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ORIGINAL ARTICLE – SARCOMA

Has the Outcome for Patients Who Undergo Resection of Primary Retroperitoneal Sarcoma Changed Over Time? A Study of Time Trends During the Past 15 years

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ABSTRACT

Background. This study aimed to investigate changes in treatment strategy and outcome for patients with primary retroperitoneal sarcoma (RPS) undergoing resection at referral centers during a recent period.

Methods. The study enrolled consecutive adult patients with primary non-metastatic RPS who underwent resection with curative intent between 2002 and 2017 at 10 referral centers. The patients were grouped into three periods according to date of surgery: t1 (2002–2006), t2 (2007–2011), and t3 (2012–2017). Five-year overall survival (OS), disease-specific survival (DSS), and crude cumulative incidence (CCI) of local recurrence (LR) and distant metastasis (DM) were calculated. Multivariable analyses for OS and DSS were performed.

Results. The study included 1942 patients. The median follow-up period after resection varied from 130 months (interquartile range [IQR], 124–141 months) in t1 to 37 months (IQR, 35–39 months) in t3. The 5-year OS was 61.2% (95% confidence interval [CI], 56.4–66.3%) in t1, 67.0% (95 CI, 63.2–71.0%) in t2, and 71.9% (95% CI, 67.7–76.1%) in t3. The rate of macroscopically incomplete resection (R2) was 7.1% in t1 versus 4.7% in t3 ($p = 0.066$). The median number of resected organs increased over time ($p < 0.001$). In the multivariable analysis resection during t3 was associated with better OS and DSS. The 90-day postoperative mortality improved

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over time (4.3% in t1 to 2.3% in t3; $p = 0.031$). The 5-year CCI of LR and DM did not change significantly over time. **Conclusions.** The long-term survival of patients who underwent resection for primary RPS has increased during the past 15 years. This increased survival is attributable to better patient selection for resection, quality of surgery, and perioperative patient management.

During the past two decades, efforts have been made to refine and standardize the management of patients with retroperitoneal sarcoma (RPS). Some centers have adopted a more extended approach to resection, reporting favorable results in terms of local control and survival.[1–4] An international collaborative, now known as the Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG), was formed in 2013 with the aim of promoting optimal care of patients with RPS through cooperative study. These efforts culminated in the development of a consensus paper that defined the principles of primary RPS treatment, aligning the views of different institutions.[5] The current study aimed to explore whether, in light of these advances, any changes have occurred in the management and outcome of patients with primary RPS resected at referral centers during the past 15 years.

METHODS

This series included all consecutive adult patients (age, $\geq$ 16 years) with primary (nonrecurrent), non-metastatic RPS who underwent surgery with curative intent between January 2002 and April 2017 at one of the following referral centers:

- Mount Sinai Hospital/Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada
- Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA
- Royal Marsden NHS Foundation Trust, London, UK
- Institut Gustave Roussy, Villejuif, France
- Institut Bergoniè, Bordeaux, France
- Institut Curie, Paris, France
- The Netherlands Cancer Institute, Amsterdam, The Netherlands
- Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
- Leiden University Medical Center, Leiden, The Netherlands
- Maria Sklodowska-Curie Institute-Oncology Center, Warsaw, Poland

The study excluded patients with a diagnosis of Ewing's family sarcoma, alveolar or embryonal rhabdomyosarcoma, gastrointestinal stromal tumor, desmoid-type fibromatosis, or gynecologic sarcoma. Data were retrieved from prospectively maintained databases in place at each participating institution.

Tumor margins were classified as macroscopically complete (R0/R1) or macroscopically incomplete (R2). The number of resected organs was defined according to the resected organ score previously described.[6] Multifocality was defined as multiple discontiguous foci of tumor separated by normal tissue, as judged by the operating surgeon. Tumor rupture was defined as disruption of the tumor pseudocapsule with any spillage of tumor or necrotic material from the mass into the abdomen.

Histologically, tumors were classified according to World Health Organization (WHO) criteria into the seven following groups: well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), leiomyosarcoma (LMS), malignant peripheral nerve sheath tumor (MPNST), solitary fibrous tumor (SFT), undifferentiated pleomorphic sarcoma (UPS), and other.[7] The Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) criteria (grades 1, 2, and 3) were applied for tumor grading.[8] When the biopsy and resected specimen tumor grades were discordant, the higher grade was recorded.

Radiotherapy (RTx), chemotherapy (CTx), or both were administered as per multidisciplinary consultation and discussion at the individual centers or as part of clinical trials. After surgery, the patients were followed up with clinical examination and computed tomography (CT) scan of the chest, abdomen, and pelvis every 4–6 months for the first 5 years, then yearly thereafter. This study was approved by local institutional review boards.

Statistical Analysis

The patients were grouped into three periods according to the date of resection: t1 (January 2002 to December 2006), t2 (January 2007 to December 2011), and t3 (January 2012 to April 2017). The main study outcomes were overall survival (OS), disease-specific survival (DSS), local recurrence (LR), and distant metastasis (DM). The study defined OS as the time between surgery and death from any cause and DSS as the time between surgery and death due to sarcoma, which included complications of sarcoma treatment. Time was censored at the date of the last follow-up visit for the patients who remained alive.

