Protocol for the Examination of Specimens From Patients With Sarcoma of the Uterus

Protocol applies to sarcomas of the uterus.

Based on AJCC/UICC TNM, 7th edition and FIGO 2009 Annual Report
Protocol web posting date: December 2013

Procedures
• Hysterectomy
• Myomectomy

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Gynecologic • Uterine Sarcoma

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Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: Uterine Sarcoma 3.0.0.0

Summary of Changes
This is a new protocol.
UTERUS: Hysterectomy and Myomectomy, With or Without Other Organs or Tissues

Select a single response unless otherwise indicated.

Specimen (select all that apply)
- Uterine corpus
- Cervix
- Right ovary
- Left ovary
- Right fallopian tube
- Left fallopian tube
- Left parametrium
- Right parametrium
- Peritoneum
- Vaginal cuff
- Omentum
- Other (specify): ___________________________
- Not specified

Procedure (select all that apply)
- Supracervical hysterectomy
- Simple hysterectomy
- Radical hysterectomy
- Myomectomy
- Right oophorectomy
- Left oophorectomy
- Right salpingectomy
- Left salpingectomy
- Right salpingo-oophorectomy
- Left salpingo-oophorectomy
- Omentectomy
- Peritoneal biopsies
- Other (specify): __________________________
- Not specified

Lymph Node Sampling (select all that apply)
- Performed
  - Pelvic lymph nodes
  - Paraaortic lymph nodes
  - Other (specify): __________________________
- Not performed
- Not known

+ Data elements preceding by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
**Specimen Integrity**
- Hysterectomy specimen (intact)
- Hysterectomy specimen without cervix
- Morcellated hysterectomy specimen
- Myomectomy (intact)
- Morcellated myomectomy specimen
- Other (specify): ____________________________

**Tumor Site**
- Fundus
- Lower uterine segment/isthmus
- Cervix
- Other (specify): ____________________________

**Tumor Size**
- Greatest dimension: ___ cm
- Additional dimensions: ___ x ___ cm
- Cannot be determined

**Histologic Type (select all that apply) (Notes B, C, D)**
- Leiomyosarcoma
- Low-grade endometrial stromal sarcoma
- Low-grade endometrial stromal sarcoma with:
  - Smooth muscle differentiation
  - Sex cord elements
  - Glandular elements
  - Other (specify): ____________________________
- High-grade endometrial stromal sarcoma
- Undifferentiated uterine/endometrial sarcoma
- Adenosarcoma
- Adenosarcoma with:
  - Rhabdomyoblastic differentiation
  - Cartilagenous differentiation
  - Osseous differentiation
  - Other heterologous element (specify): ____________________________
- Adenosarcoma with sarcomatous overgrowth
- Other (specify): ____________________________

# Low-grade endometrial sarcoma is distinguished from benign endometrial stromal nodule by infiltration into the surrounding myometrium and/or lymphovascular invasion. Minor marginal irregularity in the form of tongues <3 mm (up to 3) is allowable for an endometrial stromal nodule. This protocol does not apply to endometrial stromal nodule.

**Histologic Grade**

**Leiomyosarcoma** (Note D)
- Not applicable

**Endometrial Stromal Sarcoma** (Note C)
- Low grade
- High grade
- Cannot be assessed

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Adenosarcoma (Note B) (select all that apply)
___ Low grade
___ High grade
___ With sarcomatous overgrowth
___ Cannot be assessed

Myometrial Invasion (only for adenosarcoma)
___ Cannot be determined (explain): ______________________________
___ Tumor is limited to the endometrium or cervical surface without myometrial invasion
___ Tumor invades less than or equal to 50% (≤50%) total myometrial thickness
___ Tumor invades greater than 50% (>50%) total myometrial thickness

Involvement of Cervix
___ Cannot be determined
___ Not involved
___ Tumor involves the glandular surface of the cervix only
___ Tumor invades the cervical stromal connective tissue

