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ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Major Amputations for Extremity Soft-Tissue Sarcoma

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ABSTRACT

Introduction. With modern techniques facilitating limb conservation, amputation for extremity soft-tissue sarcoma (ESTS) is now rare. We sought to determine the indications and outcomes following major amputation for ESTS and whether amputation is prognostic of oncological outcomes in primary disease.

Patients and Methods. Patients undergoing major amputations for ESTS from 2004 to 2014 were identified from electronic patient records.

Results. The amputation rate in primary localized disease was 4.1%. Overall, 69 patients were identified, including 23 (33.3%) amputations for primary localized disease, 36 (52.2%) amputations for recurrent disease, and 10 (14.5%) amputations for metastatic disease. The local recurrence rate for localized disease at 3 years was 10.4%. Three-year overall survival (OS) was 50.3% following curative amputation, with a median survival of 41 months, and median OS following palliative amputation was 6 months. In the context of primary, localized disease, patients undergoing amputation had a greater proportion of high-grade tumors (69.6% vs. 41.1%; $p = 0.009$) of greater size (median 16.0 vs. 9.0 cm; $p = 0.003$) when compared with patients undergoing limb-conserving surgery. The rates of systemic relapse and disease-specific survival were poorer following amputation compared with limb-conserving surgery, however mode of surgery (amputation vs. limb conservation) was only prognostic for OS.

Conclusions. Amputation maintains an important role in ESTS and achieves durable local control in those unsuitable for limb-conserving surgery. Survival following amputation in the presence of metastatic disease is poor and should be reserved for patients with significant symptoms.

Amputation for extremity soft-tissue sarcoma (ESTS) has not been shown to achieve improved survival outcomes when compared with limb-conserving surgery.[1–3] Limb-conserving surgery has been shown to be associated with good functional outcomes, and as such is the surgical strategy of choice in the majority of patients, with the aim of achieving microscopically negative margins while maximizing postoperative limb function.[4–6] If microscopic negative margins are not possible due to adherence of the tumor to critical neurovascular structures or bone, a resection involving planned close or microscopically positive margins combined with neo/adjuvant radiotherapy achieves durable local control while preserving function.[7] If the size of the tumor or proximity to vital structures precludes limb-conserving surgery, induction systemic or regional chemotherapy, in the form of isolated limb perfusion, is an alternative strategy that may be used to allow the limb to be preserved.[8] In addition, with modern reconstructive techniques, more extensive soft-tissue defects following surgery can be covered, increasing the number of patients suitable for limb conservation.[9–11] However, in a minority of patients, limb-conserving surgery is not feasible and amputation maintains an important role in the management of primary, localized disease.[12] Amputation may also be necessary in recurrent disease when limb-conserving treatments have failed to gain local control, and remains a valuable palliative treatment for symptomatic, locally advanced tumors in the context of disseminated disease.

The purpose of this study was to determine the indications for, and outcomes following, major amputation for ESTS and to investigate whether amputation for primary,

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localized disease was prognostic of poorer oncological outcomes when compared with patients undergoing limb-conserving surgery.

METHODS

All patients undergoing a major amputation for ESTS at The Royal Marsden Hospital between January 2004 and January 2015 were identified from electronic patient records. In the upper limb, major amputations were defined as below elbow, above elbow, or forequarter amputations, whereas in the lower limb, major amputations were defined as below-knee, above-knee, through-hip, or hindquarter amputations.

Pathological variables of interest included maximum tumor diameter, histological subtypes, and tumor grade, with grade being determined using the French Federation of Cancer Centres Sarcoma Group Grading System.[13] Perioperative morbidity and mortality are reported at 30 days using the Clavien–Dindo scale (grades II–IV).[14] Three-year local recurrence-free survival (LRFS), distant metastases-free survival (DMFS), disease-specific survival (DSS) and overall survival (OS) were calculated and plotted using the Kaplan–Meier method and compared with the log-rank test. All oncological outcomes were defined as the time from surgery to the event. Where patients developed local recurrence and distant metastasis, both events were recorded as outcome measures.

Data regarding all patients undergoing potentially curative limb-conserving surgery for primary, localized ESTS during the same time period were retrieved from a prospectively maintained institutional database and compared with those of patients undergoing amputation for primary, localized ESTS. Multivariate Cox regression analyses were performed to evaluate the following potential prognostic factors of DMFS and DSS: patient age, tumor size, tumor grade, and surgical management (amputation vs. limb-conserving surgery). The results of the multivariate analysis are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). SPSS version 24.0 (IBM Corporation, Armonk, NY, USA) was used for all analyses.

