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CONSENSUS CONFERENCE

Consensus statement of the Hellenic and Cypriot Oesophageal Cancer Study Group on the diagnosis, staging and management of oesophageal cancer

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Abstract
In spite of recent advances in the diagnosis and management of oesophageal cancer, the overall survival of the disease worldwide remains disappointingly low. In Greece and Cyprus, this may be partly due to a failure of health care providers to implement standardised treatment protocols in clinical practice. Development of clinical practice guidelines was undertaken as a joint project between the Hellenic Society of Medical Oncology (HeSMO) and Gastro-Intestinal Cancer Study Group (GIC-SG) in an effort to provide guidance for Greek and Cypriot clinicians in all aspects of the management of oesophageal cancer. A study group was formed comprising clinicians from different disciplines with a special interest in the management of oesophageal cancer. Following extensive review of the literature, the members of the group met in person and consensus statements were developed, which were later subjected to the Delphi survey process by invited national and international experts. Statements that achieved a rate of voting consensus > 80% were adopted. Those that reached a voting consensus of < 80% were revised or rejected. In total, 46 sentences were developed and subjected to the voting process. Of those, 45 sentences achieved a rate of consensus > 80% during the first voting round. One sentence that did not reach a satisfactory rate of consensus was revised by the members of the study group and subsequently incorporated to the final statement. Forty-six recommendations covering all aspects of the management of oesophageal cancer and concise treatment algorithms are proposed by the Hellenic and Cypriot Oesophageal Cancer Study Group. In particular, centralisation of services, care by multidisciplinary teams and adherence to clinical guidelines are strongly recommended.

Keywords Adenocarcinoma · Carcinoma · Squamous cell · Esophageal neoplasms · Greece · Cyprus · Guidelines

Introduction

Oesophageal cancer (OC) is a predominantly male condition with a male to female incidence of approximately 3.6 to 1. The disease primarily affects older patients, with a peak incidence in the age group 65–74 years. The incidence of OC is trending upwards in white men with a 0.4% annual increase from 1992 to 2000. Furthermore, the 5-year survival rate is estimated at 15.4%, which is the fifth lowest among all cancers [1].

There are two major types of OC: adenocarcinoma (adenoCa) and squamous cell carcinoma (SCC). The primary known risk factors for oesophageal adenoCa are chronic gastroesophageal reflux disease (GORD), Barrett's oesophagus (BO) smoking, obesity and dietary factors [2–4]. Known risk factors for oesophageal SCC include smoking, alcohol abuse, exposure to nitrosamines, ingestion of lye, Fanconi's anaemia, Plummer–Vinson webs, and tylosis [2].

The Hellenic pathology-based cancer registry of the 5-year period 2009–2013 does not report on the incidence of OC in Greece. Possible reasons are the low incidence

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of OC in Greece and the fact that adenocarcinomas of the oesophago-gastric junction (OGJ) are often reported as gastric cancers [5]. According to the Hellenic Statistical Authority (ELSTAT) [6], 187 deaths of OC were registered in Greece in 2015.

Numerous consensus statements and guidelines for the management of OC have been developed by several medical societies worldwide [7–9]. All of them emphasise the importance of centralisation and systematic referral of OC cases to dedicated multidisciplinary teams.

Recommendation

- Centralisation of oesophageal cancer (OC) services in high-volume centres results in improved outcomes and it is strongly recommended (LOE: III, SOR: A, ROVC: 100%)

Aim

Members of the Hellenic Society of Medical Oncology (HeSMO) and the Gastro-Intestinal Cancer Study Group (GIC-SG), selected on the grounds of their experience in gastro-intestinal cancer management, founded an executive team—Hellenic and Cypriot Oesophageal Cancer Study Group (HCOC-SG)—with the task to develop a consensus statement and form guidelines on the main aspects of genetics, diagnosis, staging, treatment modalities and follow-up of oesophageal cancer. The effort and its product were based on review of the literature, the principles of evidence-based medicine and the experience and practice in other European countries, meanwhile considering the peculiarities of the Hellenic and Cypriot health care environments.

Methods

An initial effort to develop a draft with the consensus statements and recommendations for the management of OC, between December 2011 and June 2013, was not finalised due to unforeseen circumstances. The effort was resumed in June 2017: via several online communications, the members of the executive team produced a draft containing the background based on current evidence, and the consensus statements. At a face-to-face meeting in June 2018, the draft was finalised and the consensus statements were evaluated according to the Level of Evidence (LOE) and the Strength of Recommendation (SOR) (Table 1) [10].

To strengthen the opinion, all statements were subjected to the Delphi survey process [11]. One hundred and ten national and international experts were selected to participate in the survey. The procedure was scheduled to take place in two rounds of anonymous online voting for each statement, the options being "agree", "disagree", or "abstain". Abstain did not count on the overall agreement, provided it did not exceed 50% of the voters, in which case the statement was revised. The first round opened on December 6th 2018 and closed on January 15th 2019. Statements that achieved a rate of voting consensus (ROVC) of > 80% were considered of sufficient consensus. Statements that achieved an ROVC of < 80% were distributed between all members of the executive team for revision via online communication. Revised sentences entered the second round of voting, scheduled to open on February 4th 2019 and close on February 15th 2019. The LOE, the SOR and ROVC are shown in parenthesis at the end of each recommendation.

Table 1 Level of evidence (LOE) and strength of recommendation (SOR)

Level of evidence	
I	Evidence from at least one large randomised control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted RCTs without heterogeneity
II	Small RCTs or large RCTs with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts' opinions
Strength of recommendation	
A	A: Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	B: Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs…) optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Results

Of the 110 contacted experts, 75 accepted the invitation and participated in the voting process. There were 39 surgeons (52%), 19 medical oncologists (25.3%), 8 radiotherapists/medical oncologists (10.7%), 4 pathologists (5.3%), 4 radiologists (5.3%) and 1 gastroenterologist (1.4%). Forty-six sentences were subjected to the voting process. After the first round, the median rate of "abstain" was 9.3% (median 0–41.3%). Seven sentences achieved a consensus of 100%, 32 a consensus of 90–99%, 6 a consensus of 80–89%, and only 1 sentence scored a consensus of 75%. As all but one sentences achieved a consensus of more than 80%, there was no second round of voting. The sentence that scored 75% was related to the follow-up of patients with oesophageal cancer and it was revised to the full agreement of all members of the executive team.

Discussion

Genetics

Many risk factors are involved in the pathogenesis of oesophageal and oesophago-gastric junction tumours by altering the function of certain oncogenes and tumour suppressor genes leading to molecular variability. Oesophageal SCCs resemble lung SCCs with common genetic alterations, the most prominent being SOX-2 amplification [12]. In contrast, oesophageal adenocarcinomas share the same gene alterations with the remaining GI tract cancers (p53, CDKNZA, SMAD4, EGFR and HER2). HER2 gene alteration is the only one of some clinical importance [13]. Recent reports have identified the EBV-positive molecular subtype, displaying PIK3CA mutations, amplification of JAK2 and PDL-1, which might lead to a distinct therapeutic approach for this specific subtype in the future [14].

The vast majority of OC cases are sporadic. However, there is evidence that approximately 7% of patients with Barrett's oesophagus or adenocarcinoma have at least one blood relative affected. It appears that the incidence of affected cases in the families follows a pattern of autosomal dominant mode of inheritance with incomplete penetrance [15]. Microsatellite instability (MSI) has been associated with oesophageal adenoCa, and a secondary post hoc analysis of the MAGIC trial indicated that MSI was associated with a positive prognostic effect in patients treated with surgery alone and a differentially negative prognostic effect in patients treated with chemotherapy [16]. It should be emphasised, however, that only a small proportion of patients with oesophageal adenoCa display high MSI.

Prognostic factors

Stage of disease, by the TNM staging system, in patients with OC is an important prognostic factor: patients with higher stage of disease have worse outcome compared to those with lower stage [17]. Furthermore, surgical staging seems to be more accurate than preoperative clinical staging.

Another prognostic factor under consideration is the percentage of viable cancer cells in tumour specimens resected after neo-adjuvant treatment. Patients treated with preoperative chemo-radiotherapy (CRT) with less than 50% of residual viable cells in the histology specimen seem to have better survival than those with more than 50% [18]. In addition, there is evidence that the level of SUV in PET–CT scan may have prognostic value in OC [19]; in patients with localised disease, higher levels of SUV prior to any treatment [20], or after CRT [21] seem to be related to worse prognosis, although confirmatory studies are needed.

