Comparison of Amputation With Limb-sparing Operations for Adult Soft Tissue Sarcoma of the Extremity

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The use of amputation in extremity soft tissue sarcoma has been decreasing at Memorial Sloan-Kettering Cancer Center (MSKCC) over the last 15 years. In an attempt to define the efficacy and future role of amputation in extremity soft tissue sarcoma, a prospective sarcoma database compiled at MSKCC from July 1982 to January 1990, consisting of 649 patients, was analyzed in a retrospective fashion. Ninety-two patients underwent amputation, and 557 had a limb-sparing procedure. Patients selected for amputation were those who had large ($T \geq 5$ cm) high-grade tumors that invaded major vascular or nervous structures. The amputation group achieved significantly better local control than the limb-sparing group ($p = 0.007$). No survival benefit could be demonstrated, however, in the groups selected for amputation (*i.e.*, large, high-grade tumors) when compared with patients undergoing a limb-sparing procedure with similar tumors. Prevention of local recurrence by amputation also did not improve survival in this group compared with similar patients undergoing limb-sparing surgery who did develop a local recurrence. The group of patients with high-grade tumors 10 cm or larger who received chemotherapy did have a significant improvement in survival ($p = 0.01$) compared with a similar group of patients who did not receive chemotherapy, regardless of the type of operation. The prognosis of patients most likely to undergo an amputation for extremity soft tissue sarcoma (those with high-grade, large tumors) is not related to their local disease, but rather to the risk of distant metastases. Therefore, amputation in this cohort of patients can be recommended only when a limb-sparing procedure cannot achieve gross resection of tumor while still preserving a useful extremity, because amputation improves only local control and does not address distant disease. Further improvement in survival in this group of patients will be dependent on better systemic treatment for extremity soft tissue sarcoma, and not on more radical surgery.

VARIOUS AUTHORS HAVE determined the prognostic factors for survival in extremity soft tissue sarcoma. These factors include grade, size, depth, histology, distant metastases, lymph node metastases, and recurrence.[1-7] Decisions regarding surgical treatment as well as adjuvant radiation and chemotherapy have been based on these prognostic indicators.[8-14] Despite better definition of risk factors in this disease, however, tailoring of treatment to the individual patient based on these factors has been less well defined.[15,16] Surgical therapy for extremity soft tissue sarcoma at MSKCC has undergone a change in the last 15 to 20 years, with fewer amputations being performed in deference to limb-sparing procedures. From 1968 to 1978, 131 of 408 patients (32%) with extremity soft tissue sarcoma underwent amputation at Memorial Sloan-Kettering Cancer Center (MSKCC), compared with only 92 of 649 patients (14%) in 1982 to 1990 ($p = 0.05$).[10-17] This decrease in the incidence of amputations is most likely due to an improvement in local control secondary to external beam radiation therapy,[18,19] brachytherapy,[8,11-14,20-22] and doxorubicin-based (Adriamycin; Adria, Columbus, OH) chemotherapy regimens,[2,23,24] as well as a lack of evidence that amputation improved survival over limb-sparing procedures in patients considered for amputation.[1,9,17,25] As this evolution has taken place, however, the question of the efficacy and most appropriate role for amputation in extremity soft tissue sarcomas has remained unanswered.[8,26] We have attempted to answer these questions with this analysis.

Materials and Methods

A prospective sarcoma database established at MSKCC in July 1982 was analyzed in a retrospective fashion for the period of July 1982 to January 1990, with chart review, mailed questionnaire, or telephone contact used to update collected data. Type of therapy for each patient was determined by the individual surgeon based on alternatives and probability of local control and survival. Patients treated with chemotherapy received an Adriamycin-based

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regimen. Radiation therapy was delivered both by external beam and brachytherapy, as per the protocol established at MSKCC.[8,10-14,20,22] All patient tissue biopsies and tumor resections have been reviewed by a single pathologist. The database was analyzed with regard to which patients were most likely to be selected for amputation, and the results of this therapy were compared with those of limb-sparing surgery. As groups were identified as those most likely to undergo an amputation, further stratification and analysis specific for these groups was performed. Kaplan-Meier survival curves were generated, and the data were analyzed by log-rank analysis, chi square, and Fischer's exact test. Statistical significance was defined as $p < 0.05$.

