



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

Version: UterineSarcoma 4.1.0.0

Protocol Posting Date: August 2018

Includes pTNM requirements from the 8th Edition, AJCC Staging Manual, and 2015 FIGO Cancer Report

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Resection	Includes total hysterectomy and supracervical hysterectomy
Tumor Type	Description
Sarcoma	Includes leiomyosarcoma, adenosarcoma, endometrial stromal sarcoma, and undifferentiated uterine/endometrial sarcoma

This protocol is NOT required for accreditation purposes for the following:

Procedure
Biopsy, myomectomy, or removal of tumor in fragments
Primary resection specimen with no residual cancer (eg, prior myomectomy)
Cytologic specimens

The following tumor types should NOT be reported using this protocol:

Tumor Type
Carcinoma (consider the Endometrium or Cervix protocols)
Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

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Accreditation Requirements

This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- Core data elements are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is “not applicable” or “cannot be determined.”
- Conditional data elements are only required to be reported if applicable as delineated in the protocol. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- Optional data elements are identified with “+” and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards.

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (ie, secondary consultation, second opinion, or review of outside case at second institution).

Synoptic Reporting

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired "Data element: Response" format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including “Cannot be determined” if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
 - Anatomic site or specimen, laterality, and procedure
 - Pathologic Stage Classification (pTNM) elements
 - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location

Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report ie, all required elements must be in the synoptic portion of the report in the format defined above.

CAP Laboratory Accreditation Program Protocol Required Use Date: April 2019

CAP Uterine Sarcoma Protocol Summary of Changes

Version 4.1.0.0

The following data elements were modified:

Regional Lymph Nodes - Revised the format to clarify reporting involved and uninvolved nodes

Surgical Pathology Cancer Case Summary

Protocol posting date: August 2018

UTERUS:

Select a single response unless otherwise indicated.

Procedure (select all that apply)

- Total hysterectomy and bilateral salpingo-oophorectomy
- Radical hysterectomy
- Simple hysterectomy
- Supracervical hysterectomy
- Bilateral salpingo-oophorectomy
- Right salpingo-oophorectomy
- Left salpingo-oophorectomy
- Salpingo-oophorectomy, side not specified
- Right oophorectomy
- Left oophorectomy
- Oophorectomy, side not specified
- Bilateral salpingectomy
- Right salpingectomy
- Left salpingectomy
- Salpingectomy, side not specified
- Omentectomy
- Peritoneal biopsies
- Peritoneal washing
- Other (specify): _____

Note: For information about lymph node sampling, please refer to the Regional Lymph Nodes section.

+ Hysterectomy Type

- + Abdominal
- + Vaginal
- + Vaginal, laparoscopic-assisted
- + Laparoscopic
- + Laparoscopic, robotic-assisted
- + Other (specify): _____
- + Not specified

Specimen Integrity

- Intact
- Opened
- Morcellated
- Other (specify): _____

Tumor Size

- Greatest dimension (centimeters): ____ cm
- + Additional dimensions (centimeters): ____ x ____ cm
- Cannot be determined

Histologic Type (select all that apply) (Note A)

- Leiomyosarcoma
- Leiomyosarcoma, epithelioid type
- Leiomyosarcoma, myxoid type
- Endometrial stromal sarcoma, low grade[#]

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

- Endometrial stromal sarcoma with smooth muscle differentiation, low grade
- Endometrial stromal sarcoma with sex cord elements, low grade
- Endometrial stromal sarcoma with glandular elements, low grade
- Endometrial stromal sarcoma, high grade
- Undifferentiated uterine/endometrial sarcoma
- Adenosarcoma
- Adenosarcoma with rhabdomyoblastic differentiation
- Adenosarcoma with cartilaginous differentiation
- Adenosarcoma with osseous differentiation
- Adenosarcoma with other heterologous element (specify): _____
- Adenosarcoma with sarcomatous overgrowth
- Rhabdomyosarcoma
- Malignant perivascular epithelioid cell tumor
- Other histologic type not listed (specify): _____

Low-grade endometrial stromal sarcoma is distinguished from benign endometrial stromal nodule by depth of myometrial invasion ≥ 3 mm, lymphovascular invasion, or ≥ 3 foci of myometrial invasion of any depth. Minor marginal irregularity in the form of tongues < 3 mm is allowable for an endometrial stromal nodule. This protocol does not apply to endometrial stromal nodules.

