J Surg Res 2021; 4 (1): 59-67 *DOI: 10.26502/jsr.10020110*

Research Article

Retroperitoneal Soft-Tissue Sarcoma: Retrospective Study from a Cancer Hospital in Pakistan

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Received: 09 January 2021; **Accepted:** 22 January 2021; **Published:** 15 February 2021

Citation: Jibran Mohsin, Aun Jamal, Noor-ul-Mubeen, Aamir Ali Syed. Retroperitoneal Soft-Tissue Sarcoma: Retrospective Study from a Cancer Hospital in Pakistan. Journal of Surgery and Research 4 (2021): 59-67.

Abstract

Objectives: To determine the clinicopathological aspects and factors determining the recurrence and 5-year survival of patients diagnosed with retroperitoneal soft-tissue sarcoma in a Pakistani cohort of patients.

Methods: This retrospective descriptive study was conducted at the Department of Surgical Oncology, Shaukat Khanum Memorial Hospital & Research Centre (SKMCH&RC), Lahore, Pakistan. Patients who underwent surgery for retroperitoneal sarcoma from January 2011 to December 2015 were included and followed for 5 years (December 2020). A total of 54 patients was included in this study.

Results: Fifty-seven percent (n=31) cases were male with a median age at the time of presentation 43 (30-60) years. Well-differentiated liposarcoma was the most common variant. Non-compartmental resection was done in 40 (74%) of the cases. The overall 5-year survival was 74% with median Disease-Free Survival (DFS) of 14 (6-48) months. Recurrence was seen in 28 cases (52%).

Conclusions: In the Pakistani cohort of patients. retroperitoneal soft-tissue sarcoma was more commonly seen in males at the median age of 43 years. The most common presentations were abdominal pain and mass. Well-differentiated liposarcoma was the most common histological variant. The overall 5-year survival was 74% that was

affected by histological variant and grade. Recurrence was affected by histological variant and grade, margin positivity, and use of neoadjuvant therapy.

Keywords: Retroperitoneal Sarcoma; Liposarcoma; Undifferentiated pleomorphic sarcoma; Retroperitoneal tumor

1. Introduction

Retroperitoneal sarcomas (RPS) belong to a group of rare neoplasms, representing only 0.2% [1] of adult cancers and 1-2% [2] of all solid malignancies. Average annual incidence is 0.3-0.4% per 100, 000 [2] (or 2.7 cases per million) [1] population. It accounts for only 10-20% of soft tissue sarcomas. Peak incidence is seen in the 5th decade of life, although no age is immune. There are 50-70 subtypes of retroperitoneal sarcomas based on histology. Most common types vary depending on the study population but commonly documented types include liposarcomas, leiomyosarcomas [3], and malignant fibrous histiocytomas (MFH)-recently reclassified as Undifferentiated Pleomorphic Sarcoma (UPS) [4, 5]. Other relatively rare types are solitary fibrous tumors, fibrosarcomas, and malignant peripheral nerve sheath tumors [6].

The diagnosis of RPS is usually challenging and often delayed. Firstly, due to easily dismissive nonspecific symptoms such as abdominal pain or fullness [7]. Secondly, they tend to grow in large retroperitoneal potential spaces; becoming clinically detectable only when they become very large. By then, it has already involved adjacent vital organs like the kidney, bowel, and major vessels [8, 9]. Major cause of morbidity is local spread rather than distant metastasis in contrast to peripheral soft tissue sarcoma [10]. There is an increasing recognition of subtype-guided management in RPS rather than applying the same treatment strategies to all RPS. Surgery can be challenging and adequate oncological resection must be weighed against anticipated postoperative morbidity. Treatment at cancer-dedicated centers by multidisciplinary expertise including experienced surgical oncologists is recommended [11].

The preoperative evaluation must include cross-sectional imaging (Computed Tomography/Magnetic Resonance Imaging) of the Abdomen, Pelvis, and/or Chest to assess local extension, distant metastasis, and plan surgery accordingly. Multivisceral resection is often required. Nephrectomy is required in 28 to 55% of cases and colectomy in 58% of cases [10, 12]. Often multi-specialty involvement is needed [13]. It must be followed by image-guided percutaneous core needle biopsy as it is associated with minimal risk (<2%) of tumor seeding [14]. Tissue diagnosis is mandatory for initiation of neoadjuvant therapy if clinically indicated [15, 16].

