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REVIEW ARTICLE

Retroperitoneal Sarcomas: a Current Review on Management

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Abstract
Retroperitoneal sarcomas are heterogeneous tumours with variable disease biology and outcomes. The prognosis is primarily related to tumour histology and grade as well as the ability to achieve margin negative resection. Surgery involves compartment or contiguous organ resection to achieve the above goal. Careful utilization of neoadjuvant and adjuvant strategies like radiotherapy and/or chemotherapy can lead to improvement in margin status, thereby contributing to better local control and possibly reducing systemic dissemination. Use of targeted therapies has paved newer pathways of treatment integration centred on molecular and genetic targets. The aim of this review is to update the reader on all aspects of retroperitoneal sarcoma management including emphasis on pertinent and landmark trials in this regard.

Keywords Chemotherapy · Compartment resections · Multimodality · Radiotherapy · Retroperitoneal · Sarcomas

Introduction

The management of retroperitoneal sarcomas (RPS) has evolved with time. This evolution has been championed partly by the better understanding of the tumour biology and improvement in surgical and perioperative care. Histology-driven treatment allows for individualization of care. Improvements and advances in chemotherapeutic agents and radiotherapy delivery systems have contributed to betterment in recurrence rates and therefore survival. The present review aims to impress the reader about the various treatment protocols and principles thereof.

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Management

Surgery

Principles

Surgery is the only potential curative treatment in RPS and entails en bloc resection of the tumour with adjacent organs or vessels with the goal of R0 resection. The surgical procedures include wide local excision to compartmental and multiorgan eviscerations. The oncological effectiveness of adjacent organ removal should be correctly balanced with the anticipated morbidity and the chance of local recurrences, if left in situ [1–6]. Careful pre-operative assessment of the tumour in relation to surrounding structures is paramount. Routine pre-operative biopsies are not indicated, if found resectable. Though midline vertical incisions are most commonly employed for exposure, additional extensions/incisions may be warranted depending on the tumour location and extent. The first attempt at resection is the best attempt. In the disruption of the capsule or tumour rupture, both increase the risk of local recurrence (by 1.67 times) and sarcomatosis. Resection of major vessels, nerves and bone is

indicated only if there is direct invasion of these structures. Unresectability is defined by the following: (a) tumour infiltrating long segments of the superior mesenteric vessels, celiac axis, (b) spinal cord involvement, (c) extensive mediastinal involvement and (d) widespread multifocality [1–6].

Compartmental and Multivisceral Resections

Compartment (or extended) and multivisceral resections involve removing adjacent organs or vessels so as to obtain margin negative (R0) resection. When grossly involved adjacent organs are removed en bloc with the tumour, the term *selective organ resection* is used. *Compartmental resection* is one where all organs and soft tissue in that compartment are removed en bloc with the tumour irrespective of involvement (Fig. 1) which is in close proximity to the tumour. Both procedures achieve excellent local control [1–3, 5–10].

Two landmark studies [11, 12], including their combined data [13], demonstrated improved local control with a threefold reduction in local recurrences in those undergoing compartmental resections compared to wide excision or selective organ resection. The procedure was deemed safe with acceptable morbidity. As histology-driven tumour biology becomes more evident, surgical approaches tailored to specific histologies are increasingly being adopted. Table 1 depicts the published literature on multivisceral resections in RPS.

Organ resection must be individualised weighing the potential morbidity to the benefit of obtaining an R0 resection. Even if organ infiltration is not evident intraoperatively, it is wiser to resect adjacent organs to reduce the risk of margin positivity. The need for adjacent organ removal may be due to (a) suspected invasion/origin of tumour, (b) involvement of vasculature of the organ, (c) tumour encasement, (d) tumour adherence, (e) tumour lies adjacent to organ and is required for R0/R1 resection and (f) iatrogenic injury, incidental resection for another reason, etc. This classification system was propounded by the Dana Farber Cancer Institute (DFCI) [14]. Measurement of the anticipated morbidity following organ resections is done using the Resected Organ Score (ROS). The higher the score, the more is the morbidity associated with organ removal [1–3, 5–10].

Histologic Organ Invasion

Histologic organ invasion (HOI) defines the presence (or absence) of tumour deposit at the sarcoma-adjacent organ/vessel interface and therefore influences recurrence patterns and survival: A tumour with a positive HOI has an increased risk of local recurrence and reduced survival. HOI in turn is related to histology and the rationale for adjacent organ removal at surgery. The incidence of positive HOI in patients with well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS) and leiomyosarcoma (LMS) respectively is 40, 61 and 56% [8]. The risk of positive HOI is around 20–25% for tumour adhesion/encasement which increases to 65% when frank invasion is seen. Routine-adjacent organ removal may not necessarily show positive HOI. Therefore, pre-operative assessment is crucial to guide the extent of surgery. However, early pericapsular involvement cannot be identified either pre- or intra-operatively and therefore to resect or not to resect should not be solely based on frank organ invasion [3]. Fairweather et al. [14] reported a positive HOI in 26% of the organs removed in 58% of patients. The 5-year overall survival (OS) of 34% (vs 62%) in patients with a positive HOI demonstrated that HOI was an independent predictor of poor outcomes. In another study by Wang et al. [15], the authors reported that 28.5% and 35.7% of the organs resected respectively showed adjacent organ and surrounding fat infiltration.

