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ORIGINAL ARTICLE

Multivisceral resection for retroperitoneal liposarcoma-is it worth it? A 20-year single-center experience

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Abstract

Purpose Soft tissue sarcomas are rare malignant tumors. Liposarcoma constitutes the most frequent histological subtype of retroperitoneal sarcoma. The prognosis of soft tissue sarcomas depends on clinical and histologic characteristics.

Objective Evaluate variables that may be related to the overall and local recurrence-free survival in patients with retroperitoneal liposarcoma and discuss the need for visceral resection en-bloc for tumors.

Methods A retrospective analysis was conducted of the medical records of 60 patients seen between 1997 and 2017 who underwent surgical resection of retroperitoneal liposarcoma.

Results The overall survival rate at 5 years of follow-up was 75.22% (95% confidence interval [CI] 0.58–0.86). The probability of a local recurrence-free survival at 5 years of follow-up was 26.04% (95% CI 0.11–0.44). The multivariate analysis showed that dedifferentiated or pleomorphic tumors and R2/fragmented resection were associated with a shorter time to recurrence. No other characteristics markedly influenced the overall survival ($P > 0.05$).

Conclusion Patients with dedifferentiated or pleomorphic tumors and incomplete resection were associated with higher local recurrence rates than others. This study reinforces the need for complete and en-bloc resection with organs when there is clear involvement or technical surgical difficulty to maintain the tumor integrity.

Keywords Liposarcoma · Retroperitoneal space · Survival analysis · Surgical oncology · Retrospective study

Introduction

Soft tissue sarcomas (STSs) were defined by James Stephen Ewing (1866–1943) in his book *Neoplastic Diseases* (1919) as "uncommon malignant tumors composed of mesodermal or connective tissue type cells." [1] They are rare malignant tumors and account for 1% of adult solid tumors. [2]

STSs are a heterogeneous group of tumors including more than 50 histological subtypes [2] recognized by the World Health Organization (WHO) [3], with liposarcoma (LPS) accounting for approximately 20% of STSs in adults [4]. Some 15%–20% of STSs develop in the retroperitoneum (RP) [5], and of these, LPS is the most common variety [6], accounting for more than 45% of all cases. [5, 7]

The diagnosis of retroperitoneal LPS is often delayed due to its insidious growth in the retroperitoneal space, where it can reach a substantial volume before causing any symptoms or being apparent on a physical examination. Disease control through surgery remains the primary treatment when retroperitoneal LPS is localized, and complete en-bloc resection without fragmentation, including the involved structures (visceral resection is frequently needed), represents the only potential curative treatment. [5]

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The survival of patients with retroperitoneal LPS may be related to several factors, such as the tumor size, resection quality (complete or fragmented), resection of contiguous organs and histological grade. [4, 6, 7]

Objective

This study's primary purpose was to identify variables potentially related to the overall survival (OS) and local recurrence-free survival (LRFS) of patients with retroperitoneal LPS. In addition, we discuss whether or not visceral resection en-bloc with a tumor is, in fact, necessary.

Materials and methods

This is a retrospective study that analyzed the medical records of 60 patients who underwent surgical resection of their primary tumor at the Hospital das Clínicas from Faculdade de Medicina da Universidade de São Paulo (HCFMUSP) and its unit Cancer Institute of the State of São Paulo (ICESP) between 1997 and 2017. The HCFMUSP is one of the largest teaching hospitals in Latin America.

Clinical data were obtained following the Ethics Committee's approval and included patients' demographics and their disease characteristics, such as the tumor diameter, histological type, histological grade, type of resection and presence of visceral resection. This study was registered in ClinicalTrials.gov (NCT05428579).