Using the Kaplan–Meier method, OS and DSS curves were estimated, then compared using the log-rank test. The OS and DSS curves were trimmed at 100 patients at risk. Multivariable analysis for OS and DSS was performed using a Cox regression model. An additional multivariable Cox

model was fitted, including interaction terms between histology and time period, to investigate whether the prognostic effect of time period on OS varied according to histology, with adjustment for other prognostic characteristics.

Results are reported in terms of hazard ratio (HR), corresponding 95% confidence interval (CI), and p value by the Wald test.

All covariates were modeled as categorical using dummy variables. Crude cumulative incidence (CCI) curves of LR and DM were calculated in a competing risks framework. Time was calculated as the interval between surgery and the event date and censored at the date of the last follow-up visit for event-free patients.

In the analysis of LR, deaths without evidence of disease recurrence and DM, whichever occurred first, were regarded as competing events. Also, in the analysis of DM, death without evidence of disease recurrence and LR, whichever occurred first, were regarded as competing events. The patients with concomitant LR and DM were included in the DM curves. Patients undergoing R2 resection were excluded from the LR analysis. The Gray test was used to compare CCI curves.[9] The LR and DM curves were trimmed at 50 patients at risk.

To adjust for different baseline tumor and patient characteristics among the three periods, we stratified the patients into five equal-sized risk subgroups using the Sarculator prognostic nomogram for primary RPS (www.sarculator.com).[10] To address the difference in the median follow-up time between the three periods further, we calculated 3- and 5-year estimates for the current study because these were not included in the original nomogram. For each risk subgroup, the average probability of survival predicted by Sarculator was plotted against the observed survival as calculated by the Kaplan–Meier method, yielding calibration plots for each period.

Analyses were performed using R version 3.3.2 software (Institute for Statistics and Mathematics of Wirtschaftsuniversität (WU), Wien, Austria: The R Project for Statistical Computing. https://www.rproject.org/).[11] All p values lower than 0.05 (two-sided) were considered statistically significant.

RESULTS

The 1942 patients in this study underwent surgery for primary RPS with curative intent from 2002 to 2017 at the 10 participating institutions. The clinicopathologic characteristics of the patient cohort are shown in Table 1. A trend of increased patient age over time was not significant. In terms of tumor characteristics, t3 had proportionally more DDLPS (46.8% in t3 vs 39.3% in t1) and fewer WDLPS, more high-grade tumors (29.6% in t3 vs 25.3% in t1) and fewer multifocal tumors (4.4% in t3 vs 10.5% in t1). Regarding treatment-related covariates, in t3, we observed fewer tumor ruptures (3.3% in t3 vs 7.1% in t1) and a higher number of organs resected per case (median, 3 resected organs in t3 vs 2 in t1). Also in t3, the rates were lower for R2 resection (4.7% in t3 vs 7.1% in t1; $p = 0.066$) and 90-day mortality (2.3% in t3 vs 4.3% in t1; $p = 0.031$). Over time, we observed a decline in postoperative radiotherapy administration (0.4% in t3 vs 10.5% in t1; $p < 0.001$), a decrease in pre- and/or postoperative treatment with chemotherapy (12.5% in t3 vs 17.6% in t1; $p = 0.008$), and a slight increase in receipt of preoperative radiotherapy.

OS and DSS

By the end of the follow-up period, 216 patients in the t1 group, 244 patients in the t2 group, and 180 patients in the t3 group had died, including 40, 34, and 32 patients, respectively, who died without evidence of LR or DM. Kaplan–Meier curves for OS are depicted in Fig. 1A. Unadjusted OS 5 years after resection was calculated to be 61.2% (95% CI, 56.4–66.3%) in t1, 67.0% (95% CI, 63.2–71.0%) in t2, and 71.9% (95% CI, 67.7–76.1%) in t3, representing a significant increase over time ($p < 0.001$).

In the multivariable analysis of potential prognostic variables, younger patient age, female gender, smaller tumor size, lower tumor grade, macroscopically complete resection, absence of multifocality, radiotherapy administration, lack of chemotherapy administration, and resection during a more recent period all were significantly associated with a better OS (Table 2). A multivariable OS model including the same variables, except for chemotherapy and radiotherapy, showed no significant interaction between histology and time period (not shown), indicating that the survival improvement observed over time did not vary according to histologic subtype, after adjustment for other patient and tumor characteristics.

To explore the relative contributions made by various factors to the OS difference observed across the three periods, we ran two sensitivity analyses. The first analysis excluded the patients who underwent R2 resection (Fig. 2a), and the second analysis excluded the patients who died within 90 days after surgery (Fig. 2b). In both cases, OS remained significantly higher in t3 than in t1.

