Surgical morbidity in retroperitoneal sarcoma resection

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Resection of retroperitoneal sarcoma (RPS) typically involves multivisceral resection. The morbidity of RPS resection has decreased over time despite widespread adoption of radical resection. Certain patterns of resection are associated with higher complication rates and elderly patients are at increased risk of morbidity. Administration of preoperative radiotherapy does not increase morbidity, but intraoperative and brachytherapy techniques are associated with heightened toxicities. Long-term functional outcomes and quality of life scores after RPS resection are acceptable.

KEYWORDS
adverse events, mortality, quality of life, radical resection, retroperitoneal sarcoma

1 INTRODUCTION

Surgery is the mainstay of curative-intent treatment for retroperitoneal sarcoma (RPS). Given that these tumors typically grow to a considerable size prior to detection and can often involve multiple organs, definitive surgery frequently requires a complex, multivisceral resection. In order to devise tailored treatment strategies for individual patients and to counsel them accordingly, sarcoma surgeons must be able to appreciate the anticipated morbidity of a proposed procedure. The literature surrounding the short- and long-term outcomes following resection of RPS is scant and limited by considerable heterogeneity in patient populations and surgical approach. Accepting these limitations, the data available to guide decision-making are reviewed here.

2 EXTENT OF SURGERY AND SHORT-TERM MORBIDITY

Over the past decade, there has been a paradigm shift toward a radical surgical approach to RPS. In 2009, two European centers published data suggesting improved oncologic outcomes with liberal en bloc resection of organs adhering to, but not necessarily invaded by, RPS.1,2 Gronchi et al reported significantly reduced local recurrence rates with radical resection compared to an historical cohort who underwent marginal excision at the same institution. With longer follow-up, this improvement in local control was found to be associated with improved overall survival.3 The evolution toward more radical resection generated debate regarding the expectation of increased operative morbidity and whether this might offset or even negate any oncologic benefit.4,5

This question was investigated by the Transatlantic Retroperitoneal Sarcoma Working Group (TARPSWG), an international collaboration of sarcoma centers. The eight founding centers pooled their contemporary 10-year data to generate the largest reported experience of RPS resection to date.6 A total of 1007 patients underwent resection for primary, localized RPS from 2002 to 2011. All centers ascribed to a radical resection philosophy, with a median of two organs resected. The 30-day mortality rate in this series was 1.8%, with 16.4% of patients suffering a major complication (Clavien-Dindo ≥3) and 10.5% requiring reoperation. The most common adverse events were
bleeding/hematoma (2.9%), gastrointestinal (GI) anastomotic leak (2.6%), and death (1.8%). A resected organ score was devised to account for differential morbidity in organ resection. Organs were weighted according to anticipated morbidity, with pancreaticoduodenectomy assigned a higher score than nephrectomy, for example, and organs whose resection were felt to confer no added morbidity such as the appendix were weighted zero. Resected organ score was a significant predictor of morbidity, as were age >65 and transfusion requirements. This study also compared common patterns of multivisceral resection and found that those involving pancreaticoduodenectomy, vascular resection, and the combination of colon, kidney, spleen, and pancreas were associated with severe adverse events. Administration of preoperative chemo- or radio-therapy was not associated with increased post-operative morbidity, indicating that these patients can be safely treated with multimodal therapy as appropriate without impacting on the surgical strategy. Importantly, this study also demonstrated no impact of adverse events on overall survival and rates of local recurrence and distant metastases, suggesting that there is no oncologic penalty to be paid for operative morbidity.

The TARPSWG experience represents the largest series of RPS to report on operative morbidity and has the advantage of granular operative details not available in other series. It also reflects outcomes in the modern era, with advances in surgical techniques and perioperative care compared to historical series.

Three TARPSWG centers have reported separately on their short-term post-operative outcomes, with some overlap between these series and the above described collaborative data. The French and Italian sarcoma centers who published the initial series of radical resections reported their combined morbidity data to demonstrate the safety of their novel surgical approach. In this cohort of early radical resections for primary RPS, 30-day mortality was 3%, major complications (CTCAE ≥3) occurred in 18%, and 12% required reoperation. Most common complications were GI anastomotic leak (5.2%), abscess (4%), and bleeding (2.4%). Post-operative morbidity was found to increase significantly with resection of more than three organs (HR 2.75, 95% CI, 1.32-5.74; P = 0.007). Resection of stomach, small bowel (predominantly duodenum), and major vessels were associated with significantly higher rates of adverse events. The slightly better short-term post-operative outcomes seen in the TARPSWG collaborative data likely reflects the learning curve achieved once radical resection became the standard approach at these institutions.

