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Uterine Malignant and Potentially Malignant Mesenchymal Tumours Histopathology Reporting Guide

ICCR

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (select all that apply) (Note 1)

- ◯ Information not provided
- ☐ History of previous cancer, *specify*
- ☐ History of previous gynecologic biopsy/surgical excision, *specify*
- ☐ Other, *specify*

OPERATIVE PROCEDURE (select all that apply) (Note 2)

- ◯ Not specified
- ☐ Hysterectomy
  - ◯ Simple total
  - ◯ Simple supracervical/subtotal
  - ◯ Radical
  - ◯ Type not specified
- ☐ Myomectomy
- ☐ Lymph nodes, *specify site(s)*
- ☐ Other, *specify*

SPECIMEN INTEGRITY (Note 3)

- ◯ Intact
- ◯ Non-intact
- ◯ Morcellated/fragmented
- ◯ Opened

SPECIMEN(S) SUBMITTED (select all that apply) (Note 4)

- ◯ None submitted
- ☐ Ovaries
  - ☐ Left ☐ Right ◯ Not specified
- ☐ Fallopian tubes
  - ☐ Left ☐ Right ◯ Not specified
- ☐ Omentum
- ☐ Peritoneal biopsies, *specify site(s)*
- ☐ Peritoneal washings/peritoneal fluid
- ☐ Lymph nodes, *specify site(s)*
- ☐ Other, *specify*

TUMOUR SITE (select all that apply) (Note 5)

- ◯ Indeterminate
- ☐ Cervix
- ☐ Lower uterine segment
- ☐ Corpus
- ☐ Other, *specify*

MAXIMUM TUMOUR DIMENSION (Note 6)

mm

- ◯ Cannot be assessed, *specify*

BLOCK IDENTIFICATION KEY (Note 7)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

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HISTOLOGICAL TUMOUR TYPE (Note 8)

(Value list based on the World Health Organization Classification of Female Genital Tumours (2020))

- ◯ Smooth muscle tumour of uncertain malignant potential (STUMP)
- ◯ Leiomyosarcoma
- ◯ Endometrial stromal sarcoma, low grade
- ◯ Endometrial stromal sarcoma, high grade
- ◯ Undifferentiated uterine sarcoma
- ◯ Mullerian adenosarcoma without sarcomatous overgrowth
- ◯ Mullerian adenosarcoma with sarcomatous overgrowth
- ◯ Uterine tumour resembling ovarian sex cord tumour (UTROSCT)
- ◯ Perivascular epithelioid cell tumour (PEComa)
- ◯ Inflammatory myofibroblastic tumour
- ◯ NTRK-rearranged sarcoma
- ◯ SMARC-deficient uterine sarcoma
- ◯ Rhabdomyosarcoma (RMS) (embryonal and pleomorphic)
- ◯ Alveolar soft part sarcoma
- ◯ Other, *specify*

MITOTIC COUNT[a] (Note 9)

/mm^2

- ◯ Cannot be assessed

[a] *Core for leiomyosarcoma, STUMP, PEComa; non-core for all other entities but including mitotic count is strongly recommended.*

EXTENT OF INVASION (Note 10)

Myometrial or cervical stromal invasion

(Applicable to adenosarcoma only)

- ◯ Cannot be assessed
- ◯ Not identified
- ◯ ≤50%
- ◯ >50%

Uterine serosa involvement

- ◯ Cannot be assessed
- ◯ Not involved
  - Distance of tumour to uterine serosa: mm
- ◯ Involved

Parametrial involvement

- ◯ Not submitted
- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved
  - ☐ Left ☐ Right ◯ Indeterminate

Omentum[b]

- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved

Vagina[b]

- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved

Fallopian tube[b]

- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved
  - ☐ Left ☐ Right ◯ Indeterminate

Ovary[b]

- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved
  - ☐ Left ☐ Right ◯ Indeterminate

Peritoneal biopsies[b]

- ◯ Not involved
- ◯ Involved

Peritoneal washings/peritoneal fluid[b]

- ◯ Positive
- ◯ Negative
- ◯ Atypical/suspicious

[b] *If received.*

LYMPHOVASCULAR INVASION (Note 11)

- ◯ Indeterminate
- ◯ Not identified
- ◯ Present

MARGIN STATUS (Note 12)

Distal/cervical or vaginal

- ◯ Cannot be assessed
- ◯ Not involved
  - Distance of tumour from closest cervical or vaginal margin: mm
  - Specify closest margin, if possible
- ◯ Involved
  - Specify margin, if possible
  - ☐ Cervical
  - ☐ Vaginal
  - ☐ Other, *specify*

Parametrial

- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved
  - Specify laterality, if possible

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LYMPH NODE STATUS[c] (Note 13)

Pelvic nodes

- ◯ Cannot be assessed
- ◯ No nodes submitted or found

Number of nodes examined

Number of positive nodes

Size of maximum tumour deposit mm

Para-aortic nodes

- ◯ Cannot be assessed
- ◯ No nodes submitted or found

Number of nodes examined

Number of positive nodes

Size of maximum tumour deposit mm

Other lymph nodes removed, *specify site(s)*

Number of nodes examined

Number of positive nodes

Size of maximum tumour deposit mm

[c] *If resected.*

COEXISTENT PATHOLOGY (Note 14)

- ◯ None identified
- ◯ Present, *specify*

ANCILLARY STUDIES (Note 15)

- ◯ Not performed
- ◯ Performed (select all that apply)
  - ☐ Immunohistochemistry, *specify test(s) and result(s)*
  - ☐ Molecular findings, *specify test(s) and result(s)*
  - ☐ Other, *specify test(s) and result(s)*

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

PATHOLOGICALLY CONFIRMED DISTANT METASTASIS (Note 16)

- ◯ Not identified
- ◯ Present, *specify site(s)*

PROVISIONAL PATHOLOGICAL STAGING (Note 17)

FIGO (2015 edition)[d]

Leiomyosarcomas and endometrial stromal sarcomas

- ◯ I Tumour limited to uterus
  - ◯ IA Less than 5 cm
  - ◯ IB More than 5 cm
- ◯ II Tumour extends beyond the uterus, within the pelvis
  - ◯ IIA Adnexal involvement
  - ◯ IIB Involvement of other pelvic tissues
- ◯ III Tumour invades abdominal tissues (not just protruding into the abdomen)
  - ◯ IIIA One site
  - ◯ IIIB More than one site
  - ◯ IIIC Metastasis to pelvic and/or para-aortic lymph nodes
- ◯ IV Tumour invades bladder and/or rectum and/or distant metastasis
  - ◯ IVA Tumour invades bladder and/or rectum
  - ◯ IVB Distant metastasis

Adenosarcomas

- ◯ I Tumour limited to uterus
  - ◯ IA Tumour limited to endometrium/endocervix with no myometrial invasion
  - ◯ IB Less than or equal to half myometrial invasion
  - ◯ IC More than half myometrial invasion
- ◯ II Tumour extends to the pelvis
  - ◯ IIA Adnexal involvement
  - ◯ IIB Tumour extends to extrauterine pelvic tissue
- ◯ III Tumour invades abdominal tissues (not just protruding into the abdomen)
  - ◯ IIIA One site
  - ◯ IIIB More than one site
  - ◯ IIIC Metastasis to pelvic and/or para-aortic lymph nodes
- ◯ IV Tumour invades bladder and/or rectum and/or distant metastasis
  - ◯ IVA Tumour invades bladder and/or rectum
  - ◯ IVB Distant metastasis

[d] *Reprinted from Int J Gynaecol Obstet., Volume 131(Suppl 2), Prat J, Mbatani N, Uterine sarcomas, pages S105-10, 2015, with permission from Wiley.*

TNM Staging (UICC TNM 8th edition 2016)[e]

