STUMPed for a Diagnosis
Contemporary Management of Uterine Sarcomas

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Objectives—what a gynecologist should know

• Definitions
• Diagnosis
• Treatment

Disclosures
I have no financial disclosures

WHO Classification of Uterine Mesenchymal Tumors

• Endometrial stromal and related tumors
  • Endometrial stromal sarcoma, low grade
  • Endometrial stromal nodule
  • Undifferentiated endometrial stromal sarcoma
• Smooth muscle tumors
  • Leiomyosarcoma
    – Epithelioid variant
    – Myxoid variant
  • Smooth muscle tumor of uncertain malignant potential
• leiomyoma, not otherwise specified
  • Mitotically active variant
  • Cellular variant
  • Hemorrhagic cellular variant
  • Epithelioid variant
  • Myxoid
  • Atypical variant
  • Lipoleiomyoma variant
  • Growth pattern variants
WHO Classification of Uterine Mesenchymal Tumors

- Diffuse leiomyomatosis
- Dissecting leiomyoma
- Intravenous leiomyomatosis
- Metastasizing leiomyoma
- Perivascular epithelioid cell tumor
- Adenomatoid tumor
- Other benign, malignant, and miscellaneous mesenchymal tumors

- Mixed epithelial and mesenchymal tumors
  - Carcinosarcoma
  - Adenosarcoma
  - Carcinofibroma
  - Adenofibroma
  - Adenomyoma
  - Atypical polypoid variant

Carcinosarcomas are more like metaplastic carcinomas
Uterine sarcomas are heterogeneous, with different clinical presentations, responses to therapy, and outcomes

Epidemiology

<table>
<thead>
<tr>
<th>Uterine malignancies</th>
<th>Uterine sarcomas</th>
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<tbody>
<tr>
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Many premenopausal women

<table>
<thead>
<tr>
<th>Mean/Median age</th>
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<tbody>
<tr>
<td>Endometrial stromal sarcoma</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
</tr>
<tr>
<td>Undifferentiated sarcoma</td>
</tr>
<tr>
<td>Smooth muscle tumor of uncertain malignant potential (STUMP)</td>
</tr>
</tbody>
</table>
**Epidemiology**

**Risk Factors**
- Prior radiation
  - Possible association with carcinosarcoma, undifferentiated sarcoma
  - Less association with leiomyosarcoma or STUMP
  
  Giuntoli et al, Gynecol Oncol 2003  
  Guntupalli et al, Gynecol Oncol 2009
- Hormone exposure
  - Tamoxifen?
- Hereditary Predisposition
  - Hereditary leiomyomatosis and renal cell cancer (HLRCC)

**Clinical Presentation**

**Signs & Symptoms**
- Bleeding, abdominopelvic mass, presumed fibroids
- No reliable serum markers
  - CA125 elevated in 17-33%

  Park et al, J Cancer Res Clin Oncol 2008
- Endometrial sampling should be performed as appropriate
  - Up to 86% sarcomas diagnosed, with 64% specificity

  Bansal et al Gynecol Oncol 2008

**Preoperative Imaging**

- Criteria to distinguish leiomyoma from mesenchymal cancers
- **Ultrasound**
  - Single tumor
  - Non-myometrial origin
  - Absence of acoustic shadowing
  - Thickened endometrium
  - Ascites
- **MRI**
  - Poorly defined margins
  - Intermediate or high signal intensity in T1 or T2
  - Cystic alteration of tumor
  - Heterogeneity of enhancement


<table>
<thead>
<tr>
<th>Adding LDH to Dynamic MRI</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH</td>
<td>100%</td>
<td>87.7%</td>
<td>86.6%</td>
<td>38.5%</td>
<td>100%</td>
</tr>
<tr>
<td>MRI</td>
<td>100%</td>
<td>96.9%</td>
<td>97.1%</td>
<td>71.4%</td>
<td>100%</td>
</tr>
<tr>
<td>Dynamic MRI</td>
<td>100%</td>
<td>87.5%</td>
<td>90.5%</td>
<td>71.4%</td>
<td>100%</td>
</tr>
<tr>
<td>LDH + Dynamic MRI</td>
<td>100%</td>
<td>99.2%</td>
<td>99.3%</td>
<td>90.9%</td>
<td>100%</td>
</tr>
</tbody>
</table>

