Clinical Cancer Research

Predicting Survival in Patients Undergoing Resection for Locally Recurrent Retroperitoneal Sarcoma: A Study and Novel Nomogram from TARPSWG

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Abstract

Purpose: The role of surgery for first relapse locally recurrent retroperitoneal sarcoma (RPS-LR1) is uncertain. We report outcomes of the largest RPS-LR1 series and propose a new prognostic nomogram.

Experimental Design: Patients with consecutive RPS-LR1 without distant metastases who underwent resection at 22 centers (2002–2011) were included. Endpoints were disease-free and overall survival (DFS, OS) and crude-cumulative-incidence (CCI) of local/distant recurrence from second surgery. Nomograms predicting DFS and OS from second surgery were developed and validated (calibration plots); discrimination was assessed (Harrell C index).

Results: Of 684 patients identified, full prognostic variable data were available for 602. Initial surgery for primary RPS was performed at our institutions in 188 patients (31%) and elsewhere in 414 (69%). At a median follow-up of 119 months [Interquartile range (IQR), 80–169] from initial surgery and 75 months (IQR 50–105) from second surgery, 6-year DFS and OS were 19.2% [95% confidence interval (CI), 16.0–23.0%] and 54.1% (95% CI, 49.8–58.8%), respectively. Recurrence patterns and survival probability were histology-specific, with liposarcoma subtypes having the highest 6-year CCI of second local recurrence (LR, 60.2%–70.9%) and leiomyosarcoma (LMS) having higher 6-year CCI of distant metastasis (DM, 36.3%). Nomograms included age at second surgery, multifocality, grade, completeness of second surgery, histology, chemotherapy/radiotherapy at first surgery, and number of organs resected at first surgery. OS and DFS nomograms showed good calibration and discriminative ability (C index 0.70 and 0.67, respectively).

Conclusions: We developed nomograms to predict DFS and OS for patients undergoing RPS-LR1 resection. Nomograms provide individualized, disease-relevant estimations of survival for RPS-LR1 patients and assist in clinical decisions.

Introduction

Surgery is the only potential curative treatment for primary retroperitoneal sarcoma (RPS). However, the role of surgery for first relapse locally recurrent RPS (RPS-LR1) is uncertain, as further recurrence is common. Several studies demonstrated that patients undergoing surgery for RPS-LR1 have better survival than those who do not. However, such studies have inherent selection bias and cannot predict which subsets of patients may have better outcomes (1–6).

Nomograms are designed to provide disease-specific, clinically relevant prognostic models predictive of outcome measures specific to an individual patient. We and others have reported and

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

In this, the largest study on first locally recurrent retroperitoneal sarcoma (RPS-LR1), we found that the predominant pattern of subsequent recurrence was second local recurrence (LR), though its frequency and its impact on survival were histology dependent. We developed novel nomograms which, for the first time, will allow clinicians to provide personalized prognostic values for disease-free survival (DFS) and overall survival (OS) to patients undergoing surgery for RPS-LR1 at dedicated sarcoma centers.

validated single- and multi-institutional nomograms for primary RPS (2, 7–10). To date, only one single-institution nomogram, limited to retroperitoneal liposarcoma, included patients with locally recurrent RPS (2).

The TransAtlantic Retroperitoneal Sarcoma Working Group (TARPSWG) was established in 2013 as an international collaboration to collectively report outcomes (9, 11–13), propose treatment guidelines (14, 15), support clinical trials (16), and develop a prospective registry (RPS Registry, RESAR; ref. 17).

We performed an international study of the largest series of patients with RPS-LR1 undergoing surgery at TARPSWG institutions to report outcomes and develop novel nomograms to estimate disease-free (DFS) and overall survival (OS) probabilities.

Materials and Methods

Patient cohort

This study was conducted in accordance with recognized ethical guidelines and was approved by the institutional review boards (IRB) of each of the contributing centers. Patients on prospective protocols signed informed consent forms for data collection. Data on all other patients, including deceased patients, were collected with IRB approval.

Prospectively or retrospectively collected data on patients with RPS-LR1 without distant metastases undergoing surgery with curative intent at 22 dedicated sarcoma centers in eight countries from January 2002 through December 2011 were collected and analyzed. "Local recurrence" (LR) was defined as recurrence within the ipsilateral retroperitoneum, peritoneal cavity, and pelvis.

Patients who underwent initial surgery for primary RPS at institutions other than the participating centers were included, provided surgery for RPS-LR1 was performed at one of our 22 institutions. Patients with concurrent distant metastases were excluded. "Initial surgery" was defined as curative-intent surgery for primary RPS. "Second surgery" was defined as curative-intent surgery for first LR.

