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Clinico-Pathological Data and Prognostic Factors in Completely Resected AJCC Stage I-III Liposarcomas

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Background: In general, although biological behavior and prognosis of liposarcomas (LPS) are more favorable compared with most other soft tissue sarcomas (STS), prognosis can vary widely depending on tumor characteristics, especially histological subtype and tumor grade.

Patients and Methods: All consecutive, completely resected stage I-III LPS (as determined by the American Joint Committee on Cancer staging guidelines), treated at the Groningen University Hospital from 1977–2000, were analyzed.

Results: A total of 69 patients, 35 males and 34 females, median age 51 (range 11–80) years, were reviewed. After a median follow-up of 71 (range 5–231) months, the overall local recurrence and metastasis rate at five years after diagnosis were 27% and 16%, respectively. Retroperitoneal localization was a significant negative prognostic factor regarding local recurrence; dedifferentiation, grade II-III, and deep location regarding distant metastasis; and dedifferentiation, grade II-III, stage II-III, size >20 cm and non-radical resection regarding survival.

Conclusions: LPS have a relatively mild biologic behavior, with the exception of very large, deeply located, dedifferentiated and/or grade II-III LPS. Radical resection is important for disease-specific survival. LPS have a relatively mild biologic behavior, with the exception of very large, deeply located, dedifferentiated and/or grade II-III LPS.

Key Words: Soft tissue sarcoma—Liposarcoma—Epidemiology—Treatment—Survival.

The majority of soft tissue mass is composed of muscle and fatty tissue. Because adipose tissue makes up about 20% of the body weight, it seems obvious that one of the most common soft tissue sarcomas (STS) are liposarcomas (LPS).[1–4] However, LPS originate from primitive mesenchymal cells rather than mature fat cells. In fact, these tumors are rare in the subcutaneous fat, a common location of lipomas, and they are most frequently located in deeper structures.[3] Although LPS are one of the most common STS, accounting for 10–20% of all STS,[1–4] there are only limited recent data that specifically address epidemiological and treatment related aspects of this entity. Usually, these data are embedded in reports on sarcoma in general, which does not seem advisable because the biological behavior and prognosis of LPS seems to be different from most other STS.[3,5] Furthermore, there are strong indications that biological subtype determines the outcome in LPS.[6,7] This diversity in clinical behavior may not become apparent if LPS are reviewed together with other STS. The purpose of the present study was to gain an insight into the epidemiological aspects of LPS, to evaluate treatment results, and to determine prognostic factors for local recurrence, metastasis, disease-free, and disease-specific survival.

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PATIENTS AND METHODS

All consecutive liposarcomas that were diagnosed at the Groningen University Hospital, from October 1977 to January 2000, were reviewed regarding the clinicopathological data, treatment, and follow-up. Patients were followed clinically at the Groningen University

Hospital for a maximum period of 10 years. Data were retrospectively collected by chart review. For patients who were no longer being followed, data had to be collected by correspondence with the referring physician. Histopathologically, all tumors were reviewed, and if necessary revised, by one pathologist with a special interest and experience in STS (WMM). Patients with perioperative signs of regional and/or distant metastatic disease (American Joint Committee on Cancer [AJCC] stage IV) and those in whom the LPS could not be resected completely (R2-resection), were excluded from the study.

The extent of diagnostic preoperative work-up has changed during the last decades. Currently, preoperative work-up of a soft tissue tumor includes magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA) and/or computed tomography (CT) and/or ultrasonography (US) of the tumor site, followed by fine-needle aspiration (FNA), core biopsy, and/or incisional biopsy.[8] In superficially located soft tissue tumors smaller than 3 cm, and without clinical suspicion of malignancy, an excisional biopsy is performed.[9] In case of a histological diagnosis of liposarcoma, a chest CT-scan and a bone scan are performed to rule out metastatic disease.[8] We used the classification described by Enzinger,[3] and recognized four different subtypes: well-differentiated LPS (WDLPS), myxoid LPS (MXLPS), pleiomorphic LPS (PMLPS), and dedifferentiated LPS (DDLPS). Tumors were graded according to Coindre et al.,[10] and grade was assigned based on the highest grade presented. Patients were clinically staged according to the latest AJCC staging guidelines for sarcoma.[11]

After preoperative work-up, the tumor was resected with the intention to perform a wide local resection. Resection margins were classified as microscopically involved if, on histological examination, tumor cells were detected at the marked surface of the resection specimen. In recent years, in cases of microscopic involvement of the margins (R1-resection), especially in high-grade tumors, high-dose adjuvant radiotherapy (50–70 Gy) has been recommended.[8] Chemotherapy was only delivered to eligible patients who participated in different chemotherapy protocols during this time period.

