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RESEARCH ARTICLE

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Amputations for extremity soft tissue sarcoma in an era of limb salvage treatment: Local control and survival

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Background: Despite multimodality limb salvage treatment (LST) for locally advanced extremity soft tissue sarcoma (ESTS), some patients still need an amputation. Indications for amputation and oncological outcome for these patients are described.

Methods: Between 1996 and 2016, all patients who underwent an amputation for ESTS were included. Patients who underwent an amputation as primary or as non-primary treatment formed Group I and II, respectively.

Results: Thirty-nine patients were included, 16 in Group I (41%) and 23 in Group II (59%). Tumor size or local recurrence which could not be treated with LST were the two main reasons for amputation. Local recurrence free survival (LRFS) ($P = 0.396$), distant metastases free survival (DMFS) ($P = 0.965$), disease-specific survival (DSS) ($P = 0.745$), and overall survival (OS) ($P = 0.718$) were comparable for both groups. Ten-year LRFS was 90.0% versus 83.7%; DMFS was 31.0% versus 42.2%; DSS was 52.2% versus 44.1%; and OS was 44.2% versus 41.6%, for group I and II respectively.

Conclusions: Oncological outcome seems to be comparable between patients who underwent a primary or a non-primary amputation for ESTS. With the on-going possibilities concerning prosthesis and rehabilitation programs, it remains important to decide in a multidisciplinary sarcoma team meeting which treatment suits best for each individual patient.

KEYWORDS
amputation, soft tissue sarcoma, treatment

1 | INTRODUCTION

Soft tissue sarcomas (STS) are rare, malignant tumors with an incidence of 12 310 new cases in the United States and 729 in the Netherlands in 2016, resulting in 4990/300 STS related deaths in the United States and in the Netherlands in 2016.[1–3] STS form a heterogeneous group of tumors including more than 50 different histologic subtypes. The most common subtypes are pleomorphic undifferentiated sarcoma (including malignant fibrous histiocytoma), liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor, which account for a total of 76% of all STS.[4] STS can occur at any anatomic location but most often arise in the limbs (60-70%).[5–7] Despite

Abbreviations: DSS, disease-specific survival; EBRT, external beam radiotherapy; ESTS, extremity soft tissue sarcoma; HILP, hyperthermic isolated limb perfusion; IRB, institutional review board; IQR, interquartile range; LRFS, local recurrence free survival; LST, limb salvage treatment; MPNST, malignant peripheral nerve sheath tumor; OS, overall survival; STS, soft tissue sarcomas; UMCG, University Medical Center Groningen.

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complete resection, with or without (neo)adjuvant treatment, STS are known for their potential to recur locally and/or to cause distant metastases, mainly to the lungs. The available data considering the improvement of survival following (neo)adjuvant systemic chemotherapy are inconsistent and under on-going investigation.[8–10]

Amputation does not increase the survival rate of patients with extremity soft tissue sarcoma (ESTS) when compared with limb salvage surgery combined with (postoperative) radiotherapy. So, limb salvage treatment (LST) has been the treatment of choice since the early 1980s.[11–13] The comparable survival of patients treated with either amputation or LST is caused by the similar effect of systemic chemotherapy in case of metastatic disease. Future identification of new systemic chemotherapy regimens might lead to an improvement of survival in these patients.

Despite attempts to salvage the affected limb, some patients still require an amputation of the affected limb, even after successful hyperthermic isolated limb perfusion (HILP) or preoperative radiation therapy.[14–16] Several patient-related factors (age, comorbidity) and tumor-related factors (tumor size, grade, proximity to vital structures) play a role in the decision to perform an amputation.[5,6,14,17]

This study describes the indications and oncological outcome for patients who underwent an amputation for ESTS at the University Medical Center Groningen (UMCG) between 1996 and 2016.

2 | PATIENTS AND METHODS

2.1 | Patients

The Institutional Review Board (IRB) approved data collection by review of patient medical records (IRB case number 2016.675). All patients who underwent an amputation for ESTS at the UMCG between January 1996 and January 2016, were included in this study. Patients were divided into two groups: those who underwent a primary amputation (Group I) and those who underwent an amputation as non-primary treatment for ESTS (Group II).

