Leiomyosarcoma

Current Clinical Management and Future Horizons

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KEYWORDS

• Leiomyosarcoma • Soft tissue sarcoma • Uterine sarcoma • Retroperitoneum • Vascular origin • Systemic treatment • Metastasis

KEY POINTS

- Leiomyosarcomas (LMSs) are soft tissue tumors with metastatic potential that arise from smooth muscle fibers, and are derived from organs and venous structures in the pelvis and retroperitoneum.
- Uterine leiomyosarcoma is the most frequent site followed by retroperitoneal LMS.
- Surgery is the main curative treatment, which may involve a multivisceral resection and/or major vascular reconstruction.
- The high rates of metastatic failure that occur after surgical resection has prompted investigation of neoadjuvant systemic treatment strategies, with a current international phase III RCT under recruitment.
- The benefit of adjuvant treatment after surgery is limited.

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INTRODUCTION

Leiomyosarcomas (LMSs) are soft tissue tumors that develop primarily from smooth muscle in visceral organs, such as the uterus or the gastrointestinal tract, and nonvisceral structures, such as large to mid-sized veins and/or dermal pilar smooth muscle in the extremities or trunk. Their behavior has a range of outcomes, primarily based on grade, with a predilection for the development of metastasis.[1] LMSs constitute between 15% and 20% of all newly diagnosed soft tissue tumors in adults.[2]

In this review, the clinical and pathologic characteristics of LMS are described, followed by clinical considerations for the most common sites of disease: retroperitoneum and uterus. Because the development of metastasis is a common challenge, a state-of-the-art review on systemic agents is presented. Finally, future directions for advancing patient care through translational research is discussed.

CLINICAL CHARACTERISTICS OF LEIOMYOSARCOMA

The incidence of LMS increases with age, with a peak at 70 years of age. Uterine LMS (uLMS), however, occurs at a younger age with an increasing incidence at 30 years of age and a peak at 50 years of age, within the perimenopausal age group.[3] Overall, the incidence of LMS by sex varies depending on tumor location. Retroperitoneal leiomyosarcomas (RP-LMSs), particularly of the inferior vena cava (IVC), occur with a higher incidence in women,[4,5] whereas cutaneous and other LMS sites, have a slight male predominance.[6]

Ninety percent of all LMSs arise from intra-abdominal organs, such as the uterus and venous structures of the retroperitoneum (RP-LMS). LMSs account for the third most common soft tissue sarcoma (STS) after gastrointestinal stromal tumor (GIST) and liposarcoma and is the predominant sarcoma arising from large blood vessels. Within intra-abdominal LMS, uLMSs have a higher incidence compared with other RP-LMSs, with an estimated incidence of 0.64 cases per 100,000 women. They are the most common type of uterine sarcomas and account for the single largest site-specific group of LMSs.[7]

RP-LMSs account for the second most common intra-abdominal type of LMS, arising predominantly from vascular smooth muscle, such as midsize vessels including renal veins, iliac or gonadal vessels, or the IVC proper. LMS may also originate from smooth muscle of the gastrointestinal tract, but are less frequent than GIST (ratio of 1:10).[8] RP-LMSs are generally asymptomatic at presentation, although for a minority of patients, their diagnosis is defined by a veno-occlusive episode such as a deep venous thrombosis (DVT).

Extra-abdominal LMSs include tumors that develop in extremities (**Fig. 1**), superficial trunk, and head and neck structures, which account for less than 10% of LMS sites.[9] There is also a subgroup of cutaneous LMSs that originate in the dermis from the arrectores pilorum muscles of the hair follicles and from the smooth muscle surrounding sweat glands, which show a more benign tumor biology compared with deeper sites and may be referred to as "atypical intradermal smooth muscle neoplasms" when confined to the dermis to reflect their minimal metastatic risk.[9,10]

LMS can present as primary disease only or with synchronous metastases, which occurs in 20% of patients and is associated with a 5-year disease-specific survival of approximately 20%.[11] Metastatic disease is also the most common pattern of failure after curative intent treatment for both intra-abdominal and extra-abdominal LMS.[12] Recent data from expert sarcoma centers in Europe and North America report an 8-year crude cumulative incidence (CCI) for distant metastases of 50% in patients with primary retroperitoneal sarcoma (RPS) with LMS, in stark contrast to less than

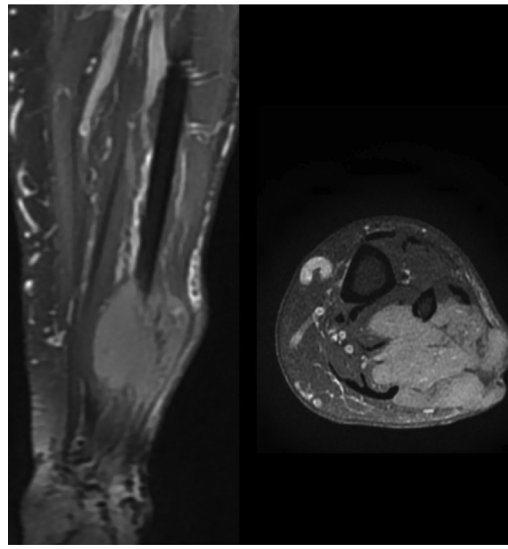

Fig. 1. Deep lower extremity LMS. Coronal and cross-section MRI with LMS involving deep and superficial left lateral compartments of leg.

10% for local recurrence after curative intent treatment.[1] The most frequent sites for first metastases are lung (49%), followed by liver (19%), soft tissue (14%), and bone (5%).[12] Lymph node involvement is exceedingly uncommon (2.7%).[13] Therefore, regional lymphadenectomy as standard of care is generally not indicated, unless clinically evident or radiologically concerning nodal disease is encountered.

