Ovarian Clear Cell Carcinoma

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- 50 year old woman with chief complaint of shortness of breath

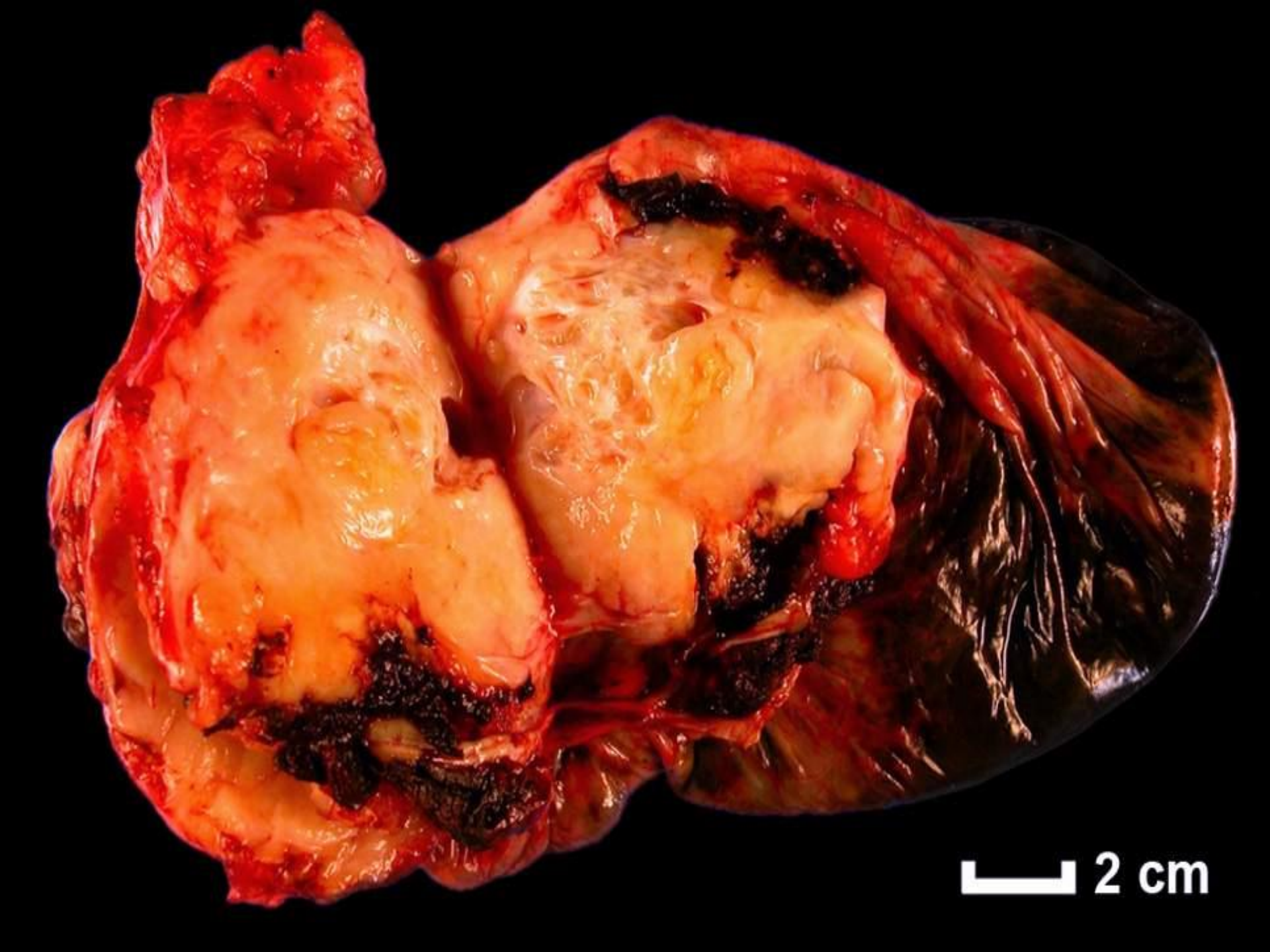
- As part of her work up; PE
- abdominal pain and abdominal distention.

- Imaging study: cystic right adnexal mass with solid and cystic features.

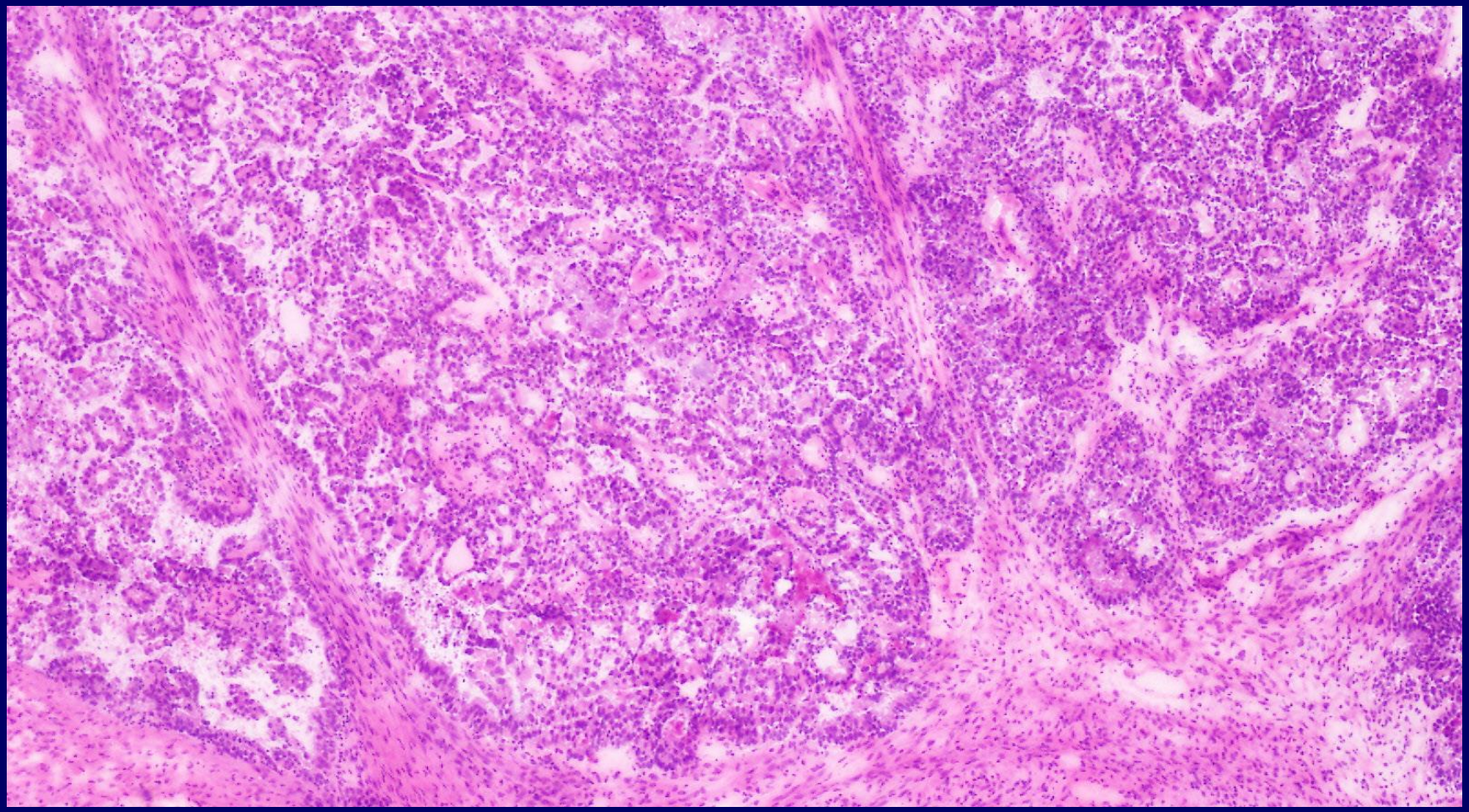
- Patient underwent surgical resection.

Intraoperative Findings

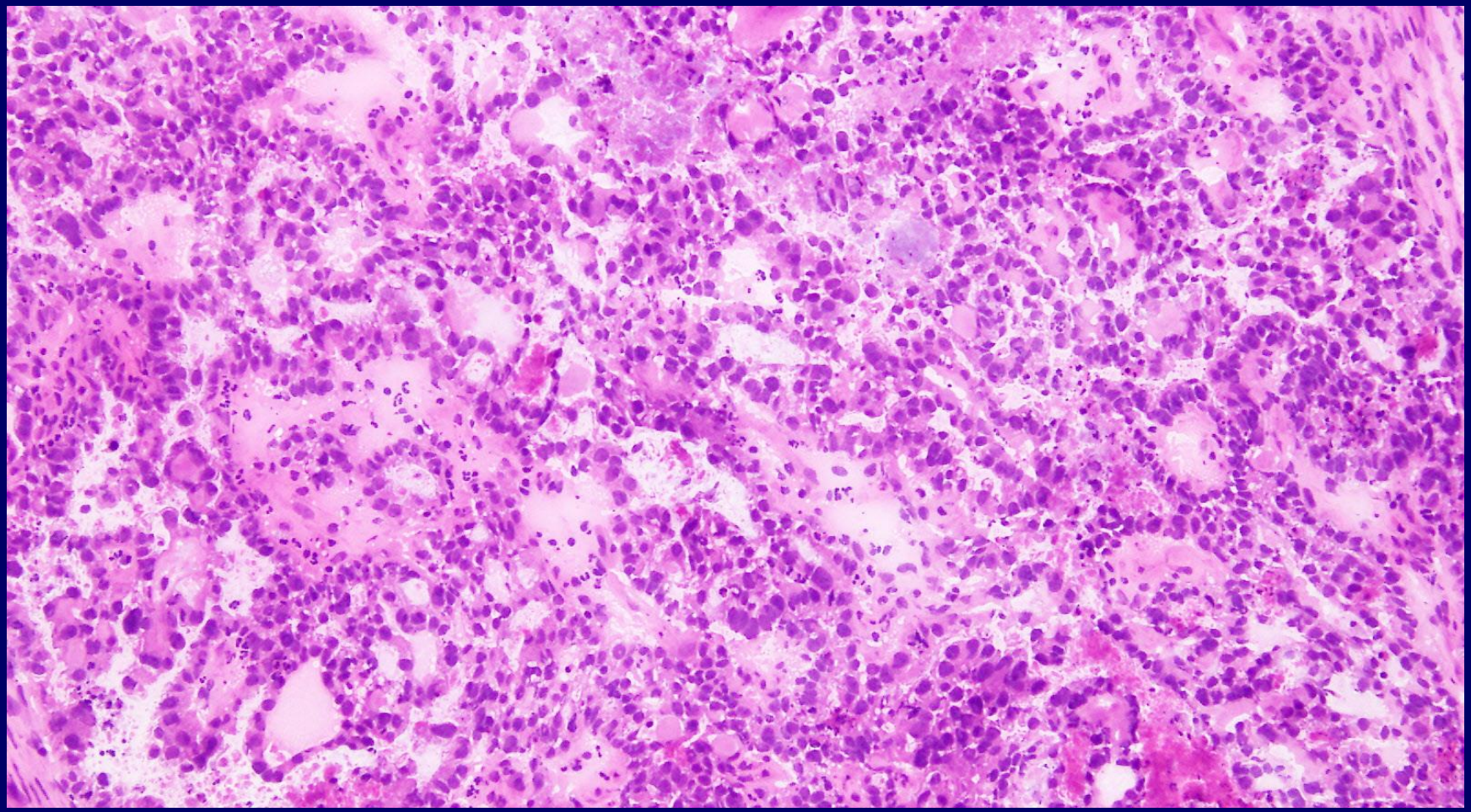
- Right adnexal mass:
  - 340 g, 9 x 8 x 6 cm, partially cystic, filled with bloody fluid..
  - The right fallopian tube was unremarkable.

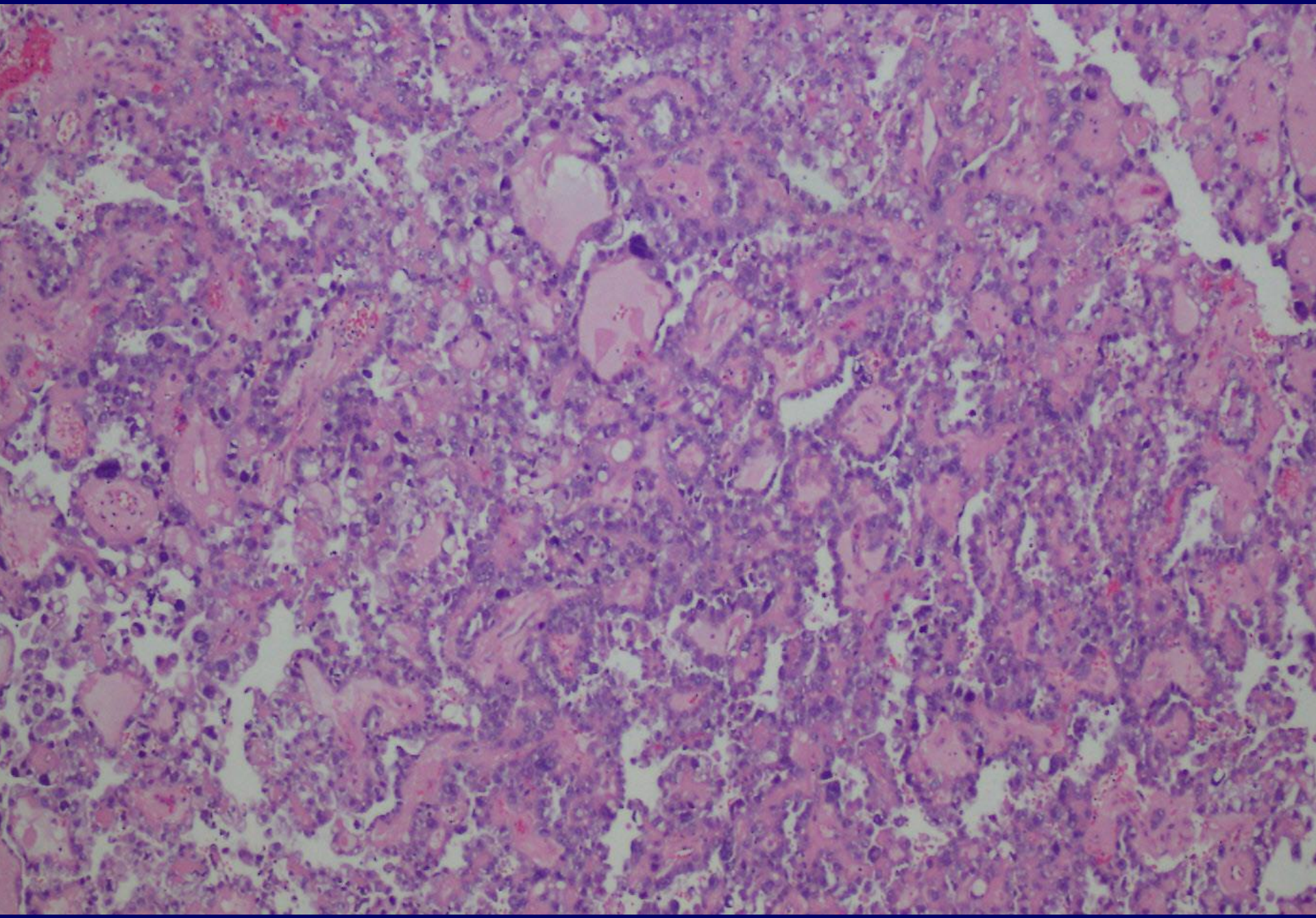

2 cm

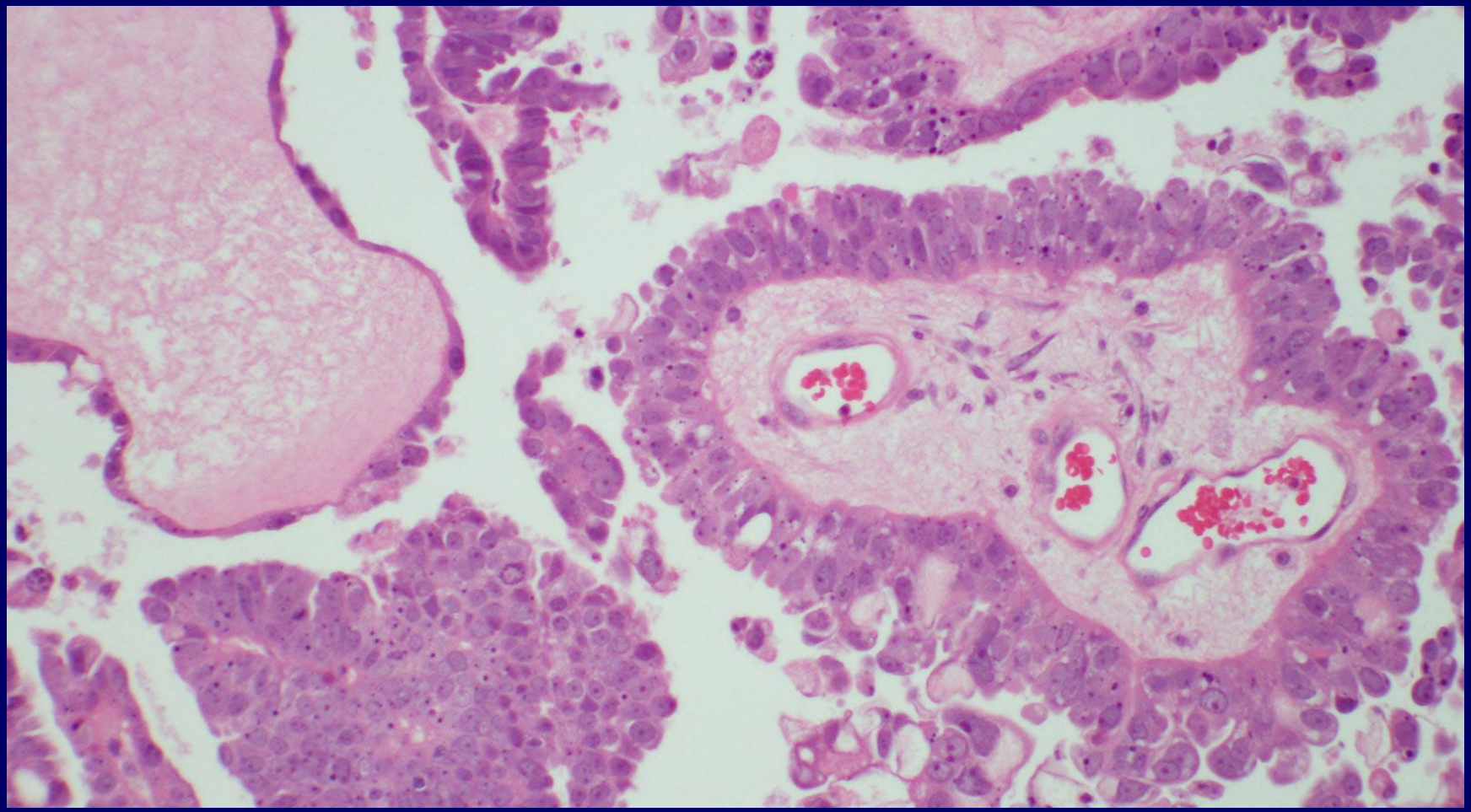
Frozen Section Diagnosis:



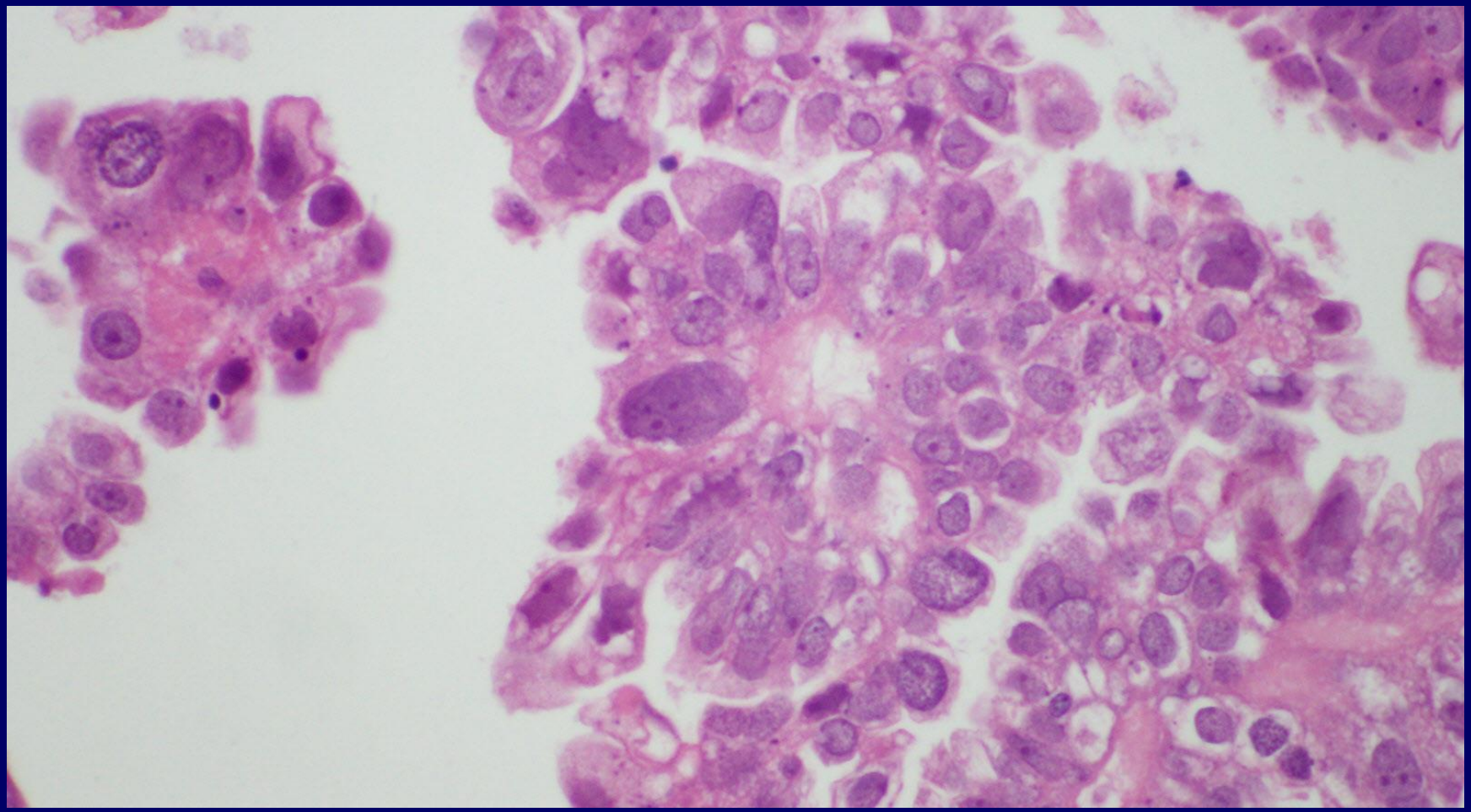
Frozen Section Diagnosis: "serous carcinoma"







Final Diagnosis:
Clear Cell Carcinoma



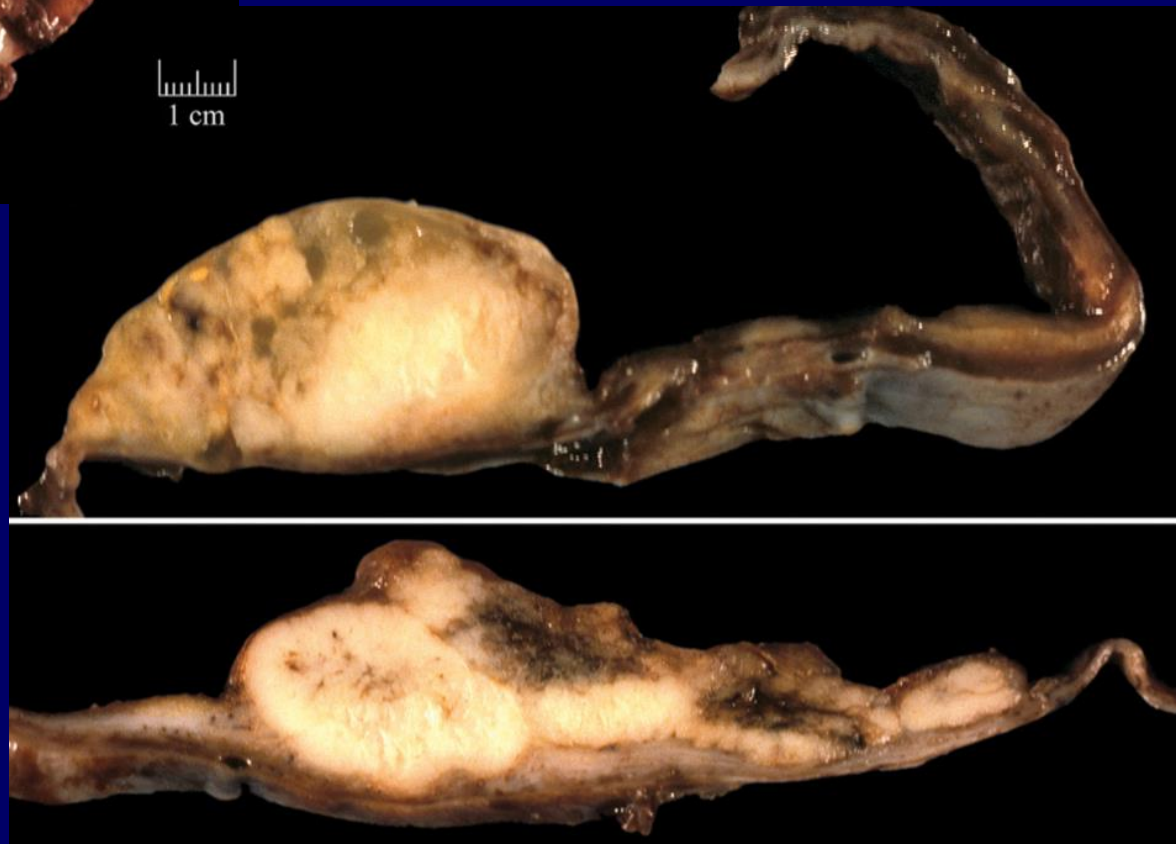
Clear Cell Carcinoma

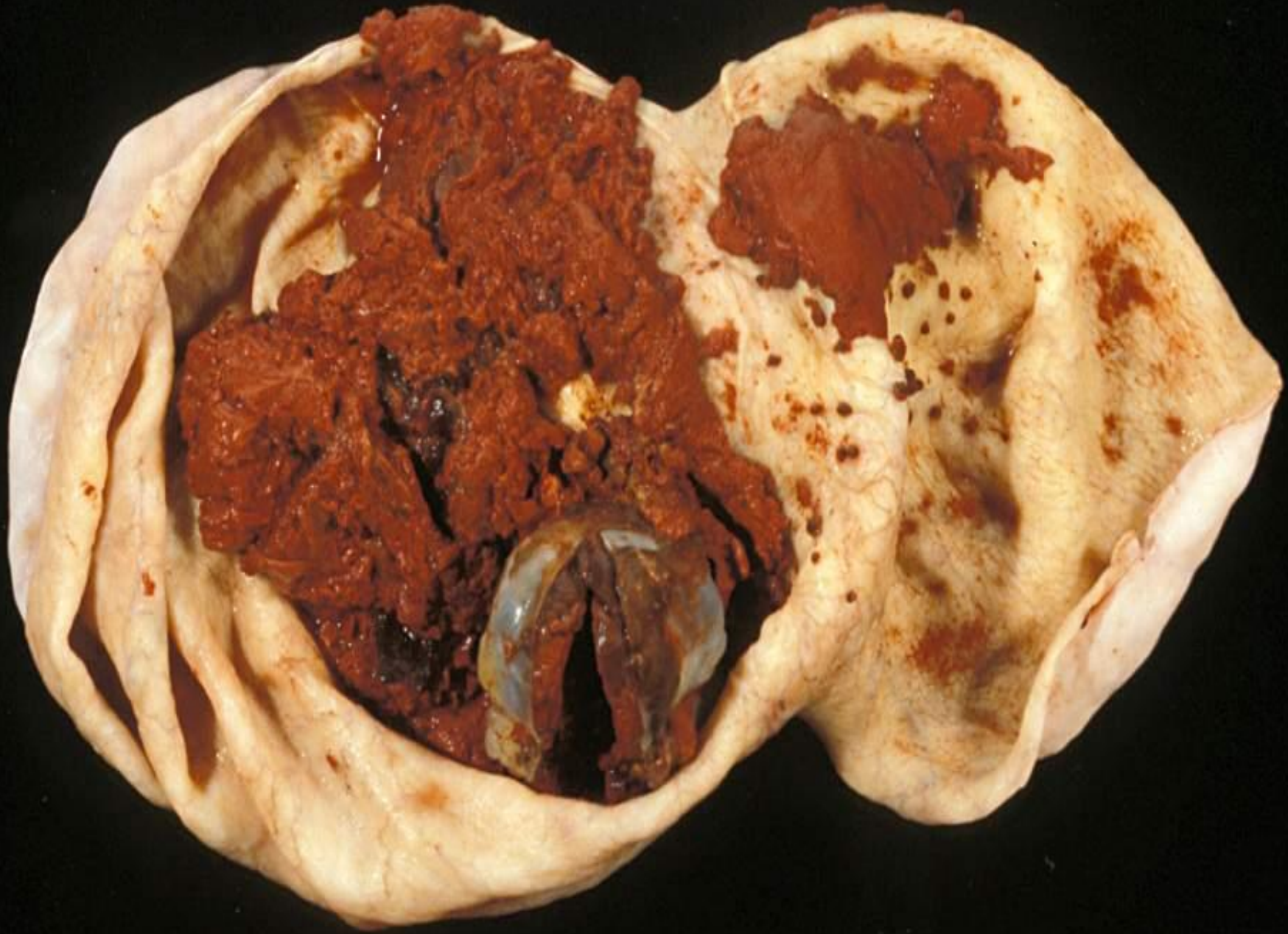
- *Most common cause for error* at frozen section & permanent section in gynecologic pathology
- Often low mitotic index
- May not show marked nuclear atypia
- May not have clear cells
- Lots of other tumors have clear cells

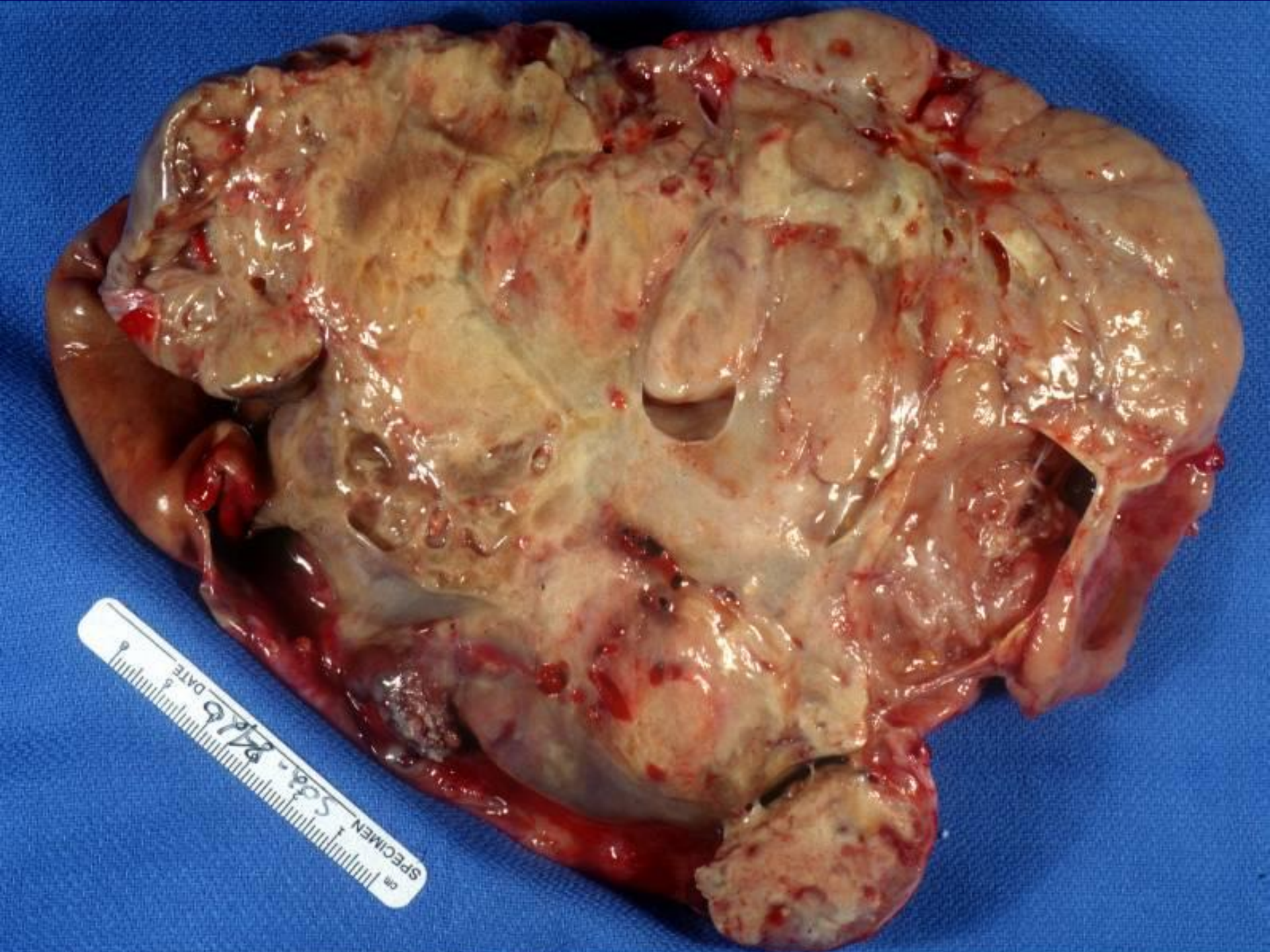
Clear Cell Carcinoma

- Second most common “surface epithelial carcinoma”
- Associated with endometriosis – ovarian and/or pelvic
- Almost always unilateral (>95%)
- Increased risk thromboembolism (x2.5)
- Poor response to cis-platinum therapy
- Presents in premenopausal age group as well as postmenopausal

