Variability in Patterns of Recurrence After Resection of Primary Retroperitoneal Sarcoma (RPS)

A Report on 1007 Patients From the Multi-institutional Collaborative RPS Working Group

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Background: Retroperitoneal sarcomas (RPS) are rare tumors composed of several well defined histologic subtypes. The aim of this study was to analyze patterns of recurrence and treatment variations in a large population of patients, treated at reference centers.

Methods: All consecutive patients with primary RPS treated at 6 European and 2 North American institutions between January 2002 and December 2011 were included. Five, 8, and 10-year overall survival (OS) and crude cumulative incidence (CCI) of local recurrence (LR) and distant metastasis (DM) were calculated. Multivariate analyses for OS, CCI of LR, and DM were performed.

Results: In all, 1007 patients were included. Median follow-up was 58 months (first and third quartile range 36–90). The 5, 8, and 10-year OS were 67% [95% confidence interval (CI), 63, 70), 56% (95% CI, 52, 61), and 46% (95% CI, 40, 53). The 5, 8, and 10-year CCI of LR and DM were 25.9 (95% CI, 23.1, 29.1), 31.3 (95% CI, 27.8, 35.1), 35% (95% CI, 30.5, 40.1), and 21% (95% CI, 18.4, 23.8%), 21.6 (95% CI, 19.0, 24.6), and 21.6 (95% CI, 19.0, 24.6), respectively. Tumour size, histologic subtype, malignancy grade, multifocality, and completeness of resection were significant predictors of outcome. Patterns of recurrence varied depending on histologic subtype. Different treatment policies at participating institutions influenced LR of well differentiated liposarcoma without impacting OS, whereas discrepancies in adjuvant systemic therapies did not impact LR, DM, or OS of leiomyosarcoma.

Conclusions: Reference centers are critical to outcomes of RPS patients, as the management strategy requires specific expertise. Histologic subtype predicts patterns of recurrence and should inform management decision. A prospective international registry is under preparation, to further define our understanding of this disease.

Keywords: leiomyosarcoma, liposarcoma, prognostic factors, retroperitoneal sarcoma, sarcoma, solitary fibrous tumor, surgery, survival

(*Ann Surg* 2016;263:1002–1009)

An effort to standardize and improve quality of surgical management of primary retroperitoneal sarcomas (RPS) has generated controversy over the past 5 years. In 2009, studies from 2 major European reference centers retrospectively demonstrated that a surgical approach incorporating the resection of uninvolved adjacent structures in the retroperitoneum was associated with an improved local outcome.[1–3] Editorials accompanying the studies[4,5] and other studies[6] highlighted open issues and uncertainties, including the fact that no survival benefit was demonstrated against a background of possibly increased postoperative morbidity. Subsequently, an improvement in overall survival (OS) was reported upon longer follow-up in 1 series, particularly for patients with low-to-intermediate–grade RPS.[7]

Other series have, however, emphasized the importance of inherent tumor biology in determining the natural history of this disease,[8–17] indicating that this should be factored into the surgical strategy. In essence, these studies suggested that patients with more indolent histologies arising in the retroperitoneum could safely and perhaps more appropriately be treated by a less extensive surgical approach.

A collaboration among many of the groups participating in this lively debate ensued, resulting in a publication on a consensus ''optimal surgical approach'' to RPS in 2012[18] and of a histology-specific nomogram for OS and disease-free survival (DFS) in 2013.[19]

A Trans-Atlantic RPS Working Group was established in 2013. Representatives from 11 high-volume centers were invited to participate. Nine agreed (6 European, 3 North American). This group contributed to the update of the European Society of Medical Oncology (ESMO) Clinical Practice Guidelines for Sarcoma and Gastrointestinal Stromal Tumor (GIST),[20] and produced a consensus

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The authors have no conflicts of interest.

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ISSN: 0003-4932/14/26105-0821
DOI: 10.1097/SLA.0000000000001447

paper on the management of primary RPS.[21] The present study reports on the combined series from 8 of the 9 centers in this collaborative group, to analyze outcomes in unprecedented depth.

METHODS

This series included all consecutive patients affected by localized primary RPS who underwent resection between January 2002 and December 2011 by high-volume sarcoma surgeons at the following centers:

(1) Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
(2) Royal Marsden Hospital NHS Foundation Trust, London, UK
(3) Institute Gustave Roussy, Villejuif, France
(4) Manheim 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, Toronto, Canada
(8) Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA

Patients affected by Ewing sarcoma, alveolar/embryonal rhabdomyosarcomas, desmoid tumors, gynecological sarcomas, and GIST were excluded.

Clinical data were collected from prospectively maintained surgical databases housed at each institution.

Surgical resections were classified as macroscopically complete (R0 or R1) or not (R2). Postoperative complications were graded according to Common Terminology Criteria for Adverse Events (CTCAE).[22] We included all events ($\geq$3) occurring either before or within 60 days after discharge. All deaths at 30, 60, and 90 days after the definitive resection were recorded regardless of whether they were related or unrelated to complications from surgery.

