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Amputation for Recurrent Soft Tissue Sarcoma of the Extremity: Indications and Outcome

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Background: Limb salvage after primary site failure of extremity soft tissue sarcoma is a challenging problem. Amputation may be the most effective treatment option in selected patients with local recurrence. We compared the outcome of patients treated with amputation versus limb-sparing surgery (LSS) for locally recurrent extremity sarcoma.

Methods: From 1982 to 2000, 1178 patients with localized primary extremity sarcoma underwent LSS. Of these, 204 (17%) developed local recurrence. Eighteen (9%) required major amputation and the remainder underwent LSS, of which 34 were selected for matched-pair analysis according to established prognostic variables. Rates of recurrence or death were estimated by the Kaplan-Meier method. Following adjustment for prognostic variables, a Mantel-Haenszel test was used to compare the outcome between the two treatment groups.

Results: Patients in each group were well matched. All patients had high-grade tumors deep to the fascia. Median time to local recurrence was similar for both groups. Median follow-up was 95 months. Amputation was associated with a significant improvement in local control of disease (94% vs. 74%; $P = .04$). We observed no difference in disease-free ($P = .48$), disease-specific ($P = .74$), or overall survival ($P = .93$) between the two groups. Median postrecurrence survival was 20 months and 5-year OS was 36% for the entire study group.

Conclusions: Limb-sparing treatment achieves local control in the majority of recurrent extremity sarcomas for which amputation is infrequently indicated. Amputation improves local disease control but not survival under these circumstances.

Key Words: Recurrent—Extremity—Sarcoma—Amputation.

Management of soft tissue sarcoma of the extremity is dependent upon anatomic location and tumor stage. Primary determinants of tumor stage include tumor size, histologic grade, and depth relative to the investing superficial muscular fascia.[1] The treatment approach to primary extremity sarcoma has shifted over the past two decades from amputation to limb-sparing resection with or without adjuvant radiotherapy. Limited prospective randomized data supports the principle that, although a more radical resection of the primary tumor improves local disease control, it does not provide a survival benefit over limb-sparing surgery (LSS) plus radiation.[2]

Despite optimal primary therapy, local recurrence rates of 10%–20% have been reported in prospective randomized trials addressing the multimodality treatment of high-grade extremity sarcomas.[3,4] Factors predicting increased risk of local recurrence have been well defined and include size >5 cm, high tumor grade, location deep to the investing muscular fascia, positive microscopic resection margins, and presentation with locally recurrent disease.[5,6] Limb salvage after primary site failure can be a challenging clinical problem in terms of resection and functional preservation.

The principal aim of treatment for isolated local recurrence is the same as that for primary tumors: local control of disease and functional limb preservation. This therapeutic aim can be achieved in most situations with limb-preserving resection with or without radiotherapy.

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Amputation, though infrequently indicated, may be the most effective treatment option in selected patients with recurrent extremity sarcoma.

In this study we examine the indications for amputation in the management of locally recurrent soft tissue sarcoma of the extremity. The primary goal of this study is to compare the oncologic outcome of patients treated with amputation or LSS as part of limb salvage therapy for primary site failure. A matched-pair analysis was conducted by stratifying patients according to established clinicopathologic prognostic factors for outcome in this well-characterized study population that was treated and followed prospectively at a single institution.

METHODS

Patients

During the period of July 1982 to January 2000, 1178 adult patients with localized primary soft tissue sarcoma of the extremity (without regional or distant metastases) underwent limb-sparing resection at Memorial Sloan-Kettering Cancer Center. Patients treated with primary amputation were not considered for this analysis. Patient information was entered into an established database and the patients were followed prospectively. Clinical follow-up visits, telephone interviews, and mailed questionnaires were used to update collected data in a prospective manner. Tumors with relatively favorable natural history, including dermatofibrosarcoma protuberans and desmoid tumors, were not included as part of the study population. Local recurrence was identified in 204 (17%) patients. Patients treated with nonoperative modalities (radiation and/or chemotherapy), patients with incomplete data sets, and those with insufficient follow-up were excluded, leaving 174 patients for analysis.

Eighteen of the 204 (9%) patients initially treated with primary LSS who later recurred locally underwent major amputation and 156 underwent limb-sparing resection with or without radiotherapy for locally recurrent extremity sarcoma. Patients undergoing minor distal extremity amputation (e.g., digit, ray, hand, ankle, and hindfoot) were not included in this analysis. Each of the patients treated with amputation was randomly matched with one or more patients from the group of 156 patients according to established prognostic factors for local and systemic relapse. Thirty-four patients (approximately twice as many as in the amputation group) were selected that most closely matched those patients treated with amputation. Thus, this prospectively followed cohort of 52 patients with locally recurrent extremity sarcomas was retrospectively stratified into two treatment groups, amputation ($n = 18$) versus resection ($n = 34$), in an effort to examine indications for amputation, determine local control, and evaluate outcome.

