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MINIREVIEWS

New trends in the surgical management of soft tissue sarcoma: The role of preoperative biopsy

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Abstract

Soft tissue sarcoma (STS) accounts for 1% of all malignant neoplasms in adults. Their diagnosis and management constitute a challenging target. They originate from the mesenchyme, and 50 subtypes with various cytogenetic profiles concerning soft tissue and bones have been recognized. These tumors mainly affect middle-aged adults but may be present at any age. Half of the patients have metastatic disease at the time of diagnosis and require systemic therapy. Tumors above 3-5 cm in size must be suspected of potential malignancy. A thorough history, clinical examination and imaging that must precede biopsy are necessary. Modern imaging techniques include ultrasound, computed tomography (CT), new magnetic resonance imaging (MRI), and positron emission tomography/CT. MRI findings may distinguish low-grade from high-grade STS based on a diagnostic score (tumor heterogeneity, intratumoral and peritumoral enhancement). A score ≥ 2 indicates a high-grade lesion, and a score ≤ 1 indicates a low-grade lesion. For disease staging, abdominal imaging is recommended to detect early abdominal or retroperitoneal metastases. Liquid biopsy by detecting genomic material in serum is a novel diagnostic tool. A preoperative biopsy is necessary for diagnosis, prognosis and optimal planning of surgical intervention. Core needle biopsy is the most indicative and effective. Its correct performance influences surgical management. An unsuccessful biopsy means the dissemination of cancer cells into healthy anatomical structures that ultimately affect resectability and survival. Complete therapeutic excision (R0) with an acceptable resection margin of 1 cm is the method of choice. However, near significant structures, *i.e.*, vessels, nerves, an R2 resection (macroscopic margin involvement) preserving functionality but having a risk of local recurrence can be an acceptable choice, after informing the patient, to prevent an unavoidable amputation. For borderline resectability of the tumor, neoadjuvant chemo/radiotherapy has a place. Likewise, after surgical excision, adjuvant therapy is indicated, but chemotherapy in nonmetastatic disease is still debatable. The five-year survival

rate reaches up to 55%. Reresection is considered after positive or uncertain resection margins. Current strategies are based on novel chemotherapeutic agents, improved radiotherapy applications to limit local side effects and targeted biological therapy or immunotherapy, including vaccines. Young age is a risk factor for distant metastasis within 6 mo following primary tumor resection. Neoadjuvant radiotherapy lasting 5-6 wk and surgical resection are indicated for high-grade STS (grade 2 or 3). Wide surgical excision alone may be acceptable for patients older than 70 years. However, locally advanced disease requires a multidisciplinary task of decision-making for amputation or limb salvage.

Key Words: Soft tissue sarcoma; Soft tissue tumors; Sarcomas; Oncology; Preoperative biopsy; Surgical management

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Core Tip: The diagnosis and treatment of soft tissue sarcoma are multidisciplinary tasks, and wide surgical resection is an absolute necessity. Modern imaging, especially magnetic resonance imaging, is valuable, and preoperative core needle biopsy is the most indicated and effective diagnostic tool. Its correct planning affects surgical management because the opposite means dissemination of cancer cells into healthy anatomical structures influencing resectability and survival. New therapeutic modalities, including chemoradiation, biological agents and immunotherapy, can improve the outcomes of the main surgical management. In any case, the management policy is personalized.

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INTRODUCTION

Soft tissue sarcomas (STSs) are rare tumors that originate from the mesenchyme (embryonic mesoderm) and affect children more often than adults[1]. They represent aggressive lesions accounting for approximately 1% of all adult malignancies and 7% of pediatric neoplasms[2,3]. Their incidence is calculated to affect 4-5 individuals *per* 100000 *per* year in Europe[4]; annually in the United States, there have been approximately 10000 new cases of soft tissue and bone sarcomas[5]. Likewise, in 2019, approximately 13000 new cases of ST and bone sarcomas were recognized in the United States with a main location (60%) in the limbs and trunk[6]. A French nationwide registry showed a continuing increase in incidence that is higher than reported and varies among different countries; however, the pathology evaluation should be made by sarcoma experts to avoid misdiagnosis which can occur in up to 30% of cases[7].