A slightly later series of 362 resections for primary RPS at the Royal Marsden Hospital from 2005 to 2014 reported 30-, 60-, and 90-day mortality of 1.4%, 1.9%, and 3.0%, respectively, severe morbidity (Clavien-Dindo ≥3) of 9%, and a 7.5% reoperation rate. While these results compare favorably to the early experience with radical resection, it should be noted that only 81% of patients underwent multivisceral resection.

Three small series of RPS resections in the pre-radical resection era report on short-term safety outcomes. Ninety-seven patients underwent surgery for primary RPS at the Mayo Clinic between 1983 and 1995. Only 22.7% of patients had more than one organ resected. In-hospital mortality was 2%, 8% suffered major complications, and 6% underwent reoperation. Van Dalen et al report on a sample of 143 patients from the Dutch national database who underwent surgery for primary RPS between 1989 and 1994. Operative details are not provided but only 63% of patients underwent complete resection (RO/R1), as compared to 93% in the French-Italian series and 95% in the TARPSWG experience. Mortality at 30 days in the Dutch population study was 4%. A single institution study from Heidelberg reported on 110 patients who underwent resection for RPS between 1988 and 2002. This series included both primary (N = 71) and recurrent (N = 39) RPS. Extent of surgery is not reported but complete resection was achieved in 70.4% of primary RPS and 61.5% of recurrent tumors. Mortality at 30 days was 6.4%, with no difference between primary RPS and recurrent disease (7.0% vs 5.1%, P = 1.0). Morbidity was not stratified by severity, but overall complication rate was 26%, again with no difference between resection for primary vs recurrent RPS (24% vs 31%, P = 0.41). The sizeable Memorial Sloan Kettering Cancer Center database includes 278 patients who underwent surgery for primary RPS between 1982 and 1997, of whom 77% had at least one organ resected. Mortality in this population was 4% at 30 days. These historical series all report higher early post-operative mortality rates than contemporary data, despite the fact that these patients for the most part underwent more conservative operations.

A more recent study compared alternative surgical approaches based on histologic subtype. A total of 135 patients underwent resection of either primary or recurrent retroperitoneal liposarcoma at MD Anderson Cancer Center from 1996 to 2007, with a more radical surgical approach adopted for dedifferentiated liposarcoma (DD LPS) than for well-differentiated liposarcoma (WD LPS). The majority (53.4%) of WD LPS was marginally resected without contiguous organs, while 71.4% of procedures for DD LPS involved visceral resection. Mortality and morbidity in the WD LPS group was 0% and 15.5%, respectively, compared to 3.9% and 35.1%, respectively, in the DD LPS group. Morbidity was not stratified according to severity of adverse events.

Given the rarity of RPS as well as the complexity and multidisciplinary nature of its treatment, it is recommended that these patients be managed within specialist sarcoma centers. The above described published series reflect outcomes from such referral centers. In contrast, Tseng et al reported on resection of retroperitoneal tumors analyzed from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database, representing 255 participating hospitals including both community and academic centers. A total of 156 patients underwent resection of retroperitoneal tumors. Of these, the vast majority (63%) were marginally resected, with only 37% of patients undergoing contiguous organ resection and only 6.4% undergoing multivisceral resection. In this series of predominantly conservative resections, 30-day mortality was 1.3%, severe morbidity 22.5%, and reoperation rate 4.5%.
3 | EFFECT OF RADIOTHERAPY ON OPERATIVE MORBIDITY

The role of radiotherapy (RT) in the multimodal treatment of RPS is extrapolated from literature in extremity soft tissue sarcoma demonstrating reduced rates of local failure and a corresponding survival benefit. The evidence in support of RT in the retroperitoneum is less robust, with no level one data to confirm improved local control compared to surgery alone.15 The EORTC STRASS trial is a randomized controlled trial undertaken to address this area of persistent clinical equipoise.16 While the final trial results remain outstanding, the safety of preoperative external beam radiotherapy (EBRT) in the treatment of RPS has been confirmed on interim safety analysis, with no increased adverse events after resection of irradiated RPS.17

