Postoperative Morbidity After Radical Resection of Primary Retroperitoneal Sarcoma

A Report From the Transatlantic RPS Working Group

Andrea J. MacNeill, MD,*† Alessandro Gronchi, MD,† Rosalba Miceli, PhD,‡ Sylvie Bonvalot, MD, PhD,§ Carol J. Swallow, MD, PhD,* Peter Hohenberger, MD,¶ Frits Van Coevorden, MD,|| Piotr Rutkowski, MD,** Dario Callegaro, MD,† Andrew J. Hayes, MD, PhD,†† Charles Honoré, MD,‡‡ Mark Fairweather, MD,§§ Amanda Cannell, BSc,¶¶ Jens Jakob, MD,¶ Rick L. Haas, MD,|||| Milena Szacht, MD,** Marco Fiore, MD,† Paolo G. Casali, MD,*** Raphael E. Pollock, MD, PhD,††† Francesco Barretta, PhD,‡ Chandrajit P. Raut, MD, MSc,§§ and Dirk C. Strauss, MD††

Objective: To investigate the safety of radical resection for retroperitoneal sarcoma (RPS).

Background: The surgical management of RPS frequently involves complex multivisceral resection. Improved oncologic outcomes have been demonstrated with this approach compared to marginal excision, but the safety of radical resection has not been shown in a large study population.

Methods: The Transatlantic Retroperitoneal Sarcoma Working Group (TARPSWG) is an international collaborative of sarcoma centers. A combined experience of 1007 consecutive resections for primary RPS from January 2002 to December 2011 was studied retrospectively with respect to adverse events. A weighted organ score was devised to account for differences in surgical complexity. Univariate and multivariate logistic regression analyses were performed to investigate associations between adverse events and number and patterns of organs resected. Associations between adverse events and overall survival, local recurrence, and distant metastases were investigated.

Results: Severe postoperative adverse events (Clavien-Dindo $\geq$3) occurred in 165 patients (16.4%) and 18 patients (1.8%) died within 30 days. Significant predictors of severe adverse events were age ($P = 0.003$), transfusion requirements ($P < 0.001$), and resected organ score ($P = 0.042$). Resections involving pancreaticoduodenectomy, major vascular resection, and splenectomy/pancreatectomy were found to entail higher operative risk (odds ratio >1.5). There was no impact of postoperative adverse events on overall survival, local recurrence, or distant metastases.

Conclusions: A radical surgical approach to RPS is safe when carried out at a specialist sarcoma center. High-risk resections should be carefully considered on an individual basis and weighed against anticipated disease biology. There appears to be no association between surgical morbidity and long-term oncologic outcomes.

Keywords: adverse events, morbidity, radical resection, retroperitoneal sarcoma, safety

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The primacy of surgery in the treatment of retroperitoneal sarcoma (RPS) has been well established. In the absence of effective systemic therapies, surgical resection represents the only possibility for cure. Over the past decade, a radical surgical approach involving en bloc resection of the tumor with adherent organs or structures has been advocated at many centers with the aim of minimizing marginality and decreasing the risk of local recurrence.[1,2] Although the oncologic outcomes of extended resection have been reported,[3,4] these are presumed to come at a cost of increased operative morbidity compared to more conservative surgical approaches. However, there is a dearth of evidence to support or refute this assumption, to specify the risk of postoperative complications, and to clarify whether these have any impact on long-term oncologic outcomes.

The Transatlantic RPS Working Group (TARPSWG) is a multi-institutional international collaboration of specialist sarcoma centers from Europe and North America. The collaboration was undertaken to generate a pooled dataset of primary RPS patients as a means of overcoming the rarity of this family of diseases. From this combined experience representing the largest published series of RPS to date, we have examined patterns of recurrence by histologic subtype and treatment strategy,[5] validated the multi-institutional RPS nomogram,[6] and evaluated outcomes after local and distant recurrence.[7] In this latest analysis of the collected series of over 1000 patients with RPS treated in the modern era, we investigate the morbidity associated with radical surgical resection and its potential relationship to oncologic outcomes.

