

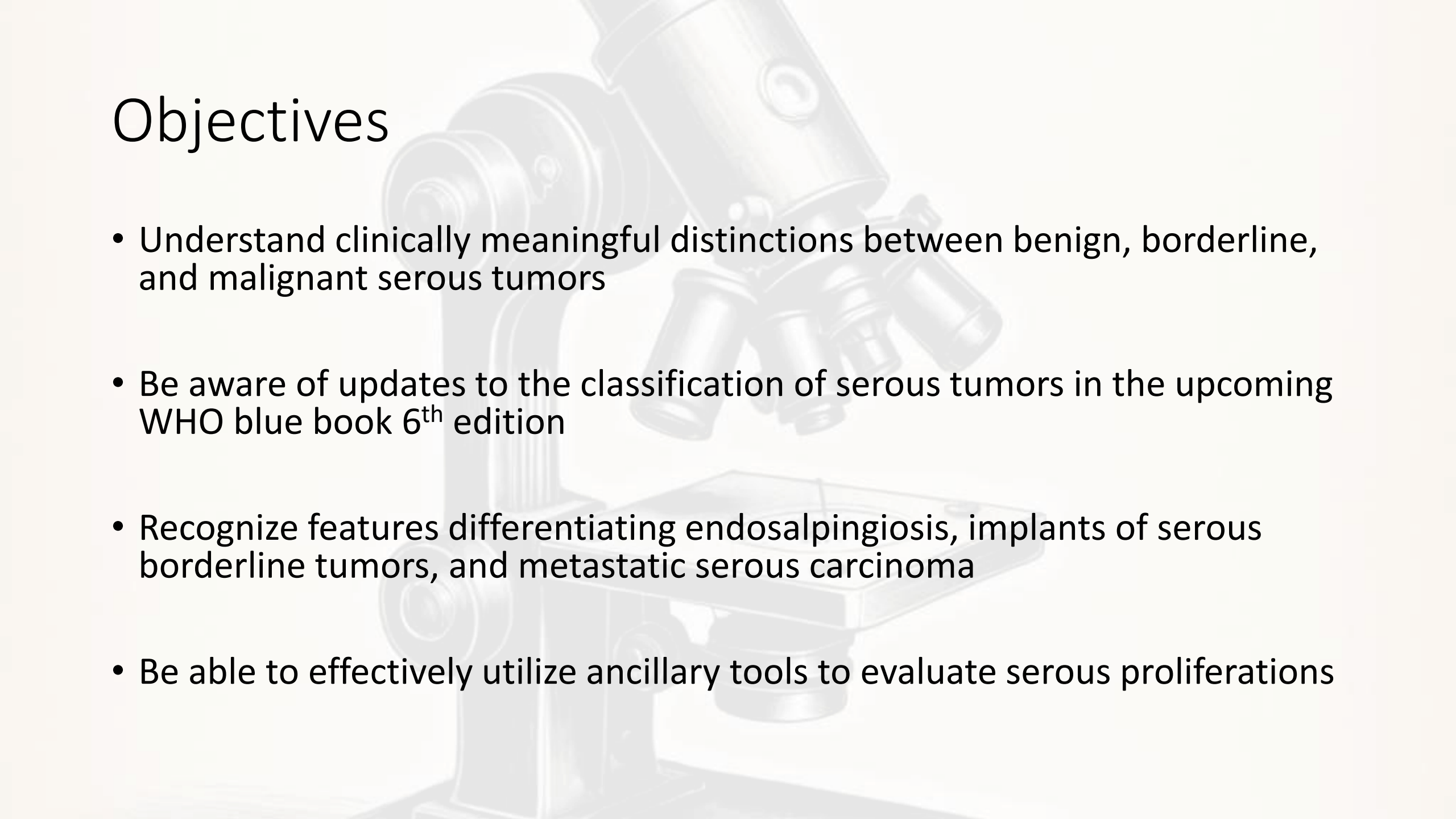
Ovarian Serous Tumors

Kyle Devins, MD

Department of Pathology

Massachusetts General Hospital

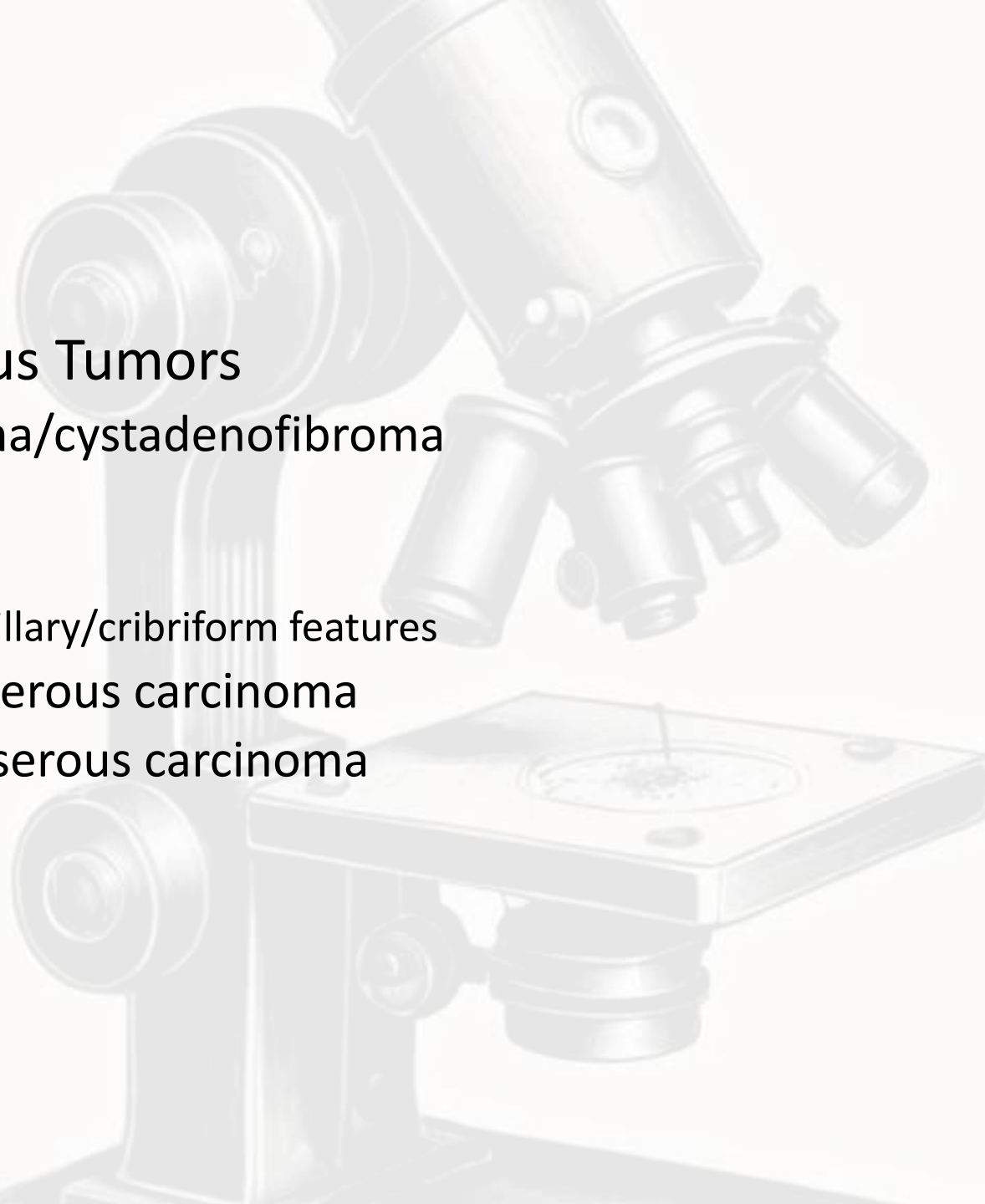
Objectives



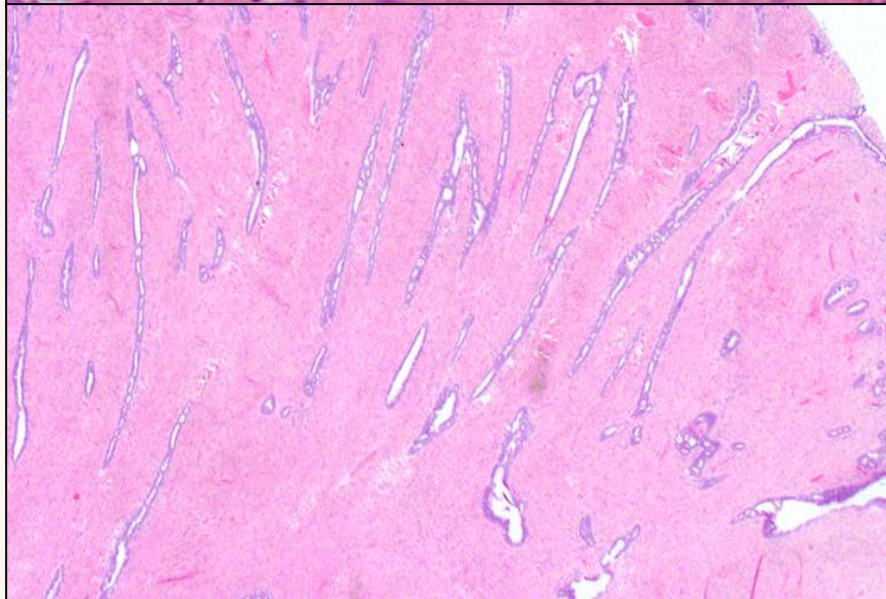
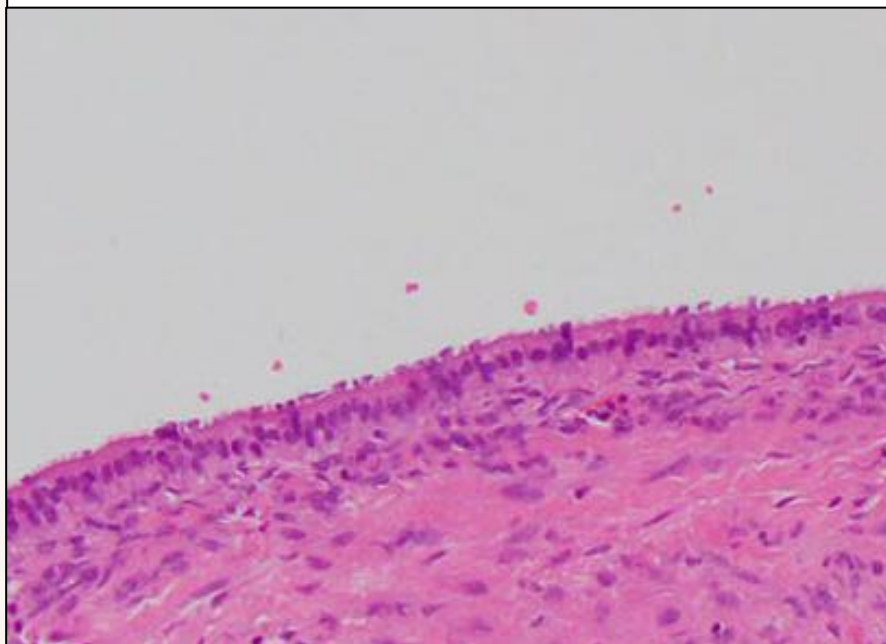
- Understand clinically meaningful distinctions between benign, borderline, and malignant serous tumors
- Be aware of updates to the classification of serous tumors in the upcoming WHO blue book 6th edition
- Recognize features differentiating endosalpingiosis, implants of serous borderline tumors, and metastatic serous carcinoma
- Be able to effectively utilize ancillary tools to evaluate serous proliferations

Agenda

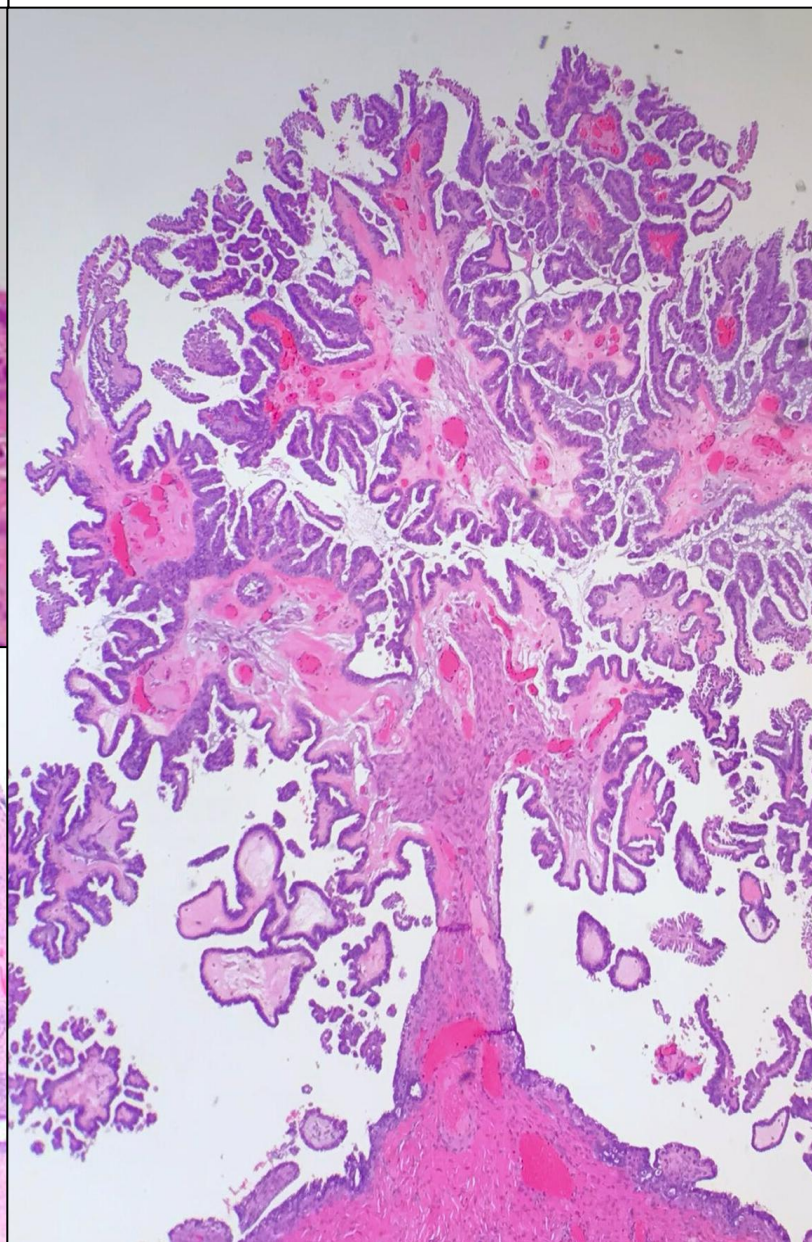
- Ovarian Serous Tumors
 - Cystadenoma/cystadenofibroma
 - Borderline
 - Implants
 - Micropapillary/cribriform features
 - Low-grade serous carcinoma
 - High-grade serous carcinoma



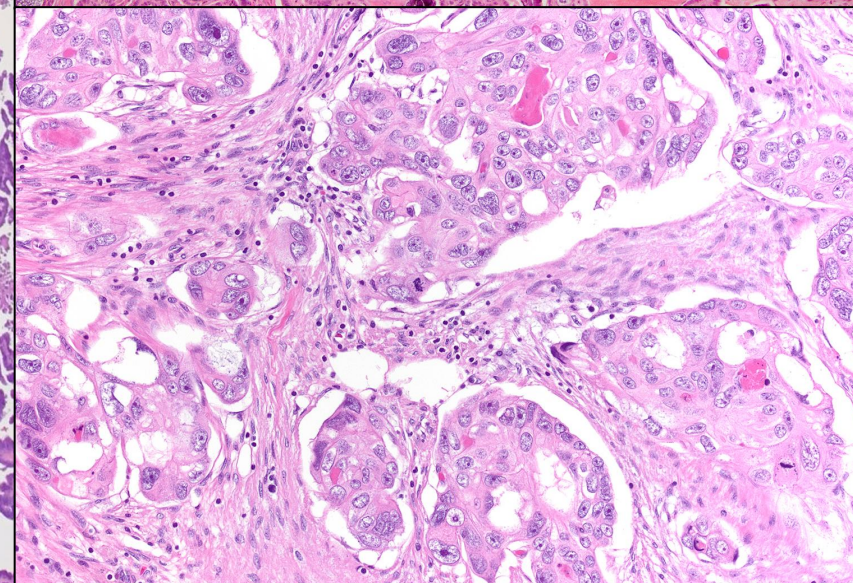
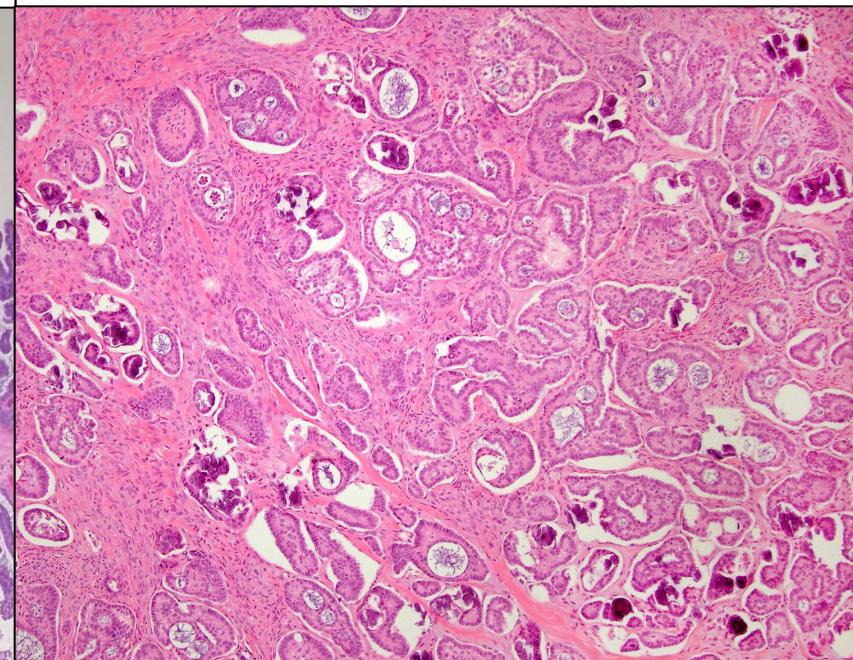
Benign



