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Oncology Outcomes in Retroperitoneal sarcomas: Prognostic factors

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Synopsis for Table of Contents: The optimal initial treatment for patients with RPS, independent of tumor size, histological subtype or grade should be based on complete resection with radical surgery, if necessary, with resection of adjacent organs to minimize the risk of residual disease.

Abstract

Introduction. Retroperitoneal sarcomas are a rare group of malignant soft tissue tumors with a generally poor prognosis. The aim of the study was to define the demographic characteristics and prognostic factors for patients with retroperitoneal sarcomas (RPS) in a Tertiary Referral Center at Mexico.

Methods. A retrospective study of patients with RPS treated from January 2005 to December 2012 at the National Cancer Institute at Mexico. Patient, tumour and treatment variables were analysed including use of adjuvant therapy and survival status. Survival and local recurrence curves were estimated using the Kaplan-Meier method

Results. Ninety-five patients with a mean age of 47 years with retroperitoneal sarcoma were included. Median follow-up was 25 months (range 1-108 months). The average tumor size was 23.7 cm . Histology, 58 (61.1 %) were liposarcoma, 14 (14.7 %) ,

leiomyosarcomas and 23 (24.2 %) were from other histologies . In 64 (67.4 %) patients were high-grade malignancies. The median survival was 51 months for patients with complete resection, 25.1 months for those with incomplete resection , and 4.4 months for those with unresectable tumors. Complete resection ($p = 0.0001$) , and liposarcoma ($p = 0.03$) were prognostic factors for overall survival.

Conclusion. In this study of patients with retroperitoneal, complete resection and liposarcoma histology are prognostic factors related to the disease-free and overall survival. Patients approached with curative intent should undergo aggressive attempts at complete surgical resection.

Keywords: retroperitoneal sarcoma, prognostic factors, complete resection, liposarcoma, recurrence, survival.

Introduction

Soft tissue sarcomas represent a heterogeneous group of rare tumors, predominantly of mesodermic origin and which represent 1–2% of all solid tumors¹. The 2014 US incidence is estimated at 12,020 new cases, causing ~4700 deaths.² Approximately 10–20% of these cases are derived from the retroperitoneum with a prevalence of ~0.3–0.4 cases/100,000 inhabitants.³ The prognosis for patients with retroperitoneal sarcomas (RPS) is relatively poor with a 36–58% 5-year overall survival (OS) and a natural history characterized by late recurrences.⁴ RPS are commonly asymptomatic until they reach great dimensions. Mean size at the time of the diagnosis is 15–18 cm.^{5,6} Due to their location and the presence of adjacent vital organs/structures (e.g., aorta, vena cava, duodenum, or head of the pancreas), the surgical and radiotherapeutic (RT) approach is complex, since the abovementioned structures and organs show poor tolerance to radiotherapy.^{7,8} However, the cornerstone of treatment for RPS is surgery with microscopically negative margins (resection R0). Despite this, after surgery alone, more than half of these tumors recur, hastening the death of these patients. Recent studies show that more aggressive surgeries together with advanced RT techniques have potentially reduced local recurrences.⁹ Also, adjuvant chemotherapy (CT) is a new therapeutic alternative for reducing the local recurrence index in certain histologies.¹⁰ Another important prognostic factor is histological grade. It has been determined that two-thirds of RPS are of intermediate or high grade and one-third are low grade.¹¹ Intermediate or high-grade tumors can metastasize to distant sites, most commonly the lung and liver. Low-grade tumors carry the risk of local recurrence, but rarely cause distant metastases.^{12,13} The objective of this review is to evaluate the most important

prognostic factors in terms of recurrence-free period and OS in a Tertiary Referral Center at Mexico in patients with RPS.

Methods

A Retrospective, descriptive data base of adult patients (older than 18 years) with RPS treated at the Instituto Nacional de Cancerologia (Mexico City) from January 2005 to December 2012. Patients with gastrointestinal stromal tumors, germinal tumors, lymphoma, dermatofibrosarcoma protuberans, and bone tumors were excluded from the study. Clinical data were acquired from the RPS database held at our facility. All data had been gathered prospectively during routine follow-up. Periodic follow-up comprised a physical examination, abdominal computed tomography (CT) scans or magnetic resonance imaging (MRI) studies, and chest x-rays, which ordinarily were planned at 4-month intervals for 2 years after surgery, twice a year for the successive 3 years, and once a year thereafter.

All patients who were included in this study underwent surgery with curative intent. All complementary treatments were administered on the basis of decisions made by the multidisciplinary institutional Board.

