Endometriosis and Associated Neoplasms of the Ovary

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Duke University School of Medicine

Outline

- Clinical Case
- Endometriosis
- Endometrioid Neoplasms of the Ovary
- Clear Cell Neoplasms of the Ovary
- Seromucinous Neoplasms of the Ovary

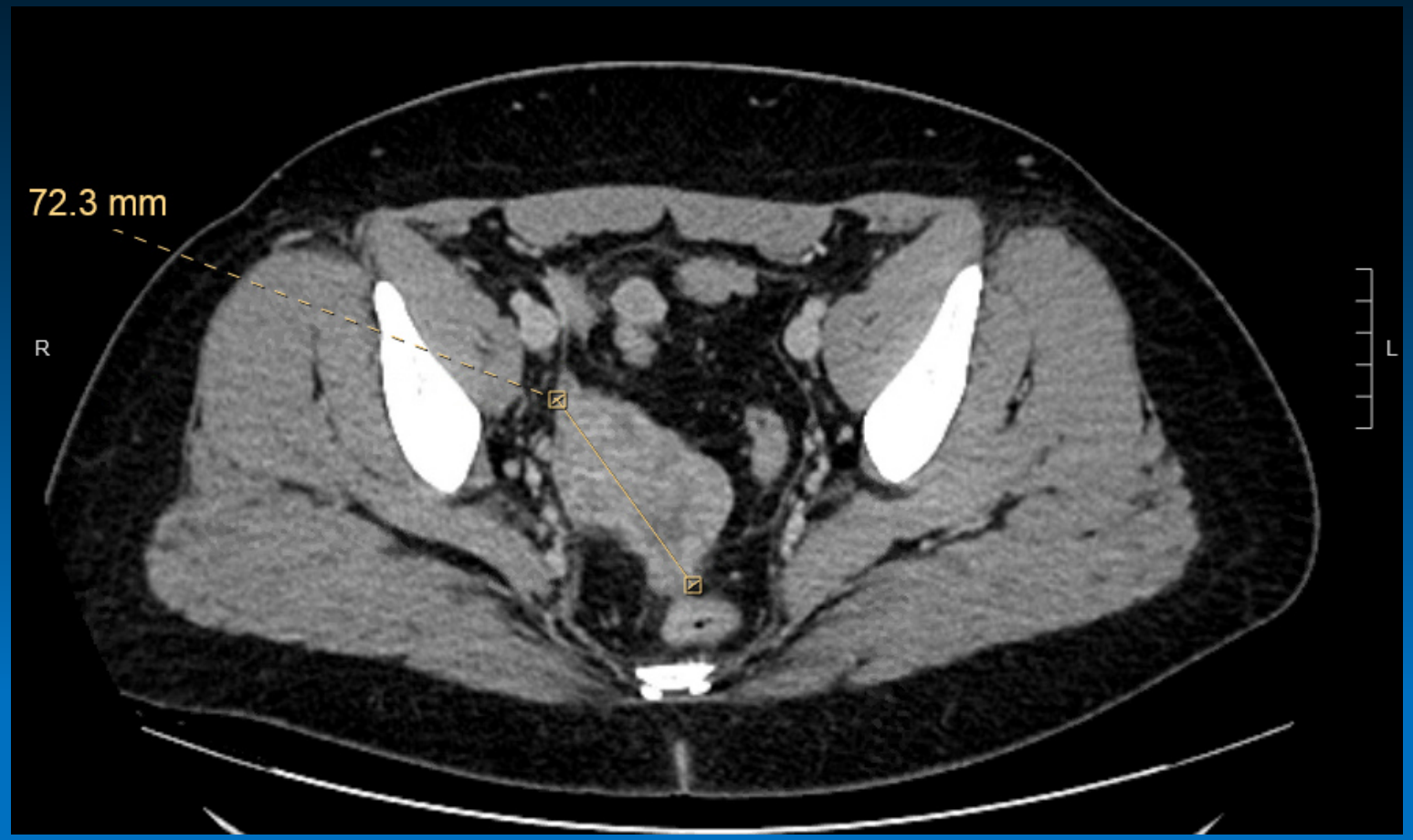
Clinical Vignette

Clinical Vignette – History

- 48 y/o female with persistent abdominal pain and pelvic pressure.
- She has a past medical history significant for papillary thyroid carcinoma, fibroids, and prior pelvic surgery for TLH for fibroids and menorrhagia (13 yr prior), cholecystitis (7 yr prior), and a left ovarian endometrioma (6 yr prior).
- Per the operative note, the right ovary appeared normal at the time of LSO.

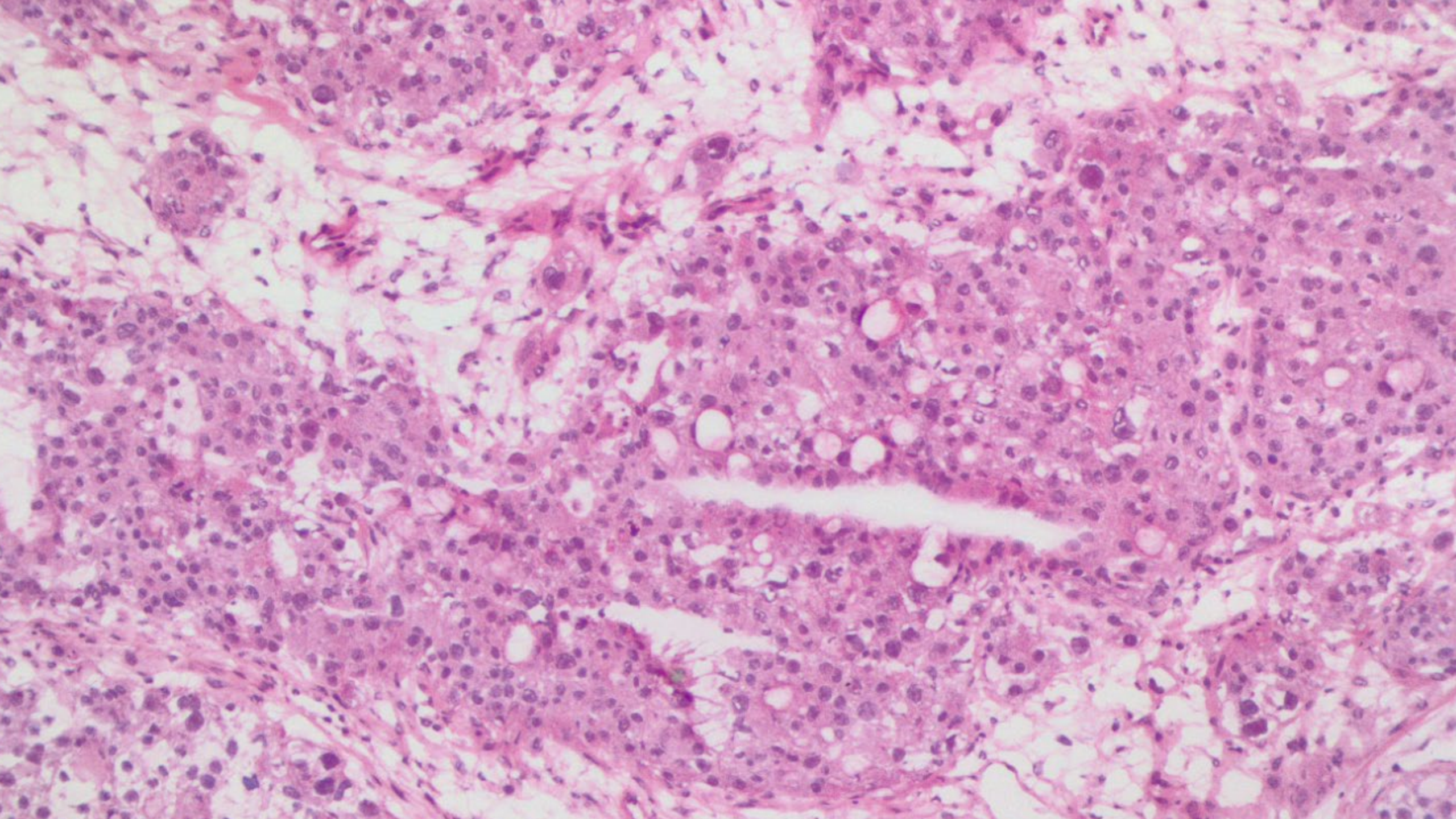
Clinical Vignette – Radiology

- A CT (GU protocol) was performed and demonstrated a large heterogeneously enhancing 7.2 cm mass in the right adnexa.
- A high density nodule measuring 1.7cm anterior to the sigmoid colon is also noted.



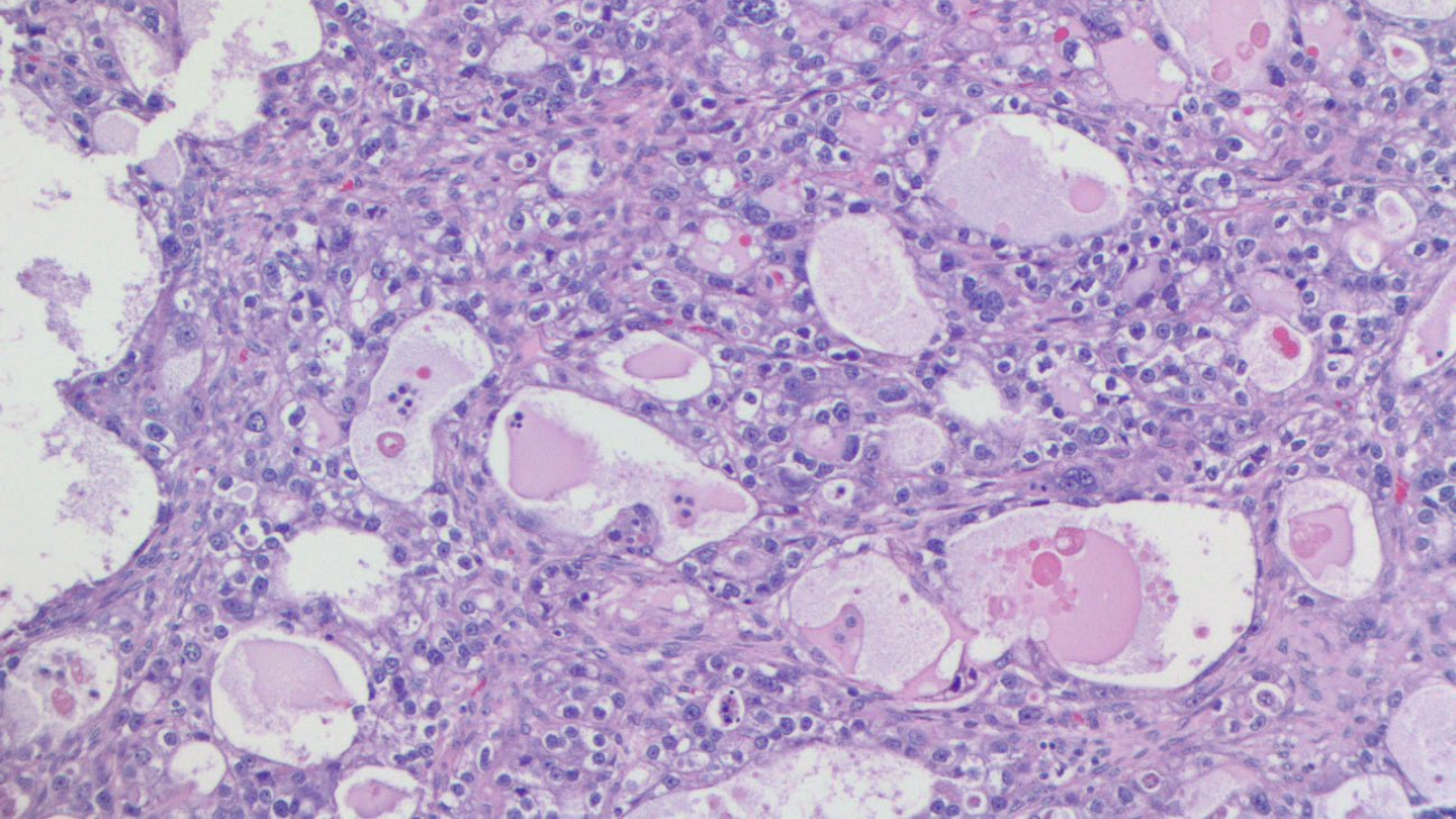
Clinical Vignette – Surgery

- The patient is taken to the OR for RSO, resection of the pelvic mass, and possible staging.

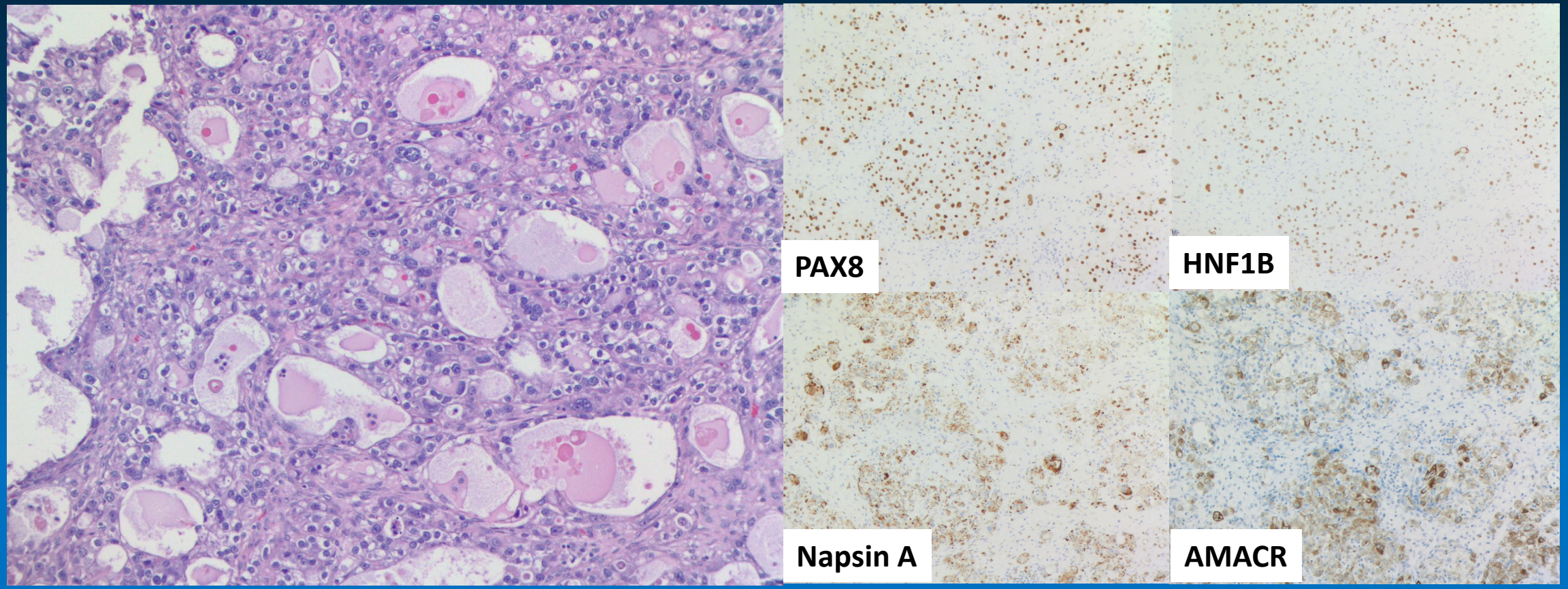


Clinical Vignette – Surgery, cont.

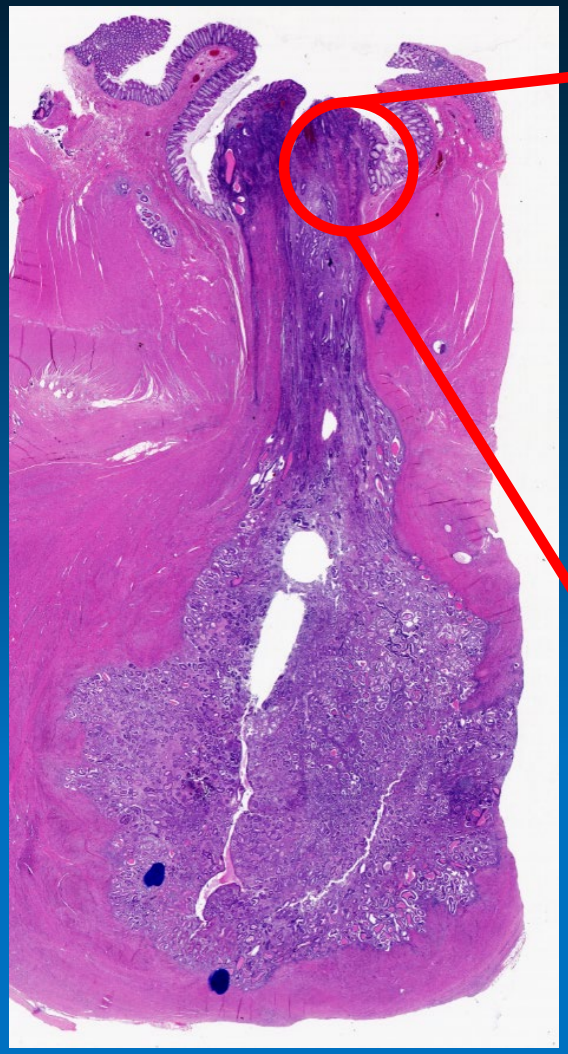
- Omentectomy, peritoneal biopsies, right pelvic lymph node dissection, right para-aortic lymph node sampling, and rectosigmoid resection with reanastomosis is performed for suspected stage 2 disease.