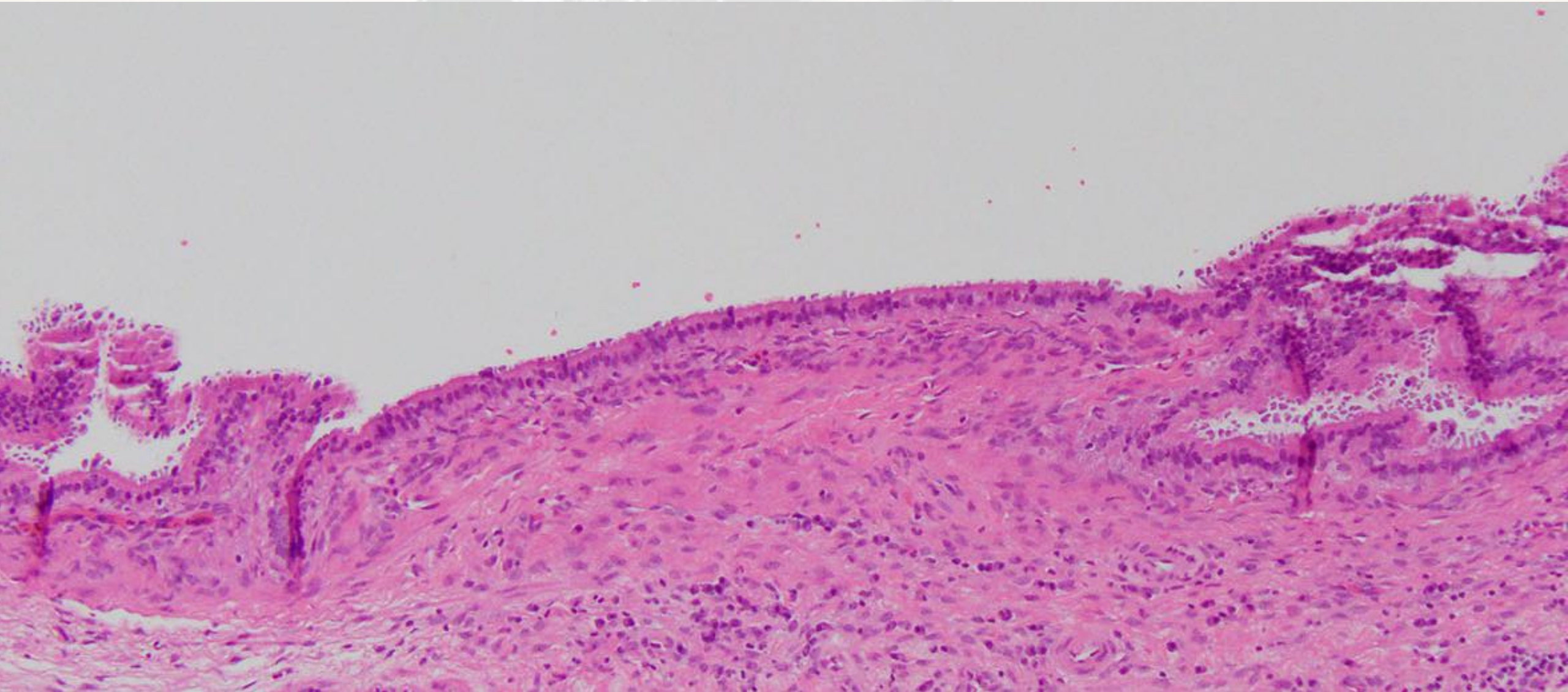
Borderline



Malignant

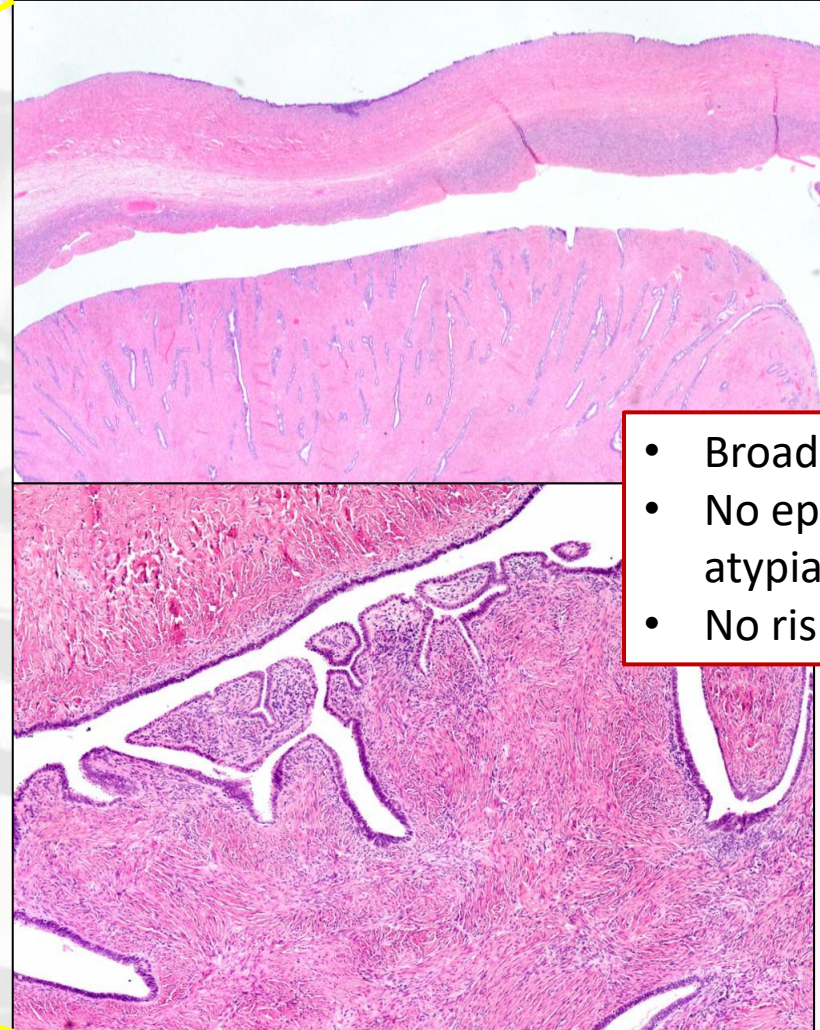
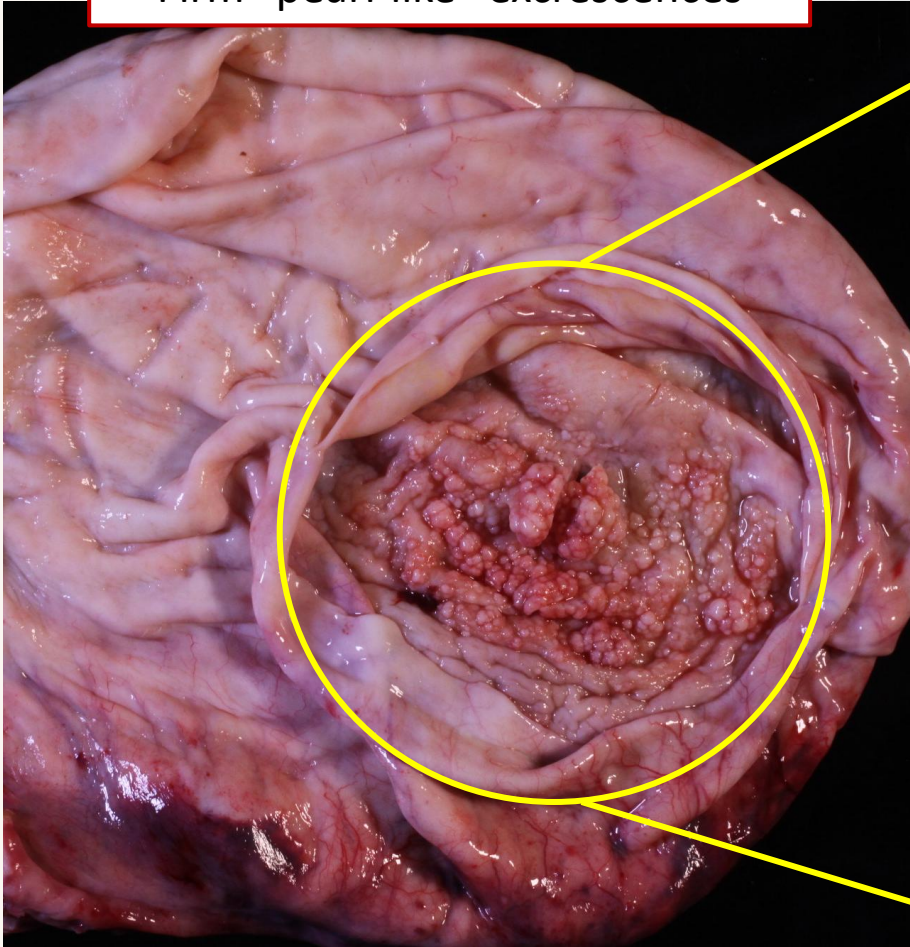


Serous Cystadenoma / Cystadenofibroma



Serous Cystadenoma / Cystadenofibroma

Firm “pearl-like” excrescences



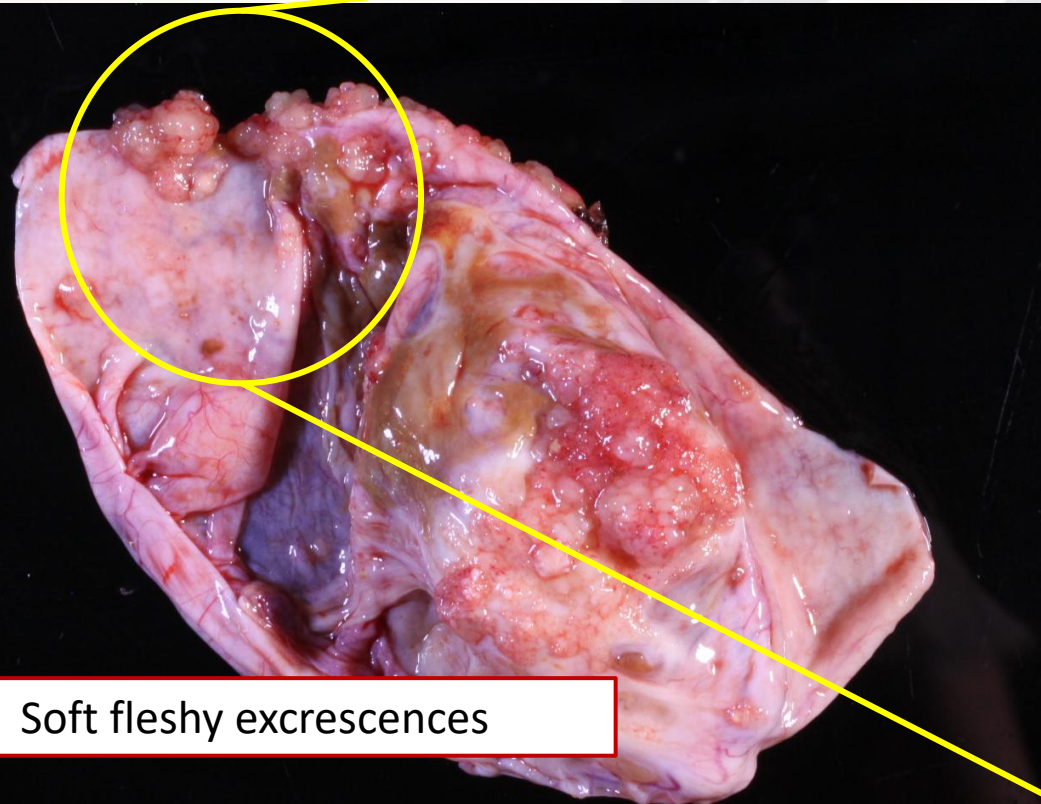
- Broad fibrous papillae
- No epithelial stratification or atypia
- No risk of aggressive behavior

Serous Borderline Tumor

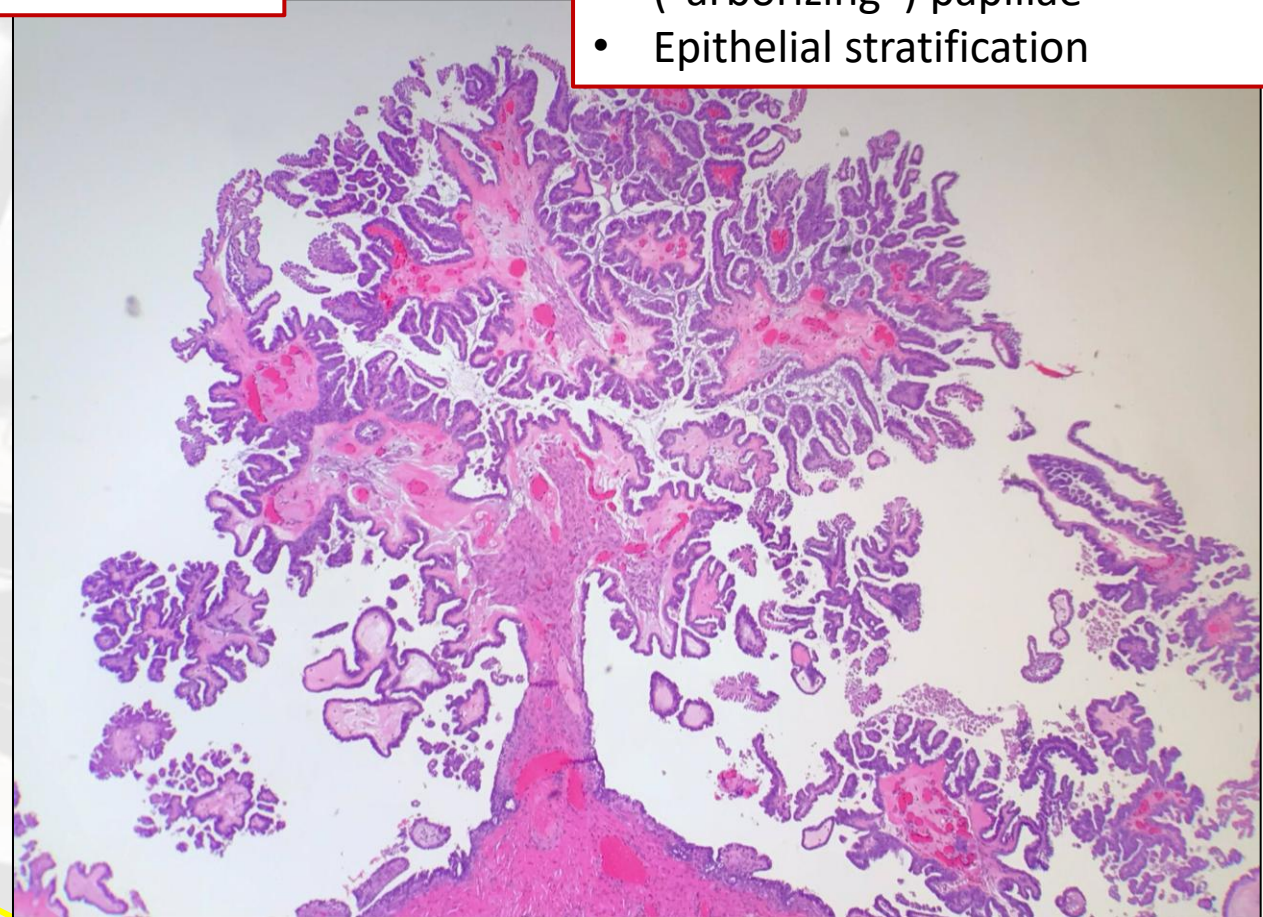
Definitions

- $>10\%$ = Serous borderline tumor
- $< 10\%$ = Serous cystadenoma with focal atypia/proliferation

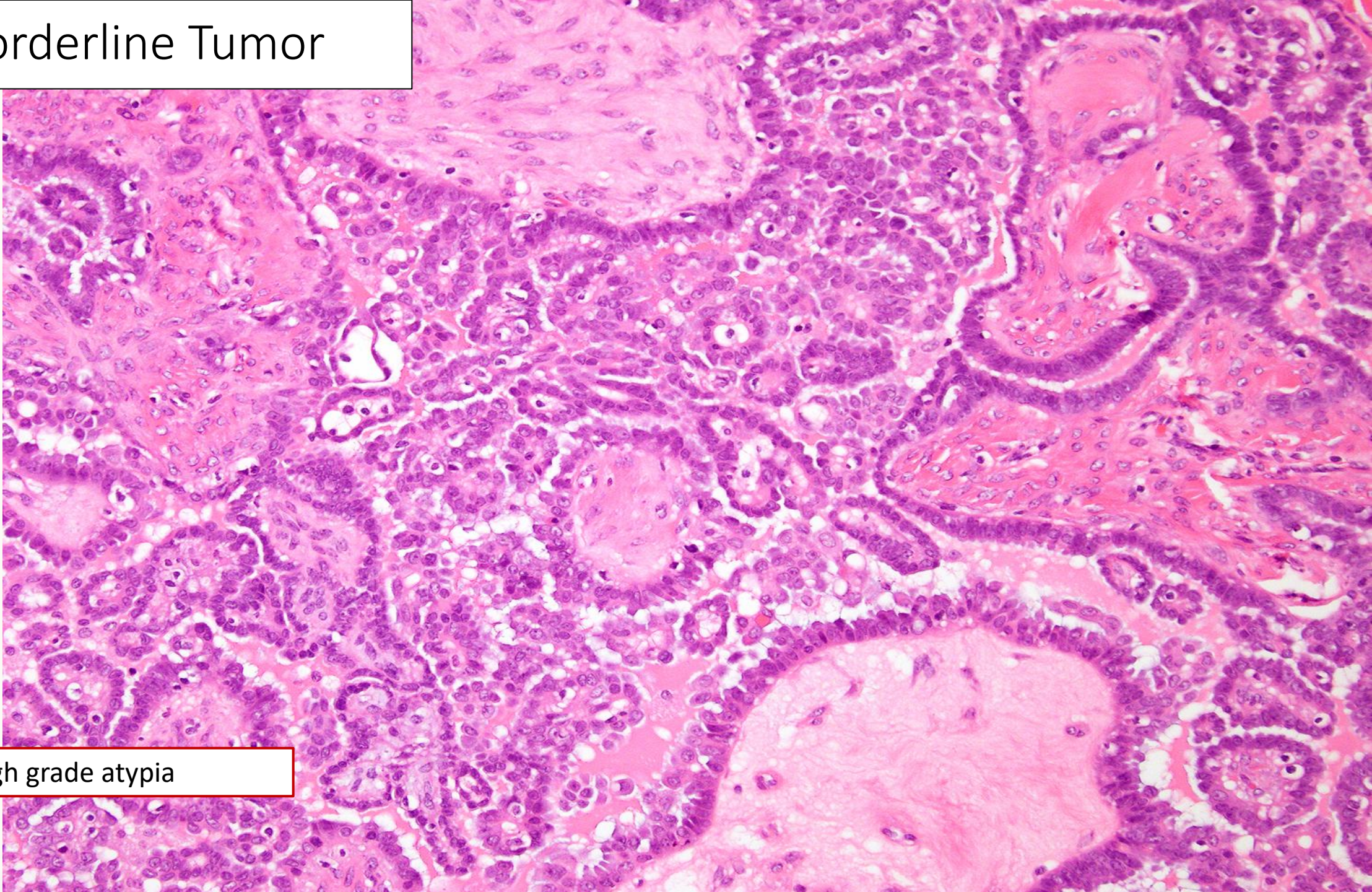
- Hierarchical branching (“arborizing”) papillae
- Epithelial stratification



Soft fleshy excrescences

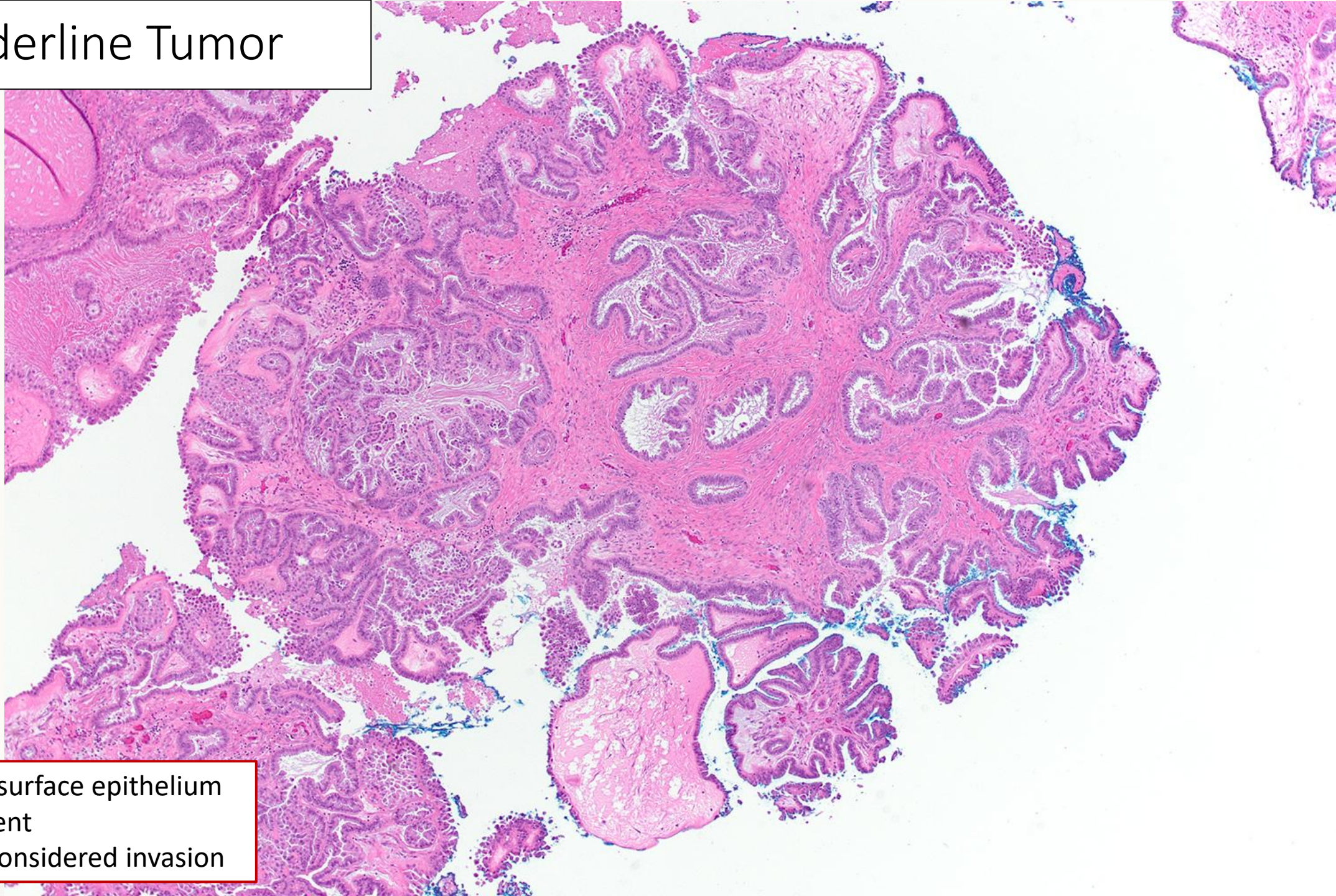


Serous Borderline Tumor



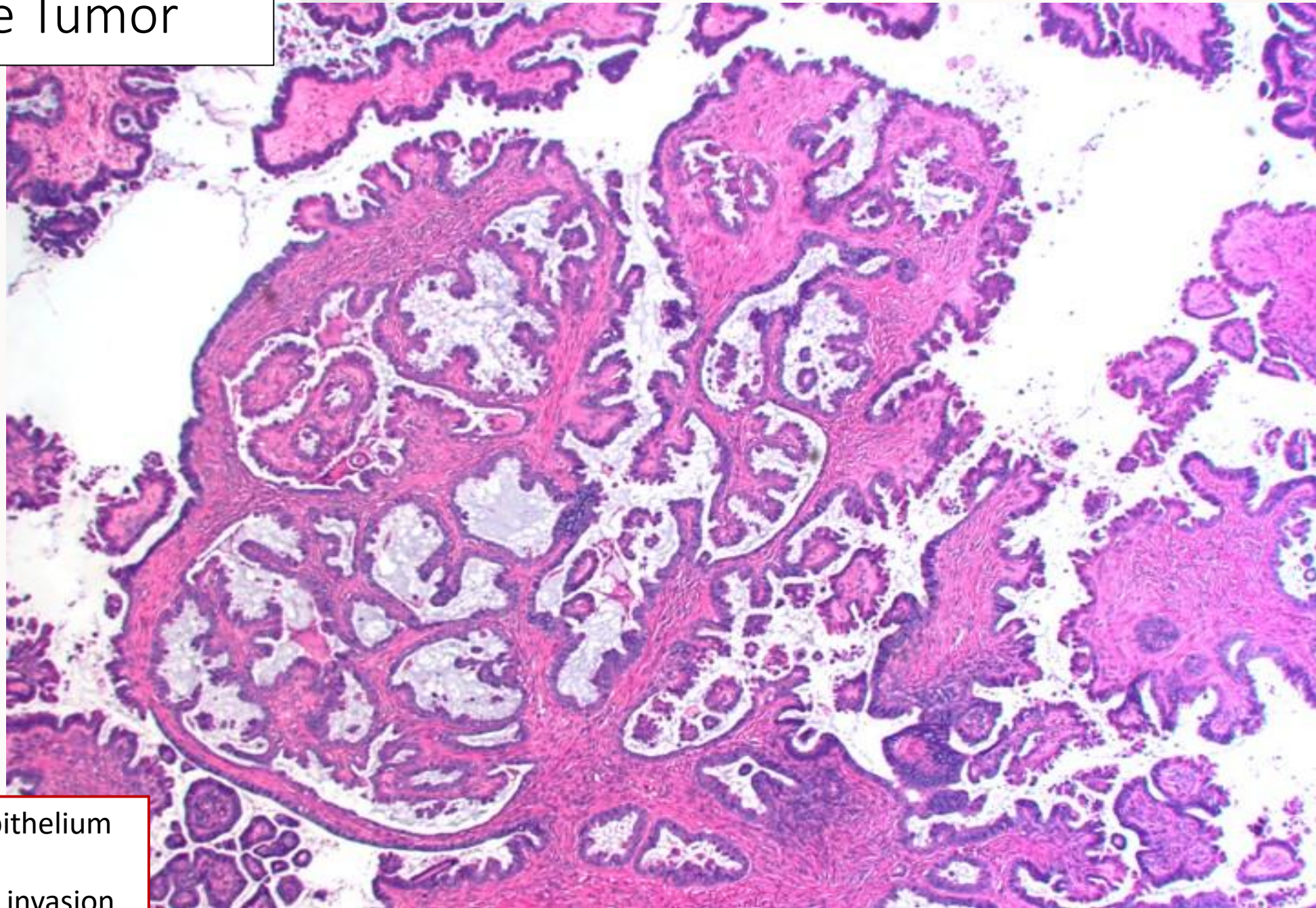
- Lacks high grade atypia

Serous Borderline Tumor



- Invagination of surface epithelium may be prominent
- Should not be considered invasion

