Soft Tissue Sarcomas (STS)

Giuseppe Badalamenti, Bruno Vincenzi, Massimiliano Cani, and Lorena Incorvaia

Soft Tissue Sarcoma, GIST and Neuroendocrine Neoplasms

Contents

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Learning Objectives

By the end of the chapter, the reader will:

- Have learned the basic concepts of epidemiology, histological subtype, and molecular profile of STS.
- Have reached in-depth knowledge of diagnosis, staging, and clinical management of STS.
- Be able to put acquired knowledge on STS into clinical practice

58.1 Introduction

Soft tissue sarcomas (STSs) represent a rare and heterogeneous group of solid tumors derived from mesenchymal progenitors and account for 1% of all adult malignancies [1]. Approximately 80% of sarcomas arise from soft tissue and viscera, whereas the remaining 20% originate from bone. STSs potentially may occur at all body anatomic sites, even though the majority arise from the extremities.

As classified by the World Health Organization (WHO), the group of STSs comprise more than 100 different histologies according to the presumptive tissue in origin [2]. Histological diagnosis is crucial in order to define staging and prognosis and to deliver appropriate therapy. Unfortunately, sometimes it causes a diagnostic challenge for pathologist, particularly when the diagnostic material is a small biopsy and when clinical information is incomplete. After the development of distant metastasis, the median overall survival (OS) is 12–19 months, and almost 20% of patients are still alive at 3 years [3].

58.1.1 Diagnosis and Pathology

There is agreement on the recommendation that the pathological diagnosis of STM should contain the following information:

- Macroscopic description
- Status of margins, so as to allow the attribution of surgical intervention to the categories "radical," "broad," "marginal," and "intralesional"
- Histotype according to WHO 2013

The malignancy grade is described by the classification of the French Federation of Cancer Centers:

- Grade 1: Low grade
- Grade 2: Intermediate grade
- Grade 3: High grade

The WHO 2013 classification of mesenchymal tumors distinguishes (1) benign lesion, (2) lesion with intermediate biological behavior, and (3) lesion with malignant biological behavior.

Intermediate lesions are defined as follows:

- Locally aggressive but not metastasizing tumors (e.g., aggressive fibromatosis)
- Tumors with a metastasis rate of less than 2% (e.g., plexiform fibrohistiocytic tumor)

58.1.2 Staging and Risk Assessment

Available staging classifications have limited relevance and should be improved. The Union for International Cancer Control (UICC) stage classification system, eighth edition, stresses the importance of the malignancy grade in sarcoma [4]. In general, in addition to grading, other prognostic factors are tumor size and tumor depth for limb sarcomas. Of course, site, tumor resectability, and the presence of metastases are also important. Nomograms are available, which can help personalize risk assessment and thus clinical decision-making, especially on adjuvant/neoadjuvant treatments [5, 6].

58.2 STS Management

58.2.1 Essential Elements Prior to the Initiation of Therapy

According to major national and international guidelines, the optimal therapeutic strategy of all soft tissue sarcomas (STS) patients should be discussed within multidisciplinary teams. Disease histology, stage, anatomical localization, and patient preferences are the most important elements for a correct decisional process [7, 9]. Notably, compliance to guidelines and relapse-free survival of sarcoma patients are significantly better when the initial treatment is guided by a pretherapeutic specialized multidisciplinary tumor board [10].

Adequate imaging of primary tumor, i.e., MRI with and without contrast +/− CT with contrast, is necessary to provide details about the size of the tumor and its contiguity to nearby visceral and neurovascular structures. A chest spiral CT scan without contrast is recommended in the US guidelines [1] and mandatory in the European ones [2]. In selected circumstances, other imaging studies might be required.

Histological diagnosis prior to therapy should be acquired whenever possible. Core needle biopsy or incisional biopsy usually provides sufficient tissue to perform a correct pathological and molecular diagnosis e must always be carried out in the case of lesions over 5 cm in diameter (Fig. 58.1).

The STS clinical presentation can be very different in relation to the place of origin. In the case of a limbs or trunk localization, the sarcoma is presented as a clini-

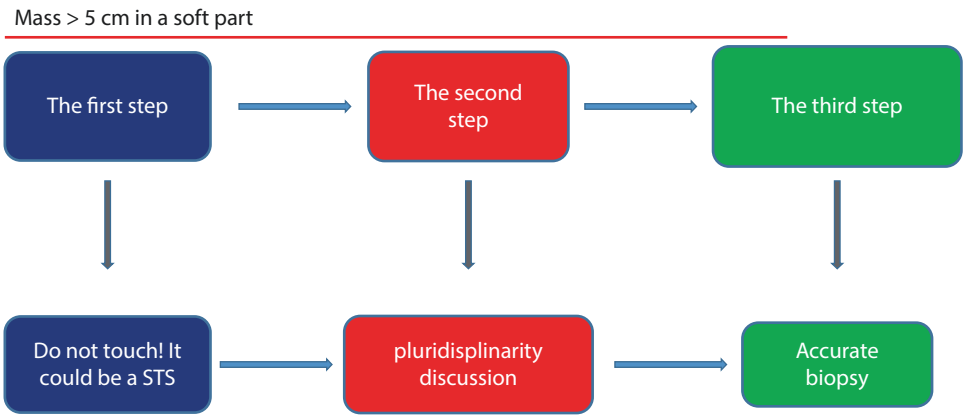


Fig. 58.1 The role of biopsy for all lesions greater than 5 cm. (Diagnosis: flow chart)