At the UMCG, all sarcoma patients are discussed in a multidisciplinary sarcoma team meeting prior to the start of treatment. This study retrospectively assessed all patients who underwent an amputation in the treatment of their ESTS. Including primary amputations, non-primary amputations, palliative amputations and amputations performed for non-oncologic factors necessitating amputation during follow-up.

To give insight in the indications for amputation among ESTS patients, the main reason/or most attributable reason for amputation was formulated for each patient in this series. Amputation levels were preoperatively discussed in the multidisciplinary sarcoma team meeting and all patients were referred to a rehabilitation specialist for evaluation of the appropriate level of amputation.

Data concerning demographics, tumor characteristics, patient treatment history, and hospitalization were collected from medical records. Demographic data included sex and age at diagnosis, type of amputation, and oncological outcome. (Follow-up ended at death or April 30, 2017). The tumor characteristics obtained from patient medical records included tumor size, tumor location, and histological subtype.

2.2 | Methods

Indications for amputation and data on each treatment modality (surgical and non-surgical) were collected. Oncological outcome was measured by local recurrence free survival (LRFS) and distant metastases free survival (DMFS) after amputation. Furthermore, disease-specific survival (DSS) and overall survival (OS) were calculated from diagnosis till end of follow-up.

2.3 | Statistical analysis

Variables were summarized with frequencies and percentages for discrete variables and medians and interquartile ranges (IQRs) for continuous variables; none of the variables were normally distributed. The Mann-Whitney U test was used to compare demographics and clinical variables. Oncological outcome was calculated using the Kaplan-Meier method and Log-rank test. P values <0.05 were considered to indicate statistical significance. SPSS Version 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) and GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego CA, www.graphpad.com) were used for statistical analysis.

3 | RESULTS

3.1 | Patients and tumors

Patient demographics and tumor characteristics are presented in Table 1. A total of 39 patients, median age 58.0 (52.0-69.0) years, 24 women (61.5%), and 15 (38.5%) men, were included in the study. A total of 16 patients (41%) underwent a primary amputation (Group I), and 23 patients (59%) underwent amputation as non-primary treatment (Group II).

The overall median tumor diameter at diagnosis was 8.7 (4.7-13.0) cm, for Group I, 11.5 (8.5-15.5) cm, and Group II, 6.1 (4.0-10.0) cm, ($P = 0.008$). The most common tumor location was the upper leg (37.5%) for Group I, and the lower leg (34.8%) for Group II. A variety of histologic subtypes were seen, including pleomorphic undifferentiated sarcoma, liposarcoma (either myxoid, dedifferentiated, or pleomorphic), and synovial sarcoma (Table 1).

3.2 | Amputations

There were 19 transfemoral amputations (48.7%), four transtibial amputations (10.3%), four transhumeral amputations (10.3%), two transradial amputations (5.1%), two interscapulothoracic amputations (5.1%), three Syme's amputations (7.7%), three hip disarticulations (7.7%), one shoulder disarticulation (2.6%), and one partial hand amputation (2.6%) among the series. The median time between the primary diagnosis and the amputation was 17.0 (9.0-94.0) weeks,