Results

From July 1, 1982 to December 31, 1989, 649 patients with extremity soft tissue sarcoma underwent an operative procedure. For purpose of analysis, the patients were divided into two groups, those undergoing an amputation (n = 92) and those with a limb-sparing procedure (n = 557). Amputation was required as a salvage procedure in 18 of the 92 patients undergoing amputation during this period. Two of these eighteen patients undergoing amputation after limb-sparing surgery presented with local recurrence and metastatic disease simultaneously, whereas 14 of the 74 patients undergoing amputation for their primary tumor had metastatic disease at their presentation. Median follow-up for all patients was 22.7 months.

As shown in Table 1, age and sex were similar in the two groups. There were, however, significant differences among the groups with regard to grade, size of tumor, invasion of major nervous or vascular structure, and selection for chemotherapy. There were significantly more patients proportionally in the amputation group with high-grade tumors, tumors 5 cm or larger, or 10 cm or larger tumors invading a major nervous or vascular structure, and tumors requiring chemotherapy. Histologic differences were limited to significantly more patients with synovial sarcomas and chondrosarcomas in the amputation group and liposarcomas in the limb-sparing group. Because synovial sarcomas are usually located in joints and tend to invade bone, this may account for the increased incidence of these tumors in the amputation group. (In our series, 25 of 31 patients with synovial sarcomas that underwent amputation had their tumor located either in the foot or a joint.) Table 1 also points out the differences between the two groups with regard to site of tumors. Significantly more patients with tumors of the upper arm and thigh underwent limb-sparing procedures, whereas patients with tumors of the lower leg and foot were more likely to be treated with an amputation. Table 1 also demonstrates the number of each type of amputation performed over this period. Because patients with high-grade, large tumors were most likely to receive amputations, these groups were further analyzed to determine if these patients benefited from amputation.

TABLE 1. *Demographic Data for Patients Undergoing an Operation for Extremity Soft Tissue Sarcoma at MSKCC from 1982–1990*

	Amputation	Limb Sparing	
	(n = 92)	(n = 557)	
Age			
Range	17–88	17–92	
Mean	45	52	
Sex			
M	48 (52%)	290 (52%)	0.97
F	44 (48%)	267 (48%)	
Size (cm)			
Range	1–36	0.5–40	
Mean	10.6	8.7	
Median	9	5	
Tumor ≥ 5 cm	66 (79%)	307 (67%)	0.04
Tumor ≥ 10 cm	44 (53%)	167 (36%)	0.007
Grade			
High	79 (86%)	353 (64%)	0.00005
Low	13 (14%)	201 (36%)	
Major nerve/vessel invasion	10 (11%)	12 (2%)	0.000003
Chemotherapy	42 (46%)	141 (25%)	0.0001
Histology			
Synovial sarcoma	31 (34%)	54 (10%)	0.000003
Liposarcoma	6 (7%)	191 (34%)	0.000004
Leiomyosarcoma	6 (7%)	41 (7%)	0.2
MFH	11 (13%)	127 (23%)	0.07
Fibrosarcoma	5 (5.4%)	55 (10%)	0.06
Chondrosarcoma	6 (7%)	11 (2%)	0.02
MPNT	8 (10%)	30 (5%)	0.06
Rhabdomyosarcoma	1 (1%)	16 (3%)	0.2
Site			
Shoulder/axilla	4 (4.3%)	62 (11%)	0.07
Upper arm	3 (3%)	46 (8%)	0.04
Elbow	4 (4.3%)	10 (2%)	0.09
Forearm	5 (5.4%)	36 (6%)	0.2
Wrist	0 (0%)	1 (0.2%)	0.8
Hand	3 (3%)	9 (1%)	0.2
Finger	1 (1%)	1 (0.2%)	0.2
Buttock	1 (1%)	27 (5%)	0.06
Groin	2 (2%)	29 (5%)	0.1
Thigh	23 (25%)	245 (44%)	0.0009
Knee	6 (7%)	23 (4%)	0.1
Lower leg	14 (15%)	47 (8%)	0.06
Foot	15 (16%)	18 (3%)	0.000006
Ankle	1 (1%)	2 (0.3%)	0.3
Toe	3 (3%)	1 (0.2%)	0.009
Extent of amputation			
Hemipelvectomy	24 (26%)		
Hip disarticulation	6 (7%)		
Above knee	23 (25%)		
Below knee	13 (15%)		
Shoulder disarticulation	1 (1%)		
Forequarter	9 (10%)		
Above elbow	8 (9%)		
Digit	8 (9%)		