Clear Cell Carcinoma Grossly

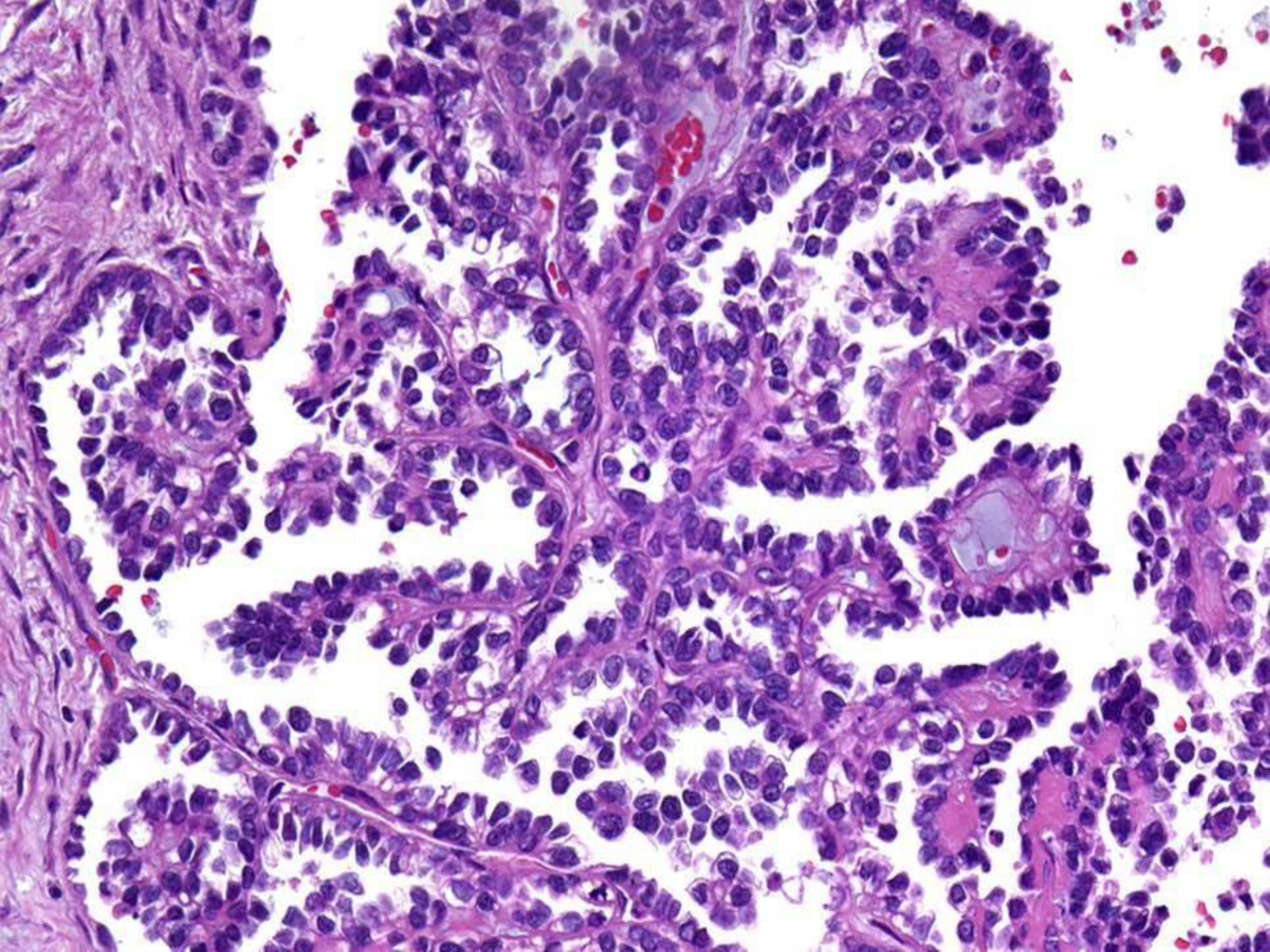

1 cm

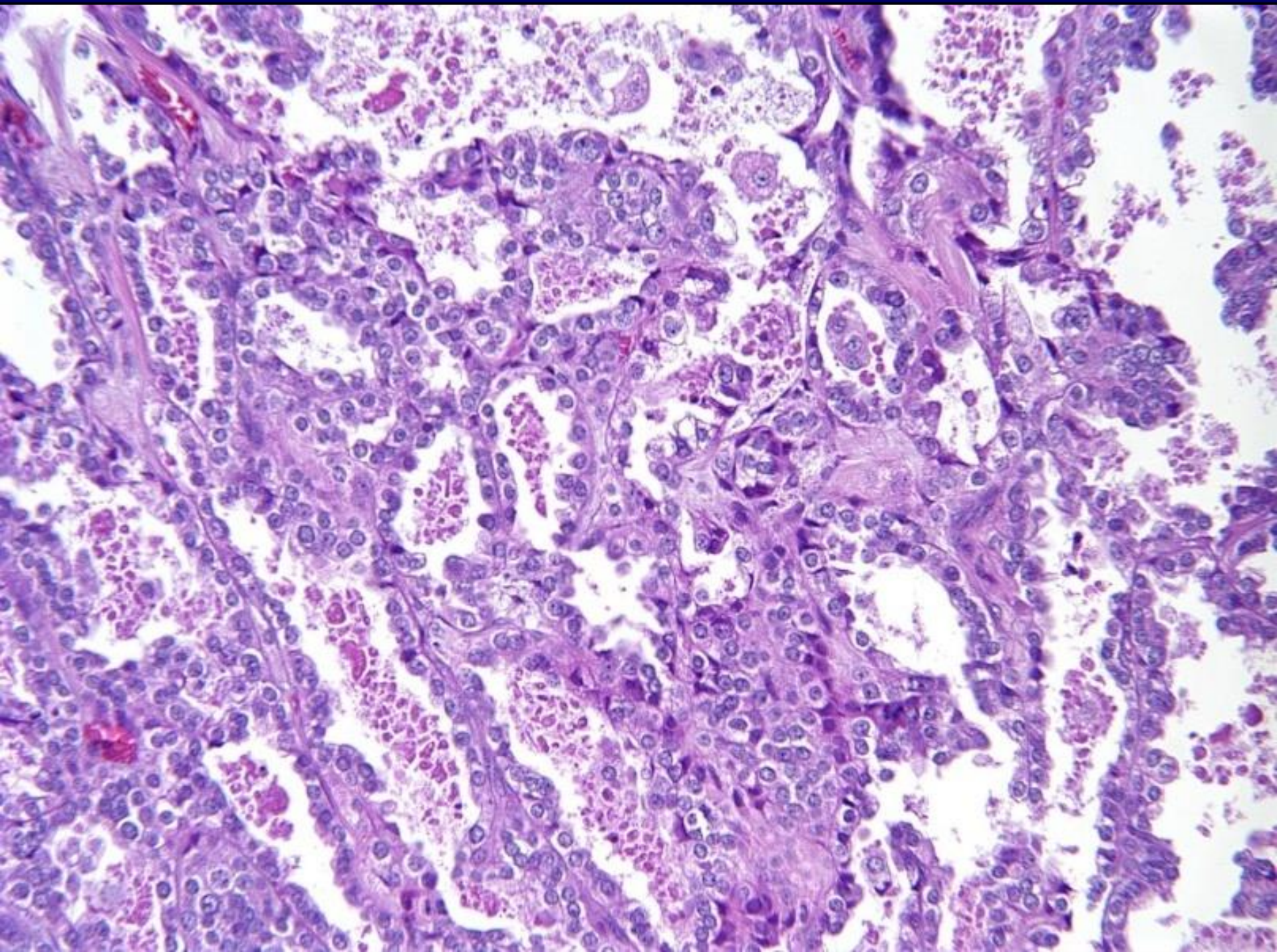


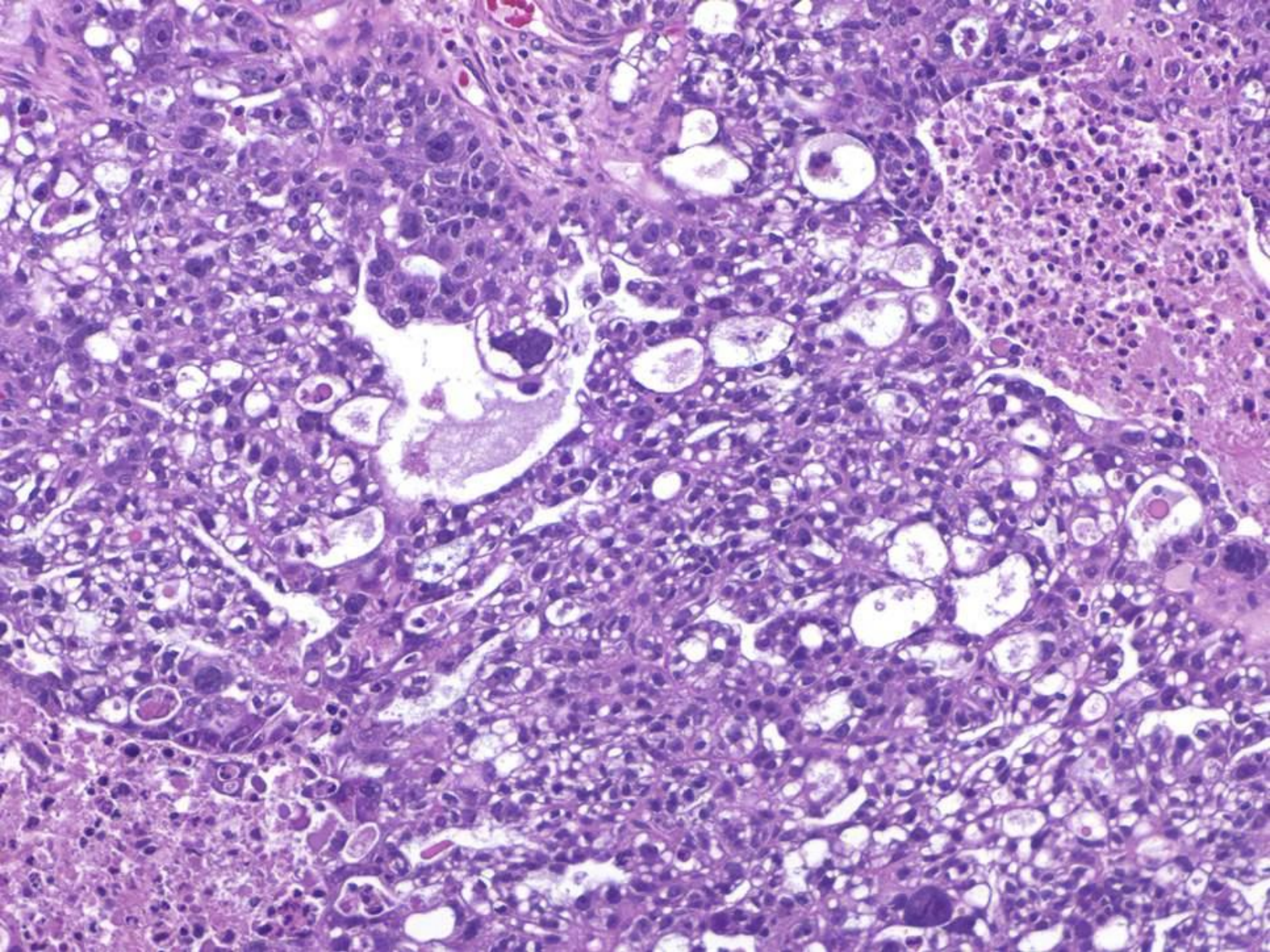

SPECIMEN
DATE

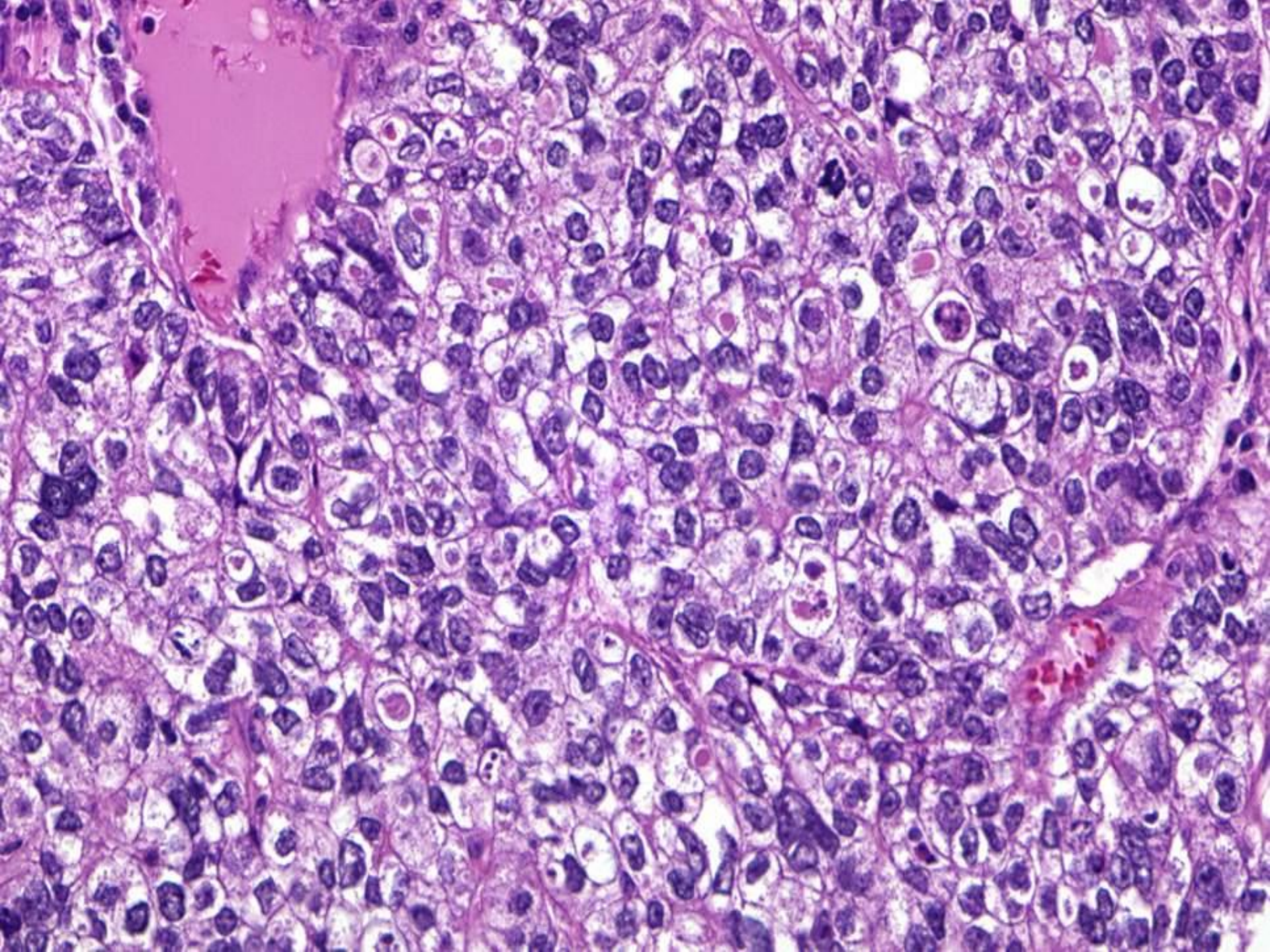
Clear Cell Carcinoma

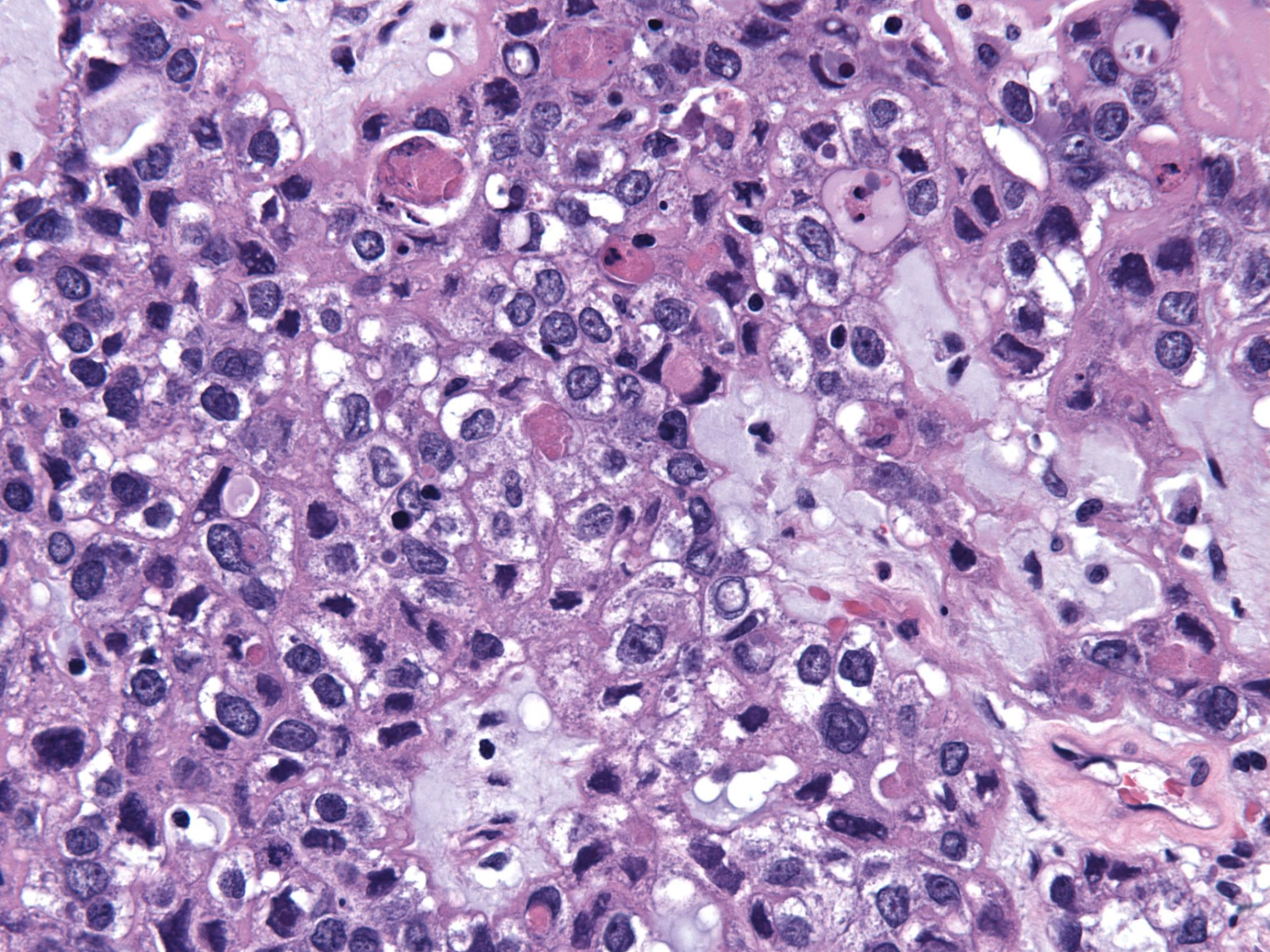
- Papillary
- Tubulocystic (or glandular)
- Cystic
- Solid
- Often prominent hyalinized stroma – or spherule-like mucoid stroma
- Fibromatous, fibroblastic, edematous stroma