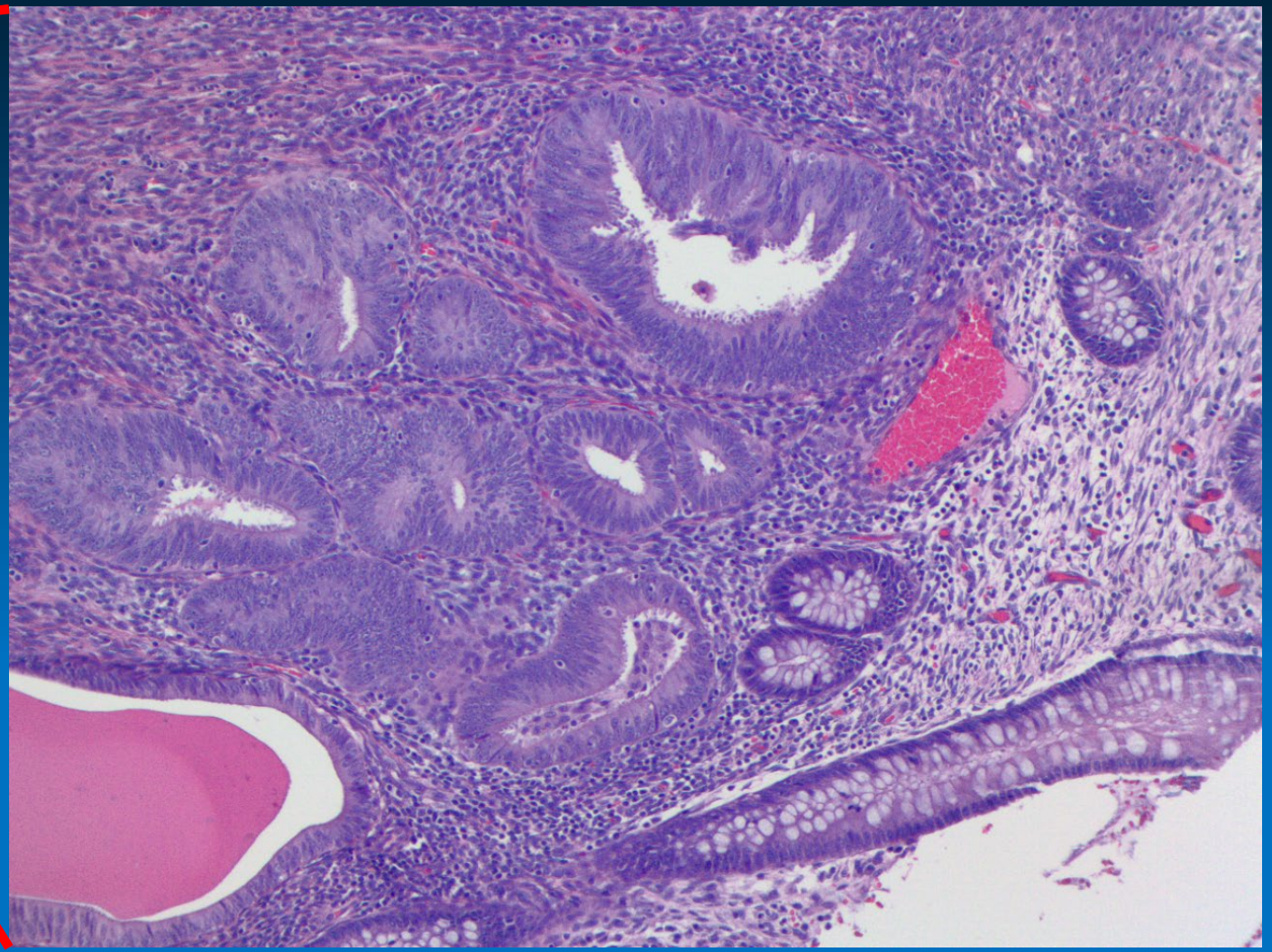


Clinical Vignette – Pathology

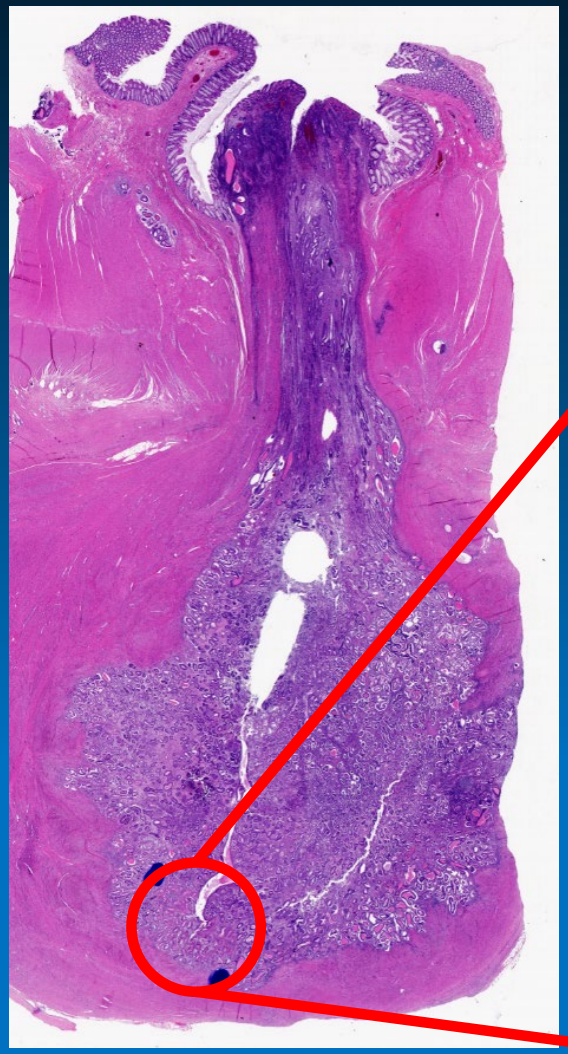


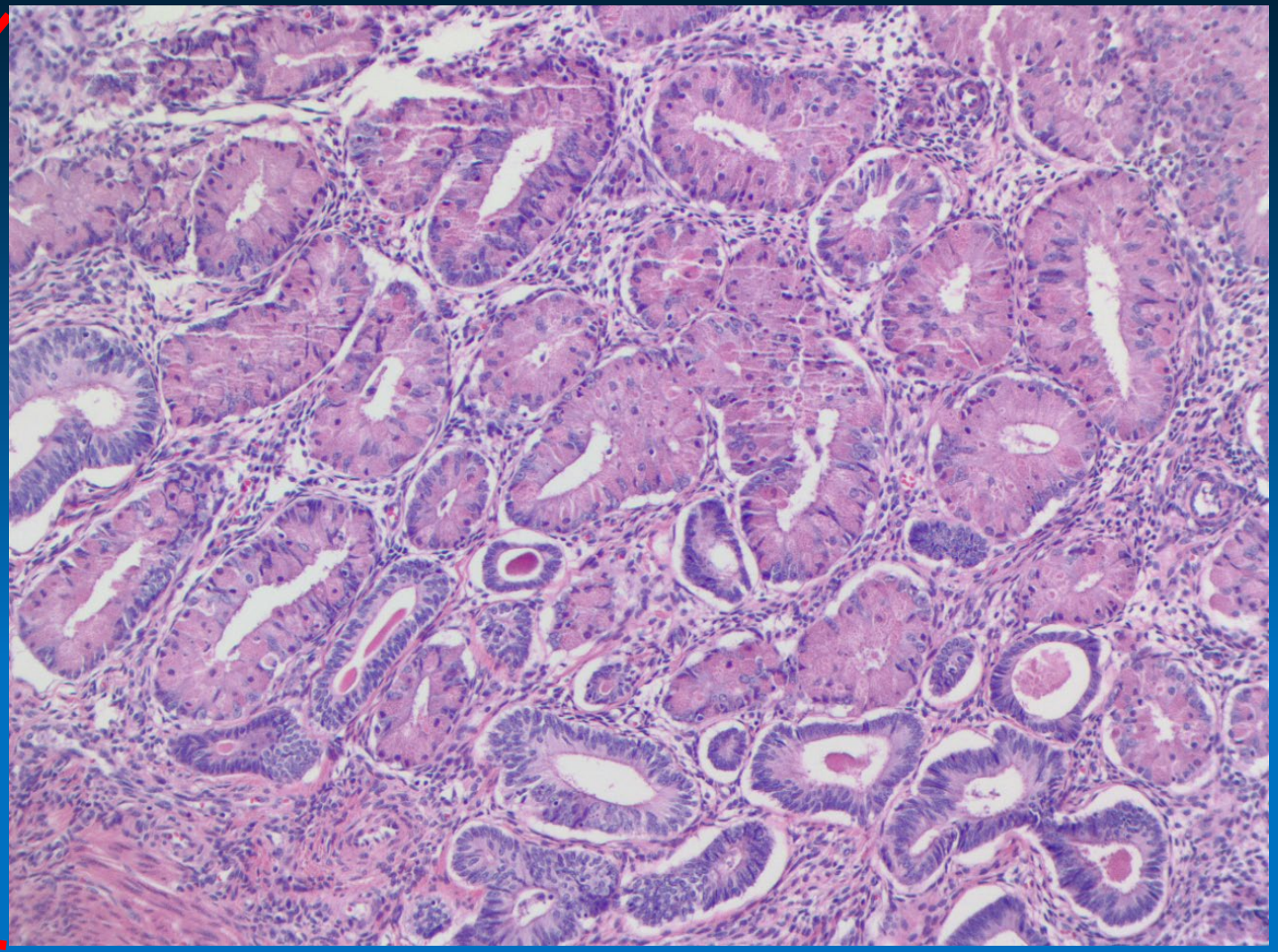
Clinical Vignette – Pathology, cont.





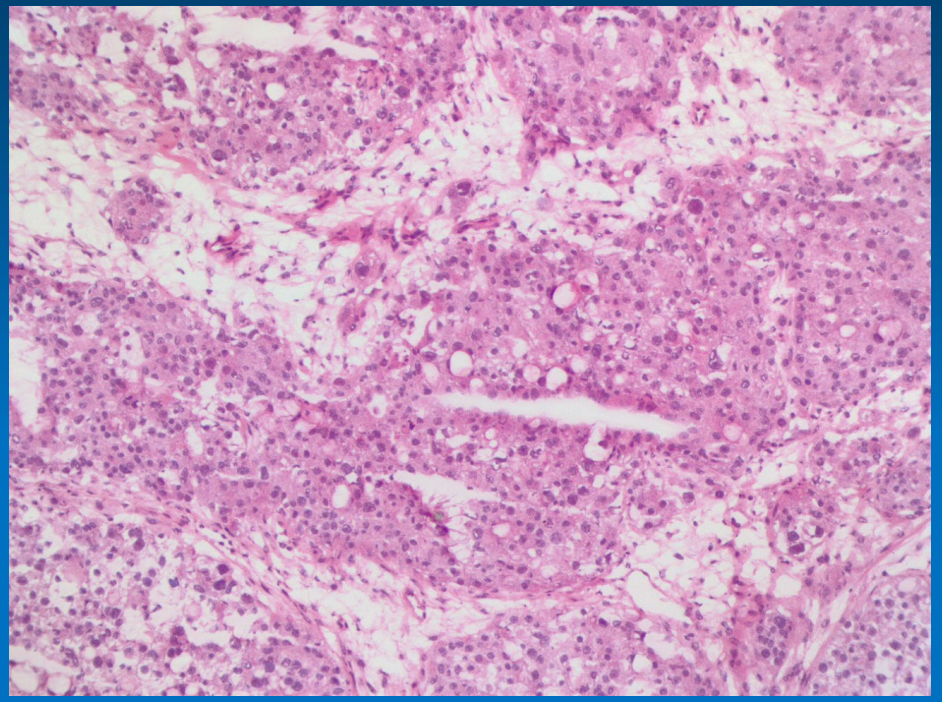
Clinical Vignette – Pathology, cont.

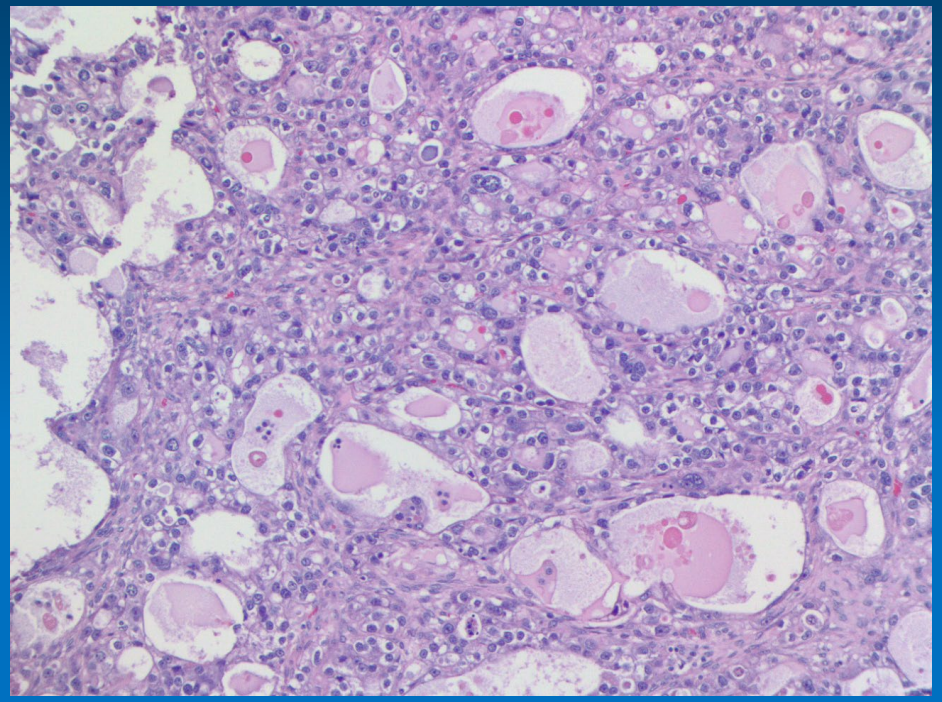




Clinical Vignette – Final Diagnosis

- Stage 1A Clear Cell Carcinoma of the Ovary
- Atypical endometriosis

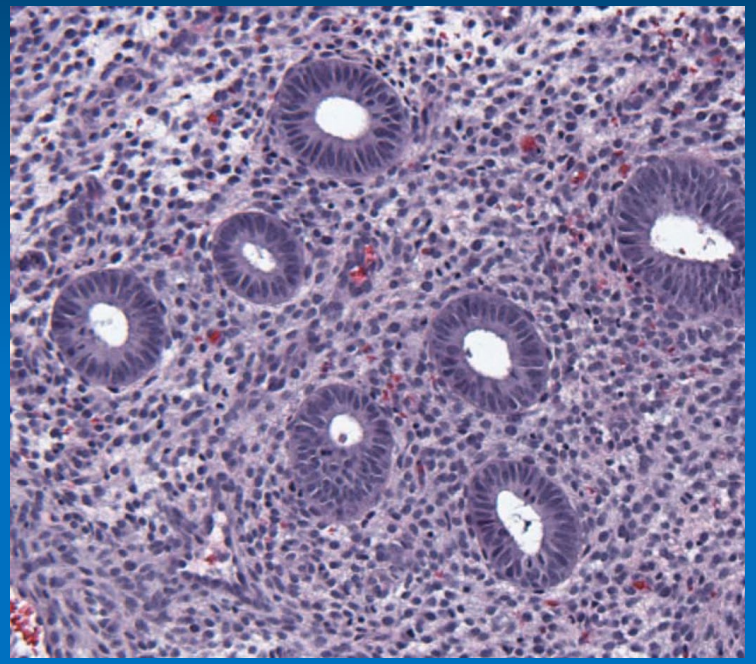


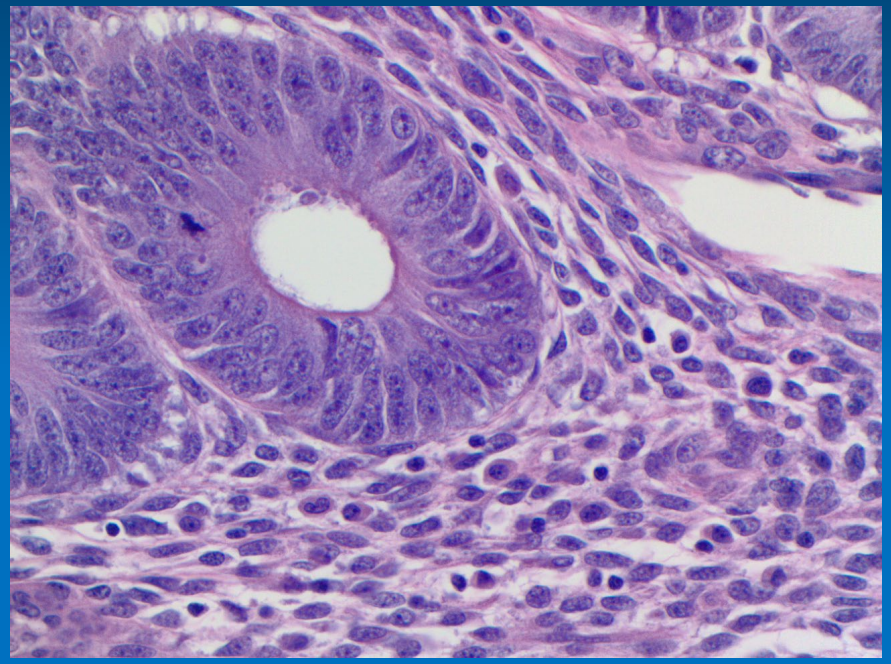


Endometriosis

Endometriosis

- The presence of endometrial glands and stroma outside of the endometrial lining and uterine musculature.





Endometriosis – Epidemiology

- True prevalence is unknown.
- ~10% of reproductive-age women (190 million women worldwide).
- Peak prevalence occurs in women age 25 to 35 yr.

Endometriosis – Risk Factors

- Asian Ethnicity
- Prolong Estrogen Exposure
- Early Age of Menarche
- Short Menstrual Cycles
- Nulliparity
- Low BMI
- Uterine Outlet Obstruction

Endometriosis – Symptoms

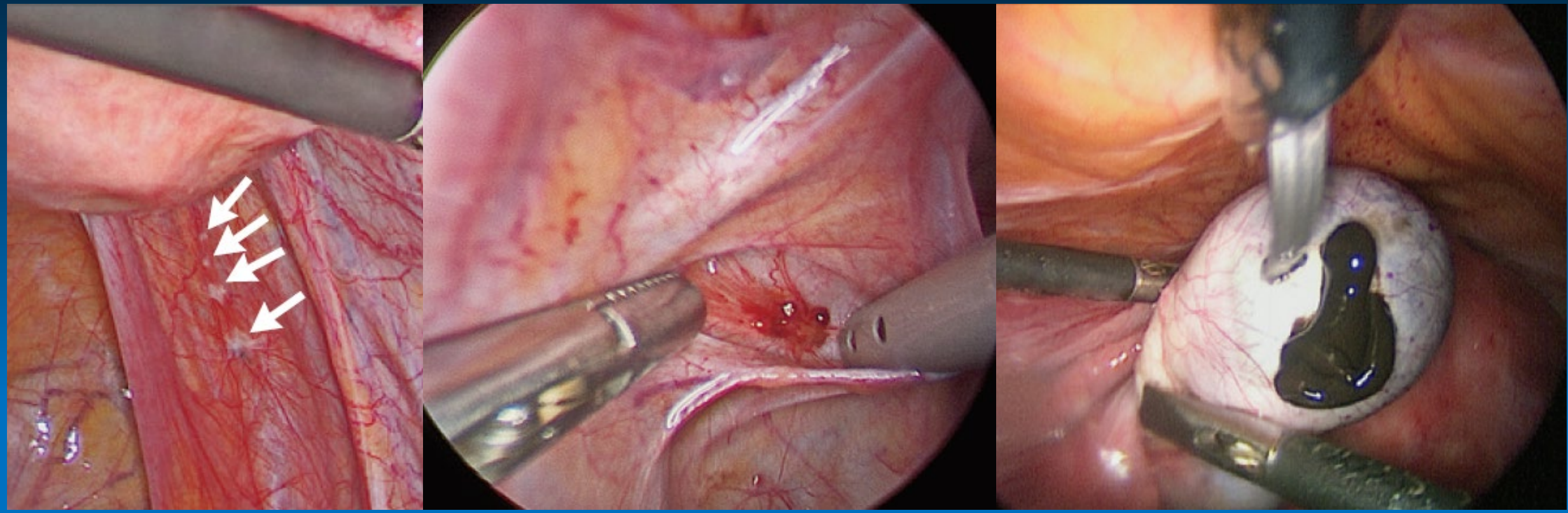
- Diagnosis is often delayed due to vague symptoms.
- Pelvic pain, infertility, or an ovarian mass are most common presentations.
- The site of endometriosis can be associated with atypical symptoms:

Bladder endometriosis

Bowel endometriosis

Thoracic endometriosis

Surgical Evaluation



Zondervan et al. *NEJM*. 2020

Surgical Staging of Endometriosis

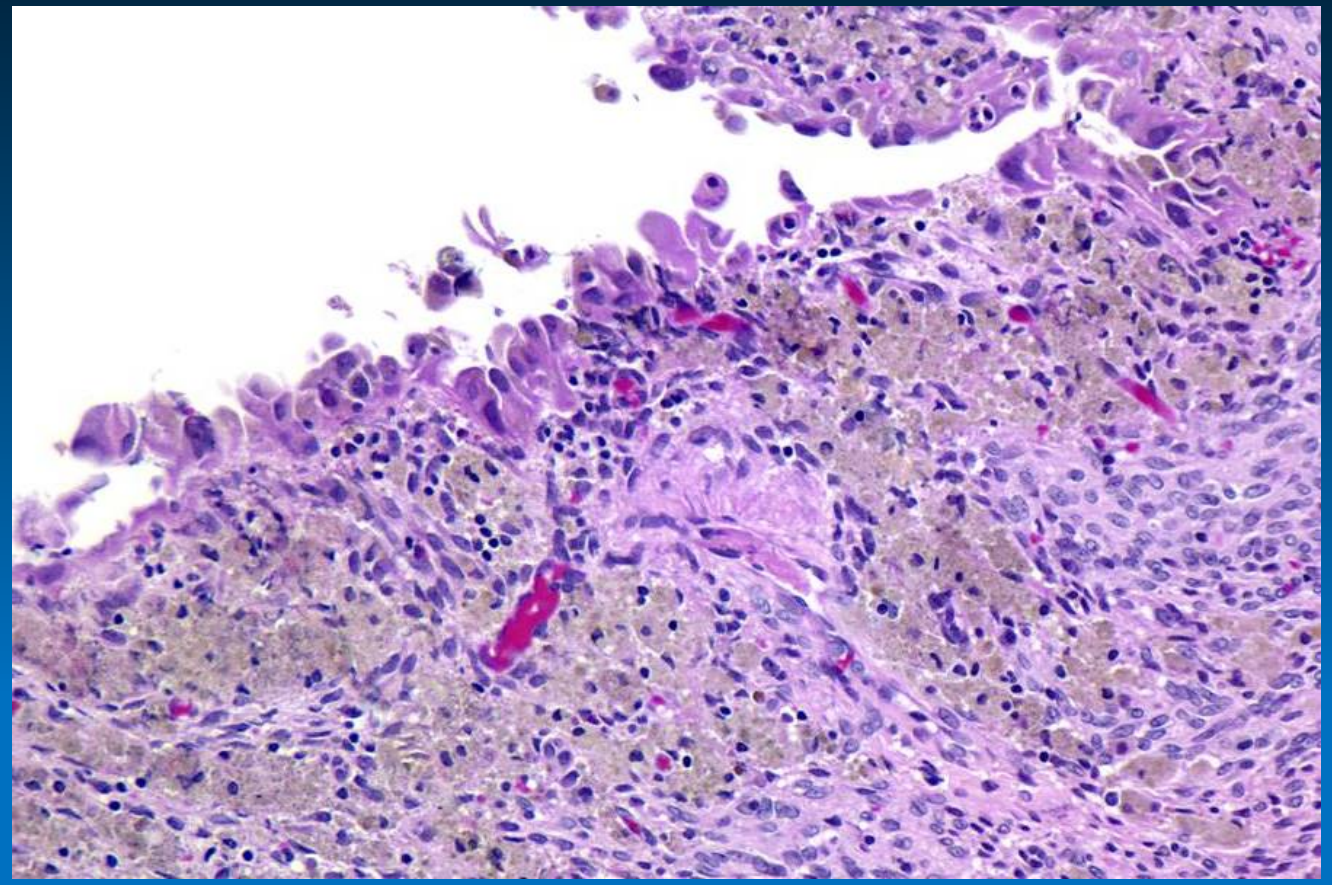
- Stage I – minimal disease with isolated implants and no significant adhesions.
- Stage II – mild disease with superficial implants less than 5 cm in aggregate with no significant adhesions present.
- Stage III – moderate disease with multiple implants both superficial and deeply invasive with peritubal and periovarian adhesions present.
- Stave IV – severe disease with multiple superficial and deep implants with filmy and dense adhesions present.

- * Symptom severity and recurrence is not correlated with stage.

