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Defining an Unresectable Primary Retroperitoneal Sarcoma

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ABSTRACT

Background: Retroperitoneal sarcomas (RPS) comprise a heterogenous group of rare mesenchymal tumours. A complete macroscopic en bloc resection of the tumour with involved adjacent structures is the only curative treatment modality. There remain no consensus criteria regarding the definition of a resectable versus unresectable RPS. This study examined the rate, rationale and outcomes for resectable and unresectable RPS from a single large tertiary referral centre.

Methods: All patients with primary non-metastatic RPS referred between January 2017 and March 2023 were identified. Patient and tumour details as well as survival analyses were compared between resectable and unresectable cohorts, and factors for unresectability were analysed.

Results: A total of 104 patients were considered for the analysis, of which 91 (87.5%) were resectable and 13 (12.5%) unresectable. Gender, age, tumour size and side were similar in both cohorts. Unresectability was determined on pre-operative imaging in seven patients (53.8%) and intra-operatively in six (46.2%) patients. The most common technical cause for unresectability was the involvement of superior mesenteric vessels (38.5%). At a median follow-up of 18 months, 84.6% of the unresectable cohort and 8.8% of the resectable cohort had died.

Conclusion: Approximately 12% of patients with primary RPS were unresectable at presentation, and in most cases, unresectability can be determined pre-operatively. Defining resectable and unresectable disease may improve the prognostication and management for patients with primary RPS.

1 | Introduction

Retroperitoneal sarcomas (RPS) are a group of rare mesenchymal tumours representing approximately 15% of patients with soft tissue sarcoma [1, 2]. The annual incidence of RPS is 0.76 per 100 000 persons, which accounts for 0.2%–0.3% of adult malignancies [3, 4]. There are several RPS subtypes; liposarcomas and leiomyosarcomas (LMS) together account for over 75% of cases [5]. Compared to sarcomas in the extremity and trunk, RPS are associated with a generally poor prognosis and relatively high rate of local recurrence as well as distant metastasis.

Surgical resection is the mainstay of treatment for patients with RPS [2, 3, 6, 7]. A complete, macroscopic en bloc resection of the tumour with involved adjacent structures is the sole curative treatment option at present [4, 5, 8]. There is limited evidence regarding the utility of radiotherapy for RPS, although it may be of value in certain subtypes [5, 9, 10]. There is no evidence to support the routine use of perioperative chemotherapy for patients with resectable RPS; however, this question is currently being studied in the STRASS 2 randomised controlled trial (clinicaltrials.gov NCT04031677). Without proven efficacy of (neo)adjuvant treatment modalities, optimal surgical planning is essential

[9, 11]. Despite the importance of surgery in the management of RPS, there are no consensus criteria defining resectability in RPS.

Current consensus from the Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG) states that major vasculature involvement, including portal vein (PV), superior mesenteric artery (SMA), coeliac axis and aorta, as well as bilateral renal involvement, are relative contraindications to surgery [12]. Due consideration to the morbidity associated with extensive retroperitoneal surgery must also be given. Immediate and delayed surgical complications, hospital admission, physical recovery and psychological impact are important factors to acknowledge.

We present a comparison of patients with primary RPS treated with curative intent who underwent resection with those who were deemed unresectable, either prior to surgery or intra-operatively, with a view to identifying which pre-operative factors best indicate unresectability.

2 | Methods

All patients with primary, non-metastatic RPS managed at Peter MacCallum Cancer Centre, Melbourne, Australia between January 2017 and March 2023 were included. Patients were excluded if there was a concurrent malignancy or if they elected for non-operative management. All patients were planned for surgery with curative intent. Patients who proceeded to surgery for recurrent disease, as well as those who had an alternative diagnosis confirmed on pathology post-operatively, were excluded from the analysis.

2.1 | Patient Data

Patient data were extracted from the medical electronic records and included: age, gender, diagnosis, anatomical location of the tumour (right, left or other), the date of the surgery, the pre-operative imaging (contrast-enhanced computed tomography [CT] of the chest, abdomen and pelvis, including the largest tumour measurement on CT from radiologist report for sizing of the tumour), pathology data (pre-operative biopsy details, the final diagnosis and the grade of the tumour). Histological subtypes were classified as per the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system [13].

