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REVIEW ARTICLE

Local recurrence of soft-tissue sarcoma: issues in imaging surveillance strategy

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Abstract

Soft-tissue sarcomas pose diagnostic and therapeutic challenges to physicians, owing to the large number of subtypes, aggressive tumor biology, lack of consensus on management, and controversy surrounding interval and duration of surveillance scans. Advances in multidisciplinary management have improved the care of sarcoma patients, but controversy remains regarding strategies for surveillance following definitive local control. This review provides an updated, comprehensive overview of the current understanding of the risk of local recurrence of soft-tissue sarcoma, by examining the literature based on features such as histological type and grade, tumor size, and resection margin status, with the aim of helping clinicians, surgeons, and radiologists to develop a tailored approach to local imaging surveillance.

Keywords Soft-tissue sarcoma · Musculoskeletal sarcoma · Imaging surveillance · Local recurrence · MRI

Introduction

Soft-tissue sarcomas (STS) are a heterogeneous group of mesenchymal neoplasms that account for about 1% of adult malignancies [1, 2]. Most cases occur in the limb or limb girdle or within the abdomen (retroperitoneal or visceral and intraperitoneal) [3]. According to the American Cancer Society, the estimated incidence of STS was 12,390 and mortality was 4,990 in the USA in 2017 [3]. This is comparable with the annual incidence of esophageal (17,500 cases) and cervical (12,000 cases) cancers [4], which illustrates that its rarity may be overestimated in clinical practice.

The initial diagnosis is often obtained by core needle biopsy, because of a low risk for complications and high diagnostic accuracy [5, 6], although unplanned excisions occur in up to 50% of some series [7]. In addition to wide surgical resection, pre- or post-operative radiation or chemotherapy may be given to augment local control, generally for larger and higher-grade tumors; amputation may be necessary when extensive vascular encasement, problems anticipated with wound closure or soft-tissue coverage or other clinical considerations render limb salvage infeasible or imprudent [3].

Local recurrence (LR) of STS portends a poor outcome [8–10]. The reported rates of LR range from 6.5% to approximately 25%; higher reported rates of local recurrence predate the widespread use of (neo)adjuvant chemoradiation therapy [11–14]. In a retrospective study involving 753 intermediate to high-grade STS patients, LR of STS was associated with the development of subsequent LRs, which significantly increased morbidity, and was the single most significant factor associated with decreased overall survival (OS), in part reflecting greater biological tumor aggressiveness [15].

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Risk factors for LR

The risk of LR is dependent on a number of factors related to tumor biology, patient demographics, and treatment strategy. These factors can be conceptually divided into those that are:

1. Intrinsic, pertaining to patient and tumor features: patient age, tumor size, anatomical location, depth within the soft tissues, and histological subtype
2. Extrinsic, related to clinical treatment and including factors such as adequacy of resection margins, contamination of the operative bed (e.g. via piecemeal excision or spillage of friable/rupture tumor, and use of perioperative radiation or chemotherapy [15]

In a study conducted at M.D. Anderson Cancer Center (MDACC), of 1,225 patients with localized primary STS, factors predictive of local recurrence included: positive or uncertain resection margins (RR: 2.5, 95% CI, 1.9–3.3; $p < 0.001$), tumors present in the head, neck or deep trunk (RR: 2.6, 95% CI, 1.8–3.6; $p < 0.001$), presence of previous recurrence (RR: 2.2, 95% CI, 1.6–3.0; $p < 0.001$), patient age > 64 years (RR: 1.8, 95% CI, 1.3–2.5; $p < 0.001$), histopathological types including undifferentiated pleomorphic sarcoma, neurogenic sarcoma or epithelioid sarcoma (RR: 1.7, 95% CI, 1.2–2.3; $p = 0.001$), a tumor size >10 cm in its greatest dimension (RR: 1.7, 95% CI, 1.2–2.4; $p = 0.002$), and high pathological grade (RR: 1.5, 95% CI, 1.1–2.2; $p = 0.013$) [16].

Size, grade, and stage

There are a number of staging systems in use for STS; the most widely used are the Enneking/Musculoskeletal Tumor Society system, which incorporates size, the tissue compartments involved, and grade [17], and the American Joint Committee on Cancer (AJCC) system, which is based on tumor, regional lymph node, metastasis (TNM) status and histological grade [18]. Previously, risk stratification was based on tumor depth, with deep tumors carrying a poorer prognosis than superficial tumors. Superficial sarcomas are often smaller in size at initial diagnosis, probably because they are more easily detected than deep sarcomas [19, 20]. However, risk stratification based on tumor depth has been eliminated in the 8th edition of the AJCC, such that, all else being equal, superficial and deep sarcomas of the same size are now considered the same stage [21].