Most surgical procedures in our institution were performed by the same surgical oncology team specialized in sarcoma (Sarcoma and Melanoma Group of the III General Surgery Division-HCFMUSP/ICESP). However, some cases were operated by the General Surgery team of the institution or by surgeons of other specialties (e.g. urology) when there was a misdiagnosis. Patients with retroperitoneal LPS who were diagnosed at other institutions were included after their histology had been revised by a pathologist experienced in sarcoma (Lima LGCA). A preoperative biopsy was not performed in all patients, only in cases for which there was diagnostic doubt or unresectability for the evaluation of systemic treatment. Cases of unresectable disease (e.g. upper mesenteric artery or vein involvement) or metastatic disease (e.g. sarcomatosis or distant disease) were excluded.

Almost all surgical cases were discussed in a weekly multidisciplinary meeting, involving not only the surgical teams but also the clinical oncology and radiotherapy teams. For surgical procedures that required complex vascular resection, the vascular surgery team was invited for a joint surgical approach.

The tumors were divided into two histology groups: well-differentiated or myxoid and dedifferentiated or pleomorphic [4]. We decided to include dedifferentiated and pleomorphic sarcomas in the same group due to their high histological grade [7] and their similar 5-year survival rates of 30–50% [4]. As these histological types have similar 5-year survival rates and the objective of the study was to evaluate the survival, it was decided to group histological types with similar survival rates only for the statistical analysis.

The resection types were divided into 2 groups: R0 or R1 and R2. We included the R0 and R1 types together because analyzing all margins of large tumors is challenging, and R1 patients can be erroneously classified as R0. Since this was a retrospective study, grouping them together helped counterweigh any inaccuracy [7]. R2 resection was defined as a residual disease or fragmentation of the tumor during the surgical procedure (assessed by the surgical report) or as evaluated by an imaging examination (computed tomography or magnetic resonance) in cases that were referred to the sarcoma group after the surgical procedure performed by some other specialty (eg gastrointestinal surgery or urology) often due to a preoperative misdiagnosis or that were referred from another hospital with the result of histopathological exam but without information from the surgical report, such as intraoperative tumor fragmentation or incomplete resection.

The OS was defined as the time between the first surgery to the date of death or last follow-up. The LRFS was defined as the time between the first surgery and abdominal recurrence by imaging tests in cases of R0 or R1 resection or residual disease progression for *R*2 resection.

Statistical analyses

The normality of the data was confirmed by the Shapiro–Wilk test. A descriptive population analysis was performed according to clinical factors using the mean and standard deviation for continuous variables and relative frequency for categorical variables. The *t*-test for independent samples was used for continuous variables and the χ^2 test or Fisher's test when necessary for categorical variables.

The probability of recurrence or death at each time point was estimated using the Kaplan–Meier Method, with a 95% confidence interval. To stratify the curves based on categorical variables, the Log-Rank test was employed. The Cox model was used to estimate the crude and multivariate effects of the variables on the risk of recurrence and death for each month. Manual data entry was conducted, with the variables inserted into the models using forward and backward methods, guided by the existing literature background. The level of significance was set at $P < 0.05$.

Statistical analyses were performed using the SPSS (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) and STATA

(StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP.) software programs.

Results

Patients' median age at the diagnosis was 55 (range: 17–76) years old, and they were predominantly female ($n = 38$, 63.3%). The first surgical procedure for LPS resection was performed at the HC-FMUSP/ICESP for 68.3% of the patients, while 31.6% had their first surgery performed at another hospital or by another surgical specialty (Table 1).

The majority of the patients had either a well-differentiated tumor (50%) or a dedifferentiated subtype (33.3%), while fewer histology reports described the pleomorphic type (11.6%) and round cells or myxoid types (5%). High-histological-grade LPS tumors (G2 and G3 by the French Federation of Cancer Centers Sarcoma Group-FNCLCC) were found in 56.6% of patients. The median largest diameter of the primary tumor was 27 (8–46) cm. R0 or R1 resection was achieved in 75% of patients, and 61.4% of patients required resection of organs en-bloc with the tumor to achieve complete resection. All patients who underwent multivisceral resection achieved complete resection (R0 or R1). The organs resected en-bloc were the spleen, kidney, liver, small intestine, colon, stomach, pancreas tail, uterus, ovary, testicle, iliac vessels, vena cava segment, diaphragm and psoas muscles.