Given the technical challenges of delivering large target volumes while minimizing toxicity to adjacent radiosensitive viscera, many investigators have hypothesized that intraoperative radiotherapy (IORT) might have a role in the treatment of RPS. Two prospective trials demonstrated promising results with respect to local control, but raised concerns regarding increased morbidity with this technique. Sindelar et al18 identified high rates of peripheral neuropathy among patients receiving IORT, and Dziewirski et al19 reported a 2% rate of early postoperative mortality and a 21.5% reoperation rate. Chronic complications occurred in 21% with an additional 2% late mortality as a result. Recently published data from The Johns Hopkins School of Medicine analyzed outcomes with IORT in 113 patients with abdominalpelvic malignancies, of which 44% were sarcomas.20 The majority of RPS were recurrent (68%) and the patients who received IORT were carefully selected on the basis of a perceived high risk of positive margins following EBRT and radical resection. Severe post-operative complications (Clavien-Dindo ≥3) occurred in 34% of patients. Similarly, an ongoing phase I/II trial of preoperative intensity-modulated radiotherapy (IMRT) followed by IORT and radical resection reported an unplanned interim safety analysis in 2014 in which 33% suffered major morbidity, 15% required reoperation, and post-operative mortality was 7%, albeit beyond 30 days.21 In both of these recent series, the morbidity following preoperative EBRT+IORT is twice that seen in the TARPSWG experience with radical resection+/− EBRT.

Smith et al reported the long-term results of a phase II trial adding postoperative brachytherapy to preoperative EBRT and found no benefit in terms of local control but prohibitive toxicities.22 Treatment-related mortality was 7.5% at 18 months median follow-up, and severe late toxicities (RTOG grade ≥3) persisted in 11% of alive patients beyond this time point. Specifically, duodenal stricture was a serious complication in patients treated with brachytherapy in the upper abdomen.

Based on these available data, a consensus document from the TARPSWG stipulated that preoperative EBRT may be considered as a neoadjuvant strategy for well-selected patients within experienced centers.23 IORT may be considered if a specific margin is considered at risk, although from a practical point of view the field often is too large for its application, and it is considered to be of no study-proven value. Finally, postoperative RT is discouraged due to excessive morbidity and the improbability of achieving a therapeutic dose.

4 | LONG-TERM MORBIDITY FOLLOWING RESECTION OF RPS

4.1 | Renal function following nephrectomy

The long-term sequelae of RPS resection, especially those involving contiguous organ resection, have not been extensively studied. As survival improves to a median of 67% at 5 years for all subtypes and more than 80% at 10 years for WD LPS,24 the long-term disability related to disease management is of increasing concern. In particular, the risk of renal failure following nephrectomy has prompted some centers to advocate for kidney-sparing resections.

A retrospective analysis of long-term renal function after RPS resection with nephrectomy has been reported in a series of 54 patients operated on at Massachusetts General Hospital.25 Median eGFR decreased from 85 mL/min to a nadir of 44 mL/min postoperatively, but partially recovered to 62 mL/min at a median follow up of 50 months. When stratified according to Chronic Kidney Disease (CKD) stage, 51% of patients with preoperative CKD stage 1-2 (normal to mildly reduced renal function) progressed to stage 3 (moderate renal function, eGFR 30-59 mL/min). Independent risk factors for progression of CKD stage were age and preoperative eGFR, even after adjusting for age at surgery. Notably, no patients developed end-stage renal disease or required dialysis. In this series, seven patients received postoperative chemotherapy, either in the adjuvant setting or for subsequent recurrence. Of these seven patients, five experienced further progression in CKD class after chemotherapy. Despite this they were able to receive a variety of systemic therapies, including nephrotoxic agents like ifosfamide.

