 135:734–8
59. Anderson DE, Badzioch MD (1992) Breast cancer risks in relatives of male breast cancer patients. J Natl Cancer Inst. 74:1114–7
60. Rosenblatt KA, Thomas DB, McTieman A et al (1991) Breast cancer in men: aspects of familial aggregation. J Natl Cancer Inst. 83:849–54
61. Demers PA, Thomas BD, Rosenblatt KA et al (1991) Occupational exposure to electromagnetic fields and breast cancer in men. Am J Epidemiol. 134:340–7
62. DiBenedetto G, Perangeli M, Bertani A (1998) Carcinoma of the male breast: an underestimated killer. Plast Reconstruct Surg. 102:696–700
63. Willsher PC, Leach IH, Ellis IO et al (1997) Male breast cancer: pathological and immunohistochemical features. Anticancer Res. 17:2335–8
64. Hill TD, Khamis HJ, Tyczynski JE, Berkel HJ (2005) Comparison of male and female breast cancer incidence trends, tumor characteristics, and survival. Ann Epidemiol. 15:773–80
65. Giordano SH, Perkins GH, Broglio K et al (2005) Adjuvant systemic therapy for male breast cancer. Cancer. 104: 2359–64
66. Cutili B (2007) Strategies in treating male breast cancer. Expert Opin Pharmacother. 8:193–202
67. Ioka A, Tsukuma H, Ajiki W, Oshima A (2006) Survival of male breast cancer patients: a population-based study in Osaka, Japan. Jpn J Clin Oncol. 36:699–703
68. El-Tamer MB, Komenaka IK, Troxel A et al (2004) Men with breast cancer have better disease-specific survival than women. Arch Surg. 139:1079–82
69. Sasco AJ, Lowenfels AB, Pasker-deJong P. (1993) Epidemiology of male breast cancer. A meta-analysis of published case-control studies and discussion of selected aetiologic factors. Int J Cancer. 53:538–49
70. Moore MP (1996) Male breast cancer. In: Harris JR, Lippman ME, Morrow M et al (eds) Diseases of the breast. Lippincott-Raven, Philadelphia, pp 859–63
71. LaVecchia C, Levi F, Luccini F (1992) Descriptive epidemiology of male breast cancer in Europe. Int J Cancer. 51:62–6
72. Hodgson NC, Button JH, Franceschi D et al (2004) Male breast cancer: is the incidence increasing? Ann Surg Oncol. 11:751–5
73. Anon (2004) Male breast cancer rates rising. Health News. 10:13
74. Stang A, Thomssen C (2008) Decline in breast cancer incidence in the United States: what about male breast cancer? Breast Cancer Res Treat. 112:595–6
75. Bagchi S (2007) Men with breast cancer have high risk of second cancer. Lancet Oncol. 8:198
76. Satram-Hoang S, Zioglas A, Anton-Culver H (2007) Risk of second primary cancer in men with breast cancer. Breast Cancer Res. 9:R10
77. Nehleh ZA, Srikantiah R, Safa M et al (2007) Male breast cancer in the veterans affairs population: a comparative analysis. Cancer. 109:1471–7
78. Saltzstein EC, Tanof M, Latomoca R (1978) Breast carcinoma of a young male. Arch Surg. 113:880–1
79. O'Malley C, Shema S, White E, Glasser S (2005) Incidence of male breast cancer in California, 1988–2000: racial ethnic variation in 1759 men. Breast Cancer Res Treat. 93: 145–50
80. Goodman MT, Tung KH, Wilkens LR (2006) Comparative epidemiology of breast cancer among men and women in the U.S., 1996-2000. Cancer Causes Control. 17:127–36
81. Crew KD, Neugut AI, Wang X et al (2007) Racial disparities in treatment and survival of male breast cancer. J Clin Oncol. 25:1089–98
82. Rosenbaum FF, Vena JE, Zielezny MA et al (1994) Occupational exposures associated with male breast cancer. Am J Epidemiol. 139:30–6
83. Mabuchi A, Bross D, Kessler II (1985) Risk factors in male breast cancer. J Natl Cancer Inst. 74:371–5
84. Fentiman IS, Fourquet A, Hortobagyi GN. (2006) Lancet. Male breast cancer. 367:595–604
85. Weiss JR, Moysich KB, Swede H (2005) Epidemiology of male breast cancer. Cancer Epidemiol Biomarkers Prev. 14:20–6
86. Tynes T (1993) Electromagnetic fields and male breast cancer. Biomed Pharmacother. 47:425–7
87. Memon MA, Donohue JH (1997) Male breast cancer. Br J Surg. 84:433–5

88. Hsing AW, McLaughlin JK, Cocco P et al (1998) Risk factors for male breast cancer. Cancer Cause Control. 9: 269–75
89. von der Weid NX (2008) Adult life after surviving lymphoma in childhood. Support Care Cancer. 16:339–45
90. Greene M, Goedert J, Bech-Hansen N et al (1983) Radiogenic male breast cancer with in vitro sensitivity to ionizing radiation and bleomycin. Cancer Invest. 1:379–86
91. Edlar S, Nash E, Abrahamson J (1989) Radiation carcinogenesis in the male breast. Eur J Surg Oncol. 15:274
92. Hauser A, Lerner I, King R (1992) Familial male breast cancer. Am J Med Genet. 44:839–40
93. Yahalom J, Petrek JA, Biddinger PW et al (1992) Breast cancer in patients irradiated for Hodgkin's disease: a clinical and pathologic analysis of 45 events in 37 patients. J Clin Oncol. 10:1674–81
94. Ron E, Ikeda T, Preston DL, Tokuoka S (2005) Male breast cancer incidence among atomic bomb survivors. J Natl Cancer Inst. 97:603–5
95. Casagrande J, Hanische R, Pike M et al (1988) A case-control study of male breast cancer. Cancer Res. 48:1326–30
96. Hirose Y, Sasa M, Bando Y et al (2007) Bilateral male breast cancer with male potential hypogonadism. World J Surg Oncol. 5:60
97. Evans DB, Critchlow RW (1987) Carcinoma of male breast and Kleinfelter's syndrome-Is there an association? CA Cancer J Clin. 37:246–50
98. Hultborn R, Hanson C, Kopf I et al (1997) Prevalence of Kleinfelter's syndrome in male breast cancer patients. Anticancer Res. 17:4293–7
99. Swerdlow AJ, Schoemaker MJ, Higgins CD et al (2005) Cancer incidence and mortality in men with Klinefelter syndrome: a cohort study. J Natl Cancer Inst. 97:1204–10
100. Woo TC, Choo R, Chandler S (2004) An unusual case of concurrent breast and prostate cancer. Can J Urol. 11: 2390–2
101. Yacoub J, Richardson C, Farmer M et al (2007) Male breast cancer during treatment with leuprolide for prostate cancer. Clin Adv Hematol Oncol. 5:555–6
102. Schlappack OK, Braun O, Maier U (1986) Report of two cases of male breast cancer after prolonged estrogen treatment for prostatic carcinoma. Cancer Detect Prev. 9: 319–22
103. Pritchard TJ, Pankowsky DA, Crowe JP et al (1988) Breast cancer in a male to female transsexual. JAMA. 259: 2278–80
104. Symmers W (1968) Carcinoma of the breast in transsexual individuals after surgery and hormonal interference with primary and secondary sex characteristics. BMJ. 2:82–5
105. Kanhai RC, Hage JJ, Biomena E et al (1999) Mammary fibroadenoma in a male-to-female transsexual. Histopathology. 35:183–5
106. Ballerini P, Recchione C, Cavalleri A et al (1990) Hormones in male breast cancer. Tumori. 76:26–8
107. Scheike O, Svenstump B, Frandson B (1973) Metabolism of estradiol 17-beta in men with breast cancer. J Steroid Biochem. 4:489–501
108. Olsson H, Aim P, Aspergren K et al (1990) Increased prolactin levels in a group of men with breast cancer: a preliminary study. Anticancer Res. 10:59–62
109. Guenel P, Cyr D, Sabroe S et al (2005) Alcohol drinking may increase risk of breast cancer in men: a European population-based case-control study. Cancer Causes Control. 15:571–80
110. Rosenblatt KA, Thomas DB, Jimenez LM et al (1999) The relationship between diet and breast cancer in men. Cancer Causes Control. 10:107–13
111. Hansen J (2000) Elevated risk for male breast cancer after occupational exposure to gasoline and vehicular combustion products. Am J Ind Med. 37:349–52
112. Cocco P, Figgs L, Dosemeci M et al (1998) Case-control study of occupational exposures and male breast cancer. Occup Environ Med. 55:599–604
113. Borgen PI, Wong GY, Vlamis V et al (1992) Current management of male breast cancer. Ann Surg. 215:451–7
114. Pagnozzi LaRaja RD, JA RRE et al (1985) Cancer of the breast in three siblings. Cancer. 55:2709–11
115. Lsson H, Anderson H, Johansson O et al (1993) Population-based cohort investigations of the risk for malignant tumors in first degree relatives and wives of men with breast cancer. Cancer. 71:1273–8
116. Kozak FK, Hall JG, Baird PA (1986) Familial breast cancer in males: a case report and review of the literature. Cancer. 58:2736–9
117. Wingren S, vanden Heuvel A, Gentile M, et al (1997) Frequent allelic losses on chromosome 13q in human male breast cancer. Eur J Cancer. 33:2393–6
118. Rubinstein WS (2004) Hereditary breast cancer in Jews. Fam Cancer. 3:249–57
119. Chodick G, Stuewing JP, Ron E, et al (2008) Similar prevalence of founder BRCA 1 and BRCA 2 mutations among Ashkenazi men with breast cancer: evidence from 261 cases in Israel. Eur J Med Genet. 51:141–7
120. Evans DG, Bulman M, Young K, et al (2008) BR/CA ½ mutational analysis in male breast cancer families from North West England. Fam Cancer. 7:113–7
121. Haralson K, Lowman N, Zhang QX et al (1998) BrCa2 germ-line mutations are frequent in male breast cancer patients without a family history of the disease. Cancer Res. 58:1367–71
122. Stratton MR, Ford O, Newhaven S (1994) Familial male breast cancer is not linked to the BrCa1 locus on chromosome 17q. Nat Genet. 7:103–7
123. Tournier I, Paillerets BB, Sobol H et al (2004) Significant contribution of germline BRCA 2 rearrangements in male breast cancer families. Cancer Res. 64:8143–7
124. Karhu R, Laurila E, Kallioniemi A, Syrjakoski K (2006) Large genomic BRCA2 rearrangements and male breast cancer. Cancer Detect Prev. 30:530–4
125. Tchou J, Ward MR, Volpe P et al (2007) Large genomic rearrangements in BRCA1 and BRCA2 and clinical characteristics of men with breast cancer in the United States. Clin Breast Cancer. 7:627–33
126. Falchetti M, Lupi R, Rizzolo P, et al (2008) BRCA1/BRCA2 rearrangements and CHEK2 common mutations are infrequent in Italian male breast cancer cases. Breast Cancer Res Treat. 110:161–7
127. Miolo G, Puppa LD, Santarosa M et al (2006) Phenotypic features and genetic characterization of male breast cancer families: identification of two recurrent BRCA2 mutations in north-east of Italy. BMC Cancer. 6:156

128. Palomba G, Cossu A, Friedman E et al (2007) Origin and distribution of BRCA2–8765delAG mutation in breast cancer. BMC Cancer. 19:132
129. Tai YC, Domchek S, Parmigiani G, Chen S (2007) Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst. 99:1811–4
130. Boyd J, Rhei E, Federici MG et al (1999) Male breast cancer in the hereditary nonpolyposis syndrome. Breast Cancer Res Treatment. 53:87–91
131. Adeyinka A, Mertens F, Bonderson L et al (2000) Cancer heterogeneity and clonal evolution in synchronous bilateral breast carcinomas and their lymph node metasta5eS from a male patient without ant detectable BRCA2 mutation. Cancer Genet Cytogenet. 118:42–7
132. LoBaccaro JM, Lumbroso S, Belon C et al (1993) Androgen receptor gene mutations in male breast cancer. Hum Mol Genet. 2:1799–802
133. Pich A, Margaria E, Chiusa L et al (1999) Androgen receptor expression in male breast cancer: lack of clinicopathological association. Br J Cancer. 79:959–64
134. Anelli A, Anelli TF, Youngson B (1995) Mutations in the p53 gene in male breast cancer. Cancer. 75:2233–8
135. Kollmorgen DR, Varanasi JS, Edge SB et al (1998) Paget's disease of the breast: a 33 year experience. J Am Coll Surg. 187:171–7
136. Pappo I, Wasserman I, Halevy A (2005) Ductal carcinoma in situ of the breast in men: a review. Clin Breast Cancer. 6:310–4
137. Anderson WF, Devesa SS (2005) In situ male breast carcinoma in the Surveillance, Epidemiology, and End Results database of the National Cancer Institute. Cancer. 104: 1733–41
138. Wadie GM, Banever GT, Moriarty KP et al (2005) Ductal carcinoma in situ in a 16 year old adolescent boy with gynecomastia: a case report. J Pediatr Surg. 40:1349–53
139. Qureshi K, Athwal R, Cropp G et al (2007) Bilateral synchronous ductal carcinoma in situ in a young man: case report and review of the literature. Clin Breast Cancer. 7:710–2
140. Harmady ZZ, Carder PJ, Brennan TG (2005) Atypical ductal hyperplasia in male breast tissue with gynecomastia. Histopathology. 47:111–2
141. Prasad V, King JM, McLeay W et al (2005) Bilateral atypical ductal hyperplasia, an incidental finding in gynecomastia-case report and literature review. Breast. 14:317–21
142. Takeucki T, Komatsuzaki M, Minesaki Y et al (1999) Paget's disease arising near a male areola without an underlying carcinoma. J Dermatol. 26:248–52
143. Bodnar M, Miller OF 3rd, Tyler W (1999) Paget's disease of the male breast associated with intraductal carcinoma. J Am Acad Dermatol. 40:829–31
144. Ucar AE, Korkukluoglu B, Ergul E, et al (2008) Bilateral paget disease of the male nipple: first report. Breast. 17:317–8
145. Choueiri MB, Otrock ZK, Tawil AN et al (2005) Inflammatory breast cancer in a male. N Z Med J. 118: U1566
146. Nishimura R, Ohsumi S, Teramoto N et al (2005) Invasive cribiform carcinoma with extensive microcalcifications in the male breast. Breast Cancer. 12:145–8
147. Burga AM, Fadare O, Lininger RA, Tavassoli FA (2006) Invasive carcinomas of the male breast: a morphologic study of the distribution of histologic subtypes and metastatic patterns in 778 cases. Virchows Arch. 449:507–12
148. Erhan Y, Erhan Y, Zekioglu O (2005) Pure invasive papillary carcinoma of the male breast: report of a rare case. Can J Surg. 48:156–7
149. Sinha S, Hughes RG, Ryley NG. (2006) Papillary carcinoma in a male breast cyst: a diagnostic challenge. Ann R Coll Surg Engl. 88(s):W3–5
150. Degirmenci B, Gulhan S, Acar M, Haktanir A (2007) Large cystic infiltrating ductal carcinoma in male breast. J Clin Ultrasound. 35:102–4
151. Poultsidis AA, Kaira S, Bobrow L, Purushotham AD (2002) Intracystic papillary carcinoma: a solid variant in a male breast-case report and review of the literature. J BUON. 7:157–9
152. Mardi K, Sharma J (2006) Invasive lobular carcinoma of the male breast-a case report. Indian J Pathol Microbiol. 49:272–4
153. Erhan Y, Zekioglu O, Erhan Y (2006) Invasive lobular carcinoma of the male breast. Can J Surg. 49:365–6
154. Yildirim E, Turhan N, Pak I et al (1999) Secretory breast carcinoma in a boy. Eur J Surg Oncol. 25:98–9
155. Bhagwandeen BS, Fenton L (1999) Secretory carcinoma of the breast in a nine year old boy. Pathology. 31:166–8
156. Titus J, Sillar RW, Fenton LE (2000) Secretory breast carcinoma in a 9-year-old boy. Aust N Z J Surg. 70:144–6
157. Kameyama K, Mukai M, Iri H et al (1998) Secretory carcinoma of the breast in a 51-year-old male. Pathol Int. 48:994–7
158. Winchester OJ (1998) Male breast carcinoma: a multiinstitutional challenge. Cancer. 83:399–400
159. Murphy CE, Carder PJ, Lansdown MR, Speirs V (2006) Steroid hormone receptor expression in male breast cancer. Eur J Surg Oncol. 32:44–7
160. Sandler B, Carman C, Perry RR (1994) Cancer of the male breast. Am Surg. 60:816–20
161. Mercer RJ, Bryan RM, Bennett RC (1984) Hormone receptors in male breast cancer. Aust NZ Surg. 54:215–8
162. Munoz de Toro MM, Maffini MY, Kass L, et al (1998) Proliferative activity and steroid hormone receptor status in male breast carcinoma. J Steroid Biochem Mol Biol. 67:333–9
163. Nahleh ZA (2006) Hormonal therapy for male breast cancer: a different approach for a different disease. Cancer Treat Rev. 32:101–5
164. Wick MR, Sayadi H, Ritter JH et al (1999) Low-stage carcinoma of the male breast: a histologic, immunohistochemical, and flow cytometric comparison with localized female breast carcinoma. Am J Clin Pathol. 111:59–69
165. American Joint Committee on Cancer. AJCC cancer staging manual. 6th ed. Philadelphia: Lippincott-Raven; 2002. p. 255–82
166. Chen L, Chantra PK, Larsen LH et al (2006) Imaging characteristics of malignant lesions of the male breast. Radiographics. 26:993–1006
167. Appelbaum AH, Evans GF, Levy KR et al (1999) Mammographic appearances of male breast disease. Radiographics. 19:559–68

168. Cooper RA, Gunter BA, Ramamurthy L (1994) Mammography in men. Radiology. 191:651–6
169. Vetto J, Schmidt W, Pommier R et al (1998) Accurate and cost-effective evaluation of breast masses in males. Am J Surg. 175:383–7
170. Patterson SK, Helvie MA, Aziz K, Nees AV (2006) Outcome of men presenting with clinical breast problems: the role of mammography and ultrasound. Breast J. 12:418–23
171. Hines SL, Tan WW, Yasrebi M et al (2007) The role of mammography in male patients with breast symptoms. Mayo Clin Proc. 82:297–300
172. Hanavadi S, Monypenny IJ, Mansel RE (2006) Is mammography overused in male patients? Breast. 15:123–6
173. Caruso G, Ienzi R, Piovana G et al (2004) High-frequency ultrasound in the study of male breast palpable masses. Radiol Med. 108:185–93
174. Gellett LR, Farmer KD, Vivian GC (1999) Tc-99m sestimibi uptake in a patient with gynecomastia: a potential pitfall in the diagnosis of breast cancer. Clin Nucl Med. 24:466
175. Du Y, Long Y, Ma R (1999) Tc-99m MIBI uptake by a male breast lymphoma accompanied by diffuse bone marrow metastases. Clin Nucl Med. 24:454–5
176. Liu M, Hussain SS, Hameer HR et al (1999) Detection of male breast cancer with Tc-99m methoxyisobutyl isonitrile. Clin Nucl Med. 24:882–3
177. Eyden BP, Shanks JH, Ioachim E et al (1999) Myofibroblastoma of the breast: evidence favoring smooth muscle rather than myofibroblastic differentiation. Ultrastruct Pathol. 23(4):249–57
178. Chalkiadakis G, Petrakis I, Chrysos E et al (1999) A rare case of benign mesenchymoma of the breast in a man. Eur J Surg Oncol. 25:96–7
179. Rice HE, Acosta A, Brown RL et al (2000) Juvenile papillomatosis of the breast in male infants: two case reports. Pediatr Surg lnt. 16:104–6
180. Talwar S, Prasad N, Gandhi S, et al (1999) Hemangiopericytoma of the adult male breast. Int J Clin Pract 53:485–6
181. Grabowski J, Saltzstein SL, Sadler GR, Blair SL (2007) Malignant phylloides tumors: a review of 752 cases. Am Surg. 73:967–9
182. Kim SH, Ezekial MP, Kim RY (1999) Primary lymphoma of the breast: breast mass as an initial symptom. Am J Clin Oncol. 22:381–3
183. Mpallas G, Simatos G, Tasidou A et al (2005) Primary breast lymphoma in male patient. Breast. 13:436–8
184. Vignot S, Ledoussai V, Nodiot P et al (2005) Non-Hodgkin's lymphoma of the breast: a report of 19 cases and review of the literature. Clin Lymphoma. 6:37–42
185. Chanan-Khan A, Holkova B, Goldenberg AS, et al (2005) Non-Hodgkin's lymphoma presenting as a breast mass in patients with HIV infection: a report of three cases. Leuk Lymphoma 46:1189–93
186. Wang ZS, Zhan N, Xiong CL, Li H (2007) Primary epithelioid angiosarcoma of the male breast: report of a case. Surg Today. 37:782–6
187. Fayette J, Martin E, Piperno-Neumann S et al (2007) Angiosarcomas, a heterogeneous group of sarcomas with specific behavior depending on primary site: a retrospective study of 161 cases. Ann Oncol. 18:2030–6
188. McLean SR, Shousha S, Francis N et al (2007) Metastatic ductal eccrine adenocarcinoma masquerading as an invasive ductal carcinoma of the male breast. J Cutan Pathol. 34:934–8
189. Ucar N, Kurt OK, Alpar S, et al (2007) Breast metastasis in a male patient with nonsmall cell lung carcinoma. South Med J. 100:850–1
190. Alzaraa A, Thomas GD, Vodovnik A, Modgill VK (2007) Merkle cell carcinoma in a male breast: a case report. Breast J. 13:517–9
191. Nair VJ, Kaushal V, Atri R (2007) Pure squamous cell carcinoma of the breast presenting as a pyogenic abscess: a case report. Clin Breast Cancer. 7:713–5
192. Kshirsagar AY, Wader JV, Langade YB et al (2006) Adenoid cystic carcinoma of the male breast. Int Surg. 91:234–6
193. deBree E, Tsagkatakis T, Kafousi M, Tsiftsis DD (2005) Breast enlargement in young men not always gynecomastia: breast cancer in a 22-year-old man. ANZ J Surg. 75:914–6
194. Gupta RK, Saran S, Dowel CS et al (1991) The diagnostic impact of needle aspiration cytology of the breast on clinical decision making with an emphasis on the aspiration cytodiagnosis of male breast masses. Diagn Cytopathol. 7:637–9
195. Das DK, Junaid TA, Mathews SB et al (1995) Fine needle aspiration cytology diagnosis of male breast lesions: a study of 185 cases. Acta Cytol. 39:870–6
196. Slavin JL, Baird LI (1996) Fine-needle aspiration cytology in male breast carcinoma. Pathology. 28:122–4
197. Sneige N, Holder PD, Katz RL et al (1993) Fine-needle aspiration cytology of the male breast in a cancer center. Diagn Cytopathol. 9:691–7
198. Joshi A, Kapila K, Verma K (1999) Fine needle aspiration cytology in the management of male breast masses: nineteen years of experience. Acta Cytol. 43:334–8
199. Cooper RA, Ramamurthy L (1996) Epidermal inclusion cysts in the male breast. Can Assoc Radiol. 47:92–3
200. Vetto JT, Pommier RP, Schmidt W et al (1995) Use of the "triple test" for palpable breast lesions yields high diagnostic accuracy and cost savings. Am J Surg. 169:519–22
201. Vetto JT, Pommier RF, Schmidt WA et al (1996) Diagnosis of palpable breast lesions in younger women by the modified triple test is accurate and cost effective. Arch Surg. 131:967–74
202. Morris A, Pommier RF, Schmidt WA et al (1998) Accurate evaluation of palpable breast lesions by the "triple test score.". Arch Surg. 133:930–4
203. Ambrogetti D, Ciatto S, Catarzi S et al (1996) The combined diagnosis of male breast lesions: a review of a series of 748 cases. Radiol Med. 91:356–9
204. Tukel S, Ozcan H (1996) Mammography in men with breast cancer: review of the mammographic findings in five cases. Aust Radiol. 40:387–90
205. Layfield LJ (1992) Can fine-needle aspiration replace open biopsy in the diagnosis of palpable breast lesions? Am J Clin Pathol. 98:145–7
206. Costa MJ, Tadras T, Hilton G et al (1993) Breast fine needle aspiration cytology: utility as a screening tool for clinically palpable lesions. Acta Cytol. 37:461–71
207. Sneige N (1994) Fine needle aspiration of the breast: a review of 1, 995 cases with emphasis on diagnostic pitfalls. Diagn Cytopathol. 9:106–12

208. Alenda C, Aranda FI, Segui FJ, Lafroga J (2005) Secretory carcinoma of the male breast: correlation of aspiration cytology and pathology. Diagn Cytopathol. 32:47–50
209. Khalbuss WE, Ambaye A, Goodison S et al (2006) Papillary carcinoma of the breast in a male patient with a treated prostatic carcinoma diagnosed by fine-needle aspiration biopsy: a case report and review of the literature. Diag Cytopathol. 34:214–7
210. Somers RG, Sandler GL, Kaplan MJ et al (1992) Palpable abnormalities of the breast not requiring excisional biopsy. Surg Gynecol Obstet. 174:325–8
211. Samdal F, Kleppe G, Amland PF et al (1994) Surgical treatment of gynecomastia: five years experience with liposuction. Scan J Plastic Reconstruct Surg Hand Surg. 28:123–30
212. McCluggage WG, Sloan S, Kenny BD et al (1999) Fine needle aspiration cytology (FNAC) of mammary granular cell tumor: a report of three cases. Cytopathology. 10:383–9
213. Deshpande AH, Munshi MM, Lele VP et al (1999) Aspiration cytology of extramammary tumors metastatic to the breast. Diagn Cytopathol. 21:319–23
214. Gupta RK (1999) Inununoreactivity of prostate-specific antigen in male breast carcinomas: two examples of a diagnostic pitfall in discriminating a primary breast cancer from metastatic prostate carcinoma. Diagn Cytopathol. 21:167–9
215. Shukla R, Pooja B, Radhika S et al (2005) Fine-needle aspiration cytology of the extramammary neoplasms metastatic to the breast. Diag Cytopathol. 32:193–7
216. Dey P, Luthra UK, Prasad A et al (1999) Cytologic grading and DNA image cytometry of breast carcinoma on fine needle, aspiration cytology smears. Anal Quant Cytol Histol. 21:17–20
217. Volpe CM, Rafetto JD, Collure DW et al (1999) Unilateral male breast masses: cancer risk and their evaluation and management. Am Surg. 65:250–3
218. Dershaw DD, Borgen PI, Deutch BM et al (1993) Mammographic findings in men with breast cancer. AJR Am J Roentgenol. 160:267–70
219. Kinne D, Hakes T (1991) Male breast cancer. In: Harris J, Hellman S, Henderson IC (eds) Breast diseases. Lippincott, Philadelphia, pp 782–9
220. Hodson GR, Urdaneta LF, AI-Jurf AS et al (1985) Male breast carcinoma. Am Surg. 51:47–9
221. Scott-Conner CE, Jochimsen PR, Menck HR et al (1999) An analysis of male and female breast cancer treatment and survival among demographically identical pairs of patients. Surgery. 126:775–80
222. Rai B, Ghoshal S, Sharma SC (2005) Breast cancer in males: a PGIMER experience. J Cancer Res Ther. 1:31–3
223. Kamila C, Jenny B, Per H, Jonas B (2007) How to treat male breast cancer. Breast. 16(Suppl 2):S147–54
224. Golshan M, Rusby J, Domingeuz F, Smith BL (2007) Breast conservation for male breast carcinoma. Breast. 16:653–6
225. Luini A, Gatti G, Brenelli F et al (2007) Male breast cancer in a young patient treated with nipple-sparing mastectomy: case report and review of the literature. Tumori. 94:118–20
226. Haid A, Knauer M, Dunzinger S et al (2007) Intra-operative sonography: a valuable aid during breast-conserving surgery for occult disease. Ann Surg Oncol. 14:3090–101
227. Hill AD, Borgen PI, Cody HS III. (1999) Sentinel node biopsy in male breast cancer. Eur J Surg Oncol. 25:442–3
228. Intra M, Soteldo J, Bassani G (2004) Sentinel node biopsy in ductal carcinoma in situ of the male breast. Breast J. 10:263–4
229. Boughey JC, Bedrosian I, Meric-Bernstam F et al (2006) Comparative analysis of sentinel lymph node operation in male and female breast cancer patients. J Am Coll Surg. 203:475–80
230. Gentilini O, Chagas E, Zurrida S et al (2007) Sentinel lymph node biopsy in male patients with early breast cancer. Oncologist. 12:512–5
231. Rusby JE, Smith BL, Dominquez FJ, Golsham M (2006) Sentinel lymph node biopsy in men with breast cancer: a report of 31 consecutive procedures and review of the literature. Clin Breast Cancer. 7:406–10
232. Camus MG, Joshi MG, Mackarem G et al (1994) Ductal carcinoma in situ in the male breast. Cancer. 74:1289–93
233. Silverstein MJ, Lagios MD, Craig PH et al (1996) Developing a prognostic index for ductal carcinoma in situ. Cancer. 78:1138–40
234. Uematsu M, Okada M, Ataka K (1998) Two-step approach for the operation of male breast cancer: report of a case at high risk for surgery. Kobe J Med Sci. 44:163–8
235. Atahan L, Yidiz F, Selek U et al (2006) Postoperative radiotherapy in the treatment of male breast carcinoma: a single institution experience. J Natl Med Assoc. 98:559–663
236. Stranzl H, Mayer R, Quehenberger F et al (1999) Adjuvant radiotherapy in male breast cancer. Radiother Oncol. 53:29–35
237. Csillag C (2005) Radiotherapy after mastectomy more common in men. Lancet Oncol. 6:547
238. Bagley C, Wesley M, Young R et al (1987) Adjuvant chemotherapy in males with cancer of the breast. Am J Clin Oncol. 10:55–60
239. Walshe JM, Berman AW, Vatas U et al (2007) A prospective study of adjuvant CMF in males with node positive breast cancer: 20 year-follow-up. Breast Cancer Res Treat. 103:177–83
240. Jaiyesimi IA, Buzdar A, Sahin A et al (1992) Carcinoma of the male breast. Ann Intern Med. 117:771–7
241. Carmona-Bayonas A (2007) Potential benefit of maintenance trastuzamab and anastrozole therapy in male advanced breast cancer. Breast. 16:323–5
242. Ribiero G, Swindell R (1992) Adjuvant tamoxifen for male breast cancer. Br J Cancer. 65:252–4
243. Agrawal A, Cheung KL, Robertson JF (2007) Fulvestrant in advanced male breast cancer. Breast Cancer Res Treat. 101:123
244. Soon Wong N, Seong Ooi W, Pritchard KI (2007) Role of gonadotropin-releasing hormone analog in the management of male metastatic breast cancer is uncertain. J Clin Oncol. 25:3787
245. Arriola E, Hui E, Dowsett M, Smith IE (2007) Aromatase inhibitors and male breast cancer. Clin Transl Oncol. 9:192–4
246. Zabolotny BP, Zalai CV, Meterissian SH (2005) Successful use of letrozole in male breast cancer: a case report and review of the hormonal therapy for male breast cancer. J Surg Oncol. 90:26–30
247. Dakin Hache K, Gray S, Barnes PJ et al (2007) Clinical and pathological correlations in male breast cancer: intratumoral aromatase expression via tissue microarray. Breast Cancer Res Treat. 105:169–75
248. Farrow J, Adair F (1942) Effects of orchiectomy on skeletal metastases from cancer of the male breast. Science. 95: 654–7

249. Singh M, Kotagiri AK, Teimory M (2007) Choroidal and optic disc metastases in a man with metachronous and metastatic breast cancer. Acta Opthalmol Scand. 85:688–9
250. Lam A, Shields CL, Shields JA (2006) Uveal metastases from breast carcinoma in three male patients. Opthalmic Surg Lasers Imaging. 37:320–3
251. Cohen VM, Moosavi R, Hungerford JL (2005) Tamoxifen-induced regression of a choroidal metastasis in a man. Arch Opthalmol. 123:1153–4
252. Ai-Ping F, Yue Q, Yan W (2007) A case report of a remote cutaneous metastasis from male breast carcinoma. Int J Dermatol. 46:738–9
253. Karakuza A, Koc M, Ozdemir S (2006) Multiple cutaneous metastases from male breast cancer. J Am Acad Dermatol. 55:1101–2
254. Fontana S, Ghilardi R, Barbaglio A et al (2007) Male breast cancer with mandibular metastasis. A case report. Minerva Stomatol. 56:225–30
255. Kesting MR, Loeffelbein DJ, Holzle F et al (2006) Male breast cancer metastasis presenting as submandibular swelling. Auris Nasus Larynx. 33:483–5
256. Hultborn R, Friberg S, Hultborn KA, et al (1987) Male breast carcinoma. II. A study of the total material reported to the Swedish Cancer Registry 1958-1967 with respect to treatment prognostic factors, and survival. Acta Oncol. 26:327–41
257. Guinee YF, Olsson H, Moller T et al (1993) The prognosis of breast cancer in males. Cancer. 71:154–61
258. Cox DR (1972) Regression models and life-tables. J R Stat Sac. 4:187–220
259. Hatschek T, Wingren S, Carstensen J et al (1994) DNA content and S-phase fraction in male breast carcinomas. Acta Oncol. 33:609–13
260. Hill A, Yagmur Y, Tran KN et al (1999) Localized male breast carcinoma and family history. Cancer. 86:821–5
261. Hemminki K, Scelo G, Boffetta P et al (2005) Second primary malignancies in patients with male breast cancer. Br J Cancer. 92:1288–92
262. Avisar E, McParland E, Dicostanzo D, Axelrod D (2006) Prognostic factors in node-negative male breast cancer. Clin Breast Cancer. 7:331–5
263. Garcia GH, Weinberg DA, Glasgow BJ et al (1998) Carcinoma of the male breast metastatic to both orbits. Opthal Plast Reconstruct Surg. 14:130–3
264. Kim JH, Benson PM, Beard JS et al (1998) Male breast carcinoma with extensive metastases to the skin. J Am Acad Dermatol. 38:995–6
265. Kreusel KM, Heimann H, Bornfeld N et al (1999) Choroidal metastasis in men with metastatic breast cancer. Am J Opthalmol. 128:253–5
266. Fullerton JT, Lantz J, Sadler GR (1997) Breast cancer among men; raising awareness for primary prevention. J Am Acad Nurse Pract. 9:211–6
267. Malkin D (1994) p53 and the Li-Fraumeni syndrome. Biochem Biophys Acta. 1198:197–213
268. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Statist Sac. 53:457–81
269. Peto R, Peto J (1972) Asymptotically efficient rank invariant test procedures. J R Statist Sac. 35:185–206
270. Fritz A (1998) SEER cancer statistics review, 1973–1995. NCI Cancer Statistics Branch, Bethesda
271. Wagner JL, Thomas CR Jr, Koh W-J et al (1995) Carcinoma of the male breast: update. Med Pediatr Oncol. 24:123–32
272. Milias S, Kalekou H, Bobos M et al (2007) Immunohistochemical investigation of CD34 antigen in male breast carcinoma. Clin Exp Med. 7:122–6
273. Rudlowski C, Schulten HJ, Golas MM, et al (2006) Comparative genomic hybridization analysis on male breast cancer. Int J Cancer. 118:2455–60
274. Andre S, Pinto AE, Laranjeira C et al (2007) Male and female breast cancer-differences in DNA ploidy, p21 and p53 expression reinforce the possibility of distinct pathways of oncogenesis. Pathobiology. 74:323–7
275. Melenhorst J, van Berlo CL, Nijhuis PH (2005) Simultaneous bilateral breast cancer in a male: a case report and review of the literature. Acta Chir Belg. 105:531–2
276. Franceschini G, D'Alba P, Costantini M et al (2006) Synchronous bilateral breast carcinoma in a 50-year-old man with 45, X/46, XY mosaic karyotype: report of a case. Surg Today. 36:71–5
277. Sosnovskikh I, Naninato P, Gatti G et al (2007) Synchronous bilateral breast cancer in men: a case report and review of the literature. Tumori. 93:225–7
278. McQueen A, Cox J, Desai S, Moore R. (2007) Multifocal male breast carcinoma: a case report. Clin Breast Cancer. 7(7):570–2
279. Joseph E, Hyacinthe M, Lyman GH et al (1998) Evaluation of an intensive strategy for follow-up and surveillance of primary breast cancer. Ann Surg Oncol. 5:522–9
280. American Society of Clinical Oncology (1997) Recommended breast cancer surveillance guidelines. J Clin Oncol. 15: 2149–56
281. The Givio Investigators (1995) Impact of follow up testing on survival and health-related quality of life in breast cancer patients: a multicenter randomised controlled trial. JAMA. 271:1587–92
282. Nahleh Z, Girnius S (2006) Male breast cancer: a gender issue. Nat Clin Practice Oncol. 3:428–37
283. Tirkkonen M, Kainu T, Loman N et al (1999) Somatic genetic alterations in BRCA2-associated and sporadic male breast cancer. Gene Chromosomes Cancer. 24:56–61
284. Struewing JP, Hartge P, Wachholder S et al (1997) The risk of cancer associated with specific mutations of BRCAI and BRCA2 among Ashkenazi Jews. N Engl J Med. 336:1401–8
285. Verhoog LC, Brekelmans CTM, Seynaeve C et al (1999) Survival in hereditary breast cancer associated with germline mutations of BRCA2. J Clin Oncol. 17:3396–402
286. Ford D, Easton DF, Stratton M et al (1998) Genetic heterogeneity and penetrance analysis of the BRCA I and BRCA2 genes in breast cancer families. Am J Hum Genet. 62:676–89
287. Storm HH, Olsen J (1999) Risk of breast cancer in offspring of male breast-cancer patients (letter). Lancet. 353:209
288. Diez O, Cortes J, Domenech M et al (2000) BRCA2 germline mutations in Spanish male breast cancer patients. Ann Oncol. 11:81–4
289. Agrawal A, Ayantunde AA, Rampaul R et al (2007) Male breast cancer: a review of clinical management. Breast Cancer Res Treat. 103:11–21
290. Donovan T, Flynn M (2007) What makes a man a man? The lived experience of male breast cancer. Cancer Nurs. 30: 464–70

291. Brain K, Williams B, Iredale R et al (2006) Psychological distress in men with breast cancer. J Clin Oncol. 24:95–101
292. Iredale R, Brain K, Williams B et al (2006) The experiences of men with breast cancer in the United Kingdom. Eur J Cancer. 42:334–41
293. Iredale R, Williams B, Brain K et al (2007) The information needs of men with breast cancer. Br J Nurs. 16:540–4
294. Allen T (2000) This man survived breast cancer. Esquire. 133:103–9
295. Parker JN, Parker PM (2002) The official patient's sourcebook on male breast cancer: a revised and updated directory for the internet age. Icon Health, San Diego
296. Landay D (2000) Be prepared: the complete financial, legal, and practical guide to living with cancer, HIV, and other life-challenging conditions. Macmillan, New York
297. Vourtsi A, Kehangias O, Antoniou A et al (1999) Male breast myofibroblastoma and MR findings. J Comp Assist Tomogr. 23:414–6
298. McCarthy P, Hurd D, Rowlings P et al (1999) Autotransplantation in men with breast cancer. ABMRT Breast Cancer Working Committee. Autologous Blood and Marrow Transplant Registry. Bone Marrow Transplant. 24: 365–8

Breast Cancer in the Elderly

26

Madhuri V. Vithala and Hyman B. Muss

26.1 Introduction

Breast cancer is the most common cancer in American women, and increasing age is the major risk factor for breast cancer. During 2001–2005, women aged 75–79 years had the highest breast cancer incidence rate of 453.1 per 100,000 [1]. Incidence and mortality data based on the Surveillance, Epidemiology, and End Results (SEER) program are shown in Fig. 26.1. The median age at diagnosis of breast cancer in the United States is 61 years, and most deaths from breast cancer now occur in women aged 65 years and older [2]. A lower incidence of breast cancer is noted in women of the age 80 years or older and may be due to lower rates of screening, detection of cancers before 80, or incomplete detection. Older women are frequently diagnosed with breast cancer at a higher stage, but survival for Stage I and Stage II breast cancer is similar across age groups [3–5]. The majority of breast cancers in younger and older patients are Stage I or Stage II. About 10% of older patients are likely to present with Stage III or Stage IV disease and some with unknown stage at diagnosis [6].

Life expectancy plays a major role in decision making in the elderly patients with breast cancer. Currently, the estimated life expectancy for a 65 year old woman in the United States is 20 years, and at 75 years women are estimated to live an additional 12.5 years [7]; decisions about treatment must be made taking into consideration this nonlinear relationship between age and life expectancy. Elderly women with breast cancer are less likely to be managed according to guidelines [6, 8] and such undertreatment may result in poorer survival [9, 10]. Moreover, older women are less likely to be enrolled in clinical trials [11, 12] but when offered the opportunity are as likely to participate as younger patients – with about 50% participation [13]. Barriers to trial participations include both physician bias about age and tolerance of toxicity and patient and family bias that treatment is not worthwhile or too toxic [13, 14]. In this chapter, we will review issues related to breast cancer in older women, including comorbidity, prevention, screening, treatment of primary breast cancer, adjuvant systemic therapy, treatment of metastatic disease, and clinical trials.

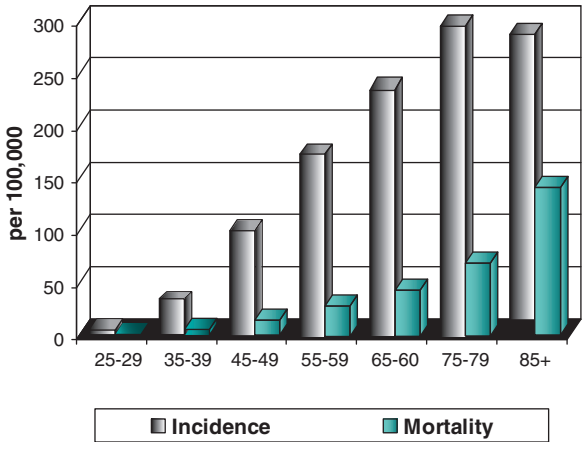

Fig. 26.1 Breast cancer incidence and mortality by age for 2001–2005 from surveillance, epidemiology, and end results (SEER) data base [1]

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases*,
DOI: 10.1007/978-3-540-69743-5_26, © Springer-Verlag Berlin Heidelberg 2010

26.2 Comorbidity in the Elderly Patient with Breast Cancer

Concurrent with a breast cancer diagnosis, older postmenopausal women are also more likely to have other coexisting illness or "comorbidity." In one major study of comorbidity, 1,800 postmenopausal women with breast cancer, diabetes, renal failure, stroke, liver disease, a previous malignant tumor, as well as smoking were significant predictors of shortened survival even when accounting for age and breast cancer stage [15]. For the 15% of patients that died during the 30-month follow-up period, breast cancer was the cause of death for 51%, heart disease for 17%, and previous cancers for 8%. All facets of breast cancer care may be effected by comorbid illness, including screening, pretreatment assessment, and the use of surgery, radiation, and systemic adjuvant therapy. For example, in an observational study of 936 women in the age group of 40–84 years with breast cancer, patients with three or more of seven selected comorbidities had a 20-fold higher rate of mortality from nonbreast cancer causes and a fourfold higher rate of all-cause mortality when compared to those without any comorbid conditions. An early diagnosis of breast cancer in this study conferred no survival advantage in women with severe comorbidity [16]. These data indicate that older women with severe comorbidity will not benefit from breast cancer prevention and screening programs. In addition, most of these chronically ill patients are unlikely to derive any major benefit from adjuvant systemic therapy. Focusing on comorbidity as opposed to "age" will remind health care professionals that life expectancy is the most important factor in managing older patients with breast cancer.

Comprehensive Geriatric Assessment (CGA) comprises a multidisciplinary evaluation of functional status, cognition, social support, psychological state, nutritional status, medication (polypharmacy), and comorbid medical conditions. CGA can accurately predict morbidity and mortality from cancer [17] and is especially helpful in the assessment of frail patients [18]. Although there is uncertainty as to whether information obtained from a detailed CGA can lead to interventions that improve survival, CGA can lead to appropriate interventions that maintain function and improve quality of life for older cancer patients [19]. It is impractical to have a CGA for all elders leading to the development of shorter but accurate instruments that can accurately predict functional decline and mortality risk [20–22]. Patients who score poorly on these instruments can be considered for a more detailed CGA [22] while healthier patients can move on with treatment. Short accurate CGA instruments might eventually prove to be accurate enough to help in the treatment selection and estimate treatment related toxicity, especially in frail patients. Recommendations for CGA have been developed by the International Society of Geriatric Oncology (SIOG) and provide useful guidelines [23].

26.3 Prevention

Primary prevention of breast cancer requires modifying factors that are associated with an increase in risk. There are few major options for primary prevention in older women. Obesity is a risk factor for breast cancer in older women [24] and may also be a predictor of increased breast cancer recurrence [25]. Although it is uncertain as to the value of weight reduction in reducing breast cancer risk, overweight elders might reduce cardiac as well as other nonbreast cancer risk by weight reduction. Older women are less likely than younger patients to be carriers of the BRCA-1 and BRCA-2 genes, but a careful family history is mandatory for all patients with breast cancer, irrespective of age, as older women may be gene carriers resulting in important management and family considerations. Although the role of exercise is controversial as a risk reducing strategy for breast cancer in older women, it should be encouraged for its other major health benefits.

Chemoprevention of breast cancer with either tamoxifen and raloxifene is an effective risk reduction strategy in high risk women [26, 27]. However, neither of these agents has been associated with improvements in survival and both are associated with increased risks of endometrial cancer and thromboembolism in older women. The benefits of tamoxifen use diminish with increasing age because older women have higher risks of mortality from competing causes of death, such as cardiovascular disease [28]. At present, only older women with an exceeding high risk for breast cancer should be considered for chemoprevention. Raloxifene may be a better choice than tamoxifen for these older patients as it is less likely to be associated with cataracts or thromboembolism [27, 29].

26.4 Screening

Mammographic screening has been shown to be effective in reducing breast cancer mortality in women aged 50–70 years [30]. For women aged older than 70 years, some studies show no association between screening and reduced breast cancer mortality whereas others show potential survival benefit [31]. The sensitivity, specificity, and positive predictive value of mammography for detecting cancer increases with age as ductal tissue is replaced by fat resulting in an increase in the radiolucency of breast tissue. The evidence of the effectiveness of mammography among older women is limited to two trials that included women older than 65 years of age. Both of these trials reported relative risk reductions of breast cancer among women 65–74 years of age (relative risk, 0.68 [CI, 0.51–0.89] [32] and 0.79 [33] among women 70–74 years of age). In one study of women of the age 80 years and older, those who obtained mammograms on a more regular basis were detected with lower stage breast cancer and had higher breast cancer-specific survival; however, deaths from other causes were also lower in women who received more frequent mammograms, suggesting a bias for mammography use among healthier patients [34].

The precise age at which to discontinue screening mammography is uncertain. Older women face a higher probability of developing and dying of breast cancer but also have a greater chance of dying of other causes, and women with comorbid conditions that limit their life expectancy to 5 years or less are unlikely to benefit from screening. The American Geriatric Society recommends that screening be individualized rather than setting guidelines by age while the American Cancer Society recommends setting no upper age limit as long as the individual is in good health and is a candidate for treatment. As prospective controlled trials are unlikely to be performed in this older age group, a reasonable option would be to offer yearly screening to women without severe comorbidities and an estimated life span of 5 years.

26.5 Treatment of Primary Breast Cancer

26.5.1 Surgery or Endocrine Therapy

Except in frail elders or those with life expectancies less than 5 years, early stage breast cancer should be treated with surgery. Older women in reasonable health tolerate surgery well and its safety is well established [35, 36]. Breast conserving therapy is now standard care for all patients with early stage breast cancer and should be offered irrespective of age. Body image is important in older women [37] and they should be told about the effects of mastectomy and breast conservation on body image. These data suggest that physician assumptions about the lack of importance of breast preservation and sexuality in elderly women are incorrect and are likely responsible for the higher mastectomy rates in older women. Older women should be offered breast conservation when appropriate.

Primary endocrine therapy with tamoxifen, and more recently aromatase inhibitors (AIs) has been shown to be effective in controlling hormone receptor positive breast cancer in older women. Compared with endocrine therapy, surgery is associated with superior local control. Although endocrine therapy may result in local control for several years, the majority of patients are likely to have tumor progression after 5 years, resulting in the need for surgery. A Cochrane meta-analysis comparing surgery with endocrine therapy in women 70 years and older has confirmed the superiority of surgery for local control but did not show a survival benefit [38]. At present, older women with surgically resectable tumors should be offered surgery. Frail patients or those with limited life to expectancies, and with hormone receptor positive tumors, can be offered endocrine therapy with either tamoxifen or an aromatase inhibitor (AI).

26.5.2 Radiation

Older women who have breast conservation surgery and an estimated life span of 5 or more years should be considered for breast irradiation. The Early Breast Cancer Trialists Collaborative Group (EBCTCG) overview showed that breast radiation after mastectomy reduced the risk of local recurrence regardless of tumor stage. In addition, this analysis showed that such radiation reduced 15-year mortality by 4–5%. Mortality benefits from radiation were limited to women where radiation resulted in a 10% or greater reduction in the 5-year local recurrence rate [39]. However, a randomized trial of radiation or not in women 70 years and older with node-negative, hormone receptor positive breast cancer 2 cm or less in diameter (T1) showed that the addition of radiation to lumpectomy and tamoxifen

had no effect on survival. Local recurrences were decreased in the radiation group (1% radiotherapy (RT) group vs. 7% lumpectomy alone) but mastectomy rates were similar (1% RT vs. 3% no RT) as some patients in the no RT group who had breast recurrence were able to be salvaged with repeat lumpectomy and breast radiation [40, 41]. This trial focused on women with low risks for local-regional recurrence irrespective of the use of breast radiation, and the survival data are in keeping with the EBCTCG results. In older women with small, node-negative breast cancers, breast radiation may be omitted without deleterious effects on survival and the pros and cons of radiation in this setting should be carefully discussed with the patient. Older women tolerate breast and postmastectomy radiation as well as younger women [42] and those with high risks for local recurrence should be considered for treatment if they have life expectancies exceeding 5 years. Partial breast radiation is also a good option for some elders as it may minimize treatment visits and reduce recurrence risk.

26.5.3 Management of the Axilla

For women with early breast cancer with clinically and radiologically negative lymph nodes the major issue is whether knowing the tumor status of the nodes will change management. For many older women, especially those with major comorbid disease or frailty, detecting axillary node involvement is not likely to change management and can be omitted. For older women however, knowing the tumor status of the axillary nodes will help in making more effective decisions about local and systemic therapies. An increasing body of data suggests that sentinel lymph node (SLN) biopsy is a safe and accurate method of evaluating the axillary nodes for metastasis, including older women. In one study of 241 patients 70 years and older, SLN was found to be a safe and accurate method of assessing axillary node status for elderly women with operable breast cancer less than 3 cm [43]. At a median follow-up time of 30 months, no axillary recurrences were noted. Axillary lymph node dissection in older patients should only be considered if there is clinical evidence of axillary node involvement. In this situation, axillary dissection plays a therapeutic as well as a staging role.

26.6 Adjuvant Systemic Therapy

26.6.1 Treatment Benefit

The overview of the EBCTCG includes 194 randomized trials of adjuvant therapy and showed that after 15 years of follow up, 5 years of tamoxifen therapy in estrogen receptor (ER) positive patients reduced the annual breast cancer mortality rate by 31% irrespective of age [44]. Moreover, about 6 months of an anthracycline containing regimen reduced the annual breast cancer death rate by about 38% in women younger than 50 years and by about 20% in women 50–69 years. These reductions were seen irrespective of tamoxifen use [44]. Unfortunately, very few patients above 70 years were entered in these trials (only about 1,200), precluding an accurate assessment of chemotherapy effects in older women. Recommendations for systemic treatment are summarized in Table 26.1 and discussed in detail below.

26.6.2 Selecting Treatment

Studies from large databases such as the San Antonio and SEER programs show that older women are more likely to have favorable tumor characteristics when compared to younger patients [45, 46]. Diab et al reported that in patients 55 years old or older, there was an association between increasing age at diagnosis and the presence of more favorable tumor characteristics, including smaller tumor size, lower likelihood of being lymph node negative, more tumors that express hormone receptors, lower proliferative rates, more diploidy, normal p53, and absence of the expression of epidermal growth factor receptor and HER-2 [45]. However, about 20–30% of older patients have ER and progesterone receptor (PR) negative tumors, a phenotype that confers a major increase in risk for early recurrence [47]. Infiltrating ductal carcinoma is the most common tumor histologic subtype, and more indolent subtypes such as mucinous and papillary carcinomas are also encountered more frequently in older age groups [48].

Selection of treatment depends on two main factors: (1) the patient's stage and the tumor's biologic characteristics (grade, hormone receptor, and HER-2 status), and (2) the patient's life expectancy (based on age and

Table 26.1 Recommendations for adjuvant systemic therapy for women 70 years and older

Estrogen and/or progesterone receptor (PR) status	HER -2 status	Nodal status	Recommendations
Positive	Negative	Negative	Endocrine therapy for most consider oncotypeDX testing
		Positive	Endocrine therapy and calculate added value of chemotherapy from adjuvant!
Any	Positive	Any	Endocrine therapy for ER+ or PR++consider chemotherapy and trastuzumab
Both negative	Negative	Any	Consider taxane-containing chemotherapy

comorbidity). We suggest that for treatment selection patients should be divided into three major subgroups: (1) ER and/or PR positive and HER-2 negative, (2) HER-2 positive (irrespective of ER and PR status), and (3) ER and PR negative and HER-2 negative (so called "triple-negative" breast cancer) groups. Estimates of recurrence and the benefits of both endocrine therapy and chemotherapy in these subgroups can be accurately made using Adjuvant! (www.adjuvantonline.com). This program can factor in age and expected life expectancy, and one can also calculate the effects of comorbidity on life expectancy. The present version does not yet easily allow for estimates of treatment benefit of trastuzumab for HER-2 positive patients nor the effect of HER-2 positive tumors on recurrence risk, but future versions of the program that are in development should remedy this. In addition, several recent reviews have provided excellent guidelines for the use of adjuvant therapy in older patients [47, 49].

26.6.3 Treatment of Older Patients with Hormone Receptor Positive, HER-2 Negative Tumors

The largest group of elders with breast cancer has ER and/or PR positive, and HER-2 negative tumors, and comprises about 70% of all new elders with invasive breast cancer. The majority of these patients will be node-negative. For these older patients with ER-positive, node-negative tumors that are 5 cm or less, the risk of metastases at 10 years can be accurately assessed using a 21 gene assay – OncotypeDx™ [50] (www.genomichealth.com). Adjuvant endocrine therapy with an AI or tamoxifen is appropriate for the majority of these patients, the exceptions being those with life spans less than 5 years or with small tumors with favorable tumor biology.

The AIs have been compared to tamoxifen using several randomized trial designs, including head on comparisons, changing to an AI for 2–3 years after a 2–3 year period on tamoxifen, and comparing an AI with placebo after 5 years of tamoxifen. In aggregate, the AIs have been found to be superior to tamoxifen, decreasing breast cancer relapse rates by about 3–5% [51, 52]. However, head-on trials comparing tamoxifen with an AI have yet to show a benefit for initiating treatment with AIs, the largest trial showing almost identical mortality rates after 100 months of follow-up [53]. Tamoxifen followed by an AI is also worthy of consideration, with one trial showing a small but significant survival benefit using this strategy [54]. For those elders at high risk of recurrence who have had 5 years of tamoxifen, consideration of extended adjuvant therapy with an AI should be given [55, 56]. The ASCO guidelines suggesting that AIs should be part of adjuvant endocrine therapy in postmenopausal patients should apply to older women as well [52]. A point in favor of the use of AIs when compared to tamoxifen is the more favorable toxicity profile of AIs in the older age group, especially the lack of an increased risk of thrombosis and endometrial cancer. In one trial comparing letrozole with placebo in elders who had 5 years of tamoxifen, no significant differences in toxicity were found between the AI and placebo [57]. Accelerated bone loss is a major concern for elders on AI therapy, and a baseline bone density prior to initiating AI should

Table 26.2 Estimation of treatment benefit and the effects of comorbidity on 10 years mortality for a 75 year old woman with a 2 cm moderately differentiated infiltrating ductal cancer and four positive lymph nodes with different levels of comorbidity (calculated from adjuvantonline.com)

Comorbidity	Treatment	% alive at 10 years
None perfect health	None[a]	53
	Endocrine therapy only[b]	61
	Endocrine + chemotherapy[c]	65
Average health for age[d]	None	41
	Endocrine therapy only	47
	Endocrine + chemotherapy	51
Major comorbidity[e]	None	14
	Endocrine therapy only	16
	Endocrine + chemotherapy	17

[a]Only surgery and/or radiation
[b]Tamoxifen or an aromatase inhibitor (AI)
[c]Chemotherapy is docetaxel and cyclophosphamide for 4 cycles [60]
[d]From www.adjuvantonline.com
[e]At least one serious illness

be done and patients managed according to accepted guidelines [58]. A downside to AI therapy is cost. AIs are considerably more expensive than tamoxifen and these issues should be discussed with patients before making a treatment decision.

There is little benefit of chemotherapy in elders with hormone receptor positive, HER-2 negative tumors. However, there are likely to be some patients in this group with node-negative tumors who might benefit from chemotherapy, and use of the 21 gene Oncotype™ assay can identify those women most likely to benefit. The role of chemotherapy for those with node-positive tumors is uncertain [59]. For those with node-positive tumors, estimates of the added value of chemotherapy can be calculated from Adjuvant! (www.adjuvantonline.com). An example of the benefits of treatment and the effects of comorbidity on outcome for patients with node-positive breast cancer calculated from Adjuvant! is shown in Table 26.2. The benefits of treatment in this example, especially chemotherapy, are small in patients with major comorbidity. A word of caution in discounting chemotherapy in these patients is needed. In the overview, chemotherapy showed similar proportional reductions in relapse in ER-positive and ER-negative patients, but only after extended follow-up. Healthy elders with estimated survivals of more than 5–10 years might ultimately derive benefit from chemotherapy, and those at high risk for recurrence are considered for such treatment. The use of nonanthracycline regimens such as docetaxel and cyclophosphamide are worthy of consideration in this setting [60]. For those with positive nodes and at high risk, more aggressive, taxane-containing regimens might be considered, as similar benefits for more aggressive and compared to less aggressive chemotherapy have been shown for older as well as younger patients [61], although with greater toxicity [62].

26.6.4 Treatment of Older Patients with HER-2 Positive Tumors

For older women with HER-2 positive breast cancer, the major issue is the use of trastuzumab with chemotherapy. Several trials have shown that trastuzumab when added to chemotherapy causes a further 50% proportional reduction in the risk of recurrence compared to chemotherapy alone [63–65]. Trastuzumab, although generally well tolerated, is associated with an increased risk of cardiac toxicity that is age related [66]. Control of hypertension, if present, and optimal management of any preexisting cardiac disease should be obtained before initiating trastuzumab. Older women with HER-2 positive tumors should be offered trastuzumab but should be closely monitored for cardiac toxicity, and in these patients, the use of nonanthracycline regimens such as docetaxel and carboplatin should be considered [67]. Patients with both node-negative and node-positive tumors benefit from trastuzumab, although the benefits in patients with small node-negative tumors (less than one cm) are likely to be very small.

26.6.5 Treatment of Older Patients with ER- and PR-Negative and HER-2 Negative Tumors

Older women with triple-negative breast cancer should be offered chemotherapy and if in good health tolerate aggressive chemotherapy regimens almost as well as younger women [68]. A recent analysis of randomized

trials of chemotherapy regimens in patients with node-positive tumors showed that more intensive, taxane-containing regimens were the most effective treatments in those with hormone receptor-negative tumors [69]. This analysis did not include HER-2 status but it is likely that most patients – probably about 80%, were HER-2 negative. A recent analysis of the EBCTG comparing chemotherapy or not in women with ER-poor tumors showed a 10-year reduction of 8% in breast cancer mortality in women younger than 50 years and a reduction of 6% in women 50–69 years [70]. Almost half of these patients received older chemotherapy regimens such as CMF (cyclophosphamide, methotrexate and fluorouracil), and recent data would suggest that current regimens would substantially improve on these results [69]. It is likely that most of the women in this meta-analysis had HER-2 negative breast cancer and thus would benefit from such treatment. Moreover, a first analysis comparing capecitabine with standard chemotherapy (either CMF or doxorubicin and cyclophosphamide) showed superiority of standard treatment in improving both relapse-free and overall survival, with the major benefit being in hormone receptor-negative patients [71].

26.7 Metastatic Disease

Metastatic breast cancer remains incurable. The goals of treatment of older women with metastatic breast cancer are the same as for younger women and include controlling the growth of cancer and maintaining the highest possible quality of life. For older women with hormone receptor-positive breast cancer, different hormonal agents should be tried until it is clear that metastases are refractory to endocrine therapy. Older patients with hormone receptor-positive metastases have previously had tamoxifen or an AI in the adjuvant setting. Those who have been off endocrine therapy for several years can be retreated with the same agent as used in the adjuvant setting, while those who develop metastases on an AI or tamoxifen can be treated with tamoxifen or an AI, respectively. For older patients with metastases resistant to both tamoxifen and AIs, trying a different AI, using a newer agent such as fulvestrant, or older agents such as megestrol acetate or high-dose estrogens, are all options that should be considered. Patients can also be retreated with agents that have been previously tried with an occasional response, provided there has been a reasonable period of time since use of the earlier agent. Using endocrine therapy until metastases are convincingly refractory to endocrine treatment allows for a delay in chemotherapy and maintenance of the highest quality of life before deciding on chemotherapeutic options [47].

Considerable debate persists as to whether to use combination or sequential single-agent chemotherapy in the treatment of metastatic breast cancer [72]. Retrospective reviews have shown that healthy older patients with metastatic breast cancer tolerate chemotherapy about as well as younger patients, including anthracycline-containing regimens [73, 74]. Sequential therapy with active single agents is generally associated with less toxicity and is more likely to maintain the highest quality of life. Most combination chemotherapy regimens are likely to be more toxic than single agents but have higher response rates and longer times to progression than single agents; however combination regimens are not associated with improved survival [47]. We recommend starting with single-agent therapy in most patients except those with rapidly progressive metastases or where even modest tumor progression will be life threatening. The exceptions are newer regimens that include single-agent chemotherapy in combination with a biologic agent [75, 76]. These regimens are generally associated with less toxic combination chemotherapy regimens and should be considered in older patients with more aggressive metastases. Even in frail elders, chemotherapy should be considered; functional status and toxicity must be closely monitored during treatment in these patients.

26.8 Clinical Trials

Older patients continue to be underrepresented in breast cancer clinical trials [12]. Available data suggest however, that when offered trials, older and younger patients have similar rates of participation, approximating 50% [13]. Healthy older women should be encouraged to participate in Phase II and III trials and efforts should be made to offer trials to such patients and encourage participation. Adding CGA as a part of these trials may also be of value in predicting treatment-related toxicity, and a short, mostly self-administered CGA instrument is now

Table 26.3 Clinical trials specifically designed for older patients with breast cancer

Trial	Treatment	N (actual)	Status
CALGB 49907 (www.calgb.org)	AC/CMF vs. Capecitabine	633	Closed
ICE (BIG) (clinicaltrials.gov) NCT00196859	Ibandronate ± Capecitabine	1,400	N ± ER + AI Closed
CASA (BIG)	Caelyx vs. none Caelyx vs. p.o. CM	Closed after 42 patients for lack of accrual	ER- and PR-
ELDA (NCI-Naples) (clinicaltrials.gov) NCT00331097	Docetaxel vs. CMF	300 (active)	Mod-high risk
ACTION (UK) (clinicaltrials.gov) UKM-CCH-ACTION	AC or EC vs. none	Closed due to poor accrual	ER- and PR-

being tested in several large National Cancer Institute sponsored cooperative group trials (CALGB 340401; www.cancer.gov**;** CHNMC-06170). Designing trials specifically for older breast cancer patients is another strategy to improve accrual; current trials for older women with early breast cancer are presented in Table 26.3. There are almost no data on the treatment of frail breast cancer patients [18], and clinical trials specifically addressing this vulnerable older group are needed.

26.9 Conclusions

Breast cancer management in elderly patients is frequently challenging. Healthy elders with 5–10 more years of life expectancy should be managed like younger postmenopausal patients, including breast conservation therapy if technically feasible, and adjuvant systemic therapy. Comorbidity must be factored into treatment recommendations, especially for frail patients. CGA can be of great help in estimating the potential for functional loss over the remaining life span and is especially helpful in frail patents where specific interventions can be made to maintain function. Older patients with significant comorbid illness or frailty may require major modifications in treatment, including surgery and chemotherapy. Accrual of healthy elders into ongoing Phase II and Phase III trials should be encouraged and trials focusing on frail elders should be developed. Overcoming physician bias in breast cancer care of older patients, as well as offering older patients clinical trial participation remains a major problem. Educational efforts focused on breast cancer care in the aged and directed at both patients and physicians need to be expanded.

References

1. Surveillance Epideliology and End Results Cancer Statisitcs Review http://seer.cance.gov/csr/1975_2005/results_merged/sect_04_breast.pdf. 2008. Ref Type: Internet Communication
2. Schairer C, Mink PJ, Carroll L, Devesa SS (2004) Probabilities of death from breast cancer and other causes among female breast cancer patients. J Natl Cancer Inst. 96: 1311–21
3. Herbsman H, Feldman J, Seldera J, Gardner B, Alfonso AE (1981) Survival following breast cancer surgery in the elderly. Cancer. 47:2358–63
4. Lyman GH, Lyman S, Balducci L, Kuderer N, Reintgen D, Cox C et al (1996) Age and the risk of breast cancer recurrence. Cancer Control. 3:421–7
5. Masetti R, Antinori A, Terribile D, Marra A, Granone P, Magistrelli P et al (1996) Breast cancer in women 70 years of age or older. J Am Geriatrics Soc. 44:390–3
6. Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW (2001) Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA. 285:885–92

7. CDC data http://www.cdc.gove/nchs/fastats/lifecpec.htm. 2008. Ref Type: Internet Communication
8. Hebert-Croteau N, Brisson J, Latreille J, Blanchette C, Deschenes L (1999) Compliance with consensus recommendations for the treatment of early stage breast carcinoma in elderly women. Cancer. 85(5):1104–13
9. Hebert-Croteau N, Brisson J, Latreille J, Rivard M, Abdelaziz N, Martin G (2004) Compliance with consensus recommendations for systemic therapy is associated with improved survival of women with node-negative breast cancer. J Clin Oncol. 22:3685–93
10. Eaker S, Dickman PW, Bergkvist L, Holmberg L (2006) Differences in management of older women influence breast cancer survival: results from a population-based database in Sweden. PLoS Med. 3:e25
11. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr, Albain KS (1999) Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med. 341: 2061–7
12. Sateren WB, Trimble EL, Abrams J, Brawley O, Breen N et al (2002) How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials. J Clin Oncol. 20:2109–17
13. Kemeny MM, Peterson BL, Kornblith AB, Muss HB, Wheeler J, Levine E et al (2003) Barriers to clinical trial participation by older women with breast cancer. J Clin Oncol. 21:2268–75
14. Trimble EL, Carter CL, Cain D, Freidlin B, Ungerleider RS, Friedman MA (1994) Representation of older patients in cancer treatment trials. Cancer. 74:2208–14
15. Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW (2001) Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA. 285:885–92
16. Satariano WA, Ragland DR (1994) The effect of comorbidity on 3-year survival of women with primary breast cancer. Ann Intern Med. 120:104–10
17. Extermann M, Hurria A (2007) Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol. 25:1824–31
18. Dittus K, Muss HB (2007) Management of the frail elderly with breast cancer. Oncology (Williston Park). 21:1727–34
19. Maas HA, Janssen-Heijnen ML, Olde Rikkert MG, Machteld Wymenga AN (2007) Comprehensive Geriatric assessment and its clinical impact in oncology. Eur J Cancer. 43:2161–9
20. Saliba D, Elliott M, Rubenstein LZ, Solomon DH, Young RT, Kamberg CJ et al (2001) The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. J Am Geriatr Soc. 49:1691–9
21. Hurria A, Gupta S, Zauderer M, Zuckerman EL, Cohen HJ, Muss H et al (2005) Developing a cancer-specific geriatric assessment: a feasibility study. Cancer. 104:1998–2005
22. Rodin MB, Mohile SG (2007) A practical approach to geriatric assessment in oncology. J Clin Oncol. 25:1936–44
23. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, Lichtman S et al (2005) Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol. 55:241–52
24. La Vecchia C, Negri E, Franceschi S, Talamini R, Bruzzi P, Palli D et al (1997) Body mass index and post-menopausal breast cancer: an age- specific analysis. Br J Cancer. 75:441–4
25. Senie RT, Rosen PP, Rhodes P, Lesser ML, Kinne DW (1992) Obesity at diagnosis of breast carcinoma influences duration of disease-free survival. Ann Intern Med. 116: 26–32
26. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM et al (1998) Tamoxifen for prevention of breast cancer: report of the national surgical adjuvant breast and bowel project P-1 Study [see comments]. J Natl Cancer Inst. 90:1371–88
27. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN et al (2006) Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA. 295:2727–41
28. Gail MH, Costantino JP, Bryant J, Croyle R, Freedman L, Helzlsouer K et al (1999) Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer [see comments] [published erratum appears in J Natl Cancer Inst 2000 Feb 2;92(3):275]. J Natl Cancer Inst. 91:1829–46
29. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN et al (2006) Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. JAMA. 295:2727–41
30. Humphrey LL, Helfand M, Chan BK, Woolf SH (2002) Breast cancer screening: a summary of the evidence for the U.S. preventive services task force. Ann Intern Med. 137:347–60
31. Nystrom L, Rutqvist LE, Wall S, Lindgren A, Lindqvist M, Ryden S et al (1993) Breast cancer screening with mammography: overview of Swedish randomised trials. Lancet. 341: 973–8
32. Andersson I, Aspegren K, Janzon L, Landberg T, Lindholm K, Linell F et al (1988) Mammographic screening and mortality from breast cancer: the Malmo mammographic screening trial. BMJ. 297:943–8
33. Tabar L, Fagerberg G, Chen HH, Duffy SW, Smart CR, Gad A et al (1995) Efficacy of breast cancer screening by age. New results from the Swedish two-county trial. Cancer. 75:2507–17
34. Badgwell BD, Giordano SH, Duan ZZ, Fang S, Bedrosian I, Kuerer HM et al (2008) Mammography before diagnosis among women age 80 years and older with breast cancer. J Clin Oncol. 26:2482–8
35. Audisio RA, Bozzetti F, Gennari R, Jaklitsch MT, Koperna T, Longo WE et al (2004) The surgical management of elderly cancer patients; recommendations of the SIOG surgical task force. Eur J Cancer. 40:926–38
36. Kemeny MM (2004) Surgery in older patients. Semin Oncol. 31:175–84
37. Figueiredo MI, Cullen J, Hwang YT, Rowland JH, Mandelblatt JS (2004) Breast cancer treatment in older women: does getting what you want improve your long-term body image and mental health? J Clin Oncol. 22:4002–9
38. Hind D, Wyld L, Beverley CB, Reed MW. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Cochrane Database Syst Rev. 2006;CD004272

39. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E et al (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 366:2087–106
40. Hughes KS, Schnaper LA, Berry D, Cirrincione C, McCormick B, Shank B et al (2004) Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med. 351: 971–7
41. Hughes KS, Schnaper LA, Berry DA, Hodgson L, Cirrincione C, McCormick B, Shank B, Champion LA, Smith BL, Shapiro C, Muss HB, Winer E, Hudis C, Wood W, Henderson IC, Sugarbaker D, Norton L. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer: a report of further follow-up. Br Ca Res Treat. 2006;100:S8. Ref Type: abstr
42. Mundt AJ (2000) Radiation therapy and the elderly. In: Hunter CP, Johnson KA, Muss HB (eds) Cancer in the elderly. Dekker, New York, pp 187–216
43. Gennari R, Rotmensz N, Perego E, dos SG, Veronesi U. Sentinel node biopsy in elderly breast cancer patients. Surg Oncol. 2004;13:193–6
44. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 365:1687–717
45. Diab SG, Elledge RM, Clark GM (2000) Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst. 92:550–6
46. Grann VR, Troxel AB, Zojwalla NJ, Jacobson JS, Hershman D, Neugut AI (2005) Hormone receptor status and survival in a population-based cohort of patients with breast carcinoma. Cancer. 103:2241–51
47. Crivellari D, Aapro M, Leonard R, von Minckwitz G, Brain E, Goldhirsch A et al (2007) Breast cancer in the elderly. J Clin Oncol. 25:1882–90
48. Toikkanen S, Kujari H (1989) Pure and mixed mucinous carcinomas of the breast: a clinicopathologic analysis of 61 cases with long-term follow-up. Hum Pathol. 20:758–64
49. Wildiers H, Kunkler I, Biganzoli L, Fracheboud J, Vlastos G, Bernard-Marty C et al (2007) Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. Lancet Oncol. 8:1101–15
50. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M et al (2004) A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. 351:2817–26
51. Ingle JN (2005) Endocrine therapy trials of aromatase inhibitors for breast cancer in the adjuvant and prevention settings. Clin Cancer Res. 11:900s–5s
52. Winer EP, Hudis C, Burstein HJ, Wolff AC, Pritchard KI, Ingle JN et al (2005) American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. J Clin Oncol. 23:619–29
53. Forbes JF, Cuzick J, Buzdar A, Howell A, Tobias JS, Baum M (2008) Effect of anastrozole and tamoxifen as adjuvant treatment for early stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol. 9:45–53
54. Coombes RC, Kilburn LS, Snowdon CF, Paridaens R, Coleman RE, Jones SE et al (2007) Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomized controlled trial. Lancet. 369:559–70
55. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ et al (2005) Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst. 97:1262–71
56. Muss HB, Tu D, Ingle JN, Martino S, Robert NJ, Pater JL et al Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG intergroup trial MA.17. J Clin Oncol. 2008;26:1956–64
57. Muss HB, Tu D, Ingle JN, Martino S, Robert NJ, Pater JL et al Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG intergroup trial MA.17. J Clin Oncol. 2008;26:1956–64
58. Hillner BE, Ingle JN, Chlebowski RT, Gralow J, Yee GC, Janjan NA et al (2003) American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol. 21:4042–57
59. Giordano SH, Duan Z, Kuo YF, Hortobagyi GN, Goodwin JS (2006) Use and outcomes of adjuvant chemotherapy in older women with breast cancer. J Clin Oncol. 24:2750–6
60. Jones SE, Savin MA, Holmes FA, O'Shaughnessy JA, Blum JL, Vukelja S et al (2006) Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol. 24:5381–7
61. Muss HB, Woolf S, Berry D, Cirrincione C, Weiss RB, Budman D et al (2005) Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. JAMA. 293:1073–81
62. Muss HB, Berry DA, Cirrincione C, Budman DR, Henderson IC, Citron ML et al (2007) Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the cancer and leukemia group B experience. J Clin Oncol. 25:3699–704
63. Hortobagyi GN (2005) Trastuzumab in the treatment of breast cancer. N Engl J Med. 353:1734–6
64. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE et al (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 353:1673–84
65. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I et al (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 353:1659–72
66. Telli ML, Hunt SA, Carlson RW, Guardino AE (2007) Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. J Clin Oncol. 25:3525–33
67. Slamon D, Eiermann W, Robert N, and et al 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide, followed by docetaxel with doxorubicin and cyclophosphamide, followed by docetaxel and

trastuzumab with docetaxel, carboplatin and trastuzumab in Her2neu positive early breast cancer patients. Br Ca Res Treat. 2006. Ref Type: abstr
68. Muss HB, Woolf S, Berry D, Cirrincione C, Weiss RB, Budman D et al (2005) Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. JAMA. 293:1073–81
69. Berry DA, Cirrincione C, Henderson IC, Citron ML, Budman DR, Goldstein LJ et al (2006) Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA. 295:1658–67
70. Group Early Breast Cancer Trialists' Collaborative, Clarke M (2008) Coates AS, Darby SC, Davies C. Gelber RD et al Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials. Lancet. 371:29–40
71. Muss HB, Berry DL, Cirrincione C, Theodoulou M, Mauer A, Cohen H, Partridge AH, Norton L, Hudis CA, Winer EP, North American Breast Cancer Intergroup. Standard chemotherapy (CMF or AC) versus capecitabine in early-stage breast cancer (BC) patients aged 65 and older: results of CALGB/CTSU 49907. J Clin Oncol. 26:8s. 5-20-2008. Ref Type: abstr
72. Miles D, von Minckwitz G, Seidman AD (2002) Combination versus sequential single-agent therapy in metastatic breast cancer. Oncologist. 7(Suppl 6):13–9
73. Christman K, Muss HB, Case LD, Stanley V (1992) Chemotherapy of metastatic breast cancer in the elderly. The Piedmont Oncology Association experience [see comment]. JAMA. 268:57–62
74. Ibrahim NK, Frye DK, Buzdar AU, Walters RS, Hortobagyi GN (1996) Doxorubicin-based chemotherapy in elderly patients with metastatic breast cancer. Tolerance and outcome. Arch Intern Med. 156:882–8
75. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA et al (2007) Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 357: 2666–76
76. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T et al (2006) Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 355:2733–43

Breast Cancer in Younger Women

27

Manuela Rabaglio and Monica Castiglione

27.1 Introduction

The definition of "young" in the context of breast cancer differs considerably according to the analyzed topics, and according to the reporting people. In general, women are considered young if diagnosed with breast cancer before 35 years of age.

Breast cancer is very rare in young women. The estimated incidence is less than 0.2 per 100.000 women below the age of 20 years, increasing to 1.4 in women 20–24 years, 7.7 in women 25–29 years, and 25.5 in women 30–34 years old [1]. A recent publication reports a doubling of the incidence of breast cancer among women under the age of forty in Geneva, during the 10 years period from 2002 to 2004 [2]. In developed countries, breast cancer represents the main cause of death among women aged 15–49 years [3, 4].

Some authors have suggested that breast cancer in young women presents biological peculiarities compared with tumors in older women: a higher histological grade, no expression of estrogen receptors, and an aggressive growth pattern [5–9]. The prognosis and survival of young women with breast cancer remains a controversial issue, with several studies showing discordant results. A worse prognosis was shown by some [9–15], whereas other studies have reported that age is not influencing disease-free or overall survival after adjustment for other prognostic factors [16–20].

Special care is needed when facing women below the age of 40 years. In particular, issues like fertility and contraception, pregnancy after cancer or cancer during pregnancy, sexuality and body image, as well as familial, genetic, and career items are peculiar for young breast cancer patients. Younger women show greater psychological morbidity than older patients. This may be due to the fact that they face a severe disease and a burdensome treatment before they had the time and chance to achieve personal targets and purposes [21].

27.2 Epidemiology

Data from the Surveillance, Epidemiology, and End Results (SEER) program of the United States show that 75% of breast tumors occur in women aged >50 years, only 6.5% in women aged <40 years, and a mere 0.6% in women below 30 years. Nevertheless, invasive breast carcinoma is the most common cancer in young women in the US, with an estimated risk of 1 in 228 individuals developing the disease by age 40. In the age group below 35, the incidence is 1.9% and the mortality is 6.4% [1].An analysis using data from 9 registries of the SEER showed that relationship between age and mortality is biphasic and for both N0 and N + patients among the T1-2 group, the analysis suggested two age components. One component shows the natural linear increase of mortality with each year of age. The other component shows higher mortality in women below 40 as compared to women around 50 years [22].

