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RESEARCH ARTICLE

Does Unplanned Excision of Soft Tissue Sarcomas Affect the Oncological Outcome: A Retrospective Study

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Received: 3 May 2025 *Accepted: 30 September 2025*

Abstract

Objectives: Soft tissue sarcoma is commonly misdiagnosed as a benign tumor and excised without appropriate precautions mandatory to deal with malignancy. Referrals after inadequate initial excision account for 19-35% of new patients in sarcoma centers. The objective of this study was to assess the oncological outcome of inappropriately treated soft tissue sarcomas in a retrospective, single-center analysis.

Methods: This study included 43 patients who had soft tissue sarcomas in the extremities and were inadequately treated. They were referred to Cairo University Hospitals, Egypt and managed from November 1999 to April 2017. The minimum follow-up period was 1 year after adequate resection. The oncological outcome was assessed regarding the incidence of local recurrence, chest metastasis as well as the overall survivorship.

Results: This study included 23 males and 20 females. 19 patients developed local recurrence (44.2%). 17 patients developed chest metastasis (39.5%). The incidence of local recurrence and chest metastasis was significantly affected by the type of the margin. Regarding the overall survival, 14 patients (32.6%) died during the follow up, while 29 patients (67.4%) were still alive by the end of the study.

Conclusion: In our study, oncological outcome was significantly affected only by the margin status. Chest metastasis affected overall survival dramatically. Although it is challenging to achieve resection with wide margin, it is mandatory to get good oncological outcome.

Level of evidence: IV

Keywords: Limb salvage, Oncological outcome, Soft tissue sarcoma

Introduction

Soft tissue sarcomas (STS) are rare malignant tumors arising from the mesoderm. STS can occur at any age; however, the most common age of diagnosis is at 56- 65 years. They may arise anywhere in the body. The extremities represent 60% of all STS cases. The commonest site is the thigh.[1]

It is a challenge to suspect STSs and to diagnose before any surgical intervention. It is commonly misdiagnosed as a benign tumor and excised without appropriate precautions mandatory to deal with malignancy. Referrals after inadequate initial excision account for 19-35% of new patients in sarcoma centers.[2-4]

Imaging should be done before the biopsy to ensure that the biopsy of potentially malignant mass is taken in a way that doesn't affect the limb salvage surgery and to avoid injury to vital structures. The main treatment of soft tissue sarcoma is resection with wide margin with or without radiotherapy.[5]

According to the Enneking *et al.*, different types of margins include intralesional margin (resection through the tumor with gross residual disease), marginal margin (resection through the pseudo-capsule), wide margin (resection with normal cuff of tissues all around) and radical margin (the tumor is resected en-bloc with the

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THE ONLINE VERSION OF THIS ARTICLE
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involved muscle compartment).[4]

Thus, the term "unplanned excision" was introduced to describe the operations performed for any excision of STSs without regard for preoperative imaging or the need to remove a wide margin. Residual tumor is the main complication in unplanned STSs which can be gross or microscopic, and this makes re-excision a challenging procedure due to presence of scar tissue, loss of anatomical normal planes, lack of palpable mass that provides a visual and tactile guide to judge resection extent, and poorly placed incisions and drains. This leads to more aggressive resection which may need reconstruction and skin flaps. Potter *et al.* found 18% to 21% difference in disease-specific survival regarding presence or absence of residual disease, and this represents a clinically important difference.[6]

Hence, they are referred to a specialized center immediately after this inadequate excision or later when they develop a recurrent mass. Accordingly, the question arises whether limb salvage for these patients would be oncologicaly safe or not.

The aim of this study was to assess the oncological outcome of patients with inadequately treated soft tissue sarcoma regarding the incidence of local recurrence, chest metastasis and overall survival.

Materials and Methods

This is a retrospective study on 43 patients who had soft tissue sarcomas in the extremities and were inadequately treated. They were referred to Cairo University Hospitals and managed from November 1999 to April 2017. Informed consent was obtained from all patients. This retrospective study was approved by the ethical committee of Cairo University Hospitals (registration number: MD-319-2020) and was conducted according to the guidelines of the Declaration of Helsinki.

