

# EIN – the final “word” in pre-malignant endometrioid neoplasia

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# Outline

- Background: Endometrioid (Type I) endometrial adenocarcinoma
- WHO 1994
- Definition of Endometrial Intraepithelial Neoplasia (EIN)
- How does one diagnose EIN?
- Why do we need EIN?
- Management of EIN
- WHO 2014
- Examples
- Diagnostic dilemmas

# Endometrioid type endometrial adenocarcinoma

- 70-80% of newly diagnosed endometrial cancer
- Associated with unopposed estrogen exposure
- Preceded by premalignant disease
- Malignancy develops through complex interactions between multiple genetic events and hormonal selection factors

# “Endometrial hyperplasia”

- Term implemented, with various qualifiers (originally stratified by degree of architectural complexity and cytologic atypia), to encompass both:
  - non-premalignant morphologic responses to a hyper-estrogenic milieu
- AND
- premalignant lesions



# The WHO classification (1994) 4-tiered system

<b>Hyperplasias (typical)</b>
Simple hyperplasia without atypia
Complex hyperplasia without atypia
<b>Atypical hyperplasias</b>
Simple atypical hyperplasia
Complex atypical hyperplasia

# Problems with WHO 1994

- Difficult to teach – entire system based on qualifiers (atypia, complexity) which have never been standardized, thus:
  - Sub-optimal interobserver reproducibility in multiple studies
  - Particularly poor reproducibility for the diagnosis of atypical hyperplasia

# Problems with WHO 1994

- Missed some clinically important lesions:
  - additional criteria (such as lesion size, threshold of gland crowding) relevant to increased cancer risk were discovered
  - The presence/absence of “atypia” is not always a reliable indicator of the presence/absence of clinical significance

# Legitimate endometrial “hyperplasias”

- Diffuse, **polyclonal** proliferations of endometrial epithelium in response to abnormal estrogenic stimulus over time
- Morphologic features depend on the extent and duration of estrogen exposure
- Do NOT represent premalignant lesions



# Legitimate endometrial “hyperplasias”

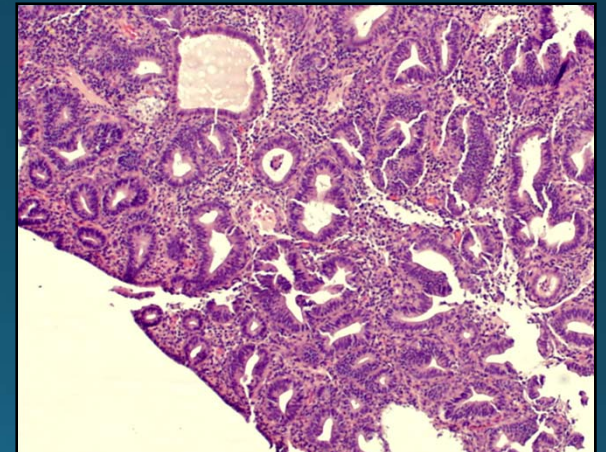
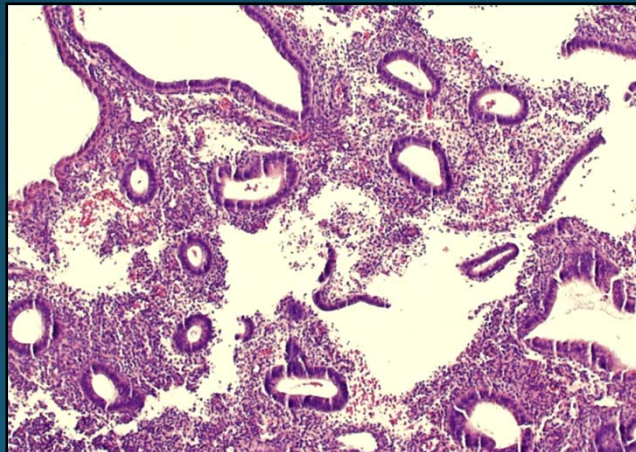
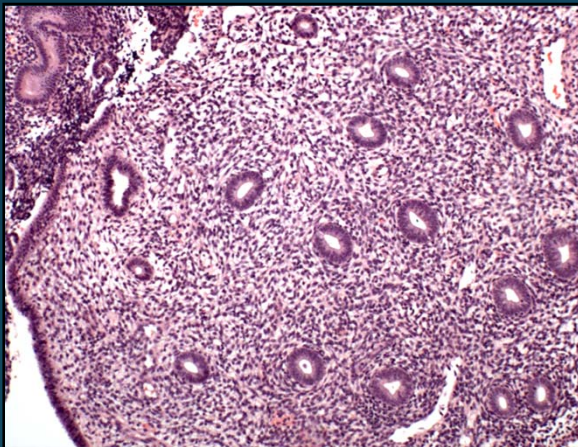
Proliferative  
endometrium



Disordered  
proliferative  
endometrium



Benign  
endometrial  
hyperplasia



Estrogen over time





# Premalignant endometrial lesion

- Endometrial cancer does NOT represent the end result of a gradual, continuous spectrum of morphologic changes
- A **localized, clonal** population of genetically-altered glands emerges as a discrete premalignant lesion (*i.e., not a hyperplasia*)

# Endometrial Intraepithelial Neoplasia (EIN)

- Monoclonal proliferation of architecturally and cytologically *altered* (not necessarily classically *atypical*) premalignant endometrial glands
- Distinct from diffuse hormonal effects (benign endometrial hyperplasia)

# Endometrial Intraepithelial Neoplasia (EIN)

- Associated with a 45-fold increased risk of endometrioid endometrial adenocarcinoma
- ~ 1/3 to 1/2 of women with EIN on biopsy will be diagnosed with cancer within a year
- Biopsies which lack EIN have a negative cancer predictive value of 99%

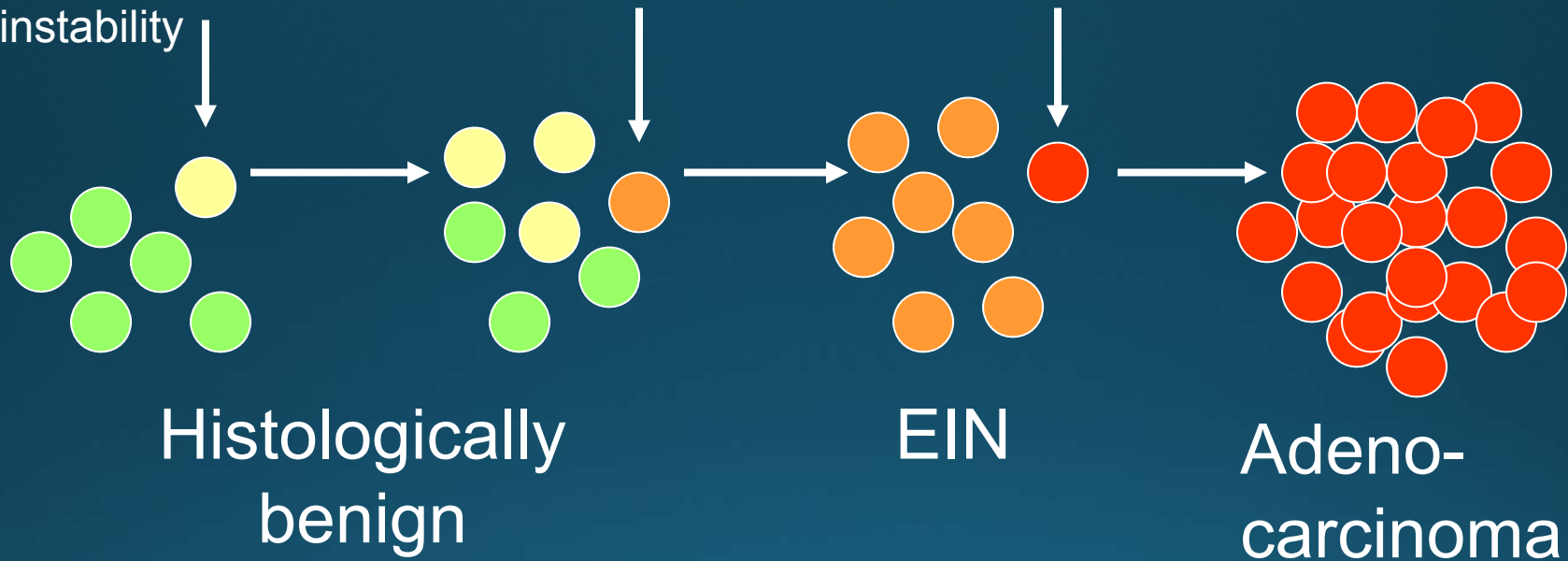


# Clonal origin of EIN

PTEN, PAX2  
inactivation,  
microsatellite  
instability

Mutations in K-ras,  $\beta$ -  
catenin, emergence  
of mutant clone

Malignant  
transformation



Adapted from Mutter GL, [www.endometrium.org](http://www.endometrium.org)

# How is EIN diagnosed?

Criterion	Comments
Architecture	Area of glands > area of stroma (often a discrete focus)
Cytology	Differs between area of gland crowding and background endometrium
Size	Focus of crowded, cytologically altered glands at least 1 mm
Benign endometrial mimics excluded	Benign endometrial hyperplasia, secretory endometrium, polyps, fragmented specimens (artifactual crowding)
Cancer excluded	Mazelike glands, solid areas, significant cribriforming = carcinoma





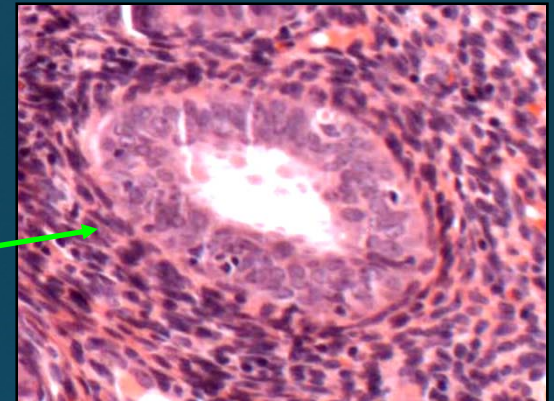
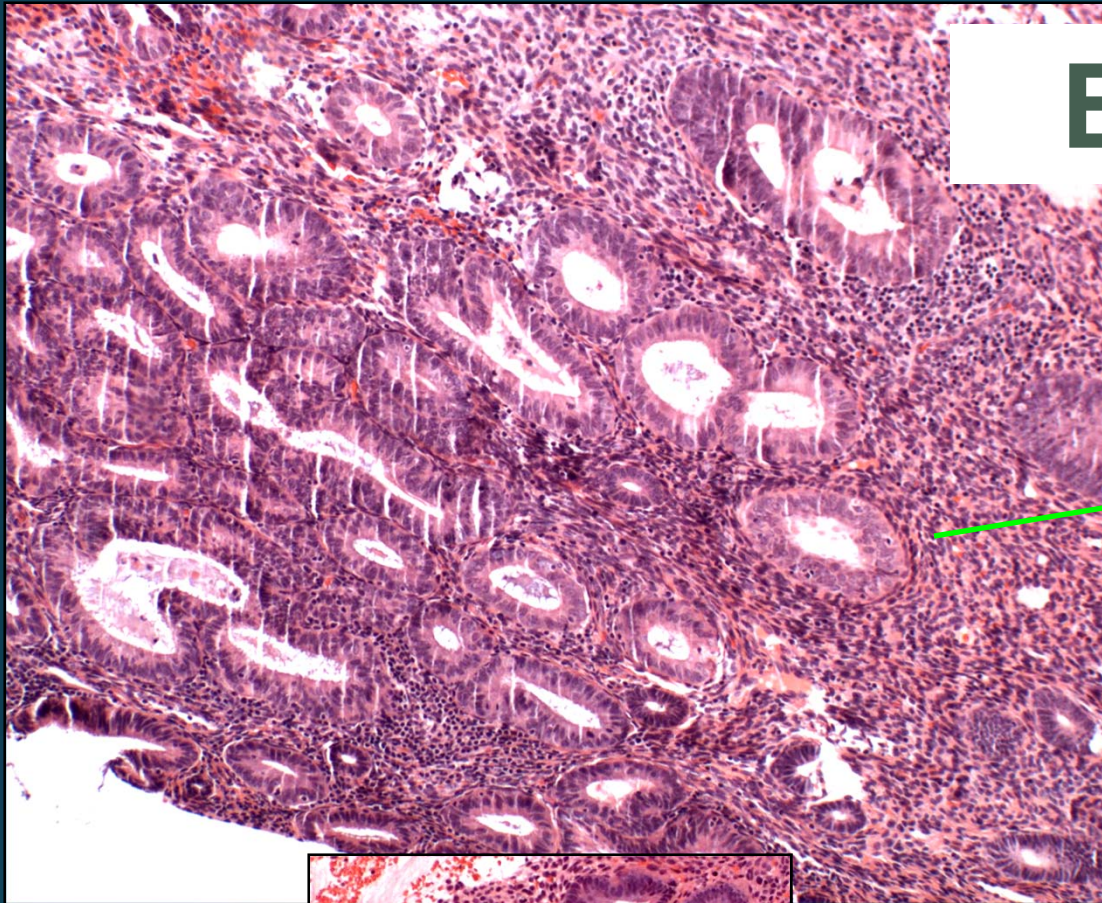
**EIN**

This histological image shows a section of endometrial tissue. The upper portion of the image is labeled 'EIN' (Endometrial Intraepithelial Neoplasia) and shows glandular structures with a thickened, dark-staining epithelial lining. The lower portion of the image shows the 'Background endometrium', which consists of more typical, less densely cellular glandular structures. An inset in the bottom left corner provides a higher magnification view of the background endometrium, showing several glands with clear, open lumens and a regular epithelial lining.

**Background endometrium**



**EIN**



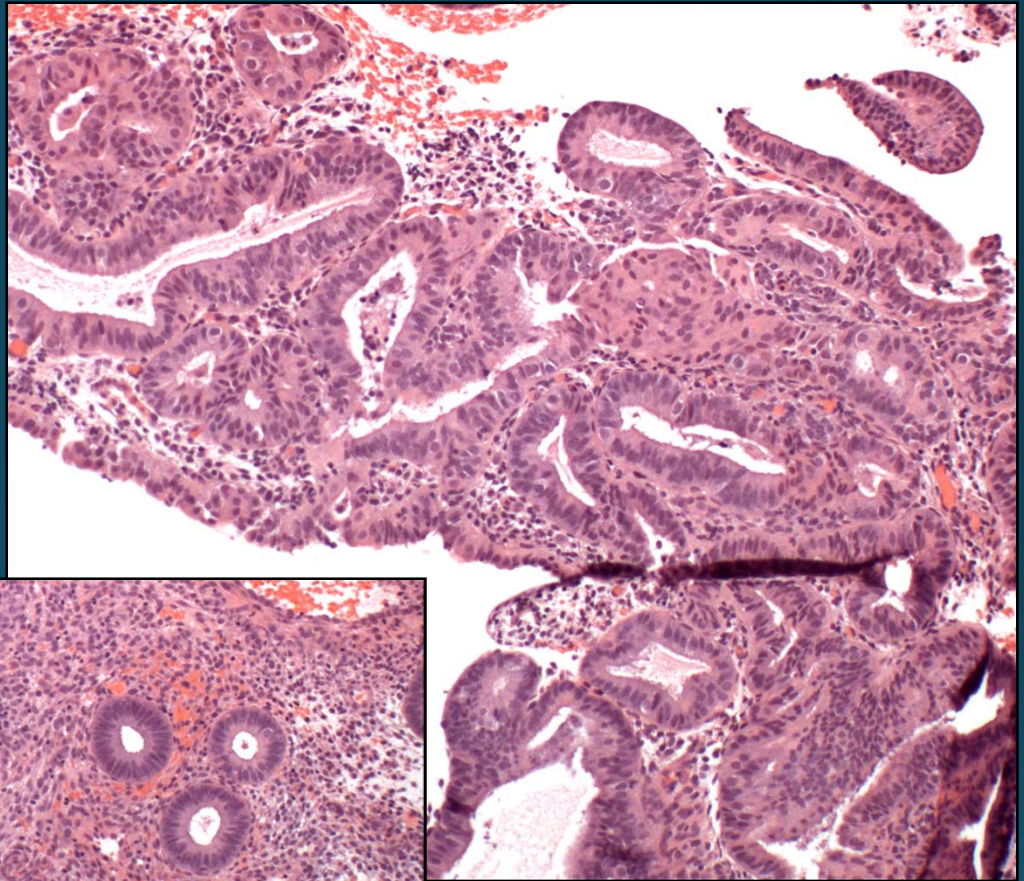
**Background endometrium**



# Volume percentage stroma

**EIN ~ 40%**

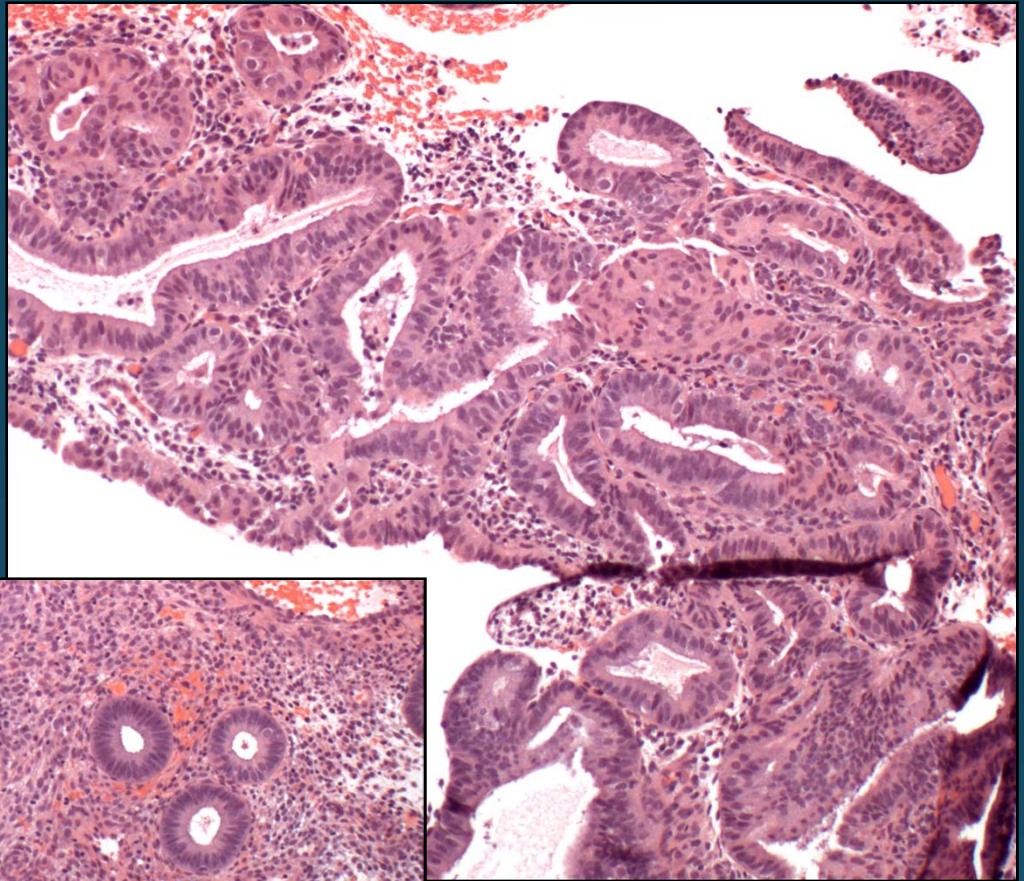
**Non-EIN ~ 75%**



# Volume percentage stroma

**EIN ~ 40%**

**Non-EIN ~ 75%**



**Bottom line: More glands than stroma**

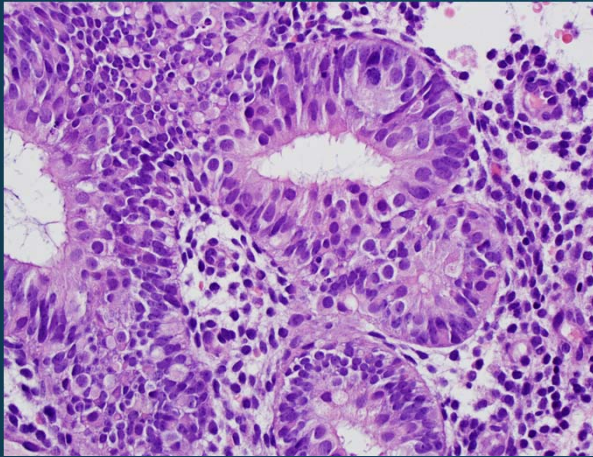
# Altered vs. “atypical” cytology

- No single cytologic appearance across all EIN lesions
- Always a comparison to background cytology
- Classic “atypia” – round non-polarized nuclei, prominent nucleoli – often present, but not required
- The cytologic change can include nuclear and/or cytoplasmic components

