Background: Retroperitoneal sarcoma is rare. Using initial specimens on biopsy, a definitive diagnosis of histological subtypes is ideal but not always achievable.

Methods: A retrospective institutional review was performed for all cases of adult retroperitoneal sarcoma from 1996 to 2015. A review of the literature was also performed related to the distribution of retroperitoneal sarcoma subtypes. A meta-analysis was performed.

Results: Liposarcoma is the most common subtype (45%), followed by leiomyosarcoma (21%), not otherwise specified (8%), and undifferentiated pleomorphic sarcoma (6%) by literature review. Data from Moffitt Cancer Center demonstrate the same general distribution for subtypes of retroperitoneal sarcoma. A pathology-based algorithm for the diagnosis of retroperitoneal sarcoma is illustrated, and common pitfalls in the pathology of retroperitoneal sarcoma are discussed.

Conclusions: An informative diagnosis of retroperitoneal sarcoma via specimens on biopsy is achievable and meaningful to guide effective therapy. A practical and multidisciplinary algorithm focused on the histopathology is helpful for the management of retroperitoneal sarcoma.

Introduction

Soft-tissue sarcomas are mesenchymal neoplasms that account for up to 1% of all newly diagnosed malignancies at a rate of 3.6 per 100,000 per year. Compared with bone or visceral sarcomas, they make up 58% of all sarcomas. Although the extremities represent the most common location of soft-tissue sarcoma, retroperitoneal sarcoma accounts for 9% to 15% of all adult soft-tissue sarcomas. For surgical pathologists, retroperitoneal tumors will be encountered in daily practice regardless of the practice setting. Retroperitoneal sarcoma presents diagnostic challenges due to its rarity, variety of tumor types, a general level of unfamiliarity among surgical pathologists, and lack of generally accepted guidelines in its diagnostic approach. In the era of personalized medicine, pathologists play a critical and central role in patient care. Demand has increased to obtain diagnostic, prognostic, and predictive information based on a relatively small amount of tissue obtained on biopsy.

In this study, we compare our experience, especially the distribution of histological subtypes, with the literature to develop a better understanding of common and rare tumor types, pertinent ancillary testing, diagnostic pitfalls, and refine a practical, multidisciplinary, and algorithmic approach to achieve an informative diagnosis to help guide the therapeutic plan.

Methods

After obtaining Institutional Review Board approval, the database Transmed (H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida) was retrospectively reviewed for all histological subtypes of retroperitoneal sarcomas from 1996 to 2015. Transmed integrates data from all patients seen at Moffitt Cancer Center since 1996 (approximately 395,000 patients, regardless of diagnosis) as well as other patients not treated at Moffitt Cancer Center but who consented to the Total Cancer Care protocol at one of 17 consortium sites (approximately 36,000 patients). This result was cross-checked by sarcoma pathologists as well as the deidentified result of another retroperitoneal sarcoma retrospective institutional review.

A systematic review of the English literature was conducted for works published between 2000 and 2015. This yielded 85 search results. Another literature search was conducted yielding an additional 444 results. After excluding case reports and studies with locations of retroperitoneal sarcoma...
ma mixed with other locations, our search yielded 54 studies from which we extracted information about the distribution of histological subtypes within each study patient population.

The meta-analysis was conducted using StatsDirect (Cheshire, United Kingdom).

Results

Literature Review
A literature search revealed the following list of most to least common histological subtypes of tumors. Percentages shown are out of all retroperitoneal sarcoma subtypes (Table 1). Our review and data analysis of retroperitoneal sarcoma studies concluded that the most common subtype of retroperitoneal sarcoma is liposarcoma, which constitutes 45.1% of all retroperitoneal sarcoma (Fig 1). The next most common subtypes are leiomyosarcoma (21.3%), other (8.2%), and malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma (6.4%; see Table 1). Well-differentiated liposarcoma and dedifferentiated liposarcoma constituted 45.8% and 44.8% of all retroperitoneal liposarcomas, respectively (Fig 2). The less common subtypes were myxoid/round cell liposarcoma and pleomorphic liposarcoma.

Institutional Results
A review of Transmed, which represents single-institution data, is summarized in Table 1. Our data for retroperitoneal sarcoma subtypes are consistent with our literature search. Liposarcomas of all subtypes at Moffitt Cancer Center make up 54.6% (168 cases) of all retroperitoneal sarcoma (307 cases), followed by leiomyosarcomas (80 cases), sarcoma not otherwise specified (15 cases), malignant peripheral nerve tumor (3 cases), and other less common subtypes (1–2 cases; see Table 1). The trend for most to least common tumor types appears to be similar (Fig 3). In Fig 4, data from Moffitt Cancer Center on the histological subtypes of retroperitoneal liposarcomas are compared with the data found during our literature search. The median age of the patients in all 54 studies was 58 years. The percentages of those who were men and women were 53.2% and 46.8%, respectively.

Gap Between Practice and Literature
Most of the literature we reviewed describes sarcoma in categories based on histological type and morphological pattern.5 Morphological features are evaluated to determine the differential diagnosis, ranking possible diagnoses from most likely to least likely in conjunction with clinical and radiological clues, and then applying ancillary testing to narrow down the diagnosis. Thus, it is important to understand the common and rare types of retroperitoneal sarcoma.