Patient and tumor variables, from both operations, included age, tumor size, grade, histologic subtype, and multifocality. Tumors were graded according to the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system (18). The following histologic subtypes were included: well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), leiomyosarcoma (LMS), malignant peripheral nerve sheath tumor (MPNST), solitary fibrous tumor (SFT), and others (including unclassified/undifferentiated pleomorphic sarcoma). Liposarcomas were classified as "well-differentiated" if no dedifferentiated component was present, and as "dedifferentiated" if such a component was present. Patients with retroperitoneal presentations of gastrointestinal stromal tumor, desmoid fibromatosis, extraosseous Ewing sarcoma/primitive neuroectodermal tumor, desmoplastic small round cell tumor, alveolar/embryonal rhabdomyosarcoma, and uterine sarcoma histologic subtypes were excluded.

Treatment variables, from both operations, included extent of resection, number of organs resected, tumor rupture, chemotherapy administration, and radiotherapy administration. Extent of resection was classified as macroscopically "complete" (R0, negative microscopic margin; or R1, positive microscopic margin) or macroscopically "incomplete" (R2). Complications were categorized using the Clavien–Dindo classification system (19). Patients were subsequently followed with clinical examination and surveillance imaging (CT scans of the chest, abdomen, and pelvis) every 3–4 months for the first 2 years, every 6 months for the following 3 years, and yearly thereafter. Patients with WDLPS had less frequent imaging at some institutions (3–6 months during the first 2–3 years postoperatively) and less routine chest CTs.

Statistical analysis

Patients were classified into two "institution subgroups" based on whether or not initial surgery for primary RPS was performed at the participating TARPSWG centers. Association between institution subgroup and patient details, tumor characteristics, and treatment variables (at both first and second surgery) was studied in a multivariable logistic model in which the response variable distinguished the institution subgroup, using the Wald test for variable testing.

Nomograms were intended to estimate 6-year DFS and OS probability, measured from date of second surgery. A 6-year estimate was chosen because median follow-up was 6 years. First LR, distant metastasis (DM), and death after second surgery were recorded as events for DFS; concomitant LR and DM were included in computations of DMs. Survival curves were estimated using the Kaplan–Meier method. The crude cumulative incidence (CCI) of LR and DM were estimated in a competing risks framework; in the analysis of LR (DM), deaths without evidence of disease and DM (LR), whichever occurred first, were regarded as competing events, and concomitant LRs and DMs were included in the estimation of the CCI curves for DM.

The putative prognostic variables were the aforementioned patient details, tumor characteristics, and treatment variables, as well as disease-free interval (DFI), defined as the time from surgery for primary RPS to time of first event (date of recurrence). To select variables for inclusion in multivariable Cox models used to derive the nomograms, multivariable random forest (RF) models were used (20). In particular, the relative importance according to the RF model was determined for each variable, a permutation procedure was applied to determine the *P* values associated to the relative importance (21), and after false discovery rate *P* value adjustment (22), the variables significant at 5% were retained. In the Cox models, the categorical variables were modelled using dummy variables, and the continuous variables were modelled using three-knot restricted cubic splines (23). Institution of initial surgery was modelled as random effect in the multivariable Cox models and removed when not significant at the likelihood ratio test. Nomogram performance was assessed by calibration plot (overall and by cohorts of institution of initial surgery), as an

indicator of internal calibration, and the Harrell C statistic, as a measure of discriminative ability, the latter adjusted for optimism by applying a bootstrap procedure (24, 25). Data for calibration plots were stratified into equally sized subgroups, as described previously (8, 9).

We also evaluated the calibration plots to compare RF predictions and Kaplan–Meier estimates. Moreover, in the multivariable Cox models, we searched for binary interactions between the selected covariates, retaining the interactions achieving a P value <5% after false discovery rate adjustment.

Association between median DFI and selected nomogram variables was tested in a multivariable quantile regression model, using the Wald test for variable testing (26).

The statistical analyses were conducted using SAS software (SAS Institute) and R software (http://www.r-project.org/).

Results

We identified 684 patients who underwent surgery for RPS-LR1 at our 22 TARPSWG institutions (Supplementary Table S1). Full data on prognostic variables were available for 602 patients constituting the study cohort (Table 1). Initial surgery for primary RPS was performed at our 22 institutions in 188 (31.2%) patients and at the referring center in 414 patients (68.8%). All curative-intent operations for RPS-LR1 were performed at the participating TARPSWG institutions.

Among patient and tumor characteristics and treatment variables, only radiation therapy at first surgery ($P = 0.003$), number of resected organs at first ($P < 0.00001$) and second surgery ($P = 0.024$), and grade ($P = 0.029$) were significantly associated with institution type of first surgery (TARPSWG vs. elsewhere). In particular, patients undergoing initial surgery at TARPSWG centers more commonly received radiotherapy at first surgery, had more organs resected at first surgery and fewer at second surgery, and had a higher frequency of grade 3 tumors (data not shown).

