Original Article

Post-relapse Outcomes After Primary Extended Resection of Retroperitoneal Sarcoma: A Report From the Trans-Atlantic RPS Working Group

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BACKGROUND: Despite a radical surgical approach to primary retroperitoneal sarcoma (RPS), many patients experience locoregional and/or distant recurrence. The objective of this study was to analyze post-relapse outcomes for patients with RPS who had initially undergone surgical resection of their primary tumor at a specialist center. **METHODS:** All consecutive patients who underwent macroscopically complete resection for primary RPS at 8 high volume centers from January 2002 to December 2011 were identified, and those who developed local recurrence (LR) only, distant metastasis (DM) only, or synchronous local recurrence and distant metastasis (LR+DM) during the follow-up period were included. Overall survival (OS) was calculated for all groups, as was the crude cumulative incidence of a second recurrence after the first LR. Multivariate analyses for OS were performed. **RESULTS:** In an initial series of 1007 patients with primary RPS, 408 patients developed recurrent disease during the follow-up period. The median follow-up from the time of recurrence was 41 months. The median OS was 33 months after LR (n = 219), 25 months after DM (n = 146), and 12 months after LR+DM (n = 43), and the 5-year OS rates were 29%, 20%, and 14%, respectively. Predictors of OS after LR were the time interval to LR and resection of LR, while histologic grade approached significance. For DM, significant predictors of OS were the time interval to DM and histologic subtype. The subgroup of patients who underwent resection of recurrent disease had a longer median OS than patients who did not undergo resection. **CONCLUSIONS:** Relapse of RPS portends high disease-specific mortality. Patients with locally recurrent or metastatic disease should be considered for resection. ***Cancer* 2017;000:000–000.** *© 2017 American Cancer Society.*

KEYWORDS: distant metastases, local recurrence, prognostic factors, retroperitoneal sarcoma, sarcoma, surgery, survival.

INTRODUCTION

Surgery is the mainstay of curative treatment for retroperitoneal sarcoma (RPS), yet a significant proportion of patients experience locoregional and/or distant disease recurrence. Mortality from RPS is predominantly due to local failure, with up to 75% of deaths occurring in the absence of distant metastasis (DM).[1-3] Improved local control has been achieved with extended surgical resection,[4,5] with evidence suggesting a corresponding survival benefit.[6] However, tumor biology remains one of the major determinants of long-term outcomes.[7-10] To date, there are minimal data to guide treatment decisions when a patient with RPS develops recurrent disease. An understanding of the consequences of disease recurrence is vital in deciding upon an appropriate management strategy.

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Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.30572, **Received:** November 3, 2016; **Revised:** December 16, 2016; **Accepted:** December 28, 2016, **Published online** Month 00, 2017 in Wiley Online Library (wileyonlinelibrary.com)

The Trans-Atlantic RPS Working Group was established in 2013 as a multi-institutional collaboration of high-volume specialist centers, as a means of improving the understanding of this family of diseases. In a combined series of 1007 patients treated over a contemporary 10-year period at 8 institutions (the largest RPS experience reported to date), we examined patterns of recurrence after resection of primary RPS as a function of histologic subtype and institutional management strategy.[11] Differences in surgical and adjuvant/neoadjuvant strategies were associated with significant variation in the rates of local recurrence (LR) for specific histologic subtypes.

In the current study, we examine in depth the subset of patients who developed recurrent disease, including both local and distant failures, to determine the consequences of relapse and to better understand the natural history and disparate biological behavior of RPS. A major question has been the outcomes following resection of recurrent RPS, which we describe here with our large combined experience.

MATERIALS AND METHODS

Patients included in this series were treated at one of the following sarcoma centers:

1. IRCCS Foundation National Cancer Institute (Milan, Italy).
2. Royal Marsden Hospital NHS Foundation Trust (London, United Kingdom).
3. Gustave Roussy Institute (Villejuif, France).
4. Mannheim University Hospital (Mannheim, Germany).
5. Netherlands Cancer Institute (Amsterdam, the Netherlands).
6. Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology (Warsaw, Poland).
7. Mount Sinai Hospital and Princess Margaret Cancer Centre (Toronto, ON, Canada).
8. Brigham and Women's Hospital and Dana-Farber Cancer Institute (Boston, Mass).