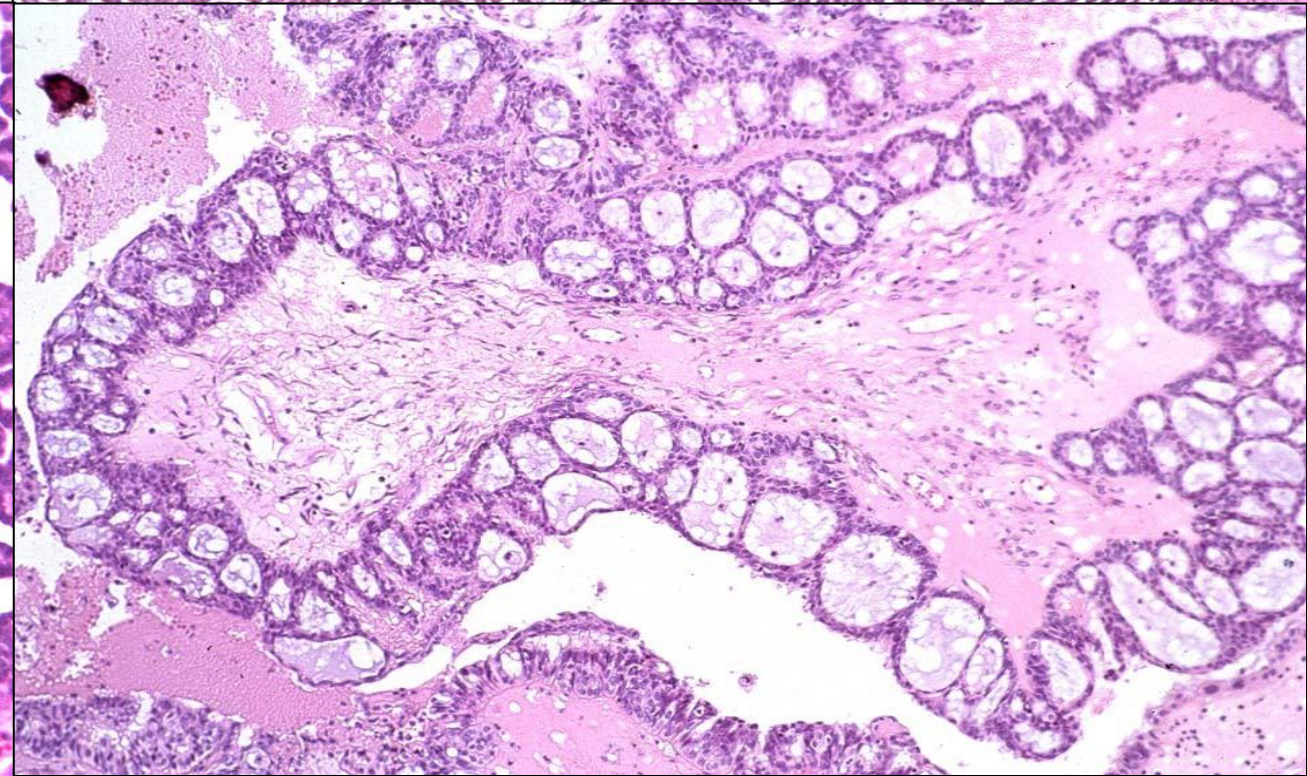
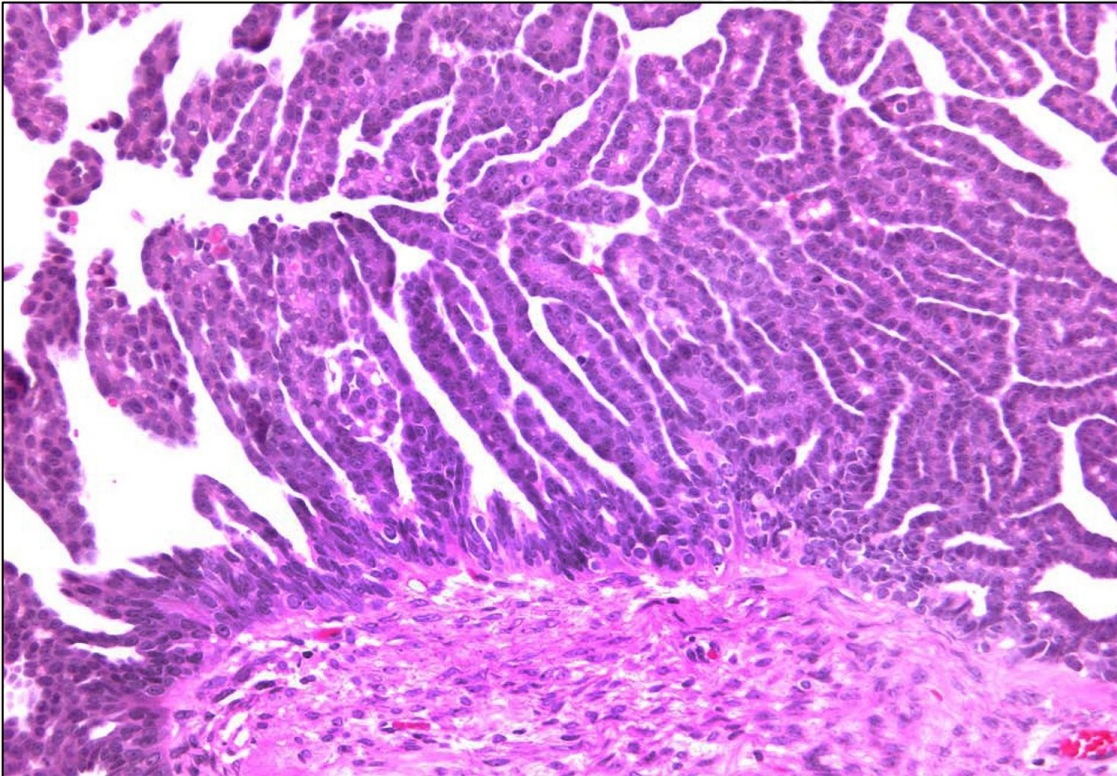
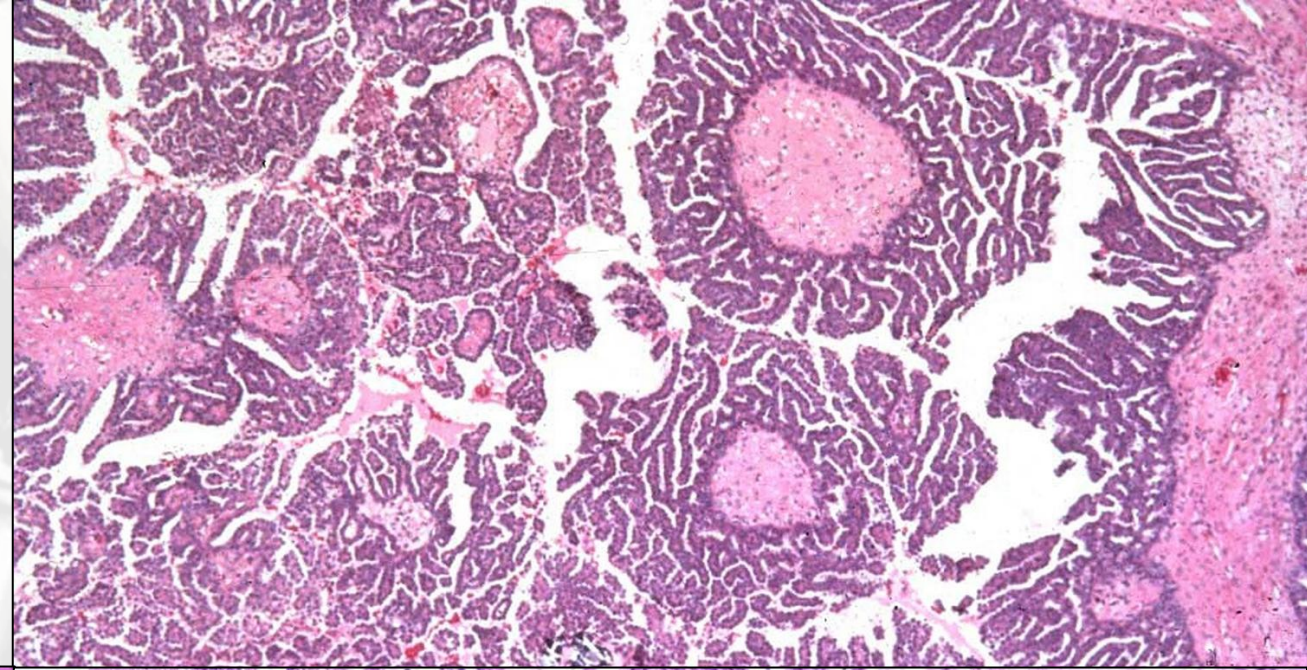
Serous Borderline Tumor



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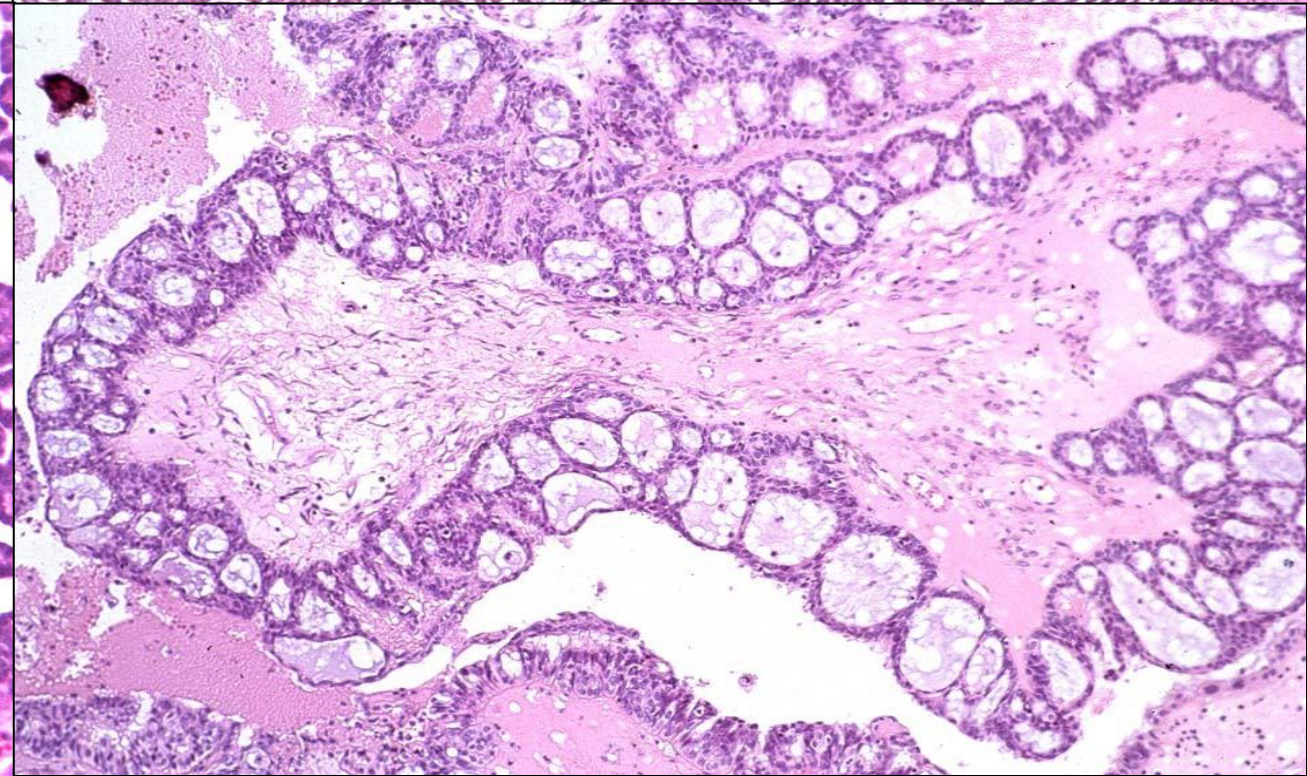
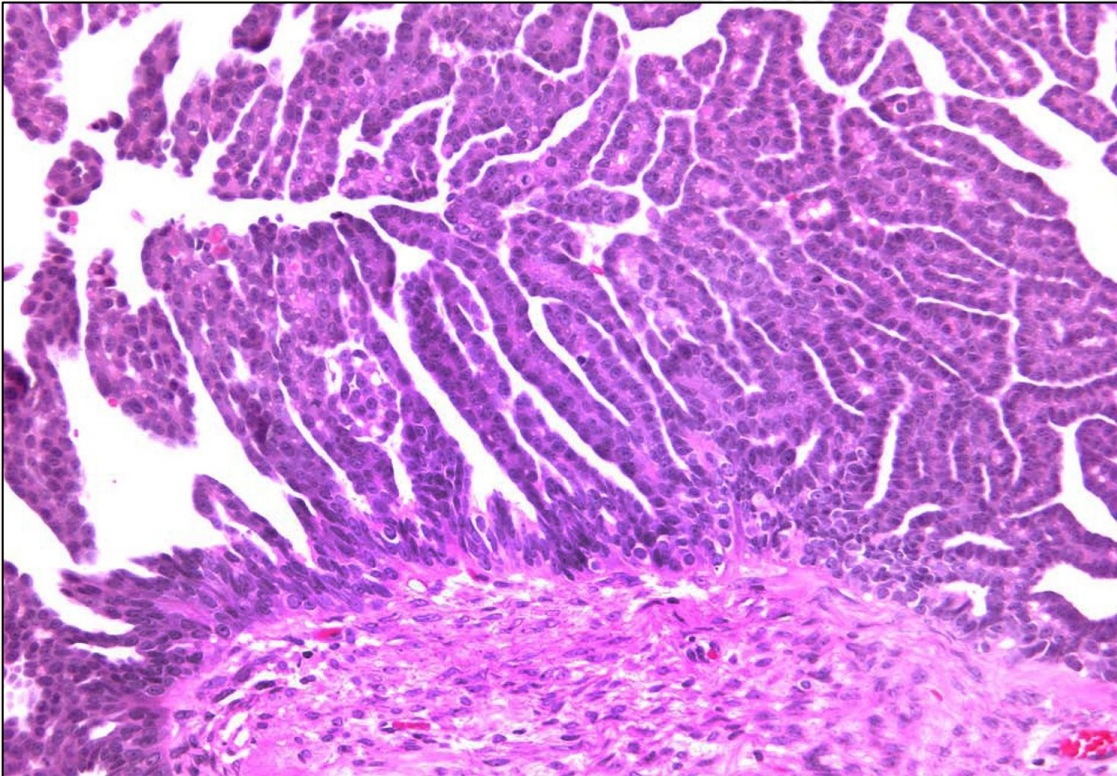
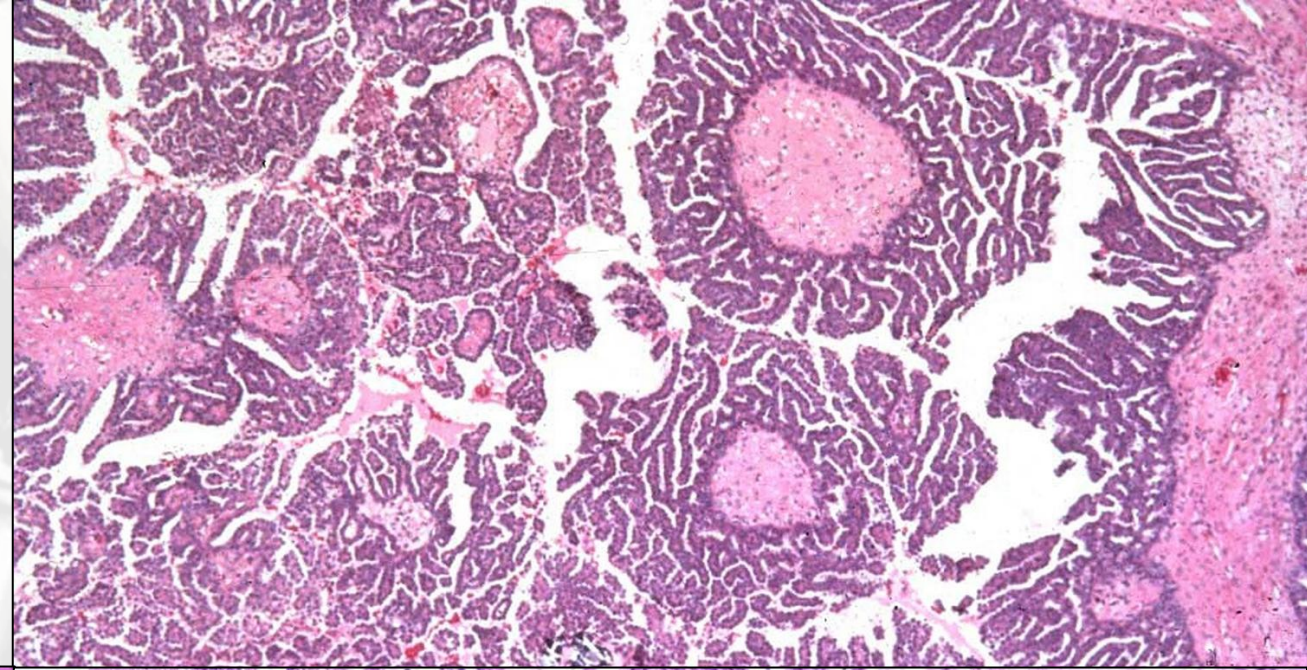
Micropapillary/Cribriform Subtype

- Micropapillae w/out fibrovascular cores
 - $\geq 5\times$ longer than width
- May be interanastomosing/cribriform
- ≥ 5 mm in size