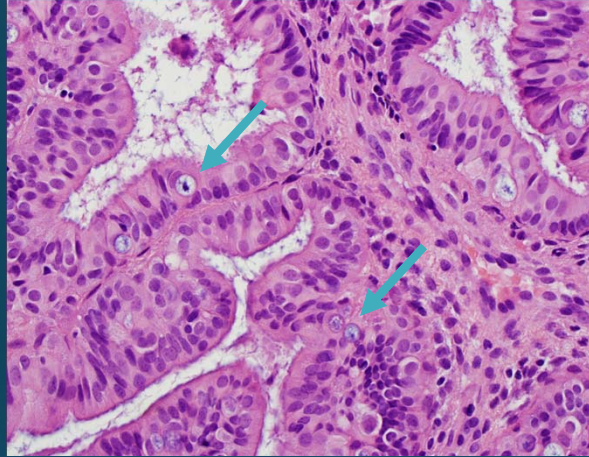


# Various patterns of metaplasia in EIN

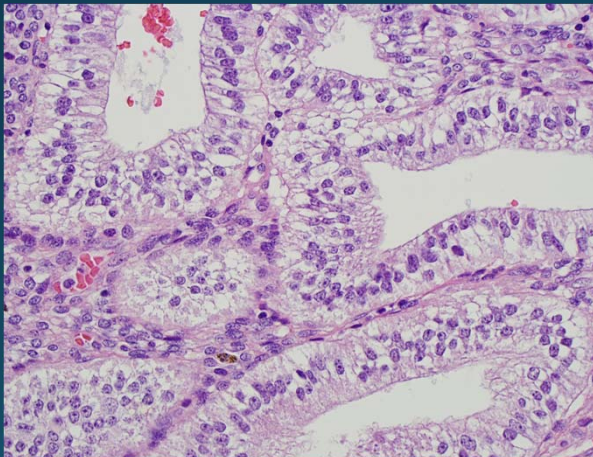
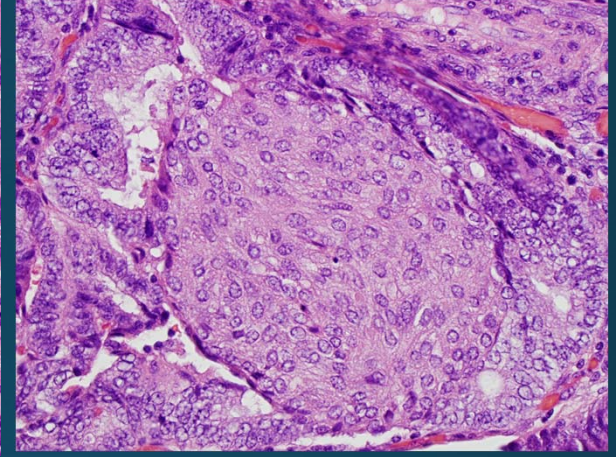
**Tubal**



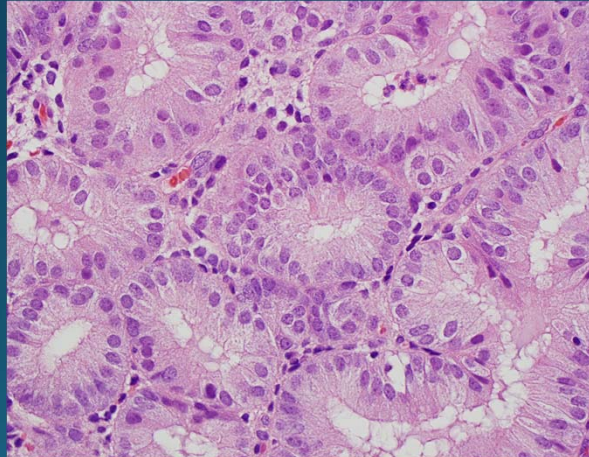
**Mucinous**



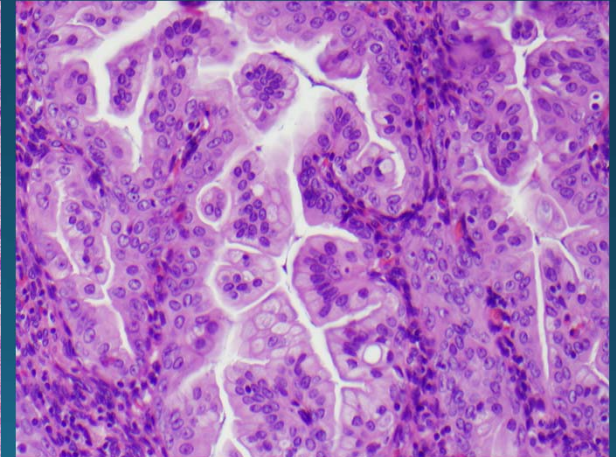
**Squamous**



**Secretory**



**Eosinophilic**



**Micropapillary**



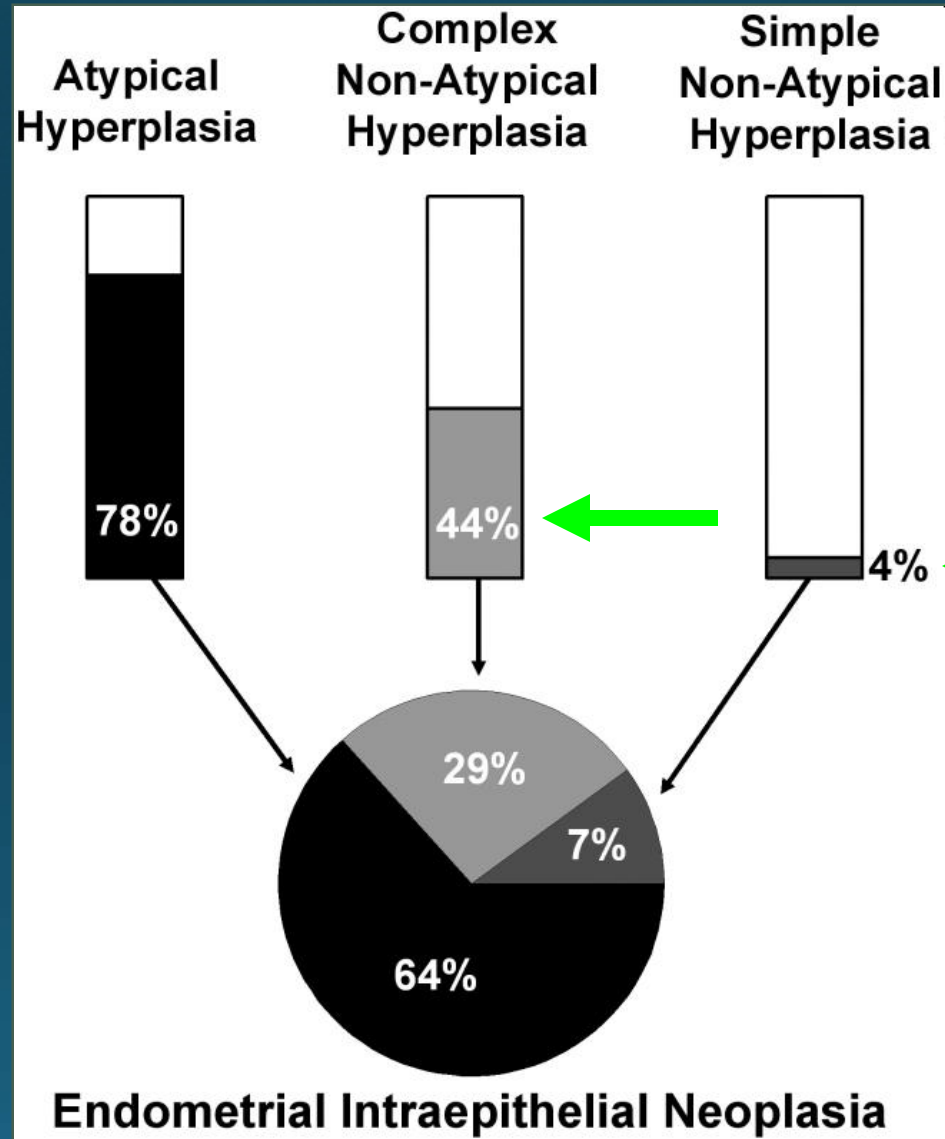
# 1mm size criterion is not arbitrary

- Confers clinical outcome predictive value
- Prevents over diagnosis of EIN
- Must be achieved in a single focus (not an aggregate measurement)

# Why do we need EIN?

- Better interobserver reproducibility than 4-tiered WHO
- Better positive cancer predictive value than 4-tiered WHO:
  - 45-fold increased cancer risk conferred by EIN
  - 14-fold increased cancer risk conferred by presence of “atypia” in WHO 1994 system

# Why do we need EIN?



# Management of EIN

- Hysterectomy
- Hormonal (progestin) therapy (young women, poor surgical candidates)
  - Up to 90% of endometrial pre-cancers may be ablated by progestin
  - Can't predict which women will respond
  - Follow-up surveillance is essential

# The WHO classification (2014) 2-tiered system

**Hyperplasia without atypia**

**Atypical hyperplasia/*Endometrioid*  
Intraepithelial Neoplasia (AH/EIN)**

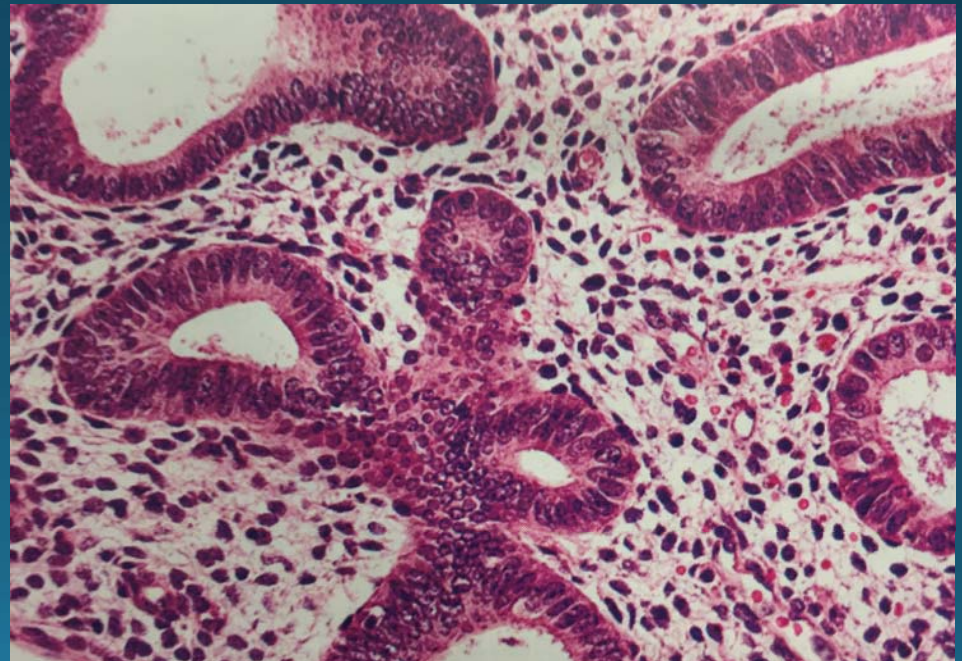
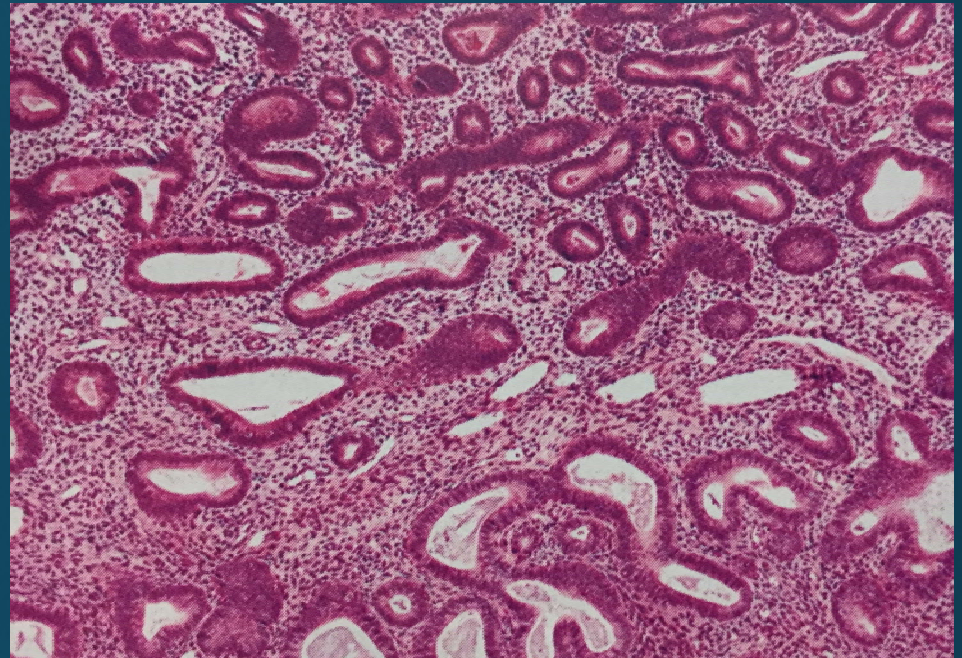
# WHO 2014

WHO 2014 Nomenclature	Topography	Functional Category	Treatment
Endometrial hyperplasia without Atypia	Diffuse	Estrogen Effect (benign)	Hormonal therapy
EIN/ Atypical Endometrial Hyperplasia	Focal progressing to diffuse	Precancer	Hormonal or surgical
Carcinoma	Focal progressing to diffuse	Cancer	Surgical



## WHO 2014: Hyperplasia without Atypia (Benign endometrial hyperplasia)

- Spectrum of changes
- Variable gland crowding, cystically dilated glands, gland branching
- Focal areas of breakdown common
- Lined by proliferating columnar epithelium, lacking cytologic atypia

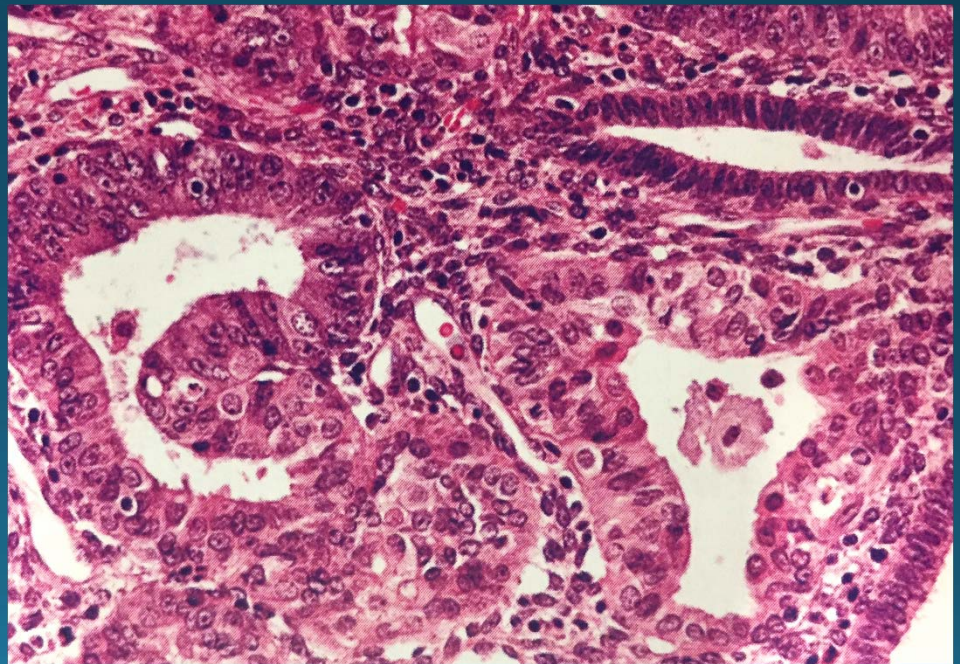
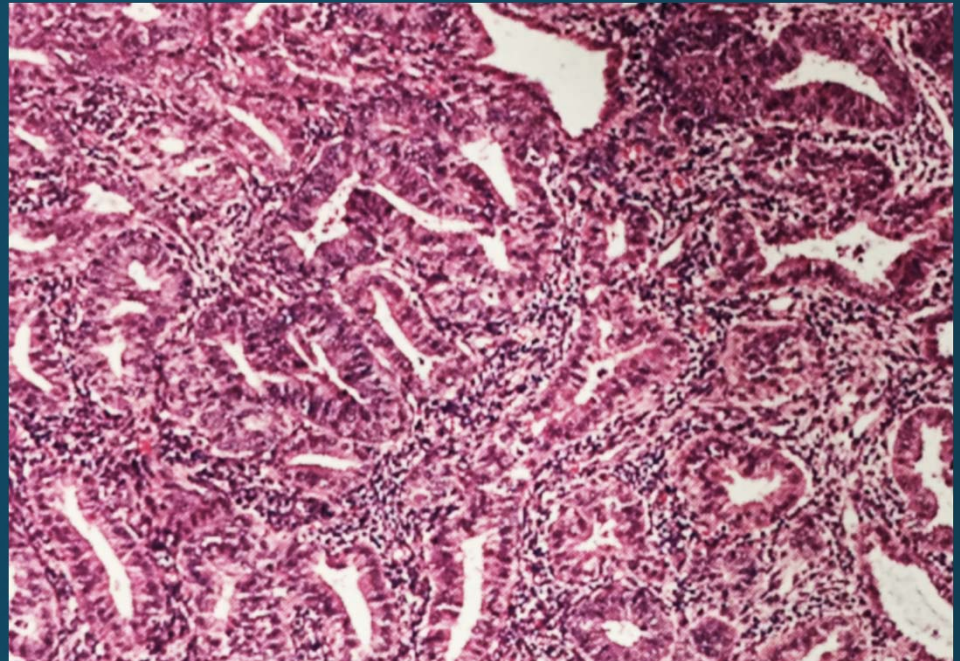


WHO 2014



## WHO 2014: Atypical Hyperplasia/Endometrioid Intraepithelial Neoplasia (EIN)

- Clonal process emerging from localized lesion in background of non-atypical hyperplasia
- Aggregates of tubular or branching glands, exceeding volume of stroma
- Distinguished from non-atypical hyperplasia by nuclear atypia (variable in degree):
  - May include “classic” features of atypia
  - May include metaplastic changes
  - Diagnosing “atypia” is based on comparison to cytology of background glands (WHO 2014 Figure 5.02)