Some sarcomas have molecular and immunohistochemical hallmarks and characteristics that can be diagnosed with a small amount of tissue acquired on biopsy; however, commonly, sarcoma does not have such a signature and morphologically overlaps with other tumors. Ancillary tests can be performed to narrow the diagnosis, with the understanding that it may not be possible to achieve a definitive diagnosis. However, it is important to realize that, when a definitive diagnosis is not achievable, an alternative option is to provide useful, diagnostic information to guide the clinical team in the next appropriate step.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Distribution From the Literature, %</th>
<th>Distribution From Moffitt, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposarcoma (all subtypes)</td>
<td>45.1</td>
<td>54.6</td>
</tr>
<tr>
<td>Well differentiated</td>
<td>23.9</td>
<td>15.3</td>
</tr>
<tr>
<td>Dedifferentiated</td>
<td>20.9</td>
<td>15.6</td>
</tr>
<tr>
<td>Myxoid/round cell</td>
<td>0.9</td>
<td>6.8</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>21.3</td>
<td>26.1</td>
</tr>
<tr>
<td>Other</td>
<td>8.2</td>
<td>0</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma</td>
<td>6.4</td>
<td>1</td>
</tr>
<tr>
<td>Sarcoma not otherwise specified</td>
<td>1.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumor</td>
<td>1.3</td>
<td>1</td>
</tr>
<tr>
<td>Solitary fibrous tumor/hemangiopericytoma</td>
<td>0.8</td>
<td>0</td>
</tr>
<tr>
<td>Fibrosarcoma (nondesmoid)</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Anaplastic sarcoma</td>
<td>&lt;0.1</td>
<td>0</td>
</tr>
<tr>
<td>Adenosarcoma</td>
<td>&lt;0.1</td>
<td>0</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>&lt;0.1</td>
<td>0</td>
</tr>
<tr>
<td>Desmoplastic small-round cell tumor</td>
<td>&lt;0.1</td>
<td>0</td>
</tr>
<tr>
<td>Epithelioid sarcoma</td>
<td>&lt;0.1</td>
<td>0</td>
</tr>
<tr>
<td>Extraskeletal osteosarcoma</td>
<td>&lt;0.1</td>
<td>1</td>
</tr>
<tr>
<td>Fibromyxosarcoma</td>
<td>&lt;0.1</td>
<td>1</td>
</tr>
<tr>
<td>Giant cell sarcoma</td>
<td>&lt;0.1</td>
<td>3</td>
</tr>
<tr>
<td>Mesenchymoma</td>
<td>&lt;0.1</td>
<td>0</td>
</tr>
<tr>
<td>Primitive neuroectodermal tumor/extraskeletal Ewing sarcoma</td>
<td>&lt;0.1</td>
<td>1</td>
</tr>
<tr>
<td>Small cell/embryonal/synovial/undifferentiated sarcoma</td>
<td>&lt;0.1</td>
<td>0</td>
</tr>
<tr>
<td>Spindle cell sarcoma</td>
<td>&lt;0.1</td>
<td>1</td>
</tr>
<tr>
<td>Undifferentiated round-cell sarcoma</td>
<td>&lt;0.1</td>
<td>1</td>
</tr>
</tbody>
</table>
for the patient’s care. In such situations, being aware of the management plan for various diagnoses is critical. Some diagnoses are managed according to established institutional pathways. The literature often focuses on achieving a definitive diagnosis, rather than realizing an informative diagnosis.

**Multidisciplinary Approach to Pathology-Focused Management**

The interdisciplinary management of retroperitoneal sarcoma involves chemotherapy, radiotherapy, and surgery, along with providing prognostic, predictive, and diagnostic information to the clinical team and the patient. The mainstay of treatment for retroperitoneal sarcoma is surgical resection. Complete resection with a microscopically negative margin (R0) remains the potential likelihood for cure.\(^6\) Surgical decision-making in retroperitoneal sarcoma is not solely based on histological subtypes, but rather on factors such as performance status, patient comorbidities, and extent of tumor involvement into adjacent organs and vascular structures.\(^1\) Adjunctive therapies such as perioperative radiotherapy and chemotherapy are also selectively used within the context of interdisciplinary review on a case-by-case basis. At this time, use of radiotherapy does not depend on histological subtypes but rather on tissue tolerance and tumor grades, with intermediate- and higher-grade tumors being more appropriate for treatment.\(^1\) Future research may enable more histology-specific decisions. We speculate that new data may suggest no role exists for radiotherapy in the treatment of leiomyosarcoma.

However, histological subtypes play a role in chemotherapy. Some subtypes may respond better to certain chemotherapeutic agents or regimens and, conversely, several different sarcoma subtypes will similarly respond to identical chemotherapy treatments (Fig 5; Table 2).\(^7\)-\(^18\) The role of chemotherapy in the management of retroperitoneal sarcoma is not well defined. The 2 most important determinants of overall survival (OS) are tumor grade and extent of resection, with subtypes having a less important role in determining prognosis.\(^6,19\) Therefore, when considering whether to pursue a definitive diagnosis for a tumor subtype, the relative costs and turnaround time of ancillary tests vs the importance or relevance of the test results in the larger context of the interdisciplinary management of retroperitoneal sarcoma must be considered; therefore, pathologists must make judicious use of their tissue samples, time, and institutional resources.

**Neoadjuvant Chemotherapy**

The role of neoadjuvant chemotherapy is not well de-
fined in retroperitoneal sarcoma due to the rarity of the disease; therefore, its role is often extrapolated from studies that include extremity sarcoma. Several case series have been reported, but no definitive prospective trials have examined OS differences in those receiving preoperative vs postoperative chemotherapy. Similarly, to date, no randomized trials exist of neoadjuvant chemotherapy vs resection alone for retroperitoneal sarcoma. Although data are limited, preoperative chemotherapy appears to be safe and occasionally induces a modest radiographic response, which may impact surgical outcomes in select patients.

The administration of systemic therapy in the neoadjuvant setting is often combination therapy with doxorubicin and ifosfamide, a regimen with potential for renal toxicity but with a higher response rate (31% vs 14% in the single-arm doxorubicin alone). As a consequence of resection, nephrectomy is often required, so chemotherapy in the neoadjuvant setting allows for use of ifosfamide, which, in combination with doxorubicin, may have a larger effect on tumor response when compared with doxorubicin alone.

