SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 15: 1799-1810, 2018

A retrospective, single-center cohort study on 65 patients with primary retroperitoneal liposarcoma

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Received August 4, 2017; Accepted September 13, 2017

DOI: 10.3892/ol.2017.7533

Abstract. Primary retroperitoneal liposarcoma (PRPLS) is the most common soft tissue malignancy of the retroperitoneum. To determine the pathological features and the curative effects of surgery in patients with PRPLS, and to elucidate key prognostic factors, the present study retrospectively analyzed the clinical cases of 65 patients with PRPLS. Immunohistochemical analysis demonstrated that vimentin and Ki-67 are better indicators for PRPLS immunohistochemical diagnosis compared with S-100 protein. S-100 protein was predominantly expressed in well-differentiated PRPLS. Positive expression of vimentin and Ki-67 were observed in almost all PRPLS samples, and Ki-67 exhibited a higher expression level in high-grade PRPLS. The level of Ki-67 expression was negatively correlated with disease-specific survival (DSS). Survival analysis revealed that the pathological subtype and histological grade were associated with DSS and local recurrence in the patients, whereas the tumor burden was associated with DSS but not local recurrence. In addition, complete tumor resection and contiguous organ resection were able to improve DSS. Microscopically positive margins did not affect DSS, whereas gross margins did. Multivariate analysis revealed that pathological subtype, histological grade and contiguous organ resection were independent prognostic factors, and that histological grade was an independent factor for local recurrence. Patient sex and age at presentation were not independent factors associated with prognosis or local recurrence. Correlation analysis demonstrated that postoperative local recurrence significantly affected DSS, and local recurrence was the most common cause of mortality among patients. Histological grade was strongly associated with the invasion of adjacent organs but not with tumor burden. Furthermore, the tumor burden was not associated with recurrence or tumor invasion of adjacent organs. Ki-67 expression was associated with prognosis. Pathological subtype, histological grade and contiguous organ resection were independent prognostic factors, while histological grade was an independent factor which affected tumor recurrence.

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Key words: disease-specific survival, local recurrence primary retroperitoneal liposarcoma, immunohistochemistry, primary tumor complete resection

Introduction

Retroperitoneal soft-tissue sarcomas located in the retroperitoneum/intra-abdominal regions account for 10-15% of all soft-tissue sarcoma cases. Liposarcomas, which are the most common histotype, account for 20-45% of the cases of retroperitoneum/intra-abdominal sarcoma, and 20% of the cases of liposarcomas are primary retroperitoneal liposarcomas (PRPLS) (1-3). PRPLS often originates from adipose tissue around the kidney. Due to the huge spaces in and the loose structure of the retroperitoneum, it is difficult to diagnose and treat owing to a lack of typical clinical symptoms. The sarcoma grows to a large size and often exhibits tumor invasion of adjacent organs by the time of diagnosis (4). The tumor usually presents as a round or oval lobulated mass, and surrounding those masses, there exist satellite lesions. Due to this, the tumor often invades proximal tissues and blood vessels. In previous years, the rate of morbidity of PRPLS has gradually increased. PRPLS tumors have a high rate of local recurrence but rarely result in distant metastases (5). Compared with other malignancies, numerous patients with PRPLS have succumbed to mortality due to the effects of local recurrence (5). This is unsurprising due to the large tumor size and its proximity to vital structures, which limit the potential to achieve negative surgical margins in surgery. Chemotherapy and radiotherapy are ineffective for the majority of PRPLS cases, with a chemotherapy response rate of <10% (6,7). Despite the large tumor size and the difficult nature of surgery due to the proximity to vital structures, complete tumor resection remains the most

effective treatment for the majority of patients with PRPLS (8). Immunohistochemistry is considered to be the most important diagnostic method for PRPLS. Evidence of the presence of PRPSL is the existence of signet-ring lipoblastomas or dendritic blood capillaries in tumor cells (9). At present, numerous immune markers are utilized in order to diagnose and identify diseases (10-12). However, it remains unclear whether the common PRPLS markers (S-100, vimentin and Ki-67) are specific for different types of PRPLS and whether increased Ki-67 expression is associated with disease-specific survival (DSS).

The present study was designed to investigate the immunohistochemical features and effects of surgical treatment of PRPLS, to retrospectively analyze DSS using clinical cases of PRPLS from a single institution, and to use the information gained to elucidate key prognostic factors that may predict which patients with PRPLS will benefit from surgical treatment.

Materials and methods

Patients. Between 1st January, 2005 and 31st March, 2015, a group of 174 patients (including 82 males and 92 females, with ages ranging from 16 to 81 years old and a median age of 51.3 years) with liposarcoma who were treated at Southwest Hospital (Chongqing, China) were identified. Of these, 99 patients were diagnosed with retroperitoneal liposarcoma, and 65 were diagnosed with PRPLS. Follow-up, via outpatient re-examination, or postal or telephone correspondence, was recorded for all 65 PRPLS patients until October 2015, with the follow-up time ranging from 3 to 114 months. Of these 65 patients, 51 patients received a complete primary tumor resection, for which the gross margins were ensured to be negative during the surgery. The remaining 14 patients received palliative surgery or biopsy. Contiguous organ resection was performed in 32 patients in order to achieve complete resection, with 22 patients exhibiting primary local recurrence following complete resection. The 65 patients diagnosed with PRPLS, including the 51 that received complete primary tumor resection, formed the basis of the present study (Table I).

Table I. Patients included in the present study.

Patient group	Patients, n
All liposarcomas treated	174
All retroperitoneal liposarcomas treated	99
All primary retroperitoneal liposarcomas treated	65
Completely resected	51
Palliative surgery or biopsy	14
Contiguous organ resection	32
Primary local recurrence following complete resection	22
Reoperation following primary local recurrence	16

