Role of radiation therapy for newly diagnosed retroperitoneal sarcoma

Lam, M.B.; Baldini, E.H.; Reijers, S.J.M.; Haas, R.L.; DeLaney, T.F.

Curr. Treat. Options in Oncol. (2021) 22: 75
DOI 10.1007/s11864-021-00877-6

Sarcoma (SH Okuno, Section Editor)

Role of Radiation Therapy for Newly Diagnosed Retroperitoneal Sarcoma

Miranda B. Lam, MD MBA[1,2,3]
Elizabeth H. Baldini, MD, MPH[1,2,3]
Sophie J. M. Reijers, MD[4]
Rick L. Haas, MD PhD[5,6]
Thomas F. DeLaney, MD[3,7,*]

Address
[1]Department of Radiation Oncology, Brigham and Women's Hospital/Dana Farber Cancer Institute, Boston, MA, USA
[2]Center for Sarcoma and Bone Oncology, Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA, USA
[3]Harvard Medical School, Boston, MA, USA
[4]Sarcoma Research and Treatment Unit, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[5]Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[6]Leiden University Medical Centre, Leiden, The Netherlands
[7]Department of Radiation Oncology, Massachusetts General Hospital, 55 Fruit Street, Boston, MA, 02114, USA
Email: tdelaney@mgh.harvard.edu

Published online: 2 July 2021

This article is part of the Topical Collection on *Sarcoma*

Keywords Retroperitoneal sarcoma · Sarcoma · Radiation therapy · Radiotherapy · External beam radiation therapy

Opinion statement

Soft tissue sarcomas (STS) are rare, aggressive, and heterogenous tumors, comprising approximately 1% of adult cancers with over 50 different subtypes. The mainstay of treatment for retroperitoneal sarcomas (RPS) includes surgical resection. The addition of radiation therapy (RT), either preoperatively or postoperatively, has been used to potentially decrease the risk of local recurrence. The recently published results from STRASS (EORTC-STBSG 62092-22092), which randomized patients to receive or not receive preoperative radiation, indicate no abdominal recurrence-free survival benefit (primary endpoint) nor overall survival benefit to date from the addition of preoperative RT prior to surgical resection in patients with RPS. Keeping in mind caveats of subgroup analyses, the data show a significant reduction in local recurrence with radiation therapy in resected patients and non-significant trends toward improved abdominal recurrence-free survival

in all patients and improved local control and abdominal recurrence-free survival in patients with liposarcoma and low-grade sarcoma. Given the high rate of local failure with surgery alone, it is possible that higher RT dose and/or selective RT dose painting may improve outcomes. Prior to treatment, the authors encourage multidisciplinary review and discussion of management options at a sarcoma center for patients with RPS. Selective use of RT may be considered for patients at high risk of local recurrence.

Introduction

Background

Sarcomas are malignant tumors arising from skeletal and extra-skeletal connective tissues. While soft tissue sarcomas (STS) are most commonly found in the extremities, other sites include the retroperitoneum, chest wall, head and neck, subcutaneous tissues, and along the peripheral nervous system. Retroperitoneal sarcomas (RPS) comprise 10–15% of STS, with an average annual incidence of 2.7 cases per million people [1, 2]. RPS arise equally in men and women, and over a wide age range, with the average patient presenting in their 50s [3–5]. The retroperitoneum includes the kidneys, adrenal glands, perirenal fat bilaterally, the aorta and its major branches, the inferior vena cava and its major tributaries, the bilateral iliac vessels, duodenum, pancreas, and parts of the ascending and descending colon. The boundaries of the retroperitoneum are paraspinous muscles posteriorly, peritoneal cavity anteriorly, diaphragm superiorly, and the bottom of the pelvis inferiorly [6].

Histologic types

The most common histologic types of RPS in adults are liposarcomas (well-differentiated and de-differentiated) and leiomyosarcomas, followed by undifferentiated/unclassified sarcomas, which include pleomorphic undifferentiated sarcomas [7, 8]. While not the focus of this review, the most common histologic types of RPS in children are extra-skeletal Ewing sarcoma/primitive neuroectodermal tumor, alveolar rhabdomyosarcoma, and fibrosarcoma [9]. Liposarcomas (LPS) consist of several variants, including well-differentiated/low-grade (most common), de-differentiated (second most common), pleomorphic, and myxoid (rare) [10]. Well-differentiated (WD) LPS rarely metastasize and are referred to as atypical lipomatous tumors when they arise in the extremities or trunk. However, these tumors in the retroperitoneum and mediastinum are referred to as WD LPS given their higher propensity to recur locally in these sites. De-differentiated (DD) LPS typically have sharply demarcated regions of non-lipogenic sarcomatous tissue within WD LPS. DD and WD LPS behave differently—DD LPS behave more aggressively with a higher local recurrence rate, the ability to metastasize, and a higher risk of death [11–14]. Retroperitoneal leiomyosarcomas (LMS) typically arise from the inferior vena cava, its tributaries, or any small vessel. LMS differ from WD/DD LPS in that metastatic disease, especially to the lungs, is more common [13, 14]. LMS can also arise from the uterus or gastrointestinal tract, and these visceral (versus retroperitoneal) tumors have a higher risk of peritoneal spread and liver metastases [15]. Other histologic types (malignant peripheral nerve sheath tumor, undifferentiated sarcoma, synovial sarcoma, solitary fibrous tumor, and desmoplastic small round cell tumor) can be seen in the retroperitoneum but are much less common [16•].

Workup

Many patients with RPS have incidentally discovered masses and are asymptomatic or minimally symptomatic. The median size of RPS tumors at diagnosis measure approximately 15 cm [4]. The minority of patients have signs or symptoms which, when present, are typically due to mass effect of the tumor or invasion of nearby structures causing pain, lower extremity edema, increased abdominal girth, gastrointestinal effects (early satiety, obstruction, bleeding), or neurologic and/or musculoskeletal symptoms. Other more rare presenting scenarios have been described (e.g., serous ascites, flu-like symptoms, paraneoplastic hypoglycemia) [17–20]. Distant metastases are seen in 10% of new diagnoses of RPS, with lung and liver metastases being most common [15].

In addition to RPS, the most common differential diagnoses of a retroperitoneal mass include lymphoma,

primary germ cell tumor, or metastatic testicular cancer. While other malignancies of visceral organs can occur (e.g., duodenum, pancreas, adrenal glands, kidneys), these are typically able to be differentiated from extravisceral retroperitoneal soft tissue tumors on radiographic studies. Schwannomas, paragangliomas, Castleman disease, and retroperitoneal fibrosis are other potential tumors in the retroperitoneum. A focused history and physical exam should be performed. Radiographic imaging evaluation is a vital aspect of a patient's workup for a new retroperitoneal mass [21•]. Computed tomography (CT) scan of the chest, abdomen, and pelvis with contrast is the recommended initial diagnostic study to evaluate the primary site as well as to determine if metastatic spread has occurred to the lung, which is typically the first site of metastasis in most RPS cases. CT is typically preferred over magnetic resonance imaging (MRI). However, in certain cases (e.g., equivocal muscle, bone or foraminal involvement on CT, or allergy to iodinated CT contrast), MRI with gadolinium may be indicated. Positron emission tomography (PET) for STS has not been established and is not routinely recommended for initial staging of RPS.

Biopsy is typically recommended as the histology can drive decisions regarding the use of each treatment modality and thus, inform the overall multidisciplinary treatment plan. The risk of tumor seeding or increasing local recurrence due to biopsy is thought to be extremely low [22–24]. Nonetheless, there are certain situations in which initial surgery without biopsy is an acceptable approach [25]. The most current RPS staging is per the eighth edition of the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (IUCC) Tumor, Node, Metastasis (TNM) system. Prior to any treatment for RPS, renal function of both kidneys should be considered.

Treatment

Given the rarity and heterogeneity of RPS, multidisciplinary evaluation at a center with sarcoma expertise is highly recommended [26•]. European Cancer Organization (ECCO) in conjunction with the Sarcoma Patients Euronet (SPAEN) Advocacy Group, the National Comprehensive Cancer Network (NCCN), and the European Society for Medical Oncology (ESMO) all strongly recommend referral of patients with sarcoma to tertiary centers [27–29]. Expert pathology and radiology review are key components of the workup that informs the decision of the dedicated sarcoma subspecialists formulating an overall treatment plan. In general, surgical resection is the mainstay of treatment for patients with RPS. Radiographic findings that indicate an unresectable tumor include extensive vascular involvement, peritoneal implants, distant metastatic disease not amenable to resection or ablation, involvement of the root of the mesentery, or spinal cord involvement [30]. Discussion at a multidisciplinary tumor board prior to treatment facilitates a multidisciplinary approach. When appropriate, participation in ongoing clinical trials is encouraged.

