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Original Article

FUNCTIONAL LIMB-SALVAGE SURGERY WITH POSTOPERATIVE RADIOTHERAPY AS A TREATMENT STRATEGY FOR ADULT SOFT TISSUE SARCOMA OF THE LOWER EXTREMITY

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ABSTRACT

Objectives: This prospective multicenter study was conducted to evaluate the outcome of patients with lower extremity soft tissue sarcoma (STS) treated with functional limb-salvage surgery (FLSS) with adjuvant radiotherapy (RT), defined as the 5-year local recurrence free rate (LRFR), distant metastasis free rate (DMFR), local recurrence/distant metastasis free rate (LR/DMFR) and survival rate (SR).

Patients and Methods: Treatment strategy was functional compartmental resection that emphases wide surgical excision with a preservation of at least one innervated muscle in a compartment to improve functional outcome combined with adjuvant postoperative RT. Excised specimens were examined histopathologically for evaluation of the surgically defined margin as free histological margin; positive microscopic resection margin was defined as tumor cells present at or within 1 mm of the inked margins of resection. Complications were assessed in terms of significant wound complication, bone fracture, and peripheral nerve damage. The study included 26 patients; 14 females and 12 males with mean age of 46.9±16 years.

Results: All managed lesions were non-central (not arising from the groin); 4 lesions (15.4%) were superficial without deep fascial invasion and 22 lesions (84.6%) were deep with a mean excised lesion diameter was 9.3±6.35. Excision margin was free in 22 specimens (84.6%) but was positive for sarcoma cells in 4 specimens (15.4%). Significant wound complications developed in 5 patients (19.2%), 2 required re-operation, bone fracture occurred only in one patient (3.8%) and three patients had nerve damage. Five patients (19.2%) developed LR after a mean duration of 27.6±4.8 months, 3 of them had positive margins; one patient required amputation, 3 patients required wide local excision plus further radiation and wide local excision alone in one patient. Distant metastasis developed in 8 patients (30.8%) after a mean duration of 27±6.5 months and 11 patients (42.3%) patients died after a mean duration of 31.6±7.5 months; all the 8 patients with distant metastasis and 2 whom had local recurrence died and one died of myocardial infarction. All determined rates showed progressive decrease throughout the follow-up period with the least LRFR (80.8%) and DMFR (73.1%) were at 36 months after surgery, while the least LR/DMFR was 50% at 42 months after surgery. The final SR was 57.7% at 48 months. There was a negative significant correlation between the postoperative 5-year local control rate and presence of free surgical margin (r=-0.562, p=0.003) and the diameter of the resected tumor, (r=-0.494, p=0.01) and a negative significant correlation between 5-year disease free rate and the diameter of the resected tumor, (r=-0.406, p=0.039).

Conclusion: The reported local recurrence rate after treatment of STS of lower extremity with functional limb salvage surgery with RT is comparable to published rates and suggested that in patients with lower extremity STS carefully performed FLSS followed by RT may serve as definitive therapy with acceptable outcome.

Key Words: Sarcoma, lower limb, limb salvage

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INTRODUCTION

Soft tissue sarcomas represent a heterogeneous group of malignant tumors arising in mesenchymal tissue and in the autonomic and peripheral nervous systems. Only 1% of all malignancies in adults are STS; most STS are localized at the extremities (50%), trunk and retroperitoneum (40%), or head and neck (10%). Rarely, these tumors arise in the gastrointestinal tract or gastrointestinal stroma, and a small percentage of these are called gastrointestinal stromal tumors.[1]

Soft tissue sarcomas constitute less than 1% of all newly diagnosed malignant diseases. Approximately 50% of the patients with STS will die of their disease. STS represent a heterogeneous group of tumors with wide variations in presentation, histologic appearance and prognosis. Although, STS are labeled and grouped by their cell of origin, in some types the origin is unknown.[2]

Soft tissue sarcomas are usually surrounded by a pseudocapsule which contains tumor cells and they can exhibit a discontinuous growth pattern. Macroscopically undetectable branches might grow along given anatomical structures, thus the whole sarcoma-related anatomic compartment should be judged as tumor-contaminated. The high rate of local resection failure is often caused by insufficiently extended primary resections[3]. Histologic grade, tumor size, and depth (superficial or deep) are well-established prognostic markers for local control and disease-free survival. Besides these parameters, nodal status and distant metastases make up the staging criteria for the current classification of STS.[4]