27.3 Risk Factors/Prognosis

Several risk factors for the development of a breast cancer have been described in the past. Among them are familiarity, endocrine factors, obesity and physical activity, exposure pesticides, and many more.

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases*,
DOI: 10.1007/978-3-540-69743-5_27, © Springer-Verlag Berlin Heidelberg 2010

Women diagnosed with breast cancer at the age of <35 years are likely to have germ-line BRCA1 or BRCA2 mutations in up to 15–30% of cases [23–26]. Typically, breast cancers occurring in BRCA-1 mutation carriers are high-grade and have a high proliferation rate, with medullary or atypical medullary cancers being over-represented. In contrast, lobular cancers and extensive intraductal cancers are more frequent in women with germline BRCA-2 mutations [27, 28]

The data presented by Bernstein [29] show that among the endocrine factors influencing the incidence of breast cancer, the use of oral contraceptives (OC) may represent an important issue in young women. Two studies conducted in Los Angeles County suggest that the relationship between oral contraceptives and breast cancer risk may have changed over time, possibly reflecting changes in pill formulation. The first study was a case–control study of women aged 37 years or younger that was completed in 1983 and showed that long-term use of combination-type OCs with a "high" content of the progestogen component before the age of 25 was associated with increased risk of breast cancer. In contrast, the use of combination-type OCs with a "low" progestogen component appears to increase breast-cancer risk little or not at all [30]. Yet, in a subsequent case–control study of women diagnosed with breast cancer more recently (1983–1989), risk was unrelated to oral contraceptive use [31]. In 1996, the Collaborative Group on Hormonal Factors in Breast Cancer published a reanalysis of data collected from 54 breast cancer studies conducted in 25 countries, which specifically gathered detailed information on oral contraceptive use [32]. In this report, a history of recent oral contraceptive use, rather than long duration of use, was related with increasing breast cancer risk. The effect of recent oral contraceptive use was the strongest among those women who first used oral contraceptives before the age of 20 years. In this pooled analysis, the breast cancers diagnosed among oral contraceptive users were at an earlier stage than those among women who had never used oral contraceptives. In individual epidemiologic studies, it was, albeit up to now, not possible to demonstrate an association between OC use and the risk of breast cancer.

In the Nurses' Health Study, in women over the age of 40 at study entry, neither long-term past OC use, nor the use prior to a first full-term pregnancy were associated with an increased breast cancer risk [33]. The same was observed in other studies as the Royal College of General Practitioners' study [34] and the one conducted by the Centers for Disease Control and Prevention, Atlanta, USA [35]. The WECARE (Women's Environment, Cancer, and Radiation Epidemiology) study, a population-based, multicenter, case–control study of 708 women with asynchronous bilateral breast cancer and 1,395 women with unilateral breast cancer, provided no strong evidence that use of oral contraceptives (OC) or postmenopausal hormones (PMH) increases the risk of a second cancer in the contralateral breast [36].The role of OC in women with a familial predisposition to breast cancer is unclear and OCs may be associated with an increased risk of breast cancer in *BRCA1* mutation carriers, but data for *BRCA2* mutation carriers are limited [37].

Physical activity may positively influence the incidence of breast cancer because of its potential effects on hormone profiles and weight gain. Strenuous physical activity is known to delay menarche and cause secondary amenorrhea and oligomenorrhea among woman athletes The analysis of data from the Nurses' Health Study II show no overall association between physical activity and risk of breast cancer among premenopausal women, but suggest that the effect of physical activity could be substantially modified by the underlying degree of adiposity [38].

Obesity in premenopausal women seems to be associated with a reduction of breast cancer risk in contrast to postmenopausal women. The effect of obesity on the nonovarian estrogen production is indeed the same in pre- and postmenopausal women, but this production adds only a small increment in the estrogen produced by the ovary during ovulatory menstrual cycles. Obese premenopausal women experience more anovulatory cycles with lower estrogen production than normal weight women, and this could explain the slightly decreased risk of breast cancer in the obese premenopausal women studies, premenopausal women with a BMI of 31 kg/m^2 or higher were 46% less likely to develop breast cancer than those with a BMI < 21 kg/m^2 [40].

It has been proposed that intrauterine exposure to high concentrations of both endogenous and exogenous estrogens during gestation will negatively influence a fetus's breast cancer risk in adult life, perhaps by influencing the number of and the degree of differentiation of breast stem cells. Fetal estrogen exposure could also increase the probability of gene mutations relevant to cancer development or alter the breast's sensitivity to hormones [41, 42]. Although not entirely consistent, some studies show that low birth weight translates into a lower breast cancer risk, as does experiencing preeclampsia in utero [43]. Birth order may also affect risk. Maternal estradiol levels are

higher in the first than in the second pregnancy, but epidemiologic studies of birth order have not consistently shown that firstborn daughters have higher risk than those with higher birth order [44].

Excess breast cancer risk has been consistently observed in association with a variety of exposures to radiation, such as the Hiroshima or Nagasaki atomic explosions [45, 46], as well as after the Chernobyl accident [47] and radiotherapy treatments for medical conditions (e.g., Hodgkin's disease) in childhood or adolescence [48, 49]. Studies on survivors of the atomic bombing of Hiroshima and Nagasaki demonstrated that the carcinogenic effect of accidental radiation is highest when exposure occurs during childhood. Exposure at a younger age increases the subsequent risk of breast cancer to a greater degree, possibly because of the unopposed oestrogen exposure, which occurs during adolescence, rendering undifferentiated breast cells maximally vulnerable to initiation by environmental carcinogens [50].

27.4 Diagnosis

The presentation of breast cancer in women under the age of 40 years may differ compared to older women. The majority of young women presents with symptoms or palpable mass [51, 52]. Older women, on the other hand, are more likely to present with breast cancer detected by screening. Clinical and radiological examinations of the breast in younger women have a limited accuracy and may delay the diagnosis [8, 53]. The denser breast tissue limits the sensitivity on screening mammography and physical examination in asymptomatic women. The use of screening ultrasound in conjunction with mammography instead of breast palpation may increase the sensitivity of cancer detection from 75% to 97% in this special population [54]. According to the guidelines of the American Cancer Society [55], screening MRI is recommended for women with an approximately 20–25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin's disease. For the other risk subgroups, including women with a personal history of breast cancer, carcinoma in situ, atypical hyperplasia, and extremely dense breasts on mammography, the available data are insufficient to recommend for or against MRI screening, and the decisions should be made on a case-by-case basis.

Breast cancer diagnosis in this young population tends to be delayed and the patients often have a longer history of palpable mass in the breast [56].

The effectiveness of physical examination is lower in very young women, as they often have dense or nodular breast tissue that is subject to cyclical hormonal changes. Also, the accuracy of mammography is low in the young women with high breast gland density, with a sensitivity of only 62.9% in women with extremely dense breasts [8, 53, 57, 58].

27.5 Tumor Characteristics

Tumors in very young women show generally a more aggressive biological behavior leading to a worse prognosis. They are reported to be less differentiated, with higher proliferation fraction and more frequently lymphovascular invasion, extensive intraductal component, necrosis, overexpression of the HER-2 oncogene, absence of the estrogen receptor, and to show more frequently, an axillary nodal involvement than those in older females [8].

In several series, age remained independently prognostic when pathological variables were taken into account [9, 10, 59]. One worldwide database review showed that women younger than 35 had more advanced disease at diagnosis and poorer 5-year survival than older premenopausal patients.

Family history of breast cancer and, in particular, mutation in BRCA1 gene seems to correlate with tumors of medullary subtypes. This was first suggested by Marcus based on the histological evaluation of 157 breast cancers from women whose families had shown evidence of genetic mutation in BRCA1 [60].

27.6 Management/Treatment of Early Breast Cancer

27.6.1 Surgery (Breast Conserving vs. Mastectomy)

Younger women show a higher incidence of local recurrences after mastectomy and after breast-conserving surgery [61].

A recent comparison of outcome after breast–conserving surgery (BCT) or mastectomy shows that

patients younger than 35 years of age have a higher local relapse rate following less extensive surgery [62]. The data of two randomized clinical trials for stage I and II breast cancer patients were pooled and a total of 1,772 patients (879 underwent breast-conserving surgery and 893 modified radical mastectomy) were analysed. Age of 35 years or less and the presence of an extensive intraductal component were associated with an increased risk of local recurrence after breast-conserving therapy. Vascular invasion causes a higher risk of local recurrence after mastectomy as well as after breast-conserving therapy, and according to the author should therefore not be used as a criterion for the choice of surgical treatment. An older trial conducted between 1960 and 1980 at Institute Curie, Paris, France [63] involving 518 patients with T1, T2, N0, N1a, invasive breast cancer treated by breast-conserving surgery with (183 patients) or without (335 patients) axillary node dissection, followed by radiation therapy to breast and nodes revealed that local control in breast was significantly impaired by young age, premenopausal status, inadequate gross surgical excision, extensive ductal in situ component, and endolymphatic extension. In a single institution report of a cohort of 1,360 patients with pT1-2 N0-1 tumors treated with BCT between 1980 and 1994 [64], age was found to be the only significant risk factor for local recurrence. Compared to patients above 65 years, patients below 45 years and patients between 45 and 65 years had a relative risk of 4.09 and 2.41, respectively, of developing local recurrence. Jobsen [65] showed in a prospective cohort study of 1,085 women with pathological T1 tumours treated with breast-conservative surgery, that the local recurrence-free survival (LRFS) was significantly different for the two age groups at 71 months follow-up, respectively, 89% for women 40 years old or younger and 97.6% for women aged more than 40 years. In a subset analysis, this significant adverse effect of young age on outcome appears to be limited to the node-negative patients and those with a positive family history. In order to analyse the possible prognostic differences between patients treated with mastectomy and breast-conserving surgery, Arriagada [66] and colleagues analyzed the characteristics and outcome of 2006 patients treated for relatively small breast cancer (<25 mm) and followed for a mean of 20 years: 717 were treated conservatively (lumpectomy and breast irradiation) and 1,289 were treated with total mastectomy. Patients with negative nodes did not receive any systemic adjuvant treatment; for node-positive women, ovarian suppression was performed by radiotherapy in 26% of the cases and chemotherapy or additive hormonal treatments were given in only 3% of the patients. For women treated with mastectomy, histological grade and extensive axillary node involvement (10 nodes or more) were significant predictive factors for local relapse. Young age, however, was not a prognostic indicator for local recurrence. In contrast, for patients treated with a conservative approach, young age (≤40 years) was the main risk factor for local relapse. These younger patients had a five-fold increased risk of developing a breast recurrence compared with patients older than 60 years. Another cohort study analysing data from the population-based Danish breast carcinoma database [67] focalized on 9,285 premenopausal women with primary breast carcinoma who were below 50 years at diagnosis. No increased risk of death was observed among women who were treated by breast-conserving surgery compared with women who underwent radical mastectomy, regardless of age at diagnosis (<35 years, 35–39 years, 40–44 years, or 45–49 years), despite the increased risk of local recurrence among young women.

These findings make the regular follow-up for young patients mandatory, in particular for signs of local recurrence.

27.6.2 Radiation

Local treatment involving radiation therapy after breast-conserving surgery has been shown to yield the same disease-free survival and overall survival as in women undergoing total mastectomy [68, 69]. In a first trial analysing the role of radiation boost, patients with a microscopically complete excision received 50 Gy of radiation to the whole breast, and thereafter, they were randomly assigned to receive either no further local treatment (2,657 patients) or an additional localized dose of 16 Gy (2,661 patients) [70]. Patients 40 years old or younger benefited most from the addition of the boost; at 5 years, their rate of local recurrence was 19.5% with standard treatment and 10.2% with additional radiation (hazard ratio, 0.46 [99% confidence interval, 0.23–0.89]; $P=0.002$). The EORTC "boost versus no boost" trial [71] showed that young patients need a 16 Gy boost after breast-conserving surgery to

reduce effectively the local recurrence rate. 5569 early stage breast cancer patients were entered in this large randomized trial. All patients underwent tumorectomy followed by whole breast irradiation with 50 Gy. Patients having a microscopically complete excision were randomized between receiving no boost or a 16 Gy boost, while patients with a microscopically residual disease were randomized between boost doses of 10 or 26 Gy. The boost significantly reduced the 5-year local recurrence rate from 7% to 4% for patients with a complete excision ($P<0.001$). No statistical differences in outcome have been shown between the complete (94% of the women) and incomplete excision (6%) groups. For patients 40 years of age or younger, the boost dose reduced the local recurrence rate from 20% to 10% ($P=0.002$). A recently published update of this trial showed that after a median follow-up period of 10.8 years, a boost dose of 16 Gy led to improved local control in all age groups, but no difference in survival could be observed. The absolute risk reduction at 10 years per age group was the largest in patients 40 years of age or younger, and severe fibrosis was statistically significantly increased in the boost group, with a 10-year rate of 4.4% vs. 1.6% [72]. The ongoing "young boost" trial conducted by the EORTC will evaluate whether a higher boost dose will further reduce the risk of local recurrence with still acceptable cosmetic outcome and without long-term side effects [73]: patients aged 50 years or less will be randomized to receive 26 Gy boost vs. 16 Gy to the tumor bed after breast-conserving therapy, following 50 Gy to the whole breast.

27.6.3 Chemotherapy

With adequate systemic treatment, the outcome of breast cancer in young women may approach the one reported for older women [74, 75]. In patients with early breast cancer, chemotherapies are better tolerated and appear to be more effective on average in younger than in older patients [76], however single trials of adjuvant chemotherapy are generally not stratified by age and if stratified, the age cut-offs are set around the natural age of menopause. The difference in the efficacy may reflect the different distribution of ER-negative and -positive cancers in younger women [8, 75–77], According to recent publication, patients with ER-negative tumors yield a higher benefit from more intensive chemotherapies than patients with ER-positive breast cancer [78]. Timing of chemotherapy start may have a relevance for young patients: an analysis of the International (Ludwig) Breast Cancer Study Group (IBCSG) Trial V at a median follow-up of 11 years suggested that early initiation (within 21 days from surgery) of adjuvant chemotherapy might improve outcome for premenopausal, node-positive patients whose tumors do not express estrogen receptors [79].

A special issue is represented by the so called triple-negative cancers, which are defined by the lack of expression of estrogen, progesterone, and ErbB2 receptors. This subgroup accounts for 15% of all breast cancer and for a even higher percentage of breast cancer arising in premenopausal Hispanic, African, and African-American women. Histologically, these cancers are poorly differentiated and most of them fall into the basal-like breast cancer subgroups, staining for basal markers such as cytokeratin 5/6. Microarray gene-expression profiling data show that they represent a homogenous group in transcriptional terms. Histologically and transcriptionally, triple-negative breast cancers have many similarities to BRCA1 associated breast cancer, suggesting a possible dysfunction in BRCA1 in this subset of sporadic cancers. This aggressive cancer group is resistant to treatments like trastuzumab and endocrine therapies. Potential targets for treatment development for this special group of breast cancers include surface receptors, such as epidermal growth factor receptors (EGFR) or c-KIT; protein kinase components of the mitogen activated protein (MAP)-kinase pathway; protein kinase components of the protein kinase B (Akt) pathway; induction of DNA damage by specific chemotherapy agents as these cancers might be more sensitive to agents that cause interstrand and double-stranded breaks like platin-containing compounds; and inhibition of already defective DNA repair, by poly ADP-ribose polymerase 1 (PARP1) inhibition [80]. A population-based study using the California Cancer Registry data Bauer [81] showed that triple-negative breast cancer affects more frequently younger, non-Hispanic Black and Hispanic women in areas of low socio-economic status. Regardless of stage at diagnosis, women with triple-negative breast cancers had poorer survival than those with other types of breast cancers. Within the population of triple-negative cancers, the patients whose cancer has the basal-like phenotype may have a particularly high probability of relapse [82].

The role and value of chemotherapy is clearly established in patients with ER-negative breast cancer.

The topical update of the EBCTCG meta-analysis [83] provides a rationale for using adjuvant chemotherapy in young patient with ER-positive breast cancer, showing a reduction of the annual breast cancer death rate by about 38%. However, the utility of chemotherapy in addition to optimal endocrine treatment (ovarian function suppression + tamoxifen) has not yet been demonstrated in clinical trials.

In recent years, new tools (genetic signature) have been developed to predict the risk of recurrence [84] and the response to chemotherapy [85, 86]. Their definite relevance is not yet established, but they will probably become more important in the future. Two randomized clinical trials investigating the role of gene-signature tools for the choice of adjuvant treatment are currently accruing patients: the TAILORx trial is comparing hormone therapy with or without combination chemotherapy in women who have undergone surgery for node-negative breast cancer. Patients are assigned to different treatment groups based on their risk of distant recurrence determined by Oncotype DX (21-gene panel) test [87]. The MINDACT (Microarray In Node-negative Disease may Avoid Chemotherapy) trial is a prospective, randomized study comparing the 70-gene signature developed in Amsterdam with the common clinical-pathological criteria in selecting patients for adjuvant chemotherapy in node-negative (planned also for node positive), hormone-sensitive breast cancer [88].

27.6.4 Endocrine Treatment

Since the St.Gallen consensus conference in 2005 [89], endocrine responsiveness has become the primary factor for the choice of the adjuvant treatment in breast cancer. This was confirmed and emphasized also at the last meeting in 2007 [90]. According to the results of the Oxford meta-analysis [76], 5 years of treatment with tamoxifen reduced the risk of recurrence by 40% and the risk of death by 32% in women with ER-positive breast cancer. This effect was similar across all age groups and was not jeopardized by prior chemotherapy. But young patients with estrogen-receptor positive disease were found to be at high risk of relapse and death following adjuvant chemotherapy in the absence of endocrine treatment [91].

Two randomized clinical trials confirmed the efficacy of tamoxifen treatment after anthracyclines-based adjuvant chemotherapy also in premenopausal women with estrogen-receptor positive disease, achieving an improvement of the disease-free survival of about 40% [92, 93].

The suppression of ovarian function by oophorectomy, radiation therapy or through gonadotropin-releasing hormone (GnRH) reduces the relative risk of recurrence by 17% and the risk of death by 13% in women younger than 40 years of age with an estrogen receptor-positive tumor, and the efficacy is larger if the suppression of the ovarian function (OFS) is not combined with adjuvant chemotherapy [76, 94]. This result is indeed expected as chemotherapy may frequently induce amenorrhea, in particular in older premenopausal women [95, 96]. Subgroup analysis of many randomized trials showed that goserelin after chemotherapy was only effective in women who did not experience ovarian failure with chemotherapy and in particular in patients younger than 40 years [93, 97].

Ovarian function suppression was at least as effective as CMF-based or antracycline-based chemotherapy in some randomized clinical trials investigating suppression alone or in combination with tamoxifen [97–105].

To date, it is not clear if the combination of ovarian suppression and tamoxifen is better than either compound alone. In the metastatic setting, the combination of ovarian suppression and tamoxifen was shown to be superior to each single agent treatment [106]. In the adjuvant setting, the ZIPP trial [107] showed a similar outcome for goserelin and tamoxifen, but the combination of both did not show a larger benefit.

The North American Intergroup trial 0142 [108] showed similar results and despite the fact that the statistical power was limited because the trial was closed early due to low accrual, the addition of ovarian ablation to tamoxifen did not result in an improved disease-free survival or overall survival but only in higher toxicity in terms of menopausal symptoms and sexual dysfunction. The ongoing SOFT trial (Suppression of Ovarian Function Trial) investigating the role of ovarian function suppression and the role of exemestane as adjuvant therapies will further help to answer the question if the addition of ovarian suppression to

tamoxifen is needed for the optimal treatment of young premenopausal women with ER-positive breast cancer.

Another open question is the role of aromatase inhibitors (AI) in the management of premenopausal patients. In the postmenopausal setting, the efficacy of the AI is well established as shown in several randomized trials. AIs do not suppress the ovarian synthesis of estrogen and may even induce recovery of the ovarian function in premenopausal women amenorrhoeic after chemotherapy [109]. AIs were shown to be also useful in stimulating ovulation in the context of in-vitro fertilization (IVF) [110, 111]. For all these reasons, their use in premenopausal patients is recommended only in combination with ovarian suppression. Three international randomized adjuvant clinical trials (ABCSG-12, SOFT and TEXT) are investigating the efficacy and feasibility of the treatment with anastrozole or exemestane vs. tamoxifen in the context of ovarian suppression [112–114]. Few data exist on the use of aromatase inhibitors in combination with ovarian function suppression in premenopausal women with advanced breast cancer. In a small study, including 16 patients [115], all previously treated with goserelin and tamoxifen, it has been shown that almost all benefited from the switch to anastrozole at progression. Another recently published trial evaluating 32 premenopausal women with T2–T4, N0–N2 breast cancer, who underwent neo-adjuvant endocrine treatment with triptorelin and letrozole [116] showed that 16 patients had a response, one complete pathological response and fifteen clinical and imaging partial responses.

The role of fulvestrant, a selective estrogen-receptor down-regulator is being investigated in at least one trial for premenopausal patients with advanced breast cancer [117]; to date, its use outside a clinical trial cannot be recommended in the adjuvant setting.

27.6.5 Targeted Treatment

An increasing number of compounds are being developed that target cellular mechanisms involved in the pathogenesis of breast cancer in a specific way. The rational use of such therapies should be based on the understanding of molecular pathways and on appropriate clinical trials with relevant endpoints.

27.7 Monoclonal Antibodies

Trastuzumab: The first widely used substance of this class was trastuzumab, a humanized monoclonal antibody, which binds to the extracellular segment of the ErbB2 receptor. Cells treated with trastuzumab undergo arrest during the G1 phase of the cell cycle, therefore reducing their proliferative activity. It has been suggested that trastuzumab induces some of its effect by downregulation of ErbB2 leading to disruption of receptor dimerization and signaling through the downstream PI3K cascade. P27Kip1 is then not phosphorylated and is able to enter the nucleus and inhibit cdk2 activity, causing cell cycle arrest [118] In addition, trastuzumab suppresses angiogenesis by both induction of anti-angiogenic factors and repression of pro-angiogenic factors. It is thought that a contribution to the unregulated growth observed in cancer could be due to proteolytic cleavage of ErbB2 that results in the release of the extracellular domain. Trastuzumab has been shown to inhibit erbB2 ectodomain cleavage in breast cancer cells [119].

Several clinical trials have shown that trastuzumab is effective as single substance and in combination with chemotherapy in the treatment of advanced [120] breast cancer overexpressing ErbB2. According to the results of five independent randomized studies in the adjuvant setting, trastuzumab combined with chemotherapy was able to reduce the risk of recurrence by at least one-third and in all but one studies [121], a reduction of the risk of death was also demonstrated [122–125]. Age did not predict the efficacy of adjuvant treatment with trastuzumab, and a subgroup analysis in two trials yielded opposing gradients of efficacy by age [122, 124].

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF) that inhibits many functions of the VEGF. This compound was shown to be active as first-line treatment of metastatic breast cancer in combination with paclitaxel [126], but not in a later phase of the disease combined with capecitabine [127]. A randomized phase III trial compared bevacizumab and paclitaxel with paclitaxel alone as first-line therapy in 772 patients with metastatic disease. Paclitaxel plus bevacizumab significantly prolonged progression-free survival as compared with paclitaxel alone (median, 11.8 vs. 5.9 months; hazard ratio for progression, 0.60; $P < 0.001$) and increased the objective response rate (36.9% vs. 21.2%, $P < 0.001$). The overall survival rate, however, was similar in the

two groups (median, 26.7 vs. 25.2 months; hazard ratio, 0.88; $P = 0.16$) [128]. The role of bevacizumab in the adjuvant treatment of breast cancer has not been investigated to date.

Pertuzumab is a monoclonal inhibitor of the dimerization of the ErbB2 protein with the epidermal growth factor receptor (EGFR; HER1) and other pathways [129]. Its mode of action differs from trastuzumab and small molecule kinase inhibitors such as gefitinib. To date, the observed activity in patients with breast cancer that does not express ErbB2 has been modest [130].

27.8 Tyrosine Kinase Inhibitors

Lapatinib is an orally active dual kinase inhibitor that reversibly inhibits the HER1 and ErbB2 kinase activities; its activity seems to be limited to breast cancers with a strong expression of ErbB2 [131]. Preliminary results indicate that lapatinib is effective in the therapy of advanced ErbB2-positive breast cancer in combination with capecitabine after failure of anthracycline-, taxane- and trastuzumab-based therapy [132].

Patients with ErbB-2–overexpressing breast cancer have been found to have a significantly higher risk of developing brain metastases [133–135]. Lapatinib, which is a small molecule capable of crossing the blood–brain barrier, has been used in clinical trials for the treatment of brain metastases. A phase II trial using lapatinib in thirty-nine patients, who developed brain metastases while receiving trastuzumab showed that one patient achieved a PR in the brain and seven patients (18%) were progression free in both CNS and non-CNS sites at 16 weeks [136].

The use of lapatinib in the adjuvant therapy is currently investigated in a randomized trial conducted by the BIG Group that will compare lapatinib with trastuzumab, as well as with sequential- and combined treatment by lapatinib and trastuzumab (ALTTO).

Temsirolimus (CCI-779) in an inhibitor of mammalian target of rapamycin (mTOR) kinase and has moderate activity as a single drug in heavily pre-treated breast cancer patients [137]. It has been investigated in combination with letrozole in postmenopausal women with advanced breast cancer; however, the development of this combination has been discontinued following the independent interim analysis of a large randomized, placebo-controlled, double-blind phase III trial, which reported that the combination showed no benefit over letrozole [138]. No specific data for young premenopausal patients are available.

Numerous other tyrosine kinase inhibitors, such as pazopanib (GW786034), a VEGF receptor-1, -2, and -3 kinase inhibitor, and erlotinib, an EGFR kinase inhibitor, are being investigated in advanced breast cancer. Neither gefitinib nor erlotinib have so far demonstrated significant single-agent activity against breast cancers refractory to chemotherapy or hormonal therapy.

The molecular crosstalk between several receptor kinases and steroid hormone receptors is likely to be involved in the resistance to antiestrogens [139, 140]; thus, modifiers of these mechanisms will potentially improve the management of hormone-sensitive breast cancer patients [141].

27.9 Vaccines

Active immunization by tumor antigens that are able to induce specific long-term antitumor immune responses is still an investigational approach in early and advanced breast cancer. Early data from clinical trials show some antitumor activity and low toxicity. Promising results have been reported from a small randomized clinical trial of active immunization with a vaccine targeting ErbB2 protein in 171 patients with early breast cancer: the vaccine significantly reduced the risk of recurrence without causing serious toxic effects. The clinical recurrence rate for the vaccinated patients was 5.6% (5/90) compared to 14.8% (12/81) for the observation patients ($p = 0.04$) at a median follow-up of 24 months [142]. The next generation of clinical studies will integrate breast cancer vaccines with standard therapies. The adjuvant setting is considered most promising as the immunosuppressive effect of bulky disease does not interfere with effective immune responses [143].

27.10 Side Effects of the Treatment

27.10.1 Surgery

Cellulitis or abscess of the breast occurs in 1–8% of women undergoing breast-conserving surgery. In two separate reports, risk factors for breast cellulitis included drainage of a hematoma, postoperative

ecchymosis, tumor stage, the volume of resected breast tissue, the number of breast seroma aspirations, breast and arm lymphedema, and removal of more than five axillary nodes [144, 145]. Cellulitis of the ipsilateral arm is a well-known complication in women who have undergone axillary lymph node dissection that typically occurs late after surgery [146]. In a retrospective analysis of 580 women treated for breast cancer between 1985 and 2004, it was shown that the overall incidence of delayed breast cellulitis (DBC) was 8% and the median time to onset of DBC from the date of definitive surgery was 226 days [145].

Seroma formation occurs in almost all patients after mastectomy. In a prospective randomized trial, extensive axillary node involvement was the greatest predictor of prolonged lymphatic drainage need after mastectomy, followed by obesity and the performance of a two-step procedure [147]. Prolonged seroma formation may be associated with delayed wound healing and an increased risk of infection [148].

Sometimes patients describe a change in chest wall sensation after mastectomy reported as "phantom breast syndrome" [149].

Differences in incidence of surgery side effects between younger and older women are not reported, and the frequency of adverse event and the cosmetic outcome are mostly related to the local situation (i.e., tumor extension in relation to the breast volume) and the surgical technique and not to age.

27.10.2 Systemic Treatment

Side effects due to endocrine therapies are in general underestimated. In particular, tamoxifen treatment in premenopausal women is associated with a variety of symptoms, including vasomotor symptoms, vaginal complaints (dryness, itching, discharge), decrease of libido, amenorrhea, insomnia and mood disturbances, leading to significant restriction in the quality of life [150, 151]. In women treated with ovarian function suppression with LHRH agonist, the menopausal symptoms appear abruptly and are severe [152], but these symptoms are partly reversible after treatment cessation [153]. Bone metabolism is highly affected by changes in ovarian function. An analysis of 89 women participating in the ZIPP trial showed that 2 years of ovarian ablation through goserelin treatment caused a significant reduction in bone mineral density, but there was a partial recovery from the bone loss 1 year after cessation of treatment. The addition of tamoxifen seems to partially counteract the demineralizing effects of goserelin [154]. In recent reports, it has been shown that women undergoing oophorectomy before the onset of menopause had an increased risk of cognitive impairment, dementia, and even Parkinsonism [155, 156]. The impact of the estrogen deprivation on cognitive function in women treated with OFS for breast cancer is not yet exhaustively clarified and needs further investigations. It is well known that there is an increase in cardiovascular disease and cardiovascular risk factors after the menopause, but it is still unclear if this is related exclusively to the ageing process or is primarly due to estrogen deprivation. No data are available about the long-term risk of cardiovascular events in young women treated with OFS, and the impact of the combination of OFS with AIs on early and late side effects in premenopausal women will be analyzed in the ongoing trials.

The short-term side effects of chemotherapy for early breast cancer in terms of gastrointestinal symptoms, bone marrow depression and infection risk do mostly not differ in dependence of age, but chemotherapies are in general better tolerated by young women in terms of acute side effects [83]. A substantial portion of women treated with adjuvant chemotherapy, but particularly, premenopausal patients gain weight during treatment. On average, with CMF they gain 2–6 kg, less with AC [157]. The weight gain may be caused by reduced basal metabolic rate, increased food intake, diminished physical activity and ovarian failure. [158, 159]. The risk of chemotherapy-induced *amenorrhea and infertility* is lower in young premenopausal women [95, 160, 161], but menopausal symptoms induced by chemical castration and endocrine treatment have a high impact on the quality of life in younger women [162].

27.10.3 Radiation Therapy

The incidence of immediate skin reaction and subsequent telangiectasia was dramatically reduced with the use of modern equipments and smaller dose per fraction with consequent minimization of the radiotherapy dose delivered to the skin [163]. The data on effect of age on side effects of radiotherapy are inconsistent, and the effect of age seems to vary by site of irradiation [164]. In a recent report of 416 women followed between June 2003 and July 2005 for outcome and

side effects of radiation therapy after breast-conserving surgery, increased age of the patient was a risk factor for the development of telangiectasia [165].

Long-term side effects like *cardiac failure* are less frequently seen in young patients, but the impact on quality of life and overall survival may be deleterious in young, otherwise healthy women [166–168].

The increased use of growth factors for dose intensification was shown to be related to an elevated risk of *secondary malignancy*, in particular acute myeloid leukemia [169–171]. Angiosarcomas arising in the irradiated breast are rare and represent about 1% of all soft tissue sarcomas, but are being reported with increasing frequency over the past 20 years, as breast-conserving therapy combined with radiation therapy to the breast has replaced modified radical mastectomy as standard of care [172].

A special issue is represented by the risk of *lymphedema*. Young patients present frequently with more advanced disease, in part due to factors leading to a later diagnosis. In addition, in young women there is a higher incidence of inflammatory breast cancer accompanied by extensive lympho-vascular invasion and nodal involvement [173]. Cyclical increase in vascularity also permits a greater vascular and lymphatic spread. Young women are also subject to more traumas to the lymphatic drainage by virtue of their greater activities as childcare, shopping, travel, sports and accidents. Furthermore, the treatment itself contributes to the development of lymphedema [174–176]. Young patients are more subject to require multiple course of intravenous chemotherapy, leading to the need of peripheral or central vascular access. These devices may induce thrombosis and infection, leading to increased risk of lymphedema of limb and breast. After breast-conserving surgery, more breast edema is observed, and moreover, younger patients undergo five-fold more breast reconstructions, which may increase the risk of lymphedema [177]. Radiotherapy (particularly extensive in case of locally advanced disease) may also affect the lymphatic drainage of the limb, and this may have a greater impact in young women [178, 179].

27.11 Follow Up Recommendations and Survivors Care

Survival of patients with breast cancer has increased during the last decade, and therefore, more breast cancer survivors treated with surgery, irradiation, and adjuvant systemic therapy are in follow-up care. The most recent ASCO guidelines for follow up of breast cancer survivors recommend annual mammography and more frequent medical history and physical examination to screen for new or locally relapsed breast cancers or symptoms of possible metastases or secondary malignancies, but no specific screening is recommended for occult metastatic disease in asymptomatic patients. [180]. Although screening breast magnetic resonance imaging (MRI) seems to be more sensitive than conventional imaging at detecting breast cancer in high-risk women, there is no evidence that breast MRI improves outcomes when used as a breast cancer surveillance tool during routine follow-up in asymptomatic patients. The decision to use breast MRI in high-risk patients should be made on an individual basis depending on the complexity of the clinical scenario.

The referral for genetic counselling is recommended for women who meet the criteria suggested by the Preventive Services Task Force and the National Comprehensive Cancer Network [181, 182]. A 10-year retrospective cohort study of breast cancer screening with mammography and clinical examination showed that the false-positive rates of mammography were higher for younger women than for older women: The percentage of mammograms that were false-positive decreased from 7.8% for women 40–49 years of age to 4.4% for women 70–79 years of age ($P = 0.001$). The false-positive rate for clinical breast examination was highest for women 40–49 years of age (6.0%) and decreased to 2.2% for women 70–79 years of age ($P = 0.001$) [183].

The consequences of premature menopause, other side effects of antiestrogen therapy and of other adjuvant therapies should be recognized and treated if indicated, but estrogen substitution therapy should possibly be avoided. Sexual dysfunction can be addressed through sexual counselling and vaginal dryness can frequently be sufficiently managed with nonhormonal preparations or with cautious use of estrogen ring preparations, recognizing that there is the potential for slight systemic absorption [184]. The role of androgen treatment in this context is still controversial [185]. Beneficial effects of testosterone on libido and sexual function were reported in naturally or treatment-induced postmenopausal women, but no data are available about the safety profile of testosterone.

Bone mineral density should be assessed, ade quate intake of calcium and vitamin D and regular

weight-bearing exercise encouraged, and bisphosphonate treatment initiated, if indicated [186].

27.12 Fertility Preservation

The increasing age at first and subsequent pregnancies in the western world and the improved survival for women diagnosed with breast cancer increases the relevance of fertility issues. Preserving fertility is frequently an important issue for younger female cancer survivors and their partners [187, 188]. In a web-based survey of 657 breast cancer patients, Partridge [189] showed fertility (after treatment) being a major concern for young women with breast cancer. In a longitudinal cohort study of 577 breast cancer patients, Ganz [190] showed that 20% were planning or hoping to have children before the diagnosis of breast cancer. 11% ($n = 61$) reported that they had considered getting pregnant since the breast cancer diagnosis. While 19% of these 61 survivors reported that they were not planning a pregnancy due to physician's recommendation, 17% said they were not planning a pregnancy because they were worried about the risk of relapse. Only 5% of women reported a pregnancy and life birth after the breast cancer diagnosis. In a multicenter survey, Thewes [191] observed highest need in fertility-related information at the time of diagnosis and treatment decision. In later stages of treatment, menopause-related information was significantly more important. Little if any attention has been paid to fertility-related needs of partners. In a case–control study conducted in Israel [192], 30 breast cancer survivors and 13 husbands were compared to 29 healthy women and 15 husbands using qualitative questions and quantitative measures, including demographic and medical questionnaire. The experience of having breast cancer did not lower the overall positive motivation toward childbirth in this population. Initial concerns that fertility preservation interventions and/or a pregnancy might increase the risk of cancer recurrence in breast cancer and gynaecological malignancies have not been confirmed to date. In 2006, the American Society of Clinical Oncology [193] recommended that involved physicians (e.g., oncologists) should discuss at the earliest point in time infertility as a potential risk of cancer treatment with patients and their partners. For patients at risk of infertility and interested in assessing their options of fertility preservation, earliest possible referral to appropriate specialists is suggested. Any decision about an appropriate therapy would ideally be supported by a team consisting of a gynaecologist, a medical oncologist, a reproductive endocrinologist, and a psychosocial care provider. The decision-making should be based on agreed written protocols that can be shared with the patients and their families.

Ovagenesis begins at approximately 3 weeks after conception. At this time, the primordial germ cells, arising from the endodermal yolk sac, begin migration to the developing ovaries. The cells undergo progressive differentiation to become primary oocytes. After birth, no more primary oocytes develop. These oocytes remain in the prophase of the first meiotic division until puberty. A woman has 200,000 oocytes at puberty. This number decreases to about 400 at the time of menopause [194]. Since many chemotherapy agents act on growing and dividing cells, both oocytes and ovarian follicles may be affected by chemotherapy.

The impact of adjuvant chemotherapy on ovarian function depends on the age of the woman, the class of drug used and the duration of treatment. Review of the published data and some prospective studies showed that patients over 40 years have a greater risk of experiencing amenorrhea during treatment, and furthermore, the amenorrhea is less often reversible [95, 96, 195]. In a prospective trial assessing acute and long-term toxicity in 796 women treated between 1974 and 1982 with doxorubicin-containing postoperative adjuvant chemotherapy [162], 80% of the premenopausal women reported amenorrhea. None of the patients under 30 years of age had menstrual abnormalities, whereas 96% of those 40–49 years old developed amenorrhea. Amenorrhea was permanent for most women over 40, but for 50% of patients under 40 years of age, it was reversible. The incidence of chemotherapy-induced amenorrhea differs with the type of chemotherapy regimen given. In general, rates of both transient and prolonged amenorrhea are higher with CMF or CEF/CAF-type regimens as compared to AC [196, 197].

Even for younger women in whom ovarian activity resumes after chemotherapy, menopause tends to happen earlier, therefore shortening the window of opportunity for conception. Furthermore, the continuation or resumption of the menses is not always equivalent with fertility. After chemotherapy, the number of anovulatoric cycles is increased [198].

The management of gonadal toxicity due to adjuvant chemotherapy for breast cancer is complex and frequently difficult. It is therefore very important to

consider the possibility of preventing ovarian failure and the therapeutic options available if infertility occurs before starting chemotherapy. It has been postulated that suppression of germ cell stimulation may lead to protection of oocytes and ovarian follicles from the toxic effects of chemotherapy. Ovarian suppression through gonadotropin-releasing hormone (GnRH) agonist or antagonist treatment during chemotherapy is still controversial as a method to maintain fertility. A small study evaluating 54 patients compared with retrospective controls suggested a benefit in preserving menstrual function from ovarian suppression with GnRH in women undergoing chemotherapy for Hodgkin's and non-Hodgkin's lymphoma [199], but a small prospective study of 18 women receiving chemotherapy for Hodgkin's lymphoma did not show a benefit for this approach [200]. The Southwest Oncology Group is currently conducting a trial aimed at preventing early ovarian failure with GnRH agonists among women with hormone receptor-negative breast cancer who receive chemotherapy (IBCSG34/Southwest Oncology Group 0230). Another randomized trial with a similar design, but using anthracycline-containg regimens, has reached the target accrual (Zoladex Rescue of Ovarian Function [ZORO]/German Breast Group) and results should be available shortly.

Small observational studies conducted in patients with Hogkin's disease also suggest that oral contraceptives may help preserve ovarian function when given during chemotherapy [201, 202]. Its use for preservation of fertility in patients with endocrine unresponsive breast cancer however remains controversial.

Embryo cryopreservation is considered an established fertility preservation method as it has routinely been used for storing surplus embryos after in vitro fertilization for infertility treatment. Because of lack of approval by health authorities and ethical bodies or insurance companies, this procedure is not available in all countries. Furthermore, a partner or sperm donor is required. This approach typically requires 2 weeks of ovarian stimulation with daily injections of follicle-stimulating hormone from the onset of menses, which may require a delay of 2–6 weeks in chemotherapy initiation. For women with hormone-sensitive tumors, alternative hormonal stimulation approaches such as letrozole or tamoxifen [110] have been used to theoretically reduce the potential risk of estrogen exposure. Short-term breast cancer recurrence rates after ovarian stimulation using letrozole or tamoxifen concurrent with follicle stimulating hormone (FSH) administration have been compared to nonrandomized controls and no increase in cancer recurrence rates has been noted [110, 203]. Live birth rates after embryo cryopreservation and implantation depend on the patient's age and the total number of embryos available and may be lower than with fresh embryos.

Oocyte cryopreservation is another option for fertility preservation, particularly in patients without a partner, or who have religious or ethical objections to embryo freezing. Ovarian stimulation and harvesting requirements are identical to those of embryo cryopreservation, and thus this technique is associated with similar concerns regarding delays of therapy and potential risks of short-term exposure to high hormonal levels. As with embryo cryopreservation, letrozole or tamoxifen can be used. Preliminary study indicates that unfertilized oocytes are more prone to damage during cryopreservation procedures than embryos, and the overall pregnancy rates may be lower than with standard in vitro fertilization procedures [204]. To date, there have been approximately 120 deliveries with this approach, and efforts to improve the efficiency of cryopreservation may increase success rates [205, 206]. Oocyte collection has the advantage that it can be performed without ovarian stimulation ("natural cycle-IVF"), but the number of viable embryo yielded is extremely low [110, 203] and this method remains experimental.

Ovarian tissue cryopreservation is an additional investigational method of fertility preservation and it has the advantage of requiring neither sperm donors nor ovarian stimulation. Ovarian tissue is removed laparoscopically and frozen. At a later time point, the ovarian tissue is thawed and re-implanted. Primordial follicles can be cryopreserved with great efficiency [207, 208], but because of the initial ischemia encountered after ovarian transplantation, a quarter or more of these follicles might be lost, as shown in xenografting studies [209]. Ovarian tissue cryopreservation has been performed in humans for less than a decade, and the first ovarian transplant procedure was reported in 2000 [210]. Ovarian tissue can be transplanted orthotopically to pelvis or heterotopically to subcutaneous areas such as the forearm or lower abdomen, and initial studies reported restoration of ovarian endocrine function after both types of transplantation [210–214]. There have been two reports of live births after orthotopic ovarian transplantation in cancer patients; one conceived spontaneously [215] and the other as a result of in vitro fertilization

[216]. One concern with the re-implantation of ovarian tissue is the potential for reintroducing cancer cells. In patients without evidence of systemic metastasis, the likelihood of occult ovarian metastasis appears to be low [217, 218], and there are no reports of cancer recurrence after ovarian transplantation, although fewer than 20 procedures are reported thus far.

The possibility that fertility preservation interventions and/or subsequent pregnancy may increase the risk of cancer recurrence is a concern for breast cancer patients and women with gynecologic malignancies. To date, the effect of subsequent pregnancy after breast cancer on prognosis has not been studied prospectively. Several case–control and retrospective cohort studies have not shown a decrement in survival or an increase in risk of recurrence with pregnancy [219, 220]. While these data are reassuring, the studies are all limited by significant biases.

27.13 Breast Cancer Associated with Pregnancy (Lactation)

Gestational or pregnancy-associated breast cancer is defined as breast cancer that is diagnosed during pregnancy or in the first postpartum year, or at any time during lactation.

Breast cancer is the most common malignancy diagnosed during pregnancy, with an estimated 1 in 3,000 to 1 in 10,000 deliveries being to pregnant breast cancer patients [221–223]. Between 0.2% and 3.8% of breast cancers diagnosed in women under age 50 are detected during pregnancy or in the postpartum period [224]. In contrast, 10–20% of breast cancers in women 30 years of age or younger are discovered during pregnancy or in the year following delivery [225]. Because the incidence of breast cancer increases with age, it has been hypothesized that the incidence of breast cancer diagnosed during pregnancy will increase as more women delay childbearing nowadays. Pregnancy itself may transiently increase an individual woman's risk of developing breast cancer, despite its long-term protective effect on the development of the disease. This was illustrated by three population-based series in which pregnancy was followed by a period of increased breast cancer risk lasting 3–10 years, which subsequently declined [226–228]. This observation has also been done for women with inherited BRCA2 mutations: the risk of breast cancer in the 2 years following a birth was 70% higher for a BRCA2 carrier compared to nulliparous controls [229]. In addition, the data of three small studies show that women with a genetic predisposition to breast cancer seem to have an increased risk for pregnancy related cancer. In a case–control study from Japan involving 343 women, a family history of breast cancer was three times more common among pregnant and lactating women with breast cancer than among controls [230]. Another small retrospective study found BRCA2 mutations in a significantly higher number of archival samples from women with pregnancy-associated breast cancer compared to samples from unmatched nonpregnant controls [231]. In a Swedish series of 302 women diagnosed with breast cancer before the age of 40 (47 from families with BRCA mutations), women with BRCA1 mutations were significantly more likely to develop breast cancer during pregnancy than those without inherited mutations [232]. Furthermore, in a matched case–control study comparing 1,260 pairs of women with known BRCA mutations with and without breast cancer, increasing parity was associated with a higher risk of breast cancer before age 50 in BRCA2, but not in BRCA1 carriers [229].

Breast cancer occurring during pregnancy presents a challenging clinical situation for the mother, the fetus, and the treating clinicians because of the complex medical, ethical, and psychological problems arising in this situation. Breast cancer during pregnancy is often perceived as a situation that puts the life of the mother in conflict with that of her unborn child. However, limited data suggest that pregnancy termination does not improve the outcome for pregnant women with breast cancer. Pregnant women should be treated according to guidelines for nonpregnant patients, with some modification to protect the fetus. Medical abortion is not usually recommended in cases of pregnancy-associated breast cancer, but may be considered during treatment planning, in particular in case of diagnosis in the first trimester. When considering management of the disease in this setting, there are two key issues: first, how the pregnancy affects the behavior of the cancer, and second, how the cancer and its treatment affect the pregnancy.

Making the diagnosis of breast cancer and performing a staging work-up is frequently more difficult due to the physiological changes in the breast that accompany pregnancy and lactation and the desire to limit radiation exposure to the unborn child.

Pregnant or postpartum women with breast cancer usually present similarly to non pregnant women with a mass or thickening in the breast. Rarely, refusal by a nursing infant of a lactating breast that harbors an occult carcinoma has been described, and termed the milk rejection sign [233]. The physiologic changes in the breast occurring during pregnancy and lactation (engorgement, hypertrophy) make physical examination more challenging and interpretation of findings more difficult, and the density of the breast may limit the utility of mammography. The malignant mammography finding of clinical suspected breast cancer was histologically confirmed in about 78% of the cases in a older report [234], and 86.7% [235] respectively 90% [236] in two recent retrospective studies.

As a result, diagnostic delays of 2 months or longer are common in women with gestational breast cancer [237] and they adversely impact outcome, since even a 1 month delay in diagnosis can increase the risk of nodal involvement by 0.9–1.8% [Nettleton, 1996 #396]. Delay in diagnosis may be responsible, at least in part, for the larger size of tumors at diagnosis in pregnant women. At presentation, about 42% of the patients are diagnosed with stage III or IV. A breast mass that persists for 2–4 weeks should always be investigated, although the majority (80%) of breast biopsies performed in pregnant women will prove to be benign [238].

Mammography is not contraindicated in pregnancy, as the average glandular dose to the breast for a two-view mammogram (200–400 mrad) provides a negligible radiation dose of 0.4 mrad to the fetus as long as abdominal shielding is used [239]. The sensitivity of the mammography is diminished by the increased water content, higher density and loss of contrasting fat in the pregnant or lactating breast. In an early series, six of eight pregnant women with histologically documented breast cancer had falsely negative mammograms [240]. Somewhat better sensitivity rates, ranging from 63% to 78%, are reported in more recent studies [230, 234–236, 241].

Breast *sonography* is often the first diagnostic test performed to evaluate a breast mass in a pregnant woman. It can distinguish between solid and cystic breast masses in almost all cases without the risk of fetal radiation exposure. A focal solid mass is observed in the majority of cases of gestational breast cancer [230, 234, 235], although in one report, two of the four malignant tumors had sonographic characteristics of a benign lesion [241]. If palpable nodes are present, axillary ultrasound and fine-needle aspiration (FNA) biopsy are important components of the initial staging evaluation.

Magnetic resonance imaging (MRI) has not been systematically studied for the diagnosis of breast masses in pregnant or lactating women. Although gadolinium-enhanced MRI appears to be more sensitive than mammography for detecting invasive breast cancer, particularly in women with dense breast tissue, the use of contrast agents such as gadolinium should be avoided during pregnancy. Gadolinium crosses the placenta, and has been associated with fetal abnormalities in rats [242, 243]. Other disadvantages of breast MRI include lack of specificity, inability to identify microcalcifications, high cost, and long examination times. MRI has been used for the diagnosis of metastases in women with newly diagnosed breast cancer during pregnancy. As long as contrast is avoided, there are no reported harmful effects from MR imaging to the pregnant woman or to the unborn child [239]. Nevertheless, some authorities recommend that all MRI scans be avoided in the first trimester [244].

There is minimal information regarding *positron emission tomography* (PET) in pregnancy. ^{18}F-FDG has been found to cross the placenta and to accumulate in fetal brain, heart, and bladder in a monkey study [245]. Healthy monkeys were born but the possibility of harms remains uncertain. The radiation dose to the uterus is 3.70–7.40 mGy, for the usual dose range of isotope injected. Recently, the case of a young woman treated for Hodgkin's disease was reported [246]. After 4 months of chemotherapy, a PET scan showed an unexplained hotspot in the right lower abdomen; 6 weeks later, the woman complained of abdominal distension and an ultrasound showed an unsuspected pregnancy with an estimated gestational age of 30 weeks. She delivered a girl by caesarian section without congenital abnormalities and at 6 years of age, she apparently has a normal development.

Although fine-needle aspiration can be used to clarify a breast mass in a pregnant patient, a core or excisional biopsy is often required for a definitive diagnosis of invasive cancer. The potential for the development of a subsequent milk fistula is overestimated and there are very few reports in the literature [247, 248]. Core, incisional or excisional biopsy can be performed relatively safely during pregnancy, preferably under local anesthesia [238]. During pregnancy and lactation, atypical cytomorphologic features are seen in normal breast tissue, and therefore interpretation of FNA samples needs

special caution and accuracy [249–252]. To avoid misinterpretation and a false-negative result in doubtful cases, a second opinion slide review at a cancer center is recommended. The risk of false-positive results is negligible in the hands of experienced cytologists [253].

Because of the potential harms to the unborn child, staging procedures should be limited to a minimum. A fetal exposition to radiation doses of less than 0.1 Gy do not cause major damage, in particular in the third trimester of pregnancy, but in case of radiation above 2.5 Gy, malformations are likely and more that 30Gy may cause abortion. The association of in utero diagnostic X-ray exposure with subsequent occurrence of childhood leukemia has been the subject of great controversy over the last 50 years. Combining the results of many case–control studies in different countries, a proportional increase in risk of about 40% for malignancy, and in particular, for ALL in childhood after a radiographic examination of the abdomen in pregnant women has been reported in the year 1956 [254]. However, subsequent cohort investigations in the United Kingdom [255] and the United States [256] reported no increase in risk of childhood leukemia linked with maternal pelvimetry during pregnancy. In addition, risks of leukemia were not increased among offspring of Japanese atomic bomb survivors, who were pregnant at the time of the bombings [257].

27.14 Fetal Exposure by Staging Procedures

Investigation	Fetal dose(mGy)
Chest X-ray	<0.01
Thoracic CT scan	0.06 (max 0.96)
Abdominal CT scan	8 (max 49)
Pelvic CT scan	8 (max 79)
Bone scintigraphy	<4.5
FDG-PET	max 8

Pregnant women with clinically positive nodes, T3 or T4 lesions or suspicion for distant metastases should undergo a complete imaging evaluation of the most common sites for distant metastatic spread (lung, liver, and bone) like nonpregnant women. In contrast, women who are asymptomatic and have clinically node-negative, early-stage breast cancer do not require formal evaluation since the incidence of unsuspected metastases is low [258]. There are no contraindications to chest radiography in pregnancy as long as abdominal shielding is used. However, the ability to evaluate the lower lung parenchyma is limited late in gestation when the gravid uterus is pressing against the diaphragm. Abdominal ultrasound is a safe procedure in pregnant women for the evaluation of liver metastases, but is significantly less sensitive than CT or MRI. CT scans are generally avoided during pregnancy because of the large cumulative radiation dose when multiple slices are obtained. MRI is preferred if further evaluation is required. MRI is also the safest and most sensitive way to scan the brain, although, as noted above, contrast agents such as gadolinium should be avoided during pregnancy. Radionuclide bone scans are reported to be safe during pregnancy but fetal exposure to radiation may result from proximity to radionuclides excreted into the maternal bladder; maternal hydration and frequent voiding can reduce this exposure but in general, bone scan procedures should better be avoided during pregnancy. MRI or plain skeletal radiographs, including spine or pelvis may be considered as alternative procedures. Alkaline phosphatase increases markedly during pregnancy due to placental production, and cannot be used as an indicator of bone metastases.

The safety of *surgery in pregnancy* was illustrated by a large retrospective study of 720,000 pregnant Swedish women in the 1970s and the 1980s. The rate of congenital malformations and unexplained stillbirths was similar between those women who underwent nonobstetric surgery requiring anesthesia (n = 5,405) and those who did not [259]. However, the rates of low birth weight infants (due to prematurity and growth retardation) and early neonatal death (death within 7 days of birth) were significantly increased in women who had had surgery. During surgery, the fetus is exposed to the transplacental effects of anesthetic agents. Commonly used anesthetics, including nitrous oxide, enflurane, barbiturates, and narcotics, have been extensively used safely in pregnancy.

Risks to the fetus during surgery are not just anesthetic related, but also include intra-operative complications, such as hypoxia and hypotension. Furthermore, decreased placental perfusion secondary to long-term positioning of the mother in the supine position is a mechanical problem in late pregnancy. Additionally,

postoperative problems, such as fever, infections, gastrointestinal problems and changes in nutritional intake, thrombosis, and pulmonary embolus could have serious adverse effects on fetal well-being. However, anxieties about anesthesia during pregnancy are probably greater than the actual risks. Prophylactic treatments to improve fetal lung maturity should be administered where surgery carries a risk of precipitating premature delivery. Nonemergency surgery in pregnancy can be scheduled for the second trimester with the least risk of fetal harm, or of inducing abortion or premature labour.

Mastectomy with axillary lymph node dissection has been the most common breast surgery for stage I, II, and some stage III breast cancers when the patient wants to continue the pregnancy [223, 260]. A major advantage of mastectomy is the elimination of the need for breast radiation therapy. If breast reconstruction is desired, it should be delayed until after delivery. Mastectomy and *breast-conserving therapy* has been demonstrated to be equivalent in terms of disease-free and overall survival in nonpregnant women. Lumpectomy with axillary lymph node dissection is feasible and safe in the pregnant woman with breast cancer, and is reported to have no adverse impact on locoregional recurrence rates [261]. However, because of the need of subsequent radiation therapy to achieve optimal local control, this approach may be contraindicated in the early pregnancy [262]. In addition, cosmetic results may be poorer because of the anatomic changes in the breast during pregnancy. Neo-adjuvant chemotherapy could be considered prior to definitive breast surgery for women with locally advanced disease at presentation or for the ones desiring breast conservation. In such cases, surgery could be performed later in the pregnancy or even postpartum.

Axillary dissection is an important component of therapy because nodal metastases are commonly detected in pregnancy-associated breast cancers, and nodal status affects the choice of adjuvant therapy. Sentinel lymph node (SLN) biopsy is being performed for axillary staging in nonpregnant patients with clinically node-negative early-stage breast cancer. The safety and test performance of sentinel node biopsy during pregnancy has not been fully evaluated. Supravital dyes such as isosulfan blue dye should not be administered to pregnant women, because of the possible risk of anaphylactic shock [263]. Some authors suggest that sentinel node biopsy is safe in pregnant patients with a minimal dose of 500–600 mCu using double filtered technetium sulfur colloid, but no supporting studies for this approach are available at the time being. Other investigators, by deriving estimates of absorbed dose at the level of epigastrium, umbilicus, and hypogastrium in nonpregnant women undergoing sentinel node biopsy for breast cancer, have concluded that expected levels of fetal exposure would be below the 50 mGy threshold absorbed dose for adverse effects [264–266].

In addition to safety issues, lymphatic pathways may be altered in the breasts of pregnant women, making identification of the sentinel node more difficult. In the only published experience, three pregnant women underwent SLN biopsy for breast cancer and a SLN was identified in all three [267]. These patients (and seven others who underwent SLN biopsy for melanoma while pregnant), all went on to have term deliveries without known adverse effects. Until further data become available, sentinel lymph node biopsy cannot generally be recommended for pregnant women with breast cancer, and some authors still consider that pregnancy represents one of the contraindications for this procedure [268].

The use of *radiation therapy* is generally avoided during pregnancy because of the risk of death, of teratogenicity to the fetus and induction of childhood malignancies and hematologic disorders [269, 270]. The amount of radiation to which the fetus is exposed depends upon the stage of pregnancy when therapeutic radiation is administered. Even with appropriate shielding, fetal exposure to therapeutic breast irradiation will increase as the fetus grows and moves closer to the diaphragm. The administration of 50 Gy external beam irradiation to the breast could result in a first trimester fetal dose of 0.04–0.15 Gy, or a third trimester dose as high as 2 Gy [271, 272]. Fetal malformations have been associated with doses of 0.1 Gy or more during the first trimester. Although there are several case reports of normal infants born after their mothers had been irradiated, including one exposed to 0.14–0.18 Gy in the third trimester, one exposed to 0.16 Gy at 24 weeks, and another exposed to 0.04 Gy in the first trimester, irradiation is generally avoided in pregnant women because absence of risk to the fetus cannot be guaranteed. As RT is generally delayed in nonpregnant women for months until after completion of chemotherapy, it seems safe to delay it also in pregnant women until after delivery.

All *chemotherapy* agents used in the treatment of breast cancer are pregnancy category D, meaning that teratogenic effects have been observed in humans. However, the risk of spontaneous abortion, fetal death, and major malformations is highest when chemotherapy is administered in the first trimester. Outside that window, most reports show a safer profile [198, 273, 274]. In general, acute side effects of chemotherapy include spontaneous abortion, teratogenesis, organ toxicity, premature birth, and low birth weight. Delayed effects of antineoplastic agents can include carcinogenesis, sterility, slow physical or mental growth and development, and teratogenic effects in the offspring's of the exposed fetus. The teratogenic and mutagenic potentials of chemotherapy agents have been studied extensively in animals, although results cannot always be extrapolated across species. Additionally, other effects such as bone marrow suppression can result in serious problems, such as infection and bleeding in both the mother and the fetus. The gastrointestinal side-effects of chemotherapy agents are also likely to be deleterious to both maternal and fetal well-being, but are difficult to quantify. Information on the effects of antineoplastic drugs administered during pregnancy has largely been derived from case reports, small case series, and collected reviews [223, 260, 274–279]. The majority of these reports focused upon the frequency of spontaneous abortion and congenital malformations in infants exposed to chemotherapy in utero for a variety of malignancies. A review of 217 pregnant women treated with cytotoxic therapies for a variety of malignancies and other medical conditions published between 1983 and 1995 [280] reported 18 newborns with congenital abnormalities: two had chromosomal abnormalities, four were stillborn, and 15 spontaneous abortions were reported. Another review of literature published between 1976 and 2001 reported on 160 women treated with anthracyclines during pregnancy [274] and showed that the fetal outcome was frequently normal (73%), but abnormalities included malformations (3%), fetal death (9%), spontaneous abortion (3%), fetal complications (8%) and prematurity (6%), and fetal death was often consecutive to maternal death due to malignancy (40%). An unfavorable fetal outcome was frequent in leukemia patients. In one of the first published review, the incidence of fetal malformations in 150 women given chemotherapy during the second or third trimesters of pregnancy was 1.3% [273]. In a case–control study, women with gestational breast cancer were significantly more likely to have a premature infant than a control group matched for maternal age. The infants had a lower mean birth weight when compared to controls, which persisted after adjustment for gestational age [281]. This is the only consistent finding associated with antenatal chemotherapy in women with breast cancer [282, 283].

The experiences of the Royal Marsden Hospital [284], of the MD Anderson Cancer Center [285] and the European Institute of Oncology [286, 287] were recently reported and they all confirmed the relative safety of adjuvant chemotherapy delivered during the second and third trimester of pregnancy.

The most commonly used regimen in pregnant women with breast cancer is doxorubicin combined with cyclophosphamide with or without fluorouracil (AC or FAC) [223, 275, 283, 285]. The most recent update of the largest prospective single-arm study in 57 pregnant breast cancer patients treated with FAC in the adjuvant ($n = 32$) or neo-adjuvant ($n = 25$) setting [285] showed that 40 women were alive and disease-free, three had recurrent breast cancer, 12 had died from breast cancer, one from other causes and one was lost to follow-up. Of the 25 patients who received neo-adjuvant FAC, six had a pathologic complete response, while four had no tumor response to chemotherapy and eventually died of their disease. All 43 women who have delivered had live births. One child has a Down's syndrome and two have congenital anomalies (club foot; congenital bilateral ureteral reflux). The other children are healthy and those in school are doing well, although two have special educational needs. The authors concluded that breast cancer can be treated with FAC chemotherapy during the second and third trimesters without significant short-term complications for the children. They also commented that longer follow-up of the children in this cohort is needed to evaluate possible late side effects such as impaired cardiac function and fertility. Whether in utero exposure to anthracyclines is cardiotoxic remains unknown. A single report in which fetal echocardiograms were performed every 2 weeks beginning at 24 weeks in a pregnant patient receiving doxorubicin and cyclophosphamide showed no abnormalities, even when postnatal echocardiograms were repeated at 2 years of age [288]. However, at least four cases of neonatal cardiac side-effects have been reported after in utero exposure to anthracyclines, and there are several cases of in utero fetal death after exposure to idarubicin or epirubicin

[282, 289–292]. Because of these reports, in the past, doxorubicin was preferred to idarubicin or epirubicin for use in pregnancy [283]. According to the data of later reports, epirubicin may be preferred to doxorubicin because of a better therapeutic index and fewer systemic and cardiac toxic effects [287, 293].

Chemotherapy should be ended/stopped 3–4 weeks before delivery to avoid transient neonatal myelosuppression and potential complications as sepsis, bleeding and death. At least one case report describes measurable tissue levels of anthracyclines in a stillborn whose mother had received doxorubicin shortly before delivery [294]. Furthermore, cyclophosphamide and doxorubicin can enter milk, therefore breastfeeding is contraindicated during chemotherapy.

Methotrexate should be avoided at all stages of pregnancy because of delayed elimination from sequestered spaces (such as amniotic fluid), as well as its abortive effect and teratogenic potential [273, 280].

The use of taxane (paclitaxel and docetaxel) in pregnancy has been described in several case reports for the treatment of breast cancer and ovarian cancer, suggesting short-term safety [282, 295–301]. Nevertheless, international guidelines for the management of breast cancer in pregnant women suggest avoiding taxanes during pregnancy because of lack of long-term safety data. In consideration of the proven efficacy in the sequential schedule, taxane administration may be postponed until after delivery. No data are available on the safety of dose-dense anthracycline-containing regimens with or without taxanes, during pregnancy.

Trastuzumab has been administered in a few cases during pregnancy [302]. In five of the seven reported cases, trastuzumab was given in the metastatic setting. Reversible oligohydramnios/anhydramnios has been reported in five cases (one in association with reversible fetal renal failure) [302–306], while in two cases, no abnormality of the amniotic fluid was observed [307, 308]. Due to these observations, the use of trastuzumab during pregnancy requires ongoing monitoring of amniotic fluid volume and fetal renal status.

There is a single case report of exposure to lapatinib during pregnancy [309]. The patient was exposed to lapatinib for 11 weeks during the first and second trimester of pregnancy, she underwent an uncomplicated delivery of a healthy female infant, and the child was developmentally normal at 18 months of age.

The great majority of women with gestational breast cancer have ER-negative/PR-negative tumors, but patients with endocrine responsive breast cancer will be candidates for hormone therapy, either in the adjuvant setting or for the treatment of metastatic disease. The use of selective estrogen receptor modulators (SERMs) such as tamoxifen during pregnancy is generally avoided as these compounds have been associated with vaginal bleeding, spontaneous abortion, birth defects and fetal death. Concerns about the use of tamoxifen in pregnancy are based on animal studies showing an increase in the incidence of abnormalities of the genital tract [310, 311] and irregular ossification of the ribs in rats [312]. In pregnant rats, tamoxifen has been associated with breast cancer in female offspring. About 50 cases of tamoxifen use during pregnancy are reported (reviewed in ref. [313]). Eight pregnancies resulted in early termination of pregnancy, 19 in healthy babies [314, 315], but 10 additional had fetal or neonatal disorders (two congenital craniofacial defects). Other rare abnormalities, such as Goldenhar's syndrome [316] and ambiguous genitalia [317] were also described. In addition, the long-term effects of tamoxifen, and whether it may increase gynecological cancers in daughters (as diethylstilbestrol does) are unknown. For women who require hormone therapy, the usual practice is to defer these agents until after delivery [318]. Data from the French National Cancer Centers (FNCLCC) showed that delayed adjuvant tamoxifen significantly improved overall survival, therefore delaying it in pregnant women seems an acceptable policy [319]. In this trial, women with early breast cancer were randomized to receive tamoxifen or placebo more than 2 years after completion of the primary treatment with surgery and chemotherapy.

Antiemetics, including promethazine (Phenergan), ondansetron [320], and droperidol combined with diphenhydramine or dexamethasone are often used to treat nausea and vomiting in pregnant women, and are generally considered safe. However, long-term dexamethasone therapy should be avoided, if possible, as chronic administration appears to increase the risk of preterm delivery due to premature rupture of membranes [321]. There may also be a slightly increased risk of oral clefts when the drugs are administered before 10 weeks of gestation [322, 323].

Although there are no randomized trials evaluating the use of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) in pregnant women, these agents are safe in the treatment of neonatal neutropenia and/or sepsis [324, 325]. Safe use of G-CSF (and recombinant

erythropoietin) in human pregnancy has been reported [326, 327].

The timing of delivery should be carefully considered in relation to chemotherapy administration. Ideally, the delivery should occur following the mother's WBC nadir to reduce the risk of infectious complications and excess bleeding from thrombocytopenia. The child should be delivered after fetal pulmonary maturity and at 34 or more weeks of gestation, at which time morbidity is relatively low.

In summary, the management of pregnancy-related breast cancer should not differ from that of nonpregnant women, with the exception of some restriction in the use of staging procedures and chemotherapies to avoid fetal risk. Radiotherapy and endocrine treatment as well as the use of antibodies and newer substances should be postponed until after delivery.

27.15 Pregnancy After Breast Cancer

Cancer survivors are often fearful that their history of cancer or its treatment will have an adverse impact on their offspring by placing them at risk for malignancy, congenital anomalies, or impaired growth and development. They are also concerned about the risks of cancer recurrence, infertility, miscarriage, and achieving a successful pregnancy outcome.

Because of the lack of data concerning breast cancer survivors, reports about pregnancy outcomes in adult survivors of childhood and adolescent cancers provide additional information [328–332]. Overall observed rates of fetal malformations (ranging from 0% to 3% minor congenital anomalies) are similar to the expected rates in offspring of the general population. Reassurance is provided by two large international cohort studies in the United States and Denmark involving almost 25,000 childhood cancer survivors who gave birth to or fathered children. In the United States series, genetic abnormalities were reported in 157 of the 4214 (3.7%) offsprings of childhood cancer survivors in contrast to 95 (4.1%) of the 2339 children of sibling controls. Similar findings were reported in the Danish series, providing further observations that cancer therapies do not confer a greater risk of inherited genetic disease in the offspring [333]. Despite the generally favorable results of pregnancy outcomes in women who have undergone chemotherapy, long-term follow-up of these offspring is limited [334]. Whether there are late cognitive or developmental abnormalities is not clear at the moment. It is encouraging that 42 children of 35 women treated for Hodgkin's disease have shown no unusual sequelae at a median follow-up time of 11 years. Concerns about an increased risk of cancer in the offspring may be relieved by data from the Five Center Study, showing that the risk of cancer in the offspring of chemotherapy-treated children and adolescents was not significantly greater than the risk observed in controls or in the general population [332].

The fear that pregnancy and all related hormonal changes subsequent to breast cancer treatment would result in activation of dormant micrometastases has not been substantiated in the literature, despite a clear link between female sex hormones and mammary carcinogenesis. Published series have, in fact, shown either no impact on survival or a slightly protective effect when women deliver after breast cancer treatment [335]. In one of these series, 94 women with early-stage disease who became pregnant after breast cancer were compared to 188 breast cancer survivors without subsequent pregnancies matched for nodal status, tumor size, age, year of diagnosis and duration of disease-free survival [219]. The risk ratio for death was significantly lower (0.44) for women who became pregnant subsequent to the diagnosis of breast cancer as compared to women with breast cancer who did not have a subsequent pregnancy. The Finnish Cancer Registry reported that among 2,536 breast cancer patients under 40 years of age, 91 women delivered a child 10 months or more after the breast cancer diagnosis. The survival rates of these women were compared to controls with no deliveries matched for stage, age, and year of breast cancer diagnosis, and who had survived at least the interval between diagnosis and delivery of the case patient. The relative risk of death was 4.8 for the controls (95% C.I. 2.2–10.3) compared to the women who had delivered a child, and survival rates at 10 years were significantly superior for the latter group (92 vs. 60%) [336]. Although these data could reflect selection bias, they are also consistent with a possible antitumor effect of the pregnancy. As the patients were matched for nodal status, tumor size and early-stage disease, a "healthy mother effect" (only patients feeling well with a good prognosis conceive and therefore show improved survival) is unlikely to be the explanation for the findings. Other authors are more cautious in the interpretation of the available data and conclude that the effect of subsequent pregnancy on breast cancer

prognosis and outcome is still unclear. The Danish Breast Cancer Cooperative Group [337] evaluated 5,725 women with primary breast cancer, aged 45 years or younger at the time of diagnosis. Among these women, only 173 became pregnant after breast cancer therapy. These women had a nonsignificantly reduced risk of death (relative risk 0.55, 95% C.I. 0.28–1.06) when compared with controls, adjusting for age and tumor stage, who had not had a pregnancy.

There are only few data regarding the influence of the interval between breast cancer diagnosis and pregnancy on survival [336, 338]. In several studies, patients who delay pregnancy more than 2 years after breast cancer diagnosis experience an enhanced survival compared to patients with shorter diagnosis-to-pregnancy intervals (<6 months) [339, 340]. The survival advantage seen in patients with longer-delayed pregnancy is not necessarily caused by the longer disease-free survival before pregnancy [338]. Physicians generally advise women to wait for at least 2 years before attempting pregnancy. The primary reason for this recommendation is that most recurrences of breast cancer occur within the first 2 years after initial diagnosis and treatment.

There are few concerns with regard to treatment and conception. As an example, the half-life of methotrexate is approximately 8–15 h and it is retained for several weeks to months in the kidney and liver, respectively. Delaying conception at least 12 weeks after stopping methotrexate has been recommended [341].

Most women who have undergone irradiation for breast cancer are able to produce milk in the affected side, the amount being frequently less than that in a nonirradiated breast, particularly if the lumpectomy site was close to the areolar complex or transected many ducts [342, 343]. However, when breast milk is produced, breast feeding from the irradiated breast is often not advisable because of the difficulties for the treatment of a possible mastitis [344]. In a retrospective survey, 11 women who experienced 13 pregnancies after breast cancer treatment were interviewed [345]. All patients reported little or no swelling of the treated breast during pregnancy. After delivery, lactation from the treated breast was possible in four instances, absent in six, and pharmacologically suppressed in three. One patient successfully breast-fed from the treated breast for 4 months. In the majority of cases, breastfeeding from the untreated breast was successful.

Beside breast cancer and benign tumors, the majority of breast surgery is performed in a fertile age. Theoretically, reduction mammaplasty and augmentation should not impair the ability to nurse, as long as there is no free transplantation of the mamilla-areola complex or an ablation of the breast gland. The average frequency of nursing after reduction mammaplasty in five studies was about 31% [346].

27.16 Psychosocial, Familial and Professional Aspects

Younger women with breast cancer experience higher levels of anxiety and depression, more psychological and financial distress, and more problems related to their psychosocial roles than older women [151, 347], The effects of a breast cancer diagnosis on interpersonal and family relations were assessed in a review of multiple studies. Age does not appear to have a direct relationship to husbands' adjustments, but younger husbands reported more problems carrying out domestic roles and a greater number of life stresses than older husbands. Studies on the impact of breast cancer on children are limited in number and scope but indicate that the effects of their mother's breast cancer vary according to the developmental level of the child [348]. A cross-sectional study used quantitative and qualitative methods to examine coping strategies used by 201 women who were aged 50 years or younger and were 6 months to 3.5 years after the diagnosis [21]. The coping strategies most frequently used were positive cognitive restructuring, wishful thinking, and making changes. For example, social support was helpful in dealing with anger or depression, whereas positive cognitive restructuring was more helpful for concerns about the future. Analyses also confirmed that most coping strategies cited in commonly administered coping scales were used frequently by these women. However, several other coping strategies were also deemed valuable, including engaging in physical activity, using meditations, and resting. These findings suggest that clinicians should identify patients' particular stressors and help with coping techniques targeting particular concerns.

In a survey conducted in 252 breast and endometrial cancer survivors, all women reported good adjustment to having had cancer, with an average of 3.7 years

since treatment completion [349]. Most differences in psychosocial adjustement between the groups were small, but younger survivors reported significantly worse adaptation than older survivors, as measured by the Hospital Anxiety and Depression Scale (HADS, $p < 0.0001$), Appearance-Orientation Scale (AOS, body image; $p = 0.02$), Fear of Recurrence ($p < 0.0001$), Distress about Long-term Treatment-Related Cancer Problems ($p = 0.01$), and Number of Sexual Problems Attributed to Cancer ($p < 0.0001$).

To date, only sparse information about fertility-related psychosocial aspects in cancer patients is available. In general, healthy women with fertility problems seem to show a higher prevalence of negative emotions than women who conceived [350]. In cancer patients, fertility-related psychosocial issues/problems comprise uncertainty about the degree of damage and anxiety of potential side effects of treatment on pregnancy and offspring, as well as potential genetic inheritance of cancer risk [151, 351]. Nevertheless, the desire for pregnancy and motherhood is an important issue for many cancer patients [189]. First investigations in this field show that breast cancer survivors who had successful pregnancies after treatment reported that it helped them to normalise their life and their transition to wellness, and having children improved their quality of life [352].

27.17 In Conclusion

- Young women have, in general, more advanced cancer at presentation.
- Preserving fertility is frequently an important issue for younger female cancer survivors and their partners.
- Management of pregnancy- related breast cancer should not substantially differ from that of nonpregnant women.
- Pregnancy after breast cancer seems to be safe.
- Tailored long-term follow-up should be warranted.
- Younger women may need special psychosocial support.

Breast cancer in young women is challenging in several aspects as medical, psychological, social issues, and the care for these patients need to take into account the peculiarities of this population.

