Multimodality Management of Extremity Soft Tissue Sarcomas—An Indian Perspective

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Abstract Soft-tissue sarcomas are a rare and heterogeneous group of tumors. The last few decades have seen rapid strides in the management of these complex lesions. The presence of a soft-tissue sarcoma in the extremity is no longer an indication for amputation. Function preserving alternatives for local control in these lesions are 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 article outlines the current understanding and emphasises the multimodality management of these challenging tumors. We also present Indian data of the incidence and oncologic outcomes of these lesions and suggest a treatment algorithm.

Keywords Multimodality · Tumor

Introduction

Soft tissue sarcomas are uncommon lesions. They represent less than 1% of all adult malignancies. More than 60% of soft-tissue sarcomas occur in the extremities making them the commonest site. Other locations are the trunk (19%), the retroperitoneum (15%), or the head and neck (9%) [1]. Due to their heterogeneous nature and rarity, most clinicians and

pathologists have limited experience in the diagnosis and complex multimodality treatment of these lesions [2].

The developments in the last few years in musculoskeletal oncology have greatly improved patient survival in sarcomas. Local management has also undergone a sea change with limb salvage being the norm rather than the exception. In spite of these exciting advances the paucity of exposure to these tumors results in most surgeons approaching them with trepidation and uncertainty.

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]. The optimal therapeutic approach includes the involvement of various disciplines at all stages of management [2]. This article outlines the current concepts and principles of multimodality management of extremity soft tissue sarcomas.

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

Soft-tissue sarcomas commonly present as a painless, slow-growing mass without any specific symptoms and signs. While sarcomas in the extremities may present earlier, diagnosis of sarcomas involving the pelvic cavity or retroperitoneum may be delayed. Their location deep within the body precludes palpation of the tumor mass early in the course of the disease thereby allowing them to often reach a large size prior to diagnosis without causing overt

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symptoms. Any soft tissue lump exhibiting any of the following four clinical features should be viewed with suspicion and considered to be malignant until proved otherwise: (i) increasing in size, (ii) size >5 cm, (iii) deep to the deep fascia, (iv) painful. The more of these clinical features present, the greater the risk of malignancy with increasing size being the best individual indicator [3].

Diagnosis and Staging

Completion of all imaging before proceeding to biopsy is advisable. Contrast-enhanced magnetic resonance imaging is the preferred method for limb lesions. Imaging 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). Nowadays needle biopsies are the preferred method for obtaining tissue for histopathological analysis. Though an open biopsy may obtain additional material which is 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 a fear that the oozing from tumor vessels after the tourniquet is released may contaminate large areas of the limb. An open biopsy requires general anaesthesia. It is less forgiving and a correct technique is of utmost importance if limb salvage is considered. Excising the scar of an open biopsy during the final procedure involves sacrifice of additional tissue which can compromise skin closure during salvage surgery. Hence core needle biopsies which are usually accomplished as an outpatient procedure under local anaesthesia are preferred. Image guided biopsies using ultrasound or CT scan are preferred in deep seated tumors which are difficult to palpate [5, 6]. Several cores should be taken to maximise the diagnostic yield. The material obtained from a core biopsy is superior (in amount and viability) compared to that obtained by FNAC and permits ancillary studies for more accurate diagnosis. The use of monoclonal antibodies in immunohistochemistry further assists the pathologist to arrive at a diagnosis. The use of molecular pathology [fluorescent in-situ hybridisation (FISH) or reverse transcription polymerase chain reaction (RT-PCR)] can be helpful in tumors characterised by a chromosomal translocation. The additional material obtained from a biopsy can always be stored for tissue banking and future research after obtaining the patient's consent. Though excision biopsies are not routinely recommended, an excisional biopsy may be the most practical option for <5 cm superficial lesions [7]. An open biopsy may be an option in selected cases where repeated core biopsies have failed to achieve a diagnosis. Biopsy should be planned in such a way that the biopsy pathway

and the scar can be safely removed on definitive surgery. All biopsies should ideally be performed by a trained surgeon, or discussed between the surgeon and the radiologist if image guidance is necessary. 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 without jeopardising 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, though 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]. The common histologic subtypes are malignant fibrous histiocytoma, leiomyosarcoma, liposarcoma and malignant peripheral nerve sheath tumors [1]. Pathologists assign grade based on number of mitoses per high-powered field, presence of necrosis, cellular and nuclear morphology and the degree of cellularity [9]. The metastatic potential of soft tissue tumors is dependent on their histologic grade rather 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, 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 with moderate to poor differentiation [11]. Nodal involvement occurs in less than 3% of patients with sarcoma [12]. Tumors likely to have nodal metastasis are epithelioid 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) which assesses the metabolic activity (FDG uptake) of the disease is helpful in detection of both loco regional and distant disease extent

simultaneously [13]. Based on standard uptake value (SUV), it can help identify the most metabolic active area in a heterogeneous lesion for a targeted biopsy. PET is still not considered as a part of routine work up of soft tissue tumors and its exact role remains to be defined.

