

SPECIAL ARTICLE

Soft tissue and visceral sarcomas: ESMO—EURACAN—GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up[☆]

A. Gronchi¹, A. B. Miah², A. P. Dei Tos³, N. Abecassis⁴, J. Bajpai⁵, S. Bauer⁶, R. Biagini⁷, S. Bielack⁸, J. Y. Blay⁹, S. Bolle¹⁰, S. Bonvalot¹¹, I. Boukovinas¹², J. V. M. G. Bovee¹³, K. Boye¹⁴, B. Brennan¹⁵, T. Brodowicz¹⁶, A. Buonadonna¹⁷, E. De Álava^{18,19}, X. G. Del Muro²⁰, A. Dufresne²¹, M. Eriksson²², F. Fagioli²³, A. Fedenko²⁴, V. Ferraresi²⁵, A. Ferrari²⁶, A. M. Frezza²⁷, S. Gasperoni²⁸, H. Gelderblom²⁹, F. Gouin³⁰, G. Grignani³¹, R. Haas^{32,33}, A. B. Hassan³⁴, S. Hecker-Nolting⁸, N. Hindi³⁵, P. Hohenberger³⁶, H. Joensuu³⁷, R. L. Jones³⁸, C. Jungels³⁹, P. Jutte⁴⁰, L. Kager⁴¹, B. Kasper³⁶, A. Kawai⁴², K. Kopeckova⁴³, D. A. Krákorová⁴⁴, A. Le Cesne⁴⁵, F. Le Grange⁴⁶, E. Legius⁴⁷, A. Leithner⁴⁸, A. Lopez-Pousa⁴⁹, J. Martin-Broto³⁵, O. Merimsky⁵⁰, C. Messiou⁵¹, O. Mir⁵², M. Montemurro⁵³, B. Morland⁵⁴, C. Morosi⁵⁵, E. Palmerini⁵⁶, M. A. Pantaleo⁵⁷, R. Piana⁵⁸, S. Piperno-Neumann⁵⁹, P. Reichardt⁶⁰, P. Rutkowski⁶¹, A. A. Safwat⁶², C. Sangalli⁶³, M. Sbaraglia³, S. Scheipl⁴⁸, P. Schöffski⁶⁴, S. Sleijfer⁶⁵, D. Strauss⁶⁶, S. Strauss⁴⁶, K. Sundby Hall¹⁴, A. Trama⁶⁷, M. Unk⁶⁸, M. A. J. van de Sande⁶⁹, W. T. A. van der Graaf^{65,70}, W. J. van Houdt⁷¹, T. Frebourg^{72†}, P. G. Casali^{27,73} & S. Stacchiotti²⁶, on behalf of the ESMO Guidelines Committee, EURACAN and GENTURIS^{*}

¹Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy; ²Department of Oncology, Royal Marsden Hospital and Institute of Cancer Research, London, UK; ³Department of Pathology, Azienda Ospedale Università Padova, Padua, Italy; ⁴Instituto Portugues de Oncologia de Lisboa Francisco Gentil, EPE, Lisbon, Portugal; ⁵Department of Medical Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India; ⁶Department of Medical Oncology, Interdisciplinary Sarcoma Center, West German Cancer Center, University of Duisburg-Essen, Essen, Germany; ⁷Department of Oncological Orthopedics, IRCCS Regina Elena National Cancer Institute, Rome, Italy; ⁸Klinikum Stuttgart-Olgahospital, Stuttgart, Germany; ⁹Centre Leon Berard and UCBL1, Lyon; ¹⁰Radiation Oncology Department, Gustave Roussy, Villejuif; ¹¹Department of Surgery, Institut Curie, Paris, France; ¹²Bioclinic Thessaloniki, Thessaloniki, Greece; ¹³Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands; ¹⁴Department of Oncology, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway; ¹⁵Paediatric Oncology, Royal Manchester Children's Hospital, Manchester, UK; ¹⁶Vienna General Hospital (AKH), Medizinische Universität Wien, Vienna, Austria; ¹⁷Centro di Riferimento Oncologico di Aviano, Aviano, Italy; ¹⁸Hospital Universitario Virgen del Rocío-CIBERONC, Seville; ¹⁹Department of Normal and Pathological Cytology and Histology, School of Medicine, University of Seville, Seville; ²⁰Integrated Unit ICO Hospitalet, HUB, Barcelona, Spain; ²¹Département d'Oncologie Médicale, Centre Leon Berard, Lyon, France; ²²Skane University Hospital-Lund, Lund, Sweden; ²³Paediatric Onco-Haematology Department, Regina Margherita Children's Hospital, Department of Public Health and Pediatrics, University of Turin, Turin, Italy; ²⁴P. A. Herzen Cancer Research Institute, Moscow, Russian Federation; ²⁵Sarcomas and Rare Tumors Unit, IRCCS Regina Elena National Cancer Institute, Rome; ²⁶Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; ²⁷Department of Cancer Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Milan; ²⁸Azienda Ospedaliera Universitaria Careggi Firenze, Florence, Italy; ²⁹Department of Medical Oncology, Leiden University Medical Center, Leiden, The Netherlands; ³⁰Centre Leon-Berard Lyon, Lyon, France; ³¹Candiolo Cancer Institute, FPO - IRCCS, Candiolo, Italy; ³²Department of Radiotherapy, The Netherlands Cancer Institute, Amsterdam; ³³Department of Radiotherapy, Leiden University Medical Centre, Leiden, The Netherlands; ³⁴Oxford University Hospitals NHS Foundation Trust and University of Oxford, Oxford, UK; ³⁵Department of Medical Oncology, Fundación Jimenez Diaz University Hospital, Advanced Therapies in Sarcoma Lab, Madrid, Spain; ³⁶Mannheim University Medical Center, Mannheim, Germany; ³⁷Helsinki University Hospital (HUU) and University of Helsinki, Helsinki, Finland; ³⁸Sarcoma Unit, Royal Marsden Hospital and Institute of Cancer Research, London, UK; ³⁹Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; ⁴⁰University Medical Center Groningen, Groningen, The Netherlands; ⁴¹St. Anna Children's Hospital, Department of Pediatrics and Medical University Vienna Children's Cancer Research Institute, Vienna, Austria; ⁴²Department of Musculoskeletal Oncology, National Cancer Center Hospital, Tokyo, Japan; ⁴³University Hospital Motol, Prague; ⁴⁴Masaryk Memorial Cancer Institute, Brno, Czech Republic; ⁴⁵Department of Cancer Medicine, Gustave Roussy, Villejuif, France; ⁴⁶Department of Oncology, University College London Hospitals NHS Foundation Trust (UCLH), London, UK; ⁴⁷Department for Human Genetics, University Hospitals Leuven, KU Leuven, Leuven, Belgium; ⁴⁸Department of Orthopaedics and Trauma, Medical University of Graz, Graz, Austria; ⁴⁹Medical Oncology Department, Hospital Universitario Santa Creu i Sant Pau, Barcelona, Spain; ⁵⁰Tel Aviv Sourasky Medical Center (Ichilov), Tel Aviv, Israel; ⁵¹Department of Radiology, Royal Marsden Hospital and Institute of Cancer Research, London, UK; ⁵²Department of Ambulatory Cancer Care, Gustave Roussy, Villejuif, France; ⁵³Department of Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; ⁵⁴Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK; ⁵⁵Department of Radiology, IRCCS Foundation National Cancer Institute, Milan; ⁵⁶Department of Osteoncolology, Bone and Soft Tissue Sarcomas and Innovative Therapies, IRCCS Istituto Ortopedico Rizzoli, Bologna; ⁵⁷Division of Oncology, IRCCS Azienda Ospedaliero-Universitaria, di Bologna, Bologna; ⁵⁸Azienda Ospedaliero, Universitaria Città della Salute e della Scienza di Torino, Turin, Italy; ⁵⁹Department of Medical Oncology, Institut Curie, Paris, France; ⁶⁰Helios Klinikum Berlin Buch, Berlin, Germany; ⁶¹Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland; ⁶²Aarhus University Hospital, Aarhus, Denmark; ⁶³Department of Radiotherapy, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; ⁶⁴Department of General Medical Oncology, University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium; ⁶⁵Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; ⁶⁶Department of Surgery, Royal Marsden Hospital, London, UK; ⁶⁷Department of Research, Evaluative Epidemiology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; ⁶⁸Institute of Oncology of Ljubljana, Ljubljana, Slovenia; ⁶⁹Department of Orthopedic Surgery, Leiden University Medical Center, Leiden; Departments of ⁷⁰Medical Oncology; ⁷¹Surgical Oncology, the Netherlands Cancer Institute, Amsterdam, The Netherlands; ⁷²Department of Genetics, Normandy Center for Genomic and Personalized Medicine, Normandie Univ, UNIROUEN, Inserm U1245 and Rouen University Hospital, Rouen, France; ⁷³Department of Oncology and Hemato-oncology University of Milan, Milan, Italy



Available online 22 July 2021

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, 6900 Lugano, Switzerland
E-mail: clinicalguidelines@esmo.org (ESMO Guidelines Committee, EURACAN and GENTURIS).

[☆]Note: Approved by the ESMO Guidelines Committee, EURACAN and GENTURIS: August 2021. This publication supersedes the previously published version – *Ann Oncol*. 2018;29(suppl 4):iv51-iv67.

[†] Deceased.

0923-7534/© 2021 European Society for Medical Oncology. Published by Elsevier Ltd. All rights reserved.

Key words: sarcoma, soft tissue sarcomas, retroperitoneal sarcoma, uterine sarcoma, desmoid, Clinical Practice Guideline.

INTRODUCTION

Soft tissue sarcomas (STSs) comprise ~80 entities defined by the World Health Organization (WHO) classification based on a combination of distinctive morphological, immunohistochemical and molecular features.¹ These ESMO–EURACAN–GENTURIS (European Society for Medical Oncology; European Reference Network for Rare Adult Solid Cancers; European Reference Network for Genetic Tumour Risk Syndromes) Clinical Practice Guidelines (CPGs) will cover STSs, with the exception of gastrointestinal stromal tumours (GISTs) that are covered in the ESMO–EURACAN–GENTURIS GIST CPGs.² EURACAN and GENTURIS are the European Reference Networks connecting European institutions, appointed by their governments, to cover rare adult solid cancers and genetic cancer risk syndromes, respectively. Extraskeletal Ewing sarcoma, round cell sarcoma with *EWSR1*-non-ETS fusion and sarcomas with *CIC* rearrangements and *BCOR* genetic alterations are covered by the ESMO–EURACAN–GENTURIS–ERN PaedCan (European Reference Network for Paediatric Oncology) bone sarcomas CPG.³ Kaposi's sarcoma, embryonal and alveolar rhabdomyosarcoma are not discussed in this manuscript, while pleomorphic rhabdomyosarcoma is viewed as a high-grade, adult-type STS. Finally, extraskeletal osteosarcoma is also considered a high-grade STS, whose clinical resemblance with osteosarcoma of bone is doubtful. The methodology followed during the consensus meeting is specified at the end of the manuscript in a dedicated paragraph.

INCIDENCE AND EPIDEMIOLOGY

Adult-type soft tissue and visceral sarcomas (excluding GISTs) are rare tumours, with an estimated incidence averaging 4–5/100 000/year in Europe.⁴ The most common STS types are liposarcomas and leiomyosarcomas (LMSs), with an incidence <1/100 000/year each, whereas the majority of sarcoma histotypes have an incidence <2/1 000 000/year.

Management in specialist reference centres

STSs can occur at any site in the body and are often managed with multimodal treatments. A multidisciplinary approach is, therefore, mandatory in all cases, involving pathologists, radiologists, surgical oncologists, orthopaedic oncologists, radiation oncologists, medical oncologists and paediatric oncologists, as well as nuclear medicine specialists and organ-based specialists, as applicable. Management should be carried out in reference centres for sarcomas and/or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually.⁵ These centres are involved in ongoing clinical trials, in which

the enrolment of sarcoma patients is common practice. Referral to a specialist centre should occur early at clinical diagnosis of a suspected sarcoma. This would mean referring all patients with an unexplained deep soft tissue mass, or with a superficial soft tissue lesion with a diameter ≥ 5 cm. Quality criteria are needed for sarcoma reference centres and, increasingly, reference networks. These criteria may vary between countries but should be based on: multidisciplinary (incorporating tools such as weekly multidisciplinary sarcoma tumour board meetings discussing cases), case volume, availability of facilities needed to properly apply CPGs, access to state-of-the-art diagnostic molecular pathology, recording and publication of outcomes and involvement in clinical and translational research.⁶

Recommendation

- Management of STSs should be carried out in sarcoma reference centres or tertiary paediatric oncology centres as appropriate for age [III, A].

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

In primary soft tissue tumours, magnetic resonance imaging (MRI) is the main imaging modality in the extremities, pelvis and trunk. Standard radiographs may be useful to rule out a bone tumour, to detect bone erosion with a risk of fracture and to show calcifications. Computed tomography (CT) has a role in calcified lesions, to rule out a myositis ossificans, in pleuropulmonary sarcomas and in retroperitoneal sarcomas (RPSs) where the performance is identical to MRI. Ultrasound may be used as first-line imaging, but if there is any suspicion for STS it should be followed by CT or MRI.