Surgery

Surgical resection has traditionally been the only potentially curative treatment for localized RPS. Complete resection (R0/R1) at initial presentation is the most important prognostic factor for overall survival (OS) [4, 5, 17, 31–36]. While an R0 resection would be ideal, this is very difficult to achieve as wide negative margins are rarely possible due to anatomic constraints. At high volume centers, complete resection (R0/R1) appears to be possible in 50–80% of cases [3–5, 37, 38]. Resection of organs adjacent to the tumor may be needed to obtain a complete oncologic resection [3, 18, 39, 40]. If a patient has unresectable disease, incomplete resection (or debulking surgery) should not be performed

(with the possible exception of WD LPS, see below) in the absence of emergent indications such as bowel obstruction or perforation as there is no survival benefit for debulking surgery. For select patients with unresectable WD LPS, debulking surgery may improve survival and palliate symptoms [41]. If preoperative RT is recommended prior to surgery, there should be close communication between the radiation oncologist and the surgeon regarding the intended surgical plan as well as the radiation fields [42].

Chemotherapy

The role of chemotherapy is controversial, without clear benefit. Adjuvant chemotherapy is not recommended outside the context of a clinical trial [43, 44]. Neoadjuvant concurrent chemotherapy and RT have not been established and are not recommended outside a clinical trial [45–47]. The role of neoadjuvant chemotherapy prior to surgery has mixed evidence. It is considered in certain cases such as for tumors which are borderline resectable, of high metastatic risk (e.g., leiomyosarcoma or DD LPS), and/or with chemosensitive histologic types (e.g., synovial sarcoma, LMS). Neoadjuvant chemotherapy appears to be safe, but data are limited in terms of the optimal regimen [48–52]. Neoadjuvant chemotherapy is currently being investigated for patients with LMS or DD LPS (EORTC STRASS-2, NCT04031677) [53•]. There is interest in the use of chemotherapy for patients with RPS given the high risk of metastatic disease, especially among certain subtypes.

Timing of RT: preoperative vs. postoperative

The use of RT among patients with RPS is variable, with studies indicating that approximately a quarter to third of patients with RPS receive RT [2, 13, 54]. Over time, there has been a shift toward the use of preoperative RT compared to postoperative RT (PORT). The interest in RT in conjunction with surgery is due to the high local recurrence rate for RPS following surgery alone. The majority of first recurrences in patients with RPS are local [55]. Distant metastases will appear in 20–30% of patients, with the liver and lung being the primary sites of spread [14, 15, 38]. High-grade tumors, LPS histology, and patients with positive surgical margins have higher local recurrence rates, and late recurrences are not uncommon among RPS patients [14, 56]. A nomogram was developed and verified to identify factors significantly predictive for recurrence, and included age, tumor size, completeness of surgical resection, tumor grade, tumor rupture, multifocality, administration of RT and/or chemotherapy, and histologic type [57]. LMS and solitary fibrous tumors have lower local failure rates while DD LPS have a higher local failure rate. RT was associated with a reduced risk of LR with a hazard ratio of 0.58 (95% CI=0.42–0.80). Factors significantly associated with distant metastases included tumor size, tumor grade, multifocality, and histologic type. LMS had the highest risk of distant metastases. These factors are considered by the multidisciplinary team when considering the addition of RT to surgery [3, 13, 57].

The first randomized trial for RPS was led by the National Cancer Institute (NCI) in the early 1990s, randomizing patients to surgery followed by PORT versus surgery and intraoperative beam RT (IORT) boost followed by PORT [58]. Median survival times were similar for both groups. The IORT group had significantly fewer local-regional recurrences and complications of radiation-

related enteritis but had higher rates of peripheral neuropathy. Two randomized trials have compared surgery alone with preoperative RT followed by surgery. The ACOSOG-Z9031 (NCT00091351) trial was prematurely closed, and the STRASS EORTC-STBSG 62092-22092 trial (NCT01344018) was recently published [59••]. No definitive data exist regarding the optimal timing of RT for RPS. Given the concern of late toxicities with PORT in RPS, a randomized trial comparing preoperative versus postoperative RT is highly unlikely to be initiated. Most sarcoma experts prefer preoperative RT when feasible [60•].

Postoperative RT

Adjuvant RT or PORT is not recommended for low-grade tumors following R0/R1 resection. In patients with higher grade tumors, PORT could be considered. However, given that normal tissues, especially bowel, fall into the space formerly occupied by the resected sarcoma and included in the PORT field, the risk for radiation-associated normal tissue morbidity is high enough that clinicians in most major sarcoma centers do not offer postop RT to most patients [42]. There is concern about late toxicity with the use of PORT in RPS. In some cases, placement of omentum or a tissue spacer at time of surgery has been utilized to displace bowel from the area of residual tumor. The studies on the use of spacers have been mixed, as the implantation of spacers has been associated with complications [60, 61]. In certain situations, IORT can be considered. However, in most cases, patients are observed because it is often not possible to deliver PORT without the risk of major side effects. There are some retrospective studies that show a decreased risk of local recurrence, but mixed impact on overall survival [4, 32, 38, 54, 55, 62–68].

Preoperative RT

Rationale and prior studies

The role of preoperative radiation therapy is still being evaluated and debated, and clinical practice consequently varies across the world. Preoperative RT has been used for RPS since the 1980s, sometimes in conjunction with intraoperative RT (IORT). Preoperative RT is thought to be safer than postoperative RT; the latter is difficult to deliver safely in the radiation dose range of 60–66 Gy typically employed postoperatively for extremity/trunk soft tissue sarcomas without significant risk of injury to radiosensitive abdominal normal tissue. There are several advantages of preoperative RT compared to postoperative RT [69]. First, the gross tumor can be precisely delineated for radiation treatment planning. Second, the tumor displaces small bowel and other organs at risk from the high-dose RT fields, allowing for higher doses to be delivered. In the postoperative setting, there is concern for bowel adhesions and the normal organs falling into the areas where the tumor previously was. Third, there may be decreased intraperitoneal tumor seeding during surgery with preoperative RT [70]. Finally, following preoperative RT, it may be possible for some patients with initially unresectable tumors to become resectable [71, 72].

Several retrospective studies investigated the outcomes of patients with RPS receiving preoperative RT [45, 65, 66, 71, 73–82]. The overall trend with preoperative RT is improvement in local control and, in some studies, overall survival as well. A large registry study from the National Cancer Database reviewed outcomes of 9068 patients with RPS who had surgery alone versus RT and surgery [83]. Using a case-controlled, propensity score-matched methodology to minimize selection bias, preoperative RT and PORT were associated with significantly improved overall survival compared to surgery alone. Median survival for patients who received preoperative RT was 110 months versus only 66 months for surgery alone (hazard ratio for death 0.70, 95% confidence interval 0.59–0.82).

STRASS

EORTC-62092 (STRASS) is currently the only randomized controlled trial comparing surgery alone versus preoperative RT followed by surgery in patients with newly diagnosed, resectable RPS and was just recently reported [59••]. Intensity-modulated RT (IMRT) or three-dimensional conformal RT (3D-CRT) was given to 50.4 Gy in 28 daily fractions. The primary outcome was abdominal recurrence-free survival (aRFS), defined as local (abdominal) or distant progressive disease during preoperative RT, tumor or patient becoming inoperable, peritoneal metastasis found at surgery, macroscopic residual disease left at surgery, or local relapse after a macroscopically complete resection. A total of 266 patients were randomized, and at a median follow-up for 43 months, median aRFS was not significantly improved by preoperative RT (4.5 vs 5.0 years, HR=1.01, 95% CI=0.71–1.44). Overall survival (OS) was similar between the two groups—84.6% (95% CI=76.5–90.1) with surgery alone versus 84% (95% CI=76.3–89.4%) with preoperative RT and surgery at 3 years and 79.4% (95% CI=69.1–86.5%) with surgery alone and 76.7% (95% CI=66.9–84.0%) with preoperative RT and surgery at 5 years. Interestingly, local recurrence rates among those resected were higher in the surgery alone group (37%) compared to the preoperative RT group (19.5%).

Initially, patients who had local progression of their tumor while receiving RT were considered to have an abdominal recurrence. However, per recommendation by the Data Monitoring Committee, a sensitivity analysis was performed such that patients with local progression of tumor during RT but were able to undergo surgery were not scored as having an abdominal recurrence. In both analyses, preoperative RT did not improve aRFS. Unplanned subgroup analysis by histologic subtype and grade suggested preoperative RT might improve outcomes in liposarcoma and in low-grade RPS, but not for LMS and higher grade RPS. Of note, there were only 31 patients with high-grade RPS in the study. The authors conclude that, at the present time, preoperative RT should not be considered standard of care for patients with newly diagnosed, localized RPS. It should be noted that median follow-up is only 43 months, and additional follow-up may show different results, as local recurrences can occur beyond 5 years. Furthermore, subgroup analyses for WD and DD LPS patients, while initially unplanned, suggested these patients may benefit from preoperative RT.