The inclusion criteria included patients with soft tissue sarcomas grade I, II, III. (American Joint Committee on Cancer System for Staging Soft Tissue Sarcomas)[7] who were inadequately treated (resected without wide margin).

Our exclusion criteria were patients with soft tissue sarcoma grade IV or previously untreated soft tissue sarcoma (De novo).

The evaluation of our patients included all the demographic data, history taking, physical examination and radiographic imaging. All excised tissues or histological slides were re-examined by an experienced pathologist to determine tumor type, grade, and resection margin status.

The surgical site was assessed carefully to note the location and orientation of surgical incision, site of drain and type of skin closure [Figure 1]. The presence of hematoma or surrounding ecchymosis was noted. Staging of the tumor was done for local and systemic disease extent. Local MRI with contrast was the study of choice to evaluate the tumor bed, to identify any gross residual tumor or to estimate the extent of tumor contamination. Systemic staging included CT chest, bone scan or PET scan.

Figure 1A-D. A case of 46-year-old female with malignant peripheral nerve sheath tumor. Patient underwent inadequate resection and received radiotherapy. The patient then presented with mass in the operative bed. A: Pre-operative radiographs showed enhanced nodules in the operative bed after inadequate resection. B: previous operative scar. C: operative bed after adequate resection. D: after coverage with Thiersch graft. The patient remained disease-free till the end of the study

Tumor bed resection typically included resection of the prior operative incision and drain site with the adjacent cuff of skin and tissues based on the prior operative report, pathology reports, physical examination, and preoperative MRI. According to the MRI, preoperative planning was done by measuring the lesion and adequate margin dimensions. Patients underwent limb salvage surgery taking into consideration adequate margin, postoperative limb function and coverage.

Neurovascular bundles within the margin were sacrificed. This occurred in 15 patients. All sacrificed bundles weren't the main supply for the limb (radial, profunda femoris, and anterior tibial and peroneal vessels). Sciatic nerve was sacrificed in one case only. All soft tissue defects were closed either primary or with soft tissue transfer including musculocutaneous flaps or skin grafts [Figure 2].