The main prognostic factors are histological grading, tumor size and surgical radicality. The operation aims at the removal of the whole tumor bearing anatomic compartment. Even wide excisions of the sarcoma surrounded by 3cm of tumor free tissue will lead to at least 60% local recurrences. Excisions along the pseudocapsule (enucleation) will most likely leave parts of the tumor behind. Insufficient surgical radicality cannot be compensated for by adjuvant therapies. The resection should be carried out without compromises.[5]

Before the 1980s, amputation was frequently considered standard treatment for soft tissue sarcoma of the extremities. This practice was changed in 1982 with the report of the randomized trial from the National Cancer Institute on the treatment of extremity sarcoma, which compared amputation with function-sparing surgery and radiotherapy. The local recurrence rate after treatment with function-sparing surgery and radiotherapy was only 15%, and there was no survival difference between the two treatment groups[6]. Thereafter, many institutions published outcome results for series of patients treated with function-sparing surgery and RT. Reported local recurrence rates ranged from 0% to 25%, with most studies documenting local recurrence rates of ≤15%.[7]

Published local recurrence rates after treatment with function-sparing surgery without adjuvant RT vary greatly and depend to a large extent on the type of surgery performed, i.e., marginal excision, wide excision, or radical excision. Marginal excision is defined as removal of the gross tumor with no attempt to remove a cuff of normal tissue; wide excision generally refers to removal of the gross tumor with at least 2cm of normal surrounding tissue; radical excision refers to removal of the entire compartment in which a tumor is located.[8] Reported rates for local recurrence after marginal excision alone have been unacceptably high, ranging from 56% to 75% in some series.[9]

The impact of timing and mode of RT was a matter of controversy; external beam radiation doses may be limited by adjacent radiosensitive tissue, intraoperative boost radiation has been devised to achieve a higher total radiation dose in combination with external beam radiotherapy; however, intraoperative RT was found associated with a higher rate of infectious complications, but the risk of death or recurrence was reduced by 40%.[6] Petersen et al.[10] found STS treated with an aggressive approach of combined external-beam RT, surgery, and intraoperative RT had improved local and distant control, with acceptable toxicity.

PATIENTS AND METHODS

This prospective multicenter Adult Sarcoma Program was instituted, 6 years ago, at General Surgery Departments, Al-Hussein, Benha and Menoufiya University Hospitals in conjunction with Radiation Oncology and Nuclear Medicine department, Al-Azhar University to evaluate the outcome of patients with lower extremity soft tissue sarcoma (STS) treated with functional limb-salvage surgery with adjuvant radiotherapy, defined as the 5-year local recurrence free rate (LRFR), distant metastasis free rate (DMFR), local recurrence/distant metastasis free rate (LR/DMFR) and survival rate (SR).

Patients' evaluation included full history and physical examination, complete blood count, and serum chemistry analyses and CT or MRI scan of the primary tumor site and chest CT were also obtained. Inclusion criteria included patients with non-metastatic STS of the extremities and for whom an amputation was believed necessary. All patients underwent incisional biopsy for confirmation of diagnosis and for histopathological typing.

Treatment strategy was functional compartmental resection that emphases wide surgical excision, wherever possible, with a preservation of at least one innervated muscle in a compartment[11] to improve functional outcome combined with adjuvant postoperative radiotherapy. Surgical technique was conducted according to that previously described by Pisters et al.[12] in brief; all visible or palpable tumors were resected. Resection was performed through normal tissue planes outside the tumor pseudocapsule along with en-bloc resection of the biopsy site. When the tumor was intermuscular or intramuscular, resection included one or more of the involved muscle bundles. The closest margins were frequently located along the main neurovascular bundle of the involved compartments. When possible, an attempt was made to save major nerves and vessels by dissecting the enveloping sheath free of the structure en bloc with the tumor specimen. When the tumor was near to bone stripping of the periosteum or resection of the adjacent part of bone may be required.

Intraoperatively, the anatomical depth of each tumor was evaluated relative to the investing fascia of the

extremity, with tumors being characterized as either superficial or deep; superficial tumor is located exclusively above the superficial fascia without invasion of the fascia, while deep tumor is located either exclusively beneath the superficial fascia, or superficial to the fascia with invasion of or through the fascia, or superficial and beneath the fascia. The tumor was considered to be in the lower extremity if it was at or beyond the groin. Tumor location was defined as central if the tumor originated in the groin area. Patients ineligible for functional compartmental resection who required radical excision or amputation were excluded off the study.

