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Survival Analysis of Patients with Primary Retroperitoneal Tumors in a Specialty Hospital in Quito-Ecuador in the Period 2009-2019

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ABSTRACT

Purpose: Primary retroperitoneal tumors (PRT) are various heterogeneous types of neoplasms that have a frequency of less than 1%. The main factors associated with survival are time with the disease, treatment received, and recurrence. This study analyzed the clinical and pathological factors that influence the survival outcomes in patients with PRT.
Methods: A retrospective cohort study and a survival analysis were conducted using the available data in the electronic clinical records of patients with a diagnosis of PRT in a specialty hospital in Quito-Ecuador between 2009 and 2019. The included patients were those coded according to the ICD-10 with the C48.0 and C48.8 code. The univariate analysis calculated frequencies, average, and dispersion measurements. Through the Kaplan-Meier method, survival time was analyzed among the different categories of included variables. These differences were shown through the log-rank test.
Results: Sarcomas were the most common type of retroperitoneal tumor found. The median survival period among patients was 14 months. Several significant variables were found to be associated with lower rates of survival, including clinical stages III and IV and status of surgical resection.
Conclusion: Most of the patients were detected in the late stages of the disease. This could be behind the higher mortality rate and low survival among patients. Variables such clinical stages and status of surgical resection were important risk factors for mortality and should be considered for the prognosis.
Key words: primary retroperitoneal tumor, sarcoma, survival analysis, Ecuador

INTRODUCTION

Primary retroperitoneal tumors (PRT) are a heterogeneous type of tumor that develop independently from the retroperitoneal organs. They represent less than 1% of all tumors (1,2), and sarcomas represent one-third of malignant neoplasms in the retroperitoneum (3).

The etiology of PRT and soft tissue tumors has not been determined; however, they are associated with genetic factors, environmental factors,

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radiation, viral infections, and immunodeficiency (4). PRT's are solid or cystic, and they may be benign or malignant depending on their appearance and histopathological characteristics (5). Approximately 75% of retroperitoneal tumors are malignant, the most common of which being sarcomas, lymphomas and neurogenic neoplasms (6).

Patients diagnosed with retroperitoneal tumors often are asymptomatic or they may exhibit various unspecific symptoms such as abdominal pain, weight loss, or a palpable mass; other complaints, are related to compression or invasion of surrounding organs (7). The diagnosis of PRT is complex and could be mistaken for metastatic disease from other primary tumors located in other organs (8). Computed tomography (CT) and magnetic resonance imaging (MRI) are currently the most reliable techniques for the diagnosis of PRT. These studies help for location, composition, and possible invasion of other organs (9). Surgery is the most effective treatment for PRT and determines overall patient survival (10). There is currently no conclusive evidence to support the adjuvant use of radiotherapy (RT) or chemotherapy. Several clinical trials are evaluating the efficacy of these therapies (11).

Recurrence is the leading cause of death by PRT. The severity of recurrence is associated with the location, the proximity of the tumors to vital organs and the histologic grade of the primary disease. Moreover, the resection of a recurrence is difficult because of the lack of access to the retroperitoneal space, compared with other more accessible anatomical areas such the extremities with other types of tumors (12).

Several factors improve the survival rate in patients with PRT. The most important of these are an early diagnosis, surgical treatment, and a rapid intervention in the case of recurrences (13). Survival of patients with PRT, including sarcomas, at one year after diagnosis is estimated to range from 40% to 80% (14,15).

MATERIAL AND METHODS

Design and Settings

This is a retrospective cohort study that analyzed the clinical and pathological factors that influence the survival rates in patients with PRT in a specialized hospital in Quito, Ecuador.

Data Source

Data source was the medical records of patients with a diagnosis of "malignant neoplasm of retroperitoneum and peritoneum" according to the International Classification of Disease tenth revision (ICD-10) C48 diagnostic code between January 1, 2009, and December 31, 2019 were analyzed.