Adjuvant/neoadjuvant treatment modalities were utilized on a case-by-case basis following multidisciplinary clinical decisions. Chemotherapy was given using standard regimens at the time or according to ongoing institutional/multi-institutional clinical studies. Radiation therapy (RT) was delivered through external beam approach, with doses ranging between 36 and 65 Gy (median 50 Gy), usually preoperatively.

In the statistical analysis, histologic types were grouped as follows: well differentiated (WD) liposarcoma (LPS), dedifferentiated (DD) LPS, leiomyosarcoma (LMS), malignant peripheral-nerve sheath tumor (MPNST), solitary fibrous tumor (SFT), undifferentiated pleomorphic sarcoma (UPS), and other sarcomas.

The Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system was applied.

Patients were prospectively followed by clinical examination and computed tomography (CT)/magnetic resonance imaging (MRI) of chest/abdomen/pelvis every 3 to 4 months for the first 2 years, then every 6 months for the following 3 years, and yearly thereafter.

Statistical Methods

The main study outcomes were OS, local recurrence (LR), and distant metastasis (DM). OS was defined as the time between surgery and death from any cause; time was censored at the date of last follow-up for patients remaining alive. OS curves were estimated using the Kaplan-Meier method and statistically compared with the log-rank test. Crude cumulative incidence (CCI) curves of LR and DM were calculated in a competing-risk framework.[23] In the analysis of LR (DM), deaths without evidence of disease and DM (LR), whichever occurred first, were regarded as competing events. In the subgroup of patients undergoing R2 resection, radiologic progression of the postsurgical residual tumor was considered as LR. Comparisons between CCI curves were carried out by means of the Gray test.[24] Concomitant LRs and DMs were included only in the estimation of the CCI curves for DM.

Multivariable analyses were based on cause-specific hazards and were therefore carried out using Cox regression models, stratified by center. Patient's age and tumor size were modeled as continuous variables using 3-knot restricted cubic splines,[25] whereas the other categorical variables used dummy variables. Cox model proportional-hazard assumption was checked and verified by relying on statistical tests based on scaled Schoenfeld residuals.[26]

The Fisher exact test was used to test the between centers difference according to categorical variables, whereas the Kruskal-Wallis test was used when continuous variables were involved in the comparison.

The statistical analyses excluded the patients with missing data and were performed using the SAS and R software [Institute for Statistics and Mathematics of Wirtschaftsuniversität (WU), Wien: The R Project for Statistical Computing. http://www.r-project.org/]. We considered a statistical test as significant when the corresponding *P* value was less than 5%.

RESULTS

Clinicopathologic Features

In all, 1007 patients were identified. Median follow-up from surgery was 58 months [interquartile range (IQR) 36–90]. The clinicopathological characteristics are shown in Table 1 and Supplemental Table 1 (http://links.lww.com/SLA/A957) and the specific organs resected en bloc with the tumor in Table 2.

Postoperative complications CTCAE grade 3 were observed in 128 patients (12.7%), grade 4 in 52 patients (5.2%), and grade 5 in 19 patients (1.9%); 106 (11%) required a surgical reintervention. Type of complications is listed in Supplemental Table 2 (http://links.lww.com/SLA/A957). Postoperative mortality at 30, 60, and 90 days was 1.8 (95% CI, 1, 2.6), 2.9 (95% CI, 1.8, 3.9), and 4.1% (95% CI, 2.9, 5.3), respectively.

Overall Survival, Local Recurrence, and Distant Metastases for the Entire Cohort

Overall Survival

In all, 332 patients died. Five, 8, and 10-year OS were 67% (95% CI, 63, 70), 56% (95% CI, 52, 61), and 46% (95% CI, 40, 53) (Fig. 1, panel A). Median time to death was 116 months. Patients' age, size of the tumor, completeness of surgical resection, malignancy grade, and multifocality significantly predicted OS (Table 3). A clear trend was also evident for histological subtype (Fig. 1, panel B).

Local Recurrence

In all, 316 patients developed LR. In 249 patients, this was the first event, whereas 47 patients developed concurrent LR and DM, and 20 patients developed LR after DM. Five, 8, and 10-year CCI of LR were 25.9 (95% CI, 23.1,29.1), 31.3 (95% CI, 27.8, 35.1), and 35% (95% CI, 30.5, 40.1), as shown in Figure 2 (panel A). The median time to first LR was 39 months. If we excluded patients who underwent macroscopically incomplete resections, 5, 8, and 10-year CCI of LR were 24% (95% CI, 21.2,27.3), 29.2% (95% CI, 25.7,33.1), and 33.1% (95% CI, 28.5,38.4), respectively. Factors significantly predicting LR were patients' age, size of the tumor, completeness of surgical resection, malignancy grade, tumor rupture, multifocality, administration of RT, and histological subtype (Table 3 and Fig. 2, panel B).

