A Review of Controversies in the Management of Soft Tissue Sarcomas

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Abstract Soft tissue sarcomas (STS) constitute a rare and challenging group of solid tumor in the field of oncology. Unlike other malignancies STS can affect a wide variety of anatomical regions in the body with varied histopathological variants and clinical outcomes. There are controversies in the diagnosis and management of STS due to rarity and heterogeneity of the disease entity. Due to dedicated research and advances made in the field of imaging, pathology, surgery, radiotherapy and chemotherapy certain controversies were laid to rest and treatment approach to STS could be standardized to a large extent in the recent past. A review of controversies related to STS was performed in this article and an attempt was made to present a balanced view pertaining to these issues.

Keywords Sarcomas · Controversies · Management

Introduction

Soft tissue sarcomas (STS) are one of the rare malignancies which constitute a heterogenous group of tumors originating from mesenchymal tissue. Even though they account for less than 1 % of total burden of solid tumors, they are highly lethal and management of these tumors is challenging. There are controversies pertaining to diagnostic workup and optimal management of STS in-view of the rarity and heterogenous clinical spectrum. These controversies mainly

revolve around the biopsy technique, imaging, histopathological evaluation, staging systems, surgical management and adjuvant therapy issues. An attempt has been made in this article to systematically review these issues and present a balanced view regarding the optimal management of STS.

Controversies in the Management of Soft tissue Sarcoma

Cell of origin

Traditionally sarcomas were named and classified based on their resemblance to mature tissue counterparts of mesenchymal origin. Liposarcomas derived from adipose cells, synovial sarcomas derived from synovial cells, leiomyosarcomas from smooth muscle cells and so on. Recent cytogenetical studies and molecular research has cleared that unlike epithelial tumors, which arise in specific organs, STS are thought to arise from undifferentiated mesenchymal stem cells that may be found virtually anywhere in the body [1]. This also explains the occurrence of certain sarcomas in anatomical sites where normally the mature mesenchymal counterpart never exists.

Type of Biopsy

More than 50 different varieties of soft tissue and bone sarcomas have been described [2, 3]. Such a heterogeneity demands a good pathological processing, histological and immune-histochemical studies for an accurate diagnosis. Various options are available for obtaining histopathological diagnosis of STS including fine needle aspiration biopsy (FNAB), Core needle biopsy, Incisional or excisional biopsy. Few major sarcoma institutions are using FNAB in the diagnosis of sarcomas. Major criticism against FNAB is its

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inability to accurately grade the tumor. Studies using FNAB in major centres have demonstrated sensitivity of 89 % in diagnosing sarcoma and 95 % accuracy in grading them [4]. Reproducible results with such a high accuracy is possible in only dedicated centres with experienced cytopathologists.

Core needle biopsy has a very high diagnostic accuracy in STS [5]. Core needle biopsy can be done safely under local anaesthesia using either manual or vacuum assisted apparatus. For better accuracy and to avoid cystic and necrotic areas in the tumor, image guided biopsies can be performed using Ultrasonography, Computerised tomography or Magnetic resonance imaging. Imaging is also useful adjunct for a core biopsy when the tumor is located in relation to vital structures. With the widespread availability of good core biopsy systems, incisional biopsy is rarely used as a diagnostic modality in STS management [6] except in situations where core biopsy is inconclusive.

In certain situations Excision biopsy is recommended for superficially located tumors of less than 3 cm in size [7]. Excisional biopsy of the entire tumor mass should only be done for small, superficial tumors that will leave a surgical bed that can readily be re-excised with a wide margin without undue morbidity should the tumor prove to be a sarcoma [8].

Principles of Biopsy Technique

An inappropriate needle or incision biopsy scars may turn a situation of limb salvage into that requiring an amputation [9]. Due to their innocuous clinical presentation as subcutaneous swelling primary level mismanagement is very common using inappropriate biopsy techniques. It is generally recommended to refer a patient to a centre with expertise for sarcoma management if there is a clinical suspicion of sarcoma [10–12]. Important considerations while doing a biopsy include planning incisions in such a way where it can be removed en bloc with the tumor without sacrificing extra skin or any vital structures during definitive surgical procedure. Longitudinal incisions are preferred in extremities. No skin flaps should be raised and haemostasis needs to be good in order to avoid dissemination of tumor.