Definitions

A primary tumor was defined as a localized lesion previously untreated or biopsied only (incisional or inadequate excisional biopsy) prior to definitive surgical therapy. A tumor was defined as a lower extremity tumor if it was in the groin, buttock, or leg. Iliac fossa tumors were excluded from the analysis. Tumors originating at or below the shoulder were defined as upper extremity primaries. Tumors originating in the axilla were included as part of the analysis.

Local recurrence was defined as a documented tumor of the same histologic type, within or contiguous to the previously excised field, 3 or more months following primary therapy for localized soft tissue sarcoma of the extremity. Patients were stratified into two study groups. Patients who developed local recurrence following primary limb-sparing therapy, and were treated with amputation with or without adjuvant chemotherapy for the recurrence, were assigned to the "amputation" group. The "resection" group consisted of patients treated with limb-sparing resection, with or without adjuvant radiation or chemotherapy, for a first local recurrence following LSS of localized primary extremity sarcoma. Time to first local or distant recurrence was calculated from the time of the primary surgical treatment. Time to second local recurrence was calculated from the time of treatment of the first local recurrence.

Tumor size was defined as the maximum diameter of the tumor at radiographic imaging or pathologic analysis. Tumors were classified as small ($\leq$5 cm), intermediate ($>$5–10 cm), and large ($>$10 cm). Tumor grade was classified as low or high based on the degree of cellularity, differentiation, vascularity, nuclear pleomorphism, number of mitosis per high power field, and amount of stromal necrosis.[4] Tumor depth was characterized as superficial or deep relative to the investing superficial muscular fascia. Bone or neurovascular involvement was defined by gross or microscopically evident invasion of these structures by sarcoma at time of surgery or pathologic assessment.

Macroscopic margins were assessed at the time of surgery and microscopic margins, histopathologically. Complete surgical resection was defined as the absence of gross residual disease following surgical excision of the tumor. Microscopic margin was defined as positive if tumor was present at the inked margin and negative if the inked margin was uninvolved by tumor.

Data

Primary study end points included time to second local recurrence, distant metastases, disease-related mortality, and overall survival (OS). Any appraisal of outcome on the basis of treatment, amputation versus limb-sparing resection, may not be related to the treatment itself. Prognosis in such a comparison between unmatched study populations is most likely based on clinical and pathologic prognostic variables. To avoid imposing modelling assumptions on this analysis, where the number of patients treated with amputation is few, we matched the patients in this study according to known prognostic variables. The selection criteria for the matched-pair analysis included the following patient-, tumor-, and treatment-related characteristics: sex; primary presentation; primary tumor site, size, depth; primary tumor histology, histologic grade, and resection margin; primary treatment, time to first local recurrence, and microscopic margin following resection of first local recurrence. The anatomic location of the primary sarcoma was evenly distributed between the two study groups; for example, the distribution of primary shoulder/axilla (17% and 20%), upper arm (6% and 9%), and forearm (11% and 9%) tumors was not significantly different between the two groups. Because patients were well matched for clinical and pathologic factors, only type of treatment for local recurrence was correlated with study end points.

Treatment

Patients were treated according to the standard of care at Memorial Sloan-Kettering Cancer Center. All patients in this study underwent primary treatment with LSS. More recently, some received adjuvant radiation and/or chemotherapy (generally doxorubicin and ifosfamide). Because adjuvant therapy was not prospectively randomized it is only reported in the treatment data but not included in any of the analyses.

Surgical treatment decisions were based on review of pathologic material obtained from biopsy or prior resections and on size and anatomic location of the recurrent tumor. Review of prior treatment included extent of resection and associated microscopic margins; type, dose, and technique of radiation; and type of chemotherapy previously administered. Locally recurrent disease was confirmed by tissue biopsy. Clinical and radiologic examination (MRI) facilitated the determination of the size, depth, and proximity of the recurrent tumor to bone or major neurovascular structures. Evidence of multifocal or multicompartment recurrence was also an important determinant of treatment strategy. Previous operative reports were reviewed to determine adjacent tissue planes potentially contaminated by tumor at time of initial surgery. Degree of pain and functional limb disturbance were considered in the treatment approach to the local recurrence.