RESULTS

A total of 69 patients undergoing a major amputation for ESTS were identified. Patient and tumor characteristics are summarized in Table 1, and further information regarding other histological subtypes in patients undergoing amputation is provided in electronic supplementary Table 1. The majority of amputations were performed in the upper limb (60.9%), for recurrent disease (52.2%) and with curative intent (85.5%). The median follow-up from the time of amputation was 20 months (range 0–139 months), with four patients lost to follow-up within 12 months of operation.

Indications for Amputation

Amputations were performed for primary localized disease in 23 patients. The most common indications for amputation in these patients were extensive involvement of the limb/limb girdle, with extension between multiple muscle compartments (65.2%), multifocality (21.7%), and unsuitability for limb-conserving surgery due to the involvement of critical structures, an entire muscle compartment, or inadequate soft-tissue coverage (13.0%). Prior treatment was uncommon in these patients, with only two receiving radiotherapy (8.7%) and one receiving systemic chemotherapy (4.3%). The median maximal tumor diameter in primary tumors was 16.0 cm (range 7.0–40.0).

Amputations were performed for recurrent localized disease in 36 patients. The most common indications for amputation in these patients were extensive involvement of the limb/limb girdle, with extension between multiple muscle compartments (44.4%), multifocality (36.1%), and unsuitability for limb-conserving surgery (16.7%). A single patient underwent amputation for a pathological fracture (2.8%). In addition to their initial resection, 27 patients had previously been treated with radiotherapy (75.0%), seven patients with systemic chemotherapy (19.4%), and a further nine patients with regional chemotherapy in the form of isolated limb perfusion with melphalan and tumor necrosis factor-α (25.0%). A total of 15 patients (41.7%) had undergone further limb-conserving surgery for recurrent disease prior to amputation. A single patient had undergone a previous amputation prior to referral, above the elbow, before proceeding to a forequarter amputation. Amputation was the initial treatment for recurrent disease in only eight patients (22.2%). Of these, three had undergone wide excision alone for primary disease, with the remaining five receiving adjuvant radiotherapy at the time of their initial surgery. The median maximal tumor diameter in recurrent tumors was 9.5 cm (range 3.9–33.0), significantly smaller than in primary disease (unpaired t test, $p = 0.007$).

A total of 59 patients had localized disease at the time of amputation and underwent surgery with curative intent. The remaining 10 patients underwent a palliative amputation (14.5%), with the indication for intervention being a fungating lesion in five patients, intractable pain in four patients, and a pathological fracture in one patient. Pulmonary metastases were present in eight patients (80.0%), accompanied by bony or subcutaneous metastases in two of

TABLE 1 Demographics and tumor characteristics of patients undergoing major amputations for extremity soft-tissue sarcoma

Variable	Primary localized	Recurrent localized	Metastatic	Overall
No. of patients	23 (33.3)	36 (52.2)	10 (14.5)	69 (100)
Median age at operation, years (range)	62 (28–86)	61 (25–83)	63.5 (17–81)	62 (17–86)
Male:female ratio	1.1 (12:11)	0.8 (22:27)	1.0 (5:5)	1.4 (40:29)
Level of amputation				
Upper limb				
Total	14 (60.8)	23 (63.9)	5 (50.0)	42 (60.9)
Above elbow	8 (34.8)	12 (33.3)	2 (20.0)	22 (31.9)
Forequarter	6 (26.1)	11 (30.6)	3 (30.0)	20 (29.0)
Lower limb				
Total	9 (39.1)	13 (30.2)	5 (50.0)	27 (39.1)
Below knee	2 (8.7)	3 (7.0)	1 (10.0)	6 (8.7)
Above knee	2 (8.7)	4 (9.3)	3 (30.0)	9 (13.0)
Through-hip	1 (4.3)	0 (0)	0 (0.0)	1 (1.4)
Hindquarter	4 (17.4)	6 (13.9)	1 (10.0)	11 (15.9)
Median tumor size, cm (range)	16.0 (7.0–40.0)	9.3 (2.8–33.0)	12.0 (5.5–21.0)	13.0 (3.9–40.0)
Histological subtype				
Undifferentiated pleomorphic sarcoma	7 (30.4)	11 (30.6)	4 (40.0)	22 (31.9)
Myxofibrosarcoma	2 (8.7)	8 (22.2)	0 (0.0)	10 (14.5)
Synovial sarcoma	1 (4.3)	2 (5.6)	1 (10.0)	4 (5.8)
Angiosarcoma	3 (13.0)	0 (0.0)	1 (10.0)	4 (5.8)
MPNST	3 (13.0)	0 (0.0)	0 (0.0)	3 (4.3)
Other	7 (30.4)	15 (41.7)	4 (40.0)	26 (36.2)
Tumor grade				
1	1 (4.3)	1 (2.8)	0 (0.0)	2 (2.9)
2	5 (21.7)	15 (41.7)	0 (0.0)	20 (29.0)
3	16 (69.6)	19 (52.8)	10 (10.0)	45 (65.2)
Unknown	1 (4.3)	1 (2.8)	0 (0.0)	2 (2.9)
Treatment preceding amputation				
Radiotherapy	2 (8.7)	27 (75.0)	4 (40.0)	33 (47.8)
Systemic chemotherapy	1 (4.3)	7 (19.4)	2 (20.0)	10 (14.5)
Regional chemotherapy	0 (0.0)	9 (25.0)	3 (30.0)	12 (17.4)

