Chapter 35
Soft Tissue Sarcomas

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Abstract Soft tissue sarcomas (STS) are a heterogeneous group of malignant tumors of mesenchymal origin, accounting for less than 1% of all adult malignancies and 15% of pediatric cancers. The most common subtypes in adults are liposarcoma (which corresponds to 20% of all STS), leiomyosarcoma and undifferentiated pleomorphic sarcoma. Based on the pattern of dissemination and the risk of distant metastases a different imaging approach may be indicated for each STS subtype as a staging workup. However, a contrast enhanced chest computed tomography is recommended for all moderate or high grade STS as a baseline imaging. Surgery is the main treatment of localized STS. It is recommended that the resection of the primary tumor includes a 2 cm margin envelope of normal tissue surrounding the lesion. The indications for radiotherapy include: high grade tumors, large (>5 cm) proximal grade 2 tumors, head and neck STS, large or high grade retroperitoneal sarcomas, local recurrences or positive margins after surgery. Adjuvant chemotherapy is still not a consensus, but there are some histologies that are better responders, like: synovial sarcoma, myxoid or pleomorphic liposarcoma, leiomyosarcoma and undifferentiated pleomorphic sarcoma. Metastatic soft tissue sarcomas are basically treated with chemotherapy. However, as there is not any highly effective treatment for the metastatic disease, the prognostic factors for prolonged survival are more related to the tumor biology than to the treatment itself.

Keywords Soft tissue sarcomas · Liposarcomas · Leiomyosarcomas · Synovial sarcomas · Limb salvage · Radiotherapy · Chemotherapy · Metastasis

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R. A. De Mello et al. (eds.), *International Manual of Oncology Practice*,
https://doi.org/10.1007/978-3-030-16245-0_35

35.1 Introduction

Sarcomas are a heterogeneous group of malignant tumors of mesenchymal origin, accounting for less than 1% of all adult malignancies and 15% of pediatric cancers [1–3]. They can be divided into 2 broad categories: soft tissue sarcomas and bone sarcomas. But with the expansion in the molecular biology, they may also be divided in simple karyotypes and highly complex karyotypes sarcomas. The simple karyotypes sarcomas have simple genetic alterations such as translocations in myxoid/round-cell liposarcoma and synovial sarcoma, APC or B-catenin mutations in desmoid tumors and KIT or PDGFRA mutations in gastrointestinal stromal tumors (GISTs) [4]. The highly complex karyotypes sarcomas include dedifferentiated and pleomorphic liposarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma and myxofibrosarcoma [4].

Although some tumors are grouped in a specific subtype, they may behave different according to the site that it arises. Retroperitoneal and intra-abdominal lesions have a much greater risk of local recurrence than extremity lesions even considering a stratification for the same subtype, which emphasizes the value of determining the aspects of biology of each tumor.

35.2 Epidemiology

According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute in the United States, the incidence of Soft Tissue Sarcomas is approximately 3.4 per 100,000 [5]. It's a rare disease, even though its true incidence is underestimated, as some visceral sarcomas are likely counted with their organ of origin rather than with soft tissue sarcomas.

It's slightly more common in males than in females by 1.4:1 and the median age at diagnosis is 59 [5]. More than 50 different histologic subtypes have been identified. The most common subtypes in adults are lipossarcoma (which corresponds to 20% of all STS), leiomyosarcoma (14% of all STS), undifferentiated pleomorphic sarcoma (UPS) (14% of all STS), GIST (9% of all STS), synovial (5% of all STS) and myxofibrosarcoma (5% of all STS) [6]. But, among elderly patients, UPS is the most common subtype. Rhabdomiosarcoma is the most common subtype in children and adolescents and is more commonly found in the head and neck region rather than the extremities. Epithelioid sarcoma is the most common subtype in the hand.

The lower extremity, which is the most common affected site, accounts for 28% of all STS. Visceral STS account for 22%, retroperitoneal sarcomas for 16%, whereas trunk and another sites account for 10% and 12%, respectively [7].

Liposarcoma is the leading type of STS on the lower extremities and on the retroperitoneum. Undifferentiated pleomorphic sarcoma (UPS) is the most common type on the upper extremities and on the trunk. Visceral STS are in their great majority gastrointestinal stromal tumors (GIST) [6].

35.3 Clinical Evaluation

Soft tissue sarcomas are usually asymptomatic masses at the beginning. But as they grow, compressive symptoms may arise, specially in case of visceral or retroperitoneal sarcomas. STS located on the extremities or on the trunk are usually first recognized by a palpable mass.

Although the clinical history and physical examination are important in the initial evaluation, symptomatology and physical findings are often nonspecific with significant overlap among presentations of neoplastic and nonneoplastic causes [8].

35.4 Risk Factors/Etiology

Sarcomas are in their great majority sporadic and idiopathic. They almost always arise de novo and not from a preexisting benign lesion. However, there are some important factors that can increase the chances to develop a sarcoma. Some recognized risk factors are: genetic predisposition (Li-Fraumeni's syndrome, neurofibromatosis and hereditary retinoblastoma), exposition to radiotherapy (RT), some chemotherapy regimens (cyclophosphamide, chlorambucil, melphalan, procarbazine and nitrosureas), infection (Kaposi's sarcoma is strongly associated with HIV and HHV8 infection), chronic lymphedema (called Stewart-Treves syndrome when associated to angiosarcoma), familial adenomatous polyposis (a major risk factor for desmoid tumors), ionizing radiation.

