

Resection outcomes for primary and local recurrent retroperitoneal liposarcoma patients

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Research

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Abstract

Aim: The clinical characteristics of primary retroperitoneal liposarcoma(PR RPLPS) and local recurrent retroperitoneal liposarcoma(LR RPLPS) cases were compared to determine related factors involved in postoperative survival.

Methods: A total of 90 patients who underwent surgery between 2006 and 2013 were included in this study. Clinicopathological data that was prospectively gathered was analyzed to identify factors associated with overall survival and progression-free survival.

Results: The PR cases showed a higher complete resection rate when compared to the LR group. The LR group showed a greater number that were poorly differentiated and highly malignant. More blood loss was observed in the LR compared to the PR group. Multivariate analysis suggested that blood loss and tumor grade were prognostic factors for OS and PFS of the PR group, but extent of resection was a prognostic factor only for OS. In the LR group, the extent of resection was a significant prognostic factor associated with OS, whereas tumor grade was associated with PFS.

Conclusions: Complete surgical resection is the most important factor for the survival of RPLPS patients. Tumor grade is an independent prognostic factor for PFS. In PR RPLPS, poor tumor classification and increased intraoperative bleeding are associated with a poor prognosis.

Introduction

Retroperitoneal liposarcoma(RPLPS) is the most common retroperitoneal sarcoma(RSTS) accounting for 20% of all soft tissue tumors[1–3]. Primary RPLPS is a rare disease and surgery is the main mode of treatment. Recurrence of the tumor is the main issue at hand and ultimately leads to death. Local recurrence occurs in 70% of cases without exhibiting distant metastases[2]. Although strategies to combat local recurrence are critical, the understanding of the cause of the primary disease still needs to be investigated and fully understood.

Here, patients undergoing primary and secondary treatment for RPLPS are analyzed to explore factors affecting the prognosis of this disease from multiple dimensions.

Materials And Methods

A total of 90 RPLPS patients undergoing surgical treatment at the PLA General Hospital (Beijing, China) from December 1, 2006 to June 1, 2013 were analyzed in this study. There were 46 cases of primary RPLPS and 44 cases showing first local recurrence. All cases were confirmed by the pathology department in the hospital.

Patient data included age, gender, tumor size, pathological classification, surgical method, intraoperative blood loss, adjuvant therapy, combined organ resection and other pathological factors. All patients

underwent CT, MRI or PET/CT. For cases where imaging diagnosis was difficult, a preoperative biopsy was performed to remove all visible tumor. A negative resection margin was defined as R0 resection and a positive postoperative margin was considered a R1 resection (positive or close margins (< 1 mm without intact fascia)). If the tumor invades surrounding organs, combined organ resection is selected. However, if the tumor invades the blood vessels, the combined resection or ligation of the blood vessels is performed. R2 (palliative) is considered if there is residual tumor observed during an operation.

Tumor size was expressed as the largest tumor diameter after a postoperative assessment (palliative resection cases). Tissue pathology was classified into grades 1, 2 and 3 according to French Federation of Cancer Centres Sarcoma Group Grading System (Fédération Nationale des Centres de LutteContre le Cancer, FNCLCC). These grades were based on tumor cell morphology, degree of differentiation, heteromorphism, mitotic images and necrosis. Adjuvant treatment included postoperative chemotherapy, intraoperative or postoperative radiotherapy, ultrasound-guided radiofrequency ablation and biological therapy.

All patients participated in follow-ups ever 3–4 months for 1 year after surgery. After one year, these follow-ups were performed every 6 months for 2–5 years post-surgery, and every year after 5 years post-surgery. Death of the patient or the follow-up date 2020-1-1 was the endpoint of the analysis. Follow-up visits included surveillance imaging (CT chest / abdomen / pelvis). If tumor recurrence was noted, a shortened follow-up interval of 3–4 months was performed. Overall survival (OS) was defined as the time from initial presentation of disease up to death. Progression-free survival (PFS) is defined as the time from diagnosis to the first occurrence of disease progression or death (date of first recurrence for those who had an R0/R1 resection, date of progression of residual disease for those who had R2 resection, or death without evidence of recurrence or progression).

