Current data suggest that radical resection remains the optimal chance for cure for patients with retroperitoneal sarcoma.

Current Diagnosis and Management of Retroperitoneal Sarcoma

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Background: Retroperitoneal sarcomas are rare neoplasms that often present with multivisceral involvement. Treatment for these tumors requires careful decision making requiring a combination of surgery, chemotherapy, and radiation therapy.

Methods: We reviewed the scientific literature pertaining to the diagnosis and management of retroperitoneal sarcomas. We also identify recent developments in treatment and discuss future trends in the care of patients with this disease.

Results: Retroperitoneal tumors often present as large, locally advanced lesions. Evaluation of these tumors requires careful consideration of a multimodality approach. Retrospective data and historical prospective series have demonstrated the survival benefit of radical resection for these tumors with en bloc resection of involved structures. Compartmental resections in the retroperitoneum along with debulking of high-grade disease and regional therapy are controversial approaches with significant morbidity that can lead to long-term survival. The application of neoadjuvant and adjuvant therapies in select tumor histologies may improve local control and survival.

Conclusions: The management of retroperitoneal sarcomas requires a multidisciplinary approach and is best accomplished at high-volume centers specializing in the care of patients with these complex malignancies. Current data suggest that radical resection remains the only chance for cure and that chemotherapy and radiation therapy may confer a survival benefit.

Introduction

Soft tissue sarcomas are mesenchymal neoplasms that, when considered in the context of all malignancies, are a rare entity. Approximately 1% of all newly diagnosed malignancies are believed to fall in under this classification.

There is generally no predominance in terms of gender or race. Age at presentation is younger compared with most other malignancies, with many being diagnosed between 54 to 65 years of age.1 These tumors can be found anywhere in the body, with 50% arising in the extremities, 10% to 15% from the trunk, less than 10% from the head and neck, and 15% in the retroperitoneum.1

This manuscript reviews the diagnosis and management of retroperitoneal masses, identifies recent changes in the diagnosis and treatment of retroperitoneal sarcomas, and discusses future trends in the multidisciplinary care of patients with this disease. While a comprehensive review of all that is written from a historical perspective is not possible here, recent developments in management of these patients are reviewed in the context of evidence-based care.
Diagnosis
The retroperitoneum offers an environment in which sarcomas can grow to a large size before they become symptomatic. Frequently, retroperitoneal sarcomas are incidentally diagnosed or identified with cross-sectional imaging as part of a workup for other problems. When patients do present with symptoms, however, the most common complaint is abdominal or back pain. Patients may also present with signs of bowel or ureteral obstruction due to either extrinsic compression or invasion of nearby structures. Other common symptoms include weight loss, anemia, and a palpable abdominal mass. Those afflicted may even notice increased abdominal girth or an uneven contour to their abdominal wall or flank.

Many patients presenting with abdominal complaints are increasingly evaluated with an imaging modality shortly after a physical examination. Modern spiral computed tomography (CT) scanners provide an excellent understanding of the relationship between nearby structures and are critical to preoperative planning. Given a patient presenting with a palpable abdominal mass, the modality of choice should be a high-resolution, thin-cut CT scan with intravenous and oral contrast. The images allow for further distinction between intra-abdominal and retroperitoneal structures. Additionally, the difference between a primary visceral retroperitoneal lesion, retroperitoneal adenopathy (possibly from another source), and a retroperitoneal sarcoma along with involvement of adjacent viscera may be ascertained. This allows for an upfront discussion of the need for biopsy if indicated, the operative plan, and the preparedness of the operative team, as well as a discussion with the patient regarding the risks and benefits. Magnetic resonance imaging (MRI) may be useful to aid in the management of lesions in close proximity to important vascular structures and to further characterize solid, cystic, necrotic, and enhancing areas. Generally, MRI is used as an adjunct to standard cross-sectional CT, with oral and intravenous contrast in select cases. Further discussion of this modality is discussed later in this manuscript.

Differential Diagnosis
Once a mass in the retroperitoneum is identified, the etiology must be determined. The differential diagnosis includes a primary neoplasm arising from a retroperitoneal visceral structure (eg, pancreas, adrenal glands, kidneys, and duodenum), a retroperitoneal sarcoma, a lymphoma, or a metastatic lesion. Adenopathy from a malignancy outside of the retroperitoneum, such as the testicles in a young male, should be considered. When a mass is discovered, the patient’s history becomes paramount to elucidating a differential diagnosis (Fig 1A-B). When B-symptoms for lymphoma or a history of scrotal pain or testicular abnormality on physical examination is obtained, attention shifts away from a primary neoplasm of the retroperitoneum. Symptoms such as hematuria, uncontrolled hypertension, or early satiety would be more indicative of a renal, adrenal, or duodenal primary malignancy, respectively.

