Tumors of the Endometrial Cavity

Endometrial Hyperplasia → Carcinoma Pathway

Proliferative Endometrium

- Straight or mildly tortuous **tubular glands**
- **Abundant stroma** (Stroma ≥ Glands)
- Columnar cells with pseudostratified hyperchromatic cigar-like nuclei and mitoses

Disordered Proliferative Endometrium

- **Variably/haphazardly shaped glands** (e.g., branching), including **cystically dilated**
- **Abundant stroma** (Gland : Stroma ratio <2:1)
- Glands/cells identical to proliferative endometrium
- Often due to anovulatory cycles

Hyperplasia (without atypia)

- **Gland crowding** (Gland : Stroma ratio >2:1)
- Can be “simple” (normal tubular glands—lowest risk) or “complex” (abnormal, irregular glands, with even less stroma—higher risk).
- **Normal nuclei/cytology** (elongate, dense, polarized, nuclei)

Hyperplasia with atypia/
Endometrial Intraepithelial Carcinoma

- **Crowded glands** (Gland : Stroma ratio >2:1)
- Typically “complex” architecture with irregular, often back-to-back glands
- **Cytologically altered nuclei**: enlarged, rounded, pleomorphic, loss of polarity, vesicular chromatin, nucleoli.

Endometrioid Carcinoma

- Distinction from CAH/EIN is based on **stromal invasion**, which is defined by one of the following
  1. **Loss of intervening stroma**: confluent growth, cribiform growth, or complex folded mazelike epithelium
  2. Irregular **infiltration of myometrium** associated with an altered fibroblastic stroma (desmoplastic response)
  3. **Solid nonsquamous epithelial growth**
  4. **Papillary architecture** or **villoglandular growth**
Complex Atypical Hyperplasia

“CAH”

Gland crowding (Gland : Stroma ratio usually >2:1), often densely crowded with only small amounts of intervening stroma and back-to-back glands.

Nuclear Atypia: relatively enlarged, rounded nuclei with loss of polarization, chromatin abnormalities (often clearing or vesicular) and variably prominent nucleoli.

Often important to compare nuclei to non-hyperplastic glands elsewhere in specimen to account for fixation artifact, etc..

If nuclear atypia is too much, consider other diagnoses like endometroid adenocarcinoma, serous carcinoma, etc...

Endometrial Intraepithelial Neoplasia (EIN)

Conceived as a true carcinoma precursor based on architectural and genetic abnormalities interpreted as neoplastic.

Diagnostic criteria:
1- Crowded glands with a gland to stroma ratio >1:1
2- Altered cytology of the crowded glands from the background epithelium (“cytologic demarcation”). This can be nuclear or cytoplasmic.
   - If no background epithelium is present, use same criteria as for CAH (above)
3- Must be > 1mm within a single tissue fragment

Although CAH and EIN are often overlapping diagnoses, they have slightly different diagnostic criteria. EIN is likely more specific, while CAH is more sensitive.

Both are acceptable by the WHO and usage often depends on local practice.
**Endometrioid Carcinoma**

**Most common** carcinoma of the endometrium.

Classically, in post-menopausal women and related to increased levels of estrogen exposure (associated with obesity, diabetes, PCOS, and certain medications) and preceded by hyperplasia.

Often presents with **vaginal bleeding** (always a concerning finding after menopause!)

**Crowded, complex glandular or villoglandular architecture.**

Cells are often columnar and **share an apical border** with eosinophilic granular cytoplasm. Nuclear atypia is often mild to moderate.

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Some cut-off’s for the extent of “confluent growth” to be more objective have been suggested:

- Kurman & Norris = 2 mm
- Longacre = 30% of total proliferation and should be able to traverse a 10x field without hitting stroma

Sometimes the cutoff of carcinoma vs CAH cutoff can be challenging. OK, to diagnose as “CAH bordering on well-differentiated endometrioid adenocarcinoma”

Frequently see **squamous differentiation** with morules, keratin pearls, and intercellular bridges.

Occasionally see **secretory changes** with glycogen vacoule or bland spindled epithelial cell component.

**Corded and Hyalinized**: has cords, clusters, and/or trabeculae of epithelioid to spindled cells embedded within hyalinized to myxoid matrix. Often associated with grade 1-2 glandular component. No prognostic significance, but sometimes confused with carcinosarcoma, leading to overtreatment.

