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Recurrence Patterns of Retroperitoneal Leiomyosarcoma and Impact of Salvage Surgery

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Abstract

Background—Optimal treatment strategies for retroperitoneal leiomyosarcoma (RPLMS), particularly recurrent disease, are unknown.

Methods—We searched the tumor registry at The University of Texas MD Anderson Cancer Center (MDACC) to identify patients with RPLMS treated between 1994 and 2013.

Results—We identified 172 patients with a diagnosis of a RPLMS. Among the 85 patients who underwent complete resection included in the survival analysis, the median overall survival (OS) was 8.3 years (95% confidence interval [CI], 5.7–12.3), 5-year local recurrence rate was 21%, and 5-year distant metastasis rate was 47%. Among 114 patients who experienced recurrence, patients who underwent salvage surgery for recurrent disease had longer OS after recurrence than patients who did not undergo salvage surgery (median survival after recurrence 5.6 vs. 3.3 years, 3-year OS rates after recurrence 72.6% vs. 58.1%, HR 0.402 [95% CI, 0.243–0.666]; $p=0.0004$). Whether salvage surgery was performed for local or distant recurrence was not associated with OS. Patients who had a longer disease-free interval (≥ 12 months) had better progression-free survival after salvage surgery than those who had a shorter interval (HR, 0.437 [95% CI, 0.244–0.783]; $p=0.0055$).

Conclusions—We recommend that salvage surgery be considered for selected patients with local or distant recurrence of RPLMS.

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Keywords

Retroperitoneal sarcoma; leiomyosarcoma; recurrence; salvage surgery; survival

Introduction

Approximately 15% of soft tissue sarcomas originate in the retroperitoneum [1]. The average annual incidence of retroperitoneal (RP) sarcoma is approximately 2.7 cases per million people [2]. RP sarcoma is a heterogeneous disease entity that consists of a large number of different histologic subtypes [3], most commonly, liposarcoma, leiomyosarcoma (LMS), undifferentiated pleomorphic sarcoma, and solitary fibrous tumor [4,5]. Each histologic subtype has unique behavioral characteristics and treatment outcomes [6]; therefore, histology should be used to guide treatment [7].

LMS accounts for 15%–30% of RP sarcomas [4,8–10], and patients with RP LMS have a significant risk of distant metastasis (>50%) but a lower risk of local recurrence than patients with other RP sarcomas [8,9], particularly in comparison to RP liposarcomas which have a predominantly local pattern of recurrence [5]. Surgical resection is the standard treatment for all localized RP sarcomas, but there is some controversy about whether resection should include uninvolved organs near the primary tumor [11]. Although a recent large study identified prognostic factors for patients who undergo surgery for primary RP sarcomas [5], information specific to RP LMS is limited. Moreover, the optimal treatment strategy for recurrent RP LMS is unknown, especially regarding whether and when resection is appropriate. We sought to investigate surgical outcomes and recurrence patterns of RP LMS and the impact of salvage surgery in treating recurrent disease.

Methods

After receiving Institutional Review Board approval, with a waiver of the informed consent requirement, we comprehensively searched the tumor registry at The University of Texas MD Anderson Cancer Center (MDACC) to identify patients who were diagnosed with RP LMS between 1994 and 2013. Patients with LMS originating in the uterus or gastrointestinal tract were excluded. All surgical specimens were examined by sarcoma pathologists at MDACC. The patients' medical records, including their pathology, radiology, and surgery reports, were reviewed retrospectively to collect clinicopathologic data. Patients who underwent primary resection at MDACC or who presented to MDACC without residual disease on radiographic imaging after primary resection and conducted follow up surveillance at MDACC were included in the survival analysis for primary resection. Patients who underwent salvage resection (resection of recurrent disease with curative intent) at MDACC, regardless of where the patients underwent primary resection, were included in the survival analysis for salvage surgery.

Overall survival (OS) was defined as the time from date of the diagnosis of the primary tumor to the time of death or last contact, and recurrence-free survival (RFS) was defined as the time from date of the diagnosis of the primary tumor to the time of disease recurrence (either local recurrence or distant metastasis), death, or last contact. Progression-free

survival (PFS) was defined as the time from salvage surgery to the time of disease progression/recurrence or death. Local and distant recurrence rates were calculated by the time from the date of the primary resection to the time of specific recurrence. Disease-free interval was defined as the time between surgical resection of the primary tumor and disease recurrence. Peritoneal recurrence was included with local recurrences because it is often difficult to distinguish peritoneal from local recurrence by radiologic assessment.