Microscopic Evaluation

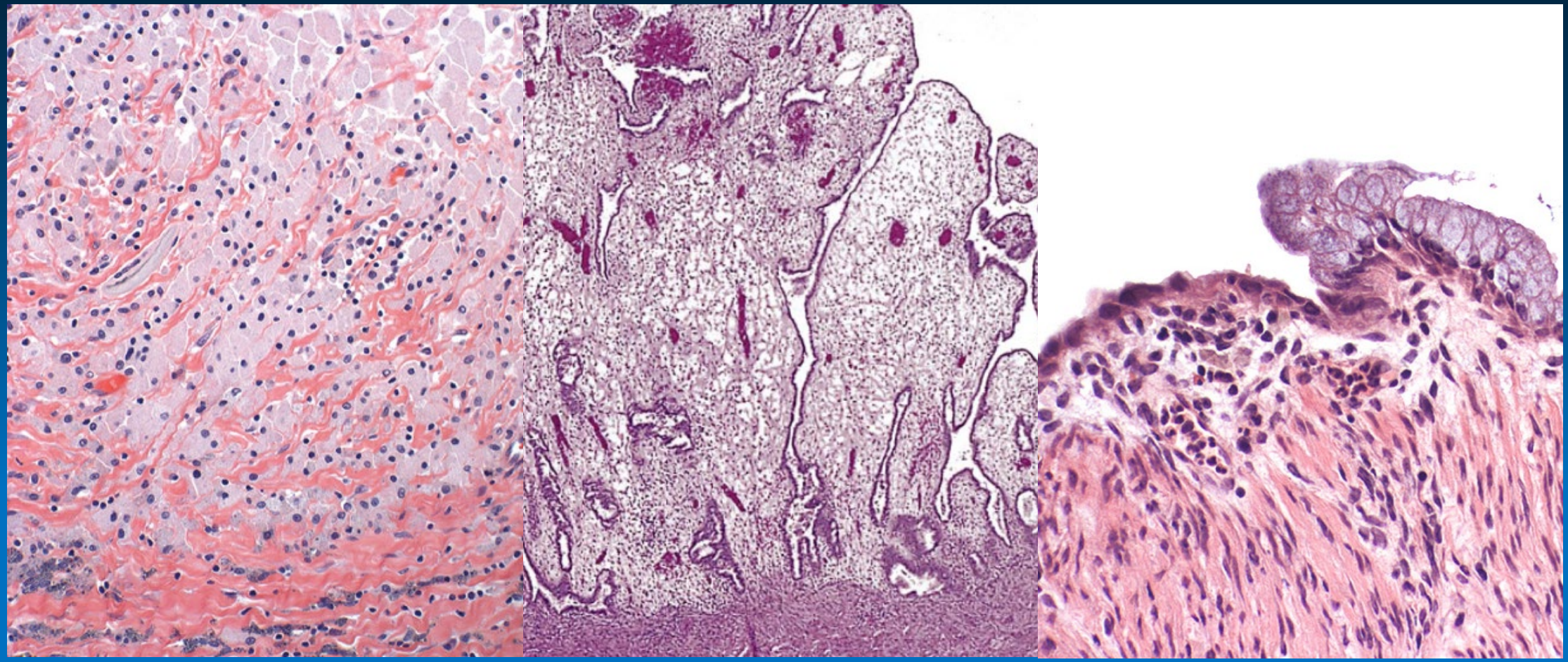
- Histologic diagnosis of endometriosis requires identification of at least 2 of the following:

1) Endometrial Glands
2) Endometrial Stroma
3) Evidence of hemorrhage (e.g. hemosiderin-laden macrophages)



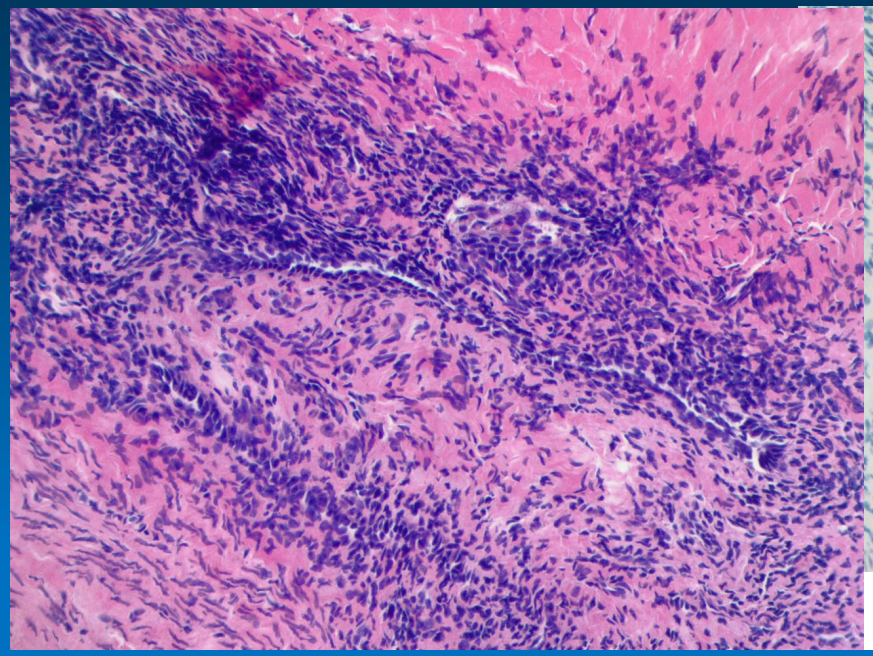
Nucci and Oliva. 2009.

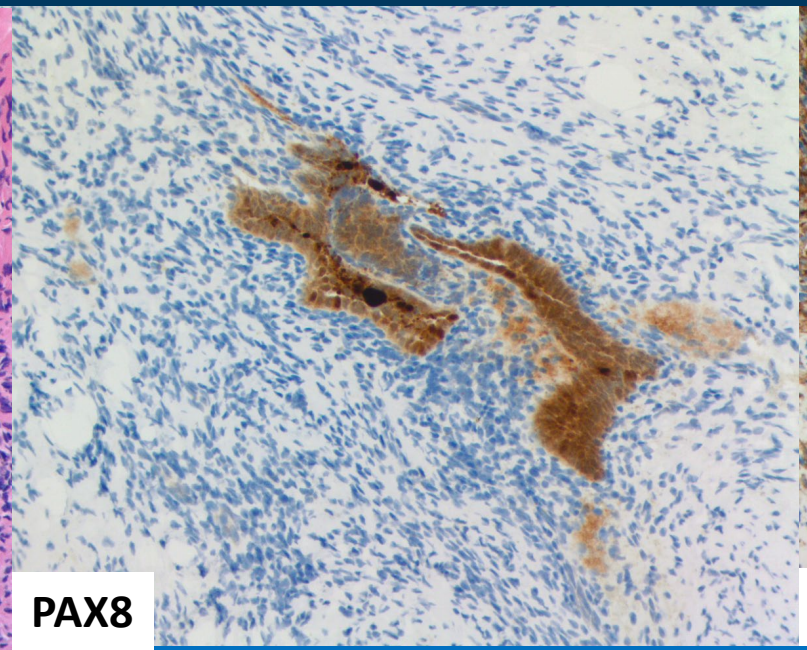
Histologic Appearance of Endometriosis

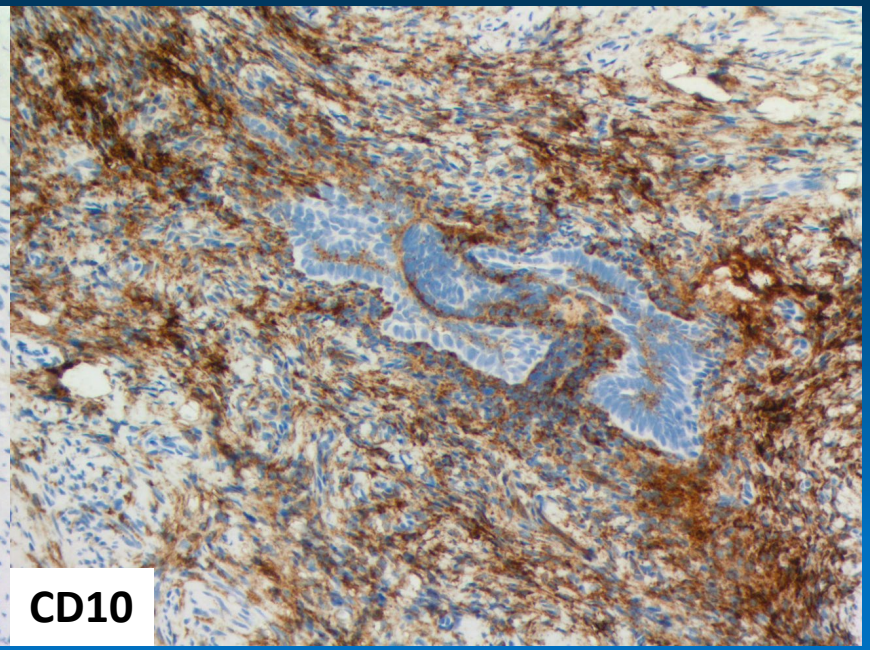


Crum et al. 3rd Edition
Mutter and Prat. 3rd Edition

Immunohistochemistry







Pathogenesis of Endometriosis

Theories include:

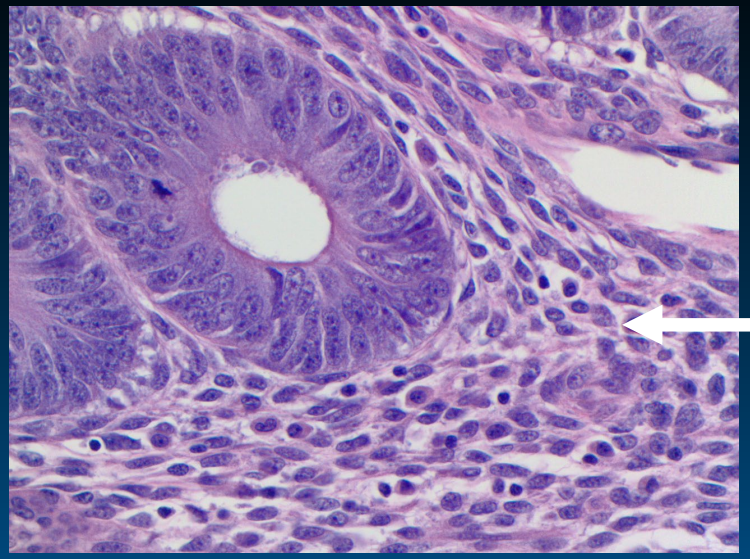
- Retrograde Menstruation and Implantation (Favored Theory)
- Metaplastic Theory (Coelomic Metaplasia)
- Benign Lymphatic/Vascular Metastasis
- Progenitor Cell Theory (Differentiation)

Endometriosis is a benign lesion but shares several characteristic with invasive cancer

1. Has the capacity to invade and damage tissues

2. Can spread to distant locations

Women with endometriosis have an increased risk of developing epithelial ovarian cancer.



Stromal Cells → Chemokines (CC and CXC)

↑ Aromatase

↑ Estradiol

↑ Inflammatory Cells

↑ Inflammatory Cytokines (TNFα, IL1β, IL6)

↑ Proangiogenic Factors (VEGF)

↑ Growth Factors

↑ Adhesion Molecules

↑ Survival and persistence of endometriotic tissue in a foreign location

– AND a ***pro-neoplastic environment***

Molecular Genetic Abnormalities in Endometriosis

- Benign endometriotic tissue harbors genetic defects that are permissive for malignant transformation.
- Loss of heterozygosity and somatic mutations in *PTEN* have been identified in 57% and 21% of endometriotic cysts, respectively (Sato et al.
- Whole exome sequencing detected somatic mutations in 79% of samples of deeply infiltrative endometriosis, with 26% harboring mutations in *KRAS*, *PIK3CA*, and *ARID1A* (Anglesio et al., *NEJM*, 2017).

Endometriosis and Risk of Ovarian Malignancy

- The frequency of malignant transformation has been estimated to be between 0.9% and 2.9% (Stern, Dash, Bentley et al. 2001).

- Women with endometriosis are predisposed to ovarian cancer, restricted to endometriod (RR 2.53) and clear cell (RR 3.37) subtypes (Brinton et al., 2000)

Malignant Transformation of Endometriosis

Pathologic criteria for establishing an origin of malignancy from endometriosis includes the following:

1) Both cancer and benign endometrial tissue should be seen in the same organ.
2) Both should have a continuous histologic relation to each other.
3) The cancer must be shown to have arisen in this tissue and not invading it from some other source.
4) The tumor should be of a histologic type known to arise in native endometrium.
5) A gradual transition from benign to malignant epithelium is helpful, or at least documented atypia in the endometriosis adjacent to the malignancy.

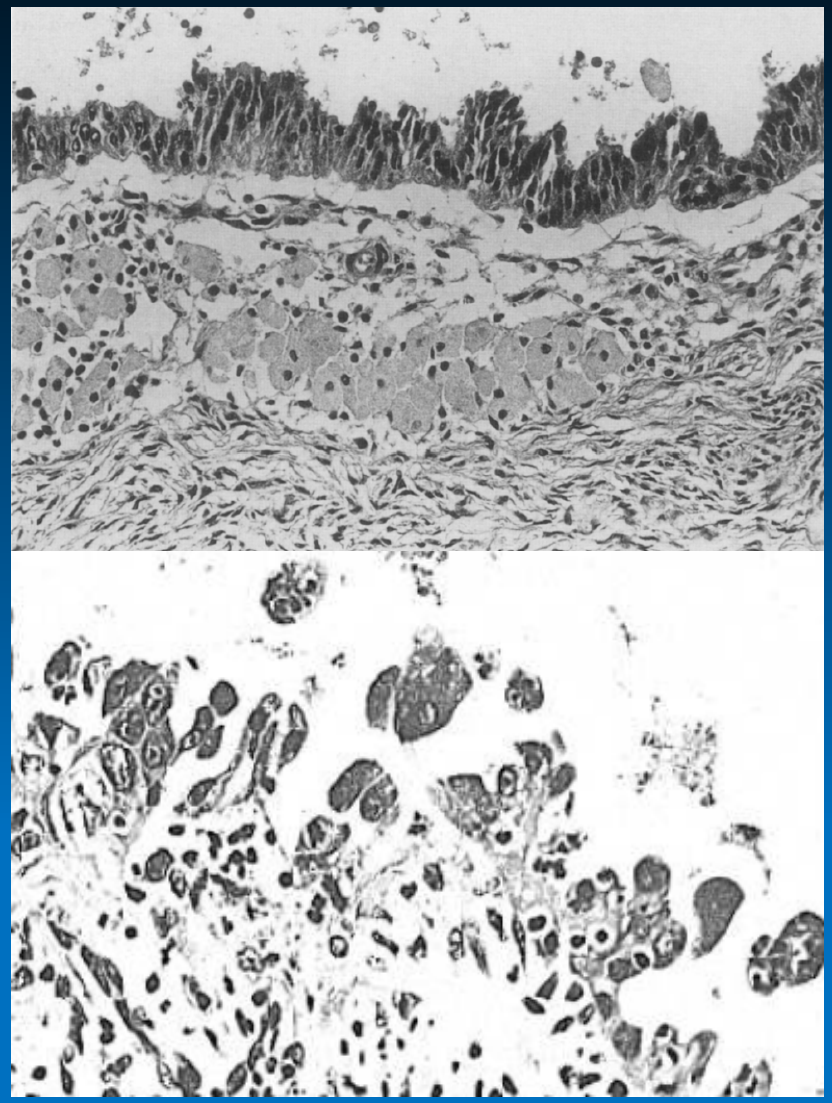
Mutter and Prat, 3rd Edition.

Atypical Endometriosis, Types

Practically speaking, there are two different histologic types of atypical endometriosis:

- Atypical Endometriosis, Endometrioid Type: Features intermediate between endometriosis and endometrioid adenocarcinoma, resembling endometrial intraepithelial neoplasia.

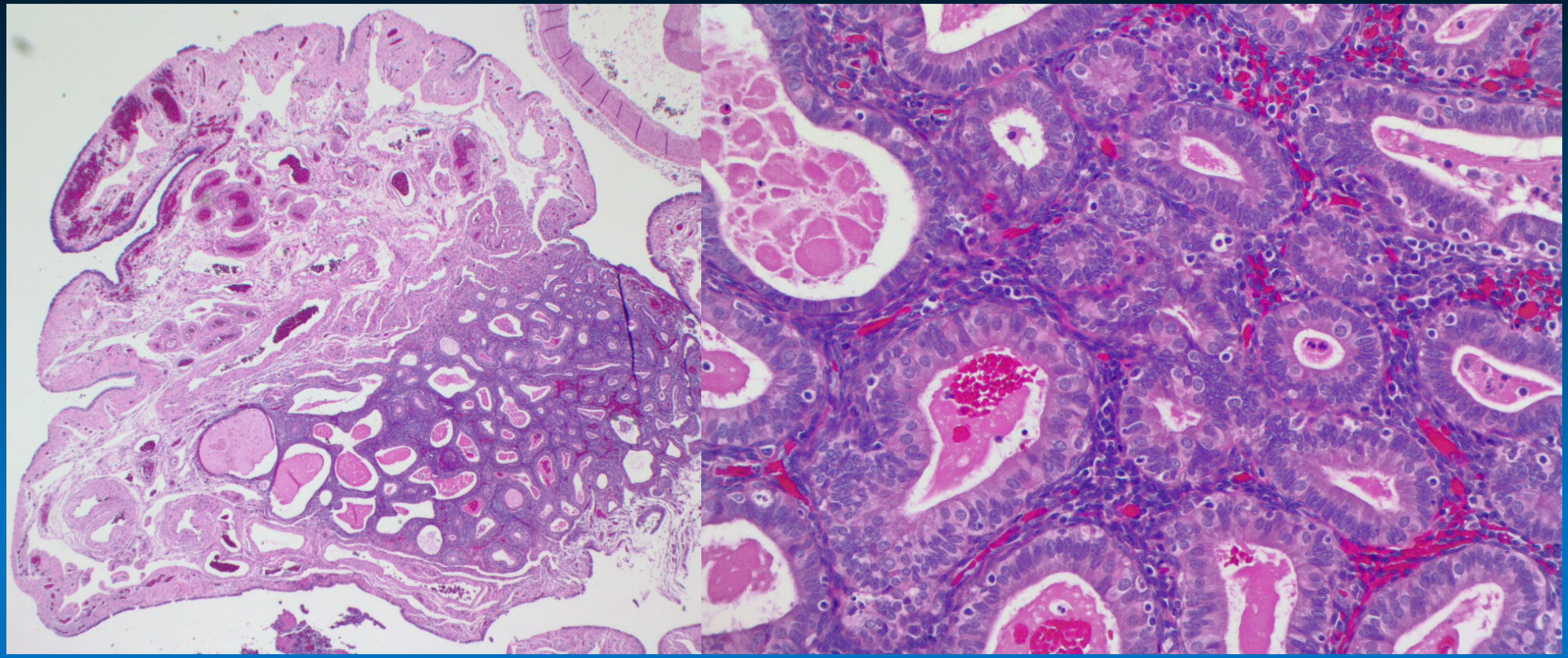
- Atypical Endometriosis, Clear Cell Type: Exfoliative atypical epithelium that is flat or hobnail like.



Mutter and Prat, 3rd Edition.

Czernobilksy and Morris, 1979.
LaGrenade and Silverberg, 1988.

Atypical Endometriosis



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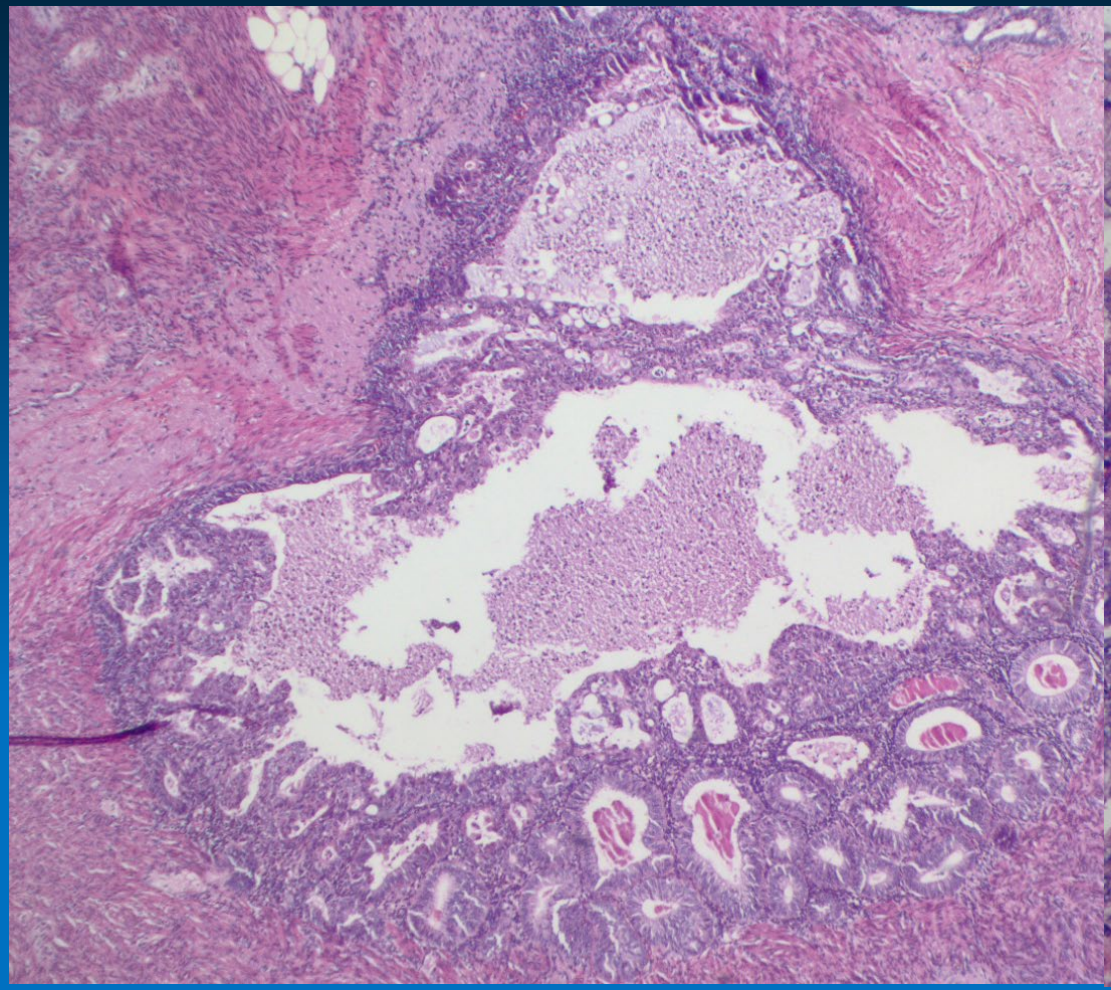