All consecutive patients who underwent surgery for primary localized RPS between January 2002 and December 2011 were identified using prospectively maintained databases from each site, after approval of the study protocol by the appropriate institutional review boards. Patients with Ewing sarcomas, alveolar/embryonal rhabdomyosarcomas, desmoid fibromatosis, gynecological sarcomas, or gastrointestinal stromal tumors were excluded. From that series of 1007 patients, those who underwent macroscopically complete resection of the primary tumor and subsequently developed recurrent disease at any time during the follow-up period were included in the current study. These patients were grouped into 3 cohorts according to the site of recurrent disease at the time of first recurrence: LR only, DM only, or both (synchronous local recurrence and distant metastasis [LR+DM]). Our previous publication reported outcomes after initial resection for the entire series of 1007 primary RPS patients[11]; the current article focuses on management and outcomes in the subset of patients who experienced recurrence (n = 408).

The completeness of resection of the primary tumor was classified dichotomously as macroscopically complete (R0/1) or incomplete (R2) according to the operative and pathology reports. Patients who underwent incomplete (R2) resection were excluded from the current study. Decisions regarding adjuvant/neoadjuvant therapies in the treatment of both primary and recurrent disease were made at the discretion of the treating oncologists after multidisciplinary discussion. Chemotherapy was administered according to standard regimens or within the context of clinical trials. External beam radiation therapy was delivered in doses of 36 to 65 Gy (median dose 50 Gy), typically in the preoperative setting for both primary and recurrent disease. Patients were selected for resection of recurrent disease after careful consideration of patient and tumor factors by the multidisciplinary specialist teams at the treating institutions. Resection of recurrent disease was performed with the goal of achieving macroscopically complete resection.

The following histologic subtypes were included: well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), leiomyosarcoma (LMS), undifferentiated pleomorphic sarcoma, malignant peripheral nerve sheath tumor, solitary fibrous tumor, and other sarcomas. The latter 4 subtypes were grouped together for the purposes of multivariate analysis because of their relatively small numbers. The 3-tiered grading system of the French National Federation of the Centers for the Fight Against Cancer (FNCLCC) was applied by local pathologists at all of the contributing centers.[12]

Postoperative surveillance regimens included clinical examination and computed tomography or magnetic resonance imaging of the chest/abdomen/pelvis every 3 to 4 months for 2 years, then every 6 months for 3 years, and yearly thereafter.

Statistical Methods

The primary study outcome was overall survival (OS), which was defined as the time from relapse to death from any cause. Disease-specific survival was reported

TABLE 1. Demographic, Clinicopathological, and Treatment Characteristics of the Three Recurrent Disease Groups

Characteristic	LR	DM	LR+DM
Total patients, No.	219	146	43
At the time of surgery for the primary tumor			
Patient age, median (IQR), y	59 (48-67)	54 (47-64)	58 (51-66)
Sex, No. (%)			
Female	102 (47)	83 (57)	16 (37)
Male	117 (53)	63 (43)	27 (63)
Histologic subtype, No. (%)			
WDLPS	53 (24)	1 (1)	—
DDLPS	123 (56)	38 (26)	22 (51)
LMS	16 (7)	78 (53)	10 (23)
UPS	9 (4)	5 (3)	4 (9)
SFT	5 (2)	5 (3)	1 (2)
MPNST	5 (2)	3 (2)	2 (5)
Other	8 (4)	16 (11)	4 (9)
FNCLCC grade, No. (%)			
I	53 (25)	10 (7)	1 (2)
II	94 (44)	59 (42)	9 (21)
III	67 (31)	73 (51)	30 (75)
Radiotherapy, No. (%)			
Given	51 (23)	66 (45)	11 (26)
Not given	168 (77)	80 (55)	32 (74)
Chemotherapy, No. (%)			
Given	39 (18)	51 (35)	14 (33)
Not given	180 (82)	95 (65)	29 (67)
At the time of recurrence			
Patient age, median (IQR), y	61 (51-70)	56 (48-65)	59 (52-67)
Time between surgery and recurrence, median (IQR), mo	23 (11-41)	12 (6-26)	7 (4-22)
Resection, No. (%)			
Done	105 (48)	53 (36)	10 (23)
Not done	114 (52)	93 (64)	33 (77)
Chemotherapy, No. (%)			
Given	68 (31)	75 (51)	33 (77)
Not given	151 (69)	71 (49)	10 (23)
Radiotherapy, No. (%)			
Given	39 (18)	19 (13)	4 (9)
Not given	180 (82)	127 (87)	39 (91)
Follow-up after surgery for the primary tumor, median (IQR), mo	76 (49-107)	59 (41-89)	70 (59-104)
Follow-up after recurrence, median (IQR), mo	37 (15-66)	42 (23-56)	65 (37-83)
Status at last follow-up, No. (%)			
AWD	74 (34)	43 (29)	7 (16)
DOC	5 (2)	4 (3)	—
DOD	106 (48)	86 (59)	35 (81)
NED	34 (16)	13 (9)	1 (2)