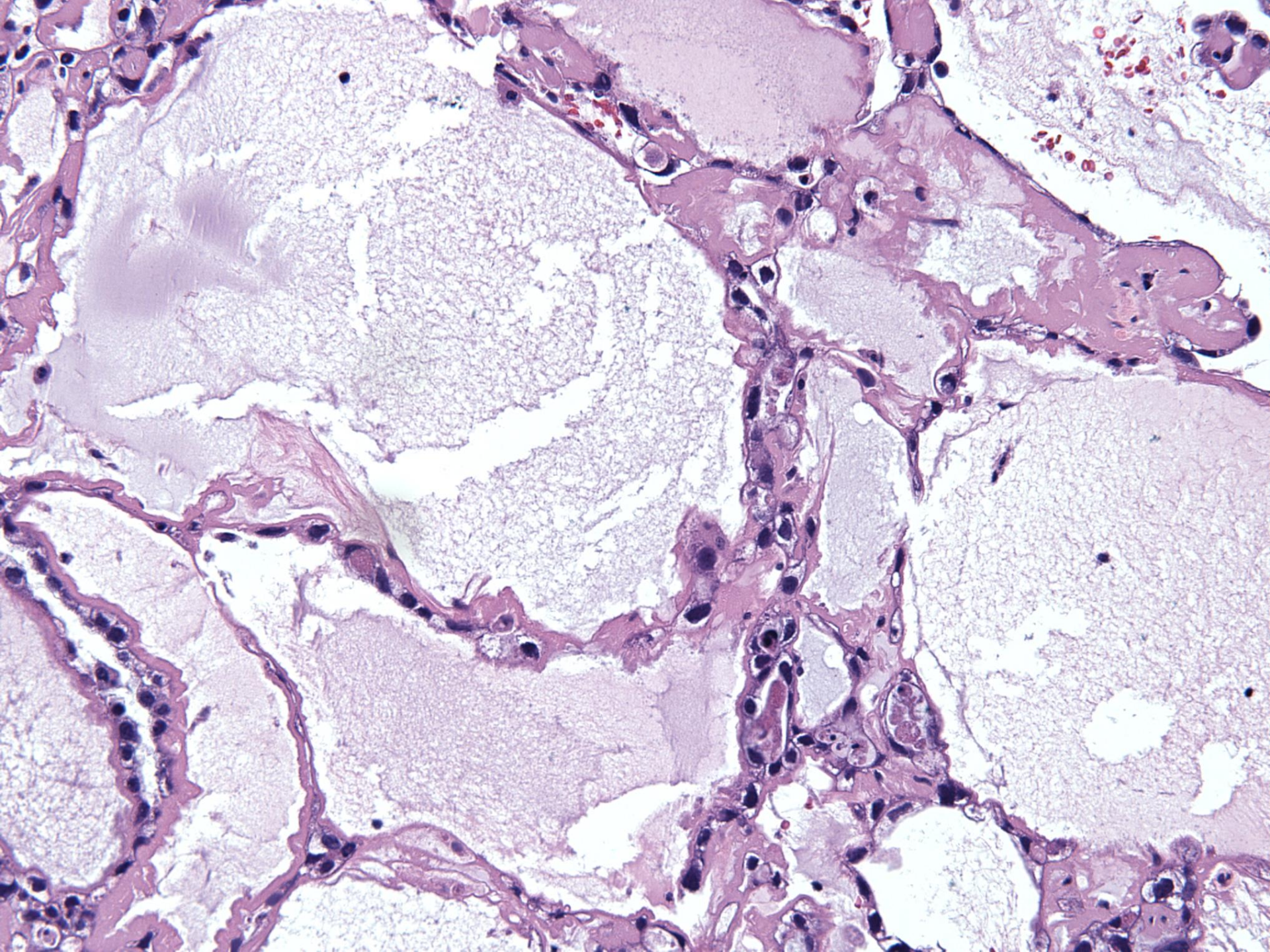


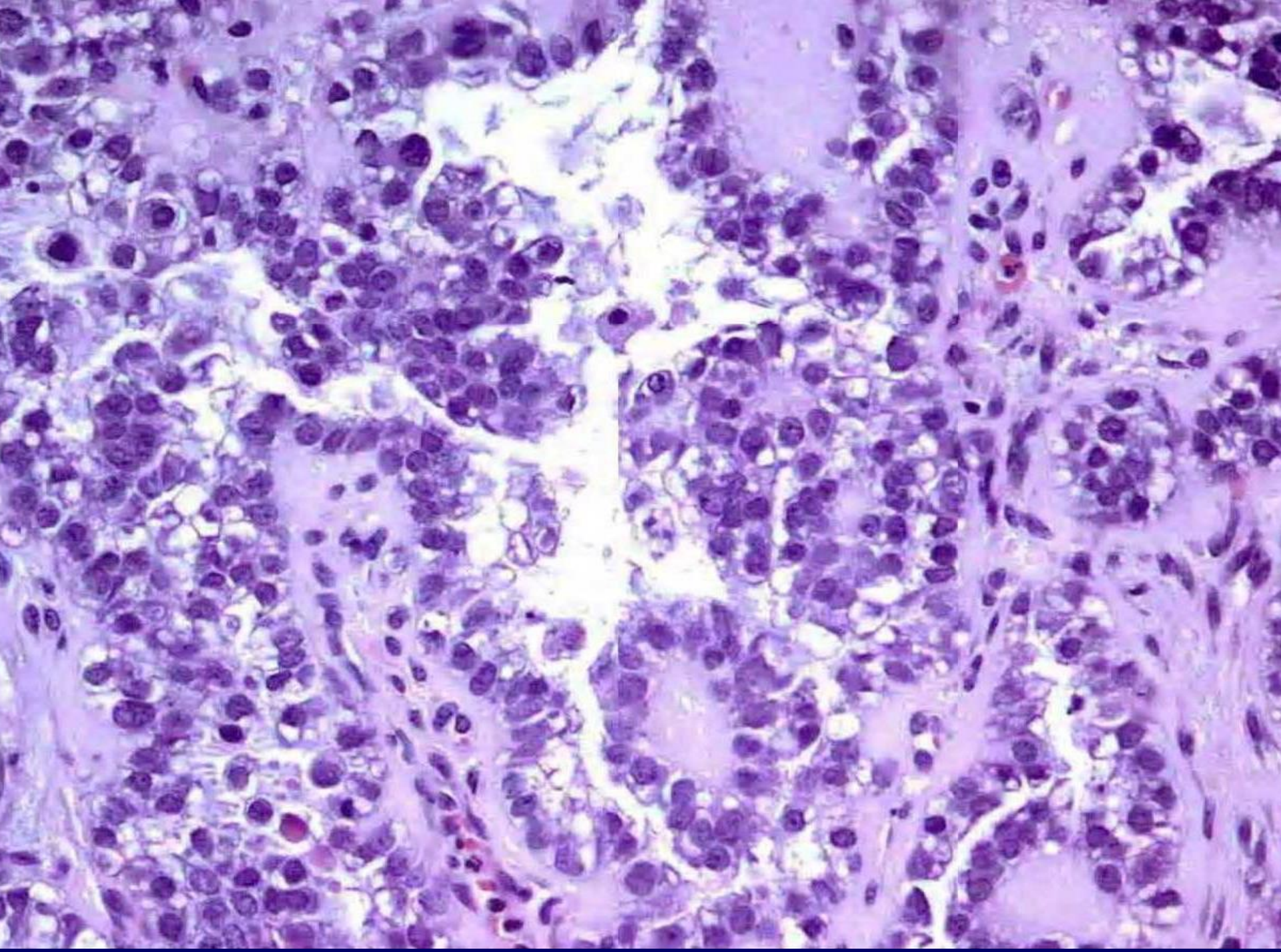


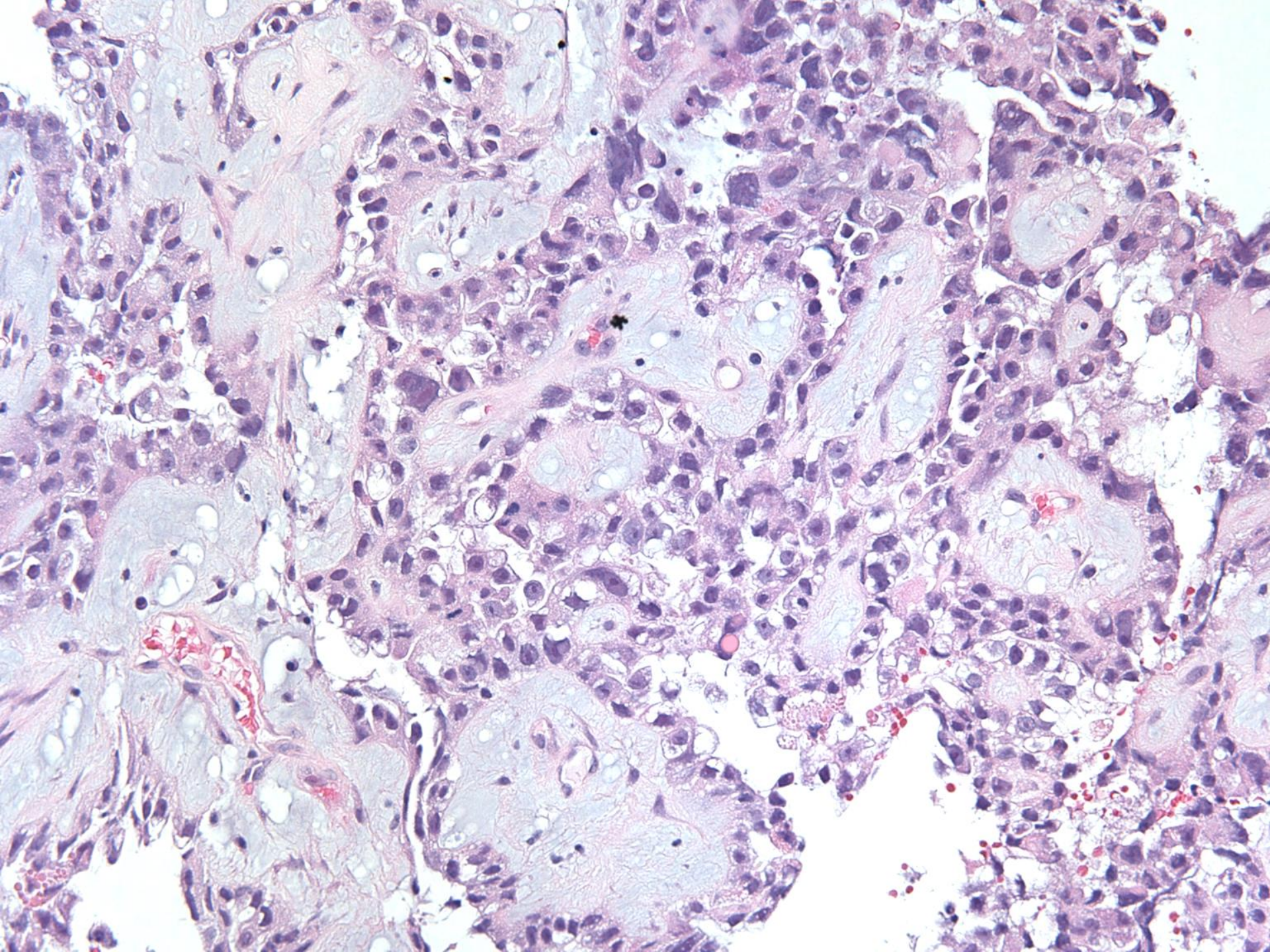






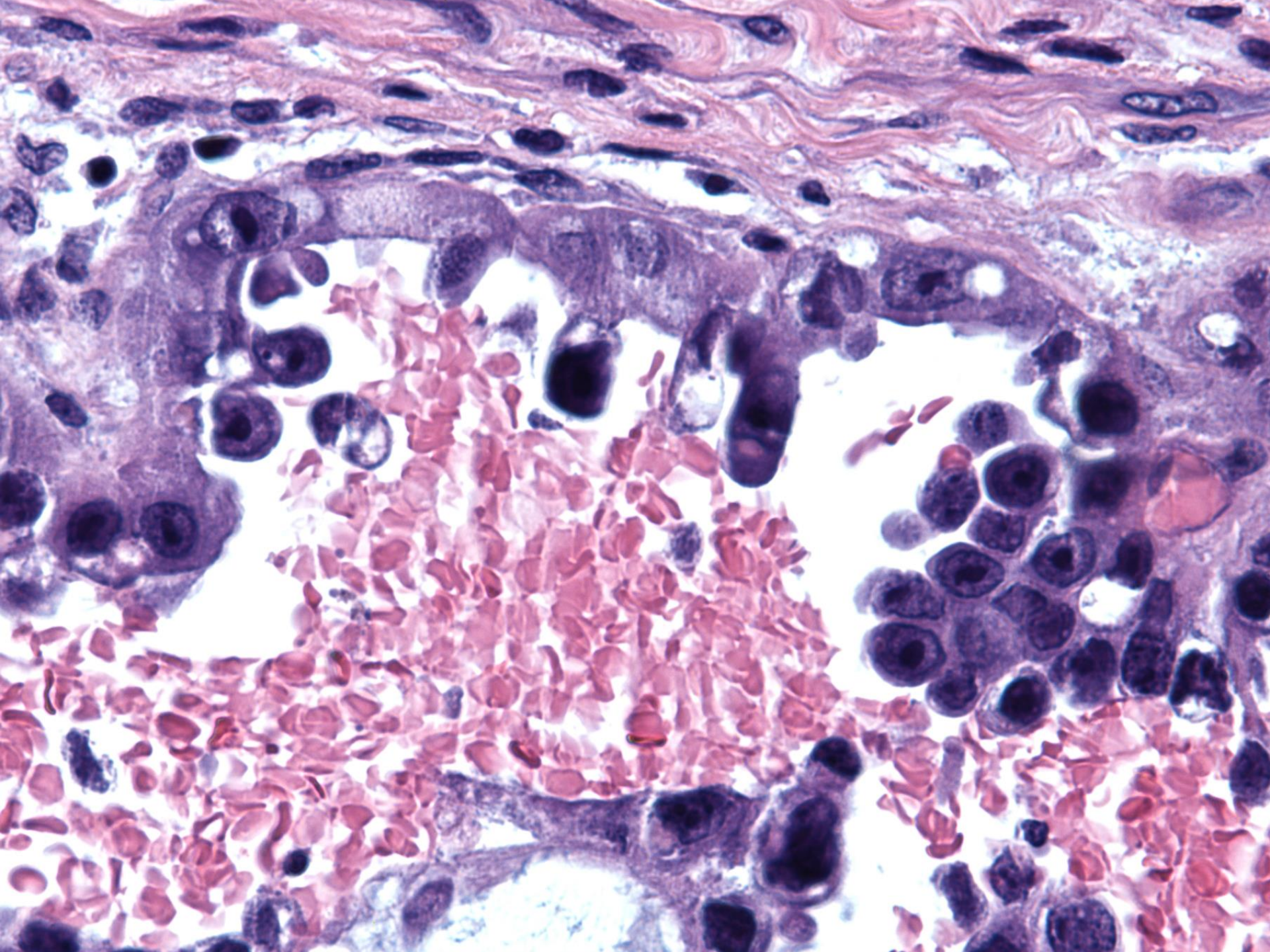


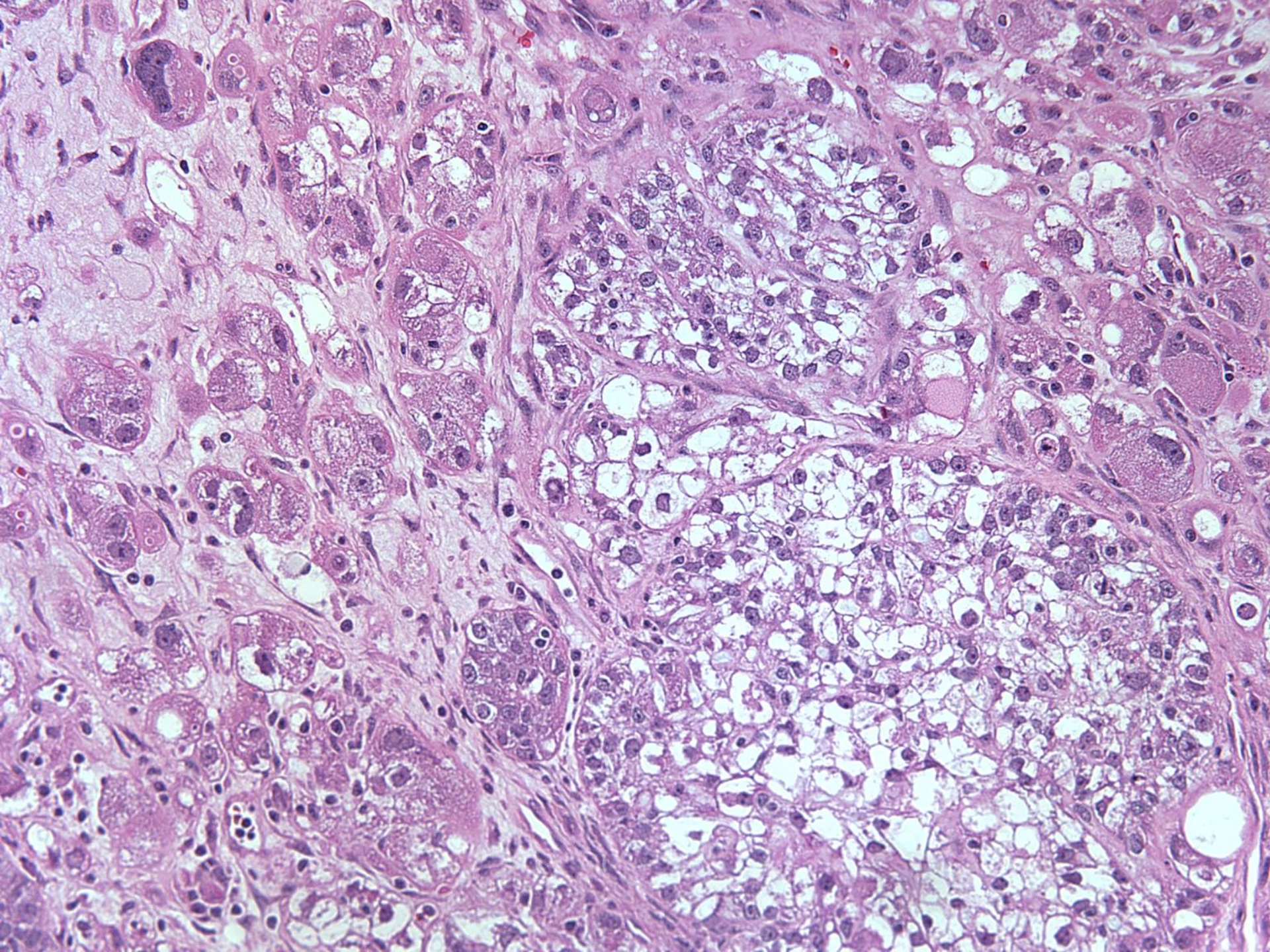


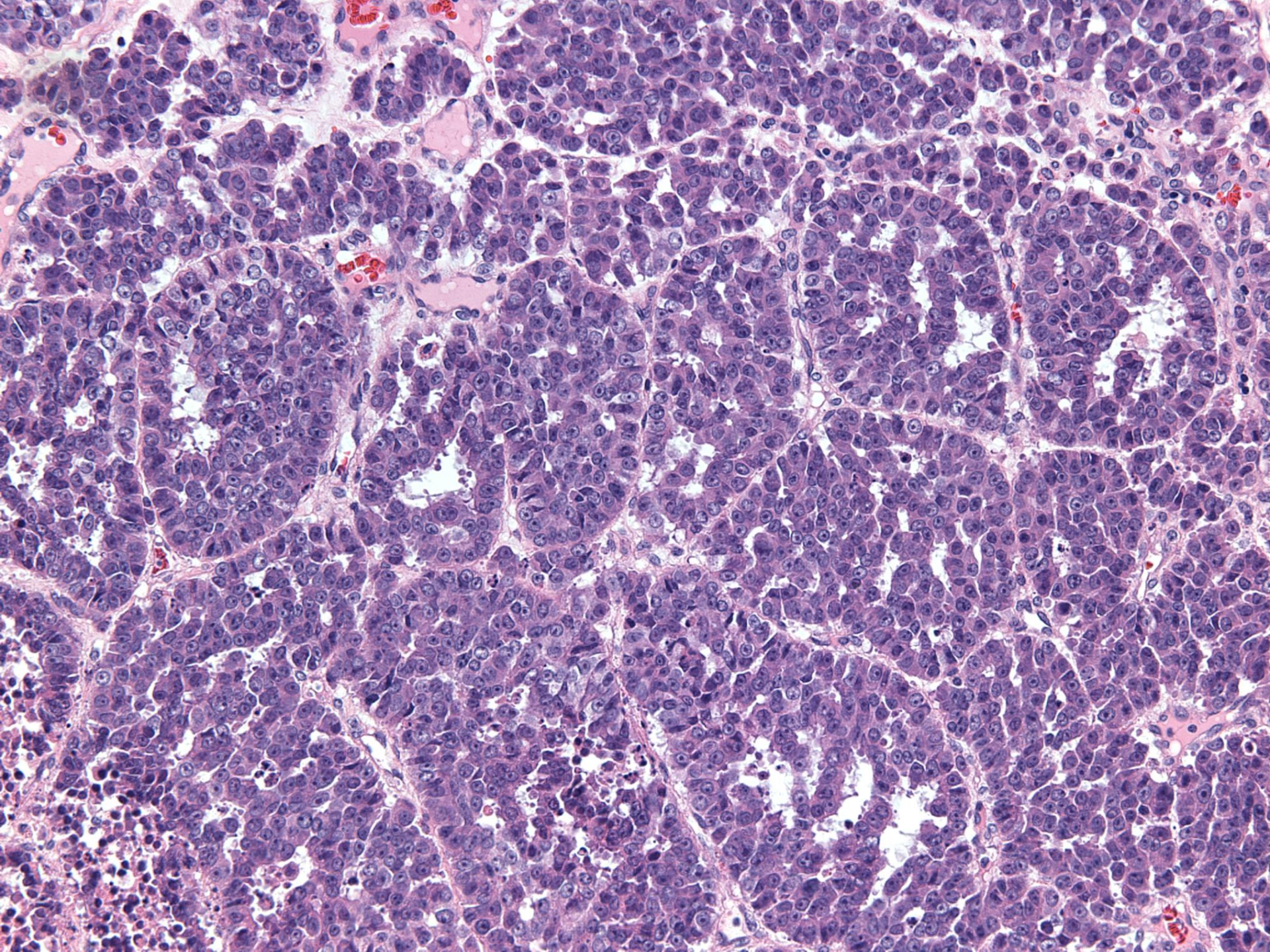


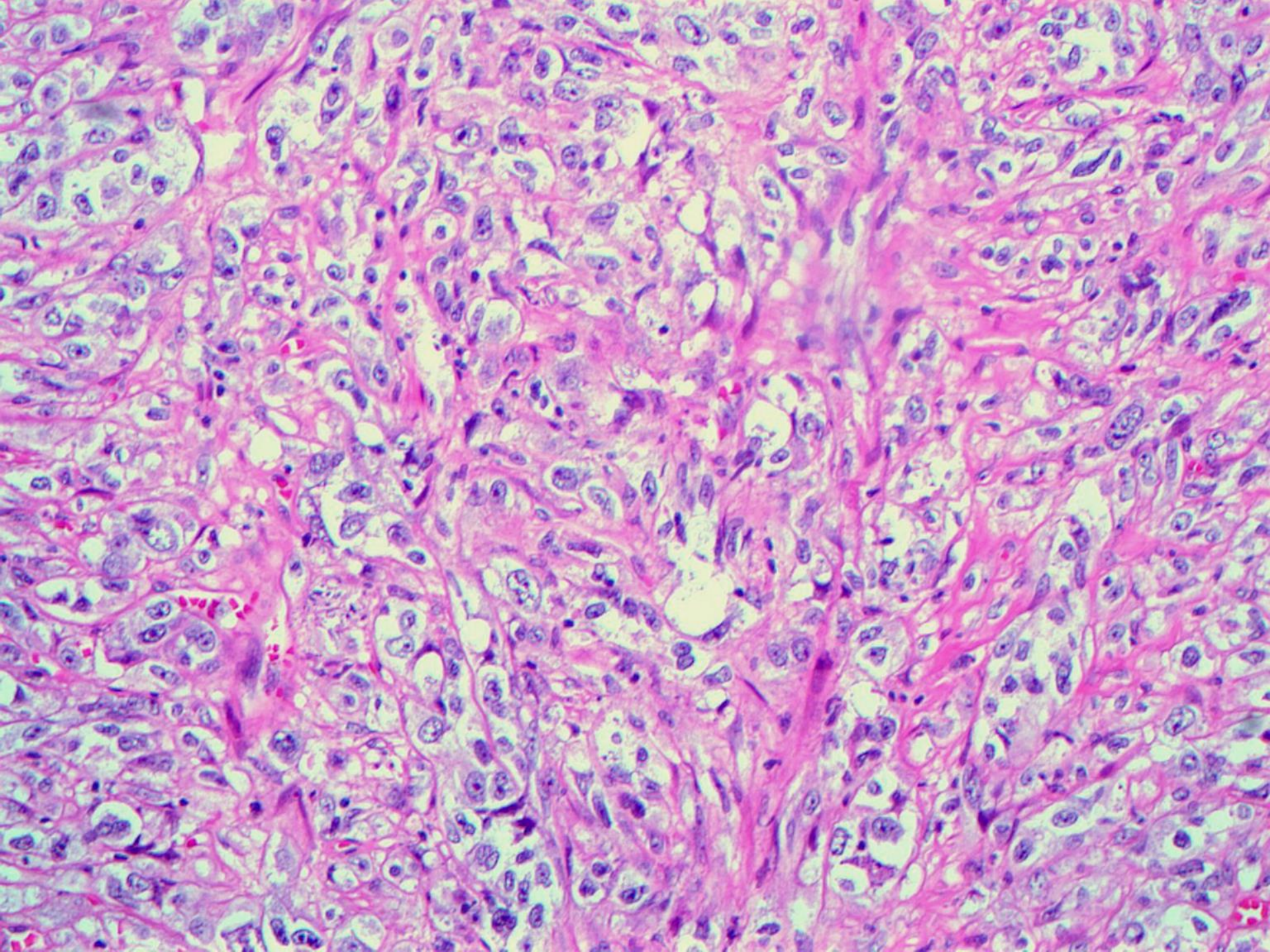
Clear Cell Carcinoma

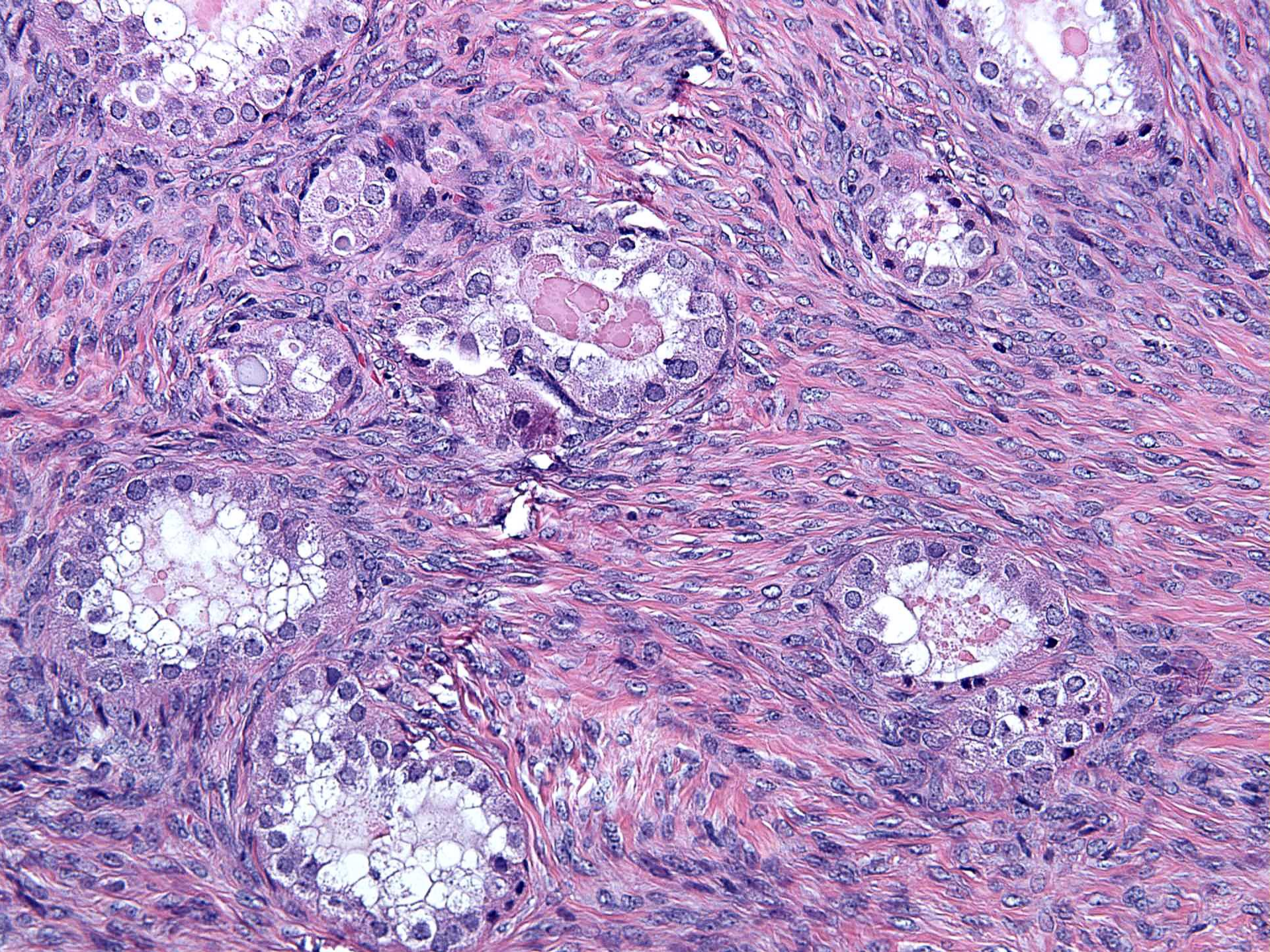
- Hobnail cells
- Clear or eosinophilic granular cytoplasm (glycogen)
- Signet ring cells containing mucin











CCC Associated with endometriosis – ovarian and/or pelvic

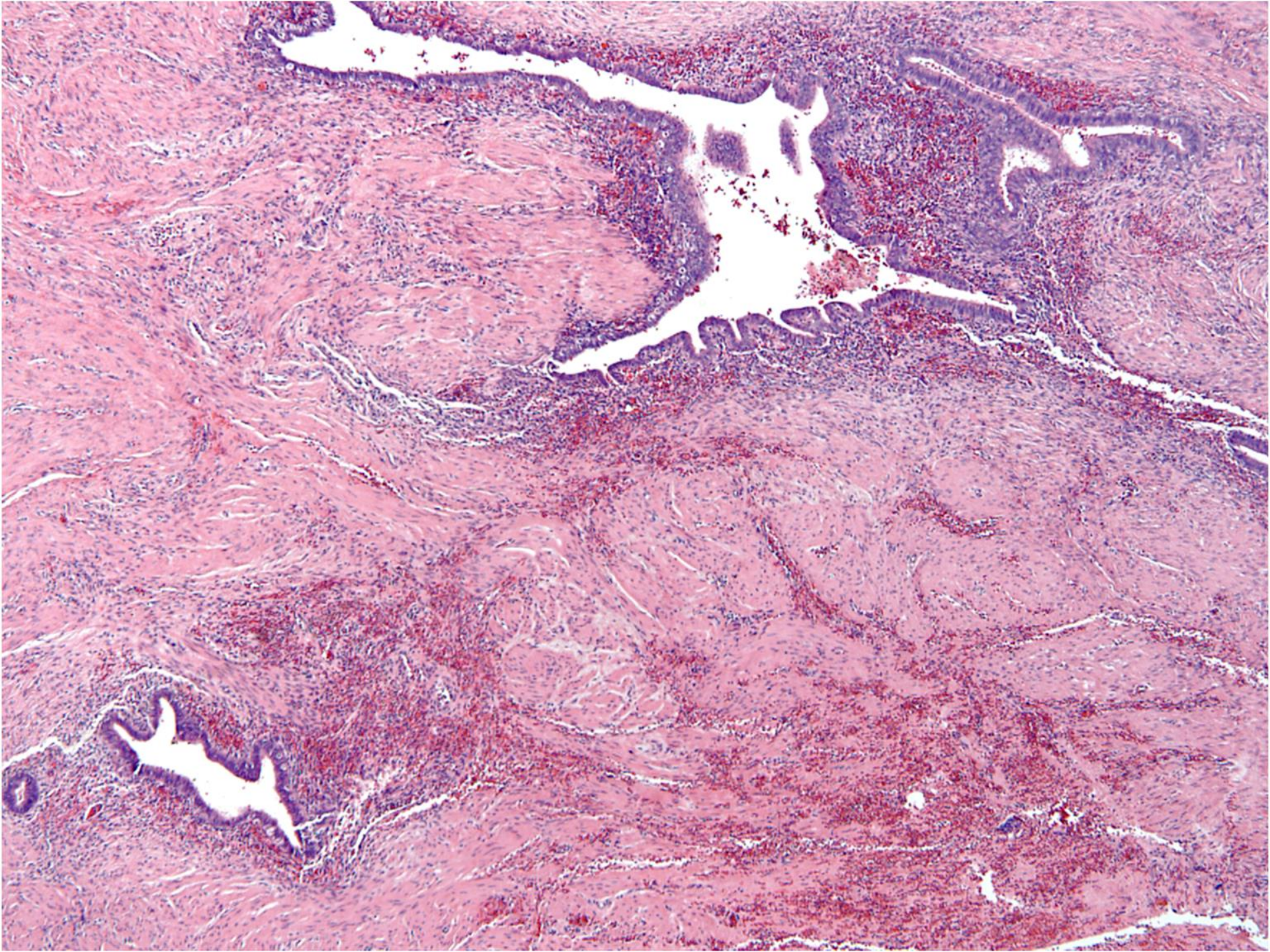
– Cohort study in Denmark (1978-1998)
– Increased risk of OC in women with endometriosis restricted to 2 histologies

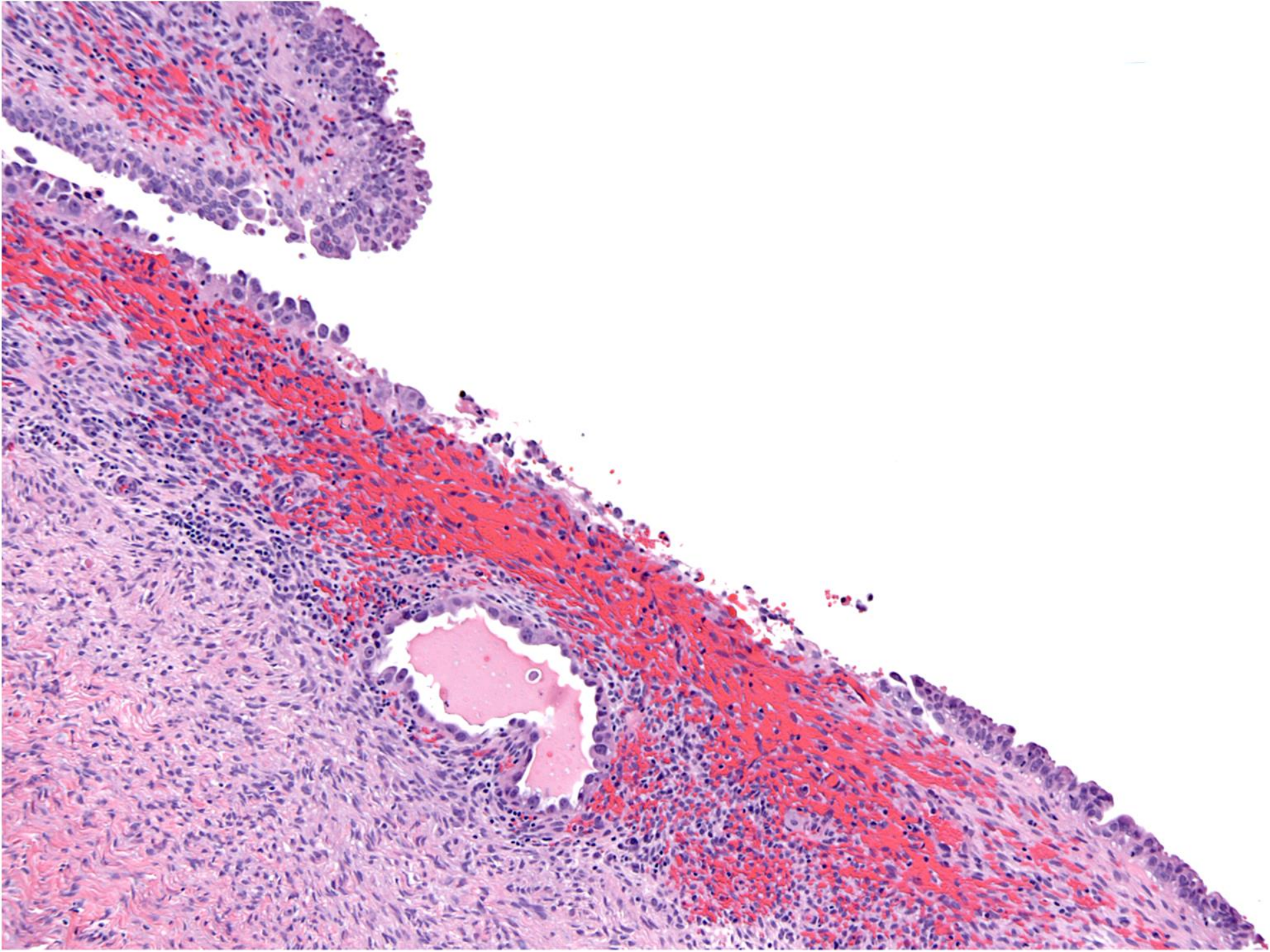
- Endometrioid (RR, 2.53; 95%CI 1.19-5.38)
- Clear cell (RR, 3.37; 95% CI 1.24-9.14)

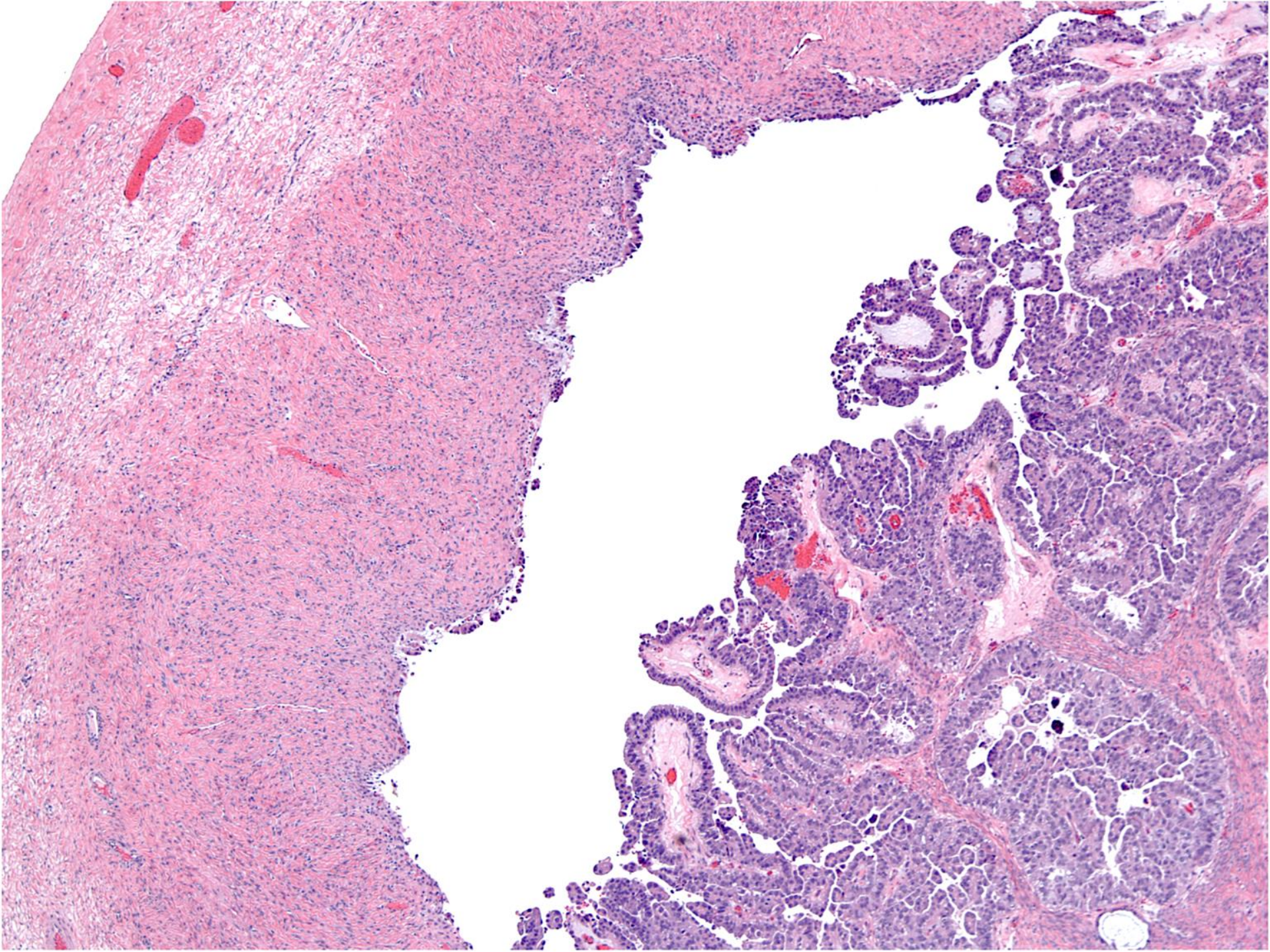
Brinton et al. Cancer Epidemiol Biomar Prev 2005;14:2929-35

CCC Associated with endometriosis – ovarian and/or pelvic

- Endometriosis in up to 70%
- Atypical endometriosis may be seen adjacent to clear cell carcinoma







International Journal of Gynecological Pathology
25:223–229, Lippincott Williams & Wilkins, Baltimore

Original Article

Patterns of Loss of Heterozygosity at 10q23.3 and Microsatellite Instability in Endometriosis, Atypical Endometriosis, and Ovarian Carcinoma Arising in Association With Endometriosis

Rouba Ali-Fehmi, M.D., Ibrahim Khalifeh, M.D., Sudeshna Bandyopadhyay, M.D., W. Dwayne Lawrence, M.D., Elvio Silva, M.D., Dezhong Liao, M.D., Ph.D., Fazlul H. Sarkar, M.D., and Adnan R. Munkarah, M.D.