Imaging Modalities
Careful consideration of the cross-sectional imaging and history is key in determining whether a biopsy of the lesion is indicated. For patients in whom preoperative systemic therapy or radiation is deemed to be potentially beneficial, a biopsy is mandatory. Aside from patients receiving preoperative therapy, preoperative CT-guided biopsy is often utilized at Moffitt Cancer Center (MCC) if the imaging and history are suggestive of a lesion other than sarcoma or if the lesion has characteristics of an intermediate- to high-grade retroperitoneal sarcoma such as large nodules, enhancement, and/or necrosis. If the lesion is arising from the stomach and may be a gastrointestinal stromal tumor, we perform a biopsy of the tumor using endoscopic ultrasound to avoid the theoretical risk of seeding the peritoneal cavity. We often do not consider a preoperative biopsy for lesions that appear to be well-differentiated retroperitoneal liposarcomas as the sensitivity of CT for low-grade lesions is nearly 100%, and there is virtually no role for preoperative therapy for these tumors.

Histologic Subtypes
Retroperitoneal sarcomas are mesenchymal neoplasms that are classified by their histology. They are grouped into
categories based on the characteristics of the mature mesenchymal tissues that they resemble. The most common histology is liposarcoma, followed by leiomyosarcoma. Other rare subtypes include fibrosarcoma and malignant peripheral nerve sheath tumors that are found in the retroperitoneum. Historically, most soft tissue sarcomas were classified as malignant fibrous histiocytomas, but recent work has demonstrated a significant proportion of these tumors are actually dedifferentiated liposarcomas. More exact diagnoses such as this are possible largely due to recent advances in immunohistochemistry (IHC) assays. Newer IHC capabilities allow the subtypes to be more clearly defined based on cell surface markers rather than histology alone. For the purposes of this review, we focus on the two common subtypes identified in the retroperitoneum: liposarcomas and leiomyosarcomas.

**Liposarcomas:** Liposarcomas are mesenchymal neoplasms with atypical adipocytes and lipoblasts in a background of mature adipose tissue. They can appear anywhere in the body. They represent a spectrum of tumors with variable behavior that ranges from a low risk of metastatic potential with well-differentiated tumors to a more aggressive biology with dedifferentiated lesions. Liposarcomas comprise the most common subtype of retroperitoneal sarcomas. Primary retroperitoneal liposarcomas carry a worse overall prognosis when compared with liposarcomas that arise from the trunk and extremities. The worse overall survival and nonretroperitoneal primaries can be explained by the earlier stage and consequent smaller size at the time of diagnosis for extremity lesions.

Liposarcomas can be subdivided into four main histologic subtypes: well-differentiated, dedifferentiated, myxoid, and round cell. The dedifferentiated category represents the subtype with a more malignant behavior and worse overall survival. This aggressive histologic subtype may present as an initial presentation or may be found in patients with disease recurrence. Liposarcoma recurrence is often more difficult to resect with negative margins due to involvement of adjacent structures and the development of dedifferentiation.

A recent study by Lahat et al examined the utility of preoperative CT imaging in determining the histologic classification of liposarcomas as either well-differentiated or dedifferentiated lesions. They reviewed the images of 78 patients and classified them as either well-differentiated or dedifferentiated based on characteristics such as their percent of fat, focal nodular/water density, ground glass opacities, and hypervascularity. Dedifferentiated lesions were more likely to be infiltrative, hypervascular lesions with areas of necrosis and focal nodular/water density. Focal nodular/water density was very sensitive (97.8%) but had a low specificity (51.5%) on final pathology. A radiologic diagnosis of a well-differentiated lesion was accurate in 100% of patients and as such may be used as a criterion to avoid preoperative biopsy.

