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Impact of primary tumor location on outcome of liposarcoma patients, a retrospective cohort study

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ABSTRACT

Background: Tumor location as a prognostic factor for patients with liposarcoma (LPS) has been studied modestly with varying outcomes. The aim was to establish the impact of tumor location on recurrence and survival of LPS patients.

Methods: A retrospective database of patients treated for LPS until December 2017 was used to assess 5-year local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS) and disease-specific survival (DSS) per tumor location using the Kaplan-Meier method and log-rank test. A multivariable Cox regression analysis was performed to adjust for other prognostic factors.

Results: In total, 518 patients were identified with a median follow-up of 68 months (interquartile range 31–138). Patients with retroperitoneal/intrathoracic WDLPS or DDLPS ($p = 0.014$), or testicular WDLPS ($p = 0.026$) developed a local recurrence more often than patients with other tumor locations. No differences between LPS subtypes and tumor location in the development of metastases ($p = 0.600$) was observed. Five-year LRFS differed significantly between tumor locations ($p < 0.001$) as well as 5y-DSS ($p < 0.001$), but 5y-DMFS did not ($p = 0.241$), with retroperitoneal/intrathoracic LPS having a worse prognosis. Patients with WDLPS in the extremity, trunk or testicular region did not die of disease, except for the rare occasion of dedifferentiation upon recurrence. After adjustment for other prognostic factors, tumor location was only of prognostic value for DSS (retroperitoneal/intrathoracic vs. extremity: HR 5.08, 95% CI 2.41–10.71, $p < 0.001$).

Conclusion: For all tumor locations, DSS mimicked DMFS except for retroperitoneal/intrathoracic LPS, where DSS mimicked LRFS and where DSS was worse than DMFS. This implies that these patients die of local disease instead of metastatic disease.

Introduction

Liposarcoma (LPS) is one of the most common subtypes of soft tissue sarcoma (STS), accounting for approximately 20% of all STS [1]. They arise from lipoblasts and adipocytes, and can therefore occur at any site of the body, but the most frequently observed locations are the extremity, the retroperitoneum and trunk [2]. Based on morphology and genetic aberrations, four subtypes can be distinguished: well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), myxoid liposarcoma (MLPS) and pleomorphic liposarcoma (PLPS) [2]. Some LPS cannot be further classified and form a residual group of LPS not otherwise specified (LPS NOS). For patients presenting with non-metastatic disease treatment usually consists of surgical removal of the tumor, optionally preceded or followed by radiotherapy, chemotherapy or an isolated limb perfusion (ILP). The choice for neoadjuvant/adjuvant treatment partially depends on the LPS subtype.

Unfortunately, a number of patients will develop a local recurrence and/or distant metastasis, or will die due to the disease. Previously identified prognostic factors for recurrence and survival include age, LPS subtype, tumor grade, tumor size and status of the resection margins [3–11], but the impact of primary tumor location

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as a prognostic factor has been studied modestly. Most of the studies compared multiple STS subtypes on one location [3–8], or just one of the LPS subtypes on multiple locations [12–15]. Until now, we identified only two articles studying primary LPS on multiple locations, but these two studies presented conflicting outcomes: one in which tumor location was of prognostic importance [16], and one in which location was not of significant importance [17]. The aim of this study was to establish the impact of tumor location in recurrence and survival in LPS patients.

Methods

Patient characteristics

Data of all patients diagnosed with and treated for LPS in the Erasmus MC Cancer Institute in Rotterdam, the Netherlands from June 1983 up to and including December 2017 were collected retrospectively. Patients with LPS NOS, distant metastases at time of diagnosis or with insufficient clinical data available were excluded.

Histological LPS subtypes were categorized according to the WHO classification and grading according to the FNCLCC [2]. Because of low numbers, tumors localized on the trunk and tumors localized in the head and neck region were combined, as well as retroperitoneal LPS with intrathoracic LPS. The resection margins were classified as R0 (microscopically negative margins), R1 (microscopically positive margins), R2 (macroscopically positive margins) or Rx (margins unknown/not assessed). During follow-up, information on vital status (alive, death of disease, death of other/unknown cause) and recurrence (local and/or distant) were obtained. In case of retroperitoneal LPS, a local recurrence was defined as recurrence of disease within the abdomen, including multifocal recurrences. Due to the retrospective nature of our data source, no distinction between a multifocal peritoneal recurrence (e.g. two peritoneal tumor depositions) and peritoneal sarcomatosis, which perhaps represents a more advanced stage of disease, could be made. Distant metastasis of retroperitoneal LPS was defined as disease outside of the abdomen. Follow-up was performed according to national and international guidelines [18].

