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SURGICAL MANAGEMENT OF RETROPERITONEAL AND PELVIC SARCOMAS

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Abstract

Management of retroperitoneal sarcomas presents technical and oncological challenges. Imaging is crucial for diagnosis and to define local tumor extent. Complete gross resection at initial presentation is the best chance for cure, but there is controversy as to how this can be best achieved. There is a long-term risk of local recurrence, which is best treated with repeat resection if feasible. The roles of radiation and chemotherapy remain undefined.

Keywords

Soft tissue sarcoma; retroperitoneal sarcoma; surgery

INTRODUCTION

Retroperitoneal soft tissue sarcomas (RPS) comprise approximately 15% of all soft tissue sarcomas (STS) and thus, the incidence of RPS in the United States is only about 1600 per year (1). The two most common histologic types are liposarcoma and leiomyosarcoma, comprising two-thirds of all RPS. Patients are most commonly diagnosed in the sixth decade, with an equal sex distribution. Median tumor size is 15–20cm (2–4). Surgery remains the primary treatment modality, with complete resection providing the only chance for cure. Local recurrence (LR), rather than distant recurrence (DR), is the major post-operative oncological concern because of the anatomical restraints of the retroperitoneum and the large size of tumors. In fact, local recurrence is the leading cause of death in patients with RPS. The roles of radiation therapy and chemotherapy remain controversial. More recent studies of more aggressive surgery and advanced radiation techniques have suggested that local recurrence can potentially be reduced, but these strategies are debatable. Newer chemotherapies and targeted agents may also play a role in the reduction of both local and

distant recurrence. This chapter will discuss the surgical evaluation and treatment of patients with RPS.

HISTOLOGY

Retroperitoneal sarcomas comprise a spectrum of histologic types/subtypes with distinct biologic behavior. Liposarcomas comprise 40–50% of all RPS in large series (2–6). They are characterized genetically by amplification of chromosome 12q, with resultant increased expression of MDM2 and CDK4 (7). The identification of this genetic alteration has allowed many tumors previously designated as malignant fibrous histiocytoma (MFH) to be reclassified as dedifferentiated liposarcoma. Retroperitoneal liposarcomas are typically either of the well-differentiated/dedifferentiated subtype, with myxoid/round cell and pleomorphic subtypes occurring very rarely (8). Well-differentiated liposarcomas (Figure 1A) appear as tumors with the density of fat, whereas dedifferentiated liposarcomas have a higher density, being hypercellular, and often occur within or adjacent to well-differentiated areas (Figure 1B). Well-differentiated liposarcomas recur locally but not distantly. Dedifferentiated liposarcomas have a higher early risk of local recurrence (within 2 years), but have an equivalent long-term cumulative risk of local recurrence compared with well-differentiated liposarcoma (8,9). Dedifferentiated liposarcomas can also metastasize to distant sites. Leiomyosarcomas are the next most common histologic type of RPS and can arise from major vessels such as the inferior vena cava (Figure 2). Almost all retroperitoneal leiomyosarcomas are high grade. The disease-specific survival for patients with high grade retroperitoneal leiomyosarcomas is almost identical to those with dedifferentiated liposarcomas, but with a lower rate *local* recurrence and a higher rate of *distant* metastasis (3). Malignant peripheral nerve sheath tumors (MPNST), constituting up to 5% of RPS (3,6), are tumors that arise from the cellular components of a normal nerve, such as Schwann cells. One-third of cases are associated with neurofibromatosis type 1 (NF1), where they commonly develop as malignant transformations of plexiform neurofibromas. NF1 patients have about a 15% lifetime risk of developing a MPNST (10). In the retroperitoneum, these tumors may arise from large nerves, such as the sciatic, and local recurrences may skip portions of normal nerve, complicating further attempts at local control. Solitary fibrous tumors (SFT), formerly known as hemangiopericytomas, also comprise approximately 5% of RPS (3,6). After complete resection, local recurrences are uncommon, but there is a significant rate of late distant metastasis, 10–20 years after initial diagnosis (11).

CLINICAL PRESENTATION AND EVALUATION

Patients often present with an asymptomatic abdominal mass or after imaging identifies an incidental retroperitoneal mass (3). When symptoms do occur, they are due to compression of adjacent intra-abdominal structures: the bowel, leading to abdominal discomfort, early satiety, weight loss, or bowel obstruction; large veins (IVC or iliac veins), causing leg swelling; or nerves, causing lower extremity pain or weakness. In one series of 500 patients, 80% of patients presented with an abdominal mass, 42% with lower extremity neurologic symptoms, and 37% with pain (3).