Finally, there are genetic predispositions associated with LMS, such as retinoblastoma and Li-Fraumeni Syndrome (LFS). Patients with retinoblastoma have a cumulative risk of 13.1% of developing secondary sarcomas after radiation therapy which are predominately LMS.[14] Patients with LFS have a lifetime LMS incidence of 7% to 8%, which occurs at a median age of 44 years. Exposure to radiation also may increase the risk of developing LMS in these patients; however, most of these are sporadic cases.

PATHOLOGIC AND MOLECULAR CHARACTERISTICS OF LEIOMYOSARCOMA

LMSs are tumors of smooth muscle differentiation, and well-differentiated tumors show typical architecture of smooth muscle with broad fascicles of plump spindle cells intersecting at right angles (**Fig. 2**).[5] Tumors may show varying degrees of hyalinization. Neoplastic spindle cells contain abundant brightly eosinophilic fibrillary cytoplasm, with distinct cell borders and cigar-shaped nuclei. Conventional LMSs also often contain scattered "monster cells" with markedly pleomorphic and hyperchromatic nuclei. More poorly differentiated tumors may show more haphazard fascicular architecture, loss of cytoplasmic eosinophilia, or may become markedly pleomorphic, with loss of histologic evidence of smooth muscle differentiation. Epithelioid and myxoid variants of LMS tend to behave more aggressively, and most commonly arise in the uterus. Rarely, heterologous elements such as fat or bone formation may be seen.

Diagnostic immunohistochemical studies are useful to confirm the diagnosis of LMS in ambiguous cases; generally, at least patchy expression of at least 2 of the following muscle markers are used to confirm smooth muscle differentiation: desmin, smooth muscle actin, muscle actin HHF-35, h-caldesmon, smooth muscle myosin, or calponin

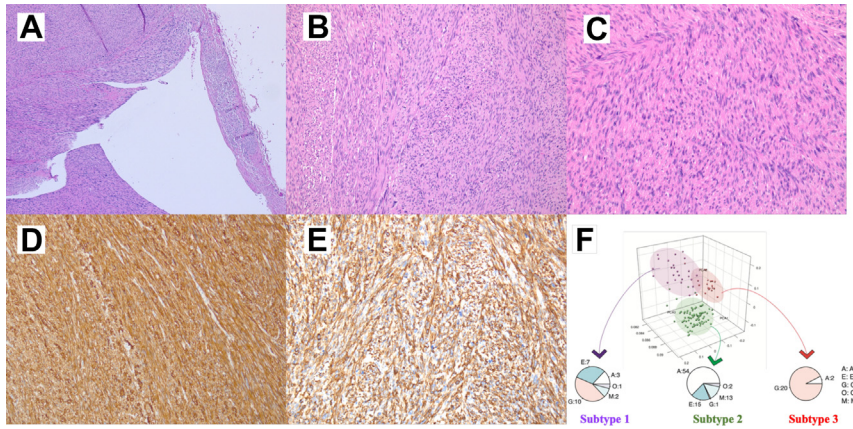

Fig. 2. Histopathologic characterization and molecular subtyping of LMS. (*A*) Low-power view showing a subcutaneous LMS arising in the wall of a small vein (at left) (hematoxylin-eosin [H&E], original magnification ×50). (*B*) Higher-power view of conventional LMS showing intersecting fascicles of brightly eosinophilic spindle cells with abundant cytoplasm and elongated ovoid nuclei. A mitotic figure is visible at center (H&E, original magnification ×100). (*C*) High-power image of conventional LMS showing intersecting fascicles of brightly eosinophilic spindle cells with abundant cytoplasm and elongated, blunt-ended ovoid nuclei (H&E, original magnification ×200). (*D*) Conventional LMS showing diffuse expression of h-caldesmon (original magnification ×100). (*E*) Conventional LMS showing diffuse expression of smooth muscle actin (original magnification ×100). (*F*) Three molecular subtypes of LMS arise following principal components analysis of transcriptomes with anatomic differences.[16]

(see Fig. 2). Immunohistochemical assessment should always be performed on the most well-differentiated appearing area of the tumor, as pleomorphic or dedifferentiated areas may lose all expression of myogenic markers. Keratin and epithelial membrane antigen are seen in up to 40% of these tumors, particularly in high-grade tumors, but is not LMS-specific.[5] Estrogen receptor (ER) and progesterone receptor (PR) expression may be seen in uLMS as well as some nonuterine retroperitoneal LMS arising in women, and rarely in extremity tumors of both sexes, but is often lost in high-grade disease. In some cases, the strong and diffuse expression of ER and PR in well-differentiated smooth muscle tumors of the abdomen/pelvis can be used to help support a diagnosis of leiomyoma of gynecologic origin versus a well-differentiated soft tissue LMS.

Tumor grade for extrauterine LMS should be scored according to the French Federation of Cancer Centers Sarcoma Group system (Federation Nationale des Centers de Lutte Contre le Cancer [FNCLCC]). The FNCLCC system categorizes tumors based on the mitotic rate, extent of necrosis, and degree of differentiation.[15] Pathologic assessment should be performed by an expert in soft tissue sarcomas, as this diagnosis can be complex and access to ancillary molecular testing may be required to secure the correct diagnosis.

LMS has been subject to comprehensive molecular profiling, including whole genome sequencing, RNA transcriptomes, and methylation profiling.[16–18] Overall, it is appreciated to be a genomically unstable tumor with evidence of complex genomic rearrangements, such as chromothripsis, followed by whole genome doubling. Mutations and dysregulation of key tumor suppressors such as TP53, RB1 are early in the molecular evolution of LMS and thus are commonly detected (>90%) with next

generation sequencing. Recently, mutational signature analysis, which examines the processes that drive tumor progression, suggest that LMS may be enriched for defects in homologous recombination (Mut sig 3). Further studies are warranted to validate how prevalent this finding is, but suggests that DNA repair inhibitors may have clinical promise. Finally, comprehensive expression analysis by RNA sequencing by multiple independent efforts has identified 3 molecular subtypes, which are associated with disease outcome, and other disease features such as site and immune involvement[16,17,19,20] (see **Fig. 2**).