**Leiomyosarcomas:** These tumors comprise the second most common histology of retroperitoneal sarcomas. They can arise anywhere in the body but are typically more aggressive when found in the retroperitoneum, major vascular structures, or intra-abdominal viscera rather than the skin or subcutaneous tissues. On histology, these tumors appear as cells in wavy sheets with cigar-shaped nuclei, and all cells stain positive for actin on IHC assays. In a review of their collective experience with leiomyosarcomas, the French Sarcoma Group found that tumors originating from large vascular structures accounted for 7% of the total cases of leiomyosarcomas. They then evaluated the outcomes of those with tumors of a vascular origin and those with leiomyosarcomas of a different origin. Based on their large experience, they found that patients with primary vascular leiomyosarcomas had a worse median overall and metastasis-free survival (2.1 years and 0.25 years, respectively) compared to patients with leiomyosarcomas of other origins (7 years and 9.6 years, respectively).

**Prognostic Factors**

Prior to planning the overall management of retroperitoneal sarcomas, as with extremity sarcomas, it is important to reflect on the characteristics that are most closely associated with the prognosis of the disease.

It is well documented that prognosis is defined by the grade of the sarcoma, regardless of histologic subtype. In most reports, mitotic activity is the major criterion used to describe the grade of tumors. Not surprisingly, the 5-year survival rate is inversely proportional to the mitotic activity within these tumors. In an elegantly designed study led by Singer et al, tumors were divided into groups based on the number of mitoses per 10 high-power fields (HPF). Groups consisted of tumors with 0 to 1 mitoses per 10 HPF, those with 1 to 9 mitoses per 10 HPF, and those with > 9 mitoses per 10 HPF. The overall survival probability for those with the most mitoses (32%) was less than those with the least (84%).

After grade as a prognostic factor, the long-term survival from retroperitoneal sarcomas is most dependent on the completeness of resection. While adjuvant and neoadjuvant therapy is used frequently for these tumors, complete resection remains the only chance for long-term survival. Many times, tumor resection involves resection of adjacent viscera with complicated reconstructions. In all cases, the surgical goal should be complete resection of the tumor with a microscopically negative margin (R0). Given the size of these tumors and their usual proximity to or effacement/invasion of vital structures, this goal is often difficult to achieve.

In a recent report from MD Anderson Cancer Center that included a large series of patients, multifocality of disease was found to be another significant prognostic factor. With a large cohort of patients and a median follow-up of 69 months, the authors found that patients...
presenting with multifocal disease had a significantly worse 5-year overall survival rate (31%) compared with those presenting with unifocal disease (60%). Upon further examination of the data, they chose a cutoff of seven lesions as a criterion to determine sarcomatosis. Multifocal disease restricts the possibility of a complete resection of all tumors, which is fundamental to long-term survival with this disease.

Treatment: Role of Surgery

The resectability of a retroperitoneal sarcoma requires careful study of high-quality preoperative cross-sectional imaging. Often these tumors will displace nearby structures; however, more locally advanced or invasive high-grade primary or recurrent lesions will invade rather than efface adjacent solid organs, hollow visceras, and major vascular structures (Fig 2A-C). Given adjacent visceral or vascular involvement and the likelihood of early distant metastasis, similar size or smaller adenocarcinomas would be considered unresectable, but the same is not generally true for sarcomas.

Some tumors are not amenable to surgical resection initially. These tumors are typically deemed as such based on the performance status of the patient and related comorbidities and the extent of involvement of multiple areas of bowel where reconstruction is not possible or will result in malabsorption and/or multiple or bilateral major vascular structures without reasonable proximal and distal targets for reconstruction, thereby compromising the viability of critical structures (Fig 3). While these lesions are often considered unresectable, some benefit may be gained with debulking symptomatic low-grade lesions in this setting.18 In some situations an aggressive operative approach is reasonable if the chance for complete resection is high, particularly with the application of neoadjuvant therapy in cases where a microscopic margin-negative resection will be difficult or challenging. The role of neoadjuvant radiation for retroperitoneal sarcomas is described later in this review.

In cases of large vessel involvement, the addition of MRI along with high-quality contrast-enhanced CT scan can be useful in identifying intraluminal tumor thrombus and/or the extent of vessel effacement or encasement.2,3 In general terms, encasement is defined as tumor involvement in > 180° of the vessel and effacement is used when < 180° of the vessel is involved without caliber change. While these terms are generally reserved for discussion of visceral malignancies (eg, pancreatic adenocarcinoma), they are also useful in a multidisciplinary discussion when sarcoma resectability is in question. Generally, a vessel can be freed from an abutting tumor, but this is less likely when a mass — particularly a high grade lesion — encases or invades the vessel wall or penetrates the lumen. This distinction, while having less bearing on resectability than in visceral malignancies of epithelial origin, is fundamental to operative planning.

