Genitourinary Sarcomas

Editors:

Reza Mehrazin, MD

Authors:

Reza Mehrazin, MD; Timothy F. Donahue, MD; Bobby Liaw, MD; Edward Y. Kim, MD; Christopher P Scally, MD; Joseph Jacob, MD; Christina L. Roland, MD

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1. Introduction

Soft tissue sarcomas arise from tissues of mesodermal origin and by themselves are rare tumors, comprising approximately 1% of all cancers.[1] Twenty percent of soft tissue sarcomas arise from the abdomen or retroperitoneum[2] with genitourinary sarcomas accounting for 2% of all soft tissue sarcomas and 1-2% of malignant tumors of the genitourinary tract.[3,4] The **spermatic cord and para-testicular tissue are the most common sites for genitourinary sarcomas** , representing about 45% of cases.

Individuals with certain germline mutations and syndromes such as Succinate Dehydrogenase (SDH) mutations, Li-Fraumeni syndrome, Familial adenomatous polyposis, Carney-Stratakis syndrome, hereditary retinoblastoma, and neurofibromatosis are at increased risk of developing sarcomas[5,6,7] (**Table 1**). Treatment of other malignancies with chemotherapy and radiation can increase the risk of developing sarcomas. Increasing radiation doses and treatment with cyclophosphamide increases the relative risk of developing a sarcoma later in life. This has been documented in the treatment and follow-up of childhood malignancies.[8,9,10,11]

The rarity of these tumors limits the ability to conduct clinical trials. Therefore, genitourinary sarcoma management is based primarily on single institution reports, registry data, and extrapolation of principles established in other soft tissue sarcomas. **Significant risk factors for tumor recurrence and progression** have been identified primarily from experience with sarcomas of the extremities and **include tumor grade, size, depth of invasion, and surgical margin status**.

The **fundamental principal of therapy** for patients with localized genitourinary soft tissue sarcomas is **complete surgical resection with grossly negative margins, denoted as an R0 resection**.[2] Patients who present with metastatic disease have a poor prognosis even when managed with combinations of surgery, systemic chemotherapy, and radiation therapy. Approximately 50% of patients will die of their disease by 2 years,[12] with sarcoma survival rates that have changed very little over time.[13]

Table 1. Risk Factors for Sarcomas

Syndromes	Li-Fraumeni Familial adenomatous polyposis Carney-Strakis Hereditary retinoblastoma Neurofibromatosis
Germline Mutations	SDH
Other	Radiation Exposure to chemicals Cyclophosphamide

2. Retroperitoneal sarcomas

2.1. Epidemiology

Retroperitoneal sarcomas are rare tumors, within an expected incidence of 0.5-1 new cases per 100,000 inhabitants per year.[14] There are more than 140 subtypes of soft tissue, sarcoma. However, within the retroperitoneum, **five main histologic goal subtypes account for 90% of the tumors including liposarcoma, leiomyosarcoma, solitary fibrous tumor, undifferentiated pleomorphic sarcoma and malignant peripheral nerve sheath tumors**.

2.2 Evaluation & Diagnosis

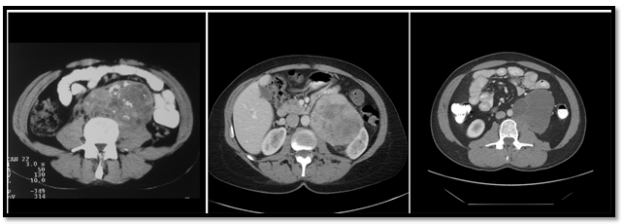

Figure 1: Percutaneous biopsy is critical to determine differential diagnosis of retroperitoneal abdominal soft tissue masses.

The initial evaluation of a retroperitoneal mass includes a detailed history and physical with specific emphasis on changes in weight, bowel function, and asking a patient if they have a personal or family history of Li-Fraumeni syndrome and neurofibromatosis, given the associated risk of multiple sarcomas at various locations with these syndromes. **Cross-sectional staging imaging studies including chest, abdominal and pelvic CT with oral and intravenous contrast should be performed with or without an abdominal pelvic MRI** .

The differential diagnosis of retroperitoneal abdominal soft tissue masses includes malignant lesions (such as soft tissue sarcoma, gastrointestinal stromal tumors, lymphoma or germ cell tumors), desmoid fibromatosis and benign lesions such as nerve sheath tumors. Often, the imaging characteristics overlap (**Figure 1**) and the primary treatment modality varies considerably depending on the diagnosis (i.e. systemic chemotherapy for lymphoma, consideration of observation for schwannoma and surgical resection for sarcoma). Therefore, a **pretreatment biopsy should be performed prior to initiating treatment or surgical resection**. **Image guided core biopsy** is safe[15] and preferred over open surgical biopsy.[16,17] Pathologic assessment of biopsies should be carried out by an experienced sarcoma pathologist and final impression should include the **specific histologic subtype and tumor grade**.

