Journal of BUON **15:** 518-523, 2010

ORIGINAL ARTICLE

Factors associated with outcome in liposarcomas of the extremities and trunk

E.E. Pakos[1], P.V. Gogou[1], N. Apostolikas[2], A. Batistatou[3], P.G. Tsekeris[1]

[1]Department of Radiation Therapy, University of Ioannina, School of Medicine, Ioannina; [2]Department of Pathology, St. Savvas Anticancer-Oncologic Hospital, Athens; [3]Department of Pathology, University of Ioannina, Medical School, Ioannina, Greece

Summary

Purpose: *Liposarcomas are malignant tumors that arise from primitive mesenchymal cells rather than mature adipose tissue. We aimed to evaluate the outcomes of patients with extremities and superficial trunk liposarcomas in relation to some clinicopathological factors.*

Methods: *Sixty-three surgically treated patients with liposarcoma, with mean age 53 years, were included in this study. The 5-and 10-year survival rates were analyzed with respect to local recurrences, distant metastases and death with the Kaplan-Meier method. Cox models estimated univariate and multivariate hazard ratios for each candidate predictor of interest.*

Results: *The 5-year overall survival was 77.8% (95% CI 65.5-87.3) and the 10-year overall survival was 63.5% (95% CI 50.4-75.3). The 5-and 10-year recurrence-free survival were 60% and 57%, respectively. The 5-and 10-year metastasis-free survival were 86% and 84%, respectively. In univariate analysis factors that were significantly associated with outcomes were grade III tumors, amputation procedures, use of chemotherapy and development of local recurrences. No significant association was observed in multivariate analysis.*

Conclusion: *Patients with liposarcoma surviving for 5 years, have also a high probability to be alive at 10 years. The development of metastases is observed within the first 5-years from diagnosis. Metastatic disease after that period is rare. The possibility of local recurrence is not negligible after the 5th year of follow up.*

Key words: extremities, liposarcoma, prognosis, survival, trunk

Introduction

Liposarcomas are malignant tumors arising from primitive mesenchymal cells rather than mature adipose tissue. They were initially described by R. Virchow in 1857. They account for approximately 10-18% of all soft tissue sarcomas [1,2] and represent the second most common type of soft-tissue sarcomas after malignant fibrous histiocytomas. Their estimated prevalence is 2.5 cases per million [3]. They are largely a disease of adults with their incidence peaking between 40 and 60 years, and show a slight male predominance [2]. The extremities and the retroperitoneum represent the commonest sites of localization [2,4]. Extremity liposarcomas account for approximately 50% of all liposarcomas and are mainly localized at the thigh and the popliteal fossa [4]. According to the degree of differentiation, liposarcomas may be classified as well differentiated, dedifferentiated, pleomorphic, myxoid, and round-cell according to the World Health Organization (WHO) Committee [5]. They usually present as painless well-circumscribed, slowly growing palpable masses, while symptoms such as pain, tenderness and functional disturbances are uncommon. The definite diagnosis is established with the histological examination of the tumor and supported by the radiological findings seen on MRI.

Surgical excision with wide margins, when this is applicable, is the treatment of choice. Radiotherapy is an effective adjunct to surgery, especially for tumors with positive surgical margins (postoperative radiotherapy) or in order to avoid amputation that would be required to obtain an adequate surgical margin to a limb-sparing operation (preoperative radiotherapy). The impact of chemotherapy remains under investigation [6]. In recent studies the reported 5-year survival

Correspondence to: Emilios E. Pakos, MD, PhD. Neohoropoulo, POB: 243, 455 00 Ioannina, Greece. Tel: +30 26510 25684, Fax: +30 26510 97853, E-mail: epakos@yahoo.gr

Received 16-08-2009; Accepted 27-09-2009

for extremity liposarcomas is approximately 75-80% [6-9]. Several prognostic factors have been reported to correlate with overall survival and disease-free survival of patients with liposarcoma such as size, grade, depth, localization, recurrent disease at presentation, positive margins and histological subtype [4,6,8,10].

The aim of this retrospective study was to present our experience on liposarcomas of the extremities and trunk and to analyze classical clinicopathological prognostic factors associated with the development of local recurrences, metastases and death.