Many times visceral or vascular resection is performed concomitantly with primary tumor extirpation. Complicated pancreatic and renal en bloc resections are described throughout the literature.9,15,19-21 In a recent controversial French study, nearly three-fourths of
the patients required concomitant visceral resection.22 Nephrectomy was most commonly performed (42%), followed by colectomy (30%). The authors advocate for “compartmental resection” rather than “shelling out of the tumor” and quote a survival difference to support this claim.22 It is clear that complete tumor extirpation is correlated with survival in many studies; however, with such a radical approach for the retroperitoneum, the potential for postoperative morbidity is high and selection bias based on the risk for increased postoperative morbidity limits this approach for all patients with retroperitoneal sarcomas. Bonvalot et al22 reported on their experience with this approach in 374 patients. After a median follow-up of 4.4 years, 47% of the patients had recurred locally. Although the authors concluded that “compartmental resection” for retroperitoneal sarcomas was safe, surgical complications developed in 16% of the patients, with half requiring re-operation. In this study, 13 patients (4%) died in the perioperative setting and 3 died intraoperatively. These numbers are high (though reportedly acceptable per the authors) and should be taken into consideration when evaluating this approach for patients with retroperitoneal sarcomas.

Another European group reported a retrospective series of patients who underwent visceral en bloc resections as a part of the primary management of retroperitoneal sarcomas.23 Due to a shift toward a more aggressive surgical approach (en bloc resection of adjacent organs) during given time periods, patients were divided into two groups. For patients who underwent surgery during the earlier time period in which less aggressive resections were performed, the 5-year local recurrence rate was 48% compared with 28% for patients treated in the recent period. It should be noted that there was no guarantee that patients had en bloc visceral resections in the more recent group; the patients were merely operated on during a time period when the institutional preference was to perform these resections. Additionally, given the nature of a retrospective review of the two time periods, the median follow-up was nearly double in the early group compared to the late group, suggesting that with longer follow-up, patients in the more radical group tend to develop recurrences equivalent to patients resected during the earlier time period.

The issue of compartmental resection in the retroperitoneum comes under debate when the operation entails resection of uninvolved organs. As noted in a recent editorial,20 the surgical plan of compartmental resection as described by Bonvalot et al22 has some fundamental flaws. First, this approach advocates radical en bloc resection of uninvolved nearby structures to obtain a negative margin; however, selection bias occurs as the complexity of resection and reconstruction increases (eg, the spine or aorta). Second, no long-term overall survival benefit has been demonstrated in the patients who have undergone resection of uninvolved organs. Others have shown no survival benefit in those with amputation for extremity sarcomas compared to those with limb preservation therapy. Finally, the data derived from the study are retrospective and span a long interval; gathering data over a 20-year period provides little to no control of confounding variables or standardized criteria for the extent of resection. It is difficult to draw meaningful conclusions based on patients treated over such a long period of time.

Although the recent European publications describing compartmental resection for retroperitoneal sarcomas remain controversial, major multivisceral resections of involved structures are often required to obtain negative surgical margins. The extent of disease in patients with retroperitoneal sarcomas can sometimes require nephrectomy at the time of primary resection. In one large series by Russo et al,24 nephrectomy was required in 20% of patients who had undergone resections. Indications for nephrectomy included gross tumor invasion or total encasement. The authors concluded that, based on a cohort of 53 patients requiring nephrectomy, the 5-year overall survival rate was significantly increased compared with a cohort of 20 historical controls who were left with macroscopic disease.

In terms of vascular invasion or in situations where the tumor arises from a major vascular structure such as the inferior vena cava or aorta, combined resection with vascular reconstruction has been described and is safe when performed at a center with expertise in these complex procedures.8,19,25 Most commonly described are patients with leiomyosarcoma arising from the inferior vena cava (IVC). Management of the IVC after resection is an area of debate regarding the need for reconstruction. The options of simple ligation vs conduit reconstruction are described, but no study to date describes an advantage of one option over the other. Based on literature reports, reconstruction of the IVC is not uniformly required, and

Fig 3. — Large desmoid tumor not amenable to resection due to involvement in small bowel mesentery and superior mesenteric artery and vein branches. Resection would have compromised blood flow to a large portion of the small bowel and resulted in infarction or short bowel syndrome.
ligation alone is generally well tolerated with a surprisingly low incidence of transient lower-extremity edema or other sequelae. The most common postoperative morbidity is lower-extremity edema and, perhaps surprisingly, acute renal failure. Avoiding this reconstruction prevents such long-term complications as graft infection and pulmonary embolism.

