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ORIGINAL ARTICLE

Tumor grade and symptoms at presentation are survival risk factors in Chinese patients with primary retroperitoneal sarcoma

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ABSTRACT

Background and Aim: No cohort studies have been performed on Chinese primary retroperitoneal sarcoma (RPS) patients. Data derived from western cohort studies may not be directly superimposable on Asian counterparts. Furthermore, the risk factors for survival of RPS are currently unknown for Chinese patients. The objectives were therefore to (1) gain insight into RPS incidence and patient demographics and clinical details; (2) determine the risk factors for overall survival (OS) and disease-free survival (DFS); and (3) critically appraise the Asian cohort data in relation to information obtained in western cohort studies.

Methods: In this retrospective cohort study, the health records of patients that had been diagnosed with primary localized RPS with curative intent between 2009 and 2020 were analyzed. Cox proportional hazards analysis was conducted to evaluate the risk factors for OS and DFS.

Results: A total of 261 patients met the inclusion criteria. Ninety-six (36.8%) patients had been diagnosed with well-differentiated liposarcoma, 63 patients (24.1%) with dedifferentiated liposarcoma, 41 patients (15.7%) with leiomyosarcoma (LMS), 22 patients (8.4%) with solitary fibroma, 7 patients (2.7%) with malignant peripheral nerve sheath tumor (MPNST), and 32 patients (12.3%) with another type of RPS. The study further revealed that (1) the 5-y OS and DFS in RPS patients was 67.8% and 51.3%, respectively, with the highest OS and DFS observed in MPNST (100% and 100%, respectively) and the lowest 5-y OS and DFS attributed to LMS (42.6% and 28.9%, respectively); (2) symptoms at presentation, Federal National Cancer Center (FNCLCC) grade, and number of combined resections are independent risk factors in OS; (3) symptoms at presentation, FNCLCC grade, chemotherapy, and hospital length of stay are independent risk factors for DFS; and (4) patients at high risk (symptoms at presentation and high-grade tumors) have less than half the chance of survival at 5 y post-diagnosis than patients with a low-risk profile.

Conclusions: Symptoms at presentation constitute a risk factor for OS and DFS. When combined with tumor grade - another risk factor for both OS and DFS - patients can be classified into a high-risk and low-risk category to gauge a patient's prognosis and, accordingly, frame an optimal clinical trajectory. Moreover, the clinicopathology and overall prognosis of RPS in Asian and Western populations are comparable and hence superimposable.

Relevance for Patients: The present study identifies the risk factors of survival in RPS and suggests symptoms at presentation should be considered in the preoperative consultation and added in prognostic grouping.

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1. Introduction

Retroperitoneal sarcoma (RPS) is a rare malignancy with 0.76 new cases/100,000 people annually in Europe [1]. Surgery with curative intent constitutes the treatment of choice for primary localized RPS. Studies have demonstrated that tumor size, pathological type, tumor grade, multifocality, number of organs involved in combined multiple organs resection, and complete resection are significant predictors of prognosis after surgery [2,3]. In 2009, a retrospective study conducted by two major European reference centers suggested that surgery with concomitant resection of uninvolved adjacent organs in RPS correlates with improved local tumor control [4,5]. However, surgery beyond the immediate resection margins around the tumor is rather contentious and controversial. Moreover, most research on RPS has been performed on western populations, while the prognosis for sarcoma patients differs among ethnic groups [6,7]. A small number of cohort studies have been conducted on Asian populations, with relatively small cohort sizes (Taiwan, n = 144; Singapore, n = 108; Singapore, n = 90; and Singapore, n = 109 included patients) [8-11]. To date, no cohort studies have been published on Chinese RPS patients. Such studies are therefore needed.

Several reports have suggested that a symptomatic visit to the clinic is a poor prognostic factor for some forms of solid tumors, including lung and gastric cancer [12,13]. RPS is generally deep-seated with a large proportion of patients experiencing compressive non-specific symptoms (e.g., abdominal distension and abdominal pain). Nevertheless, some studies have reported symptoms in RPS at diagnosis [14-18]. Accordingly, the potential prognostic value of symptoms at presentation in primary RPS also warrants further scrutiny.

Therefore, this study investigated the demographics and clinical data of RPS patients in a high-volume Chinese sarcoma center to get insight into the incidence of different RPS subtypes, comorbidities, and treatment course. Moreover, RPS risk factors in terms of overall survival (OS) and disease-free survival (DFS) were analyzed. Finally, the data were juxtaposed to study results obtained in western patient cohorts.

