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

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incidence

Adult soft tissue and visceral sarcomas (excluding gastrointestinal stromal tumor, GIST) are rare tumors, 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 pediatric oncologists, as applicable). This should be carried out in reference centers for sarcomas and/or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually. These centers are involved in ongoing clinical trials, in which sarcoma patients' enrollment is highly encouraged. This centralized 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, or arising in paediatric age.

In soft tissue tumors, magnetic resonance imaging (MRI) is the main imaging modality. Standard radiographs may be useful to rule out a bone tumor, 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 tumors, where the performance is identical to MRI.

Following appropriate imaging assessment, the standard approach to diagnosis consists of multiple core needle biopsies, possibly by using ≥16 G needles. However, an excisional biopsy may be the most practical option for <5 cm superficial lesions. An open biopsy may be another option in selected cases. An immediate evaluation of tissue viability may be considered, to ensure that the biopsy is adequate at the time it is performed. However, a frozen-section technique for immediate diagnosis is not encouraged, because generally it 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 centers. A biopsy may underestimate the tumor malignancy grade. Therefore, when preoperative treatment is an option, radiological imaging 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 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 by definitive surgery. The biopsy entrance point can be tattooed. The tumor sample should be fixed in 4% buffered formalin in due time (Bouin fixation should not be used, since it prevents molecular analysis).

Histological diagnosis should be made according to the 2002 World Health Organization (WHO) classification. A pathological expert second opinion is strongly recommended in all cases when the original diagnosis was made outside a reference center.

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 [2]. 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 pre-operative medical treatment, by which the tumor tissue undergoes major therapy-related changes (Table 1).

Tumor site should be properly recorded. Tumor size and tumor depth (in relation to the superficial fascia) should also be recorded, since they entail a prognostic value, along with

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

Tumor differentiation	Necrosis	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, 3; Grade 2: 4, 5; Grade 3: 6, 7, 8.

the malignancy grade. The pathology report after definitive surgery should mention whether the tumor was intact and should include an appropriate description of tumor margins (i.e. the status of inked margins and the distance between tumor edge and the closest inked margins). This allows the assessment of margin 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 an assessment of the histological response of the tumor. 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 hemorrhage 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 hybridisation, reverse transcription–polymerase chain reaction], especially when:

(i) the specific histological diagnosis is doubtful;
(ii) the clinical pathologic presentation is unusual;
(iii) it may have prognostic/predictive relevance.

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

The collection of fresh/frozen tissue and tumor 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 tumor tissues. Informed consent for tumor banking should be sought, enabling later analyses and research, as long as this is allowed by local and international rules.

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 [3]. In general, in addition to grading, other prognostic factors are tumor size and tumor depth for limb sarcomas. Of course, site, tumor resectability and presence of metastases are also important (Table 2).

Table 2. American Joint Committee on Cancer version 7 staging for soft tissue sarcomas [30]

Primary tumor (T)[a]				
TX	Primary tumor cannot be assessed			
T0	No evidence of primary tumor			
T1	Tumor 5 cm or less in greatest dimension			
T1a	Superficial tumor			
T1b	Deep tumor			
T2	Tumor >5 cm in greatest dimension			
T2a	Superficial tumor			
T2b	Deep tumor			
Regional lymph nodes (N)[b]				
NX	Regional lymph nodes cannot be assessed			
N0	No regional lymph node metastasis			
N1	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	N0	M0	G3
	T2b	N0	M0	G3
	Any T	N1	M0	Any G
Stage IV	Any T	Any N	M1	Any G

[a]Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor 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]The presence of positive nodes (N1) in M0 tumors is considered stage III.

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.

The surgical report, or patient chart, should provide details on: the preoperative and intraoperative diagnosis; the surgical

conduct, including possible contaminations (i.e. it should mention whether the tumor was opened, was 'seen' during the excision, etc.); surgical actual completeness vis-a-vis planned quality of margins.

treatment

localized disease

Surgery is the standard treatment of all patients with an adult type, localized STS. It must be performed by a surgeon specifically trained in the treatment of this disease [IV, A].

The standard surgical procedure is a wide excision with negative margins (R0). This implies removing the tumor 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. A marginal excision may be acceptable as an individualized option in carefully selected cases, in particular for extracompartmental atypical lipomatous tumors [IV, B].

