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

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The following recommendations apply to adult-type soft tissue sarcomas arising from limbs and superficial trunk.

Recommendations on retroperitoneal sarcomas, desmocyte fibromatosis, uterine sarcomas head and neck sarcomas

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incidence

Adult soft tissue sarcomas are rare tumours, with an estimated incidence averaging 5/100 000/year in Europe.

diagnosis

Soft tissue sarcomas are ubiquitous in their site of origin, and are often treated with multimodality treatment. A multidisciplinary approach is therefore mandatory in all cases (involving pathologists, radiologists, surgeons, radiation therapists, medical oncologists and paediatric oncologists if applicable). This 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 highly encouraged. This centralized referral should be pursued from the time of the clinical diagnosis of a suspect 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, or arising in paediatric age.

In soft tissue tumours, MR is the main imaging modality, although radiographs should be the first step to rule out a bone tumour, to detect a bone erosion with a risk of fracture and to show calcifications. CT has a role in calcified lesions to rule
out a myositis ossificans, and in retroperitoneal tumours, where the performance is identical to MR.

Following proper imaging assessment, the standard approach to diagnosis consists of multiple core needle biopsies (by using needles >16G). However, an excisional biopsy may be the most practical option for superficial lesions of <5 cm. An open biopsy may be another option in selected cases. Immediate evaluation of tissue viability may be considered, to make sure the biopsy is adequate at the time it is done. However, a frozen-section technique for immediate diagnosis is not encouraged, because generally it does not allow a complete diagnosis, especially when a 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, so that, when preoperative treatment is an option, radiological imaging may add to pathology in providing the clinician with information that helps to estimate the malignancy grade (e.g. necrosis). The biopsy should be performed by a surgeon or a radiologist, after interdisciplinary discussion, as needed. It should be planned in such a way that the biopsy pathway and the scar can be safely removed on definitive surgery. The biopsy entrance point is preferably tattooed. The tumour sample should be fixed in formalin in due time (Bouin fixation should be banned, since it prevents molecular analysis).

Histological diagnosis should be made according to the latest World Health Organization (WHO) classification. A pathological expert second opinion is recommended in all cases where the original diagnosis was made outside reference centres.

The malignancy grade should be provided in all cases in which this is feasible based on available systems. 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. Whenever possible, the mitotic rate should be provided independently. An effort should be made to improve the reliability of mitotic count as actually recorded.

Tumour site should be properly recorded. Tumour size and tumour depth (in relation to the muscular fascia) should be recorded, since they entail a prognostic value, along with 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 assessment of marginal status (i.e. whether the minimum margin is intralesional, marginal, 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 a tumour response assessment. 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 (fluorescent in situ hybridization (FISH), reverse transcription–polymerase chain reaction (RT–PCR)), especially when: (i) the clinical pathological presentation is unusual; (ii) the specific histological diagnosis is doubtful; (iii) it may have prognostic/predictive relevance.

External quality assurance programmes are encouraged for laboratories performing molecular pathology assessments. 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. Informed consent for tumour banking should be sought enabling later analyses and research, as long as this is allowed by local and international guidelines.

### Stage classification and risk assessment

The American Joint Committee on Cancer (AJCC)/International Union against Cancer (UICC) stage classification system stresses the importance of the malignancy grade in sarcoma. However, its use in routine practice is limited. In addition to grading, other prognostic factors are tumour size and tumour depth. Of course, tumour resectability is also important.

### Staging procedures

The surgical report, or patient chart, should provide details on: the preoperative and intraoperative diagnosis; the surgical conduct, including possible contamination (i.e. it should mention whether the tumour was opened, was ‘seen’ during the excision, etc.); surgical actual completeness vis-à-vis planned quality of margins.

A chest spiral CT scan is mandatory for staging purposes.

Depending on the histological type and other clinical features, further staging assessments may be recommended (i.e. regional lymph node clinical assessment for synovial sarcoma, epithelioid sarcoma, alveolar soft part sarcoma, clear cell sarcoma; abdominal CT scan for myxoid liposarcoma, etc.).

