Factors Affecting Survival in Retroperitoneal Sarcomas Treated with Upfront Surgery: A Real-World Study by Turkish Oncology Group

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ABSTRACT

Retroperitoneal sarcomas (RPS) account for approximately 15% of all soft tissue sarcomas (STS) and encompass a heterogeneous group of tumors with limited multimodality treatment options. Surgical resection with negative margins remains the standard primary treatment for patients with localized RPS. In this multicenter study, we aimed to demonstrate the real-world data on factors affecting survival in RPS treated with upfront surgery. We included a total of 197 patients who underwent curative-intent resection of a primary non-metastatic RPS between 2000-2020 at ten experienced medical oncology departments in Turkey. The median follow-up was 33 months. The median age of patients was 53 years, 57.4% of patients were female. Univariate analysis revealed that; tumor size, grade, necrosis, resection margin status, were factors affecting recurrence-free survival (RFS) (p= 0.002, p= 0.044, p= 0,024, p= 0.003 respectively). Age, tumor size, stage, resection margin status were factors affecting overall survival (OS) (p= 0.038, p= 0.001, p= 0.032, p< 0.001, respectively). In multivariate analysis, tumor size and resection margin status were independent factors affecting RFS and OS (all p-values < 0.05). Our study demonstrated that tumor size, and resection margin status were the main factors affecting survival in resected RFS. In comparison, adjuvant chemotherapy (CT), radiotherapy (RT), or multimodality treatment did not show OS and RFS advantages. We believe that advances in the molecular characterization of these tumors might help clinicians to detect the best candidates for adjuvant therapies in RPS.

Keywords: Survival, Retroperitoneal sarcoma, Adjuvant chemotherapy, Adjuvant radiotherapy, Surgery

INTRODUCTION

Retroperitoneal sarcomas (RPS) account for approximately 15% of all soft tissue sarcomas (STS) and contain a heterogeneous group of tumors with limited multimodality treatment options.[1] Surgical resection with negative margins remains a curative treatment. The majority of patients present with locally advanced disease, thus it's difficult to achieve a negative surgical margin. Therefore, the rate of locoregional recurrence is ranging from 40% to 80%.[2,3] Unlike other soft tissue sarcomas (STS), in patients with RPS, mortality is high without distant metastasis due to locoregional recurrence.[4,5]

Insufficient results with surgery alone necessitated a multimodality approach to RPS. Due to the rarity of the disease, there is a lack of data regarding treatment efficacy. The date, the majority of the studies are based on retrospective and single-institution experiences. Adjuvant radiotherapy (RT) has been shown to reduce local recurrence, particularly in extremity sarcomas, but this data has been extrapolated to limited data on RPS.[6] The role of adjuvant chemotherapy (CT) in resected RPS remains unclear. A pooled analysis from two European Organization for Research and Treatment of Cancer (EORTC) phase III clinical trials in STS failed to demonstrate a survival advantage with adjuvant doxorubicin-based CT.[7] Similarly, a recent analysis from the National Cancer Data Base (NCDB) showed the survival benefit of CT in resected RPS 8.. In the current literature, the most important predictors of local recurrence after resection of RPS are tumor grading and resection margin status.[9]

In this retrospective multicenter study, we aimed to investigate factors that affecting survival in patients with RPS who are treated with an upfront surgery

PATIENTS and METHODS

Study Population

This multicenter retrospective study included a total of 197 patients diagnosed with RPS between 2000-2020 at ten experienced medical oncology departments in Turkey. Patients who underwent curative-intent resection of a primary non-metastatic RPS without neoadjuvant therapy were identified. None of these patients had secondary primary cancer. Exclusion criteria were; aged <18 years old, metastatic disease at diagnosis, treated with neoadjuvant chemotherapy or radiotherapy for locally advanced disease, patients with a diagnosis of Ewing's family sarcoma, alveolar or embryonal rhabdomyosarcoma, gastrointestinal stromal tumor, desmoid type fibromatosis, or gynecologic sarcoma. The patients with missing data were also excluded.