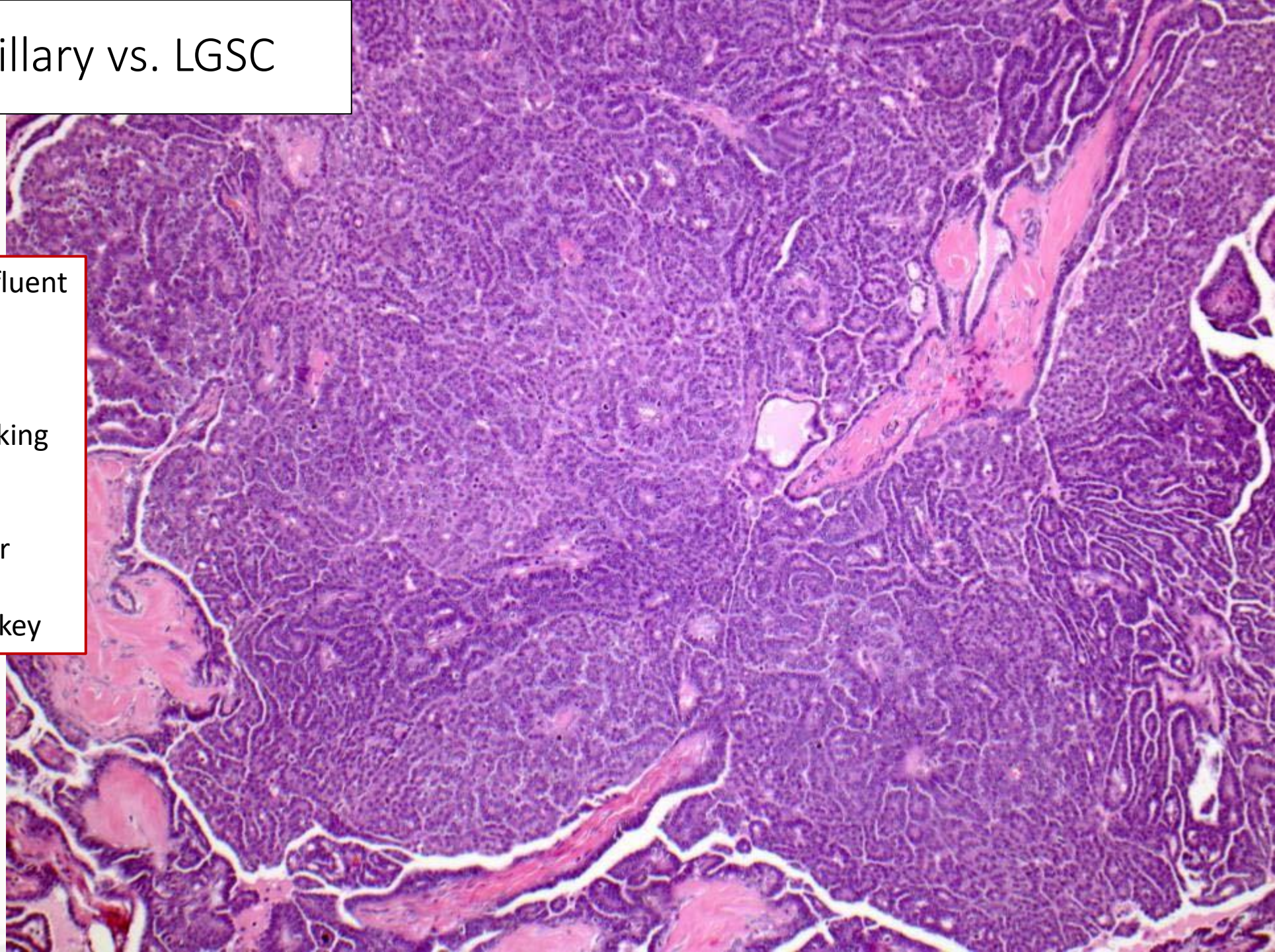
Micropapillary/Cribriform Subtype

- Should not be mistaken for LGSC
- Associated with higher risk of recurrence, progression to LGSC

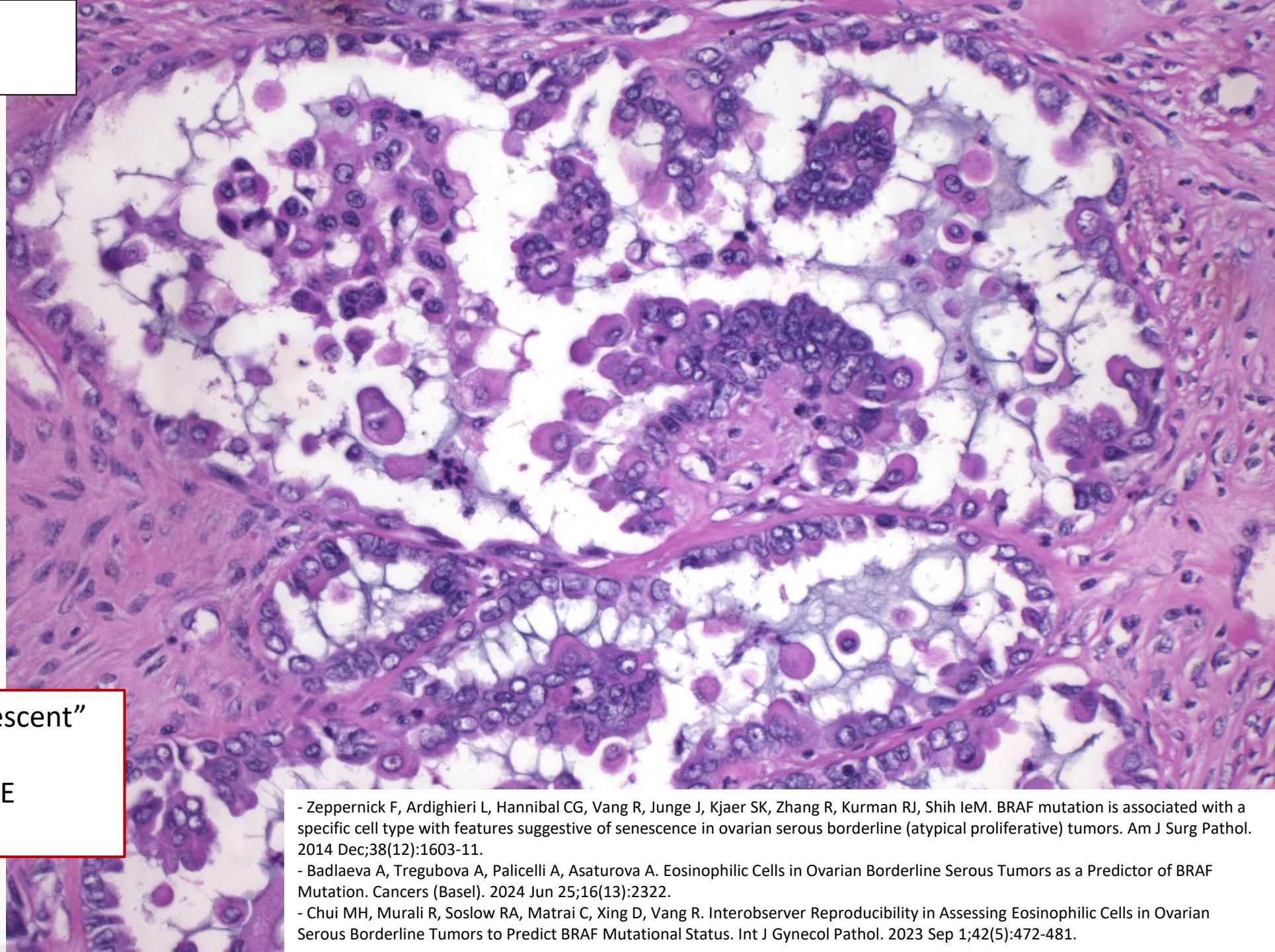


Extensive Micropapillary vs. LGSC

- Some cases may show confluent growth with extensively anastomosing papillae
- Defined cutoff for LGSC lacking for this morphology
- Often associated with other areas of discrete invasion
 - Adequate sampling is key



Eosinophilic Cells



- Thought to represent “senescent” cells
- Associated with *BRAF* V600E mutations

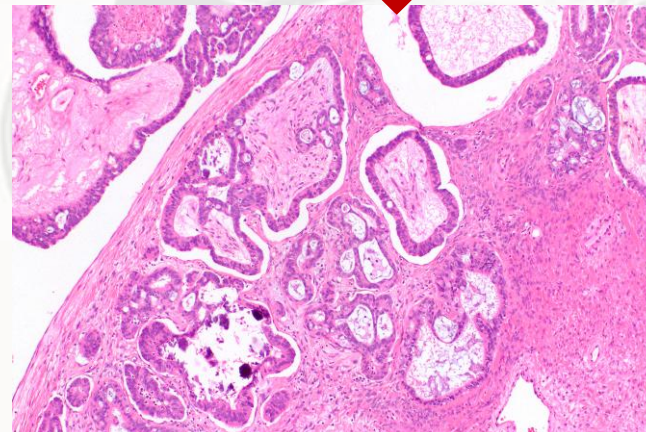
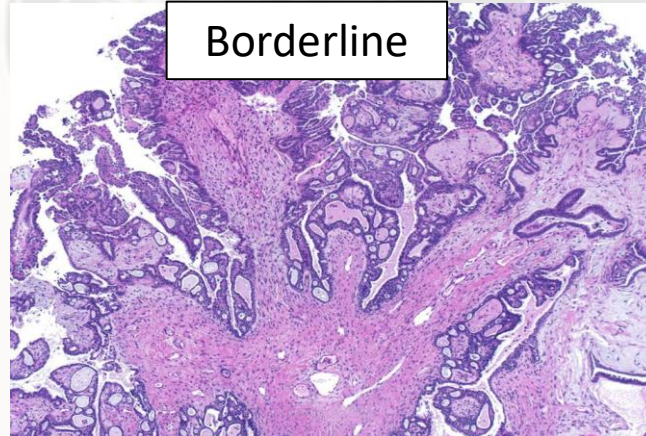
- Zeppernick F, Ardighieri L, Hannibal CG, Vang R, Junge J, Kjaer SK, Zhang R, Kurman RJ, Shih IeM. BRAF mutation is associated with a specific cell type with features suggestive of senescence in ovarian serous borderline (atypical proliferative) tumors. *Am J Surg Pathol*. 2014 Dec;38(12):1603-11.

- Badlaeva A, Tregubova A, Palicelli A, Asaturova A. Eosinophilic Cells in Ovarian Borderline Serous Tumors as a Predictor of BRAF Mutation. *Cancers (Basel)*. 2024 Jun 25;16(13):2322.

- Chui MH, Murali R, Soslow RA, Matrai C, Xing D, Vang R. Interobserver Reproducibility in Assessing Eosinophilic Cells in Ovarian Serous Borderline Tumors to Predict BRAF Mutational Status. *Int J Gynecol Pathol*. 2023 Sep 1;42(5):472-481.

Genetics and Progression of Serous Borderline Tumor

- *TP53* wild-type
- Frequent *MAPK* pathway mutations
 - *BRAF*
 - *KRAS*
 - *NRAS*



Low Grade Serous Carcinoma

- Progression to carcinoma in 4-7%
 - Usually low-grade serous carcinoma
- Adverse risk factors
 - Ovarian surface involvement
 - Micropapillary/cribriform
 - Advanced stage
 - Residual disease following surgery
- Protective factors
 - Lower risk if *BRAF* mutation (~0.5%)*
- Not predictive
 - Microinvasion
 - Lymph node involvement

*Chui MH, Kjaer SK, Frederiksen K, Hannibal CG, Wang TL, Vang R, Shih IM. BRAFV600E -mutated ovarian serous borderline tumors are at relatively low risk for progression to serous carcinoma. *Oncotarget*. 2019 Dec 3;10(64):6870-6878.

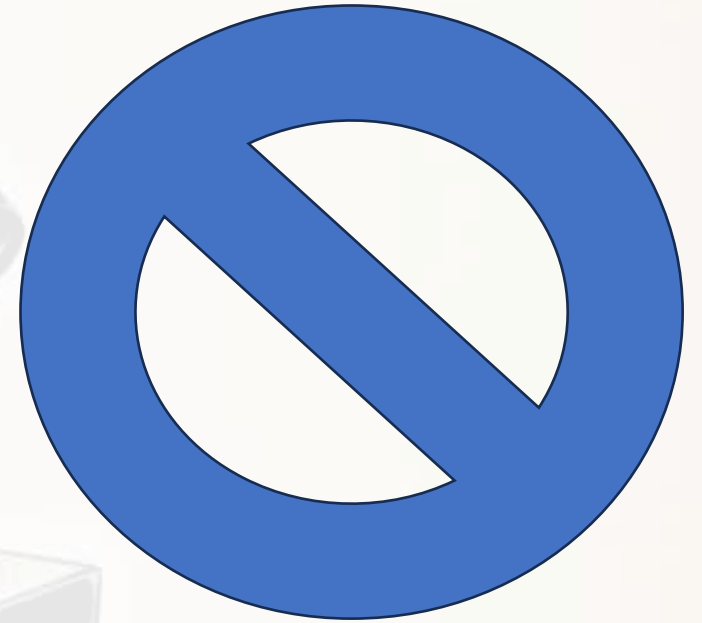
Upcoming Changes in WHO 6th Edition

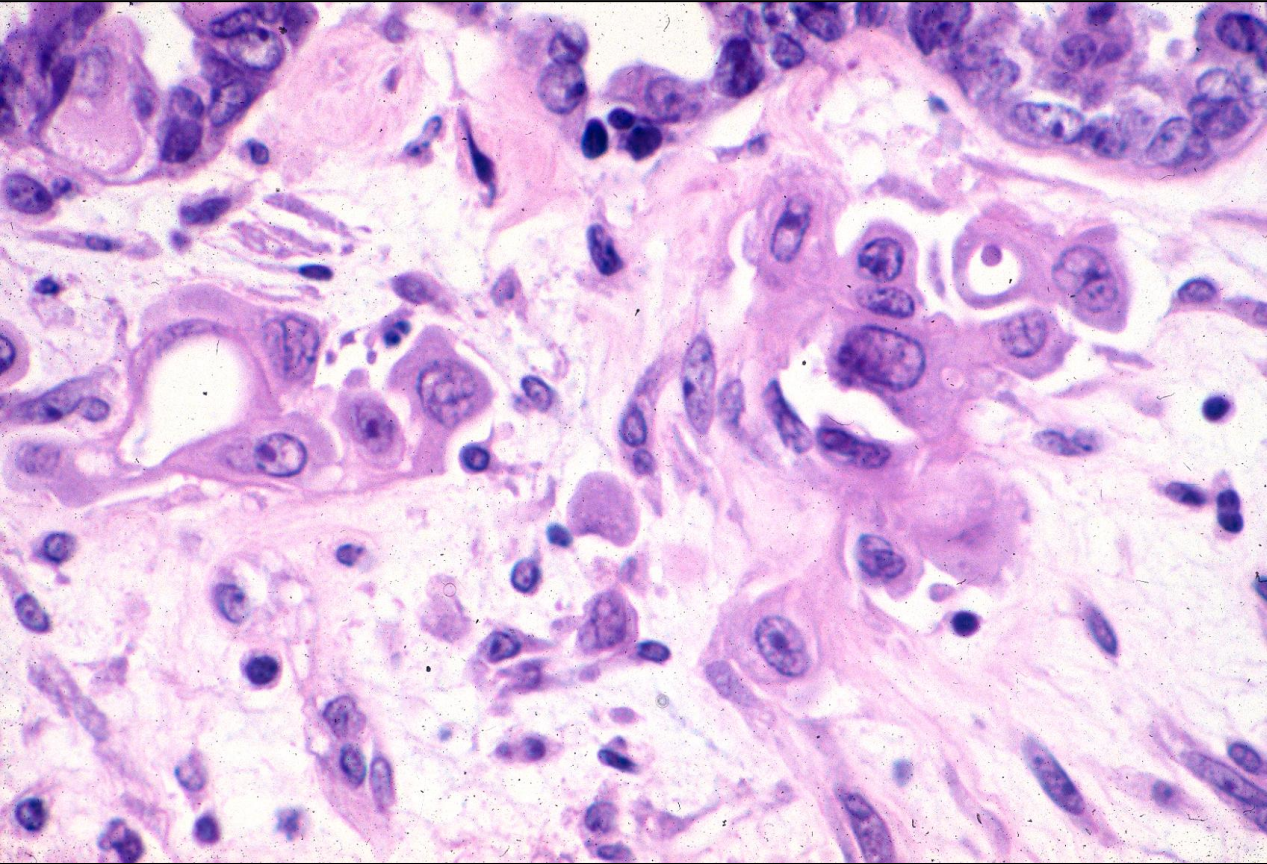
WHO 5th Edition

- Microinvasion
 - Foci of stromal invasion <5 mm in greatest dimension
 - Can have multiple foci – NOT additive

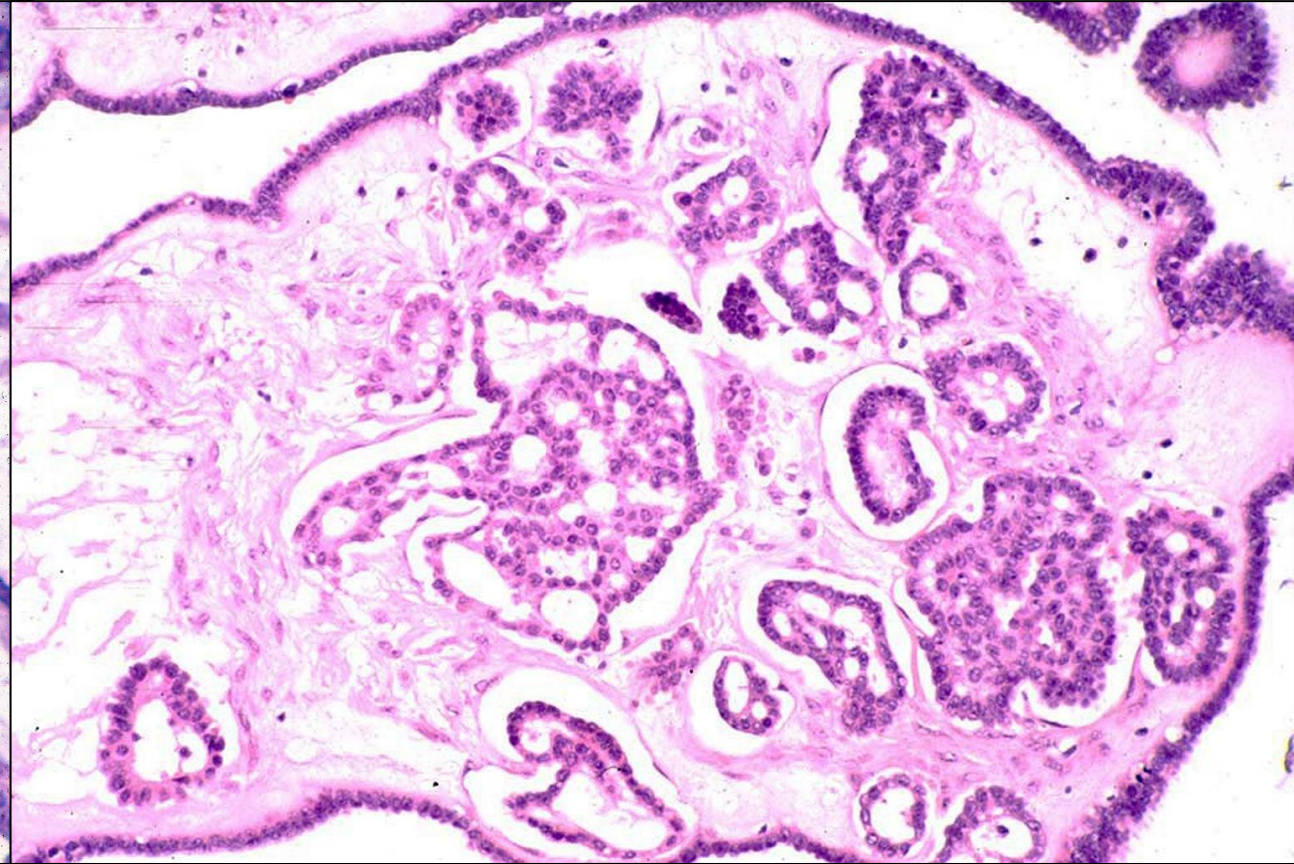
WHO 6th Edition

- Do not use the term “microinvasion”





- Minor foci (usually <5 mm) of clusters of tumour cells with abundant dense eosinophilic cytoplasm and/or small, simple papillae with cytologic features of serous borderline tumor
- Thought to be senescent – no prognostic significance
- Diagnosis: Serous borderline tumor

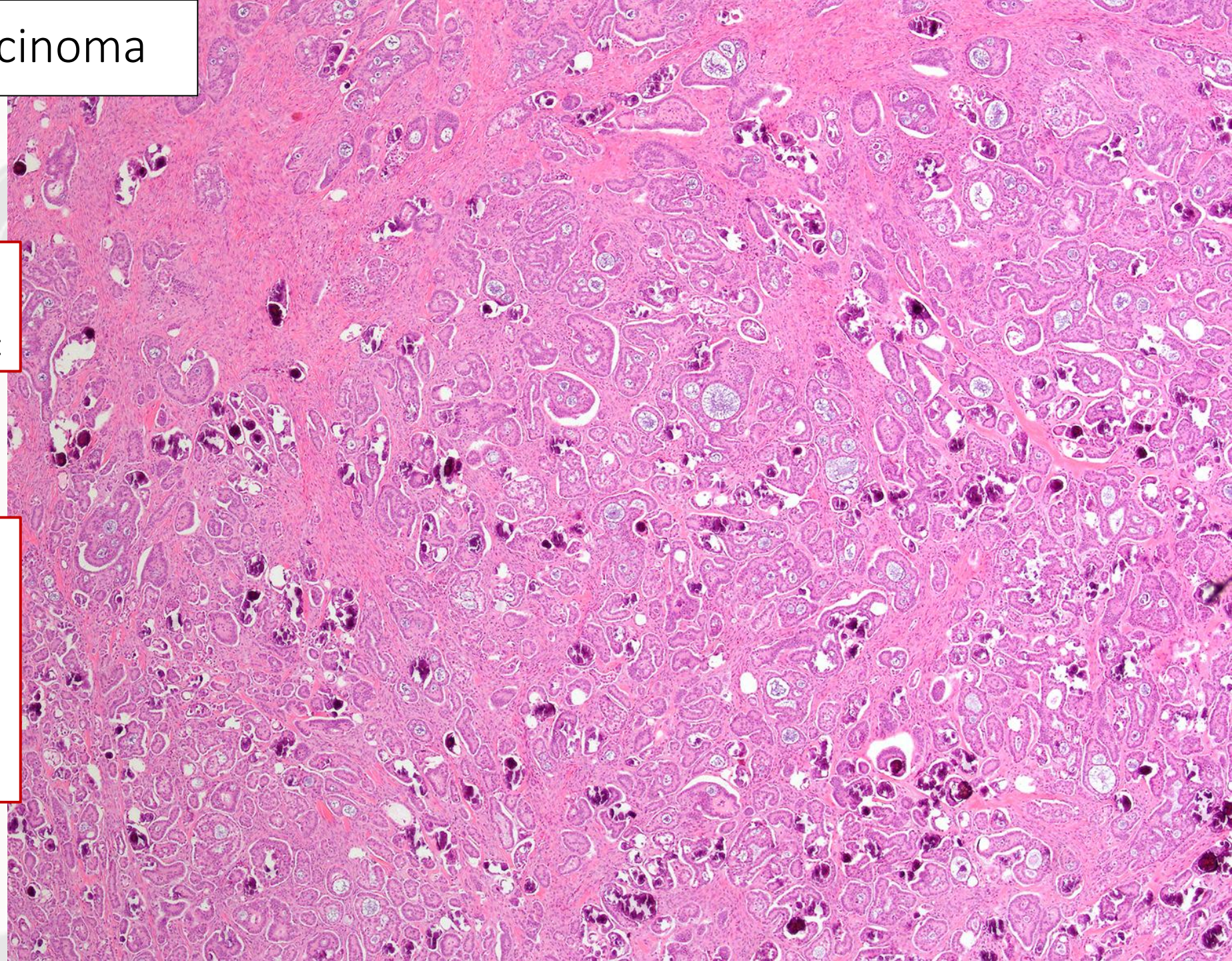


- Minor foci (<5 mm) of true invasive papillae/micropapillae or other patterns of invasion as seen in LGSC
- Diagnosis: Focal LGSC arising in serous borderline tumor

