LEIOMYOSARCOMA OF THE UTERUS: A REVIEW

An ESUN Article

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INTRODUCTION

Uterine sarcomas are a rare and aggressive form of uterine cancer. They arise from the endometrial lining or the myometrium in the uterus. Compared to the more common endometrial carcinomas, uterine sarcomas behave more aggressively and are associated with a poorer prognosis.

In this review, we shall focus on one subset - uterine leiomyosarcomas (ULMS), although it is noteworthy to mention that leiomyosarcoma can arise from other gynecological primary sites. ULMS are rare smooth muscle tumors accounting for approximately 1% of patients with uterine cancer with an estimated annual incidence of 0.64 per 100,000 women. ULMS are considered neoplasms of high metastatic potential with 5-year overall survival rates varying between 0 and 73%. These discrepancies may be attributable to inconsistent definitions and variable sample sizes for diagnostic criteria. Additionally, this adds to the dilemma of addressing survival rates given the variable time periods of these studies.

ULMS occur primarily in women 40 to 60 years of age. The most frequent presenting symptoms are abnormal vaginal bleeding and pelvic or abdominal pain. The amount of bleeding ranges from spotting to menorrhagia and is often associated with foul-smelling vaginal discharge. Less common symptoms include weight loss, weakness, lethargy, and fever. On pelvic examination, the uterus is often enlarged, and in some cases part of the tumor may prolapse through the cervical os and into the vaginal canal. Diagnosis is usually not made before surgery, thus many patients present with advanced disease.

The rarity of these tumors has prevented the performance of large epidemiological studies to identify risk factors. Data regarding parity, onset of menarche, or age at menopause as risk factors are inconclusive. Based on available United States data, there is approximately a two- to three-fold higher incidence of ULMS among African-American women compared to Caucasian women. A history of pelvic irradiation is noted in 5-10% of patients.

Benign leiomyomas (fibroids) and ULMS often coexist in the same uterus, but are genetically distinct entities (Figure 1, Table 1). ULMS are much less common and not hormonally driven.
Figure 1: A uterus has been cut showing a large, soft leiomyosarcoma with irregular borders noted to be invading the myometrium (LS, arrows) adjacent to a small, firm leiomyoma with a hemorrhagic center which is sharply demarcated (single arrow) (11).

Table 1: Gross pathological comparison of Leiomyoma and Leiomyosarcoma

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<thead>
<tr>
<th></th>
<th>Leiomyoma</th>
<th>Leiomyosarcoma</th>
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<tbody>
<tr>
<td>Usually multiple</td>
<td>Often solitary</td>
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</tr>
<tr>
<td>Variable size, 3-5cm</td>
<td>Large, often &gt;10cm</td>
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<tr>
<td>Firm, whorled surface</td>
<td>Soft, fleshy cut surface</td>
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<tr>
<td>White</td>
<td>Yellow or tan</td>
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<tr>
<td>Hemorrhage and necrosis infrequent</td>
<td>Hemorrhage and necrosis frequent</td>
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The belief that the risk of ULMS is elevated among women with a "rapidly growing" uterus or leiomyoma was proven false in a study of 1322 women admitted to two community hospitals for hysterectomy or myomectomy. Fibroids rarely, if ever, degenerate into ULMS.12
CLASSIFICATION
The Gynecologic Oncology Group (GOG) uses a classification scheme for uterine sarcomas that divides them into five categories:

- Mixed homologous mullerian sarcoma
- Mixed heterologous mullerian sarcoma
- Leiomyosarcoma
- Endometrial stromal sarcoma
- Other

Homologous refers to similarity to endometrial stroma or myometrium, while heterologous indicates similarity to other cell types, including fat, muscle, etc. Malignant mixed mullerian tumors, now called carcinosarcomas, arise from endometrial adenocarcinoma, but resemble sarcoma on histology.

The typical gross appearance is a large (>10cm), poorly circumscribed mass with a soft, fleshy consistency and a variegated cut surface that is grey-yellow to pink, with foci of hemorrhage and necrosis (Figures 2 & 3). Homologous refers to similarity to endometrial stroma or myometrium, while heterologous indicates similarity to other cell types, including fat, muscle, etc. Malignant mixed mullerian tumors, now called carcinosarcomas, arise from endometrial adenocarcinoma, but resemble sarcoma on histology.

The histologic classification of uterine sarcomas is based upon homology to normal cell types and include ULMS (analogous to myometrium), stromal sarcoma (analogous to endometrial stroma), and other heterologous cell types (i.e., osteosarcoma, liposarcoma).