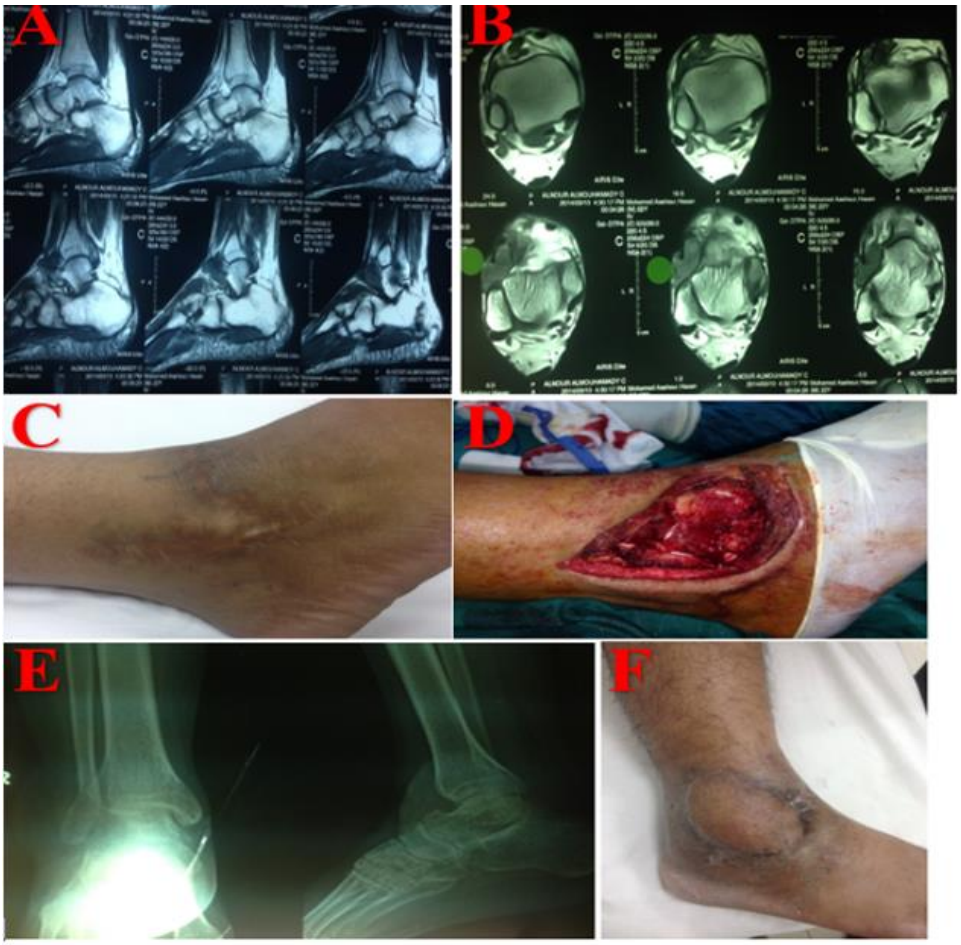

Figure 2A-F. A case of 35-year-old male with myxoid fibrosarcoma ankle and foot. The mass was excised several years before presentation and no pathology was done. A-B: Pre-operative radiographs showed enhanced signal and nodules in the operative bed. C: previous operative scar. D: operative bed after adequate resection. E: post-operative radiographs. F: healed sural flap. The patient remained disease-free for 5 years post-operative

The minimum follow-up period was 1 year after adequate resection done in our institute. The wounds were assessed after two weeks. Coverage by flaps or skin graft was observed for 6 weeks. In the first year post-operatively the patients were assessed every 6 weeks. During the second and third year, they were assessed every 3 months, then every six months during the fourth and fifth year. Initial postoperative MRI with contrast was done as baseline after 6 weeks from the adequate resection. Every three months patients did local MRI with contrast and CT chest. Operative bed was examined every visit for any masses or any complications. In cases of suspicious mass immediate local MRI with contrast was done to exclude recurrence. Patients who developed chest metastasis were sent to oncologist and oncology surgeon for either chemotherapy or metastectomy.

Data were statistically described in terms of mean ± standard deviation (± SD), median, or frequencies (number of cases) and percentages when appropriate. Survival analysis was done for the different outcome measures using Kaplan Maier statistics calculating the mean and median survival time for each group with their 95%CI and the corresponding survival graphs. Comparison was done between the different factors by Log rank method using Cox-

Mantel equation's values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

Results

This study included 23 males (53.5%) and 20 females (46.5%). Mean age was 36 years (range, 10-75 years). Regarding the age, patients were categorized into three groups. The first group (<18 years) included five patients (11.6%), second group (18-40 years) included 21 patients (48.8%), and third group (>40 years) included 17 patients (39.5%).

Our study included 11 different pathologies [Table 1]. The most common was synovial sarcoma (13 patients). 18 patients received radiotherapy (41.9%), while 11 patients only received chemotherapy. Wide margin was achieved in all cases, except three cases where marginal margin was done, as the main neurovascular bundle was adherent to the tumor.

Table 1. The frequency and percentage of patients still alive at the end of study according to pathology.

Pathology	Total N	Died during study	Censored	
			Alive	Percent
Dermatofibrosarcoma protuberans	2	0	2	100.0%
Epithelioid sarcoma	2	0	2	100.0%
Ewing sarcoma soft tissue	3	1	2	66.7%
Fibrosarcoma	3	0	3	100.0%
Leiomyosarcoma	3	0	3	100.0%
Liposarcoma	5	2	3	60.0%
Malignant fibrous histocytoma	2	0	2	100.0%
Malignant peripheral nerve sheath tumor	5	3	2	40.0%
Myxoid fibrosarcoma	2	1	1	50%
Osteosarcoma soft tissue	3	1	2	66.7%
Synovial sarcoma	13	6	7	53.8%
Overall	43	14	29	67.4%

Different tumor sites were documented [Table 2]. The most common site was the thigh (14 patients). Regarding the tumor size, patients were divided into two groups, the first group (<8cm) included 22 patients (51.2%), while the second group (>8cm) included 21 patients (48.8%). Regarding the tumor depth, 21 patients (48.8%) presented with superficial tumors, and 22 patients (51.2%) with deep tumors.