TABLE 1 Patient demographics and tumor characteristics

	Total series (*n* = 39)	Group I (*n* = 16)	Group II (*n* = 23)	*P* value
Male gender	15 (38.5)	7 (44.0)	8 (35.0)	0.740
Age at diagnosis (years)	58.0 (52.0-69.0)	57 (52.3-67.5)	59 (41.0-70.0)	0.943
Tumor size (cm)	8.7 (4.7-13.0)	11.5 (8.2-15.5)	6.1 (4.0-10.0)	0.008
Histological subtype				
Liposarcoma	5 (12.8)	3 (18.8)	2 (8.7)	
MPNST	1 (2.6)	0 (0)	1 (4.3)	
Myxofibrosarcoma	3 (7.7)	1 (6.3)	2 (8.7)	
Synovial sarcoma	7 (17.9)	3 (18.8)	4 (17.4)	
Rabdomyosarcoma	2 (5.1)	1 (6.3)	1 (4.3)	
Angiosarcoma	1 (2.6)	1 (6.3)	0 (0)	
Pleomorphic undifferentiated sarcoma	10 (25.6)	5 (31.3)	5 (21.4)	
Radiation induced sarcoma	2 (5.1)	2 (12.5)	0 (0)	
Other	8 (20.5)	0 (0)	8 (34.8)	
Tumor location				
Upper leg	8 (20.5)	6 (37.5)	2 (8.7)	
Knee	5 (12.8)	1 (6.3)	4 (17.4)	
Lower leg	11 (28.2)	3 (18.8)	8 (34.8)	
Foot	5 (12.8)	2 (12.5)	3 (13.0)	
Upper arm	3 (7.7)	3 (18.8)	0 (0)	
Lower arm	6 (15.4)	1 (6.3)	5 (21.7)	
Hand	1 (2.6)	0 (0)	1 (4.3)	
Type of amputation				
Transfemoral	19 (48.7)	6 (37.5)	13 (56.5)	
Transtibial	4 (10.3)	2 (12.5)	2 (8.7)	
Transhumeral	4 (10.3)	1 (6.3)	3 (13.0)	
Transradial	2 (5.1)	0 (0)	2 (8.7)	
Interscapulothoracic	2 (5.1)	2 (12.5)	0 (0)	
Syme's	3 (7.7)	1 (6.3)	2 (8.7)	
Hip disarticulation	3 (7.7)	3 (18.8)	0 (0)	
Shoulder disarticulation	1 (2.6)	1 (6.3)	0 (0)	
Partial hand	1 (2.6)	0 (0)	1 (4.3)	

IQR, inter quartile range; MPNST, malignant peripheral nerve sheath tumor.
Data presented as *n* (%); median (IQR); Group I, amputation as primary treatment; Group II, amputation as non-primary treatment.

Group I, 8.5 (3.0-12.8) weeks, and Group II, 80.0 (17.0-184.0) weeks ($P < 0.001$). The technique of the various amputations and amputation levels is well described by Malawer and Sugarbaker.[18]

As mentioned, the indications for amputation were discussed in the multidisciplinary sarcoma team meeting and the main reason/or most attributable reason for amputation was formulated to be able to classify the patients according to the indication for amputation. The treatment chosen for each individual patient depends on several patient and tumor characteristics. In Group I, a primary amputation was performed due to the non-resectability of the tumor caused by large tumor size in eight patients (50%), in these patients it was estimated that the extent of surgical resection necessary would have resulted in a non-functional limb. Therefore, a primary amputation was performed instead. In four patients (25%) an amputation was necessary due to bony involvement, these patients had (large) tumors with involvement of the bone in which no other treatment option was feasible. In two patients (12.5%) the involvement of the neurovascular bundle was the main reason for amputation. In the remaining two patients (12.5%) limb salvage was not possible due to abscess formation within the tumor and secondary local infection, leading to an unsuited local environment for LST. The first patient suffered from a locally advanced STS of the upper leg. After the diagnostic biopsy the patient developed a tumor perforation through the skin and a secondary infection with abscess formation within the tumor. This infection deteriorated despite the administration of antibiotics. This local environment made the intended HILP irresponsible and a primary amputation was performed instead. The second patient had been suffering from a swollen and painful foot during an entire year prior to the presentation in our center. The patient had refused to seek medical help during that year. A soft tissue mass was diagnosed which was accompanied by a large abscess of the entire foot. The abscess was drained and a core-needle biopsy of the soft tissue mass was performed simultaneously. Histopathologic examination of the biopsy showed a synovial sarcoma. Due to the abscess formation his entire foot was destructed and a primary amputation was performed. Figure 1 shows four MR-images for non-resectable ESTS necessitating primary amputation.

In Group I, one patient (6.3%) received 50 Gy preoperative external beam radiotherapy (EBRT) to facilitate a Syme's amputation of the foot. As the preoperative EBRT was given to ensure adequate margins for the primarily intended amputation, this patient was included in Group I.