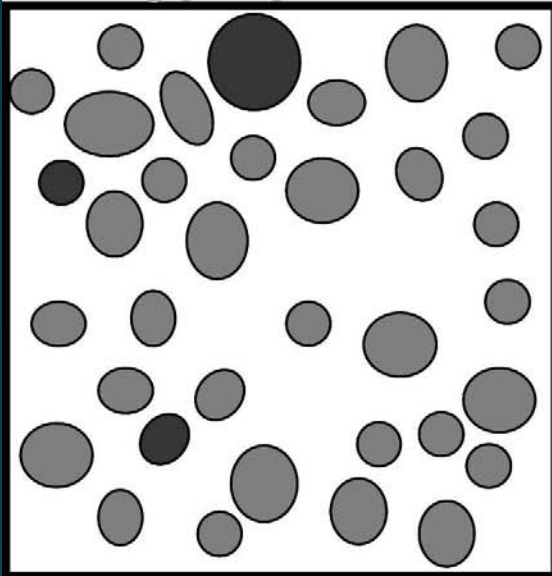


# WHO 2014

- Essentially adopted EIN (begrudgingly, perhaps?)
- Old architecture definitions (simple and complex) are stripped
- EIN definitions are the only ones that remain
- “atypical hyperplasia” = EIN makes the transition easier
  - Definition of atypia changed relative to internal standard
  - Carryforward of “hyperplasia” semantic only

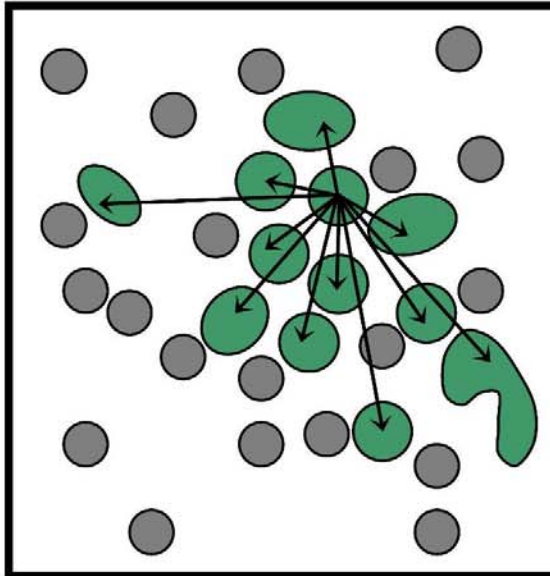
# WHO 2014 = EIN system

## Non-atypical Hyperplasia



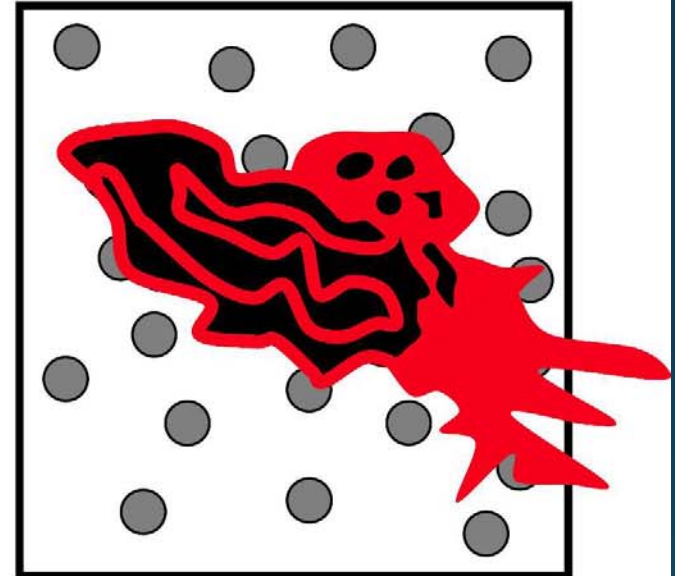
Diffuse field effect  
Regularly Irregular  
Random Metaplasias

## EIN



Expansile Clonal  
Individual glands  
Glands > Stroma  
Altered cytology

## Carcinoma



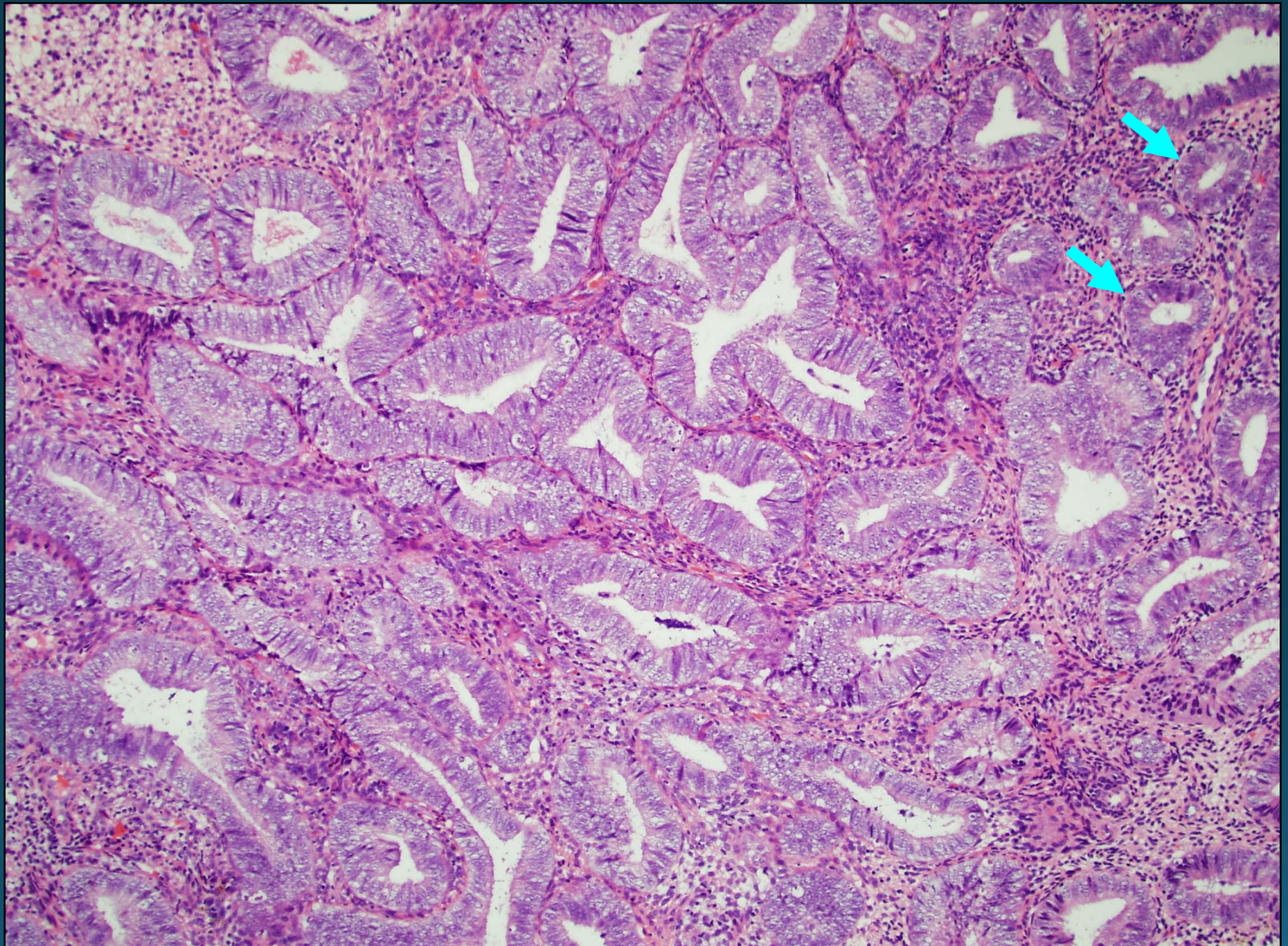
Cribriform  
Solid  
Maze-like  
Myoinvasive

# And another thing...

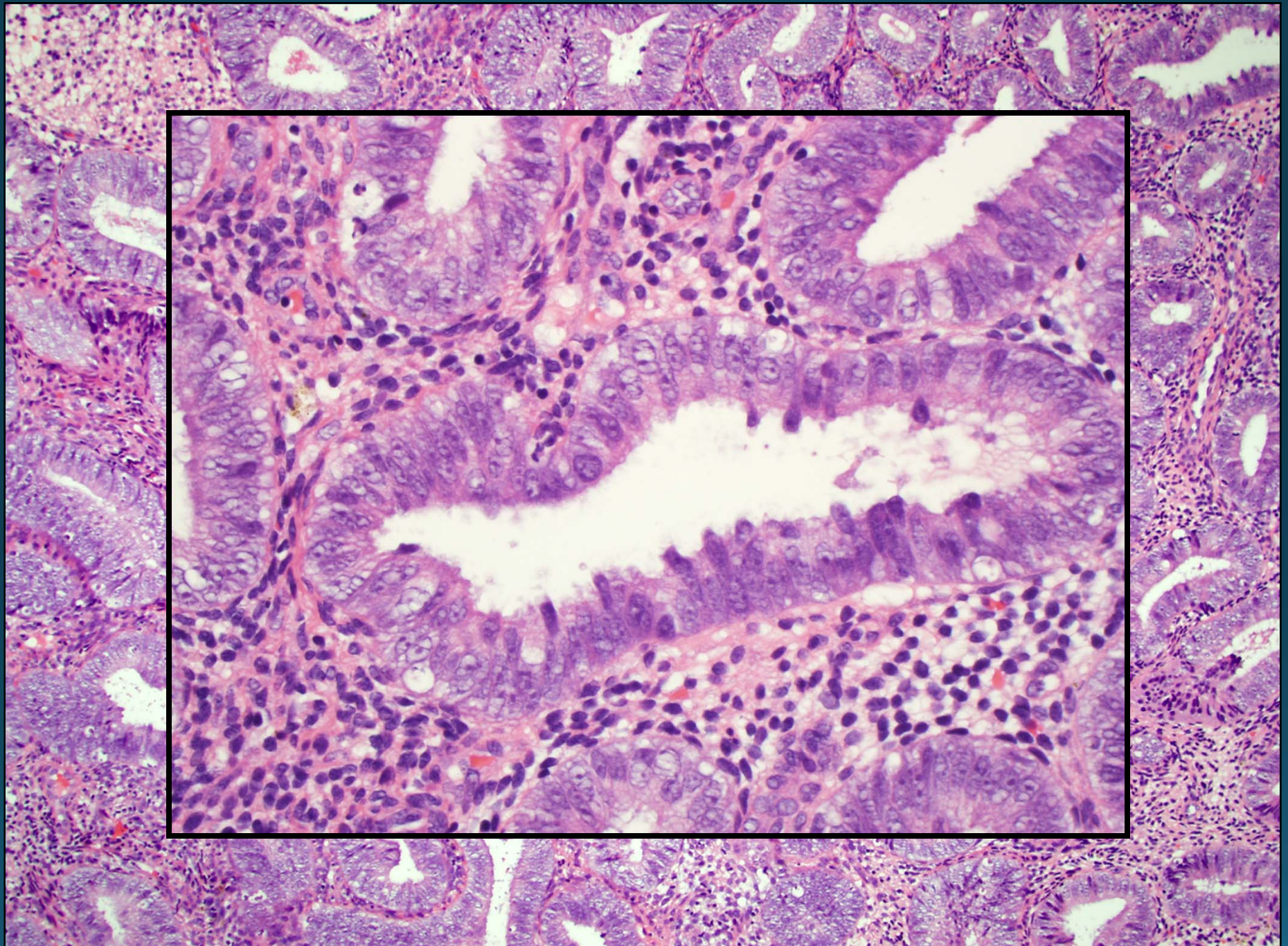
- The American College of Obstetricians and Gynecologists (ACOG) and the Society of Gynecologic Oncology (SGO) states :
  - “Pathologic diagnosis of premalignant lesions should use criteria and terminology that clearly distinguish between clinicopathologic entities that are managed differently. At present, the endometrial intraepithelial neoplasia schema is tailored most closely to this objective.”

# EIN Examples

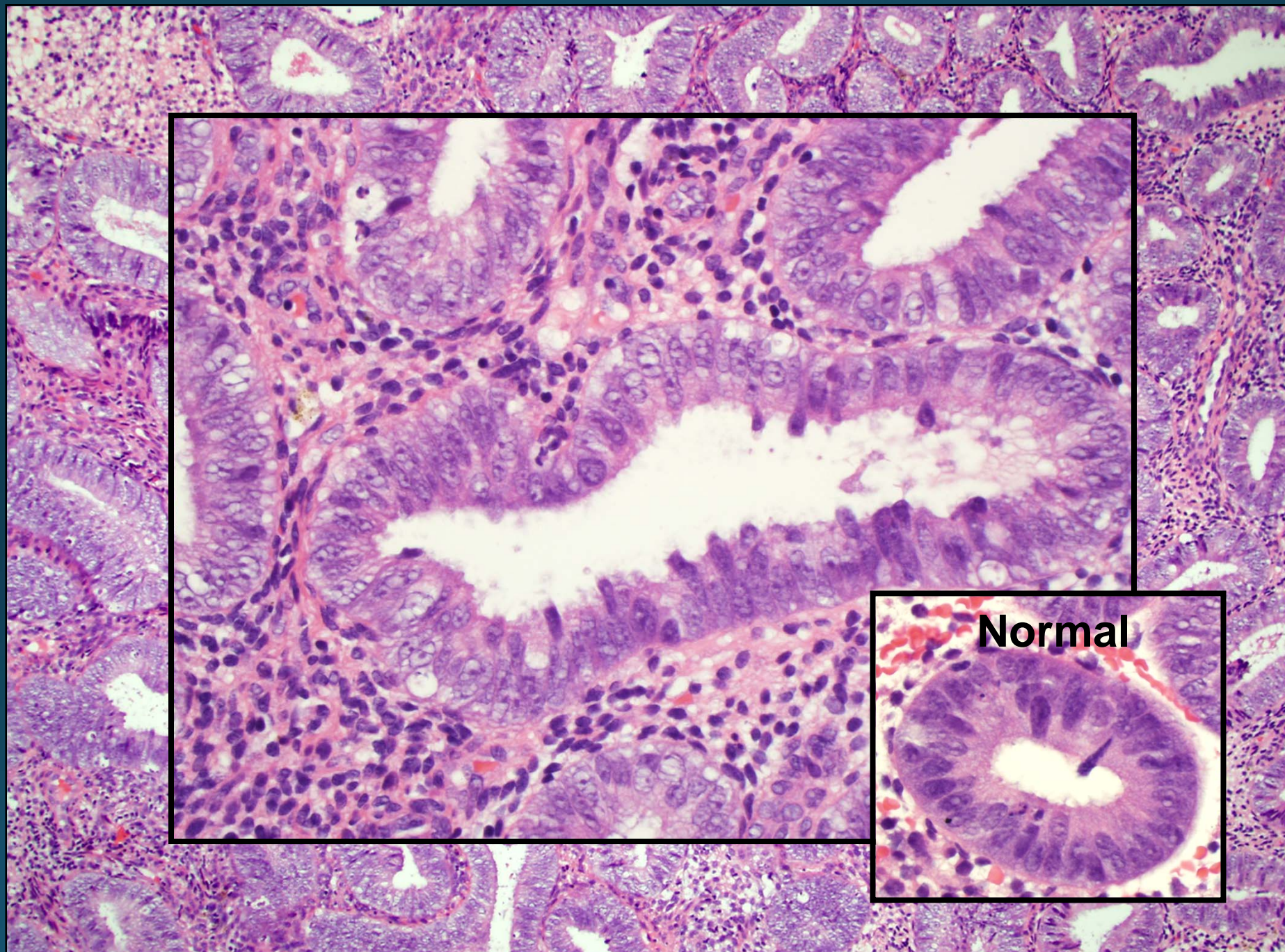














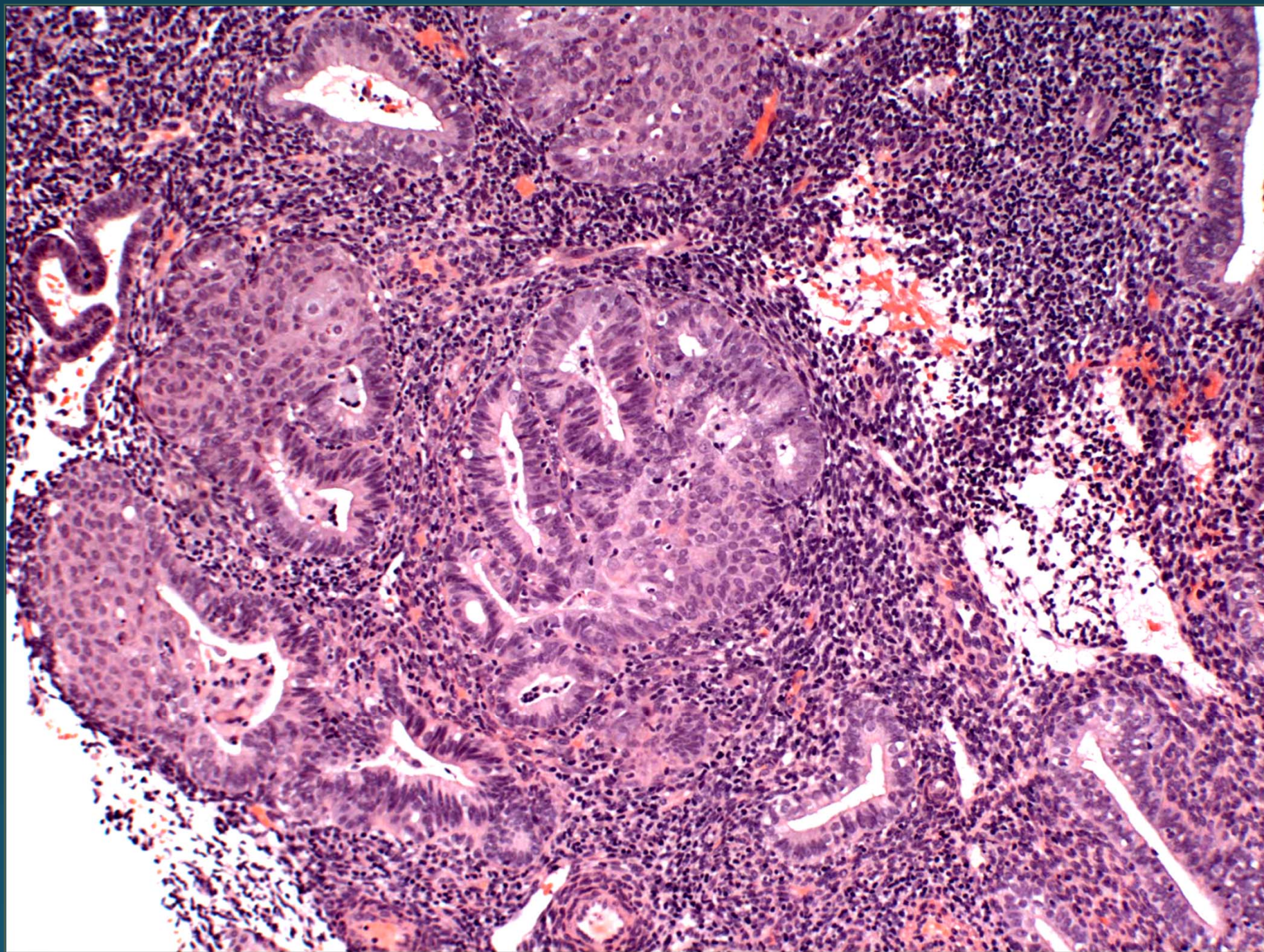


This histological image compares two types of endometrial tissue. The main image shows a large area of Endometrial Intraepithelial Neoplasia (EIN), characterized by thickened, crowded, and irregularly shaped glands with dark, hyperchromatic nuclei. A light blue box with the text 'EIN' is placed over this area. In the bottom right corner, there is a smaller, circular inset showing a cross-section of a normal endometrial gland. This inset is labeled 'Normal' in black text and shows a single, well-defined gland with a clear lumen and a single layer of columnar epithelial cells with uniform, light-colored nuclei.

