Review Article

Management of extremity soft tissue sarcomas

Ajay Puri, Ashish Gulia

Abstract

Soft-tissue sarcomas are a rare and heterogeneous group of tumors. The last few decades have seen rapid strides in surgery with function preserving alternatives for local control in these lesions becoming the norm without compromising on overall disease survival. Good functional and oncological results can be achieved with a combination of excision of the tumor, and where required, suitable adjuvant therapies. These lesions are best managed at specialty centres where the requisite multidisciplinary care can be offered to the patient to optimise results. This overview is intended as a review of current understanding and the multimodality management of these challenging tumors.

Key words: Limb salvage, multidisciplinary care, soft tissue sarcoma

Introduction

Soft tissue sarcomas are a rare and heterogeneous group of tumors, representing less than 1% of all adult malignancies. Sixty percent of soft tissue sarcomas occur in the extremities, making this the commonest site. Other locations are the trunk (19%), the retroperitoneum (15%), and the head and neck (9%).[1] Due to their uncommon nature, most clinicians and pathologists have limited experience with the extensive variability in clinical and histopathological presentation of these tumors and their complex multimodality treatment.[2]

Musculoskeletal oncology is one of the newer developing subspecialties in the country. The developments in the last few years have greatly improved not only the local management of these lesions, with limb salvage being the norm rather than the exception, but have also resulted in increased patient survival. In spite of these exciting advances, poor exposure to these tumors results in most surgeons approaching them with trepidation and uncertainty.

Department of Orthopaedic Oncology, Tata Memorial Hospital, Mumbai, India

Address for correspondence: Prof. Ajay Puri,
Room No: 26, Tata Memorial Hospital, E. Borges Road,Parel, Mumbai-400 012, India. E-mail: docpuri@gmail.com

Access this article online	
Quick Response Code:	Website: www.ijoonline.com
	DOI: 10.4103/0019-5413.82332

Approximately half of all patients with intermediate or high-grade soft tissue sarcomas develop metastatic disease and the overall survival is approximately 50% at 5 years.[3] Multidisciplinary management of these tumors is necessary to provide an optimal therapeutic approach.[2] This article outlines the current concepts and the principles of multimodality management of these challenging lesions.

Though in most patients, no specific etiology can be identified, the risk factors for soft tissue sarcomas include previous radiation therapy, exposure to chemicals (e.g., vinyl chloride, arsenic), immunodeficiency, prior injury (scars, burns), chronic tissue irritation (foreign-body implants, lymphedema), neurofibromatosis, and certain germ-line mutations like Li-Fraumeni syndrome (*p53* mutations).[1,4]

Signs and Symptoms

The soft tissue sarcomas commonly present as a painless, slow-growing mass. While sarcomas in the extremities may present earlier, diagnosis of sarcomas involving the pelvic cavity may be delayed as their location deep within the body precludes palpation of the tumor mass early in the course of the disease. Consequently, these tumors often attain large size prior to diagnosis without causing overt symptoms. Any soft tissue lump exhibiting any of the following four clinical features should be considered to be malignant until proved otherwise: (i) increasing in size, (ii) size >5 cm, (iii) location deep to the deep fascia, or (iv) pain. The more the number of these clinical features present, the greater the risk of malignancy, with increasing size being the best individual indicator.[3]