The 23 patients in Group II underwent several treatment modalities preceding the non-primary amputations. Fifteen patients (65.2%) underwent more than one treatment modality preceding the amputation, and a total of 58 treatments, median 2 (1-4) treatments per patient were performed in Group II, as follows: 35 surgical resections, 12 HILPs, 2 regimes of chemotherapy, and 9 EBRT regimes.

In Group II, the indication to perform an amputation was a local recurrence, which could not be treated with LST in 12 patients (52.2%). Other indications to perform an amputation were: tumor progression and/or no tumor response to LST in four patients (17.4%), microscopically compromised margins after LST in three patients (13.0%), and ischemia and/or secondary infection of the treated limb in four patients (17.4%) (Table 2).

A local recurrence which could not be treated with LST differs from tumor progression and/or no tumor response to LST. Hence, the patients who underwent an amputation because of a local recurrence which could not be treated with LST initially underwent successful LST. During follow-up they developed a local recurrence in which LST was not possible and therefore a non-primary amputation was performed. Whereas patients who suffered from tumor progression and/or no tumor response to limb salvage treatment underwent an attempt for LST. This attempt for LST failed and the patients suffered from tumor progression during LST or their tumor did not respond to the LST. In these patients the unsuccessful attempt for LST necessitated a non-primary amputation.

Non-oncologic factors as ischemia and/or secondary infection of the treated limb necessitated a non-primary amputation during follow-up in four patients (17.4%). However, non-oncologic factors as intolerable pain, patient dissatisfaction with functional status or patients' preference for amputation after initial LST were not found among the series.

3.3 | Follow-up

Median follow-up (time from diagnosis to end of follow-up) was 41.0 (16.0-155.0) months; Group I, 33.5 (11.5-79.8) months, and Group II, 56.0 (16.0-176.0) months ($P = 0.207$).

No significant differences in LRFS ($P = 0.396$), DMFS ($P = 0.965$), DSS ($P = 0.745$), and OS ($P = 0.718$) were found between both Groups (Figure 2). Ten-year LRFS was 90.0% versus 83.7%; DMFS was 31.0% versus 42.2%; DSS was 52.2% versus 44.1%; and OS was 44.2% versus 41.6%, for Group I and II respectively.

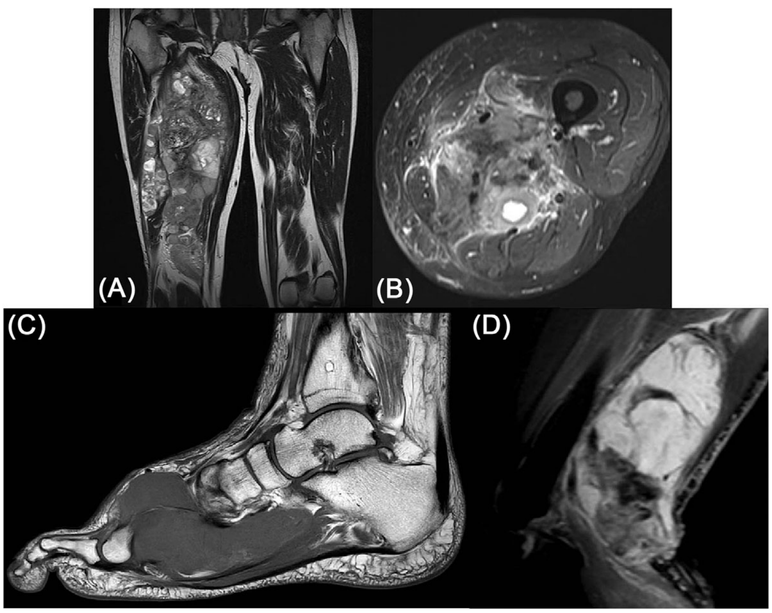

FIGURE 1 MR-images showing four examples for non-resectable ESTS necessitating primary amputation. A, Coronal image of a large ESTS of the right upper leg without involvement of the femur or the neurovascular structures. B, Transversal image of an ESTS of the left upper leg with involvement of the neurovascular structures. C, Sagittal image of an ESTS of the right foot with bony involvement. D, Sagittal image of an ESTS of the left upper leg with skin perforation, abscess formation, and secondary infection within the tumor (femur in black in this setting)