Pathology. According to the criteria of the World Health Organization (WHO) Classification of Tumors of Soft Tissue and Bone, PRPLS tumors are widely accepted to be classified into one of the five following histological subtypes, based on morphological features and cytogenetic aberrations: Well differentiated, de-differentiated, myxoid, round cell and pleomorphic (13,14). Well-differentiated PRPLS was defined as retroperitoneal fatty tumors containing mature adipocytes with occasional atypical cells and irregular hyperchromatic nuclei. Lesions with regions of non-lipogenic spindle cell sarcoma arising within a fatty tumor were labeled as de-differentiated PRPLS. Myxoid PRPLS was composed of adipocytes with different differentiation and a variable number of small lipoblasts in a prominent myxoid stroma, with or without delicate arborizing vasculature. Tumors with similar morphological small round- or oval-shaped cells and scattered adipocytes were determined to be round-cell PRPLS. Pleomorphic spindle and giant cells, as well as sheets of pleomorphic lipoblasts, were classified as pleomorphic PRPLS. The well-differentiated subtype accounts for 56% of PRPLS cases, with de-differentiated, myxoid and round-cell subtypes accounting for 37, 5 and 2% of cases, respectively. As certain myxoid liposarcomas exhibit morphological similarities to round-cell liposarcomas and are similar in terms of histological progression, these two types are difficult to distinguish from each other. Additionally, in previous studies, mixed-type PRPLS was defined by the WHO as including two or more subtypes of liposarcoma (15,16). Thus, the present study allocated patients with myxoid and round cell PRPLS into one group, and patients with pleomorphic/mixed-type PRPLS into another group. Although there are five PRPLS subtypes, histological grade may be divided into two grades (high and low), defined by histological subtype (17). The majority of mixed-type PRPLS cases include de-differentiated or pleomorphic PRPLS. Thus, the high-grade tumors include de-differentiated, pleomorphic and mixed-type cells, whereas the low-grade tumors consist of well-differentiated and myxoid/round cell types.

Immunohistochemistry. The tumor samples of 65 patients were fixed in 4% formaldehyde for 24 h at room temperature, hydrated and dehydrated with differing concentrations of ethanol (75, 85, 95 and 100%) and 100% xylene embedded in paraffin, cut into 4 μm sections and stained using the hematoxylin and eosin (H&E) method for 24 h at room temperature. Immunohistochemistry was performed by the streptavidin-peroxidase method (18) using antibodies against S-100-α2 (cat. no. bs-7873R; Bioss Antibodies, Inc., Woburn, MA, USA), vimentin (catalog no. 5741; Cell Signaling Technology, Inc., Danvers, MA, USA) and Ki-67 (catalog no. bs-2130R; Bioss Antibodies, Inc.). Positive expression was defined as brown staining in the cytosol, cytomembrane or nuclei of the tumor cells. A total of 65 H&E stained samples for S-100, vimentin and Ki-67 respectively were separated into group 1, group 2 and group 3 randomly to test for their specificity for the tumor. The Ki-67 proliferation index was also assessed using a scale reflecting the positive proportion of a total of 1,000 cells in 10 random high-power fields, as follows: +, ≥0 and <10%; ++, ≥10 and <20%; +++, ≥20 and <30%; ++++, ≥30 and <40%; and +++++, ≥40% positively stained cells.

Table II. Characteristics of 65 patients with primary retroperitoneal liposarcom[a].

Variables	Patients, n	Median survival time, months[a]	Survival rate, %
Follow-up	65	38.1±25.9	58.5
Primary tumor complete resection	51	43.3±26.8	64.7
Palliative surgery or biopsy	14	19.4±6.8	35.8
Histological subtype			
Well-differentiated	25	51.2±27.9	84.0
De-differentiated	10	20.7±12.8	50.0
Myxoid/round cell subtype	8	59.9±25.2	62.5
Pleomorphic/mixed-type	8	30.1±12.6	25.0
Histological grade			
High	18	24.9±13.2	38.9
Low	33	53.3±27.2	78.8
Contiguous organ resection	32	42.7±30.1	53.1
Primary local recurrence	22	29.2±14.2	36.4

[a]Median ± standard deviation.

Statistical analysis. The endpoints of the present study were upon patient mortality or the date of last follow-up. DSS was defined as the time from the primary treatment (time of diagnosis or time of primary resection for the 65-patient analysis) to the time of mortality or last follow-up. The endpoint for DSS was confirmed disease-associated mortality (27 of the 65 patients). The survival rate was calculated as the percentage of surviving patients among the 65 patients at the end of the follow-up period. A Wilcoxon signed-rank test was used to determine whether two dependent samples were selected from populations with the same distribution, and a Spearman's rank correlation was used to compare the correlation between two variables.

The tumor burden was defined as the diameter of the maximum dimension upon cross-sectional imaging of a single mass or the largest mass removed from the abdominal cavity, rather than other dispersive or small masses removed during primary resection. Adjacent visceral structures that were removed during resection, including those in the kidney, liver and intestines, were included in the measure of tumor burden. The 51 patients who underwent complete primary tumor resection were divided into three groups on the basis of tumor size, from small to large, as follows: Group A, ≤10 cm; group B, >10 cm and ≤20 cm; and group C, >20 cm.

The organs removed during the resection of adjacent organs, including the kidney, adrenal glands, ureter, spleen, pancreas, gall bladder, epityphlon, colon, omentum and mesentery, were recorded and organ identity was confirmed by postoperative pathological examination.

Clinical, pathological and therapeutic variables, including pathological subtype, histological grade, tumor burden, complete primary tumor resection, adjacent organ resection and the tumor margins, were examined, and the association of these factors with survival outcome were analyzed using the Kaplan-Meier method and log-rank test. Other univariate analysis and statistical associations were examined using the χ^2 test, Wilcoxon signed-rank test and Spearman's rank correlation. Multivariate factors, including age at presentation and gender, were analyzed using the Cox proportional hazards regression model.

Results

Patient, primary tumor and treatment-associated variables. Between January 2005 and March 2015, 65 patients were diagnosed with PRPLS and 51 patients underwent complete primary tumor resection at Southwest Hospital. The distribution of clinical and pathological characteristics among patients is illustrated in Table II. Of the 65 patients, 14 received palliative surgery or biopsy alone, due to the invasion of adjacent major organs or vessels by the tumor. At the endpoint of the study, 5 of these 14 patients survived. Of the 51 patients that received complete primary tumor resection, the median survival time was 43.3 months. Tumor samples from 25 patients were determined to be of the well-differentiated histological subtype, 10 were de-differentiated, 8 were myxoid/round cell and 8 were pleomorphic/mixed-type (Table II). Thus, 18 tumors were high grade and the remaining 33 tumors were low grade. Following surgery, the gross resection margins were negative for tumor tissue in all 51 patients. To achieve complete resection, 32 patients received adjacent organ resection, with 15 patients exhibiting tumor-positive microscopic margins. Following complete primary resection, 22 patients developed local recurrence and the median time to recurrence was 29.2 months (range, 3-60 months). Of these, 16 patients underwent further surgery, 4 patients received adjuvant chemotherapy or radiation, and 2 patients declined further treatment. The characteristics of the 65 patients with PRPLS are presented in Table II.