As with other diseases requiring surgical intervention, the operative treatment of sarcomas is best undertaken at a dedicated sarcoma center with physicians specifically focused on the care of patients with this disease. Outcomes in terms of survival, gross tumor resection, and postoperative complications are consistently better at high-volume centers. In fact, should a biopsy be undertaken, it is advisable that this be performed at the treatment center by the surgeon who will ultimately perform the definitive operation. Retroperitoneal sarcoma is a rare clinical event and, as such, should be managed in centers that treat the bulk of the regional cases.

Role of Chemotherapy

The role of neoadjuvant chemotherapy is not well defined in retroperitoneal sarcomas due to the rarity of the disease and therefore is often extrapolated from trials that include extremity sarcoma. Several case series have reported complications and toxicities, but no definitive prospective trials have examined survival differences in those receiving preoperative vs postoperative chemotherapy. In terms of patients who do receive preoperative therapy, the degree of tumor necrosis appears to be a factor that predicts local recurrence and overall survival. The theoretical advantage of neoadjuvant chemotherapy focuses on the potential to reduce the complexity of the proposed operation for the tumors that respond to systemic therapy. Meric et al described their experience with this approach in 65 patients. They determined that in 13% of patients, the scope of the surgery decreased with a resultant higher margin-negative resection rate and better local recurrence-free and overall survival rates compared with nonresponders. Furthermore, it appears that those receiving preoperative chemotherapy have no increase in perioperative morbidity compared with those who undergo an adjuvant regimen. At MCC, we prefer to use preoperative chemotherapy — often prior to external beam radiation — selectively for large intermediate- to high-grade lesions that will likely require nephrectomy. This is often administered with the intention of eliciting response in the primary lesion or potentially resectable metastatic lesions with combination doxorubicin/ifosfamide. Patients who may require nephrectomy are able to better tolerate higher doses of chemotherapy in the preoperative setting due to the nephrotoxic side effects of the therapy — particularly ifosfamide — on the remaining kidney postoperatively. While no prospective data are available, the retrospective case series that exist do not support the universal use of neoadjuvant chemotherapy for retroperitoneal sarcomas and, as such, we prefer to select this approach carefully for patients with biopsy-proven large, intermediate- to high-grade tumors and in the context of a multidisciplinary review.

The role of adjuvant chemotherapy has been studied as well (Table 1). Several prospective randomized trials have demonstrated decreased local recurrence rates in patients who received adjuvant regimens, but the effect on overall survival is less clear. A recent Cochrane review was undertaken to investigate the effect of adjuvant therapy in a mixed population of sarcoma patients. Upon review of 14 trials, it was determined that local recurrence and disease-free survival were both positively affected by adjuvant therapy, but the effect on overall survival could not be determined due to a lack of data. Several notable international reports of adjuvant chemotherapy have supported its use in advanced disease. The French Sarcoma Group recently reported a large retrospective cohort series of patients with grade 2 and 3 disease. In the final analysis, metastasis-free survival and overall survival were both significantly improved in patients with grade 3 disease but not grade 2. Frustaci et al reported even stronger results in the form of a retrospective study.

### Table 1. — Adjuvant Chemotherapy for Sarcoma

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>No. of Patients</th>
<th>Therapy</th>
<th>Median Follow-up (yrs)</th>
<th>Disease-Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>With chemotherapy</td>
<td>Without chemotherapy</td>
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<td></td>
<td>With chemotherapy</td>
<td>Without chemotherapy</td>
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<td>With chemotherapy</td>
<td>Without chemotherapy</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>With chemotherapy</td>
<td>Without chemotherapy</td>
</tr>
<tr>
<td>Italiano et al (2010)</td>
<td>420</td>
<td>Doxorubicin-based, various regimens</td>
<td>9</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>SMAC (2000)</td>
<td>1,568</td>
<td>Doxorubicin-based, various regimens</td>
<td>9.4</td>
<td>70% at 10 yrs</td>
<td>60% at 10 yrs</td>
</tr>
<tr>
<td>Frustaci et al (2001)</td>
<td>104</td>
<td>Doxorubicin + ifosfamide</td>
<td>4.9</td>
<td>48 mos</td>
<td>16 mos</td>
</tr>
</tbody>
</table>