In primary LPS, the follow-up period was calculated from the time of histological diagnosis. In LPS, presenting with a recurrence, the follow-up period was measured from the time of histological diagnosis of the recurrence. The local and distant recurrence rates were calculated using the Kaplan-Meier method.

Epidemiologic data were analyzed using the Mann-Whitney *U*-test and χ^2 test. Clinicopathological and treatment related factors were analyzed using a log-rank test for local recurrence, disease-free, and overall survival. A P value of <0.05 was considered statistically significant. The relative risk ratio and 95% confidence interval (95% CI) are reported.

RESULTS

Epidemiological Characteristics

The study group was composed of 35 men (51%) and 34 women (49%). Fifty-two LPS were primary tumors (75%). Seventeen patients (25%) presented with a local recurrence after earlier attempts at definitive treatment at outside institutions. In nine patients (53%), it was the first or second recurrence, in four patients (24%), it was the third recurrence, in two patients (11%), it was the fourth recurrence, in one patient (6%), the sixth recurrence, and one patient (6%) had a seventh recurrence. Overall, the median age at presentation was 51 (range 11–80) years. The median age at presentation was not significantly different in primary or recurrent LPS, 49 years (range 11–80) and 56 years (range 35–80), respectively.

Clinical Characteristics

By far, most patients (n = 57) presented with a palpable mass (83%), which in most of them (n = 46) was painless. At presentation, the median duration of symptoms was 6 months for primary LPS, and 3 months for recurrent LPS. There was no gender-related difference.

The distribution of LPS according to anatomical site is shown in Fig. 1. The majority of LPS was located in the extremities (n = 43; 62%), especially the thigh (n = 29; 42%). Although 57 tumors (83%) were palpable on clinical examination, there were site-specific differences. In the head/neck region, trunk, and extremities, most LPS were palpable (80%, 100%, 95%, respectively), whereas

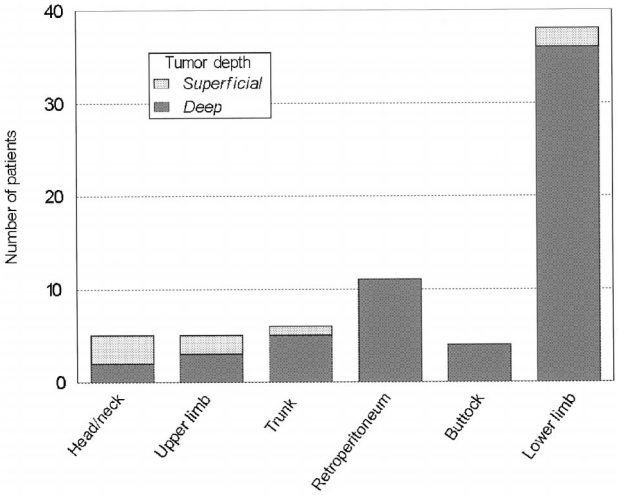

FIG. 1. Distribution of LPS according to anatomical site (n = 66).

in the retroperitoneum and buttock, respectively 64% and 50% of the tumors were undetectable on clinical examination. Overall, 61 LPS were situated beneath the fascia (88%). The relation between tumor site and tumor depth was highly statistically significant ($P = 0.002$), with the highest proportion of superficially located tumors in the head/neck region and in the upper extremity, 60% and 40%, respectively. In the retroperitoneum, buttock, and leg (nearly) all LPS were deeply seated (Fig. 1).

Preoperative Work-Up

Ultrasonography (US) of the tumor region was performed in 23 patients (33%). During the operation, information from the US appeared to be correct in only 6 of these patients (26%). CT-scan and MRI of the tumor region were performed in 40 patients (58%) and 29 patients (42%), respectively. Distant metastatic disease was excluded by plain chest film (n = 57; 83%), pulmonary CT-scan or MRI (n = 48; 70%), and bone scan (n = 37; 54%).

In 6 patients, the tumor was resected after only FNA (9%) and in 1 patient, the tumor was resected after core biopsy (1%), whereas in the remaining 62 patients, the histological diagnosis was made by biopsy (incisional: n = 31 [45%] and excisional: n = 16 [23%]) or tumor resection (n = 15, 22%). Eleven of the 15 tumors that were resected without prior histological diagnosis were recurrent LPS (73%). One patient had a primary LPS of the spermatic cord and was treated by orchidectomy. One patient had a primary LPS in the lower extremity, which was treated with surgical resection, followed by external beam radiation therapy. Two patients had a retroperitoneal LPS, which was surgically resected, en block with the left kidney and the left side of the colon in one, and en block with the left kidney in the other.

Treatment

Thirty-two patients were treated by surgical resection only (47%), 25 patients received additional radiotherapy (36%), 3 patients had additional chemotherapy (4%), and the remaining 9 patients (13%) were treated by a combined modality treatment of surgery, radiotherapy, and chemotherapy.