The vast majority of patients will not have any identifiable genetic or environmental risk factor. However, certain genetic syndromes are associated with an increased risk of developing sarcomas. Neurofibromatosis 1 (NF1, or von Recklinghausen's disease) is associated with an approximately 15% risk of developing malignant transformation of a neurofibroma into a malignant peripheral nerve sheath tumor (MPNST) (12). Individuals with NF1 also carry an increased risk of gastrointestinal stromal tumors (GIST). Hereditary retinoblastoma and Li-Fraumeni syndrome are associated with a risk of both bone and soft tissue sarcoma.

In terms of environmental factors, radiation is capable of inducing sarcomas in soft tissue and bone. The incidence of radiation-associated sarcomas increases with the post-radiation observation period (13). Following breast irradiation, the most common radiation-induced sarcomas are angiosarcomas. The actuarial frequency of radiation-associated sarcoma at 15 to 20 years is approximately 0.5% in adults treated with radiation alone to full dose. The frequency is higher following treatment of children, especially those treated with both radiation and chemotherapy, and the frequency may reach 20% to 30% many years after treatment. Chemotherapeutic agents and exposure to a few select industrial chemicals (e.g. vinyl chloride) are likewise associated with risk of sarcoma induction. Trauma is rarely a factor in the development of these tumors with the exception of desmoid tumors. The usual history is of a traumatic incident occurring shortly before awareness of the mass, suggesting that the trauma merely brought the patient's attention to the presence of the mass.

Most unifocal retroperitoneal tumors that do not arise from an adjacent organ will either be a RPS or a benign soft tissue tumor (e.g. Schwannoma). However, the differential diagnosis includes primary germ cell tumor, metastatic testicular cancer, and lymphoma. Patients with metastatic testicular cancer may have a testicular mass identified on physical examination or scrotal ultrasound. Patients with primary germ cell or testicular tumors will often have an elevated β -human chorionic gonadotropin or α -fetoprotein level. Patients with lymphoma may have B symptoms (fever, night sweats, and weight loss), additional lymphadenopathy, or an elevated LDH.

A CT scan of the abdomen and pelvis should be obtained with oral and intravenous contrast to fully evaluate the tumor and its proximity to adjacent organs, vessels, and nerves (14). For tumors that appear to consist purely of fat, the diagnosis is generally well-differentiated liposarcoma.

Two important differential diagnoses are renal angiomyolipoma and adrenal myelolipoma. Like liposarcomas, they are characterized by regions of macroscopic fat (-20 to -80 Hounsfield units). Most renal angiomyolipomas arise from the cortex and are infiltrated by a network of large vascular structures. The renal origin of exophytic angiomyolipomas may be discerned by identifying the defect in the renal capsule where the lesion is attached. Areas of hemorrhage may be present. Adrenal myelolipomas appear as well-circumscribed masses occupying the adrenal space. They have variable amounts of fat: in 50%, lesions are equal parts fat and soft tissue; in 40%, almost completely composed of fat; in 10% of lesions, they are mostly solid (15). Small punctate calcifications are seen in 25–30% of cases. Larger lesions may be associated with hemorrhage (16).

If lipomatous tumors contain areas of higher density, then these may represent areas of dedifferentiation or sclerosing components of well-differentiated liposarcoma. Conversely, it is crucial to avoid only focusing on the higher density component of the tumor and dismiss the lower density areas as normal fat. Overlooking the well-differentiated component of a mixed-density liposarcoma may lead to an incomplete resection or inappropriately small field of radiation (16). In a study from the M.D. Anderson Cancer Center, CT scan features accurately identified 60 out of 60 (100%) of well-differentiated liposarcomas but was less accurate in determining areas of hypercellular well-differentiated liposarcoma from areas of dedifferentiation (17).

After establishing the diagnosis of retroperitoneal sarcoma, the next step is to define its local extent. The relationship of the tumor with adjacent organs, vessels, nerves and bone must be assessed for abutment, invasion and/or encasement. Liposarcomas rarely invade major vessels, but leiomyosarcomas may originate from involved vessels such as the IVC, renal vein and gonadal vein. Tumor extension beyond the confines of the retroperitoneal space should be recognized. If the tumor extends across the diaphragm, into the inguinal canal, or through the obturator, sciatic or vertebral foramina, then this should be anticipated prior to resection (16). Clearly, there are some structures/organs that are easier to resect than others. Therefore, the surgeon must decide whether to aggressively excise the tumor and adjacent structures, or dissect just outside the pseudocapsule and risk leaving behind microscopic residual disease. This dilemma is a source of ongoing controversy among sarcoma surgeons on exactly how aggressive resections should be (see below).