Excised specimen was preserved till pathological analysis for tumor grading and confirmation of preoperative and intraoperative findings and evaluation of the surgically defined margin as free histological margin. Positive microscopic margin of resection was defined as tumor cells present at or within 1 mm of the inked margins of resection. Tumors were divided into three grades (low, intermediate, and high) based on an assessment of tumor differentiation, mitotic activity and amount of necrosis.[13]

Complications were assessed in terms of significant wound complication, bone fracture, and peripheral nerve damage. The significant wound complications were defined as those wound problems requiring operative revision for coverage or threatened limb loss; persistent seroma requiring repeated aspirations, drainage, or both; wound separation >2 cm; hematoma >25 ml; purulent wound discharge; or a combination of these. Peripheral nerve damage was graded according to the National Institute of Health's Common Toxicity Criteria: a) Neurosensory toxicity was defined as follows: grade 1: mild paresthesias, loss of deep tendon reflexes; grade 2: moderate sensory loss, moderate paresthesias; grade 3: severe sensory loss or paresthesias that interfere with function; and grade 4: incapacitated. Neuromotor toxicity was defined as follows: grade 1: subjective weakness without objective findings; grade 2: mild objective weakness without significant impairment of function; grade 3: objective weakness with impairment of functions; and grade 4: paralysis.

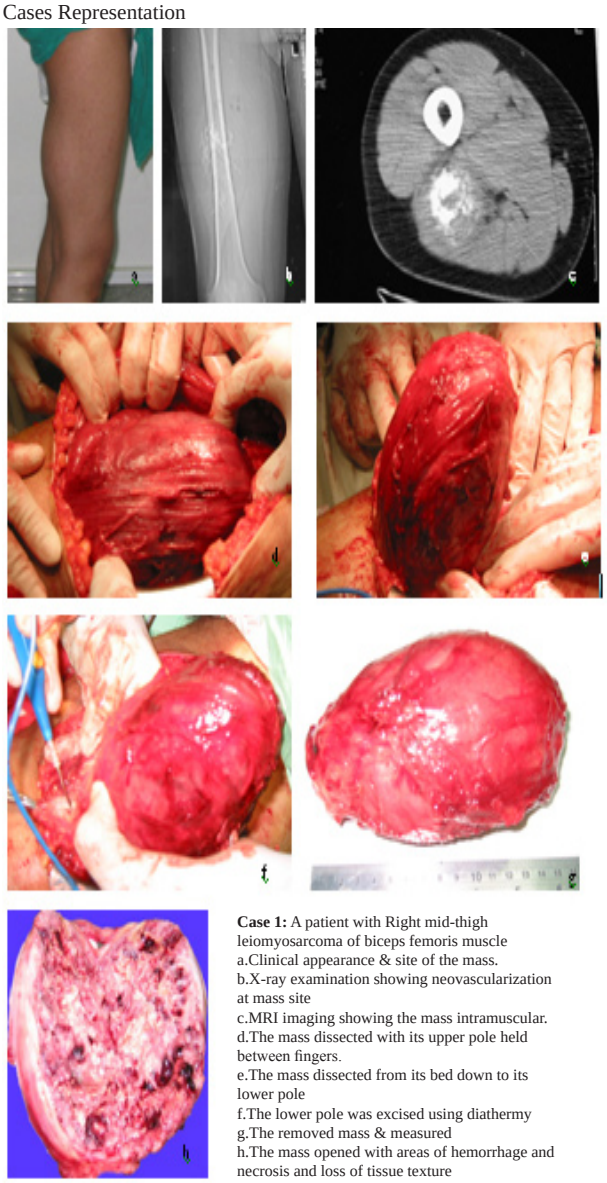
Statistical analysis:

Obtained data were presented as mean±SD, ranges, numbers and ratios. Possible relationships were investigated using Pearson linear regression to define the regression coefficient "r" and its statistical significance. Statistical analysis was conducted using the SPSS (Version 10, 2002) for Windows statistical package. P value <0.05 was considered statistically significant.