The pathologic review was performed by expert pathologists. Tumor grade was assessed according to the 3-tiered FNCLCC criteria, which take into account tumor differentiation (D), Mitotic count (M), and the presence of necrosis (N). Recurrence was defined as the presence of post-treatment sarcoma confirmed by imaging study after six months of disease-free period.

Demographic data such as age, gender, symptoms at the time of the diagnosis, symptom duration, tumor size, tumor grade and histologic diagnosis were obtained. Survival curves were created using the Kaplan-Meier method and compared using log-rank test with Bonferroni

correction according to resection status, tumor size, histology, grade, and recurrence; $p < 0.05$ was considered significant. Statistical analysis was done with SPSS v.22.0.

Results

There were 95 patients analyzed, 49 males (51.6%) and 46 females (48.4%) with a mean age of 47 years (range 18–82 years). In 87 patients (91.6%), initial symptoms included: palpable abdominal mass (31 patients, 32.6%), diffuse abdominal pain (25 patients, 26.3%), nonspecific gastrointestinal symptoms (18 patients, 18.9%), and weight loss (5 patients, 5.3%). Eight patients (8.4%) had diverse symptoms (edema, lower extremity paresthesias, increased volume in inguinal region, urinary symptoms). The remaining patients (8.4%) were asymptomatic and the tumor was incidentally discovered. Mean symptom duration was 6 months (range 1–36 months). In 12 patients (12.6%), distant metastasis were present at the time of diagnosis. Table 1 shows the clinical characteristics, size, and histology. No patient received neoadjuvant RT or CT. Oncological surgical resection was carried out in 79 patients (83.2%), while 16 patients (16.8%) were considered to have unresectable tumors, but underwent surgical biopsy. Complete resection (without residual microscopic disease and/or with negative margins) was achieved in 55 patients (69.6%). Multiorgan resection was carried out in 41 patients (52%). Of these, four (5%) required resection of more than three organs. The most frequently resected organs were kidney in 19 cases, colon in 14 cases, small intestine in 8 cases and spleen in 4. Four patients died following the procedure. The resection was incomplete (with residual macroscopic disease) in 16 patients (16.8%), three of which died following the procedure. Of the 12 patients with metastatic disease, three (25%) underwent metastasectomy after treatment of the primary tumor, 5 (41.6%) were treated with CT, and four (30%) rejected systemic treatment and only agreed

to undergo a debunking palliative surgery for the primary tumor. The mean size of the tumor in the cases operated on was 23.7cm (range 5–61 cm). The most common histological diagnosis was liposarcoma and the majority of the tumors were high grade (Table 1). Of the 51 patients who were considered for complete resection, there was recurrence in 27 patients (53%) during a mean time of 21.8 months (range 9–46 months). Of these patients, 17 (33.3%) died from the disease. Similarly, the recurrence was earlier in tumors whose histology was not liposarcoma (mean 11.6 months, 95% CI 8.5–14.7) compared with liposarcomas (mean 20.8 months, 95% CI 16.8–24.7, $p = 0.005$). Age ($p = 0.64$), tumor size ($p = 0.83$), histological grade ($p = 0.50$) and adjuvant treatment ($p = 0.2$) showed no significant difference for recurrence. OS was higher in patients with complete vs. incomplete resection (mean 55.6 vs. 28.1 months; $p < 0.0001$) or in patients with unresectable tumors (4.4 months) (Figures 1 and 2). Survival was also higher in patients with histology of liposarcoma vs. non-liposarcoma (mean 46.2 vs. 19 months; $p = 0.003$) (Figure 3). Age, histological grade, and tumor size showed no significant statistical difference in OS (Table 2). Thirty-four patients (66.6%) in the subgroups of complete resection and six patients (16.2%) in the subgroups of incomplete resection were alive at the time of the final analysis, with 30.5% 5-year OS for the complete series (Figure 4).

Discussion

RPS are rare, comprising 10% of the total of soft tissue sarcomas with a prevalence of 0.3–0.4 cases/100,000 inhabitants.³ The prognosis reported in the world literature is poor with a 5-year OS of 36–58% and a mortality largely associated with a high rate of local recurrence.⁴

The presentation of RPS in our study was uniform in both genders. The mean age at presentation was 47 years, much younger than what has been reported in other series, where they are frequently diagnosed at >60 years of age.¹⁴ More than 90% of the patients present with a palpable abdominal mass and, occasionally, symptoms include: pain, weight loss, postprandial fullness, constipation, or other vague gastrointestinal symptoms, causing the diagnosis to be made at a more advanced stage, with a mean time between symptom onset and diagnosis of 6 months.