The prognosis for patients with adult soft tissue sarcomas is multi factorial. Factors associated with a poorer prognosis include age older than 60 years, tumors >5 cm, or high-grade histology [14]. Prior intervention at a non oncology centre can adversely affect both, their local treatment and overall survival [15, 16].

Principles of Management

Multidisciplinary treatment planning involving pathologists, radiologists, surgeons, radiation therapists and medical oncologists is the current norm to optimise results for these lesions. A clinical or radiological suspicion of a soft tissue sarcoma should result in a referral to a centre with the expertise to diagnose and plan the management of these lesions as it has been shown that patients managed at specialty centres fare better [15].

Surgery

Complete surgical excision with wide margins is the mainstay of surgical treatment. With the advent of advanced imaging modalities and refinement in surgical techniques, this goal is often achievable even with function-sparing limb salvage surgery. [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, implying removal of the tumor with a rim of normal tissue around [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 decrease the incidence of local recurrence the resection should be performed outside this reactive zone if possible. Generally 2 cm beyond the tumor is used as a cut-off 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, the 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 2 cm. 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 qualitative 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. The risks of recurrence balanced against the morbidity of more radical surgery needs to be fully discussed with the patient prior to such surgeries [3]. In the case of inadequately excised tumors, reoperation should be considered if adequate margins can be achieved without major morbidity [21].

Amputations still remain a valuable tool in the armamentarium of the surgeon and are occasionally necessary. Patients with localized tumors that despite multimodality treatment 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 an 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. The dose of external beam radiotherapy can range from 45 Gy when combined with brachytherapy to 70 Gy when external beam radiotherapy alone is used in excisions with macroscopic residual disease. It may be employed as preoperative or postoperative radiation depending on institution protocols [22]. Preoperative radiotherapy can occasionally permit limb conservation of extremity sarcomas which otherwise would be inoperable or require amputation [23]. Preoperative radiotherapy has been reported to be associated with a greater risk of wound complications than

postoperative radiotherapy [22]. The incidence of such wound complications may be reduced with an increased use of local or free flaps for soft tissue coverage at index surgery. Intra operative brachytherapy either exclusively or in combination with post operative radiation is an option that is also often employed. It involves the placement of hollow tubes (for postoperative loading with radioactive iridium wires) in the tumor bed thus enabling radiation to be administered 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 with decreased morbidity, and is under investigation [25].

Chemotherapy

Chemotherapy in an adjuvant setting in soft tissue sarcomas has failed to demonstrate a significant benefit in overall survival [26]. Currently there is inadequate evidence to recommend adjuvant chemotherapy as standard for all patients of soft tissue sarcoma [27]. The histological type may play a role in the decision making to offer chemotherapy, since some types are felt to be more chemosensitive, whereas others are less so. Chemotherapy may be considered in a select population of high grade extremity sarcoma, >5 cm or recurrent high grade tumors using doxorubicin alone or a combination of doxorubicin plus ifosfamide [26]. It is best offered in the setting of prospective clinical trials.

Surveillance

Post treatment surveillance forms an important part in the overall treatment plan of patients with sarcomas. Relapses most often occur to the lungs. The risk assessment based on

Fig. 1 Age distribution of soft tissue sarcomas

Fig. 2 Kaplan Meier curve showing disease free survival

tumor grade, tumor size and tumor site may help in choosing the routine follow-up policy as there is little data supporting specific policies for follow-up [28]. High risk patients generally relapse within 2–3 years, while low risk patients may relapse later, although it is less likely. 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. [28] Ultrasonography to detect lymph node metastasis

Fig. 3 Kaplan Meier curve showing overall survival

may be applicable in tumors with a propensity for spread to lymph nodes (epitheloid sarcomas, clear cell sarcomas, rhabdomyosarcomas, angiosarcomas and synovial sarcomas). Extended surveillance may be necessary to identify and address potential late effects of surgery, radiation and chemotherapy for long term survivors.