Diagnosis and Staging

It is best to complete all local imaging prior to a biopsy (contrast enhanced magnetic resonance imaging is the preferred method for limb lesions). This helps the surgeon plan the direction of biopsy so as to minimize contamination, while targeting the most representative areas of the lesion (avoiding cystic or necrotic areas). Though the material obtained by an open biopsy is generally adequate in quantity and less challenging to the skills of the pathologist, it is a more traumatic procedure. It involves greater tissue trauma, more blood loss, and higher risk of complications such as hematoma and infection. If a tourniquet is used, there is always the fear that the oozing from tumor vessels after the tourniquet is released may contaminate large areas of the limb. An open biopsy requires general anesthesia. It is less forgiving, and a correct technique is of utmost importance if limb salvage is being considered. The skin removed at final procedure is more and can compromise closure during salvage surgery. Hence, core needle biopsies, which are usually accomplished as an outpatient procedure under local anesthesia, are preferred. Image guided biopsies are preferred in deep-seated tumors which are difficult to palpate.[5,6] Several cores should be taken to maximize diagnostic yield. The material obtained from a core biopsy is superior (in amount and viability) compared to that obtained by fine needle aspiration cytology (FNAC) and, moreover, permits ancillary studies for more accurate diagnosis. The discovery of monoclonal antibodies and their application to histopathology by way of immunohistochemistry has greatly added to the diagnostic skills of the pathologist. For those diagnoses characterized by a chromosomal translocation, the use of molecular pathology [fluorescent in situ hybridization (FISH) or reverse transcription polymerase chain reaction (RT-PCR)] can be of assistance if the histological diagnosis is doubtful. The additional material obtained by a biopsy can be used for tissue banking and research. Though excision biopsies are not routinely recommended, an excisional biopsy may be the most practical option for superficial lesions that are <5 cm in size.[7] An open biopsy may be an option in selected cases where repeated core biopsies have failed to achieve a diagnosis. All biopsies should be performed by a trained surgeon and, if it is to be image guided, after discussion between the surgeon and the radiologist. It should be planned in such a way that the biopsy pathway and the scar can be safely removed on definitive surgery. Though it does not demand great technical skills, the decision related to the performance of a biopsy requires considerable thought and experience. It is important that a clinician knows how to obtain adequate material in the least traumatic way and without jeopardizing subsequent local control of the tumor. A poorly placed biopsy incision, a poorly performed biopsy, or the complications of a biopsy may make it difficult to salvage an extremity and, in some instances, may even affect the survival of the patient.[8]

Soft tissue sarcomas are classified histologically according to the soft tissue cell of origin, although the cell type is not part of the prognostic staging system. Additional studies, including electron microscopy, histochemistry, flow cytometry, cytogenetics, and tissue culture studies may allow identification of particular subtypes within the major histologic categories.[4] Malignant fibrous histiocytoma is the most common histologic type (28%). Others are leiomyosarcoma (12%), liposarcoma (15%), synovial sarcoma (10%), and malignant peripheral nerve sheath tumor (6%).[1] Pathologists assign grade based on the number of mitoses per high power field, presence of necrosis, cellular and nuclear morphology, and the degree of cellularity.[9] The metastatic potential of soft tissue tumors is dictated more by the histologic grade than the cellular classification.

Staging has an important role in determining the treatment and prognosis of soft tissue sarcomas. The major staging system used is the one formed by the International Union against Cancer (UICC) and American Joint Committee on Cancer (AJCC).[4] This TNM system incorporates histologic grade, tumor size and depth, regional lymph node involvement, and distant metastasis.

The lungs are the most common site for metastasis of soft tissue sarcomas. Approximately 10% of patients have pulmonary metastasis at presentation.[10] Additional imaging to complete staging can include an X-ray or a computed tomographic (CT) scan of the chest and an ultrasound or CT scan of the pelvis to identify involved lymph nodes if present. CT scan of the chest is recommended for sarcomas larger than 5 cm or for those with moderate to poor differentiation.[11] Nodal involvement is rare, occurring in less than 3% of patients with sarcoma.[12] It is more likely in epitheloid sarcomas, clear cell sarcomas, rhabdomyosarcomas, angiosarcomas, and synovial sarcomas.

For complete staging, a thorough physical examination, imaging, laboratory studies, and careful review of all biopsy specimens (including those from the primary tumor, lymph nodes, or other suspicious lesions) are essential.[4]

Positron emission tomography (PET) is a relatively new imaging modality that can assess the metabolic activity (FDG uptake) of the disease and is helpful for

delineating both locoregional and distant extent of the disease simultaneously.[13] Based on the standard uptake value (SUV), it may help in differentiating benign lesions from malignant ones. It can also help identify the most metabolic active area in a heterogeneous lesion for a targeted biopsy. PET is still not considered part of the routine workup of soft tissue tumors and its exact role remains to be defined.

