

Extremity liposarcoma: prognostic indicators

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Background: Over the past 30 years, the Orthopedic Oncology Service at the Massachusetts General Hospital has treated 211 patients with liposarcomas of the extremities. **Materials & methods:** Using records maintained in a specifically designed computer system, a retrospective study was conducted that was designed to identify prognostic factors that significantly influence survival outcomes. **Results:** The overall survival rate for the group of patients was 68% with a mean follow-up of 10.5 ± 6.9 years. Patient gender had no effect on survival outcome, but age of the patient was significantly correlated with survival data, with the poorest survival for patients aged 60 years or older. The Musculoskeletal Tumor Society Stage of the lesion had a profound effect on outcome. In addition, anatomic site was correlated with survival outcomes with a 70 and 64% survival for patients with lesion about the shoulder or pelvis, compared with a 100% survival for tumors of the leg, ankle and foot, and 83% for arm, forearm and hand. Pleomorphic and dedifferentiated tumors had a poorer outcome than other forms. **Conclusion:** Liposarcoma of peripheral soft areas are sometimes difficult to treat based on the variation in outcome with site, stage and type of tumor.

Liposarcoma is a common adult soft-tissue sarcoma (STS), second only to malignant fibrous histiocytoma in frequency [1–5]. Over 9000 people in the USA are diagnosed annually with liposarcoma, which represents less than 1% of all newly diagnosed malignant tumors [2–6]. Liposarcomas arise in the supportive tissues of multiple peritoneal and retroperitoneal organs as well as nonepithelial and nonosteoid tissue, but only 45% are found in the extremities [1–3,5–8]. These tumor types occur with slightly greater frequency in men than in women [3,5,6].

The WHO currently classifies STCs based on the degree of dysplasia exhibited by the neoplasm; however, immunohistochemical data suggest that sarcomas are derived from multipotent mesenchymal cells, which differentiate into broader soft-tissue subtypes [2,5–7]. Liposarcoma has been linked to a number of genetic errors, the most common of which are *p53* mutations [1]. Togushida and colleagues screened 127 bone and STSs for *p53* and found 42 to contain the mutations [8]. *MDM2* mutations have also been implicated in the disease pathogenesis of liposarcoma due to its proposed inhibition of *p53* [9,10]. Leach and colleagues analyzed both the *p53* and *MDM2* genes in 11 malignant fibrous histiocytomas and 13 liposarcomas and found *p53* mutations in eight cases and *MDM2* mutations in a further eight [11]. These data supported the concept that an inactivation of the S-phase DNA damage

checkpoint through either mutation of *p53* or *MDM2* may be one of the implicating factors in the disease pathogenesis of liposarcoma [10,12].

Histologically, liposarcomas are classified into four basic subtypes: well-differentiated, dedifferentiated, myxoid/round cell and pleomorphic [5,6,13–16]. A somewhat confusing nomenclature is that of 'atypical lipoma', which in some centers is a term used for well-differentiated liposarcomas. Of the various subtypes, myxoid liposarcomas account for 40–50% of all liposarcomas. Pleomorphic and dedifferentiated liposarcomas have the highest rate of local recurrence and metastasis after surgical excision [6,13,14,17,18]. Common sites of metastasis include the lungs, retroperitoneum, axilla, chest wall and extremities [1,4,12,16,19]. The prognosis for patients with liposarcoma has been the subject of a number of studies [3,13,17,18,20–26]. In 1994, Gustafson and colleagues studied a group of 375 patients with liposarcomas and demonstrated that patients not referred to appropriate cancer centers for surgical treatment had a 2.4-fold higher rate of recurrence than those referred before surgery [27].

Because of the rarity of the extremity tumors, outcome data related to the anatomical site of presentation, age, stage of disease, type of tumor and postoperative recurrence rates are not clearly defined. The purpose of this study is to define and characterize the various parameters that have affected outcomes of the 211 patients with

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liposarcomas of the extremities treated by the Oncology Service of Massachusetts General Hospital (MA, USA) over the past 28 years.