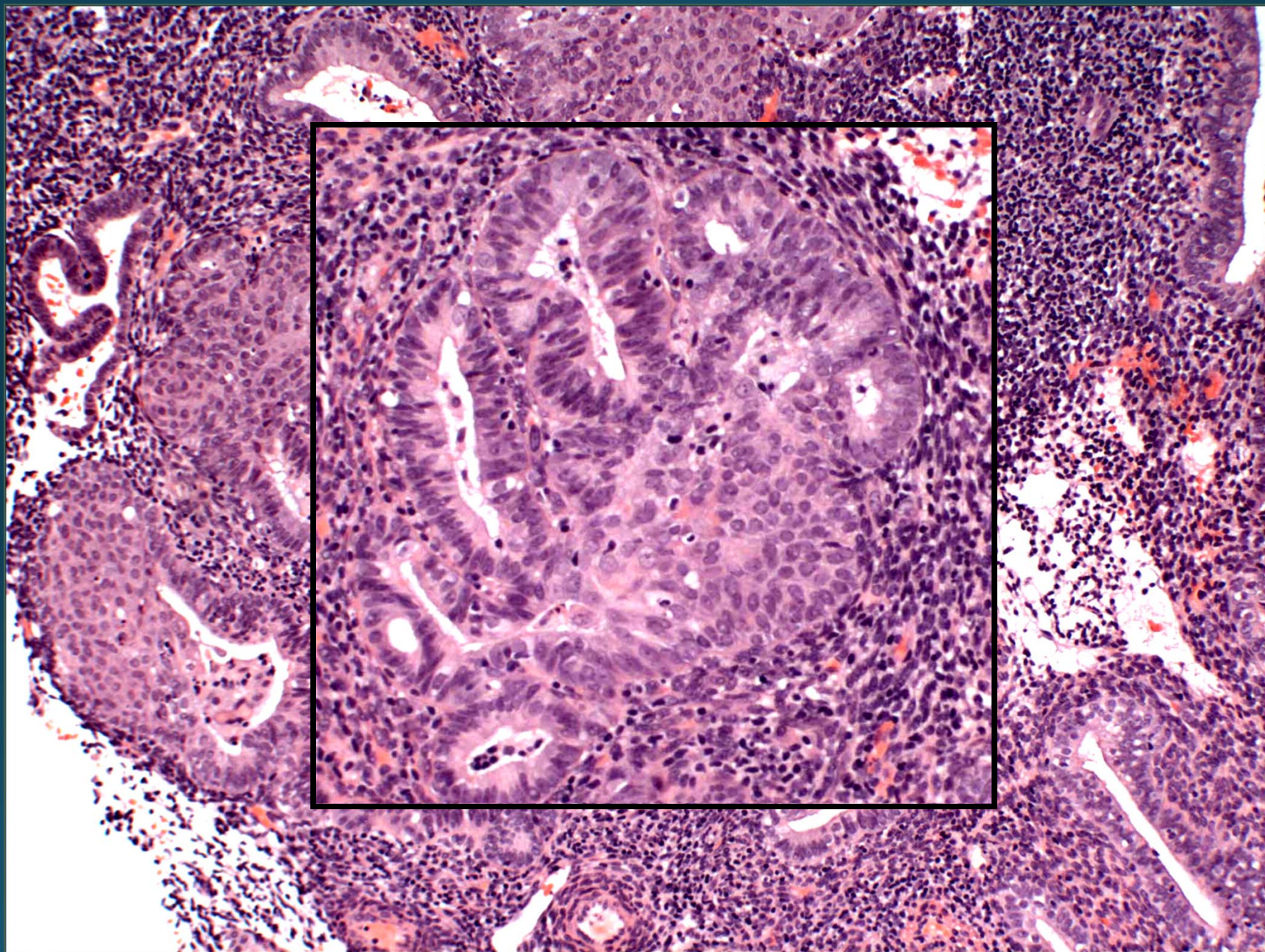
EIN

Normal

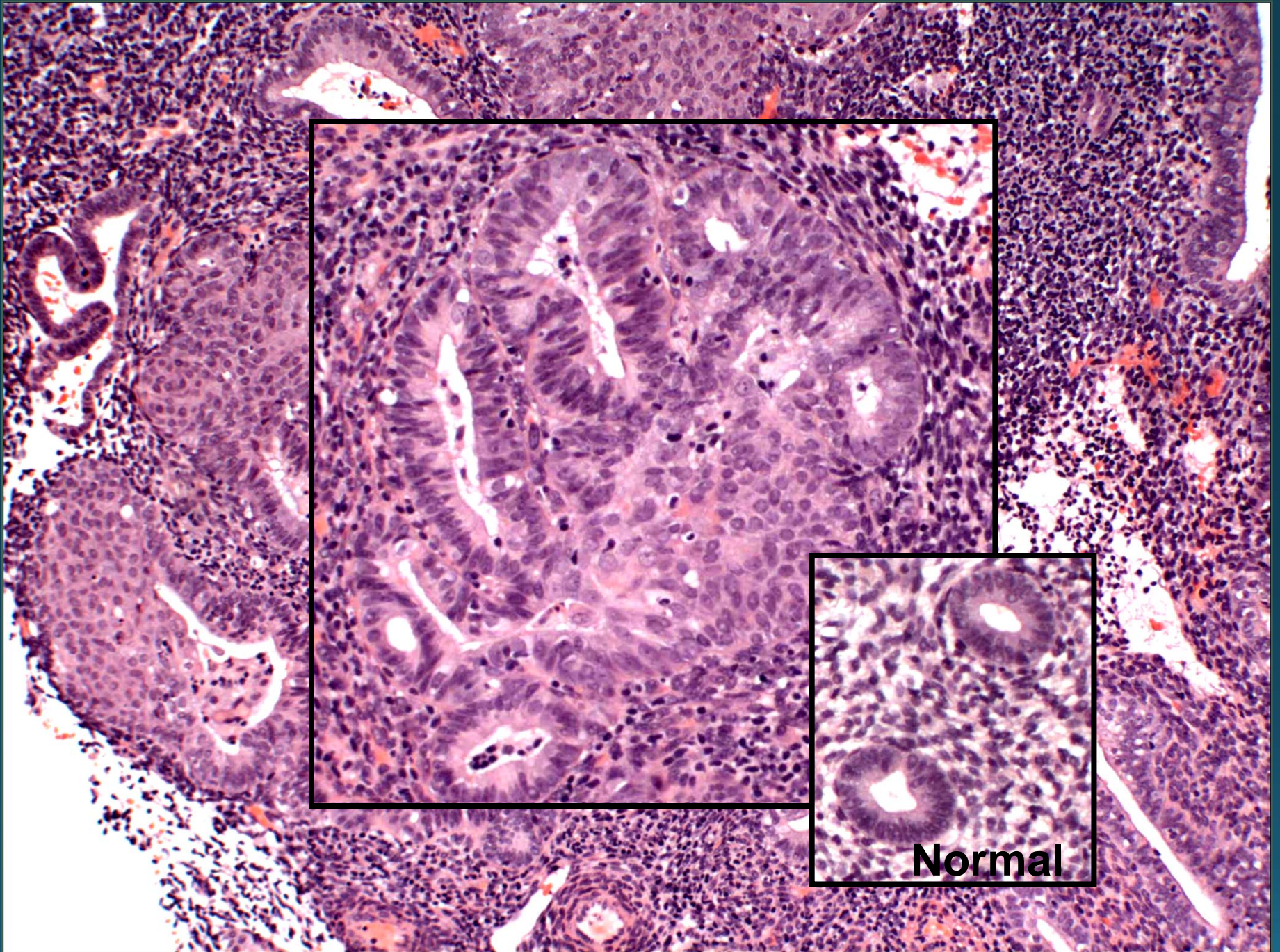












**Normal**





This histological slide shows a section of cervical tissue. The upper portion displays Ectocervical Intraepithelial Neoplasia (EIN) with squamous morules, characterized by disorganized, thickened epithelial layers. A large inset provides a magnified view of these morules. The lower right portion shows normal cervical tissue with well-organized, stratified squamous epithelium. A smaller inset provides a magnified view of this normal tissue, labeled 'Normal'.

EIN with squamous morules

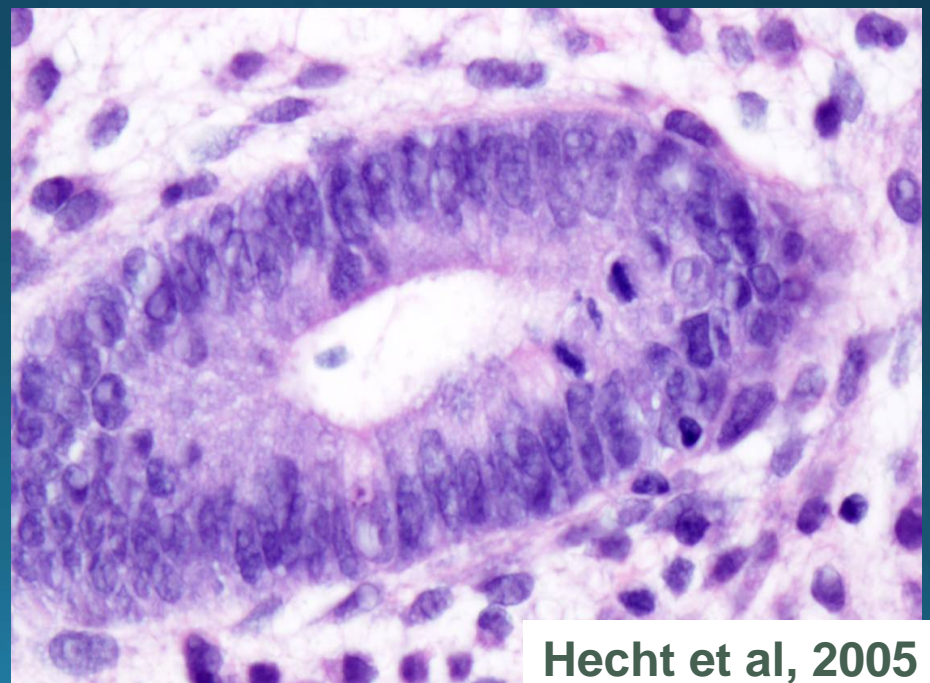
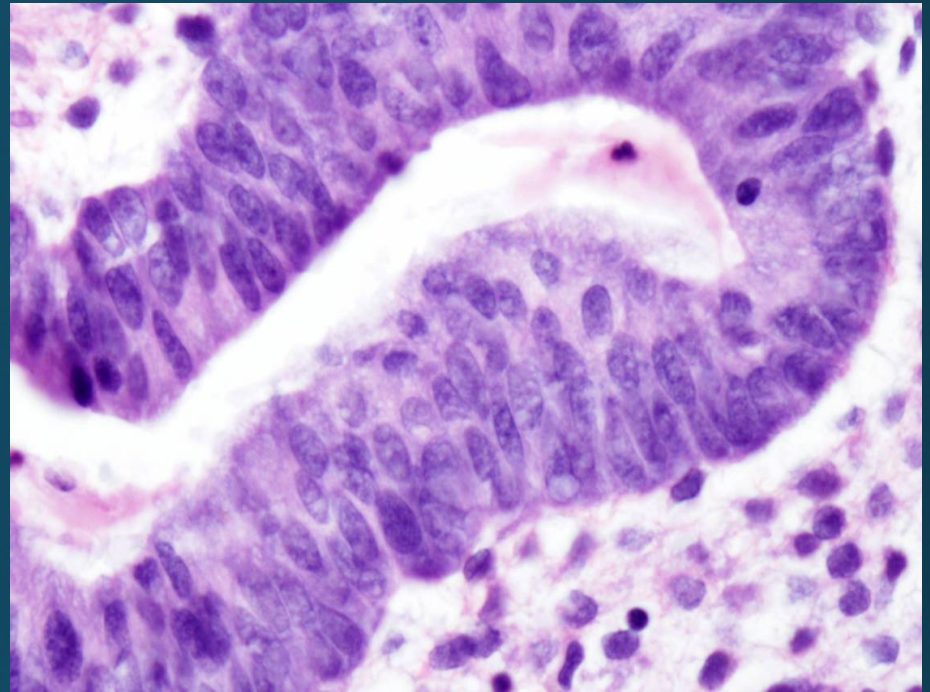
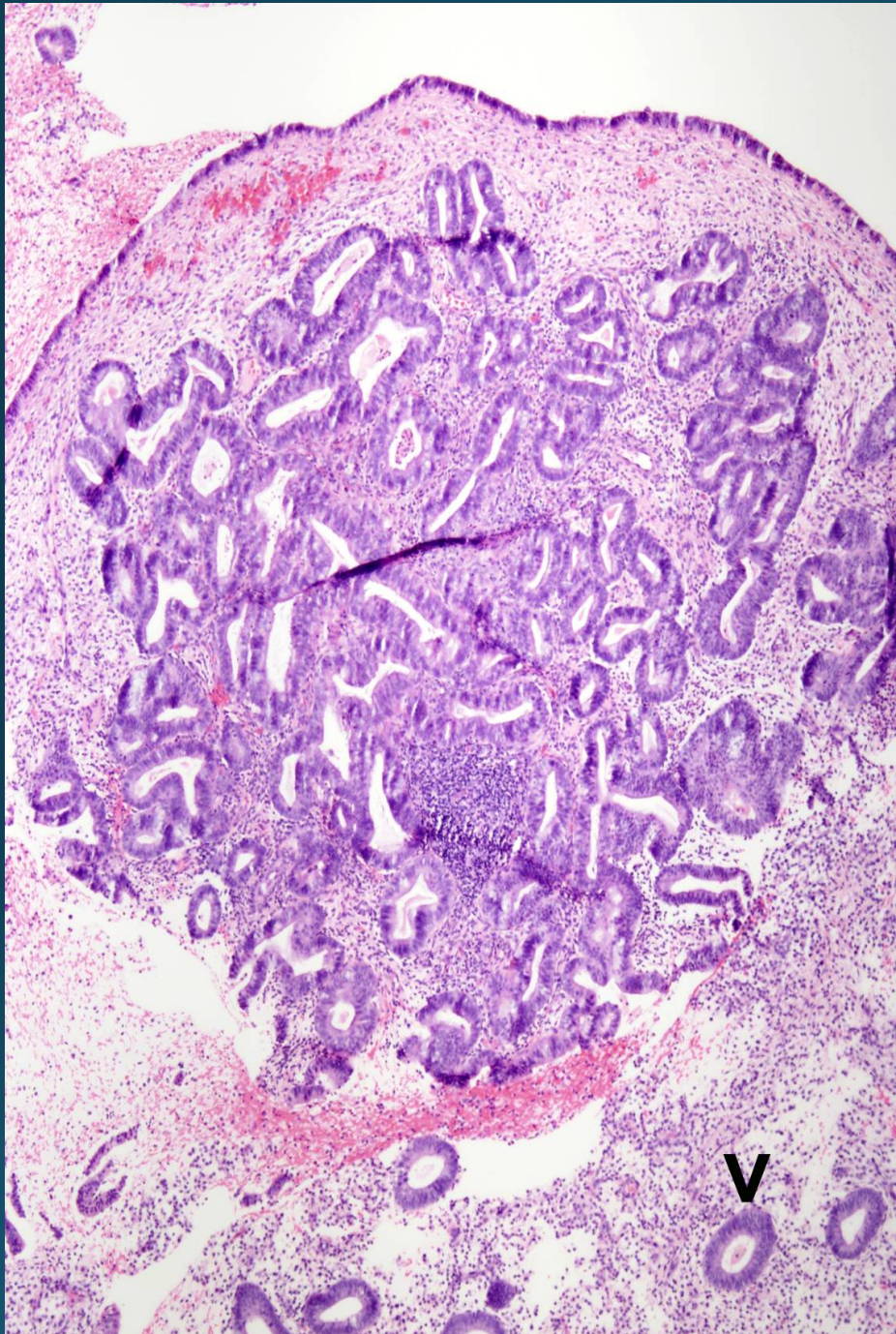
**Normal**



# EIN with squamous morules

- Can create diagnostic pitfall – peripheral “garland” of glands surrounding morule can resemble cribriforming which can be over-interpreted as carcinoma
- “Extract” the morular component when assessing the architectural nature of the glands