Statistical analysis

Categorical data were presented as numbers with percentages, and continuous data were presented as medians with corresponding interquartile ranges (IQR). Chi-square and Fisher's Exact tests were used when appropriate. The median follow-up time was calculated using the reversed Kaplan-Meier method [19].

Local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS) and disease-specific survival (DSS) were defined as time (in months) between date of diagnosis and date of local recurrence, distant metastasis or death of disease, respectively. Time was censored at 5 years of follow-up for patients remaining free of local recurrences and distant metastasis or who were alive after 5 years of follow-up. The 5-year LRFS, DMFS and DSS were estimated using the Kaplan-Meier method and differences between subgroups were tested for their significance using the log-rank test.

To adjust for other prognostic factors, multivariable Cox regression analyses for LRFS, DMFS and DSS were performed. Firstly, the factors were tested univariably, and were added to the multivariable model in case the p-value was <0.05, together with the factor coding for tumor location. The results were reported as hazard ratios (HR) with their corresponding 95% confidence intervals (95% CI). The main results of the Cox regression analyses are summarized in an overview, the complete results of both the univariable and multivariable analyses are presented in the supplemental tables. All statistical analyses were performed using SPSS (IBM SPSS Statistics, version 24).

Results

Patient characteristics

In total, 518 patients were identified who were diagnosed with and treated for LPS. There were slightly more males (56%) than females (44%), and the median age at time of diagnosis was 59 years (IQR 46–68). Most of the patients had a WDLPS (48%), followed by DDLPS (24%), MLPS (21%) and PLPS (8%). Most of the tumors were localized in one of the extremities (49%), followed by the retroperitoneum/intrathoracic cavity (29%), trunk/head and neck region (15%) and testicular/inguinal region (7%). Most tumors were low-grade, due to the large proportion of WDLPS, and the median tumor size was 16 cm (IQR 10–23). A quarter of the patients received radiotherapy, mostly adjuvant, while a small fraction received chemotherapy (4%) or an ILP (6%) as part of their primary treatment. The median follow-up time was 68 months (IQR 31–138)(Table 1).

Table 1
Patient characteristics (N = 518).

		N	%
Gender	Male	290	56.0
	Female	228	44.0
Age (years), median (IQR)		59 (46–68)	
Subtype	WDLPS	246	47.5
	DDLPS	126	24.3
	MLPS	107	20.7
	PLPS	39	7.5
Location	Extremity	254	49.0
	RPS + intrathoracic	150	29.0
	Trunk + head&neck	79	15.3
	Testis/inguinal	35	6.8
Grade	I	297	57.3
	II	36	6.9
	III	76	14.7
	Unknown	109	21.0
Resection margins	R0	149	28.8
	R1	197	38.0
	R2	45	8.7
	Rx	106	20.5
	No resection	21	4.1
Tumor size (cm), median (IQR)		16 (10–23)	
RTx	No	387	74.7
	Neoadjuvant	31	6.0
	Adjuvant	100	19.3
CTx	No	503	97.1
	Neoadjuvant	8	1.5
	Adjuvant	7	1.4
ILP	No	491	94.6
	Neoadjuvant	28	5.4
Local recurrence	No	328	63.3
	Yes	190	36.7
	TLR (months), median (IQR)	23 (10.8–58)	
Distant metastases	No	428	82.6
	Yes	90	17.4
	TSD (months), median (IQR)	23.5 (8.8–58.5)	
Survival	Alive	352	68.0
	Death of disease	122	23.6
	Death of other/unknown cause	44	8.5
	Follow-up (months), median (IQR)	68 (31–138)	

WDLPS, well-differentiated liposarcoma; DDLPS, dedifferentiated liposarcoma; MLPS, myxoid liposarcoma; PLPS, pleomorphic liposarcoma; RPS, retroperitoneal sarcoma; IQR, interquartile range; RTx, radiotherapy; ILP, isolated limb perfusion; CTx, chemotherapy; TLR, time to local recurrence; TSD, time to systemic disease.