2.3 Staging

The updated AJCC Cancer Staging Manual (8th Ed.)[18] separates sarcoma staging according to anatomic primary site in addition to histologic subtype, grade and tumor size (**Table 2**). The T category is assessed by measuring the largest diameter of the tumor in any plane. Regional nodal metastases are uncommon but are considered suspicious in the case of enlarged, rounded or necrotic appearing lymph nodes. **Lymph node biopsy is recommended for suspicious lymph nodes to confirm lymph node involvement.** Comprehensive grading of soft tissue sarcomas utilizes the grading system of the French Federation of cancer Center sarcoma group **(FNCLCC), a 3-tiered system based on tumor cell differentiation, mitotic activity and extent of necrosis**.[19]

Table 2a: TMN Staging for Soft Tissue Sarcoma of the Retroperitoneum (8th ed, 2017)[15]	
Primary Tumor (T)	
pTx	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
T1	Tumor 5 cm or less in greatest dimension
T2	Tumor more than 5 cm and less than or equal to 10 cm in greatest dimension
T3	Tumor more than 10 cm and less than or equal to 15 cm in greatest dimension
T4	Tumor more than 15 cm in greatest dimension
Regional Lymph Nodes (N)	
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastases
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 2b: Definition of Grade FNCLCC Histologic Grade	
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7, or 8

Table 2c: Anatomic Stage/Prognostic

	T	N	M	G
IA	T1	N0	M0	G1, GX
IB	T2, T3, T4	N0	M0	G1, GX
II	T1	N0	M0	G2, G3
IIIA	T2	N0	M0	G2, G3
IIIB	T3, T4	N0	M0	G2, G3
IIIB	Any T	N1	M0	Any G
IV	Any T	Any N	M1	Any G

2.4 Treatment

Anatomic constraints in the retroperitoneum limit the ability to achieve wide resection margins, making **local recurrence the leading cause of death**. However, the risk of local and distant recurrence varies by histologic subtype[19] (**Table 3**). For example, **low-grade liposarcoma almost exclusively recurs locally whereas high-grade leiomyosarcoma is prone to distant metastases with a much lower risk of local recurrence**.

Table 3: Outcomes for Primary Retroperitoneal Sarcoma by histologic subtype. Overall survival (OS), local recurrence (LR) incidence (B), distant metastasis (DM) incidence. [Adopted from Gronchi A. et al.) [19]

	5-yr OS (%)	5-yr LR (%)	5-yr DM (%)
Well-Differentiated Liposarcoma	87.4	18.6	0
Dedifferentiated Liposarcoma (grade II)	54	44.4	9.5
Dedifferentiated Liposarcoma (grade III)	40.8	33.2	44.1
Leiomyosarcoma	57.6	5.8	55.6
Malignant peripheral nerve sheath tumor	66.7	20	12.5
Solitary Fibrous Tumor	85	4.2	17.1
Other	51.8	20.4	37.1

Treatment decisions should be made by a multidisciplinary team with expertise and experience in sarcoma diagnosis and management. Management of retroperitoneal sarcoma in specialist sarcoma units is associated with reduced risk of early postoperative morbidity and with a reduced risk of postoperative mortality.[20-21] Surgical resection remains the only potentially curative treatment for retroperitoneal sarcoma, although the use of adjuvant radiation therapy or chemotherapy are considered for tumors at risk for local or distant recurrence. **The best chance for resection with curative intent to succeed is at the time of primary presentation. Complete en bloc gross resection is the cornerstone of management** and often necessitates multi-visceral resection. Detailed review of preoperative imaging should be performed to evaluate for proximity of the tumor to critical nerve, vascular structures, and bone. Preservation of specific neighboring organs should be considered on an individualized basis but **resection of all gross disease en bloc is essential for long-term survival**. Grossly incomplete resection of retroperitoneal sarcoma is of questionable oncologic benefit but may be undertaken as a palliative procedure in carefully selected patients.

While radiotherapy has a well-defined role in the management of extremity soft tissue sarcomas, the role for radiotherapy in retroperitoneal sarcomas is less well defined. Single institution retrospective series have reported favorable local control rates with the combination of surgery and radiotherapy.[22-23] **However, the only randomized phase 3 trial to examine the role of radiation in RP sarcomas (EORTC STRASS)[24] reported no difference in abdominal relapse free survival with the addition of radiation when considering all histologic subtypes**. On post-hoc sub-group analysis, in well-differentiated liposarcoma, patients treated with radiation had an improved 3-year abdominal relapse-free survival of 71.6% vs. 60.4% compared to those not treated with radiotherapy suggesting a potential benefit from radiotherapy in carefully selected **patients with well-differentiated retroperitoneal liposarcoma**.