Abbreviations: AWD, alive with disease; DDLPS, dedifferentiated liposarcoma; DM, distant metastasis; DOC, dead of complications, DOD, dead of disease; FNCLCC, French National Federation of the Centers for the Fight Against Cancer; IQR, interquartile range; LMS, leiomyosarcoma; LR, local recurrence; LR+DM, synchronous local recurrence and distant metastasis; MPNST, malignant peripheral nerve sheath tumor; NED, no evidence of disease; SFT, solitary fibrous tumor; UPS, undifferentiated pleomorphic sarcoma; WDLPS, well-differentiated liposarcoma.

as a secondary outcome. Time was censored at the date of last follow-up for patients who were still alive. OS curves were estimated with the Kaplan-Meier method and compared with the log-rank test. Crude cumulative incidence (CCI) curves of second events (LR or DM) after LR were calculated in a competing-risk framework.

Multivariate analyses were performed with Cox regression models. The time from the initial surgery to the first recurrence was modeled as a continuous variable with 3-knot restricted cubic splines to obtain a flexible fit.[13] All other variables were modeled as categorical using dummy variables.

Statistical analyses were performed with SAS (SAS Institute, Cary, NC) and R software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of the 1007 patients who underwent resection for primary RPS, 408 experienced disease recurrence. The initial site of recurrence was local only (LR) for 219 patients, distant only (DM) for 146 patients, and both local and

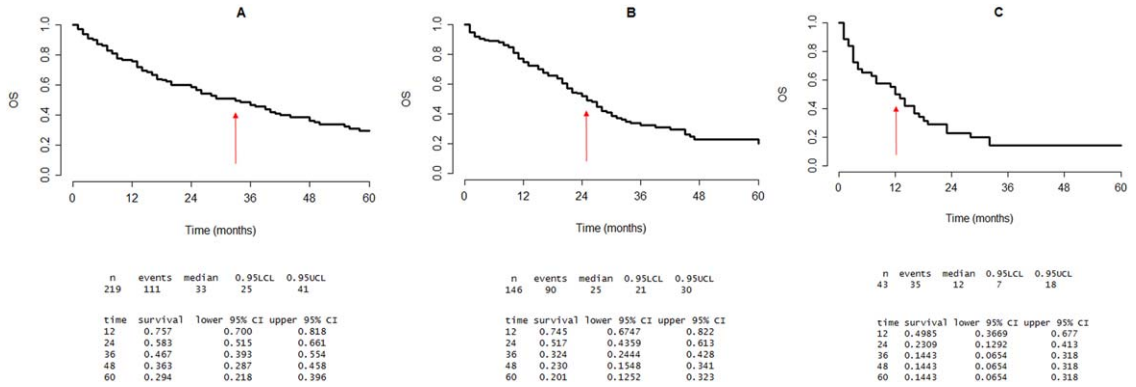


Figure 1. OS curves for patients with (A) local recurrence only, (B) distant metastasis only, and (C) synchronous local recurrence and distant metastasis. CI indicates confidence interval; LCL, lower confidence limit; OS, overall survival; UCL, upper confidence limit.