Following appropriate imaging assessment, the standard approach to diagnosis consists of multiple, core needle biopsies, possibly by using ≥ 14 –16 G needles. However, an excisional biopsy may be the most practical option for <3 cm superficial lesions. An open biopsy may be another option in selected cases, when decided within reference centres. An immediate evaluation of tissue viability using the frozen section technique may be considered to ensure that the biopsy is adequate and representative at the time it is carried out, although an immediate diagnosis is not encouraged, because frozen section technique does not allow a complete diagnosis. A biopsy may underestimate the tumour malignancy grade. Therefore, when preoperative treatment is an option, radiological imaging [including [¹⁸F]2-fluoro-2-deoxy-D-glucose positron emission tomography/CT (FDG–PET/CT)] may be useful, in addition to pathology, in providing information that helps to estimate the malignancy grade. The biopsy should be carried out by a

surgeon or a radiologist after multidisciplinary discussion. It should be planned in such a way that the biopsy tract and the scar can be safely removed by definitive surgery (except for RPSs). The biopsy entrance point can be tattooed. Even if formalin-fixed paraffin-embedded (FFPE) material allows routine molecular diagnostics, the collection of fresh snap-frozen tissue is encouraged to allow subsequent molecular assessments, particularly in the context of research. Informed consent for biobanking should be sought, enabling later research.

Pathological diagnosis should be made according to the 2020 WHO classification for soft tissue and bone tumours.¹ Since discrepancy rates between diagnosis made outside of reference centres and those made by a sub-specialised bone and soft tissue pathologist are considerable, (ranging from 8% to 11% for major discordance, and 16% to 35% for minor discordance), a pathological expert validation is required in all cases when the original diagnosis is made outside a reference centre/network.⁷

The International Collaboration for Cancer Reporting (ICCR) provides guidelines for standardised pathology reporting of STS (Supplementary Table S1, available at <https://doi.org/10.1016/j.annonc.2021.07.006>).⁸ The tumour grade should be provided in all cases in which this is feasible and applicable based on available systems, because it has prognostic and predictive meaning. The Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system is generally used, which distinguishes three malignancy grades based on differentiation, necrosis and mitotic rate.⁹ Whenever possible, the mitotic rate should be provided independently. Grading cannot be assigned after preoperative chemotherapy (ChT) and/or radiotherapy (RT), as the tumour tissue undergoes therapy-related changes.

The pathology report following definitive surgery should include whether the tumour was intact and the status of surgical margins. If margins are involved, a distinction is made between macroscopic complete resection with microscopic involvement (R1) and macroscopic incomplete resection (R2).⁹ In case of negative margins (R0), the minimum that should be documented is the distance of tumour to the closest margins. The type of tissue comprising the resection margin should also be recorded since specific tissue types (e.g. fascia) might provide more robust margins than others. In retroperitoneal liposarcomas, microscopic surgical margins have limited clinical value.

If preoperative treatment was administered, the pathology report should include an assessment of the pathological response, even though no validated systems for pathological response assessment are available for STSs. A multidisciplinary judgement is recommended, involving the pathologist and the radiologist. Preferably, post-treatment resection specimens are grossly worked up in a standardised manner as described by the European Organisation for Research and Treatment of Cancer (EORTC) consensus group.¹⁰ At the very least, the pathologist should document the microscopic proportion of viable/residual tumour cells.¹⁰ It is advised also to document the percentage of

fibrosis/hyalinisation even though the prognostic role of these parameters is still left to be investigated.

Pathological diagnosis relies on morphology complemented by immunohistochemistry and/or molecular pathology. Pathology diagnosis should be complemented by molecular pathology, especially when:

- The specific pathological diagnosis is doubtful.
- The clinical pathological presentation is unusual.
- It may have prognostic and/or predictive relevance, as exemplified by neurotrophic tyrosine receptor kinase (*NTRK*) rearrangement.
- The labels of the entity specifically refer to a distinctive molecular aberration. External quality assurance programmes are mandatory for laboratories performing molecular pathology assessments.

Recommendation

- Pathological diagnosis should be made by a sarcoma expert pathologist according to the 2020 WHO classification [IV, A].

STAGING AND RISK ASSESSMENT

Available staging classifications have limited relevance and should be improved. The Union for International Cancer Control (UICC) stage classification system, 8th edition stresses the importance of the malignancy grade in staging sarcoma.¹¹ Other prognostic factors are tumour size, tumour site, tumour resectability, the presence of metastases, quality of surgical margins and preoperative/intraoperative tumour rupture. Validated nomograms are available, which can help personalise risk assessment and aid clinical decision making, especially regarding the benefit of adjuvant/neoadjuvant treatments.¹²⁻¹⁴

A CT scan of the thorax is recommended for staging purposes. Regional lymph node (LN) metastases are usually rare (i.e. <1%); there are exceptions such as epithelioid sarcoma, clear-cell sarcoma (CCS), synovial sarcoma and angiosarcoma, for which regional assessment by CT/MRI may be added to the usual staging procedures. A CT scan of the abdomen and pelvis is recommended in the majority of sarcoma types, especially myxoid liposarcoma (MLS) and LMS [III, B]. Alternatively, a whole-body MRI can also be considered. Imaging of the brain (MRI preferred over CT) should be carried out in alveolar soft part sarcoma (ASPS) and can be considered for CCS and angiosarcoma.

FDG-PET/CT may be reserved as a problem-solving tool, for example for characterising equivocal CT findings such as LNs in relevant sarcoma types. Studies on cost-effective staging procedures are required.

The surgical report, or patient chart, should provide details on preoperative and intraoperative diagnosis, the surgical conduct, including possible contaminations (i.e. it should mention whether tumour rupture occurred either before or during surgery), the actual completeness and planned quality of margins.

Germline TP53 testing

Germline TP53 testing should be carried out, if possible, before treatment initiation in (i) patients <46 years of age with STS and at least one first- or second-degree relative <56 years of age with a TP53 core tumour (breast cancer, STS, bone sarcoma, central nervous system tumour, adrenocortical carcinoma), or (ii) patients with STS (especially in RT fields) and with another TP53 core tumour <46 years of age.¹⁵ In TP53 carriers, RT should be avoided if possible after multidisciplinary discussion,¹⁵ while an annual whole-body MRI is recommended.¹⁵

Recommendations

- Available staging classifications [UICC-American Joint Committee on Cancer (AJCC)] are of limited clinical value. Risk assessment is better obtained through the available nomograms [IV, A].
- Staging is routinely carried out with contrast-enhanced chest, abdomen and pelvis CT. Whole-body MRI may be an alternative, especially in selected histotypes. Brain CT/MRI may be indicated only in ASPS, CCS and angiosarcoma. FDG—PET/CT is indicated as a problem-solving tool in equivocal cases [IV, A].
- Surgical report should include preoperative and intraoperative diagnosis, possible contamination/tumour rupture, completeness and planned quality of microscopic margins [IV, A].
- TP53 testing should be carried out in selected patients with STS under the age of 46 years [IV, A].

MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE

This paragraph focuses on STSs arising from extremities and trunk walls (including paraspinal and head and neck locations). Special considerations about specific sites and histological types will appear later in the document. Management of local/locoregional disease located in an extremity or superficial trunk is summarised in [Figures 1](#) and [2](#). Surgery is the standard treatment for all patients with an adult-type, localised STS. It must be carried out by a surgeon specifically trained in the treatment of this disease within a sarcoma centre/network. The standard surgical procedure is an *en bloc* excision with R0 margins. This implies removing the tumour in a single specimen with a rim of normal tissue around it [II, A].¹⁶ The minimal margin on fixed tissue to be considered adequate may depend on several factors, including histological subtype, preoperative therapies and the presence of resistant anatomical barriers, such as muscular fascia, vascular adventitia, periosteum and epineurium. As an individualised option, R1 excision can be acceptable in carefully selected cases; in particular, marginal excisions along the pseudocapsule are advised for atypical lipomatous tumours [IV, B].

RT is typically added to surgery as part of the standard treatment of high-grade (G2-3) lesions [II, B].^{17,18} While

historically RT was preferably delivered post-operatively, it is now often delivered in the preoperative setting. RT is not indicated in the case of a truly compartmental resection of a tumour entirely contained within the compartment [IV, E]. RT may also be omitted after multidisciplinary discussion, considering risk factors for local recurrence, including expected/actual surgical margins, tumour size and histological type.¹⁹ This also applies to low-grade STS, which are mostly treated by surgery alone, but preoperative or post-operative RT can be considered on an individualised basis factoring histological type, tumour size and site, as well as the consequences of a local recurrence.

Local control and overall survival (OS) are not influenced by the timing of RT. However, preoperative RT is able to offset the negative prognostic impact of R1 margins much more than post-operative RT. It should always be considered when preservation of a critical structure is the goal.^{20,21} Early complications (wound complications) are more common after preoperative RT, but long-term morbidity is improved with a reduction in fibrosis, oedema, bone fracture and joint stiffness.²² RT should be delivered with the most appropriate technique available [including but not limited to intensity-modulated RT (IMRT) and particle therapy in challenging sites], to a total dose of 50 Gy in 1.8-2 Gy fractions in the preoperative setting. In the post-operative setting, doses up to 66 Gy are given, depending on presentation, age and resection margins. Neoadjuvant RT can be given in combination with ChT to the same total dose of 50 Gy in 1.8-2 Gy fractions with manageable toxicity.²³ Surgery takes place 4-8 weeks after the termination of the last cycle of ChT or the last fraction of RT. With modern RT techniques, such as image-guided RT and IMRT, the anticipated incidence of wound complications after preoperative RT may be lower than historically published incidence rates. Short-course preoperative regimens with hypofractionation have been recently reported, showing comparable effects to conventional fractionations.²⁴

Histological types such as MLS, solitary fibrous tumour (SFT), myxofibrosarcoma and extraskeletal myxoid chondrosarcoma gain the greatest benefit from RT.^{25,26} For MLS, one study has recently investigated a low dose (18 × 2 Gy), showing activity of the reduced regimen, but without comparing the efficacy with conventional doses.²⁷ Re-excision at reference centres must be considered in case of unplanned resections if adequate margins can be achieved without major morbidity, while taking into account tumour extent and tumour biology [e.g. a re-excision can be spared in atypical lipomatous tumours and classic dermatofibrosarcoma protuberans (DFSP)] [IV, A]. In case of R2 surgery, re-excision at reference centres is mandatory, possibly following preoperative treatments if adequate margins cannot be achieved, or if surgery is mutilating. When surgery may be mutilating, a multimodal treatment employing less radical surgery is an option and requires shared decision-making with the patient. Plastic surgery reconstruction and vascular grafting should be utilised as

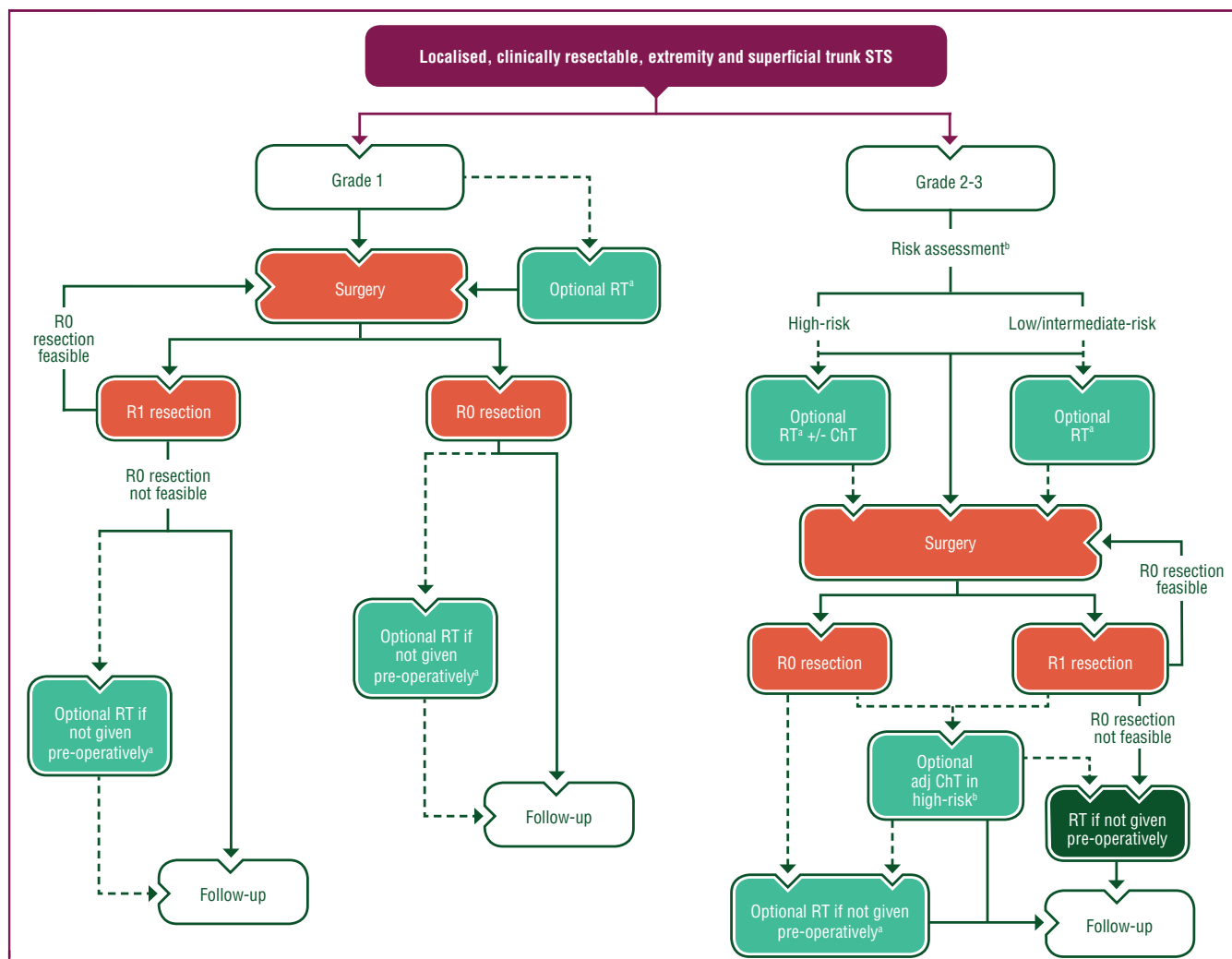


Figure 1. Management of localised, clinically resectable, extremity and superficial trunk STS.

