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SARCOMAS (SR PATEL, SECTION EDITOR)

Contemporary Management of Retroperitoneal Soft Tissue Sarcomas

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Abstract Management of retroperitoneal soft tissue sarcomas (RP STS) can be very challenging. In contrast to the more common extremity STS, the two predominant histologic subtypes encountered in the retroperitoneum are well-differentiated/dedifferentiated liposarcoma and leiomyosarcoma. Surgery remains the mainstay of treatment for RP STS. Preoperative planning and anticipation of the need for resection of adjacent organs/structures are critical. The extent of surgery, including the role of compartmental resection, is still controversial. Radiation therapy may be an important adjunct to surgery to provide locoregional disease control; this is currently being evaluated in the preoperative setting in the EORTC STRASS trial. Systemic therapy, tailored to the specific histologic subtype, may also be of benefit for the management of RP STS. Further investigation of novel therapies (e.g., targeted therapies, immunotherapy) is needed. Overall, multi-institutional collaboration is important moving forward, to continue to better understand and optimize management of this disease.

Keywords Retroperitoneal sarcoma · Liposarcoma · Leiomyosarcoma

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Introduction

Soft tissue sarcomas (STS) are rare cancers representing 1 % of all adult solid tumors. STS encompass a heterogeneous group of tumors with over 50 distinct histologic subtypes recognized by the World Health Organization [1]. Each histologic subtype has unique molecular and genetic features, clinical behavior, and response to therapy. Although STS can occur at virtually any location in the body, the majority are found in the extremities [1]. However, 15–20 % of STS develop in the retroperitoneum, a unique location that allows tumors to grow to often massive size prior to detection. In this review, we will discuss the management of retroperitoneal soft tissue sarcoma (RP STS) from diagnosis to treatment and follow-up. We will focus on patients with tumor(s) confined to the retroperitoneum and not discuss those with synchronous distant metastatic disease.

Histology and Differential Diagnosis

The most common RP STS histologic subtypes are liposarcoma and leiomyosarcoma. These are tumors of adipocyte and smooth muscle origin, respectively. In contrast to the extremities, these two histologic subtypes represent up to 80–85 % of STS found in the retroperitoneum [2]. Liposarcomas

in the retroperitoneum are almost exclusively well-differentiated (WD)/dedifferentiated (DD). Histology-confirmed myxoid liposarcoma in the retroperitoneum may represent either an incorrect diagnosis [3] or a site of distant metastasis from a primary site elsewhere in the body [4, 5].

Other less frequent primary STS histologies in the retroperitoneum include malignant fibrous histiocytoma, solitary fibrous tumor, desmoplastic small round cell tumor, and malignant peripheral nerve sheath tumor. Interestingly, reported data suggests that malignant fibrous histiocytoma, also known as undifferentiated pleomorphic sarcoma, may not exist in the retroperitoneum and, instead, may represent DD liposarcoma without an obvious WD component [6].

It is important to note, however, that two thirds of all retroperitoneal tumors are not sarcomas [2]. Other mass lesions in the retroperitoneum include lymphoma (Fig. 1a), paragangliomas and pheochromocytoma, as well as neurogenic tumors (e.g., schwannomas). In younger male patients with midline mass lesions, metastatic testicular cancer should be ruled out. Primary tumors arising from retroperitoneal organs such as the pancreas, duodenum, kidney, and adrenal must also be considered. In the perinephric area, benign myelolipomas and angiomyolipomas can often be confused with liposarcoma.

Initial Presentation

The majority of patients with RP STS are either asymptomatic or have vague, nonspecific symptoms at the time of initial presentation. Asymptomatic patients may have a mass detected on routine physical exam or found incidentally by cross-sectional imaging done for another purpose. For patients with symptoms, these may vary widely from vague abdominal discomfort or back pain to change in bowel or urinary habits. Constitutional symptoms such as fevers, night sweats, or unplanned weight loss should alert the clinician to the possibility of lymphoma as the diagnosis. Similarly, hematuria is more typical of a primary renal malignancy [7].