TABLE 1. Demographic, Clinical, and Pathological Characteristics

	n	%
Sex		
Female	483	48.0
Male	524	52.0
Patients' age, y		
Median (first and third quartile range)	58 (48–67)	
Tumor size, cm		
Median (first and third quartile range)	20 (12.9–30.0)	
FNCLCC grade		
I	329	34.1
II	370	38.3
III	267	27.6
Histological subtype		
LMS	194	19.3
DD LPS	370	36.7
WD LPS	263	26.1
MPNST	33	3.3
SFT	59	5.9
UPS	22	2.2
Other	66	6.6
Completeness of surgical resection		
R0/R1	960	95.3
R2	47	4.7
Resected organs		
Median (first and third quartile range)	2 (1–4)	
None	131	13.0
One organ	188	18.7
More than 1 organ	688	68.3
Tumor rupture		
No	945	93.8
Yes	62	6.2
Multifocality		
No	915	90.9
Yes	92	9.1
Pre/postoperative chemotherapy		
Done (pre/post/pre and postoperative)	183 (143/31/9)	18.2
Not done	824	81.8
Pre/postoperative RT		
Done (pre/post/pre and postoperative)	322 (205/90/27)	32.0
Not done	685	68.0

TABLE 2. Type and Number of Organs Resected (Percentage Calculated on the Total Number of Patients Included in the Study)

	n	%
Kidney	552	54.8%
Left colon and/or rectum	330	32.7%
Psoas muscle (partial/total)	273	27.1%
Right colon	247	24.5%
Spleen	162	16.0%
Diaphragm	140	13.9%
Abdominal wall muscles	122	12.1%
Distal pancreas	113	11.2%
Iliac vein and/or Inferior Vena Cava	110	10.9%
Adnexa and/or uterus	70	6.9%
Small bowel	67	6.6%
Major lumbar nerves	57	5.6%
Testis and/or spermatic cord and/or vas deferens	41	4.0%
Iliac artery and/or aorta	33	3.2%
Bone	24	2.3%
Liver	24	2.3%
Stomach	22	2.1%
Bladder	19	1.8%
Ureter	12	1.2%
Duodenum/head of the pancreas	10	0.9%
Duodenum or duodeno-jejunal junction	4	0.3%
Prostate	4	0.3%
Other	3	0.2%
Lung	2	0.1%

Distant Metastases

In all, 221 patients developed DM. In 195 patients, this occurred as the first event (in 47 cases accompanied also by concurrent LR, see above), whereas in 26 cases, DM followed LR. Five-, 8, and 10-year CCI of DM were 21% (95% CI, 18.4, 23.8%), 21.6 (95% CI, 19.0, 24.6), and 21.6 (95% CI, 19.0, 24.6), as shown in Figure 2 (panel C). The median time to first DM was 14 months. Factors significantly predicting DM were tumor size, malignancy grade, multifocality, and histological subtype (Table 3 and Fig. 2, panel D).

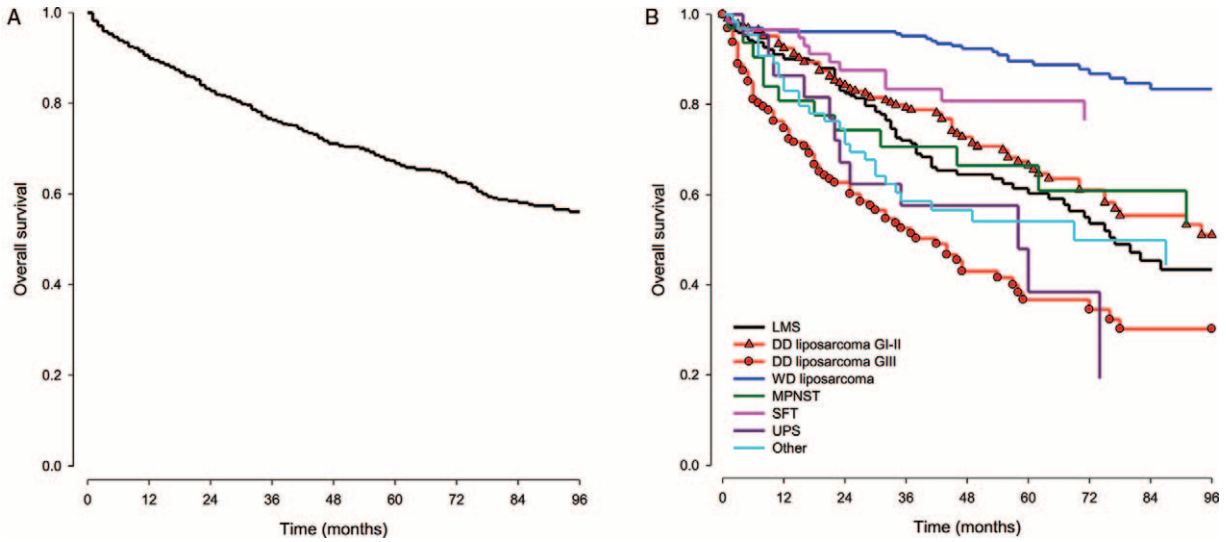

FIGURE 1. Panel A, Overall survival curve in the whole series. Panel B, Overall survival curves according to histological subtypes.