Histologic Grade (required only for adenosarcoma)

- Low grade
- High grade
- With sarcomatous overgrowth
- Cannot be assessed

Myometrial Invasion (required only for adenosarcoma)

- Not identified
- Present
 - Depth of invasion (millimeters): ____ mm
 - Myometrial thickness (millimeters): ____ mm
 - Percentage of myometrial invasion: ____%

OR, if exact percentage of invasion cannot be determined, state:

- Depth of myometrial invasion cannot be determined (explain): _____
- Myometrial thickness cannot be determined (explain): _____
- Percentage depth of myometrial invasion
- Estimated less than 50% myometrial invasion
- Estimated greater than or equal to 50% myometrial invasion
- Cannot be determined (explain): _____

Other Tissue/ Organ Involvement (select all that apply)

Note: Any organ not selected is either not involved or was not submitted.

- Not applicable
- Not identified
- Right ovary
- Left ovary
- Ovary (side not specified)
- Right fallopian tube
- Left fallopian tube
- Fallopian tube (side not specified)
- Vagina
- Right parametrium
- Left parametrium
- Parametrium (side not specified)
- Pelvic wall
- Omentum

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

___ Other organs/tissue (specify): _____
 ___ Cannot be determined (explain): _____

Margins

___ Cannot be assessed
 ___ Uninvolved by sarcoma
 + Distance of sarcoma from closest margin: ___ mm
 + Specify closest margin: _____
 ___ Involved by sarcoma
 Specify margin(s): _____

Lymphovascular Invasion

___ Not identified
 ___ Present
 ___ Cannot be determined

+ Peritoneal/Ascitic Fluid

+ ___ Not submitted/ unknown
 + ___ Negative for malignancy (normal/benign)
 + ___ Atypical and/or suspicious (explain): _____
 + ___ Malignant (positive for malignancy)
 + ___ Unsatisfactory/nondiagnostic (explain): _____
 + ___ Results pending

Regional Lymph Nodes

Note: Lymph nodes designated as pelvic (parametrial, obturator, internal iliac (hypogastric), external iliac, common iliac, sacral, presacral) and para-aortic are considered regional lymph nodes. Any other involved nodes should be categorized as metastases (pM1) and commented on in the distant metastasis section. Presence of isolated tumor cells no greater than 0.2 mm in regional lymph node(s) is considered NO(i+).

___ No lymph nodes submitted or found

Lymph Node Examination (required only if lymph nodes are present in the specimen)

___ All lymph nodes negative for tumor cells
 ___ Positive for tumor cells (select all that apply)
 Number of Nodes with Metastasis (excludes isolated tumor cells): _____
 Number of Nodes with Isolated Tumor Cells (0.2 mm or less) (if applicable): _____
 Number cannot be determined (explain): _____

Note: Reporting the number of lymph nodes with isolated tumor cells is required only in the absence of metastasis greater than 0.2 mm in other lymph nodes.

+ Nodal Site(s) with Tumor Cells (specify): _____

Number of Lymph Nodes Examined: _____
 ___ Number cannot be determined (explain): _____
 + Specify Site(s): _____

Pathologic Stage Classification (pTNM, AJCC 8th Edition) (Note B)

Note: Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. Only the applicable T, N, or M category is required for reporting; their definitions need not be included in the report. The categories (with modifiers when applicable) can be listed on 1 line or more than 1 line.

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

TNM Descriptors (required only if applicable) (select all that apply)

- r (recurrent)
 y (post-treatment)

For All Sarcomas Excluding Adenosarcoma (including 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: Tumor is limited to the uterus
 pT1a: Tumor 5 cm or less in greatest dimension
 pT1b: Tumor more than 5 cm
 pT2: Tumor extends beyond the uterus, within the pelvis
 pT2a: Tumor involves adnexa
 pT2b: Tumor involves other pelvic tissues
 pT3: Tumor infiltrates abdominal tissues
 pT3a: Tumor infiltrates abdominal tissues in one site
 pT3b: Tumor infiltrates abdominal tissues in more than one site
 pT4: Tumor invades bladder or rectum

For Adenosarcoma

Primary Tumor (pT)