The prognosis for patients with adult soft tissue sarcomas depends on several factors, including the patient's age and the size, histologic grade, and stage of the tumor. Factors associated with a poorer prognosis include age greater than 60 years, tumors >5 cm, or high-grade histology.[14] It has also been shown that prior intervention at a non-oncology center could eventually compromise both the local treatment and the overall survival.[15,16]

Principles of Management

Soft tissue sarcomas are ubiquitous in their site of origin, and are best treated with multimodality treatment. Multidisciplinary treatment planning is therefore mandatory in all cases and should involve pathologists, radiologists, surgeons, radiation therapists, and medical oncologists. This should be carried out in referral centers for sarcomas as it has been shown that patients managed at specialty centers fare better.[15]

Surgery

When feasible, function sparing surgical excision with wide margins is the cornerstone of effective treatment, the goal being preservation of a functional extremity.[17] This may be facilitated by soft tissue reconstructive surgery, including the use of local or free flaps and, occasionally, vascular and nerve resection with suitable graft reconstruction. Surgery for these lesions is best performed by a surgeon specifically trained in the treatment of this disease.[16] The standard surgical procedure is a wide excision. This implies removal of the tumor along with a rim of surrounding normal tissue.[3] In high-grade tumors, micronodules and extensions of the tumor into, and through, the reactive zone around the tumor pseudocapsule can lead to satellite and skip lesions.[18] To avoid local recurrence the resection should be performed outside this reactive zone if possible. Generally, 2 cm beyond the tumor is used as a cutoff to ensure adequate clearance, but the margin can be quantitatively less in the case of resistant anatomic barriers such as muscular fasciae, periosteum, and perineurium.[19] It is here that Kawaguchi's concept of 'barrier effects' while evaluating margins seems attractive.[20] Barrier refers to any tissue that has resistance against tumor invasion and can include muscle fascia, joint capsule, tendon, tendon sheath, epineurium, or vascular sheath. Each of these tissues can be classified as either a thick barrier or a thin barrier. A thick barrier is physically strong membranous tissue with a white tendinous lustre. A thin barrier is weaker membranous tissue of muscle fascia, periosteum of an adult, vessel sheath, and epineurium. For purposes of margin evaluation, barriers are converted into definitive thickness of normal tissue. A thick barrier is converted into the equivalent of 3 cm thickness of normal tissue. A thin barrier is considered to be equivalent to 2 cm thickness of normal tissue. A surgical margin passing just outside fascia which is separated from tumor by normal tissue also is calculated as 5 cm regardless of the barrier's actual thickness. When a tumor has adhered to a membranous barrier and the outer surface of the barrier still maintains an obvious lustre, the barrier is evaluated by deducting 1 cm from the original value. Therefore, when a lesion adheres to a thick barrier, it is evaluated as 2 cm and when a lesion adheres to a thin barrier, it is evaluated as 1 cm. By considering barrier effects translated into concrete distance equivalents, surgery can be planned at sites where barriers exist by using margins less than those mandated by true physical distance.

However, on occasion, anatomical constraints mean that a true wide resection is not possible without the sacrifice of critical anatomical structures (such as major nerves or blood vessels) and in this situation a marginal excision may be acceptable as an individualized option in highly selected cases, after having considered the risks of recurrence and the morbidity of more radical surgery and after full discussion of these factors with the patient.[3] In the case of inadequately excised tumors, reoperation should be considered if adequate margins can be achieved without major morbidity.[21]

Occasionally amputations may be considered as a surgical option. Patients with localized tumors that, despite multimodality treatments, cannot be resected completely may need an amputation to minimize the risk of distant site relapse. In addition, patients with multiple relapses, untreatable pain, bleeding, or fungation may also benefit from amputation of a limb.