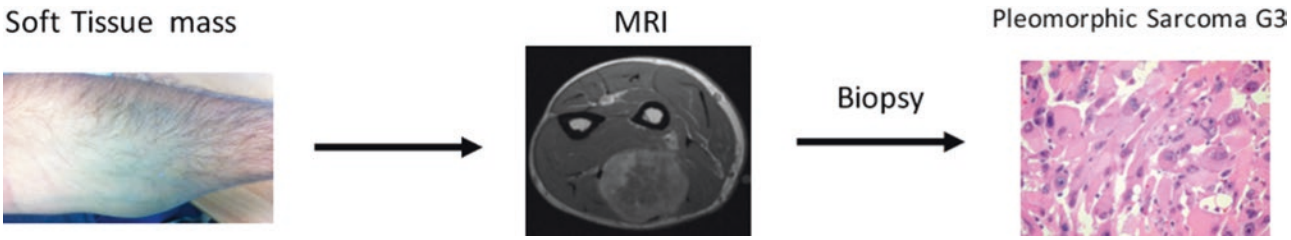


Fig. 58.2 Soft tissue mass of the forearm compatible with sarcoma; magnetic resonance imaging confirms the suspicion and the biopsy confirm pleomorphic sarcoma G3

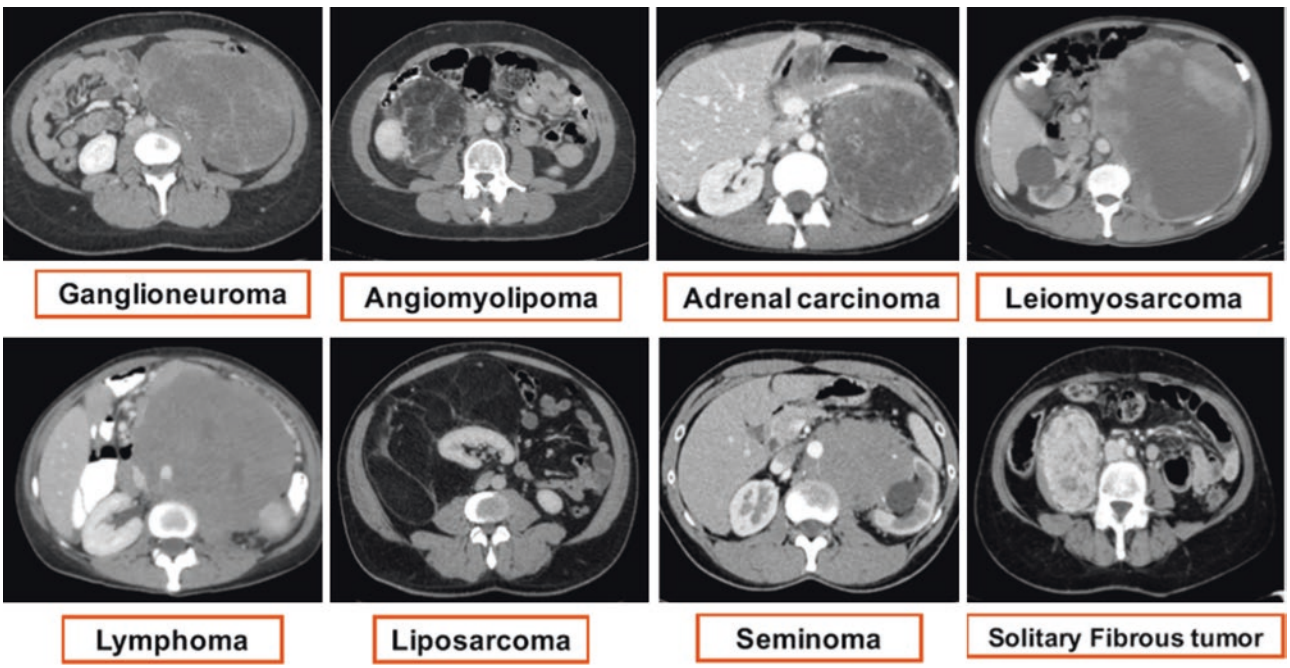


Fig. 58.3 The retroperitoneum may be the site of different type of cancers and imaging does not allow a differential diagnosis

cally evident swelling, with stretched-elastic consistency and rapid growth. In this case, only biopsy can confirm the diagnosis and define the histotype (Fig. 58.2).

Retroperitoneal sarcomas, on the other hand, can reach considerable size because they are very often asymptomatic. In this case, as in the case of the sarcomas of the limbs and of the trunk, the biopsy is mandatory. The retroperitoneum may also be the site of different type of cancers, and imaging does not allow a differential diagnosis (Fig. 58.3).

Finally, visceral sarcomas, which are much rarer and are clinically similar to the most frequent carcinomas.

Pathological review by national and international STS experts should be obtained in all cases where the histological, immunohistochemical, and molecular data do not allow a straightforward diagnosis. In fact, selected histologic subtypes characteristically display unusual biological behaviors. For example, epithelioid hemangioendothelioma is often indolent, whereas visceral Ewing(−like) sarcomas tend to be particularly aggressive. These histologic subtypes do not usually follow the principles of therapy hereby discussed.

