ANALYSIS OF NON METASTATIC SOFT TISSUE SARCOMAS OF THE EXTREMITIES IN ADULTS & ROLE OF RE-EXCISION FOR UNPLANNED EXCISION

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CERTIFICATE

This is to certify that dissertation on **"ANALYSIS OF NON METASTATIC SOFT TISSUE SARCOMAS OF THE EXTREMITIES IN ADULTS & ROLE OF RE-EXCISION FOR UNPLANNED EXCISION**" is a bonafide work done by **Dr. SIDDAPPA K.T,** in the department of Surgical Oncology, College of Oncological sciences, Cancer Institute(WIA), Chennai, under my supervision and guidance, to my satisfaction.

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CONTENTS

INTRODUCTION

Soft tissue sarcomas are rare tumors comprising less than 1% of all malignant tumors whereas extremity soft tissue sarcomas (ESTS) make up about 60% of soft tissue sarcomas [1,2]. The treatment of ESTS has changed since the 1980s from radical amputations to limb sparing surgery in combination with adjuvant radiotherapy with very similar results, which has been addressed by a prospective, randomized trial at the NCI [3]. Limb sparing excisions can be achieved in approximately 95% of patients. Adjuvant radiotherapy enhances local control, preserve function, and achieve acceptable cosmesis by contributing to tissue preservation. Because upto half of patients with sarcomas after adequate local control of the disease will develop distant metastasis, usually to the lungs. It was hoped that adjuvant chemotherapy would help to decrease the frequency of distant metastasis and increase overall survival. In meta-analysis regarding adjuvant chemotherapy was shown an absolute overall survival of 7% in the group receiving chemotherapy for extremity sarcomas. There are various controversial issues concerning the management of ESTS after unplanned resection such as patient selection for re-excision, imaging before re-excision, factors affecting local and distant recurrence, and the choice of adjuvant therapies.

REVIEW OF LITERATURE

EPIDEMIOLOGY

Sarcoma is a rare malignant tumor that represents a significant challenge to oncologists due to the large number of distinct histologies, each with its own natural history. They represent less than 1% of all malignancies in adults. They may arise in any anatomic site, although for convenience they are typically categorized into the extremity, trunk, head & neck, retroperitoneal and visceral sites [4]. STS are slightly more common in males than in females, in a ratio of 1.4:1. There are more than 50 subtypes of STS. According to the American Cancer Society, the most common types are malignant fibrous histiocytoma (28%), liposarcoma (15%), leiomyosarcoma (12%), synovial sarcoma (10%), malignant peripheral nerve sheath tumors (6%), and rhabdomyosarcoma (5%). All other types of STS occur in percentages of 3% or less [5].

According to Madras Metropolitan Tumor Registry approximately the incidence of soft tissue sarcoma per lakh population are 1% in male and 0.9% in female. According to our Cancer Institute Registry, each year from 1996 to 2005, approximately 9000 to 12000 new cancer cases were registered in our institute. Soft tissue sarcomas accounts for 2% of male and 1 % of female cases of total number of new cases registered. This includes adult sarcomas like primary, unplanned excisions, recurrent, metastatic sarcomas and some benign tumor like schwannoma, fibromatosis and DFSP and pediatric sarcomas. Adult extremity soft tissue sarcomas accounts for 40 to 50% percent of all cases.

Etiology

As with other malignant neoplasms, the pathogenesis of most soft tissue sarcomas is still unknown, although multiple associated or predisposing factors have been identified. Evaluation of the exact cause is often difficult because of the long latent period between the time of exposure and the development of sarcoma, as well as the possible effect of multiple environmental and hereditary factors during the induction period. There are many risk factors related to the development of sarcomas like radiation exposure[6,7], viruses, environmental factors, chronic lymphedema [8], chemical carcinogens, immunosuppression and genetics factors [9, 10].

Pathology

Soft tissue sarcoma probably arises from pleuripotent mesenchymal stem cell. There are wide varieties of histological subtypes of sarcomas, and clinical behavior can be subtly or significantly different depending on histological type. There are 19 histological categories and over 50 subtypes of STS described by Enzinger and Weiss [5]. Following table displays only the malignant tumors arising from the respective mesenchymal tissues according to WHO classification [11].

Table-1: Histologic Classification of Soft Tissue Tumors

FIBROUS TUMORS	SYNOVIAL TUMORS
Fibrosarcoma	Malignant giant cell tumor of tendon sheath
Adult fibrosarcoma, usual type	

Low grade fibromyxoid sarcoma	NEURAL TUMORS
Sclerosing epithelioid fibrosarcoma	Malignant peripheral nerve sheath
FIBROHISTIOCYTIC TUMORS	tumor (MPNST)(neurofibrosarcoma)
Malignant Fibrous Histiocytoma(MFH)	Malignant granular cell tumor
Follicular dendritic cell tumor/sarcoma	Primitive neuroectodermal tumors
Interdigitating reticular cell tumor	Neuroblastoma
True histiocytic sarcoma	Ganglioneuroblastoma
Inflammatory myofibroblastic tumor	PARAGANGLIONIC TUMORS
LIPOMATOUS TUMORS	Malignant paraganglioma
Liposarcoma	EXTRASKELETAL
Well-differentiated liposarcoma	CARTILAGINOUS AND OSSEOUS
Dedifferentiated liposarcoma	TUMORS
Myxoid-round cell liposarcoma	Extraskeletal chondrosarcomas
Pleomorphic liposarcoma	Extraskeletal myxoid
SMOOTH MUSCLE TUMORS	chondrosarcoma
Leiomyosarcoma	Mesenchymal chondrosarcoma
SKELETAL MUSCLE TUMORS	Extraskeletal osteosarcoma
Rhabdomyosarcoma	PLURIPOTENTIAL
Alveolar rhabdomyosarcoma	MESENCHYMAL TUMORS
Embryonal rhabdomyosarcoma	Malignant mesenchymoma
Botryoid rhabdomyosarcoma	MISCELLANEOUS TUMORS
Pleomorphic rhabdomyosarcoma	Alveolar soft part sarcoma
Rhabdomyosarcoma with ganglionic	Epithelioid sarcoma

differentiation(ectomesenchymoma) TUMORS OF BLOOD AND LYMPHATIC VESSELS Epithelioid hemangioendothelioma Angiosarcoma and lymphangiosarcoma Kaposi sarcoma PERIVASCULAR TUMORS Malignant glomus tumor (glomangiosarcoma) Malignant hemangiopericytoma / solitary fibrous tumor	Malignant extrarenal rhabdoid tumor Desmoplastic small round cell tumor Extraskeletal Ewing sarcoma Clear cell sarcoma (melanoma of soft parts) Synovial sarcoma UNCLASSIFIED TUMORS

Clinical features

Soft tissue sarcomas most commonly present as a painless swelling. The size at presentation usually depends on the location of the tumor. Tumors in the distal extremities are often small when discovered, whereas tumors in the proximal extremities are usually large and deep seated. Soft tissue sarcomas grow in a centrifugal fashion and compress surrounding normal structures, but rarely does impingement on bone or neurovascular bundles produce pain, edema, and swelling. Presence of pain is usually associated with large deep seated tumor or with hemorrhage or necrosis or involvement nerves or bone. In neglected cases tumor may ulcerate. Lung is the commonest site for distant metastasis, rarely to bone, liver and brain. Usually symptoms of lung metastasis are cough with hemoptysis or dyspnea. Bone pain and central nerves system symptoms usually seen in recurrent tumors.

Evaluation

Patients should be thoroughly evaluated with detailed history, examination, review of slides and paraffin blocks and surgical notes obtained from patients who have been treated initially elsewhere. MRI/ CT scan of local part should be done before doing biopsy. Biopsy of tumor aids in histopathological examination and ancillary test like immunohistochemistry, electron microscopy and genetic study. Local imaging with MRI or CT scan of tumor bed is done in unplanned excision. Metastatic workup includes chest x-ray and CT scan of thorax.

Biopsy:

The principal reasons for securing a preoperative tissue diagnosis in suspected soft tissue sarcoma are to distinguish these tumors from benign soft tissue tumors or metastatic carcinoma, and also to identify chemosensitive tumors such as primitive neuroectodermal tumours/ Ewing's sarcomas. Tissue for histological diagnosis can be obtained either by trucut biopsy, incision or excisional biopsy. Before biopsy local imaging should be considered where ever there is clinical suspicion of sarcoma because characterizing the lesion before distortion is better than that may accompany the biopsy. Adequate sample of tissue is necessary for definitive histology, grade and to identify prognostic factors that would alter the approach to definitive treatment. Biopsy helps plan multidisciplinary treatment and mandatory when neoadjuvant treatment is planned. Tissue obtained are subjected for

histopathological evaluation, immunohistochemistry, and, when necessary, electron microscopy and molecular markers [12].

a) Trucut biopsy:

Trucut biopsy is done using a 16 to 18F core needle. Biopsy should be done along the line future incision and nearest track to the skin and the tumor without contaminating the compartment. Adequate specimen should be taken and confirm adequacy if frozen section is available.

b) Incisional biopsies:

Play an important role in evaluation of soft tissue tumor, where decisions' regarding tissue diagnosis is doubtful. It is usually done when repeated trucut biopsy have failed. The major concern is tumor seeding and loss of tissue plane. To reduce the risk of seeding, the general guidelines of incisional biopsy should be followed:

1. Incisions oriented along the long axis of the extremity and along the line of the future incision.
2. The incision should be placed directly over the most superficial part of the tumor whenever possible, allowing a surgical approach that avoids crossing through uninvolved compartments to minimize contamination of normal tissues [13].
3. Should not elevate the flaps.