Methods

Patients

Sixty-three patients with histologically diagnosed primary liposarcoma of the extremities or the superficial trunk were included in the present study after reviewing their medical records. Patients with retroperitoneal liposarcomas were excluded from the study as well as those whose clinical data could not be found or was remotely informative. All patients were diagnosed and treated in 2 medical centers. All patients underwent either wide resection of the tumor or amputation. For each patient we recorded data on demographic characteristics, tumor location, tumor size, histological subtype, tumor grade and status of surgical margins. We also recorded data on additional therapy such as chemotherapy and radiotherapy. All patients were followed up in an outpatient basis after the end of their treatment every 3 months for the first 2 years, every 6 months for the 3rd and 4th year and annually thereafter. A chest radiograph was performed once a year. Bone scans, skeletal x-rays or MRI scans of the site of initial tumor location were obtained if indicated. All eligible patients had available follow up data concerning development of local recurrences, distant metastases and death.

Definitions - Outcomes

The maximum tumor diameter at the time of pathologic evaluation was regarded as tumor size. Tumors were classified according to size in the following 3 categories: ≤50 mm, 50-100 mm, and >100 mm. Tumors beyond the shoulder joint were classified as upper-extremity tumors and those of the groin or below were classified as lower-extremity tumors. All the other localizations were regarded as superficial trunk tumors. The type of surgery was either wide resection or amputation. The histological classification was defined according to WHO criteria [5]. The status of surgical margins was determined by the histopathologic examination of the surgical specimen. The follow-up period was calculated from the date of operation. The endpoints of the analysis were the development of metastases, local recurrence or death from any cause.

Statistical analysis

Both univariate and multivariate analyses were performed. Cox models estimated univariate and multivariate hazard ratios for each candidate predictor of interest: gender, age, tumor size, tumor location (upper extremity, lower extremity, trunk), histological type, surgical margins, tumor grade, type of surgery (resection or amputation), and use of other treatment modality (chemotherapy, radiotherapy). Only variables that had prognostic significance in the univariate analysis were included in the multivariate model. Survival, recurrence-free survival and metastasis-free survival rates were calculated according to the Kaplan-Meier method. A t-test for independent samples was used to determine whether or not there was a significant difference in the mean values between patients. Analyses were conducted using SPSS (version 14.0; SPSS, Inc., Chicago, IL). All p-values were two-tailed.

Results

Characteristics of eligible patients

Sixty-three patients with a mean (±SD) age of 53.3 (±15.1) years were included. The male/female ratio was approximately 3:1 (59% male patients). Forty-five of the tumors (71%) were located at the lower extremities, 12 at the upper extremities and 6 at the trunk. The majority of the tumors (n=39) were located at the thigh, followed by the arm and the tibia. The mean (±SD) tumor size was 96 (±4.5) mm. Twenty-seven percent of the tumors had a maximum size < 50 mm, 36% 51-100 mm and 37% > 100 mm. The majority of liposarcomas were of myxoid type (51%), followed by the well differentiated type (25%), the pleomorphic type (17%), the round cell type (2%) and the dedifferentiated type (5%). Seventy-six percent of the tumors were of low grade, 7% of intermediate grade and 17% of high grade. Fifty-three patients had available data on surgical margins. Positive surgical margins had 23% of the patients.

All patients underwent surgical intervention. Sixty patients had wide tumor resection and 3 amputation procedures. Only 8 (13%) patients received postoperative chemotherapy. Doxorubicin-based chemotherapy and ifosfamide-based chemotherapy was given in 6 and

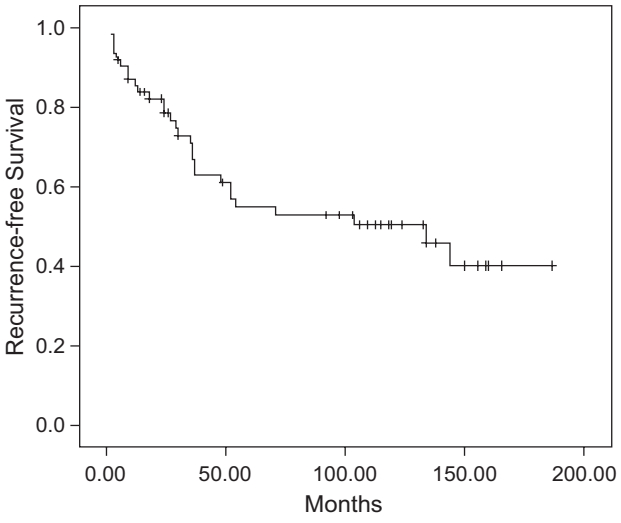

Figure 1. Recurrence-free survival in patients with liposarcoma.