  DLM

  LMS

  Goto et al, Int J Gynecol Cancer 2002
Preoperative Diagnosis is Poor

Norwegian Cohort Study, 2000-2012

- 212 cases of leiomyosarcoma, mean age 58.1
- 110 (51.9%) with abnormal bleeding
- 49 (23.1%) diagnosed pre-op, 48 (22.6%) suspected pre-op, 115 (54.2%) diagnosed postoperatively

- 55/142 (38.7%) diagnosed by curettage or biopsy
- 45/55 (81%) suggested by MRI
- 64/107 (59.8%) suggested by CT


Have an Index of Suspicion

Surgical approach

- When choosing the route and method of hysterectomy, the physician should take into consideration how the procedure may be performed most safely and cost-effectively to fulfill the medical needs of the patient. Evidence demonstrates that, in general, vaginal hysterectomy is associated with better outcomes and fewer complications than laparoscopic or abdominal hysterectomy. When it is not feasible to perform a vaginal hysterectomy, the surgeon must choose between laparoscopic hysterectomy, robot-assisted hysterectomy, or abdominal hysterectomy.

ACOG Committee Opinion 444, reaffirmed 2011

Morcellation

- Power morcellation or other techniques that cut up the uterus in the abdomen have the potential to disseminate an otherwise contained malignancy throughout the abdominal cavity. For this reason, the Society of Gynecologic Oncology (SGO) asserts that it is generally contraindicated in the presence of documented or highly suspected malignancy, and may be inadvisable in premalignant conditions or risk-reducing surgery.

- The SGO recognizes that currently there is no reliable method to differentiate benign from malignant leiomyomas (leiomyosarcomas or endometrial stromal sarcomas) before they are removed. Furthermore, these diseases offer an extremely poor prognosis even when specimens are removed intact.

SGO Position Statement, 2013
Impact of Morcellation: Occult Sarcoma

Kaiser Population Cohort study, 2009-2013
- 34,208 hysterectomies → 125 with occult uterine sarcomas
- Incidence of all sarcomas: 0.36%
- Incidence of leiomyosarcomas: 0.23%

- 111 Stage I leiomyosarcomas
  - 35 cases morcellated: 7 power, 28 non-power
  - Higher risk of death at 1 year after morcellation: 5.12 (95% CI 1.33-19.76, p = 0.02). Numbers too small for power morcellation effect.

Raine-Bennett et al, Obstet Gynecol 2016

Impact of Morcellation: Survival

Korean Cohort study, 1989-2010
- 56 cases of Stage I & II uterine leiomyosarcoma
- 25 uteri morcellated
  - Uterine size: 7.3 vs 9.8cm, p = 0.022
  - Ovarian preservation: 38.7 vs 72%, p = 0.013

Multivariate analysis for poorer overall survival
  - Stage: OR 20.34 (95% CI 1.23-325.58, p = 0.033)
  - Morcellation: OR 3.11 (95% CI 1.07-9.06, p = 0.038)

Park et al, Gynecol Oncol 2011

Uterine Preservation

Pathology dependent
Case reports only

Ovarian Preservation

Low risk to keep ovaries in Leiomyosarcoma
- Ovarian metastases:
  - Leiomyosarcoma: 3.1-3.7%
  - Carcinosarcoma: 12%
  - Endometrial stromal sarcoma: 13%, but usually not occult

- Bilateral oophorectomy recommended for Carcinosarcoma
- Ovarian preservation may impact recurrence, hormonal treatment options in Endometrial stromal sarcoma

Major et al, Cancer 1993
Giuntoli et al, Gynecol Oncol 2003
Lymphadenectomy

No known survival advantage to LND

- Lymph node metastases
  - Leiomyosarcoma: 7%, but <3% occult
  - Carcinosarcoma: 27%, 20% occult
  - Endometrial stromal sarcoma: 16%, 6% occult