Extent of Involvement of Other Organs (select all that apply)
___ Not applicable
___ Right ovary
    ___ Involved
    ___ Not involved
___ Left ovary
    ___ Involved
    ___ Not involved
___ Right fallopian tube
    ___ Involved
    ___ Not involved
___ Left fallopian tube
    ___ Involved
    ___ Not involved
___ Vaginal cuff
    ___ Involved
    ___ Not involved
___ Right parametrium
    ___ Involved
    ___ Not involved
___ Left parametrium
    ___ Involved
    ___ Not involved
___ Omentum
    ___ Involved
    ___ Not involved
___ Other (specify): ______________________________
Margins
___ Cannot be assessed
___ Uninvolved by sarcoma
    + Distance of sarcoma from closest margin: ___ mm
    + Specify margin: __________________________
___ Involved by sarcoma
    Specify margin(s): ________________________

Lymph-Vascular Invasion
___ Not identified
___ Present
___ Indeterminate

+ Peritoneal Ascitic Fluid
  + ___ Negative for malignancy
  + ___ Atypical and/or suspicious (explain): __________________________
  + ___ Malignant (positive for malignancy)
  + ___ Unsatisfactory/nondiagnostic (explain): ________________________

+ Peritoneal Washing
  + ___ Negative for malignancy
  + ___ Atypical and/or suspicious (explain): __________________________
  + ___ Malignant (positive for malignancy)
  + ___ Unsatisfactory/nondiagnostic (explain): ________________________

Lymph Nodes
___ No nodes submitted or found
Right pelvic lymph nodes:
    Number examined: ___
    ___ Number cannot be determined (explain): ________________________
    Number involved: ___
    ___ Number cannot be determined (explain): ________________________
Left pelvic lymph nodes:
    Number examined: ___
    ___ Number cannot be determined (explain): ________________________
    Number involved: ___
    ___ Number cannot be determined (explain): ________________________
Paraaortic lymph nodes:
    Number examined: ___
    ___ Number cannot be determined (explain): ________________________
    Number involved: ___
    ___ Number cannot be determined (explain): ________________________
Lymph nodes (other, specify): ____________________________
    Number examined: ___
    ___ Number cannot be determined (explain): ________________________
    Number involved: ___
    ___ Number cannot be determined (explain): ________________________

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Pathologic Staging (pTNM [FIGO])

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (posttreatment)

Leiomyosarcoma, Endometrial Stromal Sarcoma, and Undifferentiated Endometrial Sarcoma/Uterine Sarcoma

Primary Tumor (pT)
___ pTX [:] Primary tumor cannot be assessed
___ pT0 [:] No evidence of primary tumor
___ pT1 [I]: Tumor is limited to the uterus
___ pT1a [IA]: Tumor is 5 cm or less (≤5 cm) in greatest dimension
___ pT1b [IB]: Tumor is greater than 5 cm (>5 cm) in greatest dimension
___ pT2 [II]: Tumor extends beyond the uterus, but is within the pelvis (tumor extends to extrauterine pelvic tissue)
___ pT2a [IIA]: Tumor involves the adnexa
___ pT2b [IIB]: Tumor involves other pelvic tissue
___ pT3 [III]: Tumor invades abdominal tissues (not just protruding into the abdomen)
___ pT3a [IIIA]: Tumor invades abdominal tissues at one site
___ pT3b [IIIB]: Tumor invades abdominal tissues at more than one site
___ pT4 [IVA]: Tumor invades bladder mucosa and/or rectum

Regional Lymph Nodes (pN)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1 [IIIC]: Regional lymph node metastasis to pelvic lymph nodes

Distant Metastasis (pM)
___ Not applicable
___ pM1 [IVB]: Distant metastasis (excluding adnexa, pelvic and abdominal tissues)
   Specify site(s), if known: ______________________________

Adenosarcoma

Primary Tumor (pT)
___ pTX [:] Primary tumor cannot be assessed
___ pT0 [:] No evidence of primary tumor
___ pT1 [I]: Tumor is limited to the uterus
___ pT1a [IA]: Tumor is limited to the endometrium/endocervix without myometrial invasion
___ pT1b [IB]: Tumor invades less than or equal to 50% (≤50%) total myometrial thickness
___ pT1c [IC]: Tumor invades greater than 50% (>50%) total myometrial thickness
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Regional Lymph Nodes (pN)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1 [IIIC]: Regional lymph node metastasis to pelvic lymph nodes