Low-Grade Serous Carcinoma

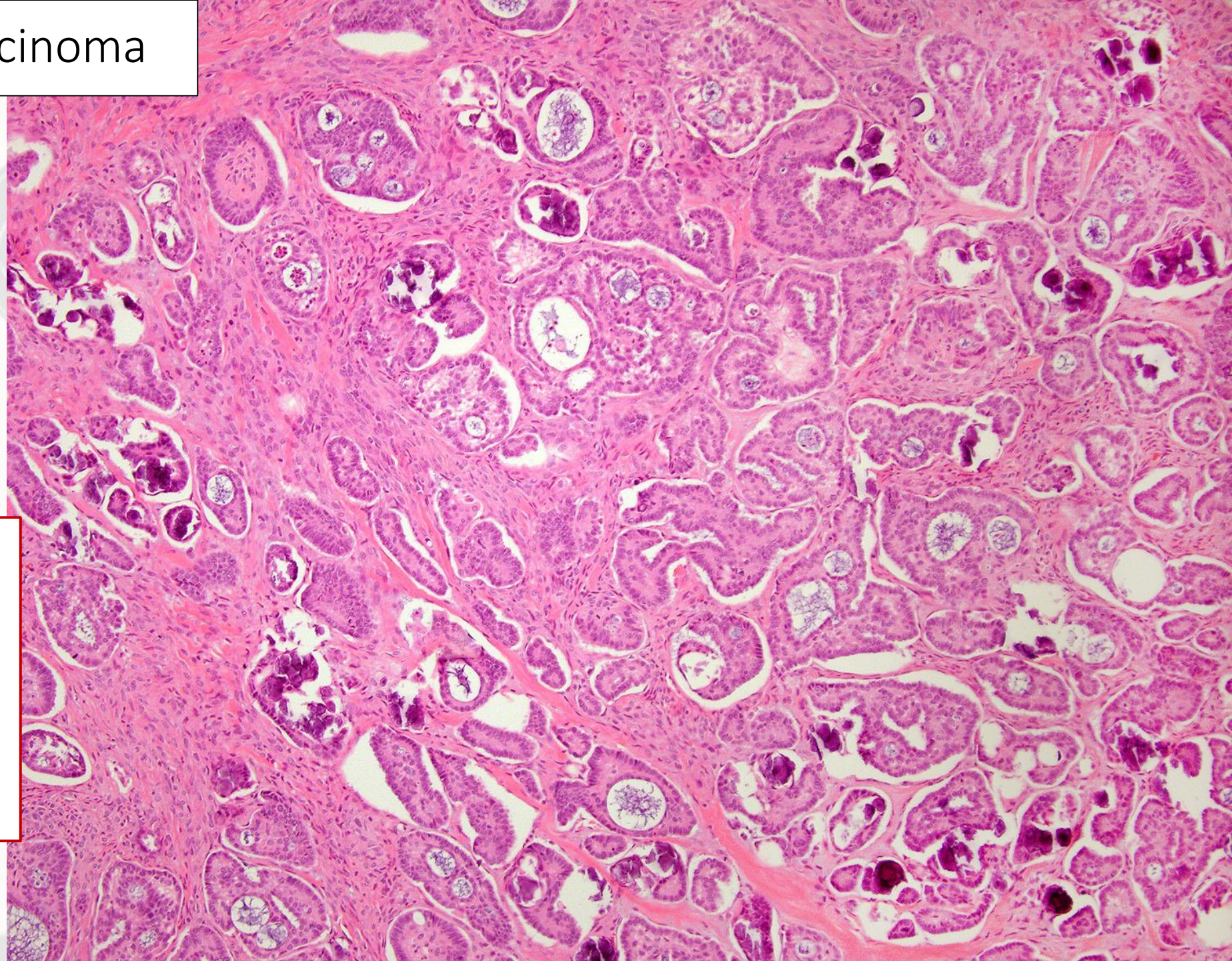
- *Often arise in association with serous borderline tumor
- *Adequate sampling is important

- Stromal invasion (no longer requires a 5 mm cutoff)
 - Nests
 - Papillae
 - Micropapillae
 - Glands
 - Solid sheets



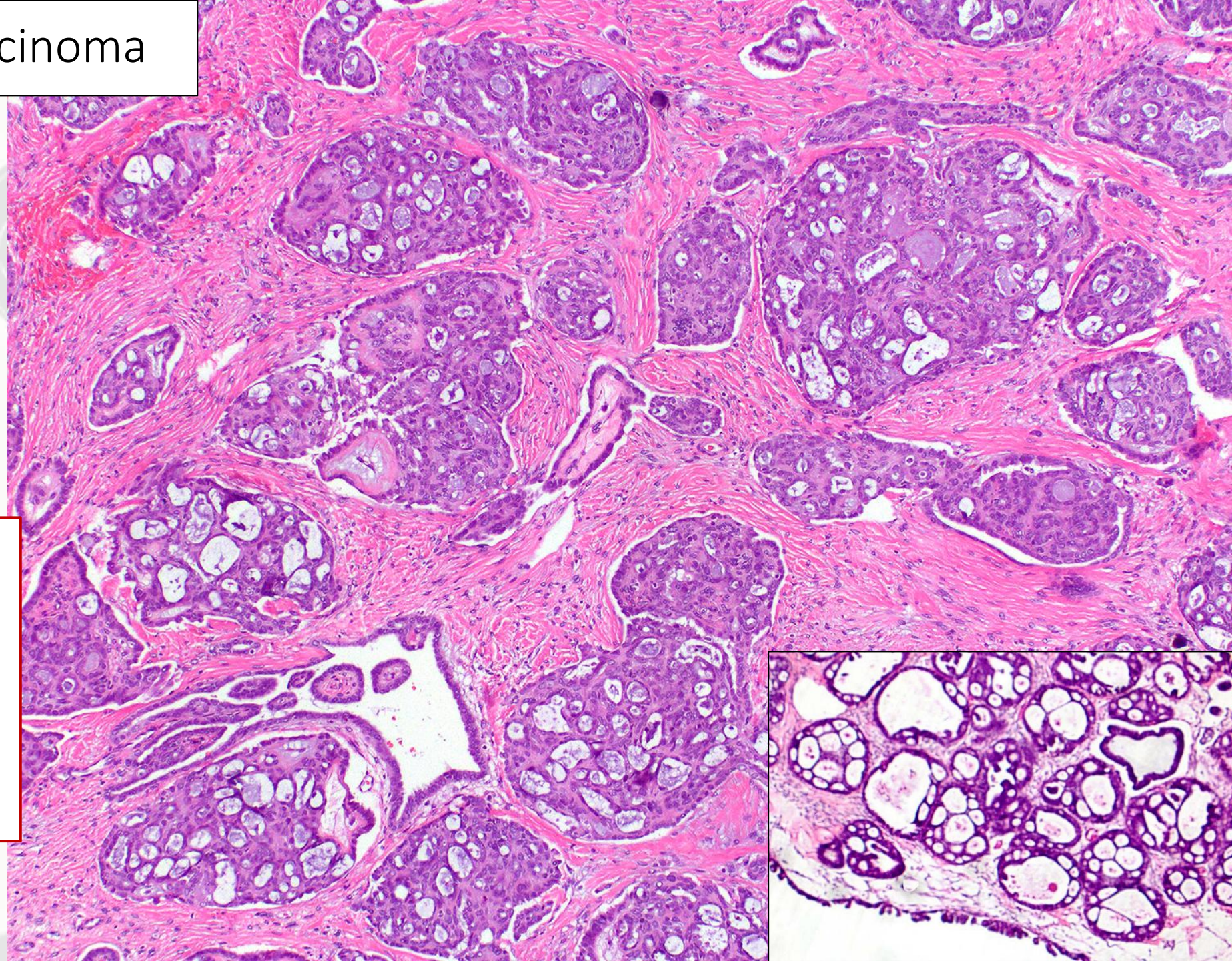
Low-Grade Serous Carcinoma

- Stromal invasion ≥ 5 mm
 - Nests
 - Papillae
 - Micropapillae
 - Glands
 - Solid sheets
- Lacks high grade atypia

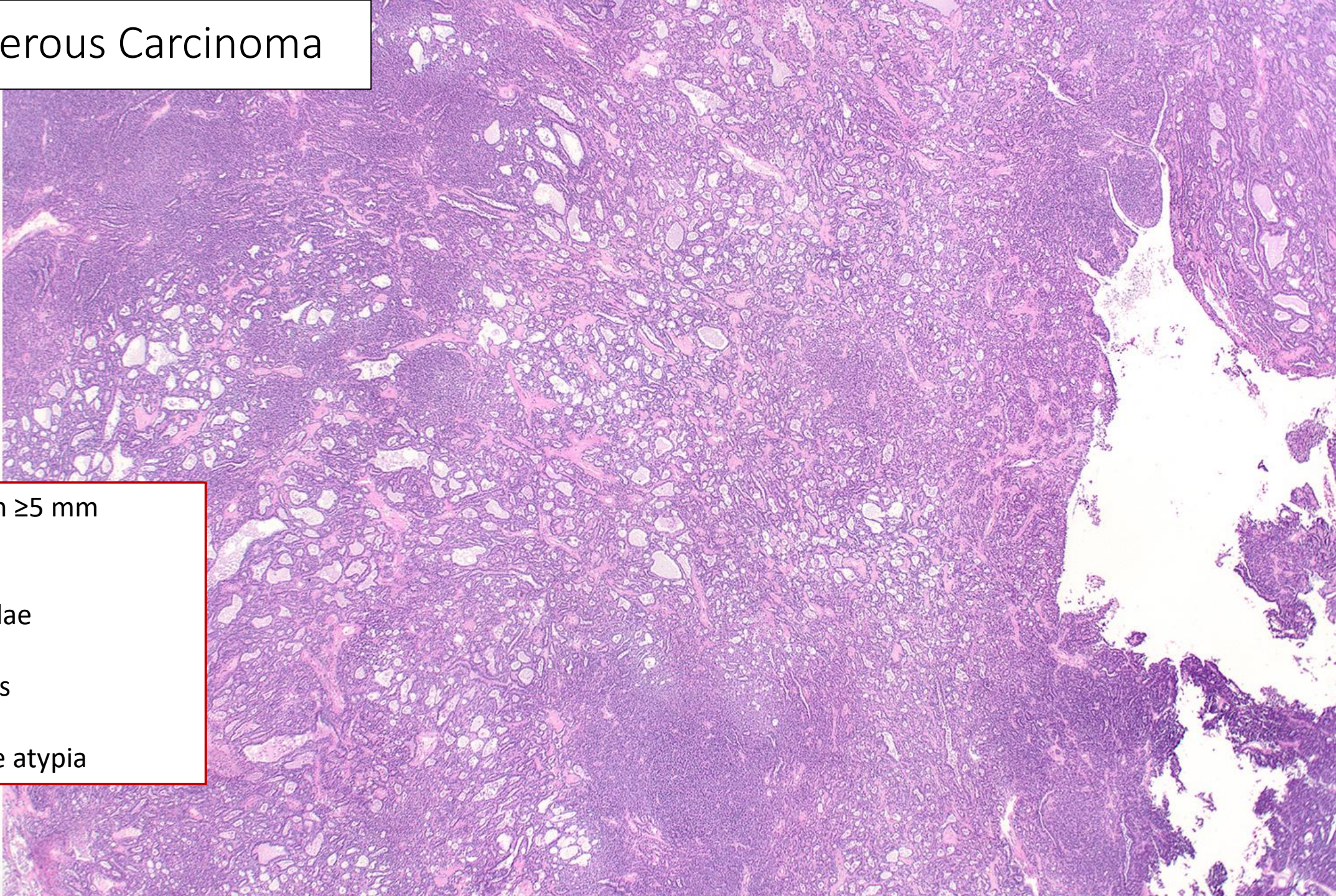


Low-Grade Serous Carcinoma

- Stromal invasion ≥ 5 mm
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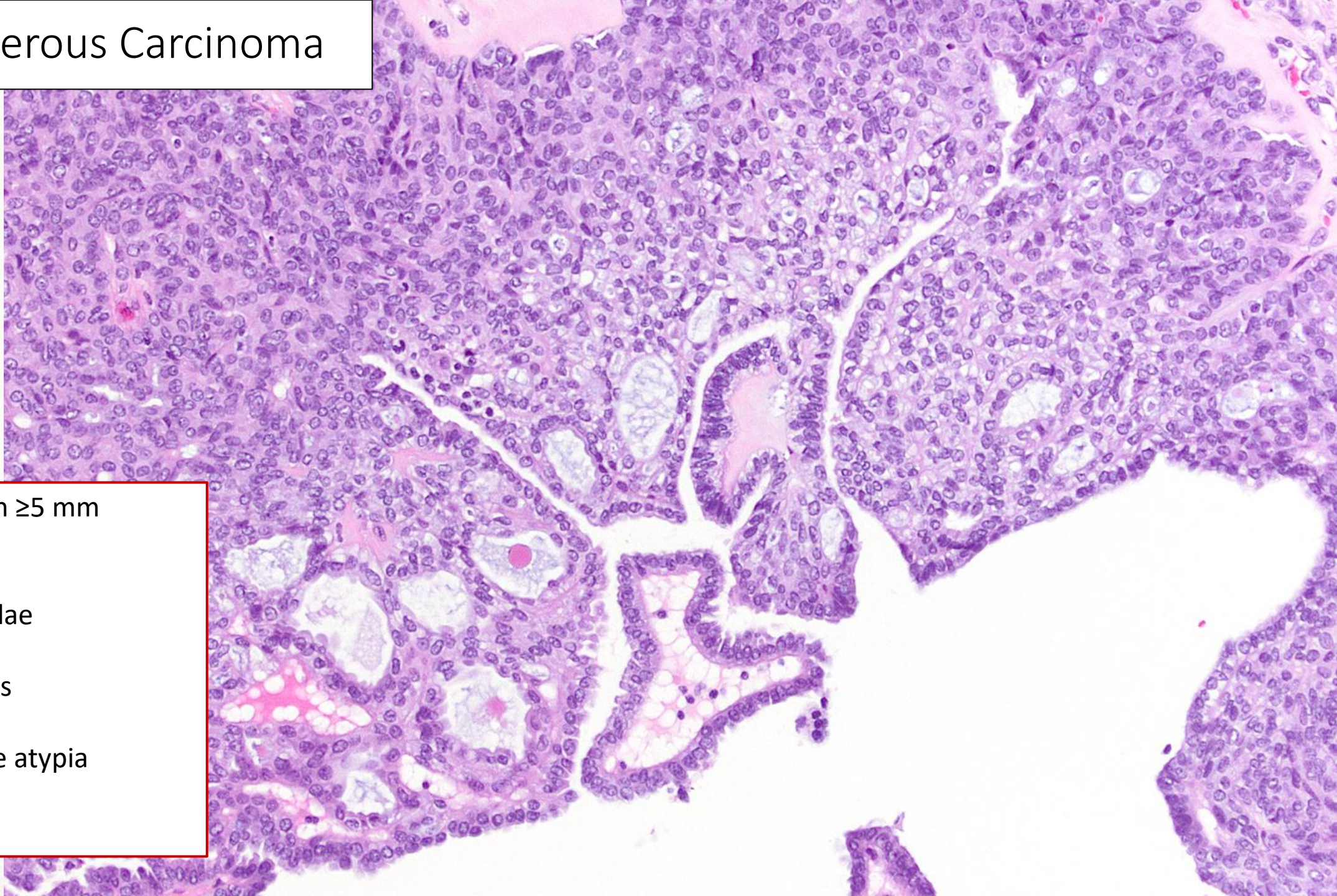


Low-Grade Serous Carcinoma



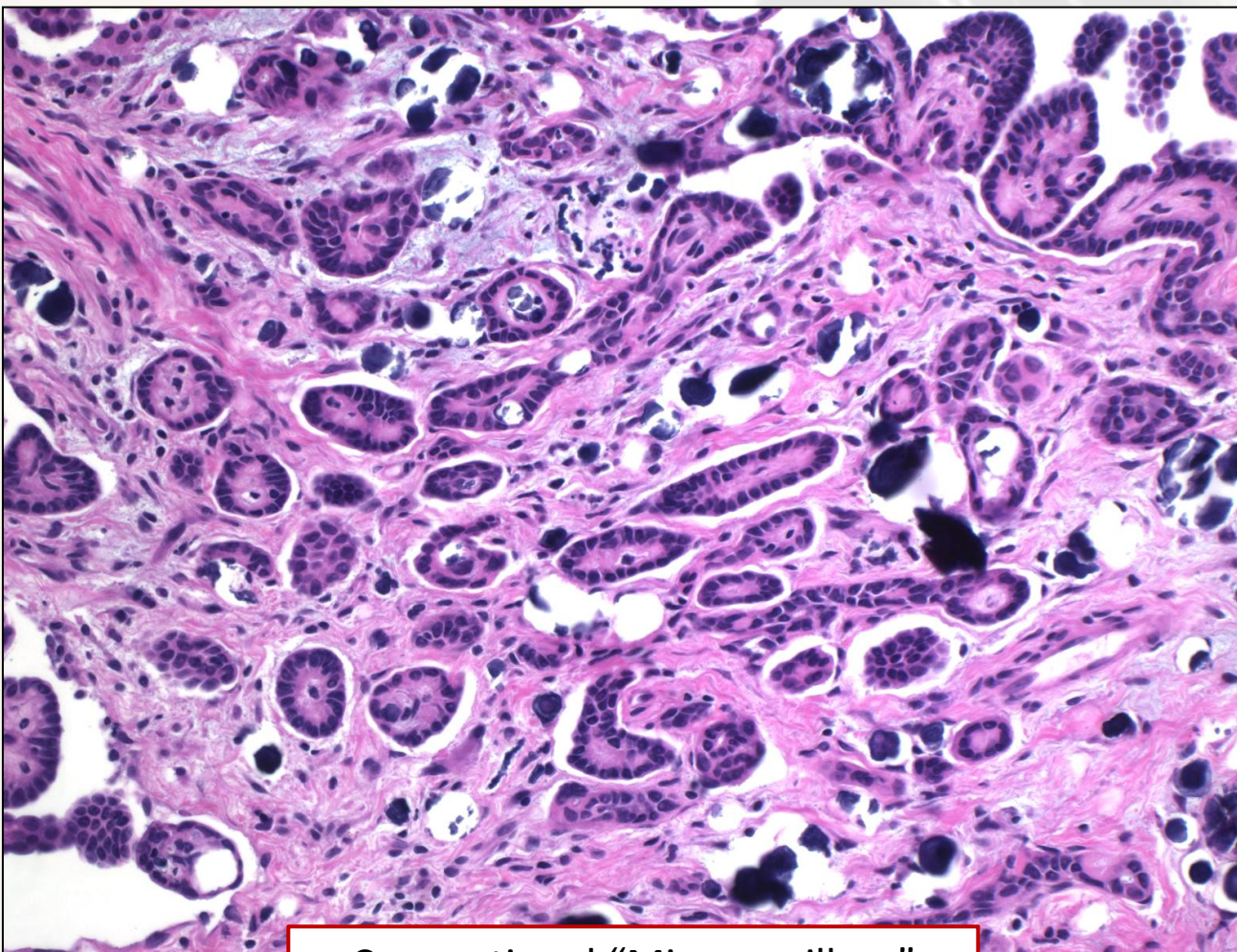
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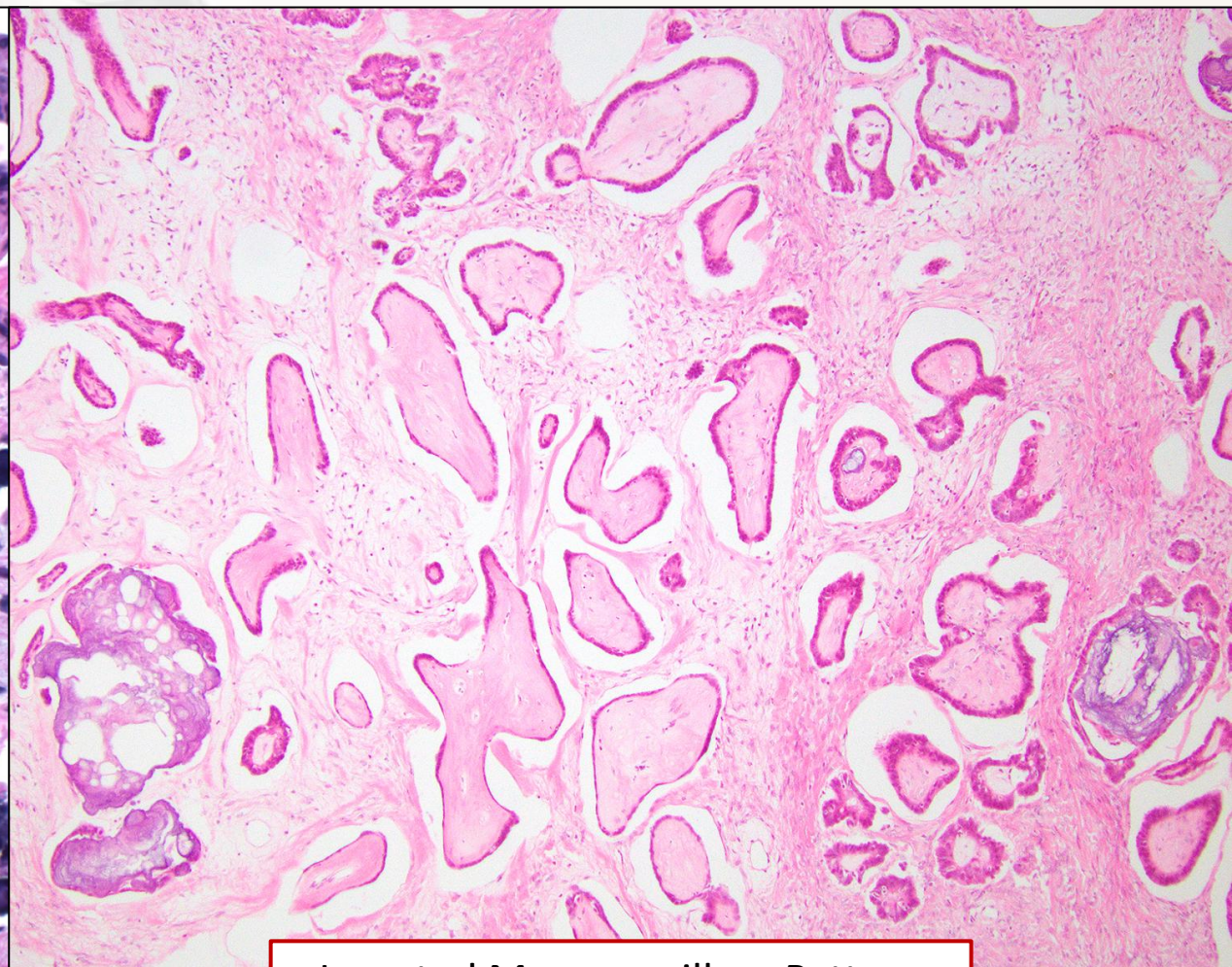