To compensate for the significant differences in baseline patient and tumor characteristics among the three periods, we stratified the patients from each period into five prognostic subgroups using a validated nomogram as described. We then compared the observed and predicted survival rates for each subgroup and for each period. The resulting calibration plots for 3-, 5-, and 7-year survival are shown in Fig. S1. In the majority of the risk-stratified subgroups, the patients who underwent resection in t3 had a better observed survival than the patients who had resection

TABLE 1 Demographic, clinical, and pathologic characteristics of the series stratified by period

	t1 (2002–2006) *n* (%)	t2 (2007–2011) *n* (%)	t3 (2012–2017) *n* (%)	*p* value
n	392	606	944	
Median follow-up period: months (IQR)	130 (124–141)	93 (90–96)	37 (35–39)	< 0.001
Median patient age: years (IQR)	58 (48–70)	60 (50–71)	62 (52–69)	0.106
Gender				
Male	205 (52.3)	302 (49.8)	497 (52.6)	0.538
Female	187 (47.7)	304 (50.2)	447 (47.4)	
Median tumor size: cm (IQR)	20.5 (13.0–30.0)	21.0 (12.9–30.0)	21.0 (14.0–30.0)	0.461
Histologic subtype				
WDLPS	100 (25.5)	156 (25.7)	190 (20.1)	< 0.001
DDLPS	154 (39.3)	233 (38.4)	442 (46.8)	
LMS	66 (16.8)	124 (20.5)	162 (17.2)	
MPNST	19 (4.8)	10 (1.7)	25 (2.6)	
SFT	24 (6.1)	33 (5.4)	48 (5.1)	
UPS	6 (1.5)	16 (2.6)	39 (4.1)	
Other	23 (5.9)	34 (5.6)	38 (4.0)	
FNCLCC grade				
1	132 (33.7)	203 (33.5)	249 (26.4)	0.048
2	147 (37.5)	219 (36.1)	359 (38.0)	
3	99 (25.3)	157 (25.9)	279 (29.6)	
NA	14 (3.6)	27 (4.5)	57 (6.0)	
Multifocality				< 0.001
Yes	41 (10.5)	43 (7.1)	41 (4.4)	
No	336 (85.7)	548 (90.4)	870 (92.1)	
NA	15 (3.8)	15 (2.5)	33 (3.5)	
Tumor rupture				< 0.001
Yes	28 (7.1)	43 (7.1)	31 (3.3)	
No	364 (92.9)	563 (92.9)	913 (96.7)	
Resected organs				< 0.001
Median (IQR)	2 (1–3)	2 (1–4)	3 (2–4)	
None	76 (19.4)	75 (12.4)	74 (7.8)	
Resection margins				0.066
R0/R1	364 (92.9)	582 (96.0)	900 (95.3)	
R2	28 (7.1)	24 (4.0)	44 (4.7)	
90-day mortality	17 (4.3)	28 (4.6)	22 (2.3)	0.031
RTx administration				< 0.001
Postop	41 (10.5)	46 (7.6)	4 (0.4)	
Preop or Intraop	68 (17.3)	168 (27.7)	193 (20.4)	
No	283 (72.2)	392 (64.7)	747 (79.1)	
CTx administration				0.008
Yes	69 (17.6)	106 (17.5)	118 (12.5)	
No	323 (82.4)	500 (82.5)	826 (87.5)	

IQR, interquartile range; WDLPS, well-differentiated liposarcoma; DDLPS, de-differentiated liposarcoma; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; SFT, solitary fibrous tumor; UPS, undifferentiated pleomorphic sarcoma; FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer; NA, R0, complete resection with microscopically negative margins; R1, complete resection with microscopically positive margins; R2, macroscopically incomplete resection; RTx, radiotherapy; CTx, chemotherapy