SPSS version 22.0 (IBM, Armonk, New York, USA) statistical software was used for data analysis. Clinical data of the PR and LR groups were compared using the Pearson chi-square or Wilcoxon-Mann-Whitney tests. OS and PFS curves were generated using the Kaplan-Meier method. Univariable and multivariable prognostic analyses were performed for OS and PFS to identify significant prognostic factors. Differences were considered statistically significant when $p < 0.05$.

Results

Clinicopathologic characteristics

Among the 90 cases of RPLPS treated, 46 cases were diagnosed as PR RPLPS and 44 cases were diagnosed as LR RPLPS. Patient demographics and tumor characteristics are listed in Table 1. The median age of patients was 54 years (ranging from 30 to 87 years) and there was a slightly higher population of men (58.9%) compared to women. The median tumor diameter was 19.5 cm (ranging from 5 to 80 cm). All cases were classified according to FNCLCC criteria. Compared to the PR group (41.3% of grade 1; 21.7% of grade 2; 37.0% of grade 3), there was an increased number of poorly differentiated and

highly malignant patients in the LR group (18.2% of grade 1; 22.7% of grade 2; 59.1% of grade 3, $p = 0.042$).

Table 1
Clinicopathological factors for 90 RPLPS patients

Characteristics	All patients	Primary retroperitoneal liposarcoma	Recurrent retroperitoneal liposarcoma	P-value ^b
	N(% of total or IQR ^a)	N(% of total or IQR ^a)	N(% of total or IQR ^a)	
Total number of patients	90(100)	46(100)	44(100)	
Age(years)				0.141
<60	63(70.0)	29(63.0)	34(77.3)	
≥60	27(30.0)	17(37.0)	10(22.7)	
Gender				0.212
Female	37(41.1)	16(34.8)	21(47.7)	
Male	53(58.9)	30(65.2)	23(52.3)	
Modus operandi				0.004*
R0 resection	46(51.1)	31(67.4)	15(34.1)	
R1 resection	30(33.3)	12(26.1)	18(40.9)	
R2 resection	14(15.6)	3(6.5)	11(25.0)	
Subtype				0.960
Well-differentiated	34(37.8)	17(37.0)	17(38.6)	
Dedifferentiated	24(26.7)	11(23.9)	13(30.0)	
Myxoid	16(17.8)	9(19.6)	7(15.9)	
Pleomorphic	9(10.0)	5(10.9)	4(9.0)	
Mixed	7(7.8)	4(8.7)	3(6.8)	
Blood loss(ml)				0.017*
<1500	60(66.7)	36(78.3)	24(54.5)	
≥1500	30(33.3)	10(21.7)	20(45.5)	
FNCLCC				0.042*
1	27(30.0)	19(41.3)	8(18.2)	
2	20(22.2)	10(21.7)	10(22.7)	
3	43(47.8)	17(37.0)	26(59.1)	
Tumor size(cm)				0.673
<20	45(50.0)	24(52.2)	21(47.7)	
≥20	45(50.0)	22(47.8)	23(52.3)	

*Significant.

^a Inter-quartile range (IQR).

^b Comparison between patients who were primary retroperitoneal liposarcoma and patients who were recurrent retroperitoneal liposarcoma using Pearson's chi-squared test for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables.

Adjuvant therapy	15(16.7)	3(6.5)	12(27.3)	0.008*
Yes	75(83.3)	43(93.5)	32(72.7)	
No				
Median adjacent organs resected	1.0(0.0–2.0)	1.0(0.0-1.3)	1.0(0.0–2.0)	0.322
*Significant.				
^a Inter-quartile range (IQR).				
^b Comparison between patients who were primary retroperitoneal liposarcoma and patients who were recurrent retroperitoneal liposarcoma using Pearson's chi-squared test for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables.				