Hecht et al, 2005

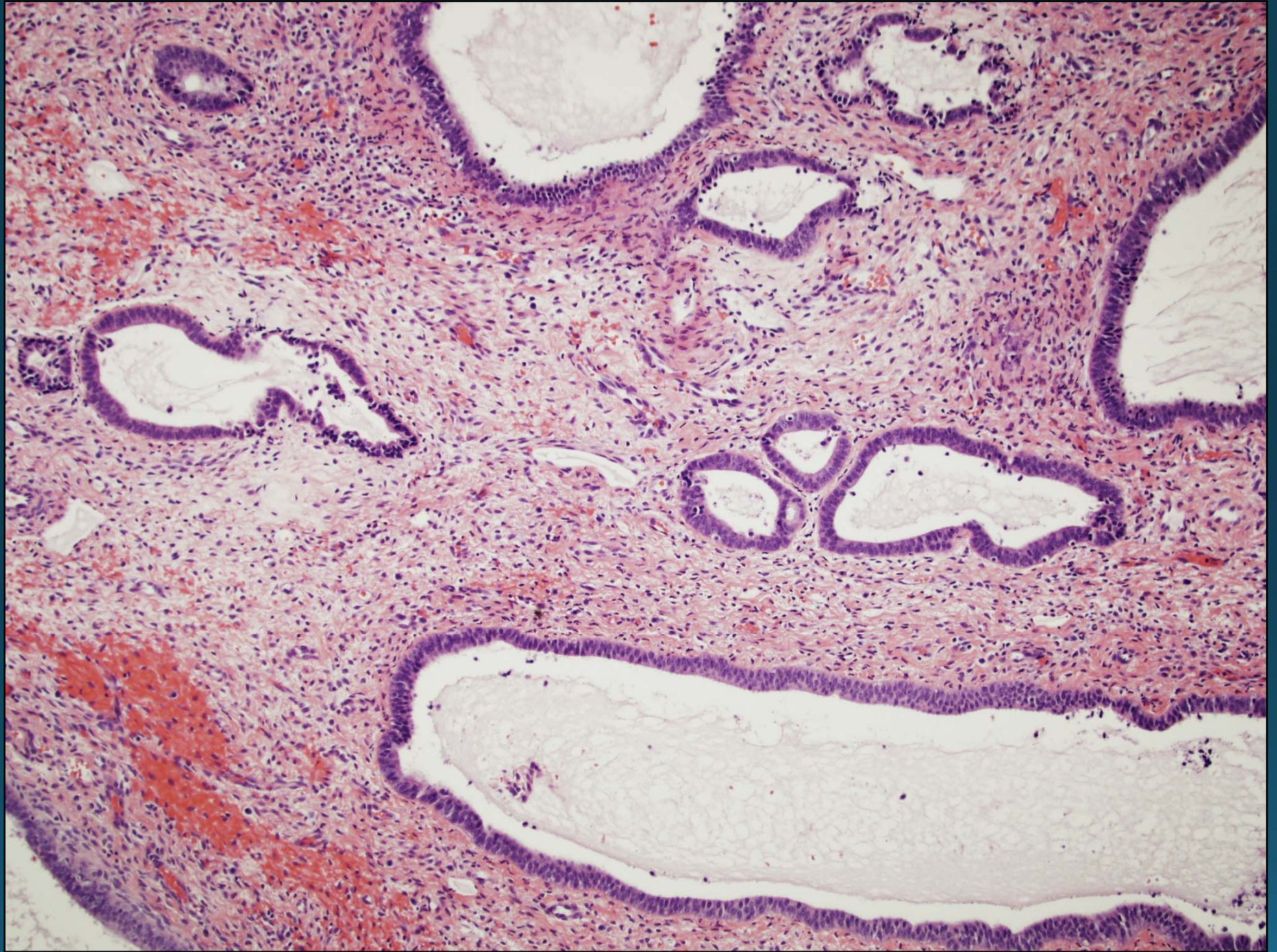


Dx: EIN by subjective diagnosis and computer morphometric analysis

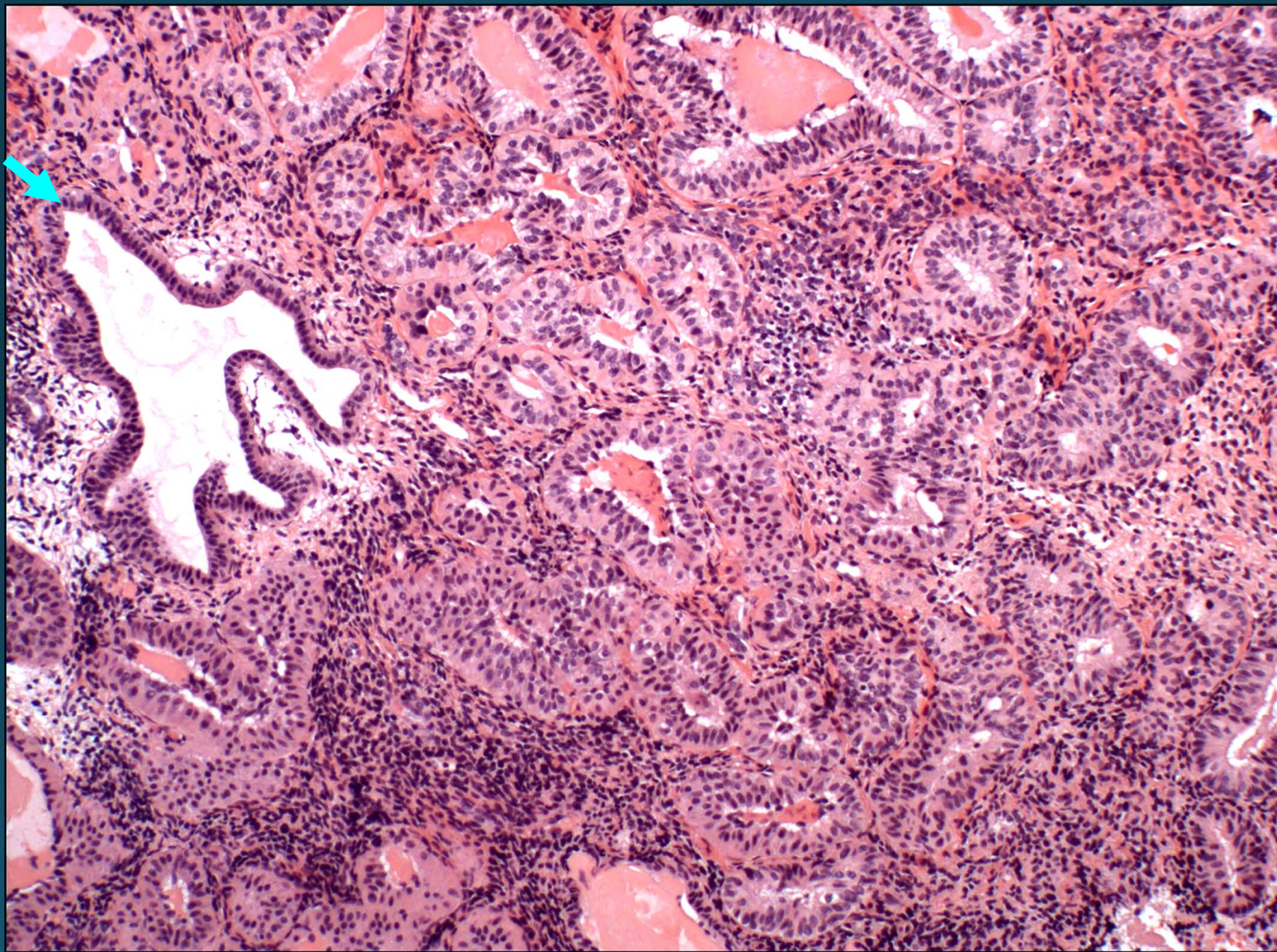
WHO 1994: Complex **non-atypical** hyperplasia

Follow-up: Endometrial adenocarcinoma 2 years later

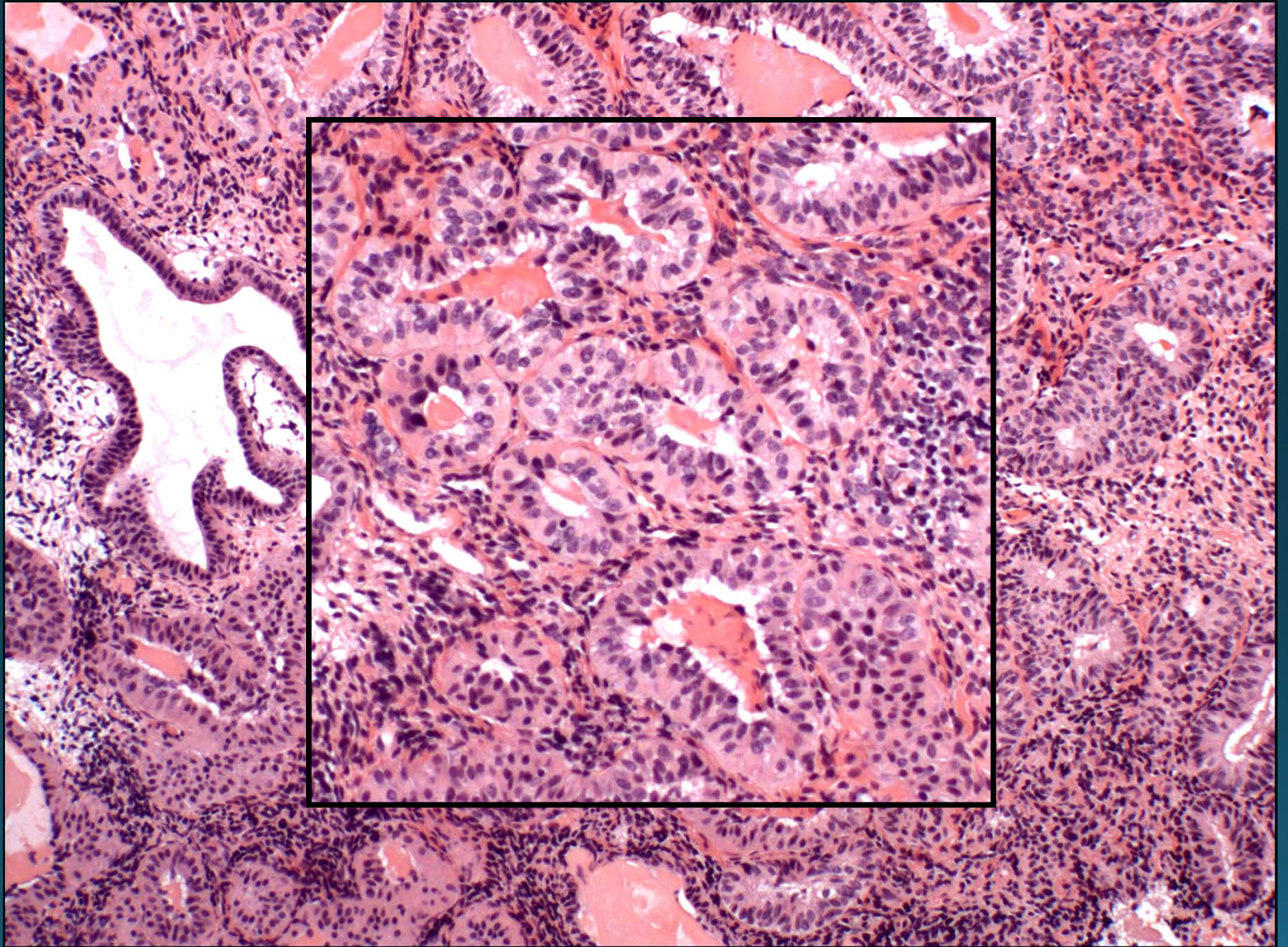






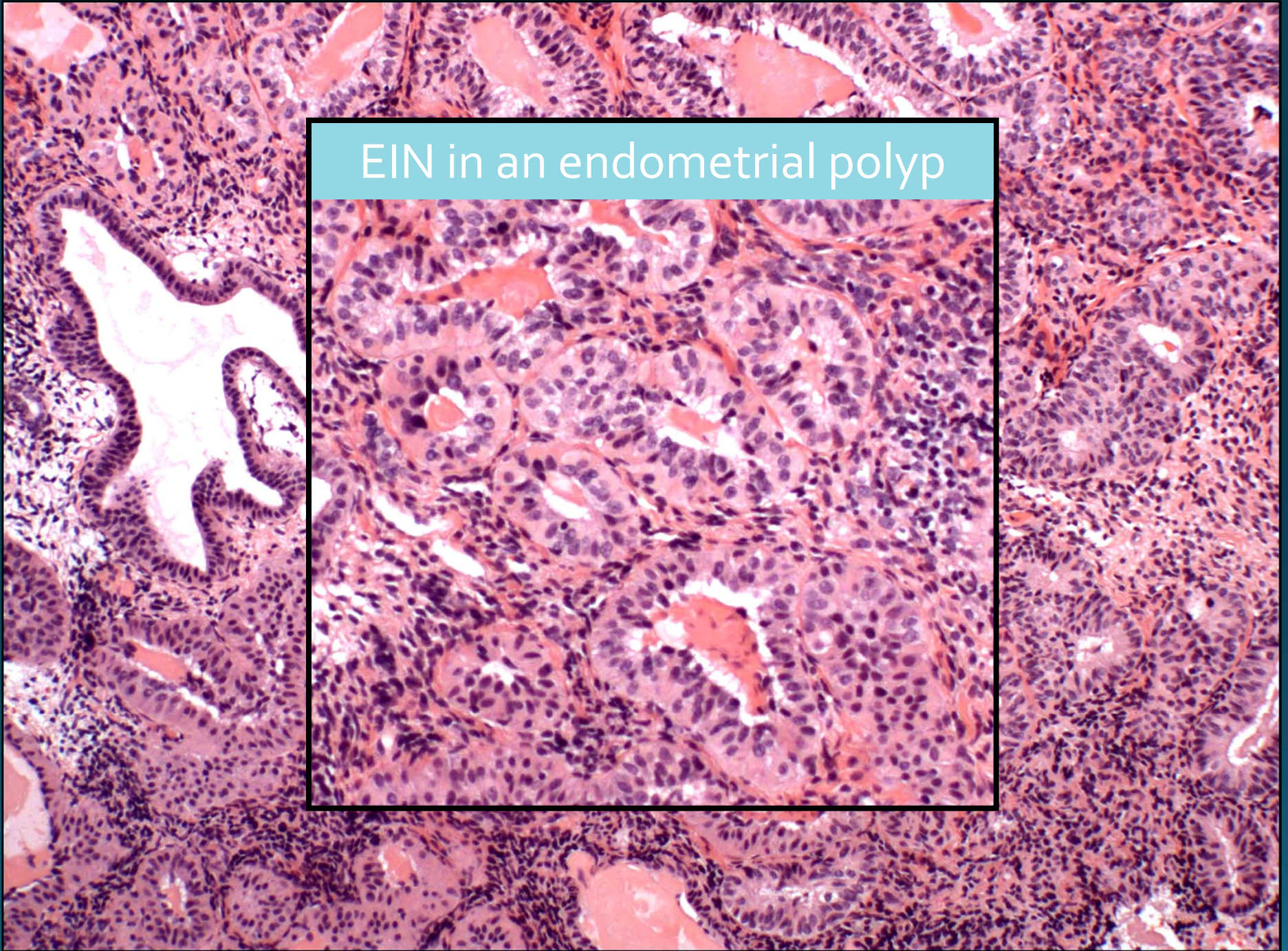








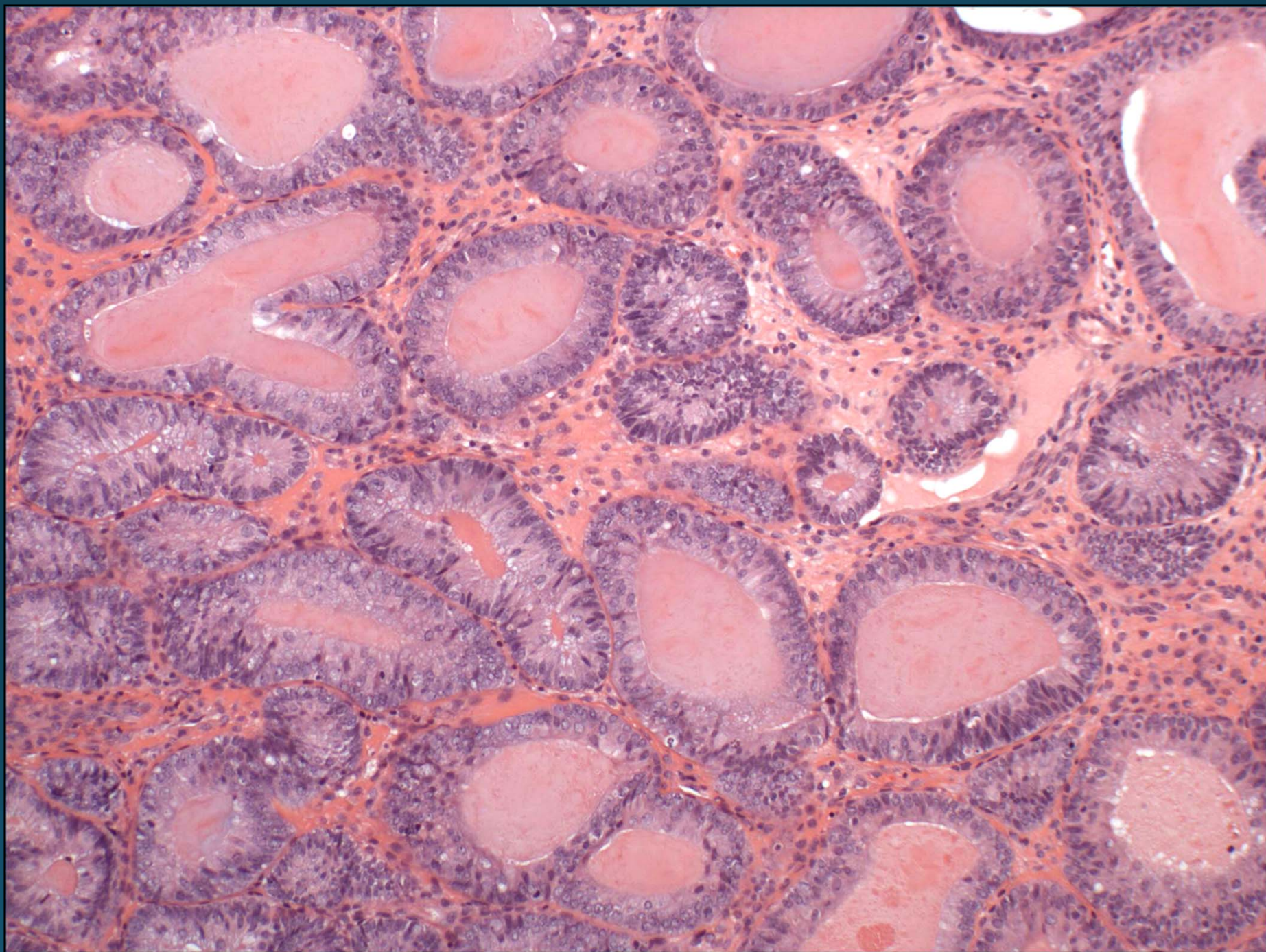
EIN in an endometrial polyp



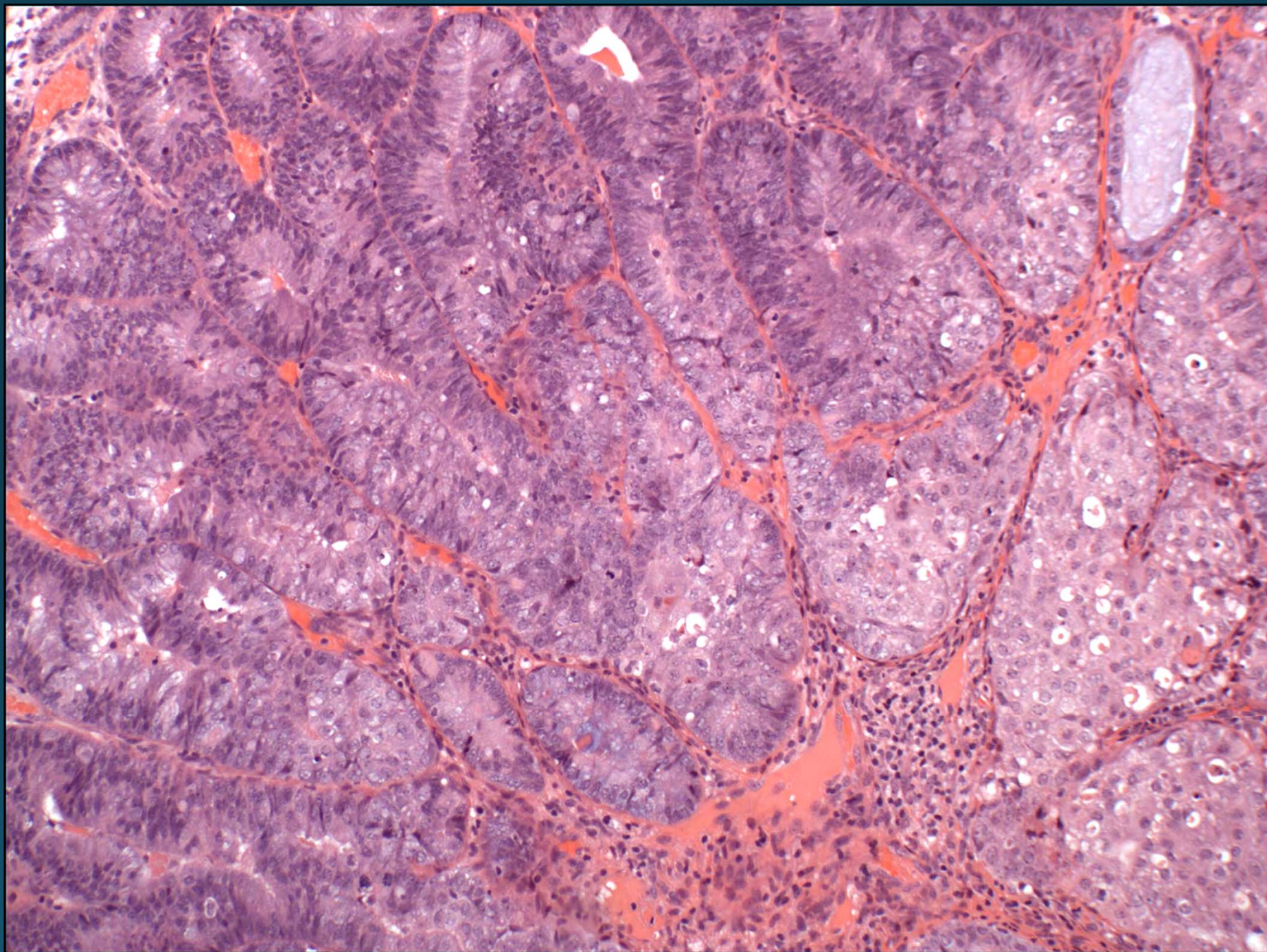


# EIN in endometrial polyps

- EIN vs. not EIN in an endometrial polyp can be tricky
  - Polyps exhibit irregularly-shaped and irregularly-distributed glands and variable cytology
- Standard diagnostic criteria for EIN apply, but the reference “background” is the polyp, not the adjacent functionalis