Limb STS has a rather better prognosis than retroperitoneal or pelvic STS. The most predominant pathologic type of STS is liposarcoma and leiomyosarcoma in adults and rhabdomyosarcoma in children[4]. Overall, 50 histopathologic subtypes with various cytogenetic profiles concerning soft tissue and bones have been recognized. The location in the vast majority concerns limbs, trunk, head and less often retro peritoneum and abdominal cavity[2]. These tumors mainly affect middle-aged adults but may be present at any age. Half of the patients have metastatic disease (first in the lungs and second in the liver) and intermediate-high grade STS at the time of diagnosis and require systemic therapy. The 5-year overall survival is approximately 55%[7-9].

Tumors above 3-5 cm in size, fast growing, deeply located, solid, cumbersome, possibly accompanied by palpable lymph nodes and causing or not causing pain must be suspected of potential malignancy. Then, an imaging evaluation [ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI)] is required and must precede biopsy[10]. Preoperative biopsy (percutaneous core needle, preferably) is a crucial diagnostic tool since there has been progress in planning multimodality management, which ensures improved outcomes[6,11]. The Ki-67 proliferation index has been proposed as a prognostic biomarker that, in addition to survival prediction, may determine the indication for lung or liver metastasectomy in carefully selected patients, improving the treatment[12].

Surgical intervention constitutes the cornerstone of management aiming at therapeutic wide excision with adequate margins[2]. Recurrence occurs in up to 50% of cases after surgery, mainly in the lungs[6]. Any effort must be made for limb salvage to avoid amputation. Neoadjuvant or adjuvant radiotherapy or chemotherapy has contributed to current progress[2]. Likewise, immunotherapy is a promising novel

therapeutic option[1]. Young age is the only known risk factor for distant metastasis within 6 mo following curative resection[13]. Diabetes mellitus has a negative influence on the clinical outcome after therapeutic excision of STS[14].

Modern imaging, including positron emission tomography (PET)/CT and regular follow-up (every 3 mo for the first 3 years, every 6 mo for the following 2 years and then once every year for the next 10 years), nomograms and artificial intelligence for local recurrence or distant metastasis after surgery, have assisted further and improved the outcome[4,12].

In this narrative review, we highlight the current data on the diagnosis and treatment of STS, providing comprehensive, complete and modern knowledge to manage them.

DIAGNOSIS

A thorough history, clinical examination and imaging are necessary requirements. Modern imaging techniques include US, CT, new MRI, and PET/CT. Imaging findings of limb STS correlate with the histopathologic findings[15]. According to the United Kingdom guidelines for the management of STS, any soft tissue lump more than 5 cm in size and, most importantly, increasing rapidly in size or painful must be considered malignant until assessed otherwise on imaging. Therefore, immediate US is mandatory. If the lesion seems to be benign, then the investigation will be terminated. Otherwise, a CT will follow and then MRI if it is indicated. When positive for malignancy or equivocal imaging findings exist, a preoperative biopsy will always be performed to confirm the diagnosis of STS[8], as described in detail below.

However, MRI is currently the method of choice. It provides accurate location, architecture, and vascularization of the tumor and determines the relationships with neighboring vital anatomic structures to plan the operative strategy and the extent of resection[16]. MRI findings may also distinguish low-grade from high-grade STS based on a diagnostic score (tumor heterogeneity, intratumoral and peritumoral enhancement). A score of 2 or 3 indicates a high-grade lesion, and a score of 0 or 1 indicates a low-grade lesion[16] . MRI radiomics and machine learning may accurately predict the tumor grade[17]. MRI is useful not only because it can guide preoperative biopsy[6] but also because high-grade sarcomas need neoadjuvant chemoradiation therapy[16]. It is known that preoperative biopsy may underassess the real grade of the definite complete specimen pathology due to the heterogeneity of STS[17]. Additionally, novel multiparametric MRI has provided promising results for the selection of patients who need neoadjuvant radiotherapy[9]. Preoperative imaging assessment of margin infiltration degree is essential for STS prognosis. MRI using the radiomics mode is a novel promising tool[18]. In addition, MRI using a deep learning radiomics nomogram can accurately predict preoperative lung metastases[19].