Materials & methods

The Oncology Service has maintained a computerized record system, which has information regarding the demographic data, diagnosis, anatomic location, treatment protocol and outcome for over 17,800 patients treated since 1972 [28]. It was possible to identify and gather data for 211 patients treated for liposarcoma of the extremities who have been followed for at least 2 years. The principal focus of the study was to define the survival rate for patients with liposarcoma of the extremities and determine which factors influenced it significantly. Although there are several systems for staging of STS [1,10,21,17,18,21], since all of the lesions in the series arose in the extremities, we chose to use the Musculoskeletal Staging System for sarcomas [29], which is designed for the staging of tumors that principally occur in the limbs. The statistical analyses used to evaluate the data included Cox regression and chi-square assessments of deviations based on the CDC Epidemiology System, which include Fisher exact test and Mantel–Haenzel systems [2,3,20,21].

Results

Table 1 shows the patient's demographic, clinical and outcome characteristics. Of the 211 patients treated by the Oncology Service, 143 (68%) are still alive with a mean follow-up of 10.5 ± 6.9 years (range: 1–28 years). A total of 68 patients died of the disease (32%) with a mean follow-up of 2.9 ± 3.2 years (range: 0.2–15.6 years). The patient who survived 15.6 years was seen in 1981 with a low-grade (Musculoskeletal Tumor Society [MSTS] stage 1B) liposarcoma of the thigh. She had three recurrences and eventually had a hip disarticulation but, ultimately, developed metastases and died, despite receiving treatment with chemotherapy and radiation.

Of the 211 patients, 57% were male and 43% were female (Table 1). The average age of the study population was 51 ± 17 years (range: 5–94 years). Patient gender did not affect survival, but the survival rate was markedly affected by patient age. For patients aged under 40 years and between the ages of 40 and 59 years, the survival rates were 84 and 73%, respectively, whereas for patients aged 60 years or older, the survival rate was only 45% ($p < 0.003$). The Musculoskeletal Tumor Society Stage had a significant

effect on survival [29]. The survival rate for the 67 patients classified as having stage IA or IB tumors was 78%, and for the 103 patients with tumors classified as stages IIA or IIB, the survival rate was 63%. For the 18 patients classified as having stage III tumors, the survival rate was only 17% ($p < 0.00001$) (Table 1).

Survival rates for anatomic site of tumor presentation showed no significant differences in outcome in relation to site. The survival rates for the 20 patients with liposarcomas of the proximal upper extremity was 50% and for the pelvis, hip or thigh was 67%. Survival for patients whose lesions occurred in the abdomen, thorax or spine was 74%. Survival for those whose tumors were in the arm, elbow, forearm or hand was 50% and, for those with the primary tumor in the leg, ankle or foot, it was 93%. It was not possible in view of the small numbers and the difficulty in obtaining data from the charts to further define the MSTS stage and subtypes for the various anatomic sites. The difference between proximal lesions and more distal ones about the foot is striking, but the numbers are insufficient to support statistical difference. This nevertheless supports the concept that lesions that arise in the foot and ankle have better survival rates than those that arise more proximally [30].

None of the tumors were located superficially and all were reported to have clear margins by the pathologist reviewing the tissue specimens. Most of the latter was related to the proximity to vital structures. However, the majority of these were performed after either a small open biopsy as a separate procedure or a core needle biopsy. Five patients had amputations, either as a primary procedure (two patients) or in relation to surgical complications (two patients) or local recurrence (one patient). The two primary amputations were chosen for patients with large lesions in the thigh and about the knee in whom the proximity of vital structures made it unlikely that the limb would survive if even marginal surgery were performed. Of the 211 patients in the series, a total of 35 developed metastases after surgery and 26 of these died of disease (26% survival; $p < 0.0001$). Eight of the patients had a local recurrence (4%). The 203 patients who did not have a local recurrence had a survival rate of 69% while, of the eight patients who had a local recurrence, only three (38%) survived. The difference was not significant (Table 1).

It was possible to determine the type of tumor for 161 of the patients, and these are shown in Table 2. The tumors arising in the majority of the

Table 1. Survival data for patients with liposarcoma.