- Subtype I LMS: represents a less differentiated form of LMS and partially overlaps in a subset of patients with undifferentiated pleomorphic sarcoma
- Subtype II LMS: expresses most genes associated with smooth muscle differentiation (conventional LMS subtype) with better oncologic outcomes and primarily occurs in the retroperitoneum
- Subtype III LMS: is the only subtype that displays a preference for a specific anatomic site and is more likely to be from the uterus

Ongoing molecular profiling efforts are under way to address what the clinical utility of these subgroups are, along with the development of novel drug therapy that specifically targets DNA damage pathways and/or cell cycle regulation.

RETROPERITONEAL LEIOMYOSARCOMA

Diagnostic Workup

Intra-abdominal/retroperitoneal leiomyosarcomas are characterized by an expansive, non-infiltrative growth pattern.[21] Diagnosis in many patients is incidental after abdominal imaging (computed tomography [CT], MRI), or can be suspected by symptoms related to major venous obstruction, including DVT or collateral abdominal venous circulation.

Intra-abdominal/RP-LMSs most commonly originate from major retroperitoneal or deep pelvic veins such as the IVC; gonadal, renal, and iliac veins; or smaller mesenteric tributaries. They are also commonly seen arising from the gastrointestinal tract, bladder, or the prostate or adrenal glands. Tumors arising from large vessels may be intraluminal, extraluminal, or a combination of both. Cross-sectional imaging is necessary to provide a detailed evaluation of the size and local extent of the tumor and to define if any metastatic disease is present. Initial investigation should include CT of the chest/abdominal/pelvis and, when appropriate, a dedicated MRI. Intravenous contrast should be administered, as they commonly exhibit avid enhancement in the venous phase but with heterogeneity due to internal hemorrhage, necrosis, or cystic changes. Calcification is uncommon.[22]

Common sites of metastasis include lung, liver, soft tissues, and bones. Lymph node metastases are uncommon but should be evaluated in preoperative imaging. Intracranial metastases are exceedingly rare and thus brain imaging is usually only warranted if focal neurologic signs are present. For retroperitoneal tumors, MRI is not as useful as CT scan in defining the vascular relationships of the tumor with major vessels in the abdomen due to its lower spatial resolution and propensity to motion artifact. It is, however, better than CT in depicting tumor relationship to adjacent organs in the pelvis and also to differentiate intravascular tumor from bland thrombus.

The use of PET-CT for disease staging in RP-LMS is not yet considered standard of care; however, several studies have explored the complementary role of fluorodeoxyglucose PET-CT in the grading of STS. Benz and colleagues[23] analyzed 120 patients with 12 different subtypes. Their study revealed a significant relationship between the

standard uptake value (SUV) at maximum SUV (SUVmax) of a lesion and the histologic grade given by the 3-tiered FNCLCC system when using a cutoff of 6.6 g/mL.

Finally, a complete diagnostic assessment requires a percutaneous biopsy, if technically feasible, as this establishes the diagnosis of LMS in most cases. Core needle biopsy of RPS is safe and does not adversely affect oncologic outcome, as recently demonstrated by several expert institutes.[24,25] The risk of needle tract seeding is approximately 0.5%.[25] A coaxial technique should be used, as it diminishes the risk of seeding. Also, the peritoneum should not be traversed if feasible. Multiple cores, preferably 5 to 10, should be obtained of the area of the tumor that appears highest grade and viable (enhancing) on imaging. Laparoscopic or open incisional biopsy should not be performed because the sample may not be representative of the higher tumor grade because of the lack of 3-dimensional image guidance. Future planes of dissection may also be altered during the incisional biopsy, or peritoneal contamination may occur,[26] and this approach is strongly discouraged.

Multidisciplinary Care in Retroperitoneal Leiomyosarcoma

Once the diagnosis of LMS of the retroperitoneum is established, patients should be evaluated by an expert sarcoma multidisciplinary team (MDT) consisting of medical, radiation, and surgical oncology. Following diagnostic imaging and pathology review, patients with this rare disease warrant a multidisciplinary discussion of care. Currently, the standard of care for resectable RP-LMS is upfront surgery, although high postoperative rates of distant metastasis has engaged the community to consider the role of neoadjuvant chemotherapy, as described later in this article. In patients with primary disease deemed borderline or unresectable, a discussion about the use of chemotherapy and/or radiation therapy should occur by the sarcoma MDT.

Although there has been a paucity of data on the utility of preoperative chemotherapy for primary RP STS,[21] this approach hypothetically may reduce distant microscopic disease and allow for completion of cytotoxic drug regimens, which may be difficult to complete after major surgery. A recently published collaborative study of 13 major sarcoma centers, exploring the benefit of neoadjuvant chemotherapy in primary RP STS has shown promising results.[27] This retrospective study included 158 patients with a median number of 3 chemotherapy cycles based on anthracycline regimens. Using RECIST criteria for tumor response, patients with partial response and stable disease (SD) after chemotherapy had significantly better overall survival (OS) compared with those with progressive disease (PD). At 5 years, OS was 26% (95% confidence interval [CI], 13%–54%) for patients with PD, 56% (95% CI, 39%–81%) for those with a partial response, and 58% (95% CI, 45%–73%) for those with SD. After comparing by histology and type of chemotherapy, the subgroup analysis showed a higher partial response rate in LMS treated with anthracycline and dacarbazine (partial response = 37%). These results suggest that there is an enhanced response with doxorubicin-based chemotherapy in combination with dacarbazine, rather than ifosfamide.[28] Further development of histology-based chemotherapy drug combinations is ongoing.