2.2 | Neoadjuvant Treatment

A proportion of patients underwent neoadjuvant therapies in accordance with institutional protocols following review in a multidisciplinary forum. Such information was included in the analysis.

2.3 | Surgical Procedure

The intra-operative decision as to whether the tumour was completely resectable or not was made by the operating surgeon. The rationale for unresectability was also recorded and formed part of the analysis.

2.4 | Statistical Analysis

Patient data and clinical information were retrieved from a prospectively maintained database. Statistical analyses were performed using STATA software for Windows (version 16.1). Categorical variables were compared with chi square test, and Student's t test and Mann–Whitney U test were utilised for continuous variables. Survival was calculated from the day of diagnosis to the last recorded clinical follow-up or death. Survival curves were estimated with the Kaplan–Meier method, with log-rank test comparison of cohorts. Analyses were two-sided, with a p-value < 0.05 taken to be statistically significant.

3 | Results

A total of 137 patients were identified, 14 of whom were excluded for recurrent tumours, seven excluded for incomplete staging or lack of biopsy, yielding a total of 116 patients considered. A further 12 patients were excluded for either concurrent malignancy precluding resection, metastatic disease, patient declining surgery or deemed not fit enough for resection, leaving a total of 104 patients for the analysis.

3.1 | Resectable and Unresectable Groups

The cohort was divided into two groups based on resectability: 91 (87.5%) patients in the resectable group and 13 (12.5%) in the unresectable group. The median age was 62 (range 21–88) years in the resectable group and 63 (range 39–86) years in the unresectable group. The median tumour size, taken as the largest tumour dimension on CT, was 173.8 mm (range 34–410 mm) in the resectable group and 159 mm (range 60–275 mm) in the unresectable group. Additional patient and tumour characteristics are summarised in Table 1.

3.2 | Tumour Subtypes and Histopathology Characteristics

Unresectable cases were most commonly DDLPS (69%) compared to WDLPS (15%) and LMS (7%). In the resectable cohort, WDLPS (42.9%) was the most common subtype, followed by DDLPS (31.9%) and LMS (19.8%). Grade 2 tumours were the most prevalent in both cohorts, comprising 54.9% of the resectable group and 38.5% of the unresectable.

3.3 | Rationale for Unresectability

Ninety-one of 104 (87.5%) patients were considered resectable and 13 (12.5%) patients were unresectable. Seven (53.8%) of the unresectable cohort were deemed so pre-operatively and the remaining six (46.2%) intra-operatively. Cross-sectional imaging from two of the patients deemed unresectable due to major vasculature involvement is demonstrated in Figures 1 and 2.

TABLE 1 | Patient and tumour characteristics for resectable and unresectable populations.

	Resectable ($n=91$)	Unresectable ($n=13$)	p
Gender			0.603
Female	42 (46.2%)	7 (53.8%)	
Male	49 (53.8%)	6 (46.2%)	
Age, year			0.772
Median	62	63	
Range	21–88	39–86	
Tumour size, mm			0.881
Median	173.8	159	
Range	34–410	60–275	
Side of disease			0.632
Left	35 (38.5%)	5 (38.5%)	
Right	47 (51.6%)	8 (61.5%)	
Other	2 (2.2%)	0 (0%)	
Histologic subtype			0.034
WDLPS	39 (42.9%)	2 (15.4%)	
DDLPS	29 (31.9%)	9 (69.2%)	
LMS	19 (20.9%)	1 (7.7%)	
SFT	1 (1.1%)	0 (0%)	
Other	3 (3.3%)	1 (7.7%)	
FNCLCC grade			0.187
1	26 (28.6%)	2 (15.4%)	
2	50 (54.9%)	5 (38.5%)	
3	13 (14.3%)	4 (30.8%)	
Unknown	2 (2.2%)	2 (15.4%)	

Abbreviations: DDLPS, dedifferentiated liposarcoma; FNCLCC, Fédération Nationale des Centres de Lutte Contre Le Cancer; LMS, leiomyosarcoma; SFT, solitary fibrous tumour; WDLPS, well-differentiated liposarcoma.