Unresectability is usually determined by vascular invasion - either of the superior mesenteric vessels or the suprahepatic IVC. If nephrectomy is anticipated, then confirmation of function of the contralateral kidney is necessary.

MRI may be useful in certain circumstances such as determining the proximity of a tumor to major nerves or in patients with a contraindication to CT scan intravenous contrast.

A minority (10–20%) of patients with RPS present with metastatic disease, with the most common sites of metastatic spread being the lung and liver (2–4). A chest CT is obtained for patients with high-grade tumors, whereas a chest X-ray is sufficient for those with low-grade tumors. Although many soft tissue sarcomas are FDG-avid, PET scans only rarely identify metastases not obvious on CT, and so their use for staging is not recommended (18).

Biopsy is not required for those patients proceeding directly to the operating room. This is particularly the case for well-differentiated liposarcomas, because of their characteristic imaging features (see above). It is reasonable to biopsy when neoadjuvant therapy is being considered, or there is diagnostic doubt, e.g. if there is concern that a retroperitoneal mass may represent lymphoma or metastatic testicular cancer (which are not treated with upfront resection). Knowledge of tumor grade and histologic subtype guides use of pre-operative radiation and/or chemotherapy. Tissue is obtained by image-guided percutaneous core biopsy. Caution should be exercised in biopsying lipomatous tumors, since histologic confirmation of well-differentiated liposarcoma can be confounded by the paucity of neoplastic cells, and sampling error, in which areas of dedifferentiation are either not

recognized or not sampled. Percutaneous biopsy may be difficult or dangerous due to a tumor's proximity to large vascular structures. The risks of needle-track and intra-peritoneal seeding are very low, and can be minimized by avoiding a transperitoneal approach. It is critical that biopsy material be reviewed by an experienced sarcoma pathologist, since 6–10% of cases originally designated as sarcoma are in fact not sarcoma, and 14–27% are initially assigned the incorrect histologic subtype (19–22).

STAGING

A detailed discussion of staging systems and nomograms for STS can be found in a separate article in this seminar series. The American Joint Committee on Cancer (AJCC) staging for RPS was derived from analysis of extremity soft tissue sarcoma (23). It includes characteristics of the primary tumor (T, size and depth), regional lymph nodes (N, negative or positive), distant metastases (M, absent or present), and grade (G1–G3). However, it does not include histologic type or subtype as a category, leading some authors to question its applicability (24–27). Nathan et al., in an analysis of 1365 RPS patients in the SEER database found that tumor grade, invasion of adjacent structures, and histologic subtype were prognostic, whereas tumor size was not (26). Anaya et al. also argued that a histology-based RPS prognostic system has major advantages over the AJCC staging system (25). This has led to the development of several post-operative nomograms specifically for patients with RPS (6,28,29). Prognostic factors in these nomograms include age, grade, histologic subtype, size, primary versus recurrent disease, multi-focality, and completeness of resection (R0/R1 vs. R2).

SURGERY

Surgical resection is the primary treatment for RPS.

Technical Aspects of Resection

Access is usually achieved through midline laparotomy. For right upper quadrant tumors displacing the right liver, a right thoracoabdominal incision will allow complete control of the inferior vena cava and right atrial access. When a tumor herniates through the midline or the left diaphragm, a left thoracoabdominal incision may be needed, unless the intra-thoracic dissection can be safely completed by enlarging the esophageal hiatus. For tumors herniating distally under the inguinal ligament, access to the external iliac and femoral vessels may be achieved either via separate S-shaped incision at the groin or by extending the midline incision distally in an oblique fashion. Where there is herniation through the sciatic notch, *en bloc* resection requires a counter-incision in the gluteal area (16). The patient is therefore positioned in contralateral decubitus to facilitate access to the pelvis anteriorly and posteriorly.

For tumors where complete gross resection is possible, leaving a negative microscopic margin around the entire tumor can be challenging. The EORTC-Soft Tissue and Bone Sarcoma Group recently described a standardized surgical approach to RPS (16). The anterior surface of these tumors is often covered by peritoneum and organs which can be resected with relatively low morbidity (e.g. colon, tail of pancreas, spleen, and kidney)