2. Patients and Methods

2.1. Patient inclusion and exclusion

This single center retrospective cohort study was approved by the medical ethics committee of South Hospital of Zhongshan Hospital/Shanghai Public Health Clinical Center under protocol number B2020-338 and was conducted in accordance with the Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (October 2013 version). All consecutive patients affected by localized primary RPS who had undergone resection with curative intent at the South Hospital of the Zhongshan Hospital/Shanghai Public Health Clinical Center, Fudan University, Shanghai, China from August 2009 to December 2020 were included in the study. Patients diagnosed with Ewing sarcoma, alveolar/embryonic rhabdomyosarcoma, desmoid tumors, gynecologic sarcoma, and gastrointestinal stromal tumors were excluded from the study.

2.2. Symptoms, grading, and interventions

The symptoms that were monitored included abdominal distension, abdominal pain, lumbodorsalgia, lower extreme discomfort, dyspepsia, and others that were classified as such. The histological subtypes included well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), leiomyosarcoma (LMS), malignant peripheral nerve sheath tumor (MPNST), solitary fibroma (SFT), and other subtypes. Tumor grades were assigned using the Federal National Cancer Center (FNCLCC) grading system. Surgical resection was classified as complete resection (R0 or R1) and incomplete resection (R2). Post-operative morbidity was graded using the Clavien-Dindo classification system [19].

2.3. Follow-up and recurrence

The post-operative follow-up included clinical and imaging examination (contrast-enhanced computed tomography or contrast-enhanced magnetic resonance imaging from the chest to the pelvis). Follow-up was standardly performed every 3 mo for the first 2 y postoperatively, every 6 months thereafter, and once a year after 5 y. Disease recurrence entailed new lesions or marked enlargement of the original lesion(s), both confirmed by imaging. The crude cumulative incidence curves (CCI) for local recurrence (LR) and distant metastases (DM) were calculated in the competitive risk framework. Death without evidence of disease recurrence and DM/LR (whichever occurred first) were considered competing events. When LR and DM concurred, only DM events were counted.

2.4. Data and statistical analysis

Data were analyzed using SPSS 22.0 (IBM, Armonk, NY, USA) and R 4.0.4 (R Foundation, Indianapolis, IN, USA). DFS and OS rates were determined using Kaplan–Meier plots and analyzed with the log-rank test. The clinicopathological factors for OS and DFS that were significant in univariable Cox proportional hazards analysis ($P < 0.05$) were used as input variables in the multivariable Cox model. Normally distributed continuous data were analyzed using the independent sample t-test, and the Mann–Whitney U test was used for non-Gaussian data sets. Differences between independent categorical variables were analyzed with the χ^2 test and Fisher's exact test. All tests were two-tailed. $P \leq 0.05$ was considered statistically significant.

3. Results

3.1. Complete cohort characteristics

A total of 261 patients met the inclusion criteria. The median (range) follow-up time for survivors was 40 (2–140) mo. Table 1

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Table 1. Demographics and medical characteristics of the retroperitoneal sarcoma study cohort (n=261).

Characteristics	N	Percentage of total
Gender		
Male	129	49.4
Female	132	50.6
Age (y) median (first and third IQR)	56	48–64
ASA score		
1	181	69.3
>1	80	30.7
Symptoms		
Yes	116	44.4
No	154	55.6
Tumor burden (cm) median (first and third IQR)	16	9–25
Histologic subtypes		
WDLPS	96	36.8
DDLPS	63	24.1
LMS	41	15.7
SFT	22	8.4
MPNST	7	2.7
Other	32	12.2
FNCLCC		
Grade 1	96	36.8
Grade 2	84	32.2
Grade 3	81	31.0
Multifocality		
Yes	20	7.7
No	241	92.3
Radiation		
Yes	21	8.0
No	240	92.0
Chemotherapy		
Yes	27	10.3
No	234	89.7
Surgical approach		
Laparoscopic surgery	5	2.0
Open surgery	164	98.0
Complete resection		
Yes	253	96.9
No	8	3.1
Number of combined resections, median (first and third IQR)	1	0-3
Operative time (h) median (first and third IQR)	3.7	2.5–4.2
Estimated blood loss (mL) median (first and third IQR)	400	100–850
Packed red blood cell transfusion		
Yes	82	31.4
No	179	68.6
Packed RBC transfusion (units) median (first and third IQR)	4	2–6
Clavien-Dindo classification		
NA	153	58.6
1–2	77	29.6
3–5	31	11.8
Postoperative hospital stay (d) median (first and third IQR)	15	11–22

IQR, interquartile range, WDLPS, well-differentiated liposarcoma; DDLPS, dedifferentiated liposarcoma; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; SFT, solitary fibroma.

lists the patient demographics and medical characteristics. The patient population was comprised of 129 (49.4%) males and 132 (50.6%) females with a median age of 56 y (first and third interquartile range [IQR], 48–64 y). Eighty patients (30.7%) had an ASA score of >1 and 116 patients (44.4%) exhibited clinical symptoms at first presentation in the hospital. The most common symptom was abdominal distension (32.7%), followed by abdominal pain (31.8%). Lumbodorsalgia, lower extreme discomfort, dyspepsia, and other symptoms accounted for 10.3%, 8.6%, 6.0%, and 10.3%, respectively.