PTEN in Ovarian CCC

- PTEN inactivation may be early event in malignant transformation of endometriosis

- Mutations occur in both endometrial and ovarian carcinomas

Histology	Inactivation (LOH)	Somatic PTEN Mutation
Endometriotic Ovarian Cyst	13/23 (56.6%)	5/23 (20.6%)
Endometrioid EOC	8/19 (42.1%)	4/19 (20%)
Clear Cell EOC	6/22 (27.3%)	2/22 (8.3%)

Sato et al. Cancer Res 2000;60:7052-6

At the molecular level

ARID1A

- AT-rich interactive domain 1A gene
- Tumor suppressor gene
- Encodes for BAF250a protein
  - Plays critical role in SWI-SNF chromatin remodeling complex present in all eukaryotes
  - Responsible for regulating critical cellular processes and gene expression

ARID1A in Ovarian CCC

- 50% of CCC and 30% of EC have mutations
- No proven clinical features/differences in outcomes associated with reduction/loss of expression of BAF250a by IHC

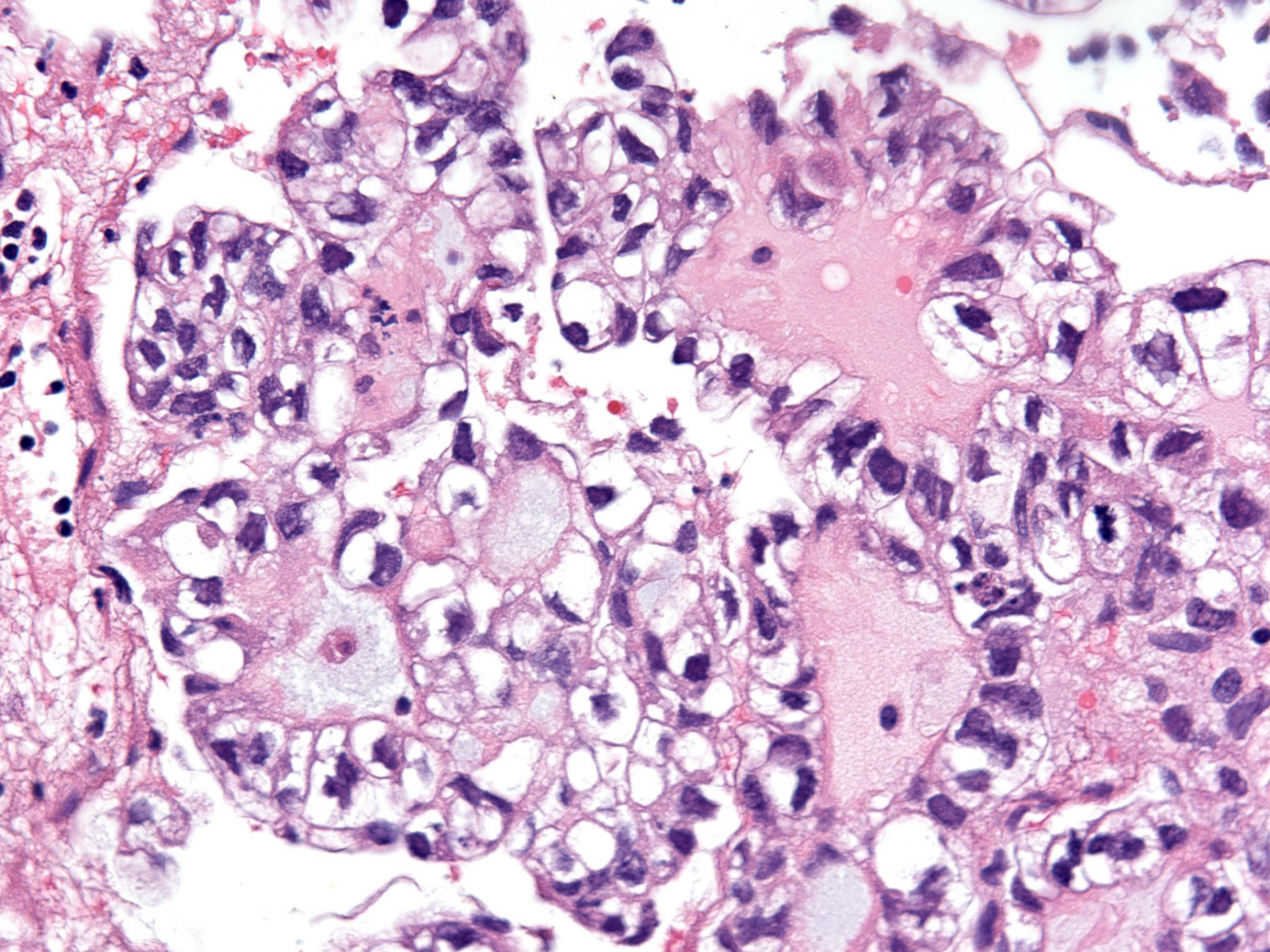
PIK3CA Mutations in Ovarian CCC

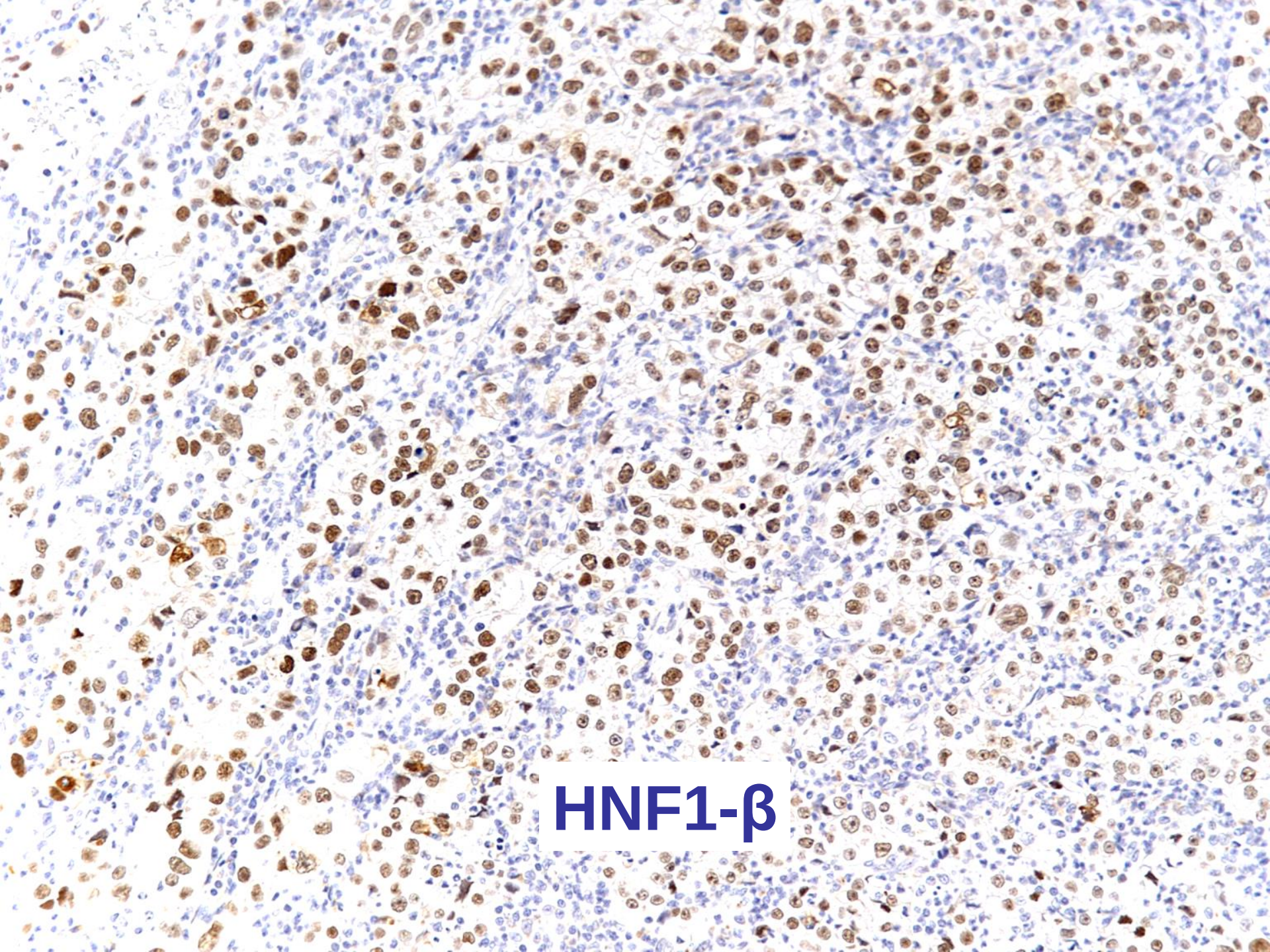
- Frequently co-mutated with ARID1A in CCC
- Observed in up to 40% of CCC
- Activation of PI3K–AKT–mTOR-HIF pathway
- Role of PI3K-mTOR inhibitors?

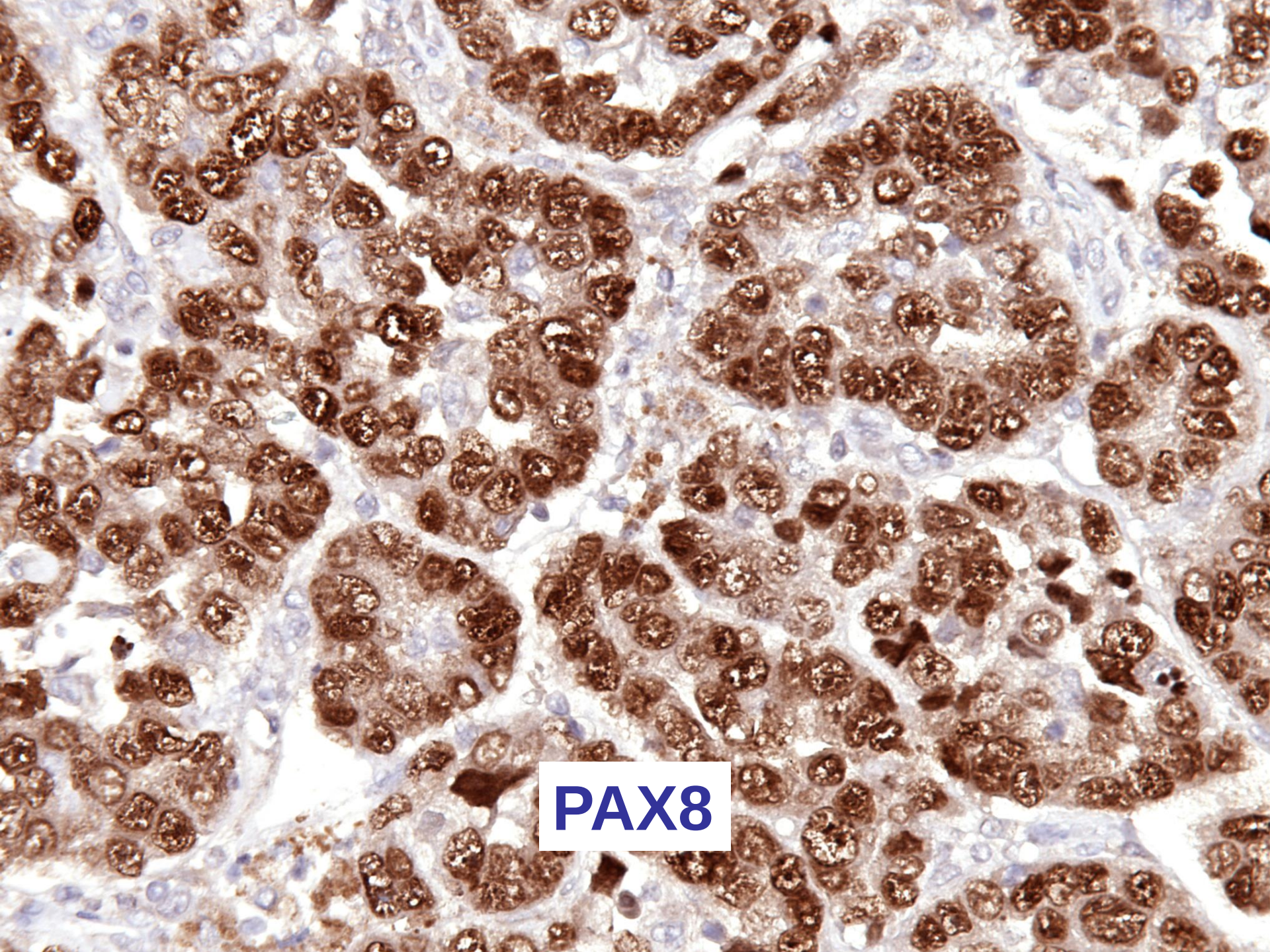
Ovarian Clear Cell Carcinoma
IHC

IHC

Negative	Positive
• ER, (90%) • WT1, (85%) • CK20, (95%) • BAF250a, (20%) • P53, (>85%)	• HNF1β, (85%) • Napsin A, (88%) • CK7, (95%) • PAX8, (85%) • PAX2, (7%)



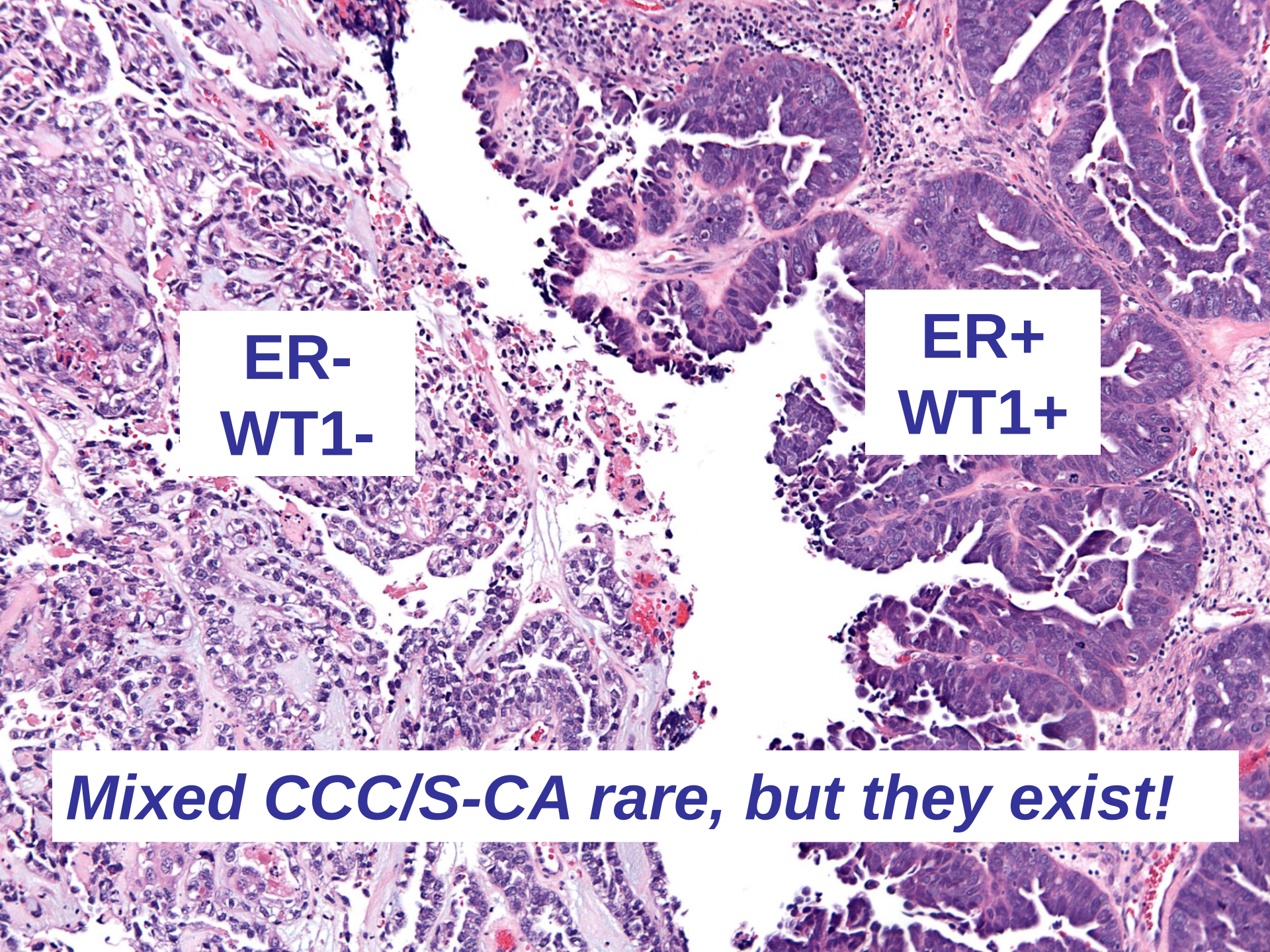

HNF1-β


PAX8

Diagnostic Reproducibly

Diagnosis	Kappa	Translation
Clear Cell Ca (CCC)	0.82	Excellent
Serous Ca (SC)	0.59	Moderate
Mixed Serous-Clear Ca (MSCC)	0.32	Fair

Am J Surg Pathol 2008;32:955-64


ER-
WT1-
ER+
WT1+
Mixed CCC/S-CA rare, but they exist!

ONCOLOGY

Prognostic analysis of ovarian cancer associated with endometriosis

Sanjeev Kumar, MD; Adnan Munkarah, MD; Haitham Arabi, MD; Sudeshna Bandyopadhyay, MD; Assaad Semaan, MD; Kinda Hayek, MD; Gunjal Garg, MD; Robert Morris, MD; Rouba Ali-Fehmi, MD

OBJECTIVE: The objective of the study was to evaluate the prognosis of ovarian cancer arising in endometriosis.

STUDY DESIGN: We retrospectively compared 42 cases of endometriosis-associated ovarian cancer (EAOC) with 184 cases of ovarian carcinoma without endometriosis (OC).

RESULTS: The median age in the EAOC group was 52 vs 59 years in OC (P .05). In comparison with OC, the EAOC patients were more likely to have low-grade (21% vs 8%; $P = .04$) and early-stage tumors (International Federation of Gynecology and Obstetrics I and II combined) (49% vs 24%; $P = .002$). Clear cell (21% vs 2%) and endometrioid (14% vs 3%) tumors were more frequent in EAOC, whereas mucinous tumors were more prevalent in OC ($P = .001$). The median survival (199 vs 62 months) and the 5 year survival (62% vs 51%) were better for EAOC when compared with OC ($P = .038$). After controlling for age, stage, grade, and treatment, association with endometriosis was not an independent predictor of better survival in ovarian cancer.

CONCLUSION: As such, EAOC has a much better survival rate than OC. This could be explained by the higher prevalence of early-stage and low-grade tumors in EAOC when compared with OC.

Key words: endometriosis, ovarian cancer, prognosis, survival

Grade in CCC

- Most exhibit range of nuclear atypia – but some feature only low to moderate pleomorphism
- Mitotic index variable – often low
- Architecture varies from well developed papillae to sheets of cells
- But, to date, no evidence that grading (nuclear, architecture, mitotic index) stratifies outcome

CCC: Cystic vs Adenofibromatous

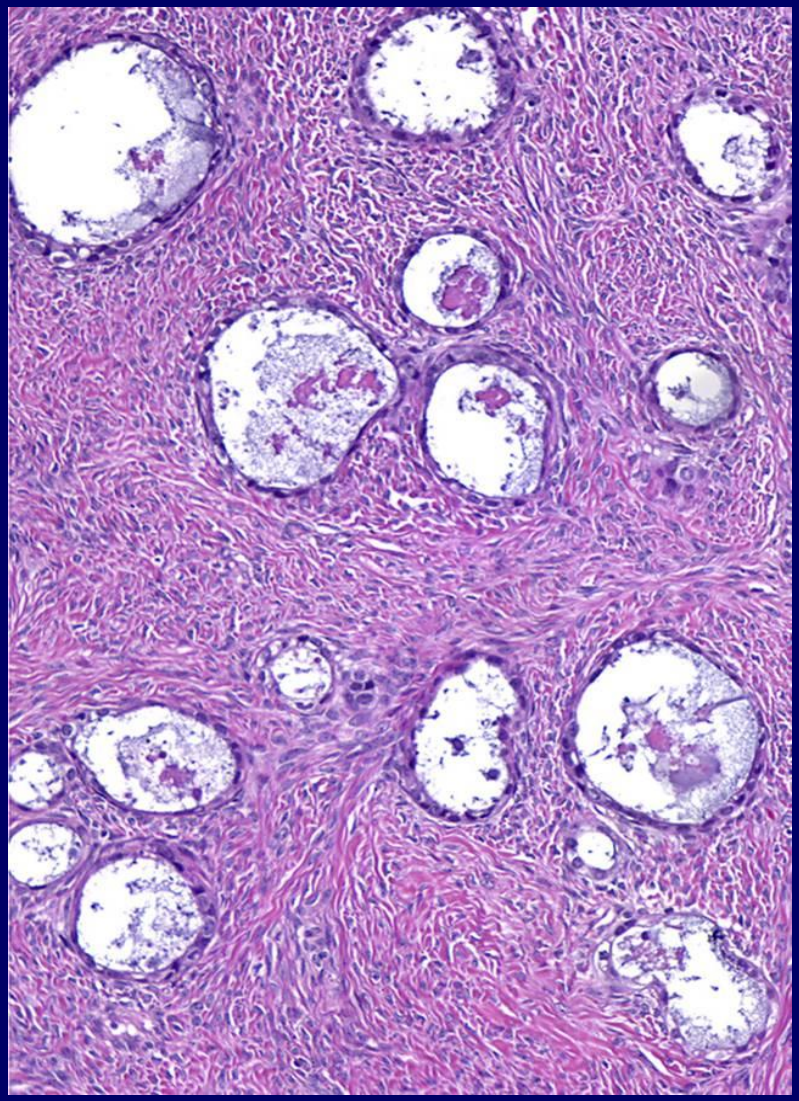
- Adenofibromatous tumors may be better, but is this reflection of borderline, low stage cases?
- Cystic tumors may be better, but is this reflection of low tumor volume?
- Endometriosis tumors probably not better, but may be worse for mixed tumors (this may be reflection of stage)?

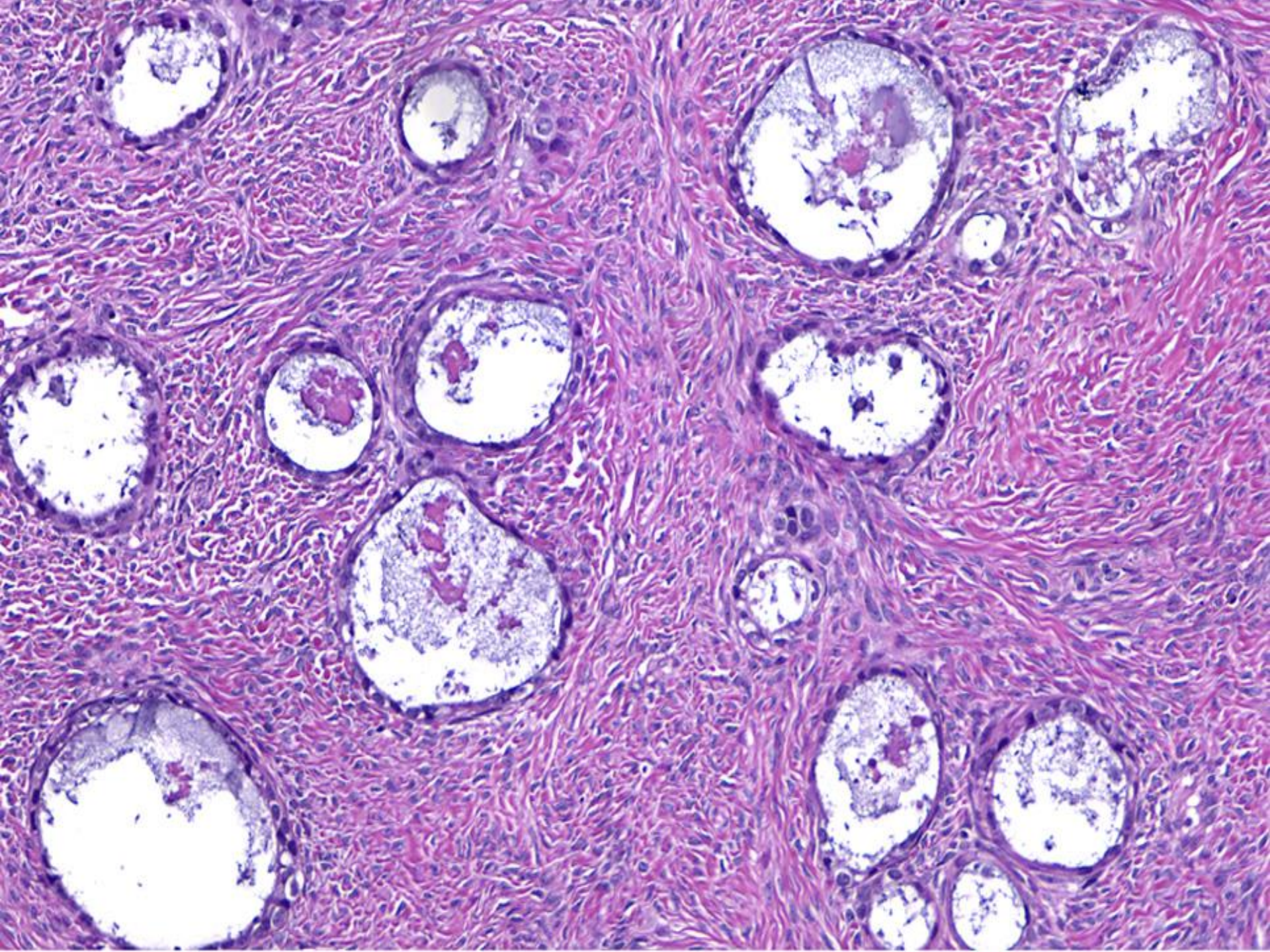
Ovarian Clear Cell Carcinoma: Diagnostic Problems

- Epithelial tumor:
- Borderline clear cell tumor
- Serous carcinoma
- Endometrioid carcinoma
- Mucinous carcinoma
- Mixed surface epithelial carcinoma
- Borderline serous tumor
- Germ line tumor:
- Yolk sac tumor
- Dysgerminoma
- Sex cord stromal tumor:
- Metastasis (esp. renal cell):

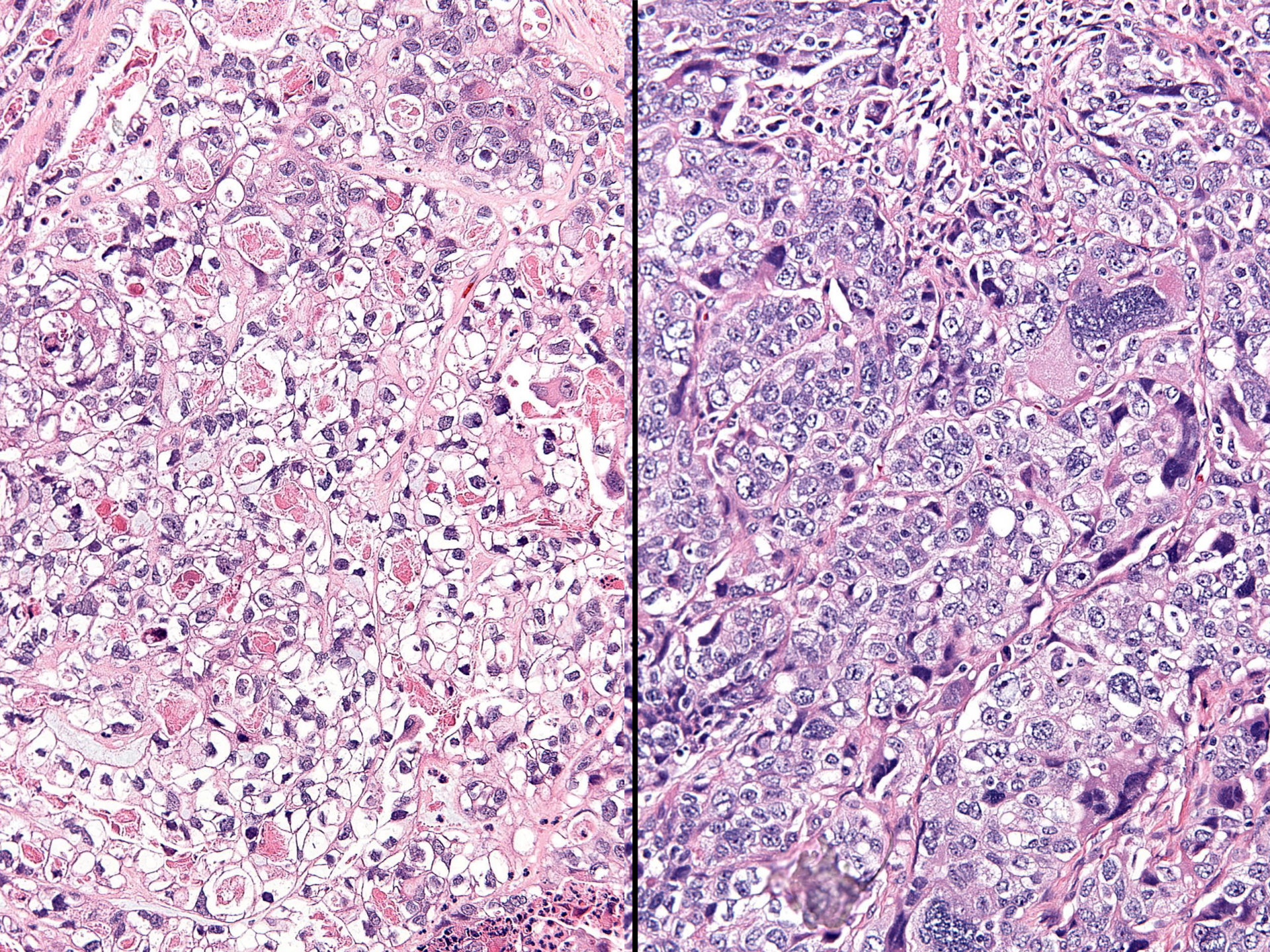
Borderline Clear Cell Tumor

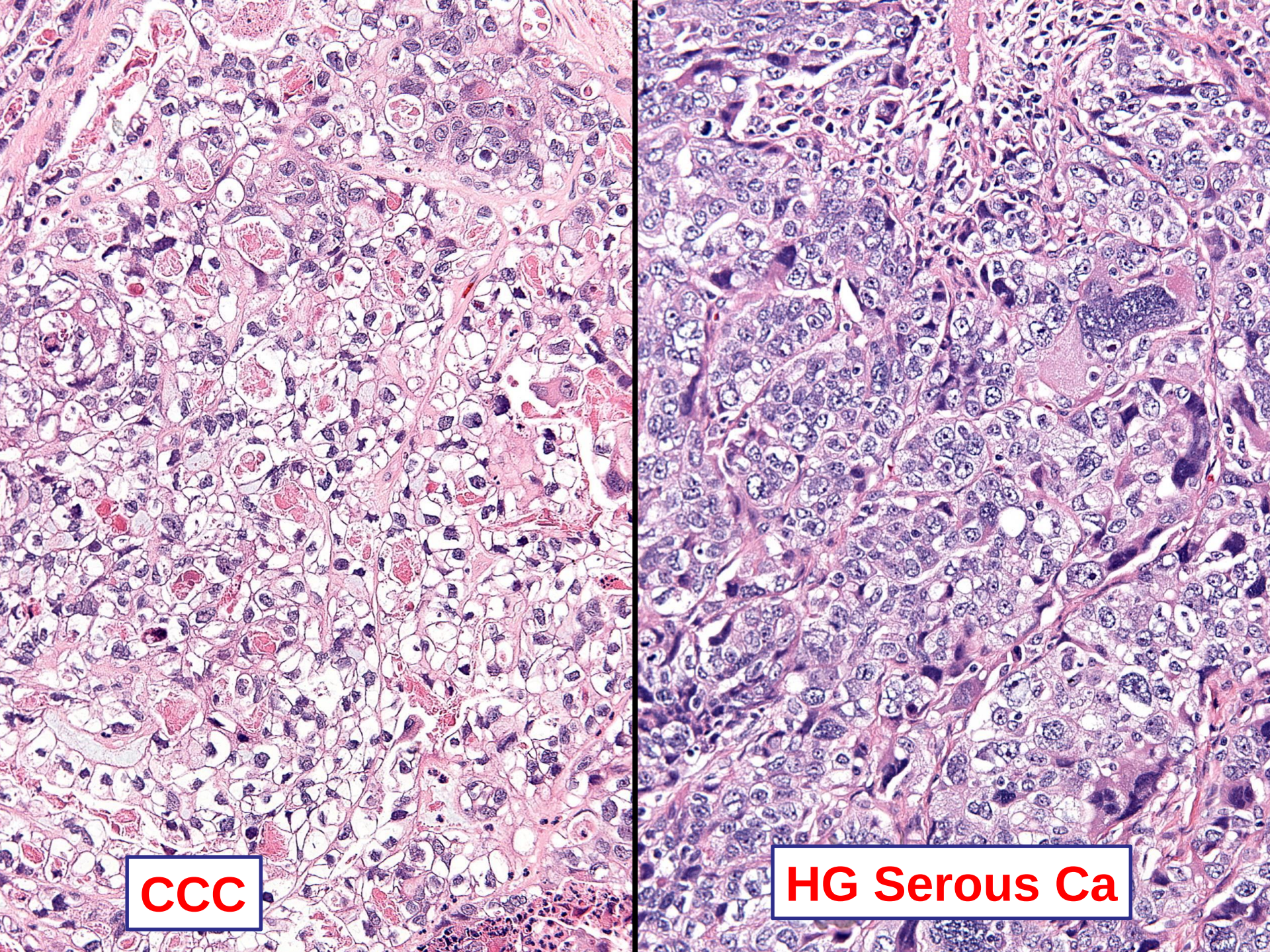
- One or two cell layers
- Minimal to mild atypia
- Prominent fibromatous stroma
- Mitotic figures <1/10 hpf
- VERY RARE





Quiz time!