Predictive factors

Several studies in the literature have investigated the predictive role of different biomarkers in OC, but no definitive conclusions can be drawn yet [22, 23]. The only exception to the above is the identification of HER2 overexpression in advanced OGJ adenoCa, where a predictive role for response to the targeted agent *trastuzumab* has been shown [24]. In addition, MSI testing is required to select patients who may benefit from anti-PDL1 immunotherapy.

Finally, the extent of FDG uptake decreases following neo-adjuvant treatment or some characteristics of the 18F-FDG uptake from the primary tumour in the baseline PET/CT seem to predict the rate of pathological complete response [25, 26]. However, the role of PET/CT in predicting the outcome of neo-adjuvant treatment remains controversial and more solid evidence is needed before definitive conclusions can be drawn.

Recommendations

- HER2 overexpression and MSI should be tested in all patients with locally advanced and/or metastatic adenoCa of the OGJ (LOE: I, SOR: A) and possibly of the oesophagus (LOE: V, SOR: C, ROVC: 96%)

Diagnosis

Alarm symptoms and signs

Most patients with OC present at a late stage with dysphagia as the predominant symptom [27]. In particular, dysphagia that progresses rapidly within few months should heighten suspicion for OC and prompt an endoscopic evaluation. Up

to 75% of patients also experience anorexia and weight loss when they seek medical attention. Other symptoms of OC include odynophagia, chest pain, or gastrointestinal bleeding. Cough aggravated by swallowing raises the possibility of an oesophago-pulmonary fistula, a devastating complication associated with a high 30-day mortality rate [28].

Diagnostic tests

The diagnosis of OC is established by flexible endoscopy with biopsy. The diagnostic yield of endoscopic biopsy reaches 100% when 6 or more samples are obtained using standard forceps [29]. In patients with advanced cancers, ultra-thin endoscopes (max diameter 6 mm) may be required to complete the examination and obtain biopsies [30], but the adequacy of such biopsy specimens has not been formally assessed. It should be noted that biopsy specimens should be of adequate volume, not only to establish diagnosis but also for genetic analysis (HER2, MSI, etc.). Brush cytology could be an alternative method of sampling tight malignant strictures, not easily accessed by conventional biopsy techniques [31, 32]. Endoscopic ultrasonography (EUS) with fine-needle aspiration (FNA) and/or trucut needle biopsy (TNB) should also be considered, when submucosal tumours are suspected or standard biopsies fail to confirm the diagnosis [33]. Radiological examination with oral contrast as an initial diagnostic test is of limited value [27]; however, it may be useful to confirm the presence of fistulas, when clinically suspected.

During an endoscopic examination, the precise location of the tumour relative to the teeth and the OGJ, the length of the tumour, the extent of circumferential involvement and the degree of obstruction should be carefully recorded to assist with treatment planning.

Endoscopic screening and surveillance of Barrett's oesophagus

Currently, endoscopic screening of the general population for the detection of BO or oesophageal adenoCa is not indicated. However, screening could be considered in patients with known risk factors (long standing typical reflux symptoms, age > 50 years, white race, male sex, obesity, first degree relative with BO or oesophageal adenoCa). In patients with columnar epithelium extending less than 1 cm above the upper end of the gastric folds (tongues or circular), in the absence of visible abnormality, endoscopic surveillance is not recommended. Targeted biopsies from this region should only be obtained in cases of visible abnormalities. In such cases, when intestinal metaplasia is confirmed histologically (previously called ultra-short BO), endoscopic surveillance is also not recommended.

Randomised controlled trials on surveillance of patients with BO are still lacking. However, retrospective studies have shown that adequate endoscopic surveillance correlates with detection of cancer at an earlier stage and with improved survival from oesophageal adenoCa [34, 35]. High definition endoscopy (endoscope, processor and screen) is recommended for endoscopic surveillance in cases of BO. Routine use of chromo-endoscopy, optical chromo-endoscopy, auto-fluorescence endoscopy or confocal laser endomicroscopy is not advised [36].

Endoscopy reports of patients with BO should include

- The presence or absence of erosive oesophagitis according to the Los Angeles classification.
- The extent of BO according to the Prague criteria (circumferential extent—C, maximum extent—M) [37].
- A description of location (in cm from the incisors) of any visible abnormality within the metaplastic epithelium, lesion size (mm) and macroscopic appearance according to the Paris classification.
- Number of biopsies taken from the metaplastic epithelium: Biopsies should be taken according to the Seattle protocol (random 4-quadrant biopsies every 2 cm within metaplastic epithelium starting from the upper end of the gastric folds). Any visible mucosal abnormalities should be sampled separately [38].
- Photo documentation.

The extent of BO and the presence and degree of dysplasia are accepted risk factors for malignant progression. Surveillance intervals for non-dysplastic BO should be stratified according to its length:

- Irregular Z-line/columnar lined oesophagus < 1 cm: no surveillance.
- Short segment BO (1-3 cm): 5 years.
- Long segment BO: 3 years. Cases with BO > 10 cm should be referred to expert centres.
- In patients older than 75 years with no previous evidence of dysplasia, further endoscopic surveillance is not indicated.

Prophylactic endoscopic therapy (i.e. ablation therapy) for non-dysplastic BO should not be performed. The average risk for cancer progression of non-dysplastic metaplastic epithelium is lower than that previously described, estimated at 0.2–0.3% per year [39]. Additionally, there is uncertainty regarding the long-term follow-up in patients with non-dysplastic BO post ablation.

Patients with the diagnosis "*indefinite for dysplasia*" confirmed by a second expert GI pathologist should be managed with optimisation of anti-reflux medication and repeat endoscopy in 6 months. If no definite dysplasia is

found in subsequent biopsies or if these biopsies are again classified as "indefinite for dysplasia", surveillance strategy should follow the recommendations for non-dysplastic BO. It should be noted, however, that an accepted definition of the term "expert GI pathologist" is lacking. When considering endoscopic treatment, confirmation by an independent pathologist from a different institution is preferable to maximize the accuracy of the diagnosis.

In 30% of patients with BO and low-grade dysplasia diagnosed at a single endoscopy, the diagnosis will not be reproduced in subsequent endoscopies [40]. Thus, it is generally advised that patients with low-grade dysplasia BO on random biopsies, confirmed by an expert GI pathologist, should have a confirmatory diagnosis within 6 months. If no dysplasia is found at second endoscopy, the interval could be broadened to 1 year. After two subsequent endoscopies negative for dysplasia, standard surveillance for patients with non-neoplastic BO is initiated. If a confirmed diagnosis for low-grade dysplasia is found in the confirmatory endoscopy, endoscopic ablation therapy should be offered. Based on the currently available literature, radiofrequency ablation (RFA), has the best efficacy and safety profile; hence, it is recommended as the treatment of choice for ablation of dysplastic BO [41].

Recommendations

- Progressive dysphagia of recent onset should prompt upper alimentary endoscopic investigation (LOE: III, SOR: A, 100%)
- Diagnosis and HER2 and MSI status of OC are established by flexible endoscopy with biopsy. The presence of BO should be mentioned at the endoscopy report (LOE: III, SOR: A, ROVC: 97%)
- Any atypia in BO should be assessed after treatment of reflux esophagitis (LOE: III, SOR: A, ROVC: 99%)

Staging

Cross-sectional imaging

Imaging plays a pivotal role at initial presentation when suspicious or confirmed at endoscopy malignancy is encountered. Initial detection and diagnosis of OC are made either at upper gastrointestinal (GI) tract contrast studies or at endoscopy examination when biopsies may also be obtained. Malignancy typically presents as a stricture or ulceration in upper GI contrast studies.

Multidetector CT (MDCT) is the workforce, standard of care modality used to provide cancer staging for multidisciplinary meeting (MDM) discussion and further management stratification, as it is most useful in identifying the presence of distant disease such as liver and/or lung metastases. A CT examination of neck, chest, abdomen and pelvis should be performed after intravenous contrast administration at fine collimation enabling multiplanar coronal and sagittal reformats to be performed with the same resolution as the axial images (slice thickness should be 2.5–5 mm) to provide accurate primary tumour length measurements. The liver should be examined in portal venous phase; with 5 mm max thickness through the abdomen considered adequate. It is considered optimal to give about 200 ml of water as oral contrast just prior to the scan for oesophageal cancer staging [42].

Asymmetric, enhancing thickening of the oesophageal wall is a typical, but non-specific, CT finding of OC. The accuracy of CT for the assessment of T stage is lower than that of EUS [43]. CT is unable to adequately differentiate between T1, T2, and T3 disease. Exclusion of T4 disease, as indicated by the preservation of fat planes between the oesophageal primary and adjacent structures (e.g. bronchus, aorta), is the most important role of CT in the determination of T status [44]. Overall accuracy of MDCT is reported to be 84–89%, while N staging accuracy is lower at around 75–80% [45].