Five of the 13 (38.5%) unresectable patients were reported unresectable secondary to involvement of superior mesenteric vessels, one pre-operatively and four intra-operatively. Two patients (15.4%) were unresectable for involvement of the aorta and coeliac axis. Other technical reasons for unresectability included extensive intra-abdominal disease not appreciated on pre-operative imaging (7.7%) and involvement of the IVC not amenable for reconstruction (7.7%). All patients were discussed in a sarcoma specialist multidisciplinary meeting, including the patients subsequently deemed unresectable at the time of the surgery. All of the four intra-operatively unresectable patients were considered resectable with curative intent treatment at the time of the initial multidisciplinary meeting. The major non-technical reason for unresectability was progression on neoadjuvant radiotherapy (30.8%). These findings are summarised in Tables 2 and 3.

In the resectable cohort 83 (91.2%) an R0/1 resection was achieved. Of the eight patients who had an R2 resection margin, five were WDLPS and three were DDLPS. Six of the eight R2 resections (75%) were for left-sided resections. Two of the patients who had R2 margins had undergone neoadjuvant radiotherapy.

3.4 | Neoadjuvant Therapies

The neoadjuvant chemotherapy regimes utilised included combinations of gemcitabine and docetaxel, doxorubicin and ifosfamide or vincristine, doxorubicin and cyclophosphamide. Six patients (5.8%) were initially considered resectable before progressing on neoadjuvant chemotherapy, which then precluded resection. Similarly, three patients (2.9%) demonstrated radiological disease progression on neoadjuvant radiotherapy and did not proceed to resection. One patient who received neoadjuvant radiotherapy was considered borderline for resection on imaging, then proceeded to surgery; however, they were found to have aortic involvement intra-operatively and were deemed unresectable.

3.5 | Survival Outcomes

The median follow-up from diagnosis for the resectable cohort was 24 months (3–59 months). At 12 months from diagnosis, six of 91 (6.6%) of the resectable cohort had died, three (3.3%) of whom were DDLPS, two (2.2%) were LMS and one was a solitary fibrous tumour. Of the six mortalities within 12 months from the resectable cohort, three patients had R0 resections and three had R1 resections. Of this same population, two patients had developed local recurrence of disease, two distant metastatic disease and one patient both local and distant metastatic disease. One mortality was in one patient without disease recurrence secondary to an unrelated medical issue. Patients with resectable WDLPS had the best survival outcomes, with 100% of patients alive at 12 months. At 18 months from diagnosis, 11 of 13 (84.6%) of the unresectable cohort had died. A survival comparison for the tumour subtypes is presented in Figure 3a,b.

4 | Discussion

RPS represent a rare group of tumours that present a surgical challenge due to their complex anatomical variation and involvement of adjacent organs. In our study, we describe the outcomes of patients presenting with primary, non-metastatic RPS deemed unresectable either on pre-operative scans or intra-operatively. The vast majority of the patients proceeded to resection with curative intent, and the main reason for inoperability was involvement of critical vascular structures. Not surprisingly, patients with unresectable tumours had a worse prognosis compared to patients who underwent complete resection. Patients with DDLPS, particularly those with high-grade disease, were associated with the worst prognosis. This is one