2 patients, respectively. Forty-five patients received postoperative external beam radiotherapy. A linear accelerator (6MV) or a Cobalt-60 unit was used. Radiotherapy was given within a median time of 30 days postoperatively (range 12-180). The daily radiation dose ranged from 1.8 to 2.0 Gy and the median total radiation dose was 5800 cGy (range 2100-6400). The shape and number of fields were modified according to the location of the primary tumor. Shrinkage technique with or without wedge filters was applied.

Table 1. Univariate analysis for risk of local recurrence in patients with liposarcoma

	Hazard ratio (95% confidence intervals)	*p-value*
Female	0.56 (0.25-1.24)	0.15
Age (per year)	1.02 (0.99-1.04)	0.25
Size (per cm)	1.01 (0.94-1.07)	0.84
Size (reference: 0-50 mm)		
51-100	0.95 (0.37-2.41)	0.91
>100	0.97 (0.37-2.54)	0.95
Location (reference: lower extremity)		
Upper extremity	1.08 (0.43-2.70)	0.88
Trunk	1.74 (0.58-5.18)	0.32
Histological type (reference: myxoid)		
Pleomorphic	1.89 (0.76-4.72)	0.17
Round cell	2.53 (0.33-19.62)	0.37
Dedifferentiated	0.97 (0.13-7.42)	0.97
Well differentiated	0.60 (0.23-1.56)	0.29
Tumor grade (reference: I)		
II	0.00 (0.00-∞)	0.99
III	1.79 (0.53-7.42)	0.31
Surgical margins (reference: negative)		
Positive	1.32 (0.55-3.14)	0.53
Type of surgery (reference: wide resection)		
Amputation	2.60 (0.33-20.58)	0.36
Chemotherapy (reference: no)		
Yes	7.88 (3.09-20.12)	<0.001
Radiotherapy (reference: no)		
Yes	1.78 (0.72-4.38)	0.21

Risk factors associated with recurrence, metastasis and mortality

The median follow up period was 103 months (range 5-215). All patients had available data during follow up. Twenty-nine (46%) patients developed local recurrence. The 5-year recurrence-free survival was 60.3% (95% confidence interval [CI] 47.2-72.4) and the respective 10-year recurrence-free survival was 57.1% (95% CI 44.1-69.5; Figure 1). One third of these patients (n=10) developed local recurrence after the 3rd year of follow up. Two of these patients developed local recurrence after 10-year follow up (134 and 144 months postoperatively). In univariate analysis (Table 1) patients who received postoperative chemotherapy had 8-fold higher risk to develop a local recurrence compared to those who did not receive chemotherapy. No other factors were statistically significant, associated with the development of local recurrence. Similarly, in multivariate analysis no factor significantly associated with local recurrence was found.

Eleven (17.7%) patients developed metastatic disease during the follow up period. In 4 patients lung metastases were observed, 4 had bone metastasis and 3 patients developed lymph node metastases. The 5-year metastasis-free survival was 85.7% (95% CI 74.6-93.3) and the 10-year metastasis-free survival was 84.1% (95% CI 72.7-92.1; Figure 2). In univariate analysis no factor was significantly associated with the development of distant

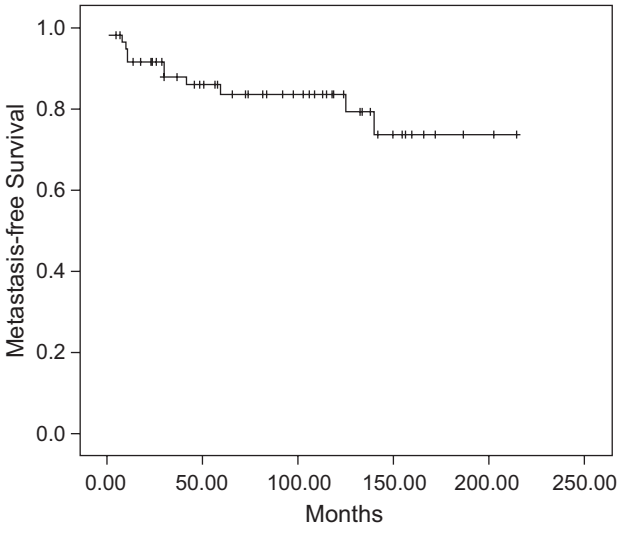

Figure 2. Metastasis-free survival in patients with liposarcoma.