Data are expressed as *n* (%) unless otherwise specified

these patients. The remaining two patients had isolated subcutaneous metastatic disease.

Perioperative Outcomes

Of the whole cohort, a total of 10 patients experienced a Clavien–Dindo grade II–IV morbidity (14.5%). A total of four patients developed wound infections–two who had undergone an above-knee amputation, and two who had undergone a hindquarter amputation. A return to theatre was required in two patients, one for drainage of a post-operative hematoma and the other following a traumatic wound dehiscence. A total of four patients developed medical complications (one urinary tract infection, one acute renal failure, and two cardiac dysrhythmias). A single patient died within 30 days of operation, giving a 30-day perioperative mortality rate of 1.4%. This patient had initially refused amputation and re-presented with sepsis secondary to an infected angiosarcoma. An emergent above-knee amputation was performed, however the patient died 15 days later from multiorgan failure.

Oncological Outcomes

For the entire cohort, the 3-year LRFS was 89.6% (95% CI 85.0–94.2), the 3-year DMFS was 44.0% (95% CI 37.2–50.8), and the 3-year OS was 49.8% (95% CI 43.0–56.6).

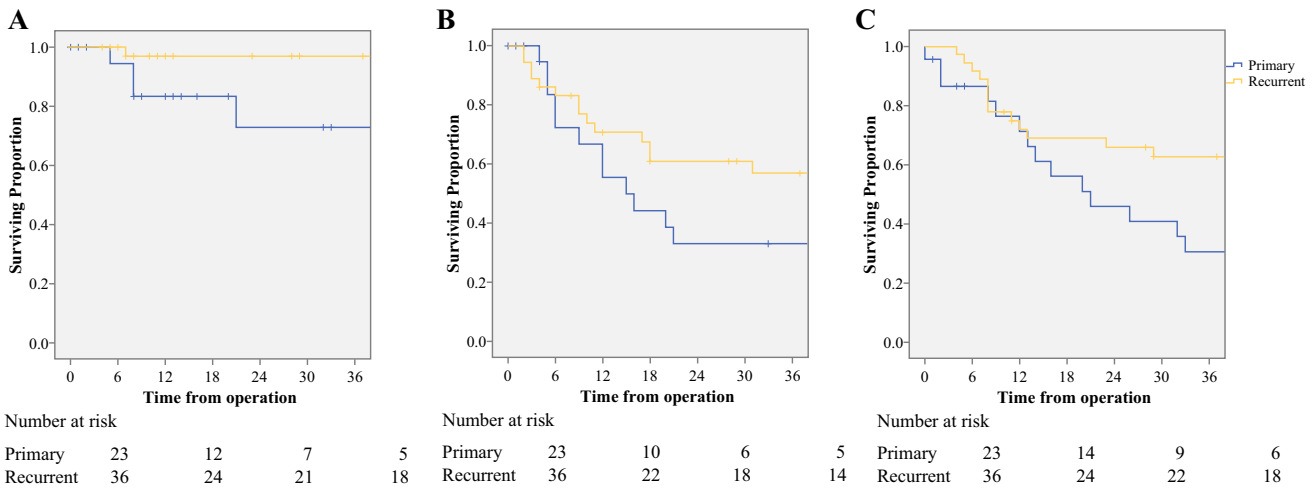

FIG. 1 **a** Local recurrence-free survival, **b** distant metastasis-free survival, and **c** overall survival following amputation for primary or recurrent localized extremity soft-tissue sarcoma

