Retrospectıve analysis of pelvic and retroperitoneal sarcomas.
Single center's experience

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Can Saracoglu*, Cebrail Akyuz**, Mehmet Gulmez*

*Department of General Surgery, Giresun University, Prof Dr A. Ilhan Ozdemir Training and Research Hospital, Giresun, Turkey
**Deparment of Gastroenterological Surgery, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey
***Department of General Surgery, Giresun University Faculty of Medicine, Giresun, Turkey

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BACKGROUND: *Retroperitoneal sarcoma (RPS) is a surgically manageable condition that can recur locally after complete macroscopical resection. Managing patients at high-volume specialized healthcare centers has positive effects on treatment outcome. The present study aimed to preoperatively, perioperatively, and postoperatively assess patients who underwent surgery for RPS.*
METHODS: *Consecutive surgical resections of RPS performed at a single healthcare center between January 2011 and December 2018 were investigated retrospectively. Histological, radiological, and clinical data were collected. In addition to local recurrence rate of patients with complex tumor resection, existing symptoms, adjuvant treatment type, and 5-year overall and disease-free survival rates were recorded and analyzed.*
RESULTS: *Extensive complete tumor resection was performed in 25 (%100) patients operated in our clinic for retroperitoneal sarcoma between 2011-2018. The mean survival time in patients undergoing R0 resection was found to be significantly higher than that in patients undergoing R1 resection(p=0.001). No statistically significant difference was found between histological grading and histological types in terms of mean survival (p=0.63 p=0.36). There was no statistically significant difference in terms of mean survival between patients who did not receive additional therapy, received adjuvant chemotherapy, and those who received adjuvant chemotherapy and radiotherapy. (p = 0.342)*
CONCLUSION: *Although extensive complete resection is the gold standard in the treatment of retroperitoneal sarcoma, the effect of adjuvant chemotherapy and radiation therapy is still under discussion. In our study, high mean survival rates were determined due to R0 resection, and the effect of tumor grade and histological subtype on survival was not observed.*

KEY WORDS: Adjuvant therapy, Overall survival, Retroperitoneal sarcoma, Surgical resection

Introduction

Retroperitoneal sarcoma (RPS) accounts for approximately 15% of all soft-tissue sarcomas, with an annual incidence of 1600 cases/year in the United States [1]. Its most common histological types, liposarcoma and leiomyosarcoma, account for two-thirds of all patients. Patients are usually diagnosed in the 6th decade of life, and the female-to-male ratio is 1:1. Tumor size can range from 15 to 20 cm 2-4. Patients usually present with painless mass, but the mass is also accompanied by pain in one-third of all patients. RPS can be of a large size because they remain asymptomatic for a long time without signs of pressure on adjacent organs. Regional lymph node involvement in RPS is extremely rare and is observed only in <5% of patients, whereas this rate is higher in synovial sarcoma, clear-cell sarcoma, epithelioid sarcoma, and epithelioid sarcoma [3,4]. The optimal treatment method is complete surgical resection, which is the only chance as a single course of treatment [5]. Local recurrence is the most important cause of death in patients with RPS. The roles of radiotherapy and chemotherapy in the treatment of patients remain controversial. Although recent studies have shown that aggressive surgery and advanced radiotherapy methods allow a decrease in the incidence of local recurrences, these treatment methods are controversial. Next-generation chemotherapy methods

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Correpondence to: Can Saracoglu, Ataturk Mahallesi, Atasehir Bulvari, 57.Ada16.Blok Daire:4, Atasehia, Istanbul, Turkey (e-mail: cansaracoglu@hotmail.com)

and targeted agents can play a role in reducing the rates of local and distant recurrences [1-4].

The present study presents a retrospective analysis of the preoperative, perioperative, and postoperative assessment of patients who were surgically treated for RPS at the University of Health Sciences Haydarpaşa Numune Training and Research Hospital's General Surgery Clinic between 2011 and 2018.

Methods

In total, 25 patients who were operated for curative purposes for RPS during 2011–2018 were retrospectively investigated. All patients had been referred to the University of Health Sciences Haydarpaşa Numune Training and Research Hospital.

