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

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Extraskeletal Ewing sarcoma is covered by other ESMO Guidelines: in general, the same principles for these tumours in children apply to adults. This is also the case for embryonal and alveolar rhabdomyosarcoma, which are exceedingly rare in adults. On the other hand, pleomorphic rhabdomyosarcoma is viewed as a high-grade adult-type soft tissue sarcoma. Gastrointestinal stromal tumours are covered by the dedicated ESMO Clinical Practice Guidelines. Kaposi's sarcoma is excluded.

incidence

Adult soft tissue and visceral sarcomas (excluding gastrointestinal stromal tumour) are rare tumours, with an estimated incidence averaging 4–5/100 000/year in Europe [1].

diagnosis

Soft tissue sarcomas (STSs) are ubiquitous in their site of origin and are often managed with multimodality treatment. A multidisciplinary approach is therefore mandatory in all cases (involving pathologists, radiologists, surgeons, radiation therapists, medical oncologists and paediatric oncologists, as well as nuclear medicine specialists, 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. These centres are involved in ongoing clinical trials, in which sarcoma patients' enrolment is common. This centralised referral should be pursued as early as at the time of the clinical diagnosis of a suspected sarcoma. In practice, referral of all patients with a lesion likely to be a sarcoma would be recommended. This would mean referring all patients with an unexplained deep mass of soft tissues, or with a superficial lesion of soft tissues having a diameter of >5 cm. Quality criteria are needed for sarcoma reference centres and, all the more, reference networks. These criteria may vary from country to country but, among others, should be based on: multidisciplinarity (incorporating tools such as weekly tumour boards discussing new cases), volume of patients, availability of facilities needed to properly apply clinical practice guidelines, recording and publication of outcomes.

In 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, and in retroperitoneal tumours, where the performance is identical to MRI. Ultrasound may be the first exam, but 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, as decided within reference centres. An immediate evaluation of tissue viability may be considered, to ensure that the biopsy is adequate at the time it is carried out. However, a frozen-section technique for immediate diagnosis is not encouraged, because it generally does not allow a complete diagnosis, particularly when preoperative treatment is planned. Fine needle aspiration is used only in some institutions, which have developed specific expertise on this procedure, and is not recommended outside these centres. A biopsy may underestimate the tumour malignancy grade. Therefore, when preoperative treatment is an option, radiological imaging (including positron emission tomography, PET) may be useful, in addition to pathology, in providing the clinician with information that helps to estimate the malignancy grade (i.e. necrosis). The biopsy should be carried out by a surgeon or a radiologist, after multidisciplinary discussion, as needed, within reference centres. It should be planned in such a way that the biopsy pathway and the scar can be safely removed by definitive surgery (except for retroperitoneal sarcomas, RPS). The biopsy entrance point can be tattooed. The tumour sample should be fixed in 4% buffered formalin in due time (Bouin fixation should not be used, since it prevents molecular analysis). The collection of fresh/frozen tissue and tumour imprints (touch preps) is encouraged, because new molecular pathology assessments could be made at a later stage in the patient's interest. In this perspective, the availability of a blood sample could add to the value of tumour tissues. Informed consent for biobanking should be sought, enabling later analyses and research, as long as this is allowed by local and international rules.

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Histological diagnosis should be made according to the 2013 World Health Organization (WHO) classification [2]. A pathological expert validation is required in all cases when the original diagnosis was made outside a reference centre/network [3].

The malignancy grade should be provided in all cases in which this is feasible based on available systems, because it has prognostic and predictive meaning. The 'Federation 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 [4]. Whenever possible, the mitotic rate should be provided independently. An effort should be made to improve the reliability of mitotic count as actually recorded. Grading cannot be assigned after preoperative medical treatment, by which the tumour tissue undergoes major therapy-related changes (Table 1).

Tumour site should be properly recorded. Tumour size and tumour depth (in relation to the superficial fascia) should also be recorded, since they entail a prognostic value, along with the malignancy grade. The pathology report after definitive surgery should mention whether the tumour was intact and should include an appropriate description of tumour margins (i.e. the status of inked margins and the distance between tumour edge and the closest inked margins). This allows the assessment of margin status (i.e. whether the minimum margin is intralesional, marginal or wide and distances from surrounding tissues). The pathological assessment of margins should be made in collaboration with the surgeon.