CCC
HG Serous Ca

CCC

- Unilateral
- Hobnail cells
- Other patterns CCC
- WT1-, ER-
- HNF-1 beta+/-

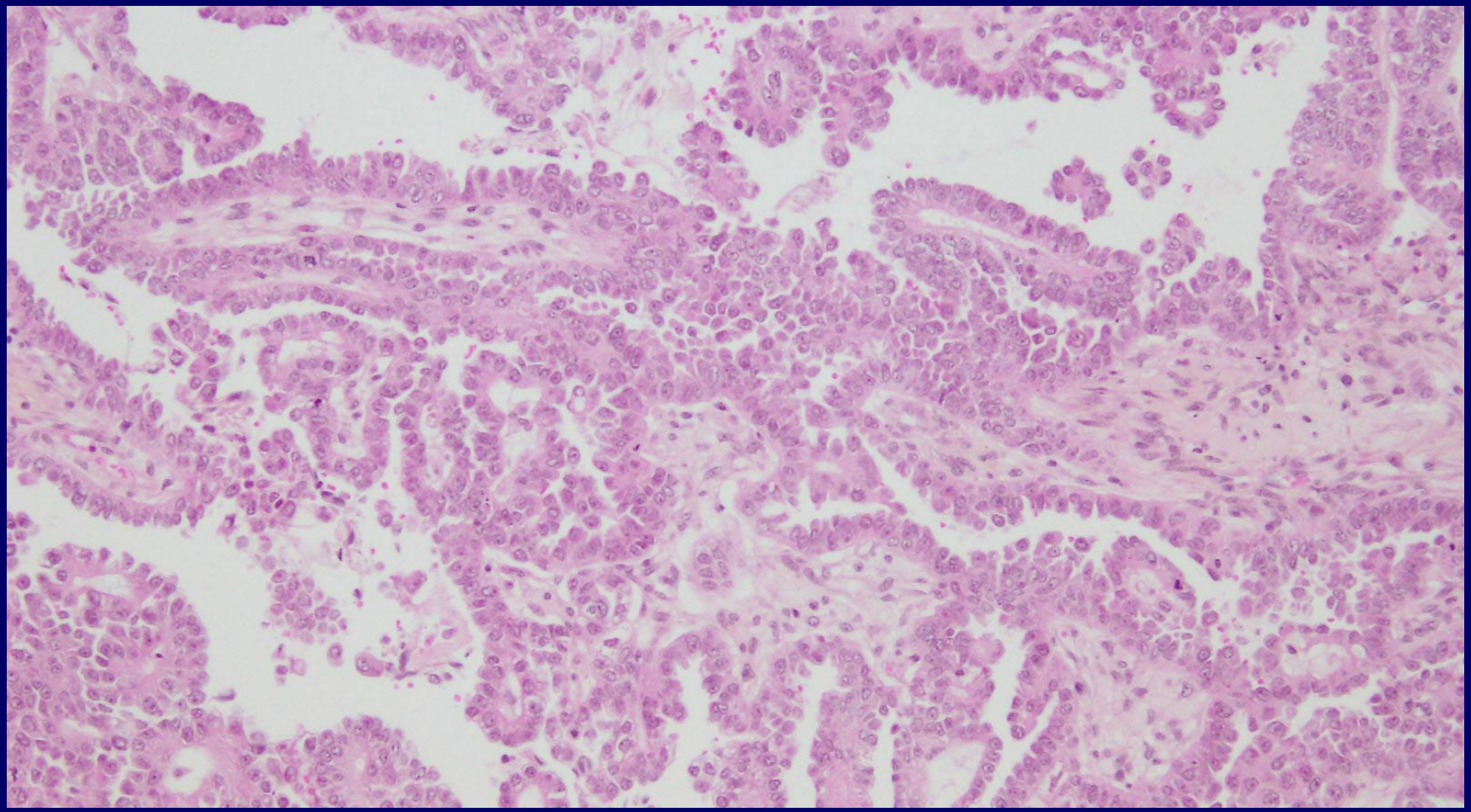
Serous-CA

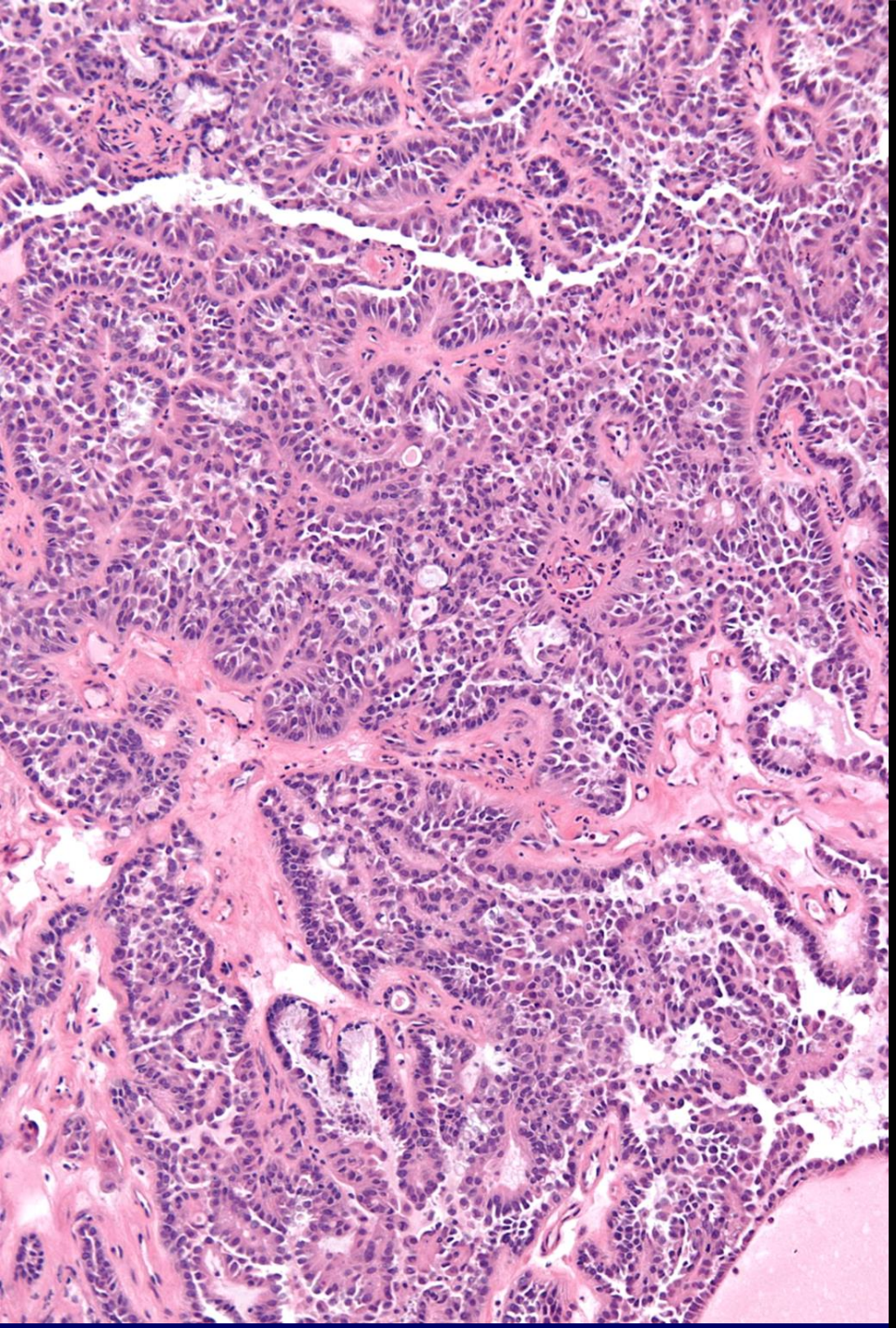
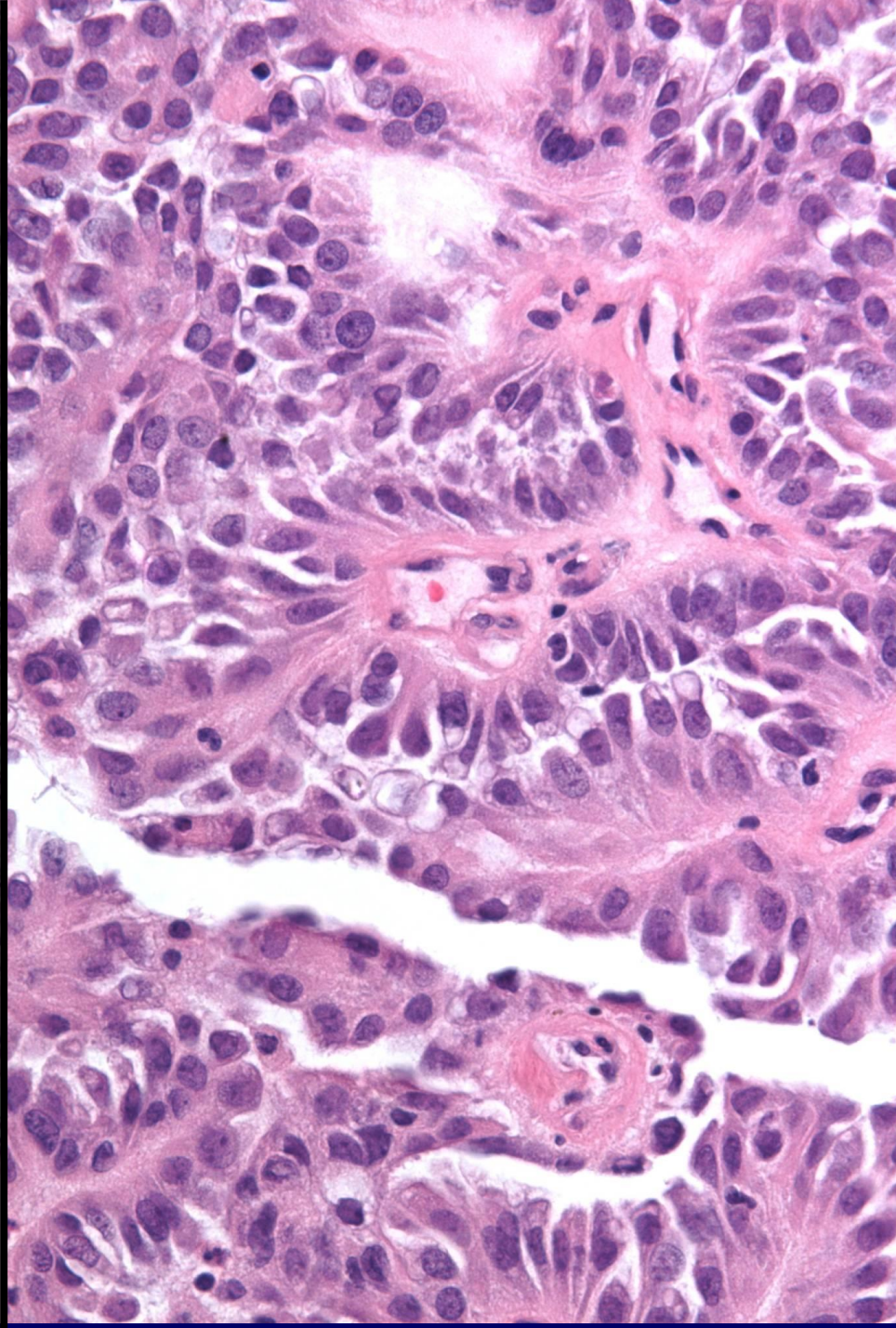
- Bilateral
- Cytoplasmic clearing
- Other patterns S-CA
- WT1+, ER+
- HNF-1 beta-/+

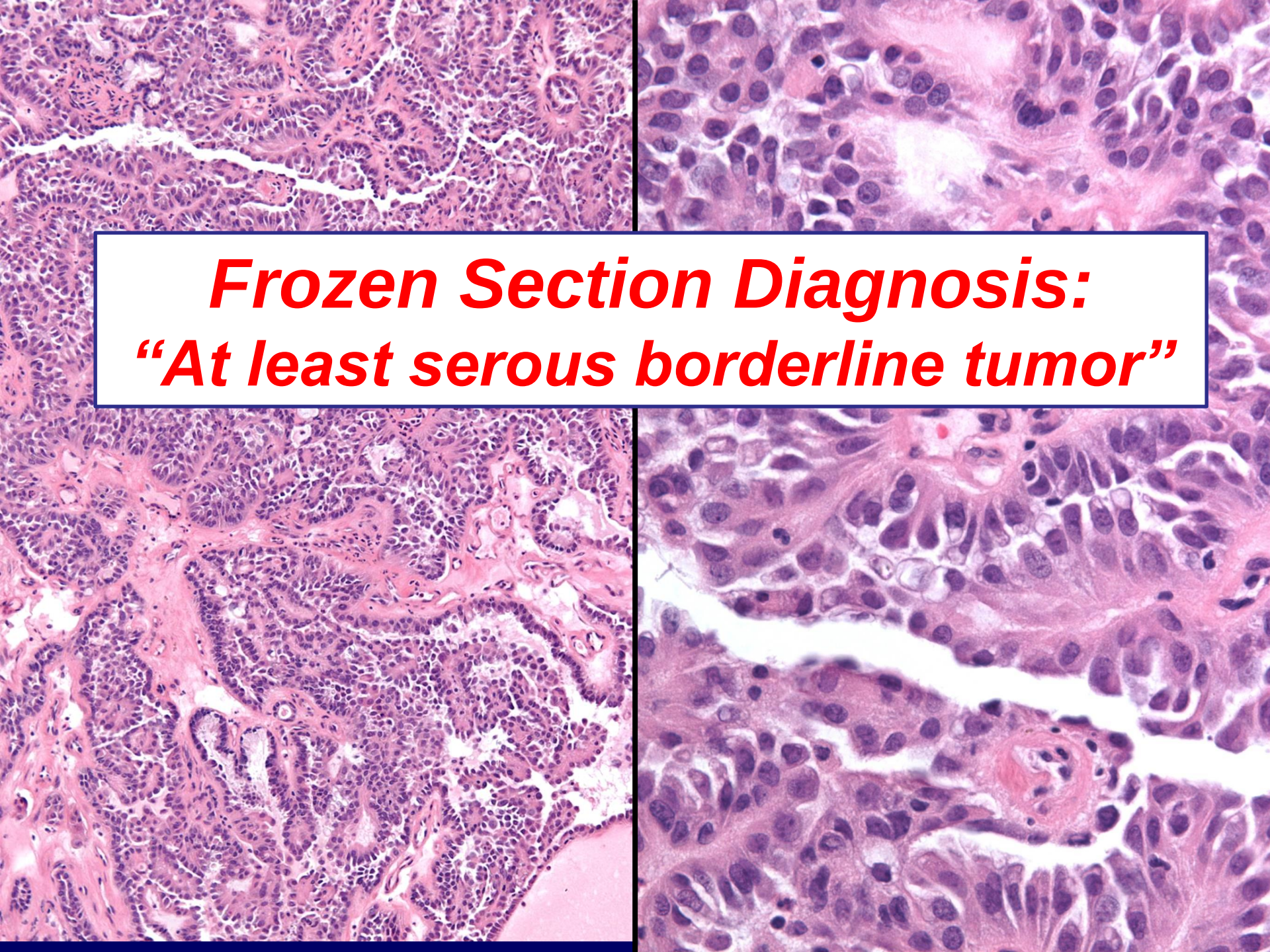
CCC vs. Ovarian Serous Carcinoma (SC)

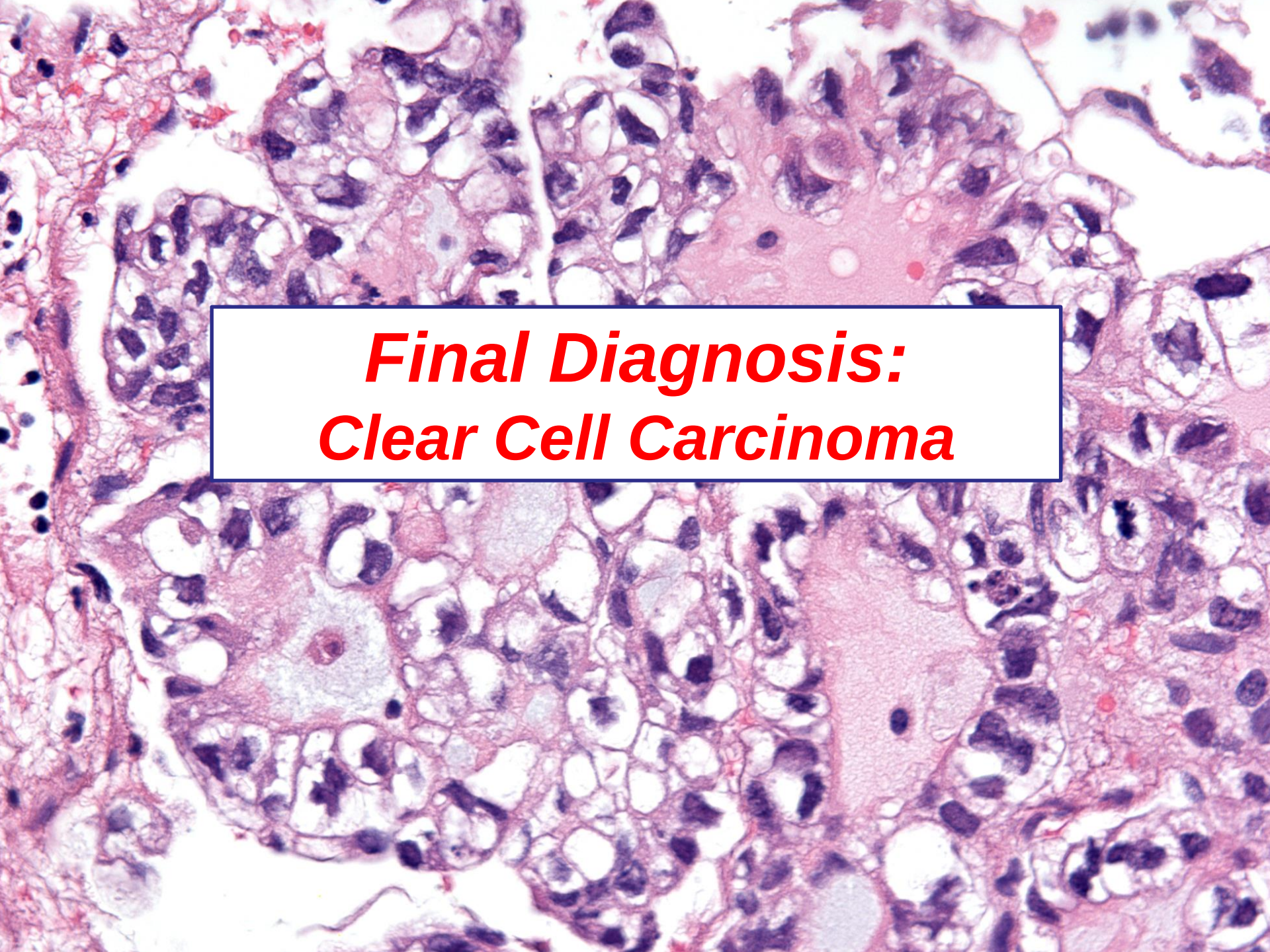
- No convincing evidence that low stage CCC is more aggressive than low stage SC – *but* low stage SC exceedingly rare
- High stage CCC does not respond to standard platinum-based therapy

Frozen Section Diagnosis:




Frozen Section Diagnosis:
"At least serous borderline tumor"


Final Diagnosis:
Clear Cell Carcinoma

Papillary CCC versus SBT

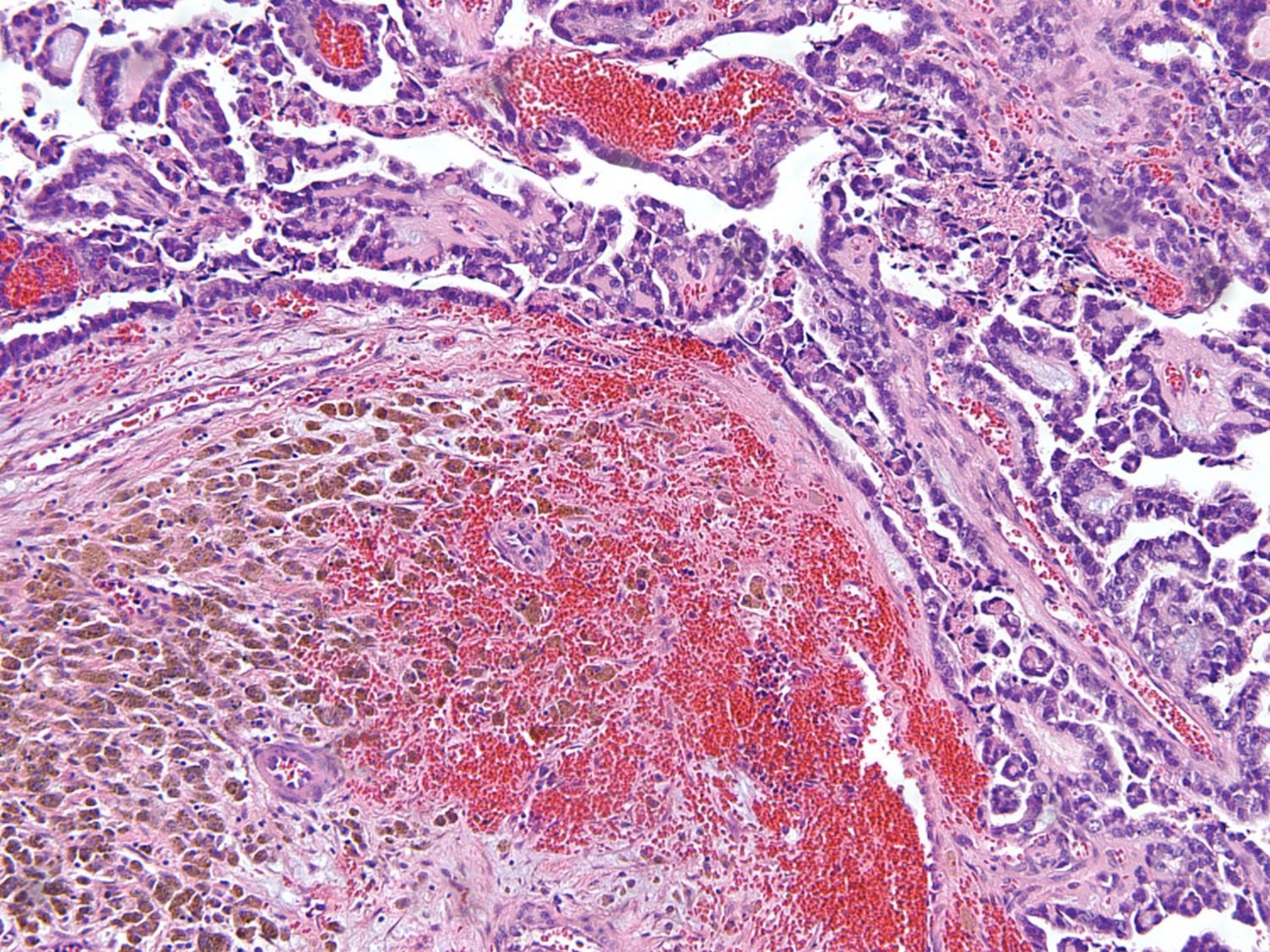
- Both may occur in younger patient population (reproductive age)
- May result in inadequate or delayed staging & therapy
- Requires extensive sectioning to determine correct diagnosis

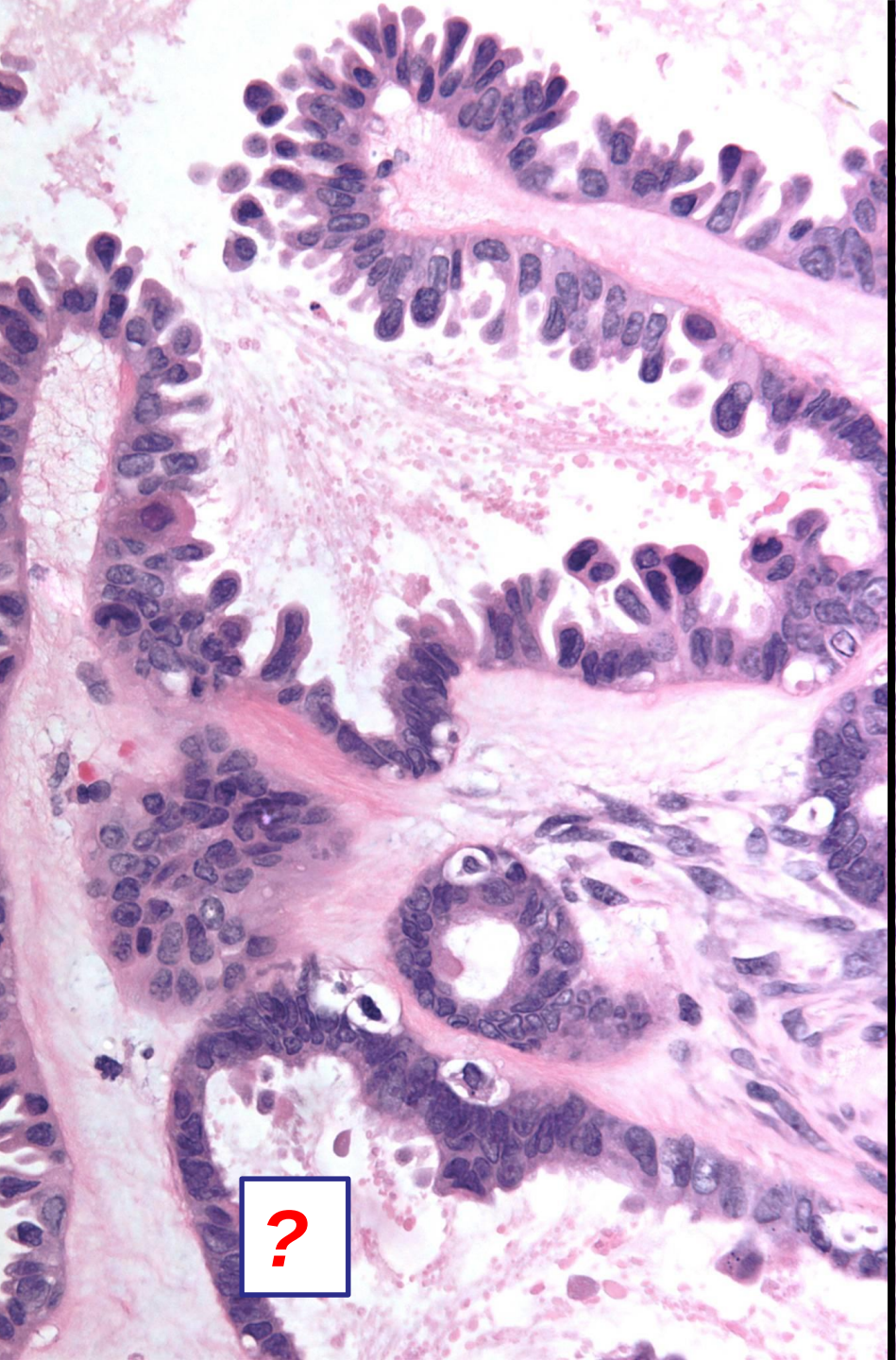
CCC

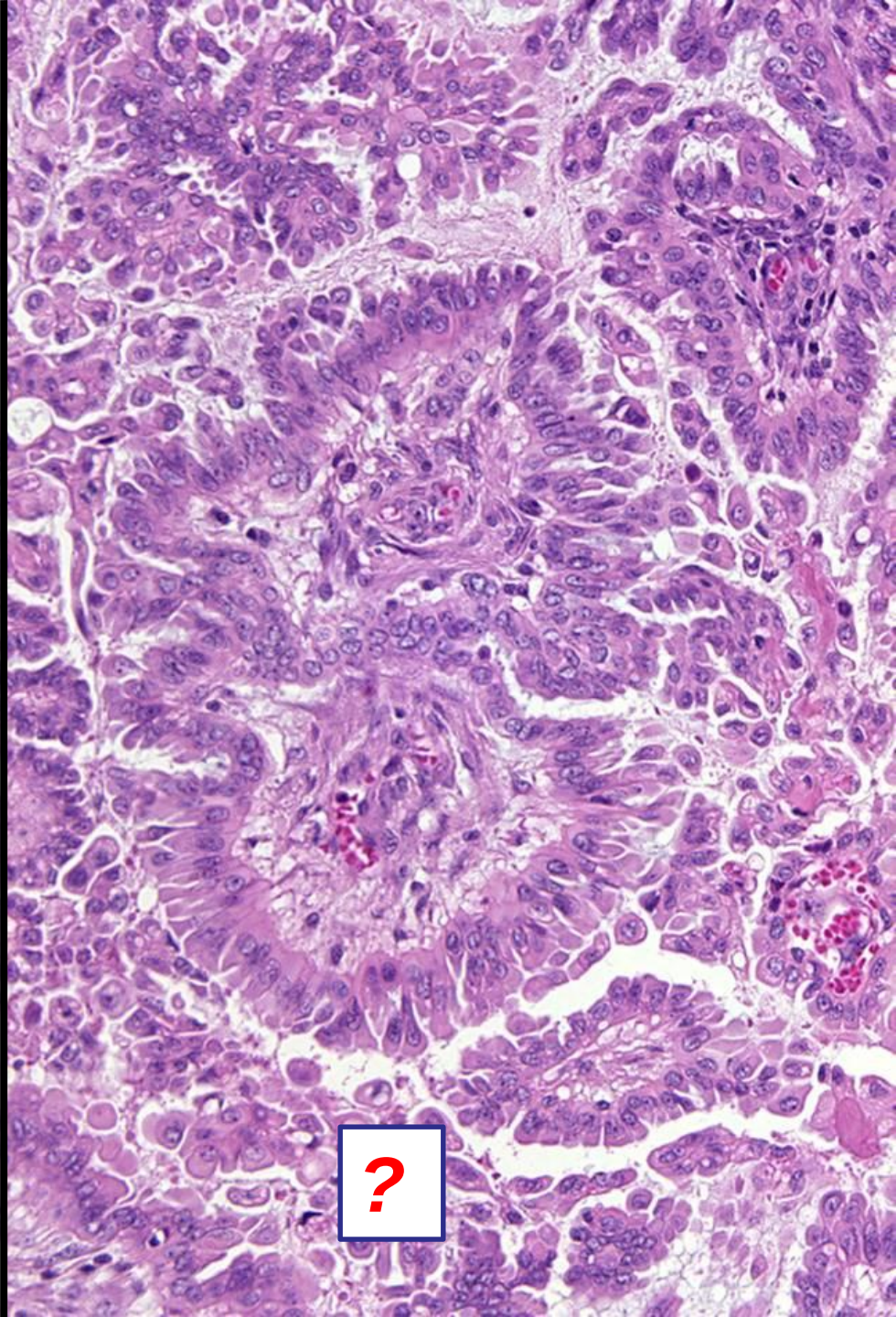
- Unilateral
- Monomorphic cell population
- Hobnail cells
- Endometriosis common
- Other patterns CCC
- WT1-/ER-

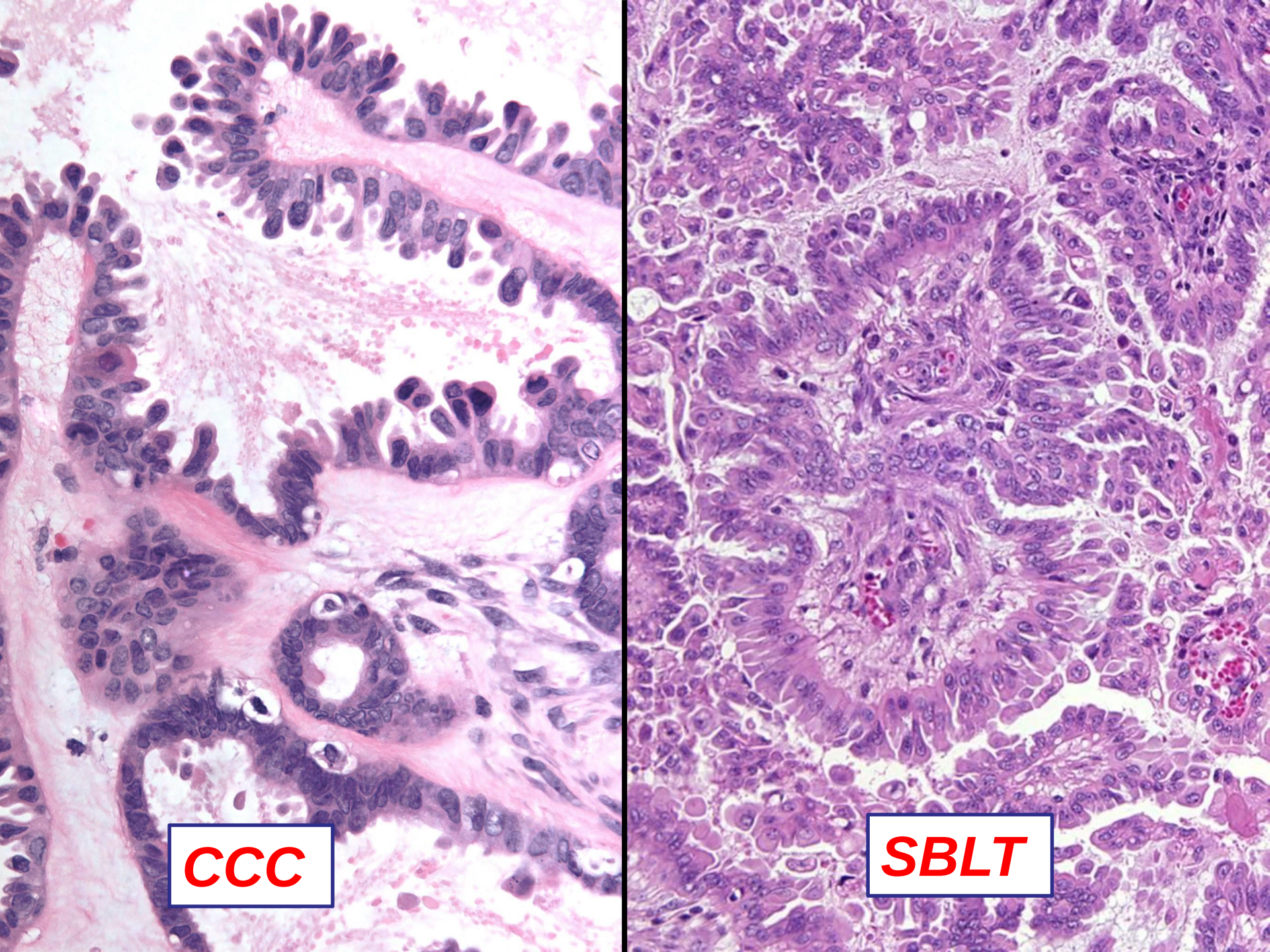
SBT

- Bilateral
- Mixed ciliated and pink cells
- Pink cell tufts
- Endometriosis uncommon
- Other patterns S-LMP
- WT1+/ER+