TABLE 2 Treatment characteristics and indications for amputation

	Total series (*n* = 39)	Group I (*n* = 16)	Group II (*n* = 23)	*P* value
Time between diagnosis and amputation	17.0 (9.0-94.0)	8.5 (3.0-12.8)	80.0 (17.0-184.0)	<0.001
Distant metastases, present prior to amputation	4 (10.3)	0 (0.0)	4 (17.4)	
Local recurrence, present prior to amputation	14 (35.9)	0 (0.0)	14 (60.7)	
Local resection prior to amputation	19 (48.7)	0 (0.0)	19 (82.6)	
Neoadjuvant radiation therapy	9 (23.1)	1 (6.3)	8 (34.8)	
Neoadjuvant chemotherapy	2 (5.1)	0 (0.0)	2 (8.7)	
Hyperthermic isolated limb perfusion	11 (28.2)	0 (0.0)	11 (47.8)	
Adjuvant radiation therapy, after amputation	2 (5.1)	1 (6.3)	1 (4.3)	
Adjuvant chemotherapy, after amputation	2 (5.1)	1 (6.3)	1 (4.3)	
Palliative radiation therapy*	7 (18.4)	1 (6.7)	6 (26.1)	
Palliative chemotherapy*	7 (17.9)	5 (31.3)	2 (8.7)	
Total amount of treatments prior to amputation	59	1	58	
Indications for primary amputation				
Tumor size		8 (50)		
Involvement of neurovascular structures		2 (12.5)		
Involvement of bone		4 (25.0)		
Abscess formation making LST irresponsible		2 (12.5)		
Indications for non-primary amputation				
Local recurrence in which LST was not possible			12 (52.2)	
Tumor progression and/or no tumor response to LST			4 (17.4)	
Microscopically comprised margins after LST			3 (13.0)	
Ischemia and/or secondary infection after LST			4 (17.4)	

IQR, inter quartile range; LST, limb salvage treatment.
Data presented as *n* (%), median (IQR), time in weeks. Group I, amputation as primary treatment; Group II: amputation as non-primary treatment.
*In Group I, one patient with widespread metastases was lost to follow up, so information regarding potential palliative treatment is missing.

In Group I, one patient (6.3%) developed a local recurrence and eight patients (50.0%) developed distant metastasis during follow-up. Six patients received palliative treatment for metastatic disease (one patient palliative EBRT and five patients palliative systemic treatment). For Group I, the median time of detection of a local recurrence or distant metastases was 13.0 (13.0-13.0) and 4.5 (1.3-17.0) months, respectively.

In Group II, four patients (17.4%) were diagnosed with distant metastases prior to the amputation, and a total of 13 patients (56.5%) developed distant metastases during follow-up after amputation. Four patients (17.4%) in Group II developed a local recurrence after amputation, of whom three were simultaneously diagnosed with distant disease. Six patients (26.1%) in Group II received palliative EBRT for metastatic disease, and a further two patients (8.7%) received palliative systemic therapy. For Group II, the median time of detection of a local recurrence or distant metastases was 18.5 (3.0-59.5) and 6.0 (2.0-24.0) months, respectively. Among the series, one patient with widespread metastases was lost to follow-up. Table 3 presents the follow-up characteristics of the time-period after diagnosis and after amputation.

As mentioned, in Group II, four patients (17.4%) were diagnosed with distant metastases prior to amputation. However, not all four patients underwent a palliative amputation. Two patients had an inguinal lymph none-metastasis accompanying their primary tumor which were treated with curative-intent by a groin lymph node dissection in addition to the local LST. Both of these patients underwent a non-primary amputation during follow-up. The third patient had a local recurrence in his upper leg and the staging chest CT-scan showed lung metastases. After careful consideration and discussion in the multidisciplinary sarcoma team meeting the complaints of the local recurrence justified the amputation. The fourth patient was diagnosed with a large sarcoma of the upper leg. After initial surgical resection a local recurrence occurred and an intra-abdominal metastasis was diagnosed simultaneously. Regrettably, the initial surgical resection comprised the blood supply of the leg which resulted in ischemia and a secondary infection of the leg necessitating the non-primary amputation.