A marginal resection was performed in 54 patients (78%), a radical resection in 13 patients (19%), and in the remaining 2 patients (3%), the tumor was resected intracapsularly. Intraoperative tumor spill occurred in 3 patients (4%), 2 of whom had a retroperitoneal LPS, and one a LPS of the thigh.

Radiotherapy was applied in 34 patients (49%), most often postoperatively (n = 30; 88%). Two patients with a LPS of the thigh received both pre- and postoperative external beam radiotherapy (EBRT) and one patient with a primary gluteal LPS received neoadjuvant EBRT, followed by intraoperative radiotherapy (IORT).[12] One patient with a second recurrence of a MXLPS of the popliteal fossa, previously treated with surgery and 64 Gy EBRT, was treated with surgical resection and 25 Gy IORT.[13] Overall, the median total radiation dose was 60 Gy, ranging from 25 (IORT)-70 Gy.

Only a small number of patients (n = 12; 17%) who participated in different protocols received chemotherapy. Radiotherapy and/or chemotherapy related complications were encountered in 17 of 37 patients (46%). By far, most were minor complications (erythema, dermatitis, epidermolysis, mucositis, and wound complications). However, four patients developed a neuropathy (11%) that was transient in two, but persisted in the other two patients.

Limb salvage was achieved in 45 of 47 limbs (96%) involved (gluteal LPS included). In one patient who presented with a recurrent LPS of the thigh, an exarticulation of the hip had to be performed. One patient with a primary gluteal LPS had to be treated by hemipelvectomy and intraoperative radiotherapy.[12] During follow-up, one additional patient who developed a local recurrence could only be salvaged by a high exarticulation of the lower limb, decreasing the cumulative limb salvage rate to 94%.

Histopathology

The revised histopathological diagnoses are presented in Fig. 2, which shows that nearly half of the tumors were MXLPS and that more than one third were WDLPS. For the various anatomical sites, tumor size, as measured by the pathologist, is presented in Fig. 3. The largest tumors were encountered in the retroperitoneum (median diameter 25 [range 12–46] cm) and lower limb (median diameter 12 [range 2–40] cm). Twenty-four of 26 WDLPS (92%) were classified as grade I LPS, the other 2 as grade II (8%), 29 MXLPS were classified as grade I (85%), and 5 MXLPS as grade II (15%). Three DDLPS

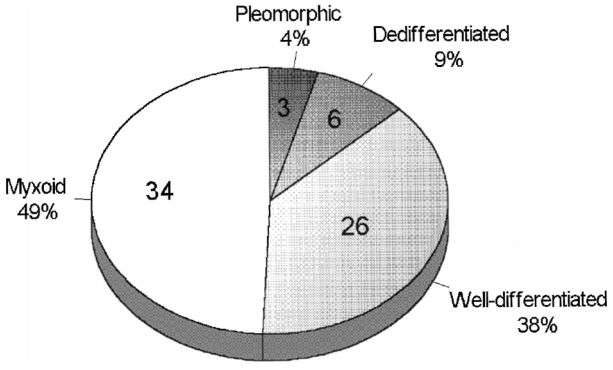

FIG. 2. Histological distribution of LPS (n = 66).

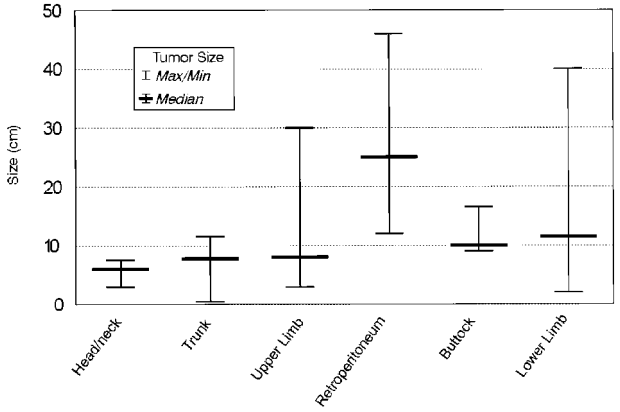

FIG. 3. Tumor size according to anatomical site.

(50%) were grade III LPS, whereas the other three were classified as grade II. Two of three PMLPS were classified as grade II, the third as grade III. The relation between histological subtype and tumor grade seemed to be highly significant ($P < 0.0001$). Overall, there was no statistically significant relation between anatomical site and tumor grade ($P = 0.19$), although retroperitoneal LPS had a significantly higher tumor grade compared to LPS at other sites ($P = 0.02$). According to the new AJCC staging guidelines,[10] 10 LPS were classified as stage Ia (14%), 3 LPS as stage Ib (4%), 52 LPS as stage IIa (76%), and 4 LPS as stage III (6%). LPS of the retroperitoneum, buttock, and thigh had significantly more stage II and III ($P = 0.01$). Microscopically, free margins (R0-resection) were achieved in 53 patients (77%); in the other 16 patients (23%) margins were microscopically involved (R1-resection). No patient had a macroscopic tumor left behind (R2-resection).