The median tumor burden was 16 cm (IQR, 9–25 cm). For histologic subtypes, 96 (36.8%) of patients had been diagnosed with WDLPS, 63 patients (24.1%) with DDLPS, 41 patients (15.7%) with LMS, 22 patients (8.4%) with SFT, 7 patients (2.7%) with MPNST, and 32 patients (12.3%) with another RPS subtype. The proportion of patients with FNCLCC grade 1, 2, and 3 was 36.8%, 32.1%, and 31.0%, respectively. Furthermore, 8.0% of patients had received external beam radiation therapy and 10.3% of patients had received chemotherapy. The tumor was completely resected in 96.9% of patients, and the median number of combined resections was 1 (IQR, 0–3). The median operative time was 3.7 h (IQR, 2.5–4.2 h), the median estimated blood loss was 400 mL (IQR, 100–850 mL), and 82 patients (31.4%) were transfused with packed red blood cells. The median length of postoperative hospital stay was 15 d (IQR, 11–22 d).

Post-operative Clavien-Dindo Class 3 complications were found in 16 patients (6.1%), 10 patients (3.8%) had Class 4 complications, and 5 patients (1.9%) exhibited class 5 complications. Among the five patients who died postoperatively, 2 patients died after reoperation due to severe abdominal infection caused by post-operative intestinal fistula, 2 patients died from cardiovascular events, and 1 patient died from multiple organ failure due to septic shock.

3.2. Symptomatic patients had higher grade tumors and experienced a more complicated clinical trajectory

A higher proportion of symptomatic patients had high-grade tumors (P = 0.003), received pre-operative radiotherapy (*P* = 0.033), and experienced a longer operation time (P = 0.038) compared to asymptomatic patients (Table 2). The symptomatic group was not subjected to more combined organ resections (median, 2 vs. 1, not significant) and comparable perioperative blood loss was noted between groups (median, 500 vs. 300 mL, not significant).

3.3. OS is negatively impacted by symptoms at presentation

For the entire cohort, 77 (29.5%) patients were deceased at the last follow-up. After 5 cases of post-operative death were removed, the OS at 1-, 2-, and 5 y was 92.9% (95% CI, 89.8–95.0%), 86.2% (95% CI, 81.7%–90.7%), and 67.8% (95% CI, 60.7–74.9%), respectively (Figure 1A). The 5-y OS for WDLPS, DDLPS, LMS, SFT, MPNST, and other subtypes was 85.8% (95% CI, 77.2–94.4%), 52.2% (95% CI, 35.0–69.4%), 42.6%

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Table 2. Demographic and medical characteristics for the symptomatic (n=116) and asymptomatic (n=145) patient cohorts.

	Symptomatic group n (%)	Asymptomatic group n (%)	*P*-value
Gender			0.506
Male	60 (51.7)	69 (47.6)	
Female	56 (48.3)	76 (52.4)	
Age (y) median (first and third IQR)	55 (46–64)	56 (49–64)	0.758
ASA score			0.696
1	79 (68.1)	102 (70.3)	
>1	37 (31.9)	43 (29.7)	
Tumor burden (cm) median (first and third IQR)	15.0 (8.2–25.0)	16.0 (9.0–25.0)	0.885
Histological subtypes			0.113
WDLPS	36 (31.0)	60 (41.4)	
DDLPS	26 (22.4)	37 (25.5)	
LMS	24 (20.7)	17 (11.7)	
SFT	8 (6.9)	14 (9.7)	
MPNST	3 (2.6)	4 (2.8)	
Other	19 (16.4)	13 (9.0)	
FNCLCC			0.003
Grade 1	32 (27.6)	63 (43.3)	
Grade 2	36 (31.0)	49 (33.8)	
Grade 3	48 (41.4)	33 (22.8)	
Radiation			0.033
Yes	14 (12.1)	7 (4.8)	
No	102 (87.9)	138 (95.2)	
Chemotherapy			0.220
Yes	15 (12.9)	12 (8.3)	
No	101 (87.1)	133 (91.7)	
Surgical approach			1.000
Laparoscopic surgery	2 (1.7)	3 (2.1)	
Open surgery	114 (98.3)	142 (97.9)	
Complete resection			0.473
Yes	111 (97.7)	142 (97.9)	
No	5 (4.3)	3 (2.1)	
Number of combined resections, median (first and third IQR)	2 (1–3)	1 (0–3)	0.357
Operative time (h) median (first and third IQR)	4.0 (3.0–4.9)	3.0 (2.0–4.0)	**0.038**
Estimated blood loss (mL) median (first and third IQR)	500 (200–975)	300 (100–800)	0.998
Packed RBC transfusion	4 (2–6)	4 (2–6)	0.136
Yes	42 (36.2)	40 (27.6)	
No	74 (63.8)	105 (72.4)	
Packed RBC transfusion (units) median (first and third IQR)			0.779
Clavien-Dindo classification			0.251
NA	70 (60.4)	83 (57.2)	
1–2	30 (25.8)	47 (32.4)	
3–5	16 (13.8)	15 (10.4)	
Post-operative hospital stay (d) median (first and third IQR)	15 (12–23)	14 (10–22)	0.204