Currently, seven patients (43.8%) are alive in Group I, five with no evidence of disease, and two with evidence of disease. In Group II, seven patients (30.4%) are still alive, six with no evidence of disease, and one with evidence of disease.

4 | DISCUSSION

Nowadays, (neo)-adjuvant treatment protocols (EBRT, HILP and/or chemotherapy) and surgery have made it possible to achieve a limb

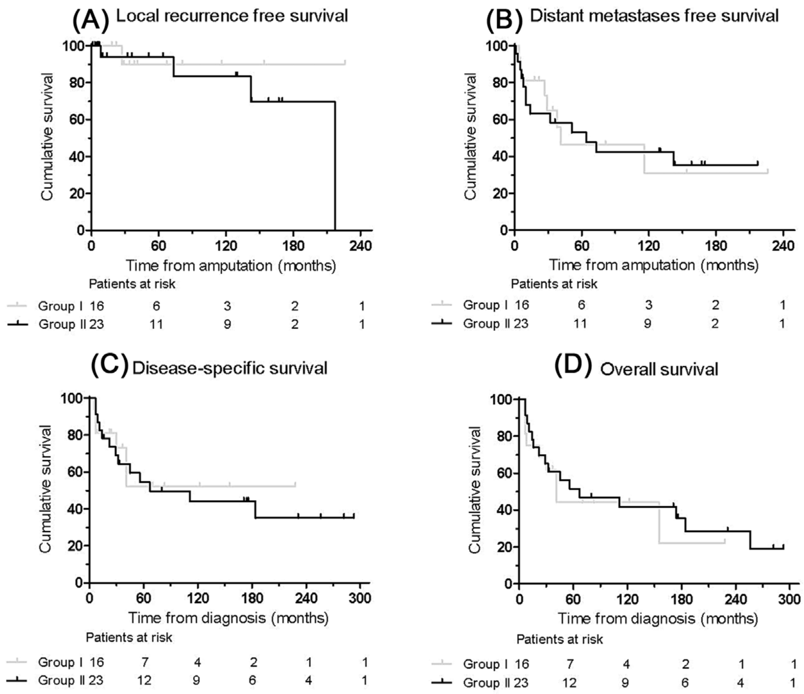

FIGURE 2 Kaplan-Meier plots showing no significant differences for: A, local recurrence free survival (*P* = 0.396); B, distant metastases free survival (*P* = 0.965) after amputation; C, disease-specific survival (*P* = 0.745); and D, overall survival (*P* = 0.718) after diagnosis

salvage rate of approximately 80-90% for ESTS.[13,19–23] However, in some cases a primary amputation is warranted for various reasons.

This study describes two groups of high risk ESTS patients in whom an amputation was performed. Group I describes the characteristics of patients who underwent a primary amputation and Group II describes the patients in whom an attempt for LST was followed by a non-primary amputation during follow-up. The non-primary amputation followed after a median of 80.0 (17.0-184.0) weeks from diagnosis, and a median of two (1-4) treatments per patient.

The predominant indications for amputation in Group I, were tumor size and involvement of bone and/or neurovascular structures. In these patients, an attempt for LST would have led to a non-functional limb. In Group II, the predominant indication for amputation was failure of the local/regional treatment, resulting in a local recurrence in which LST was no longer possible. The indications for primary and for non-primary amputation are consistent with earlier published data.[6,14,17,24,25]

In a study by Stojadinovic et al,[25] 1178 patients with localized primary STS of the extremity were identified and treated with limb salvage surgery. Of these patients, 204 (17%) developed local recurrence, of whom 18 were treated with a (non-primary) amputation whereas the remaining patients underwent another limb salvage surgery. Thirty-four of this latter group were selected for a matched-pair analysis to compare outcomes. Amputation was associated with an improvement in local control of disease (94% vs 74%; *P* = 0.04), but no significant difference in disease-free, disease-specific, or overall survival was found between the two groups.[25]

In the current series it was shown that patients who underwent an attempt at LST, that ultimately resulted in a non-primary amputation, seem to have comparable oncological outcome when compared with patients who underwent a primary amputation. The DSS and OS rates might be lower than OS rates for STS in general (10-year survival of approximately 55%).[26] However, it has to be taken into account that the patients in the UMCG series had initial ESTS with a poor prognosis, due to tumor size and/or histology.