Inclusion criteria were patients aged ≥18 years who were reported to have RPS and were treated at our healthcare center. Inoperable cases of diffuse disease; those aged <18 years; those with synchronous tumors; pregnant women; those with uncontrollable metabolic disease; and those with gynecological, skeletal or abdominal tumors such as gastrointestinal stromal tumor, small round blue cell tumor, osteosarcoma, chondrosarcoma, and fibromatosis were excluded from the study.

The present study included variables related to patients, tumor, and treatment. Patient-related variables included age, sex, symptoms, diagnostic methods, and follow-up period. Tumor-related variables included size, histological grade (high or low), and histological subtypes. Treatment-related variables included surgical methods applied, morbidity, adjuvant therapy modalities, recurrence, and secondary surgical treatment methods for recurrence.

Preoperative evaluation was performed for all patients. Initially, detailed evaluation of patient history and physical examination were performed. Chest X-ray and/or contrast computed tomography for metastatic disease was performed for all patients. Radiological examination such as angiography, intravenous pyelography, scintigraphy, and positron emission tomography were performed when needed.

Antibiotic prophylaxis and prophylactic low-molecular-weight heparin were administered to all patients. The site of surgical incision varied depending on the tumor location. Median incisions above and below the umbilical level in the supine position were preferred in most patients. Data on operation time, duration of hospital stay, morbidity rate, and mortality rate were obtained from the archive of medical files. Mortality during the initial 1-month period was considered hospital mortality. All patients underwent en bloc resection for complete tumor resection. Additional organ resections were confirmed by pathological data.

Histological subtype assessments were reviewed by a single pathologist according to the updated WHO classification. Tumor size was defined as the largest diameter of a tumor in pathological analysis. The Fédération nationale des centres de lutte contre le cancer grading system was used for tumor grading. The boundaries of macroscopic samples were expressed microscopically as R0 (clean surgical margins) and R1 (presence of tumor cells at surgical margins). R2 indicated macroscopic residual disease.

The decision concerning administration of postoperative adjuvant radiotherapy or chemotherapy was made in a council attended by a surgeon, pathologist, and oncologist. Local recurrence was defined as retroperitoneal tumor or recurrent tumor in the abdominal cavity. Metastases outside the abdominal cavity and/or metastases to organs were expressed as distant recurrence.

Patients were followed up until December 2018. Overall and disease-free survival rates as well as details of patients who were re-operated for recurring disease were recorded.

Statistical analysis was performed using SPSS 16.0 (SPSS for Windows, 2008; SPSS Inc., Chicago, Illinois, USA). The duration of overall and disease-free survival was measured from the date of surgical resection to the last follow-up visit. The effect of clinicopathological factors on survival was assessed using univariate cox proportional analysis. A p-value of <0.05 was considered statistically significant.

Results

A total of 25 patients with RPS were operated at the general surgical clinic of our hospital between 2011 and 2018. Among these, 13 (52%) were male and 12 (48%) were female. Their mean age was 57.4 ± 8.88 years. Chief complaints included abdominal pain in 14 (56%) patients, bloating in 3 (12%), and urinary obstruction in 1 (4%). In 7 (28%) patients, it was incidentally

TABLE I - *Patient characteristics*

Variable	Male	Female	Total
Patients	n= 13(52%)	n= 12(48%)	25
Age (year, mean ± SD)	54.4±8.47	60.6±7.69	57.4±8.88
Follow-up (month, mean ± SD)	33.1±17.57	33.8±14.86	33.4±16.41
Symptoms			
Abdominal pain	4(%16)	10(%40)	14(%56)
Abdominal bloating	3(%12)	-	3(%12)
Urinary obstruction	1(%4)	-	1(%4)
Incidental	5(%20)	2(%8)	7(%28)
Initial diagnosis method			
USG	4	6	10
CT	8	6	14
MRI	1	-	1