In summary, the role of preoperative RT still remains controversial. Despite the results of STRASS, some experts may continue to offer preoperative RT for patients with high risk of local recurrence [84–86]. Since patients with RPS tend to die from local recurrence more often than from distant disease, some experts feel that optimizing local control with combined modality therapy should be considered in appropriate patients. Others routinely do not recommend preoperative RT (both before and after the STRASS results), except in very select cases. We eagerly await the final publication of STREXIT, which analyzed off-trial outcomes of patients treated with and without preoperative RT at institutions participating in STRASS [87••].

RT planning and dose prescriptions

An international expert consensus guideline for preoperative RT in RPS has been published [42]. The standard radiation dose and fractionation for preoperative radiation therapy is 50.4 Gy in 1.8 Gy daily fractions or 50 Gy in 2 Gy fractions. Recommendations are for patients to undergo CT simulation in the supine position with their arms typically positioned over their heads and the use of an immobilization device (e.g., vacuum fix bag). Intravenous and/or oral contrast can be used if it will aid in the delineation of the tumor and/or organs at risk (OARs). Often, a diagnostic CT and/or MRI can be fused to the planning CT for better target and OAR delineation for contouring. 4DCT reconstruction is recommended for tumors above the pelvic brim. CT simulation slice thickness should ideally be 2–3 mm and no more than 5 mm.

RT target volumes and organs at risk

Given the rarity of RPS, the large target volume in close proximity to critical abdominopelvic normal tissues, and the magnitude of surgery required for a gross total resection of these tumors, it is advisable for preoperative RT to be performed in a center with sarcoma-specific expertise. The gross tumor volume (GTV) is first contoured on the CT planning scan; in some patients with WD LPS or mixed DD LPS with a well-differentiated component, it may be challenging to distinguish liposarcoma from retroperitoneal fat. If needed, fusion with the diagnostic CT and/or MRI can further aid in tumor delineation. For tumors below the pelvis brim where motion is not common, the GTV is contoured on the planning CT. Clinical target volume (CTV) is defined as a 1.5 cm anatomically constrained expansion around the iGTV. It is important to note that the CTV should be expanded 3 cm inferiorly if the tumor extends into the inguinal canal. The CTV is cropped at interfaces of bone, retroperitoneal compartment, liver, and kidney. If the kidney is being resected at time of surgery, then, it is not necessary to crop out the kidney from the ITV. The ITV is also cropped 3–5 mm below the skin surface and edited to expand only 5 mm into bowel and air cavities. For tumors located above the pelvic brim, there is GTV motion, and use of 4DCT planning is indicated to account for target motion secondary respiration. In this scenario, the GTV can be expanded to account for motion, named the internal GTV (iGTV), and the corresponding CTV is expanded using the iGTV, and the resulting CTV is named the internal target volume

(ITV) and edited in similar fashion to the CTV as described above. Finally, a 5–10 mm PTV expansion per institution standards is recommended to account for daily setup uncertainty. Of note, the PTV margins in the recently published STRASS trial were 9–12 mm, but 4DCT planning was not employed. When available, intensity-modulated RT (IMRT) may improve the therapeutic index by further minimizing the dose to normal tissues at risk for radiation toxicity around the tumor [88–90].

In a RT contouring study, 12 sarcoma radiation oncologists contoured two RPS cases [91]. There was a high level of agreement for the GTV, CTV, and most OARs, but only moderate agreement for the high-risk CTV (the posterior border of the tumor where surgical margins are more likely to be positive and which has been a target for selective dose escalation in some studies) and the duodenum OAR. In a follow-up study, 7 sarcoma radiation oncology and surgical oncology pairs delineated the high-risk CTV boost volumes. There was substantial to moderate agreement, with the primary differences in areas adjacent to visceral organs [92]. Furthermore, an RT quality assurance program was implemented in STRASS, and its results will be published soon.

RT side effects

Preoperative RT is overall well tolerated. Several retrospective studies, prospective trials, and the randomized STRASS-I trial indicate overall acceptable rates of acute and long-term toxicity. A study from Princess Margaret Hospital prospectively treated 41 RPS patients with preoperative external beam RT and a brachytherapy boost [65]. Acute gastrointestinal RT toxicity scores were grade 2 or less in all patients who received preoperative RT and underwent resection. No patients required hospitalization for acute toxicity, and no treatment breaks were required. However, postoperative brachytherapy was associated with unacceptable toxicity for upper abdominal tumors. Another study of 56 patients with RPS who underwent preoperative RT investigated toxicity in relation to dose to the bowel bag OAR contours [93]. Grade 3 or higher GI toxicity was seen in only 3 patients (5%). V30 appeared to be the best discriminator for toxicity, but overall, significant acute GI toxicity was very low despite bowel bag dose exceeding established constraints for most cases. Finally, in the STRASS-I trial randomizing patients to surgery alone versus preoperative RT followed by surgery, treatment-related serious adverse events occurred in 24% of the preoperative RT group compared to 10% in the surgery alone group. There was one death in the preoperative RT arm from a gastropleural fistula. The toxicity appeared to be higher in STRASS than other studies, and it has been postulated that the excess toxicity may be due in part to the low RT protocol compliance rate of 65%, including 26% major deviations [59, 84].

Other RT techniques: dose painting/boost, intraoperative RT (electrons, brachytherapy), proton RT

An innovative technique has been tested using IMRT to deliver 50 Gy in 2 Gy fractions to a preoperative clinical target volume that was limited to the contact area between the tumor mass and posterior abdominal wall,

i.e., high-risk CTV described above [88]. In doing so, the hope was to better spare critical structures without negatively impacting resectability at time of surgery. All 18 patients in the study completed preoperative RT and surgery without major complications. While longer follow-up is needed, at a median follow-up of 27 months, 2 patients had a local recurrence, and one developed metastatic disease.

Another technique that is being studied delivers a simultaneous integrated boost (SIB) to the retroperitoneal margin. In one study, 16 patients with RPS received 45 Gy in 1.8 Gy fractions to the entire preoperative tumor volume and 57.5 Gy in 2.3 Gy fractions to the retroperitoneal margin [94]. The actuarial 2-year local control was 80%, and treatment toxicities were acceptable. In another phase I study, 11 patients with RPS received intensity-modulated proton therapy (IMPT) to 50.4 GyRBE in 1.8 Gy fractions to the entire preoperative tumor and a SIB to the high-risk margin to 60.2, 61.6, and 53.0 Gy RBE in 2.15, 2.20, and 2.25 GyRBE, respectively [95•]. With a median follow-up of 18 months, there were no local recurrences, and acute toxicities were mild, requiring no RT interruptions. One patient developed hydronephrosis that required stent placement. The follow-up phase II IMPT study has limited the retained ureter(s) to 50.4 GyRBE and has completed accrual as of February 2021. A similar phase I/II IMRT trial is underway, with the phase I portion recently presented showing acceptable toxicity and no local recurrences with early follow-up [96•].

Although supportive data are limited, institutions with IORT and brachytherapy experience often offer these modalities to select patients. Those with gross disease after maximal safe surgery or areas of residual microscopic disease have been considered for IORT of 10–15 Gy. In retrospective studies, IORT with or without external beam RT appeared to improve local control but at the expense of increased toxicities, including abscess and fistula formation, and peripheral neuropathy [58, 73, 77, 80–82, 97–103]. Low-dose rate (LDR) brachytherapy delivered to the tumor bed via implanted catheters has also been investigated, but is not routinely used, especially in the upper abdomen, due to increased late toxicities in patients with upper abdominal tumors (duodenal perforation, death) [65, 78]. Permanent LDR brachytherapy seeds to the tumor bed after resection showed low local recurrence rates but a quarter of patients developed complications necessitating intervention [104]. In summary, IORT and brachytherapy show potential for improved local control but with potentially increased toxicities. It is recommended that these modalities only be used on protocol or at centers with expertise in these techniques.

Protons are increasingly being studied for RPS due to their potential dosimetric benefits [105]. With advancing technology, IMPT is now being utilized at centers with proton capabilities and is showing promise over passively scattered 3D conformal proton beam [95, 106]. Furthermore, IMPT achieves dose conformality comparable to IMRT but with the potential additional benefit of decreased integral dose. The ability to safely increase dose with IMPT or IMRT to select areas at high risk of positive margin and local recurrence may benefit patients with RPS. Finally,

utilizing IMRT or IMPT to dose escalate might reduce late toxicities seen with IORT given the ability to fractionate IMRT/IMPT.