MRI of the neck, chest and abdomen may offer additional information in locoregional staging in equivocal cases. Some studies have shown that surface-coil MRI of the oesophagus is feasible. Using a high-resolution T2-weighted sequence, the oesophageal wall layers are accurately depicted and the tumour can be identified separately from surrounding tissue. MRI has also been proven in some studies to be better than CT in the evaluation of pericardial infiltration and bone involvement by local tumour invasion [46]. In spite of this early evidence, the role of MRI in the assessment of locoregional staging should still be considered investigational.

Positron-emission tomography (PET) is of limited value in assessing T stage, as it provides little information on the depth of tumour invasion [47]. There are conflicting findings in the literature regarding the relationship between FDG uptake in the primary tumour and depth of tumour invasion. The main drawback of PET is that intense uptake of FDG by the primary tumour commonly complicates interpretation by obscuring the adjacent regional lymph node(s) [48]. Nevertheless, ^{18}F-FDG PET has a variety of potential applications ranging from improving staging accuracy, as it may detect previously unsuspected metastatic disease in up to 30% of patients at the time of initial diagnosis [49], to assisting in radiation target volume delineation.

Recommendations

- CT is the imaging staging modality of choice for determining whether the patient may undergo resection or has distant metastases (LOE: II, SOR: B, ROVC: 88%)
- MRI may add information for staging in equivocal cases (LOE: III, SOR: C, 84%)

- PET–CT should be offered to fit patients with potentially resectable disease, in order to exclude unsuspected metastases (LOE: III, SOR: A, 94%)

Endoscopic ultrasound

Endoscopic ultrasound should be performed to establish the extent of locoregional disease and guide further management. Patients with cancer confined to the mucosa or superficial submucosa can be treated using surgical resection or potentially endoscopic therapy [50, 51], whilst patients who have more advanced disease will require surgical resection with or without neo-adjuvant or adjuvant treatment [52, 53].

As EUS provides more accurate evaluation of the depth of tumour invasion (T stage) and the extent of lymph-node involvement (N stage) than both PET and CT [54, 55], the modality can offer additional information to (i) distinguish between T1a and T1b cases, the former one being amenable to endoscopic treatment, and (ii) to distinguish between T2 and T3, the latter one requiring neo-adjuvant treatment. Occasionally signs of locally spread disease (M-stage) can be detected by EUS. However, the specificity and the sensitivity for identifying lymph node disease are better when EUS is combined with FNA compared to EUS alone. For tumours smaller than 0.5 cm, high-frequency EUS transducers are used [56].

Mediastinal and perigastric lymph nodes are readily seen by EUS. Accuracy in diagnosis of lymph node invasion significantly increases with FNA [57]. FNA of suspicious lymph nodes should be performed without traversing an area of primary tumour, and only in case lymph node status is expected to influence treatment decisions.

Recommendations

- EUS can be used for initial local staging in non-obstructing lesions to guide further treatment strategy (LOE: II, SOR: A, ROVC: 97%)
- Combined use of FNA and EUS can improve the assessment of regional lymph node involvement and may be performed in equivocal cases (LOE: II, SOR: B, ROVC: 96%)

Bronchoscopy

A bronchoscopy should be carried out in all cases of oesophageal SCCs located at the level and above the carina to exclude tracheal or bronchial infiltration by the tumour and also to exclude the possibility of a second primary carcinoma of the aero-digestive tract [58, 59].

Staging laparoscopy

Several studies have indicated that staging laparoscopy and peritoneal cytology can reveal previously unsuspected serosal involvement or peritoneal metastases in cases of carcinomas of the lower oesophagus or the GOJ junction. Therefore, staging laparoscopy and peritoneal washing and cytology should be offered to patients with locally advanced (T3 or T4) adenoCa of the lower oesophagus and GOJ junction to prevent unnecessary major resections [60, 61].

Recommendation

- Staging bronchoscopy in cases with upper oesophageal SCC and staging laparoscopy in cases with locally advanced adenoCa of the lower oesophagus and OGJ should be carried out to exclude bronchial infiltration and peritoneal dissemination, respectively (LOE: III; SOR: A, ROVC: 96%)

Histopathology

In previous years, histopathologic staging after oesophagectomy was used as the only basis for cancer staging [62, 63]. Current information suggests that histopathologic staging is losing its clinical significance in locally advanced disease, as post-neo-adjuvant therapy replaces esophagectomy alone, while it remains important in early-stage lesions [64]. The 8th edition of TNM staging for cancer of the oesophagus was based on a strong 7th edition foundation, which was characterised by significant alterations compared to the previous ones (5th, 6th) [65]. The major difference between the 7th and 8th editions is the introduction of separate stage groups among pathologic (pTNM), clinical (cTNM) and post-neo-adjuvant (ypTNM) classifications [63]. In addition, histopathologic cell type, histologic grade (G-category), and tumour location (L-category) were identified as important parameters for stage grouping: (i) the difference in survival between adenoCa and SCC was best represented by creating separate stage groupings for stages I and II, (ii) histologic grade was associated with decreased survival for early-stage cancers and, therefore, was added in stages I and II in the classification of both adenoCa and SCC, and (iii) tumour location (upper and middle thoracic vs lower thoracic) was considered important for grouping T2-3N0M0 SCCs. The 8th edition of TNM and the histopathological prognostic grouping are shown in Tables 2, 3, 4, and 5 [66].

Recommendation

- The 8th edition of TNM is implemented for the histopathological staging of oesophageal cancer (SCC, adenoCa) (SOR: A, ROVC: 99%)

Table 2 TNM classification—8th edition

Primay tumour (T)
Tx: primary tumour cannot be assessed
T0: no evidence of primary tumour
Tis: high-grade dysplasia (all non-invasive neoplastic epithelium included)
T1: primary tumour invades lamina propria or submucosa
T1a: primary tumour invades mucosa or lamina propria or muscularis mucosae
T1b: primary tumour invades submucosa
T2: primary tumour invades muscularis propria
T3: primary tumour invades adventitia
T4: primary tumour invades adjacent structures
T4a: resectable primary tumour invading pleura, pericardium or diaphragm
T4b: unresectable primary tumour invading trachea, aorta, vertebral body
Regional lymph nodes (N)
Nx: regional lymph nodes cannot be assessed
N0: no regional lymph nodes metastasis
N1: metastasis to 1–2 regional lymph nodes
N2: metastasis to 3–6 regional lymph nodes
N3: metastasis to ≥7 regional lymph nodes
Distant metastasis (M)
M0: no distant metastasis
M1: distant metastasis

Management of locoregional: non-metastatic disease

The management of OC is complex and Multidisciplinary Team (MDT) meetings have been introduced in an effort to optimise patient outcomes. There is ample evidence that patients discussed at such meetings are more likely to receive more accurate diagnosis and preoperative staging compared with those treated independently by their physicians [34, 67–70]. Furthermore, it has been shown that treatment plans are altered in a significant number of patients and MDT decisions are implemented in 90–100% of cases [71, 72]. Based on those findings and although direct evidence that MDT meetings result in improved survival outcomes is still lacking, it is recommended that all patients with OC should be discussed at MDT meetings, as soon as possible after the diagnosis is confirmed and certainly before any treatment is implemented.

Oesophagectomy is one of the most complex surgical procedures associated with a significant risk of postoperative complications [73]. Several studies from different countries and health care systems have shown that short-term mortality is lower and long-term survival is higher, when oesophagectomy is carried out in high-volume hospitals and by high-volume surgeons [74–77]. Based on those differences in short- and long-term outcomes of patients, centralisation of OC services within centres of excellence is recommended.

Recommendation

- Patients with OC should be discussed at MDT meetings soon after the diagnosis is confirmed and prior to any treatment (LOE: III, SOR: A, ROVC: 100%)

Limited disease (cT1-T2 N0 M0)

In recent years, an increasing number of people with OC are diagnosed at an earlier stage because of a more liberal use of upper endoscopy for the investigation of gastrointestinal symptoms and also the establishment of surveillance programs for patients with BO. Upfront surgical resection has been the treatment of choice for all patients with limited T1-T2N0M0 tumours until recently. However, the evolution of endoscopic techniques such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) and radiofrequency ablation (RFA) over the last decade has challenged the role of surgery in the management of early-stage cancers and selection of treatment for T1 OC is now based on the depth of tumour invasion [78, 79].