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

- ☐ m - multiple primary tumours
- ☐ r - recurrent
- ☐ y - post-therapy

Primary tumour (pT)

LEIOMYOSARCOMAS AND ENDOMETRIAL STROMAL SARCOMAS[f]

- ◯ T1 Tumour limited to the uterus
  - ◯ T1a Tumour 5 cm or less in greatest dimension
  - ◯ T1b Tumour more than 5 cm
- ◯ T2 Tumour extends beyond the uterus, within the pelvis
  - ◯ T2a Tumour involves adnexa
  - ◯ T2b Tumour involves other pelvis tissues
- ◯ T3 Tumour infiltrates abdominal tissues
  - ◯ T3a One site
  - ◯ T3b More than one site
- ◯ N1 Metastasis to regional lymph nodes
- ◯ T4 Tumour invades bladder or rectum
- ◯ M1 Distant metastasis

ADENOSARCOMA

- ◯ T1 Tumour limited to the uterus
  - ◯ T1a Tumour limited to the endometrium/endocervix
  - ◯ T1b Tumour invades to less than half of the myometrium
  - ◯ T1c Tumour invades more than half of the myometrium
- ◯ T2 Tumour extends beyond the uterus, within the pelvis
  - ◯ T2a Tumour involves adnexa
  - ◯ T2b Tumour involves other pelvis tissues
- ◯ T3 Tumour involves abdominal tissues
  - ◯ T3a One site
  - ◯ T3b More than one site
- ◯ N1 Metastasis to regional lymph nodes
- ◯ T4 Tumour invades bladder or rectum
- ◯ M1 Distant metastasis

Regional lymph nodes (pN)

- ◯ NX Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Regional lymph node metastasis

[e] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 6th October 2020).*

[f] *It is recommended that all malignant uterine mesenchymal neoplasms other than adenosarcoma be staged using the staging system for leiomyosarcomas and endometrial stromal sarcomas.*

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Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement in the expert committee. An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the Dataset Authoring Committee.

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Scope

The dataset has been developed for the pathology reporting of resection specimens of the uterus for sarcomas and mesenchymal tumours with potentially malignant behaviour. The dataset is applicable to tumours of the uterine corpus and the uterine cervix.

Carcinomas, other non-mesenchymal malignancies and metastatic neoplasms are excluded from this dataset. Carcinosarcoma is also excluded as it is considered to represent a malignant epithelial tumour with divergent mesenchymal differentiation based on clinicopathologic, immunohistochemical and molecular analysis; as such, this entity is included in the International Collaboration on Cancer Reporting (ICCR) Endometrial Cancer dataset.

The authors of this dataset can be accessed here.

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Note 1 – Clinical information (Non-core)

Adequate clinical history is essential for accurate diagnoses and appropriate clinical care. It has been estimated that approximately 1% of diagnostic reports have been negatively impacted due to a lack of clinical information; in these instances, additional clinical information resulted in a change in diagnosis.[2] A history of prior malignancy, radiation or hormonal therapy (which increases risk for sarcomas), and any prior excision are considered relevant.

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Note 2 – Operative procedure (Core)

While a diagnosis of a uterine sarcoma or tumour of uncertain malignant potential may occur with limited sampling of disease (endometrial biopsy, curetting or core biopsy), a significant subset are clinically unsuspected and first diagnosed upon pathologic examination of a myomectomy or hysterectomy specimen. Hysterectomy, with or without bilateral salpingo-oophorectomy, and myomectomy can provide both diagnostic and complete surgical resection of disease, although myomectomy may be associated with residual tumour post-resection. Laparoscopic myomectomy/ hysterectomy followed by in vivo fragmentation (morcellation) affects specimen integrity, discussed below, and may be suboptimal for diagnosis because of distortion of the organ's anatomy. In general, surgical management is related to tumour site and wish for fertility preservation and the decision to perform salpingo-oophorectomy depends on the disease type and the patient's age as ovarian preservation in young patients with uterine sarcoma may not impact overall survival.[3,4] Nevertheless, hysterectomy with or without bilateral salpingo-oophorectomy is the most common and complete type of resection for malignant mesenchymal tumours. Since some sarcomas more frequently metastasize to lymph nodes than others, planning lymph node sampling or dissection is partly based on the sarcoma type (if known preoperatively), presence of clinically evident nodal disease at time of surgery, and surgeon's preference.

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Note 3 – Specimen integrity (Core)

Documentation of specimen integrity is crucial for reporting of malignant and potentially malignant uterine mesenchymal tumours as integrity affects evaluation of margins and can impact staging and prognosis of uterine sarcomas.[5-7] It is important to document morcellation, a surgical technique performed in vivo after laparoscopic myomectomy or hysterectomy to reduce the size of the specimen into fragments small enough to be removed from the patient through the laparoscopic incision sites. Recurrence of uterine sarcoma has been reported when tumours are removed laparoscopically with morcellation.[8] After this phenomenon was first documented in several series,[8-10] certain protective measures were encouraged by the gynaecology community regarding use of this particular surgical technique.[11-13]

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Note 4 – Specimen(s) submitted (Core)

The presence of accompanying organs or tissues, other than the primary tumour site specimen (myomectomy or hysterectomy) is important because it contributes to the pathological assessment of tumour extension, other than by imaging (see **Note 10 EXTENT OF INVASION**) and staging. If peritoneal washings/peritoneal fluid are submitted, this should be documented along with the presence or absence of tumour cells (see **Note 10 EXTENT OF INVASION)**.

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Note 5 – Tumour site (Core)

Uterine sarcomas can arise primarily in the cervix or corpus, and in most cases, the site can easily be assigned. If the origin of a sarcoma is equivocal and it is difficult to establish whether the tumour has arisen from the cervix or the corpus (including the isthmus), deference is typically given to a corpus origin.[14] Some tumours cannot be assigned a site of origin, for example if they are removed piecemeal, such as with morcellation, or when they efface normal anatomy and/or present at high stage. In this instance, the 'other' category can be used with an explanatory note.

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Note 6 – Maximum tumour dimension (Core)

Maximum tumour measurement requires an intact tumour as dimensions cannot be assessed on piecemeal or morcellated specimens. As such, evaluation of this element usually requires a hysterectomy or myomectomy specimen. Tumour size, which is the gross measurement across the largest dimension, is given in millimetres (mm), although International Federation of Gynecology and Obstetrics (FIGO) and TNM staging parameters require conversion to centimetres (cm).

Measurement in three dimensions is not required, nevertheless, tumour size is an important quality measure. When a case is being reviewed, it allows the reviewing pathologist to assess whether the tumour has been 'adequately' sampled. This may be particularly important in tumours with variable or undifferentiated morphology.

Tumour size is also critical for staging and may have prognostic significance. Leiomyosarcomas and endometrial stromal sarcomas confined to the uterus and measuring less than 50 mm may have a more favourable prognosis, which is reflected in the staging (FIGO Stage IA versus IB),[15] although some studies have shown no association between size and outcome for Stage I leiomyosarcoma.[16] Size ≥50 mm is one of the parameters used to assess malignant potential in perivascular epithelioid cell tumours (PEComa) of gynaecological origin.[17,18] For inflammatory myofibroblastic tumour (IMT), size >70 mm may be associated with an aggressive clinical course, although evidence is limited.[19,20]

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Note 7 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important should the need for internal or

external review arise. The reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It may be useful to have a digital image of the specimen and record of the origin of the tumour blocks in some cases.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies or clinical trials.

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Note 8 – Histological tumour type (Core)

Our knowledge of the different types of mesenchymal tumours that can occur in the uterus has expanded in the past decade, as underlying molecular abnormalities have helped define distinctive clinicopathologic entities. Proper classification of malignant and potentially malignant tumours is crucial as there are important differences in clinical management and outcome. In many instances, additional tumour sampling may be more useful than ancillary techniques; in particular, sampling of the border of tumours can be useful.