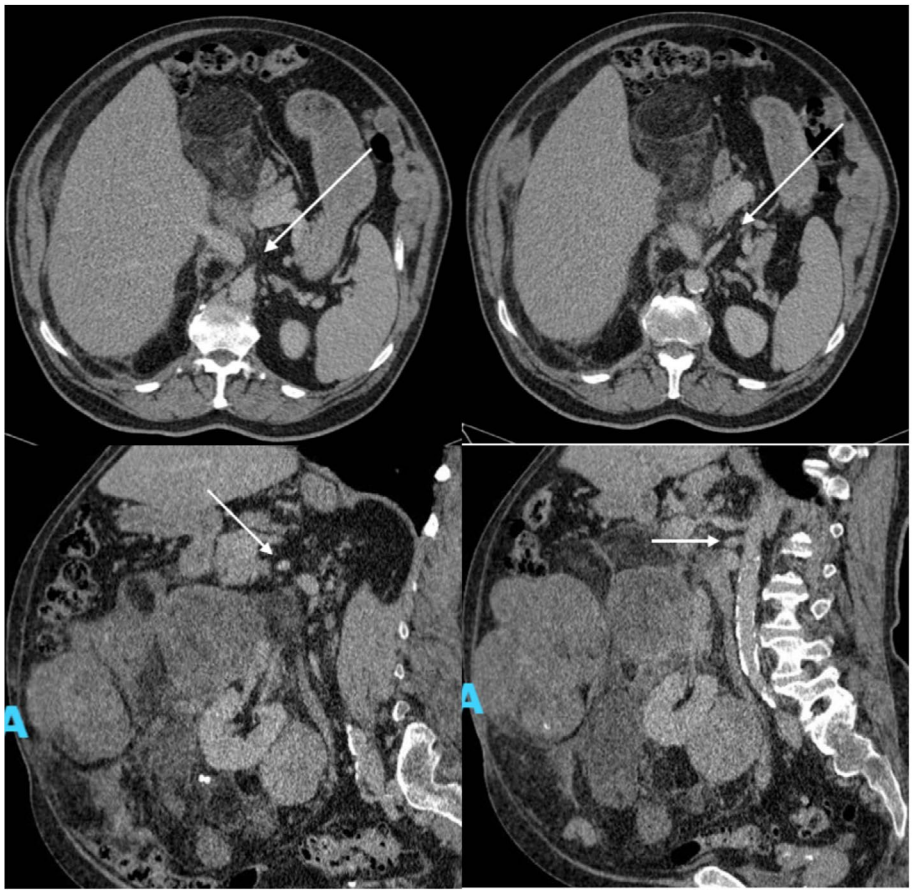

FIGURE 1 | Computer tomography (CT) axial and sagittal planar imaging demonstrating an unresectable RPS secondary to involvement of the SMA (arrow).

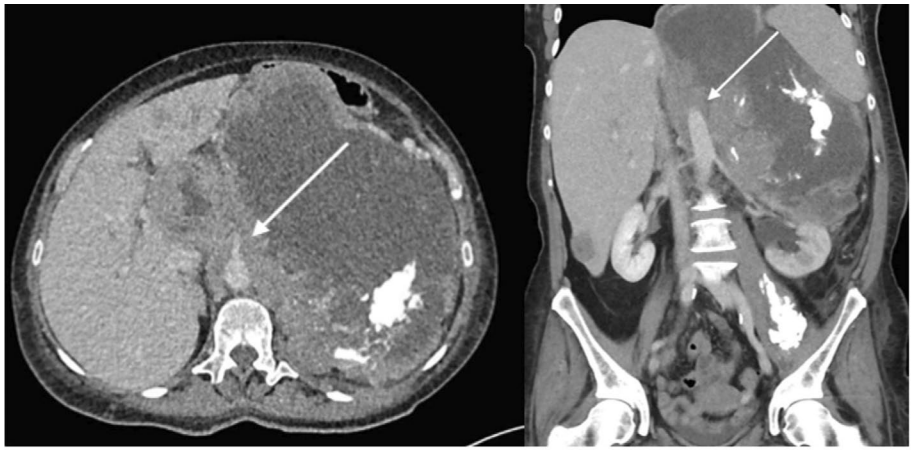

FIGURE 2 | Computer tomography (CT) axial and coronal imaging demonstrating an unresectable RPS secondary to aortic involvement (arrow).

of the first studies to detail the reasons for unresectability in patients with primary RPS.

Resectability of RPS has been previously described. The largest of these studies by Perhavec et al. [3] included 322 patients, of which 37 (11.5%) were deemed unresectable based on preoperative characteristics. Of this unresectable population, 20 (6.2%) were not considered for resection because of technical considerations, mainly involvement of major vascular structures. Deanna et al. [14] also reported on a population of 130 patients with primary RPS, of which 26% were unresectable. In their study, 13.1% of the unresectable patients were deemed so due to involvement of major vascular structures or other technical considerations. The proportion of patients in the current study deemed technically unresectable was 6.7%. Similar rates of patient comorbidities preventing resection were reported here (6.7%) when compared with Perhavec et al., 5.6%, and Deanna et al., 6.9%. This included three patients deemed medically unsuitable for multivisceral resection, as well as an 86-year-old patient deemed unfit for IVC resection and reconstruction. A

TABLE 2 | Reasons for unresectable disease.