Table 1. Cohort characteristics

	$N = 602$ (%)	
	First surgery	**Second surgery**
Gender		
Female	311 (51.7)	
Male	291 (48.3)	
Age	56.0 yrs (47.0–64.0)	59.0 yrs (50.0–67.8)
Tumor size, median (IQR)	18.0 cm (12.0–26.0)	11.0 cm (6.3–18.0)
FNCLCC grade		
1	195 (32.4)	
2	170 (28.2)	
3	237 (39.4)	
Histologic subtype		
DD LPS	266 (44.2)	
WD LPS	169 (28.1)	
LMS	73 (12.1)	
SFT	14 (2.3)	
MPNST	7 (1.2)	
Other	73 (12.1)	
Completeness of resection		
R0/R1	398 (66.1)	517 (85.9)
R2	118 (19.6)	85 (14.1)
Not available	86 (14.3)	0
Number of resected organs		
Median (IQR)	1 (0–2)	2 (1–3)
0	265 (44.0)	127 (21.1)
1	146 (24.3)	151 (25.1)
> 1	191 (31.7)	324 (53.8)
Tumor rupture		
No	363 (60.3)	521 (86.5)
Yes	77 (12.8)	67 (11.1)
Not available	162 (26.9)	14 (2.3)
Multifocality		
No	399 (66.3)	378 (62.8)
Yes	57 (9.5)	224 (37.2)
Not available	146 (24.2)	0
Chemotherapy		
Given	87 (14.5)	167 (27.7)
Preop, postop, pre- and postop, unknown	18 (3.0), 64 (10.6), 5 (0.8), 0 (0)	109 (18.1), 42 (7.0), 14 (2.3), 2 (0.3)
Given at either first and/or second surgery	226 (37.5)	
Not given	515 (85.5)	435 (72.3)
Radiotherapy		
Given	75 (12.5)	185 (30.7)
Preop, intraop, postop, pre- and postop, unknown	18 (3.0), 3 (0.5), 52 (8.6), 2 (0.3), 0	85 (14.1), 27 (4.5), 66 (11.0), 4 (0.7), 3 (0.5)
Given at either first and/or second surgery	168 (27.9)	
Not given	527 (87.5)	417 (69.3)
DFI after first surgery, median (IQR)	19.0 months (6.3–41.0)	

Oncologic outcomes

Median DFI from initial surgery to RPS-LR1 was 19 months [Interquartile range (IQR), 6–41]. Median follow-up was 119 months (IQR, 80–169) from primary RPS surgery and 75 months (IQR 50–105) from definitive surgery for RPS-LR1. Clavien–Dindo grade 3 or higher complications were observed after second surgery in 103 (17.1%) patients, and 67 (11.1%) required reoperations for complications. There were five postoperative deaths (0.8%) at 1, 3, 38, 47, and 68 days from second surgery (four treatment-related, one due to a perioperative cardiac event).

Median DFI after second surgery was 19 months (IQR, 8–57). The most common pattern of disease was a second LR (58.2%). Number of first and overall events and 6-year CCI for second LR, distant metastases, and death after second surgery are included in Supplementary Table S2 and Fig. 1A. Distant metastases as a first event were rarely detected beyond two years following second surgery, whereas risk of second LR continued progressively (Fig. 1A). Of note, 41 patients died as first event after second surgery, without documented recurrence (unknown causes). Excluding 5 patients who died of postoperative complications, median time to death was 12 months (IQR, 6–20). CCI probabilities of LR and DM by histology demonstrated that second recurrences for WDLPS/DDLPS subtypes were most commonly local and for LMS were most commonly distant metastases (Table 2; Fig. 1B and C).

Three- and 6-year DFS from second surgery were 32.6% (95% CI, 29.0%–36.7%) and 19.2% (95% CI, 16.0%–23.0%), respectively (Fig. 2A). Three- and 6-year OS were 70.2% (95% CI, 66.4%–74.1%) and 54.1% (95% CI, 49.8%–58.8%), respectively (Fig. 2A). When stratified by histology, patients with WDLPS had the most favorable DFS and OS, whereas patients with grade 3 DDLPS generally had the worst (Fig. 2B and C).

Nomogram development

RF significant predictors included in the DFS and OS nomograms were: multifocality (second surgery), grade, completeness