Purple: general categories or stratification; dark green: radiotherapy; red: surgery; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.

adj, adjuvant; ChT, chemotherapy; R0, no tumour at the margin; R1, microscopic tumour at the margin; RT, radiotherapy; STS, soft tissue sarcoma.

^a Depending upon histology and anatomical location.

^b See text.

needed, and the patient should be properly referred if necessary.

When re-excision is not possible after R1-R2 resections, post-operative RT may be considered, tailoring the decision depending on further considerations, including the impact on future surgeries.

Amputation may be the only option in certain cases. Options for limb-preserving surgery can be discussed with the patient, including ChT and/or RT [III, A], or isolated limb perfusion (ILP) with tumour necrosis factor- α (TNF- α) plus melphalan [III, A]. Perioperative regional hyperthermia combined with ChT is another option [I, B].²⁸ These options are considered in non-resectable tumours as well.

Regional LN metastases should be distinguished from soft tissue metastases in a LN basin. Regional LN metastases are rare in most subtypes and constitute an adverse prognostic factor. More aggressive multimodality treatment may be appropriate for patients with locoregional recurrences

including LN metastases, although there is a lack of formal evidence of a benefit. Radical surgery may be combined with neoadjuvant RT and neoadjuvant ChT for sensitive histological types [IV, B]. ChT may be administered as pre-operative treatment, at least in part, especially in ChT-naïve patients. ILP may be an option when easy limb- or function-sparing surgery is not possible. This modality has no impact on systemic control (but it can be combined with other modalities) [III, A].²⁹

In operable, localised STSs of extremities and the trunk wall, there is no uniform use of adjuvant and neoadjuvant anthracycline plus ifosfamide (AI) ChT among expert centres. Formally, adjuvant and neoadjuvant AI ChT is not a standard treatment. It can, however, be proposed for fit patients affected by disease at high risk of death. While published clinical controlled trials are conflicting and some large trials have shown no benefit from adjuvant and neoadjuvant AI ChT, smaller controlled

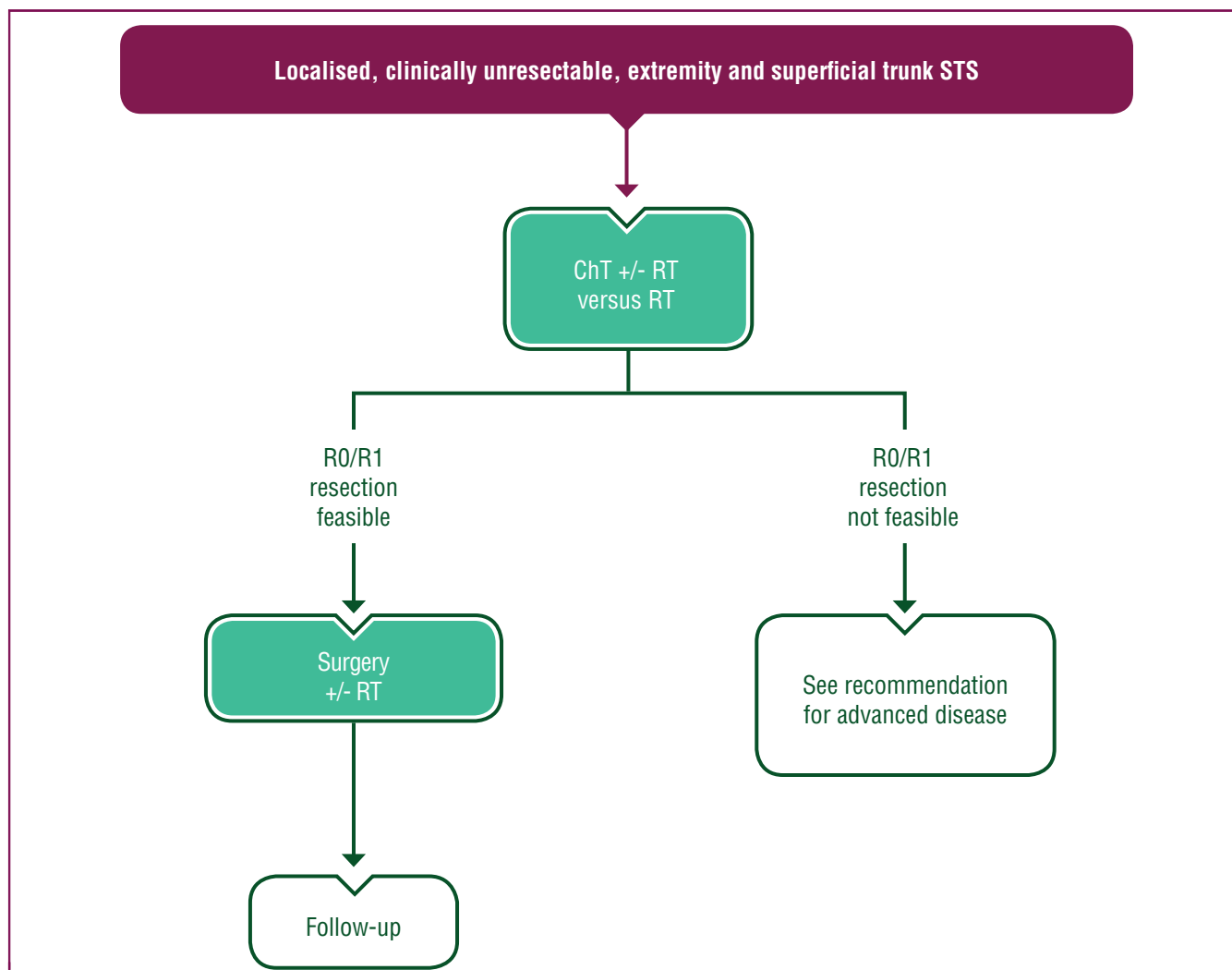


Figure 2. Management of localised, clinically unresectable, extremity and superficial trunk STS.

Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management. ChT, chemotherapy; R0, no tumour at the margin; R1, microscopic tumour at the margin; RT, radiotherapy; STS, soft tissue sarcoma.

trials and subgroup analyses of larger trials have provided data suggesting that when the risk of death is high, neoadjuvant or adjuvant AI ChT may improve relapse-free survival (RFS) and OS.³⁰⁻³²

Risk-predicting tools such as the Sarculator have identified a threshold of risk above which the administration of AI ChT may provide statistically and clinically significant benefits [II, B].^{12,33} These tools apply to the most common histological types. Patients affected by these types and with a 10-year predicted OS <60% should be selected. ChT should preferably be given in the neoadjuvant setting for at least three courses, given the non-inferiority of this shorter regimen compared with five cycles, shown in a randomised study [II, B].³⁴ The decision in patients affected by less common types needs to be made on an individual basis. Histological types known to be refractory to AI ChT in the metastatic setting (such as ASPS or CCS) should not receive adjuvant/neoadjuvant ChT.

During neoadjuvant ChT, the tumour behaviour should be monitored to exclude progression, while considering possible

patterns of non-dimensional tumour response. During neoadjuvant ChT-RT, RT should not delay the beginning of ChT, and both can be used concomitantly. Evidence has been provided about the tolerability of the combination [III, B].²³ In MLS, data from one trial suggest that trabectedin may be an alternative to AI. Evidence has also been provided on the safety profile of its combination with RT. In angiosarcoma, adjuvant/neoadjuvant ChT may be a reasonable option, since there is a high risk of local and metastatic relapse and the sensitivity to available agents (i.e. anthracyclines, ifosfamide, taxanes, gemcitabine) is high. However, definitive evidence to support this is currently lacking.

For the use of adjuvant or neoadjuvant ChT for STSs arising from primary sites other than limbs and superficial trunk, as well as for histologies not covered by available studies, a shared decision-making along with multidisciplinary tumour board discussion should be engaged.

In one large randomised phase III study (in patients with G2-3, deep, >5 cm STS), regional hyperthermia in addition

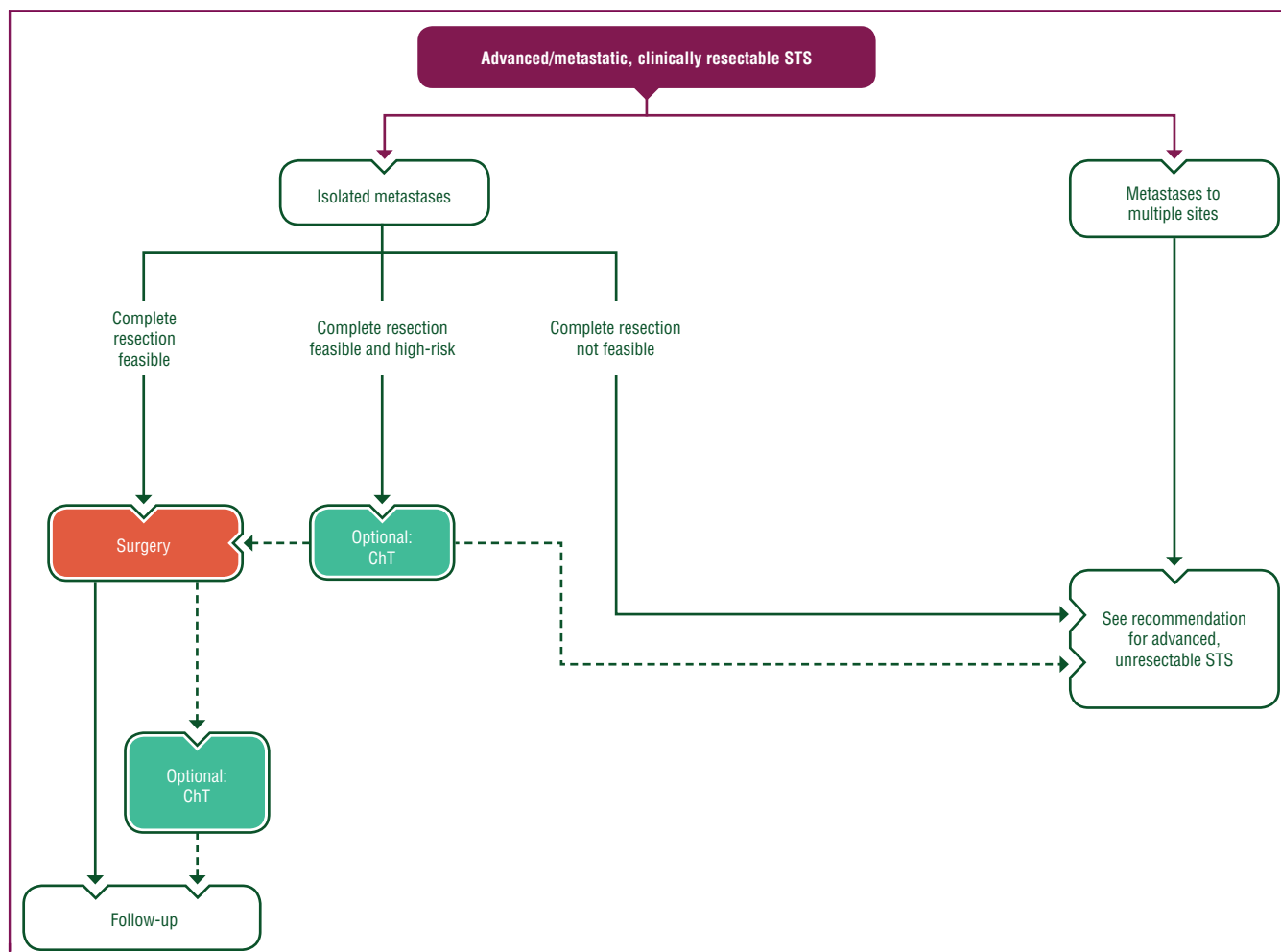


Figure 3. Management of advanced/metastatic, clinically resectable STS.

Purple: general categories or stratification; red: surgery; turquoise: combination of treatments or other systemic treatments; white: other aspects of management. ChT, chemotherapy; STS, soft tissue sarcoma.

to systemic ChT was associated with better response rates, a longer local progression-free survival (PFS), disease-free survival (DFS) and OS advantage [I, B].²⁸

In general, adjuvant ChT should never be intended to compensate for inadequate surgery.

The standard approach to local relapses parallels the approach to primary local disease, except for a wider utilisation of preoperative or post-operative RT and/or ChT, if not previously administered.

Recommendations

- Surgery is the standard treatment for all patients with an adult-type, localised STS. It must be carried out by a surgeon specifically trained in the treatment of STSs. The standard surgical procedure is an *en bloc* wide excision with R0 margins [II, A].
- Wide excision and RT are the standard treatment of high-grade (G2-3) lesions [II, B]. The sequence of the two treatments varies among institutions, but there is an overall shift towards the use of preoperative RT, especially when preserving a critical structure is one of the goals. RT can be omitted only after multidisciplinary

discussion in reference centres considering several variables.

- Options for limb-preserving surgery include ChT and/or RT [III, A], or ILP [III, A], or regional hyperthermia combined with ChT [I, B].
- Adjuvant/neoadjuvant AI ChT for at least three cycles can be proposed to patients at high risk of death [II, B].
- Neoadjuvant ChT with regional hyperthermia is another individualised option in patients at high risk of death [I, B].