Although both adenoCa and SCC limited to the mucosa (T1a) have a very low risk of lymph node metastases and can be treated endoscopically, when a tumour invades the submucosa (T1b) the risk of lymph node involvement increases to 20–30% [80–82]. Therefore, oesophagectomy with lymph node dissection is more appropriate for the latter group of patients, even though it is recognised that the majority of them (≃75%) will eventually have negative lymph nodes and would have been adequately treated with endoscopic techniques only. Attempts have been made to define factors such as depth of submucosal invasion, degree of differentiation of the tumour and presence or not of lymphovascular invasion that may predict the risk of lymph node metastases in patients with T1b tumours and subsequently tailor their management accordingly, but conflicting results have been reported so far [81, 83–86] (Fig. 1).

Several studies have shown that endoscopic treatment of T1a adenoCa can achieve equivalent to surgery oncologic outcomes with a much lower complication rate [87–92], and similar results have also been reported for T1a SCC [93–96]. Furthermore, some evidence exists that ESD may be more effective than EMR in the management of intramucosal carcinomas, albeit with a higher complication rate [96–98]. In practice, however, it is very difficult, if not impossible, to distinguish between T1a and T1b tumours preoperatively, even with the use of high-resolution Endoscopic Ultrasound (EUS), which is considered the most reliable method of assessing the depth of mural invasion [99, 100]. Therefore, patients with suspected T1 cancer should be offered EMR or ESD for completion of staging. If a well-differentiated intramucosal T1a tumour is confirmed histologically and the resection has been performed en bloc and with clear margins, the excision is considered complete and no further treatment is necessary. If, however, a submucosal T1b

Table 3 Clinical–pathological staging and prognostic grouping of squamous cell carcinoma (TNM 8th edition)

Clinical stage				Pathological stage			
Stage 0	Tis	N0	M0	Stage 0	Tis	N0	M0
Stage I	T1	N0, N1	M0	Stage IA	T1a	N0	M0
				Stage IB	T1b	N0	M0
Stage II	T2	N0, N1	M0	Stage IIA	T2	N0	M0
	T3	N0	M0	Stage IIB	T1	N1	M0
					T3	N0	M0
Stage III	T1, T2	N2	M0	Stage IIIA	T1	N2	M0
	T3	N1, N2	M0	Stage IIIB	T2	N1	M0
					T2	N2	M0
					T3	N1, N2	M0
					T4a	N0, N1	M0
Stage IVA	T4a, T4b	N0, N1, N2	M0	Stage IVA	T4a	N2	M0
Stage IVB	T any	N3	M0	Stage IVB	T4b	N any	M0
	T any	N any	M1		T any	N3	M0
					T any	N any	M1

Pathological prognostic grouping					
Group	T	N	M	Grade	Location
Group 0	T1s	N0	M0	N/A	Any
Group IA	T1a	N0	M0	1, X	Any
Group IB	T1a	N0	M0	2–3	Any
	T1b	N0	M0	Any	Any
	T2	N0	M0	1	Any
Group IIA	T2	N0	M0	2–3, X	Any
	T3	N0	M0	Any	Lower
	T3	N0	M0	1	Upper/middle
Group IIB	T3	N0	M0	2–3	Upper/middle
	T3	N0	M0	Any	X
	T3	N0	M0	X	Any
	T1	N1	M0	Any	Any
Group IIIA	T1	N2	M0	Any	Any
	T2	N1	M0	Any	Any
Group IIIB	T2	N2	M0	Any	Any
	T3	N1,2	M0	Any	Any
	T4a	N0,1	M0	Any	Any
Group IVA	T4a	N2	M0	Any	Any
	T4b	N any	M0	Any	Any
	T any	N3	M0	Any	Any
Group IVB	T any	N any	M1	Any	Any

carcinoma is found or the resection margins are involved with tumour, the patient should be offered oesophagectomy in conjunction with lymphadenectomy, provided the patient is fit for major surgery. In cases where expertise in endoscopic mucosal resection is not available locally, all fit patients with clinical T1 tumours should be offered upfront oesophagectomy (Fig. 1).

Patients with a background of BO and intramucosal adenoCa completely excised endoscopically should also be offered radiofrequency ablation of the remaining Barrett's mucosa to prevent the formation of metachronous carcinomas [101, 102]. The role of radiofrequency ablation in the management of remaining squamous dysplasia following endoscopic resection of squamous intramucosal cancer is less well defined [95, 103].

The optimal treatment for patients with clinical T2N0M0 cancers remains controversial partly because of the inaccuracy of currently available staging investigations [104, 105]. Recent studies have shown that 30–55% of patients with clinical T2N0M0 disease are found to have positive lymph nodes following oesophagectomy [106–108]. Given the high prevalence of nodal metastases among patients with cT2N0M0 disease and the fact that positive nodal status is a strongly negative prognostic factor [109, 110], it has been argued that all patients with T2 lesions should undergo neo-adjuvant treatment.

Table 4 Clinical–pathological staging and prognostic grouping of adenocarcinoma (TNM 8th edition)

Clinical stage				Pathological stage			
Stage 0	Tis	N0	M0	Stage 0	Tis	N0	M0
Stage I	T1	N0	M0	Stage IA	T1a	N0	M0
				Stage IB	T1B	N0	M0
Stage IIA	T1	N1	M0	Stage IIA	T2	N0	M0
Stage IIB	T2	N0	M0	Stage IIB	T1	N1	M0
					T3	N0	M0
Stage III	T2	N1	M0	Stage IIIA	T1	N2	M0
	T3, T4a	N0, N1	M0	Stage IIIB	T2	N1	M0
					T2	N2	M0
					T3	N1, N2	M0
					T4a	N0, N1	M0
Stage IVA	T1-T4a	N2	M0	Stage IVA	T4a	N2	M0
Stage IVB	T4b	N0, N1, N2	M0	Stage IVB	T4b	N any	M0
	T any	N3	M0		T any	N3	M0
	T any	N any	M1		T any	N any	M1

Pathological prognostic grouping

Group	T	N	M	Grade
Group 0	T1s	N0	M0	N/A
Group IA	T1a	N0	M0	1, X
Group IB	T1a	N0	M0	2
	T1b	N0	M0	1, 2
Group IC	T1 a, T1b	N0	M0	3
	T2	N0	M0	1,2
Group IIA	T2	N0	M0	3, X
Group IIB	T1	N1	M0	Any
	T3	N0	M0	Any
Group IIIA	T1	N2	M0	Any
	T2	N1	M0	Any
	T3	N0	M0	Any
Group IIIB	T2	N2	M0	Any
	T3	N1, N2	M0	Any
	T4a	N0, N1	M0	Any
Group IVA	T4a	N2	M0	Any
	T4b	N any	M0	Any
	T any	N3	M0	Any
Group IVB	T any	N any	M1	Any

Table 5 Prognostic factors for survival of oesophageal cancer

Prognostic factors	Tumour related	Host related	Treatment related
Essential	Depth of invasion Lymph node involvement Lymphovascular invasion	Performance status Age Nutritional status	MDT approach Quality of surgery
Additional	Tumour grading Tumour location	Economic status	Nutritional support
New/Promising	CEA, VEGF.C, HER2		

Observational studies, however, that addressed specifically this issue have reported contradictory results [106, 111, 112]. One recent randomised study that recruited patients with early-stage I and II OC showed no improvement in survival and increased postoperative mortality among patients who underwent neo-adjuvant CRT compared with those who had upfront surgery [113]. Furthermore, another recent well-designed, multicentre, retrospective European study showed that among patients with cT2N0M0 OC neo-adjuvant therapy had no significant effect upon survival or recurrence compared to surgery alone despite the fact that 50% of the patients had unrecognised nodal metastases at