Immunohistochemical analysis. Immunohistochemical analysis of PRPLS tumors stained for S-100, vimentin and Ki-67 is presented in Figs. 1-3. Tumors from 23 patients were positive for S-100, whereas vimentin and Ki-67 were

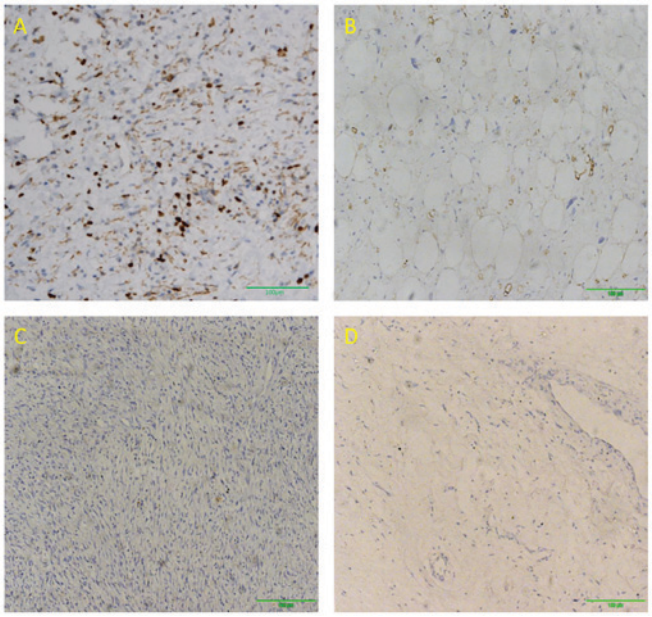

Figure 1. Positive expression of S-100 in (A) well-differentiated and (B) myxoid PRPLS. Negative expression of S-100 in (C) undifferentiated and (D) pleomorphic/mixed-type PRPLS. PRPLS, primary retroperitoneal liposarcomas.

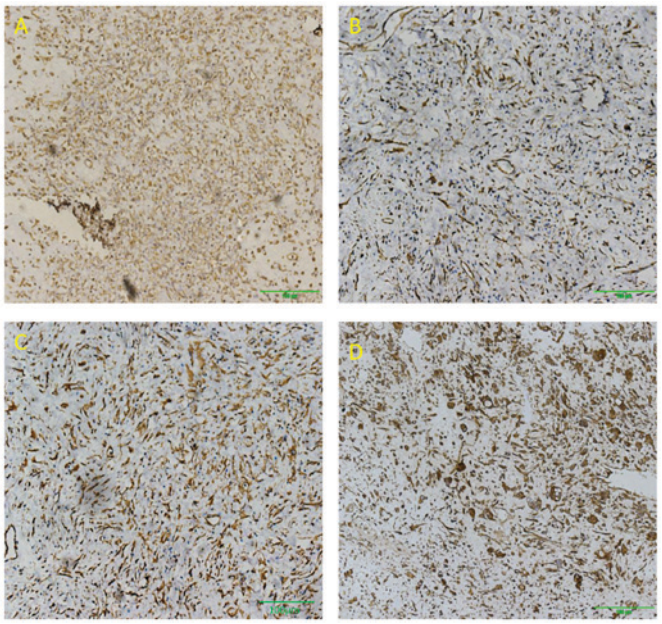

Figure 2. Positive expression of vimentin in (A) well-differentiated, (B) myxoid/round cell, (C) de-differentiated and (D) pleomorphic/mixed-type primary retroperitoneal liposarcoma tissues.

expressed in 62 and 64 patients, respectively. S-100 expression was predominantly observed in well-differentiated PRPLS. The rates of vimentin- and Ki-67-positive staining were significantly higher compared with that of S-100 (P<0.0001, P<0.0001 and P=0.157 respectively; Table III). Ki-67 was highly expressed in high-grade PRPLS, with the most pronounced expression observed in de-differentiated, pleomorphic and mixed-type tumors. Furthermore, a negative correlation was observed between Ki-67 expression index and DSS time (Table IV).

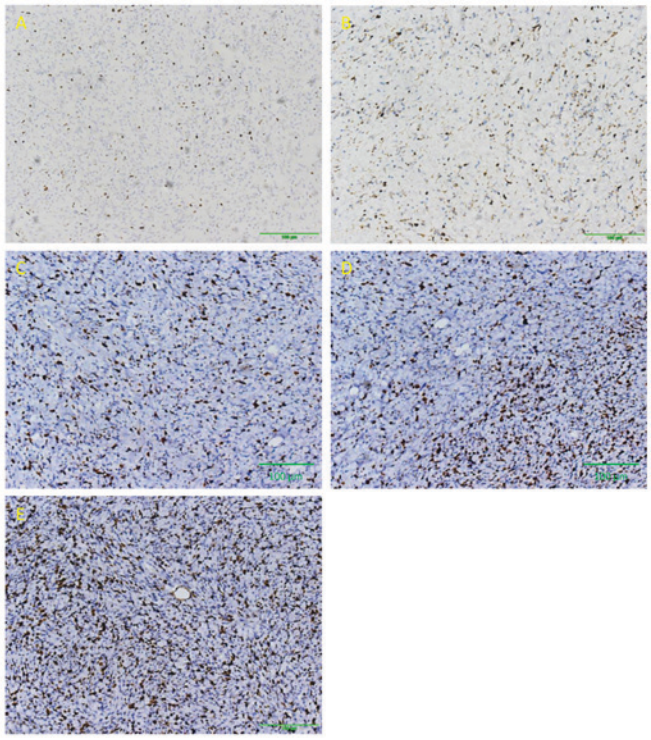

Figure 3. Positive expression of Ki-67 in primary retroperitoneal liposarcoma. Images indicate the Ki-67 proliferation indexes of (A) +, (B) ++, (C) +++, (D) ++++ and (E) +++++.

Association between pathological subtype and DSS time. The duration of follow-up period of patients ranged between 3 and 114 months. The median survival time of the 51 surgical patients was 43.3 months. The median survival time of the 25 patients with well-differentiated PRPLS was 51.2 months, and the rate of survival was 84.0%, compared with 20.7 months and 50.0% for the 10 patients with de-differentiated PRPLS. Additionally, the 8 patients with the myxoid/round cell subtype had a median survival time of 59.9 months and a survival rate of 62.5%, compared with 30.1 months and 25.0% for the 8 patients with pleomorphic/mixed-type tumors (Table II). Statistical analysis indicated that DSS time was significantly increased in patients with well-differentiated PRPLS, compared with those with de-differentiated PRPLS (χ^2=19.467, P<0.0001; Fig. 4).