MANAGEMENT OF ADVANCED DISEASE

Management of advanced disease is summarised in Figures 3 and 4. When managing patients with advanced/metastatic STS, the decision making is complex, depending on the diverse presentations and histologies, and should always be multidisciplinary. Metachronous (disease-free interval ≥ 1 year), resectable lung metastases without extrapulmonary disease are managed with surgery as standard treatment, if complete excision of all lesions is feasible, taking into account all prognostic

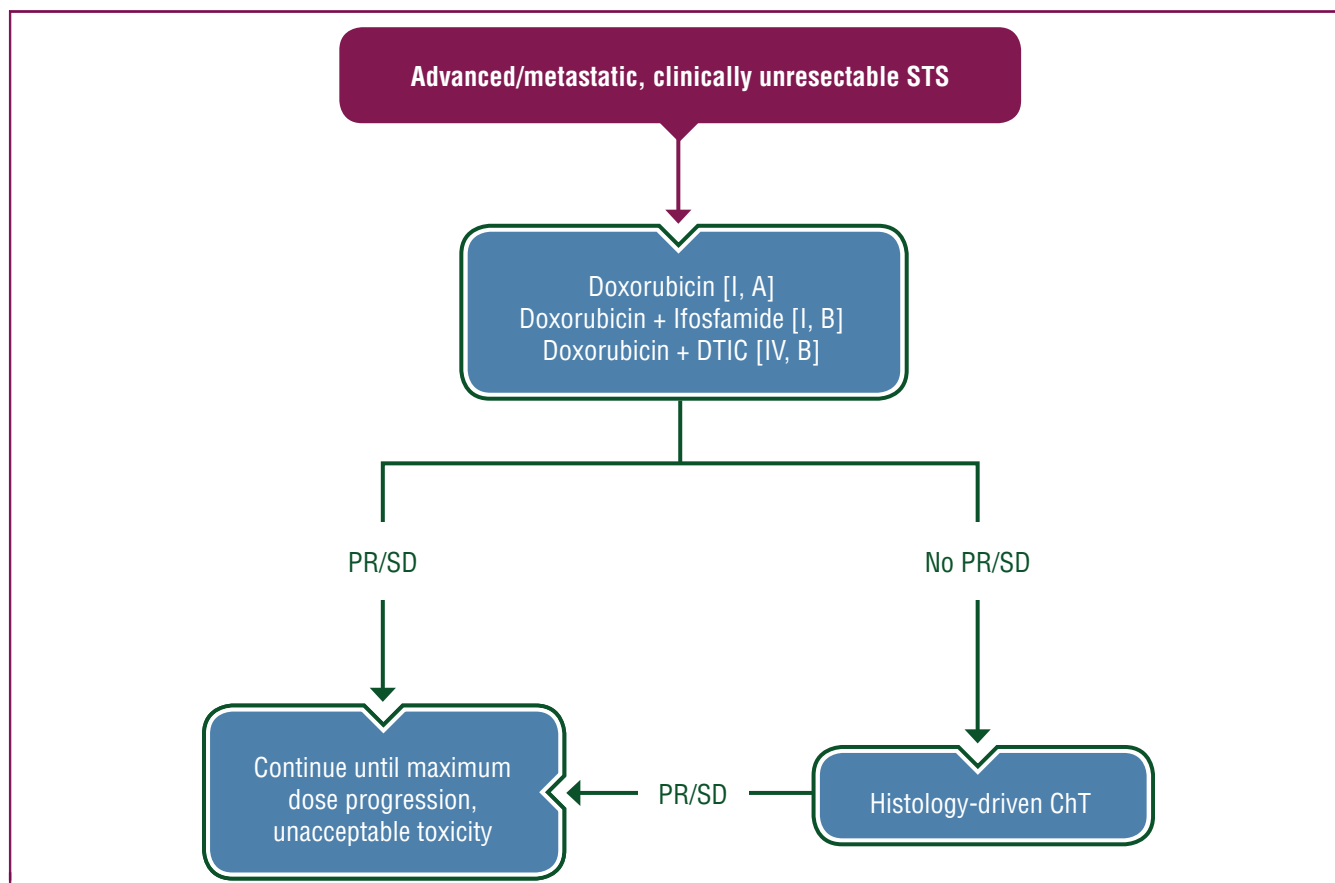


Figure 4. Management of advanced/metastatic, clinically unresectable STS.

Purple: general categories or stratification; blue: systemic anticancer therapy.

ChT, chemotherapy; DTIC, dacarbazine; PR, partial response; SD, stable disease; STS, soft tissue sarcoma.

factors [IV, B].³⁵ A minimally invasive thoracoscopic approach can be used in selected cases. Other appropriate local techniques can be considered, although surgery is the standard treatment and outcome data are required on alternative, less invasive options. When surgery of lung metastases is selected, an abdominal CT scan and a bone scan or FDG–PET are mandatory to confirm that lung metastases are ‘isolated’.

ChT may be added to surgery as an option, taking into account the prognostic factors (a short previous recurrence-free interval and a high number of lesions are adverse factors, encouraging the addition of ChT), although there is a lack of formal evidence that this improves outcome [IV, B]. ChT is preferably given before surgery to assess tumour response and modulate treatment. When lung metastases are synchronous, in the absence of extrapulmonary disease, standard treatment is ChT [III, B]. Surgery for resectable residual lung metastases may be offered as an option after ChT, especially when a tumour response is achieved. In case of isolated lung metastases, other local treatments, such as stereo-ablative RT, may also be considered.

Pulmonary non-resectable disease and extrapulmonary metastatic disease are treated with ChT as the standard of care [I, A]. Surgery or stereo-ablative RT of extrapulmonary metastases without ChT may be an option in selected cases,

especially oligometastatic disease. Surgery or RT of responding metastases may be offered as an option, taking into consideration the site, tumour extent and natural history of the disease in the individual patient.

In patients with locally advanced/metastatic, non-resectable disease, systemic treatment with an essentially palliative intent can be proposed. Anthracycline-based therapy is the standard first-line treatment [I, A]. There is no formal demonstration that multi-agent ChT is superior to single-agent ChT with doxorubicin alone in terms of OS. However, a higher response rate and longer PFS can be expected in a number of sensitive histological types according to several, although not all, randomised, clinical trials.^{36,37} Therefore, multi-agent ChT with adequate-dose AI may be the treatment of choice, particularly in histological types sensitive to ifosfamide, when a tumour response is felt to be potentially advantageous and patient performance status (PS) is good [I, B]. Doxorubicin plus dacarbazine is an option for multi-agent, first-line ChT for LMS, in which the activity of ifosfamide is far less convincing, and for SFT [IV, B].^{38,39}

A phase III study compared single-agent doxorubicin with the combination of gemcitabine-docetaxel as an upfront treatment in advanced STS patients of all types. The combination failed to show any improvement in PFS and objective response rate and is not recommended as

first-line therapy for advanced STS patients [I, D]⁴⁰ including uterine LMS.

Angiosarcoma is highly sensitive to taxanes, which can be a treatment option in this histological type [III, B].⁴¹ An alternative option is gemcitabine, alone or in combination with docetaxel [V, B].⁴²

Imatinib is standard first-line medical therapy for patients with advanced DFSP [III, A].⁴³

NTRK inhibitors are standard treatment of those rare patients with locally-advanced or metastatic *NTRK*-rearranged sarcomas; larotrectinib [III, A; European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 3]; entrectinib [III, A; ESMO-MCBS v1.1 score: 3].⁴⁴⁻⁴⁶ This treatment can also be considered in the preoperative setting, when a cytoreduction can improve morbidity and function. For *NTRK*-fusion screening, pan-NTRK immunohistochemistry has an overall sensitivity-specificity, which in STS is around 80%-75%.⁴⁵ Molecular confirmation of *NTRK* rearrangement is therefore requested in case of positive immunohistochemistry expression.

Further-line systemic therapy can be considered in fit patients with advanced STS and disease progression [II, B]. For unfit patients, no further active tumour-directed treatment may be appropriate, especially if further-line therapies have already been used. In general, patients with pretreated advanced STS should be considered for clinical trials. For patients with anthracycline-refractory disease or who are unable to receive an anthracycline, there are other options available, although high-ranking evidence is lacking:

- Patients who have already received ChT may be treated with ifosfamide if they did not progress on it previously. High-dose ifosfamide as continuous infusion 14 days (~14 g/m²) may also be an option for patients already pretreated with standard-dose (9 g/m²) ifosfamide [IV, C].^{47,48}
- Trabectedin is an option in advanced STS in second and further lines of treatment. It has proved effective in LMS and liposarcoma⁴⁹ [I, B; ESMO-MCBS v1.1 score: 2]. A high antitumour activity has been reported especially in MLS, with a peculiar pattern of tumour response. Clinical benefit with trabectedin is also described in other histological types. In selected cases trabectedin can also be combined with RT, as evidence of safety and activity across different sarcoma types was provided [III, B].⁵⁰
- A randomised trial showed a benefit in PFS averaging 3 months for pazopanib given until progression to previously treated, advanced STS patients (excluding liposarcomas).⁵¹ Thus, it is an option in non-adipogenic STS in second and further lines of treatment [I, B; ESMO-MCBS v1.1 score: 3]. The activity of pazopanib is also demonstrated in other sarcoma types within prospective phase II studies, such as SFT and extraskeletal myxoid chondrosarcoma, in which pazopanib was administered from first-line therapy [III, B].^{52,53}
- A randomised phase III trial showed that eribulin was superior to dacarbazine in patients with liposarcomas and LMSs. The median difference in OS was 2 months

[I, B], but a subgroup analysis showed that it reached 7 months in liposarcomas.⁵⁴ This led to the regulatory approval of eribulin in second and further lines of therapy [II, A; ESMO-MCBS v1.1 score: 3]. An improvement in OS was particularly seen in the pleomorphic liposarcoma subtype.⁵⁵

- One trial showed that gemcitabine-docetaxel is more effective than gemcitabine alone as second- or further-line ChT, with special reference to LMS and undifferentiated pleomorphic sarcoma, but these data are expected in a second randomised trial conducted only in LMS; in both trials, toxicity was superior with the combination of docetaxel-gemcitabine [II, C].⁵⁶ Gemcitabine showed anti-tumour activity also in LMS, angiosarcoma and epithelioid sarcomas given as a single agent.^{42,57} The combination of dacarbazine-gemcitabine was shown to improve the OS and PFS over dacarbazine in a randomised trial [II, B].⁵⁸
- Dacarbazine monotherapy has some activity as a second-line therapy (mostly in LMS and SFT).^{38,39}
- Methotrexate plus vinorelbine/vinblastine were retrospectively shown to have activity in inflammatory myofibroblastic tumour.⁵⁹

Table 1 lists systemic agents that have shown activity, either preliminary or partial, in selected sarcoma types, and have not entered standard practice and/or they are not approved/reimbursed in all European countries. Thus, if available, their use may be considered in the clinical balance within individualised patient–physician shared decisions. RT should be considered as a palliative resource in all cases as appropriate to the clinical need (e.g. bone lesions at risk of fracture).

Recommendations

- Standard treatment of metachronous (disease-free interval ≥1 year), resectable lung metastases without extrapulmonary disease is surgery, if complete excision of all lesions is feasible [IV, B].
- Standard ChT is based on anthracyclines as first-line treatment [I, A]. Multi-agent ChT with adequate-dose AI or dacarbazine may be the treatment of choice, particularly in subtypes sensitive to ifosfamide or dacarbazine, when a tumour response is felt to be potentially advantageous and patient PS is good [I, B].
- Gemcitabine-docetaxel is not generally recommended as a first-line therapy for advanced STS patients [I, D].
- Imatinib is standard medical therapy for patients with DFSP [III, A].
- NTRK inhibitors are standard treatment of patients with advanced *NTRK*-rearranged sarcomas [III, A]. They can be considered also in the preoperative setting, when a cytoreduction can improve morbidity and function [III, A; ESMO-MCBS v1.1 score: 3].
- Trabectedin is an option in advanced STS in second and further lines of treatment [I, B; ESMO-MCBS v1.1 score: 2].
- Pazopanib is an option in non-adipogenic STS in second and further lines of treatment [I, B; ESMO-MCBS v1.1 score: 3].