USG: ultrasonography, CT: computed tomography, MRI: magnetic resonance imaging

Table II - *Tumor characteristics*

N.	Sex	Age (years)	T (primary tumor)	Tumor diameter (cm)	Additional organ resection	Histological grade
1	F	59	Well-differentiated LS	37		G1
2	F	61	Well-differentiated LS	43		G1
3	F	63	Dedifferentiated LS	24	Left nephrectomy	G2
4	F	65	Dedifferentiated LS	26	Left nephrectomy	G2
5	M	61	Dedifferentiated LS	12	Distal pancreatectomy+splenectomy	G3
6	M	62	Good differentiated LS	16		G1
7	F	67	Myxoid LS	36		G3
8	F	70	Myxoid LS	26		G3
9	M	41	Well-differentiated LS	7	Right nephrectomy	G2
10	M	42	Well-differentiated LS	10		G1
11	M	68	Well-differentiated LS	35	Appendectomy	G2
12	M	53	Dedifferentiated LS	40	Right nephrectomy+right hemicolectomy	G2
13	M	44	Myxoid LS	22	Right nephrectomy+appendectomy	G3
14	F	45	Well-differentiated LS	18	Partial rib resection	G1
15	M	54	Well-differentiated LS	18	Left nephrectomy	G1
16	F	56	Myxoid LS	24		G3
17	F	69	Well-differentiated LS	6		G1
18	F	70	Myxoid LS	26		G3
19	M	55	Angiosarcoma	7	Left nephrectomy	G3
20	F	55	Well-differentiated LS	7		G1
21	M	61	Dedifferentiated LS	22	Right nephrectomy	G3
22	F	48	Dedifferentiated LS	17		G3
23	M	57	Myxoid LS	19	Right hemicolectomy	G3
24	M	51	Myxoid LS	37	Right nephrectomy+right hemicolectomy	G3
25	M	59	Well-differentiated LS	14		G1

M: male, F: female, LS: liposarcoma, G: grade

detected on radiological imaging performed for other reasons. Patient characteristics are summarized in Table I. All 25 (100%) patients underwent extensive complete tumor resection and 13 (52%) underwent additional organ resection. Nine of the patients who underwent additional organ resection underwent nephrectomy, 1 underwent distal pancreatectomy+splenectomy, 1 underwent appendectomy, 3 underwent right hemicolectomy, and 1 underwent partial resection of the 11th and 12th ribs. Details on age, sex, tumor type, tumor diameter, additional organ resection, and histological grading of patients operated for RPS are shown in Table II.

Evaluation of resection margin according to postoperative pathological data revealed that 21 (84%) patients underwent R0 resection and 4 (16%) underwent R1 resection. R2 resection was not performed in any patient. The mean survival duration was 36.3 ± 15.25 months for patients who underwent R0 resection and 18.25 ± 7.57 months for those who underwent R1 resection. Regarding mean survival rate, it was significantly higher among patients who underwent R1 resection than among those who underwent R1 resection (p = 0.001). Regarding histological grading of pathological specimens, 14 (56%) patients had grade 1 and 2 tumor and 11 (44%) had grade 3 tumor. There was no significant difference between them in terms of mean survival rate (p = 0.63). Among the 25 patients, 11 (44%) had well-differentiated liposarcoma, 7 (28%) had myxoid liposarcoma, 6 (24%) had dedifferentiated liposarcoma, and 1 (4%) had angiosarcoma. There was no significant difference among the groups of histological types in terms of survival (p = 0.36). The findings related to pathological variables are shown in Table III.

Table III - *Pathological variables*

Variable	N	Mean survival (month, mean ± SD)	P (UVA)
Resection margin			0.001
R0	21 (%84)	36.3 ± 15.25	
R1	4 (%16)	18.25 ± 7.57	
R2	-	-	
FNCLCC grade			0.63
Grades 1 and 2	14 (%56)	36.3 ± 16.63	
Grade 3	11 (%44)	29.8 ± 12.97	
Histology			0.36
IDLS	11 (%44)	36.6 ± 18.22	
MLS	7 (%28)	28.7 ± 10.85	
DDLS	6 (%24)	33.2 ± 7.80	
Other	1 (%4)	30 ± 0	

FNCLCC: Fédération nationale des centres de lutte contre le cancer, IDLS: indifferantiated liposarcoma, MLS: myxoid liposarcoma, DDLS: dedifferantiated liposarcoma

The mean operation time of the 25 patients was 259 ± 97.17 min and mean length of hospital stay was 7.76 ± 5.7 days. During the postoperative period, surgical-site infection was observed in 6 patients (24%), ileus in 6 (24%), and atelectasis in 3 (12%). Only 1 patient died due to intra-abdominal hemorrhage on postoperative day 2. The findings related to perioperative and postoperative variables are given in Table IV.