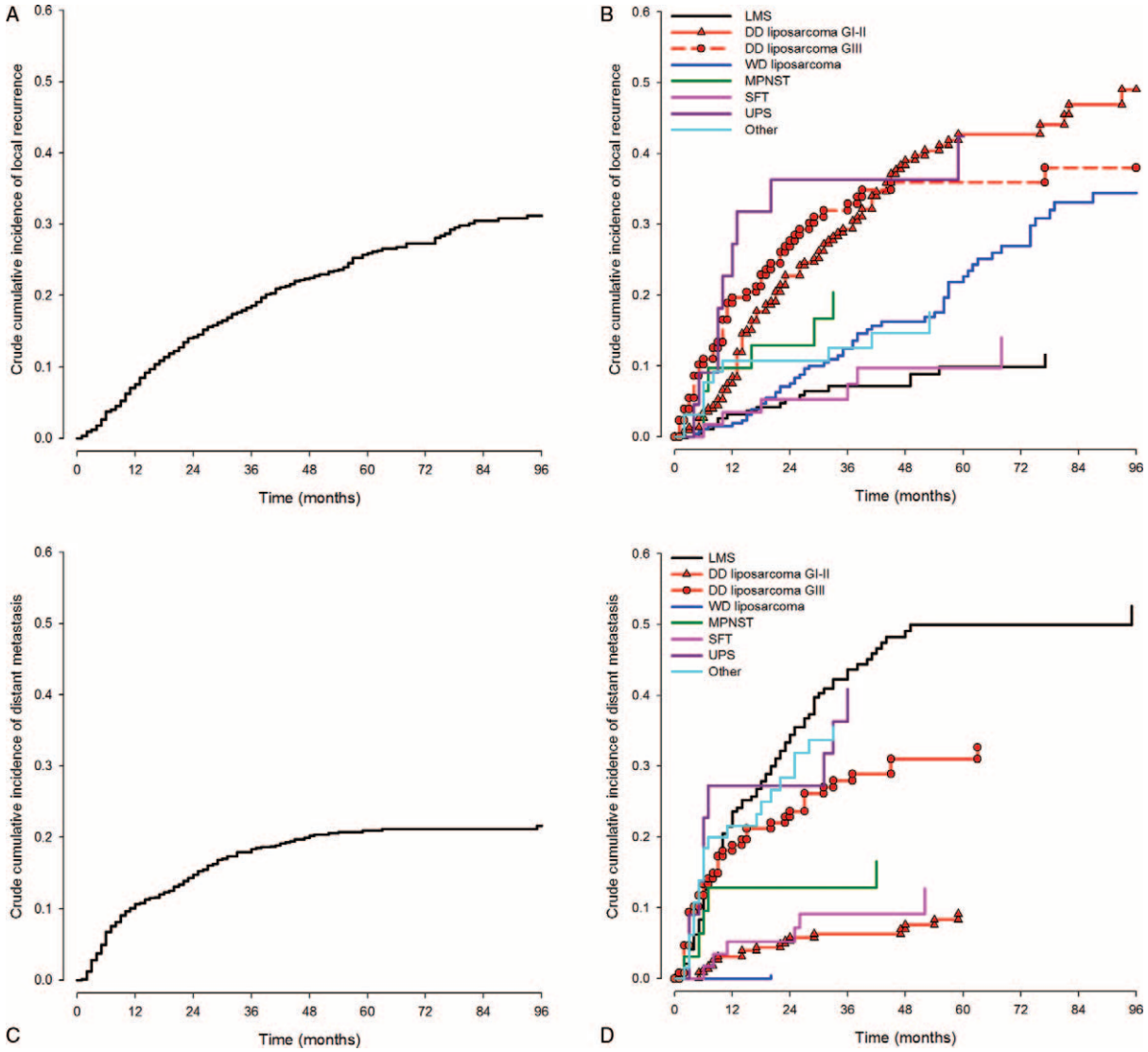

FIGURE 2. Panel A, Crude cumulative incidence of local relapse in the whole series. Panel B, Crude cumulative incidence of local relapse according to histological subtype. Panel C, Crude cumulative incidence of distant metastasis in the whole series. Panel D, Crude cumulative incidence of distant metastasis according to histological subtype.

Overall Survival, Local Recurrence, and Distant Metastases by Institution/Strategy

We selected WD LPS and LMS as the histotypes for this analysis because they represent the 2 extremes of the biological spectrum and were also the ones for which the approach differed the most amongst the 8 sites (complete data available although not shown). In Figure 3, institutions are identified by numbers and different colors. Three centers were grouped together due to limited numbers, thus resulting in 6 different sites for analysis. We chose an 8-year time point to compare outcomes, as this corresponded to the third quartile of the median follow-up.