If preoperative treatment was carried out, the pathology report should include an assessment of the histological response of the tumour. In contrast to osteosarcoma and Ewing sarcoma, however, no validated system is available at present in this regard, and no percentage of residual 'viable cells' is considered to have a specific prognostic significance. This depends on several factors, including the presence of non-treatment-related necrosis and haemorrhage and the heterogeneity of post-treatment changes. A multidisciplinary judgement is recommended, involving the pathologist and the radiologist.

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

- the specific histological diagnosis is doubtful;
- the clinical pathological presentation is unusual;
- it may have prognostic and/or predictive relevance.

Table 1. Federation Nationale des Centres de Lutte Contre le Cancer histological grading criteria

Tumour differentiation	Necrosis (macro and micro)	Mitotic count (n/10 high-power fields)
1: Well	0: Absent	1: $n < 10$
2: Moderate	1: <50%	2: 10–19
3: Poor	2: ≥50%	3: $n \geq 20$

The sum of the scores of the three criteria determines the grade of malignancy. Grade 1: 2 and 3; Grade 2: 4 and 5; Grade 3: 6, 7 and 8. Reprinted from [4] with permission of John Wiley & Sons, Inc.

External quality assurance programmes are encouraged for laboratories performing molecular pathology assessments.

stage classification and risk assessment

Available staging classifications have limited relevance and should be improved. The *American Joint Committee on Cancer* (AJCC)/*International Union against Cancer* (UICC) stage classification system stresses the importance of the malignancy grade in sarcoma [5]. In general, in addition to grading, other prognostic factors are tumour size and tumour depth for limb sarcomas. Of course, site, tumour resectability and presence of metastases are also important (Table 2).

staging procedures

A chest spiral CT scan is mandatory for staging purposes.

Regional lymph node metastases are rare, with the exception of some histologies, e.g. epithelioid sarcoma and clear cell sarcoma, for which regional assessment through CT/MRI may be added to the usual staging procedures.

Likewise, an abdominal CT scan may be added for limb myxoid liposarcoma. The brain CT scan may be added for alveolar soft part sarcoma, clear cell sarcoma and angiosarcoma.

Bone scan, whole-body MRI and PET scan are optional. Cost-effectiveness studies on their incorporation into the 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 the tumour was opened and was 'seen' during the excision, etc.); surgical actual completeness vis-a-vis planned quality of margins.

treatment

localised disease

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 this disease [III, A]. The standard surgical procedure is a wide excision with negative margins (R0). This implies removing the tumour with a rim of normal tissue around it [III, A]. The cut-off of 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 fasciae, periostium and epineurium. As an individualised option, marginal excision can be acceptable in carefully selected cases, in particular for extracompartmental atypical lipomatous tumours [IV, B].

Radiation therapy is not given in the case of a truly compartmental resection of a tumour entirely contained within the compartment [IV, A]. A wide excision is followed by radiation therapy as the standard treatment of high-grade (G2–3), deep >5 cm lesions [II, B] [6–8]. Exceptions may be made after multidisciplinary discussion taking into account several variables [9].

With exceptions to be discussed in a multidisciplinary setting, and faced with a lack of consensus across reference centres, high-grade, deep, <5 cm lesions are also treated with surgery, followed by radiation therapy [IV, A].

Table 2. American Joint Committee on Cancer (AJCC)/International Union against Cancer (UICC) TNM staging system [5]

Primary tumour (T)			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour 5 cm or less in greatest dimension[a]		
T1a	Superficial tumour		
T1b	Deep tumour		
T2	Tumour >5 cm in greatest dimension[a]		
T2a	Superficial tumour		
T2b	Deep tumour		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1[b]	Regional lymph node metastasis		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage IA			
T1a	N0	M0	G1, GX
T1b	N0	M0	G1, GX
Stage IB			
T2a	N0	M0	G1, GX
T2b	N0	M0	G1, GX
Stage IIA			
T1a	N0	M0	G2, G3
T1b	N0	M0	G2, G3
Stage IIB			
T2a	N0	M0	G2
T2b	N0	M0	G2
Stage III			
T2a, T2b	N0	M0	G3
Any T	N1	M0	Any G
Stage IV			
Any T	Any N	M1	Any G

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Handbook, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springerlink.com.

[a]Superficial tumour is located exclusively above the superficial fascia without invasion of the fascia; deep tumour is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia.

[b]Presence of positive nodes (N1) in M0 tumours is considered Stage III.

Radiation therapy is added in selected cases in the case of low- or high-grade, superficial, >5 cm and low-grade, deep, <5 cm STSs [II, B].