4. Complete hemostasis to avoid hematoma and wound complications [14]. Meticulous hemostasis to avoid hematoma and possible contamination of adjacent muscle compartments.
5. Adequate tissue for histopathology and utilize frozen section to ensure adequate tissue for diagnosis has been obtained.
6. Drain should be avoided if possible or else keep a drain close to incision so that can be excised along with scar.
7. Excision of the biopsy scar and tract is required if a sarcoma is diagnosed. Poorly planned incisions may result in increased wound morbidity during resection and lose the chance of limb salvage [15].

c) Fine-Needle Aspiration Cytology:

At present FNAC is confined to the confirmation of recurrence or rule out a metastatic focus. Even though FNAC material is sufficient to diagnose sarcoma, histological grading of tumor is not possible [16].

d) Frozen Section

It is helpful to confirm the adequacy of tissue biopsy and for diagnosis of malignancy. Frozen section is accurate, but for histopathologic subtypes and grade, it is inferior to permanent sections. It may help to confirm the margin status after resection.

Imaging of local part:

Pretreatment radiological imaging is critical for defining the local extent of a tumor, staging the disease, guiding biopsies, and aiding in diagnosis. Imaging studies are also crucial in monitoring tumor changes after treatment, especially after preoperative chemotherapy or radiation therapy, and in detecting recurrences after surgical resection. Each imaging modality, however, has a particular place in patients with soft tissue sarcomas.

Magnetic Resonance Imaging / CT scan:

Contrast enhanced CT can assess the extent of the soft tissue tumor. It also provides detailed information with respect to adjacent organs and vascular structures. Magnetic resonance images are excellent at delineating tissue planes, neurovascular structures, and characterization of soft tissue tumors without the use of radiation. MRI is better to characterize benign and malignant soft tissue tumors accurately in a high percentage of cases [17, 18, 19]. Totty et al. compared MRI with CT scanning for evaluating soft tissue tumors of the extremities [17]. The T1-weighted MR images better delineated extension of tumors into surrounding fatty tissue and the T2-weighted and spin-density MR images were superior in detecting tumor extension into muscle. Overall, the MRI yields superior resolution images to CT scanning in 33% of comparisons. The only deficiency they identified was the limited ability of MRI to demonstrate soft tissue calcification and gas. In a study comparing MRI with

CT in the evaluation of 27 extremity soft tissue tumors, Week's and associates found that MRI was able to adequately assess neurovascular involvement in 80% of cases compared with 62% of CT scans [19]. Verstraete and colleagues utilized contrast-enhanced techniques in MRI, demonstrating an improved ability to depict tissue vascularization and perfusion [18]. This advantage is relevant in biopsy planning, where the highest yield specimens are more likely to be obtained from viable, well-perfused areas. When bony involvement or destruction is of concern, CT scanning is better suited than MRI.

Metastatic workup

Sarcomas disseminate almost exclusively through the blood; lack a lymphatic system. Early lymphatic spread to regional nodes has only rarely been reported. Most common site of distant metastasis is lung for extremity sarcomas, 90% develop in lung. Although chest X-ray not as sensitive as other imaging techniques, the chest radiograph is still probably the most specific in the diagnosis of lung metastasis. As the most common surveillance tool, the chest radiograph is often the first indication of lung metastasis. CT scan chest is superior to x-ray in detecting lung metastasis [20] and it is mandatory for sarcomas according to NCCN guidelines. Ultrasound and bone scan are not necessary since chance of bone and liver metastasis in extremity sarcoma is very rare. Bone scan be considered only in symptomatic or suspected cases.

Positron emission tomography

The role of positron emission tomography (PET) has not been clearly defined. It is primarily used in the identification of unsuspected sites of metastasis in patients with recurrent high-grade tumors. It appears that tumor grade may be distinguished. Specifically for primary extremity sarcomas, PET response correlated better with outcome than did radiologic tumor size changes after treatment with neoadjuvant chemotherapy [21]. Similar results have been found for pediatric sarcomas. It is used to evaluate patients with doubtful pulmonary metastasis. It is now well recognized that PET can be used to predict response to chemotherapy [22].

Grade of tumor:

After establishing the diagnosis of sarcoma, the most critical piece of information the pathologist can provide to the clinician is histological grade. Histological grade is the most important prognostic factor for adult soft tissue sarcoma. This has been shown in several multivariate studies and is clearly stated in the World Health Organization classification. The pathologic features that define grade include cellularity, histological type and subtype and/or differentiation, pleomorphism, necrosis, and number of mitoses. Unfortunately, the criteria for grading are neither specific nor standardized. Several grading scales and systems are used: a four-grade system (Broders) [23] a three-grade system (low, intermediate, high) such as the National Cancer Institute (NCI) grading system [24] and that of the

French Federation of Cancer Centers Sarcoma Group [25] and a binary system (high vs. low) as is used at MSKCC[26].Even when there is agreement about the number of grades to be used, expert pathologists disagree about specific criteria for defining grade.

Staging

Classification based on 7th edition of International Union Against Cancer (UICC) on cancer staging. Staging includes grade of the tumor [27].

DEFINITIONS

Primary Tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Tumor 5cm or less in greatest dimension

T1a Superficial tumor

T1b Deep tumor

T2 Tumor more than 5 cm in greatest dimension

T2a Superficial tumor

T2b Deep tumor

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

Distant Metastasis (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

Histologic Grade (G)

GX Grade cannot be assessed

G1 Well differentiated

G2 Moderately differentiated

G3 Poorly differentiated

G4 Poorly differentiated or undifferentiated (four-tiered systems only)

STAGE GROUPING

IA	T1a	N0	NX	M0	G1–2	G1	Low
	T1b	N0	NX	M0	G1–2	G1	Low
IB	T2a	N0	NX	M0	G1–2	G1	Low
	T2b	N0	NX	M0	G1–2	G1	Low
IIA	T1a	N0	NX	M0	G3–4	G2–3	High
	T1b	N0	NX	M0	G3–4	G2–3	High
IIB	T2a	N0	NX	M0	G3–4	G2–3	High
III	T2b	N0	NX	M0	G3–4	G2–3	High
	Any T	N1	M0	Any G	Any G	High or Low	
IV	Any T	Any N	M1	Any G	Any G	High or Low	

Management

Surgery: The most effective single-modality treatment for localized soft tissue sarcoma is complete resection with aim to obtain a 1- to 2-cm margin of uninvolved tissue in all directions. Amputation should be reserved for tumors that cannot be resected by any other means, without evidence of metastatic disease and the potential for good long-term functional rehabilitation. This usually includes patients with large, low-grade tumors with considerable cosmetic and functional deformity, who can be rendered symptom free by a major amputation. Rosenberg and associates reported a prospective 2:1 randomized trial of 43 patients comparing limb-sparing surgery (wide excision) and postoperative radiation to amputation; all patients received postoperative systemic chemotherapy. They found that the local recurrence rate was marginally higher in the group undergoing limbsparing surgery (P = 0.06), but a large majority of patients in the limb-sparing surgery group had successful local control of their tumors. There was no statistical difference in overall survival between the two arms [3].

The basic oncological process of growth and its relation to surgery is explained by Enneking's. As sarcomas grow it compresses the normal tissue forms a pseudocapsule. At the periphery of the tumor immune reaction against the tumor cells forms the reactive zone. Through this capsule small finger like projection grows towards reactive zone. When these projections get separated from the main tumor and grow within and around the reactive zone leads to satellite nodules. When these nodule metastasis beyond 2cm from tumor in the same or different compartment it is

called as skip metastasis. There are 4 types of excision based on these oncological process explained by Enneking's [28].

1. Intracapsular resections are usually a result of "shell out" of an apparently encapsulated tumor when a malignant diagnosis was not anticipated.
2. Marginal resection, the plane of dissection is outside the pseudocapsule but before or within the surrounding reactive zone.
3. Wide resection consists of resection of surrounding normal tissue outside the reactive zone.
4. Radical resection involves amputation of limb.

Unplanned Excision

Surgeons working outside specialized oncology centers are expected to have less experience with soft tissue sarcoma. For this reason, sarcomas are frequently evaluated as benign soft tissue tumor and undergo unplanned excision. In this situation, these masses are initially treated with a marginal excision with no regard to the surgical margins and without proper preoperative use of imaging modalities.

Giuliano and Eilber introduced the term 'unplanned excision' for this type of surgical approach to soft tissue sarcomas [29]. The treatment of these patients requires special attention. The status of surgical margins, histological diagnosis, and tumor grade should be re-evaluated at the specialist center before a re-excision is performed and accurate staging of the patient should be accomplished to decide on

treatment modalities. Either computerized tomography and/or magnetic resonance imaging should be used to visualize any possible residual tumor in the extremity. If macroscopic tumor cannot be detected by radiological examination and the surgical margins are negative, further treatment with adjuvant modalities should be planned depending on the tumor properties. However, the correlation between radiological findings and residual tumor is poor after unplanned resection due to the disruption of anatomical planes, and the role of magnetic resonance imaging in the assessment of residual tumors following unplanned resection is doubtful [30]. On the other hand, Manoso *et al* reported that 90% of patients with radiological evidence of tumor positivity had residual disease, whereas this rate was 25% for patients with no radiological evidence of tumor [31]. Re-excision after an unplanned resection is a difficult task for the surgeon. Since the gross tumor has been completely removed, the surgeon has neither visual nor tactile evidence of tumor extent. In addition, the surgeon cannot determine the exact extent of tissue dissection and the area of contamination by cancer cells during the primary operation due to the presence of dense scar tissue indistinguishable from tumor tissue, even by frozen section examination. As a result, unnecessarily wide surgical resections are performed after an unplanned resection that will cause deformity in the extremity. Most of these patients will require reconstruction after re-excision and the functional outcomes, especially of the upper extremity, may be suboptimal.