21 patients needed coverage. Reconstruction with prosthesis was done in two cases; in the first case it was mandatory to resect the distal femur to achieve wide margin, while in the second case local recurrence took place after adequate limb salvage so wider margin was required.

Table 2. Different tumor sites

Site	Number of patients	Percentage
Thigh	14	32.56
Leg	9	20.93
Foot and ankle	5	11.63
Forearm	5	11.63
Knee joint	4	9.3
Elbow joint	3	6.98
Shoulder joint	2	4.65
Hand	1	2.32

Local recurrence

19 patients developed local recurrence (44.2%). 11/19 patients (57.9%) were still alive by the end of the study. The overall survival was five years and nine months while the five-year survival was 53.2% [Figure 3].

11/19 patients (57.9%) underwent re-resection after local recurrences. Eight patients (72.7%) were still alive by the end of the study. The overall survival after re-resection was seven years and five-year survival was 69.3%.

8/19 patients (42.1%) underwent amputation after local recurrence. Three patients (37.5%) were alive by the end of the study. The overall survival after amputation was four years, and the five-year survival was 33.3%.

Univariate and multivariate analysis showed that the only factor that significantly affected the incidence of local recurrence was the type of margin. All the patients who were managed by marginal margin resection (3 patients) developed local recurrence. Local recurrence was not affected by age, sex, tumor pathology, tumor size, chemotherapy and radiotherapy.

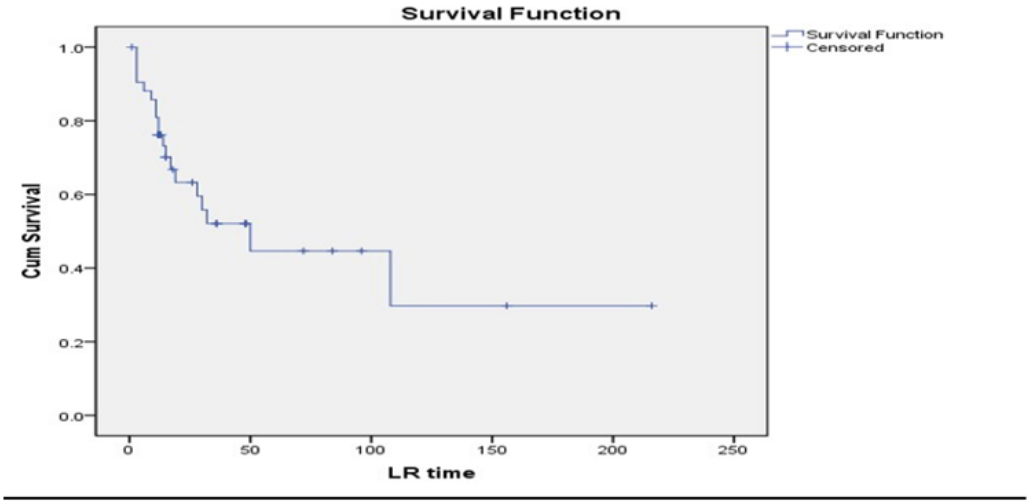

Figure 3. Kaplan Meier curve for survival in local recurrence free patients

Chest metastasis

17 patients developed chest metastasis (39.5%). Six patients received chemotherapy only (35.3%) and seven underwent metastectomy only (41.2%). Three patients received neither chemotherapy nor underwent metastectomy (17.64%). One patient received chemotherapy and underwent metastectomy. Six patients (35.3%) were still alive by the end of the study. The overall survival was 1.5 years, and the five-year survival was 11.8%.

Eight patients underwent metastectomy after chest metastasis. Two patients (25%) were alive by the end of the study. The overall survival was two years and half, and the five-year survival was 25%. Seven patients received chemotherapy after chest metastasis. Four patients (57.14%) were still alive by the end of the study. The overall survival was 3 years, and the five-year survival was 66.7%.

The overall survival of patients without chest metastasis was 10 years (95%CI=88.6-156.5). The five-year survival was 53.6%.

Local recurrence was a poor prognostic factor as it significantly affected the incidence of chest metastasis. This correlation showed that patients who developed both chest metastasis and local recurrence were 11, representing 64.7% of patients with chest metastasis and 57.9% of patients with local recurrence. This relation was statistically significant (P value 0.028) [Table 3].