Wide local excision with adequate margins, preferably outside the pseudo capsule remains the cornerstone of the treatment of nonmetastatic RPS [17, 18]. Extended or compartmental resection of adjacent uninvolved organs is also advocated in cases in which multi-visceral involvement is present [19]. Palliative resection may also be considered for symptoms in the very selected group of patients. However, most of the time it is discouraged [20, 21]. Neo-adjuvant therapy (radiation [22], chemotherapy [23, 24]) is indicated in well-selected stage II, and III patients. Adjuvant treatment can also be administered according to the pathological status of the tumor. In nutshell, the cornerstone of management is R0 resection. Most of the published work on RPS is from the west. There is a dearth of published data from the subcontinent,

especially Pakistan. This retrospective review will help in assessing the natural history and 5-year follow-up of RPS patients in the local population and determining the factors affecting survival in the Pakistani cohort of patients.

2. Material and Methods

This retrospective descriptive study was done at the Department of Surgical Oncology, Shaukat Khanum Memorial Cancer Hospital & Research Center (SKMCH&RC) Lahore, Pakistan. A total of 54 patients were included in this study. Non-probability consecutive sampling technique was used. All patients of age group 18-70 years who presented with the clinical or operative diagnosis of retroperitoneal soft-tissue sarcoma confirmed on the histopathological specimen; irrespective of gender, duration, or type of symptoms were included. All these patients underwent surgery from January 2011 to December 2015 and were followed for 5 years (December 2020). Patients who presented with retroperitoneal mass due to etiologies other than sarcomas such as lymphoma, metastatic testicular cancer with para-aortic nodal mass, renal, pancreatic, adrenal, or vertebral/spine masses were excluded from the study.

After obtaining ethical approval from the Institutional Review Board (IRB) (Ex-22-04-20-03), patients fulfilling the inclusion criteria were recruited from the Hospital Information System (HIS) of the hospital. The clinical presentation along with duration, comorbidities, age, gender, geographic origin, preoperative biopsy, preoperative imaging, and multidisciplinary board recommendations was recorded. Surgical plan (simple versus extensive/compartmental resection), blood loss, operative time, any intraoperative or postoperative complication(s), length of hospital or ICU stay, whether neoadjuvant or adjuvant therapy was given or not, recurrence (local or distant), median disease-free-survival (DFS) and overall 5-year survival (OS) were also noted. Histopathology reports indicating types of sarcomas and margins were also included in analyses.

All data were collected on a well-elaborated proforma. Data were entered and analyzed in SPSS version 26 for Windows. Continuous variables like age, duration of presenting symptoms, size of the tumor, blood loss, operative time, length of hospital stay, and disease-free survival rate were expressed as the median and interquartile range (IQR). Categorical variables like gender, presenting symptoms, comorbidities, geographic origin, histological variant, preoperative biopsy, recurrence, type of sarcoma and margins positivity, type of surgery, the number of cases that underwent neoadjuvant or adjuvant therapy, complications, recurrence, and overall 5-year survival rate were expressed as frequencies and percentages.

3. Results

Out of the total of 54 patients included in the study as per inclusion criteria, 57% (31 cases) were male and the median age at the time of presentation was 43 (30-60) years. 40 (74%) cases had no comorbidities while 8 (15%) patients were diabetic and 9 (17%) were hypertensive. The majority (n=30, 56%) of patients were from KPK - Pakistan (Khyber Pakhtunkhwa), while 15 (28%) cases were from Afghanistan and the rest (n= 9, 16%) were from Punjab - Pakistan. The initial presentation was abdominal pain in 93% (50 cases) patients, while abdominal mass was present at the time of presentation in 83% (45 patients) cases. The median duration of symptoms was 7 (3-10) months. The median size of the tumor at the initial presentation was 17 (10-26) cm (Table 1).

Preoperative radiological workup included CT scan chest/abdomen/pelvis with IV contrast. It showed no bone metastasis in 47 cases (87%) and no pulmonary metastasis in 49 cases (91%). The preoperative biopsy was done in 45 cases (83%) only as rest underwent surgery due to complications caused by mass effect or invasion like intestinal obstruction. After work-up, the cases were being discussed extensively in a Multi-Disciplinary Tumor (MDT) board specializing in the management of sarcoma patients. Thirty (55%) patients underwent neoadjuvant therapy in the form of chemotherapy (Doxorubicin and Ifosfamide), followed by radiotherapy. Rest 24 (44%) patients underwent upfront surgery followed by adjuvant chemo (radio)therapy as indicated. Noncompartmental surgery was done in the majority of patients i.e., 40 cases (74%), while 8 (15%) cases underwent nephrectomy. Colonic resection was done in 7 (13%) of the cases. The unifocal disease was seen in 42 (78%) cases. The majority (n=50, 93%) of patients were explored via midline incision with a median intraoperative blood loss of 250 (200-410) ml. The median hospital stay was 6 (4-10) days. The median operative time was 180 (140-270) minutes. No intraoperative and immediate (30 days) post-operative complication was found (0%).