From the *Department of Surgical Oncology, Mount Sinai Hospital and Princess Margaret Cancer Center, Department of Surgery, University of Toronto, Toronto, Canada; †Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; ‡Unit of Clinical Epidemiology and Trial Organization, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; §Department of Surgery, Institute Curie, Paris, France; ¶University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany; ||Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands; **Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; ††Department of Surgery, Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; ‡‡Department of Surgery, Institute Gustave Roussy, Villejuif, France; §§Department of Surgery, Division of Surgical Oncology, Brigham and Women's Hospital and Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; ¶¶Ontario Institute for Cancer Research, MaRS Center, Toronto, Canada; ||||Department of Radiation Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands.; ***Department of Cancer Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; and †††Department of Surgery, Division of Surgical Oncology, Ohio State University Medical Center, Columbus, OH.

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Reprints: Dirk C. Strauss, MD, Sarcoma/Melanoma Unit The Royal Marsden NHS Foundation Trust Fulham Rd, London, United Kingdom SW3 6JJ. E-mail: dirk.strauss@rmh.nhs.uk.

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METHODS

All consecutive patients who underwent surgery for primary localized RPS between January 2002 and December 2011 at 1 of the following 8 specialist sarcoma centers were included:

1. Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
2. Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom
3. Institut Gustave Roussy, 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 Center, Toronto, Canada
8. Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, USA.

Patients with Ewing sarcoma, alveolar/embryonal rhabdomyosarcoma, desmoid fibromatosis, gynecologic sarcomas, or gastrointestinal stromal tumor were excluded.

Completeness of resection was classified as macroscopically complete (R0/1) or incomplete (R2). Decisions regarding adjuvant/neoadjuvant therapies 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 radiotherapy was delivered between doses of 36 Gy and 65 Gy (median dose 50 Gy), typically in the preoperative setting.

Surveillance regimens included clinical examination and CT or MRI of the chest/abdomen/pelvis every 3 to 4 months for 2 years, followed by every 6 months for 3 years and yearly thereafter.

Adverse events were reported according to the Clavien-Dindo classification. Complications requiring surgical, endoscopic, or radiologic intervention (grade 3) and life-threatening complications (grade 4) within 30 days of surgery were recorded, and death (grade 5) up to 90 days after surgery. Associations between adverse events and patient characteristics, tumor characteristics, and treatments were investigated in univariate and multivariate analyses.

Primary oncologic endpoints were overall survival (OS), local recurrence (LR), and distant metastasis (DM). Associations between adverse events and OS, LR, and DM were investigated in a multivariate analysis.

Recognizing that resection of some organs or structures entails a higher risk of morbidity than others, a weighted resected organ score was devised as follows:

Weighted 0: Adrenal gland, aortocaval lymph nodes, appendix, gallbladder, inguinal ligament, omentum, psoas fascia, and skin.
Weighted 1: Adnexa and/or uterus, bladder, bone, diaphragm, distal pancreas, duodenum or duodenojejunal flexure, femoral/sciatic/obturator nerve or lumbar/sacral nerve root, iliac artery and/or aorta, iliac vein and/or IVC, kidney, left colon and/or rectum, liver, lung, parietal muscles, pericardium, posterior vaginal wall, prostate (with or without seminal vesicle), psoas muscle, right colon, small bowel, spleen, stomach, testis and/or spermatic cord and/or vas deferens, and ureter (complete or partial resection not associated with nephrectomy).
Weighted 2: Pancreaticoduodenectomy

The weighted organ score was intended to provide a more accurate representation of anticipated morbidity than simply reporting the number of organs resected. Those organs weighted 0 consist of structures often resected en passant at the time of major abdominal surgery to avoid the difficulty of later reoperation, but are not part of the en bloc multivisceral resection for RPS. Other structures weighted 0 reflect components of routine resections for RPS believed to confer minimal or no morbidity (eg. omentum, psoas fascia). The higher weighting of a pancreaticoduodenectomy compared with other resections reflects the well-established increased morbidity of this procedure.

The weighted organ score provides standardization in comparing procedures between institutions, by eliminating variability in reporting number of organs resected (eg. differential coding of the omentum as a resected organ or double counting the appendix as a separate organ in a right hemicolectomy specimen).

Patterns of resection were analyzed in association with morbidity. These were categorized as follows in order of presumed ascending morbidity:

- No organs resected or only organs weighted 0
- Other (organs weighted 1 or 0 but not included in subsequent categories)
- Colon (left/right), kidney +/− other
- Colon (left/right), kidney, spleen, pancreas +/− other
- Vascular resection (inferior vena cava or iliac vein resection) +/− other
- Pancreaticoduodenectomy +/− other

Procedures were classified according to the component of the resection conferring the highest morbidity. Thus, a "pancreaticoduodenectomy +/− other" or a "vascular resection +/− other" may include concomitant kidney and colon resection.