IQR, interquartile range, WDLPS, well-differentiated liposarcoma; DDLPS, dedifferentiated liposarcoma; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; SFT, solitary fibroma.

(95% CI, 24.6–60.6%), 83.5% (95% CI, 66.5–100%), 100.0% (95% CI, N.A.), and 65.8% (95% CI, 48.4–83.2%), respectively (Figure 1B). For the symptomatic and asymptomatic group, the 5-y OS was 54.7% (95% CI, 47.7–65.7%) and 80.0% (95% CI, 71.8–88.2%), respectively (Figure 1C).

Table 3 lists the analysis of risk factors for OS. Symptoms at first presentation (HR 1.821, P = 0.021), FNCLCC grade (HR 1.252 for Grade 2 and 2.756 for Grade 3, P = 0.021), and number of combined resections (HR 1.276, P = 0.021) constituted risk factors for OS in multivariable analysis.

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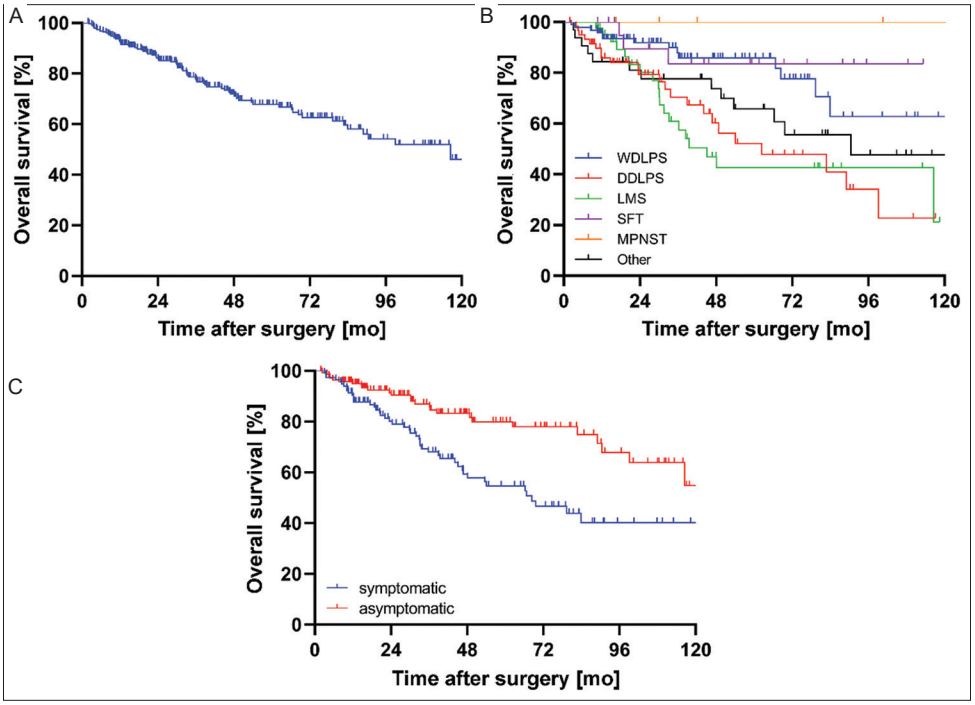

Figure 1. Overall survival in patients with primary retroperitoneal sarcoma (A) and in patients stratified for (B) histological subtype, and (C) symptomatic versus asymptomatic at first presentation. mo, months; WDLPS, well-differentiated liposarcoma; DDLPS, dedifferentiated liposarcoma; LMS, leiomyosarcoma; SFT, solitary fibroma; MPNST, malignant peripheral nerve sheath tumor.

Table 3. Univariable and multivariable analyses to determine independent predictors of overall survival of primary retroperitoneal sarcoma.