Treatments for all patients had been determined by a multidisciplinary team, including specialists in surgical oncology, medical oncology, radiation oncology, and pathology. Adjuvant/neoadjuvant treatments were used on a case-by-case basis. Frequently used cytotoxic chemotherapy regimens were doxorubicin plus ifosfamide or gemcitabine plus paclitaxel. Radiation therapy, when administered, was delivered by the external beam technique, with doses ranging from 50.4 to 56 Gy.

OS, RFS, and PFS curves were estimated using the Kaplan-Meier method. A log-rank test was performed to assess differences in survival outcomes between groups. Univariate and multivariate Cox proportional hazards regression analyses were performed to identify predictors of OS, RFS, and PFS. The SAS (version 9.2) and S-Plus (version 8.04) programs were used to perform all analyses. P-value was considered significant when it is less than or equal to 0.05.

Results

We identified 266 patients with RP LMS who were evaluated at MDACC during the period studied. Sixty-two patients had synchronous metastatic disease, and 21 patients had unresectable disease at the initial presentation. Both of these groups were excluded from the study. Of the 183 patients who underwent surgery, 11 underwent palliative (R2) resection, and 172 underwent complete resection of the primary disease. Patient and tumor characteristics are summarized in Table 1. Sixty-six patients who underwent primary resection at MDACC and 19 patients who had primary resection at other facilities were included in a cohort for survival analysis. Of those 85 total patients, 75% were female, and 74% were White. Organ resection was required in 65 (77%) patients and great vessels or iliac vessels were resected in 37 (43.5%) patients. Pathological invasion of the inferior vena cava (IVC) was found in 30 (35%), which may represent LMS arising from IVC. R0 resection was achieved in 70 (82%) patients.

Survival analysis

For the 85 patients in the survival cohort, the median follow-up was 4.1 years. The median OS was 8.3 years (95% confidence interval [CI], 5.7–12.3 years; 5-year OS rate, 73%), and the median RFS was 4.2 years (5-year RFS rate, 46%). The 5-year local recurrence rate was 21%, and the 5-year distant recurrence rate was 47%. There was no difference in OS between patients who had the primary resection at MDACC vs. at other facilities (HR 1.45, 95% CI 0.64–3.33, $p=0.376$). There was also no difference in cumulative incidence of local recurrence or distant metastasis, or RFS between 2 groups.

Prognostic factors for survival

Results of univariate and multivariate analyses to identify prognostic factors for OS and RFS are summarized in Tables 2 and 3. Since no factors remained in the models by stepwise methods, multivariate analyses were performed by entering all listed covariates. There were no variables found to be significant to predict OS or RFS.

Recurrence pattern and impact of salvage surgery

Of all 172 patients that underwent complete excision of the primary RP LMS either at MDACC or at an OSH, 114 (66.3%) patients experienced disease recurrence during the follow up period. At the time of first recurrence, 32 (18.6%) patients had local recurrence only, 72 (41.9%) patients had distant metastasis only, and 10 (5.8%) patients had simultaneous local and distant recurrence. The median disease-free interval was 18.0 months (range, 0.4–111.6 months). A total of 56 (32.6%) patients experienced local recurrence at some point during follow-up (32 had local recurrence first, 14 had local recurrence after distant metastasis, and 10 had simultaneous local and distant recurrence), and 17 (30%) of those patients had multifocal local recurrence. A total of 100 (58.1%) patients developed distant metastasis at some time during follow-up (71 had distant metastasis first, 19 had distant metastasis after local recurrence, and 10 had simultaneous local and distant recurrence). Of these patients, 76 had multifocal recurrence, and 28 had multi-organ metastasis. The most common site of metastasis was the lungs (58%), followed by the liver (38%), skin or soft tissue (20%), distant lymph nodes (10%), bone (9%), pancreas (2%), brain (1%), and spinal cord (1%).

Of the 114 patients with recurrence, 55 (48.2%) patients (19 [59.4%, 19/32] with local-only recurrence, 32 [44.4%, 32/72] with distant-only recurrence, and 4 [40.0%, 4/10] with simultaneous local and distant recurrence) underwent surgical resection of their initial recurrent tumor(s) with curative intent (i.e., salvage surgery). Of the 36 patients who underwent salvage surgery for distant metastasis, the most common organ resected was lung (16/36, 44%), followed by liver (14/36, 39%), soft tissue (4/36, 11%), distant lymph nodes (3/36, 8%), and bone (3/36, 8%). The median recurrence-to-salvage surgery interval was 2.1 months (range, 0.0–28.6 months). Of these 55 patients, 33 (60%) had multifocal recurrence, and 19 (35%) achieved R0 resection.