Imaging

Imaging of the anatomical area containing the sarcoma is required to delineate the local extent, neurovascular invasion, extent of bone involvement. Specific features such as presence of fat density and necrosis give diagnostic information about the type of tumor. Imaging should be done before any biopsy is attempted. It helps in better targeting the representative area and imaging can sometimes gives diagnostic hints to pathologist in difficult situations.

Computed Tomography (CT) is less expensive than Magnetic Resonance Imaging (MRI) and provides excellent osseous cortical detail and definition of lesion matrix mineralization patterns [13]. It is the imaging of choice in patients with contraindications to MRI. Soft tissue delineation and contrast enhancement is inferior to MRI but CT represents a cost-effective modality and is widely available [14]. As part of the diagnostic work-up in high grade sarcomas lung evaluation is required, and CT is the most sensitive technique for detecting lung metastases [15].

MRI if available is the imaging of choice for extremity soft tissue sarcomas especially when dealing with deep seated tumors in close relation to neurovascular structures. MRI gives better soft tissue delineation and aids to surgical planning in deep compartmental tumors. In addition, for post treatment evaluation, MRI is the modality of choice for detecting residual or recurrent disease [13]. Newer functional imaging modalities such as Positron emission tomography (PET) scan and Magnetic resonance spectroscopy (MRS) are evolving. Two potential areas where PET scan has shown advantage compared to conventional imaging are targeting the biopsy area in the large heterogeneous tumors [16] and assessment of tumor after neoadjuvant treatment [13]. Similarly MRS is being evaluated as a non-invasive modality to assess the grade of tumor [17].

Histopathology- Grading and Immunohistochemistry

Histological grade is the strongest predictor of patient outcome of all the known prognostic factors [18] in STS. Debate continues regarding the optimum grading system. The latest (7th) edition of AJCC staging system has changed the grading of sarcomas from 4 to 3 grades. Other grading systems include Broders classification which contains 4 grades starting from well differentiated to poorly differentiated tumors, National Cancer Institute (NCI) and French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading systems [19, 20]. All these systems use tumor differentiation, necrosis and mitotic count to assess the grade of a particular tumor. Non uniformity exists in taking the amount of necrosis in to consideration. There is no international consensus on grading system. Discordance among sarcoma expert pathologists is observed in up to 30 % as far as grade is concerned [21]. Memorial Sloan Kettering Cancer Centre (MSKCC) grading is a binary system consisting of low and high grade based on the Histopathological type of sarcoma [22]. This is a simple grading system useful in centres which lack dedicated pathologists to accurately grade the sarcoma.

Recently, battery of immunohistochemical markers have flooded the Histopathological evaluation systems [23] and positively contributed in better delineation of certain sarcomas and are also helping in planning targeted therapy in

tumors like Gastro Intestinal Stromal Tumor (GIST). Some of the important IHC markers used in sarcoma field are shown in table (Table 1).

Staging of Soft Tissue Sarcomas

Many staging systems have been proposed for soft tissue sarcomas. Most commonly used system is AJCC system of staging sarcomas. Other staging systems are MSKCC staging, Enneking staging system of the Musculoskeletal Tumor Society (MSTS). One of the major distinguishing features of STS staging is incorporation of grading in the staging system since it has a major prognostic value. Among the various staging systems the MSKCC staging [22] is a simple and practical system and can be used by majority of the centres. Table 2 shows the MSKCC staging system. In future usage of genomic and proteomic analysis and tissue microarray analysis is likely to be incorporated in STS staging which may also help in predicting disease progression, treatment response, and survival [24].

Surgical issues in the Management of Soft Tissue Sarcomas

Surgical management of STS has seen a paradigm shift from radical amputations to limb salvage procedures during the last 3 decades due to better understanding of tumor biology, advances in the field of pathology, imaging, radiotherapy, chemotherapy and refinements in surgical techniques.