Preoperative imaging, pathologic subtypes and molecular findings are crucial. Mutations in the tumor suppressor genes, *i.e.*, the *Rb1* gene (retinoblastoma 1) and *TP53* gene (tumor protein 53) can exist [12]. Liquid biopsy by detecting genomic material in serum is a novel diagnostic, prognostic and staging tool. Genetic material mainly from blood but also from other body fluids (cerebrospinal fluid, saliva, urine, or feces) may be useful for the discovery of circulating tumor cells, cell-free DNA, exosomes, or metabolites[2]. These biomarkers provide valuable information regarding the tumor genetic profile and the status of the disease to ensure optimal monitoring and to identify the mechanisms implicating treatment resistance. The preliminary results are promising despite the technical difficulties, and liquid biopsy could replace invasive tissue biopsy in the future[20]. The heterogeneity of sarcomas poses further prognostic limitations. Furthermore, circulating tumor noncoding RNAs are promising biomarkers. However, all the above research efforts are in the preclinical stage for sarcomas[21]. In addition, the genomic profile may determine the adjuvant treatment choices[22].

For disease staging, the following imaging is necessary: (1) CT chest to detect lung metastases, since they are the most common metastatic involvement; and (2) CT abdomen to detect early hepatic or pelvic metastasis, particularly for the lower limb location of the primary focus to detect retroperitoneal lymph node involvement[4,8]. Based on relevant indications, the following imaging is recommended: (1) Whole-body scintigraphy for possible bone metastases; (2) CT or preferably MRI brain for possible metastases; (3) Whole-body MRI may be useful for occult metastases[8]; and (4) Likewise, for this reason, 18F-Fluoro-2-deoxyglucose PET/CT is currently more often in use[3]. However, it is absolutely indicated before making decisions for amputation or after postoperative recurrence[8]. After neoadjuvant radiation therapy, approximately 20% of patients with limb and trunk STS require a change in the management strategy because of distant lung metastases. The followed scheme includes a total dose of 50 Gy in 25 sessions of 2 Gy within a period of five weeks and then surgical intervention after an elapse of approximately ten weeks. Therefore, chest CT is reasonable for restaging after such a long time of 15 wk[23].

Histopathologic diagnosis is based on morphological, immunohistochemical and molecular pathologic features[10]. It should be made according to the latest World Health Organization classification of soft tissue tumors. Liposarcoma, leiomyosarcoma, myxofibrosarcoma, pleomorphic undifferentiated sarcoma and synovial sarcoma constitute 75% of all STSs[15]. A second opinion of a

pathologist expert may be valuable. There are three malignancy grades based on differentiation, necrosis and mitotic rate according to the Federation of the French Cancer Centres histological grading criteria for STS[8,10]. These parameters are scored 1 to 3 for differentiation and mitotic index and 0 to 2 for necrosis. A 3-grade system is obtained by summing the scores obtained for each of these 3 parameters, as shown in Table 1[8]. The Ki-67 proliferation index grading system may be useful for the evaluation of the histological grade of STS[24]. The staging of STS is based on the Tumor-Node-Metastasis classification system according to the American Joint Committee on Cancer 8th edition, as shown in Table 2[25].

PREOPERATIVE BIOPSY

Diagnosis and management of STS should be performed by experienced centers[26]. A preoperative biopsy is necessary to establish the diagnosis after the imaging evaluation. Imaging should be performed first to avoid any interference with the anatomical integrity of the region by the biopsy manipulations. The biopsy ensures diagnosis of histological type and staging, predicts the biological behavior of the tumor, indicates the need for preoperative (neoadjuvant) or even intraoperative radiation treatment, and neoadjuvant systemic chemotherapy, determines the best planning of the operative strategy and offers better patient information (reassuring) by weighing the risks and expectations[8,10,11,27]. A preoperative frozen section for immediate diagnosis is not recommended. It has no practical value since the regular review of a core needle biopsy (CNB) will safely establish the diagnosis [10].