Reasons for unresectability	*N* (13)	% of all patients (*n* = 104)
Extensive intra-abdominal disease (pre-operative/intra-operative)	1 (0/1)	0.96
Local progression on radiotherapy	4	3.85
Involvement/invasion of SMA (pre-operative/intra-operative)	5 (1/4)	4.81
Involvement/invasion of aorta/coeliac axis (pre-operative/intra-operative)	2 (1/1)	1.92
Involvement of the IVC (pre-operative/intra-operative)	1 (1/0)	0.96

Abbreviations: IVC inferior vena cava; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

TABLE 3 | Unresectable cohort.

Age	Histology	Size (cm)	Reason for unresectability
71	Fibrosarcoma	200	SMA involvement
40	DDLPS	137	Aorta involved (intra-operative)
76	DDLPS	174	Disease progression on neoadjuvant radiotherapy
50	WDLPS	60	SMA involvement (intra-operative)
68	DDLPS	119	Disease progression on neoadjuvant radiotherapy
59	DDLPS	126	Aorta/coeliac involvement
86	DDLPS	159	IVC involvement/unfit for major vascular resection (intra-operative)
68	DDLPS	275	SMA involvement (intra-operative)
76	LMS	97	SMA involvement (intra-operative)
54	DDLPS	206	Diffuse intra-abdominal metastatic disease (intra-operative)
55	DDLPS	94	Disease progression on neoadjuvant radiotherapy
39	DDLPS	177	Disease progression on neoadjuvant radiotherapy
66	WDLPS	265	SMA involvement (intra-operative)

Abbreviations: IVC, inferior vena cava; SMA, superior mesenteric artery.

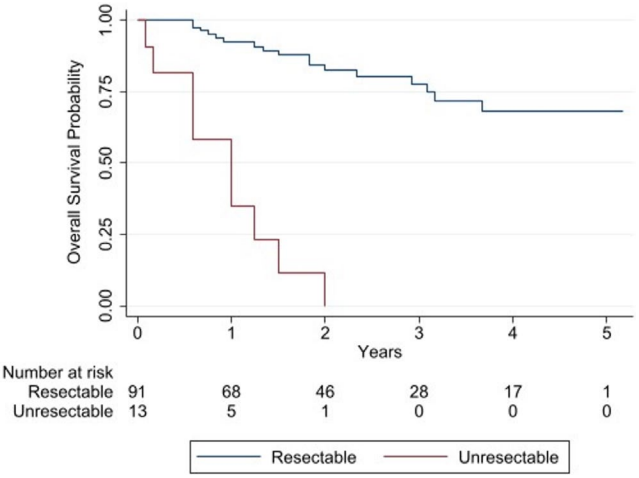

FIGURE 3 | Kaplan–Meier survival curve for (a) resectable RPS and (b) unresectable RPS.

further three patients were excluded for concurrent malignancy (metastatic melanoma, renal cell carcinoma, colorectal carcinoma). One patient who was deemed resectable but elected for non-operative management was also excluded from the unresectable cohort and the analysis. A comparison of the two prior published comparative studies of resectable and unresectable RPS with the study presented here is depicted in Table 4.

Survival outcomes are consistently better in resected cohorts within the published literature for all RPS subtypes [3, 15–18]. This was similarly demonstrated in this study, represented in Figure 4. In the cohort reported by Perhavec et al. [3] from 2021, there was 83.2% and 35.0% survival in the resectable and unresectable cohorts, respectively, with a median follow-up of 34 months. With our single institution population, we have similarly demonstrated a significant survival benefit with resection for each of the tumour subtypes. At a follow-up of 18 months, we reported 91.2% and 15.4% survival in the resectable and unresectable cohorts respectively. Of the six patients that were deemed to be unresectable intra-operatively, one was alive at 18 months. The R2 resection rate of 8.8% is at the higher end of the published literature [19, 20]. In a 2025 review of RPS management worldwide, 16 of 19 centres had R2 resection rates of less than the benchmarked 11%; however, others reported R2 resection rates of 19% and the highest 42% [21]. This speaks to both the significant heterogeneity in case mix and perceived resectability of these tumours without a standardisation.