During the postoperative period, 6 patients (24%) were administered adjuvant chemotherapy and 5 (20%) were administered adjuvant chemotherapy + radiotherapy, whereas 14 received no additional therapy. Regarding mean survival rate, there was no significant difference among these three groups of patients (p = 0.342). The findings related to postoperative variables are summarized in Table V.

Concerning survival rate, the mean disease-free survival rate of all patients operated between 2011 and 2018 was 19.36 ± 15.94 months and overall survival rate was 33.4 ± 16.41 months. Among the 25 patients, only 1 had early postoperative mortality, whereas the remaining 24 patients were alive. Survival rates are shown in Table VI. Recurrent disease was observed in 10 (40%) of the 25 patients. Among them, 8 (32%) underwent re-operation and the remaining 2 (8%) only underwent chemotherapy due to diffuse distant organ metastasis. Among these 8 patients, 6 underwent re-operation with extensive complete tumor resection and additional organ resection, 1 underwent R2 resection, and 1 underwent metastasectomy for single liver metastasis. The findings related to recurrent disease are summarized in Table VI.

Table IV - *Perioperative and postoperative variables*

Variable	
Operation time (min, mean ± SD)	259 ± 97.17
Hospital stay (days, mean ± SD)	7.76 ± 5.70
Morbidity (n)	
Surgical-site infection	6 (%24)
Ileus	6 (%24)
Atalectasia	3 (%12)
Mortality (n)	
Hemorrhage	1 (%4)

Table V - *Postoperative treatment variables*

Variables	N	Survival (month, mean ± SD)	P (UVA)
Adjuvant CT	6	27.5 ± 9.09	0.342
Adjuvant CT+RT	5	37.4 ± 8.02	
Follow-up*	14	34.64 ± 19.6	

*Patients who did not receive adjuvant treatment
UVA: ultra-variant analysis, CT: chemotherapy, RT: radiotherapy

Table VI - *Survival characteristics*

Survival (months, mean ± SD)	
Disease-free survival	19.36 ± 15.94
Overall survival	33.4 ± 16.41

Table VII - *Recurrent disease*

N.	Primary tumor	Resection margin	Adjuvant therapy	Recurrence location	Treatment
1	Well-differentiated LS	R1	CT	Retroperitoneal	Extensive complete tumor resection+right nephrectomy+partial resection of VCI
2	Dedifferentiated LS	R0	CT	Retroperitoneal	Extensive complete tumor resection+distal pancreatectomy+splenectomy
3	Dedifferentiated LS	R0	CT	Multiple metastases in the liver and lungs	CT
4	Myxoid LS	R1	CT+RT	Retroperitoneal	Extensive complete tumor resection+right nephrectomy
5	Well-differentiated LS	R0	-	Retroperitoneal	R2 resection
6	Myxoid LS	R0	CT	Retroperitoneal	Extensive complete tumor resection
7	Myxoid LS	R1	CT+RT	Retroperitoneal	Extensive complete tumor resection+right nephrectomy
8	Dedifferentiated LS	R0	CT+RT	Retroperitoneal	Extensive complete tumor resection
9	Dedifferentiated LS	R1	CT+RT	Liver metastasis	Metastasectomy
10	Myxoid LS	R0	CT	Multiple metastases in the liver	CT

LS: liposarcoma, CT: chemotherapy, RT: radiotherapy, VCI: vena cava inferior

Discussion

RPS is a rare disease and has a better survival rate than other soft-tissue sarcomas (hemangiosarcoma, malignant fibrous histiocytoma, and malignant peripheral nerve sheath tumor) [6,7] RPS is not only a singular disease but also a process involving several different neoplasms associated with a common histogenetic origin [8]. Their resection is challenging to surgeons and oncologists because they are encountered rarely and have combinations of different pathological features. Difficulty in their marginal resection and high rates of local recurrence make effective treatment of these patients difficult.