The histological grade reflects tumor-specific biology, as a morphological manifestation of genetic events that determine tumor aggressiveness, with a high tumor grade being an important negative prognostic factor for local control and OS [15]. The French Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) is the most widely used grading system for sarcoma as it is the most precisely defined, theoretically reproducible, and it correlates most closely with prognosis. The FNCLCC histological grade is determined by three factors: mitotic index, presence of necrosis, and degree of differentiation (i.e., how closely the tumor recapitulates normal adult mesenchymal tissue). Each factor is independently scored and then combined for a histological grade of 1, 2, or 3 [22, 23]. The AJCC uses a three-tiered grading system (i.e., grade 1: well-differentiated, low grade; grade 2: moderately differentiated; and grade 3: poorly differentiated, high-grade) [22]. For treatment purposes, three-tiered grading systems are frequently simplified to two tiers, with grade 1 representing low-grade tumors and grades 2 and 3 representing high-grade tumors. Although grade is an independent predictor of the probability of distant metastases, the uniformly aggressive biological behavior of some sarcoma subtypes obviates the need for classic histological grading (e.g., malignant peripheral nerve sheath tumors [MPNSTs], Ewing sarcoma, alveolar soft-part sarcoma [ASPS], rhabdomyosarcoma, clear cell sarcoma, and epithelioid sarcoma) [18, 22]. Although the aforementioned sarcoma subtypes are considered highly aggressive regardless of the attributed grade, pathologists may still grade these tumors for the purposes of treatment, and allowing for a marker for comparison in the event that the tumor subsequently metastasizes [22].

Histological type

Sarcomas are thought to arise from undifferentiated mesenchymal stem cells that partially differentiate along specific mesenchymal lineages, and they are classified based on the tissue that they most closely morphologically resemble or recapitulate. The most common histological types are liposarcoma (20%), leiomyosarcoma (14%), or fibroblastic/myofibroblastic sarcoma (which may be known as undifferentiated pleomorphic sarcoma [UPS] or, historically, malignant fibrous histiocytoma [MFH]; 14%) [18, 24]. In some instances, the histogenesis remains unclear, and the designation reflects the architectural pattern (e.g., epithelioid sarcoma, clear cell sarcoma, ASPS). Ultimately, histology should be reviewed by an experienced subspecialized pathologist as initial histological interpretation in up to 25–40% of bone sarcoma and STS is revised or reclassified upon expert consultation [25].

Of the variants of liposarcomas, atypical lipomatous tumors/well-differentiated (low-grade) liposarcomas (ALTs/WDLs) are the most common, whereas myxoid and pleomorphic liposarcomas are less common. ALTs are located in the extremity or trunk and have no metastatic ability [18], although these same tumors carry substantially increased LR and dedifferentiation risk in the retroperitoneum, mediastinum, and spermatic cord, where they are accordingly termed WDLs [21]. De-differentiated liposarcomas have higher LR

rates, the ability to metastasize, and carry a six-fold increased risk of death [26]. Thus, surveillance after ALT/WDL resection requires attention to both tumor recurrence and emergence of de-differentiation. In some instances, histology may predict metastatic pattern. For example, myxoid liposarcoma is unusual among STS in that it has a propensity to metastasize to soft tissues and bone and, as such, a careful search of even distant soft tissues must be undertaken when included on a local surveillance scan (Fig. 1). This topic is further discussed below (see Sect. Distant metastasis surveillance below).

Certain histological subtypes also influence the risk for LR. Angiosarcomas are highly aggressive sarcomas with LR rates reported from 45 to 75% [27, 28]. Additionally, the incidence of LR in leiomyosarcoma patients is approximately 60% [29], whereas the reported LR rates of myxofibrosarcoma are 55 to 65%, which may be partly because of the difficulty of achieving true-negative margins owing to a propensity for an infiltrative growth pattern (Fig. 2) [30, 31]. High rates of LR are seen with UPS as well, reported between 19 and 31%, typically in the first 1–2 years [32].

Although in general, sarcomas tend to spread hematogenously rather than through the lymphatics, some specific subtypes of sarcomas have greater propensities to involve lymph nodes. In a study from Memorial Sloan-Kettering Cancer Center (MSKCC) evaluating sarcoma patients with lymph node metastasis ($n = 1,722$), the histologies with the greatest risk for lymph node metastasis included: rhabdomyosarcoma, synovial sarcoma, epithelioid sarcoma, clear cell sarcoma, and angiosarcomas [33]. When confronted with these particular tumor subtypes, consideration of nodal drainage patterns should direct the radiologist's attention to the appropriate regional lymph nodes that may be included in the field of view when imaging is performed for local surveillance (Fig. 3).

Margin status and unplanned excision

The margin of resection and the use of radiotherapy are important for local STS disease control [34–36]. A major adverse prognostic factor is the presence of positive margins after surgical excision (Fig. 4) [37]. Two retrospective studies from the MSKCC found that margin status is an independent prognostic factor for LR and disease-specific survival [38, 39]. Patients who have had a tumor excised with positive margins reportedly have a 5.9 times increased LR rate (95% confidence interval [CI] = 3.1–11.1) for STS compared with patients with negative margins [40]. However, other studies have found evidence that microscopic positive resection margins, in terms of LR and OS, are more suggestive of aggressive tumor biology, as opposed to the adequacy of operative intervention [38, 41]. It should also be noted that occasionally a planned positive margin along a vessel or nerve may be part of a limb salvage strategy that includes adjuvant radiation therapy.