Summary and future directions

Surgical resection for patients with RPS is the only potentially curative approach. The role of chemotherapy and/or radiation therapy continues to be debated as R0 resections are difficult to achieve and there is a high risk of local recurrence. Recent data from the STRASS randomized controlled trial comparing surgery alone versus preoperative RT followed by surgery showed no statistically significant improvement in abdominal recurrence-free survival or overall survival between the two arms. Unplanned subgroup analyses show a trend toward improved local control with preoperative RT and improved overall survival in patients with WD LPS and low-grade RPS. There continues to be disagreement among sarcoma experts as to how to apply the results of this study. Some advocate selected use of preoperative RT, whereas others do not. Further studies are warranted to elucidate the role of RT for RPS. Ultimately, the decision regarding the use of RT should be a shared one between the patient, caregivers, and providers, acknowledging the available data with its limitations. Finally, given the rarity, heterogeneity, and complexity of the radiation and surgical treatments of patients with RPS, evaluation and treatment at a sarcoma center of excellence are recommended. Close collaboration and discussion between surgeons and radiation oncologists will continue to be important to determine which patients may benefit from RT for RPS.

Declarations

Conflict of Interest

Elizabeth H. Baldini has received royalty from UpToDate. Thomas F. DeLaney is a member of the Medical Advisory Board Chordoma Foundation, and has received honoraria from Elsevier, Oakstone Medical Publishing, and Best Docs and royalties from UpToDate and Wolters Kluwer Health. Miranda B. Lam declares that she has no conflict of interest. Sophie J.M. Reijers declares that she has no conflict of interest. Rick L. Haas declares that he has no conflict of interest.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Raut CP, Pisters PWT. Retroperitoneal sarcomas: combined-modality treatment approaches [Internet]. J. Surg. Oncol. J Surg Oncol; 2006 [cited 2021 Feb 18]. p. 81–7. Available from: https://pubmed.ncbi.nlm.nih.gov/16788949/

2. Porter GA, Baxter NN, Pisters PWT. Retroperitoneal sarcoma: a population-based analysis of epidemiology, surgery, and radiotherapy. Cancer [Internet]. Cancer; 2006 [cited 2021 Feb 18];106:1610–6. Available from: https://pubmed.ncbi.nlm.nih.gov/16518798/

3. Gronchi A, Casali PG, Fiore M, Mariani L, Lo Vullo S, Bertulli R, et al. Retroperitoneal soft tissue sarcomas: patterns of recurrence in 167 patients treated at a single institution. Cancer [Internet]. Cancer; 2004 [cited 2021 Feb 18];100:2448–55. Available from: https://pubmed.ncbi.nlm.nih.gov/15160351/
4. Stoeckle E, Coindre JM, Bonvalot S, Kantor G, Terrier P, Bonichon F, et al. Prognostic factors in retroperitoneal sarcoma: a multivariate analysis of a series of 165 patients of the French Cancer Center Federation Sarcoma Group. Cancer [Internet]. Cancer; 2001 [cited 2021 Feb 18];92:359–68. Available from: https://pubmed.ncbi.nlm.nih.gov/11466691/
5. Lewis JJ, Leung D, Woodruff JM, Brennan MF. Retroperitoneal soft-tissue sarcoma: analysis of 500 patients treated and followed at a single institution. Ann Surg [Internet]. Ann Surg; 1998 [cited 2021 Feb 18]. p. 355–65. Available from: https://pubmed.ncbi.nlm.nih.gov/9742918/
6. Liles JS, Tzeng CWD, Short JJ, Kulesza P, Heslin MJ. Retroperitoneal and intra-abdominal sarcoma. Curr Probl Surg [Internet]. Curr Probl Surg; 2009 [cited 2021 Feb 18];46:445–503. Available from: https://pubmed.ncbi.nlm.nih.gov/19414097/
7. Perez EA, Gutierrez JC, Moffat FL, Franceschi D, Livingstone AS, Spector SA, et al. Retroperitoneal and truncal sarcomas: prognosis depends upon type not location. Ann Surg Oncol. 2007;14:1114–22.
8. Chung L, Lau SK, Jiang Z, Loera S, Bedel V, Ji J, et al. Overlapping features between dedifferentiated liposarcoma and undifferentiated high-grade pleomorphic sarcoma. Am J Surg Pathol [Internet]. Am J Surg Pathol; 2009 [cited 2021 Mar 4];33:1594–600. Available from: https://pubmed.ncbi.nlm.nih.gov/19574885/
9. Pham TH, Iqbal CW, Zarroug AE, Donohue JH, Moir C. Retroperitoneal sarcomas in children: outcomes from an institution. J Pediatr Surg [Internet]. J Pediatr Surg; 2007 [cited 2021 Feb 18];42:829–33. Available from: https://pubmed.ncbi.nlm.nih.gov/17502193/
10. Evans HL. Atypical lipomatous tumor, its variants, and its combined forms: a study of 61 cases, with a minimum follow-up of 10 years. Am J Surg Pathol [Internet]. Am J Surg Pathol; 2007 [cited 2021 Mar 4];31:1–14. Available from: https://pubmed.ncbi.nlm.nih.gov/17197914/
11. Lahat G, Tuvin D, Wei C, Anaya DA, Bekele BN, Lazar AJ, et al. New perspectives for staging and prognosis in soft tissue sarcoma. Ann Surg Oncol [Internet]. Ann Surg Oncol; 2008 [cited 2021 Feb 18];15:2739–48. Available from: https://pubmed.ncbi.nlm.nih.gov/18521685/
12. Singer S, Antonescu CR, Riedel E, Brennan MF, Pollock RE. Histologic subtype and margin of resection predict pattern of recurrence and survival for retroperitoneal liposarcoma. Ann Surg [Internet]. Ann Surg; 2003 [cited 2021 Feb 18]. p. 358–71. Available from: https://pubmed.ncbi.nlm.nih.gov/14501502/
13. Gronchi A, Strauss DC, Miceli R, Bonvalot S, Swallow CJ, Hohenberger P, et al. Variability in patterns of recurrence after resection of primary retroperitoneal sarcoma (RPS). A report on 1007 patients from the multi-institutional collaborative RPS working group. Ann Surg [Internet]. Lippincott Williams and Wilkins; 2016 [cited 2021 Feb 26];263:1002–9. Available from: https://pubmed.ncbi.nlm.nih.gov/26727100/
14. Tan MCB, Brennan MF, Kuk D, Agaram NP, Antonescu CR, Qin LX, et al. Histology-based classification predicts pattern of recurrence and improves risk stratification in primary retroperitoneal sarcoma. Ann Surg [Internet]. Lippincott Williams and Wilkins; 2016 [cited 2021 Mar 4]. p. 593–600. Available from: https://pubmed.ncbi.nlm.nih.gov/25915910/
15. Alldinger I, Yang Q, Pilarsky C, Saeger H-D, Knoefel WT, Peiper M. Retroperitoneal soft tissue sarcomas: prognosis and treatment of primary and recurrent disease in 117 patients. Anticancer Res. 2006;26.
16.• Renne SL, Iwenofu OH. Pathology of retroperitoneal sarcomas: a brief review [Internet]. J. Surg. Oncol. John Wiley and Sons Inc.; 2018 [cited 2021 Feb 18]. p. 12–24. Available from: https://pubmed.ncbi.nlm.nih.gov/29230829/.

This provides a contemporary overview of RPS histologic types and challenges in pathologic categorization of sarcomas.

17. Storm FK, Mahvi DM. Diagnosis and management of retroperitoneal soft-tissue sarcoma. Ann Surg [Internet]. Ann Surg; 1991 [cited 2021 Feb 19];214:2–10. Available from: https://pubmed.ncbi.nlm.nih.gov/2064467/
18. Kilkenny JW, Bland KI, Copeland EM. Retroperitoneal sarcoma: the University of Florida experience. J Am Coll Surg [Internet]. J Am Coll Surg; 1996 [cited 2021 Mar 4];182:329–39. Available from: https://pubmed.ncbi.nlm.nih.gov/8605556/
19. Weiss SW, Rao VK. Well-differentiated liposarcoma (atypical lipoma) of deep soft tissue of the extremities, retroperitoneum, and miscellaneous sites: a follow-up study of 92 cases with analysis of the incidence of "dedifferentiation." Am J Surg Pathol [Internet]. Am J Surg Pathol; 1992 [cited 2021 Mar 4];16:1051–8. Available from: https://pubmed.ncbi.nlm.nih.gov/1471725/
20. Strauss G, Christensen L, Zapf J. Tumour-induced hypoglycaemia due to 'big' IGF–II. J Intern Med [Internet]. J Intern Med; 1994 [cited 2021 Mar 4];236:97–9. Available from: https://pubmed.ncbi.nlm.nih.gov/8021581/
21.• Messiou C, Moskovic E, Vanel D, Morosi C, Benchimol R, Strauss D, et al. Primary retroperitoneal soft tissue sarcoma: imaging appearances, pitfalls and diagnostic algorithm [Internet]. Eur. J. Surg. Oncol. W.B. Saunders Ltd; 2017 [cited 2021 Mar 4]. p. 1191–8. Available from: https://pubmed.ncbi.nlm.nih.gov/28057392/.

