Oncological and Clinical Outcomes following Surgery for Retroperitoneal Sarcomas of the Abdomen and Pelvis

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STATEMENT OF ORIGINALITY

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

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Dr Peter J Lee
16th September 2024

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LIST OF PUBLICATIONS ARISING FROM THIS THESIS

1. Peter J Lee, Tae Jun Kim, Lylee Ye, Yu (Sunny) Wu, Daniell Steffens, Sacha Karunaratne, Wendy Brown, Rooshdiya Karim, Peter Grimison, Angela M. Hong. SPARC - A Multi-Disciplinary Team program for Retroperitoneal Sarcoma: The Royal Prince Alfred Hospital and Chris O'Brien Lifehouse Collaboration. Retroperitoneal sarcoma surgery: the importance of a highly specialized institution and multidisciplinary team. ANZ Journal 2024. doi.org/10.1111/ans.19102

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Introduction

Retroperitoneal sarcomas (RPS) are a rare and heterogeneous group of tumours of mesenchymal origin. RPS comprise 15% of all soft tissue sarcomas (1,2). They are potentially malignant and can grow to become very large tumours within the abdomen and pelvis. Therefore, they usually present late with obstructive symptoms and pain. Obstructive symptoms depend on which organ(s) or structure(s) they abut or invade. These organs or structures may include the ureter, bladder, bowel and neurovascular structures. Management of patients with RPS is a challenge especially when they are malignant and involve these vital organs and structures. The therapeutic strategies include surgical resection, radiotherapy and chemotherapy, or a combination of these. The dilemma is which of these is the best modality, or which combination and in what order is optimal, and finally, which tumours in this heterogenous group will respond to such therapies. Additionally, due to the close vicinity of vital retroperitoneal structures and organs, including the spine and bone, an important consideration relates to preservation of quality of life by determining how much can be resected without incurring undue morbidity.

Surgical margins, like for other malignancies, are crucial and determine outcomes such as survival and recurrence. Due to the location of RPS, surgical margins of normal tissue may not be possible due to limitations in the anatomy (3). Therefore, multivisceral resection is advocated for large retroperitoneal sarcomas, especially those with negative prognostic features, such as dedifferentiation in a liposarcoma. In the literature, up to 50% of patients deemed for curative surgery may have an involved surgical margin, be it microscopic (R1) or macroscopic (R2) (4-9). Due to these challenges, local recurrence is a major problem that can influence survival. Rates of local recurrence can be high and range between 40-80%; even with

a clear surgical margin, rates of local recurrence have been reported as high as 50% (10,11). Up to 75% of patients will die with locally recurrent disease (4).

The histopathologic spectrum of sarcomas is broad as they arise from embryonic mesenchymal cells with the ability to mature into striated skeletal and smooth muscle, adipose and fibrous tissue, bone, and cartilage, among other tissues. Hence, sarcomas represent a heterogenous group of connective tissue tumours. Malignant tumours affecting peripheral nerves are included, although ectodermal in origin, because of similarities in their clinical behaviour, management, and outcome. The most common histological subtype of RPS is liposarcoma.

Recurrence can also occur in distant organs and is usually via haematogenous spread predominantly to the lung, though metastatic patterns are also linked to specific sarcoma histology. Spread to regional nodes is infrequent for soft tissue sarcomas.

A number of prognostic factors have been identified in patients with soft tissue sarcoma, the most important of which are histologic grade, tumour size, and pathologic stage at the time of diagnosis. As previously mentioned, local recurrence is a significant prognostic factor influencing survival, and hence the optimal adjunct treatments for RPS need to take these prognostic factors into account. Radiotherapy is the most widely utilized adjunct to surgery with the aim of reducing locoregional recurrence. At present, data supporting the use is limited and the increasing use of radiotherapy for RPS has largely been extrapolated from its established role for soft tissue extremity sarcomas (12,13). A recently published randomized study, EORTC-62092 STRASS I Trial (14), reported no benefit to recurrent disease-free survival with the addition of pre-operative radiotherapy. Novel chemotherapy agents are currently being trialled but more data are required to assess long term outcomes. A

collaboration of EORTC sarcoma units within Europe and non-European centres, including institutions in Australia, Royal Prince Alfred and Chris O'Brien Lifehouse Cancer Centre, have been invited to participate in the EORTC 1809 STRASS II Trial (15). This phase III randomized study will investigate the efficacy of neoadjuvant chemotherapy for dedifferentiated liposarcomas and leiomyosarcomas. In the future, collaborative databases and research should help improve the optimal management strategies for the different subtypes of RPS.

The primary aim of this thesis is to assess the oncological and clinical outcomes following surgery for retroperitoneal sarcomas, focusing on the role of multi-visceral resections, including pelvic exenterations. The secondary aim of this thesis is to assess contemporary rates of positive surgical margins following surgery for RPS, and the impact of these on oncological and clinical outcomes. Internationally, there is growing acceptance that for retroperitoneal sarcomas, especially the large to massive tumours, a microscopic involved margin (R1) and clear margin (R0) should be classified together in the reporting of resection margins, and are thus increasingly reported as such in the literature (3,4,8,10). The is because it is impossible and unfeasible to microscopically assess the large and massive tumours for every margin.

Chapter 1 is a systematic review of the literature summarising outcomes of surgery for RPS, including types of surgical resections performed and their corresponding margin status, influence of these on recurrence and survival, and the morbidity and mortality associated with aggressive, multi-visceral resections. Chapter 2 reports on our experience of the collaboration between the Royal Prince Alfred Hospital and Chris O'Brien Lifehouse Hospital, with the establishment of a formal retroperitoneal sarcoma program built on a centralised referral system and multidisciplinary team approach in the management of RPS. It assesses whether

development of a specialized and specific RPS unit within two high-volume tertiary institutions with appropriate experience and expertise can optimise clinicopathological outcomes and quality of patient care. The multidisciplinary approach includes preoperative assessment with accurate histological diagnosis and imaging investigations, consideration for neoadjuvant therapies, surgical planning, comprehensive reporting of clinicopathological outcomes, and consideration for adjuvant treatment(s). The extent of surgical resections particularly focuses on our experience with multivisceral resections including pelvic exenterations. Chapter 3 is a study assessing the role of a highly specialized surgery in the pelvis, pelvic exenteration, for retroperitoneal sarcomas. This study includes a subset of retroperitoneal sarcomas excised by the pelvic exenteration team at Royal Prince Alfred Hospital, which has utilized their experience with recurrent rectal and advanced cancers to apply the surgical and oncological principles and improve outcomes of this highly specialized pelvic surgery for this group of pelvic sarcomas.

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Chapter 1

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This systematic review was a collaborative effort from the beginning with Dr David Coker, including inception of the study design, literature search, development of the database for data extraction, writing of the initial draft, final analysis, and review of the final draft, prior to submission to the Australian and New Zealand Sarcoma Association Clinical Practice Guidelines Working Party. This review will ultimately be submitted for publication in a peer reviewed journal.

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The results of the systematic review were utilized as a background assessment of the best published international data and results, in particular of multivisceral resections, to compare and contrast the results from the two articles from our institutions (Royal Prince Alfred Hospital and Chris O'Brien Lifehouse Cancer Centre) regarding multivisceral resections (Chapter 2) and pelvic exenteration surgeries (Chapter 3) for retroperitoneal sarcomas.

The effect of multivisceral resection compared with simple resection on survival, recurrence and morbidity outcomes in primary retroperitoneal sarcoma: A systematic review

Introduction

Retroperitoneal sarcomas (RPS) are rare with an annual incidence of 0.5-5 per 100,000 people (1, 2). RPS represent a heterogeneous group of tumours of mesenchymal origin, and comprise 15% of all soft tissue sarcomas. They are potentially malignant and can grow to very large tumours with the abdomen and pelvis. Therefore, they usually present late with obstructive symptoms and pain. Obstructive symptoms depend on which organ or structure it abuts or invades. These organs or structures may include the ureter, bladder, bowel and neural structures. For patients for whom RPS is diagnosed at an earlier stage or at a relatively smaller size, they are usually identified as an incidental finding when investigative imaging is performed for a different clinical scenario, i.e. the RPS is asymptomatic.

Management of patients with RPS is a challenge especially when they are malignant and involve vital organs and structures. The therapeutic strategies include surgical resection, radiotherapy and chemotherapy, or a combination of these. The dilemma is which of these are the best modality, which combination and in which order is the optimal treatment, and which tumours in this heterogenous group will respond to such therapies. Additionally, due to the close vicinity of vital retroperitoneal structures and organs, including the spine and bone, an important consideration relates to how much can be resected without incurring too much morbidity while maintaining daily function and preserving quality of life.

Due to the infiltrative nature of RPS and the proximity to vital organs, local recurrence remains a major management issue (3). Surgery is the mainstay of curative treatment and the extent of resection of RPS remains an area of controversy. There has been a trend toward more extensive surgery over past 15 years, reflecting the limitations of both preoperative imaging, and intraoperative assessment, to accurately discern the histopathological extent of RPS; and recognizing the importance of macroscopically complete resection and maximizing the chances of histologically clear margins (4,5). Multivisceral Resections (MVR) do not have a uniform definition within the literature, which has posed a challenge in this review. However for the purposes of this review it is defined as the resection of adjacent organs abutting the tumour, even in the absence of direct invasion. This would often involve readily resectable organs contiguous with the RPS, most commonly the ipsilateral kidney, colon and psoas fascia or muscle. The varying anatomical involvements, diverse biological behaviours of the various histological subtypes, and patient factors, make complete standardisation of MVR difficult, and therefore the drawing of firm conclusions challenging.

The Australia New Zealand Sarcoma Association (ANZSA) established a multidisciplinary working party to develop a series of clinical practice guidelines to optimise patient care. Whether MVR improves outcomes for patients with primary RPS was identified as a key clinically relevant question. In this systematic review, we aimed to evaluate the impact of MVR on recurrence, survival, and perioperative morbidity in RPS.

Methods

The systematic review utilised the following PICO (population, intervention, comparison, outcome) model:

- **P**opulation: Adult patients with primary localised retroperitoneal sarcoma
- **I**ntervention: Multivisceral resection (including adjacent organs uninvolved on preoperative imaging)
- **C**omparator: Simple surgical resection
- **O**utcomes: Abdominal recurrence free survival, recurrence free survival, overall survival, perioperative morbidity

A literature search was performed in March 2021, and updated in May 2024, across multiple databases including Ovid Medline, Ovid Embase, and Cochrane Central (Wiley), of published studies in the English language meeting inclusion and exclusion criteria (Table 1). The search strategy (Figure 1) was developed after identifying MeSH terms and keywords from key publications on this topic. The literature review management software, Covidence, was utilised to facilitate the conduct of the review (6).

Two independent reviewers screened the identified studies by title and abstract for eligibility according to the PICO model. Any conflicts between reviewers were resolved through discussion with a separate senior reviewer. Following full text review by two independent reviewers to ensure suitability for the systematic review, qualitative and quantitative data extraction was performed, using a custom-designed data extraction template. The quality of each study was assessed by two independent reviewers using the NHMRC Evidence Hierarchy (7), and the Newcastle-Ottawa Quality Assessment Form for Cohort Studies (8).

Results

The PRISMA flow chart (Figure 2), demonstrates the different screening phases of the systematic review. A total of 438 studies were identified from the search strategy, and imported into Covidence for screening. The inter-rater reliability for the title and abstract screening was 88.7% and 89.7% for the full text review. Following screening, a total of 23 retrospective studies were identified addressing the clinical question (Table 2). No prospective studies were identified. The number of patients in the studies ranged from 23 to 1007 patients, with 6 studies including greater than 200 patients. Studies predominantly included patients treated in Europe and North America, with some smaller studies from Asian centres. Regarding evidence quality, when assessed by NHMRC Evidence Hierarchy, fourteen studies were level III-2, and nine were level III-3 (7) (Table 3). The quality of the studies were recorded as good (fourteen studies, 62.5%), fair (two studies) and poor quality (seven studies) according to the Newcastle-Ottawa Quality Assessment Form for Cohort Studies (8) (table 3). The sample size ranged form 56 to 1007 patients. Thirteen studies of the good quality studies were of evidence level of III-2. Gonzalez Lopez et. al. (18) reported a small cohort of 56 patients but scored highly with good quality for all three domains (selection, comparability and outcome). The one study with level III-3 evidence, Smith et. al. (11) included a large sample size of 362 patients and good quality scores for all three domains. Two studies were of fair quality (19, 24), both with level III-3 evidence and patient cohort size of 115 and 33 respectively. The remaining seven studies were of poor quality had sample sizes ranging from 34-571 patients. One study, Turner et al (28), despite a cohort of 102 patients and evidence level III-2 had poor score (of 1) for selection and therefore deemed as poor quality. The other six studies were of evidence level III-3. Schwartz et. Al. (27) reported a sample size of 571 and good scores for selection and outcome domains but had a score of 0 for comparability, thus labelled as poor quality study.

Within the context of the PICO model, and the inherent heterogeneity of MVR definition, the authors have attempted to be inclusive, as opposed to exclusive. Nevertheless, as noted in Table 3, and referenced through the manuscript, there are clearly higher quality papers which are more influential in drawing conclusions with respect to the PICO question.

Abdominal Recurrence Free Survival

Fifteen studies in the systematic review reported on the outcome on abdominal recurrence (9-23). There is significant heterogeneity in nomenclature where the synonymous term of local recurrence was often used. In addition to the heterogeneity of nomenclature, not all studies reported abdominal recurrence outcomes specifically with respect to MVR. Of the 15 studies reporting abdominal (local) recurrence outcomes, only nine reported findings specific to MVR, as are outlined below. Overall, results were conflicting, with respect to the effects of MVR on abdominal recurrence (Table 4).

In the largest study addressing abdominal recurrence, Bonvalot *et al.* (*n*=382) specifically compared compartmental resection, with simple complete resection, and resection of contiguously involved organs (9). The 3-year abdominal recurrence rates were 10% in compartmental resection (MVR), compared with 47% in simple complete resection, and 52% where macroscopically contiguously involved organ resection was performed. On multivariate analysis, there was a 2-fold increase in abdominal recurrence with simple complete resection, as compared to compartmental resection (HR 1.99, 95% CI 1.03-3.84, p=0.04).

Four studies demonstrated that MVR had no statistical significance with respect to abdominal recurrence (10-13). In the largest of these studies, Smith *et al.* (*n*=362), demonstrated that

significant predictors of local recurrence were the grade of the tumour (Grade 1 vs 3) (HR 0.09, 95% CI 0.04-0.20, p<0.001), and positive macroscopic resection margins (R2 vs R0-1) (HR 2.64, 95% CI 1.36-5.14, p=0.004)(11). Keung *et al.* (*n*=119) demonstrated that multifocal disease and R2 resection were the only independent predictors of shorter local recurrence free survival (LRFS) on multivariate analysis (HR 1.89, 95% CI 1.1-3.23, p=0.021)(12). Singer *et al.* (*n*=144), found that contiguous organ resection was associated with increased local recurrence on multivariate analysis (HR 1.70, 95% CI 1.02-2.80, p=0.04)(14). Within their multivariate analysis, the most powerful predictor of local recurrence was dedifferentiated histopathology (HR 3.6, 95% CI 2.2-6.0, p<0.0001).

Three studies examined the effect of specific organ resections, as part of MVR on abdominal recurrence (15-17). Kim *et al.* reported the outcomes of 86 patients with primary RPS abutting the pancreas (15). Resection of the distal pancreas was not associated with any difference in local recurrence. In a subgroup analysis, within those patients undergoing distal pancreatectomy, Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) histologic grade (HR 4.57, 95% CI 1.37-15.42, p=0.014) and microscopic pancreatic invasion (HR 3.23, 95% CI 1.13-9.25, p=0.029) were significant predictors of local recurrence on multivariate analysis. R2 resection was significant for local recurrence on univariate analysis, with a trend towards this outcome on multivariate analysis (HR 3.65, 95% CI 0.89-15.09, p=0.073). Cho *et al.* (*n*=114), found a trend towards en-bloc nephrectomy being associated with lower rates of local recurrence, as compared with no nephrectomy. In sub-group analysis for those patients with FNCLCC Grade 2 tumours, there was a statistically significant benefit to en-bloc nephrectomy (p=0.048), though significance was not reached for patients with Grade 1 and Grade 3 tumours (16). It should be noted however, that numbers of patients with Grade 3 tumours, were low in this cohort, with a total of only eleven patients. Spolverato *et al.* (*n*=24),

demonstrated that major vascular resection was significantly associated with higher rates of local recurrence as compared to a propensity matched cohort of RPS patients who did not undergo vascular resection (45% [95% CI 22-68] versus 24% [95% CI 3-43], p=0.05)(17).