Preoperative radiotherapy/neoadjuvant radiation is preferred over post-operative treatment as the tumor often displaces radiosensitive organs such as bowel or kidney away from the irradiated field, which may reduce the morbidity of treatment. The proximity of the field to the small bowel after surgical resection generally precludes receipt of radiation.

There are few available randomized trials comparing neoadjuvant chemotherapy to resection alone for retroperitoneal sarcoma. However, referral to medical oncology is recommended for consideration of neoadjuvant chemotherapy, particularly for cases that appear technically borderline or unresectable or for tumors that are particularly chemosensitive, such as synovial sarcoma and high-grade leiomyosarcoma (discussed in Section 6). EORTC1809/EA7211 (**STRASS2**) is an on-going randomized phase III study of neoadjuvant chemotherapy followed by surgery alone for patients with high risk retroperitoneal leiomyosarcoma and liposarcoma, that is currently accruing in Europe, Australia and Canada. Preliminary results are expected in 2025 and is a first step to address the question of neoadjuvant chemotherapy in this patient population.

Median time to recurrence, after surgical resection, of high-grade retroperitoneal sarcoma is less than 5 years, however recurrence after grossly complete resection of retroperitoneal sarcoma has been reported up to 20 years after initial resection (**Figure 1**) Current NCCN guidelines[15] recommend physical exam with chest and abdominal/pelvic imaging every 3-6 months for 2-3 years, then every 6 months for the next 2 years, then annually.

3. Paratesticular or Spermatic Cord Sarcomas

3.1 Epidemiology

The spermatic cord and paratesticular tissues are the most common sites for sarcomas of the genitourinary tract, accounting for approximately 45% of GU-related sarcomas.[24] Spermatic cord or paratesticular sarcomas arise from the **mesodermal-derived cord structures** that lie within and around the cord structures with its investing layers of fascia and cremasteric muscles. The most common histologic subtypes include liposarcoma, leiomyosarcoma, rhabdomyosarcoma, fibrosarcoma, and undifferentiated pleomorphic sarcoma (UPS) previously known as malignant fibrous histiocytoma (MFH).[25] **Liposarcomas or leiomyosarcomas are the most common histology in adults while rhabdomyosarcomas are the most common in children** .

3.2 Evaluation & Diagnosis

In adults, spermatic cord and paratesticular sarcomas often present as a unilateral painless, firm mass in the inguinal canal or scrotum and may be mistaken for a benign growth such as a lipoma or fat-containing hernia during inguinal surgery. These tumors **are distinct from the testicle** (hence **paratesticular mass**) and **do not transilluminate** on physical exam (see Core Curriculum Section: **Testis Neoplasms**). **Sonography can distinguish** whether a mass is intra- or paratesticular with excellent sensitivity, but a high index of suspicion is warranted to include spermatic cord tumor in the differential diagnosis. Radiographic characteristics differ across histologic subtypes of spermatic cord and paratesticular sarcomas, but it is not possible to differentiate subtype by ultrasound alone (see Core Curriculum Section: **Ultrasound**). In general, a **heterogeneous appearance and hypervascularity** is suggestive of a sarcoma compared to a benign lesion.[26-27] While most spermatic cord sarcomas present as asymptomatic masses, the tumors formerly referred to as Malignant Fibro Histiocytoma (MFH), now described as Undifferentiated pleomorphic sarcoma (UPS) and myxofibrosarcoma (MFS) are unique in that they may present as a **painful** mass.[28] (For GU rhabdomyosarcomas and testicular tumors in pediatrics, see Core Curriculum Sections: **Genitourinary Oncology**)