Physical examination in patients with known or suspected RP STS may reveal a definitive abdominal mass or only a subtle increase in girth, fullness, or asymmetry. From an operative planning standpoint, determination of how fixed versus mobile the mass is can, in some cases, be helpful to anticipate the ease of resectability or the need for concomitant organ resection. Motor deficits may suggest nerve (e.g., femoral, obturator) involvement by the tumor. Lower extremity edema or the presence of superficial varicosities may suggest venous obstruction due to tumor. The presence of inguinal lymphadenopathy does not completely rule out STS as there are specific histologic subtypes which can involve regional lymph nodes [8, 9], but this physical examination finding is more common with lymphoma.

Diagnostic Imaging

Cross-sectional imaging by computed tomography (CT) or magnetic resonance imaging (MRI) is mandatory for all known or suspected RP STS. Cross-sectional imaging can provide clues for histologic diagnosis, particularly for WD/DD liposarcoma (Fig. 1b). The unique "dirty fat" appearance of WD liposarcoma has been shown to have high diagnostic sensitivity up to 100 % [10]. DD liposarcoma is notable for the presence of nonfatty, focal nodular or soft tissue density components juxtaposed next to the fatty, well-differentiated component of tumor. Leiomyosarcoma, in contrast, does not have specific imaging characteristics, although tumors frequently arise from major vascular structures (Fig. 1c).

In all RP STS cases, cross-sectional imaging is critical for operative planning. In collaboration with an experienced radiologist, preoperative review of the imaging can help the surgeon to anticipate tumor involvement of adjacent organs and critical structures [11]. Although MRI may be more useful to assess tumor involvement of neurovascular structures, high-quality CT is often adequate, and to our knowledge, no robust data exists comparing the utility of the two imaging modalities for operative planning in RP STS. Preoperative review of the imaging between the surgeon and radiation oncologist can also be useful to anticipate potential close margins of resection, which, depending on institutional practice, may be useful for planning intraoperative radiation therapy.

As part of staging, all patients with RP STS should undergo at least a chest X-ray to evaluate for metastasis to the lungs, the most common site of distant disease in STS [1]. For specific histologies with the high potential for lung metastasis (e.g., leiomyosarcoma), CT of the chest is warranted. This can frequently be easily done in conjunction with the abdominal portion of the imaging study. Other imaging modalities such as positron emission tomography (PET) may be useful to rule out presence of distant metastatic disease. Emerging data also suggests that in STS, PET 18F-FDG avidity of the primary tumor may be correlated with tumor grade and potential for distant metastasis [12].

Biopsy

Preoperative biopsy is clearly indicated if (1) an alternative diagnosis for the retroperitoneal mass is suspected (e.g., lymphoma, testicular cancer) or (2) definitive histologic STS diagnosis is needed. The latter situation is relevant if a patient is being considered for neoadjuvant therapy for locally advanced disease or palliative therapy for unresectable disease. Ideally, if performed, biopsies should be done by the treating center and interpreted by an experienced soft tissue pathologist.

Recent consensus guidelines from the collaborative Trans-Atlantic Retroperitoneal Working Group strongly recommend