Patients who underwent salvage surgery had a longer median OS after recurrence (5.6 years) than did patients who did not undergo salvage surgery (3.3 years; Fig. 1A). The 3-year OS rate was 72.2% vs. 55.9% (HR, 0.402 [95% CI, 0.243–0.666]; $p=0.0004$). Of the 55 patients who underwent salvage surgery, 48 (87%; 16 [84%, 16/19] with local-only recurrence, 28 [88%, 28/32] with distant-only recurrence, and 4 [100%, 4/4] with simultaneous local and distant recurrence) experienced a second recurrence during follow-up. The median interval between salvage surgery and second recurrence was 12.4 months (range, 1.2–55.7 months).

Results of univariate and multivariate analyses performed to identify predictors of PFS after salvage surgery are shown in Table 4. The median PFS was 1.1 years. There was no difference in PFS between patients with local-only recurrence and those with distant metastasis (HR 1.539 [95%CI 0.876–2.706]; $p = 0.134$, Fig. 1B). Patients who had a longer

disease-free interval (≥ 12 months from the time of surgical resection of the primary tumor until initial tumor recurrence) had better PFS than those who had a shorter disease-free interval (HR, 0.437 [95% CI, 0.244–0.783]; $p=0.0055$), which was the only significant variable remaining in the multivariate regression model by backward-stepwise method. Median PFS was 2.7 months in the shorter disease-free interval group vs. 14.9 months in the longer disease-free interval group (Fig. IC). Multifocality, recurrence-to-salvage interval (<6 months vs. ≥ 6 months), and type of recurrence (distant vs. local) were not associated with PFS.

Discussion

We report a retrospective study of patients with surgically resected RP LMS. To our knowledge, this is the first to report surgical outcomes in patients being treated for recurrent RP LMS. We observed that following resection, RP LMS recurred more frequently at distant sites than locally and that the most common sites of recurrence were the lungs, liver, and skin or soft tissue. Salvage surgery for recurrent disease was associated with improved OS, and location (distant or local) or multifocality of the recurrent disease was not associated with OS. However, the second recurrence rate was high; cure was rare after recurrence. A disease-free interval shorter than 12 months from the time of surgical resection of the primary tumor until initial tumor recurrence was the only factor that predicted PFS, but the timing of salvage surgery (recurrence-to-salvage surgery interval, < 6 months vs. ≥ 6 months) was not associated with PFS.

Subtype-specific data are crucial for defining treatment outcomes in RP sarcomas because tumor aggressiveness, recurrence patterns, and response to adjuvant therapies such as cytotoxic chemotherapy are different for each histologic subtype [6,12]. In fact, histology-based classification of RP sarcomas predicts survival better than the American Joint Committee on Cancer staging system does [7]. However, reports of treatment outcomes of RP sarcomas generally lack data on histologic stratification [13–15], and results are skewed toward the characteristics of liposarcoma, the most common RP sarcoma subtype. Such results may mislead physicians planning treatment for patients with other RP sarcoma subtypes.

Consistent with published literature [5,6], we found that RP LMS has a distinctive recurrence pattern. Our results showed that RP LMS tends to have a high distant metastasis rate and a relatively low local recurrence rate after resection. We also found that RP LMS tended to have a high rate of metastasis to the soft tissues. A previous study reported that patients with RP LMS had longer survival after distant metastasis than those with other sarcomas [9]; this characteristic of RP LMS likely prompted surgeons at our institution to perform salvage surgery for approximately 50% of patients with distant metastasis.

In a retrospective study of 1,007 patients with RP sarcomas treated at eight high-volume sarcoma centers, Gronchi et al. compared treatment outcomes among different histologies [5]. Of these patients, 19% were LMS; these tumors had a higher risk of death than solitary fibrous tumors (HR, 1.95), a low risk of local recurrence (the 5-year local recurrence rate was lower than 10% in all eight institutions), and a high risk of distant metastasis (5-year

distant metastasis rate, 50%–60%). The 5-year local recurrence rate in our study was 15% in patients who underwent resection at MDACC; this was higher than that reported by Gronchi et al. [5] but similar to the 3-year local recurrence rate of 16% in high-grade RP LMS reported by Tan et al. from Memorial Sloan Kettering Cancer Center [6]. This variability in local recurrence rates is most likely due to different patient populations being evaluated in the respective studies. We categorized peritoneal recurrence as local recurrence because the two are difficult to distinguish.

