Leiomyosarcoma: Diagnosis, surgery and adjuvant treatment

Prof. Dr. M. Yavuz SALİHOĞLU

I.U. Istanbul Faculty of Medicine
Department of Gynaecology & Obstetrics
Division of Gynaecologic Oncology
Leiomyosarcoma: Diagnosis, surgery and adjuvant treatment

- Uterine sarcomas account for 3 - 9 percent of all uterine malignant neoplasms.

- Uterine leiomyosarcoma (uLMS) is a rare uterine malignancy that arises from the smooth muscle of the uterine wall.

- LMS is an aggressive tumor associated with a high risk of recurrence and death, regardless of stage at presentation. (The prognosis is poor, even for early-stage disease.)

- LMS usually arise de novo, but recent studies have shown that some tumors have areas with benign morphology, suggesting some progression from leiomyoma to leiomyosarcoma.

- LMS is usually a solitary, poorly circumscribed mass with a soft and fleshy consistency.

A. Histologic distribution of uterine sarcomas including carcinosarcomas

B. Histologic distribution of uterine sarcomas excluding carcinosarcomas

LMS: Leiomyosarcoma
CS: Carcinosarcoma
ESS: Endometrial stromal sarcoma

Symptoms

The most common presenting symptom of uLMS is

- Abnormal vaginal bleeding (53 %)
- (fast growing) Abdominopelvic mass (28 %)
- Abdominopelvic pain (13 %)
- Asymptomatic (6 %)
Diagnosis

• LMS,
  - is typically diagnosed postoperatively,
  - but in rare cases it is diagnosed with endometrial sampling preoperatively
  - or with frozen section intraoperatively.

• There is no single preoperative test that can reliably differentiate benign from malignant uterine disease.

Tumor Markers in uLMS

- There are no reliable serum tumor markers for uterine leiomyosarcoma.

- Serum CA-125 is elevated in 17% to 33% of leiomyosarcomas, therefore it should not be routinely used in the evaluation and diagnosis of these tumors.

- Serum lactate dehydrogenase (LDH) may be an interesting additive to imaging in the evaluation of uterine lesions concerning for uLMS.

  - Total LDH (227 - 412 IU/L) and isoenzyme LDH³ (21.2–29.8% of total LDH) increases in uLMS. however, these tests are not routinely used

(Diagnosis) Imaging

• **Preoperative imaging** is limited in differentiating benign from malignant uterine lesions, especially in the absence of obvious extruterine disease.

• Leiomyomas and uterine sarcomas appear similar; both are focal masses within the uterus and both can have central necrosis.

• Pelvic ultrasound followed by MRI is the most useful imaging strategy.

• **Sonographic evaluation →** mixed echogenic and poor echogenic parts; central necrosis; and color Doppler findings of irregular vessel distribution, low impedance to flow and high peak systolic velocity......

• However, many of these characteristics may also be found in benign leiomyomas.

Diagnosis

Imaging

- Diffusion weighted MRI may be helpful in women in whom there is a suspicion of sarcoma; however, it does not provide a definitive diagnosis.
  - High signal intensity is not a reliable indicator of uterine sarcoma.
  - A consistent finding in leiomyosarcomas is the absence of calcifications
  - Finally, the presence of intralesional hemorrhage appears to be suggestive of sarcoma

- **Computed tomography (CT) does not reliably differentiate between leiomyomas and uterine sarcomas.**

- **Positron emission tomography/CT with fluorodeoxyglucose (FDG) does not appear to be useful to distinguish between leiomyomas and uterine sarcomas.**

- **Imaging is needed to rule out metastatic disease following pathologic confirmation of the diagnosis.** *(Most of the time)*

Diagnosis

• Because LMS arises within the uterine smooth muscle, biopsy of the malignant tissue is difficult, and many lesions are found only at final pathology.

• Among women with leiomyosarcoma who underwent endometrial sampling before surgery (n = 68), the sensitivity for a diagnosis of features of a malignant smooth muscle neoplasms was 52 percent (leiomyosarcoma 35 percent and other features suspicious for malignancy 16 percent). There was no significant difference in the performance of the test between office endometrial biopsy and dilation and curettage.

• Frozen section analysis cannot definitively diagnose or exclude uterine sarcoma !!!

Staging uLMS

Staging—Uterine Sarcoma

Table 3
AJCC Tumor-Node-Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Systems for Uterine Sarcomas (includes Leiomyosarcoma and Endometrial Stromal Sarcoma)

Leiomyosarcoma and Endometrial Stromal Sarcoma

<table>
<thead>
<tr>
<th>T FIGO Stage</th>
<th>Primary Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to the uterus</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor 5 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor more than 5 cm</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor extends beyond the uterus, within the pelvis</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor involves adnexa</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor involves other pelvic tissues</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor infiltrates abdominal tissues</td>
</tr>
<tr>
<td>T3a</td>
<td>One site</td>
</tr>
<tr>
<td>T3b</td>
<td>More than one site</td>
</tr>
<tr>
<td>T4</td>
<td>Invades bladder or rectum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N FIGO Stage</th>
<th>Regional Lymph Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N0(i+)</td>
<td>Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M FIGO Stage</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis (excluding adnexa, pelvic, and abdominal tissues)</td>
</tr>
</tbody>
</table>

G Histologic Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Grade cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>G2</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>G3</td>
<td>Poorly differentiated or undifferentiated</td>
</tr>
</tbody>
</table>

Table 4. AJCC Prognostic Groups

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IC</td>
<td>T1c</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>T1-3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4</td>
<td>Any</td>
<td>N0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T</td>
<td>Any</td>
<td>M1</td>
</tr>
</tbody>
</table>
Hysterectomy

• For patients with uLMS that is confined to the uterus at time of surgery → **total hysterectomy is recommended**

• Several retrospective studies show that women with LMS diagnosed following uterine morcellation have a high risk for sarcomatosis on re-exploration and have poorer survival outcomes

  *(Avoid morcellation of uterus with suspicious fibroid)*

---

Disease confined to the uterus (FIGO Stage I)

**Ooferectomy**

- For menopausal or elderly perimenopausal women
  
  uLMS that is confined to the uterus at time of surgery \(\rightarrow\) **BSO is recommended**

  However, it is not clear if BSO influences survival in women with newly diagnosed LMS.