TABLE 2. Multivariate Cox Model Analysis of Variables Associated With Overall Survival in the Local Recurrence and Distant Metastasis Groups

	Patients With Local Recurrence			Patients With Distant Metastases		
Analyzed Variable	HR for Death	95% CI	*P*[a]	HR for Death	95% CI	*P*[a]
Months between surgery and recurrence: third vs first quartile[b]	0.36	0.22-0.58	.0001	0.40	0.23-0.69	.0052
FNCLCC grade			.0505			.2222
II vs I	1.26	0.39-4.10		1.51	0.44-5.15	
III vs I	2.27	0.70-7.36		2.20	0.68-7.11	
Histologic subtype			.3320			.0038
DDLPS vs LMS	1.33	0.62-2.86		2.30	1.27-4.14	
WDLPS vs LMS	0.48	0.11-2.16		—[c]	—	
Other vs LMS	1.44	0.60-3.47		2.53	1.35-4.73	
Surgery for recurrence: no vs yes	3.96	2.32-6.76	<.0001	1.62	0.97-2.74	.0668
Chemotherapy for recurrence: no vs yes	1.66	0.94-2.94	.0789	1.29	0.80-2.06	.2988
Radiotherapy for recurrence: no vs yes	1.76	0.98-3.18	.0583	1.03	0.46-2.28	.9447

Abbreviations: CI, confidence interval; DDLPS, dedifferentiated liposarcoma; FNCLCC, French National Federation of the Centers for the Fight Against Cancer; HR, hazard ratio; LMS, leiomyosarcoma; WDLPS, well-differentiated liposarcoma.
[a] Two-sided Wald test.
[b] The 2 values are 39 and 11 in the first subset and 26 and 6 in the second subset.
[c] One patient with a well-differentiated lipomatous tumor was included in the subgroup of patients with other histological subtypes.

distant (LR+DM) for 43 patients. Demographic, clinicopathological, and treatment details are shown in Table 1.

LR (n = 219)

In the cohort of patients whose initial site of recurrence was local only (LR), the predominant histologic subtype was liposarcoma (LPS; 80%). The majority had tumors of intermediate or high grade (75%). The median time from the initial resection to LR was 23 months. Resection of LR was performed in 105 patients (48%), and chemotherapy and radiotherapy (RT) were administered to 68 (31%) and 39 patients (18%), respectively.

For the cohort of 219 patients, the median follow-up from the time of the initial primary resection was 76 months, and the median follow-up from the time of LR was 37 months. The median OS after LR was 33 months, and the 5-year OS was 29% (95% confidence interval [CI], 21.8%-39.6%; Fig. 1A). Significant independent predictors of improved OS were a longer time interval to LR and resection of LR (Table 2). There was a trend toward significance for lower grade and for the treatment of LR with RT.

Survival for the group of patients who underwent resection of LR versus the group that did not is depicted in Figure 2A, which shows median OS of 49 and 20 months, 2-year OS of 73% (95% CI, 64.5%-83.0%) and 43% (95% CI, 33.6%-55.5%), and 5-year OS of 43% (95% CI, 32.5%-57.7%) and 11% (95% CI, 3.8%-31.5%),