Distant Metastasis (pM)
___ Not applicable
___ pM1 [IVB]: Distant metastasis (excluding adnexa, pelvic and abdominal tissues)
  Specify site(s), if known: ______________________________

+ Ancillary Studies
+ Specify: ______________________________
+ ___ Not performed

+ Comment(s)
Explanatory Notes

A. Carcinosarcoma
Carcinosarcoma (malignant mixed mullerian tumor) is excluded from the uterine sarcoma diagnostic category as it is considered in tumors of the endometrial epithelium.

B. Adenosarcoma
According to World Health Organization (WHO) criteria, mitotic activity in the mesenchymal component in excess of 2 or more per 10 high-power fields (HPFs) is required for a diagnosis of adenosarcoma, but others use a cut-off of 4 per 10 HPFs. However, given the multiple and well-known problems associated with counting mitotic figures and the fact that the number of mitoses may be variable from area to area, in practice, if the characteristic leaf-like architecture of adenosarcoma is present with periglandular cufing resulting in a cambium layer, a diagnosis of adenosarcoma should be strongly considered with mitotic counts <2 per 10 HPFs or even in the absence of mitotic figures. In adenosarcomas without sarcomatous overgrowth, it is recommended to record on the pathology report whether the stromal component is morphologically “low grade” or “high grade.” Even though there are no studies showing that this is of prognostic significance, anecdotal evidence suggests that even a small focus of “high-grade” sarcoma may result in an adverse behavior. It is suggested that the parameter of nuclear atypia be used to distinguish between low grade and high grade. In low-grade neoplasms, the atypia should be akin to that seen in low-grade endometrial stromal sarcoma. Sarcomatous overgrowth in adenosarcoma is defined as the presence of pure sarcoma, usually high grade and without an epithelial component, occupying at least 25% of the tumor.

Adenosarcomas rarely exhibit lymphovascular invasion unless associated with deep myometrial invasion or sarcomatous overgrowth.

The depth of myometrial invasion is important in the substaging of stage I adenosarcomas (tumor confined to the uterus). Stage IA tumors are limited to the endometrium or endocervix with no myometrial involvement, stage IB equates to less than or half of myometrial invasion and stage 1C equates to more than one half myometrial invasion. This staging system is similar to the 1988 FIGO staging system for carcinomas of the uterine corpus. Since low-grade endometrial stromal sarcoma and leiomyosarcoma are predominantly myometrial-based lesions, myometrial invasion per se is not used in the staging of these neoplasms.

In most adenosarcomas with a low-grade stromal component without sarcomatous overgrowth, the stromal element expresses estrogen receptor (ER), progesterone receptor (PgR), CD10, and WT1, is negative (“wild-type”) with p53 and exhibits a low MIB1 proliferation index. Thus, the immunophenotype resembles that of low-grade endometrial stromal sarcoma. Smooth muscle actin and desmin may also be positive. In areas of high-grade sarcoma and of sarcomatous overgrowth, the mesenchymal component exhibits a higher MIB1 proliferation index and may be p53 positive/aberrant. There is usually loss of expression of the cell differentiation markers ER, PgR and CD10, the immunophenotype being similar to that of an undifferentiated sarcoma. Rhabdomyosarcomatous elements in adenosarcomas express desmin and sometimes the skeletal muscle markers myogenin and myoD1. Sex cord-like elements may express inhibin and calretinin.

