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

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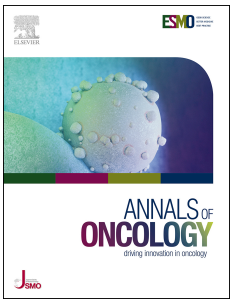

Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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Highlights:

- This Clinical Practice Guideline provides key recommendations on the management of soft tissue and visceral sarcomas.
- Recommendations have been agreed following a consensus meeting of representatives from ESMO, EURACAN and GENTURIS.
- Authorship includes a multidisciplinary group of experts from different institutions and European countries, with a representative from India and Japan.

INTRODUCTION

Soft tissue sarcomas (STSs) comprise approximately 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 a considered a high-grade STS, whose clinical resemblance with osteosarcoma of bone is doubtful. The methodology followed during the consensus 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, while 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: multidisciplinarity (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 STS 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 scan (CT) has a role in calcified lesions, to rule out a myositis ossificans, in pleuro-pulmonary 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 a 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 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 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-fluorodeoxyglucose 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%-11% for major discordance, and 16%-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).[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 system for pathological response assessment are available for STS. 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 receptor tyrosine 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 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 of the thorax is recommended for staging purposes. Regional lymph node (LN) metastases are usually rare (i.e. <1%); there are exceptions like epithelioid sarcoma, clear cell sarcoma (CCS), synovial sarcoma and angiosarcoma, for which regional assessment through CT/MRI may be added to the usual staging procedures. A CT 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 with STS under 46 years of age and at least one 1st or 2nd degree relative with a TP53 core tumour (breast cancer, STS, bone sarcoma, central nervous system tumour, adrenocortical carcinoma) under 56 years of age, or (ii) patients with STS (especially in RT fields) and another TP53 core tumour under 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-AJCC) are of limited clinical value. Risk assessment is better obtained through the available nomograms [IV, A].
- Staging is routinely performed with contrast enhanced CT chest, abdomen and pelvis. 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. [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 pseudo-capsule 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 postoperatively, 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 postoperative 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 postoperative 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 postoperative 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 (EMC) gain the greatest benefit from RT.[25, 26] For MLS, one study has recently investigated a low dose (18x2 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, reoperation 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 needed, and the patient should be properly referred if necessary.

When re-excision is not possible after R1-R2 resections, postoperative 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 preoperative treatment, at least in part, especially in chemo-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 amongst expert centres. Formally, adjuvant and neoadjuvant AI ChT is not a standard treatment. However, it can be proposed with 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 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 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 to 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, 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 patient 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 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 postoperative RT and/or ChT, if not previously administered.

Recommendations

- Surgery is the standard treatment of 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 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 and outcome data are required on alternative, less invasive options. When surgery of lung metastases is selected, an abdominal CT and a bone scan or an 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 is 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, nonresectable disease, a systemic treatment with an essentially palliative intent can be proposed. Anthracycline-based therapy is 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 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 (ORR) 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 for those rare patients with locally-advanced or metastatic *NTRK*-rearranged sarcomas; larotrectinib ESMO-Magnitude of Clinical Benefit Scale (MCBS) v1.1 score 3 [III, A; ESMO-MCBS 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/m^2) may also be an option for patients already pretreated with standard-dose (9 g/m^2) ifosfamide [IV, C].[47, 48]
- Trabectedin is an option in advanced STS from second-line. It has proved effective in LMS and liposarcoma[49] [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 be also combined to 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 advanced, previously treated, STS patients (excluding liposarcomas).[51] Thus, it is an option in non-adipogenic STS from second-line [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 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 for liposarcomas from second-line 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 (UPS), 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 antitumour activity also in LMS, angiosarcoma and epithelioid sarcomas 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 performance status (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 for 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 from second-line in STS [I, B; ESMO-MCBS v1.1 score 2].
- Pazopanib is an option in nonadipogenic STS, from second-line [I, B; ESMO-MCBS v1.1 score 3]
- 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.

Pre-treatment 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 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 rupture 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 radiotherapy (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, signals 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.

Postoperative/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 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 RPS [I, B].[28]

The value of adjuvant/neoadjuvant ChT is not established, though the rarity of the subtypes of RPSs force 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 yet. 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, whose existence 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 performed). 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 roughly 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 postoperative 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, 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-docetaxe.[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, adenosarcoma with sarcomatous overgrowth and UES are high-grade malignancies. There are no data on the value of adjuvant ChT, though their high-risk status may justify an individualized 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 for 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 (DF).

While principles for the diagnosis of STS apply also to 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 progressing cases. 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 progressing cases, 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, also HT (tamoxifen, toremifene and GnRH analogues; aromatase inhibitors), non-steroidal anti-inflammatory drugs and interferon have long been used but no prospective studies are available to understand their real activity in this disease.

Breast sarcomas (BS).

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

BS 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 postoperative RT. A targeted axillary dissection should be done in patients with clinically- and/or radiologically-concerning nodes, as the lymph node 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 in 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/postoperative RT are of no proven value in RPS. The role of adjuvant/neoadjuvant ChT is not established yet.
- 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 5th 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 in included in Supplementary Table S2. ESMO-MCBS v1.1.[84] was used to calculate scores for new therapies/indications approved by the EMA since 1 January 2016 or 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.[85] Statements without grading were considered justified standard clinical practice by the experts.

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

ALK, anaplastic lymphoma kinase; Choi, Choi criteria; m-PFS, 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.

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

Adj, adjuvant; ChT, chemotherapy; RT, radiotherapy; STS, soft tissue sarcoma.

[a] Depending upon histology and anatomical location.

[b] See text.

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

ChT, chemotherapy; RT, radiotherapy; STS, soft tissue sarcoma.

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

ChT, chemotherapy; STS, soft tissue sarcoma.

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

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

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)	NA	Phase II, single-arm
Imatinib[89]	TGCT	Any	31 (RECIST)	NA	Retrospective case-series
Nilotinib[90]	TGCT	Any	6 (RECIST)	not reached	Phase II, single-arm
PD1/-PDL1 inhibitors monotherapy[91]	Alveolar soft part sarcoma	Any	ranges from 32 to 36 (RECIST)	7-not reached (RECIST)	Phase II, singe-arm; subgroup analyses of phase II studies; case reports
PD-1/-PDL1 inhibitors[92]	Angiosarcoma	Second line and beyond	71 (RECIST)	NA	Case reports; retrospective case-series
Pexidartinib[93]	TGCT	Any	pexidartinib versus placebo 39 versus 0 (RECIST)	NA	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-adipocitic STS		11 (RECIST)	2.9 versus 1.0	
	Non-adipocitic 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 Haemangio endothelioma	Any	10.8 (RECIST)	13 (RECIST)	Retrospective case-series
Sirolimus[98]	PEComa	Any	41 (RECIST)	9 (RECIST)	Retrospective case-series
Sorafenib[99]	Epithelioid Haemangio endothelioma	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