### Localized Treatment (Curative Intent)

Retroperitoneal sarcoma is a heterogeneous group of tumors with multiple histological subtypes and grades that vary in chemosensitivity. For localized treatment, doxorubicin and ifosfamide are commonly used. Among the liposarcomas, well-differentiated liposarcoma does not respond (response rate = 0%) to chemotherapy and dedifferentiated liposarcoma responds poorly (response rate = 25%). Myxoid liposarcoma has...
the highest response rate at 48%.9 Round cell liposarcoma, a high-grade spectrum of myxoid liposarcoma, has a response rate of 17%.9 Pleomorphic liposarcoma has a response rate of 33%.1 The response rate of leiomyosarcoma to chemotherapy is 25%.10-12 For the remaining retroperitoneal sarcoma subtypes, response rates range from 21% to 31% (see Fig 5).7,9,11-14,16,26

**Table 2. Use of Chemotherapy for the Management of Retroperitoneal Soft-Tissue Sarcomas**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Chemotherapy Response Rate, %</th>
<th>Type of Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myxoid/round cell liposarcoma</td>
<td>Myxoid: 48</td>
<td>Neoadjuvant Setting</td>
</tr>
<tr>
<td></td>
<td>Round cell: 17</td>
<td>Doxorubicin/ifosfamide for localized treatment</td>
</tr>
<tr>
<td>Dedifferentiated liposarcoma</td>
<td>21–33</td>
<td>Metastatic Setting</td>
</tr>
<tr>
<td>Leiomysarcoma</td>
<td></td>
<td>Single-agent doxorubicin</td>
</tr>
<tr>
<td>Pleomorphic liposarcoma</td>
<td></td>
<td>Adjuvant Setting</td>
</tr>
<tr>
<td>Undifferentiated pleomorphic sarcoma</td>
<td></td>
<td>Adjuvant chemotherapy determined on case-by-case basis: with large high-grade tumors, adjuvant chemotherapy increases metastasis-free survival rate</td>
</tr>
<tr>
<td>Other subtypes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td></td>
<td>Histological specific treatment (not anthracycline-based) recommended</td>
</tr>
<tr>
<td>Solitary fibrous tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemangiopericytoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ewing/primitive neuroectodermal tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonpleomorphic rhabdomyosarcoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synovial sarcoma/MPNST</td>
<td>Synovial: 25–31</td>
<td>Synovial Sarcoma</td>
</tr>
<tr>
<td></td>
<td>MPNST: 21</td>
<td>Responds best to ifosfamide-based first-line therapy (doxorubicin/ifosfamide) also sensitive to radiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MPSNT Responds best to doxorubicin/ifosfamide in metastatic setting</td>
</tr>
</tbody>
</table>

Chemotherapy for Metastatic or Advanced Soft-Tissue Sarcoma (Palliative Intent)
Chemotherapy has an established role in the palliative management of metastatic or advanced soft-tissue sarcoma.6,14 In the metastatic setting, use of single-agent doxorubicin or combination doxorubicin/ifosfamide has shown a consistent response.24 However, some subtypes

**Fig 5.** Proposed algorithm for the pathology-focused management of retroperitoneal soft-tissue sarcoma.

5Team is made up of a surgical oncologist, radiologist, oncologist, and pathologist.

6CT = computed tomography, GIST = gastrointestinal stromal tumor, MRI = magnetic resonance imaging.
MDM2 identified, including systemic therapies for soft-tissue sarcoma have been receptors (critical regulators of normal adipocyte differentiation), and tyrosine kinase receptors. Other (see Fig 5).7,9,11,14,16 Although select patients with sarcoma pleomorphic rhabdomyosarcoma, and desmoid tumors Ewing sarcoma/primitive neuroectodermal tumor, non-sarcoma, solitary fibrous tumor/hemangiopericytoma, soft-tissue sarcoma with nonspecific histologies, angiosarcoma, and synovial sarcoma and malignant peripheral nerve sheath tumor (MPNST) respond best to doxorubicin/IFOSfamide.10-15,26-28 Pazopanib, a multitargeted tyrosine kinase inhibitor, has demonstrated single-agent activity in patients with advanced soft-tissue sarcoma subtypes, except for liposarcoma.16 Consensus-based recommendations for the treatment of metastatic soft-tissue sarcoma from the National Comprehensive Cancer Network provide specific therapy regimen recommendations for the following retroperitoneal sarcoma subtypes: soft-tissue sarcoma with nonspecific histologies, angiosarcoma, solitary fibrous tumor/hemangiopericytoma, Ewing sarcoma/primitive neuroectodermal tumor, non-pleomorphic rhabdomyosarcoma, and desmoid tumors (see Fig 5).7,9,11,14,16 Although select patients with sarcoma do derive substantial clinical benefit from chemotherapy, most patients develop metastatic disease that is incurable.29 In a study of 488 participants with advanced soft-tissue sarcoma who were treated with first-line chemotherapy at a single institution, 45% of them derived clinical benefit from treatment in terms of partial response (PR) or prolonged disease stabilization; the median rate of OS was 12 months.30

Furthermore, in the past decade, greater emphasis has been placed on identifying the underlying molecular drivers of sarcomas.31 Several potential novel, systemic therapies for soft-tissue sarcoma have been identified, including MDM2 targets, cyclin-dependent kinase 4 inhibitors, peroxisome proliferator-activated receptors (critical regulators of normal adipocyte differentiation), and tyrosine kinase receptors.32 Other targets reported but not yet tested include YEATS4, c-Jun, and JNK.32

Adjuvant Chemotherapy
Several prospective, randomized trials of study patients who received adjuvant regimens following surgical resection have demonstrated decreased local recurrence rates, but the effect on OS is less clear.1 The benefits of adjuvant chemotherapy must be addressed based on the individual while simultaneously taking into consideration performance status, disease location, tumor size, comorbid factors (including age), and histological subtype. The potential for benefit must be discussed in the context of expected treatment-related toxicities, including sterility in younger individuals, renal damage, secondary cancers, cardiomyopathy, and overall impairment of quality of life.16

Radiotherapy
The overall benefit of radiotherapy for use with retroperitoneal sarcoma has yet to be established, with most of the data being extrapolated from studies of soft-tissue sarcoma of the extremities.33 However, concern remains about the increased risk of treatment-related toxicity to highly radiosensitive visceral structures due to their rapidly proliferating mucosa and rich blood supply.34 The relatively low rate of radiation tolerance for surrounding normal tissues (liver, kidney, gastrointestinal tract, spinal cord) predisposes patients to risks of intestinal perforation, peritonitis, and peripheral neuropathy.35