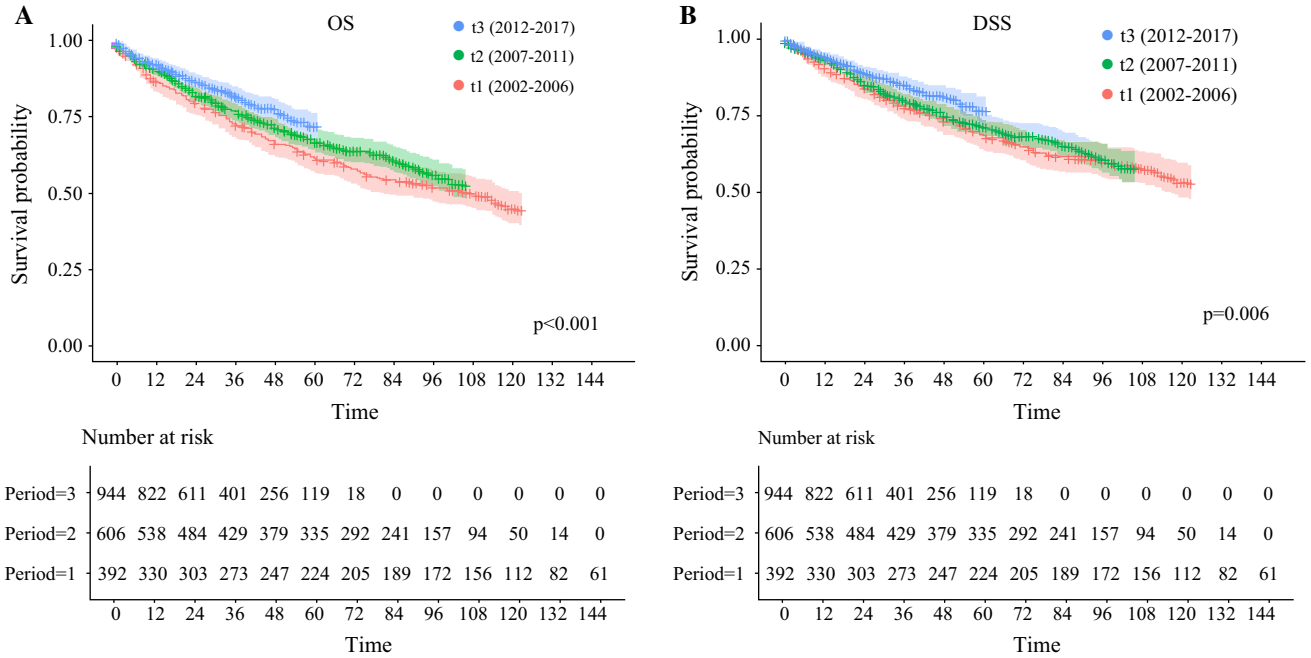

FIG. 1 Survival after resection of primary retroperitoneal sarcoma during three time periods. **a** Overall and **b** disease-specific Kaplan–Meier survival curves according to the period of resection. The 95% confidence intervals are depicted by light-colored shadowing. The curves are trimmed at 100 patients at risk

during t1 or t2. Furthermore, the patients who had resection in t3 had better observed than predicted survival in most of the risk-stratified subgroups, as demonstrated by almost all the point estimates (circles) and Kaplan–Meier 95% CIs (bars) lying well above the diagonal line. By contrast, for the patients resected in t1 and t2, a near-perfect adherence between observed and predicted survival was observed in the majority of the risk-stratified subgroups.

Similar temporal trends were observed with respect to DSS (Fig. 1B). The 5-year DSS was 68.0% (95% CI, 63.3–73.1%) in t1, 71.1% (95% CI, 67.3–75.0%) in t2, and 76.4% (95% CI, 72.4–80.6%) in t3 ($p = 0.006$). In the multivariable analysis, younger patient age, female gender, smaller tumor size, lower tumor grade, macroscopically complete resection, absence of multifocality, radiotherapy administration, lack of chemotherapy administration, and resection during a more recent period all were significantly associated with better DSS (Table 2).

LR and DM

In this study, LR occurred as a first event for 135 patients in t1, 166 patients in t2, and 189 patients t3, and DM occurred as a first event for 60 patients in t1, 100 patients in t2, and 117 patients in t3. Concomitant LR and DM occurred as a first event for 13 patients in t1, 35 patients in t2, and 44 patients in t3. Curves showing the CCI of LR for the three periods are depicted in Fig. 3A. At 5 years, the CCI of LR was 26.8% (95% CI, 22.2–31.5%) for the t1 group, 22.3% (95% CI, 18.7–25.8%) for the t2 group, and 27.6% (95% CI, 23.6–31.6%) for the t3 group ($p = 0.342$). A subgroup analysis showed no significant differences in the CCI of LR over time between histologic subtypes, except for leiomyosarcoma, in which LR was 8.5% in t3 ($n = 61$) compared with. 4.3% in t2 ($n = 124$) and 13.7% in t1 ($n = 158$) ($p = 0.045$).

Curves showing the CCI of DM for the three periods are depicted in Fig. 3B. The 5-year CCI of DM was 18.3% (95% CI, 14.3–22.2%) in t1, 21.5% (95% CI, 18.1–24.9%) in t2, and 21.6% (95% CI, 18.1–25.1%) in t3 ($p = 0.225$). For each of the three periods, OS after relapse was calculated, yielding superimposable curves (Fig. 3C).

DISCUSSION

This study found that 5-year OS after resection of primary RPS at referral centers has improved, from 61.2% for patients who had surgery between 2002 and 2006 (t1) to 71.9% for the 2012 to 2017 period (t3). Similarly, 5-year DSS has improved, from 68.0% in t1 to 76.4% in t3. The improvement in survival has not been accompanied by a corresponding decrease in the occurrence of LR or DM, but has been associated with a decrease in the proportion of patients who underwent resection for multifocal disease and a decrease in R2 resection, as well as an improvement in 90-day postoperative mortality.

Interestingly, the patients who underwent resection in t3 had less favorable baseline characteristics in terms of age (median age, 62 years in t3 vs 58 years in t1), histology

TABLE 2 Multivariable Cox model analysis of overall survival and disease-specific survival