Table 2. Univariate analysis for risk of metastasis in patients with liposarcoma

	Hazard ratio (95% confidence intervals)	*p-value*
Female	1.21 (0.37-3.98)	0.75
Age (per year)	0.99 (0.6-1.04)	0.79
Size (per cm)	0.98 (0.88-1.10)	0.75
Size (reference: 0-50 mm)		
51-100	1.15 (0.27-4.88)	0.85
>100	0.50 (0.00-3.05)	0.46
Location (reference: lower extremity)		
Upper extremity	1.03 (0.21-4.96)	0.97
Trunk	2.17 (0.45-10.53)	0.34
Histological type (reference: myxoid)		
Pleomorphic	1.08 (0.22-5.33)	0.93
Round cell	4.19 (0.49-36.00)	0.19
Dedifferentiated	2.69 (0.31-23.31)	0.37
Well differentiated	0.26 (0.04-2.43)	0.26
Tumor grade (reference: I)		
II	3.61 (0.41-31.70)	0.25
III	2.88 (0.55-15.11)	0.21
Surgical margins (reference: negative)		
Positive	2.69 (0.82-8.83)	0.10
Type of surgery (reference: wide resection)		
Amputation	0.05 (0.00-1140414)	0.73
Chemotherapy (reference: no)		
Yes	1.94 (0.42-9.04)	0.40
Radiotherapy (reference: no)		
Yes	3.76 (0.48-29.65)	0.21

metastases (Table 2). No multivariate analysis was performed due to the absence of statistically significant association in the univariate analysis.

Thirty (48%) patients died during the follow up period. The median time to death was 61.5 months (range 5-215). The 5-year survival was 77.8% (95% CI 65.5-87.3) and the 10-year survival 63.5% (95% CI 50.4-75.3). In univariate analysis (Table 3) patients with grade III tumors had a 4-fold increased risk of death compared to grade I tumors. Patients with amputation had approximately 6-fold increased risk of death compared to those with wide tumor resection. Patients with amputation had a mean (±SD) maximal tumor size of 16.5 (±11.7) cm, while those with wide resection 9.2 (±6) cm (p=0.05). Patients that received postoperative chemotherapy had 3.45-fold increased risk of death compared to those without chemotherapy. Finally, patients that developed local recurrence during the follow up period had 3.5-fold increased risk of death compared to those that did not develop any local recurrence (Figure 3). In multivariate analysis no factor significantly associated with mortality was observed.

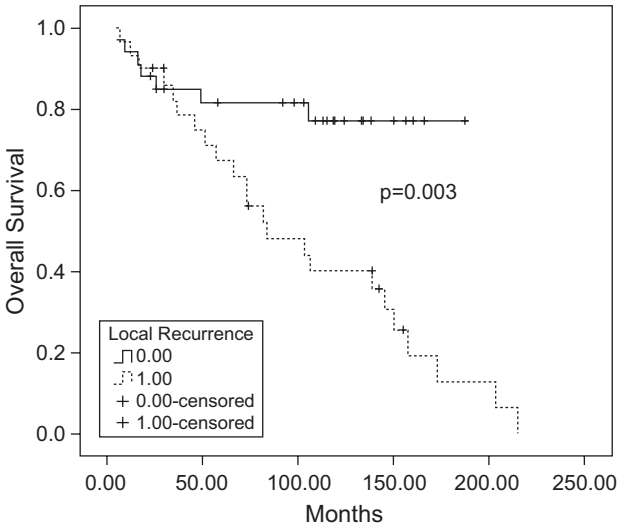

Figure 3. Overall survival of patients with liposarcoma: Comparison of survival between patients that developed local recurrences and those without.