enabling a negative anterior margin. For tumors abutting but not invading the kidney, the renal capsule may be resected *en bloc* with the tumor, without the need to sacrifice the kidney. In other instances, the anterior margin may be the head of the pancreas and duodenum, and performance of a pancreaticoduodenectomy may significantly increase morbidity. Laterally, the peritoneum and the transversalis fascia can be resected *en bloc* with the tumor. Medially, tumors can generally be dissected off of the aorta and inferior vena cava, leaving adjacent areolar tissue on the tumor as margin. The posterior margin of these tumors often abuts retroperitoneal fat and the psoas musculature, where obtaining negative margins requires visualization and sharp dissection due to the lack of anatomic dissection planes. Thus, tumors should be dissected circumferentially from anterior to posterior to optimize exposure when dissecting out the deepest parts of the tumor. Resection of major vessels, nerves, and bone is generally not necessary unless there is direct invasion. Major arteries can usually be dissected free leaving adventitia on the tumor, major nerves can be dissected free leaving epineurium on tumor, and bone can be dissected free leaving periosteum on tumor.

For IVC leiomyosarcomas, access to the tumor and the IVC is achieved using a Cattell-Braasch maneuver. After extirpation of the tumor, primary repair or autologous patching can be performed in a small subset of these tumors and is associated with minimal lower extremity edema. When this is not possible, then resection and ligation of the IVC is associated with acceptable post-operative morbidity (30). The IVC can be resected from just below the renal veins to below the bifurcation along with the right kidney without reconstruction, as long as the left gonadal and left adrenal veins are left in continuity with the left renal vein to allow collateral drainage of the left kidney. For the vast majority of patients, this results in normal left kidney function and only transient lower extremity edema, which can be mitigated by elevation and compression. While not our preference, reconstruction of the IVC has been advocated by some groups (31), but if the reconstruction thromboses, one runs the risk of clot extension into the collateral venous circulation. When IVC thrombosis is present, early intra-operative proximal control of the IVC is recommended to avoid pulmonary embolism. Placement of an IVC filter should be avoided given the risk of clot extension to the filter.

Extent of primary surgery

There is ongoing debate about how aggressive surgical resections for RPS should be, particularly regarding resection of adjacent organs and tissues. The catalysts for this debate were two European retrospective reviews analyzing the impact of more aggressive multivisceral resections on local recurrence (2,32). These “compartmental resections” comprise, for the most part, resection of adjacent kidney, colon and/or psoas, *without* increased resection rates of pancreaticoduodenectomy, hepatectomy or vascular structures. In the first study, Gronchi et al. from the Istituto Nazionale del Tumor (INT) in Milan, Italy, retrospectively examined 288 patients with primary RPS resected between 1985 and 2007 (32). Prior to 2002, adjacent organs were generally only resected if there was direct involvement by tumor. From 2002 onward, a more aggressive policy was instituted with resection of adjacent organs and tissues. Five-year actuarial local recurrence was 48% in the less aggressive surgery group and 29% in the more aggressive surgery group, with no

change in perioperative morbidity. However, the complete gross resection rate (~90%) and overall survival were the same in both time periods.

The second study is a multi-center retrospective review of 382 French patients with RPS divided patients by surgical procedure into compartmental resection of contiguous organs (32%), resection of only involved organs (35%), simple complete resection (17%), and re-excision of tumor bed (6%) (2). Complete gross resection was achieved in 73%. Margins were reported as being positive in 19%, 40% and 36% of patients undergoing compartmental resection, simple gross resection and contiguously-involved organ resection, respectively ($p<0.001$). However, when compartmental resection was performed, the resected colons or kidneys were never invaded. Rather, margins were positive where the tumor was not covered by viscera, particularly posteriorly. On multivariate analysis, the study found that compartmental resection of contiguous organs was associated with a 3.3-fold lower rate of local recurrence compared to only complete gross tumor resection.

Review of the multi-visceral resections performed in both studies reveals that they generally consisted of resection of uninvolved kidney, colon and/or psoas - structures that can be resected with low morbidity. These “compartmental resections” however, did not include other uninvolved adjacent viscera (pancreas, spleen, duodenum, liver), major vasculature (IVC, portal vein, aorta) and functionally significant muscles (diaphragm) whose resection is associated with much greater potential for morbidity and mortality. This policy of selective *en bloc* resection therefore extends to some but not all resection margins around sarcomas. As a consequence, the oncologic benefit of such resections is variable depending on the exact relationships of an individual tumor within the anatomically complex retroperitoneum. Interpretation of their results is confounded by the absence of standardization of pre-operative imaging, operative findings and pathologic review. A subsequent analysis was performed of post-operative complications of patients who underwent aggressive compartmental resections at the two highest-volume centers in the two above-mentioned articles (INT and Institut Gustave Roussy) (33). Morbidity was significant: the major complication rate was 18%, with a 12% re-operation rate and a 3% mortality rate. Resection of more than three adjacent viscera was associated with a significantly higher complication rate compared to resection of three or fewer organs (HR 2.8, 95% CI 1.3–5.7). Therefore, at this time, adoption of a frontline aggressive approach with resection of select uninvolved adjacent organs cannot be recommended given the retrospective nature of the data (fraught with selection bias), high complication rates and lack of overall survival benefit (34). There remains no consensus on the appropriate resection for RPS and no prospective trials to guide surgical practice. For operations requiring extensive organ resection or multiple surgeons from different specialties, the operation would ideally be performed at a high-volume sarcoma center. Of note, several articles on major vascular resections, liver resections, pancreaticoduodenectomies and other aggressive strategies for primary RPS have been published (30,31,35).