Ionizing radiation is a known factor that increases the risk of sarcoma development [9–12]. There is not a clear dose related to the development, but it is known that a STS may emerge within the radiation field of patients who received more than 50 Gy. They usually develop about 16 years after the RT, but this period may vary according to the histologic subtype.

The most common subtypes associated with a prior radiation are angiosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma and osteogenic sarcomas. They often develop at the edge of the radiation field and are mostly located on the chest wall or upper extremity mainly because they emerged in the area of an irradiated breast cancer and non-Hodgkin's lymphoma, which are the classic tumors associated with a further sarcoma development. Those tumors are often high-grade and have a poor prognosis.

35.5 Radiologic Assessment: Prior to the Biopsy

Diagnostic imaging plays a key role in the diagnosis and treatment. It's usually recommended that, prior to the biopsy, a radiologic evaluation is made to guide the physician to get a sample from an area with more representative material, avoiding

cystic and necrotic areas. It's also important that vascularized areas are not injured when performing the biopsy because of the risk of hematoma which can increase the volume of the lesion and change the therapeutic approach.

Several different diagnostic imaging examinations may be used in the initial evaluation of a suspected STS. The two most common modalities are the MRI (magnetic resonance imaging) and the CT (computed tomography) [13–18]. MRI provides greater soft tissue contrast than CT and therefore often allows for better definition of internal tumor soft tissue composition/intrinsec elements. MRI also provides better definition of adjacent structures, like vessels and nerves, which is of great importance for the planning of the surgery. CT better demonstrates tumor mineralization and better depicts cortical bone involvement, whereas MRI better demonstrates medullary edema [19].

35.6 Biopsy

Biopsy is essential for the diagnosis of a sarcoma. It may be obtained through open incisional or core needle. Core needle biopsy is the gold standard. However, if definitive diagnosis may require flow cytometry, cytogenetics, or molecular analysis for chromosomal translocations, a larger sample may be necessary and an incisional biopsy may be preferred. In cases where core needle biopsy is unsuccessful, an incisional biopsy is usually considered [20]. It's recommended that it is performed by an experienced surgeon, preferably by the same one who is going to operate. As the biopsy site needs to come out with the tumor, a badly planned biopsy may compromise the surgical outcome, once complications like hematomas or a biopsy which is out of a planned incision would impel a difficult excision.

Core needle is the preferred method because of its low incidence of complications and high diagnostic accuracy [21–24]. Although fine needle aspiration is not recommended for an initial approach of a suspicious lesion, it may be useful in confirming recurrences.

35.7 Staging

The American Joint Committee On Cancer (AJCC) 8th edition brought great changes into the staging for soft tissue sarcoma. There is now a different staging according to the anatomic site. An important change came with the exclusion of the depth criterion, so there is not a division by the fascia anymore (Table 35.1). Another important change was the reclassification of N1 disease into stage IV for primary sites in the extremity and trunk. For STS arising in the retroperitoneum, nodal metastases are still classified as stage III disease. As there is now a different staging for each anatomic site, a prognostic stage grouping need to be implemented for each location. Head and neck sarcomas got a new classification and needs data collection

Table 35.1 American Joint Committee On Cancer (AJCC): Definitions for T, N, M (8th edition, 2017)

	Extremity, trunk and retroperitoneum	Abdomen and thoracic visceral organs	Head and Neck
Tx	Primary cannot be assessed		
T0	No evidence for primary tumor		
T1	< 5 cm	Organ confined	< 2 cm
T2	5–10 cm	Extension into tissue beyond organ a: Invades serosa or visceral peritoneum b: Extension beyond serosa (mesentery)	2–4 cm
T3	10–15 cm	Invades another organ	> 4 cm
T4	> 15 cm	Multifocal involvement a (2 sites); b (3–5 sites); c (> 5 sites)	a: orbital invasion, skull base/dural invasion, invasion of central compartment viscera, facial skeleton or pterygoid muscles b: brain parenchymal invasion, carotid artery encasement, prevertebral muscle invasion or central nervous system involvement via perineural spread.
N	N0: No lymph node involvement or unknown status		
	N1: Lymph node involvement		
M	M0: No metastasis		
	M1: Metastases present		

before defining a stage grouping. For abdominal and thoracic visceral sarcomas there is still no recommended prognostic stage grouping. For extremetity, trunk and retroperitoneal sarcomas, the staging is shown in Table 35.2.

35.8 Staging Workup

The most common pattern of spread of the STS is hematogenous. A retrospective series reported that the proportion of lung/liver as a site of distant spread from a primary extremity sarcoma is 75:1, in contrast to primary retroperitoneal sarcoma, in which the ratio is 1:1.5, and visceral sarcomas in which the ratio is 1:10 [25].

Lymphatic spread is rare in sarcomas. However, certain subtypes, such as: synovial sarcoma, rhabdomyosarcoma, clear cell sarcoma, epithelioid sarcoma and the vascular sarcomas have a higher risk of nodal metastases. Bone metastases are more often detected in myxoid/round cell liposarcoma.