References

1. Ries L, Melbert D, Krapcho M, Stinchcomb D, Howlader N, Horner M, et al SEER Cancer Statistics Review, 1975–2005, National Cancer Institute. Bethesda, MD. 2008. http://seer-cancergov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site 2008
2. Bouchardy C, Fioretta G, Verkooijen HM, Vlastos G, Schaefer P, Delaloye JF, et al Recent increase of breast cancer incidence among women under the age of forty. Br J Cancer. 2007 Jun 4;96(11):1743–6
3. WHO World health organization.Mortality database. <http://www-depdbiarcfr/who>. Accessed 20.11.2007
4. NBCC, National Breast Cancer Coalition. Facts about breast cancer in the United States: Year 2007. <http://wwwstop-breastcancerorg/bin/indexasp?Strid=427&depid=9&nid=2>. Accessed 24.11.2007
5. Albain KS, Allred DC, Clark GM. Breast cancer outcome and predictors of outcome: are there age differentials? J Natl Cancer Inst. 1994;16:35–42
6. Althuis MD, Brogan DD, Coates RJ, Daling JR, Gammon MD, Malone KE, et al Breast cancers among very young premenopausal women (United States). Cancer Causes Control. 2003 Mar;14(2):151–60
7. Chung M, Chang HR, Bland KI, Wanebo HJ. Younger women with breast carcinoma have a poorer prognosis than older women. Cancer. 1996 Jan 1;77(1):97–103
8. Colleoni M, Rotmensz N, Robertson C, Orlando L, Viale G, Renne G, et al Very young women (<35 years) with operable breast cancer: features of disease at presentation. Ann Oncol. 2002 Feb;13(2):273–9
9. Maggard MA, O'Connell JB, Lane KE, Liu JH, Etzioni DA, Ko CY. Do young breast cancer patients have worse outcomes? J Surg Res. 2003 Jul;113(1):109–13
10. de la Rochefordiere A, Asselain B, Campana F, Scholl SM, Fenton J, Vilcoq JR, et al Age as prognostic factor in premenopausal breast carcinoma. Lancet. 1993 Apr 24; 341(8852):1039–43
11. Lethaby AE, Mason BH, Holdaway IM, Kay RG. Age and ethnicity as prognostic factors influencing overall survival in breast cancer patients in the Auckland region. Auckland Breast Cancer Study Group. NZ Med J. 1992 Dec 9;105(947):485–8
12. Nixon AJ, Neuberg D, Hayes DF, Gelman R, Connolly JL, Schnitt S, et al Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. J Clin Oncol. 1994 May;12(5):888–94
13. Swanson GM, Lin CS. Survival patterns among younger women with breast cancer: the effects of age, race, stage, and treatment. J Natl Cancer Inst. 1994:16:69–77
14. Vanlemmens L, Hebbar M, Peyrat JP, Bonneterre J. Age as a prognostic factor in breast cancer. Anticancer Res. 1998 May–June;18(3B):1891–6
15. Walker RA, Lees E, Webb MB, Dearing SJ. Breast carcinomas occurring in young women (<35 years) are different. Br J Cancer. 1996 Dec;74(11):1796–800

16. Barchielli A, Balzi D. Age at diagnosis, extent of disease and breast cancer survival: a population-based study in Florence, Italy. Tumori. 2000 Mar–Apr;86(2):119–23
17. Crowe JP, Jr., Gordon NH, Shenk RR, Zollinger RM, Jr., Brumberg DJ, Shuck JM. Age does not predict breast cancer outcome. Arch Surg. 1994 May;129(5):483–7; discussion 7–8
18. Gajdos C, Tartter PI, Bleiweiss IJ, Bodian C, Brower ST. Stage 0 to stage III breast cancer in young women. J Am Coll Surg. 2000 May;190(5):523–9
19. Kroman N, Jensen MB, Wohlfahrt J, Mouridsen HT, Andersen PK, Melbye M. Factors influencing the effect of age on prognosis in breast cancer: population-based study. BMJ (Clinical Research ed.) 2000 Feb 19;320(7233): 474–8
20. Richards MA, Gregory WM, Smith P, Millis RR, Fentiman IS, Rubens RD. Age as prognostic factor in premenopausal breast cancer. Lancet. 1993 Jun 5;341(8858):1484–5
21. Manuel JC, Burwell SR, Crawford SL, Lawrence RH, Farmer DF, Hege A, et al Younger women's perceptions of coping with breast cancer. Cancer Nurs. 2007 Mar–Apr; 30(2):85–94
22. Tai P, Cserni G, Van De Steene J, Vlastos G, Voordeckers M, Royce M, et al Modeling the effect of age in T1–2 breast cancer using the SEER database. BMC Cancer. 2005;5:130
23. Musolino A, Bella MA, Bortesi B, Michiara M, Naldi N, Zanelli P, et al BRCA mutations, molecular markers, and clinical variables in early-onset breast cancer: a population-based study. Breast. 2007;16(3):280–92
24. Peto J, Collins N, Barfoot R, Seal S, Warren W, Rahman N, et al Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. J Natl Cancer Inst. 1999 June 2;91(11):943–9
25. Robson M, Gilewski T, Haas B, Levin D, Borgen P, Rajan P, et al BRCA-associated breast cancer in young women. J Clin Oncol. 1998 May 1;16(5):1642–9
26. Turchetti D, Cortesi L, Federico M, Bertoni C, Mangone L, Ferrari S, et al BRCA1 mutations and clinicopathological features in a sample of Italian women with early-onset breast cancer. Eur J Cancer. 2000;36(16):2083–9
27. Armes JE, Trute L, White D, Southey MC, Hammet F, Tesoriero A, et al Distinct molecular pathogeneses of early-onset breast cancers in BRCA1 and BRCA2 mutation carriers: a population-based study. Cancer Res. 1999 Apr 15; 59(8):2011–7
28. Fackenthal JD, Olopade OI. Breast cancer risk associated with BRCA1 and BRCA2 in diverse populations. Nat Rev. 2007 Dec;7(12):937–48
29. Bernstein L. Epidemiology of endocrine-related risk factors for breast cancer. J Mammary Gland Biol Neoplasia. 2002 Jan;7(1):3–15
30. Pike MC, Henderson BE, Krailo MD, Duke A, Roy S. Breast cancer in young women and use of oral contraceptives: possible modifying effect of formulation and age at use. Lancet. 1983 Oct 22;2(8356):926–30
31. Ursin G, Ross RK, Sullivan-Halley J, Hanisch R, Henderson B, Bernstein L. Use of oral contraceptives and risk of breast cancer in young women. Breast Cancer Res Treat. 1998; 50(2):175–84
32. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet. 1996 June 22;347(9017): 1713–27
33. Hankinson SE, Colditz GA, Manson JE, Willett WC, Hunter DJ, Stampfer MJ, et al A prospective study of oral contraceptive use and risk of breast cancer (Nurses' Health Study, United States). Cancer Causes Control. 1997 Jan; 8(1): 65–72
34. Hannaford PC, Selvaraj S, Elliott AM, Angus V, Iversen L, Lee AJ. Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study. BMJ (Clinical Research ed.) 2007 Sept 29;335(7621):651
35. Marchbanks PA, McDonald JA, Wilson HG, Folger SG, Mandel MG, Daling JR, et al Oral contraceptives and the risk of breast cancer. N Eng J Med. 2002 Jun 27;346(26): 2025–32
36. Figueiredo JC, Bernstein L, Capanu M, Malone KE, Lynch CF, Anton-Culver H, et al Oral contraceptives, postmenopausal hormones, and risk of asynchronous bilateral breast cancer: the WECARE Study Group. J Clin Oncol. 2008 Mar 20;26(9):1411–8
37. Bermejo-Pérez M, Márquez-Calderón S, Llanos-Méndez A. Effectiveness of preventive interventions in BRCA1/2 gene mutation carriers: a systematic review. Int J Cancer. 2007;121(2):225–31
38. Colditz GA, Feskanich D, Chen WY, Hunter DJ, Willett WC. Physical activity and risk of breast cancer in premenopausal women. Br J Cancer. 2003 Sep 1;89(5):847–51
39. Key TJ, Pike MC. The role of oestrogens and progestagens in the epidemiology and prevention of breast cancer. Eur J Cancer Clin Oncol. 1988 Jan;24(1):29–43
40. van den Brandt PA, Spiegelman D, Yaun SS, Adami HO, Beeson L, Folsom AR, et al Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol. 2000 Sep 15;152(6):514–27
41. Trichopoulos D. Hypothesis: does breast cancer originate in utero? Lancet. 1990 Apr 21;335(8695):939–40
42. Schernhammer ES. In-utero exposures and breast cancer risk: joint effect of estrogens and insulin-like growth factor? Cancer Causes Control. 2002 Aug;13(6):505–8
43. Michels KB, Trichopoulos D, Robins JM, Rosner BA, Manson JE, Hunter DJ, et al Birthweight as a risk factor for breast cancer. Lancet. 1996 Dec 7;348(9041): 1542–6
44. Panagiotopoulou K, Katsouyanni K, Petridou E, Garas Y, Tzonou A, Trichopoulos D. Maternal age, parity, and pregnancy estrogens. Cancer Causes Control. 1990 Sep;1(2): 119–24
45. Carmichael A, Sami AS, Dixon JM. Breast cancer risk among the survivors of atomic bomb and patients exposed to therapeutic ionizing radiation. Eur J Surg Oncol. 2003 June; 29(5):475–9
46. Land CE, Tokunaga M, Koyama K, Soda M, Preston DL, Nishimori I, et al Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1990. Radiat Res. 2003 Dec;160(6):707–17
47. Pukkala E, Kesminiene A, Poliakov S, Ryzhov A, Drozdovitch V, Kovgan L, et al Breast cancer in Belarus and Ukraine after the Chernobyl accident. Int J Cancer. 2006 Aug 1;119(3):651–8

48. Guibout C, Adjadj E, Rubino C, Shamsaldin A, Grimaud E, Hawkins M, et al Malignant breast tumors after radiotherapy for a first cancer during childhood. J Clin Oncol. 2005 Jan 1;23(1):197–204
49. Kenney LB, Yasui Y, Inskip PD, Hammond S, Neglia JP, Mertens AC, et al Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. Ann Intern Med. 2004 Oct 19;141(8):590–7
50. Korenman SG. The endocrinology of breast cancer. Cancer. 1980 Aug 15;46(4 Suppl):874–8
51. Agnese DM, Yusuf F, Wilson JL, Shapiro CL, Lehman A, Burak WE Jr. Trends in breast cancer presentation and care according to age in a single institution. Am J Surg. 2004 Oct;188(4):437–9
52. Foxcroft LM, Evans EB, Porter AJ. The diagnosis of breast cancer in women younger than 40. Breast (Edinburgh, Scotland). 2004 Aug;13(4):297–306
53. Di Nubila B, Cassano E, Urban LABD, Fedele P, Abbate F, Maisonneuve P, et al Radiological features and pathological-biological correlations in 348 women with breast cancer under 35 years old. Breast. 2006;15(6):744–53
54. Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27, 825 patient evaluations. Radiology. 2002 Oct;225(1):165–75
55. Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, et al American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA: Cancer J Clin. 2007 Mar–Apr;57(2):75–89
56. Ashley S, Royle GT, Corder A, Herbert A, Guyer PB, Rubin CM, et al Clinical, radiological and cytological diagnosis of breast cancer in young women. Br J Surg. 1989 Aug; 76(8):835–7
57. Ballard-Barbash R, Taplin SH, Yankaskas BC, Ernster VL, Rosenberg RD, Carney PA, et al Breast Cancer Surveillance Consortium: a national mammography screening and outcomes database. Am J Roentgenol. 1997 Oct 1;169(4): 1001–8
58. Buist DSM, Porter PL, Lehman C, Taplin SH, White E. Factors Contributing to Mammography Failure in Women Aged 40–49 Years. J Natl Cancer Inst. 2004 October 6; 96(19):1432–40
59. Dubsky PC, Gnant MF, Taucher S, Roka S, Kandioler D, Pichler-Gebhard B, et al Young age as an independent adverse prognostic factor in premenopausal patients with breast cancer. Clin Breast Cancer. 2002 Apr;3(1):65–72
60. Marcus JN, Watson P, Page DL, Narod SA, Lenoir GM, Tonin P, et al Hereditary breast cancer: pathobiology, prognosis, and BRCA1 and BRCA2 gene linkage. Cancer. 1996 Feb 15;77(4):697–709
61. Kurtz JM, Jacquemier J, Amalric R, Brandone H, Ayme Y, Hans D, et al Why are local recurrences after breast-conserving therapy more frequent in younger patients? J Clin Oncol. 1990 Apr;8(4):591–8
62. Voogd AC, Nielsen M, Peterse JL, Blichert-Toft M, Bartelink H, Overgaard M, et al Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. J Clin Oncol. 2001;19(6):1688–97
63. Fourquet A, Campana F, Zafrani B, Mosseri V, Vielh P, Durand JC, et al Prognostic factors of breast recurrence in the conservative management of early breast cancer: a 25-year follow-up. Int J Radiat Oncol Biol Phys. 1989 Oct; 17(4):719–25
64. Elkhuizen PH, van de Vijver MJ, Hermans J, Zonderland HM, van de Velde CJ, Leer JW. Local recurrence after breast-conserving therapy for invasive breast cancer: high incidence in young patients and association with poor survival. Int J Radiat Oncol Biol Phys. 1998;40(4):859–67
65. Jobsen JJ, van der Palen J, Meerwaldt JH. The impact of age on local control in women, with pT1 breast cancer treated with conservative surgery and radiation therapy. Eur J Cancer. 2001 Oct;37(15):1820–7
66. Arriagada R, Le MG, Contesso G, Guinebretiere JM, Rochard F, Spielmann M. Predictive factors for local recurrence in 2006 patients with surgically resected small breast cancer. Ann Oncol. 2002 Sep;13(9):1404–13
67. Kroman N, Holtveg H, Wohlfahrt J, Jensen MB, Mouridsen HT, Blichert-Toft M, et al Effect of breast-conserving therapy versus radical mastectomy on prognosis for young women with breast carcinoma. Cancer. 2004;100(4): 688–93
68. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Eng J Med. 2002 Aug 22;347(8):567–75
69. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Eng J Med. 2002;347(16): 1227–32
70. Bartelink H, Horiot JC, Poortmans P, Struikmans H, Van den Bogaert W, Barillot I, et al Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Eng J Med. 2001 Nov 8;345(19): 1378–87
71. Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot JC, Jager JJ, et al Can patient-, treatment- and pathology-related characteristics explain the high local recurrence rate following breast-conserving therapy in young patients? Eur J Cancer. 2003 May;39(7):932–44
72. Bartelink H, Horiot J-C, Poortmans PM, Struikmans H, Van den Bogaert W, Fourquet A, et al Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. J Clin Oncol. 2007 August 1;25(22):3259–65
73. Radiation dose intensity study in breast cancer in young women. The Netherlands Cancer Institute. ClinicalTrials.gov Identifier:NCT00212121
74. Kroman N, Melbye M, Mouridsen HT. Prognostic influence of age at diagnosis in premenopausal breast cancer patients. Scand J Surg. 2002;91(3):305–8
75. Rapiti E, Fioretta G, Verkooijen HM, Vlastos G, Schafer P, Sappino AP, et al Survival of young and older breast cancer patients in Geneva from 1990 to 2001. Eur J Cancer. 2005 Jul;41(10):1446–52
76. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effects of chemotherapy and hormonal therapy

for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. Lancet. 2005 May 14–20; 365(9472):1687–717
77. Polychemotherapy for early breast cancer: an overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 1998 Sept 19;352(9132):930–42
78. Berry DA, Cirrincione C, Henderson IC, Citron ML, Budman DR, Goldstein LJ, et al Estrogen receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA. 2006 Apr 12;295(14):1658–67
79. Colleoni M, Bonetti M, Coates AS, Castiglione-Gertsch M, Gelber RD, Price K, et al Early start of adjuvant chemotherapy may improve treatment outcome for premenopausal breast cancer patients with tumors not expressing estrogen receptors. The International Breast Cancer Study Group. J Clin Oncol. 2000 Feb;18(3):584–90
80. Cleator S, Heller W, Coombes RC. Triple-negative breast cancer: therapeutic options. Lancet Oncol. 2007 Mar;8(3): 235–44
81. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007 May 1;109(9):1721–8
82. Rakha EA, El-Sayed ME, Green AR, Lee AH, Robertson JF, Ellis IO. Prognostic markers in triple-negative breast cancer. Cancer. 2007 Jan 1;109(1):25–32
83. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. Lancet. 2005; 365: 1687–717
84. Glas AM, Floore A, Delahaye LJ, Witteveen AT, Pover RC, Bakx N, et al Converting a breast cancer microarray signature into a high-throughput diagnostic test. BMC Genom. 2006;7:278
85. Andre F, Pusztai L. Molecular classification of breast cancer: implications for selection of adjuvant chemotherapy. Nat Clin Pract. 2006 Nov;3(11):621–32
86. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 2006 August 10;24(23):3726–34
87. Phase III randomized study of adjuvant combination chemotherapy and hormonal therapy versus adjuvant hormonal therapy alone in women with previously resected axillary node-negative breast cancer with various levels of risk for recurrence (TAILORx Trial). PDQ:NCT00310180
88. MINDACT (Microarray In Node-negative Disease may Avoid Chemotherapy): a prospective, randomized study comparing the 70-gene signature with the common clinical-pathological criteria in selecting patients for adjuvant chemotherapy in node-negative breast cancer. PDQ: NCT00433589
89. Goldhirsch A, Glick JH, Gelber RD, Coates AS, Thurlimann B, Senn HJ. Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol. 2005 Oct;16(10):1569–83
90. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thurlimann B, Senn HJ. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol. 2007 Jul; 18(7):1133–44
91. Goldhirsch A, Gelber RD, Yothers G, Gray RJ, Green S, Bryant J, et al Adjuvant therapy for very young women with breast cancer: need for tailored treatments. J Natl Cancer Inst. 2001;30:44–51
92. Colleoni M, Gelber S, Goldhirsch A, Aebi S, Castiglione-Gertsch M, Price KN, et al Tamoxifen after adjuvant chemotherapy for premenopausal women with lymph node-positive breast cancer: International Breast Cancer Study Group Trial 13–93. J Clin Oncol. 2006 Mar 20;24(9):1332–41
93. Davidson NE, O'Neill AM, Vukov AM, Osborne CK, Martino S, White DR, et al Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). J Clin Oncol. 2005 Sep 1;23(25): 5973–82
94. Arriagada R, Le MG, Spielmann M, Mauriac L, Bonneterre J, Namer M, et al Randomized trial of adjuvant ovarian suppression in 926 premenopausal patients with early breast cancer treated with adjuvant chemotherapy. Ann Oncol. 2005 Mar;16(3):389–96
95. Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N. Risk of menopause during the first year after breast cancer diagnosis. J Clin Oncol. 1999 Aug;17(8):2365–70
96. Petrek JA, Naughton MJ, Case LD, Paskett ED, Naftalis EZ, Singletary SE, et al Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: a prospective study. J Clin Oncol. 2006 Mar 1;24(7): 1045–51
97. Castiglione-Gertsch M, O'Neill A, Price KN, Goldhirsch A, Coates AS, Colleoni M, et al Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: a randomized trial. J Natl Cancer Inst. 2003 Dec 17;95(24): 1833–46
98. Ejlertsen B, Mouridsen HT, Jensen MB, Bengtsson NO, Bergh J, Cold S, et al Similar efficacy for ovarian ablation compared with cyclophosphamide, methotrexate, and fluorouracil: from a randomized comparison of premenopausal patients with node-positive, hormone receptor-positive breast cancer. J Clin Oncol. 2006 Nov 1;24(31):4956–62
99. Jakesz R, Hausmaninger H, Kubista E, Gnant M, Menzel C, Bauernhofer T, et al randomized adjuvant trial of Tamoxifen and Goserelin versus Cyclophosphamide, Methotrexate, and Fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer – Austrian Breast and Colorectal Cancer Study Group Trial 5. J Clin Oncol. 2002 December 15;20(24):4621–7
100. Jonat W, Kaufmann M, Sauerbrei W, Blamey R, Cuzick J, Namer M, et al Goserelin versus Cyclophosphamide, Methotrexate, and Fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: the Zoladex Early Breast Cancer Research Association Study. J Clin Oncol. 2002 December 15;20(24):4628–35
101. Roché H, Kerbrat P, Bonneterre J, Fargeot P, Fumoleau P, Monnier A, et al Complete hormonal blockade versus epirubicin-based chemotherapy in premenopausal, one to three node-positive, and hormone-receptor positive, early breast cancer patients: 7-year follow-up results of French

Adjuvant Study Group 06 randomized trial. Ann Oncol. 2006 Aug;17(8):1221–7
102. Roché H, Mihura J, de Lafontan B, Reme-Saumon M, Martel P, Dubois J, et al Castration and tamoxifen vs chemotherapy (FAC) for premenopausal, node and receptors positive breast cancer patients: a randomized trial with a 7 years follow-up. Proc Am Soc Clin Oncol. 1996;15:117
103. Schmid P, Untch M, Kosse V, Bondar G, Vassiljev L, Tarutinov V, et al Leuprorelin acetate every-3-months depot versus Cyclophosphamide, Methotrexate, and Fluorouracil as adjuvant treatment in premenopausal patients with node-positive breast cancer: The TABLE Study. J Clin Oncol. 2007 June 20;25(18):2509–15
104. Scottish Cancer Trials Breast Group and ICRF Breast Unit. Adjuvant ovarian ablation versus CMF chemotherapy in premenopausal women with pathological stage II breast carcinoma: the Scottish trial. Lancet. 1993;341:1293–8
105. von Minckwitz G, Graf E, Geberth M, Eiermann W, Jonat W, Conrad B, et al CMF versus goserelin as adjuvant therapy for node-negative, hormone receptor-positive breast cancer in premenopausal patients: a randomized trial (GABG trial IV-A-93). Eur J Cancer. 2006 Aug;42(12): 1780–8
106. Klijn JG, Blamey RW, Boccardo F, Tominaga T, Duchateau L, Sylvester R. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol. 2001;19(2):343–53
107. Baum M, Hackshaw A, Houghton J, Rutqvist, Fornander T, Nordenskjold B, et al Adjuvant goserelin in pre-menopausal patients with early breast cancer: results from the ZIPP study. Eur J Cancer. 2006 May;42(7):895–904
108. Robert N, Wang M, Cella D, Martino S, Tripathy D, Ingle J, et al Phase III comparison of tamoxifen versus tamoxifen with ovarian ablation in premenopausal women with axillary node-negative receptor-positive breast cancer <= 3 cm. Proc Am Soc Clin Oncol. 2003;22:5
109. Smith IE, Dowsett M, Yap YS, Walsh G, Lonning PE, Santen RJ, et al Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol. 2006 Jun 1;24(16):2444–7
110. Oktay K, Buyuk E, Libertella N, Akar M, Rosenwaks Z. Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. J Clin Oncol. 2005;23(19):4347–53
111. Oktay K, Hourvitz A, Sahin G, Oktem O, Safro B, Cil A, et al Letrozole reduces estrogen and gonadotropin exposure in women with breast cancer undergoing ovarian stimulation before chemotherapy. J Clin Endocrinol Metab. 2006 Oct;91(10):3885–90
112. Phase III randomized study of ovarian function suppression in combination with Tamoxifen versus ovarian function suppression in combination with Exemestane versus Tamoxifen alone in premenopausal women with endocrine-responsive breast cancer: SOFT/IBCSG24-02. PDQ: NCT00066690
113. Phase III randomized study of Triptorelin and Exemestane versus Triptorelin and Tamoxifen in premenopausal women with endocrine-responsive breast cancer: TEXT/IBCSG25-02. PDQ:NCT00066703
114. Tamoxifen vs. Anastrozole, alone or in combination with zoledronic acid, in premenopausal, hormone receptor-positive breast cancer patients: ABCSG-12. PDQ:NCT00295646
115. Forward DP, Cheung KL, Jackson L, Robertson JF. Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer. Br J Cancer. 2004 Feb 9;90(3):590–4
116. Torrisi R, Bagnardi V, Pruneri G, Ghisini R, Bottiglieri L, Magni E, et al Antitumour and biological effects of letrozole and GnRH analogue as primary therapy in premenopausal women with ER and PgR positive locally advanced operable breast cancer. Br J Cancer. 2007 Sep 17;97(6): 802–8
117. Dana-Farber Cancer Institute. Fulvestrant in premenopausal women with hormone receptor-positive breast cancer, 2005. ClinicalTrials.gov Identifier:NCT00146601
118. Kute T, Lack CM, Willingham M, Bishwokama B, Williams H, Barrett K, et al Development of Herceptin resistance in breast cancer cells. Cytometry Part A. 2004;57A(2): 86–93
119. Albanell J, Codony J, Rovira A, Mellado B, Gascon P. Mechanism of action of anti-HER2 monoclonal antibodies: scientific update on trastuzumab and 2C4. Adv Exp Med Biol. 2003;532:253–68
120. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Eng J Med. 2001;344(11): 783–92
121. Joensuu H, Kellokumpu-Lehtinen P-L, Bono P, Alanko T, Kataja V, Asola R, et al Adjuvant Docetaxel or Vinorelbine with or without Trastuzumab for breast cancer. N Engl J Med. 2006 February 23;354(8):809–20
122. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Eng J Med. 2005 Oct 20;353(16):1659–72
123. Robert N, Eiermann W, Pienkowski T, Crown J, Martin M, Pawlicki M, et al BCIRG 006: Docetaxel and trastuzumab-based regimens improve DFS and OS over AC-T in node-positive and high-risk node-negative HER2-positive early breast cancer patients: Quality of life (QOL) at 36 months follow-up. J Clin Oncol, 2007 ASCO Annual Meeting Proceedings Part I. 2007;Vol 25(June 20 Suppl):18S
124. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, et al Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Eng J Med. 2005;353(16):1673–84
125. Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, et al 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomized controlled trial. Lancet. 2007; 369(9555): 29–36
126. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez E, et al A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: a trial coordinated by the Eastern Cooperative Oncology Group (E2100). Breast Cancer Res Treat. 2005;94(Suppl 1):3

127. Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, et al Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol. 2005;23(4):792–9
128. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, et al Paclitaxel plus Bevacizumab versus Paclitaxel Alone for Metastatic Breast Cancer. The New England journal of medicine. 2007 December 27;357(26): 2666–76
129. Agus DB, Gordon MS, Taylor C, Natale RB, Karlan B, Mendelson DS, et al Phase I clinical study of pertuzumab, a novel HER dimerization inhibitor, in patients with advanced cancer. J Clin Oncol. 2005;23(11):2534–43
130. Cortes J, Baselga J, Kellokumpu-Lehtinen P, et al Open label, randomized, phase II study of pertuzumab (P) in patients (pts) with metastatic breast cancer (MBC) with low expression of HER2. J Clin Oncol. 2005;ASCO Annual Meeting Proceeding (Part II); 23 (1 June Suppl):3068
131. Spector NL, Xia W, Burris H 3rd, Hurwitz H, Dees EC, Dowlati A, et al Study of the biologic effects of lapatinib, a reversible inhibitor of ErbB1 and ErbB2 tyrosine kinases, on tumor growth and survival pathways in patients with advanced malignancies. J Clin Oncol. 2005;23(11):2502–12
132. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Eng J Med. 2006 Dec 28;355(26):2733–43
133. Bendell JC, Domchek SM, Burstein HJ, Harris L, Younger J, Kuter I, et al Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer. 2003;97(12):2972–7
134. Clayton AJ, Danson S, Jolly S, Ryder WD, Burt PA, Stewart AL, et al Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. Br J Cancer. 2004 Aug 16;91(4):639–43
135. Lin NU, Winer EP. Brain Metastases: The HER2 Paradigm. Clin Cancer Res. 2007 March 15;13(6):1648–55
136. Lin NU, Carey LA, Liu MC, Younger J, Come SE, Ewend M, et al Phase II trial of Lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2008 Apr 20;26(12):1993–9
137. Chan S, Scheulen ME, Johnston S, Mross K, Cardoso F, Dittrich C, et al Phase II study of temsirolimus (CCI-779), a novel inhibitor of mTOR, in heavily pretreated patients with locally advanced or metastatic breast cancer. J Clin Oncol. 2005 Aug 10;23(23):5314–22
138. Gligorov J, Azria D, Namer M, Khayat D, Spano JP. Novel therapeutic strategies combining antihormonal and biological targeted therapies in breast cancer: focus on clinical trials and perspectives. Crit Rev Oncol Hematol. 2007;64(2): 115–28
139. Arpino G, Wiechmann L, Osborne CK, Schiff R. Crosstalk between the estrogen receptor and the HER tyrosine kinase receptor family: molecular mechanism and clinical implications for endocrine therapy resistance. Endocr Rev. 2008 Apr 1;29(2):217–33
140. Osborne CK, Shou J, Massarweh S, Schiff R. Crosstalk between estrogen receptor and growth factor receptor pathways as a cause for endocrine therapy resistance in breast cancer. Clin Cancer Res. 2005 January 15;11(2):865s–70
141. Milano A, Dal Lago L, Sotiriou C, Piccart M, Cardoso F. What clinicians need to know about antioestrogen resistance in breast cancer therapy. Eur J Cancer. 2006 Nov; 42(16):2692–705
142. Peoples G, Khoo S, Dehqanzada Z, Mittendorf E, Hueman M, Gurney J, et al Combined clinical trial results of a HER2/neu (E75) vaccine for prevention of recurrence in high-risk breast cancer patients. Breast Cancer Res Treat. 2006;1:S6
143. Curigliano G, Spitaleri G, Pietri E, Rescigno M, de Braud F, Cardillo A, et al Breast cancer vaccines: a clinical reality or fairy tale? Ann Oncol. 2006 May;17(5):750–62
144. Brewer VH, Hahn KA, Rohrbach BW, Bell JL, Baddour LM. Risk factor analysis for breast cellulitis complicating breast-conservation therapy. Clin Infect Dis. 2000 Sep;31(3):654–9
145. Indelicato DJ, Grobmyer SR, Newlin H, Morris CG, Haigh LS, Copeland EM 3rd, et al Delayed breast cellulitis: an evolving complication of breast conservation. Int J Radiat Oncol Biol Phys. 2006 Dec 1;66(5):1339–46
146. Simon MS, Cody RL. Cellulitis after axillary lymph node dissection for carcinoma of the breast. Am J Med. 1992 Nov;93(5):543–8
147. Petrek JA, Peters MM, Nori S, Knauer C, Kinne DW, Rogatko A. Axillary lymphadenectomy. A prospective, randomized trial of 13 factors influencing drainage, including early or delayed arm mobilization. Arch Surg. 1990 Mar; 125(3):378–82
148. Budd DC, Cochran RC, Sturtz DL, Fouty WJ Jr. Surgical morbidity after mastectomy operations. Am J Surg. 1978 Feb;135(2):218–20
149. Jamison K, Wellisch DK, Katz RL, Pasnau RO. Phantom breast syndrome. Arch Surg. 1979 Jan;114(1):93–5
150. Ganz PA, Kwan L, Stanton AL, Krupnick JL, Rowland JH, Meyerowitz BE, et al Quality of life at the end of primary treatment of breast cancer: first results from the moving beyond cancer randomized trial. J Natl Cancer Inst. 2004 March 3;96(5):376–87
151. Knobf MT. The influence of endocrine effects of adjuvant therapy on quality of life outcomes in younger breast cancer survivors. Oncologist. 2006 Feb;11(2):96–110
152. Schover LR. Premature ovarian failure and its consequences: vasomotor symptoms, sexuality, and fertility. J Clin Oncol. 2008 February 10;26(5):753–8
153. Nystedt M, Berglund G, Bolund C, Fornander T, Rutqvist LE. Side effects of adjuvant endocrine treatment in premenopausal breast cancer patients: a prospective randomized study. J Clin Oncol. 2003 May 1;21(9):1836–44
154. Sverrisdottir A, Fornander T, Jacobsson H, von Schoultz E, Rutqvist LE. Bone mineral density among premenopausal women with early breast cancer in a randomized trial of adjuvant endocrine therapy. J Clin Oncol. 2004 September 15;22(18):3694–9
155. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, et al Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology. 2007 September 11;69(11):1074–83

156. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, et al Increased risk of parkinsonism in women who underwent oophorectomy before menopause. Neurology. 2008 January 15;70(3):200–9
157. Shapiro CL, Recht A. Side effects of adjuvant treatment of breast cancer. N Eng J Med. 2001 Jun 28;344(26): 1997–2008
158. Demark-Wahnefried W, Hars V, Conaway MR, Havlin K, Rimer BK, McElveen G, et al Reduced rates of metabolism and decreased physical activity in breast cancer patients receiving adjuvant chemotherapy. Am J Clin Nutr. 1997 May;65(5):1495–501
159. Demark-Wahnefried W, Winer EP, Rimer BK. Why women gain weight with adjuvant chemotherapy for breast cancer. J Clin Oncol. 1993 Jul;11(7):1418–29
160. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. J Clin Oncol. 1996 May;14(5):1718–29
161. Del Mastro L, Venturini M, Sertoli MR, Rosso R. Amenorrhea induced by adjuvant chemotherapy in early breast cancer patients: prognostic role and clinical implications. Breast Cancer Res Treat. 1997 Apr;43(2):183–90
162. Hortobagyi GN, Buzdar AU, Marcus CE, Smith TL. Immediate and long-term toxicity of adjuvant chemotherapy regimens containing doxorubicin in trials at M.D. Anderson Hospital and Tumor Institute. NCI Monogr. 1986;(1):105–9
163. Sainsbury JRC, Anderson TJ, Morgan DAL. ABC of breast diseases: breast cancer. BMJ (Clinical Research ed.) 2000 September 23;321(7263):745–50
164. Bentzen S, Overgaard J. Patient-to-patient variability in the expression of radiation-induced normal tissue injury. Semin Radiat Oncol. 1994 Apr;4(2):68–80
165. Lilla C, Ambrosone C, Kropp S, Helmbold I, Schmezer P, von Fournier D, et al Predictive factors for late normal tissue complications following radiotherapy for breast cancer. Breast Cancer Res Treat. 2007;106(1):143–50
166. Bird BRJH, Swain SM. Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. Clin Cancer Res. 2008 January 1;14(1):14–24
167. Jones LW, Haykowsky MJ, Swartz JJ, Douglas PS, Mackey JR. Early breast cancer therapy and cardiovascular injury. J Am Coll Cardiol. 2007 October 9;50(15):1435–41
168. Perez EA, Suman VJ, Davidson NE, Kaufman PA, Martino S, Dakhil SR, et al Effect of Doxorubicin plus Cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial. J Clin Oncol. 2004 Sept 15;22(18):3700–4
169. Hershman D, Neugut AI, Jacobson JS, Wang J, Tsai W-Y, McBride R, et al Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte colony-stimulating factors during breast cancer adjuvant chemotherapy. J Natl Cancer Inst. 2007 February 7;99(3):196–205
170. Le Deley M-C, Suzan F, Cutuli B, Delaloge S, Shamsaldin A, Linassier C, et al Anthracyclines, Mitoxantrone, radiotherapy, and granulocyte colony-stimulating factor: risk factors for leukemia and myelodysplastic syndrome after breast cancer. J Clin Oncol. 2007 January 20;25(3): 292–300
171. Smith RE, Bryant J, DeCillis A, Anderson S. acute myeloid leukemia and myelodysplastic syndrome after Doxorubicin-Cyclophosphamide adjuvant therapy for operable breast cancer: The National Surgical Adjuvant Breast and Bowel Project Experience. J Clin Oncol. 2003 Apr 1;21(7): 1195–204
172. Monroe AT, Feigenberg SJ, Price Mendenhall N. Angiosarcoma after breast-conserving therapy. Cancer. 2003;97(8):1832–40
173. Osteen RT, Cady B, Friedman M, Kraybill W, Doggett S, Hussey D, et al Patterns of care for younger women with breast cancer. J Natl Cancer Inst. 1994;16:43–6
174. Gomide LB, Matheus JPC, Candido dos Reis FJ. Morbidity after breast cancer treatment and physiotherapeutic performance. Int J Clin Pract. 2007;61(6):972–82
175. Purushotham AD, Bennett Britton TM, Klevesath MB, Chou P, Agbaje OF, Duffy SW. Lymph node status and breast cancer-related lymphedema. Ann Surg. 2007 Jul; 246(1):42–5
176. van der Veen P, De Voogdt N, Lievens P, Duquet W, Lamote J, Sacre R. Lymphedema development following breast cancer surgery with full axillary resection. Lymphology. 2004 Dec;37(4):206–8
177. Pain SJ, Purushotham AD. Lymphoedema following surgery for breast cancer. Br J Surg. 2000 Sep;87(9): 1128–41
178. Perbeck L, Celebioglu F, Svensson L, Danielsson R. Lymph circulation in the breast after radiotherapy and breast conservation. Lymphology. 2006 Mar;39(1):33–40
179. Senkus-Konefka E, Jassem J. Complications of breast-cancer radiotherapy. Clin Oncol (Royal College of Radiologists (Great Britain)). 2006 Apr;18(3):229–35
180. Khatcheressian JL, Wolff AC, Smith TJ, Grunfeld E, Muss HB, Vogel VG, et al American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. 2006 Nov 1;24(31):5091–7
181. National Comprehensive Cancer Network. Clinical practice guidelines in oncology, 2007. http://www.nccn.org
182. US Preventive Services Task Force. Genetic risk assessment and brca/BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation statement. Ann Intern Med. 2005 Sept 6;143(5):355–61
183. Elmore JG, Barton MB, Moceri VM, Polk S, Arena PJ, Fletcher SW. Ten-year risk of false positive screening mammograms and clinical breast examinations. N Engl J Med. 1998 Apr 16;338(16):1089–96
184. Roche N. Follow-up after treatment for breast cancer in young women. Breast (Edinburgh, Scotland). 2006 Dec; 15(Suppl 2):S71–5
185. Krychman ML, Stelling CJ, Carter J, Hudis CA. A case series of androgen use in breast cancer survivors with sexual dysfunction. J Sexual Med. 2007;4(6):1769–74
186. Hayes DF. Follow-up of patients with early breast cancer. N Engl J Med. 2007 June 14;356(24):2505–13
187. Schover LR. Psychosocial aspects of infertility and decisions about reproduction in young cancer survivors: a review. Med Pediatr Oncol. 1999 Jul;33(1):53–9
188. Wenzel L, Dogan-Ates A, Habbal R, Berkowitz R, Goldstein DP, Bernstein M, et al Defining and measuring

reproductive concerns of female cancer survivors. J Natl Cancer Inst. 2005;34:94–8
189. Partridge AH, Gelber S, Peppercorn J, Sampson E, Knudsen K, Laufer M, et al Web-based survey of fertility issues in young women with breast cancer. J Clin Oncol. 2004 Oct 15;22(20):4174–83
190. Ganz PA, Greendale GA, Petersen L, Kahn B, Bower JE. Breast cancer in younger women: reproductive and late health effects of treatment. J Clin Oncol. 2003 Nov 15; 21(22):4184–93
191. Thewes B, Meiser B, Taylor A, Phillips KA, Pendlebury S, Capp A, et al Fertility- and menopause-related information needs of younger women with a diagnosis of early breast cancer. J Clin Oncol. 2005 Aug 1;23(22):5155–65
192. Braun M, Hasson-Ohayon I, Perry S, Kaufman B, Uziely B. Motivation for giving birth after breast cancer. Psycho-Oncol. 2005;14(4):282–96
193. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, et al American Society of Clinical Oncology Recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006 June 20;24(18):2917–31
194. Coulam C. Neuroendocrinology and ovarian function. In: Scott JR, DiSaia PJ, Hammond CB, et al, editors.Danforth's obstetrics and gynecology. 6th ed. Philadelphia, PA: Lippincott, 1990. p.57–73
195. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. J Clin Oncol. 2006 Dec 20;24(36):5769–79
196. Parulekar WR, Day AG, Ottaway JA, Shepherd LE, Trudeau ME, Bramwell V, et al Incidence and prognostic impact of amenorrhea during adjuvant therapy in high-risk premenopausal breast cancer: analysis of a National Cancer Institute of Canada Clinical Trials Group Study – NCIC CTG MA.5. J Clin Oncol. 2005 Sept 1;23(25):6002–8
197. Stearns V, Schneider B, Henry NL, Hayes DF, Flockhart DA. Breast cancer treatment and ovarian failure: risk factors and emerging genetic determinants. Nat Rev. 2006 Nov;6(11):886–93
198. Sutton R, Buzdar AU, Hortobagyi GN. Pregnancy and offspring after adjuvant chemotherapy in breast cancer patients. Cancer. 1990 Feb 15;65(4):847–50
199. Blumenfeld Z, Avivi I, Linn S, Epelbaum R, Ben-Shahar M, Haim N. Prevention of irreversible chemotherapy-induced ovarian damage in young women with lymphoma by a gonadotrophin-releasing hormone agonist in parallel to chemotherapy. Hum Reprod (Oxford, England). 1996 Aug;11(8):1620–6
200. Waxman J. Preserving fertility in Hodgkin's disease. Baillieres Clin Haematol. 1987 Mar;1(1):185–90
201. Behringer K, Breuer K, Reineke T, May M, Nogova L, Klimm B, et al Secondary amenorrhea after Hodgkin's lymphoma is influenced by age at treatment, stage of disease, chemotherapy regimen, and the use of oral contraceptives during therapy: a report from the German Hodgkin's Lymphoma Study Group. J Clin Oncol. 2005 Oct 20; 23(30):7555–64
202. Chapman RM, Sutcliffe SB. Protection of ovarian function by oral contraceptives in women receiving chemotherapy for Hodgkin's disease. Blood. 1981 Oct;58(4):849–51
203. Oktay K. Further evidence on the safety and success of ovarian stimulation with letrozole and tamoxifen in breast cancer patients undergoing in vitro fertilization to cryopreserve their embryos for fertility preservation. J Clin Oncol. 2005 Jun 1;23(16):3858–9
204. Oktay K, Cil AP, Bang H. Efficiency of oocyte cryopreservation: a meta-analysis. Fertil Steril. 2006 Jul;86(1): 70–80
205. Borini A, Bianchi V, Bonu MA, Sciajno R, Sereni E, Cattoli M, et al Evidence-based clinical outcome of oocyte slow cooling. Reprod Biomed Online. 2007 Aug;15(2):175–81
206. Kuwayama M. Highly efficient vitrification for cryopreservation of human oocytes and embryos: the Cryotop method. Theriogenology. 2007 Jan 1;67(1):73–80
207. Meirow D, Baum M, Yaron R, Levron J, Hardan I, Schiff E, et al Ovarian tissue cryopreservation in hematologic malignancy: ten years' experience. Leukemia Lymphoma. 2007 Aug;48(8):1569–76
208. Poirot C, Vacher-Lavenu MC, Helardot P, Guibert J, Brugieres L, Jouannet P. Human ovarian tissue cryopreservation: indications and feasibility. Hum Reprod (Oxford, England). 2002 June;17(6):1447–52
209. Newton H. The cryopreservation of ovarian tissue as a strategy for preserving the fertility of cancer patients. Human reproduction update. 1998 May–June;4(3):237–47
210. Oktay K, Karlikaya G. Ovarian function after transplantation of frozen, banked autologous ovarian tissue. N Eng J Med. 2000 Jun 22;342(25):1919
211. Oktay K, Buyuk E, Rosenwaks Z, Rucinski J. A technique for transplantation of ovarian cortical strips to the forearm. Fertil Steril. 2003 Jul;80(1):193–8
212. Oktay K, Buyuk E, Veeck L, Zaninovic N, Xu K, Takeuchi T, et al Embryo development after heterotopic transplantation of cryopreserved ovarian tissue. Lancet. 2004 Mar 13;363(9412):837–40
213. Radford JA, Lieberman BA, Brison DR, Smith AR, Critchlow JD, Russell SA, et al Orthotopic reimplantation of cryopreserved ovarian cortical strips after high-dose chemotherapy for Hodgkin's lymphoma. Lancet. 2001 Apr 14;357(9263):1172–5
214. Tryde Schmidt KL, Yding Andersen C, Starup J, Loft A, Byskov AG, Nyboe Andersen A. Orthotopic autotransplantation of cryopreserved ovarian tissue to a woman cured of cancer - follicular growth, steroid production and oocyte retrieval. Reprod Biomed Online. 2004 Apr;8(4):448–53
215. Donnez J, Dolmans MM, Demylle D, Jadoul P, Pirard C, Squifflet J, et al Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet. 2004 364(9443): 1405–10
216. Meirow D, Levron J, Eldar-Geva T, Hardan I, Fridman E, Zalel Y, et al Pregnancy after transplantation of cryopreserved ovarian tissue in a patient with ovarian failure after chemotherapy. N Engl J Med. 2005 Jul 21;353(3): 318–21
217. Kim SS, Radford J, Harris M, Varley J, Rutherford AJ, Lieberman B, et al Ovarian tissue harvested from lymphoma patients to preserve fertility may be safe for autotransplantation. Hum Reprod (Oxford, England). 2001 Oct;16(10):2056–60
218. Sonmezer M, Shamonki MI, Oktay K. Ovarian tissue cryopreservation: benefits and risks. Cell Tissue Res. 2005 Oct;322(1):125–32
219. Gelber S, Coates AS, Goldhirsch A, Castiglione-Gertsch M, Marini G, Lindtner J, et al Effect of pregnancy on overall

survival after the diagnosis of early stage breast cancer. J Clin Oncol. 2001 Mar 15;19(6):1671–5
220. Loibl S, Kohl J, Kaufmann M. Reproduction after breast cancer: what advice do we have for our patients? Zentralbl Gynakol. 2005 Jun;127(3):120–4
221. Antonelli NM, Dotters DJ, Katz VL, Kuller JA. Cancer in pregnancy: a review of the literature. Part II. Obstet Gynecol Surv. 1996 Feb;51(2):135–42
222. Antonelli NM, Dotters DJ, Katz VL, Kuller JA. Cancer in pregnancy: a review of the literature. Part I. Obstet Gynecol Surv. 1996 Feb;51(2):125–34
223. Berry DL, Theriault RL, Holmes FA, Parisi VM, Booser DJ, Singletary SE, et al Management of breast cancer during pregnancy using a standardized protocol. J Clin Oncol. 1999 Mar;17(3):855–61
224. Wallack MK, Wolf JA Jr, Bedwinek J, Denes AE, Glasgow G, Kumar B, et al Gestational carcinoma of the female breast. Curr Probl Cancer. 1983 Mar;7(9):1–58
225. Anderson BO, Petrek JA, Byrd DR, Senie RT, Borgen PI. Pregnancy influences breast cancer stage at diagnosis in women 30 years of age and younger. Ann Surg Oncol. 1996 Mar;3(2):204–11
226. Albrektsen G, Heuch I, Kvale G. The short-term and long-term effect of a pregnancy on breast cancer risk: a prospective study of 802, 457 parous Norwegian women. Br J Cancer. 1995 Aug;72(2):480–4
227. Lambe M, Hsieh C, Trichopoulos D, Ekbom A, Pavia M, Adami HO. Transient increase in the risk of breast cancer after giving birth. N Eng J Med. 1994 Jul 7;331(1):5–9
228. Wohlfahrt J, Andersen PK, Mouridsen HT, Melbye M. Risk of late-stage breast cancer after a childbirth. Am J Epidemiol. 2001 Jun 1;153(11):1079–84
229. Cullinane CA, Lubinski J, Neuhausen SL, Ghadirian P, Lynch HT, Isaacs C, et al Effect of pregnancy as a risk factor for breast cancer in BRCA1/BRCA2 mutation carriers. Int J Cancer. 2005 Dec 20;117(6):988–91
230. Ishida T, Yokoe T, Kasumi F, Sakamoto G, Makita M, Tominaga T, et al Clinicopathologic characteristics and prognosis of breast cancer patients associated with pregnancy and lactation: analysis of case-control study in Japan. Jpn J Cancer Res. 1992 Nov;83(11):1143–9
231. Shen T, Vortmeyer AO, Zhuang Z, Tavassoli FA. High frequency of allelic loss of BRCA2 gene in pregnancy-associated breast carcinoma. J Natl Cancer Inst. 1999 October 6;91(19):1686–7
232. Johannsson O, Loman N, Borg A, Olsson H. Pregnancy-associated breast cancer in BRCA1 and BRCA2 germline mutation carriers. Lancet. 1998 Oct 24;352(9137):1359–60
233. Saber A, Dardik H, Ibrahim IM, Wolodiger F. The milk rejection sign: a natural tumor marker. Am Surg. 1996 Dec;62(12):998–9
234. Liberman L, Giess CS, Dershaw DD, Deutch BM, Petrek JA. Imaging of pregnancy-associated breast cancer. Radiology. 1994 Apr 1;191(1):245–8
235. Ahn BY, Kim HH, Moon WK, Pisano ED, Kim HS, Cha ES, et al Pregnancy- and lactation-associated breast cancer: mammographic and sonographic findings. J Ultrasound Med. 2003 May;22(5):491–7; quiz 8–9
236. Yang WT, Dryden MJ, Gwyn K, Whitman GJ, Theriault R. Imaging of breast cancer diagnosed and treated with chemotherapy during pregnancy. Radiology. 2006 Apr 1;239(1):52–60
237. Barthelmes L, Davidson LA, Gaffney C, Gateley CA. Pregnancy and breast cancer. BMJ (Clinical Research ed.) 2005 June 11;330(7504):1375–8
238. Collins JC, Liao S, Wile AG. Surgical management of breast masses in pregnant women. J Reprod Med. 1995 Nov;40(11):785–8
239. Nicklas AH, Baker ME. Imaging strategies in the pregnant cancer patient. Semin Oncol. 2000 Dec;27(6):623–32
240. Max MH, Klamer TW. Pregnancy and breast cancer. South Med J. 1983 Sep;76(9):1088–90
241. Samuels TH, Liu FF, Yaffe M, Haider M. Gestational breast cancer. Canadian Association of Radiologists journal = Journal l'Association canadienne des radiologistes. 1998 June;49(3):172–80
242. Frank G. Shellock EK. Safety of magnetic resonance imaging contrast agents. J Mag Reson Imaging. 1999;10(3):477–84
243. Shao-Pow Lin JJB. MR contrast agents: physical and pharmacologic basics. J Magn Reson Imaging. 2007;25(5):884–99
244. Shellock FG, Crues JV. MR procedures: biologic effects, safety, and patient care. Radiology. 2004 Sep;232(3):635–52
245. Benveniste H, Fowler JS, Rooney WD, Moller DH, Backus WW, Warner DA, et al Maternal-fetal in vivo imaging: a combined PET and MRI Study. J Nucl Med. 2003 Sept 1;44(9):1522–30
246. ten Hove CH, Zijlstra-Baalbergen JM, Comans EI, van Elburg RM. An unusual hotspot in a young woman with Hodgkin's lymphoma. Haematologica. 2008 Jan 1;93(1):e14–5
247. Barker P. Milk fistula: an unusual complication of breast biopsy. J R Coll Surg Edinb. 1988 Apr;33(2):106
248. Schackmuth EM, Harlow CL, Norton LW. Milk fistula: a complication after core breast biopsy. AJR. 1993 Nov;161(5):961–2
249. Bottles K, Taylor RN. Diagnosis of breast masses in pregnant and lactating women by aspiration cytology. Obstet Gynecol. 1985 Sep;66(3 Suppl):76S–8S
250. Mitre BK, Kanbour AI, Mauser N. Fine needle aspiration biopsy of breast carcinoma in pregnancy and lactation. Acta Cytologica. 1997 July–Aug;41(4):1121–30
251. Novotny DB, Maygarden SJ, Shermer RW, Frable WJ. Fine needle aspiration of benign and malignant breast masses associated with pregnancy. Acta Cytologica. 1991 Nov–Dec; 35(6):676–86
252. Shannon J, Douglas-Jones AG, Dallimore NS. Conversion to core biopsy in preoperative diagnosis of breast lesions: is it justified by results? J Clin Pathol. 2001 Oct;54(10):762–5
253. Loibl S, von Minckwitz G, Gwyn K, Ellis P, Blohmer JU, Schlegelberger B, et al Breast carcinoma during pregnancy. Cancer. 2006;106(2):237–46
254. Stewart A, Webb K, Giles D. Malignant disease in childhood and diagnostic irradiation in utero. Lancet. 1956;2:447
255. Court Brown WM, Doll R, Hill RB. Incidence of leukaemia after exposure to diagnostic radiation in utero. Br Med J. 1960;2(5212):1539–45
256. Diamond EL, Schmerler H, Lilienfeld AM. The relationship of intra-uterine radiation to subsequent mortality and

development of leukemia in children. A prospective study. Am J Epidemiol. 1973 May;97(5):283–313
257. Delongchamp RR, Mabuchi K, Yoshimoto Y, Preston DL. Cancer mortality among atomic bomb survivors exposed in utero or as young children, October 1950–May 1992. Radiat Res. 1997 Mar;147(3):385–95
258. Puglisi F, Follador A, Minisini AM, Cardellino GG, Russo S, Andreetta C, et al Baseline staging tests after a new diagnosis of breast cancer: further evidence of their limited indications. Ann Oncol. 2005 Feb 1;16(2):263–6
259. Mazze RI, Kallen B. Reproductive outcome after anesthesia and operation during pregnancy: a registry study of 5405 cases. Am J Obstet Gynecol. 1989 Nov;161(5): 1178–85
260. Woo JC, Yu T, Hurd TC. Breast cancer in pregnancy: a literature review. Arch Surg. 2003 Jan;138(1):91–8; discussion 9
261. Kuerer HM, Gwyn K, Ames FC, Theriault RL. Conservative surgery and chemotherapy for breast carcinoma during pregnancy. Surgery. 2002 Jan;131(1):108–10
262. Ruo Redda MG, Verna R, Guarneri A, Sannazzari GL. Timing of radiotherapy in breast cancer conserving treatment. Cancer Treat Rev. 2002 Feb;28(1):5–10
263. Sprung J, Tully MJ, Ziser A. Anaphylactic reactions to Isosulfan blue dye during sentinel node lymphadenectomy for breast cancer. Anesth Analg. 2003 Apr 1;96(4): 1051–3
264. Gentilini O, Cremonesi M, Trifiro G, Ferrari M, Baio SM, Caracciolo M, et al Safety of sentinel node biopsy in pregnant patients with breast cancer. Ann Oncol. 2004 Sept 1;15(9): 1348–51
265. Keleher A, Wendt R, 3rd, Delpassand E, Stachowiak AM, Kuerer HM. The safety of lymphatic mapping in pregnant breast cancer patients using Tc-99m sulfur colloid. Breast J. 2004 Nov–Dec;10(6):492–5
266. Pandit-Taskar N, Dauer LT, Montgomery L, St. Germain J, Zanzonico PB, Divgi CR. Organ and fetal absorbed dose estimates from 99mTc-sulfur colloid lymphoscintigraphy and sentinel node localization in breast cancer patients. J Nucl Med. 2006 July 1;47(7):1202–8
267. Mondi MM, Cuenca RE, Ollila DW, Stewart JHIV, Levine EA. Sentinel lymph node biopsy during pregnancy: initial clinical experience. Ann Surgl Oncol. 2007 Jan 1;14(1): 218–21
268. Lyman GH, Giuliano AE, Somerfield MR, Benson AB, III, Bodurka DC, Burstein HJ, et al American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early stage breast cancer. J Clin Oncol. 2005 Oct 20;23(30):7703–20
269. Greskovich JF Jr, Macklis RM. Radiation therapy in pregnancy: risk calculation and risk minimization. Semin Oncol. 2000 Dec;27(6):633–45
270. Kal HB, Struikmans H. Radiotherapy during pregnancy: fact and fiction. Lancet Oncol. 2005 May;6(5):328–33
271. Antypas C, Sandilos P, Kouvaris J, Balafouta E, Karinou E, Kollaros N, et al Fetal dose evaluation during breast cancer radiotherapy. Int J Radiat Oncol Biol Phys. 1998 Mar 1; 40(4):995–9
272. Petrek JA. Breast cancer during pregnancy. Cancer. 1994 Jul 1;74(1 Suppl):518–27
273. Doll DC, Ringenberg QS, Yarbro JW. Antineoplastic agents and pregnancy. Semin Oncol. 1989 Oct;16(5):337–46
274. Germann N, Goffinet F, Goldwasser F. Anthracyclines during pregnancy: embryo-fetal outcome in 160 patients. Ann Oncol. 2004 Jan;15(1):146–50
275. Byrd BF Jr, Bayer DS, Robertson JC, Stephenson SE Jr. Treatment of breast tumors associated with pregnancy and lactation. Ann Surg. 1962 Jun;155:940–7
276. Murray CL, Reichert JA, Anderson J, Twiggs LB. Multimodal cancer therapy for breast cancer in the first trimester of pregnancy. A case report. JAMA. 1984 Nov 9;252(18):2607–8
277. Turchi JJ, Villasis C. Anthracyclines in the treatment of malignancy in pregnancy. Cancer. 1988 Feb 1;61(3): 435–40
278. Wiebe VJ, Sipila PE. Pharmacology of antineoplastic agents in pregnancy. Crit Rev Oncol Hematol. 1994 Apr; 16(2):75–112
279. Williams SF, Schilsky RL. Antineoplastic drugs administered during pregnancy. Semin Oncol. 2000 Dec; 27(6):618–22
280. Ebert U, Loffler H, Kirch W. Cytotoxic therapy and pregnancy. Pharmacol Ther. 1997;74(2):207–20
281. Zemlickis D, Lishner M, Degendorfer P, Panzarella T, Burke B, Sutcliffe SB, et al Maternal and fetal outcome after breast cancer in pregnancy. Am J Obstet Gynecol. 1992 Mar;166(3):781–7
282. Giacalone PL, Laffargue F, Benos P. Chemotherapy for breast carcinoma during pregnancy: A French national survey. Cancer. 1999;86(11):2266–72
283. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. Lancet Oncol. 2004 May;5(5):283–91
284. Ring AE, Smith IE, Jones A, Shannon C, Galani E, Ellis PA. Chemotherapy for breast cancer during pregnancy: an 18-year experience from five London teaching hospitals. J Clin Oncol. 2005 Jun 20;23(18):4192–7
285. Hahn KM, Johnson PH, Gordon N, Kuerer H, Middleton L, Ramirez M, et al Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. Cancer. 2006 Sep 15;107(6):1219–26
286. Gentilini O, Masullo M, Rotmensz N, Peccatori F, Mazzarol G, Smeets A, et al Breast cancer diagnosed during pregnancy and lactation: biological features and treatment options. Eur J Surg Oncol. 2005;31(3):232–6
287. Peccatori F, Martinelli G, Gentilini O, Goldhirsch A. Chemotherapy during pregnancy: what is really safe? Lancet Oncol. 2004;5(7):398
288. Meyer-Wittkopf M, Barth H, Emons G, Schmidt S. Fetal cardiac effects of doxorubicin therapy for carcinoma of the breast during pregnancy: case report and review of the literature. Ultrasound Obstet Gynecol. 2001 Jul;18(1):62–6
289. Achtari C, Hohlfeld P. Cardiotoxic transplacental effect of idarubicin administered during the second trimester of pregnancy. Am J Obst Gynecol. 2000 Aug;183(2):511–2
290. Peres RM, Sanseverino MT, Guimaraes JL, Coser V, Giuliani L, Moreira RK, et al Assessment of fetal risk associated with exposure to cancer chemotherapy during pregnancy: a multicenter study. Braz J Med Biol Res. 2001 Dec;34(12):1551–9
291. Reynoso EE, Huerta F. Acute leukemia and pregnancy–fatal fetal outcome after exposure to idarubicin during the second trimester. Acta Oncol. 1994;33(6):709–10
292. Siu BL, Alonzo MR, Vargo TA, Fenrich AL. Transient dilated cardiomyopathy in a newborn exposed to idarubicin and all-trans-retinoic acid (ATRA) early in the second tri-

mester of pregnancy. Int J Gynecol Cancer. 2002 July–Aug; 12(4):399–402
293. Eedarapalli P, Biswas N, Coleman M. Epirubicin for breast cancer during pregnancy: a case report. J Reprod Med. 2007 Aug;52(8):730–2
294. Karp GI, von Oeyen P, Valone F, Khetarpal VK, Israel M, Mayer RJ, et al Doxorubicin in pregnancy: possible transplacental passage. Cancer Treat Rep. 1983 Sep;67(9):773–7
295. De Santis M, Lucchese A, De Carolis S, Ferrazani S, Caruso A. Metastatic breast cancer in pregnancy: first case of chemotherapy with docetaxel. Eur J Cancer Care (Engl). 2000 Dec;9(4):235–7
296. Gainford MC, Clemons M. Breast cancer in pregnancy: are taxanes safe? Clinical Oncol (Royal College of Radiologists (Great Britain)). 2006 Mar;18(2):159
297. Gonzalez-Angulo AM, Walters RS, Carpenter RJ Jr, Ross MI, Perkins GH, Gwyn K, et al Paclitaxel chemotherapy in a pregnant patient with bilateral breast cancer. Clin Breast Cancer. 2004 Oct;5(4):317–9
298. Mendez LE, Mueller A, Salom E, Gonzalez-Quintero VH. Paclitaxel and carboplatin chemotherapy administered during pregnancy for advanced epithelial ovarian cancer. Obstet Gynecol. 2003 Nov;102(5 Pt 2):1200–2
299. Nieto Y, Santisteban M, Aramendia JM, Fernandez-Hidalgo O, Garcia-Manero M, Lopez G. Docetaxel administered during pregnancy for inflammatory breast carcinoma. Clin Breast Cancer. 2006 Feb;6(6):533–4
300. Potluri V, Lewis D, Burton GV. Chemotherapy with taxanes in breast cancer during pregnancy: case report and review of the literature. Clin Breast Cancer. 2006 Jun;7(2):167–70
301. Sood AK, Shahin MS, Sorosky JI. Paclitaxel and platinum chemotherapy for ovarian carcinoma during pregnancy. Gynecol Oncol. 2001 Dec;83(3):599–600
302. Pant S, Landon MB, Blumenfeld M, Farrar W, Shapiro CL. Treatment of breast cancer with trastuzumab during pregnancy. J Clin Oncol. 2008 March 20;26(9):1567–9
303. Bader AA, Schlembach D, Tamussino KF, Pristauz G, Petru E. Anhydramnios associated with administration of trastuzumab and paclitaxel for metastatic breast cancer during pregnancy. Lancet Oncol. 2007 Jan;8(1):79–81
304. Fanale MA, Uyei AR, Theriault RL, Adam K, Thompson RA. Treatment of metastatic breast cancer with trastuzumab and vinorelbine during pregnancy. Clinical Breast Cancer. 2005 Oct;6(4):354–6
305. Sekar R, Stone PR. Trastuzumab use for metastatic breast cancer in pregnancy. Obstet Gynecol. 2007 Aug; 110(2 Pt 2):507–10
306. Watson WJ. Herceptin (trastuzumab) therapy during pregnancy: association with reversible anhydramnios. Obstet Gynecol. 2005 Mar;105(3):642–3
307. Shrim A, Garcia-Bournissen F, Maxwell C, Farine D, Koren G. Favorable pregnancy outcome following Trastuzumab (Herceptin) use during pregnancy – case report and updated literature review. Reprod Toxicol (Elmsford, NY). 2007 June;23(4):611–3
308. Waterston AM, Graham J. Effect of adjuvant trastuzumab on pregnancy. J Clin Oncol. 2006 Jan 10;24(2): 321–2
309. Kelly H, Graham M, Humes E, Dorflinger LJ, Boggess KA, O'Neil BH, et al Delivery of a healthy baby after first-trimester maternal exposure to lapatinib. Clin Breast Cancer. 2006 Oct;7(4):339–41
310. Chamness GC, Bannayan GA, Landry LAJ, Sheridan PJ, McGuire WL. Abnormal reproductive development in rats after neonatally administered Antiestrogen (Tamoxifen). Biol Reprod. 1979 Dec 1;21(5):1087–90
311. Iguchi T, Hirokawa M, Takasugi N. Occurence of genital tract abnormalities and bladder hernia in female mice exposed neonatally to tamoxifen. Toxicology. 1986; 42(1):1–11
312. Tucker M, Adam H, Patterson J. Tamoxifen. In: Laurence DR, McLean AEM, Wetherall M, editors. Safety testing of new drugs laboratory predictions and clinical performance. Academic, London; 1984. p. 125–61 [chapter 6]
313. Barthelmes L, Gateley CA. Tamoxifen and pregnancy. Breast. 2004;13(6):446–51
314. Andreadis C, Charalampidou M, Diamantopoulos N, Chouchos N, Mouratidou D. Combined chemotherapy and radiotherapy during conception and first two trimesters of gestation in a woman with metastatic breast cancer. Gynecol Oncol. 2004 Oct;95(1):252–5
315. Isaacs RJ, Hunter W, Clark K. Tamoxifen as systemic treatment of advanced breast cancer during pregnancy–case report and literature review. Gynecol Oncol. 2001 Mar; 80(3):405–8
316. Cullins SL, Pridjian G, Sutherland CM. Goldenhar's syndrome associated with tamoxifen given to the mother during gestation. JAMA. 1994 June 22–29;271(24): 1905–6
317. Tewari K, Bonebrake RG, Asrat T, Shanberg AM. Ambiguous genitalia in infant exposed to tamoxifen in utero. Lancet. 1997 Jul 19;350(9072):183
318. Goldhirsch A, Gelber RD. Life with consequences of breast cancer: pregnancy during and after endocrine therapies. Breast. 2004;13(6):443–5
319. Delozier T, Switsers O, Genot JY, Ollivier JM, Hery M, Namer M, et al Delayed adjuvant tamoxifen: ten-year results of a collaborative randomized controlled trial in early breast cancer (TAM-02 trial). Ann Oncol. 2000 May 1;11(5):515–9
320. Einarson A, Maltepe C, Navioz Y, Kennedy D, Tan MP, Koren G. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. BJOG. 2004 Sep;111(9):940–3
321. Cowchock S. Prevention of fetal death in the antiphospholipid antibody syndrome. Lupus. 1996 Oct;5(5):467–72
322. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. Am J Med Genet. 1999 Sep 17;86(3):242–4
323. Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, et al Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology. 2000 Dec;62(6):385–92
324. Bilgin K, Yaramis A, Haspolat K, Tas MA, Gunbey S, Derman O. A randomized trial of granulocyte-macrophage colony-stimulating factor in neonates with sepsis and neutropenia. Pediatrics. 2001 Jan;107(1):36–41
325. Schibler KR, Osborne KA, Leung LY, Le TV, Baker SI, Thompson DD. A randomized, placebo-controlled trial of granulocyte colony-stimulating factor administration to newborn infants with neutropenia and clinical signs of early-onset sepsis. Pediatrics. 1998 Jul;102(1 Pt 1):6–13
326. Sangalli MR, Peek M, McDonald A. Prophylactic granulocyte colony-stimulating factor treatment for acquired chronic severe neutropenia in pregnancy. Aust NZ J Obstet Gynaecol. 2001 Nov;41(4):470–1

327. Ghosh A, Ayers KJ. Darbepoetin alfa for treatment of anaemia in a case of chronic renal failure during pregnancy–case report. Clin Exp Obstet Gynecol. 2007;34(3):193–4
328. Byrne J, Rasmussen SA, Steinhorn SC, Connelly RR, Myers MH, Lynch CF, et al Genetic disease in offspring of long-term survivors of childhood and adolescent cancer. Am J Hum Genet. 1998 Jan;62(1):45–52
329. Dodds L, Marrett LD, Tomkins DJ, Green B, Sherman G. Case-control study of congenital anomalies in children of cancer patients. BMJ (Clinical Research ed.) 1993 July 17;307(6897):164–8
330. Edgar AB, Wallace WHB. Pregnancy in women who had cancer in childhood. Eur J Cancer. 2007;43(13):1890–4
331. Li FP, Fine W, Jaffe N, Holmes GE, Holmes FF. Offspring of patients treated for cancer in childhood. J Natl Cancer Inst. 1979 May;62(5):1193–7
332. Mulvihill JJ, Myers MH, Connelly RR, Byrne J, Austin DF, Bragg K, et al Cancer in offspring of long-term survivors of childhood and adolescent cancer. Lancet. 1987 Oct 10;2(8563):813–7
333. Winther JF, Boice JD Jr, Mulvihill JJ, Stovall M, Frederiksen K, Tawn EJ, et al Chromosomal abnormalities among offspring of childhood-cancer survivors in Denmark: a population-based study. Am J Hum Genet. 2004;74(6):1282–5
334. Hensley ML, Reichman BS. Fertility and pregnancy after adjuvant chemotherapy for breast cancer. Crit Rev Oncol Hematol. 1998;28(2):121–8
335. Calhoun K, Hansen N. The effect of pregnancy on survival in women with a history of breast cancer. Breast Dis. 2005;23:81–6
336. Sankila R, Heinavaara S, Hakulinen T. Survival of breast cancer patients after subsequent term pregnancy: "healthy mother effect". Am J Obst Gynecol. 1994 Mar;170(3): 818–23
337. Kroman N, Jensen MB, Melbye M, Wohlfahrt J, Mouridsen HT. Should women be advised against pregnancy after breast-cancer treatment? Lancet. 1997 Aug 2;350(9074): 319–22
338. Harvey JC, Rosen PP, Ashikari R, Robbins GF, Kinne DW. The effect of pregnancy on the prognosis of carcinoma of the breast following radical mastectomy. Surg Gynecol Obstet. 1981 Nov;153(5):723–5
339. Clark RM, Chua T. Breast cancer and pregnancy: the ultimate challenge. Clin Oncol (Royal College of Radiologists (Great Britain)). 1989 Sept;1(1):11–8
340. Mueller BA, Simon MS, Deapen D, Kamineni A, Malone KE, Daling JR. Childbearing and survival after breast carcinoma in young women. Cancer. 2003 Sep 15;98(6):1131–40
341. Donnenfeld AE, Pastuszak A, Noah JS, Schick B, Rose NC, Koren G. Methotrexate exposure prior to and during pregnancy. Teratology. 1994 Feb;49(2):79–81
342. Wobbes T. Effect of a breast-saving procedure on lactation. The European journal of surgery = Acta Chirurgica. 1996 May;162(5):419–20
343. Findlay PA, Gorrell CR, d'Angelo T, Glatstein E. Lactation after breast radiation. Int J Radiat Oncol Biol Phys. 1988 Aug;15(2):511–2
344. Hassey KM. Pregnancy and parenthood after treatment for breast cancer. Oncol Nurs Forum. 1988 Juyl–Aug;15(4): 439–44
345. Higgins S, Haffty BG. Pregnancy and lactation after breast-conserving therapy for early stage breast cancer. Cancer. 1994 Apr 15;73(8):2175–80
346. Zimpelmann A, Kaufmann M. Breastfeeding nursing after breast surgery. Zentralbl Gynakol. 2002 Nov;124(11):525–8
347. Mor V, Malin M, Allen S. Age differences in the psychosocial problems encountered by breast cancer patients. J Natl Cancer Inst. 1994;16:191–7
348. Northouse LL. Breast cancer in younger women: effects on interpersonal and family relations. J Natl Cancer Inst. 1994;16):183–90
349. Kornblith AB, Powell M, Regan MM, Bennett S, Krasner C, Moy B, et al Long-term psychosocial adjustment of older vs younger survivors of breast and endometrial cancer. Psycho-Oncol. 2007;16(10):895–903
350. Oddens BJ, den Tonkelaar I, Nieuwenhuyse H. Psychosocial experiences in women facing fertility problems – a comparative survey. Hum Reprod (Oxford, England). 1999 Jan;14(1):255–61
351. The Ethics Committee of the American Society for Reproductive Medicine Fertility preservation and reproduction in cancer patients. Fertil Steril. 2005;83(6):1622–8
352. Dow KH. Having children after breast cancer. Cancer Pract. 1994 Nov–Dec;2(6):407–13

Psychological Support for the Breast Cancer Patient

28

Donna Greenberg

A woman confronted by the diagnosis of breast cancer faces the challenges of a life-threatening illness. The seriousness of the diagnosis, the nature of treatment, and the natural history of illness defines the challenge to coping. Each woman looks to her physician first for clarification of the medical treatment. Since treatment often requires breast surgery, a combination of chemotherapy and radiation, and antiestrogen treatment that hastens menopause, the psychological effects are different for premenopausal women married with children, women concerned about their physical attractiveness or who want to preserve fertility, and women concerned about the effect on their partners. The diagnosis has one meaning for a woman with a family history of breast cancer who suffered in her adolescence as her mother died of breast cancer, and another if she is married to a man who lost his mother to breast cancer.

The medical plan, the first method of coping, clarifies the diagnosis and formulates a medical treatment to keep the threat of malignancy at bay. For each woman, the psychological challenge depends on psychiatric history, her other burdens, and her temperament. Women tend, more than men, to seek and accept care for psychiatric and psychological needs, and psychiatry and psychology offer tools to help women cope as they go forward. The trained professional brings to the bedside of women technical skills in listening and the recognition of biological and psychological syndromes that simultaneously affect mood.

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28.1 Diagnosis

Most women are quite alarmed when a mammogram is abnormal. Anxiety persists for several weeks even when the abnormality is a false positive. The more quickly the outcome is clarified, the better [1]. With a lump in the breast or an abnormal mammogram, the radiologist's and surgeon's effort to make the diagnosis can require several procedures with unclear answers or unclear margins. The patient continues being alarmed and anxious. Delays that are minor in a healthcare system are major for each woman's alarm system. A diagnosis of in situ cancer or malignancy means that the woman may undergo a limited resection or mastectomy and consider breast reconstruction. Chemotherapy implies visible hair loss, fatigue, malaise, and menopausal symptoms. Antiestrogen medications augment menopausal symptoms. These treatments affect a woman's sexual confidence and fertility. She worries about babies not yet born, her children's risk of losing their mother, and the risk that the children themselves will be vulnerable to breast cancer.

Delay in diagnosis and guilt about delay have sometimes been associated with the patient's psychological profile. Not disclosing the breast symptom to another was a strong factor that predicted delay in diagnosis in a systematic review of factors implicated in delay. Three studies found that psychiatric history explained delay in diagnosis but one did not. Poor social support was considered significant in three of four studies [2]. Delay was also more common with older age, fewer years of education, nonwhite ethnic origin, breast symptoms other than a lump, and not attributing breast symptoms to breast cancer. Data was insufficient to judge the importance of psychological factors in delay and prognosis.

I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_28, © Springer-Verlag Berlin Heidelberg 2010

28.2 Psychological Assessment

Once a diagnosis is made, we are often asked to consult on issues of decision making, anxiety, depression, insomnia, fatigue, and adaptation. The first challenge is to hear the patient explain what the diagnosis means, what worries her, and what her burdens were before the diagnosis. Understanding her very individual considerations, age and developmental challenges, and past psychiatric history, allows us to put in context any plan. Her ability to cope is related to how recently she has become aware of the diagnosis and need for treatment. Initial shock and denial give way, with the help of medical staff and other support, to recognition that there are some emergency issues and then a marathon of medical challenges. Sometimes, emotional issues are on the back burner until the medical challenges are met. Specific worries may relate to surgical procedures, radiation treatment, and changes in body image. Standard anticancer drugs like cyclophosphamide and adriamycin cause catabolism, hair loss, weight gain and fatigue. There is a prolonged focused period of treatment and partial disability. Taxanes like paclitaxel can also add neuropathic pain and numbness. Intermittent dexamethasone used to prevent hypersensitivity and vomiting has effects on mood, sleep and weight. Depending on the patient's age, menopausal symptoms are temporary at first and then become permanent, sooner than would have occurred without treatment. Concerns about loss of control and the possibility of recurrence punctuate treatment.

28.3 Effect of Hormonal Treatment on Mood

The plan for hormonal treatment directly affects psychological status; as a woman tries to cope with serious illness, her emotions are modulated by estrogen deficiency. Women who are taking estrogen/progesterone hormone replacement usually stop abruptly at the time of diagnosis. Dysphoria, insomnia and hot flashes may also develop abruptly if the plan includes ovariectomy or leuprolide treatment. These changes come more gradually if adjuvant chemotherapy suppresses ovarian function and antiestrogen treatments are added later.

By the time women with estrogen-positive tumors are about to receive hormonal treatments, more than half have mood alterations, word finding problems and loss of libido. Tamoxifen or aromatase inhibitors are then added. In one study comparing exemestane and tamoxifen [3], exemestane caused more difficulty with sleep. Hot flashes increased in frequency for 3 months but decreased thereafter. On an average, women who took tamoxifen had more hot flashes at 1 year than women on exemestane. There was no difference in mood alteration, impaired word finding or low energy [4]. At 1 year, libido was worse with exemestane. Hot flashes tended to decrease with time with either tamoxifen or exemestane. Low energy was a problem for 75% of women. For those intolerant to tamoxifen, letrozole or exemestane has been shown to improve side effects, including mood in the short term [5].

28.4 Adherence to Hormonal Medications

Most, but not all, women adhere to the prescribed many years of antiestrogen treatment; adherence reports vary widely. Psychological support and clarification of the role of antiestrogen medications may be critical to disease outcome. Women tend to overestimate their faithfulness to a tamoxifen regimen [6]. About 23% of women taking tamoxifen failed to achieve optimal adherence of 80% days covered by filled prescriptions [7]. A 5-year course was not completed by 31%. Overall, the likelihood that a woman would continue these treatments depends on whether they have a positive view of tamoxifen at the outset and an improving view as time goes on [8]. In one study, older women were less apt to persist with tamoxifen if they had less support than needed, if they wanted more of a role in decision making, if they had no input about tamoxifen from a physician, and if they were not told about side effects in advance [9]. Many women with early-stage breast cancer who were prescribed adjuvant anastrozole may also not take it faithfully. Mean adherence over the first 12 months of therapy ranged from 82–88%; the mean adherence decreased each year, dropping to 62–79% in the third year [10].

28.5 Anxiety

Some patients have a history of anxiety disorder or phobia. Phobia of needles or claustrophobia during radiation treatment or magnetic resonance imaging can interfere with diagnosis and treatment. Some patients have a chronic tendency to expect the worst or to "catastrophize." They may always be preoccupied with planning the future and anticipating the next threat. For those with anxiety disorder, higher levels of anxiety, panic attacks and phobias prior to breast cancer anxiety itself interferes with quality of life. Loss of control is a dominant theme when prognosis is uncertain. Anxiety begins a week or a month before each scan undertaken to check the status of the illness, so that there is little peaceful time between tests. While every woman must face anxiety about new symptoms following diagnosis and seek reassurance from their physician, a subgroup may be preoccupied and unable to be reassured that new pains are not a signal of recurrent cancer. Generalized anxiety, panic disorder, or excessive worry about every physical symptom can be treated by medications and/or cognitive behavioral treatments specific for anxiety. Antidepressants, specific serotonin reuptake inhibitors, in particular, in low dose can reduce the chronic level of anxiety that a patient faces. When anxiety is chronic, antidepressants are preferred over benzodiazepines. In addition, patients can learn strategies to reduce anxious thoughts about recurrence or medical complications by relaxation, distraction, thought stopping, substitution, or other techniques of cognitive treatments. Specific cognitive behavioral techniques have been developed for anxiety disorders, and these may be modified for the conditions of cancer treatment.

28.6 Sleep

Insomnia is a major complaint of women treated for breast cancer (Table 28.1). The alarm of a new diagnosis often disrupts sleep, especially in the first few months. Subsequently, the course of estrogen deficiency may intervene with nighttime hot flashes. Anxious worry about not falling asleep is a psychophysiologic cause of insomnia; anxiety about falling asleep can prevent falling asleep. For one woman, the cascade of thoughts about sleep followed from her desire to do everything she could on behalf of getting well. If she did not fall asleep, she would not sleep well; and she felt she would be damaging her effort against cancer. This assumption and the vicious cycle was a psychophysiologic cause of insomnia. Often, anxiety about falling asleep and sleep disorder predates breast cancer.

Table 28.1 Causes of insomnia in breast cancer patients

New threat of diagnosis or recurrence
Estrogen deficiency with hot flashes
Worry about not falling asleep
Physiologic dependency on benzodiazepines
Side effects of antiemetic phenothiazines (akathisia)
Anticipatory anxiety about repeat scans
Dexamethasone treatment with chemotherapy
Caffeine, decongestants, alcohol
Sleep apnea

Several factors associated with chemotherapy can disrupt sleep. Women who have been taking benzodiazepines like lorazepam as a medication to facilitate chemotherapy and prevent nausea may have rebound insomnia when they stop hypnotics intermittently. Patients who take prochlorperazine for nausea may develop the extrapyramidal side effect, akathisia or restless legs that prevent sleep. Because nausea is so common during chemotherapy, patients often fail to mention that they are using a phenothiazine like prochlorperazine, which can unexpectedly cause restlessness. Anticipatory anxiety associated with the next scan or the next chemotherapy treatment also prevents sleep. During chemotherapy, dexamethasone to prevent delayed nausea and vomiting or early emesis with chemotherapy is another cause of insomnia. Steroids are also added to prevent hypersensitivity to taxanes. Side effects of dexamathasone to prevent delayed nausea include insomnia, agitation, and depression post-cessation [11]. Caffeine, decongestants and alcohol can also contribute to insomnia. Sleep-disordered breathing and sleep apnea must also be considered. Nocturnal oxygen desaturation may be a clue that a sleep study is needed [12–14].

Insomnia is a feature of the estrogen deficiency. About 65% of postmenopausal women treated for breast cancer have hot flashes. About three-quarters

have hot flashes in the first 10 years after their last menstrual period, and half have hot flashes even later. These are more severe in younger tamoxifen users who had chemotherapy [15].

A hot flash begins with sweating, tachycardia and increased peripheral blood flow. Evaporation of sweat may lead to cooling. Sometimes an aura of anxiety or thirst precedes the flash. The wave of heat spreads over the body, particularly the upper part. Menopausal women without breast cancer report trouble falling asleep, waking frequently at night, feeling unusually tired [16]. Savard found more wake time in the 10-min periods around hot flashes and more stage changes to lighter sleep in breast cancer survivors. Compared to nights without hot flashes, there was a lower percentage of stage II sleep and a longer rapid eye movement (REM) latency. Overall, hot flashes were found to be associated with less efficient, more disrupted sleep [17].

While menopausal women treated with hormones sleep better, this option is not available to women with breast cancer. Antidepressants have been used as an alternative for vasomotor symptoms and sleep. Benefit has been documented for a number of antidepressants, both specific serotonin reuptake inhibitors: paroxetine [18], fluoxetine [19], and the specific serotonin norepinephrine reuptake inhibitor venlafaxine [20]. Serotonin mediation of hot flashes has been suggested. Gabapentin at 900 mg per day also reduces hot flashes in women with breast cancer [21]. Vasomotor symptoms and worse depressive symptoms were meaningful predictors of insomnia in women less than 4 years from stage I to IIIA breast cancer [22].

28.7 Cognitive Difficulties

Troubles with working memory and concentration are a common complaint of patients who receive adjuvant chemotherapy for breast cancer. Specific neurocognitive deficits do not typically match subjective reports. Patients who are more distressed report more cognitive failures. In the acute setting, benzodiazepines, steroids, anticholinergic medications affect cognition and attention. The catabolism and fatigue associated with chemotherapy further impairs function. In breast cancer as opposed to other tumors, the course of estrogen withdrawal also may add to cognitive dysfunction [23–25]. Broken sleep, anxiety and low mood further contribute.