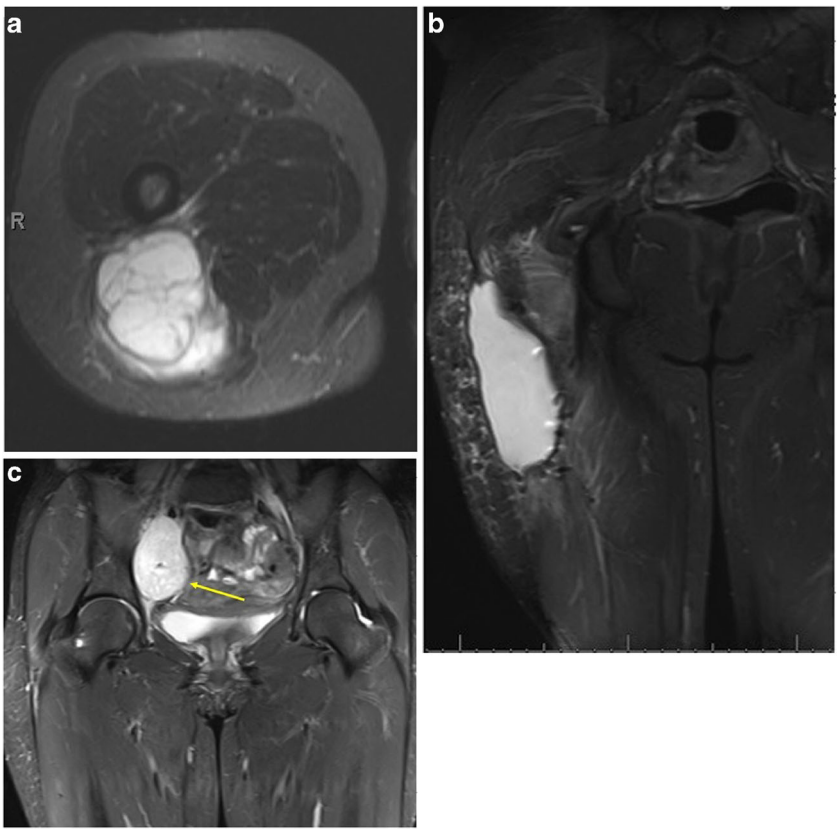

Fig. 1 A 43-year-old woman with a posterior thigh grade 2 myxoid liposarcoma with a round cell component; this case highlights tumor-specific patterns of recurrence and metastasis. **a** Axial fat-suppressed PD shows a hyperintense lobular mass in the posterior lateral aspect of the right thigh. **b** Coronal fat-suppressed proton density from routine surveillance MRI 2 years later revealed post-operative seroma in the thigh. **c** Coronal post-contrast T1-weighted fat-suppressed image from the same scan also revealed an avidly enhancing retroperitoneal solid soft-tissue mass in the right pelvis (*arrow*). Although the location raised the possibility of a solid ovarian neoplasm, myxoid liposarcoma has a propensity to metastasize to soft tissues and was thus suspected, and later confirmed histologically

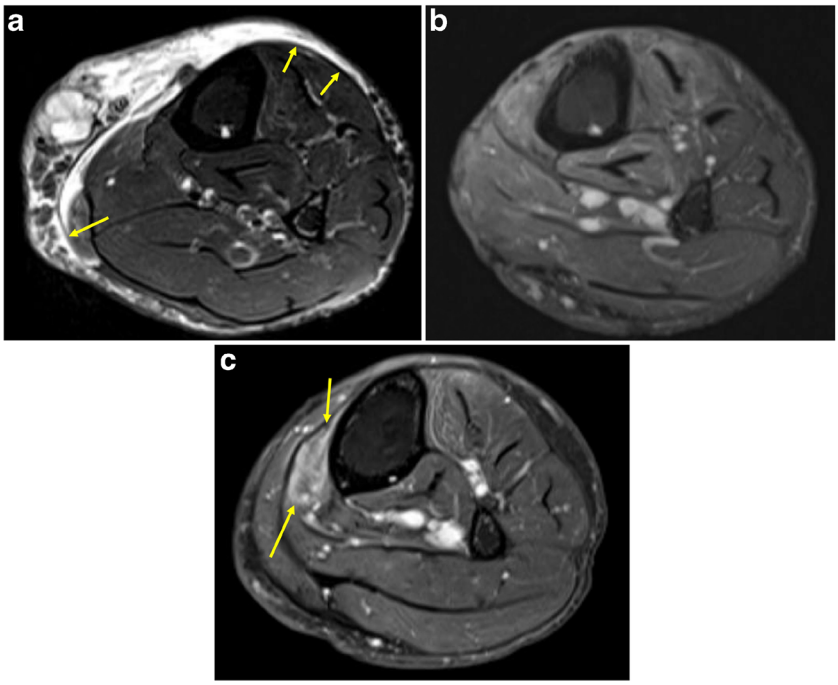

Fig. 2 An 84-year-old woman with recurrent myxofibrosarcoma in the lower leg. **a** Axial T2-weighted fat-suppressed image in the lower leg shows an ill-defined mass centered in the medial aspect of the lower leg; note the infiltrative tails of peritumoral edema (*arrows*) extending across midline anteriorly, and posteromedially. Peritumoral edema or enhancement in this infiltrative fashion reflects an underlying myxofibrosarcoma growth pattern, and may thwart achievement of wide negative margins; in this case, the final closest margin was 1 mm. **b** Axial post-contrast T1-weighted fat-suppressed image 6 months post-operatively during routine surveillance shows changes related to medial gastrocnemius flap reconstruction, but no evidence for recurrent disease. **c** Axial post-contrast T1-weighted fat-suppressed image 21 months post-operatively during routine surveillance demonstrates a new, mass-like area of heterogeneous enhancement (*arrows*) ultimately proven to be recurrent myxofibrosarcoma in the muscle flap; this tumor was not clinically palpable. It should be noted that because of the tumor matrix and its idiosyncratic growth pattern, myxofibrosarcoma recurrence may exhibit little or no internal enhancement [30], and may be mistaken for post-operative collection or radiation effects

