WHO Classification of tumors of the *uterine corpus* (2014)

• Epithelial tumors and precursors
  – Precursors
    • Hyperplasia without atypia
    • Atypical hyperplasia/Endometrioid intraepithelial neoplasia 8380/2*
Hyperplasia without atypia

- Exaggerated proliferation of glands of irregular size and shape, with an associated increase in the gland to stroma ratio compared with proliferative endometrium, but without significant cytological atypia

- Synonyms
  - Benign endometrial hyperplasia
  - Simple non-atypical endometrial hyperplasia
  - Complex non-atypical endometrial hyperplasia
  - Simple endometrial hyperplasia without atypia
  - Complex endometrial hyperplasia without atypia

- 1-3% progression to WD endometrial carcinoma
Fig. 8.1
Simple hyperplasia (without atypia). Glands are only minimally crowded but are dilated and have outpouchings.
Fig. 8.2
Simple hyperplasia (without atypia). Glands are mildly crowded and some are cystically dilated
Fig. 8.8
Simple hyperplasia (without atypia). Nuclei are elongated, oriented perpendicular to the basement membrane, and have even chromatin
Fig. 8.3
Simple hyperplasia (without atypia). Glands are mildly crowded and dilated, with some exhibiting outpouchings and simple branching.
Fig. 8.5
Complex hyperplasia (without atypia). Branching and tubular glands are sufficiently crowded for classification as complex hyperplasia, despite the presence of some glands with simple tubular profiles.
Fig. 8.6
Complex hyperplasia (without atypia). Glands are sufficiently crowded for classification as complex hyperplasia, despite the presence of glands having only simple tubular profiles.
Fig. 8.7
Complex hyperplasia (without atypia). Dilated glands resemble those seen in simple hyperplasia but are sufficiently crowded for classification as complex hyperplasia.
Fig. 8.9
Complex hyperplasia (without atypia). Nuclei are elongated, oriented perpendicular to the basement membrane, and have even chromatin
Fig. 8.10
Complex hyperplasia (without atypia). Nuclei are elongated, oriented perpendicular to the basement membrane, and are evenly hyperchromatic.
Fig. 8.11
Complex hyperplasia (without atypia). Nuclei are elongated, oriented perpendicular to the basement membrane, and are evenly hyperchromatic.
Atypical hyperplasia/Endometrioid intraepithelial neoplasia

• Cytological atypia superimposed on endometrial hyperplasia (EIN)
• Synonyms
  – Complex atypical endometrial hyperplasia
  – Simple atypical endometrial hyperplasia
  – Endometrial intraepithelial neoplasia (EIN)
• Coexists with carcinoma in approximately 25-40% of women; 1/4 to 1/3 of women with a biopsy of AH/EIN will be diagnosed with cancer at immediate hysterectomy or during the first year of follow-up
• Long term risk: 14-fold in classic, early studies of AH to 45-fold in EIN studies
Atypical hyperplasia/Endometrioid intraepithelial neoplasia

- Nuclear atypia:
  - enlargement, pleomorphism, rounding, loss of polarity and nucleoli
  - Nuclear atypia is variable, both qualitatively and quantitatively
  - As these features are somewhat subjective, intraobserver and interobserver variability remains problematic
  - AH/EIN often accompanied by metaplastic changes which adds to the difficulty in diagnosis
Atypical hyperplasia/Endometrioid intraepithelial neoplasia

• Histogenesis
  – Continuous unopposed estrogenic stimulation leads to progression of hyperplasia without atypia to AH/EIN
  – AH/EIN emerges as a clonal process that begins as a localized lesion usually in a background of hyperplasia without atypia