This provides an overview on important radiologic characteristics of RPS.

22. Binitie O, Tejiram S, Conway S, Cheong D, Temple HT, Letson GD. Adult soft tissue sarcoma local recurrence

after adjuvant treatment without resection of core needle biopsy tract tumor. Clin Orthop Relat Res [Internet]. Springer New York LLC; 2013 [cited 2021 Mar 4]. p. 891–8. Available from: https://pubmed.ncbi.nlm.nih.gov/22968531/

23. Wilkinson MJ, Martin JL, Khan AA, Hayes AJ, Thomas JM, Strauss DC. Percutaneous core needle biopsy in retroperitoneal sarcomas does not influence local recurrence or overall survival. Ann Surg Oncol [Internet]. Springer New York LLC; 2015 [cited 2021 Mar 4];22:853–8. Available from: https://pubmed.ncbi.nlm.nih.gov/25190132/

24.• Berger-Richardson D, Swallow CJ. Needle tract seeding after percutaneous biopsy of sarcoma: risk/benefit considerations [Internet]. Cancer. John Wiley and Sons Inc.; 2017 [cited 2021 Mar 4]. p. 560–7. Available from: https://pubmed.ncbi.nlm.nih.gov/27859013/.

This paper discusses the low risk of biopsy for RPS.

25. Lahat G, Madewell JE, Anaya DA, Qiao W, Tuvin D, Benjamin RS, et al. Computed tomography scan-driven selection of treatment for retroperitoneal liposarcoma histologic subtypes. Cancer [Internet]. Cancer; 2009 [cited 2021 Mar 4];115:1081–90. Available from: https://pubmed.ncbi.nlm.nih.gov/19156920/

26.• Bonvalot S, Gaignard E, Stoeckle E, Meeus P, Decanter G, Carrere S, et al. Survival benefit of the surgical management of retroperitoneal sarcoma in a reference center: a nationwide study of the French Sarcoma Group from the NetSarc Database. Ann Surg Oncol [Internet]. Springer New York LLC; 2019 [cited 2021 Mar 4];26:2286–93. Available from: https://pubmed.ncbi.nlm.nih.gov/31065964/.

This provides key points regarding the surgical management of RPS.

27. Esmo T, Sarcoma Network Working Group E. Soft tissue and visceral sarcomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol [Internet]. Oxford University Press; 2014 [cited 2021 Mar 4];25:iii102–12. Available from: www.springerlink.com.

28. NCCN Clinical Practice Guidelines in Oncology [Internet]. [cited 2014 Nov 20]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

29.• Andritsch E, Beishon M, Bielack S, Bonvalot S, Casali P, Crul M, et al. ECCO essential requirements for quality cancer care: soft tissue sarcoma in adults and bone sarcoma. A critical review [Internet]. Crit. Rev. Oncol. Hematol. Elsevier Ireland Ltd; 2017 [cited 2021 Mar 5]. p. 94–105. Available from: https://pubmed.ncbi.nlm.nih.gov/28109409/.

This provides a review of important considerations in the treatment of patients with STS.

30. Jaques DP, Coit DG, Hajdu SI, Brennan MF. Management of primary and recurrent soft-tissue sarcoma of the retroperitoneum. Ann Surg [Internet]. Lippincott Williams and Wilkins; 1990 [cited 2021 Mar 4];212:51–9. Available from: https://pubmed.ncbi.nlm.nih.gov/2363604/

31. Hassan I, Park SZ, Donohue JH, Nagorney DM, Kay PA, Nasciemento AG, et al. Operative management of primary retroperitoneal sarcomas: a reappraisal of an institutional experience [Internet]. Ann. Surg. Ann Surg; 2004 [cited 2021 Feb 19]. p. 244–50. Available from: https://pubmed.ncbi.nlm.nih.gov/14745333/

32. Catton CN, O'Sullivan B, Kotwall C, Cummings B, Hao Y, Fornasier V. Outcome and prognosis in retroperitoneal soft tissue sarcoma. Int J Radiat Oncol Biol Phys [Internet]. Int J Radiat Oncol Biol Phys; 1994 [cited 2021 Feb 19];29:1005–10. Available from: https://pubmed.ncbi.nlm.nih.gov/8083069/

33. Lehnert T, Cardona S, Hinz U, Willeke F, Mechtersheimer G, Treiber M, et al. Primary and locally recurrent retroperitoneal soft-tissue sarcoma: local control and survival. Eur J Surg Oncol [Internet]. Eur J Surg Oncol; 2009 [cited 2021 Feb 19];35:986–93. Available from: https://pubmed.ncbi.nlm.nih.gov/19138832/

34. Anaya DA, Lev DC, Pollock RE. The role of surgical margin status in retroperitoneal sarcoma [Internet]. J. Surg. Oncol. J Surg Oncol; 2008 [cited 2021 Feb 19]. p. 607–10. Available from: https://pubmed.ncbi.nlm.nih.gov/19072853/

35. Pierie JPEN, Betensky RA, Choudry U, Willett CG, Souba WW, Ott MJ. Outcomes in a series of 103 retroperitoneal sarcomas. Eur J Surg Oncol [Internet]. Eur J Surg Oncol; 2006 [cited 2021 Feb 19];32:1235–41. Available from: https://pubmed.ncbi.nlm.nih.gov/16919908/

36. Avancès C, Mottet N, Mahatmat A, Chapuis E, Serre I, Culine S. Prognostic factors for first recurrence in patients with retroperitoneal sarcoma. Urol Oncol Semin Orig Investig [Internet]. Elsevier Inc.; 2006 [cited 2021 Feb 19];24:94–6. Available from: https://pubmed.ncbi.nlm.nih.gov/16520270/

37. Van Dalen T, Hoekstra HJ, Van Geel AN, Van Coevorden F, Albus-Lutter C, Slootweg PJ. Locoregional recurrence of retroperitoneal soft tissue sarcoma: second chance of cure for selected patients. Eur J Surg Oncol [Internet]. W.B. Saunders Ltd; 2001 [cited 2021 Feb 19];27:564–8. Available from: https://pubmed.ncbi.nlm.nih.gov/11520090/

38. Mendenhall WM, Zlotecki RA, Hochwald SN, Hemming AW, Grobmyer SR, Cance WG. Retroperitoneal soft tissue sarcoma [Internet]. Cancer. Cancer; 2005 [cited 2021 Feb 19]. p. 669–75. Available from: https://pubmed.ncbi.nlm.nih.gov/16003776/

39. Russo P, Kim Y, Ravindran S, Huang W, Brennan MF. Nephrectomy during operative management of retroperitoneal sarcoma. Ann Surg Oncol [Internet]. Lippincott Williams and Wilkins; 1997 [cited 2021 Mar 4];4:421–4. Available from: https://pubmed.ncbi.nlm.nih.gov/9259970/

40.• Fairweather M, Wang J, Jo VY, Baldini EH, Bertagnolli MM, Raut CP. Surgical management of primary retroperitoneal sarcomas: rationale for selective organ resection. Ann Surg Oncol [Internet]. Springer New York LLC; 2018 [cited 2021 Mar 4];25:98–106. Available