In the case of low-grade, deep, >5 cm STSs, radiation therapy should be discussed in a multidisciplinary fashion, considering the anatomical site and the related expected sequelae versus the histological aggressiveness.

Local control and survival are not influenced by the timing of radiotherapy, but early and late complications are. If it is anticipated that wound complications will be severe, surgery followed by adjuvant radiotherapy may be the best option. Radiation therapy should then be administered, with the best technique available, to a total dose of 50 Gy in 1.8–2 Gy fractions, possibly with a boost up to 66 Gy, depending on presentation and resection margins. If it is anticipated that wound complications will be a manageable problem, neoadjuvant radiotherapy, possibly in combination with chemotherapy [10] to a total dose of 50 Gy in 1.8–2 Gy fractions, followed by surgery may be considered. In addition, by means of modern radiotherapy techniques such as image guided radiotherapy and intensity modulated radiotherapy the anticipated incidence of wound complications after preoperative radiotherapy is lower than historically published. The main advantage of preoperative radiotherapy is that, with prolonged follow up, late morbidity (fibrosis, bone fracture, etc.) is lower, translating into improved functional outcome and quality of life.

Reoperation in reference centres must be considered in the case of R1 resections, if adequate margins can be achieved without major morbidity, taking into account tumour extent and tumour biology (e.g. re-excision can be spared in extracompartmental atypical lipomatous tumours, etc.) [IV, A]. In the case of R2 surgery, reoperation in reference centres is mandatory, possibly

following preoperative treatments if adequate margins cannot be achieved, or surgery is mutilating. In the latter case, the use of multimodal therapy with less radical surgery requires a shared decision-making with the patient in cases of uncertainty. Plastic repairs and vascular grafting should be used as needed, and the patient should be properly referred as necessary.

Radiation therapy will follow marginal or R1–R2 excisions, if these cannot be rescued through re-excision, tailoring the decision depending on further considerations, including impact on future surgeries, etc.

Mutilating surgery may be of choice in some cases. Options for limb-preserving surgery can be discussed with the patient, including chemotherapy and/or radiotherapy [III, A], or isolated hyperthermic limb perfusion with tumour necrosis factor-alpha + melphalan [III, A], if the tumour is confined to an extremity, or regional hyperthermia combined with chemotherapy [I, B] [11]. These options are resorted to in non-resectable tumours as well, i.e. in the truly locally advanced disease.

Regional lymph node metastases should be distinguished from soft tissue metastases involving lymph nodes. They are rare and constitute an adverse prognostic factor in adult-type STSs. More aggressive treatment planning is therefore felt to be appropriate for these patients, although there is a lack of formal evidence to indicate that this improves clinical results. Surgery through wide excision (mutilating surgery is exceptionally done given the prognosis of these patients) may be coupled with adjuvant radiation therapy and adjuvant chemotherapy for sensitive histological types, as the standard treatment of these presentations [IV, B]. Chemotherapy may be administered as preoperative treatment, at least in part. Given the paucity of published data on adjuvant radiotherapy after lymph node dissections in regional metastatic STS, the indication should probably be reserved for patients with a relatively large number of tumour-positive lymph nodes and/or extranodal spread in the absence of haematogenic metastases. The increase in local control should be balanced against toxicity (especially peripheral lymphoedema). These treatment modalities adding to surgery should not be viewed as truly 'adjuvant', the context being in fact that of a likely systemic disease. In one large randomised phase III study (in patients with G2–3, deep, >5 cm STSs), regional hyperthermia in addition to systemic chemotherapy was associated with a local and disease-free survival (DFS) advantage when compared with chemotherapy alone [I, B]. Isolated limb perfusion may be an option in this patient population. In itself, this modality has obviously no impact on systemic control (but it can be combined with other modalities) [III, A] [12].