Residual tumor in re-excision specimens:

he extent of surgery during unplanned resection is vital since it will determine the amount of residual tumor tissue directly affecting the chance of local recurrence. However, the clinical significance of right width of surgical margins for resections with wide margins is controversial [28]. Previous studies have reported a residual tumor rate of 24% to 63% after unplanned resections [29, 32-34]. Soft tissue sarcomas are expected to have extensions into the surrounding tissues macroscopically undetectable during surgery. Hence, tumor spreading beyond the natural boundaries such as the fascial planes is highly probable during an unplanned resection. Re-excision removes the unappreciated residual tumor that extends beyond the pseudocapsule of the primary tumor and was performed in 24% to 100% of patients in previous studies [29, 32, 33, 35-37]. During re-excision, all skin and subcutaneous tissue overlying the contaminated wound as identified by imaging modalities should be removed. The presence of residual disease in re-excision specimens is reported to be a risk factor for local recurrence and has no effect on prognosis [35 to 37]. In addition, residual tumor has been detected less frequently after unplanned resections, if patients with macroscopic tumors were excluded [31, 41]. High rates of residual tumor justify further surgery in order to decrease the rate of local recurrence. The factors that determine for residual disease in re-excision specimens are not clear but patients with positive and uncertain margins after unplanned resection should definitely undergo re-excision. Re-excisions should be avoided when the boundaries of the contaminated surgical bed are unclear, when improvement in surgical margins is unlikely due to the proximity to vital structures

and/or neurovascular bundle, and when further surgery would lead to increased morbidity [42].

Local recurrence and survival:

tudies evaluating extremity STS patients identified a link between positive microscopic margins at initial resection and local recurrence [43-46]. However, the association between local recurrence and subsequent systemic metastases and tumor related death is less clear. There are studies stating that positive margin status or microscopic residual disease after re-excision may affect systemic metastases and survival [37, 38, 46, 47]. In this scenario, either local recurrence may contribute to the occurrence of distant metastases and poor patient survival, or an aggressive tumor may predispose to both local recurrence and distant metastases at the same time. Prognostic factors affecting local recurrence were reevaluated in patients with ESTS treated with an initial unplanned resection in previous studies. Local control is improved with repeated wide margin resections after incomplete primary surgery [35, 37, 39, 48]. On the other hand, local recurrence rate increases in patients initially treated with an unplanned resection outside the specialized centers compared to those primarily treated at specialized centers [49]. In contrast to this, local outcome is reported to be similar in patients treated at specialized centers with definitive resection or re-excision after unplanned resection [35, 37]. However, patient selection bias may have played a role as small, benign looking, and superficially located masses are usually treated with an unplanned resection outside the specialized centers whereas masses that are malignant in appearance are initially

referred to oncology centers. Previous studies have reported a 5-year survival rate of 62% to 84% for patients treated at a referral center starting with a core needle or incisional biopsy followed by planned wide excisions and adjuvant therapies. Although tumor seeding along the anatomical planes can be controlled by postoperative radiotherapy, the possibility of distant metastases may increase resulting in a decrease in overall survival. For these reasons, re-excision after an unplanned resection decreases distant metastases and improves overall survival [35, 37, 38]. The final margin status after re-excision is an independent predictor of disease-free and overall survival. Achieving negative surgical margins is the most effective factor to control distant spread and survival after an unplanned resection [37]. Re-excision after unplanned resection in the case of negative margins should be performed cautiously. In the study by Atalay *et al* [40], after an unplanned resection, patients were grouped as those with positive microscopic margins and those with negative microscopic margins treated with re-excision or without further surgical therapy. In multivariate analysis, low tumor grade and adjuvant radiotherapy were the independent prognostic factors prolonging disease-free survival, however, only re-excision without radiations in the case of negative margins decreased overall survival after unplanned resection [40]. An explanation for the difference in survival may be the selection or treatment biases. Since surgery is unavoidable, more radical surgery could have been performed for patients with positive surgical margins. Even if this was the case, survival was longer in patients with negative margins treated without further surgery compared to those with positive margins.

Adjuvant treatment

Radiotherapy

he goals of adjuvant radiotherapy in the management of soft tissue sarcoma are to enhance local control, preserve function, and achieve acceptable cosmesis by contributing to tissue preservation. Adjuvant radiotherapy is indicated in tumor size more than 5cm of any grade, but the role of radiotherapy for high grade tumor less than 5cm is not defined. The benefit of adjuvant radiotherapy in enhancing local control with conservative surgical resection in soft tissue sarcoma overall has been demonstrated in two randomized clinical trials, one using EBRT and the other using Brachytherapy, with corroboration in a third trial with high local control that compared two EBRT strategies [50- 52].

External Beam Radiation Therapy:

BRT is the most popular adjuvant radiotherapy approach, perhaps because there is less reliance on special technical and operational requirements than are needed for Brachytherapy, which include specific collaboration between surgical and radiation oncologists. EBRT requires comprehensive and multidisciplinary pretreatment consultation and accurate pathologic and radiologic assessment. Radiation can be given pre-operatively or post operatively.

Rationale for Preoperative External-Beam Radiation Therapy: The hypothetical principle in pre-operative radiotherapy is that radiotherapy given with intact vascular supply and microenvironment with a relative absence of actively proliferating tumor clonogens and radioresistant hypoxic cells, which results in a need for lower doses in pre-operative radiotherapy. At a median of 3.3 years of follow-up, local control was identical (93%) in both arms of the study, but a small advantage in overall survival in favor of preoperative radiotherapy was statistically significant [53]. This has not been substantiated with 5-year results. The 5-year results for preoperative versus postoperative treatment, respectively, were as follows: local control, 93% versus 92%; metastatic-relapse free, 67% versus 69%; recurrence-free survival, 58% versus 59%; overall survival, 73% versus 67% (P = .48), cause-specific survival, 78% versus 73% (P = .64). Only resected margins were significant for local control. Tumor size and grade were the only significant factors for metastatic-relapse, overall survival, and cause-specific survival. Grade was the only consistent predictor of recurrence-free survival.

Rationale for Postoperative External-Beam Radiation Therapy: It is rational and convenient to sterilize microscopic nests of residual disease without postponing surgery. Its use is supported by numerous single-institution studies, and it has been shown to enhance local control in a randomized trial that compared conservative surgery and radiotherapy to conservative surgery alone [51]. Canadian Sarcoma Group randomized trial demonstrated that preoperative radiotherapy doubles the risk of early acute wound complication compare to post operative radiotherapy (29%vs 14%). This observation seems to apply almost exclusively to

lower limb lesions [52]. The significant limitations of postoperative EBRT are related to the less precise target volumes compared to those of preoperative EBRT. Postoperative volumes are larger and associated with higher doses, both of which increase the late tissue morbidity. Late morbidity in the same trial includes increased tissue fibrosis and edema mediated by larger doses and larger irradiated volumes in the postoperative setting. Late bone fracture may be related in part to higher radiotherapy doses and larger volumes associated with the timing of radiotherapy.

Relative advantages and disadvantages exist to the use of preoperative and postoperative EBRT (Table-1).

Table-2: Advantages and disadvantages of Pre-operative and Post-operative radiotherapy in soft tissue sarcoma
Pre-operative radiotherapy
Advantages
• Permits radiation volumes and better tissue sparing possible
• Total dose lower than with adjuvant radiotherapy
• Reduces tumor dissemination during surgery
• Better blood supply: possibly lower dose needed to control disease
• Requires preoperative multidisciplinary assessment (major benefit)
• Potential to reduce micrometastasis, may confer survival advantage
Disadvantages
• Complications and side effects are increased

• Overall survival is not improved
• Interpretation of histology can be more difficult after surgery
Post-operative radiotherapy
Advantages
• Wound complications are less
• Less requirement for preoperative multidisciplinary assessment
• Final margins available to help determine need for radiotherapy
• No delay in surgery because of complications from radiotherapy
Disadvantages
• Requires treatment of larger volumes
• Increased late tissue morbidity (dose and volume related)
• Does not improve overall survival

Dose and volume of radiation: The dose of radiotherapy represents an additional unexplored area. Postoperative radiotherapy volumes are significantly larger because they encompass all surgically manipulated tissues and because anatomic planes are disrupted and no longer provide containment barriers to tumor growth and must be considered high risk. Subsequently, the volume is reduced to the immediate area of origin of the tumor, with recognition that this is impossible in some anatomic sites due to the proximity of critical anatomy. These guidelines follow those of the American Brachytherapy Society of at least 2- to 5-cm longitudinal margin beyond the CTV and at least 1 cm beyond the lateral edge of the CTV.