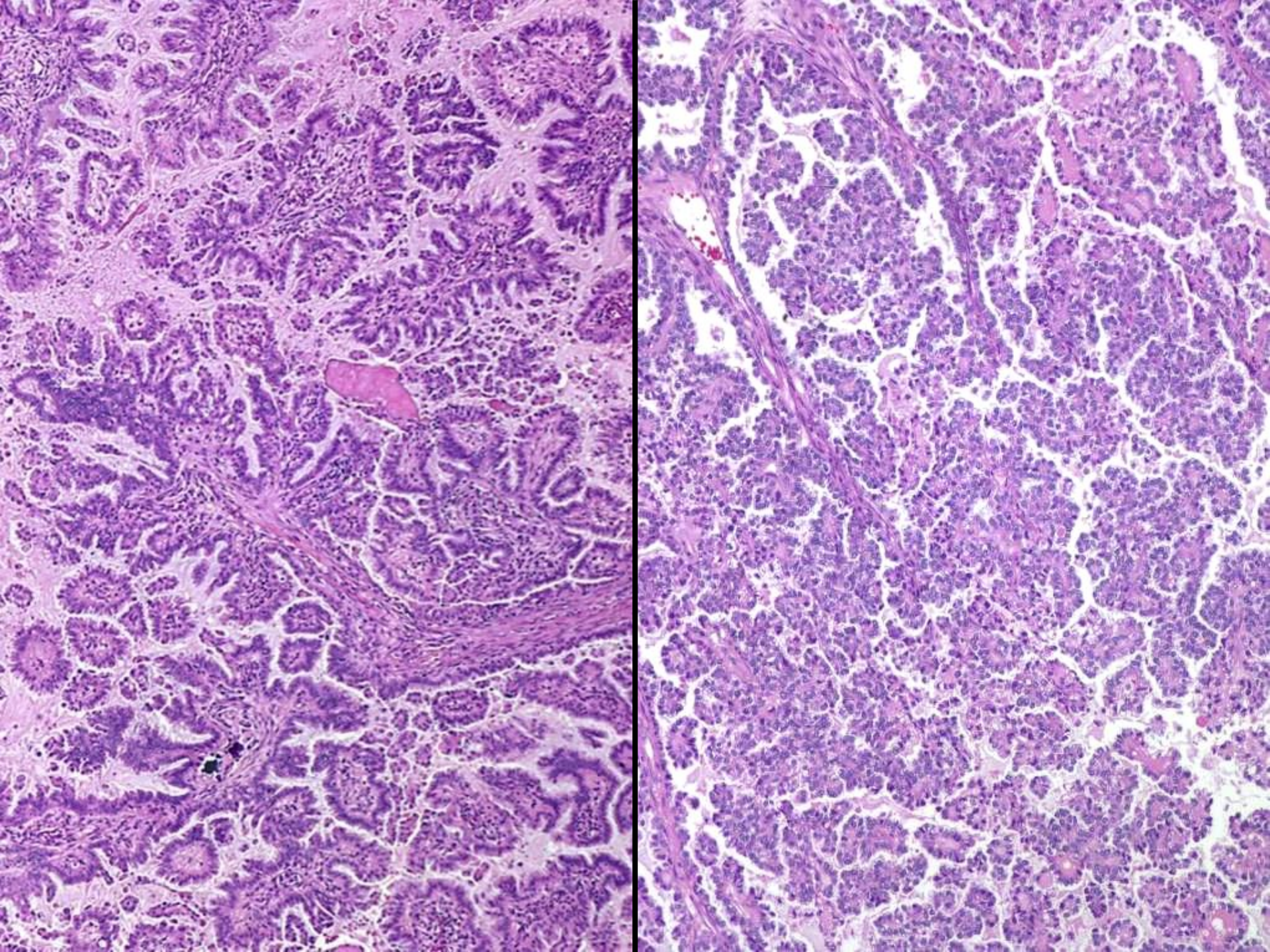


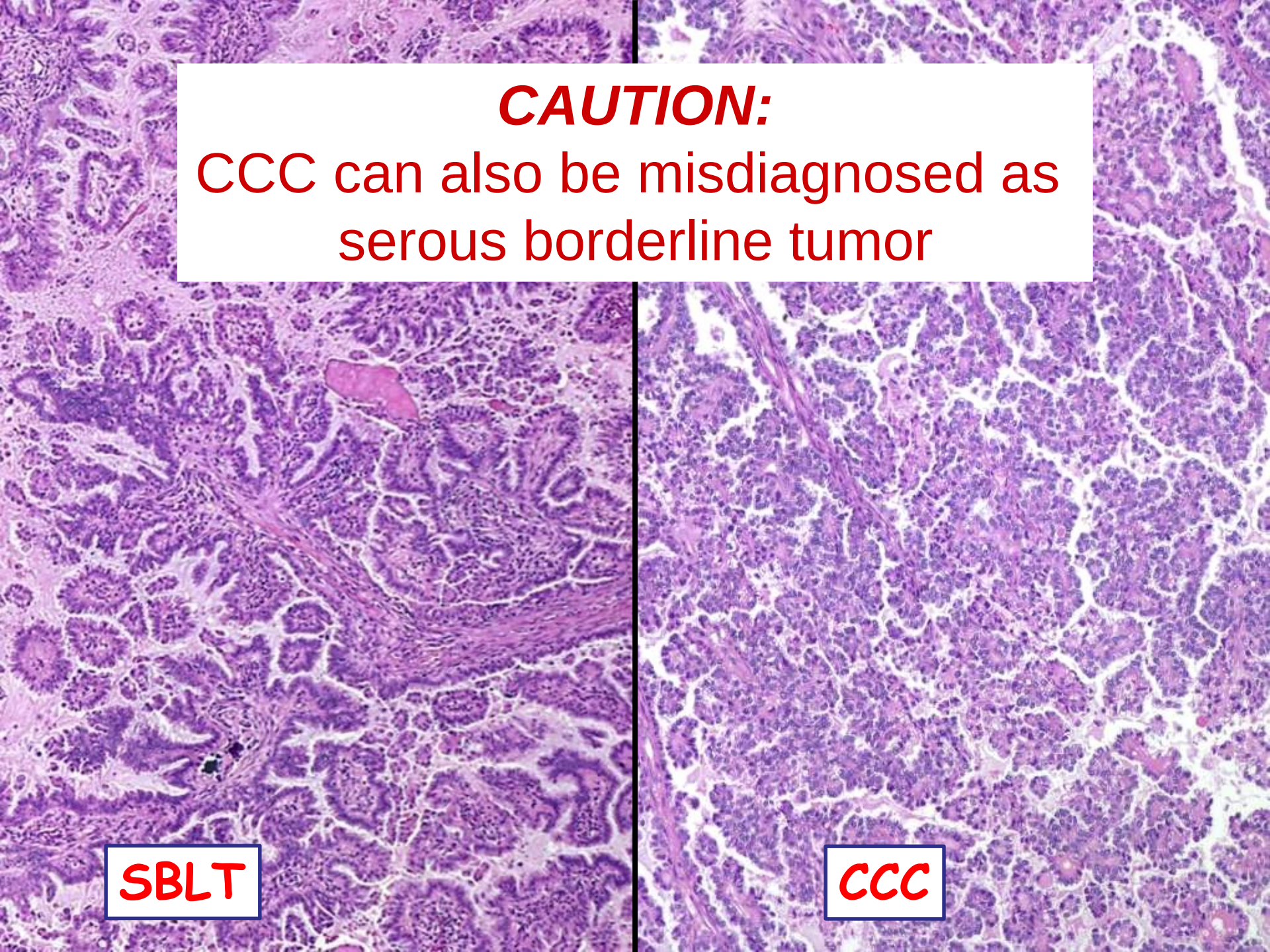


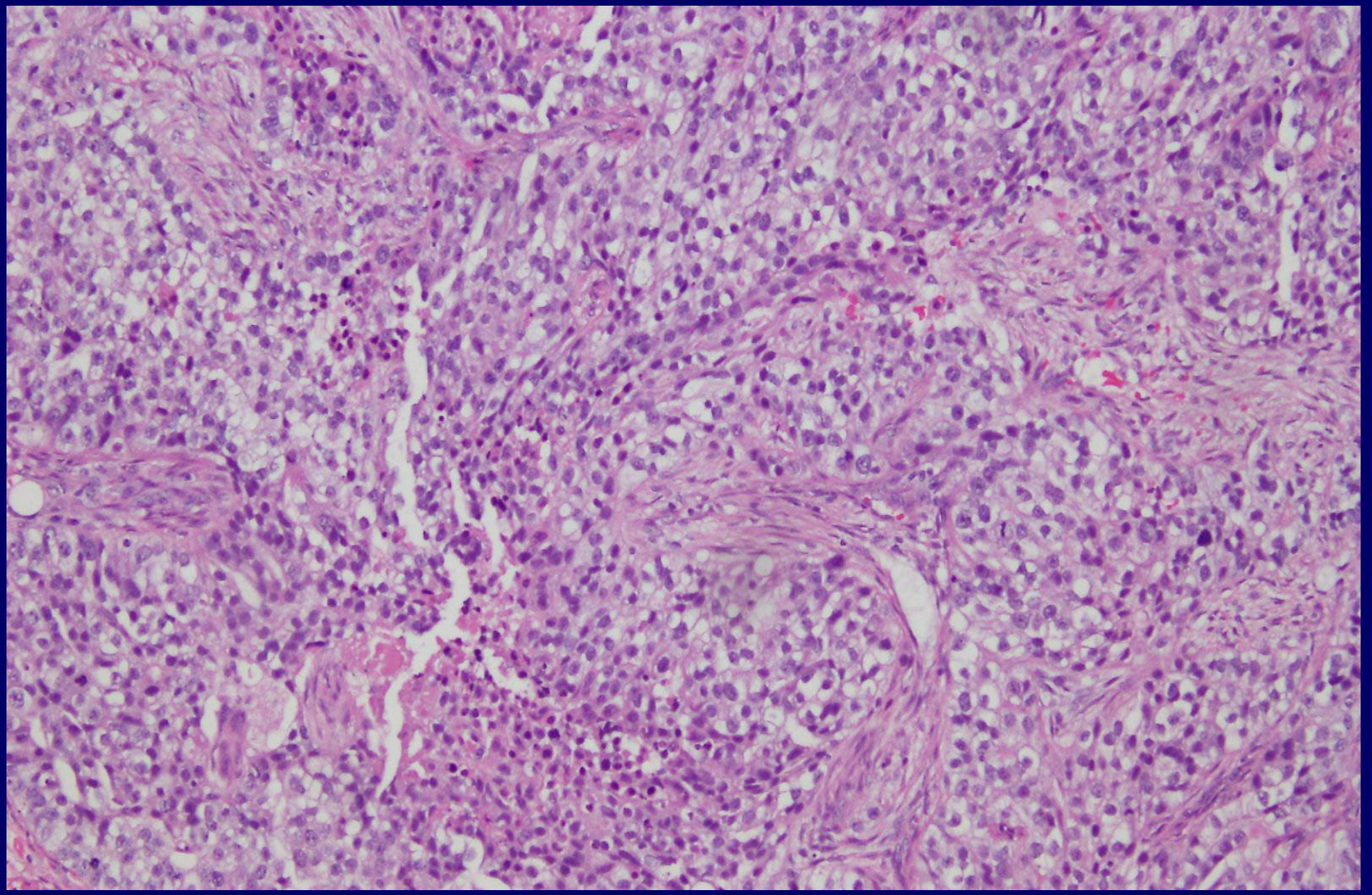


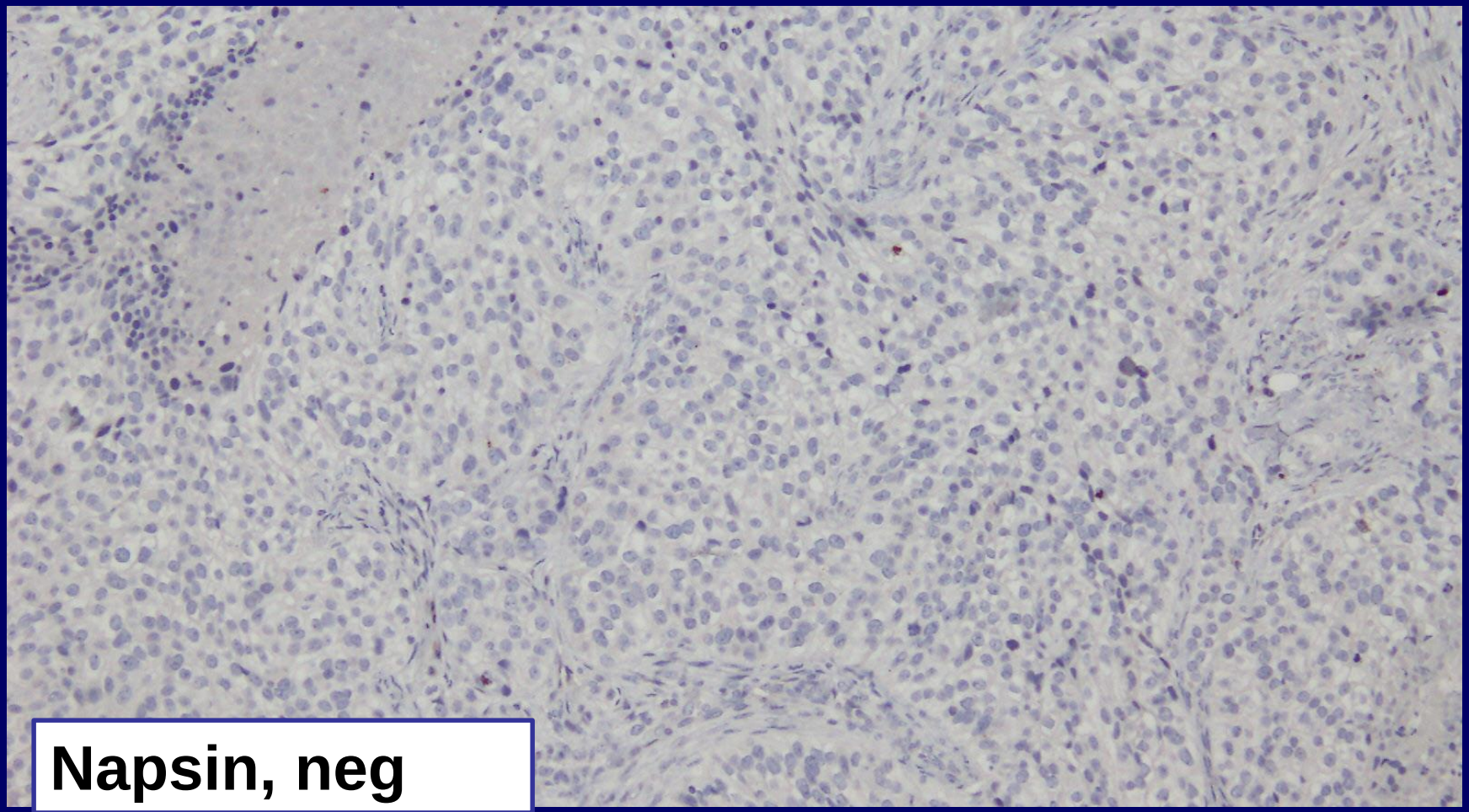

CCC
SBLT

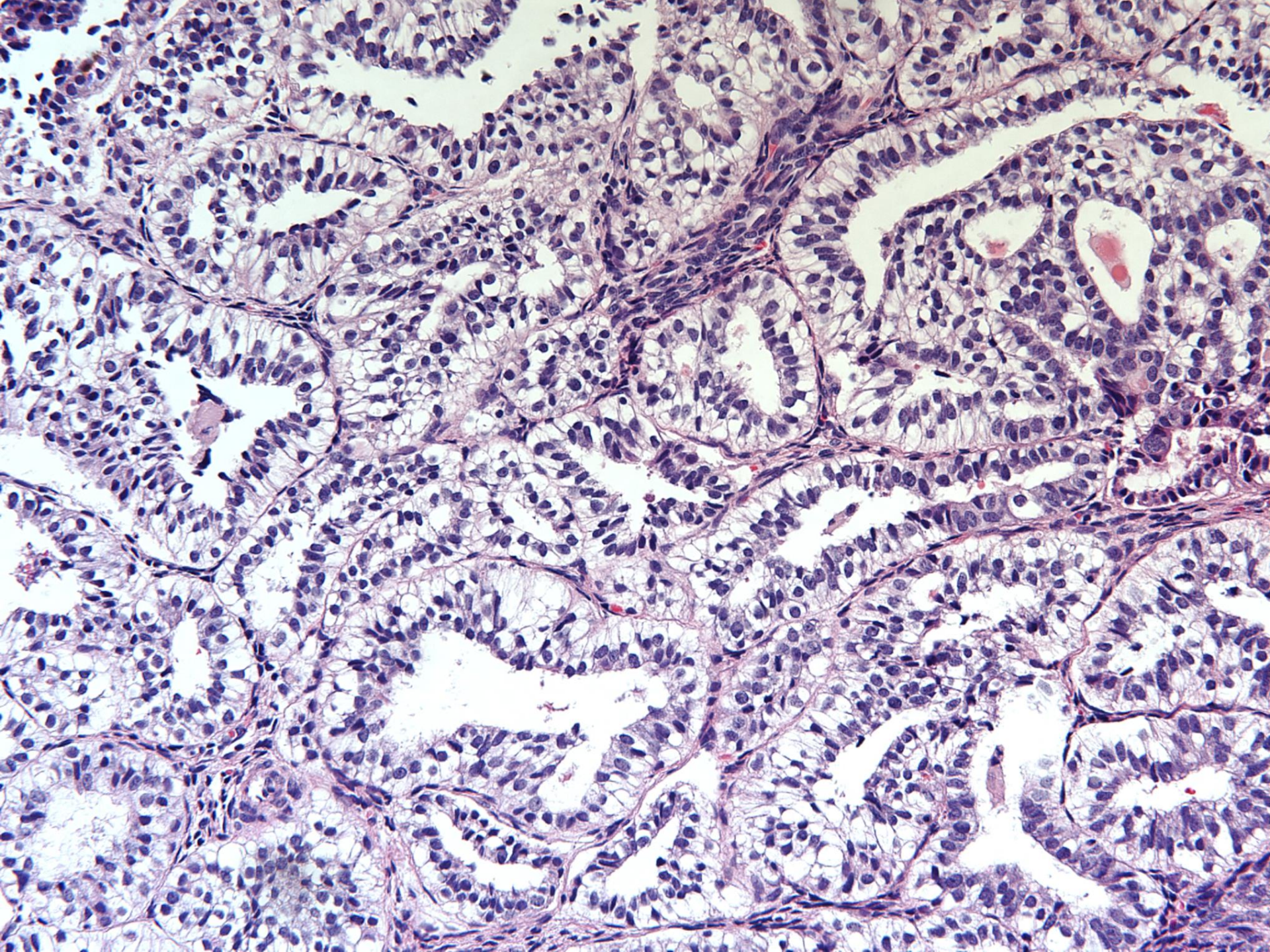

Serous Borderline

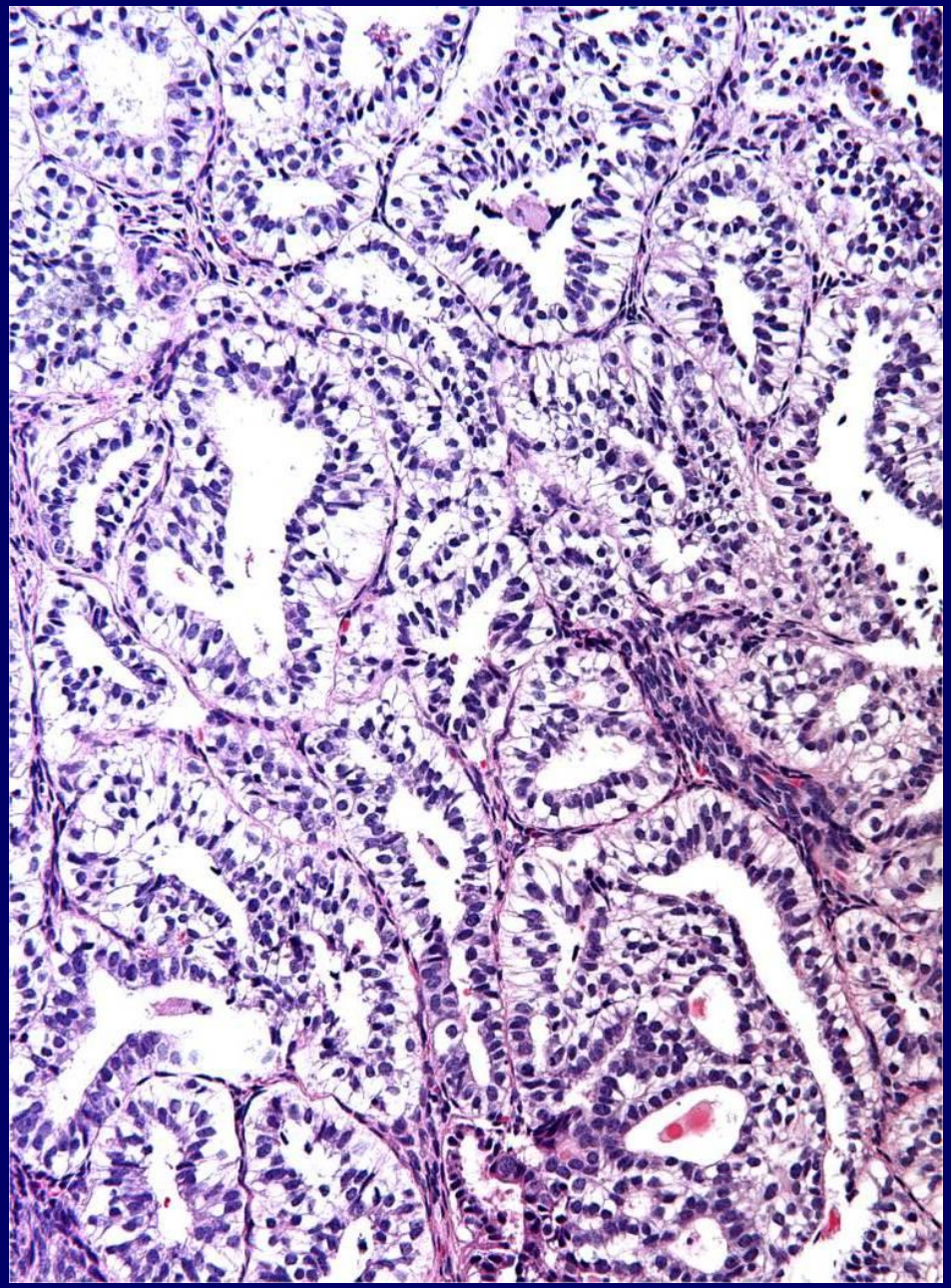


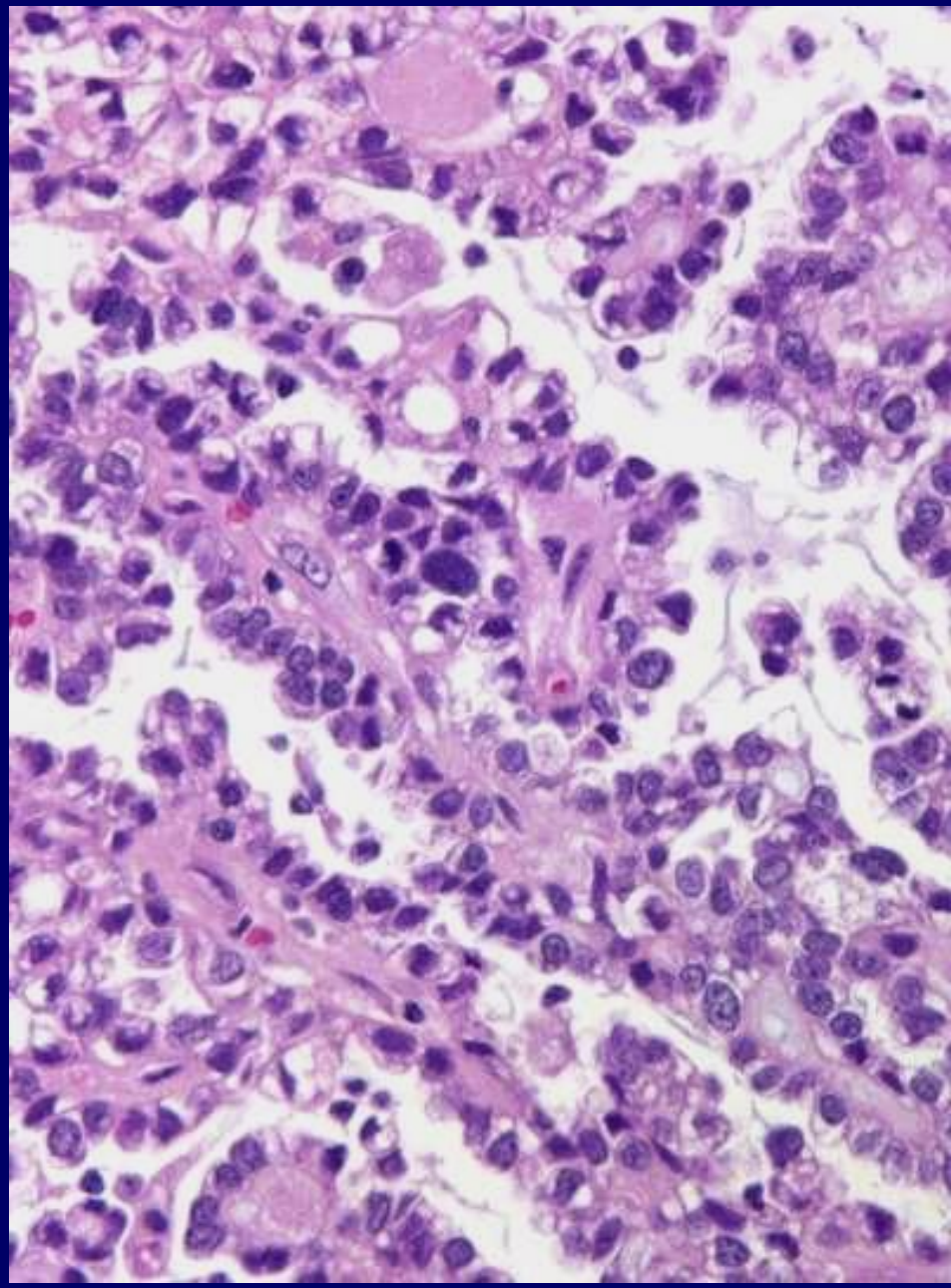

CAUTION:
CCC can also be misdiagnosed as serous borderline tumor
SBLT
CCC

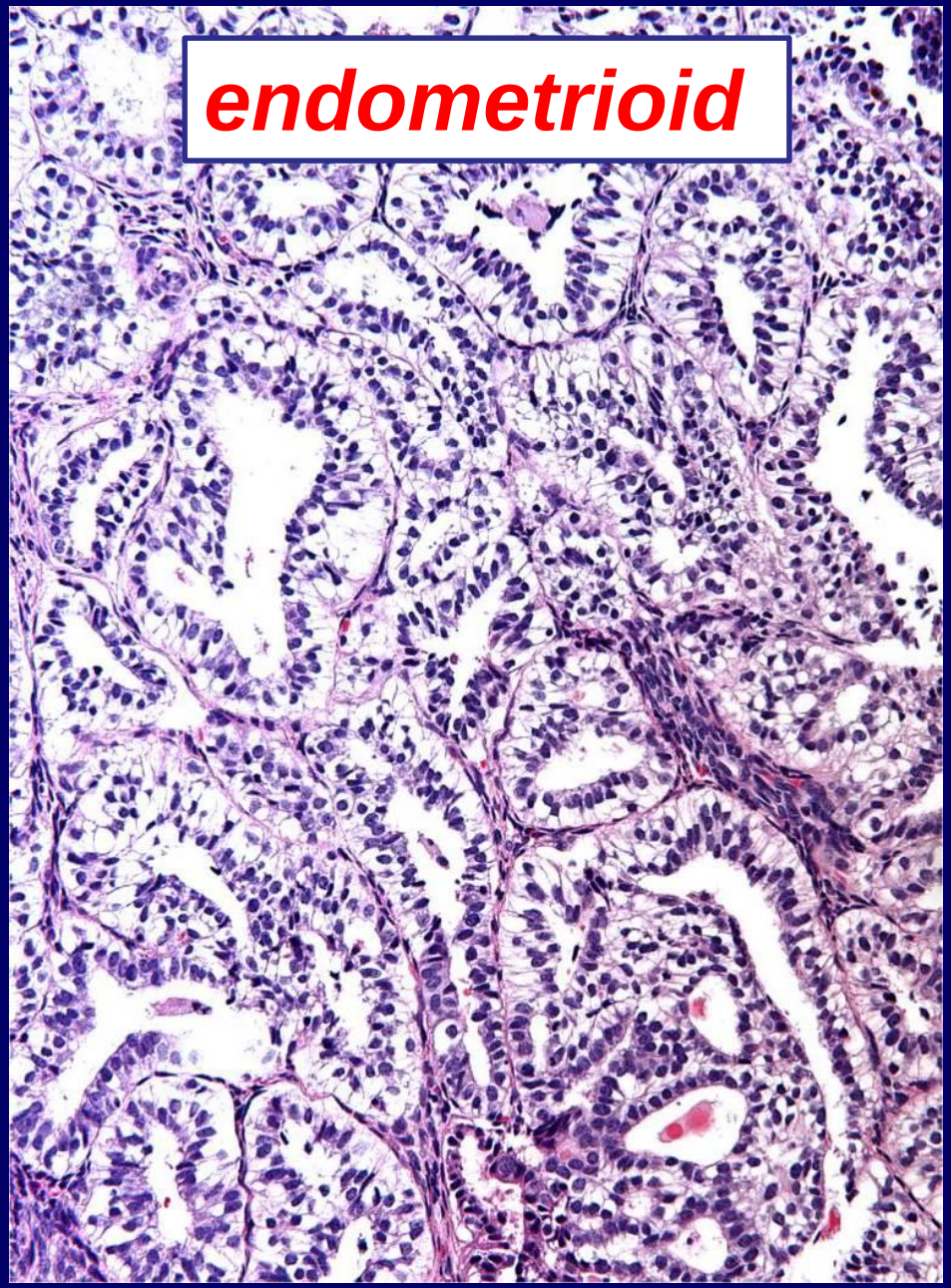


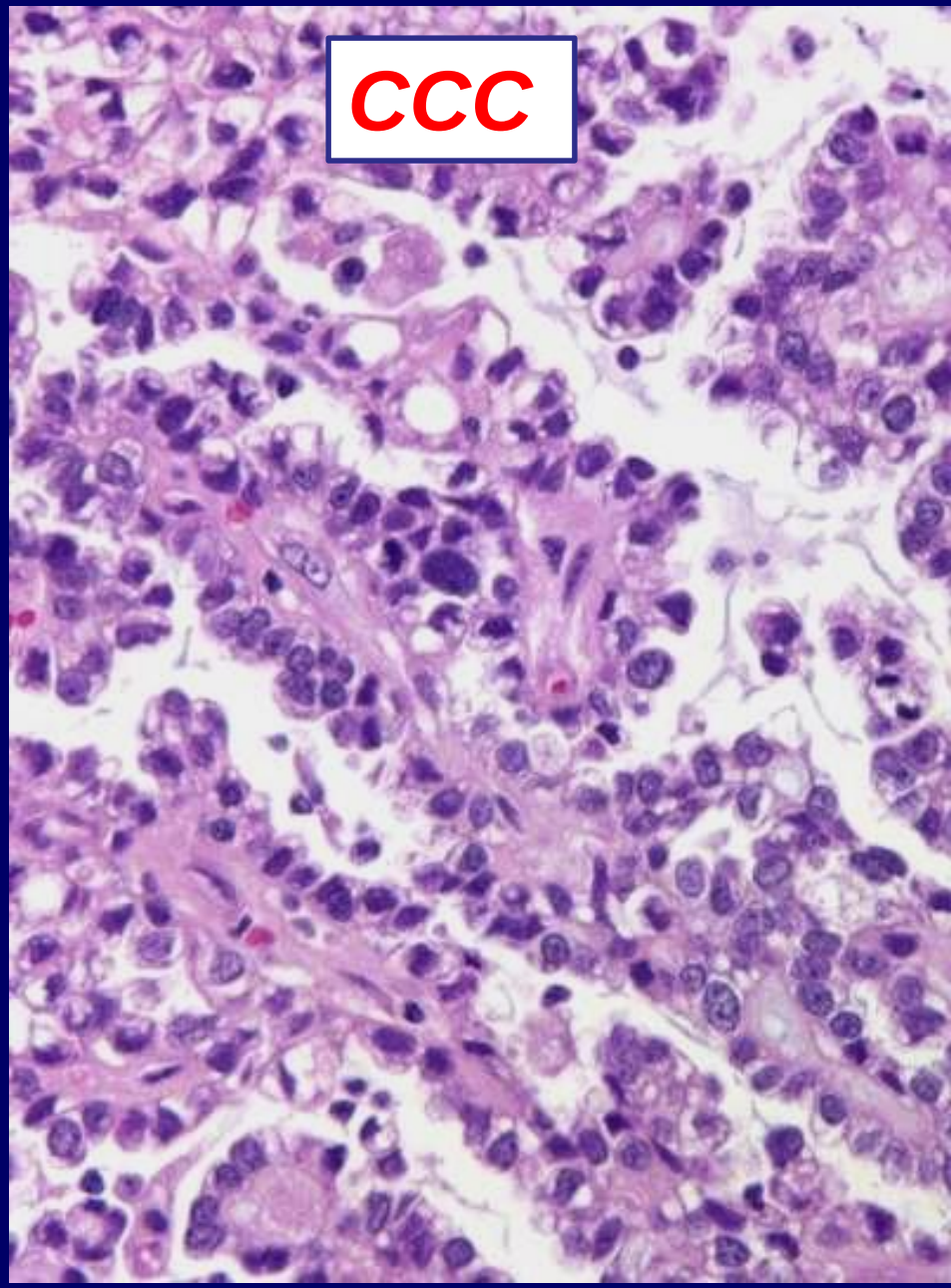

Napsin, neg








endometrioid


CCC

CCC

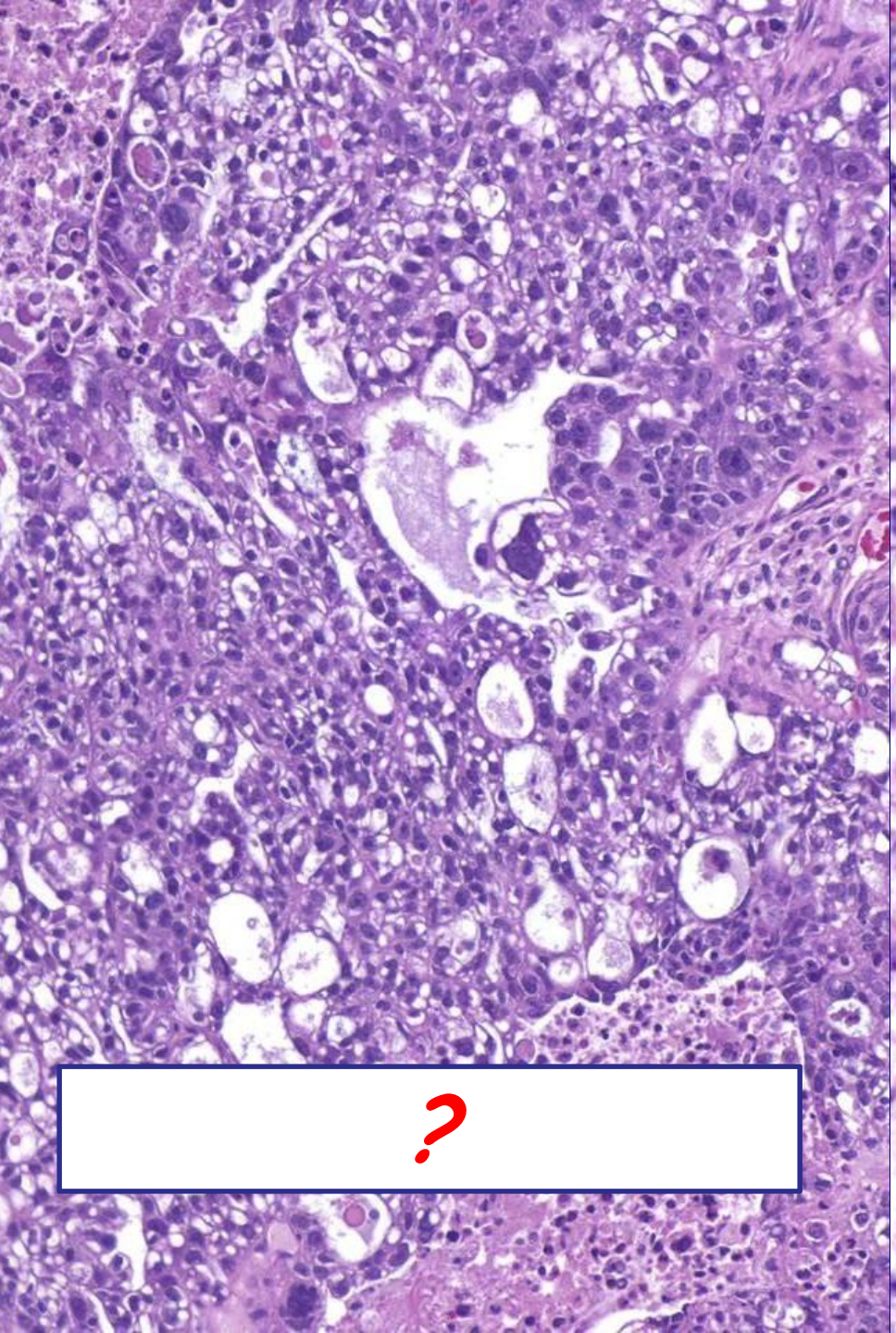
- Unilateral
- Hobnail cells
- Other patterns CCC
- WT1-, ER-
- HNF-1 beta+/-