In patients with localized disease, no difference in oncological outcomes was noted between those undergoing amputation for primary or recurrent disease (Fig. 1). The 3-year LRFS was 97.0% (95% CI 94.0–99.9) in those with recurrent disease, and 72.9% (95% CI 60.5–85.3) in those with primary disease ($p = 0.127$, log-rank test), while the DMFS was 57.2% (95% CI 48.3–66.1) in those with recurrent disease and 33.4% (95% CI 22.3–44.5) in those with primary disease ($p = 0.082$, log-rank test). Of the 59 patients with localized disease at the time of surgery, 29 developed metastatic disease (49.2%), with a median time to first metastasis of 10 months. The most common site of first metastasis was the lung, accounting for 22 of these patients (75.9%). Two patients presented with intra-abdominal metastases and one patient presented with a retroperitoneal lesion. Of the remaining four patients, two presented with bony metastases and two presented with subcutaneous metastases. The OS at 3 years was 62.8% (95% CI 54.6–71.0) in those with recurrent disease, and 30.5% (95% CI 20.1–40.9) in those with primary disease ($p = 0.076$).

The 3-year OS following amputation in the context of localized disease was 50.3% (95% CI 43.4–57.2). Survival following palliative amputation in the context of metastatic disease was significantly shorter, with a median OS of 6 months and no patients surviving over 24 months ($p < 0.001$, log-rank test) (Fig. 2).

Impact of Amputation on Oncological Outcomes in Primary, Localized Extremity Soft-Tissue Sarcoma

A total of 23 patients underwent amputation for primary localized disease. During the same time period, a total of 556 patients with primary, localized ESTS underwent a potentially curative resection at our institution, giving an amputation rate of 4.1%.

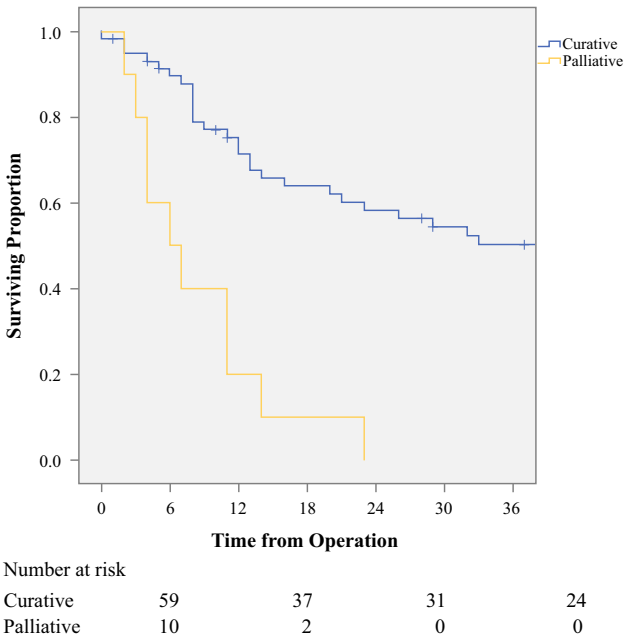

FIG. 2 Overall survival following amputation for extremity soft-tissue sarcoma when performed with curative or palliative intent

There was no difference in the age of patients at operation in those undergoing amputation or limb-conserving surgery (median age 62 vs. 63 years, Mann–Whitney test; $p = 0.413$). With regard to histological subtype, undifferentiated pleomorphic sarcomas (31.9 vs. 30.4%), myxofibrosarcomas (14.5 vs. 9.8%), and synovial sarcomas (4.3 vs. 3.2%) accounted for similar proportions of tumors in each cohort. Well-differentiated liposarcomas (11.7%), myxoid liposarcomas (11.7%), and leiomyosarcomas (7.2%) were the most frequent other subtypes in the limb-conserving cohort, but accounted for no patients undergoing amputation. Angiosarcomas (13.0 vs. 0.6%) and

MPNSTs (13.0 vs. 2.0%) were more frequent in the amputation cohort. Patients with primary disease undergoing amputation had significantly larger tumors than those treated with limb-conserving surgery (median size 16.0 vs. 9.0 cm, unpaired *t*-test; $p = 0.003$), and a greater proportion had high-grade tumors (69.6 vs. 41.1%, χ^2 test; $p = 0.009$). Those undergoing amputation also had a greater proportion of upper limb tumors (60.8 vs. 23.2%, χ^2 test; $p < 0.001$).