Factor studied	Number	Number surviving	Percentage	Statistics*
Number of patients	211	143	68	
Gender				
Males	120	79	66	
Females	91	64	70	NS
Age (years)				
<40 years of age	57	48	84	
Aged 40–59	92	70	73	
Age ≥60	62	34	45	p < 0.003
MSTS stage (23 had no stage cited)				
Stages IA, IB	67	58	78	
Stages IIA, IIB	103	65	63	
Stage III	18	3	17	p < 0.00001
Anatomic site				
Proximal upper extremity	20	10	50	
Distal upper extremity	5	3	60	
Spine, thorax and abdomen	19	14	74	
Pelvis, thigh, hip and knee	152	102	67	
Distal lower extremity	15	14	93	NS
Recurrence after surgery				
No local recurrence	203	51	69	
Local recurrence	8	3	38	NS
Metastases after surgery				
No metastases	176	134	76	
Metastases	35	9	26	p < 0.0001

*Statistical assessments are based on Cox regression and CDC Epidemiology System.

MSTS: Musculoskeletal Tumor Society; NS: Nonsignificant.

patients in our series were classified as myxoid liposarcoma, most of which were thought to be Grade 1 or 2 on a scale of 3 [1–3,6,10,18] (Figure 2). A total of 47 patients were thought to have atypical lipomas or low-grade liposarcomas (Grade 1 or 2) (Figure 1) [31,32,33]. A total of 17 patients had pleomorphic and 17 dedifferentiated liposarcomas (all Grade 2 or 3) (Figure 2). The histologic studies were performed by our musculoskeletal oncologic pathology specialists, who were considered authoritative. The data shown in Table 2 demonstrate that the pleomorphic and dedifferentiated tumors have a much poorer prognosis than the other types ($p < 0.00003$). Of the myxoid round-cell group, only the round-cell tumors differed slightly in outcome compared with the myxoid ($p < 0.03$).

It was possible to obtain information about tumor size for only 40 patients. Regrettably, the charts for this study, which goes back many years, were not always available or were incomplete. The average tumor size for the 40 patients studied was

$5069 \pm 662 \text{ mm}^3$ (range: 4110–6900 mm^3). For those 23 patients that survived, the value was $5061 \pm 721 \text{ mm}^3$ (range: 4110–6900 mm^3) and for those 17 that died it was $5080 \pm 574 \text{ mm}^3$ (range: 4340–6295 mm^3). There was no statistical difference between the two groups.

A total of 41 patients had flow-cytometric studies, which showed 14 tumors with aneuploidy and 27 that remained diploid [34]. There was no difference in the survival rates for the two groups with different DNA characteristics.

A total of 87 patients received adjunctive therapy [20,25,26,33,35]. Generally, the large lesions in areas close to the vessels and nerves receive pre-operative radiation and postoperative radiation was administered for lesions in which the surgical resection was marginal. Chemotherapy was administered for high-grade lesions or those that were MSTS stage III.

A total of 55 patients received radiation (survival rate 60%) and 28 had both radiation and chemotherapy (survival rate 63%). Only two

Table 2. Survival data by histologic tumor type.		
Tumor type*	Survival data	
	No. of patients	Percentage
Atypical and low grade	47	72
Myxoid†	52	81
Round‡	9	44
Mixed (round and myxoid)†	19	68
Pleomorphic§	17	12
Dedifferentiated§	17	52

*Histologic type was not available for 50 of the patients who were treated early in the study.
†The statistical analysis for the myxoid, round and mixed was just barely significant by chi-square at $p < 0.03$ and did not differ from the atypical and low grade.
‡The statistical difference for pleomorphic and differentiated tumors when compared with the others in the series was highly significant (chi-square at $p < 0.00003$).

had chemotherapy alone and 122 patients had neither (survival rate 76%). These data show no significant difference.

Cox regression studies showed that only site, age, MSTS stage and tumor type displayed independent significant statistical differences. Thus, patients with high MSTS stage pleomorphic or dedifferentiated liposarcomas of the thigh who are 60 years or older have a potentially very poor outcome [36].

Discussion & conclusion

The 211 patients with extremity liposarcoma had an overall survival rate of 68% with a mean follow-up of 10.5 ± 6.9 years. These data seem to be somewhat better than some of the other forms of

primary STSs, as noted in a review article published in 2005, which suggests that the survival rates for 65 patients with leiomyosarcoma were 51% and, for 22 with clear-cell sarcoma, 59% [3]. The results for 471 patients with malignant fibrous histiocytoma, 146 patients with synovial sarcoma, 100 with fibrosarcoma and 87 with malignant schwannoma were not statistically different from those for liposarcoma reported here [3].