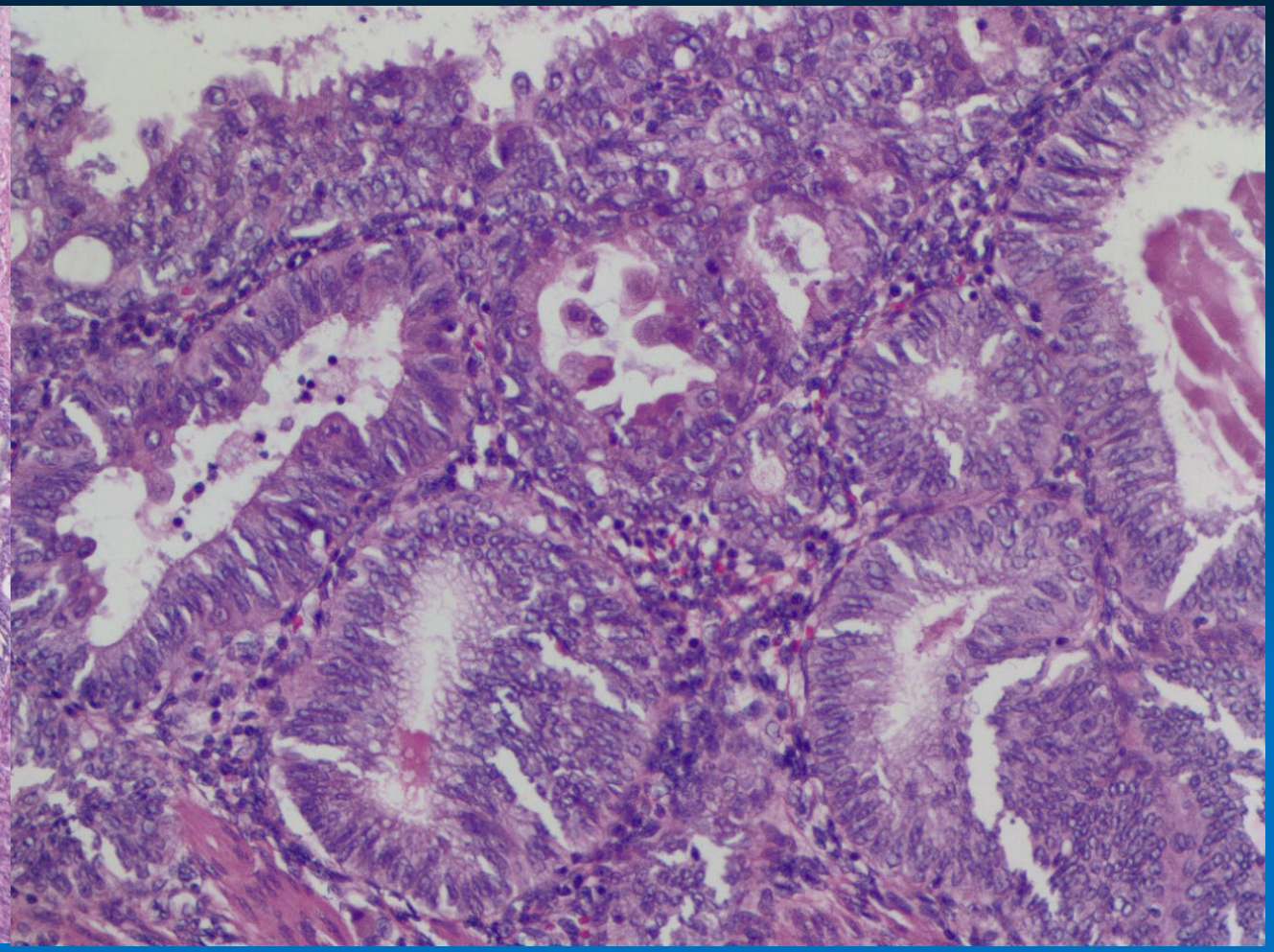

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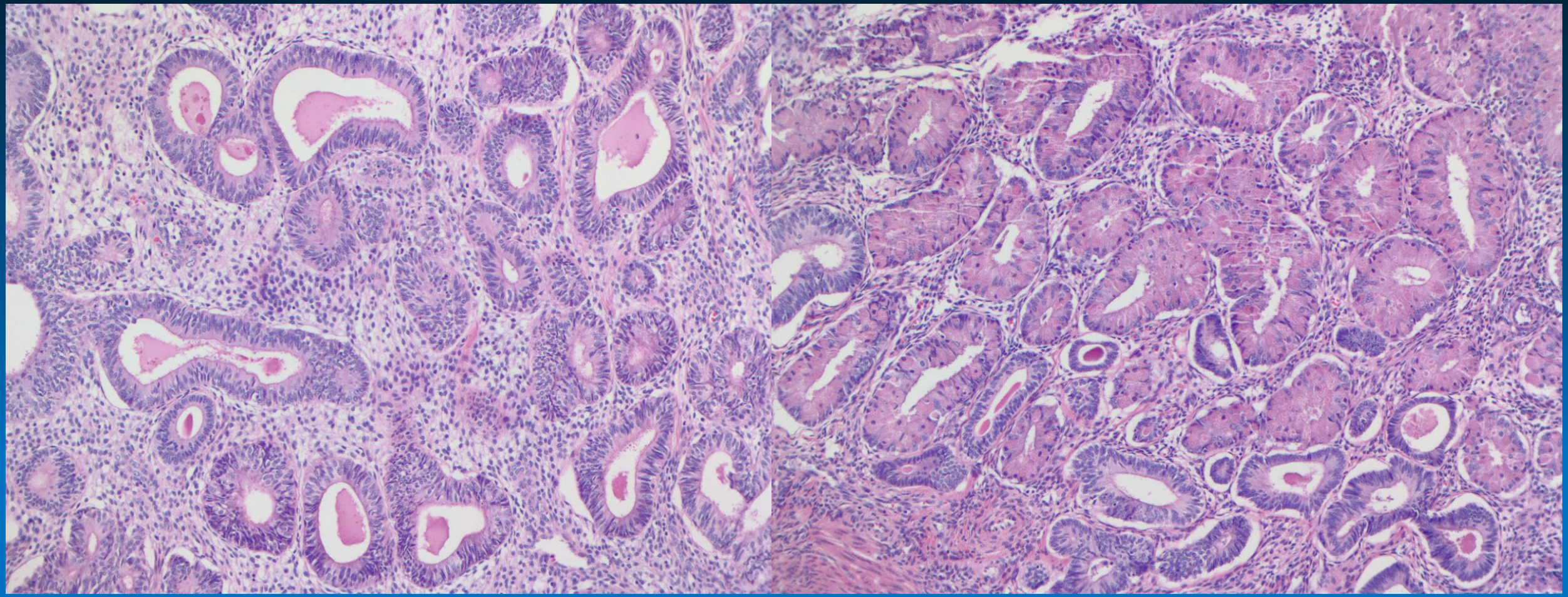

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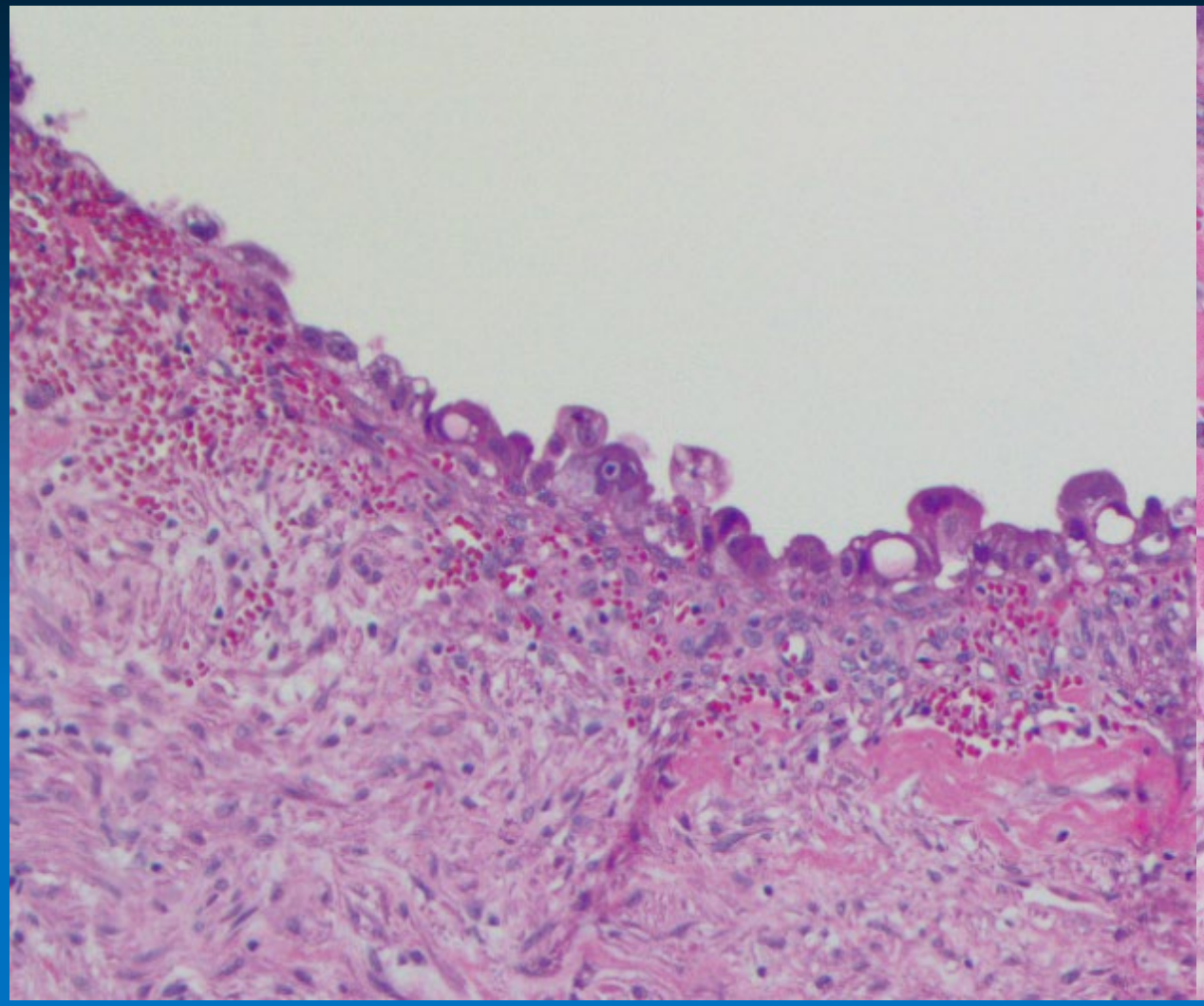
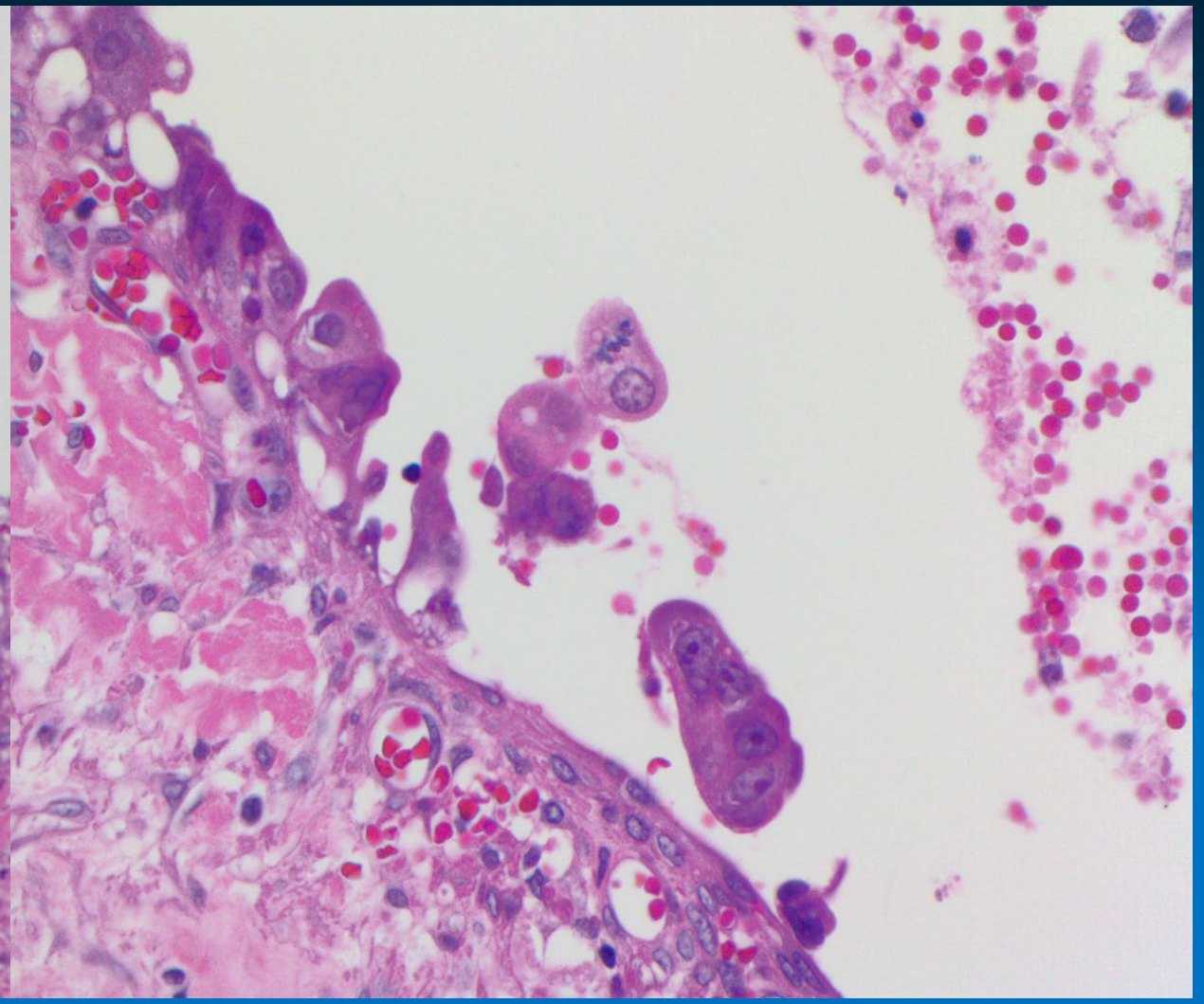
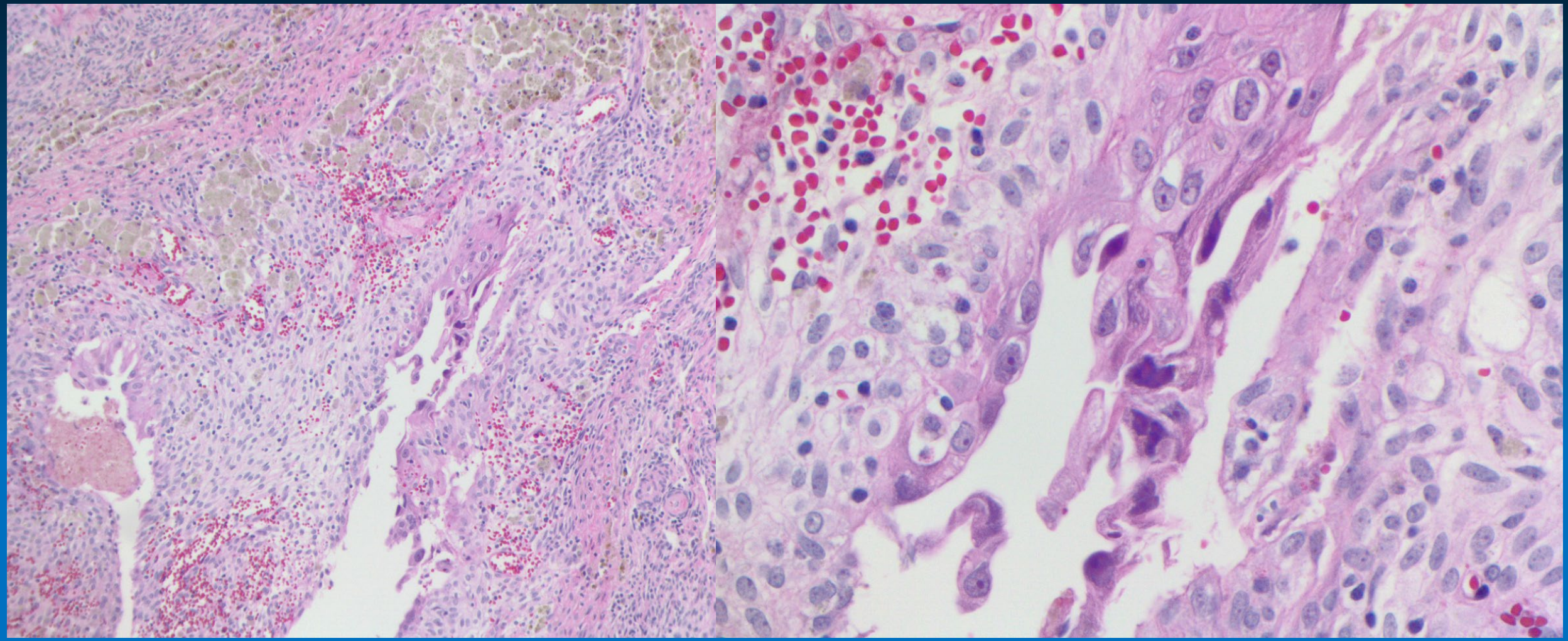




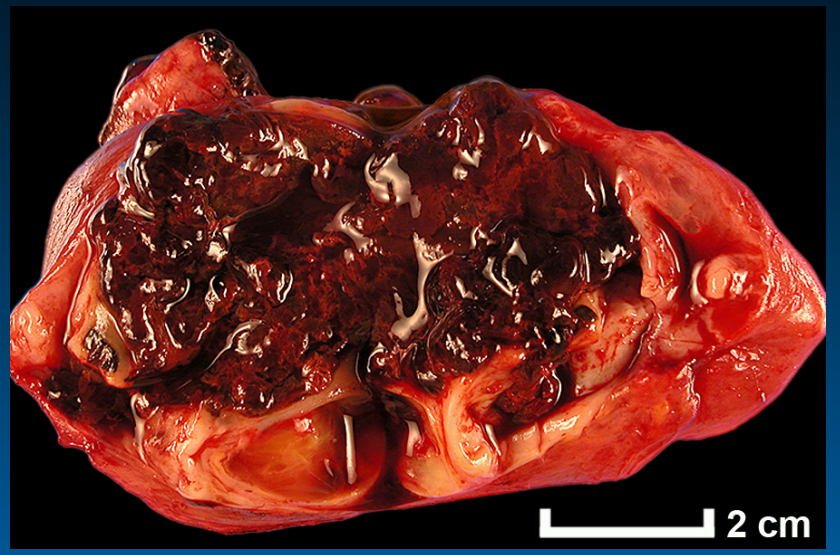
Atypical Endometriosis

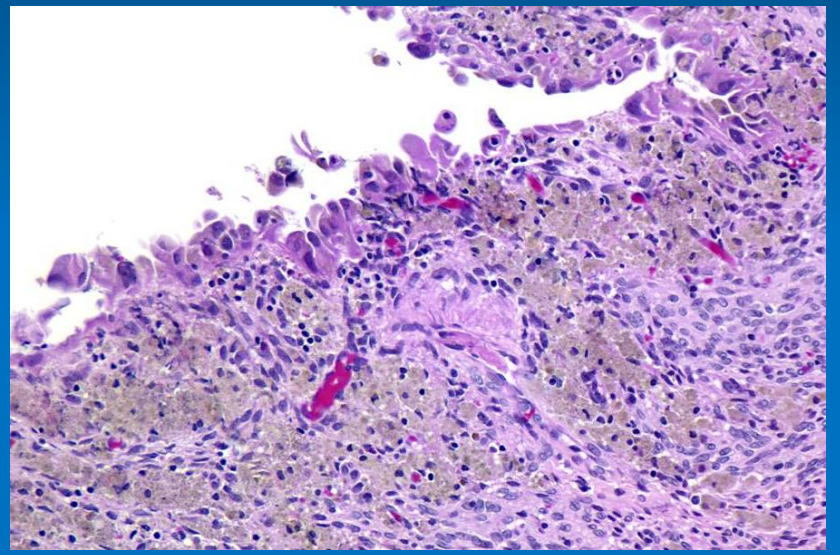


Endometrioid Tumors of the Ovary

Endometrioma

- Cystic forms of endometriosis, may or may not be associated with endometriosis elsewhere in the pelvis.
- A common cause of ovarian enlargement in 30's and 40's.
- Can present with pain.
- Cyst contents are typically dark brown due to old hemorrhage (chocolate cyst).
- Cysts are lined by endometrial epithelium overlying endometrial stroma. Hemosiderin-laden macrophages and fibrosis are seen.
- Harbor genetic mutations seen in endometrioid adenocarcinomas and clear cell carcinomas of the ovary, suggesting they are precursors.
- Risk of malignancy increases with age.



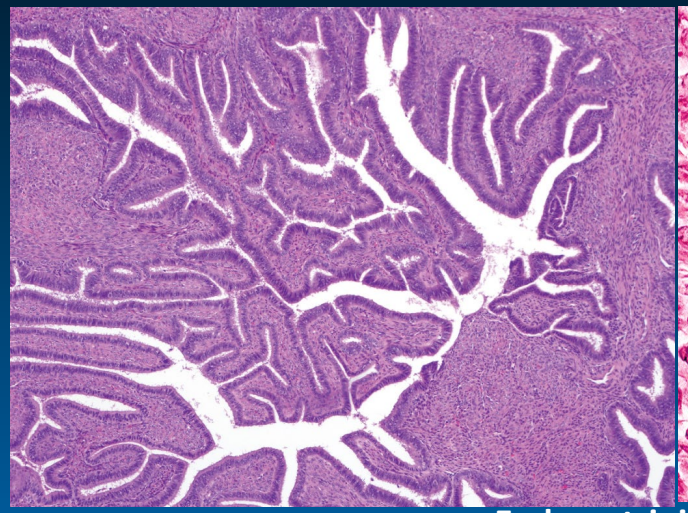


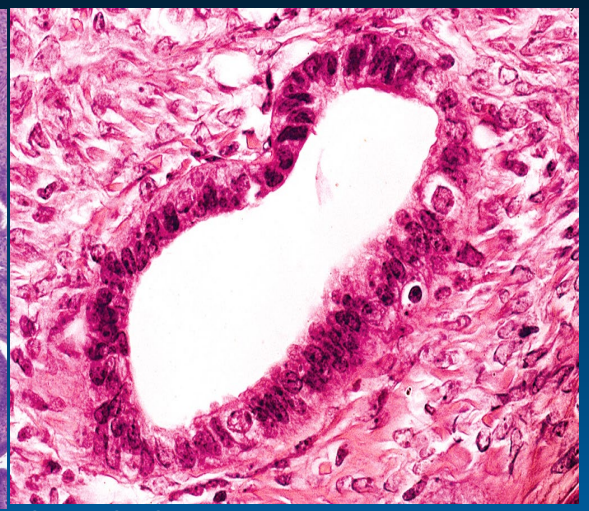
Nucci and Oliva. 2009.

Endometrioid Borderline Tumor

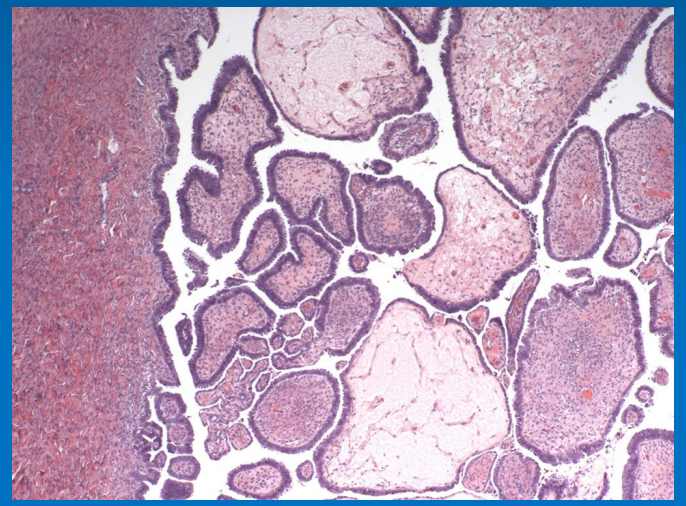
- Benign endometrioid tumors are really rare (<1% of all benign ovarian tumors)
- Mean age 55 years (28-86)
- 63% associated with endometriosis
- Prognosis is excellent.