### Treatment

#### Limited disease

Surgery is the standard treatment for all patients with adult-type, localized soft tissue sarcomas. It must be performed by a surgeon specifically trained in the treatment of this disease. The standard surgical procedure is a wide excision with negative margins (R0). This implies removing the tumour with a rim of normal tissue around. One centimetre has been sought enabling later analyses and research, as long as this is allowed by local and international guidelines.

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individualized option in highly selected cases, in particular for extracompartmental atypical lipomatous tumours.

Wide excision followed by radiation therapy is standard treatment in high-grade, deep lesions, >5 cm. Radiation therapy is not given in the case of a truly compartmental resection of a tumour entirely contained within the compartment. With exceptions to be discussed in a multidisciplinary setting, and in the face of a lack of consensus across reference centres, also high-grade, deep, <3 cm lesions are treated with surgery followed by radiation therapy. Radiation therapy is added in selected cases in the case of low-grade, superficial, >5 cm, and low-grade, deep, <5 cm soft tissue sarcoma. In the case of low-grade, deep, >5 cm soft tissue sarcoma, radiation therapy should be discussed in a multidisciplinary fashion, considering the anatomical site and the related expected sequelae versus the histological aggressiveness. Overall, radiation therapy has been shown to improve local control, but not overall survival. Radiation therapy should be administered postoperatively, with the best technique available, at a dose of 50–60 Gy, with fractions of 1.8–2 Gy, possibly with boosts up to 66 Gy, depending on presentation and quality of surgery. Alternatively, radiotherapy may be carried out preoperatively, normally using a dose of 50 Gy. Intraoperative radiation therapy (IORT) and brachytherapy are options in selected cases.

Re-operation 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. it may be spared in extracompartmental atypical lipomatous tumours, etc.). In the case of R2 surgery, re-operation is mandatory, possibly with 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 shared decision-making with the patient under conditions of uncertainty. Plastic repairs and vascular grafting should be used as needed, and the patient should be properly referred if necessary. Radiation therapy will obviously follow marginal or R1–R2 excisions, if these cannot be rescued through re-excision, even outside the usual indications (see above). In non-resectable tumours, or those amenable only to mutilating surgery (in this case, on an individualized basis after sharing the decision with the patient in conditions of uncertainty), chemotherapy and/or radiotherapy, or isolated hyperthermic limb perfusion with tumour necrosis factor-α (TNFα) + melphalan, if the tumour is confined to an extremity, or regional hyperthermia combined with chemotherapy, are options.

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 soft tissue sarcomas. 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 standard treatment for these presentations. Chemotherapy may be administered as preoperative treatment, at least in part. 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 randomized phase III study (in patients with G2–3, deep, >5 cm soft tissue sarcomas), regional hyperthermia in addition to systemic chemotherapy was associated with a local and disease-free survival advantage. Isolated limb perfusion may be an option in this patient population, along with chemotherapy and radiation therapy.

Data have been provided that adjuvant chemotherapy might improve, or at least delay, distant and local recurrence in high-risk patients. A meta-analysis found a statistically significant, limited benefit in terms of both survival and relapse-free survival. However, studies are conflicting, and a final demonstration of efficacy is lacking. It is also unknown whether adjuvant chemotherapy may be especially beneficial in specific subgroups. Therefore, adjuvant chemotherapy is not standard treatment in adult-type soft tissue sarcomas, and can be proposed as an option to the high-risk individual patient (having a >G1, deep, >5 cm tumour) for shared decision-making with the patient [II, C]. Adjuvant chemotherapy is not used in histologies 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. A local benefit may be gained, facilitating surgery. In one large randomized phase III study (in patients with G2–3, deep, >5 cm soft tissue sarcomas), regional hyperthermia in addition to systemic chemotherapy was associated with a local and disease-free survival advantage (no survival benefit demonstrated). If used, adjuvant chemotherapy should consist of the combination chemotherapy regimens proven to be most active in the advanced disease.

The standard approach to local relapse parallels the approach to primary local disease, except for a wider resort to preoperative or postoperative radiation therapy, if not previously performed.