Association between histological grade and DSS time. Analysis of tumor grade and DSS was performed using the follow-up data of the 51 patients with PRPLS who received complete primary resection. Histological subtype was used to define the histological grade, which included de-differentiated and pleomorphic/mixed-type subtypes and low-grade included well-differentiated and myxoid/round cell subtypes. The median survival time of the 18 patients with high-grade PRPLS was 24.9 months and the overall survival rate was 38.9%, compared with 53.3 months and 78.8% for the 33 patients with low-grade PRPLS (Fig. 4). DSS was significantly increased in the patients with low-grade PRPLS compared with patients with high-grade PRPLS (χ^2=19.053, P<0.001).

Association between tumor burden and DSS time. The present study investigated the association of tumor burden with

Table III. Analysis on the specificity of S-100, vimentin and Ki-67 staining.

Groups	Positive, n	Negative, n	Positive rate, %	Z-value	P-value[a]
Group 1				-6.245	<0.0001
S-100	23	42	35.4		
Vimentin	62	3	95.4		
Group 2				-6.403	<0.0001
S-100	23	42	35.4		
Ki-67	64	1	98.5		
Group 3				-1.414	0.157
Vimentin	62	3	95.4		
Ki-67	64	1	98.5		

[a]Wilcoxon Signed Ranks Test.

Table IV. Correlation between the intension of Ki-67 expression and survival time.

Ki-67 staining intensity				
Threshold (%)	Symbol	Patients, n	R-value	P-value[a]
≤0 and 10	+	29	-0.542	0.0001
≤10 and 20	++	13		
≤20 and <30	+++	8		
≤30 and <40	++++	8		
>40	+++++	6		

[a]Spearman's rank correlation.

postoperative survival time. In the 51 patients that received complete primary resection, the total median tumor burden was 18.0 cm (range, 3-45 cm). There were 7 patients in group A (tumor size, ≤10 cm), with a median survival time of 52.1 months. There were 28 patients in group B (tumor size, >10 cm and ≤20 cm), and the median survival time was 45.6 months, compared with 35.3 months for the 16 patients in group C (tumor size, >20 cm). Statistical analysis demonstrated that tumor burden was significantly associated with DSS (χ^2=6.826, P=0.033; Fig. 4).

Association between the DSS time of patients and complete resection or palliative surgery/biopsy. The median survival time of the 51 patients that received complete resection was 43.3 months and the survival rate was 64.7%, compared with 19.4 months and 35.7% for the 14 patients that underwent palliative surgery or biopsy. Thus, complete tumor resection was demonstrated to be significantly associated with increased DSS time (χ^2=15.471, P<0.0001), and also observably improved the survival rate and survival time (Fig. 4).

Association between DSS time and contiguous organ resection or palliative surgery/biopsy. To achieve complete tumor resection, contiguous resection was performed where necessary. The median survival time following contiguous organ resection (32 patients) was 42.7 months and the rate of survival was 53.1%, compared with 19.4 months and 35.8% following palliative surgery or biopsy (14 patients). Analysis demonstrated that DSS time was significantly increased in patients who received contiguous organ resection, compared with those who underwent only palliative surgery or biopsy (χ^2=7.130, P=0.008; Fig. 5).

Margin of resection. Of the 51 patients who underwent complete resection, all had negative gross margins. The median survival time for these patients was 43.3 months and the rate of survival was 64.7%, compared with 19.4 months and 35.7% in the 14 patients who received palliative surgery or biopsy with tumor-positive gross margins. Of the 32 patients who underwent contiguous organ resection, 15 patients had tumor-positive microscopic margins. The median survival time for these patients was 36.9 months and the survival rate was 46.7% in these 15 patients. There was no statistically significant difference between the DSS of patients with tumor-negative gross margins and positive microscopic margins (χ^2=2.240, P=0.134; Fig. 6). However, the status of the gross margins was associated with prognosis based on a comparison of the DSS of the 51 patients with negative gross margins and the 14 patients with positive gross margins who received palliative surgery or biopsy (χ^2=15.471, P<0.0001; Fig. 5).

Association between DSS time, gender and age at diagnosis. Among the 65 patients included in the present study, the 35 males had a median survival time of 36.1 months and a 60.0% survival rate, compared with a 40.5-month median survival time and 56.7% survival rate in the 30 female patients. Analysis demonstrated that gender did not affect DSS time (χ^2=0.005, P=0.821; Fig. 5). For patients with age <60 years (n=40), the median survival time was 37.1 months, and the survival rate was 57.5%, compared with 38.9 months and a 60.0% survival rate for patients with age ≥60 years (n=25). The age at diagnosis did not affect DSS (χ^2=0.005, P=0.671; Fig. 5).