All mesenchymal tumours of the uterus should be typed according to the most recent edition of the World Health Organization (WHO) Classification of Tumours of Female Genital Tumours, 5th edition, 2020 (Table 1).[21] The ICCR dataset includes 5th edition Corrigenda, June 2021.[22] The most commonly encountered sarcomas - leiomyosarcoma, endometrial stromal sarcoma and Müllerian adenosarcoma - will be discussed first.

Table 1: World Health Organization classification of mesenchymal tumours of the uterine corpus.[21]

Descriptor	ICD-O codes[a]
Mesenchymal tumours specific to the uterus	
Smooth muscle tumour of uncertain malignant potential (STUMP)	8897/1
Leiomyosarcoma	8890/3
Endometrial stromal sarcoma, low grade	8931/3
Endometrial stromal sarcoma, high grade	8930/3
Undifferentiated uterine sarcoma	8805/3
Uterine tumour resembling ovarian sex cord tumour (UTROSCT)	8590/1
Perivascular epithelioid cell tumour (PEComa)	8714/3
Inflammatory myofibroblastic tumour	8825/1
Mixed epithelial and mesenchymal tumours	
Adenosarcoma	8933/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2).[23] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries. Incorporates all relevant changes from the 5th Edition Corrigenda June 2021.

Smooth muscle tumours

Classification of smooth muscle tumours primarily relies on histologic assessment of several parameters. This assessment, however, can be challenging as benign, malignant and tumours classified as of uncertain malignant potential can share overlapping morphologies. For example, a high degree of cellularity may be seen in both benign (cellular leiomyoma) and malignant (leiomyosarcoma) tumours. Nevertheless, using the most recent edition of the WHO Classification, most uterine smooth muscle neoplasms are readily diagnosed either as benign or malignant.[24] The type of leiomyosarcoma (spindle, epithelioid, myxoid) should be included in the report.

Leiomyosarcoma with spindle cell differentiation is diagnosed when there are at least two of the following three histological parameters: diffuse, moderate to severe nuclear atypia, mitotic count ≥10 per 2 mm^2 (≥10 mitoses per 10 high power fields (HPF) if field diameter is 0.55 mm) and tumour cell necrosis.[24] The criteria for diagnosis of malignancy in epithelioid and myxoid smooth muscle tumours are stricter. Epithelioid leiomyosarcoma usually contains ≥4 mitoses per 2 mm^2 (≥4 mitoses per 10 HPFs if field diameter is 0.55 mm) moderate to severe nuclear atypia and/or tumour cell necrosis.[25-27] Myxoid leiomyosarcomas usually have an infiltrative border, and either moderate to severe nuclear atypia, tumour cell necrosis, or >1 mitosis per 2 mm^2 (>1 mitoses per 10 HPFs if field diameter is 0.55 mm).[28]

Tumours which show morphological features that exceed the criteria for leiomyoma but fall below the threshold for leiomyosarcoma may be diagnosed as smooth muscle tumour of uncertain malignant potential (STUMP).[29,30] The category of STUMP should be used sparingly and before making a diagnosis of STUMP, every effort should be made to establish a diagnosis of either a leiomyoma subtype, leiomyosarcoma, or one of the recently described mesenchymal tumours with deceptively bland cytology as included in this dataset (i.e., perivascular epithelioid cell tumour, IMT, and neurotrophic tyrosine receptor kinase (NTRK)-rearranged spindle cell sarcoma). Besides epithelioid and myxoid neoplasms, the most common histologic subtypes of leiomyoma which may give rise to diagnostic difficulties are leiomyoma with bizarre nuclei and cellular leiomyoma. In order to make a distinction from leiomyosarcoma, accurate assessment of the number of mitoses in leiomyoma with bizarre nuclei is important but this is not straightforward because karyorrhectic nuclei may mimic mitoses.[31,32] Fumarate hydratase (FH)-deficient morphology can be seen in leiomyoma with bizarre nuclei as well as conventional and cellular leiomyomata. In FH-deficient leiomyomata, the nuclei are often arranged in chains, have eosinophilic cytoplasmic inclusions, prominent eosinophilic nuclei, and perinucleolar haloes. The presence of these features, often accompanied by staghorn blood vessels and alveolar-pattern edema, particularly in a smooth muscle tumour occurring in a young woman, should prompt consideration of association with fumarate hydratase deficiency. Loss of FH staining by immunohistochemistry supports the diagnosis. Of note, a subset of these tumours are characterised by intact expression of FH (corresponding to the presence of FH protein that is non-functional). With either loss or a non-functional FH protein, accumulation of 2-SC and a positive 2-SC stain confirms the diagnosis. Although the majority of these cases seems to be sporadic, hereditary leiomyoma and renal cell carcinoma syndrome needs to be ruled out in the appropriate clinical setting.[33-36] As high cellularity may be observed in benign and malignant smooth muscle tumours, as well as endometrial stromal neoplasms, tumours considered cellular leiomyoma should not contain microscopic features which exceed the WHO criteria for leiomyoma.[24]

Smooth muscle tumour of uncertain malignant potential (STUMP) is an applicable diagnosis if a spindle cell smooth muscle tumour has focal/multifocal or diffuse nuclear atypia, 5-9 mitoses per 2 mm^2 (5-9 mitoses per 10 HPFs if field diameter is 0.55 mm) and lacks tumour cell necrosis. Approximately 12-17% of such tumours have recurred. The STUMP diagnosis is also applicable to any bland smooth muscle tumour with tumour cell necrosis or necrosis of an uncertain type. Approximately 28% of such tumours have recurred. Tumours lacking cytological atypia and tumour cell necrosis, but with ≥15 mitoses per 2 mm^2 (≥15 mitoses per 10 HPFs if field diameter is 0.55 mm) are

also considered STUMPs. Although none of such cases has recurred, the experience with these tumours is limited.[30,37] In addition to the Stanford criteria,[37] other helpful parameters that may be included in the assessment of recurrent potential in smooth muscle neoplasms are atypical mitoses, vascular involvement, and infiltrative/irregular margins.[38] Epithelioid and myxoid STUMPs are rare, and it is important to exclude their respective benign and malignant variants by integrating gross, microscopic and molecular findings.

Endometrial stromal sarcoma

The classification of endometrial stromal sarcoma has evolved over time due to a better understanding of its morphologic spectrum and underlying recurrent molecular abnormalities. While it was historically separated into low and high grade categories based on mitotic count, the category of high grade endometrial stromal sarcoma was removed from the 2003 WHO Classification as there was a lack of clinical relevance in separating tumours that morphologically resembled proliferative phase endometrial stroma into low and high grade categories based on mitotic count alone.[39] It is worth noting that the category of high grade endometrial stromal sarcoma at that time represented a heterogeneous group of tumours including those that resembled endometrial stroma and those with more nuclear pleomorphism. Currently, two categories of endometrial stromal sarcoma are recognised by the most recent WHO Classification.[21] While they maintain the same lexicon used in the past - low grade and high grade endometrial stromal sarcoma - they represent two distinct clinicopathologic entities with differing morphology, biologic behaviour and molecular findings.[39-45]

Low grade endometrial stromal sarcoma is composed of cells which morphologically resemble proliferative-phase endometrial stroma, i.e., cells have uniform round to ovoid nuclei and scant cytoplasm and they are associated with a delicate spiral arteriole-like network. This tumour has a characteristic growth pattern as it typically permeates the myometrium in a 'finger-like' or 'tongue-like' fashion; lymphovascular invasion (LVI) is frequent and sometimes prominent. Smooth muscle, sex cord-like, fibrous and myxoid variant morphology is not uncommon. Most, but not all tumours, harbour gene fusions most commonly *JAZF1-SUZ12.* Tumours with sex cord-like differentiation often harbour fusions involving *PHF1*. Patients with low grade endometrial stromal sarcoma typically have an indolent and protracted course.