The preoperative dose used in most institutions is approximately 50 Gy in daily fractions of 1.8 to 2.0 Gy over approximately 5 weeks. A postoperative boost is administered only if the surgical margins are positive, although it is unclear whether this is beneficial. Stoeckle et al. described that there is no benefit in giving post operative boost to tumor bed in margin positive [54]. Quality of life and limb function, however, depend on achieving a good local control and on radiation dose and technique. Radiotherapy also is appropriate in resected STS with positive margins. In such cases better local control is obtained with doses higher than 64 Gy and in superficial locations on the extremities [55].

Brachytherapy (BRT):

Brachytherapy is an attractive approach because patients usually leave the hospital having completed all their treatment in about 2 weeks compared to a 6- to 7-week course of EBRT [56]. Radiation will be delivered through the catheters which are place during the time off surgery usually after sixth postoperative day to allow enough time for wound healing. Unlike in postoperative external beam radiation, no attempts are made to treat large margins or to include the scar and the drainage site, although it is acknowledged that this approach has not been formally compared with EBRT in similar cases. The rapid dose fall-off with BRT usually spares more normal tissue than EBRT, except when precision techniques such as IMRT are used. In patients treated with BRT alone, the dose is usually 45 Gy given over 4 to 6 days, and when given as a boost, the dose is usually 15 to 20 Gy plus 45 to 50 Gy with EBRT. The most commonly used isotope is low-dose-rate iridium-192; however,

high-activity iodine-125 is occasionally used in young patients or to protect the gonads. High-dose-rate iridium-192 has been advocated to take advantage of its radiation safety and dose-optimization capabilities.

Adjuvant BRT was evaluated in a randomized trial to determine its role after complete gross resection. The 10-year actuarial local control rates were 81% and 67% (P = 0.03) in the BRT and no-BRT groups, respectively [50]. This improvement in local control, however, was limited to patients with histologically high-grade tumors with local control of 89% and 64% (P = .001) in the BRT and no-BRT groups, respectively. No benefit in low grade tumor. At MSKCC, EBRT is added to BRT only when the geometry of the implant is suboptimal or there is a positive surgical margin. The American Brachytherapy Society has also recommended that BRT should not be used as a sole treatment modality in several situations like:

1. If the CTV cannot be adequately encompassed in the implant geometry.
2. When the proximity of critical anatomy is anticipated to prevent administration of a meaningful dose.
3. When the resection margins are positive, and
4. If there is skin involvement.

In such situations use of external-beam radiotherapy alone or with BRT may be used. One of the most attractive aspects of BRT is the ability to deliver further radiation in previously irradiated patients who may otherwise need amputation to obtain good local control. The Brachytherapy CTV may be difficult to define, but in

general it is represented by the volume of tissue considered at risk for microscopic extension of tumor and includes the tumor bed visualized on radiographic studies and under direct inspection intraoperatively. The dose of radiotherapy represents an additional unexplored area.

Adjuvant Chemotherapy:

STS always have been considered to be less chemosensitive. Approximately 50% of patients develop distant metastasis even with adequate local control of disease, usually to the lungs (extremity sarcomas) or liver (abdominal primary), it was expected that adjuvant chemotherapy would help to decrease the frequency of distant metastasis and increase overall survival. Many randomized trials have used anthracyclines, adriamycin alone (epirubicin, which is less cardiotoxic) or in combination with others like ifosfamide, cyclophosphamide, dacarbazine, actinomycin, methotrexate, and cisplatin. The small size of most other adjuvant chemotherapy trials makes interpretation on an individual basis difficult because most studies had no statistical power to detect small changes in overall survival. Hence role of adjuvant chemotherapy was analyzed in the STS Meta-Analysis Collaboration's of 14 trials of chemotherapeutic regimens using doxorubicin and was found to improve the local recurrence–free interval (6%), the distant relapse–free interval (10%) and recurrence-free survival (10%) from 45% to 55% at 10 years, but its effect on overall survival was only a trend. There was a higher benefit for tumors localized to the extremities, with a significant increase in survival rate (7%) [57]. After this meta-analysis, three more randomized studies using combinations

adriamycin and ifosfamide were undertaken to clarify the still-controversial results concerning adjuvant chemotherapy. These studies, with a wide interstudy variability, failed to demonstrate an improvement in survival [58-60].

Preoperative chemotherapy

Beginning in the 1970s in the United States and the 1980s in Europe, studies have been conducted to evaluate the advantages of preoperative (or neoadjuvant) chemotherapy, which in theory would lead to the rapid and measurable volumetric reduction of primary tumor, would measure in vivo chemosensitivity to the prescribed drugs, and would act immediately on possible occult micrometastases. The studies are few, and the number of patients in the studies is low. Nevertheless, the results seem to demonstrate the same advantages observed with postoperative chemotherapy. As Pisters [61] noted, ‘‘ it is important to bear in mind that one of every two patients will live at least 5 years without pre- or postoperative chemotherapy.’’ The retrospective analyses of the role of chemotherapy for stage III sarcomas from the experience gained at the MSKCC and at the MD Anderson Cancer Center (Houston, Texas) have yielded interesting results [62,63]. The clinical benefits associated with doxorubicin-based chemotherapy seem not to be sustained beyond 1 year, suggesting caution in the interpretation of adjuvant chemotherapy trial. The MSKCC investigators retrospectively compared the treatment of primary high-grade sarcomas with neoadjuvant chemotherapy (doxorubicin, ifosfamide, and Mesna) or with surgery alone. There was a significant improvement in disease-specific survival in patients who had sarcomas larger than 10 cm in the group treated with chemotherapy [63].

Chemoradiation

A possible synergistic effect of combined radiation and chemotherapy has been tried. Combined therapy has been investigated continually for almost 20 years, and studies have confirmed the drastic reduction in the number of amputations, the reduction of recurrences, and the possibility of achieving complete response. High-risk soft tissue sarcomas (i.e., those of large size, deep location, and high tumor grade) present a significant dual threat locally and at distant anatomic sites. In Massachusetts General Hospital, interdigitating courses of chemotherapy and a lower total dose of radiotherapy were used: three courses of doxorubicin, ifosfamide, mesna, and dacarbazine and two 22-Gy courses of radiation (11 fractions each) for a total preoperative radiation dose of 44 Gy. An additional 16-Gy boost dose (in eight fractions) was delivered for microscopically positive surgical margins [64]. The 5-year actuarial local control, distant metastasis-free survival, and overall survival rates for the chemoradiation group were 92%, 75%, and 87%, respectively. Local and systemic toxicity included significant and expected wound-healing complications in the lower limbs evident in 29% [65]. A multicenter study that included 64 patients analyzed using the same protocol has shown significant toxicity, with 3 patients (5%) having experienced fatal grade 5 toxicities consisting of myelodysplasia in 2 and sepsis in 1. Moreover, another 53 patients (83%) experienced a variety of grade 4 toxicities, and 5 patients required amputation [66]. Concurrent chemoradiation can be used in highly selected patients with caution.

Intra arterial chemotherapy

Concept of this technique to improve local control and convert borderline operable tumor where radical procedures culminant into limb loss. Intra-arterial chemotherapy has the potential benefit of providing higher doses of chemotherapy to the affected limb as first pass. Single agent adriamycin/cisplatine or in comination chemotherapy have been used in many studies in conjunction with radiation and surgery. Intra-arterial chemotherapy has been used in conjunction with radiation. In a neoadjuvant study at UCLA, patients received 3 days of intra-arterial doxorubicin before administration of 35-Gy external-beam radiation over 10 days or 17.5 Gy administered over 5 days [67]. Patients were then randomly assigned to receive postoperative doxorubicin intravenously or no further chemotherapy. No difference in survival or local control was noted in this study. Thereafter, a randomized trial by the same group examined preoperative intravenous versus intra-arterial chemotherapy before radiation (28 Gy given over 8 days) followed by wide excision. There was no difference in local recurrence or survival between the 45 patients receiving intra-arterial doxorubicin and the 54 patients receiving intravenous doxorubicin Limb salvage conversion was marginal with high rate of complications in intra-arterial chemotherapy. There was no difference in local recurrence or survival between the patients receiving intra-arterial doxorubicin and the patients receiving intravenous doxorubicin in randomized trial [68]. The complication were high both types including thromboembolism, infection, gangrene, and problems with wound healing, requiring amputation. Pathologic fractures have been reported in patients receiving chemotherapy and relatively larger doses of radiation. At present intra-arterial chemotherapy has a limited role in the treatment of extremity sarcomas.