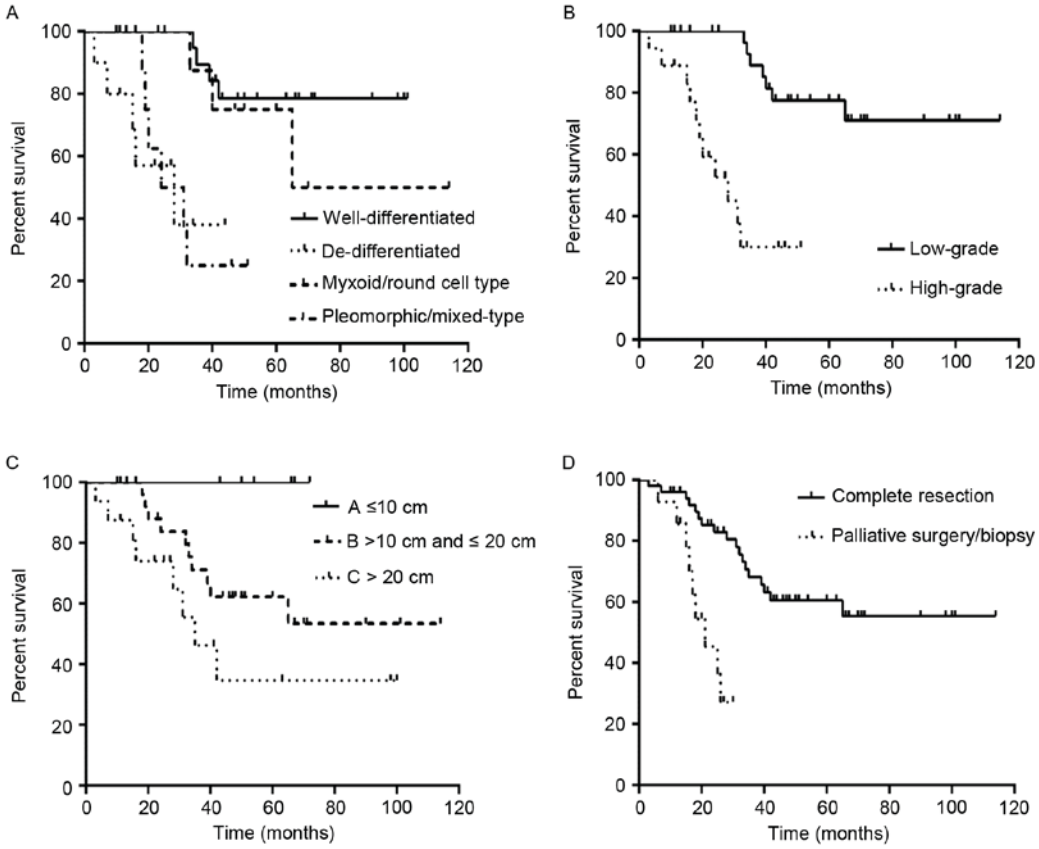

Figure 4. Analysis of patient prognosis. Association between disease-specific survival and (A) pathological subtype (P<0.0001), (B) histological grade (P<0.0001), (C) tumor burden (P=0.033) and (D) complete resection (P<0.0001) are shown.

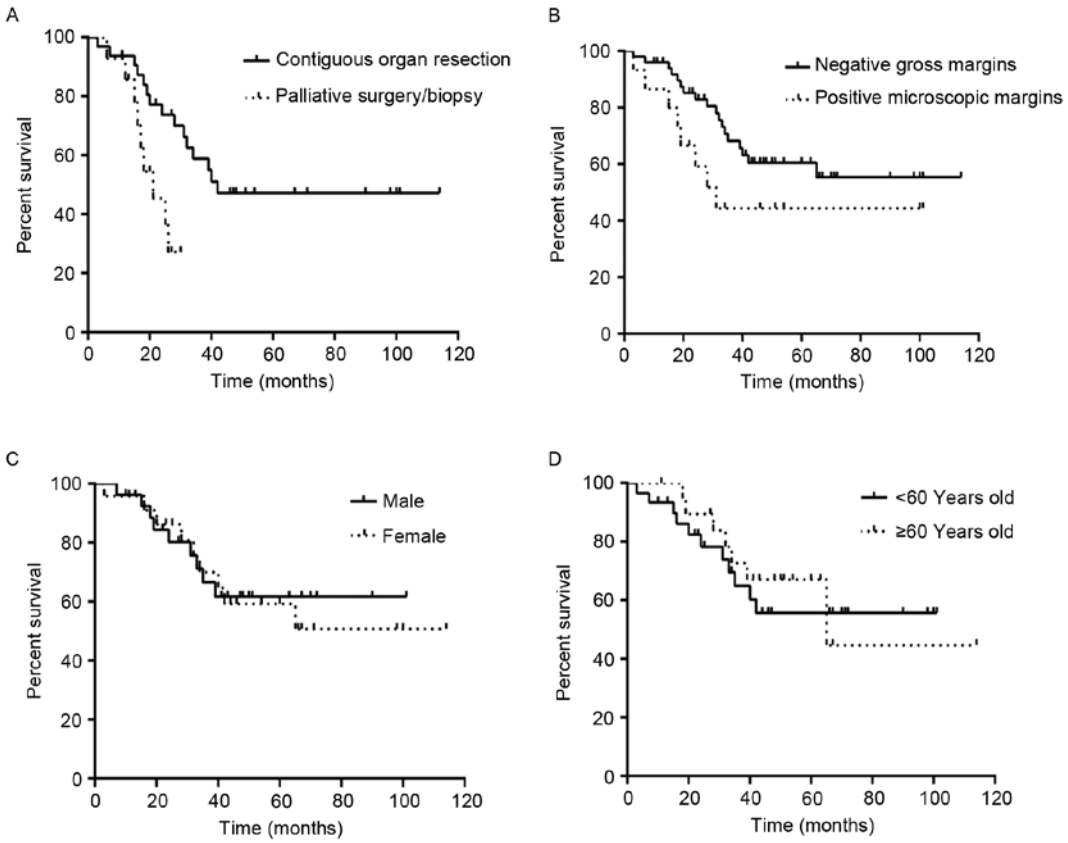

Figure 5. Analysis of prognosis. Association between disease-specific survival and (A) contiguous organ resection (P=0.008), (B) microscopic margin (P=0.134), the gross margin (P<0.0001), (C) gender (P=0.821) and (D) age at presentation (P=0.671) are shown.