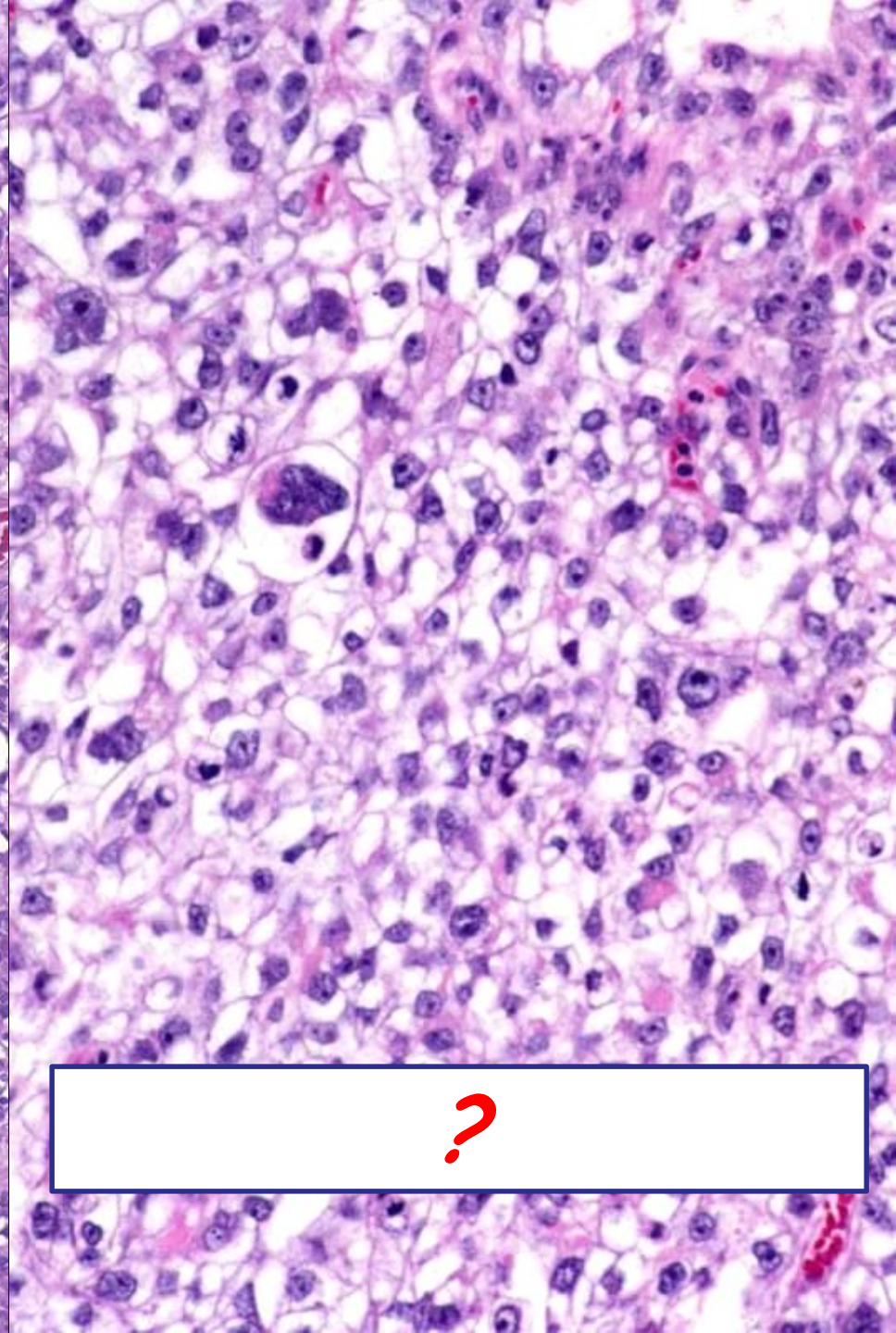
Endometrioid-CA

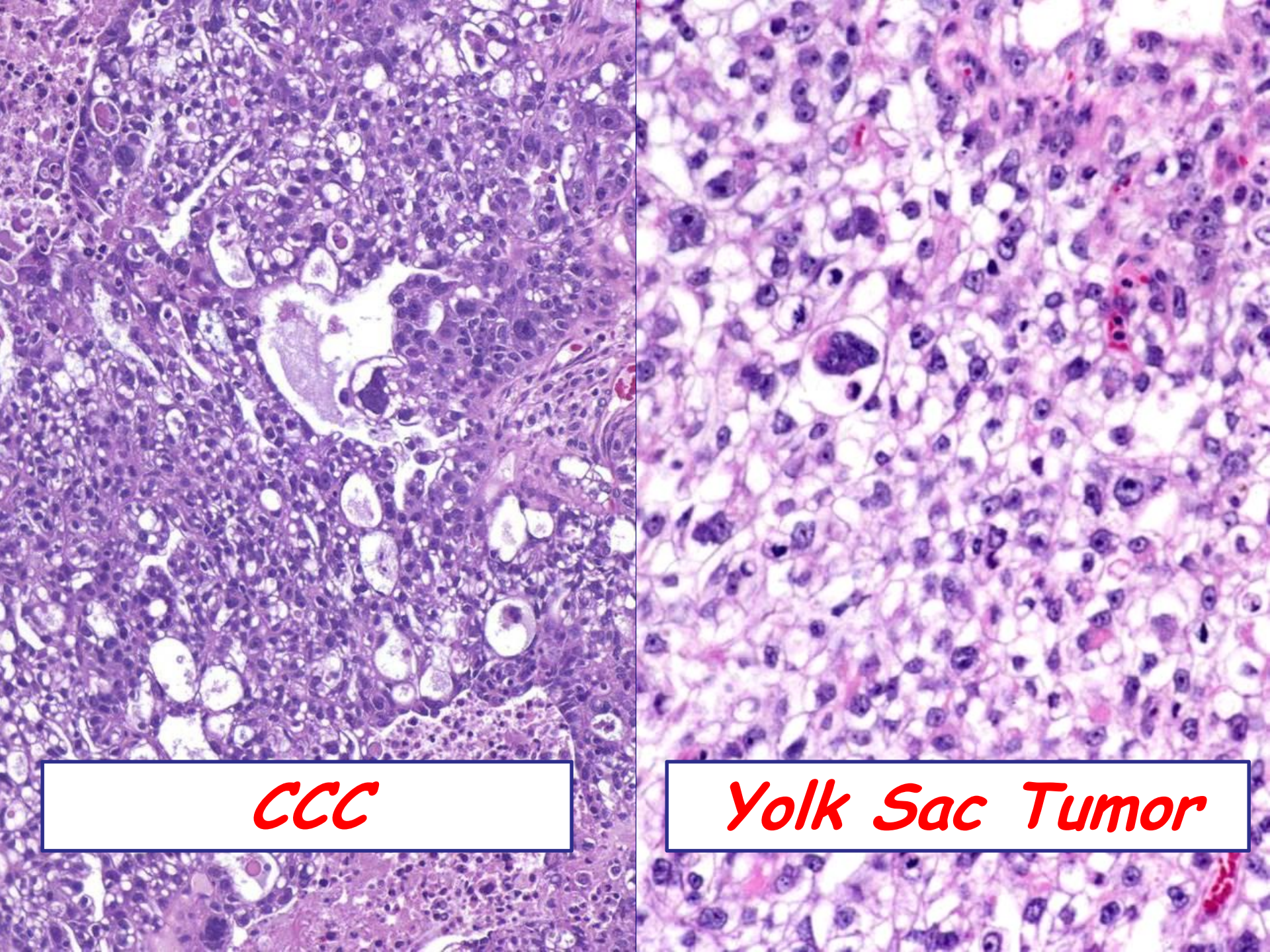
- Unilateral, but may be bilateral
- Cytoplasmic clearing
- Other patterns E-CA
- WT1-, ER+
- HNF-1 beta-/+

Endometrioid Carcinomas with Clear Cytoplasm

- “Secretory” carcinoma - subnuclear and supranuclear vacuoles, most of the time has low grade (nuclear grade 1-2) cytology
- Endometrioid carcinoma with clear cytoplasm, due to glycogen, lipid, other
- Squamous glycogenization has other areas of classic squamous differentiation

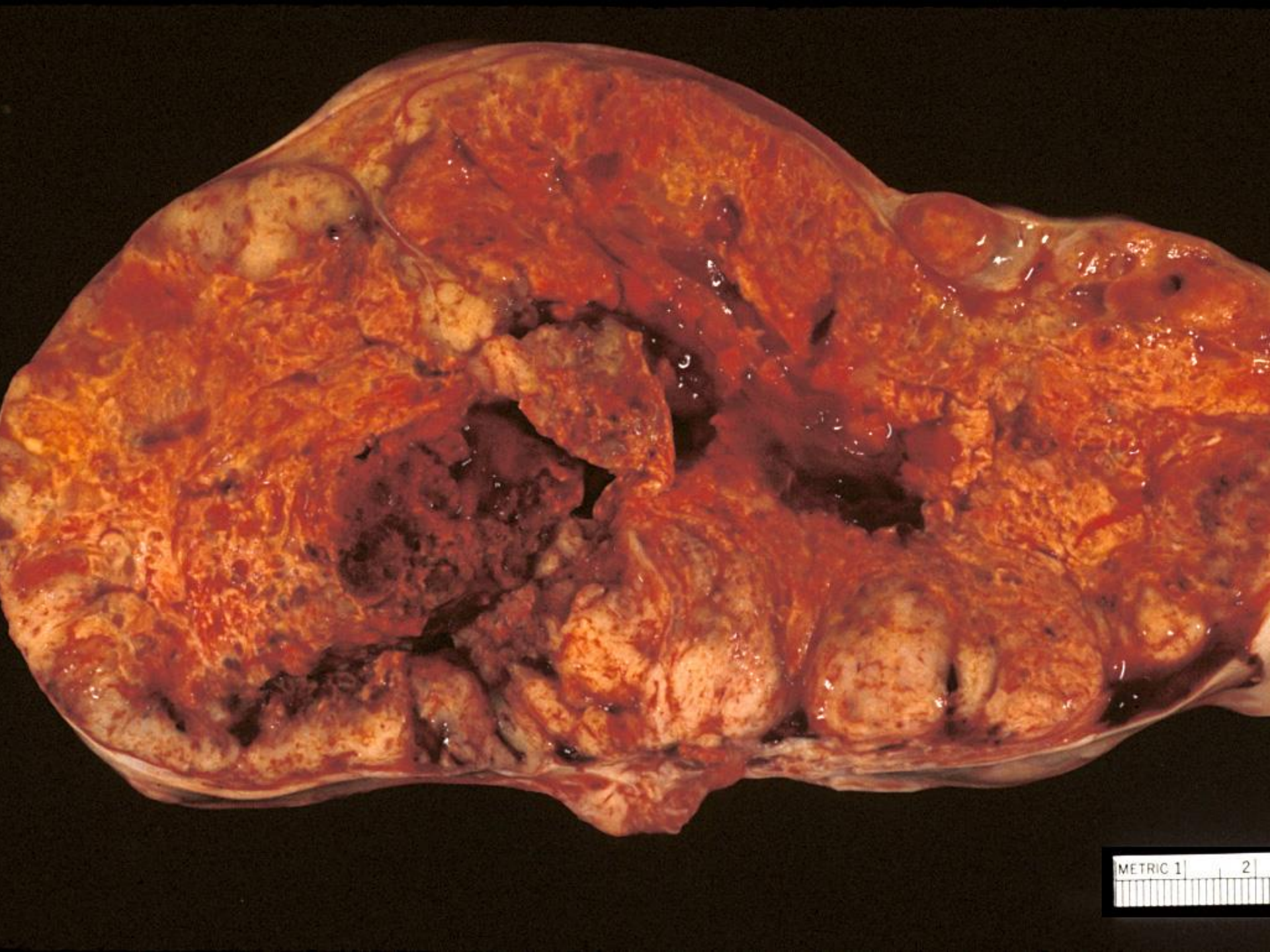


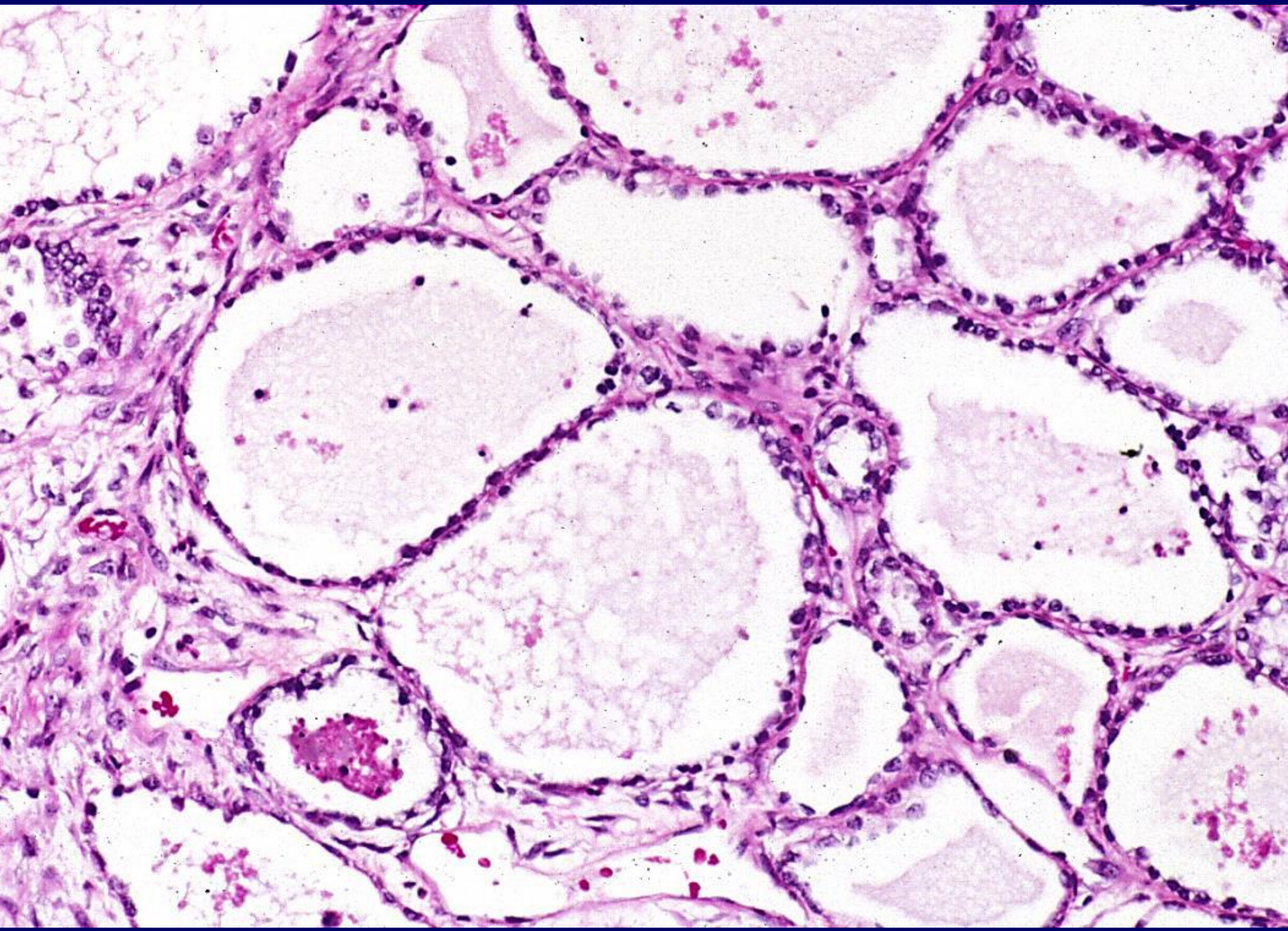



CCC
Yolk Sac Tumor

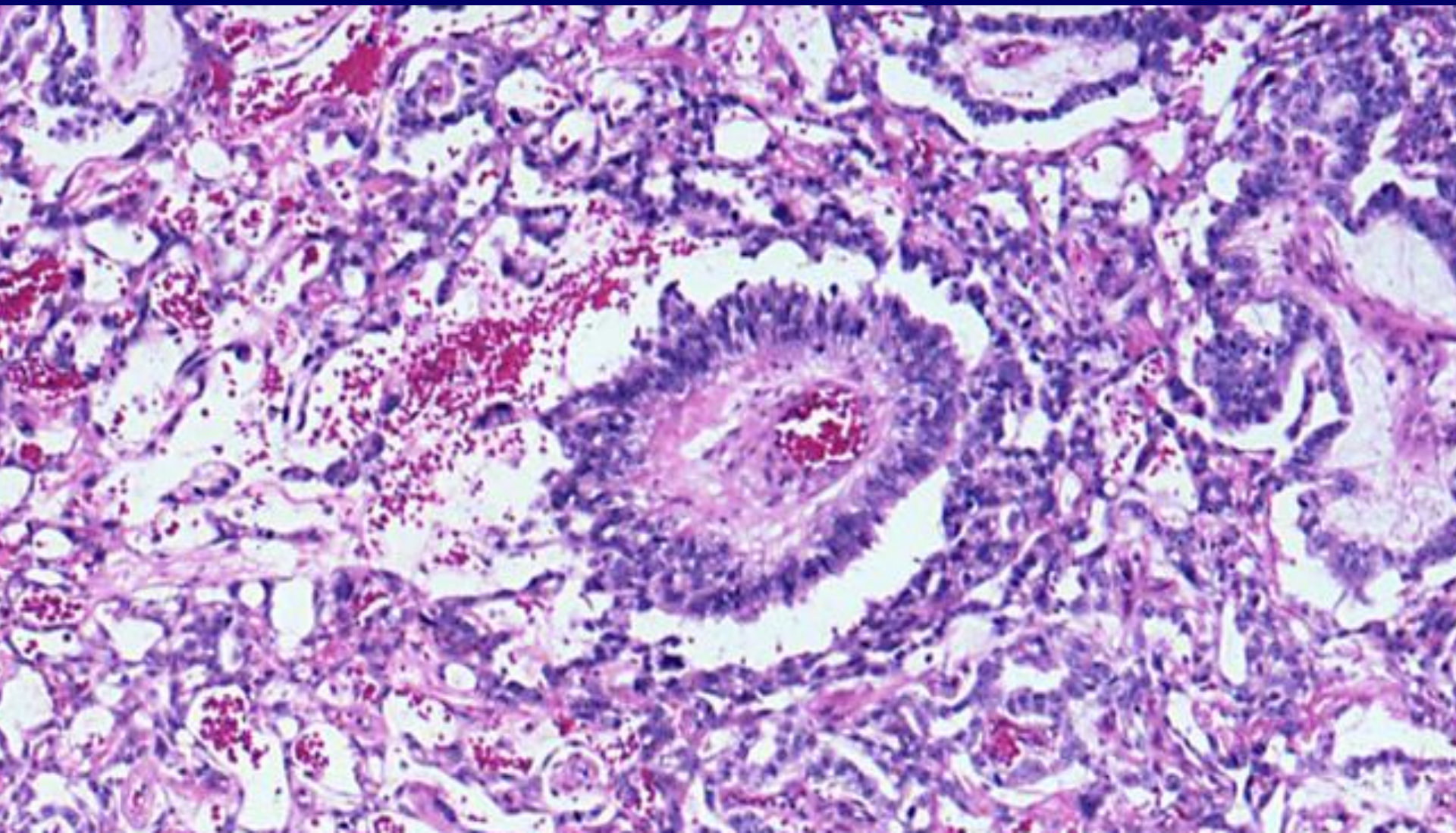
Intraoperative Consultation Issues

- In the reproductive years, misdiagnosing yolk sac for CCC is especially problematic.
- Yolk sac: Limited, reproductive conservation surgery is standard of care. Chemotherapy is highly effective.
- CCC: Full cancer staging operation


METRIC 1
2



Yolk Sac Tumor

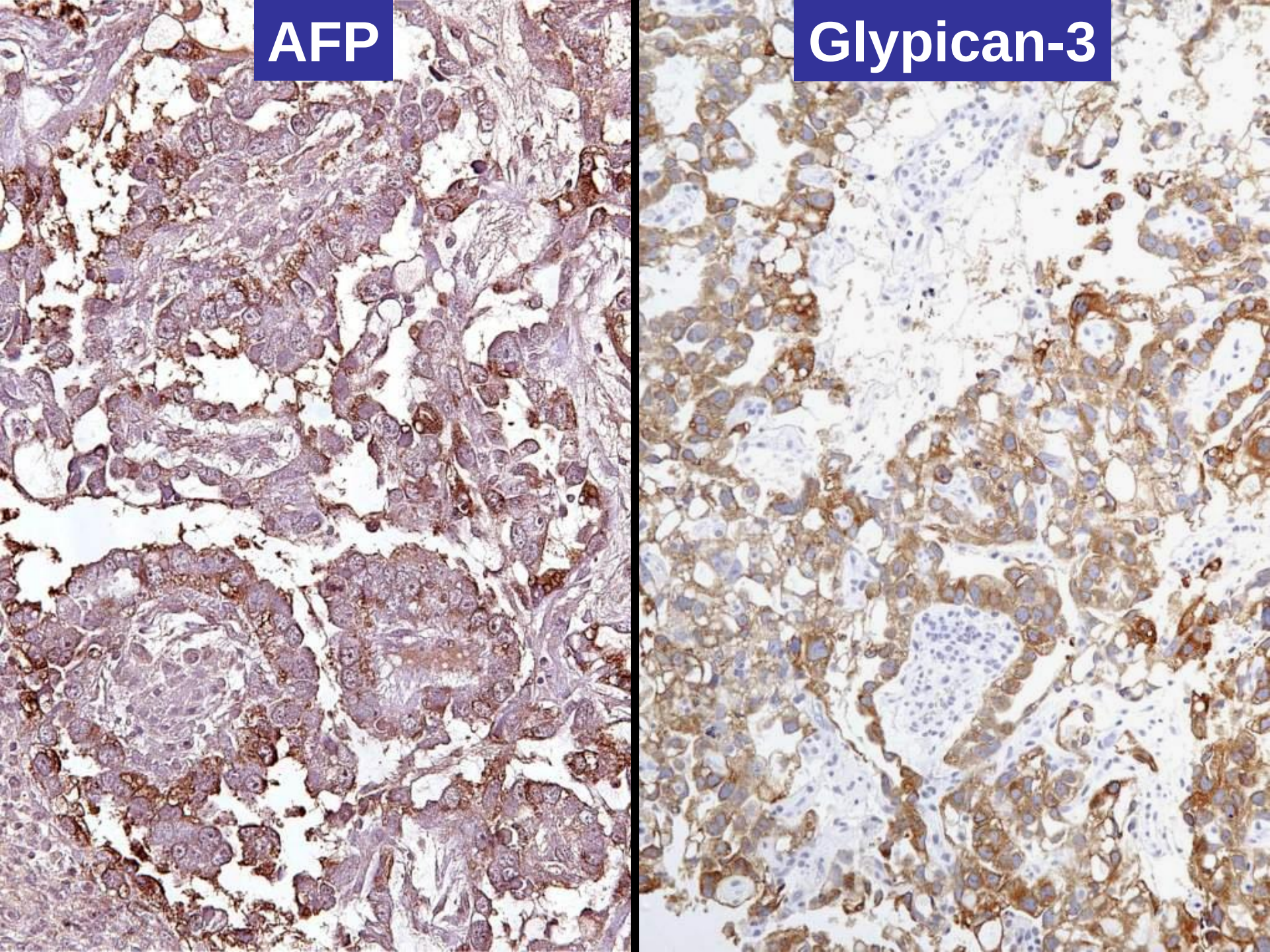


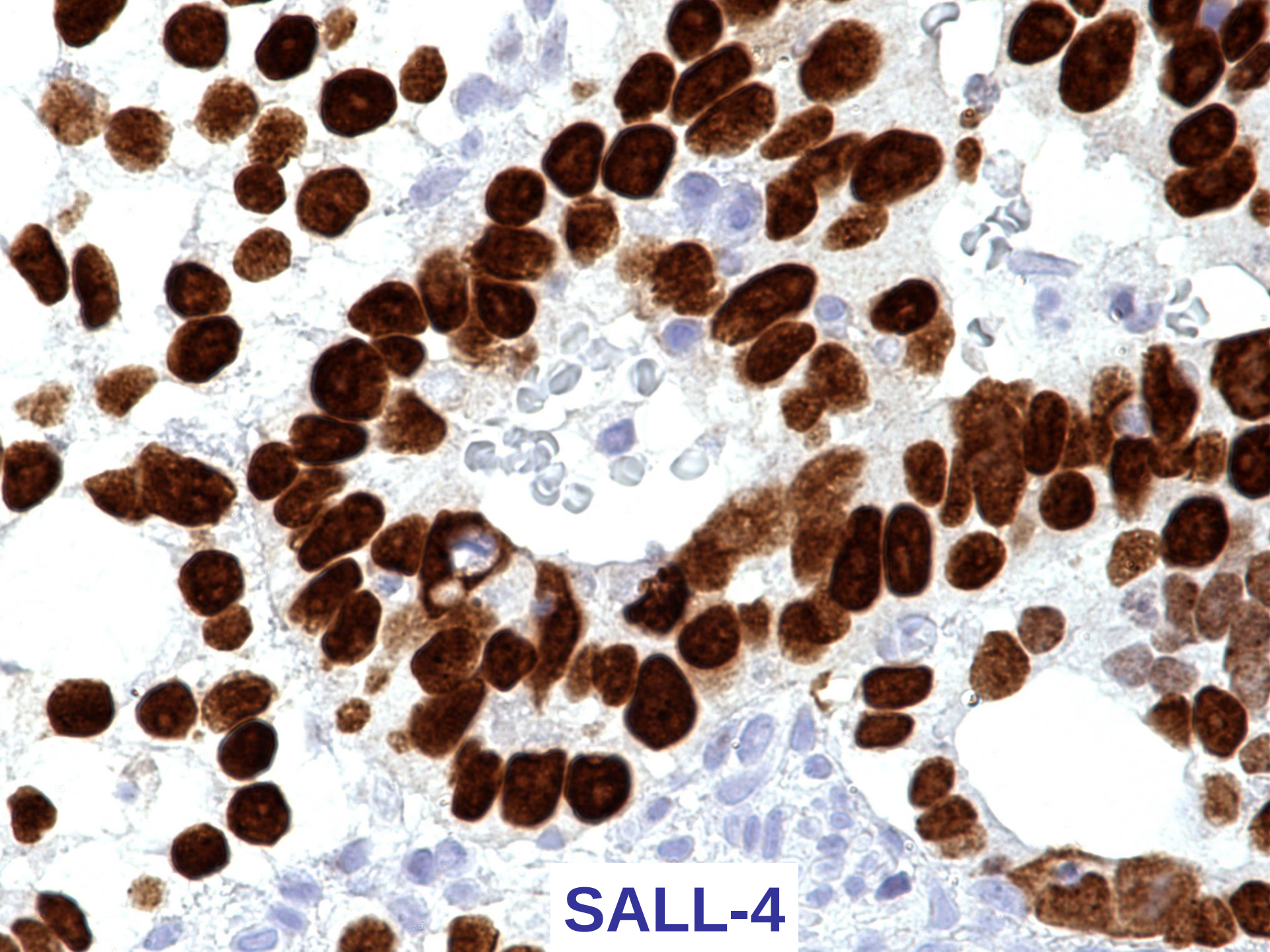
CCC

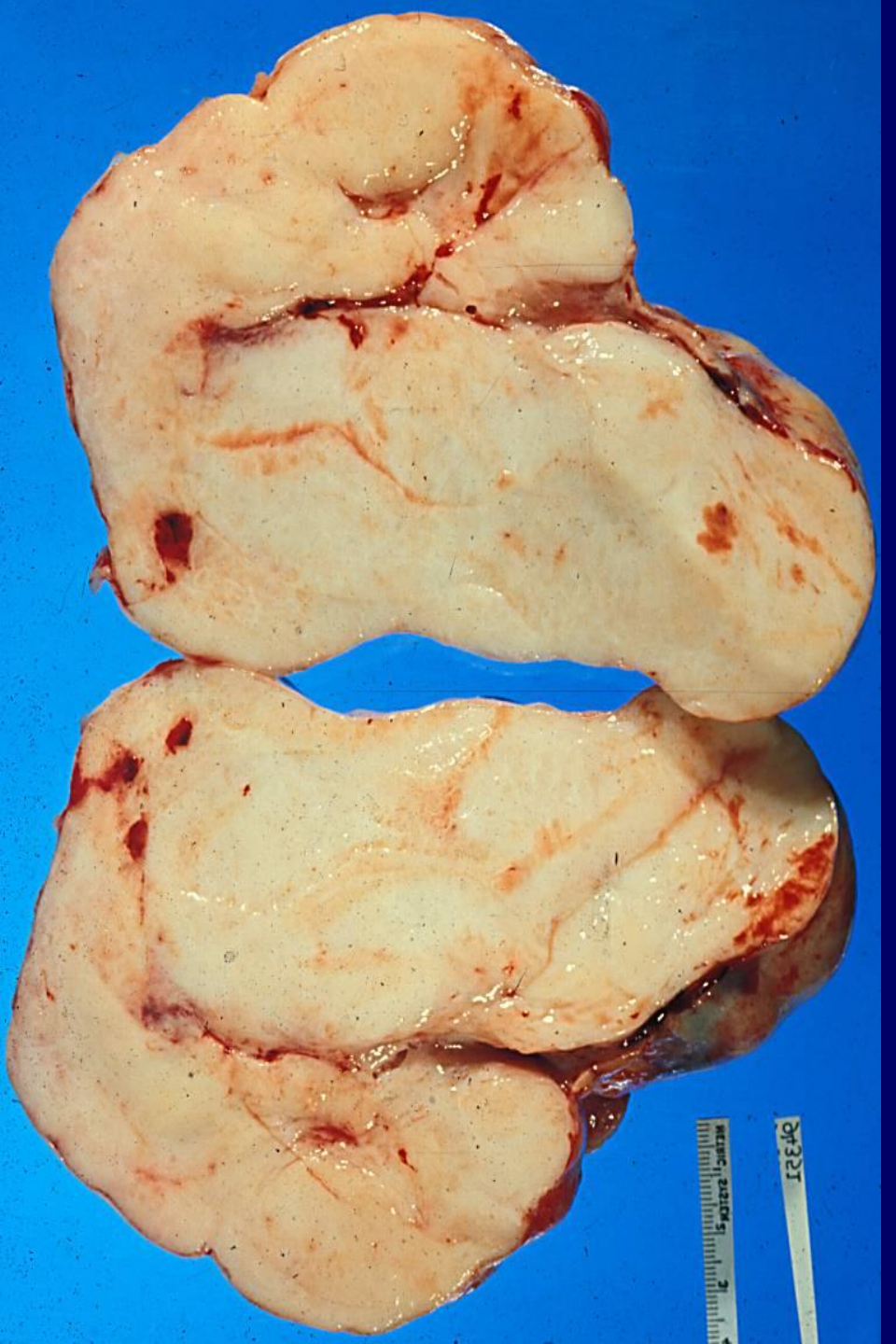
- AFP, negative
- CK-7, positive
- Glypican-3, negative
- HNF1-beta, positive
- SALL4, negative