Data Collection

Data were retrieved from prospectively maintained databases in place at each participating institution. Clinical and demographic features including age, gender, histological subtype, pathological grade according to FNCLCC (Fédération Nationale des Centres de Lutte Contre Le Cancer) grading system, surgical margin status, tumor size, stage (According to AJCC 8. edition), and presence of adjuvant RT, or CT. Tumor margins were classified as complete (R0) or incomplete (R1/R2). The OS was defined as the time from the diagnosis to the death or last follow-up. The RFS was defined as the time from the diagnosis to the recurrence or metastasis.

This multicenter retrospective study was performed in accordance with the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the University of Erzincan Binali Yıldırım University School of Medicine (33216249-50.01.02).

Statistical Analysis

IBM SPSS 25 (Statistics Program for Social Scientists) (USA) program was used for statistical analysis. Kolmogorov Smirnov test was used ort he compatibility of the data to normal distribution. Non-parametric continuous data were given as median (range), and categorical data as frequency (percentage). Survival analysis was performed using the Kaplan – Meier method. Log-Rank test was used to compare survival times between groups. The independent prognostic factors for OS and RFS were determined by Cox regression analysis. The time from diagnosis to death due to any reason OS; The time from diagnosis to disease relapse or

Table 1. All the patients' general and clinical characteristics

Age, year, median (range)	53 (18-85)
Gender, n (%)	
Male	84 (42.6)
Female	113 (57.4)
Tumor size, n (%)	
< 10 cm	101 (51.3)
≥ 10 cm	96 (48.7)
Tumor grade, n (%)	
1	45 (22.8)
2	72 (36.5)
3	80 (40.6)
Necrosis	
Yes	61 (31.0)
No	136 (69.0)
Stage, n (%)	
IA,B	38 (19.3)
II	59 (29.9)
IIIA	56 (28.4)
IIIB	44 (22.3)
Tumor histology, n (%)	
Liposarcoma	66 (33.5)
Leomyosarcoma	64 (32.5)
Sinovial sarcoma	14 (7.1)
Undifferantiated pleomorphic sarcoma	12 (6.1)
Mixofibrosarcoma	11 (5.6)
Spindle cell sarcoma	10 (5.1)
MPNST	3 (1.5)
Other	17 (8.6)
R0 resection, n (%)	
Yes	130 (66.0)
No	67 (34.0)
Treatment modality, n (%)	
Surgery	49 (24.8)
Surgery + CT	62 (31.5)
Surgery + RT	21 (10.7)
Surgery + CT + RT	65 (33.0)

Abbrevation: *CT= Chemotherapy, RT= Radiotherapy, RFS= Relapse free survival; OS= Overall survival*

death was defined as RFS. All statistical tests were done bilaterally and p< 0.05 was considered statistically significant.

RESULTS

Clinicopathological Features and Treatment

A total of 197 patients diagnosed with RPS between 2000-2019 were included in this study. Median follow-up was 33 months (range: 3-209 months). Demographic and clinical characteristics of the patients are described in Table 1. The median age of the patients was 53 years (range: 18-85). Of 113 (57.4%) patients were female and 84 (42.6%) were male. Tumor size was < 10 cm in 51.3% of the patients. Forty point six percent of patients had grade 3 disease, 36.5% had grade 2, and 22.8% had grade 1 disease. Necrosis was found in 31% of the patients. Stage IA and IB disease were found in 19.3% of the patients, 29.9% had stage II, 28.4% had stage IIIA, 22.3% had stage IIIB disease. In our cohort, 33.5% of patients had liposarcoma, 32.5% leiomyosarcoma, 7.1% synovial sarcoma, 6.1% undifferentiated pleomorphic sarcoma, 5.6% myxofibrosarcoma, 5.1% spindle cell sarcoma, 1.5% had malignant peripheral nerve sheet tumor (MPNST), and 8.6% had other histological types. In the study population, 66% of patients had R0 resection, and 34% of patients had R1/R2 resection. According to the treatment modality, 24.8% of patients had surgery alone, 31.5% had surgery and CT, 21% had surgery and RT, 33% had surgery, RT, and CT.