Neoadjuvant systemic therapies for RPS are an area of ongoing research, in particular with the STRASS2 trial (an ongoing randomised controlled trial of neoadjuvant therapy for patients at high risk of metastatic disease). The majority of treatment regimens are extrapolated from extremity sarcoma, despite the recognition of different behaviour, growth and metastatic patterns in RPS [2]. There are a number of recognised hypothetical benefits from neoadjuvant systemic therapy, including potential downstaging of tumours, reducing microscopic tumour burden as well as better tolerance in the neoadjuvant as opposed to the adjuvant setting, although this is yet to be recognised by way of improved survival outcomes [7]. Furthermore, as surgery for RPS often involves nephrectomy, neoadjuvant chemotherapy

TABLE 4 | Key studies in unresectable and resectable primary RPS.

	Year of publication	Country	Number of patients	% of total cohort unresectable	Pre-operative vs. intra-operative decision	Anatomical consideration	Patient unfit for surgery
Deanna	2018	Canada	130	34 (26%)	34/0	22 (16.9%)	12 (9.2%)
Perhavec	2021	Italy	322	37 (11.5%)	37/0	20 (6.2%)	17 (5.3%)
Tai	2025	Australia	104	13 (12.5%)	7/6	8 (7.7%)	7 (6.7%)

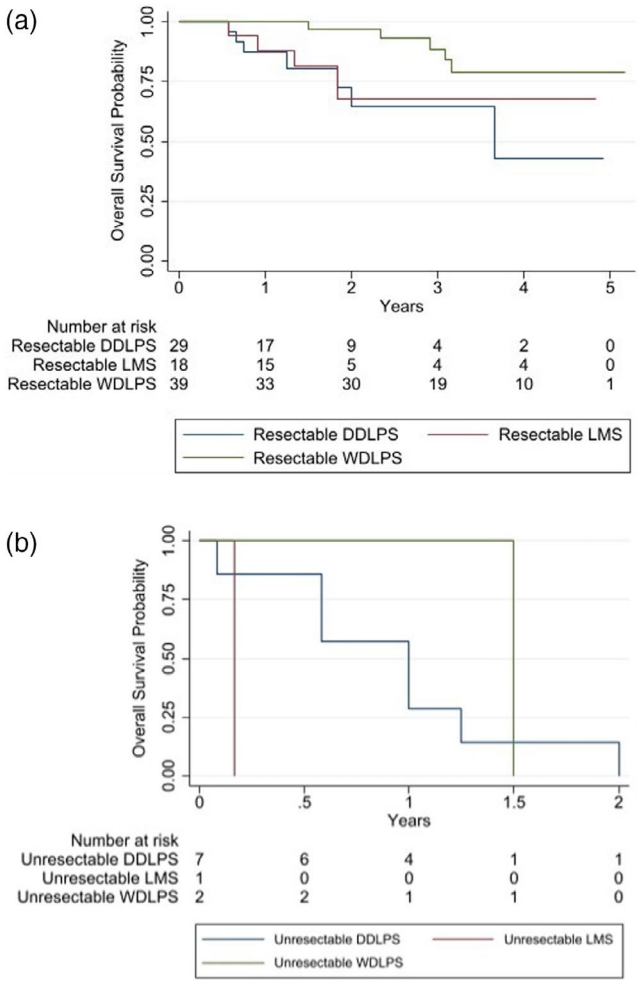

FIGURE 4 | Kaplan–Meier survival curve comparing resectable versus unresectable disease.

allows administration of chemotherapy whilst the patient has two kidneys functioning. In 2021, Tseng et al. [6] reported on outcomes following neoadjuvant systemic therapy from a number of centres from the TARPSWG. They reported a clinical benefit in 79% of cases with this approach, with the suggestion that most benefit was likely to be seen in the population of high-risk primary disease [6]. Concurrent neoadjuvant radiotherapy, given in 46% of cases, was not associated with a higher rate of pathological complete response [6]. Similarly to resectability, there is a no consensus as to the most effective systemic therapy for the diverse range of RPS [1, 7]. Combination anthracycline and ifosfamide was the most common regimen adopted in this multicentre study, although there was marked heterogeneity [6]. Combination neoadjuvant chemotherapy and radiotherapy is also not standard of care for RPS. De Sanctis et al. [22] published on the relapse-free survival and overall survival of 83 patients with both primary and locally recurrent RPS who were administered high-dose ifosfamide with concurrent radiotherapy prior to resection. In this cohort, the 7-year overall survival was 63.2% and disease-free survival 46.6%, demonstrating feasibility; however, they were unable to comment on efficacy without a comparison arm.