Hyperthermia and limb perfusion

Limb perfusion in STS of the extremities is a practice dating back to the 1970s .Here limb perfusion requires isolation of the arterial and venous system of the limb by means of a tourniquet and obtaining access to arteries and veins supplying the limb. The arterial and venous supplies of the limb are connected to an extracorporeal circulation system to isolate the limb from the rest of the body. Recirculation of the blood from the limb is performed by a heart-lung machine to reoxygenate the blood. Care is taken after isolation of the limb to ensure that there is no leakage of the circuit into the systemic circulation; technetium-labeled albumin is injected into the circuit, and a probe is used over the heart to ensure isolation of the bypass circuit. Because mild hyperthermia makes chemotherapy more effective hence the blood of the circuit is often warmed to 39°C to 40°C [69]. A number of chemotherapeutic agents have been used for limb perfusion, such as melphalan, nitrogen mustard, dactinomycin, and doxorubicin. The most effective agent has been melphalan when given with tumor necrosis factor (TNF). After isolation of the extremity, melphalan (10 to 13 mg/L limb volume) was perfused into the limb with a dose of TNF ten times the lethal dose for humans, under mild hyperthermic conditions [69]. In early studies interferon- α was included in the regimen, but it was later dropped because it did not appear to improve results over melphalan and TNF alone. Both components of the regimen appeared important; the omission of TNF led to a decrease in tissue dose of melphalan, probably from its effects on the tumor vasculature. Surgery to remove residual tumor was performed 2 to 4 months after limb perfusion. With a median follow-up of 3 years, 71% of patients had successful

limb salvage, 71% of patients had successful limb salvage following isolated limb perfusion. It is difficult to compare this approach to standard chemotherapy, given the heterogeneity of patients in the two types of studies. In aggregate, the response rate does appear to be higher in the perfusion studies than in the infusion studies. However, isolated limb perfusion requires substantial expertise and specialized dedicated equipment. Complications of this technique are high including shock (from systemic leak of TNF); infection; chronic damage to skin, muscles, and nerve; persistent edema; and arterial or venous thrombosis.

Hyperthermia has been used in other ways to enhance the effects of chemotherapy in patients with locally advanced disease. Whole-body hyperthermia using extracorporeal heating of blood has been combined with ifosfamide and carboplatin intravenous chemotherapy. Regional hyperthermia has demonstrated partial and complete responses in patients with locally advanced and metastatic soft tissue sarcoma. Regional hyperthermia provided through an external electromagnetic field (phased array) has been examined in combination with ifosfamide and etoposide, as well as other combinations of chemotherapy. Studies have demonstrated partial and complete responses in patients with locally advanced and metastatic soft tissue sarcoma. The hyperthermia used in these protocols is more aggressive than that used with limb perfusion; higher temperatures have led to a higher rate of local complications. Doxorubicin, ifosfamide, and etoposide chemotherapy with or without regional hyperthermia has shown superior local progression-free survival and disease-free survival on the hyperthermia arm with out over all survival benefit [70].

Prognostic Factors

An analysis of prospective data collected from 1,041 patients older than 16 years with localized soft tissue sarcoma of the extremity with long-term follow-up determined the clinical and pathologic factors that influence local recurrence, distant recurrence, and disease-specific and overall survival [44]. The 5-year survival rate was 76%, with a median follow-up of 4 years. Factors that increased the risk of recurrence are shown in table-3 [71]. Recurrent tumors, positive margins, in elderly patients, with histology of fibrosarcoma and MPNST were associated with high chance of local recurrence. Histologic subtype of liposarcoma was favorable for decreased distant recurrence rate when compared with other histologic types. Factors that increased distant recurrence rates were tumor size larger than 5 cm, high histological grade, deep location, recurrent disease at the time of presentation, and histologic subtype of leiomyosarcoma.

Table-3: Relative Risk Influence on Recurrence of Localized Extremity Soft Tissue Sarcoma

Variables	Local Recurrence (P)	Distant Recurrence (P)	Disease-Free Survival (P)
Age	1.6 (.001)	-	-
Recurrent presentation	2.0 (.001)	1.5 (.02)	1.5 (.033)
Fibrosarcoma	2.5 (.006)	-	-
Malignant peripheral nerve tumor	1.8 (.001)	-	1.9 (.008)
Size >5 cm	-	1.9 (.0001)	2.1 (.0001)
Margin positive	1.8 (.0001)	-	1.7 (.011)
Depth	-	2.5 (.0007)	2.8 (.0002)
High grade	-	4.3 (.0001)	4.0 (.0001)
Leiomyosarcoma	-	1.7 (.024)	1.9 (.012)

French Federation of Cancer Centers Sarcoma Group. Cancer 2001;91:1914

For disease-specific mortality, large tumor size, high histological grade, deep location, recurrent disease at presentation, positive histological margins at the time of resection of the primary, lower-extremity site, and the histological types of leiomyosarcoma and malignant peripheral nerve tumor were all influential factors. Patients with a local recurrence of greater than 5 cm in less than 16 months had a 4-year disease-specific survival of 18%, compared to 81% for patients with a local recurrence of 5 cm or less in more than 16 months [72]. Grade is a dominant factor in early metastasis most of them occur within 24 months, but in late recurrence initial size becomes equally important.

Management of distant metastasis:

Approximately 20% of patients with a soft tissue sarcoma of an extremity develop pulmonary metastases, and in the majority, the lung remains the only clinically evident site of metastasis. Most metastases are detected in follow-up, although 80% develop within 2 years of diagnosis. Median survival from the time metastases are recognized is on the order of 8-12 months [73]. The most common tumors to develop metastases to the lung were, by order of frequency, leiomyosarcoma 21%, malignant fibrous histiocytoma 18%, synovial sarcoma 14%, and liposarcoma 12%. Although metastasis from soft tissue sarcoma, like those from osteogenic sarcoma, is usually confined to the lung, the results of resection are less favorable. In general these tumors are less sensitive to chemotherapy than osteosarcoma, which renders metastasectomy even more compelling. No data have suggested that neoadjuvant therapy improves resectability or survival. Hence,

patients who meet standard criteria for resectability should undergo metastasectomy. Metachronous metastasis prognosis depends on disease free survival, number metastasis, histology, grade and complete resection of metastasis. A meta-analysis of 255 patients by the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Sarcoma Group reported 3-year and 5-year overall postmetastasectomy survival rates of 54% and 38% respectively, suggesting that such treatment can be considered if complete resection of the metastasis is possible [74]. Similar results was found later at the Memorial Sloan-Kettering Cancer Center, complete resection, disease-free interval greater than 12 months, and low-grade histology were significant favorable prognostic factors, whereas an age older than 50 years and a diagnosis of liposarcoma or malignant peripheral nerve tumor were unfavorable prognostic factors. Of 213 patients undergoing metastasectomy, 161 patients had a complete resection and achieved a 3-year survival of 46% and a 5-year survival of 37%. [75]. These results were significantly better than for patients who had an incomplete resection or who did not undergo surgery.

Recurrence in the lung develops in approximately half of the patients who have complete pulmonary resection of soft tissue sarcoma metastases. Median disease-free interval between metastasectomy and lung recurrence is 4 to 6 months. Experience with repeated thoracotomies is limited, with only a few reports in the literature. The National Cancer Institute and M. D. Anderson Cancer Center reported their experiences with 43 and 39 patients, respectively, and found a median survival of 25 and 28 months, respectively, after the second thoracotomy if complete resection is achieved. Complete resection, a single lung metastasis, and a disease-free

interval greater than 18 months were associated with improved survival when compared to patients with incomplete resection or without surgical options. In a series of 86 patients undergoing lung re-resection for metastatic soft tissue sarcoma, Weiser et al found an estimated 5-year survival of 36%. Poor prognostic indicators included more than three pulmonary nodules, nodules greater than 2 cm, and high-grade histopathology of the primary tumor.

The next step was to assess when chemotherapy could be effective in patients undergoing metastasectomy. A European retrospective study at the Department of Surgery, Istituto Portugues de Oncologia Francisco Gentil (Lisbon, Portugal) analyzed prognostic factors in 85 patients who had undergone resection of pulmonary metastasis. In a multivariate analysis, only metastasis dimension and involvement of surgical margins were found to be independent factors associated with survival. Adjuvant chemotherapy was associated with survival only at univariate analysis [76]. A study conducted at the MSKCC of the effects of perioperative chemotherapy in patients undergoing pulmonary resection for metastatic STS of the extremities suggests that systemic chemotherapy has minimal, if any, long-term impact on outcome for these patients [78].

Complications of Primary Treatment

Wound Complications:

Both radiation and chemotherapy decreases the wound healing capacity. They suggested that radiation or antineoplastic drugs delivered more than 7 days before or

after the surgery were accompanied by minimal inhibition of wound healing [79]. The incidence of surgical wound complications was no different for patients undergoing preoperative chemotherapy than for patients undergoing surgery alone [79, 80]. There is definite increase in wound complication rates with radiation alone or in combination with chemotherapy.

Postoperative radiations volumes are larger and associated with higher doses, hence the late tissue morbidity are high. The late effects are increased tissue fibrosis and edema. Late bone fractures due to osteoporosis are related in part to higher radiotherapy doses and larger volumes associated with the timing of radiotherapy. Stinson et al. reported on 145 patients with soft tissue sarcoma who underwent limb-sparing surgery and postoperative radiation with or without chemotherapy and found a 6% fracture rate [81]. In preoperative radiotherapy the targeted volume is known hence radiation field can be planned to reduce the dose to normal tissue. The risks of acute wound complication are high compared to postoperative radiotherapy but late toxicity is less. The risk of wound complication appears to be almost entirely confined to lower-extremity lesions in randomized trials [52,82]

In the MSKCC study wound complications were high in the randomized BRT trial [84]. The overall complication rate was 24% in the BRT arm, compared to 15% in the control arm (P = .18). The rate of reoperation was higher in the BRT group, 9% versus 1% (P = .03). In the Canadian trial comparing preoperative and postoperative irradiation, the wound complication were higher in preoperative radiation arm (35% vs. 17%; P = .01) [52]. The manner in which the wound was

closed, comorbidity, age, smoking history, and treatment center had no apparent influence on the risk.