WD LPS

Median size was 27 cm, similar across all 6 sites. Surgery was macroscopically complete in all cases, but the number of organs resected and administration of RT varied significantly between 1 (IQR 0–2) and 5 (IQR 4–7), and 0% to 72%, respectively (Fig. 3, $P < 0.0001$). The corresponding CCI of LR at 8 years was 5% (95% CI, 0.7, 35.5%) in the institution where extended surgery and RT were employed, 34.8% (95% CI, 19.7, 61.4) in the one where RT was not employed, but surgery was extended, and 42.5% (95% CI, 28.9, 62.4) in the one where RT was not employed at all and surgery was more limited (Fig. 3, panel C, center 5, 3, and 2, respectively); the difference of LR by institution was statistically significant ($P = 0.048$). Postoperative morbidity and mortality were similar in these 3 sites. No differences in 8-year OS were observed amongst the 6 sites (Fig. 3, panel D).

LMS

Median size was 12 cm, similar across all 6 sites. Surgery was macroscopically complete in all cases, with significant variation in the median number of organs resected amongst centers between 1 (IQR 0–2) and 4 (IQR 1–7) ($P < 0.0001$) (Fig. 4, panel A). In

TABLE 3. Results From the Multivariable Cox Models on the 3 Endpoints Analyzed

	OS			LR			DM		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age, y			<0.001			0.001			0.059
67 vs 48*	1.52	(1.28, 1.81)		1.30	(1.10, 1.55)		1.22	(1.01, 1.48)	
Sex			0.153			0.668			0.225
Male vs female	1.19	(0.94, 1.50)		1.05	(0.83, 1.34)		1.18	(0.90, 1.53)	
Tumor size, cm			0.011			0.045			0.040
30 vs 13*	1.34	(1.05, 1.70)		1.38	(1.07, 1.78)		1.06	(0.81, 1.39)	
Completeness of surgical resection			0.001			<0.001			0.211
R2 vs R0/R1	2.36	(1.45, 3.84)		2.81	(1.76, 4.49)		1.61	(0.76, 3.38)	
FNCLCC grade			<0.001			<0.001			<0.001
II vs I	2.52	(1.45, 4.38)		2.57	(1.52, 4.32)		2.33	(1.33, 4.08)	
III vs I	6.47	(3.70, 11.30)		4.58	(2.62, 8.00)		4.83	(2.74, 8.49)	
Histological subtype			0.072			0.012			<0.001
LMS vs SFT	1.95	(0.94, 4.02)		1.07	(0.48, 2.40)		2.90	(1.37, 6.17)	
DD LPS vs SFT	1.58	(0.78, 3.20)		1.94	(0.91, 4.14)		1.07	(0.50, 2.31)	
WD LPS vs SFT	1.16	(0.50, 2.69)		2.25	(1.00, 5.07)		0.57	(0.22, 1.48)	
MPNST vs SFT	1.65	(0.67 4.09)		1.07	(0.38, 3.01)		0.95	(0.33, 2.77)	
UPS vs SFT	2.26	(0.92, 5.53)		3.40	(1.29, 8.93)		2.46	(0.94, 6.48)	
Other vs SFT	2.78	(1.28, 6.05)		1.62	(0.66, 4.03)		2.30	(1.01, 5.26)	
Tumor rupture			0.647			0.019			0.819
Yes vs no	1.11	(0.72, 1.72)		1.67	(1.09, 2.57)		0.93	(0.52, 1.67)	
Multifocality			0.001			<0.001			0.002
Yes vs no	1.85	(1.30, 2.63)		2.05	(1.43, 2.94)		1.94	(1.27, 2.97)	
Chemotherapy			0.314			0.271			0.492
Yes vs no	1.17	(0.86, 1.57)		1.22	(0.86, 1.74)		1.12	(0.81, 1.55)	
RT			0.864			0.001			0.210
Yes vs no	0.98	(0.73, 1.30)		0.58	(0.42, 0.80)		0.82	(0.61, 1.11)	

*The 2 values are, respectively, the third and first quartiles of the variable distribution.

addition to variability in administration of RT, receipt of chemotherapy also varied significantly from 0% to 63% ($P < 0.0001$) (Fig. 4, panel B). The corresponding CCI of LR at 8 years was below 10% for all sites (Fig. 4, panel C). The corresponding 8-year CCI of DM was not influenced by the different approaches (Fig. 4, panel D). Similarly, no significant differences in 8-year OS were seen amongst the 6 sites.

DISCUSSION

In this series of over 1000 patients with primary RPS, treated at 8 European/North American sarcoma reference centers over a contemporary 10-year period, 5 and 10-year OS rates were 67% and 46%, LR were 26% and 35%, and DM were 21% and 22%, respectively. When compared with population-based results published in 2009 using the Surveillance, Epidemiology, and End Results (SEER) database,[27] a 20% difference in OS in favor of the present series at the 5, 8, and 10-year time points was apparent. Tumor grade, complete surgical resection, multifocality, tumor rupture, age, and preoperative RT have previously been established as prognostic factors for RPS. In this study, histologic subtype significantly influenced the pattern of failures and the final outcome, as recently reported by a large single-institution series.[28] Different treatment policies at participating reference institutions influenced the LR outcomes of WD LPS without impacting OS, whereas differences in the use of adjuvant systemic therapies did not impact LR, DM, or OS outcomes of LMS. Short-term morbidity was consistent with previous studies on RPS and comparable with the other major abdominal cancer surgeries.[3,8,9,27–29]

Several limitations must be acknowledged. First, the study is retrospective, albeit based on data collected from prospectively maintained datasets. Second, the case mix was different across countries and centers. Third, differences in surgical strategy could not be evaluated objectively. For instance, number of organs resected is not an accurate surrogate for extent of resection. Fourth, chemotherapy and RT administrations varied broadly among the different centers. Fifth, no formal comparison with low-volume centers could be made. Finally, no quality-of-life assessment was done in this analysis.