Some low grade endometrial stromal tumours are classified as having 'limited' infiltration. These represent tumours that lack overt myometrial permeation but have more margin irregularity than allowed for designation as an endometrial stromal nodule.[46,47] Although most behave in benign fashion, a subset of tumours classified as such have metastasized. Thus, these tumours should be regarded as potentially malignant and be classified as low grade endometrial stromal sarcomas with limited infiltration.[48]

High grade endometrial stromal sarcoma encompasses tumours that have distinctive clinical, histologic and molecular findings that differs from low grade endometrial stromal sarcoma.[43,45,49-51] This tumour type occurs over a wide age range and shows a variable morphology but typically contains at least a focal characteristic round cell component (if associated with *YWHAE*-rearrangement), or myxoid spindle cell component (if associated with *BCOR*-rearrangement, most commonly *ZC3H7B-BCOR*, or internal tandem duplications). Patients with high grade endometrial stromal sarcoma more commonly present at higher stage in comparison to patients with low grade endometrial stromal sarcoma. Histologically, they can show expansile, permeative, or more commonly destructive infiltration of the myometrium; LVI can also be prominent. Tumours associated with *YWHAE*-rearrangement often, but not always, have a morphologically low grade component often akin to the fibromyxoid variant of low grade endometrial sarcoma. *BCOR*-associated tumours can closely mimic the appearance of myxoid leiomyosarcoma as tumour cells are often spindled with mild to moderate nuclear atypia and set in a prominent myxoid stroma. Limited clinical data suggest that high grade endometrial stromal sarcomas, regardless of the underlying genetic abnormality, are more likely to

pursue an aggressive clinical course with earlier recurrences and metastasis, in comparison to low grade endometrial stromal sarcoma.[43,45,49,51]

Although rare, a scenario worth mentioning is the potential for low grade endometrial stromal sarcoma to 'transform' to a high grade tumour. In this scenario, the tumour may have the appearance of a high grade endometrial stromal sarcoma or undifferentiated uterine sarcoma but harbour translocations characteristic of conventional low grade endometrial stromal sarcoma.[52]

Müllerian adenosarcoma

Müllerian adenosarcoma is a biphasic neoplasm composed of a benign, non-neoplastic Müllerian epithelial component and a malignant sarcomatous component which is usually, but not always, morphologically low grade. These tumours are uncommon, representing less than 1% of all uterine malignancies and approximately 10% of uterine sarcomas. They present over a wide age range, most commonly in postmenopausal women, but a significant subset occurs in younger adults. Patients typically present with abnormal uterine bleeding. Other findings may include an enlarged uterus, pelvic mass, or polyp (either endocervical or endometrial in origin). Gross examination may show multiple large, soft polypoid masses filling the uterine cavity; tumours may invade the myometrium or cervical stroma, a finding more commonly associated with sarcomatous overgrowth. Characteristic histologic findings include a leaf-like growth pattern (also often described as phyllodes-like as the appearance is akin to a phyllodes tumour of the breast), with intraglandular stromal polypoid projections, and cuffing of the glands by hypercellular stroma. However, not all adenosarcomas show phylloidiform growth with some being composed of variably sized rounded glands surrounded by hypercellular stroma ('rigid cysts'); a combination of these appearances is not uncommon. The stromal cells may show variable amounts of nuclear atypia in the form of nuclear enlargement with irregular nuclear contour or nuclear hyperchromasia. Mitoses are typically identified (usually >1 per 2 mm^2 (>1 mitosis per 10 HPFs if field diameter is 0.55 mm) but may be sparse or, in rare cases, absent. The stromal component is most commonly homologous, i.e., it has the appearance of endometrial or cervical stroma, but may also show heterologous differentiation, most commonly rhabdomyosarcoma. Sex cord-like differentiation may also occur. Sarcomatous overgrowth is defined as the presence of greater than 25% of the tumour composed solely of a neoplastic stromal component without epithelium; sex-cord-like differentiation is not considered in the assessment of stromal overgrowth.[53,54] Sarcomatous overgrowth often shows aberrant p53 immunoreactivity and loss of hormone receptor positivity.[55,56] It is important to note that the non-neoplastic epithelial component typically has a banal appearance, sometimes with various types of epithelia (tubal, endometrioid, mucinous, squamous); occasionally the epithelial component may show some cytologic atypia in the form of nuclear enlargement and hyperchromasia. In this latter scenario, additional sampling may be prudent to exclude carcinosarcoma. Features associated with an unfavourable outcome include sarcomatous overgrowth, deep myometrial invasion, and extrauterine extension; morphologically high grade nuclear atypia (marked nuclear enlargement and hyperchromasia) that shows mutation-type staining pattern for p53 may also be an adverse prognostic feature.[56]

Undifferentiated uterine sarcomas (Unclassifiable sarcomas)

Sarcomas which cannot be classified are considered undifferentiated uterine sarcoma. This is a diagnosis of exclusion after other malignancies, such as undifferentiated carcinoma, carcinosarcoma, leiomyosarcoma, and high grade endometrial stromal sarcoma have been excluded. As many of the tumours in the differential diagnosis may have areas of morphologic overlap, the diagnosis of undifferentiated uterine sarcoma is best rendered on a complete excision specimen as a more limited specimen may lack the diagnostic features of other uterine malignancies. It is worth noting that undifferentiated uterine sarcoma can be separated into two different types based on their morphologic appearance: uniform and pleomorphic.[57] With advanced molecular techniques and newly reported molecular abnormalities, the former are increasingly categorised as high grade endometrial stromal sarcomas whereas the pleomorphic type likely mostly represent sarcomas that are so poorly

differentiated that cannot be classified.[58] Some of these tumours may represent carcinosarcomas in which only the sarcomatous component is seen, and thus before making a diagnosis of an undifferentiated uterine sarcoma, additional sampling should be considered which may reveal diagnostic areas. Prior to rendering the diagnosis of undifferentiated uterine sarcoma in an excision specimen, extensive tumour sampling, immunohistochemical staining, and if possible, molecular testing may be needed to exclude other neoplasms.

Potentially malignant mesenchymal tumours of the uterus are those in which prognostication requires assessment of various clinical and pathologic parameters to determine biologic potential. Tumours within this category include uterine tumour resembling ovarian sex cord tumour, perivascular epithelioid cell tumour, and IMT.

Uterine tumour resembling ovarian sex cord tumour (UTROSCT)

Uterine tumour resembling ovarian sex cord tumour (UTROSCT) is an uncommon uterine tumour whose histologic features recapitulates the appearance of an ovarian sex cord tumour. Historically, the term UTROSCT included tumours entirely composed of sex cord elements as well as endometrial stromal tumours with extensive sex cord differentiation; the latter are no longer considered in this category based on morphologic as well as molecular differences. UTROSCT exhibit a wide range of morphologic appearances with diffuse, corded, trabecular, tubular, retiform and/or nested growth. Tumour cells have variable amounts of cytoplasm ranging from inconspicuous to abundant, which may be pale, foamy or eosinophilic; rhabdoid morphology may be seen and can be extensive. Nuclei are usually uniform with minimal cytologic atypia and the mitotic count is low. Nuclear atypia in the form of nuclear enlargement and hyperchromasia, as well as brisk mitotic activity, may be seen. UTROSCT is characterised by recurrent gene fusions involving *NCOA1-3*, *GREB1* and *ESR1*.[59-62] These tumours are considered to be of uncertain malignant potential. Although data is limited, features that may be associated with aggressive behaviour include a mitotic count >2 per 2 mm^2 (>2 mitoses per 10 HPFs if field diameter is 0.55 mm), necrosis, extensive (>50%) rhabdoid morphology and potentially tumours with *GREB1* rearrangement.[60-63]

Perivascular epithelioid cell tumour (PEComa)