The goal of surgical treatment of locally recurrent soft tissue sarcoma of the extremity was excision of the tumor with negative gross and microscopic margins of resection and with preservation of a functional limb whenever possible. Treatment of locally recurrent disease could be achieved in over 90% of patients with limb-sparing techniques. During the operation, dissection of the tumor was performed through uninvolved tissue at a distance from the grossly palpable lesion, including biopsy incisions and needle biopsy tracts where appropriate. For those patients undergoing limb-sparing resection, intra- or intermuscular tumor was resected en bloc with involved muscle bundles. In this group, tumors in proximity to major neurovascular anatomy were resected with margins limited by the paucity of nonvital surrounding soft tissues. With multimodality treatment options available, amputation was infrequently indicated for the treatment of our patients with locally recurrent sarcoma of the extremity. The specific indications for amputation in this setting will be defined later. In general, amputation was performed for tumors so extensive that resection, short of amputation, could not possibly achieve complete extirpation of the disease with a reasonable functional outcome. Patients were treated with primary adjuvant radiotherapy based on prognostic factors predicting an increased risk of local recurrence at the discretion of the Multidisciplinary Soft Tissue Sarcoma group or as part of clinical trials. Techniques employed to deliver radiotherapy included external beam radiotherapy and brachytherapy with iridium-192 seed implantation. For patients receiving adjuvant brachytherapy, radioactive iridium was not loaded into the brachytherapy catheters until after the fifth postoperative day. This practice is based on our earlier experience that demonstrated an increased risk of wound complications when catheters were loaded during the proliferative phase of wound healing, during the first 5 days after surgery. Total adjuvant radiation dose ranged from 4,350–6,500 cGy. Patients with locally recurrent disease who received prior external beam radiotherapy were generally treated with resection followed by brachytherapy. Over half of the patients with locally recurrent tumors previously treated with resection alone underwent resection followed by radiotherapy (brachytherapy or external beam radiation).

Statistics

Summary statistics were obtained using established methods. Associations between categorical variables were evaluated using the χ^2 test,[7] with a P value $< .05$ considered significant. Treatment groups were matched on the basis of factors known to influence disease-specific survival. This matched-pair analysis was conducted in an attempt to ensure that comparisons of interest, in this case treatment of local recurrence, could be properly made within the confines of a small group of individuals receiving amputation and retrospectively stratified study groups. Time to local and distant recurrence and disease-related mortality were calculated for both treatment groups. Initial local recurrence-free survival was defined as time to local recurrence of extremity sarcoma from time of first surgery. Time to second local recurrence was calculated from time of treatment for first local recurrence. Disease-free survival was calculated from time of treatment of first local recurrence to subsequent disease recurrence (local or distant). Deaths that were confirmed to be due to sarcoma were treated as end points for disease-specific survival. Disease-specific survival was calculated from time of treatment of first local recurrence to time of sarcoma-related death. All other deaths were regarded as censored events. OS was defined as the time from first local recurrence surgery to death from any cause. The rate of recurrence or death was estimated using the product-limit method of Kaplan and Meier.[8]

To compare the outcome between patients treated with amputation to those who underwent limb-sparing resection, matching each patient who received an amputation to patients with resection created strata defined by clinical and pathologic prognostic factors for local and distant recurrence and tumor-related mortality. A Mantel-Haenszel test[9] was used to test the null hypothesis: survival functions between patients treated with amputation and resection for locally recurrent disease are no different. The survival comparison was restricted to the time of observation from July 1982 to January 2000. The indicated P value following second local recurrence-free, disease-specific, and OS comparisons was based on the comparison of the survival curves. Statistical analysis was performed using JMP® software (JMP, Cary, NC). A P value $< .05$ was considered statistically significant.

TABLE 1. *Local recurrence: Amputation vs. limb sparing surgery, matched-pair analysis*

Factor	Amputation n = 18	Resection n = 34
Sex		
F	8	16
M	10	18
Primary presentation		
Pimary, no treatment	3	4
Primary, incomplete WLE	7	13
Primary, complete WLE	0	1
Primary, biopsy only	8	16
Site		
Upper extremity	10	17
Lower extremity	7	16
Trunk (buttock)	1	1
Primary size		
< 5	7	11
5–10 cm	5	10
> 10 cm	6	13
Primary depth		
Superficial	0	0
Deep	18	34
Histology		
MFH	4	10
Liposarcoma	2	9
Synovial	4	3
Rhabdomyosarcoma	2	0
Leiomyosarcoma	1	1
Chondrosarcoma	1	0
Epitheloid	1	1
Ewing's extraosseous	1	1
Fibrosarcoma (non-desmoid)	0	3
Hemangiopericytoma	0	1
MPNT	1	5
Undifferentiated	1	0
Primary histologic grade		
Low	0	0
High	18	34
Primary resection microscopic margin		
Negative	9	25
Positive	9	9
Primary procedure		
Resection	18	34
Amputation	0	0
Primary radiotherapy		
Yes	11	20
No	7	14
Primary chemotherapy		
Yes	10	15
No	8	19
LR microscopic margin		
Negative	15	20
Positive	3	10

WLE, wide local excision; depth is defined relative to the superficial investing muscular fascia; MFH, malignant fibrous histiocytoma; MPNT, malignant peripheral nerve sheath tumor; LR, local recurrence; patients undergoing amputation for primary extremity sarcoma were excluded from the study; $P > 0.05$ for all comparisons between the two study groups.