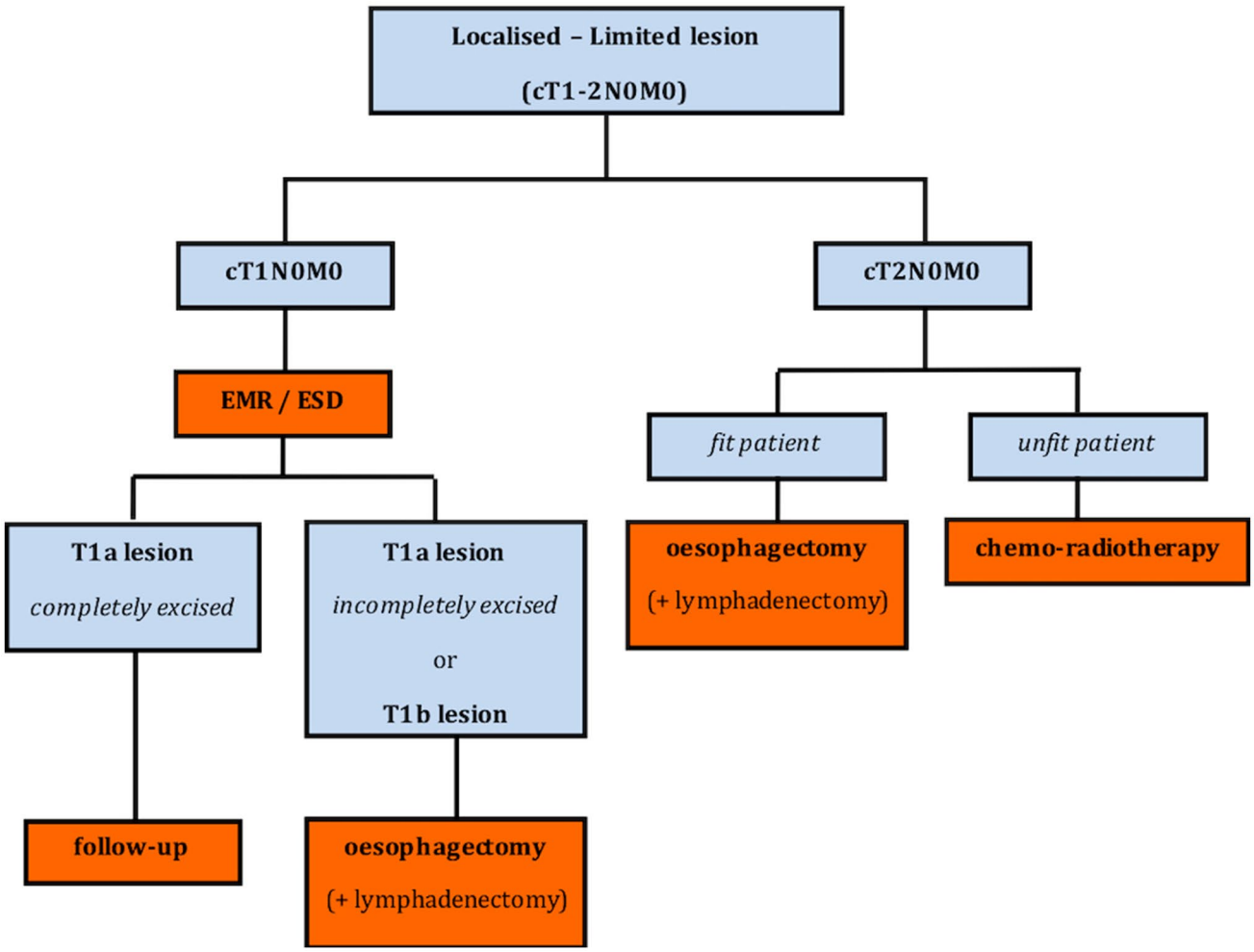

Fig. 1 Treatment flowchart of localised oesophageal cancer

the time of surgery [114]. Until more conclusive data from randomised studies becomes available, it is recommended that patients with clinical T2N0M0 tumours should be offered upfront surgery.

Several prospective randomised studies [115–117] and a recent Cochrane review [118] have shown that CRT appears to be at least equivalent to surgery in terms of survival in patients with resectable oesophageal SCC who are fit for surgery. Therefore, patients with localised SCC of the upper third of the thoracic oesophagus should be given the choice of radical CRT or transthoracic 3-stage oesophagectomy combined with lymphadenectomy. In case of persistent disease or local recurrence following radical CRT, salvage oesophagectomy can be offered with relatively good results [119, 120]. For patients with localised SCC of the cervical oesophagus, radical CRT is the treatment of choice [121]. Definitive chemo-radiotherapy should also be considered as an alternative to surgery for patients with localised OC who are not fit or not willing to undergo surgery (Fig. 1).

Controversy still exists regarding the optimal surgical strategy in terms of operative approach, surgical technique and extent of lymphadenectomy in patients with operable OC [122]. Several studies have shown that resection of the tumour with clear margins (R0 resection) is an important prognostic factor [123, 124]. Tumour-free margins, however, can be accomplished with a number of different approaches including right transthoracic, left thoraco-abdominal and transhiatal approach using open or minimally invasive surgical techniques. It has been argued that transthoracic approaches allow for more radical oncological resection of the tumour and adjacent lymph nodes that may result in a survival benefit. Indeed, subgroup analysis of the late results from a large, well-designed, randomised study [125, 126] have confirmed a trend towards improved survival for patients with adenoCa of the lower oesophagus, who underwent transthoracic oesophagectomy compared with those who had transhiatal approach, and significantly improved survival for a subgroup of those patients who had limited

number of positive lymph nodes (1-8 nodes). Furthermore, a number of cohort studies have shown that the higher number [127, 128] and the location [129, 130] of lymph nodes that are normally removed via a transthoracic but not a transhiatal approach are important prognosticators of improved survival following surgery for oesophageal and OGJ carcinomas. Although other cohort studies [131, 132] and some meta-analyses [133, 134] have questioned these conclusions, on balance available evidence suggests that patients with resectable carcinomas of the middle or the lower third of the oesophagus including those with Siewert type I or II adenoCa of the OGJ should be offered transthoracic, 2-stage oesophagectomy combined with 2-field mediastinal and upper abdominal lymphadenectomy (Ivor Lewis procedure).

The role of minimally invasive techniques in OC surgery has been explored in recent years. Two large cohort studies [135, 136], two prospective randomised studies [137, 138] and a recent meta-analysis [139] have shown that the use of minimally invasive techniques to perform oesophagectomy for cancer is associated with a modest improvement in perioperative outcomes without compromising long-term survival. Therefore, it is recommended that the use of minimally invasive or hybrid techniques to perform oesophagectomy can be considered depending on local expertise and surgeon's preference.

Recommendations

- Patients with suspected cT1 OC should be offered endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR) for staging. For patients with pT1a lesions completely excised endoscopically, no further intervention is required (LOE: III, SOR: B, ROVC: 93%)
- Patients with histologically confirmed pT1a oesophageal adenoCa, following complete endoscopic resection of the tumour, should be offered endoscopic radiofrequency ablation of remaining Barrett's mucosa (LOE: III, SOR: A, ROVC: 92%)
- Following endoscopic resection for staging, oesophagectomy and lymphadenectomy should be offered to patients with submucosal pT1b cN0 lesion and to those with intramucosal pT1a cN0 tumours incompletely excised, provided they are fit for major surgery (LOE: III, SOR: A, ROVC: 97%)
- Upfront oesophagectomy for fit patients with suspected cT1 lesion should be considered, if expertise in endoscopic mucosal resection is not available (LOE: III, SOR: A, ROVC: 97%)
- Upfront surgery, without neo-adjuvant treatment, could be offered to patients with cT2N0M0 lesions (LOE: II, SOR: B, ROVC: 93%)
- Transthoracic, 2-stage oesophagectomy, combined with 2-field lymphadenectomy (Ivor Lewis procedure) or 3-stage oesophageactomy with 2-filed lymphadenectomy, depending on tumour location and surgeon' s preference, should be offered to patients with operable middle or lower third OC and to those with Siewert type I and II cancers of the OGJ (LOE: II, SOR: B, ROVC: 95%)
- Oesophagectomy with 3-field lymphadenectomy is feasible in fit patients, but not beneficial in terms of disease control and survival (LOE: III, SOR: B, ROVC: 88%)
- Siewert type III tumours of the OGJ should be treated as gastric carcinomas, with extended total gastrectomy and D2 lymphadenectomy (LOE: II, SOR: A, ROVC: 96%)
- Minimally invasive or hybrid oesophagectomy could be offered to patients with operable oesophageal cancer depending on local expertise and surgeon's preference (LOE: II, SOR: B, ROVC: 92%)
- Patients with resectable SCC of the upper thoracic oesophagus should be offered the choice of radical CRT or transthoracic 3-stage resection combined with lymphadenectomy (LOE: II, SOR: A, ROVC: 83%)
- Radical CRT should be offered to patients with localised SCC of the cervical oesophagus (LOE: III, SOR: A, ROVC: 97%)
- Definitive CRT could be considered for patients with resectable OC, who are not fit or not willing to undergo surgery (LOE: III, SOR: A, ROVC: 100%)

Locally advanced disease (cT3-T4 or cN1-N3 M0) (Fig. 2)

The management of local–regional oesophageal and OGJ cancer has undergone a major evolution over the past 15 years. The majority of patients now undergo some form of combined modality therapy rather than local therapy alone, which is associated with poor oncological outcomes. However, the optimal management of these patients remains controversial. The main factors for selecting primary treatment are tumour stage and location, histological type and the medical condition, as well as the requests of the patients. Preoperative treatment, either chemotherapy (CT) or combined CRT is clearly indicated in locally advanced resectable carcinoma (cT3-T4 or cN1-N3 M0). CRT should be delivered with modern radiotherapy techniques (IMRT, VMAT) (Fig. 2).