The primary method of the first choice is CNB with needles of 14-18 gauges. Several needle samples (4-10) are required to increase the maximum chance of a correct diagnosis[6,8,10,28]. It was performed under imaging guidance (US, CT) and achieved adequate specimens for complete histopathologic evaluation along with immunohistochemical assays. Most cases are performed under local anesthesia, but sedation may be required in some cases. The complications (hemorrhage or infection) are minimal [11]. A large series from Royal Marsden Hospital United Kingdom including 530 cases of CNB performed under local anesthesia showed that it was diagnostic in 93% of cases, needed to be repeated in 7% of cases, had a complication rate of 0.4%, had a diagnostic accuracy rate of 97.6% in distinguishing STS from benign lesions (sensitivity of 96.3%, specificity of 99.4%, positive predictive value of 99.5%, negative predictive value of 95.1%) and had a grade accuracy rate of 86.3%[29]. Adequate tissue samples must be obtained in different directions within the tumor through a single skin incision; to avoid rare needle tract recurrence, the selection of the biopsy site should be planned so that it is included in the subsequent resection, if required[29].

Preoperative CT-guided CNB is accurate and valuable for intraabdominal and retroperitoneal sarcomas[30]. A recent study from the United States based on the National Cancer Database including 2620 patients who underwent surgery for nonmetastatic retroperitoneal sarcoma showed that preoperative biopsy (performed in 42.4% of cases) was proven useful with better outcomes and improved survival[31].

Fine needle aspiration does not provide tissue samples and offers cytologic rather than histologic information. Its utility is limited only to recurrence cases of an already known STS[11]. Open biopsy techniques include incisional biopsy by removing a small part of the tumor. It is associated with a 2% possibility of complications (inflammation, hematoma) but most importantly dissemination of malignant cells and delay in the treatment. Its rare indication is limited to failure of CNB. Excisional biopsy by whole tumor removal does not have any place in suspected STS but only in superficial small soft tissue tumors (less than 2 cm in size), which have minimal malignant potential. The basic principles of open biopsy are meticulous hemostasis and avoidance of drain placement[8,11].

MANAGEMENT

The management of abdominal STS at an experienced center with a multidisciplinary approach provides improved outcomes and better prognosis[32]. The initial referral, even based on suspicion, to such a center is of great importance to ensure the optimal chance in accurate diagnosis and proper management[22]. Surgery is the standard treatment and must be performed by an experienced surgeon. Wide excision with adequate margins at least 1 cm or even 2 cm, free of involvement, constitutes the operative target to achieve a residual zero (R0) resection[2,33-35]. However, vital neighboring anatomical structures may sometimes restrict the resection margin, and microscopic infiltration may be found within it (R1 resection). Further treatment is needed for positive resection margins to restrict recurrence[36]. It has been reported that high-grade tumors have a negative effect on overall survival, but resection margins do not. The 5-year overall survival was 71.1% for R0 resection and 70.2% for R1 resection[37]. Lymph node metastases are rare in STS, and sentinel lymph node biopsy and lymphadenectomy are limited and debatable[38]. Neoadjuvant radiotherapy and wide excision have been widely used but are associated with wound complications[39], reaching up to 39%[40]. This rate is limited to

Table 1 Federation of the French Cancer Centres histological grading criteria

Differentiation (score)	Necrosis (score)	Mitotic count (score)
Well (1)	Absent (0)	$n < 10^1$ (1)
Moderate (2)	< 50% (1)	$n = 10–19^1$ (2)
Poor (anaplastic) (3)	≥ 50% (2)	$n \geq 20^1$ (3)

[1]Number of mitoses *per* 10 high power fields.
After summing the three scores, grade 1 is defined as a total score of 2 or 3; grade 2 as a total score of 4 or 5; and grade 3 as a total score of 6 to 8.