No difference in LRFS was noted between patients undergoing amputation or limb-conserving surgery (log-rank test; $p = 0.064$); however, patients undergoing amputation had significantly shorter DMFS (log-rank test; $p < 0.001$) and OS (log-rank test; $p < 0.001$) (Fig. 3). On multivariate analysis, amputation was not found to be independently prognostic of systemic relapse, with the only independent prognostic factors being tumor size and grade (Table 2). Amputation was found to be prognostic of OS, alongside tumor size, grade, and patient age. However, while these other factors were also prognostic of DSS, amputation was not.

DISCUSSION

With the widespread adoption of limb-conserving techniques, amputation for primary, localized ESTS is now rare. The amputation rate in the current series was 4.1%, with rates published in other series ranging from 6 to 10%.[15–17] Although it is recognized that amputation is still necessary in selected patients, with the available techniques for limb conservation it is now achievable for amputation rates in primary, localized ESTS to be no higher than 5%.

In the context of localized disease, when amputation is performed for primary disease, it is, for the most part, in patients presenting with large, high-grade tumors. The median tumor size in patients undergoing amputation in the current series was almost double that of those managed with limb-conserving surgery, as was the proportion of patients with high-grade tumors. This trend towards greater size and higher grade has also been reported in previous series of amputation, both in those exclusively comprised of primary tumors and those including recurrent sarcomas.[3,15,18] This emphasizes the need for early recognition and treatment of ESTS, not only as this may reduce the requirement for amputation in primary disease but also as size is a well-recognized prognostic factor for survival.[16,19–22]

Patients who undergo amputation for recurrent disease have typically been heavily pretreated and conservative techniques to secure local control have failed. In the current series, less than one-fifth of patients with recurrent disease proceeded directly to amputation, of which more than half had received radiotherapy following their primary operation. Size appears to be less of a factor precluding limb-salvage in recurrent disease, with these tumors being significantly smaller than primary tumors requiring amputation. Rather, it is found that with subsequent recurrences, preservation of a heavily pretreated limb becomes increasingly challenging. When limb-conserving surgery is not possible, specialized techniques such as isolated limb perfusion may be considered as a stand-alone palliative treatment in truly irresectable disease, and may allow the limb to be preserved in a significant proportion of cases, although the extent and duration of treatment response is variable.[23,24] In addition, the effectiveness of regional chemotherapy is probably less in a heavily pretreated recurrent sarcoma than in primary untreated disease. In those patients who are unsuitable for regional chemotherapy, or have an inadequate response to treatment, major