28.8 Overlap of Symptoms of Estrogen Deficiency and Depression

The diagnosis of clinical depression is complicated by the overlap of symptoms that make up the syndrome of major depressive disorder (MDD) and those symptoms associated with breast cancer treatment, but the psychological and biological stressors associated with treatment also make MDD more likely. Low mood, poor concentration, fatigue, insomnia, thoughts of death, and prominent anxiety often come with breast cancer treatment. Insomnia is a core symptom of MDD. Patients with MDD have trouble falling asleep and staying asleep [11]. They have less delta sleep, broken sleep, and alterations in timing, amount, and composition of REM sleep [12, 13]. In addition to waking at night, the night is spent in dysphoria, anxiety, and hopelessness. In the setting of breast cancer, patients often attribute their unhappiness to the diagnosis of cancer and the natural concerns that come from the diagnosis. However, persistent insomnia, anhedonia, constant awareness of the diagnosis without the ability to concentrate on other things or to enjoy what is normally enjoyed become markers for the syndrome of MDD. History of MDD and/or anxiety disorder, in other words, life-time history, should add heavily to the assessment of the diagnosis. A history of anxiety disorder predisposes to depressive disorder.

As breast cancer treatment often moves a premenopausal or perimenopausal woman further toward menopause, dysphoria is often associated with menopausal symptoms. Independent of the psychological adjustment to breast cancer, some women are particularly sensitive to mood changes from female hormones. Postpartum or premenstrual changes have been linked with clinical mood syndromes that depend on the individual sensitivity of women to specific changes in female hormones [26]. Epidemiological studies have suggested that women approaching menopause are more at risk for MDD. Clinical depression has been associated with the transition to menopause [27]. Schmidt found a 14-fold increased risk for depressive symptoms in the 2 years surrounding menopause compared to the time of regular cycles. Irritability, nervousness, and frequent mood changes are common in the transition [28]. Both antidepressants and hormones ameliorate the symptoms. In one study in women without breast cancer, aged 40–60, who were perimenopausal or menopausal, escitalopram

as well as estrogen/progesterone improved sleep and vasomotor symptoms, but escitalopram had a better effect on depressive mood [29, 30]. Other antidepressants also benefit mood in menopausal women; these include mirtazapine, fluoxetine, citalopram, paroxetine, and venlafaxine.

Clinical depression is more common with surgical menopause, suggesting that the risk of depression is greater with sudden cessation of estrogen. In breast cancer patients, this would occur with ovariectomy, leuprolide treatment, or abrupt cessation of hormone replacement treatment.

28.9 Fatigue

Treatment for breast cancer, particularly with adjuvant chemotherapy, is fatiguing. Fatigue comes from catabolic effects of treatment, loss of hormones, sleep impairment, and stress. The majority of women undergoing adjuvant chemotherapy, who have cancer-related fatigue, do not have clinical depression [31]. The diagnosis of MDD was established in only 17% of those who met a case definition of cancer-related fatigue. Another 2% who did not meet the case definition met criteria for MDD. History of MDD and prevalence and incidence of cancer-related fatigue were significantly related to the diagnosis of depression at posttreatment assessment. The tendency to catastrophize and increase in the body mass index have been noted to be significant predictors of fatigue in the 6 months after treatment [32].

A minority of breast cancer patients report fatigue and impairment comparable to that seen in women with chronic fatigue syndrome. These women tend to score higher on measures of depression, interpersonal sensitivity, and obsessive-compulsive behavior [33]. Fatigue correlates strongly with self-reported neuropsychological function but not with objective neuropsychological function in a laboratory setting [34].

Persistent fatigue is a marker for women who tend to feel overwhelmed. Persistent fatigue was predicted by high anxiety, high impairment in role function, and low sense of control over fatigue symptoms at baseline assessment [35]. Women who experience depressive symptoms in the first years after diagnosis are at risk for long-term fatigue regardless of how tired they were at the outset [36].

The best treatment for MDD is critical for those with persistent cancer-related fatigue. In addition to antidepressant medication, cognitive behavioral treatment and graded exercise, which has been important in the treatment of chronic fatigue syndrome, might also be important for the subset of breast cancer patients with persistent fatigue and comorbid depressive disorder [37]. Cognitive behavioral techniques and programs of energy conservation have been used for cancer-related fatigue [38, 39].

28.10 Prevalence of Major Depressive Disorder in Breast Cancer Patients

A recent review of the prevalence of MDD in breast cancer patients estimated 10–25%, but came to the conclusion that the precise rate is difficult to determine because of the use of symptom screening tools, the different causes of similar symptoms, and the rare use of Diagnostic Statistical Manual case definition in previous studies [40]. Life time history of affective disorder becomes an important factor in diagnosis.

In Denmark, where there is both a psychiatric registry and tumor registry, between 1970 and 1993, breast cancer patients had a significantly increased incidence of psychiatric admission with affective disorders and anxiety disorders compared to other women [41]. The risk of nonnatural mortality was increased in the first year after diagnosis [42]. Suicide risk tended to increase with depression and age. An international population-based study of more than 700,000 women found that the suicide risk remained elevated among women diagnosed between 1990 and 2001 and throughout follow-up. It was highest among black women [43].

28.11 Treatment

For women who have MDD, particularly if they have a history of previous episodes of MDD, antidepressant medications are the standard of treatment. (Tables 28.2 and 28.3) These drugs may have additional benefit for cognitive, sleep, fatigue, and vasomotor symptoms, as already noted. Antidepressant medications have not

Table 28.2 Syndromes treated by antidepressant medication

Panic disorder
Anxiety disorder with preoccupation about somatic symptoms
Hot flashes
Generalized anxiety disorder
Perimenopausal mood disorder
Major depressive disorder (MDD)

Table 28.3 Antidepressant medications

	Starting dose	Maintenance dose
Citalopram (Celexa)	10 mg/day	20–40 mg/day
Escitalopram (Lexapro)	5–10 mg/day	10–20 mg/day
Sertraline (Zoloft)	25–50 mg/day	50–150 mg/day
Mirtazapine (Remeron)	15 mg h	15–45 h sedating, weight gain
Venlafaxine (Effexor)	37.5 mg/day	75–300 mg/day XR is daily
Wellbutrin[a]	75 mg/day	150 SR b.i.d. or 300 XL
Duloxetine[a]	30 mg/day	60 mg q.d.
Fluoxetine[a]	10 mg/day	20–60 mg/day
Paroxetine[a]	10 mg/day	20–60 mg/day

[a]Consider 2D6 inhibition as a factor that may affect tamoxifen metabolism

been associated with increased risk of breast cancer in epidemiological studies [44, 45]. In general, there is no *a priori* reason to pick one antidepressant over another except to take advantage of the side-effect profile or to reduce side effects in a given patient. If the patient is taking tamoxifen, CYP 2D6 inhibition may lower the effective level of tamoxifen metabolites [46]. Whether this interaction is clinically meaningful is still unclear [46–49]. In that context, for instance, citalopram or venlafaxine may be preferred.

Combination of antidepressant medication with tailored psychotherapy has a better outcome. Antidepressants are often all the more effective for clinical depression when combined with cognitive behavioral treatment or other psychotherapy in patients without cancer [50]. In those women who have cancer, even those not clinically depressed, psychosocial interventions focused on the challenge of the cancer itself – group therapy, cognitive behavioral therapy, supportive-expressive formats, relaxation techniques, and individual therapy – can reduce distress and increase coping [51, 52]. These interventions have strengthened the patient's feeling of control and reduced vulnerability and distress as she faces the uncertainty of cancer. With group and individual treatment, she is less alone. She may be more able to confront the existential plight and the difficult practical challenges that come with negotiating progressive illness. Education and support offer tools for expressing her wishes, using energy wisely, and living fully on her own terms. Social skills like ability to speak effectively with family and medical staff can improve. How to live with the change in breasts, how to grapple with dating and options for children, worries about genetics of the cancer are topics within psychotherapy. Group psychosocial interventions per se have not increased survival in metastatic breast cancer patients [53–57].

28.12 Patients with Psychotic Illness

There is no increased risk of breast cancer in patients with schizophrenia or bipolar disorder [58]. If the patient is noted to have a psychotic disorder, it is important to consider how her particular delusions and ability to comply with treatment will affect her outcome. Many patients with psychoses have difficulty with abstract thinking. Explanations should be concrete. These patients may not trust family or physicians, and may be more sensitive to feeling controlled. They may have more difficulty with simple decisions. Each decision should be made with respect, with alternatives of no treatment, with short deadlines to decision. The physician can emphasize how he thinks cancer is best treated and what he would suggest. When the patient's own executive function is impaired, a plan to sustain adherence both to psychiatric and medical treatment is all the more important.

28.13 Conclusion

Expert care would mean that each woman has the opportunity to be heard, to grapple with the existential plight, and to have syndromes of psychiatric diagnosis treated. Full treatment of MDD and anxiety disorder should also alleviate symptoms of hot flashes, insomnia, and fatigue. Antidepressant medications should be

used methodically. Since response may take several weeks, how long the patient has taken a specific dose of antidepressant should be noted. If a benefit does not occur after 1 or 2 months, the regimen should be adjusted. In those women taking tamoxifen, antidepressant medications with less cytochrome P450 2D6 inhibition would be the first choice.

Expert psychopharmacological care should be augmented by appropriate cognitive behavioral, individual, or group treatments. For those who do not require the best specific treatments for psychiatric syndromes, coping strategies are strengthened by access to psychoeducation, relaxation, and expert group or individual interventions tailored to the treatments for best cancer care.

MDD is a relapsing syndrome with grave morbidity and mortality that must occur in some women who are treated for breast cancer [59]. It has a lifetime prevalence of 16.2% and 12-month prevalence of 6.6% in adults. It is more common in women than men, with a risk ratio of 1.7–1.0 over a lifetime [60]. Risk factors also include personal or family history of depressive disorder, prior suicide attempts, lack of social supports, stressful life events, and current substance abuse. It is worth taking note of these risk factors when considering which women with breast cancer need surveillance for depression. We are bound to treat what is serious and treatable.

Most patients with breast cancer do not develop MDD, but the adjustment to the diagnosis, hormonal changes associated with menopause and further antiestrogen treatments cause dysphoria, sleep disruption, fatigue, poor concentration, and anxiety. Some women are more susceptible to these hormonal changes than others. Some women have a history of MDD or anxiety disorder that adds to their difficulty coping with medical illness. Psychosocial interventions help patients to adjust to the uncertainty of cancer, the loss of fertility and body image; however, the best psychosocial interventions include optimal treatment for MDD.

References

1. Barton MB, Morley DS, Moore S, Allen JD, Kleinman KP, Emmons KM, Fletcher SW (2004) Decreasing women's anxieties after abnormal mammograms: a controlled trial. J Natl Cancer Inst. 96:529–38
2. Ramirez AJ, Westcombe AM, Burgess CC, Sutton S, Littlejohns P, Richards MA (1999) Factors predicting delayed presentation of symptomatic breast cancer: a systematic review. Lancet. 353:1127–31
3. Jones SE, Cantrell J, Vukelja S, Pippen J, O'Shaughnessy J et al (2007) Comparison of menopausal symptoms during the first year of adjuvant therapy with either exemestane or tamoxifen in early breast cancer: report of a tamoxifen exemestane adjuvant multi-center trial substudy. J Clin Oncol. 25:4765–71
4. Fallowfield L, Cella D, Cuzick J et al (2004) Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in combination (ATAC) adjuvant breast trial. J Clin Oncol. 22:4261–71
5. Thomas R, Williams M, Marshall C, Walker L (2008) Switching to letrozole or exemestane improves hot flushes, mood and quality of life in tamoxifen intolerant women. Brit J Cancer. 98:1494–9
6. Waterhouse DM, Calzone KA, Mele C, Brenner DE (1993) Adherence to oral tamoxifen: a comparison of patient self-report, pill counts, and microelectronic monitoring. J Clin Oncol. 11:1189–97
7. Partridge AH, Wang PS, Winer EP et al (2003) Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. J Clin Oncol. 21:602–6
8. Lash TL, Fox MP, Westrup JL, Fink AK, Silliman RA (2006) Adherence to tamoxifen over the five-year course. Breast Cancer Res Treat. 99:215–20
9. Kahn KL, Schneider EC, Malin J, Adams JL, Epstein AM (2007) Patient-centered experiences in breast cancer: predicting long-term adherence to tamoxifen use. Med Care. 45:431–9
10. Partridge AH, LaFountain A, Mayer E, Taylor BS, Winer E, Asnis-Alibozek A (2008) Adherence to initial adjuvant anastrozole therapy among women with early stage breast cancer. J Clin Oncol. 26:556–62
11. Grunberg SM (2007) Antiemetic activity of corticosteroids in patients receiving cancer chemotherapy: dosing, efficacy, and tolerability analysis. Ann Oncol. 18:233–40
12. Buysse DJ, Reynolds DC III, Hauri PJ et al (1994) Diagnostic concordance for DSM IV sleep disorders: a report from the APA/NIMH DSV-IV field trial. Am J Psychiatry. 151:1351–60
13. Benca RM, Obermeyer WH, Thisted RA et al (1992) Sleep and psychiatric disorders: a meta-analysis. Arch Gen Psychiatry. 49:651–68
14. Weilburg JB, Stakes JW, Roth T. (2008) Sleep Disorders. In: Stern TA, Rosenbaum JF, Fava M, Biederman J. Rauch SL, editors. Comprehensive Clinical Psychiatry. Mosby Elsevier; p. 285–99
15. Carpenter JS, Andrykowski MA, Cordova M, Cunningham L, Studts J, McGrath P, Kenady D, Sloan D, Munn R (1998) Hot flashes in postmenopausal women treated for breast carcinoma: prevalence, severity, correlates, management, and relation to quality of life. Cancer. 82:1682–91
16. Kronenberg F (1994) Hot flashes: phenomenology, quality of life, and search for treatment options. Exp Gerontol. 29: 319–36
17. Savard J, Davidson JR, Ivers H, Quesnel C, Rioux D, Dupere V, Lanier M, Smard S, Morin CM (2004) The association between nocturnal hot flashes and sleep in breast cancer survivors. J Pain Sympt Manage. 27:513–22
18. Stearns V, Beebe KL, Lyengar M, Dube E (2003) Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. JAMA. 289:2827–34

19. Loprinzi CL, Sloan JA, Perez EA, Quella SK, Stella PJ, Mailliard JA et al (2002) Phase III evaluation of fluoxetine for treatment of hot flashes. J Clin Oncol. 20:1578–83
20. Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA et al (2000) Venlafaxine in management of hot flashes in survivors of breast cancer: a randomized controlled trial. Lancet. 356:2059–63
21. Pandya KJ, Morrow GR, Roscoe JA, Zhao H et al (2005) Gabapentin for hot flashes in 420 women with breast cancer: a randomized double-blind placebo-controlled trial. Lancet. 366:818–24
22. Bardwell WA, Profant J, Casden DR, Dimsdale JE, Ancoli-Israel S, Natarajan L, Rock CL, Pierce JP (2008) The relative importance of specific risk factors for insomnia in women treated for early stage breast cancer. Psychooncology. 17:9–18
23. Jenkins V, Shilling V, Deutsch G et al (2006) A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. Br J Cancer. 94:828–34
24. Joffee H, Hall JE, Gruber S et al (2006) Estrogen therapy selectively enhances prefrontal cognitive processes: a randomized, double-blind, placebo-controlled study with functional magnetic resonance imaging in premenopausal and recently postmenopausal women. Menopause. 12:411–22
25. Silverman DH, Dy CJ, Castellon S, Lai J, Pio BS, Abraham L, Waddell K, Petersen L, Phelps ME, Ganz PA (2007) Altered frontocortical cerebellar and basal ganglia activity in adjuvant treated breast cancer survivors 5–10 years after chemotherapy. Breast Cancer Res Treat. 103:303–11
26. Schmidt P, Nieman LK, Danaceau MA, Adamas LF, Rubinow DR (1998) Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. N Engl J Med. 338:209–16
27. Cohen LS, Soares CN, Otto MW, Vitonis AF, Harlow BL (2006) Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Arch Gen Psychiatry. 63:385–90
28. Schmidt PJ, Haq N, Rubinow MD, David R (2004) A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. Am J Psychiatry. 161:2238–44
29. Soares CN, Helga A, Joffe H, Bankier B, Cassano P, Petrillo LF, Cohen LS (2006) Escitalopram versus ethyinyl estradiol and norethindrone acetate for symptomatic peri- and postmenopausal women: impact on depression, vasomotor symptoms, sleep, and quality of life. Menopause. 13:780–6
30. Soares CN, Almeida OP, Joffe H, Cohen LS (2001) Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. Arch Gen Psychiatry. 58:529–34
31. Andrykowski MA, Schmidt JE, Salsman JM, Beacham AO, Jacobsen P (2005) Use of a case definition approach to identify cancer-related fatigue in women undergoing adjuvant therapy for breast cancer. J Clin Oncol. 23:6613–22
32. Donovan KA, Small BJ, Andrykowski MA, Munster P, Jacobesen PB. (2007) From: Utility of a cognitive-behavioral model to predict fatigue following breast cancer treatment. Health Psychol.26:464–72
33. Servaes P, Verhagen S, Bleijenberg G (2002) Determinants of chronic fatigue in disease-free breast cancer patients: a cross-sectional study. Ann Oncol. 13:589–98
34. Servaes P, Verhagen CA, Bleijenberg G (2002) Relations between fatigue, neuropsychological functioning and physical activity after treatment for breast carcinoma. Cancer. 95:2017–26
35. Servaes PM, Gielissen MF, Verhagen S, Bleijenberg G (2007) The course of severe fatigue in disease-free breast cancer patients: a longitudinal study. Psycho Onology. 16:787–95
36. Bower JE, Ganz PA, Desmond KA, Bernards C, Rowland JH, Meyerowitz BE, Belin TR (2006) Fatigue in long-term breast carcinoma survivors: a longitudinal investigation. Cancer. 106:751–8
37. Sharpe M, Hawton K, Simpkin S, Surawy C, Hackmann A, Klimes I, Peto T, Warrel D, Seagroatt V (1996) Cognitive behaviour therapy for chronic fatigue syndrome: a randomized controlled trial. Br Med J. 312:22–6
38. Gielissen MF, Verhagn S, Witjes F, Bleijenberg G (2006) Effects of cognitive behavioral therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavioral therapy: a randomized controlled trial. J clin Oncol. 42:4882–7
39. Barsevick AM, Dudley W, Beck S et al (2000) A randomzied clinical trial of energy conservation for patients with cancer-related fatigue. Cancer. 100:1302–10
40. Fann JR, Thomas-Rich AM, Katon WJ, Cowley D, Pepping M, McGregor BA, Gralow J (2008) Major depression after breast cancer: a review of epidemiology and treatment. Gen Hosp Psychiatry. 30:112–26
41. Hjerl K, Andersen EW, Keiding N, Mortensen PB, Jorgensen T (2002) Increased incidence of affective disorders, anxiety disorders, and non-natural mortality in women after breast cancer diagnosis: a nation-wide cohort study in Denmark. Acta Psychiatrica Scandinavica. 105:258–64
42. Yousaf U, Christensen M-LM, Engholm G, Storm HH (2005) Suicides among Danish cancer patients 1971–1999. Br J Cancer. 92:995–1000
43. Schairer C, Brown LM, Chen BE, Howard R, Lynch CF et al (2006) Suicide after breast cancer: an international population-based study of 723810 women. J Natl Cancer Inst. 98:1416–9
44. Gonzalez-Perez A, Rodriquez LAG (2005) Breast cancer risk among users of antidepressant medications. Epidemiology. 16:101–5
45. Haque R, Enger SM, Chen W, Petitti DB (2004) Breast cancer risk in a large cohort of female antidepressant medication users. Cancer Lett. 221:61–5
46. Jin Y, Desta Z, Stearns V, Ward B, Ho H, Lee KH et al (2005) CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst. 97:30–9
47. Lim HS, Lee HJ, Lee KS, Lee ES, Jang IJ, Ro J (2007) Clinical implications of CYP2D6 genotypes predictive of tamoxifen pharmacokinetics in metastatic breast cancer. J Clin Oncol. 25:3837–45
48. Goetz MP, Knox SK, Suman VJ, Safgren SL, Ames MM, Visscher DW et al (2007) The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. Breast Cancer Res Treat. 101:1213–21
49. Ratliff B, Dietze EC, Bean GR, Moore C, Wanto S, Seewaldt VL (2004) Correspondence: Re: active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. J Natl Cancer Inst. 96:883

50. Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ et al (2000) A comparison of nefazadone, the cognitive behavioral –analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med. 342:1462–70
51. Fawzy FI, Fawzy NW, Arndt LA et al (1995) Critical review of psychosocial interventions in cancer care. Arch Gen Psychiatry. 52:100–13
52. Leubbert K, Dahme B, Hasenbring M (2001) The effectiveness of relaxation training in reducing treatment-related symptoms and improving emotional adjustment in acute non-surgical cancer treatment: a meta-analytic review. Psycho Oncol. 10:490–502
53. Spiegel D, Butler LD, Giese-Davis J, Koopman C, Miller E et al (2007) Effects of supportive-expressive group therapy on survival of patients with metastatic breast cancer. Cancer. 110:1130–8
54. Kissane DW, Li Y (2008) Effects of supportive-expressive group therapy on survival of patients with metastatic breast cancer: a randomized controlled trial. Cancer. 112:443–4
55. Kissane D, Grabsch B, Clarke DM et al (2007) Supportive-expressive group therapy for women with metastatic breast cancer: survival and psychosocial outcome from a randomized controlled trial. Psychooncology. 16:277–86
56. Classen PJ, Butler LD, Koopman C et al (2001) Supportive-expressive group therapy and distress in patients with metastatic breast cancer: a randomized clinical intervention trail. Arch Gen Psychiatry. 58:494–501
57. Goodwin PJ, Leszcz M, Ennis M et al (2001) The effect of group psychosocial support on survival in metastatic breast cancer. N Engl J Med/ 345:1719–26
58. Hippisley-Cox J, Vinogradova Y, Coupland C, Parker C (2007) Risk of malignancy in patients with schizophrenia or bipolar disorder: nested case-control study. Arch Gen Psychiatry. 64:1368–76
59. Greenberg DB (2004) Barriers to the treatment of depression in cancer patients. J Natl Cancer Inst Monogr. 32:127–35
60. Kessler RC, Berglund P, Bemler O, Jin R, Koretz D, Merkangas KR et al (2003) The epidemiology of major depressive disorder. JAMA. 289:3095–105

Management of the Patient with a Genetic Predisposition for Breast Cancer

29

Vickie L. Venne and Saundra S. Buys

29.1 Hereditary Breast Cancer

Women who have close relatives with breast cancer have an increased risk of developing breast cancer themselves. Familial clustering of breast cancer may occur for several reasons. Breast cancer is a common disease, and clustering may be coincidental. Shared environmental or lifestyle factors may result in multiple cases of breast cancer within a family, particularly among siblings. Genes that regulate estrogen metabolism or that otherwise indirectly influence the incidence of breast cancer may be important in some familial cases. Finally, a small percent of familial clusters are caused by mutations in major breast cancer predisposition genes that are inherited in an autosomal dominant fashion. Of all women with breast cancer, about 25–30% have a close family member with cancer [1], but only about 5–10% of breast cancer is due to highly penetrant inherited predisposition gene mutations [2, 3]. This chapter will review the basics of cancer genetics, outline selected breast cancer family syndromes, and discuss the importance of the family and personal history in identifying those who may have an inherited predisposition to breast cancer. Models for assessing the risk of developing cancer and of having a genetic predisposition to cancer will be described. Management of individuals at high risk for developing breast cancer will be discussed, including genetic counseling and testing, interpretation of results, and options for modifying risk in those with a family history of breast cancer, with or without an identifiable gene mutation.

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29.1.1 Somatic and Germline Genetics

All cancer is genetic; that is, all cancer is caused by the accumulation of genetic mutations in a specific somatic cell line. Only rarely, however, is cancer the result of an inherited gene mutation. Cancer can occur in any cell, either somatic or germline, that contains a nucleus, but heritability requires a mutation in the germline. Mutations in the germline (either egg *or* sperm) are passed to the offspring at the time of conception, resulting in the mutation being present in each somatic cell in the body. Persons with an inherited predisposition to cancer, therefore, require one less acquired mutation before a given cell becomes malignant. Because genetic material is halved during maturation of the egg and sperm, half of the germ cells (and consequently half of offspring) will have the mutation. Families with an inherited predisposition to cancer usually have more cases of cancer than would be expected by chance; cancer in several generations and cancer at earlier ages than are typical.

29.2 Breast Cancer Syndromes

There are more than 60 genes that, when mutated in the germline, confer a significant risk for cancer, including several that increase the risk for breast cancer. The most common of these is Hereditary Breast and Ovarian Cancer, associated with mutations in the *BRCA1* or *BRCA2* genes. Table 29.1 identifies the major syndromes that include breast cancer, the causative genes, and organ sites that may be affected [4]. Most germline mutations that predispose to breast cancer are inherited in an autosomal dominant fashion,

I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases*,
DOI: 10.1007/978-3-540-69743-5_29, © Springer-Verlag Berlin Heidelberg 2010

Table 29.1 Breast cancer syndromes

Syndrome	Gene (chromosome) location	Organ sites involved
Hereditary breast/ovarian cancer syndrome	*BRCA1*(17q21)	Breast, ovary, prostate
Hereditary breast/ovarian cancer syndrome	*BRCA2*(13q12.3)	Breast, ovary, breast cancer in males, prostate, melanoma, pancreas
Cowden syndrome	*PTEN*(10q22.3)	Hamartomas of intestine; skin lesions; cancers of breast, endometrium, thyroid (nonmedullary)
Peutz-Jeghers syndrome	*STK11/LKB1*(19p13.3)	GI polyps and cancers, pancreas, uterine, ovary, cervix, breast, lung; also abnormal melanin deposits
Li-Fraumeni syndrome	*TP53*(17q13.1)	Breast, brain, adrenal cortex, sarcomas, leukemia

such that a mutation from either parent increases the risk for cancer. Spontaneous mutations are rare. Therefore, if an individual has a mutation, one of the parents is almost always a carrier, and siblings and children are at 50% risk of inheriting the familial mutation. Most of the genes are tumor suppressor genes which, when working properly, reduce the risk of developing cancer. When mutated, however, the protective function is lost and the risk of cancer is increased.

The risk for the development of cancer associated with mutations in these genes varies depending on the specific gene and the population analyzed. Early studies, which evaluated families based on a clinical ascertainment of four or more breast cancers, suggested a higher penetrance [5] than subsequent studies in families with a more modest family history [6]. Population-based studies test all individuals diagnosed with breast cancer for gene mutations, without regard to family history. In these studies, the risk for cancer in relatives is still lower [7]. It is likely that modifying genes or environmental factors affect penetrance from family to family. Clinic-based ascertainment may select for families in which there is not only a breast cancer gene mutation, but other genetic or environmental factors at play. Since most patients seek genetic testing because of a family history of breast cancer, it is likely that the risk for cancer in these individuals more closely mirrors clinic-based risk estimates than population-based risk estimates.

A *BRCA1* or *BRCA2* mutation is found in approximately 1 per 400 non-Jewish Caucasians [7] and about 1 in 50 Ashkenazi Jews [8]. The rate in other ethnic groups is not well defined, although specific founder mutations have been identified in many countries, including the Netherlands [9] and Iceland [10]. *BRCA1* mutations are associated with a lifetime risk for breast cancer of about 60–80% in women and 2% in men [11, 12], as well as a risk of around 40% for ovarian cancer [8, 13–15]. The rates for *BRCA2* mutation carriers are about 50–60% for female breast cancer, 5–7% for male breast cancer, and 10–30% for ovarian cancer [11–14, 16]. *BRCA1*-associated cancers are typically high grade, often with medullary features, usually estrogen and progesterone receptor negative, and do not overexpress HER2/neu (so-called "triple negative" breast cancer) [17]. *BRCA2*-associated breast cancers are generally estrogen receptor positive and of no specific histologic type [18, 19]. There is no evidence that prognosis is different in *BRCA*-associated cancers compared with non*BRCA* cancers of similar grade, stage, and histologic type [20]. The ovarian cancers in *BRCA* mutation carriers are epithelial in origin and usually of serous histology [21, 22]. Fallopian tube cancers and primary peritoneal cancers are also prevalent [23].

Mutations in the *BRCA1* and *BRCA2* genes confer risks for cancers other than breast and ovarian. *BRCA2* mutations are associated with an increased risk of melanoma, pancreatic cancer, and possibly prostate cancer [5, 24, 25] Prostate cancer occurring in both *BRCA1* and *BRCA2* mutation carriers may be more aggressive than prostate cancers in the general population [26, 27].

Cowden syndrome is caused by a mutation in the *PTEN* gene. It is often first recognized because of skin lesions and intestinal hamartomas [28], but is also associated with an increased risk of early-onset breast cancer that ranges from 25 to 50%. Annual mammograms and breast magnetic resonance imaging (MRI) are

recommended beginning at age 30–35, or 5–10 years earlier than the earliest breast cancer in the family [29]. Besides breast cancer, nonmedullary thyroid cancer, endometrial cancer, and possibly renal cancer may be increased. Benign findings that occur frequently include benign thyroid disease, trichilemmomas, which are flesh-colored bumps on the face and tongue [30], and macrocephaly above the 97th percentile.

Li-Fraumeni syndrome is a rare disorder, with only about 400 families in the reported literature. It is caused by a mutation in *TP53*, the "guardian of the genome," that prevents cells with DNA damage from proceeding through cell cycle. Somatic mutations in *TP53* are found in about half of all cancers. When present as a germline mutation, risk for cancer is extremely high [31, 32]. Approximately 50% of individuals with mutations have developed cancer by age 30, and the prevalence by age 70 is 90% [33]. Osteosarcomas, soft tissue sarcomas, brain tumors, leukemia and adrenal cortical carcinomas are the characteristic tumors, with breast cancer found in 25% of those who do not die of childhood tumors [34]. Breast cancer tends to occur very early, often in the 20s. Virtually every other solid tumor is also found at very early ages in this population, with multiple primary tumors found in 57% in a 30-year follow-up study [35]. The recommended screening for breast cancer includes annual mammograms and MRI starting at age 20–25, as well as risk-reducing surgery if appropriate [29].

Peutz-Jeghers syndrome is associated with a mutation in *SKT11*. It is usually diagnosed based on distinctive hamartomatous polyps [36] and the presence of benign pigmented spots on the lips and buccal mucosa. The lifetime risk for cancer is up to 80% in these families, with breast cancer being the most common at around 45% [37, 38]. Since breast cancer can be seen in women in their 30s, breast screening with annual mammograms and MRI is recommended beginning at age 25 [39].

29.3 Identification of High-risk Individuals

29.3.1 Family History

A woman's risk of developing breast cancer is strongly related to the number of affected relatives, their genetic proximity, and ages at which they were diagnosed. Collecting an accurate family history is the single most cost-effective approach to identifying individuals with hereditary breast cancer [40]. A three-generation family history should be collected on individuals who have a suspected predisposition to cancer and should include all first-degree relatives (children, siblings, parents) and second-degree relatives (uncles and aunts, nieces and nephews, grandparents), as well as more distant relatives who have cancer [41]. For each family member, essential information includes current age or age and cause of death, medical history including types of cancer and age of onset, ethnicity/country of origin, and other syndrome-specific features, for example multiple gastrointestinal polyps. A graphic representation of the family history using recognized pedigree nomenclature outlined in Fig. 29.1 allows assessment of inheritance patterns and permits this information to be communicated to other clinicians and to patients in a clear and consistent manner [42].

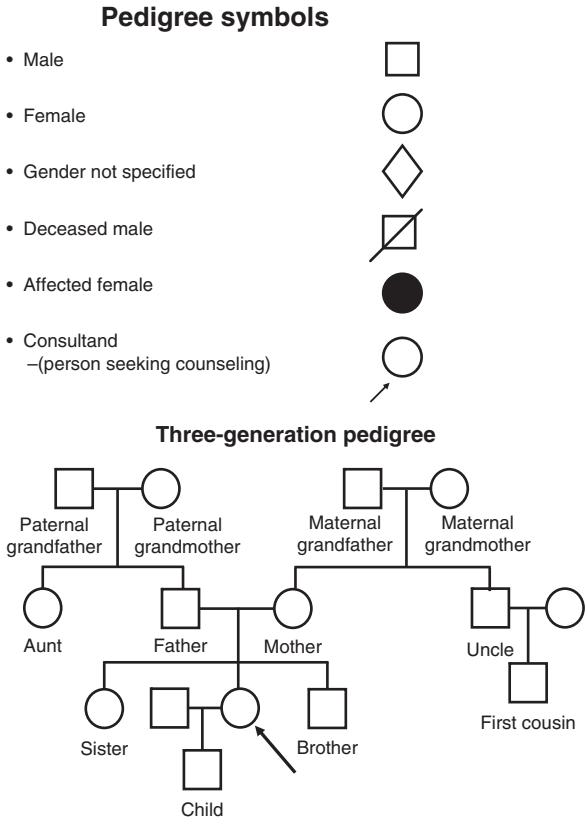

Fig. 29.1 Pedigree symbols and structure (represented by two slides). By using recognized pedigree nomenclature and structure, family history information can be communicated to other clinicians and patients in a clear and concise manner

The cancer pedigree should include at least the number and gender of individuals in each generation, whether affected with cancer or not, so the ratio of affected to unaffected family members can be incorporated into the assessment. A common breast cancer genetic myth is that "you don't have to worry about breast cancer on your father's side of the family." It is essential to collect *both* maternal and paternal histories of cancer, since germline mutations are equally likely to be inherited paternally as maternally.

Knowledge of breast cancer in first-degree relatives is generally accurate [43], but is less reliable in more distant relatives [44, 45]. Knowledge of cancers in other organs is often less precise. Gastric cancer and ovarian cancer may both be reported as "stomach cancer," and cervical, uterine, and ovarian all reported as "female cancer." Ovarian cysts may also be misreported as cancer. Questioning the patient about outcomes may be helpful in determining the accuracy of the diagnosis. For example, a report of a relative with long-term survival after a diagnosis of "ovarian cancer" or "pancreatic cancer" should raise questions about the accuracy of the diagnosis since these cancers have low long-term survival rates. Family medical histories are dynamic, and it is important to remind the patient that if additional cases of cancer are diagnosed or discovered, she should recontact the provider because the new information may alter the risk calculation and subsequently alter recommendations for risk management [46].

Taking a detailed family history takes time. Some centers use a questionnaire that can be mailed prior to an appointment or completed in a waiting room. Several web-based questionnaires in both English and Spanish are readily available from resources such as the Centers for Disease Control and Prevention (http://www.hhs.gov/familyhistory/). In some cases, small family size, adoption, and misidentified paternity complicate the analysis of a family history [47]. Despite these difficulties, obtaining an accurate family history reduces the likelihood of either overlooking the possibility of a hereditary cancer syndrome, which in turn leads to lost opportunities for cancer risk management and risk reduction in the patient as well as extended family members; or of inappropriately performing genetic testing. After obtaining an initial family history, referral to a cancer genetic service may be the most appropriate way to obtain a complete family history and risk assessment.

29.3.2 Personal Health History

In addition to information about the extended family, a cancer risk assessment includes a personal health history. The presence of cancer, cancer site, age of onset, the existence of multiple primaries or bilaterality, history of previous biopsies and whether the biopsy showed proliferative breast disease are important. Hormone-related factors such as age at menarche, nulliparity or age at first birth, number of pregnancies, duration of breast-feeding, age of menopause, and exogenous hormone use (oral contraception, hormone replacement therapy) also have an impact on the risk of developing cancer. Diet and exercise play a significant role in the development of breast cancer, not least of which is the impact of obesity on the increased rate of breast cancer in postmenopausal women [48]. Alcohol ingestion is also positively associated with breast cancer [49, 50]. Mammographic breast density is an increasingly recognized risk factor for breast cancer, and may be more strongly correlated with a risk for the development of breast cancer than any factors except for age, gender, and the presence of a breast cancer predisposition gene mutation [51]. Finally, radiation exposure, particularly during childhood and adolescence, increases the risk of breast, thyroid and other cancers [52]. Radiation was commonly administered in the 1940s through early 1970s for acne vulgaris, tinea capitis, hemangiomas, and enlargement of the tonsils or thymus, as well for Hodgkin's disease and other malignancies [52, 53]. The identification of a woman with both breast and thyroid cancer may suggest Cowden's syndrome, but in the presence of a history of radiation therapy, an environmental cause would be far more likely than an inherited one.

29.4 Risk Assessment

Two different but related risks are important to the individual patient: the risk of developing breast cancer, and the risk of carrying a mutation in a breast cancer predisposition gene.

Communication of risk requires an understanding of ways to present risk, the various models used to assess risk, the manner in which numbers can be interpreted, and the factors that are necessary to put them

into context of the patient's perception of her risk. Most women with a family history of breast cancer significantly overestimate their risk [54].

29.4.1 Absolute Risk

An absolute risk is the probability of an event occurring during a specific interval. For example, a well-known risk figure associated with breast cancer is 11%, a cumulative incidence statistic, which means that about one in nine women in the general population will develop breast cancer at some point in her lifetime [55]. Unless she has a breast cancer predisposition gene mutation, a woman who is presenting for risk assessment at age 30 has an absolute risk of developing breast cancer in the next 5 years of about 0.1%, or one in a thousand, far less than the 11% lifetime statistic [56].

29.4.2 Relative Risk

Most population-based studies of familial cancer report absolute risk, which compares the frequency of cancers within affected families to the frequencies expected in the general population. An observed-to-expected ratio (odds ratio) is used to quantify the risk [57] based on the particular environmental factor (parity, oral contraceptive use, diet, pesticide exposure) or the genetic proximity of an affected relative (sister, mother, aunt, grandmother). The risk is typically described as x-fold over that of the general population (Table 29.2). This may also be reported as a percent increase. Hormone replacement therapy may confer a relative risk of 1.2, for example, which is accurately reported as a 20% increase in the risk. That concept is not always well understood by patients who are confused and call their doctors wondering if their risk has increased from 11 to 31% by their use of postmenopausal hormone replacement therapy, when a 1.2 relative risk has only increased their risk from 11 to 13%.

Table 29.2 Selected lifetime risk ratios for breast cancer based on family history

Relationship of affected relative	Risk ratio
Mother	1.7–4
Sister, premenopausal	3.6–5
Sister, postmenopausal	2
Sister and mother	2.5
Second degree	1.4–2
Third degree	1.35

Modified from [124], with permission

29.4.3 Predicting Development of Breast Cancer: Gail Model and Claus Tables

Several mathematical models have been developed to estimate the risk of developing breast cancer. The Gail model computes individualized absolute risk in Caucasian women receiving routine mammograms [58]. It uses five specific risk factors (age at evaluation, age at menarche, age at first live birth, number of prior breast biopsies, and number of first degree relatives with breast cancer) to estimate 5-year and lifetime risk. A modification also includes the presence of proliferative breast disease on biopsy, and newer analyzes of the data include risks for non-Caucasian women [59]. Although the model is a useful tool for defining risk estimates in the general population, it has several limitations in the context of a high-risk setting. It does not address the risk for women under age 35 or for those who are not undergoing regular mammograms. Most relevant to a high-risk population, the Gail model includes only first-degree relatives and therefore does not include paternal history, nor does it include a family history of ovarian cancer or age of onset of cancers. Therefore, it is not an appropriate model to assess risk for women in families with a known or suspected inherited cancer predisposition gene mutation.

The Claus tables [2] were subsequently developed based solely on family relationships and are more appropriate for estimating risk in women with a family history of breast cancer. This model includes first-and second-degree relatives and can be used to estimate cumulative risk over 10-year intervals. It includes relatives in only one lineage (either maternal or paternal) but not both. The model uses a single locus dominant genetic assumption, but those cases are limited to only about 5–10% of breast cancers.

29.4.4 Models for Predicting Presence of a BRCA Gene Mutation: BRCAPro and BOADICEA

The most significant risk for breast cancer, except for gender and age, is the presence or absence of a specific germline mutation. Therefore, an important step in the risk assessment is to determine the likelihood that the family has a recognizable genetic syndrome, as outlined in Table 29.1 and discussed above. *BRCA* gene mutations are the most prevalent of the genetic syndromes associated with an increased risk for breast cancer, especially in certain populations such as Ashkenazi Jews.

Several models have been developed to assess the likelihood of carrying a *BRCA1/2* mutation. The most commonly used model in the U.S. is BRCAPro, which includes age-specific cancer as well as positive and negative family history information of both first-and second-degree relatives from both sides of the family [60–62]. The information is then evaluated using a Bayesian approach to calculate carrier probabilities. Free registration for online access to this model is available at http://astor.som.jhmi.edu/BayesMendel/brcapro.html. Another model, used widely in the U.K. and Australia, is BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), which was developed based on segregation analysis of breast and ovarian cancer and recently updated to include male breast, prostate and pancreatic cancers and to allow for the risk of multiple cancers [63]. A user-friendly web-based program (http://www.srl.cam.ac.uk/genepi/boadicea_home.html) is available. Myriad Genetic Laboratory, the only laboratory licensed to provide clinical *BRCA* testing, has a simple web-based questionnaire, which provides basic information regarding appropriateness for offering testing specific to *BRCA1/2* (http://www.myriadtests.com). In general, it is reasonable to offer genetic testing to individuals with a 10% or greater *a priori* likelihood of having a mutation [29, 64, 65].

29.5 Genetic Testing

Genetic testing for a breast cancer predisposition gene mutation is complicated in many ways and should not be considered "just a blood test." On the most basic level, it is expensive. The cost may or may not be covered by insurance and in either case, care should be taken to assure that the right person is tested for the right gene mutation. Depending on the circumstances of testing, a negative test does not always lower the risk for breast cancer and should not always be considered "good news." Many families deemed to be appropriate for genetic testing have a sufficiently strong family history that warrants enhanced screening, even if no mutation is found [66]. A positive test result carries with it recommendations for expensive and potentially morbid therapies. Patients seek genetic testing for many reasons, and the impact of the test result – whether positive, negative, or uninformative – on psychological health, social relationships and medical care needs to be explored prior to testing [67]. In addition, the test result has implications not only for the individual being tested, but for family members. As such, there is an ethical requirement to inform family members, and a strategy for doing so must be developed. Despite the ease of ordering a genetic test, doing so carries with it an obligation to assure that patients are well served by the testing process [67]. Due to the complexities of genetic testing and the significant implications of the test results on patients and their family members, in most cases, referral to a genetic professional is appropriate. A list of genetic counselors can be found at www.nsgc.org or a cancer center can be located at the National Cancer Institute's website (http://www.cancer.gov/search/geneticsservices/).

In general, referral for genetic testing is appropriate for an individual diagnosed with breast cancer under age 40, bilateral breast cancer, male breast cancer, or both breast and ovarian cancer. Families with two or more individuals with breast cancer under age 50, breast cancer under age 50 and ovarian cancer at any age, or three or more individuals with breast cancer at any age are also appropriate for genetic counseling and testing [29, 65]. Some families have fewer cases of cancer but have a small number of women, or have related cancers such as pancreatic cancer or melanoma. These may also be appropriated for genetic testing [47]. Ashkenazi Jewish women with breast cancer at a later age are also appropriate for genetic testing [29]. Ideally, the first person to receive genetic testing in a family should be someone affected with cancer, because if there is a mutation in the family, that person is more likely to carry the mutation than unaffected individuals. If a mutation is identified, testing for that

specific gene mutation can then be performed in relatives, both male and female, based on the inheritance pattern of the particular gene.

If a mutation is identified in a family, it is ideal from a scientific and psychosocial perspective to test other branches of the family, starting with the oldest generation alive. For example, rather than testing all cousins of a mutation carrier, testing aunts and uncles provides information for their descendants. If a parent has a mutation, all children, regardless of their cancer status, become testing candidates; if there is no mutation, subsequent generations do not need to be tested. From a psychosocial perspective, there are also advantages to testing a member of the oldest generation first, because it is often easier to share information from a parent to a child than from a child to a parent [68].

Genetic testing for breast cancer predisposition gene mutations is conducted on a blood specimen or, under some circumstances, a buccal sample obtained from a cheek swab. Clinical testing for the *BRCA1* and *BRCA2* genes in the U.S. is currently available only through Myriad Genetic Laboratory (http://www.myriadtests.com), which holds a patent on these genes. For the initial person tested in a family, the test involves sequencing the entire gene and is relatively expensive. In the Ashkenazi Jewish population, recognized high-frequency mutations can be evaluated initially; if one of the three founder mutations is not identified, based on the strength of the family history, it may then be necessary to request a full-sequence analysis [69]. Once a mutation is identified in a family, specific mutation analysis, which is much less expensive, can be offered to other family members. A resource to help identify available laboratories for other cancer-related germline tests is GeneTests (www.genetests.org), available free of charge to registered users. This website, developed by the University of Washington, Seattle with funding from the National Library of Medicine and Maternal and Child Health Bureau, is an information resource that includes a directory of clinical and research laboratories that offer specific medical genetic tests.

29.5.1 Genetic Education and Counseling

Prior to having a blood specimen obtained for genetic testing, genetic counseling is recommended [65]. The purpose of genetic education is to provide factual information about cancer etiology, including environmental and genetic factors. Verbal discussion, written information, and video or computer programs may be used to explain reasons for the family having an excess of cancer; the potential syndromes under consideration; basic genetics including carcinogenesis and heritability; the ability to test for predisposition gene mutations; and the implications of the result in terms of cancer risk, heritability, and options for medical management [67].

Genetic counseling, as opposed to genetic education, is interactive and addresses psychosocial as well as factual issues. Components of genetic counseling include obtaining an individual and family social and health history; assessing the risks of cancer or of having an identifiable mutation; ensuring that the patient understands those risks as well as the laboratory and clinical procedures and options for testing and screening, as well as the risks, benefits, and limitations of the various options; assessing psychosocial needs and intervening when appropriate; determining the reason for pursuing genetic testing; counseling to facilitate medical decision making; providing anticipatory grief or crisis counseling; and facilitating medical screening, testing, or management options as desired [67]. The possible test results (positive, negative, or variant of uncertain significance) should be outlined and the patient's response to the various results discussed. Individuals differ in their belief on whether the identification of a mutation is good or bad news. For a woman with breast cancer, having a mutation may be good news in that it explains the etiology of her cancer. On the other hand, an unaffected woman who is the only one of her four sisters without a mutation may experience survivor guilt and see her result as bad news. Exploring the potential reactions to all these results, as well as how ready the patient is to hear the result, is an important part of the pretest session.

Pretest counseling should also include a discussion about options available if the woman decides to forgo testing. There are several reasons why women might not want to be tested. Some women are hesitant to consider genetic counseling and testing because of concerns regarding genetic discrimination [70]. Although a few court cases have tested them, laws have been passed in many states that protect genetic privacy. In May 2008, the Genetic Information Nondiscrimination Act was signed into law, and went into effect in May

2009 related to health insurance and in November 2009 related to workplace issues [71]. Although the consequences of genetic discrimination may be significant, there are few documented cases of such discrimination, and the risk is likely to continue to diminish as genetic testing for adult conditions becomes more common. Other women may choose not to be tested because of the high cost of testing when not covered by insurance, or because the medical management options they would choose would not be affected by mutation status.

Families may ask about testing children for the familial gene mutation. In the absence of documented medical benefit, offering genetic testing to minors may compromise the autonomy of the child. Psychological consequences could include stigmatization of the child, or viewing the child as fragile [72, 73]. Testing for *BRCA1* and *BRCA2* should not be performed on minors because there is virtually no risk of cancer developing in minors and medical management would not be affected. Testing for *TP53* mutations associated with Li-Fraumeni Syndrome is much more complicated since many of the cancers present during childhood. However, efficacy of screening is still not clear, and genetic testing should be performed by a healthcare professional with expertise in cancer risk assessment and management.

29.5.2 Interpretation of Test Results

Positive (presence of a deleterious mutation): A positive test result indicates that an individual has a mutation that increases the risk of developing breast cancer, as well as other cancers or benign conditions associated with that mutation. This result also means that other family members are candidates for genetic testing.

Negative (absence of a deleterious mutation): The significance of a negative test result depends on whether or not there is a known mutation in the family. If the mutation in the family is already identified, this result is a true-negative test result and means (with greater than 99% accuracy) that the patient did not inherit that mutation and therefore, would have a risk of developing cancer similar to the risk of a woman in the general population. Although some have suggested that individuals in mutation-carrying families have an increased risk of developing cancer even if they do not carry the familial mutation [74], others do not support this conclusion and in general, recommendations for mutation-negative individuals in mutation-carrying families are the same as for the general population [75, 76]. Management recommendations should incorporate other risk factors for breast cancer, including those assessed by the Gail model as well as breast density and family history of breast cancer on the other side of the family.

The predictive value of a negative test is lower if the patient is the first one in the family being offered testing. There are a number of possible explanations for a negative test result in this case, including the possibility that the cancers in the family are not due to an inherited gene mutation but rather chance occurrences; that limitations of the technology do not allow a mutation to be identified; that the mutation is in a gene different from the one analyzed; or that the susceptibility gene that is predisposing to cancer in that family has not yet been discovered. Another possibility is that there is a familial gene mutation accounting for the apparent increase in breast cancer; but that the individual tested does not have the mutation (i.e., is a phenocopy). In the presence of a striking family history, it may be appropriate to offer testing to a second affected family member.

A negative test result in an unaffected individual from a family that has not been previously tested provides limited information to the individual. Recommendations for risk management for this woman should be based on the family history [75].

Variants of uncertain significance: *BRCA1* and *BRCA2* are large genes with hundreds of recognized deleterious mutations as well as many variants that may or may not increase the risk of breast cancer, currently classified as variants of uncertain significance. As more research is completed, most of these will be reclassified as either polymorphisms of no clinical significance or deleterious mutations. Until the mutation is reclassified, individuals with variants of uncertain significance should be managed based on family history. Unless testing is done in a research setting in an attempt to clarify the significance of the mutation, testing other family members for the variant is discouraged since no clinically relevant interpretation can be derived from the result.

29.6 Medical Management of High-Risk Individuals

Recommendations for medical management of individuals at increased risk for developing breast cancer,

either because of family history or because of the presence of a known gene mutation, are based primarily on consensus and clinical judgment rather than randomized clinical studies [29]. Although the details vary, management of risk generally includes enhanced screening, chemoprevention and surgical risk reduction.

29.6.1 Medical Management of a Woman with No Identifiable Mutation

Women without an identifiable mutation, who have a family history that includes only breast cancer, will have a risk of developing breast cancer based on empiric personal and family history data, such as that obtained from the Gail model, Claus tables, or data such as that presented in Table 29.2. The Gail model is most appropriate for women if there are only a few women who were diagnosed at relatively late ages [59]. In these families, first- and second-degree relatives of women with breast cancer should initiate annual mammograms 5–10 years younger than the earliest diagnosis in the family or age 40, whichever is youngest, but not before age 25. For women with a lifetime risk of developing cancer over 20%, the American Cancer Society recommends that MRI screening be conducted annually as well [77]. MRI examinations have higher sensitivity, but lower specificity, resulting in a higher rate of false positives. A number of studies have suggested that MRI surveillance would benefit high-risk women [78–80], although this has not yet been fully evaluated clinically in a randomized trial. In addition, since mammographic breast density makes interpretation of mammograms more difficult and also increases the risk of developing breast cancer [51], breast MRI or ultrasound may be an appropriate complement to mammogram in women with dense breasts and a family history of breast cancer, even if the risk does not reach 20% by available mathematical models [80, 81]. In addition, chemoprevention or risk-reducing mastectomy, as discussed below, may be appropriate for some of these women [82]. Since the risk of ovarian cancer is not appreciably increased in breast-only histories, ovarian screening is not recommended.

29.6.2 Medical Management of Breast Cancer Predisposition Gene Mutation Carriers

As in high-risk women without identifiable gene mutations, the options for management include surveillance, chemoprevention and risk-reducing surgery. Most data comes from carriers of mutations in *BRCA1* and *BRCA2,* but are generally appropriately applied to those with Cowden, Peutz-Jeghers, and Li-Fraumeni syndromes, except as noted. The efficacy of various options in reducing mortality is still being defined, and enrollment of high-risk subjects into research resources and clinical trials should be encouraged.

29.6.3 Screening for Breast Cancer in Women

In the general population, mammographic screening for breast cancer in women over age 50 has been proven to be effective in reducing breast cancer mortality. Screening between the ages 40 and 49 is controversial but generally recommended [83, 84]. Women with identifiable *BRCA1* or *BRCA2* mutations should undergo annual mammograms [29] and breast MRI starting at age 25 [77, 80]. The age at initiation differs based on the syndrome. In Cowden syndrome, screening can start as late as 35, although it should begin 5–10 years earlier than the earliest breast cancer in the family [29]. Since breast cancer may occur earlier in women with Li-Fraumeni syndrome, screening begins at age 20–25 [35]. Breast MRI should be performed in a center that has a dedicated breast coil, experience in interpreting breast MRI and the ability to perform MRI-directed breast biopsies. Most centers alternate mammograms and MRI evaluations so that women receive some type of imaging every 6 months.

The risk of annual mammograms in women with gene mutations has been the subject of some discussion. It is not clear whether the potential benefit of early detection outweighs the actual risk of radiation-induced neoplasia [85]. Because the incidence of breast cancer at this age is very low and the carcinogenic risk of breast radiation is higher in younger women, it is not clear whether the reduction in mortality will outweigh the risk of radiation-induced

cancer [86]. Caution should be used in recommending mammograms under age 25.

Although there is no proof that breast self-examination or clinical breast examination reduces mortality from breast cancer in women either with or without a genetic predisposition to breast cancer, they are recommended components of screening for breast cancer [87]. The current recommendation is that breast self examination be performed monthly from age 18 and clinical breast exam twice yearly starting at age 25 [29]. The usefulness of clinical breast examination is related to the amount of time spent on the exam. In general, examination of both breasts should take approximately 3 min.

29.6.4 Screening for Breast Cancer in Men

Men with a breast cancer predisposition gene mutation should be instructed to perform breast examination monthly and undergo clinical breast exam annually or semi-annually. Baseline mammogram may be considered in the presence of gynecomastia [29]. Although men with a mutation have a much higher risk of breast cancer than the general male population, it is less than half the risk for women in the general population, so routine imaging with mammograms or MRI is not currently part of the screening protocol in most centers.

29.6.5 Screening for Ovarian Cancer

The efficacy of screening for ovarian cancer is poor in the general population [88]. However, because of the higher incidence of ovarian cancer in mutation carriers, these women constitute a group for whom screening may provide some benefit. Yearly screening with transvaginal ultrasound (TVU) and serum CA-125 has been demonstrated to be ineffective [89]. Therefore, despite the absence of data, the National Comprehensive Cancer Network suggests that for women who elect screening rather than the preferred risk-reducing oophorectomy, screening for ovarian cancer with CA125 and TVU should be performed every 6 months starting at age 35 or 5–10 years earlier than the earliest ovarian cancer diagnosed in the family [29].

29.6.6 Risk-reducing Mastectomy

The most effective means of reducing the risk of breast cancer is with mastectomy. The seminal manuscript studied 639 women with a family history of breast cancer and found a 90% reduction in breast cancer incidence compared with the incidence in sisters of women who did not have such surgery [90], and subsequent studies have confirmed the efficacy of this option [91, 92]. Mutation status in women in the seminal study was not known, but the reduction of risk was seen both in those with a moderate family history as well as those with a strong family history suggestive of a genetic predisposition. Most women in this series underwent subcutaneous mastectomy, a procedure that preserves the nipple-areolar complex and therefore leaves more breast tissue than a total mastectomy [90]. Options for risk-reducing mastectomy include total mastectomy, which removes the nipple-areolar complex, or total skin-sparing mastectomy in which the nipple is retained. If the latter procedure is performed, surgeons should remove as much breast tissue as possible from the underside of the nipple. Women considering mastectomy should understand the morbidity of the surgery, including surgical risks and loss of sensation, options for reconstruction, the small risk of developing breast cancer in residual breast tissue, and the possibility of finding unsuspected cancer [93]. A preoperative mammogram and/or MRI should be performed since identifying an unsuspected cancer may alter the type of surgery that is performed, and specifically allows for cancer staging with a sentinel node biopsy rather than a full axillary dissection.

Risk-reducing mastectomy is appropriate for some women and not for others, based primarily on the women's own beliefs and values. Many women are clear that identification of a mutation would lead them to choose immediate mastectomy, and others are equally clear about their wish to avoid the procedure. For those who are undecided, several principles may assist in making a decision about this procedure.

- Prior diagnosis of breast cancer. Because not all women with breast cancer predisposition gene mutations develop breast cancer at all, some may wish to defer risk-reducing mastectomy until they are diagnosed with breast cancer, and then undergo therapeutic mastectomy on the affected side and contralateral risk-reducing mastectomy. The devel-

opment of breast cancer in a woman with a *BRCA* gene mutation increases the 5-year risk of a contralateral breast cancer to around 20%, and many women choose bilateral mastectomy at the time of diagnosis. However, most women will have a significantly greater risk of mortality from a prior breast cancer than from a breast cancer that has yet to be discovered, and the prognosis of the prior (or current) cancer should be considered in making this decision. The short- to intermediate-term risk of cancer recurrence in women with high-risk disease may be substantially higher than the risk of developing a second primary tumor. However, women with higher-risk cancers may be more likely to request bilateral mastectomy (or contralateral prophylactic mastectomy), and even if this does not improve prognosis, the procedure may provide sufficient peace of mind to be warranted.

- Risk of developing breast cancer. Most women who consider risk-reducing mastectomy have gene mutations and are therefore at a high-enough risk to warrants mastectomy. Women may also wish to undergo mastectomy because of a combination of family history and personal risk factors defined by Gail [82], such as the need for prior breast biopsies based on suspicious mammograms or breast exams, and the presence of proliferative breast disease. Assuring that the woman understands her age-specific risks, as well as her lifetime risks, is also important. Although the lifetime risk of developing breast cancer may be, for example, 70%, a 50-year old woman has a risk that is less than that since she has already lived past some of that risk. Describing risk in quantifiable terms per year (usually around 0.5–1.5% per year for women with mutations) may be helpful. Some women wish to undergo mastectomy because of an inflated sense of the risk of cancer, in which differentiating the age-specific and lifetime risk is useful.
- Ease of cancer detection. Breast cancer may be more or less difficult to detect, depending on the density of breast tissue on physical exam and imaging [51]. Detection is much easier in women with fatty-replaced breasts than in women with extremely dense breasts. Women may choose mastectomy over screening if screening tools are less likely to detect cancer at an early stage.
- Chemoprevention options. Risk reduction with tamoxifen or raloxifene may be an option instead of mastectomy. The degree of risk reduction in mutation carriers has not been evaluated in prospective trials, but is certainly less than with prophylactic mastectomy. Nevertheless, this option should be discussed.
- Psychological factors. Women consider prophylactic mastectomy for many reasons. For some, the family culture is to have risk-reducing surgery, and the pressure to undergo the procedure may be significant. These women should be supported if they wish to have surveillance alone. Other women have cared for family members with terminal cancer and may wish to spare their own families. Some fear developing cancer or are extremely anxious about screening, and the probability of early detection is not reassuring. All these issues should be explored in depth. Counseling or grief therapy may be appropriate in some cases. There is no absolute medical indication for this procedure, and the final decision about risk-reducing surgery is always therefore a psychological one.

29.6.7 Risk-Reducing Oophorectomy

Ovarian cancer is generally less common in families with *BRCA1* and *BRCA2* mutations than is breast cancer. Some families have a preponderance of ovarian cancer, which may be related to specific *BRCA* gene mutations or to modifying genes. The lifetime incidence is about 40% in *BRCA1* mutation carriers and 10–30% in *BRCA2* mutation carriers. Oophorectomy is estimated to reduce the risk of ovarian cancer by greater than 90% [94], although there is still a risk of primary peritoneal carcinoma, which has the same microscopic appearance and biology as epithelial ovarian cancer [89]. The clinical issues in women contemplating risk-reducing oophorectomy include the appropriate age to undergo the procedure, the extent of the surgery, and the use of postoophorectomy hormone replacement therapy [95].

The age-specific risk of ovarian cancer in mutation carriers increases sharply after age 40, although the risk per year is still low at that age. If risk-reducing surgery is to be performed, it is reasonable to consider this between age 35 and 40. Healthy women in their 70s may still accrue a benefit from this procedure, although the absolute benefit decreases with age. Several studies have demonstrated the added

advantage of reducing breast cancer risk if the ovaries are removed before menopause. This seems to be particularly true in women with *BRCA2* gene mutations, probably related to the fact that *BRCA2*-associated breast cancers are usually estrogen receptor positive [94]. Breast cancer risk reduction is observed even in women who take hormone replacement therapy after surgery.

Risk reducing oophorectomy in mutation carriers should be performed by a gynecologic oncologist or other surgeon experienced in performing oophorectomy for risk reduction in high-risk women. Surgical staging with multiple peritoneal biopsies and washings should be performed to detect an unexpected ovarian or primary peritoneal cancer [96]. The ovaries should be multiple-sectioned, and examined by an experienced pathologist. The fallopian tubes should be removed and carefully examined since tubal carcinomas are increased in mutation carriers. The role of hysterectomy is less clear, as there seems to be no increased risk of endometrial cancer associated with *BRCA* mutations. However, women who wish to take tamoxifen may choose to undergo hysterectomy in order to reduce the risk of tamoxifen-associated endometrial hyperplasia [97]. Women who are planning on taking estrogen may also choose hysterectomy to avoid the need for progestins. In general, salpingo-oophorectomy can be performed laparoscopically with less morbidity than if hysterectomy is also performed. If hysterectomy would require an open procedure and tamoxifen or estrogen are not planned, it is reasonable to perform salpingo-ooporectomy alone.

The use of estrogen following risk-reducing oophorectomy is a subject of debate [98, 99]. Oophorectomy in young women has been associated with increased mortality due to cardiovascular and bone effects of estrogen depletion [100, 101]. Estrogen replacement therapy should therefore be strongly considered in younger premenopausal women undergoing risk-reducing oophorectomy [95]. Particularly if estrogen is used without progestin, breast cancer risk is still reduced after oophorectomy. One reasonable approach is to use estrogen (with cyclic progestin or a progestin-containing IUD in women with a uterus) from the time of oophorectomy until around age 45–50, and then consider tamoxifen for 5 years. In general, women who have had breast cancer should not take estrogen, and this decision should be made in consultation with the woman's oncologist.

29.6.8 Chemoprevention for Breast Cancer

Tamoxifen is a selective estrogen receptor modulator that has been used for more than 30 years for treatment of breast cancer, both as adjuvant therapy and treatment of advanced disease. Women treated with tamoxifen were found to have a reduction in the incidence of contralateral breast cancer. This observation led to studies of tamoxifen as a breast cancer chemoprevention agent in women who were at high risk but did not have breast cancer. The largest such study, conducted by the National Surgical Adjuvant Breast and Bowel Project, demonstrated approximately a 50% risk reduction in incidence of both invasive and in situ breast cancer in women who had an *a priori* 5-year risk of 1.7% or greater as calculated by the Gail model [82, 102]. Only estrogen receptor-positive cancers are reduced with tamoxifen. There was no difference in the number of estrogen receptor-negative cancers [102]. This study led to approval of tamoxifen by the US Food and Drug Administration in October 1998 as a means to reduce risk of breast cancer. Tamoxifen is associated with a doubling of the risk of endometrial cancer (from one to two cases per 1,000 women per year) and a tripling of risk of pulmonary embolism (from 0.23 to 0.69 per 1,000 women per year), both primarily in postmenopausal women. A second study, The Study of Tamoxifen and Raloxifene (STAR) demonstrated that raloxifene, another selective estrogen receptor modulator, provided benefits similar to tamoxifen in reducing the risk of invasive breast cancer, although *in situ* cancer was not reduced [103]. The significance of this finding is not clear, but raloxifene has been approved for use as a chemopreventive agent and carries with it a lower risk of thromboembolic disease and endometrial hyperplasia than tamoxifen.

The use of tamoxifen or raloxifene in women with gene mutations is not well studied [104]. It is probably of benefit in women with *BRCA2* mutations, since these cancers are usually estrogen receptor positive. Because a disproportionate number of cancers in *BRCA1* mutation carriers are estrogen receptor negative, tamoxifen may not reduce risk in these women. In women with a family history of breast cancer but without an identifiable breast cancer predisposition gene mutation, either tamoxifen or raloxifene is recommended if the risk by the Gail model is over 1.7%. Women with a family history of breast cancer, but no

affected first-degree relatives, or women with dense breast tissue, may have a calculated risk lower than 1.7%, but chemoprevention may still be appropriate.

29.6.9 Chemoprevention for Ovarian Cancer

Women who have been taken oral contraceptives for at least 5 years have a 50% reduction in risk of developing ovarian cancer [105]. There has been some concern that use of oral contraceptives may increase the risk of breast cancer [106, 107], but others have demonstrated no impact [108–110]. It appears that modern low-dose estrogen pills have minimal impact on the risk of breast cancer, probably reduce the risk of ovarian cancer even in women with mutations, and are an acceptable means of contraception and risk reduction in women with mutations. Use of oral contraceptives does not need to be continuous to provide benefit [109]. It is reasonable to initiate these agents several years prior to first childbirth, then resume following childbirth, although one study demonstrated some increased risk in breast cancer if taken prior to the first full-term pregnancy [109]. Progestins and other inhibitors of ovulation may be similarly effective, although data are lacking. Current studies are evaluating this question.

29.6.10 Medical Management of Mutation Carriers Diagnosed with Breast Cancer

BRCA gene mutations have little influence on the management of breast cancer although several studies are exploring new agents. Many women with mutations choose bilateral mastectomy if a unilateral cancer is found in order to reduce the substantial risk of developing a contralateral breast cancer. Lumpectomy with radiation therapy, however, has been demonstrated to provide good control of cancer with no increase in the risk of ipsilateral breast tumor recurrence in the first 6–7 years after treatment [111], but longer-term follow-up is lacking.

Women who are newly diagnosed with breast cancer and judged to be testing candidates because of family history, age, or ethnicity are often required to make decisions about testing and cancer treatment simultaneously [112]. Unless surgical treatment of the cancer itself is impacted by mutation status, there is little reason to perform testing in a woman who is not able to make a thoughtful decision about undergoing testing in a rushed situation. Test results are usually available within 2 weeks. The major impact of genetic testing is usually surgical and not systemic therapy [113, 114]. Women with breast cancer who would choose lumpectomy over mastectomy if no mutation was found, can undergo lumpectomy, proceed with chemotherapy, and then make the decision to undergo mastectomy or postlumpectomy radiation, depending on the result of the genetic test.

29.7 Information for Extended Family Members

Although the focus of this chapter has been the patient who presents with concerns about her particular family history, genetic testing is different from other medical testing in that it has implications for the extended family members. Most obviously, a woman who has an identifiable mutation has the chance of passing that mutation to her children, and since she almost certainly inherited it from a parent, her siblings also have a 50% chance of having the mutation. However, extended family members can also be at risk for having the mutation, and several mechanisms, such as model letters, can be provided to patients to help them communicate with the appropriate testing candidates. Studies reveal that the majority of women share their mutation status with their families, especially with those members they believe are also at risk [115–117].

Women who do not have mutations can also provide useful information to extended family members [118]. In the case of individuals who are members of a family in which there is a known mutation, the children would have a risk of developing cancer similar to others in the general population. However, if the individual is a member of a family in which there is not a known mutation, the empiric risk information would be relevant to children, siblings, and possibly extended family members. Typically, the responsibility to share the implications of this information is given to the patient, after appropriate education, to preserve patient confidentiality.

29.8 Direct-to-Consumer Genetic testing

With the anticipated promises of the Human Genome Project, along with consumer interest in self-directed health management, many companies are beginning to offer genetic testing directly to the public. This appeals to individuals who have concerns about genetic discrimination, and advocates claim that this knowledge allows them to make treatment and lifestyle decisions[119].

There are two ways in which direct-to-consumer (DTC) testing is promoted: one which increases the public's awareness while still requiring that the test be ordered by a physician who receives the result [120]; and the other is purchased, and ordered by the consumer, with results going directly to that consumer [121]. Both models have been used to promote breast cancer genetic testing.

In 2002, Myriad Genetic Laboratories piloted an advertising campaign in Atlanta and Denver, and in 2007, launched a larger campaign in New York, Connecticut, Rhode Island, and Massachusetts. The ads encouraged women to talk to their doctors about their family history or call a toll-free number (directed to the laboratory) to learn if they were appropriate testing candidates. Although advocates believe that this helps educate women and their physicians, many in the genetics community are concerned that ads lead to overuse of the test [120, 122, 123].

Other companies offer genetic testing for a wide variety of conditions, including breast cancer. Currently, these companies do not offer testing for the genes discussed in this chapter, which typically confer a five to tenfold increased risk of developing cancer. Instead, their panels of single nucleotide polymorphism include many that confer a two to fourfold increased risk. As more genes are identified that are associated with an increased risk, they will likely be added to these panels. The current question is within the molecular findings will lead to a management plan that is different from that which would be offered based only on a family history assessment [122, 123].

29.9 In summary

As the public becomes more aware of and informed about the genetics of breast cancer, there will be an increasing demand for genetic counseling and clinical testing. Whether as part of a comprehensive clinical breast cancer clinic or as a primary practitioner's service, high-risk families will be identified and should be offered appropriate services. A variety of resources from both the oncology and genetic communities are available to provide specialized care to women and their families who need genetic counseling, result interpretation, or psychological support related to testing and subsequent management decisions [Table 29.3]. The future of genetic testing will be a team effort, involving the primary care physician, the cancer center and the cancer genetic service, whether it is obtaining a family and personal health history to determine the magnitude of risk, conducting genetic counseling and/or testing, or facilitating long-term medical management of the patient and her extended family members.

Table 29.3 Additional resources: websites

Facing our risks of cancer empowered (FORCE):www.facingourrisk.org. This website is a resource for individuals and families who have a strong family history of breast cancers or are carriers of a mutation that confers an increased risk of developing cancer. General information, chat rooms, a blog, and discussion board are available on-line, while a national meeting in May of each year allows participants to gather, and local chapters are developing in several states
Gene clinics:www.geneclinics.org. This website is a companion to gene tests, funded by the National Institutes of Health and developed at the University of Washington, Seattle. Gene clinics is a clinical information resource relating genetic testing to the diagnosis, management, and genetic counseling of individuals and families with specific inherited disorders. It contains information related to molecular testing, genetic counseling and management options for specific diseases
National society of genetic counselors:www.nsgc.org. This site is the resource for the genetic counseling profession and contains a resource link to assist consumers and professional local genetic counseling services
National institutes of health:http://www.cancer.gov/search/geneticsservices/. Cancer Net PDQ contains information about cancer, clinical trials and providers of cancer genetic services
National comprehensive cancer network:www.nccn.org. National comprehensive cancer network (NCCN) is an alliance of cancer centers and was established in 1995 to provide state-of-the-art guidelines in cancer prevention, screening, diagnosis, and treatment through excellence in basic and clinical research. This site contains practice guidelines for identification and management of genetically high-risk patients

References

1. Lynch HT, Lynch JF (1986) Breast cancer genetics in an oncology clinic: 328 consecutive patients. Cancer Genet Cytogenet. 22(4):369–71
2. Claus EB et al (1996) The genetic attributable risk of breast and ovarian cancer. Cancer. 77(11):2318–24
3. Madigan MP et al (1995) Proportion of breast cancer cases in the United States explained by well-established risk factors. J Natl Cancer Inst. 87(22):1681–5
4. Lindor NM, et al (2008) Concise handbook of familial cancer susceptibility syndromes – second edition. J Natl Cancer Inst Monogr. (38):1–93
5. Ford D et al (1994) Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet. 343(8899): 692–5
6. Frank TS et al (1998) Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family history and ovarian cancer risk. J Clin Oncol. 16(7):2417–25
7. Ford D, Easton DF, Peto J (1995) Estimates of the gene frequency of BRCA1 and its contribution to breast and ovarian cancer incidence. Am J Hum Genet. 57(6):1457–62
8. Struewing JP et al (1997) The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med. 336(20):1401–8
9. Petrij-Bosch A et al (1997) BRCA1 genomic deletions are major founder mutations in Dutch breast cancer patients. Nat Genet. 17(3):341–5
10. Johannesdottir G et al (1996) High prevalence of the 999del5 mutation in Icelandic breast and ovarian cancer patients. Cancer Res. 56(16):3663–5
11. Liede A, Karlan BY, Narod SA (2004) Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. J Clin Oncol. 22(4):735–42
12. Tai YC et al (2007) Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst. 99(23): 1811–4
13. Ford D et al (1998) Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet. 62(3):676–89
14. Antoniou A et al (2003) Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 72(5): 1117–30
15. Gayther SA et al (1997) Variation of risks of breast and ovarian cancer associated with different germline mutations of the BRCA2 gene. Nat Genet. 15(1):103–5
16. Satagopan JM et al (2002) Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Clin Cancer Res. 8(12):3776–81
17. Schneider BP et al (2008) Triple-negative breast cancer: risk factors to potential targets. Clin Cancer Res. 14(24): 8010–8
18. Lakhani SR et al (2002) The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. J Clin Oncol. 20(9):2310–8
19. Bane AL et al (2007) BRCA2 mutation-associated breast cancers exhibit a distinguishing phenotype based on morphology and molecular profiles from tissue microarrays. Am J Surg Pathol. 31(1):121–8
20. Foulkes WD et al (2004) Estrogen receptor status in BRCA1- and BRCA2-related breast cancer: the influence of age, grade, and histological type. Clin Cancer Res. 10(6): 2029–34
21. Lu KH et al (2000) Occult ovarian tumors in women with BRCA1 or BRCA2 mutations undergoing prophylactic oophorectomy. J Clin Oncol. 18(14):2728–32
22. Sherman ME et al (1999) Histopathologic features of ovaries at increased risk for carcinoma. A case-control analysis. Int J Gynecol Pathol. 18(2):151–7
23. Levine DA et al (2003) Fallopian tube and primary peritoneal carcinomas associated with BRCA mutations. J Clin Oncol. 21(22):4222–7
24. Anon (1999) Cancer risks in BRCA2 mutation carriers. The Breast Cancer Linkage Consortium. J Natl Cancer Inst. 1999;91(15):1310–6
25. Domchek SM, Weber BL (2006) Clinical management of BRCA1 and BRCA2 mutation carriers. Oncogene. 25(43): 5825–31
26. Agalliu I et al (2009) Associations of high-grade prostate cancer with BRCA1 and BRCA2 founder mutations. Clin Cancer Res. 15(3):1112–20
27. Narod SA et al (2008) Rapid progression of prostate cancer in men with a BRCA2 mutation. Br J Cancer. 99(2):371–4
28. Schreibman IR et al (2005) The hamartomatous polyposis syndromes: a clinical and molecular review. Am J Gastroenterol. 100(2):476–90
29. National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian.2008; V.1.2008
30. Pilarski R, Eng C (2004) Will the real Cowden syndrome please stand up (again)? Expanding mutational and clinical spectra of the PTEN hamartoma tumor syndrome. J Med Genet. 41(5):323–6
31. Olivier M et al (2003) Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. Cancer Res. 63(20):6643–50
32. Varley JM (2003) Germline TP53 mutations and Li-Fraumeni syndrome. Hum Mutat. 21(3):313–20
33. Lustbader ED et al (1992) Segregation analysis of cancer in families of childhood soft tissue sarcoma patients. Am J Hum Genet. 51(2):344–56
34. Birch JM et al (2001) Relative frequency and morphology of cancers in carriers of germline TP53 mutations. Oncogene. 20(34):4621–8
35. Hisada M et al (1998) Multiple primary cancers in families with Li-Fraumeni syndrome. J Natl Cancer Inst. 90(8):606–11
36. Giardiello FM et al (1987) Increased risk of cancer in the Peutz-Jeghers syndrome. N Engl J Med. 316(24):1511–4
37. Hearle N et al (2006) Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res. 12(10): 3209–15
38. Mehenni H et al (2006) Cancer risks in LKB1 germline mutation carriers. Gut. 55(7):984–90
39. Giardiello FM, Trimbath JD (2006) Peutz-Jeghers syndrome and management recommendations. Clin Gastroenterol Hepatol. 4(4):408–15

40. Bennett IC, Gattas M, Teh BT (2000) The management of familial breast cancer. Breast. 9(5):247–63
41. Hoskins KF et al (1995) Assessment and counseling for women with a family history of breast cancer. A guide for clinicians. JAMA. 273(7):577–85
42. Bennett RL et al (2008) Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Couns. 17(5):424–33
43. Schneider KA et al (2004) Accuracy of cancer family histories: comparison of two breast cancer syndromes. Genet Test. 8(3):222–8
44. Kerber RA, Slattery ML (1997) Comparison of self-reported and database-linked family history of cancer data in a case-control study. Am J Epidemiol. 146(3):244–8
45. Ziogas A, Anton-Culver H (2003) Validation of family history data in cancer family registries. Am J Prev Med. 24(2):190–8
46. Acheson LS et al (2000) Family history-taking in community family practice: implications for genetic screening. Genet Med. 2(3):180–5
47. Weitzel JN et al (2007) Limited family structure and BRCA gene mutation status in single cases of breast cancer. JAMA. 297(23):2587–95
48. Calle EE et al (2003) Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 348(17):1625–38
49. Boffetta P, Hashibe M (2006) Alcohol and cancer. Lancet Oncol. 7(2):149–56
50. Boffetta P et al (2006) The burden of cancer attributable to alcohol drinking. Int J Cancer. 119(4):884–7
51. Boyd NF et al (2007) Mammographic density and the risk and detection of breast cancer. N Engl J Med. 356(3):227–36
52. Zheng T et al (2002) Radiation exposure from diagnostic and therapeutic treatments and risk of breast cancer. Eur J Cancer Prev. 11(3):229–35
53. El-Gamal H, Bennett RG (2006) Increased breast cancer risk after radiotherapy for acne among women with skin cancer. J Am Acad Dermatol. 55(6):981–9
54. Hopwood P et al (2003) Do women understand the odds? Risk perceptions and recall of risk information in women with a family history of breast cancer. Community Genet. 6(4):214–23
55. Jemal A et al (2007) Cancer statistics, 2007. CA Cancer J Clin. 57(1):43–66
56. Woloshin S, Schwartz LM, Welch HG (2002) Risk charts: putting cancer in context. J Natl Cancer Inst. 94(11): 799–804
57. Prasad K et al (2008) Tips for teachers of evidence-based medicine: understanding odds ratios and their relationship to risk ratios. J Gen Intern Med. 23(5):635–40
58. Gail MH, Benichou J (1994) Validation studies on a model for breast cancer risk. J Natl Cancer Inst. 86(8):573–5
59. Rockhill B et al (2001) Validation of the Gail et al model of breast cancer risk prediction and implications for chemoprevention. J Natl Cancer Inst. 93(5):358–66
60. Berry DA et al (2002) BRCAPRO validation, sensitivity of genetic testing of BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes. J Clin Oncol. 20(11): 2701–12
61. Gilpin CA, Carson N, Hunter AG (2000) A preliminary validation of a family history assessment form to select women at risk for breast or ovarian cancer for referral to a genetics center. Clin Genet. 58(4):299–308
62. Parmigiani G, Berry D, Aguilar O (1998) Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. Am J Hum Genet. 62(1):145–58
63. Antoniou AC et al (2006) BRCA1 and BRCA2 mutation predictions using the BOADICEA and BRCAPRO models and penetrance estimation in high-risk French-Canadian families. Breast Cancer Res. 8(1):R3
64. American Society of Clinical Oncology (2003) American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. J Clin Oncol. 21(12):2397–406
65. Nelson H et al (2005) Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation statement. Ann Intern Med. 143(5): 355–61
66. Singer ME, Cebul RD (1997) BRCA1: to test or not to test, that is the question. Health Matrix Clevel. 7(1):163–85
67. Trepanier A et al (2004) Genetic cancer risk assessment and counseling: recommendations of the National Society of Genetic Counselors. J Genet Couns. 13(2):83–114
68. Claes E et al (2003) Communication with close and distant relatives in the context of genetic testing for hereditary breast and ovarian cancer in cancer patients. Am J Med Genet A. 116(1):11–9
69. Ferla R et al (2007) Founder mutations in BRCA1 and BRCA2 genes. Ann Oncol. 18(Suppl 6):vi93–8
70. Hudson KL et al (1995) Genetic discrimination and health insurance: an urgent need for reform. Science. 270(5235): 391–3
71. Hudson KL, Holohan MK, Collins FS (2008) Keeping pace with the times–the Genetic Information Nondiscrimination Act of 2008. N Engl J Med. 358(25):2661–3
72. Bradbury AR et al (2007) How often do BRCA mutation carriers tell their young children of the family's risk for cancer? A study of parental disclosure of BRCA mutations to minors and young adults. J Clin Oncol. 25(24):3705–11
73. Bradbury AR et al (2008) Should genetic testing for BRCA1/2 be permitted for minors? Opinions of BRCA mutation carriers and their adult offspring. Am J Med Genet C Semin Med Genet. 148C(1):70–7
74. Smith A et al (2007) Phenocopies in BRCA1 and BRCA2 families: evidence for modifier genes and implications for screening. J Med Genet. 44(1):10–5
75. Goldgar D, et al (2007) BRCA phenocopies or ascertainment bias? J Med Genet. 2007;44(8):e86; author reply e88
76. Katki HA, Gail MH, Greene MH Breast-cancer risk in BRCA-mutation-negative women from BRCA-mutation-positive families. Lancet Oncol. 8(12):1042–3
77. Saslow D et al (2007) American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 57(2):75–89
78. Leach MO et al (2002) The UK national study of magnetic resonance imaging as a method of screening for breast cancer (MARIBS). J Exp Clin Cancer Res. 21(3 Suppl): 107–14
79. Morris EA et al (2003) MRI of occult breast carcinoma in a high-risk population. AJR Am J Roentgenol. 181(3): 619–26

80. Warner E et al (2004) Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA. 292(11):1317–25
81. Plevritis SK et al (2006) Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. JAMA. 295(20):2374–84
82. Gail MH et al (1999) Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. J Natl Cancer Inst. 91(21):1829–46
83. Hendrick RE, et al (1997) Benefit of screening mammography in women aged 40-49: a new meta-analysis of randomized controlled trials. J Natl Cancer Inst Monogr. (22): 87–92
84. Moss SM et al (2006) Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomized controlled trial. Lancet. 368(9552): 2053–60
85. Berrington deGonzalez A, et al (2009) Estimated risk of radiation-induced breast cancer from mammographic screening for young BRCA mutation carriers. J Natl Cancer Inst. 101(3):205–09
86. Landier W et al (2004) Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group Long-term Follow-up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. J Clin Oncol. 22(24):4979–90
87. Baxter N (2001) Preventive health care, 2001 update: should women be routinely taught breast self-examination to screen for breast cancer? CMAJ. 164(13):1837–46
88. Buys SS et al (2005) Ovarian cancer screening in the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial: findings from the initial screen of a randomized trial. Am J Obstet Gynecol. 193(5):1630–9
89. Greene MH et al (2008) A prospective study of risk-reducing salpingo-oophorectomy and longitudinal CA-125 screening among women at increased genetic risk of ovarian cancer: design and baseline characteristics: a Gynecologic Oncology Group study. Cancer Epidemiol Biomark Prev. 17(3):594–604
90. Hartmann LC et al (1999) Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med. 340(2):77–84
91. Hartmann LC, Degnim A, Schaid DJ (2004) Prophylactic mastectomy for BRCA1/2 carriers: progress and more questions. J Clin Oncol. 22(6):981–3
92. Rebbeck TR et al (2004) Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE study group. J Clin Oncol. 22(6): 1055–62
93. Brandberg Y et al (2008) Psychological reactions, quality of life, and body image after bilateral prophylactic mastectomy in women at high risk for breast cancer: a prospective 1-year follow-up study. J Clin Oncol. 26(24):3943–9
94. Kauff ND et al (2008) Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. J Clin Oncol. 26(8):1331–7
95. Rebbeck TR et al (2005) Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE study group. J Clin Oncol. 23(31):7804–10
96. Powell CB et al (2005) Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: role of serial sectioning in the detection of occult malignancy. J Clin Oncol. 23(1): 127–32
97. Gabriel CA et al (2009) Use of total abdominal hysterectomy and hormone replacement therapy in BRCA1 and BRCA2 mutation carriers undergoing risk-reducing salpingo-oophorectomy. Fam Cancer. 8(1):23–8
98. Rossouw JE et al (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 288(3):321–33
99. Anderson GL et al (2004) Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 291(14):1701–12
100. Domchek SM et al (2006) Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Lancet Oncol. 7(3):223–9
101. Shuster LT et al (2008) Prophylactic oophorectomy in premenopausal women and long-term health. Menopause Int. 14(3):111–6
102. Fisher B et al (1998) Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 90(18):1371–88
103. Vogel VG et al (2006) Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA. 295(23):2727–41
104. King MC et al (2001) Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA. 286(18):2251–6
105. Whittemore AS et al (2004) Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations. Br J Cancer. 91(11):1911–5
106. Kelsey JL, Gammon MD, John EM (1993) Reproductive factors and breast cancer. Epidemiol Rev. 15(1):36–47
107. Ursin G et al (1997) Does oral contraceptive use increase the risk of breast cancer in women with BRCA1/BRCA2 mutations more than in other women? Cancer Res. 57(17): 3678–81
108. Brohet RM et al (2007) Oral contraceptives and breast cancer risk in the international BRCA1/2 carrier cohort study: a report from EMBRACE, GENEPSO, GEO-HEBON, and the IBCCS Collaborating Group. J Clin Oncol. 25(25): 3831–6
109. Haile RW et al (2006) BRCA1 and BRCA2 mutation carriers, oral contraceptive use, and breast cancer before age 50. Cancer Epidemiol Biomark Prev. 15(10):1863–70
110. Milne RL et al (2005) Oral contraceptive use and risk of early-onset breast cancer in carriers and noncarriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomark Prev. 14(2):350–6
111. Pierce LJ et al (2006) Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. J Clin Oncol. 24(16): 2437–43
112. Ardern-Jones A, Kenen R, Eeles R (2005) Too much, too soon? Patients and health professionals' views concerning the impact of genetic testing at the time of breast cancer

diagnosis in women under the age of 40. Eur J Cancer Care (Engl). 14(3):272–81
113. Schwartz MD et al (2004) Impact of BRCA1/BRCA2 counseling and testing on newly diagnosed breast cancer patients. J Clin Oncol. 22(10):1823–9
114. Weitzel JN, et al (2003) Effect of genetic cancer risk assessment on surgical decisions at breast cancer diagnosis. Arch Surg. 138(12):1323–8; discussion 1329
115. Patenaude AF et al (2006) Sharing BRCA1/2 test results with first-degree relatives: factors predicting who women tell. J Clin Oncol. 24(4):700–6
116. MacDonald DJ et al (2007) Selection of family members for communication of cancer risk and barriers to this communication before and after genetic cancer risk assessment. Genet Med. 9(5):275–82
117. McGivern B et al (2004) Family communication about positive BRCA1 and BRCA2 genetic test results. Genet Med. 6(6):503–9
118. Forrest LE et al (2008) Increased genetic counseling support improves communication of genetic information in families. Genet Med. 10(3):167–72
119. Hogarth S, Javitt G, Melzer D (2008) The current landscape for direct-to-consumer genetic testing: legal, ethical, and policy issues. Annu Rev Genomics Hum Genet. 9: 161–82
120. Myers MF et al (2006) Genetic testing for susceptibility to breast and ovarian cancer: evaluating the impact of a direct-to-consumer marketing campaign on physicians' knowledge and practices. Genet Med. 8(6):361–70
121. Gollust SE, Wilfond BS, Hull SC (2003) Direct-to-consumer sales of genetic services on the Internet. Genet Med. 5(4): 332–7
122. Geransar R, Einsiedel E (2008) Evaluating online direct-to-consumer marketing of genetic tests: informed choices or buyers beware? Genet Test. 12(1):13–23
123. Wasson K (2008) Consumer alert: ethical issues raised by the sale of genetic tests directly to consumers. Am J Bioeth. 8(6):16–8
124. Slattery ML, Kerber RA (1993) A comprehensive evaluation of family history and breast cancer risk; the Utah Population Database. JAMA. 270:1563

Chemoprevention of Breast Cancer

30

Kathrin Strasser-Weippl and Paul E. Goss

30.1 Introduction

Breast cancer is the most common cancer affecting women worldwide. Approximately 210,000 new cases are reported annually in the United States, and there are about 1.2 million incident cases [1]. Globally, the incidence is rising rapidly, coincident with rising socioeconomic development, as exemplified in Southeast Asia. Early detection and treatment of breast cancer have resulted in an important but modest reduction in mortality [2]. Furthermore, despite data implicating diet and other environmental risk factors discussed in this and other chapters, no specific lifestyle changes have yet been shown to significantly reduce the risk of breast cancer. It is thus logical to explore chemoprevention as a way to address this urgent public health issue.