Statistical Analyses

Adverse events were analyzed as a dichotomous variable (Clavien-Dindo ≤ 2 or ≥ 3). Univariate and multivariate logistic regression analyses were performed to investigate associations between adverse events and clinicopathologic characteristics including age at diagnosis, tumor size, operative time, transfusion requirement, resected organ score, and pattern of organs resected (the latter were alternately included in the multivariate model because of their association), and administration of preoperative chemotherapy and pre- and/or intraoperative radiotherapy.

As previously reported, 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 who were still alive. OS curves were estimated using the Kaplan-Meier method. Crude cumulative incidence (CCI) curves of LR and DM were calculated in a competing-risk framework. Concomitant LR and DM were included in the estimation of the CCI curves for DM.[5] Associations between adverse events and OS, LR, and DM were investigated with multivariate Cox models, adjusting for patient and disease characteristics. Death times of patients with Clavien-Dindo 5 were censored. Proportional-hazard assumptions were verified using scaled Schoenfeld residuals.

In all models, center was modeled as a random effect whereas patient age, tumor size, and resected organ score were modeled as continuous variables using 3-knots restricted cubic splines.[8] All other variables (including age in univariate logistic model) were modeled as categorical using dummy variables. Missing data were excluded from the analyses. Statistical analyses were performed with SAS (SAS Institute, Cary, NC) and R software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 1007 patients underwent resection for primary RPS at 1 of 8 referral centers. Median follow up from the time of surgery

TABLE 1. Demographic, Clinical, and Pathological Characteristics

	N	%
Sex		
Female	483	48
Male	524	52
Age, yrs		
Median (1st and 3rd quartile)	58 (48–67)	
Tumor size, cm		
Median (1st and 3rd quartile)	20 (12.9–30.0)	
FNCLCC grade		
I	329	32.7
II	370	36.7
III	267	26.5
Not available	41	4.1
Histological subtype		
DD LPS	370	36.7
WD LPS	263	26.1
LMS	194	19.3
SFT	59	5.9
MPNST	33	3.3
UPS	22	2.2
Other	66	6.6
Operative time, min*		
Median (1st and 3rd quartile)	240 (162–330)	
Transfusion requirement, unit of packed red blood cells†		
Median (1st and 3rd quartile)	1 (0–3)	
Completeness of surgical resection		
R0/R1	960	95.3
R2	47	4.7
Resected organs		
Median (1st and 3rd quartile)	2 (1–4)	
None	131	13
One	188	18.7
More than one	688	68.3
Tumor rupture		
No	945	93.8
Yes	62	6.2
Multifocality		
No	885	87.9
Yes	92	9.1
Not available	30	3
Chemotherapy		
Given	183	18.2
(pre/post/pre and postoperative)	(143/31/9)	(14.2/3.1/0.9)
Not given	824	81.8
Radiotherapy		
Given	322	32
(preintra/post/preintra and postoperative)‡	(216/90/16)	(21.4/8.9/1.4)
Not given	685	68

DD indicates dedifferentiated; FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer; IQR, interquartile range; LMS, leiomyosarcoma; LPS, liposarcoma; MPNST, malignant peripheral nerve sheath tumor; R0, macroscopically complete resection with negative microscopic margins; R1, macroscopically complete resection with positive microscopic margins; R2; macroscopically incomplete resection; SFT, solitary fibrous tumor; UPS, undifferentiated pleomorphic sarcoma; WD, well differentiated.

*Data not available for 199 patients (19.8%).

†Data not available for 157 patients (15.6%).

‡Of the 216 patients reported in the category preintraoperative RT, 3 received intraoperative RT only and 8 pre- plus intraoperative RT; of the 16 patients reported in the category preintra and postoperative RT, 10 received intraoperative RT.

was 58 months. Demographic, clinicopathologic, and treatment details are given in Table 1.

Median tumor size was 20 cm (interquartile range, IQR: 12.9–30.0) and complete resection was achieved in 95% of cases. Median number of organs resected en bloc with the tumor was 2 (IQR: 1–4).