NR = not reported, SMAC = Sarcoma Meta-analysis Collaboration.
They found a nearly three-fold increase in the disease-free survival for patients who received adjuvant therapy. More importantly, there was an absolute difference of 29 months between the median overall survival of patients receiving adjuvant chemotherapy and those who did not. It should be noted that these reports include patients with soft tissue extremity sarcoma and little data are available for the routine use of adjuvant chemotherapy in the subset of patients with retroperitoneal sarcomas. Data from soft tissue extremity sarcomas are often generalized to retroperitoneal sarcomas. This is a usual approach because of the rare incidence of retroperitoneal sarcomas and the limitations of designing a clinical trial with such a small and profoundly heterogenous patient population. For these reasons, we generally do not advocate adjuvant systemic therapy outside of a protocol or in the setting of a multidisciplinary review at a sarcoma center.

For patients with overwhelming intra-abdominal recurrence, or sarcomatosis, the role of hyperthermic intraperitoneal chemotherapy (HIPEC) has been investigated. This is typically delivered in the operating room after a maximal amount of tumor debulking has been completed. The chemotherapy is delivered via large bore catheters directly to the temporarily closed peritoneal cavity. The chemotherapy is typically platinum-based (eg, cisplatin or oxaliplatin) and always delivered at hyperthermic temperatures of about 42°C. Principles of this therapy are based largely on specific patient selection. For maximal benefit, only patients with peritoneal disease (not recurrent solid organ) should be selected, and maximal cytoreductive surgery should be completed prior to administration of HIPEC. Patients treated outside of these parameters will have poorer outcomes.

Few randomized trials have evaluated HIPEC in patients with sarcomatosis, and most of these studies have demonstrated no benefit over debulking alone. A French group recently published a randomized trial with significant follow-up that showed no improvement in overall survival for patients following debulking and peritoneectomy after receiving HIPEC compared with those who did not. Local relapse-free and metastasis-free survival were identical between the groups as well. Interestingly, the group reported a low incidence of morbidity associated with the therapy, which is contradicted in many other reports.

Remaining reports in the literature are case series, either described retrospectively or prospectively. These are single-institution reports that describe survival outcomes and the toxicity of the operation (Table 2). All reports indicate that cytoreductive surgery followed by HIPEC is a safe procedure, but the overall effectiveness cannot be determined due to the lack of randomized controls. The final conclusion from each report is essentially that although the procedure is safe, the effect on survival cannot be formally determined until a prospective randomized trial is conducted.

Given the paucity of data and the marginal response of a select group of patients, HIPEC should, at this time, be delivered only at centers with significant experience in this modality and only in the setting of clinical protocol. With the recent organization of the American Society of Peritoneal Surface Malignancies, there will likely be forthcoming criteria for agents and regimens that will be tested in a prospective randomized trial.

**Role of Radiation Therapy**

Although commonly applied for retroperitoneal sarcomas in either the neoadjuvant or adjuvant setting, there is no level I evidence for radiation therapy in the specific management of retroperitoneal sarcomas, so data from extremity soft tissue sarcomas are generally extrapolated. Decisions about dose and timing need to be modified due to not only the potential for toxicity to nearby structures, but also the potential effects relating to the anatomic confines of this space. Specific concerns remain with the potential for bowel toxicity. In treating soft tissue sarcomas, prescribing doses in the range of 60 Gy to 90 Gy is not uncommon, but the bowel exhibits significant signs of toxicity at doses greater than 45 Gy. For this reason, regimens must be modified.

Fundamentally, the choice for preoperative vs postoperative radiation therapy must be made with consideration of wound complications as well as the impact on local recurrence and survival (Table 3). No study has shown a survival benefit for patients receiving preoperative radiation compared with those receiving postoperative radiation. These same studies do show an increase in postoperative complications, most often wound infections or dehiscence. With no survival benefit and an increase in postoperative complications, preoperative radiation therapy should be used in highly selected patients in the setting of a high-volume, multidisciplinary program focusing on sarcoma.