Perivascular epithelioid cell tumours (PEComas) are unusual mesenchymal neoplasms that are composed of a distinctive population of cells, termed perivascular epithelioid cells, which co-express smooth muscle and melanocytic markers. These tumours have wide anatomic distribution and the uterus is the most common site when they occur in the female genital tract.[17,18,64-66] Most tumours occur sporadically with only a small subset being associated with tuberous sclerosis. Histologically, tumours most commonly are composed of epithelioid and spindle cells but can sometimes be solely or predominantly epithelioid or spindled. Tumours often, but not always, show a characteristic perivascular pattern of growth in which the tumour cells are radially arranged around the vasculature. In some tumours, the neoplastic cells can be seen within the muscular wall of the vessel. Another distinctive aspect of these tumours is their cytologic appearance; the cells are remarkable for abundant granular eosinophilic or clear cytoplasm although predominantly spindled tumours may show less abundant cytoplasm. When epithelioid, the tumour cells grow in sheets, nests and/or trabeculae that are surrounded by a delicate capillary vasculature. Spindled tumours often exhibit fascicular growth and can mimic smooth muscle neoplasia, the distinctive morphologic difference being the granular appearance of the cytoplasm. Of note, *TFE3*-associated PEComas often are composed of epithelioid cells that have predominantly clear cytoplasm; extensive melanin deposition may also occur. Assessment of potential malignant behaviour for PEComa of the female genital tract is based on the following parameters: tumour size ≥50 mm, high nuclear grade, mitotic count of >1 mitosis per 12 mm^2, presence of necrosis and presence of vascular invasion. If a tumour has three or more of these features, it is best classified as malignant. Only tumours that lack all features could potentially be considered benign. Any tumour with one or two features should be considered of uncertain malignant potential.

Inflammatory myofibroblastic tumour (IMT)

Inflammatory myofibroblastic tumour (IMT) is a myofibroblastic/fibroblastic neoplasm characterised by a variably myxoid stroma with an accompanying variably intense inflammatory infiltrate, primarily composed of lymphocytes and plasma cells. This tumour shows a wide anatomic distribution with the uterine corpus being the most common location in the female genital tract; less commonly it involves the cervix.[19,67-69] Occasionally, IMT may be identified at the time of delivery and in some cases may be adherent to the maternal surface of the placenta or be associated with the placental membranes.[70,71] Microscopically, the tumour borders can be well demarcated or irregular, either showing permeative (stromal sarcoma-like) or infiltrative margins. A number of different morphologies may be seen and are often intermixed: myxoid, leiomyoma-like, or hyalinised. The myxoid pattern is characteristically hypocellular with individual cells dispersed in an abundant myxoid matrix, a feature that imparts a fasciitis-like appearance on low power magnification. The leiomyoma-like areas are composed of spindled cells in intersecting fascicles or showing storiform growth; the former closely mimics smooth muscle neoplasia. The hyalinised pattern is remarkable for an abundant hyalinised and collagenous stroma containing scattered spindled cells. The tumour cells in the fasciitis-like areas are spindled with eosinophilic to amphophilic cytoplasmic processes and ovoid to tapered nuclei with open dispersed chromatin, features that closely resemble the appearance of the spindled cells of nodular fasciitis. The spindled cells in the leiomyoma-like areas have features indistinguishable from smooth muscle neoplasia with eosinophilic cytoplasm and more oblong nuclei with blunt ends. The epithelioid variant of IMT, which typically occurs in the abdominal cavity and is characterised by a predominant component of epithelioid cells with eosinophilic cytoplasm and vesicular nuclei, has yet to be described in the uterus, but has been reported in the ovary.[72,73] An inflammatory infiltrate, often present at the periphery of the tumour but also dispersed throughout, is typically composed of lymphocytes and plasma cells although other inflammatory cells can be seen; the amount and distribution of inflammatory cells vary but inflammation is typically a reproducible finding and characteristic of IMT. Assessment of potential malignant behaviour for IMT of the female genital tract is not well established. Some tumours present at high stage and should be considered malignant. Pathologic features which have been associated with aggressive behaviour include large tumour size (>150 mm), marked nuclear atypia, LVI and tumours with high mitotic counts (>10 per 2 mm^2 which corresponds to >10 mitoses per 10 HPFs if field diameter is 0.55 mm). These features are not invariably associated with adverse outcome and conversely tumours as small as 62 mm or with mitotic counts of only 1 per 2 mm^2 (1 mitosis per 10 HPFs if field diameter is 0.55 mm) have recurred. Recurrence of IMT at all anatomic sites is estimated at 25% and is related to resectability.[74] As complete resection is typically achieved with hysterectomy, this may partially explain the overall good outcome for most patients with uterine neoplasms.

Rhabdomyosarcoma

Less common uterine sarcomas include rhabdomyosarcoma and alveolar soft part sarcoma. Different types of rhabdomyosarcoma have been described in the female genital tract; in the uterus, embryonal rhabdomyosarcoma (ERMS) and pleomorphic rhabdomyosarcoma are the most likely to be encountered.[75-78] Histologically, ERMS characteristically shows alternating cellularity with hypocellular myxoid zones and hypercellular foci of spindled rhabdomyoblasts, often condensing underneath the overlying epithelium (cambium layer). Heterologous cartilaginous differentiation is commonly seen. Pleomorphic rhabdomyosarcoma is composed of sheets of highly atypical spindled, polygonal or rhabdoid cells with large irregular, frequently multinucleated cells and eosinophilic cytoplasm. Mitoses are frequent and often atypical. Both subtypes of rhabdomyosarcoma are positive for desmin, myoD1 and myogenin. ERMS is associated with high frequency of *DICER1* mutation which may be somatic or germline. Adult patients with ERMS have a less favourable prognosis than children.[75] Patients with pleomorphic rhabdomyosarcoma have a poor prognosis.[78] Some of these tumours may represent rhabdomyosarcomatous overgrowth in an adenosarcoma or carcinosarcoma; thus, extensive sampling should be undertaken to exclude an epithelial component before diagnosing a pleomorphic rhabdomyosarcoma.

Alveolar soft part sarcoma (ASPS)

Alveolar soft part sarcoma (ASPS) can occur at any location in the female genital tract; uterine tumours can occur in the corpus or cervix.[79-82] Histologically, they are composed of nests of large, polygonal epithelioid cells with abundant eosinophilic granular cytoplasm containing an eccentric or centrally located nucleus with vesicular nuclei and prominent nucleolus. Characteristically, the nests are enveloped by a delicate sinusoidal vascular network and the cells often show dyscohesion resulting in an alveolar-like appearance. Cytoplasmic clearing and rhabdoid cells may be seen. Intracytoplasmic granules and/or rhomboid crystals may be seen, which can be highlighted by periodic acid-Schiff stain and are diastase resistant. Mitoses are typically sparse. ASPS is characterised by *TFE3* rearrangements as a result of chromosomal translocation t(x;17)(p11;q25). As a consequence, tumour cells typically show strong and diffuse nuclear staining for TFE3. The prognosis of ASPS at all anatomic sites appears to be related to resectability, which may explain the relative better prognosis for ASPS of the gynaecologic tract in comparison to those that arise elsewhere.

It is worth noting that many different types of sarcoma more commonly encountered in other anatomic locations can also rarely arise in the uterus, such as liposarcoma[83] and angiosarcoma.[84-86] Prior to making the diagnosis of a pure unusual type of sarcoma of the uterus, additional sampling of the lesion should be performed to exclude the possibility that it represents the component of a more commonly encountered uterine neoplasm, such as sarcomatous overgrowth of an adenosarcoma or the mesenchymal component of a carcinosarcoma.