There is no consensus on the current role of adjuvant chemotherapy. Study results are conflicting, in the presence of negative results from the largest studies, though data are available from smaller studies suggesting that it might improve, or at least delay, distant and local recurrence in high-risk patients [13, 14]. A meta-analysis found a statistically significant limited benefit in terms of both survival- and relapse-free survival [15]. It is unknown whether adjuvant chemotherapy may be particularly beneficial in specific subgroups or even detrimental in others. Therefore, adjuvant chemotherapy is not standard treatment in adult-type STS. It can be proposed as an option to the high-risk individual patient (high-grade, deep, >5 cm tumour) for a shared decision-making with the patient [II, C] or within clinical trials. A randomised trial showed no differences between three (preoperative) and five (pre- and postoperative) courses of full-dose chemotherapy [16]. A trial is ongoing comparing standard preoperative chemotherapy versus histology-driven chemotherapy. Adjuvant chemotherapy should never be intended to rescue inadequate surgery. In any case, adjuvant chemotherapy is not used in histological subtypes known to be insensitive to chemotherapy. If the decision is made to use chemotherapy as upfront treatment, it may well be used preoperatively, at least in part [III, B]. A local benefit may be gained, facilitating surgery. When employed, adjuvant chemotherapy should consist of the combination chemotherapy regimens proved to be most active in advanced disease. Radiation therapy should not delay the start of chemotherapy and can be used preoperatively. In one large randomised phase III study (in patients with G2–3, deep, >5 cm STSs), regional hyperthermia in addition to systemic chemotherapy was associated with a local progression-free survival (PFS) and DFS advantage [I, B] [11].

The standard approach to local relapses parallels the approach to primary local disease, except for a wider resort to preoperative or postoperative radiation therapy and/or chemotherapy, if not previously carried out.

advanced disease

The decision-making is complex, depending on 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 [17] [IV, B]. A minimally invasive thoracoscopic approach can be resorted to in selected cases. Other appropriate local techniques can be resorted to, though surgery is the standard and data are required on alternative less invasive options. Decisions must also consider the feasibility of the various options. When surgery of lung metastases is selected, an abdominal CT scan and a bone scan or a fluorodeoxyglucose (FDG)-PET are mandatory to confirm that lung metastases are 'isolated'.

Chemotherapy 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 chemotherapy), although there is a lack of formal evidence that this improves outcome [IV, B]. Chemotherapy is preferably given before surgery in order to assess tumour response and thus modulate treatment.

In cases where lung metastases are synchronous, in the absence of extrapulmonary disease, standard treatment is chemotherapy [III, B]. Surgery of completely resectable residual lung metastases may be offered as an option, especially when a tumour response is achieved.

Extrapulmonary metastatic disease is treated with chemotherapy as the standard treatment [I, A].

In highly selected cases, surgery of responding metastases may be offered as an option following a multidisciplinary evaluation, taking into consideration their site and the natural history of the disease in the individual patient.

Surgery, or ablations, or radiation therapy, of extrapulmonary metastases may be an option without chemotherapy in highly

selected cases (e.g. some patients with myxoid liposarcoma, solitary fibrous tumour, etc.) [7].

Standard chemotherapy is based on anthracyclines as the first-line treatment [I, A]. As of today, there is no formal demonstration that multiagent chemotherapy is superior to single-agent chemotherapy with doxorubicin alone in terms of overall survival (OS). However, a higher response rate can be expected, in particular in a number of sensitive histological types, according to several, although not all, randomised clinical trials [18, 19]. Therefore, multiagent chemotherapy with adequate-dose anthracyclines plus ifosfamide may be the treatment of choice, particularly when a tumour response is felt to be potentially advantageous and patient performance status is good.

In angiosarcoma, taxanes are an alternative option, given their high antitumour activity in this specific histological type [20] [III, B]. An alternative option is gemcitabine ± docetaxel [21] [V, B].

Doxorubicin plus dacarbazine is an option for multiagent first-line chemotherapy of leiomyosarcoma, where the activity of ifosfamide is far less convincing in available retrospective evidence, or solitary fibrous tumour [22] [V, B].

Imatinib is standard medical therapy for those rare patients with dermatofibrosarcoma protuberans who are not amenable to non-mutilating surgery or with metastases deserving medical therapy [23, 24] [III, A].

After failure of anthracycline-based chemotherapy, or the impossibility to use it, the following criteria may apply, although high-level evidence is lacking:

- Patients who have already received chemotherapy may be treated with ifosfamide, if they did not progress on it previously. High-dose ifosfamide (around 14 g/m^2) may be an option also for patients who have already received standard-dose ifosfamide [25, 26] [IV, C].
- Trabectedin is a second-line option [II, B] and is approved for advanced previously treated STS in the EU. It has proved effective in leiomyosarcoma and liposarcoma [27]. In myxoid liposarcoma, a high antitumour activity was described. A peculiar pattern of tumour response has been reported, with an early phase of tissue changes preceding tumour shrinkage [28]. Clinical benefit with trabectedin was also obtained in other histological types.
- One trial showed that gemcitabine + docetaxel is more effective than gemcitabine alone as second-line chemotherapy, with special reference to leiomyosarcoma and undifferentiated pleomorphic sarcoma, but data are conflicting and toxicity is different [29] [II, C]. Gemcitabine was shown to have anti-tumour activity in leiomyosarcoma and angiosarcoma also as a single agent.
- Dacarbazine has some activity as a second-line therapy (mostly in leiomyosarcoma and solitary fibrous tumour). The combination of dacarbazine and gemcitabine was shown to improve the OS and PFS over dacarbazine in a randomised trial [30] [II, B].
- A randomised trial showed a benefit in PFS averaging 3 months for pazopanib given up to progression to advanced, previously treated, STS patients (excluding liposarcomas) [31]. Thus, it is an option in non-adipogenic STS [I, B].

Best supportive care alone is an alternative for pre-treated patients with advanced STS, especially if further-line therapies have already been used in the patient.

Radiation therapy should be used as a palliative resource in all cases as appropriate to the clinical need (e.g. bone lesions at risk of fracture, etc.).

In general, advanced previously treated patients are candidates for clinical trials.

With reference to selected histological types, there is anecdotal evidence of activity of several molecular targeted agents, building on consistent preclinical data. Examples are:

- mammalian target of rapamycin inhibitors in malignant perivascular epithelioid cell tumours (PEComas), which are often associated with the loss of tuberous sclerosis complex 1 (TSC1)/TSC2 [32];
- crizotinib in inflammatory myofibroblastic tumour associated with anaplastic lymphoma kinase translocations [33];
- sunitinib and cediranib in alveolar soft part sarcoma, where the molecular target is as yet unclear [34, 35]
- sunitinib in solitary fibrous tumours, where the molecular target is as yet unclear [36].

These patients can be sent to reference centres, to be treated accordingly, preferably within clinical studies or prospective clinical recordings [III, C].

follow-up

There are few published data to indicate the optimal routine follow-up policy of surgically treated patients with localised disease [37].

The malignancy grade affects the likelihood and speed at which relapses may occur. The risk assessment based on tumour grade, tumour size and tumour site therefore helps in choosing a routine follow-up policy. High-risk patients generally relapse within 2–3 years, whereas low-risk patients may relapse later, although it is less likely. Relapses most often occur to the lungs. Early detection of local or metastatic recurrence to the lungs may have prognostic implications, and lung metastases are asymptomatic at a stage in which they are suitable for surgery. Therefore, the routine follow-up may focus on these sites. Although the use of MRI to detect local relapse and CT to scan for lung metastases is likely to pick up recurrences earlier, it has not been demonstrated that this is beneficial, or cost effective, compared with the clinical assessment of the primary site and regular chest X-rays.

That said, while prospective studies are needed, a practical approach in place at several institutions is as follows: Surgically-treated intermediate-/high-grade patient 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 for local relapse every 4–6 months, with chest X-rays or CT scan at longer intervals in the first 3–5 years, then annually.

special presentations and entities

retroperitoneal sarcomas

Patients with suspected RPS need to be referred to high-volume sarcoma centres [38].

Chest, abdomen and pelvis IV contrast-enhanced CT are standard for staging. IV contrast-enhanced MRI is an option, especially for pelvic tumours, to assess specific aspects of tumour

extent. Functional assessment of contralateral kidney is necessary. Pre-treatment biopsy for pathological diagnosis should be carried out, to allow tailored present and future therapeutic decisions, unless otherwise indicated by a sarcoma tumour board. A multiple core biopsy with an adequate coaxial needle of sufficient size (14–16 G) is the standard procedure. Risk of needle track seeding is minimal and should not be a reason to avoid a biopsy. Nonetheless, the pathway of the biopsy should be carefully planned to minimise contamination and complications, and should not be carried out transperitoneally. Open or laparoscopic biopsies must be avoided.

Comprehensive imaging evaluation is critical, to accurately assess extent of tumour. Certain areas (e.g. inguinal canal, retrohepatic vena cava, diaphragm, neural foramina, etc.) are particularly challenging to evaluate and may require additional specialised radiological input. Specific appreciation of the well-differentiated versus the dedifferentiated component(s) of liposarcoma is critical to surgical decision-making.