3.3 Treatment

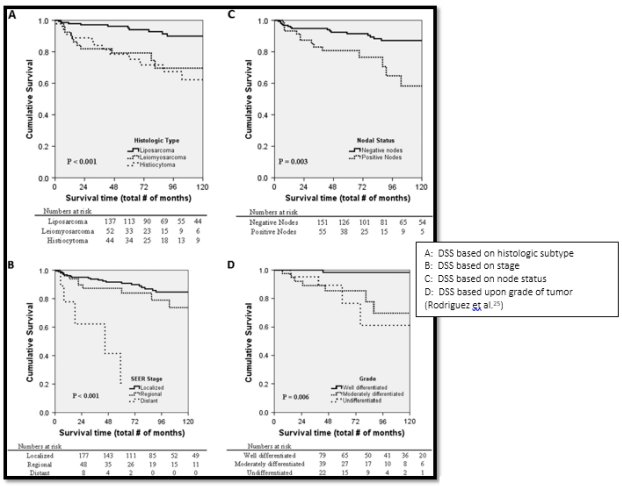

Figure 2: Differences in survival rates have been reported based upon histology, local and regional versus metastatic disease, tumor grade, and lymph node involvement. Liposarcomas are associated with the best disease-specific survival rates at 5 and 10 years (95% and 90%, respectively), followed by leiomyosarcoma (77% and 66%, respectively), while histiocytomas have the worst survival (77% and 61%, respectively; p<0.001). Those with local and regional disease have better DSS at 5 and 10 years (91% to 83% and 86% to 73%, respectively) compared to those with distant disease (33% to 33%; p<0.001). Well differentiated tumors have better DSS at 5 and 10 years (95% and 90%) compared to moderately and undifferentiated tumors (84% to 70% and 88% to 56%, respectively; p<0.009). Similarly, lymph node involvement is associated with worse survival (91% to 87% versus 78% to 57% at 5 and 10 years, respectively; p<0.001[25]). Used with permission

Surgical management of soft tissue sarcomas requires complete surgical resection with gross and microscopic negative margins. Soft tissue sarcomas are commonly incidentally discovered; therefore, the diagnosis may be confirmed on final histology. As such, many patients do not undergo an initial wide local resection of the tumor and may have positive margins. Thus, wide local reresection including radical inguinal orchiectomy is advocated for patients with incidentally discovered spermatic cord or paratesticular sarcomas.[2] The recommended surgical approach in this setting involves extending the initial resection **from the level of the internal ring to the ipsilateral scrotum, removing all cord remnants and adjacent soft tissues, including en bloc excision of the overlying skin and scar from the first surgery**. The internal ring is opened and the immediate soft tissue and fat removed with the goal of widely excising the at-risk mesodermal-derived layers. A hemiscrotectomy is performed if the initial tumor involved the skin or if the original specimen was removed via a trans-scrotal approach. [24] When operating, it is important to recognize that the **underlying disease represents a field defect** rather than a process involving just the visualized and palpable mass; therefore **wide resection of local soft tissues to achieve a negative margin is paramount to minimize the risk of local recurrence**.

Murray et al.[24] reported on outcomes in 72 patients with surgically managed localized spermatic cord or paratesticular sarcomas. Wide reresection was performed in 48 (67%) of patients. Lack of receipt of wide re-resection was associated with a 30.7% (95% CI 9.8%-51.7%) reduction in recurrence-free survival at 2 years (44.1%; 95% CI 19.9%-68.3% at 5 years) (p<0.0001). In this cohort, **positive surgical margins on the pathologic specimen obtained at reresection were strongly associated with both disease recurrence (HR 5.56, 95% CI 1.14-27.11; P=0.034) and cancer-specific death** (HR 6.16, 95% CI 1.25-30.29; P=0.025).

A systemic retrospective review of 178 patients with paratesticular liposarcoma showed that those who underwent high inguinal orchiectomy had significantly higher rate of recurrence free survival, compared to those who underwent simple tumorectomy. Similar to prior reports, microscopic positive surgical margin was a risk factor for recurrence. They also reported that adjuvant radiation therapy had no statistically significant effect on recurrence-free survival, even in subgroup analysis of patients with positive margins.[29]

Pathologic features associated with risk of recurrence include histology, positive margins, tumor size, inguinal location, depth of invasion (Figure 2).[30] **Tumor grade does not have a significant influence of local recurrence, with low grade tumors recurring as often as high grade**.[30] The **pattern of tumor spread is primarily local** with contiguous spread along the cord through the inguinal canal into the abdomen/retroperitoneum. **Lymphatic and hematogenous spread are extremely rare in spermatic cord and paratesticular sarcoma.** Therefore, lymphadenectomy should not be routinely performed without documented evidence of lymph node involvement. One exception to this rule is rhabdomyosarcoma which has a **higher propensity for both lymphatic and hematogenous spread**. Thus, unilateral pelvic and retroperitoneal lymph node dissection is recommended in the case of **rhabdomyosarcomas**.[31-32]

Local recurrence rates after surgery alone are as high as 50% in some series,[33,34,35,36,37] which has generated interest in the role of adjuvant radiation therapy for these patients. Prospective, randomized data from patients with soft tissue sarcomas of the extremities where **adjuvant radiation** was performed after surgery **demonstrated improvements in rates of local recurrence but not overall survival**.[34,35,36,37,38,39] Similarly, observational reports in patients with spermatic cord and soft tissue sarcomas treated with adjuvant radiation therapy suggest a benefit in terms of local control but not overall survival. Advocates for radiation therapy recommend 60-65 Gy administered over six weeks to the inguinal canal, ipsilateral nodes and adjacent pelvic tissues, and ipsilateral hemiscrotum.[37,38,40,41]

