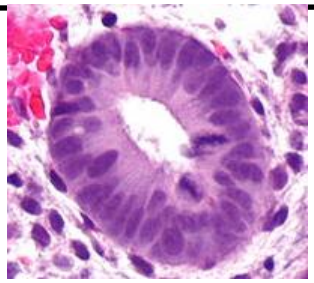
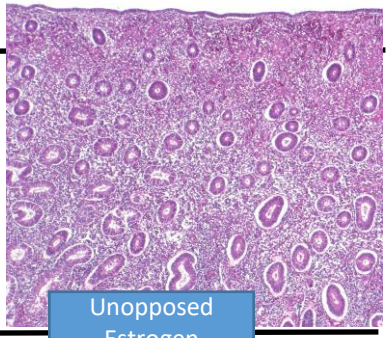
Endometrial Tumors

Endometrial Hyperplasia→ Carcinoma Pathway

Proliferative Endometrium

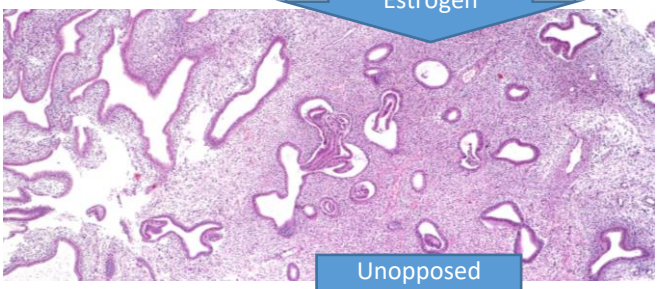




Straight or mildly tortuous **tubular glands**
Abundant stroma (Stroma ≥ Glands)
Columnar cells with pseudostratified hyperchromatic cigar-like nuclei and mitoses

Unopposed Estrogen

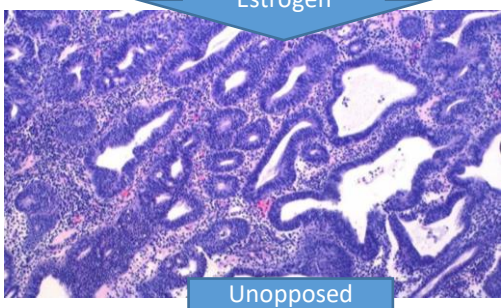
Disordered Proliferative Endometrium



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

Unopposed Estrogen

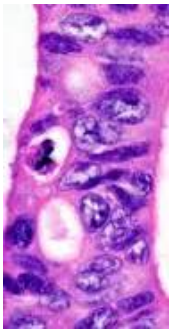
Hyperplasia (*without* atypia)

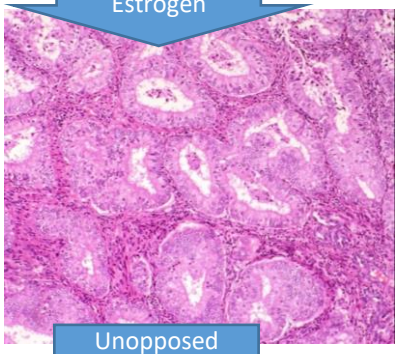


Gland crowding (Gland : Stroma ratio >2:1)
Can be "simple" (normal tubular glands—lowest risk) or "complex" (abnormal, irregular glands, with even less stroma—higher risk).
Normal nuclei/cytology (elongate, dense, polarized, nuclei)

Unopposed Estrogen

Endometrial Atypical Hyperplasia/ Endometrial Intraepithelial Neoplasia

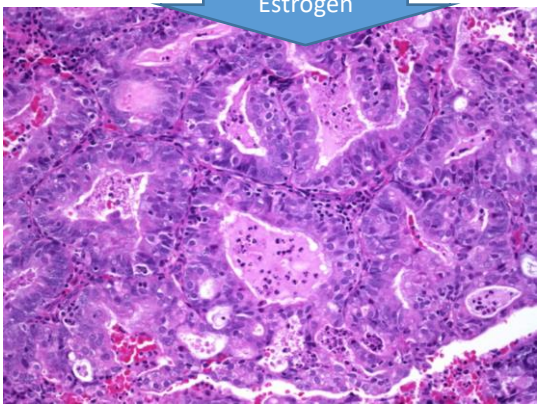




Crowded glands (Gland : Stroma ratio >2:1)
Typically "complex" architecture with irregular, often back-to-to back glands
Cytologically altered nuclei: enlarged, rounded, pleomorphic, loss of polarity, vesicular chromatin, nucleoli.

Unopposed Estrogen

Endometrioid Carcinoma



Distinction from EAH/EIN is based on **stromal invasion,** which is defined by one of the following

1- **Loss of intervening stroma**: confluent growth, cribriform growth, or complex folded mazelike epithelium

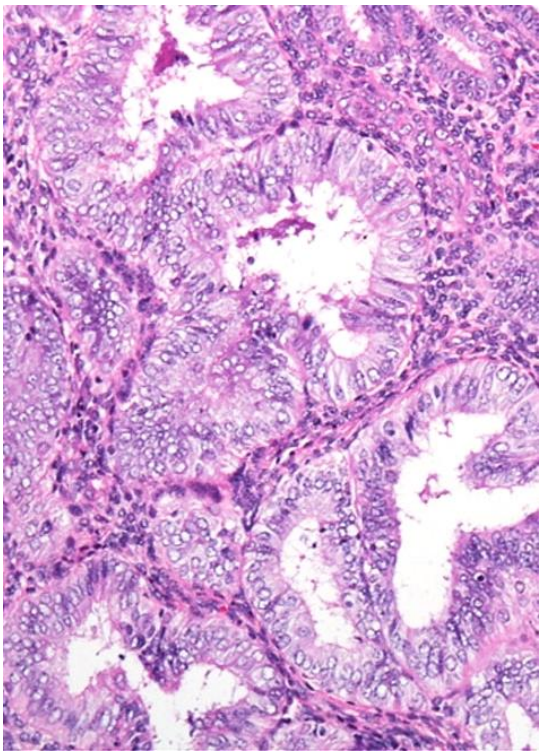
2- Irregular **infiltration of myometrium** associated with an altered fibroblastic stroma (desmoplastic response)

3- **Solid non-squamous epithelial growth**

4- **Papillary architecture** or **villoglandular growth**

EAH/EIN start as a localized clonal expansion→ Precursor to endometrioid carcinoma and has many of the same molecular changes (e.g., MMR, PTEN, KRAS, CTTNB1). ~1/3 risk of endometrial cancer on immediate hysterectomy or within the next year. Treatment: Hysterectomy or Hormones.