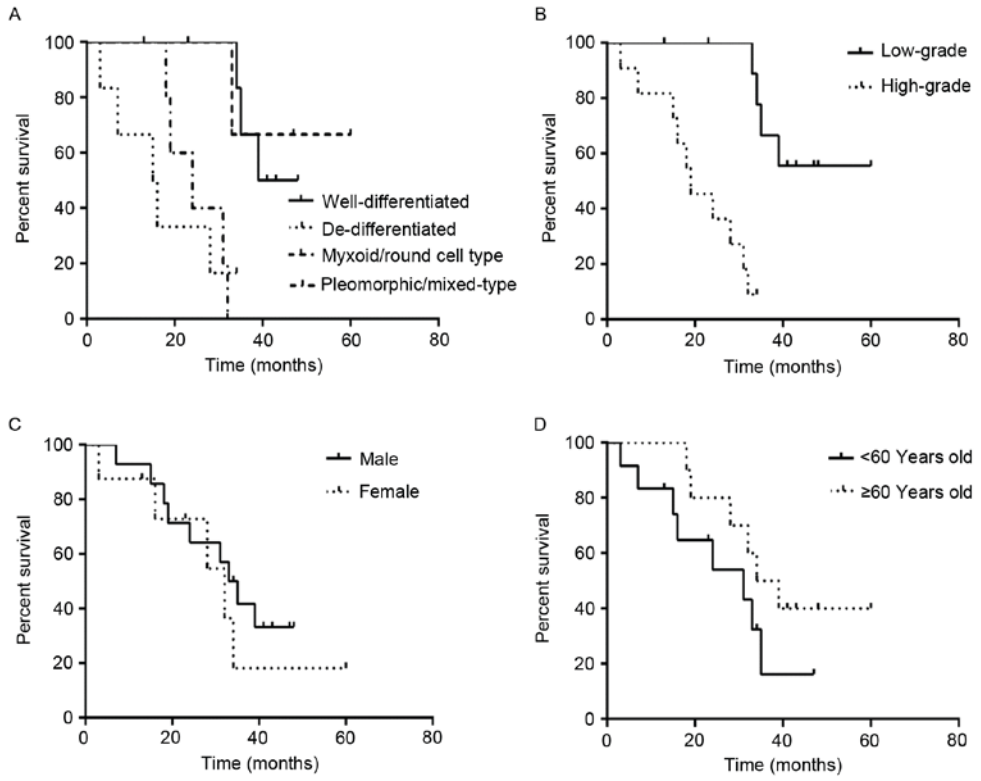

Figure 6. Analysis of primary local recurrence. Association between disease-specific survival and (A) pathological subtype (P=0.002), (B) histological grade (P<0.0001), (C) gender (P=0.466) and (D) age at presentation (P=0.186) are shown.

Multivariate analysis of factors affecting prognosis. The pathological subtype, histological grade, tumor burden, contiguous organ resection, local recurrence, tumor margins, gender and age at presentation were analyzed using the Cox proportional hazards regression model. The results revealed that pathological subtype, histological grade and contiguous organ resection were independent factors that affected prognosis, whereas the remaining variables were not (Table V).

Association between pathological subtype and DSS time in patients with primary local recurrence. Of the 51 patients who underwent complete resection, 22 experienced primary local recurrence. The median time to recurrence of the 8 patients with well-differentiated PRPLS was 34.5 months and the survival rate was 62.5%, compared with 17.2 months and 16.7% for the 6 patients with de-differentiated PRPLS. Additionally, the 3 patients with myxoid/round cell tumors exhibited a median time-to-recurrence of 46.7 months and survival rate of 66.7%, compared with 24.8 months and 0% survival rate in the 5 patients with pleomorphic/mixed-type PRPLS. Statistical analysis demonstrated that, in patients with primary local recurrence, the pathological subtype was associated with DSS (χ^2=14.995, P=0.002; Fig. 6).

Association between histological grade and DSS in patients with primary local recurrence. Of the 22 patients with primary local recurrence, the median time to recurrence of the 11 patients with high-grade PRPLS was 20.6 months and the rate of survival was 9.1%, compared with 37.8 months and 63.6% in the 11 patients with low-grade PRPLS. Analysis demonstrated that the DSS time was significantly higher among patients with low-grade PRPLS, compared with those with high-grade PRPLS (χ^2=14.810, P<0.0001; Fig. 6).

Multivariate analysis of factors affecting local recurrence. The pathological subtype, histological grade, tumor burden, gender and age at presentation were examined in the patients who exhibited local recurrence following resection (n=22) using the Cox proportional hazards regression model. The analysis demonstrated that histological grade was an independent factor affecting local recurrence, while the remaining variables were not independently associated with recurrence (Table VI).

Correlation between local recurrence and DSS time. Of the 51 patients who received complete resection, 22 developed primary local recurrence, with a survival rate of 36.4%. By comparison, the survival rate was 86.2% for the 29 patients without local recurrence. This finding demonstrated that local recurrence strongly affected DSS, and statistical analysis indicated that there was a negative association between local recurrence and DSS (R=0.517, P=0.000; Table VII). Thus, local tumor recurrence following complete resection was the predominant cause of mortality in patients with PRPLS.

Correlation between tumor burden and histological grade. Of the 51 patients who underwent complete tumor resection, the median tumor burden was 18.0 cm. The median tumor burden of the 33 patients with low-grade PRPLS was 17.2 cm, and value was 19.4 cm in the patients with high-grade PRPLS. Statistical analysis revealed that histological grade was not correlated with tumor burden (R=0.222, P=0.117; Table VIII).

Table V. Multivariate analysis of patient prognosis[a].

Variables	B	SE	Wald	df	P-value	Exp (B)	95% CI
Histological subtype	-0.491	0.247	3.952	1	0.047	0.612	0.377-0.993
Histological grade	2.262	0.385	12.172	1	<0.0001	9.602	2.695-34.219
Tumor burden	0.141	0.283	0.249	1	0.618	1.151	0.662-2.003
Contiguous organ resection	-1.115	0.451	6.117	1	0.013	0.328	0.135-0.793
Primary local recurrence	0.944	0.541	3.046	1	0.081	2.570	0.890-7.419
Margin	-0.549	0.578	0.903	1	0.342	0.577	0.186-1.793
Gender	-0.044	0.385	0.013	1	0.908	0.957	0.450-2.036
Age	0.305	0.419	0.529	1	0.467	1.357	0.596-3.087

[a]Cox proportional hazards regression model. B, regression coefficient; SE, standard error; Wald, statistical magnitude; df, degree of freedom; Exp (B), relative risk; CI, confidence interval.

Table VI. Multivariate analysis of local recurrence[a].

Variables	B	SE	Wald	df	P-value	Exp (B)	95% CI
Histological subtype	0.064	0.306	0.044	1	0.834	1.066	0.586-1.941
Histological grade	2.506	0.963	6.772	1	0.009	12.260	1.857-80.958
Tumor burden	1.006	0.582	2.992	1	0.084	2.736	0.875-8.557
Gender	-0.155	0.752	0.042	1	0.837	0.857	0.196-3.740
Age	-0.006	0.723	0.007	1	0.993	0.994	0.241-4.099

[a]Cox proportional hazards regression model. B, regression coefficient; SE, standard error; Wald, statistical magnitude; df, degree of freedom; Exp (B), relative risk; CI, confidence interval.

Table VII. Correlation between disease-dependent survival and local recurrence.

Parameter	Patients, n	Median survival rate, %	R-value	P-value[a]
Primary local recurrence			0.517	<0.001
Yes	22	36.4		
No	29	86.2		

[a]Spearman's rank correlation.

Table VIII. Correlation between tumor burden and histological grade, tumor invasion of adjacent organs or local recurrence.

Parameters	Patients, n	Median tumor burden, cm	R-value	P-value[a]
Histological grade			0.222	0.117
High	18	19.4±5.1		
Low	33	17.2±8.4		
Adjacent organ invasion			0.225	0.112
Yes	32	19.3±7.2		
No	19	15.9±7.6		
Primary local recurrence			0.159	0.265
Yes	22	18.6±5.7		
No	29	17.5±8.6		

[a]Spearman's rank correlation.