Statistical Analysis

Our analysis considers the following variables: sex, level of education, comorbidities, history of diabetes, history of hypertension, smoking, alcohol consumption, symptoms, histological type of the tumor, tumor differentiation grade, clinical stage of cancer, tumor size, presence of recurrence, surgical treatment, surgical resection type, chemotherapy, radiotherapy, palliative care, and death.

The Kaplan-Meier method was used to plot survival curves. These graphs serve to test the proportional hazard assumption. Using the Kaplan-Meier survival curves followed by the log-rank tests, the survival time after initial diagnosis among the different categories of included variables was calculated.

A Cox proportional hazard regression model was used to compare survival time for each variable to determine the variables that had a p value of 0.25 or under. Variables that met the criteria or any other variables that were considered clinically relevant in our saturated Cox regression model were included. By backward variable reduction, the final model obtained included the variables sex, presence of urinary symptoms, gastrointestinal bleeding, surgical resection type, and clinical stage at diagnosis. A sensitivity analysis was then performed. Stata Version 14 and Microsoft Excel were used for the statistical analysis.

RESULTS

Characteristics of the Sample

The analysis included 77 patients with a diagnosis of retroperitoneal sarcomas between 2009 and 2021. *Table 1* shows the characteristics of the patients. The male sex was more frequent with 62.34% (48/77) vs 37.66% for females (29/77). The mean age was 57 years, ranging from 21 to 81 years of age, and the groups between 51 and 65 years and more than 65 years of age were most affected, 32.46% (25/77) and 36.36% (28/77), respectively. Comorbidities were present in 36.36% (28/77) patients, hypertension and diabetes mellitus type 2 were frequent, 25.97% (20/77) and 12.98% (10/77), respectively. Abdominal pain, 77,92% (60/77), and the presence of an abdominal mass, 51.95% (40/77) were the most predominant symptoms in the patients.

Table 1 - Characteristics of the sample

Sample	n (%)
Sex	
Male	48 (62.34)
Female	29 (37.66)
Age of patients	
18-35	6 (7.79)
36-50	18 (23.37)
51-65	25 (32.46)
> 65	28 (36.36)
Education	
Primary	19 (24.67)
Secondary	38 (49.35)
Higher education	17 (22.07)
None	3(3.89)
Comorbidity	
Yes	28 (36.36)
No	49 (63.63)
Diabetes history	
Yes	10 (12.98)
No	67 (87.02)
Hypertension history	
Yes	20 (25.97)
No	57 (74.03)
Smoking history	
Yes	9 (11.69)
No	68 (88.31)
Alcohol history	
Yes	13 (16.88)
No	64 (83.12)
Principal symptom	
Abdominal pain	60 (77.92)
Abdominal mass	40 (51.95)
Weight loss	31 (40.26)

Table 2 - Tumor characteristics

Sample	n (%)
Histological Type	
Sarcoma	58 (75.32)
Other	19 (24.67)
Type of Sarcoma	
Liposarcoma	26 (44.83)
Undifferentiated pleomorphic sarcoma (UPS)	14 (24.14)
Leiomyosarcoma	7 (12.07)
Malignant peripheral nerve sheath tumor (MPNST)	4 (6.90)
Synovial sarcoma	2 (3.45)
Embryonal Rhabdomyosarcoma	1 (1.72)
Fibroblastic sarcoma	1 (1.72)
No information	3 (5.17)
Tumor Differentiation Grade	
High grade	31 (40.25)
Low grade	14 (18.18)
No information	32 (41.55)
Stage of cancer	
I	1 (1.29)
II	14 (18.18)
III	30 (38.96)
IV	9 (11.68)
No information	23 (29.87)
Tumor size	
Less than 5cm	2 (2.59)
5-10 cm	11 (14.28)
More than 10 cm	40 (51.94)
No information	24 (31.16)
Recurrence	
Yes	17 (22.07)
No	60 (77.92)
Resection Type	
Complete (RO)	27 (35.06)
Incomplete (R1 and R2)	46 (59.74)
No information	4 (5.20)
Chemotherapy	
Yes	35 (45.45)
No	42 (54.54)
Radiotherapy	
Yes	7 (9.09)
No	70 (90.90)
Palliative care	
Yes	12 (15.58)
No	65 (84.41)
Total	77 (100)