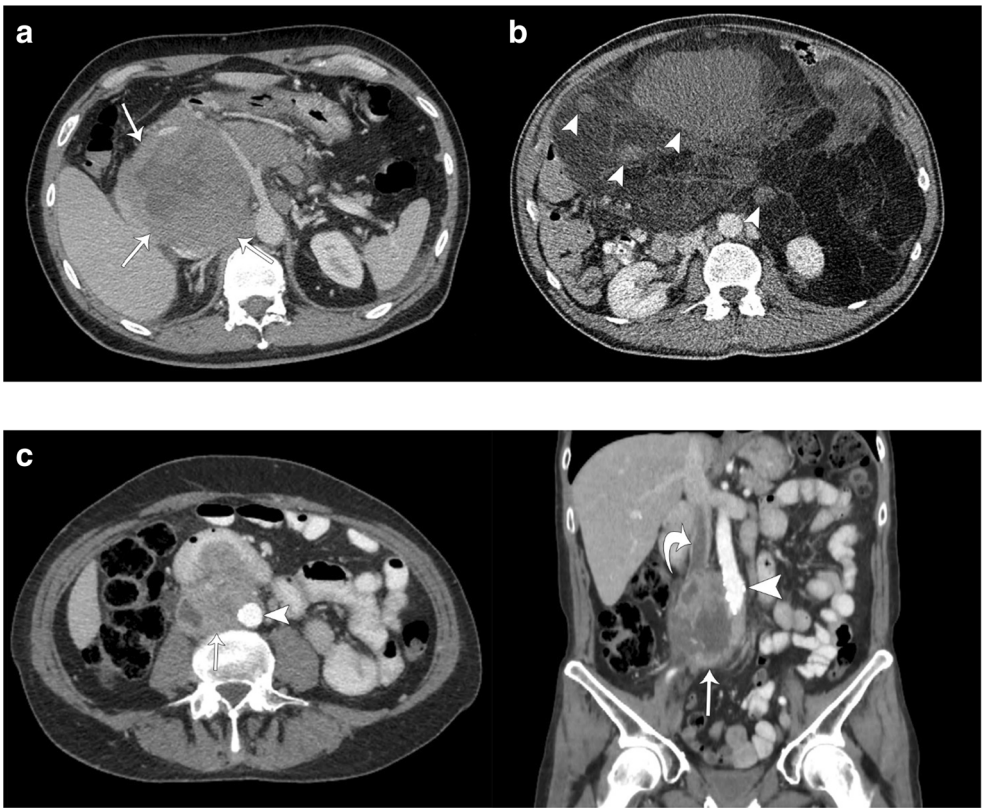

Fig. 1 CT image of a 57-year-old man with diffuse large B cell lymphoma (*arrows*), which could easily be confused with a retroperitoneal sarcoma (**a**). CT image of 46-year-old woman with a retroperitoneal liposarcoma. Some areas of soft tissue attenuation nodularity are present within the mass (*arrowheads*), concerning for regions of dedifferentiation (**b**). CT images of a 64-year-old man with a leiomyosarcoma of the inferior vena cava (IVC). Transverse CT image with intravenous contrast (*left*) and coronal (*right*) reformation demonstrate a large heterogeneous retroperitoneal mass replacing the IVC (*arrows*) with mass effect on the abdominal aorta (*arrowheads*). There is thrombus within the infrarenal IVC superior to the tumor (*curved arrow*) (**c**)

image-guided core needle (14 or 16 gauge) biopsy for all suspected RP STS [13••]. In fact, if a histologic diagnosis is not determined with initial biopsy, repeat core biopsy is encouraged by the Working Group guidelines. Sampling of well-perfused areas on contrast-enhanced cross-sectional imaging or 18F-FDG-avid areas of tumor on PET (if available) is also encouraged. Open surgical biopsy through laparotomy, however, should be avoided as this can distort the natural tissue planes and potentially contaminate the peritoneal cavity. Laparoscopic biopsy carries similar risks.

An exception to the need for preoperative biopsy, however, is in cases with diagnostic imaging that is pathognomonic for liposarcoma (Fig. 1b), as already discussed. In lipomatous tumors with a nonfatty component, preoperative biopsy to confirm DD disease may be potentially helpful for patient counseling and treatment decision making; however, recent data actually suggests that diagnosis of DD by percutaneous core biopsy has very low accuracy [14].

Staging

STS in general can be staged based on the American Joint Committee on Cancer (AJCC) TNM staging system [15]. Tumor size is categorized as less than (T1) or greater than (T2) 5 cm, and the importance of histologic grade is recognized. For RP STS, the AJCC TNM system, however, is not particularly relevant as the vast majority of tumors are over 5 cm and none of the two predominant histologic subtypes (liposarcoma, leiomyosarcoma) spread via the lymphatic system, obviating the need for N staging. Understandably, due to the rarity of these tumors, there is no RP STS-specific staging system.

As an alternative to the TNM staging system, nomograms have been developed in STS to predict clinical outcomes [16–20]. Recently, data collected from four major sarcoma centers was used to develop an RP STS-specific nomogram that was shown to predict postoperative disease-free and overall survival [21••]. In addition to patient age, tumor size, and grade, this nomogram also includes histologic subtype and, unique to RP STS, the presence of multifocality, defined as two or more tumors.