Correlation between tumor burden and tumor invasion of adjacent organs. Of the 51 PRPLS patients who underwent complete resection, 32 underwent resection of adjacent organs as a result of tumor invasion. The median tumor burden in patients who received adjacent organ resection was 19.3 cm, compared with 15.9 cm in the 19 patients without tumor invasion of adjacent organs. Statistical analysis demonstrated that there was no significant correlation between tumor burden and tumor invasion of adjacent organs (R=0.225; P=0.112; Table VIII).

Correlation between tumor burden and local recurrence. Following complete primary surgical resection, 22 patients developed primary local recurrence and the median tumor burden was 18.6 cm, compared with 17.5 cm in the 29 patients that did not exhibit local recurrence. Statistical

Table IX. Correlation between adjacent organs invasion and histological grade.

Parameter	Patients, n	Median integral number of organs invaded[a]	R-value	P-value[b]
Histological grade			0.666	<0.001
High	27	2±1		
Low	38	1±1		

[a]Rounding-off method; [b]Spearman's rank correlation.

analysis indicated that tumor burden was not correlated with the development of local recurrence (R=0.159, P=0.265; Table VIII).

Correlation between tumor invasion of adjacent organs and histological grade. Of all 65 patients with PRPLS, a median of 1 organ was invaded in each of the 38 patients with low-grade PRPLS, compared with 2 in the 27 patients with high-grade PRPLS. Statistical analysis demonstrated that there was a positive correlation between tumor invasion of adjacent organs and tumor histological grade (R=0.666, P<0.001; Table IX). Thus, the histological grade was strongly associated with tumor invasion of adjacent organs.

Discussion

RPLS is the most common soft tissue malignancy of the retroperitoneum and accounts for ~40% of cases of primary soft tissue sarcoma in the retroperitoneum (1-3). PRPLS typically occurs in patients of 40-60 years, with a 1:1 ratio between male and female patients (1,19). Primary liposarcoma most commonly develops in the arms, legs, retroperitoneum (20) or the bottom of pelvic cavity (21). PRPLS lacks typical clinical symptoms, meaning it is difficult to diagnose. The majority of patients with PRPLS are diagnosed at an advanced disease stage, therefore PRPLS tumors often grow to a large size and have invaded adjacent organs upon diagnosis (22).

The benefits of using adjuvant chemotherapy and radiation therapy to treat PRPLS remains controversial (23,24). A number of studies have suggested that chemotherapy may worsen patient prognosis (25,26). Other studies have reported that chemotherapy has limited effectiveness for PRPLS, but is beneficial for liposarcomas originating from the lower or upper extremities (23,27). Radiation can result in clinical complications, including nerve lesions, hydronephrosis, ureteral fistula and ileus (28). For PRPLS, due to the deep location in the enterocoelia and close proximity to important visceral organs, damage to the viscera by radiation must be considered when deciding upon treatment modalities.

According to the criteria of the WHO Classification of Tumors of Soft Tissue and Bone (29), the histological tumor subtype defines the histological grade: High-grade includes de-differentiated, pleomorphic and mixed cell subtypes, whereas low-grade comprises well-differentiated, myxoid and round cell subtypes, with histological subtype predicting DSS (17,26). In previous reports, well-differentiated and myxoid PRPLS cases exhibited low rates of local recurrence, and long intervals between treatment and recurrence compared with other subtypes of PRPLS (17,30). The present study, which was based on a Chinese population from a single medical center, comprised 49.0% cases of well-differentiated, 19.6% cases of de-differentiated and 15.7% cases of myxoid/round cell PRPLS. The percentage of PRPLS histological subtypes was approximately consistent with previous reports (14,17). The biological behavior of these tumors indicated that well-differentiated tumors grew slowly. By contrast, de-differentiated tumors grew faster and centrifugally. It is more likely for de-differentiated tumors to lead to increased invasion of adjacent organs. In the present study, the histological tumor grade was significantly associated with tumor burden, as the majority of PRPLS cases exhibited expansive growth and formed a pseudocapsule. However, histological grade was associated with tumor invasion of adjacent organs. This may be due to the highly invasive nature of high-grade tumors and the ability of some of the tumor cells to pass through the tumor pseudocapsule to invade adjacent organs.

Pathological diagnosis currently remains the gold standard for the diagnosis of PRPL. Common markers for investigating the clinicopathological features and biological behavior in immunohistochemical analysis of PRPL tumors include S-100, vimentin and Ki-67 (31-34). S-100 is an acidic calcium-binding protein that is predominantly present in the cytosol of astroglial cells of the central nervous system. Vimentin is an intermediate filament protein that is expressed in mesenchymal cells and is closely associated with the occurrence and metastasis of tumors (35). Ki-67 is a proliferation-associated nuclear antigen and may be used to measure the proliferative activity of tumor cells (36). Ki-67 is specifically expressed in the cytoplasm (membrane) of adipocytes and in the nuclei of other tumor cells. The results of the present study demonstrated that vimentin and Ki-67 were more sensitive markers for PRPLS diagnosis compared with S-100. S-100 protein was predominantly expressed in well-differentiated PRPLS. Furthermore, vimentin and Ki-67 were expressed in the majority of the PRPLS cases, and there was a higher expression of Ki-67 in high-grade PRPLS, including de-differentiated, pleomorphic and mixed-type PRPLS. By contrast, in low-grade tumors, ~20.0% of the cell population was Ki-67-positive. However, the Ki-67-positive cell population ranged from 20.0 to 60.0% in high-grade PRPLS. These results demonstrated that Ki-67 expression reflected the proliferative activity of the tumor cells, and its positive expression was associated with DSS.

In recent years, certain reports have indicated that de-differentiated liposarcoma is associated with poor prognosis, whereas the sclerotic subtype has the best prognosis in well-differentiated PRPLS cases (30). Tseng *et al* (37) reported that the 5-year survival rate of patients with differentiated retroperitoneal liposarcoma was 20.0%, compared with 83.0% for those with well-differentiated PRPLS. In the present study, the survival times for patients with well-differentiated and myxoid/round cell PRPLS were improved compared with those with de-differentiated and pleomorphic/mixed-type tumors. Additionally, the prognosis for patients with low-grade PRPLS was improved compared with those with

high-grade. Furthermore, survival analysis demonstrated that the pathological subtype and histological grade were important prognostic factors for DSS, and that there was a positive association between tumor invasion of adjacent organs and histological grade.