It is important to distinguish planned from unplanned excisions when evaluating prognosis of STS recurrence. Because of surgeon inexperience, misleading clinical findings, or a deceptive radiological appearance, STS may be removed as an unplanned excision (UPE), without the goal of achieving tumor-free margins, in up to 30–50% of STS cases [7]. Compared with planned excisions, patients with UPE generally present at stage I–II disease (64% vs 40% of cases; $p < 0.05$), smaller tumor size (5 vs 12 cm; $p < 0.05$), and are more likely to have an intermediate- or high-grade sarcoma [42–44]. Furthermore, unplanned excisions may be performed in a piecemeal fashion, resulting in contamination of the surgical bed. Consequently, UPE of STS have higher LR rates and decreased disease-specific survival rates, as opposed to planned excisions [45].

Neoadjuvant and adjuvant therapy

The incidence of metastatic disease after successful local control of the primary tumor increases to 40–50% with a tumor size >5 cm [39, 46]. In a study involving 316 patients with STS, the 5-year survival rates for distant metastases in high-grade tumors, based on tumor size, was 84, 70, 50, and 33% for tumor size subgroups of <5 cm, 5–10 cm, 10–15 cm, and >15 cm respectively [47]. Although still controversial, data such as these support the use of neoadjuvant chemotherapy in an attempt to reduce disease-specific mortality in STS. The extent to which neoadjuvant chemotherapy reduces local recurrence rates is difficult to define, but can aid in down-staging the primary tumor, inducing tumor shrinkage away from vital structures such as nerves and vessels, and facilitating wide surgical margins.

Radiation therapy (RT) may be administered in the neoadjuvant or adjuvant setting, depending on a variety of considerations, including patient and surgeon preference. In general, a neoadjuvant strategy leverages a definable tumor target to enable smaller treatment volumes and a lower dose to adjacent displaced tissues; surgeons, on the other hand, may prefer post-operative radiation to reduce the risk for operative complications, such as infection and wound dehiscence (Fig. 5) [48, 49]. Several prospective, randomized, controlled trials (RCTs) using external beam RT or brachytherapy for STS treatment have shown improved local control after treatment, although survival did not improve [37, 50–52]. In two retrospective studies