The best chance of cure is at the time of primary presentation, and an individualised management plan should be made, following discussion at a multidisciplinary sarcoma case conference on both imaging and pathological findings. The standard treatment of primary lesions is surgery, to be carried out by a surgeon with specific sarcoma expertise. Surgery should be aimed at achieving macroscopically complete resection in one specimen bloc and minimising microscopically positive margins. This is best done by resecting the tumour en bloc with adherent structures, even if not overtly infiltrated (III, A) [39–42]. Preservation of specific organs (i.e. kidney, head of the pancreas and/or liver) should be considered on an individualised basis and mandates a specific expertise in the disease to make the right decisions. Judgement must be used in deciding which neurovascular structures to sacrifice, weighing the potential for local control against the potential for long-term dysfunction.

Grossly incomplete resection of RPSs is of questionable benefit and 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.

Although no randomised trials of neoadjuvant therapy versus resection alone for RPS have been reported to date, neoadjuvant therapy, in the form of chemotherapy, external beam radiation, regional hyperthermia or combinations, is safe in well-selected patients and may be considered after careful review by a multidisciplinary sarcoma tumour board [43]. This is particularly relevant in the case of technically unresectable/borderline resectable RPS that could potentially be rendered resectable by downsizing, and also in chemosensitive histologies such as synovial sarcoma. The sensitivity of solitary fibrous tumour to radiation therapy should also be considered. In one large randomised phase III study (in patients with G2–3, deep, >5 cm STSs), regional hyperthermia in addition to systemic chemotherapy was associated with a local PFS and DFS advantage [44] [I, B].

Preoperative radiation therapy in resectable tumours is being investigated in a currently accruing prospective randomised clinical trial. Preoperative treatments are not intended to change the extent of surgery, but to improve the quality of surgical margins.

Postoperative/adjuvant external beam radiation following complete gross resection is of limited value, and is associated with significant short- and long-term toxicities. A therapeutic radiation treatment dose can be achieved in a minority of patients following resection. In selected cases, it may be an option in well-defined anatomical areas felt to be at high risk. Brachytherapy is of unproven value and is associated with significant short- and long-term complications. Intraoperative radiotherapy is of unproven value.

The value of adjuvant chemotherapy is not established. However, one can make the same considerations which apply to extremity STSs.

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, or to patients experiencing a response to medical therapies.

uterine sarcomas

The group of uterine sarcomas includes leiomyosarcomas, endometrial stromal sarcomas (ESS, formerly low-grade ESSs) and undifferentiated endometrial sarcomas (UESs). Carcinosarcomas (malignant Müllerian mixed tumours) are currently viewed as epithelial cancers, and treatment should be tailored accordingly. Thus, before a final diagnosis of sarcoma is made, the pathologist should be certain that an epithelial component is absent, through proper immunohistochemical analysis.

At the moment, we do not have clinical and radiological criteria to differentiate leiomyomas from malignant uterine tumours. Thus, procedures resulting in potential tumour cell spillage, such as morcellation out of endobags, entail a high risk of worsening patient prognosis if malignancy is the post-operative pathological diagnosis [45, 46].

Smooth tumours of undefined malignant potential constitute a negative definition, which is resorted to when both a leiomyoma and a leiomyosarcoma cannot be diagnosed with certainty [47]. There are remarkable variations with this diagnosis amongst pathologists. Some of these lesions might represent 'low-grade' leiomyosarcomas. Due to the uncertainty, hysterectomy is an option, but there is room for individualised decision-making with an informed patient.

Standard local treatment of uterine leiomyosarcoma, ESS and UES (when localised) is en bloc total hysterectomy (including laparoscopy/assisted or robotic surgery, provided the tumour is resected with the same criteria as for open surgery). With a diagnosis of sarcoma, fertility-preserving surgery in young women is not supported by any evidence and should not be regarded as standard, though of course it may be the choice made by an informed patient. The added value of bilateral salpingo-oophorectomy is not established, particularly in premenopausal women, and lymphadenectomy has not been demonstrated to be useful in the lack of macroscopic involvement. In ESS, however, lymph nodes may be positive in roughly 10% of cases. Although in uterine leiomyosarcoma retrospective studies suggested a possible decrease in local relapses, radiation therapy has not improved survival and relapse-free survival in a prospective randomised trial, and therefore is not recommended [48]. The use of radiation therapy as an adjuvant to surgery can be an option in selected cases, after shared decision-making with the patient, following multidisciplinary discussion taking into account special risk factors, including: local relapse, cervical

involvement, parametral involvement, serosal involvement and UES histology [IV, C]. The value of adjuvant chemotherapy in uterine leiomyosarcoma is undetermined. Uncontrolled studies suggest a benefit in comparison with external controls for gemcitabine + docetaxel × 4 courses followed by doxorubicin × 4 courses, as well as for gemcitabine + docetaxel × 4 courses [49, 50]. A prospective randomised trial with a no-treatment control arm versus gemcitabine + docetaxel × 4 courses followed by doxorubicin × 4 courses is ongoing.