Treatment—Surgery

The mainstay of treatment for RP STS is surgery with the goal of complete resection whenever possible [7, 13••, 22]. As these tumors are often massive in size (Fig. 1), surgery can be challenging. In addition, tumors may be "pushing" into or directly invading adjacent visceral organs or critical structures. En bloc resection of tumor with adjacent organ resection, most commonly the kidney and colon, is frequently needed to achieve complete resection [22]. Preoperative anticipation of

potential operative scenarios is therefore critical, and to facilitate complete and safe resection, a multidisciplinary surgical team (e.g., surgical oncology and vascular surgery) and use of adjunct procedures (e.g., ureteral stent placement) may be required [11, 13••]. Although preoperative cross-sectional imaging can suggest tumor invasion, definitive assessment of the relationship between the tumor and an adjacent organ/structure often cannot be made until exploration at surgery. These and additional technical considerations for RP STS resection have been described by the Trans-Atlantic Retroperitoneal Working Group [23••]. Overall, given the rarity of the disease and often complex nature of these operations, treatment outcomes for RP STS are better at experienced sarcoma referral centers [24].

Interestingly, two studies have actually examined the extent of tumor invasion into resected adjacent organs on a histological level. In patients with concomitant en bloc nephrectomy for RP STS, Russo et al. found that the majority of cases (73 %) demonstrated no tumor invasion into the renal capsule [25]. By contrast, a more recent study by Mussi et al. demonstrated microscopic involvement of adjacent organs in 61 % of cases [26]. The authors categorized involvement as either "infiltrative" (clear focal or diffuse infiltration of nests or single tumor cells into organ tissue) versus "pushing or expansive" (ill-defined borders between tumor and organ tissue without clear infiltration). True "infiltration" was only seen in 42 %; therefore, among all cases studied by Mussi et al., only 25 % of resected organs actually had histologic evidence of tumor invasion.

With any type of resection for RP STS, the limits of resectability are important to recognize. RP leiomyosarcoma can frequently arise from the inferior vena cava; resection and reconstruction of this major structure can be done safely with reasonable outcomes, typically in collaboration with a vascular surgeon [27, 28]. Although less common, aortic resection and reconstruction have also been described [27, 29]. To facilitate major vascular resection, at some institutions, patients are placed under cardiopulmonary bypass [30]. Tumor involvement of the vertebral spine and in particular, the spinal cord, however, is considered a contraindication for resection. In addition, tumor involvement of the bowel mesenteric root would also be viewed by many sarcoma surgeons as a contraindication for resection as this would place the patient at risk of short gut syndrome and chronic total parenteral nutrition. In rare instances, RP STS may involve both kidneys. The need for bilateral nephrectomy, which would place the patient on permanent dialysis, would also preclude resection.

For patients with resectable RP STS, the completeness of resection has been shown to be a significant predictor for both recurrence-free and overall survival across multiple studies [7, 21••]. One area of ongoing controversy in the surgical management of RP STS is the extent of resection needed to truly achieve complete resection. In 2009, two independent reports were published advocating extended or compartmental resection, in which adjacent organs or structures were removed even without gross evidence of tumor invasion at the time of surgery [31, 32]. Both groups reported improved locoregional disease control. Gronchi et al. found lower 5-year locoregional recurrence rates in a more recent cohort of patients who had undergone compartmental resection (28 %) versus a prior cohort of patients with simple complete resection (48 %). Similarly, Bonvalot et al. demonstrated that within a contemporary cohort of matched patients, those with compartmental resection had a threefold lower rate of locoregional recurrence compared to those with simple complete resection. Subsequent follow-up data reported by Gronchi et al. has demonstrated the durability of locoregional disease control and importantly, improved 5 year overall survival (67 vs. 48 %) in the compartmental resection group [33]. The histologic subtype also appears to impact locoregional disease control and patterns of failure after compartmental resection [34••]. Specifically, leiomyosarcoma appears to have very low rates of 5-year locoregional recurrence (5 %) after compartmental resection; however, these patients are at high risk for distant metastasis (55 %).