Recurrence and Survival

The duration of follow-up for this cohort of patients ranged from 5 to 251 months with median and mean follow-up of 79 and 87 months, respectively.

Local Recurrence

During follow-up, 18 of 69 patients (26%) developed a local recurrence after 2–101 months. A total of 28% of local recurrences was evident by 1 year, 44% by 2 years, 72% by 3 years, 78% by 4 years, and 89% by 5 years. There were two very late local recurrences after 81 and 101 months. Multiple recurrences were common and occurred in 67% of patients who developed a local recurrence after initial presentation with a primary LPS and in 83% of patients who presented with a recurrent LPS.

On univariate analysis, retroperitoneal localization was associated with a significantly shorter local recurrence-free interval (Table 1, Fig. 4). Retroperitoneal LPS recurred after a median recurrence-free interval of 48 months. At the end of the study period, five of the patients who had had a retroperitoneal LPS had no signs of recurrent disease. Four patients died from unresectable local recurrences in absence of distant metastases, and one patient died from an unresectable local recurrence and metastases to the lung, vertebrae, and soft tissues. One patient is still alive but has an unresectable local recurrence without distant metastases and is likely to suffocate in the near future.

Distant Metastases

Within a range of 4–103 months, 11 patients (16%) developed distant metastases. Of these, 27% were evident by 1 year, 55% by 2 years, 82% by 3 years, and 91%

TABLE 1. *Local recurrence-free interval according to potential prognostic factors*

Clinicopathological factor		RR	95% CI
Gender	Male vs. female	0.69	0.27–1.74
Histological subtype	WDLPS vs. all other subtypes	2.39	0.79–7.3
	All other subtypes vs. DDLPS	1.04	0.14–7.8
Primary vs. recurrent presentation		1.36	0.51–3.63
Anatomical site	All other sites vs. retroperitoneum	3.22*	1.21–8.6
Depth	Superficial vs. deep	2.69	0.36–20.2
Type of resection	R1 vs. marginal	1.01	0.32–3.18
	R1 vs. radical	1.25	0.28–5.56
Tumor diameter	≤10 cm vs. 10–20 cm	1.64	0.53–5.07
	≤10 cm vs. >20 cm	2.92	0.94–9.0
Grade	I vs. II	1.11	0.32–3.85
	I vs. III	2.05	0.27–15.6
Stage	I vs. II	5.32	0.71–40.7
	I vs. III	8.55	0.53–137
Treatment	Surgery vs. surgery + radiotherapy	0.54	0.19–1.54
	Surgery vs. surgery + chemotherapy	0.85	0.11–6.55
	Surgery vs. surgery + radiotherapy + chemotherapy	0[a]	

* Significance, $P < .05$.
[a] Numbers too small to draw conclusions.

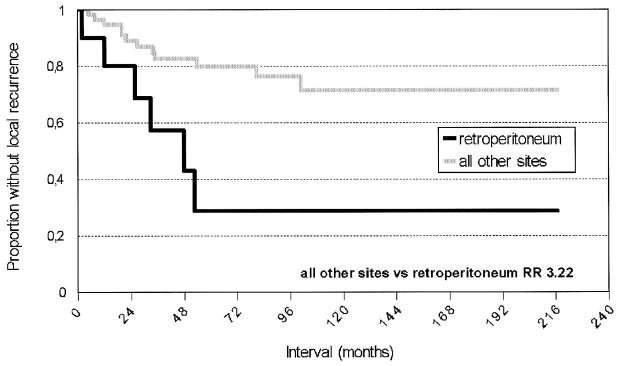

FIG. 4. Local recurrence-free interval according to anatomical site.