The medical treatment of advanced leiomyosarcomas, UES and adenosarcoma with sarcomatous overgrowth parallels that for adult-type STSs. It should be kept distinct from malignant Müllerian mixed tumours, which are currently treated with therapies for epithelial tumours. As for all leiomyosarcomas, doxorubicin, dacarbazine, trabectedin 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 leiomyosarcomas.

ESSs are 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 the rare EPC1-PHF1 or JAZF1-PHF1 transcripts. Adjuvant hormonal therapy 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. The systemic treatment of metastatic low-grade ESS exploits their sensitivity to hormonal therapies [V, B]. Therefore, progestins, aromatase inhibitors and Gn-RH analogues (for pre-menopausal patients) can be used [51]. Tamoxifen is contraindicated due to a possible agonist activity, as is hormonal replacement therapy (HRT) containing oestrogens. Chemotherapy may be an option when hormonal therapy has failed. Surgery of lung metastases is an option, even in presentations which might not be surgically approached in other STS, given the long natural history of the disease. This may apply to pelvic disease as well, even in the presence of metastatic disease.

Currently, a subgroup of high-grade ESS is recognised, which is defined by specific cytogenetics, marked by the (10;17) translocation, carrying the YWHAE-FAM22 transcript [52]. Their behaviour is more aggressive. Currently, their sensitivity to hormonal therapies is not defined, so cytotoxic chemotherapy is considered appropriate in the metastatic setting, though data are lacking.

High-grade ESS, adenosarcoma with sarcomatous overgrowth and UES are high-grade malignancies. There are no data on the value of adjuvant chemotherapy, though their high-risk status may justify a shared decision with the patient in conditions of uncertainty, especially in UES. Hyperthermic peritoneal chemotherapy 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 hormonal therapy (as for ESS) a resource for progressing disease and surgery. The same applies to peritoneal leiomyomatosis, if non-mutilating surgery is not feasible.

For pelvic aggressive angiomyxoma, surgery is the treatment of choice if not mutilating, with observation thereafter. In progressing disease, hormonal therapy, or interruption of any ongoing stimulation with oestrogens, may allow mutilating surgery to be avoided and the disease to be kept under control [53].

desmoid-type fibromatosis

While principles for the diagnosis of STS apply also to desmoids, beta-catenin mutational analysis may be useful when the pathological differential diagnosis is difficult.

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 watchful waiting policy can be proposed [54, 55] [III, B]. This should follow a shared decision-making with the patient, with 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 signal is not meaningful with regard to the disease evolution.

For progressing cases, optimal strategy needs to be individualised on a multidisciplinary basis and may consist of surgery (without any adjuvant therapy), radiation therapy, observation, isolated limb perfusion (if the lesion is confined to an extremity) or systemic therapy (see below) [56] [V, B]. Systemic therapies include: hormonal therapies (tamoxifen, toremifene and Gn-RH analogues), non-steroidal anti-inflammatory drugs; low-dose chemotherapy, such as methotrexate + vinblastine or methotrexate + vinorelbine; sorafenib; imatinib; interferon; full-dose chemotherapy (using regimens active in sarcomas, including liposomal doxorubicin) [57–63]. It is reasonable to employ the less toxic therapies before the more toxic ones in a stepwise fashion. A comprehensive clinical judgement of progression should be used. Hormonal contraception should be discussed with the patient, and definitely stopped in case of progressing disease.

breast sarcomas

These patients should be referred to sarcoma units.

Breast sarcomas 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. those having >10 mitoses/10 HPF and marked stromal overgrowth) have a 20%–30% metastatic rate. On the other hand, metaplastic breast carcinomas, also known as carcinosarcomas, are epithelial neoplasms, whose treatment should be tailored to their mainly epithelial nature.