Lewis et al. published one of the largest series, which evaluated almost 500 cases of retroperitoneal tumors and found that 80% present as an asymptomatic abdominal tumor, 42% with neurological symptoms in the lower extremities and 37% with pain.¹⁵ With regards to recurrence, the main site is the peritoneal cavity. In our study it was 40%, less than in other series, which report a rate of ~58% at 2 years.¹⁶ However, the high frequency of patients with advanced disease at the time of the diagnosis and with tumors deemed unresectable (by imaging or during the initial laparotomy) correlates with a the very high mortality index (69.5%) observed in our series, and is not necessarily associated with the recurrence. Gyorki et al.¹⁷ published a systematic review of the largest series of RPS in which an 80% index of resection is reported and where a complete resection was achieved in >50% of the cases. Macroscopic positive margins have been defined as important

predictors of recurrence. It is important to highlight that it is difficult for the pathologist to review the totality of the tumor; therefore, a definition of an R0 or microscopically negative margin should be taken with caution. It is better to define resection as macroscopically complete or incomplete.¹⁷ In our institute, a rate of complete resection of 57.9% is attained. Tumor-only resections comprised 43.2% of patients, while resection of adjacent organs was necessary in 56.8% of cases.

An association between the histological subtype and OS has been demonstrated repeatedly with better results for patients with liposarcomas than those with other histologies (leiomyosarcoma, pleomorphic sarcoma, malignant tumor of the peripheral nerve sheath, synovial sarcoma and others).¹⁸ In fact, the group of patients with liposarcoma could be divided into well-differentiated, undifferentiated, myxoid and rounded cells. Lu et al.¹⁹ showed that well-differentiated and myxoid liposarcoma patients have more prolonged survival rates than the undifferentiated variants. In our series, non-liposarcoma histology was one of the independent variables associated with worse OS and with a shorter recurrence-free period. However, it can be assumed that the well-differentiated and myxoid variant or rounded cells are those with better survival rates. Analysis of the subgroup of liposarcomas should be carried out to establish with greater precision the variable that impacts on better survival and longer disease-free period.

Avancés et al.²⁰ demonstrated that tumor grade is another risk factor associated with recurrence and with poor survival. It has been commented that tumor grade is related with resections with residual macroscopic disease; however, in our study this was not the case. Histological grade was not a factor in recurrence or in OS even though the percentage of high-grade tumors was 67.4%.

Another variable to take into consideration is adjuvant treatment. We mention RT as a treatment option once complete resection has been carried out with the goal of prolonging the recurrence-free period.²¹ Nonetheless, in our population, this was not a viable alternative for most patients with complete resection. It was administered only in those patients with macroscopically positive disease or incomplete resection, second recurrences or high-grade and large tumors. This suggests that because of the low number of patients and their poor prognosis, adjuvant treatment was not significant in the analysis of recurrence. In general, regardless of size, histology and grade of presentation of RPS, complete resection with or without contiguous organs continues to be the main independent variable for recurrence-free period and OS.

We have found several limitations to our study: The retrospective design, the fact that surgical techniques are highly individualized based on patient and tumor characteristics; not analyzed concomitant pathologies; and most important of all, results are based on a small number of patients operated in a single institution

Conclusion

Based on the results of this study, RPS presents itself on our population in younger patients when compared with the international literature, mainly in an Anglo-Saxon population. The optimal initial treatment for patients with RPS, independent of tumor size, histological subtype or grade should be based on complete resection with radical surgery and, if necessary, with resection of adjacent organs to minimize the risk of residual disease. In patients with non-liposarcoma histology and in those where the margins were not able to be properly established in the pathological analysis of the surgical specimen, a closer follow-up with clinical examination and follow-up with computerized tomography would be beneficial for early detection of recurrences and for early treatment. Optimal treatment of recurrences has not been entirely elucidated and continues to be researched in detailed studies. In our population, tumor size and grade are not variables that affect the recurrence or OS. However, an analysis of the different subgroups should be carried out to define their potential roles in resectability, considering that complete resection is the principal prognostic factor for recurrence and OS. Adjuvant therapy (CT or RT) has not been considered the standard of care, and efforts are still ongoing to select a therapy with less toxicity and better efficacy in decreasing recurrence, mainly locally. In the present study, although it was not one of the main objectives, adjuvant therapy was not a variable in the recurrence-free period. Therefore, its use after the first complete resection could be limited to those cases with residual disease or non-liposarcoma histology, regardless of the tumor grade.