	Overall survival			Disease-specific survival		
	HR	95% CI	*p* value	HR	95% CI	*p* value[a]
Age (years)[b]			< 0.001			0.003
≥ 62 versus < 62	1.55	(1.31–1.83)		1.30	(1.08–1.55)	
Sex			< 0.001			0.030
Male versus female	1.37	(1.16–1.62)		1.25	(1.04–1.50)	
Tumor size (cm)			0.047			0.009
10–20 versus < 10	1.41	(1.00–1.69)		1.48	(1.10–2.01)	
> 20 versus < 10	1.30	(1.06–1.87)		1.65	(1.20–2.28)	
FNCLCC grade			< 0.001			< 0.001
2 versus 1	2.46	(1.65–3.65)		3.25	(2.04–5.15)	
3 versus 1	5.44	(3.62–8.16)		7.46	(4.64–11.99)	
Histologic subtype			0.078			0.124
WDLPS versus SFT	1.04	(0.57–1.89)		1.28	(0.63–2.64)	
DDLPS versus SFT	1.49	(0.90–2.49)		1.74	(0.96–3.18)	
LMS versus SFT	1.72	(1.02–2.90)		2.06	(1.12–3.82)	
MPNST versus SFT	1.73	(0.90–3.32)		1.93	(0.91–4.10)	
UPS versus SFT	1.73	(0.93–3.22)		2.13	(1.05–4.33)	
Other versus SFT	2.09	(1.16–3.78)		2.50	(1.26–5.00)	
Tumor rupture			0.080			0.072
Yes versus no	1.34	(0.97–1.84)		1.37	(0.98–1.93)	
Completeness of resection			< 0.001			< 0.001
R2 versus R0/1	2.24	(1.64–3.07)		2.55	(1.84–3.54)	
Multifocality			< 0.001			< 0.001
Yes versus no	1.56	(1.19–2.04)		1.68	(1.26–2.24)	
Chemotherapy			0.021			0.011
Yes versus no	1.27	(1.03–1.56)		1.33	(1.26–1.66)	
Radiotherapy			0.042			0.013
Yes versus no	0.79	(0.66–0.95)		0.73	(0.58–0.90)	
Period			< 0.001			< 0.001
t1 versus t3	1.68	(1.35–2.10)		1.58	(1.24–2.02)	
t2 versus t3	1.44	(1.17–1.78)		1.48	(1.18–1.89)	

HR, hazard ratio; CI, confidence interval; WDLPS, well-differentiated liposarcoma; SFT, solitary fibrous tumor; DDLPS, dedifferentiated liposarcoma; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; UPS, undifferentiated pleomorphic sarcoma; R2, macroscopically incomplete resection; R0, complete resection with microscopically negative margins; R1, complete resection with microscopically positive margins

[a]*p* value by the Wald test

[b]The lowest value is the 1st quartile and the highest are the 3rd quartiles of the variable distribution

(more DDLPS and UPS and less WDLPS in t3), and grade (more high-grade tumors in t3). Nevertheless, we observed an absolute increase of 10.7% in 5-year OS between t1 and t3. In the multivariable analysis, resection performed in t1 was associated with worse OS (HR, 1.68) and DSS (HR, 1.58).

The survival of the patients who had surgery during the initial 5-year period (5-year OS, 61%) compared favorably with that for the patients with primary RPS who underwent resection in the 1990s (range of 40% to 60% across major series).[1,12–16] In t3, the 5-year OS of 72% and the 5-year DSS of 76% were higher than the survival rates published for recent series of patients with primary RPS who had surgery at referral centers.[17,18]

A risk-stratified analysis (Fig. S1) showed that the improvement in survival over time was homogeneously distributed in each risk subgroup but more evident for the patients with a lower predicted survival. This is understandable considering the timing of recurrence in RPS. The patient groups with inferior predicted survival comprise