Treatment strategy

A total of 51.1% (46/90) of patients underwent R0 resection, 33.3% (30/90) underwent R1 resection and 15.6% (14/90) underwent R2 resection. The primary group (R0 67.4%, R1 26.1%, R2 6.5%) showed a higher complete resection rate compared to the relapsed group (R0 34.1%, R1 40.9%, R2 25%) ($p = 0.004$). In order to obtain a higher rate of complete tumor resection or to reduce tumor burden, 65.6% (59/90) of patients underwent at least 1 adjacent organ resection during surgery (Table S1). The most frequent organ resection performed was for the colon (32.2%), followed by the kidney (18.9%), spleen (10.0%) and small intestine (7.8%). The median blood loss in the PR group was 800 ml (95% CI 897.7, 1541.3) and 1200 ml (95% CI 1127.1, 2811.6) in the LR group. Assigning 1500 ml of blood volume as a boundary, the LR group was more prone to blood loss during the operation ($p = 0.009$). In 16 patients, tumors were closely associated with abdominal blood vessels, including the iliac vessels (11.1%), inferior vena cava (8.9%) and abdominal aorta (5.6%). Postoperative complications included hemorrhagic shock (3cases), postoperative abdominal infections (3cases), pancreatic fistulas (2cases), intestinal fistula (1case), ureteral fistula (1case) and incisional liquefaction (2cases). Adjuvant therapy was performed on 15 patients (12 in the relapse group), where 5 were treated with intraoperative radiotherapy, 6 with radiofrequency ablation, and 4 with chemotherapy.

Outcomes

Median follow-up time was 28 months. A total of 59 patients who underwent R0 / R1 resection showed recurrence at a rate of 77.6%, with median recurrence time being 12 months. A total of 57 patients passed away, including 43 who died of relapse after R0 / R1 resection and 14 patients who passed away after R2 resection. The OS at 1, 3 and 5 years were 68.9%, 45.6%, and 33.3%, respectively. The PFS at 1, 3 and 5 years were 50.0%, 32.2%, and 18.9%, respectively. Due to a differential course of the disease, the OS in the PR group was 80.4%, 60.9%, and 45.7% at 1, 3 and 5 years, respectively, while the OS in the LR group was 56.8%, 29.5% and 20.5%, respectively. Differences between the two groups were statistically significant ($p = 0.004$, Fig. 1A). Similarly, the PFS at 1, 3 and 5 years in the PR group were 63.0%, 43.5% and 28.3%, compared to 36.4%, 15.9% and 9.1% in the LR group ($p = 0.015$, Fig. 1B).

Among the 46 cases diagnosed with PR RPLPS, univariate analysis (Table S2) revealed that R0 resection results in longer OS than R1 and R2 resections (R0 resection median OS, 65 months, 95% CI 50.02–69.52 months vs. R1 resection median OS, 19 months, 95% CI 13.53–56.14 months vs. R2 resection median OS, 8 months, 95% CI 1.24–20.09 months, $p < 0.001$). Similarly, the median PFS of patients in the R0 resection group was 53 months (95% CI 36.77–58.06 months) and 12 months for the R1 resection group (7.18–38.0 months). Assigning 1500 ml of blood loss as a limit, a large amount of intraoperative bleeding indicates poor prognosis (OS, $p = 0.006$; PFS, $p = 0.008$). The FNCLCC subtype was also a significant indicator of the postoperative survival time. The median OS times observed for FNCLCC grades 1, 2 and 3 were 70 (58.23–80.93), 66 (34.42–75.38) and 20 (13.28–37.54) months ($p < 0.001$), respectively. The median PFS were 55 (37.17–61.57), 36 (14.73–60.07) and 12 (8.51–33.14) months ($p = 0.022$), respectively. Multivariate analysis using the Cox proportional hazards model revealed that blood loss (OS: $p = 0.003$, Fig. 2B; PFS: $p = 0.035$, Fig. 2D) and tumor grade (OS: $p = 0.000$, Fig. 2C; PFS: $p = 0.027$, Fig. 2E) were significant prognostic factors associated with the postoperative survival time. However, extent of resection was a prognostic factor associated with OS ($p = 0.035$, Fig. 2A), but not with PFS (Table 2).

Table 2

Multivariate associations between clinicopathologic and treatment factors and survival for PR RPLPS patients.