C. Endometrial Stromal Sarcoma
Even though in the past endometrial stromal sarcomas (ESS) were classified as low grade (LG) and high grade (HG) based on mitotic activity, the largest and most comprehensive review of these tumors by Chang and colleagues in 1999 showed that mitotic activity was not predictive of outcome in stage I tumors. Thus, the diagnosis of HG-ESS was discouraged in those tumors that resemble proliferative-phase endometrial stroma but in which the mitotic index exceeded 10 per 10 HPFs. Currently many expert gynecologic pathologists, without any proven basis outside of personal experience, make the
diagnosis of HG-ESS when there is a transition from high-grade undifferentiated sarcoma to areas that can be recognized as conventional LG-ESS. However, recently, a subset of cases previously diagnosed as HG-ESSs has been histologically and genetically defined by Lee, Nucci and colleagues. These tumors, the high-grade areas are characterized by cells with a round cell-epithelioid appearance and high-grade cytologic features which often are associated with areas that have the appearance of the fibroblastic variant of low-grade conventional ESS. These tumors have been shown to have a novel genetic fusion between YWHAE and FAM22A/B and harbor t(10;17)(q22;p13). The high-grade areas of the tumor express cyclin D1 but lose CD10, ER, and PgR expression (in contrast to the conventional low-grade areas) consistent with a high-grade sarcoma. It is important to recognize these tumors as they have an intermediate prognosis between LGESS and undifferentiated uterine sarcoma (UUS) and appear not to respond to the usual treatment for low-grade ESS.

Low-grade ESS, high-grade ESS and UUS all exist and should be separately diagnosed, although UUS should be a diagnosis of exclusion (leiomyosarcomas and other high-grade sarcomas, for example rhabdomyosarcoma, should be excluded). Molecular testing is diagnostically unnecessary in conventional ESS and in USS, but is useful in confirming the diagnosis of HG-ESS in tumors with a round cell-epithelioid appearance that can be associated with areas that have the appearance of the fibroblastic variant of conventional LG-ESS.

D. Leiomyosarcoma

By definition, uterine leiomyosarcoma (LMS) is a highly malignant neoplasm with survival rates depending upon the extent of spread. For tumors confined to the uterine corpus, size plays a significant role in prognosis. Despite differences in survival rates, it is clear that stage is a significant factor related to outcome. Histologic grade, however, has not been consistently identified as a significant prognostic parameter. The utility of grading uterine LMS is controversial and no universally accepted grading system exist. In 2011, Veras et al. tried to characterize “low-grade uterine leiomyosarcomas” as a clinicopathological entity but came to the conclusion that this can be diagnosed only retrospectively at present. Furthermore, when the Stanford criteria are strictly applied, all tumors classified as leiomyosarcomas, should be regarded intrinsically as high grade.

Conventional uterine LMS is a cellular tumor composed of fascicles of spindle-shaped cells exhibiting smooth muscle differentiation with moderate to severe pleomorphism. Usually coagulative tumor cell necrosis (CTCN) is present and mitoses exceed 10-15/10 HPF. Two LMS subtypes included in the WHO classification deserve special attention as their pathologic features differ from those of ordinary spindle cell LMS. Epithelioid leiomyosarcoma (E-LMS) is composed predominantly of round or polygonal cells with eosinophilic to clear cytoplasm exhibiting nested, plexiform or cored growth patterns. Nuclear atypia may be only mild and necrosis may be absent. Mitotic rate is generally ≤3/10 HPF and most tumors infiltrate adjacent myometrium. Myxoid leiomyosarcoma (M-LMS) may be grossly gelatinous, microscopically hypocellular with a predominant myxoid stroma and often has a low mitotic rate. In the absence of severe cytologic atypia and high mitotic activity, both epithelioid and myxoid LMS are diagnosed as sarcomas based on their infiltrative borders.

Ancillary Studies in the Differential Diagnosis

Immunoreactivity for smooth muscle actin, muscle specific actin, calponin, desmin, h-caldesmon and heavy chain smooth muscle myosin are commonly seen in uterine LMS. Desmin expression may be focal. Similarly, E-LMS and M-LMS may demonstrate lesser degrees of immunoreactivity for these markers. Cell cycle related markers Ki-67, p53, and p16 are usually overexpressed in LMS compared to leiomyoma. Cytokeratins and EMA may be focally positive in LMS, especially in the epithelioid variant.