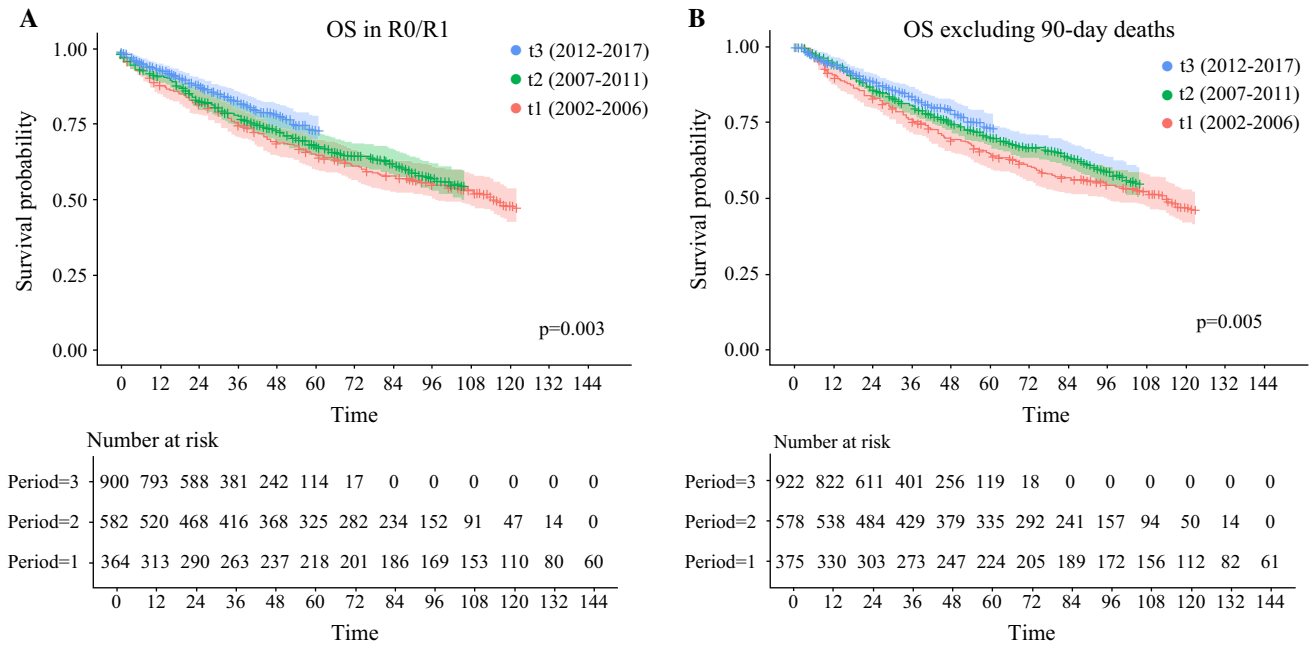

FIG. 2 Sensitivity analysis of overall survival during three time periods. Overall survival curves according to time period of resection are shown, excluding **a** R2 patients and **b** patients who died within 90 days after surgery

those with high-grade DDLPS or high-grade LMS. For both groups, the risk of recurrence is highest in the first few years of follow-up evaluation, then begins to level off. In contrast, the patients with higher predicted survival include mainly those with SFT or WDLPS. The cumulative risk of recurrence for the latter increases slowly but steadily with time. The cumulative risk of recurrence for the latter increased slowly but steadily with time. Therefore, a nomogram with a prediction spanning 3 and 7 years might not be able to exhibit a difference.

Interestingly, the observed survival improvement from t1 to t3 was not associated with any consistent difference in occurrence of LR and DM. Post-relapse survival was similar between t1 and t3, indicating that the change in survival could not be attributed to more effective post-relapse therapies. We performed two sensitivity analyses that excluded the patients who either had R2 resection or had died within 90 days after surgery, and whereas the curves did not separate as much, the difference in survival during the three periods persisted (Fig. 2), indicating that although the drop in R2 rate and the lower 90-day mortality contributed to the survival improvement over time, they did not fully account for it.

In terms of what could account for the improvement, one possibility is that the decrease in the R2 rate and intraoperative tumor rupture may reflect superior quality of resection, whereas the decrease in 90-day mortality may reflect improved perioperative patient care. During the past 15 years, patient pre-habilitation, fast-track protocols, adoption of surgical checklists, and advances in anesthesia and intensive care unit (ICU) care have been associated with a better short-term outcome for other types of cancer surgery and might have played a role for the RPS patients as well.[19–21]

In addition, however, the time-trend in these same parameters also could result from better patient selection. Up to 20% of patients referred to a high-volume center with a primary RPS do not undergo surgery with curative intent.[22,23] The decision to pursue curative-intent surgery is based on technical resectability, tumor biology, and patient factors (comorbidities, performance status).[24] Because the current study did not include patients who were referred to these sarcoma centers during the same period but did not undergo curative-intent surgery, we could not discern whether the improvement in surgical quality outcomes should be primarily attributed to better patient selection or to improved operative and perioperative management. Both likely played a role.

This study also explored changes in resection strategy over time. We observed an increase in the number of organs resected from t1 to t3, but no differences over time in tumor size or proportion of liposarcomas, features that drive the resection strategy.[5,25,26] Therefore, it is likely that the observed increase in the median number of organs