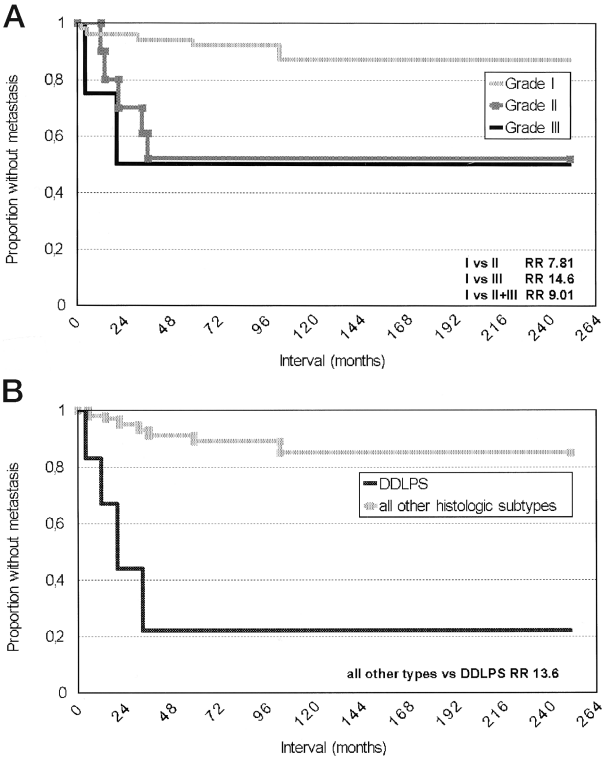

FIG. 5. (A) Metastasis-free interval according to tumor grade. (B) Metastasis-free interval according to histological subtype.

by 5 years. One patient developed distant metastases after 103 months. Four patients (36%) with distant metastases also experienced a local recurrence. In three of them, the local relapse preceded the distant failure by a median interval of 47 (range 4–91) months. In one patient, local and distant relapse occurred simultaneously.

The lung was the most common site for metastases (72%), followed by vertebrae (36%), soft tissues (27%), liver (18%), and brain (9%). None of the 26 WDLPS developed distant metastases, whereas 3 out of 6 metastasizing MXLPS (50%) did so to the soft tissues. Three patients (all MXLPS) developed extrapulmonary metastases only (soft tissue, spine, and brain).

A univariate analysis of prognostic factors with regard to metastasis-free interval is presented in Table 2. Deep tumor location, DDLPS (RR 13.6), and tumor grade II and III (RR 7.8 and 14.6, respectively) were associated with a significantly shorter metastasis-free period (Fig. 5a,b). After 5 years, DDLPS had a metastasis rate of 78%, with a median metastasis-free interval of 20 months. After 5 years, grade I, II, and III LPS had a metastasis rate of 8%, 49%, and 50%, respectively. The median metastasis-free interval in grade II and III LPS

TABLE 2. *(Distant) metastasis-free interval according to potential prognostic factors*

Clinicopathological factor		RR	95% CI
Gender	Male vs. female	0.36	0.10–1.37
Histological subtype	All other subtypes vs. DDLPS	13.6*	4.0–47
Primary vs. recurrent presentation		0.28	0.04–2.15
Anatomical site	All other sites vs. retroperitoneum	0.53	0.07–4.2
Depth	Superficial vs. deep	∞*	
Type of resection	R1 vs. marginal	3.83	0.49–30.3
	R1 vs. radical	1.57	0.10–25.1
Tumor diameter	≤10 cm vs. 10–20 cm	1.57	0.39–6.26
	≤10 cm vs. >20 cm	1.93	0.43–8.6
Grade	I vs. II	7.81*	2.10–29.1
	I vs. III	14.6*	2.67–80
	I vs. II + III	9.01*	2.64–31
Stage	I vs. II + III	0.66	0.17–2.49
Treatment	Surgery vs. surgery + radiotherapy	0.34	0.07–1.66
	Surgery vs. surgery + chemotherapy	1.23	0.15–10.0
	Surgery vs. surgery + radiotherapy + chemotherapy	0.59	0.15–2.80

* Significance, $P < .05$.

was 36 and 20 months, respectively. The relative risk of DDLPS was not influenced by tumor depth (RR 11.9, 95% CI, 3.49–40.7), nor by grade (RR10.3, 95% CI, 3.01–35.2). The relative risk of tumor grade II and III lost significance, when adjusted for DDLPS (RR 2.82, 95% CI, 0.76–10.5 and RR 1.45, 95% CI, 0.27–7.9, respectively). None of the superficially located tumors metastasized to distant sites.

Survival

A univariate analysis with regard to disease-free interval is presented in Table 3, demonstrating a significantly longer disease-free interval in WDLPS, grade I LPS, stage I LPS, and in tumors ≤10 cm. When corrected for tumor size and stage, WDLPS still had a better disease-free interval (RR 4.4 and 3.6, respectively). When adjusted for grade, WDLPS lost its significance (RR 2.7). Tumor grade I remained a significant factor when adjusted for tumor size (RR 2.6), but lost independence when adjusted for histological subtype (RR 1.3) or stage (RR 1.7). Tumor stage I, corrected for histological subtype, tumor grade, or tumor size, lost significance (RR 6.9, 5.2, and 4.2, respectively). Tumor size lost significance when adjusted for grade (RR 1.96) or stage (RR1.74), but was not influenced by histological subtype WDLPS (RR 4.2).