Currently, there is no defined role for chemotherapy in patients with spermatic cord and paratesticular sarcomas with the exception of pediatric rhabdomyosarcomas where response rates have been demonstrated with the combination of vincristine, cyclophosphamide, and doxorubicin. Routine adjuvant chemotherapy is not recommended for patients with spermatic cord sarcomas and has been limited to the palliative or salvage setting in patients with metastatic disease.

Due to high recurrence rates, patients with spermatic cord and paratesticular sarcomas should be surveilled closely after surgery, especially over the first 3-5 years after initial treatment. Imaging of the chest with a plain radiograph and cross-sectional imaging with CT or MRI of the abdomen and pelvis to include the primary site of disease should be performed every 3-6 months for the first 2-3 years after surgery, every 6 months for the next two years, and then annually. For patients with radiographic evidence of disease recurrence, imaging of the known sites of disease should be performed every 2-3 months. The interval between imaging is eventually extended but lifelong periodic imaging is recommended since late recurrences at 15 years and beyond have been reported. [40] Follow up evaluations include physical exam, chest x-rays, cross-sectional imaging, and other studies as indicated by the presence of symptoms.

4. Adult Prostate Sarcomas

4.1 Epidemiology

Prostate sarcoma originates from the prostate stroma rather than glandular elements, which give rise to the more common adenocarcinoma. Prostate sarcomas are rare and account for less than 0.1% of all primary prostate malignancies.[12] These tumors are divided into different histologic subtypes, including **prostate leiomyosarcoma, rhabdomyosarcoma, fibrosarcoma, and spindle cell sarcoma** (in descending order of frequency). **Prostate stomal lesions that do meet the diagnostic criteria for sarcoma have been designated as prostate STUMP (stromal tumor of unknown malignant potential)**.[42]

4.2 Evaluation & Diagnosis

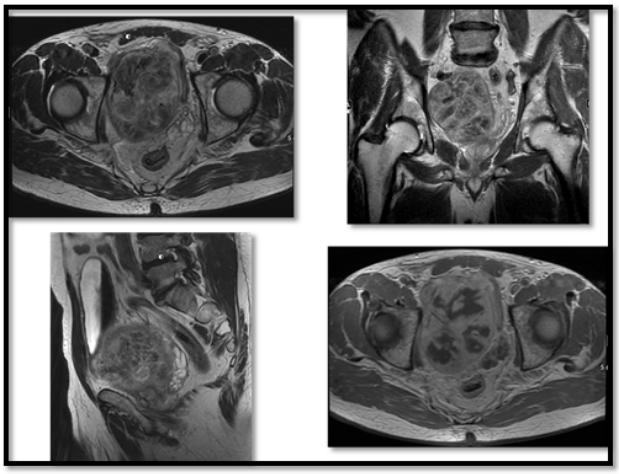

Figure 3: MRI of Prostate sarcoma
Images courtesy of H. Alberto Vargas-Alvarez, M.D.

Patients with prostate sarcoma often present with signs and symptoms associated with **urinary obstruction**. Perineal pain, hematuria, ejaculatory pain, constipation, and weight loss are commonly reported as well. The **serum PSA is often normal**, as expected due to the non-epithelial origin of the tumor. Tumors can be quite large at the time of initial presentation (**Figure 3**) and the diagnosis of often made at the time of prostate biopsy or transurethral resection. [12,43,44] Most prostate sarcomas have a very aggressive clinical course and the prognosis remains poor with most patients having a very short overall survival.[43,44]

4.3 Treatment

Similar to spermatic cord sarcomas, management of this rare tumor is based upon small case series from institutions, registry data, and extrapolation from experience with other sarcomas. The **most important prognostic factors for survival are (1) achieving negative surgical margins** at the time of resection and (2) the **absence of metastases at initial presentation**. **Tumor size, grade, and histologic subtype do not appear to influence overall survival, which is typically less than a year in most patients**.[45,46] Outcomes in adults contrast with the experience with rhabdomyosarcomas in children in which the prognosis associated with this tumor is better compared to other subtypes and where chemotherapy has an established effective role. Musser et al. reported on 38 patients with prostate sarcomas over 30 years at their institution. Leiomyosarcoma (34%) and rhabdomyosarcoma (32%) were the most common tumor types with rhabdomyosarcoma having lower CSS (HR 3.00; 95% CI 1.13-7.92; p=0.027) than was observed in