In Group II, prior to a non-primary amputation, 10 patients underwent a surgical resection as initial treatment of their ESTS. Seven of these 10 patients underwent their initial surgical resection at an outside institution (ie, accidental marginal resection). Although oncological outcome following an accidental marginal resection may be similar, these patients require wider resections.[27,28] In the current series, all seven patients underwent a re-resection at our center and none of these patients had to undergo an amputation due to inadequate initial treatment. Most of these patients developed a local recurrence necessitating amputation during follow-up.

In the current study, only one patient in Group I developed a local recurrence, in contrast to four local recurrences (17.4%) in Group II. Three patients out of these latter four were simultaneously diagnosed with distant metastases, so the clinical significance of these "local failures" is questionable, for example, expression of metastatic disease. Furthermore, the LRFS and DMFS were found to be comparable between the two groups.

Among the series, four patients (10.3%) were diagnosed with distant disease prior to the amputation. As mentioned, two of these patients were treated with curative-intent while the other two patients underwent a palliative amputation. The median OS following amputation was 5.5 months for these four patients and 1 month following the two palliative amputations performed. This poor median

TABLE 3 Follow-up after diagnosis and after amputation

	Total series (*n* = 39)	Group I (*n* = 16)	Group II (*n* = 23)	*P* value
Follow-up after diagnosis				
Time between diagnosis and end of follow up	41.0 (16.0-155.0)	33.5 (11.5-79.8)	56.0 (16.0-176.0)	0.207
Survival, patients alive at end of follow up	14 (35.9)	7 (43.8)	7 (30.4)	
Follow-up after amputation				
Local recurrence, developed after amputation	5 (12.8)	1 (6.3)	4 (17.4)	
Median time of detection	13.0 (4.0-50.0)	13.0 (13.0-13.0)	18.5 (3.0-59.5)	
Histological subtype				
Liposarcoma	1 (20.0)	0 (0)	1 (25.0)	
MPNST	1 (20.0)	0 (0)	1 (25.0)	
Radiation induced sarcoma	1 (20.0)	1 (100.0)	0 (0)	
Other	2 (40.0)	0 (0)	2 (50.0)	
Treatment of local recurrence				
Curative re-resection + radiation therapy	1 (20.0)	0 (0)	1 (25.0)	
Curative re-amputation	2 (40.0)	0 (0)	2 (50.0)	
Palliative radiation therapy	1 (20.0)	1 (100)	0 (0)	
Palliative comfort care	1 (20.0)	0 (0)	1 (25.0)	
Distant metastasis, developed after amputation	21 (53.8)	8 (50.0)	13 (56.5)	
Median time of detection	6.0 (2.0-18.5)	4.5 (1.3-17.0)	6.0 (2.0-24.0)	
Histological subtype				
Liposarcoma	3 (14.3)	1 (12.5)	2 (15.4)	
Myxofibrosarcoma	3 (14.3)	1 (12.5)	2 (15.4)	
Synovial sarcoma	2 (9.5)	1 (12.5)	1 (7.7)	
Rabdomyosarcoma	2 (9.5)	1 (12.5)	1 (7.7)	
Pleomorphic undifferentiated sarcoma	5 (23.8)	2 (25.0)	3 (23.1)	
Radiation induced sarcoma	2 (9.5)	2 (25.0)	0 (0)	
Other	4 (19.0)	0 (0)	4 (30.8)	

IQR, inter quartile range; MPNST, malignant peripheral nerve sheath tumor.
Data presented as *n* (%), median (IQR), time in months. Group I, amputation as primary treatment; Group II, amputation as non-primary treatment.