Limb Salvage Versus Amputation

Traditionally amputation was the established surgical therapy for STS. In the last 3 decades, rates of amputations have

Table 1 Showing patterns of IHC marker positivity in different sarcomas

Immuno HistoChemistry markers	Type of Sarcoma
Desmin	Sarcomas (smooth, skeletal muscle, endometrial stromal)
CD 31, CD34, S 100	Vascular sarcomas
Vimentin	Sarcomas with neural, lipomatous, chondroid differentiation
Cytokeratin, Epithelial membrane antigen, CD99, Bcl 2	Many sarcomas, Non specific
CD117	Synovial sarcoma
CD 57, Vimentin	Gastrointestinal stromal tumor
CD 99, S100, NET, Vimentin	Chondrosarcoma
Cytokeratin, CD 99, NET, Desmin	PNET/Ewing's sarcoma
CD 57, EMA, vimentin	Desmoplastic round cell tumos
	Osteosarcoma

Table 2 Showing MSKCC staging system for STS

Good prognostic features	Poor prognostic features	Staging
Low Grade	High Grade	Stage 0 – No poor prognostic feature
Tumor Size <5 cm	Tumor size >5 cm	Stage 1 – 1 Poor prognostic feature
Superficial Tumors	Deep tumors	Stage 2 – 2 Poor prognostic feature
		Stage 3 – 3 Poor prognostic feature
		Stage 4 – Metastatic sarcoma

reduced as more patients are being considered for limb salvage. As the literature about sarcomas accumulated, it was realised that radical resections including amputation did not improve the overall survival of patients [25]. In a landmark prospective Randomised trial at National Cancer Institute, Dr Rosenberg randomised 43 patients in to either limb salvage surgery followed by radiotherapy or amputation. He concluded that there is no significant difference in the disease free or overall survival between patients undergoing radical margin negative resection with radiotherapy and patients undergoing amputation [26]. Majority of cancer centres all over the world currently report 80 to 90 % limb salvage rates for STS. Debate continues between biological aggressiveness of tumor versus surgical margins and local control as the main determinants of overall survival of sarcoma patients [27–29]. However surgeons should be familiar with the contra indications to limb salvage surgery which includes - involvement of more than one compartment, neurovascular involvement, infiltration of bone, extensive skin/soft tissue involvement and sarcoma in a diseased limb.

Optimum Margins in Sarcoma Surgery

In the era of limb salvage surgery the role of conservative wide excision and adjuvant radiotherapy is established as equivalent to amputation. However the debate continues regarding ideal margin and role adjuvant therapy in STS. Enneking [30] in the year 1980 described a classification to define the types of resection in relation to margins in sarcoma. In Intrlesional excision the resection plane goes through the tumor with gross residual disease and in marginal excision the plane of resection is through the pseudocapsule with inevitable residual microscopic disease. Both these procedures are associated with more than 40 % local recurrence and are not recommended in the management of STS. Only wide excision and radical compartment resections are recommended limb salvage procedures in sarcoma

management [31, 32]. As per NCCN guidelines the optimal STS resection margin has been defined as the amount of tissue necessary to obtain a negative-margin resection [33]. In practice, the margin should at least be 1 to 2 cm of grossly normal tissue around the tumor and beyond the pseudocapsule especially in the setting of limb salvage surgery in combination with post op radiotherapy. This can be relaxed in presence of a biological barrier such as joint capsule or deep fascia and in the vicinity of neurovascular structures [34].

Management of Patients with Prior Surgical Intervention and Unknown or Positive Margins

The fact has been already highlighted that a significant proportion of sarcoma patients undergo unplanned non oncologic surgical intervention prior to referral to a tertiary care centre. This is a common problem not only in developing countries but also in major western centres. Various studies have shown that previous unplanned resection with unknown or positive margin can affect the ultimate limb salvage rate and survival [35]. Residual tumour has been identified in as many as 30 % of patients undergoing re-excision. Hence a re-wide excision to excise the tumour bed with negative margins along with the scar is recommended in such patients.

Role of Palliative Surgery in Extremity and Retroperitoneal Sarcomas

Sometimes patients with aggressive sarcomas can present with synchronous distant metastases. A palliative resection/amputation is indicated in such patients suffering from bleeding, intractable pain, fungation and infection. A debulking surgery can improve quality of life in patients with retroperitoneal tumors, especially in low grade tumors (well differentiated liposarcoma) since margin negative resection may not be feasible in certain situations.

Role of Major Vascular and Soft Tissue Reconstruction

Major vascular involvement is considered relative contraindication for limb salvage surgery. Similarly extensive soft tissue involvement especially in the setting of previous unplanned resections with bad scars is also relative contraindications. With the advent of microvascular techniques and advances in vascular and prosthetics field, more and more limb preserving surgeries are being attempted in the current era using vascular and soft tissue reconstruction techniques [36, 37]. However the experience is limited and patient selection plays a crucial role in such situations. Patients with isolated and limited vascular involvement do well with vascular reconstruction provided a good margin negative resection can be achieved. Availability of soft

tissue reconstruction expertise can help in planning wider resections without fear of not achieving a primary closure. Local rotation advancements and muscle flaps can be used efficiently in STS to improve margin status, achieve good wound closure and healing and thereby improving long-term oncologic control and functional results.