Use of preoperative radiotherapy is currently being investigated in an accruing, prospective, randomized, multicenter trial (NCT01344018). This type of trial is investigating the potential for external beam radiotherapy (EBRT) to reduce local regional failure.36 Proponents of preoperative radiation cite the potential benefits of potentially using lower doses, while the tumor displaces radiosensitive viscera outside the field of radiation.37 Proponents also claim gross tumor volume can be more adequately defined, which would allow for more accurate preoperative treatment planning.37

Use of postoperative EBRT has been studied but largely abandoned due to its toxic effects of the remaining organs within the tissue bed after resection, with no apparent improvement in survival.37 Another concern with postoperative radiation suggests the difficulty in defining a precise area of the tumor bed to apply EBRT.17

Our experience at Moffitt Cancer Center favors use of preoperative EBRT for intermediate- to high-grade tumors, especially in more radiosensitive tumors, such as extraosseous Ewing sarcoma/primitive neuroectodermal tumor. The more common subtypes, such as well-differentiated liposarcoma and leiomyosarcoma, are generally unresponsive to radiation.18 Thus, concern remains about the increased risk of treatment-related toxicity to visceral structures.

Pathological Prognostic Factors
The most important prognostic factors for survival are extent of tumor resection and histological grade, although histological subtype is also emphasized as an important factor.38 Other factors influencing prognosis include tumor stage, patient age, tumor size, and multifocality. Nomograms have been developed and validated to more accurately predict postoperative survival based on these and other factors.39 Well-differentiated liposarcomas have the most favorable outcome, whereas leiomyosarcomas, pleomorphic sarcoma/malignant fibrous histiocytoma, MPNST, and dedifferentiated liposarcomas exhibit the least favorable outcomes.38

Other prognostic concerns include risks for locore-
Regional recurrence and metastasis. Local regional relapse is the main cause of disease-related death and, in conjunction with retroperitoneal sarcoma, the risk for developing abdominal sarcomatosis also results in death, even in the absence of systemic dissemination. Tumor grade and histological subtypes are major prognostic factors related to metastatic occurrence. Toulemonde et al reviewed the data of 586 study patients with retroperitoneal sarcoma during a multicenter analysis, looking at patterns of care at diagnosis and prognostic factors, with a focus on main histological subtypes. Those findings are summarized in Table 3.

Proposed Algorithm for Management

A patient’s clinical and radiological information is first assessed by an interdisciplinary team that generally includes a surgical oncologist, radiologist, medical and radiation oncologists, and a pathologist — preferably all of whom have expertise in soft-tissue sarcoma (see Fig 5). Cross-sectional imaging, including computed tomography (CT) or magnetic resonance imaging (MRI), preferably with intravenous contrast, can demonstrate predictable displacement of retroperitoneal structures, allowing for localization of a tumor to the retroperitoneum rather than the peritoneal cavity. When a mass is detected in the retroperitoneum, the differential diagnoses may include primary retroperitoneal soft-tissue sarcomas, metastatic disease, including lymphadenopathy from primary sites of disease elsewhere, lymphoma, primary neoplasms arising from retroperitoneal viscera such as the pancreas, kidneys, ureters, adrenal glands, duodenum, or ascending/descending colon such as adenocarcinoma or gastrointestinal stromal tumor (GIST), paraspinal neurogenic tumors, and retroperitoneal fibrosis. Clinical symptomatology, such as B symptoms in cases of lymphoma or findings on physical examination such as a palpable testicular abnormality, which may be associated with retroperitoneal lymphadenopathy, will direct diagnostic consideration away from primary retroperitoneal sarcoma.

Other symptoms such as hematuria, uncontrollable hypertension, or early satiety may raise concern for a primary tumor of a retroperitoneal origin rather than primary retroperitoneal sarcoma.

Findings on cross-sectional imaging may also help assess the internal composition of the tumor, allowing for the preoperative prediction of tumor histopathology and assessment of local extent of disease; these may have an impact on neoadjuvant treatment, surgical planning, or both. Tumor staging should include imaging of the chest to evaluate for pulmonary metastatic disease and is typically performed with CT.

Of all the retroperitoneal sarcoma subtypes, well-differentiated liposarcomas make up 24% and are comprised of simple-appearing fat that has a characteristic appearance on cross-sectional imaging (Fig 6). For lesions demonstrating typical imaging findings of well-differentiated retroperitoneal liposarcoma, biopsy is typically not indicated given the high rate of diagnostic sensitivity of CT for low-grade adipocytic lesions and no role for neoadjuvant therapy with these tumors.

If imaging findings do not suggest well-differentiated liposarcoma, then image-guided core needle biopsy or fine needle aspiration (FNA) is required and is preferred to open surgical biopsy. However, core needle biopsy is preferred to FNA due to the difficulty that exists in discerning histological subtype by FNA.

If results on biopsy suggest retroperitoneal sarcoma, then surgery is the mainstay treatment for all subtypes (see Fig 5). If the tumor is partially resectable, then neoadjuvant radiotherapy and chemotherapy become more important for treating the periphery of the lesion because it will abut critical structures; both types of therapy have the intent of consolidating the peritumoral reactive zone and rendering close margins sterile. Neoadjuvant chemotherapy is also important for tumors with chemosensitive histologies. For the palliative management of metastatic or advanced soft-tissue sarcoma, chemotherapy has an established role.

### Table 3. Risk by Subtype for Local Regional Relapse, Metastasis, and OS Rates

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Risk for Locoregional Relapse</th>
<th>OS</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiomyosarcoma</td>
<td>Piecemeal resection predictive of relapse</td>
<td>Adjacent organ involvement associated with worst OS</td>
<td>Exceptions to typical pattern of metastatic disease</td>
</tr>
<tr>
<td>Well-differentiated liposarcoma</td>
<td>Piecemeal resection predictive of relapse</td>
<td>Adjacent organ involvement associated with worst OS</td>
<td>Commonly metastasizes to liver, lung</td>
</tr>
<tr>
<td>Dedifferentiated liposarcoma</td>
<td>Surgeon specialization and perioperative radiotherapy associated with lower risk of relapse</td>
<td>Grade 3 associated with worst OS</td>
<td>Nearly all recur locoregionally, not via metastasis</td>
</tr>
</tbody>
</table>