### Table 2. — Reports of Hyperthermic Intraperitoneal Chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Regimen</th>
<th>Median Follow-up (mos)</th>
<th>Median Overall Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berthet et al (1999)</td>
<td>43</td>
<td>Multiple</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Elber et al (1999)</td>
<td>54</td>
<td>Mitoxantrone</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>Rossi et al (2004)</td>
<td>60</td>
<td>Cisplatin/doxorubicin</td>
<td>28</td>
<td>34</td>
</tr>
<tr>
<td>Bonvalot et al (2005)</td>
<td>19</td>
<td>Cisplatin/doxorubicin</td>
<td>60</td>
<td>29</td>
</tr>
<tr>
<td>Lim et al (2007)</td>
<td>28</td>
<td>Cisplatin/mitoxantrone</td>
<td>NR</td>
<td>5.5</td>
</tr>
</tbody>
</table>

NR = not reported.
Preoperative radiation therapy has been studied largely in the setting of pilot studies on an institutional basis. Reports from large-volume centers focus on the safety and feasibility of this therapy. A report from the University of Alabama, the largest report from a single institution, indicates that dose escalation is important.52 Patients received a total of 45 Gy, with a boost of 57.5 Gy to areas predicted as high probability for positive margins. The authors suggest that higher doses may be possible. All patients underwent surgical resection nearly all having a complete macroscopic resection. Another report from MD Anderson Cancer Center indicated that preoperative chemotherapy combined with neoadjuvant radiation may be of benefit.20 In this series of 35 patients, 83% underwent surgical resection and 90% of those underwent a complete macroscopic resection. These reports indicate that it is safe, but no comparative studies exist and thus long-term survival conclusions are not possible.

At our center, preoperative radiation is used for highly selected cases — generally for intermediate- to high-grade lesions — following a discussion with an interdisciplinary team experienced in the management of these complex cases. Patients with large tumors are typically given preoperative radiation under the theory that (1) the gross tumor volume can be accurately addressed only preoperatively, (2) the neoplasm itself actually protects the surrounding viscera (generally bowel or kidney) by displacing these structures, and (3) tumors with a rich blood supply have a better response to the radiation.31 We tend not to use adjuvant radiation therapy for these patients as the exact surgical margins are more difficult to assess, even with intraoperative marking using surgical clips, and the collateral damage to the remaining viscera can be much higher.

Studies have been reported that focus on ancillary adjuvant treatments. In one such report of brachytherapy following resection and neoadjuvant radiotherapy, the authors believe brachytherapy to be generally safe but advocate its use only to the lower abdomen, given the high toxicity of delivery to the upper abdomen.53 Another report of intraoperative radiotherapy describes the modality as safe, with a radiation-related morbidity of 14%.54 In both of these reports, the sample size was small and the follow-up was insufficient to allow for conclusions regarding the impact on survival. Even with the use of radical surgery and pre- or postoperative chemoradiotherapy, approximately half of patients will have a local recurrence at a median of 45 months.7 Management of recurrent sarcoma is difficult and should warrant referral to a high-volume center.

### Recurrent Disease

#### Local Recurrence

The overwhelming majority of patients will manifest local recurrence at some point. Management of this recurrent disease should involve a coordinated plan of care among medical, radiation, and surgical oncologists. In the setting of locally recurrent disease, complete

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>No. of Patients</th>
<th>Therapy</th>
<th>Median Follow-up</th>
<th>% Local Recurrence Rate</th>
<th>% Overall Survival (yrs)</th>
</tr>
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<tr>
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<td></td>
<td></td>
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<td>With XRT</td>
<td>Without XRT</td>
</tr>
<tr>
<td><strong>Adjuvant Therapy</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pisters et al47 (1996)</td>
<td>164</td>
<td>Surgery ± brachytherapy</td>
<td>6.3 yrs</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td>Yang et al49 (1998)</td>
<td>141</td>
<td>Chemotherapy ± EBRT</td>
<td>9.6 yrs</td>
<td>1.5</td>
<td>23.3</td>
</tr>
<tr>
<td>Alektiar et al49 (2008)</td>
<td>41</td>
<td>Surgery + IMRT</td>
<td>35 mos</td>
<td>4.8</td>
<td>NR</td>
</tr>
<tr>
<td>Koshy et al50 (2010)</td>
<td>2,830</td>
<td>Surgery ± XRT</td>
<td>5 yrs</td>
<td>NR</td>
<td>NR</td>
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<td><strong>Neoadjuvant Therapy</strong></td>
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<tr>
<td>Caudle et al34 (2007)</td>
<td>14</td>
<td>Neoadjuvant XRT</td>
<td>11 mos</td>
<td>50</td>
<td>N/A</td>
</tr>
<tr>
<td>Kraybill et al13 RTOG 9514 (2010)</td>
<td>64</td>
<td>Neoadjuvant chemotherapy, XRT + adjuvant chemotherapy</td>
<td>2.57 yrs</td>
<td>10.1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

EBRT = external beam radiation therapy, IMRT = intensity-modulated radiation therapy, NR = not reported, NA = not applicable.
operative extirpation should be the goal. Given that many of those patients will have undergone an extensive operation for their primary disease, the decision to re-enter the abdomen should not be taken lightly. Anatomic planes will be destroyed and, perhaps, due to significant reconstructions, uninvolved organs may be displaced and therefore more easily injured on reoperation. For these reasons, reoperation for recurrence should be undertaken if there is evidence of progression and when it is believed that the complete resection of the recurrent disease can be accomplished safely.