Table 2
LPS subtype per primary tumor location.

	Extremity	RPS + intrathoracic	Trunk + head&neck	Testis	Total
WDLPS	130 (51)	57 (38)	46 (58)	13 (37)	**246 (48)**
DDLPS	18 (7)	82 (55)	7 (9)	19 (54)	**126 (24)**
MLPS	86 (34)	7 (5)	13 (17)	1 (3)	**107 (21)**
PLPS	20 (8)	4 (3)	13 (17)	2 (6)	**39 (8)**
Total	**254 (100)**	**150 (100)**	**79 (100)**	**35 (100)**	**518 (100)**

WDLPS, well-differentiated liposarcoma; DDLPS, dedifferentiated liposarcoma; MLPS, myxoid liposarcoma; PLPS, pleomorphic liposarcoma; RPS, retroperitoneal sarcoma.

Tumor location versus liposarcoma subtype

More than half of the tumors localized in one of the extremities were WDLPS (51%), a third of the tumors MLPS (34%) and only a small proportion were DDLPS (7%) or PLPS (8%). Retroperitoneal/intrathoracic LPS were mostly of the DDLPS (55%) and WDLPS (38%) subtype, while tumors localized on the trunk/head and neck region were mostly WDLPS (58%) and less often MLPS (17%) or PLPS (17%). At last, testicular/inguinal tumors were mainly DDLPS (54%) and WDLPS (37%), and rarely PLPS (6%) or MLPS (3%)(Table 2).

Recurrence versus tumor location

In total, 36.7% of the patients developed a local recurrence (median time to local recurrence 23 months, IQR 11–58) and 17.4% developed distant metastasis (median time to metastasis 24 months, IQR 9–59)(Table 1). Since local recurrence and distant metastasis rates differ between LPS subtypes, the impact of tumor location was analyzed per subtype (Table 3). Patients with WDLPS developed significantly more often a local recurrence when the tumor was localized retroperitoneal/intrathoracic (53%) or in the testicular region (46%) than with tumors localized in the extremity (29%) or trunk/head and neck (30%, $p = 0.014$). Also patients with retroperitoneal/intrathoracic DDLPS experienced significantly more often a local recurrence (62%) than patients with other locations of DDLPS (extremity 33%, trunk/head and neck 29%, testicular 37%, $p = 0.026$). In patients with MLPS ($p = 0.274$) and PLPS ($p = 0.703$) no differences in local recurrence rates between the different tumor locations were observed (Table 3).

Using Kaplan-Meier analysis, 5y-LRFS differed significantly between the different tumor locations ($p < 0.001$, Fig. 1A), with 5y-LRFS rates of 73.9% for patients with extremity LPS, 70.3% for patients with trunk/head and neck LPS, 64.5% for patients with testicular LPS and 35.8% for patients with retroperitoneal/intrathoracic LPS. After adjustment for other prognostic factors (LPS subtype, age, tumor size, status of the resection margins, neo-adjuvant/adjuvant radiotherapy, chemotherapy and ILP) in a multivariable Cox regression analysis, tumor location was no longer of prognostic value (Table 4, Supplemental Table S1).

With regard to the distant metastasis rate, no significant differences between the different tumor locations in any of the LPS subtypes were observed (WDLPS: $p = 0.773$, DDLPS: $p = 0.321$, MLPS: $p = 0.556$, PLPS: $p = 0.512$, overall: $p = 0.600$)(Table 3). Additionally, there were no differences in the 5y-DMFS between the different tumor locations, with 5y-DMFS rates of 89.0% for patients with trunk/head and neck LPS, 84.8% for patients with extremity LPS, 80.1% for patients with testicular LPS and 77.3% for patients with retroperitoneal/intrathoracic LPS ($p = 0.241$, Fig. 1B). Also in the multivariable analysis no significant impact for tumor location was observed (Table 4, Supplemental Table S2).

Remarkably, 7 of the patients with WDLPS developed metastatic disease, while this subtype is known for its lacking metastatic potential, unless the tumor undergoes dedifferentiation at recurrence. This was indeed the case for five out of the seven patients with metastatic 'WDLPS'. The sixth patient had multiple local recurrences which were all WDLPS, but at time of the last (multifocal)

Table 3
Number of patients with a local recurrence (LR) and/or distant metastasis (DM).

