

Research Article

Indications of amputation after limb-salvage surgery of patients with extremity-located bone and soft-tissue sarcomas: A retrospective clinical study

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ABSTRACT

Objective: This study aimed to investigate amputation-related factors after limb-salvage surgery (LSS) in patients with extremity-located bone and soft-tissue sarcomas and determine the relationship between these factors and patient survival.**Methods:** In this retrospective study at our institution, patients in whom LSS was first performed because of an extremity-located musculoskeletal sarcoma, and subsequently amputation was carried out for various indications were included. Patient and tumor characteristics, details of surgical procedures, indications of amputation, number of operations, presence of metastasis before amputation, and post-amputation patient survival rates were analyzed.**Results:** A total of 25 patients (10 men, 15 women; mean age=41.96±21.88 years), in whom amputation was performed after LSS as initial resection of an extremity sarcoma or re-resection(s) of a local recurrence, were included in the study. The leading oncological indication for amputation was local recurrence that occurred in 18 (72%) patients. Non-oncological indications included prosthetic infection in 5 (20%), mechanical failure in 1 (4%), and skin necrosis in 1 (4%) patient. The patients underwent a median of 2 (range, 1–4) limb-salvage procedures before amputation. Distant organ metastasis was detected in 22 (88%) patients during follow-up; in 13 (52%) of these patients, metastasis was present before amputation. A total of 11 (44%) patients were alive at the time of study with no evidence of the disease (n=3) or with disease (n=8), and 14 (56%) patients died of disease. The mean overall and post-amputation survival were 47±20.519 (range, 11–204) months and 22±4.303 (range, 2–78) months, respectively. The median follow-up was 27 (range, 6–125) months.**Conclusion:** The most common causes of amputation after LSS were local recurrence and prosthetic infection. Patients who underwent amputation after LSS developed a high rate of distant organ metastasis during follow-up and had reduced survival.**Level of Evidence:** Level IV, Therapeutic Study

Introduction

Limb-salvage surgery (LSS) preserves a better quality of life and functional capacity than amputation in the treatment of malignant musculoskeletal tumors (1). However, there is no difference between these 2 surgical treatment modalities in terms of survival and relapse of the disease when appropriate surgical margins are obtained (1).

Although amputation has been frequently performed for treatment of malignant bone and soft-tissue tumors in the past, currently LSS has become the standard of care with the advances in chemotherapy regimens, improvements in imaging studies, and accumulation of experience in musculoskeletal reconstructive surgery (1-3). There are 2 key factors to be considered for LSS: wide surgical margins should be obtained to ensure that the survival of the patient is better than that with amputation, and the reconstructed extremity should function satisfactorily (4, 5). LSS is only occasionally an option for management of recurrent bone and soft-tissue sarcomas because appropriate surgical margins can be usually obtained by an amputation (2, 3).

The factors that can affect extremity survival after LSS have been reported in the literature (6-8). However,

there is limited research investigating the overall and post-amputation survival of these patients. This study mainly aimed to determine the frequency of amputation after LSS of extremity-located bone and soft-tissue sarcomas at a tertiary musculoskeletal oncology center. The effect of tumor- and surgery-related factors on amputation, oncological or non-oncological indications, number and type of surgical interventions before amputation, and association of distant organ metastasis with amputation were also investigated in addition to overall and post-amputation survival.

Materials and Methods

This retrospective study included patients who underwent LSS owing to an extremity-located musculoskeletal sarcoma and required amputation during follow-up for various indications at our institution. Patients, who underwent a primary amputation because of malignant bone and soft-tissue tumors of the extremities, including malignant skin tumors, were excluded. The study protocol was approved by the local ethics committee of Marmara University School of Medicine (09.2020.8).

The demographic characteristics of patients (age and sex), tumor characteristics (diagnosis, localiza-

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tion, depth, size, and histopathological grade), status of the surgical margins (wide, marginal, or intralesional), wound closure method (primary, skin graft, or free flap), indications of amputation (local recurrence, prosthetic infection, mechanical failure, or skin necrosis), number of operations before amputation, presence of metastasis before amputation and during follow-up, survival of patients after initial LSS (overall survival) and amputation (post-amputation survival), and duration of follow-up were accessed from the archived files and digital hospital records. All patients in this study were treated with a multidisciplinary approach according to the decision of the Bone and Soft Tissue Tumors Council of Marmara University Pendik Training and Research Hospital.