Recurrence Free Survival

Eleven studies reported varying recurrence free survival (RFS) outcome measures, including disease free survival (DFS) and distant recurrence free survival (DRFS) (5, 10-14, 17-20, 27). Of these 11 studies that reported recurrence free survival outcomes, only 6 studies reported specific MVR outcomes. Keung *et al.* found in their cohort of 119 patients with dedifferentiated liposarcoma (DDLPS) that MVR was not predictive of distant recurrence free survival. Rather, R0/R1 resection was a significant predictor of distant recurrence free survival, compared to R2 resection (HR 3.18, 95% CI 1.32-7.64, p=0.010)(12). When only the 80% of patients in that cohort with R0/R1 resection were sub-analysed, intact tumour specimen resection was a significant predictor of DRFS, compared with fragmented tumour resection (HR 3.93, 95% CI 1.92-8.05, p<0.001). Lopez *et al.* (*n*=56), reported en-bloc resection to have significantly improved DFS as compared to enucleation, defined as removal of the tumour within its pseudocapsule, and therefore analogous to simple resection (p<0.01); though they did not quantify this improvement in DFS further within the paper (18).

Abdelfatah *et al.* (*n*=115), found that it was only once five or more organs were resected that the risk of overall recurrence was significantly elevated (HR 17.8, 95% CI 3.77-84.5, p<0.001)(19). Of note only eight patients had five or more organs resected in this series. Other significant predictors of disease recurrence were R1 margins as compared to R0, size (>15cm), and leiomyosarcoma or histology other than liposarcoma. Schwartz *et al.* (*n*=571), found on multivariate analysis that larger en-bloc resections (3-4 organs compared with 0 organs) were

predictive of shorter DFS (HR 1.56, 95% CI 1.03-2.37, p=0.04) (27). Other variables predictive of shorter DFS were high-grade tumours (HR 2.66, 95% CI 1.88-3.77, p<0.01) and node-positive disease (HR 2.08, 95% CI 1.22-3.52, p<0.01). MVR was found to have no significant effect on DFS in two papers (10, 20).

Overall Survival

Twenty of the 23 studies reported survival outcomes (Table 2). The majority of studies reported overall survival (OS) and median survival (in months), whilst only in a few studies reported on disease-specific survival (DSS). Overall, there is conflicting evidence as to the effect of MVR on OS and DSS.

The study by Bonvalot *et al.* (*n*=382) was regarded as the study with the greatest power to address this PICO question for a multitude reasons including, the numbers in the cohort, that it considered all relevant histopathology and was assessed to be of high quality (Table 3)(9). In this paper, the authors were able to retrospectively compare simple resection, resection of contiguously involved organs, and compartmental resection (defined as a systematic resection of uninvolved contiguous organs performed to obtain a rim of normal tissue surrounding the tumour). The type of resection was not a prognostic factor for OS (compartmental resection versus simple complete resection, HR 0.62, 95% CI 0.34-1.13, p=0.11). Similarly, compartmental resection compared with resection of contiguously involved organs was not predictive of OS (HR 0.87, 95% CI 0.54-1.41, p=0.57). In the multivariate analysis, independent predictive factors associated with shorter OS were high grade tumours, tumour rupture, gross residual disease, and positive margins. Complete resection was a statistically significant prognostic factor for longer OS (HR 1.7 for R1 resection vs R0 resection, 95% CI 1.07-2.72, p=0.03). A further seven studies demonstrated non-statistically significant results with respect to MVR and survival outcomes (5, 9-11, 18, 25, 28). In four of these studies,

positive resection margin and higher tumour grade were both significant predictors of worse OS (9, 11, 24, 27).

A small but good quality study, by Morizawa *et al.* (*n*=23), suggests OS benefit of MVR compared to simple resection (26). demonstrated in multivariate analysis that simple resection, as opposed to extended resection encompassing the tumour and adjacent organs, was predictive of shorter OS (HR 3.80, 95% CI 1.25-16.59. p<0.04).

Two studies focused on liposarcoma of the retroperitoneum only and found an inferior association with DSS and OS, when MVR was compared to simple resection (12, 14). Singer *et al.* (*n*=177), demonstrated that contiguous organ resection (excluding nephrectomy), compared to no contiguous organ resection, was associated with a decreased DSS (HR 1.9, 95% CI 1.01-3.5, p=0.05)(14). Margin status (i.e. macroscopic [R2] versus negative [R0]), however, was a stronger predictor of DSS (HR 3.8, 95% CI 2.0-7.4, p<0.0001); and similarly, DDLPS was associated with significantly worse DSS when compared to well differentiated liposarcoma (HR 6.0, 95% CI 3.3-10.9, p<0.0001). In a study specifically looking at DDLPS (*n*=119), Keung *et al.* demonstrated on univariate analysis that in patients with an R0/R1 resection, there was a statistically significant difference in median OS where fewer than two organs were resected compared to resection of two or more (74.3 months, 95% CI 42.9-79.8, vs 59.3 months, 95% CI 40.8-91.3, p=0.045)(12). However, on multivariate analysis this was not independently prognostic. Furthermore, on multivariate analysis there were no statistically significant factors with respect to OS within the cohort, who had macroscopically resected DDLPS.

Three studies stratified the number of organs resected, or the types of organs resected (11, 17, 19). Abdelfatah *et al.* (*n*=115), demonstrated a statistically significant increased risk of death, where five or more organs were resected, albeit in a total of only eight cases (7% of the cohort), as compared to no organs resected (HR 6.25, p=0.005)(19). However, this was not significant for 1-2 or 3-4 organs resected. Smith *et al.* (*n*=362), showed an increased risk of death where three or more organs were resected on univariate analysis (HR 4.11, p<0.001), however this did not reach significance on multivariate analysis, with only higher tumour grade associated with shorter OS (11). In a propensity-matched analysis of 24 patients, vascular resection was associated with shortened OS (HR 5.17, 95% CI 1.41-18.99, p=0.013)(17).

Four studies reported the effects of specific organ resections and survival outcomes (14-17). Cho *et al.* (*n*=114), found no difference in 5-year cancer-specific survival (CSS) when comparing patients who underwent nephrectomy as part of their resection with those patients that did not undergo nephrectomy (75% vs 71%) (16). However, on subgroup analysis there was a trend towards better CSS where nephrectomy was performed for FNCLCC grade 2 tumours (p=0.077). Those patients undergoing nephrectomy, had a statistically significant increase in contiguous organ resections (35 cases with nephrectomy [53%] vs 11 cases without nephrectomy [22%], p=0.002); and were significantly more likely to have a liposarcoma as opposed to another histology (p<0.001). No difference in disease-specific survival was seen when nephrectomy was analysed by Singer *et al.*(14). Kim *et al.* (*n*=88), reported the effect of distal pancreatectomy and found no statistically significant effect on OS (15). Patients who underwent distal pancreatectomy were more likely to have DDLPS, and a higher number of contiguous organs resected (3.8±0.9 vs 1.0±0.9, p<0.001). Spolverato *et al.* found a similar trend towards a higher number of contiguous organs resected in those patients undergoing vascular resection (p=0.089), though in this series, no trend was observed towards any specific histopathology (17).

Perioperative Morbidity

Thirteen publications identified in the systematic review, reported perioperative morbidity outcomes (5, 9, 12, 15-18, 20, 22, 23, 25, 30, 31). Of these 13 studies, eight reported perioperative morbidity outcomes that compared MVR with simple resection, and are discussed below. These included the three largest retrospective cohorts within the systematic review (5,25,30). MacNeill *et al.* reported the largest cohort with 1,007 patients from the TARPSWG collaboration (25). Perioperative morbidity was reported using the Clavien-Dindo classification, and a unique 'weighted organ score' was developed in recognition that resection of some organs or structures entails an inherent higher risk of morbidity; and would therefore more accurately represent anticipated morbidity. Patterns of resection were categorised, to enable further standardisation and analysis. Severe postoperative complications occurred in 16.4% of patients in the cohort, with 10.5% requiring reoperation, and a 1.8% mortality within 30 days of surgery. On multivariate analysis, the resected organ score was a significant predictor of severe adverse events when a score of 8 was compared with 0 (OR 3.00, 95% CI 1.24-7.29, p=0.007); it was not significant when a score of 4 was compared with 1 (OR 1.21, 95% CI 0.85-1.73). When patterns of resection were analysed, no pattern reached statistical significance. In a separate analysis, using the same TARPSWG cohort of patients, Gronchi *et al.* reported no difference in postoperative morbidity and mortality when comparing different extents of resection across major European and North American centres (5).

There are two large cohorts derived from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) that focus on postoperative morbidity (30, 31). Tseng *et al.* (*n*=156) analysed the ACS-NSQIP data from 2005 to 2007, and compared contiguous organ resection with no contiguous organ resection (31). They reported no

difference in overall morbidity (p=0.7), severe morbidity (Clavien-Dindo classification grade 3 or higher) (p=0.79), and mortality (p=1.0) when contiguous organ resection was performed, as compared to simple resection. Multivariate analysis similarly found no difference where contiguous organ resection was compared to simple resection in either overall morbidity (OR 1.38, 95% CI 0.49-3.89, p=0.54), or severe morbidity (OR 0.78, 95% CI 0.05-13.18, p=0.86). Judge *et al.* performed a similar study using a larger cohort (*n*=564, 233 MVR) of ACS-NSQIP data from 2012-2015 (30). On multivariate analysis, there was no difference in overall morbidity (OR 0.72, 95% CI 0.38-2.36, p=0.31), or severe morbidity (OR 1.18, 95% CI 0.55-2.52, p=0.67) when MVR was performed compared to simple surgical resection.

Of the remaining publications reporting morbidity outcomes, Ikoma *et al.* (*n*=83) observed that simple resection was significantly associated with Clavien-Dindo classification grade 3 or higher complication, when compared with MVR (OR 0.11, 95% CI 0.02-0.58, p=0.01) (20). Postoperative complications occurred in 26% where organ resection occurred, versus 4% where no organ resection occurred.

With respect to specific organ resections, Cho *et al.* (*n*=114), demonstrated that nephrectomy was associated with a significant decrease in postoperative renal function (acute kidney injury in nephrectomy cohort 52%, versus no nephrectomy cohort 4%, p<0.001). There was no difference between the two groups in terms of decline of long term renal adaptation, where ultimate GFR was reduced to less than 60% of preoperative GFR (nephrectomy cohort 25%, versus no nephrectomy cohort 10%, p=0.086) (16). Distal pancreatectomy was not associated with significant difference in terms of complications and severe complications (15). In contrast, vascular resection was associated with an increase in severe complications (54% vs 25%, p=0.002)(17).

Discussion

There are challenges within this review of multi-visceral resections due to the variations and non-standardized techniques in surgery, the anatomical variations, and the biological diversity of histology and tumour grade leading to different patterns of tumour behaviour.

The definition of multi-visceral resection itself is not universal and somewhat controversial. However, the surgical principle of a single en-bloc resection with adjacent organs and structures has been adopted over the last two decades to achieve the highest probability of a clear surgical margin (32,36). Bonvalot (9) defined resections as simple, contiguously involved organ resection, and complete compartmental resection. The difference between the latter two multi-visceral resections is that complete compartment resection is a more extensive and aggressive resection which includes organs that are not macroscopically involved.

There is growing consensus and recommendation from leading international institutions that the extent of resection should be tailored to the biological behaviour of the retroperitoneal sarcoma in terms of its propensity for local and distant recurrence, as well as its histological type and grade (5,32,33,34). The histological type and grade are posited to have a far greater impact with respect to distant recurrence and therefore overall survival, than the extent of surgery. For low to intermediate grade RPS with a lower risk of distant recurrence as compared to local recurrence, MVR should be considered to reduce abdominal recurrence as the review suggests that MVR appears to improve histologic margins, which would correlate with improved local recurrence free survival (9). Ultimately, where surgery offers the only chance of cure, an aggressive approach to resectable disease should be considered.

The retroperitoneum is a large area encompassing many vital structures and organs of the abdomen and pelvis where the primary tumour can arise. The organs and structures can be

significantly different according to which side of the body the tumour arises. Hence, the numerous sites other than arising from a specific organ include the soft tissues of the hypochondrium, iliac fossa, psoas muscle, mesentery and can extend from or to the region below the inguinal ligament and lower limb. This leads to the vast differences in what an en-bloc resection involves.

Retroperitoneal sarcomas are rare and due to the different histological subtypes within a category, for example the different subtypes for a liposarcoma (well differentiated, de-differentiated, pleomorphic, myxoid), and the biological variations in behaviour, there are further challenges in comparing outcomes and drawing recommendations from the available literature. Furthermore, there are patient factors that require consideration. Quality of life by preserving function for the patient is crucial in the decision making and planning of surgery, and hence "tailoring of surgery" is an important patient factor that could lead to compromise of surgical margins (e.g. preserving superior mesenteric vessels may lead to R1 margin, but the alternative, R0, may lead to short bowel syndrome with life-long total parental feeding or even death). Finally, performing a randomized controlled trial would be ideal in terms of robustness of evidence and to draw solid conclusions, but tremendously impractical and for the most part unfeasible due to the forementioned challenges in diversity and specificity.

Survival

Overall survival and disease-free survival were reported in twenty studies (table 2). The key factors that influenced survival were tumour subtype and grade, surgical resection margin, extent of disease (i.e. number of organs involved) and integrity of tumour maintained with delivery of the specimen (i.e. no tumour rupture intra-operatively). Extent of surgical resection did not convey a favourable overall survival outcome.

Margin Status

Surgical margin is a significant factor that influences disease recurrence. The influence of surgical margin on survival is contentious with R1 resection margin. A macroscopic involved margin (R2) was a significant negative prognostic indicator for overall survival or disease specific survival in five studies (table 6). Morizawa (26) compared R1-2 with R0 status and showed no difference in overall survival in the two groups (HR: 3.35; 95% CI: 0.42 to 26.90, p=0.26). This was a small cohort study (n=23) and the R1 status was significantly higher with 17 patients (R0=4, R2=2). Interesting, the Abdelfatah (19) showed no difference in median survival when R1 and R0 were compared. Therefore, in Morizawa's study, if the R1 was classified and survival calculated with R0 (rather than R2), would the survival show a difference. Furthermore, the study demonstrated in multivariate analysis that simple resection, as opposed to extended resection encompassing the tumour and adjacent organs, were predictive of decreased OS (HR 3.80, 95% CI 1.25-16.59). This means that if eleven out of the seventeen R1 patients did not have an extended resection then they would most likely would have had an R2 resection thus lead to worse OS.

Extent of surgical resection

The principle of extent of surgical resection is to achieve the optimal surgical margin, which is a clear margin (R0) in the aim to improve survival. Four studies (24,26,29,37) demonstrated improved survival with extended resections compared to simple resections or palliative resections. Unsurprisingly, the more significant outcomes by Wu (29) and Makela (37) ($p=0.008$ and $p<0.0118$ respectively) were shown when the comparison was a palliative resection. Two studies reported worse survival with extended resections.

Conversely, two studies showed worse survival outcomes with more aggressive and multiorgan resections. Singer showed that contiguous organ resection for retroperitoneal liposarcomas compared to no contiguous organ resection, the survival (excluding nephrectomy) was worse (HR: 1.90; 95% CI: 1.01-3.50, p=0.05). Unfortunately, the distribution of histology subtypes for the two groups of resections was not reported but the author concluded that the contiguous organ resection group (except nephrectomy) had an increased risk of local and distant recurrences (11). This would suggest, contiguous organ resections included a higher proportion of the aggressive histology subtype and hence the more extensive operation. Similarly, Abdelfatah (19) showed worse overall survival when multiple organs were resected, the highest risk in the group with five or more organs resected compared to no organ resection (HR:6.25; 95% CI: 1.73 to 22.60, p=0.005). This group was small (8 cases, 7% of cohort). When less than 5 organs were resected, there was no significant difference in survival. Four other studies showed no difference in survival. Smith, with the largest cohort of 362 patients, showed that 2 or more organs resected compared to none resected did not influence disease specific survival (table 3.5.1). Similarly, Cho (n=114) reported on extended resections with nephrectomy versus no nephrectomies and showed no difference in 5-year cancer specific survival (75% vs 71%, p=0.554).