MFH, malignant fibrous histiocytoma; MPNT, malignant peripheral nerve tumor.

Survival curves for patients with tumors of at least 5 cm or at least 10 cm were generated (Figs. 1 and 2) to determine if patients with large tumors received a survival

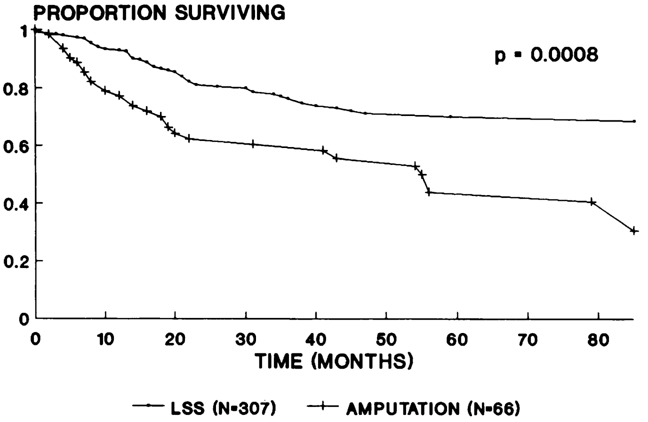

FIG. 1. Kaplan–Meier survival curves for patients who have tumors 5 cm or larger and who undergo limb-sparing surgery (LSS) *versus* amputation.

benefit from their amputation compared with patients with similar-sized tumors undergoing limb-sparing surgery. From Figures 1 and 2, it is clear that amputation for large tumors did not improve survival. In fact, survival was significantly worse in the group of patients who underwent amputation for tumors 5 cm or larger or 10 cm or larger.

To explain this survival difference, this cohort of patients (T ≥ 5 cm or T ≥ 10 cm) was analyzed for grade of tumor. As shown in Table 2, patients with large tumors requiring an amputation had proportionally more high-grade lesions compared with patients undergoing limb-sparing procedures with large tumors ($p < 0.02$). This significant difference in grade among these two groups accounts for the significantly worse survival in the patients undergoing an amputation for tumors 5 cm or larger or 10 cm or larger.

The next factor that was significantly more predominant in the amputation group was high-grade lesions.

TABLE 2. *Number of Large Tumors (≥5 cm or ≥10 cm) That are Also High Grade*

	Amputation (n = 92)	Limb Sparing (n = 557)	p
Tumor ≥ 5 cm, high grade	55/66 (83%)	208/307 (68%)	0.01
Tumor ≥ 10 cm, high grade	33/37 (89%)	61/86 (70%)	0.02

Survival curves again were generated for patients undergoing amputation *versus* limb-sparing surgery for high-grade lesions, and as can be seen in Figure 3, amputation did not improve survival. Survival was actually significantly better ($p = 0.001$) in the limb-sparing group compared with patients having an amputation.

This survival difference again can be accounted for by a difference in the two groups. There were significantly more tumors 10 cm or larger in the group with high-grade lesions requiring amputation (86%) compared with the limb-sparing group with high-grade lesions (64%), $p = 0.00005$.

To control for these differences between the two groups, the survival in patients with high-grade, large tumors undergoing amputation was compared with survival from limb-sparing surgery for similar lesions (Figs. 4 and 5). As before, there was no survival benefit for patients undergoing amputation for high-grade, large tumors.