Results of large series and prognostic factors

Table 1 summarizes the three largest, contemporary surgical series of primary RPS, one each from Memorial Sloan-Kettering Cancer Center (New York, USA), the Instituto

Nazionale Tumori (Milan, Italy), and the multicenter French Sarcoma Group (2,4). Each series is the most recent update from that institution/group's sarcoma database. Consistent across these series are median age at presentation of 55–60 years, maximal tumor diameter of 15–20cm, with approximately 70% of tumors being of intermediate or high grade. Complete gross resection was achieved in 75–90% of cases, with contiguous organ resection performed in 58–91%. Use of pre-/post-operative radiation and chemotherapy ranged from 14%–37% and 16%–40%, respectively. Despite variations in both operative philosophies (as described above) and utilization of adjunctive therapies, five-year overall survival (59–66%), local recurrence (31–46%), and distant recurrence (21–24%) did not vary greatly between the three studies.

Multiple series have identified prognostic factors. For overall survival, worse outcome is associated with histologic type, higher grade, multifocality, and incomplete or piecemeal resection (2,4,6,36–38). Risk factors for local recurrence include histologic subtype, grade, radiation, and type of surgery to be prognostic factors (2,3,32,38). Only one study (2) found margin to be prognostic while another study did not (3). Prognostic factors for distant recurrence (found in one or more studies) included histologic subtype, grade, and complete gross resection (3,32,36–38).

Debulking operations for primary disease

Surgeons should be wary of attempting surgery if complete surgical resection cannot be performed. In some series, incomplete resection has resulted in the same overall survival as patients undergoing biopsy alone (3,39,40). However, there may be some role for debulking unresectable RPS in very select circumstances such as for very slow growing tumors (e.g. well-differentiated liposarcomas) or for the relief of symptoms. MSKCC studied 55 patients with unresectable liposarcomas and found increased survival (26 versus 4 months) in patients receiving partial resection compared to biopsy alone (41). The majority of benefit for partial resection was seen in patients with primary disease, and patients undergoing partial resection of local recurrence showed significantly decreased survival compared to after partial resection of primary disease (17 versus 46 months). Several studies have shown that approximately 75% of patients report symptomatic improvement after palliative surgery (41–43). This improvement, however, can be short-lived. One study showed 71% of patients had symptomatic improvement at 30 days but this fell to 54% by 100 days (43). Also in this study, palliative operations had a morbidity rate of 29% and mortality rate of 12%. Thus selection of patients and surgical judgment is critical as these operations are often extensive and may not provide prolonged alleviation of symptoms.

RADIATION THERAPY

There is a lack of high quality studies to define the role of radiation in the management of patients with RPS. Numerous retrospective and non-randomized prospective studies exist, with some finding an association between adjuvant radiation and local disease control (44), while others have shown a delay in local recurrence but ultimately no difference in rate of local control (45). This controversy is reflected in clinical practice, with some institutions reporting very low (<15%) use of radiation (46), while in others, 70% of patients receive radiation (32).

Only one prospective randomized trial of radiation has been published (47), in which 35 patients with RPS were randomized to receive either 20 Gy of intra-operative radiation (IORT) with 35–40 Gy of postoperative external beam radiation therapy (EBRT) or 50–55 Gy of post-operative EBRT. Median survival was not significantly different between the groups (45 months for IORT vs. 52 months for EBRT only), but local recurrence was significantly lower in the group receiving IORT (40% vs 80%). Patients in both arms of the trial experienced very high rate of toxicity. Disabling radiation enteritis occurred in 50% of the EBRT only group compared to 13% in the IORT group. On the other hand, the IORT group had increased rates of peripheral neuropathy (60% vs 5%).