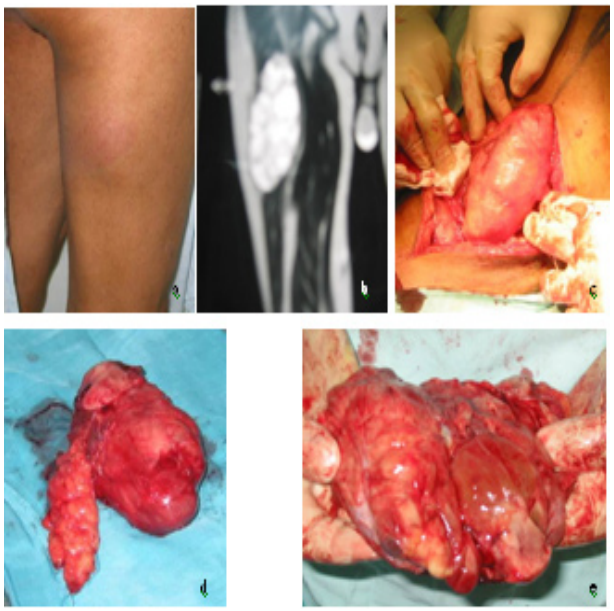
RESULTS

The study included 26 patients; 14 females (53.8%) and 12 males (46.2%). Patients had mean age of 46.9±16; range of 19-75 years. Non of the managed lesions were central (arising from the groin); 10 cases (38.5%) were in mid-thigh (Case 1 & 2), 10 cases (38.5%) were in the upper thigh; in 2 cases (7.7%) the mass was encroaching on the buttock and in 8 cases the mass was not encroaching on the buttock (Case 3), 5 lesions (19.2%) were located in lower thigh and not involving the popliteal fossa (Case 4) and one case (3.8%) had an extensive lesion involving from the mid-thigh to the upper leg encroaching on the popliteal fossa (Case 5).

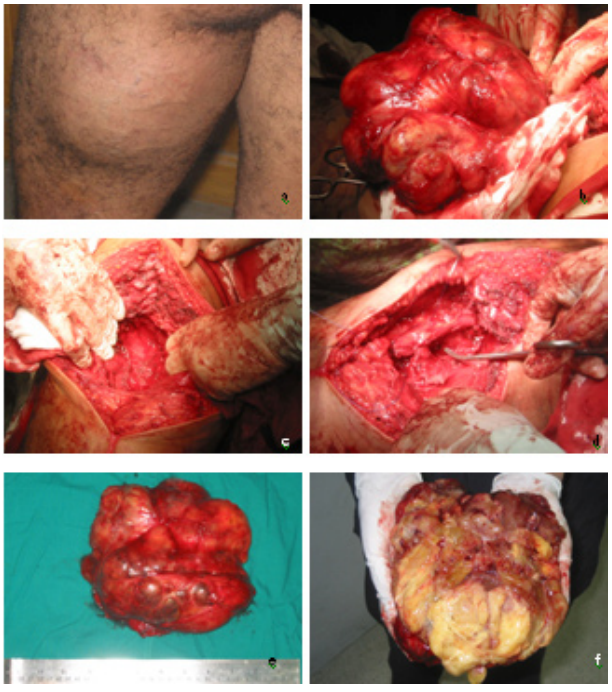
Cases Representation



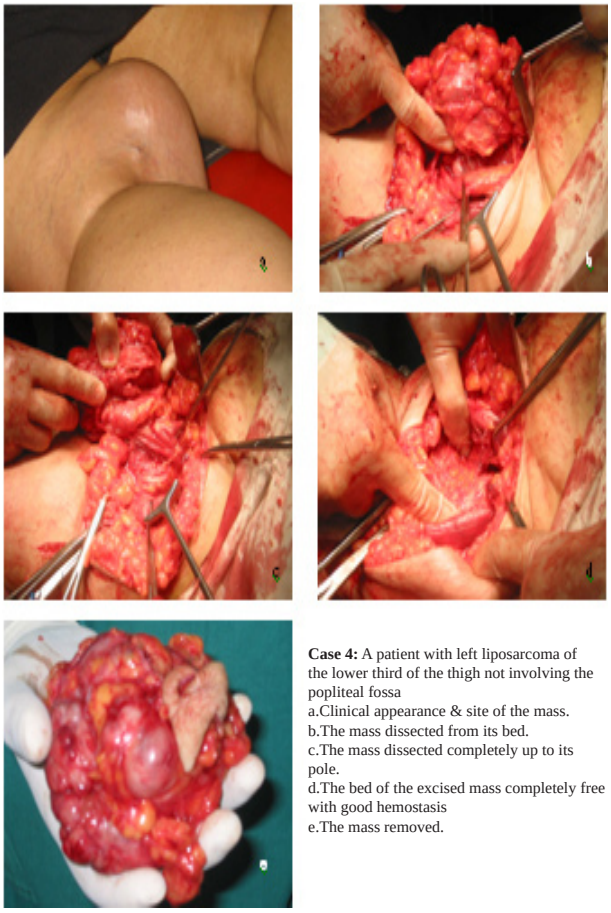
Case 1: A patient with Right mid-thigh leiomyosarcoma of biceps femoris muscle
a.Clinical appearance & site of the mass.
b.X-ray examination showing neovascularization at mass site
c.MRI imaging showing the mass intramuscular.
d.The mass dissected with its upper pole held between fingers.
e.The mass dissected from its bed down to its lower pole
f.The lower pole was excised using diathermy
g.The removed mass & measured
h.The mass opened with areas of hemorrhage and necrosis and loss of tissue texture