TABLE 2. Number of Organs Resected According to Patterns of Single and Multivisceral Resection

Resection Patterns	N (%)	Number of Organs Resected	
		Median	IQR
No organs resected or organs weighted 0*	142 (14.1)	0	0–0
Other†	397 (39.4)	2	1–3
Colon, kidney +/− other	259 (25.7)	3	2–4
Colon, kidney, spleen, pancreas +/− other	82 (8.1)	5	4–6
Vascular resection +/− other	117 (11.6)	3	2–4
Pancreaticoduodenectomy +/− other	10 (1.0)	5	4.25–6.75

IQR indicates interquartile range.

*Including 131 patients with no organs resected and 11 patients whose resection score was 0.

†Organs not included in other patterns of resection.

Type of organs resected either individually or as part of a multivisceral resection is shown in Supplementary Table 1, http://links.lww.com/SLA/B213. The most commonly resected organs were kidney (54.8% of patients) and colon or rectum (57.2%), and the combination of kidney and colon was the most common multivisceral resection, performed in 41% of patients. Table 2 shows the median (IQR) number of organs removed according to each single and multivisceral resection. Median operative time was 240 minutes (IQR: 162–331), and there was a significant correlation between resected organ score and operative time (Fig. 1). The median transfusion requirement was one unit of packed red blood cells (IQR: 0–3).

Severe postoperative adverse events (classified as Clavien-Dindo 3 or higher) occurred in 165 patients (16.4%). The most common adverse events were bleeding/hematoma (2.9%), bowel anastomotic leak/fistula (2.6%), and death (1.8%) (Table 3). Reoperation was required in 106 patients (10.5%). Cumulative mortality at 30, 60, and 90 days from surgery was 1.8%, 2.9%, and 4.1%, respectively (data not shown).

On univariate logistic analysis (Table 4, left panel), the probability of suffering a severe postoperative adverse event increased significantly with age (Fig. 2A; $P = 0.003$) and resected organ score (Fig. 2B; $P = 0.042$). To estimate the adverse event risk in the elderly, we used a cut-off of 65 years as defined by the WHO. The odds ratio of a severe adverse event in patients 65 years of age or older compared to those under 65 was 1.50 (95% CI: 1.06–2.13; $P = 0.031$). A significant association was also detected between severe adverse events and pattern of resection (Fig. 3; $P = 0.042$). Three of the patterns of resection studied were associated with an increased risk of severe adverse events: pancreaticoduodenectomy, vascular resection, and the combination of colon, kidney, spleen, and pancreas

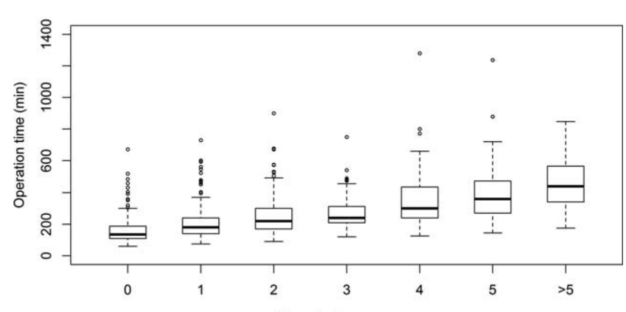

FIGURE 1. Box-plots of operative time according to resected organ score.

TABLE 3. Type and Incidence of All Severe Complications (Clavien-Dindo ≥3) Within 30 Days of Surgery

	N	%
Postoperative bleeding/hematoma	29	2.9
Bowel anastomotic leak/bowel fistula/gastric fistula	26	2.6
Death	18	1.8
Abscess	17	1.7
Respiratory failure/pneumonia/pneumothorax/pleural effusion	14	1.4
Wound infection/wound healing complications	11	1.1
Bowel obstruction/ileus	10	1.0
Sepsis	10	1.0
Dehiscence/evisceration	9	0.9
Abdominal/retroperitoneal collection	8	0.8
Chylous fistula/lymphatic collection	8	0.8
Pancreatic leak/fistula/pancreatitis	8	0.8
Renal failure	7	0.7
Cardiac ischemia/infarct/failure	5	0.5
Bile leak/fistula	4	0.4
Urine leak	4	0.4
Venous thromboembolism	4	0.4
Others	45	4.5
Patients with severe postoperative adverse event (s)	165	16.4