- Stromal invasion ≥ 5 mm
 - Nests
 - Papillae
 - Micropapillae
 - Glands
 - Solid sheets
- Lacks high grade atypia
- p53 wild-type

Low-Grade Serous Carcinoma



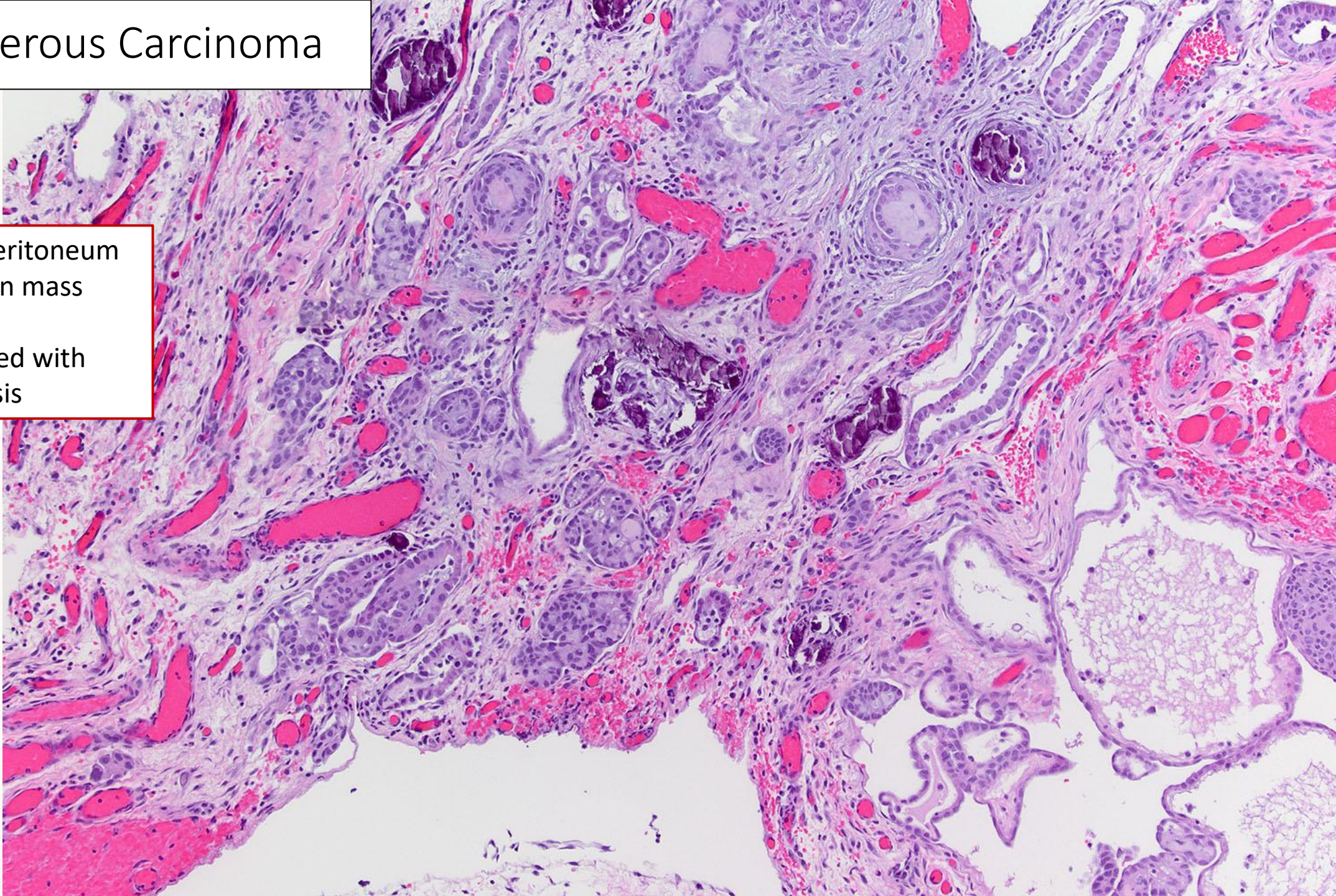
Conventional "Micropapillary"
Invasive Pattern



Inverted Macropapillary Pattern

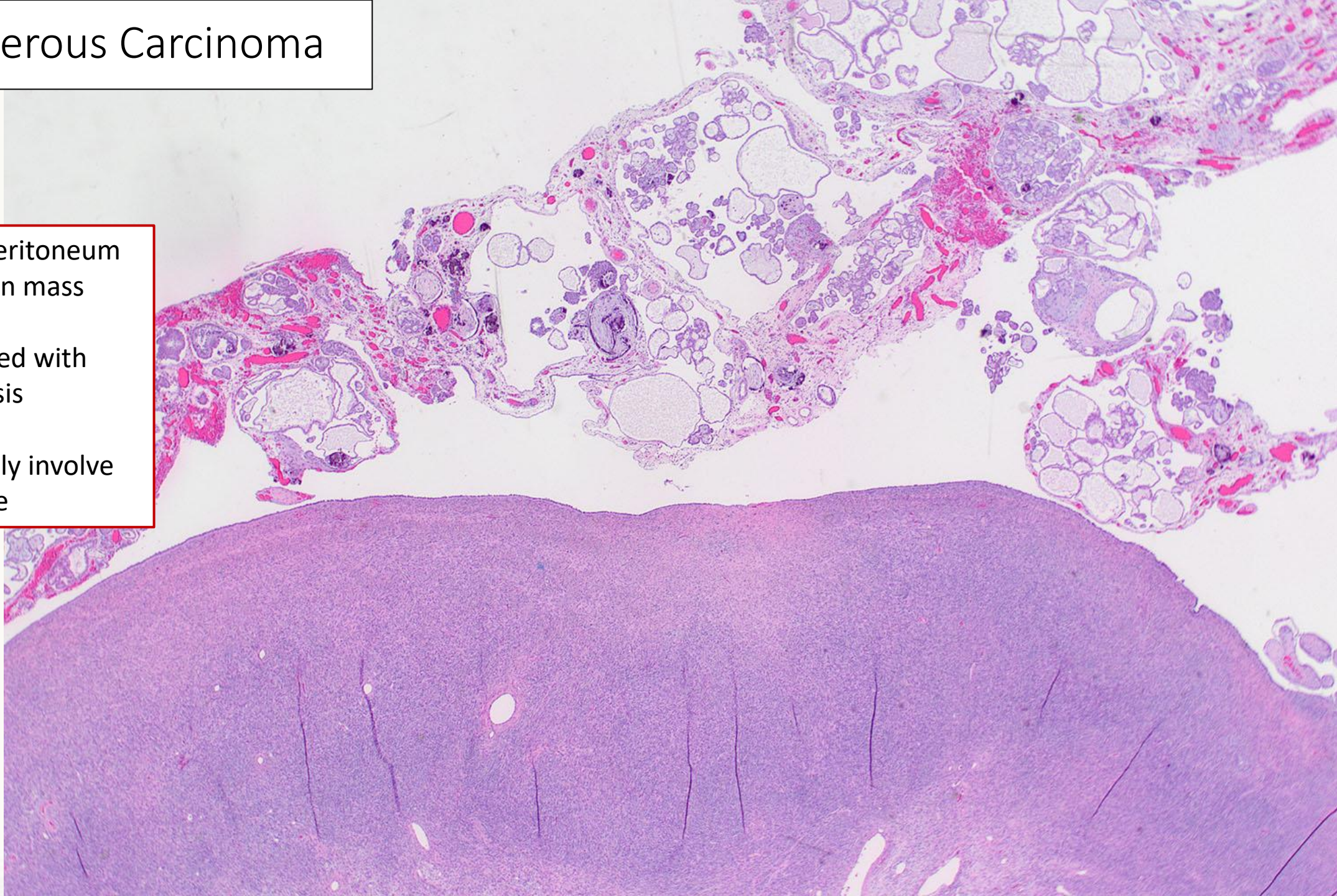
Low-Grade Serous Carcinoma

- May arise in peritoneum without ovarian mass
- Often associated with endosalpingiosis



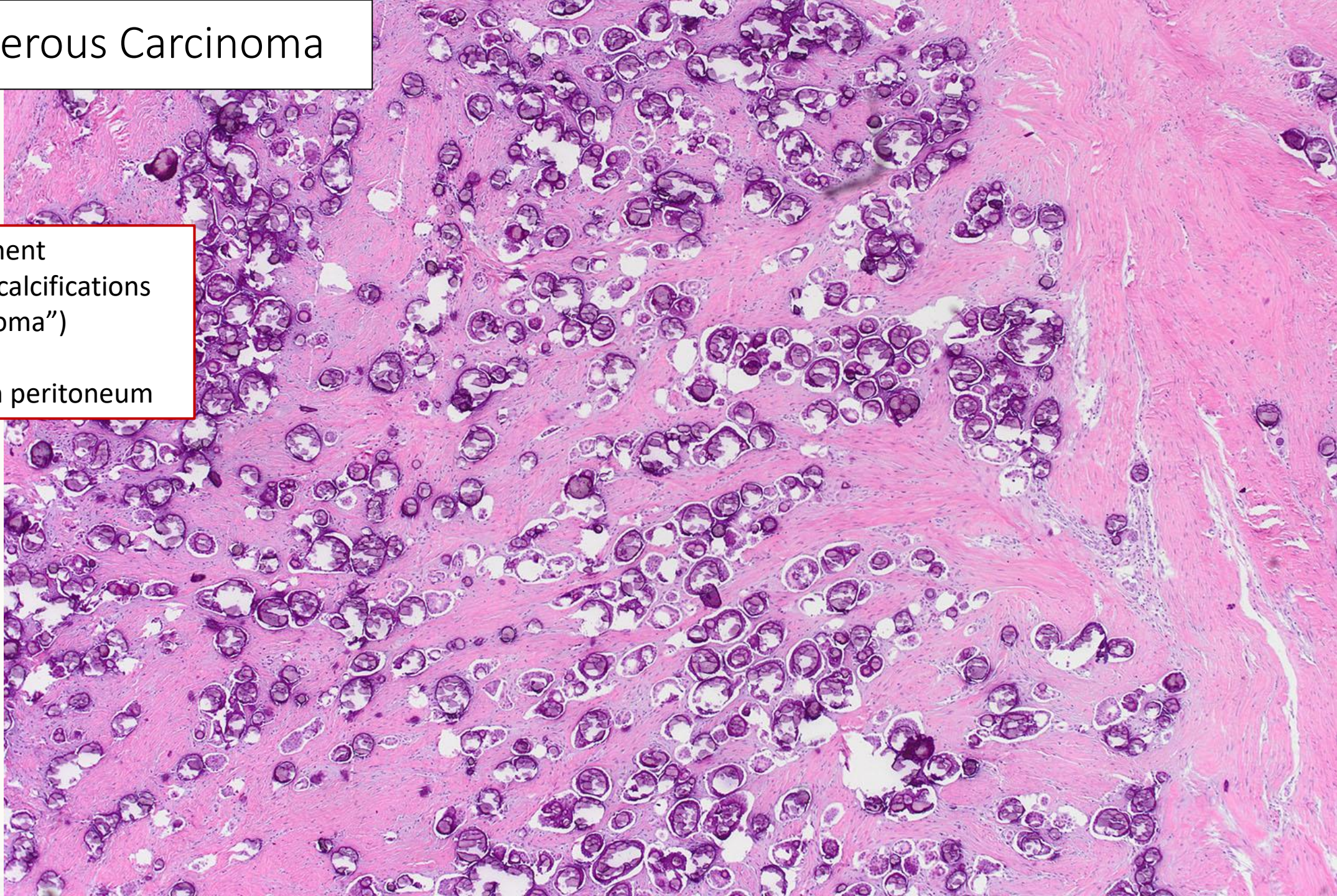
Low-Grade Serous Carcinoma

- May arise in peritoneum without ovarian mass
- Often associated with endosalpingiosis
- May secondarily involve ovarian surface



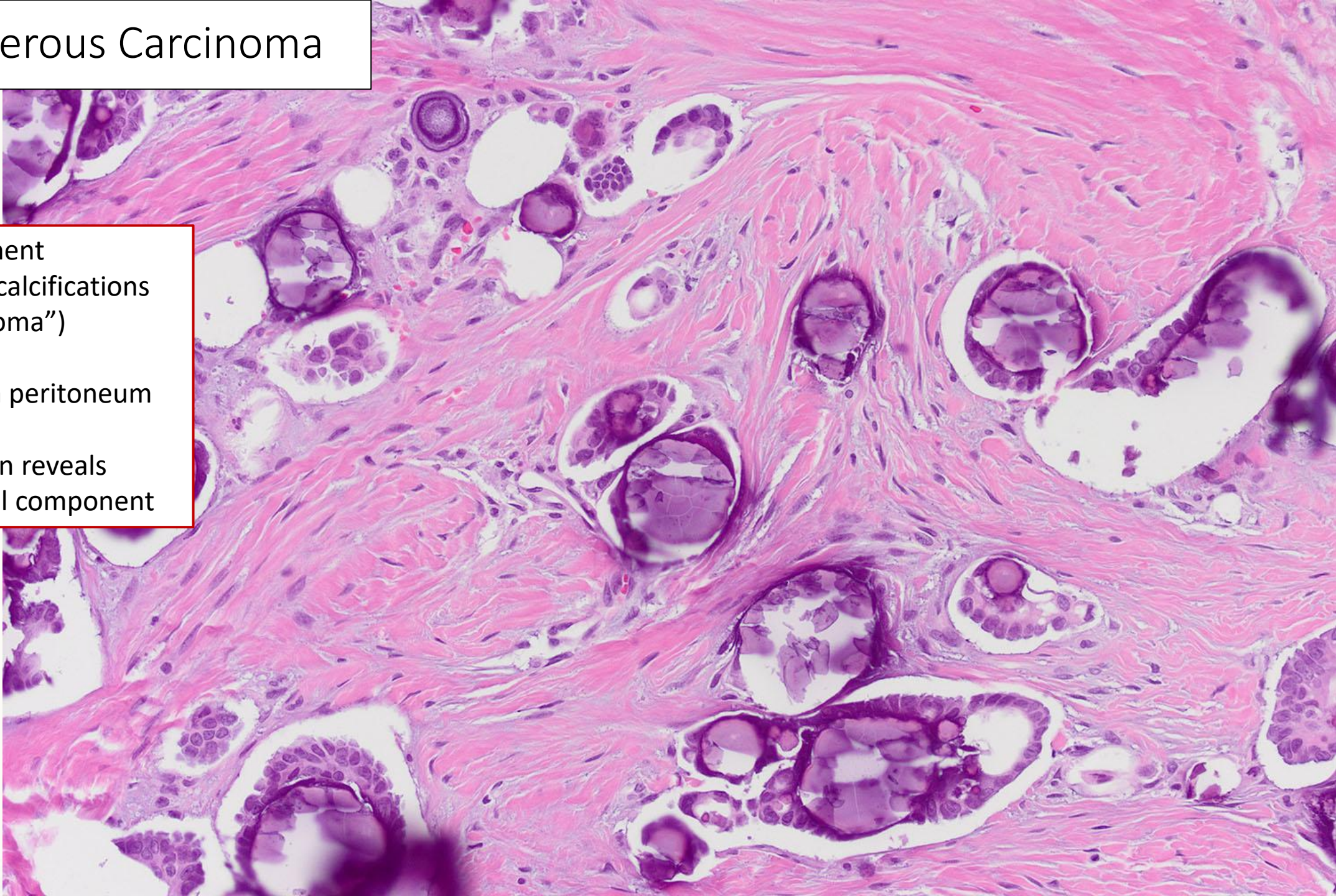
Low-Grade Serous Carcinoma

- May have prominent psammomatous calcifications (“psammocarcinoma”)
- More common in peritoneum



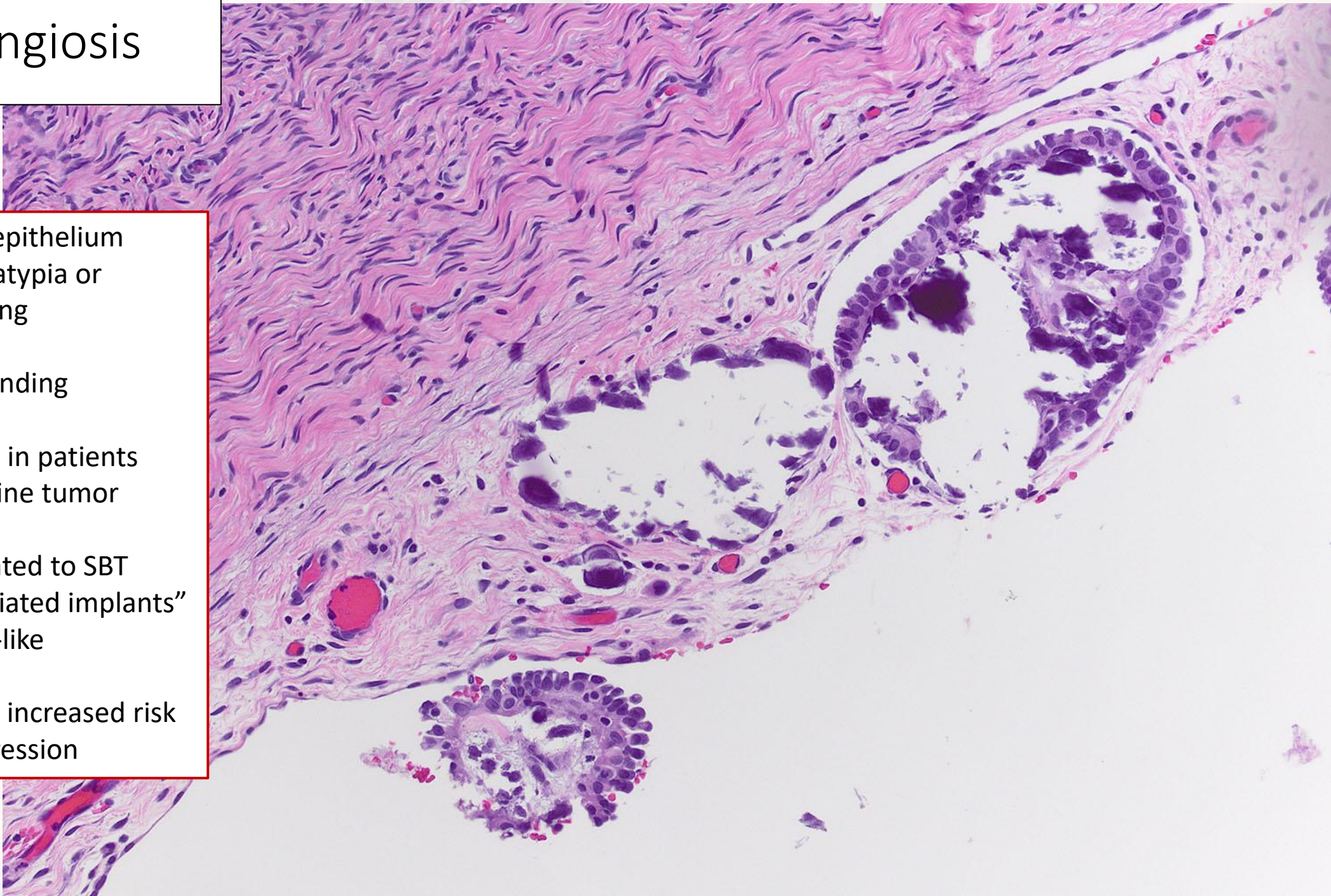
Low-Grade Serous Carcinoma

- May have prominent psammomatous calcifications (“psammocarcinoma”)
- More common in peritoneum
- Close examination reveals invasive epithelial component