Table 2 American Joint Committee on Cancer classification and staging for soft tissue sarcoma, 8th Edition

TNM classification	Stage
T1: Tumor ≤ 5 cm	IA: T1; N0; M0; G1
T2: Tumor > 5 cm and ≤ 10 cm	IB: T2, T3, T4; N0; M0; G1
T3: Tumor > 10 cm and ≤ 15 cm	II: T1; N0; M0; G2/3
T4: Tumor > 15 cm	IIIA: T2; N0; M0; G2/3
N0: No regional lymph node metastasis or unknown lymph node status	IIIB: T3, T4; N0; M0; G2/3
N1: Regional lymph node metastasis	IV: Any T; N1; M0; any G Any T; any N; M1; any G
M0: No distant metastasis	
M1: Distant metastasis	

G expresses the histological grading sum score. TNM: Tumor-Node-Metastasis.

half at experienced centers[40]. Neoadjuvant radiotherapy tends to replace adjuvant radiotherapy and is strongly recommended[41,42]. Concurrent neoadjuvant chemoradiation therapy increases the chance of R0 resection[43]. For high-grade deep tumors, T2 or more (stage II or III), wide excision and adjuvant radiation therapy (external beam 60-76 Gy) for local control is the indicated policy[2,10,44,45]. Limb sparing surgery combined with radiotherapy is the current preferable method for such tumors of limbs [46]. It must precede preoperative traditional fractioned radiotherapy of 50-50.4 Gy with a daily dose of 1.8-2 Gy over 5-6 wk[47-49]. Generally, a daily dose > 2.2 Gy is usually hypofractionated radiotherapy [47]. Novel techniques for radiotherapy, including intensity-modulated radiation therapy, proton beam therapy, intraoperative electron radiotherapy and postoperative brachytherapy (*via* catheters in the surgical field), promise to decrease the side effects of standard radiotherapy while achieving better local control[2,8,10,50].

Chemotherapy with doxorubicin alone or in combination with ifosfamide is the basic scheme as a neo-adjuvant or adjuvant[2]. However, there have been conflicting aspects for adjuvant chemotherapy after R0 resection[51]. Tyrosine-kinase inhibitors (pazopanib, sunitinib, imatinib) have been indicated in some specific types[2]. In advanced metastatic cases, gemcitabine has been used in combination with docetaxel, vinorelbine, or dacarbazine, but with limited results[2]. Isolated hyperthermic limb perfusion (IHLP) with tumor necrosis factor-alpha and melphalan is another proposed option for limb STS[2,52]. A recent nationwide multicenter study from the Netherlands showed that in unresectable limb STS, preoperative IHLP or neoadjuvant radiotherapy avoided both amputations with acceptable oncological outcomes[53]. Wide surgical excision alone without neoadjuvant or adjuvant chemotherapy may be acceptable for patients over 70 years of age, providing comparable survival[54]. Frail very elderly patients (more than 80 years old) can tolerate an operative intervention for limb STS well[55,56].

Overall, unplanned excisions were 18.2% among 2187 primary operations for STS in the Netherlands Cancer Registry database[57]. It is known that unplanned surgical excision is related to an increased risk of local recurrence despite any adjuvant oncologic therapy[58]. For this reason, reresection is an option after positive or uncertain resection margins, but it is associated with increased morbidity and residual disease, which requires complete information for the patient[59]. However, a recent large study from Japan including 4483 operations (4128 planned excisions and 355 unplanned excisions) for limb STS showed that additional excision after unplanned excision was not associated with increased mortality and local recurrence compared to planned excision[60]. Furthermore, in the case of R1 or even R2 resection, reresection in combination with perioperative radiotherapy must be considered[61]. Surgical resection of lung metastases has improved overall survival (49 mo median and 42% 5-year). However, R1 resection of the primary tumor and ≥ 2 metastases decrease it[62]. Pulmonary metastasectomy

improves the prognosis compared to conservative treatment[63].