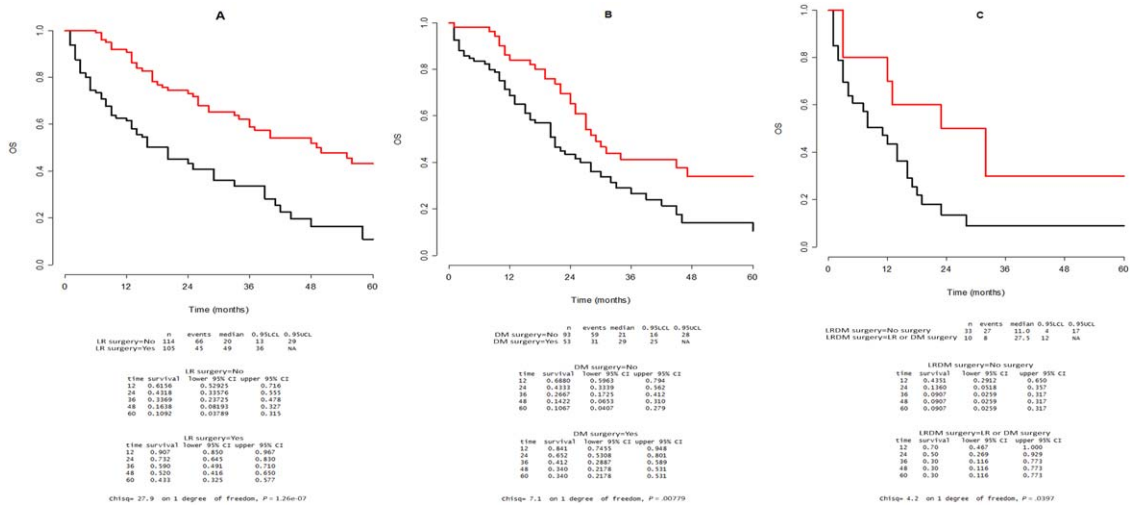
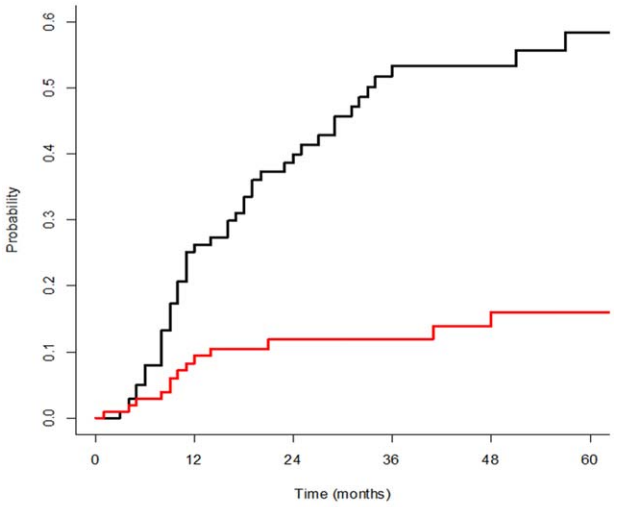


Figure 2. OS curves for resected patients (red lines) and nonresected patients (black lines) with (A) LR only, (B) DM only, and (C) LR+DM. CI indicates confidence interval; DM, distant metastasis; LCL, lower confidence limit; LR, local recurrence; LR+DM, synchronous local recurrence and distant metastasis; NA, not available; OS, overall survival; UCL, upper confidence limit.



	Event	time	CCI	lower 95% CI	upper 95% CI
1	LR	12	0.263	0.187	0.3692
2	LR	24	0.400	0.309	0.5183
3	LR	36	0.533	0.433	0.6574
4	LR	48	0.533	0.433	0.6575
5	LR	60	0.584	0.475	0.7176
6	DM	12	0.094	0.050	0.1767
7	DM	24	0.119	0.068	0.2088
8	DM	36	0.119	0.068	0.2089
9	DM	48	0.160	0.094	0.27210
10	DM	60	0.160	0.094	0.272

Figure 3. CCI curves for further local recurrence (black line) and DM (red line) as second events after the resection of the first local recurrence. CCI, crude cumulative incidence; CI, confidence interval; DM, distant metastasis.

respectively ($P < .0001$). The CCI of further LR for the 105 patients who underwent resection of LR was calculated to be 40% (95% CI, 30.1%-51.8%) at 2 years and 58% (95% CI, 47.5%-71.8%) at 5 years. The CCI of DM in this group was 12% (95% CI, 6.8%-20.9%) at 2 years and 16% (95% CI, 9.4%-27.2%) at 5 years (Fig. 3).

DM (n = 146)

The majority of the patients who developed DM as the first site of failure had LMS (53%), whereas 27% had LPS (almost all DDLPS). The vast majority of the patients in this cohort had tumors of an intermediate or high grade (93%). The median time from the initial resection of the primary RPS to DM was 12 months. Resection of DM was performed in 53 patients (36%), and chemotherapy was administered to 75 (51%).

The median follow-up from the time of the initial primary resection was 59 months, and the median follow-up from the time of the detection of DM was 42 months. The median OS after DM was 25 months, and the 5-year OS was 20% (95% CI, 12.5%-32.3%; Fig. 1B). Significant independent predictors of improved OS were a longer time interval to DM and LMS histology (Table 2), and resection of DM approached significance ($P = .0668$). Resection of DM was a significant predictor of improved disease-specific survival ($P = .035$; Supporting Table 1 [see online supporting information]). Survival in the group of patients who underwent resection of DM (n = 53) was longer than in patients who did not (n = 93), with median OS of 29 and 21 months, 2-year OS of 65% (95% CI, 53.1%-80.1%) and 43% (95% CI, 33.4%-56.2%), and 5-year OS of 34% (95% CI,

21.8%-53.1%) and 11% (95% CI, 4.1%-27.9%), respectively ($P = .008$; Fig. 2B).