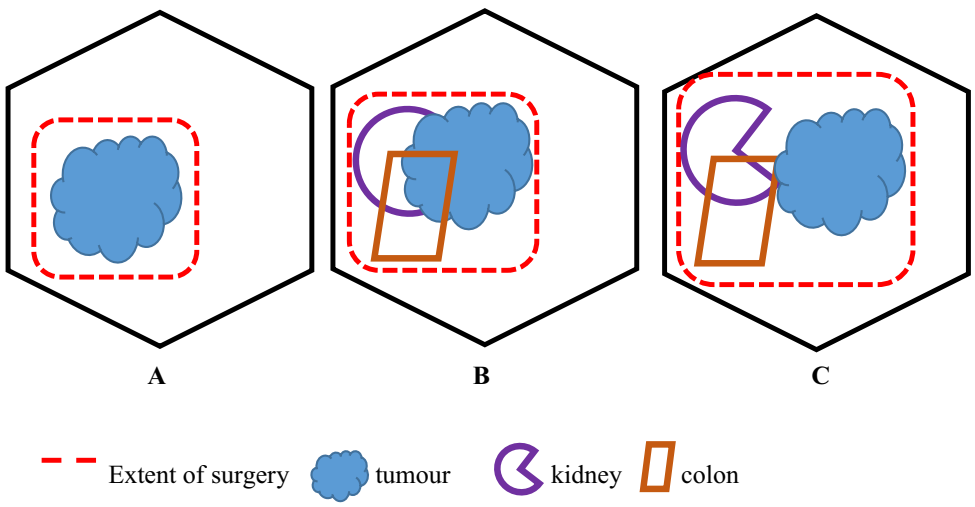

Fig. 1 Diagrammatic representation of wide excision (A), selective organ resection (B) and compartmental resection (C)

Table 1 Published studies on compartmental and multivisceral resections in RPS

Author/year	Period	*n*	MVR (%)	Tumour size (median, cm)	R0 + / − R1 resections	F/U (mo.)	Recurrences	Survival	Post-op morbidity
Gronchi [11] 2009	1985–2007	136 vs 152	20 vs 50	15 vs 18	88 vs 91%	58, 120 vs 32	LR: 48 vs 28% DM: 13 vs 22%	5 y OS: 51 vs 60%	NA
Bonvalot [12] 2009	1985–2005	382	Comp.: 31.4 Cont.: 34	18	75%	56.8	LR: 49% DM: 34%	5 y OS: 57%	16%; 3% deaths
Bonvalot [13] 2010	2000–2008	249	1 organ: 16 > 1: 74	17	93%	37	LR: 22.3% DM: 24%	5 y OS: 65.4%	18%; 3% deaths
Gronchi [50] 2012	1985–2008	331	24 vs 63	15 vs 18	90 vs 94%	127 vs 48	LR: 49 vs 28% DM: 12 vs 25%	5 y OS: 48 vs 66%	NA
Gronchi [51] 2013	1999–2009	523	1 organ: 34 > 1: 57	16	90.8%	45	LR: 24.5% DM: 17.8%	5 y OS: 56.8% 5 y DFS: 39.4%	NA
Toulmonde [52] 2014	1988–2008	486	Comp.: 24 ≥ 1: 65	17	76%	78	LR: 54% DM: 22%	5 y OS: 66%	NA
Panda [53] 2015	2008–2010	23	26	10	61%	24	LR: 39.1%	5 y OS: 60%	1 death
Tan [54] 2016	1982–2010	675	1 organ: 53 > 1: 47	17	85%	39.6	LR: 45% DM: 29%	10 y DSS: 55%	NA
Hogg [55] 2016	1997–2013	79	> 1:70	20.5 mean	89%	61	LR: 41% DM: 12.2%	5 y OS: 55.3%	3 deaths
Abdelfatah [54, 56] 2016	1994–2010	131	51.3 Vascular: 16	12.3	84.4%	NA	NA	Median OS: 48.7 mo	NA
Guiliano [57] 2016	2002–2012	2920	39.5	15	NA	NA	LR: 4.6% DM: 14.6%	5 y OS: 58.4%	33.6% CSM
Fair-weather [14] 2017	2002–2011	99/ 118	1 organ: 84	15–17	84%	33.6	LR: 48% DM: 22 and 46%	5 y OS: 34–62% (HOI + ve vs HOI − ve)	NA
Petrou [58] 2017	2002–2016	108	67 Cont.: 73.3 Comp.: 6.67	10–33	95%	83	43.3%	5 y and 10 y OS: 88 and 79% 5 y and 10 y DFS: 65 and 59%	NA
TARPSWG [59] 2017	2002–2011	1007	≥ 1: 87	20	95.3%	58	LR: 25.9% DM: 21%	5 y OS: 67% 10 y OS: 46%	16.4% 1.8% deaths
Ng WJ [60] 2017	2000–2014	85	1 organ: 50 > 1: 9.4	16.5	50%	46	59%	Median OS: 45 mo	NA
Stahl [61] 2017	1998–2011	4015	NA	16	64.6%	67	NA	5 y OS: 64.7%	NA
Chiappa [62] 2018	1994–2015	83	64	10–20	74%	84	NA	5 y OS: 51% 5 y DFS: 58%	24%
Snow [63] 2018	2008–2016	88	Kidney: 43 Colon: 36 Others < 10	13	97%	36	LR: 35%	5 y OS: 66%	NA
Malinka [64] 2019	2005–2015	61	28 (vascular)	NA	84% (+R1)	74	LR: 41%	5 y OS: 58% 5 y DFS: 34%	31%
Patkar [65] 2020	2008–2017	100	Cont.: 43 Vascular: 7	15	83%	25.3	LR: 35% DM: 20%	5 y OS: 62%	29%

Comp. compartmental resection, *cont.* contiguous resection, *MVR* multivisceral resection, *LR* local recurrence, *DM* distant metastases, *mo.* months, *NA* not available, *OS* overall survival, *DFS* disease-free survival, *CSM* cause-specific mortality

Metastasectomy

The risk of distant metastases in RPS is related to two important factors: histology and grade of the tumour and recurrent disease. The concept and data for metastasectomy for RPS is not very robust unlike extremity sarcomas. Various small studies have reported or suggested some survival benefit with a caveat that patient selection

is extremely important to achieve these outcomes. The prerequisites for performing a metastasectomy are (a) low volume disease at recurrence, (b) ability to achieve R0 resection, (c) disease-free interval (DFI) of > 12 months, (d) stable disease at recurrence for > 6 months irrespective of chemotherapy use, (e) good performance status with normal hepatic/pulmonary function and (f) LMS histology. The presence of multifocal intra-abdominal recurrences/metastases is a contraindication for metastasectomy.