To address the utility of neoadjuvant chemotherapy for resectable RP-LMS, an open-label multicenter, randomized phase III trial, STRASS 2, sponsored by the European Organisation for Research and Treatment of Cancer (EORTC) has recently opened (NCT04031677). It is currently recruiting patients in the EU and Canada with plans to open in Australia, Japan, and possibly the United States. This trial was specifically designed to investigate whether preoperative chemotherapy improves the prognosis of patients with high-risk RP–dedifferentiated liposarcoma (DD-LPS) or RP-LMS (G1-G3) followed by curative intent surgery (**Fig. 3**). Patients who meet

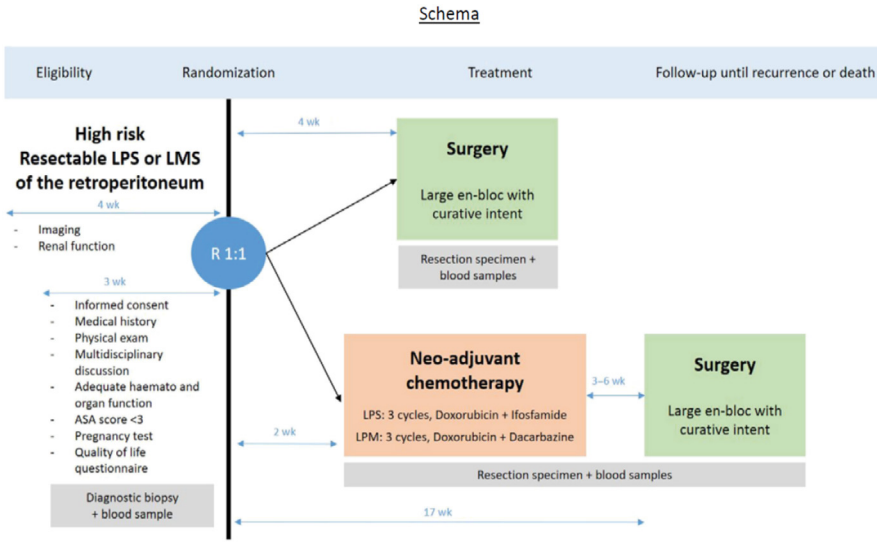

Fig. 3. Study schema for STRASS 2: neoadjuvant chemotherapy plus surgery versus surgery only for resectable LMS of the retroperitoneum.

inclusion criteria will be randomized to the standard arm (upfront en bloc curative intent surgery within 4 weeks after randomization) or the experimental arm. The experimental arm consists of 3 cycles of neoadjuvant anthracycline-based chemotherapy starting within 2 weeks after randomization. Combination therapy will be histotype-directed with dacarbazine or ifosfamide for LMS or DD-LPS, respectively.

Whether there is a benefit to adding neoadjuvant radiation therapy to this patient population was recently addressed by the phase-3 randomized clinical trial, STRASS.[29] Unlike STRASS 2, this study included most major sarcoma types, in which 14% (38 of 266) were RP-LMS. Overall, the 3-year analysis showed no statistically significant difference in abdominal recurrence-free survival (ARFS) for all histology types; 58.7% (95% CI 49.5–66.7) in the surgery group and 60.4% (51.4–68.2) in the radiotherapy plus surgery group. Importantly, post hoc analyses of ARFS demonstrated no significant difference for RP-LMS.[29] Given the increasing data that there is a lower incidence of local recurrence in RP-LMS (8-year CCI <10%),[1] along with randomized data from the STRASS trial, these data have been interpreted that neoadjuvant radiation for resectable primary RP-LMS is unlikely to provide benefit.

Surgical Treatment

Surgery is the mainstay for curative intent treatment in LMS. For intra-abdominal/retroperitoneal lesions, this usually consists of a multivisceral resection of adjacent organs with the goal of achieving an en bloc R0 resection. Curative intent multivisceral surgery for primary RP-LMS can be planned in 3 clinical settings: (1) resectable disease, (2) borderline resectable, and (3) primary tumor with synchronous oligometastatic disease.

Multivisceral surgery for retroperitoneal and pelvic LMS generally includes resection and possible reconstruction of major vascular structures, such as the IVC, renal veins. or iliac vessels, determined by the vascular origin of these tumors. Overall, the goal is to achieve a complete resection, which may require either partial resection followed by

primary vascular closure repair or a complete segmental resection with a biological or polytetrafluoroethylene (PTFE) graft reconstruction, depending on the extent of tumor involvement.

Because the IVC is a common site of origin, en bloc resection of these tumors requires resection and possible reconstruction of the IVC and other major venous tributaries, depending on the location, intravascular tumor extent, and collateral venous drainage at the time of surgery (**Fig. 4**). In IVC-LMS, tumor location has been previously described based on the segment of IVC involved and distance to the main iliac confluence, renal veins, and retrohepatic segment of the IVC.[30] The complexity and risk of this reconstruction increases as the retrohepatic segment of the IVC is included in the resection, particularly when major hepatic veins or the right atrium of the heart are involved. These highly challenging resections may require a hepatic mobilization, including major liver resection or even extracorporeal bypass circulation. Thus, preoperative surgical planning with appropriate surgical expertise is key to achieve optimal oncologic resection and mitigate perioperative morbidity and mortality.[30–34] RP-LMS also can arise in the gonadal vessels, and depending on their location, a kidney-sparing procedure may be feasible (**Fig. 5**).

Borderline resectability is often defined by the proximity or involvement of major vascular structures that may not be possible to resect or reconstruct, along with the extent of other viscera that would require resection to achieve a grossly negative result. For borderline resectable disease, an initial neoadjuvant systemic treatment approach, followed by neoadjuvant radiation therapy, or trimodal approach, may aid in defining patients who will succumb early to metastatic disease, while also providing the opportunity to potentially cytoreduce technically challenging tumors, which may result in less morbid procedures. Although radiation therapy does not appear to help with local control rates based on the STRASS data, its utility here is potentially facilitating resectability.