LR+DM (n = 43)

The histologic profile of this group (51% DDLPS and 23% LMS) was a composite of the 2 extremes represented by the LR and DM groups. The median time from the primary surgery to relapse was 7 months. Ten of the patients underwent resection: both local and distant sites in 5, LR only in 4, and a distant site only in 1. For the group of 43 patients, the median follow-up was 70 months from the initial primary surgery and 65 months from the detection of recurrence; the median OS was 12 months (95% CI, 7-18 months), and the 5-year OS was 14% (95% CI, 6.5%-31.8%; Fig. 1C). Patients who underwent resection of recurrent disease (n = 10) had longer survival than patients who did not (n = 33) with median OS of 28 and 11 months, 2-year OS of 50% (95% CI, 26.9%-92.9%) and 14% (95% CI, 5.2%-35.7%), and 5-year OS of 30% (95% CI, 11.6%-77.3%) and 9% (95% CI, 2.6%-31.7%), respectively ($P = .04$; Fig. 2C). Given the small number of patients in this group, multivariate analysis was not performed.

DISCUSSION

This series of 408 patients from the Trans-Atlantic RPS Working Group represents the largest experience of recurrent RPS published to date. In the original description of 1007 consecutive primary RPS patients treated at high volume specialist centers, we reported a 5-year OS of 67%.[11] The data that we present here confirm that survival following recurrence of RPS is poor: the 5-year OS was 29% after LR, 20% after DM, and 14% after LR+DM. Although 10-year post-relapse follow-up has not yet been reached, it is anticipated that OS after LR will continue to decline over time, as the risk of LR persists long term and survival with recurrent disease can be prolonged. In the original series of 1007 primary RPS patients, the CCI of LR was calculated to be 35% at 10 years versus 26% at 5 years. In contrast, the CCI of DM was 22% at 10 years versus 21% at 5 years, indicating that the risk of distant failure plateaus roughly 5 years after primary resection, with the resultant possibility of long-term survival or possibly cure. Thus, the better prognosis associated with LR versus DM that we have shown here may be diminished with longer follow-up.

The management of recurrent RPS is complex and requires multidisciplinary evaluation and planning. Resection of recurrent disease offers the only possibility of long-term survival and can result in prolonged OS for carefully selected patients.[14-17] A recent report of treatment for recurrent or residual RPS detailed selection criteria for resection and noted that the development of concomitant LR and DM, multifocal recurrence, poor performance status, and technical unresectability were all considerations in determining which patients might benefit from operative management of disease failure.[18] An earlier collaboration between 2 of the participating centers in the current series suggested that after extended resection for primary disease, the benefit of reoperation for LR may be limited.[19] However, this was based on a small number of patients. In the current study of a much larger cohort, we demonstrate a significant association between resection and survival for patients with locally recurrent disease. The association was less pronounced for resection of metastatic disease because the cause of death in this cohort was more widely varied, but resection of DM was significantly associated with improved disease-specific survival. Patients selected for surgery in this series tended to be younger, and were more likely to be female and to have had a longer interval between the resection of their primary tumor and the detection of recurrence (Supporting Tables 2-4 [see online supporting information]). In the LR group, selection seemed to favor WDLPS histology and lower grade tumors. Since surgery is generally offered to patients with a better performance status and favorable tumor biology, the survival benefits demonstrated may reflect these variables as much as the treatment itself. Even so, the current data indicate that resection of recurrent RPS in well-selected patients can be associated with prolonged survival and should be considered.