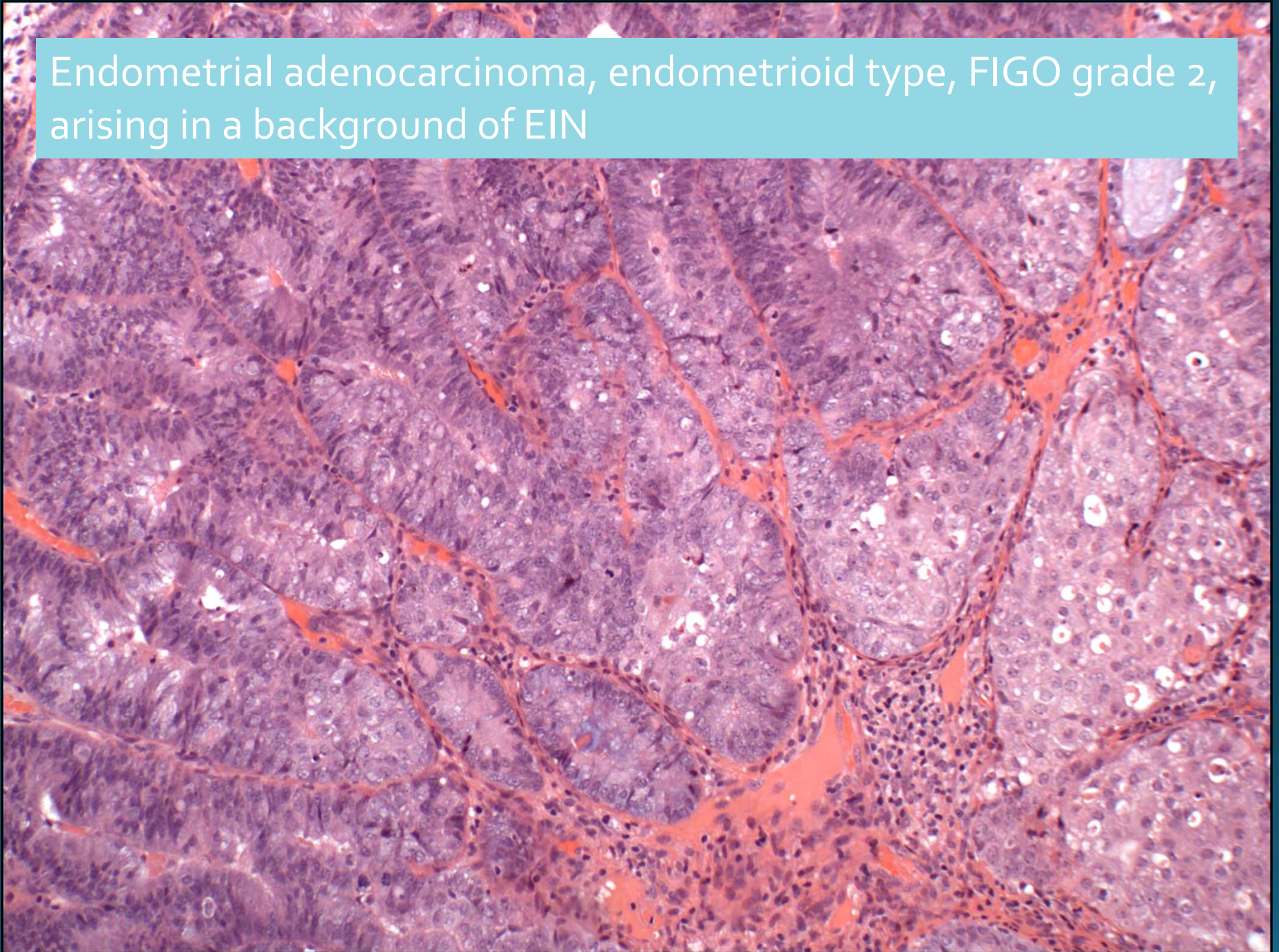




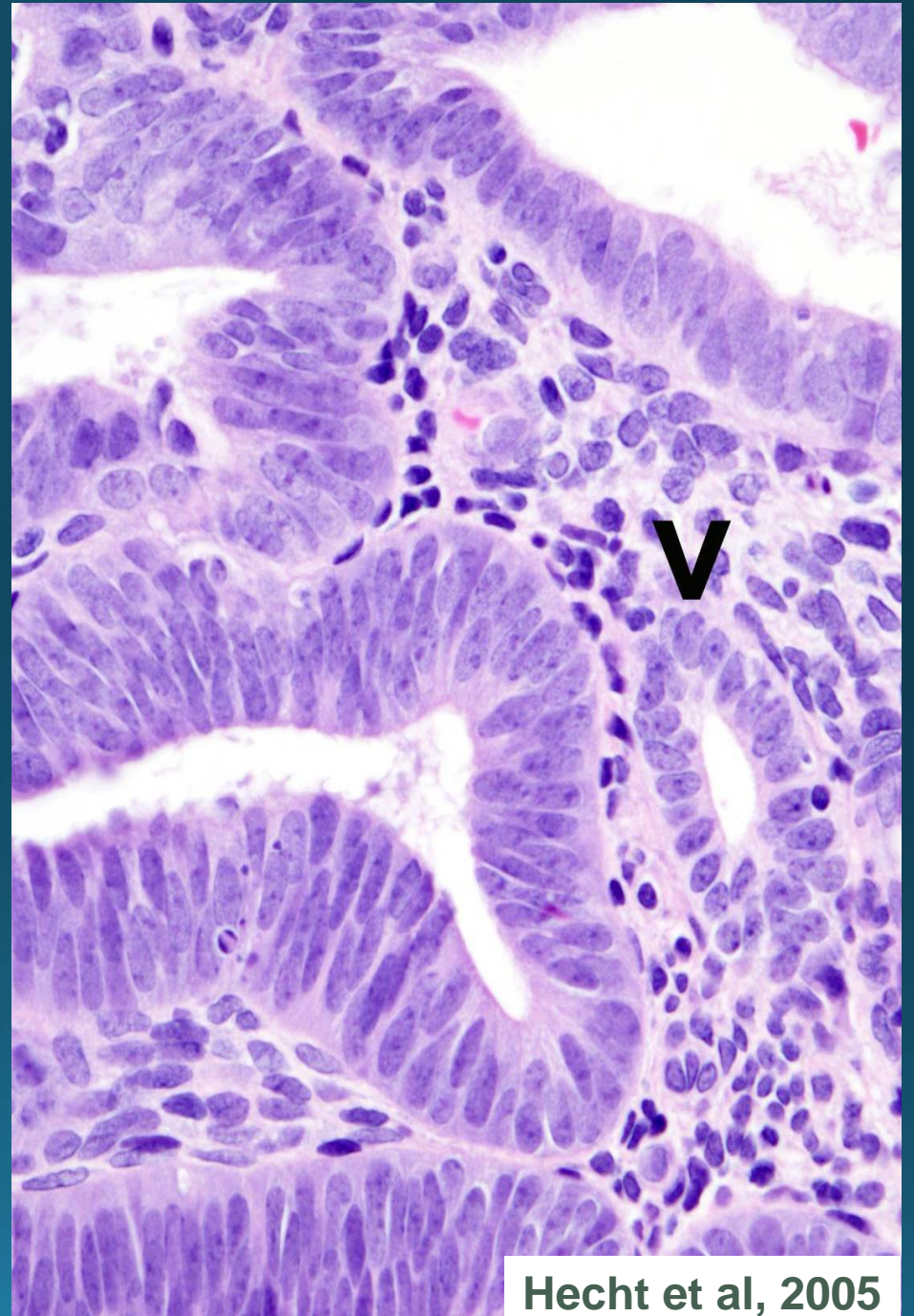
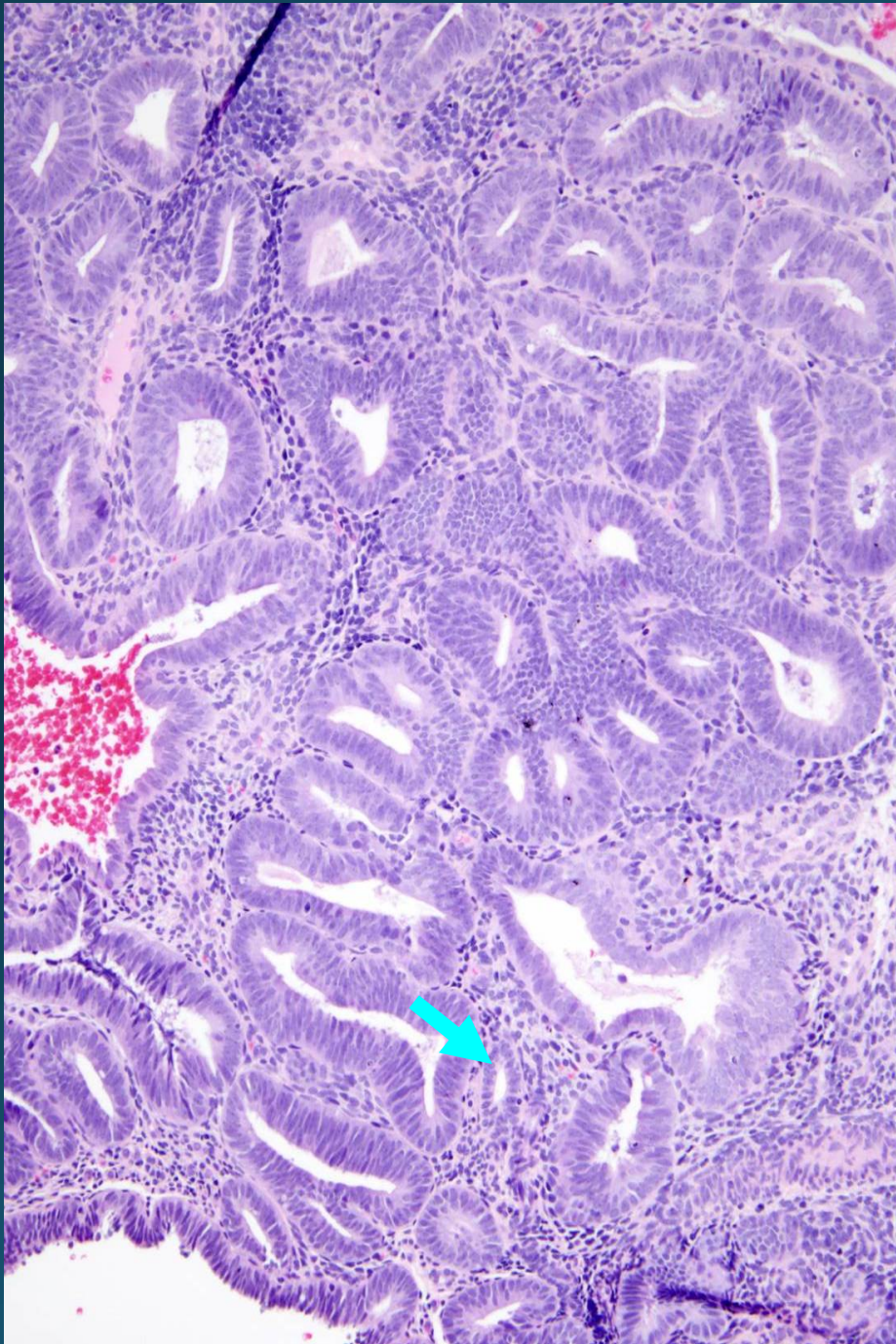




Endometrial adenocarcinoma, endometrioid type, FIGO grade 2,  
arising in a background of EIN







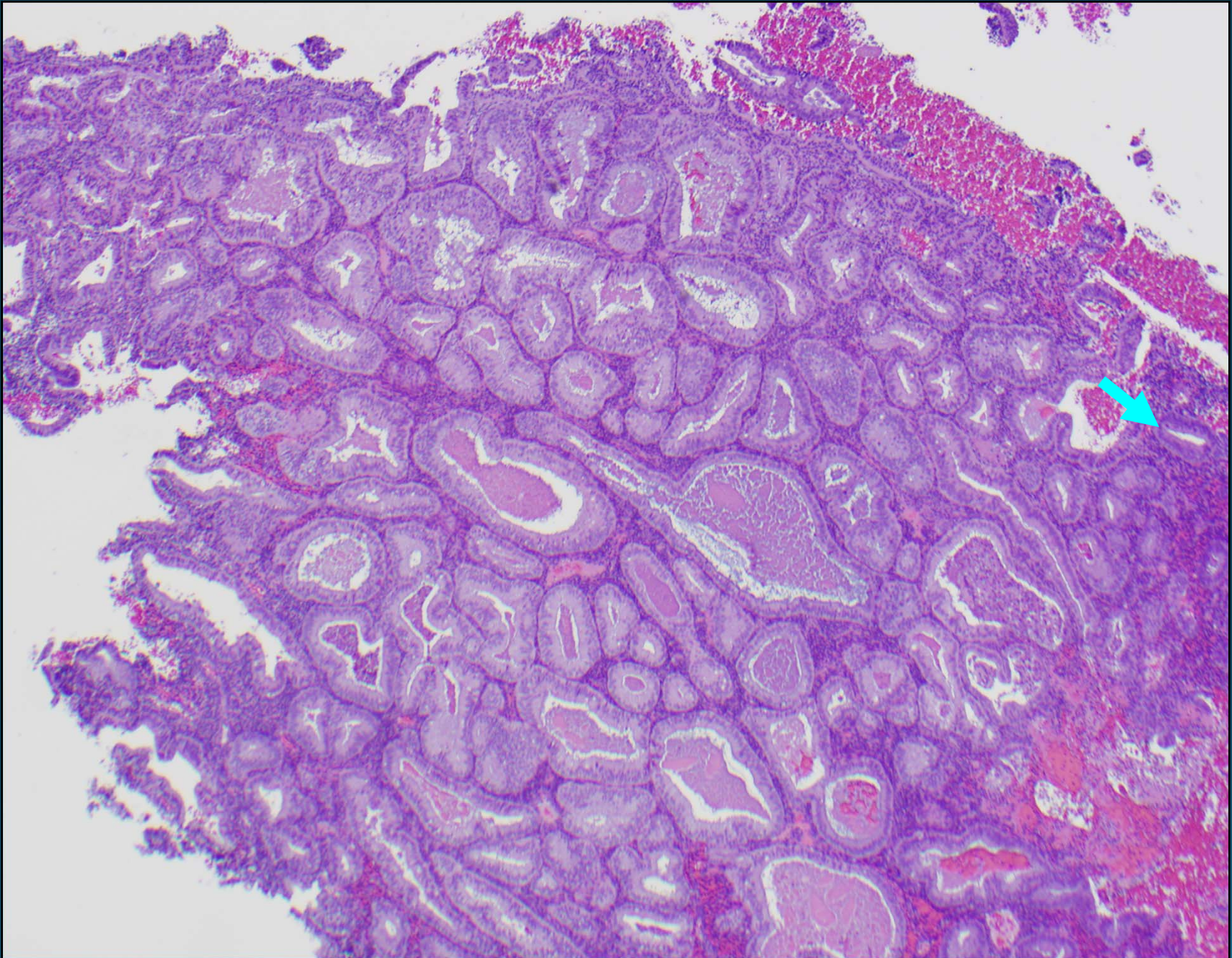
Hecht et al, 2005



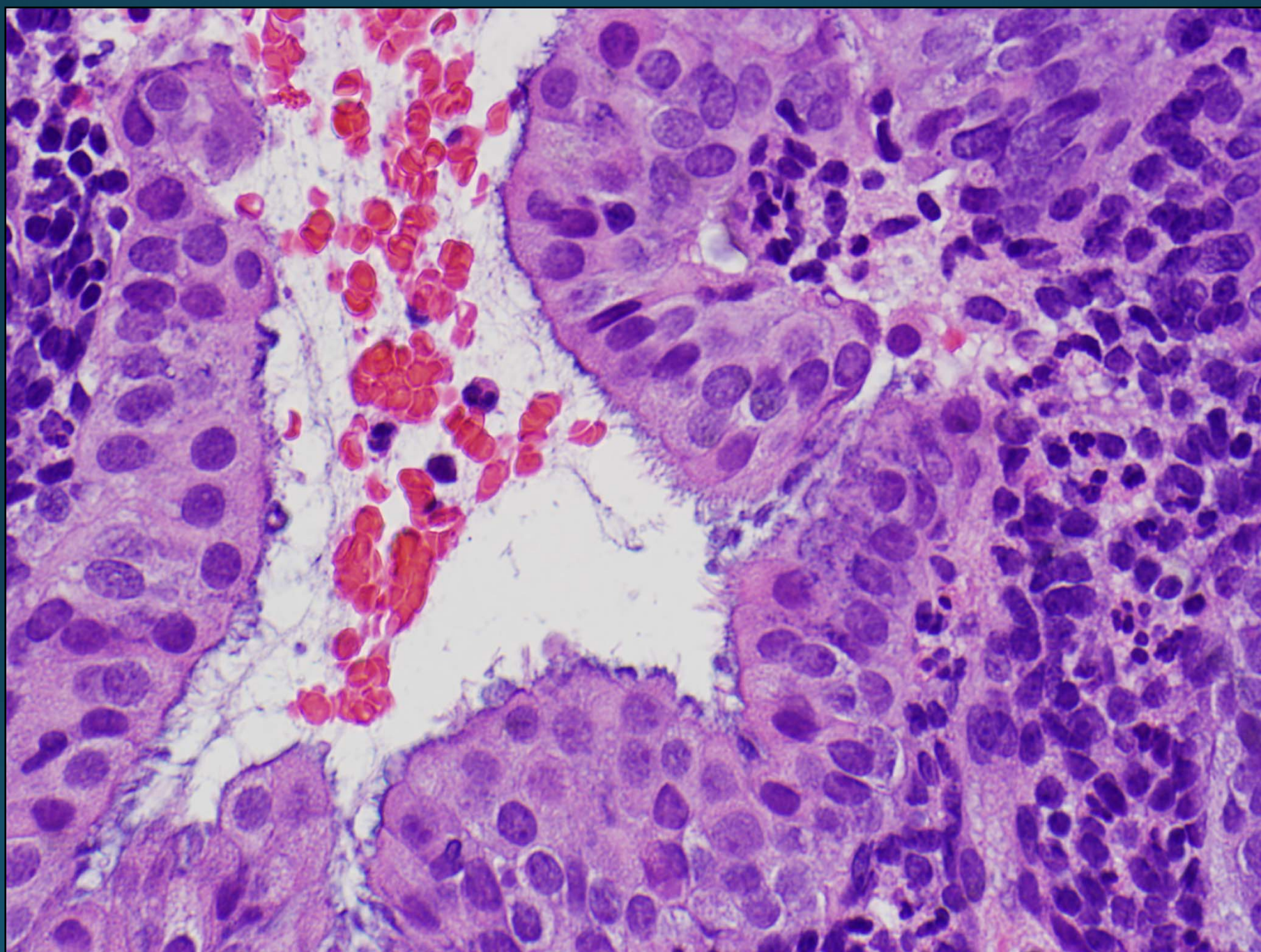
Dx: EIN by subjective diagnosis and computer morphometric analysis