Table 35.2 AJCC: Anatomic stage/prognostic groups (8th edition, 2017)

Stage	T	N	M	Grade
IA	T1	N0	M0	G1, GX
IB	T2	N0	M0	G1, GX
	T3	N0	M0	G1, GX
	T4	N0	M0	G1, GX
II	T1	N0	M0	G2, G3
IIIA	T2	N0	M0	G2, G3
IIIB	T3	N0	M0	G2, G3
	T4	N0	M0	G2, G3
	Any T	**N1** (for retroperitoneal sarcomas, N1 disease means stage III)	M0	Any G
IV	Any T	Any N	M1	Any G
	Any T	**N1** (for extremity or trunk sarcomas, N1 disease means stage IV)	M0	Any G

Table 35.3 Additional imaging that need to be done at some specific subtypes of STS, besides the chest CT and the local imaging evaluation

Imaging approach	Subtype of STS
Abdominal/pelvic CT	Myxoid/round cell liposarcoma
	Epithelioid sarcoma
	Angiosarcoma
	Leiomyosarcoma
MRI of total spine	Myxoid/round cell liposarcoma
Central Nervous System MRI or CT	Alveolar soft part sarcoma
	Angiosarcoma

Thus, based on the pattern of dissemination and the risk of distant metastases a different imaging approach may be indicated for each STS subtype, although a contrast enhanced chest computed tomography (CT) is recommended for all moderate or high grade STS as a baseline imaging.

Myxoid/round cell liposarcoma, for example, has a totally different pattern of dissemination than well differentiated or pleomorphic liposarcomas. While those other liposarcomas often metastasize to the lungs, the myxoid/round cell subtype has a predilection for bones, specially hematopoietic bones, which justifies the need for an MRI of total spine (which has shown to be superior to bone scintigraphy or even PET-CT for depicting its bone metastases) and for fatty sites like the mediastinum, justifying the chest CT (lung metastases may also occur but are not so common as in other subtypes like the well differentiated/dedifferentiated or the pleomorphic liposarcomas) and the abdominal/pelvic CT (to rule out a retroperitoneal/abdominal involvement) [26].

In Table 35.3 below is shown the different imaging evaluations that need to be done at some specific subtypes of STS, besides the chest CT and the local imaging evaluation.

35.9 Surgery

Surgery is the main treatment of localized STS. It is recommended that the resection of the primary tumor includes a 2 cm margin envelope of normal tissue surrounding the lesion [27]. However, the exact width of the negative margin necessary for an optimal local control is hard to know, because of the retraction of the tissues when removed.

The biopsy site needs to be excised en bloc with the surgical specimen. Care must be taken not to violate the tumor, which is associated with a higher local failure rate even if radiation therapy is used [28]. If closed suction drainage is necessary, the drains should exit the skin close to the edge of the surgical incision, because an eventual re-resection or radiotherapy (RT) of that area may be necessary. Surgical clips should be placed to mark the periphery of the surgical field and other relevant structures to help guide potential RT, especially if resections with microscopically positive or grossly positive margins are anticipated.

It is also recommended that the fascia is resected, even for superficial lesions. But as it confers an adequate barrier against dissemination, thinner (1 to 2 mm) margins of fascia are likely adequate. The periosteum can also be used as a margin and so in the absence of frank bone invasion, resection up to and possibly including the periosteum (without further damage to the cortical bone) may be acceptable [29]. Resection of the periosteum should be limited to tumors abutting it. It is known that periosteal stripping may increase the risk of a later radiation-related pathologic fracture, but it may be done in order to achieve negative margins, once a margin free surgery is the main goal of the treatment [30–32].

The perineurium may also be used as margin when resecting a STS. The tumor can be resected away from a neurovascular bundle with the perineurim as margin. If an artery is involved, arterial reconstruction may be done, preferably using venous grafts, which had a significantly higher patency rate than reconstruction with artificial venous substitutes [33]. Although a venous reconstruction is not essential, it can be done in order to reduce the postoperative edema.

Some tumors associated with high rates of local recurrence, like myxofibrosarcoma and dermatofibrosarcoma need special care regarding the surgery. They both have microscopic components that extends beyond the visible tumor and so an extended margin may be necessary. But the myxofibrosarcoma is usually multifocal and have an infiltrative tail, which can be seen on MRI. The 2 cm margin for those lesions should be planned circumferentially around the tumor and these tails [34].

35.10 Lymphadenectomy

Nodal metastases are rare in STS and therapeutic lymphadenectomy is indicated only if clinically positive nodes are present or in sarcomas that emerged from a lymph node basin. But certain subtypes like rhabdomyosarcoma, angiosarcoma, clear cell sarcoma and epithelioid sarcomas have a higher rate of nodal involvement.

For those cases, sentinel lymph node biopsy is being studied, although, until now, its role remains unclear because prospective studies did not show any survival advantage and only a 5% to 7% rate of occult lymph node metastases with these high risk subtypes [35].

35.11 Limp Perfusion/Infusion

Patients who have advanced local disease with involvement of major neurovascular bundles or multifocality are candidates for isolated limb perfusion or infusion, which can provide higher doses of chemotherapy to the limb. Isolated limb perfusion with melphalan and tumor necrosis factor-alpha (TNF) is the recommended option based on recent studies. The Rotterdam group performed a study with 197 patients using melphalan plus TNF and achieved limb salvage rate of 87% with a perioperative mortality of 0.5% [36]. However, isolated limb perfusion with melphalan alone had limited success [37].

The limb perfusion normally uses hyperthermic solutions in a high flow rate and requires the dissection of the limb's major vessels. Isolated limb infusion is a less invasive alternative (with normothermic solutions in low flow rate) but a less effective technique, as showed in a phase 2 clinical trial, which included 32 patients using isolated limb infusion with melphalan plus dactinomycin and showed a 53% of significant response (25% had complete response and 28% a partial response) [38].

35.12 Surgical Management of Metastatic Disease

Although surgical metastasectomy for STS has been studied only in retrospective series, it offered longer median overall survival (OS) compared with historical controls [39–42]. But only medically fit patients with a controlled primary, limited and resectable metastatic disease are candidates for a metastasectomy [43].