The wide excision is followed by radiation therapy as standard treatment of high-grade (G2–3), deep >5 cm lesions [II, B].

Radiation therapy is not given in the case of a truly compartmental resection of a tumor entirely contained within the compartment [IV, A].

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

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. Overall, radiation therapy has been shown to improve local control, but not overall survival (OS).

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 and brachytherapy are options in selected cases. The decision should be made on a multidisciplinary basis, taking into consideration the pros and cons of various options.

Re-operation in reference centers must be considered in the case of R1 resections, if adequate margins can be achieved without major morbidity, taking into account tumor extent and tumor biology (e.g. it is spared in extracompartmental atypical lipomatous tumors, etc.) [IV, A]. In the case of R2 surgery, re-operation in reference centers 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 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.

In non-resectable tumors, or those amenable only to mutilating surgery (in this case, on an individualized basis after sharing the decision with the patient in cases of uncertainty), available options are chemotherapy and/or radiotherapy [III, A], or isolated hyperthermic limb perfusion with tumor necrosis factor-alpha + melphalan [III, A], if the tumor is confined to an extremity, or regional hyperthermia combined with chemotherapy [I, B] [4].

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 standard treatment of these presentations [IV, B]. 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 STSs), regional hyperthermia in addition to systemic chemotherapy was associated with a local and disease-free survival 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].

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 [5]. However, study results are conflicting. It is also unknown whether adjuvant chemotherapy may be particularly beneficial in specific subgroups. Therefore, adjuvant chemotherapy is not standard treatment in adult-type STS and can be proposed as an option to the high-risk individual patient (high-grade, deep, >5 cm tumor) for shared decision-making with the patient [II, C]. A randomized trial showed no differences between 3 (pre-operative) and 5 (pre- and postoperative) courses of full-dose chemotherapy [6].

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. If used, adjuvant chemotherapy should consist of the combination chemotherapy regimens proven to be most active in advanced disease. Radiation therapy should not delay the start of chemotherapy. In one

large randomized 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 disease-free survival advantage [I, B].

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

advanced disease

Metachronous (disease-free interval ≥1 year) resectable lung metastases without extrapulmonary disease are managed with surgery, if complete excision of all lesions is feasible, as standard treatment [7] [IV, B]. A minimally invasive thoracoscopic approach can be resorted to in selected cases. When surgery of lung metastases is selected, an abdominal CT scan and a bone scan or a FDG-positron emission tomography 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 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 tumor 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 tumor response is achieved.

Extrapulmonary metastatic 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.

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 tumor, etc.) [7].

Standard chemotherapy is based on anthracyclines as first-line treatment [8] [I, A]. At the time of writing these Guidelines, there is no formal demonstration that multiagent chemotherapy is superior to single-agent chemotherapy with doxorubicin alone in terms of OS. 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 adequate-dose anthracyclines plus ifosfamide may be the treatment of choice, particularly when a tumor 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 high antitumor activity in this specific histological type [9] [III, B]. An alternative option is gemcitabine ± docetaxel [V, B].

Doxorubicin plus dacarbazine is an option for multiagent first-line chemotherapy of leiomyosarcoma, where the activity of ifosfamide is far less convincing on available retrospective evidence [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 [10] [III, A].

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

(i) Patients who have already received chemotherapy may be treated with ifosfamide, if they did not receive it previously. High-dose ifosfamide (around 14 g/m^2) may be an option also for patients who have already received standard-dose ifosfamide [11] [IV, C].
(ii) 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 [12]. In myxoid liposarcoma, a high antitumor activity was described. A peculiar pattern of tumor response has been reported, with an early phase of tissue changes preceding tumor shrinkage [13]. Clinical benefit with trabectedin was also obtained in other histological types.
(iii) One trial showed that gemcitabine + docetaxel is more effective than gemcitabine alone as second-line chemotherapy, but data are conflicting and toxicity is different [14] [II, C]. Gemcitabine was shown to have antitumor activity in leiomyosarcoma also as a single agent.
(iv) Dacarbazine has some activity as second-line therapy (mostly in leiomyosarcoma). The combination of dacarbazine and gemcitabine was shown to improve the OS and PFS over dacarbazine in a randomized trial and is therefore an option in leiomyosarcoma [15] [II, B].
(v) A randomized trial showed a benefit in PFS averaging 3 months for pazopanib given up to progression to advanced, previously treated, STS patients (excluding liposarcomas) [16]. If commercially available, this will be an option in non-adipogenic STS [I, B]. Its clinical efficacy in selected subgroups is still to be determined through further studies, to optimize the clinical use.
(vi) A randomized trial showed a benefit in PFS averaging 3 weeks for ridaforolimus given up to progression as maintenance therapy to advanced, previously treated, STS patients with a partial/complete response, or stable disease, after induction with optimal chemotherapy [17] [I, C]. Its clinical efficacy in selected subgroups is still to be determined through further studies.