Statistical analysis

Data analysis was carried out using the Statistical Package for Social Sciences version 22.0 software (IBM SPSS Corp.; Armonk, NY, USA). The study data were evaluated using descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum). Survival curves were calculated using the Kaplan-Meier method.

Results

A total of 57 (8.7%) of 654 patients with a diagnosis of extremity-located primary bone or soft-tissue sarcoma underwent amputation at our institution between 2009 and 2018. Of these, 32 (4.9%) patients underwent a primary amputation at first surgery to achieve appropriate surgical margins, and these patients were not included this study. Amputation was performed after LSS in 25 (3.8%) patients, which was done as initial resection of an extremity sarcoma or re-resection(s) of a local recurrence. Of these 25 patients, 12 had their initial LSS at another center and 13 at our institution.

Table 1 summarizes a descriptive analysis of the demographic characteristics of the patients, tumor characteristics, details of surgical procedure, indications for amputation, existence of metastasis before amputation or at follow-up, survival status, and follow-up of the patients. Table 2 gives the localization of the tumors and amputation levels of the extremities in detail.

Local recurrence was the leading oncological indication for amputation and occurred in 18 (72%) patients. Non-oncological indications included prosthetic infection in 5 (20%), mechanical failure in 1 (4%), and skin necrosis in 1 (4%) patient. A total of 4 (22.2%) patients with local recurrence had amputation after first local recurrence. In the remaining 14 (78.8%) patients, amputation was indicated after the second or subsequent local recurrences. Patients experienced a median of 2 (range 1–4) limb-salvage procedures before amputation.

Distant organ, particularly lung, metastases was detected in 22 (88%) patients during follow-up. In 13 (52%) patients, metastatic involvement was already present before amputation (in 5 patients at initial

Table 1. Descriptive analysis of demographic characteristics of the patients and tumor characteristics

		n (%)
Age (years)	Min-max (median)	1–71 (44)
	Mean±SD	41.96±21.88
Sex	Female	10 (40.0)
	Male	15 (60.0)
Diagnosis	Osteosarcoma	9 (36.0)
	Ewing sarcoma	3 (9.0)
	Pleomorphic sarcoma	3 (9.0)
	Chondrosarcoma	2 (8.0)
	Fibrosarcoma	2 (8.0)
	Dermatofibrosarcoma protuberans	1 (4.0)
	Leiomyosarcoma	1 (4.0)
	Myofibroblastic sarcoma	1 (4.0)
	Myxofibrosarcoma	1 (4.0)
	Rabdomyosarcoma	1 (4.0)
	Synovial Sarcoma	1 (4.0)
Tumor localization	Upper extremity	6 (24.0)
	Lower extremity	19 (76.0)
Tumor depth	Superficial	0 (0.0)
	Deep	25 (100.0)
Tumor size (cm)	Min-max (median)	4–30 (9)
	Mean±SD	10.20±5.45
Tumor grade	Grade 1	4 (16.0)
	Grade 2	3 (12.0)
	Grade 3	18 (72.0)
Surgical margin	Wide	16 (64.0)
	Marginal	5 (20.0)
	Intralesional	4 (16.0)
Closure of wound	Primary	18 (72.0)
	STSG	3 (12.0)
	Free flap	4 (16.0)
Indications of amputation	Oncological indications	
	Local recurrence	18 (72.0)
	Non-oncological indications	
	Prosthetic infection	5 (20.0)
	Mechanic failure	1 (4.0)
Number of operations before amputation	Skin necrosis	1 (4.0)
	Min-max (median)	1–4 (2)
	Mean±SD	2±0.76
Amputation decision for oncological indications	1 st local recurrence	4 (22.2)
	2 nd local recurrence	11 (61.1)
	>2 nd local recurrence	3 (16.7)
Metastasis before amputation	Yes	13 (52.0)
	No	12 (48.0)
Metastasis at follow-up	Yes	22 (88.0)
	No	3 (12.0)
Survival status	Alive	11 (44.0)
	Dead	14 (56.0)
Follow-up (month)	Min-max (median)	6–125 (27)
	Mean±SD	39.88±31.59

SD: standard deviation; STSG: split thickness skin graft.