Palliative Surgery

The role of palliative surgery in RPS is controversial and incompletely understood. Palliative surgery can be classified as planned or unplanned [2]. The former includes tumour debulking in patients otherwise deemed incurable where it is done to ameliorate symptoms of pain, obstruction, etc. so as to improve quality of life. The latter includes patients in whom intra-operative findings alter the intent of treatment, although such decisions were not intended pre-operatively. The decision to pursue palliative surgery requires thorough assessment of the plausible benefits, including improvement in symptoms to the substantial morbidity (around 30% with 12% mortality) of surgery in the setting of metastatic disease [5, 16]. Therefore, these decisions have to be made in a multidisciplinary setting [1]. Furthermore, any surgical intervention is likely to delay chemotherapy which is the standard of care in a metastatic scenario [1] and patients with multifocal intra-abdominal recurrences rarely benefit from debulking.

Minimally Invasive Surgery

The use of minimally invasive surgery (MIS) in RPS surgery is evolving. Using the NCDB, Gani et al. [17] studied the association of clinical outcomes and MIS in patients undergoing surgery for RPS. Post-operative outcomes and survival were similar between the MIS and open groups. The authors concluded that clinical outcomes of MIS were comparable to open surgery, although the need for further randomised trials to evaluate outcomes was highlighted. However, oncological end points were not reported. The potential criticisms for use of MIS routinely in RPS are (a) higher risk of R + resections, especially in liposarcomas due to tumour multifocality, (b) need for large incisions to retrieve the tumour (especially those undergoing multivisceral resections), (c) absence of robust oncological benefit or equivalence of MIS over open surgery till date and (d) inadequate or incomplete surgery at the first attempt can jeopardise future treatment and outcomes in these patients. Therefore, routine use of MIS cannot be recommended [18].

Surgical Quality

There has been a paradigm shift in the surgical approaches and techniques involved during the treatment of RPS. The adage 'first is the best' holds maximum relevance in RPS surgery. Going by these trial results, it can be concluded that surgeries performed in high volume centres lead to (a) more margin negative resections, (b) more surgical oriented decisions, (c) reduction in risk of disease related deaths by at least twofold and (d) possible improvement in overall survival. Table 2 depicts the various studies on surgical quality and outcomes in RPS.

Recurrent Disease and Salvage Surgery [1, 2, 5, 8, 19–24]

The rate of recurrent disease, despite R0 resections in RPS, is substantial, varying between 22 and 85%. Recurrences can be local (50–60%), distant (15–35%) or a combination of above (20%). From the Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG) study, the 5-year OS was 29%, 20% and 14% respectively after local, distant or combined recurrences. Local recurrence (LR) can influence distant failures as well. LR is generally encountered within the first 2–3 years after treatment, although in 40%, it can be seen beyond 5 years and up to 25 years. The risk factors for recurrence include (a) histology and grade of tumour, (b) prior R0 resection status, (c) use of prior radiotherapy, (d) tumour rupture and piece meal resection, (e) tumour focality, (f) tumour growth rate and (g) DFI between initial treatment and recurrence. The presence of favourable factors like prior R0 resection, low-grade tumours, long interval to recurrence (DFI more than 1–2 years), absence of tumour rupture at initial surgery, unifocality and slow growing tumours (< 0.9 cm/month) can be subjected to finite periods of observation with caveat of repeated imaging and close follow-up.

Salvage surgery gives a window of opportunity to improve overall survival by resecting the recurrent focus completely (R0 resection). The decision-making for salvage surgery is complex involving careful assessment of pros and cons of another operative procedure in a scarred abdomen that increases morbidity and mortality. The timing for performing salvage surgery is controversial. While one study [8] reported increased risk of re-recurrence (hazard ratio [HR]: 2.72) if the interval between the recurrence and salvage surgery was more than 3 months with a 5-year OS of 13.4%, another study [21] favoured a longer delay to salvage, in order to assess disease biology and identify a new foci of recurrent disease at remote areas in the abdomen. A subsequent study [22] noted that 86% of patients on surveillance protocol underwent surgery after a median delay of 20 months. However, a delay meant increase in adjacent

Table 2 Published studies on surgical quality and outcomes in RPS

Author/year	Groups	Period	*n*	Findings	Survival	Conclusions
Maurice [66] 2017	High volume (> 10th percentile) vs low volume centre	2004–2014	3141 (70% undergo surgery)	R0: 67.6% R0 + 1: 93%	Median OS: 71.1 vs 68.9 mo	High volume centres: 1.9 × more surgery, 2.5 × more R0 + 1 and 1.8 × more R0 resection
Berger [67] 2018	Academic cancer centre vs community cancer centre	2004–2013	1642 vs 1120	R0: 55.9 vs 47% OR: 0.83 for positive margins	OS: similar (HR: 0.91)	Academic cancer centre: higher margin negative resections; not significant for survival
Bagaria [68] 2018	< 5 cases: low 5–10: medium > 10: high vol. centre	2004–2013	5407 (70% undergo surgery)	R0: 68 vs 65 vs 82%	5 y OS:56 vs 57 vs 66%	Low vol: 1.56 × higher mortality; high vol: 4 × lower 30-day mortality (2.4 vs 0.5%)
Keung [69] 2018	< 10 cases: low > 10: high vol. centre	1998–2011	6950	30-day readmission rates: 1.8 vs 3.4%; 30-day mortality: 1.9 vs 3.1%; 90-day mortality: 3.2 vs 5.7%	5 y OS:52 vs 58%; median OS longer by 12 months HR for death: 0.77	High vol: lower 30-day readmission, 30-day and 90-day mortality rate, longer 5-year survival and lower risk of death
Adam [4] 2019	< 5 cases: low 6–10: intermediate > 10: high vol. centre	1998–2012	5340 [86% treated in low vol. centre]	OR, 90-day mortality: 0.25 and positive margins: 0.58 in high vol centre	Better survival HR for OS: 0.61	High vol: more high-grade tumours; lower 90-day mortality and positive margin; improved OS
Sandrucci [70] 2018	High vol: > 100 cases obs./yr Low vol: < 100 High surgeon case vol.: > 20/yr Low surgeon case vol: < 5/yr	2006–2011	138	R0: 60% (high vol. centre)	OS: 65 vs 31% (based on resection status) in high vol. centre	Low vol: surgical reports missing important prognostic data; surgical quality poor; no data on tumour diameter, pre-op biopsy, etc Lesser tumour fragmentation in cancer centres. Surgeon-based vol. influence outcomes
Bonvalot [71] 2019	NetSarc (26 centre) database vs others	2010–2017	2945 (36.6% under NetSarc)	First R0: 41.9% vs 12.3%	2 y OS: 87% vs 70%	Surgeries done within NetSarc: 2 × lower risk of death
Villano [72] 2020	High volume (> 13 cases/yr.) vs low volume (< 13 cases/yr.) centre	2004–2015	8721	90-day mortality among both groups: 1–2%	OS (median): 139 mo. vs 94 mo	Reduction in overall mortality by 4% per case up to 13 cases/yr. No further reduction beyond 13 cases

OS overall survival, *vol* volume, *yr.* year

organ resections at salvage and use of frequent imaging to monitor the tumour growth.