The effect of amputation on survival in patients with low-grade, large lesions compared with limb-sparing surgery is shown in Figure 6. Again there is no survival advantage in this group of patients for amputation.

The question of local recurrence and its influence on survival is addressed in Table 3 and Figures 7, 8, 9, and 10. From Table 3 it can be seen that amputations resulted in significantly better local control ($p = 0.007$). Distant metastases, however, were more common in the ampu-

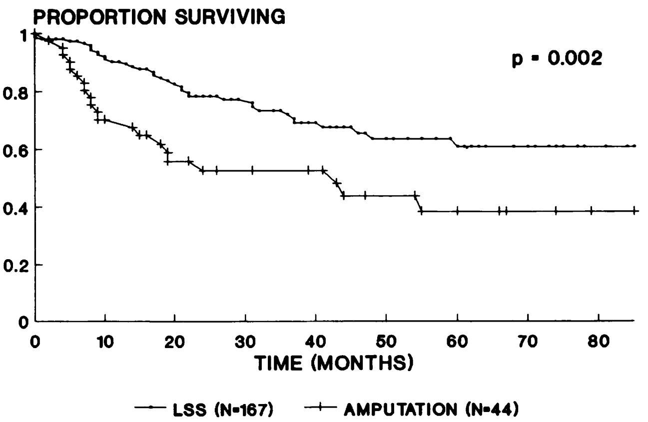

FIG. 2. Kaplan–Meier survival curves for patients who have tumors 10 cm or larger and who undergo limb-sparing surgery (LSS) *versus* amputation.

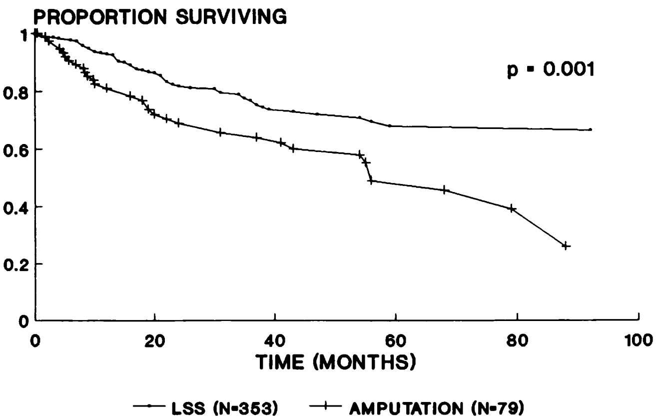

FIG. 3. Kaplan–Meier survival curves for patients who have high-grade tumors and who undergo limb-sparing surgery (LSS) *versus* amputation.

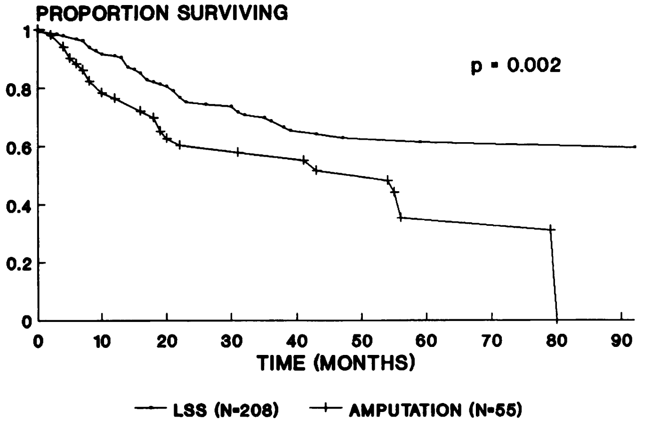

FIG. 4. Kaplan-Meier survival curves for patients who have high-grade tumors 5 cm or larger and who undergo limb-sparing surgery (LSS) *versus* amputation.