IHC: (+)CK7, PAX8; (-)CK20; Cup-like vimentin staining. Low-grade often ER/PR +;

**Grade using the FIGO system**: based on the amount of solid growth. Be sure to exclude squamous morules from this calculation. The grade can be increased by 1 based on severe nuclear atypia in the majority of the cells. A confluent microacinar pattern is often counted as solid.

<table>
<thead>
<tr>
<th>FIGO grade</th>
<th>% Solid Growth</th>
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<tbody>
<tr>
<td>1</td>
<td>≤5%</td>
</tr>
<tr>
<td>2</td>
<td>6-50%</td>
</tr>
<tr>
<td>3</td>
<td>&gt;50%</td>
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### Molecular Classification

#### Ultramutated (POLE mutated) subtype (~5%)
Mutations of DNA polymerase ε result in an extremely high tumor mutation rate → lots of neoantigens in tumor cells → recognized by immune system → lots of tumor infiltrating lymphocytes → **Excellent prognosis**. Often younger patients. Often grade 3 with intratumoral heterogeneity and giant tumor cells. Broad invasive front with low clinical stage.

#### Hypermutated/Microsatellite Instability (MSI) subtype (~25%)

#### Copy Number High/Serous-like subtype (~25%)
Genomically unstable → high somatic copy number alterations. Very high rate of TP53 mutations. Often Grade 3 with diffuse high nuclear grade, slit-like spaces, hobnailing, and destructive invasion. Often older patients and advanced stage. Poor prognosis.

#### Copy Number Low/Microsatellite Stable (MSS) subtype (~45%)
Most common type. Often Grade 1-2, ER/PR+ with squamous differentiation. Associated with unopposed estrogen exposure (as is seen in obesity). Overall low mutation rate. Very frequent PTEN mutations. Intermediate prognosis (depends largely on stage).

Generally, frequent mutations (can be seen all groups) in **PTEN, PIK3CA, ARID1A, CTNNB1, and KRAS**

### In general:
Low-grade (FIGO 1/2): map to the copy number low and MSI-H categories
High-grade (FIGO 3): map to all 4 categories, but least to the copy number low group

#### Familial syndromes:
**Lynch Syndrome**: germline mutations in mismatch repair (MMR) proteins → MSI-subtype → ~50% lifetime risk (similar to risk of colon cancer).

**PTEN-hamartoma tumor syndrome/Cowden syndrome**: Germline PTEN mutation → no specific morphology

### Molecular Classification Algorithm:

#### How do you separate serous carcinoma from serous-like endometrioid carcinoma?
Primarily by morphology (e.g., if there is squamous differentiation → serous-like endometrioid). However, both are TP53-mutated and are aggressive, and this can be morphologically challenging, so this distinction is likely not too important at this time.
Myoinvasion

Can be very challenging to identify/measure! **Measure from endomyometrial junction to the deepest point of invasion.**

Report as % (depth of invasion/total myometrial thickness).

**Critical clinical cutoff point = 50%** (inner vs outer ½)

Myometrial invasion often (but not always!) includes irregular angular glands *eliciting a desmoplastic response or loose granulation tissue* with inflamed edematous fibrous stroma

It can be helpful to look for compressed *non*-neoplastic glands to determine the level of the endomyometrial junction.

Carcinoma involving **adenomyosis** or within vessels do *not* count as invasion. So, look for surrounding benign glands and stroma to rule out colonization of adenomyosis

**Challenging patterns of myometrial invasion:**

"**Pushing**" Invasion — broad, expansile front with a mild or absent stromal reaction. Helpful to submit adjacent normal endometrium to determine level of endomyometrial junction (if present).


**Diffusely infiltrative “melter” pattern**—individual well-formed glands with mild to moderate atypia that diffusely infiltrate the myometrium with minimal stromal reaction (sort of like “adenoma malignum” of the cervix). Often wide-spread throughout uterus. Make Dx on low-power from architecture. Can be extremely challenging to evaluate for superficial invasion, but good prognosis if stage 1, so less important.

**Lymphovascular Invasion**

Frequently seen with MELF pattern. Sometimes intravascular cells can appear “histiocytoid,” requiring stains to confirm that they are tumor.