In this study, we didn't identify any factors which effectively predicted OS or RFS of RP LMS after curative-intent primary resection, likely due to a small number of study patients. Gladdy et al. from Memorial Sloan Kettering Cancer Center reported recurrence patterns and risk factors for recurrence of 353 patients with primary resectable LMS, which included 144 (41%) patients with abdominal/RP LMS. They reported similar distant-predominant pattern of recurrence (5-year distant recurrence rate was 43% among abdominal/RP LMS patients), and lung was the most common site of recurrence, followed by the liver. Multivariate analysis of risk factors for recurrence showed that size >10 cm and R1 resection were associated with local recurrence, and size >10cm and high grade histology were associated with distant recurrence. The benefit of perioperative therapy was not assessed [16].

We observed an association between salvage surgery for recurrent RP LMS and improved survival in this study; however, the true benefit of salvage surgery for recurrent RP sarcomas remains controversial. There are a few reports that have analyzed the potential benefit of salvage surgery for RP sarcomas; however, these reports do not distinguish amongst histologic subtypes. Evidence specific to salvage surgery for RP LMS is limited. In a retrospective study of 377 RP sarcoma patients, including 59 (15.6%) LMS patients, from two European institutions that encouraged extended primary resection, Gronchi et al. did not show a survival benefit for salvage surgery in recurrent RP sarcomas [9]. Of the 76 patients who experienced local recurrence, 21 (27.6%) underwent salvage surgery, but only 2 of those patients had RP LMS. Gronchi et al. reported that extended primary resection optimized local control (5-year local recurrence rate, 5%) and concluded that a second surgery was of limited benefit when local recurrence followed extended resection [9]. In contrast, in a single-institution retrospective study in which 57% of 61 patients with RP sarcomas who experienced local recurrence underwent salvage surgery [17], Lewis et al. reported that salvage surgery was the most significant predictor of survival following local recurrence (median survival, 60 months vs. 20 months for those who did not undergo salvage surgery) [17]. Again, however, lack of histological specification in that study limits the application of their results to RP LMS patients. Most recently, the Trans-Atlantic RP Sarcoma Working Group reported their retrospective study of 408 patients with RP sarcomas who underwent curative intent resection and subsequently experienced disease recurrence. Among patients with local recurrence, lack of salvage surgery was associated with shorter OS (HR 3.96, 95%CI 2.32–6.76; $p<0.001$); this association was not statistically significant among patients with distant metastases (HR 1.62, 95% CI 0.97–2.74; $p=0.067$) [18]. However, since the current consensus is that the biologic behavior of sarcomas is unique to each histologic subtype, it would have been more informative to stratify the patient results in this study by histologic subtype. In our study, approximately 50% of patients with recurrent

RP LMS were able to undergo potentially curative salvage surgery, and patients who underwent salvage surgery had a median survival of 5.6 years after recurrence. The lack of an OS difference after salvage surgery between patients with local or distant recurrence should encourage surgeons to consider salvage surgery for selected patients with RP LMS recurrence at distant sites as well as those with local recurrence. Similarly, multifocal recurrent disease was not associated with a decreased OS in this study and, therefore, patients with multifocal recurrent RP LMS should not be excluded for consideration of salvage surgery on that finding alone.

While surgical resection is the only potentially curative therapy, the benefit of perioperative systemic therapy in RP LMS remains unclear. The clinical benefit of perioperative radiation therapy seems to be limited in view of the high distant recurrence risk and low local recurrence risk after resection of RP LMS. In a recently published analysis of 8,653 patients with surgically resected RPS from the National Cancer Database, 1,525 (18%) patients received perioperative chemotherapy. Chemotherapy was more frequently given to patients with tumors classified as intermediate-/high-grade, leiomyosarcoma, or UPS histology, and to patients who had R2 resection. After propensity score matching, perioperative chemotherapy was associated with shorter OS (40 vs. 52 months; $p=0.002$) [19]. However, owing to innate selection bias associated with this retrospective analysis, the clinical benefit of perioperative therapy remains unclear. Future prospective study is warranted, and researchers should be aware that response to chemotherapy is distinct among different histologic subtypes of RP sarcomas.