OS following palliative amputation seems to be comparable with the 6 months median OS recently reported by Smith et al.[29]

The current study shows that patients who underwent a non-primary amputation underwent 58 treatment modalities (median 2 treatments per patient) preceding the amputation. Although this figure of median 2 treatments modalities prior to the amputation in the 23 patients in Group II seems low, a previous study has shown that the psychological impact of regional tumor treatment (HILP in this study) is large, resulting in post-traumatic stress syndrome in 20% of patients.[30] In contrast, other studies did not show differences in quality of life and functional outcome when comparing amputation with LST in the treatment of ESTS.[31,32] Another study shows that 80% of the patients who underwent a non-primary amputation did not regret undergoing the initial attempt at LST.[33]

In the last decades, many options for prosthesis parts have entered the market, including improved socket designs, technological advances such as microprocessor-equipped prosthesis components (ankle and knee), and a wider choice in foot selection. A better prosthetic rehabilitation program also offers patients a better quality of life. Since the 1990s, osseointegration (Swedish) techniques, to ensure a stable fixation of the titanium implant into the bony tissue of the amputation stump, have evolved to become more standardized, too.[34,35] With this technique, the human-prosthesis interface has been optimized, gait optimization has been achieved, and functional outcome has been improved. With the development of evidence-based guidelines, the amputee patient can have a standardized protocol for a rehabilitation program, which in the end leads to a better functional result.[36–38] Considering the implications of ablative surgery, there are no data available comparing patients' self-sufficiency after an upper versus lower limb amputation is performed. However, it seems logical that lower limb amputations have a smaller impact on one's daily routine than upper limb amputations do. Due to the fact that the upper limb harbors much more subtle tactile functions and fine motor skills as the lower limb, prosthetic options after an upper limb amputation are less and the implications on the patients' life are substantial. The finding that primary amputations were performed for larger and more proximally located ESTS might be caused by the fact that these tumors are diagnosed in a later stadium due to a naturally larger limb-circumference, that is, limb volume, of the proximal limbs. Accordingly, ESTS of the distal limbs might be diagnosed earlier leading to more LST options as these tumors might be less extensive at time of diagnosis. Still, the development of a local recurrence or failure of the LST might result in a non-primary amputation for some of these distal ESTS.

This study has some limitations, the retrospective character of this study encompasses the risk of retrospective selection bias. However, this study includes all patients who underwent an amputation in the treatment of their ESTS, patients in Group I all had tumors necessitating a primary amputation. Whereas, patients in Group II had tumors in which an initial (or several) attempt for LST was considered to be possible. Furthermore, it was chosen to exclude tumor grade from this manuscript, as almost one-third of data considering tumor grades was missing. Due to the retrospective nature of this study it was impossible to retrieve the tumor grade for these 12 patients. Whereas, the remaining 27 patients all suffered from a high grade (grade 2 or 3) ESTS.

In summary, patients with ESTS for whom an amputation is indicated have a worse prognosis than patients with STS in general. However, patients who underwent a primary or a non-primary amputation for ESTS seem to have comparable oncological outcomes. Given this comparable oncological outcome, the need is urgent on behalf of the patient for amputation levels to be chosen adequately and for optimal rehabilitation to be provided by surgeons and rehabilitation specialists.[39,40]

5 | CONCLUSION

The timing of amputation does not seem to affect the oncological outcome of ESTS patients. Therefore LST remains the treatment of choice, even for locally advanced ESTS. Attempts to achieve local control with LST in patients with ESTS can result in multiple intensive treatments per patient. However, the time between diagnosis and amputation was significantly longer for Group II when compared with Group I (80.0 [17.0-184.0] vs 8.5 [3.0-12.8] weeks, $P < 0.001$). Despite all efforts, some patients will need a non-primary amputation because of a local recurrence, failure of LST or LST-related complications. Ongoing possibilities are being realized in prosthesis and rehabilitation programs, therefore it remains important to decide in a multidisciplinary fashion which treatment suits best for each individual patient.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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