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Figure Legends

Figure 1. Survival curve in patients related to the type of resection.

Figure 2. Relapse-free survival curve in patients related to the type of resection.

Figure 3. Survival curve in patients based on histologic diagnosis.

Figure 4. Five-year overall survival curve.

Table 1. Characteristics of the 95 patients with retroperitoneal sarcoma

Characteristics	N (%)
Gender	
Male	49 (51.6%)
Female	46 (48.4%)
Stage*	
IB	25 (26.3%)
IIA	1 (1.1%)
IIB	2 (2.1%)
III	55 (57.9%)
IV	12 (12.6%)
Symptoms to diagnosis	
Yes	87 (91.6%)
No	8 (8.4%)
Tumor size	
<20 cm	46 (48.4%)
>20 cm	49 (51.6%)
Histology	
Liposarcoma	58 (61.1%)
Well-differentiated	24 (41.37%)
Undifferentiated	28 (48.25%)
Myxoid	3 (5.17%)
Pleomorphic	3 (5.17%)
Leiomyosarcoma	14 (14.7%)
Others**	23 (24.2%)
FNCLCC grade	
I	29 (30.5%)
II	2 (2.1%)
III	64 (67.4%)
Resectability***	
Unresectable	16 (16.8%)
Incomplete resection	24 (25.3%)
Complete resection	55 (57.9%)
Resection of adjacent organs	
Yes	54 (56.8%)
No	41 (43.2%)

*AJCC 2010

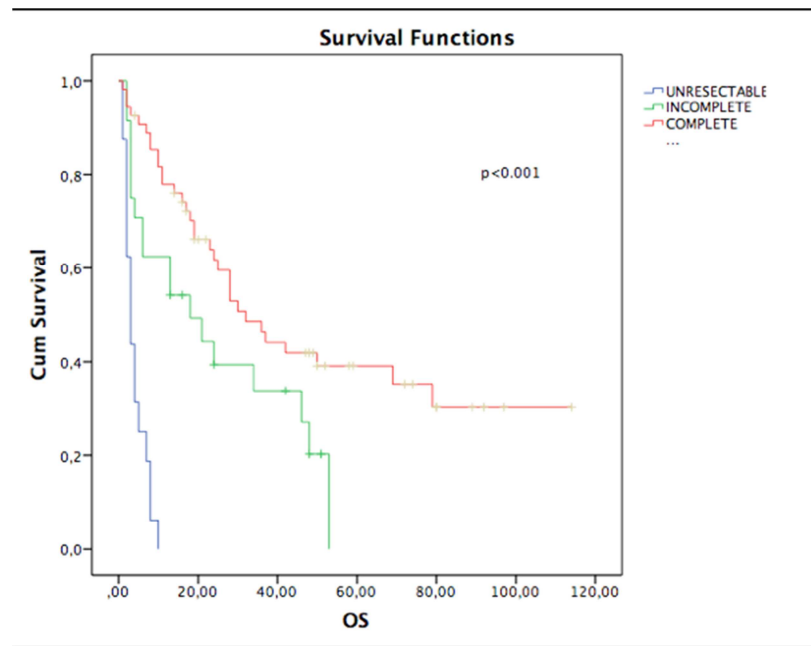
*Other includes pleomorphic sarcoma, synovial sarcoma, fibrosarcoma, rhabdomyosarcoma, tumors of peripheral nerve sheath, desmoid tumors.

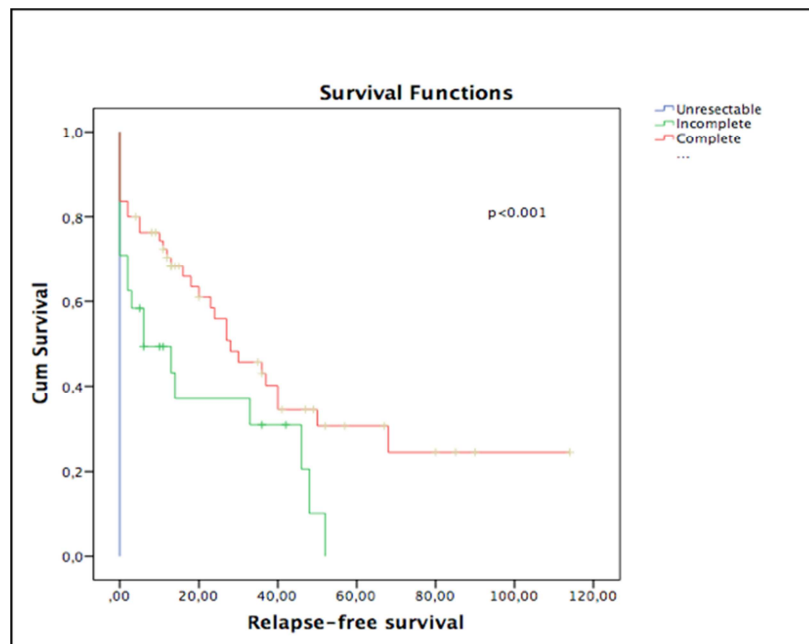
** Surgical resection was classified as complete (R0 or R1) or not (R2).