• Genetic profiles
  – AH/EIN contains many of the genetic changes seen in endometrioid endometrial carcinoma (microsatellite instability, PAX2 inactivation and PTEN, KRAS and CTNNB1 (β-catenin) mutation
Complex atypical hyperplasia (AH). Glands with complex profiles and papillary infoldings are crowded in a back-to-back fashion, compressing intervening normal endometrial stroma.
Fig. 8.12
Complex atypical hyperplasia. Nuclei are rounded and have vesicular chromatin
Fig. 8.13
Complex atypical hyperplasia. Nuclei are rounded, have vesicular chromatin, and display stratification and loss of polarity.
Fig. 8.14
Complex atypical hyperplasia. Nuclei are enlarged and rounded, have vesicular chromatin with fine granularity, and display stratification and loss of polarity.
Fig. 8.15
Complex atypical hyperplasia. Nuclei vary from ovoid to rounded, have even chromatin with evident nucleoli and mitotic figures, and display some stratification and loss of polarity.
Fig. 8.16
Complex atypical hyperplasia. Nuclei are enlarged and rounded, have vesicular chromatin with fine granularity and evident nucleoli, and display stratification and loss of polarity.
Endometrial intraepithelial neoplasia (EIN)

Diagnostic criteria

- **Architecture**
  
  Area of glands greater than stroma

- **Cytology**
  
  Cytology differs between architecturally crowded focus and background, or clearly abnormal

- **Size > 1mm**
  
  Maximum linear dimension exceeds 1mm

- **Exclude mimics**
  
  Benign conditions with overlapping criteria: basalis, secretory, polyps, repair, etc.

- **Exclude cancer**
  
  Carcinoma if mazelike glands, solid areas, polygonal ‘mosaic-like’ glands, myoinvasion or significant cribriforming
Fig. 17.5 Clonal origin of EIN. The first genetic changes (such as PTEN inactivation) which initiate endometrial carcinogenesis are unaccompanied by any phenotypic alterations at the light microscopic level. This ‘latent’ phase of cytologically and architecturally normal but genetically altered cell may persist for years in a normally menstruating woman. Low cancer risk, combined with lack of a rational therapeutic response, are reasons that systematic screening and treatment of these ‘latent’ phase lesions is unwarranted at present. As additional genetic damage accumulates, higher-risk morphologically altered mutant clones declare themselves by demonstrating those architectural and cytologic alterations that distinguish EIN. Malignant transformation of EIN lesions, which occurs at least 46-times more frequently than benign endometrial disease, is the trigger for clinical malignancy.
Fig. 17.6 Schematic topography of EIN. Benign, premalignant and malignant endometrial processes have differing large-scale architectures and distribution within the endometrial compartment. Reparative or degenerative changes lead to epithelial piling up and loss of polarity in regions of stromal breakdown or offending stimulus. Benign systemic effects (such as unopposed estrogens) tend to induce changes throughout the endometrial field, with responsive individual glands randomly scattered throughout. In contrast, EIN lesions begin at a single point in space, growing outwards as a compact mass of individual glands with altered cytology. Initially they have the appearance of a physical 'patch' or geographic domain composed of glands with altered cytology and architecture, eventually overtaking the entire endometrial compartment. Malignant types of cancer...
WHO Classification of tumors of the uterine corpus (2014)

• Endometrial carcinomas
  – **Serous endometrial intraepithelial carcinoma**  8441/2*
  – Neuroendocrine tumors
    • Low-grade neuroendocrine tumor
      Carcinoid tumor  8240/3
    • High-grade neuroendocrine tumor
      Small cell neuroendocrine carcinoma  8041/3
      Large cell neuroendocrine carcinoma  8013/3
  – Mixed cell adenocarcinoma  8323/3
    (Type I & Type II (>=5%))
Serous endometrial intraepithelial carcinoma (SEIC)

- Frequently develops directly on a polyp or in atrophic endometrium
- Confined to the epithelium, even in the absence of demonstrable invasion, this is a carcinoma that can shed cells and metastasize widely to extra-uterine sites
- p53 intense and diffuse staining of at least 75% of the tumors or complete absence of p53 immunoreactivity correlates with a TP53 mutation, very high Ki-67 labeling index
- Since the distinction of SEIC from early stromal invasion by serous carcinoma is often impossible, it is recommended that these lesions in biopsies be termed “minimal uterine serous carcinoma”
Neuroendocrine tumors