Radiotherapy

Radiotherapy complements adequate surgery as standard treatment of intermediate and high-grade deep tumors with a diameter of >5 cm. It can consist of preoperative or postoperative radiation, depending on institution protocols.[22] Preoperative radiotherapy can occasionally permit limb conservation of extremity sarcomas that otherwise would be inoperable or require amputation.[23] Reports suggest that preoperative radiotherapy is associated with a greater risk

of wound complications than postoperative radiotherapy.[22] Intraoperative brachytherapy, either exclusively or in combination with postoperative radiation, is an option that is also often employed. Here, the radiotherapist places hollow tubes (for postoperative loading with radioactive iridium wires) in the tumor bed. This enables radiation to be administrated to the surgical bed while irradiation of healthy tissue is minimized. Radical brachytherapy alone, when used judiciously, has demonstrated good local control and functional outcomes, with reduced treatment-related morbidity.[24] Intensity-modulated radiation therapy (IMRT) has the potential to better target the delivered radiation dose; it is associated with less morbidity and is currently under investigation.[25]

Chemotherapy

The role of chemotherapy in soft tissue sarcomas is still debatable. A quantitative meta-analysis of updated data from 1568 individual patients from 14 trials of doxorubicin-based adjuvant therapy showed an absolute benefit from adjuvant therapy of 6% for local relapse free interval, 10% for distant relapse free interval, and 10% for recurrence free survival; however, there was no overall survival benefit at 10 years.[26] The histological type may play a role during decision making on whether to offer chemotherapy, since some types are felt to be more chemosensitive than others. High-grade tumors that are >5 cm in diameter have the greatest tendency to metastasize and patients with such tumors are most likely to benefit with adjuvant chemotherapy.[4] Chemotherapy in soft tissue sarcomas is best offered in the setting of prospective clinical trials.

Surveillance

Post treatment surveillance forms an important part of the overall treatment plan in patients with sarcomas. There are no published data supporting specific policies for follow up of surgically treated patients with localized disease. Relapses most often occur to the lungs. The risk assessment based on tumor grade, size, and site may help in choosing the routine follow up policy.[27] High-risk patients generally relapse within 2–3 years and, while low-risk patients may relapse later, it is less likely. The best method of follow-up has not been established. Although the use of MRI to detect local relapse and CT to scan for lung metastases is likely to pick up recurrence earlier, it is yet to be demonstrated that this is beneficial or cost-effective compared with clinical assessment of the primary site and regular chest X-rays.[27]

Management of subsequent metastases

Soft tissue sarcomas have a predilection for developing pulmonary metastases at some point in their natural history. Studies have shown that a select subset of these patients will benefit from complete excision of these metastases provided the primary disease is controlled. The primary selection criteria for considering a patient for pulmonary metastasectomy have largely remained unchanged over the years;[28] the criteria are as follows:

1. Complete resection should be technically possible
2. Primary disease should be controlled or controllable
3. Extrapulmonary metastatic disease must be absent
4. The patient should have the physiological reserve to withstand the procedure