Well-differentiated liposarcoma was the most common histopathological variant seen in 40 (74%) of the cases, followed by undifferentiated sarcoma in 10 (19%) and leiomyosarcoma in 4 (7%) cases. Pathological margins were clear (> 1 cm) in 48 cases (89%) i.e. R0 resection. The overall 5-year survival was 74%. Since histological subtype and grading is the major prognostic indicator, it was noticed that 37 out of 40 cases (92%) of well-differentiated liposarcoma, 2 out of 10 (20%) undifferentiated pleomorphic sarcoma, and 1 out of 4 cases (25%) of leiomyosarcoma were alive at 5 years follow up (Table 2).

PARAMETERS		
Age (years), Median (IQR)	43 (30-60)	
Gender, n (%)		
Male	31 (57)	
Female	23 (43)	
Co morbidities, n (%)	None	40 (74)
	Diabetes mellitus	8 (15)
	Hypertension	9 (17)
Geographic origin, n (%)	KPK	30 (56)
	Afghanistan	15 (28)
	Punjab	9 (16)
Presentation, n (%)	Abdominal pain	50 (93)
	Abdominal mass	45 (83)
Duration of symptoms (months), Median (IQR)	7 (3-10)	
Size of tumor (cm), Median (IQR)	17 (10-26)	

Table 1: Demographics and clinical presentation.

PARAMETERS			
Overall 5-year survival rate, n (%)	40 (74)		
Histology wise 5-year survival rate, n (%)			
Well differentiated liposarcoma	37 (92)		
Undifferentiated liposarcoma	2 (20)		
Leiomyosarcoma	1 (25)		
Recurrence, n (%)	28 (52)		
Histology wise recurrence, n (%)	**Local recurrence**	**Distant recurrence**	
Well differentiated liposarcoma (n=40)	18 (45)	1 (2.5)	19 (47.5)
Undifferentiated liposarcoma (n=10)	1 (10)	4 (40)	5 (50)
Leiomyosarcoma (n=4)	1 (25)	3 (75)	4 (100)
	20 (71)	8 (29)	
Disease-free survival, Median (IQR)	14 (6-48)		
Risk factors, n (%)			
Recurrence in margin positive cases	4 (100)		
Recurrence in margin negative cases	24 (48)		
Recurrence in patients without neo-adjuvant therapy (n=24)	20 (83)		
Recurrence in patients with neo-adjuvant therapy (n=30)	8 (27)		
Recurrence in compartment resection (n=14)	5 (36)		
Recurrence in non-compartment resection (n=40)	23 (58)		

Table 2: Survival parameters.

Recurrence was seen in 28 cases (52%). Amongst them, 20 (71%) patients had a local recurrence (18 out of 40 (45%) cases of well-differentiated liposarcoma, 1 out of 10 (10%) of undifferentiated sarcoma, 1 out of 4 (25%) of leiomyosarcoma) and 8 (29%) had a distant recurrence (3 out of 4 (75%) cases of leiomyosarcoma, 4 out of 10 (40%) of undifferentiated sarcoma, 1 out of 40 (2.5%) of well-differentiated sarcoma). All 4 cases with margin positivity had a recurrence (100%). Median disease-free survival was 14 (range 6-48) months. All recurrent cases were treated by non-operative modalities like chemotherapy, radiotherapy, or palliative/ supportive care.

4. Discussion

Retroperitoneal soft-tissue sarcoma is a rare disease with several histological variants [1-3]. Its diagnosis is often delayed due to its vague presentation and non-specific symptoms [7]. The median size at presentation is often more than 20 cm in 50% of the cases. It needs a complete and detailed preoperative workup to assess the grade, stage, resectability, and histological type [15, 16]. Limited published data from cancer dedicated

centers of the subcontinent especially Pakistan on clinicopathological aspects of patients diagnosed with the retroperitoneal soft-tissue sarcoma made the need for such study necessary.

Surveillance, Epidemiology, and End Results (SEER) database results showed 47.7% of patients with RPS were male, while National Soft Tissue Sarcoma Registry showed 52% were male. In comparison, the percentage of male patients was slightly high i.e. 57% in this study. The median age at the time of presentation was 43 (range 30-60) years in this study, which was younger than that seen in the SEER database with a median age of 60 (40-72) [1, 2]. Due to the nature of the disease, the main clinical presentation is abdominal pain in the initial stage of disease or abdominal mass in later stages due to a local increase in the size of the tumor [9, 10]. The presence of abdominal mass at the time of presentation was seen more frequently in this study i.e. 45 cases (83%) in comparison to 43% seen in Dutch Network and National Database for Pathology [7]. This difference was most likely due to low public awareness leading to late clinical presentation.