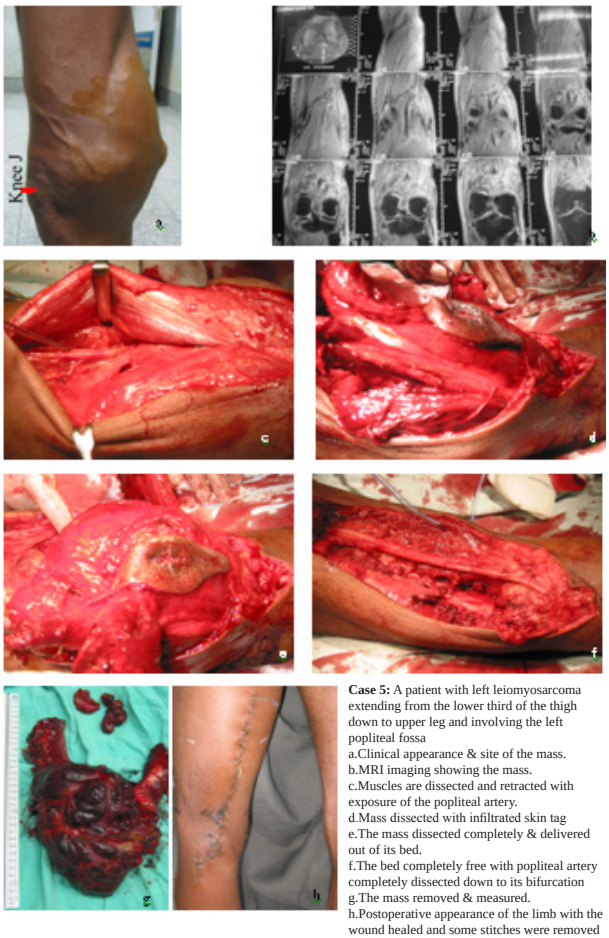
Case 2: A patient with Right mid-thigh liposarcoma
a.Clinical appearance & site of the mass.
b.MRI imaging showing the mass extramuscular.
c.The mass dissected from its bed.
d.The removed mass
e.The mass opened with areas of hemorrhage and necrosis and loss of tissue texture



Case 3: A patient with left leiomyosarcoma of the upper third of the thigh not encroaching on the buttock
a.Clinical appearance & site of the mass.
b.The mass dissected from its bed.
c.The bed of the excised mass completely free with good hemostasis
d.The removed mass & measured
e.The mass opened with areas of hemorrhage and necrosis and loss of tissue texture



Case 4: A patient with left liposarcoma of the lower third of the thigh not involving the popliteal fossa
a.Clinical appearance & site of the mass.
b.The mass dissected from its bed.
c.The mass dissected completely up to its pole.
d.The bed of the excised mass completely free with good hemostasis
e.The mass removed.



Case 5: A patient with left leiomyosarcoma extending from the lower third of the thigh down to upper leg and involving the left popliteal fossa
a.Clinical appearance & site of the mass.
b.MRI imaging showing the mass.
c.Muscles are dissected and retracted with exposure of the popliteal artery.
d.Mass dissected with infiltrated skin tag
e.The mass dissected completely & delivered out of its bed.
f.The bed completely free with popliteal artery completely dissected down to its bifurcation
g.The mass removed & measured.
h.Postoperative appearance of the limb with the wound healed and some stitches were removed

Four lesions (15.4%) were superficial without deep fascial invasion and the other 22 lesions (84.6%) were deep; 13 lesions were superficial to the fascia but invading it, 5 lesions were superficial to the fascia and invading through it and the other 4 lesions were superficial and extending beneath it. In 2 patients (7.7%), resection of the major branches of an adjacent nerve was needed to obtain a complete gross resection, while in the other 24 patients only small nerves were resected with complete dissection and resection of the neurovascular bundle enclosing sheath. Stripping of the periosteum was needed for adequate resection in only one patient (3.8%) and resection of part of the adjacent bone was needed in another patient (3.8%) of patients. Only one patient (3.8%) required tissue transfer for wound closure while in the other 25 patients (96.2%) the wound was primarily closed (Table 1).