Other Complications

The development of bony fracture has been reported but the data are scant. The rate of fracture varies from 4% to 10% in radiation arm compared to 0% in the surgery alone arm [83,86]. Some authors suggested that prophylactic intramedullary fixation of the femur should be considered for patients undergoing resection of large tumors in the anterior compartment of the thigh requiring extensive periosteal stripping and adjuvant radiation therapy. Lin et al. evaluated 205 patients with soft tissue sarcoma of the thigh to determine the factors contributing to pathologic fracture of the femur in patients treated with adjuvant radiation (115 patients were treated with BRT alone, EBRT was used in 59, and 31 received a combination of EBRT and BRT)[85]. The 5-year actuarial risk was 8.6%, which on univariate analysis correlated with periosteal stripping (P = .0001), location in the anterior compartment (P = .008), female gender (P = .01), the use of chemotherapy (P = .02), age of 50 years or older (P = .03), and the use of EBRT instead of BRT (P = .04). On multivariate analysis only periosteal stripping retained significance (P = 0.01). The data from Princess Margaret Hospital, where a long-term follow up of patients with combined EBRT and limb-salvage surgery (without adjuvant chemotherapy) showed a significantly higher rate of pathologic fractures with higher radiotherapy doses (60 or 66 Gy; rate of 10%) than with lower doses (50 Gy; rate of 2%) and a higher rate of fracture when radiation therapy was given postoperatively than when it was given

preoperatively [86]. The other complication encountered with adjuvant radiation is peripheral nerve damage. Le Pechoux et al. reported a rate of 1.6% of peripheral nerve damage in 62 patients treated with postoperative radiation [78]. Wound complications necessitating reoperation were seen more in patients who received BRT. Patients treated with postoperative radiotherapy have deteriorating rates of fibrosis and peripheral edema compared to those receiving preoperative radiotherapy, and it is conceivable that their risk of fracture ultimately may be greater.

Follow up

Standard guideline for surveillance helps in identification of recurrence that is potentially curable and limb function can still be salvaged. The majority (90%) of extremity local recurrences occur during the first 5 years after treatment, of which up to two-thirds are detected during the first 2 years [87]. In a retrospective review of surveillance for follow-up of patients with high-grade extremity sarcomas, Whooley and associates evaluated the efficacy and cost-effectiveness of chest radiographs, CT scans of chest, imaging of the affected extremity, and blood tests [88]. Follow-up evaluations were performed every 3 months during the first 2 years, every 4 to 6 months during the third posttreatment year, every 6 months for years 4 to 5, and annually thereafter. Their review found that physical examination was the most common method of detection of local recurrence (97%), with only one recurrence detected solely by surveillance MR (3%). Pulmonary metastasis was identified in 40% of patients, but only 37% of these patients with pulmonary had symptoms as a basis for detection. Asymptomatic patients had their pulmonary metastasis initially

detected with chest radiographs in 83% of cases. In the remainder of patients, pulmonary metastases were detected solely with CT scanning.

NCCN guidelines [89] recommend that patient should be followed up as shown in table-4. Periodic imaging of primary site with MRI or CT scan should be considered if risks of recurrence are high, especially if the location or depth of the lesion makes physical examination unreliable for this determination. Ultrasound can be used in this setting as well. Local imaging may not be necessary after 5 years of treatment because the chance of local recurrence is smaller.

TABLE -4: Surveillance guidelines for extremity soft tissue sarcomas (NCCN).

Stage I	Stage II and III
• History & Physical examination every 3–6mo for 2–3y, then annually. • Consider imaging surgical site with scan annually based on estimated risk of locoregional recurrence. • Consider baseline imaging after primary therapy. • Consider chest X-ray every 6–12mo.	• History & Physical examination every 3–4mo for 3y, then every 6mo for next 2y, then annually. • Imaging of primary site (MRI, CT, consider US). • Chest imaging (plain radiograph or chest CT) every 3–6mo for 5y, then annually

In our institute we follow up the patient every month in 1st year with clinical examination and chest X ray. Once in two months in 2nd year, once in 3 months in 3rd year and then every 6 monthly thereafter till 5 years. After five year annual follow up

chest X-ray and clinical examination, CT thorax was considered only if there was any abnormality in chest X-ray. In our institute metastectomy is considered only if disease free interval was there for more than 6 months with good performance status with few metastases. No chemotherapy will be given following metastectomy. Patients who fail in lung or distant organ within 6 months after treatment or multiple bilateral metastases will be considered for best supportive therapy.

OBJECTIVES

1. To analyze the patient characteristics, tumor characteristics and prognostic factors in patients with non metastatic soft tissue sarcoma of the extremities in adults.
2. To study the role of re-excision for the previously unplanned excision.

MATERIALS AND METHODOLOGY

From January 1996 to December 2005, 145 consecutive cases of non-metastatic adult soft tissue sarcomas of the extremities were included in the study. We excluded all pediatric sarcomas, Rhabdomyosarcoma, Ewing's sarcomas and Primitive neuroectodermal tumors and stage IV disease at presentation or on evaluation. Others like Dermatofibrosarcoma protuberans and aggressive fibromatosis were also excluded.

Out of 145 patients 74 (51%) patients had undergone unplanned resection of a primary sarcoma at a nonspecialized center and were subsequently referred to our institution for further treatment. These were further categorized into re-excision and non re-excision group depending on the review of operative notes, Pathology report, clinical and radiological findings. a) Re-excision group contains 52(36%) patients, out of which 20 patients had clinical or radiological presence of residue disease and the remaining 32 patients had only scar. b) Non re-excision group contains 22 patients of which, 19 were considered for adjuvant radiation and 3 were kept under surveillance without re-excision.

All patients were thoroughly evaluated with detail history, physical examination, review of slides, paraffin blocks and surgical notes (if treated initially elsewhere). Metastatic workup includes chest X-ray and CT-scan of thorax. Extent of local disease was assessed by contrast CT-scan or MRI.

Wide local excision with 2cm normal tissue margin all around is the main surgical resection technique. Radiotherapy was given if the size is more than 5 cm, high grade tumor and unplanned excision suspected to have contamination. External beam radiation was used in all such cases with doses ranging from 50 to 60 Gy with 1.8 to 2 Gy fraction per day. In one patient brachytherapy was used. Chemotherapy was administered at the discretion of the multidisciplinary board. Anthracycline based chemotherapy was given only in young, high grade tumours.

As per our institute protocol lung metastectomy is considered only if disease free interval was there for more than 6 months with good performance status with few metastases. No chemotherapy is given following metastectomy. Patients who failed in lung or distant organ within 6 months after treatment or multiple bilateral lung metastases will be considered for best supportive therapy.

Patients were followed up till august 2009. The recurrence pattern and the time for the tumor to recur were studied at follow up. Prognostic factors such as age group, grade, size, and histology, type of surgery and adjuvant treatment were studied that influence the survival. The prognostic effect of re-excision for the previous unplanned surgeries was studied. The analysis was done for entire 145 patients and those had unplanned excision using the SPSS statistical package (version-10).

RESULTS

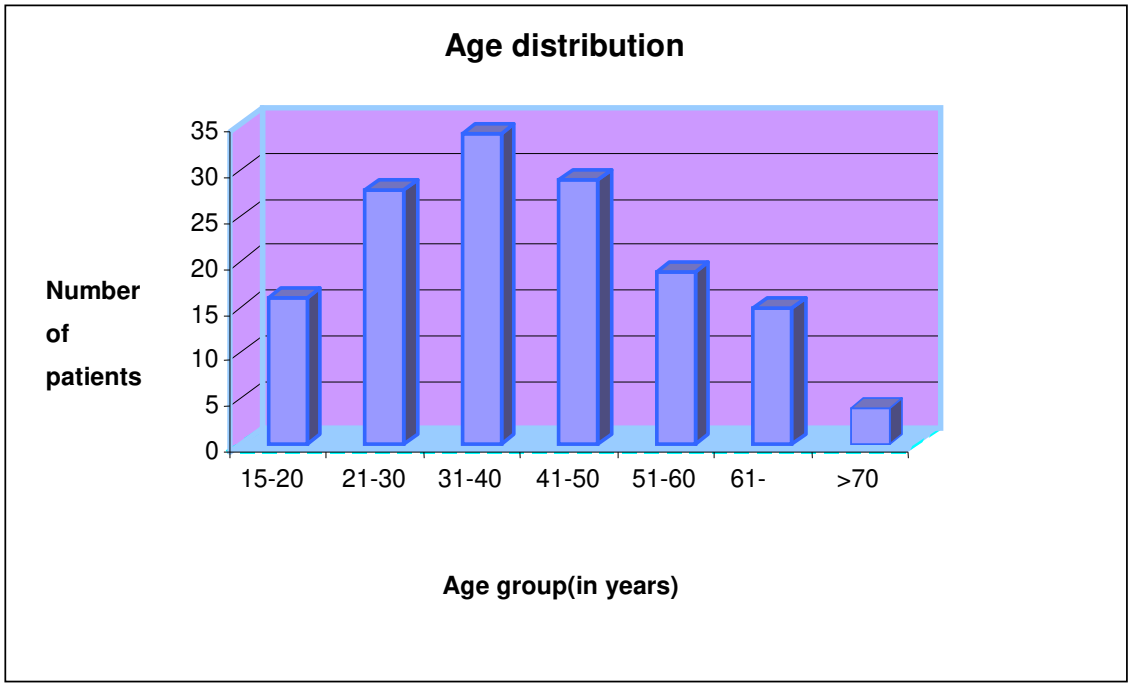


Chart -1: Age distribution

Results:

From January 1996 to December 2005, 145 consecutive adult patients diagnosed with non-metastatic extremity soft tissue were studied and followed up till August 2009. Mean duration of follow-up is 59months (2 - 142months). There were 95 men and 50 women; their mean age was 40.7 years (median age 39years; range 16 to 84).