For pulmonary metastases, there are two major prognostic factors: a margin-negative metastasectomy and a longer disease-free interval (DFI), preferably greater than 1 year, between resection of the primary and the metastases [44]. Others prognostic factors are number of metastatic pulmonary nodules (resection of more than 8 nodules being probably futile), tumor grade, tumor size (primary <= 10 cm is a positive prognostic factor) and patient age (older than 50 confers a worst prognosis) [44–47]. Histologic subtype is not defined as a prognostic factor, once many reports could not find a difference in OS between sarcoma subtypes [48–50]. However, a recent study with 155 patients with STS and pulmonary metastases found longer OS for leiomyosarcoma and shorter for liposarcoma or synovial sarcoma [51].

Despite aggressive surgical management, recurrence rates are still above 50% following the resection of pulmonary metastases [52]. However, some series have

shown improved OS with repeated resection of recurrent metastasis [50]. Regarding the operation, the pulmonary metastasectomy used to be mainly an open surgery, even because manual palpation identifies up to 25% more pulmonary metastases than CT [53]. But minimally invasive resections are not associated with shorter OS or greater recurrence compared with open surgery, even because it is mostly used for peripheral, low-volume metastatic disease [54].

Patients with synchronous pulmonary metastases do not benefit from metastasectomy and chemotherapy may be the initial treatment [55]. Only the ones who benefits from chemotherapy should be considered for surgery. Chemotherapy and radiotherapy may be used preoperatively or postoperatively, but they need to be discussed on a case-by-case basis.

Hepatic metastases are more common in visceral or retroperitoneal sarcomas, specially leiomyosarcomas [56]. Hepatic metastasectomy is still not a consensus and should be restricted to medically fit patients, with a long DFI and an oligometastatic disease [57, 58].

35.13 Radiotherapy

Amputation used to be the standard treatment for STS, but with the emergence of radiotherapy, the rate of amputation has been reduced to approximately 1% without any measurable fall in overall survival [59–64]. The indications for RT in STS include: high grade tumors, large (>5 cm) proximal grade 2 tumors, head and neck STS, large or high grade retroperitoneal sarcomas, local recurrences or positive margins after surgery. If available, brachytherapy should be considered for extremity STS and intraoperative RT followed by external RT for retroperitoneal sarcomas.

The optimal timing of RT is still motive of debate. The benefits of a preoperative radiation include delivery of a lower total dose (usually 50 Gy compared with 60–70 Gy after resection) to an oxygenated lesion in a smaller field (the postoperative field needs to cover the operative bed, surgical wound and drain sites) and besides that, it may reduce the seeding during surgical manipulation and thicken the pseudocapsule, easing the resection [65–67]. The postoperative radiation is favored if there is need for pathologic confirmation, concern for wound healing or radiation complications to delay definitive resection. The myxoid-round cell liposarcomas are particularly more sensitive to radiation than others STS histologies, including their metastatic lesions; which can be effectively palliated with RT.

In summary, preoperative RT is preferred for larger lesions specially involving critical structures and for extremities, since few acute wound healing complications occured in upper extremity STS and the wound complications with lower extremity STS can usually be managed. Surgery is usually performed 3–6 weeks after the completion of radiation and care must be taken to examine the pathologic specimen for positive margins, which may necessitate consideration of a postoperative boost. In contrast, postoperative therapy (at least 60 Gy) is usually preferred after an unplanned excision or

unexpectedly difficult resection, failure to obtain negative margins, or possibly when wound closure is expected to be under greater tension.

Although adjuvant RT at higher doses can also improve outcomes in patients with positive margins, local control is still worse with positive as compared with negative margins and reresection to negative margins is preferred if additional conservative surgery can be performed.

35.14 Chemotherapy: Adjuvant

Adjuvant chemotherapy is still not a consensus. However, two important meta-analyses showed benefit, especially for recurrence- free survival [68, 69]. The SMAC (Sarcoma Meta-Analysis Collaboration) study from 1997 showed a slight benefit in OS for the group of adjuvant chemotherapy but only for extremity and trunk STS [70]. Another meta-analysis, published in 2008 and which included 18 trials with 1953 patients, showed a statistically significant benefit in overall survival but only for the group that used doxorrubicin plus ifosfamide (the doxorrubicin alone group showed benefit as well but not statistically significant) [68].

However, the results of individual studies are controversial. Frustaci et al. [70] in 2001 brought a study with 104 patients comparing 5 cycles of epirubicin 120 mg/m^2 plus ifosfamide 9 g/m^2 versus observation and showed a gain in disease-free survival (48 months for the adjuvant therapy versus 16 months for the observation group) and OS (75 months for the adjuvant therapy versus 46 months for the observation group). However, the EORTC (European Organisation for Research and Treatment of Cancer) 62931 [71] study, which randomized 351 patients comparing 5 cycles of doxorubicin 75 mg/m^2 plus ifosfamide 5 g/m^2 every 3 weeks versus observation, showed no benefit in relapse-free survival or OS.

There are some histologies that are better responders to chemotherapy like: synovial sarcoma, myxoid or pleomorphic liposarcoma, leiomyosarcoma and undifferentiated pleomorphic sarcoma. But the results of the studies comparing adjuvant chemotherapy for those chemosensitive histologies are also controversial [72–74]. In 2014, the EORTC and the Soft Tissue and Bone Sarcoma Group (STBSG) coordinated two large trials of adjuvant chemotherapy in localized high-grade STS. As both studies failed to demonstrate benefit in OS, they tried to identify subgroups of patients from those trials who could benefit from adjuvant chemotherapy. They concluded that adjuvant chemotherapy is not associated with better OS in any pathology subgroup and that adjuvant chemotherapy for STS remains an investigational procedure and is not a routine standard of care.