The role of curative intent surgery for RP-LMS in the setting of synchronous oligometastases is a matter of debate. The role of surgery applies most commonly to lung metastases; however, similar principles could be extrapolated to limited hepatic, soft tissue, and/or rarely isolated bone metastases. When analyzing prognostic factors involved in the survival benefit of surgery for oligometastasis, timing of metastases (synchronous vs metachronous), progression-free interval, number of lesions, and complete metastases resection, are prognostic, with the caveat of patient selection in these retrospective studies.[35,36]

Surveillance

RP-LMSs, as previously discussed, demonstrate a high rate of metastatic recurrence.[1,12,37] This pattern of recurrence can be exclusively metastatic, or local and metastatic after many years following resection. Late local and distant recurrences (5–10 years after diagnosis) may occur in 27% and 9%, respectively, in RP-LMS.[12] Clinical follow-up must therefore include a CT series of chest, abdomen, and pelvis for the remainder of the patient's life, as late recurrences of more than 25 years have been documented. In most expert centers, follow-up intervals for RP-LMS is cross-sectional imaging every 4 months for 2 years after surgery, every 6 months between 2 and 5 years postoperatively, and then yearly.[21]

UTERINE LEIOMYOSARCOMA

uLMS is an aggressive tumor arising from smooth muscle and is the most common site of disease. Although it accounts for only 1% to 2% of uterine malignancies, it

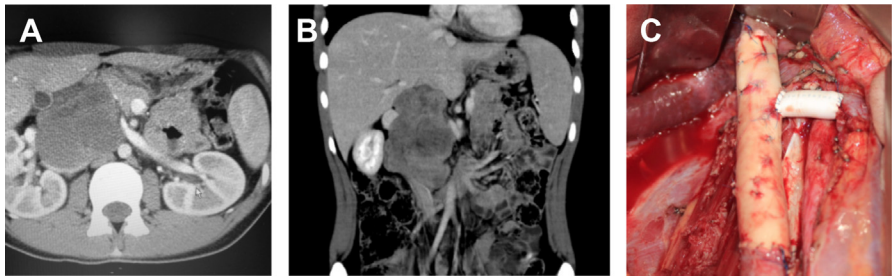

Fig. 4. IVC-LMS resection with major vascular reconstruction. (*A*) Cross-sectional and (*B*) coronal CT scan of grade 2 IVC-LMS involving IVC and right renal vein. (*C*) En bloc resection including IVC reconstruction with cadaveric aortic graft and left renal vein reimplantation with PTFE graft.

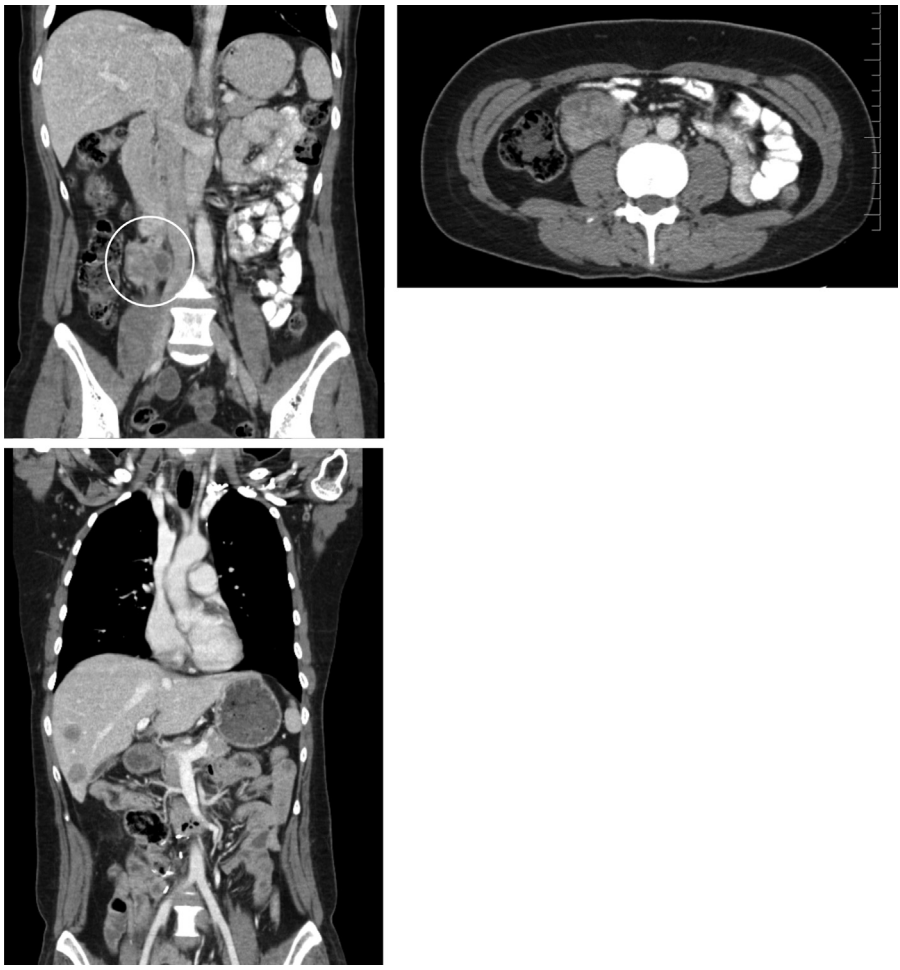

Fig. 5. Gonadal vein LMS. A grade 3 LMS was resected en bloc with a mid-ureteric repair (top left coronal image, top right axial image). Hepatic metastasis developed within the first postoperative year (bottom left coronal image).

has a poor prognosis, with overall 5-year survival ranging from 15% to 65%.[38–40] Women with uLMS should be clinically managed in specialty centers with expertise in gynecology oncology and sarcoma; however, unfortunately these referrals often occur postoperatively after hysterectomy or myomectomy for presumed benign uterine leiomyomas.[41]

Preoperative Assessment

uLMS is challenging to diagnose preoperatively given its radiologic resemblance to benign uterine leiomyomas, low utilization of preoperative biopsy for diagnosis, and sampling error in those few tumors that are biopsied preoperatively. This distinction between leiomyoma and LMS is important to make, as en bloc hysterectomy is the surgical standard of care for uLMS, whereas procedures such as morcellation and myomectomy are strictly reserved for leiomyomas. Although there is currently no clinical or serologic test to confidently distinguish between the 2 pathologies, certain clinical assessments may provide some value.