Serio *et al* (38) proposed that the complete resection of PRPLS (according to the gross margins) was an effective surgical treatment for PRPLS. Previous studies reported that ~80.0% of patients with PRPLS that required aggressive treatment were suitable for complete surgical resection, and this treatment strategy resulted in a median survival time of 83 months and a 5-year DSS of 60.0% (39-41). Singer *et al* (17) reported 3- and 5-year survival rates of 73.0 and 60.0%, respectively, when complete resection was performed. Additionally, Milone *et al* (42) reported a 5-year survival rate of 85.7%. The rate of complete primary tumor resection was 78.5% in the present study, compared with 81.0% in a previous report (17). This discrepancy may be due to the fact that 46 patients in the present study presented with tumor invasion of adjacent organs. However, there was no significant difference in the prognosis of patients with negative gross margins during operation compared with that of patients with positive microscopic margins postoperatively. It is hypothesized that this may be because these PRPLS tumors had complete pseudocapsules and exhibited local expansive growth. However, tumor-positive gross margins strongly affected DSS.

In the present study, the tumor burden was associated with DSS. However, tumor burden did not directly affect tumor invasion of adjacent organs and local recurrence. This is potentially due to ~80.0% of patients exhibiting a tumor burden of >10 cm, indicating that the tumor grew expansively and the majority of the tumor pseudocapsules were complete. A previous study has reported that the 5-year survival rate of patients who underwent complete tumor resection was 75.0%, compared with 34.0% for patients who underwent palliative surgery or biopsy (43). This effect on survival rate was also observed in the present study. However, the follow-up period of certain patients was short, and long-term survival must also be evaluated. Biopsy is not generally recommended for patients without the ability to undergo complete resection due to the likelihood of tumor seeding (44). Shibata *et al* (45) observed that, for patients with PRPLS that were not able to undergo complete resection, palliative surgery is able to increase the survival time compared with simple biopsy and reduce 75.0% of the clinical symptoms. Neuhaus *et al* (25) reported similar results.

To achieve a complete removal of the tumor, 57.0-83.0% of patients with PRPLS required contiguous organ resection (25,46), and the resected organs included kidney, adrenals, ureter, colon, small intestine, omentum, spleen and other celiac organs (47). Patients appear to benefit from this aggressive approach. Furthermore, complete resection that includes resection of tumor-invaded adjacent organs has been shown to be beneficial for the prevention of local recurrence (17). In the present study, 32 patients received contiguous organ resection. The prognosis of these patients was improved compared with the 14 patients who received palliative surgery or biopsy.

Multivariate analysis demonstrated that the pathological subtype and histological grade of the tumors were independent markers of prognosis, therefore, the greater the differentiation of the tumor, the better the prognosis of the patient. Additionally, contiguous organ resection was an independent prognostic factor; if patients exhibited tumor invasion of the adjacent organs, the prognosis of patients who received contiguous organ resection was improved compared with patients who received palliative surgery. However, although tumor burden affected DSS, it was not an independent prognostic marker. The likely reason for this is that larger tumors are able to infiltrate adjacent organs more easily. Additionally, the rate of complete resection was lower in patients with a larger tumor burden. In the present study, gender and age were not independent prognostic markers for DSS.

Clinical practice demonstrates that PRPLS has a very high local recurrence rate following surgery (5). The majority of patients succumb to disease as a result of local recurrence. Thus, the majority of patients with local recurrence require reoperation (25). It is generally considered that the cause of recurrence is the presence of pseudocapsules containing malignant cells, which can be observed in the majority of cases of PRPLS, and the rapid growth of the tumor to oppress the surrounding normal structures. PRPLS frequently recurs *in situ* (48). The probability of recurrence doubles over time (48). Certain studies have reported that first, second and third complete resections were 57, 22 and 10.0%, respectively, in primary local recurrence of PRPLS following the first resection (39,49). For patients with recurrence who cannot undergo complete resection, the aim of treatment is to attenuate symptoms, remove oppression of the surrounding organs and obstruction of the tumor, maintain visceral function, extend survival time and improve the quality of life. A previous study indicated that if the speed of growth of a recurrent tumor is >0.9 cm per month, multiple surgeries do not improve the survival rate (50).

Research has demonstrated that local recurrence of liposarcomas is closely associated with tumor grade. In the present study, of the 22 patients with local recurrence, half of original primary tumors were high grade and almost all cases exhibited tumor invasion of adjacent organs, which is in accordance with the literature (17,44). Tumor burden was not associated with local recurrence, and it was observed that almost all the tumors had whole pseudocapsules and grew expansively. Of the patients with local recurrence, 30 underwent further surgery and only 8 survived to the end of the study, with a survival rate of 36.4%, compared with 86.2% in patients without recurrence. According to the present study, local recurrence was negatively correlated with DSS time. Thus, postoperative local recurrence is considered to be the most common cause of mortality in patients with PRPLS. Multivariate analysis demonstrated that histological grade was an independent factor that affected local recurrence, whereas tumor burden was not an independent prognostic factor, potentially as the majority of patients exhibited recurrence had primary tumors >10 cm and over half of these patients exhibited tumor invasion of adjacent organs. Furthermore, half of the patients that developed recurrence had high-grade primary tumors. Gender and age at presentation were not independent factors.

In conclusion, despite the high rate of recurrence and mortality of PRPLS, surgical resection is the most effective treatment. Local recurrence is the predominant cause of mortality in PRPLS. Staining for vimentin and Ki-67 demonstrated higher

sensitivity for PRPLS diagnosis compared with S-100 protein. S-100 protein was predominantly expressed in well-differentiated PRPLS, whereas vimentin and Ki-67 exhibited positive expression in almost all PRPLS samples. Additionally, Ki-67 was highly expressed in high-grade PRPLS. Notably, there was a negative association between the Ki-67 expression index and DSS. DSS was strongly associated with pathological subtype, histological grade, tumor burden, complete primary tumor resection and contiguous organ resection. Positive microscopic margins did not affect DSS, whereas the status of gross margins was strongly associated with DSS. Pathological subtype, histological grade and contiguous organ resection were independent markers of prognosis. Pathological subtype and histological grade were associated with local recurrence, with histological grade demonstrated to be an independent marker for local recurrence. Patient age at presentation and gender were not useful markers of prognosis or local recurrence.

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