Although male dominance is evident in patients with RPS in the literature, the male-to-female ratio was 1:1 in the present study (52%-48%). In other studies, the mean age at tumor detection was 3rd-4th decades of life, whereas that in the present study was 57.4 ± 8.88 years (9). Unlike in the literature, common findings included abdominal pain and bloating (68%). In 7 patients (28%), tumor detection was incidental [10]. Computed tomography and ultrasonography were useful for early diagnosis as well as for the assessment of local and distant metastases of the disease.

In the present study, none of the patients underwent preoperative biopsy. For several patients with sarcomas, a biopsy can be recommended, i.e., if a neoadjuvant therapy protocol is followed at clinics or if there is a need for oncological treatment in the presence of local or metastatic diseases that are unresectable. Preoperative biopsy is not required for all patients with RPS [11].

The rarity of RPS indicates that prognostic factors have not been clearly identified yet. In general, it is recognized that the most important factor affecting survival outcome is complete tumor resection [12,13]. Although the complete tumor resection rate reportedly varies from 38% to 74%, its reported average is 53% [14-16]. In the present study, the complete tumor resection rate (R0) was 84%, R1 resection rate was 16%, and R2 resection rate was 0%, and these rates were found to be considerably higher than those reported in the literature. The mean survival rate was 36.3 ± 15.25 months in patients who underwent R0 resection and 18.25 ± 7.57 months in those who underwent R1 resection, which revealed a significant difference ($p = 0.001$).

The most important factor determining survival after complete tumor resection is histological grade (8,17,18). Histological grade varies depending on the number of mitosis, degree of cellular and nuclear atypia, and presence of necrosis [8,17,19]. According to the AJCC grading system, the grade of soft-tissue sarcomas directly determines disease stage. Tumor size is the second most important determinant of disease stage [8,17,20]. In the present study, 14 patients (56%) had grade 1 and 2 tumors and 11 (44%) had grade 3 tumors. There was no significant difference between these groups in terms of mean survival rate (29.8 ± 12.97 vs. 36.3 ± 16.63 months; $p = 0.63$), which do not confirm to previous findings. In a study by Singer et al [21] that included 177 patients with RPS treated for curative purposes, histological subtype was associated with survival. Although the mortality rate for dedifferentiated liposarcoma was found to be six times higher than that for well-differentiated liposarcoma, there was no significant difference among patients with well-differentiated liposarcoma, myxoid liposarcoma, and dedifferentiated liposarcoma in terms of survival ($p = 0.36$).

Although in of RPS, tumor invasion into adjacent organs is well-known, studies on RPS report that direct organ involvement is rare and that they are of a "pressing" character [22]. Mussi et al. reported that the rate of adjacent organ resection was 62.3% in patients who patients resection for liposarcoma [23]. In the present study, 13 patients (52%) underwent adjacent organ resection.

The effectiveness of treatment modalities other than surgery such as chemotherapy and radiotherapy remains controversial. Although chemotherapy for liposarcoma of the lower or upper extremities is shown to be useful, studies showing its effectiveness on RPS are few in number [24,25]. Although some studies report that radiotherapy is useful for RPS, its effect on survival is controversial. Due to the toxic effect of radiotherapy on adjacent organs, its use is limited and has significant effects on morbidity and mortality [26,27]. In the present study, it was found that 6 patients (24%) were administered adjuvant chemotherapy, 5 (20%) were administered adjuvant chemotherapy+radiotherapy, and 14 (56%) were not administered additional therapy. There was no significant difference between the patients who were administered adjuvant therapy and those who were not in terms of survival ($p = 0.342$).