Endometrial Atypical Hyperplasia *"EAH"*



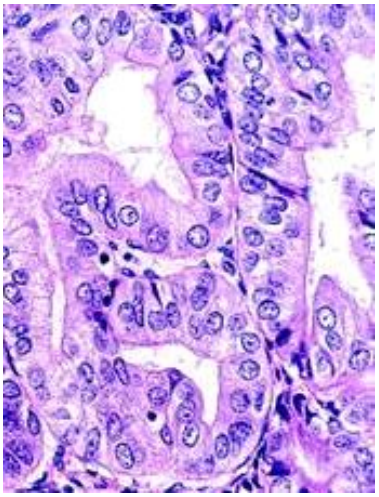
Formerly, "Complex Atypical Hyperplasia" ("CAH")

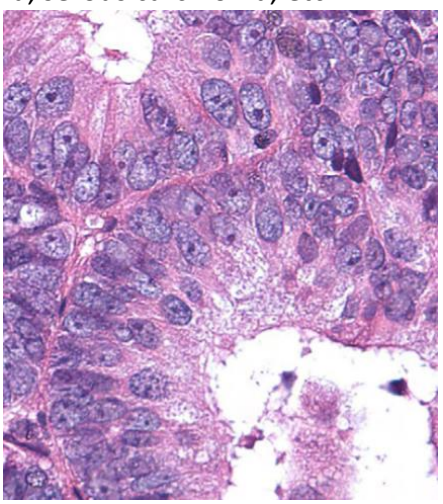
Gland crowding (Gland : Stroma ratio usually >2:1), often densely crowded with only small amounts of intervening stroma and back-to-back glands

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…





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

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

Endometrial Intraepithelial Neoplasia (EIN)

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

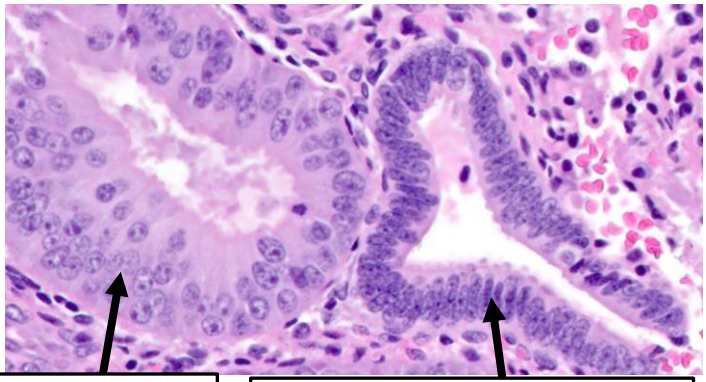
Diagnostic criteria:

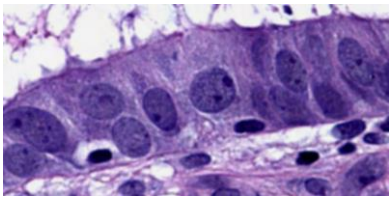
1- **Crowded glands with a gland to stroma ratio >1:1**

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 EAH (above)

3- **Must be > 1mm within a single tissue fragment**





EIN/EAH: **Nuclei are enlarged and rounded with chromatin clearing and loss of polarity**

Proliferative Endometrium: **Cigar-like dense nuclei with basal, often pseudostratified, arrangement**

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.

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

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

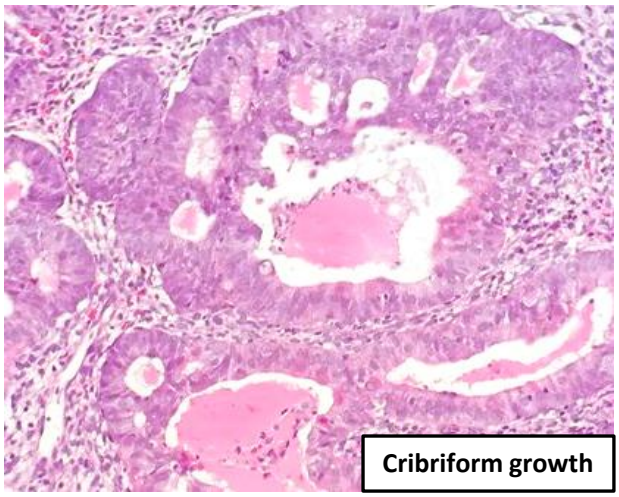
Sometimes the cutoff of carcinoma vs EAH cutoff can be challenging. OK, to diagnose as "EAH bordering on well-differentiated endometrioid adenocarcinoma"

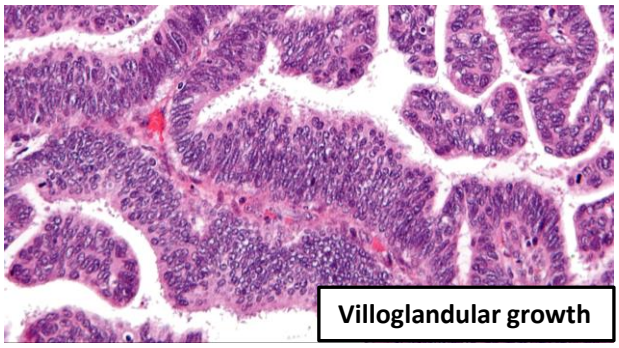
Frequently see **squamous differentiation** with morules, keratin pearls, and intercellular bridges.