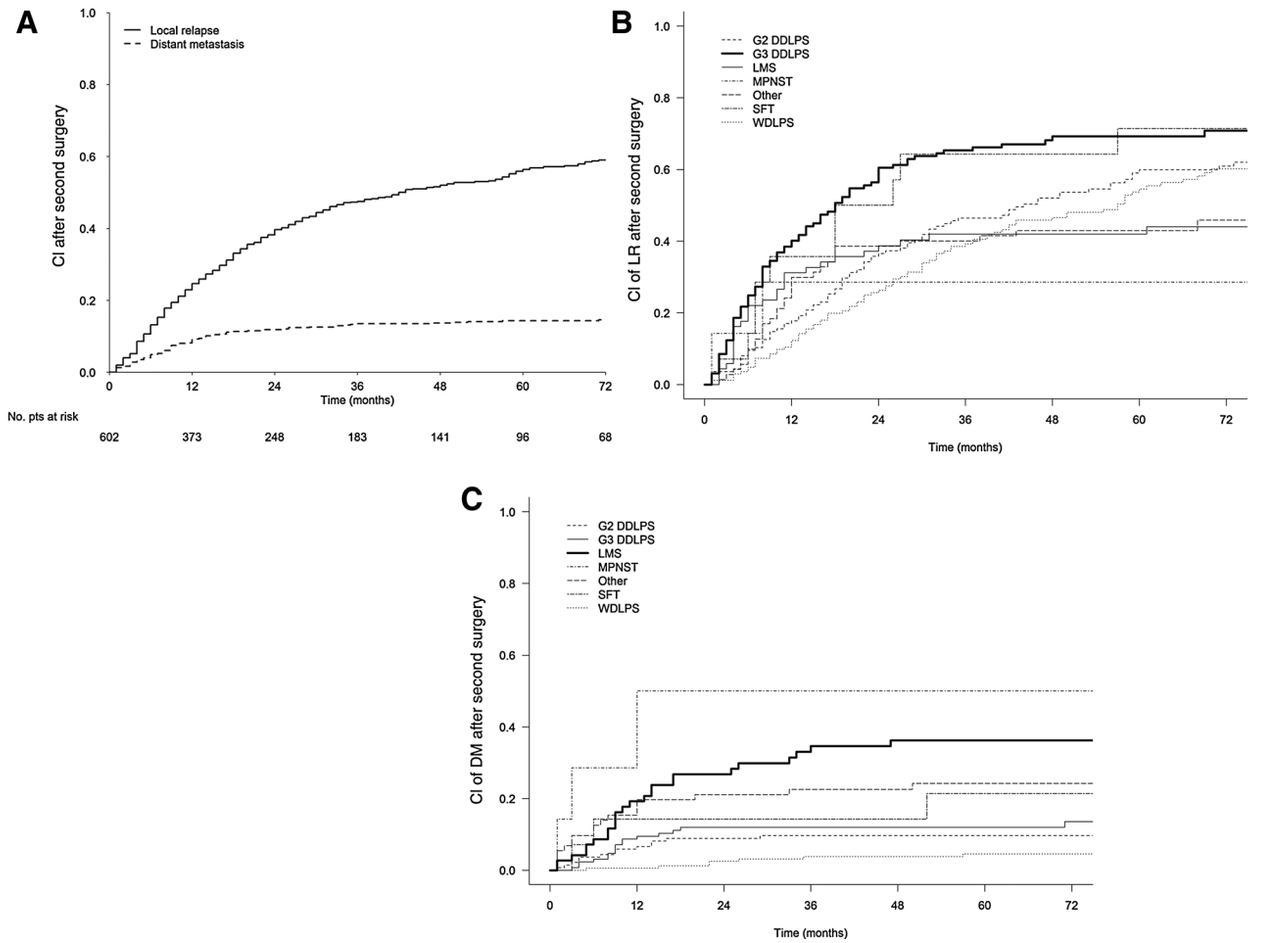

Figure 1.
CCI curves of LR and DM as first events after second surgery (**A**), of LR by histology (**B**), of DM by histology (**C**).

of second surgery, histology, and radiotherapy (first surgery; Supplementary Table S3). Chemotherapy at first surgery was independently predictive of DFS, whereas age at second surgery was significant for OS. The number of organs resected at first surgery was significant in the RF DFS model ($P = 0.033$) and, even though it achieved a P value of 0.095 in the OS model, we included it as a predictive variable in the OS nomogram for the reasons below. The variables above were included in multivariable Cox models used to develop the nomogram (Table 3). Institution type (TARPSWG vs. elsewhere) was initially modelled as random effect but was removed, as it was not statistically significant ($P = 0.462$ for DFS, $P = 0.950$ for OS).

If we removed three of the four selected variables significantly associated with the institution type (i.e. radiotherapy at first surgery, number of resected organs at first surgery, and grade) from the Cox models, then institution of initial surgery reached statistical significance ($P = 0.003$ for DFS, 0.038 for OS). This could mean that such variables had succeeded in modeling the institution heterogeneity, thus reinforcing our idea of keeping number of resected organs in the OS nomogram. DFI was excluded because of its strong association with other nomogram-selected variables, such as age at second surgery ($P = 0.003$), number of organs resected at first surgery ($P = 0.037$), grade ($P = 0.0003$), histology ($P = 0.033$), and radiotherapy ($P = 0.0004$) or chemotherapy at