Currently, most radiation oncologists with expertise in treating RPS prefer delivering EBRT *pre*-operatively rather than post-operatively (48). Pre-operative radiation therapy has several potential advantages: (1) the target tumor volume can be clearly delineated; (2) adjacent normal tissue (especially bowel) is displaced out of the treatment field; (3) there is better oxygenation of the radiation field pre- vs post-operatively; (4) intra-operatively, there is a small risk of tumor seeding and peritoneal sarcomatosis (49,50). Retrospective and non-randomized prospective studies have demonstrated that p-pre-operative radiation is better tolerated than post-operative radiation, when administered to a comparable treatment volume (51). Recently, Bartlett et al. reviewed 696 RPS patients in the American College of Surgeons NSQIP database (52). After adjustment for confounding variables, the 70 patients (10%) who underwent pre-operative radiation were not found to have increased in morbidity or mortality compared to those who did not receive radiation. A phase III multi-institutional prospective randomized trial of preoperative radiation and surgery versus surgery alone for RPS was attempted in the United States through the American College of Surgeons Oncology Group (ACOSOG 9031), but failed due to lack of accrual. The failure of this trial has been attributed to institutional biases for or against the use of radiation, and a lack of consensus on the optimal neoadjuvant radiation regimen. The European Organisation for Research and Treatment of Cancer (EORTC) is currently accruing a similar trial (“STRASS”; EORTC 62092).

The data is conflicting about combining pre-operative with intra-operative radiation. Gieschen et al treated 29 patients with RPS with preoperative radiation to a median dose of 45 Gy and patients then underwent complete gross resection (53). 10–20 Gy IORT was delivered to 16 of the 29 patients. Local control at 5 years was 83% for patients who received both preoperative radiation and IOERT and 61% for those who received only preoperative radiation. Similar results in local control for RPS treated with EBRT and IOERT have been reported from the Mayo Clinic (54). However, no benefit to IORT could be found on analysis of two prospective, non-randomized trials that utilized preoperative radiation therapy as well as either IORT or brachytherapy (55). Of the 72 patients with intermediate- or high-grade tumors in the study, pre-operative therapy was completed in 57 patients; 54 patients went on to complete surgical resection. Of these, 22 patients received IORT, 12 post-operative brachytherapy, and 20 no additional boost. During this trial, use of brachytherapy to the upper abdomen was associated with grade 3 toxicity in nearly 40% of patients including two deaths and one life-threatening illness (56). In this study, the 5-year local recurrence-free, disease-free, and overall survival rates were 60%, 46%, and 61%,

respectively. There was no association between disease-free survival and use of either IORT or brachytherapy.

Newer radiation therapy technologies have been applied to patients with RPS in order to decrease treatment-related morbidities. These technologies, including 3D conformal, intensity-modulated (IMRT) and proton-beam (PBRT) (57–60), can more precisely target the tumor and critical margins, and thereby decrease delivery of radiation to adjacent organs and structures. Short-term follow-up of small series of patients treated with these technologies has established their safety and promising efficacy in decreasing LR (19,54,61,62). For example, dose escalation to presumed high-risk tumor margins using IMRT could help reduce LR (62,63).

In summary, use of radiation therapy for RPS is sharply polarized. Those against it cite the absence of data demonstrating a survival benefit and its considerable toxicities, especially in the post-operative setting. On the other hand, advocates argue that radiation improves local control, which is the major determinant of outcome in RPS, and the lower morbidity rates associated with pre-operative radiation. There is, however, widespread agreement that pre-operative radiation is favored over post-operative radiation, and that radiation has a greater role in the management of recurrent disease.

CHEMOTHERAPY AND CHEMORADIATION

The efficacy of neoadjuvant or adjuvant chemotherapy for soft tissue sarcomas is largely based on randomized trials and meta-analyses where the primary sites were predominantly the extremity and trunk. Typically, patients with high-risk lesions (higher grade, larger size [typically >5cm]) were eligible. Several early prospective studies using doxorubicin-based chemotherapy failed to show an improvement in disease-free or overall survival in patients receiving postoperative chemotherapy compared with surgery alone (64). A meta-analysis of 14 randomized trials of doxorubicin-based adjuvant chemotherapy versus no chemotherapy in STS was performed in 1997 (65). The adjuvant chemotherapy group had a statistically significant higher rate of local recurrence-free survival (81% vs. 75%, $P = .016$), distant recurrence-free survival (70% vs. 60%, $P = .003$), and overall recurrence-free survival (55% vs. 45%, $P = .001$). However, overall survival differed only by 4% (54% vs. 50%), and this difference did not attain statistical significance. Four subsequent randomized trials examined the benefit of anthracycline and ifosfamide-based combination adjuvant chemotherapy in extremity STS, and two of them suggested a possible survival benefit for adjuvant chemotherapy. An updated meta-analysis was published in 2008 of 18 randomized trials of 1953 patients (66). Similar results were found in terms of local recurrence and distant recurrence compared to the earlier meta-analysis, but in this analysis the combination of doxorubicin and ifosfamide was found to increase overall survival from 59% to 70%. Most recently, however, the European Organization for Research and Treatment of Cancer (EORTC) reported final results of a trial that randomized 351 patients to adjuvant doxorubicin and ifosfamide or no chemotherapy (67). Extremity sarcomas comprised 80% of patients accrued, with the actual number of retroperitoneal sarcomas not stated. Histologically, one-third of patients had either liposarcoma or leiomyosarcoma (the predominant histologies in the retroperitoneum), but the proportion of well- and de-