Table 1. Systemic agents associated with evidence of activity in selected sarcoma types

Regimen	Sarcoma type	Treatment line	ORR (%)	mPFS (months)	Study type
Axitinib ⁸⁶	SFT	Any	5.9 (Choi)	5.1 (Choi)	Phase II, single-arm
Bevacizumab Temozolomide ⁸⁷	SFT	Any	79 (Choi)	9.7 (Choi)	Retrospective study
Crizotinib ⁸⁸	Inflammatory myofibroblastic tumour	Any	ALK-positive patients: 50 ALK-negative patients: 14 (RECIST)	N/A	Phase II, single-arm
Imatinib ⁸⁹	TGCT	Any	31 (RECIST)	N/A	Retrospective case series
Nilotinib ⁹⁰	TGCT	Any	6 (RECIST)	Not reached	Phase II, single-arm
PD-1/PD-L1 inhibitors monotherapy ⁹¹	Alveolar soft part sarcoma	Any	Ranges from 32 to 36 (RECIST)	7-not reached (RECIST)	Phase II, single-arm; subgroup analyses of phase II studies; case reports
PD-1/PD-L1 inhibitors ⁹²	Angiosarcoma	Second-line and beyond	71 (RECIST)	N/A	Case reports; retrospective case-series
Pexidartinib ⁹³	TGCT	Any	Pexidartinib versus placebo 39 versus 0 (RECIST)	N/A	Phase III, randomised
Regorafenib ^{94,95}	Leiomyosarcoma	Second-line and beyond	0 (RECIST)	Regorafenib versus placebo (RECIST) 3.7 versus 1.8	Phase II, randomised
	Synovial sarcoma		8 (RECIST)	5.6 versus 1.0	
	Other non-adipocytic STS		11 (RECIST)	2.9 versus 1.0	
	Non-adipocytic STS	Further-line, after pazopanib	0 (RECIST)	2.1 versus 1.1	Phase II, randomised
Selumetinib ⁹⁶	Neurofibromatosis type 1-related neurofibroma	Any	70 (volumetric assessment)	Not reached	Phase II, single-arm
Sirolimus ⁹⁷	Epithelioid Haemangioendothelioma	Any	10.8 (RECIST)	13 (RECIST)	Retrospective case series
Sirolimus ⁹⁸	PEComa	Any	41 (RECIST)	9 (RECIST)	Retrospective case series
Sorafenib ⁹⁹	Epithelioid Haemangioendothelioma	Any	13.3 (RECIST)	6 (RECIST)	Phase II, single-arm
Sunitinib ¹⁰⁰	SFT	Any	48 (Choi)	6 (RECIST)	Retrospective case series
Tazemetostat ¹⁰¹	Epithelioid sarcoma	Any	15 (RECIST)	5.5 (RECIST)	Phase II, single-arm

ALK, anaplastic lymphoma kinase; Choi, Choi criteria; mPFS, median progression-free survival; N/A, not available; ORR, overall response rate; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PEComa, perivascular epithelioid cell tumour; RECIST, Response Evaluation Criteria in Solid Tumours; SFT, solitary fibrous tumour; STS, soft tissue sarcoma; TGCT, tenosynovial giant cell tumour.

- Eribulin is an option in patients with liposarcomas [II, A; ESMO-MCBS v1.1 score: 3].
- The combination of dacarbazine-gemcitabine or gemcitabine-docetaxel is an option in doxorubicin-pretreated patients [II, B].

FOLLOW-UP

There are few published data to indicate the optimal routine follow-up policy of surgically-treated patients with localised disease.⁶⁰

The tumour grade affects the likelihood and interval at which relapses may occur. Risk assessment based on histological type, tumour grade, size and site help in choosing a routine follow-up policy. High-risk patients generally relapse within 2-3 years, whereas low-risk patients may relapse later. Relapses most often occur in the lungs. The use of MRI to detect local relapse in the extremities and superficial trunk and CT for lung metastases is likely to pick up recurrences earlier than other assessment/imaging modalities.

While prospective studies are needed, a practical approach in place at several institutions is as follows:

after completion of treatment, intermediate-/high-grade patients may be followed every 3-4 months in the first 2-3 years, then twice a year up to the fifth year, and once a year thereafter; low-grade sarcoma patients may be followed every 6 months for the first 5 years, then annually.

SPECIAL PRESENTATION AND ENTITIES

Retroperitoneal sarcoma

Pretreatment biopsy for pathological diagnosis should be carried out, to allow tailored therapeutic decisions, unless otherwise indicated by the multidisciplinary board. Risk of needle track seeding is minimal and should not be a reason to avoid a biopsy. The preferred route should be a retroperitoneal approach if technically possible rather than transperitoneal. Open or laparoscopic biopsies must be avoided.

Comprehensive imaging evaluation is critical to accurately assess the extent of the tumour. Specific appreciation of the well-differentiated versus the dedifferentiated component(s) of liposarcoma is critical to surgical decision making. Histology-specific nomograms for RPS patients are

available, which can help personalise risk assessment and assist clinical decision making.¹³

The best chance of curative resection is at primary presentation. The standard treatment of primary lesions is surgery. Surgery should be aimed at achieving a single *en bloc* specimen and macroscopically complete resection minimising R1 margins. This is best done by resecting the tumour *en bloc* with adherent structures [III, A].⁶¹⁻⁶⁴ Preservation of specific organs (i.e. kidney, head of the pancreas and/or liver, neurovascular structures, etc.) should be considered on an individualised basis. Preoperative/intraoperative tumour ruptures are associated with a poor prognosis.

Grossly incomplete resection of RPSs is potentially harmful and can only be regarded as potentially palliative in carefully selected patients. Grossly incomplete resection is to be avoided by imaging review, thoughtful planning and referral to appropriate centres.

Neoadjuvant treatment, in the form of ChT, external beam RT (EBRT), regional hyperthermia or combinations, can be considered in the case of technically unresectable/borderline resectable, i.e. RPS that could be surgically converted by downsizing, and in chemosensitive histologies such as synovial sarcoma.²⁶

Preoperative RT in resectable tumours did not improve RFS and OS in one randomised clinical trial [I, D].⁶⁵ However, signs of efficacy were observed in the liposarcoma subgroup and low-intermediate malignancy grade. Therefore, in patients with a low-intermediate grade liposarcoma preoperative RT can be discussed. On the contrary, no effect was seen in resectable LMS and high-grade dedifferentiated liposarcoma. Therefore, in patients affected by these sarcoma types preoperative RT should not be considered.

The value of preoperative RT in other rarer histological types is less established. However, the activity of RT in SFT should be factored into the decision.²⁶ For all other histological types an individualised decision with a higher degree of uncertainty can be made based on size of the tumour, its local risk and the expected quality of surgery.

Post-operative/adjuvant EBRT following complete gross resection is of limited value and is associated with significant short- and long-term toxicities, because a therapeutic RT dose can be achieved in only a minority of patients. In selected cases, it may be an option in well-defined anatomical areas thought to be at high risk. Brachytherapy is of unproven value and is associated with significant short- and long-term complications. Intraoperative RT is of unproven value.

In a large, randomised phase III study (in patients with G2-3, deep, >5 cm STSs), regional hyperthermia in addition to systemic ChT was associated with PFS, DFS and OS advantage in the subgroup of RPSs [I, B].²⁸

The value of adjuvant/neoadjuvant ChT is not established, though the rarity of the subtypes of RPSs forces extrapolation of the data available in other settings.

Surgery of local recurrences could be offered on an individualised basis, especially to patients affected by well-differentiated liposarcoma and having a long disease-free interval between initial resection and subsequent

recurrence, and possibly to patients experiencing a response to medical therapies.⁶⁶

Uterine sarcomas

Uterine sarcomas include LMS, endometrial stromal sarcomas (ESSs, formerly low-grade ESSs), undifferentiated endometrial sarcomas (UESs) and adenosarcoma with sarcomatous overgrowth (ASS). Carcinosarcomas (malignant Müllerian mixed tumours) are currently viewed as epithelial cancers, and treatment should be tailored accordingly. Thus, before a final diagnosis of a sarcoma is made, the pathologist should be certain that an epithelial component is absent.

Clinical and radiological criteria to confidently differentiate leiomyomas from malignant uterine tumours are not available. Thus, procedures resulting in potential tumour cell spillage, such as morcellation out of endoscopic bags, are discouraged because they entail a high risk of worsening patient prognosis when malignancy is the post-operative pathological diagnosis.⁶⁷

Smooth muscle tumours of undefined malignant potential (STUMPs) constitute a negative definition, which is used when both leiomyoma and LMS cannot be diagnosed with certainty.⁶⁸ There are remarkable variations with this diagnosis among pathologists that imply a degree of subjectivity. Some of these lesions might actually represent 'low-grade' LMS, the existence of which is disputed. Due to the uncertainty about their prognosis, a hysterectomy is usually proposed to patients with a diagnosed STUMP, but there may be room for individualised decision making. Careful follow-up is then recommended.

Standard local treatment of localised uterine LMS (U-LMS), ESS and UES is *en bloc* total hysterectomy (including laparoscopy/assisted or robotic surgery, provided the tumour is resected with the same criteria as for open surgery and morcellation is not carried out). With a diagnosis of sarcoma, systematic lymphadenectomy has not been demonstrated to be useful. The added value of bilateral salpingo-oophorectomy is not established, particularly in premenopausal women, so possible ovarian preservation is feasible. There are studies suggesting that ovarian preservation may be an option even in cases of International Federation of Gynaecology and Obstetrics (FIGO) stage I ESS.⁶⁹ With a diagnosis of sarcoma, fertility-preserving surgery in young women should not be regarded as a standard procedure. In ESS, however, LNs may be positive in ~10% of cases. RT has not improved RFS and OS in the only prospective randomised trial and is not recommended [I, D].⁷⁰ The use of post-operative RT can be an option in selected cases, following multidisciplinary discussion considering special risk factors, including: local relapse, cervical involvement, parametral involvement, serosal involvement and UES histology [IV, C]. Adjuvant ChT in U-LMS is not standard treatment, since its value is undetermined [IV, C]. Uncontrolled studies suggested a benefit in comparison with external controls for four courses of gemcitabine-docetaxel

followed by four courses of doxorubicin, as well as four courses of gemcitabine-docetaxel.⁷¹ A prospective, randomised trial with a no-treatment control arm versus four courses of gemcitabine-docetaxel followed by four courses of doxorubicin was attempted but closed early due to lack of accrual (International Rare Cancers Initiative (IRCI) 001, NCT01533207).

The systemic treatment of advanced U-LMS, UES and ASS parallels that for adult-type STSs. As for all LMSs, doxorubicin, dacarbazine, trabectedin, gemcitabine alone or in combination with docetaxel and pazopanib are active agents and may be used in a stepwise fashion. There is retrospective evidence that ifosfamide may be less active as a single agent in LMS.³⁸

ESSs are histologically low-grade tumours, with a consistent pathological appearance. The diagnosis is supported by typical cytogenetics, marked by a chromosomal translocation (7;17) with *JAZF1-SUZ12* or related translocations joining *EPC1-PHF1* or *JAZF1-PHF1* genes. Adjuvant hormonal therapy (HT) is not standard, though it may be an option, given retrospective evidence suggesting its role in decreasing relapses. However, the sensitivity of the advanced disease to hormones makes the benefit questionable overall [IV, C]. The systemic treatment of metastatic low-grade ESSs exploits their sensitivity to HT [V, B]. Therefore, progestins, aromatase inhibitors and gonadotropin-releasing hormone (GnRH) analogues (for premenopausal patients) can be used.⁶⁷ Tamoxifen is contraindicated due to a possible agonist activity, as is hormonal replacement therapy containing oestrogens. ChT may be an option when HT has failed. Surgery of lung metastases is an option, even in presentations which might not be surgically approached in other STSs, given the long natural history of the disease. This may apply to pelvic disease as well, even in the presence of metastatic disease.

A subgroup of high-grade ESS is recognised, which is defined by specific cytogenetics, marked, in most cases, by the *YWHAE-FAM22* transcript.⁷² Other less common molecular alterations can be detected, including *ZC3H7B-BCOR* fusion and *BCOR* internal tandem duplication.¹ They are often insensitive to HT, and cytotoxic ChT is considered appropriate in the metastatic setting, with notable responses reported with anthracycline-based regimens [IV, B].⁷³

High-grade ESS, ASS and UES are high-grade malignancies. There are no data on the value of adjuvant ChT, though their high-risk status may justify an individualised decision especially in UES [V, C]. Hyperthermic peritoneal ChT has not been shown to be effective and is an experimental-only option.

For benign metastasising leiomyomas, clinical observation is the treatment of choice at diagnosis, with HT (as for ESS) being standard treatment of progressing disease and surgery. The same applies to peritoneal leiomyomatosis if non-mutilating surgery is not feasible.

For pelvic aggressive angiomyxoma, surgery may be the treatment of choice if not debilitating, with observation thereafter. In progressing disease, HT, or interruption of any ongoing stimulation with oestrogens, may allow mutilating

surgery to be avoided and the disease to be kept under control.⁷⁴

Desmoid-type fibromatosis

While principles for the diagnosis of STS apply also to desmoid-type fibromatosis (DF), mutational analysis of β -catenin and the *APC* gene in β -catenin-negative cases may be useful when the pathological differential diagnosis is difficult. In patients affected by β -catenin, wild-type DF familial adenomatous polyposis should be ruled out.

Given the unpredictable natural history of the disease (with the possibility of long-lasting stable disease and even occasional spontaneous regressions, along with a lack of metastatic potential) and functional problems implied by some tumour anatomical locations, an initial active surveillance policy can be proposed [III, A].⁷⁵ This should follow a careful monitoring of potentially life-threatening extra-abdominal locations (e.g. head and neck region) and intra-abdominal desmoids (mesenteric fibromatosis). Under such a policy, treatment is reserved for progressive disease. The preferred imaging modality is MRI, taking into consideration that the tumour imaging appearances may not be meaningful with regard to the disease evolution or patient symptoms.

For progressive disease, the optimal strategy needs to be individualised on a multidisciplinary basis and may consist of further watchful waiting, systemic therapies or local therapies such as percutaneous cryoablation (extra-abdominal cases) [IV, C], ILP (if the lesion is confined to an extremity) [IV, C] and surgery in favourable locations (i.e. abdominal wall) [IV, C].⁷⁵ Definitive RT should be considered after multiple failed lines of treatment or for tumours in critical anatomical locations where surgery would involve prohibitive risk or functional impairment, especially in elderly patients [III, C].⁷⁵ When a systemic therapy is chosen, available options include: low-dose ChT (such as methotrexate-vinblastine or methotrexate-vinorelbine; oral vinorelbine; taxanes); sorafenib [II, B]; pazopanib; imatinib; and full-dose ChT (using regimens active in sarcomas, including liposomal doxorubicin).⁷⁶⁻⁸³ In addition, HT (tamoxifen, toremifene and GnRH analogues; aromatase inhibitors), nonsteroidal anti-inflammatory drugs and interferon have also long been used, but no prospective studies are available to understand their real activity in this disease.