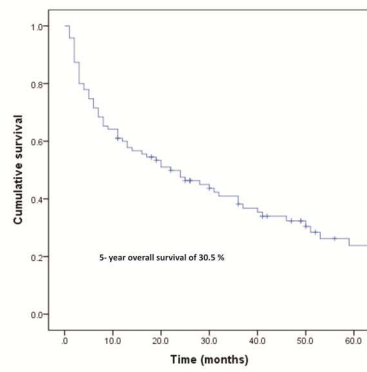
Table 2. Analysis Estimates From the Cox Proportional Hazards Models on Survival Types

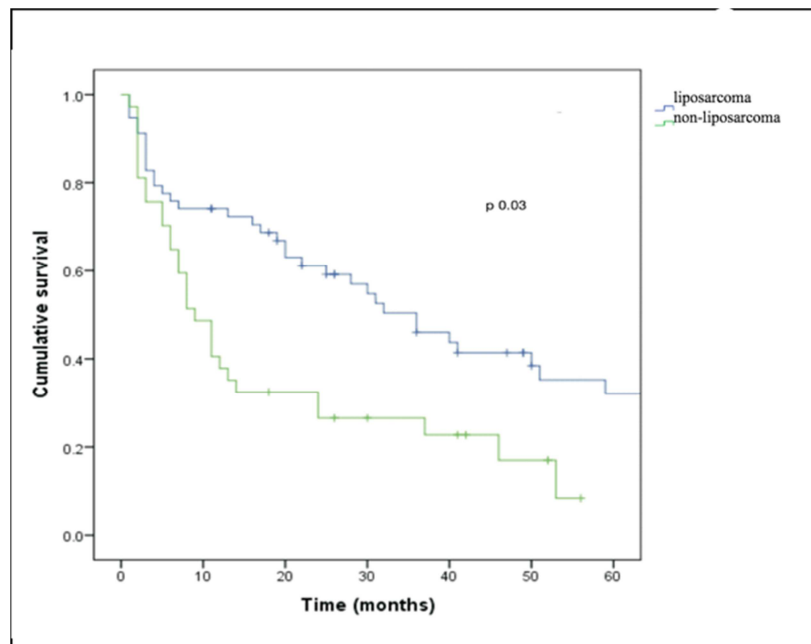
Category	OS			RFS		
	HR	95% CI	P	HR	95% CI	P
<i>Age</i>			NS			NS
<45	0.55	0.35-0.88		0.71	0.3-1.2	
>45	1.4	0.6-1.85		1.2	0.91-2.1	
<i>Size(cm)</i>			NS			NS
<20	1.9	1.7-5.46			0.84-2.26	
>20	1.6	0.8-2.04			0.92-2.65	
<i>Histology</i>			0.03			0.05
<i>Liposarcoma</i>	38.8	0.85-1.47		3.02	2.02-4.01	
<i>Others**</i>	33.5	1.68-2.47		2.74	1.44-4.05	
<i>Graade FNCLCC</i>			NS			NS
<i>G1</i>	5.76	3.81-7.72		5.27	3.17-7.38	
<i>G2</i>	0.25	0.7-1.12		19.5	4.8-34.2	
<i>G3</i>	0.52	0.41-2.208		22.8	15.7-29.9	
<i>Resection</i>			<0.001			<0.001
<i>Unresectable</i>	3.4	2.7-5.4		2.91	1.4-5.9	
<i>Incomplete resection</i>	2.1	1.58-3.33		11.9	5.53-25.6	
<i>Complete resection</i>	5.12	4.05-6.603		2.06	1.11-3.81	

Abbreviations: OS, overall survival; RFS, relapse-free survival;









Highlights

- Retroperitoneal sarcomas are rare neoplasms , in Latin America there are few studies showing oncological outcomes in this population
- We present the results of treatment of retroperitoneal sarcomas in the most important cancer center in Latin America.
- The overall 5-year survival in our patients was 30.5 slightly higher than in other publications.
- Local disease recurrence remains the main cause of mortality.