Pre-operative radiotherapy is offered selectively for patients with RPS [9, 22]. The STRASS and subsequent STREXIT study [10] demonstrated that neoadjuvant RT was most likely to be of benefit in those patients at the lowest risk of developing distant metastatic disease, namely patients with well-differentiated liposarcoma and Grade 1 and Grade 2 dedifferentiated liposarcoma.

The optimal management of RPS is provided by a specialised multidisciplinary team [18, 23, 24]. The TARPSWG consensus paper [12] on the management of primary RPS highlighted the importance of collaboration and of multispecialty surgical input to optimise perioperative outcomes. Importantly, the role of further research was also emphasised. The recommendation for said multidisciplinary team included radiologists, pathologists and medical, radiation and surgical oncologists to share complex decision-making around management. All patients included within this study were discussed in a multidisciplinary meeting and were consulted by specialist sarcoma surgeons.

Higher rates of local recurrence with limited resection led to the adoption of more aggressive surgical resections for RPS [17, 25]. In 2009, Gronchi et al. [17] published a 48% 5-year survival with an aggressive surgical strategy involving en bloc resection of adjacent organs compared with a 28% 5-year survival managed with a more conservative surgical approach. Similarly, in 2010, Bonvalot et al. [16] reported a 5-year survival rate of 65.4% with a compartmental resection strategy which, with other contemporary research, informed the TARPSWG recommendations for surgical management. This consensus was for complete, macroscopic en bloc resection of the tumour with involved organs [4, 5, 18]. As surgical techniques develop in efficacy and safety, the definitions of resectable and unresectable RPS will likely shift. It is critical that there is a framework from which to build on these definitions. This will further promote higher-quality research, objectivity in decision making, and improved

patient outcomes. RPS resection involving vascular reconstruction in particular has higher rates of morbidity [26–28]. Tzanis et al. [26] published a review on vascular reconstructive options in RPS, making note of careful patient selection with appropriate pathology in a high-volume, specialised centres as predictive factors for improved outcomes. One proposed model to base the criteria of resectability on, with a similar focus on major vessel involvement, is that of pancreatic cancer [3, 29]. In principle, translating these unresectable or borderline characteristics to the RPS population would be beneficial not only in reducing the subjective decision making on an individual patient basis but also standardising the definitions from a research perspective. Whilst this model would be beneficial in consideration of anatomic relationship to vasculature for RPS, unresectability may also relate to numerous tumour-organ relationships [12, 29]. Notably, the biology of pancreatic ductal adenocarcinoma is markedly different from the heterogeneous RPS cohort and, as such, the implications of the technically resectable imaging findings may not translate to the same treatment intent for RPS.

This study is a retrospective analysis and there are therefore significant limitations. The main limitation relates to a thorough understanding of the primary reason for unresectability, particularly in those cases which were technically resectable but did not proceed due to patient preference or comorbidities. However, patients were prospectively enrolled in a comprehensive registry and all patients were discussed in a high-volume multidisciplinary meeting and underwent surgery at a quaternary high-volume referral centre.

5 | Conclusion

Surgical resection is the gold standard for curative treatment of primary RPS, and dedicated efforts are required to define the limitations of this treatment. This will not only improve the surgical experience but also facilitate multidisciplinary management as advances in systemic therapy continue to be made. The current study highlights that the majority of patients presenting with primary RPS have resectable disease. The most common technical reason for unresectability is involvement of critical vasculature. More clearly defined criteria for resectability will improve patient selection for upfront surgery or for systemic therapy options.

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Disclosure

The authors have nothing to report.

Ethics Statement

Study approval was awarded by the institutional human research ethics committee.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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