OS = overall survival.
Fig 5 summarizes relevant information regarding subtypes and perioperative therapy considerations. Myxoid/round cell liposarcoma as a primary malignancy is rare in the retroperitoneum (< 0.9% of all retroperitoneal sarcoma subtypes), and physical examination and imaging of the extremities to rule out a primary site in an extremity with distant retroperitoneal metastasis are indicated. Primitive neuroectodermal tumors, Ewing sarcoma, and alveolar/embryonal rhabdomyosarcoma are radiosensitive and chemosensitive, so they should not be considered for first-line surgery. Because primary chemotherapy is always given, the strategy for these tumors significantly differs from that undertaken for adult-type soft-tissue sarcoma. Subsequent surgery is then considered for responsive tumors to achieve complete resection of all visible tumors; however, adjacent viscera is only included if true invasion is evident. Our experience with GIST is that neoadjuvant tyrosine kinase inhibitor therapy for large lesions and abutting critical structures should be used to reduce tumor size and limit the complexity of the procedure. Reduction of tumor size due to effective preoperative imatinib occurs in the majority of patients. In such a scenario, proper therapy is warranted for larger tumors that may require multivisceral resection.

Determination of Tumor Types With Radiological and Histological Correlation
Well-Differentiated and Dedifferentiated Liposarcoma
CT or MRI can be used to recognize well-differentiated liposarcoma (see Fig 6). Histomorphological findings that support a diagnosis of well-differentiated liposarcoma include proliferation of mature adipocytes with marked variation in cell size and a focal nuclear atypia in both adipocytes and stromal cells. Identification of lipoblasts does not make (or is required for) a diagnosis of liposarcoma. Lipoblasts may be seen in benign lesions such as lipoblastoma, pleomorphic lipoma, and chondroid lipoma.

Based on morphology, 4 main subtypes exist: adipocytic (lipoma-like), sclerosing, inflammatory, and spindle cell. The sclerosing subtype of well-differentiated liposarcoma tends to occur in the retroperitoneum and microscopically demonstrate scattered, hyperchromatic, bizarre stromal cells set in extensive fibrillary collagenous stroma. With the exception of the spindle-cell subtype, well-differentiated liposarcoma has been found by molecular and cytogenetic studies to harbor a characteristic ring and giant marker chromosomes containing amplification of the 12q13-15 region, including MDM2. Several other genes located in the 12q14-15 region, including CDK4 and HMGA2, are frequently coamplified with MDM2.

Immunohistochemically, expressions of MDM2 and CDK4 are present in most cases and are in keeping with gene amplification. Molecular, cytogenetic, and immunohistochemistry applications help distinguish well-differentiated liposarcoma from benign adipose tumors. Well-differentiated liposarcoma is locally aggressive and lacks metastatic potential. Unless it becomes dedifferentiated (dedifferentiated liposarcoma), well-differentiated liposarcoma is potentially curable with complete excision when located in the extremities; however, sites like the retroperitoneum and mediastinum pose difficulty in obtaining a microscopically negative margin (R0). The differential diagnosis of well-differentiated liposarcoma from benign adipose tumors in a limited specimen, such as specimens from core needle biopsies, can be difficult. MDM2 fluorescence in situ hybridization is sensitive and specific to identify MDM2 amplification in morphologically atypical and typical lesional cells. The immunohistochemistry performance of MDM2 decreases when working with limited specimens on biopsy, a rate typically attributed to the focal staining seen within the majority of well-differentiated liposarcoma on whole-tissue sections.

MDM2 has been useful in identifying dedifferentiated liposarcomas in addition to well-differentiated liposarcoma. Several studies have reported that most poorly differentiated sarcomas arising in the retroperitoneum are, in fact, dedifferentiated liposarcoma and can be diagnosed on the basis of MDM2 amplification even without an atypical adipocytic component. Like well-differentiated liposarcoma, dedifferentiated liposarcoma harbors the ring or giant marker chromosomes, whereas MDM2 (12q15) is consistently amplified and overexpressed.
Histologically, dedifferentiated liposarcoma contains a well-differentiated liposarcoma component juxtaposed to areas of either low- or high-grade nonlipogenic sarcoma (dedifferentiation). The dedifferentiated component may exhibit a wide variety of morphology from high-grade sarcoma resembling undifferentiated pleomorphic sarcoma or high-grade myxofibrosarcoma to low-grade dedifferentiation resembling fibromatosis or fibrosarcoma. Historically, many dedifferentiated liposarcomas were diagnosed as malignant fibrous histiocytoma, particularly de novo dedifferentiated liposarcomas. Dedifferentiated liposarcoma commonly occurs in the retroperitoneum, with more than 90% arising de novo, whereas less than 10% represent recurrences.

Radiologically, the presence of a nonlipogenic soft-tissue mass within an otherwise fatty tumor would be consistent with dedifferentiation (Fig 7). Given the internal heterogeneity, it is important to correlate the histopathological findings with radiological imaging because results on tissue sampling may yield low-grade lipomatous tissue or high-grade sarcoma depending on the target of the biopsy. Surgically, the dedifferentiated part of the tumor is regarded as the only part needed to be excised, whereas surrounding well-differentiated liposarcoma is regarded as normal tissue. Therefore, dedifferentiated liposarcoma is rarely excised with margins free of well-differentiated liposarcoma. Dedifferentiation is associated with a 15% to 20% metastatic rate; however, the mortality rate is more often related to uncontrolled local recurrences than to metastatic spread. A case illustration of dedifferentiated liposarcoma appears in Fig 8.

Other Subtypes of Liposarcoma

Myxoid/round cell liposarcoma and pleomorphic liposarcoma constitute 0.9% and 0.4% of all retroperitoneal soft-tissue sarcomas, respectively (see Table 1). Myxoid liposarcoma demonstrates areas of myxomatous tissue that appear similar to fluid (low density on CT; high signal intensity on T2-weighted MRI) prior to
administering intravenous contrast. However, myxoid elements will be enhanced as opposed to non-enhanced fluid in areas of cystic degeneration or tumor necrosis. Occasionally, liposarcoma may demonstrate areas of mineralization or ossification. More than 95% of cases of myxoid liposarcoma demonstrate a classical t(12;16)(q13;p11) or t(12;22)(q13;q12) translocation, which results in fusion of FUS-CHOP or EWSR1-CHOP, respectively. A diagnosis of primary retroperitoneal myxoid liposarcoma should be made with caution, because such cases represent either metastatic myxoid liposarcoma or well-differentiated/dedifferentiated liposarcoma with myxoid stromal change. 