58.2.2 Principles of Multidisciplinary Therapeutic Approach

58.2.2.1 Surgery

Surgical resection with appropriately negative margins is the standard treatment for most patients with STS. Dissection should be through grossly normal tissue planes uncontaminated by tumor and should be performed by a surgeon specifically trained in the treatment of STS. In fact, the volume and expertise of the center where the surgery is conducted does significantly impact overall and progression-free survival [4]. The biopsy site should be excised en bloc with the definitive surgical specimen, to minimize the risk of seeding. Currently, there is no universal agreement on the dimensions of the margins, ideally >2 cm. Closer margins might be necessary to preserve bones, joints, major vessels, or nerves, especially in extremity STS. Surgical clips might be placed to mark the periphery of the surgical field to help guide potential future radiotherapy, particularly for retroperitoneal and abdominal sarcomas.

In extremity STS, limb-sparing surgery should be performed, whenever possible. Stage I disease of the extremities should be treated with radical surgery and oncologically appropriate margins. In case of appropriate margins, patients should be evaluated for rehabilitation and start clinical and radiological follow-up. In case of positive surgical margins, surgical re-resection is strongly advised; if the reintervention does not significantly affect organ function [5], adjuvant RT should be considered. Patients with stage II, III resectable disease might follow several therapeutic strategies according to size, histologic subtype, and localization.

Appropriate multimodal strategies include the following:

1. Surgery followed by adjuvant RT +/− chemotherapy
2. Preoperative (chemo)RT followed by surgery +/− adjuvant chemotherapy
3. Preoperative chemotherapy followed by surgery + adjuvant RT +/− chemotherapy.

Preoperative RT and/or chemotherapy should be considered to reduce the likelihood of a local relapse and to improve the outcomes of surgery [6]. In selected cases, either resectable with adverse functional outcome or unresectable, regional limb therapy (perfusion and infusion) with chemotherapy +/− TNF-alpha can be considered in institutions with experience [7]. Amputation should be performed for patient preference or if the gross total resection of the tumor is expected to render the limb nonfunctional [8].

For STS of the retroperitoneum, the standard surgical treatment is multi-visceral en bloc resection, often including nephrectomy, partial colectomy, and resection of vascular and muscular structures. This type of surgery is considered safe when carried out at a specialist sarcoma center. High-risk resections should be carefully considered on an individual basis and weighed against anticipated disease biology [9].

Notably, patients with limited metastasis confined to a single organ and limited tumor bulk that are amenable to local therapy should receive primary tumor management as described for stage II or III tumors and consider metastasectomy +/− chemotherapy +/− RT [10] (Fig. 58.4).

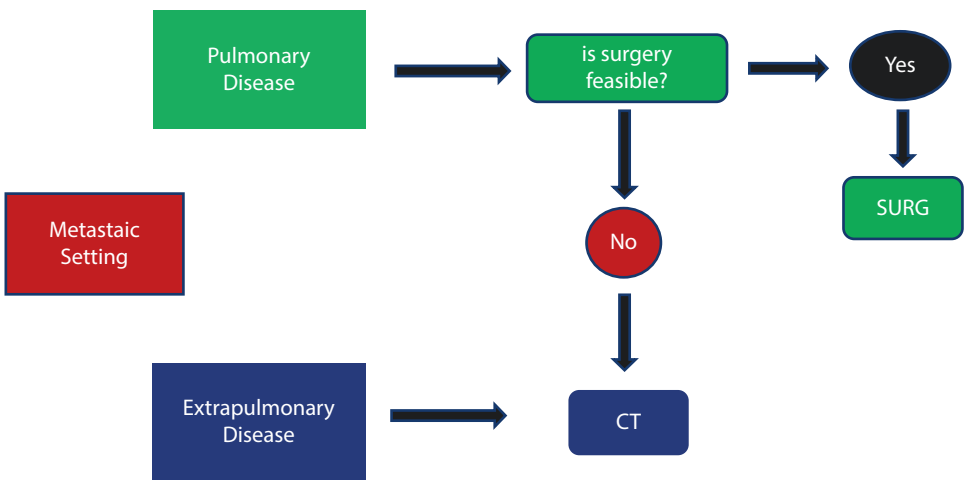


Fig. 58.4 Therapeutic approach in advanced disease

58.2.2.2 Radiotherapy

Radiotherapy is widely used in the treatment of STS patients. Adjuvant (i.e., postoperative) external beam RT (50 Gy + a variable boost dose based on margin status) should be considered for a close soft tissue margin (10–16 Gy boost) or a microscopically positive margin on bone, major blood vessels, or a major nerve (16–18 Gy boost). Randomized clinical trial data support the use of adjuvant RT to reduce local relapse, although there is no clear improvement in overall survival rates [11]. Preoperative RT is believed to reduce the risk of seeding due to surgical manipulation of the tumor. It is usually administered at a dosage of 50 Gy in 1.8–2 Gy fractions. Preoperative and adjuvant RT does not differ in terms of local or global disease control. Compared to adjuvant RT, preoperative RT is associated to greater risk of wound complications [12], but usually targets smaller radiation fields, reducing side effects, such as fibrosis, joint stiffness, and oedema [13]. A recent meta-analysis combining 16 studies also supports the use of external beam RT (both pre- and postoperative) for local tumor control in patients with resectable STS, both in the extremities and in the retroperitoneum [14]. Brachytherapy can also be considered in selected patients as an alternative to external beam RT [15].