RESULTS

Between July 1982 and January 2000, 1178 patients with localized primary sarcoma underwent LSS. Of these, 204 (17%) developed local recurrence. Thirty-four patients were excluded from the analysis. Eighteen (9%) patients were treated with amputation for local recurrence of extremity sarcoma. No patient treated with

amputation for locally recurrent disease was excluded. One hundred fifty-six patients were treated with limb-sparing resection with or without adjuvant radiotherapy during the period of observation. Of these, 34 patients were randomly selected based on stratification of clinicopathologic prognostic variables that most closely matched those patients in the amputation study arm. Median follow-up for those patients who are alive as of last follow-up is 95 months. Median age of the patients in the amputation group was 39 years and in the resection group, 58 years. Table 1 demonstrates the comparison between study groups according to clinical and pathologic variables. There were no significant differences between the study groups in terms of sex, primary presentation, site, histopathology, tumor size, grade and depth, stage, primary and recurrent margin of resection, primary adjuvant therapy, and number of distant recurrences.

All patients in this study had primary tumors of high histologic grade located deep to the investing superficial muscular fascia of the extremity. All patients underwent complete tumor resection at time of primary surgery and the rate of microscopic margin involvement did not differ between the two study groups. Although rate of microscopic margin involvement was not significantly different between the two groups, patients in the amputation group had more frequent margin-positive resections (9 of 18 vs. 9 of 34) at time of initial operation. This was attributable to focally involved periosteum, perineurium, or vascular adventitia by primary sarcoma. The proportion of patients receiving primary adjuvant chemoradiotherapy was similar between the two groups.

Indications for amputation in the 18 patients with recurrent extremity sarcoma are listed in Table 2. The principal reasons for amputation include multiple local recurrences or multicompartment disease and major neurovascular or bone invasion by recurrent tumor. Figure 1 is an MR image of a large, multifocal recurrent forefoot mass that encases and destroys the metatarsals. In general, amputation was undertaken when the nature of the recurrence made it impossible to achieve complete surgical clearance of the disease with the expectation of a reasonable functional outcome. Our treatment approach for patients who have synchronous local recurrence and distant metastases is determined by the extent of distant disease. For those patients with limited resectable—typically pulmonary—metastases, amputation or LSS was performed as indicated in conjunction with metastasectomy. In rare circumstances, a palliative amputation can be justified in the setting of distant disease with the goal of relieving symptoms due to uncontrolled local disease progression.

Forty-one of the 52 patients in this study developed distant metastases. Three of 18 patients in the amputation group and 3 of 34 in the resection group developed distant metastases prior to their first local recurrence. Median time to first distant recurrence from primary treatment for these six patients was 9.3 months. Four of the six had resectable lung metastases and were rendered disease-free with metastasectomy. One patient had an isolated sternal metastasis that was completely resected. One patient with epithelioid sarcoma of the upper extremity developed subcutaneous in-transit forearm metastases and was rendered free of clinically evident disease by resection and isolated

TABLE 2. *Indications for amputation for locally recurrent extremity sarcoma*

Patient	Indication for amputation	Site	Level of amputation
1	Multifocal, bone + neurovascular invasion	Leg	Above knee
2	Disabling pain, sciatic nerve invasion	Buttock	Hemipelvis
3	Large, multifocal, invading femur	Thigh	Above knee
4	Pain, useless arm, invading humerus/scapula	Arm	Forequarter
5	Large, pain, invading scapulo-humeral joint	Axilla	Forequarter
6	Fungating, bleeding, multifocal in-transit	Forearm	Proximal humerus
7	Invading elbow joint/humerus	Arm	Proximal humerus
8	Large, invading brachial plexus	Axilla	Forequarter
9	Bone invasion	Hand	Forearm
10	Femur and femoral artery invasion	Thigh	Above knee
11	Uncontrollable, neurovascular invasion	Forearm	Proximal humerus
12	Multifocal, invading elbow joint	Elbow	Proximal humerus
13	Large, fungating, multifocal	Leg	Above knee
14	Pain, useless arm, brachial plexus invasion	Arm	Forequarter
15	Fungating, invading pelvis/femoral vessels	Thigh	Hemipelvis
16	Invading tibia/popliteal fossa	Leg	Above knee
17	Multifocal, invading bone	Forearm	Above elbow
18	Bone and neurovascular invasion	Thigh	Above knee