Microscopically, most ULMS are overtly malignant, with hypercellularity, coagulative tumor cell necrosis, abundant mitoses (>10 to 20 mitotic figures (mf) per 10 high power fields (hpf)), atypical mitoses, cytologic atypia, and infiltrative borders (Figures 4 & 5, Table 2). Mitotic rate is the most important determinant of malignancy, but is modified by the presence of necrosis and cytologic atypia. The diagnosis of ULMS may be made in the presence of tumor necrosis and any mitoses. In the absence of tumor necrosis, the diagnosis can be made with moderate to severe cytologic atypia and a mitotic index greater than 10mf/10hpf. Without tumor necrosis and significant atypia, a high mitotic index is compatible with a benign clinical course, however, data is limited.
Coagulative Tumor cell necrosis: abrupt transition from viable tumor to necrotic tumor seen in tissue.

Mitotic Index: a measure for the proliferation status of a cell population. It is the ratio between the number of cells in mitosis and the total number of cells. Mitotic figures per 10 high power fields in the mitotically most active areas.

One study looked at the expression of particular markers that are of interest in gynecological cancers (p53, Epidermal Growth Factor, and Platelet Derived Growth Factor) in tissue samples from patients who had ULMS or benign leiomyomas. Their data demonstrated significant and molecular differences between benign and malignant smooth muscle tumors of the uterus. The study also suggested a prognostic interrelationship between expression of p53 and stage in ULMS.

Figure 4: Tumor necrosis consists of ghosts (no nuclei) of tumor and an abrupt transition from live to dead tumor (left panel) without an inflammatory response. Degenerative changes contain either liquefaction necrosis (no cell ghosts as seen in the lower panel here), edema, or an inflammatory response at the boundary with viable tissue. Courtesy of Jonathan L. Hecht, MD, PhD (Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA).

Figure 5 (left): Mitosis (center of slide). Criteria for malignancy relies on necrosis, and mitotic count. Figure 6 (right): Atypia is seen characteristically and lowers the required number of mitoses to meet criteria for malignancy. Atypical (a.k.a. symplastic) leiomyoma is a benign smooth muscle tumor with atypia only, lacking mitoses or necrosis. Photos courtesy of Jonathan L. Hecht, MD, PhD (Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA).
### Table 2: Diagnostic Criteria for LMS, Adapted from 2003 WHO Guidelines (14)

<table>
<thead>
<tr>
<th>Criteria for LMS</th>
<th>Standard smooth muscle Differentiation</th>
<th>Epithelioid differentiation</th>
<th>Myxoid differentiation</th>
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<tbody>
<tr>
<td><strong>Histology</strong></td>
<td>Cigar-shaped spindled cells with scanty to abundant eosinophilic cytoplasm</td>
<td>Rounded cells with central nuclei, and clear to eosinophilic cytoplasm</td>
<td>Spindle shaped cells set within an abundant myxoid matrix</td>
</tr>
<tr>
<td><strong>Any coagulative tumor cell necrosis</strong></td>
<td>Any coagulative tumor cell necrosis</td>
<td>Any coagulative tumor cell necrosis</td>
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<tr>
<td><em><em>In the absence of tumor cell necrosis, the diagnosis required diffuse, moderate to severe cytological atypia and a mitotic index of &gt; 10mf/10hpf</em>. If the mitotic index is &lt; 10mg/10hpf, the chance of recurrence is low (less than 2-3%).</em>*</td>
<td>In the absence of tumor cell necrosis, the diagnosis requires diffuse, moderate to severe cytological atypia and a mitotic index of &gt;5mf/10hpf.</td>
<td>In the absence of tumor cell necrosis, the diagnosis requires diffuse, moderate to severe cytological atypia and a mitotic index of &gt;5mf/10hpf.</td>
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<tr>
<td><strong>In the absence of coagulative tumor cell necrosis and significant atypia, a high mitotic index is compatible with a benign clinical course.</strong></td>
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<td>*<strong>mf/hpf = mitotic figures/high power fields</strong></td>
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A subset of smooth muscle tumors will not be easily classified based on the criteria and are designated as smooth muscle tumors of uncertain malignant potential (STUMP). The literature is unresolved on whether special studies such as proliferation index or stains for p53 add to the discriminating power of the basic criteria of mitoses, necrosis and cytologic atypia in determining the malignant potential of STUMP lesions. In practice, however, these stains are uncommonly used, and definitive diagnosis of sarcoma is never reported based on these stains alone.16,17

Limited data has allowed some tumors, formerly classified as STUMP, into the leiomyoma category and should be distinguished from their sarcomatous counterparts.