In univariate analysis, dedifferentiation, grade II and III, non-radical resection, and stage II and III were associated with a worse disease-specific survival (Table 4). None of the stage I patients died of the disease, but the numbers are too limited to reach statistical significance. After correction for radicalness of resection, DDLPS and grade II-III LPS continued to have a significantly worse disease-specific survival (RR 10.2 and 7.9, respectively), but when corrected for each other, both factors lost significance. After a radical resection, no patient died of the disease.

DISCUSSION

Liposarcoma (LPS) is the second or third most common soft tissue sarcoma (STS) of adult life and the incidence of LPS is estimated at 10–20% of all STS.[1–4] This tumor is primarily a tumor of adult life, and generally shows a slight preference for the male sex.[7,14,15] In this series, the median age at presentation with a primary or recurrent LPS was 49 and 56 years, respectively, and the male/female ratio was 1.03. Liposarcoma most often occurs in the lower extremity (13–68%) and the retroperitoneum is the second most common site (10–36%).[7,16,17] This was confirmed in our series in which 38 of 69 LPS (55%) were situated in the lower extremity, primarily in the thigh (n = 29). The retroperitoneum was the second most frequent anatomical site (16%). Characteristically, most LPS are deeply seated, and the majority seem to take origin from large intermuscular connective tissue spaces. Localization in the subcutaneous tissue is rare. However, noteworthy excep-

TABLE 3. *Disease-free survival according to potential prognostic factors*

Clinicopathological factor		RR	95% CI
Gender	Male vs. female	0.56	0.25–1.25
Histological subtype	WDLPS vs. PMLPS	2.80	0.31–25.1
	WDLPS vs. MXLPS	3.21*	1.07–9.7
	WDLPS vs. DDLPS	13.0	0.86–10.4
	WDLPS vs. all other subtypes	3.88*	1.33–11.3
Primary vs. recurrent presentation		1.04	0.43–2.50
Anatomical site	All other sites vs. retroperitoneum	1.92	0.76–4.79
Depth	Superficial vs. deep	3.91	0.53–28.9
Type of resection	R1 vs. marginal	1.48	0.55–3.95
	R1 vs. radical	0.26	0.03–2.20
Tumor diameter	≤10 cm vs. 10–20 cm	1.92	0.74–4.99
	≤10 cm vs. >20 cm	3.03*	1.14–8.09
Grade	I vs. II	2.80*	1.14–6.87
	I vs. III	5.39*	1.56–18.6
	I vs. II + III	3.27*	1.47–7.3
Stage	I vs. II	7.10	0.96–52.8
	I vs. III	23.9*	2.48–229
	I vs. II + III	7.79*	1.05–57.6
Treatment	Surgery vs. surgery + radiotherapy	0.69	0.28–1.75
	Surgery vs. surgery + chemotherapy	2.21	0.50–9.8
	Surgery vs. surgery + radiotherapy + chemotherapy	0.97	0.63–2.44

* Significance, $P < .05$.

TABLE 4. *Overall (disease-specific) survival according to potential prognostic factors*

Clinicopathological factor		RR	95% CI
Gender	Male vs. female	0.41	0.13–1.33
Histological subtype	All other subtypes vs. DDLPS	14.40*	4.72–44.1
Primary vs. recurrent presentation		0.50	0.11–2.28
Anatomical site	All other sites vs. retroperitoneum	2.76	0.85–8.9
Depth	Superficial vs. deep	∞	
Type of resection	R1 vs. marginal	2.34	0.52–10.6
	R1 vs. radical	0*	
Tumor diameter	≤10 cm vs. 10–20 cm	1.91	0.51–7.1
	≤10 cm vs. >20 cm	2.60	0.65–10.4
Grade	I vs. II	8.01*	2.26–28.4
	I vs. III	31.7*	7.1–142
	I vs. II + III	10.7*	3.29–34.6
Stage	I vs. II + III	∞	
Treatment	Surgery vs. surgery + radiotherapy	1.43	0.41–5.0
	Surgery vs. surgery + chemotherapy	1.95	0.23–16.7
	Surgery vs. surgery + radiotherapy + chemotherapy	2.34	0.38–7.4

* Significance, $P < .05$.

tions are the shoulder and head/neck area where tumors of smaller size, and shorter duration of symptoms, may extend into subcutaneous fat.[18,19] In this series, 8 of 69 LPS (12%) were subcutaneously seated, with the highest relative frequency in the head/neck region (60%), and the lowest in the lower extremity, buttock, and retroperitoneum (5%, 0%, and 0%, respectively) (Fig. 1).