Variables	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Gender (female vs. male)	0.610 (0.407–1.051)	0.042	0.599 (0.346–1.034)	0.066
Age (continuous)	1.071 (0.998–1.036)	0.072		
ASA score (>1 vs. 1)	1.164 (0.704–1.923)	0.554		
Symptoms (yes vs. no)	2.393 (1.476–3.879)	<0.001	1.821 (1.095–3.026)	0.021
Tumor burden (continuous)	1.013 (0.991–1.036)	0.241		
Histological subtypes		0.006		0.988
DDLPS vs. WDLPS	2.902 (1.493–5.641)		1.229 (0.510–2.960)	
LMS vs. WDLPS	3.071 (1.540–6.138)		1.094 (0.404–2.962)	
SFT vs. WDLPS	0.719 (0.206–2.505)		0.904 (0.227–3.607)	
MPNST vs. WDLPS	0.000 (0.000–E+195)		0.000 (0.000–E+221)	
Other vs. WDLPS	1.987 (0.931–4.243)		1.404 (0.542–3.640)	
FNCLCC		<0.001		0.021
Grade 2 vs. grade 1	1.884 (0.936–3.791)		1.252 (0.518–3.023)	
Grade 3 vs. grade 1	4.456 (2.360–8.415)		2.756 (1.067–7.116)	
Radiation (yes vs. no)	0.465 (0.169–1.277)	0.137		
Chemotherapy (yes vs. no)	2.848 (1.581–5.131)	<0.001	1.990 (0.904–4.384)	0.088
Surgical approach (laparoscopic vs. open)	0.048 (0.000–273.3)	0.492		
Complete resection (no vs. yes)	0.554 (0.332–0.923)	0.023	0.343 (0.105–1.124)	0.077
Number of combined resections (continuous)	1.355 (1.173–1.566)	<0.001	1.276 (1.037–1.570)	0.021
Operative time (continuous)	1.220 (1.040–1.431)	0.014	0.915 (0.694–1.207)	0.529
Estimated blood loss (continuous)	1.000 (1.000–1.000)	0.003	1.000 (1.000–1.000)	0.701
Packed RBC transfusion (yes vs. no)	2.084 (1.307–3.324)	0.002	1.506 (0.799–2.842)	0.206
Clavien-Dindo classification (3–5 vs. NA/1–2)	2.397 (1.287–4.463)	0.006	1.479 (0.671–3.260)	0.332
Postoperative hospital stay (continuous)	1.021 (1.010–1.033)	<0.001	1.002 (0.992–1.025)	0.332

WDLPS, well-differentiated liposarcoma; DDLPS, dedifferentiated liposarcoma; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; SFT, solitary fibroma

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3.4. DFS depends on RPS subtype and is shorter in symptomatic patients

For the whole group, 108 (41.4%) patients relapsed. The median time to recurrence was 19.6 (95% CI, 12.7–25.5) mo, and the DFS at 1-, 2-, and 5 y was 84.0% (95% CI, 79.5–88.5%), 71.8% (95% CI, 65.9–77.7%), and 51.3% (95% CI, 43.7–58.9%), respectively (Figure 2A). The 5-y CCI for LR and DM was 38.5% (95% CI, 31.2–45.8%) and 8.1% (95% CI, 4.4–11.8%), respectively (Figure 2B). The 5-y DFS rate for WDLPS, DDLPS, LMS, SFT, MPNST, and other RPS subtypes was 50.6% (95% CI, 45.5–65.7%), 37.4% (95% CI, 20.3–54.5%), 28.9% (95% CI, 12.8–45.0%), 86.1% (95% CI, 71.6–100%), 75.0% (95% CI, 32.5–100%), and 56.7% (95% CI, 38.9–74.5%), respectively (Figure 2C). The 5-y DFS was 40.3% (95% CI, 30.1–50.5%) and 62.7% (95% CI, 51.7–73.7%) for the symptomatic and asymptomatic group, respectively (Figure 2D).

Table 4 lists the analysis of risk factors for DFS. The result indicated that the symptoms at the visit (HR: 1.928, P = 0.002), FNCLCC grade (P = 0.026), chemotherapy (HR: 2.828, P = 0.001), and post-operative hospital stay (HR: 1.022, P = 0.001) were significantly correlated with DFS in multivariable Cox analysis.

FNCLCC grade and symptoms constituted both DFS and OS risk factors. In a subsequent analysis, patients with high-grade tumors (FNCLCC Grade 3) and symptoms at presentation were assigned to the high-risk group (n = 48), while the rest were assigned to the low-risk group (n = 213). The 5-y OS was 33.1% (95% CI, 16.6–49.7%) for the high-risk group and 77.1% (95% CI, 70.0–84.2%) for the low-risk group (Figure 3A). The 5-y DFS for patients in high-risk and low-risk group was 22.5% (95% CI, 9.6–35.1%) and 59.1% (95% CI, 50.5–67.7%), respectively (Figure 3B).