Quality of Life

Quality of life (QOL) is increasingly being recognised as an important parameter to analyse in RPS patients. Although extensive data on this subject in RPS is lacking [2], few studies have documented the same. Wong et al. [25] prospectively studied 48 patients treated with neoadjuvant radiotherapy to identify the impact of radiotherapy and surgery on QOL using the EORTC-QLQ-C30. There was a significant improvement in QOL 1 month post-radiotherapy, although 54% had gastrointestinally related acute toxicity at radiotherapy completion. At the end of 3 years, 88% of the patients had chronic toxicities. Patients with no evidence of disease at the end of 3 years had better QOL. Patient's age, gender, tumour size or dose of radiotherapy had no bearing on QOL. Callegaro et al. [26] reported that majority of patients were indeed symptomatic prior to treatment especially with regard to neuropathy and chronic pain. Lim et al. [27] reported better functioning scores in treated patients compared to other cancers. Hence, patient-related outcomes are important during follow-up.

Radiotherapy

Adjuvant Radiotherapy

The main indications of adjuvant radiotherapy include margin positive resections, recurrent tumours and those with adverse pathological risk factors viz. larger tumour size (> 10 cm), high-grade tumours and aggressive histologies. The standard dose of adjuvant radiotherapy is 50–55 Gy. The relative radio-responsiveness of individual histological subtypes as well as the incidence of local recurrence associated with each are important factors. As majority of RPS patients succumb from unresectable local disease rather than distant failures, a reduction in such local recurrences could probably translate to improved overall survival [28]. For example, WDLPS and DDLPS are most likely to recur locally while LMS predominantly fails systemically [29]. A systematic review reported that LPS and LMS were radio-responsive in only half the cases when radiotherapy was administered while malignant peripheral nerve sheath tumour (MPNST) and undifferentiated pleomorphic sarcomas (UPS) were poorly responsive to radiotherapy [30]. Table 3 shows the various studies on adjuvant radiation in RPS.

Many studies have reported reduction in local recurrences and thus an improvement in local control with radiotherapy. However, caution must be exercised when interpreting these results as results obtained from extremity sarcomas are difficult to reproduce in the retroperitoneum owing to larger tumour masses, close vicinity of critical structures and increased acute and late toxicity with standard radiotherapy doses [28]. The plausible advantages of adjuvant radiotherapy is that there is no delay in curative surgery and adjuvant treatment can be tailored based on histology, margins and other prognostic factors as per the histopathology report [31]. The potential disadvantages are the absence of clear-cut survival advantage with an added risk of both acute and late toxicities. Therefore, adjuvant radiotherapy for RPS is limited to treatment of recurrent disease and is sparingly utilised owing to increased morbidity and lower chance achieving a therapeutic dose [5, 28, 32].

Neoadjuvant Radiotherapy

The concept of neoadjuvant radiotherapy (NART) in RPS is derived from extremity sarcoma trials which showed improved local control with lower long term toxicity with NART over adjuvant radiotherapy [5, 29]. The anticipated advantages [5, 28, 29, 33] of NART include (a) clear delineation of target volume of tumour, (b) reduced surrounding toxicity as tumour would have pushed the adjacent organs aside, (c) intact tumour vasculature improves tumour oxygenation and hence RT effects, (d) potentially sterilises 'at-risk' margins near critical structures that could reduce local recurrence rates, (e) achieve reduction in tumour size, (f) results in formation of pseudo-capsule around the tumour improving R0 resection rates and reducing tumour rupture intra-operatively and (g) possible improvement in survival secondary to reduced R + resection, tumour rupture and improved local control. The potential disadvantages of NART are (a) need for pre-treatment biopsy, (b) delay in curative surgery and (c) absence of prognostic factors to tailor treatment. Table 4 depicts the various neoadjuvant radiotherapy studies in RPS. The standard pre-operative dose is 50–50.4 Gray (Gy) in 1.8–2 Gy fractions [29]. Local control after NART is around 49–75% [31].

Two important trials viz. ACOSOG 9031 [34] and STRASS [35] were conducted to study the precise role of NART in RPS. While the former did not accrue sufficient patients to push the trial forward secondary to institutional biases to radiotherapy usage and lack of consensus on the optimal NART regimen [5], the latter was a randomised, multicentre trial in which 266 patients were randomised to NART followed by surgery vs surgery alone. The primary end point of the trial was abdominal recurrence–free survival (ARFS). Of patients, 74.5% were LPS. The 3-year ARFS was 60.4% vs 58.7% (HR: 1.01) in the NART vs surgery alone group. Complication rates were similar in both groups. The authors finally concluded the trial failed to demonstrate a benefit of NART for RPS. However, in an exploratory analysis, LPS subgroup was found to show benefit with NART. Finally, a systematic review of radiotherapy in RPS