R0: no residual tumor, R1: microscopic residual tumor, R2: macroscopic residual tumor

Table 2 exhibits tumor characteristics; the predominant histologic types of tumors were sarcomas with 75.32% (58/77) and others type of tumors in 24.67% in (19/77). Among the patients in the sarcoma group, 44.83% (26/58) had a histological diagnosis of liposarcoma, 24.14% (14/58) had undifferentiated pleomorphic sarcomas (UPS), and 12.07% (7/58) had leiomyosarcoma. Other primary retroperitoneal tumors were 26.32% (5/19) gastrointestinal stromal tumors, 15.79% (3/19) mesenchymal tumors, 10.53% (2/19) extragonadal germ cell tumors, 10.53% (2/19) primitive neuroectodermal tumors, 5.26% (1/19) paragangliomas, 5.26% (1/19) retroperitoneal pseudomyxoma and 26.32% (5/19) unspecified tumors.

Tumors greater than 10 cm represented 51.94% (40/77), and the stage III cancer was the most frequent, in 38.96% (30/77) of patients. 40.25% (31/77) of tumors were high grade differentiated. 59.74% (46/77) had an incomplete resection (R1 and R2). Additional treatments to surgery were chemotherapy and radiotherapy, prescribed to 45.45% (35/77) and 9.09% (7/77) of patients, respectively.

Survival Analysis

The median survival time of the patients was 14 months and the 25th percentile of survival time was 3 months. The total time at risk was 2385 months and the total follow-up time was 154 months, in which 52 patients died. The rest of the population survived beyond the follow-up period. The overall incidence rate was 0.02 (*fig. 1*).

The probability of survival in the first year after diagnosis was 54.63% (95% CI: 0.43 - 0.65). The probability