Can see frequent vascular “pseudoinvasion” with laparoscopic hysterectomy specimens, which is thought to be artifactual/iatrogenic. So, if it is a low-grade, non-invasive tumor that was removed laparoscopically, it’s probably “pseudoinvasion.”
An Approach to Difficult Endometrial Lesions

High-Grade Cytology?

- No
  - Architecture
    - Low-risk
      - CAH/EIN
    - Intermediate-risk
      - <30% CAH/EIN
    - High-risk
      - ≥30% CAH/EIN

- Yes
  - Adenocarcinoma

Be sure to consider:
- Serous
- Clear cell

Note: If the proliferation has a papillary or labyrinthine growth pattern, there is no % requirement.

Architectural Patterns:

High-risk Patterns: Carcinoma
- Glandular confluence without intervening stroma (10x field)
- Extreme, meandering or labyrinth pattern
- Macroglands with well-developed secondary branching or multiple generations of bridging forming a cribriform pattern
- Villous and nonvillous papillae containing second and third degree branching and/or cribriform budding

Intermediate-risk Patterns: Borderline

Low-risk Patterns: Hyperplasia
- Simple budding into small glands
- Macroglands with simple, non-branching nonvillous papillae or minimal bridging
- Simple non-branching villous and nonvillous papillae

### Benign Endometrial Polyp

Localized, disorganized altered glands and stroma.

**Glands:** tubules that may be simple, branched, or cystically dilated. Lined by inactive epithelium.

**Stroma:** often collagen-rich containing characteristic thick blood vessels

Often solitary. Can be anywhere in uterus.

Small polyps are often asymptomatic.

Large polyps may cause bleeding.

May have superimposed metaplasia, hyperplasia, or carcinoma (particularly SEIC in postmenopausal)

### Atypical Polypoid Adenomyoma “APA”

Three key features:
1) **Endometrial glands** with some architectural complexity and cytologic atypia
2) Prominent squamous morules
3) Surrounding prominent cellular fibromuscular stroma

Often centered in **lower uterine segment**, ~2cm.

Associated with MLH-1 promoter methylation (~1/2)

Can be confused with myoinvasive endometrioid adenocarcinoma, but APA fibromuscular stroma is P16+ (whereas desmoplastic stroma/myometrium is P16-)

Although benign, can progress or be associated with atypical hyperplasia/EIN or endometrioid adenocarcinoma

### Adenosarcoma *(Think: Phyllodes tumor)*

Mixed epithelial and mesenchymal tumor with a **benign epithelial component** and **low-grade malignant stroma**.

**Papillary/polypoid projections** of cellular stroma into dilated gland lumens. Often with condensation, “collaring” around benign surface glands. Stroma resembles endometrial stroma but is often more fibroblastic.

Often post-menopausal but can be any age.

Can show heterologous elements and sarcomatous overgrowth. When ≥25% of tumor is a high-grade sarcoma, “Adenosarcoma with sarcomatous overgrowth”

IHC: Stroma (+) CD10, ER, PR.

Prognosis: Recurring potential. If sarcomatous overgrowth, more aggressive → can metastasize.
Other Endometrial Carcinomas

Serous Carcinoma

Epithelial cells with **large atypical nuclei, prominent nucleoli, and scant cytoplasm. Numerous mitoses.**

Often complex papillary architecture. Can be solid or glandular. Luminal surfaces often appear **scalloped** (no common apical border as is seen in endometrioid). Grading not applicable. Often infiltrates in “gaping” to slit-like (non-solid) glands.

Typically **post-menopausal** women presenting with bleeding. Often grossly inconspicuous on the **surface of a polyp.** Background endometrium often atrophic.

**Serous Endometrial Intraepithelial Carcinoma** ("SEIC")—non-invasive precursor to serous carcinoma; confined to the epithelium (e.g., surface of a polyp). Malignant: Can still undergo transtubal metastasis to pelvis.

Molecular: Frequent TP53 mutations. Associated with BRCA1/2. IHC: **p53 mutant** (either diffuse or null), P16 block positive.

Prognosis depends on stage (advanced = very bad).

Clear Cell Carcinoma

**Polygonal or hobnail-shaped cells with clear cytoplasm** (or sometimes eosinophilic) and **prominent nuclear atypia**

Tubulocystic, papillary, or solid architecture with hyalinized stroma and eosinophilic extracellular **hyaline globules.**

Often atrophic background.