differentiated liposarcomas was not detailed. Overall, no differences were found in overall or recurrence-free survival at a median follow-up of 8 years. So, the utility of adjuvant chemotherapy for soft tissue sarcomas remains unclear. The applicability of this data specifically to *retroperitoneal* sarcomas also remains uncertain. On the one hand, most RPS are high grade and larger than 5cm. On the other hand, very few patients with RPS were included in the above RCTs, and sarcomas of the retroperitoneum may have a unique biology and response to treatment compared to sarcomas at other sites.

Unfortunately, there are no randomized trials of neoadjuvant or adjuvant chemotherapy for RPS. Meric et al examined whether pre-operative chemotherapy could decrease the extent of resection in 65 patients with STS, 23 of whom had RPS (68). In the RPS subgroup, no patients had a response significant enough to allow organ salvage, with one patient progressing to unresectability while on chemotherapy. Donahue et al treated 55 patients with high grade RPS with neoadjuvant chemotherapy (69). Before 1990, patients received doxorubicin-based therapy; after 1990, patients with leiomyosarcomas received dacarbazine or gemcitabine/docetaxel-based therapy while patients with other histologies received ifosfamide-based therapy. One-quarter of patients had >95% tumor necrosis. After a median follow-up of 68 months, 5-year disease-specific survival (DSS) was 47%, not significantly different than the 37% survival predicted by the MSKCC nomogram. However, in the 25% of patients who demonstrated a pathologic response, 5-year DSS was 83%. Thus, chemotherapy is controversial for RPS given its heterogeneous nature and the lack of compelling clinical trials data. It is now well accepted that histologic subtype significantly governs outcome in RPS, and different histologies (e.g. leiomyosarcoma) are known to carry higher risk of metastasis.

Newer agents and strategies are currently being investigated. Targeted agents, especially inhibitors of CDK4 and MDM2 for well- and de-differentiated liposarcomas, have recently been developed and show promise in early clinical trials (70).

The addition of radiation-sensitizing agents to pre-operative radiation has also been studied. A phase I trial from MDACC reported 35 patients with RPS treated with neoadjuvant doxorubicin and concurrent dose-escalation EBRT with or without IOERT (71). This neoadjuvant treatment was completed in 89% of patients. In the group receiving 50 Gy radiation (6 patients), significant nausea and neutropenia occurred in two patients each. Six (17%) patients progressed to unresectability while on the neoadjuvant protocol. Of the remaining patients who underwent resection, two had 50–90% tumor necrosis and three had 10–49% necrosis. Gronchi et al treated 83 patients with upfront resectable RPS pre-operatively with high-dose long-infusion ifosfamide and 3D conformal radiation (72). One-third of patients could not complete the phase I/II protocol. A RECIST partial response was observed in 7 patients (8%). Four patients progressed to unresectability. Pathologic response rates were not reported. Yoon et al combined pre-operative radiation with bevacizumab to treat 20 patients with intermediate or high grade STS (four of whom had RPS) (73). There were no grade 4 toxicities, 20% had grade 3 toxicities. Nine of 20 (45%) tumors had 80% necrosis, which was more than twice the historical rate seen with radiation alone.

In summary, use of chemotherapy (either adjuvant or neoadjuvant) has **not** been conclusively shown to provide significant downsizing or survival benefit in RPS. Further studies, particularly in the neoadjuvant setting, are constrained by the small but defined rate of progression to unresectability and associated toxicities. Progress will likely depend on targeted rather than cytotoxic therapies.