Tumour subtype

Ikoma (20) reported on well differentiated sarcomas and hence a longer median survival whereas Wu (29) included the more aggressive type in the spectrum of liposarcomas, such as dedifferentiated, myxoid/round cell and pleomorphic liposarcoma subtypes. Singer (14) showed a significant difference in disease specific survival when the tumour was well differentiated compared to dedifferentiated tumours (HR: 0.17; 95% CI:0.09 to 0.30, p<0.0001).

Tumour grade

Tumour aggressiveness or tumour grade is an important factor for survival. All eight studies (table 5) reporting on tumour grade and survival outcomes showed worse prognosis with high grade tumours. Three studies (11,14, 29) comparing well differentiated liposarcoma with dedifferentiated liposarcomas showed significantly worse survival in the more aggressive or higher in grade subtypes (dedifferentiated, or grade 2/3). Smith (11) examined the three different grades and reported grade 3 tumours had a significantly worse disease specific survival when compared to grade 1 (HR: 33.33; 95% CI: 8.33 to 100, $p<0.001$) and grade 2 (HR: 3.57; 95% CI: 2.00 to 6.25).

Recurrence

Like survival outcomes (as forementioned), recurrence rates were reviewed in terms of tumour subtype and grade, margin status and extent of surgery.

Tumour Subtype

Tumour type is an important factor that influences different rates of local and distant recurrences. Smith *(*11), reported significant differences in recurrences between liposarcomas both well differentiated and de-differentiated subtypes, and leiomyosarcomas. Leiomyosarcomas showed a significant higher rate of distant disease whereas liposarcomas were most likely to recur locally. Singer (14) showed recurrence for dedifferentiated liposarcomas was significantly higher than well differentiated liposarcoma, both locally and for distant disease.

Tumour Grade

The higher the grade of tumour the more likely for local and distant recurrence (table 7). Bonvolat (9), Turner (28) and Smith (11) showed grade three tumours had the highest chance of local recurrence. Smith also reported higher distant recurrence with grade 3 tumours when compared to grade 1 and 2 separately. Wu showed well differentiated tumours recurred locally later compared to de-differentiated tumours (34.5 vs 17.2 months).

Margin Status

Margin status is a significant prognostic factor for recurrence rates. Four studies (9,11,19,18) that reported resections with involved surgical margins conveyed an increased risk of recurrence. Abdelfatah (19) also showed recurrences occurred earlier when the margin was incomplete. Interestingly, there was no difference in the median recurrence free interval when 1-2 were resected compared to 5 or more organs resected (17.5 and 14.7 months respectively). However, when no organs were resected this increased to 70.1 months but not statistically significant (p=0.0830)

Extent of surgical resection

More extensive surgery reduced the rates of local or distant recurrence. Bonvolat (9) showed compartmental resection, the most aggressive of all resections, lowered recurrence compared to simple complete resections. The 3-year recurrence rate was reduced to 10%, from 50% for standard resections. However, the overall survival rate was not improved by compartmental resection, since further operation(s) were performed for those who developed recurrences following non-compartmental resections (9). Hence, some authors argue against compartmental resections and argue that if R0/R1 could be achieved with similar survival rates then less aggressive surgery should be supported (19).

Patients who underwent surgery for recurrent disease has worse prognosis than primary sarcomas (22,29,37) and more likely to have further recurrences (Rossi, 38).

The fundamental principle and teaching for retroperitoneal sarcoma surgery is to aim for wider margins and hence, an approach of multivisceral resection has been advocated in the pursuit of higher rates of clear margin resections. However, R0 is clearly not the only important factor for survival but tumour biology, subtype and grade must also be included. Hence, surgery should be tailored to all these factors in addition to R0 resection (or R1 at the worst). R0 is crucial for local control and there is some evidence of improved prognosis and reduced rates of recurrence. At the same time, it is just as important that the outcome of surgery also maintains function and thus quality of life. Liposarcomas tend to recur locally (even despite a R0 margin) and the intra-operative challenge is identifying "tumour related fat" to "normal fat". Therefore, some would advocate a more extensive and maximally invasive approach. However, if the tumour abuts the femoral nerve and lumbosacral trunk, then the author would advocate preservation to maintain lower limb function and preserving quality of life over the risk of local recurrence. Similarly, if the tumour lies adjacent to vital structures that cannot be sacrificed, such as the superior mesenteric artery and vein (SMA/V), then there is risk of a positive margin despite complete resection of the tumour. If these vessels were resected for a higher chance of R0 margin, then the patient would suffer with short gut syndrome or could even lead to death due to global small bowel infarction. Likewise, as leiomyosarcomas have a higher risk of distant metastases causing lower survival (16), compartmental surgery may not be the answer to improve survival and thus, surgery should be tailored to maximise outcome including quality of life. Larger tumours, tumour perforation or rupture intra-operatively, surgery at low volume centres or non-specialized sarcoma units, debulking of tumour, vascular invasion and poorly differentiated sarcomas are also factors with worse prognosis (9,17,19).

This review did not include neoadjuvant and post operative therapies due to the confounding bias. In particular, post-operative radiotherapy complicates and makes surgery for recurrence more challenging with increased risk of bleeding, organ injury and iatrogenic bowel perforation. More importantly the STRASS trial (21) did not show a clear benefit in neoadjuvant radiotherapy and the STRASS II trial is currently recruiting (39).

Perioperative morbidity

The systematic review analysis consistently demonstrated that MVR does not increase morbidity in a significant manner. This finding is in keeping with the findings of Bonvalot *et al.* (*n*=249) who looked at compartmental resections in France and Italy, and found an overall rate of 18% severe morbidity (Clavien-Dindo grade 3 or higher) (35). There was a significant effect on the rate of severe complications when more than three organs were resected, as compared with three or fewer organs resected. When considering the most common organs resected (colon, kidney and psoas muscle), none were associated with increase in morbidity. Significantly higher morbidity was seen where major vessels (17) and the stomach were resected. It is well documented that longer operative times leads to higher grade of complications and Tseng supported this finding (31). There was no evidence to suggest that post-operative adverse events negatively affected oncological outcomes, including survival and recurrence.

Concerns regarding perioperative morbidity should not alone be a contraindication to MVR. The oncologic benefit of multivisceral resection should be assessed and balanced against the expected perioperative morbidity in individual patients, within the context of pathology and

technical factors. This discussion is recommended to be performed within the context of an expert multidisciplinary team meeting.

Limitations of the systematic review

Available evidence has several fundamental limitations. Critically, the definition of MVR is not standard, and varies throughout the studies. Secondly, available evidence is entirely retrospective and thus known limitations of retrospective evidence, including selection bias, must be considered. Patient selection, specifically the decision for MVR including resection of adjacent organs versus simple resection, and including whether there was evidence of invasion on preoperative imaging, was not able to be assessed. Ultimately, the overall intent of MVR is not possible to be ascertained with retrospective data and is a major confounder. Prospective data collection through the Trans-Atlantic RetroPeritoneal Sarcoma Working Group (TARPSWG) collaboration will hopefully clarify this question in the future.

Utilization of the results of the systematic review

Definitions and standardization of care for retroperitoneal sarcoma will always be a challenging. This variability is also seen with other surgical disciplines, for example pelvic exenteration surgery, where the definition of what should be included or excluded in the definitions of care are still up for debate in the international literature. Hence systematic reviews and meta-analyses, continue to be a challenge in the delivery of accurate data and results due to the heterogeneity of study inclusions as well as designs.

As such, the systematic review (Chapter 1) included only retrospective evidence. The data and results were of great value to establish our collaboration between the two institutions, allowing the creation of a prospective database of the most important parameters, in particular the extent

of surgery, number of organs involved for both multivisceral retroperitoneal resection and pelvic exenteration. Additionally, quality of life data has been sparse in the literature including the articles in the systematic review. Quality of life prospective data for the patients' undergoing surgery for retroperitoneal sarcomas were therefore included.

Recurrence and survival rates, surgical margins, histopathological grade and subtypes are prospectively included in our institution's database, to contribute to future multi-centre studies in collaboration with the TARPSWG. This will be vital for clarification in determining the best surgical approach for the different subtypes of RPS and thus standardizing the management for RPS.

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Figure 1. Database Search Strategy

1 exp Retroperitoneal Neoplasms/ (9416)

2 exp sarcoma/ (140856)

3 1 and 2 (2419)

4 ((retroperitone* adj3 (sarcoma* or liposarcoma or leiomyosarcoma*)) or rpls).mp. (2186)

5 3 or 4 (3314)

12 (multi-visceral or multivisceral or mvr or extended resection* or compartmental resection* or compartmental surg* or complete resection* or complete surg*).mp. (24136)

13 5 and 12 (312)

14 limit 13 to (english language and yr="1990 -Current") (244)

36 (animal* or rat o rats or swine or mouse or mice or dog or dogs or canine*).mp. (7221056)

37 (case reports or systematic review or editorial).pt. (2892347)

38 (case report* or systematic review*).ti,ab. (590940)

39 35 or 36 or 37 or 38 (10160509)

41 14 not 39 (182)

search updated 25/5/22 to include 2021-current publications as per requirement of c.4. of technical report

**line 12 of Strategy for t2q2 changed on 03/05/23 to: multi-visceral or multivisceral or mvr or extended resection* or compartmental resection* or compartmental surg* or (complete* adj2 resection*) or complete surg*

Figure 2. PRISMA flow diagram of the systematic review.

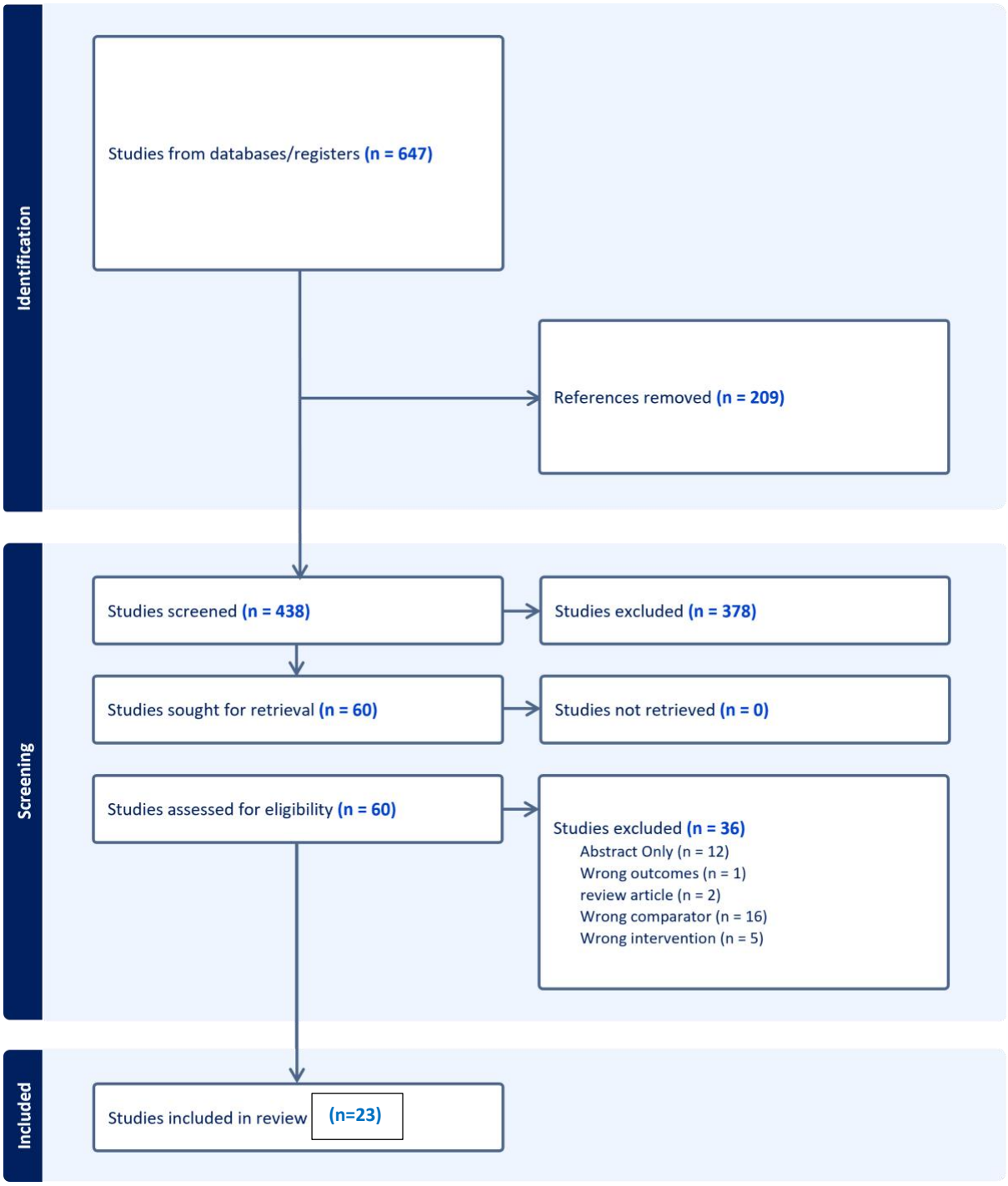

Table 1. Inclusion and exclusion criteria for title and abstract screening

Inclusion criteria	Exclusion criteria
• **P**opulation: Adult patients with primary retroperitoneal sarcoma • **I**ntervention: Multivisceral resection (including adjacent organs uninvolved on preoperative imaging) • **C**omparator: Simple surgical resection • **O**utcomes: Overall survival, abdominal recurrence free survival, recurrence free survival, perioperative morbidity	• Case Reports • Conference Abstract Only • Not Sarcoma • Excluded Sarcoma Type (Kaposi Sarcoma, GIST, Dermatofibrosarcoma protuberans (DFSP), Adenosarcoma, • Carcinosarcoma, Endometrial stromal tumours, Phyllodes tumour, gliosarcoma, uterine sarcoma) • Not Retroperitoneal Sarcoma • Not Relevant to research question • Review

Table 2. List of articles included in the systematic review

	Author, Year	Population	Country	Years	Sample Size	Multivisceral Resection	Recurrence Outcomes	Survival Outcomes	Perioperative Morbidity
1	Abdelfatah, 2016	RPS (primary, unifocal, without sarcomatosis)	USA	1994-2010	115	0 Organs *n*=21 1-2 Organs *n*=59 3-4 Organs *n*=27 >5 Organs *n*=8	Analysis of 87 patients with R0/R1 resection. Median overall recurrence free survival 20.0 months.	Median survival 62.7 months.	Not reported
2	Bonvalot, 2009	Primary RPS	France	1985-2005	382	Compartmental complete resection *n*=120 Simple complete resection *n*=65 Contiguously involved organ resection *n*=130	5-year abdominal recurrence rate 49% 5-year distant recurrence 34%	Median survival 6 years. 5-year OS 59%	85 patients (22%) had CD≥2.
3	Chiappa, 2006	Primary (and recurrent) RPS	Italy	1994-2006	34	Contiguous organ resection *n*=21 Simple resection *n*=7	Analysis of 23 patients with R0/R1 resection. 5-year disease free survival 60%	5-year survival 55%	Significant morbidity in 6 patients (22%)
4	Chiappa, 2018	Primary (and recurrent) RPS	Italy	1994-2015	83	Contiguous organ resection *n*=53 (31/46 with primary RPS)	5-year disease free survival 68% in primary RPS	5-year survival 63%	Significant post-operative complications 20 patients,

									of whom 17 underwent MVR.
5	Cho, 2018	RPS located in the perirenal space or with suspected ureter invasion	Korea	1996-2015	114	Nephrectomy group, underwent en-bloc resection of organs within 1cm of the tumour, and locoregional peritonectomy n=65	Analysis of 84 patients with R0/R1 Figures not reported in paper. No difference between groups.	5-year cancer specific survival, 75% nephrectomy group and 71% no-nephrectomy (simple resection) group	AKI nephrectomy group 52%, versus 4% in no-nephrectomy group. No other morbidity outcomes reported
6	Eroglu, 1999	Primary (and recurrent) RPS	Turkey	1990-1996	33	Simple resection *n*=19 Multivisceral resection *n*=14	Recurrence (local or distant) in 73% Mean disease free survival 18 months.	Median survival 58 months. 5-year survival 49%	Not reported
7	Gronchi, 2016	Primary RPS	Europe and North America	2002-2011	1007	Various resection policies across major European and North American centres, including extended resection.	5-year local recurrence 24% 5-year distant recurrent 21%	5-year overall survival 67%	No statistically significant difference between different extents of resection. Reported in text, no data.
8	Ikoma, 2018	Primary RPS (WDLPS)	USA	1995-2011	83	Concomitant organ resection *n*=38	Analysis of 76 patients, who underwent R0/R1 resection.	Analysis of 76 patients, who underwent R0/R1 resection.	Post-operative complication 26% concomitant organ

							5-year local recurrence rate 38%	5-year overall survival 86%	resection versus 4% no organ resection.
9	Judge, 2019	Primary RPS	USA	2012-2015	564	Multivisceral resection *n*=233	Not reported	Not reported	Severe morbidity (CD≥3) 11% in MVR versus 8% in simple resection.
10	Keung, 2014	Primary RPS (DDLPS)	USA	1998-2008	119	0 organs *n*=7 1 organ *n*=32 2 organs *n*=29 3 organs *n*=13 4 organs *n*=12 5 organs *n*=7 6 organs *n*=9 7 organs *n*=3 Unknown *n*=7	5-year local recurrence free survival *n*=15% 5-year distant recurrence free survival *n*=33%	5-year overall survival 42%	Not reported
11	Kim, 2021	RPS in the left upper quadrant	South Korea	2001-2020	86	Distal pancreatectomy (DP) *n*=33	5-year recurrence free survival 37.5% DP group, versus 39.7% non-DP group (NS)	5-year overall survival 45.8% DP group, versus 59.3% non-DP group (NS)	No difference in morbidity outcomes between groups.