Given that the possibility of cure after recurrence is low, it is important to carefully consider the potential morbidity of reoperation in the individual patient. At the centers represented in this study, a relatively conservative approach is taken to resection of recurrent RPS after an extended primary procedure, in that the aim is to excise the recurrent tumor and directly invaded organs, rather than performing a wider excision as might be done for primary RPS. As far as we are aware, no published study has specifically addressed the morbidity of resection for recurrent RPS, but it could reasonably be anticipated to be at least on par with other major abdominal procedures such as distal pancreatectomy and segmental colectomy. Importantly, the incidence of further recurrence after resection of the first LR is substantial. In our series, 58% of patients developed a second LR within 5 years and 16% developed DM. However, 24% of patients who underwent resection of the first LR remained persistently disease-free at the 5-year time point, albeit with an

ongoing risk of late LR. The likelihood of curing patients with recurrent disease is low, but in appropriately selected patients long-term disease control can be achieved, warranting the risk of morbidity in patients with good performance status.

The selection of patients for reoperation should also take into account tumor biology. The latter has been previously estimated on the basis of tumor growth rate.[3] In the current study, as in others,[20] the time interval to disease recurrence correlated significantly with subsequent OS, which reflects a combination of favorable biology and patient selection for aggressive treatment. Histologic subtype is an important predictor of the pattern of recurrence and is also predictive of OS, as shown in our original series of 1007 patients as well as another large, contemporary series.[21] In keeping with other published literature, we found that the importance of histology was diminished after LR, but it remained a significant predictor of OS in the context of DM. This is likely attributable to the preponderance of LMS among patients with DM because this histologic subtype represents more of a systemic than a local threat, and to the availability of multiple lines of chemotherapy and biological agents active against LMS. In contrast, the systemic treatments available for LPS are less numerous and effective, so patients with metastatic LPS have a poorer outcome. Retroperitoneal LPS is primarily a disease of local failure, as clearly shown by the experience we report here as well as others.[1,2,14] Because of this pattern of recurrence and the paucity of effective systemic therapies for LPS, it is apparent that local control should ideally be pursued at the time of primary treatment, with careful attention to the quality of the resection.

Local control may be optimized not only by extended primary resection but potentially also by the delivery of preoperative RT. Nonrandomized observational studies have suggested that RT may improve local control; this hypothesis is being examined in an ongoing international randomized clinical trial.[22] In the experience that we report here, it is possible that differential use of RT contributed to the pattern of local versus distant failure. Of the patients who developed DM, 45% received RT as part of their primary treatment, compared to only 26% in the LR and LR+DM groups. The latter group had particularly poor outcomes, with a 5-year OS of only 14%. It is possible that this group harbored the same unfavorable biology as the DM group but with inferior local control, and that this precluded resection as a treatment option.

Although we acknowledge the limitations of a retrospective study, our results support a role for resection of locally recurrent or distant metastatic disease in carefully selected patients, while highlighting the poor prognosis associated with the recurrence of RPS, whether or not the patient undergoes resection. A consensus guideline on the management of recurrent RPS has been published by the members of the Trans-Atlantic RPS Working Group with the goal of helping to guide decision making for this complex disease presentation,[23] and a prospective registry has been established to improve the quality of evidence going forward.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Andrea J. MacNeill: Data interpretation and writing. **Rosalba Miceli**: Data analysis, data interpretation, and writing. **Dirk C. Strauss**: Concept and study design, data interpretation, and writing. **Sylvie Bonvalot**: Concept and study design, data interpretation, and writing. **Peter Hohenberger**: Concept and study design, data interpretation, and writing. **Frits Van Coevorden**: Concept and study design, data interpretation, and writing. **Piotr Rutkowski**: Concept and study design, data interpretation, and writing. **Dario Callegaro**: Data collection, data interpretation, and writing. **Andrew J. Hayes**: Data collection, data interpretation, and writing. **Charles Honoré**: Data collection, data interpretation, and writing. **Mark Fairweather**: Data collection, data interpretation, and writing. **Amanda Cannell**: Data collection, data interpretation, and writing. **Jens Jakob**: Data collection, data interpretation, and writing. **Rick L. Haas**: Data collection, data interpretation, and writing. **Milena Szacht**: Data collection, data interpretation, and writing. **Marco Fiore**: Data collection, data interpretation, and writing. **Paolo G. Casali**: Concept and study design, data interpretation, and writing. **Raphael E. Pollock**: Concept and study design, data interpretation, and writing. **Chandrajit P. Raut**: Concept and study design, data interpretation, and writing. **Alessandro Gronchi**: Concept and study design, data interpretation, and writing. **Carol J. Swallow**: Concept and study design, data interpretation, and writing.

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