- pTX: Primary tumor cannot be assessed
 pT0: No evidence of primary tumor
 pT1: Tumor limited to the uterus
 pT1a: Tumor limited to the endometrium/endocervix
 pT1b: Tumor invades to less than half of the myometrium
 pT1c: Tumor invades one half or more of the myometrium
 pT2: Tumor extends beyond the uterus, but within the pelvis
 pT2a: Tumor involves adnexa
 pT2b: Tumor involves other pelvic tissues
 pT3: Tumor infiltrates abdominal tissues
 pT3a: Tumor infiltrates abdominal tissues in one site
 pT3b: Tumor infiltrates abdominal tissues in more than one site
 pT4: Tumor invades bladder and/or rectum

For All Sarcomas

Regional Lymph Nodes (pN)

- pNX: Regional lymph nodes cannot be assessed
 pN0: No regional lymph node metastasis
 pN0(i+): Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
 pN1: Regional lymph node metastasis

Distant Metastasis (pM) (required only if confirmed pathologically in this case)

- pM1: Distant metastasis (excluding adnexa, pelvic and abdominal tissues)
 Specify site(s), if known: _____

+ For All Sarcomas Excluding Adenosarcoma (Including Leiomyosarcoma, Endometrial Stromal Sarcoma, and Undifferentiated Endometrial Sarcoma/Uterine Sarcoma)

+ FIGO Stage (2015 FIGO Cancer Report)

- + I: Tumor limited to uterus
 + IA: Less than or equal to 5 cm

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

- + ___ 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: 1 site
- + ___ IIIB: More than 1 site
- + ___ IIIC: Metastasis to pelvic and/or para-aortic lymph nodes
- + ___ IV: Tumor invades bladder and/or rectum and/or distant metastasis
- + ___ IVA: Tumor invades bladder and/or rectal mucosa
- + ___ IVB: Distant metastasis

+ For Adenosarcoma

- + FIGO Stage (2015 FIGO Cancer Report)
- + ___ I: Tumor limited to uterus
- + ___ IA: Tumor limited to endometrium/endocervix with no myometrial invasion
- + ___ IB: Less than or equal to half myometrial invasion
- + ___ IC: More than half myometrial invasion
- + ___ II: Tumor extends beyond the uterus, within the pelvis
- + ___ IIA: Adnexal involvement
- + ___ IIB: Tumor extends to extrauterine pelvic tissue
- + ___ III: Tumor invades abdominal tissues (not just protruding into the abdomen).
- + ___ IIIA: 1 site
- + ___ IIIB: More than 1 site
- + ___ IIIC: Metastasis to pelvic and/or para-aortic lymph nodes
- + ___ IV: Tumor invades bladder and/or rectum and/or distant metastasis
- + ___ IVA: Tumor invades bladder and/or rectal mucosa
- + ___ IVB: Distant metastasis

+ **Ancillary Studies**

- + Specify: _____
- + ___ Not performed

+ **Comment(s)**

Explanatory Notes

A. Histologic Type

Carcinosarcoma

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

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 (HPF) is required for a diagnosis of adenosarcoma, but others use a cut-off of 4 per 10 HPF.¹⁻⁵ 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 cuffing resulting in a cambium layer, a diagnosis of adenosarcoma should be strongly considered with mitotic counts <2 per 10 HPF 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 neoplasms. 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.⁶

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).⁷ 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 (ESS) 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.^{2,4} 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.

Endometrial Stromal Sarcoma

Low-grade endometrial stromal sarcoma, in contrast to endometrial stromal nodule, demonstrates myometrial invasion from the nodule or tumor mass of ≥ 3 mm, lymphovascular invasion, or ≥ 3 foci of myometrial invasion of any depth. About 60% of ESS have a translocation of the short arm of chromosome 7 and the long arm of chromosome 17 [t(7;17)], resulting in a fusion between 2 zinc finger genes (*JAZF1/JJAZ1*).⁸ However, this is not specific to ESS and may be demonstrated in the benign variant known as ESN (endometrial stromal nodule).⁹ Other rearrangements are a t(6;7), resulting in the *PHF1/JAZF1* fusion gene, and t(6;10), resulting in the *EPC1/PHF1* fusion.²

Even though in the past endometrial stromal sarcomas 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

1990 showed that mitotic activity was not predictive of outcome in stage I tumors.¹⁰ 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 HPF. 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.¹¹ However, recently, a subset of cases previously diagnosed as HG-ESSs has been histologically and genetically defined by Lee et al^{12,13} and Nucci et al (2007). In 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.¹² 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.¹² It is important to recognize these tumors as they have an intermediate prognosis between LG-ESS 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.