HIGHLIGHTS

- The most common causes of amputation after limb-salvage surgery (LSS) were local recurrence and prosthetic infection.
- Large, deeply located, and high-grade sarcomas of the lower extremities were more commonly associated with local recurrence and, eventually, an amputation after LSS.
- Patients who underwent amputation after LSS developed a high rate of distant organ metastasis during follow-up and had reduced survival.

presentation and in 8 patients during the period between initial presentation and amputation). Distant organ metastasis was detected after amputation in the remaining 9 (36%) patients. A total of 11 (44%) patients were alive at the time of the study with no evidence of the disease (n=3) or with disease (n=8), and 14 (56%) patients died of the disease. Of the 14 patients who died, 9 died within a median of 5 (range, 2–8) months after amputation, and only 5 survived for a

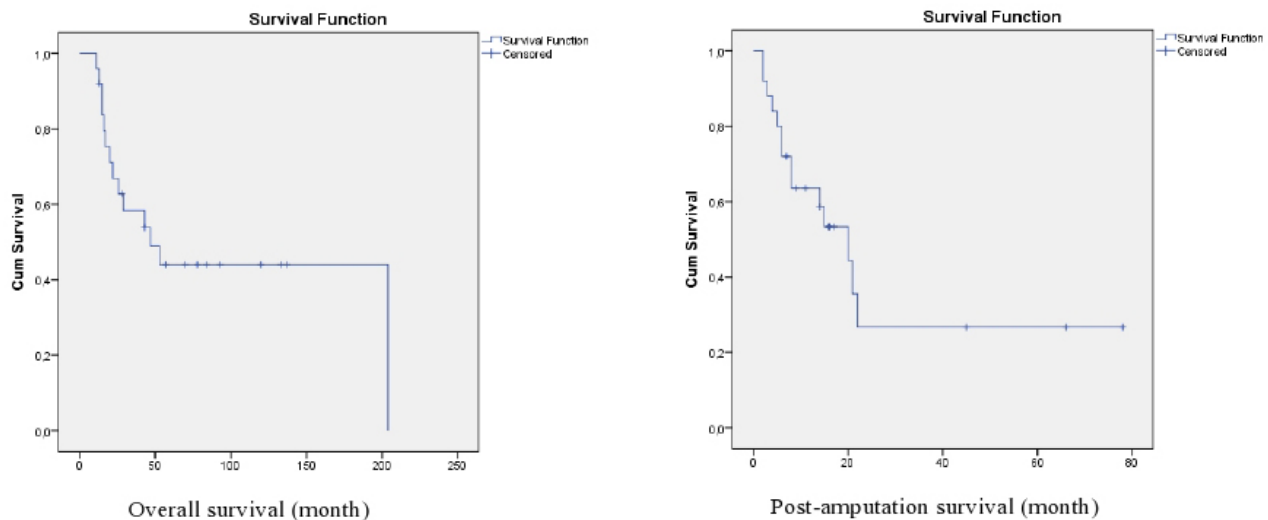


Figure 1. The Kaplan-Meier analysis of overall and post-amputation survival of patients

Table 2. Descriptive analysis of tumor localization and amputation level

Tumor localization	n	%
Thigh	2	8
Distal femur	6	24
Knee	1	4
Proximal tibia	5	20
Ankle	2	8
Foot	3	12
Shoulder	1	4
Arm	4	16
Forearm	1	4
Amputation level	n	%
Hip disarticulation	6	24
High transfemoral	2	8
Above knee	5	20
Below knee	5	20
Ray amputation	1	4
Forequarter	5	20
Transhumeral	1	4

median of 22 (range, 14–30) months. The mean overall and post-amputation survival durations of the patients were 47 ± 20.519 (range, 11–204) months and 22 ± 4.303 (range, 2–78) months, respectively. The Kaplan-Meier analysis of overall and post-amputation survival demonstrated that patients who underwent amputation after LSS had reduced survival rates (Figure 1). The median duration of follow-up was 27 (range, 6–125) months.

Discussion

A search of our database, including the time period of the study, revealed that patients who required secondary amputation (amputation after LSS) constituted 3.8% (25/654) of our extremity-located musculoskeletal sarcoma cohort. The tumors were usually larger than 5 cm, were deeply located, and were of high grade. Local recurrence and prosthetic infections were the leading oncological and non-oncological indications for amputation, respectively. Patients experienced a median of 2 (range, 1–4) limb-salvage procedures before amputation. A high percentage of patients (88%; 22/25) were found to develop distant organ metastases during follow-up. The mean values of over-

Table 3. Comparison of the characteristics of disease and patients undergoing amputation after limb-salvage surgery for extremity sarcomas