Table 2. Histology-specific patterns of recurrence and survival

Histology	% 6-Year CCI, LR (95% CI)	% 6-Year CCI, DM (95% CI)	% 6-Year DFS (95% CI)	% 6-Year OS (95% CI)
WDLPS ($N = 169$)	60.2 (52.4–69.0)	4.6 (2.2–9.5)	30.3 (23.4–39.1)	77.1 (70.1–84.7)
DDLPS, grade 1–2 ($N = 137$)	61.0 (52.9–70.2)	9.7 (5.8–16.2)	22.6 (16.2–31.3)	54.6 (46.3–64.6)
DDLPS, grade 3 ($N = 129$)	70.9 (62.9–79.8)	13.6 (8.4–22.0)	6.5 (3.0–14.5)	32.2 (23.9–43.5)
LMS ($N = 73$)	44.0 (33.3–58.2)	36.3 (26.2–50.1)	12.4 (6.4–24.2)	45.4 (33.8–60.8)
MPNST ($N = 7$)	28.6 (7.8–100.0)	50.0 (17.8–100.0)	21.4 (4.2–100.0)	35.7 (8.3–100.0)
SFT ($N = 14$)	71.4 (48.9–100.0)	21.4 (7.1–64.6)	7.1 (10.8–47.2)	56.2 (35.2–90.0)
Other ($N = 73$)	45.9 (35.0–60.3)	24.2 (15.9–36.8)	17.7 (10.0–31.2)	48.3 (37.1–62.8)

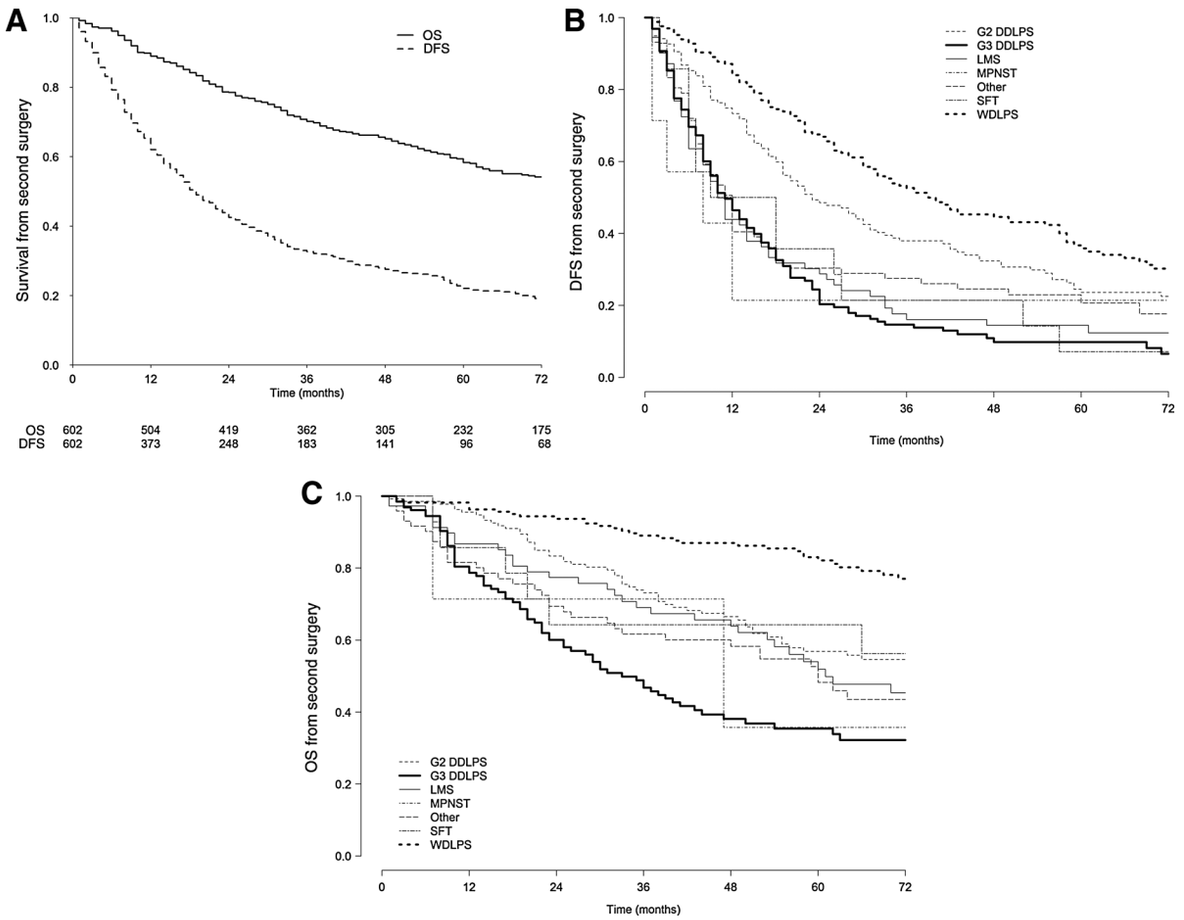

Figure 2.
Kaplan–Meier curves of DFS and OS after second surgery (**A**), of DFS by histology (**B**), of OS by histology (**C**).

first surgery ($P = 0.029$), from the multivariable quantile regression model. In particular, high median DFI corresponded to older age, higher number of resected organs, low grade, SFT or other histology, and radiotherapy or chemotherapy administration.