Survival

Univariate analysis revealed that; tumor size, grade, necrosis, resection margin status, were significantly associated with RFS (p= 0.002, p= 0.044, p= 0.024, p= 0.003 respectively). Age, tumor size, stage, resection margin status were associated with OS (p= 0.038, p= 0.001, p= 0.032, p< 0.001 respectively) (Table 2). The patients with R0 resection had statistically significant longer RFS compared to R1/R2 resection (47 months vs. 20 months, p= 0.003) (Figure 1A). R0 resection also was associated with improved OS compared to R1/R2 resection (122 months vs. 55 months p< 0.001) (Figure 1B). The patients with tumor size < 10 cm had statistically significant longer RFS compared to patients with ≥ 10 cm tumor size (54 months vs. 20 months, p= 0.002) (Figure 2A). The patients with a tumor size of < 10 cm had statistically significant longer OS compared to patients with ≥ 10 cm tumor size (122 months vs. 70 months, p= 0.001) (Figure 2B).

In multivariate analysis tumor size (hazard ratio [HR] 1.545, 95% CI 1.031-2.316 p= 0.035) and resection margin status (HR 1.568, 95% CI 1.041-

Table 2. Univariate Analysis of factors affecting OS and RFS

		RFS, months (95% CI)	p	OS, months (95% CI)	p
Age	<65	46 (47.3-64.6)	0.076	103 (78.9-127.0)	0.038
	≥65	25 (12.4-37.5)		40 (27.1-52.9)	
Gender	Male	35 (20.5-49.4)	0.484	103 (29.4-176.6)	0.225
	Female	34 (8.3-59.6)		99 (84.3-113.6)	
Tumor size	<10 cm	54 (28.6-79.3)	0.002	122 (80.7-163.3)	0.001
	≥10 cm	20 (12.4-27.6)		70 (48.1-91.9)	
Tumor grade	1-2	46 (25.2-66.8)	0.044	122 (64.6-179.4)	0.215
	3	24 (5.8-42.2)		95 (66.2-123.8)	
Necrosis	Yes	20 (10.0-29.9)	0.024	122 (72.1-171.8)	0.063
	No	47 (29.9-64.1)		78 (41.9-114.1)	
Stage	I-II	48 (28.4-67.5)	0.096	122 (56.8-187.2)	0.032
	III	25 (14.8-35.2)		99 (57.6-140.4)	
R0 resection	Yes	47 (27.6-66.4)	0.003	122 (93.7-150.3)	<0.001
	No	20 (12.9-27.0)		55 (15.2-94.8)	
Treatment modality	Surgery	17 (8.6-25.4)	0.215	100 (78.7-121.3)	0.421
	Surgery + CT	35 (24.2-45.8)		95 (61.1-128.9)	
	Surgery + RT	70 (1.4-138.6)		NR	
	Surgery + CT + RT	50 (23.5-76.5)		74 (62.6-128.9)	

Abbrevation: *CT=Chemotherapy, RT=Radiotherapy, RFS: Relapse free survival OS=Overall survival*

2.363 p= 0.032) were independent factors affecting RFS. Also tumor size (HR 1.545, 95% CI: 1.117-3.441 p= 0.019) and resection margin status (HR 2.139 95% CI: 1.222-3.744 p= 0.008) were indipendently affecting OS (Table 3).