	Stojadinovic et al., 2001	Smith et al., 2017	Erstad et al., 2018	Present Study
Age (Median)	39	61	52	44
Amputation after LSS	18	36	22	25
Amputation decision for first recurrence	18 (100.0)	21 (58.3)	18 (81.8)	4 (16.0)
Tumor size				
<5 cm	7 (38.9)	Nr	4 (18.2)	2 (8.0)
5-10 cm	5 (27.8)	Nr	10 (45.5)	14 (56.0)
>10 cm	6 (33.3)	Nr	7 (31.8)	9 (36.0)
Nr	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)
Median	Nr	9.3	Nr	9
Tumor grade				
Low grade	0 (0.0)	1 (2.8)	1 (4.6)	4 (16.0)
Intermediate grade	0 (0.0)	15 (41.7)	2 (9.1)	3 (12.0)
High grade	18 (100.0)	19 (52.7)	16 (72.7)	18 (72.0)
Nr	0 (0.0)	1 (2.8)	3 (13.6)	0 (0.0)
Tumor localization				
Upper extremity	10 (55.6)	23 (63.9)	6 (27.3)	6 (24.0)
Lower extremity	7 (38.9)	13 (36.1)	14 (63.6)	19 (76.0)
Trunk	1 (5.5)	0 (0.0)	2 (9.1)	0 (0.0)
Tumor margin				
Negative	9 (50.0)	Nr	10 (45.5)	16 (64.0)
Positive	9 (50.0)		12 (54.5)	9 (36.0)
Tumor depth				
Superficial	0 (0.0)	Nr	5 (22.7)	0 (0.0)
Deep	18 (100.0)		16 (72.7)	25 (100.0)
Nr	0 (0.0)		1 (4.6)	0 (0.0)
Metastasis before amputation	3 (16.7)	Nr	4/17 (23.5)	13 (52.0)
Metastasis after amputation	13 (72.2)	Nr	17 (77.3)	22 (88.0)
Amputation indication				
Oncological indication	18 (100.0)	36 (100.0)	17 (77.3)	18 (72.0)
Non-oncological indication	0 (0.0)	0 (0.0)	5 (22.7)	7 (28.0)
Post-amputation local recurrence	1 (5.5)	Nr	2/17 (11.8)	0 (0.0)

Nr: not recorded; LSS: limb-salvage surgery.

all and post-amputation survival of patients were 47 ± 20.519 and 22 ± 4.303 months, respectively. Patients who underwent amputation after LSS developed a high rate of distant organ metastasis during follow-up and had reduced survival.

Table 3 gives the comparative data of the previous related studies (6-8) and this study, which evaluated patients with sarcoma requiring amputation after LSS, in terms of the amputation rate, patient and tumor characteristics, surgical margins, rate of metastatic involvement before and after amputation, and indications for amputation. In the literature, the rate of amputation after LSS has been reported between 9% and 14% (6, 9, 10). This rate was 3.8% (25/654) in this study, and only 0.6% (4/654) of patients underwent amputation after the first local recurrence. We put forward 2 main reasons to explain this low rate of secondary amputation in our extremity-located musculoskeletal sarcoma cohort. First, the sociocultural structure of the society in the country in which this study was conducted strictly prevents patients from agreeing to an amputation. Second, the progressively increasing experience and collaboration of our multi-disciplinary team, which included experienced cardiovascular and reconstructive surgeons, expanded the range of our indications for LSS, particularly in re-resections of local recurrences and revision of bone reconstructions. It should also be mentioned that all patients in these situations were informed about the consequences of re-resections and revisions and the possibility of a secondary amputation.

A comparison of the previous studies in the literature with our study revealed that similar tumor characteristics, including size larger than 5 cm, deep location, and high grade, were associated with extremity sarcomas requiring amputation after LSS (6-8). Malignant bone and soft-tissue tumors with these features had a worse prognosis than that of small-sized, superficial, and low-grade sarcomas (11). We speculate that after LSS of an extremity sarcoma with aggressive radiological and histopathological features, short- or long-term complications, including local recurrence, are more likely.

A study by Stojadinovic et al. and Smith et al. has reported that a large number of tumors located in the upper extremities required amputation after LSS (6, 8). These tumors could invade or expand very close to major neurovascular structures; therefore, surgical margins frequently may remain marginal or intralesional, leading to local recurrence and subsequent re-resection or amputation (2). However, non-oncological causes of amputation, mainly prosthetic infections or mechanical failures, were seen very rarely after upper extremity reconstructions.