The nomograms to predict 6-year DFS and OS for patients undergoing curative-intent surgery for RPS-LR1 are shown in Fig. 3A and B and their scoring system are presented in Supplementary Table S4 and S5. At internal validation, both nomograms showed good calibration (Supplementary Fig. S1A– S1F), independently from the sets used for validation (patients undergoing initial surgery at TARPSWG institutions and patients undergoing surgery elsewhere). The discriminative ability, according to the Harrell C index, was 0.70 for OS nomogram and 0.67 for DFS nomogram.

Table 3. Multivariable analysis

	DFS After second surgery		OS After second surgery	
Factor	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Resected number of organs at first surgery	1.31 (1.04–1.63)	0.001	1.57 (1.17–2.11)	0.002
Age at second surgery	—	—	1.33 (1.10–1.59)	0.005
Multifocality at second surgery, yes vs. no	1.87 (1.54–2.27)	<0.001	1.78 (1.39–2.28)	<0.001
Grade – 3 vs. 1–2	1.51 (1.21–1.87)	<0.001	1.82 (1.37–2.40)	<0.001
Completeness of surgery at second surgery, incomplete vs. complete	1.65 (1.27–2.15)	<0.001	2.14 (1.55–2.96)	<0.001
Histology		0.013		0.001
LMS vs. DDLPS	1.14 (0.85–1.54)		0.79 (0.54–1.15)	
WDLPS vs. DDLPS	0.66 (0.51–0.85)		0.46 (0.32–0.66)	
MPNST vs. DDLPS	1.53 (0.62–3.77)		1.21 (0.37–3.98)	
Other vs. DDLPS	1.11 (0.82–1.50)		1.02 (0.70–1.49)	
SFT vs. DDLPS	0.94 (0.54–1.66)		0.51 (0.24–1.11)	
Chemotherapy administered at first surgery, yes vs. no	1.22 (0.93–1.61)	0.145	—	—
Radiotherapy administered at first surgery, yes vs. no	1.06 (0.80–1.41)	0.679	1.15 (0.82–1.62)	0.407

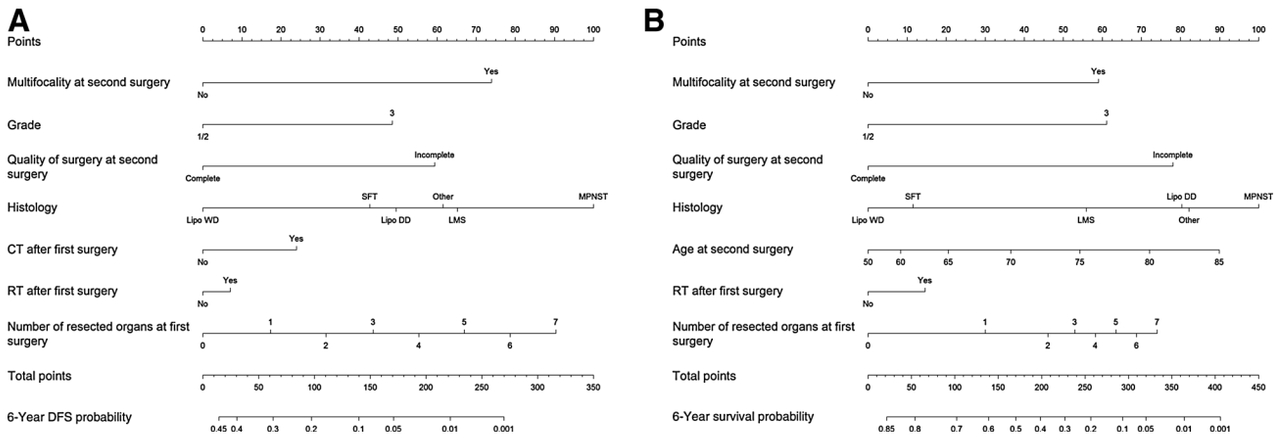

Figure 3.

Nomograms to predict 6-year DFS (**A**) and OS (**B**) after second surgery in patients with recurrent RPS . Instructions: each nomogram provides a method of calculating the 6-year DFS or OS probability on the basis of a patient's combination of covariates. For instance, in the DFS nomogram, locate the patient-specific multifocality at second surgery, draw a line straight up to the "Points" axis to determine the associated score. Repeat for the other nomogram variables, sum the scores, and locate the total score on the "Total Points" axis. Draw a line straight down to the "6-year DFS Probability" axis to obtain the probability.