from: https://pubmed.ncbi.nlm.nih.gov/29067605/.
This paper provides an important contemporary discussion of surgical approaches for RPS.
41. Shibata D, Lewis JJ, Leung DH, Brennan MF. Is there a role for incomplete resection in the management of retroperitoneal liposarcomas? J Am Coll Surg [Internet]. J Am Coll Surg; 2001 [cited 2021 Mar 4];193:373–9. Available from: https://pubmed.ncbi.nlm.nih.gov/11584964/
42. Baldini EH, Wang D, Haas RLM, Catton CN, Indelicato DJ, Kirsch DG, et al. Treatment guidelines for preoperative radiation therapy for retroperitoneal sarcoma: preliminary consensus of an international expert panel. Int. J. Radiat. Oncol. Biol. Phys. Elsevier Inc.; 2015. p. 602–12.
43. Le Cesne A, Ouali M, Leahy MG, Santoro A, Hoekstra HJ, Hohenberger P, et al. Doxorubicin-based adjuvant chemotherapy in soft tissue sarcoma: pooled analysis of two STBSG-EORTC phase III clinical trials. Ann Oncol [Internet]. Oxford University Press; 2014 [cited 2021 Mar 4];25:2425–32. Available from: https://pubmed.ncbi.nlm.nih.gov/25294887/
44. Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer [Internet]. Cancer; 2008 [cited 2021 Mar 4];113:573–81. Available from: https://pubmed.ncbi.nlm.nih.gov/18521899/
45. Pisters PWT, Ballo MT, Fenstermacher MJ, Feig BW, Hunt KK, Raymond KA, et al. Phase I trial of preoperative concurrent doxorubicin and radiation therapy, surgical resection, and intraoperative electron-beam radiation therapy for patients with localized retroperitoneal sarcoma. J Clin Oncol [Internet]. J Clin Oncol; 2003 [cited 2021 Mar 4];21:3092–7. Available from: https://pubmed.ncbi.nlm.nih.gov/12915599/
46. Gronchi A, De Paoli A, Dani C, Merlo DF, Quagliuolo V, Grignani G, et al. Preoperative chemo-radiation therapy for localised retroperitoneal sarcoma: a phase I-II study from the Italian Sarcoma Group. Eur J Cancer [Internet]. Eur J Cancer; 2014 [cited 2021 Mar 4];50:784–92. Available from: https://pubmed.ncbi.nlm.nih.gov/24316063/
47. Eilber F, Eckardt J, Rosen G, Forscher C, Selch M, Fu YS. Preoperative therapy for soft tissue sarcoma. Hematol. Oncol. Clin. North Am. W.B. Saunders; 1995. p. 817–23.
48.• Tseng WW, Barretta F, Conti L, Grignani G, Tolomeo F, Albertsmeier M, et al. Defining the role of neoadjuvant systemic therapy in high-risk retroperitoneal sarcoma: a multi - institutional study from the Transatlantic Australasian Retroperitoneal Sarcoma Working Group. Cancer [Internet]. John Wiley and Sons Inc; 2020 [cited 2021 Mar 4];127. Available from: https://pubmed.ncbi.nlm.nih.gov/33206381/.
This study investigates the role of chemotherapy in RPS.
49. Meric F, Milas M, Hunt KK, Hess KR, Pisters PWT, Hildebrandt G, et al. Impact of neoadjuvant chemotherapy on postoperative morbidity in soft tissue sarcomas. J Clin Oncol [Internet]. American Society of Clinical Oncology; 2000 [cited 2021 Mar 4];18:3378–83. Available from: https://pubmed.ncbi.nlm.nih.gov/11013278/
50. Meric F, Hess KR, Varma DGK, Hunt KK, Pisters PWT, Milas KM, et al. Radiographic response to neoadjuvant chemotherapy is a predictor of local control and survival in soft tissue sarcomas. Cancer [Internet]. Cancer; 2002 [cited 2021 Mar 4];95:1120–6. Available from: https://pubmed.ncbi.nlm.nih.gov/12209699/
51. Wendtner CM, Sultan Abdel-Rahman, Krych M, Baumert J, Lindner LH, Baur A, et al. Response to neoadjuvant chemotherapy combined with regional hyperthermia predicts long-term survival for adult patients with retroperitoneal and visceral high-risk soft tissue sarcomas. J Clin Oncol [Internet]. J Clin Oncol; 2002 [cited 2021 Mar 4];20:3156–64. Available from: https://pubmed.ncbi.nlm.nih.gov/12118030/
52. Donahue TR, Kattan MW, Nelson SD, Tap WD, Eilber FR, Eilber FC. Evaluation of neoadjuvant therapy and histopathologic response in primary, high-grade retroperitoneal sarcomas using the sarcoma nomogram. Cancer [Internet]. Cancer; 2010 [cited 2021 Mar 4];116:3883–91. Available from: https://pubmed.ncbi.nlm.nih.gov/20564145/
53.• van Houdt WJ, Raut CP, Bonvalot S, Swallow CJ, Haas R, Gronchi A. New research strategies in retroperitoneal sarcoma. The case of TARPSWG, STRASS and RESAR: making progress through collaboration [Internet]. Curr. Opin. Oncol. NLM (Medline); 2019 [cited 2021 Mar 4]. p. 310–6. Available from: https://pubmed.ncbi.nlm.nih.gov/30893150/.
This paper provides a helpful review and future directions for clinical research in RPS.
54.• Bates JE, Dhakal S, Mazloom A, Constine LS. The benefit of adjuvant radiotherapy in high-grade nonmetastatic retroperitoneal soft tissue sarcoma. Am J Clin Oncol Cancer Clin Trials [Internet]. Lippincott Williams and Wilkins; 2018 [cited 2021 Mar 5];41:274–9. Available from: https://pubmed.ncbi.nlm.nih.gov/26703813/.
This paper discusses the potential role of adjuvant radiation therapy in RPS.
55. Heslin MJ, Lewis JJ, Nadler E, Newman E, Woodruff JM, Casper ES, et al. Prognostic factors associated with long-term survival for retroperitoneal sarcoma: implications for management. J Clin Oncol [Internet]. American Society of Clinical Oncology; 1997 [cited 2021 Mar 4];15:2832–9. Available from: https://pubmed.ncbi.nlm.nih.gov/9256126/
56. Toulmonde M, Le Cesne A, Mendiboure J, Blay JY, Piperno-Neumann S, Chevreau C, et al. Long-term recurrence of soft tissue sarcomas: prognostic factors and implications for prolonged follow-up. Cancer [Internet]. John Wiley and Sons Inc; 2014 [cited 2021 Mar 4];120:3003–6. Available from: https://pubmed.ncbi.nlm.nih.gov/24942887/

57. Gronchi A, Miceli R, Shurell E, Eilber FC, Eilber FR, Anaya DA, et al. Outcome prediction in primary resected retroperitoneal soft tissue sarcoma: histology-specific overall survival and disease-free survival nomograms built on major sarcoma center data sets. J Clin Oncol [Internet]. American Society of Clinical Oncology; 2013 [cited 2021 Mar 11];31:1649–55. Available from: http://ascopubs.org/doi/10.1200/JCO.2012.44.3747

58. Sindelar WF, Kinsella TJ, Chen PW, Delaney TF, Tepper JE, Rosenberg SA, et al. Intraoperative radiotherapy in retroperitoneal sarcomas: final results of a prospective, randomized, clinical trial. Arch Surg [Internet]. Arch Surg; 1993 [cited 2021 Feb 25];128:402–10. Available from: https://pubmed.ncbi.nlm.nih.gov/8457152/

59.•• Bonvalot S, Gronchi A, Le Péchoux C, Swallow CJ, Strauss D, Meeus P, et al. Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol [Internet]. Lancet Publishing Group; 2020 [cited 2021 Feb 5];21:1366–77. Available from: https://pubmed.ncbi.nlm.nih.gov/32941794/.

This is the first randomized controlled trial investigating the role of neoadjuvant radiation therapy prior to surgery for RPS patients.

60.• Reid J, Smith R, Borg M, Dobbins C, Gowda R, Chryssidis S, et al. Feasibility of spacers to facilitate postoperative radiotherapy for retroperitoneal sarcomas. J Med Imaging Radiat Oncol [Internet]. Blackwell Publishing; 2017 [cited 2021 Mar 5];61:812–8. Available from: https://pubmed.ncbi.nlm.nih.gov/28741839/.

This paper describes the potential role of spacers for adjuvant radiation therapy in RPS.

61. Park H, Lee S, Kim B, Lim DH, Choi Y La, Choi GS, et al. Tissue expander placement and adjuvant radiotherapy after surgical resection of retroperitoneal liposarcoma offers improved local control. Med (United States) [Internet]. Lippincott Williams and Wilkins; 2016 [cited 2021 Mar 5];95. Available from: https://pubmed.ncbi.nlm.nih.gov/27512857/

62. DeLaney TF, Kepka L, Goldberg SI, Hornicek FJ, Gebhardt MC, Yoon SS, et al. Radiation therapy for control of soft-tissue sarcomas resected with positive margins. Int J Radiat Oncol Biol Phys [Internet]. Int J Radiat Oncol Biol Phys; 2007 [cited 2021 Mar 4];67:1460–9. Available from: https://pubmed.ncbi.nlm.nih.gov/17394945/

63. Tseng WH, Martinez SR, Do L, Tamurian RM, Borys D, Canter RJ. Lack of survival benefit following adjuvant radiation in patients with retroperitoneal sarcoma: a SEER analysis. J Surg Res [Internet]. J Surg Res; 2011 [cited 2021 Mar 5];168. Available from: https://pubmed.ncbi.nlm.nih.gov/21470630/

64. Bonvalot S, Rivoire M, Castaing M, Stoeckle E, Le Cesne A, Blay JY, et al. Primary retroperitoneal sarcomas: a multivariate analysis of surgical factors associated with local control. J Clin Oncol [Internet]. J Clin Oncol; 2009 [cited 2021 Mar 4];27:31–7. Available from: https://pubmed.ncbi.nlm.nih.gov/19047280/

65. Jones JJ, Catton CN, O'Sullivan B, Couture J, Heisler RL, Kandel RA, et al. Initial results of a trial of preoperative external-beam radiation therapy and postoperative brachytherapy for retroperitoneal sarcoma. Ann Surg Oncol [Internet]. Springer Science and Business Media LLC; 2002 [cited 2021 Mar 4];9:346–54. Available from: https://pubmed.ncbi.nlm.nih.gov/11986186/

66.• Albertsmeier M, Rauch A, Roeder F, Hasenhütl S, Pratschke S, Kirschneck M, et al. External beam radiation therapy for resectable soft tissue sarcoma: a systematic review and meta-analysis. Ann Surg Oncol [Internet]. Springer New York LLC; 2018 [cited 2021 Feb 26];25:754–67. Available from: https://pubmed.ncbi.nlm.nih.gov/28895107/.