Emerging entities

Emerging uterine mesenchymal entities include *NTRK*-rearranged sarcoma, *PDGFR*-rearranged sarcoma and *SMARCA4*-deficient uterine sarcoma. *NTRK*-rearranged sarcoma has been recently described to occur in the uterine cervix and lower uterine segment.[87-90] Histologically, *NTRK*-rearranged sarcomas typically have an infiltrative border and are composed of a proliferation of spindled cells exhibiting either a patternless architecture or showing (often haphazard) fascicular or herringbone growth. Entrapped endocervical glands may be encircled by the neoplastic cells, sometimes with polypoid projections simulating adenosarcoma; however, there is typically no periglandular stromal condensation. The spindle cells have eosinophilic cytoplasm and generally show mild to moderate nuclear enlargement with nuclei that are ovoid with dispersed chromatin and small nucleoli; epithelioid change and foci of marked atypia may be seen. The vascular component can be composed of delicate capillaries or vessels with variably thickened walls often with prominent hyalinisation. The mitotic count is variable ranging from 0 to 50 per 2 mm^2 (0-50 mitoses per 10 HPFs if field diameter is 0.55 mm) atypical mitotic figures and necrosis may be seen. Other findings that may be encountered include focal myxoid matrix, focal hemangiopericytoma-like vasculature and a prominent lymphocytic infiltrate. These tumours show positivity for pan-TRK, but this marker is not specific for the gene fusion. Patients with *NTRK*-rearranged sarcoma typically present with Stage I disease; however, approximately one third have developed recurrence or metastatic disease.[87-90] Targeted therapy against tropomyosine kinase receptors has shown clinical benefit in patients with *NTRK*-associated sarcomas.[91]

RET fusion positive neoplasms may also exhibit fibroblastic or neural-like differentiation and have phenotypic overlap with *NTRK*-related neoplasms.[92] Recently a cervical sarcoma with a novel *RET-SPECC1L* fusion has been described.[93] Rare spindle cell sarcomas with recurrent *MEIS1-NCOA2* fusions have also been recently described.[94]

COL1A1-PDGFB rearranged uterine sarcomas are rare and data is limited.[89,95] These tumours are composed of a cellular proliferation of spindle cells that typically exhibit a storiform or herringbone growth pattern although one tumour has been described as showing a fascicular 'leiomyoma-like' growth pattern. Overall, it is interesting to speculate that these tumours could be the uterine counterpart of dermatofibrosarcoma protuberans, as they show morphological overlap (including

fibrosarcomatous areas), a similar immunophenotype (focal loss of CD34 staining in 'fibrosarcomatous areas'), as well as sharing the same gene fusion.

SMARCA4-deficient uterine sarcoma (SDUS) is a recently described entity that shares morphologic overlap with undifferentiated endometrial carcinoma but has distinctive clinicopathologic and molecular differences.[96-98] Tumours characteristically show a diffuse growth of large epithelioid cells with round vesicular nuclei and exhibit prominent rhabdoid morphology; other features which may be focally present include phyllodiform architecture, vague cording or nesting associated with stromal hyalinisation, small cell or spindled morphology, and focal myxoid stromal change. Brisk mitoses (usually >20 per 10 HPFs/0.24 mm^2), necrosis and LVI are common. Patients with SDUS have a poor prognosis.[96-98]

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Note 9 – Mitotic count (Core)

The clinical significance of mitotic activity depends on the specific tumour-type involved. Documentation of mitotic activity (highest mitotic count) is required for leiomyosarcoma, STUMP and PEComa, and strongly recommended for UTROSCT, IMT, solitary fibrous tumour and undifferentiated uterine sarcoma. It is optional for other sarcoma types. The 5th edition of the WHO Classification of Tumours[21] considers both HPFs and mm^2 for counting of mitoses. In addition, the size of the objective field is mentioned.

For leiomyosarcoma and STUMP, mitotic activity constitutes part of the diagnostic definition together with other histologic features including nuclear atypia and tumour cell necrosis. Mitotic count ≥10 mitoses per 2 mm^2 (≥10 mitoses per 10 HPFs if field diameter is 0.55 mm) is used for spindle cell smooth muscle tumours, whereas mitotic count ≥4 mitoses per 2 mm^2 (≥4 mitoses per 10 HPFs if field diameter is 0.55 mm) and ≥2 mitoses per 2 mm^2 (≥2 mitoses per 10 HPFs if field diameter is 0.55 mm) are used for epithelioid and myxoid smooth muscle tumours, respectively.[21] For STUMP, mitotic activity forms part of the diagnostic definition under two scenarios based on the 2020 WHO Classification:[21] 1) tumours with focal/multifocal or diffuse nuclear atypia, and 5-9 mitoses per 2 mm^2 (5-9 mitoses per 10 HPFs if field diameter is 0.55 mm) but lacking tumour cell necrosis; and 2) tumours showing ≥15 mitoses per 2 mm^2 (≥15 mitoses per 10 HPFs if field diameter is 0.55 mm) and lacking nuclear atypia and tumour cell necrosis. It is important to note that degenerative nuclear changes/ karyorrhexis may mimic mitotic figures, particularly atypical mitotic figures. It is generally recommended that a formal mitotic count should rely predominantly if not exclusively on counting of typical bipolar mitoses. For PEComa, the presence of any mitotic activity, together with tumour size (≥50 mm), high grade atypia, necrosis and LVI form the criteria for malignancy in the gynaecologic tract.[17,64,99] For other rare uterine sarcoma types in which mitotic count is part of the risk stratification (e.g., solitary fibrous tumour), mitotic activity should also be documented.

For IMT, there is limited evidence that mitotic count and large tumour size may be associated with more aggressive clinical behaviour.[20,28] For UTROSCT, there is also limited evidence that elevated mitotic counts and necrosis are associated with malignant behaviour.[63] Mitotic activity is generally brisk for undifferentiated uterine sarcoma and mitotic count has been shown to be prognostically relevant in undifferentiated uterine sarcomas (lacking endometrial stromal sarcoma genetic fusions) with tumours showing a mitotic count of >25 mitoses per 2 mm^2 (>25 mitoses per 10 HPFs if field diameter is 0.55 mm) being associated with decreased survival.[100,101]

For adenosarcoma, most tumours demonstrate stromal mitoses (>1 mitosis per 2 mm^2 (>1 mitosis per 10 HPFs if field diameter is 0.55 mm)) but mitotic activity may be minimal or even absent in some

cases.[102,103] There is currently no evidence that mitotic count alone is prognostically significant, in contrast to the presence of sarcomatous overgrowth and/or deep myometrial invasion which are associated with worse prognosis.[104-106] With regard to endometrial stromal sarcomas, while low grade endometrial stromal sarcomas tend to exhibit lower mitotic counts than high grade endometrial stromal sarcomas, there is overlap in the range of mitotic activity and the number of mitoses is not used for diagnostic classification. However, most low grade endometrial stromal sarcomas display a mitotic rate of <5 mitoses per 2 mm^2 (<5 mitoses per 10 HPF if field diameter is 0.55 mm) and a finding of high mitotic rate (particularly >10 mitoses) should prompt more thorough tumour sampling and careful histologic evaluation as well as consideration of ancillary studies to exclude high grade endometrial stromal sarcoma or other tumour types. The degree of mitotic activity has no diagnostic or known prognostic significance for recently recognised entities including *SMARCA4*-deficient uterine sarcoma and *NTRK*-rearranged sarcoma. Mitotic activity is typically high in *SMARCA4*-deficient uterine sarcoma and is variable in *NTRK*-rearranged sarcoma.

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Note 10 – Extent of invasion (Core)

Myometrial or cervical stromal invasion

The depth of myometrial invasion is an essential parameter in the staging of adenosarcomas located in the uterine corpus or cervix (see **Note 17 PROVISIONAL PATHOLOGICAL STAGING**). According to the current FIGO Staging System,[107] Stage IA adenosarcoma is limited to the endometrium/endocervix; Stage IB invades ≤50% of the myometrium or cervical stroma; and Stage IC invades more than 50% of the myometrium or cervical stroma.[108,109] Myometrial infiltration is also an important prognostic factor in uterine adenosarcoma for overall survival and recurrence.[15,56,110]

Because the staging of low and high grade endometrial stromal sarcomas, leiomyosarcoma and undifferentiated uterine sarcoma (and other sarcomas) is not based currently on myometrial infiltration, the depth of myometrial infiltration is not relevant.