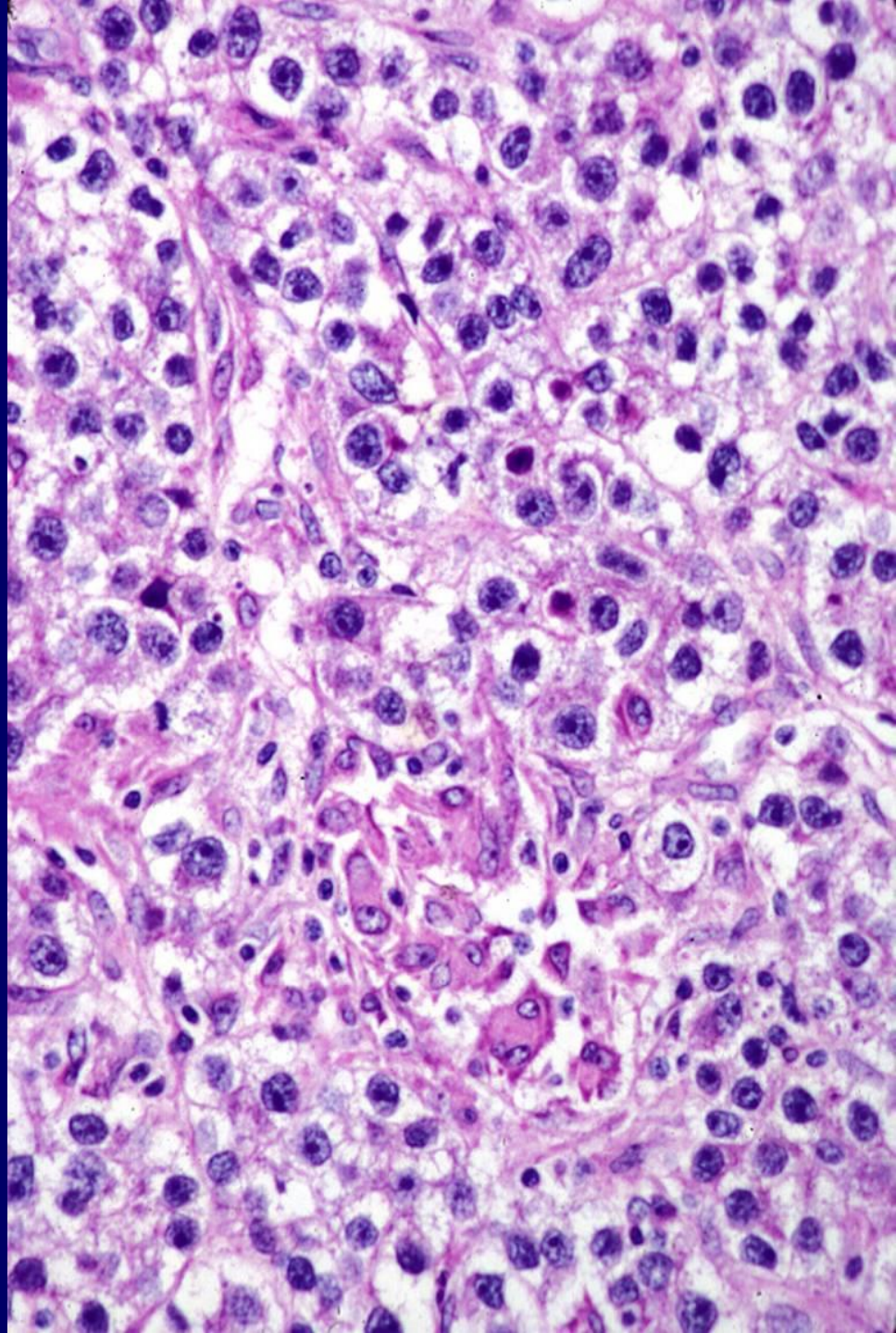
Yolk Sac Tumor

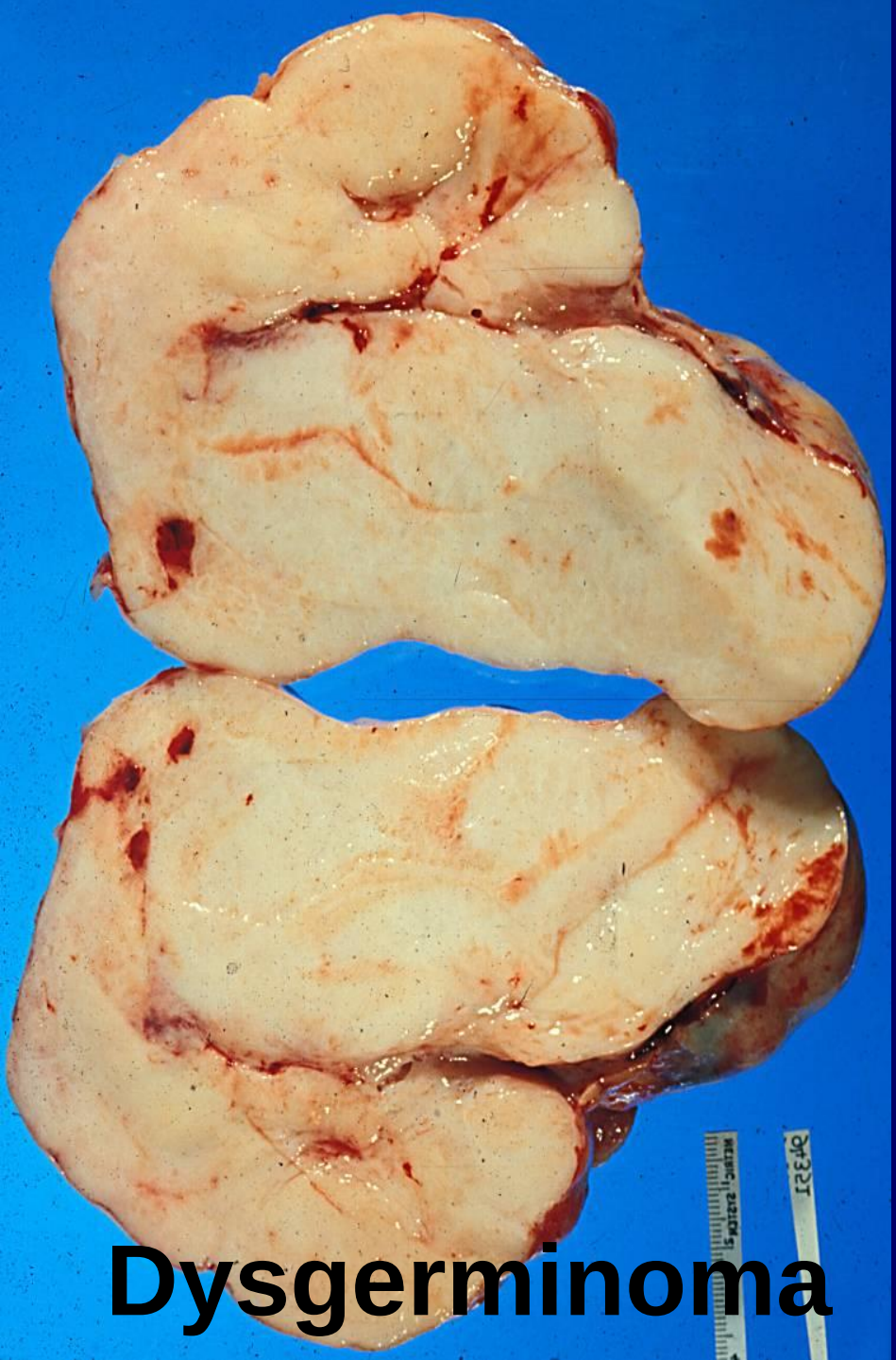
- AFP, positive
- CK-7, negative
- Glypican-3, positive
- HNF1-beta, positive
- SALL4, positive


AFP
Glypican-3

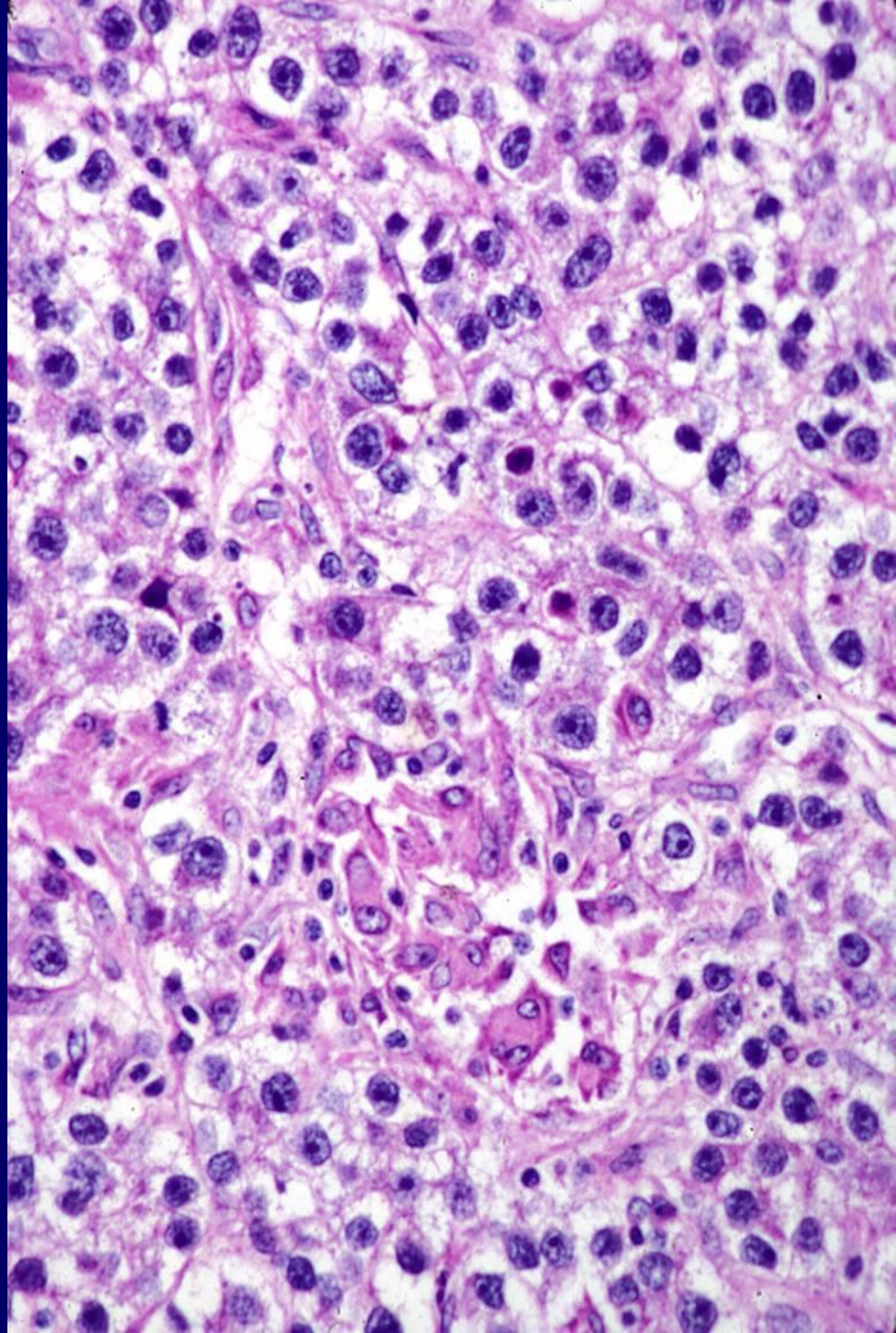

SALL-4







Dysgerminoma

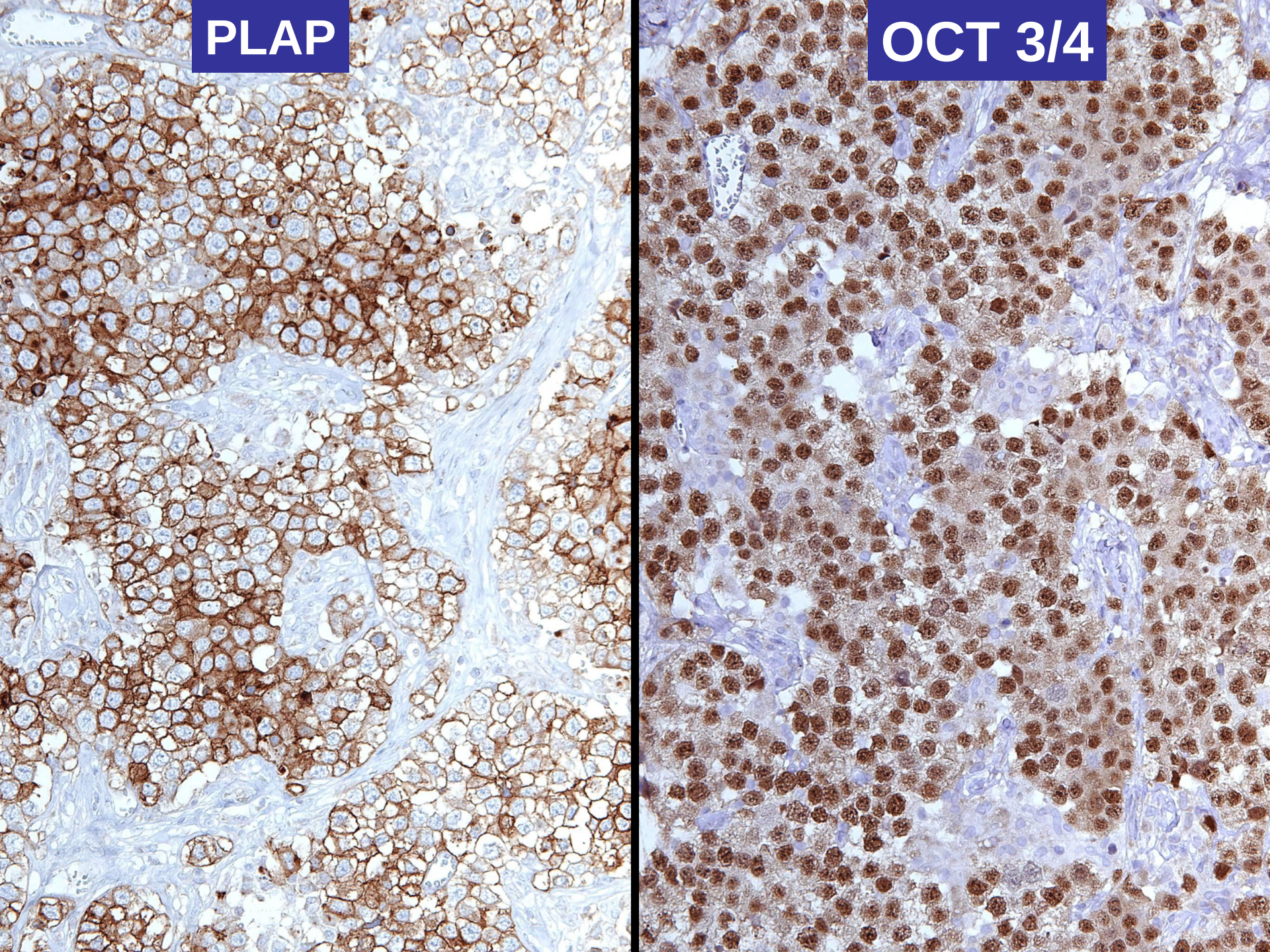


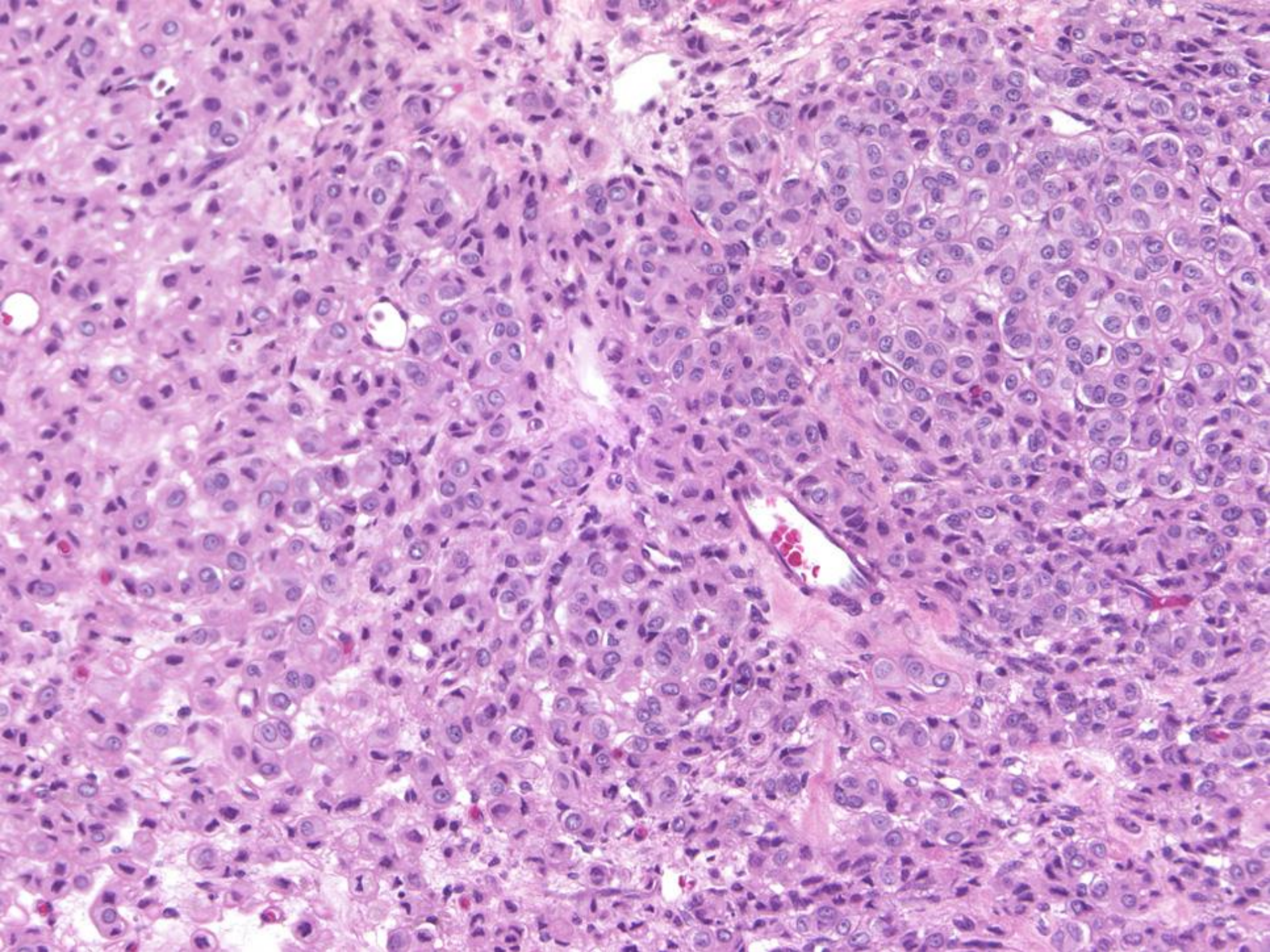
Solid CCC

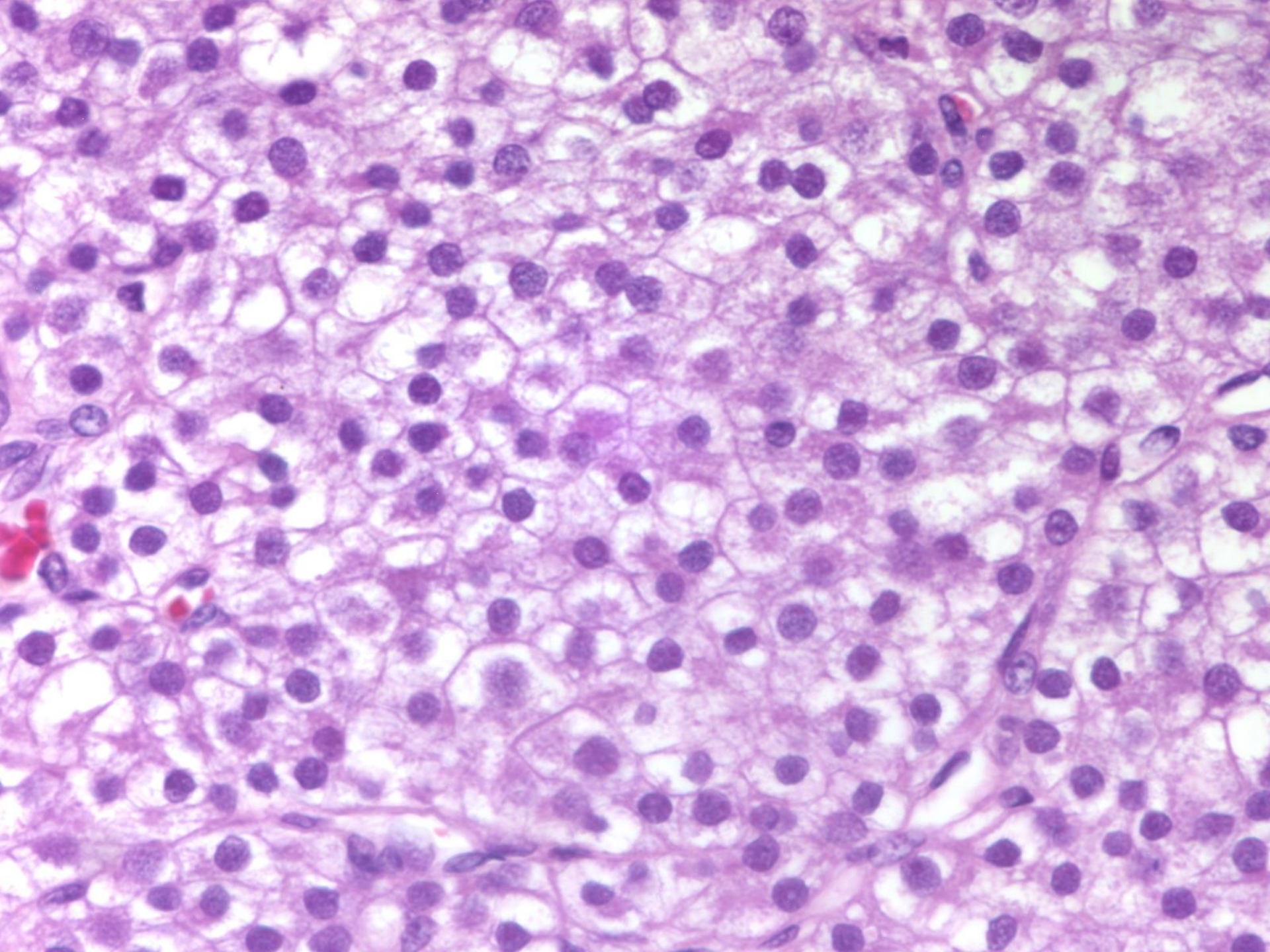
- Polyhedral nuclei w/ inconspicuous nucleoli
- Lymphocytes and plasma cells
- PLAP-negative
- OCT3/4-negative
- CK7-positive

Dysgerminoma

- Central, rounded nuclei w/ 1-4 nucleoli
- Lymphocytes and granulomas
- PLAP-positive
- OCT3/4-positive
- CK7-negative


PLAP
OCT 3/4





CCC

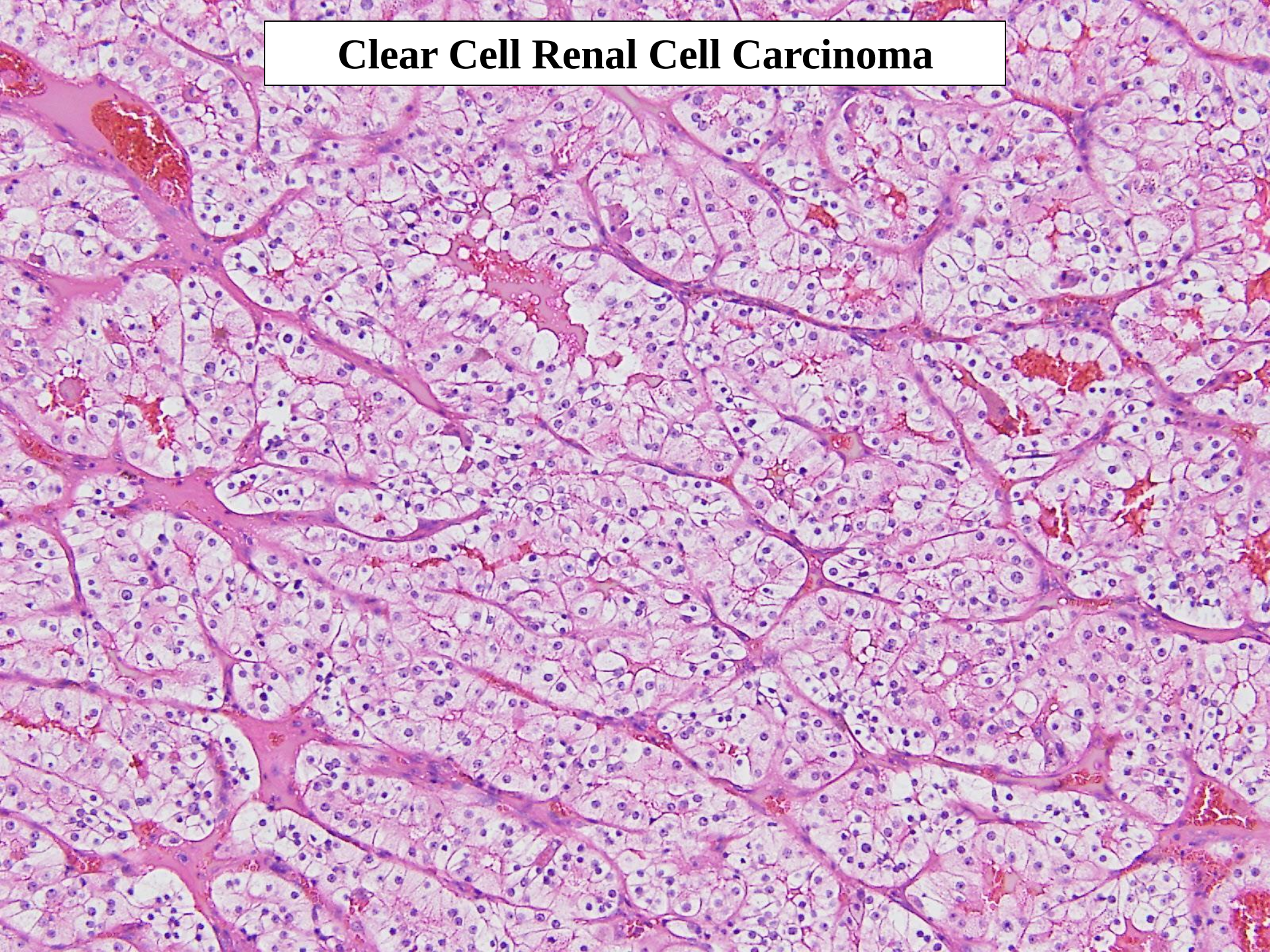
- Unilateral
- Yellow
- Other CCC patterns
- Cytokeratin pos
- Inhibin neg
- Calretinin neg

Steroid cell tumor

- Unilateral
- Yellow
- Uniform pattern

- Cytokeratin ?
- Inhibin pos
- Calretinin pos

Clear Cell Renal Cell Carcinoma



When To Actively Exclude RCC

- Prior history of renal cell carcinoma
- Suspicion of a retroperitoneal mass
- Family history or renal cell carcinoma or evidence of hereditary renal cell carcinoma syndrome
  - von Hippel-Lindau
  - Hereditary leiomyomatosis

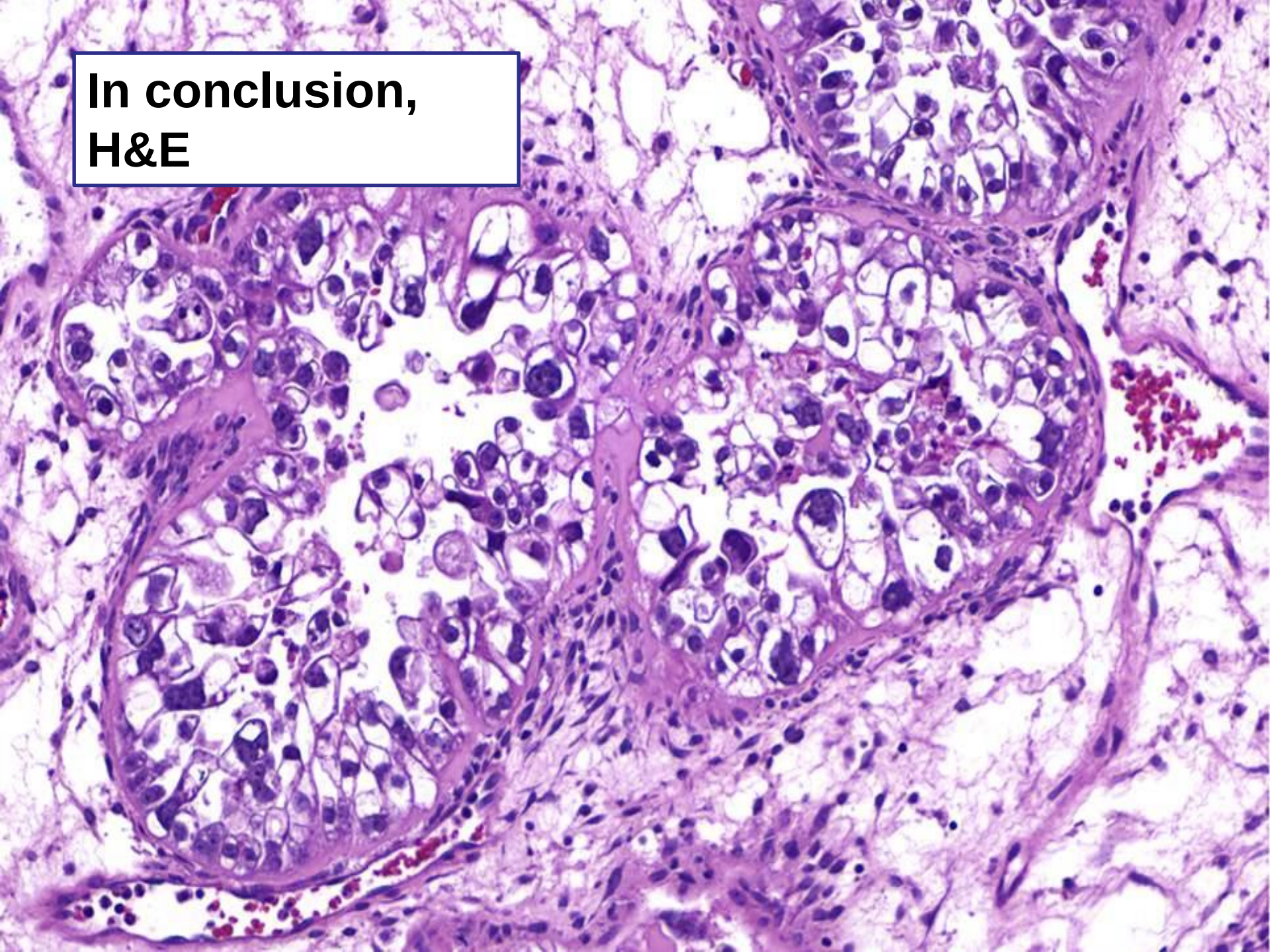
Rare, but need to keep in consideration

CCC

- PAX8+
- PAX2+ (<10%)
- HNF1β+
- Unilateral
- Endometriosis

Renal Cell CA

- PAX8+
- PAX2+ (77%)
- HNF1β+
- May be bilateral
- Renal mass or history of RCC


In conclusion,
H&E

Thanks

Endometriosis-Associated Ovarian Cancer: A Distinct Clinical Entity?

- Younger
- Diagnosed at earlier stage
- Lower grade lesions
- Better prognosis
  (even when adjusting for stage)