Best supportive care alone is an option for pretreated 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 fractures, 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 (mTOR) inhibitors in malignant perivascular epithelioid cell tumors (PEComas), which are often associated with the loss of tuberous sclerosis complex 1 (TSC1)/TSC2 [18];
- crizotinib in inflammatory myofibroblastic tumor associated with anaplastic lymphoma kinase (ALK) translocations [19];
- sunitinib and cediranib in alveolar soft part sarcoma and solitary fibrous tumors, where molecular target is yet unclear [20, 21].

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

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 occur. The risk assessment based on tumor grade, tumor size and tumor 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, 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 is yet to be 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. 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 longer intervals in the first 3–5 years, then annually.

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 tumors, if no preoperative treatment is planned.

The standard treatment of localized lesions is surgery, which is best performed through a retroperitoneal quasi-compartmental resection, i.e. a complete excision of the mass, along with en bloc visceral resections of adjacent organs and tissues covering the tumor [22, 23] [IV, B].

The value of preoperative treatments in resectable tumors is not established. Available options include radiation therapy, chemotherapy, chemo-radiation therapy and 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, post-operative radiation therapy to the whole tumor bed at doses recommended for sarcomas is not feasible at an acceptable toxicity. In selected cases, it may be an option in well defined anatomical areas felt to be at high risk. The value of preoperative radiation therapy is not established, and a prospective randomized trial is ongoing.

uterine sarcomas

This group includes leiomyosarcomas, endometrial stromal sarcomas (formerly, low-grade endometrial stromal sarcomas), undifferentiated endometrial sarcomas and pure heterologous sarcomas [24]. Carcinosarcomas (malignant mullerian mixed tumors) are mixed epithelial and mesenchymal neoplasms, whose treatment should be tailored to their mainly epithelial nature.

Standard treatment of all these tumors, 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 tumors [IV, C]. However, as far as leiomyosarcomas and high-grade undifferentiated sarcomas are concerned, bilateral salpingo-ophorectomy, particularly in premenopausal women, and also lymphadenectomy are not demonstrated to be useful in the lack of macroscopic involvement.

Although retrospective studies suggested a possible decrease in local relapses, radiation therapy has not improved survival and relapse-free survival in a randomized trial, and therefore is not recommended in uterine leiomyosarcoma [25]. Therefore, its use as an adjuvant to surgery may only be an option in selected cases, after a shared decision-making with the patient following multidisciplinary discussion, taking into account special risk factors for local relapse [IV, C].

The value of adjuvant chemotherapy in uterine leiomyosarcoma is undetermined, as for all adult STS [26]. Uncontrolled studies suggest a benefit in comparison with external controls for gemcitabine + docetaxel × four courses followed by doxorubicin × four courses, as well as for gemcitabine + docetaxel × four courses. A prospective randomized trial with a no-treatment control arm versus gemcitabine + docetaxel × four courses followed by doxorubicin × four courses is ongoing.

The systemic treatment of metastatic endometrial stromal sarcomas exploits their sensitivity to hormonal therapies [V, B]. Therefore, progestins, aromatase inhibitors and Gn-RH analogues (for pre-menopausal patients) can be used. Tamoxifen is contraindicated, as well as hormonal replacement therapy (HRT) 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 STSs. In any case, it should be kept distinct from malignant mullerian mixed tumors.

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 tumor anatomical locations, an initial watchful waiting policy can be proposed [27] [III, B], after a 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. The preferred imaging modality is MRI, taking into consideration that the tumor signal is not meaningful with regard to the 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) [28, 29] [V, B]. Systemic therapies include: hormonal therapies (tamoxifen, toremifene, Gn-RH analogues), nonsteroidal anti-inflammatory drugs; low-dose chemotherapy, such as methotrexate + vinblastine or methotrexate + vinorelbine; low-dose interferon; imatinib; sorafenib; full-dose chemotherapy (using regimens active in sarcomas, including liposomal doxorubicin). It is reasonable to employ the less toxic therapies before the more toxic ones in a stepwise fashion.

breast sarcomas

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 behavior than other histological types, while malignant phyllodes tumors (i.e. those having >10 mitoses/10 HPF and marked stromal overgrowth) have a 20%–30% metastatic rate. On the other hand, 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 tumor 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 performed in the absence of the clinical evidence of involvement.