Breast sarcomas

These patients should be referred to sarcoma units and managed jointly within breast units. Metaplastic breast carcinomas, also known as carcinosarcomas, are epithelial neoplasms, the treatment of which should be tailored to their mainly epithelial nature.

Breast sarcomas (BSs) encompass radiation- and non-radiation-induced sarcomas. Therefore, sarcomas of the skin of the breast area should be conceptually distinguished from mammary gland sarcomas. Angiosarcoma has a more aggressive behaviour than other histological types, while malignant phyllodes tumours (i.e. >10 mitoses/10

high-power field and marked stromal overgrowth) have a 20%-30% metastatic rate.

In general, breast-conserving surgery may be carried out, depending on the quality of margins versus the size of the tumour and the breast, along with the feasibility of RT in primary BS, while wide excision of the RT field and immediate plastic surgical reconstruction is often necessary in radiation-induced BS. In angiosarcomas of the mammary gland the tendency to recur is high and mastectomy (involving the muscular fascia and the whole previously irradiated field) is recommended in most cases, even in combination with post-operative RT. A targeted axillary dissection should be done in patients with clinically- and/or radiologically-concerning nodes, as the LN metastatic risk in angiosarcoma is higher than average (5%-15%).

As far as adjuvant/neoadjuvant ChT is concerned, there is a higher degree of uncertainty, although one may use the same principles of STS at other sites. Considering the high risk of angiosarcoma to develop local and systemic relapses, preoperative treatments including ChT and RT may be used. Re-irradiation can be considered in radiation-associated angiosarcomas.

Recommendations

- Patients with suspected RPS, uterine sarcoma, DF and BS need to be referred to high-volume sarcoma centres [III, A].
- Standard treatment of RPS consists of surgical resection *en bloc* with adherent organs [V, A].
- Neoadjuvant RT has shown signs of efficacy in primary low-/intermediate-grade retroperitoneal liposarcoma [II, B].
- Intraoperative/post-operative RT is of no proven value in RPS. The role of adjuvant/neoadjuvant ChT is not yet established.
- Standard local treatment of localised U-LMS, ESSs and UESs is *en bloc* total hysterectomy [IV, A]. Adjuvant RT is not recommended [I, D].
- Active surveillance is the first-line strategy for all newly diagnosed primary DF, without life-threatening presentations [III, A].
- For progressing DF, the optimal strategy needs to be individualised on a multidisciplinary basis and may even consist of the continuation of the active surveillance, systemic therapies, local therapies, such as percutaneous cryoablation, ILP (if the lesion is confined to an extremity), surgery in favourable locations or RT [IV, C].

METHODOLOGY

This CPG has been developed by ESMO in partnership with EURACAN—GENTURIS during a virtual consensus meeting which was held on 5 December 2020. The CPG was developed in accordance with the ESMO standard operating procedures for CPG development <http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology>. Recommended interventions are intended to correspond to the ‘standard’ approaches for diagnosis, treatment and survivorship on sarcomas, according to current consensus among the

European multidisciplinary sarcoma community of experts. This community was represented by the members of the ESMO Sarcoma Faculty and experts appointed by all institutions belonging to the Sarcoma domain of EURACAN—GENTURIS. Experimental interventions considered to be beneficial are labelled as ‘investigational’. Other non-standard approaches may be proposed to the single patient as ‘options’ for a shared patient-physician decision in conditions of uncertainty, as long as some supporting evidence (though not conclusive) is available. Algorithms accompany the text, covering the main typical presentations of disease, and are meant to guide the user throughout the text. The relevant literature has been selected by the expert authors. An ESMO-MCBS table with ESMO-MCBS scores is included in [Supplementary Table S2](#), available at <https://doi.org/10.1016/j.annonc.2021.07.006>. ESMO-MCBS v1.1.⁸⁴ was used to calculate scores for new therapies/indications approved by the EMA since 1 January 2016 or the Food and Drug Administration (FDA) since 1 January 2020 (<https://www.esmo.org/Guidelines/ESMO-MCBS>). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. Levels of evidence and grades of recommendation are applied using the system shown in [Supplementary Table S3](#), available at <https://doi.org/10.1016/j.annonc.2021.07.006>.⁸⁵ Statements without grading were considered justified standard clinical practice by the experts.

ACKNOWLEDGEMENTS

Patient representatives Markus Wartenberg and Gerard van Oortmerssen from Sarcoma Patients EuroNet (SPAEN) who attended the consensus meeting as observers and contributed the valuable perspectives of patients to the consensus process. The authors thank Louise Green and Richard Lutz of the ESMO Guidelines staff for their support throughout the whole consensus process and Jackie Jones of JJ Medical Communications Ltd for her logistical support during the virtual consensus meeting. This support was funded by ESMO. Manuscript editing support was provided by Richard Lutz, Catherine Evans and Louise Green (ESMO Guidelines staff). Nathan Cherny, Chair of the ESMO-MCBS Working Group, Urani Dafni ESMO-MCBS Working Group Member/Frontier Science Foundation Hellas and Giota Zygoura of Frontier Science Foundation Hellas provided review and validation of the ESMO-MCBS scores. Nicola Latino (ESMO Scientific Affairs staff) provided coordination and support of the ESMO-MCBS scores and preparation of the ESMO-MCBS table.

FUNDING

No external funding has been received for the preparation of these guidelines. Production costs have been covered by ESMO from central funds.

DISCLOSURE

AG has received honoraria for participation in advisory boards for Novartis, Pfizer, Bayer, Lilly, PharmaMar,

SpringWorks and Nanobiotix, invited speaker for Lilly, PharmaMar and research grant from PharmaMar; APDT has received honoraria for participation in advisory boards for Bayer and Roche, invited speaker for PharmaMar and Novartis; NA Non-remunerated leadership and advisory roles for Sociedade Portuguesa de Cirurgia; JB has no personal financial disclosure, received research grants (institutional) from Eli Lilly, Novartis, Roche, Samsung Bioepis, Paxman Coolers Ltd, Sun Pharma and non-remunerated advisory role for Novartis, non-remunerated leadership activities for Immuno-oncology society of India, Indian society of Medical and Paediatric Oncology, Teenage and Young Adult Cancer Foundation and Indian cooperative oncology network; SB has received honoraria for participation in advisory boards for Deciphera, Blueprint Medicines, Lilly, Novartis, Daiichi-Sankyo, Plexxikon, Roche, GlaxoSmithKline (GSK), invited speaker fees from Pfizer and PharmaMar, institutional research grant from Novartis, institutional research as principal investigator (PI) for Daiichi-Sankyo, Roche, Deciphera, Lilly, Novartis, Blueprint Medicines, Bristol-Myers Squibb (BMS), Incyte, non-remunerated activities for Federal Institute for Drugs and Medical Devices (BfArm) and founding member of German Sarcoma Foundation; RB reports non-remunerated activities as PI for IRCSS Galeazzi Orthopedic Institute and IRE-ISG Regina Elena Institute, participation at the Clinical Experience Exchange Meeting, III IDBN National Congress 2019, Italian Association of Medical Oncology (AIOM), IRE-ISG Regina Elena Institute and Lazio Association of Orthopaedic Hospital Traumatologists (ALOTO); SBI has received honoraria for participation in advisory boards from Bayer Healthcare, Boehringer Ingelheim, Clinigen, Hoffmann-La Roche, Ipsen, Eli Lilly and Sensorion, non-remunerated activities for Bayer and membership of the German Paediatric Oncology Society and European Musculoskeletal Oncology Society; JYB received research support from Merck Sharp & Dohme (MSD), Roche, GSK, Novartis, Bayer, PharmaMar outside the present work; SBon has received honoraria for advisory board from Nanobiotix and as invited speaker for PharmaMar, trial research grant from the Institut National du Cancer (INCa); IB has received honoraria for participation in advisory boards for Roche, Lilly, Sanofi, Pierre Fabre, Ipsen, and as invited speaker for Amgen, BMS, Novartis, Leo Pharma, AstraZeneca and Genesis, member of Board of Directors for Hellenic Society of Medical Oncology, Hellenic Society of Sarcomas and Rare Tumors, Hellenic Oncology Research Group (HORG), PI trial research support from Novartis, BMS, Regeneron, MSD, Lilly and Roche; JVMGB receives royalties from UpToDate and Wolters Kluwer, and direct research funding from TRACON pharmaceuticals; KB has received honoraria for expert testimony and advisory boards for Bayer, invited speaker fees and research grant from Eli Lilly, PI for Deciphera and Novartis; TB has received honoraria for participation in advisory boards for Bayer and Eli Lilly, invited speaker fees from PharmaMar and Novartis; EDÁ has received honoraria for participation in advisory board for Bayer, invited speaker for Lilly, PharmaMar and Roche, institutional research support from Pfizer, Roche and

AstraZeneca; XGDM has received honoraria for participation in advisory boards for Ipsen, EusaPharma, BMS, Pfizer, Roche and PharmaMar, invited speaker for Lilly, Astellas Pharma, Eisai and Pfizer and institutional research grant from AstraZeneca; ME has received honoraria for participation in advisory boards for Clinigen and Bayer, consulting fees from Blueprint Medicines, institutional research funding from Novartis as PI; AF has received honoraria for participation in advisory board for Novartis and invited speaker fees for MSD and Amgen; VF has received honoraria for participation in advisory boards and speaker fees for BMS, Novartis and MSD and speaker fees from Pierre Fabre; SG has reported institutional research for Blueprint Medicines and member of American Society of Clinical Oncology (ASCO) and AIOM; HG has reported PI research for Daiichi, Deciphera and Novartis, Co-ordinating PI for Boehringer Ingelheim and AmMax Bio; FG has received honoraria for participation in advisory board for Amgen and expert testimony for Deciphera, stock ownership for Atlanthera, licensing fees from Zimmer, non-remunerated activities for 3D-Side and INCa DGOS funding and member of the board of NetSarc the French clinical reference network for soft tissue and visceral sarcomas; GG has received honoraria for participation in advisory boards for Lilly, Eisai, Merck, Bayer and GSK, invited speaker fees from PharmaMar and Novartis, institutional grants from PharmaMar, Bayer and Novartis; RH has received Honoraria from GSK; ABH is a member of Board of Directors for EIT Health UK and Ireland, received or currently receives direct research funding as a PI from Roche, performs work in clinical trials or contracted research for the Institution and Clinical Director of the Oncology and Haematology Directorate, Oxford Cancer Centre; SHN received invited speaker fee from University Hospital Basel, Switzerland for Swiss sarcoma symposium, reports institutional research role as deputy PI for Eisai, non-remunerated activity for Harmonization International Bones Sarcoma Consortium (HIBISCus), membership of European Society for Paediatric Oncology (SIOP), German, Swiss, Austrian Society of Paediatric Oncology and Hematology (GPOH) and German Society of Pediatrics and Adolescent Medicine (DGKJ); NH has received honoraria as expert testimony and invited speaker from PharmaMar, performs work in clinical trials or contracted research for which his/her institution received financial support from PharmaMar, Lilly, Adaptimmune Therapeutics, AROG Pharmaceuticals, Bayer, Eisai, Lixte, Karyopharm, Deciphera, GSK, Novartis, Blueprint Medicines, Nektar Therapeutics, Forma, Amgen and Daiichi-Sankyo, non-remunerated leadership roles for Grupo Español de Investigación en Sarcomas (GEIS) and SELNET, and has non-remunerated membership or affiliation with ESMO, Sociedad Española de Oncología Médica (SEOM), ASCO, Connective Tissue Oncology Society (CTOS) and European Organisation for Research and Treatment of Cancer (EORTC); PH has received honoraria for participation in advisory boards for Pfizer, Roche and GSK, invited speaker fees from PharmaMar and Lilly, clinical expert fees from Boehringer Ingelheim, institutional research funding for

clinical trials from Siemens, Novartis, Blueprint Medicines and meeting sponsorship from PEKKIP Oncology, non-remunerated activities for the German Sarcoma Foundation (DSS), German Interdisciplinary Sarcoma Group (GISG) and Interdisciplinary Working Party on Sarcomas (IAWS) of the German Cancer Society (DKG), advisory role for the German Cancer Aid (DKH) Committee on Health Technology Assessment and Sarcoma Patients EuroNet (SPAEN); HJ has received honoraria for participation in advisory boards for Orion Pharma, Neutron Therapeutics and Maud Kuistila Memorial Foundation, had full-time or part-time employment at Orion Pharma, until 31 August 2020, stocks in Orion Pharma and Sartar Therapeutics; RLJ has received honoraria for expert testimony consultancy for Adaptimmune, Bayer, Boehringer Ingelheim, Blueprint Medicines, Clinigen, Eisai, Epizyme, Daiichi, Deciphera, Immunodesign, Lilly, SpringWorks, TRACON, UpToDate, PharmaMar, advisory board for Athenex, institutional research grant from MSD; CJ has received travel grants from Ipsen and PharmaMar; LK has received honoraria for participation in advisory boards for Bayer, Novartis and Agios; BK has received honoraria for participation in advisory boards for Bayer, Blueprint Medicines, Boehringer Ingelheim, SpringWorks, GSK and PharmaMar, institutional research support from PharmaMar and SpringWorks, member of EORTC and Chair of the EORTC soft tissue and bone sarcoma group (STBSG); AK has received honoraria for participation in advisory boards for Daiichi-Sankyo and Otsuka and invited speaker fees from Novartis, Taiho and Eisai; KK has received honoraria for participation in advisory board for Bayer and expert testimony for Eli Lilly and Roche; ALC has received honoraria for participation in advisory boards for Deciphera and Lilly, invited speaker fees from PharmaMar and Bayer; EL received honoraria from SpringWorks Therapeutics for scientific advisory board participation and member of the European Reference Network GENTURIS; AL has received institutional research grants from Johnson & Johnson, Alphamed, Medacta and Implantec, non-remunerated activities for European Musculoskeletal Society (EMSOS), Austrian Society of Orthopaedic Surgeons (OGO) and membership of CTOS; AL-P has received honoraria as invited speaker for PharmaMar, institutional research funding from the Spanish Health Ministry, reported non-remunerated activities as PI for PharmaMar, Cebiotex, Deciphera, Lilly, GSK, Daiichi, Epizyme, Advenchen Laboratories, Novartis, Karyopharm, Blueprint Medicines, GEIS and other activity for EORTC; JMB has received honoraria for expert testimony for Lilly, PharmaMar, Eisai, Bayer, invited speaker fee from PharmaMar, institutional research for PharmaMar, Eisai, Novartis, Immix Biopharma, Lixte, Karyopharm, Bayer, Celgene, Pfizer, BMS, Blueprint Medicines, Deciphera, Nektar Therapeutics, Forma, Amgen, Daiichi-Sankyo, Lilly, AROG Pharmaceuticals, Adaptimmune and GSK; OM has received honoraria for participation in advisory boards for MSD, Megapharm, AstraZeneca, Takeda and Progenetics, invited speaker fees from MSD and Roche; CM has performed non-remunerated activities for International Cancer Imaging Society and EORTC STBSG; OMi has

