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Clinical course and prognostic factors of patients with dedifferentiated liposarcoma: a retrospective analysis

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Abstract

Introduction Dedifferentiated liposarcoma (DDLPS) is a fairly common subtype of soft tissue sarcoma, but relatively little is known about the clinical course and prognostic factors of this mesenchymal malignancy.

Methods We performed a retrospective analysis of patients diagnosed with DDLPS at the University Hospital Leuven, Belgium between 1991 and 2022 based on an established clinical database and patient records.

Results We identified 259 patients with DDLPS, with the retroperitoneum as most common location of the primary tumor (47.5%). 204/259 patients (78.8%) patients had primary surgery. Radiotherapy was administered in the pre- (46/259, 17.8%) or postoperative setting (51/259, 19.7%). At diagnosis 28/259 (10.8%) patients presented with locally inoperable disease and 26/259 (10.0%) with synchronous metastasis. In patients who had primary surgery, local relapses were seen in 114/259 (44.0%) patients and 80/259 (30.9%) patients developed metachronous metastasis. A total of 48/259 (18.5%) patients developed both local relapse and metastasis. Patients with inoperable or metastatic disease were often treated with systemic therapy. The most common first-line systemic therapies were doxorubicin (51/98, 52.0%), doxorubicin combined with ifosfamide (12/98, 12.2%) and different types of experimental treatments (18/98, 18.4%). The median overall survival from first diagnosis of DDLPS to death of all causes was 70.5 months (95% confidence interval [CI] 56.6–98.6) for all patients, 10.9 months (95% CI 3.6–29.2) in patients with inoperable disease, 28.4 months (95% CI 1.3-199.3) for patients with local relapse and only 9.4 months (95% CI 1.2–25.9) for patients with metastatic disease. We identified lower age, primary surgery, absence of synchronous metastasis, absence of local relapse and treatment with experimental therapy as statistically significant favorable prognostic factors.

Conclusions DDLPS is a subtype of soft tissue sarcoma with an aggressive clinical course and very poor prognosis, especially in patients with inoperable or metastatic disease. The results with classic chemotherapy are poor, and experimental treatments may be a preferred choice for individual patients. Data from this retrospective series can inform the design of future prospective and ongoing trials in this setting.

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Keywords Dedifferentiated liposarcoma, Treatment modalities, Prognostic factors

Introduction

Liposarcomas are malignant tumors originating from precursors of adipose tissue and represent a relatively common subfamily of soft tissue sarcomas (STS). Liposarcoma accounts for approximately 15–20% of all mesenchymal malignancies [1, 2].

The latest World Health Organization classification of soft tissue and bone tumors describes 5 subtypes of liposarcoma: atypical lipomatous tumor/well differentiated liposarcoma, dedifferentiated liposarcoma (DDLPS), myxoid liposarcoma, pleomorphic liposarcoma and myxoid pleomorphic liposarcoma [3].

According to the Belgian Cancer Registry the incidence of liposarcoma in Belgium is around 0.9–1.5/100.000/year [4]. The disease occurs more commonly in males then in females (ratio 1.8/1). The incidence increases with age, with a peak of newly diagnosed cases occurring around the age of 75 years. The most common subtype of liposarcoma is DDLPS. According to Belgian figures DDLPS accounts for 39% of all liposarcomas [4]. These findings are comparable with French data, where an incidence of liposarcoma of 1.3/100.000/year was described in 2020, with approximately 41.4% cases of DDLPS [5]. A group in the United States found an incidence of liposarcoma of 1.1/100.000/year, with 21.0% cases of DDLPS [6]. The incidence of liposarcoma seems to increase over time, compared with a few decades ago [5, 6]. This can be partially explained by more accurate diagnostic criteria, increasing use of molecular tools for diagnostics, but also an interaction with environmental and lifestyle factors has been proposed [6]. The majority of DDLPS cases are diagnosed in middle-aged and older adults. In children and young adults DDLPS is very rare [7].

The World Health Organization defines DDLPS as "an atypical lipomatous tumor/well-differentiated liposarcoma showing progression, either in the primary or in a recurrence, to (usually non-lipogenic) sarcoma of variable histological grade" [8]. Classically, the tumor is a mixture of well differentiated and dedifferentiated components. In some cases the well differentiated component cannot be identified. It is generally believed that up to 90% of DDLPS occur *de novo*, while the other cases arise from recurrences of a well differentiated liposarcoma [9]. There is still considerable uncertainty about this concept.

In theory DDLPS can occur everywhere in the body, but in contrast with other subtypes of liposarcoma DDLPS has a predilection for the retroperitoneum, where it tends to spread within the abdominal cavity, but it can also metastasize to distant sites [1]. If the disease occurs in the extremities, it is usually located proximally in the deep soft tissue. Other typical primary locations of DDLPS are the spermatic cord, trunk and head and neck region [7]. The most common clinical presentation is that of a large, painless mass slowly increasing in size over time. Often DDLPS is an incidental finding, especially for retroperitoneal primaries, which can be very large at time of diagnosis. Symptoms like abdominal pain or distention, intestinal or urinary obstruction are reported in some patients [9].

DDLPS is a high grade, aggressive disease, similar to other dedifferentiated or pleomorphic sarcomas. The local recurrence rate after surgery is approximately 40% [7]. Metastatic spread is seen in about 15–30% of cases during the course of the disease [7]. DDLPS is considered poorly sensitive to chemotherapy [10]. Of note, there are hardly any prospective data on the typical clinical course of DDLPS and only few data on the responsiveness of DDLPS to systemic therapy in the literature, as most historical trials have pooled DDLPS together with multiple other mesenchymal malignancies. The exception here are some data reported from the registration trials for the drugs trabectedin and eribulin, which had a focus on liposarcomas, but pooled multiple subtypes of adipocytic malignancies [11–14]. The 5-year survival counted from the first diagnosis of DDLPS is about 50–60% [4, 15], but is remarkably lower in cases with unresectable or metastatic disease.

Based on the few published prognostic data, patients with DDLPS have poorer prognosis in case of positive resection margins after primary surgery, a primary tumor location in deep trunk/retroperitoneum or head and neck, a larger size of the primary tumor, higher pathologic grade, presence of metastasis and old age at diagnosis [15]. DDLPS arising in the extremities has a more favorable prognosis as compared to other primary sites [7].

Cytogenetically, DDLPS is characterized by supernumerary ring and giant marker chromosomes (Fig. 1), called "neochromosomes", with amplified sequences of chromosome 12q13-15. These neochromosomes do not possess real centromeres and are therefore distributed unequally during mitosis. Genetically there is a consistent amplification of the *murine double minute 2 (MDM2)* and *cyclin-dependent kinase 4 (CDK4)* genes, both located on chromosome 12, in DDLPS, which can be helpful in distinguishing this disease from other types of poorly differentiated sarcoma [8]. MDM2 immunohistochemistry and/or fluorescence in situ hybridization are routinely used for diagnostic purposes. MDM2 targets tumor protein p53 (TP53) for proteasomal degradation, and therefore prevents apoptosis. CDK4 causes enhanced progression of cells through the cell cycle. DDLPS

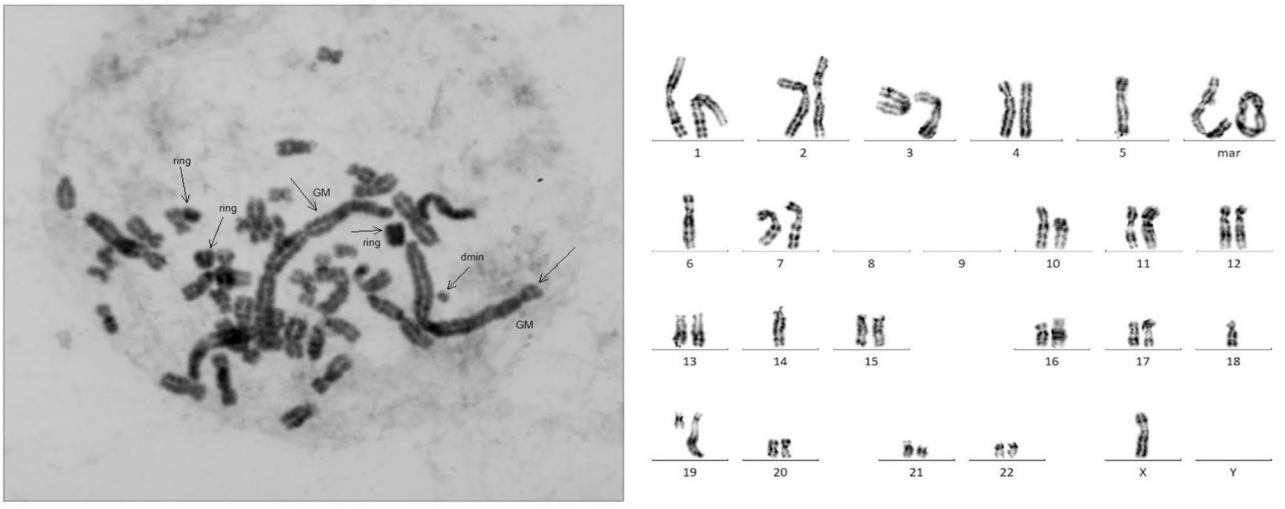

Fig. 1 Supernumerary ring and giant marker chromosomes

harbors a higher number of point mutations, rearrangements and copy number alterations than its well-differentiated counterpart [16]. High mutational burden and an increased number of gene copy number alterations are associated with poor prognosis [16].

For localized disease, surgical resection with clear margins is the standard of care and the only way to cure DDLPS [9]. For retroperitoneal DDLPS a systematic resection of noninvolved contiguous organs (compartmental resection) is the preferred surgical treatment [17]. Additional radiotherapy, often given postoperatively, can be considered for large DDLPS of the extremities to improve local disease control [7]. For retroperitoneal sarcoma the prospective trial EORTC-62092 (STRASS) failed to demonstrate a significant benefit of preoperative radiotherapy. However, a post hoc sensitivity analysis in the subgroup with liposarcoma did show a 10% absolute abdominal recurrence free survival benefit at 3 years (65% vs. 75%) [18]. The pooled data from the STRASS trial and the off-trial STREXIT cohort did show a benefit in abdominal recurrence-free survival in grade 1 and 2 DDLPS with a hazard ratio (HR) of about 0.6. For grade 3 DDLPS no statistically significant difference was found. Nevertheless, no clear benefit in overall survival (OS) was observed so far [19].

Unresectable, locally advanced tumors, inoperable relapses and metastatic cases of DDLPS are often treated with palliative chemotherapy, with anthracycline-based therapy as the first choice. Some experts challenge the activity of anthracyclines in DDLPS. Other systemic treatment options include drugs such as ifosfamide, trabectedin, eribulin or gemcitabine/docetaxel [7]. Promising experimental treatment options include MDM2 antagonists and CDK4 inhibitors [7]. Multiple trials are currently investigating the use of MDM2 antagonists in DDLPS [20].

In general the systemic treatment of DDLPS has very poor clinical efficacy. The median overall survival (mOS) for patients with metastastic DDLPS is around 10.2 months [15]. In a retrospective analysis of patients with liposarcoma, 82% of whom had DDLPS, the majority of patients received anthracyclines in first or later lines of treatment (82%). The objective response rate was 12% for all patients, with a median progression-free survival (mPFS) of 4.6 months and a mOS of 15.2 months [21].

Traditionally various types of STS have been pooled together when performing clinical trials or analyzing epidemiological data. Reliable prospective data on the natural course, clinical evolution, drug sensitivity or resistance of specific sarcoma subtypes such as DDLPS are very limited. More recent clinical trials tested new treatments using a more subtype-specific approach, but the lack of reference data from prospective analyses is a limitation for designing research projects that can ultimately lead to improvement in treatment outcomes. Considering the relative lack of prospective outcome data in patients with DDLPS we performed a comprehensive, retrospective analysis of the clinical features, treatment options, prognosis and potential prognostic factors in patients with this malignancy treated at the University Hospitals in Leuven (Belgium).

Methods

For the purposes of this retrospective analysis we identified patients with DDLPS diagnosed between 1991 and 2022 at the University Hospitals in Leuven by searching an institutional research database containing information on patients with mesenchymal tumors (LECTOR, reference number S51495). After obtaining ethics approval

(reference number MP024913) for the project, we collected and analyzed relevant patient data including age at diagnosis and gender, and tumor data, such as primary tumor site (retroperitoneum, trunk/head/neck, extremities, unknown), initial tumor presentation (local, locally inoperable, metastasized) and anatomical site(s) of metastasis. Patients with missing survival data were excluded from the analysis.

Locally inoperable DDLPS was defined as DDLPS without known distant metastatic spread via the blood vessels or the lymphatic system. An inoperable DDLPS (retroperitoneal or elsewhere in the body) was considered locally advanced disease. Metastatic DDLPS was defined as DDLPS with documented distant metastases. A relapse of retroperitoneal DDLPS after earlier surgery with or without radiotherapy was considered as local relapse. Site of metastasis was here defined as the number of organs affected by metastasis.

For local disease data on the treatment of the primary tumor (type of surgery, completeness of resection, radiotherapy, perioperative systemic treatment) and about local and metastatic relapse were collected. Primary surgery was defined as surgery on the primary tumor, without any evidence of metastatic disease. For locally inoperable and metastatic disease we collected information about palliative systemic treatments, progression and best response. Perioperative systemic treatment for local disease was not considered as first line systemic treatment for advanced disease. The assessment of best response to systemic treatment was based on patient records. We did not review historical radiological images for the purpose of this retrospective, mainly descriptive analysis.

OS was defined as the interval between the date of diagnosis of DDLPS as indicated in the patient file and the date of death (all-cause mortality). Progression-free survival (PFS) was calculated as the interval between the start of a systemic treatment and the date of reported progression.

The Kaplan Meier method was used for estimating mOS and mPFS. Cox regression models were used to estimate the prognostic effect of baseline characteristics. Metastasis and local relapse were analyzed as time-varying predictors, and data were analyzed using a counting process data format. Results are presented as hazard ratios with 95% CI. P-levels < 0.05 were considered as statistically significant. mOS could not be estimated for time-varying variables (metastasis and local relapse). Analyses were performed using SAS software (version 9.4 of the SAS System for Windows).

Results

Patient and tumor characteristics

We identified 264 patients with DDLPS. Five patients were excluded because of missing survival data, so we included 259 patients in this analysis. They had a median age at diagnosis of 61.6 years (range 24–89). There was a slight male predominance (57.5%).

Primary tumor sites were located in the retroperitoneum (123/259 patients, 47.5%), head and neck and trunk [without retroperitoneum] (87/259 patients, 33.6%) and extremities (47/259 patients, 18.1%). In two cases the primary origin of the tumor was unknown (0.8%), both of them had synchronous metastasis.

At time of the diagnosis 28/259 patients (10.8%) presented with locally inoperable disease and 26/259 (10.0%) with synchronous metastasis. During the course of the disease, 114/259 patients (44.0%) presented with a local relapse after initial local treatment. The mean interval between the first local treatment and local relapse was 35.5 months (range 1.7-196.5 months).

A total of 80/259 patients (30.9%) developed metachronous metastasis, and 48/259 patients (18.5%) developed both local relapse and metachronous metastatic disease. The mean interval between the first local treatment and metachronous metastatic relapse was 40.1 months (range 1.6-170.6 months).

In total 106/259 patients (40.9%) had metastatic disease, either at diagnosis or later during the further evolution of the disease. At first diagnosis of metastasis 64/106 patients (60.4%) had only one organ affected by metastasis, 42/106 (39.6%) had two or more metastatic sites. The most frequent anatomical sites of metastasis were lung (57.4% of metastatic patients), liver (17.6%), lymph node (15.7%), peritoneum (11.1%) and bone (10.2%).

The key demographics and tumor characteristics are summarized in Table 1.

Treatment of localized disease and general prognosis of localized disease

Of the 259 patients included in this analysis, 217 (83.8%) underwent surgical treatment for DDLPS during the course of their disease, the vast majority at first diagnosis (213/217 patients, 98.2%), including patients with more advanced disease. In 204/233 patients (87.6%) with local disease only at first diagnosis, primary surgery could be performed. In patients with a primary tumor localization in the extremities, 42/47 patients (89.4%) had primary surgery, whereas in the group of head and neck and trunk only 68/87 patients (78.2%) had primary surgery. In patients with retroperitoneal DDLPS 103/123 (83.7%) had primary surgery. A total of 29/233 patients with local disease at diagnosis (12.4%) did not receive primary surgery, most of them because of technical irresectability of the tumor (17/29 patients, 58.6%), but also due

Table 1 Demographics and tumor characteristics

Characteristic	Number of patients (%)
Mean age at diagnosis (years)	61.6 (24–89)
Gender	
Male	149 (57.5)
Female	110 (42.5)
Primary tumor site	
Retroperitoneum	123 (47.5)
Head and neck and trunk	87 (33.6)
Extremities	47 (18.2)
Unknown	2 (0.8)
Locally inoperable disease at diagnosis	28 (10.8)
Metastatic disease	106 (40.9)
Synchronous	26 (10.0)
Metachronous	80 (30.9)
Number of organs affected by metastasis (at first diagnosis of metastasis)	
1	64 (24.7)
≥2	42 (16.2)
Site of metastasis	
Lung	62 (23.9)
Liver	19 (7.3)
Lymph node	17 (6.6)
Bone	14 (5.4)
Peritoneum	12 (4.6)
Other	73 (28.2)[a]

[a]Others: pleural, retroperitoneal, muscles, mesenterial, omental, pancreas, abdominal wall, spleen, jejunum, colon, subcutaneous, adrenal gland, skin, breasts, spinal canal, stomach

to factors such as age/presence of comorbidities (5/29 patients, 17.2%), development of metastasis in the interval between diagnosis and surgery (4/29 patients, 13.8%) and/or the decision of the patient (3/29 patients, 10.3%). In retroperitoneal DDLPS 65/103 patients (63.1%) received a compartmental resection, this is 31.9% of all patients who received primary surgery. Other types of surgery performed in primary setting were hemicrotectomy (16/204, 7.8%), wide excision of a tumor of the extremities (39/204, 19.1%) and abdominal resection of tumor and involved organs (75/204, 36.8%). A total of 9 out of 204 patients (4.4%) had a different or unknown type of surgery. Among all patients who received primary surgery, 68/204 patients (33.3%) had a complete R0 resection, 29/204 patients (14.2%) had an R1 resection and 4/204 patients (1.2%) had an R2 resection. In 67/204 patients (32.8%) the completeness of resection could not be estimated properly on the surgical resection piece (R0/R1 resection). For 36/204 patients (17.6%) the completeness of resection was unknown.

A total of 76/114 patients (66.7%) who presented with a local relapse had subsequent surgery and 25/106 patients (23.6%) with metastatic disease had at least one metastasectomy. The most frequent site of metastasectomy was the lung (13/25 patients, 52.0%).

Table 2 Radiotherapy treatment

Radiotherapy	Number of patients	%
Any	107	100
Primary tumor		
Neoadjuvant	66	61.7
Adjuvant	30	28.0
Neoadjuvant and adjuvant	32	29.9
Definitive	2	1.9
Local relapse	31	29.0
Neoadjuvant	14	13.1
Adjuvant	17	15.9
Palliative radiotherapy	20	18.7

Radiotherapy was given in 107/259 patients (41.3%), mainly in the adjuvant (51/107, 47.7%) or neoadjuvant setting (46/107, 43.0%), both for primary tumors (66/107, 61.7%) and for relapsing DDLPS (31/107, 29.0%). Two patients (1.9%) had both neoadjuvant and adjuvant radiotherapy in primary setting. Two patients (1.9%) were treated with radiotherapy for local disease without subsequent surgery, both could not undergo surgery due to rapid development of metastasis. A total of 20/107 patients (18.7%) underwent palliative radiotherapy. The median radiation dose used for adjuvant therapy was 57 Gy (range, 45–70), in the neoadjuvant situation 49 Gy (range, 25–70) and in the palliative setting 39 Gy (range, 8–70). Hypofractionation was frequently used, especially in the palliative setting. A summary of radiotherapy treatments is given in Table 2. Only 7/204 patients (3.4%) received perioperative systemic therapy (neoadjuvant/adjuvant) for a primary, non-metastatic tumor.

In total 206/259 patients (79.5%) received local primary therapy (primary surgery and/or radiotherapy). The relapse rate after local treatment was 70.9% (146/206 patients) and relapses occurred after a median interval of 20.0 months after initiation of local treatment (range 0.6-196.5 months). A total of 93/146 patients (63.7%) had a local relapse, 41/146 patients (28.1%) developed metastatic disease and 12/146 (8.2%) had both a local and a metastatic relapse. For retroperitoneal localization the local relapse rate after primary surgery was highest (62/103 patients, 60.2%), for localization in head and neck and trunk 32/68 patients (47.1%) developed a local relapse. Patients with tumor localization in the extremities had the lowest local relapse rate after primary surgery (11/42 patients, 26.2%). After surgery alone the median time to relapse was 19.4 months (141 patients, range 0.6-196.5 months). With both surgery and perioperative radiotherapy the median time to relapse was 24.3 months (64 patients, range 2.4-142.5 months) and with radiotherapy alone (2 patients) the median time to (metastatic) relapse was only 2.1 months.

The different treatment modalities are summarized in Table 3.

Treatment and prognosis of inoperable and/or metastatic disease

In total 98 patients with inoperable or metastatic disease received at least one line of palliative systemic therapy (39.0% of the total population, 73.2% of the patients with inoperable or metastatic disease).

The most frequently used systemic treatment regimens in first line were doxorubicin ($n=51$, 52.0%), doxorubicin-ifosfamide ($n=12$, 12.2%) and different types of experimental therapy ($n=18$, 18.4%). A complete summary of all first line therapies is shown in Table 4.

With doxorubicin monotherapy the best response was partial response in 6/51 patients (11.8%) and stable disease in another 12/51 patients (23.5%). A total of 27/51 patients (52.9%) showed disease progression as best response. In the other patients we had no information about the best response. The mPFS was 2.1 months. With doxorubicin-ifosfamide the best response was partial response in 2/12 patients (16.7%) and stable disease in 2/12 patients (16.7%), while 7/12 patients (58.3%) showed disease progression. In one other patient we had no information about the best response. The mPFS with combination treatment was 2.4 months. With experimental therapy the best response was a partial response in 4/18 patients (22.2%) and stable disease in 5/18 patients (44.4%). Another 5/18 patients (27.8%) showed disease progression as best response. In the other patients we had no information about the best response. The mPFS with experimental treatments was 5.8 months. Early progression on systemic therapy was a common observation. Some patients did not even have follow-up scan due to this.

In total 58 patients received second line palliative systemic therapy (22.0% of the entire population, 42.0% of the patients with inoperable or metastasized disease). The agents most frequently used here were trabectedin (16/58, 27.6%), ifosfamide (11/58, 19.0%), eribulin (9/58, 15.5%) and experimental therapy (11/58, 19.0%). In total 19/58 (32.8%) of those patients had stable disease and 6/58 (10.3%) had a documented partial response with second line systemic therapy. Response rates were highest in the group receiving experimental therapy, where 3/11 patients (27.3%) reached a partial response. The mPFS with all second line therapies was 2.8 months.

A total of 36 patients received third or higher line palliative systemic therapy. The therapy regimens most frequently used were trabectedin (16 patients), eribulin (13 patients) and the oral angiogenesis inhibitor pazopanib (6 patients). A total of 11 patients were treated in clinical trials. In third or higher line a partial response was seen in 8.2% of patients, stable disease as best response in 39.3% of cases.

Table 3 Surgery, radiotherapy, systemic therapy

Treatment	Setting	Number of patients, *n* (%)
Surgery	Any	217 (83.4)
	For primary tumor	213 (82.2)
	For local relapse	76 (29.3)
	Metastasectomy	25 (9.7)
Radiotherapy	Any	107 (41.3)
	Preoperative	46 (17.8)
	Postoperative	51 (19.7)
	Palliative	20 (7.7)
Systemic therapy	Any	100 (38.7)
	Preoperative	5 (1.9)
	Postoperative	7 (2.7)
	1st line palliative	98 (37.8)
	2nd line palliative	58 (22.4)
	3rd line palliative	36 (13.9)
	> 3rd line palliative	13 (5.0)

Table 4 Overview on the most frequently used first line palliative systemic therapies

First line therapy	Number of patients (%)	mPFS (months)[a]	ORR (%)[b]
Doxorubicin	51 (52.0)	2.1	11.8
Doxorubicin-ifosfamide	12 (12.2)	2.4	16.7
Experimental therapy[c]	18 (18.4)	5.8	22.2
Others[d]	17 (17.3)		

[a]median progression-free survival, counted from start of systemic treatment

[b]overall response rate

[c]Docetaxel + gemcitabine + MORAB-004/placebo, doxorubicin + olaratumab, trabectedin + tTF-NGR, brigimadlin

[d]others: trabectedin, eribulin, ifosfamide, pazopanib, liposomal doxorubicin, cisplatin-etoposide, etoposide, cyclophosphamide, doxorubicin-dacarbazine

Prognostic factors

Prognostic factors are summarized in Table 5.

In the entire cohort the mOS from first diagnosis of DDLPS to death from all causes was 70.5 months (95% CI 56.63;98.60), with a 5-year survival of 55.8% (Fig. 2). Younger patients (< 65 years) had a statistically significant better OS (mOS 135.2 months, 95% CI 81.4;166.7) then older patients (≥ 65 years, 41.3 months, 95% CI 26.8;62.9, $p<0.0001$). There was no significant difference in mOS comparing male and female DDLPS patients.

With respect to the anatomical localization of the primary tumor, retroperitoneal tumors tended to have the best mOs (77.0 months, 95% confidence interval (CI) 60.1;128.3), DDLPS of the extremities the worst (66.9 months, 95% CI 30.9;151.5), but this differences was not statistically significant.

For patients with localized disease who underwent primary surgery the mOS was 101.9 months (95% CI 75.8;135.2). Patients who had primary surgery had a

Table 5 Prognostic factors

Prognostic factor	Number	mOS (months, 95% CI)	Hazard ratio	*p* value
All patients	259	70.5 (56.6;98.6)		
Age at diagnosis			2.173 (1.565;3.019)	< 0.0001
<65 years	140	135.2 (81.4;166.7)		
≥65 years	119	41.3 (26.8;62.9)		
Gender			0.884 (0.641;1.219)	0.4531
Male	149	66.9 (42.8;103.2)		
Female	110	76.0 (56.5;101.9)		
Anatomical sites				0.3499
Retroperitoneum	123	77.0 (60.1;128.3)		
Head/neck/trunk	87	70.3 (42.5;103.8)	0.947 (0.657;1.365)	
Extremities	47	66.9 (30.9;151.5)	0.922 (0.593;1.434)	
Unknown	2	21.2 (4.90;.)	3.427 (0.835;14.063)	
Local relapse			3.689 (2.539;5.361)	< 0.0001
Yes	114			
No	145			
Metastasis			8.828 (6.405;12.166)	< 0.0001
Yes	106			
No	153			
Pattern of metastasis			2.414 (1.463;3.985)	0.0006
Metachronous	80	21.3 (9.4;26.9)		
Synchronous	26	4.9 (2.8;9.4)		
Number of sites of metastasis			1.165 (0.746;1.817)	0.5021
1	64	12.7 (6.9;26.9)		
≥2	42	9.7 (3.3;18.2)		
Primary surgery at diagnosis			0.149 (0.087;0.257)	< 0.0001
Yes	204	101.9 (75.8;135.2)		
No	28	10.9 (3.8;29.2)		
Type of surgery				0.3049
Abdominal resection	75	83.4 (62.9;123.8)		
Compartmental resection	65	135.2 (77.1;.)	0.674 (0.410;1.107)	0.1189
Excision limb	39	101.9 (43.67;.)	0.715 (0.428;1.194)	0.1997
Hemiscrotectomy	16	103.2 (56.53;.)	0.452 (0.163;1.251)	0.1261
Other/Unknown	9	. (8.8;.)	0.711 (0.257;1.968)	0.5109
Completeness of resection				0.0326
R0	68	66.4 (42.5;142.9)		
R0/1	67	130.1 (77.1;166.7)	0.774 (0.474;1.263)	0.3048
R1	29	81.4 (63.0;101.9)	1.185 (0.655;2.145)	0.5742
R2	4	9.3 (2.93;.)	5.598 (1.304;24.031)	0.0205
Unknown	36	164.8 (87.5;215.8)	0.650 (0.378;1.115)	0.1178
Perioperative radiotherapy			1.185 (0.780;1.800)	0.1996
Yes	63	76.0 (62.0;151.5)		
No	144	123.8 (83.4;146.1)		
Perioperative systemic therapy			2.397 (0.973;5.907)	0.0575
Yes	7	30.9 (8.57;.)		
No	210	98.6 (72.7;130.9)		
Type of first-line palliative systemic treatment				0.0063
Doxorubicine	51	11.9 (7.4;18.0)		
Doxorubicine-ifosfamide	12	8.7 (0.4;21.2)	1.661 (0.815;3.384)	0.1621
Experimental therapy	18	37.9 (6.70;.)	0.340 (0.152;0.758)	0.0083
Best response to first-line palliative systemic treatment				
Complete response	0	NA		
Partial response	14	16.1 (3.8–92.0)		
Stable disease	26	14.6 (1.4–61.2)		

Table 5 (continued)

Prognostic factor	Number	mOS (months, 95% CI)	Hazard ratio	*p* value
Progressive disease	47	9.7 (0.4–98.6)		
Unknown/not assessable	11	2.8 (0.4-.)		

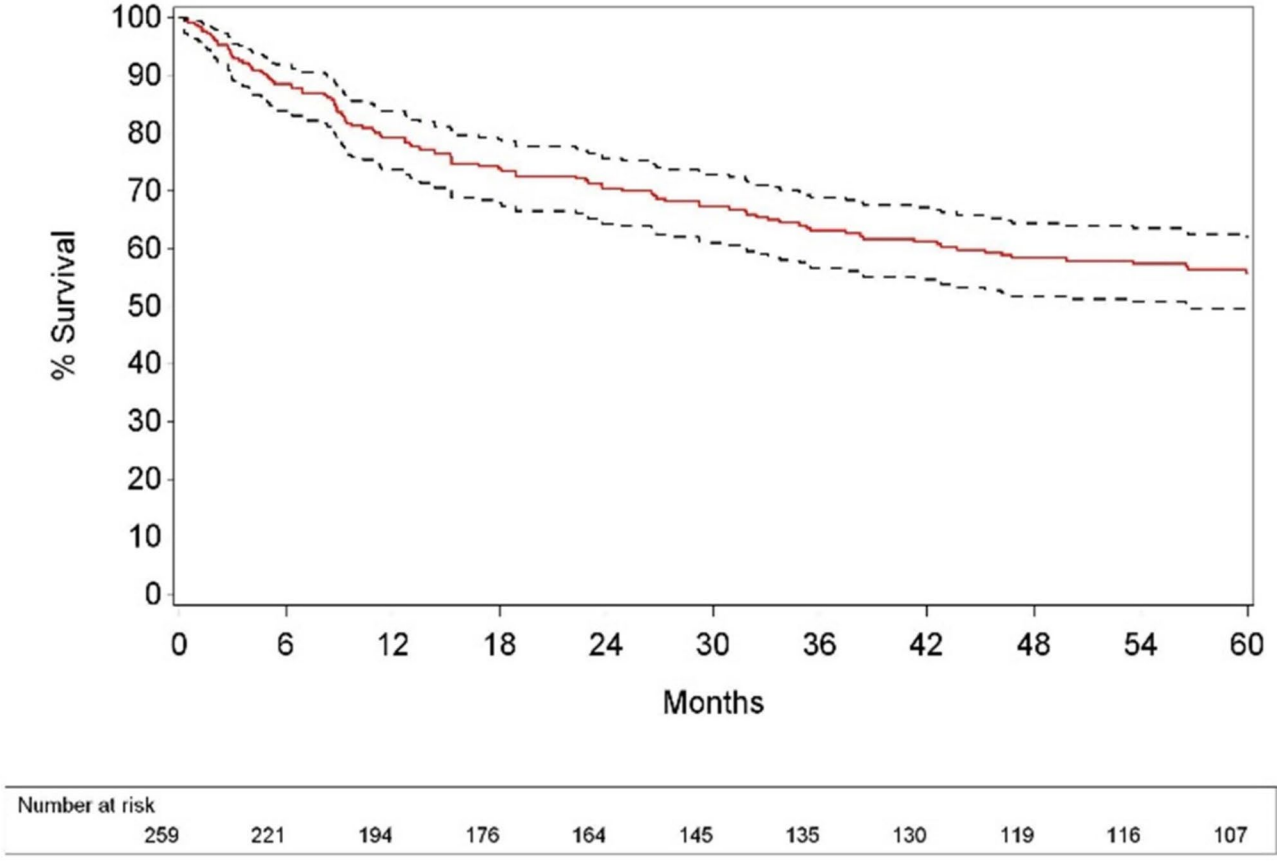

Fig. 2 Kaplan Meier estimate for overall survival of all patients (+ 95% confidence interval)

better mOS as compared to patients with no surgery for the primary tumor ($p < 0.0001$). Numerically there was a trend towards better mOS with compartmental resection than with more limited abdominal resection (135.2 versus 83.4 months), but these differences were not statistically significant. R2-resection was found to be a negative prognostic factor (p 0.0205) for mOS. There was no significant difference comparing R0-, R0/R1- and R1-resection. Perioperative radiotherapy and perioperative systemic treatment did not seem to have any statistically significant influence on OS.

For patients with inoperable disease at diagnosis mOS was only 10.9 months (95% CI 3.8;29.2). For metastatic disease the OS was 9.4 months since diagnosis of first metastasis (range 1–99 months), with a 5-year survival for these patients of only 8.3%. The mOS was significantly better in the group with metachronous metastasis then in patients with synchronous metastasis (21.3 vs. 4.9 months). The number of sites of metastasis did not seem to have an impact on the mOS. The occurrence of a local relapse after primary treatment was a poor prognostic factor is this dataset ($p < 0.0001$).

We found no difference in mOS (counted from start of first line systemic palliative treatment) comparing doxorubicin and doxorubicin-ifosfamide as first line systemic treatment for inoperable or metastatic disease (11.9 versus 8.7 months respectively, p 0.16). Experimental therapy however showed a statistically significant better mOS (37.9 months, p 0.01) as compared with doxorubicin. OS and PFS for all patients receiving first line systemic palliative treatment and for patients receiving an anthracycline-based regimen in first line is shown in Fig. 3. For all patients receiving first line systemic therapy mOS was 14.3 months (95% CI 9.2;21.2) and mPFS 3.0 months (95% CI 2.0;4.3), counted from the start of systemic treatment. For patients receiving an anthracycline-based regimen mOS was 10.4 months (95% CI 7.8;15.3) and the mPFS 2.7 months (95% CI 1.7;3.2). Best response

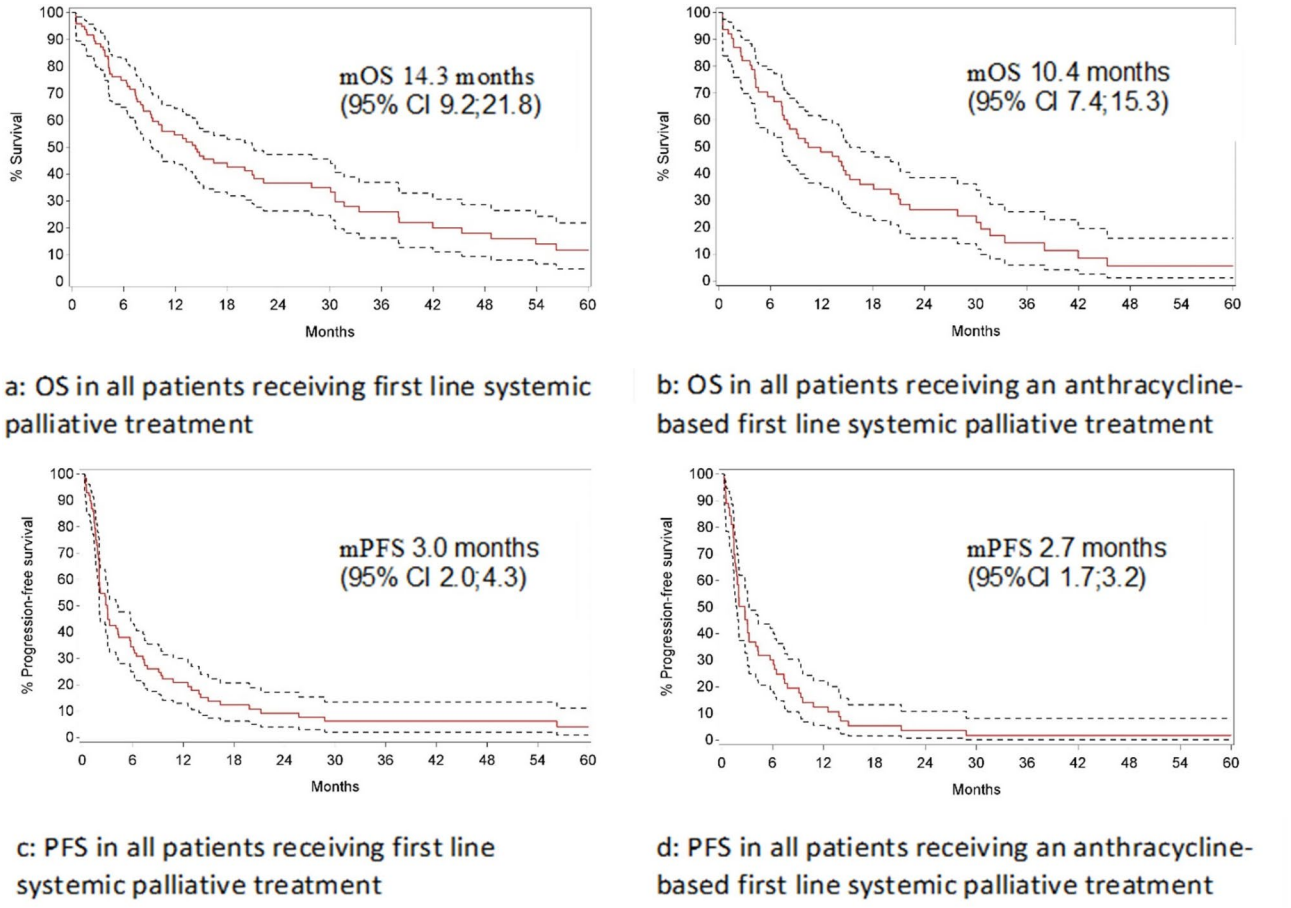

Fig. 3 Kaplan-Meier estimate for overall survival (OS) and progression-free survival (PFS) with first line systemic therapy

to first line therapy numerically seemed to influence the mOS, with partial response as a positive predictive factor. However no statistical analysis was possible, given the high risk of immortal time bias and the low number of responses.

Discussion

Liposarcoma is a heterogenous group of tumors that originate from adipocytic tissue. Most historical studies have pooled data of different subtypes of liposarcoma together, but these subtypes show very different clinical characteristics, genetic background and disease courses. In this retrospective analysis we focused on the subgroup of DDLPS.

Our demographic data were similar to those reported in the literature [5, 6, 22]. There was a slight male predominance and the median age at diagnosis of DDLPS was 61.6 years. We noticed a predilection for the retroperitoneal localization (123/259 patients, 47.5%), comparable to what has been reported in the literature [15].

DDLPS has an aggressive disease course, with a high percentage of local recurrence (114/259 patients, 44.0%) and metastasis (106/259 patients, 40.9%). In the literature the locale relapse rate was similar (41%), but the metastatic rate was lower than in our data set (15–30%) [9].

The vast majority of patients had primary surgery (204/259, 78.8%), which currently is the only curative treatment available [7]. Radiotherapy was mostly performed perioperatively in the primary setting (66/259, 25.5%), but also as perioperative radiotherapy after local relapse (31/259, 12.0%). For retroperitoneal DDLPS preoperative radiotherapy is able to prevent local abdominal relapse, especially in grade 1 and 2 disease [18, 19]. It is also commonly used to obtain better local control of primary extremity DDLPS [7]. Perioperative systemic treatment was only used in 7 patients in the primary setting (2.7%). This seems to be consistent with the literature, as there are only very limited data on perioperative systemic therapy strategies in this setting [15].

For advanced DDLPS most patients received an anthracycline-containing regimen in first line (63/98 patients, 64.3%), historically the most important agent for treatment of DDLPS [15]. There was no significant difference between single-agent treatment with doxorubicin and the combination of doxorubicin with ifosfamide. The response rate of 11.8% with doxorubicin is very similar

to response rates reported earlier in the treatment of different types of STS [23]. Interestingly the second most common therapy in first line were different kinds of experimental treatments (18/101, 17.8%). Survival was better with experimental therapy, which provides a strong rationale for inclusion of patients with DDLPS in clinical trials, also in early treatment lines. Of note, the assessment of response to experimental treatment in trials was based on established criteria such as Response Evaluation Criteria in Solid Tumors (RECIST). Response data in those patients were therefore more objective than in patients treated in clinical routine. In third or higher line 6 patients in our dataset received pazopanib, even though this has never been formally approved for liposarcoma [24].

In the literature we have only limited data about prognostic factors for DDLPS specifically. We found a better (but not statistically significant) OS for primary localization in the retroperitoneum, compared to the extremities [7]. A possible explanation is the relatively high number of patients who received primary surgery in our data set (83.7%). We noticed a statistically better OS for younger patients (<65 years) and in patients that received primary surgery. The better prognosis in patients who received primary surgery cannot be explained by an absence of metastasis, since only patients with localized disease at diagnosis were included in this analysis. These prognostic factors have been described previously [15]. Compartmental resection showed a trend towards better OS, compared with more limited abdominal surgery, but this was not statistically significant. R2-resection had a significantly worse prognosis compared to R0-resection, but there was no significant difference found between R0- and R1-resection, even though data in the literature show completeness of resection is an important prognostic factor [15]. There was a numerical advantage in mOS for R0/R1-resection (retroperitoneal localization), this was probably again related to the application of compartmental resection, where the pathology report cannot assess the completeness of resection accurately (R0/R1) because of the size of the resection piece. Local relapse rates were highest for retroperitoneal tumors, and lowest in tumors of the extremities. Perioperative radiotherapy or perioperative systemic therapy did not significantly alter the survival rates, but there was a trend towards poorer survival after perioperative systemic therapy, probably due to selection of more advanced cases. For advanced disease, the main determinant of survival seemed to be the response to first line palliative systemic treatment, even though these data may have been affected by immortal time bias [25]. In the literature larger tumor size is a known poor prognostic factor [15]. Because of too many missing data on primary tumor size, it was not possible to analyze this factor in our cohort.

Our study does have inherent limitations. The most important limitation is its retrospective character, with a potential impact of reporting and selection bias. Prospective data are required to evaluate the added value of radiotherapy or systemic therapy in the perioperative setting and to identify the best first line systemic treatment. We also cannot exclude that changes in practices over the past three decades may have influenced the prognosis over time. On the other hand, we do believe that our study can contribute to the understanding of this prevalent subtype of liposarcoma, especially given the relatively large sample size.

Conclusions

DDLPS is a subtype of STS with an aggressive clinical course and very poor prognosis, especially in patients with inoperable or metastatic disease. The results with classic chemotherapy are poor, and experimental treatments may be a preferred choice for individual patients. Data from this retrospective series can inform the design of future prospective and ongoing trials in this setting.

Abbreviations

STS	soft tissue sarcoma
DDLPS	dedifferentiated liposarcoma
MDM2	murine double minute 2
CDK4	cyclin-dependent kinase 4
HR	hazard ratio
mOS	median overall survival
mPFS	median progression free survival
CI	confidence interval
RECIST	response evalution criteria in solid tumors
ORR	overall response rate

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Author contributions

J.C. and P.S. helped with the concept and design of the study, acquisition of data, analysis and interpretation of data, drafting and revising article. I.T. and A.L. helped with the acquisition of data, analysis and interpretation of data, preparation of Figs. 2 and 3. D.H., T.D., R.S., M.C. and H.W. helped with the acquisition of data, analysis and interpretation of data, drafting and revising article. All authors reviewed and approved the manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

For this retrospective analysis we used an institutional research database at the University Hospitals of Leuven, containing information on patients with mesenchymal tumors (LECTOR, reference number S51495), after obtaining ethics approval from our institutional ethics committee: Research Ethics Committee UZ/KU Leuven (reference number MP024913). The Committee confirms that they work in accordance with the ICH-GCP principles (International Conference on Harmonisation Guidelines on Good Clinical

Practice), with the most recent version of the Helsinki Declaration, and with applicable laws and regulations. Informed consent from individual participants was deemed unnecessary according to this framework.

Consent for publication
Not applicable.

Competing interests
PS has a consulting or advisory role at Ellipses Pharma, Deciphere, Transgene, Exelixis, Boehringer Ingelheim, Studiecentrum voor Kernenergie, Adcendo, PharmaMar, Merck Healthcare KGaA, Medpace, Cogent Biosciences, Eisai, Curio Science, LLX Solutions, SERVIER, Genmab, Sanofi, Regeneron, Moleculin Biotech, Avacta Life Sciences, Amryt Pharma, UCB, Boxer Capital, NEC OncoImmunity AS, Sonata Therapeutics, IDRx, Telix Pharmaceuticals. He received research funding from CoBioRes NV, Eisai, G1 Therapeutics, PharmaMar, Genmab, Merck, Sartar Therapeutics, ONA Therapeutics, Adcendo. The other authors declare that they have no competing interests.

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