(OR > 1.5). Severe adverse events were independent of tumor size ($P = 0.354$) but were significantly correlated with transfusion requirements ($P < 0.001$). Administration of preoperative chemotherapy ($P = 0.201$) or pre- and/or intraoperative radiation ($P = 0.997$) did not increase the risk of postoperative adverse events. On multivariate logistic analysis, age ($P = 0.012$), transfusion requirements ($P < 0.001$), and resected organ score ($P = 0.007$) were significant predictors of severe adverse events (Table 4, right panel). In the alternative multivariate model including pattern of resection instead of resected organ score, the former did not achieve statistical significance (Supplementary Table 3, http://links.lww.com/SLA/B213; $P = 0.082$).

Five and 10-year OS was 68.1% (95% CI: 64.8%–71.5%) and 46.7% (95% CI: 40.5%–53.8%), respectively. CCI of LR and DM at 5 years was 25.9% and 21.0% (95% CI: 23.1%–29.1% and 18.4%–23.8%), respectively, and at 10 years 35.0% and 21.6% (30.5%–40.1% and 19.0%–24.6%), respectively (data not shown). In multivariate Cox models, there was no impact of postoperative adverse events on overall survival, or on rates of LR and DM (Supplementary Table 2, http://links.lww.com/SLA/B213).

DISCUSSION

RPS remains predominantly a surgical disease. With few effective systemic therapies and no proven survival benefit to radiotherapy, surgical resection represents the only curative therapeutic modality for RPS. Thus, outcomes from RPS remain tightly correlated to quality of surgery. Complete resection has been repeatedly demonstrated to be one of the most important predictors of local recurrence and overall survival from this disease.[9–13] Attempts to elevate the quality of surgery have resulted in many sarcoma centers adopting a policy of more radical resection of the tumor and adjacent organs, with reported improvements in oncologic outcomes.[1,3,4,14] This approach is described in a consensus document from the TARPSWG regarding the preferred surgical management of primary RPS.[15] In this study, we attempt to address the question of whether radical resection entails additional surgical morbidity, and if so, if this is justified by improved oncologic outcomes.

In this series of 1007 patients with primary RPS treated at specialist sarcoma centers, we found that 16.4% suffered a serious complication after surgery (Clavien-Dindo ≥3), 10.5% required reoperation, and 1.8% died within 30 days of surgery. These results compare favorably with historical series of surgery for RPS before the adoption of radical resection, in which morbidity ranged from 8% to 31%, and early postoperative mortality from 0% to 7%.[12,16–19] It should be noted that severity of postoperative complications is not systematically reported in these series, making direct comparison with the current study difficult. In our series, mortality increased

TABLE 4. Results From the Univariate and Multivariate Logistic Models for Severe Complications (Clavien-Dindo ≥3 vs <3)

	Univariate Models			Multivariate Model		
	OR	95% CI	P	OR	95% CI	P
Age, yrs			0.003			0.012
67 vs 48*	1.52	1.20–1.93		1.42	1.11–1.83	
Tumor size, cm			0.354			0.653
30 vs 13*	1.24	0.93–1.67		0.91	0.65–1.28	
Resected organs score			0.042			0.007
4 vs 1*	1.51	1.10–2.07		1. 21	0.85–1.73	
8 vs 0†	4.33	1.96–9.57		3.00	1.24–7.29	
Transfusion requirement (blood units)			<0.001			<0.001
1–3 vs 0	2.74	1.68–4.46		2.56	1.53–4.26	
3+ vs 0	5.80	3.52–9.54		5.59	3.30–9.46	
Unknown vs 0	2.02	0.94–4.37		1.44	0.59–3.55	
Radiotherapy			0.997			0.622
Preintraoperative‡ vs no	1.16	0.74–1.82		1.19	0.73–1.94	
Only postoperative vs no	0.85	0.45–1.57		0.89	0.46–1.74	
Chemotherapy			0.201			0.209
Prepostoperative§ vs no	0.88	0.54–1.44		0.81	0.47–1.38	
Only postoperative vs no	0.16	0.02–1.18		0.19	0.02–1.45	

CI indicates confidence interval; DD LPS, dedifferentiated liposarcoma; FNCLCC, French National Federation of the Centers for the Fight Against Cancer; LMS, leiomyosarcoma; OR, odds ratio; WD LPS, well differentiated liposarcoma.