On the opposite side of the debate, the original studies of compartmental resection have been criticized for their retrospective design and the lack of standardized methodology for patient selection [35]. Specifically, there is the potential for "selective" resection of adjacent organs (e.g., the psoas muscle but not the aorta) [36]. The complication rates for compartmental resection can also be significant. Bonvalot et al. originally reported that 22 % of patients in their series had one or more surgical or medical complications and among those with surgical complications, half required reoperation [32]. Subsequently, two other groups have evaluated compartmental resection and reported similarly high rates of complications (30–31 %) and need for reoperation (11–15 %) [37, 38].

The indications for compartmental resection may be dependent on tumor histology [39]. Tseng et al. demonstrated that for WD/DD liposarcoma, multifocal tumors and tumors in remote locations (outside field) can occur within the retroperitoneum and intra-abdominal cavity [40]. This finding raises the possibility of a "field defect" in the patient's fat, a concept originally proposed by Neuhaus et al. [41]. To provide adequate locoregional control for this specific histology, in theory, would require clearance of all the retroperitoneal and intra-abdominal fat (including mesentery), which is not practical and fraught with complications.

Treatment—Radiation Therapy

Even after macroscopic complete surgical resection, locoregional recurrence develops in 20–75 % of patients, and this is the predominant driver for cancer-related mortality

in RP STS [42]. The possibility of residual microscopic disease as suggested by the high locoregional failure rate observed after surgery forms the rationale for adding perioperative radiation therapy (RT) in this disease.

Multiple retrospective single-institution series have shown improved locoregional disease control with the addition of postoperative RT after tumor resection [43–45]. A more recent analysis of the National Oncology Database of 261 patients who received definitive surgery for RP STS similarly showed a significant improvement in local failure-free survival at 5 years (79 v 64 %) with the addition of postoperative RT [46].

Intraoperative radiation therapy (IORT, typically ranging 10–20 Gy) can also be combined with postoperative external beam radiation therapy (EBRT) to give additional dose to the tumor bed. Dose limiting toxicities from IORT, however, include neuropathy and gastrointestinal toxicities. A single prospective randomized trial found a significantly improved locoregional disease control rate of 60 % using a combination of 20 Gy IORT and 35–40 Gy postoperative EBRT compared to 20 % control with 50–55 Gy postoperative EBRT alone [47].

Preoperative RT offers several theoretical advantages compared with postoperative RT. The most important is that the intact tumor in the retroperitoneum and intra-abdominal cavity often displaces the radiosensitive organs (e.g., small bowel) out of the field of radiation, minimizing toxicity and potentially allowing for higher dose delivery to the tumor. Results from single-institution, prospective, single-arm phase I/II trials and retrospective studies using preoperative RT with or without IORT have shown the 5-year locoregional control rates of 60–89 % [48–52].

There is, however, a lack of data from prospective randomized trial comparing radiation in combination with surgery versus surgery alone for RP STS. The planned randomized control trial ACOSOG Z9031 examining the effect of preoperative RT plus surgery versus surgery alone was closed prematurely due to slow patient accrual. EORTC 62092 (STRASS) is a similar phase III randomized study of preoperative RT plus surgery versus surgery alone. This trial opened in 2012 and is currently actively accruing patients. Other ongoing trials are examining the feasibility, tolerability, and efficacy of dose-escalated preoperative RT beyond 50 Gy using intensity modulated radiation therapy or IMRT techniques. Charged particles, such as protons, have different physical and radiobiological properties and, in theory, are better in sparing normal organs, with higher efficacy than conventional photon therapy radiation. Currently, there are also several active trials assessing the role of proton therapy for RP STS.

Treatment—Systemic Therapy

Chemotherapy either in the preoperative or postoperative setting provides an additional treatment modality for RP STS that could potentially lower the rates of locoregional recurrence and improve survival. Unfortunately, little data exists to evaluate the efficacy of chemotherapy for RP STS; moreover, chemotherapy is not unequivocally recommended for use by established consensus guidelines [53]. Despite this, several studies, with mostly data extrapolated from STS patients with advanced/metastatic disease or tumors at other anatomic sites, are important to mention. In addition, several histology subtype-specific studies have been reported that may also help to guide treatment in RP STS. Ultimately, these treatment decisions should be made by a multidisciplinary team at an experienced sarcoma center.