Table 3. Univariate analysis for risk of death in patients with liposarcoma

	Hazard ratio (95% confidence intervals)	*p-value*
Female	0.85 (0.40-1.82)	0.69
Age (per year)	1.01 (0.98-1.03)	0.54
Size (per cm)	1.03 (0.97-1.10)	0.33
Size (reference: 0-50 mm)		
51-100	0.72 (0.27-1.93)	0.51
>100	1.19 (0.47-3.03)	0.72
Location (reference: lower extremity)		
Upper extremity	0.86 (0.32-2.31)	0.77
Trunk	1.77 (0.60-5.26)	0.30
Histological type (reference: myxoid)		
Pleomorphic	1.35 (0.54-3.54)	0.52
Round cell	1.25 (0.16-9.65)	0.83
Dedifferentiated	2.61 (0.58-11.79)	0.21
Well differentiated	0.43 (0.14-1.29)	0.13
Tumor grade (reference: I)		
II	1.67 (0.21-13.26)	0.63
III	4.07 (1.21-13.64)	0.02
Surgical margins (reference: negative)		
Positive	1.24 (0.53-2.91)	0.62
Type of surgery (reference: wide resection)		
Amputation	5.89 (1.73-20.11)	0.005
Chemotherapy (reference: no)		
Yes	3.47 (1.45-8.30)	0.005
Radiotherapy (reference: no)		
Yes	0.85 (0.37-1.99)	0.72
Development of local recurrence (reference: no)		
Yes	3.61 (1.53-8.54)	0.003

Discussion

This study represents the experience of 2 medical centers regarding liposarcomas of the extremities and trunk. Overall survival of the whole patient group was 52%, while the recurrence free survival and the metastasis free survival were 54% and 83% respectively during a median follow-up period of 103 months. Patients with liposarcoma that will survive for 5 years, have also a high probability to be alive at 10 years. The development of metastases is observed within the first 5 years from diagnosis, and metastases after that period are a rare phenomenon. The possibility of local recurrence is not negligible after the 5th year of follow up. In our series half of the patients developed recurrences after 3 years, although the majority of them were developed within the first 5 years. It has been reported that high risk period for the development of local recurrence in limb liposarcomas are the first 3 years after definite surgery [11]. In univariate analysis only the use of chemotherapy was significantly associated (8-fold) with increased risk for local recurrence. The development of distant metastases was not statistically associated with any factor. Grade III tumors, amputation, use of chemotherapy and development of local recurrence were significantly associated with decreased survival. Multivariate models did not show any statistically significant association of any of the examined factors with either local recurrences, distant metastases or death in patients with liposarcomas.

Our study demonstrated a statistically significant association of grade III tumors with decreased overall survival compared to grade I tumors. This association has also been reported in previous studies. Weitz et al. [12] in a large study of mixed populations of 1,261 soft tissue sarcomas (STS) of the extremities including 340 liposarcomas reported a doubled risk of death in patients with high grade tumors. However, the population was mixed and the authors did not display separate results for liposarcomas. Chang et al. [13] found a significant increment in local failure in patients with high grade liposarcomas. High tumor grade showed statistically significant correlation with the development of local recurrences and distant metastases in a recent study based on the Scandinavian Sarcoma Group Register [8]. The authors did not report whether this correlation was also observed in respect with overall survival as well. Bispo Junior et al. [14] reported that high tumor grade was significantly associated with increased risk for recurrence, metastasis and death in their series of 50 extremities liposarcomas. Finally, Singer et al. [15] also found that tumor grade was a significant predictor of survival (52% in grade III vs. 98% in grade I), but their study had also a mixed population of STS, with 36 liposarcomas included.

The statistically significantly decreased survival observed in patients who underwent amputation compared to those who underwent wide resection procedures has not been reported till know in the literature. Amputation procedures have been selected for larger tumors and probably for patients with advanced-stage disease, so the observed association might reflect the above parameters. Moreover, the possibility that the results could be due to chance cannot be excluded, since only 3 patients underwent amputation. Similarly, the association of chemotherapy usage with increased mortality has not been reported yet and might reflect the advanced disease of the patients that were administered chemotherapy. Those that received chemotherapy were regarded as high-risk patients with grade III tumors and size over 5 cm. The impact of chemotherapy on survival of patients with primary liposarcomas of the extremities remains controversial. Eilber et al. [6] compared doxorubicin-based with ifosfamide-based chemotherapy in 245 high risk patients with primary extremities liposarcomas and found that ifosfamide-based chemotherapy was associated with improved disease survival, while doxorubicin-based chemotherapy had no impact on survival. In our series the majority of patients received doxorubicin-based chemotherapy.