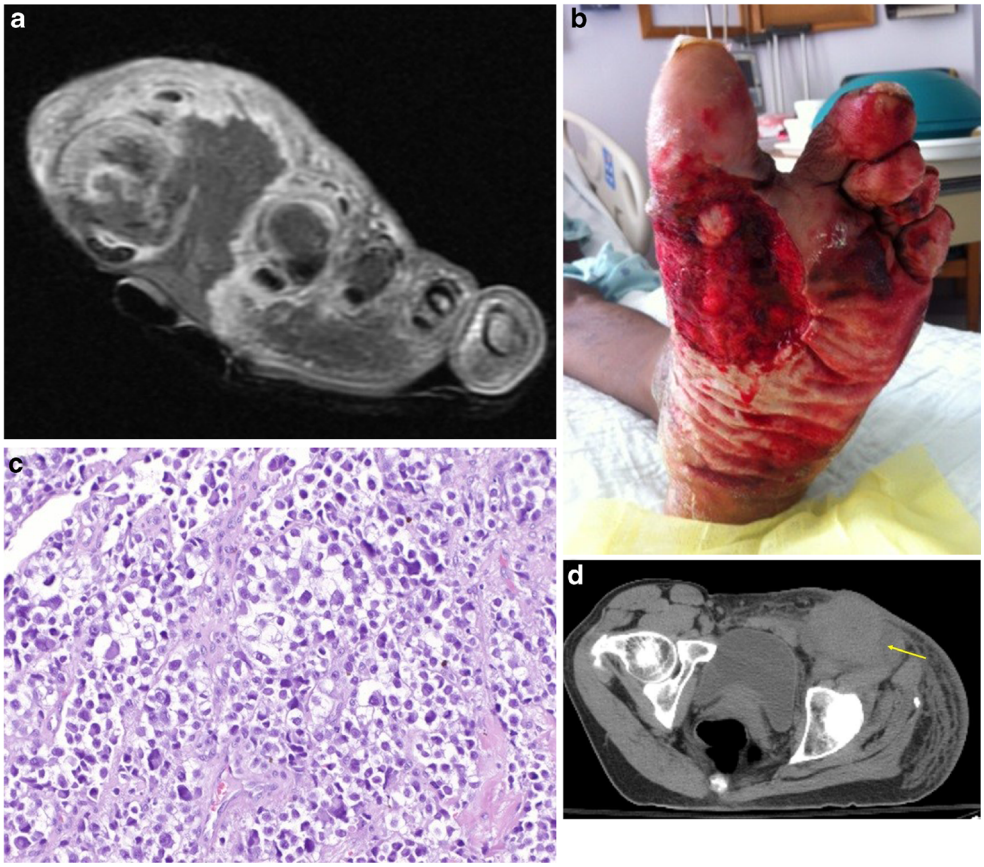

Fig. 3 A 47-year-old man with fungating clear cell sarcoma of the foot also highlights tumor-specific patterns of recurrence and metastasis. **a** Coronal post-contrast fat-suppressed T1-weighted image shows the fungating mass with open plantar ulceration, and osseous erosion into the plantar aspect of the proximal phalanx of the great toe. Lack of enhancement centrally is consistent with spontaneous tumor necrosis or abscess formation. **b** Corresponding gross photo. **c** Hematoxylin and eosin showing histology of clear-cell sarcoma, with nests of epithelioid tumor cells and characteristic clear cytoplasm. **d** Axial unenhanced CT obtained approximately 1 year after multiple recurrences following both Syme amputation and below knee amputations (not shown) revealed a third recurrence in a large inguinal node metastasis (*arrow*). Clear-cell sarcoma is one of the few sarcomas with a propensity to metastasize via the lymphatics, requiring surveillance of the draining nodal basins

involving 174 patients (high- and low-grade sarcoma) who received neoadjuvant or adjuvant RT, results showed a decreased risk of LR in high-grade STS patients (p= 0.005), improved recurrence-free survival (p = 0.069) and OS (p = 0.003) [53], and that neoadjuvant RT provided similar rates of local control compared with adjuvant RT [54]. In a retrospective review of 94 patients with extremity STS, there was no difference in the rate of LR, distant metastasis, or death in patients who received neoadjuvant and adjuvant radiation therapy versus neoadjuvant therapy alone ($p < 0.05$) [55]. This supports the concept that neoadjuvant RT does not necessitate additional RT post-operatively.

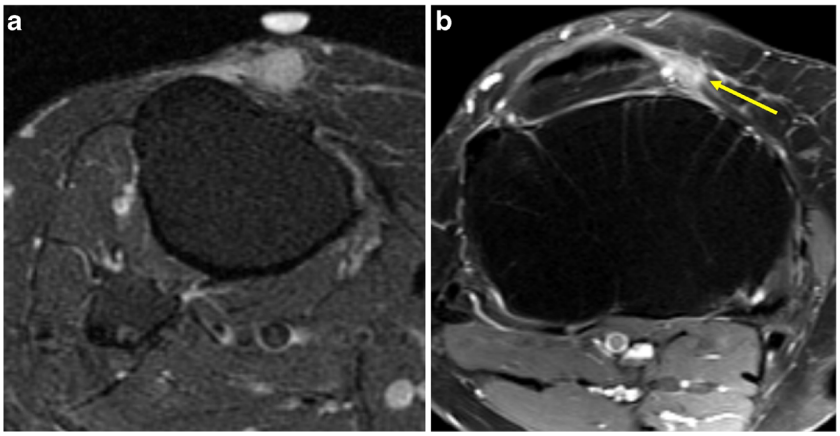

Fig. 4 A 69-year-old woman with an indeterminate soft-tissue mass in the anterior pretibial soft tissues, highlighting how unplanned excision increases risk of local recurrence (LR). **a** Pre-operative axial fat-suppressed proton density-weighted (PD) image shows the small 1.5-cm mass in the pretibial subcutaneous soft tissues. The patient underwent unplanned excision at an outside facility. **b** Axial post-contrast fat-suppressed T1-weighted image from routine surveillance MRI 3 years later revealed nodular enhancement in the surgical bed (*arrow*) along the inferior medial patellar retinaculum, which was subsequently biopsied and confirmed as sarcoma recurrence. Morphologically, the sarcoma was of intermediate grade, and resembled a variant of synovial sarcoma, malignant myoepithelioma or malignant glomus tumor; because immunohistochemical and genetic studies were inconclusive, the final pathology was that of an unclassified sarcoma