Uterine serosa involvement

Uterine serosal involvement should be documented as it is an adverse prognostic factor in uterine leiomyosarcoma.[111] Although evidence for clinical relevance for other uterine sarcomas is limited, the ICCR Uterine Sarcoma Dataset Authoring Committee (DAC) considers it to represent a core element in reporting.

Tumour-free distance to uterine serosa refers to the distance between the deepest point of tumour within the myometrium and the nearest serosal surface and is considered a non-core element.

Parametrial involvement

Parametrium is defined as the fibro-adipose connective tissue located laterally in the supracervical portion of the uterus. Most hysterectomies for uterine sarcoma will be simple hysterectomies without parametrial resections. If parametrial tissue is removed, the presence or absence of parametrial involvement should be documented as best practice. Although evidence for clinical relevance of parametrial involvement in uterine sarcomas is limited, the DAC considers it to represent a core element in reporting.

Omentum

Omental involvement should be documented as it contributes to the staging assessment. FIGO Stage IIIA equates to one site of abdominal involvement and IIIB to more than one site.[107]

Vagina

A total hysterectomy can have a vaginal cuff which should be measured. The presence or absence of vaginal involvement in such cases should be documented on the report.

Fallopian tube

The presence or absence of adnexal (ovarian/fallopian tube) involvement should be documented. Adnexal involvement affects the tumour stage (FIGO Stage IIA) which remains the most powerful prognostic factor for uterine sarcomas,[15,109,112,113] and may occur as a result of direct extension or metastatic spread of tumour.

Ovary

The presence or absence of adnexal (ovarian/fallopian tube) involvement should be documented. Adnexal involvement affects the tumour stage (FIGO Stage IIA) which remains the most powerful prognostic factor for uterine sarcomas,[15,109,112,113] and may occur as a result of direct extension or metastatic spread of tumour.

Peritoneal biopsies

Peritoneal involvement should be documented as it contributes to the staging assessment. Pelvic peritoneal involvement equates to FIGO Stage IIB while abdominal peritoneal involvement equates to FIGO Stage IIIA or IIIB depending on the number of sites involved.[107]

Peritoneal washings/peritoneal fluid

The presence or absence of tumour cells in peritoneal fluid/washings should be documented if this specimen type is submitted. There is only limited data suggesting that positive peritoneal cytology may be an adverse prognostic factor in uterine sarcomas with one study suggesting that positive peritoneal cytology may be a prognostic factor for mortality in uterine sarcomas, particularly in leiomyosarcoma.[114] Accrual of this data prospectively will facilitate future study regarding the prognostic significance of positive peritoneal fluid.

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Note 11 – Lymphovascular invasion (Core)

The presence or absence of lymphovascular invasion (LVI) in uterine sarcomas should be documented. For some tumours, such as low grade and high grade endometrial stromal sarcoma, LVI is frequently encountered; in contrast, other tumours, such as adenosarcomas, uncommonly demonstrate LVI unless associated with deep myometrial invasion and/or sarcomatous overgrowth. The presence of LVI may carry prognostic significance in leiomyosarcoma, particularly when early stage,[115,116] and in adenosarcoma.[117-119]

One study evaluated specific patterns of vascular involvement by low grade endometrial stromal sarcoma, high grade endometrial stromal sarcoma, leiomyosarcoma, and undifferentiated uterine sarcoma and divided patterns into 'true' vascular invasion versus 'intrusion' into lymphovascular spaces.[120] True LVI was characterised by dyscohesive clusters of tumours cells with irregular edges,

lacking vasculature within the intravascular tumour and/or lack of immunohistochemically proven endothelial cells surrounding the intravascular tumour focus. Vascular intrusion, which was considered to be 'pseudoinvasion', was characterised by cohesive intravascular tumour with smooth contours and lined by endothelial cells. Pre-existing vascular spaces were frequently identified within the intravascular tumour in the cases of vascular intrusion and such foci were often in direct communication with the main tumour mass.[120]

While usually straightforward, the assessment of LVI may be difficult in a minority of cases, for which the reasons may include (but are not limited to) suboptimal fixation or cauterization artefacts. In such cases, examination of multiple levels and/or immunostaining for endothelial or lymphatic markers (such as CD31, CD34, D2-40 and ERG) may be employed to assist with the decision-making. Cases that are still equivocal after taking additional steps may be reported as 'indeterminate' for LVI, but this designation should only be sparingly used and it is useful to provide the reason in a comment in the report.

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Note 12 – Margin status (Core and Non-core)

Margins of resection are an important parameter to include in reporting as they may guide post-surgical treatment with chemotherapy and/or radiation therapy depending on tumour type. In addition, positive margins have been shown to be a negative prognostic factor for a variety of different uterine sarcomas including low and high grade endometrial stromal sarcoma,[121] leiomyosarcoma,[122] and Müllerian adenosarcoma.[123] The most relevant margin is usually the distal cervicovaginal resection margin. However, the status of other surgical margins, such as the parametrium (when removed) including laterality, should also be documented.

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Note 13 – Lymph node status (Core)

The anatomic location and number of lymph nodes dissected, the number containing tumour and the size of the largest tumour deposit should be accurately documented in the pathology report. According to TNM8,[124] nodal involvement should be recorded as the presence of isolated tumour cells (ITC, <0.2 mm), micrometastases (MIC, 0.2-2 mm) or macrometastases (MAC, >2 mm). MAC are regarded as pN1, MIC as pN1 (mi) and ITCs are pN0 (i+); ITCs do not upstage a neoplasm. Involvement of pelvic and/or para-aortic lymph nodes by uterine sarcoma will upstage the sarcoma. The number of lymph nodes examined and number of lymph nodes involved by tumour should be reported for regional lymphadenectomies, if performed.

Because of the low risk of metastatic disease in lymph nodes, routine lymph node dissection is typically not undertaken in low stage uterine leiomyosarcomas.[125-127] Moreover, lymphadenectomy is not routinely undertaken for uterine leiomyosarcoma as it does not appear to impact overall survival.[122,127,128] Nevertheless, lymph node resection should be performed if the lymph nodes appears enlarged or suspicious.[129] The reported frequency of lymph node involvement in low grade endometrial stromal sarcomas ranges from 3.6% to 10%,[121,130,131] and from 10.2% to 44% for high grade endometrial stromal sarcoma.[121,132] The prognostic importance of lymphadenectomy for endometrial stromal sarcomas has been a subject of debate,[112,130,133-135] although a recent meta-analysis concluded that for localised endometrial stromal sarcoma and leiomyosarcoma, lymphadenectomy is not recommended.[128]

Lymph node metastasis is a significant prognostic factor in uterine adenosarcoma.[136] However, lymphadenectomy is not typically performed unless lymph nodes appear enlarged and/or suspicious as the rate of nodal metastasis is low (6.5%).[137]

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Note 14 – Coexistent pathology (Non-core)

There are no known precursor lesions of uterine sarcomas. Unrelated incidental conditions can be documented.