• A diverse group of neoplasms that share a morphological neuroendocrine phenotype

• Synonyms
  – For carcinoid: WD endocrine tumor, grade 1
  – For small cell neuroendocrine carcinoma: small cell carcinoma, neuroendocrine carcinoma, small cell type, grade 3
  – For large cell neuroendocrine carcinoma: neuroendocrine carcinoma, large cell type, grade 3

• (No grade 2 ?)
WHO Classification of tumors of the uterine corpus (2014)

• Mesenchymal tumors
  – Endometrial stromal and related tumors
    • Endometrial stromal nodule 8930/0
    • Low grade endometrial stromal sarcoma 8931/3
    • High grade endometrial stromal sarcoma 8930/3
      (undifferentiated endometrial sarcoma 8930/3)
      UES, monomorphic type
      UES, pleomorphic type
    • Undifferentiated uterine sarcoma 8805/3
    • Uterine tumor resembling ovarian sex cord tumor 8590/1*
High-grade endometrial stromal sarcoma

- A malignant tumor of endometrial stromal derivation with high-grade, round cell morphology sometimes associated with a low-grade spindle cell component that is most commonly fibromyxoid

- Histopathology
  - May have typical infiltrative growth and vasculature of its low-grade counterpart
  - High grade round cell usually predominant
  - Rarely, a high-grade sarcoma is seen in association with areas that have the appearance of conventional low-grade ESS and also can be diagnosed as high-grade ESS
High-grade endometrial stromal sarcoma

- The high-grade component of tumors with t(10;17) \((YWHAE-FAM22\) genetic fusion as a result of \(t(10;17)(q22;p13)\) \((t(7;17)(p15;q21)---JAZF1-SUZ12\) in low-grade ESS\) is CD10, ER and PR negative but shows strong diffuse cyclin D1 positivity (>70% nuclei)
- The high-grade component also c-Kit positive but DOG1 negative
- The low-grade spindle cell component typically strongly and diffusely CD10, ER and PR positive and shows variable, heterogeneous cyclin D1 expression (<50%)
- Dedifferentiated vs de Novo
Undifferentiated uterine sarcoma

- A tumor arising in the endometrium or myometrium, lacking any resemblance to proliferative-phase endometrial stroma, with high-grade cytological features and with no specific type of differentiation

- Synonyms
  - Undifferentiated endometrial sarcoma (not recommended)

- Histopathology
  - Variably CD10 positive and ER and PR weakly positive or negative, focal SMA, desmin, EMA or CK may be seen
  - Cyclin D1 can be diffusely positive but in those cases the tumors are also typically positive for CD10 (which excludes YWHAE-FAM22 sarcomas)
YWHAE-FAM 22 (YWHAE-NUTM2)
Sarcomas

- **Histopathology**
  - Myopermeative tumor with LVI (similar to LGESS)
  - High grade epithelioid/Round cell area (present in nearly all cases)
  - Admixed with low grade area (present in ~50%)

- **Immunophenotypic features**
  - High grade area: ER/PR negative; CD10 negative; positive for cyclin D1, Cd117/Kit, CD99
  - Low grade area: ER/PR positive; CD10 positive; overlap with LGESS
  - Both areas: negative for CK, DOG1, HMB45, S100, desmin, SMA, caldesmon
**UES**

- Complex karyotype
- High mitotic activity
- Tumor necrosis
- Poor prognosis

**ESS**

- High-grade
  - YWHAE-FAM22
- Low-grade
  - JAZF1-SUZ12
  - JAZF1-PHF1
  - EPC1-PHF1

- ↑ Nuclear size/Irregularity in nuclear contour
- ↑ Mitotic activity
- Tumor necrosis