58.3 Medical Therapy

58.3.1 Neoadjuvant Chemotherapy

The cornerstone of the medical therapy for most STS patients in all settings is represented by anthracyclines (doxorubicin and epirubicin), alone or in association to other drugs.

In the last few years, the efficacy of neoadjuvant treatment has been evaluated in different trials. The advantages of a neoadjuvant treatment are different: tumor shrinkage with the possibility of a conservative surgery, early control of micrometastases, and in vivo evaluation of treatment activity (Fig. 58.5).

In this setting, the data are conflicting and the benefit of chemotherapy seems to be limited to patients with high-grade large tumours [16]. Importantly, in patients with high-risk localized STS, three cycles of full-dose pre-operative CT are not inferior to five cycles [17]. Recently, it was reported that neoadjuvant full-dose epirubicin + ifosfamide was superior to histotype-tailored chemotherapy for most histological STS subtypes [18]. Among the histology-driven regimens, the use of trabectedin in high-grade myxoid liposarcoma has shown particularly interesting results, with response rates comparable to the standard epirubicin regimen [18]. Neoadjuvant therapy is proposed in experienced centers high risk to patients where primary surgical treatment would not be feasible or would be only feasible with adverse functional outcome.

In specific histologies, neoadjuvant chemoradiotherapy treatment may be particularly active and must be considered before surgery (Fig. 58.6).

Neoadjuvant treatment: Theoretical advantages

- Tumor cytoreduction
- Immediate treatment of micrometastases
- Early indication as to the effectiveness of chemotherapy/radiotherapy

Fig. 58.5 Theoretical advantages of neoadjuvant treatment

58.3.2 Adjuvant Chemotherapy

The finality of adjuvant treatment in STS is to improve overall survival (OS) and relapse-free survival (RFS) (Fig. 58.7).

The role of adjuvant chemotherapy in STS therapy is debatable [19]. Large meta-analysis including several trials conducted up to the year 2000 showed a statistically significant 6–10% increase in recurrence-free survival at 10 years, associated to a non significant 4% increase in overall survival [20]. In a 2001 Italian trial, restricted selection criteria for high-risk cases and high-dose intensities of doxorubicin and ifosfamide resulted in a positive impact on the disease-free survival and overall survival [21]. A second, updated meta-analysis published in 2008 confirmed a significant, although marginal, efficacy of chemotherapy in localized resectable soft-tissue sarcoma with respect to local recurrence, distant recurrence, overall recurrence and overall survival. These benefits are further improved with the addition of ifosfamide to doxorubicin-based regimens, but must be weighed against associated toxicities [22]. Notably, in 2012, the randomized clinical trial EORTC 62931 showed no significant benefit deriving from an adjuvant chemotherapy with doxorubicin, ifosfamide, and granulocyte colony-stimulating factor [23]. This study, however, was limited by a long period of accrual, a large number of ineligible patients, inadequate dosing of ifosfamide, and inclusion of patients with leiomyosarcoma, an histology known to be poorly responsive to ifosfamide. Currently, adjuvant chemotherapy is generally considered for young fit patients with high-grade disease after discussion of risk-benefit ratio [24].

The Italian AIOM guidelines and European ESMO guidelines suggest an adjuvant treatment in the case of lesions greater than 5 centimeters in diameter, G3, and with deep localization.

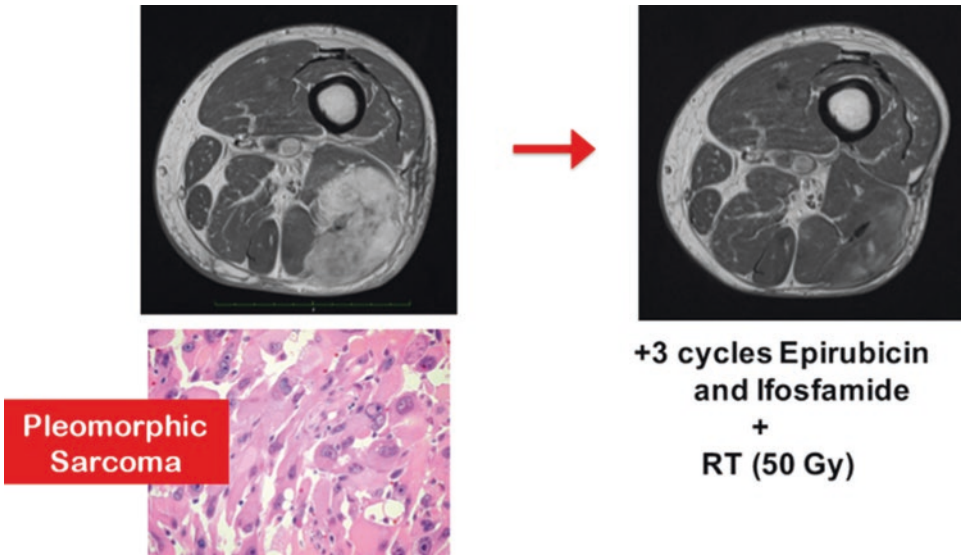


Fig. 58.6 Pleomorphic Sarcoma: good response after neoadjuvant chemoradiotherapy treatment