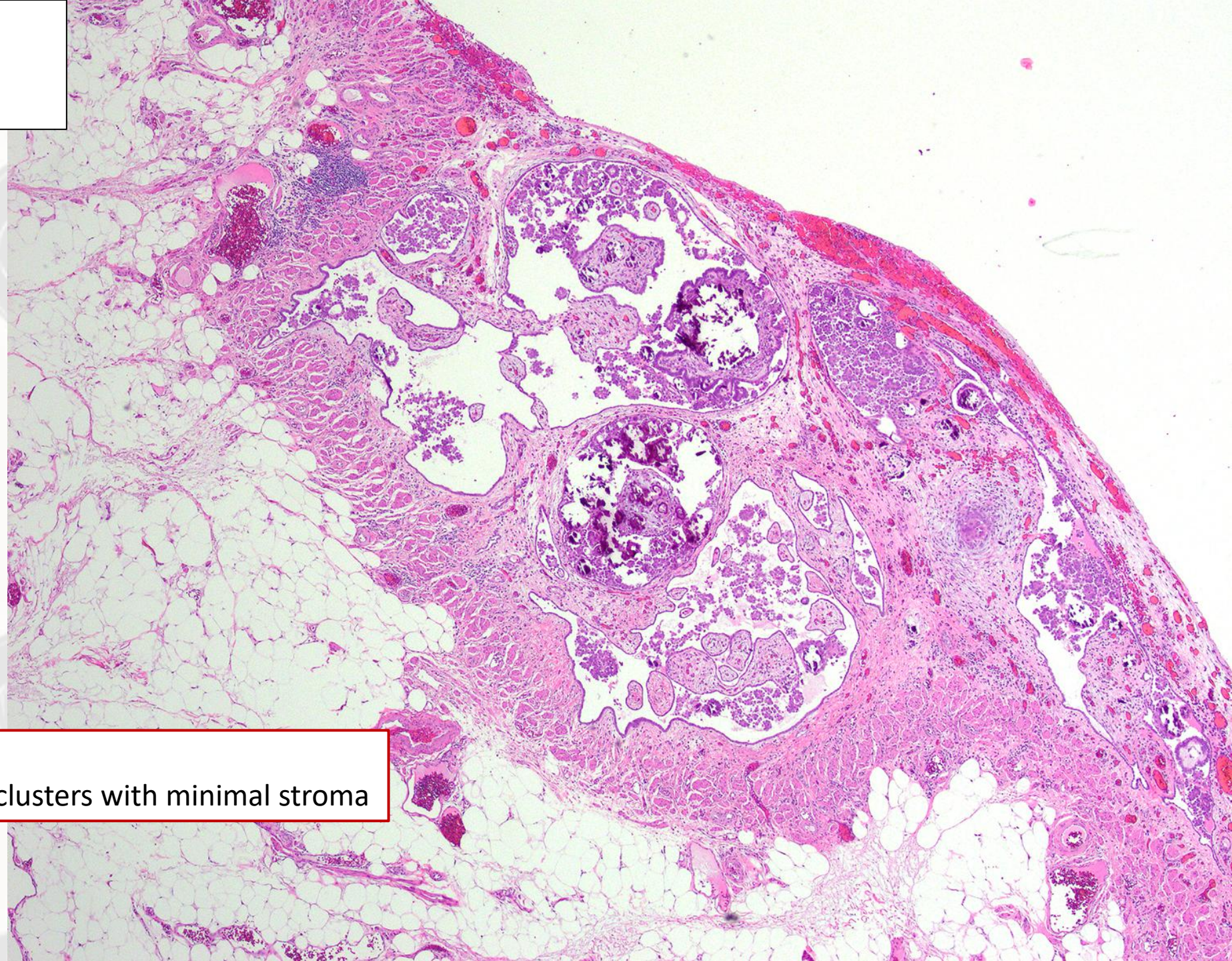


Endosalpingiosis

- Ciliated tubal-type epithelium without significant atypia or hierarchical branching
- May be incidental finding
- Increased incidence in patients with serous borderline tumor
- May be clonally related to SBT
 - “Well differentiated implants”
 - Endometriosis-like
- Not associated with increased risk of recurrence/progression

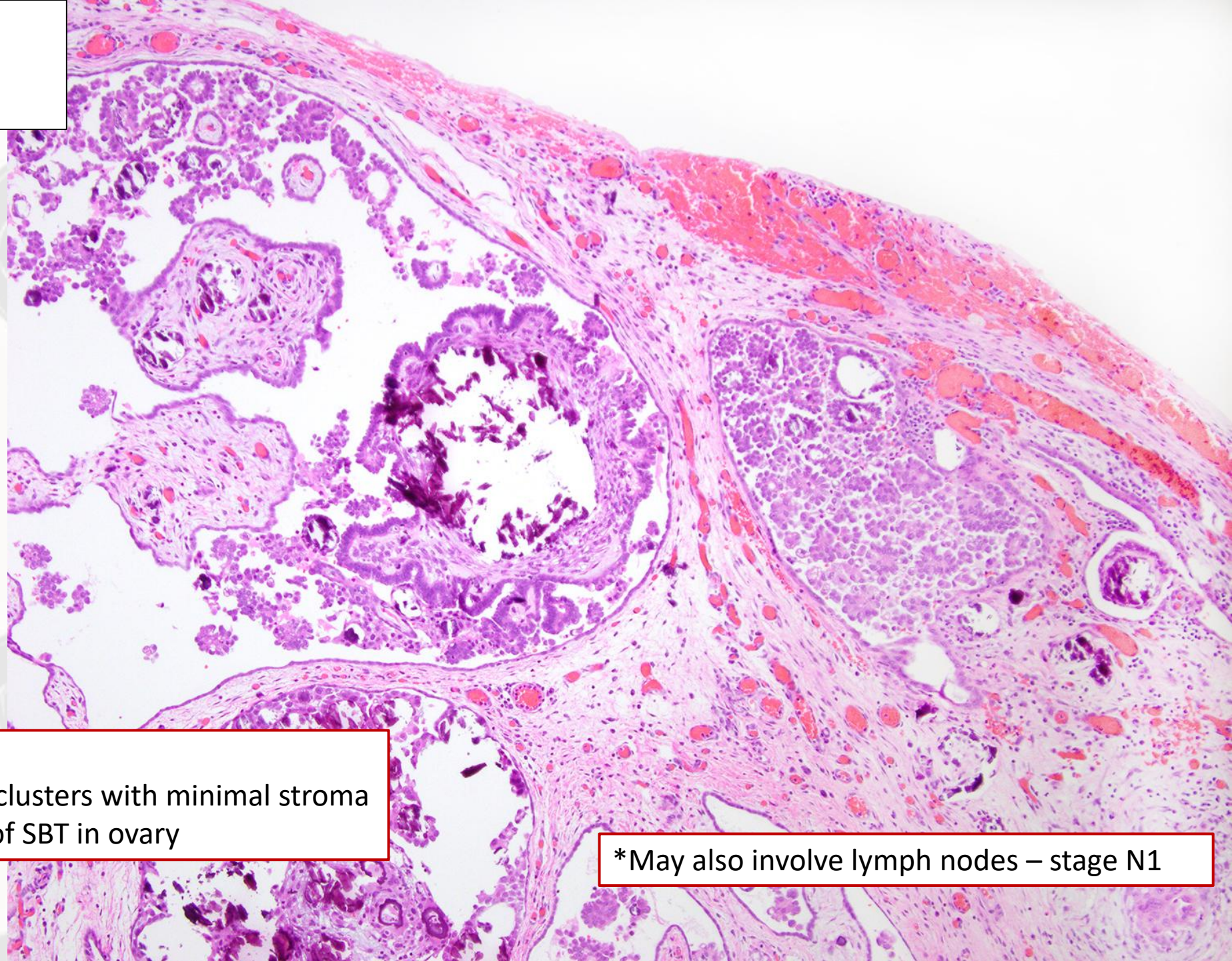


SBT Implants (non-invasive)



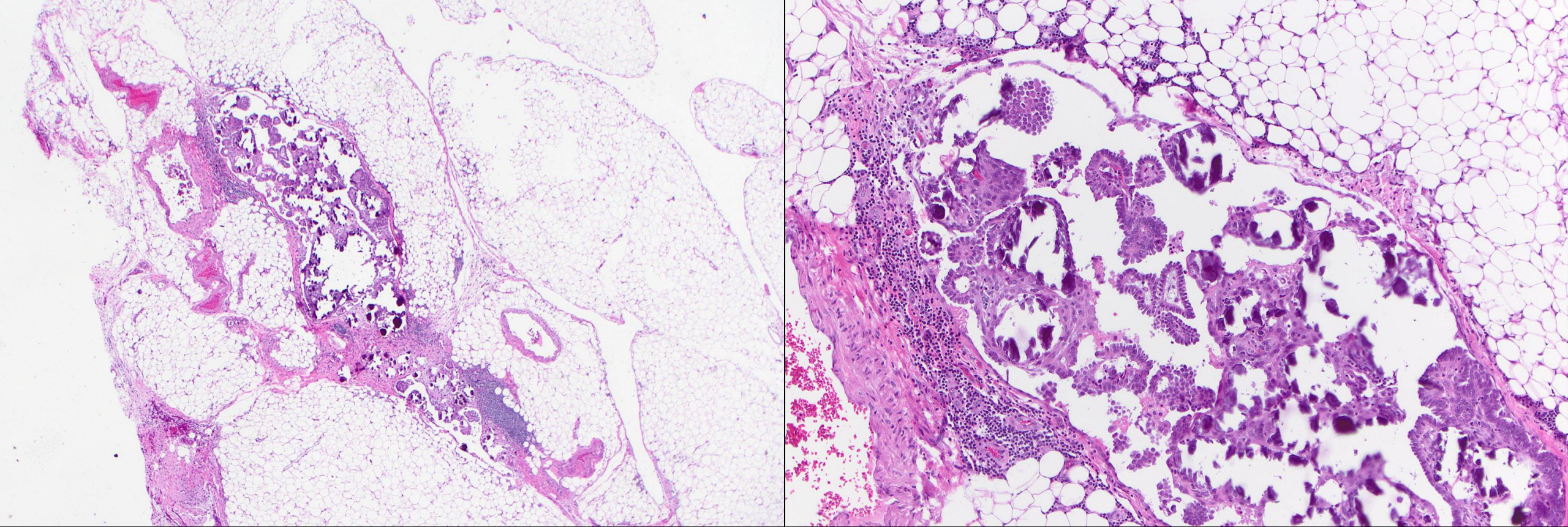
- Epithelial implants
 - Branching papillae or cell clusters with minimal stroma

SBT Implants (non-invasive)



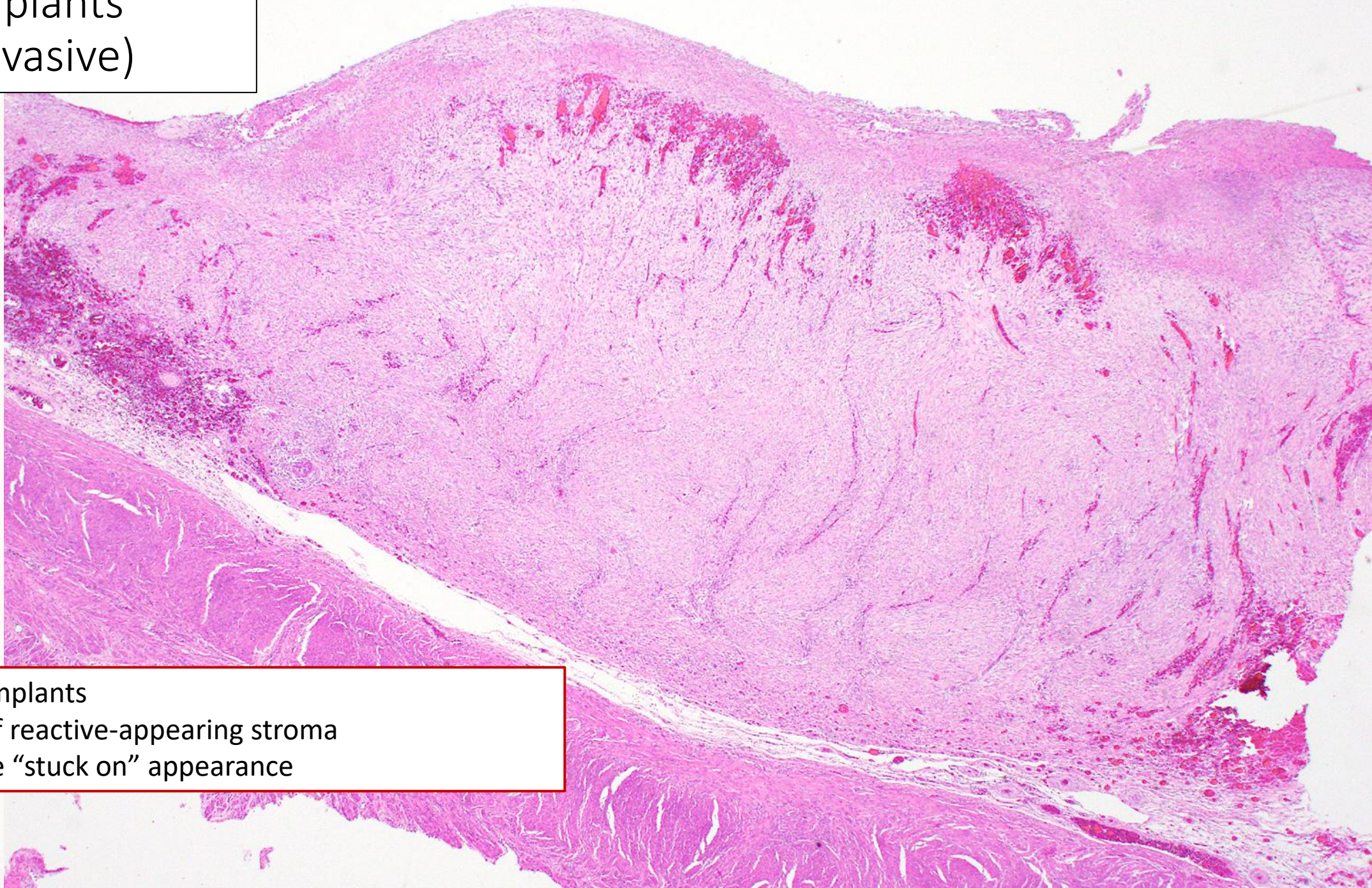
- Epithelial implants
 - Branching papillae or cell clusters with minimal stroma
 - Features similar to those of SBT in ovary

*May also involve lymph nodes – stage N1



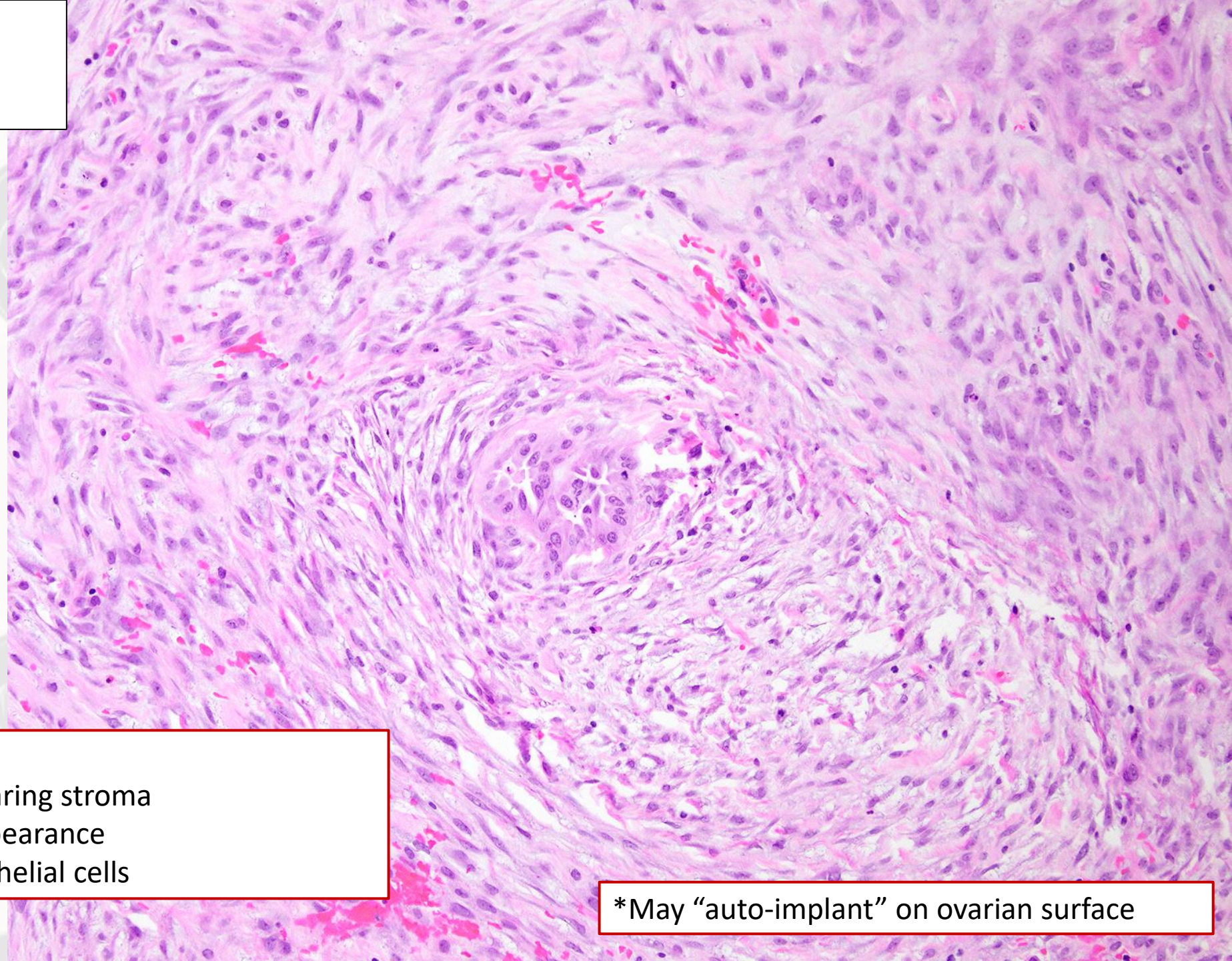
- Epithelial implants
 - Branching papillae or cell clusters with minimal stroma
 - Features similar to those of SBT in ovary
 - May involve septae in omentum
 - Lack infiltration into surrounding tissue

SBT Implants (non-invasive)



- Desmoplastic implants
 - Nodules of reactive-appearing stroma
 - Often have “stuck on” appearance