leiomyosarcoma. [44] Of these 38 patients, 19 (50%) were treated surgically. All patients with positive surgical margins (3 of 19) experienced recurrence and died due to disease progression. Neoadjuvant chemotherapy and radiation therapy were used in 12 patients with localized disease to downsize the tumor to facilitate surgical resection. Seventeen patients presented with metastatic disease and were treated with protocols including vincristine, dactinomycin, cyclophosphamide (VAC), or mesna, Adriamycin, ifosfamide, dacarbazine (MAID) although no durable response was seen with any systemic therapies. Fifteen of 17 patients died of disease, while the remaining two with disease progression were lost to follow up at 11 and 13 months. Consolidative surgery was attempted in 8 patients with limited metastatic disease. All eight patients progressed systemically and died of disease at a median of 1.7 years after surgery. For this reason, these authors caution against consolidative surgery in patients who present with metastatic disease. In this series, overall median CSS was 2.9 years with 7.7 years for those with clinically localized disease and 1.5 years for patients presenting with metastatic disease. [46]

5. Adult Bladder and Renal Sarcoma

5.1 Epidemiology

There is a paucity of literature regarding adult sarcomas of the bladder, kidney, and ureter. Men appear to be more commonly diagnosed with sarcoma of the bladder and kidney with a significantly higher prevalence seen in Whites as compared to Blacks and Hispanics.[47-48] Bladder sarcomas do not appear to be as highly associated with a history of smoking compared to urothelial carcinoma.[49] In a SEER database study that analyzed approximately 3,000 patients with genitourinary sarcoma, bladder sarcomas accounted for 27% of cases. Kidney sarcomas accounted for 25% of cases while ureteral sarcomas were exceedingly rare. [47-50] In a large institutional study, ureteral sarcoma only accounted for 1 case of the 131 genitourinary sarcomas diagnosed over 25 years.[1]

5.2 Evaluation & Diagnosis

All patients should undergo a thorough history and physical exam. Most patients are symptomatic and present with **gross hematuria, local urinary symptoms, pain, or microscopic hematuria**.[49] Complete clinical staging includes a CT of the chest, abdomen, and pelvis with intravenous contrast. Image-guided core needle biopsy is recommended to obtain a diagnosis prior to definitive treatment. Genetic counseling or germline genetic testing are not recommended on a routine basis. Histologic evaluation by an experienced pathologist is critical and can be augmented with molecular testing such as fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR).

Various bladder and kidney subtypes of sarcoma have been described. The **most frequently described subtypes of renal sarcomas are leiomyosarcoma and liposarcoma. Carcinosarcoma appears to be the most commonly described sarcoma of the bladder followed by leiomyosarcoma**.[13,47,48]

Similar to all sarcomas, the prognosis of bladder and renal sarcomas is primarily associated with stage and the completeness of the resection.[1,2,47,51] Low grade soft tissue sarcomas of the kidney such as leiomyosarcoma and low grade liposarcoma exhibit limited metastatic potential but have a high rate of local recurrence. **Certain renal sarcoma subtypes such as high-grade rhabdomyosarcoma, vascular sarcoma, clear cell sarcoma, and epithelioid sarcoma have a predilection for lymph node metastasis**. Other subtypes such as **PNET and Ewing's sarcoma are considered systemic conditions** based on their high rates of metastatic disease.[51]

Carcinosarcoma or sarcomatoid carcinoma of the bladder is a rare malignancy defined by the presence of malignant epithelial and mesenchymal elements. Although histogenesis is unclear, these tumors are generally considered to be in the sarcoma family and usually present with **extravesical disease and have a 5-year cancer specific survival of 20%**. Median cancer-specific survival was only 14 months in a SEER database analysis and only stage was associated with CSS. [52,53] In the largest available institutional series, the positive margin rates for renal and bladder sarcomas were 32-86%. Unfortunately, the associated prognosis was extremely poor with 40-75% of patients found to be dead of disease at last follow-up.[13,48]

5.3 Treatment/Surveillance

Treatment of bladder and renal sarcomas should follow the same oncologic principles applied to other abdominal soft tissue sarcomas. Due to the small amount of data describing the treatment of bladder and renal sarcomas, no specific organ site recommendations can be made. **Similar to all sarcomas, complete resection with negative surgical margins should be the goal of therapy as margin status is significantly associated with oncologic outcomes. The NCCN guidelines recommend complete surgical resection with or without intraoperative radiation**. Preoperative chemotherapy and/or radiotherapy can be considered to facilitate an R0 resection. **Re-resection is recommended for local recurrence**. Since recurrence rates are high, recommended surveillance is intensive: the NCCN guidelines recommend cross-sectional imaging every 3 to 6 months for the first 2 to 3 years and every 6 months for the next 2 years, then annually thereafter (see reference PDF **here**).[15]