WHO 1994: Simple **non-atypical** hyperplasia

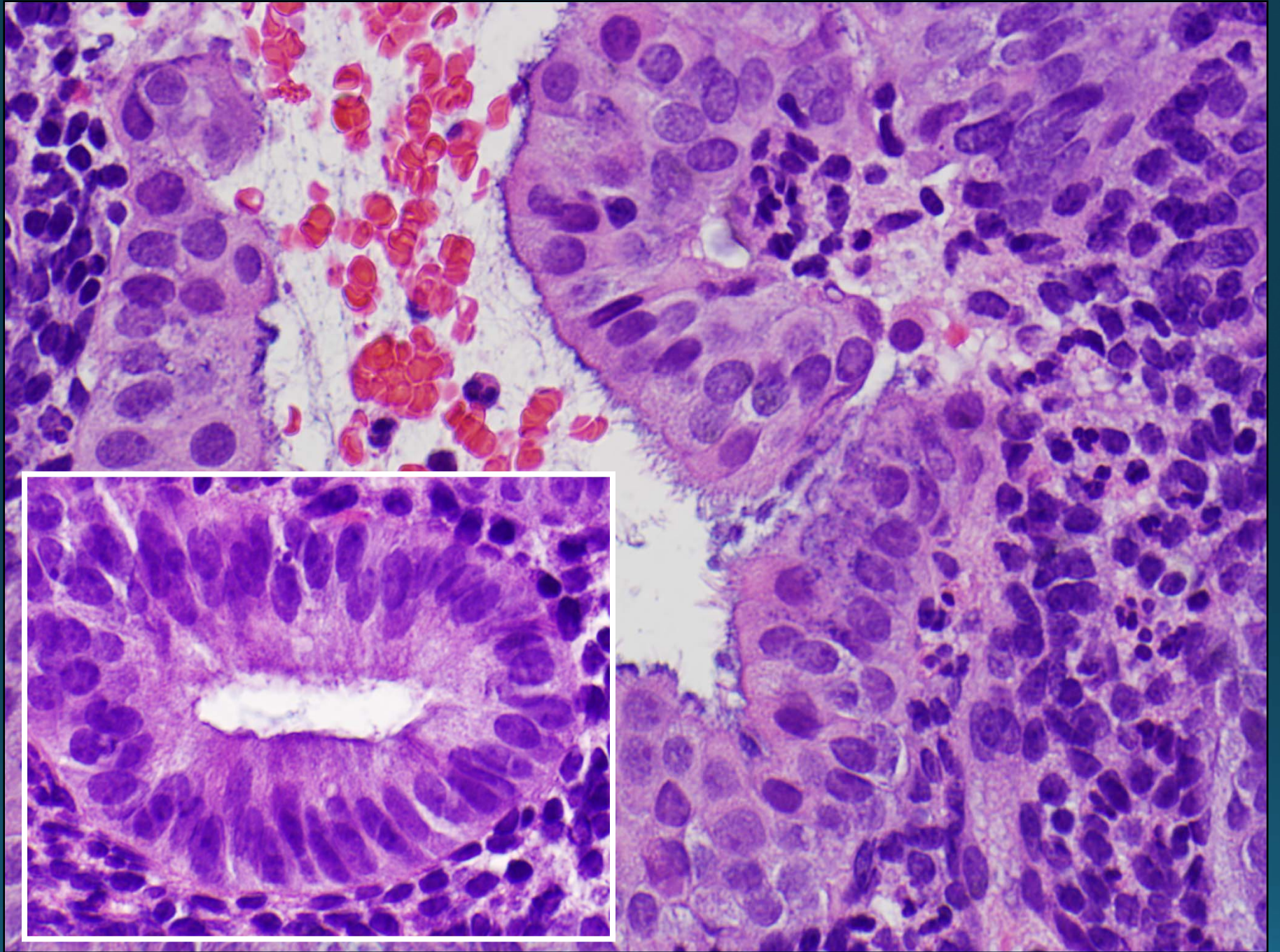
Follow-up: Endometrial adenocarcinoma 8 months Later