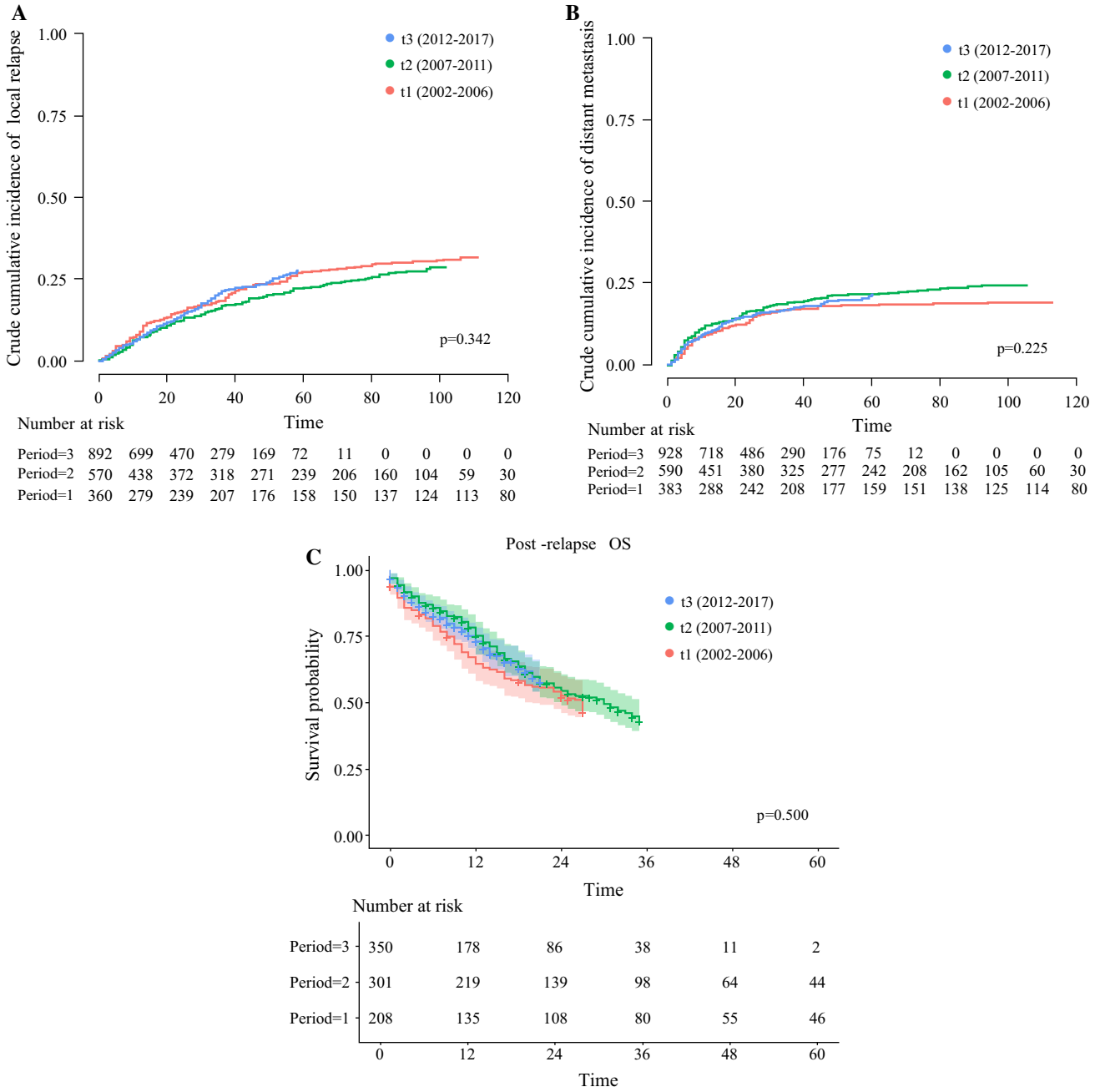

FIG. 3 Local relapse, distant relapse, and post-relapse overall survival (OS) after resection of primary retroperitoneal sarcoma during three time periods. **a** Crude cumulative incidence of local relapse and **b** crude cumulative incidence of distant metastasis according to period of resection are shown as well as **c** post-relapse OS curves according to period of resection

resected genuinely reflects the adoption of a more comprehensive resection approach rather than a different case-mix.

Overall, more patients were treated with preoperative RTx over time, but more important was the dramatic decline in the use of postoperative RTx, from 10.4% in t1 to 0.4% in t3. Both the STRASS (EORTC 62092) trial of preoperative RTx versus surgery alone in primary RPS, which started recruiting in 2012, and the publication of consensus guidelines recommending that if RTx is to be administered it should be done preoperatively rather than postoperatively may have contributed to this shift.[5,27–29]

The size of this series of primary RPS patients, one of the largest in the literature, allowed us to estimate survival differences during three periods using high-quality data collected in prospectively-maintained databases, with

details regarding date and site of recurrence, and use of CTx/RTx, which are typically missing in population-based datasets.

The main limitations of this study were its retrospective design and the shorter follow-up period for the more recent cohort. We mitigated this inevitable bias by comparing survival at time points when at least 100 patients were at risk and by comparing OS in risk-stratified subgroups according to a nomogram adapted to a short (5- and 3-year) prediction window. The results of this study might not apply to low-volume centers, where the majority of primary RPS patients continue to be treated in some jurisdictions despite less favorable outcomes than experienced by patients at high-volume centers.[30]

In conclusion, post-resection 5-year survival was superior for the patients with primary RPS who had resection during a recent 5-year period compared with 10 to 15 years ago in the same group of referral centers. This survival improvement was not linked to a decrease in the rate of sarcoma recurrence, but rather appeared attributable to a combination of better patient selection, better quality of surgery, and better perioperative management.