6. Systemic Therapy Options for Sarcoma:

Due to the scarcity of genitourinary soft tissue sarcomas (GU STSs) cases, there are limited prospective data as it comes to optimally guiding the use of systemic therapy in this heterogenous group of rare tumors. As en-bloc complete surgical resection with negative margins still offers the best chance at cure, **GU STSs remain primarily surgically managed**. Guidance on use of systemic therapy in the neoadjuvant and adjuvant settings to improve upon surgical outcomes come primarily through extrapolation of data from STS of other sites, or through retrospective data analyses. **The choice of chemotherapeutic regimen in the management plan for GU STS, whether in the peri-operative arena, or for recurrence/metastasis, depends mostly on sarcoma histology, rather than the site of GU primary**. The most common histologies reported in GU sarcomas are leiomyosarcoma, liposarcoma, rhabdomyosarcoma, for which the systemic management options are discussed here (**Table 4**).

Table 4. Incidence and recommended systemic therapy options based on different subtype.

Histology	Incidence (n/year)	Systemic Therapy	
Liposarcoma	0.5-1/100,000 persons (~2,000/year in US) 60%	Neoadjuvant/Adjuvant*	Metastatic
Well-Differentiated		none	palbociclib
Dedifferentiated		doxorubicin +/- ifosfamide	doxorubicin +/- ifosfamide Trabectedin Eribulin pazopanib
Leiomyosarcoma	15%	doxorubicin +/- dacarbazine or Ifosfamide	doxorubicin +/- dacarbazine or Ifosfamide gemcitabine/docetaxel Trabectedin pazopanib
Rhabdomyosarcoma	<5%	Vincristine/dactinomycin/cyclophosphamide (VAC)	vincristine/dactinomycin/cyclophosphamide (VAC) vinorelbine/cyclophosphamide topotecan/cyclophosphamide
Other high-grade RP Sarcoma (UPS, MPNST)	20%	doxorubicin +/- ifosfamide	doxorubicin +/- ifosfamide
Solitary Fibrous Tumor	5%	none	Temozolomide + bevacizumab

6.1 Leiomyosarcoma

6.1.1 Adjuvant

Adjuvant chemotherapy has demonstrated limited utility in the setting of leiomyosarcoma of uterine and other soft tissue origin. These experiences provide some insights regarding the utility of adjuvant chemotherapy in GU leiomyosarcomas.

A study of 6 months of adjuvant doxorubicin in stage I and II uterine sarcomas, for which the majority were leiomyosarcomas, showed no significant improvement in PFS or OS.[54] Another study of 4 cycles of adjuvant gemcitabine/docetaxel in high-grade uterine leiomyosarcoma yielded 2-year PFS rates that appeared superior to historical controls,[55] but the lack of a control arm makes these findings difficult to interpret. Some promising data for 2- and 3-year PFS was shown in the phase II SARC 005 study, by intensifying the adjuvant regimen to 4 cycles of gemcitabine/docetaxel followed by 4 cycles of doxorubicin.[56] However, the phase III study of this regimen suffered from poor enrollment, limited analysis of available study data did not show a superior outcome to OS or RFS with adjuvant chemotherapy as compared to observation alone.[57]

A 2008 meta-analysis of localized soft tissue sarcoma of the extremity and trunk demonstrated improvement in local, distant, and overall recurrence, as well as overall survival with doxorubicin and ifosfamide-based adjuvant chemotherapy.59 However, there are limited data regarding the benefits of systemic chemotherapy for patients with intra-abdominal or retroperitoneal sarcoma. Inclusion of chemotherapy in the multidisciplinary management of high-grade STS >5cm may be considered, as these tumors have a propensity for distant recurrence, rather than local relapse (**Figure 1**).

6.1.2 Neoadjuvant

Neoadjuvant chemotherapy can be considered in patients with localized leiomyosarcomas not amenable to upfront surgical resection, although the benefits of neoadjuvant chemotherapy are unclear. Anthracycline- and **ifosfamide-based regimens** are predominantly considered for neoadjuvant use. These cases are best discussed in a multidisciplinary setting, as concurrent neoadjuvant radiation therapy may also be considered to reduce local recurrence. Sequential vs. concurrent use of chemotherapy and radiation therapy remains controversial and utilization is institution-dependent.