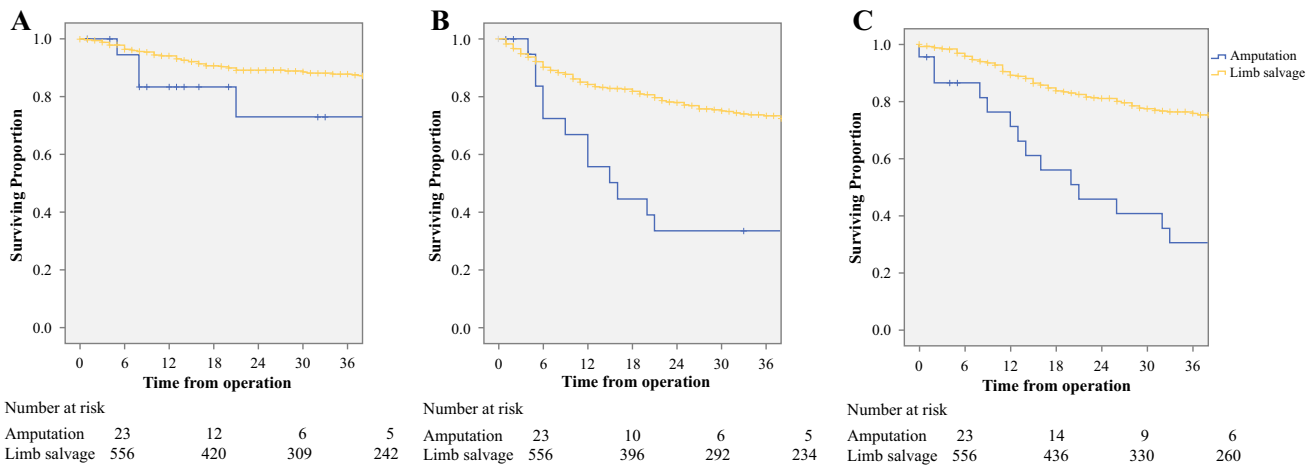

FIG. 3 **a** Local recurrence-free survival, **b** distant metastasis-free survival, and **c** overall survival following amputation or limb-conserving surgery for primary localized extremity soft-tissue sarcoma

TABLE 2 Multivariate analysis of independent prognostic factors of oncological outcome in patients with primary, localized extremity soft-tissue sarcoma

	Distant metastases-free survival		Overall survival		Disease-specific survival	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Amputation vs. limb-conserving surgery	1.71 (0.96–3.06)	0.70	2.13 (1.25–3.64)	0.006	1.48 (0.79–2.78)	0.221
Tumor size, cm	1.08 (1.06–1.11)	<0.001	1.07 (1.05–1.10)	<0.001	1.07 (1.04–1.10)	<0.001
Tumor grade						
I vs. III	0.04 (0.02–0.11)	<0.001	0.11 (0.05–0.21)	<0.001	0.10 (0.05–0.19)	<0.001
II vs. III	0.51 (0.35–0.74)	<0.001	0.60 (0.42–0.86)	0.005	0.59 (0.41–0.85)	0.005
Patient age (years)	1.01 (0.99–1.02)	0.212	1.04 (1.02–1.05)	<0.001	1.03 (1.02–1.05)	<0.001

HR hazard ratio, *CI* confidence interval

amputation can achieve durable local control, with a local recurrence rate of <5% at 3 years in the current series.

In spite of durable local disease control, patients undergoing amputation have significantly higher rates of metastatic spread and poorer survival than those undergoing limb-conserving surgery, as has been previously reported in the literature.[3,15] The mode of initial surgery, be it limb conservation or amputation, was not identified as a prognostic factor for distant relapse in the current series or in a previous series that also investigated this association,[15] nor was it found to be prognostic of DSS in the current series. Rather, the need for amputation appears to represent a selection bias towards patients with more biologically aggressive tumors who are destined to have poorer outcomes. This has implications not only for the counseling of these patients prior to amputation but also on the frequency and mode of their surveillance postoperatively. The majority of metastases in ESTS occur within the first 2 years following surgery, with a median time to first metastasis of 10 months in the current series.[25] Although the current systemic treatments for metastatic sarcoma are of limited efficacy, there is some evidence that metastasectomy for isolated pulmonary metastases may benefit selected patients.[26–29] Consideration should be given to radiological surveillance every 3 months in the first 2 years following amputation, with the aim of identifying patients who go on to develop systemic metastasis in this high-risk group.

The survival of patients undergoing amputation in the presence of metastatic disease is poor. The median survival of such patients in the current series was 6 months, and no patients undergoing amputation in the context of metastatic disease survived more than 2 years from operation. Although the previous series reporting survival following amputation in the context of metastatic disease also include pathologies other than sarcoma, survival outcomes are similarly poor, ranging from a median of 3–13 months.[30–33] In light of such poor survival, palliative amputation in the presence of metastatic sarcoma should be reserved for patients with severe symptoms in whom all other conservative palliative treatments have been exhausted.

The authors acknowledge the limitations of this study. As a retrospective series, information regarding quality of life and functional assessments following amputation are lacking. Previous series have reported that both quality of life and postoperative function are greater following limb-conserving surgery than amputation, and, as may be expected, higher levels of amputation are associated with poorer postoperative function.[34,35] Although the length of follow-up in this series appears short, this may be due to earlier relapses and subsequent death in this cohort of high-risk patients. However, the potential for late relapse in soft-tissue sarcoma is well-recognized and longer follow-up may provide more information regarding the outcomes of those patients not relapsing within the first 2 years postoperatively.

CONCLUSION

Amputation maintains an important role in the management of ESTS, whether in the context of primary, recurrent, or metastatic disease. However, patients undergoing amputation have poorer outcomes compared with limb-conserving surgery, and the initial consultation and postoperative surveillance should be tailored accordingly.

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