This is a comprehensive review and meta-analysis for patients receiving RT for STS.

67. Choi AH, Barnholtz-sloan JS, Kim JA. Effect of radiation therapy on survival in surgically resected retroperitoneal sarcoma: a propensity score-adjusted seer analysis. Ann Oncol [Internet]. Elsevier; 2012 [cited 2021 Mar 4];23:2449–57. Available from: http://www.annalsofoncology.org/article/S0923753419351877/fulltext

68. van Doorn RC, Gallee MPW, Hart AAM, Gortzak E, Rutgers EJT, van Coevorden F, et al. Resectable retroperitoneal soft tissue sarcomas. The effect of extent of resection and postoperative radiation therapy on local tumor control. Cancer [Internet]. Cancer; 1994 [cited 2021 Mar 4];73:637–42. Available from: https://pubmed.ncbi.nlm.nih.gov/8299085/

69. Nielsen OS, O'Sullivan B. Retroperitoneal soft tissue sarcomas: a treatment challenge and a call for randomized trials [Internet]. Radiother. Oncol. Radiother Oncol; 2002 [cited 2021 Mar 4]. p. 133–6. Available from: https://pubmed.ncbi.nlm.nih.gov/12464440/

70. Van Der Werf-Messing B. Carcinoma of the bladder treated by suprapubic radium implants. The value of additional external irradiation. Eur J Cancer [Internet]. Eur J Cancer; 1969 [cited 2021 Mar 4];5:277–85. Available from: https://pubmed.ncbi.nlm.nih.gov/4977652/

71. Daylami R, Amiri A, Goldsmith B, Troppmann C, Schneider PD, Khatri VP. Inferior vena cava leiomyosarcoma: is reconstruction necessary after resection? J Am Coll Surg [Internet]. J Am Coll Surg; 2010 [cited 2021 Mar 4];210:185–90. Available from: https://pubmed.ncbi.nlm.nih.gov/20113938/

72. Ito H, Hornick JL, Bertagnolli MM, George S, Morgan JA, Baldini EH, et al. Leiomyosarcoma of the inferior vena cava: survival after aggressive management. Ann Surg Oncol [Internet]. Ann Surg Oncol; 2007 [cited 2021 Mar 4];14:3534–41. Available from: https://pubmed.ncbi.nlm.nih.gov/17896156/

73. Zlotecki RA, Katz TS, Morris CG, Scott Lind D, Hochwald SN. Adjuvant radiation therapy for resectable retroperitoneal soft tissue sarcoma: the University

of Florida experience. Am J Clin Oncol Cancer Clin Trials [Internet]. Am J Clin Oncol; 2005 [cited 2021 Mar 4];28:310–6. Available from: https://pubmed.ncbi.nlm.nih.gov/15923806/

74. Yoon SS, Chen YL, Kirsch DG, Maduekwe UN, Rosenberg AE, Nielsen GP, et al. Proton-beam, intensity-modulated, and/or intraoperative electron radiation therapy combined with aggressive anterior surgical resection for retroperitoneal sarcomas. Ann Surg Oncol [Internet]. Springer New York; 2010 [cited 2021 Mar 4];17:1515–29. Available from: https://pubmed.ncbi.nlm.nih.gov/20151216/

75. Bremjit PJ, Jones RL, Chai X, Kane G, Rodler ET, Loggers ET, et al. A contemporary large single-institution evaluation of resected retroperitoneal sarcoma. Ann Surg Oncol [Internet]. Springer New York LLC; 2014 [cited 2021 Mar 4];21:2150–8. Available from: https://pubmed.ncbi.nlm.nih.gov/24615180/

76. Pawlik TM, Pisters PWT, Mikula L, Feig BW, Hunt KK, Cormier JN, et al. Long-term results of two prospective trials of preoperative external beam radiotherapy for localized intermediate- or high-grade retroperitoneal soft tissue sarcoma. Ann Surg Oncol [Internet]. Ann Surg Oncol; 2006 [cited 2021 Mar 4];13:508–17. Available from: https://pubmed.ncbi.nlm.nih.gov/16491338/

77. Willett CG, Suit HD, Convery K, Tepper JE, Mankin HJ, Rosenberg AL, et al. Intraoperative electron beam radiation therapy for retroperitoneal soft tissue sarcoma. Cancer [Internet]. Cancer; 1991 [cited 2021 Feb 21];68:278–83. Available from: https://pubmed.ncbi.nlm.nih.gov/1906369/

78. Petersen IA, Haddock MG, Donohue JH, Nagorney DM, Grill JP, Sargent DJ, et al. Use of intraoperative electron beam radiotherapy in the management of retroperitoneal soft tissue sarcomas. Int J Radiat Oncol Biol Phys. 2002;52:469–75.

79. Kelly KJ, Yoon SS, Kuk D, Qin LX, Dukleska K, Chang KK, et al. Comparison of perioperative radiation therapy and surgery versus surgery alone in 204 patients with primary retroperitoneal sarcoma: a retrospective 2-institution study. Ann Surg [Internet]. Lippincott Williams and Wilkins; 2015 [cited 2021 Feb 26];262:156–62. Available from: https://pubmed.ncbi.nlm.nih.gov/26061213/

80.• Hull MA, Molina G, Niemierko A, Haynes AB, Jacobson A, Bernstein KDA, et al. Improved local control with an aggressive strategy of preoperative (with or without intraoperative) radiation therapy combined with radical surgical resection for retroperitoneal sarcoma. J Surg Oncol [Internet]. John Wiley and Sons Inc.; 2017 [cited 2021 Feb 26];115:746–51. Available from: https://pubmed.ncbi.nlm.nih.gov/28127762/.

This paper investigates preoperative RT with or without intraoperative RT with surgical resection for RPS.

81. Ove R, Wallner K, Badiozamani K, Korjsseon T, Sutlief S. Long-term results of intraoperative electron beam radiotherapy for primary and recurrent retroperitoneal soft tissue sarcoma. Int J Radiat Oncol Biol Phys [Internet]. Int J Radiat Oncol Biol Phys; 2001 [cited 2021 Feb 21];50:127–31. Available from: https://pubmed.ncbi.nlm.nih.gov/11316555/

82. Ballo MT, Zagars GK, Pollock RE, Benjamin RS, Feig BW, Cormier JN, et al. Retroperitoneal soft tissue sarcoma: an analysis of radiation and surgical treatment. Int J Radiat Oncol Biol Phys [Internet]. Int J Radiat Oncol Biol Phys; 2007 [cited 2021 Mar 4];67:158–63. Available from: https://pubmed.ncbi.nlm.nih.gov/17084545/

83. Nussbaum DP, Rushing CN, Lane WO, Cardona DM, Kirsch DG, Peterson BL, et al. Preoperative or postoperative radiotherapy versus surgery alone for retroperitoneal sarcoma: a case-control, propensity score-matched analysis of a nationwide clinical oncology database. Lancet Oncol [Internet]. Lancet Publishing Group; 2016 [cited 2021 Feb 26];17:966–75. Available from: https://pubmed.ncbi.nlm.nih.gov/27210906/

84.•• Chowdhary M, Spraker MB. Preoperative radiotherapy for retroperitoneal sarcoma [Internet]. Lancet Oncol. Lancet Publishing Group; 2021 [cited 2021 Feb 25]. p. e2. Available from: https://pubmed.ncbi.nlm.nih.gov/33387501/.

This response letter to the STRASS trial highlights important considerations of the trial.

85.•• DeLaney T, Mullen JT, Wang D, Goldberg SI, Kirsch DG. Preoperative radiotherapy for retroperitoneal sarcoma [Internet]. Lancet Oncol. Lancet Publishing Group; 2021 [cited 2021 Mar 5]. p. e1. Available from: https://pubmed.ncbi.nlm.nih.gov/33387499/.

This response letter to the STRASS trial highlights important considerations of the trial.