A limitation of our study was its retrospective design, which results in unavoidable selection bias. Selection bias likely affected our finding of longer survival in patients who underwent salvage surgery. To address the rarity of RP LMS, we included patients who underwent initial primary resection at other facilities, but this strategy may have also contributed to the selection bias. However, given the excellent survival after salvage surgery (median OS after recurrence, >5 years), we believe it would be inappropriate to perform a randomized controlled trial to test the benefit of salvage surgery in patients with recurrent RP LMS. Clearly, patient selection for salvage surgery is of paramount importance, and the results of our analysis should help such patient selection.

Strengths of our study are its single-institution design and our institution's status as a high-volume cancer center, which allowed us to include a relatively large number of patients with this rare disease. We believe that our findings, which are specific to RP LMS, will help guide treatment strategies, especially for patients with recurrent disease.

In conclusion, we observed that RP LMS had a relatively low local recurrence rate and a high distant metastasis rate, supporting previous findings in smaller series. Salvage surgery for recurrent RP LMS was associated with OS. Short disease-free interval (<12 months) was a risk factor for PFS after salvage surgery, whereas multifocality, recurrence-to-salvage interval (<6 months vs. ≥6 months), and type of recurrence (distant vs. local) were not. We recommend that surgeons consider salvage surgery for patients with recurrent RP LMS, particularly when the recurrence occurs after a disease-free interval longer than 12 months from the time of initial tumor resection even if multifocal recurrent disease is present.

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Synopsis

Retroperitoneal leiomyosarcomas frequently recur at distant sites. Patients who underwent salvage surgery after recurrence had longer overall survival than did those who did not.

Figure 1.

(A) Overall survival (OS) of patients with retroperitoneal leiomyosarcoma after recurrence comparing patients who underwent salvage surgery and those who did not undergo salvage surgery. (B) OS after salvage surgery comparing patients who underwent salvage surgery for local recurrence and those who underwent salvage surgery for distant metastasis. (C) Progression free survival comparing patients with disease-free interval ≥ 12 months and those with disease-free interval <12 months from the time of surgical resection of the primary tumor until initial tumor recurrence.

TABLE 1

Characteristics of patients with retroperitoneal leiomyosarcoma who underwent curative surgical resection (N=172)

	Total	Survival cohort
Variable	N (%)	N (%)
Number of patients	172	85
Age at diagnosis, median (IQR)	55.5 (47–63)	58 (48–65)
Sex		
Female	129 (75.0)	64 (75.3)
Male	43 (25.0)	21 (24.7)
Ethnicity		
White	133 (77.3)	63 (74.1)
Black	16 (9.3)	12 (14.1)
Hispanic	16 (9.3)	9 (10.6)
Asian	3 (1.7)	1 (1.2)
Other	4 (2.3)	0
Tumor grade		
Low	9 (5.2)	7 (8.2)
Intermediate	29 (16.9)	18 (21.2)
High	82 (47.7)	34 (40.0)
Unknown	52 (30.2)	26 (30.6)
Organ resections	120 (69.8)	65 (76.5)
Kidney/ureter/adrenal	61 (35.5)	24 (28.2)
Great vessels/Iliac vessels	49 (28.5)	37 (43.5)
GI tract	16 (9.3)	10 (11.8)
Pancreas	6 (3.5)	5 (5.9)
Spleen	4 (2.3)	2 (2.4)
Liver	4 (2.3)	1 (1.2)
Pathologic IVC involvement		
Yes	36 (20.9)	30 (35.3)
Tumor size		
<10 cm	91 (52.9)	56 (65.9)
10 cm	62 (36.1)	26 (30.6)
Unknown	19 (11.1)	3 (3.5)
Resection		
R1 or unknown	60 (34.9)	15 (17.7)
R0	112 (65.1)	70 (82.4)
Chemotherapy		
Neoadjuvant	39 (22.7)	37 (43.5)
Adjuvant	27 (15.7)	9 (10.6)

	Total	Survival cohort
Variable	N (%)	N (%)
None	104 (60.5)	39 (45.9)
Unknown	2 (1.2)	0
Radiation therapy		
Neoadjuvant	19 (11.1)	16 (18.8)
Adjuvant	15 (8.7)	1 (1.2)
None	136 (79.1)	68 (90.0)
Unknown	2 (1.2)	0
Status at last follow-up		
Alive	87 (50.6)	49 (57.7)
Dead	85 (49.4)	36 (42.4)

Abbreviations: IQR, interquartile range; R0, negative margins; R1, microscopic residual tumor; MDACC, The University of Texas MD Anderson Cancer Center.