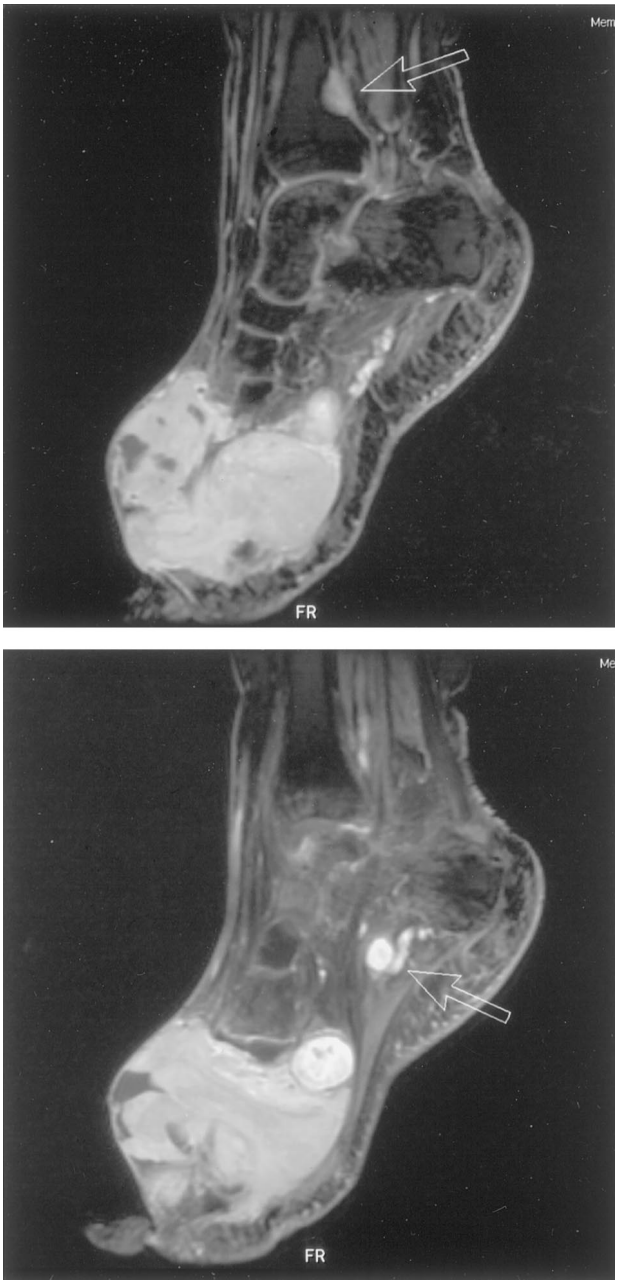

FIG. 1. Magnetic resonance image of a large, multifocal, recurrent forefoot mass that encases and destroys the metatarsals. Arrows indicate sites of multifocal disease involving bone and soft tissues.

limb perfusion. All six of these patients were free of distant disease at the time of their first local recurrence. Median time to local recurrence from treatment of first distant recurrence was 28.5 months. There were 35 patients who developed distant disease failure following treatment of local recurrence, 13 in the amputation and 22 in the limb-sparing group. In these patients, median time to first distant recurrence was 11 months.

TABLE 3. *Complete resection rates in patients with locally recurrent soft tissue sarcoma of the extremity*

Reference	Year	N	No. (%) completely resected
Giuliano[10]	1982	38	33 (87)
Potter[11]	1986	21	20 (95)
Sauter[12]	1993	30	27 (90)
Current series	2001	52	49 (94)

Local Control and Disease-Free Survival

Treatment for those patients in the amputation group included amputation alone in 12 patients and amputation plus chemotherapy in 6 patients. The distribution of treatment in the limb-sparing treatment arm is as follows: resection only (n = 15), resection plus radiotherapy (n = 15), resection plus chemotherapy (n = 2), resection plus chemoradiotherapy (n = 2). Median time to first local recurrence in the amputation and limb-sparing groups was similar, 15.2 and 17.8 months following primary therapy, respectively (P = NS). Fifty patients in this study could be completely resected. All patients treated with amputation had complete surgical resections. Three patients in the limb-sparing arm had incomplete surgical resection with focal areas of macroscopic disease remaining adjacent to critical neurovascular structures; two of these patients received adjuvant radiotherapy and did not developed a second recurrence during the period of follow-up. One patient is alive with persistent local disease. Our rate of complete resection of gross disease (94%) for patients with local recurrence compares favorably with that reported elsewhere[10–12] (Table 3). Three patients in the amputation group and 10 in the limb-sparing arm had a single focus of involved microscopic margin by tumor (P = .17). None of the three with positive microscopic margins in the amputation group developed a subsequent local failure. Four of the 10 patients with microscopic margin-positive limb-sparing resection of first local recurrence developed subsequent local disease failure. Ten patients developed second local recurrences of which four had positive and six had negative histologic margin involvement at time of resection of first recurrence. Microscopic margin status following resection of first recurrence was not a significant predictor of subsequent recurrence when the two groups were analyzed together (P = .32) or when the limb-sparing group was analyzed separately (P = .30).