Table 3 Published studies on adjuvant radiotherapy in RPS

Author/year	Groups/method	Dose (med./Gy)	Period	*n*	F/U (mo.)	R0 + R1 (%)	LC	Failure	Survival	Toxicity	Comment
Surgery vs surgery + PORT											
Sampath [73] 2010	Surgery vs surgery + PORT	50.2	1982–2003	192 vs 51	59	42 (R0)	5 y: 64 vs 79%	37.2%	5 y DSS: 73% OS: 55%	NA	PORT: improved LFFS
Trovik [74] 2014	Surgery vs surgery + PORT	50	1988–2009	55 vs 37	56.4	55.7 (R0)	5 y: 39 vs 77%	LR: 48% DM: 40%	5 y OS: 52 vs 71%	Acute: 2 Late: 1	PORT: improved LFFS, OS
Bates [75] 2015	Surgery vs surgery + PORT	NA	1973– 2010	339 vs 144	NA	NA	NA	NA	Median OS: 27 vs 36 mo	NA	PORT: improved OS in high-grade tumours
Kim [76] 2018	Surgery vs surgery + PORT	54 (60 if R1/2)	1994–2015	42 vs 38	37.1	86.2%	5 y: 24.3 vs 74.2%	58.8%	5 y OS: 70.6 vs 71.6%	Acute: 63% Late: 5.26%	PORT: improved LFFS; Benefit in R +
Nazzani [77] (SEER) 2018	Surgery vs surgery + PORT	NA	2004–2014	854 vs 372	33	NA	NA	NA	Lower mortality with PORT HR: 0.73	NA	PORT: lower CSM in large and high-grade tumours
Surgery vs surgery + IORT + PORT											
Stucky [78] 2014	Surgery vs Surgery + IORT + PORT	10–12	1996–2011	26 vs 37	45	89%	46 vs 89%	NA	OS: 60 vs 60%	Stricture: 1	IORT: improved local control
Hager [79] 2017	Surgery vs surgery + IORT	15	2001–2014	23 vs 23	55.5	84.8%	NA	43.5 vs 47.8%	5 y DSS: 58.6 vs 82.3%	NA	IORT: improved DSS
Surgery + PORT vs surgery + IORT + PORT											
Sindelar [80] 1993	Surgery + PORT vs surgery + IORT + PORT	Post: 50–55 IORT: 20 Post: 35–40	1993	20 vs 15	96	NA	20 vs 60%	LR: 80 vs 40%	Median OS: 52 vs 45 mo. DFS: 38 vs 19 mo	IORT: more neuropathy	IORT: similar survival; better local control
Gieschen [81] 2001	Surgery + PORT vs surgery + IORT + PORT	Post: 45 IORT: 10–20	1980–1996	17 vs 20	38	78%	60.6 vs 83%	LR: 13 DM: 18	OS: 30 vs 74.4%	20%	IORT: excellent local control, survival
Pezner [82] 2011	Surgery + PORT vs surgery + IORT + PORT	NA	1990–2008	13 vs 20	15	NA	NA	LR: 12% RR: 26%	NA	GI: 10 and 27%	Less toxicity with IMRT
Surgery + IORT vs surgery + IORT + PORT											

Table 3 (continued)

Author/year	Groups/method	Dose (med./Gy)	Period	*n*	F/U (mo.)	R0+R1 (%)	LC	Failure	Survival	Toxicity	Comment
Coelho [39] 2018	Surgery+IORT vs Surgery+IORT+PORT	IORT:15 Combined: 12	2004–2015	12/41 27 vs 17	97.2	88%	5 y: 62% 8 y: 62%	LR: 5 DM: 5	5 y OS: 15%	Acute: 31% Late: 7%	Good local control

PORT post-operative radiotherapy, *IORT* intra-operative radiotherapy, *LR* local recurrence, *RR* regional recurrence, *DM* distant metastases, *DFS* disease-free survival, *OS* overall survival, *DSS* disease-specific survival, *NA* not available, *mo.* months, *HR* hazard ratio, *LFFS* local failure–free survival, *CSM* cancer-specific mortality, *y* years

which included 10 trials concluded that the median OS and the 5-year survival were significantly increased in patients treated with radiotherapy and surgery compared to patients treated with surgery alone [36]. The median recurrence-free survival (RFS) was also significantly better in the radiotherapy arms (pre- or post-operative) compared to surgery alone with similar R0 resection rates.

Newer Techniques

Intensity Modulated Radiotherapy.

Intensity modulated radiotherapy (IMRT) has led to improved RT delivery to the tumour with reduced toxicity. Besides, it allows for selective dose escalation for high-risk margins, thereby reducing overall dose to surrounding critical organs [31] and could reduce local recurrence rates by sterilizing these 'high-risk' margins [5, 29].

Proton Beam Therapy.

The rationale for using proton therapy stems from the point that RPS are large tumours at presentation with critical structures in the vicinity and lower off target scatter due to 'Bragg peak' [29]. By using sharp dose gradients between the tumour and normal tissues, toxicity is reduced [28].

Use of Spacer Devices.

Studies have looked at using spacers as fillers between the tumour and surrounding tissue and documented lesser complications with optimum local control [15].

Use of Selective Dose Escalation to 'At-Risk' Margins.

In an elegant study by Tzeng et al. [37], selective escalation of radiation dose was performed not to the entire tumour, but only to margins which were deemed to be at a high risk of positivity after surgery. The authors reported a subsequent R0 resection rate of 80% with a 2-year local control of 80%. Of tumours, 75% responded with size reduction. There was no treatment related or post-operative morbidity.

Intra-operative Radiotherapy

Intra-operative radiotherapy (IORT) for RPS was adopted as part of the therapeutic armamentarium in the late 1980s after studies depicted higher rates of bowel-related complications (chronic enteritis/fistula) with conventional external beam radiotherapy (EBRT). As most RPS are large tumours at the time of presentation, often close to critical structures, IORT serves as a promising modality for radiation delivery [33, 38].