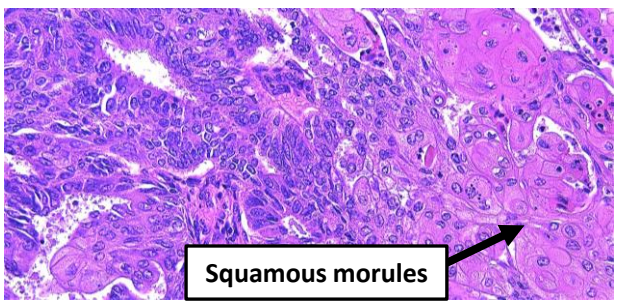
Occasionally see **secretory changes** with glycogen vacuole or bland spindled epithelial cell component.

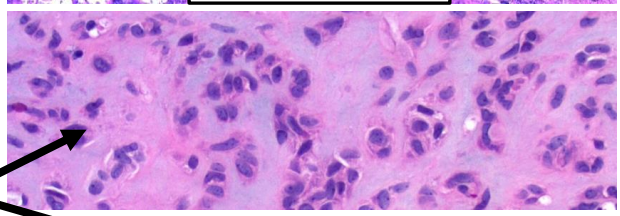
Corded and Hyalinized: has cords, clusters, and/or trabeculae of epithelioid to spindled cells embedded within hyalinized to myxoid matrix. Often associated with grade 1-2 glandular component. No prognostic significance, but sometimes confused with carcinosarcoma, leading to overtreatment. IHC: Nuclear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

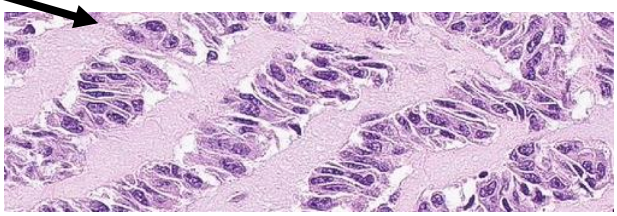
IHC: (+)CK7, PAX8; (-)CK20; Cup-like vimentin staining. Low-grade often ER/PR +;











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.
Grades 1-2= Low-grade; Grade 3= High-grade

FIGO grade	% Solid Growth
1	≤5%
2	6-50%
3	>50%

Endometrioid Carcinoma *(continued)*

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%): Mutations in mismatch repair proteins result in a high mutation rate → lots of neoantigens in tumor cells→ recognized by immune system→ lots of tumor infiltrating lymphocytes. Intermediate prognosis despite TILs. Often Grade 3, substantial LVI, MELF-pattern of invasion. Often located in lower uterine segment. Associated with Lynch Syndrome.

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.

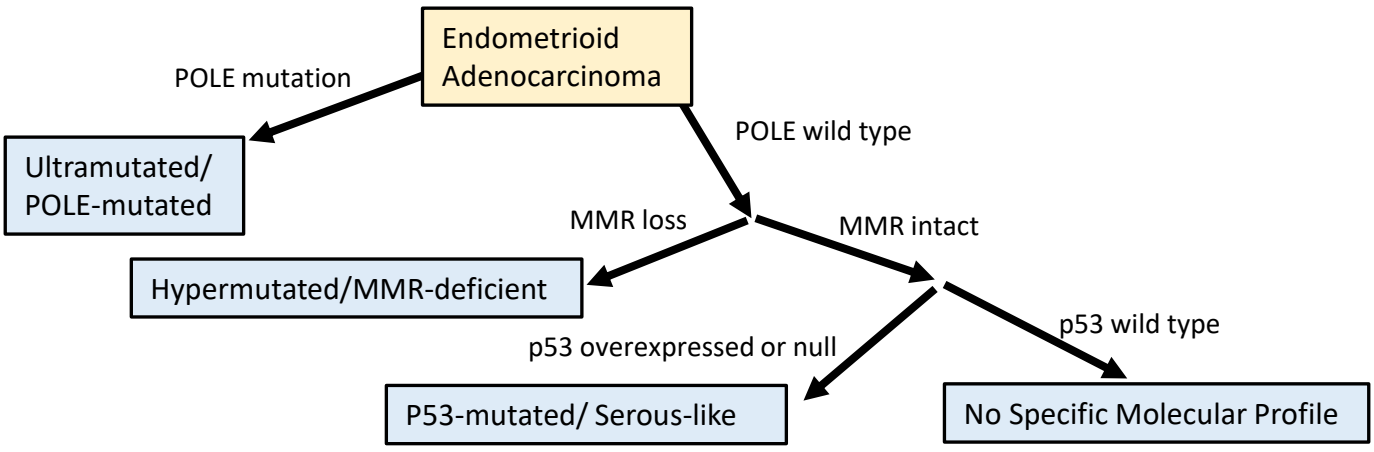
No Specific Molecular Profile (NSMP) (~45%): Most common type. Often Grade 1-2, ER/PR+ with squamous differentiation. Associated with unopposed estrogen exposure (as is seen in obesity). Overall low mutation rate. Very frequent PTEN mutations. Intermediate prognosis (depends largely on stage).