Often postmenopausal women with vaginal bleeding.

Grading not applicable.

Relatively poor prognosis.

Mucinous Carcinoma

An endometrial carcinoma in which > 50% of the neoplasm is mucinous. Very rare. (Most tumors that are mucinous are endometrioid adenocarcinoma with mucinous differentiation)

Often low-grade with glandular or villoglandular architecture and uniform mucinous columnar cells with minimal stratification/atypia. Frequent KRAS mutations. Can still grade using FIGO System.

Relatively good prognosis.

Be sure to consider endocervical origin on biopsy!

Mixed Carcinoma

The term mixed carcinoma should be used when two or more distinctive subtypes of endometrial carcinoma are identified, each representing at least 5% of the tumor.
**Dedifferentiated Endometrial Carcinoma**

Two distinct components:
1. **Low-grade (FIGO 1-2) endometrioid carcinoma**
2. **High-grade undifferentiated carcinoma** (see above)

Each component has the IHC/molecular of that component (e.g., undifferentiated component has SWF/SNF mutations).

Very aggressive.

**Undifferentiated Carcinoma**

Malignant epithelial neoplasm with **no differentiation**.

Sheets of medium-sized relatively **uniform, monotonous, discohesive cells** with often **condensed chromatin**. No gland formation (resembles lymphoma). Numerous mitoses. Often numerous **tumor-infiltrating lymphocytes** (TIL).

Often form large, polypoid masses within uterine cavity.

Molecular: Often MMR-deficient (some Lynch-associated); Frequent mutations of SWF/SNF pathway (SMARCA4, SMARCA1/INI-1, ARID1B de-activation)

IHC: Loss of MLH1/PMS2. Loss/focal Cytokeratins, EMA, ER, PAX8. (+)CD34

Very aggressive.

**Carcinosarcoma**

Biphasic tumor with two components:
1. **High-grade carcinoma** (epithelial) and
2. **Sarcoma** (mesenchymal)

Typically **post-menopausal women** presenting with vaginal bleeding. Often a large pelvic mass that **prolapses out of the cervix** in ~1/2 of cases.

Often intimate admixture of carcinoma and sarcoma elements.

Carcinoma is **often serous or endometrioid carcinoma**

Sarcoma is often high-grade non-specific sarcoma, but “heterologous” elements can be seen including: rhabdomyosarcoma, chondrosarcoma, and osteosarcoma (which look/stain like they do elsewhere)

Molecular: Frequent TP53 mutations.

**Poor prognosis.** Frequent pelvic recurrences and lymph node metastases (of carcinomatous component)
Helpful Tables

Carcinoma Immunohistochemistry

<table>
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<tr>
<th></th>
<th>Endometrioid (Low-grade)</th>
<th>Serous</th>
<th>Clear Cell</th>
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<tbody>
<tr>
<td>ER/PR</td>
<td>+</td>
<td>-/+</td>
<td>-/+</td>
</tr>
<tr>
<td>p53</td>
<td>Wild-type</td>
<td>Abnormal</td>
<td>Wild-type, usually</td>
</tr>
<tr>
<td>P16</td>
<td>-/patchy</td>
<td>Block-positive</td>
<td>-/patchy</td>
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<tr>
<td>PTEN</td>
<td>Loss</td>
<td>Intact</td>
<td>Intact</td>
</tr>
<tr>
<td>NapsinA</td>
<td>-</td>
<td>-/+</td>
<td>+</td>
</tr>
<tr>
<td>HNF1β</td>
<td>-</td>
<td>-/+</td>
<td>+</td>
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However, as always, there are exceptions. For example, grade 3 endometrioid carcinomas may exhibit a “serous” immunophenotype with p53 mutations via dedifferentiation and rare clear cell carcinomas may also stain with p53.

Endometrial Polyp Classification and Treatment

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<th>Stroma</th>
<th>Management</th>
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<td>Benign Endometrial Polyp</td>
<td>Benign</td>
<td>Benign, Fibrous</td>
<td>Polypectomy</td>
</tr>
<tr>
<td>Polypoid adenomyoma</td>
<td>Benign</td>
<td>Benign, Muscle</td>
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<td>Hysterectomy or Hormones</td>
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