Discussion

Management of patients with first locally recurrent RPS is a challenging conundrum encountered frequently in high-volume sarcoma centers. There are no evidence-based guidelines drawn from any large studies to guide the clinicians. This is the largest study to report outcomes, and the first to propose new nomograms predictive of DFS and OS for patients undergoing curative-intent second surgery for RPS-LR1. These nomograms provide individualized and disease-relevant estimation of DFS and OS and will assist in clinical decision-making. Both nomograms were internally validated and perform well for patients irrespective of the site of initial surgery for primary RPS. Thus, they can be implemented in real-world clinical encounters.

The strengths of our study are its size (602 patients), breadth (22 centers), scope (all common RPS histologies), and focus (only RPS-LR1). Only one prior study, limited to patients with RP LPS, proposed a nomogram which incorporated both patients with primary and locally recurrent RPS (2). Interestingly, recurrent RPS was significant on univariate but not multivariate analysis in that study, likely due to other relevant confounding variables (multifocality, histology). Nevertheless, it remained in the model, given other studies reporting its significance and improved calibration accuracy without affecting concordance. However, that nomogram included only 102 patients with recurrent disease and was not designed to distinguish prognostic factors within a cohort of patients with recurrent RPS.

Several points from our study warrant further comment. First, we found that higher number of organs resected at initial surgery was a negative prognostic factor for both DFS and OS after second surgery. This should not be interpreted as endorsing a less aggressive resection at initial presentation simply to increase the probability of improving DFS and OS at recurrence. Rather, this more likely suggests that patients who undergo an extensive multivisceral resection initially and subsequently recur have aggressive tumor biology, whereas those who undergo an initial simple excision and recur may still have disease that can be salvaged by a more extended procedure. Essentially, it is an indirect measure of the ability for surgical salvage at first recurrence, predicated on the extent of initial treatment and tumor biology.

Second, DFI was not selected as a predictive variable in either nomogram. This may be a composite variable, because some patients identified early as locally recurrent may in fact have had low-volume persistent disease (such as indolent WDLPS in perinephric fat), whereas others truly had rapid recurrence with worse outcome. This may explain DFI's strong association with many nomogram variables (number of organs resected, grade, histology, etc.), which led to its exclusion from the nomogram variables set.

Third, grade 3 DDLPS was the histologic subtype associated with the worst DFS and OS outcomes. Compared with primary grade 3 DDLPS, which may both recur locally and spread systemically, patients with first locally recurrent grade 3 retroperitoneal DDLPS amenable to a second surgical procedure tend to recur again locally. Their metastatic risk is comparatively low. Moreover, although DFS of grade 3 DDLPS and LMS was similar and poor, OS of LMS was better, which may be related to the broader armamentarium of systemic agents for LMS (27). Of note, chemotherapy and radiotherapy administration at second surgery were removed from the model, as both appeared to represent selection bias.

Fourth, treatment practices for patients with primary RPS and recurrent sarcoma have changed over the period of this study and may vary between centers, including extent of surgery, chemotherapy regimens, and radiation delivery. No differences were noted between TARPSWG centers in terms of number of organs resected at second surgery and use of chemotherapy or radiation. Although more contemporary chemotherapy regimens improve survival in patients with metastatic disease, their impact in this study population is uncertain, and thus, our data are valid irrespective of treatment era.

Fifth, the fact that site of initial surgery for primary RPS has no impact on outcome after second surgery (for RPS-LR1) may be surprising. It suggests that salvage surgery for first recurrence may balance out the inadequacy of first surgery. This may be due to more aggressive second surgery. Of 414 patients undergoing first

surgery elsewhere, 225 (54.3%) had multivisceral resections at second surgery. In contrast, only 75 of 188 (38.3%) patients undergoing both operations at our institutions underwent multivisceral resection at second surgery. We previously demonstrated that surgery for primary RPS performed at high-volume sarcoma centers was associated with improved OS (11). There is an inherent selection bias given that we selected for patients who were candidates for surgery, so we lack data on those who underwent first surgery elsewhere and were not candidates for second surgery upon recurrence. Therefore, we still stress that initial surgery at dedicated sarcoma centers is associated with better outcomes when measured from initial treatment. Nonetheless, this study suggests that for patients undergoing initial surgery at a nonspecialized center who develop resectable RPS-LR1 and who are both candidates for and undergo second surgery at a dedicated sarcoma center, DFS and OS may still match that of patients undergoing both the initial and second surgery at the dedicated sarcoma centers.