SCC

Several meta-analyses have addressed the benefit of trimodality treatment (surgery and CRT), over surgery alone for SCC [140, 141]. One of the most recent meta-analysis demonstrated higher rates of complete tumour resection after combined treatment (55–100% after preoperative CRT vs 37–100% after surgery alone). Survival rates were also significantly higher after neo-adjuvant CRT with no

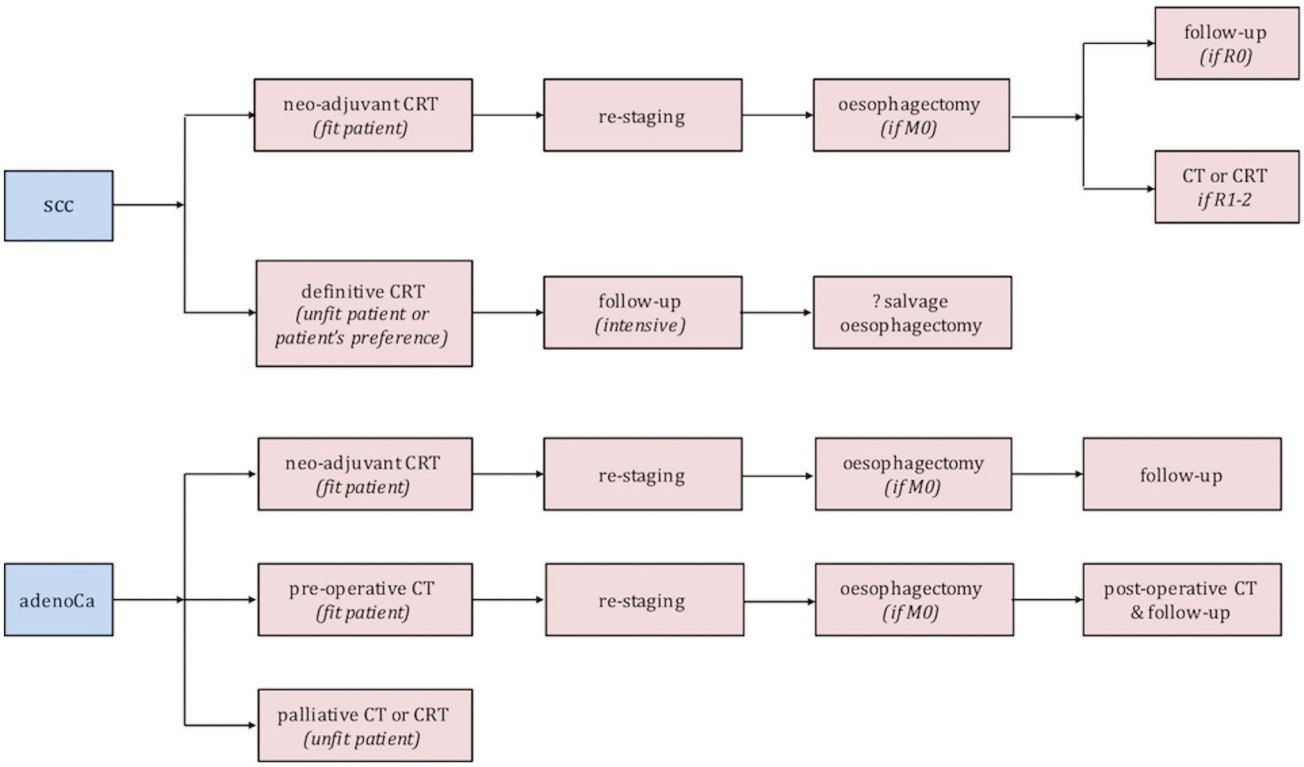

Fig. 2 Algorithm for the treatment of locally advanced oesophageal cancer (cT3-4 or any cT, cN1-3, cM0)

increase in morbidity rate. The benefit of neo-adjuvant treatment was greater for preoperative CRT in comparison to preoperative CT alone [140]. None of the trials included in this meta-analysis demonstrated any significant survival benefit of definitive CRT compared with neo-adjuvant treatment followed by surgery or surgery alone. The CROSS trial [142] established preoperative CRT as the standard of care modality. The trial randomised patients with resectable tumours (adenoCa or SCC) to receive surgery alone or weekly administration of carboplatin and paclitaxel for 5 weeks and concurrent radiotherapy (RT) (41.4 Gy/23 fractions) followed by surgery.

Preoperative CRT doubled median survival and had higher complete resection rates and survival, whilst postoperative complication rates were similar between the two treatment groups. Although health-related quality of life (HRQOL) declined during neo-adjuvant CRT, no such effect was apparent on postoperative HRQOL as compared with surgery alone [143]. Furthermore, two randomised studies showed that adding surgery to CRT improves local tumour control, but does not increase survival of patients with locally advanced oesophageal SCC, who respond well to induction treatment [115, 116].

Overall, preoperative CRT with surgery or definitive CRT and salvage surgery are both acceptable therapeutic approaches for locally advanced, resectable SCC. Definitive CRT is recommended for cervical tumours.

AdenoCa

Meta-analyses of locally advanced oesophageal cancer have established perioperative CT or neo-adjuvant CRT as standard of care for adenoCa of the oesophagus or oesophagogastric junction [144, 145]. The CROSS trial that included both adenoCa and SCC established the use of preoperative carboplatin/paclitaxel with RT [142]. The combination showed a survival advantage with favourable toxicity profile.

The addition of RT to neo-adjuvant CT may result in higher histological complete response rate, higher R0 resection rate, and a lower frequency of lymph-node metastases, without any significant effect on survival [146]. Even after complete tumour response to preoperative treatment, patients with adenocarcinoma should proceed to surgery.

Recommendations

- Preoperative treatment is clearly indicated in locally advanced resectable OC (cT3-T4 or cN1-N3 M0) (LOE: I, SOR: A, ROVC: 97%)
- For patients with SCC of the oesophagus, preoperative CRT, according to the CROSS protocol, is associated

with higher rates of complete tumour resection and better survival compared with surgery alone (LOE: I, SOR: A, ROVC: 99%)
- For patients with SCC of the oesophagus, preoperative CRT with surgery or definitive CRT and salvage surgery are both acceptable therapeutic approaches, while definitive CRT is recommended for cervical tumours (LOE: II, SOR: B, ROVC: 99%)
- For patients with oesophageal adenoCa, perioperative CT or preoperative CRT are both acceptable therapeutic approaches (LOE: II, SOR: A, ROVC: 90%)
- Even after complete tumour response to preoperative therapy, patients with oesophageal adenoCa should proceed to surgery (LOE: III, SOR: A, ROVC: 96%)

Restaging: assessment of therapeutic response

Concerning imaging assessment of therapeutic response to RT or CT, MDCT is not considered accurate. However, as this is a comparative examination and may take place also during treatment, MDCT allows discrimination of responders from non-responders by identifying downsizing or stable appearances. According to many systematic reviews, the accuracy of EUS in the assessment of therapeutic response is higher than that of MDCT but inferior to that of FDG PET, specifically after RT [147].

FDG PET–CT currently seems to be the best imaging modality for the assessment of response to neo-adjuvant therapy in patients with OC if primary tumour was metabolically active at baseline examination. Recent studies suggest that the quantitative decrease in FDG uptake seen after neo-adjuvant therapy correlates closely with patient survival and with pathologic response to therapy [25]. In addition, FDG PET–CT may have a post-therapeutic role in detecting interval distant metastases, which have been reported in 8–17% of cases [148, 149].

Adjuvant treatment

Perioperative CT or preoperative CRT is the preferred therapeutic strategy in localised adenoCa of the oesophagus or OGJ. Survival benefit from the addition of adjuvant CRT over surgery alone has not been proven in randomised trials. However, there is evidence of reduced locoregional recurrence rate after the addition of CRT [150, 151]. One retrospective study including 213 matched pairs with squamous histology indicated that oesophagectomy with postoperative chemo(cisplatin/5FU)-radiotherapy was associated with longer survival and lower recurrence rates, especially at a locoregional level, compared with surgery alone [152]. Another retrospective study of patients with surgically treated lymph node positive OC (80% adenoCa; 20% SCC) indicated that the addition of sequential chemo(cisplatin/5-fluorouracil ± epirubicin)-radiotherapy resulted in an OS of 47.5 months (surgery alone: 14.1 months) [153]. A recent database analysis of 1095 oesophageal SCC treated with radical surgery indicated a survival benefit for patients treated with adjuvant fluoropyrimidine-based CRT compared to those who had surgery alone, particularly for those with pT3/4 stage, N + tumours, larger tumour size, poorly differentiated tumours, and R1/2 resections [154].