Eleven patients underwent R2 resection. In the analysis of the surgical specimens, three of them showed a well-differentiated/myxoid histology, while eight showed an undifferentiated/pleomorphic type. However, it should be noted that the histology of the unresected component may be different from that removed. This is possible in some cases in which the surgeon confuses the well-differentiated component with normal retroperitoneal tissue, resecting only the higher-grade component, which usually presents as a more solid and well-defined lesion. To confirm the histology of the residual component, it would be necessary to perform a biopsy in the postoperative period, which is rarely done.

In the 5 years of follow-up, 31 patients had a recurrence of LPS. Table 2 describes the characteristics comparing patients with and without recurrence. Patients were followed for a median of 52 months after surgery (Fig. 1). During the five-year follow-up, nine patients died after having their LPS resected. The OS at 5 years of follow-up was 75.22% (95% CI 0.58–0.86).

There were no significant differences in the OS between male and female patients ($P = 0.307$), among different

Table 1 Clinicopathologic characteristics of patients with retroperitoneal liposarcoma ($n = 60$)

Variable	*n* (% or range)
Median age, y	55 (17–76)
Sex	
Female	38 (63.3)
Male	19(31.6)
First surgical procedure resection	
HC-FMUSP/ICESP	41 (68.3)
Another hospital	19 (31.6)
Type of tumor	
Well differentiated	30 (38.3)
Deddiferentiated	20 (33.3)
Plemorphic	7 (11.6)
Myxoid	3 (5)
Histological grade	
G1	23 (38.3)
G2/G3	34 (56.6)
Unknown	3 (5)
Median size,cm	27 (8–46)
Completenes of ressection	
R0/R1 resection	45 (75)
R2/fragemented ressection	11 (18.3)
Unknowm	4 (6.6)

Table 2 Clinicopathologic characteristics of patients with and without recurrence ($n = 60$)

Variables	No recurrence	Recurrence	*P*
Age, years	54.0 ± 13.2	59.2 ± 10.4	0.905
Sex, Male %	34.5	38.7	0.734
High grade, %	53.6	67.9	0.274
Size > 25 cm, %	48.1	57.1	0.799
Dedifferentiated or pleomorphic, %	37.9	51.6	0.287
R2 or fragmented resection, %	0.0	37.9	< 0.001

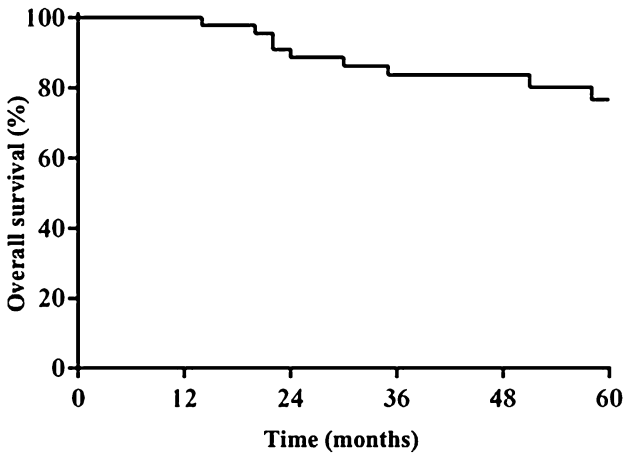

Fig. 1 The overall survival from LPS resection ($n = 60$)