The most important aim of surgical treatment is the prevention of local recurrence of RPS [6,28]. Anatomical localization and tumor size are the main factors in determining tumor resectability. The surgeon who performs the first resection should achieve the widest resection possible, including neighboring organs, to ensure complete tumor resection.

In the literature, 5-year recurrence rates for complete and incomplete tumor resection were 30.76% and 68.42%, respectively [29]. In the present study, recurrence was observed in 28.57% of patients who underwent R0 resection and in those who underwent R1 resection. Our results are comparable to the recurrence rates of similar patients treated at large-scale healthcare centers. In the present study, 32% of the patients were re-operated for complete surgical resection due to local recurrence. In 8% of the patients, adjuvant chemotherapy was administered due to diffuse distant organ metastasis. Among patients followed up during the 5-year period, 1 had early mortality due to hemorrhage, whereas other patients were alive.

In the present study, the average survival rate was of 96% (24 of 25 patients) and mean follow-up period was

33.4 ± 16.41 months. Milone et al. [30] reported a 5-year survival rate of 85.7% after complete tumor resection. In a study by Chae et al., the 5-year survival rate was 82.2% [31]. According to the literature, this proportional significant difference can be attributed to the small number of patients and the extent of complete tumor resection (R0) rate.

The present study has some limitations such as small sample size and analysis based on retrospective data, which limit access to prognostic and predictive factors.

Conclusion

RPS are the most common histological type of malignant retroperitoneal tumors. Many studies have been published on RPS, and complete tumor resection is the gold standard for its treatment, which increases survival rate and decreases recurrence rate. It remains controversial whether adjuvant chemotherapy or radiation therapy is effective. Disease recurrence is common even after complete tumor resection, and complete tumor resection after recurrence is recommended.

The present study reports higher survival rates than those reported in the literature, which can be attributed to complete tumor resection (R0). Although tumor grade and histological subtype are defined as prognostic factors, the present study found these variables to not have an impact on survival. Even in the presence of effective systemic agents, surgical resection remains the main basis for primary treatment.

Riassunto

Il sarcoma retroperitoneale (RPS) è una condizione gestibile chirurgicamente che può ripresentarsi localmente dopo la resezione macroscopica completa. La gestione dei pazienti in centri sanitari specializzati ad alto volume ha effetti positivi sull'esito del trattamento. Il presente studio mira a valutare preoperatorio, perioperatorio e followup di pazienti sottoposti a intervento chirurgico per RPS.

Sono state investigate retrospettivamente le resezioni chirurgiche consecutive di RPS eseguite in un unico centro sanitario tra gennaio 2011 e dicembre 2018. Sono stati raccolti dati istologici, radiologici e clinici. Oltre al tasso di recidiva locale dei pazienti con resezione tumorale complessa, sono stati registrati e analizzati i sintomi esistenti, il tipo di trattamento adiuvante e i tassi di sopravvivenza globale e libera da malattia a 5 anni.

Risultati: un'ampia resezione completa del tumore è stata eseguita in 25 (% 100) pazienti operati nella nostra clinica per sarcoma retroperitoneale tra il 2011 e il 2018. Il tempo medio di sopravvivenza nei pazienti sottoposti a resezione R0 è risultato essere significativamente più alto rispetto a quello nei pazienti sottoposti a resezione R1 (p = 0,001). Nessuna differenza statisticamente significativa è stata trovata tra la classificazione istologica e tipi istologici in termini di sopravvivenza media (p = 0,63 p = 0,36). Non c'era alcuna differenza statisticamente significativa in termini di sopravvivenza media tra i pazienti che non hanno ricevuto terapia aggiuntiva, che hanno ricevuto chemioterapia adiuvante e quelli che hanno ricevuto chemioterapia e radioterapia adiuvanti (p = 0,342)

In conclusione: sebbene un'ampia resezione completa sia il gold standard nel trattamento del sarcoma retroperitoneale, l'effetto della chemioterapia adiuvante e della radioterapia è ancora in discussione. Nel nostro studio, sono stati determinati tassi di sopravvivenza medi elevati a causa della resezione R0 e non è stato osservato l'effetto del grado di tumore e del sottotipo istologico sulla sopravvivenza.

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