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.¹⁴ The utility of grading uterine LMS is controversial, and no universally accepted grading system exists.⁵ 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.¹⁵ Furthermore, when the Stanford criteria are strictly applied, all tumors classified as leiomyosarcomas should be regarded intrinsically as high grade.^{15,16}

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 to 15 per 10 HPF.¹⁶ 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 corded growth patterns. Nuclear atypia may be only mild and necrosis may be absent. Mitotic rate is generally greater than 3 per 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.¹⁴

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.¹⁷⁻¹⁹ 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.²⁰ Cytokeratins and EMA may be focally positive in LMS, especially in the epithelioid variant.

Undifferentiated Uterine/Endometrial Sarcoma

Undifferentiated uterine/endometrial sarcoma 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. Nucci et al proposed that high-grade ESS with the novel fusion gene *YWHAE-FAM22* should be distinguished from undifferentiated uterine/endometrial sarcoma.¹⁸

Other Tumor Types

Other differential diagnostic considerations included in spindle/sarcomatous lesions primary to the uterus include perivascular epithelioid cell tumor (PEComa) and rhabdomyosarcoma. PEComa belongs to a group of tumors characterized by both melanocytic and smooth muscle differentiation, and should be recognized separately from smooth muscle tumors.²¹⁻²³ Rhabdomyosarcoma is rare but is the most common uterine heterologous sarcoma.²⁴ Pleomorphic and embryonal subtypes are most frequent, while the alveolar and spindled variants are extremely rare.²⁵ Rhabdomyosarcomas are usually positive for desmin, muscle-specific actin, myogenin, Myo D1, and myoglobin, and negative for smooth muscle actin. Pleomorphic and alveolar subtypes have a worse prognosis than the embryonal subtype.²⁴

B. Pathologic Stage Classification

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.²⁶

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. Single tumor cells or small clusters of cells not more than 0.2 mm in greatest diameter are classified as isolated tumor cells. These may be detected by routine histology or by immunohistochemical methods and are designated N0(i+). 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.

TNM Descriptors

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

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).

T Category Considerations

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

TNM Category	FIGO Stage	Definition
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Primary Tumor

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 1 site
pT3b	[IIIB]:	Tumor invades abdominal tissues at more than 1 site
pT4	[IVA]:	Tumor invades bladder mucosa and/or rectum

Regional Lymph Nodes (pN)[#]

pNX:		Cannot be assessed
pN0:		No regional lymph node metastasis
pN0(i+):		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
pN1	[IIIC]:	Regional lymph node metastasis to pelvic lymph nodes

[#] Regional lymph nodes include the pelvic, obturator, internal iliac (hypogastric), external iliac, common iliac, para-aortic, 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 Category	FIGO Stage	Definition
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Primary Tumor

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% ($\leq 50\%$) total myometrial thickness
pT1c	[IC]:	Tumor invades greater than 50% ($> 50\%$) total myometrial thickness
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

[#] Regional lymph nodes include the pelvic, obturator, internal iliac (hypogastric), external iliac, common iliac, para-aortic, 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)