Tumors now in the leiomyoma category include: mitotically active, cellular, epithelioid, myxoid, atypical (pleomorphic, bizarre, or symplastic) tumors. Mitotically active leiomyomas can occur in pre-menopausal women and have the typical macroscopic and histologic appearance of a leiomyoma with the exception that they have > 5mf/hpf. Cellular leiomyomas tend to have hypercellularity and can suggest the diagnosis of ULMS, but they lack tumor cell necrosis, cytologic atypia and mitotic figures. Epithelioid leiomyomas are yellow or grey and may contain visible areas of hemorrhage and necrosis, and tend to be solitary and softer than the usual leiomyoma. Myxoid leiomyomas have myxoid material separating the tumor cells. They are soft...
and translucent with circumscribed margins with neither cytologic atypia nor mitotic figures. Atypical leiomyomas lack all the other components with the exception of atypia and have little recurrence potential (Figure 6).\textsuperscript{14}

Unlike smooth muscle tumors at other sites, uterine smooth muscle tumors are generally not graded. Rather, clinical behavior is defined by the designation to categories of ULMS, leiomyoma, or STUMP. The distinction is important since grading ULMS based on criteria at other body sites is misleading.

**DIAGNOSTIC EVALUATION**

Patients with abnormal uterine bleeding or a suspicious uterine lesion should undergo endometrial sampling. Imaging studies and/or clinical findings are not specific for ULMS versus other uterine tumors. Ultrasound examination, magnetic resonance imaging (MRI), or computed tomography (CT) do not reliably distinguish between sarcoma, leiomyoma, endometrial cancer, lymphoma, intravenous leiomyomatosis, or adenomyosis.\textsuperscript{18}

**MRIs and Diagnosis:** The utility of MRI for diagnosis is being addressed in case reports. Contrast resolution in soft tissues (better than ultrasonography) and lack of ionizing radiation show great promise as an imaging tool to evaluated LMS. The findings of atypical degeneration with irregular contours should bring LMS into the differential when evaluating leiomyomas (or other pelvic masses). One study looked at patients (including nine patients with pathologically proven LMS and three with STUMP) in order to study the magnetic resonance characteristics of non-benign uterine smooth muscle tumors. Additionally, they analyzed twelve cases of benign leiomyomas in which the gynecologists had suspected LMS. Size, location, signal intensity, and contrast enhancement of the tumors were studied on an individual basis. With some exceptions, the authors concluded that more than 50% of high signal on T2-weighted images and the presence of any small high-signal areas on T1-weighted images with un-enhanced pockets were considered MRI suggestive for STUMPS and LMS.\textsuperscript{22}

**STAGING**

Staging is based on surgical, not clinical findings. Extensive local growth is a hallmark of ULMS and spread of these tumors occur by local, lymphatic, and hematogenous routes (Figure 2). Metastasis frequently involves the lung. If the diagnosis of ULMS is known preoperatively, chest imaging is necessary to evaluate for metastatic disease.

Surgical staging for ULMS is the same as for endometrial carcinoma (Figure 7). The surgery includes peritoneal washings for cytology, extrafascial total abdominal hysterectomy, bilateral salpingo-oophorectomy, removal of enlarged lymph nodes, and biopsy or any suspicious areas. Some oncologists recommend omentectomy and pelvic and paraaortic lymph node sampling.
Figure 7: The International Federation of Gynecology and Obstetrics (FIGO) Staging of ULMS

<table>
<thead>
<tr>
<th>Stage I Tumor confined to corpus uteri</th>
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<tbody>
<tr>
<td>IA Tumor limited to the endometrium</td>
</tr>
<tr>
<td>IB Tumor invades up to or less than 50% of the myometrium</td>
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<td>IC Tumor invades more than 50% of the myometrium</td>
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<table>
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<th>Stage II Tumor invades cervix but does not extend beyond uterus</th>
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<tr>
<td>IIA Endocervical glandular involvement only</td>
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<tr>
<td>IIB Cervical stroma invasion</td>
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<tr>
<th>Stage III Local and/or regional spread</th>
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<tr>
<td>IIIA Tumor involves uterine serosa and/or adnexa (direct extension or metastasis)</td>
</tr>
<tr>
<td>IIIB Vaginal involvement (direct extension or metastasis)</td>
</tr>
<tr>
<td>IIIC Metastasis to the pelvic and/or para-aortic lymph nodes</td>
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<th>Stage IV</th>
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<tr>
<td>IVA Tumor invades the bladder mucosa and/or bowel mucosa</td>
</tr>
<tr>
<td>IVB Distant metastasis (excluding metastasis to vagina, pelvic serosa, or adnexa. Including metastasis to intra-abdominal lymph nodes other than para-aortic, and/or inguinal lymph nodes)</td>
</tr>
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</table>

LMS should be grouped with regard to the degree of differentiation as follows:

- G1 5 percent or less of a nonsquamous or nonmorular solid growth
- G2 6 percent to 50 percent of a nonsquamous or nonmorular solid growth
- G3 More than 50% of a nonsquamous or nonmorular solid growth

TREATMENT FOR LOCALIZED DISEASE

Surgical Treatment

At a minimum, surgical treatment of a patient with a ULMS of the uterus should include a total hysterectomy and removal of the cervix.