		LR, n (%)			DM, n (%)		
		No	Yes	p	No	Yes	p
WDLPS	Extremity	92 (71)	38 (29)	0.014	127 (98)	3 (2)	0.773
	RPS + intrathoracic	27 (47)	30 (53)		55 (96)	2 (4)	
	Trunk + head&neck	32 (70)	14 (30)		44 (96)	2 (4)	
	Testis	7 (54)	6 (46)		13 (100)	0 (0)	
	Total	**158 (64)**	**88 (36)**		**239 (97)**	**7 (3)**	
DDLPS	Extremity	12 (67)	6 (33)	0.026	16 (89)	2 (11)	0.321
	RPS + intrathoracic	31 (38)	51 (62)		58 (71)	24 (29)	
	Trunk + head&neck	5 (71)	2 (29)		5 (71)	2 (29)	
	Testis	12 (63)	7 (37)		12 (63)	7 (37)	
	Total	**60 (48)**	**66 (52)**		**91 (72)**	**35 (28)**	
MLPS	Extremity	65 (76)	21 (24)	0.274	59 (69)	27 (31)	0.556
	RPS + intrathoracic	4 (57)	3 (43)		5 (71)	2 (29)	
	Trunk + head&neck	10 (77)	3 (23)		10 (77)	3 (23)	
	Testis	0 (0)	1 (100)		0 (0)	1 (100)	
	Total	**79 (74)**	**28 (26)**		**74 (69)**	**33 (31)**	
PLPS	Extremity	17 (85)	3 (15)	0.703	10 (50)	10 (50)	0.512
	RPS + intrathoracic	3 (75)	1 (25)		3 (75)	1 (25)	
	Trunk + head&neck	9 (69)	4 (31)		9 (69)	4 (31)	
	Testis	2 (100)	0 (0)		2 (100)	0 (0)	
	Total	**31 (79)**	**8 (21)**		**24 (62)**	**15 (38)**	
Total		**328 (63)**	**190 (37)**	**<0.001**‡	**428 (83)**	**90 (17)**	**0.600**‡

‡χ^2-test, all other tests were Fisher's Exact tests.
WDLPS, well-differentiated liposarcoma; DDLPS, dedifferentiated liposarcoma; MLPS, myxoid liposarcoma; PLPS, pleomorphic liposarcoma; RPS, retroperitoneal sarcoma; LR, local recurrence; DM, distant metastasis.

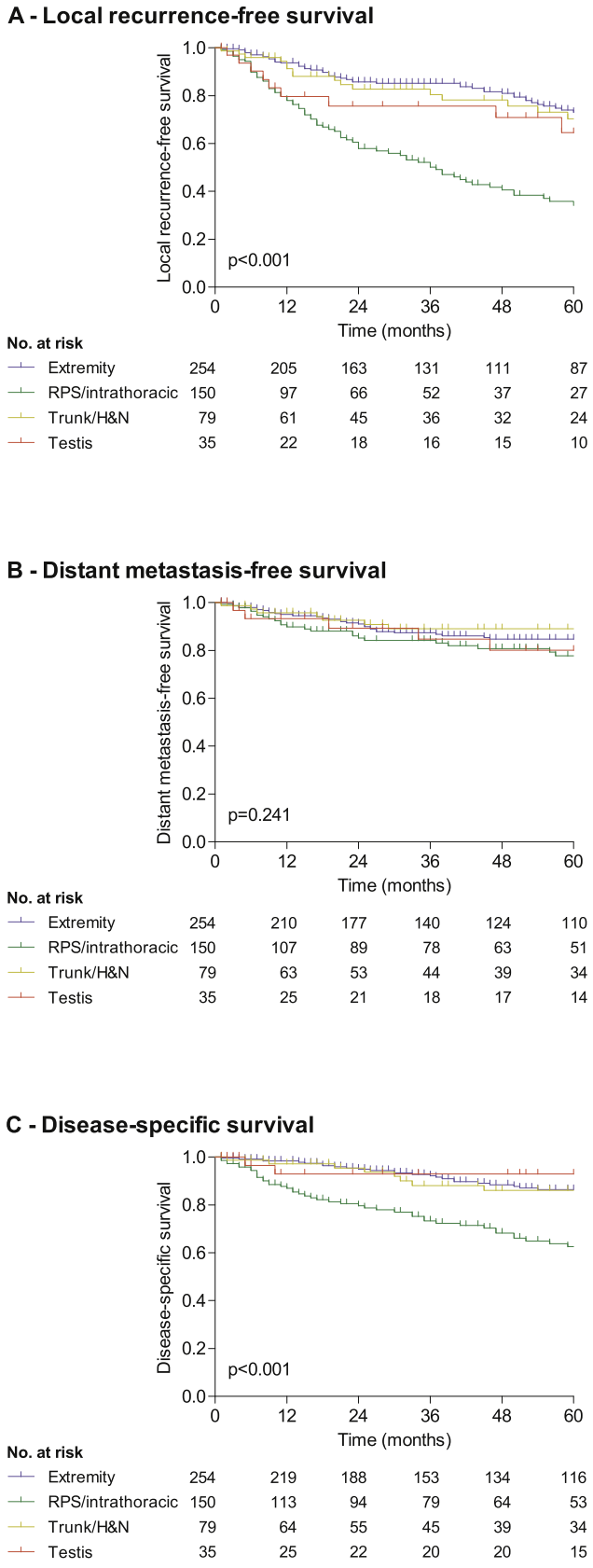

Fig. 1. Five-year local recurrence-free survival (**A**), 5-year distant metastasis-free survival (**B**) and 5-year disease-specific survival (**C**) per tumor location of all patients diagnosed with and treated for liposarcoma. P-values were calculated using the log-rank test. RPS: retroperitoneal liposarcoma, H&N: head & neck.

Table 4
Impact of tumor location in local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS) and disease-specific survival (DSS) after adjustment for other prognostic factors. Complete results of the Cox regression analyses are shown in supplemental tables S1, S2 and S3.

		N	HR	95% CI	P
LRFS	Extremity	223	Ref		
	RPS + intrathoracic	135	1.46	0.92–2.32	0.110
	Trunk + head&neck	68	1.16	0.66–2.05	0.604
	Testis/inguinal	30	1.29	0.62–2.70	0.503
DMFS	Extremity	254	Ref		
	RPS + intrathoracic	150	1.78	0.86–3.70	0.123
	Trunk + head&neck	79	1.08	0.53–2.21	0.838
	Testis/inguinal	35	1.64	0.66–4.03	0.285
DSS	Extremity	223	Ref		
	RPS + intrathoracic	135	5.08	2.41–10.71	<0.001
	Trunk + head&neck	68	1.87	0.81–4.30	0.142
	Testis/inguinal	30	1.15	0.32–4.14	0.826

LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; RPS, retroperitoneum; RTx, radiotherapy; CTx, chemotherapy; ILP, isolated limb perfusion; Tx, treatment; HR, hazard ration; 95% CI, 95% confidence interval.

local recurrence also multiple lung lesions suspected for metastases were discovered. However, no biopsy or resection was performed on either the local recurrence or one of the lung lesions. A few months after the diagnosis of lung metastases the patient died. So, in our opinion it was likely that dedifferentiation also had occurred in this patient. The last patient developed a local recurrence and a paravertebral lesion simultaneously. The local recurrence was biopsied and showed WDLPS without any signs of dedifferentiation, but no biopsy of the paravertebral lesion was obtained. The patient is still alive, after 'palliative' radiotherapy of 24Gy, with a follow-up period of 60 months (42 months after discovery of the paravertebral lesion), so we doubt if this atypical paravertebral lesion indeed was a metastasis.

Survival versus tumor location

The 5y-DSS differed significantly between the different tumor locations ($p < 0.001$, Fig. 1C), with the best prognosis for patients with testicular LPS (5y-DSS 93.0%), patients with extremity LPS (86.4%) and trunk/head and neck LPS (86.1%). Patients with retroperitoneal/intrathoracic LPS had a worse prognosis with a 5y-DSS rate of 62.2%. Also after adjustment for other prognostic factors, a retroperitoneal/intrathoracic tumor location had a worse prognosis compared to tumor location in the extremity (HR 5.08, 95% CI 2.41–10.71, $p < 0.001$, Table 4, Supplemental Table S3).

Since the group of retroperitoneal/intrathoracic LPS mainly consisted of patients with WDLPS or DDLPS (total 93%, Table 2), an additional DSS analysis for these two LPS subtypes was performed to explore whether the worse prognosis was due to large proportion of DDLPS in this subgroup. As expected, DDLPS patients with a retroperitoneal/intrathoracic location had the worst prognosis (5y-DSS 50.3%), together with patients with a DDLPS on the trunk/head and neck (44.4%), followed by DDLPS patients with a location in the extremity (84.0%) and testis (88.2%, $p = 0.023$, Supplemental Fig. S1A). Also when analyzing patients with WDLPS, patients with retroperitoneal/intrathoracic WDLPS had a worse prognosis (5y-DSS 80.5%), while WDLPS patients with tumor locations in the extremity (99.2%), trunk/head and neck (100%) or testis (100%) had an excellent prognosis ($p < 0.001$, Supplemental Fig. S1B). Only one patient with non-retroperitoneal WDLPS died of disease within 5 years of follow-up, which turned out to be treatment-related (5 days after ILP). In the total follow-up period, 4 patients with non-retroperitoneal WDLPS died of disease (after 75, 179, 210 and 226

months), all after dedifferentiation upon recurrence. Only of one patient with multiple local recurrences and lung metastases, dedifferentiation was not pathologically confirmed.

Neoadjuvant/adjuvant treatment in LPS

Neoadjuvant/adjuvant treatment of the primary tumor was also included in the Cox regression analyses for LFRS, DMFS and DSS. For LRFS, radiotherapy as well as chemotherapy and ILP tested significantly in univariable analysis, but only radiotherapy remained of significant influence in the multivariable analysis, reducing the risk of a local recurrence (HR 0.19, 95% CI 0.11–0.35, $p < 0.001$, Supplemental Table S1). Also for DMFS all three treatment modalities tested significantly in univariable analysis, but none of them remained significant in multivariable analysis (Supplemental Table S2). For DSS, only CTx and ILP tested significantly in univariable analysis, but again both lost their prognostic value in multivariable analysis (Supplemental Table S3).

Discussion

The results of this study show that primary tumor location has an impact on local recurrence-free survival and disease-specific survival, while no differences in distant metastasis-free survival were observed.

Despite that there was no difference in DMFS, patients with retroperitoneal/intrathoracic LPS have a worse prognosis than patients with a LPS localized elsewhere. Generally, patients with cancer die because of metastatic disease, but these data confirmed that retroperitoneal/intrathoracic LPS is one of the few entities where patients also can die because of local disease, as indicated by the worse LRFS. This is further underlined by Fig. 1, showing that the DSS is worse than the DMFS and that the DSS curve of patients with retroperitoneal/intrathoracic LPS mimics the LRFS curve. For the other tumor locations, the DSS curves resemble the DMFS curves more. The worse prognosis of these patients might be explained by the large proportion of patients with DDLPS or a higher percentage of irradical resections (R1/R2) in this subgroup. However, after adjusting for the status of resection margins and for LPS subtype in a multivariable analysis, still a worse DSS for patients with retroperitoneal/intrathoracic tumors was observed. Additionally, we separately analyzed the patients with WDLPS, and patients with a retroperitoneal/intrathoracic tumor location again had a worse prognosis than patients with WDLPS on other locations (Supplemental Fig. S1). Multiple explanations for the worse prognosis of retroperitoneal/intrathoracic LPS can be thought of, including delayed detection because of a lack of symptoms, allowing the tumor to grow silently and resulting in more complex and extensive surgery, but it is still unclear if it is indeed a matter of time or whether there is a biological reason for an unfavorable clinical outcome.

Since patients with retroperitoneal/intrathoracic LPS die because of local disease and local control proved to be essential, we might need to reconsider the local treatment options, consisting of 1) surgery and 2) radiotherapy. Evidently, the goal of surgery is complete resection of the tumor, but especially for retroperitoneal sarcomas there is an ongoing discussion regarding the appropriate extent of resection. Usually, a 'simple' complete resection is performed, enucleating the tumor, sometimes in combination with en-bloc resection of an involved adjacent organ. However, there are clues that a compartmental resection, during which also uninvolved adjacent organs are resected to ensure wide margins, is associated with lower recurrences rates and improved overall survival [20–22]. However, these studies were based on retrospective data, which inherently leads to selection and information bias amongst others, and compartmental resections might lead to higher complications rates. Secondly, the use of neoadjuvant/adjuvant radiotherapy in this patient group might be reconsidered. Neoadjuvant/adjuvant radiotherapy as part of the primary treatment had no significant effect on DMFS or DSS, but did have a protective effect on LRFS in multivariable analysis in this study. Additionally, a previous study on extremity LPS also showed that an aggressive treatment approach (resection with wide margins and radiotherapy) resulted in excellent local control in extremity WDLPS, but also that this did not result in better disease-specific survival [23]. Given its toxicity, varying effectivity and missing effect on survival, we are currently reluctant in giving radiotherapy in our center, despite the better local control. Only a quarter of the patients received radiotherapy in this cohort, whereas this percentage might be higher in other centers/cohorts [23]. However, since local control appears to be crucial in retroperitoneal/intrathoracic LPS, the use of radiotherapy for the sake of local control needs to be reevaluated, which is currently being done in the STRASS trial. Although the first results of the STRASS trial – randomizing between neoadjuvant radiotherapy plus surgery versus surgery alone for patients with retroperitoneal sarcoma – overall showed no benefit of neoadjuvant radiotherapy in terms of abdominal recurrence-free survival, a subgroup analysis demonstrated that neoadjuvant radiotherapy might benefit the LPS subgroup [24]. However, the final results, including data on overall survival, are pending and needed to see whether the improved abdominal recurrence-free survival will result in improved overall survival.

To the best of our knowledge, there were only two studies comparing the outcomes of the different LPS subtypes taking all tumor locations into account: one study in which tumor location was not of prognostic value [17] and one study in which it was of prognostic value [16]. In the latter study, patients with retroperitoneal disease also had a worse prognosis than patients with tumors in the lower extremity, upper extremity or trunk. This study confirms these results, but contradicts the results of the other study. Possible explanations for the different outcomes could be the distribution of LPS subtypes, the distribution of the different tumor locations or the number of included patients. The distribution of LPS subtypes was comparable between the two studies and our study, but in the study of Knebel et al. [17] only 130 patients were included, of whom almost 85% had a tumor localized in the extremity, approximately 10% in the retroperitoneum/pelvis, and only 4.5% in the trunk/head and neck region and 1% in the spermatic cord. On the contrary, Dalal et al. [16] included 801 patients with a distribution of the tumor locations comparable to ours, with 56.5% of the tumors localized in the extremity, 28% in the retroperitoneum and 11% in the trunk.

The survival rates observed in this study are comparable to the survival rates reported in literature. For retroperitoneal LPS, 5-year overall survival (5y-OS) rates of 60% (all LPS) [11], 57% (only 50% LPS included) [20] and 54% (58% LPS) [8]have been reported, compared to 5y-DSS of 62% in this study. For extremity LPS, a 5y-DSS rate of 80% [9], 12y-DSS rate of 87% for the upper extremity and 82% [16] for lower extremity LPS have been reported, compared to 5y-DSS of 86% in our study.

Evidently, our study has some limitations. Because of the retrospective nature, which is inevitable when studying rare diseases, selection bias and information bias may have been introduced. We tried to minimize the selection bias by including all LPS patients without any exclusion criteria except for insufficient available data and metastatic disease at diagnosis. Strengths of this study are the large number of included patients and that the results are based on daily clinical practice.

Currently, treatment is more or less similar for the different LPS

subtypes or tumor locations, but more and more evidence is becoming available showing STS and even LPS is not a single entity. For each STS/LPS subtype, and maybe even for each tumor location, a different treatment approach might be needed and preferable.

Conclusion

A retroperitoneal/intrathoracic tumor location had a negative effect on disease-specific survival of LPS patients. These patients also developed local recurrent disease more often than patients with other tumor locations, but no differences in distant metastases were observed. This implies that these patients die of local disease instead of metastatic disease and that the local treatment options, including the extent of surgery and radiotherapy, should be reevaluated. Radiotherapy improved local control, but had no effect on distant metastasis-free survival or disease-specific survival in this cohort. Therefore, pending the final results on overall survival of the STRASS trial, the use of radiotherapy in retroperitoneal/intrathoracic LPS should be reconsidered, since in this patient group local control proved to be of essential importance. Lastly, patients with WDLPS in the extremity, trunk or testicular region did not die of disease, except for rare cases in whom the tumor had dedifferentiated upon recurrence.

Conflicts of interest

None of the authors declare any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.08.026.

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