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

note

These Clinical Practice Guidelines have been developed following a consensus process based on a consensus event organized by ESMO in Milan, Italy in January 2012 and refined afterwards. 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 panel worked on the text of ESMO Guidelines of previous years, whose authorship should also be credited.

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 GIST], which are therefore not specifically covered. Specific histological types, however, may deserve specific approaches, not necessarily covered hereafter, given the scope of these Guidelines. Extraskeletal Ewing sarcoma is covered by other ESMO Guidelines: in general, the same principles for these tumors 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 STS. GISTs are covered by dedicated ESMO Guidelines. Kaposi's sarcoma is excluded.

Consensus Panel ESMO Guidelines 2012

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conflict of interest

Prof. Blay has reported: consultancy/honoraria: Novartis, Roche, GlaxoSmithKline, PharmaMar; research funding: PharmaMar. Dr. Boukovinas has reported: royalty fees from Novartis. Dr. Casali has reported: consultancy/honoraria: Bayer, GlaxoSmithKline, Janssen Cilag, Merck Sharp & Dohme, Novartis, Pfizer, PharmaMar, and Sanofi-Aventis. Prof. De Alava has reported: research funding from PharmaMar. Dr. Dei Tos has reported: consultancy for Novartis, Pfizer, and GlaxoSmithKline; research grant from Novartis. Dr. Eriksson has reported: honoraria from Novartis, Swedish Orphan Biovitrum, GlaxoSmithKline, Merck Sharp & Dohme, and Pfizer. Dr. Fedenko has reported: speakers' bureau for Roche, Jansen, Lilly. Dr. Ferrari has reported: research funding: Amgen, MolMed, PharmaMar, Infinity; consultancy: Takeda and Merck. Dr. Gelderblom has reported: research funding from Pfizer, Novartis, PharmaMar, Eisai, GlaxoSmithKline, and Infinity. Mr. Grimer has reported: speakers' bureau for Takeda. Dr. Gronchi has reported: honoraria and advisory board compensation from Novartis Pharma; honoraria and travel coverage from PharmaMar; honoraria from Pfizer. Prof. Hassan has reported: investigator-initiated, early phase trials with Takeda and Astellas; conference chair for Takeda satellite symposia; scientific board of Sarcoma UK; grants with Cancer Research UK and EU FP7. Prof. Hohenberger has reported: research funding: Novartis, GlaxoSmithKline, PharmaMar; Advisory Boards for Novartis, PharmaMar, GlaxoSmithKline, and Pfizer. Prof. Joensuu has reported: research support from Novartis. Prof. Jurgens has reported: institutional research grants: Roche, Pfizer, and Takeda. Prof. Kager has reported: advisory board for Takeda. Dr. Le Cesne has reported: honoraria: Pfizer, PharmaMar, Novartis. Prof. Nishida has reported: research funding from Novartis. Dr. Picci has reported: advisory boards for Merck and Takeda. Dr. Reichardt has reported: advisory board: Novartis, Pfizer, PharmaMar, Bayer, Merck Sharp & Dohme; Honoraria: Novartis, Pfizer, PharmaMar, Merck Sharp & Dohme, Amgen. Dr. Rutkowski has reported: honoraria and speakers' bureau and advisory board for Novartis; honoraria from Pfizer. Dr. Schlemmer has reported: research funding and honoraria from Novartis. Dr. Sleijfer has reported: Research funding: Novartis, GlaxoSmithKline, Bayer, Pfizer. Dr. Stacchiotti has reported: research and travel support from Amgen Dompé; advisory role, research support, and honoraria from Novartis; research support and honoraria from Pfizer; and research support from Bayer, Merck Sharp & Dohme, GlaxoSmithKline, Infinity, Lilly, Molmed, PharmaMar, Sanofi-Aventis, and Schering Plough. Prof. Wardelmann has reported: honoraria and grants from Novartis.

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