Adjuvant radiotherapy

The benefit of postoperative adjuvant radiotherapy (RT) in ULMS is unclear. The European Organization for Research and Treatment of Cancer (EORTC) randomly assigned 222 patients with stage I or II uterine sarcoma (including 103 patients with ULMS) to pelvic external beam radiation or observation. The preliminary report in 2003 suggested a lower rate of local recurrence in the irradiated group but no improvement in overall survival. Retrospective studies provide conflicting data. Most studies that group all uterine sarcomas together note better pelvic control with adjuvant RT. In GOG protocol 20, women with stage I or II uterine sarcoma were randomized to a trial of adjuvant doxorubicin with or without adjuvant RT. The majority of these patients had carcinosarcoma. Results showed that the irradiated group of patients had a significantly lower rate of pelvic failure, but no improvement in overall survival. Retrospective studies suggest the possibility of a survival benefit as well as an improvement in local control. The largest series evaluated 103 women with stage I-IV uterine sarcoma (42% ULMS) who received RT at the discretion of their physician. Irradiated patients had a significantly better five-year pelvic control (76% versus 36%) and overall survival (73% versus 37%). The significance of improved survival and pelvic control remained in multivariate analysis after controlling for stage, histology, tumor grade, and presence of lymphvascular invasion.
A major obstacle with ULMS is that even if pelvic control is achieved, the majority of women develop distant extraabdominal metastases.31

Guidelines from the National Comprehensive Cancer Network (NCCN) suggest that adjuvant RT can be considered for all women with resected stage I or stage II ULMS. For stage III ULMS with positive lymph nodes, the NCCN recommends consideration of adjuvant chemotherapy and pelvic RT, vaginal brachytherapy, and/or adjuvant chemotherapy.32

The use of RT needs to be balanced with the negative effects of therapy. Short term or immediate side effects include vaginal bleeding, vaginal discharge, skin reactions, hair loss, urinary problems, diarrhea and pain. Long term side effects include changes in bowel/bladder function and sexual function.

**Adjuvant Chemotherapy**

With the high rate of distant metastatic spread in ULMS, adjuvant systemic therapy is controversial. Some observational studies suggest a benefit,33,34 while most do not.32,35-38 To date, no prospective studies are available that focus on patients with ULMS, and there is no definitive evidence that adjuvant chemotherapy improves overall survival. Therefore, it cannot be recommended as the standard of care, and should be considered in individual circumstances.

Three observational studies suggest that the combined use of postoperative RT and chemotherapy may provide benefit after resection of uterine sarcoma. Two of the studies involved patients with carcinosarcomas. The third study had 41 patients with uterine sarcoma who received either pelvic RT or RT plus adjuvant chemotherapy. Three-year survival rates were significantly better in the chemotherapy group (66% versus 36%).39

Neoadjuvant chemotherapy can be used to improve respectability of advanced disease, in the appropriate setting. The data is limited, at best.

**Treatment for Recurrent, Advanced, or Metastatic Disease**

**Surgery**

Recurrent ULMS is diagnosed by the new development of symptoms. Most relapses occur in the pelvis, followed by the lung and abdomen. Bone and brain metastases are uncommon.21 Surgical resection should be considered in patients with localized single foci recurrences, either local or metastatic. In a report of 41 women who underwent resection for recurrent uterine ULMS (29% pulmonary, 41% pelvis), two-year survival was 71 percent among those who had a disease-free interval between resection of the primary and the development of metastatic disease of 12 months or longer.40-42 In a study evaluating metastatic disease, Lenvenback et al showed that 71% had unilateral lesions, 51% had one lesion, and 70% had nodules greater than 2 cm. After pulmonary resection, unilateral versus bilateral disease was a significant predictor of survival (p = 0.02). Size, number of metastases, disease-free interval, and patient age were not significant.42

With regard to Radiofrequency Ablation (RFA) and Video Assisted Thoracic Surgery (VATS), there is limited literature on sarcomas and more studies are needed prior to recommendations.
Radiofrequency Ablation (RFA) and Video Assisted Thoracic Surgery (VATS): There are a small number of case reports in the literature of RFA and VATS for metastatic lesions to the liver and lung. Most of these studies have small numbers and within those, even fewer with lesions from a uterine primary. Nevertheless, these approaches provide an alternative local therapy for metastatic lesions and more studies will be needed to establish its role in LMS.