Table 1: Tumor characteristics.

Variable		No.	%
Location	Non-central	26	100
	Central	0	0
Site	Mid-thigh	10	38.5
	Upper thigh encroaching on the buttock	8	30.8
	Upper half of the thigh, not encroaching on the buttock	2	7.7
	Lower thigh encroaching on the popliteal fossa	5	19.2
	Mid-thigh to the upper leg	1	3.8
Depth	Superficial	4	15.4
	Deep		
	Superficial to the fascia but invading it.	13	50
	Superficial to the fascia and invading through it	5	19.2
	Superficial to the fascia and extending beneath it	4	15.4
Size (in cm)	≤5	9	34.6
	>5	17	65.4
Margin	Free (negative)	22	84.6
	Positive	4	15.4

The mean excised lesion diameter was 9.3±6.3; range: 1-25 cm; 8 lesions (30.8%) had diameter of ≤5 cm with a mean diameter of 3.8±1.4 cm and 18 lesions (69.2%) had diameter of >5cm with a mean diameter of 11.8±6.1 cm. Histopathological examination of margin of excision was free in 22 excised specimens (84.6%) but was positive for sarcoma cells in 4 specimens (15.4%). Significant wound complications developed in 5 patients (19.2%) and wound complication requiring re-operation was seen in only 2 patients (7.7%) (Table 2). Bone fracture occurred only in one patient (3.8%) in whom bone resection was performed. Nerve damage was reported only in 3 patients (11.5%); one patient (3.8%) had grade 1 neuromotor toxicity, another had grade 1 neurosensory toxicity and the third had grade 2 neurosensory toxicity (Table 3).

Table 2: Postoperative wound complications.

Complications	NO.	%
No significant complications	21	80.7
Significant, not requiring re-operation	3	11.6
Significant, requiring re-operation	2	7.7

Table 3: Postoperative bone and nerve complications.

Bone fracture			1	3.8
Nerve damage	Neuromotor toxicity	grade 1	1	3.8
	Neurosensory toxicity	grade 1	1	3.8
		grade 2	1	3.8

Histopathological study of preoperative excisional biopsy that confirmed postoperatively revealed that malignant fibrous histocytoma, liposarcoma and leimyosarcoma were the commonest types with a total prevalence of 65.5% of studied cases (Table 4).

Table 4: Histological types of soft-tissue sarcomas.

Histological type	No.	%
Malignant fibrous histocytoma (MFH)	7	27
Liposarcoma	6	23.1
Leiomyosarcoma	4	15.4
Synovial sarcoma	2	7.7
Fibrosarcoma	1	3.8
Malignant schwannoma	1	3.8
Angiosarcoma	1	3.8
Extra-skeletal osteosarcoma	1	3.8
Other types	3	11.6
Total	26	100

Five patients (19.2%) developed local recurrence after a mean follow-up duration of 27.6±4.8; range: 20-32 months from the date of initial operation. The margins of resection were positive in 3 of 5 patients with local recurrences; in 2 patients the tumor cells were present at the margin and within 1 mm in the third patient. Four patients with local recurrence had deeply seated lesion and only one had superficial lesion developed local recurrence. One patient required amputation, three patients required wide local excision plus further radiation and wide local excision alone in one patient. Distant metastasis developed in 8 patients (30.8%) after a mean follow-up duration of 27±6.5; range: 18-39 months from the date of initial operation. Eleven patients (42.3%) patients died after a mean follow-up duration of 31.6±7.5; range: 18-45 months from the date of initial operation. All the 8 patients whom had distant metastasis and 2 whom had local recurrence died and one had myocardial infarction and also died (Table 5).