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REFERENCES

1. Gronchi A, Lo Vullo S, Fiore M, et al. Aggressive surgical policies in a retrospectively reviewed single-institution case series of retroperitoneal soft tissue sarcoma patients. *J Clin Oncol.* 2009;27:24–30.
2. Bonvalot S, Rivoire M, Castaing M, Stoeckle E, Le Cesne A, Blay JY, Laplanche A. Primary retroperitoneal sarcomas: a multivariate analysis of surgical factors associated with local control. *J Clin Oncol.* 2009;27:31–7.
3. Bonvalot S, Miceli R, Berselli M, et al. Aggressive surgery in retroperitoneal soft tissue sarcoma carried out at high-volume centers is safe and is associated with improved local control. *Ann Surg Oncol.* 2010;17:1507–14.
4. Gronchi A, Miceli R, Colombo C, et al. Frontline extended surgery is associated with improved survival in retroperitoneal low- to intermediate-grade soft tissue sarcomas. *Ann Oncol.* 2012;23:1067–73.
5. Trans-Atlantic RPS Working Group. Management of primary retroperitoneal sarcoma (RPS) in the adult: a consensus approach from the Trans-Atlantic RPS Working Group. *Ann Surg Oncol.* 2015;22:256–63.
6. MacNeill AJ, Gronchi A, Miceli R, et al. Postoperative morbidity after radical resection of primary retroperitoneal sarcoma: a report from the Transatlantic RPS Working Group. *Ann Surg.* 2018;267:959–64.
7. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F. WHO classification of tumours of soft tissue and bone. Lyon: International Agency for Research on Cancer; 2013.
8. Trojani M, Contesso G, Coindre JM, et al. Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. *Int J Cancer.* 1984;33:37–42.
9. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat.* 1988;16:1141–54.
10. Gronchi A, Miceli R, Shurell E, et al. Outcome prediction in primary resected retroperitoneal soft tissue sarcoma: histology-specific overall survival and disease-free survival nomograms built on major sarcoma center data sets. *J Clin Oncol.* 2013;31:1649–55.
11. R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2012. ISBN 3-900051-07-0. Retrieved 31 August 2015 at http://www.R-project.org/.
12. Ferrario T, Karakousis CP. Retroperitoneal sarcomas: grade and survival. *Arch Surg.* 2003;138:248–51.
13. Lewis JJ, Leung D, Woodruff JM, Brennan MF. Retroperitoneal soft tissue sarcoma: analysis of 500 patients treated and followed at a single institution. *Ann Surg.* 1998;228:355–65.
14. Hassan I, Park SZ, Donohue JH, et al. Operative management of primary retroperitoneal sarcomas: a reappraisal of an institutional experience. *Ann Surg.* 2004;239:244–50.
15. Stoeckle E, Coindre JM, Bonvalot S, et al. Prognostic factors in retroperitoneal sarcoma: a multivariate analysis of a series of 165 patients of the French Cancer Center Federation Sarcoma Group. *Cancer.* 2001;92:359–68.
16. van Dalen T, Plooij JM, van Coevorden F, et al. Long-term prognosis of primary retroperitoneal soft tissue sarcoma. *Eur J Surg Oncol.* 2007;33:234–8.
17. Tan MC, Brennan MF, Kuk D, et al. Histology-based classification predicts pattern of recurrence and improves risk stratification in primary retroperitoneal sarcoma. *Ann Surg.* 2016;263:593–600.
18. Gronchi A, Strauss DC, Miceli R, et al. 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. *Ann Surg.* 2015;263:1002–9.
19. Trépanier M, Minnella EM, Paradis T, et al. Improved disease-free survival after prehabilitation for colorectal cancer surgery. *Ann Surg.* 2019;270:493–501.
20. Mayer EK, Sevdalis N, Rout S, et al. Surgical checklist implementation project: the impact of variable WHO checklist compliance on risk-adjusted clinical outcomes after national implementation: a longitudinal study. *Ann Surg.* 2016;263:58–63.
21. Visioni A, Shah R, Gabriel E, Attwood K, Kukar M, Nurkin S. Enhanced recovery after surgery for noncolorectal surgery? A systematic review and meta-analysis of major abdominal surgery. *Ann Surg.* 2018;267:57–65.
22. Maurice MJ, Yih JM, Ammori JB, Abouassaly R. Predictors of surgical quality for retroperitoneal sarcoma: volume matters. *J Surg Oncol.* 2017;116:766–74.
23. Ng D. Why were non-metastatic primary retroperitoneal sarcomas not resected? Connective tissue oncology society 2018 annual meeting.
24. Ng D, Swallow CJ. Decision-making for palliative versus curative-intent treatment of retroperitoneal sarcoma (RPS). *Chin Clin Oncol.* 2018;7:40.
25. Bonvalot S, Raut CP, Pollock RE, et al. Technical considerations in surgery for retroperitoneal sarcomas: position paper from E-Surge, a master class in sarcoma surgery, and EORTC-STBSG. *Ann Surg Oncol.* 2012;19:2981–91.
26. Casali PG, Abecassis N, Aro HT, et al. Gastrointestinal stromal tumours: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment, and follow-up. *Ann Oncol.* 2018;29:iv267.
27. Bonvalot S, Gronchi A, Le Péchoux C, et al. Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS):

amulticentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2020;21(10):1366–1377.
28. Bonvalot S, Gaignard E, Stoeckle E, et al. Survival benefit of the surgical management of retroperitoneal sarcoma in a reference center: a nationwide study of the French Sarcoma Group from the NetSarc database. *Ann Surg Oncol.* 2019;26:2286–93.
29. Keung EZ, Chiang YJ, Cormier JN, Torres KE, Hunt KK, Feig BW, Roland CL. Treatment at low-volume hospitals is associated with reduced short-term and long-term outcomes for patients with retroperitoneal sarcoma. *Cancer.* 2018;124:4495–503.
30. Adam MA, Moris D, Behrens S, et al. Hospital volume threshold for the treatment of retroperitoneal sarcoma. *Anticancer Res.* 2019;39:2007–14.