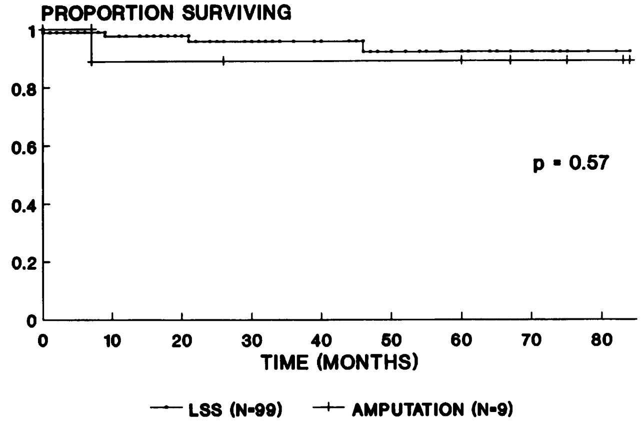

FIG. 6. Kaplan-Meier survival curves for patients with low-grade tumors 5 cm or larger and who undergo limb-sparing surgery (LSS) *versus* amputation.

tation group compared with limb-sparing surgery (p = 0.000003), because they were more likely to have high-grade, large tumors, consistent with previous reports of high-grade tumors being associated with metastatic spread.[5,7,27,28]

The effect of local recurrence on survival can be seen in Figure 7, which compares survival in patients undergoing an amputation who do not develop local recurrence with those having a limb-sparing procedure who do develop local recurrence. Again, in the group of patients who underwent a limb-sparing procedure and developed a local recurrence, their survival was still better than the group with no local recurrence after an amputation.

Figures 8, 9, and 10 stratify the groups for grade (Fig. 8), large size (Fig. 9), and grade plus large size (Fig. 10), while again comparing the survival in patients undergoing an amputation who do not develop a local recurrence with patients undergoing a limb-sparing procedure who do develop a local recurrence. Despite stratifying for grade and size, there still is no survival advantage to achieving local control with an amputation in these cohorts of patients.

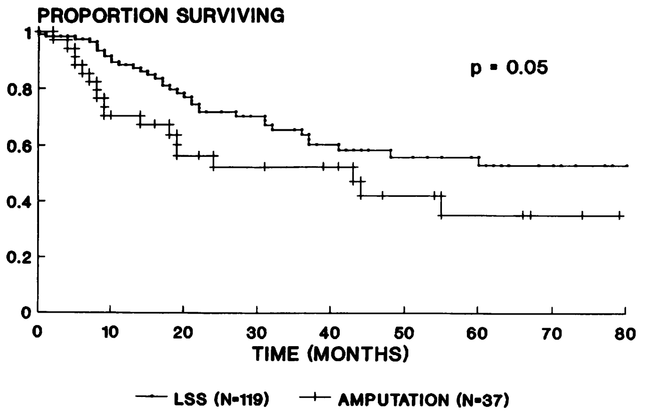

FIG. 5. Kaplan-Meier survival curves for patients who have high-grade tumors 10 cm or larger and who undergo limb-sparing surgery (LSS) *versus* amputation.

Because better local control of the tumor in the amputation group did not lead to improved survival, the question of control of systemic disease with chemotherapy in this group is addressed in Figure 11. This figure compares the effect of chemotherapy on survival in all patients (undergoing either an amputation or limb-sparing surgery) with high-grade tumors 10 cm or larger. The survival in this group of patients who received chemotherapy was significantly better than in those patients not receiving chemotherapy, regardless of the type of operation.

Discussion

From the data presented, the patients selected to undergo an amputation for extremity soft tissue sarcoma at MSKCC from 1982 to 1990 were those thought to have the worst risk factors[1-7,9-14,27,29,30] (*i.e.*, high-grade, large tumors) and thus the worst prognosis. These patients were also more likely to receive chemotherapy. Based on the survival analysis for this cohort of patients (those with high-grade, large tumors), however, it is clear that these patients were not benefited from amputation as compared with limb-sparing procedures, despite stratifying the risk factors to make the groups as similar as possible.