Variable	Analyses by survival type					
	OS			PFS		
	HR	95% CI	p Value	HR	95% CI	p Value
Modus operandi (R0 vs R1 vs R2resection)			0.035*			0.326
R0 vs R1	3.02	0.96-9.48	0.058	1.69	0.68-4.23	0.260
R0 vs R2	6.89	1.49-31.86	0.014*	2.51	0.65-9.67	0.182
Blood loss (< 1500 ml vs ≥ 1500 ml)	0.19	0.06-0.57	0.003*	2.59	0.16-0.94	0.035*
FNCLCC (1 vs 2 vs 3)			0.000*			0.027*
1 vs 2	4.08	0.87-19.21	0.075	1.57	0.57-4.29	0.383
1 vs 3	17.68	4.70-66.56	0.000*	3.06	1.35-6.93	0.007*
*Significant.						
FNCLCC, French Federation of Cancer Centers Sarcoma Group; OS, overall survival; PFS, progression-free survival; R0 resection, Complete resection + clean microscopic margins; R1 resection, Complete resection + positive microscopic margins; R2 resection, macroscopically incomplete resection.						

Among the 44 cases diagnosed as LR RPLPS, univariate analysis (Table S3) showed that a R0 resection results in longer OS (median OS, 61 months, 95% CI 38.32–72.61 months) and PFS (median PFS, 26 months, 95% CI 20.44–53.29 months). Patients with tumor diameters < 20 cm showed longer OS than patients with tumor diameters ≥ 20 cm (median OS, 30 months, 95% CI 25.27–51.97 months vs. 9 months, 95% CI 8.80-32.59 months, $p = 0.024$). Differences of PFS between the two groups were not statistically significant ($p = 0.077$). Patients with low-grade disease showed favorable OS and PFS compare to those with intermediated-grade and high-grade disease (median OS: 72 months, 95% CI 42.55–94.95 months vs. 23 months, 95% CI 9.00-45.40 months vs. 12 months, 95% CI 10.31–25.46 months, $p = 0.001$; median PFS: 60 months, 95% CI 25.56–79.44 months vs. 12 months, 95% CI 5.58-18.43 months vs. 8.5 months, 95% CI 7.00-21.30 months, $p = 0.005$). Multivariate analysis using the Cox proportional hazards model revealed that resection extent was a significant prognostic factor associated with OS ($p = 0.001$, Fig. 3A), whereas tumor grade was associated with PFS ($p = 0.044$, Fig. 3B) (Table 3).

Table 3

Multivariate associations between clinicopathologic and treatment factors and survival for LR RPLPS patients.

Variable	Analyses by survival type					
	OS			PFS		
	HR	95% CI	p Value	HR	95% CI	p Value
Modus operandi (R0 vs R1 vs R2 resection)			0.001*			0.157
R0 vs R1	3.94	1.32-11.78	0.014*	2.21	0.99-4.94	0.054
R0 vs R2	10.51	3.16-34.96	0.000*	0.00	0.00-5.74	0.963
Tumor size (< 20 cm vs ≥ 20 cm)	0.49	0.22-1.09	0.081	0.73	0.34-1.58	0.422
FNCLCC (1 vs 2 vs 3)			0.090			0.044*
1 vs 2	4.82	0.55-42.46	0.157	5.58	1.29-24.14	0.021*
1 vs 3	8.19	1.03-65.40	0.047*	4.14	1.27-13.53	0.019*
*Significant.						
FNCLCC, French Federation of Cancer Centers Sarcoma Group; OS, overall survival; PFS, progression-free survival; R0 resection, Complete resection + clean microscopic margins; R1 resection, Complete resection + positive microscopic margins; R2 resection, macroscopically incomplete resection.						

Discussion

RPLPS continues to pose a challenge to diagnosis, prediction of clinical behavior and treatment for disease recurrence within the intra-abdominal and retroperitoneal space. Due to the low overall incidence of this disease and variability between patients, little research has been describing RPLS in the Asian population[4–6].

Most patients diagnosed with RPLS have no obvious clinical symptoms in the early stage, and do not show signs until the tumor enlarges and causes symptoms. The relationship between tumor size and postoperative survival time remains controversial. One group [7] believes that RPLPS is difficult to completely surgically remove, affecting survival time after surgery. In this study, patients with a tumor diameter ≥ 20 cm accounted for 50% of all cases(45/90). In the PR RPLPS group, there was no significant

correlation between tumor size and survival prognosis. In the LR RLPPS group, the OS of patients with a tumor diameter ≥ 20 cm was significantly shorter than seen in patients with small tumor burden ($p = 0.024$). However, this was not an independent risk factor for prognosis by multivariate analysis.