- For young premenopausal women
  
  These subpopulation may wish to retain their ovaries for fertility preservation. In addition, oophorectomy in these patients will result in premature menopause, which may impact quality of life.

  **Recommendations regarding BSO must be individualized for them**

LMS confined to the uterus with estrogen and/or progesterone receptor-positivity \(\rightarrow\) **BSO is recommended**

---

Complete Cytoreduction

- For patients with uLMS that is confined to the uterus at time of surgery → **Complete cytoreduction was significantly associated with disease-free survival.**

- For patients with uLMS that is confined to the pelvis at time of surgery → **Complete cytoreduction may have a potential role!**

- Although the data are limited to small patient series, an optimal cytoreduction (to no gross residual disease) is associated with improved overall survival compared with women with residual disease at the end of surgery.

Women with LMS confined to the uterus have a low incidence of lymph node involvement (less than 5%)!!!

- For patients with uLMS that is confined to the uterus at time of surgery → **Lymphadenectomy is not recommended.**

- For patients with uLMS that is confined to the uterus at time of surgery with bulky lymph nodes → **Lymphadenectomy is recommended.**

- For patients with uLMS that is confined to the pelvis at time of surgery with bulky lymph nodes → **Lymphadenectomy may be considered as a part of complete cytoreduction.**

Advance stage (FIGO stage III)

• For women with disease not amenable to an optimal cytoreduction (including those with metastatic disease extending beyond the pelvis) → there is no benefit to surgery.

• In at least one study, the presence of residual disease following surgery was associated with a poor prognosis compared with a complete cytoreduction. In addition, surgery may delay the start of systemic treatment.

• Therefore, in the absence of high quality data showing a benefit to surgical cytoreduction → initiate medical therapy rather than surgical cytoreduction.

Surgery The Basics

Metastatic Disease (FIGO Stage IV)

Surgery may be reasonable in the following scenarios:

- Total hysterectomy may serve as palliation for women experiencing significant pelvic symptoms (i.e., pain or vaginal bleeding).

- Total hysterectomy and resection of metastatic disease may be considered for selected patients with a relatively low disease burden beyond the peritoneal cavity (e.g., isolated metastatic disease in the lung or liver). Complete resection in these patients may be possible with limited morbidity.

For women whose specimen was found postoperatively to be LMS, a second surgical procedure for the sole purpose of staging was not required → Postop. CT of the chest, abdomen, and pelvis to help guide postoperative treatment. HOWEVER !!!

• For women who underwent a supracervical hysterectomy → removal of the cervix with BSO is recommended.
• For women who underwent myomectomy → hysterectomy combined with BSO is recommended.
• For women in whom the tumor was morcellated → surgical exploration and staging is recommended to ensure any residual peritoneal disease is resected.

Oduyebo T et al. The value of re-exploration in patients with inadvertently morcellated uterine sarcoma. Gynecol Oncol 2014
Adjuvant Treatment
Early-stage disease:

• Observation is the standard of care following resection of a uterus-limited, intact specimen. While chemotherapy or pelvic radiation is sometimes considered following surgery for LMS, no form of adjuvant therapy has demonstrated improvement in survival outcomes compared with observation.

• Randomized trials comparing regimens (Docetaxel, gemcitabine and doxorubicin) with observation did not show improvement in recurrence rates or survival outcomes.

• These data support surveillance/observation for women with stage I, uterus-limited LMS rather than chemotherapy

• The use of adjuvant radiotherapy (RT) has no impact on survival outcomes for women with early-stage LMS

Hensley ML et al. Adjuvant therapy for high-grade, uterus-limited leiomyosarcoma: results of a phase 2 trial (SARC 005). Cancer 2013
Adjuvant Treatment

Advanced disease:

• Women with intra-abdominal involvement of disease (stage III) or distant metastases (stage IV) who have undergone complete resection of disease have a high risk of disease progression following surgery alone. Therefore, adjuvant chemotherapy is offered rather than postoperative surveillance, although whether treatment improves survival has not been established.

• For women with advanced LMS, the administration of combined-modality treatment (eg, pelvic radiation plus chemotherapy) is investigational.

• Compared with pelvic RT only, the addition of combination chemotherapy to RT was associated with the following non-statistically significant trends.
  • A lower incidence of recurrence (39 versus 62 percent)
  • Higher PFS at three years (52 versus 41 percent)
  • Improvement in OS at three years (80 versus 67 percent)

Leiomyosarcoma: Diagnosis, surgery and adjuvant treatment

Prof. Dr. M. Yavuz SALİHOĞLU
I.U. Istanbul Faculty of Medicine
Department of Gynaecology & Obstetrics
Division of Gynaecologic Oncology

Thank You