12	Lopez, 2014	RPS	Spain	2000-2010	56	En-bloc resection of the tumour and contact structures	Simple resection median disease free survival 17.3 months En-bloc resection median disease free survival 23.4 months	Simple resection median overall survival 47.9 months En-bloc resection median overall survival 57.3 months	Severe morbidity CD≥3, Simple resection (enucleation) 14.8%, versus en-bloc resection 27.6%
13	MacNeil, 2018	Primary RPS	Europe and North America`	2002-2011	1007	Weighted organ score used to standardise the comparison of procedures	5-year local recurrence 25.9% 5-year distant metastases 21%	5-year overall survival 68!%	Severe complications CD≥3 16.4%
14	Morizawa, 2016	Primary RPS	Japan	2002-2014	23	Extended resection, tumour mass and adjacent organs *n*=14	Not reported	Median overall survival 52 months	Not reported
15	Ng, 2017	Primary (and recurrent) RPS	Singapore	2000-2014	85 (55 primary RPS)	Contiguous organ resection *n*=45	Median disease free survival 21 months	Median overall survival 45 months	Not reported
16	Schwartz, 2019	Primary RPS	USA	2000-2016	571	0 organs resected *n*=140 1-2 organs resected *n*=315 3-4 organs resected *n*=82 ≥5 organs resected *n*=34	Median disease free survival 35.3 months	Median overall survival 81.6 months	Not reported

17	Singer, 2003	Primary RPS (liposarcoma and malignant fibrous histiocytoma)	USA	1982-2001	177	Contiguous organ resection *n*=47	Median time to local recurrence 45 months. 5-year local recurrence free survival 41% 5-year distant recurrence free survival 89%	Median time to sarcoma-specific death 83 months (DSS) 5-year disease-specific survival 60%	Not reported
18	Smith, 2015	Primary RPS	UK	2005-2014	362	Resection included a contiguous organ *n*=292	3-year local recurrence free survival stratified by histological subtype WDLPS 98%, DDLPS 56.7%, and LMS 80% 3-year distant metastases free survival stratified by grade of tumour, grade I 98.9%, grade II 83%, grade III 61%	3-year disease specific survival 81.2%	30-day mortality 1.4% 30-day Clavien-Dindo grade II-IV morbidity 15.7%
19	Spolverato, 2021	Primary RPS (LPS)	Italy	2002-2019	425	Vascular resection 24 (5%) patients	5-year local recurrence 45% vascular resection cohort versus 24% propensity matched cohort	5-year overall survival 60% vascular resection cohort versus 81%	Major complications (Clavien-Dindo ≥3) 54% vascular resection versus

							5-year distant recurrence 20% vascular resection cohort versus 0% propensity matched cohort	propensity matched cohort	25% propensity matched cohort
20	Tseng, 2011	Primary RPS	USA	2005-2007	156	Contiguous organ resection *n*=58 (37%)	Not reported	Not reported	Overall 30-day morbidity, severe morbidity (composite outcome measure), and mortality in 26%, 11.5%, and 1.3% respectively.
21	Turner, 2019	Primary (and recurrent) RPS	Canada	1990-2014	102	Multivisceral resection *n*=76	Cumulative recurrence 55%	Not reported	Not reported
22	van Doorn, 1994	RPS	Netherlands	1973-1990	34	Extended resection *n*=8	Recurrence free survival in extended resection 50%, versus 24% marginal resection	Not reported	Not reported
23	Wu, 2018	Primary RPS (LPS)	China	2005-2015	51 (complete primary tumour resection)	Contiguous organ resection *n*=32	Median time to local recurrence 29.2 months	Median survival 43.3 months	Not reported

CD – Clavien Dindo Classification

Table 3. Quality assessment of the individual studies

Study	Title	NHMRC Level of Evidence	Risk of Bias (Newcastle Ottawa scale for cohort study)			
			Selection	Comparability	Outcome	Overall
Abdelfatah, 2016	Long-term outcomes in treatment of retroperitoneal sarcomas: A 15 year single-institution evaluation of prognostic factors.	III-3	2	1	3	Fair Quality
Bonvalot, 2009	Primary retroperitoneal sarcomas: A multivariate analysis of surgical factors associated with local control.	III-2	4	2	3	Good Quality
Chiappa, 2006	Primary and recurrent retroperitoneal soft tissue sarcoma: Prognostic factors affecting survival.	III-3	3	0	1	Poor Quality
Chiappa, 2018	Aggressive surgical approach for treatment of primary and recurrent retroperitoneal soft tissue sarcoma	III-3	3	0	1	Poor Quality

Cho, 2018	Clinical benefit and residual kidney function of en-bloc nephrectomy for perirenal retroperitoneal sarcoma.	III-2	4	2	2	Good Quality
Eroglu, 1999	Retroperitoneal soft tissue sarcoma: Effect of hyperthermic total abdominal perfusion.	III-3	2	1	2	Fair Quality
Gronchi 2016	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	III-2	3	2	3	Good Quality
Ikoma, 2017	Concomitant organ resection does not improve outcomes in primary retroperitoneal well-differentiated liposarcoma: A retrospective cohort study at a major sarcoma centre.	III-2	4	2	3	Good Quality
Judge, 2019	Morbidity, mortality and temporal trends in the surgical management of retroperitoneal sarcoma: An ACS-NSQIP follow-up analysis.	III-2	4	2	3	Good Quality
Gonzalez Lopez, 2014	Differences between en-bloc resection and enucleation of retroperitoneal sarcomas.	III-2	3	2	2	Good Quality

Keung 2014	Predictors of outcomes in patients with primary retroperitoneal dedifferentiated liposarcoma undergoing surgery	III-2	3	2	3	Good Quality
Kim, 2021	Postoperative outcomes of distal pancreatectomy for retroperitoneal sarcoma abutting the pancreas in the left upper quadrant.	III-2	4	2	3	Good Quality
MacNeill, 2018	Postoperative morbidity after radical resection of primary retroperitoneal sarcoma.	III-2	4	2	3	Good Quality
Morizawa, 2016	Extended resection including adjacent organs and Ki-67 labelling index are prognostic factors in patients with retroperitoneal soft tissue sarcoma.	III-2	4	2	3	Good Quality
Ng, 2017	Tumour biology remains the main determinant of prognosis in retroperitoneal sarcomas: a 14-year single centre experience.	III-3	2	0	3	Poor Quality
Schwartz, 2019	Predictors of disease-free and overall survival in retroperitoneal sarcomas: A modern 16-year multi-	III-3	3	0	3	Poor Quality

	institutional study from the United States Sarcoma Collaboration (USSC).					
Singer, 2003	Histologic subtype and margin of resection predict pattern of recurrence and survival for retroperitoneal liposarcoma.	III-2	4	1	3	Good Quality
Smith, 2015	Outcome following resection of retroperitoneal sarcoma.	III-3	4	1	3	Good Quality
Spolverato, 2021	Oncological outcomes after major vascular resections for primary retroperitoneal liposarcoma.	III-2	4	2	3	Good Quality
Tseng, 2010	Contiguous organ resection is safe in patients with retroperitoneal sarcoma: An ACS-NSQIP analysis.	III-2	4	2	3	Good Quality
Turner, 2019	Neoadjuvant radiotherapy followed by surgery compared with surgery alone in the treatment of retroperitoneal sarcoma: a population-based comparison.	III-2	1	1	3	Poor Quality
van Doorn, 1993	Resectable retroperitoneal soft tissue sarcomas.	III-3	1	0	2	Poor Quality
Wu, 2017	A retrospective, single-centre cohort study on 65 patients with primary retroperitoneal liposarcoma.	III-3	2	0	1	Poor Quality

Table 4. Summary of Abdominal Recurrence Outcomes

Author, year	Sample size	Recurrence Measure	Recurrence Outcome	Summary
Bonvalot, 2009	382	Abdominal recurrence	Simple Resection associated with increased abdominal recurrence, HR 1.99 (95% CI 1.03-3.84) compared with Compartmental Resection.	Favour MVR, and more specifically compartmental resection. Statistically significant finding ($p<0.05$).
			Contiguously Involved Organs associated with increased abdominal recurrence, HR 2.17 (95% CI 1.19-3.94) compared with Compartmental Resection.	
van Doorn, 1994	34	Local recurrence	Local recurrence 50% in extended resection, versus 76% after marginal resection.	Trend toward MVR, in small numbers. Not statistically significant.
Keung, 2014	119	Local recurrence free survival	LRFS with <2 organs resected, median survival 25.1 months, versus LRFS with >2 organs median survival 21.1 months.	No difference between simple resection and MVR. ($p=0.982$).

Ng, 2017	85	Local recurrence	In text, contiguous organ resection stated to be not statistically significant predictor of LR.	No statistical significance.
Smith, 2015	362	Local recurrence	Resection of >3 organs not associated with increased local recurrence, HR 1.52 (95% CI 0.74-3.13) versus resection of 0 organs.	No statistical significance (p=0.259).
Singer, 2003	177 (33 patients with R2 resection excluded)	Local recurrence	Contiguous organ resection associated with increased local recurrence, HR 1.07 (95% 1.02-2.8) versus no organ resection.	Favour simple resection. Statistically significant finding (p=0.04).
Cho, 2017	114 (30 patients with R2 resection excluded)	Local recurrence	Nephrectomy versus no nephrectomy, no difference in cumulative recurrence at 5 – years. Subgroup analysis, for FNCLCC grade 2 tumours, recurrence in nephrectomy 55%, versus no nephrectomy 63%.	Trend towards MVR, and en-bloc resection. No difference in 5-year local recurrence (p=0.429). Statistically significant trend in subgroup analysis for FNCLCC grade 2 tumours for improved LR outcomes with MVR(p=0.048).

Kim, 2021	86	Local recurrence	Distal pancreatectomy versus no distal pancreatectomy, no difference in LR.	No statistical significance (p=0.863).
Spolverato, 2021	24 patients with major vascular resections, propensity matched analysis with 425 consecutive patients who underwent resection retroperitoneal liposarcoma resection.	Local recurrence	Major vascular resection 5-year LR 45%, versus no major vascular resection 24%	Statistically significant worsened LR with major vascular resection (p=0.05).

Table 5. The impact of tumour grade on survival outcomes

Author, year	Tumour Characteristics/Treatments		Measured Survival Outcome	Outcome Groups		P-Value	Summary
	Group 1 (N)	Group 2 (N)		Outcome Group 1	Outcome Group 2		
Makela, 2000	High grade	Low grade	Median survival	10.0 months	42.0 months	*Not reported*	
Abdelfatah, 2016	High grade (69)	Low/Intermediate grade (50)	Overall survival	HR: 2.01; 95% CI: 1.06 to 3.79		p=0.0320	
Chiappa, 2018	High grade	Low grade	5-year overall survival rate	14.00%	57.00%	p=0.0004	
Eroglu, 1999	High-grade (18)	Low-grade (10)	5-year overall survival rate	HR: 11.10; 95% CI: 2.50 to 48.80		p=0.0014	
Turner, 2019	Grade 2 (14)	Grade 1 (37)	Overall survival	HR: 4.00; 95% CI: 1.21 to 13.17		p=0.0200	
Turner, 2019	Grade 3 (42)	Grade 1 (37)	Overall survival	HR: 3.30; 95% CI: 1.09 to 9.96		p=0.0300	
Schwartz, 2019	Grade 2-3 (326)	Grade 1 (131)	Overall survival	HR: 2.44; 95% CI: 1.60 to 3.74		p<0.0100	
Wu, 2018	High-grade (18)	Low-grade (33)	Disease specific survival	24.9 months	53.3 months	p<0.0010	
Smith, 2015	Grade 3 (77)	Grade 1 (100)	Disease specific survival	HR: 33.33; 95% CI: 8.33 to 100.00		p<0.0010	
Smith, 2015	Grade 3 (77)	Grade 2 (148)	Disease specific survival	HR: 3.57; 95% CI: 2.00 to 6.25		p<0.0010	

 Group 1 tumour characteristics/treatments have significantly better survival outcomes than group 2 tumour characteristics/treatments.

 Group 2 tumour characteristics/treatments have significantly better survival outcomes than group 1 tumour characteristics/treatments.

 No significant difference in survival outcomes between group 1 and group 2 tumour characteristics/treatments.

Extended resection; a surgical resection of tumour mass and adjacent organs. Radical resection; all tumour macroscopically removed. Palliative resection; macroscopic or microscopic tumour remaining after resection. HR; Hazard-ratio.

Table 6: The impact of histological margins of resections on survival outcomes							
Author, year	**Tumour Characteristics/Treatments**		**Measured Survival Outcome**	**Outcome Groups**		**P-Value**	**Summary**
	Group 1 (N)	**Group 2 (N)**		**Outcome Group 1**	**Outcome Group 2**		
Abdelfatah, 2016	R2 (18)	R0-1 (92)	Median survival	10.1 months	73.5 months	p<0.0010	⊖
Ng, 2017	R1 (31)	R0 (31)	Median survival	36.0 months	111.0 months	p=0.0400	⊖
Bonvalot, 2009	R1 (103)	R0 (176)	Overall survival	HR: 1.70; 95% CI: 1.07 to 2.72		p=0.0300	⊖
Bonvalot, 2009	R2 (46)	R0-1 (336)	Overall survival	HR: 3.14; 95% CI: 1.67 to 5.92		p=0.0004	⊖
Schwartz, 2019	R2 (45)	R0-1 (512)	Overall survival	HR: 2.41; 95% CI: 1.57 to 3.69		p<0.0100	⊖
Singer, 2003	R2 (33)	R0 (77)	Disease specific survival	HR: 3.80; 95% CI: 2.00 to 7.40		p<0.0001	⊖
Rossi, 2013	R1 (58)	R0 (15)	5-year overall survival rate	45.00%	93.00%	p=0.0130	⊖
Rossi, 2013	R1-2 (63)	R0 (15)	5-year overall survival rate	HR: 3.47; 95% CI: 1.06 to 11.41		p=0.0400	⊖
Morizawa, 2016	R1-2 (19)	R0 (4)	Overall survival	HR: 3.35; 95% CI: 0.42 to 26.90		p=0.2600	=
Abdelfatah, 2016	R1 (56)	R0 (36)	Median survival	*Not reported*	*Not reported*	p=0.8620	=

⊕ Group 1 tumour characteristics/treatments have significantly better survival outcomes than group 2 tumour characteristics/treatments.

⊖ Group 2 tumour characteristics/treatments have significantly better survival outcomes than group 1 tumour characteristics/treatments.