Role of Isolated Limb Perfusion (ILP)

Isolated limb perfusion is a specialized technique of delivering high dose of chemotherapy to involved limb and sparing the remaining normal body of chemotoxicity. These techniques can be used in patients with advanced or recurrent sarcoma not suitable for upfront limb salvage surgery. Specialized equipment including a pump and perfusionist are required for such an approach. Hyperthermia has been used along with chemotherapy (melphalan, Cisplatin) with good outcomes in some studies. Few dedicated centres have reported a good limb salvage rate in advanced or recurrent sarcoma patients using isolated limb perfusion [38, 39].

Role of Pulmonary Metastasectomy in STS

Despite achieving a good local control with surgery and radiotherapy approximately 50 % of high grade STS patients develop lung metastases and ultimately succumb to the disease. Various treatment modalities have been tried and Pulmonary Metastasectomy is an option in some patients with good pulmonary function and favourable disease biology. Disease biology is assessed by post treatment recurrence free interval, number of metastatic nodules, histology and site of primary tumor and presence of extra pulmonary sites of metastasis. Majority of studies in the literature are retrospective in nature and few studies have shown 30 to 40 % 5 survival undergoing pulmonary metastasectomy [40]. A wedge resection of lung metastases using staplers can be achieved with minimal morbidity and mortality. Bilateral lung metastases can be tackled with staged thoracotomies and VATS is not indicated due to high chance of missing the metastases.

Role of Radiotherapy in the Management of STS

The role of radiotherapy (RT) is well established in the modern limb salvage protocols for extremity STS. Radiotherapy is indicated in all sarcoma patients undergoing wide excision except for low grade superficial tumors of size less than 5 cm in diameter in which an adequate margin of 1–2 cm is obtained [41]. RT is also indicated in patients with unknown margins and, recurrent sarcomas. Radiotherapy can be given either pre operatively or post operatively. Practical advantages of preoperative RT are reduced field of volume to be irradiated, lower dose, and improved rates

of margin negative resections. At the same time preoperative RT can increase the acute wound problems following surgery. A prospective randomised study to address the issue of timing of radiotherapy and its effect on wound morbidity was conducted [42]. The study concluded that acute wound complications were significantly high in preoperative RT compared to postoperative RT. A recent update of the study [43] showed no significant difference in recurrence rates or survival between pre or postoperative RT. However post operative radiotherapy is widely practiced because of the availability of complete tumor related information including type, grade and margin status and minimal microscopic tumor burden to be treated Peri-operative Brachytherapy has been used successfully by some centres to deliver a tumor bed boost in patients with high grade sarcoma and tight margins with excellent local control rates [41].

Role of Chemotherapy in the Management of STS

Apart from well established indications of chemotherapy in Ewnigs sarcoma and Rhabdomyosarcoma, the role of chemotherapy in STS continues to be debated. Sarcomas are a group of tumors with varying sensitivity to chemotherapy. Also due to rarity and heterogeneity of tumors accrual of patients and comparing outcomes is difficult. Various trials have reported either no benefit or minimal survival benefit using adjuvant chemotherapy in sarcomas. The Sarcoma Meta-Analysis Collaboration (SMAC) addressed this issue by conducting a Meta analysis after taking individual patient details of small studies which used adjuvant Adriamycin based chemotherapy [44]. It showed significant reduction in both local and distant recurrences but only a modest statistically insignificant improvement in overall survival. Recently an update of SMAC was published which included additional trials of adjuvant chemotherapy [45]. This included 5 studies using ifosfamide along with Adriamycin. Significant reductions in local and distant failures along with improved overall survival was noted which was statistically significant mainly in high-grade sarcoma patients. Based on these studies adjuvant chemotherapy can be recommended in high grade sarcomas especially synovial sarcoma [46] and high grade liposarcoma [47]. Unlike in osteosarcoma in which the role of neoadjuvant chemotherapy is well established, studies have failed show any advantage of neoadjuvant chemotherapy in soft tissue sarcomas except in Ewing's sarcoma and embryonal Rhabdomyosarcoma.

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