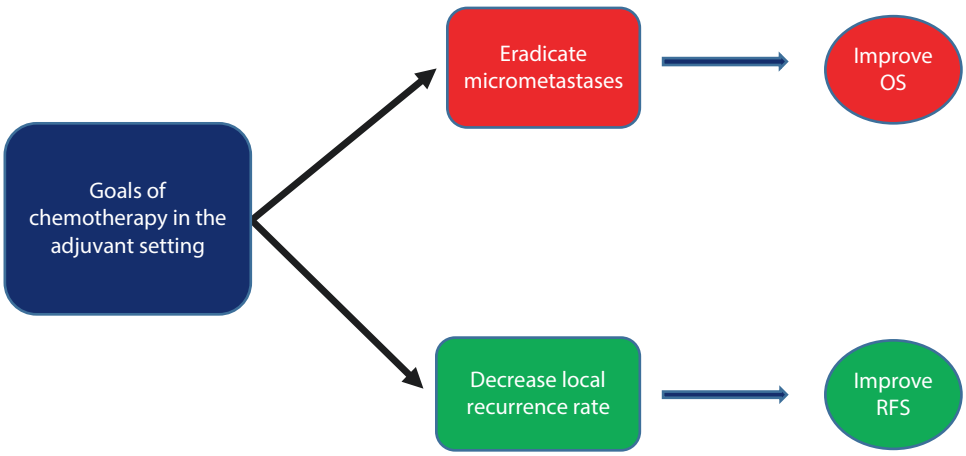


Fig. 58.7 Benefits of adjuvant chemotherapy

Age, performance status, and sensitivity to chemotherapy are further parameters to be evaluated (Fig. 58.8).

58.3.3 Palliative Chemotherapy

The benefit of doxorubicin in metastatic STS patients was first reported by Benjamin et al. in 1975 [25]. Median survival for patients with metastatic STS treated with doxorubicin-containing regimens is however only 12–16 months, and the 2-year survival rate is ~30% [26, 27]. It must be noted that the addition of ifosfamide to doxorubicin does not significantly increase overall survival, but is associated to higher response rates and longer progression-free survival, with usually manageable increases in toxicity [26].

Two other chemotherapeutic regimens, i.e., doxorubicin + evofosfamide, a hypoxia-activated prodrug similar to ifosfamide [28], and gemcitabine + docetaxel [29], have been recently studied as potential first-line therapies in randomized controlled phase III trials, both with no benefit in survival compared to doxorubicin alone. Alternative regimens should be proposed if anthracyclines are contraindicated (e.g., in case of reached cumulative dose due to previous chemotherapy for other cancers, in presence of known cardiologic morbidity) or based on patient preference [30].

In second line, based on the specific histologic subtypes, other drugs and regimens can be chosen (see), for example, gemcitabine+/−docetaxel or dacarbazine in leiomyosarcomas [31, 32], trabectedin in liposarcoma and leiomyosarcoma [33], and the multi-tyrosine kinase inhibitor pazopanib for non-adipocytic sarcomas [35]. Among these agents, eribuline showed impressive results with improved overall survival, particularly in liposarcomas [34].

Moreover, in selected histologies, targeted therapies should be considered based on their molecular specificity [36], e.g., in dermatofibrosarcoma protuber-

ans (a subtype driven by PDGF-β/PDGFR signaling), the multi-tyrosine kinase inhibitor imatinib has strong activity [37, 38]; and in myofibroblastic inflammatory tumor, a subtype often driven by ALK translocation, ALK inhibitors can be used [39, 40] (Table 58.1).

Immunotherapy in STS is not approved yet, although recently promising results have been observed with pembrolizumab in a limited number of histologies. [41]

Figure 58.9 shows the treatment flow chart in the case of metastatic disease (Fig. 58.10).

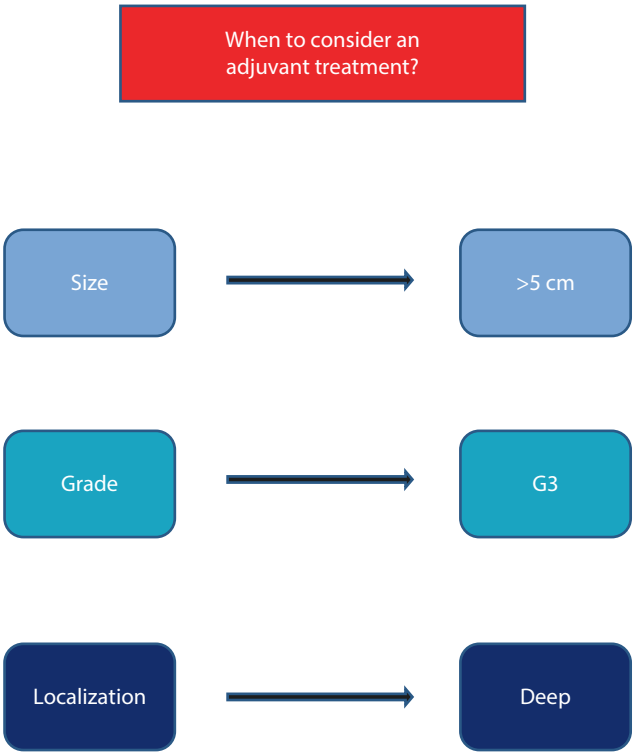
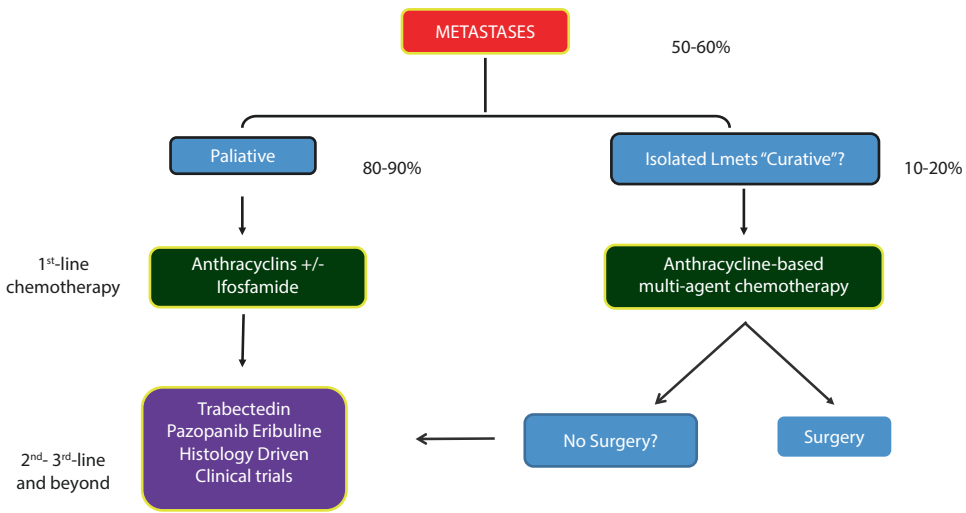