It is difficult to compare the distribution of histological subtypes in the literature because different classifications have been used and anatomical distributions often vary. Undoubtedly, the myxoid type is by far the most common LPS. It is described most frequently in the literature[7,14,19] and was present in almost half of our patients (49%). The distribution of the other histological subtypes was in accordance with the series from the University of Texas M.D. Anderson Cancer Center (MDACC) published by Evans.[7] The relative frequency of PMLPS in our and the MDACC series was relatively low (4–5%), compared with some reports in the literature.[2,14] However, the latter series, which reports 23–26% PMLPS, has a different distribution of anatomical sites and/or did not recognize the dedifferentiated subtype.

After 5 years of follow-up, the overall local recurrence rate in this series was 27%, which seems to be in accordance with other reports, although the figures should be interpreted with caution because length of follow-up and distribution of histological subtypes and anatomical sites vary widely.[2,15,17] One of the highest local recurrence rates (85%) is reported in a series by Evans, comparable with this present series, but that study had a much longer follow-up with a minimum of 10 years.[7] This very long follow-up may be responsible for the high local recurrence rate because in LPS, which is different from other STS, (very) late recurrences are common.[2,17,19] In this series, only 44% of all local recurrences were evident by 2 years, whereas 11% occurred after 5 years, the latest of which even occurred 8.5 years after treatment. From the literature, histological subtype (DDLPS and PMLPS),[19,20] retroperitoneal localization,[15,21] recurrent presentation,[19,21] and involved surgical margins[17,19] have been reported as independent negative prognostic factors with regard to local recurrence. In the current series, retroperitoneal localization was the most important significant factor impairing the local recurrence-free interval (Table 1). No local recurrences were encountered after multimodality treatment (surgery, radiotherapy, and chemotherapy), but numbers were too small to draw conclusions. Histological subtype, tumor grade and size, recurrent presentation, margin status, and stage were not significant prognostic factors for local control.

Once LPS recurred, multiple recurrences were common (overall 72%). LPS tends to recur uncontrollably, especially in the retroperitoneum, and may be fatal through local effects, as reported by others.[22,23] Dedifferentiation in recurrence is reported in well-differentiated retroperitoneal LPS and is associated with a poor outcome.[6,7,15,22] This feature was encountered in 2 of 18 local recurrences (11%), both of which were retroperitoneal WDLPS. Both patients died from an unresectable local recurrence, in the absence of distant metastases.

After 5 years of follow-up, the overall metastasis rate was 16%. Most metastases became evident within the first 3 postoperative years (72%), as reported by others.[2,19] Late distant failures appeared to be relatively rare,

because nearly all metastases were evident by 5 years. As expected, the lung was the most common site for metastases (72%). This relative frequency is comparable with the results of Kindblom,[6] but is high compared to others (38–57%).[2,7] The high tendency of MXLPS to metastasize to extrapulmonary soft tissue sites, reported in the literature (38–88%),[2,7,19,20,24] was confirmed in our series, in which 50% of metastasizing MXLPS did so to soft tissues. WDLPS did not metastasize to distant sites.

From the literature, high tumor grade,[2] pleomorphic subtype,[19,20] round cell subtype (a poorly differentiated form of MXLPS),[24,25] and tumor necrosis[2] have been reported as independent factors associated with impaired metastasis-free interval. As shown in Table 2, and Fig. 5a,b, DDLPS, tumor grade II and III, and deep tumor location were significant determinants of metastatic outcome in the present series. After 5 years, grade II and III LPS had the highest metastatic rate (49% and 50%, respectively), with the shortest median metastasis-free interval ($\leq$ 3 years). Superficially located tumors did not metastasize.

Because several different classification systems for LPS have been used, it is very difficult to compare survival data from the literature. Reported independent

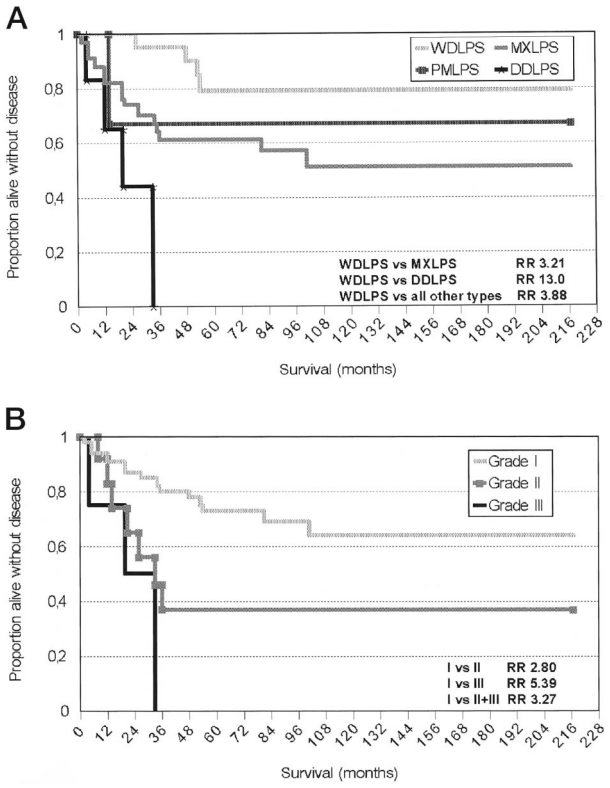

FIG. 6. (A) Disease-free survival according to histological subtype. (B) Disease-free survival according to tumor grade.