In time, a detailed understanding of the initiation, promotion and growth of breast cancer, and identification of risk factors that are able to identify specific individuals at risk will likely provide the rationale upon which to base optimal prevention strategies. In the interim, chemoprevention has focused on applying the antiestrogens tamoxifen, an established treatment in breast cancer patients, and raloxifene approved for the treatment and prevention of osteoporosis. Cohorts of women identified at high risk for breast cancer have been studied. In this chapter, we review known breast cancer risk factors, in particular the role of estrogen in the pathogenesis of the disease, and preclinical models of chemoprevention. Data related to breast cancer prevention from clinical trials with tamoxifen, raloxifene and the novel antiestrogen lasofoxifene are presented. The potential for new agents and strategies in chemoprevention is discussed. Ongoing and possible future clinical trial designs are outlined.

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30.2 Estrogen and Breast Cancer Risk

30.2.1 Estrogen in the Pathogenesis of Breast Cancer

The exact mechanisms involved in estrogen-induced carcinogenesis are not yet fully elucidated. Exogenous estrogens cause breast cancer in rat mammary tumor models (see next section), increasing both the number of breast tumors and the rapidity of their growth [3]. Endogenous or exogenous estrogens may enhance cell proliferation, which increases the number of cell divisions and thereby the number of mutations [4]. With an enhanced rate of proliferation, the time available for DNA repair is reduced. The single-stranded DNA present during cell division is particularly susceptible to damage (see also Chap. 11) [5]. Research is ongoing into the role of the metabolism of estrogens to genotoxic metabolites as a mechanism of carcinogenesis [6–10].

30.2.2 Epidemiological Factors

Epidemiological evidence strongly favors a role for estrogens in the development and growth of breast cancers. The almost 150-fold incidence of breast cancer in women compared with men reflects the relationship between female sex steroids and breast cancer. The model proposed is that total exposure to estrogens

I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases*,
DOI: 10.1007/978-3-540-69743-5_30, © Springer-Verlag Berlin Heidelberg 2010

during a lifetime is related to breast cancer risk. Thus, known risk factors, which have been shown to positively correlate with breast cancer risk, such as earlier age at menarche and late age at menopause, high bone mass, obesity in menopause, long-term use of hormone replacement therapy, high free levels of estradiol in postmenopausal women and possibly breast density, may all be considered as measures of estrogen exposure in the breasts [11–23]. Taken together, these data suggest that antagonizing the effects of estrogen is a logical target for breast cancer chemoprevention.

In addition to these estrogen-related factors, results from a study in Scandinavia suggest that the number of inches in height grown around puberty, which in turn correlates with onset of menarche, is related to the risk of breast cancer in later life [9].

30.2.3 Cohort Selection

As an attempt to translate these risk factors into a useful clinical selection tool for chemoprevention trials, a model of relative risks for various combinations of these and other factors was developed, and later extended, by Gail et al. [24]. The risk factors used in this model include age at menarche, age at first live birth, number of previous breast biopsies and number of first-degree relatives with breast cancer. With the Gail model, the chance of a woman of a given age and with specific risk factors of developing breast cancer over a specified period of time can be determined (Fig. 30.1). The Gail model of risk assessment was used in the most definitive breast cancer prevention trials (National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1) and the NSABP P-2, STAR trial as described below (see also Sect. 5) [25–27].

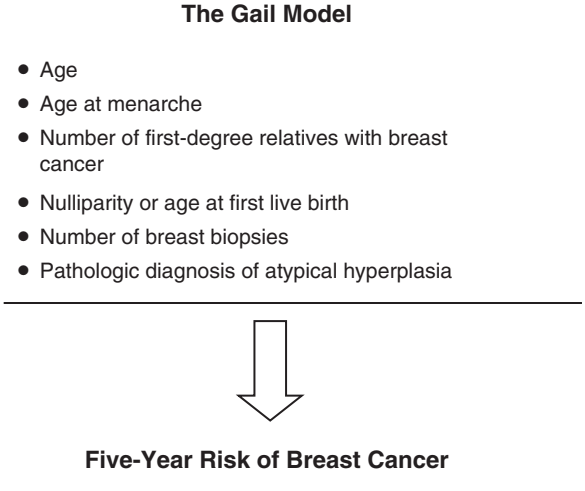

Fig. 30.1 Variables included in the original Gail Model

30.3 Preclinical Models of Potential Chemopreventatives

30.3.1 Breast Cancer Xenografts

In breast cancer research, the most widely used hormone-dependent human tumor cell line is MCF-7. These cells can be inoculated in the mammary fat pad of cycling "athymic nude mice." Being immunodeficient, these animals are not able to reject the human xenograft. MCF-7 breast cancer xenografts are hormone dependent and similar to human breast tumors with respect to many histological and phenotypic features. Therefore, the ability of novel endocrine agents to shrink established tumors or to prevent tumor formation by newly inoculated cells can be usefully studied in this model [28].

In another model of postmenopausal, hormone-dependent breast cancer in nude mice, MCF-7 cells transfected with the aromatase gene (MCF-7_{CA}) are inoculated in ovariectomized nude mice. The cells then serve as a source of estrogen in the "postmenopausal" mouse and produce sufficient estrogen to form tumors. This model is particularly useful to determine the effects of both antiestrogens and estrogen synthetase (aromatase) inhibitors on tumor growth [29, 30].

An important limitation of human xenograft models is that cells might have adapted to growth in vitro before being inoculated, and might not fully reflect human disease [10].

30.3.2 Carcinogen-induced Rat Mammary Tumors

The two most widely used chemical carcinogens for tumor induction in the rat mammary gland are 12-dimethylbenz(a)anthracene (DMBA) and N-methylnitrosurea (MNU). The tumors induced by these agents occur with latencies between 8 and 21 weeks and final tumor incidences are close to 100%. Tumor latency is in general inversely related to carcinogen dose, whereas tumor incidence is directly related, if an

earlier endpoint is used. As is the case with MCF-7 xenografts, these tumors have also been shown to be strongly hormone-dependent for both induction and growth. Investigational antiendocrine chemopreventatives can be given to animals prior to carcinogen administration (prevention of tumor initiation) or following it (inhibition of tumor promotion) [31].

30.4 SERMs in the Chemoprevention of Breast Cancer

The term selective estrogen receptor modulator (SERM) is an abbreviation for selective estrogen receptor (ER) modulator. These agents bind to the ER and exert either estrogenic or antiestrogenic effects depending on the specific end-organ. The most widely studied SERM is tamoxifen, a nonsteroidal antiestrogen, which has been shown in a large randomized trial to be effective in the chemoprevention of breast cancer. For raloxifene, a similar effect has been documented. Raloxifene and other selective estrogen receptor modulators (SERMs) discussed later in this section, show estrogenic and antiestrogenic effects on end-organs, which differ in part from those caused by tamoxifen. The efficacy and multiorgan effects of tamoxifen and raloxifene are presented and compared in detail below.

30.4.1 Tamoxifen

30.4.1.1 Tamoxifen and Breast Cancer Risk Reduction

Several studies of tamoxifen in early stage breast cancer (adjuvant clinical trials) have shown that when given once daily over 5 years, it reduces local and distant treatment failures compared to placebo. In addition, the incidence of tumors in the contralateral breast also decreased. These findings strongly supported the hypothesis that tamoxifen might serve as a tumor-preventive agent [32–35].

In 1992, the NSABP initiated the P-1 trial, which randomly assigned women at increased risk for breast cancer to receive either tamoxifen 20 mg daily or placebo for 5 years (Fig. 30.2). Women were deemed at increased risk either because they were 60 years of age or older or 35–59 years of age with a predicted 5-year-risk for breast cancer of at least 1.66%, or if they had a history of lobular carcinoma in situ (LCIS) [26]. The algorithm for estimating 5-year-risk was based on the work of Gail et al. with the average risk of breast cancer in P-1, as measured in the Gail model, being 3.2% over 5 years [25]. The duration of 5 years of tamoxifen was selected because previous trials had shown that there was a significant trend toward increased benefit (fewer contralateral cancers) with longer tamoxifen duration (up to 5 years) in the adjuvant setting [36, 37]. Through the duration of P-1, 78% of the 13,388 participants continued on therapy. When the trial was terminated in 1997, tamoxifen was found to have reduced the overall risk of invasive breast cancer by 49% ($P<0.00001$), with cumulative incidence rates through 69 months of follow-up of 43.4 vs. 22.0 per 1,000 women in the placebo and tamoxifen groups, respectively. When age, history of LCIS, history of atypical hyperplasia, and levels of predicted risk of breast cancer were taken into consideration, tamoxifen was found to be effective in all subgroups. The reduction in breast cancer incidence was confined to ER-positive tumors (69% less in the tamoxifen group) with no demonstrable difference in ER-negative disease. The greatest differences were seen in small tumors (less than 2 cm in size) and breast cancers without axillary involvement, with only small benefits from tamoxifen in larger tumors or higher nodal status. Importantly, a reduction of 50% ($P<0.002$) in noninvasive breast cancer (ductal carcinoma in situ (DCIS) and LCIS) was also noted. The results of the P-1 trial are shown in figure (Fig.30 3) [26].

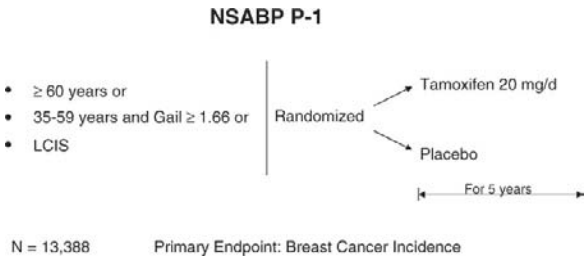

Fig. 30.2 Design of the NSABP P-1 Study

Two European trials also evaluated tamoxifen use in breast cancer chemoprevention [38, 39]. Overall, both failed to show any effect on breast cancer incidence. In the Italian trial, 5,408 women who had had a total hysterectomy for reasons other than neoplasm were randomized to receive tamoxifen 20 mg daily or a placebo, both orally for 5 years. Eligibility criteria in this study did not include any risk factors and HRT

Type of Event	Placebo	Tamoxifen	Risk Ratio
Invasive breast cancer	175	89	0.51
Non-invasive breast cancer	69	35	0.50
Invasive endometrial cancer	15	36	2.53
Fractures[1]	137	111	0.81
Stroke	24	38	1.59
Transient ischemic attack	25	19	0.76
Pulmonary embolism	6	18	3.01
Deep vein thrombosis	22	35	1.60

Fig. 30.3 Numbers of events in NSABP P-1. [1]Hip, spine, radius Colles' and other lower radius

(hormone replacement therapy) was allowed. Tamoxifen's lack of effect on the incidence of breast cancer in this trial can be explained by the relatively small size compared to P-1, the low-risk population (48.3% had had a bilateral oophorectomy and no specific risk factors were required) and the limited compliance, with only 149 participants completing 5 years of treatment. Interestingly, in this study, a subset analysis showed a definite trend toward chemoprevention of breast cancer on tamoxifen in women taking concurrent HRT [26, 38].

In the UK trial, 2,494 women with a strong family history of breast cancer were randomized to reveive tamoxifen 20 mg/day orally or a placebo for up to 8 years. Postmenopausal women taking HRT were eligible without having to stop such therapy and were also allowed to initiate concurrent HRT for relief of symptoms while on study. A number of possible explanations have been offered for the apparently contradictory results of the UK trial as compared to P-1. One reason could relate to the study populations, with the risk assessment of the UK trial being predominantly based on a strong family history of breast cancer, whereas in NSABP P-1, the entry criteria were based mostly on nongenetic risk factors. In addition, there was a considerable difference in the duration of follow-up between the two trials. The average follow-up for P-1 was only 3.5 years compared to the UK median of nearly 6 years. One other reason for failure of the European studies to show a positive result could be the fact that 41% of the participants in the UK trial and 14% in the Italian trial received HRT [26, 38, 39].

Based on the encouraging results of the P-1 trial, a second prevention trial using tamoxifen was initiated. Within the IBIS-I study, 7,145 women aged 35–70 years and at increased risk of breast cancer were randomly assigned to receive either tamoxifen (20 mg/day) or placebo for 5 years [40]. After a median follow-up of 96 months, significantly fewer women in the tamoxifen group had developed invasive breast cancer (RR > 0.73, $P > 0.004$). Interestingly, the prophylactic effect of tamoxifen was constant for the entire follow-up period, and no diminution of benefit was observed for up to 10 years. Not unexpectedly, the two arms did not differ in the risk of ER-negative invasive tumors (35 in each arm) across the entire follow-up period, but importantly, the risk of ER-positive invasive breast cancer was 34% lower in the tamoxifen arm (RR > 0.66). [40] This greater reduction in ER+ cancers in the 5 years following the 5 years of prior tamoxifen has not generally been taken into consideration when discussing the benefits and risks of preventative tamoxifen, but is clearly of importance to women considering chemoprevention with this agent.

30.4.1.2 Tamoxifen Effects other than on the Breast

Endometrial Cancer Risk. In P-1, participants who received tamoxifen had a 2.53 times greater risk of developing invasive endometrial cancer (95% CI 1.35–4.97). This was more common in women over 50 years of age compared with younger women (RR 4.01 vs. 1.21). All invasive endometrial cancers that occurred in the group receiving tamoxifen were FIGO stage I, none of which resulted in death [26]. In the IBIS trial, the risk ratio for endometrial cancer on tamoxifen was 1.55 (95% CI 0.68–3.05) [40]. The overview of adjuvant breast cancer trials by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [37] has confirmed this tamoxifen-related endometrial cancer risk. An annual excess of death from endometrial cancer of about 0.2 per 1,000 postmenopausal women treated with tamoxifen, who had not been hysterectomized, was observed. In general, the absolute increase in endometrial cancer was about half the decrease in contralateral breast cancer in these adjuvant trials [37].

Lipid Metabolism and Cardiovascular Risk. Although for over a decade tamoxifen has been thought to favorably influence lipid levels, a benefit on cardiovascular mortality has not consistently been demonstrated. While in retrospective analyzes of three randomized breast cancer trials, a reduction in coronary heart

disease (CHD) was observed, no benefit was demonstrated in P-1 or IBIS [26, 40–44]. In the EBCTCG overview of 1998, it was reported that mortality rates for causes "not attributed to breast or endometrial cancer" were nearly identical in patients receiving tamoxifen or placebo in the adjuvant setting [37]. Therefore, it remains to be established whether tamoxifen's favorable influence on lipid metabolism translates into a reduction in CHD.

Bone Metabolism and Fracture Risk. Tamoxifen has been shown to preserve bone mineral density (BMD) in postmenopausal breast cancer patients [45–47]. P-1 is the only prospective trial, which has evaluated the effect of tamoxifen on bone fractures and it showed a reduction in the risk of long bone and symptomatic vertebral fractures of borderline statistical significance (RR > 0.81, 95% CI 0.63–1.05) [26], while in the IBIS trial, no effect during active treatment could be shown (RR > 1.02, 95% CI 0.68–1.54). To date, tamoxifen has not been evaluated in a prospective trial in women with osteoporosis. However, the fracture risk was identical between raloxifene and tamoxifen in the STAR trial, confirming that they have very similar bone preserving effects [27].

Coagulation and Thromboembolic Risk. In the tamoxifen group of P-1, pulmonary embolism was three times as frequent (RR > 3.01, 95% CI 1.15–9.27) and strokes nearly twice as common among women ≥50 years of age (RR 1.75; 95% CI 0.98–3.20). In addition, more women receiving tamoxifen developed deep vein thrombosis (RR 1.6; 95% CI 0.91–2.86). A similar trend for pulmonary embolism, retinal vein thrombosis and superficial thrombophlebitis was observed in IBIS (see below). [40] Overall, the increase in vascular events on tamoxifen was comparable to that seen with hormone replacement therapy [26, 48].

Cataract Incidence. An additional risk of tamoxifen that was identified during P-1 was a small excess risk of cataracts (RR 1.14;95% CI 1.01–1.29) [26].

Quality of Life. Day et al. analyzed health-related quality of life in the P-1 study. Tamoxifen significantly increased bothersome hot flashes and vaginal discharge, but this did not affect overall physical and emotional well-being as reported by study participants. Importantly, weight gain and depression, two side effects commonly believed to be tamoxifen related, were not confirmed [49].

Overall, side effects due to tamoxifen seem to be much lower after the completion of the active treatment period than during active treatment. For example, in the IBIS-1 study, deep-vein thrombosis and pulmonary embolism were statistically significantly higher in the tamoxifen arm than in the placebo arm during active treatment (52 vs. 23 cases, RR > 2.26, 95% CI > 1.36–3.87) but not after tamoxifen was stopped (16 vs. 14 cases, RR > 1.14, 95% CI > 0.52–2.53. As the risk-reducing effect of tamoxifen appears to persist for at least 10 years, and most side effects of tamoxifen do not continue after the 5-year treatment period, this implies an improved risk-benefit ratio after the drug has been stopped.

On October 29, 1998, the FDA approved tamoxifen "for reducing the incidence of breast cancer in women at high risk for the disease." It should be noted however that the effect of tamoxifen on overall or breast cancer-specific survival has not been ascertained from these studies. While experience with tamoxifen in the adjuvant breast cancer setting suggests a favorable impact on survival, these results cannot yet be projected to the chemoprevention setting.

30.4.2 Raloxifene

30.4.2.1 Raloxifene and Breast Cancer Risk Reduction

Raloxifene hydrochloride is a SERM chemically distinct from tamoxifen. It appears to act as an estrogen antagonist in breast tissue, but as an estrogen agonist with respect to its effects on circulating lipids and bone and minimal agonist effects on the uterus.

On the basis of the initial laboratory studies and subsequent clinical evaluation, raloxifene received FDA approval for the prevention of osteoporosis in postmenopausal women in 1997.

In the Multiple Outcomes of Raloxifene Evaluation (MORE) study, 7,705 postmenopausal women with existing osteoporosis and no history of breast or endometrial cancer were randomized to receive either raloxifene (60 or 120 mg) or placebo daily (Fig. 30.4). The MORE trial was designed to test whether raloxifene would lower the risk of fractures in this patient population. Participants were also monitored for the occurrence of breast cancer, a secondary endpoint of the trial. After a median follow-up of 40 months, there were 12 ductal carcinomas in situ and 40 invasive tumors

Fig. 30.4 Design of the MORE randomized trial

Type of Event	Placebo N = 2576	Raloxifene N = 5129	Risk Ratio
Invasive breast cancer	27	13	0.24
Invasive endometrial cancer	4	6	0.8
New vertebral fracture	10.1%	5.4/6.6%[1]	0.7/0.5[1]
Deep vein thrombosis and pulmonary embolism	8	55	3.1

Fig. 30.5 Results of the MORE randomized trial [1]for groups receiving raloxifene 60 mg/d and 120 mg/d, respectively

reported. There were substantially fewer invasive cancers in women receiving raloxifene (RR > 0.24; 95% CI 0.13–0.44; $P < 0.001$). This difference was entirely attributable to a 90% reduction in ER-positive invasive breast cancers (RR > 0.1; 95% CI 0.04–0.24) with no difference in the occurrence of ER-negative tumors (Fig. 30.5) [50]. At the 1998 American Society of Clinical Oncology meeting, a partially overlapping analysis reviewing data from nine raloxifene trials (including MORE) was presented. Taken together, these studies could also demonstrate a significant reduction in newly diagnosed breast cancers in women on raloxifene [51].

On the basis of the data coming from the MORE study, the STAR trial, comparing tamoxifen with raloxifene in the prevention setting, was launched [27]. In this study, 19,747 postmenopausal women with a mean age of 58.5 years having an increased 5-year breast cancer risk (mean risk, 4.03%) were randomized to receiving 20 mg of tamoxifen or 60 mg of raloxifene daily for 5 years The results of this study showed that raloxifene is as effective as tamoxifen in preventing invasive breast cancer (RR 1.02). With respect to noninvasive breast cancers, there was a nonsignificant trend favoring tamoxifen. Regarding side effects, patients on raloxifene had significantly fewer cataracts (RR 0.79) and thromboembolic events (RR 0.70) than those on tamoxifen.

30.4.2.2 Raloxifene Effects other than on the Breast

Endometrial Cancer Risk. Preclinical studies suggest that raloxifene may have limited effects on endometrial proliferation. In the initial clinical reports, endometrial thickening was unchanged during raloxifene therapy compared to placebo [52, 53]. Raloxifene did not increase the risk of endometrial cancer (RR > 0.8; 95% CI 0.2–2.7) during the first 3 years of the MORE trial, but the total number of cases was small. In the women who underwent transvaginal ultrasound, endometrial thickness was increased by 0.01 mm in the raloxifene arm and decreased by 0.27 mm in the placebo group ($P < 0.01$) [50]. It has not yet been established whether animal models and clinical endometrial proliferation are reliable predictors of endometrial cancer, especially in view of limited follow-up.

In the STAR trial, the risk of endometrial cancer on raloxifene was not significantly reduced compared to tamoxifen (RR > 0.62, 95% CI 0.35–1.08), but there was a significant reduction in hyperplasia in women on raloxifene compared to tamoxifen (RR > 0.16, 95% CI 0.09–0.29) [27].

Bone metabolism and fracture risk. Raloxifene is approved for the prevention of osteoporosis in postmenopausal women because the MORE trial showed a significant increase in BMD of the lumbar spine in women on raloxifene [54]. In the STAR trial, the effects of tamoxifen and raloxifene were similar on bone [27].

Lipid Metabolism and Cardiovascular Risk. Like tamoxifen, raloxifene has also been shown to influence serum lipid levels in a favorable way [52, 55, 56]. In the STAR trial, there was no difference between raloxifene and tamoxifen in ischemic heart disease (RR > 1.10, 95% CI 0.85–1.43) [27]. In the prospective, placebo-controlled RUTH (Raloxifene Use for The Heart) trial, raloxifene is being tested for its effects on CHD in high-risk postmenopausal women.

Coagulation and Thromboembolic Risk. The study of tamoxifen and raloxifene has provided a direct comparison between tamoxifen and raloxifene on vascular

events such as pulmonary embolism and deep vein thrombosis. The available data indicate that raloxifene causes significantly fewer thromboembolic events than tamoxifen (RR > 0.70, 95% CI 0.54–0.91). On the other hand, the risk of stroke or transient ischemic attack was similar in both groups [27].

Quality of Life. A pooled analysis from several clinical trials demonstrated a tamoxifen-like effect for raloxifene on symptoms of menopause in postmenopausal women [57]. As the greatest increase in hot flashes in the tamoxifen group of P-1 was seen in premenopausal women, a similar effect of raloxifene can be expected in this setting [26]. Alternative SERMs

Apart from tamoxifen and raloxifene, several other SERMs have been, or are being evaluated. Toremifene, an analog of tamoxifen, has been shown to have equivalent efficacy in metastatic breast cancer compared with tamoxifen, and is approved at a 20 mg-dose for this indication [58, 59]. Currently, several adjuvant trials with toremifene are in progress. Interim analyzes have shown no difference between tamoxifen and toremifene in terms of efficacy and side effects [60, 61]. In two other trials, toremifene appeared to have a more favorable effect on lipid metabolism than tamoxifen but was less bone preserving [62, 63]. Attempts to find improved SERMs as chemopreventatives lead/led to clinical testing of droloxifene, levormeloxifene and idoxifene, but development has been discontinued for all three of these agents. Droloxifene did not show beneficial effects compared to tamoxifen in breast cancer patients and both levormeloxifene and idoxifene caused somewhat unexpected gynecological effects [64, 65]. EM-800 (SCH 57050) and its derivative SCH 57068, originally thought to be pure antiestrogens, have now been shown to have SERM properties. They have potent antibreast cancer effects in preclinical models, cause uterine atrophy and have a positive effect on bone metabolism. This profile gives these compounds the potential to be better chemopreventatives than tamoxifen. SCH 57068 is likely to be the agent tested as it does not cause a reduction in serum-free carnitine levels, known to be a problem with the parent SCH 57050 [66–70]. Likewise, lasofoxifene (CP 336156) and the raloxifene analog LY 117018 have profiles in preliminary preclinical and clinical studies to make them promising chemopreventatives with improved end-organ profiles [71–74]. For lasofoxifene, data on its chemopreventive effect in 8,556 postmenopausal women have been published recently, showing a hazard ratio, for the development of ER-positive invasive breast cancer after 5 years, of 0.19 (CI 0.07–0.56, $P < 0.01$) [75].

30.5 Other Possible Agents for Future Chemoprevention Trials

30.5.1 Pure Antiestrogens

Fulvestrant (Faslodex), the most potent known steroidal antiestrogen, is an analog of estradiol without agonist activity. In athymic nude mice, inhibitory effects of fulvestrant on the growth of MCF-7 human breast cancer xenografts have been demonstrated [68], and fulvestrant has shown efficacy as a second-line agent after tamoxifen failure in advanced breast cancer. Unexpectedly, fulvestrant produced no significant changes in bone density and gonadotropin levels [76–78]. Further evaluation of this potent antiestrogen is warranted. It may have a role in chemoprevention if its therapeutic index is favorable but one definite disadvantage is the need to administer it parenterally.

30.5.2 Aromatase Inhibitors

Antagonizing the effects of estrogen on the breast is a principle of chemoprevention that has been established by tamoxifen and other SERMs. In addition, catecholestrogens, metabolites of estrogen, are thought to be genotoxic and tumorigenic [10]. Therefore, targeting estrogen synthesis is a way of preventing estradiol from stimulating the receptor and reducing the formation of these cancer-causing metabolites. To this end, estrogen synthetase (aromatase) inhibitors have been developed. Aromatase is the enzyme complex responsible for the final step in estrogen biosynthesis: the conversion of androgens to estrogens. Preclinical experiments have been conducted to determine the chemopreventive efficacy of new, potent and selective aromatase inhibitors. For example, vorozole decreased tumor incidence from

100 to 10% and tumor multiplicity from 5 to 0.1 tumors per animal in the MNU-induced rat mammary tumor model and showed similar effects in the DMBA-induced tumor model [79, 80]. Similarly, letrozole inhibited new mammary tumor development in the DMBA rat model [81, 82]. Clinical development of aromatase inhibitors has, to date, focused on their use in postmenopausal women with hormone receptor-positive breast cancer [83]. The third-generation aromatase inhibitors, letrozole, anastrozole, and exemestane are all approved for use as adjuvant therapy for women with early breast cancer [84–86]. Reduction of contralateral breast cancer in these trials has provided the first clinical data on the potential chemopreventative effects of this class of compounds. For example, in the ATAC trial comparing anastrozole to tamoxifen in the adjuvant setting, the aromatase inhibitor contralateral tumors were noted in 20 cases in the anastrozole arm and in 35 cases in the tamoxifen arm (odds ratio, 0.57; 95% CI, 0.33– 0.98; P _ 0.044) [87, 88]. Similarly, a significantly reduced rate of contralateral breast cancer was reported for women starting letrozole late after breast cancer diagnosis – and after tamoxifen treatment – vs. those taking placebo [89].

Several large, ongoing prevention trials are studying the effect of aromatase inhitors on breast cancer incidence in healthy women. For example, in the randomized, double-blind, placebo-controlled NCIC-CTG MAP.3 trial (ExCel), exemestane is compared with placebo in a 1:1 ratio in 4,560 postmenopausal women who are 35 years or older in age and at increased risk of developing breast cancer. The primary endpoint of this study is breast cancer incidence, with clinical bone fractures, cardiovascular events, quality of life, tolerability and safety, and incidence of other malignancies being secondary endpoints. Similarly, in the IBIS-2 study, anastrozole is compared with placebo in 6,000 postmenopausal women at an increased breast cancer risk. In the second part of this study (IBIS-2 DCIS), anastrozole is compared with tamoxifen in 4,000 women after a diagnosis of DCIS. In the NSABP B-35 study, anastrozole and tamoxifen are also compared with each other in women having had a diagnosis of DCIS.

Several trials of aromatase inhibitors in combination with fulvestrant vs. aromatase inhibitors alone are pending in metastatic breast cancer. If this combination proves effective in breast cancer treatment, it could be of interest in breast cancer prevention studies in the future.

30.5.3 Retinoids

Retinoids are a class of compounds, which include vitamin A and its analogs. Although their mechanisms of action at the molecular level are largely unknown, it is evident that retinoids influence cell differentiation, apoptosis and cell proliferation [90].

Exogenous retinoids have been shown to inhibit the proliferation of human breast cancer cells in vitro and in animal models [90]. Furthermore, in preclinical breast cancer prevention studies, the addition of retinoids to both tamoxifen and raloxifene resulted in a decrease in mammary tumor incidence as compared with the use of SERMs alone [91, 92]. However, their chronic toxicity and poor pharmacodynamic profile limit the administration of pharmacologically active doses of exogenous retinoids in humans. Despite the synthesis of thousands of new retinoids in the past 20 years, these obstacles have not been overcome. In a clinical trial, the efficacy of adjuvant fenretinide, a new retinoid, in preventing a second breast malignancy in women with breast cancer was evaluated. After a median follow-up of 97 months, no statistically significant reduction in the occurrence of contralateral breast cancer could be shown as compared with the no-treatment arm [90, 91].

More recently, retinoic acid metabolism blocking agents (RAMBAs) have been developed. They act by inhibiting the catabolism of retinoic acid and unlike retinoids, they do not induce their own metabolism. Consequently, they increase both tissue and plasma levels of endogenous retinoids [93, 94]. The first member of this class of compounds, liarozole fumarate, is not only a RAMBA but also a powerful third-generation aromatase inhibitor [93, 95, 96]. Liarozole has been shown to have antitumor activity against ER-positive and ER-negative breast cancer in the preclinical and clinical setting [97, 98]. RAMBAs, therefore, may be the preferable approach to investigate the chemopreventive effects of retinoic acid.

30.5.4 Dietary Prevention

Dietary modification as a possible approach to breast cancer prevention is obviously attractive. To date, numerous compounds in food have been shown to have anticancer effects in animal studies, yet only few of

them have been investigated in humans as potential chemopreventatives.

30.5.4.1 Flaxseed

Flaxseed is a source of plant lignans, which are estrogenic compounds in plants called phytoestrogens. Epidemiologic evidence suggests that breast cancer incidence is low among populations with high flaxseed consumption and urinary lignan levels [99]. Flaxseed has been shown to have chemopreventive effects on mammary tumor development in the preclinical setting [100]. It has been suggested that some of its effects may be mediated by influence on endogenous hormone metabolism. The lignans, enterolactone and enterodiol bind the ER and weakly inhibit aromatase [101]. Flaxseed also increases total urinary estrogen excretion and lengthens the luteal phase of the menstrual cycle in humans [102, 103]. Given the strong association between estrogen levels and breast cancer risk (see also Sect. 2), this influence on sex-steroid metabolism together with its other antiestrogen effects makes dietary flaxseed ingestion a chemoprevention strategy worth exploring. Currently, there are several ongoing studies examining the effects of dietary flaxseed intake on surrogate markers for breast cancer chemoprevention, such as breast density.

30.5.4.2 Soya

Soy beans contain isoflavones, which are converted to antiestrogenic and antioxidative compounds in the bowel. They have been shown to have cytostatic activity in mammary cancer cell lines and inhibit growth and progression of mammary tumors in rodents [104–106]. In addition, soy milk supplements have been reported to reduce serum estradiol levels in premenopausal women [107]. Therefore, like flaxseed, soy protein appears to be a dietary component suitable for clinical trials to investigate a potential breast cancer chemopreventive effect [108].

30.5.4.3 Vitamin E

Vitamin E is a lipid-soluble antioxidant with the potential to protect breast tissue from oxidant damage, which has been proposed as a possible cause of breast cancer [109]. In preclinical studies, vitamin E has been shown to reduce proliferation of breast cancer cell lines and to decrease mammary carcinogenesis in the DMBA-induced mammary tumor model [110, 111]. The influence of vitamin E on breast cancer risk has been explored in several clinical studies, some of which found an inverse association of dietary intake of vitamin E and breast cancer incidence [112].

30.5.5 Oophorectomy

The estrogen-antagonizing strategies discussed under SERMs and aromatase inhibitors may be of advantage in premenopausal women as well but probably most effectively employed in conjunction with ovarian function ablation. The most likely cohort of premenopausal women in whom preventative strategies would be used are those at genetic risk for breast cancer.

Oophorectomy has been known for a long time to prevent recurrence of breast cancer after primary diagnosis and to reduce the risk of second, new primaries [36]. Chemical oophorectomy with LHRH-analogs such as goserelin and buserelin that inhibit the production of LH and FSH in the pituitary gland is a reversible alternative to oophorectomy. Thus, an LHRH-analog with an SERM or an aromatase inhibitor might prove to be a chemoprevention strategy for high-risk young women. As premature loss of ovarian function is of particular concern in young women, the use of a bone-preserving and lipid-lowering SERM in combination with an LHRH-analog is most attractive (see also Chap. 23).

30.6 Considerations for Future Chemoprevention Trials

The positive results of the P-1 and IBIS I tamoxifen prevention trials were of major significance. Not only were they "proof of concept" that antiendocrine agents can substantially reduce the risk of breast cancer, but also raise important issues with respect to future chemoprevention studies. Improved agents, alternative cohort selection and different trial designs merit consideration. Figure 30.6 illustrates parameters affecting

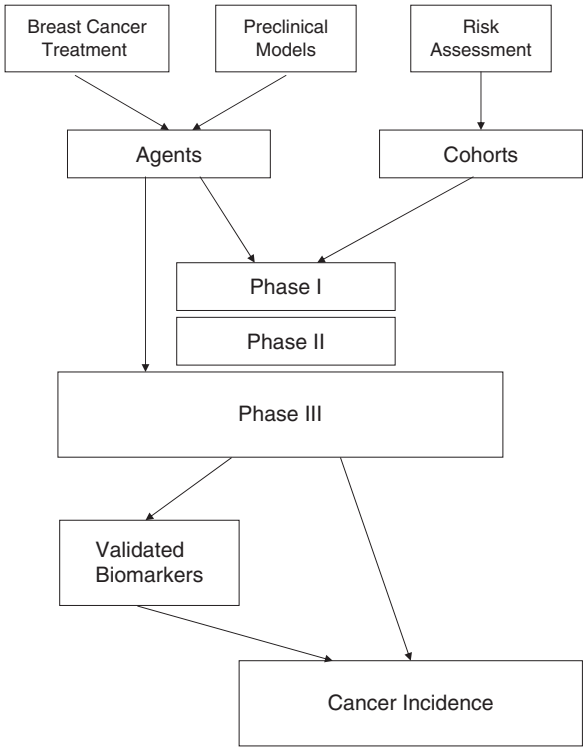

Fig. 30.6 Key parameters in chemoprevention trials

the clinical development of future chemopreventatives, and some key questions pertaining to them are discussed in more detail below.

What is optimal risk assessment for breast cancer? The prevention trials conducted to date have been based on identification of women at higher than average risk for breast cancer. The term "high risk," however, has not yet been unanimously agreed upon and many risk factors that might be included into an estimation of an individual's risk have been proposed. In the P-1 trial, for example, "high risk" was defined as a Gail score of over 1.66, although the Gail model has been criticized for omitting or incompletely accounting for additional factors such as BRCA1/2 status, ethnicity and family history of male breast and ovarian cancer [25, 26]. Differences in risk assessment might explain the discrepant North American and European tamoxifen prevention trial results. In future clinical studies, it will be necessary to decide whether women with different risk factors should be included in the same trials as in P-1 and STAR, or whether the target populations should be confined to specific risk factors. This decision is in part based on whether the selected agent is believed to act similarly in women with diverse risks. Furthermore, the addition of newly identified clinical markers of risk such as breast density, bone density, elevated plasma estrogen levels and single nucleotide polymorphisms associated with breast cancer risk may be used as entry criteria for future chemoprevention trials. Finally, a study subject's perception of risk also influences the conduct of the trial in terms of compliance and the final evaluation of the therapeutic index of a study drug.

What are the features of an ideal chemopreventive drug? Originally, the term "chemoprevention" was defined as the use of specific natural or synthetic chemical agents to reverse, suppress or prevent carcinogenic progression to invasive cancer [113]. It has been debated as to whether the P-1 study has shown tamoxifen to be "chemopreventive" rather than treating incident cases of cancer. From a clinical standpoint however, it may not be relevant whether an agent prevents the initiation of a cancer or inhibits its promotion or both, as reduction in the incidence of cancer is clearly of importance. The pharmacologic profile of an ideal breast cancer chemopreventive agent should include oral availability, an excellent therapeutic index and absence of long-term toxicities, the two latter points being difficult to evaluate without costly long-term exposure and follow-up in clinical trials. Ideally, unlike tamoxifen, and apparently raloxifene, it should also reduce the incidence of both ER-positive and ER-negative tumors.

How can potential chemopreventive agents be identified? Two major tools have been used to assess potential breast cancer chemopreventatives viz. preclinical models (see also Sect. 2) and efficacy in the treatment of breast cancer patients. Results obtained with the currently used preclinical models have not always been predictive of efficacy in humans. Thus, improving these models is an important future challenge as it could help to select successful agents and shorten the interval between discovery of a new agent and its ultimate clinical application.

A positive effect of an agent in breast cancer treatment is obviously a powerful piece of evidence to support its potential as a chemopreventative. This was exemplified by the activity of tamoxifen in advanced disease, in the adjuvant setting and most importantly, in the prevention of contralateral new primary breast cancer. For the selection of future agents however, this lengthy and costly model may not be necessary. Efficacy against advanced breast cancer may not be realistic for some agents, in which case, this should not

be inappropriately used as a selection tool. Where it is, a simple phase II response trial may be adequate to select a promising agent. In any case, outstanding questions will always remain from breast cancer studies and additional clinical trials will be necessary. This subsequent clinical trial path, helpful in selecting an agent, is discussed next.

What studies are necessary and feasible to move forward to a large breast cancer prevention trial? In the case of tamoxifen, phase I and II trials in healthy women were not performed prior to the definitive prevention study. That left several issues unanswered at the end of the trial. Is 20 mg the minimal effective dose for chemoprevention; is the duration of 5 years and the continuous once daily administration the optimal chemoprevention strategy? For future agents, phase I and II dose finding studies for safety and efficacy on other end-organs should be conducted in healthy women. These could be stand-alone trials or assessed in a vanguard cohort within the context of phase III trials [114]. Ultimately, long and costly phase III trials with breast cancer occurrence as an endpoint will always be required unless truly validated surrogate markers can be identified and relied upon for the registration of a new chemopreventative [115, 116]. Should this happen, then the clinical trial strategy could focus on dose-finding, schedule-optimizing studies in healthy women, and the definitive trials could be much shorter. For example, an ongoing trial examining the chemopreventive potential of celecoxib is using Ki-67 modulation in ductal lavage or fine needle aspiration of the breast as the primary endpoint after a treatment duration of 12 months only.

What are possible secondary endpoints in breast cancer chemoprevention? Most agents evaluated in breast cancer chemoprevention to date have been endocrine agents with secondary effects on other organs like bone, lipid metabolism, the cardiovascular system and the uterus. Chemoprevention trials should evaluate these endpoints and cohorts should be selected with regard to risk factors in organs such as osteoporosis, high plasma lipid levels, history of myocardial infarction or history of endometrial malignancy. Matching designer drugs with specific end-organ effects to cohorts with specific profiles of risk such as osteoporosis or cardiovascular disease may be feasible in the future.

Other Future Considerations: It will remain difficult but desirable to define the duration of cancer risk reduction (prevention) with future agents in novel cohorts. The risk of ER-negative breast cancer has not been reduced by either tamoxifen or raloxifene, and in addition, this form of breast cancer carries a greater risk of death. Thus, finding ways to prevent these tumors is imperative, and ultimately, reduction in breast cancer mortality not just incidence must be achieved. This might require combinations or sequences of endocrine agents with or without other novel classes of drugs. Of course, in addition to achieving these important goals, the benefit of chemopreventatives must be shown both to clearly outweigh the risks and to be affordable within the context of a healthcare budget. These critical questions will continue to challenge researchers attempting to prevent breast cancer in the foreseeable future.

References

1. Jemal A, Thun MJ, Ries LA et al (2008) Annual report to the nation on the status of cancer, 1975–2005, featuring trends in lung cancer, tobacco use, and tobacco control. J Natl Cancer Inst. 100(23):1672–94
2. Chu KC, Tarone RE, Kessler LG et al (1996) Recent trends in U.S. breast cancer incidence, survival, and mortality rates. J Natl Cancer Inst. 88(21):1571–9
3. Hulka BS, Liu ET, Lininger RA (1994) Steroid hormones and risk of breast cancer. Cancer. 74(3 Suppl):1111–24
4. Brzozowski AM, Pike AC, Dauter Z et al (1997) Molecular basis of agonism and antagonism in the oestrogen receptor. Nature. 389(6652):753–8
5. Santen RJ, Yue W, Naftolin F, Mor G, Berstein L (1999) The potential of aromatase inhibitors in breast cancer prevention. Endocr Relat Cancer. 6(2):235–43
6. Bugano DD, Conforti-Froes N, Yamaguchi NH, Baracat EC (2008) Genetic polymorphisms, the metabolism of estrogens and breast cancer: a review. Eur J Gynaecol Oncol. 29(4):313–20
7. Eliassen AH, Missmer SA, Tworoger SS, Hankinson SE (2008) Circulating 2-hydroxy- and 16alpha-hydroxy estrone levels and risk of breast cancer among postmenopausal women. Cancer Epidemiol Biomark Prev. 17(8):2029–35
8. Justenhoven C, Hamann U, Pierl CB et al (2008) CYP2C19*17 is associated with decreased breast cancer risk. Breast Cancer Res Treat. 115(2):391–6
9. Ahlgren M, Melbye M, Wohlfahrt J, Sorensen TI (2004) Growth patterns and the risk of breast cancer in women. N Engl J Med. 351(16):1619–26
10. Yager JD, Liehr JG (1996) Molecular mechanisms of estrogen carcinogenesis. Annu Rev Pharmacol Toxicol. 36:203–32
11. Boyd NF, Byng JW, Jong RA et al (1995) Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J Natl Cancer Inst. 87(9):670–5
12. Zhang Y, Kiel DP, Kreger BE et al (1997) Bone mass and the risk of breast cancer among postmenopausal women. N Engl J Med. 336(9):611–7

13. Toniolo PG, Levitz M, Zeleniuch-Jacquotte A et al (1995) A prospective study of endogenous estrogens and breast cancer in postmenopausal women. J Natl Cancer Inst. 87(3):190–7
14. Byrne C, Schairer C, Wolfe J et al (1995) Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst. 87(21):1622–9
15. Goss PE, Sierra S (1998) Current perspectives on radiation-induced breast cancer. J Clin Oncol. 16(1):338–47
16. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R (2000) Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA. 283(4): 485–91
17. Adami HO, Signorello LB, Trichopoulos D (1998) Toward an understanding of breast cancer etiology. Semin Cancer Biol. 8(4):255–62
18. Cauley JA, Lucas FL, Kuller LH, Vogt MT, Browner WS, Cummings SR (1996) Bone mineral density and risk of breast cancer in older women: the study of osteoporotic fractures. Study of osteoporotic fractures research group. JAMA. 276(17):1404–8
19. Cauley JA, Lucas FL, Kuller LH, Stone K, Browner W, Cummings SR (1999) Elevated serum estradiol and testosterone concentrations are associated with a high risk for breast cancer. Study of Osteoporotic Fractures Research Group. Ann Intern Med. 130(4 Pt 1):270–7
20. Hsieh CC, Trichopoulos D, Katsouyanni K, Yuasa S (1990) Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: associations and interactions in an international case-control study. Int J Cancer. 46(5):796–800
21. Easton D, Ford D, Peto J (1993) Inherited susceptibility to breast cancer. Cancer Surv. 18:95–113
22. Anon. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet. 1997;350(9084):1047–59
23. Colditz GA, Hankinson SE, Hunter DJ et al (1995) The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med. 332(24):1589–93
24. Gail MH, Costantino JP, Pee D et al (2007) Projecting individualized absolute invasive breast cancer risk in African American women. J Natl Cancer Inst. 99(23):1782–92
25. Gail MH, Brinton LA, Byar DP et al (1989) Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 81(24):1879–86
26. Fisher B, Costantino JP, Wickerham DL et al (1998) Tamoxifen for prevention of breast cancer: report of the national surgical adjuvant breast and bowel project P-1 study. J Natl Cancer Inst. 90(18):1371–88
27. Vogel VG, Costantino JP, Wickerham DL et al (2006) Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. JAMA. 295(23):2727–41
28. Clarke R (1996) Human breast cancer cell line xenografts as models of breast cancer. The immunobiologies of recipient mice and the characteristics of several tumorigenic cell lines. Breast Cancer Res Treat. 39(1):69–86
29. Banks WA (2006) The blood-brain barrier in psychoneuroimmunology. Neurol Clin. 24(3):413–9
30. Lu Q, Liu Y, Long BJ, Grigoryev D, Gimbel M, Brodie A (1999) The effect of combining aromatase inhibitors with antiestrogens on tumor growth in a nude mouse model for breast cancer. Breast Cancer Res Treat. 57(2):183–92
31. Russo J, Russo IH (1996) Experimentally induced mammary tumors in rats. Breast Cancer Res Treat. 39(1):7–20
32. Fisher B, Costantino J, Redmond C et al (1989) A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen receptor-positive tumors. N Engl J Med. 320(8):479–84
33. Rutqvist LE, Cedermark B, Glas U et al (1991) Contralateral primary tumors in breast cancer patients in a randomized trial of adjuvant tamoxifen therapy. J Natl Cancer Inst. 83(18):1299–306
34. Anon. Adjuvant tamoxifen in the management of operable breast cancer: the Scottish trial. Report from the breast cancer trials committee, Scottish cancer trials office (MRC), Edinburgh. Lancet. 1987;2(8552):171–5
35. Fisher B, Redmond C (1991) New perspective on cancer of the contralateral breast: a marker for assessing tamoxifen as a preventive agent. J Natl Cancer Inst. 83(18):1278–80
36. Anon. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early breast cancer trialists' Collaborative Group. Lancet. 1992;339(8785):71–85
37. Anon. Tamoxifen for early breast cancer: an overview of the randomized trials. Early breast cancer trialists' Collaborative Group. Lancet. 1998;351(9114):1451–67
38. Veronesi U, Maisonneuve P, Costa A et al (1998) Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomized trial among hysterectomized women. Italian Tamoxifen Prevention Study. Lancet. 352(9122):93–7
39. Powles T, Eeles R, Ashley S et al (1998) Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomized chemoprevention trial. Lancet. 352(9122):98–101
40. Cuzick J, Forbes JF, Sestak I et al (2007) Long-term results of tamoxifen prophylaxis for breast cancer–96-month follow-up of the randomized IBIS-I trial. J Natl Cancer Inst. 99(4):272–82
41. McDonald CC, Stewart HJ (1991) Fatal myocardial infarction in the Scottish adjuvant tamoxifen trial. The Scottish breast cancer committee. BMJ. 303(6800):435–7
42. Costantino JP, Kuller LH, Ives DG, Fisher B, Dignam J (1997) Coronary heart disease mortality and adjuvant tamoxifen therapy. J Natl Cancer Inst. 89(11):776–82
43. McDonald CC, Alexander FE, Whyte BW, Forrest AP, Stewart HJ (1995) Cardiac and vascular morbidity in women receiving adjuvant tamoxifen for breast cancer in a randomized trial. The Scottish cancer trials breast group. BMJ. 311(7011):977–80
44. Rutqvist LE, Mattsson A (1993) Cardiac and thromboembolic morbidity among postmenopausal women with early stage breast cancer in a randomized trial of adjuvant tamoxifen. The Stockholm Breast Cancer Study Group. J Natl Cancer Inst. 85(17):1398–406
45. Love RR, Barden HS, Mazess RB, Epstein S, Chappell RJ (1994) Effect of tamoxifen on lumbar spine bone mineral density in postmenopausal women after 5 years. Arch Intern Med. 154(22):2585–8

46. Love RR, Mazess RB, Barden HS et al (1992) Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. N Engl J Med. 326(13):852–6
47. Love RR, Mazess RB, Tormey DC, Barden HS, Newcomb PA, Jordan VC (1988) Bone mineral density in women with breast cancer treated with adjuvant tamoxifen for at least two years. Breast Cancer Res Treat. 12(3):297–302
48. Chlebowski RT, Collyar DE, Somerfield MR, Pfister DG (1999) American society of clinical oncology technology assessment on breast cancer risk reduction strategies: tamoxifen and raloxifene. J Clin Oncol. 17(6):1939–55
49. Day R, Ganz PA, Costantino JP, Cronin WM, Wickerham DL, Fisher B (1999) Health-related quality of life and tamoxifen in breast cancer prevention: a report from the National Surgical Adjuvant Breast And Bowel Project P-1 Study. J Clin Oncol. 17(9):2659–69
50. Cummings SR, Eckert S, Krueger KA et al (1999) The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple outcomes of raloxifene evaluation. JAMA. 281(23):2189–97
51. Jordan VC, Glusman JE, Eckert S. Raloxifene reduces incident primary breast cancer: integrated data from multicenter, double-blind, placebo-controlled, randomized trials in postmenopausal women. Breast Cancer Res Treat. 1998;50(3): 227. Ref Type: abstr
52. Delmas PD, Bjarnason NH, Mitlak BH et al (1997) Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med. 337(23):1641–7
53. Boss SM, Huster WJ, Neild JA, Glant MD, Eisenhut CC, Draper MW (1997) Effects of raloxifene hydrochloride on the endometrium of postmenopausal women. Am J Obstet Gynecol. 177(6):1458–64
54. Ettinger B, Black DM, Mitlak BH et al (1999) Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple outcomes of raloxifene evaluation (MORE) investigators. JAMA. 282(7):637–45
55. Draper MW, Flowers DE, Huster WJ, Neild JA, Harper KD, Arnaud C (1996) A controlled trial of raloxifene (LY139481) HCl: impact on bone turnover and serum lipid profile in healthy postmenopausal women. J Bone Miner Res. 11(6): 835–42
56. Walsh BW, Kuller LH, Wild RA et al (1998) Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. JAMA. 279(18):1445–51
57. Glusman JE, Lu Y, Huster WJ. Raloxifene effecst on climacterial symptoms compared with hormone or estrogen replacement therapy (HRT or ERT).). Proc North Am Menopause Soc 8th Annual Meeting Program. 1997. Ref Type: abstr
58. Buzdar AU, Hortobagyi G (1998) Update on endocrine therapy for breast cancer. Clin Cancer Res. 4(3):527–34
59. Hayes DF, Van Zyl JA, Hacking A et al (1995) Randomized comparison of tamoxifen and two separate doses of toremifene in postmenopausal patients with metastatic breast cancer. J Clin Oncol. 13(10):2556–66
60. Holli K (1997) Evolving role of toremifene in the adjuvant setting. Oncology (Williston Park). 11(5 Suppl 4):48–51
61. Holli K (1998) Adjuvant trials of toremifene vs tamoxifen: the European experience. Oncology (Williston Park). 12(3 Suppl 5):23–7
62. Saarto T, Blomqvist C, Ehnholm C, Taskinen MR, Elomaa I (1996) Antiatherogenic effects of adjuvant antiestrogens: a randomized trial comparing the effects of tamoxifen and toremifene on plasma lipid levels in postmenopausal women with node-positive breast cancer. J Clin Oncol. 14(2):429–33
63. Marttunen MB, Hietanen P, Tiitinen A, Ylikorkala O (1998) Comparison of effects of tamoxifen and toremifene on bone biochemistry and bone mineral density in postmenopausal breast cancer patients. J Clin Endocrinol Metab. 83(4):1158–62
64. Bruning PF (1992) Droloxifene, a new anti-oestrogen in postmenopausal advanced breast cancer: preliminary results of a double-blind dose-finding phase II trial. Eur J Cancer. 28A(8–9):1404–7
65. Haarstad H, Lonning PE, Gundersen S, Wist E, Raabe N, Kvinnsland S (1998) Influence of droloxifene on metastatic breast cancer as first-line endocrine treatment. Acta Oncol. 37(4):365–8
66. Simard J, Labrie C, Belanger A et al (1997) Characterization of the effects of the novel non-steroidal antiestrogen EM-800 on basal and estrogen-induced proliferation of T-47D, ZR-75–1 and MCF-7 human breast cancer cells in vitro. Int J Cancer. 73(1):104–12
67. Simard J, Sanchez R, Poirier D et al (1997) Blockade of the stimulatory effect of estrogens, OH-tamoxifen, OH-toremifene, droloxifene, and raloxifene on alkaline phosphatase activity by the antiestrogen EM-800 in human endometrial adenocarcinoma Ishikawa cells. Cancer Res. 57(16):3494–7
68. Labrie F, Labrie C, Belanger A et al (1999) EM-652 (SCH 57068), a third-generation SERM acting as pure antiestrogen in the mammary gland and endometrium. J Steroid Biochem Mol Biol. 69(1–6):51–84
69. Luo S, Sourla A, Labrie C et al (1998) Effect of twenty-four-week treatment with the antiestrogen EM-800 on estrogen-sensitive parameters in intact and ovariectomized mice. Endocrinology. 139(5):2645–56
70. Tremblay A, Tremblay GB, Labrie C, Labrie F, Giguere V (1998) EM-800, a novel antiestrogen, acts as a pure antagonist of the transcriptional functions of estrogen receptors alpha and beta. Endocrinology. 139(1):111–8
71. Rosati RL, Da Silva JP, Cameron KO et al (1998) Discovery and preclinical pharmacology of a novel, potent, nonsteroidal estrogen receptor agonist/antagonist, CP-336156, a diaryltetrahydronaphthalene. J Med Chem. 41(16): 2928–31
72. Ke HZ, Paralkar VM, Grasser WA et al (1998) Effects of CP-336, 156, a new, nonsteroidal estrogen agonist/antagonist, on bone, serum cholesterol, uterus and body composition in rat models. Endocrinology. 139(4):2068–76
73. Curiel MD, Calero JA, Guerrero R, Gala J, Gazapo R, de la Piedra C (1998) Effects of LY-117018 HCl on bone remodeling and mineral density in the oophorectomized rat. Am J Obstet Gynecol. 178(2):320–5
74. Hodsman AB, Drost D, Fraher LJ et al (1999) The addition of a raloxifene analog (LY117018) allows for reduced PTH(1–34) dosing during reversal of osteopenia in ovariectomized rats. J Bone Miner Res. 14(5):675–9
75. LaCroix AZ, Cummings SR, Thompson DJ, et al Effects of 5 years of treatment with lasofoxifene on the incidence of breast cancer in older women. Breast Cancer Res Treat. 69(2suppl). 2008. Ref Type: abstr

76. Howell A, DeFriend DJ, Robertson JF et al (1996) Pharmacokinetics, pharmacological and anti-tumour effects of the specific anti-oestrogen ICI 182780 in women with advanced breast cancer. Br J Cancer. 74(2):300–8
77. Howell A, DeFriend D, Robertson J, Blamey R, Walton P (1995) Response to a specific antioestrogen (ICI 182780) in tamoxifen-resistant breast cancer. Lancet. 345(8941): 29–30
78. Nicholson RI, Gee JM, Manning DL, Wakeling AE, Montano MM, Katzenellenbogen BS (1995) Responses to pure antiestrogens (ICI 164384, ICI 182780) in estrogen-sensitive and -resistant experimental and clinical breast cancer. Ann N Y Acad Sci. 761:148–63
79. Lubet RA, Steele VE, Casebolt TL, Eto I, Kelloff GJ, Grubbs CJ (1994) Chemopreventive effects of the aromatase inhibitors vorozole (R-83842) and 4-hydroxyandrostenedione in the methylnitrosourea (MNU)-induced mammary tumor model in Sprague-Dawley rats. Carcinogenesis. 15(12):2775–80
80. De Coster R, Van Ginckel RF, Callens MJ, Goeminne NK, Janssens BL (1992) Antitumoral and endocrine effects of (+)-vorozole in rats bearing dimethylbenzanthracene-induced mammary tumors. Cancer Res. 52(5):1240–4
81. Bhatnagar AS, Hausler A, Schieweck K, Lang M, Bowman R (1990) Highly selective inhibition of estrogen biosynthesis by CGS 20267, a new non-steroidal aromatase inhibitor. J Steroid Biochem Mol Biol. 37(6):1021–7
82. Schieweck K, Bhatnagar AS, Batzl C, Lang M (1993) Antitumor and endocrine effects of non-steroidal aromatase inhibitors on estrogen-dependent rat mammary tumors. J Steroid Biochem Mol Biol. 44(4–6):633–6
83. Goss PE, Winer EP, Tannock IF, Schwartz LH (1999) Randomized phase III trial comparing the new potent and selective third-generation aromatase inhibitor vorozole with megestrol acetate in postmenopausal advanced breast cancer patients. North American Vorozole Study Group. J Clin Oncol. 17(1):52–63
84. Baum M, Buzdar A, Cuzick J et al (2003) Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early stage breast cancer: results of the ATAC (arimidex, tamoxifen alone or in combination) trial efficacy and safety update analyses. Cancer. 98(9):1802–10
85. Coombes RC, Hall E, Gibson LJ et al (2004) A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med. 350(11):1081–92
86. Thuerlimann B, Keshaviah A, Mouridsen H, et al BIG 1-98: randomized, double-blind phase III study to evaluate letrozole (L) vs. tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. Proc Am Soc Clin Oncol. 24, No. 511. 2005. Ref Type: abstr
87. Osborne CK, Coronado-Heinsohn EB, Hilsenbeck SG et al (1995) Comparison of the effects of a pure steroidal antiestrogen with those of tamoxifen in a model of human breast cancer. J Natl Cancer Inst. 87(10):746–50
88. Buzdar A. The ATAC ('arimidex', tamoxifen, alone or in combination) trial in postmenopausal women with early breast cancer – updated efficacy results based on a median follow-up of 47 months. Breast Cancer Res Treat. 77, 295. 2003. Ref Type: abstr
89. Goss PE, Ingle JN, Pater JL et al (2008) Late extended adjuvant treatment with letrozole improves outcome in women with early stage breast cancer who complete 5 years of tamoxifen. J Clin Oncol. 26(12):1948–55
90. Miller WH Jr (1998) The emerging role of retinoids and retinoic acid metabolism blocking agents in the treatment of cancer. Cancer. 83(8):1471–82
91. Veronesi U, De Palo G, Marubini E et al (1999) Randomized trial of fenretinide to prevent second breast malignancy in women with early breast cancer. J Natl Cancer Inst. 91(21): 1847–56
92. Anzano MA, Byers SW, Smith JM et al (1994) Prevention of breast cancer in the rat with 9-cis-retinoic acid as a single agent and in combination with tamoxifen. Cancer Res. 54(17):4614–7
93. Van WJ, Van NG, Coene MC et al (1992) Liarozole, an inhibitor of retinoic acid metabolism, exerts retinoid-mimetic effects in vivo. J Pharmacol Exp Ther. 261(2):773–9
94. Van Wauwe JP, Coene MC, Goossens J, Cools W, Monbaliu J (1990) Effects of cytochrome P-450 inhibitors on the in vivo metabolism of all-trans retinoic acid in rats. J Pharmacol Exp Ther. 252(1):365–9
95. Bruynseels J, De CR, Van RP et al (1990) R 75251, a new inhibitor of steroid biosynthesis. Prostate. 16(4):345–57
96. Van WJ, Coene MC, Cools W et al (1994) Liarozole fumarate inhibits the metabolism of 4-keto-all-trans-retinoic acid. Biochem Pharmacol. 47(4):737–41
97. Goss PE, Oza A, Goel R et al (2000) Liarozole fumarate (R85246): a novel imidazole in the treatment of receptor-positive postmenopausal metastatic breast cancer. Breast Cancer Res Treat. 59(1):55–68
98. Goss PE, Strasser K, Marques R et al (2000) Liarozole fumarate (R85246): in the treatment of ER negative, tamoxifen refractory or chemotherapy resistant postmenopausal metastatic breast cancer. Breast Cancer Res Treat. 64(2):177–88
99. Ingram D, Sanders K, Kolybaba M, Lopez D (1997) Case-control study of phyto-oestrogens and breast cancer. Lancet. 350(9083):990–4
100. Serraino M, Thompson LU (1992) The effect of flaxseed supplementation on the initiation and promotional stages of mammary tumorigenesis. Nutr Cancer. 17(2):153–9
101. Wang C, Makela T, Hase T, Adlercreutz H, Kurzer MS (1994) Lignans and flavonoids inhibit aromatase enzyme in human preadipocytes. J Steroid Biochem Mol Biol. 50 (3–4):205–12
102. Haggans CJ, Hutchins AM, Olson BA, Thomas W, Martini MC, Slavin JL (1999) Effect of flaxseed consumption on urinary estrogen metabolites in postmenopausal women. Nutr Cancer. 33(2):188–95
103. Serraino M, Thompson LU (1991) The effect of flaxseed supplementation on early risk markers for mammary carcinogenesis. Cancer Lett. 60(2):135–42
104. Lamartiniere CA, Moore JB, Brown NM, Thompson R, Hardin MJ, Barnes S (1995) Genistein suppresses mammary cancer in rats. Carcinogenesis. 16(11):2833–40
105. Hawrylewicz EJ, Zapata JJ, Blair WH (1995) Soy and experimental cancer: animal studies. J Nutr. 125(3 Suppl):698S–708S
106. Barnes S (1995) Effect of genistein on in vitro and in vivo models of cancer. J Nutr. 125(3 Suppl):777S–83S
107. Lu LJ, Anderson KE, Grady JJ, Nagamani M (1996) Effects of soya consumption for one month on steroid hormones in

premenopausal women: implications for breast cancer risk reduction. Cancer Epidemiol Biomark Prev. 5(1):63–70
108. Stoll BA (1997) Eating to beat breast cancer: potential role for soy supplements. Ann Oncol. 8(3):223–5
109. Baum M, Ziv Y, Colletta A (1991) Prospects for the chemoprevention of breast cancer. Br Med Bull. 47(2):493–503
110. Knekt P (1991) Role of vitamin E in the prophylaxis of cancer. Ann Med. 23(1):3–12
111. Charpentier A, Groves S, Simmons-Menchaca M et al (1993) RRR-alpha-tocopheryl succinate inhibits proliferation and enhances secretion of transforming growth factor-beta (TGF-beta) by human breast cancer cells. Nutr Cancer. 19(3): 225–39
112. Kimmick GG, Bell RA, Bostick RM (1997) Vitamin E and breast cancer: a review. Nutr Cancer. 27(2):109–17
113. Lippman SM, Benner SE, Hong WK (1994) Cancer chemoprevention. J Clin Oncol. 12(4):851–73
114. Goodman GE (1992) The clinical evaluation of cancer chemoprevention agents: defining and contrasting phase I, II, and III objectives. Cancer Res. 52(9 Suppl):2752s–7s
115. Lippman SM, Lee JS, Lotan R, Hittelman W, Wargovich MJ, Hong WK (1990) Biomarkers as intermediate end points in chemoprevention trials. J Natl Cancer Inst. 82(7): 555–60
116. Schatzkin A, Freedman LS, Schiffman MH, Dawsey SM (1990) Validation of intermediate end points in cancer research. J Natl Cancer Inst. 82(22):1746–52

Design, Implementation, and Interpretation of Clinical Trials

31

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31.1 Introduction

The findings from Phase III randomized clinical trials (RCTs) conducted since the 1950s have lead to major advances in the clinical treatment and prevention of breast cancer. The impact of these clinical trials is best evaluated by examining the substantial decline in mortality attributed to breast cancer in countries that have accepted and applied the results from Phase III clinical trials in the broader clinical setting [1]. Concomitant with the wider acceptance of the merits of RCTs for testing new therapeutic interventions, there have been important developments in the biostatistical methods utilized in RCTs that reflect recognition of the integral role of statistical science in clinical research.

The purpose of this chapter is to summarize salient features of the design, conduct, and analysis of modern cancer clinical trials, particularly those in breast cancer. The emphasis is on concepts and methods that are deemed essential for assuring that clinical trials incorporate optimal scientific, clinical, statistical, ethical, and practical considerations from the time an idea for an RCT surfaces until the results are reported. Within this chapter we illustrate major design considerations and issues that have arisen in breast cancer clinical trials based on our experience with landmark trials of the National Surgical Adjuvant Project for Breast and Bowel Cancers (NSABP), as well as, when appropriate, citing examples from other clinical trial groups that have made substantive contributions in the development of clinical trial methodology. Our focus is on fundamental principles that are essential for conducting RCTs and methods that are most relevant for multicenter RCTs. In order to have the material serve as a practical guide for clinical and basic scientists, we have minimized the use of statistical notation and technical jargon. For readers who may desire more statistical details on particular concepts or methods, the references with each topic should prove useful. In addition, two papers by Peto et al. [2, 3] provide a particularly insightful introduction to fundamental concepts in the design and conduct of cancer RCTs.

31.1.1 Highlights in the Evolution of Clinical Trials

Inherent in the experimental design of a clinical trial is the notion of a comparative (control) group against which a new intervention is tested. The earliest appreciation of the importance of a controlled clinical trial is generally credited to Daniel (in the Book of Daniel, Chapter 1: Verses 12–15) in the Old Testament of the Bible [4]. Daniel believed that he and his fellow Israelites would be defiled by consuming the food and wine provided by the Babylonian king, Nebuchadnezzar. He requested that the Israelites receive only pulse (leguminous plants, such as peas or beans) and water for 10 days, following which their "countenances" were to be compared to the "countenances" of those men who ate the king's diet. The conclusion of the trial, as reported in the Book of Daniel is:

> And at the end of 10 days their countenances appeared fairer, and they were fatter in the flesh, than all the youths that did eat of the king's food (Daniel 1:15).

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases*,
DOI: 10.1007/978-3-540-69743-5_31, © Springer-Verlag Berlin Heidelberg 2010

In the 14th century, Petrarch, who was skeptical of the clinical approaches of the time, wrote a letter to Boccaccio, in which he envisioned a comparative trial of two equal sized groups of men with similar age, environment, lifestyle, and temperament, and who had developed the same disease within the same time frame. The group assigned to the current physicians' "prescriptions" would then be compared to those taking no medicine to evaluate who "escapes" the disease. In his hypothetical trial Petrarch states: "I have no doubt as to which half would escape." [5].

An inadvertent clinical trial occurred in 1537 when the surgeon, Ambroise Paré, resorted to the application of a digestive concoction of egg yolks, rose oil, and turpentine to wounds received during battle when the usual treatment consisting of pouring boiling oil over wounds was in short supply [143]. He employed what he regarded was likely to be an ineffective therapy, but to his surprise he observed that:

> Those to whom I applied the digestive medicament feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish and with much pain and swelling about their wounds (Translation in [6]).

Based on his clinical impressions, Paré decided to abandon the standard treatment in favor of more humane approaches to treating battle wounds.

Paré's description of his findings does not include a statistical summary of how many soldiers received each of the two treatments or whether there were any soldiers who did not show a better result with the new therapy. However, Paré's personal observations on an unspecified number of wounded soldiers were dramatic enough to convince him to change his clinical approach to treating battle wounds at a time prior to the development of formal statistical methods.

In the 18th eighteenth century, James Lind [7] carried out his now famous clinical trial of six dietary treatments on seamen suffering from scurvy. He conducted a trial of 12 seamen with scurvy whose "cases were as similar as I could make them," in which two of the men received two oranges and one lemon daily. Therefore, the original evidence for the use of citrus fruit in the prevention and treatment of scurvy, which was shown many years later to be a sequellae of vitamin C deficient diets during long sea voyages, was based on a sample size of two men.

Whether "numerical methods" had an essential role in evaluating the effectiveness of treatments became a topic for debate in the mid 1800s. In his *Essay on Clinical Instruction* published in 1834, P.C.A. Louis, a noted physician and pathologist, strongly recommended the use of the numerical method in clinical research, while acknowledging the difficulties in implementation:

> The only reproach which can be made to the numerical method … is that it offers real difficulties in its execution. It neither can, or ought to be applied to other than exact observations, and these are not common; and on the other hand, this method requires much more labour and time than the most distinguished members of our profession can dedicate to it [8].

Louis's enthusiasm for the use of statistics in evaluating therapeutic interventions was not necessarily shared by other physicians. F.J. Double, in an article entitled "The inapplicability of statistics to the practice of medicine," which appeared in the London Medical Gazette, stated:

> Individuality is an invariant element in pathology…. Numerical and statistical calculations, open to many sources of fallacy, are in no degree applicable to therapeutics [9].

In his response entitled "The applicability of statistics to the practice of medicine," which was published in the same issue of the London Medical Gazette, P.C.A. Louis stated:

> A therapeutic agent cannot be employed with any discrimination or probability of success in a given case, unless its general efficacy, in analogous cases, has been previously ascertained; therefore, I conceive that without the aid of medical statistics nothing like real medical science is possible [8].

An invaluable contribution to the development of clinical trial methodology was the concept of randomization among treatments, which Sir Ronald A. Fisher introduced in agricultural experiments [10, 11]. As initially applied in clinical trials, patients were split into groups depending on the number of treatments and then the groups were randomly allocated to a particular treatment. However, statisticians soon noted that allocation of individuals between treatments was better because the replication afforded the opportunity to calculate an error term. A number of early clinical trials used a systematic allocation approach, such as alternately assigning patients between a control and experimental treatment, but this method has a potential for bias since the treatment assignments can be predicted prior to entry of the patient into the clinical trial.

The Medical Research Council (MRC) Streptomycin Trial published in the *British Medical Journal* [12],

which ushered in the modern era in clinical trial methods, is generally cited as the first example of a "properly randomized clinical trial [13]." In the MRC trial, patients were randomly allocated between treatments utilizing random sampling numbers. Sir A. Bradford Hill, the distinguished medical statistician, was recognized for his role in the conceptualization and conduct of this seminal trial. He did much to bring attention to the importance of assuring that sound scientific principles were incorporated into future clinical trials.

A bibliography and many original documents related to these and other early developments in clinical trials are available online through the James Lind Library at the University of Edinburgh. The Lind Library is a valuable annotated resource for individuals interested in the evolution of fundamental concepts in clinical trial methods.