All determined rates showed progressive decrease throughout the follow-up period with the least LRFR (80.8%) and DMFR (73.1%) were at 36 months after surgery, while the least LR/DMFR was 50% reported at 42 months after surgery (Table 6, Figure 1). The final

survival rate was 57.7% and reported at 48 months, (Figure 1). There was a negative significant correlation between the postoperative 5-year local control rate and presence of free surgical margin (p=0.003) and the diameter of the resected tumor, (p=0.01). Moreover, there was a negative significant correlation between the postoperative 5-year disease free rate and the diameter of the resected tumor, (p=0.039), while the correlation was negative non-significant with the presence of free surgical margin, (p>0.05).

Table 5: Follow-up data.

Local recurrence	**No. (%)**		**5 (19.2%)**
	Free duration (months)		27.6±4.8 (20-32)
	Margin	Positive	3 (11.6%)
		Negative	2 (7.7%)
	Depth of lesion	Superficial	1 (3.8%)
		Deep	4 (15.4%)
	Management	Amputation	1 (3.8%)
		Wide excision & radiation	3 (11.6%)
		Wide excision alone	1 (3.8%)
Distant Metastasis	Number (%)		9 (34.6%)
	Free duration (months)		27.2±6.1 (18-39)
Mortality	Number (%)		11 (42.3%
	Death associated with distant metastasis		9 (34.6%)
	Death associated with local recurrence		2 (7.7%)

Table 6: Postoperative Follow-up Outcome rates.

	LRFR	**DMFR**	**LR/DMFR**
6-m	100%	100%	100%
12-m	100%	100%	100%
18-m	96.2%	96.2%	92.3%
24-m	92.3%	84.6%	76.9%
30-m	88.5%	76.9%	65.4%
36-m	80.8%	73.1%	53.8%
42-m	80.8%	69.2%	50%
48-m	80.8%	69.2%	50%
54-m	80.8%	69.2%	50%
60-m	80.8%	69.2%	50%

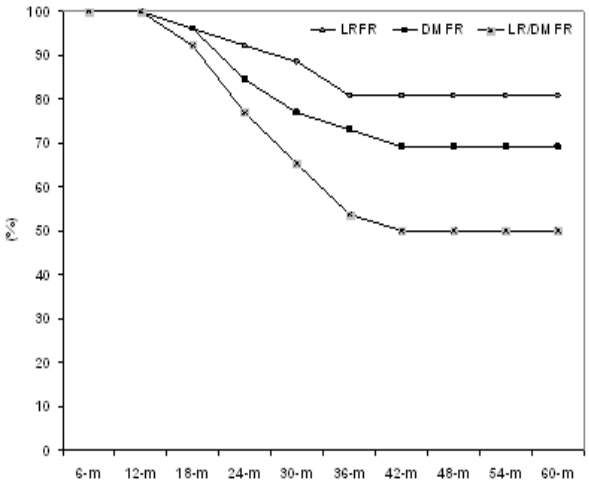


Fig.1: Postoperative follow-up rates.

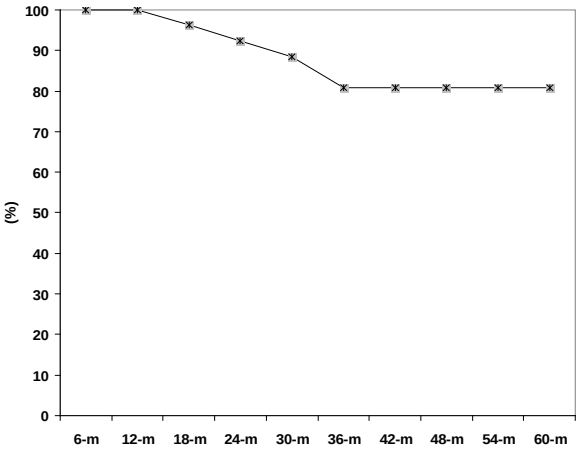


Fig. 2: The reported survival rates throughout the follow-up period

DISCUSSION

Limb-sparing surgery, consisting of wide-margin tumor resection and preoperative or postoperative radiotherapy/chemotherapy, has become the surgical treatment of choice for extremity sarcomas. However, adequate tumor resection can sometimes compromise crucial limb function, necessitating functional restoration surgery[14]. This study aimed to evaluate the outcome of patients with lower extremity soft tissue sarcoma (STS) treated with functional limb-salvage surgery with adjuvant

radiotherapy, defined as the 5-year local recurrence free rate, distant metastasis free rate, local recurrence/distant metastasis free rate and survival rate.