For those in whom it is believed that surgical resection will not be possible or that an R2 resection is likely, systemic therapy should be considered and exploration of the abdomen reserved for palliative intent. Shibata et al.19 studied the role of incomplete resection of retroperitoneal liposarcomas and determined that tumor debulking may be beneficial in patients with unresectable primary disease; however, this benefit is marginal at best for those with unresectable recurrent disease. Furthermore, a recent report by Park et al.55 studied the growth rate of 105 patients with locally recurrent retroperitoneal liposarcomas. They concluded that the size of the locally recurrent disease, primary histologic variant, grade, and local recurrence growth rate were independent predictors of disease-specific survival. Improved survival was identified in those patients with a growth rate of less than 0.9 cm per month.

**Metastatic Disease**

As with radiation therapy, there is a paucity of data regarding resection of metastatic disease for retroperitoneal sarcoma. Some important points can be drawn from evaluations of metastasectomy for extremity soft tissue sarcoma. Blackmon et al.56 recently reported their results on pulmonary metastasectomy from soft tissue sarcoma. The authors reported that the 5-year survival rate in this highly selected group of patients was nearly doubled, from 13.5% to 35%, in the patients who underwent resection of pulmonary metastases compared to those without resection.

The surgical management of hepatic metastases has been studied in similar fashion. There are several reports of extended survival in those who undergo resection of hepatic metastases.57-59 With a recent study by Marudanayagam et al. reporting a 32% 5-year overall survival rate in patients who underwent resection of hepatic metastases. A review of metastasectomy studies seems to indicate that the disease-free interval is the strongest predictor of benefit from hepatic metastasectomy. Several studies have also investigated the resection of noncolorectal nonneuroendocrine hepatic metastases. In these patients as well, there is a survival advantage following resection of the liver lesions.60

At MCC, we tend to treat patients with a shorter disease-free interval or multiple sites of metastasis with standard systemic therapy or a clinical trial. Metastasectomy in this setting may be undertaken after determining disease response in patients with acceptable performance status. Patients with a long disease-free interval, oligometastatic disease, and excellent performance status are more suitable candidates for metastasectomy with curative intent. Although several centers report a survival advantage after metastasectomy for sarcoma, this approach may not be advantageous for patients with multiple sites of disease or a short disease-free interval. Careful patient selection in this setting is critical to minimize treatment-related complications and improve outcomes.

**Palliative Procedures**

Given the proximity of the primary lesion to bowel and other viscera, it is not surprising that patients with unresectable recurrent disease or widely disseminated disease will require a palliative operation at some point. The Memorial Sloan-Kettering experience found that a majority of palliative operations were for gastrointestinal complaints.61 More than half of the patients had initial relief of their symptoms at 30 days, but the effect was short-lived. When operating on patients with palliative intent, the axiom of “first do no harm” should be paramount.

**Conclusions**

The presentation and the extent of disease in a patient with retroperitoneal sarcoma are perhaps more varied than in patients with any other clinical entity. Furthermore, the rarity of retroperitoneal sarcomas makes organizing appropriately powered prospective studies difficult. Many reports are retrospective, single-institution reports based on historical controls. Problems encountered with these studies include the varied clinical approaches over a time period with a rapidly changing clinical milieu. Larger collaborative prospective controlled studies among sarcoma centers need to be conducted in order to establish more powerful conclusions regarding the management of these complex neoplasms.

The treatment of retroperitoneal sarcomas is based on surgical resection. All diagnostic algorithms and other treatment modalities should be managed by a multidisciplinary team at a high-volume center that focuses on the care of patients with sarcoma. The decision for preoperative therapy — chemotherapy or radiation — should be based on optimizing the patient for surgical resection. Therapies that do not enhance the fitness of the patient or the likelihood of complete gross tumor resection will not improve long-term survival.

**References**

56. Blackmon SH, Nipam S, Roth J, et al. Resection of pulmonary and