Considering all that have been published, adjuvant chemotherapy should be administered with doxorubicin plus ifosfamide in high dosages and may be considered for high risk patients (tumors greater than 5 cm in diameter, high grade and deep to the fascia) with chemosensitive histologies (specially myxoid-round cell liposarcoma and synovial sarcoma) but needs to be discussed on a case-by-case basis once its benefits are still not a consensus.

35.15 Chemotherapy: Neoadjuvant

There are no randomized trials comparing neoadjuvant chemotherapy (with no adjuvant chemotherapy) versus observation. The Italian and the Spanish Sarcoma Group developed an international multicentric randomized phase 3 clinical trial [75] with extremity and trunk STS that compared 3 preoperative cycles of epirubicin 120 mg/m^2 and ifosfamide 9 g/m^2 versus this same preoperative scheme plus two postoperative cycles. The non-inferiority of 3 cycles of a full-dose conventional chemotherapy in comparison to five was confirmed. A retropective series [76] showed that neoadjuvant chemotherapy did not increase postoperative morbidity and could also be used to assess the tumor response to chemotherapy.

Another phase 3 clinical trial, the ISG-STS 1001, showed the superiority of the neoadjuvant administration of standard chemotherapy (epirubicin 120 mg/m^2 plus ifosfamide 9 g/m^2) to a histotype-tailored regimen [77]. However, the benefit with the standard chemotherapy suggests that this might be the added value of neoadjuvant chemotherapy itself in patients with high-risk STS [77].

Since the neoadjuvant approach may reduce the tumor burden (which can be better evaluated by PET-CT [78]), it is basically indicated for large or unresectable tumors, especially for extremity STS in order to make a posterior attempt of a conservative surgery.

35.16 Management of Local Recurrences

For local recurrences, it is important to know what kind of treatment was used on the first approach. For patients with no prior radiation, conservative surgery associated with radiotherapy is recommended. The RT may be done pre-operatively or post-operatively and this decision must be individualized. For patients with prior radiation, conservative surgery with re-irradiation also needs to be discussed on a case-by-case basis. If re-irradiation is considered, a brachytherapy or intensity-modulated RT is usually the choice in order to reduce the risk of toxicity.

Although conservative surgery is the first surgical option for local recurrences, approximately 10–25% of patients with local recurrence will have involvement of a great neurovascular bundle or bone or even a great ammount of soft tissue and skin, making a conservative surgery not viable [79–81]. For those cases, the same options used for a primary attempt of resection may be used and schemes of chemotherapy and/or RT pre-operatively should be considered, as well as limb perfusion/infusion techniques.

Special consideration needs to be made for low grade retroperitoneal liposarcoma recurrences and desmoid tumors recurrences (or even primaries as well), which can be followed symptomatically and if surgery is considered in unresectable cases, even an incomplete resection can provide prolongation in survival and successful symptom palliation.

35.17 Soft Tissue Sarcoma: Metastatic

Metastatic soft tissue sarcomas are basically treated with chemotherapy. However, as there is not any highly effective treatment for the metastatic disease, the prognostic factors for prolonged survival are more related to the tumor biology than to the treatment itself [82].

The standard chemotherapy regimen is based on anthracyclines as first-line treatment. Although the studies with anthracycline-based combination regimens (doxorubicin or epirubicin with ifosfamide and or dacarbazine) have shown controversial results regarding overall survival, they are also valid as first-line options for medically fit patients [83].

New drugs are being tested in randomized phase 2 studies, such as the olaratumab. The combination of olaratumab with doxorubicin in patients with advanced STS achieved a significant improvement of 11.8 months in OS; median OS was 26.5 months with olaratumab plus doxorubicin and 14.7 months with doxorubicin alone. Another drug that have been tested is the aldoxorubicin, a novel albumin-binding prodrug of doxorubicin. Aldoxorubicin improved progression-free survival and tumor response, but it did not show an increase in OS [84].

As second-line treatment, new drugs such as pazopanib, trabectedin, eribulin and gemcitabine are acceptable options. Pazopanib is a multi-targeted tyrosine kinase inhibitor which is active in patients with advanced non-adipocytic STS. The PALETTE study, a phase 3 trial, compared pazopanib 800 mg once daily with placebo in non-adipocytic STS [85]. The OS was 12.5 months with pazopanib versus 10.7 months with placebo. However, 3.3% of the patients in the PALETTE study and 14% of the patients of a more recently published case report [87] developed a difficult to treat pneumothorax. Trials with pazopanib in renal cell carcinoma, urothelial carcinoma and cervix carcinoma did not report pneumothorax, suggesting it is a specific adverse event in STS patients [86].

A phase 3 study compared eribulin plus dacarbazine versus dacarbazine alone in advanced liposarcoma and leiomyosarcoma patients [87]. It showed that the combination improved OS by 2 months (13.5 months for the combination versus 11.5 months for observation). Another phase 3 multicenter clinical trial involving liposarcomas and leiomyosarcomas studied trabectedin versus dacarbazine after a prior therapy with an anthracycline and at least one additional systemic regimen [88]. Although trabectedin did not improve OS over dacarbazine (12.4 months for trabectedin versus 12.9 months for dacarbazine), it showed superior disease control.