WD/DD Liposarcoma

For cytotoxic chemotherapy, Italiano et al. reported the largest retrospective review of advanced WD/DD liposarcoma patients treated with mostly anthracycline-containing regimens [54]. Unfortunately, no impact of chemotherapy on progression-free or overall survival was noted and objective tumor response rate was only 12 % in total (all DD) and 0 % in WD. More recently, single-agent high-dose ifosfamide has been shown to have some activity against WD/DD liposarcoma with an objective response rate of 23–25 % [55, 56]. As another nonanthracycline alternative, the combination of gemcitabine and docetaxel is used in STS in general; however, no data exists to assess efficacy specifically in liposarcoma, to our knowledge.

Other systemic therapies, including targeted therapies, have also been evaluated in WD/DD liposarcoma. Eribulin mesylate, a marine-derived microtubule inhibitor, was reported to have selective activity in DD liposarcoma [57]. Other potentially promising novel therapies in WD/DD liposarcoma that are being actively investigated include MDM2 inhibitors [58] and CDK4 inhibitors [59–61]. These and other novel systemic therapies in liposarcoma are reviewed elsewhere [62].

Leiomyosarcoma

Leiomyosarcoma is an STS subtype that can also be responsive to cytotoxic chemotherapy. In a phase II study of gemcitabine and docetaxel in leiomyosarcoma patients, an objective response was observed in 53 % of patients, with three patients experiencing a complete response [63]. The vast majority of these patients, however, had leiomyosarcoma of uterine origin. Maki et al. reported a subsequent randomized phase II study in advanced STS patients comparing gemcitabine alone to gemcitabine and docetaxel [64]. Among the leiomyosarcoma patients, which included both uterine and nonuterine origin disease, objective response was seen in 1 out of 9 (11 %) in the single-arm group and 5 out of 29 (17 %) in the combination arm. These more modest response rates

(14 %) were also seen in the French TaxoGem study which included both uterine and nonuterine leiomyosarcoma [65].

Pazopanib, a multikinase inhibitor and anti-angiogenesis agent, is another potential systemic therapy option available for treatment of leiomyosarcoma. Pazopanib has been approved by the United States Food and Drug Administration as second-line therapy in patients with high-grade STS after demonstration of improved progression-free survival in the PALETTE study [66]. This agent appears to have selective activity for leiomyosarcoma when compared to liposarcoma [66, 67].

Treatment of Multifocal Disease

Multifocal disease confined to the retroperitoneum and intra-abdominal cavity is a unique situation that can be encountered in RP STS. By definition, these patients have two or more tumors, and as expected, compared to patients with only a single tumor, those with multifocal disease have worse outcome. Anaya et al. reported a twofold difference in 5-year overall survival (31 vs. 60 %) in patients with unifocal vs. multifocal disease [68]. In patients with seven or more tumors, 5-year survival decreased to 7 %.

Systemic therapy is a potential treatment option in multifocal RP STS. Several groups, however, have explored the role of surgery in these patients, often in combination with intraperitoneal chemotherapy either at the time of resection or immediately after resection [69••]. Similar to techniques used for other peritoneal surface malignancies (e.g., appendiceal carcinoma, mesothelioma), surgery, referred to as cytoreduction, attempts to remove all of the macroscopic tumor including peritonectomy and often visceral organ resection, while intraperitoneal chemotherapy is designed to eliminate microscopic residual disease [70–72]. Intraperitoneal chemotherapy is heated (hyperthermic) to 42 °C to enhance tissue penetration and drug cytotoxicity.

Rossi et al. reported combined results from four institutions in Italy for 60 patients with multifocal disease, all of whom underwent cytoreduction surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) using doxorubicin and cisplatin [73]. The median time to progression in these patients was 22 months and the median overall survival was 34 months. Lim et al. reported on 28 patients from MD Anderson Cancer Center with peritoneal sarcomatosis treated with cytoreduction surgery and HIPEC using cisplatin with and without mitoxantrone [74]. Overall survival was poor (17 months for cisplatin alone, 6 months for combination) and the authors concluded that HIPEC was of limited clinical benefit. In both studies, the toxicity associated with HIPEC was substantial.