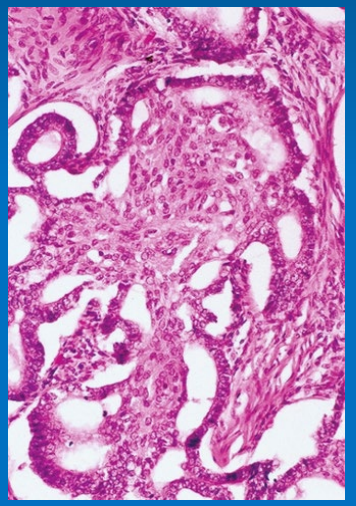
Endometrioid Adenofibroma





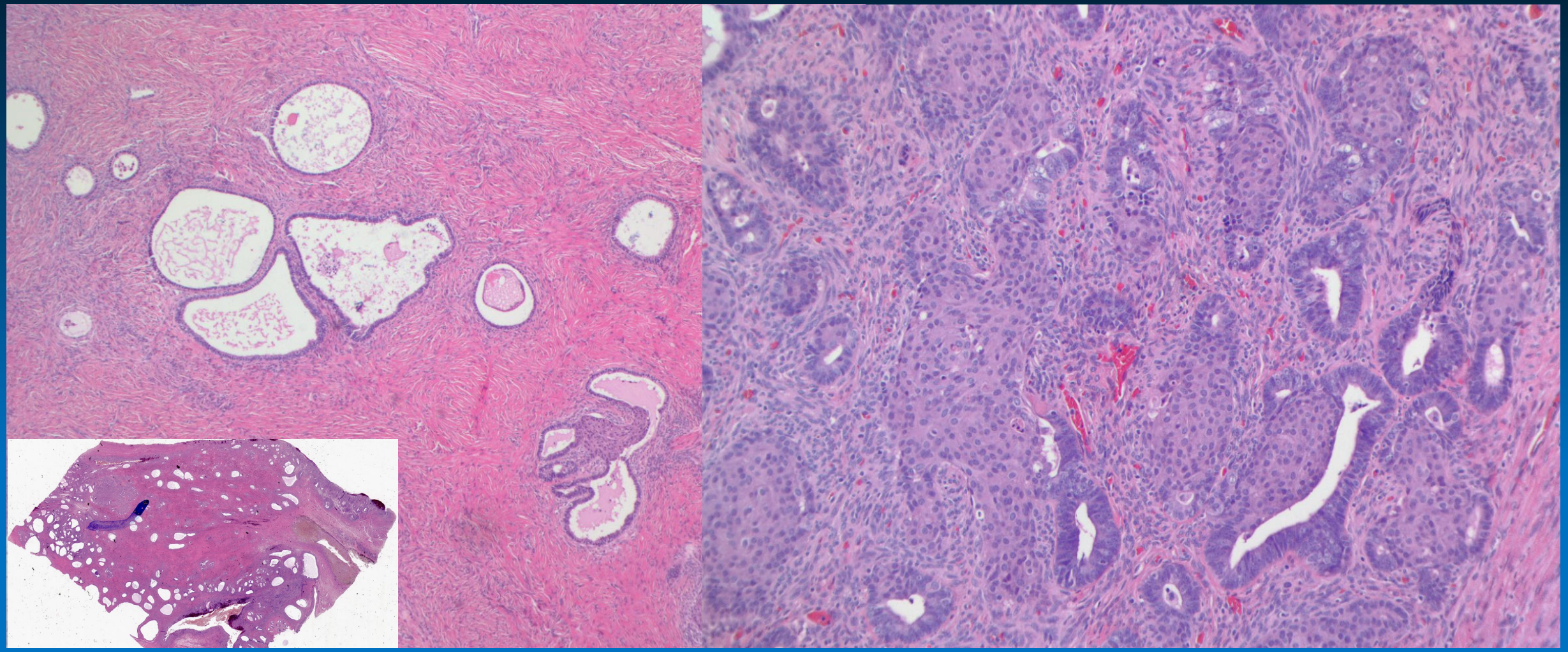
Endometrioid Borderline Tumor



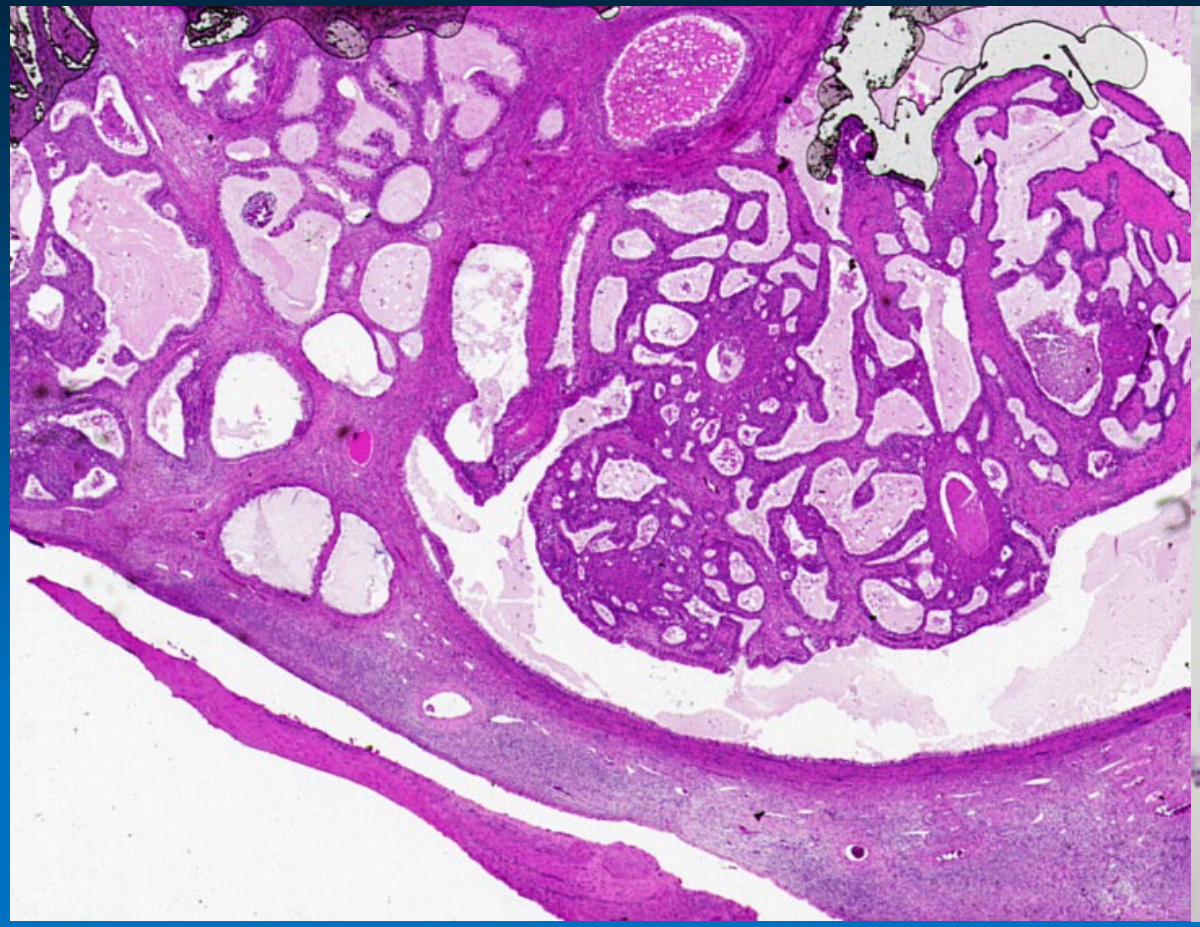


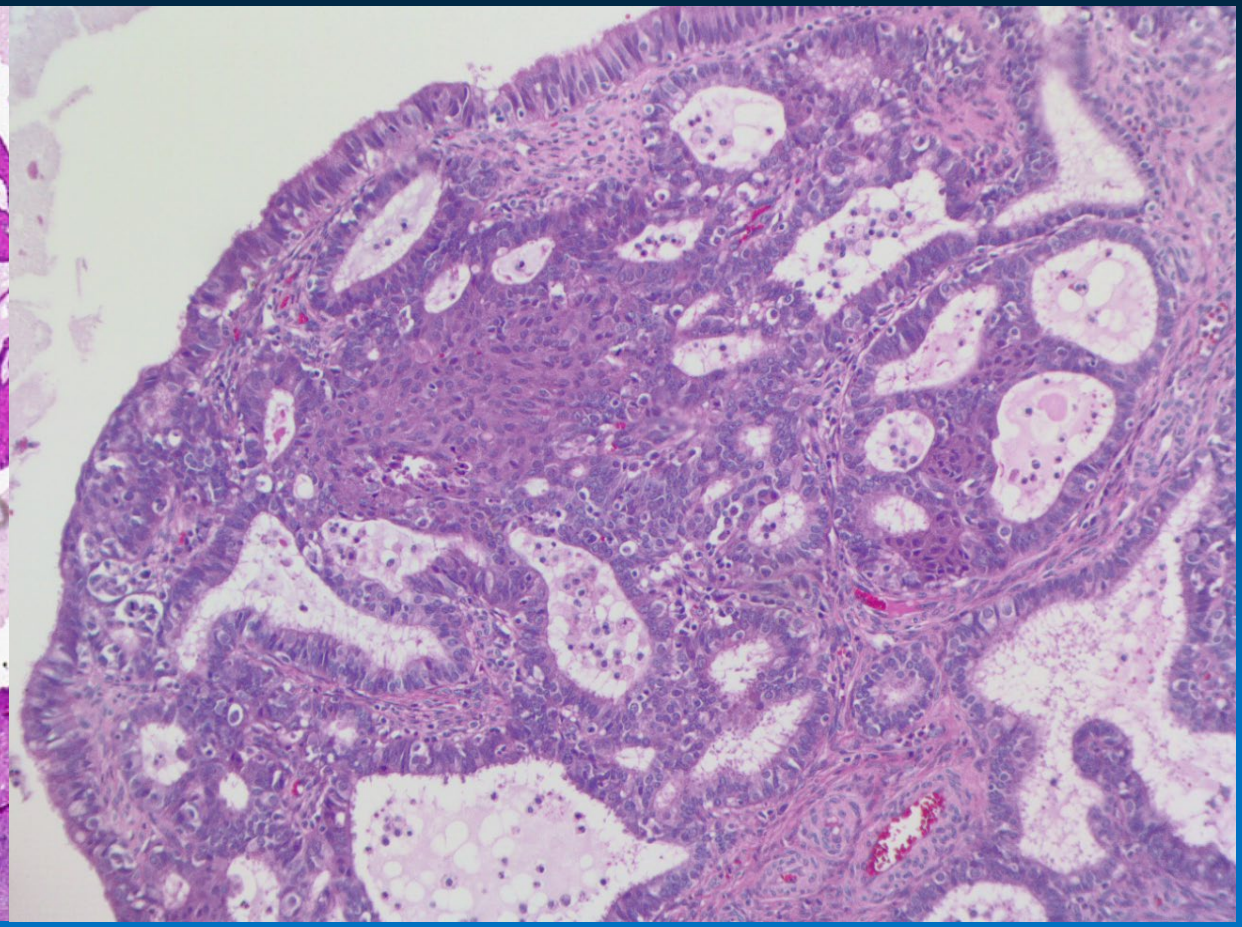
Crum *et al.*, 3rd Edition

Endometrioid Borderline Tumor

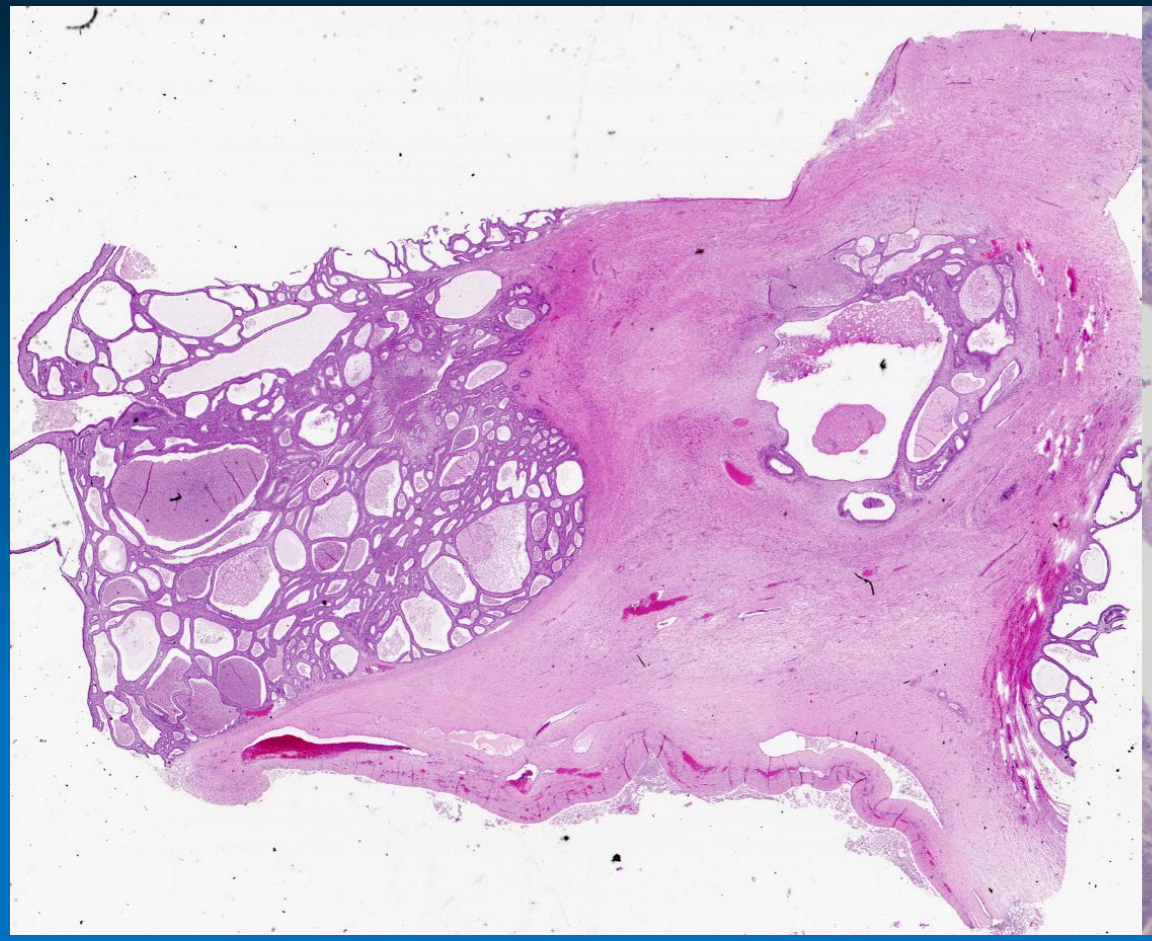


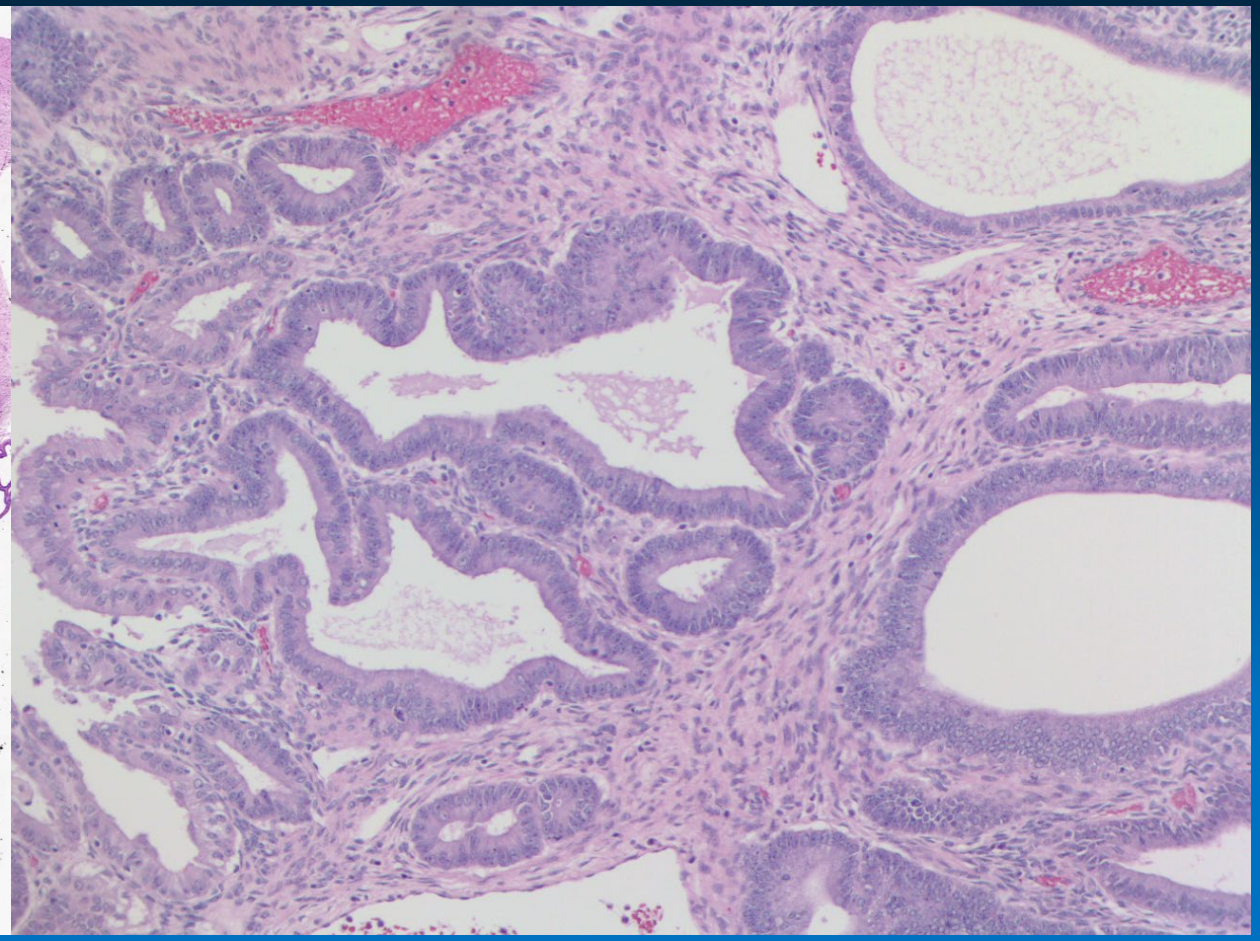
Endometrioid Borderline Tumor





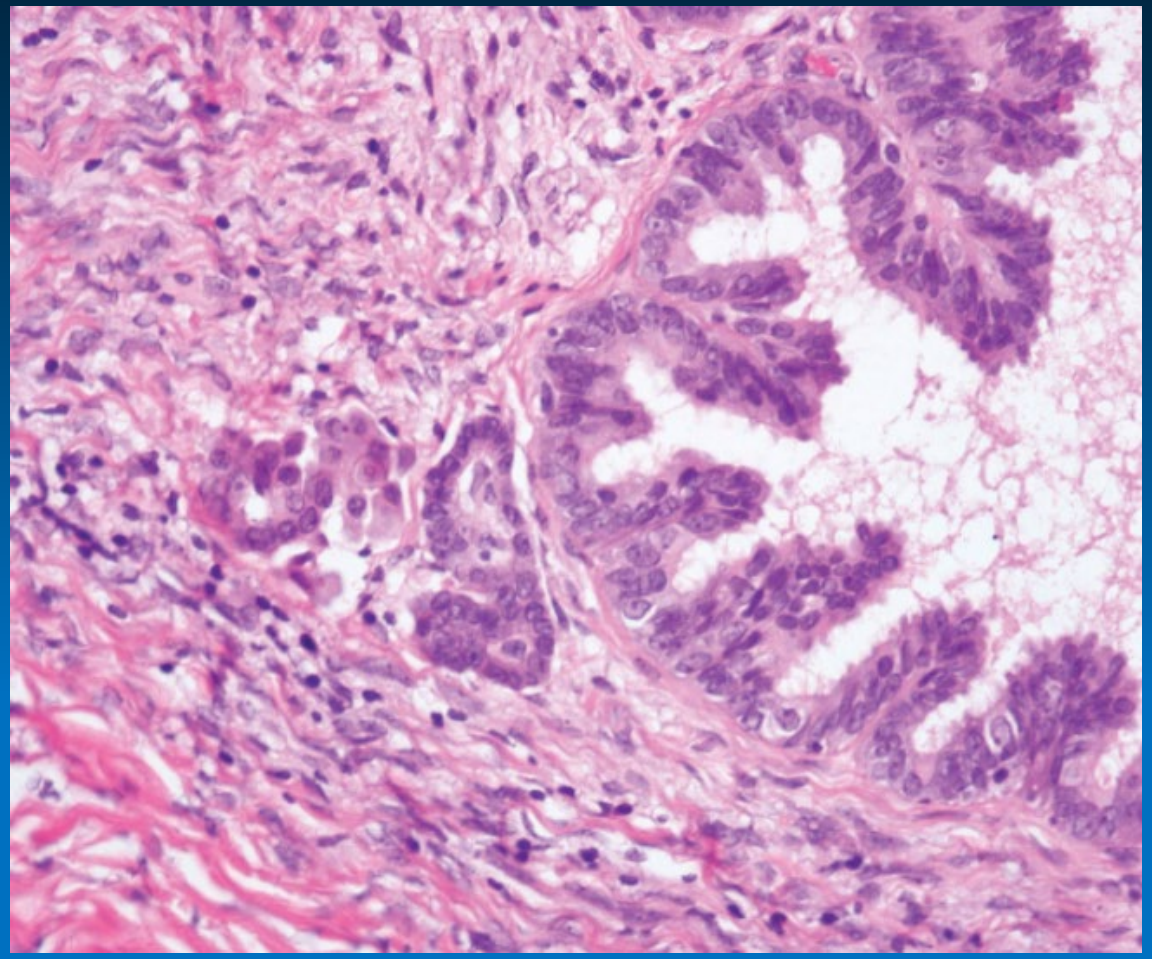
Endometrioid Borderline Tumor





Microinvasion in Borderline Tumors

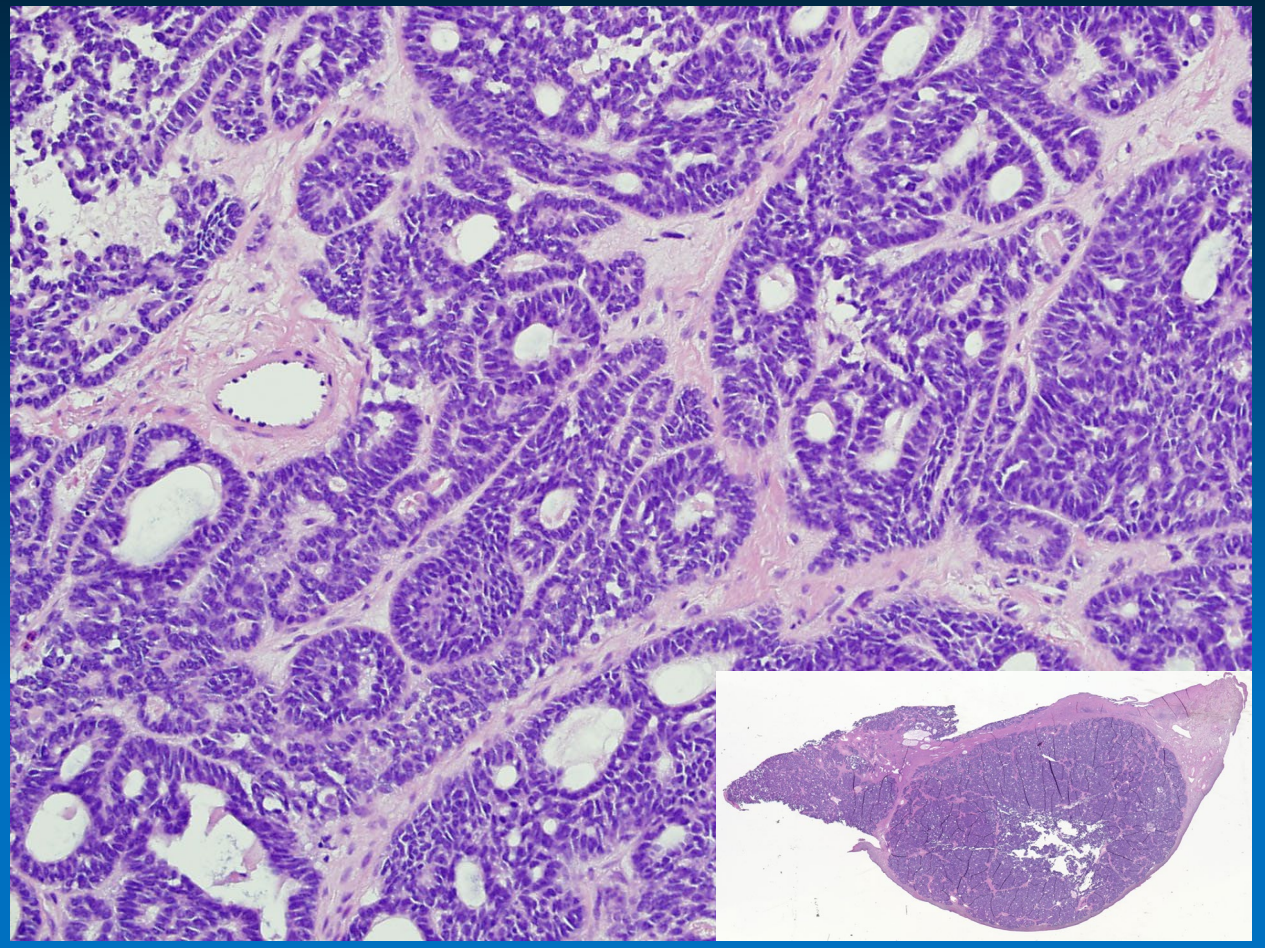
- Cells invading the stroma of a borderline tumor measuring < 5 mm in greatest dimension.
- Can be multifocal
- Should prompt additional sampling.
- No adverse outcomes



Crum *et al.*, 3rd Edition

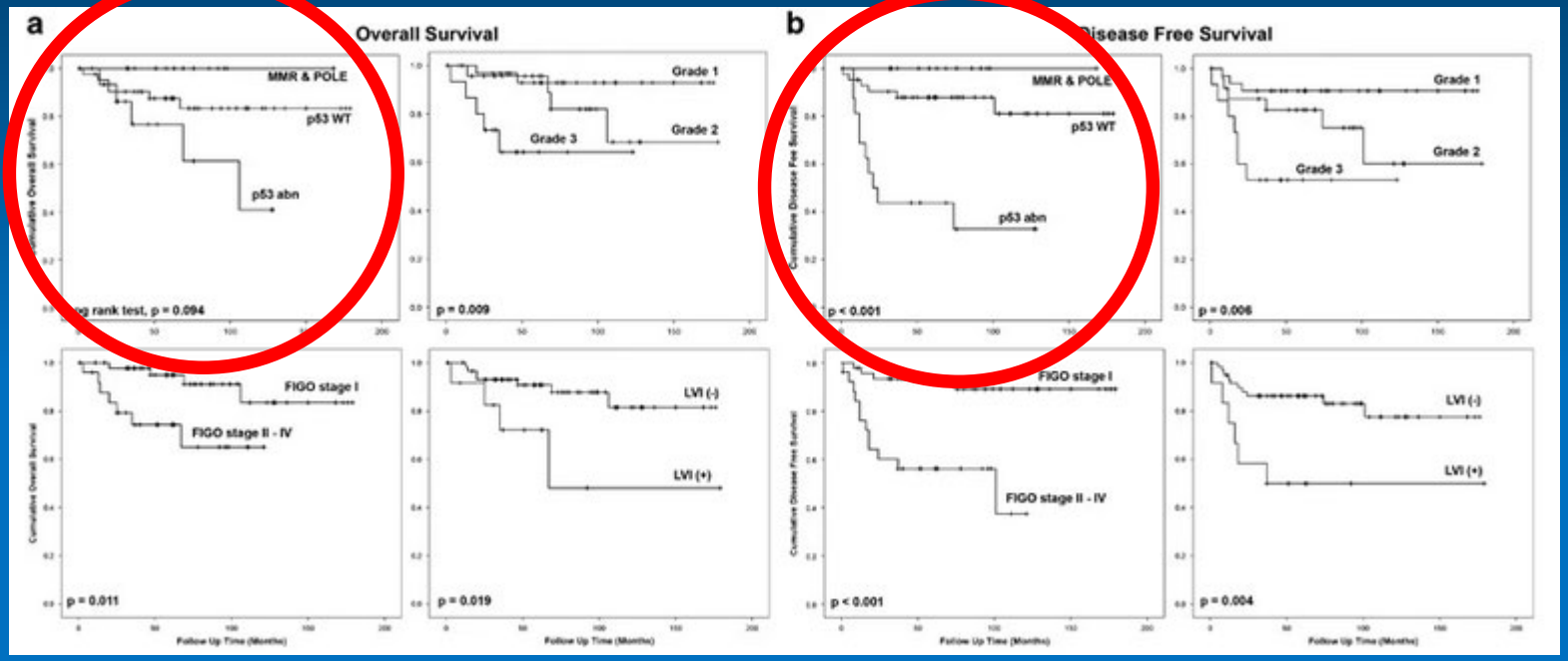
Endometrioid Adenocarcinoma of the Ovary

- Account for 10-15% of ovarian carcinomas
- Common in 40's and 50's.
- ~40% are associated with endometriosis
- Genetic alterations in beta-catenin, PTEN, and PIK3CA.



Prognosis of Endometrioid Adenocarcinomas of the Ovary

- Prognosis mimics 4-subtype molecular classification system of endometrial adenocarcinomas by TCGA, including MMR-deficient, POLE-mutated, p53 abnormal, and p53-wildtype tumors with no specific molecular profile.



Parra-Herran et al., *Mod Pathol, 2017*.

Treatment Considerations for Ovarian Endometrioid Adenocarcinomas

- Grade 1 Tumor, Stage I: Observation