Pleomorphic liposarcoma often presents as a nonspecific soft-tissue mass without obvious fat evident by results on imaging mimicking other high-grade retroperitoneal sarcomas. Pleomorphic liposarcoma exhibits pleomorphic lipoblasts without well differentiation or other types of liposarcoma. This is a rare type of high-grade liposarcoma that can be differentiated from dedifferentiated liposarcoma by the absence of MDM2 amplification. Pleomorphic liposarcoma also has a different clinical metastatic rate than other pleomorphic or high-grade sarcoma types (Table 4). 

**Retroperitoneal Leiomyosarcoma**

Retroperitoneal leiomyosarcomas typically arise from smooth muscle within the soft tissues of the retroperitoneum itself or within the walls of large retroperitoneal vessels such as the inferior vena cava, aorta, or gonadal veins. Radiographically, the most helpful diagnostic clue may be identification of a mass associated with one of these vascular structures. Typically, retroperitoneal leiomyosarcomas are hypervascular solid tumors with minimal necrosis and a notable absence of internal fat compared with liposarcomas. Mineralization is rarely seen. Compression of the underlying vessel may result in venous thrombosis, and intraluminal extension of disease is not uncommon.

Retroperitoneal leiomyosarcoma shows a high propensity of occurrence in women. When arising from large blood vessels, it commonly occurs from the inferior vena cava and its major tributaries. Grossly, leiomyosarcomas may exhibit either a grey-to-white whorled appearance or form fleshy, tan-white masses with hemorrhage, necrosis, and/or cystic change indistinguishable from other sarcomas. Typical histomorphology consists of intersecting fascicles of spindle cells with elongated and blunt-ended nuclei and eosinophilic cytoplasm. Nuclear hyperchromasia and pleomorphism (ranging from mild to severe) can be observed. Pleomorphism in leiomyosarcoma may resemble undifferentiated pleomorphic sarcoma. Mitoses, including atypical mitotic figures, are usually present. Occasionally, retroperitoneal leiomyosarcoma may have areas exhibiting epithelioid cytomorphology, multinucleated giant cells, prominent inflammatory infiltrate, or exuberant myxoid change. Rarely, leiomyosarcoma contains granular cytoplasmic change. Leiomyosarcoma, specifically of soft-tissue origin, is considered malignant when some degree of nuclear atypia and mitotic activity, which may be very low (<1/10 hpf), are present. Antibodies to smooth-muscle actin, desmin, and caldesmon are positive in most types of leiomyosarcoma, and may be expressed in myoepithelial cells. Aberrant cytokeratin is frequent and epithelial membrane antigen expression may also be seen. S100, CD34, estrogen, and progesterone receptors may also be positive in leiomyosarcoma. Hormone-receptor expression can be seen in leiomyosarcoma of a uterine origin but is not specific for leiomyosarcoma of a gynecological origin.

**Undifferentiated Pleomorphic Sarcoma**

Undifferentiated pleomorphic sarcoma was previously referred to as malignant fibrous histiocytoma. It has no identifiable line of differentiation when analyzed by current technologies and represents a diagnosis of exclusion. Undifferentiated pleomorphic sarcoma typically presents as a large, nonspecific, heterogeneous, enhancing soft-tissue mass with internal necrosis and intratumoral hemorrhage, often with lobulated morphology and well-defined margins due to the presence of a pseudocapsule. Occasionally, internal fibrous tissue may be identified as areas of low signal intensity on T1- and T2-weighted MRI (Fig 9). Myxoid elements may be seen as regions of increased T2-weighted signal with enhanced intravenous contrast. Tumor heterogeneity, including hemorrhage, is typical of undifferentiated pleomorphic sarcoma. Given the propensity for hemorrhage, underlying neoplasms, including undifferentiated pleomorphic sarcoma, must be consid-
erred in any patient presenting with spontaneous hematoma. When arising in the retroperitoneum, these tumors tend to be larger than when they occur in the extremities. Adjacent bone invasion is more common than in liposarcoma or leiomyosarcoma and may help suggest the diagnosis. Undifferentiated pleomorphic sarcoma represents the most common soft-tissue sarcoma following prior radiotherapy.

When encountering a retroperitoneal soft-tissue tumor with the appearance of undifferentiated pleomorphic sarcoma, pathologists must exclude possible pleomorphic sarcoma of a specific type (eg, pleomorphic leiomyosarcoma, pleomorphic liposarcoma), a dedifferentiated component of another type of sarcoma (eg, dedifferentiated liposarcoma), and other sarcomatoid carcinomas. Rarely, sarcomatoid mesothelioma, dedifferentiated melanoma, and anaplastic lymphoma can also occur.

The histology of undifferentiated pleomorphic sarcoma is variable and may reveal several morphological patterns, from storiform areas composed of spindle cells to pleomorphic areas composed of large, rounded, fibroblastic-like cells with marked nuclear atypia and bizarre, multinucleated-tumor giant cells. Mitotic activity is prominent with atypical mitotic figures. The background stroma is usually collagenous, but, rarely, the stroma may have metaplastic osteoid or chondroid material. Some cases of undifferentiated pleomorphic sarcoma have prominent background xanthomatous and neutrophilic infiltrates.

Prominent stromal myxoid change may be present in undifferentiated pleomorphic sarcoma, either focally within the tumor or as large areas abutting cellular zones. Tumors with cytomorphology indicative of undifferentiated pleomorphic sarcoma with prominent myxoid stroma and features such as multinodular growth pattern and prominent curvilinear vascular pattern, even focally, should be diagnosed as high-grade myxofibrosarcoma.