TABLE 3. *Number of Patients Who Have Local and Distant Recurrences After Surgery*

Recurrence	Amputation (n = 92)	Limb Sparing (n = 557)	p
Local	6 (6%)	87 (15%)	0.007
Distant	36 (43%)	80 (14%)	0.000003
Total	42 (45%)	157 (28%)	0.001

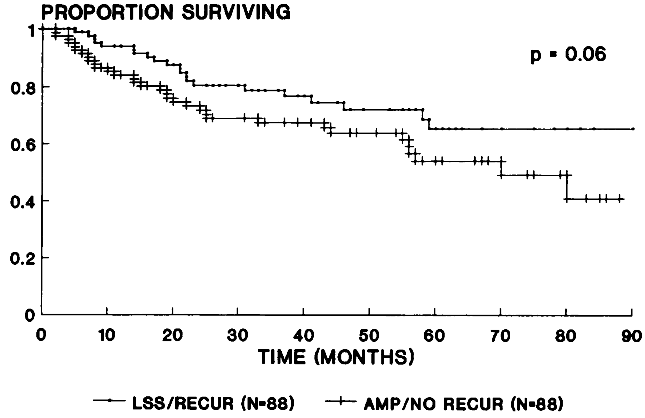

FIG. 7. Kaplan-Meier survival curves for patients who undergo a limb-sparing procedure (LSS) and who have a local recurrence (RECUR) *versus* patients who undergo amputation (AMP) and who do not have a local recurrence (NO RECUR).

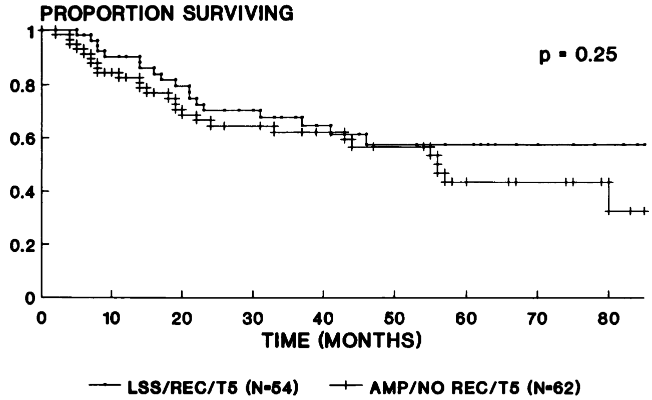

FIG. 9. Kaplan-Meier survival curves for patients who have tumors 5 cm or larger and who undergo a limb-sparing procedure (LSS) and have local recurrence (REC) *versus* patients who undergo amputation (AMP) for tumors 5 cm or larger and who do not have a local recurrence (NO REC).

Because any surgical procedure impacts only on the local disease, amputation proved significantly superior to limb-sparing surgery in local control and preventing locally recurrent disease.[25,26,31,32] Despite controlling the disease locally, however, amputation still did not improve survival over patients undergoing limb-sparing surgery in this series and others,[2,23,30] even if the patients undergoing limb-sparing surgery developed local recurrence and despite stratifying for risk factors. We and others have reported previously[9,17,27,33] that local recurrence did have a significant effect on survival in patients requiring an amputation for extremity soft tissue sarcoma. It is important to understand this apparent discrepancy of the effect local recurrence has on survival, because it points out the magnitude of the effect a lack of control of distant metastases has on this cohort of patients. In our previous report,[17] survival in patients undergoing amputation for extremity soft tissue sarcoma who developed a local recurrence was compared with patients with no recurrence (local or distant), leading to the apparent negative effect of local recurrence on survival. Figures 7 through 10, however, compare patients with limb-sparing surgery who develop a local recurrence only, with patients undergoing an amputation with no evidence of a local recurrence. These latter patients, however, may (and often did [Table 3]) still develop distant metastases. (Patients developing distant metastases in the study by Williard et al.[17] were censored for the analysis of local recurrence.) Explanation of this discrepancy highlights that survival in patients most likely to undergo an amputation (those with high-grade, large tumors) is dictated by the development of distant metastases and not by the development of a local recurrence. Thus, this apparent discrepancy points out the need for systemic control in these patients requiring amputation