In the present study 26 patients with STS treated with function-sparing surgery with adjuvant RT, the 5-year local recurrence rate was 19.2%, the 5-year distant metastasis rate was 26.9% and the 5-year disease specific survival rate was 61.5% but the overall survival rate was 57.7%; with a negative significant correlation between the postoperative duration free of local recurrence and presence of free surgical margin and the diameter of the resected tumor and a negative significant correlation between the postoperative duration free of distant metastasis and the diameter of the resected tumor. For patients with local recurrence only one patient required amputation, 3 patients required wide local excision plus further radiation and wide local excision alone in one patient.

These findings agreed with that reported in literature; Peiper et al.[2] reported a local recurrence rate of 31% after a median of 13 months and distant metastases occurred in 30% of patients and that the tumor size significantly influenced disease-free survival and positive microscopic margins and subfascial tumors were associated with an increased local recurrence rate. Gronchi et al.[5] reported that size, malignancy grade, depth, histotype are statistically significant prognostic factors with an extra risk was observed for patients with positive margins after 3 to 5 years. Yildiz et al.[15] who reported a 5-year local recurrence rate of 12.5% and 5-year survival rate of 51% and found a significant correlation between negative surgical margins and local control; and between tumor grade and survival and concluded that achievement of negative surgical margins promotes local control in extremity soft tissue sarcomas, Khanfir et al.[16] reported a 5-year local relapse-free survival rate of 78% in patients underwent wide resection and adjuvant radiotherapy for soft-tissue sarcomas of the extremities. Zagars et al.[17] reported a 5-year local control rate of 83% and freedom from metastasis at 5 years was 71% and the and concluded that prognostic factors for local recurrence, metastatic recurrence, lymph node recurrence, disease free survival, and disease specific survival are different. Also, Alektiar et al.[18] reported a 5-year local control rate in patients with lower extremity STS was 86%.

The reported 5-year survival rate goes in hand with Karakousis et al.[19] and Vraa et al.[20] who reported a 5-year disease specific survival rate of 66% and 67%, respectively after treatment of thigh sarcoma. Moreover, the obtained results agreed with that reported previously by Pisters et al.[21] and Vraa et al.[22] who reported that soft-tissue sarcomas in the lower extremities had the worst prognosis and attributed this to the fact that many deep-seated sarcomas in the thigh are not detected for a longer time than tumors in, e.g., the upper extremity, and therefore they are usually larger and may have had a greater risk of dissemination. In support of such attribution, the present study included only 4 superficial lesions (15.4%) without deep fascial invasion and the other 22 lesions (84.6%) and the higher frequency of distant metastasis in comparison to the frequency of local recurrence reported throughout the follow-up period.

On contrary to the obtained survival rate, Peiper et al.[2] found after a median follow-up of 4.5 years a cumulative 5-year survival rate of 70%, Yildiz et al.[15] reported a 5-year disease specific survival rate of 51% and Zagars et al.[17] reported that the disease specific survival rate at 5 years was 73%. This discrepancy of reported disease specific survival rates could be attributed to multiple factors studies including sarcoma patients in general had better survival rates or the study groups may have been composed of a higher percentage of patients with large, deep, and high-grade tumors. Further differences may be related to the definition of wide excision; for instance, some studies describe surgery that attempted to attain at least 2cm gross margins around the tumor, often such attempted wide excisions are limited by the fact that, in one dimension, the margin is necessarily close due to a critical normal structure, such as a neurovascular bundle or bone.

In the current study, significant wound complications developed in 5 patients (19.2%) and wound complication requiring reoperation was seen in only 2 patients (7.7%), such figures agreed with but was superior to that reported by Alektiar et al.[18] who found a wound re-operation rate of 11% in patients with lower limb STS managed with limb-sparing surgery and postoperative RT. Bone fracture occurred only in one patient (3.8%) in whom bone resection was performed. This finding goes in hand with Livi et al.[23] who assessed the occurrence of long-bone fracture in patients underwent radical excision for STS of the limb followed by postoperative irradiation and reported a frequency of 3.3% throughout the follow-up period. Nerve damage was reported only in 3 patients (11.5%), this rate of treatment concomitant nerve damage agreed with that reported by Schwartz et al.[24] who reported a nerve damage rate of 8.6% after adjuvant radiotherapy in patients treated by surgical resection for peripheral or torso STS.

Conclusion reported local recurrence rate after treatment of STS of lower extremity with function-sparing surgery with RT is comparable to published rates and suggested that in patients with lower extremity STS carefully performed FSS followed by RT may serve as definitive therapy with acceptable outcome.

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