The study Alliance A091401 [89], a randomised phase 2 trial, investigated the efficacy of nivolumab plus ipilimumab versus nivolumab alone in metastatic STS with a primary endpoint of objective response. The nivolumab alone does not warrant further study due to its limited efficacy. But nivolumab combined with ipilimumab demonstrated promising efficacy in certain subtypes (alveolar sarcoma, leiomyosarcoma, UPS, myxofibrosarcoma and angiosarcoma).

Questions

1. Soft tissue sarcomas comprises a heterogeneous group of rare diseases. In most cases, there is no known etiologic factor. However, literature describes some well established risk factors. Which of the following statements about these risk factors is not true?

   (a) Previous exposition to ionizing radiation is related to the risk of development of a subgroup of radiation-induced sarcomas that are diagnosed most often until 5 years after exposition.
   (b) Viral infections may be related to some specific sarcoma subtypes (Kaposi's sarcoma).
   (c) Some genetic predisposition syndromes are major risk factors, among them: Li-Fraumeni, neurofibromatosis and familial adenomatous polyposis (FAP) syndrome.
   (d) Stewart-Treves syndrome consists of an angiosarcoma related to chronic lymphedema (idiophatic, infectious or postoperative).

Answer: (a)

(a) Radiation-induced sarcomas are most often diagnosed after 16 years, although this period may vary depending on the subtype that will arise.

2. Soft tissue sarcomas are rare and comprises 1% of all malignancies in adults. They can affect virtually any anatomic site, occurring more frequently in some locations. About sarcomas, which of the following is not true?

   (a) The retroperitoneum is one of the most common sites of origin, comprising 16% of the cases.
   (b) The extremities are the most affected anatomic location, specially the upper extremity (arm and forearm).
   (c) The visceral sites are commonly affected, GIST being the most common histologic subtype in this region.
   (d) Sarcomas are malignant tumors of mesenchymal origin, with more than 50 histological subtypes. Liposarcoma, leiomyosarcoma and undifferentiated pleomorphic sarcoma are the most common ones.

Answer (b)

(b) The lower extremity, which is the most common affected site, accounts for 28% of all STS

3. About the radiation induced sarcomas, which of the following is correct?

   (a) They often develop at the edge of the radiation field.
   (b) They usually have a better prognosis.
   (c) Angiosarcoma is the only subtype associated.
   (d) They usually develop at the extremities.

Answer (a)

They often develop at the edge of the radiation field, suggesting incomplete repair of normal tissue.

They usually have a poorer prognosis.
Angiosarcoma, osteogenic sarcomas and UPS are the most common subtypes that are associated.
They are mostly located on the chest wall or upper extremity mainly because they emerged in the area of an irradiated breast cancer and non-Hodgkin's lymphoma, which are the classic tumors associated with a further sarcoma development.

4. A 60-year-old man presented with a slow growing, palpable mass in his right thigh, noted 3 years ago. During physical examination, you notice a deep, firm, immovable 9.0 cm tumor in the lateral aspect of the right thigh. What is the most appropriate next step for diagnosis?

   (a) Enhanced contrast CT to study the nature, localization of the tumor and assess femur medullary involvement.
   (b) Incisional biopsy under sedation.
   (c) Fine-needle aspirate.
   (d) MRI to study the tumor composition and relation to adjacent structures, which may allow a better planning of the biopsy and surgery.

Answer (d)
CT better demonstrates tumor mineralization and better depicts cortical bone involvement, whereas MRI better demonstrates medullary edema.
Core needle biopsy is now the gold standard, with the incisional biopsy reserved for when a bigger sample is needed.
Fine needle aspirate is most of the times not diagnostic for soft tissue sarcomas.
It's usually recommended that, prior to the biopsy, a radiologic evaluation is made so it can guide the physician to get a sample from an area with more representative material, avoiding cystic and necrotic areas. It's also important that vascularized areas are not injured when performing the biopsy because of the risk of hematoma which can increase the volume of the lesion and change the therapeutic approach.

5. About the soft tissue sarcomas, which of the following is correct?

   (a) Desmoid tumors are high grade lesions that usually present with lung metastases
   (b) Myxoid/round cell liposarcomas are chemosensitive and radiosensitive lesions
   (c) Neoadjuvant chemotherapy with 3 cycles showed inferior results compared to a 5 cycles scheme combining 3 cycles pre-operatively and 2 cycles postoperatively.
   (d) Nodal metastases for retroperitoneal sarcomas mean stage IV disease

Answer (b)
Desmoids are low grade lesions which does not metastasize.
An international multicentric randomized phase 3 clinical trial with extremity and trunk STS that compared 3 preoperative cycles of epirubicin 120 mg/m^2 and ifosfamide 9 g/m^2 versus this same preoperative scheme plus two postoperative

cycles. The non-inferiority of 3 cycles of a full-dose conventional chemotherapy in comparison to five was confirmed

Nodal metastases for extremity sarcomas mean stage IV disease, but for retroperitoneal sarcomas it means a stage III disease.

6. A 70- year-old man was diagnosed with an undifferentiated pleomorphic sarcoma (UPS) on the right arm. The complete imaging staging revealed synchronic pulmonary metastases. Which of the following is not true about the soft tissue sarcomas?

   (a) UPS is the most common sarcoma on the upper extremities
   (b) UPS is the most common subtype among elderly patients
   (c) The best treatment option would be the resection of the primary followed by pulmonary metastasectomy.
   (d) The baseline imaging staging for UPS is composed of a chest CT and a MRI/CT of the primary site.