The most common presenting symptom was painless swelling. The duration of symptoms varied from 1 to 240 months with mean duration of 30 months. Most common histology were Synovial sarcoma (23.4%), MFH (19.3%), Liposarcoma(7.6%), Pleomorphic sarcoma(8.3%) and not classified (spindle cell sarcoma- 21.3%). The characteristic of patients is shown in table-5.

Table-5: Characteristics of patient, tumor and treatment

Variables	Number of patients (percentage)
Age in yrs, median	**39 (15-84)**
Age < 40yrs	74 (50.9%)
Age ≥ 40yrs	71 (49.1%)
Sex	
Male	95 (65.5%)
Female	50 (34.5%)

Size , median in cm	**8 (3-44)**
Unknown	21 (14.5%)
T≤5cm	35 (24.1%)
T>5cm	89 (61.4%)
Tumors > 10 cm	**36 (24.8%)**
Grade	
Low grade	24 (16.5%)
High grade	121(83.5%)
Stage	
Unknown	21 (14.5%)
Stage I	22 (15.2%)
Stage II	26 (17.9%)
Stage III	75(51.7%)
Amputation	53 (36.5%)
Positive margins	4 (2.7%)
Adjuvant treatment	
No adjuvant	67 (46.2%)
Radiation only	54 (37.2%)
Chemotherapy± radiation	24 (16.6%)

Surgical resection was done with 2cm margin all around except when tumor is close to the nerves, vessels and bone where perineurium, periostium and sheath covering vessels were taken as margin.

Surgery is the main treatment. Limb salvage surgery was done in 92 patients (64 %). Fifty three patients (36%) had major amputation. Adjuvant radiation was given in 54 patients, chemotherapy and radiation in 12 and chemotherapy alone in 12 and 67 did not receive any adjuvant treatment. Five patients treated with neo-adjuvant therapy, 2-radiation, 2- chemotherapy and 1-chemoradiation. Out of these 2 were salvaged and 3 underwent amputation.

Recurrence: Totally 47(32.4%) patients had recurrence including local recurrence in 13 cases(9%) , local recurrence with regional node metastases in 3(2%), failed only in regional lymph nodes in 4(2.7%), with both local and distant metastasis in 2(1.3%) and remaining 25(17.3%) failed in distant site alone as shown in table-13.

Median time for distant metastasis was 4 month (1- 44) and 90% had recurrence in lung. Lymph node metastasis in our study was 4.8% seen in synovial sarcoma, pleomorphic sarcoma, leiomyosarcoma, MFH and unclassified spindle cell sarcoma.

Table- 6: Number of recurrence and effect of grade, size and radiation on recurrence.

Factors	Local recurrence	Regional recurrence	distant metastasis
Total Number of recurrence 47(32.4%)	13(9%)	7(4.7%)	27(18.6%)
Grade			
Low (24)	2 (8.3%)	Nil	Nil
High (121)	11 (9.0%)	7 (5.8%)	27 (22.3%)
Size			
Tx (21)	3 (14.2%)	2 (9.5%)	2 (9.5%)
≤ 5cm (35)	4(11.4%)	1 (2.8%)	7 (20%)
>5cm (89)	6 (6.7%)	4 (4.5%)	18 (20.3%)
(Excluding amputation)			
Without RT (24)	3(12.5%)	Nil	1(4.15%)
With RT (54)	6(11.1%)	2 (3.7%)	7(13%)

Recurrence was treated according to site, extent, number, disease free interval and ECOG performance status. 12 patients with local recurrence were salvaged with wide local excision and one patient received palliative radiation only. One patient with lymph node metastasis underwent nodal clearance and lung metastectomy was done in 4 cases. Twenty five were sent on supportive care and 2 defaulted for treatment.

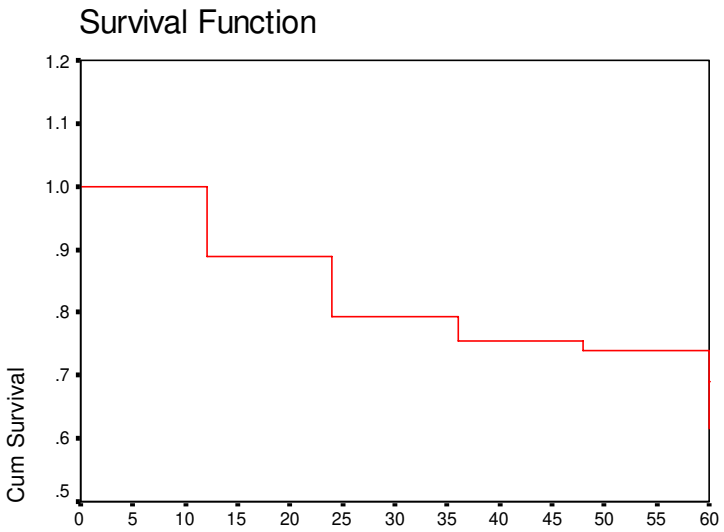
Reconstruction: Primary closure of wound was possible in 127 patients, remaining 18 need reconstruction like local advancement flap in 5, gastrocnemius flap + split skin graft in 2, gracilis muscle flap in 1, posterior interosseous flap, pectoralis major muscle flap, tensor fascia lata flap, anterolateral thigh flap in one each cases and split skin grafting in six.

Complication: Postoperative complication was noted in 11 % (16/145) cases. Two major complications were flap failure requiring reconstruction with free flap. Others like wound infection in 4, wound gaping in 3, marginal necrosis in 3, hematoma, abscess and skin graft loss in one cases each was seen.

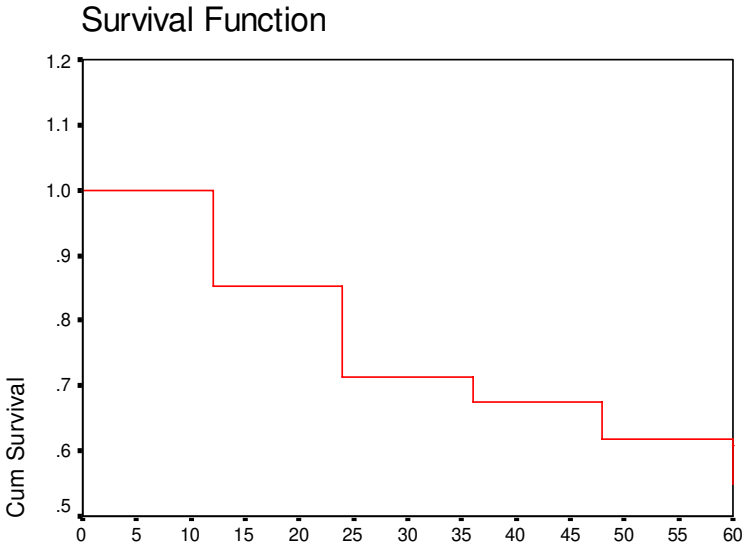
The principal host, tumor-related and treatment prognostic factors that predict for overall survival were assessed include sex, age group, histological grade, tumor size, and adjuvant treatment were analyzed for 145 patients as shown in the table-7.

The five year disease free and overall survival for 145 Patients is 60.1% and 69.2% respectively is shown in graphs.

Overall survival and disease free survival graphs for 145 patients with non-metastatic extremity soft tissue sarcomas.



Graph-1: 5 years overall survival



Graph-2: 5 year disease free survival

Table -7: univariate analysis for entire 145 patients:

Variables	Number of patients (%)	Overall survival (%)	p-value
Age group			
< 40 yrs	74 (50.9%)	80.04	0.0183
≥40 yrs	71 (49.1%)	57.53	
Sex			
Male	95 (65.5%)	66.53	0.940
Female	50 (34.5%)	73..08	
Size			
Tx	21 (14.5%)	83.95	
T1	35 (24.1%)	81.30	0.012
T2	89 (61.4%)	60.47	
Grade			
Low	24 (16.5%)	95.65	0.0037
High	121(83.5%)	63.70	
Adjuvant treatment (excluding amputation)			
Without Radiation	24 (16.5%)	63.77	0.446
With Radiation	54 (37.2%)	78.78	

High grade tumors, size more than 5cm and in patients aged more 40 yrs had significantly lower survival. Chemotherapy (p-0.428) and histological type (p-0.606) did not affect the survival. Margin positivity (0.464) did not effect the survival expect increased risk of local recurrence (50% recurred)

Table-8: multivariate analysis.