Despite these caveats, this study represents an unprecedented collaboration among 8 high-volume trans-atlantic reference centers that has resulted in the largest retrospective series of RPS reported. The amalgamation of institutional experiences provides relevant contemporary historical control data for future studies, and also some insights into the treatment of RPS. Moreover, the comparison of outcomes amongst participating centers has generated hypotheses for future studies.

Retroperitoneal sarcoma is not a single disease, and the spectrum of histologies is quite variable. At one end is WD LPS, whose 8-year OS was in excess of 80%. As the metastatic risk was virtually nil, deaths were all related to locoregional recurrences, which were observed in nearly one-third of patients as the only mode of failure. This emphasizes the need to refer RPS patients to specialized centers to provide an individualized optimal management approach. However, the LR risk even in experienced centers seems to remain constant over time, save for the center favoring tumor resection en bloc with adjacent visceral organs and RT (Fig. 3, center 5), which had the highest local control rate, holding over time, and similar postoperative morbidity and mortality. OS rates were superimposable at the 8-year time point in all 8 participating institutions (Fig. 3), as most local recurrences of WD LPS can be managed by subsequent resections, especially when the first one had been limited. It is likely that these patients will succumb later to locoregional recurrences. Whether such an improved local control by extended local resection and RT translates into cure remains an open