Immunohistochemistry serves as a method to exclude other pleomorphic tumors. Undifferentiated pleomorphic sarcoma often shows patchy to rare cells positive for cytokeratin, actin, desmin, or epithelial membrane antigen. Vimentin and CD34 may be positive but are of no diagnostic value. Over the years, complex cytogenetic aberrations have been identified in undifferentiated pleomorphic sarcoma, but they are nonspecific. Similarities between undifferentiated pleomorphic sarcoma and leiomyosarcoma have been reported from comparative genomic hybridization analyses, suggesting a possible shared lineage. Furthermore, Carneiro et al reported that losses of 4q13 (encompassing SMAD1) and 18q22 were independent predictors of metastasis.

**Neurogenic Tumors**

Neurogenic tumors, including nerve sheath tumors (both benign and malignant), are more common in the extremities, but they have been known to occur in the retroperitoneum, often in paraspinal or presacral locations. Neurogenic tumors tend to demonstrate a fusiform shape, increased T2-weighted signal intensity, and intravenous contrast enhancement. Bony erosions and scalloping, including widening of the neural foramina, are commonly associated osseous findings. Differentiation of benign and malignant neoplasms can be difficult, but increased size, rapid growth, internal necrosis, and increased vascularity all favor malignancy. Malignant neurogenic tumors also tend to demonstrate greater fluorodeoxyglucose uptake than benign tumors on positron emission tomography/CT. Malignant tumors are often seen in the setting of type 1 neurofibromatosis.

**Ganglioneuroma** is a rare, benign, differentiated neoplasm of the sympathetic nervous system that contains no immature neuroblastic elements. Ganglioneuromas predominantly arise within the posterior mediastinum and retroperitoneum. They are well-circumscribed tumors with a fibrous capsule, and cut sections are gray to yellow with a whorled-like pattern similar to leiomyoma. Histologically, this tumor consists of Schwann cells with scattered deposits of ganglion cells, isolated, or small clusters. Surgical excision is appropriate. Ganglioneuromas rarely recur. Malignant transformation into MPNST has been reported.

**Schwannoma**, a peripheral nerve sheath tumor consisting of well-differentiated Schwann cells, is usually encapsulated, and its cut surfaces have a pink, white, or yellow appearance. Retroperitoneal tumors are large and may have areas of cystic degeneration.
and calcification. Classic histology shows a pattern of alternating Antoni A (cellular areas of spindle cells with occasional palisading) and Antoni B (loose myxoid areas with scattered spindle cells and thick-walled, hyalinized vessels) areas.

Retroperitoneal schwannomas may be exclusively or predominantly composed of Antoni A tissue.\(^{26,27}\) Schwannomas with increased cellularity and occasional mitoses are referred to as cellular schwannomas, a variant of schwannoma.\(^{26-28}\) Degenerative changes such as cyst formation, calcification, hemorrhage, and hyalinization may be present in retroperitoneal schwannomas, especially if the tumor has been present for a long time. Marked nuclear atypia characterized by Schwann cells with large, hyperchromatic nuclei are usually associated with schwannomas with degenerative change (ancient schwannoma). They behave similar to conventional schwannomas. \(^{260}\) S100 is strongly and diffusely expressed in schwannomas.\(^{97,98}\) SOX10, a marker of neural crest differentiation, exhibits nuclear staining in schwannomas.\(^{99,100}\) Of note, retroperitoneal schwannomas may express cytokeratin AE1/3 due to cross-reactivity with GFAP.\(^{46}\)

MPNST is an aggressive sarcoma arising from a peripheral nerve (eg, sciatic nerve, brachial plexus, sacral plexus) or preexisting benign nerve sheath tumor (eg, neurofibroma). Nearly 50% of MPNSTs occur in patients with type 1 neurofibromatosis and the remainder sporadically occurs.\(^{46,66}\) Retroperitoneal involvement is rare.\(^{99,100}\) Grossly, MPNSTs arising from a nerve form a large fusiform mass and often measure more than 5 cm and have a tan-white, fleshy cut surface with areas of hemorrhage and necrosis.\(^{46}\) Tumor histomorphology is diverse. Classic cases of MPNST exhibit spindle cells arranged in densely cellular fascicles alternating with less cellular, myxoid areas, creating a marble-like effect.\(^{46}\) The cells can have a whorling or, rarely, palisading architecture with large areas of necrosis. The spindle cells have hyperchromatic nuclei and pale cytoplasm. Mitoses are readily seen. Occasionally, MPNSTs demonstrate marked pleomorphism, simulating high-grade, undifferentiated pleomorphic sarcoma. Skeletal muscle differentiation, glandular differentiation, and heterologous elements have been reported in MPNSTs.\(^{101,102}\) Between 50% and 90% of cases of MPNST are positive for S100, which demonstrates focal staining, and 2% to 15% show weak expression of TLE1.\(^{97,103-108}\) SOX10 has recently been reported to show better sensitivity and specificity for the diagnosis of MPNST than S100.\(^{109}\) A rare variant, epithelioid MPNST, is not associated with type 1 neurofibromatosis and commonly arises from preexisting schwannoma.\(^{46}\) Histologically, epithelioid MPNST is composed of short cords of large epithelioid cells arranged in a vague, nodular pattern.\(^{46}\) The cells have large, round nuclei with prominent nucleoli. They may be associated with myxoid matrix. They can resemble melanoma or carcinoma. Immunohistochemically, epithelioid MPNSTs show strong and diffuse S100 positivity, one-half of cases lack SMARCB1 staining, and rare cases show keratin positivity.\(^{110,111}\) MPNST may also have rhabdomyoblastic differentiation (malignant triton tumor), which has a worse prognosis than conventional MPNST.\(^{112}\)

Cellular schwannoma may be misdiagnosed as MPNST due to it hypercellularity. Significant institutional data do not exist to address how to differentiate MPNST from cellular schwannoma in the retroperitoneum. One large study suggested that certain features distinguish cellular schwannoma from MPNST, but only in general and not specifically to the retroperitoneum (Table 5).\(^{113}\)