31.1.2 History of Cancer Clinical Trial Cooperative Groups

The Cancer Cooperative Groups Program in the United States had its origins when Dr. Sidney Farber, Mrs. Albert Lasker and others persuaded Congress to allocate an additional $5 million for the National Cancer Institute (NCI) to fund the Cancer Chemotherapy National Service Center (CCNSC). The NCI was fortunate to have several individuals with much foresight involved with planning for the new initiative. Foremost among these were Dr. Kenneth Endicott, Head, CCNSC, Dr. Gordon Zubrod, Clinical Director, National Cancer Institute, and Dr. Marvin Schneiderman, Chief, Biometrics Section, CCNSC. Their vision for the CCNSC was to form cooperative networks of institutions that had established clinical cancer research programs encompassing medical specialties such as medical oncology, radiation oncology, and surgical oncology, who in partnership with biostatisticians as full collaborators, would carry out controlled clinical trials to address important questions about cancer treatment. These outstanding NCI leaders were able to attract some of the most talented clinical researchers and statisticians of that era to organize and participate in the original cancer cooperative groups program. From the inception of CCNSC, the organizers recognized the need to establish, in conjunction with the formation of the clinical groups, Statistical Centers that would provide resources essential for the conduct of clinical trials that incorporate sound scientific principles. The earliest cancer clinical cooperative groups were organized according to geographic areas within the United States [14].

Several specialty cooperative groups also were initiated in the latter half of the 1950s as part of the CCNSC. Among these was the NSABP, a cancer clinical cooperative group of surgeons established in 1957 under the leadership of Dr. I. S. Ravdin, and dedicated to carrying out RCTs in patients with operable breast cancer. By 1960 there were nine funded NCI clinical cooperative groups. Eventually, in succeeding years, more than 30 clinical cooperative groups were formed, but due to consolidation and attrition, there are today only ten cancer clinical cooperative groups. The Veteran's Administration (VA) Cooperative Studies Program for VA Medical Centers, which was organized in 1945, expanded its scope considerably during the time when the CCNSC was being initiated by adapting approaches developed by the early NCI groups to accommodate the VA system [15]. Following the initiation of the cancer clinical cooperative groups in the United States, clinical collaborative groups with organizational structures similar to the CCNSC program were also established in Western Europe. For example, the European Organization for Research and Treatment of Cancer (EORTC), which is a cooperative endeavor among several European countries, was formally established in 1974 with assistance from several American statisticians and support from NCI [16].

The first trials conducted by these groups consisted of short-term chemotherapy trials in patients with advanced disease and utilized tumor response as the primary endpoint. In these early trials, patient follow-up was very short and mortality was not considered as the endpoint of choice. However, these trials advanced several essential features that provided a strong foundation for the cancer clinical trials that would follow the earliest endeavors. Each of the investigators participating in the original groups had to agree:(1) to follow a predefined common protocol that specified inclusion and exclusion criteria for patients who could be entered into the clinical trial; (2) that patients entered into the protocols would be randomly allocated among treatments using a proper randomization procedure in order to provide unbiased comparisons; (3) to centralize clinical and pathologic data collection for quality control, monitoring, as well as a program for long-term follow-up; and (4) to centralize statistical analysis and collaborative reporting of the findings of

the RCTs. These guiding principles remain as relevant today as they were in the initial founding of the clinical trials cooperative group program [17].

The concurrent establishment of ongoing Statistical Centers to collaborate with each of the cancer cooperative groups fostered: (1) major new and innovative developments in statistical methodology tailored to address questions relevant to cancer clinical trials; (2) access to and increased use of high speed computational facilities and creation of specialized software packages for database management and statistical analysis; and (3) creation of professional specialties, such as data managers, to support the collection, processing, and quality control of clinical trial data [18, 19].

31.2 Fundamental Features

31.2.1 Collaboration

Clinical trials involve collaborations among many disciplines, but a strong collaborative relationship between the lead clinical scientist and the primary biostatistician for a major trial is essential to ensure that an RCT adheres to the best scientific and ethical principles and methods throughout its course. At the inception of the modern era in RCTs, Hill [20] recognized the necessity for this ongoing collaboration:

> (T)he statistically designed clinical trial is above all a work of collaboration between the clinician and the statistician and that collaboration must prevail from start to finish [20].

Today the need for statistics and statisticians in modern clinical trial research is no longer a topic for debate, as it was in the time of P.C.A. Louis. There is an acceptance of the role of statistical methods and there are many fine examples of highly successful collaborations in breast cancer clinical trials. Unfortunately, there also is unevenness in the extent to which optimal statistical methods are evident in published clinical trial reports, indicating that there is still opportunity for improvement in the collaborations. Biostatisticians and clinical scientists have written extensively about how to foster collaborative relationships. However, collaboration in practice relies on a complex mixture of factors relating to the key investigators, which include not only academic qualifications and professional competencies, but also less easily defined factors such as leadership and management styles, effectiveness in communication in interdisciplinary settings, and mutual commitment to establishing working environments that encourage cross-disciplinary interactions.

There are numerous reasons why some trials fail to achieve the expectations of ongoing collaboration between the clinical specialists and the biostatisticians involved throughout the course of a clinical trial. One overarching reason may be that statistical concepts and issues utilized in the conduct of clinical trials are still not well understood by many nonstatisticians. Approaches considered essential by the statistician in order to have a statistically sound RCT may be regarded by clinical colleagues as being unnecessarily time consuming, non–cost-effective, or simply irrelevant rather than fundamental for the scientific validity of the trial or to assure the quality of the data. In addition, some concepts that are promoted as important in clinical trials, for example, intention-to-treat analysis, are counterintuitive to nonstatistical scientists and may become contentious issues in specifying analytic methods and interpretation of clinical trials. There is a difference as well in how physicians and statisticians are trained to think. In medicine, emphasis is on the individual patient and tailoring a treatment prescription to a particular patient, as eloquently expressed by Double in the debate with P.C.A. Louis over 150 years ago. Whereas physicians evaluate the individual patient by a process of tests and clinical judgment that leads to a differential diagnosis and treatment, statisticians rely on summarizing groups of patients with certain characteristics in common in order to identify treatments that are useful on average for a specific group of patients.

Ellenberg [21] presents an excellent summary of the broad scope of biostatistical collaboration in medical research. Our collaborations in numerous NSABP cancer clinical trials lead us to the following recommendations for promoting collaborative relationships that produce RCTs of highest scientific quality.

First and foremost, key investigators in an RCT, including the primary trial biostatistician, should agree at the initiation to accept shared authority and responsibility for the scientific integrity of the research conducted. Biostatisticians who are content to be consulted to write the statistical considerations for a protocol that has already been drafted except for defining the statistical hypothesis to be tested, calculating the sample

size, and outlining the analytic approaches to interim and final analysis are not full collaborators. Clinical scientists who visualize their interaction with the biostatistician as one in which the biostatistician provides sample size justifications, randomization scheme, and analytic plans when the protocol is designed and then has no major participation until it is time for the data analysis are not fulfilling the expectations associated with collaborative relationships in clinical trials. It may be difficult for busy investigators, including the primary biostatistician, to find the time for discussions during the initial conceptual phases in designing a protocol, but it is the most critical time for assuring that the design is scientifically sound and consistent with the best methodology currently available. Moreover, working together in drafting sections of a protocol, such as the statement of the primary aims of the study, definitions of study outcomes, and detailed follow-up schedules enables the primary biostatistician not only to have a more informed understanding of factors important for developing the statistical considerations section, but also provides opportunities to make a contribution to other sections that leads to more rigorous design overall.

Second, all key collaborators in a trial should meet together during the early phases of clinical trial planning and discuss the rationale and other major facets important for the study. In-person meetings are especially crucial during the preliminary phases of trial design in order to discuss and agree upon major elements important for the conduct of the trial. The biostatistician should enter into the discussions asking insightful questions of the investigators and be prepared to discuss at an appropriate time what the critical issues are from the statistical standpoint. These meetings are likely to be most productive when all parties have read the relevant background material, such as the reports of findings from the early phase trials in advance of the meetings.

Third, even though individual investigators will have assignments for drafting particular portions of the protocol for a clinical trial, all key collaborators, including the biostatistician, should review and agree on the entire final draft of the protocol, as well as substantive changes that are made subsequently during the conduct of the RCT. An analogous process should be followed when reports or publications of results are in preparation.

Finally, while the establishment of independent statistical and data coordinating centers, in conjunction with governance structures that facilitate shared authority and shared responsibilities in the conduct of RCTs, have done much to stimulate collaboration among clinical and statistical disciplines, the best collaborations depend also on interpersonal and work environment factors. Although it may be impossible to specify all the intangible factors that contribute to optimal collaborations, written protocols and publications serve as evidence post facto as to whether the RCT has been a joint intellectual research endeavor among the key investigators.

31.2.2 Phases in Development and Testing of New Drugs

For many years following their creation, the cancer cooperative groups defined three stages, referred to as Phases I, II, and III, necessary to evaluate new drugs in studies with human subjects [18]. The three phases develop evidence important for recommending a drug's use as a clinical treatment. Preclinical invitro studies on parts of living organisms, such as tissue samples, and in vivo animal studies provide vital information on potential efficacy, likely toxicities, pharmacokinetics, and initial dose estimates that guide researchers in the design of the human studies. The objective of Phase I studies is to obtain data on dosing and safety concerns, with collection of preliminary data on biological activity against the disease. In contrast with many disease conditions, where Phase I studies may recruit healthy volunteers to test new drugs because they are anticipated to have limited toxicity, usually patients with advanced, end-stage cancer, are the participants in Phase I studies of new cancer drugs which tend to have greater toxicity. Phase I trials do not have control groups; the goal is to define an estimate of the maximum tolerated dose (MTD).

Following completion of Phase I studies to establish a tolerable dose level for use in future trials, investigators recruit patients for Phase II trials that have as their primary objective to evaluate whether a drug shows sufficient promise of efficacy to move forward to testing in comparative trials against the current standard therapy. The earliest Phase II trials typically set some estimate of efficacy, based on clinical judgment and historical experience with current standard therapies, of what response rate is necessary for the drug to

go forward to Phase III trials. Patients in Phase II trials are usually patients with metastatic disease and may have had extensive treatment with other drug regimens. The outcome used for the response rate usually is some early indicator that the drug is active against the metastases, such as the extent to which the tumor shrinks in size or disappears following administration of the test drug. Phase IIA designs, which test a single drug, may have one or multiple stages. The most popular design for Phase II trials is a two-stage design, in which drugs that demonstrate little or no activity against the tumor can be dropped earlier when fewer patients have been treated [22]. If a drug shows sufficient activity during the first stage, then additional patients are treated in order to obtain a sufficiently precise estimate of the response rate to use in the design of a Phase III trial. Phase IIB generally refers to trials in which one or more new treatments are compared to the standard therapy. Patients may be randomly allocated among the treatments. It is sometimes difficult to distinguish between a Phase IIB design and a Phase III trial other than the sample size is not adequate for testing with a definitive outcome. There are some Bayesian approaches to Phase I and Phase II trials that merit consideration [23, 24]. Some recently developed approaches for Phase II two stage designs take into account both efficacy and safety outcomes jointly in deciding about early termination of the trial (see, e.g., [25]).

The Phase III trial entails comparisons of the promising new regimen to the best available standard therapy, and relies upon a more definitive outcome measure such as mortality. The participants in Phase III trials are generally those who have earlier stage disease or have not received prior treatment for advanced disease.

Scientific and statistical considerations for the design and conduct of each of the three stages in the development of new therapies are different. Table 31.1 summarizes some of the salient features of each of the phases. There has been a tendency, particularly in the design and conduct of Phase I and Phase II studies, to rely upon statistical methods established many years ago. Some newer methods, which have some attractive statistical properties, have been proposed and merit further evaluation in carefully monitored clinical trials in order to determine whether they will provide more optimal approaches for successful drug development.

Table 31.1 Summary of various phases of clinical trials on human subjects

	Phase 0	Phase I	Phase II	Phase III	Phase IV
Definition	First studies on human subjects to understand the path of a drug (small amount) in the body	Studies on clinical pharmacology and toxicity to establish a safe dose and schedule of drug administration	Initial clinical investigation for treatment effect and toxicity	Full scale studies to determine efficacy of a new treatment,as well as to compare severity of side effects, relative to standard therapy	Final step for evaluating new therapies (postmarketing surveillance)
Outcome	Pharmacokinetics; Pharmacodynamics	MTD (maximum tolerated dose)	Proportion of patients responding; average blood or tissue levels of a drug	Time to events with possible censoring; toxicity grades from CTCAE (common terminology criteria for adverse events)	Proportion of patients experiencing long-term side effects such as cardiac toxicity
Sample size	10–15	20–50	50–100	Substantial number of patients from multicenter (several hundreds to several thousands)	Substantial number of patients from multicenter (several hundreds to several thousands)
Statistical methods	Exploratory analysis such as ranking the outcome measurements	CRM(Continual Reassessment Method) [136];	Early stopping of ineffective therapies [137]; Two-stage design [22]	Kaplan-Meier method [75]; Log-rank test [73]; Cox's proportional hazards model [74]	Statistical inference based on, say, the proportion

It is difficult to carry out new, more complex designs, in busy clinical settings, but some commitment of resources is merited if a new statistical approach has the potential to reduce the number of patients exposed to adverse risks and/or to be more cost effective than the classical methods. The types of therapies under development today, such as targeted therapies or vaccines, differ from the classical drug trials. Statisticians are active in developing methods that are tailored for these new therapies, although most of the published clinical trials do not yet incorporate these advances in statistical approaches.

In recent years, as regulatory agencies have moved to more rapid approval of drugs, there has been added a requirement for continuation of safety surveillance and technical support on the part of the drug company for a period following the approval for marketing of the drug. The collection of data on patients receiving the drug following approval by the regulatory body is referred to as a Phase IV trials or Post Marketing Surveillance Trial. These postmarketing studies have many serious limitations, which include lack of appropriate comparison groups to discriminate between adverse events associated with the disease condition or the drug and incomplete reporting of adverse events.

As an alternative to the phases in drug development discussed above, some statisticians prefer to refer to the stages as translational, treatment mechanism (TM), dose-finding (DF), dose-ranging, safety and activity (SA), comparative (CTE), and expanded safety (ES) ([26], Section 6.3, pp. 132–134).

31.2.3 Explanatory and Pragmatic Considerations

Different viewpoints frequently occur among key investigators regarding basic features that need to be specified when planning a clinical trial. For instance, a common clinical approach, analogous to what is done in laboratory experiments, is to minimize the heterogeneity among patients who are eligible for the RCT in order to limit the accrual to patients in whom it is believed that the experimental treatment is likely to be most beneficial. Other collaborators may advocate the use of the fewest possible eligibility criteria that are medically necessary for assuring known safety concerns in order to test the treatment on as heterogeneous a group of patients as possible, thereby increasing the generalizability of the trial results. These two approaches, referred to as explanatory and pragmatic respectively, arise when the rationale for the trial includes a biological hypothesis that the researchers are interested in testing within the framework of the Phase III trial. Usually the biological hypothesis may already have been formulated based on findings from laboratory animal experiments or *translational* studies in humans. On the other hand, if the main stated objective of the clinical trial is to decide which treatment is better overall for patients rather than to test an underlying biological hypothesis, this leads to different design and analytic approaches. Schwartz and Lellouch [27] discussed the issues associated with these two philosophies toward designing clinical trials, and there have been numerous papers since their paper elaborating on the "explanatory" and "pragmatic" approaches to RCTs. Table 31.2 lists the contrasting features that are associated with these two different philosophical approaches to the design of RCTs.

Lellouch and Schwartz pointed out that, since RCTs involve human subjects, ethical, as well as statistical considerations, often lead to a pragmatic approach in the overall design. Ethical concerns (as discussed below) direct us to choose a design that will have the greatest potential for benefiting the patients who consent to participate in the trial and future patients to whom the treatment might be given. The pragmatic

Table 31.2 Contrasting features of pragmatic and explanatory philosophies in RCTs (Based on [27])

Pragmatic	Explanatory
Generalizability	Efficiency
Heterogeneity	Homogeneity
Broad entry criteria	Narrow entry criteria
Larger sample size	Smaller sample size
Real world	Laboratory
Equalized	Optimal
Treatment	Biology
Typical treatment effect	Maximal treatment effect
All patients randomized	Patients adhering to protocol
Unbiased	Potential for bias
Intention-to-treat (ITT)	Treated per protocol (TPP)
Decision	Understanding

approach, which enhances the ability to generalize the findings of the trial to the broadest population of patients, is consistent with the rationale for carrying out large collaborative clinical trials that encompass many clinical centers.

Therefore, the stated primary aim of a Phase III study generally is a clinical, rather than a biological, hypothesis. When there is a biological hypothesis of interest, the use of a pragmatic design does not necessarily preclude obtaining valuable information relating to an explanatory hypothesis. Optimally designed clinical trials incorporate features that provide for obtaining scientifically valid information relating to biological questions of interest. Additional study aims can be formulated to evaluate the relationships between the treatment outcomes and host-tumor factors of interest, when ethical or other considerations do not preclude collecting measurements that are needed for testing the underlying biological hypothesis. RCT designs that are pragmatic, but also have a biological rationale that can be tested, are more complex to design than those that simply provide a decision about treatment.

NSABP Protocol B-06, which was a randomized clinical trial consisting of three treatment groups that compared total mastectomy to lumpectomy (the control arm) to lumpectomy with or without postoperative radiation therapy, had major pragmatic and explanatory features to consider in the study design [28]. At the time of the initiation of the B-06 protocol in 1976, principles put forth by the distinguished surgeon, Dr. William Halstead, had dominated the approach to treatment of primary operable breast cancer for more than 75 years. Surgeons considered the radical mastectomy, which consisted of removal of not only the breast but also regional axillary nodes and chest muscle, necessary in order to prevent the further spread of the cancer. The untested belief that the radical mastectomy would "cure" more patients with operable breast cancer was based on anatomical and mechanistic principles relating to how breast cancer metastasizes. However, long-term follow-up of women apparently cured of the primary breast cancer indicated that breast cancers continued to recur at distant body sites many years after the initial surgery. Laboratory studies, conducted during the 1960s, of how breast cancer metastasizes, as well as clinical observations on the history of the disease in women following surgery, indicated that there was not an orderly progression in the pattern of dissemination of tumor cells to distant parts of the body and that it was likely that clinically occult metastases have occurred in many women prior to the clinical detection of the primary breast cancer. Dr. Bernard Fisher, Group Chairman of the NSABP, proposed that these differing views relating to breast cancer metastases must be tested in a rigorous manner in a well-designed RCT. The appropriate outcome for comparing the biological hypothesis scientifically, as well as for the pragmatic aim of determining whether less surgery was equivalent to more extensive surgery, was survival. It is noteworthy that the outcome of interest in NSABP Protocol B-06 involved designing a trial to evaluate equivalence, rather than the more usual RCTs of drug therapies where the test question is whether the experimental drug is superior to the standard therapy. This chapter presents in subsequent sections some of the unique challenges that occurred in designing and conducting this paradigmatic surgical RCT.

Another example of a pragmatic trial incorporating seminal biological hypotheses is NSABP Protocol B-09. Protocol B-09 evaluated long-term administration of tamoxifen, an anti-estrogenic drug, as adjunct therapy with chemotherapy for women with Stage II operable breast cancer. In the 1970s when NSABP Protocol B-09 was initiated, it was biologically and clinically important to assess the extent that responsiveness to tamoxifen therapy related to the quantitative levels of estrogen and progesterone receptors (ER and PR) in the primary tumor. In order to evaluate the role of these hormone receptors in a scientifically sound manner, determinations of the receptor values on tumor specimens from all patients entered into NSABP B-09 were made either at a central laboratory or at laboratories that had been approved based on their demonstrated capability to conduct the hormone receptor assays in a valid and reproducible manner. Two papers published 25 years ago in the *Journal of Clinical Oncology* were the first to conclusively demonstrate in unbiased comparisons from almost 2,000 patients entered into NSABP B-09 [29, 30] that therapeutic response to tamoxifen was related to quantitative hormone levels. These articles, recently featured in an invited commentary in the *Journal of Clinical Oncology*, utilized statistical models to estimate the relationship between ER and PR levels and disease free survival, while simultaneously controlling for other known prognostic factors [31]. Because there has been a requirement in all NSABP protocols for centralized review of histopathological features, the

multivariable analyses also gave insights into the close correspondence between the degree of morphologic differentiation in tumors and the presence of hormone receptors.

In summary, as shown by the two examples above, optimally designed RCTs can achieve primary aims that encompass both explanatory and pragmatic aspects. Even if the findings of such trials are nonpositive with respect to the experimental therapy, the inclusion of the explanatory aim provides valuable biological insights that are useful in enhancing understanding of disease and/or treatment mechanisms.

31.2.4 Selection of the Primary Question for Investigation

The primary question that the trial will be designed to answer must be clearly stated from the outset in designing a clinical trial. While this may seem to be self-evident, it is imperative that the question be sufficiently important to utilize the time and resources of numerous professionals required to design and conduct the clinical trial, as well as justifying that human subjects take on risks or discomforts for uncertain clinical benefits to themselves or future individuals who may suffer from the same disease condition. It would seem that ongoing cancer cooperative groups need to be particularly vigilant in choosing research questions that are the most relevant, timely, and innovative rather than proposing trials that represent minor departures from previously conducted studies that have not resulted in major improvements in therapy. Most Phase III RCTs in breast cancer require 5 or more years devoted to recruitment and follow-up to complete the trial. There may be a plethora of questions available for further study, but questions, which if successfully answered, would have the most impact on curing or reducing morbidity from the disease should receive first consideration by experienced clinical trial investigators. The choice of a novel question that has a strong rationale for study usually requires a substantial amount of discussion among collaborators and time invested to develop a study plan that is scientifically sound, clinically feasible, and ethically appropriate. In Phase III studies there has to be sufficient background information available on safety concerns and potential for substantial efficacy to provide support for study on a large number of patients. From the statistician's perspective the question must be amenable to developing a testable statistical hypothesis, with sufficient information available to specify important statistical aspects of the study design, such as the primary outcome and sample size considerations.

The philosophy followed by the NSABP has been that the choice of the primary aim for a protocol should be formulated only after actively seeking the counsel of knowledgeable scientists from a variety of disciplines regarding questions that are believed to be the most likely to provide answers that have both clinical and biological importance for the treatment of breast cancer. While a small number of additional secondary aims can be incorporated, if they fit well with the primary study aim, a protocol with numerous secondary aims selected because of the interests of the investigators participating in the clinical trial is to be avoided as such "appeasement protocols" tend to divert attention and resources from the primary aim, lead to overly complex protocol designs that become difficult to follow in practice, and may jeopardize the completion of the trial [32].

31.3 Design Considerations

31.3.1 Assuring Precision and Eliminating Bias

Most clinical trials involve testing for treatment effects that are small or moderate in size. Two universal concerns that must be taken into account in such trials are how to avoid random errors and systematic errors.

In order to obtain reliable estimates of treatment effects, it is necessary to control appropriately the extent of random variation present. Control of random error is achieved by assuring that a trial has an adequate sample size. Unfortunately, some previous RCTs in breast cancer have had inadequate sample sizes to identify small, but important, treatment effects on outcomes, such as mortality. Inadequate control of random error was a major problem in early trials of tamoxifen or chemotherapy carried out during the 1970s that were designed to consider whether systemic therapy prolonged disease-free survival. Although the trials showed large effects of systemic therapies in

preventing recurrences, the sample sizes were inadequate to provide reliable results on mortality.

Systematic errors, which result in biased estimates of the treatment effect, may arise due to an improper study design or may be introduced during the course of the study due to unforeseen events that affect differential loss of data between treatment groups. An important tool available for avoiding moderate biases is randomization. Properly randomized trials that employ appropriate methods for analysis and emphasize the overall findings in the interpretation of the trial are utilizing the best approaches to prevent serious biases in the conclusions from the trial. Other important features that can reduce or eliminate systematic biases include: (1) blinding of treatments; (2) centralized classification of endpoints using objectively defined criteria; and (3) minimizing exclusion of patients after randomization. Statistical bias inherent in some analytic methods frequently can be eliminated computationally or may be inconsequential relative to other sources of error. Systematic overviews of all relevant trials also are useful in preventing moderate biases since they prevent an overemphasis in the literature on the results of subjectively selected RCTs.

31.3.2 Defining Study Outcomes

The specific aims of the clinical trial determine the outcomes (also referred to as endpoints) that will be measured and analyzed. Although the stated objectives and specific aims of the clinical trial lead directly to the choice of an outcome in a general sense, defining the specific outcome, as it will be measured in the trial, is not always as straightforward. When using the classical frequentist approach to the statistical elements of design, the objective for the trial is usually restated in the form of a statistical hypothesis for testing. In order to specify a testable hypothesis, the outcome measure must be defined carefully with consideration given to its clinical relevance, objectivity, quantifiability, validity, and reproducibility. Typically, there may be a number of outcomes or interest, but in most Phase III studies there is a single primary outcome selected. Of course, there are occasions when there is more than one outcome that may be of major interest, leading to specification of more than one "primary" outcome, but the usual approach is to select the most meaningful clinical outcome as primary, and other important clinical outcomes as secondary. There are also trials in which a composite outcome may be constructed to accommodate a combination of outcomes as a single summary measure. Hard outcomes, such as mortality, are generally preferred for evaluating responses to treatment over "softer" outcomes such as tumor regression. In order to calculate the power of the study to detect a clinically important difference between treatments, it is necessary to select a single primary outcome measure; the power associated with the secondary outcomes then is a passive consequence of the sample size specified for the primary outcome. Piantadosi [26] gives an insightful discussion of issues associated with selection of the primary outcome.

Since time-to-event outcomes, such as survival, disease-free survival, recurrence-free interval, progression-free interval, etc., are the most common outcomes used in breast cancer clinical therapeutic trials, it is worthwhile to discuss some of the considerations related to such measures. Time-to-event outcomes have become widely used, replacing binomial outcomes such as 5-year survival probability as a measure of response to therapy. There are two numerical values that must be specified for each subject's outcome for time-to-event at the time when an analysis is done.

First, there is a binary variable for each subject that indicates whether the person has experienced the event of interest. For example, if the outcome is survival, then each subject is classified as alive or dead at the time of the last recorded follow-up. Generally, there is an indicator variable coded as 0 (alive) or 1 (dead) associated with the vital status of each person at the end of follow-up. The second numerical value is the actual time from randomization (initial treatment) until death or, if not dead, time from randomization until the last follow-up time. Study subjects alive at the last regular follow-up scheduled time are generally referred to as censored. Some study subjects may not have continued under observation throughout the course of the study for various reasons, so there is not up-to-date information on their vital status.

Statisticians distinguish between those who are administratively censored because of a planned analysis and those whose follow-up is delinquent, referring to the latter as "lost-to-follow up." Since patients are generally accrued into a clinical trial over some period of time, often several years, until the requisite sample size is achieved and then followed for the outcome for

some additional years, the censoring times will vary for patients who have not yet died. It is reasonable to assume that patients with short observation periods due to their late entries may have similar treatment response rates as those with longer follow-ups, whereas patients with shorter follow-up times due to some lack of compliance to the study (lost-to-follow-up) may not have responses that are independent of the study outcome, which could introduce a bias in the estimation of treatment effect. Study subjects who do not adhere to the follow-up schedule may also not have adhered to the treatment schedule when treatment consists of receiving therapy over time. There is also a particular concern if the loss rates differ between the treatment groups. If there are a substantial proportion of patients with incomplete observation times due to "lost-to-follow-up," then the analysis needs to take into account potential for bias in the treatment outcomes. Many sample size formulas have the capability to specify a rate of lost-to-follow-up in the calculation, but it is important in the design and conduct of the study that the proportion of losses be kept low in order to avoid the potential bias. Sections on sample size and analysis considerations below provide additional insights into issues that arise in defining outcome measures.

Because of the lengthy study period required to observe the primary outcomes of direct interest (death or recurrence) in early stage breast cancers, investigators may think of using a "surrogate" outcome that occurs earlier in the course of follow-up. Surrogate outcomes have considerable clinical appeal because they usually are associated with some biological change caused by the treatment that it is believed will eventually be reflected in the treatment effect on the longer term outcome. Moreover, surrogate outcomes, when valid and reliable, can lead to more efficient trials due to smaller sample size requirement, as well as shorter follow-up times to observe the surrogate outcome. Surrogate outcomes are commonly employed in the earliest phases of testing on humans. Unfortunately, surrogate outcomes often have serious limitations and uncertain validity in comparative trials so that statisticians will generally discourage their use in Phase III RCTs. Fleming and DeMets [33] provide an excellent overview of surrogate outcomes and the serious problems that can arise. It is often worthwhile, however, to consider including the surrogate outcome as a secondary explanatory aim in the Phase III trial, since the resulting information can be valuable for enhancing understanding of the biological role of the surrogate outcome in determining the definitive outcome of the trial.

31.3.3 Choice of Control Group

The design of clinical trials always involves decisions about the appropriate comparison against which the experimental intervention will be evaluated. The earliest phases of development in new therapies typically do not entail randomized control groups. As noted above, Phase IIA cancer trials do not have concurrent or randomized control groups incorporated in the design, but rather rely upon assumptions derived from historical experience with the standard therapies, to evaluate the probable efficacy of an experimental therapy.

Randomization serves several valuable purposes in assuring the scientific integrity of the clinical trial design. Randomization helps to distinguish between association, which is what is measured in observational studies, and causation so that differences in outcome between treatment groups can be attributed to the therapy. As noted earlier, randomization has a role in the elimination of bias in the treatment comparisons. When sample sizes are adequate, randomization tends to assure balance in the distributions of prognostic factors across the treatment groups. An important feature of randomization, that is not inherent in other methods such as statistical adjustment to control for potential confounding effects of imbalances in prognostic factors, is that randomization balances not only known prognostic factors, but also balances unknown (or unmeasured) prognostic factors. The balance on prognostic factors tends to improve with increasing sample size. Finally, random allocation of participants to treatment groups guarantees the validity of the statistical tests comparing the interventions. Although the focus in this chapter is on drawing inferences from clinical trials based on the classical frequentist methods of statistical design and analysis, it is worthy of mention that randomization is also relevant for the Bayesian and likelihood approaches. For example, in the Bayesian approach to analysis, randomization is necessary in order to assure the absence of confounding [34].

Although the majority of clinical trialists now accept the RCT as the gold standard for comparing a

standard to an experimental therapy, some researchers have been proponents of the use of other comparison groups, such as historical or nonrandomized concurrent controls, as an alternative to randomization for many trials. They argue that there is no ethical dilemma in treating patients in a historically controlled trial (HCT) and that an HCT requires a smaller sample size. They generally rely on multivariable modeling to adjust for known prognostic variables to alleviate potential bias in comparisons.

Most Phase III breast cancer clinical trials seek to identify small or moderate differences between treatments. There are serious concerns about biases that may remain due to unknown or unmeasured prognostic factors associated with diseases, such as breast cancer, for which all factors associated with the clinical outcome are still not well understood. The philosophy that has guided the NSABP relating to randomization has been:

> When ethical issues do not preclude its use, the appropriate focus should be upon how the principles may be best utilized rather than upon what the alternative approaches to the randomized clinical trial might be [35].

The numerous examples in the literature of uncontrolled studies, studies with historical controls or nonrandomized concurrent controls that have created at times undue enthusiasm for treatments subsequently determined to be of little worth, provide a strong practical justification for randomization in clinical trials. When considering the value of RCTs, it is good to be aware of the lessons learned recently from the Women's Health Trial, in which the hormone replacement treatment (HRT) arm was discontinued early, due to the surprising result that there was a harmful cardiovascular effect of the treatment rather than the potentially strong benefit for heart disease, which was predicted based on the findings of earlier observational studies (WHI [36]).

31.3.4 Masking and Placebos

The rationale for masking is that the investigators, who recruit patients, administer treatments, or collect and evaluate data on outcomes, or the patients will not make judgments relating to the conduct of the study based on knowing the treatment received by individual patients. Among the numerous biases that masking helps to prevent are patient biases in reporting of subjective outcomes or side effects, physician bias in patient management, bias in evaluation of clinical response to treatment, bias in data management within the clinic, and bias in decisions related to interim monitoring of a trial.

Placebos are inactive chemical compounds formulated to resemble the active test drug in terms of taste, smell, and appearance that are given to patients allocated to the nonexperimental therapy. Sometimes "sham" procedures that resemble the actual treatment are also done to disguise which patients receive test medical procedures. Approaches to assure masking can become quite elaborate; therefore, it is worthwhile to provide details of how masking was achieved for studies involving masking. Although ethical questions have been raised with the use of placebos, if the procedures employed include careful attention to details, such as when and how the patient will be unmasked and which investigators have access to unmasked data, these concerns can be largely addressed. Members of interim data monitoring committees (DMCs) should always retain the right to review unmasked data in masked trials, since their primary responsibility is to ensure the safety of the participants and cannot rely on statistical guidelines as the sole means of distinguishing benefit from harm. Another caution is that masking does not guard against biases important in equivalence trials, since masking cannot provide protection against concluding equivalence when actually one treatment is superior (Day, Biostatistics in Clinical Trials, 2001).

In the majority of breast cancer RCTs, it is not feasible to mask the clinical investigators who treat patients or the participants to the treatments that are being received, since they are of a disparate nature in terms of the administration or the adverse effects. However, there are some trials in which it is not only possible to mask the treatment allocation, but also is important to protect the scientific integrity of the trial from biases that may be introduced following randomization. The first NSABP trial of long-term chemotherapy (NSABP B-05) compared the oral drug, l-phenylalanine mustard (LPAM) to placebo in a double-blinded RCT. The blinding was useful in assuring that subjective side effects were reported in an unbiased fashion. During the design of Protocol B-14, which was the first NSABP RCT in women with pathologically Stage I breast cancer, the biostatisticians strongly recommended the use of a placebo so

that the trial would be double-masked in evaluating patients' response to the drug tamoxifen. The trials of tamoxifen that had been conducted by other groups had generally had a control arm that had no further therapy following surgery for breast cancer. The primary reason for a placebo was a concern that there was a potential for patients to be crossed over to the tamoxifen group during the course of the study. The power of the study to identify a difference in survival could be seriously compromised if the "drop-ins" to the tamoxifen group were not kept to a minimum since the mortality difference predicted was relatively modest given the favorable prognosis of women eligible for the trial. The placebo encouraged investigators to adhere to the protocol and provided a means of monitoring carefully unmasking for nonprotocol specified reasons. The masking proved to be very worthwhile also in assuring unbiased reporting of rare adverse effects, such as thromboembolic events, and subjective side effects, such as the frequency and severity of hot flashes, which are increased by tamoxifen, but which are common also in women who do not receive tamoxifen.

When it is not possible to mask the study interventions, it is still desirable to consider whether it is possible to mask the clinical staff who will assess the clinical outcome, particularly when the outcome is something other than overall survival. Another approach to maintain objectivity in determination of outcomes is to have a committee that reviews and classifies all outcome data without knowledge of the treatments that patients have received.

31.4 Sample Size and Study Power

31.4.1 Statistical Inference and Sample Size Considerations

Biostatisticians may choose among several approaches for developing statistical design considerations and for drawing conclusions from clinical trials. Statisticians differ among themselves about which forms of statistical inference are preferable for particular studies. While some statisticians may want to choose one inferential approach for general use, the dogmatic selection of a single approach may not lead always to optimal designs and analyses. Furthermore, it can strengthen the conclusions when several trials, using different inferential approaches, support and enhance the overall conclusions about a therapy. As discussed briefly below, frequentist, Bayesian, and likelihood inferential approaches derive from different ways of thinking about variation when estimating population parameters based on samples drawn from populations.

The classical frequentist approach, which is the most commonly employed in practice, regards the underlying values that we are attempting to estimate from samples, such as the treatment effect, as fixed constants (parameters). The statements about the precision around the sample estimate of the parameter are based on what would occur theoretically in repetitive experiments if samples of a fixed sample size are drawn. Investigators make probability statements about the data conditional on tests of specific hypotheses that have been formulated in advance about the parameters of interest. These hypotheses are referred to as the null and alternative hypotheses. The clinical trial design specifies Type I error (probability of a falsely rejecting the null hypothesis) and Type II error (probability of falsely rejecting the alternate hypothesis) for H_0 (null hypothesis) and H_A (alternate hypothesis) which establishes a cutoff for rejection of H_0. The cutoff level for rejection of H_0 is the significance level of the test, while one minus the Type II error is referred to as the power of the test. The result of the clinical trial is usually reported in terms of the significance test in which the null hypothesis is rejected or fails to be rejected. Since the parameters of interest are considered to be "fixed constants," we cannot directly make probabilistic conclusions about their actual values, but rather state what proportion of the time the confidence interval will contain the true parameter value. For example, the interpretation of the 95% confidence interval is that it will include the true value of the parameter 95% of the time. Statements about confidence intervals are not intuitive, so that their interpretation is frequently misstated in published reports.

In the Bayesian approach, Bayes theorem is the basis for inverting conditional probabilities. Statisticians utilize probability models both for the sample data and for the unknown parameters, so that the parameters are also viewed as random variables. Therefore, probability statements can be made about the parameters prior to the conduct of the trial. There is considerable flexibility and subjective judgment that

may be employed in specifying these prior probabilities. The choice of optimistic, skeptical, or noninformative priors plays a role in determining the conclusions at the end of the trial.

The likelihood approach to statistical inference uses the likelihood principle and the statistical likelihood function, which has a natural interpretation based on quantifying the relative evidence for the treatment comparisons. It is a more recently developed approach than either the frequentist or Bayesian and there remain various methodological issues that have not been fully resolved. Nonetheless, it provides a useful method of inference applicable for many RCTs, especially for those with time-to-event outcomes.

Fundamental principles in experimental design provide the basis for determining sample size. There will be a choice of designs and the selection of an optimal clinical trial design depends on many factors. Sample size may vary considerably, depending on the type of outcome variable (e.g., continuous, binary, ordinal, categorical, count, or time-to-event), and whether the comparisons of outcomes are expressed on an additive scale as differences, on a multiplicative scale as ratios, or some more complex formulation. Even after specification of the type of outcome variable and comparisons of interest, there are generally multiple statistical tests, each with somewhat different assumptions to choose for calculating sample size and primary analysis. Regardless of which sample size formula the statistician selects from among the reasonable choices for a given trial, the statistician provides justification of the reasons for the choice.

Sample size formulas for different designs have similarities across all designs with modifications tailored to features of the experimental design. The formula given below is a common sample size expression that we use here to illustrate the major components needed for sample size calculations.

A sample size formula, based on using the normal approximation for the distribution of sample means, is:

$$N = c^2(Z_{1-\alpha}\sigma_0 + Z_{1-\beta}\sigma_A)^2 / \Delta^2$$

where N is the total sample size for the two groups and c is a constant, Z_α is the standard normal deviate whose probability of being exceeded corresponds to α, the Type I error. In the formula above, α is assumed to be associated with a one-sided hypothesis. (If a two-sided hypothesis is specified, then $\alpha/2$ replaces α.) Z_β is the standard normal deviate corresponding to β, the Type II error. Δ is the hypothesized treatment effect that corresponds to the difference between the standard and experimental treatment means, and σ_0 and σ_A are the standard deviations under the null and alternative hypotheses respectively.

31.4.2 Clinical Significance vs. Statistical Significance

Choice of the treatment effect (Δ) for the sample size calculation is a critical decision in the design of an RCT. This decision entails careful deliberation among the key investigators about what treatment effect would be sufficient to have a clinically important impact. It is necessary to keep in mind that the apparent treatment effect that is observed in the clinical trial will be less than what would be achievable in an idealized experiment because of issues related to patient adherence and follow-up. The clinical impact, if the experimental treatment is superior to the standard therapy, will therefore be less than the true efficacy of the treatment. While larger sample sizes will detect smaller differences as statistically significant, treatment effect sizes should be selected, based on consideration of the smallest clinically meaningful effect size. The choice of a clinically meaningful effect size, which is done collaboratively among investigators, is one of the most challenging issues in the design of an RCT. The biostatistician can facilitate the discussion about what constitutes a clinically meaningful difference by preparing tables that show the number of deaths or recurrences that will be prevented for treatment differences of various size for patients in the trial and when findings from the trial are generalized to similar patients in the general population. Ultimately, however, it is the clinical investigators who have the lead role and assist the statistician in making this decision. Once the choice is made, it will not only affect the total sample size needed, but also other factors, such as number of clinical sites needed, anticipated duration of recruitment, and total length of time to complete the clinical trial. It is not scientifically sound to design a trial in which the effect sizes anticipated are smaller than there is good statistical power to identify.

31.4.3 Statistical Significance and Study Power

The selection of values for the Type I (α) and Type II (β) error rates in sample size calculations for breast cancer treatment trials often relies upon conventions that have become established in medical research. Conventional values of 0.05 or 0.01 (two-sided) for α and 0.20 or 0.10 for β are selected most often as the error rates in comparative trials. While these values may be acceptable for many clinical trials, statistical considerations should explicitly address selection of their values as part of developing sample size considerations for a clinical trial. The choice of Type I and Type II error rates is an opportunity to weigh issues relating to risks and benefits of the control and experimental treatments. The balancing of benefits and risks in selection of error rates also depends upon whether the patients have advanced disease, early stage disease, or are healthy volunteers at increased risk of disease participating in a breast cancer prevention trial.

The question of when one-sided or two-sided Type I error rates are appropriate has also been a topic for some debate in the literature. When the standard therapy is a systemic therapy against which a new experimental therapy is to be compared, there is general agreement that the sample size and statistical test should use Type I error values corresponding to two-sided tests of the alternate hypothesis. When the standard group is a placebo or control arm that does not receive any drug, then some statisticians would favor a one-sided statistical hypothesis. When there is a placebo, the question is not which drug is better (two-sided) but rather whether the test drug is better than no drug. In the latter circumstance it is still possible to use a lower, more stringent, α, such as 0.025 or 0.01, which in a practical sense obviates the argument over whether the test should be one or two sided.

31.4.4 Baseline Outcome Rates and Population Measures of Variability

Often one does not know precisely all the parameters needed in the equation for calculating sample size. There may be uncertainty about what the baseline outcomes will be in the group on standard therapy which will affect the sample size needed. The formula also assumes that we know the value of the standard deviation (measure of variability) in the population, but frequently we can only approximate it from available preliminary data or sometimes can only guess at a likely range of values. Therefore, we may choose a range of values for the uncertain parameters and then using some conservative assumptions calculate a sample size that seems feasible and likely to achieve the scientific objectives of the study.

31.4.5 Sample Sizes for Other Common Experimental Designs

The sample size formula above was for a trial in which the hypothesis of interest was a test of the superiority of an experimental therapy as compared to the standard therapy. When the hypothesis is that the experimental therapy has an outcome that is similar to that of the standard therapy, i.e., equivalence trial, no difference must be defined by specifying the largest acceptable difference, say δ, as part of the null hypothesis. This specified difference plays a role in the P value at the end of the trial and whether the nominal significance level is attained.

31.4.6 Time-to-Event Outcomes

The most common definitive outcomes in breast cancer clinical trials are time-to-event outcomes, such as survival or disease-free survival (DFS). For time-related outcomes, the power of the statistical tests is related to the number of events (deaths, recurrences) that have occurred at the time the analysis is performed rather than the number of patients that have been randomized. One simple approach to sample size calculations uses the ratio of the hazard (mortality) rates and assumes that the corresponding survival curves will follow an exponential curve, i.e., that the hazard rate is constant over time. If $\Delta = \lambda_1/\lambda_2$ where λ_1 and λ_2 are the hazard rates for the control and experimental groups respectively, then the maximum likelihood estimates of λ will be the number of events observed divided by the total

time followed (at risk). Using this method one can solve for the number of events needed for the trial given specified Type I and Type II error rates.

31.4.7 Sample Size Adjustments

Other more complex formulas that accommodate nonconstant hazard rates and adjust the treatment effect size projected for noncompliance (nonadherence to treatment allocation such as drop-ins or drop-outs and losses to follow-up) or a phasing in of the treatment effect over time have been developed. Since the impact of noncompliance is to reduce the apparent treatment effect observed in the RCT, there is a need to inflate the sample size. Simple, conservative adjustment based on the proportion (p_m) of anticipated noncompliance is to use the factor $1/(1 - p_m)$. If p_m is 0.20, then sample size needs to be inflated by 56% to maintain power. If noncompliance is as high as 0.30, then the sample size required is approximately doubled (2.04). Because of issues about bias associated with noncompliance, we try to reduce noncompliance as much as possible, but still need to take noncompliance into account in determining sample size [37].

Lakatos and Lan [38] have developed methods for sample size calculation utilizing the most common test for time-to-event outcomes, the logrank statistic, and incorporating flexibility in the adjustment for nonuniform accrual patterns, nonconstant and nonproportional hazard rates, lags in treatment effects, loss to follow-up and dropouts. For a detailed presentation of sample size formulae and compendium of sample size tables, the book by Shuster [39] is a useful reference. Software is readily available for calculating sample sizes that take into account anticipated accrual patterns, more than two treatment groups, and adjustments for noncompliance and other factors to ensure that the trial will have adequate power. The statistical package, PASS, is a relatively inexpensive package for estimating sample sizes or study power for the majority of clinical trials (NCSS, PASS, and GESS, http://www.ncss.com). There are also numerous useful programs that can be downloaded freely from trustworthy Websites of clinical trial biostatisticians, such as the departmental Website of Biostatistics and Applied Mathematics, at MD Anderson Cancer Center (http://biostatistics.mdanderson.org/SoftwareDownload/) and the National Cancer Institute Website (http://www.cancer.gov/statistics/tools).

Further adjustment of sample size can be done to accommodate plans for interim data monitoring during the conduct of the trial based on group sequential designs. Such adjustments can be quite complex. EaST is a more sophisticated, albeit costly, software package that provides the capability to take into account the plans for interim monitoring of data (Cytel: Statistical Software and Services, http://www.cytel.com).

There is also freeware that can be found on various Websites for sample size calculations and simulating the outcomes of trials under varying assumptions about the design parameters.

31.5 Randomization Methods

The biostatistician works closely with the clinical investigators prior to the initiation of the clinical trial in specifying all aspects of the randomization process in order to ensure that the implementation proposed is appropriate and feasible. In addition, the process should be carefully documented thoroughly throughout the trial. Detailed written procedures of the process and training of all personnel involved in randomizing participants are important. It is also essential that procedures are in place for backing up randomization when computers fail. If the trial is blinded, there should be a well-defined plan that includes who has access to unblinded treatment allocations, how blinding is maintained, the indications for unblinding a participant, and who will be contacted to unblind (including a sequence of backup staff for times when the primary person is unavailable). Often, it is necessary to provide coverage for randomization and unblinding on a 7 day, 24 h basis. Although unblinding of patients in most RCTs is an uncommon, sporadic occurrence, NSABP has experience with rare events related to young children (or even on one occasion, the pet dog) who accidentally swallowed some of a patient's pills on a weekend evening with the consequence that there was a the need to unblind immediately to determine whether the pills were a harmless placebo or active drug. All deviations from the randomization procedures and handling of voided randomizations or other violations should be documented fully for interim and final reporting of the trial findings.

Randomization should be centralized at a data coordinating center outside the clinical setting whenever feasible. The randomization list, if generated in advance of the trial, should be prepared by a qualified person (usually study biostatistician) who is not involved with recruitment or treatment of trial subjects. During the conduct of the study, the details of the generation of the randomization lists should not be disclosed to any of the clinical personnel involved with the trial participants. (Generally access to the randomization lists is restricted to only a few individuals who have a need to know for protection of subjects and to assure backup in the event that the biostatistician who generated the list is not available.)

Random allocation for all subjects is often done prior to the initiation of recruitment for early phase experiments of healthy volunteers, experiments with dietary manipulations, or vaccine trials with closed populations. Alternatively, random allocation may be done sequentially as the participants enter the trial. This approach is done in many Phase III cancer trials that have a prolonged recruitment period. In trials of operable breast cancer, participants are not known in advance and may not have been diagnosed with the condition until sometime during the course of the RCT. The randomization process may be stepwise. In some trials, randomization is done for groups of individuals (cluster or group randomization) rather than for each individual. Group randomization may be the method of choice when the intervention is administered in clinical settings to groups of patients, such as an educational program or a dietary intervention. Random allocation of the clusters makes this approach scientifically acceptable as long as the cluster remains the unit for statistical analysis.

Statisticians no longer rely upon tables of random numbers and preparation of sealed envelopes containing the treatment allocations that are opened in sequence at the clinical site when a patient agrees to participate in a clinical trial (as was done for the NSABP B-04 and B-06, the surgical RCTs conducted in the 1970s). Use of randomized assignments in sealed envelopes at clinical sites should be avoided. While this was a common method in the past for randomization, it is questionable, especially when the study is not blinded since the investigator can either deliberately or by mistake invalidate the randomization process. Further, with modern communication methods such as fax or Web-based randomization programs that permit the randomization to occur in real time (when no problems are identified following a check of the eligibility criteria prior to randomization), there is generally no justification for envelope randomization. Any new system for randomization should be fully pretested prior to the randomization of the first patient. Software for Web-based systems is now available, but it should be pretested in the actual context of the trial prior to adoption.

The random allocation should occur as close in time to the initiation of the intervention as practically feasible. Delays between randomization and initiation of therapy can increase the number of dropouts or subjects who do not receive the allocated therapy. Omitting from analysis the patients who do not receive the allocated therapy can lead to bias. Bias may not occur related to the delay if the treatments are blinded, but should be suspected in unblinded studies. To avoid bias associated with dropouts occurring following randomization, but before initiation of therapy, analysis should include outcomes for all participants as randomly allocated regardless of whether treatment was actually received, i.e., intention-to-treat.

Patients may be stratified into groups based on important prognostic factors and randomly allocated to treatment groups within the strata in order to ensure balance on critical prognostic factors. For example, in clinical trials of operable breast cancer, it is common to stratify on the number of positive axillary nodes because number of positive nodes is the strongest prognostic factor in determining outcomes such as disease-free survival and survival. Another prognostic factor of interest for stratification in trials of early stage breast cancer is the age of the patient at diagnosis, since outcomes differ by age group with younger (premenopausal) women tending to have more aggressive tumors that have a poorer outcome. It is desirable, as well in multicenter studies to balance treatment allocations by clinical site in the design, in order to assure that the numbers of patients allocated to each treatment group within centers are balanced overall, as well as at times of interim data analysis during the course of the RCT. In addition, there may be heterogeneity among the clinical centers, not only with respect to the patient prognostic factors, but also in the adherence rates to the study treatments and the follow-up of patients which make stratification or balancing on clinical centers.

The next step in the process is to create the randomization within each stratum. The random allocations may

be generated in a number of ways. According to Wittes [34]: "The ideal device (for randomized allocation) is a perfectly unbiased coin tossed by an angel." A person tossing a coin is fallible and there may be problems with validating the process, such as filing to record all tosses if a particular toss does not agree with the desired treatment allocation. Random and "haphazard" treatment allocations are not the same. For example, assignment by alternating sequences of the treatment is not a proper method for random allocation although supporters of this method have argued that since patients enroll in a chance order, an alternating assignment of treatments to patients will result in groups roughly at equal risk. However, the person doing the randomization can influence which participants receive a specific therapy. Even when therapy is blinded using alternative sequences, one inadvertent unblinding of treatment reveals the entire sequence of treatment allocations (see [26], p. 335). Similarly, a scheme that allocates patients to different treatments based on alternating days has problems. Once clinical staff becomes aware of the sequence, they can control which patients are randomized to which therapy. This allocation procedure is subject especially to bias when used for nonemergency conditions. Under emergency conditions, if all patients are randomized, the bias issue may be minimal since treatment cannot be delayed until the next day. However, the statistical problem relating to the two outcomes still applies.

Most clinical trials today rely on computer generated treatment assignments. Computers generate "pseudorandom" numbers, not random numbers. The common algorithm for generating a pseudorandom sequence is the linear congruential method [40] which may lead to sequences that are serially correlated and have repetitive series if algorithm's parameters are not appropriately chosen. There is a need to choose a "good" random number generator and to evaluate the program thoroughly before initiating randomization and during the course of a large trial to ensure that the program is not looping back improperly and, therefore, generating repetitive sequences. Statistical tests should be performed to verify the validity of the randomization sequence. Proper randomization is one of the most crucial features in assuring the scientific integrity of an RCT. If it is discovered at the conclusion of a trial that there was a serious problem with the random allocation, the study can be criticized as invalid.

A simple randomized sequence has no memory of previous treatment assignments. However, it may have imbalance in the treatment assignments, which can be particularly problematic when number randomized is small or moderate in size. There is a nonnegligible probability of some imbalances between treatments and a small probability of serious imbalances. Imbalance increases the variance of the estimated treatment effect, but the amount of the increase will be slight if the imbalance is not severe. The treatment allocation may be relatively balanced and still have problems with imbalances in major prognostic factors.

To alleviate potential treatment imbalances that occur with simple randomization, statisticians will often employ a constrained randomization scheme that helps to assure balance in the numbers on each treatment. Random permuted blocks is a method of restricted randomization to ensure exactly equal treatment numbers at certain equally spaced points in the sequence of patient assignment. Block sizes are multiples of the number of treatment groups. For each block of patients we use a different random ordering of the assignments for each treatment. For example, if there are two treatments and the designated block size is four, there will be six possible orderings of the treatments within a block. The randomization consists of selecting at random (with replacement) strings of the blocks. Sometimes treatment allocation sequences are generated with blocks of varying size to reduce the predictability of the sequence of treatments, but the block size should be relatively small to assure balancing of the treatments. Imbalances may still occur with this approach, the extent of imbalance is less due to the balance within blocks. The random permuted blocks is an appropriate randomization scheme in RCTs when there is an expectation of relatively large numbers accrued from each of the clinical center.

It is common in breast cancer treatment trials that there are many clinical centers, but the majority of centers may accrue only a small number of patients to the RCT. In order to assure that the numbers of patients are balanced by treatment and major prognostic factors, cancer biostatisticians have often preferred to use an adaptive (dynamic) method of allocating patients to treatments while controlling for balance on pre-specified major prognostic factors. Efron [41] introduced the notion of "biased coin" randomization as a procedure to control imbalances. The implementation of this adaptive randomization approach that is most popular in cancer clinical trials is usually referred to as minimization method [42, 43].

31.5.1 An Example of Biased Coin Algorithm

The following is a specific example of the biased-coin algorithm adopted by the National Adjuvant Breast and Bowel Project (NSABP).

1. Obtain the number of patients on each treatment arm for the current protocol at the current institution.
2. Calculate the difference in number of patients between the treatment arm(s) with the fewest number of patients (first group) and the treatment arm(s) with the highest number of patients. Define the second group as one including all the treatment arms that have the number of patients greater than the minimum.
3. If the difference is greater than two patients, then the treatment is then assigned with a $\gamma\%$ ($\gamma > 0.5$) probability that it will be a treatment from the first group, and a $(1 - \gamma)\%$ probability that it will be a treatment from the second group. Within the groups, the probability for each treatment is evenly divided.

Example 1: Suppose an institution had the following patients currently:

	# Patients
Arm 1	5
Arm 2	6
Arm 3	8

The biggest difference in patients is three. Thus, assuming $\gamma = 70$, Group 1 will consists only of Arm 1 with 70% probability, and Group 2 will consist of Arm 2 and Arm 3 with 30% probability. Therefore the probabilities for the individual treatment arms break down as follows:

Arm 1: 70% probability of being the assigned treatment arm

Arm 2: 15% probability of being the assigned treatment arm

Arm 3: 15% probability of being the assigned treatment arm

4. If the difference in number of patients between the treatment arm(s) with the fewest number of patients and the treatment arm(s) with the highest number of patients is less than or equal to 2 then
   a. Calculate a score for each treatment arm by adding the number of patients on that arm on the current protocol at each of the patient's stratification levels multiplied by a pre-assigned weight for each stratum variable (See Example 2 below).
   b. If all treatment arms have the same score, then generate a random number between 1 and the number of treatment arms on the current protocol and assign the treatment accordingly.
   c. If all treatment arms do not have the same score, then divide the treatment arms into two groups, the first group consisting of all treatment arm(s) with the lowest score, and the second group containing all other treatment arms. Within the groups, the probability for each treatment is evenly divided.

Example 2: Suppose there are three stratification factors to be used for designing a new study; age (dichotomous), nodal status (negative, positive), and estrogen receptor (ER) (negative, positive). Suppose the protocol had the following distribution of patients across three arms at the current stage:

	Age	Nodalstatus	ERstatus
Arm1	Younger: 5 patients Older: 4 patients	Negative: 4 patients Positive: 5 patients	Negative: 6 patients Positive: 3 patients
Arm2	Younger: 4 patients Older: 4 patients	Negative: 5 patients Positive: 3 patients	Negative: 3 patients Positive: 5 patients
Arm3	Younger: 4 patients Older: 4 patients	Negative: 5 patients Positive: 3 patients	Negative: 2 patients Positive: 6 patients

Now suppose that the patient being randomized has these stratification levels as younger, node-negative, and ER-positive. Assuming that the weight given to each stratification variable is 1, the score for each treatment is shown below:

Score for Arm 1 = $(5 \times 1) + (4 \times 1) + (3 \times 1) = 12$,
Score for Arm 2 = $(4 \times 1) + (5 \times 1) + (5 \times 1) = 14$,
Score for Arm 3 = $(4 \times 1) + (5 \times 1) + (6 \times 1) = 15$.

So Group 1 would include only Arm 1 with 70% probability and Group 2 would consist of Arm 2 and Arm 3 with 30% probability. Therefore the probabilities for the patient to be randomized to each arm break down as follows:

Arm 1: 70% probability of being the assigned treatment arm

Arm 2: 15% probability of being the assigned treatment arm

Arm 3: 15% probability of being the assigned treatment arm

31.6 Ethical and Related Considerations

A fundamental responsibility of clinical trial researchers is to assure the conduct of RCTs that are ethical in all features from the design through the final closeout of the study. Ethical considerations are interwoven with many of the scientific facets involved with clinical trials. This section deals mainly with ethical concerns that predominate in the planning of an RCT as they relate to specific design elements. Although we do not present in detail the evolution of protections for human subjects in clinical research studies, all staff involved with the conduct of clinical trials should be knowledgeable about the background and content of major codes, laws, guidelines and principles, such as the Nuremberg Code [44], Declaration of Helsinki [45], Belmont Principles [46], and regulations that pertain to national and international studies that conduct research with human participants. The elements of informed consent should also be familiar to all investigators and staff, not just those who are responsible for recruitment of subjects to clinical trials. The National Institutes of Health (NIH) and other funding bodies require training in the principles and legal requirements for research involving human subjects and Institutional Research Boards must approve research protocols and review adverse events on an annual basis.

Clinical thinking about an ethical requirement for signed informed consent of participants in clinical trials has changed greatly in many countries since the 1960s when, at a meeting of the Medical Research Council (MRC) to consider the legal and ethical concerns regarding RCTs, the attendees:

> …decided that there was no obligation on the part of an investigator to inform a patient that he was participating in a trial. Particularly is this so in the trial of methods of treatment for desperate cases of advanced disease. If the trial is ethically the criteria outlined and if therefore the choice of treatments is really being made by the 'toss of a coin,' it is not to be considered to be the best part of doctoring to inform a patient so gravely ill that we do not know how to treat her, and that the choice of treatment is being so determined [47].

Zelen [48] proposed as a design for the RCT that, when a standard therapy is to be compared to a new experimental therapy, it is ethical to randomize and then seek informed consent only from the patients who are randomly allocated to the experimental therapy, since the patients allocated to the standard therapy would be treated in the same manner as if there had been no clinical trial. Although this design, sometimes referred to as the "informed consent" design, has generally been deemed as not ethical, it is worthy of mention because it stimulated consideration of the possibility of some modifications in the approach to obtaining informed consent such as the "pre-randomization" approach employed in the NSABP Protocol B-06 lumpectomy trial, as discussed in more detail below.

Current procedures for ethical conduct of clinical trials incorporate two important protections for human subjects. Ethics Committees, or Institutional Review Boards (IRBs) as they are referred to in the United States, are independent bodies which must follow various legal and ethical requirements that protect human subjects in research studies. IRBs are charged with reviewing and approving protocols prior to implementation, annual review and approval of study progress, as well as intervening substantive protocol changes. Unexpected adverse events occurring during the course of the trial are also reported to the IRB for their review and approval of actions taken.

With few exceptions, such as when the situation does not permit (e.g., heart or stroke victims requiring immediate emergency treatment) or in the case of minors or others unable to give informed consent, signed informed consent must be obtained from all subjects prior to enrolling them in a trial. Thus, the approach to clinical trials today strongly affirms that it is an ethical obligation of the investigators to obtain informed consent from *all* participants in a clinical trial. The informed consent process involves providing the potential participant with complete, accurate information on several aspects, including: (1) a clear statement that the participant is being requested to become a participant in a research study; (2) explanation of the purpose of the research and the procedures that will be followed in the study; (3) description of experimental procedures; (4) potential benefits for the participant; (5) expected risks and discomforts that are known or suspected; (6) alternative methods available for treatment of the disease; (7) anticipated duration of the study; (8) availability and willingness of the investigator to answer questions about the study; and (9) the right of the participant to withdraw consent at any time during the course of the trial without any adverse consequences affecting future treatment. The informed

consent should be constructed in language that is informative and understandable to the populations from which the participants are to be recruited. In multicenter clinical trials, this may entail that the consent form is translated into several languages and written in clear simple words that the public can understand rather than technical or legalistic terms.

Although there is now general agreement that participants in clinical trials should be given complete information and the opportunity to consent voluntarily to become a part of a clinical trial, issues can still arise about the process used in obtaining informed consent, particularly in clinical trials where the patient must simultaneously cope with a serious newly diagnosed disease such as breast cancer. Signatures and initials on multiple pages of a consent form are not an adequate substitute for dedicated and knowledgeable clinical trial staff that spends time with potential participants discussing the study and answering their questions in words that they can understand. With respect to the implementation of these tremendous gains in the protections of human subject protections, we have expressed the following caution:

> …..There is no dichotomy of purpose between preservation of human rights and dignity and freedom of inquiry. There must be strict vigilance to ensure that there is no serious conflict between the forces defending subjects rights and those defending freedom of inquiry. In such a confrontation, once again, 'winners may become losers' [32]

NIH and FDA require interim data monitoring plans for protection of human subjects during the conduct of the trial. As discussed below in the section on interim data monitoring, most Phase III have independent data monitoring committees. In spite of the many formal procedures in place to protect human subjects who participate in RCTs, those who design and conduct the trials should give thoughtful attention to addressing ethical concerns that arise. As illustrated in the examples below, ethical issues that arise may be complex and there may be disparate viewpoints regarding what is an ethical solution.

To be ethical a study must be scientifically sound. Rutstein [49] summarized this principle well:

> It may be accepted as a maxim that a poorly or improperly designed study involving human subjects… is by definition unethical. Moreover when a study is in itself scientifically invalid, all other ethical considerations become irrelevant. There is no point in obtaining informed consent to perform a useless study [49].

Clinical trial investigators have an ethical obligation to: (1) ask relevant important clinical questions; (2) use the best possible research design and methods throughout the conduct of the trial; (3) assure that the projected sample size is adequate to achieve clinically meaningful findings; (4) obtain informed consent of all participants; (5) implement quality assurance, as appropriate, in protocol requirements and data collection; (6) monitor accumulating data during the course of trial to identify known, as well as unexpected, adverse events of treatment and early evidence of treatment benefit or harm; (7) analyze data relating to all patients entered into the RCT, i.e., follow "intention-to-treat" principle; and (8) publish and disseminate the findings at the conclusion of the trial.

Similarly, the research team at institutional sites needs to be trained by experienced trial leadership in their responsibilities for ethical and scientific conduct of the trial, which include: (1) careful evaluation of potential participants for protocol eligibility to minimize errors in subject recruitment; (2) explain the protocol appropriately and obtain informed consent of participants prior to entering them into the trial; (3) be knowledgeable and comply with all protocol requirements relating to eligibility, treatment, and follow-up; (4) promote adherence of participants by providing high quality care and a supportive clinical environment; (5) submit complete, accurate data in a timely manner; (6) report serious adverse events immediately to the appropriate personnel and agencies, e.g. the Food and Drug Administration (FDA) for trials funded by or conducted in the United States; and (7) work collaboratively with the trial management staff to resolve problems that arise during the conduct of the trial.

31.6.1 Ethical Concerns Relating to Randomization

Until a drug has been established as efficacious and adequately safe, or ineffective with adequate safety, or simply ineffective, the principle of "equipoise" can apply to justify randomization, provided that the participant has been fully informed of potential benefits and risks and consents freely to participate. Thus, the participant accepts uncertainties about individual benefits and risks. There is a fragile balance between individual and collective ethics. Individual ethics involves

considering what is best for the individual patient, whereas collective ethics entails consideration of advancements in medicine and public health through careful scientific experimentation.

Opponents of randomization contend that "equipoise" seldom applies by the time a Phase III trial is conducted because there is evidence from animal studies and Phase I/II trials indicating that the therapy is efficacious with an acceptable level of toxicity [144]. However, the rejection of the ethical nature of an RCT leads to acceptance of therapies with limited comparative evidence and/or further observational studies to establish effectiveness of therapy involving historical comparisons or concurrent nonrandomized controls [140].

Those of us who consider randomization the method of choice argue that without randomization there will be limited advancement of medical science. Those who strongly support randomization believe that there should be a global standard of evidence that is based on randomized controlled clinical trials. Random allocation of patients to treatment groups has become accepted as the "gold standard" by the majority of biomedical researchers. Most clinical trial statisticians are strong advocates for the use of RCTs.

Moreover, with respect to the issue about when patients should be offered the opportunity to participate in an RCT, we recommend that clinical investigators adopt the "uncertainty principle," which has been endorsed by many researchers as an ethical approach. The uncertainty principle states that randomization should be offered when both the physician and patient are uncertain which treatment is better for the patient. Using this as the guiding principle for randomization of a patient places the emphasis on the individual patient rather than a group of patients with particular prognostic factors, and is, thus, more consistent with the usual clinical approach. The drawback for some physicians is that they must be able to discuss uncertainties in medical practice with the patient.

31.6.2 Ethical Controversies in Randomization and NSABP Protocol B-06

NSABP Protocol B-06 had as its primary hypothesis that survival following conservative surgery (lumpectomy) is comparable to that following more extensive surgery (total mastectomy). There was much controversy surrounding the conduct of this clinical trial. Although the radical mastectomy was the standard therapy for operable breast cancer in the United States at the time this protocol was initiated, a small number of surgeons believed that a lumpectomy was indeed as good as a radical mastectomy. They envisioned no ethical dilemma with doing a lumpectomy on patients with early stage breast cancer in the absence of a definitive direct comparison with the standard operation. A second important therapeutic question incorporated in the lumpectomy trial was whether patients in whom the breast was spared should also receive radiation therapy for the control of local recurrences. The leadership of the NSABP and many NSABP clinical investigators believed fervently that the ethical approach to resolve these controversial clinical questions was to conduct a multicenter RCT that was scientifically well-designed in all respects to test both the relevant clinical and biological hypotheses. Accordingly, they developed a protocol with three treatment groups (mastectomy, lumpectomy, and lumpectomy with radiation to the breast) for women diagnosed with operable breast cancer that was 4 cm. or less and whose tumors were amenable to a cosmetically acceptable result. Axillary dissection was done in all three treatment groups, primarily to obtain pathologic information on whether the axillary nodes contained tumor cell, which was necessary since at that time systemic therapy was given only to women with pathologically Stage II breast cancer.

NSABP Protocol B-06 opened for accrual in April 1976 utilizing an envelope randomization scheme with treatments balance achieved within an institution using a classic Greco-Latin square design. The investigators discussed the protocol with eligible patients prior to surgery and obtained informed consent in the conventional manner without knowledge of which treatment the patient would receive if she agreed to enter the trial. The adoption of a noncentralized randomization was due to the clinical practice at that time of doing the surgery for removal of the cancer with the initial biopsy to establish the diagnosis of breast cancer. (An analogous randomization process had been successfully employed in the predecessor surgical trial, NSABP Protocol B-04.) Following the biopsy and availability of immediate pathologic diagnosis of breast cancer by frozen section, the surgeon would have staff open the next envelope in the sequence available at the site and would proceed to carry out the operation specified. The

NSABP utilized this conventional randomization scheme for Protocol B-06 until 1978, when, due to chronic low accrual to the Protocol B-06 that threatened the capability to complete this paradigm shifting trial, discussions evolved about whether modifications to the randomization could be made that would make the trial more acceptable to both physicians and patients. As noted above, Zelen [48] had proposed an approach in which randomization between a standard and experimental therapy would be done prior to seeking informed consent and only patients who were randomly allocated to the experimental therapy would be approached to obtain informed consent. We rejected the Zelen approach, since it was deemed unethical to enter any patient into a research protocol without properly informing her about her participation in the research. However, Zelen's paper stimulated considerations as to whether it might be possible to modify the conventional randomization to enhance the accrual rate in a manner that was ethical and did not seriously jeopardize the ability to answer the scientific questions.

Some idea of how different physicians rationalized the uncertainties in the surgical treatment of breast cancer existing at that time are reflected in comments to a survey querying reasons why surgeons did not consider participation in an RCT of mastectomy vs. lumpectomy [50]. One surgeon, who performed radical mastectomies on his patients, stated: "I don't fear the remorse of removing a breast unnecessarily as I do the remorse of losing one patient unnecessarily because of the trial," whereas another surgeon, who was a proponent of segmental mastectomy (the term for lumpectomy used in Protocol B-06) said:

> I have performed the segmental mastectomy over the past few years and have no reason to regret the surgery. If I honestly believe that there is no choice between the operations and that I do not know which is better, then why, obviously, should my patients subject themselves to the mutilating mastectomy (Taylor, 1984)."

These two surgeons obviously could not ethically participate in an RCT to test different surgeries because of their strong clinical opinions favoring one or the other therapies. However, some surgeons, who participated in NSABP and believed that an RCT was both ethically and scientifically necessary to resolve the uncertainties associated with the surgical treatment of breast cancer, still had difficulties with recruiting patients to NSABP Protocol B-06. They did not feel comfortable with presenting a clinical trial in which the patient had to make a choice between two such disparate surgeries at a time when the patient did not have a definite cancer diagnosis and would undergo surgery not knowing whether she would have her breast removed or only a portion of the breast involved with tumor. These concerns of NSABP clinical investigators lead us to consider modifications to the randomization approach in Protocol B-06. Eventually, after much discussion and debate, both within and external to the NSABP, the decision was made to change from an envelope randomization to a centralized randomization and to adopt an approach to obtaining informed consent that enabled the surgeon to tell the patient which surgery she would have prior to the actual operation. This novel approach, which was named "prerandomization," was a compromise reached in order to alleviate ethical concerns of some investigators and at the same time preserve the ability of the trial to be completed in a manner that preserved its scientific objectives. Interestingly, there were also investigators who believed the conventional randomization was entirely ethical and continued to recruit patients to the trial using that approach even after the introduction of prerandomization.

There were a number of critical aspects in the procedures for the implementation of the prerandomization process to preserve the ethical and scientific integrity of the trial. First, patients entered into the trial had to have a known diagnosis of invasive breast cancer, which meant that a biopsy had to be done prior to and separate from the definitive surgery. The protocol was changed from the usual one stage procedure for diagnosis and definitive surgery that was done during that era to a two stage procedure. Because it was essential to monitor that the randomization process was appropriately conducted, central randomization replaced randomization by envelopes at the institutions. Having established that a patient had operable invasive breast cancer and satisfied other protocol inclusion and exclusion criteria, the site investigator could initiate the randomization process by telephoning the NSABP Biostatistical Center at the time when the patient was scheduled for a visit to discuss the options available for further treatment. During the telephone call a checklist verifying eligibility, including that the diagnosis of invasive breast cancer had been made. Following verification of eligibility, the random treatment assignment for that patient was provided to the investigator. The second step was for the investigator to present the protocol to the patient, providing all

the treatment options in detail including potential risks and benefits. If the patient was receptive to entering the clinical trial, the third step was an explanation that the treatments were assigned by chance. The patient was informed which of the treatments she would receive based on the random assignment already provided to the surgeon if she agreed to participate in the trial. The patient received the information about the randomly allocated treatment prior to signing of informed consent. All other elements of the informed consent process were unchanged.

In contrast to the approach proposed by Zelen [48], the NSABP approached all potential participants for informed consent. Because of the prerandomization, there were some patients, who when informed of the treatment allocation prior to signing informed consent, refused the treatment assignment. In order to be able to evaluate whether patients who agreed to the treatment allocation differed from those who refused on important prognostic factors, patients refusing the treatment allocation were asked for consent to clinical follow-up for study outcomes. Most patients refusing the randomly allocated treatment because of a preference for the alternative treatment agreed to be followed within the trial.

The prerandomization also generated debate based on both scientific and ethical grounds. A scientific concern is that it is less efficient than a conventional randomization approach. Because the trial now included patients who refused the allocated treatment, there was a need to re-evaluate and increase the sample size to ensure that there would be adequate numbers entered who agreed to the random treatment allocation. Scientifically, prerandomization is inefficient relative to conventional randomization. An ethical concern is that knowledge of the treatment assignment before obtaining informed consent of the patient might lead a physician, who wishes to promote the acceptance rate, to tailor the presentation of the treatment options in a manner to influence the patient's decision.

Because the sample size inflation factor (>1) increases rapidly as the refusal rate increases, it was essential that the refusal rate be kept as low as possible. For example, if the refusal rate were 10%, 20%, or 30%, then the corresponding sample size inflation factors would be around 1.6, 2.8, and 6.3, respectively. The accrual rate increased sufficiently following the initiation of prerandomization to complete accrual to the trial although the accrual was extended over more years than most NSABP trials. When the trial closed accrual in 1984, more than 2,100 patients had been randomized in equal numbers to the three treatment groups. Of the 2,105 patients enrolled in the Protocol B-06 trial who consented to be followed and had follow-up information, 172 (8.2%) refused their assigned therapy. The refusal rates varied somewhat across the three treatment groups with 11.3% of patients refusing allocated treatment in the total mastectomy group, 5.2% refusing in the lumpectomy alone group, and 8.1% in the lumpectomy plus radiation therapy group. The initial findings from the trial published in the *New England Journal of Medicine* in 1985 provided physicians and women for the first time scientific evidence indicating that survival was essentially equivalent for women receiving lumpectomy to those receiving a mastectomy [28]. These results have subsequently been confirmed through 8, 12, and 20 years of follow-up in subsequent publications in the NEJM [51–54].

There were no easy resolutions to the complex ethical considerations involved with Protocol B-06. There was an unfailing belief among the leadership and clinical investigators that Protocol B-06 was a crucial trial to complete regardless of difficulties and criticisms encountered. More than 2,000 dedicated women were willing to commit to participate in a trial spanning almost a decade in spite of the ongoing controversies. Fortunately, with the changes made in the trial design, the original aims were fulfilled. In hindsight, one could pose a number of questions about the ethics of RCTs with highly controversial treatment options based on the experience with Protocol B-06. Are there circumstances where it is better to rely on "expert opinion" or choices favored by the popular media as an alternative to conducting a controversial RCT? Would the patients' or public's interest have been better served by discontinuing the trial because of too slow an accrual rate using conventional randomization and publishing the findings, albeit unreliable, based on an inadequate sample size? Would the patients' or public's interests have been better served to continue to accrue patients utilizing conventional randomization even if the trial was prolonged for several more years? The NSABP response to these questions is apparent in their commitment to complete the RCT and to modify the sequence of steps in their randomization. The conclusions from this trial lead to dramatic alterations in the treatment options available after 1985 to women

diagnosed with operable invasive breast cancer. In this instance the prerandomization alleviated sufficiently some ethical concerns of patients and physicians and provided for a paradigm changing trial to be completed. In spite of the success with prerandomization in NSABP B-06, however, classical approaches to randomization and informed consent are the preferred method.

Although there were more ethical issues associated with Protocol B-06 than there are with the typical RCT involving the comparisons of drug interventions, nonetheless investigators conducting major clinical trials can expect that they will be confronted with complex ethical issues. With close collaboration between the clinical scientists and the statisticians for the trial, often resolutions to ethical concerns can be found that still preserve the scientific integrity of the trial.

31.6.3 Data Integrity

The importance of ensuring the integrity of data collected in clinical trials cannot be overemphasized. While findings from laboratory studies are likely to be eventually challenged if subsequent experiments fail to reproduce the results, it is often infeasible and ethically questionable to consider independent replication of a clinical trial that has been very costly in money, time, and other resources. Therefore, for many reasons it is essential that an RCT provide convincing and credible evidence that can be relied upon for clinical implementation, as well as planning future RCT.

Clinical trials carried out by major cancer cooperative groups have in place many procedures for checking data submitted on an ongoing basis throughout the course of the clinical trial. However, it can be difficult to discriminate between errors in data generation or reporting, which can be prevalent due to misunderstanding or carelessness, and instances of sporadic data falsification or fabrication, which are relatively uncommon. Statistical procedures can be useful for detecting some forms of fraud (see, for example, [55]). Clinical settings are not always optimal for data quality endeavors since RCTs which take many years to conduct must deal with attrition in key staff and/or changes in dedication to the objectives of the RCT.:

> It is infinitely more difficult to maintain a level of enthusiasm year after year so that data is collected as meticulously and as thoroughly at the fifth year of study, for example, as at the fifth week. It is the obligation of those who institute and carry out a trial, as well as those who participate, to develop and cooperate in mechanisms to ensure the integrity of the data. Such efforts should not be considered by the investigator as adversary or demonstrating lack of trust. Rather, they are to achieve impeccability ([32], p. 269).

In spite of dedicated commitment to the principles above, the NSABP had occasion during the 1990s to experience first hand the devastating controversy that can arise when the principles of data integrity, as articulated above, were found to have been violated by Dr. Roger Poisson, a surgeon at St. Luc Hospital in Montreal. It is beyond the scope of this chapter to relate the chronology of events and give our perspectives on the impact of events following the discovery that Dr. Poisson had fabricated or falsified data relating to eligibility on about 7% of the approximately 1,500 patients that he had entered on 22 NSABP trials. The NSABP discovered the problem, the leadership reported it to the appropriate governmental agencies, and assisted throughout the lengthy 3 year governmental investigation that ensued. The NSABP also re-analyzed promptly all trials in which Dr. Poisson had randomized patients which resulted in findings that were nearly identical to those in publications and substantiated the validity of the original conclusions. Although the NSABP had provided convincing information to other academicians and governmental agencies that the findings from NSABP trials were not sensitive to the inclusion or exclusion of data on St. Luc patients, an article published in the Chicago-Tribune in March, 1994, raised controversies and spread doubt about the results of NSABP trials, especially Protocol B-06, the lumpectomy trial. Events subsequent to the media frenzy that ensued lead to government hearings and serious disruptions to completion of several major NSABP clinical trials, including the first large scale prevention trial (NSABP P-01). Although eventually the NSABP was able to successfully complete the trials in progress at that time and to continue with its primary mission, the effect of the Poisson episode were profound, not just for NSABP and its leadership, but for all involved in clinical trials. For a more detailed account and insightful perspectives on the nature of what transpired and the consequences for RCTs, we refer the reader to the article by Peto et al. [56] and the discussion in [26] (pp. 553–560).

31.7 Conduct of the Clinical Trial

The written protocol for a clinical trial provides clinical investigators and other professional staff with important information relating to the rationale and conduct of the clinical trial. The protocol helps to assure that the staff at all clinical centers follow common procedures in carrying out the major features of the clinical trial. The protocol is the major document relied upon by review committees in decisions relating to approval and funding. It also contains information relied upon by Ethics Committees or IRBs to ensure that patients rights and safety are well-protected, as well as guidance for independent Data Monitoring Committees (DMCs). Different organizations have developed their own preferred formats for the content of a clinical trial protocol, so that there is not one standardized template that can be recommended for breast cancer clinical trials. [26], pp. 160–164) outlines 29 items essential for most protocols describing RCTs and provides a brief discussion of the content for each item. The majority of features are universal within the protocols of all groups that carry out multicenter clinical trials, so that the novice clinical trialist can readily adapt a template in recent use by one of the major cancer cooperative clinical trial groups for the development of a planned RCT.