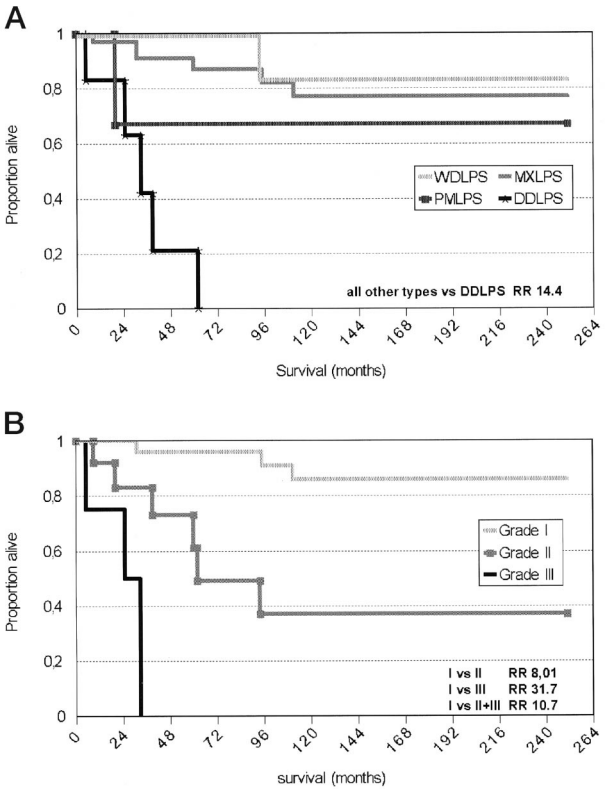

FIG. 7. (A) Disease-specific survival according to histological subtype. (B) Disease-specific survival according to tumor grade.

negative prognostic factors are high tumor grade,[21,26] tumor necrosis,[2] tumor size $\geq$ 5 cm[19,26] and $\geq$ 10 cm,[21] histological subtype (PMLPS, DDLPS, round cell MXLPS)[14,18–20,24,25,27], recurrent presentation,[21] and retroperitoneal localization.[14,15,17,21] In the current series, four factors (histological subtype, tumor size, tumor grade, and tumor stage) were significantly associated with disease-free survival (Table 3, Fig. 6a,b). Patients with WDLPS, tumors $\leq$10 cm, grade I LPS, and AJCC stage I LPS had a significantly longer disease-free survival, but these factors appeared to be associated with each other.

Three factors that significantly determined disease-specific survival were histological subtype, tumor grade, and type of resection (Table 4, Fig 7a,b). DDLPS, grade II-III, and non-radical resections had a significantly worse disease-specific survival. After radical resection, no patient died of the disease. Even when adjusted for type of resection, DDLPS and grade II-III LPS continued to have a significantly worse disease-specific survival, although both factors were associated with each other.

In the current series, we did not study the influence of the round cell subtype, a poorly differentiated variation of MXLPS, because round cell LPS was not recognized as a separate entity. Although strict criteria defining the

prognostic significance of the round cell component in MXLPS have not been established,[27] there are reports showing that a round cell component varying from >25% to even >5% is associated with a poor prognosis.[25,28] Tumor necrosis was also not analyzed as a separate prognostic factor. However, this factor, together with tumor differentiation and mitosis count, is one of the cornerstones of tumor-grade classification, as described by Coindre et al.[10] The prognostic importance of retroperitoneal localization could not be demonstrated in this series, but this may be a time-dependent issue, because at the end of the study period, 4 of 11 patients (45%) with retroperitoneal LPS had died from their disease; 1 patient (9%) had an unresectable local recurrence at the end of the study period, which will be fatal in the near future. Moreover, in those patients with retroperitoneal STS without evidence of disease, the duration of follow-up was relatively short.

Conclusion

This series of 69 consecutive patients with completely resected, AJCC stage I-III LPS confirms that liposarcoma is a quite heterogeneous disease, and that its outcome is determined to a significant degree by histological subtype, grade, size, stage, depth, and type of resection. Compared with other soft tissue sarcomas, LPS has a relatively mild biological behavior, with the exception of large, deeply located, dedifferentiated and/or grade II-III LPS. With regard to local failure, retroperitoneal localization was an additional negative prognostic factor. However, in contrast to some reports in the literature, we were not (yet) able to demonstrate a significant influence of retroperitoneal localization on survival.

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