Finally, our choice to derive the nomograms from multivariable Cox models instead of directly using the RF models predictions may be criticized. Predicted probabilities may be obtained directly with a RF model (accommodating complex interactions between the covariates), which can be interpreted as an advantage. However, this was not the case with our data. The calibration was only slightly improved when using RF models (e.g., the calibration plot for RF DFS probabilities in Supplementary Fig. S2, to be compared with the calibration plot for Cox model DFS probabilities in Fig. 1A; the RF model overestimated the observed DFS in the third subgroup and underestimated DFS in the seventh subgroup). Instead, we tried to incorporate the covariate interactions in the Cox models; the models including the significant interactions (see statistical analysis section) gave a slight calibration improvement (Supplementary Fig. S3 for the DFS model) against the increase of model degrees of freedom (17 additional interaction terms for the DFS model), with consequent overfitting problems.

Few studies have reported prognostic factors in patients with locally recurrent RPS undergoing surgery. Several reported that patients with RPS-LR1 undergoing surgery had better survival than those that did not (1, 3, 4, 28). Gyorki and Brennan identified resectability of LR as the most significant predictor of outcome (4). Grobmeyer and colleagues identified high grade and no resection as negative prognostic factors (28). Ikoma and colleagues found that patients with recurrent retroperitoneal LMS, who underwent salvage surgery, had better OS than those who did not, regardless of whether the recurrence was local or distant (3). Park and colleagues reported that patients with locally recurrent retroperitoneal LPS with growth rates of less than 9 mm per month, who underwent resection, had better disease-specific survival than those with the same growth rate that did not undergo resection or with a faster growth rate regardless of whether surgery was performed (6). Yang and colleagues identified additional factors, such as higher histologic grade and DFI of less than 1 year, as poor prognostic factors among 50 patients with RPS-LR1 undergoing surgery (29). Likewise, a previous study by Gronchi and colleagues on a series of 377 patients undergoing surgery showed that WDLPS histology subtype and DFI were independent predictor of postrelapse outcome (21). These studies generally reflect selection bias favoring patients undergoing surgery who may have lower volume disease, less vascular involvement, longer DFIs, more favorable histologies, and other favorable markers of tumor biology.

Importantly, our data do not justify surgery in all patients with RPS-LR1. In fact, in our previously reported experience, 52% of patients with RPS-LR1 did not undergo surgery. Our new nomograms can help identify patients, amongst a cohort of those with resectable recurrences, who potentially have more favorable outcomes.

There are several limitations to our study. First, because these data were analyzed retrospectively (though some of the databases were maintained prospectively), we did not collect data on indications for surgery, such as symptoms, which could skew the outcomes. We are currently conducting a prospective primary RESAR, which will further characterize indications for surgery (17). Second, pathology was not reviewed centrally. Therefore, there may be some discrepancy amongst pathologists about issues such as FNCLCC grade in DDLPS. Third, this nomogram is not applicable to all patients with locally recurrent or metastatic RPS or with second or later recurrences. It is based on and designed for patients undergoing surgery for RPS-LR1 disease. Fourth, just as there is a selection bias in studies reporting that patients with RPS-LR1 disease undergoing surgery have better outcomes than those that do not, our study also has an inherent selection bias. All patients underwent second surgery at TARPSWG institutions, and thus, it is possible that our nomograms provide at best an upper limit on potential outcomes of individuals with RPS-LR1 undergoing surgery. Nevertheless, the nomograms will help clinicians predict survival outcomes in patients considered operable, but cannot compare outcomes with and without surgery for individual patients. Finally, although most contemporary sarcoma studies focus on histology (usually nonretroperitoneal sites), we still included all histologies in the retroperitoneum, albeit modeled separately and accounted for in the model. The rarity of RPS has, to date, limited our ability to parse data about the different RPS histologies. However, our TARPSWG collective now has datasets that can help future studies focus on individual RPS histologies.

These nomograms were constructed from a large group of institutions, and as such, they are broadly applicable. The nomograms have been added to the "Sarculator" app (http://www.sarculator.com) for mobile devices and are being used by the authors in patient consultations.

In conclusion, we found that the predominant pattern of subsequent recurrence was second LR, though this was histology dependent. Similarly, DFS and OS were histology dependent. New nomograms will, for the first time, allow clinicians to provide personalized prognostic values for DFS and OS to patients undergoing surgery for RPS-LR1 disease at dedicated sarcoma centers.

Disclosure of Potential Conflicts of Interest

D. Callegaro reports receiving speakers bureau honoraria from Eli Lilly and Company. P. Rutkowski reports receiving speakers bureau honoraria from Novartis, Bristol-Myers Squibb, Pfizer, and Eli Lilly, and is a consultant/advisory board member for Novartis, MSD, Blueprint Medicines, Bristol-Myers Squibb, and Roche. N. Ahuja reports receiving commercial research grants from Astex and Cepheid, and holds ownership interest (including patents) in IBM. G. Grignani is a consultant/advisory board member for Pharmamar, Lilly, Novartis, and EISAI. No potential conflicts of interest were disclosed by the other authors.

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