Chest metastasis was also significantly affected by the type of margin, as all the patients with marginal margin resection developed chest metastasis. However, it was not affected by age, sex, tumor size, pathology, chemotherapy and radiotherapy.

Patient survivorship

Regarding the overall survival, 14 patients (32.6%) died during the follow up, while 29 patients (67.4%) were still alive by the end of the study. The estimated overall survival was 7.5 years. The estimated overall five-year survival was 59.8% [Figure 4]. Regarding disease-free survival, 18 patients had no evidence of disease (41.9%). Overall survival for those patients was 8 years (95%CI=55.69-155.84). The five-year survival was 30.3%.

The overall survival after wide margin was 12 years (95%CI=111.6-177.4) while in marginal margin was 3 years (95%CI=23.1-56.9). The five-year survival was 62.7% in wide margin and 33.3% in marginal margin. The P value 0.388 was statistically insignificant.

Table 3. Cross table for local recurrence versus chest metastasis

Chest metastasis and local recurrence cross table					
			Local recurrence		Total
			No	Yes	
Chest metastasis	No	*Count*	18	8	26
		% within Chest mets	69.2%	30.8%	100.0%
		% within LR	75.0%	42.1%	60.5%
	Yes	*Count*	6	11	17
		% within Chest mets	35.3%	64.7%	100.0%
		% within LR	25.0%	57.9%	39.5%
Total		*Count*	24	19	
		% within Chest mets	55.8%	44.2%	100.0%
		% within LR	100.0%	100.0%	100.0%

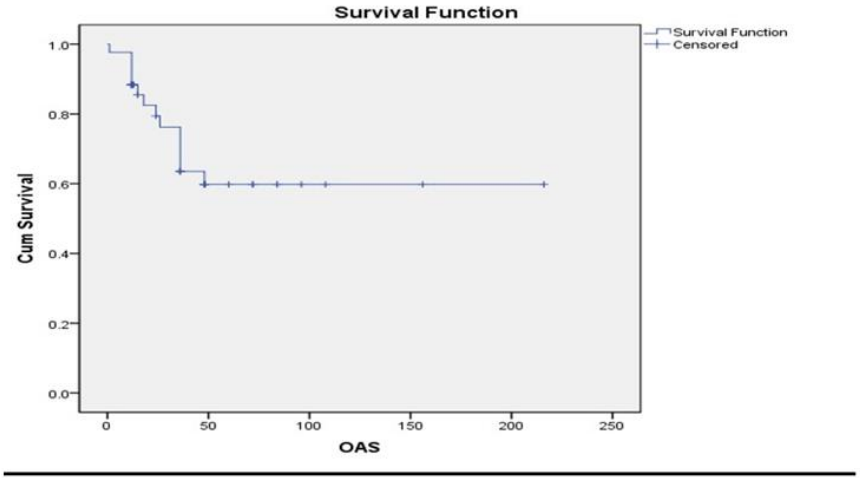

Figure 4. Kaplan Meier curve showing the overall survival of all patients in the study

Regarding disease-free survival, in the wide margin group, 18 patients (45%) were disease-free while in the marginal margin group, no patients were disease-free. The overall survival in the wide margin group was 9 years and half, while in the marginal margin group was eight months. The five-year survival was 33.1% in the wide margin group and 0% in the marginal margin group. The P value 0.026 was statistically significant [Figure 5].

Patients in the wide margin group who didn't develop chest metastasis were 26 (65%), while in the marginal margin group, all patients developed chest metastasis. The overall survival of patients with wide margin was 11 years (95%CI=99.3-168.4), while that of marginal margin patients was 1 year and two months (95%CI=5.5-22.5). Five-year survival was 59.2% in wide margin and 0% in marginal margin. The P value 0.03 was statistically significant.

Tumor size, pathology, chemotherapy and radiotherapy did not significantly affect the survival of the patients.

Discussion

In the current study, we retrospectively analyzed a single-center cohort regarding patients with previously inadequately treated (not resected with wide margin) soft tissue sarcomas. We assessed the oncological outcome and the prognostic factors of STSs patients after re-excision and limb salvage.