All patients were discussed in sarcoma/GI-multidisciplinary board meetings. Regarding surgery, the median operative time in our study was 180 (140-270) minutes, comparable to the median operative time of 316 minutes seen in a study conducted at the University of California San Francisco Medical Center. The median intraoperative blood loss in this study was 250 (200-410) ml, which was less than noted in the study conducted at the University of California San Francisco Medical Center i.e. median 500 ml. The same study showed R0 resection in 95% slightly higher than 89% seen in this study [13]. The need for nephrectomy (15% versus 42%) and colectomy (13% versus 30%) were less in this study as compared to French retrospective study reported by Bonvalot et al. [17]. The same study and an Italian study by Gronchi et al showed no significant difference in survival when compartmental resection was compared to noncompartmental resection [10]. The median hospital stay in this study was 6 (4-10) days which was comparable to the median hospital stay of 7 days noted by Tseng et al. [13]. Well-differentiated liposarcoma, the most common variant, was seen in 74% of cases in this study. This was higher than the study conducted at the University of California San Francisco Medical Center i.e. 55%. The same pattern noticed about the median size of the tumor at initial presentation i.e. 17 (10-26) cm in this study versus a median of 14 cm in a study conducted by Tseng et al. [13].

In this study, the overall 5-year survival rate was 74% (40 cases). Histological variants wise 5-year survival was comparable to MD Anderson Cancer Centre (MDACC) Database [well-differentiated liposarcoma (92% in this study versus 95%), leiomyosarcoma (25% versus 43%), and undifferentiated sarcoma (20% versus 25%)] [25]. The recurrence rate in this study was noted to be 52% that was slightly less than that was noted by MDACC i.e. 66%. Retrospective studies from Memorial Sloan Kettering-Cancer Centre (MSKCC) and European Multi-Institutional Collaborative RPS Working group showed well-differentiated liposarcoma was associated with 30-60% local recurrence in comparison to 60% distant metastatic potential in leiomyosarcoma [25]. These findings were also seen in this study i.e., 45% local recurrence was seen in well-differentiated liposarcoma and 75% distant recurrence in the case of leiomyosarcoma.

According to the MDACC database, a 5-year local control rate was double if margin positive resection was done (33% versus 62%) [25]. According to a study conducted at MSKCC, median survival was 18 months with incomplete resection or no resection versus 103 months with complete resection. In this study, 100% recurrence seen in margin positive patients confirmed these findings.

In this study, recurrence was higher in standard resection as compared to extensive or compartmental resection (58% versus 36%). An Italian study done by Gronchi et al showed similar recurrence rates (28% in compartmental and 48% in standard resection). Similar findings were noted in a French study conducted by Bonvolat in 2009 i.e. local recurrence rate was 44% with compartmental resection that was 3.29 times lower than standard resection. But there was no impact on the overall 5-year survival rate. Hence, it was recommended to resection adjacent organs only in case of invasion [25].

The effect of neoadjuvant therapy was seen in this study i.e., 27% recurrence rate in the case of neoadjuvant therapy versus 83% recurrence without neoadjuvant therapy. The study conducted by Nussbaum et al also showed improvement in overall survival with the use of multi-modality therapy [22]. Two prospective trials at MDACC also showed similar findings in terms of 60% local recurrence control rate at 5 years with the use of preoperative radiotherapy. A study conducted by Stucky et al at Mayo Clinic showed an 89% 5-year local control rate with preoperative radiation as compared to 46% local control rate in case of surgery alone. Prospective randomized phase III study STRASS trail (EORTC 62092) is ongoing to further assess the role of preoperative radiation [25].

According to the Medical College of Wisconsin (National Cancer Database), Singer et al and Bremjit et al median overall survival was shortened with the use of preoperative chemotherapy [9, 25]. But due to innate selection bias, these studies couldn't be used as a standard of care. On the other hand, MDACC established the safety and benefits of preoperative chemotherapy in terms of better local recurrence rate. The same findings were also noted in this study (27% recurrence rate with neoadjuvant therapy versus 83% surgery alone).

In conclusion, although standard resection in comparison to compartmental resection affects the recurrence rate but has no effect on the overall survival rate. Secondly, neoadjuvant therapy in the form of chemotherapy and radiotherapy has proven benefit on the recurrence rate and hence survival. The limitation of this study included a small sample size and a single-center study. There is a need for multicenter analyses of the management of such patients and prospective study with a larger sample size before any formal conclusion or guidelines established.

Retroperitoneal sarcoma is a rare disease with varied presentations and needs complex management. The management includes integration of surgery, chemotherapy, and radiation. These management decisions should be taken in high volume centers that regularly treat sarcomas as it leads to the best possible outcomes.

5. Conclusions

In the Pakistani cohort of patients. retroperitoneal soft-tissue sarcoma was more commonly seen in males at the median age of 43 years. The most common presentations were abdominal pain and mass. Well-differentiated liposarcoma was the most common

histological variant. The overall 5-year survival was 74% that was affected by histological variant and grade. Recurrence was affected by histological variant and grade, margin positivity, and use of neoadjuvant therapy.

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