DISCUSSION

This multicenter study was conducted to investigate the factors affecting survival in RPS patients treated with upfront curative-intent surgery. Patients with RPS usually present in their 50s, and the frequency is approximately equal in men and women.[10,11] In our study, the median age was 53, with a female predominance. Similarly, in the current literature, the most common histological subtypes were liposarcomas and leiyomyosarcomas.[12,13]

Surgical resection with negative margins remains the standard curative treatment for patients with localized RPS. It is difficult to compare and interpret resectability rates in different institutions due to the heterogenity of the criteria used to determine which patients undergo surgical exploration.[14,15] Grossly complete resection for patients with primary lesions is possible in up to 78% of cases.[16] In our study, the R0 resection rate was 66%. The relationship between margin status and overall survival is well defined in STS. A recent European report on 411 patients undergoing resection for STS revealed that margin status distance defined by R-classification and UICC-classification were independent predictors of local reccurence.[17] Gronchi et al. demonstrated that extensive visceral resection for RPS improved OS and decreased local reccurence.[18] Several studies investigated the prognostic factors for RPS by univariate and multivariate analysis.[19-21] For patients with non-metastatic disease, complete surgical resection, and histologic grade were the main determinants of survival in several recent analyses.[5,22] In our population, the histological grade was not related to survival. Dalton et al. reported that larger tumor size (> 10 cm) and fixation to adjacent retroperitoneal structures were adversely correlated with survival.[23] We found that patients with tumors > 10 cm had worse OS and RFS compared to patients with < 10 cm tumor. Histological subtypes didn't show the difference in OS and RFS.