Patients with locally recurrent RPLPS are managed similarly to patients with primary RPLPS. Examination of suspected local recurrence requires abdominal CT (sometimes MRI). Abdominal CT is not only the main preoperative diagnosis method, but also provides a basis for preoperative tumor classification [89]. CT examination determines tumor invasion in surrounding organs, blood vessels and other tissues, which is critical for pre-surgery analysis in order to properly achieve R0 resection. In this study, the colon was the most commonly removed organ (32.2%), followed by the kidney (18.9%). We observed that combined organ resection did not directly affect survival after surgery, which is similar to what was observed in previous work [310]. The use of preoperative percutaneous biopsies in RPLPS patients is controversial [1112]. In cases where the diagnosis is not clear or the tumor is unresectable, biopsies can be used to confirm diagnosis and determine the histological type, providing additional information for adjuvant therapy.

One group [13] retrospectively analyzed 110 RSTS patients and found that intraoperative bleeding > 1500 ml was an independent risk factor for poor postoperative survival. Another group [14] found that retroperitoneal dedifferentiated liposarcoma (RP DDLPS) patients, higher levels of intraoperative bleeding predicted a poor survival prognosis (HR 3.302, 95% CI 1.231–8.858, $p = 0.018$). In this study, univariate analysis revealed that intraoperative bleeding < 1500 ml indicates better OS and PFS, but the effect of multivariate analysis was not significant in PR RPLPS. Although resection of RPLPS is more difficult and is associated with more bleeding ($p = 0.009$), no significant correlation exists between the amount of bleeding and postoperative survival in LR RPLPS.

Generally, active surgical resection is recommended to ensure clean margins that can effectively improve overall survival for RSTS [15]. However, for RPLPS cases, especially recurrent liposarcoma cases, the relationship between the marginal status and local recurrence is not clear. One study [6] has suggested that a negative resection margin was associated with a reduction in local recurrence rate (HR = 0.18, $p = 0.001$) and improved disease-specific survival (HR = 0.14, $p < 0.001$). Another [16] reported 119 RP DDLPS cases that showed no significant relationship between resection margin status and local recurrence. Univariate analysis of our study showed that surgical marginal status significantly affected OS and PFS, and multivariate analysis showed an R2 resection (as compared to an R0 resection) was associated with an increased risk for OS (PR RPLPS: HR 6.89, $p = 0.014$; LR RPLPS: HR 10.51, $p = 0.000$). The association of margin size on oncologic outcomes for RPLPS is based on limited data and varying definitions of the definition of a positive margin.

Previous studies [1718] confirmed that histological grade is an important prognostic factor for retroperitoneal tumors, but relatively few studies have targeted liposarcomas, especially those that are recurrent. One group [6] has suggested that low-grade RPLP tumors were significantly associated with a reduced risk of local recurrence and improved survival. Another group [16] studied 119 cases of RP

DDLPS, showing that patients with intermediate grade RP DDLPS showed a better prognosis than those with high grade RP DDLPS. Altogether, these results support the FNCLCC classification[19], where differences between grade 1 and 3 tumors significantly affect OS and PFS, regardless of whether these tumors are primary or recurrent.

Due to the heterogeneity of tumor tissue, different tissue types often predict survival time [20]. Some studies[21] have shown that myogenic differentiation significantly predicted the outcome of RPLPS. Even though in this study, tumor histological type is not an independent risk factor for survival time after surgery, it is worth noting that transformation from RP WDLPS to RP DDLPS occurs where there is an evolution of mutations following each recurrence[3]. These mutations may also result in changes in tumor grade and affect patient survival. Therefore, the impact of different tumor histological types on the prognosis of RPLP requires further research.

Although surgery is considered the most effective treatment for RPLPS, some studies have also tried new adjuvant treatments. These studies shown that preoperative neoadjuvant radiotherapy can prolong the survival of RPLPS, especially in patients with high-risk pathological types [22], and reduce the possibility of local recurrence[23]. MD Anderson Cancer Center reported that combined chemotherapy in patients with RP DDLPS produced a response rate of 24% [24]. Since new adjuvant treatment methods have not been widely practiced in the clinic, they are given to refractory or complicated liposarcoma cases. This, we did not discuss adjuvant treatment for the typical RPLPS case in our work.