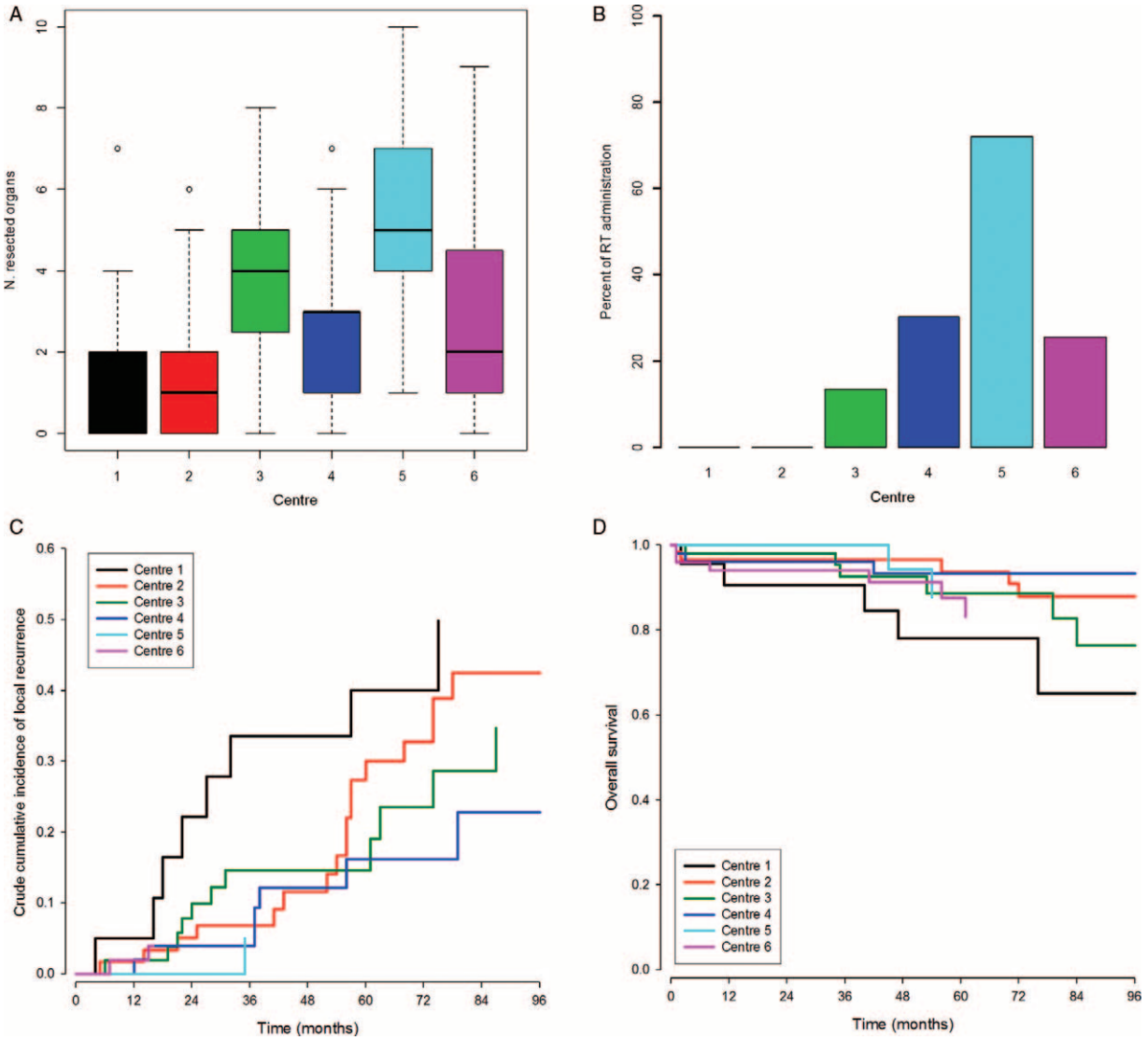

FIGURE 3. Well differentiated liposarcoma. Panel A, Box plot showing the distribution of the number of organs resected according to center (median: bold lines). Panel B, Plot showing the percent of RT administration according to institution. Panel C, Crude cumulative incidence of local relapse according to institution. Panel D, Overall survival curves according to institution.

question, which a longer follow-up of this series and, possibly the ongoing randomized study on preoperative RT,[30] will help to clarify. A comparison between different strategies has to include quality-of-life assessment and the number of operations over the patient's lifetime, which could not be accurately measured retrospectively. A prospective RPS registry currently in preparation will be instrumental in further improving our understanding of the role of preoperative RT and extended resections in this subset of RPS. Thus, in the absence of any demonstrable OS benefit with different treatment strategies, the optimal management of patients with retroperitoneal WD LPS in terms of extent of resection and use of RT needs to be further studied.

At the other end of the spectrum of RPS is LMS, with an 8-year OS of 40%. As the LR risk was in the 10% rate, most deaths in patients with RP LMS were related to metastatic spread, occurring in as many as 50% of patients. Interestingly, in contrast with the LR risk of WD LPS, which is mainly related to anatomic constraints, the metastatic risk is linked to the biology of the disease and seemed to flatten out after 5 years. In other words, patients with a retroperitoneal LMS who survived without any disease recurrence for 8 years were likely cured. When comparing strategies amongst institutions, we found less variability in surgical strategy than was seen with WD LPS, although variations in the administration of RT were still present. Nevertheless, no difference in local control was seen. The use of adjuvant/neoadjuvant chemotherapy was very variable, with one institution employing chemotherapy in more than 60% of LMS patients, but with no impact on the incidence of DM detected (Fig. 4). Although a formal comparison between the 2 strategies could not be made, it seemed that the administration of systemic chemotherapy in this series was not beneficial. New studies are needed to improve the outcome of these patients by both reinforcing available therapies and identifying more active compounds.

Solitary fibrous tumor and DD LPS displayed a pattern of LR and DM that lay within the biological spectrum of behavior defined