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Note 15 – Ancillary studies (Non-core)

Ancillary testing (chiefly immunohistochemistry and/or molecular testing) may be of value in the diagnosis of uterine malignant and potentially malignant mesenchymal tumours. The results of ancillary tests should be interpreted in the overall context of the clinical setting, macroscopic pathology and microscopic pathology. The most recent WHO Classification[21] defines two potential roles for ancillary tests for certain tumours: 1) to serve as essential diagnostic criteria, required for establishing the diagnosis; or 2) to serve as supportive criteria that are desirable but not essential to establish the diagnosis. To harmonise with the latest WHO Classification,[21] the DAC recommends adopting a similar strategy, acknowledging that some of these ancillary tests may not be available in all practice settings. Discussion of the detailed immunophenotype of the various uterine sarcomas or use of ancillary testing to resolve specific differential diagnoses is beyond the scope of these recommendations. Among the tumours with a defining molecular alteration, gene fusion is the main pathologic mechanism; thus, fluorescent in situ hybridisation or RNA sequencing are the primary types of molecular diagnostic tools, with a few rare exceptions of tumours characterised by inactivating mutations.

Leiomyosarcoma and STUMP are expected to exhibit a smooth muscle immunophenotype (positive for desmin, h-caldesmon, smooth muscle myosin and smooth muscle actin), although it is not uncommon for only some of the smooth muscle stains to be positive or for staining to be patchy, particularly in myxoid and epithelioid variants. While mutation of *TP53*, *MED12*, and/or *ATRX* occur in a minority of leiomyosarcomas, these alterations are not specific to leiomyosarcoma. A recent study has shown that p53 immunohistochemistry may be useful in distinguishing translocated associated sarcomas from other non-translocated associated sarcomas with the former more often showing wild-type staining.[138] A minority of myxoid leiomyosarcoma may exhibit PLAG1 immunoreactivity and *PLAG1* fusion. Low grade endometrial stromal sarcoma is expected to exhibit diffuse strong CD10 and estrogen receptor (ER) immunoreactivity The diagnosis can be supported by demonstrating a gene fusion involving *JAZF1* and/or *PHF1* but since only about two-thirds of these tumours harbor such a gene fusion, molecular testing is not essential for the diagnosis nor does a negative result exclude the diagnosis. High grade endometrial stromal sarcoma encompasses a range of tumours that are subclassified by one of a variety of distinct gene fusions, thus requiring molecular testing for their diagnosis. The high grade component of *YWHAE-NUTM2A/B* high grade endometrial stromal sarcoma typically exhibits absent CD10 and ER immunoreactivity, positive cyclin D1, CD117, CD56, CD99 and BCOR immunoreactivity,[139] and the *YWHAE-NUTM2A/B* gene fusion. *ZC3H7B-BCOR* high grade endometrial stromal sarcoma retains CD10 immunoreactivity, exhibits variable ER immunoexpression, positive cyclin D1 immunoreactivity, variable BCOR immunoreactivity, and *ZC3H7B-BCOR* gene fusion. High grade endometrial stromal sarcoma with *BCOR* internal tandem duplication (ITD) exhibit variable CD10

immunoexpression, loss of ER immunoreactivity, positive cyclin D1 and BCOR immunoreactivity, and *BCOR* ITD by molecular sequencing techniques.

SMARCA4-deficient uterine sarcoma is defined by loss of SMARCA4 (BRG1) immunoreactivity or, rarely, loss of SMARCB1 (INI1) immunoreactivity. The diagnosis can be supported by demonstrating inactivating mutation or deletion of *SMARCA4.* IMT is defined by positive ALK immunoreactivity; demonstration of *ALK* fusion by molecular testing can support the diagnosis but is not essential if the ALK immunostain is positive. PEComa is defined by dual melanocytic (HMB45, cathepsin K, melan A, MITF, and/or PNL2) and myoid (smooth muscle actin, desmin, h-caldesmon) immunoreactivity. It is recommended that at least two melanocytic markers be positive given the lack of specificity of any one marker for PEComa. The subset of PEComas that harbour a *TFE3* fusion exhibit TFE3 immunoreactivity along with melanocytic marker immunoreactivity, although smooth muscle marker immunoreactivity may be limited or absent. The diagnosis of PEComa can be supported by demonstration of an inactivating mutation of *TSC1* or *TSC2* or by demonstrating *TFE3* or *RAD51B* fusion.[140] UTROSCT is characterised by polyphenotypic immunoreactivity of epithelial markers (keratin, epithelial membrane antigen (EMA)), sex cord markers (FOXL2, SF1, calretinin, inhibin, WT1, and/or melan A), myoid markers (smooth muscle actin, desmin and h-caldesmon) and hormone receptors (ER and progesterone receptor (PR)). The diagnosis can be supported by demonstrating *ESR1* or *GREB1* fusion; however such alterations are not present in all cases, so a negative result does not exclude the diagnosis. *NTRK* uterine sarcoma is defined by a gene fusion involving *NTRK1, NTRK2,* or *NTKR3.* S100 and CD34 are usually positive and immunoreactivity of these markers can be used as a screening tool to identify tumours that merit *NTRK* molecular testing; smooth muscle markers, CD10 and hormone receptors are usually negative. Pan-TRK immunoreactivity can also be used to triage testing for a *NTRK* fusion. However, high grade endometrial stromal sarcoma may show NTRK immunoreactivity in the absence of an *NTRK* fusion.[141] Uterine adenosarcomas do not have a unique immunophenotype and so the diagnosis is mainly based on morphologic criteria. The tumour cells usually exhibit CD10 and ER immunoreactivity but these markers may be absent in areas of high grade stroma/sarcomatous overgrowth. Rhabdomyosarcoma is expected to exhibit immunoreactivity of desmin, myogenin, and/or myoD1. Both rhabdomyosarcoma and adenosarcoma with rhabdomyosarcomatous differentiation may harbor *DICER1* mutations.

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Note 16 – Pathologically confirmed distant metastasis (Core)

Documentation of known metastatic disease is an important part of the pathology report. Such information, if available, should be recorded with as much detail as is available including the site, whether the specimen is a histopathology or cytopathology specimen and with reference to any relevant prior surgical pathology or cytopathology specimens.

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Note 17 – Provisional pathological staging (Core)

The pathological staging must be provided on the pathology report and is therefore a core element. The term 'provisional pathological staging' is used in this dataset to indicate that the stage that is provided may not represent the final tumour stage which should be determined at the multidisciplinary tumour board meeting where all the pathological, clinical and radiological features are available.[107,124,142]

The latest version of either FIGO *or* TNM staging, *or* both, can be used depending on local preferences.[107,124,142] The FIGO Staging System is in widespread use internationally and is the system used in most clinical trials and research studies. However, Union for International Cancer Control (UICC) or American Joint Committee on Cancer (AJCC) versions of TNM are used or mandated in many parts of the world.[124,142] With regards to updating of staging systems, there is collaboration between FIGO and those agencies responsible for TNM with an agreement to adopt changes to FIGO staging. Following the introduction of a new FIGO Staging System, this is usually incorporated into TNM (both UICC and AJCC versions) at a later date. Apart from minor discrepancies in terminology, the UICC and AJCC systems are broadly concurrent.

There are two staging systems for uterine sarcomas. One is to be used specifically for adenosarcomas and the other is for leiomyosarcomas and endometrial stromal sarcomas.[107] It is recommended that the latter staging system be used for other malignant uterine mesenchymal neoplasms, such as undifferentiated sarcoma and rhabdomyosarcoma; it is not recommended to provide a pathological stage for STUMPs. It is controversial as to whether a pathological stage should be applied to other mesenchymal tumours of uncertain malignant potential which are discussed in this dataset, such as UTROSCT, PEComa and IMT. However, a stage may be applied for those neoplasms which fulfil the criteria for malignancy in the individual tumour types, although this is not mandated.

A tumour should be staged following diagnosis using various appropriate modalities (clinical, radiological, pathological). While the original tumour stage should not be altered following treatment, TNM systems allow staging to be performed on a resection specimen following non-surgical treatment (for example chemotherapy, radiotherapy); in such cases, if a stage is being provided on the pathology report (this is optional), it should be prefixed by 'y' to indicate that this is a post-therapy stage. The reference document TNM Supplement: A commentary on uniform use, 5th Edition (C Wittekind et al. editors) may be of assistance when staging.[143]

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