4. Discussion

RPS is a rare but highly heterogeneous disease, accounting for 15% of all soft tissue sarcomas [20]. No retrospective case studies had been published on Chinese RPS patients before, so there was a knowledge gap in terms of incidence, demographics, medical details, and prognostic factors. This gap was filled by the current study, which was performed on the largest Asian cohort to date [8-11]. Our study revealed that (1) the incidence of RPS subtypes proceeded in the order of WDLPS > DDLPS > LMS > other subtypes > SFT > MPNST; (2) the 5-y OS and DFS in Chinese RPS patients was 67.8% and 51.3%, respectively, with the highest OS and DFS observed in MPNST (100% and 100%, respectively) and the lowest 5-y OS and DFS attributed to LMS (42.6% and 28.9%, respectively); (3) symptoms at presentation, FNCLCC grade, and number of combined resections are independent risk factors in OS; (4) symptoms at presentation, FNCLCC grade, chemotherapy, and hospital length of stay are independent risk factors for DFS; and (5) patients at high risk (symptoms at presentation and high-grade tumors) have less than half the chance of survival at 5 y post-diagnosis than patients with a low-risk profile.

A key finding was that patients who presented with symptoms had a significantly worse prognosis. It is known that symptoms constitute a prognostic factor for certain solid cancers [12,13],

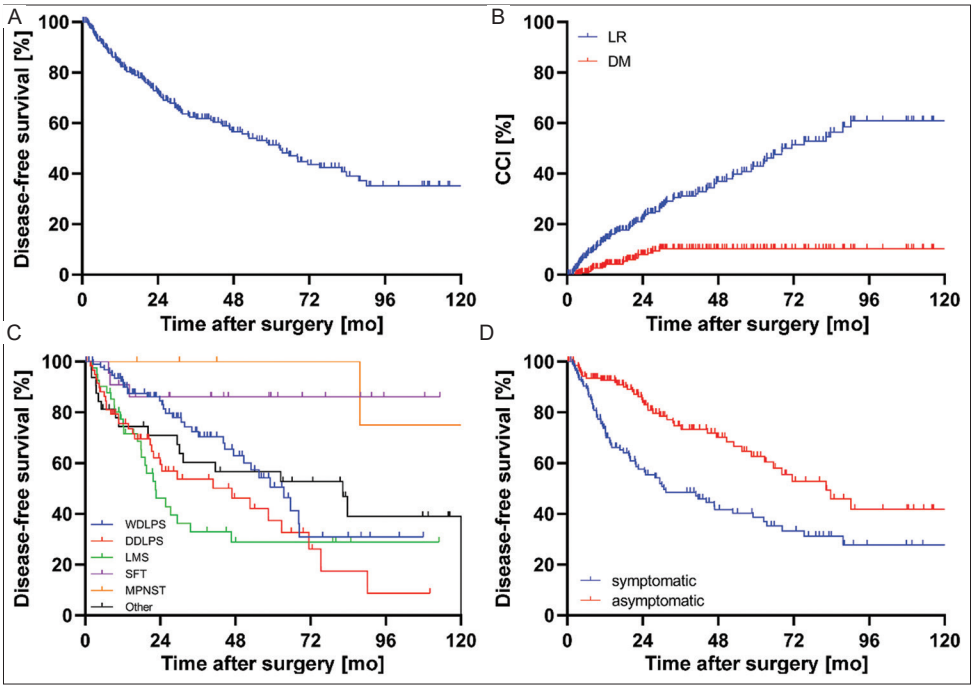

Figure 2. Disease-free survival in patients with primary retroperitoneal sarcoma (A) and in patients stratified for (B) local recurrence and distant metastasis, (C) histological subtype, and (D) symptomatic versus asymptomatic presentation. mo, months; CCI, crude cumulative incidence; LR, local recurrence; DM, distant metastasis; WDLPS, well-differentiated liposarcoma; DDLPS, dedifferentiated liposarcoma; LMS, leiomyosarcoma; SFT, solitary fibroma; MPNST, malignant peripheral nerve sheath tumor.

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Table 4. Univariable and multivariable analyses to determine independent predictors of disease-free survival of primary retroperitoneal sarcoma.