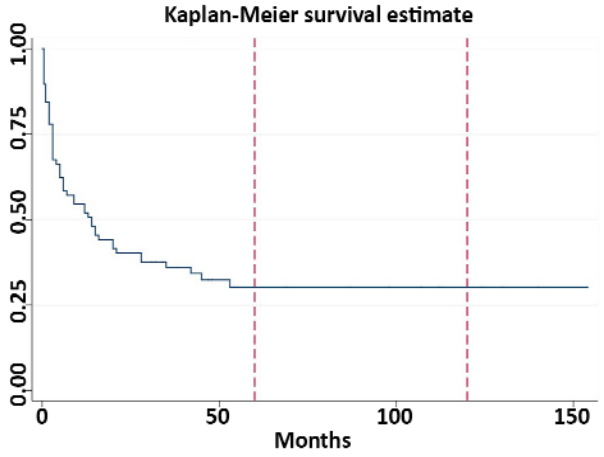

Figure 1 - Global survival in patients for PRT

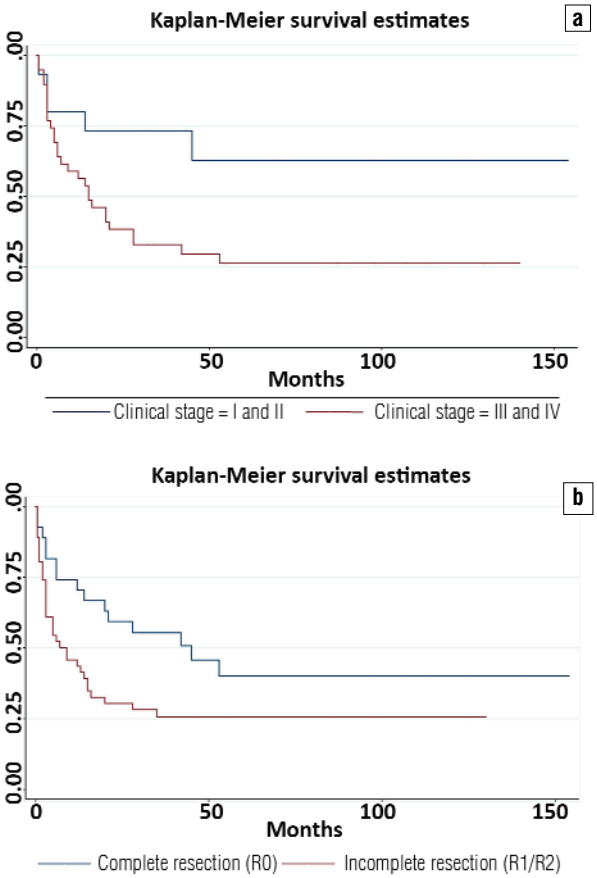

Figure 2 - Kaplan-Meier curves for the variables related with survival

(a) Survival by clinical stage: Patients with a diagnosis of stage I or II have a significantly higher survival than those with stages III and IV. (b) Survival by state of resection: Patients that had an incomplete resection had a significantly lower survival time (7 months) than those with a complete resection (45 months).

of survival after five years of follow-up was 15.63%. The annual probability of survival is depicted in *table 3*.

The univariate analysis of the patient characteristics exhibited several significant relationships with survival rate (*table 4*). The main variables that were associated with a lower rate were the male gender (p=0.04), presence of weight loss (p=0.04), history of diabetes mellitus (p=0.01), the clinical stage (p=0.02), the type of procedure (p=0.05), and the incomplete resection of the tumor (p=0.03). *Fig. 2* shows the survival estimates using Kaplan-Meier curves for the variables related with survival.

Cox-Proportional Hazard Model

The multivariable Cox proportional hazards regression model using a p-value for significance < 0.05 and 95% confidence interval in a multivariate analysis showed that the clinical stages III and IV had significantly higher probabilities of dying (HR: 3.92, 95%CI 1.37-11.23, p=0.011). Additionally, the presence of urinary symptoms showed a higher rate (HR: 3.59,

Table 3 - Annual probability of survival in 12-month intervals

Months	Total patients at beginning of interval	Deaths	Lost	Survival	Standard Error	95% CI.
0-12	77	35	0	0.546	0.057	0.428-0.649
12-24	42	11	0	0.403	0.056	0.293-0.509
24-36	31	8	0	0.299	0.052	0.201-0.402
36-48	23	7	0	0.208	0.046	0.126-0.304
48-60	16	4	0	0.156	0.041	0.086-0.245
60-72	12	1	0	0.143	0.040	0.076-0.230
84-96	11	1	0	0.130	0.038	0.067-0.215
96-108	10	3	0	0.091	0.033	0.040-0.168
108-120	7	2	0	0.065	0.028	0.024-0.135
120-132	5	3	0	0.026	0.018	0.005-0.081
132-144	2	1	0	0.013	0.013	0.001-0.062
144-156	1	1	0	0.546	0.057	-