One of the 18 (6%) patients treated with amputation developed a second local recurrence at the amputation stump. This patient was initially treated with resection

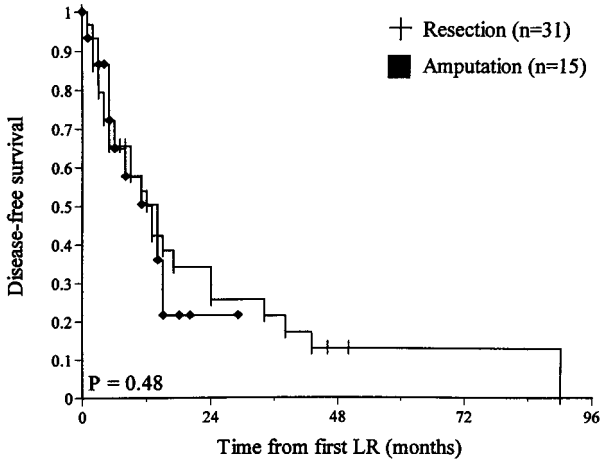

FIG. 2. Disease-free survival (DFS) for patients treated with amputation and limb-sparing resection for locally recurrent (LR) extremity sarcoma. DFS was calculated from time of treatment of first LR to time of subsequent recurrence.

for a localized primary synovial sarcoma of the foot that locally recurred 19 months later and was treated with below-knee amputation and adjuvant chemotherapy. Pulmonary metastases and a stump recurrence were completely resected 29 and 31 months following treatment of first local recurrence. He was treated with a second amputation (above-knee) for the stump recurrence. He died of disease 2 years hence. Nine of 34 (26%) patients developed a second local recurrence following limb-sparing treatment. Of these nine patients, six had resection plus radiotherapy and three had resection alone as treatment for their initial local recurrence. These findings represent a significant improvement in local control of disease with amputation for locally recurrent high-grade extremity sarcoma (94% vs. 74%; $P = .04$).

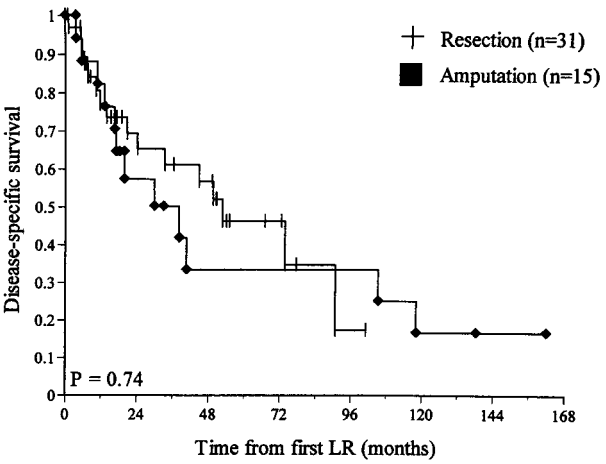

FIG. 3. Postrecurrence disease-specific survival (DSS) for locally recurrent (LR) extremity sarcoma treated with amputation or resection. Deaths resulting from disease were treated as an end point for DSS, which was calculated from time of treatment for first LR to sarcoma-related death.

We observed no difference in the overall disease-free survival between the two study groups when the analysis was confined strictly to those patients who developed a local recurrence first (n = 46; $P = .48$)(Fig. 2). Thus, three patients in each group who developed a first distant recurrence prior to failing locally were excluded. The results were no different when the three patients with incomplete resections were excluded from the analysis. Median disease-free interval following amputation or limb-sparing treatment for first local recurrence was 9.5 and 12.0 months, respectively.

Disease-Specific and Overall Survival

Disease-specific survival rates were calculated and survival curves generated as shown in Fig. 3. Median disease-specific survival for the amputation and limb-sparing groups was 19.6 and 28.3 months, respectively. Corresponding actuarial 5-year disease-specific survival rates were 30.5% and 46.5%, respectively. Median disease-specific survival for the entire cohort was 22.3 months. We observed no statistically significant difference in overall tumor-related mortality between the two study groups ($P = .74$).