1. *Clinical features.* Although both benign and malignant entities can present with uterine bleeding, a uterine mass, or pelvic pain, new or growing fibroids in postmenopausal women who are not using hormonal replacement therapy are concerning for malignancy.[38,41] Rapid fibroid growth or large uterine size in premenopausal women do not correlate with an increased risk of malignancy.[39,41]
2. *Endometrial biopsy.* Sampling of the endometrium has limited value, as sensitivity and specificities were found to be of 35% to 80% and 30% to 65%, respectively, with no difference between office biopsy and curettage as a sampling method,[39,41,42] which is likely because of difficulty in sampling the deeper uterine smooth muscle where these tumors originate.
3. *Laboratory markers.* Several markers have been investigated to discern between LMS and leiomyomas. None are clinically effective. Lactate dehydrogenase is a nonspecific marker, as it has been previously shown to have a sensitivity of 47% to 74% and specificity of 85% to 100% at various cutoff values in one study.[43]
4. *MRI.* In terms of imaging, MRI with contrast appears more informative than sonography and CT. Sensitivity and specificity were reported as 77% to 96%[39]; however, the generalizability of such results is limited. Valuable findings include dark and homogeneous mass in T2-weighted images having a high negative predictive value for LMS, presence of calcifications associated with fibroids, and ill-defined margins associated with LMS[41] (**Fig. 6**).
5. *Morcellation.* Leiomyomas are a common reason for gynecologic surgery, and morcellation has allowed women with enlarged fibroids to benefit from minimally invasive surgery.[41] The low incidence of LMS diagnosis in presumed benign leiomyomas is estimated at 0.007% to 0.2%,[39–41] and this is because of limitations in preoperative assessment tools, as there is genetic evidence that most uLMSs arise independently of fibroids.[39,41] If LMS diagnosis occurred after myomectomy, hysterectomy is necessary to complete surgical management.[44]

Subsequent to a "black box" warning issued by the Food and Drug Administration in 2014 regarding electromechanical morcellator devices, this practice changed throughout North America and varies between gynecologic departments from no morcellation at all to carefully selected patients to in-bag only morcellation.[39] This concern is related to risk of occult malignancy dissemination, as well as increased rates of recurrence and decreased survival.[39,40,45] As such, if LMS diagnosis occurs after morcellation, National Comprehensive Cancer Network (NCCN) guidelines recommend imaging and to consider reexploration surgery.[44]

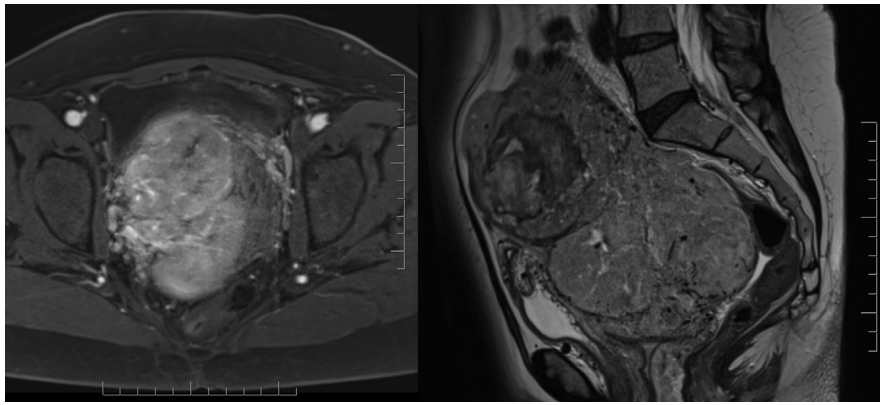

Fig. 6. MRI features of uterine mass concerning for LMS. A large heterogenous uterine mass demonstrates irregular boarders on axial T1 images with enhancement (left) and greater than 50% T2 signal on sagittal images (right). Right pelvic sidewall extension and suspicious posterior bladder involvement are present.

There are no studies looking at survival and recurrence rates in LMS treated by myomectomy without morcellation and subsequent hysterectomy. Interestingly, evidence of muscle cells present in peritoneal fluid was found after myomectomies even before morcellation.[46] The need for adjuvant treatment in cases of inadvertent LMS morcellation is unknown, and one study found no benefit for adjuvant chemotherapy, chemoradiation, or radiation to improve survival or recurrence outcomes.[47]

Surgical Standard

uLMS is surgically staged according to the 2017 International Federation of Gynecology and Obstetrics (FIGO) staging for uLMS and endometrial stromal sarcomas (**Table 1**). The surgery involves total hysterectomy,[39,44] with controversies surrounding need for lymphadenectomy and oophorectomy. If pathologic diagnosis occurs after hysterectomy, the NCCN recommends imaging with CT of the chest, abdomen, and pelvis, and to consider surgical reexploration.[44]