- Suggest lymphadenectomy for carcinosarcoma
- Consider lymphadenectomy for endometrial stromal sarcoma
- Resect bulky lymph nodes

Major et al, Cancer 1993
Shah et al, Obstet Gynecol 2008

Staging—Leiomyosarcomas & Endometrial Stromal Sarcomas (FIGO 2009)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor limited to uterus</td>
</tr>
<tr>
<td>IA</td>
<td>Less than or equal to 5cm</td>
</tr>
<tr>
<td>IB</td>
<td>More than 5cm</td>
</tr>
<tr>
<td>II</td>
<td>Tumor extends beyond the uterus, within the pelvis</td>
</tr>
<tr>
<td>IIA</td>
<td>Adnexal involvement</td>
</tr>
<tr>
<td>IIB</td>
<td>Involvement of other pelvic tissues</td>
</tr>
<tr>
<td>III</td>
<td>Tumor invades abdominal tissues (not just protruding into abdomen)</td>
</tr>
<tr>
<td>IIIA</td>
<td>One site</td>
</tr>
<tr>
<td>IIIB</td>
<td>More than one site</td>
</tr>
<tr>
<td>IIIC1</td>
<td>Metastasis to pelvic and/or para-aortic lymph nodes</td>
</tr>
<tr>
<td>IIIA</td>
<td>Tumor invades bladder and/or rectum</td>
</tr>
<tr>
<td>IIIB</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>

Staging—Adenosarcomas (FIGO 2009)

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<tr>
<th>Stage</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor limited to uterus</td>
</tr>
<tr>
<td>IA</td>
<td>No myometrial invasion</td>
</tr>
<tr>
<td>IB</td>
<td>Less than or half myometrial invasion</td>
</tr>
<tr>
<td>IC</td>
<td>More than half myometrial invasion</td>
</tr>
<tr>
<td>II</td>
<td>Tumor extends beyond the uterus, within the pelvis</td>
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<tr>
<td>IIC</td>
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</tr>
<tr>
<td>IVA</td>
<td>Tumor invades bladder and/or rectum</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastases</td>
</tr>
</tbody>
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Staging—Carcinosarcomas are staged as endometrial carcinomas (FIGO 2009)

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<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>No or less than half myometrial invasion</td>
</tr>
<tr>
<td>IB</td>
<td>Invasion equal to or more than half of the myometrium</td>
</tr>
<tr>
<td>II</td>
<td>Tumor invades the cervical stroma but does not extend beyond the uterus</td>
</tr>
<tr>
<td>IIA</td>
<td>Tumor invades serosa of the corpus uterus and/or adnexae</td>
</tr>
<tr>
<td>IIIB</td>
<td>Vaginal and/or parametral involvement</td>
</tr>
<tr>
<td>IIIC1</td>
<td>Metastasis to pelvic lymph nodes</td>
</tr>
<tr>
<td>IIIC2</td>
<td>Metastasis to para-aortic lymph nodes, with or without positive pelvic nodes</td>
</tr>
<tr>
<td>IVA</td>
<td>Tumor invades bladder and/or bowel mucosa</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastases including intra-abdominal and inguinal lymph nodes</td>
</tr>
</tbody>
</table>
Stage Distribution

5 Year Overall Survival—Stage I
- ESS: 97%
  - All stages ESS: 92%
  - Leiomyosarcoma: 57%
  - Carcinosarcoma: 62%
  - Undifferentiated sarcoma: 52%
  - Adenosarcoma
    - IA: 84%
    - IB: 65%

EORTC Randomized Phase III trial—1988-2001
- 224 patients with Stage I or II uterine sarcomas from 36 institutions
  - 99 LMS, 92 CS, 30 ESS, 3 other
- Randomization of pelvic RT 5040cGy versus observation
- Overall relapse rate: 47% vs 50%
- Locoregional relapse rate: 21% vs 40%, p = 0.0004
  - Carcinosarcomas: 24% vs 47%, p < 0.05
  - Leiomyosarcomas: 20% vs 24%
- Overall survival, carcinosarcomas: HR 1.58, 95% CI 0.83-3.01