IORT utilises a single high dose of radiation to the tumour bed with the goal of eliminating microscopic disease, thereby improving local control [39]. IORT is used in isolation or usually combined with EBRT: 10–15 Gy of IORT with 45–50 Gy of EBRT [29]. It can be administered as high-dose radiation (HDR-IORT) using Ir^{192} or using electrons. The potential advantages are precise and targeted

Table 4 Published trials on neoadjuvant radiotherapy in RPS

Author/year	Groups/method	Dose (med./Gy.)	Period	*n*	F/U (months)	R0 + R1	LC	Failure	Survival	Toxicity	Comment
NART + surgery vs surgery											
Nussbaum [33] 2014 (NSQIP)	Surgery vs NART + surgery	NA	2005–2011	714 vs 71	NA	NA	NA	NA	NA	26.4 vs 29.2%	NART: no increase in short-term (30-day) morbidity, mortality
Nussbaum [83] 2015 (NCDB)	Surgery vs NART + surgery	NA	1998–2011	10,628 vs 696	NA	85.9 vs 90.7%	NA	NA	5 y OS: 53.2% vs 54.2%	Low	NART: improved survival only in high grade
Ecker [84] 2016 (NCDB)	Surgery vs NART + surgery ± IORT/PORT	50	2004–2013	1908 vs 139 + 35	52	83.6%	NA	NA	5 y OS: 67.4 vs 91.7%	NA	NART: **better OS**; especially with high-risk path features
Turner [85] 2019	Surgery vs NART + surgery	49	1990–2014	62 vs 40	90	30.6% vs 72.5%	Median LRFS: 28.4 vs 89.3 mo	63% vs 43%	Median OS: 75.9 vs 119.4 mo	NA	NART: higher LRFS and OS
NART + surgery vs surgery + PORT											
Zlotecki [86] 2005	NART + surgery vs surgery + PORT	Pre: 50.4 Post: < 50	1974–2003	15 vs 25	31.6	85% vs 57%	61 vs 65%	LR: 4 + 2 L + D: 3 + 2 DM: 3 + 4	5 y OS: 69%	Acute: 36 vs 80% Post-op: 24%	NART: improves local control
Pippa [31] 2017	NART + surgery vs surgery + PORT	Pre:55 Post: 60.4	2006–2015	11 vs 19	36.3	80%	100 vs 69%	LR: 17% (all PORT) DM: 43%	5 y OS: 54 vs 48%	Acute: 7% Late: 3.3%	NART: better local control
NART + surgery vs NART + surgery + IORT ± PORT											
Pierie [87] 2006	NART + surgery vs NART + surgery + IORT + PORT	Pre:45IORT:10–20	1973–1998	103	27	62/103	NA	LR: 19%	5 y OS: 45 vs 77%	IORT: 28.6% Total: 5/103	IORT: improved local control, survival
Pawlik [88] 2006	NART + surgery vs NART + surgery + IORT ± PORT	Pre:45 IORT:15	1996–2002	23 vs 34	40	95%	60 vs 51%	LR: 17 DM: 8 L + D: 3	5 y DFS: 46%	NA	IORT: trend towards better DFS

Table 4 (continued)

Author/year	Groups/method	Dose (med./Gy.)	Period	*n*	F/U (months)	R0 + R1	LC	Failure	Survival	Toxicity	Comment
Hull [89] 2017	NART + surgery vs NART + surgery + IORT	Pre: 50.4 IORT: 10	2003–2013	30 vs 16	53	98%	72%	LR: 10.9% DM: 17%	5 y OS: 81% 5 y DSS: 63%	Post-op: 22%	Good local control; high DM
NART + surgery + PORT vs NART + surgery + IORT ± PORT											
Kirste [90] 2019	NART + surgery + IORT + PORT vs NART + surgery + PORT	Pre: 19.8 Post: up to 45 IORT:10–15	2009–2011	2 vs 3	61	100%	80%	LR: 1 DM: 1	NR	Acute: 1 Chr: 1	Effective and feasible
NART + surgery + IORT vs surgery + IORT + PORT											
Ballo [91] 2007	NART + surgery + IORT vs surgery + IORT + PORT	Pre:50 Post: 55 IORT:15	1960–2003	50 vs 33	47	52%	46% vs 51% (IORT not used vs used)	LR: 60% DM: 33%	5 y DSS: 44%	10%	No improvement in outcomes with PORT/IORT
Surgery vs surgery + IORT ± PORT vs NART + surgery											
Nussbaum [92] 2016	Surgery vs surgery + PORT vs NART + surgery	NA	2003–2011	6290 vs 2215 vs 563	42–3	NA	NA	NA	Median OS: 66 vs 89 vs 110 months	NA	Both pre- or post-op RT: improved survival
Surgery vs NART + surgery vs NART + surgery + IORT ± PORT											
Kelly [93] 2015	Surgery vs NART + surgery vs NART + surgery + IORT ± PORT	50 IORT:10	2003–2011	172 vs 17 vs 15	38.7	61% vs 45% (R0)	65 vs 91% (no RT vs RT)	LR: 52 DM: 12	5 y DSS: 85 vs 93%	Post-op: 17 vs 41%	RT: improves local control; no survival benefit

NART neoadjuvant radiotherapy, *PORT* post-operative radiotherapy, *IORT* intra-operative radiotherapy, *LR* local recurrence, *DM* distant metastases, *DFS* disease-free survival, *OS* overall survival, *DSS* disease-specific survival, *NA* not available, *mo.* months, *LRFS* local recurrence–free survival, *L + D* combine locoregional and distant failure, *y* years

delivery of high-dose radiation to the tumour bed, limiting toxicity to adjacent vital structures (that is generally displaced by the tumour), achieving dose escalation which is difficult with conventional EBRT and option of re-irradiation for recurrent disease. Thus, the therapeutic ratio is higher compared to EBRT alone [38]. However, IORT is associated with toxicities like peripheral neuropathy, stricture formation, hydronephrosis, bowel perforation, fistulisation and abscess formation [5]. Also, evidence for improved outcomes after IORT is lacking [29]. Furthermore, availability of expertise and resources is a common constraint for usage and should be considered only where such facilities are available [29]. Currently, its use is not recommended outside clinical trials [28, 29]. The RETROWTS trial in Germany is currently underway to evaluate its role in RPS [40]. Table 5 depicts the published studies of IORT in RPS.

Chemotherapy

Adjuvant Chemotherapy

The role of adjuvant chemotherapy in RPS stems from trials conducted for extremity soft tissue sarcomas, few of which had RPS as a subset (Table 6).