1. *Lymphadenectomy.* Lymphadenectomy is not usually necessary[38,44] given that the main LMS dissemination mechanism is hematogenous. The incidence of positive lymph nodes is low at 6.6% to 11% overall,[38,39,48] and less than 5% for early stages.[39] Omitting lymphadenectomy was not associated with decreased OS in the literature,[48] and a suggested surgical approach is to inspect and remove only grossly enlarged nodes.[39,40]
2. *Bilateral oophorectomy.* Oophorectomy is recommended for postmenopausal women, with improved OS demonstrated for patients older than 51 years in a National Cancer Database study.[48] NCCN and FIGO permit ovarian preservation in selected patients with early-stage LMS who wish to retain hormonal function.[38,44] This is controversial due to a speculative hormonal effect, because LMSs are often positive for ER and PR,[38,40] which contrasts with the cardiac and overall health beneficial effects of estrogen. In premenopausal women, oophorectomy for early LMS was not associated with an OS benefit.[39,48]
3. *Complete debulking and lung metastasectomy.* For patients with extrauterine resectable disease, complete surgical debulking is the recommended treatment by FIGO and NCCN.[38,44] Because LMS response to adjuvant treatment including

Table 1
International Federation of Gynecology and Obstetrics staging for uterine sarcomas

Stage	Definition
Leiomyosarcomas and endometrial stromal sarcomas	
I	Tumor limited to uterus
IA	<5 cm
IB	More than 5 cm
II	Tumor extends beyond the uterus within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvic tissues
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than 1 site
IIIC	Metastasis to pelvic and/or para aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

systemic therapy and/or radiation is limited,[38,44] complete debulking to no gross residual disease, including resection of isolated pulmonary metastases, was shown in some studies to have a better outcome.[39,40] Similarly for recurrent uLMS, surgical resection when feasible was described to prolong survival with a median OS of 54 months (24–83 months) when complete resection was achieved.[49] Best candidates for secondary resection have localized recurrences and prolonged progression-free intervals of 12 to 18 months.[40] A recently explored avenue is the use of hyperthermic intraperitoneal chemotherapy for patients with primary or recurrent LMS sarcomatosis. A review including 68 patients showed a median OS of 29 to 37 months, but a perioperative death rate of 4%.[50]

SYSTEMIC THERAPY IN LEIOMYOSARCOMA

Adjuvant Chemotherapy

In LMS, approximately 50% of patients with localized disease will develop distant metastases and die of their disease, despite optimal local treatment.[51] The use of adjuvant chemotherapy, in an attempt to reduce the risk of disease recurrence in STS (which included patients with LMS) was evaluated in several trials with conflicting results. For example, a large randomized controlled trial (n = 351; EORTC STBSG 62931) compared adjuvant doxorubicin + ifosfamide versus observation in patients with STS. This study failed to demonstrate any impact in terms of both recurrence-free survival and OS.[52] In contrast, an Italian trial (n = 104) that randomized patients with STS to adjuvant epirubicin + ifosfamide versus observation demonstrated a 4-year OS benefit favoring chemotherapy use (69% vs 50%).[53] Unfortunately, these adjuvant STS trials suffer from the fact that treatment was deployed in a heterogeneous population of patients with STS, and some trials were also underpowered.

Meta-analysis of adjuvant chemotherapy studies in STS were not surprisingly encouraging for routine treatment. The initial meta-analysis by the Sarcoma Meta-Analysis Collaboration demonstrated no OS benefit with chemotherapy use.[54] However, an updated 2008 meta-analysis of 18 randomized trials (n = 1953) showed a

significant benefit of OS favoring chemotherapy (OR for death 0.56; 95% CI, 0.36–0.85; $P < .05$).[55] This meta-analysis, however, did not include the EORTC STBSG 62931 mentioned previously. Subsequently, a pooled analysis of the 2 largest adjuvant chemotherapy EORTC studies (n = 819) failed to show OS benefit, apart from patients with R1 resection.[56]

Given the incongruous results, adjuvant chemotherapy use in STS (including LMS) varies across institutions and remains controversial. International guideline recommends discussing the option of adjuvant chemotherapy with patients affected by high-risk STS of extremity and trunk wall in the context of ambiguous evidence.[57]

Systemic Treatment Options in Metastatic Leiomyosarcoma

The rate of metastasis occurrence in patients with LMS treated for localized disease can vary by disease site of origin (31% in extremity, 58% in the abdomen, 53%–71% in the uterus).[12,38] In advanced or metastatic setting, the outcomes for patients with LMS are poor, with a varied median OS of 12 to 24 months.[58,59]

The main treatment option for patients with LMS with advanced/metastatic disease remains chemotherapy. No specific trials for LMS have been reported in first-line setting, but patients with LMS are represented in 20% to 40% of the STS trials population.[60–63] First-line chemotherapy for advanced, metastatic, or unresectable STS is typically based on doxorubicin monotherapy, with a response rate of 15% to 20%, with a further 30% to 40% of patients experiencing disease stabilization.[57,60–63] The median progression-free survival (PFS) of doxorubicin monotherapy is approximately 4.5 to 6 months.[60–63]

Several clinical studies comparing single-agent doxorubicin with doxorubicin combinations, such as doxorubicin + ifosfamide, doxorubicin + olaratumab, and gemcitabine + docetaxel, failed to show an OS advantage, although combination therapy may result in an improvement of response rates and PFS when compared with doxorubicin alone.[60] Combination treatments generally do come at a cost, as they are associated with elevated levels of toxicities and decreased treatment tolerability.[60–63] Despite this, it is worth noting that combination therapy is still routinely used in clinic. For example, gemcitabine and docetaxel combination, although not superior to doxorubicin, is commonly used in the first-line setting where doxorubicin cannot be used or in the second-line treatment setting.[3,64,65]

Several other regimens have also shown activity in LMS, beyond first-line treatment. These include agents such as trabectedin and eribulin. In a phase III trial, trabectedin demonstrated superiority over dacarbazine in PFS but failed to show advantage in OS.[66,67] In another phase III trial, OS superiority of eribulin, when compared with dacarbazine was reported in liposarcoma and LMS populations (median OS 13.5 vs 11.5 months; $P = .0169$), but this advantage is lost when analyzing the treatment effect in the LMS cohort alone.[68] Other treatment options for subsequent lines of therapy in LMS include dacarbazine, gemcitabine single agent, and liposomal doxorubicin[66–70] (**Table 2**).