Variables	**Number of patients**	**p-value**
Size	≤5cm(35)	0.076
	>5cm (89)	
Grade	Low (24)	0.012
	High (121)	
Age group	< 40yrs (74)	0.010
	≥40yrs (71)	

Analysis of unplanned excision:

Out of 74 patients who had unplanned excision elsewhere; 52 patients underwent re-excision here, 19 were considered for adjuvant radiation and 3 were kept under surveillance without re-excision (after reviewing surgical and pathological reports). The residual disease was found in 50% (26 /52). Of the 52 patients, thirty two patients had only scar without any palpable lump and with normal imaging of which 37.5% (12/32) had microscopic residual disease. Disparity between the clinical and pathological residual disease is shown in table-9:

Table -9: clinical and pathological residual correlation in re-excision group

Total 52 patients	Pathological residue present % (no of patients)	Pathological residue absent % (no of patients)
Clinically or radiologically residue present (20)	70% (14)	30% (6)
Clinically or radiologically residue absent (32)	37.5% (12)	62.5% (20)

Table-10: Recurrence pattern between two groups:

Group	Number of patients	Local	Regional	Distant
Re-excision done	52	1(1.9%)	1(1.9%)	8(15.4%)
No re-excision	22	8(36.4%)	1(4.5%)	2(9%)
Total number	74	9 (12.2%)	2 (2.7%)	10(13.5%)

Local recurrences were high in those who did not undergo re-excision for unplanned excisions. The 5-year disease free survival and overall survival is shown in table-11, the 5-year disease free survival for re-excision group was 77.8 % versus 56.6% for those who did not undergo re-excision (p-0.014), which is statistically significant. In re-excision group there is trend towards increase overall survival but it was not statically significant (0.464).

Table-11: disease free survival and overall survival

Variables(No of patients)	Disease free survival (%)	p-value	Overall survival (%)	p-value
Re-excision done(52)	77.88	0.0148	83.75	0.464
No re-excision (22)	56.63		79.91	

Table-12: 5yr disease free survival in unplanned excision group.

Variables	Re-excision done (%)	No Re-excision (%)	p-value
Size			
≤5cm	78.54	71.43	0.317
>5cm	73.20	62.50	0.504
Grade			
Low	100.00	100.00	0.312
High	73.20	51.92	0.030

In low grade tumors re-excision did not affect the local recurrence or survival but in high grade tumors re-excision has shown significant disease free survival. In re-excision group there is trend towards increasing survival in tumors more than 5cm but it was not statically significant.

Prognostic effect of residual disease: The prognostic effect of residual disease in the pathologic specimen was studied in the subset of patients who underwent re-excision. Presence or absence of residual disease following re-excision did not have an impact on disease free survival or over all survival.

Table-13: significance of residual tumor on survival

Re-excision	**Number of cases**	**5yr disease free survival**	**5yr overall survival**	**p-value**
Pathological residue				
Present	50% (26/52)	75.17%	77.75%	0.1477
Absent	50% (26/52)	81.17%	89.86%	

DISCUSSION

Soft tissue sarcomas (STS) are rare tumors; the crude incidence for male is 1 per lakh and 0.9 per lakh for female according to Madras Metropolitan tumor registry [90]. According to our hospital based registry, soft tissue tumors accounts 2% of male and 1 % of female cases for total number of new cases registered approximately 9000 to 12000 annually [91]. Approximately 30% have metastatic disease at presentation. The world wide incidence is 1 to 2 cases per 100,000 per year [1, 2].

Synovial sarcoma is the most common histology in our study compared to others series, where MFH is being common [29, 32, 35]. Histological subgroup did not show any survival difference, probably due to small number in each group with varying degree of grade and size.

In our study, limb salvage surgery was possible in 64 percent of patients while 36% of the patients underwent amputation. This is probably due to delay in presentation and large size at diagnosis. In our study 61 % of patients had tumors more than 5cm and 24 % had more than 10 cm.

In the our study, we found that sarcomas larger than 10 cm in size carried a 2.5 -fold greater probability of death compared with sarcomas that were less than 5 cm in size ($p = 0.017$).

The benefits of adjuvant radiation therapy after surgery for soft tissue sarcomas of the extremities have been shown in randomized clinical trials comparing conservative resection alone with resection followed by adjuvant radiation therapy [51, 52, and 53]. In our study, a patient who received adjuvant radiation there was a trend towards increased survival but it was not statistically significant. In Sarcoma Meta-analysis Collaboration, adjuvant chemotherapy has showed significant survival benefit of 7% in extremity soft tissue sarcomas. In our study out of 121 high grade soft tissue sarcomas, only 24 patients received adjuvant chemotherapy. There was no statistically significant survival benefit for adjuvant chemotherapy. This may be because of selection bias and small sample size receiving adjuvant chemotherapy.

In our series, univariate analysis for low grade, size less than 5cm and age less than 40years were identified as important prognostic factors. In multivariate analysis, statistically significant survival advantage was found for grade of tumors and age less than 40 years. Size, gender, histopathological subtypes and adjuvant therapy did not show any statistical significance.

Some series of extremity sarcomas have shown that grade, size, age, and Histologic subtype were important prognostic factors in predicting overall survival [92, 93, and 94]. In Berlin et al series the mean mitotic activity was an additional risk factor for local recurrence and survival [93].

Lymph node metastases were seen in 4.7% (7/145) of patients in our study in tumors like synovial sarcoma, pleomorphic sarcoma, leiomyosarcoma, MFH and unclassified spindle cell sarcoma. In other literature nodal metastasis varied from 3.4 to 15% [96, 97]

Unplanned excision:

Most of the soft tissue tumors are benign; the incidence being malignant is 1 in 100 cases of benign tumors [5]. Probably this is the reason why STS are often thought to be benign and are excised without adequate margins in nonspecialist centers and without oncological expertise. These suspicious masses should be subjected to further investigation before definitive excision. In our study 70% had a treatment in nonspecialist centre.

The correlation between radiological findings and residual tumor is poor after unplanned resection due to the disruption of anatomical planes, and the role of magnetic resonance imaging in the assessment of residual tumors following unplanned resection is doubtful [30]. In our study 30% of patients did not have any pathological residue which was reported on imaging with CTscan or MRI. Manoso *et al* reported that 90% of patients with radiological evidence of tumor positivity had residual disease, whereas this rate was 25% for patients with no radiological evidence of tumor [31]. In our study among patients who underwent unplanned excision with post excision local imaging being normal, 37.5 % had microscopic residual disease on re-excision.

The rate of re-excisions in our series is 37.2% which is similar to other published series shown in table-14. Re-excision of unplanned surgeries was performed in 24% to 100% of patients in previous studies [29, 33, 35, 37-39]. Various studies have reported a residual tumor rate of 24% to 63% after unplanned resections [29, 32-39]. The residual disease rate in our series is 50%, which is almost similar to other series.

Table-14: Rate of re-excision and residual disease in the re-excised specimen in major published series

Study	No. of patients	Site	Presentation	Re-excision	Residual disease
Giuliano 1985	90	Ext	Primary	90 (100%)	51%
Lewis, 2000 ,MSKCC	1092	Ext	Primary	407(37%)	39%
M. Fiore , 2006	597	Ext	Primary	318 (53%)	24%
Zornig,1995	189	Ext , trunk	NS	67(35%)	45%
Karakousis 1999	194	Ext	Any	104(43%)	40%
Zagars 2003	1225	Any	Any	295(25%)	45%
Present study Cancer institute (WIA) 2010	145	Ext	Primary	52(37.2%)	50%

Ueda et al. [95] described that the local recurrence rate was higher in patients who received inadequate initial resection than in patients who received successful primary tumor resection in the same institution.

In our study, out of 74 unplanned excisions, 22 patients did not under go re-excision, of which 19 had adjuvant radiotherapy. Despite being margins negative and receiving adjuvant radiotherapy, 36% (8/22) of these patients developed local recurrence. On contrary, recurrence rate was 1.9% (1/52) among the patients who had re-excision after an unplanned excision. This indicates re-excision should be considered in all cases undergoing unplanned excision.

CONCLUSIONS

A patient with any soft tissue swelling, which raises a suspicion of soft tissue sarcoma, should be referred to a specialist centre, where a multidisciplinary team with good experience will be available.

Surgery is the main treatment modality. Grade and age were found to be significant prognostic factors for survival.

All patients who have undergone unplanned excision for soft tissue sarcomas should be followed by wide re-excision because substantial number patients will have residual disease even with normal imaging and re-excision has shown a significant decrease in risk of local recurrence.

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PROFORMA

Name: **Age:** **Sex:**

OP no: CI no:

Date of admission:

Personal history:

Smoking:

Comorbid condition:

Family history:

Treated in other institution (unplanned excision): Yes / No

Diagnosis:

Margins:

Recurrent: Yes / No

Diagnosis:

Primary: Yes / No

Presenting symptoms:

Swelling:

Pain:

Ulcer:

Neurological symptoms:

Other:

Clinical features:

Location:

Size:

Skin:

Neurovascular status:

Regional nodes:

Imaging:

Chest X-ray:

CT Chest:

Imaging local part

CT scan

MRI:

Bone scan:

Biopsy

Trucut biopsy:

Open biopsy:

Repeat biopsy:

Out side treated slide review:

Final diagnosis:

IHC:

Treatment:

Neoadjuvant treatment:

Surgery:

Date of surgery

Type of surgery

Defect:

Reconstruction:

Morbidity:

Date of discharge:

Post operative histopathology:

Margins:

Re- excision for positive margins:

Adjuvant treatment:

Date of completion of treatment:

Status at first follow up:

Date of recurrence:

Status at recurrence: symptomatic/ asymptomatic

Type of recurrence:

Treatment of recurrence:

Date of last follow up:

Status at present: