Malignant adipocytic tumours: A 20-year single-centre retrospective study

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Abstract. Adipocytic tumours are the most common soft tissue neoplasms. Among them, liposarcoma is the most frequent malignant neoplasm. However, to the best of our knowledge, no previously published study has assessed the evolution and oncological prognosis of the different subtypes of liposarcoma at the retroperitoneal level compared with at other locations. The present study is a retrospective observational study in which all patients were operated on between October 2000 and January 2020 with a histological diagnosis of liposarcoma. Variables, such as age, sex, location, histological type, recurrence, type of treatment and mortality, among others, were analysed. The patients were divided into two groups: Group A (retroperitoneal location) and group B (non-retroperitoneal location). A total of 52 patients with a diagnosis of liposarcoma (17 women and 35 men) and a mean age of 57.2±15.9 years were assessed. A total of 16 patients were classified into group A and 36 into group B. The OR of recurrence was 1.5 (P=0.02) for R1 vs. R0 resection in group A. The OR of recurrence in group B for R1 vs. R0 resection was 1.8 (P=0.77), whereas for R2 vs. R0 resection, the OR was 69 (P=0.011). In conclusion, 52 cases of malignant adipocytic tumours collected during 2000-2020 were analysed with the new World Health Organization classification (updated 2020). Although its recurrence potential and capacity for distant metastasis depended on each histological type, surgical treatment with unaffected margins was the main prognostic factor for survival. The present study identified differences in relation to the survival of each histological subtype and its location, finding greater survival in dedifferentiated liposarcoma, myxoid liposarcoma and pleomorphic liposarcoma located at the extraperitoneal level than in the retroperitoneal location. Resectability was not influenced by liposarcoma location.

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Abbreviations: WHO, World Health Organization; WDL/ATL, atypical/well-differentiated liposarcoma; DDL, dedifferentiated liposarcoma; MLP, myxoid liposarcoma; PLP, pleomorphic liposarcoma; MRI, magnetic resonance imaging; CT, computed tomography; MDM2, murine double minute-2

Key words: liposarcoma, dedifferentiated, retroperitoneal sarcoma, soft tissue tumours, local recurrence

Introduction

Lipomatous tumours represent a category of neoplasms with a broad spectrum and clinical behaviour (1). Liposarcomas are the most common malignant tumours of soft tissue of mesenchymal origin (2,3). They can be located in any part of the body with fatty tissue (4).

Several histological types have been described and their classification has changed over the last two decades, with new clinical entities appearing. The importance of diagnosis after histology is relevant to predict tumour behaviour and prognosis.

From the first description by Rudolf Virchow in 1857 of a tumour originating from adipose tissue with mixed features, which he called 'myxoma lipomatodes lesion', to the current concept of liposarcoma, several classifications have emerged (5-7) (Table I). Currently, the fifth WHO

classification of Tumors of Soft Tissue and Bone, published in 2020, establishes atypical lipomatous tumour as a tumour of intermediate grade of malignancy and well-differentiated liposarcoma (WDL) with its variants (lipoma-like, sclerosing and inflammatory), dedifferentiated liposarcoma (DDL), myxoid liposarcoma (MLP) and pleomorphic liposarcoma (PLP) as malignant adipocytic tumours. It also introduces two histological subtypes not described in the previous classifications: atypical spindle cell/pleomorphic lipomatous tumour (ASC) and pleomorphic myxoid liposarcoma (MP) (8,9). While ASC originates as a superficial lipomatous mass predominantly in the extremities with a low recurrence rate, distant metastasis as well as dedifferentiation phenomena, MP is characterised by large lesions predominantly in young patients, located in the mediastinum with a highly aggressive character (high local recurrence, distant metastatic capacity with affinity for lung and bone and low survival rate) (10-12).

WDL/ATL together with DDL represent the most frequent types of liposarcoma. WDL/ALT accounts for 40% of all liposarcomas (3,13). The terms WDL and ALT are used interchangeably to refer to tumours with identical histology but different anatomical location. According to the WHO classification of these lesions, ALT will be used for those liposarcomas located in the extremities or superficial trunk while WDL would be reserved for those located in the retroperitoneum, mediastinum or paratesticular (14).

We present a series of patients operated on in our centre, carrying out a descriptive and analytical statistical analysis with the aim of studying the main prognostic factors of these tumours with respect to recurrence and survival.

Materials and methods

Retrospective observational study. All patients operated on at the Hospital Universitario Príncipe de Asturias de Alcalá de Henares in Alcalá de Henares, Madrid, Spain, during the period from October 2000 to January 2020 were collected.

Due to changes in the WHO classification of bone and soft tissue tumours, the Anatomical Pathology Department was asked to review the tissues and their classification according to the fifth WHO classification.

The inclusion criteria were: final histological diagnosis of liposarcoma (any of its variants), resected disease with curative intent and patients over 18 years of age. Patients with a previous history of liposarcoma and those with soft tissue lesions in which immunohistochemical or molecular studies were negative for liposarcoma were excluded. In addition, other soft tissue tumours such as solitary fibrous tumour, soft tissue sarcomas, gastrointestinal stromal tumours or lipomas were excluded.

The diagnosis of liposarcoma was determined by the Department of Pathology, through the microscopic and macroscopic study of the submitted specimen. To distinguish between the different histological subtypes (WDL/ALT, DDL and MLP) the determination of murine double minute-2 (MDM2) and cyclin-dependent kinase 4 (CDK4) was performed. The amplification of MDM2 and CDK4 was based on fluorescence *in situ* hybridization (FISH) analysis (15). Prior to 2016, we did not have this amplification technique in our centre, so it has only been determined in the cases of establishing the differential diagnosis of the histological subtype from that year on in the study patients. The determination of the Ki-67 cell replacement index was performed by immunohistochemistry, using MIB-1 monoclonal assays, specific for the Ki67 nuclear protein (16). To carry out the evaluation of the immunohistochemical expression of Ki-67, three random fields of representative sections of each lesion were selected. The positive cell count was performed using a x400 magnification microscope objective. After, all visualized brown nuclear staining was interpreted as positive immunohistochemical expression for Ki67. The total cells of each cell population and the number of stained cells were counted, in order to obtain the total percentage of stained cells per cell population and a total percentage of the expression of each marker of the analyzed specimen.

Variables. Epidemiological variables (age, sex, comorbidities), location of the lesion, form of presentation, diagnosis, tumour size, histological subtype, degree of differentiation, as well as those related to the surgical intervention (average length of stay, associated surgery, recurrence, type of recurrence, relapse, presence of distant metastasis or type of surgical resection) or type of adjuvant treatment were collected. All variables were collected in a Microsoft Excel 2020® spreadsheet.

The odds ratio (OR) was calculated to describe the risk the recurrence from histology tumour or type of surgery (R0/R1/R2 resection). The OR determines an estimate (with confidence interval) for the relationships between dichotomic variables. The significance level used to calculate the confidence level was 0.05 (alpha level), which indicates a confidence level of 95%. Fisher's test was used to study whether there was an association between two qualitative variables.

In the case of categorical variables, the proportion of each category with respect to the total number of patients was calculated. For qualitative variables, the distribution of phenomena was studied, while for quantitative variables, the mean and standard deviation were studied.

Survival (calculated in months) of the patients included in the study was estimated using the Kaplan-Meier method. It was performed both for patients with a histological diagnosis of WDL/ALT based on their location (retroperitoneal vs. non-retroperitoneal), to compare patients with histology other than WDL/ALT (non-WDL/ALT, which includes DDL, PLP and MLP) depending on its location (retroperitoneal or non-retroperitoneal) and to compare survival regardless of the histological subtype of liposarcoma, establishing location as a variable (retroperitoneal and non-retroperitoneal).

Ethical approval. The present study was approved by the Ethics Committee of the Fundación para la Investigación del Hospital Universitario Príncipe de Asturias (protocol number: OE 49/2020) on 23rd February 2021, with a favourable opinion, exempting the informed consent of the patients included as it was a retrospective study.

Results

Patients. Fifty-two patients (17 females (59.3±13.7) and 35 males (57.1±16.7 years) diagnosed with liposarcoma in the described period were studied. The overall mean age was 57.2±15.9 years.

Table I. Evolution of the WHO classification of liposarcomas.

1994	2002	2013	2020
	Intermediate aggressiveness		Intermediate aggressiveness
Well-differentiated liposarcoma	Well-differentiated liposarcoma	Well-differentiated liposarcoma	Well-differentiated /atypical lipomatous tumour (WDL/ALT)
Adipocyte lipoma-like			Malignant adipocytic tumours
Sclerosing	Malignant adipocytic tumours		Adipocyte lipoma-like
Inflammatory			Inflammatory
Myxoid liposarcoma	Myxoid liposarcoma	Myxoid liposarcoma	Myxoid liposarcoma
Round cell liposarcoma			Sclerosing
Pleomorphic liposarcoma	Pleomorphic liposarcoma	Pleomorphic liposarcoma	Pleomorphic liposarcoma
Dedifferentiated liposarcoma	Dedifferentiated liposarcoma	Dedifferentiated liposarcoma	Dedifferentiated liposarcoma
			Atypical spindle cell[a]
			Pleomorphic myxoid liposarcoma[a]

[a]New histological subtypes.

In the study we decided to divide patients into two groups according to location (group A (retroperitoneal location) and group B (non-retroperitoneal location, dependent on superficial fatty tissue).

Group A (retroperitoneal location) consisted of 16 patients (30.7%). Within group B, the most frequent locations were: lower limb (22 patients; 42.3%), upper limb (5 patients; 9.6%), dorsal (2 patients; 3.8%), inguinal (4 patients; 7.7%), head and neck (2 patients; 3.8%) and perianal (1 patient; 1.9%).

Retroperitoneal location. Group A consisted of 16 patients (mean age 60.6±13.3 years), divided into 6 males (mean age 61.7±16.1 years) and 10 females (mean age 60±12.3 years). The clinical characteristics in relation to presentation, diagnosis, tumour size, degree of differentiation and histology are shown in Table II. In all patients the diagnosis was made by CT scan with intravenous contrast. In only 2 patients, MRI was performed as an adjunct (12.5%).

Histopathological study revealed 6 atypical/well differentiated liposarcomas (WDL/ATL), 37.5%, 5 dedifferentiated (DDL), 31.2%, 4 myxoid liposarcomas (MPL) (25%) and 1 pleomorphic liposarcoma (PLP) (6.2%).

Regarding histology, we observed that the mean age of presentation for WDL/ATL was 56.3±14 years (67% men), DDL was 65±14.8 years (20% men), PLP 46 years (100% male) and MLP of 65.25±10.2 years (100% female).

Three patients died during follow-up (18.7%) related to disease progression. Surgery was a complete resection with unaffected surgical margins (R0) in 9 patients (56.2%) and with microscopic involvement (R1) in 7 patients (43.7%). No surgical resections with macroscopically affected margins (R2) were described. The mean length of stay was 12.62±6.3 days.

In 87.5% (14 patients), surgery required at least one visceral resection due to tumour involvement. A colectomy (right or sigmoidectomy) was associated in 9 patients (56.2%), 1 nephrectomy (6.2%), 1 orchiectomy (6.2%), 1 adrenalectomy (6.2%) and 2 splenectomies (12.5%).

Overall survival was 61.4±57.2 months. Regarding histological type survival was 71.4±56.5 months (WDL/ATL), 22.7±7.5 months (DDL), 100.1±78.2 months (MLP) and 41.3 months (PLP).

Six patients had recurrence (3 WDL/ATL and 3 LPM) after surgery (37.5%), 3 of them died during follow-up. The overall disease-free interval was 29.8±12 months. A disease-free interval of 36.1±13.8 months was observed for WDL/ATL and 23.5±7.3 months for MLP (Fig. 1).

The OR was calculated as a function of recurrence in relation to histology (OR (WDL/ATL) 1.3 (95% CI P=0.736) and OR (MLP) 2 (95% CI P=0.441). The OR for recurrence was 1.5 (95% CI P=0.02) for R1 vs. R0 resection.

All patients in whom recurrence was described, it was detected locally in the peritoneum where the original tumour was located. Only 1 patient showed pulmonary metastasis. Three patients received adjuvant treatment with systemic chemotherapy (first-line adriamycin-based regimens). Only one patient received intraperitoneal hyperthermic chemotherapy with doxorubucin in conjunction with cytoreduction surgery. Of the two patients with local recurrence, one underwent salvage surgery and is currently free of disease, while the other patient was not considered for further treatment due to advanced age.

Non-retroperitoneal location. Group B consisted of 36 patients (mean age 57.2±15.9 years), divided into 17 females (mean age 58.9±14.8 years) and 19 males (53.6±17.1 years). The characteristics of each liposarcoma (diagnostic presentation, size, grade and histology) are listed in Table II.

In 16 patients MRI was sufficient to approximate the diagnosis and to study the relationship with neighbouring

Table II. Clinical features of patients with retroperitoneal and non-retroperitoneal liposarcomas.

Patient	Sex	Age, years	Location	Clinical presentation	Group	Diagnosis	Size, cm	Histology
Patient 1	Female	45	Retroperitoneal	Tumour	Group A	CT	22x16	WDL/ALT
Patient 2	Male	69	Upper limb	Tumour	Group B	US	7x6x3	WDL/ALT
Patient 3	Male	33	Upper limb	Tumour	Group B	CT + US	7x8	MLP
Patient 4	Male	53	Upper limb	Tumour	Group B	CT	6	PLP
Patient 5	Female	47	Upper limb	Local pain	Group B	MRI	9X6	WDL/ALT
Patient 6	Male	63	Lower limb	Tumour	Group B	US	10x8x5	WDL/ALT
Patient 7	Female	47	Back	Tumour	Group B	US	7.5x3.2x3.7	WDL/ALT
Patient 8	Male	49	Back	Tumour	Group B	US	14x6.5x2	WDL/ALT
Patient 9	Female	54	Lower limb	Tumour	Group B	US	3x3x1.5	WDL/ALT
Patient 10	Male	43	Lower limb	Tumour	Group B	US	6x4x3.5	WDL/ALT
Patient 11	Female	41	Upper limb	Tumour	Group B	US	7x3.5x3	WDL/ALT
Patient 12	Male	82	Lower limb	Tumour	Group B	US	10	WDL/ALT
Patient 13	Male	69	Lower limb	Tumour	Group B	CT+MRI	11x9x8	MLP
Patient 14	Male	81	Lower limb	Tumour	Group B	CT	15x10x8	WDL/ALT
Patient 15	Female	57	Retroperitoneal	Tumour	Group A	CT	15x9	MLP
Patient 16	Female	28	Lower limb	Tumour	Group B	US + MRI	20x10x15	WDL/ALT
Patient 17	Male	22	Lower limb	Tumour	Group B	MRI	8x5x2	MLP
Patient 18	Female	50	Lower limb	Tumour	Group B	CT + MRI	10x5.5	MLP
Patient 19	Female	63	Lower limb	Tumour	Group B	MRI	13x6x2	MLP
Patient 20	Female	71	Lower limb	Tumour	Group B	MRI	20x13x6	WDL/ALT
Patient 21	Male	54	Lower limb	Tumour	Group B	US + MRI	18x10x10	WDL/ALT
Patient 22	Male	40	Lower limb	Tumour	Group B	US + MRI	19x11x8	MLP
Patient 23	Female	49	Lower limb	Tumour	Group B	US + MRI	12.5x8.5x7	WDL/ALT
Patient 24	Female	65	Lower limb	Tumour	Group B	CT	11x6x3	WDL/ALT
Patient 25	Female	84	Lower limb	Tumour	Group B	MRI	21x17x7	MLP
Patient 26	Male	41	Lower limb	Tumour	Group B	US	11x5	DDL
Patient 27	Female	61	Lower limb	Tumour	Group B	US	4x1.2x1	PLP
Patient 28	Female	69	Lower limb	Tumour	Group B	MRI	12.4x10.3	PLP
Patient 29	Male	58	Lower limb	Tumour	Group B	MRI	24x19x3	WDL/ALT
Patient 30	Female	68	Lower limb	Tumour	Group B	US	7x6x4	WDL/ALT
Patient 31	Female	58	Lower limb	Local pain	Group B	MRI	11x9x5	WDL/ALT
Patient 32	Female	86	Lower limb	Tumour	Group B	MRI	23x12x16	WDL/ALT
Patient 33	Female	61	Lower limb	Tumour	Group B	MRI	9x4	WDL/ALT
Patient 34	Male	71	Perianal	Tumour	Group B	MRI	8x6x3	WDL/ALT
Patient 35	Male	33	Lower limb	Tumour	Group B	MRI	8x3x1	MLP
Patient 36	Male	58	Cervical	Tumour	Group B	US	3.3x2.5x2	MLP
Patient 37	Male	62	Cervical	Tumour	Group B	US	5x5x3	WDL/ALT
Patient 38	Female	72	Retroperitoneal	Abdominal pain	Group A	CT + US	20x13x10	MLP
Patient 39	Female	56	Retroperitoneal	Tumour	Group A	CT	28x25x15	MLP
Patient 40	Female	49	Retroperitoneal	Tumour	Group A	CT	24.5x16x6	WDL/ALT
Patient 41	Female	76	Retroperitoneal	Tumour	Group A	CT	9x6.5x7	MLP
Patient 42	Male	82	Retroperitoneal	Incidental	Group A	CT	4x2x2	WDL/ALT
Patient 43	Male	45	Retroperitoneal	Tumour	Group A	CT	14x13x4	WDL/ALT
Patient 44	Male	58	Retroperitoneal	Abdominal pain	Group A	CT + MRI	16x11x13	WDL/ALT
Patient 45	Male	46	Retroperitoneal	Tumour	Group A	CT	33x20x15	PLP
Patient 46	Male	80	Retroperitoneal	Ascites	Group A	CT	25x18x12	DDL
Patient 47	Female	64	Retroperitoneal	Anaemia	Group A	CT	21x18x13	DDL
Patient 48	Male	59	Retroperitoneal	Tumour	Group A	CT	8x7x7.5	WDL/ALT
Patient 49	Female	42	Retroperitoneal	Asthenia	Group A	CT + US	20x12x8	DDL

Table II. Continued.

Patient	Sex	Age, years	Location	Clinical presentation	Group	Diagnosis	Size, cm	Histology
Patient 50	Female	76	Retroperitoneal	Abdominal pain	Group A	CT + US	12x10x3	DDL
Patient 51	Female	63	Retroperitoneal	Abdominal pain	Group A	CT + MRI	18x15x12	DDL
Patient 52	Male	76	Testicular	Tumour	Group B	US	3x3x2	DDL

CT, computed tomography; US, ultrasound; MRI, magnetic resonance imaging; WDL/ALT, well-differentiated/atypical lipomatous tumour; DDL, dedifferentiated liposarcoma; PLP, pleomorphic liposarcoma; MLP, myxoid liposarcoma.

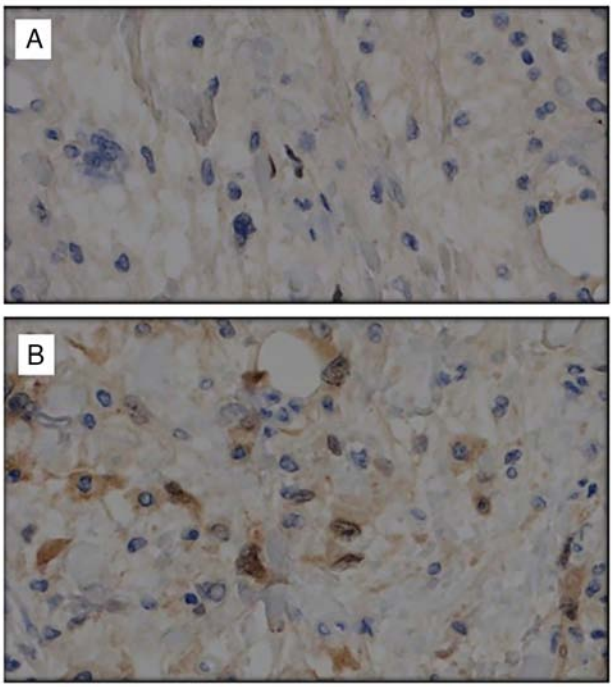

Figure 1. Atypical/well differentiated liposarcoma. (A) Immunohistochemical study, these cells express CDK4 focally. (B) Immunohistochemical study, these cells express MDM2 focally and CDK4 diffusely. CDK4, cyclin-dependent kinase 4; MDM2, murine double minute-2.

structures. In 6 patients, CT was performed, while ultrasound was performed in 9 patients as the only imaging test. Only 9 patients underwent surgery without imaging.

Histopathological study revealed 22 atypical/well-differentiated liposarcomas (WDL/ATL), 61%, 2 dedifferentiated (DDL), 5.5%, 9 myxoid liposarcomas (MLP) (25%) and 3 pleomorphic liposarcomas (PLP) (8.3%). Histological markers (MDM-2, CK4, Ki67) were obtained from only 20 patients (Table III).

The mean age of presentation for WDL/ATL was 59.4±14 years (45% men), DDL was 58.5±24.7 years (100% men), PLP 61±8 years (33% male) and MLP of 50.22±20.4 years (100% male).

Surgery was a complete resection with unaffected surgical margins (R0) in 22 patients (61.1%), with microscopic involvement (R1) in 12 patients (33.3%) and with macroscopic involvement (R2) in 2 patients (5.5%). In all patients in whom surgery was not an R0, margins of the surgical site were widened except in two patients (given their advanced age, 84 and 86 years respectively) and in 3 others in whom, due to the tumour location, complementary postoperative radiotherapy was decided.

The mean length of stay was 2±3.2 days. Only two patients died during follow-up in relation to progression of their oncological disease (1 patient with a history of MLP and 1 patient with PLP

The overall survival of the patients described in group B was 87.9±65.2 months. Regarding histological type survival was 62.9±45.9 months (WDL/ATL), 48.3±35.1 months (DDL), 146.0±78.7 months (MLP) and 123.4±38.6 months (PLP). Overall survival was assessed using Kaplan-Meier curves. Survival was analysed by comparing the influence of the location (retroperitoneal vs. non-retroperitoneal) of the WDL/ATL liposarcomas in our series (Fig. 2). Improved survival was observed in patients with a non-retroperitoneal location. We also analysed the survival of the two groups in relation to their location (retroperitoneal vs. non-retroperitoneal), regardless of histological type (Fig. 3). We observed that patients operated on with a diagnosis of liposarcoma located at the retroperitoneal level had a lower survival than those whose location was extraperitoneal, regardless of histological subtype. Finally, we studied the influence of location (retroperitoneal vs. non-retroperitoneal) without taking WDL/ATL histology into account, defining a group (non-WDL/ATL) made up of DDL, PLP and MLP histologies (Fig. 4). In our study, we found that survival was lower in those patients who underwent surgery with a diagnosis of liposarcoma located at the retroperitoneal level in relation to the DDL, MLP and PLP subtypes compared to extraperitoneal location.

During follow-up only 2 recurrences with two deaths were described. The recurrence interval in these patients was 100.4±72.7 months. One patient was treated with postoperative radiotherapy and the other patient was treated with chemotherapy (several lines of treatment; adriamycin, trabectadine and ifosfamide), with progression of the disease at the pulmonary level and death of both patients. In relation to recurrence, the relative risk was analysed according to histological type: OR (MLP): 7.73 (P=0.225) and OR (PLP): 21 (95% CI P=0.07) as well as the type of surgical resection: OR (R1): 1.8 (95% CI P=0.77) and OR (R2): 69 (95% CI P=0.001).

Table III. Histological markers (MDM-2, CK4, Ki67) of liposarcomas.

Patient	MD M2	CD K4	Sex	Age, years	Location	Group	Grade (FNC LCC)	Histological subtype	Ki67
Patient 7	(+)	(-)	Female	47	Back	Group B	1	WDL/ALT	1%
Patient 8	(+)	(-)	Male	49	Back	Group B	1	WDL/ALT	Not performed
Patient 11	(-)	(-)	Female	41	Upper Limb	Group B	1	WDL/ALT	Not performed
Patient 14	(-)	(+)	Male	81	Lower Limb	Group B	2	WDL/ALT	5-10
Patient 20	(-)	(+)	Male	71	Perianal	Group B	1	WDL/ALT	<1%
Patient 21	(+)	(+)	Female	54	Lower Limb	Group B	1	WDL/ALT	<1%
Patient 23	(-)	(+)	Female	49	Lower Limb	Group B	1	WDL/ALT	<1%
Patient 27	(+)	(+)	Female	61	Lower Limb	Group B	1	WDL/ALT	5%
Patient 29	(+)	(+)	Male	58	Retroperitoneal	Group A	2	WDL/ALT	20-25%
Patient 30	(-)	(+)	Female	68	Lower Limb	Group B	1	WDL/ALT	<1%
Patient 32	(-)	(+)	Female	86	Lower Limb	Group B	1	WDL/ALT	<1%
Patient 37	(+)	(+)	Male	62	Retrocervical	Group B	1	WDL/ALT	<1%
Patient 45	(+)	(+)	Male	46	Retroperitoneal	Group A	2	PLP	Not performed
Patient 46	(+)	(+)	Male	80	Retroperitoneal	Group A	3	DDL	70%
Patient 47	(+)	(+)	Female	64	Retroperitoneal	Group A	2	DDL	12-16%
Patient 48	(+)	(+)	Male	59	Retroperitoneal	Group A	1	WDL/ALT	6-9%
Patient 49	(+)	(+)	Female	42	Retroperitoneal	Group A	2	DDL	20%
Patient 50	(+)	(+)	Female	76	Retroperitoneal	Group A	1	DDL	Not performed
Patient 51	(+)	(+)	Female	63	Retroperitoneal	Group A	2	DDL	0.02%
Patient 52	(+)	(+)	Male	76	Testicular	Group B	2	DDL	Not performed

MDM2, murine double minute-2; CDK4, cyclin-dependent kinase 4; WDL/ALT, well-differentiated /atypical lipomatous tumour; DDL, dedifferentiated liposarcoma; PLP, pleomorphic liposarcoma.

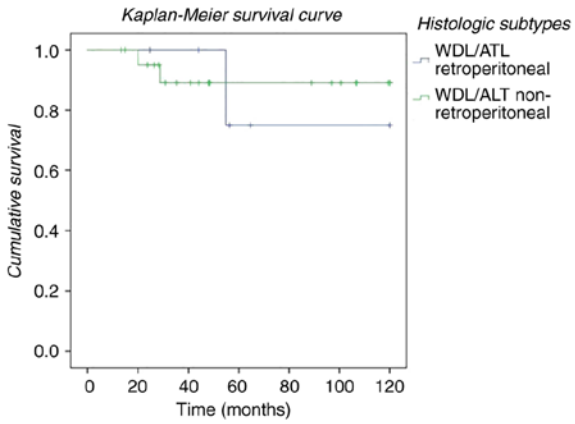

Figure 2. Kaplan-Meier survival curve of non-retroperitoneal WDL/ALT and retroperitoneal WDL/ALT liposarcomas. WDL/ALT, well-differentiated liposarcoma/atypical lipomatous tumour.

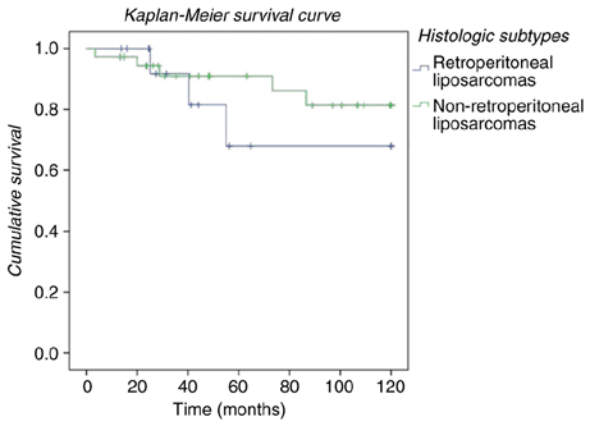

Figure 3. Kaplan-Meier survival curve of retroperitoneal and non-retroperitoneal liposarcomas.

Discussion

Liposarcoma is the most common mesenchymal malignancy of soft tissue. They can be located in any part of the body where there is fatty tissue (17). They all have lipoblasts (hyperchromatic cells with indented nucleoli and vacuolated cytoplasm) that can complete adipogenesis like their predecessor the adipocyte (18).

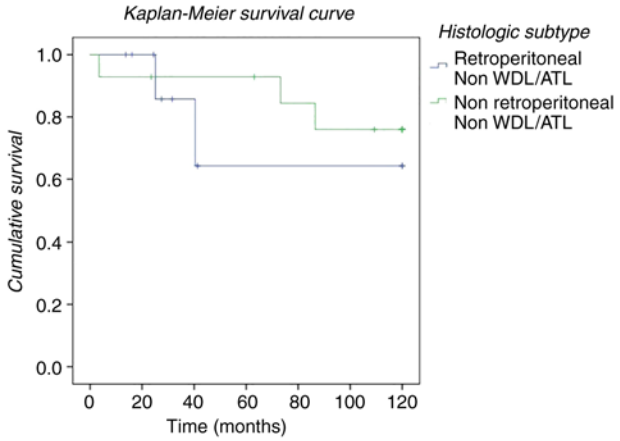

Figure 4. Kaplan-Meier survival curve of non-WDL/ALT and WDL/ALT liposarcomas. WDL/ALT, well-differentiated liposarcoma/atypical lipomatous tumour.

Genetic and molecular alterations in liposarcomas have been described. The most frequently described alterations are amplifications in the 12q 13-15 region that involve the MDM2 and CDK4 genes and that have implications not only for establishing the diagnosis of malignancy but also for the prognosis of this tumours.

Each type of liposarcoma is associated with its own genetic mutation and histopathological findings (19). WDL and DDL are associated with a high level of 12q.13.15 amplifications as well as MDM2 and CDK4 positivity (3) (Fig. 1). (DDL also has amplifications of 6q23 and 1p32), while the myxoid type lacks these in favour of expressing FUS/EWSR1-DDIT3) (8). In our series, the possibility to perform MDM2 and CDK4 determination became available in 2016, so it was only obtained in 20 patients (Table III). These immunohistochemical techniques serve to establish the differential diagnosis between the different types of LPS. Thus, co-expression of MDM2 and CDK4 is very common in DDL. In our series, all DDL that underwent immunohistochemistry against MDM2 and CDK4 were positive. However, only 38% expressed both proteins in WDL (20,21).

DDL can arise spontaneously or be the result of malignant transformation of a pre-existing WDL/ALT. It accounts for 18% of all liposarcomas and is up to 5 times more frequent in the retroperitoneum than in the extremities. In our series, we found a greater number of cases of DDL in the peritoneum (31%) compared to the extraperitoneal location (5.5%). This could be explained by the fact that undifferentiated liposarcoma (DDL) is a subtype of high-grade liposarcoma, which progresses from a previous well-differentiated liposarcoma (WDL/ATL) and this presents a higher frequency of retroperitoneal location. On the other hand, we have observed in our series a higher number of extraperitoneal WDL/ATL (61%) compared to retroperitoneal location (37.5%). This could be explained by the small number of cases in our series or by the fact that it is the most frequent extraperitoneal histology.

Unlike WDL/ALT, which has a local recurrence of less than 50%, no distant metastases and close to 100% survival, DDL has a higher potential for distant metastases (15-20%) with a predominance in the lung, recurrence rates of 40-80% and 5-year survival of 30% (1,18). While DDL and WDL/ALT occur in the sixth and seventh decade of life, MLP (<20% of all liposarcomas) is typical of younger patients (fourth and fifth decade of life), with no sex predominance and extremity location. In contrast to other liposarcomas, they have a good response to treatment with chemotherapy and radiotherapy. Finally, PLP (5-15% of all liposarcomas) occurs in older patients (seventh decade of life), predominantly in men and mainly located in the extremities (1,5).

In our series we have observed a similar distribution with respect to the age of presentation of WDL/ATL and DDL and location. MLP was found in older patients (sixth and seventh decade of life) whereas non retroperitoneal PLP were founded in seventh decade of life with female gender predisposition.

The form of presentation of these tumours is directly related to their size and location. They may present as slowly and progressively growing masses of adipose tissue (sometimes painful), while in other cases they may be an incidental finding after an imaging test, as occurs when they are located in the retroperitoneum. Symptoms such as abdominal pain, early satiety, neurological or obstructive symptoms due to compression (14).

The differential diagnosis is made both with other benign soft tissue tumours (spindle cell lipoma, inflammatory myofibroblastic tumour or even with lipomas with areas of necrosis after trauma) and with malignant tumours such as carcinomas of the gastrointestinal tract, gastrointestinal stromal tumours (GIST) or even with solitary fibrous tumour (3,14).

For diagnosis, many authors consider thoraco-abdominopelvic CT to be the gold standard, both to determine the characteristics of the tumour and to determine the presence of distant metastasis or its relationship with neighbouring structures. According to Kim and Munk, the degree of differentiation of the liposarcoma can be estimated after the CT scan. Low grade liposarcomas present as radiolucent masses while intermediate grade liposarcomas are associated with the presence of septa. High-grade liposarcomas present as heterogeneous, dense masses with contrast uptake (22,23). MRI is reserved for assessing neurovascular invasion or muscle involvement in these lesions, presenting as a hypointense signal on T1 and hyperintense on T2 (1,14). All retroperitoneal tumours were examined with CT scan in order to check the relationship with neighbouring organs. A little cases were studied by MRI. In case non retroperitoneal tumours, CT scan were not necessary and ultrasound and MRI were preferred (Table II).

In general, there is no lymphatic involvement at the time of diagnosis. Treatment is mainly surgical. However, there is no consensus on the most appropriate margin of resection for WDL/ALT of the trunk and extremities, differentiating between a marginal excision (excision of the tumour along its pseudocapsule) and a wide excision (wide excision of tissue that includes a margin of at least 1 to 2 cm of tissue or tumour-affected tissue) (13). Although recurrence described in the literature is higher after marginal excision (11.9% vs. 3.3%), there are insufficient studies that have demonstrated an increased mortality associated with recurrence. On the contrary, other authors have shown that the free margin has an impact on survival in retroperitoneal liposarcomas (19). Although it seems logical to think that an R2 resection has a higher recurrence rate than an R0 or R1 resection, authors

such as Keung *et al* describe in their work that patients with affected margins are not significantly associated with worse local recurrence, although it was associated with a higher rate of distant metastases and a lower disease-free interval (24). In our series, we did find a significant association between resection margin involvement and risk of recurrence in both series.

In contrast to patients diagnosed with non-retroperitoneal WDL/ATL, patients with retroperitoneal WDL/ATL had a shorter survival (blue line, Fig. 2). We compare both groups (retroperitoneal and non-retroperitoneal), and patients with non-retroperitoneal liposarcomas had a better overall survivor and disease free interval (Fig. 3). Finally, despite the fact that the survival of patients with DDL, MLP, or PLP histology is lower than patients with WDL/ATL, we observed that survival in this group was higher in patients with extraperitoneal location (Fig. 4).

Other manuscripts describe an overall survival of up to 70% after R0 or R1 resection compared to those patients undergoing R2 (16%) (4). In our study, patients who underwent surgery for liposarcoma in a non-retroperitoneal location (R1 resection) had 100% survival compared to those who underwent R2 resection (0% survival). At the retroperitoneal level, the survival of patients who underwent R0 resection was also 100%, while those who underwent R1 resection had 71.4% survival.

In our study, we decided to divide the patients into two groups according to tumour location (retroperitoneal and non-retroperitoneal). Although it is well known that prognosis is directly related to complete resection with free margins in all subtypes, location can be a variable to take into account in those cases in which adjuvant or neoadjuvant treatment is required. For example, abdominal involvement may be treated by cytoreduction surgery and HIPEC and include excision of nearby organs depending on tumour infiltration. On the other hand, liposarcomas located in the extremities have better delimitation and better response to radiotherapy, with less morbidity. In addition, in recent years, a type of treatment consisting of intra-arterial infusion of chemotherapy has obtained good results with a decrease in the number of amputations (25).

The role of radiotherapy and chemotherapy (adjuvant or neoadjuvant) is currently controversial. According to the European Society for Medical Oncology (ESMO), neoadjuvant chemotherapy is an alternative for tumours that are initially unresectable (26). Anthracycline-based chemotherapy schedules (such as doxorubucin at doses of 75 mg/m^2 have shown better responses without a significant impact on survival in selected patients. In addition, MLP has a high sensitivity to chemotherapy along with a high response rate to these regimens in contrast to WDL/ALT and DDL which are chemoresistant. Cytoreductive surgery with intraperitoneal chemotherapy administration (HIPEC) has also been employed in selected patients, associated with significant toxicity and limited clinical benefit (27-29). In our series, one patient underwent cytoreduction surgery and HIPEC after peritoneal recurrence of WDL/ALT with no recurrence during follow-up to date.

Finally, preoperative radiotherapy has been shown to have a relevant role in potentially resectable patients, who do not require urgent surgery, using a lower dose of radiation with a consequent lower toxicity than that which would be used after the operation.

The current WHO classification for bone and soft tissue tumours has recently been updated in 2020 by introducing two more histological types with different characteristics. Total 52 cases of malignant adipocytic tumours collected during 2000-2020 were analysed with the new WHO classification updated 2020. The involvement of the resection margins together with the histological type myxoid liposarcoma was the main indicator in our series.

Treatment is mainly surgical, and the use of radiotherapy and chemotherapy is currently controversial. In our study we have found differences in relation to the survival of each histological subtype and its location, finding greater survival in DDL, LPM and LPP located at the extraperitoneal level. Resectability (R0) was not influenced by liposarcoma location.

In addition, in our study we have observed that the retroperitoneal location negatively influences the prognosis, probably in relation to the involvement of the surgical margins and the need to extend the surgery to neighbouring organs due to local infiltration.

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Availability of data and materials

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

Authors' contributions

FMM, BMG, AQV, LDG, ABM, CVM, EOM, CDC, MDA, FGMN, AGC, MAM and MAO contributed to the design of the study. FMM was a major contributor in the writing of the manuscript. BMG and MDA confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Fundación para la Investigación del Hospital Universitario Príncipe de Asturias (protocol code: OE 49/2020).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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