**Solitary Fibrous Tumor/Hemangiopericytoma**

Solitary fibrous tumor is a mesenchymal tumor of fibroblastic origin that occurs in deep soft tissue such as the thigh, pelvis, retroperitoneum, and serosal surfaces.\(^{114}\) Solitary fibrous tumor typically demonstrates marked enhancement when viewed with intravenous contrast and presents as a solid, enhancing soft-tissue mass with prominent tortuous and serpentine vessels extending to and seen within the periphery of the mass. Central necrosis is common. The cut surface of the tumor is gray-white to red-brown in color and hemorrhage or cystic degeneration may be seen.\(^{46}\) Histologically, solitary fibrous tumors

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**Table 5. — Distinguishing Features Between Cellular Schwannoma and Malignant Peripheral Nerve Sheath Tumor**

<table>
<thead>
<tr>
<th>Cellular Schwannoma</th>
<th>Malignant Peripheral Nerve Sheath Tumor</th>
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<tbody>
<tr>
<td>Free of metastasis</td>
<td>Malignant</td>
</tr>
<tr>
<td>Disease-specific–related deaths</td>
<td></td>
</tr>
<tr>
<td>Schwannian whorls</td>
<td>Perivascular hypercellularity</td>
</tr>
<tr>
<td>Peritumoral capsule</td>
<td>Tumor herniation into vascular lumens</td>
</tr>
<tr>
<td>Subcapsular lymphocytes</td>
<td>Necrosis</td>
</tr>
<tr>
<td>Macrophage-rich infiltrates</td>
<td></td>
</tr>
<tr>
<td>Fascicles absent</td>
<td>Expression of (p75NTR) observed in 80% of tumors*</td>
</tr>
<tr>
<td>Expression of (p75NTR) observed in 31% of cellular schwannomas*</td>
<td></td>
</tr>
<tr>
<td>Complete loss of SOX10*</td>
<td></td>
</tr>
<tr>
<td>Neurofibromin or p16 expression*</td>
<td></td>
</tr>
<tr>
<td>Presence of EGFR immunoreactivity is specific*</td>
<td></td>
</tr>
<tr>
<td>Ki-67 labeling indices &gt; 20% highly predictive (87% sensitivity, 96% specificity)</td>
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</tbody>
</table>

*In general, not specific to the retroperitoneum.  
*\(P < .001.\)
can demonstrate a variable appearance, from being highly cellular to densely hyalinized and hypocellular tumors. Cellular, solitary fibrous tumors show a patternless architecture composed of tightly packed, bland-appearing, spindle- to fusiform-shaped cells with indistinct cytoplasmic borders arranged around prominent dilated, branched vessels. Myxoid change is common, as is stromal and perivascular hyalinization. Mitoses are scarce.

A solitary fibrous tumor variant, the fat-forming solitary fibrous tumor, often affects the thigh and retroperitoneum.16 It contains a variable amount of mature adipocytes that should not be confused with well-differentiated liposarcoma. Solitary fibrous tumors can be malignant, and these cases demonstrate dense cellularity, increased mitoses (> 4 mitoses/10 hpf), variable cytological atypia, tumor necrosis, and/or infiltrative margins.115,116 Tumor cells are typically positive for CD34 (70%), BCL2 (30%), epithelial membrane antigen (30%), and actin (20%).117-123 Desmin, cytokeratin, and S100 are usually absent.117 Recently, NAB2/STAT6 was identified in solitary fibrous tumors, strongly suggesting that this type of tumor is a translocation-associated neoplasm and that STAT6 immunostain is a sensitive and specific marker for solitary fibrous tumor.124,125

**Other Rare Considerations**

GIST in the retroperitoneum is rare: One case report has been documented in the literature,126 Characteristic immunostain pattern of CD117, CD34, and DOG1 immunoreactivity is helpful in confirming the diagnosis.46 Ewing sarcoma in the retroperitoneum is also rare. Hallmark translation (EWSR1/FLI1 or EWSR1/ERG) detection is helpful in confirming Ewing sarcoma in the majority of cases.46

Retroperitoneal desmoid tumor has been described in 11 articles since 1991.127-135 These tumors are characterized by proliferation of spindle (fibroblast) cells, with a moderate amount of collagen fibers, bland cellular appearance, scant mitosis, and lack of metastasis.130,135 Expression of beta catenin in tumor cells is helpful for confirming the diagnosis.18

Most sporadic cases of aggressive fibromatosis contain a somatic mutation in either APC or CTNNB1.128 Lazar et al138 reported 3 discrete mutations (ACC-41GCC, TCT45TTT, and TCT45CCT) in 2 codons of CTNNB1 exon 3. Targeted therapy for desmoid tumor/ fibromatosis may be a potential treatment option in the future.135

Retroperitoneal lipoma is a rare benign tumor of mature adipocytes occurring in the retroperitoneum. Eighteen cases of retroperitoneal lipoma have been described in the literature since 1980.139-155 Retroperitoneal lipoma may not be distinguishable from well-differentiated liposarcoma on imaging and findings on biopsies are often inconclusive. Molecular testing is recommended to support a diagnosis of retroperitoneal lipoma confirming the absence of MDM2 amplification; however, a negative result does not exclude the possibility of well-differentiated liposarcoma. Amplification varies in individual tumors and among different cells in the same tumor. Additional research is necessary to understand the etiology and genetic mechanisms of retroperitoneal lipomas. Close and regular follow-up is recommended for such cases.

**Conclusions**

When a definitive diagnosis of retroperitoneal sarcoma, including its histological tumor type and grade, is achievable, then such a diagnosis can help provide useful prognostic and predictive information to help guide effective therapy. However, not all tumors of the retroperitoneum must be biopsied, subjected to work up by ancillary testing, or both methods to achieve a definitive diagnosis. Certain tumor types may call for specific neoadjuvant therapeutic regimens that might produce excellent responses, thus warranting a definitive diagnosis with judicious ancillary testing. By contrast, other tumor types may share similar therapeutic regimens, but neoadjuvant therapy may not provide any benefit to the patient. In such cases, an informative diagnosis should be rendered as an alternative, which includes meaningful and useful information to guide the next best step in management, especially when there is a small amount of tissue on biopsy available for analysis. A definitive diagnosis can be deferred and then be rendered at resection following a full examination of the entire tumor. This type of multidisciplinary, pathology-focused approach is practical and, in our experience, works well to serve the needs of patients with retroperitoneal sarcoma.

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**References**