- Grade 2/3 Tumor, Any Stage: Chemotherapy
- Grade 1 Tumor, Stage II: Chemotherapy, Maintenance Hormonal Tx

5-year survival for stage I carcinomas is 78%, for stage II is 63%, stage III 24%, and stage IV 6%.

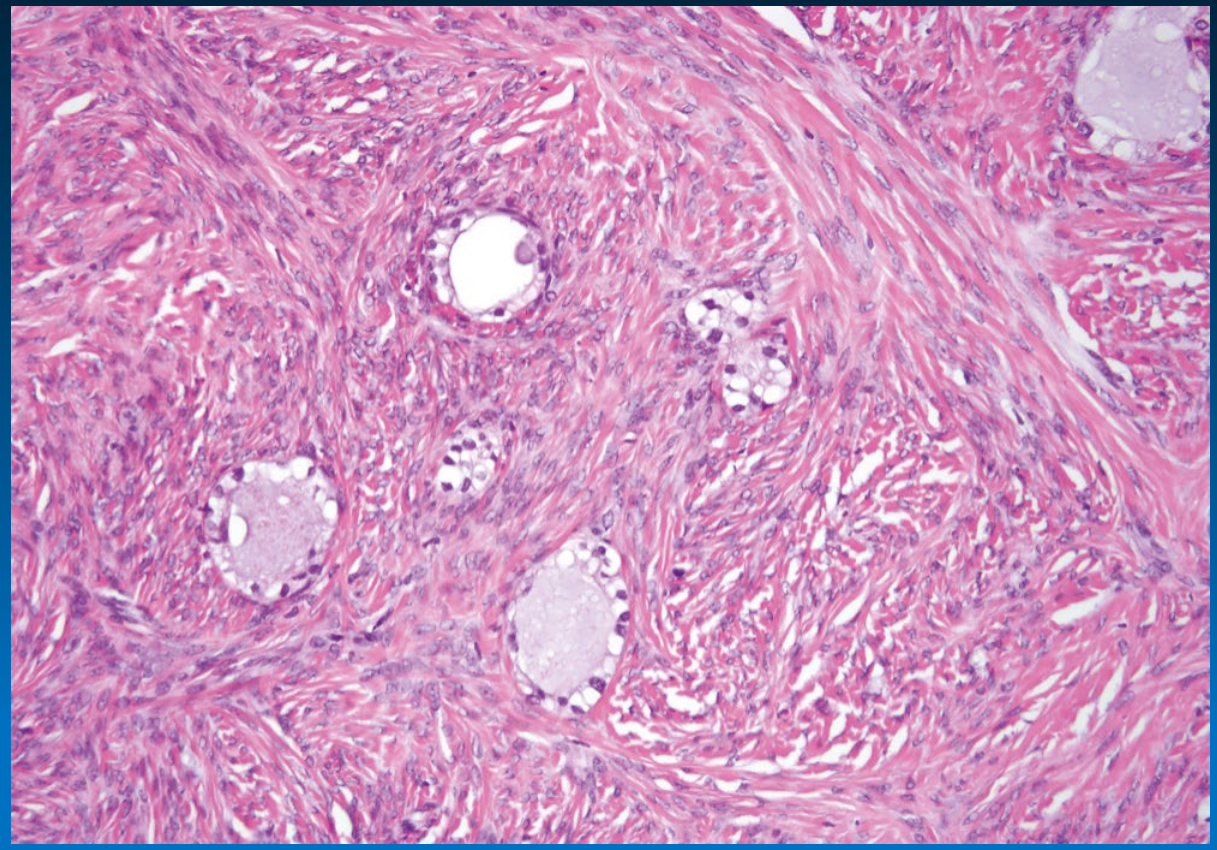
Concurrent Endometrioid Carcinomas of the Ovary and Uterus

- Features which favor synchronous primaries:
  - Well-differentiated tumor
  - Superficial myoinvasion
  - Unilateral ovarian involvement
- Features which favor ovarian metastasis:
  - High grade cytology
  - Bilateral involvement
  - Surface involvement
  - LVI
  - Multinodular growth pattern
  - Absence of ovarian endometriosis

Clear Cell Tumors of the Ovary

Clear Cell Cystadenoma/Adenofibroma

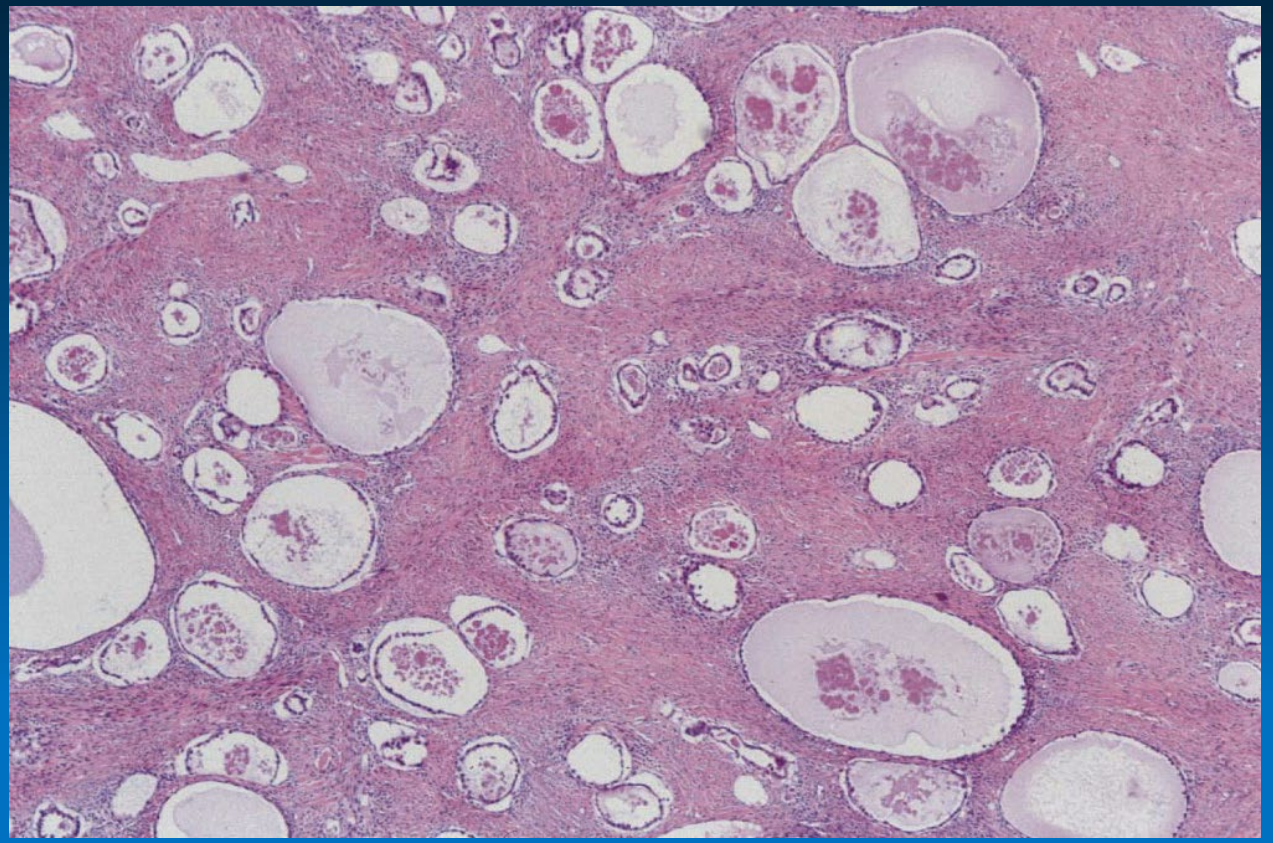
- Clear cell adenofibromas are extremely rare and may be found associated with other types of adenofibromas.
- Fibromatous stroma with widely spaced glands lined by bland cuboidal epithelium.
- Tumors should be carefully sampled to exclude a borderline or malignant component.



Crum *et al.*, 3rd Edition

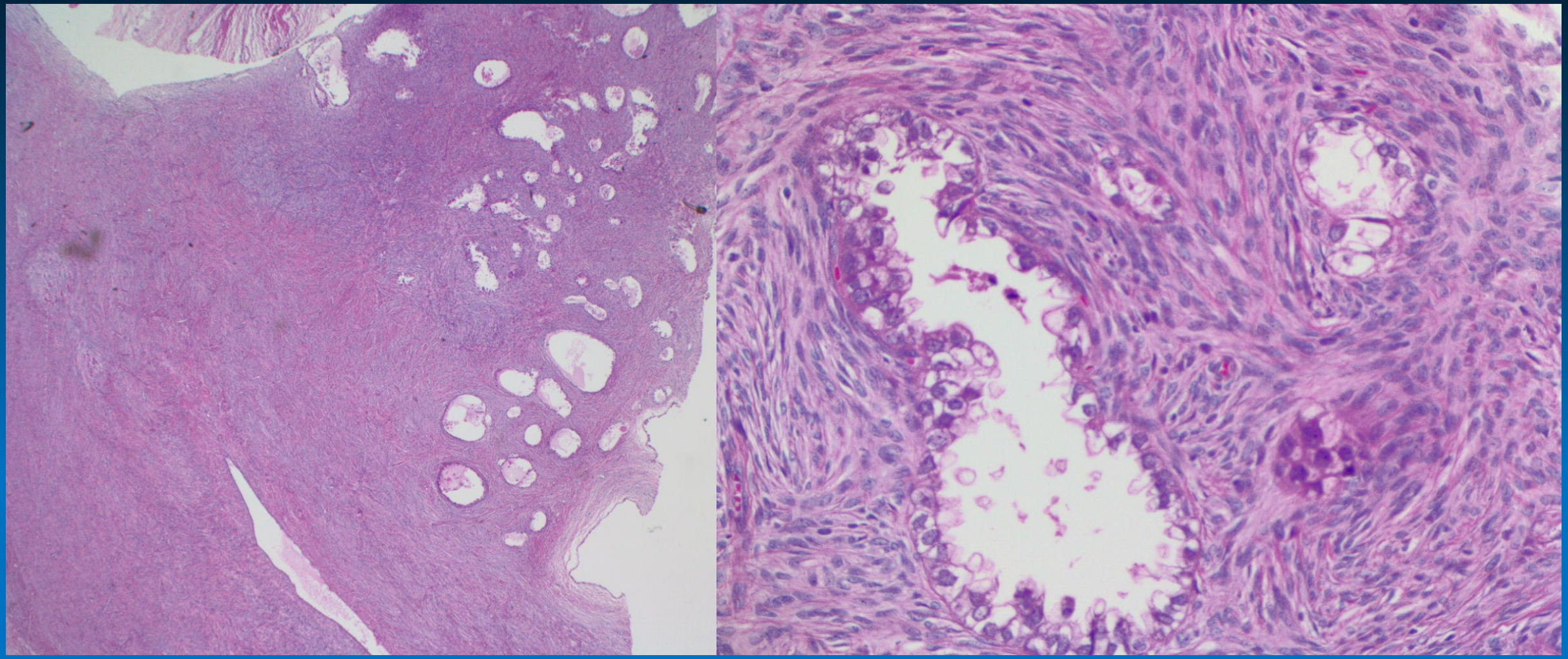
Clear Cell Borderline Tumor

- Rare – account for less than 1% of all borderline tumors.
- A clear cell adenofibroma is considered borderline if there is atypia of the glandular component.
- Cytologic atypia includes nuclear enlargement, hyperchromasia, and prominent nucleoli

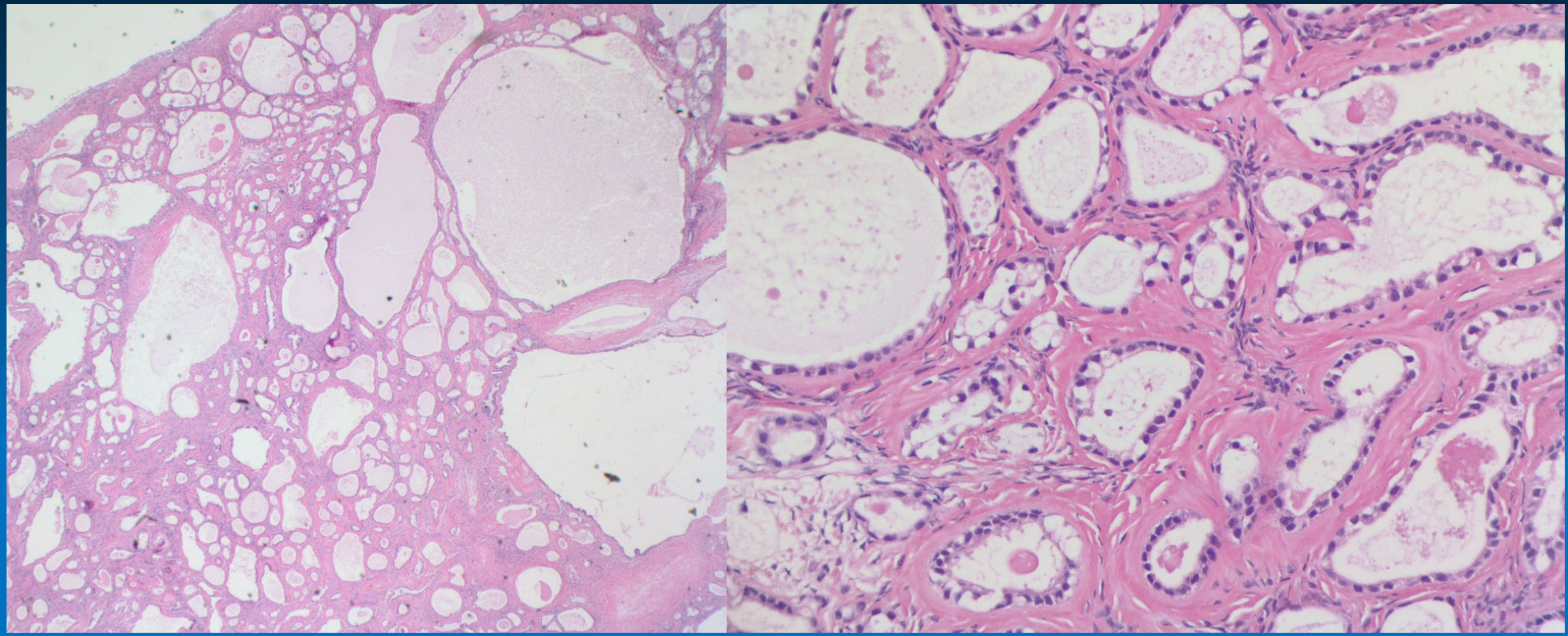


Mutter and Prat, 3rd Edition.