**extensive disease**

Metachronous resectable lung metastases without extrapulmonary disease are managed with complete excision of all lesions as standard treatment [IV, B]. Chemotherapy may be added as an option, taking into account the prognostic factors (a short previous 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 results. Chemotherapy is preferably given before surgery, in order to assess tumour response and thus modulate the length of treatment. In the case of lung metastases being synchronous, in the absence of extrapulmonary disease, standard treatment is chemotherapy [IV, B]. Especially when a patient benefit is achieved, surgery of completely resectable lung metastases may be offered as an option.

Extrapulmonary disease is treated with chemotherapy as 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.

Standard chemotherapy is based on anthracyclines as first-line treatment [I, A]. There is no formal demonstration that
multiagent chemotherapy is superior to single-agent chemotherapy with doxorubicin alone in terms of overall survival. However, a higher response rate may be expected, in particular in a number of sensitive histological types, according to several, although not all, randomized clinical trials. Therefore, multiagent chemotherapy with anthracyclines plus ifosfamide may be the treatment of choice, especially when a tumour response is felt to be able to give an advantage and patient performance status is good.

In angiosarcoma, taxanes are an alternative option, given their antitumour activity in this specific histological type [III, B]. Imatinib is standard medical therapy for those rare patients with dermatofibrosarcoma protuberans who are not amenable to non-mutilating surgery or with metastases requiring medical therapy [III, B].

After failure of anthracycline-based chemotherapy, or impossibility of using it, the following criteria may apply, although in the lack of high-level evidence.

Patients who have already received chemotherapy may be treated with ifosfamide, if they did not receive it previously. High-dose ifosfamide (~14 g/m²) may be an option also for patients who have already received standard-dose ifosfamide [IV, C].

Trabectedin is a second-line option [II, B]. It has proved effective in leiomyosarcoma and liposarcoma. In myxoid liposarcoma a peculiar pattern of tumour response has been reported, with an early phase of tissue changes preceding tumour shrinkage. Responses to trabectedin have also been obtained in other histological types, including synovial sarcoma.

One trial showed that gemcitabine + docetaxel is more effective than gemcitabine alone as second-line chemotherapy, but data are conflicting and toxicity is different [II, C]. Gemcitabine was also shown to have antitumour activity in leiomyosarcoma as a single agent.

Dacarbazine has some activity as second-line therapy (mostly in leiomyosarcoma). It could also be combined with gemcitabine.

Best supportive care is an option for pretreated patients with advanced soft tissue sarcoma, all the more if further-line therapies have already been used in the patient. In general, advanced pretreated patients are candidates for clinical studies.

With reference to selected histological types, there is anecdotal evidence of activity of some molecular targeted agents, possibly in the face of preclinical consistent data. These patients can be sent to reference centres, to be treated accordingly, preferably within clinical studies.

**follow-up**

There are no published data to indicate the optimal routine follow-up policy of surgically treated patients with localized disease.

The malignancy grade affects the likelihood and speed at which relapses may take place. 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, while 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, 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 is yet to be demonstrated that this is beneficial, or cost effective, compared with 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. The 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 more relaxed intervals in the first 3–5 years, then yearly.

**special presentations and entities**

**retroperitoneal sarcomas**

Core needle biopsies are the standard procedure for diagnosis in retroperitoneal sarcomas. They should not be performed through the peritoneum. An open biopsy may be an option in selected cases. In both cases, the pathway of the biopsy should be carefully planned to avoid contamination and complications. However, radiological imaging may be sufficient for the diagnosis of lipomatous tumours, if no preoperative treatment is planned. Standard treatment for localized lesions is surgery, which is best performed through a retroperitoneal quasi-compartmental resection, that is a complete excision of the mass, along with en-bloc visceral resections of adjacent organs and tissues covering the tumour [IV, B]. The value of preoperative treatments in resectable tumours is not established. Thus, while not standard they are available options, including radiation therapy, chemotherapy, chemoradiation therapy, regional hyperthermia in addition to chemotherapy. If given, preoperative treatments are not meant to change the extent of surgery. Likewise, the value of adjuvant chemotherapy is not established. In general, postoperative radiation therapy to the whole tumour bed at doses recommended for sarcomas is not feasible at an acceptable toxicity. In selected cases, it may be an option for well-defined anatomical areas felt to be at high risk.