*Third versus first quartile.

†Maximum versus minimum value.

‡including patients with preoperative, intraoperative, pre- and intraoperative and intra- and postoperative radiotherapy.

§including patients with preoperative or pre- and postoperative CT.

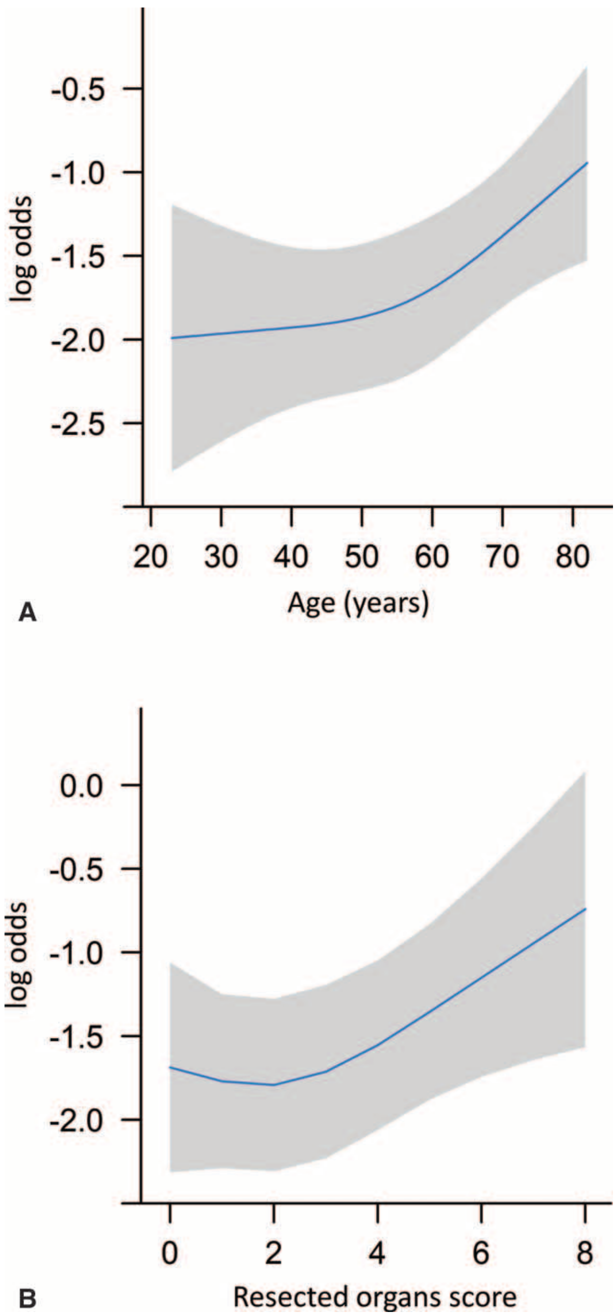

FIGURE 2. Log-odds of severe postoperative adverse event (Clavien-Dindo ≥3) according to age (A) and score of organs resected (B).

from 1.8% at 30 days to 4.1% at 90 days. Although early postoperative deaths are attributable to adverse events, the latter figure represents a combination of surgical morbidity and early disease recurrence.

Lahat et al[20] postulated that radical resection might be warranted for aggressive locally recurrent tumors like dedifferentiated liposarcoma whereas marginal excision might be appropriate for the more indolent well-differentiated liposarcoma. In their comparison of the 2 techniques, marginal excision was associated with 0% mortality and 15.5% morbidity, whereas radical resection entailed 3.9% mortality and 35.1% morbidity. In our series, the morbidity of radical resection more closely approximates that of marginal excision in this historical comparison.

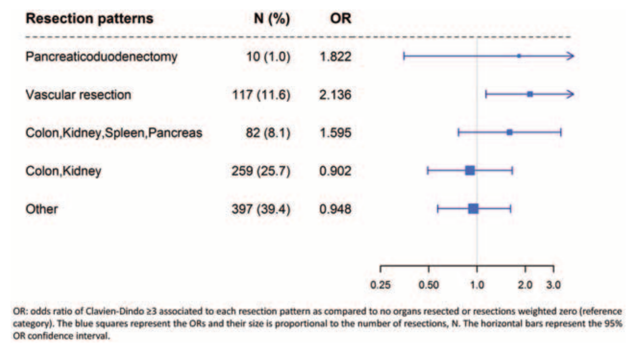

FIGURE 3. Results of univariable logistic model depicting the association between severe adverse events and patterns of resection.