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 NSMP and MSI-H categories
High-grade (FIGO 3): map to all 4 categories, but least to the copy number low group

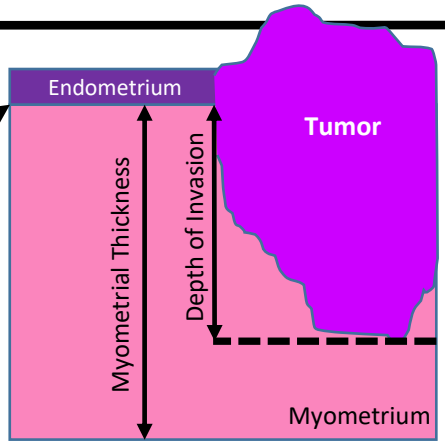
Familial syndromes:
Lynch Syndrome: germline mutations in mismatch repair (MMR) proteins → MSI-subtype
~50% lifetime risk (similar to risk of colon cancer).
PTEN-hamartoma tumor syndrome/Cowden syndrome: Germline PTEN mutation→ no specific morphology

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). β-catenin nuclear expression supports Endometrial carcinoma, but this has limited sensitivity. Regardless, 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



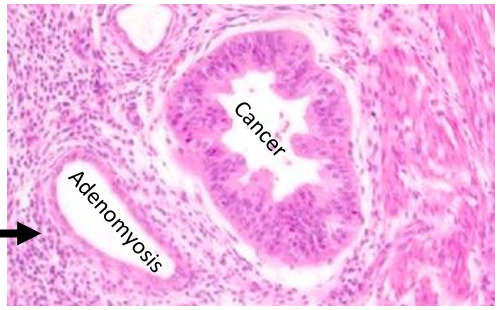
Can be very challenging to identify/measure!
<u>Measure from endomyometrial junction to the deepest point of invasion.</u>

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

<u>Critical clinical cutoff point = 50%</u> (inner vs outer ½)

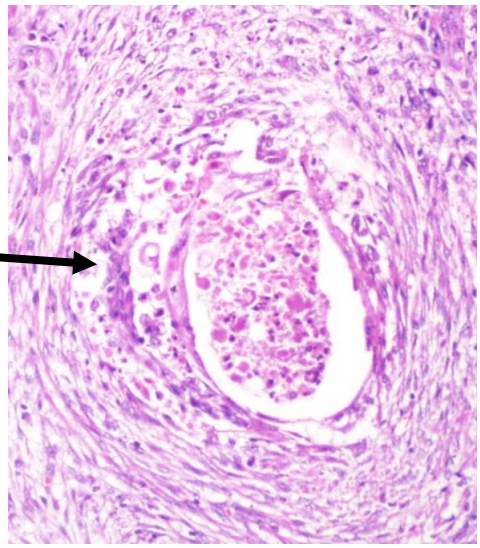
Myometrial invasion often (but not always!) includes irregular angular glands **eliciting a <u>desmoplastic response</u> or loose granulation tissue** with inflamed edematous fibrous stroma

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



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

<u>Challenging patterns of myometrial invasion:</u>

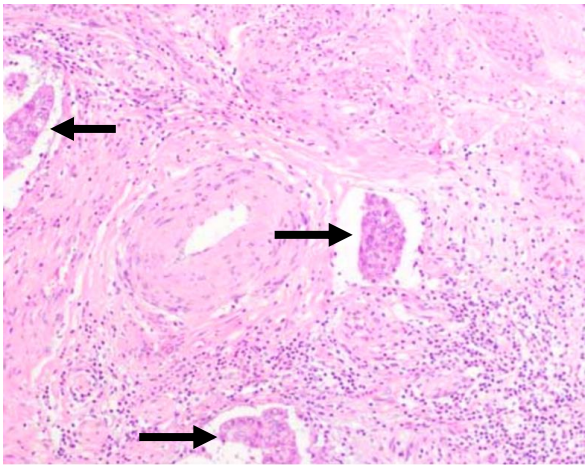


"Pushing" Invasion—broad, expansile front with a mild or absent stromal reaction. Helpful to submit adjacent normal endometrium to determine level of endomyometrial junction (if present).

"Microcystic, Elongated, and Fragmented" (MELF)— invasive glands often lined by a single, flattened layer of epithelium with eosinophilic, squamoid cytoplasm. Simulate vascular spaces. Associated edematous, inflamed stroma. Very sneaky!! Associated with LVI. Frequently MMR deficient. More aggressive.

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



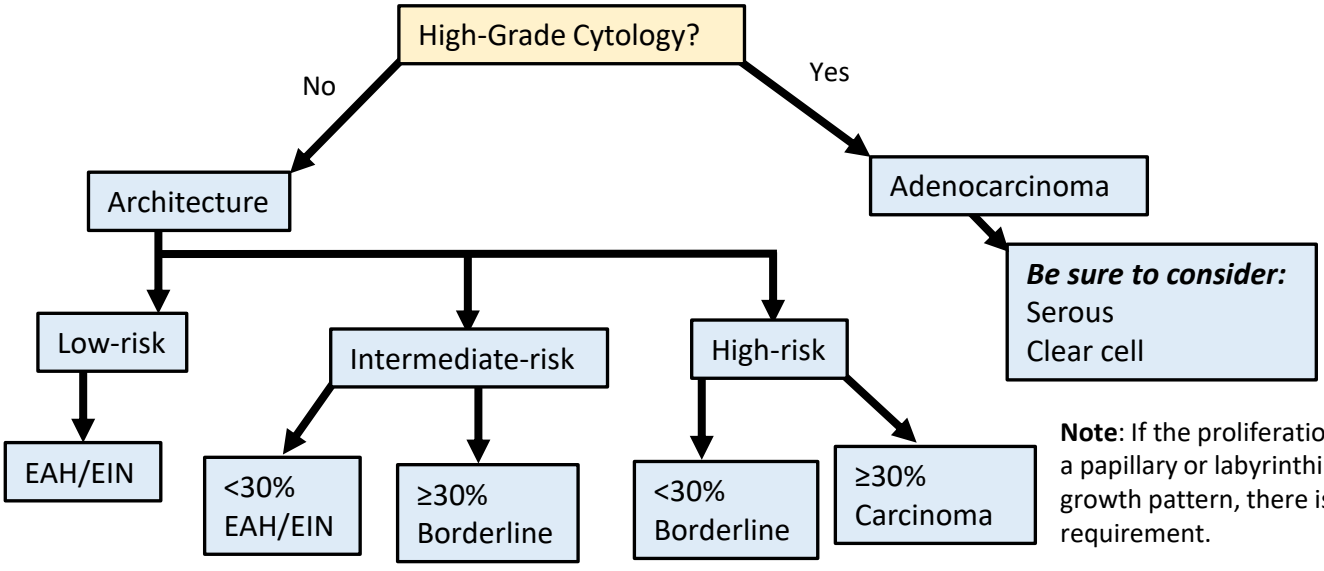
Frequently seen with MELF pattern.