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 [29].

1. Complete resection should be technically possible
2. Primary disease should be controlled or controllable
3. Absence of extrapulmonary metastatic disease
4. Patient should have the physiological reserve to withstand the procedure

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

Function preserving alternatives for local control in soft tissue sarcomas have become the norm without compromising on overall disease survival. The advent of better imaging modalities, more effective adjuvant modalities, a better understanding of anatomy with continuous refinement in surgical techniques have all played a part in achieving this goal. Good functional and oncological results can be achieved with a combination of excision of the tumor, and where required, suitable adjuvant therapies. Multidisciplinary care offered to the patient at specialty centres helps to optimise results in these challenging tumors.

An Indian Perspective

Incidence

A prospective observational study done at our institute documented all patients presenting in the bone and soft tissue OPD from 01/01/2010 to 31/12/2010. Of a total 2007 patients, 723 (36%) had a soft tissue lesion which included both benign and malignant tumors of mesenchymal and cutaneous origin. Of the 491 soft tissue mesenchymal extremity tumors, 413 (84%) were malignant soft tissue sarcomas. These tumors were commoner in adults, affecting

Fig. 4 Treatment algorithm for non metastatic extremity sarcomas

Chemotherapy may be offered to patients with high grade lesions $> 5\text{cm}$ or recurrent lesions after discussion in multidisciplinary clinic, preferably in a trial setting

patients in the third to fifth decade (Fig. 1). Males (69%) were predominantly affected. The thigh was the most common site (40%) involved. Synovial sarcoma (22%) was the most common tumor seen followed by spindle cell sarcoma (18%), soft tissue Ewing's sarcoma (12%), pleomorphic sarcoma and leiomyosarcoma (8% each) and liposarcoma (6%).

Staging data was available in 372 patients. 32% were metastatic at presentation with the lung being the most common site of metastasis.

The limitation of this study is that there is an obvious selection bias. Our institute is a tertiary referral cancer centre, hence these numbers are more representative of a hospital based registry and not a true reflection of absolute numbers/incidence in the population.

Outcome Data of Extremity Soft Tissue Sarcomas (STS)

A set of 142 patients with extremity STS non metastatic at presentation were enrolled in a prospective randomized controlled trial at our institution between January 2006 and June 2010 to evaluate the effectiveness of follow up strategies. One hundred and ten of these had a minimum 2 year follow up. There were 78 males and 32 females. The age range was from 7 to 66 years with a mean age of 35 years. There were 56 primary lesions and 46 recurrent tumors. Eight patients underwent scar excision for unknown margins after excision of a high grade STS elsewhere. There were 98 high grade lesions and 12 low grade tumors. These included 50 synovial sarcomas, 26 spindle cell sarcomas, 7 soft tissue Ewing's sarcoma, 8 pleomorphic sarcomas, 7 liposarcomas, 2 dermatofibrosarcomas, 4 extra skeletal chondrosarcoma, 1 clear cell sarcoma, 1 round cell tumour, 1 Myxofibrosarcoma, 2 Leiomyosarcoma, 1 epithelioid sarcoma. Forty eight lesions were greater than 10 cms (maximum dimension) in size and 62 were less than 10 cms. Ninety seven patients had limb salvage whereas 13 had an amputation. Of the 97 patients with limb salvage 26 (24%) needed a flap at index surgery to ensure adequate soft tissue cover. In all except two patients, the margins after resection were uninvolvement on histopathological evaluation. Decisions regarding adjuvant therapy were made on a case to case basis. Twenty three patients had no adjuvant therapy, 53 had radiotherapy, 25 had a combination of chemotherapy and radiotherapy and 9 cases had only chemotherapy.

One hundred cases available for follow up were analysed for oncologic results. The follow up in these 100 patients ranged from 3 to 64 months with a mean of 33 months. There were 6 isolated local recurrences, 26 distant recurrences and 11 patients had combined recurrence. At the time of last review 65 patients have no evidence of disease, 32 are dead and 3 patients are alive with disease. The disease free survival (DFS) at 5 years was 51% and the overall survival

(OS) at 5 years was 62% (Figs. 2 and 3). Patients with low grade tumors and those with lesions less than 10 cms in size showed a trend for better OS when compared to those with high grade lesions and lesions greater than 10 cms but this did not reach statistical significance.

Based on our experience we have proposed a suitable algorithm for the management of these lesions (Fig. 4) [30].

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