FOLLOW-UP

The median time to local recurrence for patients with RPS is 22 months (74). Post-operatively, the National Comprehensive Cancer Network (NCCN) guidelines recommend physical exam and CT scan of the abdomen and pelvis every 3–6 months for two years, then annually. Chest CT should be added for those patients with high grade tumors (75). There remains a risk of delayed recurrence (five years after resection) particularly for low grade tumors. Therefore, our practice is to follow patients with low grade tumors indefinitely, but to stop follow-up of high-grade tumors after five years.

LOCAL RECURRENCE

LR is the primary mode of recurrence after complete resection of retroperitoneal sarcoma, and may occur late: up to 40% of patients will recur beyond 5 years (44). Synchronous local and distant recurrence occurs in about 20%, and is associated with poor prognosis (median survival 12 months) (42). With close post-operative follow-up, most recurrences are detected at an asymptomatic stage by radiologic surveillance. Symptomatic patients will present with abdominal pain (52%), abdominal fullness (18%), and abdominal cramping/nausea (18%) (42).

The most significant prognostic variable following local recurrence is resectability of the recurrent disease (3). Median survival is 60 months in resected patients, compared with just 20 months for unresected patients. Approximately half of patients will have unresectable disease, defined as peritoneal implants (sarcomatosis) or extensive vascular involvement. Other prognostic factors include tumor grade, multifocality and tumor growth rate (42,76).

Surgery for local recurrence

Resection of locally recurrent RPS is generally significantly more difficult than resection for primary disease, and the risk of another local recurrence is even higher than that for primary disease. Each subsequent recurrence is associated with lower rate of successful re-resection and shorter disease-free interval (3,42,76,77). In studies specifically addressing resection of locally recurrent RPS, rates of complete resection ranged between 44–60% and complete resection was significantly associated with increased survival (40,42,74). Reported 5-year overall survival after complete resection are between 30–46% compared to 27% or less in unresectable patients. Park et al. examined 105 patients who had local recurrence of RP sarcoma (76). After a median follow-up of 65 months, local recurrence size, local recurrence growth rate, histologic subtype, and grade with independent predictors of disease-specific survival. Local recurrence growth rate for the first local recurrence was defined as the tumor size divided by the time from primary resection to local recurrence. Patients with a local

recurrence growth rate <1cm per month had improved survival following resection of the local recurrence.

There are limited data to guide decision-making for locally-recurrent disease. For patients with resectable disease where further increase in tumor size would render the disease unresectable, an operation is typically indicated. On the other hand, a strategy of close observation may be considered in those with aggressive biology (as demonstrated by a short recurrence-free interval and multiple prior resections), in high-risk patients with significant co-morbidities, or in those with low grade, slowly-progressive biology. Employing such a strategy allows the surgeon to select out those patients unlikely to benefit from attempted resection (78). Patients with recurrent high grade tumors should be encouraged to enroll in trials of investigational chemotherapy. The multifocal nature of recurrent disease in most patients limits use of radiation therapy.

SUMMARY

Management of RPS presents complex challenges. Referral to a high volume sarcoma center is recommended. Complete gross resection at initial presentation is the best chance for cure, but controversy continues as to how this can be best achieved. There is a long-term risk of local recurrence, which is best treated with repeat resection if feasible. The role of pre-operative radiation is controversial, but the subject of an ongoing randomized trial in Europe. As our understanding of the genetic alterations grows, so too will the development and use of targeted systemic agents.

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Figure 1.

Well differentiated/dedifferentiated liposarcoma. (A) Axial image of right retroperitoneal well-differentiated liposarcoma which appears as an area of abnormal appearing fat (arrows). (B) Coronal image showing area of dedifferentiation, which appears as a more solid area within or adjacent to abnormal appearing fat (arrowheads).

Figure 2. Inferior vena cava leiomyosarcoma. (A) Axial image of an IVC leiomyosarcoma at the level of the renal veins. (B) Coronal image showing extension of tumor from liver to bifurcation.

TABLE 1

Selected Surgical Series

Institution/Group	MSKCC*	French Sarcoma Group (2)	INT/MDACC/UCLA (6)
Time period	1982–2010	1988–2008	1999–2009
Year published	2014	2014	2013
Median follow-up (months)	52	78	45
Number of patients	675	586	523
Median age (years)	60	57	57
Primary tumors	100%	100%	100%
Median tumor size (cm)	17	17	16
Intermediate- or high-grade	64%	72%	72%
Complete gross resection	85%	76%	90%
Mortality	3%	3%	NR
Pre-/post-op radiation	14%	29%	37%
Pre-/post-op chemotherapy	16%	17%	40%
5-year local recurrence	39%	46%	31%
5-year distant recurrence	24%	22%	21%
5- year overall survival	59%	66%	57%

* submitted for publication; NR, not recorded.