The MacDonald Intergroup Trial 0116 investigated the role of postoperative chemo(5FU and leucovorin) radiotherapy in 556 patients (20% OGJ adenoCa; 80% gastric adenoCa) and found that the OS in the surgery-only group was 27 months, as compared with 36 months in the CRT group [155].

Recommendations

- Postoperative fluoropyrimidine-based CT in combination with RT is recommended for oesophageal SCC (LOE: II; SOR: A) and adenoCa (LOE: III; SOR: A) staged T3-4a, or N + , in fit patients, who have not received preoperative treatment after R0 resection (ROVC: 83%)
- After R1 and R2 resection, postoperative fluoropyrimidine-based CT for all patients plus RT for those who had no preoperative CRT is recommended (LOE: III, SOR: B, ROVC: 95%)

The resected specimen: histopathological assessment

The role of histopathology in the management of oesophageal carcinoma is to produce accurate histological assessment that provides the clinicians with information about prognosis and the need for additional treatment. Although there is no consensus in the current literature regarding the pathological examination of the esophagectomy specimens, there is a general tendency for using standardised protocols. Of those, the AJCC/TNM staging system-based pathology cancer synoptic report from the College of the American Pathologists (CAP) is the most commonly used [156].

Completeness of resection

The initial pathological evaluation of the oesophagectomy specimen often begins while the patient is still under anaesthesia, to provide significant information regarding the status of the proximal and distal margins. Since adenocarcinomas often grow underneath the uninvolved mucosa, it is very important to evaluate a full thickness section of both margins. In cases where the lesion appears with a longitudinal margin < 1 cm, it is preferable to take perpendicular sections that include both the lesion and the margin.

Macroscopic assessment

The surgical specimen is preferably sent to the pathology department immediately after removal from the patient, not embedded in formalin, to optimise orientation and sampling. The specimen should be accompanied by full clinical information. The length of the oesophagus shortens after removal and fixation by at least a quarter and pinning could be helpful in this regard. The outer surface of the oesophagus should be painted before opening. There are two recommended methods for opening the oesophagus; the longitudinal dissection and the "bread-sliced", the latter being proposed for tumours with circumferential growth. The following parameters are recorded: (a) specimen dimensions (length of oesophagus and length of stomach), (b) tumour location, (c) macroscopic appearance of the tumour (ulcerated, plaque-like, polypoid, flat), (d) distance of tumour from proximal and distal resection margins, (e) distance from OGJ, (f) distance from circumferential margin of the oesophagus, (g) maximum tumour dimension, (h) depth of invasion, (i) involvement of any adjacent structures, (j) presence or absence of Barrett mucosa or other lesions and (k) number of lymph nodes [156]. Worldwide data recommend the dissection of as many lymph nodes as possible and that more nodes should be dissected with increasing pT stage (≥ 10 for T1; $\geq 20$for T2; and ≥ 30 for T3 and T4) [157].

Microscopic assessment

During histological evaluation of the tumour, the following parameters are recorded: (a) histological type, (b) histological grade, (c) pattern of growth (expanding or infiltrating), (d) depth of invasion (in mm), (e) status of serosa, (f) status of distal and proximal resection margins, (g) status of circumferential resection margin, (h) presence of vascular and perineural invasion, (i) number of involved lymph nodes, (j) presence of Barrett metaplasia and/or dysplasia, and (k) pTNM (Table 1) [63, 156].

The WHO *histological classification* is the most widely used and classifies oesophageal tumours into SCC, verrucous carcinoma, basaloid SCC, adenoCa, adenoid cystic carcinoma, muco-epidermoid carcinoma, adeno-squamous carcinoma, undifferentiated carcinoma, small cell carcinoma and others [158]. SCC and adenoCa are classified according to the differentiation into well, moderate and poorly differentiated carcinomas [63, 159, 160].

Following neo-adjuvant CRT, the use of a *tumour regression grading* (TRG) score for the assessment of response to treatment is recommended [160, 161]. The status of *circumferential resection margin* (CRM) represents a significant prognostic factor, according to some authors. Involvement of CRM or the presence of neoplastic cells within 1 mm of the CRM is considered a poor prognostic factor [17, 160].

In case of *BO*, proximal margin at squamous-Barrett mucosa junction and presence or not of dysplasia should be reported. If the proximal margin demonstrates the presence of gastric mucosa, any helicobacter-associated gastritis or atrophy should also be mentioned [160, 162, 163].

All lymph nodes excised should be thoroughly examined, and the number of the involved over the total number of lymph nodes should be reported [17, 42, 160–162, 164]

The endoscopic submucosal dissection specimens are handled carefully to collect information regarding (a) histological type, (b) histological grade, (c) pattern of growth (expanding or infiltrating), (d) depth of invasion (in mm), (e) status of distal and proximal resection margins, (f) presence of muscularis propria invasion and (g) the presence of vascular and perineural invasion [165].

Recommendation

- The following parameters should be recorded and included in the pathology report: (i) maximum tumour diametre, (ii) tumour location and distance from margins and OGJ, (iii) macroscopic appearance of the tumour, (iv) maximum depth of invasion (anatomical layer), (v) histological type, (vi) histological grade, (vii) serosal involvement (gastric, pleural or pericardial), (viii) resection margins (proximal, distal and circumferential), (ix) vascular and perineural invasion, (x) number and status of lymph nodes, (xi) formal assessment of the response to neo-adjuvant treatment using TRG scoring system and (xii) pathologic staging (pTNM, according to 8th edition of TNM) (SOR: A, ROVC: 100%)

Post-treatment follow-up

Controversy still exists regarding the need for surveillance of patients with oesophageal cancer undergoing treatment with curative intent [166–171]. With the exception of patients submitted to endoscopic resection for early lesions or definitive CRT for SCC, there is no sufficient evidence to suggest that regular follow-up after initial treatment improves survival in the majority of cases. Therefore, monitoring of patients following radical surgery should focus on symptoms, clinical examination, dietary advice and psychosocial support. Endoscopy or cross-sectional imaging should be performed selectively and based on clinical findings.

Patients with Tis or T1a tumours who undergo EMR or ESD have a significant risk of local recurrence or residual disease and should be monitored very closely [88–90, 92, 93, 95, 172]. Although the frequency of endoscopic surveillance has not been studied specifically, a reasonable schedule would include endoscopies every 3 months for the first year, six monthly the second year and annually thereafter. Endoscopic surveillance should also include a search for the

presence of BO, and four-quadrant biopsies should be taken to detect residual or recurrent dysplasia. Biopsies of the neosquamous mucosa should be taken even in the absence of mucosal abnormalities, as dysplasia may occasionally be present beneath the squamous mucosa. Ablation of residual or recurrent high-grade and low-grade dysplasia should also be considered.

Similarly, patients with SCCs of the proximal oesophagus who undergo definitive CRT and no surgery have an increased risk of local recurrence or residual disease. Therefore, these patients should also be offered intensive follow-up with endoscopy, biopsies and CT every 3 months in the first year and six-monthly thereafter. In the cases where isolated local recurrence or residual disease is detected, salvage surgery can be carried out with relatively good results [119, 120, 173].

Recommendations

- Regular follow-up with endoscopy and cross-sectional imaging is the usual practice for patients undergoing surgery with curative intent, although there is no sufficient evidence that such practice results in improvement of survival (LOE: IV, SOR: B, ROVC: 75%)
- Endoscopic follow-up with biopsies on regular 3-month intervals is recommended after ablative treatment of BO or EMR of Tis lesions (LOE: III, SOR: B, ROVC: 94%)
- Intensive follow-up with endoscopy, biopsies and CT every 3 months in the first year and every 6 months thereafter should be offered to patients with complete response following definitive CRT (LOE: III, SOR: A, ROVC: 91%)
- Endoscopy combined with EUS could accurately detect local postoperative recurrence. FNA should be performed, especially if local recurrence cannot be proven by other means of investigation (LOE: IV, SOR: B, ROVC: 95%)

Treatment of metastatic disease

Chemotherapy

Palliative treatment is the only option for patients with advanced OC with the goal of controlling cancer-related symptoms and prolonging survival without compromising patient's quality of life. Although SCCs represent a small minority of patients enrolled on most clinical trials, histologic subtype does not seem to play a major role in response rate or survival duration in patients treated with a variety of regimens. As a result, systemic therapy regimens recommended for advanced oesophageal and OGJ adenoCa and SCC of the oesophagus can be used interchangeably, except as indicated. Regimens are commonly chosen on the basis of performance status, comorbidities and possible treatment-associated toxicities.