NCCN Sarcoma Chemo Options
Clinical Trials strongly recommended
- Combo:
  - Docetaxel/gemcitabine (LMS)
  - Doxorubicin/ifosfamide
  - Doxorubicin dacarbazine
  - Gemcitabine/dacarbazine
  - Gemcitabine/vinorelbine
- Hormonal (for LGESS, ER/PR (+) & uLMS)
  - Medroxyprogesterone acetate
  - Megestrol acetate
  - Aromatase inhibitors
  - GnRH analogs
- Single agent
  - Dacarbazine
  - Doxorubicin
  - Epirubicin
  - Gemcitabine
  - Ifosfamide
  - Doxil
  - Pazapanib
  - Temozolomide
  - Vinorelbine (cat 2B)
  - Docetaxel (cat 3)

Treatment--Hormones
- ER & PR in about 56% of sarcomas
  - Mostly in Endometrial Stromal Sarcomas
  - Many case series of hormonal therapies
    - Megestrol acetate
    - Other progestational agents
    - GnRH analogues
    - Aromatase inhibitors
- Trials in Leiomyosarcomas ongoing.
Molecular Considerations

The Cancer Genome Atlas Project

- Carcinosarcomas: most resemble serous endometrial or ovarian cancers.
  - Extensive copy number variation
  - Recurrent mutations in p53, FBXW7, PIK3CA, PPP2R1A, PTEN
- 7 sarcoma subtypes under study
  - Uterine and non-uterine leiomyosarcoma
  - Dedifferentiated liposarcoma, desmoid sarcoma, malignant peripheral nerve sheath tumor, myxofibrosarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma

So what is a STUMP?

- “Uterine Smooth Muscle Tumors that no one talks about”
- Smooth muscle tumors
  - Leiomyosarcoma
  - Epithelioid variant
  - Myxoid variant
- Smooth muscle tumor of uncertain malignant potential

Not Quite a Leiomyosarcoma

- Two diagnostic features are required to make the diagnosis of leiomyosarcoma
  - Significant and diffuse cytologic atypia
  - At least 10 mitoses per 10 high powered fields
  - Coagulative tumor necrosis
- Excision required for thorough histologic examination
- Differential: metastasizing leiomyoma, metastatic low grade leiomyosarcoma

Characterizing STUMPs

- MD Anderson case series, 1990-2005
  - 41 patients, mean age 43 (range 25-75)
  - 10 patients had myomectomy, others hysterectomy
  - Mean follow-up time 45 months (1-171 months)
  - 7.3% recurrence
    - PFS: 13, 47, 68 months
    - All were diagnosed at hysterectomy
    - All 3 alive and disease free at median follow-up of 128 months

Gyntupalli et al, Gynecol Oncol 2009
STUMPed for a diagnosis

- Bland histologic appearance
- Synchronous or metachronous involvement of different anatomic sites
  - Pelvis, lung, soft tissue, bowel, omentum, lymph nodes, bone
- Typical treatment: Excision
- Consider hormone blockade.
- Pay attention to recurrences
- Subsequent tumors may be more aggressive
  - More aggressive tumors may warrant chemo

Benign Metastasizing Leiomyoma

Diffuse Leiomyomatosis

Intravenous Leiomyomatosis

Taftaf et al, Case Rep Oncol Med 2014

Dim et al, Niger Med J 2012

Tenzer et al, J Clin Gynecol Obstet 2015
A rose by any other name…

- Many tumors are called sarcomas, some are mesenchymal tumors, but not high grade sarcomas
- Have a level of suspicion for occult lesions
- Ovaries and lymph nodes might be important, but can be readdressed on final pathology
- Get a review by a Gynecologic Pathologist
- Refer to Gynecologic Oncologist if consultation needed
- Molecular characteristics may unlock answers in the future