Table 4 - Univariate analysis of patient variables

Variable	n (%)	50th percentile survival (months)	p value
Sex			0.048
Male	48 (62.34)	9	
Female	29 (37.66)	28	
Age of patients			0.449
18-35	6 (7.79)		-
36-65	43 (55.83)	16	
> 65	28 (36.36)	6	
Comorbidity			0.875
Yes	28 (36.36)	5	
No	49 (63.63)	14	
Diabetes history			0.017
Yes	10 (12.98)	2	
No	67 (87.02)	15	
Hypertension history			0.753
Yes	20 (25.97)	5	
No	57 (74.03)	14	
Smoking history			0.472
Yes	9 (11.69)	6	
No	68 (88.31)	14	
Alcohol history			0.352
Yes	13 (16.88)	3	
No	64 (83.12)	15	
Abdominal pain			0.858
Yes	60 (77.92)	12	
No	17 (22.08)	14	
Weight loss			0.056
Yes	31 (40.26)	6	
No	46 (59.74)	20	
Abdominal mass			0.682
Yes	40 (51.95)	12	
No	37 (48.05)	14	
Digestive symptoms			0.142
Yes	23 (29.87)	6	
No	54 (70.13)	16	
Urinary symptoms			0.043
Yes	8 (10.39)	3	
No	69 (89.61)	15	
Gastrointestinal bleeding			0.043
Yes	3 (3.90)	3	
No	74 (96.10)	14	
Tumor differentiation			0.128
High	28 (66.67)	15	
Low	14 (33.33)	.	
Clinical Stage			0.024
I and II	15 (27.78)	.	
III and IV	39 (72.22)	15	
Chemotherapy			0.875
Yes	28 (41.18)	14	
No	40 (58.82)	9	
Radiotherapy			0.212
Yes	7 (9.09)	.	
No	70 (90.91)	12	
Tumor resection			0.119
Yes	35 (45.45)	28	
No	41 (53.25)	9	
Size of tumor			0.429
< 5 cm	2 (2.60)	.	
5 cm to 10cm	11 (14.29)	42	
> 10 cm	40 (51.95)	21	
Type of tumor			0.985
Sarcoma	58 (75.32)	14	
Other	19 (24.67)	12	
Type of procedure			0.059
Needle biopsy (non-surgical procedure)	19 (24.68)	5	
Surgery	55 (71.43)	21	
Other	3 (3.90)	1	
State of resection			0.035
Complete resection (R0)	27 (36.99)	45	
Incomplete resection (R1 and R2)	46 (63.01)	7	
Recurring Tumor			0.482
Yes	17 (22.07)	42	
No	60 (77.92)	13	

R0: no residual tumor, R1: microscopic residual tumor, R2: macroscopic residual tumor

95%CI 1.15-11.21, p=0.027). Moreover, patients with a prior incomplete resection of their tumor had a higher risk of death and female patients have a lower risk (*table 5*).

DISCUSSION

Primary retroperitoneal tumors represent approximately 1% of all malignant tumors in adults. Diagnosis and treatment can be challenging due to the late clinical presentation and the particular location of the

Table 5 - Cox-proportional hazards model.

Factor	Hazard ratio	95%CI	p value
Sex (female vs. male)	0.61	0.27-1.37	0.239
Urinary Symptoms (yes vs. no)	3.59	1.15-11.21	0.027
Gastrointestinal bleeding (yes vs. no)	6.20	0.69-55.18	0.102
Surgery resection (incomplete vs. complete)	1.95	0.88-4.30	0.095
Clinical stage (III/IV vs. I/II)	3.92	1.37-11.23	0.011

tumor, as the retroperitoneum is a compliant space and the tumor may be asymptomatic for a long time (16).

Our findings show that PRT are more frequent in older patients. This is comparable to other studies, where data reveal that these tumors often are diagnosed between the sixth and seventh decade of life (17-19). Even though evidence shows no difference in the incidence between males and females, we found a slight predominance in males (20). In our study, 36.36% patients had comorbidities, which is comparable to 39.6% reported by Garcia et al. (21).

Symptoms of PRT present themselves late in life, most commonly by the presence of an abdominal mass or discomfort. We found that symptoms such as abdominal pain, abdominal mass, and weight loss were the most frequently reported. These results echo those reported by Hueman et al. (22). In our case series, 51.94% tumors were greater than 10 cm, which is relatively smaller than those reported by other studies, where the size of tumors greater than 20 cm was more frequent (23,24).

In our study, sarcomas were the most frequent type of PRT in 75.32% patients. These data are similar to the 83.7% described by Viserda et al. (25), a study of 10-year follow-up, and the 79.2% reported by Garcia et al. (23). The subtype of sarcoma most commonly found were liposarcomas in 44,83% of patients, which was slightly lower than those reported in other studies where at least half of the cases were this type of sarcoma (17,18,26,27). Most of the cases were detected in the late stages of the disease, similar to other studies (27-29).