Bonvalot et al. conducted a randomized trial of cytoreduction surgery followed by postoperative intraperitoneal chemotherapy versus surgery alone for patients with peritoneal sarcomatosis [75]. After complete resection leaving no macroscopic residual disease, the authors found no difference in survival between patients that received intraperitoneal chemotherapy and those that did not.

The role of cytoreduction surgery and intraperitoneal chemotherapy in patients with multifocal RP STS therefore remains to be defined. The major studies reported to date have included patients with gastrointestinal stromal tumor or GIST and not a pure population of RP STS patients. In addition, there are wide variations in the extent of disease burden, completeness of cytoreduction, and chemotherapy regimens used. Importantly, treatment responses may vary by histologic subtype. As an example of this, Baratti et al. found that with cytoreduction and HIPEC, patients with liposarcoma seemed to derive no benefit (100 % had peritoneal recurrence), whereas those with leiomyosarcoma seemed to have better locoregional control and a higher proportion of long-term survivors [76]. Recently, Hayes-Jordan et al. reported that for children and young adults with intra-abdominal desmoplastic small round cell tumor, complete cytoreduction and HIPEC led to exceptional median overall survival of 63 months [77].

Surveillance

For unifocal and multifocal disease, patients with RP STS are at high risk for locoregional recurrence after resection, as already discussed. Early detection may improve resectability and prevent the development of tumor complications such as bowel obstruction and malignant ascites. Although the majority of recurrences occur in the first 2–3 years after initial resection, late recurrences are common and in fact, occur even after 10–15 years [13••].

Guidelines for appropriate surveillance strategies, however, are not well defined and are in need of further study [78]. Consensus guidelines from the National Comprehensive Cancer Network suggest that for postoperative follow-up, a history and physical examination with cross-sectional imaging (e.g., CT) should be performed every 3–6 months for 2–3 years, then every 6 months for the next 2 years, then annually without a defined end point. The European Society of Medical Oncology provides surveillance guidelines for STS based on low-, intermediate-, and high-risk disease, but does not provide specific recommendations by tumor location (e.g., retroperitoneum) [79]. Guidelines from the Trans-Atlantic Retroperitoneal Sarcoma Working Group recommend postoperative follow-up initially every 3–6 months up to five years, then annually; patients should be followed indefinitely [13••].

Treatment of Recurrent Disease and Symptom Palliation

For patients who develop recurrent disease, surgery still remains the mainstay of treatment in the absence of distant metastatic disease. The decision to operate in the setting of recurrent disease, however, is often more complicated. Multiple studies have also shown that the rates for complete resection are significantly lower in the setting of recurrent versus primary disease, ranging from 50 to 60 versus 70 to 80 %, respectively [80, 81]. Reoperative surgery is also more challenging, often requires additional lysis of adhesions, and has increased potential for complications (e.g., enterotomy).

An important consideration in the decision for surgery in recurrent RP STS is the disease biology. This includes the disease-free interval from the time of initial resection. A short interval (e.g., less than a year) suggests more aggressive disease and, depending on the histology, may indicate the potential for occult distant metastatic disease, in which systemic therapy prior to surgery may be more optimal. For retroperitoneal WD/DD liposarcoma, Park et al. also found that the rate of disease progression had a significant impact on outcomes after resection for recurrent disease [82]. Improved survival was seen in patients with recurrent tumor growth rates of less than 0.9 cm per month, and the authors concluded that this cutoff could be used to select patients for resection.