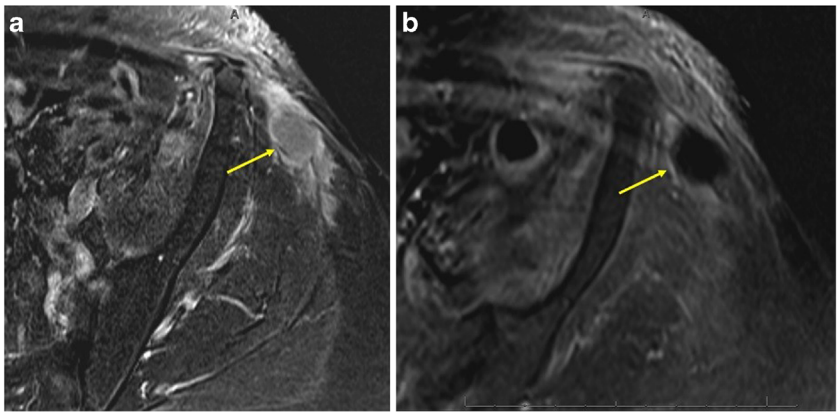

Fig. 5 A 48-year-old man with locally recurrent inflammatory fibroblastic/myofibroblastic sarcoma in the lateral gluteal soft tissues, highlighting this tumor subtype's aggressive biological behavior and infiltrative growth pattern. **a** Axial subtraction post-contrast fat-suppressed T1-weighted image obtained 3 months post-operatively shows the enhancing 5-cm, locally recurrent sarcoma with ill-defined peritumoral enhancement in the adjacent soft tissues (*arrow*). Although the enhancing tails are nonspecific and could be due to postoperative changes, tumor extension, or a combination of both, they are similar to those seen in myxofibrosarcoma, and when composed of tumor impede margin-free resection, increasing the risk for local recurrence (closest margin had been 3 mm at original resection). **b** Axial subtraction post-contrast fat-suppressed T1-weighted image after radiation therapy shows no central enhancement (*arrow*), indicative of complete tumor necrosis. Responses like this buttress the belief that adjuvant radiation reduces the risk of local recurrence by eradicating residual microscopic viable tumor after STS excision, although this has been difficult to prove empirically in unplanned excisions

The practice of adjuvant RT for planned excisions of intermediate- or high-grade STS is well-adopted, whereas it remains unestablished for UPE [56–59]. DeLaney et al. showed that STS patients ($n = 154$) with positive margins after surgery who received >64 Gy had higher 5-year local control, disease-free survival, and OS rates of 85, 52.1, and 67.8% versus 66.1, 41.8, and 62.9% if given <64 Gy ($p < 0.04$) respectively[60]. Several studies have shown that although adjuvant RT, in the absence of tumor bed excision, is not optimal management for preventing LR [57–59], its use in conjunction with tumor bed excision demonstrates improved local control [59, 61]. Thus, even in the event of aggressive tumor bed excision of high-grade STS with adjuvant RT, local control is not equivalent to planned primary excision and adjuvant RT [59].

Imaging modality

According to the American College of Radiology (ACR) Appropriateness Criteria guidelines, magnetic resonance imaging (MRI) is the most appropriate imaging test for LR of malignant or aggressive musculoskeletal soft-tissue tumors [62], ideally with gadolinium contrast enhancement [63–67]. However, this recommendation is not without debate, with several studies showing a lack of clear benefit [11–14, 68–70]. For instance, in a retrospective cohort of 168 patients, Cheney et al. found that only one clinically unsuspected STS recurrence was discovered by surveillance MRI, the remainder being identified by the patient or clinician on physical examination [11]. On the other hand, Chou et al. reported that in their series 3 out of 6 recurrences were clinically unsuspected, and were detected at routine MRI surveillance [71]. Advanced imaging sequences can supplement standard MRI protocols, including functional MRI with dynamic contrast enhancement (DCE) and diffusion-weighted imaging (DWI), to increase the sensitivity and specificity in identifying LR [63]. Positron emission tomography (PET) may also play an important role in local surveillance, particularly as a problem-solving modality in cases where MRI findings are equivocal, or where MRI is contra-indicated or may be nondiagnostic owing to metal artifact [72–74].

The use of MRI after surgical resection of an STS is to help differentiate recurrent tumor from post-surgical seroma, hematoma, inflammation, and scarring [11, 12]. Postoperative changes in the surgical bed can manifest characteristics similar to those of recurrence with conventional T1-weighted, T2-weighted, and static post-contrast sequences [63]. The complete absence of fluid signal in the surgical bed is a specific, if infrequently observed, indicator of no recurrence [66, 75]. Occasionally, sarcoma recurrence may demonstrate low signal intensity on fluid-sensitive images [76]. Tumor recurrence can be characterized by areas of architectural distortion on T1-weighted sequences, and intravenous contrast medium can improve tumor conspicuity by revealing nodular or mass-like areas of enhancement [76]. Chou et al. showed that the incremental value of administering contrast medium was training-level-dependent, but primarily driven by increased sensitivity for recurrence detection, ranging from 69% without contrast medium, to 90% when contrast-enhanced sequences were reviewed [71]. Although Chou et al. specifically assessed for the presence of nodular or mass-like enhancement on post-contrast sequences as an indicator of recurrent tumor, low specificity and sensitivity of nodular enhancement was recently demonstrated in the setting of previous UPE [77].

Radiologists should be aware that not all tumors recur as nodular tissue or masses; both undifferentiated pleomorphic sarcoma and myxofibrosarcoma may recur as plaque-like "tails" of tumor on MRI [30, 78].

Fludeoxyglucose positron emission tomography (FDG-PET)/CT has shown high sensitivity in the detection of distant recurrence [79], but findings are often nonspecific in the operative bed of the resected primary tumor owing to post-surgical or post-radiation inflammatory changes that can persist for years following treatment. In two meta-analyses involving studies evaluating the use of PET/CT for STS, PET/CT was found to be superior for the detection of nodal/soft-tissue metastases, as opposed to CT or MRI [80, 81].