In conclusion, we found that complete surgical resection is an independent favorable prognostic factor of OS for RPLPS (both primary and local recurrent). In PR RPLPS, intraoperative blood loss ≥ 1500 ml and FNCLCC grade 3 predicted a poor prognosis (OS and PFS). LR RPLPS surgical resections are more difficult than PR RPLPS surgical resections, and show more intraoperative blood loss as well as worse pathological grade. Tumor grade is an independent risk factor for PFS in LR RPLPS. We expect that further prospective studies and multi-center collaborations can provide strong support for clinical decision-making for RPLPS treatment strategies.

Abbreviations And Acronyms

RPLPS = retroperitoneal liposarcoma

PR RPLPS = primary retroperitoneal liposarcoma

LR RPLPS = local recurrent retroperitoneal liposarcoma

RSTS = retroperitoneal sarcoma

FNCLCC = Fédération Nationale des Centres de LutteContre le Cancer

OS = overall survival

PFS = progression-free survival

CI = confidence interval

RPDDLPS = retroperitoneal dedifferentiated liposarcoma

RPWDLPS = retroperitoneal well-differentiated liposarcoma

Declarations

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because they are derived from the patient database of the center and hence subject to confidentiality but are available from the corresponding author on reasonable request.

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Authors' contributions

Y.Y. and X.D. conceived and designed the study. Y.Y., S.H. and D.T. analyzed and interpreted the data. Y.Y., S.X., and S.L. wrote the manuscript. Y.W. and R.L. played a supplementary role in this study. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

This study was approved by the Protection of Human Subjects Committee of the Chinese People's Liberation Army (PLA) General Hospital. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Informed consent for publication was obtained.

Competing interests

The authors declare that they have no competing interests.