Going by these aforementioned trials, it is evident from extremity sarcoma trials that the benefit of adjuvant chemotherapy is proportional to the variability in the sensitivity of histological subtypes to the standard anthracycline and ifosfamide regimen as well as propensity of recurrence [28, 41]. Many newer studies have propounded the need for histologically driven chemotherapy regimen to improve response and survival outcomes [41]. One study looked at the addition of hyperthermia to standard adjuvant chemotherapy after complete resection and found that the combination resulted in improved local control and DFS without increasing surgical complications [42]. The SMAC meta-analysis [43] in 1997 demonstrated improvement in RFS in the chemotherapy-treated patients with a trend in improvement in OS. However, there was criticism due to possible dilution of the beneficial effects of chemotherapy due to inadequate sample size, variable exclusion of patients and including heterogeneous group with respect to site, grade, chemosensitivity and drugs used [28, 44]. In 2008, an update on the meta-analysis that included 18 randomised trials with 1953 patients with localised and resectable soft tissue sarcomas conclusively demonstrated an improvement in the local, distant and overall RFS in the chemotherapy arm, with the odds ratio [OR] of 0.73 (95% CI: 0.56–0.94), 0.67 (95% CI: 0.56–0.82) and 0.67 (95% CI: 0.56–0.82) respectively. Overall survival was beneficial in those receiving ifosfamide and doxorubicin doublet chemotherapy (OR for death: 0.56 (95% CI: 0.36–0.85)). The criticism of the meta-analysis was the exclusion of the negative EORTC trial [28, 44, 45].

Table 5 Published studies of IORT in RPS

Author/year	Period	*n*	IORT dose (median Gy)	IORT type	EBRT	EBRT dose (median Gy)	R0 + R1	F/U (mo.)	Local control	Survival	Toxicity
Alketiar [94] 2000	1992–1996	32	12–15	HDR	Yes	45–50.4	93.7%	33	5 y: 62%	5 y OS: 18%	18% (GI); 9% (fistula); 6% (neuro); 3% (HUN)
Peterson [95] 2002	1981–1995	87	8.75–30	Electrons	Yes	48.6	82.8%	42	5 y: 59%	5 y OS: 47%	13.8% (GI); 8% (fistula); 10% (neuro)
Bobin [96] 2003	1988–2001	24	15	Electrons	Yes	45–50	92%	52.6	5 y: 46%	5 y OS: 56%	25%(neuro); 8.3% (chronic)
Krempien [97] 2006	1991–2004	67	12–20	Electrons	Yes	45	82%	30	5 y: 40%	5 y OS: 64%	10% (GI); 8% (neuro); 3% (stenosis)
Dziewirski [98] 2006	1998–2004	46	20	HDR	Yes	50	85%	20	5 y: 51%	5 y OS: 55%	21.5% (post-op)
Sweeting [99] 2013	2002–2009	18	12.5	Electrons	Yes	45	100%	43	5 y: 64%	5 y OS: 72%	NA
Roeder [100] 2014	2007–2003	27	12	Electrons	Yes	50	96%	33	5 y: 72%	5 y OS: 74%	15% (acute); 33% (post-op)

IORT intra-operative radiotherapy, *Gy* Gray, *EBRT* external beam radiotherapy, *HDR* high-dose radiation, *OS* overall survival, *HUN* hydroureteronephrosis, *NA* not available, *GI* gastrointestinal, *y* years, *neuro* neurological

Table 6 Published trials of adjuvant chemotherapy in sarcomas

Author/year	Period	*n*	Arms	Chemo	F/U mo	Comments
EORTC 62,771 [101] 1979	1977–1988	468	Surgery alone vs surgery + chemo (8 cycles)	Doxorubicin + vincristine + dacarbazine + cyclophosphamide	80.4	No benefit Trend for improved OS in grade III tumours
SMAC meta-analysis [43] 1997	1997	1568 [14 trials]	No chemo vs adjuvant chemo	Adriamycin based	112.8	Adjuvant chemotherapy improves RFS Trend towards improved OS No effect on truncal sarcomas
Brodowicz [102] 2000	NA	59	Surgery + RT vs surgery + RT + chemo	Adriamycin + dacarbazine + ifosfamide (6 cycles)	42	No significant difference in terms of DFS or OS
Frustaci [103] 2001	1992–1996	104	Surgery alone (51) vs surgery + chemo (53)	Doxorubicin + ifosfamide	59	Absolute benefit: 13% at 2 y and 19% at 4 y
Petrioli [104] 2002	1985–1996	88	Surgery ± RT (43) vs surgery + chemo ± RT (45)	Epirubicin + ifosfamide	93.6	Possible advantage of epirubicin-based adjuvant chemotherapy
Updated meta-analysis [45] 2008	2008	1953 [18 trials]	No chemo vs adjuvant chemo	Doxorubicin + ifosfamide (5/18 trials) or doxorubicin alone	NA	Marginal efficacy for local, distant and overall recurrences Better OS with doublet therapy (11% reduction in death)
French sarcoma group [105] 2010	1980–1999	1513	Adjuvant chemo	Adriamycin based	108	13% reduction in risk of death 9% reduction in distant metastases in grade III
EORTC 62931 [106] 2012	1995–2003	351	Surgery alone vs surgery + chemo	Adriamycin + ifosfamide (5 cycles)	94.8	No significant difference in terms of DFS or OS
Angele [42] 2014	1997–2006	149/341	Adjuvant chemo (73) vs adjuvant chemo + RHT (76)	Etoposide + ifosfamide + doxorubicin	99	Improved local control with RHT Similar OS

DFS disease-free survival, *OS* overall survival, *mo.* months, *LR* local recurrence, *DR* distant recurrence, *OR* odds ratio, *LRFS* local recurrence–free survival, *DRFS* distant recurrence–free survival, *RFS* recurrence-free survival, *RHT* regional hyperthermia, *HR* hazard ratio, *RT* radiotherapy, *y* years

At present, adjuvant chemotherapy in RPS remains debatable [5]. The most appropriate indications for (neo) adjuvant chemotherapy are good ECOG performance status, relatively young patients with chemo-sensitive histologies, high-grade and large tumours wherein recurrence risk is higher and/or upfront surgery can be extremely morbid/suboptimal. The decision should be taken in a multidisciplinary tumour board, and patient should be involved in discussion regarding the apparent benefit vis-a-vis the chemotherapy-related potential toxicity [28, 44].