The comprehensive assessment of recurrence risk has led to an increasing number of personalized management tools[64], including surgical operation, radiotherapy, novel promising targeted biological agents and immunotherapy (monoclonal antibodies, cellular therapies with modified T cells and natural killer cells, or vaccines)[1,2,12,65,66]. For retroperitoneal STS, aggressive surgical management has been recommended, since it showed satisfactory results for primary tumors but not for recurrence[67-70]. Likewise, for abdominal STS, surgery is the standard treatment[71]. Operative intervention and radiotherapy maximize local control[72]. For abdominal wall STS, extensive surgery is indicated for local control despite the rate but acceptability of incisional hernia[73]. For metastatic STS, systemic therapy and local control by surgical resection, usually or recently by stereotactic body radiation therapy, have been recommended[74]. MRI-guided radiotherapy is another recent alternative modality [75]. For advanced retroperitoneal liposarcoma, the most common subtype of retroperitoneal STS, treatment based on targetable molecular pathways may be the future perspective[76].

A recent systematic review showed that patients with hepatic, abdominal or retroperitoneal metastasis undergoing metastasectomy have a survival benefit for a long period of time compared with those undergoing chemotherapy[4]. A multicenter retrospective cohort study from the United States using the National Cancer Database including 8953 cases showed that younger adult patients under 40 years old had a notable proportion (14.3%) of limb STS and more challenging management. They received chemotherapy more often than radiotherapy *vs* older patients[77]. A study including 1124 patients with distant metastases at diagnosis, stage IV STS, from the United States National Cancer Database showed that metastasectomy after resection of the primary site increased survival[78]. In any case, regardless of the subsequent kind of metastasis management, primary tumor resection is necessary to improve survival[79].

Visceral obesity is common in retroperitoneal and trunk sarcoma, and it has a negative effect on surgical results but not on oncologic outcomes[80]. A recent international multicenter study using clinical data as prognostic factors of 493 patients with STS found that increased modified Glasgow prognostic score (used in various malignancies and based on preoperative C-reactive protein and albumin levels to calculate a score from 0 to 2), tumor size, grade, neutrophil/lymphocyte ratio, and recurrence were associated with reduced survival[81]. Likewise, another study found a predictive effect on survival of retroperitoneal STS using body mass index, total protein serum levels and blood white cell count by performing prognostic models[82].

The 5-year survival for limb and trunk STS was found to be 71.6% in local recurrence-free patients, 75.7% in metastasis-free and 84.7% in disease-specific[83]. The 3-year overall survival for head and neck STS was 68%, for disease specific 71% and recurrence free 61%. Higher tumor grade and tumor size greater than 5 cm were associated with reduced disease-specific survival[26].

CONCLUSION

Any suspected soft tissue lump above 5 cm in size must be investigated thoroughly, first by US and CT. For further detailed information, if needed, modern MRI prevails among the imaging modalities and constitutes the method of the first option. Preoperative CNB, always after imaging, is essential in confirming the diagnosis and determining the staging with prognosis and the optimal planning of the management policy. Liquid biopsy and genomic profiling will likely be useful in diagnosis, prognosis and treatment. A multidisciplinary approach is valuable and mandatory. Wide surgical excision with an acceptable healthy margin of 1 cm is the method of choice in management. In locally borderline tumors affecting limb vessels or nerves, modern neoadjuvant or adjuvant chemoradiation therapy may ensure limb savings by downstaging the tumor, thus avoiding amputation. Additionally, this therapy in the advanced metastatic stage improves surgical outcomes after mandatory primary tumor excision. Novel targeted biological agents and immunotherapy may contribute further. Detailed follow-up for a long time is recommended because of the outstanding possibility of recurrence, in which the chance of reresection or stereotactic radiotherapy exists. However, in any case, the management of STS should be personalized and performed by an expert team.

FOOTNOTES

Author contributions: Pavlidis TE designed research, contributed new analytic tools, analyzed data and review; Pavlidis ET performed research, analyzed data review and wrote the paper.

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