Median OS for the amputation and limb-sparing groups was 19.6 and 22.3 months, respectively. The 5-year OS rate was 25.1% in the amputation group and 40.2% in the limb-sparing group. There was no significant OS difference between those undergoing amputation and limb-sparing treatment of locally recurrent extremity sarcoma ($P = .93$). Median overall postrecurrence survival is 20 months, and 5-year overall postrecurrence survival is 36% for the entire study group. The results were no different when the three patients with incomplete resections were excluded from the analysis. At last follow-up, four patients treated with amputation and eight patients following limb-preserving treatment are alive without evidence of disease. Twelve and 16 have died of disease following amputation and limb-sparing resection, respectively.

When the outcome comparison of treatment was conducted between patients undergoing amputation and the total unmatched population (n = 156) having limb-sparing treatment for locally recurrent soft tissue sarcoma of the extremity, we observed a significant difference in disease-specific ($P = .009$) and OS ($P = .003$) favoring the limb-sparing group. Suspecting that the outcome difference was related to clinicopathologic factors other than treatment, we conducted the same analysis exclud-

ing those patients with high-grade superficial and those with low-grade tumors in the limb-sparing group. When the 75 patients with locally recurrent, high-grade, deep primary tumors treated with limb-sparing salvage therapy were compared with similar patients undergoing amputation (n = 18), the difference in disease-specific ($P = .21$) and OS ($P = .21$) was no longer evident. This suggests that the outcome appraisal in our initial matched-pair analysis may be associated with the treatment modality, given that known prognostic variables were controlled for, in the stratification prior to survival comparisons being made.

DISCUSSION

The aim of this study was to elucidate the indications for and the influence of amputation as salvage therapy for locally recurrent soft tissue sarcoma of the extremity. Matched-pair analysis was conducted of a well-characterized study cohort followed prospectively at a single institution over a median surveillance period of 95 months. Stratification by clinical and pathologic prognostic variables resulted in well-matched comparison groups. Treatment of locally recurrent soft tissue sarcoma of the extremity was achieved in over 90% of patients with limb-sparing techniques. The findings of this study demonstrate that amputation, though rarely indicated for locally recurrent sarcoma of the extremity, is associated with a significant improvement in local control compared with limb-preserving treatment (94% versus 74%). The effect of treatment on postrecurrence disease-specific and OS identified in this study is consistent with the findings of others comparing amputation to LSS for primary extremity sarcomas.[2,13,14] We found that the improvement in local control with amputation did not translate into any statistically significant change in disease-free, disease-specific, or overall survival.

Our data does not support the superiority of amputation over LSS for recurrent sarcoma of the extremity. Because the number of patients in this study was limited, our ability to verify a statistically significant decrement in survival associated with amputation is low. Although not statistically significant, patients treated with limb salvage had longer median disease-specific (28.3 versus 19.6 months) survival when compared with those treated with amputation. Both treatment groups were comparable, but despite a significant improvement in local control, the amputation group had a worse survival. For soft tissue sarcoma of the extremity, distant metastases govern survival. Sixteen of 18 (89%) patients in this study treated with amputation developed distant disease failure, higher than the corresponding rate for patients treated with limb salvage (25 of 34, 73%), despite adjuvant therapy being used more than twice as often in the former group. Though systemic failure was more frequent despite chemotherapy being given twice as often in the amputation group, it is possible that treatment facilitated the distant spread of disease or that the diseases that necessitated amputation were worse biologically. The data underscore the finding that outcome in patients who require amputation for locally recurrent extremity sarcoma is dictated by the development of distant metastasis and not by local control of disease. Regardless of whether or not amputation is associated with worse survival, the prognosis for this entire cohort of large, high-grade locally recurrent extremity sarcoma was very poor, with high rates of distant relapse and death despite good local control rates.

Review of our experience, and that of others, with local salvage of extremity soft tissue sarcoma following primary site failure shows that amputation is performed in 9%–14% of such circumstances (Table 4) and that the indications for amputation are limited. Amputation is a reasonable treatment option for patients with multifocal or multicompartmental extremity recurrences and for those who have significant bone, joint, or neurovascular involvement precluding complete functional limb-preserving resection. Large, proximal lower extremity recurrences can be challenging clinical problems in terms of resection and reconstruction and may be best treated with amputation.

Distal lower limb amputations are very functional due to advances in lower limb prosthetics. Upper extremity prosthetics and amputees' function remains poor. Unreconstructable limbs may require amputation, nevertheless. Certainly, those patients with a painful, functionally impaired limb associated with local disease failure are poor candidates for limb-sparing salvage therapy. It is recommended that the duration of pain be limited to <3 months in those patients requiring amputation in an effort to limit the incidence of subsequent phantom limb pain.[15] Amputation should further be considered for patients who have either failed or are no longer candidates for further radiotherapy. The treatment-related toxicity associated with re-irradiation is an important factor in the

TABLE 4. *Treatment for locally recurrent soft tissue sarcoma of the extremity*

Reference	Year	Limb-sparing treatment (%)	Amputation (%)
Giuliano[10]	1982	22 (88)	3 (12)
Sauter[12]	1993	12 (86)	2 (14)
Current series	2001	186 (91)	18 (9)

therapeutic decision analysis for patients who fail locally after primary surgery and radiation.[16] An important consideration for distal lower extremity recurrences is that the functional outcome with below-knee amputation may be superior to a limb impaired by extensive re-resection and radiation.[17,18] One alternative to amputation for locally advanced extremity sarcoma is isolated limb perfusion using tumor necrosis factor and melphalan.[19] This treatment modality is in the investigational stage of clinical application.