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."

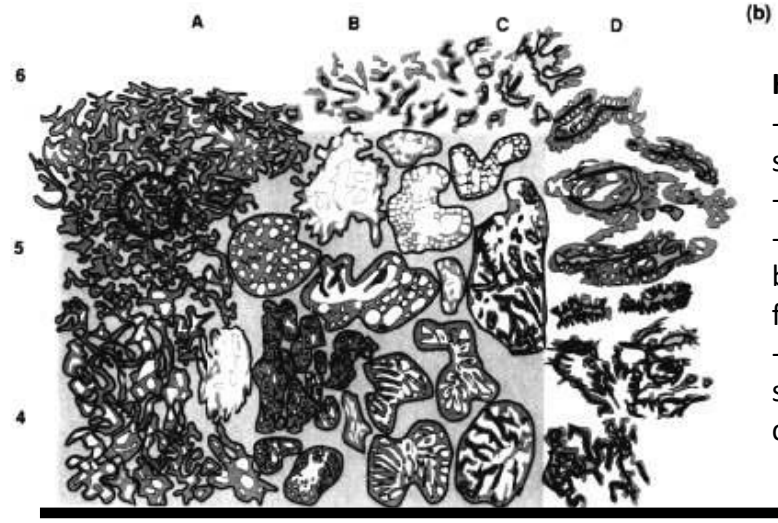
An Approach to Difficult Endometrial Lesions

Modified from: Mills and Longacre. Surg Pathol Clin. 2011 March



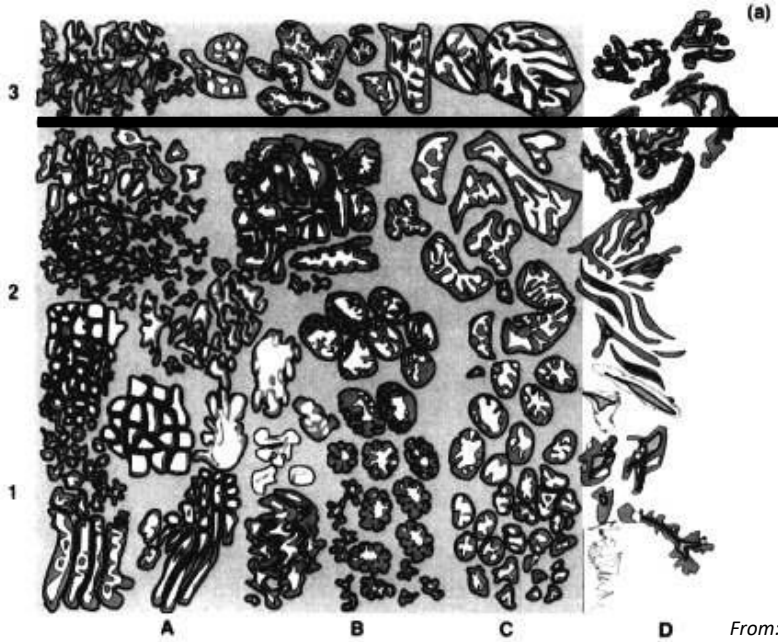
Note: If the proliferation has a papillary or labyrinthine growth pattern, there is no % requirement.

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



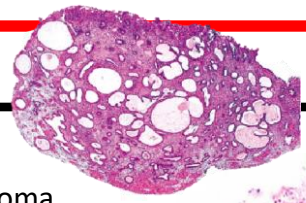
Intermediate-risk Patterns: Borderline

Low-risk Patterns: Hyperplasia

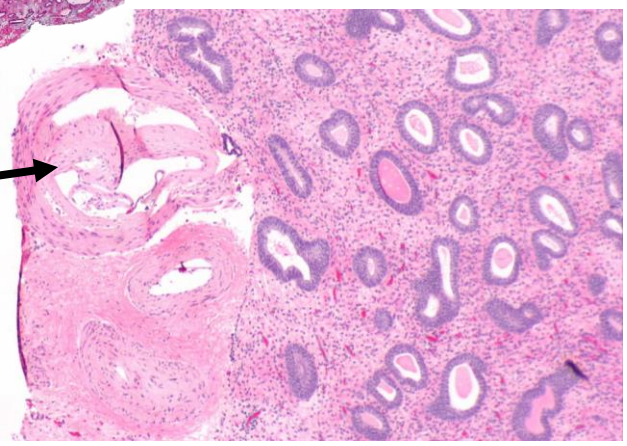
- Simple budding into small glands
- Macroglands with simple, non-branching nonvillous papillae or minimal bridging
- Simple non-branching villous and nonvillous papillae

From: Longacre et al. Am J Surg Pathol. 1995 Apr;19(4):371-406.

Polyps



Benign Endometrial Polyp



Localized, disorganized altered glands and stroma.