In our study, the rate of local recurrence was 44.2%. The five-year survival of patients who developed local recurrence was 53.2%. Our recurrence rate was similar to Dapper *et al.* (45%).[8] Potter *et al.* stated that the local recurrence rate was 34%. The five-year survival in patients who didn't develop local recurrence was 89.7%. He stated that the local

recurrence rate was higher in patients with residual tumor in the resected tumor bed. In patients who had gross residual disease in the resected tumor bed, the five-year survival was 66.7%.[6] This also may justify our results as our study included only high-grade tumors and all the patients had residual disease in the resected tumor bed.

Davis *et al.* reported that recurrence rates were 16.6% of the patients with residual disease and only 1.6% in patients without residual disease.[9] Tomoki Nakamura *et al.* reported the least local recurrence rate in literature (7.6%) and highest five-year survival 91% in patients who didn't develop local recurrence.[10]

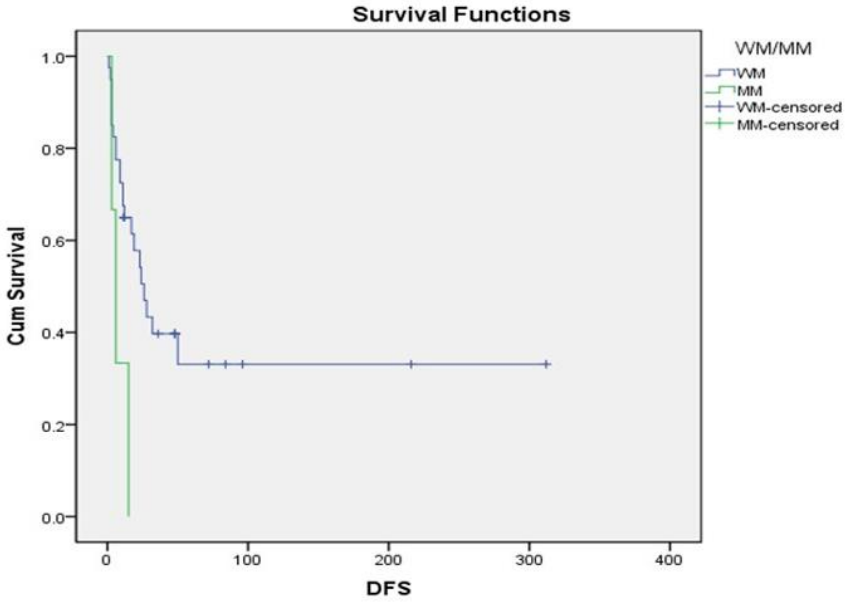

Figure 5. Kaplan Meier curve showing disease free survival according to margin status

In our study, the incidence of chest metastasis was 39.5%. The five-year survival was 53.6% in patients who didn't develop chest metastasis. While the patients who developed chest metastasis had five-year survival 11.8%. Hanasilo CEH *et al.* studied 29 patients with planned excision and 23 patients with unplanned excision. In unplanned excision, patients with low-grade tumors were 17.4% and with high-grade tumors were 82.6%. The rate of distant metastasis was 34.8% in patients who underwent unplanned excision. This rate of metastasis is almost similar to our study as our study included only patients with unplanned excision. The five-year survival was 74.9% in patients who didn't develop chest metastasis in the unplanned group. He stated that chest metastasis rate and five-year survival in patients who didn't develop chest metastasis was better in the unplanned group than planned one.[11] This result was similar to Arai *et al.*, Quershi *et al.,* and Fiore *et al.*[12-14]

M. Venkatesan *et al.* studied 42 patients. Re-resection was done in 35 patients, amputation in 5 and 2 patients underwent re-resection but declined any further surgery. The rate of chest metastasis was 4.8%.[15] T. Morri *et al.* reported no chest metastasis.[16]

In the current study, the five-year survival was 59.8% which is the lower than most of the literature. The survival rate of STSs is multifactorial and depends on different parameters, such as grading, tumor size, surgical experience/resection margins, metastatic status, different subtypes and local recurrence; therefore, the study cohorts are not easy to compare. Daniel A. Jones *et al.* studied 44 patients. The tumor grade was low in 8 (18%) patients, intermediate in 4 (9%) patients and high in 32 (73%). The AJCCT (tumor) stage was T1a in 27 patients (61%), T1b in 2 (5%), T2a in 13 (29%), and T2b in 2 (5%). The five-year survival was 95%.[17]