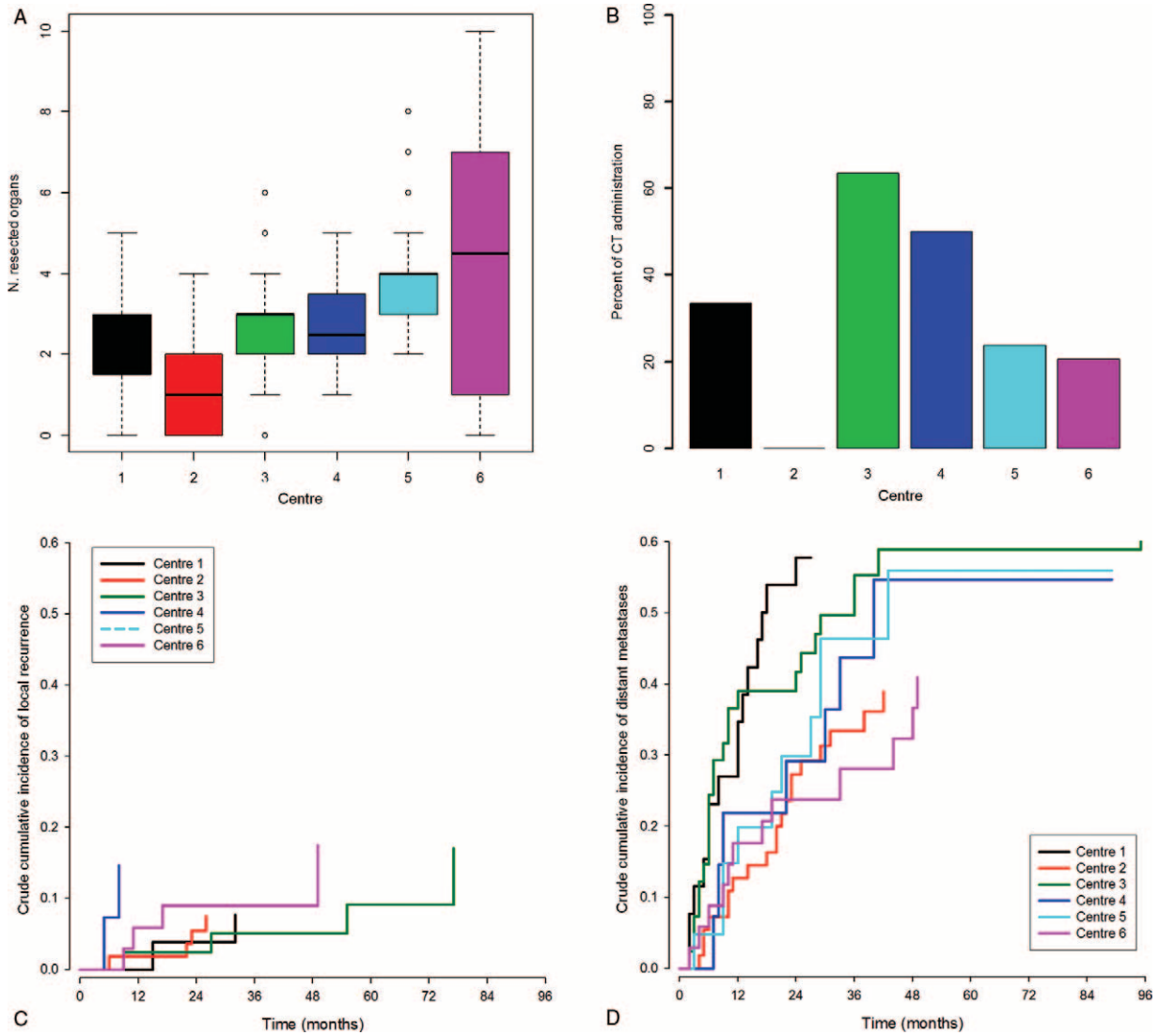

FIGURE 4. Leiomyosarcoma. Panel A, Box plot showing the distribution of the number of organs resected according to center (median: bold lines). Panel B, Plot showing the per cent of CT administration according to center. Panel C, Crude cumulative incidence of local relapse according to institution. Panel D, Crude cumulative incidence of distant metastases according to institution.

by WD LPS and LMS. The 8-year OS of SFT was in excess of 75%, with low LR and DM rates. This reflects the predominance of the classical variant of SFT at this site, although a longer follow-up may be needed to rule out late recurrences, which are known to occur even after 10 years (Figs. 1 and 2). DD LPS was the most common histology, accounting for 35% of all cases. Eight-year OS of DD LPS was 43.9%. Deaths were more related to the LR risk, which was over 40% at 8 years, whereas the DM risk was less than 20%. Interestingly, grading the dedifferentiated component was very helpful to further delineate 2 distinct entities. Grade II DD LPS was associated with an 8-year OS of 50%, almost exclusively related to LR risk (which was approximately 50%, compared with a DM risk of less than 10%). Patterns of failure were similar to WD LPS, although disease intervals were shorter and the likelihood of death at the 8-year time point was higher. Grade III DD LPS was associated with a 30% 8-year OS, the worst of the entire group of RPS. At variance with WD LPS and GII DD LPS, deaths were both related to LR and DM. In fact, the latter was over 30% at 8 years, similar to LMS (Figs. 1 and 2). The use of combined locoregional therapies needs to be studied prospectively as in the randomized trial on preoperative RT.[30] Other approaches such as preoperative combined deep-wave hyperthermia and systemic chemotherapy that were proposed to improve LR-free survival[31] must be re-evaluated in the light of more aggressive surgery of today, whereas new studies are needed to address the systemic risk of this subset.

In conclusion, the choice of treatment strategies is important to maximize chances of cure and should be tailored to the specific histology. This emphasizes the importance of a preoperative biopsy, so that use of neoadjuvant and adjuvant treatments and extent of surgical resection can be more specific to the presenting histology. Implicit in this is the need to centrally refer these patients. The best chance of resection with curative intent is at the time of primary presentation. The balance between the expected morbidity and the possible improvement in oncologic outcome should be factored in

the management algorithm and tailored to the patient. Oncologic outcomes in this large series of patients, which anecdotally are superior to those reported in population-based analyses (albeit with all of the caveats of such comparisons), cannot provide further hard evidence to recommend the concentration of RPS patients in ''few'' specialist sarcoma reference centers per country, but they could serve as the basis of in-depth discussions with national authorities on RPS in the years to come. They are in line with recent data reported by the French Sarcoma Group, showing a better outcome for patients treated at a ''specialized'' center.[29,32] This is consistent with what has been reported for other cancers or diseases requiring complex procedures.[33–35] The National Institute for Health and Care Excellence (NICE) in the UK also recently published a Sarcoma Quality Statement recommending people with a RPS be referred to a specialized sarcoma center before having any treatment.[36] The next step in addressing this advance in health policy would involve crafting a definition of RPS center, specifying the minimum number of RPS cases that should be treated annually to be considered a reference center. Collaboration among large RPS reference institutions is critical to make progress. The Trans-Atlantic RPS Working Group is expanding to include other centers in Europe and North America. A prospective international registry is under preparation and will further define our understanding of this disease.

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