Answer (c)

Patients with synchronous pulmonary metastases do not benefit from metastasectomy; and chemotherapy may be the initial treatment.

7. A 45-years-old woman underwent resection of a 5 cm soft tissue mass from her back. Pathological report revealed an undifferentiated pleomorphic sarcoma, with positive margins. Staging workup was negative for metastasis. What is the most appropriate next step?

   (a) Observation
   (b) Radiotherapy
   (c) Doxorubicin based chemotherapy
   (d) Reresection

Answer (d)

Although adjuvant radiation may be an option, the main goal of the treatment for most STS is a resection with negative margins.

8. Which of the following statements is not true about the staging of soft tissue sarcomas?

   (a) Unlike extremity localized tumors, retroperitoneal sarcomas with nodal metastasis are grouped in stage III
   (b) The location in relation to the fascia (superficial or deep) remains an important staging criterion
   (c) Head and neck sarcomas have a proper staging system, similar to other malignant head and neck tumors
   (d) Histological grade remains a relevant factor in staging.

Answer (b)

The American Joint Committee on Cancer (AJCC) – 8th edition brought great changes into the staging for soft tissue sarcoma. There is now a different staging

according to the anatomic site. An important change came with the exclusion of the depth criterion, so there is not a division by the fascia anymore

9. A 63-years-old man presented with a fast-growing mass in his right axillary region. He sought medical attention and was submitted to adequate imaging workup and core needle biopsy. Pathology and staging revealed an 8.0 cm synovial sarcoma with no metastatic disease. He underwent wide resection and axillary lymphadenectomy. Pathological report demonstrated an 8.0 cm synovial sarcoma, resected with free margins and three lymph nodes harboring sarcoma metastasis. Which of the following depicts the most appropriate statement?

   (a) There is no need for lymphadenectomy, since nodal metastases are rare in soft tissue sarcomas.
   (b) The patient should be referred to medical oncology, once nodal metastasis characterizes stage III disease
   (c) The patient should be referred to radiotherapy, to evaluate adjuvant treatment, and medical oncology to discuss, on a case-by-case basis, the benefit of adjuvant chemotherapy regimen in this high-risk patient
   (d) The treatment is complete and the patient should be followed every 6 months

Answer (c)

Synovial sarcoma is a high grade and a chemosensitive sarcoma subtype. As this is a high risk (> 5 cm, high grade sarcoma with nodal metastasis) patient, adjuvant chemotherapy may be indicated. The lymph node dissection showed 3 metastatic lymph nodes, making it reasonable to irradiate this area in order to try to achieve a better local control.

10. Nodal metastases in soft tissue sarcomas are a rare event. However, they exist, and may be associated with specific sarcoma subtypes. Which of the following contains the subtypes of greater risk for nodal dissemination?

   (a) Synovial sarcoma, clear cell sarcoma and malignant nerve sheath tumor
   (b) Epithelioid sarcoma, lymphangiosarcoma and liposarcoma
   (c) Angiosarcoma, leiomyosarcoma and fibrosarcoma
   (d) Rhabdomyosarcoma, angiosarcoma and clear cell sarcoma

Answer (d)

Synovial sarcoma, rhabdomyosarcoma, clear cell sarcoma, epithelioid sarcoma and the vascular sarcomas have a higher risk of nodal metastases.

11. Which one of the following is the most common subtype of extremity soft tissue sarcomas?

   (a) Undifferentiated pleomorphic sarcoma
   (b) Liposarcoma
   (c) Leiomyosarcoma
   (d) Myxofibrosarcoma

Answer (b)
Liposarcoma is the most common subtype in the extremities, particularly in the lower extremities.

12. Some soft tissue sarcomas metastases have a predilection for central nervous system. Which of the following alternatives contains one of these sarcoma subtypes?

    (a) Epithelioid sarcoma
    (b) Desmoid tumors
    (c) Leiomyosarcoma
    (d) Alveolar soft part sarcoma

Answer (d)
Alveolar soft part sarcoma and angiosarcoma are the subtypes most commonly associated to central nervous system metastasis.

13. Myxoid/Round cell liposarcoma needs to be properly staged with a lot more than just a physical examination. Which of the following contains the complete baseline imaging approach for those tumors?

    (a) Chest CT only
    (b) Chest and abdominal/pelvic CT
    (c) Chest and abdominal/pelvic CT plus MRI of total spine
    (d) Chest and abdominal/pelvic CT plus Central Nervous System MRI

Answer (c)
Myxoid/round cell liposarcoma has a totally different pattern of dissemination than well differentiated or pleomorphic liposarcomas. While those other liposarcomas often metastasize to the lungs, the myxoid/round cell subtype has a predilection for bones, specially hematopoietic bones, which justifies the need for an MRI of total spine (which has shown to be superior to bone scintigraphy or even PET-CT for depicting its bone metastases) and for fatty sites like the mediastinum, justifying the chest CT (lung metastases may also occur but are not so common as in other subtypes like the well differentiated/dedifferentiated or the pleomorphic liposarcomas) and the abdominal/pelvic CT (to rule out a retroperitoneal/abdominal involvement).

14. A 70- year-old female patient just had a 5 cm, high grade, undifferentiated pleomorphic sarcoma removed from her arm. The pathological report showed compromised microscopic margin. What is the most appropriate approach for this case?

    (a) Reresection to negative margins
    (b) Adjuvant radiotherapy
    (c) Adjuvant chemotherapy
    (d) Observation and if it relapses, reresection

Answer (a)

Although adjuvant radiotherapy or even adjuvant chemotherapy may be options, the main goal of the treatment of most high-grade sarcomas is to obtain negative margins whenever possible.