References

- Clement PB, Scully RE. Mullerian adenosarcoma of the uterus: a clinicopathologic analysis of 100 cases with a review of the literature. *Hum Pathol.* 1990;21:363-381.
- Gallardo A, Prat J. Mullerian adenosarcoma: a clinicopathologic and immunohistochemical study of 55 cases challenging the existence of adenofibroma. *Am J Surg Pathol.* 2009;33:278-288.
- McCluggage WG. Mullerian adenosarcoma of the female genital tract. *Adv Anat Pathol.* 2010;17:122-129.
- Soslow RA, Ali A, Oliva E. Mullerian adenosarcomas: an immunophenotypic analysis of 35 cases. *Am J Surg Pathol.* 2008;32:1013-1021.
- Kurman RJ, Carcangiu ML, Harrington CS, Young RH, eds. *WHO Classification of Tumors of the Female Reproductive Organs.* Geneva, Switzerland: WHO Press; 2014. *World Health Organization Classification of Tumors.* 4th ed.
- Clement PB. Mullerian adenosarcomas of the uterus with sarcomatous overgrowth: a clinicopathological analysis of 10 cases. *Am J Surg Pathol.* 1989;13:28-38.
- Prat J. FIGO Cancer Report. Uterine sarcomas *Int J Gynecol Obstet.* 2015;131 (Suppl 2); S105-S110.
- Koontz JI, Soreng AL, Nucci M, et al. Frequent fusion of the JAZF1 and JAZ1 genes in endometrial stromal tumors. *Proc Natl Acad Sci U S A.* 2001;98(11):6348-6353.
- Chiang S, Ali R, Melnyk N, et al. Frequency of known gene rearrangements in endometrial stromal tumors. *Am J Surg Pathol.* 2011;35(9):1364-1372.
- Chang KL, Crabtree GS, Lim-Tan SK, Kempson RL, Hendrickson MR. Primary uterine endometrial stromal neoplasms: a clinicopathologic study of 117 cases. *Am J Surg Pathol.* 1990;14:415-438.
- Ohta Y, Suzuki T, Omatsu M, et al. Transition from low-grade endometrial stromal sarcoma to high-grade endometrial stromal sarcoma. *Int J Gynecol Pathol.* 2010;29:374-377.
- Lee CH, Marino-Enriquez A, Ou W, et al. The clinicopathologic features of YWHAE-FAM22 endometrial stromal sarcomas: a histologically high-grade and clinically aggressive tumor. *Am J Surg Pathol.* 2012;36:641-653.
- Lee CH, Ou WB, Marino-Enriquez A, et al. 14-3-3 fusion oncogenes in high-grade endometrial stromal sarcoma. *Proc Natl Acad Sci U S A.* 2012;109:929-934.
- Nucci MR. Tumors of the female genital tract, part d myometrium. In: Fletcher C, ed. *Diagnostic Histopathology of Tumors.* Philadelphia, PA: Churchill Livingstone Elsevier; 2007:683-696.

15. Veras E, Zivanovic O, Jacks L, Chiappetta D, Hensley M, Soslow R. "Low-grade leiomyosarcoma" and late-recurring smooth muscle tumors of the uterus: a heterogeneous collection of frequently misdiagnosed tumors associated with an overall favorable prognosis relative to conventional uterine leiomyosarcomas. *Am J Surg Pathol*. 2011;35:1626-1637.
16. Bell SW, Kempson RL, Hendrickson MR. Problematic uterine smooth muscle neoplasms: a clinicopathologic study of 213 cases. *Am J Surg Pathol*. 1994;18:535-558.
17. D'Angelo E, Spagnoli LG, Prat J. Comparative clinicopathologic and immunohistochemical analysis of uterine sarcomas diagnosed using the World Health Organization classification system. *Hum Pathol*. 2009;40:1571-1585.
18. Nucci MR, Harburger D, Koontz J, Dal Cin P, Sklar J. Molecular analysis of the JAZF1-JJAZ1 gene fusion by RT-PCR and fluorescence in situ hybridization in endometrial stromal neoplasms. *Am J Surg Pathol*. 2007;31:65-70.
19. Oliva E, Young RH, Amin MB, Clement PB. An immunohistochemical analysis of endometrial stromal and smooth muscle tumors of the uterus: a study of 54 cases emphasizing the importance of using a panel because of overlap in immunoreactivity for individual antibodies. *Am J Surg Pathol*. 2002;26:403-412.
20. Chen L, Yang B. Immunohistochemical analysis of p16, p53, and Ki-67 expression in uterine smooth muscle tumors. *Int J Gynecol Pathol*. 2008;27:326-332.
21. Argani P, Aulmann S, Illei PB, et al. A distinctive subset of PEComas harbors TFE3 gene fusions. *Am J Surg Pathol*. 2010;34:1395-1406.
22. Folpe AL, Mentzel T, Lehr HA, Fisher C, Balzer BL, Weiss SW. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. *Am J Surg Pathol*. 2005;29:1558-1575.
23. Hornick JL, Fletcher CD. PEComa: what do we know so far? *Histopathology*. 2006;48:75-82.
24. Ferguson SE, Gerald W, Barakat RR, Chi DS, Soslow RA: Clinicopathologic features of rhabdomyosarcoma of gynecologic origin in adults. *Am J Surg Pathol*. 2007;31:382-389.
25. Fadare O. Heterologous and rare homologous sarcomas of the of the uterine corpus: a clinicopathologic review. *Adv Anat Pathol*. 2011;18:60-74.
26. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.