Prognostic factors that have been reported to correlate with outcomes of liposarcomas of the extremities and were not confirmed by the present study were age [4,6-9], tumor size [6,8,12], histological subtype [6-9,14] and surgical margins [6,8,9,12]. The lack of any association of the above parameters with liposarcoma outcomes in our study is probably due to the limited number of eligible patients, the considerable extent of missing data in some parameters such as tumor grade, and the inhomogeneous follow up of patients.

Taking into account the different biological behavior, not only of each type of soft tissue sarcoma, but in particular between extremities and retroperitoneal liposarcomas [16], future investigations should target the establishment of large homogeneous studies to recognize prognostic factors associated with extremities and superficial trunk liposarcomas.

References

1. Peterson JJ, Kransdorf MJ, Bancroft LW, O'Connor MI. Malignant fatty tumors: classification, clinical course, imaging appearance and treatment. Skeletal Radiol 2003; 32: 493-503.
2. Enzinger FM, Weiss SW (Eds). Liposarcoma. In: Soft Tissue Tumors, (3rd Edn). St. Louis, 1995, Mosby, pp 431-466.

3. Kindblom LG, Angervall L, Svendsen P. Liposarcoma: a clinicopathologic, radiographic and prognostic study. Acta Pathol Microbiol Scand 1975; 253 (Suppl): 1-271.
4. Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 1996; 14: 1679-1689.
5. Fletcher CDM, Unni KK, Mertens F. Pathology and Genetics of Tumours of Soft Tissue and Bone. WHO Classification of Tumours, vol. 5, Lyon, France: IARC Press; 2002: 35-46.
6. Eilber FC, Eilber FR, Eckardt J et al. The impact of chemotherapy on the survival of patients with high-grade primary extremity liposarcoma. Ann Surg 2004; 240: 686-697.
7. Pearlstone DB, Pisters PW, Bold RJ et al. Patterns of recurrence in extremity liposarcoma: implications for staging and follow-up. Cancer 1999; 85: 85-92.
8. Engström K, Bergh P, Gustafson P et al. Liposarcoma: outcome based on the Scandinavian Sarcoma Group register. Cancer 2008; 113: 1649-1656.
9. Dalal KM, Kattan MW, Antonescu CR, Brennan MF, Singer S. Subtype specific prognostic nomogram for patients with primary liposarcoma of the retroperitoneum, extremity, or trunk. Ann Surg 2006; 244: 381-391.
10. Zagars GK, Goswitz MS, Pollack A. Liposarcoma: outcome and prognostic factors following conservation surgery and radiation therapy. Int J Radiat Oncol Biol Phys 1996; 36: 311-319.
11. Issakov J, Soyfer V, Kollender Y, Bickels J, Meller I, Merimsky O. Liposarcoma in adult limbs treated by limb-sparing surgery and adjuvant radiotherapy. J Bone Joint Surg Br 2006; 88: 1647-1651.
12. Weitz J, Antonescu CR, Brennan MF. Localized extremity soft tissue sarcoma: improved knowledge with unchanged survival over time. J Clin Oncol 2003; 21: 2719-2725.
13. Chang HR, Hajdu SI, Collin C, Brennan MF. The prognostic value of histologic subtypes in primary extremity liposarcoma. Cancer 1989; 64: 1514-1520.
14. Bispo Junior RZ, de Camargo OP, de Oliveira CR, Filippi RZ, Baptista AM, Caiero MT. Prognostic factors and expression of MDM2 in patients with primary extremity liposarcoma. Clinics 2008; 63: 157-164.
15. Singer S, Corson JM, Gonin R, Labow B, Eberlein TJ. Prognostic factors predictive of survival and local recurrence for extremity soft tissue sarcoma. Ann Surg 1994; 219: 165-173.
16. Linehan DC, Lewis JJ, Leung D, Brennan MF. Influence of biologic factors and anatomic site in completely resected liposarcoma. J Clin Oncol 2000; 18: 1637-1643.