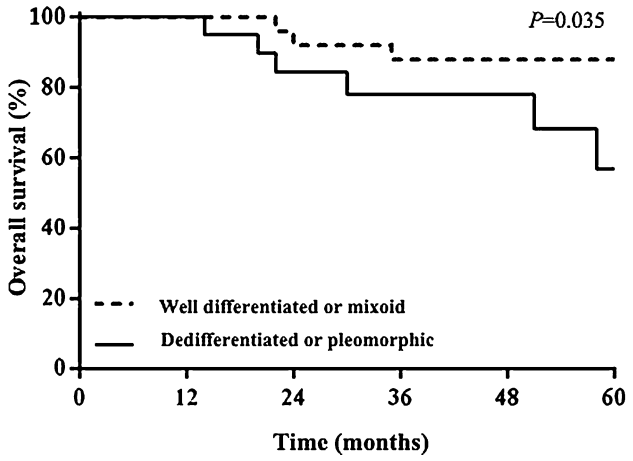

Fig. 2 Differences in the OS between patients with dedifferentiated or pleomorphic tumors (n = 27) and patients with well-differentiated or mixoid tumors ($n = 33$)

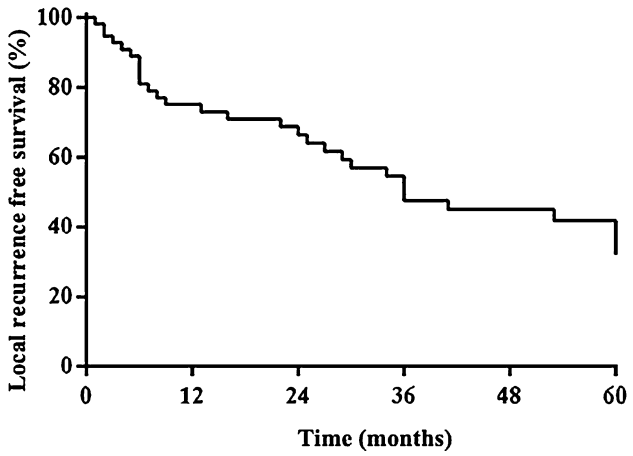

Fig. 3 The local recurrence-free survival after LPS resection ($n = 60$)

histological grades ($P = 0.306$), or based on recurrence ($P = 0.175$), resection type ($P = 0.802$) or the presence of visceral resection ($P = 0.187$). Figure 2 shows the OS of patients with dedifferentiated or pleomorphic tumors compared to other histological types, showing that the former had a lower survival rate than the latter (55% [95% CI 0.24–0.77] vs. 88% [95% CI 0.67–0.96], $P = 0.035$).

During the five-year follow-up, 31 patients relapsed with LPS. After 5 years of follow-up, 26.04% (95% CI 0.11–0.44) of the patients were in remission (Fig. 3).

Patients with dedifferentiated or pleomorphic tumor had a worse LRFS (11%, 95% CI 0.01–0.46) than those with well-differentiated or mixoid tumors (35%, 95% CI 0.14–0.56, $P = 0.018$) (Fig. 4a). The LRFS was also compared between the two resection types, and patients with R0 and R1 resection had a greater LRFS (35%, 95% CI 0.14–0.56) than those with R2 or fragmented resection (11%, 95% CI 0.01–0.46, $P < 0.001$) (Fig. 4b). When adjusting the LRFS curves for sex ($P = 0.579$), histological grade ($P = 0.147$) and presence of visceral resection ($P = 0.941$), there was no significant difference between groups.

The Cox regression analysis for the LRFS and OS showed that dedifferentiated or pleomorphic tumors ($P = 0.023$) and the type of tumor resection ($P < 0.001$) were significant in LRFS (Table 3). No variable was significant in OS ($P > 0.05$).

The results of a multivariate analysis (Table 4) showed that dedifferentiated or pleomorphic tumors and the R2 fragmented resection type were associated with time to recurrence after adjusting for confounding variables. The reason the authors used two models in the multivariate analysis was to minimize confounding variables.

Discussion

The differential diagnoses for retroperitoneal tumors should include lymphoma, germ cell tumors, undifferentiated carcinomas, and sarcomas. LPS is the most common type of retroperitoneal sarcoma, but its behavior, diagnosis and treatment continue to be challenging.