Variables	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Gender (female vs. male)	0.934 (0.639–1.366)	0.726		
Age (continuous)	1.012 (0.997–1.028)	0.105		
ASA score (>1 vs. 1)	0.994 (0.652–1.517)	0.979		
Symptoms (yes vs. no)	2.225 (1.506–3.286)	<0.001	1.928 (1.272–2.923)	0.002
Tumor burden (continuous)	1.006 (0.988–1.024)	0.520		
Histological subtypes		<0.001		0.354
DDLPS vs. WDLPS	1.908 (1.163–3.129)		1.055 (0.535–2.080)	
LMS vs. WDLPS	2.152 (1.065–3.659)		1.096 (0.506–2.373)	
SFT vs. WDLPS	0.218 (0.089–0.922)		0.365 (0.107–1.247)	
MPNST vs. WDLPS	0.218 (0.030–1.611)		0.244 (0.032–1.838)	
Other vs. WDLPS	1.122 (0.610–2.064)		0.764 (0.351–1.665)	
FNCLCC		<0.001		0.026
Grade 2 vs. Grade 1	1.619 (0.959–2.733)		1.009 (0.550–1.854)	
Grade 3 vs. Grade 1	3.196 (1.975–5.173)		2.926 (0.947–3.915)	
Radiation (yes vs. no)	0.826 (0.417–1.638)	0.584		
Chemotherapy (yes vs. no)	3.328 (2.012–5.504)	<0.001	2.828 (1.496–5.349)	0.001
Surgical approach (laparoscopic vs. open)	0.586 (0.082–4.209)	0.595		
Complete resection (no vs. yes)	0.787 (0.442–1.400)	0.414		
Number of combined resections (continuous)	1.264 (1.123–1.423)	<0.001	1.152 (0.979–1.356)	0.089
Operative time (continuous)	1.230 (1.081–1.398)	0.002	1.016 (0.823–1.256)	0.880
Estimated blood loss (continuous)	1.000 (1.000–1.000)	0.028	1.000 (1.000–1.000)	0.938
Packed RBC transfusion (yes vs. no)	1.401 (0.943–2.083)	0.095		
Clavien-Dindo classification (3–5 vs. NA/1–2)	1.540 (0.823–2.880)	0.177		
Post-operative hospital stay (continuous)	1.028 (1.017–1.039)	<0.001	1.022 (1.008–1.035)	0.001

WDLPS: Well-differentiated liposarcoma, DDLPS: Dedifferentiated liposarcoma, LMS: Leiomyosarcoma, MPNST: Malignant peripheral nerve sheath tumor, SFT: Solitary fibroma

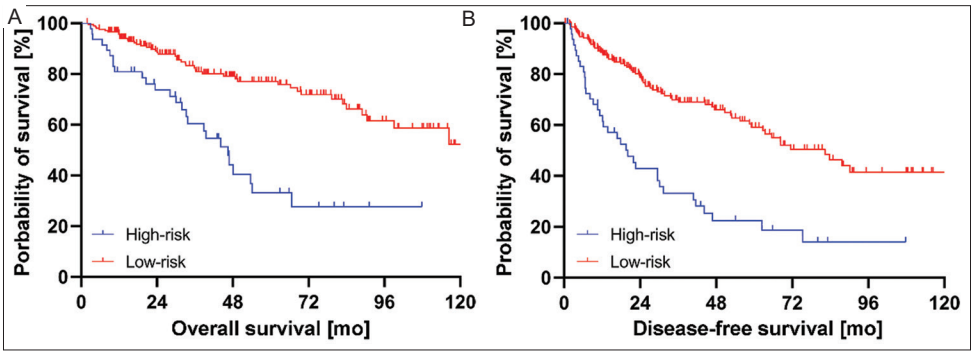

Figure 3. Overall survival (A) and disease-free survival (B) in patients with primary retroperitoneal sarcoma stratified for risk. Differences between groups in both data sets were significant ($P < 0.001$).

which has been equivocal in regard to RPS. There are only five studies that have investigated the symptoms-prognosis relationship [14-18]. The largest sample size was reported by Xiao *et al*. [15], which included 57 patients with primary retroperitoneal liposarcoma, who found that that this RPS subtype was correlated with lower DFS in univariable analysis. However, multivariable analysis was not performed due to limited cohort size. In a study by Luo *et al*. [17] featuring 35 cases of retroperitoneal SFT, the 5-y DFS of symptomatic and asymptomatic patients was 56.4% and 65.0%, respectively, but the difference was not statistically significant. The study was likely underpowered. In 2016, Taguchi *et al*. [16] concluded that a symptomatic visit is an independent prognostic factor for primary retroperitoneal liposarcoma, but this conclusion was based on a cohort size of only 24 patients. The retroperitoneum encompasses a relatively large, malleable space, so patients with RPS commonly present with a considerable tumor burden that triggers them to visit the doctor. Thus, in the aforementioned studies, the mass effect of

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the tumor was most likely the chief cause of the symptoms. In this study, however, no difference was observed in the tumor size between the symptomatic and asymptomatic groups (Table 2). In fact, the symptomatic group was characterized by a higher FNCLCC grade only, while combined organ resection, perioperative bleeding, and operative time did not differ between symptomatic and asymptomatic patients. Accordingly, a higher tumor grade seems to be associated with more deleterious tumor biological behavior that is revealed through symptoms at clinical presentation, which in turn negatively affects prognosis. Rapid tumor growth and invasion into neighboring tissues lie at the basis of the symptomatic manifestation. Corroboratively, RPS with organ invasion is associated with worse prognosis [21]. Unfortunately, RPS is often diagnosed during regular check-ups or not acted on in time due to misattribution of symptoms to non-oncological, benign origin (e.g., bloating, which can have numerous other causes). Consequently, patients present at the hospital with advanced tumors, which debilitates effective treatment.