Fig. 58.8 Indications for adjuvant treatment

Table 58.1 Histology-driven treatment

Histotypes	specific treatments
Non myxoid liposarcoma	Doxorubicin +/– ifosfamide
Myxoid liposarcoma	Trabectedin
Leiomyosarcoma	Doxorubicin + DTIC, Gem-TAX, Gem-DTIC
Synovialosarcoma	High-dose Ifosfamide
UPS	Ifosfamide. Gem-TAX
Angiosarcoma	Taxol, gemcitabine
MPNST	Etoposide-HD ifosfamide
GIST, dermatofibrosarcoma	Imatinib
Pecomas	mTOR inhibitors
Alveolar soft tissue sarcoma	Anti-VEGFR agents
Endometrial Stromal sarcoma	Hormonal treatment (aromatase inhibitor)

Fig. 58.9 Flow chart treatment in metastatic setting



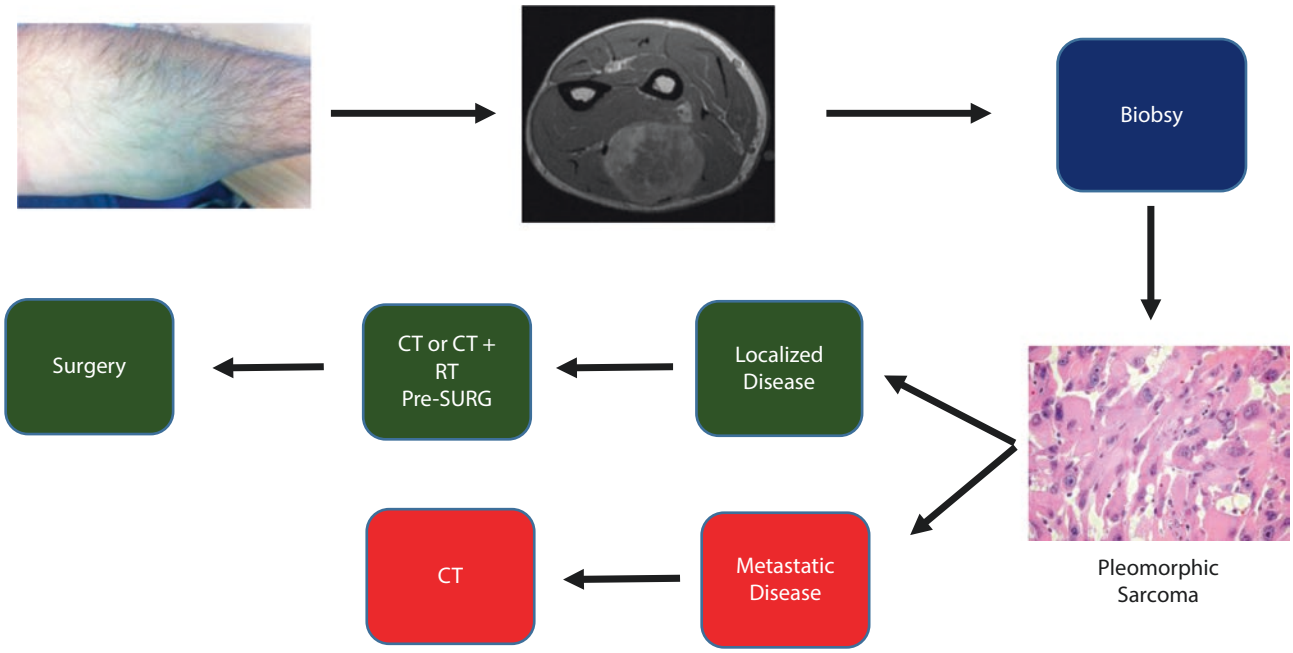


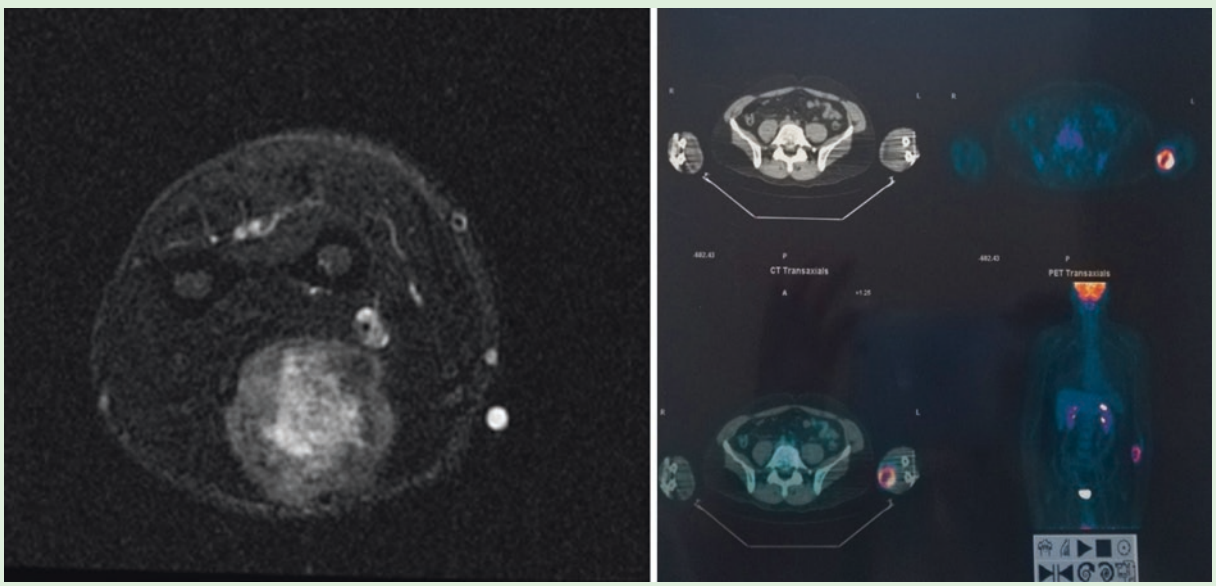
Fig. 58.10 Global therapeutic approach in a patient with a mass of soft tissues. First, biopsy. Second, staging. If localized disease, consider neoadjuvant treatment and then surgery. If metastatic disease, palliative chemotherapy