When exploring nonchemotherapy, targeted treatment options for LMS, pazopanib (small-molecule inhibitor against vascular endothelial growth factor) demonstrated modest efficacy in STS, with PFS benefit alone.[71] In a subgroup analysis of patients with uLMS across 2 trials, a response rate of 11% PFS at 3 months and an OS of 17.5 months were observed).[72] Other nonchemotherapy options include antihormone therapies with ER/PR-positive LMS. These tumors may be characterized with indolent clinical course and demonstrated 12-week PFS rate of 50% with a median duration of treatment of 2.2 months, when treated with letrozole.[73,74]

Table 2
Chemotherapy types used for progressive lines of treatment in patients with advanced LMS

Study	Drug/ Combination Tested	Treatment Line	Phase	Number of Patients/ LMS Patients	RR (%)	PFS (month) >	OS (month)
Demetri et al,[66] 2012	Trabectedin vs Dacarbazine	>1	III	518/378	9.9 vs 6.9	4.2 vs 1.5	12.4 vs 12.9
Patel et al,[67] 2016	Trabectedin vs dacarbazine	>1	III	577/423	10 vs 7	4.3 vs 1.6	13.7 vs 13.1
Maki et al,[69] 2007	Gemcitabine vs gemcitabine + docetaxel	>1	IIR	122/38	8 vs 16	3 vs 6.2	11.5 vs 17.9
Schoffski et al,[68] 2016	Eribulin vs dacarbazine	>1	III	122/38	4 vs 5	2.6 vs 2.6	13.5 vs 11.5
Sutton et al,[70] 2005	Liposomal doxorubicin	>1	II	32/32*	16.1	NA	NA

Abbreviations: LMS, leiomyosarcoma; NA, not applicable; PFS, progression-free survival; OS, overall survival; RR, response rate.

Targeted agents are also recently or currently being evaluated in patients with LMS. Monotherapy with checkpoint inhibitors, such as pembrolizumab or nivolumab, showed low clinical activity in this tumor subtype with no responses and short-term clinical benefit were reported (PFS of 1.4–1.8 month).[75,76] Given the lack of activity in monotherapy trials, combination immunotherapy strategies are currently being explored. A recent retrospective study demonstrated a 45% overall response rate and a median PFS of 14.4 months among responders in patients with LMS treated with nivolumab and ipilimumab.[77] A prospective trial that included the preceding combination in STS has also been reported showing promising results of the combination.[78] In another study, combination therapy with durvalumab (PD L-1 inhibitor) with either olaparib (PARP inhibitor) or cediranib (anti-angiogenic inhibitor) resulted in disease stabilization in 30% of patients with LMS, some of whom were durable (DAPPER Trial-NCT03851614), again highlighting the value to exploring combination therapy with checkpoint inhibitors. Currently, there are several endeavors interrogating biomarkers that are associated with response or resistance to immunotherapy in sarcomas. These include genetic profiling to analyze tumor-immune micro-environment as well as inflammation signatures.[77–80] One other area of emerging interest, in terms of novel drug usage, is the discovery of homologous recombination defects in LMS, as previously discussed.[16] A recent phase 2 study demonstrated the combination of temozolamide and olaparib resulting in a response rate of 27% in heavily pretreated patients with uLMS (NCT03880019). Together with the DAPPER study, there is now ample justification to explore PARP-inhibitor combinations in LMS.

In summary, the use of adjuvant chemotherapy in resected LMS remains uncertain and controversial. In the metastatic setting, first-line therapy is still dominated by doxorubicin-based therapies. In recent years, there has been an expansion of therapeutic options beyond first-line therapy to include agents such as trabectedin, eribulin, and pazopanib. Current trials are ongoing, with interrogation of immunotherapy combination strategies. In addition, PARP inhibition may be a useful and important therapeutic strategy for LMS.

FUTURE DIRECTIONS

As the biology of LMS becomes more comprehensively assessed by both histotype specific care and molecular profiling, the field has several promising directions to improve patient outcomes.[81] First, the diagnostic challenges of diagnosing uLMS has shown promise with the advent of circulating tumor DNA. Ongoing efforts by several groups to aid in establishing an accurate diagnosis are under way, and this approach could alleviate the challenges patients face when diagnosed postoperatively.[82–84] Second, our ability to determine higher versus low metastatic risk is also being addressed by cooperative group efforts.[83] We will learn more from the neoadjuvant STRASS 2 trial whether the use of neoadjuvant chemotherapy will benefit RP-LMS. Finally, because metastatic disease is the main clinical challenges patients face, new drug therapies are emerging in the DNA damage inhibitor space with promising phase 2 clinical trials.[85] Certainly, by understanding which patients with LMS require multidisciplinary therapy early in their course and by developing more effective systemic agents, improving patient outcomes should be realized in the future.

CLINICS CARE POINTS

- LMS can present as primary disease only, or with advanced disease.
- Diagnostic assessment should include a percutaneous biopsy.
- Staging workup should include a CT of chest/abdomen/pelvis, and/or MRI in pelvic or extremity tumors.
- Patients should be evaluated by an expert sarcoma multidisciplinary team to define the role of multimodal treatment.
- Surgery is the mainstay for curative intent treatment.
- Extent and complexity of these multivisceral resections may require multiple surgical teams, including surgical oncology, hepato-pancreato-biliary/transplant, and/or vascular surgery.
- Doxorubicin-based treatment is the mainstay for patients with metastatic LMS. The role of neoadjuvant regimens is currently under investigation.

DISCLOSURE

The authors have nothing to disclose.

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