Histologically, according to World Health Organization's classification, liposarcomas are divided into four types well-differentiated, dedifferentiated, myxoid or round cells and pleomorphic [3]. The extent of differentiation, reflected by the histological grade, is important to determine the evolution of the disease and patient's prognosis after resection [4]. Retroperitoneal LPS are almost exclusively well-differentiated and dedifferentiated. Myxoid LPS in the RP is very rare and may represent a misdiagnosis or metastasis in the RP of a distant myxoid LPS [8]. Furthermore, both well-differentiated and dedifferentiated LPS can present with myxoid stromal components, which may cause a misdiagnosis of myxoid LPS. [9]

The survival of patients diagnosed with retroperitoneal LPS depends on multiple factors, including but not limited to the tumor size, resection quality (complete or fragmented), resection of continuous organs, type and histological grade [4, 6, 7]. Well-differentiated LPS has a high risk of local recurrence and very low metastatic potential, with a 5-year survival of up to 90% [4]. Dedifferentiated tumors have a similar local effect but have a greater capacity to present with systemic metastasis (10–15%) [4]. The 5-year OS in our study was 75.22% (95% CI 0.58–0.86). This result was similar to the findings of the international series. In the series by Brennan et al. [4], the 3- and 5-year disease-specific survival rates were 73% and 60%, respectively, and 56% of patients had well-differentiated tumors. In a study performed with dedifferentiated tumors at Dana Faber Hospital, the OS was 42% at 5 years [7]. In our cohort, patients

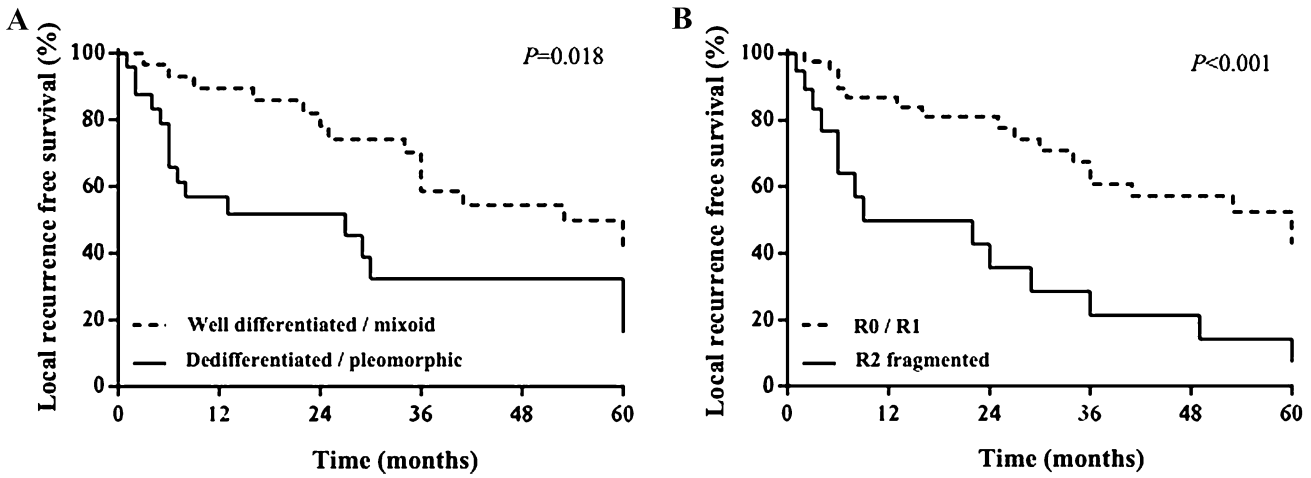

Fig. 4 **A** The LRFS of patients with dedifferentiated or pleomorphic tumors (continuous line; $n=27$) and patients with well-differentiated or mixoid tumors (dashed line; $n=33$), $P=0.018$. **B** The LRFS according to resection type: R2 (continuous line; $n=11$) and R0 or R1 (dashed line; $n=45$), $P<0.001$