Neoadjuvant Chemotherapy/Chemoradiation

The use of neoadjuvant chemotherapy (NACT) or chemoradiotherapy (CT/RT) is increasingly being utilised in RPS, the main rationale being reduction in the incidence of distant failures and improvement the margin negative (R0) resections [5]. Although there are no trials directly comparing NACT/chemoradiation to surgery to make robust conclusions [28], the usage of NACT appears promising for certain high-grade and/or chemo-sensitive histologies like DDLPS, LMS, UPS, myxoid LPS, synovial sarcomas, rhabdomyosarcomas (RMS) and extra-skeletal Ewing sarcomas. Even though standardised chemotherapy protocols exist for RMS and extra-skeletal Ewing sarcoma, these histologies are rare in the retroperitoneum per se [28].

The standard chemotherapeutic regimen includes anthracycline with ifosfamide-based combination chemotherapy for most histologies with the exception of LMS where doxorubicin and dacarbazine [3] or docetaxel are commonly used. Many of these agents also have radio-sensitizing properties, thereby making chemoradiotherapy a promising option [28].

The main advantages of neoadjuvant treatment include the use of relatively nephrotoxic agents (e.g. ifosfamide)

prior to major surgery that often predisposes a patient to a potential nephrectomy that could increase the risk of pushing such patients to nephrotoxicity with therapeutic doses post-operatively. Besides, neoadjuvant treatment serves as an assessor for in vivo tumour sensitivity to chemotherapy, which potentially reduces the risk of micrometastases and provides useful prognostic and research information in patients responding to neoadjuvant treatment [2, 6, 28]. Tumour down-staging is also the goal of treatment; however, the extent of surgery does not reduce following treatment. Some authorities believe that chemotherapy could possibly lead to lesser need for MVR, thereby reducing the complexity of surgery [46].

The potential drawbacks of neoadjuvant therapy are a possible delay in curative surgery and a small but definite risk of tumour progression during chemotherapy. Furthermore, in liposarcomas that constitute the major bulk of RPS, the main cause of mortality remains local progression rather than metastatic spread [28]. Therefore, caution must be used when instituting chemotherapy in liposarcomas. Lastly, UPS is considered a relatively chemoresistant histology portending an unfavourable outcome irrespective of neoadjuvant therapy [46]. A number of trials have studied the role of neoadjuvant therapy in RPS and are outlined below (Table 7).

The main caveats that one must remember is that although survival in the chemotherapy subsets in these studies is lower, this may be attributed to larger and/or high-grade histologies that confer aggressive biology for which neoadjuvant treatment is used and that 'one size fits for all' concept of using anthracycline + ifosfamide chemotherapy may not be 'histologically driven'. In fact, in the Italian Sarcoma trial [47], patients with myxoid LPS had similar survival both in the trabectedin and epirubicin + ifosfamide doublet arms, adding food for thought that less toxic regimen may be more beneficial in the long term. This is further being investigated in the STRASS-2 study that aims to evaluate neoadjuvant chemotherapy in exclusively high-grade RPS (DDLPS and LMS) with the objective of reduction in incidence of distant metastases [6].

Palliative Systemic and Targeted Therapy

Palliative chemotherapy forms the mainstay of treatment in metastatic sarcomas. Anthracycline-based chemotherapy is most commonly employed in this setting as first-line therapy [6, 28]. With response rates of 20–30%, the median survival hovers around 12–15 months [48]. In the second-line setting, agents such as gemcitabine/docetaxel combination, high-dose ifosfamide, trabectedin, pazopanib and eribulin have been utilised with some benefit [6]. Trabectedin, which interferes with DNA repair mechanism, has been used in the treatment of advanced round cell/myxoid liposarcomas and LMS. Likewise, pazopanib, an oral tyrosine kinase inhibitor, has been used in the setting of advanced sarcomas, with benefit spanning across all histologies barring for liposarcoma [49]. Newer agents like CDK inhibitors, cabazitaxel, olaratumab, ridaforolimus and vorinostat are currently being investigated in various phase II/III trials [6, 49].

Table 7 Published trials of neoadjuvant therapy in sarcomas

Author	Period	Arms	Drugs	*n*	Findings
Miura [107] 2015	1998–2011	a. NACT b. Adj c. Periop d. None	Variety of regimen	163 490 12 7128	Reduced median OS (40 vs 68.2 months) in chemotherapy group compared to surgery alone
Italian Sarcoma group [47] 2016	2011–2016	NACT	3# epirubicin + ifosfamide vs 3# histologically tailored regimen (gemcitabine + docetaxel: UPS; trabectedin: myxoid LPS; high-dose infusion ifosfamide: SS; etoposide + ifosfamide: MPNST; gemcitabine + dacarbazine: LMS)	287 (97:UPS 65: LPS [myxoid]; 70: SS; 27: MPNST; 28: LMS)	Higher probability of RFS (0.62 vs 0.38) and OS (0.89 vs 0.64) at 46 months compared to histology-tailored regimen
Sanctis [108, 109] 2017, 2018	2003–2010	NACTRT	3 cycles high-dose infusional ifosfamide + 50.4 Gy RT	83	RFS: 46.6% (7 y) OS: 63.2% (7 y); 32 patients died LR after NACTRT: infield

NACT neoadjuvant chemotherapy, *Adj* adjuvant chemotherapy, *NACTRT* neoadjuvant chemoradiation, *UPS* undifferentiated pleomorphic sarcoma, *SS* synovial sarcoma, *LPS* liposarcoma, *LMS* leiomyosarcoma, *MPNST* malignant peripheral nerve sheath tumour, *RFS* recurrence-free survival, *OS* overall survival, *LR* local recurrence, *periop* perioperative, *y* years

Conclusions

Treatment of retroperitoneal sarcomas has evolved over the decades, with more complex multivisceral resections being increasingly performed for tumour extirpation. Obtaining margin negative resection (R0 resection) and judicious use of radiotherapy, either neoadjuvant or adjuvant, to sterilise at-risk margins can help reduce local recurrence and could possibly lead to improved survival rates. The most appropriate indications for (neo) adjuvant therapy are good ECOG performance status, relatively young patients with chemosensitive histologies and higher grade and larger tumours where recurrence rates can be high. Tumour histology plays an important role in personalizing treatment options. The use of targeted therapy could further improve outcomes even in the metastatic setting.

Declarations

Conflict of Interest The authors declare no competing interests.

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