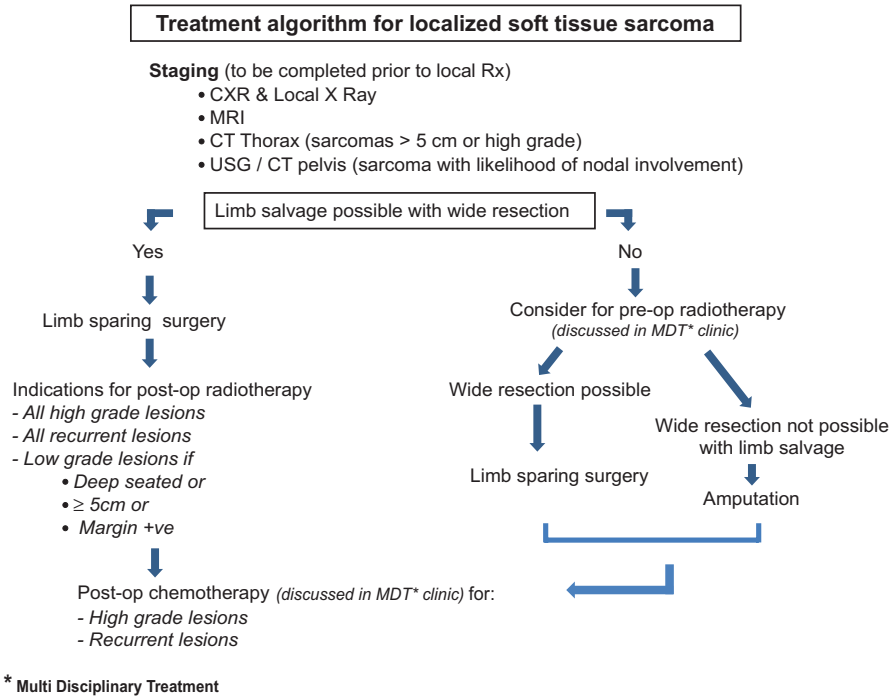

Figure 1: Treatment algorithm for localized soft tissue sarcoma

Palliative chemotherapy may be beneficial in some patients with advanced metastatic soft tissue sarcoma. It has been established that good performance status, young age, and absence of liver metastasis may possibly improve survival time.[28]

Conclusion

The presence of a soft tissue sarcoma in the extremity is no longer an indication for amputation.[29] The last few decades have seen rapid strides in surgery and function preserving alternatives for local control in these lesions have become the norm, without compromising on overall disease survival. The advent of better imaging modalities and more effective adjuvant modalities, along with better understanding of anatomy and the continuous refinement in surgical techniques, have all played a part in achieving this goal. Good functional and oncological results can be achieved by using a combination of tumor excision and, where required, suitable adjuvant therapies. A suitable algorithm for the management of these lesions is suggested in Figure 1.