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Figures

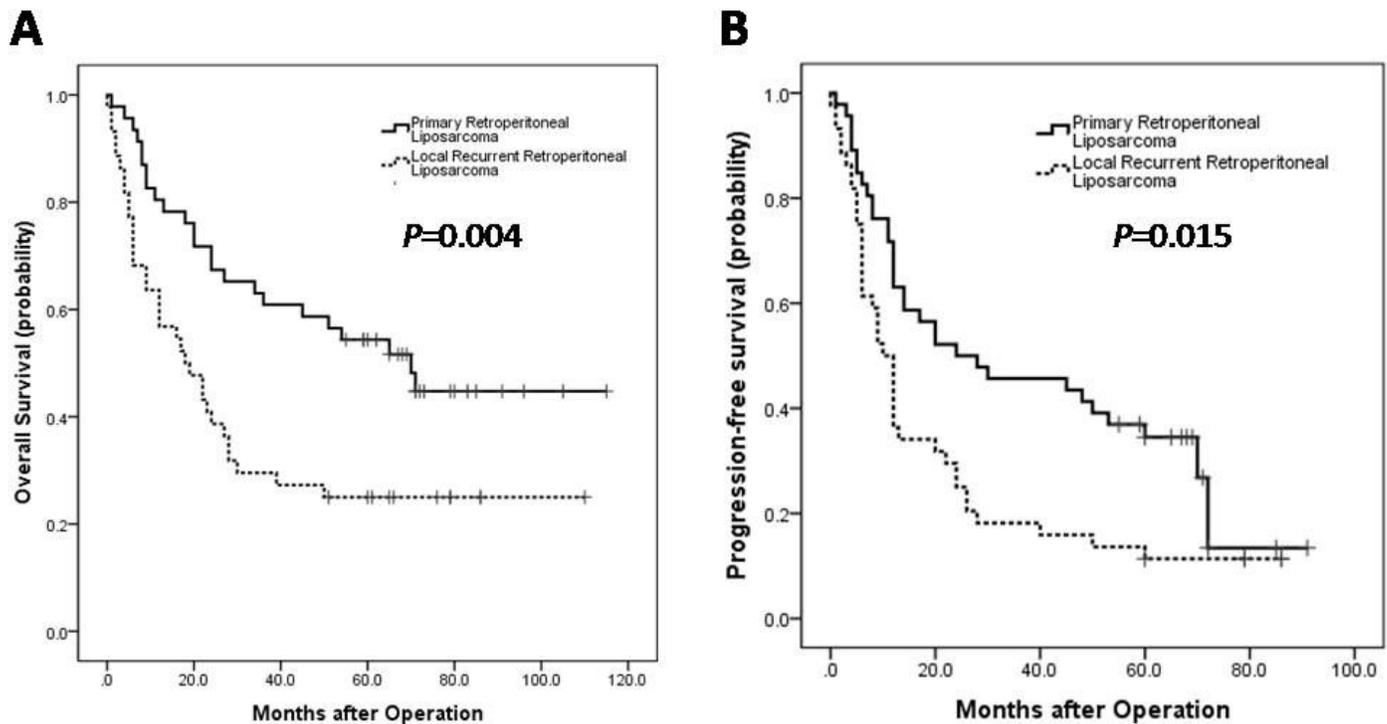


Figure 1

A postoperative survival curve for RPLPS patients stratified by referral status for primary tumor vs. local recurrent tumor cases. A. Overall survival after operation; B. Progression-free survival after operation.