The diagnostic accuracy of ultrasound in the detection of tumor recurrence has been reported with an overall sensitivity and specificity of 0.83–0.88 and 0.93–0.94 respectively, although no studies have shown the superiority of the use of ultrasound over MRI in LR surveillance when the two imaging modalities were compared [82, 83]. Ultrasound may be beneficial in the presence of hardware and if recurrence is clinically suspected. Doppler interrogation may aid in distinguishing recurrent tumor from avascular fibrous tissue at the postoperative site [62], although hypovascular tumor recurrence could mimic benign findings.

Frequency and duration of surveillance scans for local recurrence

With the advent of multimodality therapy and limb-sparing surgery, LR rates have been reported to be as low as 9–12% at 5 and 10 years post-surgical treatment [84]. The ACR Appropriateness Criteria for local surveillance follow-up of malignant or aggressive soft-tissue tumors recommends that follow-up is, interestingly, agnostic to histological tumor grade. A typical strategy consisting of cross-sectional imaging every 3–4 months for the first 3 years, then every 6 months up to the 5th year, and annually throughout the 10 years after treatment [85, 86], is structurally similar to that advocated by the ACR [73]. The fact that most recurrences occur within 2 years following treatment justifies more intensive surveillance early in the post-treatment period, particularly in high-risk patients. Although late LR may be observed beyond 10 years and lifetime recurrence risk never vanishes, discontinuing surveillance scans 5–10 years after treatment in a low-risk context would be a reasonable approach for most patients [62]. A summary of recommendations for surveillance is provided in Table 1, although it must be re-emphasized that such guidelines allow for variation as dictated by clinical judgment.

Several recent studies even suggest that clinical examination alone may be sufficient for local surveillance. In a retrospective review involving 174 patients with STS of the limb who underwent follow-up by oncologists in a single center

Table 1 Surveillance scan recommendations for extremity soft-tissue sarcoma local recurrence and pulmonary metastasis from The National Comprehensive Cancer Network (*NCCN*) [87], American College of Radiology (*ACR*) [62], MD Anderson Cancer Center (*MDACC*) [88], and the European Society for Medical Oncology (*ESMO*)/European Sarcoma Networking Group (*ESNG*) [85]. Some guidelines offered the caveat that although MRI and chest CT may detect local recurrence (*LR*) and lung metastases earlier, benefit and cost-effectiveness have not been proven. Moreover, they stress that surveillance considerations should be individualized, and may be influenced by externalities such as the reliability of the physical examination, and the initial depth of the tumor

	NCCN	ACR	MDACC	ESMO/ESNG
Modality	Clinical; supplemented with "periodic imaging (MRI, CT, or ultrasound)… based on the estimated risk for locoregional recurrence"	MRI favored over PET, CT, ultrasound	Low risk: clinical High risk: MRI, CT, or ultrasound	MRI or clinical
LR frequency	Low risk: q3–6 months for 2–3 years, then annually High risk: q3–6 months for 2–3 years, then q6 months for 2 years, then annually	q3–6 months	Low risk: q3–4 months for 2 years, then q4–6 months for 2 years, then yearly High risk: MRI, CT, or ultrasound q3 months for 2 years, then q4 months for 2 years, then q6 months for year 5, then annually	Low risk: q4–6 months for 3–5 years, then annually High risk: q3–4 months for 2 years, then q6 months up to year 5, then annually (total of 8–10 years)
Chest modality	Chest X-ray or CT	CT	Chest X-ray	Chest X-ray or CT
Chest frequency	Low risk: q6–12 months High risk: q3–6 months for 2–3 years, then q6 months for 2 years, then annually	q3–6 months	Same as for local site	q3–4 months for 2 years, then q6 months for 1 year, then q6–12 months up to year 5, then annually

from 2003 to 2009, local recurrences were detected clinically in 30 of the 31 patients, whereas MRI detected only 1 case [13]. Another retrospective study found that surveillance MRI infrequently detected asymptomatic LRs following limb-salvage surgery with RT, and should be reserved for tumor sites that are inaccessible on clinical examination [11]. These data appear to challenge the notion that active imaging surveillance consistently results in earlier recurrence recognition, although an alternative interpretation that surveillance imaging should be even more frequent for the highest risk patients could be drawn. Large prospective studies would be required to establish improved outcome with frequent radiological follow-up, or conversely, that clinical examination alone offers parity versus imaging surveillance.

Distant metastasis surveillance

In a study at MDACC, factors that were predictive of metastatic recurrence included: a tumor size >5 cm, a high-tumor grade, and specific histopathology subtypes (leiomyosarcoma, rhabdomyosarcoma, synovial sarcoma, or epithelioid sarcoma) [16]. According to the ACR Appropriateness Criteria for the evaluation of metastatic disease to the lung from a primary sarcoma, high-risk patients should undergo follow-up chest CT without contrast medium every 3–4 months for the first 2–3 years, then every 6 months for up to 5 years, and then annually [62]. Low-grade STS patients should have CT without contrast surveillance scans every 4–6 months for 3–5 years, then annually. The NCCN bases surveillance scans on the stage of the tumor, with stage I STS patients receiving chest imaging every 6–12 months for 2–3 years, stage II–IV patients receiving chest imaging every 3–6 months for 2–3 years, then annually [87].