received honoraria for participation in advisory boards for Bayer, Blueprint Medicines, MSD, Pfizer, invited speaker fees from BMS, Eli Lilly, Ipsen, Roche and Servier, institutional research for Blueprint Medicines, Bayer, Epizyme and Eli Lilly; BM has received honoraria from Clinigen as invited speaker; EP has received honoraria for participation in advisory boards for SynOx, Daiichi-Sankyo and Deciphera Pharmaceuticals and invited speaker fees from Peer View Educational; MAP has received honoraria for participation in advisory boards for Roche, invited speaker fees from Eli Lilly, Pfizer and Novartis, expert testimony from Blueprints Medicine and institutional research grant from Novartis; SPN has received honoraria for participation in advisory board for Immunocore; PR has received honoraria for participation in advisory boards for Bayer, Clinigen, Roche, MSD, Deciphera, Mundibiopharma, PharmaMar, Blueprint Medicines, invited speaker fees from Lilly, PharmaMar, institutional research for PharmaMar, Karyopharm, SpringWorks, AROG Pharmaceuticals, Blueprint, Deciphera, Amgen, Astellas, Epizyme, Lilly, MSD, Pfizer, Novartis and Philogen, membership of German Sarcoma Foundation; PRu has received honoraria for participation in advisory boards for MSD, BMS, Pierre Fabre, Merck, Sanofi, Blueprint Medicines, invited speaker fees from MSD, BMS, Pierre Fabre, Merck, Sanofi, Novartis, institutional research funding from Pfizer, BMS and non-remunerated activities for the Polish Society of Surgical Oncology and ASCO; MS has received honoraria for travel grant from PharmaMar and writing engagement for Lilly; SS has reported a research grant from Johnson & Johnson and research funding from Roche Austria; PS has received honoraria for participation in advisory boards for Deciphera, Blueprint Medicines, Boehringer Ingelheim, Ellipses Pharma, Transgene, Exelixis, Medscape, Guided Clarity, Ysios, Modus Outcomes, Studiecentrum voor Kernenergie, Curio Science, institutional honoraria for advisory boards for Blueprint Medicines, Ellipses Pharma, Intellisphere, expert testimony for Advanced Medical/Teladoc Health, institutional research funding from CoBioRes NV, Eisai, G1 Therapeutics, Novartis and PharmaMar; SSI Chair of Centre for Personalised Cancer Treatment and Route Personalised Medicine, Dutch Science Agenda, Member of supervisory board for SkylineDX and Scientific advisory committee Pan-Cancer T BV; SSt has received honoraria for participation in advisory board for GSK; KSH reports non-remunerated activity for CTOS as President 2020 and membership of the Scandinavian Sarcoma Group; MAJvdS has performed work in clinical trials or contracted research for which the institution received financial support from Daiichi-Sankyo, Implantcast and Carbofix; WTAvdG has received institutional honoraria for participation in advisory boards of Bayer and GSK, institutional research grants from Novartis and Lilly, and consultancy work for SpringWorks; WJvH has received institutional honoraria for participation in advisory board for Belpharma, invited speaker fees from Amgen, expert testimony for Sanofi and MSD, personal travel grant from Novartis and institutional research grant from BMS; TF reported institutional research funding from the Foundation ARC and Ligue

Régionale contre le Cancer, leadership role for ERN GENTURIS; PGC has received honoraria for participation in advisory board for Bayer, institutional research funding from Amgen Dompé, Advenchen, Bayer, Blueprint, Deciphera, Eli Lilly, Epizyme, Daiichi, GSK, Karyopharm, Novartis, Pfizer, PharmaMar, SpringWorks, AROG Pharmaceuticals and Eisai, non-remunerated activities for the Italian Sarcoma Group, European School of Oncology, Federation of Italian Cooperative Groups and Rare Cancers Europe; SSa has received honoraria for participation in advisory boards for Bayer, Deciphera, Eli Lilly, Daiichi, Maxivax, Novartis, invited speaker fees from GSK and PharmaMar, expert testimony fee from Bavarian Nordic and Epizyme, institutional research funding from Amgen Dompé, Advenchen, Bayer, Blueprint Medicines, Deciphera, Eli Lilly, Epizyme, Daiichi, GSK, Karyopharm, Novartis, Pfizer, PharmaMar, SpringWorks and Hutchinson MediPharma International Inc., non-remunerated activities for CTOS, Chordoma Foundation, Epithelioid Haemangioendothelioma Foundation, Desmoid Foundation, EORTC STBSG and Italian Sarcoma Group Onlus; AAS, AB, ABM, AD, AFer, AMF, AT, BB, CMo, CS, DAK, DS, FF, FLG, MM, MU PJ, RP and SBo have declared no conflicts of interests.

REFERENCES

- WHO Classification of Tumours Editorial Board. *Soft Tissue and Bone Tumours*. 3. 5th ed. Lyon: IARC; 2020. Available at <https://publications.iarc.fr/588>. Accessed May 1, 2021.
- Casali PG, Blay JY, Abecassis N, et al. Gastrointestinal stromal tumours: ESMO—EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021.
- Strauss SJ, Frezza AM, Gronchi A, et al. Bone sarcomas: ESMO—EURACAN-GENTURIS-ERNPaedCan Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021.
- Gatta G, Capocaccia R, Botta L, et al. Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet — a population-based study. *Lancet Oncol*. 2017;18(8):1022-1039.
- Blay JY, Soibinet P, Penel N, et al. Improved survival using specialized multidisciplinary board in sarcoma patients. *Ann Oncol*. 2017;28(11):2852-2859.
- Andritsch E, Beishon M, Bielack S, et al. ECCO essential requirements for quality cancer care: soft tissue sarcoma in adults and bone sarcoma. A critical review. *Crit Rev Oncol Hematol*. 2017;110:94-105.
- Ray-Coquard I, Montesco MC, Coindre JM, et al. Sarcoma: concordance between initial diagnosis and centralized expert review in a population-based study within three European regions. *Ann Oncol*. 2012;23(9):2442-2449.
- Dei Tos AP. *Soft Tissue Sarcoma Histopathology Reporting Guide Resection Specimens*. Sydney, Australia: International Collaboration on Cancer Reporting; 2021.
- Trojani M, Contesso G, Coindre JM, et al. Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. *Int J Cancer*. 1984;33(1):37-42.
- Wardelmann E, Haas RL, Bovee JV, et al. Evaluation of response after neoadjuvant treatment in soft tissue sarcomas; the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) recommendations for pathological examination and reporting. *Eur J Cancer*. 2016;53:84-95.
- Brierley JD, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours*. 8th ed. Oxford: John Wiley & Sons; 2016.
- Callegaro D, Miceli R, Bonvalot S, et al. Development and external validation of two nomograms to predict overall survival and occurrence of distant metastases in adults after surgical resection of localised soft-tissue sarcomas of the extremities: a retrospective analysis. *Lancet Oncol*. 2016;17(5):671-680.
- Gronchi A, Miceli R, Shurell E, et al. Outcome prediction in primary resected retroperitoneal soft tissue sarcoma: histology-specific overall survival and disease-free survival nomograms built on major sarcoma center data sets. *J Clin Oncol*. 2013;31(13):1649-1655.
- Callegaro D, Miceli R, Bonvalot S, et al. Development and external validation of a dynamic prognostic nomogram for primary extremity soft tissue sarcoma survivors. *EClinicalMedicine*. 2019;17:100215.
- Frebourg T, Bajalica Lagercrantz S, Oliveira C, et al. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes. *Eur J Hum Genet*. 2020;28(10):1379-1386.
- Rosenberg SA, Tepper J, Glatstein E, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. *Ann Surg*. 1982;196(3):305-315.
- Pisters PW, Harrison LB, Leung DH, et al. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *J Clin Oncol*. 1996;14(3):859-868.
- Beane JD, Yang JC, White D, et al. Efficacy of adjuvant radiation therapy in the treatment of soft tissue sarcoma of the extremity: 20-year follow-up of a randomized prospective trial. *Ann Surg Oncol*. 2014;21(8):2484-2489.
- Fiore M, Ford S, Callegaro D, et al. Adequate local control in high-risk soft tissue sarcoma of the extremity treated with surgery alone at a reference centre: should radiotherapy still be a standard? *Ann Surg Oncol*. 2018;25(6):1536-1543.
- Dagan R, Indelicato DJ, McGee L, et al. The significance of a marginal excision after preoperative radiation therapy for soft tissue sarcoma of the extremity. *Cancer*. 2012;118(12):3199-3207.
- Gundle KR, Kafchinski L, Gupta S, et al. Analysis of margin classification systems for assessing the risk of local recurrence after soft tissue sarcoma resection. *J Clin Oncol*. 2018;36(7):704-709.
- O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet*. 2002;359(9325):2235-2241.
- Palassini E, Ferrari S, Verderio P, et al. Feasibility of preoperative chemotherapy with or without radiation therapy in localized soft tissue sarcomas of limbs and superficial trunk in the Italian Sarcoma Group/Grupo Espanol de Investigacion en sarcomas randomized clinical trial: three versus five cycles of full-dose epirubicin plus ifosfamide. *J Clin Oncol*. 2015;33(31):3628-3634.
- Kalbasi A, Kamrava M, Chu FI, et al. A phase II trial of 5-day neoadjuvant radiotherapy for patients with high-risk primary soft tissue sarcoma. *Clin Cancer Res*. 2020;26(8):1829-1836.
- Callegaro D, Miceli R, Bonvalot S, et al. Impact of perioperative chemotherapy and radiotherapy in patients with primary extremity soft tissue sarcoma: retrospective analysis across major histological subtypes and major reference centres. *Eur J Cancer*. 2018;105:19-27.
- Haas RL, Walraven I, Leconte-Artzner E, et al. Extrameningeal solitary fibrous tumors-surgery alone or surgery plus perioperative radiotherapy: a retrospective study from the global solitary fibrous tumor initiative in collaboration with the Sarcoma Patients EuroNet. *Cancer*. 2020;126(13):3002-3012.
- Lansu J, Bovée JVMG, Braam P, et al. Dose reduction of preoperative radiotherapy in myxoid liposarcoma: a nonrandomized controlled trial. *JAMA Oncol*. 2021;7(1):e205865.
- Issels RD, Lindner LH, Verweij J, et al. Effect of neoadjuvant chemotherapy plus regional hyperthermia on long-term outcomes among patients with localized high-risk soft tissue sarcoma: the EORTC 62961-ESHO 95 randomized clinical trial. *JAMA Oncol*. 2018;4(4):483-492.
- Deroose JP, Eggermont AM, van Geel AN, et al. Long-term results of tumor necrosis factor alpha- and melphalan-based isolated limb perfusion in locally advanced extremity soft tissue sarcomas. *J Clin Oncol*. 2011;29(30):4036-4044.
- Frustaci S, Gherlinzoni F, De Paoli A, et al. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. *J Clin Oncol*. 2001;19(5):1238-1247.