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

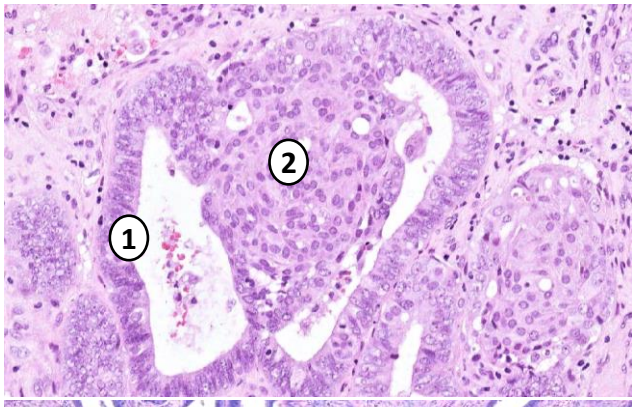
Stroma: often collagen-rich containing **characteristic thick blood vessels**

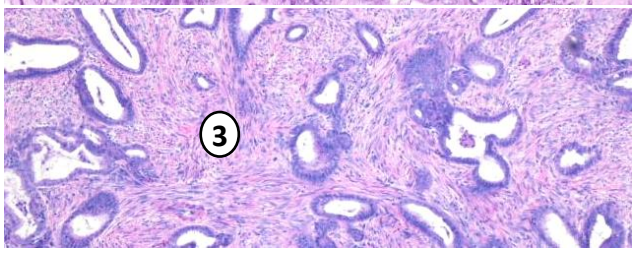
Often solitary. Can be anywhere in uterus.

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**

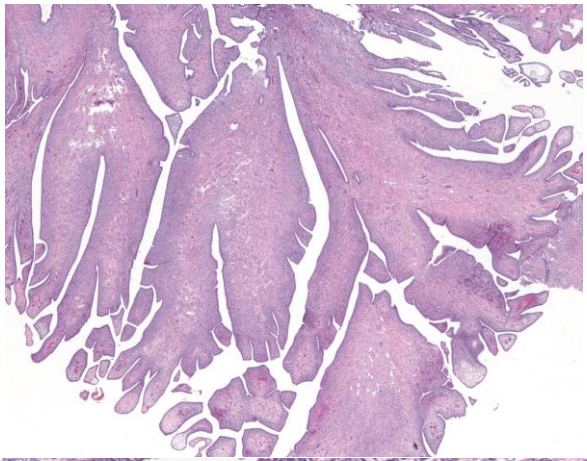
Often centered in **lower uterine segment**. ~2cm.

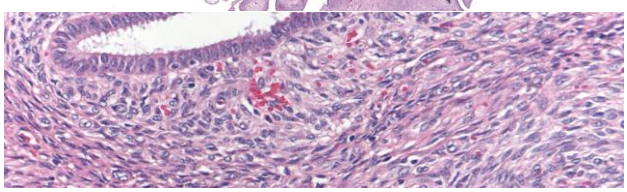
Associated with MLH-1 promoter methylation (~1/2)

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.

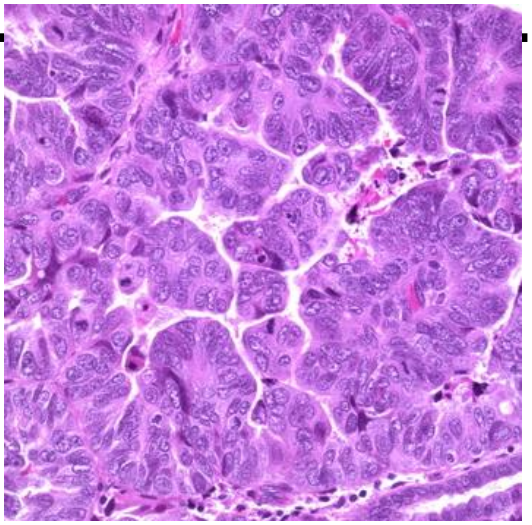
Can show heterologous elements and sarcomatous overgrowth. When ≥25% of tumor is a high-grade sarcoma, "Adenosarcoma with sarcomatous overgrowth"

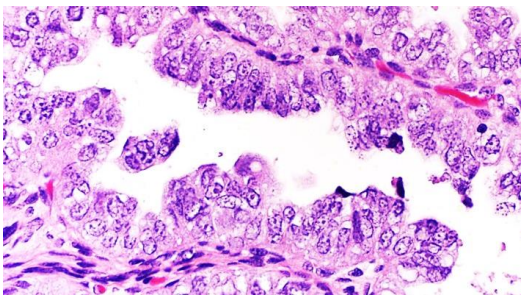
IHC: Stroma (+) CD10, ER, PR.

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

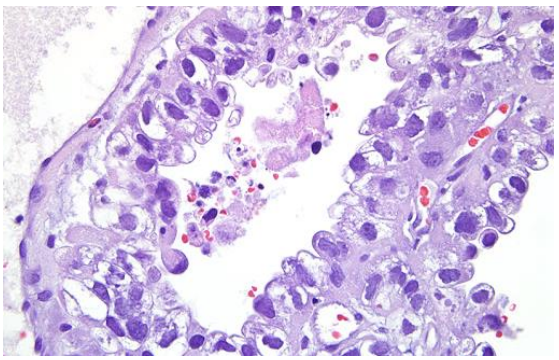
Typically **post-menopausal** women presenting with bleeding. Often grossly inconspicuous on the **surface of a polyp**. Background endometrium often atrophic.

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. Sometimes HER2 amplified
IHC: **p53 mutant** (either diffuse or null), p16 block positive.
WT-1 Negative (compared to Tubo-ovarian, which is usually +)

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. Not many mitoses.

Often postmenopausal women with vaginal bleeding.

Grading not applicable. Relatively poor prognosis.