= No significant difference in survival outcomes between group 1 and group 2 tumour characteristics/treatments.

Extended resection; a surgical resection of tumour mass and adjacent organs. Radical resection; all tumour macroscopically removed. Palliative resection; macroscopic or microscopic tumour remaining after resection. HR; Hazard-ratio.

Supplementary table 7. The impact of tumour grade on recurrence outcomes						
Author, year	**Tumour Characteristics/Treatments**		**Measured Recurrence**	**Outcome Groups**		**P-Value**	**Summary**
	Group 1 (N)	**Group 2 (N)**		**Group 1**	**Group 2**		
Turner, 2019	Grade 1 (37)	Grade 3 (42)	Local recurrence	HR: 0.23; 95% CI: 0.08 to 0.60		p=0.0030	⊕
Turner, 2019	Grade 1 (37)	Grade 2 (14)	Local recurrence	HR: 0.18; 95% CI: 0.07 to 0.51		p=0.0010	⊕
Smith, 2015	Grade 2 (148)	Grade 3 (77)	Local recurrence	HR: 0.35; 95% CI: 0.22 to 0.56		p<0.0010	⊕
Smith, 2015	Grade 1 (100)	Grade 3 (77)	Local recurrence	HR: 0.09; 95% CI: 0.04 to 0.20		p<0.0010	⊕
Smith, 2015	Grade 2 (148)	Grade 3 (77)	Distant recurrence	HR: 0.26; 95% CI: 0.13 to 0.52		p<0.0010	⊕
Smith, 2015	Grade 1 (100)	Grade 3 (77)	Distant recurrence	HR: 0.00; 95% CI: 0.00 to 0.42		p=0.0200	⊕
Schwartz, 2019	Grade 1 (131)	Grade 2-3 (326)	Disease-free survival	HR: 0.38; 95% CI: 0.27 to 0.53		p<0.0100	⊕
Bonvalot, 2009	Grade 1 (123)	Grade 3 (112)	Abdominal recurrence	HR: 0.39; 95% CI: 0.22 to 0.68		p=0.0008	⊕
⊕	Group 1 tumour characteristics/treatments have significantly better recurrence outcomes than group 2 tumour characteristics/treatments.						
⊖	Group 2 tumour characteristics/treatments have significantly better recurrence outcomes than group 1 tumour characteristics/treatments.						
〓	No significant difference in recurrence outcomes between group 1 and group 2 tumour characteristics/treatments.						
HR; Hazard-ratio.							

CHAPTER 2

SPARC - A Multi-Disciplinary Team program for Retroperitoneal, Intra-Abdominal and Pelvic Sarcoma: The Royal Prince Alfred Hospital and Chris O'Brien Lifehouse Collaboration. Retroperitoneal Sarcoma Surgery: The Importance of a Highly Specialised Institution and Multidisciplinary Team

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Abstract

Introduction and Aim:

The Royal Prince Alfred Hospital (RPAH) and Chris O'Brien Lifehouse (COBLH) established a formal Sarcoma of the Pelvic and Abdominal Retroperitoneum Collaboration (SPARC) in November 2020. An established multidisciplinary team (MDT) with the aims to centralise patient referrals and treatment, establish database and research, coordinate surgical resections is critical in improving patient outcomes and quality of life.

Methods:

A prospective database was established in October 2021. Clinical, pathological and radiological data points were recorded for all patients since the inception of SPARC. Quality of Life questionnaires were included and follow-up planned regularly for 5 years.

Results:

From November 2020 to Feb 2024, 294 new referrals were discussed at the MDT meeting. Majority were from the metropolitan area (182) followed by regional NSW (87), interstate (20) and five internationals. 141 operations were performed during this period compared to 119 operations from 2010 to November 2020 in RPAH. The inception of the SPARC program has resulted in exponential growth in operations, improving from the previous rate of 15 cases annually to 35. Liposarcomas followed by leiomyosarcomas are the most common types of sarcomas resected. The majority were extended resections (81.6%) and 22% were pelvic exenterations. Overall R0 rate is 54.6%, R1 38.3% and R2 1.4% (131 (92.9%) had R0/R1 resections. Overall complication rate was 35.5% with one in-hospital mortality.

Conclusion:

Success and expansion of a robust retroperitoneal sarcoma program requires a collaborative surgical approach, an MDT meeting, centralized referral process, and a research team in specialized tertiary institutions.

Introduction

Retroperitoneal sarcomas (RPS) are a rare and heterogeneous group of tumours of mesenchymal origin (1,2). The current Australia clinical practice guidelines for the management of sarcoma recommends patients with suspected sarcoma be referred to specialized sarcoma centre early for management, including a preoperative biopsy (3,4). RPS comprise 15% of all soft tissue sarcomas (1,5) and can grow to become very large tumours within the abdomen and pelvis.

Management of patients with RPS is a challenge due to tumour proximity to vital organs. Obstructive symptoms depend on which organ or structure it abuts or invades, which can include the ureter, bladder, bowel and neural structures. The therapeutic strategies include surgical resection, radiotherapy, and chemotherapy, or a combination of these (2,6–8). Surgical margins, like in other malignancies, are crucial and determine outcomes such as survival and recurrence rates (9,10). Negative surgical (R0) margins may not be possible in RPS due to the limitations of the anatomy (11). Additionally, due to the close vicinity of vital retroperitoneal structures and organs, including the spine and bone, multi-visceral resections are advocated (12,13) but how much can be resected without undue morbidity and with preservation of quality of life should always influence the planning of surgery and the overall treatment.

Hence, a multidisciplinary team (MDT) approach is crucial with the aim to minimise risk of local and distant recurrence and minimise significant morbidity that can compromise the

patient's quality of life. The expertise and experience shared in the discussions during these meetings amongst radiologists, surgeons, medical oncologists, radiation oncologists and pathologists, is paramount to successful treatment and improving survival outcomes. Additionally, the MDT is an effective way for centralising referrals, streamlining the pathways of care (especially for regional or interstate referrals), and identifying potential patients for clinical trials and other research studies. Complementing the MDT with an established prospective database to audit, examine and assess the outcomes promotes the success of any surgical program. Data analysis and dissemination of outcomes leads to further development of the program by targeting areas of improvement, and ultimately, further expansion and growth of the program to support the increasing referral network and MDT meetings.

The Royal Prince Alfred Hospital (RPAH) and Chris O'Brien Lifehouse (COBLH) formalised the Sarcoma of the Pelvic and Abdominal Retroperitoneum Collaboration (SPARC) in November 2020 with the aims to centralise referrals, facilitate multi-disciplinary discussion, establish a database and facilitate research with the ultimate goal of improving patient outcomes and quality of life. This article illustrates the early outcomes identified in the implementation of this multi-disciplinary framework in a quaternary public health institution.

Methods:

The structure and governance of the Retroperitoneal, Intra-abdominal and Pelvic Sarcoma Program

The structure and governance of the Retroperitoneal Sarcoma Program is led by the Chief Executive Officer of the Sydney Local Health District (SLHD) (**Figure 1**). The academic direction is led by the Institute of Academic Surgery of SLHD and the clinical direction under the Advanced Gastro-Intestinal Surgery Program (AGISP) at RPAH, with collaboration with

the COBLH. Research is undertaken through the Surgical Outcomes Research Centre (SOuRCe). The lead of the SPARC program chairs the MDT and research meetings, and the monthly SPARC planning and development meetings.

The MDT meeting

Fortnightly MDT meetings have been occurring since November 2020, coordinated by the Retroperitoneal Sarcoma Clinical Nurse Consultant (CNC) through centralised referral to the CNC. For each patient, their imaging, diagnostic histopathology, surgical planning including detailed proposed operation and post-operative histopathology, and adjunctive systemic and radiotherapy treatments are discussed at the MDT meeting. As this program started during the COVID pandemic, a virtual MDT meeting was initiated. This has continued due to the success with high levels of attendance by radiologists, surgeons, medical oncologists, radiation oncologist and pathologists. The virtual platform also provides the opportunity of allowing colleagues from other metropolitan and rural institutions to attend and present their patients. A formal MDT outcome letter is produced for each case discussed and sent to the relevant clinicians especially the referring or treating consultant and general practitioner. One of the strengths of this MDT meeting is the surgical planning by multiple surgical disciplines. The images are reviewed by a dedicated sarcoma radiologist and a detailed operation is planned during this meeting. All patients discussed at the MDT meeting are recommended for tissue diagnosis prior to definitive treatment. The exception is when tissue biopsy poses risks of complication due to location, outweighing the benefit. Additionally, the post-operative histopathology is discussed to ensure maximal and appropriate post-surgical treatment(s), adjuvant radiotherapy and chemotherapy, and appropriate surveillance are determined.

Research

A prospective database with a research manager for the SPARC program was established after receiving Ethics and Governance approval, obtained from the Sydney Local Health District Ethics Review Committee (RPAH Zone) in July 2021. Separate Governance approval was received from COBLH in August 2022. During the initial consultation with the treating clinician, patients are invited to participate and provide informed consent for research including preoperative quality of life (QoL) questionnaires. Comprehensive data on clinical, pathological, and radiological factors are recorded. Postoperative questionnaires are collected prior to discharge and regularly distributed to patients for up to 5 years via telephone, mail or email based on their preference using unique SLHD REDCap linked to the participant. An algorithm of management pathway was produced as seen in **Figure 2**. Importantly, patients who did not proceed to surgery, due to being determined "not resectable" or due to the patient's wishes not proceed to surgery, were also included.

The database at inception was designed to allow for collaboration with other established retroperitoneal sarcoma organisations for ethically approved projects. The database format is readily accessible to other established sarcoma databases including the Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG), RESAR and Desmoid studies (14), and the Australia and New Zealand Sarcoma Association (ANZSA) Australian Comprehensive Cancer Outcomes and Research Database (ACCORD) database.

Quality of life data are collected using the Short Form-36 Version 2 (SF-36v2) Health Survey (14), the European Organisation for Research and Treatment of Cancer-Quality of Life – Core Questionnaire C30 (EORTC QLQ-30) questionnaire (15), and the EuroQoL-5D (16) instrument. Work and healthcare utilisation, financial concerns, distress (using the Distress

Thermometer where a score of ≥4 indicates clinically significant levels of distress) (17), pain (measured using the Leeds assessment of neuropathic symptoms and signs or LANSS pain scale) (18), and patient in-hospital experience data are also captured.

Results:

Referrals:

From November 2020 to 9th Feb 2024, 294 new referrals were presented at the MDT meeting. There were 532 discussions including re-discussions of patients in this period. The purposes of re-discussions following initial MDT recommendations include review of additional imaging, tissue diagnosis with core biopsies, clinical evaluation for the appropriateness of treatment especially extensive surgery and review of histopathology (when the initial biopsy is performed at a different pathology department other than RPAH).

The most common source of referrals was from metropolitan referrers (*n*=182 patients, 61.9%) followed by rural (*n*=87, 29.6%), interstate (*n*=20, 6.8%) and international (*n*=5, 1.7%) referrals. Referrals were made by surgeons (*n*=132, 44.9%), medical oncologists (*n*=69, 23.5%), other specialists including general practitioners (*n*=68, 23.1%), gynae-oncologists and radiation oncologists (*n*=24, 8.2%), and presentation to the emergency department (*n*=1, 0.3%).

Caseload:

There have been 141 sarcoma operative cases performed since November 2020. **Figure 3** demonstrates the number of surgeries performed each year before and after the inception of the SPARC program, illustrating the significant growth in caseload since implementing a dedicated program. The division of caseloads between RPAH and COBLH have been 89 and 52 respectively. Since its inception, per financial year status, caseloads have increased from 24 in

2020/2021, to 37 in 2021/2022, to 45 in 2022/2023 and currently at 35 in 2023/2024, at the time of publication. Prior to establishing the SPARC database, there were 119 operative cases across the from November 2010 to November 2020, averaging 12 cases annually.

There were a combined 29 (20.6%) cases with the upper gastrointestinal surgical team due to involvement of foregut structures, and 31 (22.0%) cases requiring pelvic exenteration. The centralised MDT process allowed for timely surgical co-ordination to ensure specific surgeons were available to provide the essential service.

Patient demographics:

The median age of the 141 operative cases was 59.6 years (IQR 49.1 – 71.3 years), with 67 patients (47.5%) being male. Tumour types included 71 primary sarcomas (50.4%), 25 recurrent sarcomas (17.7%), 5 residual sarcomas (3.5%), 7 metastatic sarcomas (5.0%) and 33 (23.4%) non-sarcomas. Tumour sites were retroperitoneal (*n*=67, 47.5%), abdominal (*n*=22, 15.6%), and pelvic (*n*=52, 36.9%). The pathologies of sarcomas are included in **Figure 4**. The most common diagnoses were liposarcoma (30.5%), leiomyosarcoma (13.5%) and other sarcomatous histology (11.3%) including angiomyxoma, rhabdomyosarcoma, undifferentiated pleomorphic sarcoma, and desmoplastic small round cell tumours. Other soft tissue tumours such as schwannoma, desmoid tumours and gastrointestinal stromal tumours were included in the database.

Adjunctive treatments:

Adjunctive treatments included neoadjuvant chemotherapy (*n*=5, 3.6%), adjuvant chemotherapy (*n*=8, 5.7%), and adjuvant radiotherapy (*n*=7, 5.0%). For the five patients who received neoadjuvant chemotherapy, there were two cases of liposarcoma, one case of desmoid

tumour, one case of desmoplastic small round cell tumour (classified as “Other sarcoma”), and one case of suspected local recurrence of Ewing’s Sarcoma which ended up being radiotherapy induced change (classified as “Other Non-Sarcoma”). Of the three sarcoma cases, two were retroperitoneal primaries and one was a residual sarcoma in the retroperitoneum after incomplete previous resection.

Eight patients received adjuvant chemotherapy for three cases of leiomyosarcoma (two retroperitoneal primaries, one pelvic primary), two cases of gastrointestinal stromal tumour (one pelvic primary, one abdominal primary), two cases of “other sarcoma” including rhabdomyosarcoma (retroperitoneal metastasis) and desmoplastic small round cell tumour (retroperitoneal primary), and one case of liposarcoma (retroperitoneal primary).

Adjuvant radiotherapy was given to seven patients, with two cases of liposarcoma (one retroperitoneal recurrence, one pelvic recurrence), two cases of leiomyosarcoma (one pelvic recurrence, one retroperitoneal metastasis given with palliative intent), two cases of “other sarcoma” including myxofibrosarcoma (abdominal primary) and hybrid sclerosing epithelioid fibrosarcoma/low grade fibromyxoid sarcoma (pelvic primary), and one case of chordoma (pelvic primary).

Surgical Outcomes:

The goal of RPS surgery is to achieve en-bloc resection of the tumour along with any involved adjacent structures to maximally clear the disease. The type of resection can be defined as R0 (complete resection with negative microscopic margins), R1 (complete resection with positive microscopic margins, <1mm), or R2 (macroscopic evidence of disease or incomplete resection). Although R0 resection is the optimal goal, this is frequently difficult or sometimes

impossible to achieve and to assess pathologically (due to the massive retroperitoneal sarcomas) therefore, the consensus of sarcoma surgeons is aimed at R0/R1 resection (15,16). **Table 1** outlines the surgical margin outcomes. Of the 141 operative cases, the outcome was R0 in 77 (54.6%), R0 or R1 resections in 131 (92.9%). Two patients (1.4%) had a R2 resection. The other eight patients (5.7%) did not have a surgical resection margin grading due to a non-cancer diagnosis or fragmented tissue preventing accurate analysis. 97.2% (*n*=69) of primary sarcomas underwent a R0/R1 resection, as did 100% of recurrent (*n*=25), residual (*n*=5) and metastatic (*n*=7) sarcomas. The R0 rate was 60.6% (*n*=43) of primary sarcomas, 44.0% (*n*=11) for recurrent sarcomas, 40.0% (*n*=2) for residual sarcomas and 42.9% (*n*=3) for metastatic sarcomas.

The median operative time was 4.2 hours (IQR 2.3 – 6.8 hours) with a median length of stay of 10 days (IQR 5 – 17 days) including length of intensive care unit stay of 2 days (IQR 1.2 – 3.8 days). The median blood loss calculated in collaboration with the anaesthetic team at time of surgery was 500mL (IQR 125 – 1500mL). 37.6% (*n*=53) of cases required blood transfusions intraoperatively.