The knowledge that symptoms at presentation comprise a risk factor for survival can be exploited for optimal clinical management in several ways. First, we recommend a comprehensive biopsy for symptomatic patients to ensure greater diagnostic acuity. Given that symptomatic patients have more invasive tumors and a worse prognosis, adjuvant therapy should be considered for certain RPS subtypes (e.g., undifferentiated pleomorphic sarcoma). Second, this study showed that symptomatic patients had a greater tendency to undergo a combined resection of more organs and experience more bleeding during surgery compared to asymptomatic patients, albeit the trends were not statistically significant. Nevertheless, these factors should be taken into account during preoperative work-up, and where necessary, a postoperative transfer to the ICU should be secured. It is important to emphasize that the presence or absence of symptoms should not be the basis for a more aggressive surgical strategy, and that the extent of the resection should be comprehensively considered alongside the surgical exploration, pathological subtype, and other pertinent factors [22]. Third, the postoperative follow-up should be more frequent and profound for the symptomatic patients given the more than doubled probability of death during the 5 y after diagnosis compared to asymptomatic patients.

FNCLCC classification was also an independent risk factor for OS and DFS in the multivariable analysis. Its prognostic role in RPSs has been established [23]. We combined the FNCLCC classification and the symptoms of RPS patients and stratified the patients into a high-risk group and a low-risk group. The 5-y DFS of patients in the high-risk group and the low-risk group was 22.5% (95% CI, 9.6–35.1%) and 59.1% (95% CI, 50.5–67.7%), respectively, whereas the 5-y OS was 33.1% (95% CI, 16.6–49.7%) and 77.1% (95% CI, 70.0–84.2%), respectively. Accordingly, the combination of the two indicators can be employed to better prognosticate the clinical course of RPS patients and can serve as an evaluation tool for outpatient consultation as well as screening of patients during clinical trial enrollment.

Compared to the multicenter western cohort of 1007 patients reported by the Trans-Atlantic RPS Working Group in 2016 [3], the Asian cohort (this study cohort) was characterized by a higher proportion of WDLPS (26.1% vs. 36.8%, respectively) and a lower tumor burden (median, 20 vs. 16 cm, respectively). The OS was comparable (5-y OS of 67.0 vs. 67.8%), whereas the Asian cohort had a higher 5-y CCI in terms of LR (25.9 vs. 38.5%, respectively). The DM rate was lower in the Asian cohort (21.0 vs. 8.1%, respectively). Compared with the Memorial Sloan Kettering Cancer Center (MSKCC) cohort of 675 primary RPS [2], the Asian cohort was characterized by a lower age (median, 60 y vs. 56 y, respectively) and a higher incidence of WDLPS (28% vs. 36.1%, respectively), whereas the median tumor size was similar (17 vs. 16 cm, respectively). With respect to prognostic factors, the 5-y disease-specific survival, CCI of LR, and CCI of DM were 69%, 39%, and 24%, respectively, in the MSKCC cohort. Survival was comparable to that of the Asian cohort, whereas the proportion of DM was higher. The lower CCI of DM in the Asian cohort may be ascribed to the higher proportion of WDLPS, since the recurrence of WDLPS is generally local and without DM [24]. Taken together, the clinicopathological characteristics and prognosis of primary RPS patients in the Asian population and Western populations were largely identical.

Our study had several limitations. First, nearly 10% of patients who presented with localized primary RPS were not resected [25] and were excluded from this study, somewhat limiting the generalizability of our findings. Second, due to underrepresentation in our cohort, the findings on rare histological subtypes (e.g., MPNST; n = 7) were difficult to validate.

5. Conclusions

This largest single-center RPS cohort study with Asian patients demonstrated that symptoms at presentation constitute a risk factor for OS and DFS. When combined with tumor grade, patients can be classified into a high-risk and low-risk category to gauge a patient's prognosis and, accordingly, frame an optimal clinical trajectory. Moreover, the clinicopathology and overall prognosis of RPS in Asian and Western populations are comparable and hence superimposable. Most of the study conclusions based on European and American populations can therefore be applied to Asian populations.

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of the South Hospital of Zhongshan Hospital/Shanghai Public Health Clinical Center. All patients signed a universal consent form allowing for inclusion in research activities.

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