The presence of symptoms may also help guide the management of recurrent RP STS. Symptoms alone may push the surgeon to resection, particularly for recurrent tumors that appear to be easily resectable by cross-sectional imaging

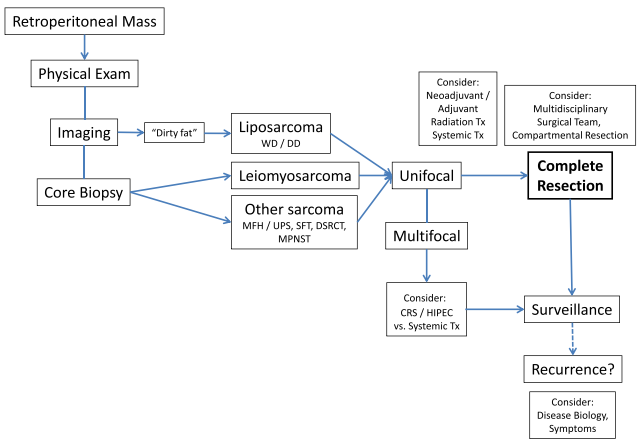

Fig. 2 Proposed algorithm for the management of patients with retroperitoneal soft tissue sarcoma. Management of this disease should ideally take place at an experienced sarcoma referral center by a multidisciplinary team (surgical oncologist, medical oncologist, radiation oncologist, etc.). *WD* well-differentiated, *DD* dedifferentiated, *MFH* malignant fibrous histiocytoma, *UPS* undifferentiated pleomorphic sarcoma, *SFT* solitary fibrous tumor, *DSRCT* desmoplastic small round cell tumor, *MPNST* malignant peripheral nerve sheath tumor, *Tx* treatment, *CRS* cytoreduction surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy

[81]. If not easily resectable or if resection may be associated with high morbidity, symptom palliation may also be achieved by nonsurgical options such as radiation therapy (if unifocal recurrence) or systemic therapy. In WD/DD retroperitoneal liposarcoma, Shibata et al. also demonstrated that incomplete resection may also be of benefit. These patients achieved symptom palliation and in addition, had significantly improved survival compared to exploration or biopsy only (median overall survival of 26 versus 4 months) [83].

Conclusions

The management of RP STS from diagnosis to treatment and follow-up is complex and can be very challenging. As this review highlights, management of this disease should ideally take place at an experienced center by a multidisciplinary sarcoma team. Recognition of the specific tumor histology is critical, with well-differentiated/dedifferentiated liposarcoma and leiomyosarcoma as the two predominant subtypes encountered in the retroperitoneum. In addition to histology, each case must be evaluated on an individual basis for operative planning, the potential role of radiation therapy and systemic therapy, as well as for unique situations such as multifocal disease, recurrence, and symptom palliation. A proposed algorithm for management is provided (Fig. 2).

Investigation into other novel therapies for retroperitoneal STS is needed. For STS in general, tumor analysis has identified molecular and genetic aberrations that may be suitable targets for therapy [84, 85]. These aberrations are likely conserved within a histologic subtype; however, differences in frequency and response to therapy by anatomic site (e.g., extremity versus retroperitoneum) may exist. An example, already discussed, is the response to gemcitabine and docetaxel in uterine versus nonuterine leiomyosarcoma. Certainly in the retroperitoneum, where tumors are typically massive in size, there is typically ample tissue for molecular and genetic studies. Tseng et al. reported histology- and retroperitoneum-specific studies of the tumor immune microenvironment in WD/DD liposarcoma [86, 87••]. The presence of an adaptive immune response, including cytotoxic CD8 T cells, was seen within retroperitoneal tumors. Importantly, these T cells were shown to have high expression of PD-1, an immunotherapy target that when exploited in melanoma and other solid tumors, has demonstrated remarkable efficacy [88].

Overall, given the rarity of these tumors, to continue to better understand and optimize management of retroperitoneal STS, multi-institutional collaboration is very important moving forward. An example of this is the Trans-Atlantic Retroperitoneal Sarcoma Working Group, led by Dr. Alessandro Gronchi. These efforts have already led to consensus guidelines for surgery and the overall management of this disease

[13••, 23••]. Future efforts will be aimed at establishing a large clinical database with access to tissue for research purposes.

Compliance with Ethics Guidelines

Conflict of Interest Yuliya Olimpiadi, Suisui Song, James Hu, George Matcuk, Shefali Chopra, Burton Eisenberg, Stephen Sener, and William Tseng declare that they do not have conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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