The surgical resection of PRT is difficult because of the lack of access to the retroperitoneal space. We found a R0:R+ resection ratio of 37%:63%, which means that more than half of the cases did not achieve complete surgical resection. These data are different to those reported by other studies in which the complete surgical resection was higher, 48%:35%, 50%:50%, and 83%:17% (30-32). Incomplete surgical resection of PRTs is the primary cause of local recurrence. In our case series, 22% of patients had recurrences; however, our result is lower than that reported by Ferrario et al., which was 41% (33).

The probability of survival in the first year after diagnosis was 54.6%, and the probability of survival at 5 years was 15.6%, in contrast to other studies in which the range of survival at 5 years was between 22 and 66% (19,27,34). This can be explained because most of the patients that we included in our study were in the late stages of the disease. In agreement with our findings, previous studies support that sex, clinical stage, type of procedure, and incomplete tumor resection should be considered as an important predictor of survival (35-37).

Surgical resection of localized tumors with gross negative margins remains the standard of care, with 5-year survival rates ranging above 50% (38). Bonvalot et al. (12) showed that the surgical factors associated with local control in a cohort of 382 patients with PRTs were mostly high grade of differentiation, tumor rupture, and gross residual disease (R2 status). In our multivariate analysis, the incomplete resection was an independent predictor of inferior overall survival, which has been consistently reported in several studies (37,39-41). These results indicate that the presence of gross residual tumor is associated with worse patient outcomes, highlighting the importance of achieving macroscopically complete resection. Additionally, we found that patients with stage III/IV had poorer overall survival rates than those in stage I/II. These results are similar to others reported in the literature; patients with advanced clinical stages have tumors invading adjacent structures and may be more likely to develop residual microscopic or gross disease even after resection (42-44).

The clinical manifestations of retroperitoneal tumors are nonspecific. The presence of an asymptomatic abdominal mass found incidentally on abdominal examinations is the most common presentation. However, neurologic, musculoskeletal, and urinary /intestinal obstructive symptoms may be present in local invasion or compression of retroperitoneal structures (45,46). No studies were identified in which the presence of urinary symptoms could be related to overall survival of PRT. Nevertheless, Taguchi et al. (47) reported that any patients presenting symptoms at diagnosis were significantly more likely to develop recurrence and die due to sarcoma compared to asymptomatic patients.

The analysis of these results must consider some limitations. First, as with all single-institution retrospective studies, the study had small sample size, and the results cannot be extrapolated to the general population. Second, data for some explanatory factors were missing and some were recorded incorrectly, which could have been useful in adjusting the model. Some of the records had missing or incomplete histopathological information. Finally, the selection criteria for the diagnosis of PRT was the ICD-10 code classification and it is possible that we missed some patients because of inappropriate codification. Nonetheless, to our knowledge, this is the first survival analysis study in a cohort of patients with PRTs followed

for 10 years in Ecuador and it provides information about the dynamic survival of these patients.

CONCLUSION

The survival of patients with PRT is related to the clinical stage of the disease and the status of surgical resection. Other risk factors that should be considered in estimating patient survival and prognosis are the male sex and the presence of urinary and digestive symptoms.

Author's Contributions

Andrés Moreno: Conceptualization, Methodology, Software, Writing - Original draft preparation Xavier Sánchez.Data curation, Methodology, Software, Writing- Original draft preparation. Ricado Manosalvas: Data curation. Luciana Armijos: Methodology, Writing - Original draft preparation. Ruth Jimbo-Sotomayor: Methodology, Writing- Original draft preparation Oscar Jaramillo: Validation, Writing - Reviewing and Editing: Alfredo Viloria: Validation, Writing - Reviewing and Editing.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Hospital Carlos Andrade Marín (IESS-HCAM-CEISH-2021-0026-DF).

Consent to participate

The Ethics Committee established that there was no need for informed consent for this study. All methods were carried out in accordance with relevant guidelines and regulations. The information of the patients came from secondary data and the database was properly anonymized before its use.

Data Availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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