Clear Cell Borderline Tumor

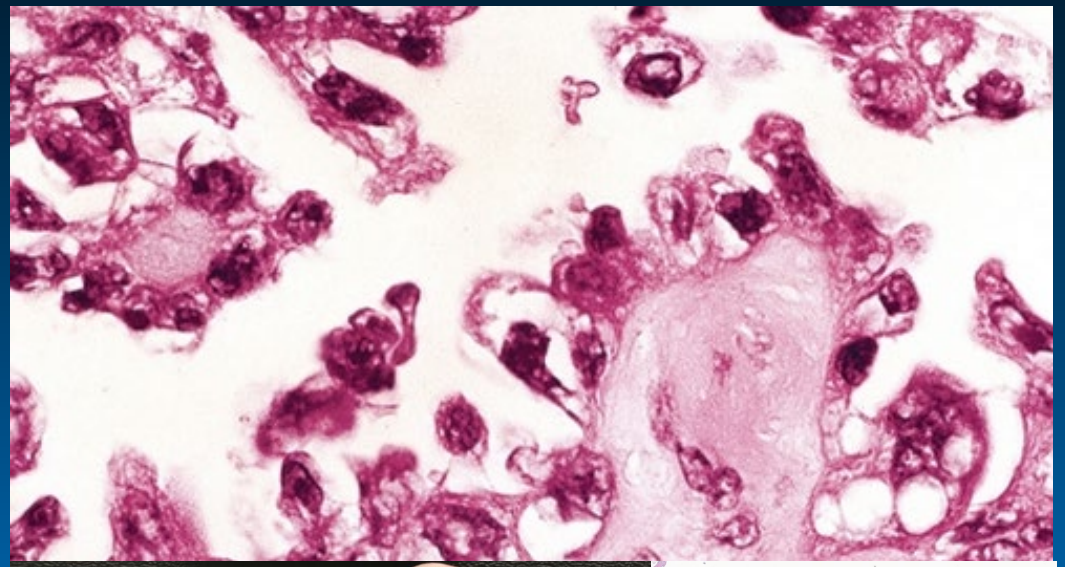


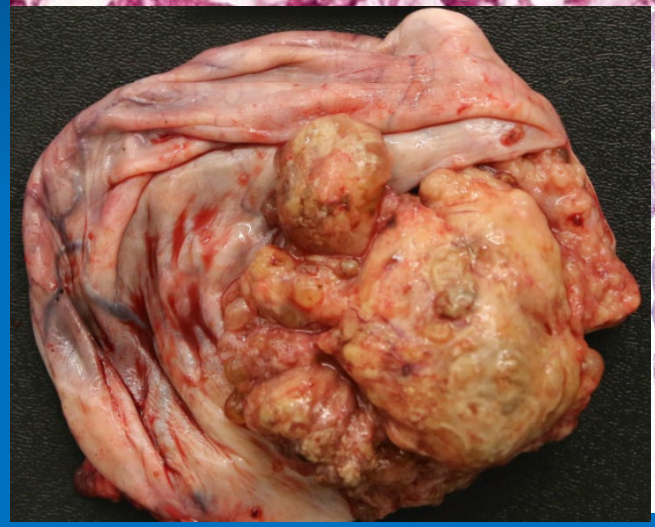
Clear Cell Borderline Tumor

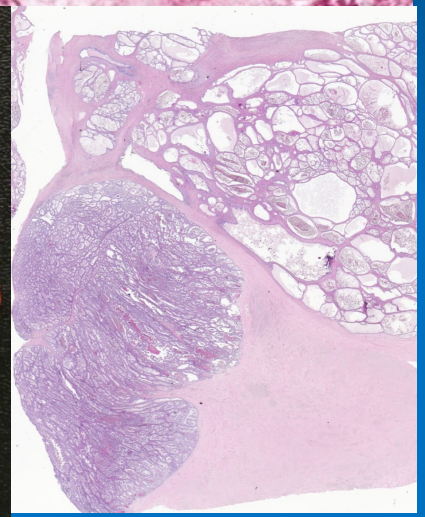


Clear Cell Adenocarcinoma of the Ovary

- A malignant tumor composed of clear, eosinophilic and hobnail cells, displaying papillary, tubulocystic, and solid patterns.
- Mean age is 55 years
- 50-70% associated with endometriosis.
- Common mutations include *PTEN, ARID1A*, and *PIK3CA*.

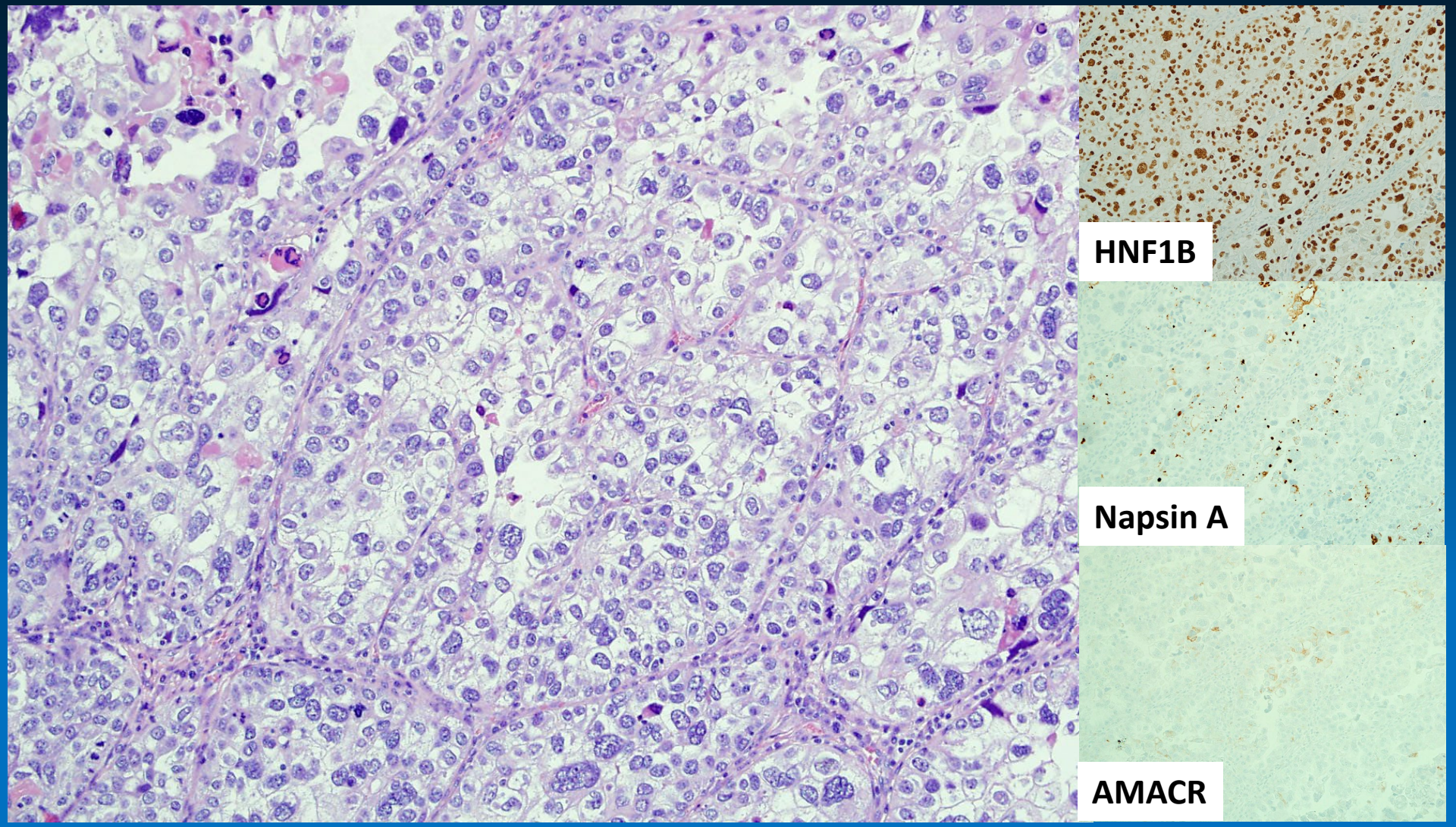






Crum *et al.*, 3rd Edition

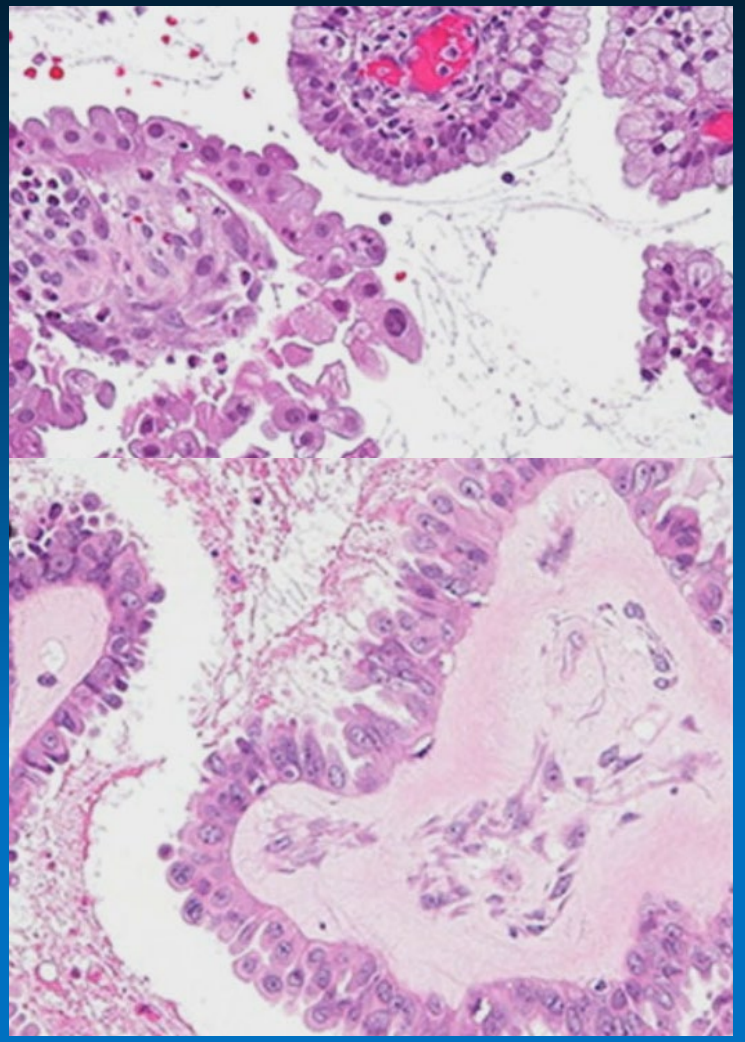
Markers of Clear Cell Differentiation



Seromucinous Tumors of the Ovary

Seromucinous Neoplasms

- Introduced to WHO in 2014
- First described in 1976
- Also known as mixed Müllerian epithelial tumors
- Seroumucinous tumors are characterized by ***an admixture of various cell types, including endocervical-type mucinous, endometrioid, ciliated, and squamous type epithelium***
- 1/3rd are associated with endometriosis

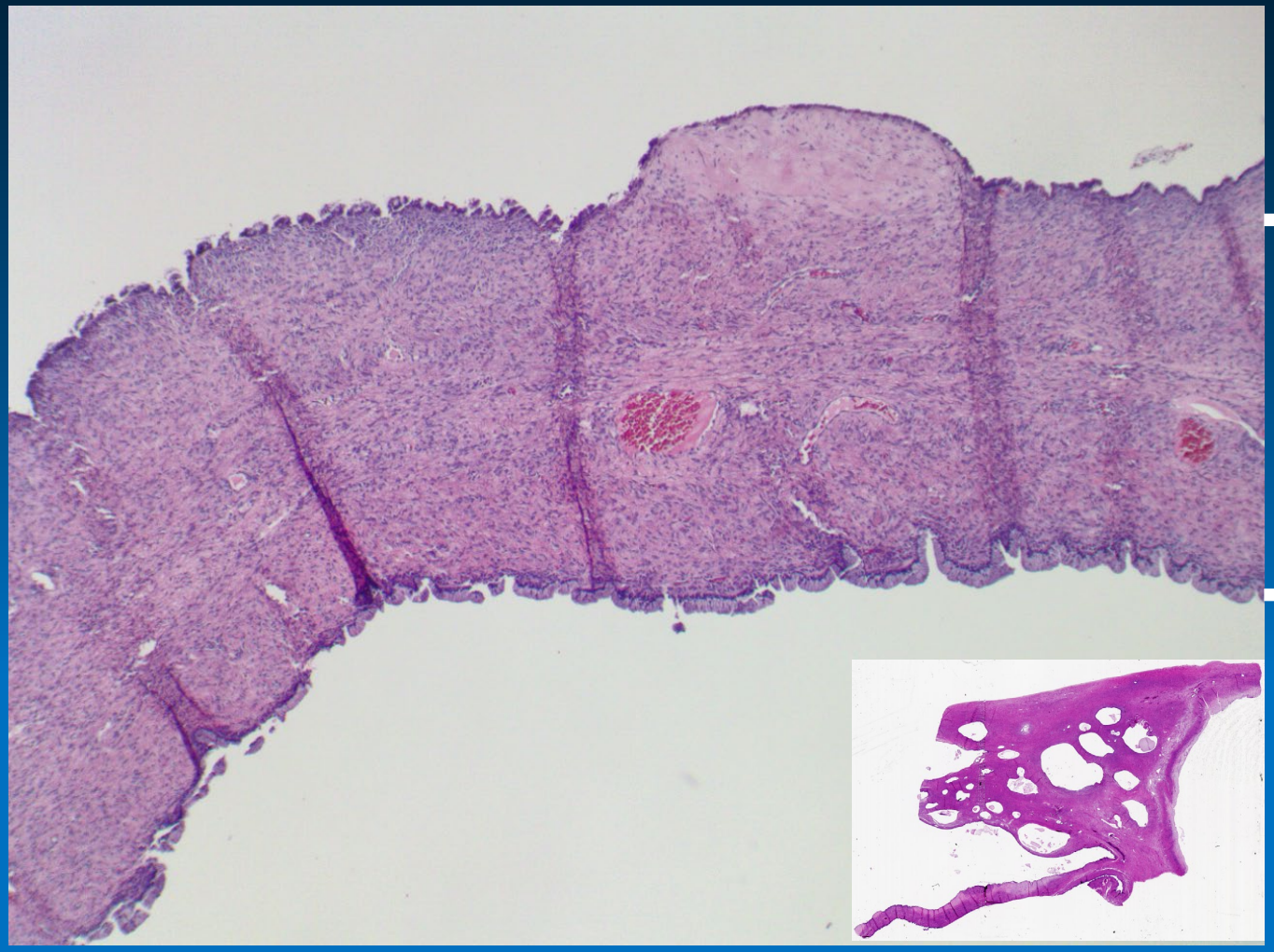


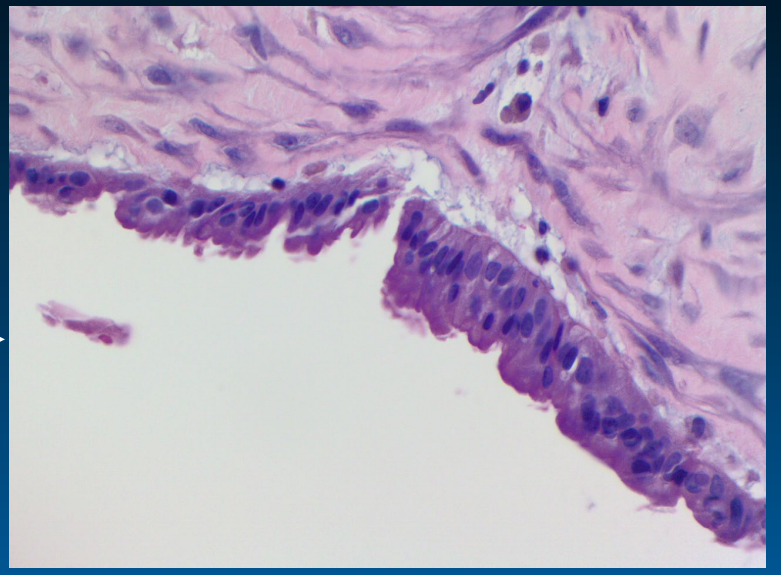
Kurman and Shih, IJGP, 2017.

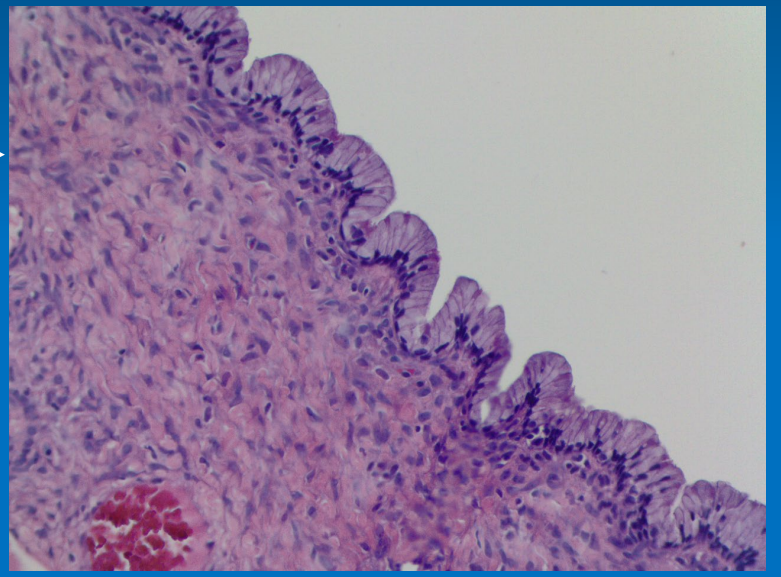
Seromucinous Cystadenoma

- Benign cystic neoplasms
- Contain two or more Müllerian cell types (at least 10%)
- Uncommon