E. Undifferentiated Uterine/Endometrial Sarcoma

Undifferentiated uterine/endoemetrial sarcoma (UUS) is a high-grade sarcoma that lacks specific differentiation. Histopathologically these tumors show marked cellular pleomorphism and abundant
mitotic activity with atypical forms. They lack the typical growth pattern and vascularity of low-grade ESS and displace the myometrium in contrast to the infiltrative pattern of low-grade ESS. They often resemble the sarcomatous component of a carcinosarcoma. These sarcomas are most often aneuploid with an S-phase fraction greater than 10%, and are negative for ER and PgR.10 Nucci et al proposed that high-grade ESS with the novel fusion gene YWHAE-FAM22 should be distinguished from undifferentiated uterine/endometrial sarcoma.

F. Other
Other differential diagnostic considerations included in spindle/sarcomatous lesions primary to the uterus include perivascular epithelioid cell tumor (PEComa). PEComa belongs to a group of tumors characterized by both melanocytic and smooth muscle differentiation, and should be recognized separately from smooth muscle tumors.19-21

The TNM staging system for uterine sarcoma endorsed by the American Joint Committee on Cancer (AJCC) and the parallel system formulated by the International Federation of Gynecology and Obstetrics (FIGO) are recommended, as shown below.

According to AJCC/International Union Against Cancer (UICC) convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically infeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

It is important to note that in uterine sarcoma, as in cancer of other organs, the validity of T stage depends upon the adequacy and completeness of the surgical staging.

### TNM Classification and FIGO Staging System for Leiomyosarcoma, Endometrial Stromal Sarcoma and Undifferentiated Uterine Sarcoma

<table>
<thead>
<tr>
<th>TNM Category</th>
<th>FIGO Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>pTX</td>
<td>[-]:</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>pT0</td>
<td>[-]:</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>pT1</td>
<td>[I]:</td>
<td>Tumor is limited to the uterus</td>
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<td>[IA]:</td>
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<tr>
<td>pT1b</td>
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<tr>
<td>pT2</td>
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<td>Tumor extends beyond the uterus, but is within the pelvis (tumor extends to extraperitoneal pelvic tissue)</td>
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pT3 [III]: Tumor invades abdominal tissues (not just protruding into the abdomen)  
pT3a [IIIA]: Tumor invades abdominal tissues at one site  
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pT4 [IVA]: Tumor invades bladder mucosa and/or rectum

Regional Lymph Nodes (pN)*  
pNX: Cannot be assessed  
pN0: No regional lymph node metastasis  
pN1 [IIIC]: Regional lymph node metastasis to pelvic lymph nodes

* Regional lymph nodes include the pelvic, obturator, internal iliac (hypogastric), external iliac, common iliac, paraaortic, presacral, and parametrial lymph nodes.

Distant Metastasis (pM)  
pM0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)  
pM1 [IVB]: Distant metastasis (excluding adnexa, pelvic and abdominal tissues)

Adenosarcoma

TNM FIGO  
Category Stage Definition

Primary Tumor  
pTX [--]: Primary tumor cannot be assessed  
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pT1 [I]: Tumor is limited to the uterus  
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Distant Metastasis (pM)  
pM0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)  
pM1 [IVB]: Distant metastasis (excluding adnexa, pelvic and abdominal tissues)

TNM Stage Groupings  
Stage 0 Tis N0 M0
Stage IA*  T1a  N0  M0  
Stage IB*  T1b  N0  M0  
Stage IC**  T1c  N0  M0  
Stage II  T2  N0  M0  
Stage IIIA  T3a  N0  M0  
Stage IIIB  T3b  N0  M0  
Stage IIIC  T1-T3  N1  M0  
Stage IVA  T4  Any N  M0  
Stage IVB  Any T  Any N  M1  

* Stage IA and IB for adenosarcoma differ from those applied to leiomyosarcoma and endometrial stromal sarcoma  
** Stage IC does not apply for leiomyosarcoma and endometrial stromal sarcoma.

TNM Descriptors

For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or after initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor before multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval and is identified by the “r” prefix: rTNM.

The “a” prefix designates the stage determined at autopsy: aTNM.

Additional Descriptors

Residual Tumor (R)
Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX  Presence of residual tumor cannot be assessed  
R0  No residual tumor  
R1  Microscopic residual tumor  
R2  Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).
References

Bibliography