Surgery type in relation to surgical outcomes:

Of the 141 cases, 27 (19.1%) were tumour-alone (simple) excisions and 115 (80.9%) were extended resections. Extended resections also included 31 (22.0%) pelvic exenterations. Of the simple excisions, 23 (85.2%) had R0/R1 resection and the other 4 (14.8%) could not be graded in its resection margin due to its benign nature or fragmented tissue. Of the 114 extended resections, 108 (94.7%) had a R0/R1 resection, and 2 (1.8%) had a R2 resection. The R0 rate was 52.6% in the extended resections. Of the 31 pelvic exenteration cases, 30 (96.8%) had a

R0/R1 resection with 22 (71%) having a R0 resection. One case could not be assessed as resection margin grade due to fragmented tissue.

Complications

Table 2 outlines the complications. The overall postoperative complication rate was 35.5% (*n*=50) and all cause 30-day mortality was 0.7% (*n*=1). Postoperative complications were classified according to the Clavien-Dindo Classification System, using a grading of I to V with severe defined as Clavien-Dindo grades III and IV and mortality as Clavien-Dindo grade V. For each patient, the most severe complication was graded according to the Clavien-Dindo grading system and some patients experienced more than one observed postoperative complication. Of all the 50 patients who experienced postoperative complications, 27 patients (54%) had Clavien-Dindo grade I and II complications, and 22 patients (44%) had grade III and IV complications. From the 101 total observed number of complications, the most common complications included 17 patients (16.8%) with gastrointestinal complications including ileus or infection, 16 patients (15.8%) with wound related complication including superficial dehiscence and infection, and 15 patients (14.8%) with urological complications including acute kidney injury or urinary tract infections. The one 30-day mortality was a patient who died on day 5 post-operation with a massive pulmonary embolism despite venous thromboembolism chemical prophylaxis.

Discussion:

Since the inception of the SPARC program, there has been a dedicated retroperitoneal sarcoma team aiming to improve access to a centralised surgical referral service, surgical outcomes, and patient-related care at RPAH and COBLH. As seen in the results, the annual surgical caseload prior to the SPARC program was 12 cases per year from 2009 to 2019, increasing to over 35

cases per year following SPARC inception, thus nearly tripling the annual caseload and continuing to grow each year. There is a large body of evidence showing surgery at specialised sarcoma centres is associated with improved patient outcomes (3). In a recent study of the US National Cancer Database using outcome data of 5407 patients with RPS treated in the US, there was a clear volume-outcome relationship for 30-days mortality and overall survival (17). In that study, a threshold of 10 cases per year was used as a definition for a high-volume centre and only 0.4% (3/678 centres) met the criteria. The increasing surgical caseload with the SPARC program strengthens the concept of specialised sarcoma care and will likely to translate to better patient outcomes in the longer term.

Critical components of the success of the SPARC program include a dedicated Retroperitoneal Sarcoma MDT meeting and centralised referral via the clinical nursing consultant (CNC). As recognised in **Figure 1**, all internal and external referrals are received by the Retroperitoneal Sarcoma CNC who co-ordinates the fortnightly RPS MDT meeting that determines the recommended treatment algorithm for each patient. The MDT meeting allows allied health staff (psychologists, physiotherapists, occupational therapists, dieticians and stomal therapists), physicians (medical and radiation oncologists, radiologists) and surgeons (upper gastrointestinal surgeons, colorectal surgeons, surgical oncologists) to identify and provide recommendations to streamline patients who require operative intervention, systemic therapy, radiotherapy, clinical treatment recruitment and best supportive care. The centralised MDT process also facilitates timely surgical co-ordination to ensure specific surgeons are available to provide the essential service.

In regards to surgical outcomes, the SPARC program achieved a R0/R1 resection rate of 92.9%. Being within a centre that also performed a high volume of pelvic exenteration, we were able

to perform 31 pelvic exenterations that had a 71% R0 or 96.8% R0/R1 resection margin. The overall R2 resection was 1.4%. Studies show that R0 resection confers a significant improvement in overall survival and increased disease free survival. Some studies have shown that R0/R1 resections have better overall survival than R2 (13,16). Our R2 resection rate was low which indicates a marker of quality preoperative planning and surgical management. The complication rate in our series was similar to those in literature between 27-34% with a Clavien-Dindo grade III and IV rate at 15.6% (22 from 141 cases) (13).

Challenges exist in managing the diverse histology, including non-sarcoma related malignancies, within the database. Moreover, several non-malignant cases were appropriately referred due to initial concerns for a sarcoma based on imaging and biopsy (with final histopathology proving it to be a benign process), and were worked up accordingly, the inclusion of this data can skew surgical outcomes, as evidenced by the number of cases that have non-applicable grading of resection margins. On the other-hand, as the program continues to grow, a separate database from the "sarcoma" should be maintained. An established database for other common soft tissue tumours such as schwannomas, desmoid tumours and GISTs will prove very useful as they have not been formally recruited in a prospective database in the past in our institution. Additionally, referrers in the past did not know who to refer their patients with these nevertheless challenging diagnosis and treatment. Therefore, we have included these histology to demonstrate the importance of a database for future reporting and analysis.

The concept of the prospective database has been an excellent resource for research. As the database continues to expand, we hope to achieve publications looking at oncological outcomes, adjust treatment algorithms, quality of life trajectory and add to established databases globally.

Conclusion:

The establishment of a dedicated retroperitoneal and pelvic sarcoma service termed SPARC (Sarcoma of the Pelvis, Abdominal Retroperitoneum Collaboration) has centralised patient referrals and treatment, established a prospectively collected database and research, and co-ordinated surgical resections with all the surgical subspecialties as well as adjunctive treatments at RPAH and COBLH. This provides timely access to a formalized management pathway for patients to receive highly specialised care, especially access to the MDT meeting. Whilst in its early stages of development, there is ongoing endeavour for improvement and expansion.

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TABLES

TABLE 1: Surgical margin outcomes across all retroperitoneal, abdominal and pelvic sarcoma resections

	Overall (*n*=141)			
Type of procedure	**R0**	**R1**	**R2**	**N/A**
Simple Excision (*n*=27, 19.1%)	17 (63.0%)	6 (22.2%)	0 (0%)	4 (14.8%)
Extended Resection (*n*=114, 80.9%)	60 (52.6%)	48 (42.1%)	2 (1.8%)	4 (3.5%)
Pelvic Exenteration (*n*=31, 22%)	22 (71%)	8 (25.8%)	0 (0%)	1 (3.2%)
Non-Pelvic Exenteration (*n*=110, 78%)	55 (50%)	46 (41.8%)	2 (1.8%)	7 (6.4%)

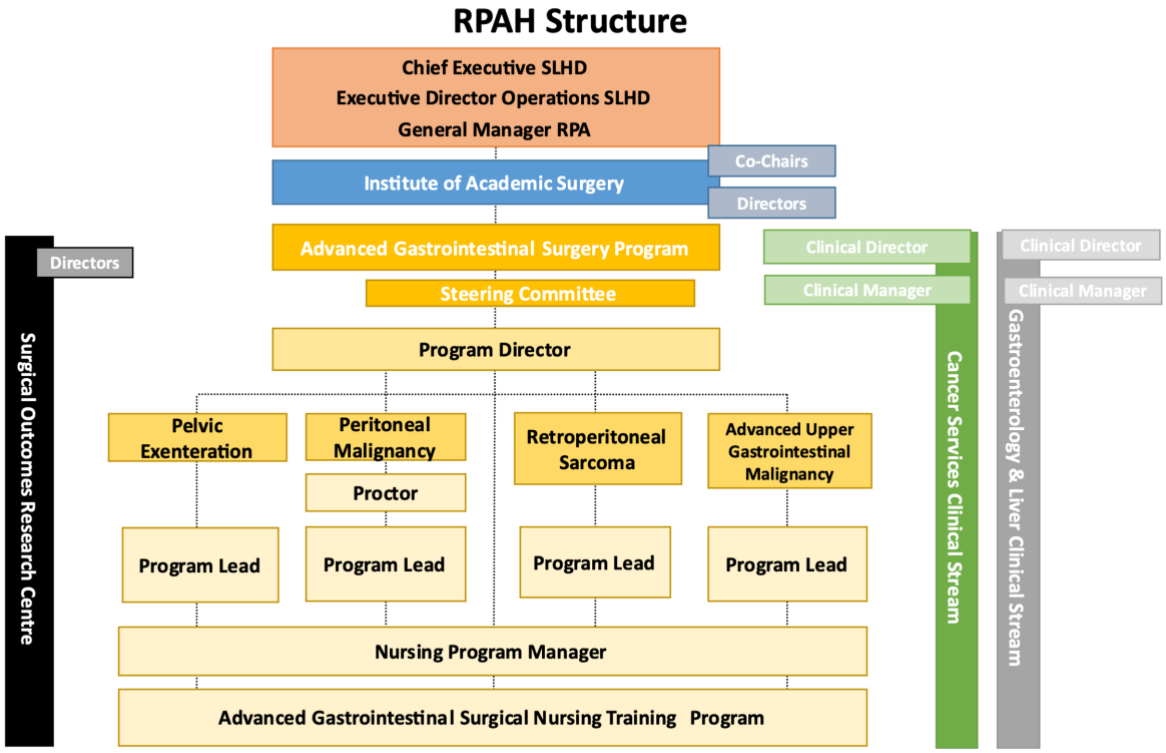
TABLE 2: Complications according to the Clavien-Dindo Classification System

Complications	**Overall (*n*=141)**	**Observed Postoperative Complications (*n*=101)**
Number of Patients Experiencing a Postoperative Complication	50 (35.5%)	Gastrointestinal 17 (16.8%) Wound 16 (15.8%) Urological 15 (14.8%) Infection 14 (13.9%) Respiratory 12 (11.9%) Abscess 8 (7.9%) Thrombosis/Embolism 6 (5.9%) General 5 (5.0%) Cardiac 5 (5.0%) Neurological 3 (3.0%)
Clavien Dindo I-II	27 (54.0%)	
Clavien Dindo III-IV	22 (44.0%)	
Clavien Dindo V (30-day)	1 (2.0%)	

The highest Clavien-Dindo grade was given to a single patient who experienced a postoperative complication. Some patients were observed to have more than one complication.

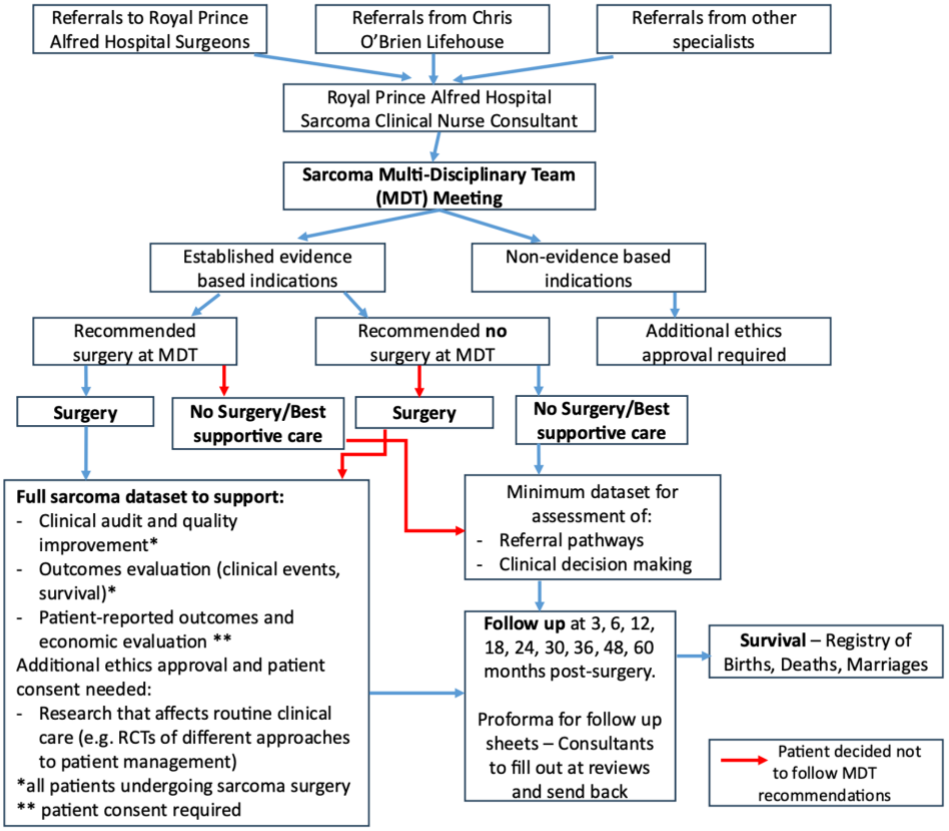
FIGURES

FIGURE 1: The Structure and Governance of the Retroperitoneal, Intra-Abdominal and Pelvic Sarcoma Program



SLHD = Sydney Local Health District; RPA = Royal Prince Alfred Hospital

FIGURE 2: SPARC algorithm of management pathway



SPARC= Sarcoma of the Pelvis, Abdominal Retroperitoneum Collaboration, RCT = Randomised control trial

FIGURE 3: Demonstrating the number of surgeries performed each year before and after the inception of the SPARC program, illustrating the significant growth in caseload since having a dedicated program