31. Woll PJ, Reichardt P, Le Cesne A, et al. Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial. *Lancet Oncol*. 2012;13(10):1045-1054.
32. Gronchi A, Palmerini E, Quagliuolo V, et al. Neoadjuvant chemotherapy in high-risk soft tissue sarcomas: final results of a randomized trial from Italian (ISG), Spanish (GEIS), French (FSG), and Polish (PSG) sarcoma groups. *J Clin Oncol*. 2020;38(19):2178-2186.
33. Pasquali S, Pizzamiglio S, Touati N, et al. The impact of chemotherapy on survival of patients with extremity and trunk wall soft tissue sarcoma: revisiting the results of the EORTC-STBSG 62931 randomised trial. *Eur J Cancer*. 2019;109:51-60.
34. Gronchi A, Stacchiotti S, Verderio P, et al. Short, full-dose adjuvant chemotherapy (CT) in high-risk adult soft tissue sarcomas (STS): long-term follow-up of a randomized clinical trial from the Italian Sarcoma Group and the Spanish Sarcoma Group. *Ann Oncol*. 2016;27(12):2283-2288.
35. Blackmon SH, Shah N, Roth JA, et al. Resection of pulmonary and extrapulmonary sarcomatous metastases is associated with long-term survival. *Ann Thorac Surg*. 2009;88(3):877-884. discussion 884-875.
36. Antman K, Crowley J, Balcerzak SP, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. *J Clin Oncol*. 1993;11(7):1276-1285.
37. Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol*. 2014;15(4):415-423.
38. D'Ambrosio L, Touati N, Blay JY, et al. Doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, or doxorubicin alone as a first-line treatment for advanced leiomyosarcoma: a propensity score matching analysis from the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *Cancer*. 2020;126(11):2637-2647.
39. Stacchiotti S, Tortoreto M, Bozzi F, et al. Dacarbazine in solitary fibrous tumor: a case series analysis and preclinical evidence vis-a-vis temozolomide and antiangiogenics. *Clin Cancer Res*. 2013;19(18):5192-5201.
40. Seddon B, Strauss SJ, Whelan J, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDis): a randomised controlled phase 3 trial. *Lancet Oncol*. 2017;18(10):1397-1410.
41. Penel N, Bui BN, Bay JO, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. *J Clin Oncol*. 2008;26(32):5269-5274.
42. Stacchiotti S, Palassini E, Sanfilippo R, et al. Gemcitabine in advanced angiosarcoma: a retrospective case series analysis from the Italian Rare Cancer Network. *Ann Oncol*. 2012;23(2):501-508.
43. Rutkowski P, Klimczak A, Lugowska I, et al. Long-term results of treatment of advanced dermatofibrosarcoma protuberans (DFSP) with imatinib mesylate — the impact of fibrosarcomatous transformation. *Eur J Surg Oncol*. 2017;43:1134-1141.
44. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med*. 2018;378(8):731-739.
45. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol*. 2020;21(2):271-282.
46. Demetri GD, Antonescu CR, Bjerkeheggen B, et al. Diagnosis and management of tropomyosin receptor kinase (TRK) fusion sarcomas: expert recommendations from the World Sarcoma Network. *Ann Oncol*. 2020;31(11):1506-1517.
47. Le Cesne A, Antoine E, Spielmann M, et al. High-dose ifosfamide: circumvention of resistance to standard-dose ifosfamide in advanced soft tissue sarcomas. *J Clin Oncol*. 1995;13(7):1600-1608.
48. Martin-Liberal J, Alam S, Constantinidou A, et al. Clinical activity and tolerability of a 14-day infusional ifosfamide schedule in soft-tissue sarcoma. *Sarcoma*. 2013;2013:868973.
49. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. *J Clin Oncol*. 2016;34(8):786-793.
50. Martin-Broto J, Hindi N, Lopez-Pousa A, et al. Assessment of safety and efficacy of combined trabectedin and low-dose radiotherapy for patients with metastatic soft-tissue sarcomas: a nonrandomized phase 1/2 clinical trial. *JAMA Oncol*. 2020;6(4):535-541.
51. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2012;379(9829):1879-1886.
52. Martin-Broto J, Stacchiotti S, Lopez-Pousa A, et al. Pazopanib for treatment of advanced malignant and dedifferentiated solitary fibrous tumour: a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2019;20(1):134-144.
53. Stacchiotti S, Ferrari S, Redondo A, et al. Pazopanib for treatment of advanced extraskeletal myxoid chondrosarcoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2019;20(9):1252-1262.
54. Schoffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2016;387(10028):1629-1637.
55. Demetri GD, Schoffski P, Grignani G, et al. Activity of eribulin in patients with advanced liposarcoma demonstrated in a subgroup analysis from a randomized phase III study of eribulin versus dacarbazine. *J Clin Oncol*. 2017;35(30):3433-3439.
56. Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. *J Clin Oncol*. 2007;25(19):2755-2763.
57. Frezza AM, Jones RL, Lo Vullo S, et al. Anthracycline, gemcitabine, and pazopanib in epithelioid sarcoma: a multi-institutional case series. *JAMA Oncol*. 2018;4(9):e180219.
58. Garcia-Del-Muro X, Lopez-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. *J Clin Oncol*. 2011;29(18):2528-2533.
59. Baldi GG, Brahm M, Lo Vullo S, et al. The activity of chemotherapy in inflammatory myofibroblastic tumors: a multicenter, European retrospective case series analysis. *Oncologist*. 2020;25(11):e1777-e1784.
60. Rothermundt C, Whelan JS, Dileo P, et al. What is the role of routine follow-up for localised limb soft tissue sarcomas? A retrospective analysis of 174 patients. *Br J Cancer*. 2014;110(10):2420-2426.
61. Swallow CJ, Strauss DC, Bonvalot S, et al. Management of primary retroperitoneal sarcoma (RPS) in the adult: an updated consensus approach from the Transatlantic Australasian RPS Working Group. *Ann Surg Oncol*. 2021. <https://doi.org/10.1245/s10434-021-09654-z>.
62. Bonvalot S, Raut CP, Pollock RE, et al. Technical considerations in surgery for retroperitoneal sarcomas: position paper from E-Surge, a master class in sarcoma surgery, and EORTC-STBSG. *Ann Surg Oncol*. 2012;19(9):2981-2991.
63. Gronchi A, Miceli R, Colombo C, et al. Frontline extended surgery is associated with improved survival in retroperitoneal low- to intermediate-grade soft tissue sarcomas. *Ann Oncol*. 2012;23(4):1067-1073.
64. Angele MK, Albertsmeier M, Prix NJ, et al. Effectiveness of regional hyperthermia with chemotherapy for high-risk retroperitoneal and abdominal soft-tissue sarcoma after complete surgical resection: a subgroup analysis of a randomized phase-III multicenter study. *Ann Surg*. 2014;260(5):749-754. discussion 754-746.

65. Bonvalot S, Gronchi A, Le Pechoux C, et al. Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2020;21(10):1366-1377.
66. Trans-Atlantic RPS Working Group. Management of recurrent retroperitoneal sarcoma (RPS) in the adult: a consensus approach from the Trans-Atlantic RPS Working Group. *Ann Surg Oncol*. 2016;23(11):3531-3540.
67. Kho KA, Nezhat CH. Evaluating the risks of electric uterine morcellation. *JAMA*. 2014;311(9):905-906.
68. Ip PP, Cheung AN. Pathology of uterine leiomyosarcomas and smooth muscle tumours of uncertain malignant potential. *Best Pract Res Clin Obstet Gynaecol*. 2011;25(6):691-704.
69. Nasioudis D, Mastroyannis SA, Latif NA, et al. Effect of bilateral salpingo-oophorectomy on the overall survival of premenopausal patients with stage I low-grade endometrial stromal sarcoma; a National Cancer Database analysis. *Gynecol Oncol*. 2020;157(3):634-638.
70. Reed NS, Mangioni C, Malmstrom H, et al. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). *Eur J Cancer*. 2008;44(6):808-818.
71. Hensley ML, Wathen JK, Maki RG, et al. Adjuvant therapy for high-grade, uterus-limited leiomyosarcoma: results of a phase 2 trial (SARC 005). *Cancer*. 2013;119(8):1555-1561.
72. Lee CH, Ou WB, Marino-Enriquez A, et al. 14-3-3 fusion oncogenes in high-grade endometrial stromal sarcoma. *Proc Natl Acad Sci U S A*. 2012;109(3):929-934.
73. Hemming ML, Wagner AJ, Nucci MR, et al. YWHAE-rearranged high-grade endometrial stromal sarcoma: Two-center case series and response to chemotherapy. *Gynecol Oncol*. 2017;145:531-535.
74. Schwartz PE, Hui P, McCarthy S. Hormonal therapy for aggressive angiosarcoma: a case report and proposed management algorithm. *J Low Genit Tract Dis*. 2014;18(2):E55-E61.
75. Desmoid Tumor Working Group. The management of desmoid tumours: a joint global consensus-based guideline approach for adult and paediatric patients. *Eur J Cancer*. 2020;127:96-107.
76. Palassini E, Frezza AM, Mariani L, et al. Long-term efficacy of methotrexate plus vinblastine/vinorelbine in a large series of patients affected by desmoid-type fibromatosis. *Cancer J*. 2017;23(2):86-91.
77. Skapek SX, Anderson JR, Hill DA, et al. Safety and efficacy of high-dose tamoxifen and sulindac for desmoid tumor in children: results of a Children's Oncology Group (COG) phase II study. *Pediatr Blood Cancer*. 2013;60(7):1108-1112.
78. Constantinidou A, Jones RL, Scurr M, et al. Pegylated liposomal doxorubicin, an effective, well-tolerated treatment for refractory aggressive fibromatosis. *Eur J Cancer*. 2009;45(17):2930-2934.
79. Szucs Z, Messiou C, Wong HH, et al. Pazopanib, a promising option for the treatment of aggressive fibromatosis. *Anticancer Drugs*. 2017;28(4):421-426.
80. Kasper B, Gruenwald V, Reichardt P, et al. Imatinib induces sustained progression arrest in RECIST progressive desmoid tumours: final results of a phase II study of the German Interdisciplinary Sarcoma Group (GISG). *Eur J Cancer*. 2017;76:60-67.
81. Broto JM, Hindi N, Redondo A, et al. 1624MO Weekly nab-paclitaxel for progressive or symptomatic desmoid tumors: a multicenter single arm phase II trial from the Spanish Group for Research on Sarcoma (GEIS). *Ann Oncol*. 2020;31:S975.
82. Mir O, Honore C, Chamseddine AN, et al. Long-term outcomes of oral vinorelbine in advanced, progressive desmoid fibromatosis and Influence of CTNNB1 Mutational Status. *Clin Cancer Res*. 2020;26(23):6277-6283.
83. Gounder MM, Mahoney MR, Van Tine BA, et al. Sorafenib for advanced and refractory desmoid tumors. *N Engl J Med*. 2018;379(25):2417-2428.
84. Cherny NI, Dafni U, Bogaerts J, et al. ESMO-magnitude of clinical benefit scale version 1.1. *Ann Oncol*. 2017;28(10):2340-2366.
85. Dykewicz CA, Centers for Disease Control and Prevention (U.S.); Infectious Diseases Society of America, et al. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2001;33(2):139-144 (Adapted from: Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. *Clin Infect Dis*. 1994;18:421).
86. Stacchiotti S, Simeone N, Lo Vullo S, et al. Activity of axitinib in progressive advanced solitary fibrous tumour: results from an exploratory, investigator-driven phase 2 clinical study. *Eur J Cancer*. 2019;106:225-233.
87. Park MS, Patel SR, Ludwig JA, et al. Activity of temozolomide and bevacizumab in the treatment of locally advanced, recurrent, and metastatic hemangiopericytoma and malignant solitary fibrous tumor. *Cancer*. 2011;117(21):4939-4947.
88. Schoffski P, Sufliarsky J, Gelderblom H, et al. Crizotinib in patients with advanced, inoperable inflammatory myofibroblastic tumours with and without anaplastic lymphoma kinase gene alterations (European Organisation for Research and Treatment of Cancer 90101 CREATE): a multicentre, single-drug, prospective, non-randomised phase 2 trial. *Lancet Respir Med*. 2018;6(6):431-441.
89. Verspoo FGM, Mastboom MJL, Hannink G, et al. Long-term efficacy of imatinib mesylate in patients with advanced Tenosynovial Giant Cell Tumor. *Sci Rep*. 2019;9(1):14551.
90. Gelderblom H, Cropet C, Chevreau C, et al. Nilotinib in locally advanced pigmented villonodular synovitis: a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2018;19(5):639-648.
91. Shi Y, Cai Q, Jiang Y, et al. Activity and safety of gepanolimab (GB226) for patients with unresectable, recurrent, or metastatic alveolar soft part sarcoma: a phase II, single-arm study. *Clin Cancer Res*. 2020;26(24):6445-6452.
92. Florou V, Rosenberg AE, Wieder E, et al. Angiosarcoma patients treated with immune checkpoint inhibitors: a case series of seven patients from a single institution. *J Immunother Cancer*. 2019;7(1):213.
93. Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. *Lancet*. 2019;394(10197):478-487.
94. Mir O, Brodowicz T, Italiano A, et al. Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol*. 2016;17(12):1732-1742.
95. Penel N, Mir O, Wallet J, et al. A double-blind placebo-controlled randomized phase II trial assessing the activity and safety of regorafenib in non-adipocytic sarcoma patients previously treated with both chemotherapy and pazopanib. *Eur J Cancer*. 2020;126:45-55.
96. Gross AM, Wolters PL, Dombi E, et al. Selumetinib in children with inoperable plexiform neurofibromas. *N Engl J Med*. 2020;382(15):1430-1442.
97. Stacchiotti S, Simeone N, Lo Vullo S, et al. Activity of sirolimus in patients with progressive epithelioid hemangioendothelioma: a case-series analysis within the Italian Rare Cancer Network. *Cancer*. 2021;127(4):569-576.
98. Sanfilippo R, Jones RL, Blay JY, et al. Role of chemotherapy, VEGFR inhibitors, and mTOR inhibitors in advanced perivascular epithelioid cell tumors (PEComas). *Clin Cancer Res*. 2019;25(17):5295-5300.
99. Chevreau C, Le Cesne A, Ray-Coquard I, et al. Sorafenib in patients with progressive epithelioid hemangioendothelioma: a phase 2 study by the French Sarcoma Group (GSF/GETO). *Cancer*. 2013;119(14):2639-2644.
100. Stacchiotti S, Negri T, Libertini M, et al. Sunitinib malate in solitary fibrous tumor (SFT). *Ann Oncol*. 2012;23(12):3171-3179.
101. Gounder M, Schoffski P, Jones RL, et al. Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: an international, open-label, phase 2 basket study. *Lancet Oncol*. 2020;21(11):1423-1432.