The protocol does not usually contain detailed information on the organizational structure, administrative procedures, or many of the technical processes relating to data collection, management, and quality control for a clinical trial. These aspects become part of a separate written document, often referred to as the Manual of Operations (MOP). The MOP serves an important role in assisting all trial personnel with conducting the protocol in a manner consistent with the intent of the protocol. A carefully detailed MOP serves a major purpose in assuring the soundness of the data derived in the conduct of the clinical trial. The study protocol and MOP, which may serve for numerous clinical trials conducted by the same cooperative group, require time consuming careful, often tedious, attention to details by experienced staff. The preparation of these documents prior to implementing a clinical trial may take several months of effort if no prototype is available from a prior trial, but the time involved can help prevent problems during the course of the trial that would lead to substantial delays and changes in approach that can jeopardize the scientific integrity of the clinical trial. Meinert's book *Clinical Trials: Design, Conduct, and Analysis* [57] contains detailed guidance on practical day-to-day aspects of conducting RCTs. The checklists provided in the book can also be utilized when writing the protocol and MOP to ensure that the implementation of a trial is comprehensive in scope.

Over time many features of cancer clinical trials have tended to become standardized across the cooperative clinical trial groups in order to facilitate data completeness and quality, as well as to provide for consistency in comparisons of outcomes across clinical trials utilizing similar patient populations. The International Conference on Harmonization (ICH), which is a collaborative effort of the United States, the European Union, and Japan, has developed numerous useful guidelines that encompass general considerations for clinical trials (ICH E8), good clinical practices (ICH E6), choice of control groups (ICH E10), and sound statistical principles (ICH E9). All guidelines can be readily accessed through their Website (URL: http://www.ich.org). Trials of patients with advanced disease now generally rely on the RECIST criteria for assessing the responsiveness of tumors to treatment, duration of complete response, and duration of overall response [58].

31.7.1 Interim Data Monitoring

Well-defined plans for interim monitoring of data during the course of a clinical trial are essential for the conduct of clinical trials. The primary rationale for interim data monitoring relates to ethical concerns, but there are also scientific concerns that are a part of interim monitoring. Interim monitoring establishes a mechanism to terminate the trial early for several reasons, including: (1) undue serious toxicity occurs; (2) the benefit of the experimental therapy is clearly established; (3) it becomes apparent that there is little or no chance for a clinically important benefit to occur based on the data that have already been accumulated (futility); (4) findings from other clinical trials have affected the need for the ongoing trial; or (5) design or conduct issues have arisen that have compromised the scientific integrity of the trial.

Interim monitoring also serves a role in quality assurance and quality control of the data. There are many potential problems that can occur in data collection and conduct that only become manifest when there is ongoing review of the emerging data in a clinical trial. Incompleteness or inaccuracies in reporting of critical data items that are not identified during routine data editing often become manifest during interim data analyses. Corrective measures can then be undertaken so that the scientific integrity of the entire trial is not jeopardized.

Meinert [59] has listed four monitoring models, which he characterized as: (1) blissful ignorance (nobody looks); (2) ask the statistician (statistical stopping rules decision making); (3) treater investigator monitoring (monitoring performed by the collective set of study investigators; and (4) watertight separation (monitoring entrusted to a committee independent of the trial investigators). The first model is ethically untenable for the vast majority of cancer clinical trials, since most treatments have the potential for serious adverse events. There are situations in which accrual and treatment may be completed over too short an interval of time to permit interim monitoring of outcomes that leads to an early termination of accrual or ineffective therapy, but these are rare exceptions. The majority of Phase III breast cancer RCTs have a few years of accrual that are followed by additional years of observation for study outcomes.

Both NIH and the FDA have policies relating to interim data monitoring in clinical trials. Since 1998 NIH has required that all clinical trials must have a written approved data and safety monitoring plan. All Phase III trials must have an independent Data Monitoring Committee (DMC). The FDA recommends an independent DMC for "Pivotal" Phase III trials and trials with mortality or irreversible morbidity outcomes.

An independent DMC consists of clinical and basic scientists from relevant disciplinary areas, epidemiologists, biostatisticians and ethicists or consumer (patient) representatives who are not affiliated with the clinical trial or those individuals who are conducting the clinical trial. The DMC deals with the complex issue of how much evidence in support of the superiority (or inferiority) of one of the treatments should be allowed to accumulate before a trial is stopped and the findings reported. The role of the DMC is particularly challenging when there are multiple outcomes of major interest and/or serious known or potential acute or long-term adverse effects associated with treatment. Usually, the results of statistical tests, where the significance level has been appropriately adjusted for the multiple comparisons involved with interim looks at the data, provide guidance to the DMC in making decisions about whether a trial should continue or not. One objective is to permit early termination of a trial that has a beneficial effect by means of conservative stopping guidelines so that a trial will not stop prior to answering the primary study hypotheses. There are various organizational structures for DMCs, but usually the DMC has responsibilities to the participants in the trial, the study investigators, the sponsor, local IRBs, and regulatory agencies.

The DMC meeting to review interim data generally has four parts. There is an open session that is attended by the sponsor, the Principal Investigator and other key investigators involved with the conduct of the trial, the lead biostatistician for the trial and other Statistical and Data Coordinating Center staff. The trial investigators report on the status of the trial providing information on accrual, data submission, protocol adherence, and other aspects including any serious problems that may have been encountered. There are three practices followed relating to presentation of interim outcome data during the open session. One approach is to present no outcome data. A second approach is to present outcome data for the combined treatment groups. A third approach is to present the outcome data for the treatment groups but to mask the treatment assignments. The third approach may be problematic as differences in treatment begin to emerge during the course of interim monitoring if the behavior of trial investigators is affected by speculation about which treatment group is doing better. Therefore, our preference is not to show outcome data by treatment group, even if masking is maintained, during the open session of the DMC meeting. The second part of the DMC meeting is a closed session during which the DMC reviews unmasked data by treatment group. The trial biostatistician and a representative of the sponsor may be in attendance at the closed session, but typically the trial PI and other clinical investigators are not present for the closed session. Following its review of outcome data during a closed session, the DMC members meet in an executive session to develop their final recommendations based on their review of interim data and other information about the trial. (Sometimes, the

formulation of recommendations may be done within the closed session if the DMC does not have major issues to address.) The DMC recommends one of the following options: (1) continue the trial as designed; or (2) continue the trial, but make modifications to the protocol or operational aspects to deal with safety concerns or other addressable problems; or (3) stop the trial. There are many factors that DMCs take into account in formulating recommendations, such as whether the trial is meeting accrual goals, comparability of treatment groups, protocol adherence, study outcomes, safety concerns, coherence of the emerging data and consistency of findings with those from other trials that are available, net benefit based on weighing the benefits and risks, clinical and public import of interim data, and statistical considerations. The book *Data Monitoring Committees in Clinical Trials: A Practical Perspective* by Ellenberg, Fleming, and DeMets [60] is a valuable nontechnical reference for researchers who would like to become more familiar with the role, responsibilities, and procedures for independent DMCs.

Usually the lead biostatistician for the trial, in consultation with the DMC, develops the detailed plan for interim data analysis. Important considerations include: (1) deciding which outcomes should be monitored; (2) determining how often interim outcome analysis should be performed; and (3) deciding which nonoutcome variables, such as compliance, acute toxicity, long-term adverse events, quality of life, etc., should be included in interim data analyses.

Statistical issues arise in interim data monitoring that relate to repeated significance testing. If the significance level (*P*-value) for each interim analysis is the same as the *P*-value for the final analysis, then the Type I error will increase with each analysis conducted. For example if a significance level of 0.05 is used for each interim analysis, then by the fifth interim analysis, the true Type I error will be 0.14. If there are ten interim analyses, then the error will be 0.20 by the tenth analysis.

Statistical methods have been developed that adjust the Type I error for the number of interim analyses. The earliest approaches to adjusting for multiple tests were the sequential monitoring methods such as SPRT in which statistical testing is done after each study outcome occurs. These methods can be especially useful when the outcome can be evaluated within a short interval of observation following treatment. In most cancer trials, however, interim analysis is done based on group sequential designs that have been adapted to trials in which the outcomes are delayed. The book by Jennison and Turnbull [61] is an excellent resource on the most common statistical approaches to interim monitoring. A typical approach to group sequential monitoring is to monitor the primary outcome once or twice per year after some pre-specified minimum number of outcomes has been reported. There is a significance level at each interim analysis determined such that the overall experiment-wise Type I error will be maintained at the desired level, say, e.g., 0.05. The data monitoring plan specifies in advance the maximum number of planned interim analyses, which may be based on the projected amount of information (outcomes) projected or on the projected meeting schedule of the DMC.

Some common conventional monitoring techniques are: (1) Pocock's [62] approach, which specifies the same lower nominal significance level at each pre-specified interim analysis and final analysis; (2) Haybittle-Peto [63] approach, which specifies the same lower nominal significance level at each pre-specified interim analysis with the overall significance level at the final analysis; (3) O'Brien and Fleming [64] approach in which the nominal significance levels are lowest for the earliest pre-specified interim analysis which increases toward the overall significance level at the final analysis; and (4) Lan and Demets [65]) alpha spending function approach, which provides flexibility in the number and timing of interim analyses. Bayesian methods have also been proposed for interim data monitoring of RCTs, although Bayesian approaches have not been as widely used as the frequentist methods presented above.

Specific methods have also been developed for data monitoring that can be utilized to evaluate when the DMC should consider stopping the trial because the interim outcome data show that it would be unlikely or impossible for the final analysis to have a statistically significant positive result. The statistical approaches for such futility analysis are stochastic curtailment or conditional power [66, 67].

Often the statistical procedures for interim data monitoring are called stopping rules. However, most experienced biostatisticians and DMC members prefer to call them guidelines or flags that are used to inform the DMC about when there should be serious discussion of the emerging data relative to the continuation of the trial rather than as strict rules for when the trial

should stop, since there are other important factors to consider in addition to the primary efficacy outcome when deciding where to stop a trial and report the findings. The usual statistical interim monitoring strategy will have stopping guidelines for primary efficacy outcomes and may have stopping guidelines for serious adverse outcomes, although the latter may also be monitored without any formal statistical testing relying on the expert judgment of the DMC about when to consider stopping a trial because of undue risk to participants. During its review of the interim analyses the DMC generally relies on ad hoc weighing of the findings for the different outcomes.

The NSABP Breast Cancer Prevention Trial (BCPT), which tested 5 years of tamoxifen vs. placebo in double-blind RCT of more than 13,000 women at increased risk of breast cancer, adopted an innovative alternative approach to data monitoring when there are multiple outcomes in a clinical trial [68]. The BCPT, presented complex challenges for interim data monitoring due to the large number of outcomes, both beneficial and deleterious, that the DMC needed to consider in the interim data monitoring. The interim monitoring strategy that was developed incorporated both guidelines for individual outcomes and a composite global index that weighted the individual outcomes according to their life-threatening potential. This more comprehensive strategy which includes formal statistical considerations of net benefit for a treatment may also have advantages for data monitoring in cancer treatment trials.

As another more recent example, the NSABP B-31 study was an interesting phase III 2-stage randomized trial. It was designed to evaluate an incremental effect in overall survival (OS) of a trastuzumab (Herceptin) to a chemo regimen (AC → Taxol) among positive-node and HER2 gene positive patients. Since there was strong evidence of cardiac toxicity due to Herceptin, the B-31 trial was planned as a two-stage study. In the first stage, 1,000 patients were to be randomized to AC followed by Taxol (ACT) or AC followed by Taxol + Herceptin (ACTH) to compare the cardiac toxicities. If the observed difference in proportion of cardiac events would be less than 4%, then the second stage would be initiated to accrue an additional 1,700 patients for the efficacy analysis of Herceptin based on the OS endpoint. Three formal statistical comparisons were planned to assess excessive cardiotoxicity on the experimental arm.

To design the second stage of the study, it was assumed that the addition of Herceptin would reduce the annual mortality rate by 25%. It was also assumed that 5% of patients who were randomized to ACTH arm would fail to begin Herceptin, and an additional 10% will discontinue their Herceptin therapy uniformly over the 1-year course. These noncompliance assumptions further attenuated the 25% reduction to 22.8%. To detect this reduction in mortality with 80% power, using a two-sided 0.05-level log-rank test, would require that the number of deaths be 480. Thus, if 2,700 patients were accrued over 4 years and 9 months, the number of required events would be reached approximately 2 years and 9 months after the closure of accrual, i.e., 7 years and 6 months after the initiation of the study. However, the accrual to this study has stopped early due to strong evidence of efficacy of Herceptin [69]. The cardiac toxicity of Herceptin was reported in Tan-Chiu et al. [70].

Four interim analyses were scheduled prior to the definitive analysis: after 96, 192, 288, and 384 deaths. Asymmetric stopping boundaries were employed based on the O'Brien-Harrington-Fleming method [71]. Because these analyses must be timed to coincide with the semiannual meetings of the NSABP Data Monitoring Committee (DMC), in practice, the numbers of events at each interim analysis usually differ slightly from the plan. If significant deviations were necessary, the nominal levels of significance were to be adjusted by alpha-spending [65].

The NSABP B-31 design did not have the futility [66, 67] component in it, but it would be informative for the Data Monitoring Committee to consider stopping a trial when there is a strong trend that patients in the experimental arm are doing worse than ones in the control arm. To include the futility component, at each interim analysis, consideration may be given to dropping the experimental arm if it is significantly worse than the control arm, e.g. if the estimated hazard ratio vs. control exceeds 1, at a pre-specified nominal level.

31.8 General Analysis Considerations

The statistical design considerations and operational definitions of the outcome guide the statistical analysis of the primary outcome of the clinical trial. The

statistical considerations in the protocol specify the analytic strategy for the primary outcome and major secondary outcomes of the clinical trial.

In order to prevent biased treatment comparisons the primary analysis performed for the majority of trials is the "intention-to-treat (ITT)" analysis which should also be pre-specified in the study protocol. Three fundamental principles apply to the ITT analysis. They are: (1) participants in intervention comparisons should be counted in their randomly allocated group; (2) all participants randomly allocated to the intervention group should be counted in the denominator for that treatment; and (3) all events should be included in the intervention comparison for the primary outcome measure. Even for RCTs in which the "Treated Per Protocol (TPP)" analysis has been specified as the primary analysis, as may be done in equivalence trials, there is a need to conduct the ITT analysis and compare the finding to that of the TPP to evaluate possible biases in the TPP analysis. The well-written protocol will contain sufficient information for ITT analysis and TPP analysis datasets.

If a RCT has been well-designed and carefully conducted in accordance with a detailed protocol, then the analysis for the primary outcome is often straightforward, although attention to data quality control checks and simple tabular and graphical summaries are important during the preliminary analysis phase to guide specific details of the analysis. Frequently, data inconsistencies not identified during routine editing of the data forms will surface during the preliminary analytic process, particularly when the biostatistician begins looking at multiple cross-tabulations of variables of interest.

The practice of the NSABP Biostatistical Center has been to create analysis files containing all variables that will be analyzed for a specified data cutoff date. The file includes not only original values of variables, but also some variables that are formed by combining information from several variables on the original data forms to facilitate the primary analyses, such as creation of flags and follow-up times for time-to-event analyses, specification of cutoff values for forming categories of interest for continuous variables, transformed data values indicated for certain analyses, etc. These analysis files are helpful for the statistician during the original analysis, and also provide documentation for any subsequent validation of an analysis. A useful preliminary analytic technique is to compute event rates (hazard rates) or outcomes, such as hazard rates for time-to-event outcomes or proportion of events within each level of baseline covariates in order to screen for main prognostic effects and potential interactions of major covariates with the intervention. These screening tabulations provide information useful in developing appropriate strategies to deal with issues, such as colinearity, sparseness in some data categories, missing observations, and unusual combinations of variables in the distributions, in multivariable modeling. For readers who desire more guidance on how to approach preliminary data analyses, Pocock's book, *Clinical Trials: A Practical Approach*, especially Chapters 13 and 14 [72], is a basic, easily understood reference.

Although the possible outcomes employed in clinical trials may encompass variables of all types, including continuous, binary, categorical, etc., the majority of major RCTs in breast cancer have a time-to-event outcome, such as overall survival or disease-free survival as the primary outcome.

The brief summary of methods in this chapter focuses on some of the relevant considerations for trials where the definitive outcome is analyzed as a time-to-event. There are numerous books and journal articles that provide comprehensive treatment of the theoretical and technical background needed for the conduct of such analyses, and numerous software packages that perform these analyses appropriately, including SAS (SAS Institute Inc., http://www.sas.com), STATA (StataCorp LP, http://www.stata.com), and S-PLUS (Insight Corp., http://www.insightful.com). We summarize below several conceptual features of the techniques that are most commonly utilized in practice and provide a few illustrative examples of analytic approaches that have broad applicability in modern breast cancer clinical trials.

There is an extensive history of the evolution of methods for survival analysis, but, as noted earlier, the development of methodology employed in cancer trials analyzing event times was greatly stimulated by the establishment of the NCI Cooperative Group Program in the 1950s. The major analytic approaches developed from the late 1950s through the seminal papers by Peto and Peto [73] and [74]) provided the fundamental approaches that continue to be used in most clinical trials today for testing differences in survival curves and estimating treatment response.

Summarization of time-to-event data typically involves display of data for each treatment in life table

format as well as calculation of a test statistic to determine whether the differences between the control group and the experimental group(s) are statistically significant. Two joint outcome variables are associated with each participant in the trial at the calendar date chosen as the cutoff for the analysis. In the simplest example, if the outcome of interest is mortality (and all individuals have been observed until death or the last protocol scheduled follow-up, if alive), then one calculates the observed survival time for each patient from the time of entry to the study using some suitable unit of observation time. For breast cancer clinical trials, it has been customary to use months as the time unit for survival curves. The second variable, referred to as a "dummy variable," is given a value of "0" or "1" depending on whether the patient was alive or dead at the time of last observation. Formally, the term censored is used for patients with a code "0" since if the observation time were extended indefinitely, all patients would eventually die. Since patients enter clinical trials over a period of time, often several years duration, at the time of analysis, patients may be censored administratively at various times due to the early termination of their observation time, but they can contribute to the denominator in calculating a death rate until the time when they are censored at which time they are taken out of the denominator in calculating subsequent event rates.

The classical Kaplan and Meier [75] method for estimating life table survival utilizes the exact death and censoring times, resulting in the familiar step function graphs found in many publications, where the downward steps in the curve occur when there are deaths. The product-limit estimator for the Kaplan-Meier survival is

$$\hat{S}(t_k) = \prod_{i=1}^{k} [1 - d_i / N_i]$$

with variance estimated as

$$\hat{V}\{\hat{S}(t_k)\} = \hat{S}(t_k)^2 \sum_{i=1}^{k} \{d_i / N_i (N_i - d_i)\},$$

where N_i is the number of individuals who are at risk at time t_i, d_i is the number of individuals who have an event at time t_i, and d_i/N_i is an estimate of the probability of an event at time t_i given survival to a point just prior to time t_i.

If there were no censoring then the Kaplan-Meier survival curve would be the same as a plot based on the binomial distribution. The Kaplan-Meier life-table assumes that censoring is noninformative about the outcome, which is a reasonable assumption for individuals whose times are curtailed because of an arbitrary selection of a study cutoff date for analysis. However, when there are individuals whose follow-up is incomplete because they have not adhered to the protocol follow-up schedule or who have discontinued participation in the clinical trial, there is a question about whether such observations should be considered censored in the usual manner since it is not known whether their death rates are similar to those who have continued to participate in protocol follow-up. Indeed, there are numerous papers that have been published indicating that participants who did not adhere to protocol treatment and follow-up schedules are more likely to have less favorable outcomes than those who continue to participate in the protocol. Similarly, when the outcome of interest is recurrence rather than death, follow-up time may be terminated due to intercurrent deaths from causes other than breast cancer. We are making a strong assumption that cannot be tested when we assume that participants who die of nonbreast cancer causes without a prior recurrence of disease would have had a similar outcome for breast cancer if they had not experienced an earlier death from other causes. Statistical approaches have been developed to deal with situations in which there are multiple outcomes that can occur that handle a potential lack of independence that may be associated with the more complex considerations regarding "multiple events" in time-to-event analysis.

The Kaplan-Meier life-table is most appropriate when the number of events is not too large, but in trials where there are large sample sizes with many events, it may be useful to group the data in time intervals during which multiple events and censored observations occur rather than calculate the survival curve based on exact times. The classical paper by Cutler and Ederer [76] presents the method for computing the life table from grouped data, which is often denoted as an actuarial life-table.

Statistical testing to compare the treatment groups is generally based on some version of the logrank or a related test, as shown below for grouped data. It is convenient to consider the data as a sequence of 2 × 2 tables, in which each table displays, for control and experimental treatment groups, the number of events and censored observations for a particular ordered interval of time as follows:

$$\begin{array}{ll} \text{Group A: } d_{iA} & n_{iA} - d_{iA} \\ \text{Group B: } d_{iB} & n_{iB} - d_{iB} \end{array}$$

where d_{iA} is the number of deaths in group A at failure time t_i, d_{iB} is the number of deaths in group B at failure time t_i, n_{iA} is the number of people at risk in group A at failure time t_i, and n_{iB} is the number of people at risk in group B at failure time t_i.

The test statistic $Z = (O_A - E_A)/\sqrt{V_A}$, where

$$O_A = \sum_i w_i d_{iA},$$

$$E_A = \sum_i w_i \frac{n_{iA} d_i}{n_i},\ d_i = d_{iA} + d_{iB}$$

$$V_A = \sum_i w_i^2 d_i \frac{(n_i - d_i) n_{iA} n_{iB}}{(n_i - 1) n_i^2},$$

can be shown to be approximately a normally distributed variable.

If $w_i = 1$, the test is the usual logrank test statistic. (The logrank test sometimes includes other designations in recognition of statisticians who developed the earliest versions of the test prior to the publication of the more theoretically motivated presentation in the classical paper by Peto and Peto [73]. For example, the modification of the Mantel and Haenszel [77] by Mantel [78] is a version of the logrank test.) There are also alternative test statistics that can be chosen, which have been shown to be similar to the logrank test, but with a different weighting factor. Perhaps, the best known alternative to the logrank test is the version developed by Gehan [79], as a modification of the nonparametric Wilcoxon test to take censoring into account. The statistic above becomes the Gehan Wilcoxon test (also sometimes called Gehan Breslow test) when the weight, $w_i = n_i$ is used in the above formulae. Alternatively, the statistic becomes the Tarone and Ware test [80] when $w_i = \sqrt{n_i}$. The latter two tests are reasonable alternatives to the logrank for some trials, but it is important that the rationale and choice of the test statistic be a part of the written Statistical Considerations in the protocol.

When stratified randomization has been used, then intervention effects should be summarized within strata and then a combined test across strata utilized when computing the test statistics. Properties of many tests and estimation procedures often depend on "large sample theory" to provide approximations, as well as often other assumptions relating to normality and equality of variances among the treatment groups. Software for exact statistical tests, such as XACT and LOGXACT, are also now available for testing when sample sizes are not sufficiently large for use of large sample theory (Cytel: Statistical Software and Services, www.cytel.com). Resampling methods can be used for obtaining standard errors or confidence intervals when exact inference is not available or assumptions are violated [81].

31.8.1 Modeling Treatment Effects with Multivariable Models

The major utility of modeling treatment effects often relates to the testing of pre-specified biological hypotheses about the relationship between patient prognostic factors and outcome, such as in the NSABP trials relating hormone receptors to treatment effectiveness in the trials employing tamoxifen, or adjusting the treatment effect for selected patient prognostic factors. Generally, the logrank analysis, as described above, appropriately taking into account any stratification variables, will be the primary analysis. However, there is often a desire to adjust other prognostic factors for any imbalances as a supportive analysis using multivariable models. There may also be an interest in examining whether there are any treatment interactions with selected prognostic factors. A well-written protocol will include discussion about the rationale for models and details of whether they will be utilized in testing pre-specified hypotheses or for exploratory analyses. The Statistical Considerations should incorporate how the models will be estimated, what approaches will be utilized for evaluating fit, and details on how the experimental error will be controlled.

Evaluation of potential subgroups should be based on findings of interaction tests, preferably pre-specified, not on findings in subgroup comparisons of treatment effects. Quantitative interactions in treatment effects with covariates are expected to occur frequently and are model dependent. Qualitative interactions of covariates with treatment effects, in which some patients have a positive response and other patients a negative treatment response, are not model dependent, but do not occur frequently in practice. Statisticians are generally very cautious in approaching subgroup analyses,

particularly when hypotheses about interactions have not been specified in advance of the analysis.

The Cox proportional hazards model has become the most popular for modeling time-to-event data since the publication of the paper by Cox [74]. Prior to that time there were a number of parametric models based on distributions such as the exponential, Weibull, or logistic model (choosing a fixed binary outcome, e.g., 5 year survival), that incorporated prognostic factors as covariates. There are several reasons why the Cox model has nearly universal appeal to statisticians. The most important rationale for its use is that it is an extension of the logrank test statistic. Briefly, if $\lambda_0(t)$ is the event rate in the control group, $\lambda_1(t)$ is the event rate in the experimental treatment group, and X_{ij} is the jth covariate for the ith patient, then

$$\lambda_1(t_i) = \lambda_o(t_i)\exp\left(\sum_{j=1}^{k} \beta_j x_{ij}\right).$$

The flexibility of this model is great since, unlike the earlier parametric models, the baseline event (or hazard) rate is arbitrary and can be separated from modeling of the covariates; therefore, the event rates in both groups may vary over time and only the "relative risk" (i.e., ratio of event rates) is assumed to be constant with time. In spite of its popularity, there are still circumstances in which the proportionality assumption is questionable or when other models may be preferred, such as when a mechanistic model is suggested based on an underlying biological rationale. The proportional hazards model can be used to compare treatment groups adjusting for covariates and to test for statistical interaction of treatment with specific covariates as an assist in identifying subgroups. Several NSABP Protocols have entailed extensive multivariable modeling to characterize interactions between prognostic factors and treatment outcome to test biological hypotheses. One notable example is NSABP Protocol B-09 in which an apparent qualitative interaction between hormone receptors and mortality emerged in multivariable modeling [82]. Although the subgroup analyses were anticipated at the time of protocol design, the qualitative nature of the interaction was unexpected, necessitating considerable additional analyses and cautious interpretation about whether the findings were a rare chance occurrence or could be attributable to the treatment. Interestingly, the findings also motivated the development of new methods for testing specifically for qualitative interaction [83].

Additional considerations apply in modeling variables that vary over time following randomization. Failure to recognize and/or analyze appropriately time-related variables has occurred and may have contributed to a confusing literature on some important questions in breast cancer clinical trials. In 1981 a paper in the *New England Journal of Medicine* presented an analysis of total dose of chemotherapy received by breast cancer patients in a clinical trial of chemotherapy vs. control that concluded that the size of the treatment effect was related to the total amount of chemotherapy received over multiple courses of therapy [84]. Unfortunately, the statistical method employed did not take into account the time-related nature of the total dose received. In order to receive a high total dose, patients had to survive free of recurrence for most of the time planned for courses of therapy. We published a commentary and showed results for patients receiving placebo in an NSABP trial, using the method apparently employed in the paper. We illustrated that the outcome and amount of drug were inextricably linked such that even patients who received more placebo did better than patients who received less placebo. When more appropriate methods, such as a Cox model with a time-varying covariate, were used, the apparent dose response for the placebo, as well as that for the chemotherapy treated patients, was no longer present [85]. A second example, where a time-varying covariate analysis provided useful insights into a biological hypothesis, was in the analysis of ipsilateral breast cancer reoccurrence in patients treated with or without irradiation to the breast following lumpectomy (NSABP Protocol B-06) [86].

31.8.2 Multiplicity Considerations

Issues of multiplicity which influence the validity of the statistical significance tests arise in many contexts in clinical trials. They are often an important concern in interpreting the statistical tests and estimated treatment effects properly. Some of the typical situations in which multiplicity can become problematic, if not recognized and properly addressed in the analyses, include more than two treatment groups, multiple outcome measures, measurements over time of the same

outcome measure, subgroup analyses, and interim data analyses. One of the most common approaches in the past used to control the Type I error probability was the Bonferroni inequality in which the nominal significance level was divided by the number of statistical tests employed. The resulting value was then used for each of the pairwise statistical tests to preserve the overall experimental error at the desired significance level. More recent papers have shown that the Bonferroni approach is more conservative than desirable in most multiplicity testing situations. The papers by Hochberg [87] and Cook and Farewell [88] provide relevant discussion of multiplicity considerations and approaches useful for current clinical trials.

31.8.3 Analysis of Multiple Outcomes Under Competing Risks

In clinical trial data, one of the popular primary outcomes is disease-free survival (DFS), defined as any first events consisting of local, regional, or distant recurrence of the original cancer, a new cancer other than the original one, and deaths prior to any aforementioned diseases. However, investigators are often more interested in making statistical inference on a subset of those first events, which needs to be cast over the competing risks setting. For example, radiation oncologist may be only interested in looking at the local or regional recurrences, to investigate whether irradiation could help reducing the recurrence rate in local areas around the original cancer [89]. Also in breast cancer studies, investigators may be interested in knowing whether a new therapy could reduce the rate of breast cancer-related death alone in the presence of nonbreast cancer deaths.

31.8.3.1 One Sample Case

Investigators sometimes are interested in estimating proportions of cause-specific events in one group. For example, in the NSABP B-14 protocol that studied the efficacy of the hormonal therapy with tamoxifen, a serious side effect was endometrial cancer. Estimation of the proportion of the endometrial cancer in tamoxifen group in this case would require consideration of other events that may have precluded the event of interest, such as death prior to developing the endometrial cancer. Statistical inference on a subset of the DFS events is usually based on the cumulative proportion of the events of particular interest (cause-specific events). One possible, but misleading, approach would be to censor the other events of no interest at their event times and estimate the cumulative probability of cause-specific events by using 1-Kaplan-Meier (1-KM) estimates. It is, however, well known that this approach overestimates the true probabilities [90–93]. One way of removing the bias is to use the cumulative incidence function [94]. Gooley et al. [95] nicely provide a more intuitive interpretation of the 1-Kaplan-Meier approach and the cumulative incidence function approach. Another naïve way of removing the bias would be to rearrange the observed survival data, pretending that the events of no interest had never happened [96], so that they are always in the risk sets at observed failure times. The following example compares the 1-KM and nonparametric cumulative incidence methods.

31.8.3.2 Comparing 1-KM Method and Nonparametric Cumulative Incidence Approach in NSABP B-04 Data

In this example, we use a dataset from one of the Phase III trials conducted by the NSABP (B-04 study). The NSABP B-04 study evaluated the endpoint of overall survival to investigate whether a less aggressive surgical procedure (total mastectomy) is equivalent to the traditional mastectomy. The patients in this trial have been followed more than 30 years for cancer recurrence and mortality, so the B-04 follow-up data are often viewed as a natural history in breast cancer mortality without any adjuvant therapy. [53, 54]) presented an analysis result of the 25-year follow-up data from the B-04 study.

A total of 1,665 patients (1,079 node-negative; 586 node-positive) were originally randomized to five treatment groups; three groups in node-negative (radical mastectomy, total mastectomy + irradiation, total mastectomy) and two groups in node-positive (radical mastectomy, total mastectomy + irradiation). A subset of 586 node-positive patients will be used in this example.

Investigators in breast cancer research are often interested in evaluating an effect of a therapeutic agent in terms of reducing breast-cancer-related deaths only,

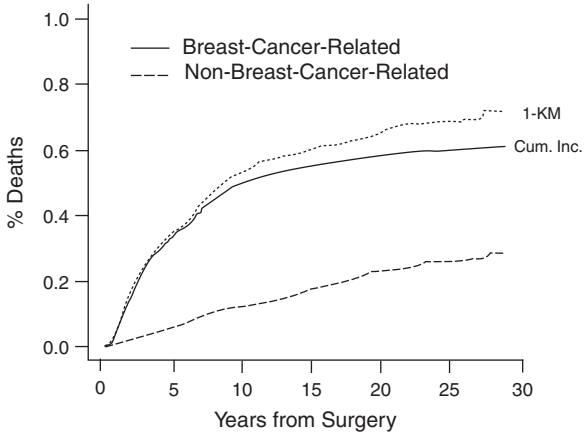

Fig. 31.1 Comparison of the 1-KM estimates and cumulative incidence estimates in NSABP B-04 data

in the presence of other causes of deaths. In this analysis, we will define deaths following the breast cancer events to be breast-cancer-related deaths, and non-breast-cancer-related deaths otherwise. Figure 31.1 shows the comparison between the two methods in terms of estimating the proportion of breast-cancer-related deaths as a function of time in the presence of competing nonbreast-cancer-related deaths (dashed line). As mentioned earlier, the estimated curve from the 1-KM approach (dotted line) tend to overestimate the proportion of breast-cancer-related-deaths compared to one from the cumulative incidence approach (solid line).

There also have been efforts to parameterize the cumulative incidence function completely [97–99] or partially [100] by using popular distributions such as exponential or (extended) Weibull distributions. The key idea in parameterizing the cumulative incidence function is that the overall events are partitioned into different types of cause-specific events under competing risks, so the maximum proportion of each type of cause-specific events is less than 1 (improper). When the parametric assumption is correct, the parametric approach provides more accurate results in terms of bias and variation of the estimator compared to the nonparametric methods [98, 100]. The major advantage of the nonparametric approach is no need for an assumption for the baseline distribution of true failure time distribution. Therefore, nonparametric approaches may merit the designing stage of a study under competing risks while parametric methods may provide more accurate inference for ad hoc analysis of competing risks data if the parametric assumption can be justified.

31.8.3.3 Two-Sample Comparison

Investigators are often interested in comparing two or more failure time distributions with censoring under competing risks. For example, in randomized breast cancer studies, a new treatment may be given to one group of patients whereas the patients in the other group are on a conventional therapy or in placebo. The investigators may be interested in whether the new therapy delayed local or regional recurrences by comparing the cumulative probabilities of local or regional recurrences over time between the two groups. Pepe and Mori [93] proposed a two-sample test statistic for this type of comparison. Earlier Gray [96] proposed a (stratified) *K*-sample test statistic to compare the subdistribution cumulative probabilities, which has been implemented as a procedure *cuminc* in the *cmprsk* software package in R (http://www.r-project.org).

31.8.3.4 Regression on Cumulative Incidence Function

Regression model is useful in evaluating the effects of important prognostic factors in breast cancer on the subdistributions of cause-specific events, or evaluating interactions between treatment and prognostic factors. Fine and Gray [101] proposed a semiparametric proportional hazards model for subdistributions. This approach has been implemented as a function *crr* in the *cmprsk* software package in R. Jeong and Fine [102] proposed a parametric regression model on cumulative incidence function by assuming the Gompertz distribution [103, 104] for the baseline cumulative hazard function under the generalized odds rate model [105].

31.8.3.5 Design Under Competing Risks; Sample Size and Loss of Power

Recently, the primary endpoints in breast cancer clinical trials have been more specifically defined such as breast cancer recurrence [106]. In such designs, it would be more efficient to consider pattern of other competing events in the designing stage. Latouche et al. [107]

provides a sample size formula under competing risks as

$$n = \frac{(u_{\alpha/2} + u_{\beta})^2}{(\ln\theta)^2 \, p\,(1-p\,)\psi}.$$

In the formula above, p is the proportion of patients randomly allocated to the experimental group, the parameter θ is the subdistribution hazard ratio, and the parameter ψ controls the proportion of cause-specific events of interest. Thus the sample size will be affected by both the subdistribution hazard ratio and proportion of cause-specific events of interest. For example, if there is no other competing events such as in the DFS endpoint that typically includes any first event, the hazard ratio can be estimated from the previously observed distribution of DFS events, and ψ will be 1. However, if only a subdistribution of local or regional events is considered, $\psi < 1$ and the subdistribution hazard ratio will be affected by the pattern of other competing events. Even when it is assumed that the subdistribution hazard ratio in local or regional events and the hazard ratio in DFS are almost identical, a bigger sample size is still needed if $\psi < 1$, or in other words, the power will decrease if the sample size is calculated by assuming $\psi = 1$ in this case. In general, a substantial increase in sample size, or substantial loss of power, would be expected, if the absolute value of the hazard ratio in local or regional events is smaller than the hazard ratio in DFS *and* the proportion of cause-specific events is also small.

31.8.4 Building and Validating Prediction Models

After a clinical trial is conducted, it would be meaningful to build a prediction model to guide physicians how to treat their patients or design future studies. A simple example can be modeling the effects of patients' baseline characteristics on development of cardiac events, as in the NSABP B-31 study, such as congested heart failure or cardiac death in cardio-toxic treatment regimen [70]. In another example, a model can be built to predict the recurrence rate among tamoxifen-treated patients given information on their gene signatures [108]. A simplest approach would be to evaluate each gene effect on time-to-recurrence in the univariate Cox proportional hazards model (supervised) and select top genes to be included in the prediction model based on a stringent criterion such as the false discovery rate (FDR; [109, 139]) approach, adjusting for multiple comparisons. In case that the number of selected genes is large, a principal component regression modeling has been recently proposed to account for a possible correlation structure among genes [110]. After analyzing the multivariate Cox model including the final list of genes or principal components, a linear combination of the estimates of regression coefficients and covariate values from the analyzed cohort can be rescaled between 0 and 100 as a score. So when a patient visits a clinic, a score can be calculated based on the developed model to predict his/her recurrence probability, which might facilitate evaluation of risk/benefit aspects of a potentially toxic chemo- or hormonal therapy regimen.

Once a prediction model is built, it needs to be validated. The internal model validation process usually evaluates the abilities of calibration and discrimination of the developed model [142]. Both calibration and discrimination measure the degree of agreement between the predicted and observed outcomes. Specifically calibration refers to bias. For example, if an *average* predicted probability of breast cancer recurrence in a group of patients is very close to the observed counterpart, the prediction model is considered to have good calibration ability. Discrimination measures the association at a more *individualized* level. For example, a commonly used quantity for evaluating the discrimination ability is so-called *C*-index [111], which measures the proportion of all possible usable pairs of patients in which the predictions and observed outcomes are concordant. For survival data, the usable pairs only include ones, at least one of whom has experienced an event. The *C*-index can be also interpreted as the area under the receiver operating characteristics (ROC) curve [112], ranging from 0.5 to 1 [113]. The *C*-index value closer to 1 would imply a better ability of discrimination of the model. Once a model is validated internally, including a bias correction step, the final model can be validated externally in a new data set collected from the similar population.

31.8.5 Interpretation

Interpretation of findings from RCTs should adhere to the ITT principle that guides the analysis of data. If randomized subjects are withdrawn from the analyses,

there is a concern about the potential for biased results. Interpretation of the findings should always focus on the primary hypothesis tested with reliance on the overall estimated intervention effect and its confidence intervals. Adverse effects of treatment should also be discussed fully in a manner that elucidates the net benefit of the treatment. The CONSORT statements, which are referred to in Sect. 9 below, provide many additional insights into the appropriate manner to summarize and interpret the findings from RCTs.

Subgroup analyses have been an ongoing topic for debate in clinical trials methodology. Recent articles in clinical journals highlight the need for improvement in strategies for the conduct and reporting of subgroup analyses [138, 114]. Subgroup analyses of baseline characteristics should be limited in number, preferably pre-specified, secondary to the overall study conclusion, and supported by formal statistical interaction tests. In other words, tests of significance within individual subgroups are not appropriate for deciding when to show individual subgroups. Issues of multiplicity of testing, as discussed in Sect. 8.2 above, are important to take into account. Subgroup analyses of post randomization variables, such as adherence to protocol medication or intermediate disease markers, should be approached cautiously utilizing methods that have been developed for time varying covariates or serial markers. Unless the RCT has been specifically designed to test variables such as total dose, dose intensity or dose timing, analyses of these factors should be interpreted as exploratory in nature. They may provide directions for hypotheses that are testable in future clinical trials. Subgroup findings other than those that have been predefined in the protocol should also be considered as hypothesis generating. At no stage in the analysis should the randomized treatment allocation be compromised.

31.9 Reporting and Publication

There has been a coordinated effort over the past 10 years to improve the quality of journal articles reporting the primary findings of RCTs. Most notable among these initiatives has been the Consolidated Standards of Reporting Trials (CONSORT) statement, which incorporates a systematic checklist recommended for structuring a publication that encompasses the contents of the title, abstract, introduction, methods, results, and discussion. The CONSORT statement also recommends inclusion of a flow chart that describes in detail the flow of patients in the trial from initial registration and randomization, as well as the reasons for attrition in the number of patients included in the analyses of the completed trial. Since publication of the original CONSORT statement which dealt with guidelines for parallel group trials, the CONSORT investigators have developed analogous guidelines for reporting noninferiority and equivalence trials [141, 145], cluster-randomized trials [115], nonpharmacologic treatments [116, 117], reporting results of harmful effects [146], and constructing informative abstracts [118, 119]. The CONSORT guidelines for parallel group designs have undergone some revisions since their original publication [120]; therefore, it is important to consult the most recent versions of the guidelines when preparing a paper for publication ([121–124]; and the Website http://www.consort-statement.org/) for the most recent versions of guidelines.

Following the publication of the original CONSORT guidelines several major journals, such as *Lancet* and the *New England Journal of Medicine*, require that papers reporting the findings of RCTs that are submitted for publication adhere to the CONSORT guidelines. Regardless of whether a specific journal requires following the CONSORT guideline, key investigators and biostatisticians who participate in the preparation of manuscripts should be familiar with the CONSORT statement and make every effort to adhere to the principles embodied in their conceptualization. Even for RCTs in which there are complex designs that may not conform exactly to the specific content provided in some of the CONSORT guidelines, they provide much useful guidance that can be adapted to enhance the quality of the manuscript.

31.10 Clinical Trial Overviews

The Early Breast Cancer Treatment Collaborative Group (EBCTCG), established by Sir Richard Peto, Oxford University, in the 1980s pools data from all known RCTs in order to determine which, if any, adjuvant therapies have an impact on survival. The first systematic overview demonstrated that there were indeed improvements in survival associated with systemic adjuvant tamoxifen and chemotherapy. The EBCTCG has continued to compile data from new

RCTs and update follow-up information on all RCTs every 5 years. The papers from the EBCTCG, which synthesize, the worldwide data on various treatment questions, have been influential both in clinical practice and in providing information useful for designing new RCTs ([125–134]; Website, http://www.ctsu.ox.ac.uk/projects/ebctcg). The merits of the overviews depend upon having data from all properly randomized clinical trials that have followed all patients randomized for many years. Helpful guidelines are available for conducting overviews for researchers who wish to conduct formal statistical review of evidence from related RCTs [135].

Ultimately, the most convincing evidence on specific interventions comes from well-designed and conducted randomized trials on breast cancer that have sufficient numbers of patients to identify small to moderate sized differences in survival outcomes.

References

1. Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20–69 years. Lancet. 2000;355(9217):1822
2. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer. 1976;34(6):585–612
3. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer. 1977;35(1):1–39
4. Lilienfeld AM. Ceteris paribus: The evolution of the clinical trial. Bull Hist Med. 1982;56:1–18
5. Witkosky, SJ. The evil that has been said of doctors: Extracts from early writers. Trans. with Annotations by T.C. Minor. The Cincinnati Lancet-Clinic. 1889; 41/New Series 22: 447–48
6. Bull JP. The historical development of clinical therapeutic clinical trials. J Chronic Dis. 1959;10:218–48
7. Lind J. A treatise of the scurvy. In three parts. Containing an inquiry into the nature, causes and cure, of that disease. Together with a critical and chronological view of what has been published on the subject. Edinburgh: Printed by Sands, Murray and Cochran for A Kincaid and A Donaldson, 1753
8. Louis PCA. The applicability of statistics to the practice of medicine. Lon Med Gazette. 1837;20:488–91
9. Double M. The inapplicability of statistics to the practice of medicine. Lon Med Gazette, 1837
10. Fisher RA. The arrangement of field experiments. J Ministry Agric. 1926;33:503–13
11. Fisher RA, McKenzie, WA. Studies in crop variation. II the manurial response of different potato varieties. J Agric Sci. 1923;13:315
12. Medical Research Council. Streptomycin in Tuberculosis Trials Committee. Streptomycin treatment of pulmonary tuberculosis. Br Med J. 1948;2:769–83
13. Armitage P. Trials and errors: the emergence of clinical statistics. J Roy Stat Soc, Series A. 1983;146:321–34
14. The National Program of Cancer Chemotherapy Research. Cancer Chemotherapy Rep. 1960;1:5–34
15. Henderson WG, Lavori PW, Peduzzi P, Collins JF, Sather MR, Feussner JR. Cooperative Studies Program, US Department of Veterans Affairs. In: Redmond CK, Colton T, editors. Biostatistics in clinical trials. Wiley; 2001. pp. 99–115
16. Sylvester R. European Organization for Research and Treatment of Cancer (EORTC). In: Redmond CK, Colton T, editors. Biostatistics in clinical trials. Wiley; 2001. P. 191
17. Fisher B. NSABP and advances in the treatment of breast cancer. In: Redmond CK, Colton T, editors. Biostatistics in clinical trials. Wiley; 2001. pp. 310–21
18. Schneiderman MA, Gehan EA. History, early cancer and heart disease trials. In: Redmond CK, Colton T, editors. Biostatistics in clinical trials. Chichester: Wiley; 2001. pp. 227–35
19. Zelen M, Gehan E, Glidewell O. Biostatistics. In: Hoogstraten, editor. Cancer research: Impact of the cooperative groups. Paris: Masson; 1980. pp. 291–312
20. Hill Sir AB. The clinical trial III. In: Statistical methods in clinical and preventive medicine. London: E And S Livingstone; 1962. p. 291
21. Ellenberg JH. Biostatistical collaboration in medical research. Biometrics. 1990;46:1–32
22. Simon R. Optimal two-stage designs for Phase II clinical trials. Control Clin Trials. 1989;10:1–10
23. Thall PF, Simon R. Practical Bayesian guidelines for Phase IIB clinical trials. Biometrics. 1994;50:337–49
24. Thall PF, Simon R. A Bayesian approach to establishing sample size and monitoring criterion for Phase II clinical trials. Control Clin Trials. 1994;15:463–81
25. Bryant J, Day R. Incorporating toxicity considerations into the design of two-stage Phase II clinical trials. Biometrics. 1995;51:1372–83
26. Piantadosi S. Clinical trials: A methodologic perspective. Second Edition. Wiley-Interscience; 2005
27. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. J Chronic Dis. 1967;20:637–48
28. Fisher B, Bauer M, Margolese R, Poisson R, Pilch Y, Redmond C, et al Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Eng J Med. 1985;312:665–73
29. Fisher B, Redmond C, Brown A, Wickerham, DL, Wolmark N, Allegra J, Escher G, Lippman M, Savlov E, Wittliff J et al Influence of tumor estrogen and progesterone receptor levels on the response to tamoxifen and chemotherapy in primary breast cancer. J Clin Oncol. 1983a:1(4):227–41
30. Fisher B, Wickerham DL, Brown A, Redmond CK. Breast cancer estrogen and progesterone receptor values: their distribution, degree of concordance, and relation to number of positive axillary nodes. J Clin Oncol. 1983;1(6):349–58
31. Fisher B, Redmond CK, Fisher ER. Evolution of knowledge related to breast cancer heterogeneity: A 25-year retrospective. J Clin Oncol. 2008;26:2068–71

32. Redmond CK, Fisher B. Design of the controlled clinical trial. In: Pilch YF, editor. Surgical oncology. McGraw-Hill; 1984. pp. 254–72
33. Fleming TR, DeMets DL. Surrogate endpoints in clinical trials: Are we being misled? Ann Int Med. 1996;125:605–13
34. Wittes, J. Randomized treatment allocation. In: Redmond CK, Colton T, editors. Biostatistics in clinical trials. Wiley; 2001. pp. 384–92
35. Rockette HE, Redmond CK, Fisher B. Impact of randomized clinical trials on therapy of primary breast cancer: The NSABP overview. Control Clin Trials. 1982;3:209–25
36. Investigators Writing Group WHI. Risks and benefits of estrogen plus progesterone in healthy postmenopausal women. J Am Med Assoc. 2002;288:321–33
37. Latakos E. Sample size determination. In: Colton T, Redmond CK, editors. Biostatistics in clinical trials. Wiley; 2001
38. Lakatos E, Lan KKG. A comparison of sample size methods for the logrank statistic. Stat Med. 1992;11:179–91
39. Shuster JJ. CRC handbook of sample size guidelines for clinical trials. CRC Press: Boca Raton FL; 1990
40. Press WH, Teukolsky SA, Vetterling WT, Flannery BP. Numerical recipes in C: The art of scientific computing. 2nd ed. Cambridge: Cambridge University Press; 1992
41. Efron B. Forcing a sequential experiment to be balanced. Biometrika. 1971;58:403–17
42. Begg CB, Iglewicz BA. A treatment allocation procedure for sequential clinical trial. Biometrics. 1980;36:81–90
43. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics. 1975;31:103–15
44. The Nuremberg Code, 1947. Br Med J. 1996;313:1449
45. World Medical Association. Declaration of Helsinki (1964, 1975, 1983, 1989, 1996). Br Med J. 1996;313:1449–50
46. National Commission for Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, DC: DHEW Publication Number (OS) 78-0012. Appendix I, DHEW Publication No. (OS) 78-0013; Appendix II, DHEW Publication No. (OS) 78-0014, 1978
47. Hill Sir, AB. Medical ethics and controlled trials. Br Med J. 1963;1:1043
48. Zelen M. A new design for randomized clinical trials. New England of Medicine. 1979;300:1242
49. Rutstein DR. Ethical aspects of human experimentation. Daedalus. J Am Acad Arts Sci. 1969; Spring:523
50. Taylor KM, Margolese RG, Soskolne CL. Physicians' reasons for not entering eligible patients in a randomized clinical trial of surgery for breast cancer. N Eng J Med. 1984;310: 1363–7
51. Fisher B, Redmond C, Poisson R, Margolese R, Wolmark N, Wickerham DL, et al Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. N Eng J Med. 1989;320:822–8
52. Fisher B, Anderson S, Redmond C, Wolmark N, Wickerham DL, Cronin W. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. N Eng J Med. 1995;333(22): 1456–61
53. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH, Wolmark N. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Eng J Med. October 17, 2002; 347(16):1233–1241
54. Fisher B, Jeong J, Anderson S, et al Twenty-five year findings from a randomized clinical trial comparing radical mastectomy with total mastectomy and with total mastectomy followed by radiation therapy. N Eng J Med. 2002;347: 567–75
55. Buyse M, Evans S. Fraud in clinical trails In: Redmond C and Colton, TE, editors. Biostatistics in clinical trials. Wiley; 2001. p. 200–8
56. Peto R, Collins R, Sackett D, et al The trials of Dr. Bernard Fisher: A European perspective on an American episode. Control Clin Trials. 1997;18:1–13
57. Meinert, CL. Clinical trials. Design, conduct and analysis. New York: Oxford University Press; 1985
58. Therasse P, Arbuck SG, Eisenhauer EA, et al New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst. 2000;92:205–16
59. Meinert, CL. Workshop on interim data monitoring. Annual Meeting of the Society for Clinical Trials, 1996
60. Ellenberg S, Fleming T, DeMets D. Data monitoring committees in clinical trials: A practical perspective. West Sussex, England: Wiley; 2002
61. Jennison C, Turnbull BW. Group sequential methods with applications to clinical trials. Chapman & Hall/CRC; 2000
62. Pocock, SJ. Group sequential methods in the design and analysis of clinical trials. Biometrika. 1977;64:191–99
63. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. Br J Radiol. 1971;44:793–7
64. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979;35:549–56
65. Lan KG, Demets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70:659–63
66. Pepe MS, Anderson GL. Two-stage experimental designs: early stopping with a negative result. J Roy Stat Soc, Series C (Applied Statistics). 1992;41:181–90
67. Wieand S, Schroeder G, O'Fallon JR. Stopping when the experimental regimen does not appear to help. Stat Med. 1994;13:1453–8
68. Redmond CK, Costantino JP, Colton T. Challenges in monitoring the breast cancer prevetion trial. In: DeMets DL, Furberg CD, Friedman L, editors. Data monitoring in clinical trials: A case studies approach. Springer; 2006. pp. 118–35
69. Romond EH, Perez EA, Bryant J, et al Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Eng J Med. 2005;353:16,1673–84
70. Tan-Chiu E, Yothers G, Romond E, et al Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, Human Epidermal Growth Factor Receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol. 2005;23: 7811–9
71. Fleming TR, Harrington DP, O'Brien PC. Designs for group sequential tests. Control Clin Trials. 1984;5:348–61
72. Pocock SJ. Clinical trials: A practical approach. New York: Wiley; 1983

73. Peto R, Peto J. Asymptotically efficient rank invariant test procedures (with discussion). J Roy Stat Soc, Series A (Statistics in Society). 1972;135:185–206
74. Cox DR. Regression models and life-tables (with discussion). J Roy Stat Soc, Series B. 1972;34:187–202
75. Kaplan EL, Meier P. Nonparametric estimator from incomplete observations. J Am Stat Assoc. 1958;53:457–81
76. Cutler SJ, Ederer F. Maximum utilization of the life table method in analyzing survival. J Chronic Dis. 1958;8: 699–712
77. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies for disease. J Natl Cancer Inst. 1959;22:719–48
78. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemotherapy Rep. 1967;50:163–70
79. Gehan EA. A generalized two sample Wilcoxon statistic for comparing arbitrarily censored data. Biometrika. 1965;52: 650–3
80. Tarone RE, Ware J. On distribution free tests for equality of survival functions. Biometrika. 1977;64:156–60
81. Efron B. Bootstrap methods: Another look at the jackknife. Ann Stat. 1979;7:1–26
82. Fisher B, Redmond C, Brown A, et al Treatment of primary breast cancer with chemotherapy and tamoxifen. N Eng J Med. 1981;305:1–6
83. Gail M, Simon R. Testing for qualitative interactions between treatment effects and patient subsets. Biometrics. 1985;41: 361–72
84. Bonadonna G, Valagussa P. Dose-response effect of adjuvant chemotherapy in breast cancer. N Eng J Med. 1981;34: 10–5
85. Redmond C, Fisher B, Wieand HS. The methodologic dilemma in retrospectively correlating the amount of chemotherapy received in adjuvant therapy protocols with disease-free survival. Cancer Treatment Rep. 1983;67:519–26
86. Fisher B, Anderson S, Fisher ER, Redmond C, et al Significance of ipsilateral breast tumor recurrence after lumpectomy. Lancet. 1991;338:327–31
87. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 1988;75:800–2
88. Cook RJ, Farewell VT. Multiplicity considerations in the design and analysis of clinical trials. J Roy Stat Soc, Series A. 1996;159:.93–110
89. Taghian A, Jeong J, Anderson S, et al Pattern of loco-regional failure in patients with breast cancer treated by mastectomy and chemotherapy (+/- tamoxifen) without radiation: results from five NSABP randomized trials. J Clin Oncol. 2004;22: 4247–54
90. Gaynor JJ, Feuer EJ, Tan CC, et al On the use of cause-specific failure and conditional failure probabilities: Examples from clinical oncology data. J Am Stat Assoc. 1993;88: 400–9
91. Korn EL, Dorey FJ. Applications of crude incidence curves. Stat Med. 1992;11:813–29
92. Lin DY. Non-parametric inference for cumulative incidence functions in competing risks studies. Stat Med. 1997;16: 901–10
93. Pepe MS, Mori M. Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data? Stat Med. 1993;2:37–751
94. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: Wiley; 1980
95. Gooley TA, Leisenring W, Crowley J, et al Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999;18:695–706
96. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat. 1988;16:1141–54
97. Benichou, J, Gail, MH. Estimates of absolute cause-specific risk in cohort studies. Biometrics 1990;46:813–26
98. Jeong J. A new parametric distribution for modeling cumulative incidence function: Application to breast cancer data. J Roy Stat Soc, Series A (Statistics in Society). 2006;169: 289–303
99. Jeong J, Fine J. Direct parametric inference for cumulative incidence function. J Roy Stat Soc, Series C (Applied Statistics). 2006;55:187–200
100. Bryant J, Dignam JJ. Semiparametric models for cumulative incidence functions. Biometrics. 2004;60:182–90
101. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94: 496–509
102. Jeong J, Fine J. Parametric regression on cumulative incidence function. Biostatistics. 2007;8:184–96
103. Garg ML, Rao BR, Redmond CK. Maximum-likelihood estimation of the parameters of the Gompertz survival function. J Roy Stat Soc, Series C (Applied Statistics). 1970;19:152–9
104. Gompertz B. On the nature of the function expressive of the law of human mortality, and on the new mode of determining the value of life contingencies. Phil Trans Roy Soc London. 1825;115:513–80
105. Dabrowska DM, Doksum KA. Estimation and testing in a two-sample generalized odds-rate model. J Am Stat Assoc. 1998;83:744–9
106. Goss PE, Ingle JN, Martino S, et al A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Eng J Med. 2003;349:1793–802
107. Latouche A, Porcher R, Chevret S. Sample size formula for proportional hazards modeling of competing risks. Stat Med. 2004;23:3263–74
108. Paik S, Shak S, Tang G, et al A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Eng J Med. 2004;351:2817–26
109. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J Roy Statistical Soc, Series B 1995;57:289–300
110. Bair E, Tibshirani R. Semi-supervised methods to predict patient survival from gene expression data. PLoS Biol. 2004;2:511–22
111. Harrell FE, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. J Am Med Assoc. 1982;247:2543–6
112. Hanley JA, McNeil BJ. The meaning and use of the area under the receiver operating characteristic (ROC) curve. Radiology. 1982;143:29–36
113. Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. Stat Med. 2004;23:2109–23
114. Wang R, Lagakos, SW, Ware JH, Hunter, DJ, Drazen, JM. Statistics in medicine – reporting of subgroup analyses in clinical trials. N Eng J Med. 2007;357:2189–94

115. Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster randomised trials. Br Med J. 2004;328(7441):702–8
116. Boutron I, Moher D, Altman DG, Schulz K, Ravaud P, for the CONSORT group. Methods and processes of the CONSORT Group: Example of an extension for trials assessing nonpharmacologic treatments. Ann Int Med. 2008;W60–W67
117. Boutron I, Moher D, Altman DG, Schulz K, Ravaud P, for the CONSORT group. Extending the CONSORT Statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. Ann Int Med. 2008;295–309
118. Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, Schulz KF and the CONSORT Group. CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. PLoS Med 5(1): e20. doi:10.1371/journal, 2008
119. Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, Schulz KF, the CONSORT Group. CONSORT for reporting randomised trials in journal and conference abstracts. Lancet. 2008;371:281–83
120. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al Improving the quality of reports of randomized controlled trials: the CONSORT Statement. J Am Med Assoc. 1996;276:637–9
121. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Int Med. 2001;134(8):663–94
122. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet. 2001;357(9263):1191–4
123. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. J Am Med Assoc. 2001;285(15):1987–91
124. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. Ann Int Med. 2001;134(8):657–62
125. Early Breast Cancer Trialists' Collaborative Group. Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer: an overview of 61 randomized trials among 28, 896 women. N Eng J Med. 1988;319: 1681–91
126. Early Breast Cancer Trialists' Collaborative Group. Treatment of early breast cancer. Vol. I: Worldwide evidence 1985-1990. Oxford University Press, 1990
127. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Lancet. 1992;339:1–15 & 71–85
128. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: an overview of the randomized trials. N Eng J Med. 1995;333: 1444–55
129. Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation in early breast cancer: overview of the randomised trials. Lancet. 1996;348:1189–96
130. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet. 1998;351:1451–67
131. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet. 1998;352:930–42
132. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Lancet. 2000;355:1757–70
133. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005a;365:1687–717
134. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and on 15-year survival: an overview of the randomised trials. Lancet. 2005b;366:2087–106
135. Moher D, Cook DJ, Eastwood, S, Olkin I, Rennie D, Stroup, DF, for the QUOROM Group. Improving the quality of reports of meta-analyses of randomized controlled trials: the QUOROM statement. Lancet 1999;354:1896–1900
136. O'Quigley J, Pepe M, Fisher L. Continual reassessment method: A practical design for phase I clinical trials in cancer. Biometrics. 1990;46:33–48
137. Gehan EA. The determination of the number of patients required in a preliminary and follow-up trial of a new chemotherapeutic agent. J Chronic Dis. 1961;13:346–53
138. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analyses and other misuses of baseline data in clinical trials. Lancet. 2000;355:1064–9
139. Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. Ann Stat. 2001;29:1165–88
140. Byar DP. The use of data bases and historical controls in treatment comparisons. Recent Results in Cancer Res. 1988;111:95–8
141. Elbourne DR, Altman DG, Pocock SJ, Evans SJW. Reporting of noninferiority and equivalence randomized trials: An extension of the CONSORT statement. J Am Med Assoc. 2006;295:1152–60
142. Harrell FE, Lee, KL, Mark, DB. Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1966;15:361–87
143. Paré A. Les oeuvres de M. Ambroise Paré conseiller, et premier chirurgien du Roy avec les figures & portraicts tant de l'Anatomie que des instruments de Chirurgie, & de plusieurs Monstres, Paris: Gabriel Buon 1575
144. Royall RM, Bartlett RH, Cornell RG. Ethics and statistics in randomized clinical trials. Stat Sci. 1991;6:52–88
145. Piaggio G, Elbourne DRY Altman DG, Pocock SJ, Evans SJW. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA. 2006;295:1152–60
146. Ioannidis JP, Evans, Gotzsche PC, O'Neil RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med. 2004;141:781–8

Structure of Breast Care Center

32

David P. Winchester

32.1 Introduction

Recent reports indicate a plateau in the incidence and a decrease in the mortality rate of breast cancer in the United States, but evaluation and management of benign and malignant breast disease continue to be a major health problem. The American Cancer Society (ACS) estimated that there would be 178,480 patients diagnosed with invasive breast cancer in the United States in 2007. Approximately 62,030 additional women would be diagnosed with in situ carcinoma of the breast, 85% of whom would have ductal carcinoma in situ [1].

The annual incidence of breast cancer in most developed countries can be accurately tracked through cancer registration systems. Contrariwise, there are no comprehensive databases to estimate the incidence of benign breast disease in the United States. This annual number likely runs in the millions. Countless patients seek evaluation and management of a broad spectrum of benign disease, which must be differentiated from breast cancer. The threat of breast cancer and broad media coverage combine to heighten the level of anxiety and concern among women with breast cancer symptoms and findings. These include breast pain, lumps, nipple discharge, the itching breast, mastitis, axillary node enlargement and abnormal imaging findings such as cystic and solid masses, the asymmetric density, microcalcifications, skin thickening and enhancing lesions seen on breast MRI. Thus, millions of consistently anxious women around the world present with self-discovered findings or physician-detected abnormalities through physical exam or imaging studies. This places a significant burden on healthcare systems to conduct top quality, multidisciplinary evaluation and management in an optimally organized setting.

Silverstein recognized that the evaluation and management of breast patients was often fragmented, inefficient and time-consuming. He firmly believed that these patients should be promptly evaluated and test results communicated as quickly as possible. He also recognized the need to navigate patients through this complex environment. The result was the establishment of a multidisciplinary breast clinic at UCLA in 1973. Further refinements and philanthropic support led to the opening of the Van Nuys Breast Center, the first free-standing, multidisciplinary breast center in the United States [2]. Since that time, breast centers, hospital-based or free-standing, have rapidly proliferated.

32.2 The National Accreditation Program for Breast Centers

The American College of Surgeons has a long and distinguished history of accrediting cancer and trauma programs in the United States. More recently, the College has organized a bariatric accreditation program.

The American College of Surgeons was founded in 1913. Within 10 years, the first cancer registry in the United States was introduced and a cancer accredi tation program took root. The Commission on Cancer, as presently constituted, consists of representatives from 47 national professional organizations committed to decreasing the morbidity and mortality of cancer patients through standard setting and the monitoring of

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I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases,*
DOI: 10.1007/978-3-540-69743-5_32, © Springer-Verlag Berlin Heidelberg 2010

outcomes. Thirty-six multidisciplinary standards must be met by accredited facilities verified at the time of triennial survey. Between 70–80% of all newly diagnosed cancer patients in the United States are cared for in the Commission on Cancer-accredited programs. These 1,450 centers are required to submit comprehensive data on all analytic cancer patients to the National Cancer Database (NCDB). The NCDB was initially organized in 1988 and now contains comprehensive information on over 25 million cancer patients. This has provided, through the years, a firm foundation for tracking patterns of care on a longitudinal basis and effecting change to keep pace with evidence-based changes in evaluation and management.

The practice of medicine in the United States is undergoing transformation to a more transparent system of quality management and outcomes of cancer patients through accredited facilities and individual physician reporting. The large network of Commission on Cancer-accredited programs and the robust NCDB have formed an excellent framework to address these changes.

The idea of a National Accreditation Program for Breast Centers (NAPBC) was conceived in this transformational medical delivery system in the year 2005. The experience and success of the Commission on Cancer provided early guidelines for the NAPBC development. There was recognition, at the outset, that diseases of the breast, including breast cancer, required a multidisciplinary team for optimal patient evaluation and management. The Board of Regents of the American College of Surgeons approved seed funding in 2006 to support program development. A formal governing board of the NAPBC was organized and has been meeting regularly for the past 3 years. The board consists of representatives from 16 national, professional organizations (Table 32.1). In addition, six working committees were organized as outlined in Table 32.2. Thus, the NAPBC is an organization of organizations, housed and staffed at the American College of Surgeons national headquarters in Chicago but governed by the NAPBC board. The mission statement for this program states that "The NAPBC is a consortium of national, professional organizations dedicated to the improvement of the quality of care and monitoring of outcomes for patients with diseases of the breast." To meet this mission, five objectives were agreed upon (Table 32.3).

Table 32.1 Member Organizations

American Board of Surgery[a]
American Cancer Society (ACS)
American College of Surgeons
American Society of Breast Disease
American Society of Breast Surgeons (ASBS)
American Society of Clinical Oncology (ASCO)
American Society of Therapeutic Radiology and Oncology
Association of Cancer Executives
Association of Oncology Social Work
College of American Pathologists (CAP)
The Joint Commission
National Cancer Institute (NCI)[a]
National Cancer Registrars Association
National Consortium of Breast Centers
Oncology Nursing Society
Society of Surgical Oncology
Members-at-Large

[a]Liaison Board Membership

Table 32.2 NAPBC committees

Executive committee
Quality improvement and measurement
Access and utilization
Center criteria and approvals process
Education and dissemination
Information technology and outcomes

Table 32.3 Mission objectives

Consensus development of standards for breast centers and a survey process to monitor compliance
Strengthen the scientific basis for improving quality care
Establish a national breast cancer database to effect quality improvement
Reduce the morbidity and mortality of breast cancer by improving access to screening and comprehensive care, promoting risk reduction and prevention and advocating for increased access and participation in clinical trials
Expand programs of quality improvement measurement and benchmark comparison

The original design of the NAPBC called for three categories of breast centers. The centers could be housed in a single geographic area or recognized as centers without walls as long as the breast center leadership had control of provided services. If provided services were not available on site, referred services were required within reasonable distance for breast patients.

The clinical breast center (CBC) was designed to initiate clinical decision-making for patients presenting with breast symptoms or abnormal breast imaging findings. The breast evaluation and management center (EMC) was to provide the essential services to patients with breast disease seeking definitive evaluation and management, whereas the comprehensive breast and evaluation management center (CEMC) was designed to provide comprehensive services to patients with breast disease seeking definitive evaluation and management.

After 18 months of deliberation by the NAPBC board, there was consensus on the establishment of 27 standards for breast center accreditation.

In order to field test and validate center categories, components, standards and the survey process, 18 voluntary pilot site surveys were conducted across the United States. Many lessons were learned. The 27 standards have undergone substantial revisions. Several deficiencies were encountered but appeared to be readily correctable through education. The structure of the centers confirmed the heterogeneous settings in which evaluation and management are conducted. A common model was community-based, consisting of private practitioners in general surgery, medical oncology, radiation oncology, radiology and pathology working together to deliver high-quality evaluation and management of their patients. Some services, such as breast imaging, surgery, systemic therapy and radiation therapy were provided on-site while other services, such as genetic counseling, plastic surgery and survivorship programs were referred to nearby locales. Another common model encountered within or without walls was nonteaching hospitals or academic/teaching hospitals. In these settings, there were more provided services and fewer referred services. It was our observation that patients received excellent care, irrespective of the center model because they were afforded the full-range of services, whether provided or referred.

The experience of the pilot surveys led the NAPBC board to approve a single category for accreditation. The board reasoned that as long as breast patients were afforded the full range of services for evaluation and management and all of the 27 standards were met, a single accreditation category would be inclusive rather than exclusive.

32.3 NAPBC Standards

The categories for standards include center leadership, breast cancer data management and registry operations, clinical management, research, community outreach, professional education and quality improvement.

32.4 Center Leadership

Purpose: The standard establishes the medical director and/or co-directors, or interdisciplinary steering committee as the Breast Program Leadership (BPL) responsible and accountable for breast center activities.

32.4.1 Level of Responsibility and Accountability

Standard 1.1 The organizational structure of the breast center gives the BPL responsibility and accountability for provided breast center services.

Leadership is the key element in an effective breast center and its success depends on effective BPL. The BPL is responsible for goal setting, as well as planning, initiating, implementing, evaluating and improving all breast-related activities in the center.

The center or medical staff formally establishes the responsibility, accountability and multidisciplinary membership required for the BPL to fulfill its role. The center documents the breast program leader's responsibility and accountability using a method appropriate to the center's organizational structure. Examples include, but are not limited to, the following:

- The center bylaws designate the breast program leader as having defined authority.
- Policies and procedures for the center define authority of the breast program leader.

- Policies and procedures for the medical staff define authority of the breast program leader.

Other methods that are consistent with the center organization and operation are acceptable.

The BPL is responsible for an annual audit of the following:

- Interdisciplinary Breast Cancer Conference Activity (Standard 1.2)
- Database Quality Assurance (Standard 1.3)
- Breast Conservation Rate (Standard 3.3)
- Sentinel Lymph Node Biopsy Rate (Standard 3.4)
- Needle Biopsy Rate (Standard 3.9)

Documentation:

The center completes the on-line Survey Application Record (SAR) and documents the following information in the text box provided:

- Briefly describe the organizational structure of the breast center and leadership roles and responsibilities.

Provide the surveyor with the following documents 2 weeks prior to survey:

- A copy of a roster of the breast center steering committee, if applicable.
- A copy of the minutes from the most recent steering committee meeting, if applicable.
- Center bylaws or policy and procedures, or other facility-approved methods used to document the level of responsibility and accountability designated to the breast program leader, if applicable. For example, private practice offices may not have policy and procedures documented, but are requested to define the structure.

32.4.2 Cancer Conference

Standard 1.2 The BPL monitors and evaluates the interdisciplinary breast cancer conference frequency, multidisciplinary attendance, prospective case presentation and total case presentation annually, including AJCC staging and discussion of nationally accepted guidelines. CME credit is recommended.

Conferences that include case presentations should be available to the entire medical staff and are the preferred format. Consultative services are optimal when physician representatives from diagnostic radiology, pathology (including AJCC staging), surgery, medical oncology and radiation oncology participate in the breast conference.

Setting the Interdisciplinary Breast Conference frequency and format allow for prospective review of breast cancer cases and encourages multidisciplinary involvement in the care process. Breast cancer conferences are integral to improving the care of breast cancer patients by contributing to the patient management process and outcomes, and providing education to physicians and other staff in attendance.

The Interdisciplinary Breast Conference is focused on treatment planning for newly diagnosed and recurrent breast cancer patients, and should include discussion of tumor stage and relevant, nationally accepted breast cancer patient care guidelines developed by national organizations. This conference should be designed for breast surgeons, medical oncologists, and radiation oncologists to provide a comprehensive update on new data and recent advances in surgery and systemic/local therapy that are critical to the optimal management of breast cancer patients. Radiologists and pathologists provide essential expertise in diagnosis. Nurses, fellows, and pharmacists in the oncology field are also invited to attend.

Conference frequency is dependent upon annual caseload. Seventy-five percent (75%) of all breast cancer cases (stage 0, I, II) shall be discussed prospectively in order to meet compliance with this standard.

Prospective case reviews include, but are not limited to, the following:

- Imaging and pathology reviews.
- Newly diagnosed breast cancer and treatment not yet initiated.
- Newly diagnosed breast cancer and treatment initiated, but discussion and additional treatment is needed.
- Previously diagnosed, initial treatment completed, but discussion of adjuvant treatment or treatment recurrence or progression is needed.
- Previously diagnosed, and discussion of supportive or palliative care is needed.

Monitoring of breast cancer conference activity by the BPL ensures that conferences provide consultative services for patients, as well as offer education to physicians and allied health professionals.

Documentation:

The BPL determines the method for documenting breast conference activity based on facility requirements and the needs of the program. A breast cancer conference grid, calendar, or tracking tool that shows the annual conference schedule may be used.

The center completes the on-line SAR and provides the following in the text box provided:

- Briefly describe the breast cancer conference program to include frequency, attendance, and case presentation.
- Attach a copy of the breast cancer conference schedule/calendar from the last complete year.

The surveyor attends a breast cancer conference to observe the multidisciplinary involvement in case discussions, at the time of survey.

32.4.3 Evaluation and Management Guidelines

Standard 1.3 The BPL identifies and references evidence-based breast care evaluation and management guidelines.

Patient management and treatment guidelines promote an organized approach to providing care. The BPL should review and adopt breast care evaluation and management guidelines developed by national organizations appropriate to the patients that are diagnosed and treated by the center. Examples of referencing these guidelines could include:

- PowerPoint presentations or handouts at cancer conferences or BPL meetings of relevant, nationally accepted breast care guidelines.

National organizations that have developed breast care guidelines include, but are not limited to, the following:

- American Cancer Society (ACS)
- American Society of Clinical Oncology (ASCO)
- American Society for Therapeutic Radiology and Oncology (ASTRO)
- National Quality Forum (NQF)
- National Comprehensive Cancer Network (NCCN)

Guidelines adopted by the BPL for use by the center are documented. This is in addition to patient management and treatment guidelines required by the NAPBC.

The BPL establishes the concordance rate for adherence to adopted guidelines being used by the center, and monitors utilization through review of a random sample of cases for which these guidelines are applicable. The monitoring activity is reported to the BPL on a regular basis. The BPL addresses compliance levels that fall below the established concordance rates.

Documentation:

The center completes the on-line SAR and provides the following in the text box provided:

- Submit a list of breast care evaluation and management guidelines utilized by the center; identifying the originating organization, i.e., institutional, national, etc.

32.5 Clinical Management

Purpose: The standards identify the scope of clinical services needed to provide quality breast care to patients. The managing physician is essential to coordinating a multidisciplinary team approach to patient care.

32.5.1 Interdisciplinary Patient Management

Standard 2.1 After a diagnosis of breast cancer, the patient management is conducted by an interdisciplinary team, as appropriate. Physician team members should be board certified or eligible.

Breast cancer is a disease requiring interdisciplinary evaluation and management. The NAPBC has identified 17 components in the spectrum of breast cancer diagnosis, treatment, surveillance, and rehabilitation/support.

An example to clarify “as appropriate” may include; A 90 year old woman with co-morbid conditions presents with a small breast cancer could be appropriately managed without the review of an interdisciplinary discussion.

Documentation:

The center completes the on-line SAR and provides the following:

- Select the types of physicians that conduct the initial patient evaluation and management, indicating if the physicians are board certified or eligible, and if they are available on-site or by referral (check all that apply)

The surveyor will discuss the process for patient evaluation and management, at the time of survey.

32.5.2 Patient Navigator

Standard 2.2 A patient navigator process is in place to guide the patient with a breast abnormality through provided or referred services.

The primary function of the patient navigation process is to coordinate services and guide patients through the health care system by assisting with access issues, identifying resources, providing educational materials and developing relationships with service providers.

The patient navigation process should include a consistent care coordinator throughout the continuum of care able to assess the physical, psychological and social needs of the patient. The results are enhanced patient outcomes, increased satisfaction, and reduced costs of care. This may involve different individuals at each point of care.

The following organizations provide patient navigation information and resources:

- American Cancer Society
- Patient Navigation in Cancer Care
- Educare

Examples of patient navigation include, but are not limited to, the following:

- Provide education, support and coordination to assist patients to get to appointments.
- Provide educational resources on breast health, breast cancer and breast care.
- Connect patients and families to resources and support services.
- Promote communication between the patient and health care providers.
- Coordinate services throughout the continuum of breast care.
- Enhance the patient's quality of life, sense of autonomy, and self-determination for managing her own health.

Qualifications of a patient navigator may include:

- Successful completion of a recognized patient navigator training program.
- Documentation of the requisite knowledge and skills from previous education and experience to provide patient navigation.

Documentation:

The Center completes the on-line SAR and provides the following in the text box provided:

- Identify the individual(s) who provides patient navigation in the center along with their qualifications and role.

The surveyor will discuss the patient navigation process at the time of survey.

32.5.3 Breast Conservation

Standard 2.3 A proportion of at least 50% of patients with early stage breast cancer (Stage 0, I, II) is offered and/or treated with breast conserving surgery, and compliance is evaluated annually.

Breast-conserving surgery for patients with early stage breast cancer is a nationally accepted standard of care in appropriately selected patients. Most centers exceed the 50% level and this level should not be used as benchmark. Fifty percent is considered the minimum standard in order to meet NAPBC compliance. Published data confirm high utilization rates for breast-conserving surgery and are all in excess of 50%. Compliance is evaluated annually.

Guidelines for breast-conserving surgery are available from the following organizations:

- American Cancer Society
- American College of Radiology (ACR)

Documentation:

The center completes the on-line SAR and provides the following:

- Complete the table summarizing the percent of early-stage breast cancer patients receiving breast-conserving surgery.
- Document when the annual evaluation of compliance was conducted by the BPL.

The surveyor will review a random sample of breast cancer patient medical records to evaluate the appropriate use of breast-conserving surgery at the time of survey.

32.5.4 Sentinel Node Biopsy

Standard 2.4 Sentinel lymph node biopsy is performed when appropriately indicated for invasive breast cancer, and compliance is evaluated annually.

Patients currently considered candidates for sentinel lymph node biopsy include those with resectable primary breast cancers and clinically negative axillary nodes.

This technique most commonly utilizes a combination of radionuclide and blue dye, although some centers utilize radionuclide alone.

Documentation:

The center completes the on-line SAR and provides the following:

- Complete the table summarizing the percent of sentinel lymph node biopsies.
- Document when the annual evaluation of compliance was conducted by the BPL.

The surveyor will review a random sample of breast cancer patient medical records to evaluate the appropriate use of sentinel lymph node biopsy at the time of survey.

32.5.5 Breast Cancer Surveillance

Standard 2.5 A process is in place for assuring follow-up surveillance of breast cancer patients.

Follow up surveillance includes history, clinical examination, upper extremity lymphedema measurements and imaging studies. Frequency of follow-up will vary from patient to patient. Bone scan, PET scan, and other tests are the responsibility of the managing physician and are generally ordered for evaluation of symptoms or restaging.