86.•• Izzuddeen Y, Sharma DN. Preoperative radiotherapy for retroperitoneal sarcoma [Internet]. Lancet Oncol. Lancet Publishing Group; 2021 [cited 2021 Feb 25]. p. e3. Available from: https://pubmed.ncbi.nlm.nih.gov/33387503/.

This response letter to the STRASS trial highlights important considerations of the trial.

87.•• Callegaro D, Raut CP, Ajayi Taiwo A, Swallow CJ, Gronchi A, Bonvalot S. Pre-operative radiotherapy in patients with primary retroperitoneal sarcoma: trial (STRASS) vs off-trial (STREXIT) results. 2020. Annual Virtual Meeting Connective Tissue Oncology Society (CTOS); abstract 17; 2020.

This abstract discussed initial results to patients with RPS treated off-trial at STRASS institutions. Final publication pending.

88. Bossi A, De Wever I, Van Limbergen E, Vanstraelen B. Intensity modulated radiation-therapy for preoperative posterior abdominal wall irradiation of retroperitoneal liposarcomas. Int J Radiat Oncol Biol Phys [Internet]. Elsevier Inc.; 2007 [cited 2021 Mar 4];67:164–70. Available from: https://pubmed.ncbi.nlm.nih.gov/17084556/

89. Koshy M, Landry JC, Lawson JD, Staley CA, Esiashvili N, Howell R, et al. Intensity modulated radiation therapy for retroperitoneal sarcoma: a case for dose escalation and organ at risk toxicity reduction. Sarcoma

[Internet]. Sarcoma; 2003 [cited 2021 Mar 4];7:137–48. Available from: https://pubmed.ncbi.nlm.nih.gov/18521378/

90. Musat E, Kantor G, Caron J, Lagarde P, Laharie H, Stoeckle E, et al. Étude théorique d'une radiothérapie postopératoire avec modulation d'intensité d'un sarcome rétropéritonéal. Cancer/Radiotherapie [Internet]. Cancer Radiother; 2004 [cited 2021 Mar 4];8:255–61. Available from: https://pubmed.ncbi.nlm.nih.gov/15450519/

91. Baldini EH, Abrams RA, Bosch W, Roberge D, Haas RLM, Catton CN, et al. Retroperitoneal sarcoma target volume and organ at risk contour delineation agreement among NRG sarcoma radiation oncologists. Int J Radiat Oncol Biol Phys [Internet]. Elsevier Inc.; 2015 [cited 2021 Feb 24]. p. 1053–9. Available from: https://pubmed.ncbi.nlm.nih.gov/26194680/

92. Baldini EH, Bosch W, Kane JM, Abrams RA, Salerno KE, Deville C, et al. Retroperitoneal sarcoma (RPS) high risk gross tumor volume boost (HR GTV boost) contour delineation agreement among NRG sarcoma radiation and surgical oncologists. Ann Surg Oncol [Internet]. Springer New York LLC; 2015 [cited 2021 Feb 24];22:2846–52. Available from: https://pubmed.ncbi.nlm.nih.gov/26018727/

93. Mak KS, Phillips JG, Barysauskas CM, Lee LK, Mannarino EG, Van Benthuysen L, et al. Acute gastrointestinal toxicity and bowel bag dose-volume parameters for preoperative radiation therapy for retroperitoneal sarcoma. Pract Radiat Oncol [Internet]. Elsevier Inc.; 2016 [cited 2021 Feb 21];6:360–6. Available from: https://pubmed.ncbi.nlm.nih.gov/27009922/

94. Tzeng CWD, Fiveash JB, Popple RA, Arnoletti JP, Russo SM, Urist MM, et al. Preoperative radiation therapy with selective dose escalation to the margin at risk for retroperitoneal sarcoma. Cancer [Internet]. Cancer; 2006 [cited 2021 Mar 4];107:371–9. Available from: https://pubmed.ncbi.nlm.nih.gov/16752414/

95.• DeLaney TF, Chen YL, Baldini EH, Wang D, Adams J, Hickey SB, et al. Phase 1 trial of preoperative image guided intensity modulated proton radiation therapy with simultaneously integrated boost to the high risk margin for retroperitoneal sarcomas. Adv Radiat Oncol [Internet]. Elsevier Inc; 2017 [cited 2021 Feb 25];2:85–93. Available from: www.advancesradonc.org.

This phase 1 trial investigated the safety of preoperative proton RT with a simultaneously integrated boost to the high risk surgical margin for RPS.

96.• DeLaney TF, Wang D. Phase I/II trial of preoperative dose-painted intensity modulated radiation treatment for retroperitoneal sarcoma with high-dose (simultaneously integrated) boost. Rome, Italy: Connective Tissue Oncology Society (CTOS); 2018.

This presentation reviewed the preliminary results of a phase 1/2 trial investigating preoperative photon RT with a simultaneously integrated boost to the high risk surgical margin for RPS.

97. Pezner RD, Liu A, Chen YJ, Smith DD, Paz IB. Full-dose adjuvant postoperative radiation therapy for retroperitoneal sarcomas. Am J Clin Oncol Cancer Clin Trials [Internet]. Am J Clin Oncol; 2011 [cited 2021 Mar 5];34:511–6. Available from: https://pubmed.ncbi.nlm.nih.gov/21127412/

98. Gilbeau L, Kantor G, Stoeckle E, Lagarde P, Thomas L, Kind M, et al. Surgical resection and radiotherapy for primary retroperitoneal soft tissue sarcoma. Radiother Oncol [Internet]. Radiother Oncol; 2002 [cited 2021 Mar 5];65:137–43. Available from: https://pubmed.ncbi.nlm.nih.gov/12464441/

99. Trovik LH, Ovrebo K, Almquist M, Haugland HK, Rissler P, Eide J, et al. Adjuvant radiotherapy in retroperitoneal sarcomas. A Scandinavian Sarcoma Group study of 97 patients. Acta Oncol (Madr) [Internet]. Informa Healthcare; 2014 [cited 2021 Mar 5];53:1165–72. Available from: https://pubmed.ncbi.nlm.nih.gov/25000415/

100. Gunderson LL, Nagorney DM, McIlrath DC, Fieck JM, Wieand HS, Martinez A, et al. External beam and intraoperative electron irradiation for locally advanced soft tissue sarcomas. Int J Radiat Oncol Biol Phys [Internet]. Int J Radiat Oncol Biol Phys; 1993 [cited 2021 Feb 21];25:647–56. Available from: https://pubmed.ncbi.nlm.nih.gov/8454483/

101. Krempien R, Roeder F, Oertel S, Weitz J, Hensley FW, Timke C, et al. Intraoperative electron-beam therapy for primary and recurrent retroperitoneal soft-tissue sarcoma. Int J Radiat Oncol Biol Phys [Internet]. Int J Radiat Oncol Biol Phys; 2006 [cited 2021 Feb 21];65:773–9. Available from: https://pubmed.ncbi.nlm.nih.gov/16682152/

102. Bishop AJ, Zagars GK, Torres KE, Hunt KK, Cormier JN, Feig BW, et al. Combined modality management of retroperitoneal sarcomas: a single-institution series of 121 patients. Int J Radiat Oncol Biol Phys [Internet]. Elsevier Inc.; 2015 [cited 2021 Mar 5];93:158–65. Available from: https://pubmed.ncbi.nlm.nih.gov/26130233/

103. Le Péchoux C, Musat E, Baey C, Al Mokhles H, Terrier P, Domont J, et al. Should adjuvant radiotherapy be administered in addition to front-line aggressive surgery (FAS) in patients with primary retroperitoneal sarcoma? Ann Oncol [Internet]. Elsevier; 2013 [cited 2021 Mar 5];24:832–7. Available from: http://www.annalsofoncology.org/article/S092375341937142X/fulltext

104. Fairweather M, Wang J, Devlin PM, Hansen J, Baldini EH, Ready JE, et al. Safety and efficacy of radiation dose delivered via iodine-125 brachytherapy mesh implantation for deep cavity sarcomas. Ann Surg Oncol [Internet]. Springer New York LLC; 2015 [cited 2021 Mar 5];22:1455–63. Available from: https://pubmed.ncbi.nlm.nih.gov/25341749/

105. Delaney TF, Haas RLM. Innovative radiotherapy of sarcoma: proton beam radiation. Eur J Cancer [Internet]. Elsevier Ltd; 2016 [cited 2021 Mar 5];62:112–23. Available from: https://pubmed.ncbi.nlm.nih.gov/27258968/

106. Chung CS, Trofimov A, Adams J, Kung J, Kirsch D, Yoon S, et al. 207. Int J Radiat Oncol [Internet]. Elsevier; 2006 [cited 2021 Mar 5];66:S116. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0360301606014763

Publisher's note