15. A 40- year-old male patient was diagnosed with a 5 cm myxoid/round cell liposarcoma in his right thigh, but distant to the neurovascular bundle. Physical examination revealed enlarged lymph nodes in the right groin, whose biopsy was positive for metastatic sarcoma. The complete imaging staging showed a metastatic disease only to the lymph nodes in right groin. Which of the following items contains the correct clinical stage and treatment?

    (a) Stage IV / Chemotherapy only
    (b) Stage III / Resection of the primary and lymphadenectomy
    (c) Stage IV / Neoadjuvant chemotherapy followed by resection of the primary with no lymphadenectomy
    (d) Stage IV / Resection of the primary and lymphadenectomy

Answer (d)

N1 for extremity sarcomas means a stage IV disease (for retroperitoneal sarcomas it means a stage III disease)

Although many options of treatment are available in this case, like neoadjuvant chemotherapy (myxoid/round cell liposarcoma is particularly a chemosensitive subtype); the resection of the primary to negative margins with lymphadenectomy (since no other distant disease is present) is the most important part of the treatment.

16. About soft tissue sarcomas, which of the following is not true?

    (a) Limb perfusion with melphalan alone showed to be non-inferior to limb perfusion with melphalan and TNF.
    (b) Isolated limb infusion is a less invasive alternative (with normothermic solutions in low flow rate) but a less effective technique, as showed in recent phase 2 clinical trials.
    (c) Epithelioid sarcoma is the most common subtype in the hand.
    (d) Rhabdomiosarcoma is the most common subtype in children and adolescents and are more commonly found in the head and neck region rather than the extremities.

Answer (a)

Isolated limb perfusion with melphalan and tumor necrosis factor-alpha (TNF) is the recommended option based on recent studies. The Rotterdam group performed a study with 197 patients using melphalan plus TNF and achieved limb salvage rate of 87% with a perioperative mortality of 0.5% (36). However, isolated limb perfusion with melphalan alone had limited success.

Clinical Case

A 62-year-old female patient was referred to our service with an asymptomatic palpable mass on her right thigh. She brought an ultrasound that revealed a

hypoechoic mass with some internal debris and measuring 5.6 x 12 x 6.1 cm in the middle of the quadriceps muscle. After a complete physical examination which showed clinically positive lymphnodes in the right groin, a magnetic resonance of the right thigh was ordered, which showed a complex lesion with some areas of necrosis but with no neurovascular bundle or bone involvement. A core needle biopsy of the lesion was performed and revealed a pleomorphic liposarcoma. Fine needle aspiration of the lymphnodes in the groin was positive for neoplastic cells. A chest CT was ordered and did not show any metastatic implants.

1. Question: What would be your next step? What's the staging of this disease? Lymphadenectomy would be indicated in this case?

Answer:

1. The patient has a stage IV disease with isolated regional (ipsilateral groin) disease.
2. Lymphadenectomy is indicated. Therapeutic lymphadenectomy is indicated only if clinically positive nodes are present or in sarcomas that emerged from a lymph node basin.
3. Next step would be the resection of the primary with lymphadenectomy. As it is an undoubtedly resectable lesion (as shown in the MRI), we prefer an upfront surgery instead of using neoadjuvant approaches with chemotherapy or radiotherapy, although both neoadjuvant approaches are reasonable and may have been indicated. Neoadjuvant chemotherapy or radiotherapy is more frequently used when the primary is unresectable or resectable with adverse functional outcomes.

The patient was then treated with the resection of the primary to negative margins and with a right pelvic and inguinal lymphadenectomy. The pathological report confirmed a pleomorphic liposarcoma with 12cm in its greatest dimension. It also revealed 3 (out of 10) metastatic lymphnodes in the groin and 1 (out of 14) in the pelvis.

2. Question: What's your next step? Is radiotherapy/chemotherapy indicated?

Answer:

1. Radiotherapy is indicated. The indications for radiotherapy in STS include: high grade tumors, large (>5cm) proximal grade 2 tumors, head and neck STS, large or high grade retroperitoneal sarcomas, local recurrences or positive margins after surgery).
2. Chemotherapy is indicated. Adjuvant chemotherapy should be administered with doxorubicin plus ifosfamide in high dosages and may be considered for high risk patients (tumors greater than 5cm in diameter, high grade and deep to the fascia) with chemosensitive histologies (specially myxoid-round cell liposarcoma and synovial sarcoma) but needs to be discussed on a case-by-case basis once its benefits are still not a consensus. Although pleomorphic liposarcoma is not a chemosensitive histology, the patient had a large and high-grade primary with a stage IV disease.

Radiotherapy was then applied. Also, adjuvant chemotherapy was used with doxorubicin and ifosfamide in high dosages. The patient was followed and on the 6th month she presented at the office with a resectable local recurrence.

3. Question: What's your next step?

Answer:

1. New re-staging with a complete history and physical examination and a chest CT as baseline imaging staging.
2. If the new re-staging shows only the local recurrence, resection to negative margins is the most appropriate recommendation.
3. For patients with prior radiation, conservative surgery with re-irradiation needs to be discussed on a case-by-case basis. If re-irradiation is considered, a brachytherapy or intensity-modulated radiotherapy is usually the choice in order to reduce the risk of toxicity.

New re-staging was done and revealed a local recurrence only. So new resection to negative margins was performed. The patient is then being followed with a 3/3 months consultation.

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