The approach to patients with synchronous distant metastases is guided by the extent of systemic disease. For those with limited, resectable metastases and life expectancy exceeding 6 months, it is reasonable to pursue salvage therapy of the local recurrence in conjunction with metastasectomy. Patients who develop systemic recurrence following a short disease-free interval, and have extensive systemic disease with limited life expectancy, are better served by palliative systemic chemotherapy and nonoperative palliative (radiation) treatment of the synchronous local recurrence. Under such circumstances, amputation is rarely indicated for palliation of uncontrolled local disease failure.

A fundamental change in the treatment of primary extremity sarcomas was prompted by a prospective randomized trial conducted at the National Cancer Institute between 1976 and 1981. In this study, patients with high-grade primary extremity sarcomas were randomized to receive either amputation or limb-sparing resection and adjuvant radiotherapy.[2] None of the 16 patients randomized to the amputation arm developed local recurrence, whereas 4 of 27 (15%) undergoing limb-sparing resection developed local recurrence. This significant improvement in local control with amputation did not translate into better disease-free or overall survival (5-year OS, 88% vs. 83%).

Williard and colleagues[13,14] later documented the paradigm shift in the treatment of primary extremity sarcomas by comparing two time periods, 1968 to 1978 and 1982 to 1990. A significantly decreasing role of amputation was observed that the authors attributed to the application of more effective multimodality, limb-preserving treatment administered during the latter period of time. The decreased use of amputation was not associated with any decrement in survival.

The role of multimodality limb-sparing treatment was further defined by a prospective randomized controlled trial of surgery only versus surgery and adjuvant brachytherapy for patients with primary and recurrent extremity and superficial trunk soft tissue sarcomas treated and followed over a median of 76 months at a single institution.[4] Brachytherapy was associated with a significant improvement in local control (89% vs. 66%; $P = .025$) for patients with high-grade tumors only. However, the disease-specific survival was similar between the two treatment arms (84% vs. 81% at 5 years).

The findings of the current study that examines the role of amputation as salvage therapy for locally recurrent extremity sarcomas are similar to other studies comparing amputation to limb-sparing treatment for primary disease. That is to say, amputation for local recurrence provides enhanced local disease control (94% vs. 74%; $P = .04$); this reduction in the rate of subsequent local recurrence, however, was not associated with any significant difference in survival. The relatively short median disease-free interval (9.5–12 months) for this patient cohort reflects the aggressive biology of these large, high-grade, deeply situated, recurrent tumors and is consistent with previous reports.[20] The substantially worse prognosis for these patients with local recurrence and even amputation failed to be associated with better survival. It remains unknown what the outcome would have been if amputated patients had undergone a limb salvage procedure. Nevertheless, a complete resection can be performed in most cases (87%–95%) (Table 3). However, in this setting, the main outcome predictor is control of systemic disease. The limited number of patients in this study limits the analysis of the effect of adjuvant chemotherapy on outcome. Larger, nonrandomized studies have found that survival for patients receiving chemotherapy following resection of high-grade, large (>10 cm) extremity sarcomas, regardless of type of surgery, was significantly longer than in those who did not receive chemotherapy.[14] Our current practice is to consider preoperative chemotherapy in large recurrent high-grade extremity sarcomas and those patients with synchronous metastatic disease.

CONCLUSION

Local control of extremity sarcoma that fails at the primary site is often a challenging problem. In most cases, multimodality limb-preserving treatment approaches are successful in establishing local disease control. Amputation is infrequently required under such circumstances. Patients who require amputations have biologically aggressive tumors at a high risk of distant failure. The principal indication for amputation is local disease so extensive that complete surgical clearance is impossible to achieve with the expectation of a reasonable functional outcome. Although more radical surgical resections provide better local control of disease, there does not appear to be an associated survival benefit. The majority of patients (41 of 52, 79%) with high-grade,

deep tumors that recur locally will develop clinically apparent systemic disease, and over 60% will ultimately die of disease. Local recurrence appears to be an indicator, and distant metastases a determinant, of outcome. Despite advances in treatment for locally recurrent extremity sarcoma, systemic disease and consequent tumor-related mortality remain a formidable challenge.

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