Bone and soft-tissue sarcomas occur more commonly in the lower extremities (12). Besides oncological indications, non-oncological complications, including prosthetic infection, mechanical failure of an endoprosthesis, or insufficient soft-tissue coverage may result in amputation after LSS. Erstad et al. have reported a higher number of amputations after LSS of lower extremity sarcomas (7). In this study, 76% (16/25) of the tumors requiring amputation after LSS were located in the lower extremities. The leading oncological indication for amputation was local recurrence that occurred in 18 (72%) patients. Non-oncological indications included prosthetic infection in 5 (20%), mechanical failure in 1 (4%), and skin necrosis resulting in insufficient soft-tissue coverage for bone reconstruction in 1 (4%) patient.

A high rate of tumor-positive surgical margins, ranging from 50% to 54.5%, has been reported in patients who require amputation because of local recurrence after LSS (6, 7). The rate of tumor-positive surgical margins was also high in this study; 36% (9/25) of patients

with marginal or intralesional surgical margins had a local recurrence and subsequently underwent amputation during follow-up, demonstrating the negative effect of inappropriate resections on extremity survival.

The main complications after LSS include instability, soft-tissue insufficiency, mechanical failure, infection, local recurrence, and non-union or graft resorption for biological reconstructions (1, 4, 13). Local recurrence and infection were found to be the 2 most common causes of amputation (4). In this study, the most common indication leading to amputation after LSS was local recurrence followed by prosthetic infection, and these findings were consistent with the literature.

Bone defects occurring after resection of malignant bone and soft-tissue tumors in the lower extremities are often reconstructed with a mega-prosthesis (2, 3). Prosthetic joint infections (PJI) are divided into 3 groups; early onset (<3 months), delayed onset (>3 months, <12 months), and late onset (>12 months) (14). In our study, 20% (5/25) of patients required amputation after LSS because of a delayed-onset (3/25) or late-onset (2/25) infection of a mega-prosthesis. A two-staged revision is the most preferred surgical treatment for late infections of mega-protheses (15). We followed a similar approach and performed a two-stage revision in the management of 5 patients with delayed or late-onset PJI. Soft-tissue reconstruction was provided by local pediculated or free flaps when required. However, eventually an amputation was required because of recurrent infections and insufficient soft-tissue coverage.

The rate of distant organ metastasis before amputation has been reported between 16.7% and 23.5% in patients with previous LSS (6, 7). In addition, considerably increased metastases rates have been reported at follow-up, particularly in patients with local recurrence (16, 17). In this study, the rate of distant organ metastasis before amputation and during follow-up was 52% (13/25) and 88% (22/25), respectively. We believe that this high rate of distant metastasis was related to the high percentage (72%; 18/25) of local recurrences in our patient cohort, which required amputation after LSS. We can also argue subjectively that our low rate of amputation after the first local recurrence may have increased the development of distant metastasis.

Amputations performed on patients with sarcoma with distant organ metastasis are known as palliative amputations in the literature (8). Smith et al. have reported a mean survival of 6 months in patients undergoing palliative amputation (8). The study by Stojadinovic et al. has reported a median survival of 19.6 months and a low rate of distant organ metastasis before the first recurrence (6). In this study, the rate of palliative amputation was 52% (13/25). We believe that distant organ metastasis is a significant parameter affecting patient survival.

The rates of local recurrence after amputation have been reported to be between 5.5% and 11.8% (6, 7) with no local recurrence observed after amputation in this study. Achieving appropriate surgical margins with amputation could be an important factor. In addition, as most of the patients had metastatic disease, follow-up after amputation was short for development of a recurrence.

This study had some limitations. First, it was a retrospective study with a small number of patients treated in a single center. Second, there was no control group. Third, a subgroup analysis was not possible owing to the heterogeneous diagnoses and localization of the tumors. However, it is one of the rare studies scrutinizing the etio-

logical factors and the effect of amputation on survival in patients requiring amputation after LSS of extremity-located malignant bone and soft-tissue tumors.

In conclusion, the initial management and follow-up of extremity-located musculoskeletal sarcomas require a multidisciplinary approach. In our study, the most common oncological and non-oncological causes of amputation after LSS were local recurrence and prosthetic infection, respectively. The large, deeply located, and high-grade sarcomas of the lower extremities were more prone to local recurrence and, eventually, amputation after LSS. Patients who underwent amputation after LSS developed a high rate of distant organ metastasis during follow-up and had reduced survival.

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethics committee of Marmara University School of Medicine (09.2020.8).

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