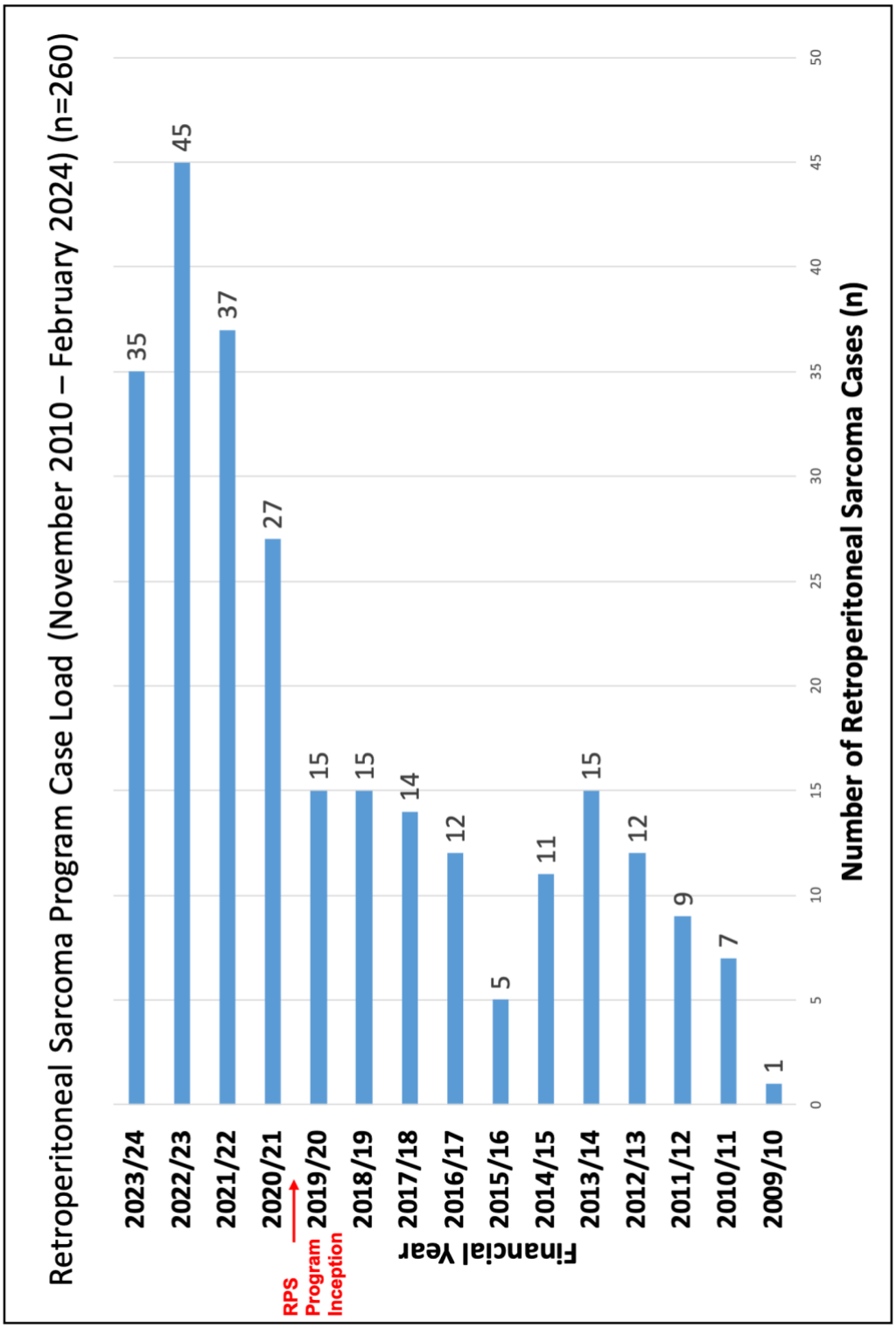
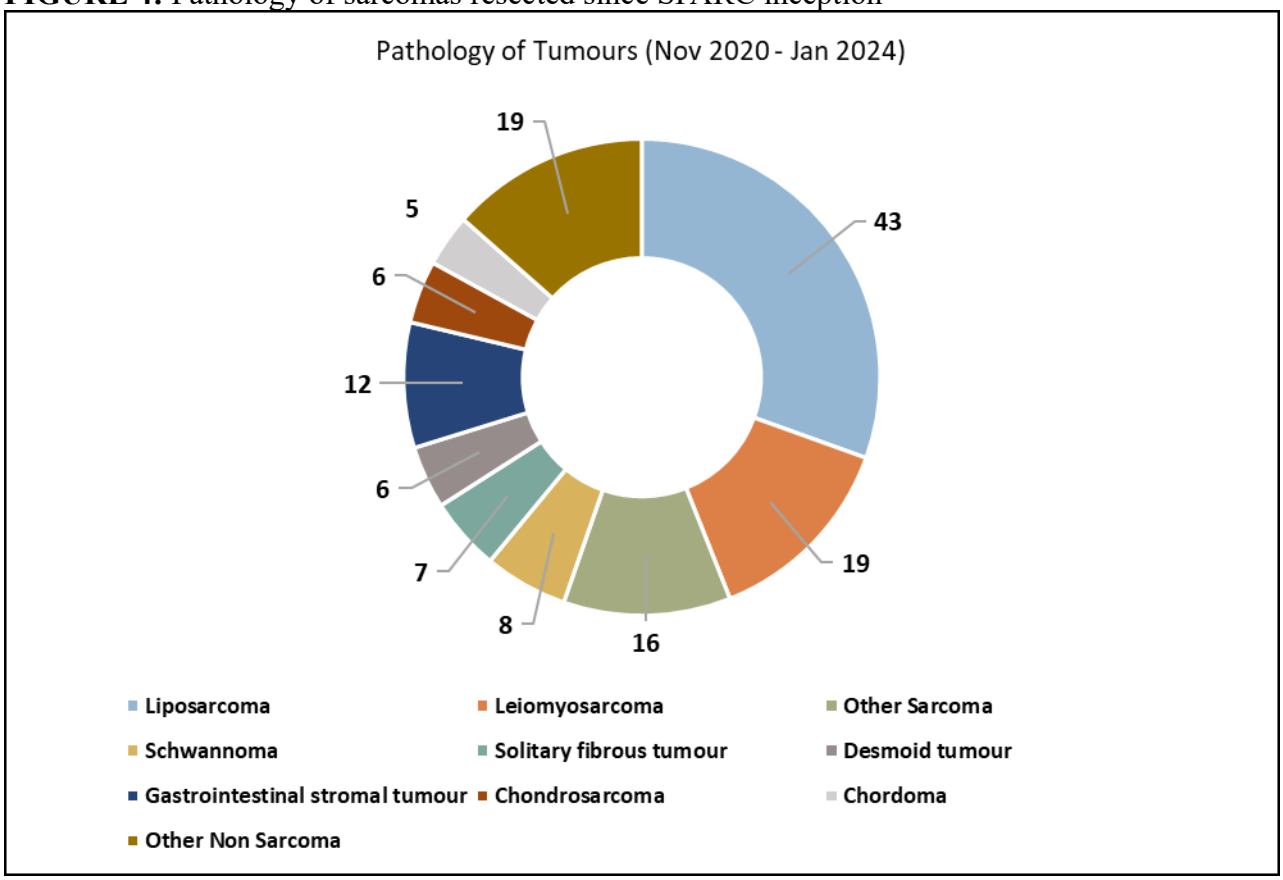


FIGURE 4: Pathology of sarcomas resected since SPARC inception



CHAPTER 3

Survival and Morbidity after pelvic exenteration for pelvic sarcoma: an institutional series.

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ABSTRACT

Background:

To describe our institutional experience in the management of locally advanced primary, and recurrent pelvic sarcoma through pelvic exenteration (PE).

Methods:

Patients undergoing PE for locally advanced primary or recurrent pelvic sarcoma between 2003 and 2017 were identified from a prospectively maintained database at a single quaternary referral hospital in Sydney, Australia, and were eligible for this retrospective review. The primary outcomes measured were surgical resection margin and survival. Secondary outcome measures included 30-day morbidity, in hospital length of stay (LOS), and return to theatre.

Results:

There were 29 patients who underwent PE for pelvic sarcoma during the study period, with 55% (*n*=16) having advanced primary tumours and 45% (*n*=13) having recurrent disease. The R0 resection rate was 52% (*n*=15); and five-year-survival of 38% (*n*=11). The R0 resection was noted to be higher in patients having primary advanced tumours (56%) compared to those with recurrent disease (46%), however this failed to reach statistical significance in this cohort. There was no recorded 30-day mortality. Grade 3 or higher Clavien-Dindo complications were uncommon (14%), but more likely in patients undergoing surgery for recurrent disease (75%).

Conclusion:

In our cohort of patients with locally advanced and recurrent disease, more than 50% achieved an R0 resection. Recurrent disease makes R0 resection more difficult and can lead to higher morbidity, need for 30-day re-intervention and longer in hospital LOS. PE surgery remains the only curative option for locally advanced, and recurrent sarcoma in the pelvis, and can be performed with acceptable survival and morbidity outcomes.

Keywords:

Pelvic Exenteration; Sarcoma; Survival; Margins of Excision; Morbidity

Introduction:

Sarcomas are an uncommon malignant tumour arising from mesenchymal tissue. Less than 5% of all sarcomas are located in the pelvic region, often producing little or no symptoms until they have grown large and extensively involve pelvic organs [1]. En-bloc surgical resection with clear margins is the treatment of choice, giving patients the best chance of survival and decreasing the risk of local recurrence [2-4]. Extended radical surgery with or without bony

resection provides such an option in patients with pelvic sarcomas. Although such surgeries have been extensively evaluated in the setting of primary advanced and recurrent rectal cancers [5-7], there remains a paucity of literature on such extensive surgery for pelvic sarcomas.

Aggressive management of primary and recurrent pelvic sarcoma is now possible with PE due to advances in perioperative radiological assessment and surgical techniques. The utility of preoperative magnetic resonance imaging (MRI) has allowed for more accurate operative planning. This combined with a greater understanding of the surgical anatomy of the pelvis has allowed for surgeons to explore complex resections, with bone, muscular and neurovascular dissection and resection [8].

Figure 1, demonstrates the compartments of the pelvis as viewed from inferiorly. Central PE, represents the basis of exenteration surgery with resection of the rectum and surrounding involved organs. Refinement of techniques facilitating 'higher and wider' resections in the pelvis [9], have enabled extended resections in the posterior, anterior and lateral compartments [10]. The posterior compartment is characterised by resection of the sacrum. Sacral transection below the level of the sacroiliac joint is performed transabdominally in our institution [11], whereas for more proximal sacral resections the patient is re-positioned prone following the abdominoperineal phase of the resection. The anterior compartment is characterised by resection of the bladder and/or pubic bone [10], with urological reconstruction dependent upon the degree of bladder resection. Urinary complications represent a major source of post-operative morbidity, most commonly from infection or urinary leak [12]. The presence of major neurovascular structures within the confines of the bony pelvis makes the lateral compartment a challenge in PE surgery. Austin and Solomon have published a technique of en bloc resection of the pelvic sidewall, allowing safe access to a more lateral plane than previously, which has

improved oncological outcomes [13]. Where the tumour involves common or external iliac vessels, they are resected en bloc, and reconstructed [14]; internal iliac vessels are resected en bloc or ligated for control and access.

Patients with locally advanced or recurrent pelvic sarcomas have a poor prognosis without surgery due to limited alternative management options [4,15]. With extended radical surgery and a R0 resection margin, five-year survival rates beyond 50% are achievable [6]. Furthermore, if R0 resection is achieved, recent studies of pelvic exenteration suggest that patients long term quality of life (QoL) is better at 12 months following surgery, and that their QoL returns to baseline before 6 months post-operatively [5,7,16].

Extended radical surgery in the pelvis can be associated with significant morbidity depending on how radical the resection has to be to achieve an R0 resection margin [5]. For this reason, appropriate patient selection and decision-making within experienced, multi-disciplinary units is essential to ensure survival and QoL benefits for these patients [17]. In this article we present the outcomes and survival of pelvic exenteration (PE) surgery for patients with primary advanced and recurrent pelvic sarcomas from our institution.

Methods:

Population

Following institutional ethics approval, a review of the prospectively maintained PE database was performed to identify all patient who underwent PE for locally advanced primary or recurrent pelvic sarcoma between January 2003 to December 2017. The suitability of patients for surgery was determined by preoperative MRI and PET scans, and discussion at a multidisciplinary PE specific meeting. Patients who had technically resectable disease were

offered surgery, with a discussion of what that entails, relevant risks and benefits, and long-term sequelae. All clinical data with respect to PE was routinely collected as part of the prospective clinical database.

The primary outcomes measured were surgical resection margin and survival. Secondary outcomes included post-operative morbidity and length of in hospital stay. Patients were followed up at 3, 6 and 12 months post-operatively and annually thereafter. Imaging was the primary means of surveillance for patient follow-up for sarcoma. All complications were recorded in the prospectively maintained database.

Data Collection

Data were retrieved from the prospective database and confirmed with review of surgical case files and electronic and paper hospital medical records. Demographic, clinical, operative, and complication data were collected for each patient. These included age, sex, preoperative ASA (American Society of Anaesthesiology) score, concurrent surgical procedures, resection intent (curative or palliative), operating time, intraoperative blood loss and length of stay.

Pathological completeness of resection was defined as R0 (complete resection of tumour), R1 (microscopic tumour remnant at the margin, <1mm), and R2 (macroscopically involved margin, usually performed in a palliative context). Tumour invasion to lymph nodes, adjacent organs and cortical bone invasion were also recorded.

Complications within 30-days after surgery were recorded using the Clavien-Dindo classification, and any intervention for these were also recorded. Death status was determined from medical records and the New South Wales Births, Deaths and Marriages Department.

These data were confirmed for all patients by periodic updates from the state-wide registry of births and deaths as is done for all exenteration patients through an ethics approved database protocol.

Statistical Analysis

Survival analysis was performed by using the Kaplan-Meier analysis. Subgroup analysis was not performed because of the small number of patients. Comparisons of variable means was done using Kruskal-Wallis rank test, and Pearson's chi-squared was used for comparison of three-year survival data. A *p*-value of less than 0.05 was considered significant. Data were analysed using Stata v13.

Results:

Demographics

In the 15-year study period, 29 patients underwent PE for advanced primary or recurrent pelvic sarcoma. Sixteen patients were operated for advanced primary, and 13 for recurrent disease. Demographic data are presented in Table 1.

The majority of patients were female representing 66% of patients in the study population. The median age was 53 years (range, 14 - 84). Twelve patients (75%) had neoadjuvant therapy for the management of their primary tumour, with six (46%) of the recurrent cohort undergoing neoadjuvant therapy. The intent of surgery was curative in 93% (*n*=27) of the patients.

Two patients (7%) underwent surgery for symptom control in a palliative context. One had primary disease, and the other recurrent disease; both had known distant disease. Both

presented symptomatically with a bowel obstruction, and in the case of the patient with recurrent disease there was bowel perforation. The patient with recurrent disease underwent central compartment resection only, whilst the patient with primary disease had resection of both the central and anterior compartments.

The majority of patients (79%) were diagnosed after symptomatic presentation. Their symptoms included abdominal pain, neurological- and vascular compromise. The remaining 21% of patients were incidentally diagnosed in the context of imaging for another indication.

The most common pelvic compartment involved with tumour in our cohort of patients was the posterior compartment (*n*=14), followed by lateral compartment (*n*=11) and central compartment (*n*=10) (Table 2). Eleven patients required urological reconstruction with an ileal conduit, with three of the four patients with anterior compartment resection requiring a conduit. Twelve patients required bone resection, either sacrectomy, pubic bone, or ischial bone. There were nineteen patients who required vascular resection, the majority of whom had primary disease; ten patients required vascular reconstruction of common or external iliac vessels.

The most common histological subtype in our patient cohort was de-differentiated sarcoma (34%), followed by leiomyosarcoma (24%). Table 3 outlines the different histological subtypes in patients with primary and recurrent tumours.

Morbidity and Mortality

In our series, there was no 30-day mortality. The overall mean in hospital length of stay (LOS) was 33 days (range 8-109), with shorter mean LOS for patients undergoing surgery for primary tumours compared to recurrences (Table 4).

The mean intra-operative blood loss for all patients was 3,575mL (range minimal-24,000mL), with little difference noted between patients undergoing surgery for primary and recurrent tumours (Table 4).

While post-operative morbidity was ubiquitous, serious post-operative complications which required radiological or surgical intervention were for intra-abdominal sepsis, small bowel obstruction, ureteric leak, wound debridement and bleeding (Table 5). One patient who had surgery for advanced primary tumour required radiological drainage of a pelvic collection. There were three patients who required post-operative surgical intervention, all of whom had surgery for recurrent tumours. Two of these patients required intervention for ureteric anastomotic leaks and the other due to entero-enteric anastomotic leak.

Resection margins and survival

The overall R0 rate was 51.7% (*n*=15) and R1 rate 48.3% (*n*=14), with no recorded R2 resections in the studied cohort. While more R0 resections were noted in the primary advanced group (56% vs 46%), this difference was not statistically significant. The resection margins when broken down across the compartments involved do not reveal a trend with respect to R0 rate (Table 4).

The median post-operative survival for all patients was 44.7 months (range 2-178). Patients who underwent surgery for palliation had a median survival of 7 months (range 2-12) compared to 47.5 months (range 3-178) for patients having curative intent surgery.

Patients who had R0 resections had a mean survival of 51.8 months (range 3-178) and those with R1 resections mean survival of 37.1 months (range 2-92). Kaplan-Meier survival curves for R-status and primary compared with recurrent tumours are shown in Figures 2 and 3.

At three years follow up, 48% (*n*=14) of patients were still alive and there was no statistically significant difference in three-year survival between primary and recurrent sarcoma patients or for resection margin status.

Discussion:

Recent literature indicates that approximately 5% of PE performed for non-rectal malignancies are for pelvic sarcomas [18]. In our quaternary referral centre, there were 29 patients who underwent PE for locally advanced primary, and recurrent pelvic sarcomas over a 15-year period, with the majority having surgery with curative intent. The rarity of these advanced and recurrent tumours highlight one of the many challenges when trying to select which patients are likely to benefit from such extensive surgery, and the importance of specialized centres to oversee patient management.

While the majority of tumours in this series involved the posterior compartment, there was extensive involvement of multiple compartments in most cases. Approximately, one-third required vascular reconstruction and just over 40% of patients required bone resection. The involvement of multiple compartments and need for bony resection and/or vascular reconstruction necessitates radical resection, and contributes to longer operative time, increased blood loss and increased post-operative morbidity, as well as potentially leading to higher rates of positive resection margins [5,6,14,18].

Despite the extensive nature of tumours and extended resections in this series, an R0 rate of 51.7% was achievable, with no recorded 30-day mortality. It is noted that patients with recurrent tumours were more likely to have significant post-operative morbidity. This is in keeping with other studies which report morbidity rates of >80% for PE and increased rate when surgery is performed for recurrence or after previous pelvic irradiation [19,20]. The need for urinary diversion has also been identified as a major risk factor for post-operative morbidity [19, 21]. In our series, all patients who required further surgical intervention suffered complications of urinary diversion, either due to ureteric anastomotic leak from their ileal conduit or the entero-enteric anastomosis after formation of the ileal conduit. Brown *et al.*, have previously reported on the high rates of post-operative morbidity associated with urological reconstruction in the context of PE [12]. It is our institutional practice to re-operate where a ureteric leak is identified within the first week post-operatively.