**Prognosis**

- Intermediate prognosis
- Good prognosis
High grade endometrial stromal sarcoma
Cyclin D-1 (>70% positive)
CD10 (+)
Cyclin D-1 (>70% positive)
WHO Classification of tumors of the uterine corpus (2014)

- Mesenchymal tumors
  - Miscellaneous mesenchymal tumors
    - Rhabdomyosarcoma 8900/3
    - **Perivascular epithelioid cell tumor**
      - Benign 8714/0*
      - Malignant 8714/3*
PEComa

- Perivascular epithelioid cell tumor
  - a mesenchymal tumor typically containing epithelioid cells with clear to eosinophilic, granular cytoplasm demonstrating melanocytic and smooth muscle differentiation, thought to be derived from the so-called perivascular epithelioid cells
  - IHC: HMB-45 (92%); Melan-A (72%), MiTF (50%)
  - Malignancy (2 or more worrisome features): >5 cm, infiltrative margin, high-grade nuclei, cellularity, mitosis (>1/50 HPF), necrosis, vascular invasion
<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>Tumors showing: &lt; 5 cm, noninfiltrative, non–high-grade nuclear features,</td>
</tr>
<tr>
<td></td>
<td>no necrosis or vascular invasion and a mitotic rate $\leq 1/50$ HPF</td>
</tr>
<tr>
<td>Uncertain malignant</td>
<td>Tumors with only 1 of the following:</td>
</tr>
<tr>
<td>potential</td>
<td>nuclear pleomorphism or multinucleated giant cells</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>gross size $\geq 5$ cm</td>
</tr>
<tr>
<td>Malignant</td>
<td>Tumors with 2 or more features:</td>
</tr>
<tr>
<td></td>
<td>gross size $&gt; 5$ cm, infiltrative growth, high-grade nuclear features,</td>
</tr>
<tr>
<td></td>
<td>necrosis, vascular invasion, or a mitotic index $\geq 1/50$ HPF</td>
</tr>
</tbody>
</table>
TNM and FIGO classification of uterine sarcomas (2014)

- Leiomyosarcoma, Endometrial stromal sarcoma

<table>
<thead>
<tr>
<th>TNM</th>
<th>FIGO</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>I</td>
<td>Tumor limited to the uterus</td>
</tr>
<tr>
<td></td>
<td>T1a</td>
<td>IA</td>
</tr>
<tr>
<td></td>
<td>T1b</td>
<td>IB</td>
</tr>
<tr>
<td>T2</td>
<td>II</td>
<td>Tumor extends beyond the uterus, within pelvis</td>
</tr>
<tr>
<td></td>
<td>T2a</td>
<td>IIA</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>IIB</td>
</tr>
<tr>
<td>T3</td>
<td>III</td>
<td>Tumor involves abdominal tissues</td>
</tr>
<tr>
<td></td>
<td>T3a</td>
<td>IIIA</td>
</tr>
<tr>
<td></td>
<td>T3b</td>
<td>IIIB</td>
</tr>
<tr>
<td>N1</td>
<td>IIIC</td>
<td>Metastasis to regional LNs</td>
</tr>
<tr>
<td>T4</td>
<td>IVA</td>
<td>Tumor invades bladder or rectal mucosa</td>
</tr>
<tr>
<td>M1</td>
<td>IVB</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>
TNM and FIGO classification of uterine sarcomas (2014)

- Leiomyosarcoma, Endometrial stromal sarcoma
- Note: Simultaneous tumors of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors
<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>Stage IC*</td>
<td>T1c</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2a</td>
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<td>Stage IIB</td>
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<td>M0</td>
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<tr>
<td>Stage IIIA</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>T1,2,3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Note: Stage IC does not apply for leiomyosarcoma and ESS (Adenosarcoma: IA (EM), IB (<1/2 wall), IC (>1/2 wall)) (IA, IB ?)