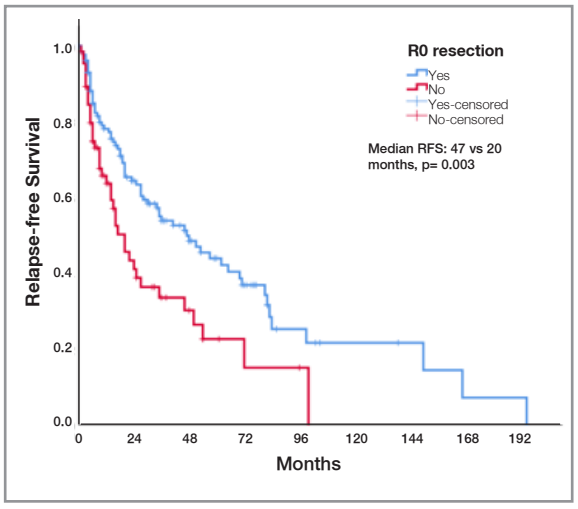

Figure 1A. Relapse free survival by R0 resection

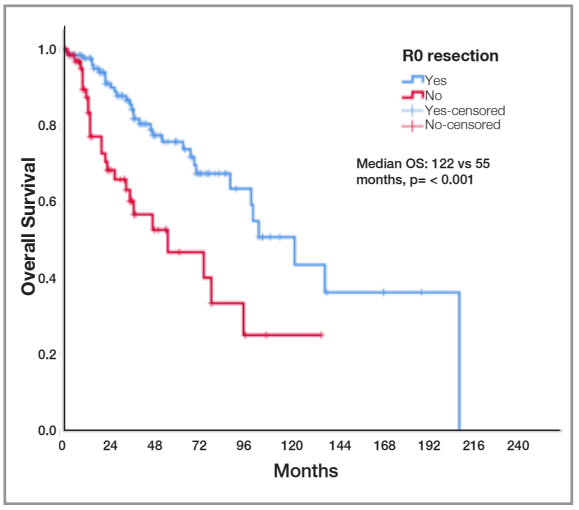

Figure 1B. Overall survival by R0 resection

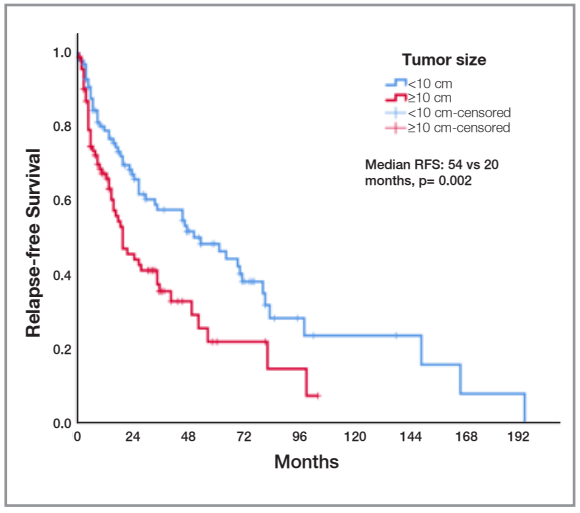

Figure 2A. Relapse Free survival by tumor size

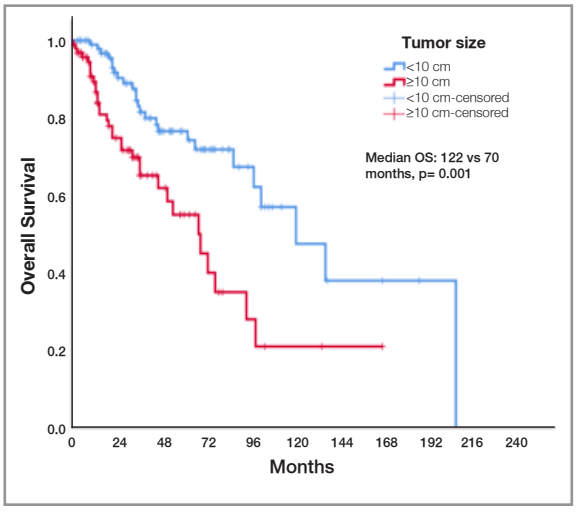

Figure 2B. Overall survival by tumor size

The role of adjuvant chemotherapy in resected RPS remains obscure. A recent propensity score modeling of retrospective cohort study demonstrated that adjuvant CT following curative-intent resection of RPS did not confer a survival benefit.[8] Whether postoperative RT is beneficial for survival is controversial. Postoperative RT has been associated with improved RFS in retrospective non-randomized studies with no improvement in OS.[22,24,25] A recent study reported that multimodality therapy has no impact on overall survival in patients with RPS compared to surgery alone.[21] In our cohort, there was no significant difference in RFS and OS between treatment modalities consisting of only surgery; surgery plus RT; surgery plus CT; surgery, sequential CT, and RT.

There are some limitations in our multicentre study. First of all, it is a retrospective analysis of patients from various medical oncology departments all over the country. Histopathological evaluations of the patients may vary depending on the experience of institutions. Lack of central pathological assessment is a potential limitation of this study. On the other hand, we did not have data on whether the adjacent organs were resected during resection, and if so, which organs were resected. We didn't have a molecular evaluation in our patients.

Table 3. Multivariate Analysis of factors affecting OS and RFS

		RFS		OS	
		HR (95% CI)	**p**	**HR (95% CI)**	**p**
Age	< 65	Reference	0.142	Reference	0.066
	≥ 65	1.467 (0.880-2.445)		1.904 (0.958-3.784)	
Tumor size	< 10 cm	Reference	0.035	Reference	0.019
	≥ 10 cm	1.545 (1.031-2.316)		1.960 (1.117-3.441)	
Tumor grade	1-2	Reference	0.155	Reference	0.380
	3	1.327 (0.899-1.958)		1.279 (0.738-2.217)	
Necrosis	No	Reference	0.072	Reference	0.244
	Yes	1.432 (0.968-2.118)		1.378 (0.804-2.362)	
Stage	I-II	Reference	0.750	Reference	0.123
	III	1.070 (0.706-1.622)		1.545 (0.889-2.685)	
R0 resection	Yes	Reference	0.032	Reference	0.008
	No	1.568 (1.041-2.363)		2.139 (1.222-3.744)	

Abbrevation: *RFS= Relapse free survival; OS= Overall survival*

In conclusion, our multicenter study indicates that adjuvant CT, RT, or multimodality treatment did not show OS and RFS advantage in the resected RPS. Tumor size and resection margin status were the main factors affecting survival. We believe that advances in the molecular characterization of these tumors might help clinicians to detect the best candidates for adjuvant therapies in RPS. Therefore, further studies with randomized clinical trials are needed.

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