These results are similar to those reported in the Royal Marsden Hospital experience, in which 113 patients who underwent nephrectomy as part of their RPS resection were followed with respect to renal function.8 The median preoperative eGFR of 89.2 mL/min declined to a nadir of 46 mL/min post-operatively but later rebounded to 58.1 mL/min at a median follow-up of 20.2 months. As in the Massachusetts General Hospital cohort, approximately half (49%) of patients with stage 1-2 CKD progressed to stage 3. One patient progressed to stage 4 CKD and one to stage 5, the latter requiring temporary dialysis. All patients with stage 3 CKD preoperatively remained in this class.

Renal function after multivisceral resection for RPS was also documented by the Milan group in a retrospective analysis of 95 long-term survivors.26 Nephrectomy was performed in 67% of cases. After nephrectomy, creatinine concentration was within 1.5 times the upper reference limit in 91% of patients both at 4 months after surgery and at a distant time point (median 49 months). In multivariable analysis, adjusting for patient age and baseline levels, creatinine did not differ between patient who underwent nephrectomy and those who did not.

4.2 | Pain, function, and quality of life

Callegaro et al reported long-term functional and quality of life (QOL) outcomes after radical resection of RPS.26 Among surviving
patients, 76% reported having suffered some degree of neuropathy involving the lower limb and/or groin. Sensory disturbances were persistent in 62% of patients at the time of survey completion (median 49 months after surgery). This long-term change occurred more frequently in patients who underwent complete or partial resection of the psoas muscle (93%) than in those who had only the psoas fascia resected (53%). Patients with complete psoas resection also demonstrated reduced motor function in the lower limb as assessed by the Lower Extremity Function Scale (LEFS). Similarly, reduced LEFS scores were seen in patients who experienced severe early postoperative complications (Clavien-Dindo ≥3). Sexual dysfunction was reported as loss of libido by 31% of patients, dyspareunia in 22% of woman, erectile dysfunction and retrograde ejaculation in 27% and 9% of men, respectively.

Chronic pain after surgery was investigated by the Brief Pain Inventory (BPI). The mean value for average pain within the previous 24 h was 2.0 on a 0-10 scale. Pain scores of at least five were reported by 21% of interviewed patients. Legs were the most common site of pain (39%), followed by abdomen and back (30%). Pain interference with daily activities was overall low in patients who reported mild pain in the previous 24 h (score 1-4). In patients with moderate to severe pain, interference with daily activities was seen mainly in general activity, mood, walking, and ability to work.

The limited available data regarding function and QOL are all retrospective in nature. The above described data are further limited by the lack of baseline evaluations of function and QOL scores. Prospectively-collected QOL metrics are awaited from the EORTC STRASS trial, and additional prospective studies addressing QOL are ongoing.

The only available QOL data prospectively collected at baseline in primary RPS patients proceeding to surgery were recently presented by Fiore et al.27 Sixty consecutive patients were enrolled of whom 25% received neoadjuvant treatment (7 radiotherapy, 6 chemotherapy, 2 chemo + radiotherapy). Prior to surgery, Global Health Status (GHS) scores were evaluated by the EORTC QLQ-C30, on a scale from 0 to 100. The median score was 58.3/100 (interquartile range, 41.7-70.8). Overall, GHS scores did not differ significantly from EORTC QLQ-30 reference values for all cancer patients when stratified for gender and age. Median scores for most QLQ symptoms were zero, with the exception of fatigue, insomnia, pain, and urinary symptoms. Pain was reported by 68% of patients at baseline. Interestingly, functional impairment and neuropathic pain in the lower limb were also documented before surgery: 50% of patients reported neuropathic symptoms and median LEFS score was 65.5/80 (IQR 45.5-76.25). This value may not be significantly different from the LEFS value of 60 reported by Callegaro et al in operated patients at distant follow up. The possibility that postoperative lower limb dysfunction could be partially attributed to the tumor itself requires further investigation. Mean pain intensity within the 24 h before surgery was overall mild, although 17% of patients reported severe pain scores requiring daily analgesics.

5 | SURGERY FOR RPS IN THE ELDERLY

Given the extent of surgery required for complete resection of RPS and the above described operative risks, careful preoperative assessment is required to ensure that patients are suitable candidates and are optimized for the procedure. Advanced age is of concern in undertaking any major abdominal operation and the elderly deserve particular attention in discussion of surgery for RPS.