Table 3 Results of a crude Cox regression analysis of the LRFS and OS at five years of follow-up after liposarcoma resection ($n=60$)

Variables	LRFS[a]			OS[b]		
	HR[c]	95%	*P*	HR[c]	95%	*P*
Age (years)	1.012	0.98–1.04	0.425	1.044	0.99–1.10	0.137
Diameter (cm)	1.023	0.98–1.07	0.283	1.004	0.94–1.08	0.919
Sex			0.586			0.317
Male	1.227	0.59–2.56		1.885	0.55–6.52	
Female	Ref			Ref		
Histological grade			0,157			0.320
High grade	1,794	0.80–4.03		2.220	0.46–10.70	
Low grade	Ref			Ref		
Dedifferentiated and pleomorphic			0.023			0.051
Present	2.347	1.13–4.90		3.884	1.00–15.14	
Absent	Ref			Ref		
Visceral resection			0.942			0.207
Yes	0.972	0.45–2.10		2.714	0.58–12.79	
No	Ref			Ref		
Resection type			<0.001			0.803
Fragmented R2	5.298	2.42–11.60		1.218	0.26–5.75	
R0 or R1	Ref			Ref		
Recidivate						0.195
Yes				2.789	0.59–13.16	
No				Ref		

[a]LRFS = local recurrence-free survival

[b]OS = overall survival

[c]HR = a hazard ratio

with dedifferentiated or pleomorphic tumors had a lower OS in a univariate analysis than patients with well-differentiated tumors (55% vs. 88%). These data were corroborated by other studies that showed that, in multivariate analyses, dedifferentiated tumors had a lower global survival rate with a hazard ratio of 6 ($p<0.0001$). [4]

Local recurrence is common and increases morbidity. During the 5-year follow-up in the present study, 31 patients

Table 4 Multivariate Cox models for LRFS[a]

Variables	Model 1			Model 2		
	HR[b]	95% CI	*P*	HR[b]	95% CI	*P*
Age (years)	1.005	0.98–1.04	0.728			
Diameter (cm)	1.023	0.98–1.08	0.273	1.037	0.99–1.09	0.147
Sex			0.240			
Male	1.917	0.65–5.67				
Female	Ref					
Histological grade			0.701			0.867
High grade	1.257	0.39–4.04		0.916	0.33–2.55	
Low	Ref			Ref		
Dedifferentiated or pleomorphic			0.030			0.011
Yes	3.187	1.12–9.08		3.741	1.36–10.32	
No	Ref			Ref		
Resected organs			0.701			0.488
Yes	0.818	0.39–4.04		0.736	0.32–1.72	
No	Ref			Ref		
Resection type			< 0.001			< 0.001
Fragmented R2	19.696	5.30–73.14		16.204	4.71–55.75	
R0 or R1	Ref			ref		
Likehood ratio (χ^2 test)	30.4				28.9	
P		< 0.001			< 0.001	

Model 1—adjusted for age, diameter, sex, histological grade, type of tumor, presence of resected organs and type of resection. Model 2—adjusted for diameter, histological grade, tumor type, presence of resected organs and type of resection

[a]LRFS = local recurrence-free survival

[b]HR = a hazard ratio

relapsed with LPS, and the presence of R2 or fragmented resection was higher in relapsed patients (37.9%) than in patients without recurrence (0%). Therefore, all patients with fragmented resection or R2 had disease progression, further supporting the need to perform en-bloc resection without tumor fragmentation.