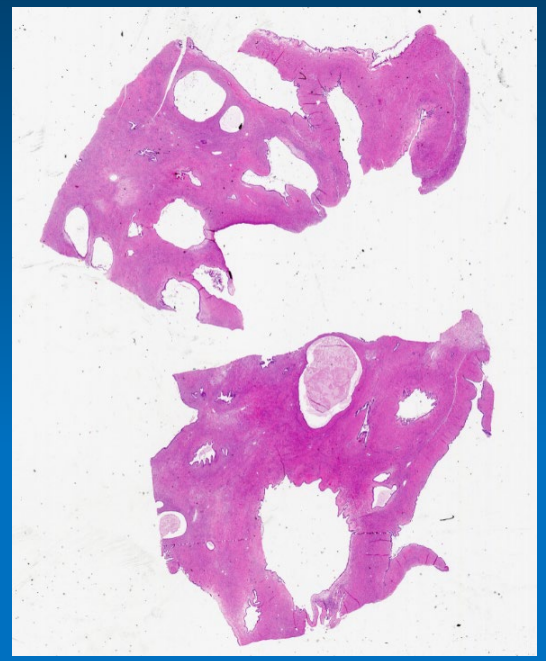
Seromucinous Cystadenoma

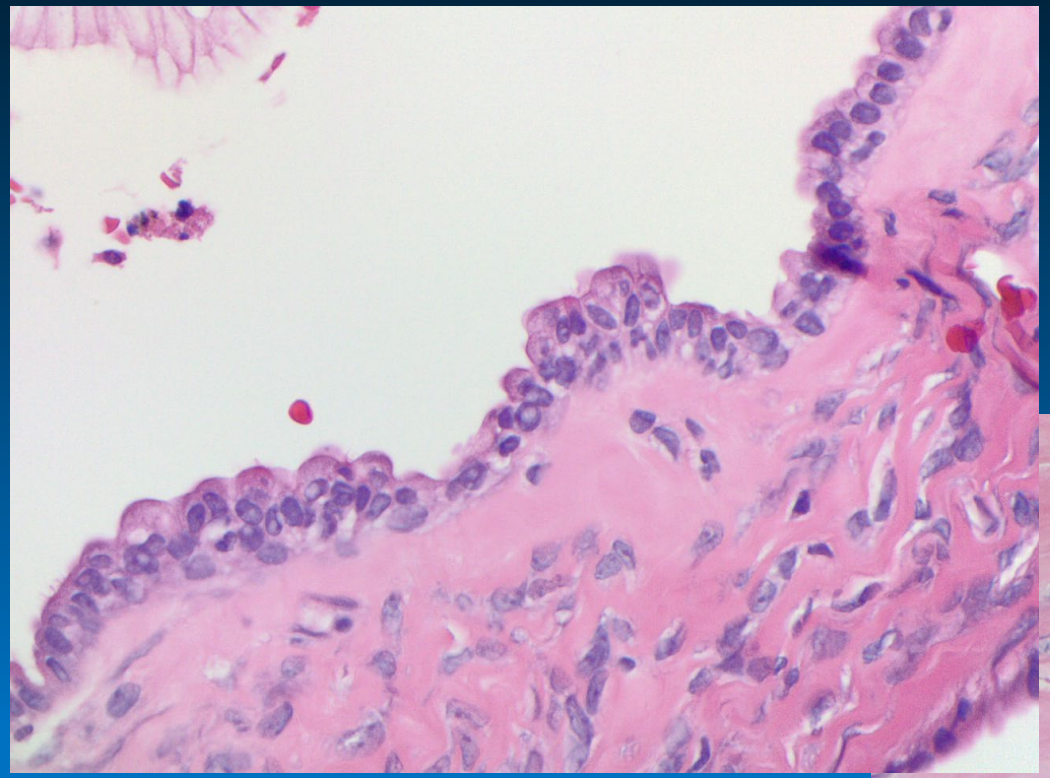


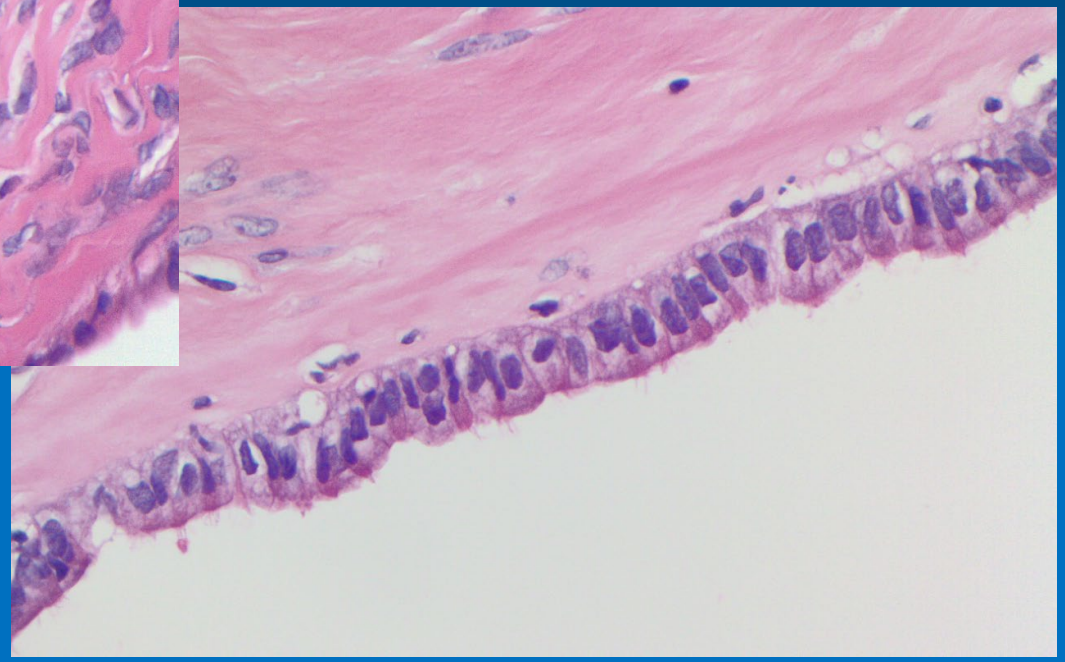




Seromucinous Cystadenofibroma



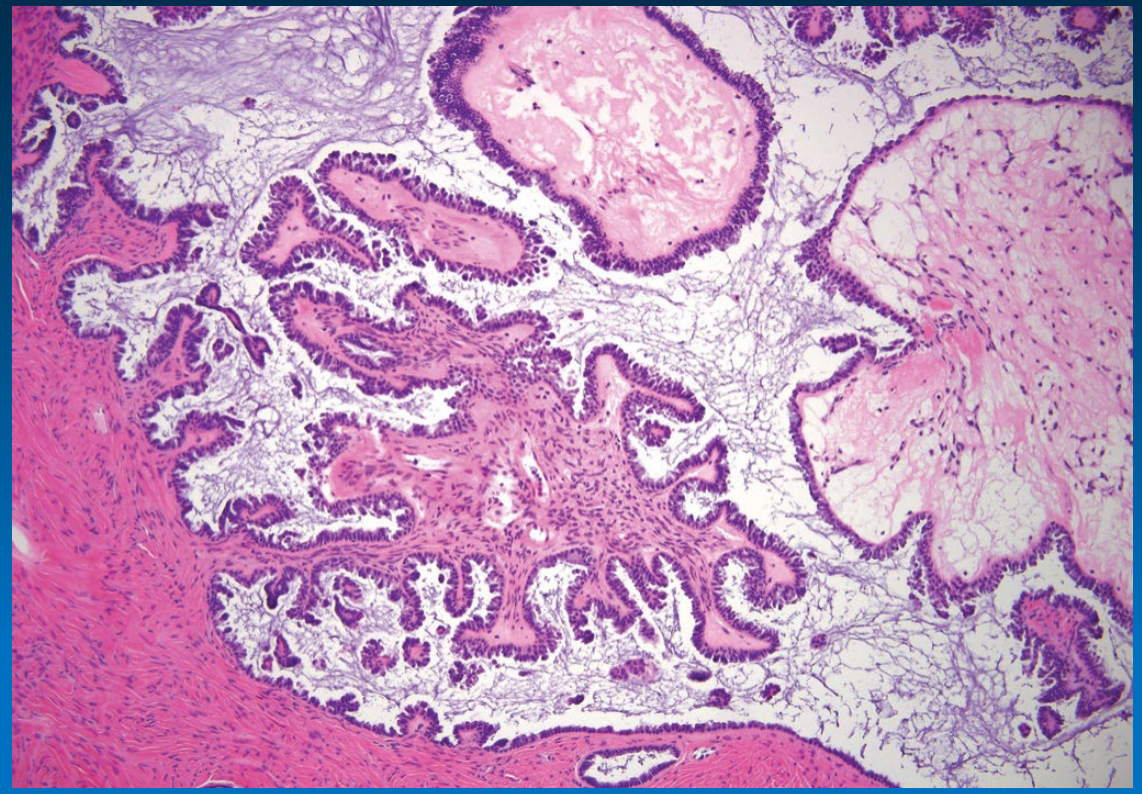




Seromucinous Borderline Tumors

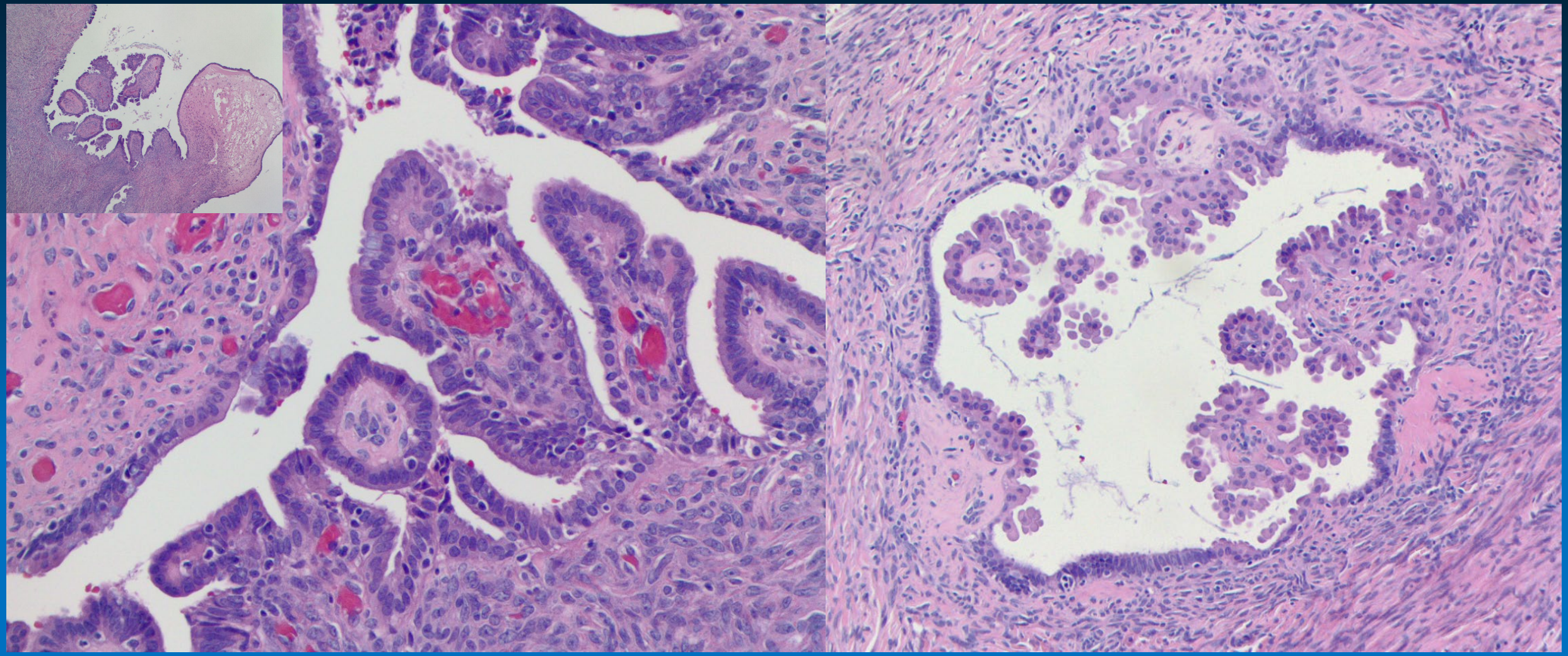
- In the past, known as a subset of mucinous tumors.
- 15% of borderline mucinous tumors.
- Average age 33-44 yr.
- Papillary growth with hierarchical branching; cells with conspicuous eosinophilic cytoplasm
- Tumors are associated with an excellent prognosis.

Seromucinous Borderline Tumor

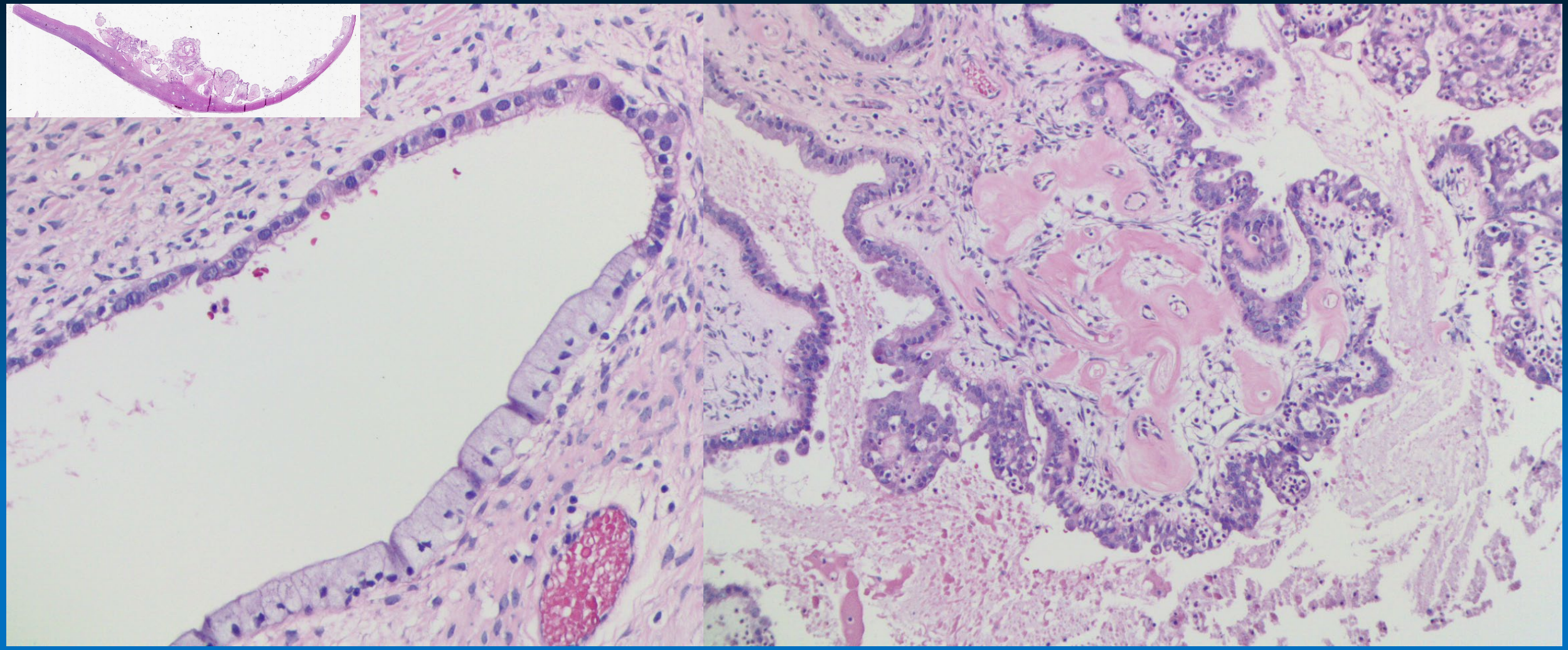


Crum *et al.*, 3rd Edition

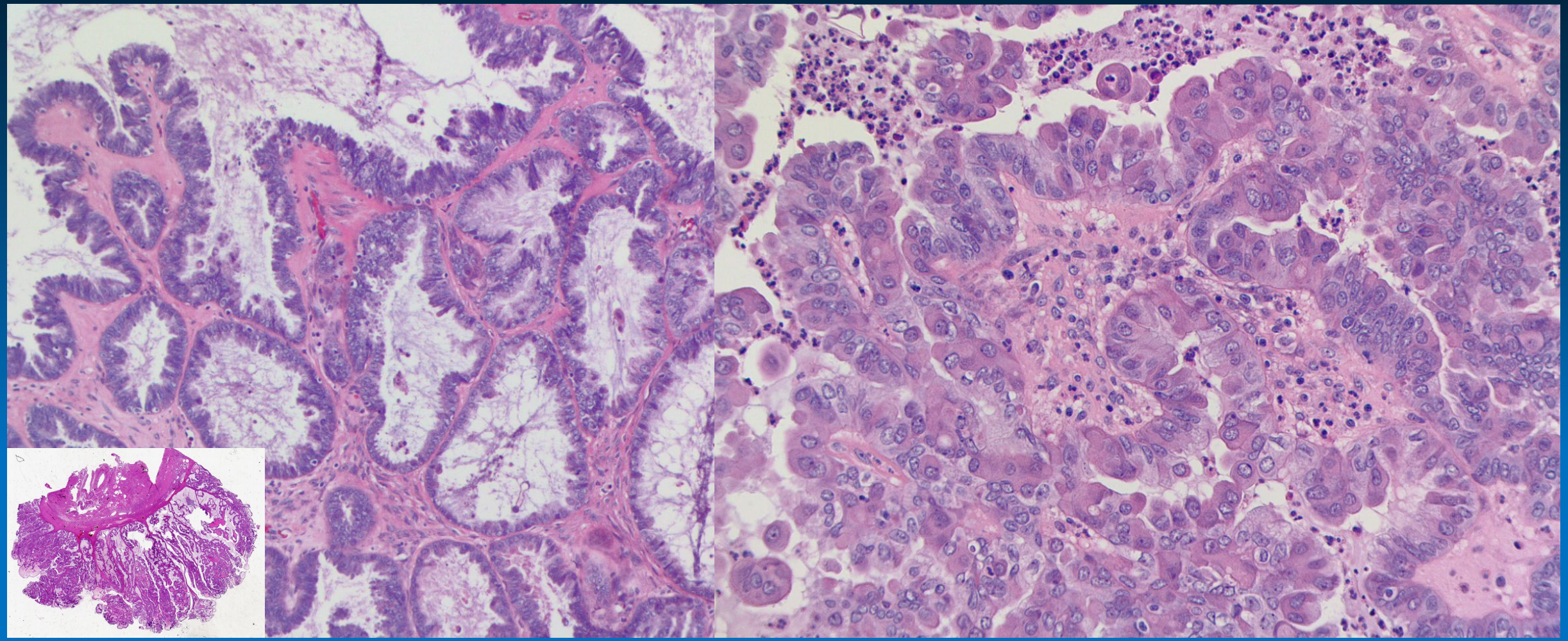
Seromucinous Borderline Tumor



Seromucinous Borderline Tumor



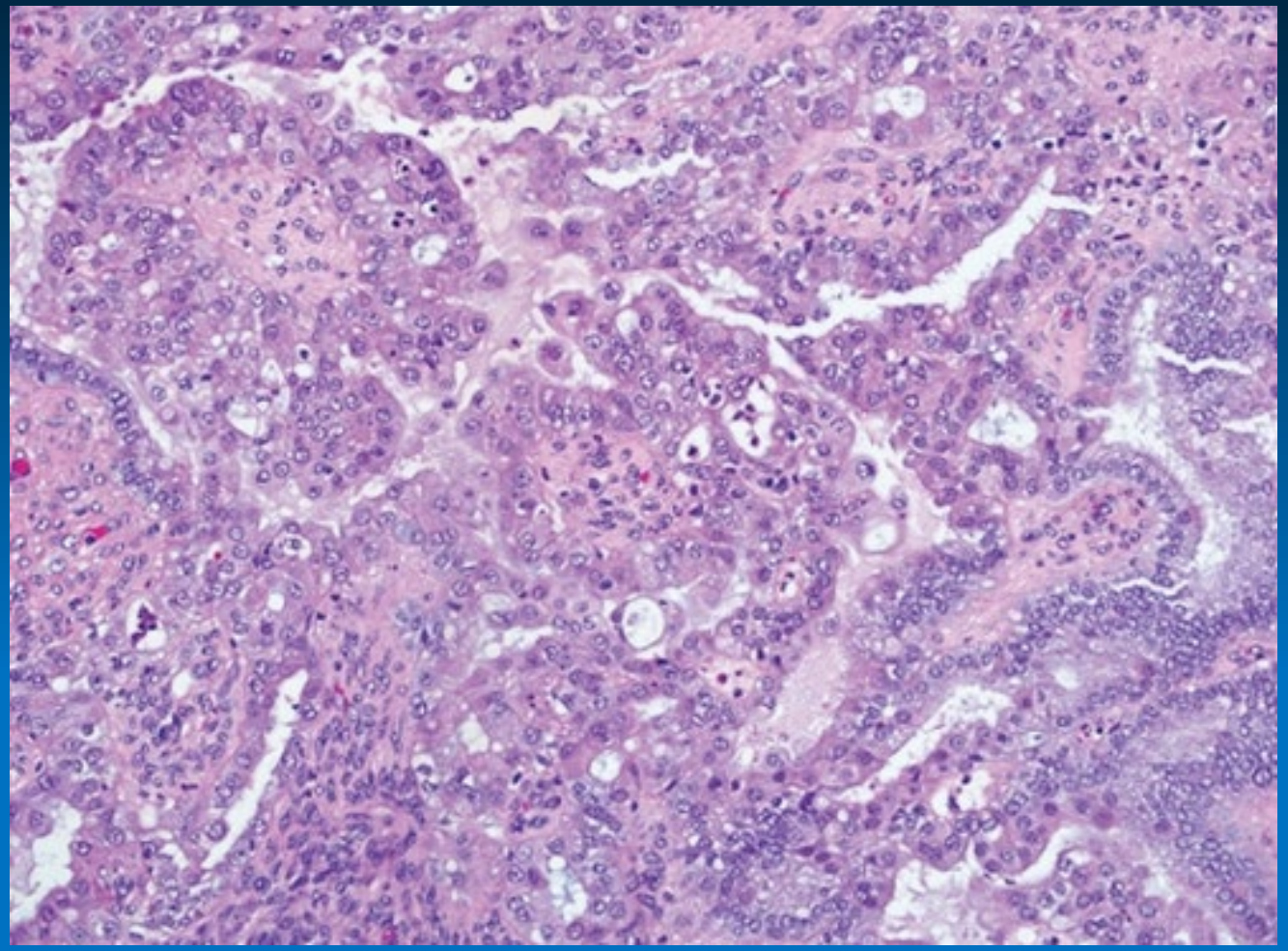
Seromucinous Borderline Tumor



Seromucinous Adenocarcinomas

- Predominantly composed of serous and endocervical type mucinous epithelium.
- Uncommon
- Most common presentation is a pelvic mass.

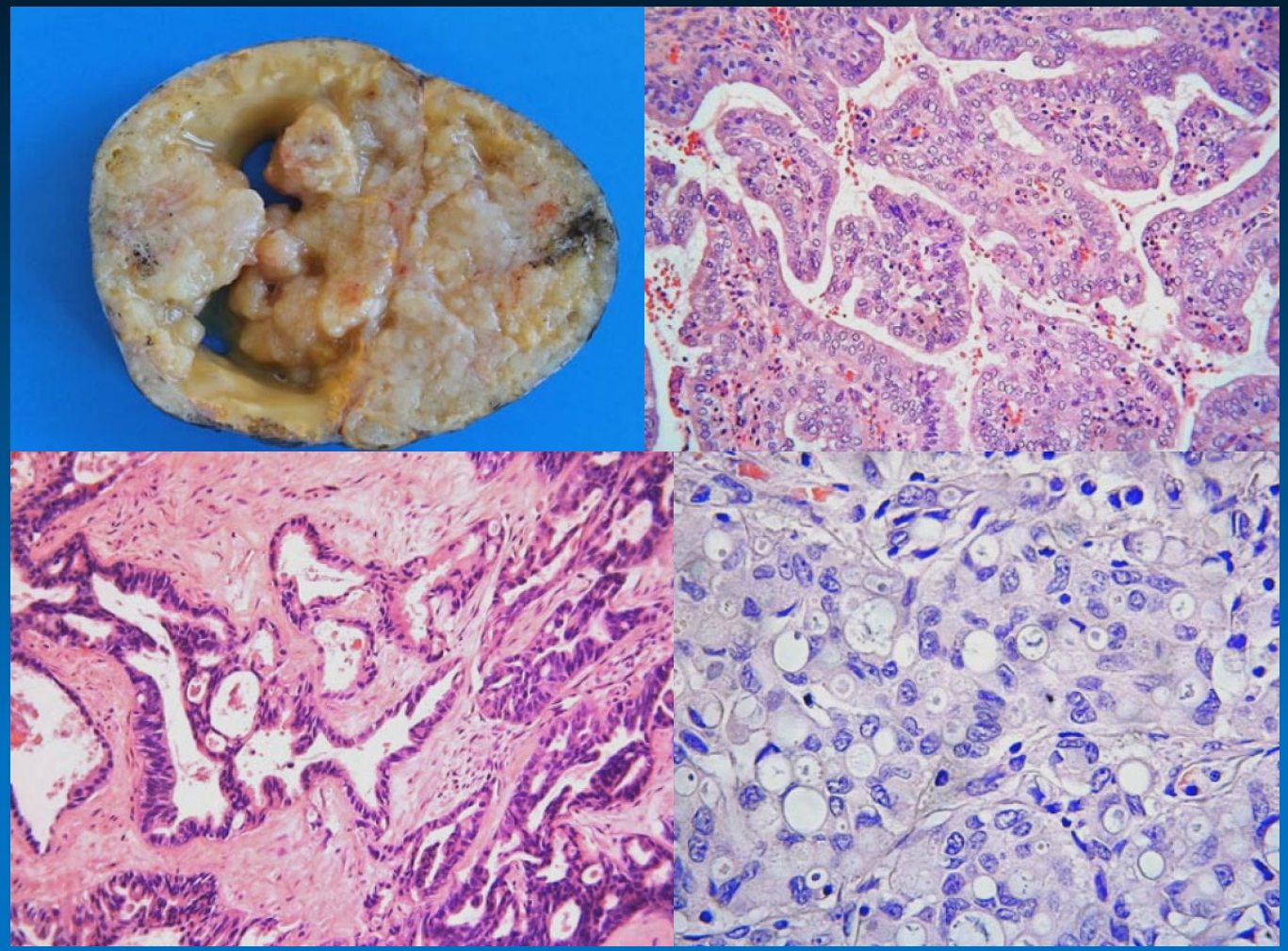
Seromucinous Carcinoma



Crum *et al.*, 3rd Edition

Seromucinous Adenocarcinoma

- Largest study (n=19)
- Age range 16-79 yr.
- ~80% were stage 1
- Expansile papillary growth, destructive infiltration, and solid growth
- Endometriosis in 52%



Taylor and McCluggage, *Am J Surg Pathol,* 2015.

Endometriosis and Associated Neoplasms of the Ovary

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October 20, 2020

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