In 70–80% of STS cases, metastasis is to the lung; however, there are notable exceptions to this pattern of metastatic spread [89, 90]. Myxoid liposarcomas and ASPS can present with extrapulmonary metastases to the bone (mainly the spine), retroperitoneum, abdomen, muscles, and paraspinal soft tissue [91, 92]. Additionally, myxofibrosarcoma may metastasize to the pleura, adrenal glands, soft tissue, and mesentery [30]. Given this specific metastasis spread, surveillance includes MRI of the spine, bone scintigraphy, and CT abdomen/pelvis at the discretion of the referring physician [93, 94]. Leiomyosarcomas and dedifferentiated liposarcomas can metastasize to the soft tissues, lung, and the liver. Although retroperitoneal liposarcomas (most often the well-differentiated/dedifferentiated subtypes) recur locally or are never able to be completely excised, CT is an important tool to monitor the dedifferentiated soft-tissue density component in particular [95].

As mentioned above, several histological types have a propensity to metastasize to lymph nodes, particularly rhabdomyosarcoma, angiosarcoma, clear-cell sarcoma, and epithelioid sarcoma; in fact, failure to assess nodal status in these subtypes has been associated with inferior OS rates [96]. The use of lymphoscintigraphy in conjunction with a sentinel lymph node biopsy can be used in the staging work-up of these STS [97], and their draining nodal basins should be carefully scrutinized on follow-up surveillance imaging. Ecker et al. [97] showed that standardized approaches to regional lymph node examinations showed a significant difference in median OS following pathological identification of nodal disease for epithelioid sarcoma ($p = 0.001$) and clear cell sarcoma ($p < 0.001$), supporting the notion that nodal evaluation can be considered a quality measure in the delivery of care for this subset of sarcoma patients [96], although it should be noted that given their relative frequency among sarcoma subtypes, leiomyosarcoma, liposarcoma, and undifferentiated pleomorphic sarcoma still account for the largest absolute number of nodal metastases [98].

In patients with a primary STS, a CT of the chest without contrast medium should be performed to evaluate for pulmonary metastasis at initial staging. Several studies show that spiral CT is the most accurate imaging study for evaluating lung metastases [80, 81]. Depending on risk factors, surveillance chest CT can be performed as frequently as every 3–6 months for the first 10 years, although less intensive CT surveillance, or strategies employing radiographs staggered with CTs may be adopted [62, 85].

In the event that the MRI is equivocal, FDG-PET/CT may be appropriate and useful [99]. It is particularly useful when suboptimal imaging is attained with MRI, owing to orthopedic hardware. The role of FDG-PET/CT beyond a problem-solving tool has not been widely supported in the literature [99]. As noted previously, the main drawback of PET/CT is the inability to use it in the first 3 postoperative months because of hypermetabolic changes post-surgically [99].

Patient outcomes

The rate of LR increases with STS stage. In a study by MSKCC evaluating outcomes and stage, patients with stage I lesions ($n = 137$) had a 12% LR rate, disease-free survival (DFS) of 86%, and OS of 90%. Of those with stage II disease ($n = 491$), 18% had LR, the DFS was 72%, and the OS was 81%. The rate of LR increased to 17% for stage III ($n = 469$) patients, with decreased DFS (52%) and OS (56%) [100].

The impact of STS LR on survival has been variably estimated in the literature [99]. Several studies have found that LR and microscopically positive surgical margins were directly correlated with worsened survival [10, 15, 101], and achievement of negative margins at definitive surgery was shown to improve 5-year survival (47%) versus patients with positive margins (36%; $p = 0.01$) [102]. OS has been shown to depend on local control of tumor, and local relapse was influenced by surgical margins, radiation therapy, and histological subtype

[9]. Although LR has been associated with decreased OS (hazard ratio 2.1 vs no LR) [103], Alamanda et al. offered conflicting evidence that local recurrence did not affect disease-specific survival [104]. Even if the premise that routine imaging surveillance infrequently detects clinically unsuspected local recurrence is accepted, many best practice guidelines are predicated on the belief that early recognition and eradication of locally recurrent disease ultimately improves quality of life, even if survival benefit has been difficult to firmly establish.

The STS has a distant metastatic rate of 22–36% [50, 105], most often to the lung, with an average OS rate of 12 months once metastatic [106]. One study ($n = 443$) found that patients with LR of STS were at an increased risk for distant metastasis (hazard ratio [HR] = 8.4; 95% CI, 4.3–16.5; $p < 0.001$) and death (HR = 3.4; 95% CI, 2.1–5.6; $p < 0.001$) [107]. Metastatic disease to the lymph nodes is associated with a 5-year OS of 20–60% [108–110]. The 5-year survival for STS patients who develop pulmonary metastases is approximately 10% and it is about 15–52% for patients with a disease-free interval [111–113].

Conclusion

Close monitoring after STS resection is warranted to detect LR, with the hope that early detection will facilitate local control, decrease risk of metastatic spread, and ultimately improve chances of re-achieving disease-free status. Although there is considerable variation in the recommended frequency of surveillance scanning, high-risk patients will benefit most from more intensive surveillance schedules (i.e., at least every 3 months during the first 2 years after initial local control). Considering both intrinsic (such as tumor histology, grade, and size) and extrinsic (margin status and surgical bed contamination) risk factors helps to risk-stratify patients in a more targeted approach to achieving favorable clinical outcomes.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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