In the Royal Marsden Hospital series of RPS resections from 2005 to 2014, the only significant predictor of 30-day mortality was age >75.8 This prompted further investigation into decision-making regarding surgery for RPS in the elderly, as well as outcomes in this population. Smith et al reported a significantly higher rate of non-operative management for RPS in patients >65 (41.8% vs 12.0%, P < 0.001) despite similar rates of unresectable tumors as compared to younger patients.28 This disparity was attributed to comorbidities and patient preference. Elderly patients who did undergo surgery suffered significantly higher rates of post-operative complications than patients <65 (28.3% vs 9.5%, P < 0.001), although mortality was the same. Importantly, oncologic outcomes were nonetheless equivalent between the two groups. Similarly, the TARPSWG collaboration identified age >65 as a significant prognostic factor for postoperative morbidity (OR 1.50, 95% CI 1.06-2.13; P = 0.031) and concluded that patients must not be excluded from consideration for RPS resection on the basis of age alone, but that the increased risks associated with advanced age warrant specific patient counselling.

An attempt to risk-stratify patients undergoing resection for RPS using the modified frailty index (mfi) was recently reported by Park et al.29 Using data from the ACS-NSQIP database, RPS patients were found to have low mfi scores (ie, few comorbidities). Select mfi scores were associated with severe morbidity but did not predict 30-day mortality. Overall this was not shown to be a robust tool for the RPS population.

6 | SURGERY FOR RECURRENT RPS

To date, radical multivisceral resection has only been shown to be of value in primary RPS. Decision-making regarding resection of recurrent RPS is complex and multifactorial. When appropriate, the goal of surgery is complete resection (RO/1), with contiguous organs removed only as necessary.30 Despite re-resection, post-relapse outcomes are poor, with the vast majority of patients developing further recurrence.24 For this reason, decisions regarding resection of recurrent disease must carefully weigh anticipated morbidity against the perceived benefit, taking into account that the probability of cure is extremely low.

Data regarding morbidity of resection for recurrent RPS are extremely scant. In the Heidelberg series, there was no difference in morbidity and mortality for primary versus recurrent RPS, although differences in surgical approach are not described.11
CONCLUSIONS

The usual large size of RPS at presentation in combination with the anatomic constraints of the retroperitoneum typically necessitate complex multivisceral resection to achieve negative margins. In order to accurately assess patients’ operative risk and counsel them accordingly, surgeons must be able to estimate the morbidity of a planned procedure. Operative morbidity associated with resection of RPS has not been evaluated in a systematic, prospective manner but multiple retrospective series over the past two decades have documented an improvement in short-term perioperative outcomes, despite a shift toward more extensive resections. This improvement is undoubtedly multifactorial, attributable in part to advances in surgical technique and perioperative care. It likely also reflects a mature learning curve as radical resection was adopted as the standard approach at specialist centers in the early 2000s. Furthermore, recent data documenting improved operative outcomes reflect increasing regionalization of patients to specialist centers, underscoring the need for referral to high-volume institutions with extensive experience in the management of this disease.

Despite gradual and ongoing improvement in perioperative outcomes, the morbidity and mortality associated with radical resection of RPS remain considerable. Certain patterns of resection are predictably associated with higher risks of post-operative complications, particularly those involving pancreatic and vascular resection. Elderly patients are at increased risk of postoperative morbidity and must be counseled accordingly. Importantly, postoperative complications entail no oncologic penalty in terms of rates of local and distant failure and overall survival.

Long-term functional outcomes following resection of RPS remain poorly understood, although the limited retrospective evidence available appears to demonstrate acceptable morbidity. Renal function following nephrectomy is adequate, with typically only mild impairment of no functional consequence. Subjectively reported rates of sensory disturbance and pain are high and require further investigation, both to document these phenomena prospectively and to investigate surgical techniques that might modify these risks (eg, nerve preservation). Quality of life data are scant but promising.

The systematic and prospective collection of metrics for short- and long-term morbidity, functional outcomes, and QOL should be undertaken by all sarcoma centers in order to achieve an accurate and comprehensive understanding of the impacts of RPS and its treatment. This will require the development or validation of specific instruments for this disease. Simultaneously, sarcoma centers should be continuously refining and improving surgical techniques, actively advancing learning curves, and ensuring the highest quality standards in perioperative management.

CONFLICT OF INTEREST

The authors have no disclosures.

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