This should be a RARE diagnosis→ most clear endometrial tumors will either be endometrioid or serous. Should see varied architecture. IHC: **(+) NapsinA**, HNF1β, AMACR; (-/+) p53; usually (-)ER.

Mucinous Carcinoma

Now just a pattern of Endometrioid Carcinoma in which > 50% of the neoplasm is mucinous. Very rare.

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.

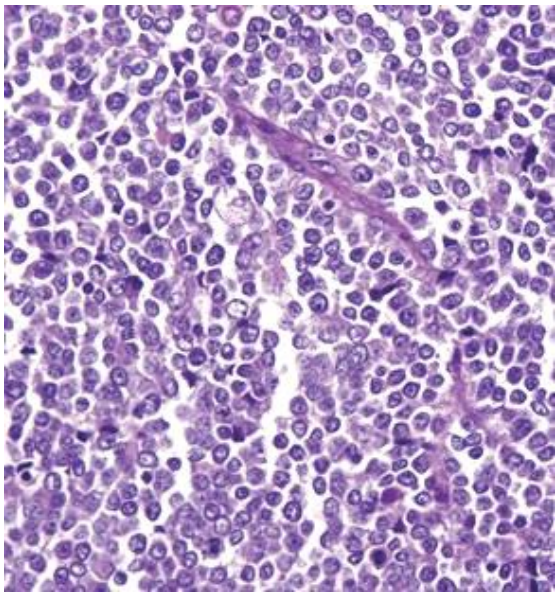
Relatively good prognosis.

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, where at least one is Serous carcinoma or Clear cell carcinoma. Excludes Dedifferentiated carcinoma and carcinosarcoma.

Undifferentiated Carcinoma



Malignant epithelial neoplasm with **no overt differentiation**.

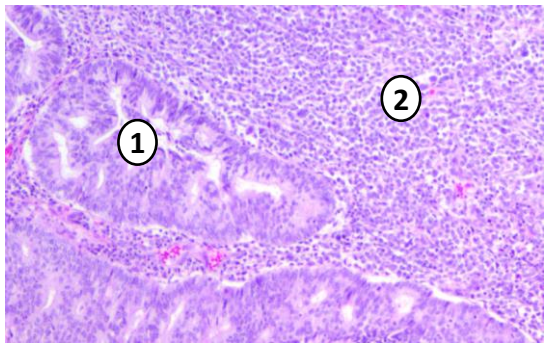
Sheets of medium-sized relatively **uniform, monotonous, discohesive cells** with often **condensed chromatin**.
No gland formation (resembles lymphoma). Numerous mitoses. Sometimes rhabdoid. Often numerous tumor-infiltrating lymphocytes (TIL)
Often form large, polypoid masses within uterine cavity.

Molecular: Often MMR-deficient (some Lynch-associated); Frequent mutations of SWF/SNF pathway (SMARCA4 (BIRG1), SMARCB1 (INI-1), ARID1A/B de-activation)

IHC: Loss of MLH1/PMS2 and/or BIRG1.
Loss/focal Cytokeratins, EMA, ER, PAX8. (+/-)CD34

Very aggressive.

Dedifferentiated Endometrial Carcinoma

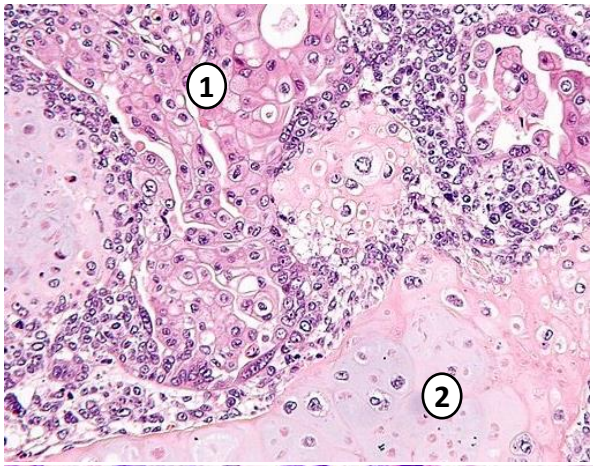


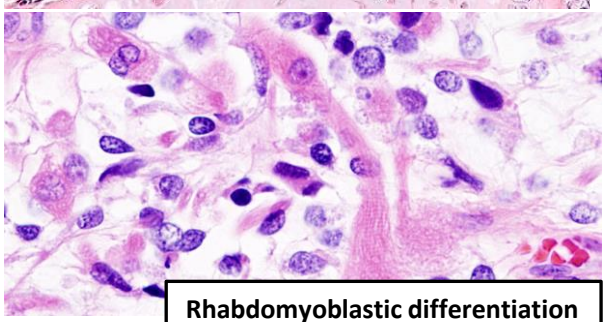
Two distinct, but clonally related, components, often with an abrupt transition:
1) **Low-grade (FIGO 1-2) endometrioid carcinoma**
2) **High-grade undifferentiated carcinoma** (see above)

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

Very aggressive.

Carcinosarcoma





Rhabdomyoblastic differentiation

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

Sarcoma represents a transdifferentiation (epithelial-mesenchymal transition) of epithelial component during tumor evolution.

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 both elements.