58

Case Study

Man, 50 years old

- *Family history* negative for malignancy
- *APR:* hypertension
- *APP:* contusive trauma on the left forearm with the appearance of a rapidly growing lesion
- *Objective examination*: stretch-elastic swelling of soft parts
- *Blood tests*: normal blood tests



- *RMI mdc*: In correspondence of the proximal third of the fly side of the forearm, round formation with sharp margins. DT max 3.8 cm × 5.6 cm
- *FDG-PET:* metabolic radiocomposed localized in correspondence of the left forearm, with a diameter of 38 mm and with an SUV = 12.1
- *CT-scan: negative for distant metastases*

Question

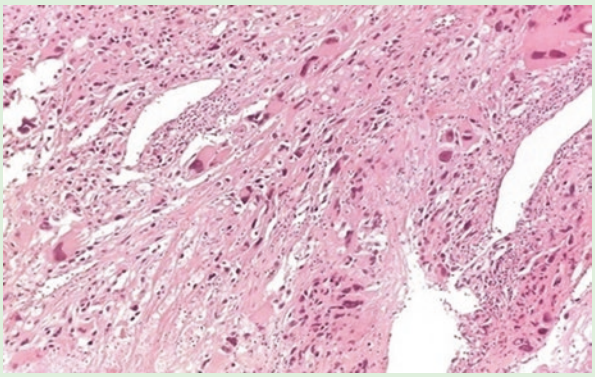
What action should be taken?

1. Surgery
2. Biopsy
3. Other

Answer

Biopsy

Pleomorphic saroma G3



Question

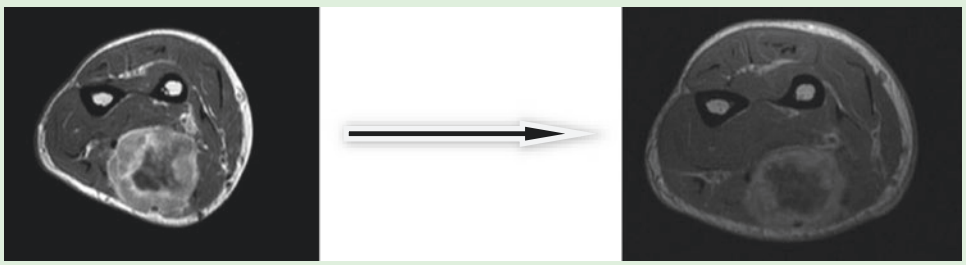
What action should be taken?