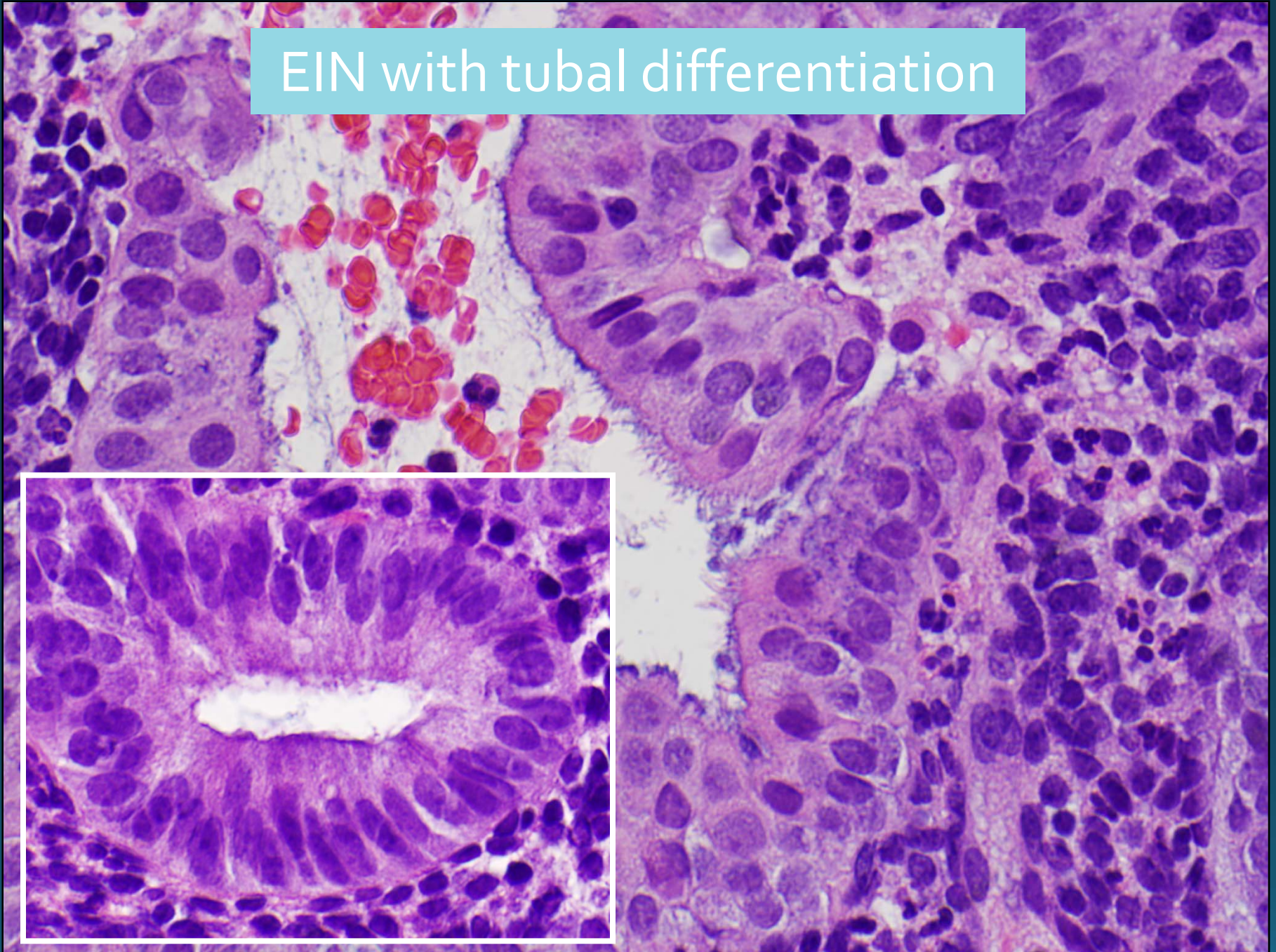




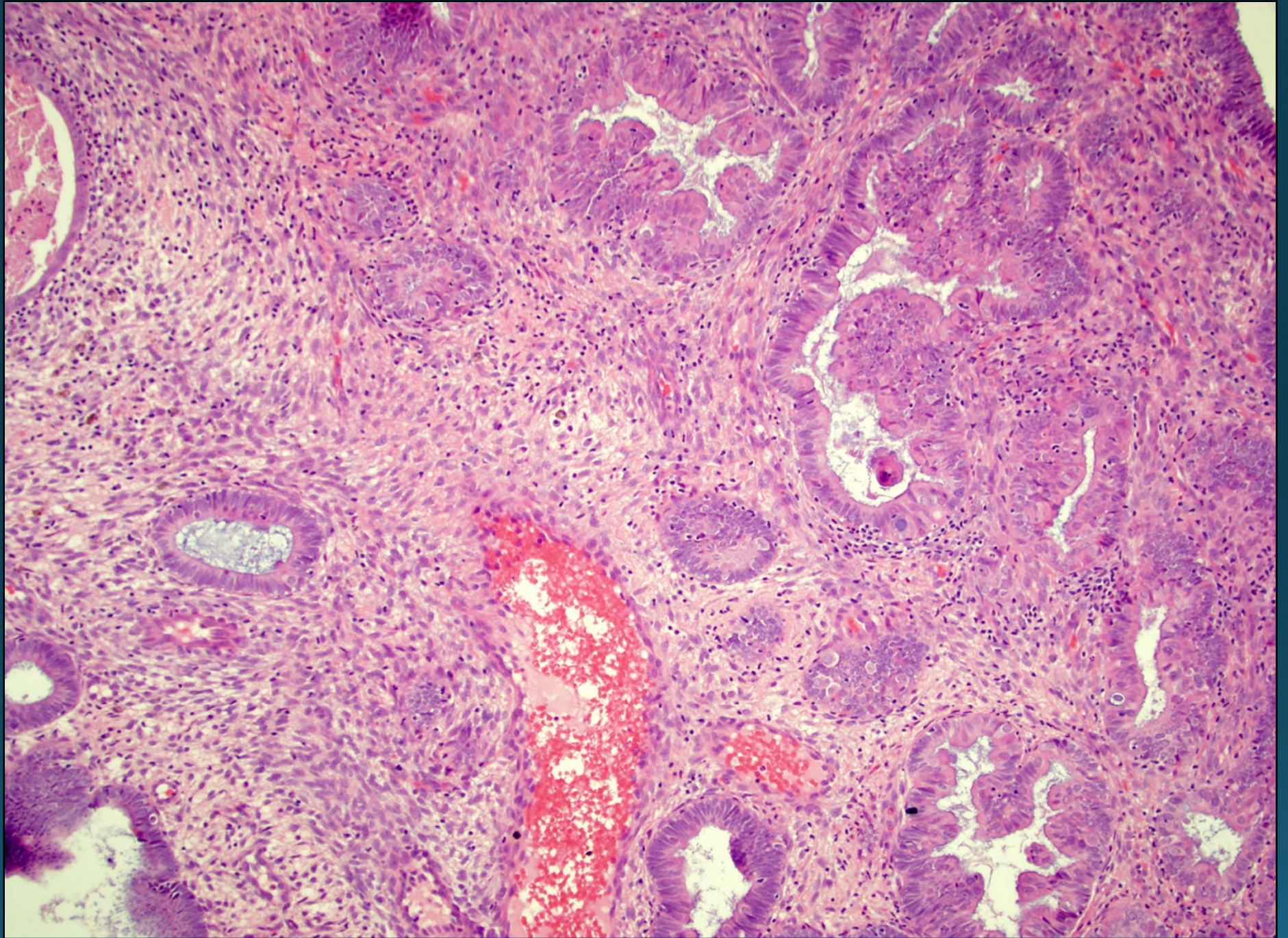




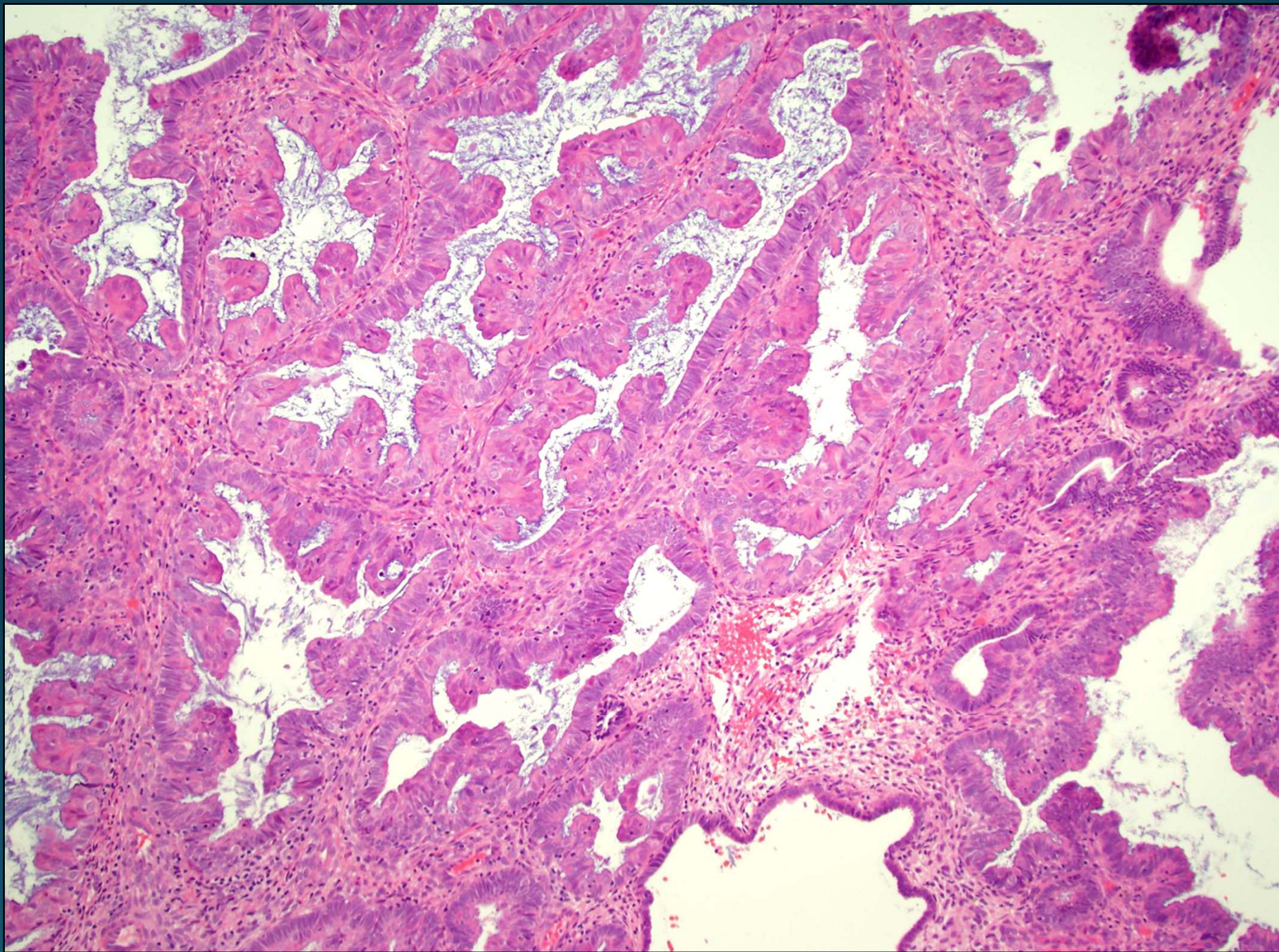
## EIN with tubal differentiation



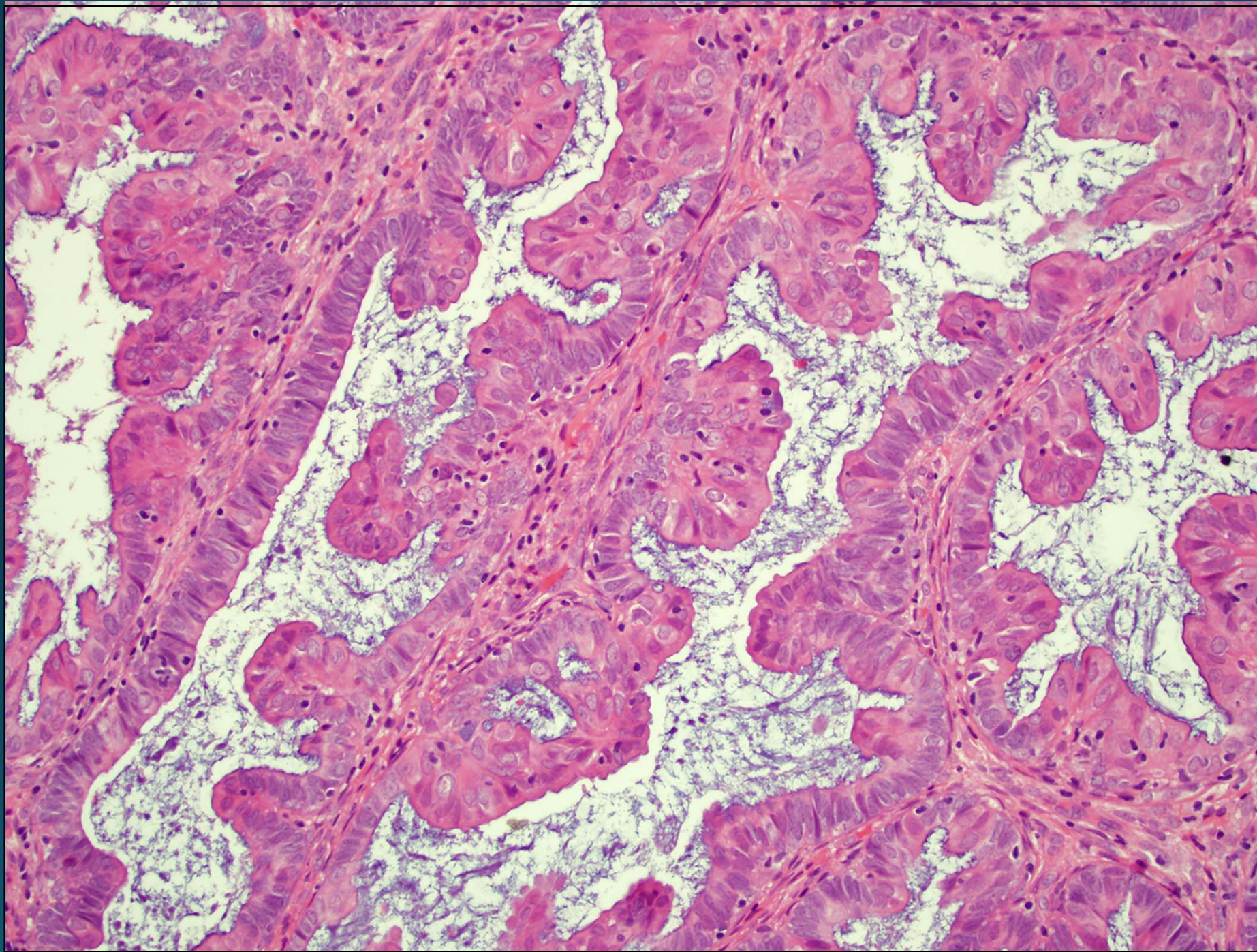






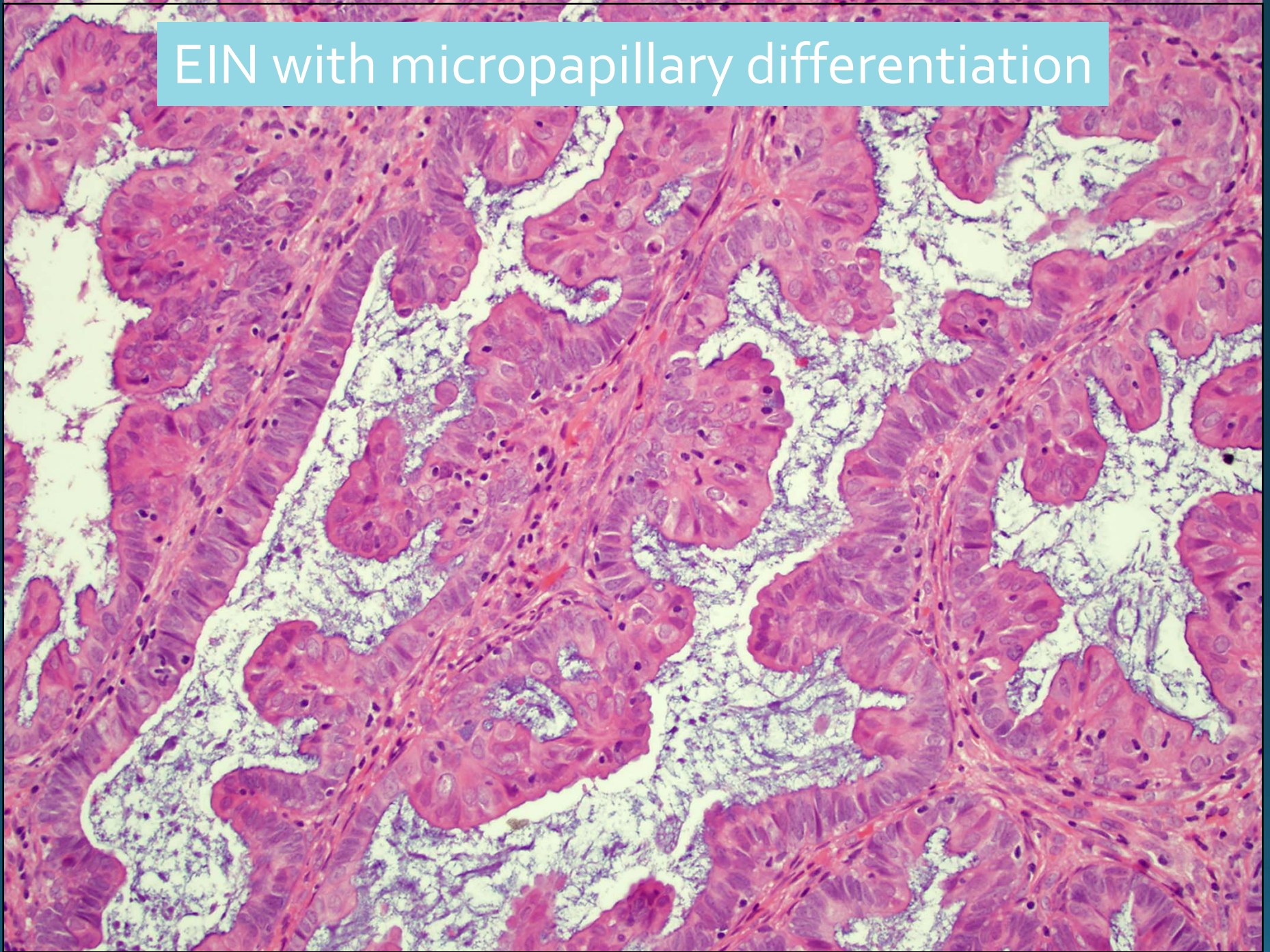








## EIN with micropapillary differentiation





# EIN with micropapillary differentiation

- Gland crowding, architectural complexity, cytology is often bland
- Can mimic secretory endometrium
- Can mimic adenocarcinoma when luminal tufting is especially exuberant



# Common diagnostic dilemmas – ambiguous “gland crowding”

- Focal (cytologically altered) gland crowding, subdiagnostic of EIN:
  - Size criterion of 1 mm not met
  - Excessively fragmented specimen: focus < 1 mm, on edge of fragment
  - Glands not sufficiently crowded
  - Deeper levels may help



# Subdiagnostic "Gland Crowding"



1 mm

Non-EIN (too small)



# Subdiagnostic EIN: “Gland Crowding”

n=143 (0.3% of 71,579 specimens)

- Altered cytology
- Size < 1mm
- Glands < stroma
- Outcomes (n=143)
  - 77% Benign
  - 19% EIN
  - 4% Cancer
- Dx: “Crowded focus of cytologically altered glands (see comment).  
Comment: Resampling is recommended within 6-12 months”

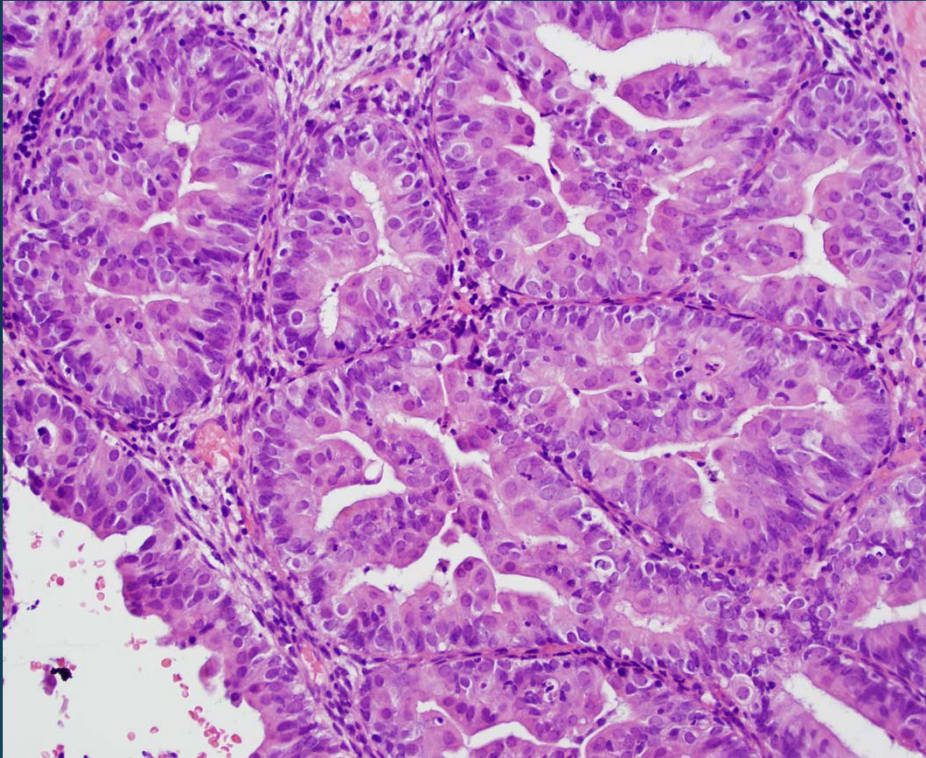


# Common diagnostic dilemmas – High dose progestin therapy

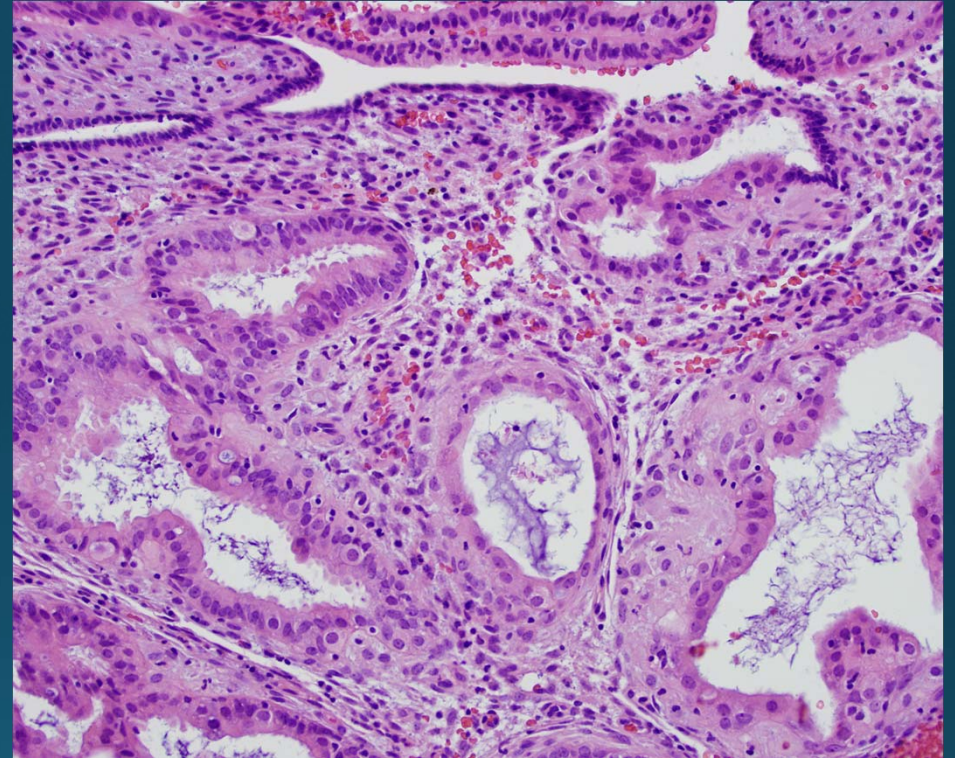
- Stromal expansion decreases gland density
- Makes neoplastic cytology bland
- Nuclear rounding in normal cells



# Progestin effect on architecture



PRE-Rx

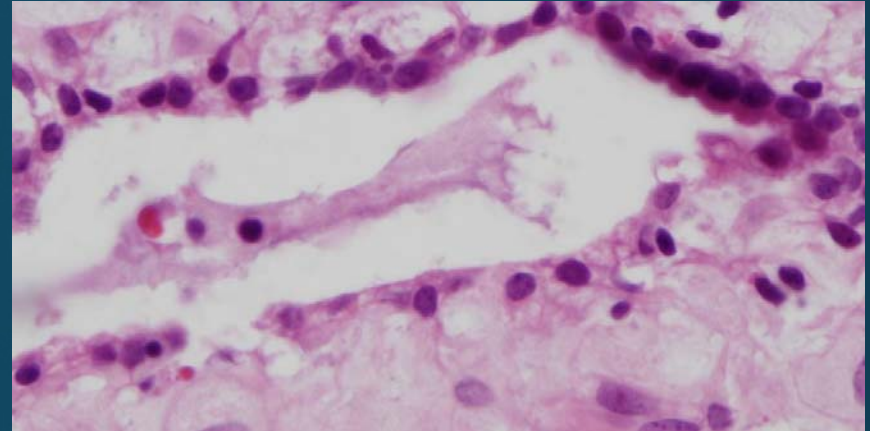
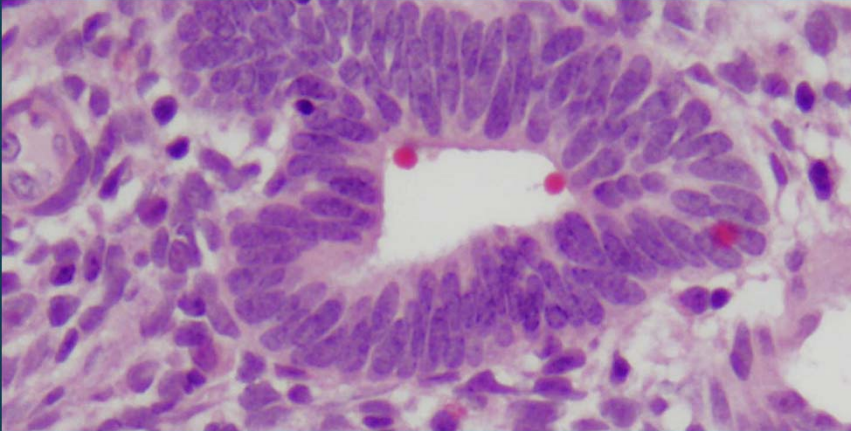


POST-Rx

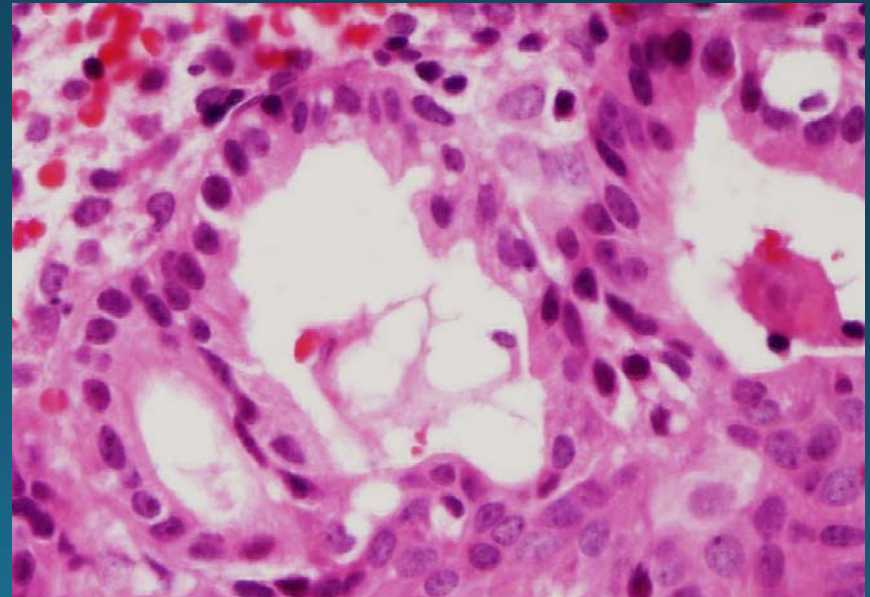
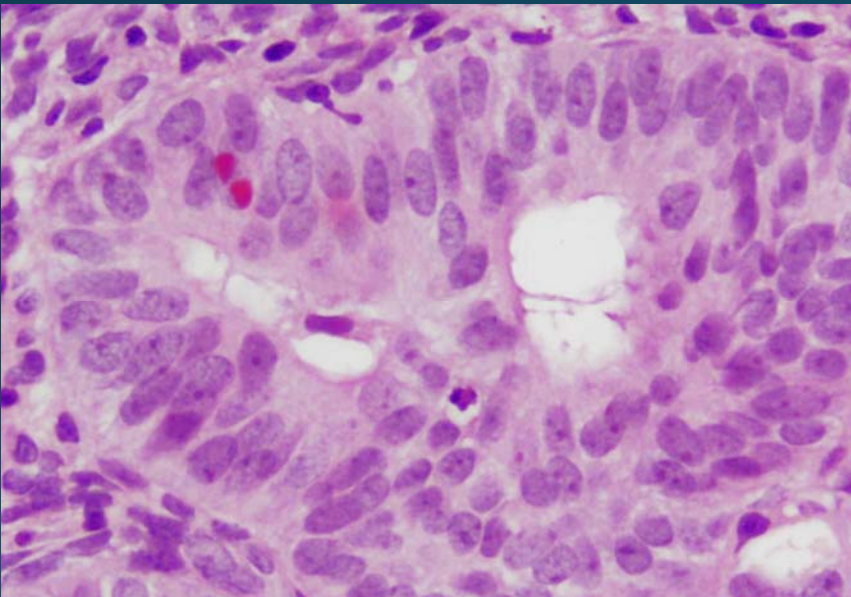


# Progestin effect on cytology

NL



EIN



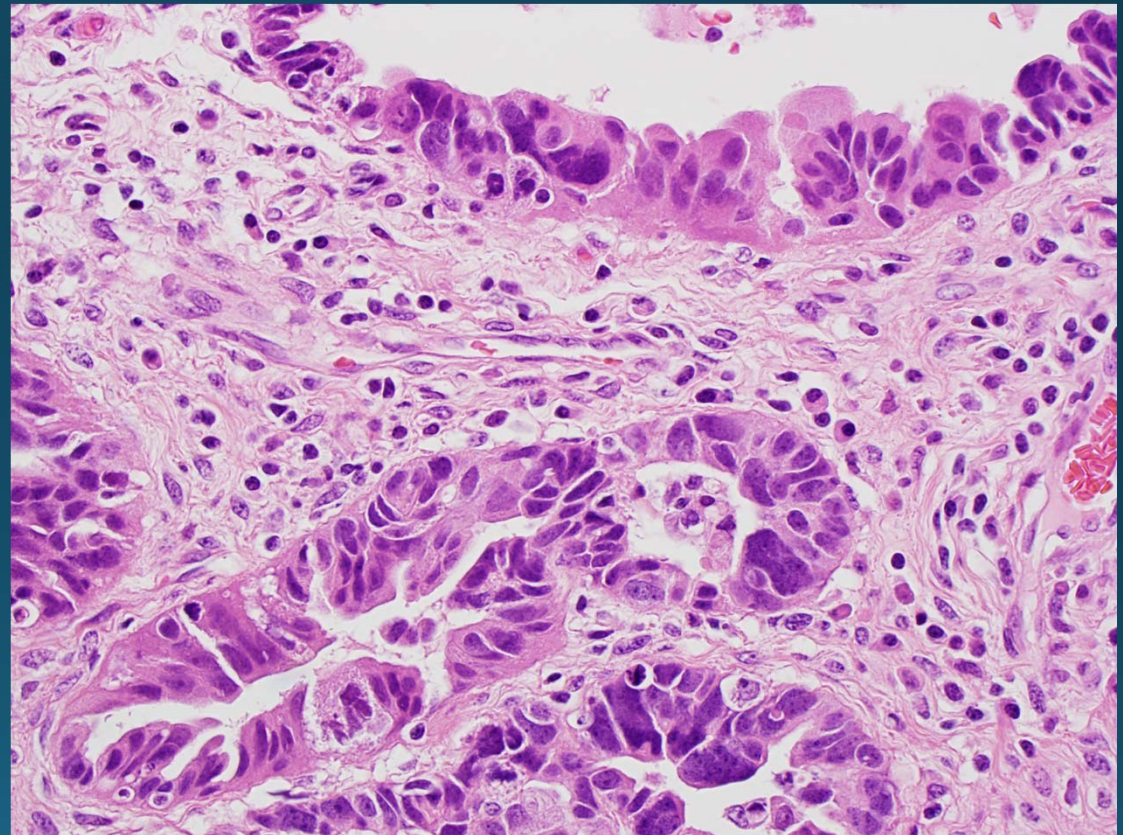
PRE-Rx

POST-Rx



# Potential diagnostic dilemma – Serous endometrial intraepithelial carcinoma (EIC)

- Completely unrelated to EIN
- Putative precursor of serous adenocarcinoma
- Isolated EIC does not behave like a precancer; can spread causing disseminated abdominal disease
- Must exclude EIC when considering dx of EIN





# EIN take home points

- No need to struggle over “atypia” in the classical sense
- Many lesions which were hard to classify with WHO 1994 translate easily to EIN
- Some clinically important lesions missed with WHO 1994 are picked up using EIN
- WHO 2014 adopted EIN – some semantic carryover, but legacy criteria are gone
- At last, down to a 2-class hormonal/precancer system
- Published record of criteria/outcomes all under “EIN” moniker



# EIN take home points

- Make everyone happy in your report:
  - “Endometrial intraepithelial neoplasia (atypical hyperplasia)”
  - “Benign endometrial hyperplasia (hyperplasia without atypia)”



# EIN take home points

- The EIN vs WHO war is over (or really should be)



# References

- Committee on Gynecologic Practice, Society of Gynecologic Oncology. The American College of Obstetricians and Gynecologists Committee Opinion no. 631: Endometrial intraepithelial neoplasia. *Obstet Gynecol* 125(5):1272-8, 2015
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# Objective vs. subjective EIN diagnosis