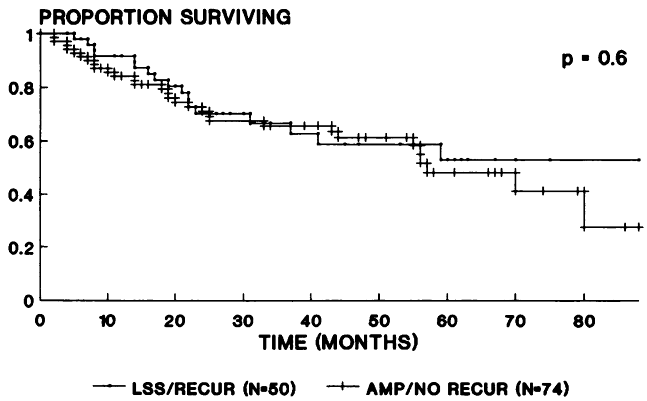

FIG. 8. Kaplan-Meier survival curves for patients who have high-grade lesions and who undergo a limb-sparing procedure (LSS) and have local recurrence (RECUR) *versus* patients who undergo amputation (AMP) for high-grade lesions and who do not have a local recurrence (NO RECUR).

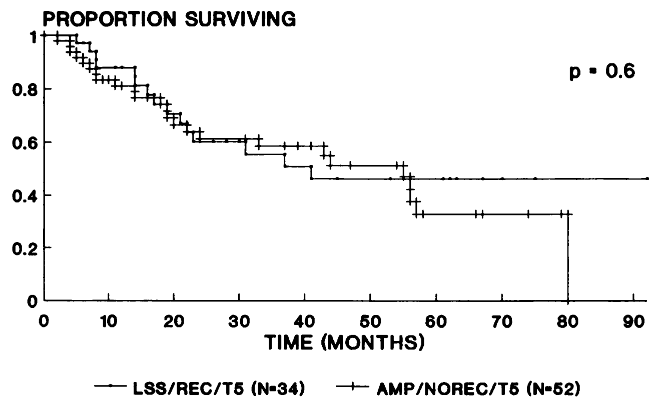

FIG. 10. Kaplan-Meier survival curves for patients with high-grade tumors 5 cm or larger who undergo limb-sparing surgery (LSS) and have local recurrence (REC) *versus* patients who undergo amputation for high-grade tumors 5 cm or larger and who do not have local recurrence (NO-REC).

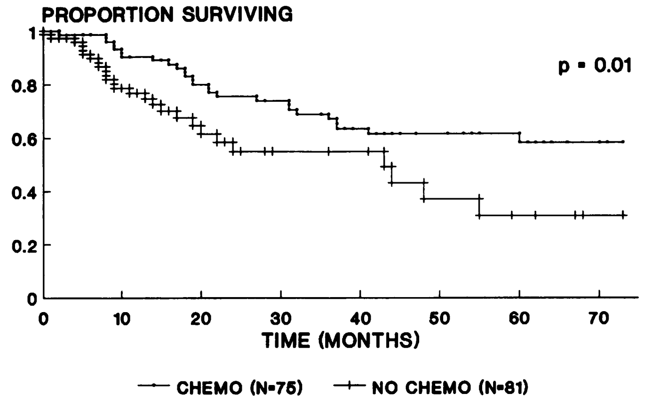

FIG. 11. Kaplan-Meier survival curves for patients who have high-grade tumors 10 cm or larger and who receive chemotherapy (CHEMO) *versus* patients who have high-grade tumors 10 cm or larger and who receive no chemotherapy (NO CHEMO) (amputation and limb-sparing groups are combined).

for extremity soft tissue sarcoma (because 43% of the amputation group developed distant metastases whereas only 6% developed a local recurrence [Table 3]), and shows local control to be of much less importance.