**uterine sarcomas**

This group includes leiomyosarcomas, endometrial stromal sarcomas (formerly, low-grade endometrial stromal sarcomas), undifferentiated endometrial sarcomas and pure heterologous sarcomas.

Carcinosarcomas (malignant Mullerian mixed tumours) are mixed epithelial and mesenchymal neoplasms, whose treatment should follow their mainly epithelial nature.

Standard treatment for all these tumours, when localized, is total abdominal hysterectomy. The added value of bilateral salpingo-oophorectomy is not established. In endometrial stromal sarcoma bilateral salpingo-oophorectomy is generally performed, due to the hormonal sensitivity of these tumours, and lymphadenectomy may be an option, given the possible...
higher incidence of nodal involvement [IV, D]. However, as far as leiomyosarcomas and high-grade undifferentiated sarcomas are concerned, bilateral salpingo-oophorectomy, particularly in premenopausal women, as well as lymphadenectomy, is not demonstrated to be useful in the absence of macroscopic involvement.

Although retrospective studies have suggested a possible decrease in local relapses, radiation therapy did not improve survival and relapse-free survival in a randomized trial, and therefore is not recommended in leiomyosarcoma [II, C]. Therefore, its use as an adjuvant to surgery may only be an option in selected cases, after shared decision-making with the patient following multidisciplinary discussion, taking into account special risk factors for local relapse.

The systemic treatment of metastatic endometrial stromal sarcomas exploits their sensitivity to hormonal therapies [V, D]. Therefore, progestins are generally used, along with gonadotrophin-releasing hormone (GnRH) analogues and aromatase inhibitors. Tamoxifen is contraindicated, as well as hormonal replacement therapy containing estrogens. Surgery of lung metastases is an option, given the natural history of the disease.

The medical treatment of leiomyosarcomas, undifferentiated endometrial sarcomas and pure heterologous sarcomas parallels that for adult-type soft tissue sarcomas. In any case, it should be kept distinct from malignant Mullerian mixed tumours.

desmoid-type fibromatosis
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, a watchful waiting policy may be the best option [IV, B], after shared decision-making with the patient, with the exclusion 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. Preferred imaging is MRI, though considering that the tumour signal is not meaningful with regard to disease evolution.

For progressing cases, optimal treatment needs to be individualized on a multidisciplinary basis and it 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) [V, D]. Systemic therapies include: hormonal therapies (tamoxifen, toremifene, GnRH analogues), non-steroidal anti-inflammatory drugs; low-dose chemotherapy, such as methotrexate + vinblastine or methotrexate + vinorelbine; low-dose interferon; imatinib; full-dose chemotherapy (using regimens active in sarcomas). It is reasonable to employ the less toxic therapies before the more toxic ones in a stepwise fashion.

head and neck sarcomas
These are sarcomas arising at a difficult anatomical location. Cases should be dealt with through a multidisciplinary approach, also involving head and neck surgeons. Radiation therapy is widely resorted to, given the surgical margins generally achievable.

breast sarcomas
Breast sarcomas encompass radiation- and non-radiation-induced sarcomas. Then sarcomas of the skin of the breast area should be conceptually distinguished from mammary gland sarcomas. Finally, angiosarcoma has a more aggressive behaviour than other histological types, while malignant phyllodes tumours [i.e. those having >10 mitoses/10 high-power fields (HPF) and marked stromal overgrowth] have a 20%–30% metastatic rate.

The best treatment of breast sarcomas is far from being defined, given their rarity and heterogeneity. In general, breast-conserving surgery may be used, 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 generally preferred, even in combination with postoperative radiotherapy. Lymphadenectomy is not performed in the absence of clinical evidence of involvement.

As far as adjuvant chemotherapy is concerned, the same principles as for soft tissue sarcoma apply. One may consider the high risk of local and systemic relapse of angiosarcoma in making a decision.

note
These Clinical Practice Guidelines have been developed following a consensus process based on a consensus event organized by ESMO in Lugano in November 2009. This involved experts from the community of the European sarcoma research groups, sarcoma networks of excellence 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 EU-funded network of excellence CONTCANET (CONnective Tissue Cancers NETwork) and EUROBONET (EUROpean BOne NETwork) also financially supported the consensus process.

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