Another important issue is the duration of the study. The first patient treated in this group had surgery in 1975 and there were a total of 62 patients treated prior to 1990 whose survival rate was 56%. A total of 157 patients have been treated since 1990 and their survival rate is 67% ($p < 0.02$). These data suggest that the treatment protocols in the earlier days were not as effective as they are currently; or possibly that some of the current group have not been followed long enough to establish the true survival rate.

In treating STSs of the extremities, the major therapeutic goals are long-term survival, avoidance of a local recurrence, maximizing function and minimizing morbidity [3,18,24–27,31,32]. Until recently, and certainly for our patients treated from 1975 to 1990, amputation for extremity sarcomas represented an important therapeutic option, especially for recurrence located in a previously irradiated field [18,26,31,32,37]. The patients in this series were treated almost entirely by wide local resection and only five had an amputation. This is certainly reflective of the current planning protocol, which suggests that surgical resection of the primary tumor remains an essential component of treatment for virtually all patients [3,17,20,24,26,27,31,32]. In some reports, the combination of surgery and radiation therapy have demonstrated better outcomes than either treatment alone for almost all STSs over 5 cm in greatest dimension [3,18,20,25,26,38]. Surgery with low-dose rate brachytherapy, delivering highly localized radiation, with a minimal dose to healthy surrounding tissues, has also been shown to be feasible, particularly for surgery for local recurrences [3,25,33,39,40,41].

Willett and colleagues studied 27 patients with STS who had had preoperative radiotherapy, limb-sparing marginal surgical resection and whole-mount tumor histological analysis [40]. They found grade and size of STSs to be important predictors of response to radiotherapy, and preoperative twice-daily radiotherapy may more likely permit the conservative surgical excision of sarcomas of borderline resectability [42]. When a conservative treatment

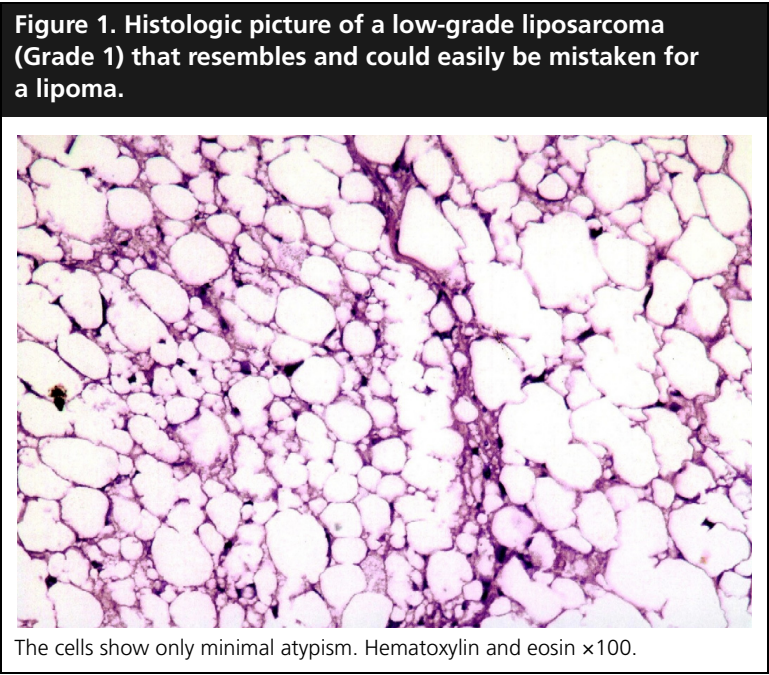
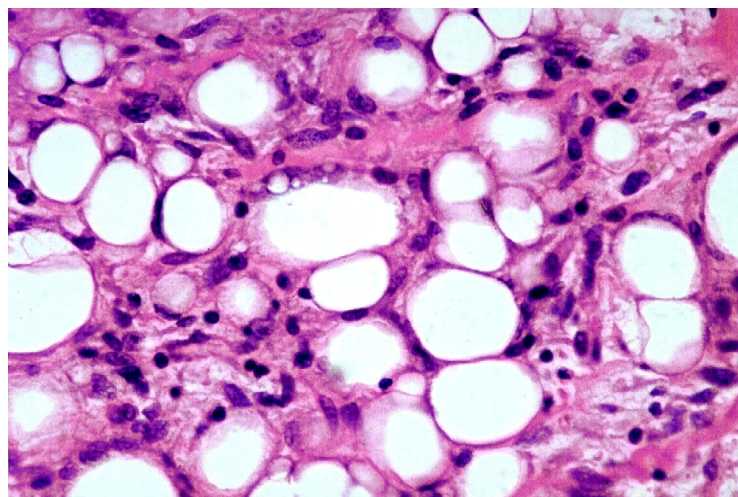