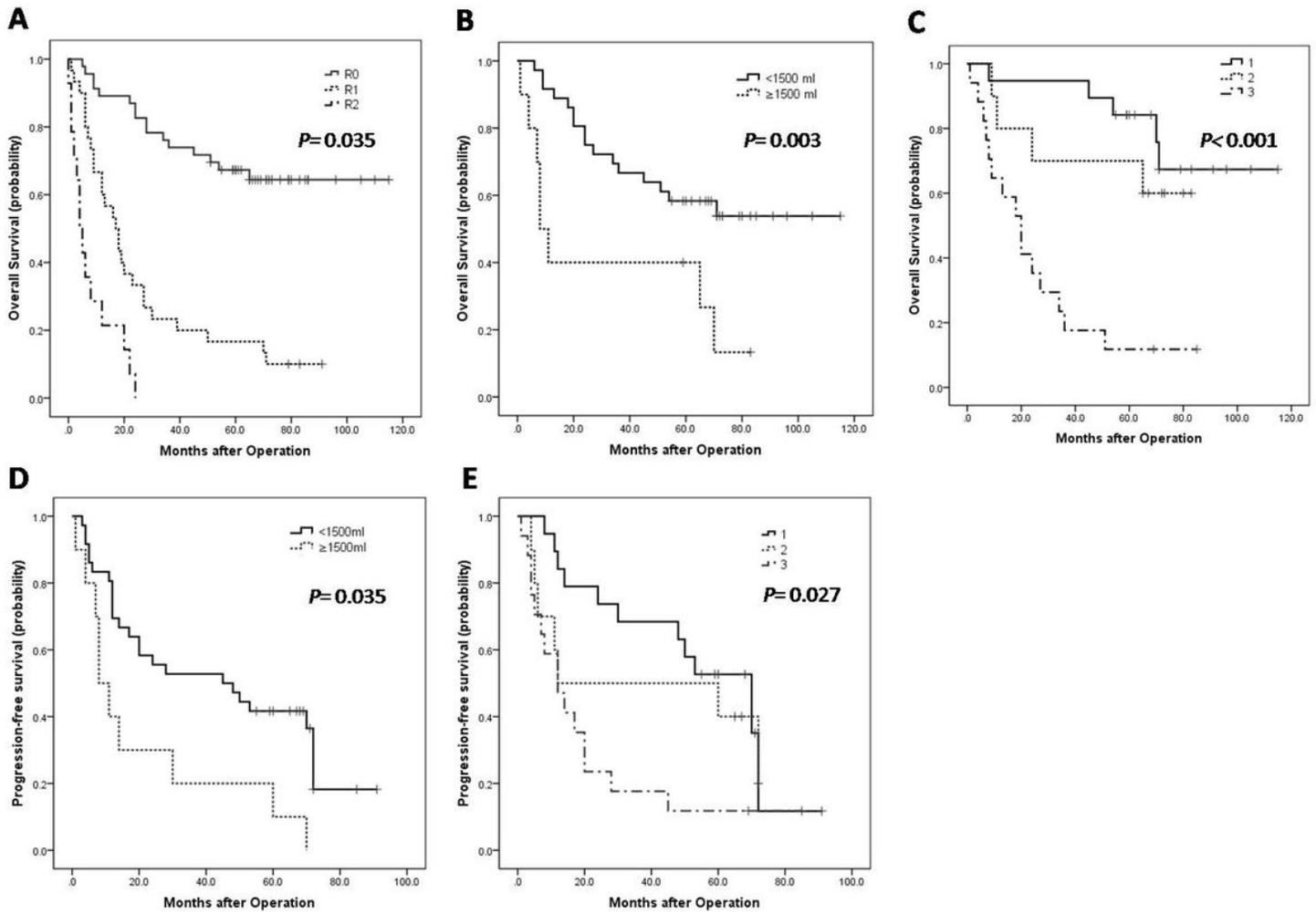


Figure 2

Resection outcomes for PR RPLPS cases according to resection margin status (A. Overall survival), blood loss (B. Overall survival; D. Progression-free survival) and tumor grade (C. Overall survival; E. Progression-free survival).

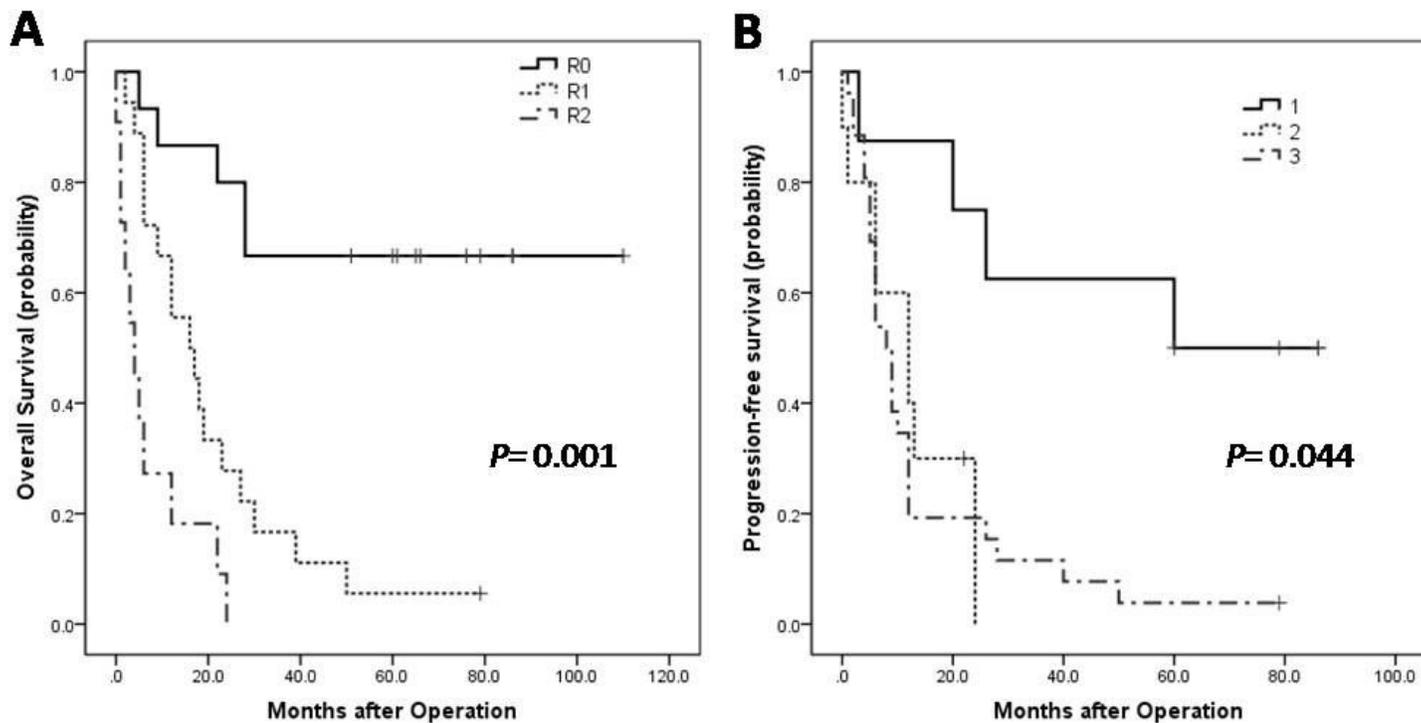


Figure 3

Resection outcomes for LR RPLPS cases according to resection margin status (A. Overall survival) and tumor grade (B. Progression-free survival).

Supplementary Files

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