TABLE 2

Univariate and multivariate analysis of prognostic factors for overall survival

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, ≥65 vs <65 years	1.32 (0.62–2.83)	0.472	1.83 (0.71–4.73)	0.215
Sex, female vs male	0.71 (0.35–1.45)	0.349	0.74 (0.34–1.61)	0.450
Tumor size, >10 cm vs ≤10 cm	1.65 (0.81–3.35)	0.165	2.07 (0.94–4.58)	0.071
Tumor grade, High vs low/intermediate	1.18 (0.59–2.35)	0.632	1.20 (0.54–2.66)	0.652
Organ resection, yes vs no	1.13 (0.46–2.75)	0.791	1.70 (0.52–5.52)	0.378
IVC involvement, yes vs no	1.37 (0.70–2.69)	0.361	0.89 (0.33–2.41)	0.821
R0 resection, yes vs no	0.43 (0.14–1.31)	0.138	0.37 (0.09–1.48)	0.161
Chemotherapy, yes vs no	0.94 (0.49–1.83)	0.866	0.95 (0.45–2.01)	0.899
Radiation therapy, yes vs no	0.82 (0.37–1.80)	0.622	0.75 (0.25–2.24)	0.607
Institution of primary resection, MDACC vs other	1.45 (0.64–3.33)	0.376	1.42 (0.43–4.65)	0.567

Abbreviations: HR, hazard ratio; CI, confidence interval; R0, negative margins

TABLE 3

Univariate analysis of prognostic factors for recurrence-free survival

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, ≤65 vs >65 years	0.71 (0.36–1.38)	0.314	0.84 (0.37–1.92)	0.685
Sex, female vs male	0.90 (0.48–1.69)	0.739	0.90 (0.46–1.79)	0.772
Tumor size, >10 cm vs ≤10 cm	1.24 (0.68–2.28)	0.479	1.32 (0.69–2.54)	0.405
Tumor grade, High vs low/intermediate	1.13 (0.64–2.03)	0.669	1.12 (0.60–2.10)	0.722
Organ resection, yes vs no	1.36 (0.66–2.79)	0.408	2.14 (0.86–5.30)	0.102
IVC involvement, yes vs no	0.98 (0.54–1.78)	0.948	0.77 (0.37–1.59)	0.483
R0 resection, yes vs no	0.63 (0.28–1.45)	0.279	0.57 (0.21–1.50)	0.252
Chemotherapy, yes vs no	0.90 (0.52–1.56)	0.704	0.89 (0.48–1.66)	0.722
Radiation therapy, yes vs no	0.81 (0.42–1.59)	0.543	0.68 (0.31–1.52)	0.350
Institution of primary resection, MDACC vs other	0.95 (0.50–1.82)	0.882	0.86 (0.36–2.03)	0.723

Abbreviations: HR, hazard ratio; CI, confidence interval; R0, negative margins

TABLE 4

Univariate and multivariate analysis of prognostic factors for progression-free survival in patients with recurrent retroperitoneal leiomyosarcoma who underwent salvage surgery for 1st recurrence

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age at salvage surgery, ≥ 65 (n=12) vs <65 years (n=55)	0.83 (0.35–1.96)	0.673		
Sex, female (n=47) vs male (n=8)	0.63 (0.30–1.30)	0.209		
Tumor grade, low/intermediate (n=11) vs high (n=28)	1.18 (0.57–2.42)	0.660		
R0 resection, yes (n=38) vs no (n=21)	0.81 (0.46–1.42)	0.467		
Multifocal recurrence, yes (n=33) vs no (n=22)	1.64 (0.94–2.88)	0.084		
Site of recurrence, distant (n=19) vs local (n=36)	1.54 (0.88–2.71)	0.134		
Recurrence-to-salvage interval, ≥ 6 months (n=18) vs <6 months (n=37)	1.13 (0.64–2.00)	0.680		
Disease free interval, ≥ 12 months (n=38) vs <12 months (n=17)	0.44 (0.24–0.78)	0.0055	0.44 (0.24–0.78)	0.0055

Abbreviations: HR, hazard ratio; CI, confidence interval; R0, negative margins.