References

1. Kasper B, Gil T, D'Hondt V, Gebhart M, Awada A. Novel treatment strategies for soft tissue sarcoma. Crit Rev Oncol Hematol 2007;62:9-15.
2. Jansen-Landheer ML, Krijnen P, Oostindier MJ, Kloosterman-Boele WM, Noordijk EM, Nooij MA, *et al*. Improved diagnosis and treatment of soft tissue sarcoma patients after implementation of national guidelines: A population-based study. Eur J Surg Oncol 2009;35:1326-32.
3. Grimer R, Judson I, Peake D, Seddon B. Guidelines for the management of soft tissue sarcomas. Sarcoma 2010;2010:506182.
4. National Cancer Institute: Adult Soft Tissue Sarcoma Treatment (PDQ®) 2011. Available from: http://www.cancer.gov/cancertopics/pdq/treatment/adult-soft-tissue-sarcoma/HealthProfessional [updated on 24 Jan 2011].
5. Narvani AA, Tsiridis E, Saifuddin A, Briggs T, Cannon S. Does image guidance improve accuracy of core needle biopsy in diagnosis of soft tissue tumours? Acta Orthop Belg 2009;75:239-44.
6. Heslin MJ, Lewis JJ, Woodruff JM, Brennan MF. Core needle biopsy for diagnosis of extremity soft tissue sarcoma. Ann Surg Oncol 1997;4:425-31.
7. Casali PG, Jost L, Sleijfer S, Verweij J, Blay JY. Soft tissue sarcomas: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009;20(Suppl 4):132-6.
8. Pollock RC, Stalley PD. Biopsy of musculoskeletal tumours--beware. ANZ J Surg 2004;74:516-9.
9. Daugaard S. Current soft-tissue sarcoma classifications. Eur J Cancer 2004;40:543-8.
10. Cormier JN, Huang X, Xing Y, Thall PF, Wang X, Benjamin RS, *et al*. Cohort analysis of patients with localized, high-risk, extremity soft tissue sarcoma treated at two cancer centers: chemotherapy-associated outcomes. J Clin Oncol 2004;22:4567-74.
11. Christie-Large M, James SL, Tiessen L, Davies AM, Grimer RJ. Imaging strategy for detecting lung metastases at presentation in patients with soft tissue sarcomas. Eur J Cancer 2008;44:1841-5.
12. Fong Y, Coit DG, Woodruff JM, Brennan MF. Lymph node metastasis from soft tissue sarcoma in adults: Analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg 1993;217:72-7.
13. Okazumi S, Dimitrakopoulou-Strauss A, Schwarzbach MH, Strauss LG. Quantitative, dynamic 18F-FDG-PET for the evaluation of soft tissue sarcomas: Relation to differential diagnosis, tumor grading and prediction of prognosis. Hell J Nucl Med 2009;12:223-8.
14. Vraa S, Keller J, Nielsen OS, Sneppen O, Jurik AG, Jensen OM. Prognostic factors in soft tissue sarcomas: The Aarhus experience. Eur J Cancer 1998;34:1876-82.
15. Bhangu AA, Beard JA, Grimer RJ. Should soft tissue sarcomas be treated at a specialist centre? Sarcoma 2004;8:1-6.
16. Abellan JF, Lamo de Espinosa JM, Duart J, Patino-Garcia A, Martin-Algarra S, Martinez-Monge R, *et al*. Nonreferral of possible soft tissue sarcomas in adults: A dangerous omission in policy. Sarcoma 2009;2009:827912.
17. Watson DI, Coventry BJ, Langlois SL, Gill PG. Soft-tissue sarcoma of the extremity: Experience with limb-sparing surgery. Med J Aust 1994;160:412-6.
18. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop Relat Res 1980;153:106-20.
19. Novais EN, Demiralp B, Alderete J, Larson MC, Rose PS, Sim FH. Do surgical margin and local recurrence influence survival in soft tissue sarcomas? Clin Orthop Relat Res 2010;468:3003-11.
20. Kawaguchi N, Ahmed AR, Matsumoto S, Manabe J, Matsushita Y. The concept of curative margin in surgery for bone and soft tissue sarcoma. Clin Orthop Relat Res 2004;429:165-72.
21. Manoso MW, Frassica DA, Deune EG, Frassica FJ. Outcomes of re-excision after unplanned excisions of soft-tissue sarcomas. J Surg Oncol 2005;91:153-8.
22. O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, Chabot P, *et al*. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: A randomised trial. Lancet 2002;359:2235-41.
23. Robinson MH, Ball AB, Schofield J, Fisher C, Harmer CL, Thomas JM. Preoperative radiotherapy for initially inoperable extremity soft tissue sarcomas. Clin Oncol (R Coll Radiol) 1992;4:36-43.
24. Laskar S, Bahl G, Puri A, Agarwal MG, Muckaden M, Patil N, *et al*. Perioperative interstitial brachytherapy for soft tissue sarcomas: Prognostic factors and long-term results of 155 patients. Ann Surg Oncol 2007;14:560-7.
25. Stewart AJ, Lee YK, Saran FH. Comparison of conventional radiotherapy and intensity-modulated radiotherapy for post-operative radiotherapy for primary extremity soft tissue sarcoma. Radiother Oncol 2009;93:125-30.
26. Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults. Cochrane Database Syst Rev 2000;4:CD001419.
27. Cool P, Grimer R, Rees R. Surveillance in patients with sarcoma of the extremities. Eur J Surg Oncol 2005;31:1020-4.
28. Alexander J, Haight C. Pulmonary resection for solitary metastatic sarcomas and carcinomas. Surg Gynecol Obstet 1947;85:129-46.
29. Rosenberg SA, Tepper J, Glatstein E, Costa J, Baker A, Brennan M, *et al*. The treatment of soft-tissue sarcomas of

the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg 1982;196:305-15.

How to cite this article: Puri A, Gulia A. Management of extremity soft tissue sarcomas. Indian J Orthop 2011;45:301-6.

Source of Support: Nil, **Conflict of Interest:** None.