Guidelines for follow-up surveillance are available at:

- Agency for Healthcare Research and Quality (AHRQ)
- National Lymphedema Network (NLN)

Documentation:

The center completes the on-line SAR and provides the following in the text box provided:

- Describe the process in place to assure patient follow-up, or attach a copy of the follow-up surveillance plan.

The surveyor will discuss follow-up surveillance at the time of survey.

32.5.6 AJCC Staging

Standard 2.6 AJCC staging (clinical and/or pathologic) is accurately recorded on 90% of newly diagnosed breast cancer patients and noted in the medical record.

Proper staging of cancer allows the physician to determine appropriate treatment. Staging enables the reliable evaluation of treatment results and outcomes reported to various institutions on a local, regional, and national basis.

When using the AJCC system, either clinical or pathological staging is assigned to each primary. Both should be assigned and recorded in the medical record, if appropriate. Use the criteria for clinical and pathological staging outlined in the current edition of the *AJCC Cancer Staging Manual* [3] to determine the appropriate stage.

A designation of M_x makes the patient unstageable and this designation should not be used. The managing physician should designate whether the patient is M0 or M1.

The assignment of staging is most appropriate by the managing physician, who is ultimately responsible for planning the patient's treatment. The patient's managing physician evaluates all available staging information (X-rays, scans, laboratory tests, and operative and pathology reports), records the staging elements (TNM and Stage Group) in the medical record. Tumor registrars participate in documentation, if available.

Documentation:

The center completes the online SAR and indicates below/the following:

- Check whether AJCC staging is recorded in the medical record.

- Attach a report of the breast cancer stage distribution for the last complete year.

The surveyor will review a random sample of breast cancer patient medical records to evaluate the accuracy of clinical and pathologic staging at the time of survey.

32.5.7 Pathology Reports

Standard 2.7 The College of American Pathologists' (CAP) Cancer Committee guidelines are followed for all invasive breast cancers, including estrogen and progesterone receptors, and Her2 status [4].

Patient management and treatment guidelines promote an organized approach to providing quality care. The NAPBC requires that 90% of breast cancer pathology reports will contain the scientifically validated data elements outlined on the surgical case summary checklist of the (CAP) publication *Reporting on Cancer Specimens* [4].

Guidelines for surgical pathology reporting are available by:

- College of American Pathologists (CAP)While synoptic reporting is strongly advised, it is not mandatory. Imaging studies should be correlated with pathology when feasible.

Documentation:

The center completes the on-line SAR and indicates the following:

- Check whether synoptic reporting is being utilized

The surveyor will review a random sample of breast cancer patient medical records to evaluate pathology reporting at the time of survey.

32.5.8 Diagnostic Imaging

Standard 2.8 Mammographic screening, diagnostic imaging, and breast MRI are conducted through Mammography Quality Standards Act (MQSA)-certified radiologists.

Federal law mandates that mammography must be conducted and interpreted by a MQSA-certified radiologist.

MQSA information is available from:

- U.S. Food and Drug Administration (FDA)

ACR Guidelines for mammographic screening, diagnostic imaging, and breast MRI are available from:

- American College of Radiology
  - Guidelines for the Performance of Screening Mammography.
  - Guidelines for the Performance of Diagnostic Mammography.
  - Guidelines for the Performance of Magnetic Resonance Imaging (MRI) of the Breast.

Documentation:

The center completes the on-line SAR and indicates the following:

- Check all imaging services provided or referred.

MQSA certification will be validated by the surveyor at the time of survey.

32.5.9 Needle Biopsy

Standard 2.9 Palpation-guided or image-guided needle biopsy is the preferred initial diagnostic approach rather than open surgical biopsy.

Either fine needle aspiration for cytologic evaluation or core needle biopsy (preferred) constitute the initial diagnostic approach for palpable or occult lesions. Open surgical biopsy as an initial approach should be avoided as it does not allow for treatment planning and is associated with a high reexcision rate. Compliance is reviewed annually with BPL.

Documentation:

No documentation is required.

The surveyor will review a random sample of breast cancer patient medical records to evaluate the appropriate use of palpation or image-guided needle biopsy at the time of survey.

32.5.10 Ultrasonography

Standard 2.10 Diagnostic ultrasound and/or ultrasound-guided needle biopsy are performed by an ACR-certified, American Society of Breast Surgeon (ASBS)-certified, or American Institute of Ultrasound in Medicine (AIUM)-certified physician.

The NAPBC requires physician certification for the performance of diagnostic ultrasound and/or ultrasound-guided needle biopsy. Voluntary certification programs are available from the ACR, ASBS and the American Institute of Ultrasound Medicine. Physicians performing these procedures in centers applying for NAPBC accreditation will need to demonstrate that they are enrolled in or working toward certification by one of the organizations mentioned above. At the time of the next survey, physicians performing the procedures in NAPBC-accredited centers will need to provide documentation of certification.

The following organizations provide guidelines and/or certification programs for physicians performing diagnostic ultrasound and/or ultrasound-guided needle biopsy:

- American College of Radiology
- American Society of Breast Surgeons (ASBS)
- American Institute of Ultrasound Medicine (AIUM)

Documentation:

The surveyor will review documentation confirming certification, as available, at the time of survey.

The surveyor will discuss the process underway for certification of those physicians in the center performing diagnostic ultrasound and/or ultrasound-guided biopsy, at the time of survey.

32.5.11 Stereotactic Core Needle Biopsy

Standard 2.11 Stereotactic core needle biopsy is performed by radiologists, surgeons or other physicians under the standards and requirements developed by the ACR and the American College of Surgeons (ACS) or certified by the ASBS.

Stereotactic core needle biopsy is most commonly used to diagnose suspicious microcalcifications and hould be done with dedicated equipment. It is also used to biopsy masses and/or architectural distortions not visible on ultrasonography.

The NAPBC requires physician certification for the performance of stereotactic core needle biopsy. Voluntary certification programs are available from the ACR and American College of Surgeons, and the ASBSs. Physicians performing this procedure in centers applying for NAPBC accreditation will be required to demonstrate that they are enrolled in or working toward certification by one of the organizations mentioned above. At the time of the next survey, physicians performing the procedure in NAPBC-accredited centers will need to provide documentation of certification.

The following organizations provide guidelines and/or certification programs for physicians performing stereotactic core needle biopsy:

- American College of Radiology
- American Society of Breast Surgeons

Documentation

The surveyor will review documentation confirming certification, as available, at the time of survey.

The surveyor will discuss the process underway for certification of those physicians in the center performing stereotactic core needle biopsy, at the time of survey.

32.5.12 Radiation Oncology

Standard 2.12 Radiation oncology treatment services are provided by or referred to board certified/eligible radiation oncologists, and the breast cancer quality measure endorsed by the NQF for radiation therapy is utilized.

Radiation therapy is a primary component of multidisciplinary treatment, and should be administered by board certified/eligible physicians. Board certification for radiation oncology took effect in 1969. Radiation oncologists demonstrating competence and privileged by their facility can be considered "grandfathered" prior to 1969. In addition, the NAPBC requires that the following standard of care endorsed by the NQF related to radiation therapy is utilized:

- Radiation therapy is administered within 1 year (365 days) of diagnosis for women under age 70 receiving breast-conserving surgery for breast cancer.

Documentation

The center completes the on-line SAR and indicates the following:

- Check all radiation oncology treatment services provided or referred.

The surveyor will confirm board certification/eligibility, and review a random sample of breast cancer patient medical records to evaluate the appropriate use of the radiation therapy quality measure, at the time of survey.

32.5.13 Medical Oncology

Standard 2.13 Medical oncology treatment services are either provided by or referred to board certified/eligible medical oncologists, and the breast center quality measures endorsed by the NQF for medical oncology are utilized.

Medical oncology (systemic therapy) is a primary component of multimodality treatment, and should be administered by board certified/eligible physicians. In addition, the NAPBC requires that the following standards of care endorsed by the NQF related to medical oncology are utilized:

- Combination chemotherapy is considered or administered within 4 months (120 days) of diagnosis for women under the age of 70 with AJCC T1c, Stage II or III hormone receptor-negative breast cancer.
- Tamoxifen or third-generation aromatase inhibitor is considered or administered within 1 year (365 days) of diagnosis for women with AJCC T1c, Stage II and III hormone receptor-positive breast cancer.

Documentation:

The center completes the on-line SAR and indicates the following:

- Check all medical oncology treatment services provided or referred.

The surveyor will confirm board certification/eligibility, and review a random sample of breast cancer patient medical records to evaluate the appropriate use of the medical oncology quality measures, at the time of survey.

32.5.14 Nursing

Standard 2.14 Nursing care is provided by nurses with specialized knowledge and skills in diseases of the breast. Nursing assessment and interventions are guided by evidence-based standards of practice and symptom management.

The complex needs of cancer patients and their families require specialized oncology nursing knowledge and skills to achieve optimal patient care outcomes. The oncology nurse is an integral member of the multidisciplinary breast team.

In larger centers, ONS-certified nurses are preferred. In smaller centers or private practice offices, ONS-certified nurses are optional, but nursing care should be provided by those with experience in breast diseases.

A clinical expert in oncology nursing can be:

- An oncology clinical nurse specialist with a master's degree.
- A certified nurse practitioner with a Master's degree.
- An oncology-certified nurse (OCN).

Oncology nursing resources are available:

- Oncology Nursing Society
- Oncology Nursing Certification Corporation

Documentation:

The center completes the online SAR and indicates the following:

- Enter the total number of oncology-trained nurses on staff at the center, and enter the total number of Oncology Nursing Society (ONS)-certified nurses on staff, if applicable.

The surveyor will discuss the nursing assessment and intervention process, at the time of survey.

32.5.15 Support and Rehabilitation

Standard 2.15 Support and rehabilitation services are provided or referred.

Comprehensive breast cancer care is multidisciplinary and includes medical health professionals addressing patient needs identified along the breast cancer continuum from diagnosis through survivorship. Supportive services help patients and their families cope with the day-to-day details of a breast cancer diagnosis. These resources address emotional, physical, financial, and other needs of the breast cancer patient.

Supportive services address the needs of the majority of patients, as well as provide for special populations or needs. The supportive services offered on site will vary depending upon the scope of the facility, local staff expertise, and patient mix. Supportive services not provided on site are provided through referral to other facilities and/or local agencies. Supportive services should be evaluated annually.

Advocacy organizations include:

- American Cancer Society
- Susan G. Komen for the Cure
- National Lymphedema Network
- Y-Me

Supportive services include, but are not limited to, the following:

- Assisting patients and family members with adjusting to or accepting a breast cancer diagnosis
- Lymphedema care and prevention
- Career counseling
- Grief counseling
- Nutritional counseling
- Palliative care
- Support groups
- Transportation services
- Lymphedema prevention and/or treatment
- Range of motion physical therapy

Patient education in lymphedema by a physical therapist/nurse will empower each patient undergoing axillary surgery and help patients and family members in the day-to-day precautions.

Documentation:

The center completes the on-line SAR and indicates the following:

- Check all support and rehabilitation services provided or referred.The surveyor will discuss the support and rehabilitation services available, at the time of survey.

32.5.16 Genetic Counseling

Standard 2.16 High-risk counseling, genetic counseling, and testing services are provided or referred to a board certified/eligible genetic counselor.

Genetic counseling is a primary component of multidisciplinary treatment, and should be administered by a board certified/eligible genetic counselor. Genetic professionals work as members of health care teams providing information and support to individuals and/or families that are deemed high risk for breast cancer. Genetic professionals:

- Assess the risk of a genetic disorder by researching a family's history and evaluating medical records.
- Weigh the medical, social and ethical decisions surrounding genetic testing.
- Provide support and information to help a person make a decision about testing.
- Interpret the results of genetic tests and medical data.
- Provide counseling or refer individuals and families to support services.
- Serve as patient advocates.
- Explain possible treatments or preventive measures.
- Discuss screening and prevention options.

32.5.17 Genetic Counseling for Breast Cancer

The Cancer Genetics Program offers a comprehensive cancer risk assessment that focuses on family history and genetics, along with environmental and lifestyle factors.

Breast cancer education and individualized risk assessment is initiated by evaluation of one's personal risk factors. Individuals meet with a genetic counselor to review their family's history and construct a family tree to uncover cancer patterns. Lifestyle factors and attitudes about cancer risk are explored. A personalized cancer risk profile with strategies to lessen the likelihood of developing the disease is developed.

By identifying risks for the disease and detecting cancers early, genetic counseling can dramatically improve the chances of surviving breast cancer.

32.5.18 Genetic Testing for Breast Cancer

Genetic testing for BRCA 1, BRCA 2, or other breast cancer susceptibility genes can be elected. Mutations in these genes increase the lifetime risk of breast, ovarian and associated cancers. The value of genetic testing is very much dependent on a woman's individual preference after full education about benefits and risks. From the information gained during this process, personally designed prevention and early detection strategies can be developed. Recommendations for genetic risk assessment and BRCA mutation testing for breast cancer susceptibility are available from the U.S. Preventive Services Task Force:

- Agency for Healthcare Research and Quality (AHRQ)

32.5.18.1 Breast Cancer Education for Women at Risk

Genetic counselors may also organize seminars, support groups, opportunities to enroll in ongoing research projects, and free lectures.

Documentation:

The center completes the on-line SAR and indicates the following:

- Check the counseling services provided or referred.

The surveyor will review and discuss the genetic counselor(s) training and experience at the time of survey.

32.5.19 Educational Resources

Standard 2.17 Culturally appropriate educational resources are available for patients along with a process to provide them. The materials provided are appropriately adjusted for the patient population.

Centers should provide patients with educational information covering the entire spectrum of evaluation and management of breast disease. Some centers have patient education libraries, while others provide printed materials that are either locally generated or provided by national organizations. Audiovisual education is a very effective delivery method.

In centers dealing with culturally diverse populations, educational resources should be available in various languages.

Educational resources are appropriately adjusted based on the patient population.

Documentation:

The center completes the on-line SAR and indicates the following:

- Check the types of educational resources available to patients. If other culturally appropriate educational resources are available, please specify.
- Describe the processes for providing educational resources to patients.

The surveyor will review samples of educational resources provided to patients, at the time of survey.

32.5.20 Reconstructive Surgery

Standard 2.18 Plastic/reconstructive surgery is either provided by or referred to board certified/eligible plastic/reconstructive surgeons.

Patients undergoing mastectomy should be afforded a discussion on the options of breast reconstruction with a board certified/eligible plastic/reconstructive surgeon. There is an increasing trend in immediate breast reconstruction utilizing tissue expanders, implants, or autologous tissue transfer. Some patients may desire delayed reconstruction. Patients need to understand that breast reconstruction does not interfere with surveillance or detection of local recurrence.

Consideration needs to be given to the timing of reconstruction with respect to systemic adjuvant chemotherapy or radiation therapy.

Documentation:

The center completes the on-line SAR and indicates the following:

- Check the types of plastic and reconstructive services provided or referred.

Board certification/eligibility will be confirmed by the surveyor, at the time of survey.

32.5.21 Evaluation and Management of Benign Breast Disease

Standard 2.19 Evaluation and management of benign breast disease follows nationally recognized guidelines.

Benign breast disease is defined as breast findings found on clinical breast examination deemed non-suspicious by the examiner or a BIRADS category one or two on breast imaging.

If the mass is cystic and tender, needle aspiration may be done at the time or deferred until breast imaging is done. If ultrasound is available to the initial examining physician, confirmation of the cyst and complete aspiration with ultrasound guidance is preferred. Palpation-guided cyst aspiration is acceptable. The mass should completely resolve and follow-up options should be discussed. The fluid, if benign in appearance, should be discarded. Incomplete resolution of the mass and/or bloody fluid are indications for submission of the cyst fluid for cytologic evaluation.

A clinically benign, but solid mass requires additional evaluation. Mammography and ultrasound, unless recently performed, should be done to confirm the solid, but benign characteristics of the palpable mass. Office-based fine needle aspiration or core needle biopsy can be palpation and/or ultrasound-guided. Ultrasound-guided needle biopsy would be expected in a radiology department setting. If a benign diagnosis, without atypia, is confirmed, the patient may be observed or excisional biopsy performed, depending on circumstances and patient/physician preferences.

Occult, asymptomatic cysts, found with mammography/ultrasound require no intervention but thorough discussion with the patient. BIRADS 3 findings are usually managed with a 3–6 month imaging follow-up and clinical breast exam. This applies to both benign masses and micro calcifications.

Documentation:

Appropriate evaluation and management of benign breast disease is documented in the medical record.

The surveyor will review a random sample of breast patient medical records to evaluate adherence to national guidelines for the evaluation and management of benign breast disease, at the time of survey.

32.6 Research

Purpose: The standards promote advancement in prevention, early diagnosis and treatment through the provision of clinical trial information and patient accrual to breast cancer-related clinical trials and research protocols.

32.6.1 Clinical Trial Information

Standard 3.1 Information about the availability of breast cancer-related clinical trials is provided to patients through a formal mechanism.

By providing information about the availability of breast cancer-related clinical trials, the facility offers patients the opportunity to participate in the advancement of evidence-based medicine.

The following organizations offer patient information and resources related to clinical trials:

- American Cancer Society
- National Cancer Institute
- U.S. Food and Drug Administration
- Coalition of Cancer Cooperative Groups

A formal process is in place to provide information about breast cancer-related clinical trials to patients seen at the center. Methods of providing information include, but are not limited to, the following:

- Access to the internet or Intranet search services through the patient library.
- Articles in facility newsletters.
- Pamphlets or brochures in patient waiting rooms or patient packets.
- Physician/nurse education.

Documentation:

The center completes the on-line SAR and indicates the following:

- Check the appropriate boxes indicating the types of clinical trial materials provided to patients.
- In the text box, describe the process to provide clinical trial materials to patient.

The surveyor will review samples of educational resources provided to patients and discuss the process in place to provide them, at the time of survey.

32.6.2 Clinical Trial Accrual

Standard 3.2 Two percent (2%) or more of eligible breast cancer patients are accrued to treatment-related breast cancer clinical trials and/or research protocols in regional centers. The standard is encouraged but not required for community centers.

Clinical research advances science and ensures that patient care approaches the highest possible level of quality.

Facilities must accrue patients to breast cancer-related clinical research at the minimum percentage rate of 2%. Patients eligible to meet this standard are those patients

- Seen at the center for diagnosis and/or treatment and placed on a clinical trial through the facility.
- Seen at the center for diagnosis and/or treatment and placed on a trial through the office of a staff physician.
- Seen at the center for diagnosis and/or treatment and placed on a trial through another facility.
- Seen at the center for any reason and placed on a prevention or breast cancer control trial.

Basic science, clinical, and prevention and control research is generally conducted in cancer centers supported by grants from the National Cancer Institute (NCI) or in academic health centers. Research in community hospitals typically involves therapeutic and nontherapeutic trials.

Treatment-related clinical trial groups include, but are not limited to, the following:

- NCI-sponsored programs such as the Community Clinical Oncology Program (CCOP).
- Cooperative trial groups such as the American College of Surgeons Oncology Group (ACOSOG).
- University-related research.
- Pharmaceutical company research.
- Locally developed, peer-reviewed studies.

Cancer control research studies include, but are not limited to, the following:

- Primary prevention.
- Early Detection.
- Quality of life.
- Economics of care.

Centers participating in clinical research show that an independent review mechanism consistent with national standards is in place and used. Research projects involving participation by human subjects must be approved by an internal or external institutional review board (IRB). Patients participating in clinical trials must give their informed consent.

A study coordinator, data manager, or other clinical research professional is available to assist in enrolling patients, monitoring patient accrual, and identifying and providing information and/or education about new trials.

Patient accrual is monitored, and the results are documented.

Information about breast cancer clinical trials is available through:

- National Cancer Institute (NCI)

Documentation:

The center completes the online SAR and indicates the following:

- Complete the table indicating those trial groups of which your center is a member and/or accrues patients, and the number of patients accrued for the last complete year.

The surveyor will discuss the clinical trials program with the breast cancer team, at the time of survey.

32.7 Community Outreach

Purpose: The standards ensure that prevention and early detection opportunities are provided to the community, patients, and their families.

32.7.1 Prevention and Early Detection Programs

Standard 4.1 Each year, two or more breast cancer prevention and/or early detection programs are provided by the center or coordinated with other facilities or local agencies targeted to the community with expectations for follow-up of positive findings.

Prevention programs identify risk factors and use strategies to modify attitudes and behaviors to reduce

the chance of developing breast cancer. Early detection programs apply screening guidelines to detect cancers at an early stage, which improves the likelihood of increased survival and decreased morbidity.

Prevention and early detection programs are offered at scheduled intervals as defined by the BPL. Prevention and early detection programs are provided by the center or are coordinated with other facilities and/or local agencies such as the ACS. Programs provided by the center could include:

- Electronic educational programs/website resources.
- Risk reduction through lifestyle modification or chemoprevention.
- Breast cancer awareness.
- Breast self-examination.
- Breast care education.
- Genetic counseling to high-risk population.
- Screening mammography and clinical examination.

Documentation:

The center completes the online SAR and indicates the following:

- List all programs provided either onsite or coordinated with other facilities or local organizations.
- In the text box, describe the process used to follow-up with patients found to have positive findings during breast cancer prevention and/or early detection programs.

The surveyor will review documentation of the annual prevention and/or early detection programs, and discuss the community outreach program, at the time of survey.

32.8 Professional Education

Purpose: The standard promotes increased knowledge of breast cancer program staff through participation in local, regional, or national educational activities.

32.8.1 Breast Program Staff Education

*Standard 5.1 A*ll professionally certified/credentialed members of the breast center participate in local (including breast cancer conference attendance), state, regional, or national breast-specific educational programs annually.

The breast cancer care team members should include, but is not limited to, the following professionals:

Radiologist	Nursing staff
Pathologist	Patient navigator
Surgeon	Social worker
Medical oncologist	Physical therapist
Radiation oncologist	Plastic/reconstructive surgeon
Genetic counselor	

Educational activities ensure that members of the breast cancer care team possess current knowledge of breast cancer prevention, early detection, diagnosis, treatment, and follow-up care. All members of the breast cancer care team participate in ongoing breast cancer-related education at the local, state, regional, or national level annually. Educational activities include, but are not limited to, the following:

- A breast cancer-related lecture.
- A local, state, regional, or national breast cancer meeting or workshop.
- A breast cancer-related video conference.
- A breast cancer-related web-based training module or webconference.
- Journal CME.

CME is recommended, and documentation of participation is required.

Documentation:

The center completes the on-line SAR and indicates the following:

- Complete the table describing the educational program(s) attended by the professionally certified/credentialed members of the breast center on an annual basis.

The surveyor will discuss the breast center staff education, at the time of survey.

32.9 Quality Improvement

Purpose: The standard ensures that breast services, care, and patient outcomes are evaluated and improved continuously.

32.9.1 Quality and Outcomes

Standard 6.1 Each year, the BPL conducts or participates in two or more studies that measure quality and/or outcomes and the findings are communicated to the breast center staff or interdisciplinary conference.

The annual evaluation of services and care provide a baseline to measure quality and an opportunity to correct or enhance patient outcomes. Quality improvement is a multidisciplinary effort and must include support and representation from all clinical, administrative, and patient perspectives. Successful participation in quality improvement programs/initiatives from other breast-related health care organizations can meet some, or all, of these quality and outcomes requirement to be an approved breast center. The following are examples of recommended quality improvement programs/initiatives:

- The ASBS Mastery of Breast Surgery Program
- The National Outcomes and Analysis Database Project of the ASBS – www.breastsurgeons.org [5]
- The Committee on Quality and Safety of the ASBS establishes standards for breast surgery quality – www.breastsurgeons.org [5]
- Participation in the National Consortium of Breast Centers' Quality Initiatives benchmarks available for performance comparison – www.breastcare.org [6]
- The NQFs breast cancer measures – www.qualityforum.org [7]
- The American College of Surgeons, Commission on Cancer, National Cancer Data Base breast cancer benchmarks – www.facs.org/cancer [8]

The ASBS with the American College of Surgeons is developing an education-based quality improvement program for surgeons delivering breast care. This voluntary quality initiative will be based on prior and ongoing educational activity, participation in meeting defined standards, and contributing to data collection for certain defined standards.

The relationship between the ASBSs Mastery of Breast Surgery Program and the NAPBC will be defined when the development of the Mastery of Breast Surgery Program is complete.

The breast center leadership focuses on the quality-related issues relevant to the center and local patient population. Studies of quality may include structure, process, and outcome variables, and may be selected at the discretion of the breast center leadership. Examples include, but are not limited to, the following domains:

Domain	Descriptor
Structure	Development of systems that monitor delivery of breast care. For example, development of a recording system whereby the time from positive biopsy to initial therapeutic intervention is systematically recorded on all patients
Process	Evaluation and interpretation of breast care delivery data for the purposes of quality assessment and improvement. For example, study of proportion of patients undergoing recommended breast-conservative surgery, sentinel node biopsy and/or adjuvant therapy
Outcomes	Concrete disease-related outcome variables such as breast cancer-specific mortality, local recurrence rates and/or treatment-related morbidity and mortality

Quality improvement studies should include, but are not limited to:

- Process.
- Scope of the issue.
- Reason why issue needs to be addressed.
- Available data define the issue, opportunity, or area requiring investigation or improvement.
- Factors contributing to the issue.
- Initiatives/interventions needed for resolution.

A summary of the analysis of data, findings, and recommendations of each study, as well as the process to implement changes in program activities, is documented and communicated to the breast center staff. The documentation includes the following:

- The study topic.
- A summary of the findings.
- The actions recommended.
- Follow-up steps to monitor the actions implemented.

Documentation:

The center completes the on-line SAR and indicates the following:

- Complete the table documenting the type of studies conducted and the methods utilized to communicate and discuss results with the breast center staff.
- Provide documentation of participation in a national quality improvement initiative related to breast cancer care, and the methods utilized to communicate and discuss results with the breast center staff.

The surveyor will discuss the quality improvement initiatives, at the time of survey.

32.10 Survey Process

To facilitate a thorough and accurate evaluation of the breast center, the center must complete or update an online SAR. Each year, the facility is notified of the areas of the SAR requiring annual updates.

In addition to capturing information about breast center activity, the individuals responsible for completing portions of the SAR will perform a self-assessment and rate compliance with each standard using the Breast Center Standards Rating System.

The survey is conducted by one trained surveyor with a major interest in diseases of the breast. The survey requires approximately 5–6 h. Approximately 1 h is allotted for the surveyor to speak/meet with the breast center leadership and key staff responsible for various aspects of the program to assess compliance with each standard through review of the survey application. Two hours are allotted for the surveyor to review at least 20 charts containing information on patients diagnosed with breast cancer for AJCC staging and compliance with the CAP protocol for breast pathology reports, and ten charts containing information for patients diagnosed with benign breast disease. One hour is spent for the breast conference, with the remaining time allotted to touring the center and a summation with the breast center team.

32.11 Accreditation Awards

Accreditation decisions are based on consensus rating from the surveyor, NAPBC staff and Center Criteria and Approvals Process Committee. Table 32.4 describes the accreditation award matrix.

Appeals to the accreditation award are reviewed by the Center Criteria and Approvals Process Committee.

32.12 European Accreditation of Breast Units

Blamey outlined the requirements of a specialist breast unit in 2000 and described the most recent progress in the European Society of Mastology (EUSOMA) in 2006 [9]. Several European countries have embraced the guidelines and strongly support the concept of breast center accreditation. This is a voluntary program but one which is needed in order for patients and referring doctors to recognize centers meeting specified standards for quality evaluation and management.

A multidisciplinary Accreditation Board is responsible for final decisions on accreditation awards.

Seven basic criteria are required for accreditation as a breast unit.

- A single integrated unit
- Sufficient cases to allow effective working and continuing expertise
- Care by breast specialists in all the required disciplines
- Working in multidisciplinary fashion in all areas
- Providing all the services necessary – from genetics and prevention, through the treatment of the primary tumor, to care of advanced disease and palliation
- Patient support
- Data collection and audit

An important component of the EUSOMA accreditation is data collection to fulfill audit requirements. Initial accreditation is awarded to qualified units whereas full accreditation becomes available when a center has 5 years of appropriate data.

The survey process involves a maximum of four multidisciplinary individuals focusing on imaging, standards, breast pathology, patient support and care rendered by surgery, medical oncology and radiation oncology.

The multidisciplinary meeting is considered one of the important requirements, which is monitored during the survey. There are many similarities between NAPBC and EUSOMA as outlined in Table 32.5.

32.13 Benefits of being a NAPBC Accredited Center

Accreditation by the NAPBC offers many notable benefits that will enhance a breast center and its quality of patient care. NAPBC-accredited programs offer the following:

Table 32.4 Accreditation award matrix

	Three-year/full accreditation	Three-year/provisional accreditation	Accreditation deferred
Thirty-one standards	Ninety percent or more of eligible standards are met. Full accreditation awarded with recommendation for improvement in any deficient standards within a 12-month period	Less than 90% of eligible standards are met. Full accreditation withheld until correction of deficient standards is documented within a 12-month period	Less than 75% of eligible standards are met. Full accreditation deferred until correction of deficient standards and resurvey in 12 months

- A model for organizing and managing a breast center to ensure multidisciplinary, integrated, and comprehensive breast care services.
- Self-assessment of breast program performance based on recognized standards.
- Recognition by national healthcare organizations as having established performance measures for high-quality breast healthcare.
- Free marketing and national public exposure.
- Participation in a National Breast Cancer Registry – a nationwide breast cancer database for breast centers and hospitals in the United States.
- Access to breast center comparison benchmark reports containing national aggregate data and individual facility data to assess patterns of care and outcomes relative to national norms.

From a patient's perspective, obtaining care at a NAPBC-accredited center ensures that one will receive the following:

- Quality care close to home.
- Comprehensive care offering a range of state-of-the-art services and equipment.
- A multidisciplinary, team approach to coordinate the best care and treatment options available.
- Access to breast cancer-related information, education, and support.
- Breast cancer data collection on quality indicators for all subspecialties involved in breast cancer diagnosis and treatment.
- Ongoing monitoring and improvements in care.
- Information about clinical trials and new treatment options.

Table 32.5 Comparison of NAPBC and EUSOMA

	NAPBC	EUSOMA
Specific standards	Yes	Yes
Multidisciplinary executive committee	Yes	Yes
Initial accreditation	No	Yes
Center with or without walls	Yes	Yes
Online application	Yes	Yes
Number of surveyors	One	Four-maximum
Length of survey	5 h	5 h
Survey periodicity	3 years	5 years
Multidisciplinary breast conference	Yes	Yes

References

1. American Cancer Society Cancer Facts and Figures 2007, Atlanta: American Cancer Society; 2007
2. Silverstein MJ (2003) The Van Nuys breast center. The first free-standing multidisciplinary breast center. Surg Oncol Clin North Am. 9(2):159–76
3. AJCC. Cancer Staging Manual Sixth Edition. Springer, New York; 2002
4. College of American Pathologists Reporting on Cancer Specimens, Northfield, IL 2005; 16
5. http://www.breastsurgeons.org/
6. http://www.breastcare.org/
7. http://www.qualityforum.org/
8. http://www.facs.org/cancer/
9. Blamey RW, Cataliotti L (2006) EUSOMA accreditation of breast units. Eur J Cancer. 42:1331–7

Medicolegal Pitfalls in Breast Cancer Diagnosis and Management

33

Janet R. Osuch and Vence L. Bonham

33.1 Introduction

Breast cancer is the most common cancer in women [1], and failure to diagnose it in a timely manner has been documented as the most common reason for a successful medical malpractice claim [2, 3]. Knowledge of the common allegations made when a malpractice suit is filed for failure to diagnose breast cancer can provide insight into the risk management of a physician's practice and simultaneously minimize errors in patient care. Many physicians are unaware of the legal process involved in a malpractice suit until it affects them or a close colleague. At this point, an objective perspective is often impossible. Nonetheless, it is inevitable that many, if not most, physicians will find themselves a defendant in a medical malpractice suit at some point in their career for a less-than-perfect patient outcome, whether medical negligence has occurred or not. This chapter is intended to outline the common allegations of misdiagnosis or mismanagement of breast cancer, to review the process of legal proceedings common to a medical malpractice suit, to review the issues likely to arise in the defense of a case, and to provide recommendations on the steps to take when facing malpractice litigation.

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33.1.1 Magnitude of the Problem

The Physician's Insurance Association of America (PIAA) has published three reports from their Data Sharing Project, summarizing the indemnity claims history of the PIAA between January 1985 and June 2008 [2–4]. These reports provide the best overview of the magnitude of the malpractice problem as the data source was national (and international) rather than regional or local, and by 2001, PIAA provided medical malpractice insurance to over 100,000 physicians. During this time, over 185,400 claims for medical malpractice were filed and 52,200 closed [3]. Cases related to breast cancer have represented the most common condition resulting in a successful medical malpractice suit, second only to neurologically impaired newborns with respect to indemnity dollars paid [3]. The 1995 report reviewed the three most common diagnostic or treatment errors resulting in successful claims by specialty: the rank-order for (1) General Surgery, was breast cancer, appendicitis, and spinal fracture; (2) Radiology, was breast cancer, lung cancer, and spinal fracture; (3) Obstetrics and Gynecology, was breast cancer, ectopic pregnancy, and pregnancy; (4) Family Practice, was myocardial infarct, breast cancer, and appendicitis, and (5) Internal Medicine, was lung cancer, myocardial infarct, and breast cancer [5]. This list provides insight into medical malpractice claims in general, and into reasons why breast cancer-related allegations are so common. The conditions listed are notorious for being difficult to diagnose, lacking definitive or immediate diagnostic criteria in many cases, and/or result in a devastating impact on the life of the person affected by the condition. A 2003 report by the American Academy of Family Physicians cited failure

I. Jatoi, M. Kaufmann (eds.), *Management of Breast Diseases*,
DOI: 10.1007/978-3-540-69743-5_33, © Springer-Verlag Berlin Heidelberg 2010

to diagnose as the top reason family physicians are sued, with breast cancer being the most common disease in this allegation [6].

It should not be surprising that radiologists, surgeons and obstetricians/gynecologists have breast cancer diagnostic failures as number one in rank-order frequency for claims paid. The sheer numbers of women undergoing screening mammography for breast cancer, coupled with the prevalence of the disease, would predict for a high frequency of medical malpractice suits among radiologists. Because general surgeons are most responsible for the management of symptomatic breast problems, the number-one rank order for this discipline can also intuitively be explained on the basis of prevalence. However, prevalence alone does not account for the frequency of allegations for failure to diagnose breast cancer. Kern, in a nationwide study of 338 cases of missed diagnosis of cancer, demonstrated that the frequency of allegations for failure to diagnose breast cancer, as compared with allegations for other cancers, is twice as high as ought to exist when considering the proportion of breast cancer cases in relation to all cancer cases in the general population [7]. Part of the explanation for this relates to the mistaken expectation of the public that if a diagnosis of breast cancer is made in a timely fashion, that cure is guaranteed, and if it is not, then survival has been compromised. In addition, all three reports from the PIAA demonstrated that women most likely to sue are much younger than the average woman who is diagnosed with breast cancer, and are more likely to have a negative or equivocal mammogram finding [2–4]. This latter fact accounts for obstetricians/gynecologists, who see a large number of young women in their practices, having breast cancer diagnostic failures as number one in rank-order frequency for claims paid for their discipline.

33.1.2 Common Allegations in the Diagnosis or Management of Breast Cancer

Although physicians are not immune from treatment-related allegations, the vast majority of malpractice claims related to breast cancer allege a failure in the diagnosis rather than a treatment-related problem. However, successful suits have been filed when physicians fail to provide "reasonable skill and care" in the administration of drugs, radiation therapy, or surgery for breast cancer treatment, just as with any medical condition. In addition, litigation for claims of unnecessary surgery is reported, especially if nonsurgical treatment alternatives were not disclosed [8]. There are many states that have laws that require physicians to provide patients with a standardized written summary of their treatment options if breast cancer is diagnosed, and some specify penalties for noncompliance with the legislation [8]. By example in this latter instance, a patient might sue her physician for lack of informed consent if she did not receive the standardized materials required in her state, and if she had a mastectomy for treatment and later learned that she may have been a candidate for breast-preservation therapy. In this scenario, and if the physician believed that the patient had received full disclosure, the standardized brochure could become a strong part of the physician's defense, if it had been provided. On the other hand, a patient who was eligible for and chose breast-preservation therapy would be far less likely to succeed in a claim for lack of informed consent, even if the standardized written materials were not provided to her, unless she could claim and prove harm related to her treatment [8]. The legal principles behind these scenarios will be discussed in a later section.

The best source citing common allegations related to failure to diagnose breast cancer come from the PIAA Study cited earlier. The 2002 study, which documented paid claims from January 1995 through May of 2001, reported on 450 cases from 25 member companies [3]. The most frequent diagnostic error in the 2002 study was the misreading of a mammogram (37.8% as opposed to 22.7% of claims in the 1995 study). This allegation also accounted for the highest amount of indemnity, over $57 million. This is in contrast to prior reports, which alleged failure to be impressed with physical findings as the most common error, (35.5% as opposed to 28.7% in the 2002 study). Negative mammogram reports, failure to refer to a specialist, and communication errors among providers ranked third, fourth and fifth in the frequency of errors in the 2002 study. These physician-related errors resulted in an average delay in diagnosis of 16.3 months, compared to 12.7 and 14 months in the 1990 and 1995 studies, respectively [3].

Patient delays also occur. Even in recent studies, the average patient delay from symptom to medical consultation is about 3 months [9, 10]. In the 2002 PIAA

Study, no patient delay was documented in 67.3% of cases. There were a variety of reasons listed for patient delays that did occur, including procrastination, failure to keep follow-up appointments, or other health problems. Many physicians are surprised to learn that once a patient-physician relationship is established, the failure of the patient to keep appointments does not excuse their responsibility in an allegation of diagnostic delay. This issue relates to the topic of duty, the first of four components of a medical malpractice case.

33.2 Elements of Medical Malpractice

Medical malpractice law has been viewed by some as convoluted in its rules and regulations [11]. This view reflects the fact that the comprehension of the topic by those not trained in law is, at best, challenging. One legal scholar describes medical malpractice law as follows: "The debate, in its most caricatured (and perhaps most common) form, pits the champions of predictability, rationality and affordable medical care against emotional, biased juries and injured plaintiffs" [11]. Nonetheless, understanding the current elements of medical malpractice is necessary to those that it may affect. Although some physicians may believe that they are immune from malpractice litigation because they practice exemplary medicine, this is an incorrect assumption. Any physician involved in the practice of medicine may find herself or himself a defendant in a medical malpractice lawsuit, and becoming knowledgeable about the litigation process before such an occurance will serve him/her better than denial.

The liability of physicians is governed by general negligence principles. Malpractice is usually defined as unskillful practice resulting in injury to the patient, and failure to exercise the required degree of care, skill, and diligence under the circumstances [12]. To have a claim of negligence, four elements must be present: (1) Duty; (2) Breach of the Standard of Care; (3) Causation; and (4) Damages.

Duty. A duty in negligence cases may be defined as a legal obligation, statutory or common-law, to conform to a particular standard of conduct or standard of care toward another [13]. A patient–physician relationship establishes a duty for the physician to provide care in compliance with the standard of care for a reasonable physician of that specialty. A patient–physician relationship exists when a doctor renders professional services to a person who has contracted for such services [14], and this is both a professional and a legal obligation. A duty does not exist to provide care if there is no physician–patient relationship. The plaintiff (patient) must prove that a duty by the physician existed [14–16]. The existence of the relationship is a question of fact to be determined by a jury, but the courts have recognized that the acceptance or undertaking of treatment of the patient by a physician creates the physician-patient relationship [17]. The issue of duty is not an area of dispute in the majority of medical malpractice cases.

Standard of Care. Once the patient–physician relationship is established, the physician has a duty to exercise the same degree of care and skill in managing the patient as would be exercised by a competent physician in a similar situation. Courts refer to the degree of care and skill that should be exercised as the "standard of care" [16]. To establish a breach of duty, also termed negligence, the patient must prove that the physician failed to comply with the standard of care.

Proximate Cause. An essential element of the patient's medical malpractice action is that there be causal connection between the act or omission of the doctor and the harm that the patient has suffered. This connection is usually handled by the courts by what is called "proximate cause" or "legal cause" [13]. The test for a direct causal connection or cause-in-fact between the patient's injury and the doctor's negligence is usually described by the courts in terms of the "but for" test. The patient must prove that "but for" the doctor's act(s) or omission(s), the patient's injuries would not have occurred. Under the "but for" test, a patient cannot establish proximate cause unless an improved outcome (greater than 50%) was more likely than not, absent the physician's actions. This test of causation has been problematic in delay-of-diagnosis cases, and many states have established different causation tests [12, 18, 19]. Alternatives include the substantial factor test and the loss of chance doctrine. These will be discussed in more detail in an upcoming section of this chapter.

Damages. If a plaintiff can prove that a duty existed and that the duty was breached and was the cause of an injury or harm, then a defendant will be liable for compensatory damages. There are two types of compensatory damages – special and general damages. Actual or special damages represent reimbursement for actual

economic payment for medical care and related expenses, incurred losses and disability [20, 21]. General noneconomic damages are losses due to pain, suffering, inconvenience, physical impairment, or physical disfigurement that cannot be measured exactly in monetary terms [21]. As part of malpractice tort reform, some states have put a cap on noneconomic losses. Each state has developed its own statutory basis for limiting damages.

33.2.1 Malpractice Issues Related to Breast Cancer

Standard of Care: Legal and Clinical Issues. In medical malpractice cases, physicians are held to an objective standard of care specific to the case in question. It has been recognized by the courts that perfection is neither realistic nor expected in the practice of medicine, but it has been simultaneously acknowledged that it is not enough for physicians to do their best if their conduct does not rise to the level of care required of similar members of the profession, practicing under circumstances similar to the case in question [22].

The standard of care to which a physician is held is a national standard in most state courts. The court has established that "The duty of care… takes two forms: (a) a duty to render a quality of care consonant with the level of medical and practical knowledge the physician may reasonably be expected to possess and the medical judgment he may be expected to exercise, and (b) a duty based upon the adept use of such medical facilities, services, equipment and options as are reasonably available" [23].

Rarely, a court will impose its own value judgment on physicians; an example is the case of *Helling vs. Carey*. The trial court ruled that compliance with customary practice within the medical profession is not conclusive evidence that a physician was not negligent [24]. It is unusual for a court to expressly disagree with the standard of care that prevails among physicians. *Helling vs. Carey* is important because it is not the rule but an aberration. Most courts reject the *Helling* court approach of establishing the standard of care as a matter of law. Typically, the standard of care is not set by the judge or the jury, but by the medical profession [11, 25]. This is done through expert witness testimony.

In recent years, one of the tools used by expert witnesses includes the citing of clinical practice guidelines published by professional organizations. Medical and legal commentators have been debating the role of clinical practice guidelines in the establishment of the standard of care since guidelines became widely used. Since clinical practice guidelines are not written to include the circumstances of individual clinical scenarios, expert witness testimony is necessary to establish the standard of care, as is reflected in the following statement from a health law treatise:

> American physicians and specialty groups have expended substantial efforts on standard settings in recent years, specifying treatments for particular diseases. … Such guidelines provide a particularized source of standards against which to judge the conduct of the defendant physician and their production by national medical specialty societies and the government will be influential. A widely accepted clinical standard may be presumptive evidence of due care, but expert testimony will still be required to introduce the standard and establish its sources and its relevancy [12]

It is thought by some commentators that the use of clinical guidelines as practice standards may benefit physicians by providing definition as to the standard of care, and thus limit lawsuits for bad outcomes. Others believe that using clinical guidelines to establish the standard of care will restrict the practice of medicine. It is likely that in cases of medical malpractice, clinical guidelines will be taken into consideration as expert witnesses describe the standard of care. The standard of care changes with the individual circumstances of a case, advances in medicine over time and changes in societal expectations.

Medical malpractice lawsuits alleging a delay in the diagnosis of breast cancer often become a battle of the experts regarding the definition of the standard of care. Expert witnesses are hired by opposing sides of a case and are often at odds with one another regarding the conduct of a physician, and whether that conduct meets the standard of care for an individual case. As a consequence, an "expert witness" serves a far more important function than what one usually thinks of when one thinks of the word "witness." Not simply an observer of events (as in a marriage), or as one who substantiates the truth (as in a criminal trial), the expert witness establishes the standard of care for the court. Because the expert witness helps establish the standard of care for a given case, her or his testimony has a profound influence on its outcome. Expert witnesses have a professional responsibility to provide objective and unbiased opinions based on medical fact and judgment

rendered as a result of meticulous preparation of a case. Whether an individual expert is hired by the plaintiff's or the defendant's attorney should not matter, because the testimony of that expert should be the same for the circumstances of a given case. One of the ways that a defendant physician may have input into her or his case of medical malpractice involves the careful consideration of which expert witnesses should be used to assist in defense of the case. Those capable of giving ethical, objective, and credible testimony will be of greatest advantage to the defendant physician. This will be considered in more detail later.

Proximate Cause: Legal Issues. Establishing causation is a primary focus in a breast cancer medical malpractice suit. Historically, the "but for" definition has been applied to establish causation and has already been discussed. An alternative definition established by some state courts is called the substantial factor test, which allows recovery when the breach of the standard of care is a substantial factor in producing injury, even if the plaintiff's chances at a better outcome in the absence of the negligent action was less than 50%. This definition was first applied by the New Jersey Supreme Court in a delay in the diagnosis of breast cancer case [26]. This case has been recognized for expanding the causation rules for breast cancer diagnostic delay cases [27].

Another alternative definition of causation is referred to as the loss of chance doctrine. This represents a legal doctrine to establish causation when the plaintiff cannot prove that, but for the doctor's actions or omissions, the patient's injury (decrease in chance of survival or death) would not have occurred. The doctrine was specifically designed to address problems arising in medical malpractice cases, and its use has been limited almost exclusively to such cases [28]. When a physician is negligent in diagnosing a disease, and the resulting delay reduces the plaintiff's chances of survival (even though the chance of survival was below 50% before the missed diagnosis), many states have adopted a "loss of a chance" doctrine. The rationale for adaptation of this principle was discussed in a law review article as follows: "The loss of chance doctrine developed partly as an alternative…in proving causation in medical malpractice cases. Whereas … a plaintiff would have to prove that failure to recover was more likely than not caused by the defendant's negligence, under the loss of chance doctrine, the plaintiff would not have to prove causation by a preponderance of the evidence. The doctrine also was the courts' response to the inherent unfairness in the situation of a patient with both underlying injuries and tort injuries [29]." In a typical "lost chance" case, a patient is initially at risk for some injury or perhaps death, through no fault of the defendant. Some negligent act by the defendant physician, however, causes the plaintiff to incur an increase in risk for that same injury, and the plaintiff in fact, subsequently, suffered the injury. The most difficult cases are those in which the plaintiff had a very high initial risk of injury (over 50%), and experts are unable to testify with a reasonable degree of medical certainty that the defendant's negligence (as opposed to the preexisting condition) caused the plaintiff's injury [30]. This doctrine is particularly important in delay in diagnosis of breast cancer cases.

Regardless of the legal guidelines adapted by the state regarding causation, the expert witness hired to testify regarding proximate cause will be asked to predict the survival of the patient from the disease, both at the time when it could have been diagnosed and the time when it was diagnosed. Predictions of survival will then be estimated based on circumstances of no diagnostic delay and compared with those of the case under consideration. The heterogeneous behavior of breast cancer makes these estimates of probability less definitive than the simplistic view of breast cancer biology that is often taken. In this regard, the public health message encouraging women to obtain yearly breast cancer screening correctly communicates that a diagnosis in an asymptomatic phase of the disease can result in improved survival. That mammography in asymptomatic women reduces mortality from breast cancer is often erroneously equated with the notion that a delayed diagnosis will automatically result in increased mortality. Survival from breast cancer is a complicated issue, and definitive predictions regarding the disease course in an individual patient are very difficult. It is even more difficult to convey these concepts to those (e.g., juries) that must weigh the evidence to determine the legal issue of proximate cause. Because of this, the defense of a case will be much easier if it can be proven that the standard of care was not violated. However, it is important to understand the issues that will be raised by the expert witnesses surrounding the issue of proximate cause.

Proximate Cause: Clinical Issues. Proximate cause, as discussed, refers to the burden of proof that the

plaintiff must establish to prove that she was harmed in a direct way by the defendant's actions. In other words, it is not enough that the plaintiff's attorney proves that the defendant physician violated the standard of care, but it must also be proved that the violation resulted in harm to the patient. For example, assume that a 1 cm mammographic abnormality is followed for a year, and biopsied with free margins when it reaches 1.2 cm. Histologically, the lesion is composed entirely of ductal-carcinoma-in-situ. It is possible that a patient who has experienced such a delay may contemplate suit, alleging, perhaps, that the biopsy should have been done in a more timely fashion. Even if the plaintiff was able to successfully establish that allegation as true, it would be extremely difficult to prove that any harm had occurred directly linked to the diagnosis of a disease that has no ability to metastasize and for which she would have the full complement of treatment options available. Under these circumstances, the case would have likely been dismissed.

The establishment of proximate cause is dependent on the biology of the disease in question and is typically linked to treatment and survival. For some diseases, this might be relatively straight-forward, but such is not the case for breast cancer. This has to do with the complexity of treatment options available for breast cancer, as well as the heterogeneous biology of the disease. In the past, treatment arguments often centered on the issue of whether or not a patient would have needed chemotherapy if her diagnosis would have been made in a more timely manner. This is less often an issue currently, since it has become standard for most women with invasive disease of 1 cm in size or more to receive some form of systemic therapy [31]. Arguments are often made, however, about the length, cost, and the side effects of the drugs deemed necessary to treat the disease at the time that it was diagnosed, especially if the delayed diagnosis resulted in a staging change.

Proximate cause arguments may take local treatment forms if it has been necessary for a patient to have a mastectomy rather than breast preservation for treatment, and that necessity can be proved to be linked to a delayed diagnosis, as has already been discussed. The same can be said for the need for radiation treatment following a mastectomy. Regardless of treatment issues related to proximate cause, however, survival predictions are almost always considered in cases alleging a delay in diagnosis. These predictions become critical in the calculation of damages, should the prior components of the allegations be proved.

Prognosis and Survival. The question that the court will be attempting to answer during proximate cause arguments centers on the prediction of an individual patient's prognosis and survival. There is no prognostic measure short of clinical evidence of metastatic disease that will predict for this with certainty. Instead, the expert witness will rely on a battery of prognostic indicators to predict the biological behavior of the tumor in a given case. The most common of these include time between symptom onset and diagnosis, tumor size at symptom onset and at diagnosis, axillary lymph node status and number of lymph nodes involved, tumor stage according to the TNM system of classification, tumor grade, nuclear grade, estrogen and progesterone receptor status and HER-2/neu oncogenes expression [32]. Not all of these markers are independent of one another, and not all carry the same level of evidence in terms of their predictive ability for survival from breast cancer. Many other markers are available with even less evidence of usefulness [33]. Each of these factors will, however, help the expert estimate the biological behavior of the individual tumor and the likelihood of survival. Knowledge of these factors, as well as a thorough understanding of the complexity of the natural history of breast cancer and the biologic heterogeneity of its behavior, is critical to the credible testimony of a given expert. Adjuvant! Online [34] is a decision-making tool that is available to assist physicians with estimates of ten-year mortality from breast cancer (and all causes), and the effect that treatment may have on mortality rates. Although it does not consider all of the prognostic factors, it does include some of those most important, including patient age, comorbidity status, tumor size in centimeters (0.1–1.0, 1.1–2.0, 2.1–3.0, 3.1–5.0, >5.0), number of lymph nodes involved (0, 1–3, 4–9, >9), estrogen receptor status, and tumor grade. It is an evidence-based program that uses the San Antonio Data Base and draws on information from the SEER data base, overviews of clinical trials, individual clinical trial results, and the literature in general [35]. Other tools are in development and will become available in the future as well.

Proximate Cause, Screening, and the "Early Diagnosis" of Breast Cancer. It is important for the expert witness to have a clear concept of the strengths and limitations of breast cancer screening as it relates

to the concept of the early diagnosis of breast cancer. Prior to mammography, the diagnosis depended on physical signs such as a lump in the breast or nipple discharge. This period is referred to as the "clinical phase" of the disease. All diseases also have a period during which the biological processes causing the eventual symptoms are present but not clinically apparent. This period is referred to as the "latent phase." Some diseases have an extremely short latent phase, notably bacterial infectious diseases. In contrast, the latent period for most cancers, including breast cancer, evolves over years of time. Diseases with a long latent phase are possible candidates for screening tests, whose goal is to diagnose the disease during the asymptomatic, or preclinical phase. The preclinical phase is that portion of the latent phase during which the disease is detectable using the screening test. One of the most important criteria in the decision to use a test to detect a disease in an asymptomatic population is the ability to intervene in the natural history of the disease and effect outcome by reducing mortality [36] The results of multiple, randomized controlled clinical trials evaluating screening mammography have demonstrated an average 26% mortality reduction in women aged 40 and above [37, 38]. These facts are often used in medical malpractice cases to establish that an earlier diagnosis would have resulted in a better prognosis. What the logic of this argument fails to recognize is that the inverse is also true. A 25% reduction in mortality in screened women by mammography also implies that in 75% of the screened population destined to die from breast cancer, mammography makes no difference in outcome. What accounts for this? To answer that question, the concepts of angiogenesis, metastasis and "biological predeterminism" must be introduced.

Angiogenesis and Biological Predeterminism. Breast cancer mortality is directly linked to metastasis, or the spread of the cancer to distant organ sites. Just as with any cancer, not all breast cancer cases possess the biological ability to metastasize [39]. In fact, a complex, ten-step process is involved. This process depends upon (1) the proliferation of cancer cells following neoplastic transformation, which depends on the presence of growth factors; (2) the process of angiogenesis, that is, the formation of new blood vessels, to support the growth of a tumor mass beyond 1–2 mm; (3) invasion of tumor cells into the stroma of the organ of origin, and subsequent vascular invasion; (4) embolization of tumor cells from the vasculature to larger vessels; (5) survival of tumor cells in the circulation; (6) adherence of tumor cells in the capillary beds of distant organs; (7) extravasation of tumor cells into the parenchyma of distant organs; (8) proliferation of tumor cells in the parenchyma of distant organs; (9) evasion of immune mechanisms of the host at the primary and distant sites; (10) neovasculization of the tumor bed at the distant sites [39]. This complicated process depends upon the proper microenvironment at each step. If the cascade is interrupted at any one step, metastasis cannot be established.

Whether or not a tumor possesses the necessary biological components to establish the metastatic process is not obvious at the point of diagnosis of most cases of breast cancer, and metastasis can occur even 40 years after the initial treatment [40]. This makes the establishment of proximate cause problematic. Conversely, biologically, metastasis can occur long before it is clinically detectable. Tumor neovascularization, which is necessary for tumor growth and metastatic potential, has been shown to be established when a tumor is still in-situ [41], and well before our current detection capabilities. These principles relate directly to the concept of biological predeterminism, which were originally developed by MacDonald. In a study in 1951, he observed that 56% of breast tumors that were 1 cm or less in size had already spread to axillary lymph nodes, whereas 23% of tumors that were 5 cm or more had not done so [42]. This paradox caused him to question the generally held belief that tumor size and lymph node status were a cause-and-effect phenomenon. He postulated that many tumors had already developed the ability to metastasize before their primary diagnosis. This concept was expanded upon by Heuser et al. and applied to the Breast Cancer Detection Demonstration Project data, a study conducted in the 1970s and focused on breast cancer screening [43]. The authors concluded that some of the cancers diagnosed in the study grew extremely slowly and essentially never would have metastasized, whereas others grew so fast that no matter what intervention was applied, death would have been the eventual outcome. In other words, metastasis would have been biologically impossible even in the clinical phase of the disease in the former case, and biologically established even before the preclinical phase of the disease in the latter. In either case, screening mammography would have made no difference on the disease outcome. The

25% mortality reduction with the use of screening mammography is a laudable accomplishment in breast cancer control, but the large number of women who undergo the screening test and for whom the test makes no difference in outcome points to the need for more efficacious detection tools for breast cancer. The studies related to screening have helped define the biology of the disease, and have underscored the concept that the biological behavior of breast cancer is complicated and difficult to predict with certainty [44].

Diagnostic Delay, Survival, and Symptomatic Breast Cancer. Although allegations of failure to screen occur, allegations of failure to diagnose breast cancer in a timely manner occur more often in the setting of an abnormal mammogram with or without a palpable mass [3]. The concept that a diagnostic delay automatically predicts for a decrease in an individual woman's life expectancy has been debated for years. Hundreds of studies have been done with conflicting results. An excellent discussion of the individual studies and their conclusions can be found in a textbook chapter written by Kern [45]. Two large studies of the topic, both from the United Kingdom but conducted in quite different ways, were published in the same journal in 1999. These two studies reached opposite conclusions. The first, by Sainsbury et. al., examined over 35,000 patients with breast cancer listed in the Yorkshire Cancer Registry between 1976 and 1995, approximately 4–5% of whom had diagnostic delays of greater than 90 days. The study found no adverse effect of diagnostic delay on survival. In fact, it found that those patients treated within 30 days had a decreased survival compared with the rest of the patients [46]. The other study was a systematic review of 87 observational studies of over 100,000 patients with a diagnostic delay of breast cancer. In the 38 studies and over 50,000 patients in whom a quantitative survival outcomes analysis could be done, the authors found that patients with delays of 3 months or more had a 12% lower 5-year survival as compared with the group with shorter delays, and that those with delays between 3 and 6 months had a 7% lower survival as compared with those with shorter delays [47]. The study found that in this first group, which included studies from 1907–1996, those that included inoperable disease and those that included only operable disease, had similar results. This contrasted with the second group of studies analyzed, (21 studies and over 25,000 patients), all of which were conducted after 1970. This group did not include the actual 5-year survival data. Fourteen studies confirmed that delay in diagnosis of 3 months or more resulted in shorter survival than delays of less than 3 months (both inoperable and operable cases). Seven studies in this group showed no decreased survival, and four of these seven included only operable patients. The third group of studies analyzed in this review included 28 studies of over 20,000 patients; 25 of these analyzed operable disease only. Ten of these 25 studies showed worse survival in those with diagnostic delays, whereas 15 of the 25 showed no impact of delay on survival. The authors also tested a secondary hypothesis that longer delays were associated with more advanced stage. The 13 studies that were analyzed supported the hypothesis, but in three studies that analyzed survival within individual stages, none found a decrease in survival among patients with stage I disease, and one study found an improved survival among those patients with stage III disease. Correcting for lead-time bias, the overall conclusions of the authors is a decrease in survival of about 5% for those with diagnostic delays of 3–6 months. The authors acknowledge that for many patients, a diagnostic delay of 3–6 months will have no impact on survival, but that it will for a minority. This group is theorized to be the group in which the disease progresses to a more advanced stage during the diagnostic delay. This may or may not be the correct conclusion. There is most certainly a group of patients in whom a diagnostic delay is of no consequence because the disease remains without metastatic potential, and a group in whom metastasis is established in the preclinical phase of the disease and therefore cannot be influenced by early detection efforts (it is possible that this is the reason for worse outcomes in the study of Sainsbury et al. in the patients treated promptly). There is a third group of patients with varying biologic behavior, some of whom may be harmed by diagnostic delay. The challenge in a given case is to predict which patients may fall into this category, and knowledgeable and well-intentioned experts for plaintiffs and defendants often disagree over the causation issue. Disagreement aside, the biological complexities of causation arguments are difficult to explain for experts and difficult for a jury to comprehend. It therefore is in a defendant's best interest to avoid breaches in the standard of care whenever possible, and to consider settling cases during which negligence has occurred.

33.3 The Litigation Process

Doctors often misunderstand the litigation process. The process is cumbersome, drawn out and too often not clearly explained to the parties of a lawsuit. For purposes of understanding the legal process, it can be divided into six phases.

1. The Preinitiation of the Lawsuit,
2. The Filing of the Lawsuit,
3. The Discovery Phase,
4. The Motion Practice,
5. Trial, and,
6. Appeal.

Litigation in the United States is a method of using a formal system to resolve disputes. For many individuals, when they think of "litigation," they think of a trial seeking truth. Only 3.8% of the delay in the diagnosis of breast cancer cases reported to the PIAA were decided at a trial by a jury [3]. Most lawsuits are resolved prior to trial, by the claims either being dismissed voluntarily or settled by the parties based upon a judicial decision.

The *prediscovery phase* of litigation is a phase of informal discovery of the facts. In this phase of litigation, the plaintiff and her or his lawyer analyze whether they believe the matter is meritorious, determining whether they believe the elements for a medical malpractice claim have been met. This phase involves obtaining and reviewing the primary medical records in the case, and consulting with a physician expert to determine whether the claim is meritorious. A reference book for lawyers on litigation and trial techniques states: "Discovery may be a good way to learn what a witness will say and may be a good way to hold a witness or a party to a particular version of the facts, but it is a very inefficient way to get information. The suggestion is not to ignore discovery, but rather to stop ignoring informal methods of investigation. … Instead, this discussion is about learning facts in other ways – by doing ... "trolling," or nosing about for essential information. Doing it well is one of the marks of a good trial lawyer" [48]. This process of informal discovery is important to a plaintiff's lawyer to determine whether there is merit to filing a lawsuit. Tort reform laws in many states require a greater level of evidence of violation of the standard of care before a cause of action or lawsuit can be initiated [49].

The *filing* of the lawsuit is the second phase of the litigation process, which begins with serving of the summons and complaint to the defendant. A summons is an instrument used to commence a civil action. The summons may be personally served by a process server or can be mailed to the defendant depending on the laws of an individual state. Many physicians have heard horror stories of sheriffs going to their offices, disrupting the staff and patients to serve a summons. This is not a common occurrence. It is more likely that the summons and complaint will be mailed to the physician, or an individual will, in a professional manner, personally serve the Summons and Complaint.

The Complaint and Answer are called pleadings, which are the formal allegations by the parties of their respective claims and defenses [50]. A complaint is the initial pleading, which sets forth a claim for relief. A complaint shall set forth the allegations that are the basis of the lawsuit and is the plaintiff's general statement of the allegations. Most medical malpractice cases are decided by state courts. The defendant must respond to the allegations in a legal document that is called the Answer. The Answer is a concise response to each allegation made in the complaint. These two pleadings, the complaint and the answer, begin the formal litigation process.

The third phase of litigation is the *discovery phase*. This phase is where the parties discover the facts and the arguments of both parties. Parties may obtain discovery of any relevant, unprivileged information, unless the court limits discovery. This may include information, which is not by itself admissible, as long as it may lead to admissible evidence. Thus the scope of discovery is very broad [51]. This is the stage of the litigation process that often takes the longest period of time and involvement of both parties. Various tools are used for discovery, including interrogatories, depositions, request for documents and request for admission. Interrogatories are a set or series of written questions submitted to an opposing party in a lawsuit as part of discovery [50]. They are an inexpensive method of discovery and are binding on the person giving the answers [51]. A deposition is a discovery device by which one party asks oral questions of the other party or of a witness for the other party. A deposition is recorded testimony taken under oath. The person who is deposed is called the deponent. A court reporter or stenographer is present to record the testimony. A word-for-word transcript is made of the

deposition. This is a common discovery technique. A request for documents is a discovery tool that is often used to obtain production of medical records, office policies, clinical guidelines, contractual arrangements and other documents related to the medical practice and the care provided to the patient. A request for admission is a written statement of facts concerning the case, which is submitted to the opposing party. That party then is required to admit or deny the statement. The statements are treated by the court as having been established and need not be proved at trial [50].

The fourth phase is described as *motion practice*. A motion is a written or oral application to the court for a ruling or order. Various types of motions can be made to the court, including motions to add parties, motions to amend the complaint and motions for summary judgment. A motion for summary judgment is a motion that there is no dispute of fact and based upon the law, the moving party is entitled to prevail as a matter of law. Motions are argued orally before the court. Some motions include written legal arguments by the parties that are presented to the judge, who makes a ruling based upon the law.

The fifth phase is the *trial*, during which a jury makes a determination about whether there was a violation of the standard of care that caused an injury to the patient. A medical malpractice trial is not substantially different from other civil trials. Between 7 and 10% of medical malpractice cases go to trial [52]. The remainder of cases are resolved by the plaintiff voluntarily dismissing the lawsuit, the Court dismissing the case, or the parties reaching an out-of-court settlement.

The sixth phase is the *Appeal Process*. Most medical malpractice cases that go to trial will not be appealed, because after final judgment by the trial court, an appeal can be taken only on questions of law and not on questions of fact. Typically, questions of law relate to the trial judge's rulings and the admissibility of evidence [51].

33.3.1 What are the Common Questions that Lawyers Ask?

Understanding the common questions asked by plaintiff [53] or defense attorneys can help provide insight into good risk management practices. Examples of common questions include:

1. Did you document all complaints made by a patient?
2. Do you have a system to track mammograms and diagnostic reports?
3. Do you have a system to follow-up with your patients?
4. What was the date the problem was discovered and what were all prior and subsequent examination dates?
5. If the problem was a breast mass, what was the size and location of the mass at each visit?
6. Who was present in the examining room on each visit?
7. What was said and done by the doctor and any nurses on each visit?
8. Were breast self-examination instructions given to the patient?
9. Did you document all patient interactions with the office, including telephone calls?
10. Did the time from the first complaint to diagnosis result in increase in the stage of the disease?

33.3.2 Patient-Physician and Physician-Physician Communication

Effective communication between the patient and her physician is an important aspect of the physician-patient relationship. The patient is much more likely to feel satisfied with her care if she feels her complaints have been taken seriously, that she has reason to be concerned, and that the provider shares her concern [16]. Recommendations should be communicated clearly, and reasons should be provided for the recommendations.

Gallagher et al. have shown that patients desire honesty and compassion, as well as an apology from their physician when an error occurs, and that failing to provide patients with desired information could increase the chances of a decision to sue [54]. This viewpoint has been underscored by Stelfox et al., who states "results demonstrate that physicians who received low patient satisfaction ratings were more likely to have complaints from patients and malpractice lawsuits than those with high ratings. Physicians with high rates of complaints from patients were also more likely to have malpractice lawsuits than were physicians with low rates" [55]. These same authors

have shown that the length of routine primary care visits is predictive of malpractice risk and that physicians with shorter routine visits are more likely to have been sued compared to those having longer visits [55].

It is important to recognize communication problems and take affirmative action to improve the patient-physician relationship. When this becomes impossible, referral to a physician who may be able to establish a more positive relationship with the patient is advised. Poor communication, and the failure to establish an effective patient-physician relationship, too often is at the root of a decision to sue a physician [16]. Communication with the patient is necessary in understanding the patient's complaints. In this regard, many women who have breast complaints are not really sure that they feel a mass and are filled with fear and apprehension. Many seek reassurance rather than problem confirmation [16]. This being said, it must be recognized that the majority of women who file suit for failure to diagnose breast cancer discovered the mass themselves [3]. Assisting a patient in determining whether a mass is present or not, initiating appropriate work-up and follow-up of findings and communication of work-up and follow-up plans are the keys to patient satisfaction of care in this setting.

In addition to patient-physician communication, communication between providers is essential to providing quality care and managing risk of liability [16]. Failure for providers to communicate diagnostic results or treatment plans to one another can potentially result in a successful claim alleging a delay in the diagnosis of breast cancer.

In summary, there are a variety of medical errors that can occur in the diagnosis or treatment of breast cancer, but all too commonly, the errors are ones of communication, follow-up, or tracking. Common allegations related to the failure to diagnose breast cancer, and recommended steps in managing risk and improving quality of care, are identified in Table 33.1 [16].

33.3.3 Coping with a Lawsuit

Being sued can have a significant impact on the personal and professional life of a physician. Shapiro et al. have shown that sued physicians find the practice of medicine more challenging, rewarding and satisfying prior to being sued, and that after a claim against them, sued physicians find the practice of medicine more frustrating [56]. They also demonstrated that the more personally involved the physician felt, the stronger the self-reported anger, inner tension, depression and sense of defeat engendered in the physician by the claim [56].

It is important to recognize that the filing of a malpractice lawsuit is not evidence of a failure to provide quality care, nor does it denote physician incompetence. Errors occur in medicine, as in any profession, and litigation is a part of our society in the United States.

33.3.4 What to do When You Are Sued

Receiving a summons and complaint or being contacted by a plaintiff's lawyer should trigger certain steps on the part of a defendant physician:

1. If you receive a letter or telephone call from an attorney advising you that he or she represents your patient and wants information, contact your insurer and advise them of the letter or communication.
2. If you receive a notice of intent to sue or a summons and complaint, contact your insurer immediately. There are time limits that must be addressed in response to the complaint.
3. Do not alter any medical records under any circumstances. This includes removing words, progress note sections, reports, or any other records. Additions to the medical record, even if intended as clarifications, should also be avoided under all circumstances.
4. Discuss the selection of your attorney with your insurer. You have a right to participate in the selection of your attorney. Obtain recommendations on good defense malpractice attorneys from other physicians.
5. Do not discuss the patient and the case with your colleagues and friends, as it may become an issue in the litigation. Any conversations with a colleague or friend may be discoverable.
6. Cooperate with your lawyer and your insurer.
7. Do not expect that you can bring a counterclaim against your patient.
8. Be an active participant in your case. Educate your lawyer about the clinical aspects of it.

Table 33.1 Common allegations for failure to diagnose breast cancer and recommend steps in risk management

Allegation	Recommendations for risk management
Failure to screen	Perform clinical breast exam according to guidelines
	Order mammography according to guidelines
	Teach patients breast self-exam
	Communicate recommendations
	Document each step above
Failure to correctly interpret an abnormal mammogram	Double read mammograms
	Follow mammography audit results
Failure to have knowledge of abnormal mammogram results	Track results of tests
	Communicate abnormal results and recommendations to the patient
	Document each step above
Failure to follow-up on a complaint; failure to take patient complaint seriously	Perform a focused history and physical exam with any breast complaint
	Follow complaint to resolution or refer
	Communicate findings/recommendations
	Track patient follow-up
	Document each step above
Failure to verify a patient complaint on physical exam	Perform careful history and exam
	Examine specific area of concern
	Repeat exam at best phase of menstrual cycle if ovulating
	Communicate findings/recommendations
	Follow complaint to resolution or refer
	Document each step above
Failure to follow-up on a physical exam with abnormal findings	Follow physical finding to resolution
	Communicate findings/recommendations
	Track patient need for follow-up
	Refer if problem persists
	Establish follow-up responsibility with referring provider and patient
	Document each step above
Failure to refer	Establish follow-up responsibility
	Document each step above
Misinterpretation of abnormal findings of physical exam as benign or breast lump with normal mammogram as benign	Refer any persistent breast abnormality to a specialist, no matter what the mammogram result
	Communicate area of concern to patient and specialist
	Establish follow-up responsibility
	Document each step above
Failure to perform a biopsy	Perform a biopsy for any persistent abnormality
	If surgical intervention is deferred, establish a clear follow-up plan
	Communicate the plan to patient and provider
	Establish follow-up responsibility
	Document each step above

9. Have input when expert witnesses are selected to defend your case. Do not choose friends and close colleagues to defend your case, but respected physicians in the field with whom you do not have a personal relationship. Chosen experts should be able to demonstrate respect for the legal process, be familiar with the current medical literature, testify for both plaintiffs and defendants, and be able to articulate their opinions well.
10. Keep everything in perspective. Being sued does not equate with being an incompetent physician.

33.3.5 Summary

The diagnosis and management of breast cancer requires an understanding of the common allegations of negligence in the care of patients with breast cancer. Taking steps to manage your risk of liability will reduce your risk of misdiagnosis of breast cancer and mismanagement of your patient, and will improve the quality of care you provide your patients. Being sued for delay in diagnosis of breast cancer is one of the most common reasons primary care physicians and surgeons are sued. Understanding the litigation process, and actively participating with your lawyer in your defense, may increase your chances of a satisfactory outcome when faced with malpractice litigation.

References

1. Jemal A, Siegel R, Ward E et al (2008) Cancer statistics, 2008. CA Cancer J Clin. 58:71–96
2. Physician's Insurance Association of America (1995) Breast cancer study. PIAA, Washington, DC
3. Physician's Insurance Association of America (2002) Breast cancer study. PIAA, Washington, DC
4. Physician's Insurance Association of America (1990) Breast cancer study. PIAA, Washington, DC
5. Physician's Insurance Association of America (1995) Data sharing reports, executive summary. PIAA, Washington, DC
6. Roberts RG (2003) Seven reasons family doctors get sued and how to reduce your risk. Fam Pract Manag. 10(3):29–34
7. Kern KA. Medicolegal analysis of the delayed diagnosis of cancer in 338 cases in the United States. Arch Surg. 1994;129(4):397–403; discussion 4
8. Arnold R, Klingman R (1995) Medical malpractice liability for errors in breast cancer diagnosis and treatment. In: Donegan W, Spratt J (eds) Cancer of the Breast., 4th edn. W.B. Saunders, Philadelphia, pp 795–808
9. Anderson B, Cacioppo J (1995) Delay in seeking a cancer diagnosis: delay stages and psychophysiological comparison processes. Br J Social Psychol. 34:33–52
10. Lauver D (1994) Care-seeking behavior with breast cancer symptoms in Caucasian and African-American women. Res Nurs Health. 17(6):421–31
11. Kacmar D (1994) The impact of computerized medical literature databases on medical malpractice litigation: time for another Helling vs. Carey wake up call? Ohio St LJ. 58:617
12. Furrow B, Greany T, Johnson S, Jos T, Schartz R (1995) Health law. West, St. Paul, MN
13. Prosser W (1978) Law of torts. West, St. Paul, MN
14. Oja v. Kim, 229 Mich App 184, 581 NW2d 739; 1998
15. Mastroianni AC (2006) Liability, regulation and policy in surgical innovation: the cutting edge of research and therapy. Health Matrix Clevel. 16(2):351–442
16. Osuch JR, Bonham VL (1994) The timely diagnosis of breast cancer. Principles of risk management for primary care providers and surgeons. Cancer. 74(Suppl 1):271–8
17. Rigelhaupt J (2000) What constitutes patient-physician relationship for malpractice purposes. ALR. 17:132
18. Glicklich v Spievack, 16 MASS App 488; 1983
19. Allen C (2003) Loss of Chance in Wyoming: alive, but for how long? Wyo L Rev. 6:533–58
20. Sandbar S, Gibofsky A, Firestone M, LeBlang T (1995) Legal medicine. Mosby, St. Louis
21. Schwartz V, Kelly K, Partlett D (eds) (2005) Torts case and materials., 11th edn. Foundation, Stamford, Connecticut
22. King R (1999) Reconciling the exercise of judgement and the objective standard of care in medical malpractice. Okla L Rev. 52:49–84
23. Hall v Hinton, 466 S0.2d 856 872-873 (Miss. 1992)
24. Helling v Carey, 519P.2d 981 (Wash. 1974)
25. Hines N (2006) Why technology provides compelling reasons to apply a Daubert analysis to the legal standard of care in medical malpractice cases. Duke Law Technol Rev.
26. Evers v. Dollinger, 95 N.J. 399; 1984
27. JH G (1993) The Evers case: 1984 decision has lasting impact. N Jersey Med. 90:536–7
28. Anon. The palpable breast lump: information and recommendations to assist decision-making when a breast lump is detected. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Canadian Association of Radiation Oncologists. CMAJ. 1998;158(Suppl 3):S3–8
29. Ellis L (1993) Loss of chance as technique: toeing the line at fifty percent. Tex L Rev. 72:369–402
30. Walker V (1994) Direct inference in the lost chance cases: factfinding constraints under minimal fairness to parties. Hofstra L Rev. 23:247–307
31. National Institutes of Health Consensus Conference (1991) Treatment of early stage breast cancer. JAMA. 265:391–5
32. Gonzalez-Angulo AM, Morales-Vasquez F, Hortobagyi GN (2007) Overview of resistance to systemic therapy in patients with breast cancer. Adv Exp Med Biol. 608:1–22
33. ASCO Expert Panel (1998) 1997 update of recommendations for the use of tumor markers in breast and colorectal cancer. J Clin Oncol. 16:793–5

34. Adjuvant! Online. www.adjuvantonline.com. Accessed 5 May 2008
35. Ravdin PM, Siminoff LA, Davis GJ et al (2001) Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. J Clin Oncol. 19(4): 980–91
36. Miller AB (1996) Fundamental issues in screening for cancer. In: Schottenfeld D, Fraumeni JF Jr (eds) Cancer epidemiology and prevention. Oxford University, New York, pp 1433–52
37. Freedman DA, Petitti DB, Robins JM (2004) On the efficacy of screening for breast cancer. Int J Epidemiol. 33(1):43–55
38. Humphrey LL, Helfand M, Chan BK, Woolf SH (2002) Breast cancer screening: a summary of the evidence for the U.S. preventive services task force. Ann Intern Med. 137(5 Part 1):347–60
39. Fidler IJ (1990) Critical factors in the biology of human cancer metastasis: twenty-eighth G.H.A. Clowes Memorial Award Lecture. Cancer Res. 50:6130–8
40. Rutqvist LE, Wallgren A (1985) Long-term survival of 458 young breast cancer patients. Cancer. 55(3):658–65
41. Folkman MJ (2004) Angiogenesis and breast cancer. In: Bland KI, Copeland EM (eds) The breast comprehensive management of benign and malignant disorders., 3rd edn. Saunders, St. Louis, MO, pp 563–86
42. MacDonald I (1951) Biological predeterminism in human cancer. Surg Gynecol Obstet. 92:443–52
43. Heuser L, Spratt JS, Polk HC Jr (1979) Growth rates of primary breast cancers. Cancer. 43(5):1888–94
44. Tabar L, Duffy SW, Vitak B, Chen HH, Prevost TC (1999) The natural history of breast carcinoma: what have we learned from screening? Cancer. 86(3):449–62
45. Kern K (2004) The delayed diagnosis of symptomatic breast cancer. In: Ba C (ed) The breast comprehensive management of benign and malignant disorders., 3rd edn. Saunders, St. Louis, MO, pp 1597–628
46. Sainsbury R, Johnston C, Haward B (1999) Effect on survival of delays in referral of patients with breast cancer symptoms: a retrospective analysis. Lancet. 353(9159): 1132–5
47. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ (1999) Influence of delay on survival in patients with breast cancer: a systematic review. Lancet. 353(9159): 1119–26
48. McElhaney J (1987) McElhaney's trial notebook., 2nd edn. American Bar Association, Chicago, pp 31–2
49. Anon. Tamoxifen for early breast cancer: an overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 1998;351(9114):1451–67
50. Black H (2004) Law dictionary., 8th edn. West, St. Paul, MN
51. Danner D, Varn L, Mathias S (1994) Medical malpractice: checklist and discovery. CBC, New York
52. Vidmar N (1995) Medical malpractice and the American Jury. The University of Michigan, Ann Arbor, MI
53. Ellerin I, Frieder M, Hillerich G. Handling a failure to diagnose breast cancer. Trial. 1996:31–7
54. Beckman HB, Markakis KM, Suchman AL, Frankel RM (1994) The doctor-patient relationship and malpractice. Lessons from plaintiff depositions. Arch Intern Med. 154(12):1365–70
55. Levinson W, Roter DL, Mullooly JP, Dull VT, Frankel RM (1997) Physician-patient communication. The relationship with malpractice claims among primary care physicians and surgeons. JAMA. 277(7):553–9
56. Shapiro RS, Simpson DE, Lawrence SL, Talsky AM, Sobocinski KA, Schiedermayer DL (1989) A survey of sued and nonsued physicians and suing patients. Arch Intern Med. 149(10):2190–6

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