Patients with R0 or R1 resection had a relatively high recurrence rate of 62.1%. Sarcomas are characterized by a high rate of recurrence even when all macroscopic disease has been removed [6], and relapse occurs in approximately 60% to 70% of these patients. [7] Negative margins are frequently not feasible due to anatomic constraints. In several retrospective assessments of patients with retroperitoneal sarcomas, complete surgical excision (R0 or R1) was achieved in only 40% to 60% of patients, and while incomplete or debulking (R2) resection may improve local symptoms, it does not improve the survival [10]. Incomplete resection has also been associated with a risk of developing distant metastasis that is almost four-fold higher than in those who undergo complete resection [10]. In an analysis of 500 patients with retroperitoneal sarcoma treated at MSKCC, the median survival duration of patients who underwent complete resection was 103 months versus 18 months for patients who underwent incomplete resection, showing no marked difference from the survival rates in patients treated with observation without resection, thus demonstrating that there is no survival benefit from debulking procedures. [10]

Our institutional strategy for managing recurrent retroperitoneal LPS is individualized. In general, when there is local recurrence and a surgical procedure with low morbidity and mortality is feasible, surgery is discussed. When there are multiple lesions or in locations that require complex resection (such as multivisceral resection of the gastrointestinal tract, urological, vascular or neurological systems that carries a high risk of morbidity), surgery is not indicated, and the clinical oncologist considers other treatment modalities.

The 5-year LRFS in the present study was 26.04% (95% CI 0.11–0.44), and it was worse for patients with dedifferentiated or pleomorphic tumor ($P = 0.023$) and the fragmented or incomplete resection type ($P < 0.001$) than in others, according to univariate and multivariate analyses. Other studies have also shown an association between disease-free survival or progression and dedifferentiated tumors, fragmented resection or compromised margins. [4]

Several questions remain concerning the extent of surgery and the need for organ resection, depending on the histological type. Although our study did not indicate the statistical significance of visceral resection, it is well stablished

that complete resection without fragmentation of the tumor remains the most important predictor of local recurrence and global survival [4]. A previous study of nephrectomy for retroperitoneal sarcoma (all histologic types) demonstrated that renal capsular invasion was present in 15% of patients, renal parenchymal invasion in 9% and renal vein invasion in 3% of patients, with 73% of patients having no evidence of direct kidney invasion [11]. This raises the question of whether or not there is any benefit to resecting the kidney or other organs.

Since the tumor is quite similar to normal retroperitoneal tissue and fat, it is challenging to determine the limits of the lesion, so the risk of tumor fragmentation and dissemination of neoplastic cells is high. If it occurs, evidence points to a poor prognosis [7].The treatment of patients with retroperitoneal LPS remains challenging, and there is presently no way to achieve a cure with chemotherapy or radiotherapy. The perioperative use of chemotherapy or radiation therapy has been applied for retroperitoneal sarcoma to improve the outcome, mainly based on data from limited retrospective studies and extrapolated from extremity sarcoma cases. STRASS (EORTC 62092), a phase III randomized study, failed to demonstrate the benefit of pre-operative radiotherapy for retroperitoneal sarcoma, but in the exploratory analysis, preoperative radiotherapy was suggested to benefit the LPS subgroup, although this should be confirmed in future studies. [12]

The development of targeted therapies, such as CDK4 inhibitors, may improve the efficacy of systemic therapy for STSs, since CDK4 is a cyclin-dependent kinase frequently overexpressed in LPSs. Dickson et al. from MSKCC recently published the results of a phase II trial of a CDK4 inhibitor administered to 60 patients with LPSs (47 dedifferentiated and 13 well-differentiated). The overall progression-free survival at 12 weeks was 57% [13]. MDM2 inhibitors for the treatment of LPSs are also being investigated.

Conclusion

Despite the limitations of its retrospective nature and the limited number of patients, the results of our study were similar to those of other studies in which dedifferentiated or pleomorphic tumors and incomplete resection were associated with poor local recurrence rates. This underscores the need for complete en-bloc resection with organs if there is clear involvement or if there is technical surgical difficulty to maintain the integrity of the tumor. In our group, there is a tendency to maximize resection because of the absence of effective perioperative therapies. Finally, because of the rarity of this disease, it is important to discuss these complex cases in multidisciplinary team meetings.

Declarations

Conflict of interest Frederico Ribeiro Teixeira Jr and other co-authors have no conflict of interest.

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