Chemotherapy

Though unproven in the adjuvant setting, single agent doxorubicin is an effective drug for advanced ULMS. Objective response rates are between 16 and 25 percent, lasting generally less than 6 months. 43-47

Two randomized trials have examined the benefit of doxorubicin single agent therapy versus in combination. Doxorubicin alone was compared to doxorubicin plus cyclophosphamide. Response rates were similar in both arms for patients with measurable disease (19%), as was the progression-free and median overall survival (median 11.6 versus 10.9 months). 48-52

The second trial compared doxorubicin with and without dacarbazine, Although combined therapy was associated with a significantly higher response rate overall, there were no significant differences between the two groups in terms of progression-free survival or overall survival (7.7 versus 7.3 months). Combination therapy was associated with more hematologic and gastrointestinal toxicity. 53

Ifosfamide has limited activity as a single agent with a response rate of 17%. 53 Its combination with doxorubicin increased the objective response but added substantial toxicity. 54,55

The combination of gemcitabine and docetaxel is the most effective chemotherapy regimen for ULMS patients with advanced disease described to date. In one report, patients with unresectable uterine or other primary site ULMS received gemcitabine plus docetaxel and granulocyte colony stimulating factor. Of the 34 patients in the study, complete response was seen in 3 patients and partial response in 15, for an overall response rate of 53%. Seven patients had stable disease. Despite the use of granulocyte colony stimulating factor, grade 3 or 4 neutropenia and febrile neutropenia developed in 21 and 6 percent, respectively. The toxicity profile was otherwise mild. 53

A second series with 35 patients reported 7 of 12 patients (2 with ULMS) had a response. 56

To date, there has not been a phase III trial comparing doxorubicin plus ifosfamide versus gemcitabine plus docetaxel. Historical comparison shows at least equivalent response, with improved toxicity with gemcitabine plus docetaxel. Therefore gemcitabine plus docetaxel can be considered for first line use in the appropriately selected patient.

Temozolomide is also modestly active. In an observational series with 12 patients (most of whom had received two prior chemotherapy regimens), one patient had a prolonged partial response and one a near complete response after 13 months. 57 In a second study, responses were seen in 5 of 11 patients with gynecologic ULMS. 58 Response lasted for longer than one year in four patients.

A potentially new agent being investigated in the treatment of soft tissue sarcomas is Trabectedin (ecteinascidin), or ET-743. It is the active component of extracts from Caribbean tunicate, Ecteinascidia tubinata. ET-743 binds to the guanine residue within the minor groove of DNA causing a bend in the major groove which interferes with the DNA binding proteins and transcription factors in the cancer cell. Several phase II studies have demonstrated some activity in advanced soft tissue sarcomas, including ULMS. Response rates range between 4-17%. 59
drug and its potential future combination with additional active agents will be investigated in a future GOG phase II trials.

Certain uterine tumors are responsive to hormonal therapy because they express estrogen and/or progesterone receptors. However, this is not the case in ULMS and adjuvant hormonal therapy is not recommended for any stage of ULMS.

Patients with metastatic ULMS have limited options with regards to chemotherapy and enrollment in clinical trials is appropriate. Chemotherapy is palliative and should be used to relieve symptoms. Options include single agent doxorubicin, doxorubicin and ifosfamide, single agent gemcitabine, and gemcitabine and docetaxel. Considering that there is no survival benefit with our current chemotherapeutic options, toxicity versus symptom management should be evaluated on a case by case basis with full informed consent.

**SUMMARY AND RECOMMENDATIONS**

ULMS are rare tumors with a limited body of literature to help guide treatment. Patient care should be individualized. Further investigation is needed to improve the treatment options for our patients with this disease.

**Surveillance (32)**

- Physical exam every 3 months for 2 years, then every 6-12 months.
- Chest imaging every 3-6 months for 2 years, then annually.
- CT/MRI as clinically indicated.
- Patient education regarding symptoms.

**Surgical**

- Extrafascial total abdominal hysterectomy with bilateral salpingo-opherectomy and formal surgical staging.
- Fertility-sparing in young women who wish to preserve childbearing potential with low grade ULMS may be considered.

**Adjuvant Therapy**

- RT appears to improve local control while it is unclear whether it provides survival benefits. Adjuvant chemotherapy is of uncertain benefit.
REFERENCES