1. Surgery
2. Neoadjuvant treatment

Answer

Neoadjuvant treatment

- *Response evaluation after three cycles with epirubicin and ifosfamide:* partial response (Choi criteria)



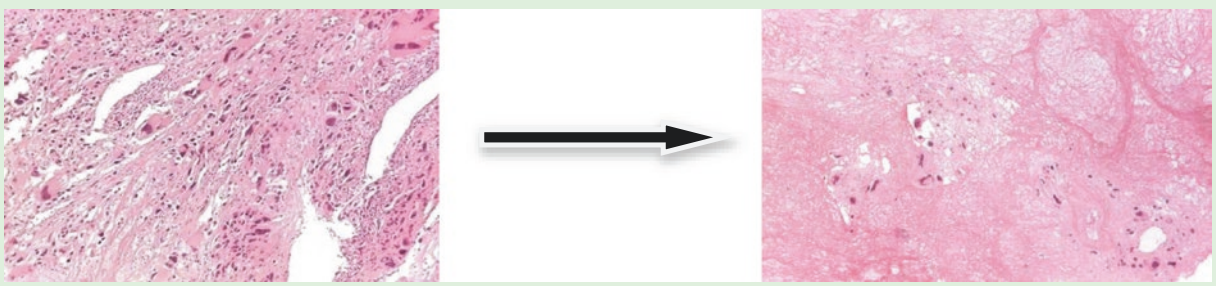
Question

What action should be taken?

1. Surgery
2. Radiotherapy
3. Continue chemotherapy

Answer

Surgery: Undifferentiated pleomorphic sarcoma with a high degree of malignancy, largely necrotic, with residual groups of vital cellular elements. Necrosis 95%. HWOS grade 3.



Pre-chemotherapy

Post-chemotherapy

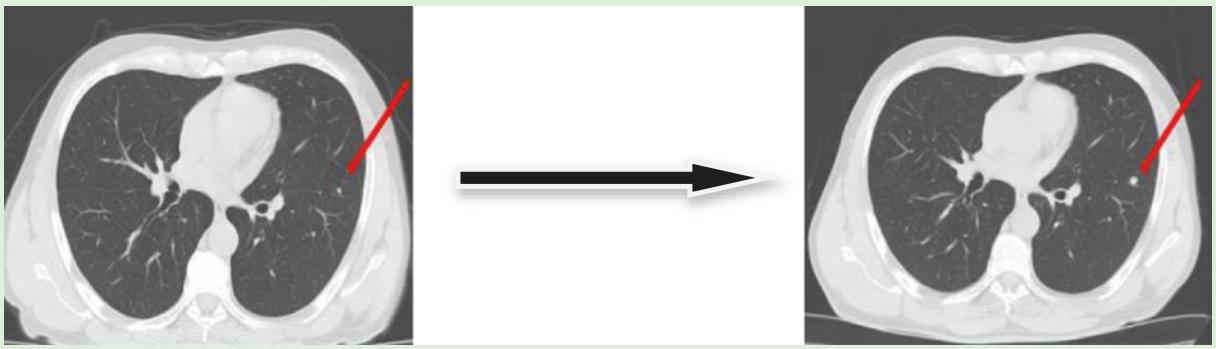
Key Points

- The importance of a correct diagnosis: biopsy is essential
- Considers a neoadjuvant treatment in the case of high grade sarcomas over 5 cm in diameter

Case Study

Man, 45 years old

- *Family history* negative for malignancy
- *APR:* 2 years ago, surgery for a leiomyosarcoma of the right arm followed by adjuvant chemotherapy
- *APP:* in the course of the follow up finding of a single growing pulmonary nodule



Question

What action should be taken?

1. Surgery
2. Radiotherapy
3. Chemotherapy
4. Biopsy

Answer

Surgery: Thoracotomy and transsegmental resection of the left lower lobe with diagnosis of metastases from leiomyosarcoma G2

Question

What action should be taken?

1. Follow up
2. Radiotherapy
3. Chemotherapy

Answer

Follow up

Key Points

- In case of single pulmonary metastases, consider surgery
- After pulmonary metastasectomy, chemotherapy is not a standard

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Expert Opinion

Giuseppe Badalamenti

Key Points

- Soft tissue sarcomas (STSs) include over 80 histological rare entities, with even more molecular subsets, characterized by a low to very low incidence in all populations.
- A multidisciplinary approach is mandatory in all cases, involving pathologists, radiologists, surgeons, radiation therapists, medical oncologists, and pediatric oncologists, as well as nuclear medicine specialists and organ-based specialists.
- Surgery is the standard treatment of all patients with an adult type, localized STS. The standard surgical procedure is a wide excision with negative margins (no tumor at the margin, R0).
- Surgery (wide excision) can be completed with adjuvant RT in case of STS >5 cm diameter, G3, and deep localization.
- There is no consensus on the current role of adjuvant chemotherapy. Study results are conflicting, though some data available from smaller studies suggesting that adjuvant ChT might improve, or at least delay, distant, and local recurrence in high-risk patients. The choice of an adjuvant treatment must therefore be individualized especially in the case of chemosensitive histology.
- In the advanced/metastatic disease, the goal is palliative, and the decision-making is complex, depending on diverse presentations and histologies and should always be multidisciplinary. Monotherapy with anthracyclin remains the gold standard. The histology-driven treatment is an option in particular cases.

- (Ref. ESMO Clinical Practice Guidelines – Soft Tissue and Visceral Sarcomas)

Hints for Deeper Insight and Suggested Reading

- Soft Tissue and Visceral Sarcomas: ESMO-EURACAN Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. P.G. Casali, N. Abecassis et al., on behalf of the ESMO Guidelines Committee and EURACAN. Annals of Oncology 29 (Supplement

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