The best treatment of breast sarcomas is far from being defined, given their rarity and heterogeneity. In general, breast-conserving surgery may be resorted to, depending on the quality of margins versus the size of the tumour and the breast, along with the feasibility of radiation therapy. In addition, angiosarcomas of the mammary gland have such a tendency to recur that mastectomy (involving the muscular fascia) is recommended in most cases, even in combination with postoperative radiation therapy. Lymphadenectomy is not carried out in the absence of clinical evidence of involvement.

As far as adjuvant and neoadjuvant chemotherapy is concerned, the same principles of STS apply. One may consider in particular the high risk of angiosarcoma to develop local and

Table 3. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System)[a]

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

[a]By permission of the Infectious Diseases Society of America [64].

systemic relapses, so that preoperative treatments may be resorted to, including chemotherapy, radiation therapy, etc. Re-irradiation should be considered in radiation-induced angiosarcomas.

note

Levels of evidence and grades of recommendation have been applied using the system shown in Table 3. Statements without grading were considered justified standard clinical practice by the panel members. The above recommendations apply to adult-type STSs arising from limbs and the superficial trunk. Guidelines on retroperitoneal sarcomas, desmoid-type fibromatosis, uterine sarcomas, and breast sarcomas are provided separately at the end of the chapter with regard to those main aspects by which they differ from more frequent STSs. In general, the main principles of diagnosis and treatment may well apply to all STSs, including the rarest presentations (e.g. visceral sarcomas other than gastrointestinal stromal tumour), which are therefore not specifically covered. Specific histological types, however, may deserve specific approaches, not necessarily covered hereafter, given the scope of these guidelines.

consensus panel ESMO Guidelines 2014

These Clinical Practice Guidelines have been developed following a consensus process based on a consensus event organised by ESMO in Milan, Italy, in December 2013 and refined by July 2014. This involved experts from the community of the European sarcoma research groups and ESMO faculty. Their names are indicated hereafter. The text reflects an overall consensus among them, although each of them may not necessarily find it consistent with his/her own views. The panel worked on the text of ESMO Guidelines of previous years, whose authorship should also be credited.

- Paolo G. Casali, Italy (*Moderator*)
- Jean-Yves Blay, France (*Moderator*)
- Alexia Bertuzzi, Ireland
- Stefan Bielack, Germany
- Bodil Bjerkehagen, Norway
- Sylvie Bonvalot, France
- Ioannis Boukovinas, Greece
- Paolo Bruzzi, Italy
- Angelo Paolo Dei Tos, Italy
- Palma Dileo, UK
- Mikael Eriksson, Sweden
- Alexander Fedenko, Russian Federation
- Andrea Ferrari, Italy
- Stefano Ferrari, Italy
- Hans Gelderblom, Belgium
- Robert Grimer, UK
- Alessandro Gronchi, Italy
- Rick Haas, Netherlands
- Kirsten Sundby Hall, Norway
- Peter Hohenberger, Germany
- Rolf Issels, Germany
- Heikki Joensuu, Finland
- Ian Judson, UK
- Axel Le Cesne, France
- Saskia Litière, Belgium
- Javier Martin-Broto, Spain
- Ofer Merimsky, Israel
- Michael Montemurro, UK
- Carlo Morosi, Italy
- Piero Picci, Italy
- Isabelle Ray-Coquard, France
- Peter Reichardt, Germany
- Piotr Rutkowski, Poland
- Marcus Schlemmer, Germany
- Silvia Stacchiotti, Italy
- Valter Torri, Italy
- Annalisa Trama, Italy
- Frits Van Coevorden, Netherlands

- Winette Van der Graaf, Netherlands
- Daniel Vanel, Italy
- Eva Wardelmann, Germany

A consensus meeting was specifically held on retroperitoneal sarcoma, whose output was a separate position paper but which also contributed to the retroperitoneal sarcoma paragraph of the ESMO Guidelines. In addition to some of the above mentioned experts, it was also made up by the following panellists:

- Chiara Colombo, Italy
- Marco Fiore, Italy
- Luigi Mariani, Italy
- Rosalba Miceli, Italy
- Raphael E. Pollock, USA
- Chandrajit P. Raut, USA
- Dirk Strauss, UK
- Carol J. Swallow, Canada

A consensus meeting was specifically held on Uterine sarcoma, whose output was a separate position paper but which also contributed to the Uterine sarcoma paragraph of the ESMO Guidelines. In addition to some of the above mentioned experts, it was also made up by the following panellists:

- Angiolo Gadducci, Italy
- Suzanne George, USA
- Martee L. Hensley, USA
- Roberta Sanfilippo, Italy

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conflict of interest

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