Tseng et al[21] investigated the safety of radical resection using data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). In this study, which was not limited to specialist sarcoma centers, 63% of patients underwent marginal excision and 31% had only one organ resected with the tumor, leaving only 6% of patients having undergone a true multivisceral resection. Results from the entire cohort reveal 1.3% mortality, 26% morbidity, and 11.5% severe morbidity, with no difference between patients undergoing marginal excision and those having radical resection. The current series of patients undergoing radical resection demonstrates lower morbidity and comparable mortality with the ACS-NSQIP reported experience of predominantly marginal excisions.

The combined French-Italian experience of radical resection reported 3% mortality, 18% major morbidity, and a 12% reoperation rate.[4] Smith et al[13] reported a 10-year experience with radical resection in which mortality at 30, 60, and 90 days was 1.4%, 1.9%, and 3.0%, respectively. Severe adverse events (Clavien-Dindo ≥3) occurred in 9% of patients and 7.5% required reoperation. These results closely approximate the findings of the current, larger collaborative study.

In comparison to the existing literature, our results indicate that there is no additional morbidity or mortality associated with extended resection of RPS, but rather that short-term surgical outcomes are comparable to, and in some cases better than, historical and contemporary series of less radical resections. Although advances in surgical technique and perioperative care may be partially responsible for these improved outcomes, the majority of the above-described literature has been published within the last decade, and is thus representative of the modern era. A more probable explanation lies in the fact that the current series of patients were treated at sarcoma referral centers with extensive experience in the surgical management of RPS.

In this series we found that age, transfusion requirements, and resected organ score were significant predictors of postoperative severe adverse events. Elderly patients (≥65) had a 1.5-fold risk of severe adverse events compared with younger patients. This should nuance the preoperative discussion but it does not represent a prohibitive risk and in fact lends support to aggressive surgical management of older patients. The association of blood transfusion with postoperative complications is undoubtedly multifactorial. Intraoperative or early postoperative transfusion may be an indicator of a technically challenging procedure with a heightened risk of adverse events unrelated to blood loss itself. Alternatively, requirement for transfusion may result from major hemorrhage in which associated hypotension and development of hematomas predispose to other adverse events. As might be expected, morbidity increases with complexity of resection, as seen in the association of weighted organ score with severe adverse events, as well as the identification of higher risk resections including those involving pancreatectomy and splenectomy, major vascular resection, and pancreaticoduodenectomy. This is consistent with Bonvalot et al,[4] who identified in a smaller cohort of patients a threshold of 3 organs as the point above which severe adverse events were more likely. As the above described higher risk resections represent only 21% of the current series, most patterns of radical resection were in fact equivalent in terms of operative risk. Resections known to entail higher morbidity should be undertaken only after thoughtful consideration of the relative risks involved in achieving local control in the context of the overall tumor extent and anticipated disease biology.[22]

Importantly, preoperative treatment with chemo- or radiotherapy did not increase operative risk. The EORTC STRASS trial that is currently underway will shed further light on the specific impact of neoadjuvant radiation on operative morbidity in a randomized, controlled setting.[23] The second interim safety analysis has been conducted and did not show any increase in morbidity associated with preoperative radiotherapy.[24]

This is the first study to investigate the potential impact of postoperative complications on long-term oncologic outcomes. In this patient cohort, we found no association between surgical morbidity and local or systemic failure, or OS. Thus, although avoidance of surgical morbidity is of great importance from a patient quality of life perspective, we can be reassured that there is no oncologic penalty to be paid for postoperative complications.

We have previously reported OS and LR/DM data from this large, international experience of RPS, suggesting that treatment of RPS by specialist multidisciplinary teams is associated with improved oncologic outcomes. Although subject to all of the limitations of a retrospective study, we can now confirm the safety of a radical surgical approach when carried out within the context of a specialist sarcoma center. As surgery remains the mainstay of curative-intent treatment for RPS and complex multivisceral resection is frequently required, referral of these patients to specialist centers is strongly advocated.

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