Another report by Emrich et al.[33] also stated that local recurrence significantly decreased survival in patients with high-grade extremity soft tissue sarcomas, with a 5-year survival rate of 44% in patients without a local recurrence *versus* 26% in patients who developed a local recurrence. Of the 184 patients who developed local recurrences in this study (a retrospective review), 141 had documented distant metastases. The authors cannot provide data regarding time of appearance of distant metastases in relation to the time of development of the local recurrence, but conclude: ". . . it is likely that a lack of local control of the tumor results in distant metastases, ultimately leading to a shorter survival time."[33] Again based on our data in Table 3, however, we would argue that most distant metastases arise from the primary tumor and are not secondary to a local recurrence that metastasizes. This conclusion is also supported by data from Huth and Eilber,[34] showing that development of a local recurrence—13 of 255 patients (5%)—was much less frequent than development of distant metastases—72 of 255 patients (28%)—among their patients with extremity soft tissue sarcoma. Heise et al.[7] reported similar results, with local recurrence in 100 of 594 patients (17%) *versus* 231 of 594 patients (39%) with distant metastases or simultaneous local recurrence and distant metastases. (We would propose that the simultaneous "detection" of local recurrence and distant metastases was from residual local microscopic disease as well as distant microscopic disease, present at the time of the initial resection and detectable only at a later date, because both cell populations increased in number at similar rates.) Thus, this would indicate that most patients with high-grade, large tumors requiring amputation already have systemic disease at the time of operation, and will not be benefited in terms of survival from a more radical procedure to control local disease.

The finding that the survival in patients receiving chemotherapy after resection of a high-grade tumor 10 cm or larger was significantly better than in those patients not receiving chemotherapy, regardless of the type of surgery, also lends support to the above premise. This observation is also supported by the only prospective, randomized trial reported in the literature,[23] with a recent update,[24] comparing limb-sparing surgery and adjuvant radiation therapy with amputation in patients with high-grade tumors, both groups being randomized to postoperative chemotherapy. The authors were able to show no survival advantage for amputation *versus* limb-sparing surgery in these patients with high-grade tumors, despite an increase in local recurrence in the limb-sparing surgery group. Also, patients receiving chemotherapy (doxorubicin, cyclophosphamide, and methotrexate) did have significantly improved survival regardless of their initial surgical procedure. Potter et al.,[2] with a similar patient population, reported similar data and conclusions. These findings support the concept of control of systemic disease as the primary predictor of outcome, with local control assuming a lesser role in these patients in terms of survival. Until better systemic therapy is developed to control distant disease, local control in extremity soft tissue sarcoma for high-grade, large lesions is not the issue.

One might reason that low-grade, large lesions, with a lower propensity for distant spread but with the difficulty in removing the entire tumor with clear margins with a limb-sparing procedure, would be better treated with an amputation. Our data suggest that these lesions are just as well treated by limb-sparing procedures, however, and that amputation does not offer a survival advantage in this group. This suggests that local recurrence, although morbid, can be dealt with by re-resection without increasing the mortality rate in patients with low-grade, large lesions. Again, multiple authors support this point, citing evidence that re-resection of local recurrences can render patients disease free and without worsening their prognosis.[2,3,34] Potter et al.[2] rendered seven of seven patients disease free after re-resection of a local recurrence, whereas Huth and Eilber[34] successfully re-resected 9 of 13 patients with local recurrence, with no subsequent evidence of systemic disease.

The role of amputation in extremity soft tissue sarcoma has been decreasing over the past 15 to 20 years. Clearly the groups this procedure is targeted at (those patients with high-grade, large lesions) have not obtained a survival benefit from this procedure. The prognosis of this cohort of patients is determined by their systemic disease (on which amputation obviously has no effect), and not their local tumor burden. The question of local recurrence leading to the development of distant disease is not definitively answered by this analysis, but the evidence supports that most patients considered for amputation (patients with large, high-grade tumors) will develop distant metastases from their primary tumor, without a local recurrence, and amputation of their extremity will not improve their survival. Because no group of patients could be demonstrated to obtain a survival advantage from amputation, we can only recommend this procedure for the patient whose tumor cannot be grossly resected with a limb-sparing procedure while still preserving a useful extremity. Further progress in the treatment of this disease awaits the development of more effective chemotherapeutic agents to address the systemic component of this disease. Until more effective systemic agents or other treatment modalities become available for these patients, the question of best local control will remain a secondary one, with equal or better survival being obtained with limb-sparing surgery when compared with amputation for patients with extremity soft tissue sarcoma.

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