6.1.3 Metastatic

Doxorubicin-based regimens are typically considered in the first-line setting for treatment of metastatic leiomyosarcomas, although gemcitabine-based regimens can be used in those who have contraindications to use of an anthracycline. The phase III GeDDiS trial randomized patients with unresectable or metastatic soft tissue sarcomas to receive either gemcitabine/docetaxel or doxorubicin as first-line therapy, with similar PFS and OS observed in both arms. 58 Multiple antineoplastic agents demonstrate activity in metastatic leiomyosarcoma in the second-line setting and beyond, with varying degrees of responsiveness and durability of disease control. Trabectedin, dacarbazine, ifosfamide, temozolomide, and pazopanib all have data to support its use.

6.2 Liposarcoma

6.2.1 Neoadjuvant/Adjuvant

The different subtypes of liposarcoma respond variably to chemotherapy, leading to subtype-specific recommendations for neoadjuvant and adjuvant therapy. In a retrospective analysis of 88 liposarcoma patients that received first-line chemotherapy, a significantly **higher response rate was observed in myxoid liposarcoma, as compared with well-differentiated and dedifferentiated liposarcomas** (48% vs. 11%).[59] This finding has been replicated in other studies evaluating myxoid and round cell subtypes.[60-61] The relative chemosensitivity of myxoid and round cell liposarcomas to chemotherapeutic agents such as doxorubicin and trabectedin has resulted in increased consideration for peri-operative chemotherapy use, although the published clinical experience remains inconclusive. **Decisions on whether neoadjuvant or adjuvant chemotherapy should be employed in myxoid/round cell liposarcoma cases should be evaluated in a multidisciplinary setting, and individualized based on patient risk and clinical context** .

Given the **poor response rates seen with well-differentiated and dedifferentiated liposarcomas to systemic therapies**,[59] neoadjuvant/adjuvant use of chemotherapy in these patients is not strongly recommended. Pleomorphic liposarcomas exhibit similar histologic findings and response to treatment as undifferentiated pleomorphic sarcomas, and in that context, neoadjuvant/adjuvant therapy with doxorubicin/ifosfamide, can be considered on an individualized basis.

6.2.2 Metastatic

Doxorubicin-based regimens are used in the metastatic setting as first-line therapy across liposarcoma subtypes. In the second-line setting, there are high response rates of myxoid/round cell liposarcomas to trabectedin,[62] although it has demonstrated efficacy and improved disease control over dacarbazine across all liposarcoma subtypes in phase III testing.[63] Eribulin was associated with an OS benefit vs. dacarbazine in a phase III trial that enrolled both leiomyosarcoma and liposarcoma patients.[64] Subgroup analysis validated the finding that eribulin is associated with improved OS across all liposarcoma subtypes.[65]

Other systemic options that have demonstrated efficacy include gemcitabine-based regimens, dacarbazine, ifosfamide, and pazopanib.

6.3 Rhabdomyosarcoma

6.3.1 Neoadjuvant/Adjuvant

The management of rhabdomyosarcoma in adults is similar to that in the pediatric population, where it is a relatively more prevalent disease, and data from randomized trials have shaped the standard of care. In children, the prognostic risk groups for rhabdomyosarcoma are determined by age, size,

stage, presence of nodal and metastatic involvement, and site of primary tumor. **Paratesticular rhabdomyosarcoma is considered a favorable primary site, whereas bladder, prostate, retroperitoneum, and pelvis are considered unfavorable. Systemic chemotherapy plays an important role in the management of localized disease, as local therapy with surgery or radiation alone is associated with low rates of long-term survival**. The selection of chemotherapy regimen is dependent on prognostic risk group in the pediatrics population. The chemotherapy regimen depends on the pediatric prognostic risk group. Those with low risk disease and excellent prognosis have the option of reduced dose chemotherapy regimens to minimize toxicity. [66-67]

All adults with genitourinary rhabdomyosarcomas, regardless of the site of primary, are considered poor risk due to their age. As such, they are at high risk for relapse and multidrug chemotherapy regimen as well as clinical trial participation is recommended. Outside of a clinical trial the **current standard of care for patients in the perioperative period is vincristine/dactinomycin/cyclophosphamide (VAC)**.[68]

6.3.2 Metastatic

There is currently no preferred chemotherapy regimen in the metastatic setting for rhabdomyosarcoma, and **clinical trials should be considered**. Regimens such as VAC, if not previously used in the localized disease setting, may have activity, although treatment associated toxicity and how it impacts QOL would need to be carefully considered. Other regimens such as vinorelbine/cyclophosphamide,[69] topotecan/cyclophosphamide,[70] and vinorelbine monotherapy are other options that may strike a better balance between disease response and toxicity in incurable patients.

Presentations

Genitourinary Sarcomas Presentation 1

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