Potter *et al.* studied 203 patients. 139 patients had planned resection whereas 64 patients had unplanned resection. After resection of tumor bed in patients who had unplanned resection, microscopic residual tumor was found in 40 (63%) patients, gross residual tumor was found in 6 (9%) patients and no residual tumor was found in 18 (28%) patients. The overall five-year survival was 74%. He stated that residual disease affected the survival rate.[6] This can explain our low five-year survival rate as residual tumor was found in all patients.

We correlated the impact of several factors on oncological outcome. Superficial lesions had better oncological outcomes than deep lesions, but it was statistically insignificant. Muehlhofer *et al.* also found no statistical significance between superficial and deep lesions for overall survival.[18] Morii *et al.,* Potter *et al.* and M. Venkatesan *et al.* stated that superficial lesions had better oncological outcomes than deep lesions.[6,15,16]

We found that wide margin, unlike marginal margin, had

less incidence of local recurrence and chest metastasis. It was statistically significant. In contrast to our study, Ramu *et al*. and Clarkson *et al*. stated that there was no difference in local and systemic recurrence rates when marginal margin was done to save major neurovascular structures.[19,20] O'Donnell *et al*. also stated that even positive margin was accepted to save major neurovascular bundle and had no impact on local and systemic recurrence.[21]

We found that patients who received radiotherapy developed chest metastasis more than those who didn't receive. This can be explained by bias in selecting patients who received radiotherapy. Most of them either had a large tumor size or there are doubtful margins. Local recurrence was less in patients receiving radiotherapy.

Manoso *et al.* and Potter *et al*. reported that radiotherapy didn't affect local recurrence rate after reresection of operative bed with negative margins after inadequately treated soft tissue sarcoma. [4,6] In contrast, Kepka *et al*. reported 12% local recurrence rate after radiotherapy treatment without tumor bed resection after unplanned excision.[22]

We correlated the relation between local and systemic recurrence. We found that among patients with local recurrence, 64.7% developed systemic recurrence while patients with chest metastasis, 57.9% developed local recurrence. In contrast to our study, Gustafson *et al*. studied 375 patients with soft tissue sarcoma including primary, unplanned excision and complicated. He stated that there was no relation between local recurrence and chest metastasis.[23]

Limitations of our study included lack of full data about previous surgeries, mixed tumor subtypes which could directly affect the potential capability of metastasis and oncological outcome, being retrospective, lack of control group (e.g. patients underwent amputation) as well as potential selection bias in treatment allocation. Points of strength included long follow-up period, good documentation of cases and statistical correlation between all factors.

Conclusion

In our study, oncological outcome was significantly affected only by margin status. Chest metastasis affected overall survival dramatically. Although it is challenging to achieve wide resection, it is mandatory to get good oncological outcome. Radiotherapy may decrease the incidence of local recurrence, but it did not affect systemic failure and the overall survival. Further prospective studies with a larger number of cases are required.

Acknowledgement

N/A

Authors Contribution: Authors who conceived and designed the analysis: Wael Sadek and Walid Ebeid/Authors who collected the data: Ahmed Gamal and Wessam Abou Senna/Authors who contributed data or analysis tools: Wael Sadek and Ahmed Gamal/Authors who performed the analysis: Wael Sadek/Authors who wrote the paper: Wael Sadek and Walid Ebeid

Declaration of Conflict of Interest: The author(s) do NOT have any potential conflicts of interest for this manuscript.

Declaration of Funding: The author(s) received NO financial support for the preparation, research, authorship, and publication of this manuscript.

Declaration of Ethical Approval for Study: This retrospective study was approved by the ethical committee of Cairo University Hospitals (registration number: MD-319-2020) and was conducted according to the guidelines of the Declaration of Helsinki.

Declaration of Informed Consent: There is no information (names, initials, hospital identification numbers, or photographs) in the submitted manuscript that can be used to identify patients.

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