Figure 2. Histological picture of a dedifferentiated liposarcoma (Grade 3).



The cells are atypical with evidence of active DNA synthesis and marked pleomorphism. Hematoxylin and eosin $\times 100$.

is feasible, it should therefore combine surgical resection and radiotherapy with brachytherapy possibly being best suited for previously irradiated patients [25,41,42].

Using Cox regression analysis, the current study shows that MSTS stage, age and type of tumor can be used as prognostic factors for the survival of patients with liposarcoma. Based on the information obtained from our data, it is possible to predict that any patient with a primary lesion in the leg, ankle or foot, regardless

of MSTS stage, age or gender, is likely to have a good prognosis (93%), whereas a patient with a primary tumor of the pelvis, proximal femur, scapula or shoulder, is less likely to survive. Furthermore, patients with MSTS stage III at outset have a very poor outcome. The latter patient groups should undergo a more aggressive treatment regimen, possibly with radiation and chemotherapy, while patients with leg, ankle or foot, arm or wrist, or hand tumor, might undergo a more conservative treatment regimen [30]. However, all patients with extremity liposarcoma should continue to be closely monitored since the time to metastasis is on the average of 1.6 ± 2.9 years (range: 0–11 years) [6,12,16–19].

It should be apparent that we still have much to learn about liposarcomas of the extremities. The success rate for treatment is not really as good as it could be and we should try to devise some techniques to identify patients who are at high risk for metastasis and death. Evaluating the *p53* and *MDM2* mutations might be an important addition as well as assessing the tumors and the patients for genetic abnormalities [1,8–12]. These studies might be helpful in deciding who should be treated with adjuvant or neoadjuvant treatment to improve outcome.

Future perspective

It is apparent, based on our study and the currently available literature, that liposarcomas of the extremities are difficult to treat. The success rate for treatment is quite poor. In the coming

Executive summary

- Using the data from our computerized file system, it was possible to analyze data for 211 cases of liposarcoma of the extremities treated by one institution over a 30-year period.
- From the data, we were able to determine the age, gender, type of tumor, site, Musculoskeletal Tumor Society (MSTS) stage, treatment systems and outcome for the patients.
- The overall survival rate for the entire series was 68%.
- Gender did not have an effect on survival, but patients aged over 60 years of age did less well than those of a younger age (45% survival).
- Patients with MSTS stage III (metastases at the time of discovery) had a very poor outcome (17% survival).
- Pleomorphic or dedifferentiated liposarcomas (12 and 52%, respectively) had a much poorer outcome than others. Atypical, low-grade and myxoid types of tumors did much better (72 and 81%, respectively).
- Anatomic site had no effect on outcome, except for patients with distal lower extremity tumors who did considerably better (95% success).
- Adjunctive treatment with radiation and chemotherapy of 87 patients did not seem to materially affect outcome.

years, we should focus on devising techniques to identify patients who are at high risk for metastasis and death. Furthermore, on the basis of biologic studies, it may be possible in the future to treat some of the patients with agents, which will improve the outcome or better define the need for adjuvant or neoadjuvant treatment.

Disclosure

None of the authors have received any rewards or contributions for this effort. The computer system utilized for this study has received approval from the Institutional Review Board of the Hospital. The patients described in this study were reviewed anonymously and no violation of patient confidentiality has occurred.

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