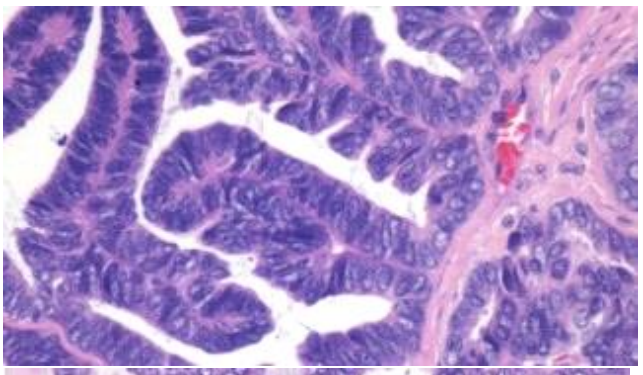
Carcinoma is **often serous or endometrioid carcinoma**

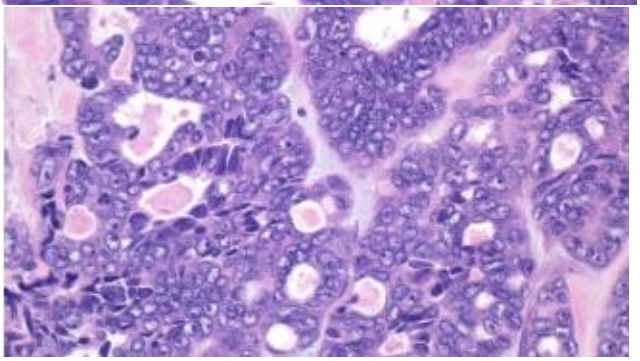
Sarcoma is often high-grade non-specific sarcoma, but "heterologous" elements can be seen including: rhabdomyosarcoma, chondrosarcoma, and osteosarcoma (which look/stain like they do elsewhere)

Molecular: Frequent TP53 mutations.

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

Mesonephric-like Adenocarcinoma





Adenocarcinoma with mesonephric-like differentiation.

Tubular, glandular, slit-like, papillary, and solid growth.
Can have eosinophilic **colloid-like material**.
Dense to vesicular nuclei
Can arise in uterine wall (as opposed to endometrial cavity)

IHC: (+) TTF1, GATA3, CD10 (luminal), PAX8, calretinin
(-) ER, PR, WT1; Wild-type p53

Molecular: frequent KRAS mutations

Seem to be **aggressive**.

If there are mesonephric remnants, then you can drop the "-like" and just call it mesonephric carcinoma.

Consider this Dx if you ever have something that looks endometrial but is ER negative!

Gastric (Gastrointestinal)-type endometrial adenocarcinoma

A mucinous carcinoma with gastric/gastrointestinal features, resembling gastric epithelium.
Rare. Aggressive.

Low nuclear grade. May contain goblet cells. PMID: 31567280

Must exclude:
1) Endometrioid carcinoma with mucinous differentiation→ so sample well.
2) Endocervical adenocarcinoma→ so consider P16 IHC and/or HPV ISH
3) A gastrointestinal metastasis.

Squamous cell carcinoma

An endometrial carcinoma with *exclusively* squamous differentiation.

Usually obviously malignant, but can be deceptively bland with a broad front abundant glycogenation.

Associated with chronic inflammatory conditions, longstanding pyometra, and ichtyosis uteri (keratinizing squamous metaplasia of the endometrium).

Must exclude:
1) Endometrioid carcinoma with extensive squamous morules/differentiation→ so take lots of sections looking for a glandular component.
2) Cervical squamous cell carcinoma→ Look for CIN and do IHC for P16 and/or HPV ISH.

Helpful Tables

Carcinoma Immunohistochemistry

	Endometrioid (Low-grade)	Serous	Clear Cell
ER/PR	+	-/+	-/+
p53	Wild-type	Abnormal	Wild-type, usually
P16	-/patchy	Block-positive	-/patchy
PTEN	Loss	Intact	Intact
NapsinA	-	-/+	+
HNF1β	-	-/+	+

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

Based on a session by Dr. Anthony Karnezis, UC Davis

Diagnosis	Epithelium	Stroma	Management
Benign Endometrial Polyp	Benign	Benign, Fibrous	Polypectomy
Polypoid adenomyoma	Benign	Benign, Muscle	Polypectomy
EAH/EIN in a polyp	Atypical/Crowded	Benign, Fibrous	Hysterectomy or Hormones
Atypical Polypoid Adenomyoma (APA)	Atypical/Crowded	Benign, Muscle	Hysterectomy or Hormones
Adenosarcoma	Benign	Malignant	Hysterectomy
Carcinoma	Malignant	Benign	Hysterectomy
Carcinosarcoma	Malignant	Malignant	Hysterectomy

Architectural DDX:

Based on a talk by Dr. Joe Rabban, UCSF, at USCAP 2021

Papillary

Benign:
Surface Papillary Syncytial metaplasia
Papillary Proliferation of the Endometrium

Malignant:
Villoglandular endometrioid carcinoma
Serous carcinoma
Clear cell carcinoma
Endocervical adenocarcinoma

Clear

Benign:
Arias Stella reaction,
Gestational endometrium

Malignant:
Endometrioid carcinoma with squamous or secretory change
Clear cell carcinoma.

Mucinous

Benign:
Contamination by endocervix
Mucinous metaplasia

Malignant:
Endometrioid carcinoma with mucinous metaplasia
Endocervical adenocarcinoma
Metastatic GI carcinoma
Gastric (Gastrointestinal)-type endometrial adenocarcinoma

Sometimes on biopsy can only say “Complex glandular mucinous proliferation” and then in a comment explain the DDX of mucinous metaplasia, contamination, or under sampled carcinoma (need further sampling).

Squamous

Benign:
Squamous morular metaplasia
Granulomatous endometritis
Placental site nodule

Low-Risk or Malignant:
Endometrioid carcinoma with squamous metaplasia
Atypical Polypoid Adenomyoma (APA)
Cervical HSIL/Squamous cell carcinoma
Trophoblastic tumors
Endometrial squamous cell carcinoma
Epithelioid mesenchymal tumor

Solid

Benign:
Endometrial stromal nodule
Morular metaplasia

Malignant:
High-grade endometrioid carcinoma (grade 3)
Undifferentiated carcinoma
Corded and hyalinized endometrioid carcinoma
Endometrial stromal sarcoma
Leiomyosarcoma
Carcinosarcoma