Two-drug regimens are preferred for patients with advanced disease because of lower toxicity, whereas three drug cytotoxic regimens should be reserved for medically fit patients with good performance status and frequent access to toxicity evaluation. Cisplatin and 5FU CT is the most investigated and most commonly applied doublet resulting in response rates of 25–50%. The combination of leucovorin, fluorouracil and oxaliplatin (FLO) was associated with significantly less toxicity and improved median PFS (5.8 vs 3.9 months) compared with leucovorin, fluorouracil and cisplatin (FLP) in a phase III study including patients with metastatic OGJ cancer [174]. Although no significant difference was seen in OS, the subgroup of patients > 65 years receiving FLO had better response rates, PFS and OS (13.9 vs 7.2 m). The REAL-2 study involving anthracycline containing triplets, compared oxaliplatin to cisplatin and capecitabine to fluorouracil and found that capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin, respectively, in patients with previously untreated advanced OGJ adenoCa [175]. Other available options include paclitaxel with a platinum agent [176, 177], docetaxel with cisplatin [178], 5FU with irinotecan [179], ECF and ECF modifications [180] and DCF (docetaxel, fluorouracil and a platinum agent) [181].

Single agent chemotherapy has very low response rate (15%) and no survival benefit. In patients with HER-2 positive metastatic tumours from OGJ adenoCa, the addition of trastuzumab to chemotherapy confers a survival benefit (see Targeted agents).

Targeted agents

Ramucirumab

Based on the RAINBOW phase III study, ramucirumab is administered in advanced gastric or OGJ adenoCa in the second or subsequent line setting in combination with paclitaxel [182]. Single agent ramucirumab can be offered, in the second line setting and after prior platinum or fluoropyrimidine cCT, in patients for whom paclitaxel is not appropriate.

Trastuzumab

Trastuzumab should be added to first-line chemotherapy for HER2 overexpressing metastatic gastric or OGJ adenoCa in combination with either fluoropyrimidine and cisplatin [24] or with other chemotherapeutic agents but not with anthracyclines. Two other anti-HER2 drugs, T-DM1 and lapatinib in combination with capecitabine and oxaliplatin, had negative results in advanced or metastatic gastric cancer [183, 184].

Pembrolizumab

Pembrolizumab can be administered to patients with metastatic dMMR adenoCa of OGJ in the second or subsequent line [185].

Recommendations

- Cytotoxic CT in selected patients with advanced and metastatic OC, irrespective of histology, could be offered, because it can provide symptom palliation, improve quality of life and prolong survival (LOE: III, SOR: B, ROVC: 97%)
- Regimens should be chosen in the context of performance status, medical comorbidities, toxicity profile and HER-2 status (for adenoCa only) (SOR: A, ROVC: 100%)
- Elderly patients with metastatic OC and with a poor performance status may be treated with monotherapy (LOE III, SOR: B, ROVC: 89%)
- Ramucirumab can be used in the second or subsequent line setting in combination with paclitaxel, or as single agent for the treatment of metastatic or advanced OGJ adenoCa (LOE: I, SOR: A, ROVC: 98%)
- Trastuzumab can be added to first-line CT for HER2 overexpressing metastatic OGJ adenoCa in combination with fluoropyrimidine and cisplatin (LOE: I, SOR: A, ROVC: 100%)
- Pembrolizumab can be offered as a second or subsequent line of treatment to patients with metastatic dMMR adenoCa of the oesophagus (LOE: II, SOR: A, ROVC: 93%)

Surgery

Despite some encouraging results presented from centres of excellence in liver surgery, metastatic oesophageal disease remains a contraindication for surgery [186–188]. These limited case series are not providing solid evidence, regarding the benefit of liver resection in these patients but they can give rise to larger multicentre studies, to explore the role of metastatic disease resection.

Recommendations

- Resection of metastatic disease alone is not indicated in OC patients outside clinical trials (LOE: IV, SOR: A, ROVC: 92%)

Palliative treatment

General considerations

In patients with unresectable or locally advanced OC, palliative interventions provide relief of symptoms and may also prolong life and improve nutritional status and overall quality of life. Dysphagia is one of the most common symptoms in patients with oesophageal cancer. Palliative methods for relieving dysphagia include endoscopic therapies, RT, brachytherapy, CT or surgery.

Endoscopic palliation

Endoscopic palliative treatments include dilatation, laser ablation, endoscopic injection, endoscopic mucosal resection, photodynamic therapy and prosthetic stenting of the obstructing tumour. The optimal management is not clear and still debated. The choice of the individual palliative method should be based upon anatomical features of the lesion, patient status and preference, and expertise availability [189].

Chemotherapy and radiotherapy

External beam radiotherapy (EBRT) has traditionally been used as a non-invasive means for the palliation of dysphagia in patients with incurable, metastatic oesophageal cancer. Several series reported significant and long-lasting relief in 60–75% of patients [190]. Short RT courses (30 Gy in 10 fractions) offer favourable responses with minimal toxicities and are more appropriate for patients with limited prognosis [191]. Accumulating evidence supports the use of intraluminal brachytherapy (BT) to palliate persistent dysphagia and bleeding with response rates of 50–80% and median dysphagia-free survival of 3–10 months [192]. The combination of EBRT and BT appears superior to BT alone for longer symptom relief and PFS [193]. In addition, BT offers better symptom control with fewer complications compared to stent insertion as reported by two randomised trials [194].

The combination of RT with CT can also be beneficial for symptom relief in metastatic oesophageal cancer patients, with several series reporting improvement of dysphagia in 60–80% of patients [195, 196]. However, palliative platinum/5-FU CT combined with a short course of RT in the TROG 03.01 randomised trial showed a modest, but not statistically significant, increase in dysphagia relief rate compared with RT alone, but at a cost of increased toxicity [197].

Recommendations

- A short course of palliative RT should be offered to patients with advanced symptomatic OC. Feeding tube insertion for nutritional support is recommended (LOE: III, SOR: B, ROVC: 91%)
- Palliative CRT could be considered for patients with advanced symptomatic OC and good performance status. Feeding tube insertion for nutritional support or stenting

of the lesion for immediate dysphagia relief may also be offered (LOE: II, SOR: B, ROVC: 94%)

Conclusions

Current evidence and practice suggest that patients with oesophageal cancer should be managed at highly specialised centres with adequate case volume, in order to optimise outcomes in terms of morbidity, mortality, local recurrence and survival. Multidisciplinary teams comprising surgeons, oncologists, pathologists, radiotherapists and radiologists should care for these patients at every stage of their treatment from the initial evaluation to the post-treatment follow-up and in accordance with the recommendations listed above.

Audit and quality control of therapeutic services require compulsory collection and registration of all patients' data according to regional or national programmes. Registered data should include all preoperative characteristics, intraoperative outcomes and quality of surgery parameters as well as postoperative morbidity and mortality, follow-up details and oncological outcomes as defined above. A case mix adjusted feedback is crucial in the whole process of the "quality assurance" concept. If suboptimal performance is encountered, the responsible treating team should be instructed to improve results by further and more intensive training or to cease treating such cases.

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Compliance with ethical standards

Conflict of interest Dr. KALOGERIDI reports non-financial support from Sanofi, outside the submitted work; Dr. XYNOS reports non-financial support from Johnson & Johnson, outside the submitted work; Dr. SOUGLAKOS reports grants from Amgen, grants and personal fees from Roche, grants and personal fees from Sanofi, personal fees from Servier, personal fees from MSD, personal fees from Merck Serono, personal fees from CellGene, outside the submitted work.

Human participants and/or animals No human participants or animals were involved during the execution of this research project.

Informed consent For this type of article, informed consent is not required.

Legal disclaimer The study group considers adherence to these guidelines to be voluntary. The ultimate determination regarding their application is to be made by the physician in light of each patient's individual circumstances. In view of the consulting and non-binding nature, these guidelines cannot form the basis for legal action or litigation for compliance or absence of compliance in the clinical practice setting, but can only be considered as general guidelines based on best available evidence for assistance in decision making. Any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. HCGC-SG makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way. In addition, these guidelines describe evaluations and administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that such clinical studies are designed to test innovative management strategies in a disease for which better treatment is sorely needed. However, by reviewing and synthesising the latest literature, this practice guideline serves to identify questions for further research and the settings in which investigational therapy should be considered.

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