The three-year survival rate after R0 resection for pelvic sarcomas suggested by other studies is 48.1% [18], which concords with our findings. Due to the small cohort of patients, we cannot clearly identify which factors are associated with improved survival. Previous collaborative studies have suggested that R0 resection is the main determining factor in improving survival rates [18], which is reflected in our results although statistical significance was not achieved. Furthermore, our data would suggest that patients with recurrent disease would have the same benefit of survival as those with primary advanced tumours if an R0 is achieved. Patients with recurrent disease who have potential for complete resection, therefore, should be considered for a pelvic exenteration.

The use of neoadjuvant and adjuvant radiotherapy and chemotherapy in our heterogenous cohort of pelvic sarcoma is reflective of both the distinctive and retrospective nature of this

cohort. There are little randomised data on the efficacy of pre- and post-operative strategies in retroperitoneal sarcoma (RPS) [15], from which neoadjuvant and adjuvant therapy can be extrapolated in pelvic sarcoma. The significant exception to this lack of randomised data, is the STRASS I trial which demonstrated that there was no benefit to recurrence free survival through the routine use of neoadjuvant radiotherapy [22]. An international collaborative phase III trial (EORTC 1809 STRASS II) assessing neoadjuvant chemotherapy in dedifferentiated liposarcoma and leiomyosarcoma will be of great interest, noting that these were the most common histology in our cohort. Adjuvant radiotherapy following gross resection is not of proven benefit and is associated with substantial toxicity [23-24]. Adjuvant chemotherapy after complete gross resection is not of proven benefit in RPS [25]; there may be a role in selected cases following consideration within experience multidisciplinary units [15]. All patients with complex pelvic sarcoma require discussion at an experienced multidisciplinary team meeting to ensure individual treatment decisions are made in line with the best available evidence.

The dictum of success in PE surgery, in terms of objective measures such as survival and recurrence, and subjective measures including quality of life and health economics has been stated to be ‘two-thirds decision-making and only one-third surgical technique’ [17]. This dictum is equally applicable to complex sarcoma surgery. In both PE and RPS, the centralisation of services where there is multidisciplinary expertise in the management of these complex patients, is supported by evidence of improved outcomes for patients [26-27]. It is these centralised, quaternary centres that participate in multinational research collaborations with both prospective databases and randomised controlled trials.

The authors acknowledge the limitations in our study, particularly the small number within the cohort, and its retrospective nature. One area where the retrospective nature of the study had

an impact was on the inability to analyse details of the initial resection in the recurrent cohort of patients, which was not captured in the database. Whilst the small numbers in the cohort likely mean the study is underpowered to identify statistically significant factors associated with survival outcomes; the feasibility of PE for pelvic sarcoma is demonstrated, as is that outcomes in a quaternary Australian unit appear equivalent with those reported in international collaborations.

Conclusion:

PE remains the only possible curative option for patients with advanced primary or recurrent pelvic sarcomas. Improved imaging, surgical planning and increasing multi-disciplinary expertise in PE in quaternary centres, are essential in facilitating appropriate patient selection. In those patients R0 resection rates and five-year survival of more than 50% can be achieved.

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TABLES

TABLE 1. Demographic Information of Patients Undergoing Extended Radical Surgery for Pelvic Sarcoma (*n*=29)

Sex	
Male	10
Female	19
Age	53 (14-82)
Primary Tumor Management	
Neoadjuvant Therapy	
Radiotherapy	5
Chemotherapy	7
Adjuvant Therapy	
Radiotherapy	3
Chemotherapy	1
ASA Score	
1	3
2	15
3	10
4	1
Neoadjuvant Therapy for Recurrence	
Radiotherapy	1
Chemotherapy	5

TABLE 2. Presenting Complaint

Abdominal Pain	6
Altered Bowel Habit	5
Bowel Obstruction	2
Neurologic – motor deficit	2
Vascular	2
Urinary	5
Bowel Perforation	1
Detected on routine surveillance	6

TABLE 3. Type of Sarcoma

Advanced Primary	**16**
Sacral/Pelvic Sarcoma	6
Leiomyosarcoma	4
Pleomorphic Sarcoma	2
Myofibroblastic Sarcoma	1
Liposarcoma	1
Osteosarcoma	1
Prostatic Sarcoma	1
Recurrent	**13**
Sacral/Pelvic Sarcoma	4
Leiomyosarcoma	3
Myofibroblastic Sarcoma	1
Chondrosarcoma	2
Osteosarcoma	1
Ovarian/Endometrial	2

TABLE 4. Clinical Characteristics and Outcomes by Advanced primary Versus Recurrent pathology

	Primary Advanced	Recurrent	Overall	*p*-value
Curative intent	14 (88%)	11 (85%)	25/29	
Pelvic Compartment Excised				
Anterior	2	2	4	
Posterior	6	8	14	
Central	4	6	10	
Right Lateral	4	3	7	
Left Lateral	4	3	7	
Complete	3	2	5	
Resection margins				0.6
R0	9	6	15	
R1	7	7	14	
Length of Stay (days)	27	40	33	0.32

Mean intraoperative blood loss (mL)	3744	3369	3575	0.97
Mean survival (months)	41.2	49	44.7	0.2
Post Operative mortality (30 days)	0	0	0	
Stoma	8	6	14	
Ileal conduit	4	7	11	
Bone(total) Sacrectomy* Pubic bone Ischial bone	5 3 3 3	7 4 3 3	12 7 6 6	
Vascular Internal iliac vessels Common/Ext reconstruction	13 13 7	6 4 3	19 17 10	
Vertical Rectus Abdominus musculo-cutaneous flap (VRAM)	0	2	2	

*Of the sacrectomies performed, there were two that were high (S2 or above) , one in each of locally advanced and recurrent tumours.

TABLE 5. Complications by Advanced primary Versus Recurrent pathology

Complications	Primary Advanced (n=16)	Recurrent (n=13)	Overall (n=29)	
Wound				
Infection	2	6	8	
Superficial Dehiscence	1	4	5	
Pressure ulcer	1	3	4	
Pelvic collection	4	5	9	
Gastrointestinal				
Prolonged ileus	1	4	5	
Small bowel obstruction	2	1	3	
Enterocutaneous fistula	1	1	2	
High output ostomy	2	0	2	
Neurological				

Lower limb deficit	2	2	4	
Sensory deficit	3	4	7	
Urology				
Ureteric leak	0	2	2	
Incontinence	1	1	2	
Cardiovascular				
Arrhythmia	2	4	6	
Deep venous thrombosis	1	4	5	
Pulmonary embolism	0	1	1	
Respiratory				
Atelectasis	5	5	10	
Pneumonia	1	1	2	
Sepsis				
Intrabdominal	0	3	3	
Chest	1	0	1	
IV line related	1	1	2	
Wound	0	3	3	
Urological	0	3	3	
Reoperation	2	5	7	
Small bowel obstruction	1	0	1	
Wound debridement	1	2	3	
Ureteric anastomosis	0	2	2	
Major Vascular	0	1	1	

FIGURES

FIGURE 1. Compartments of the pelvis

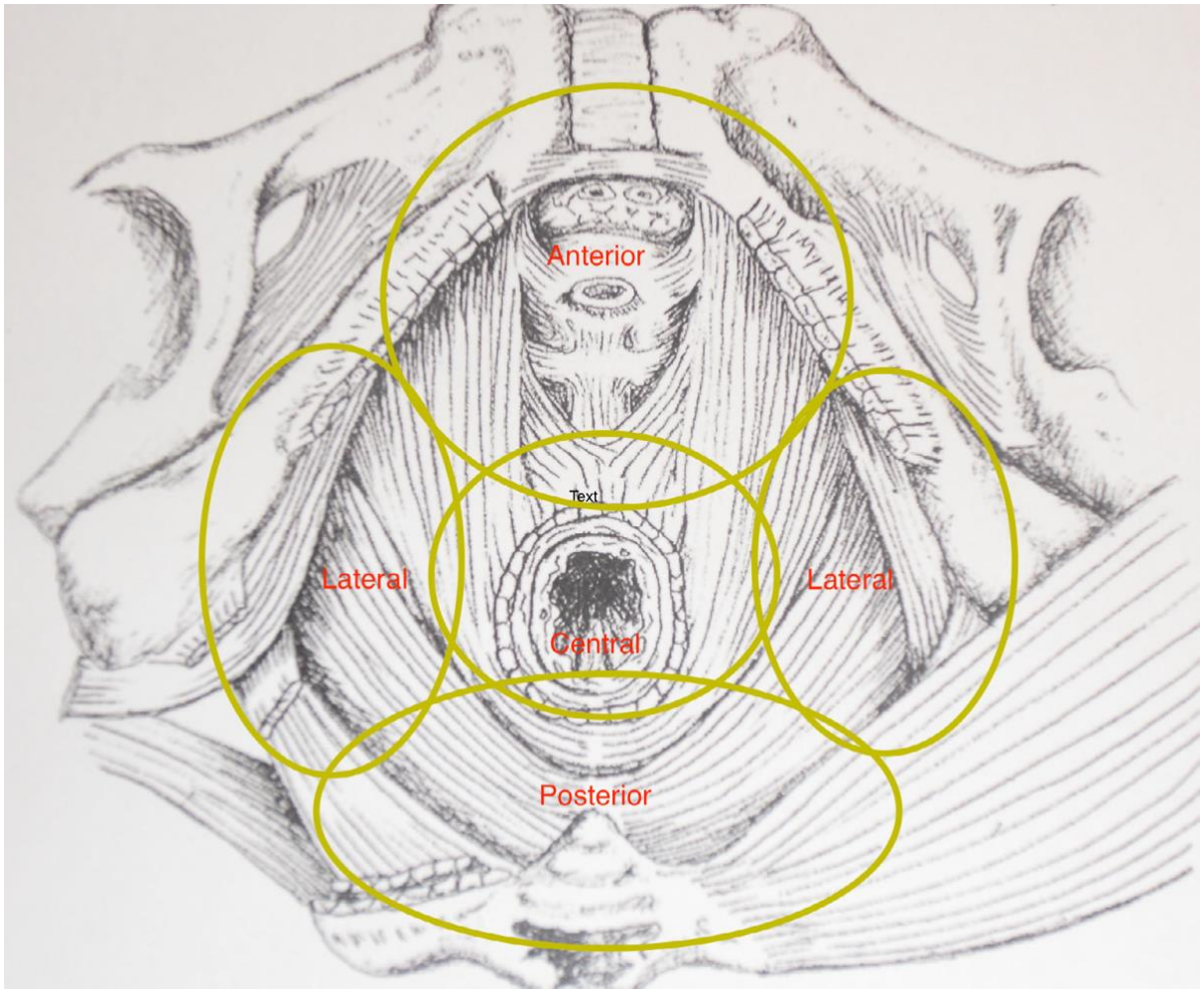
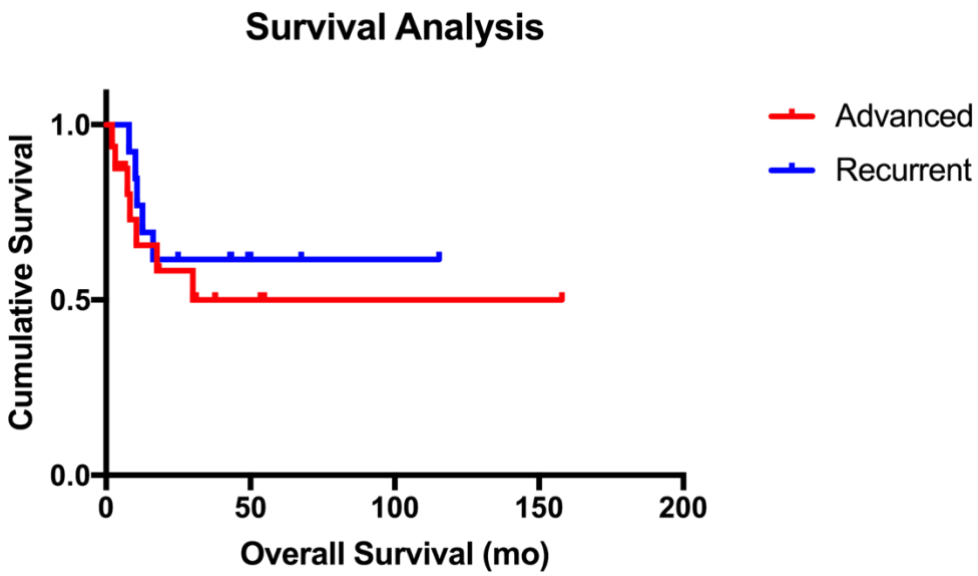


FIGURE 2. Overall Survival (p=0.4766)



Conclusion and future directions

RPS is a rare condition with many different histological subtypes and grades involving in different areas of the abdomen and pelvis. This has historically resulted in small cohort studies with many heterogenous variables for analysis and thus a challenge to draw strong conclusions. Most of the studies include only retrospective evidence, thus the move towards a collaborative approach with the TARPSWG's prospective database is a positive step forward for future studies. Additionally, conducting a cost analysis alongside a quality of life study would be beneficial to further substantiate the findings and their implications. Ultimately, this will help establish the standardisation of care for RPS patients.

The definition of MVR remains a challenge. With the results of the systematic review and evidence from the chapters of this thesis, MVR (including pelvic exenteration) is the recommended approach to achieving the best possible surgical margin, as well as recurrence survival and overall outcome. Its impact on overall survival is still contentious, and while there is heterogenous evidence to support MVR to improve overall survival, survival also depends on the histological subtype and grade.

Multivisceral retroperitoneal resection and pelvic exenteration should always be discussed and performed after an MDT meeting to discuss the risk of morbidity and mortality. As surgeons, we need to take into consideration the patients' quality of life following surgery, especially for the long term, and tailor treatment to the individual.

APPENDIX 1: STATEMENT OF CONTRIBUTIONS

Candidate declaration

Chapter 2 titled "SPARC - A Multi-Disciplinary Team program for Retroperitoneal Sarcoma: The Royal Prince Alfred Hospital and Chris O'Brien Lifehouse Collaboration. Retroperitoneal sarcoma surgery: the importance of a highly specialised institution and multidisciplinary team" has been published (ANZ Journal 2024. doi.org/10.1111/ans.19102). The candidate is the corresponding author.

The nature of the candidate's contribution is as follows:

• Study concept and design

• Data collection and analysis

• Data interpretation

• Manuscript preparation and drafting

• Final approval of manuscript

The nature of contribution by the co-authors is as follows:

Tae Jun Kim– data collection and analysis, data interpretation, preparation of manuscript, final approval of manuscript

Lylee Le- data collection and analysis, data interpretation, revision of manuscript

Yu (Sunny) Wu- data collection and analysis, data interpretation, revision of manuscript

Daniel Steffens- data interpretation, critical revision of manuscript, final approval of manuscript

Sacha Karunaratne- data interpretation, critical revision of manuscript, final approval of manuscript

Wendy Brown- data interpretation, critical revision of manuscript, final approval of manuscript

Rooshdiya Karim- data interpretation, critical revision of manuscript, final approval of manuscript

Peter Grimison- data interpretation, critical revision of manuscript, final approval of manuscript

Angela M. Hong- data interpretation, critical revision of manuscript, final approval of manuscript

Chapter 3 titled “Survival and Morbidity after Pelvic Exenteration for Pelvic Sarcoma: An Institutional Series” has been published (ANZ Journal 2021. doi: 10.1111/ans.17275). The candidate is the corresponding author.

nature of the candidate’s contribution is as follows:

• Study concept and design

• Data collection and analysis

• Data interpretation

• Manuscript preparation and drafting

• Final approval of manuscript

The nature of contribution by the co-authors is as follows:

Babak Meshkat– data collection and analysis, data interpretation, manuscript preparation and drafting, final approval of manuscript

Prashanth Sasidharan- data collection and analysis, data interpretation, revision of manuscript

Assad Zahid- data collection and analysis, data interpretation, revision of manuscript

David Coker- revision of manuscript, final approval of manuscript

Michael J Solomon- data interpretation, critical revision of manuscript, final approval of manuscript

Peter Jun Myung Lee

25/09/2024

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Prof Michael Solomon

25/09/2024