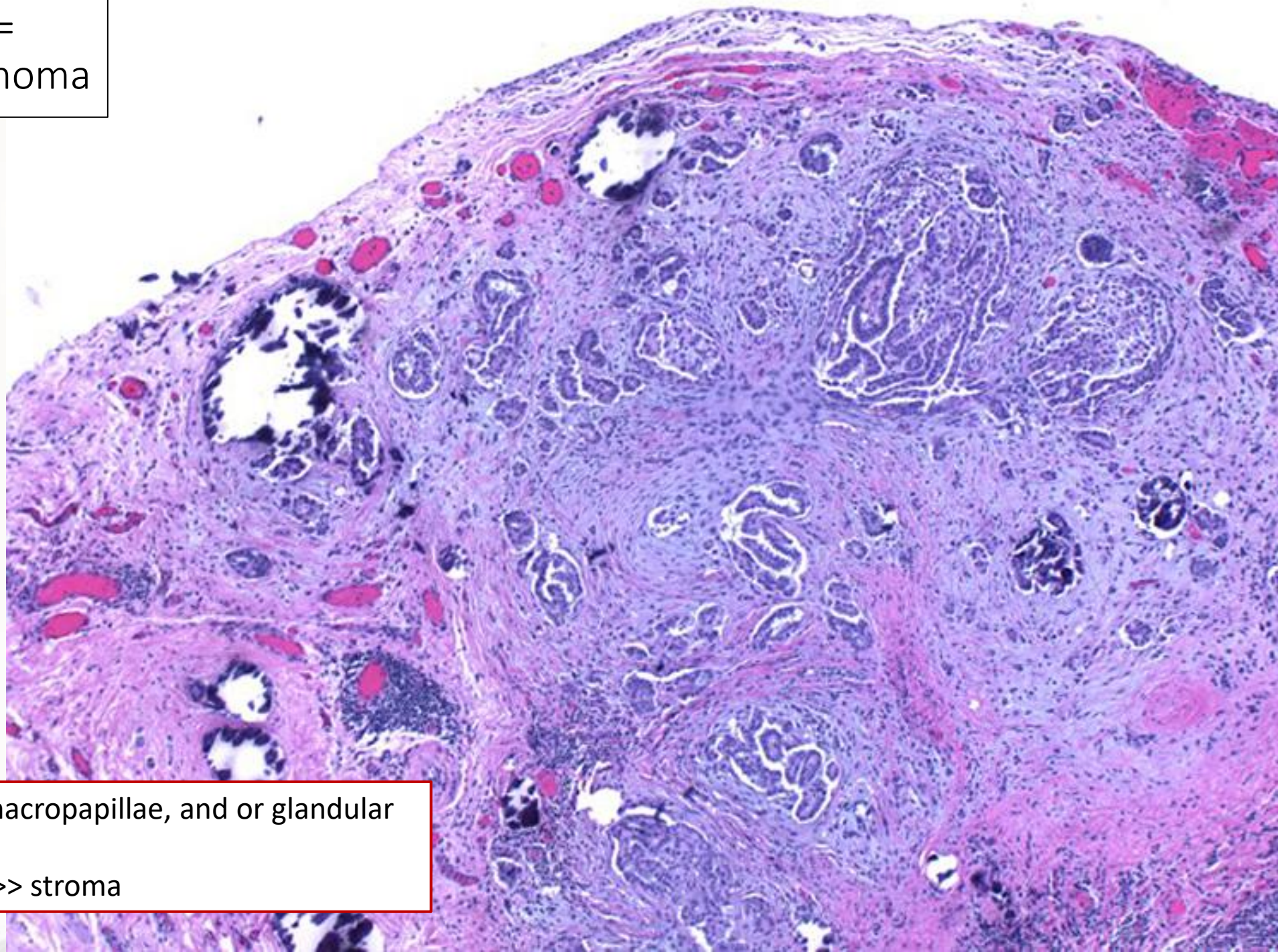
SBT Implants (non-invasive)



- Desmoplastic implants
 - Nodules of reactive-appearing stroma
 - Often have “stuck on” appearance
 - Few clusters or single epithelial cells

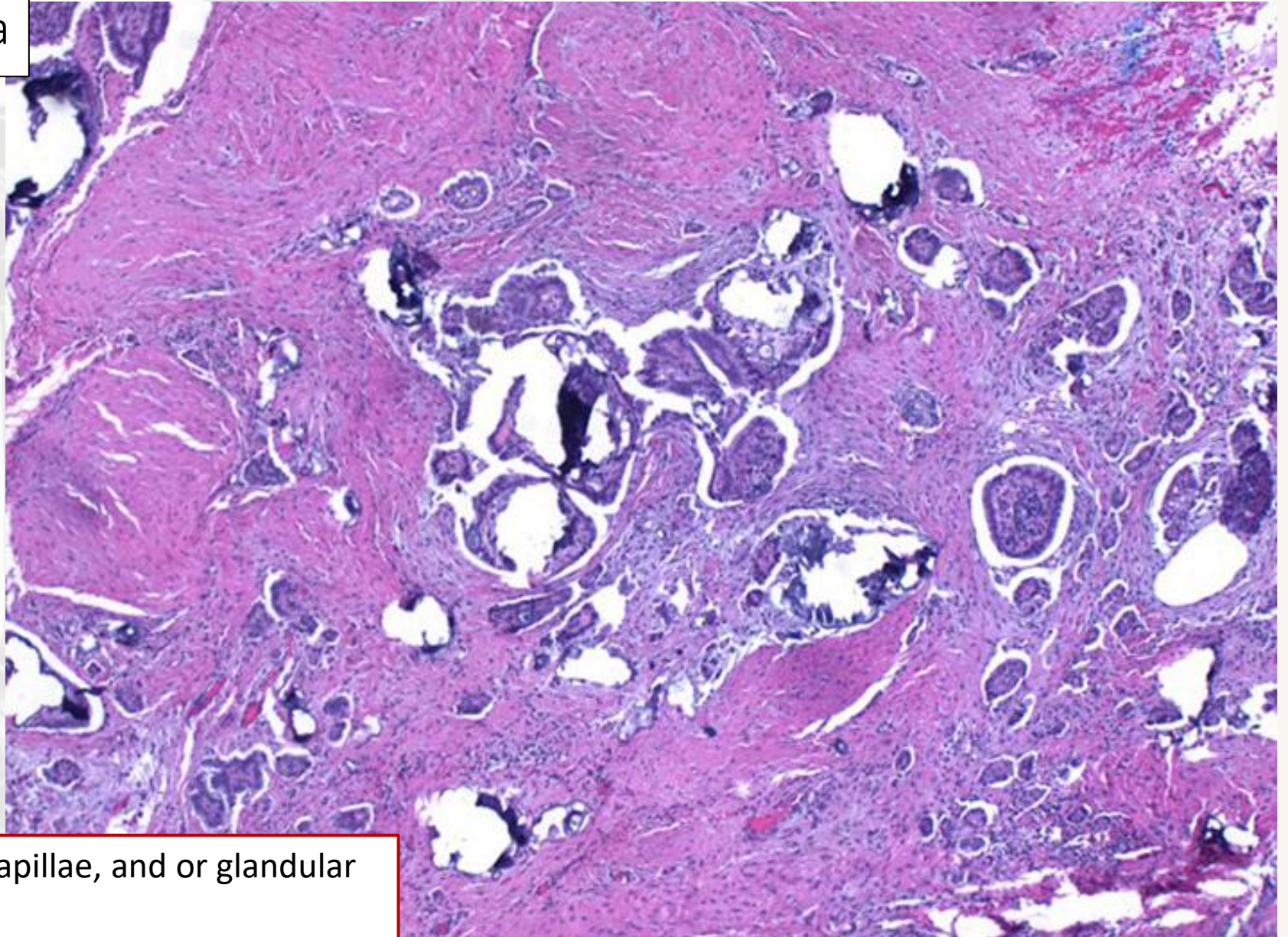
*May “auto-implant” on ovarian surface

“Invasive implant” =
Low-grade serous carcinoma



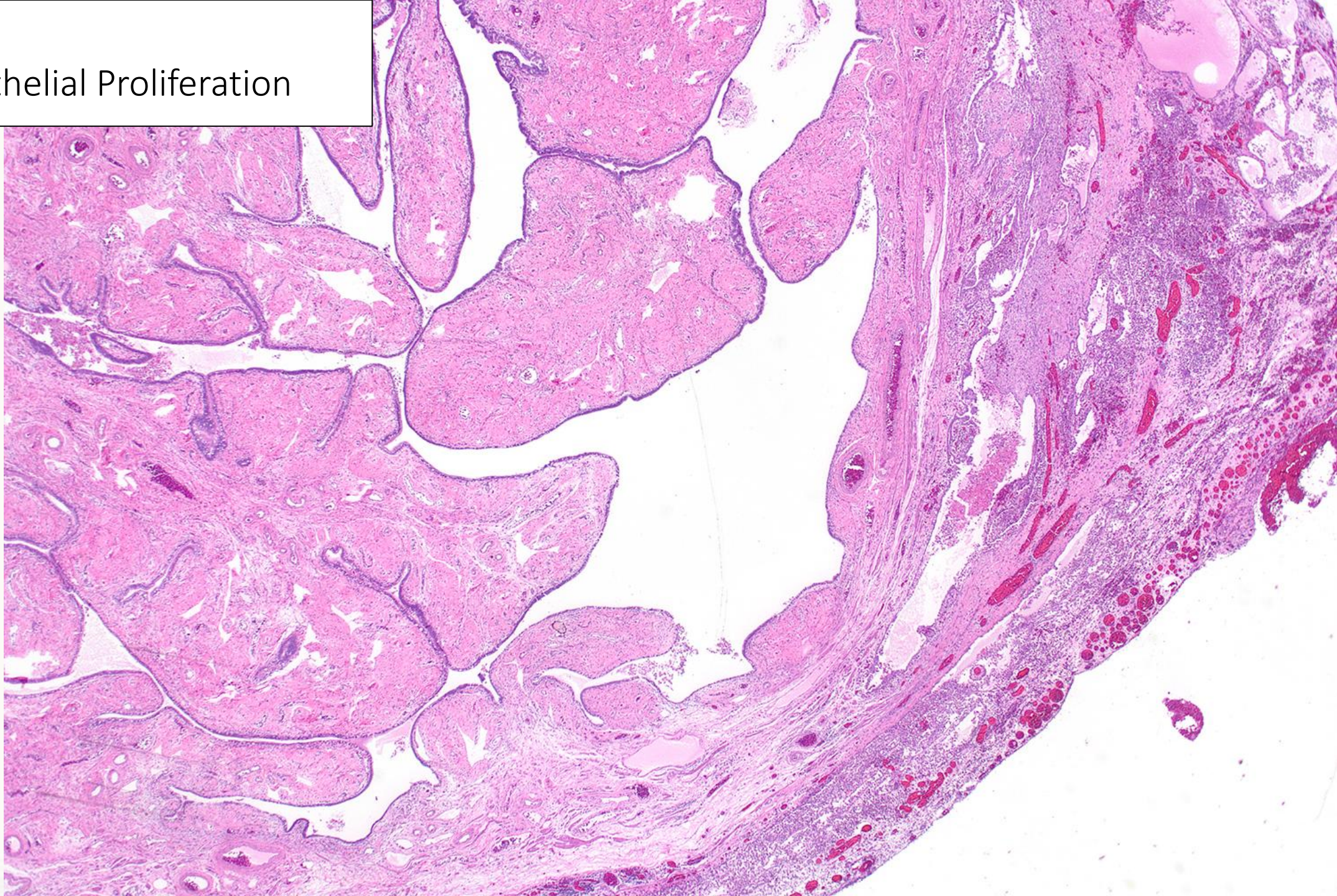
- Infiltrative nests, papillae, macropapillae, and or glandular patterns
- Epithelial elements usually >> stroma

“Invasive implant” =
Low-grade serous carcinoma

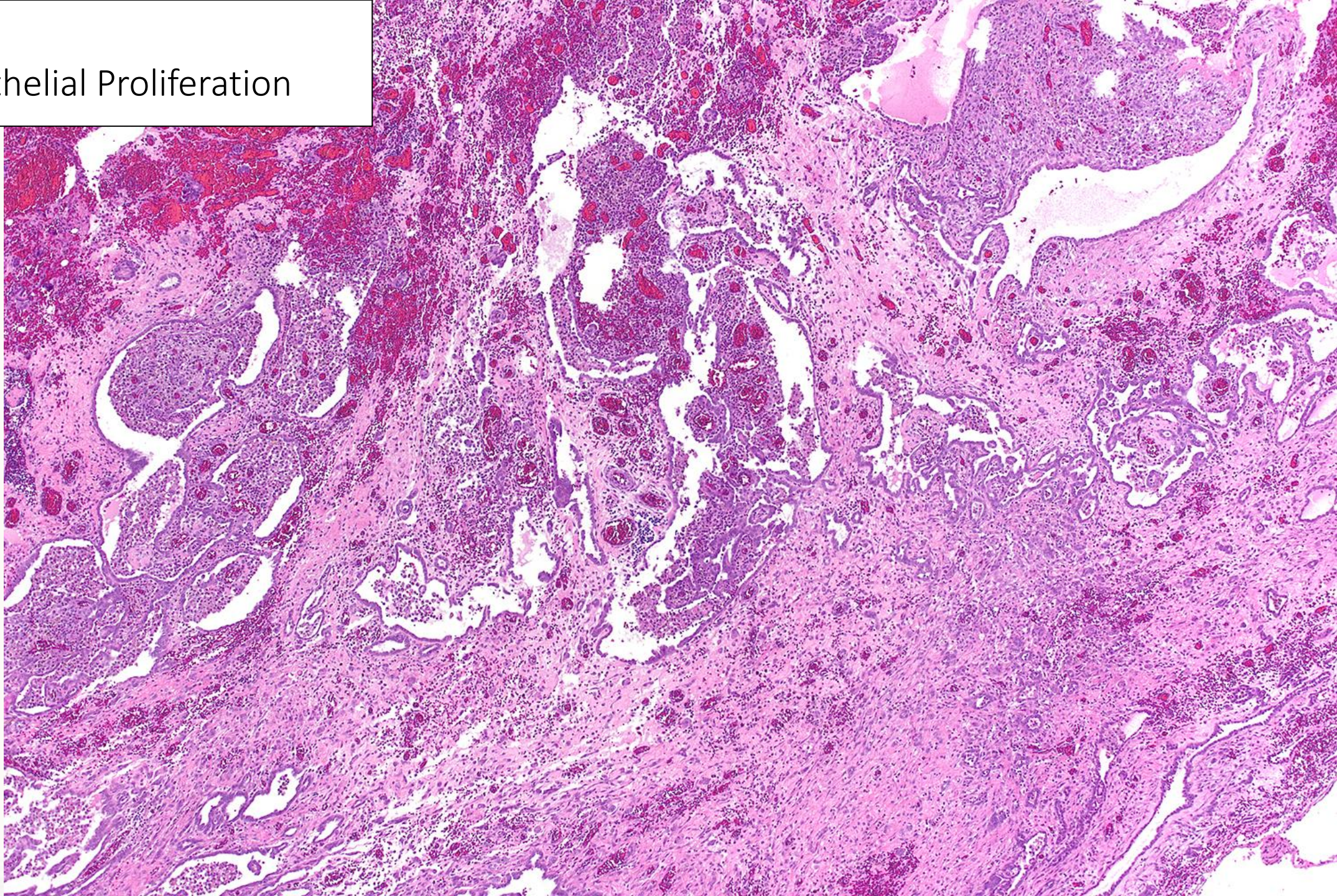


- Infiltrative nests, papillae, macropapillae, and or glandular patterns
- Epithelial elements usually >> stroma

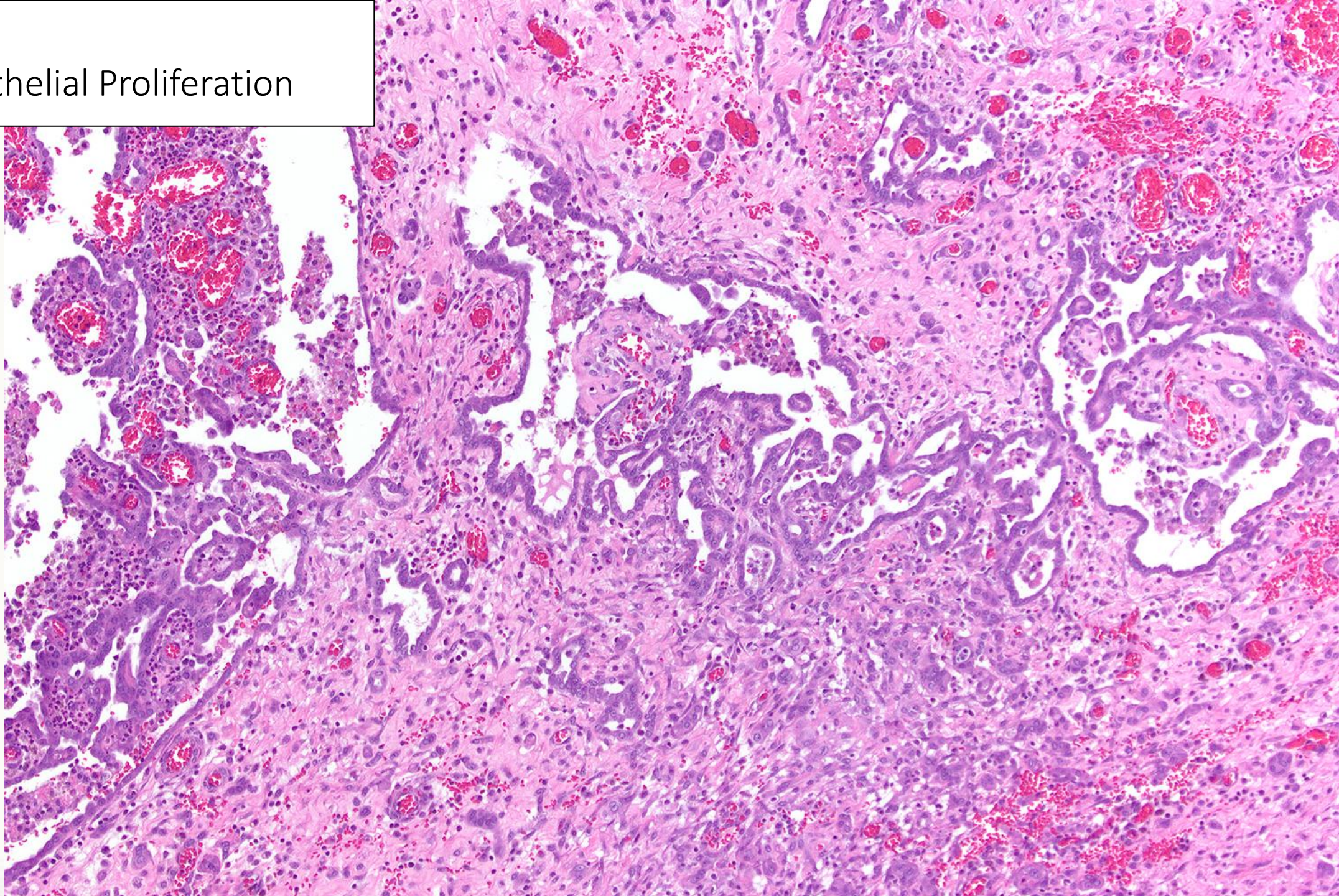
Mimic of LGSC:
Reactive Mesothelial Proliferation



Mimic of LGSC:
Reactive Mesothelial Proliferation

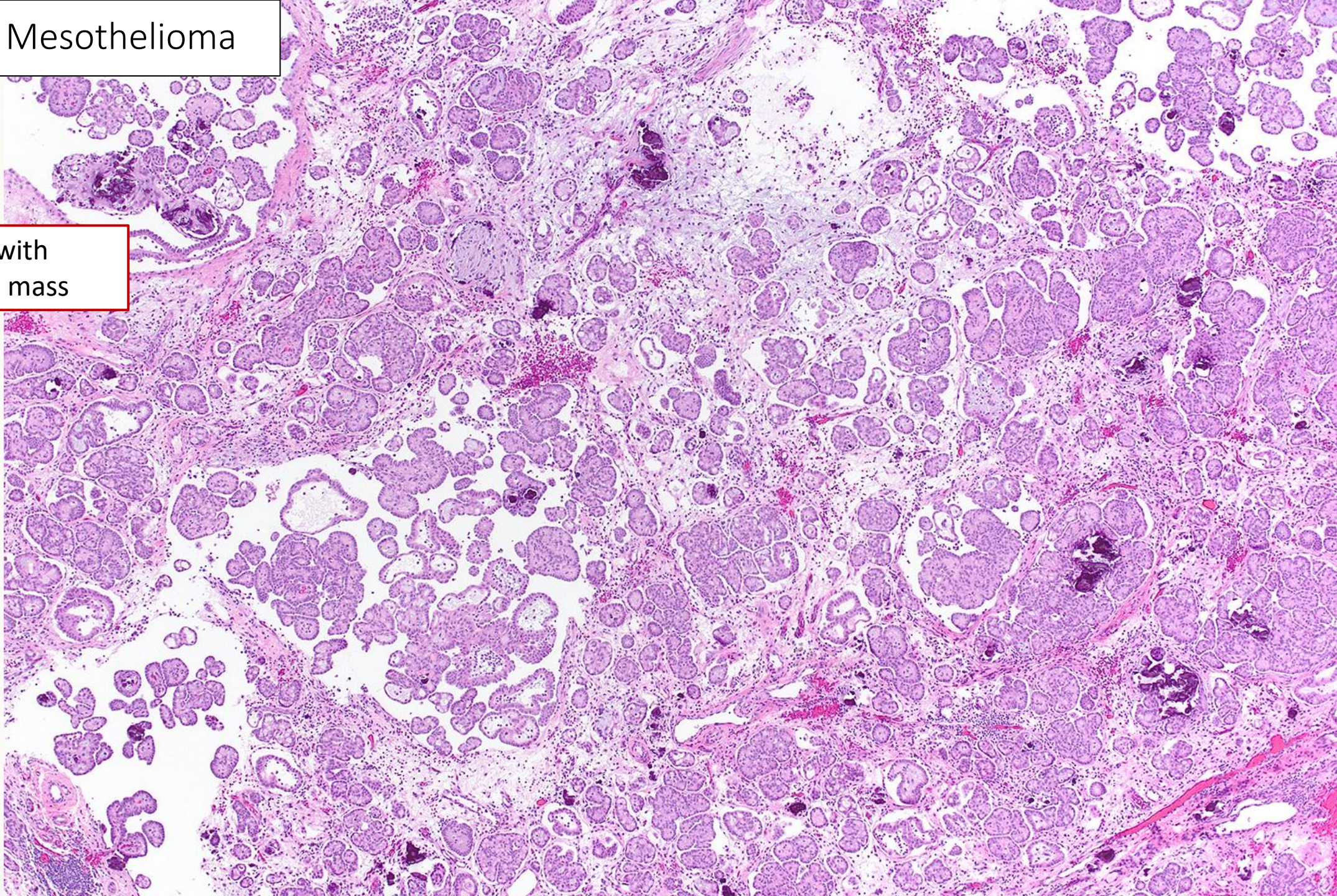


Mimic of LGSC:
Reactive Mesothelial Proliferation



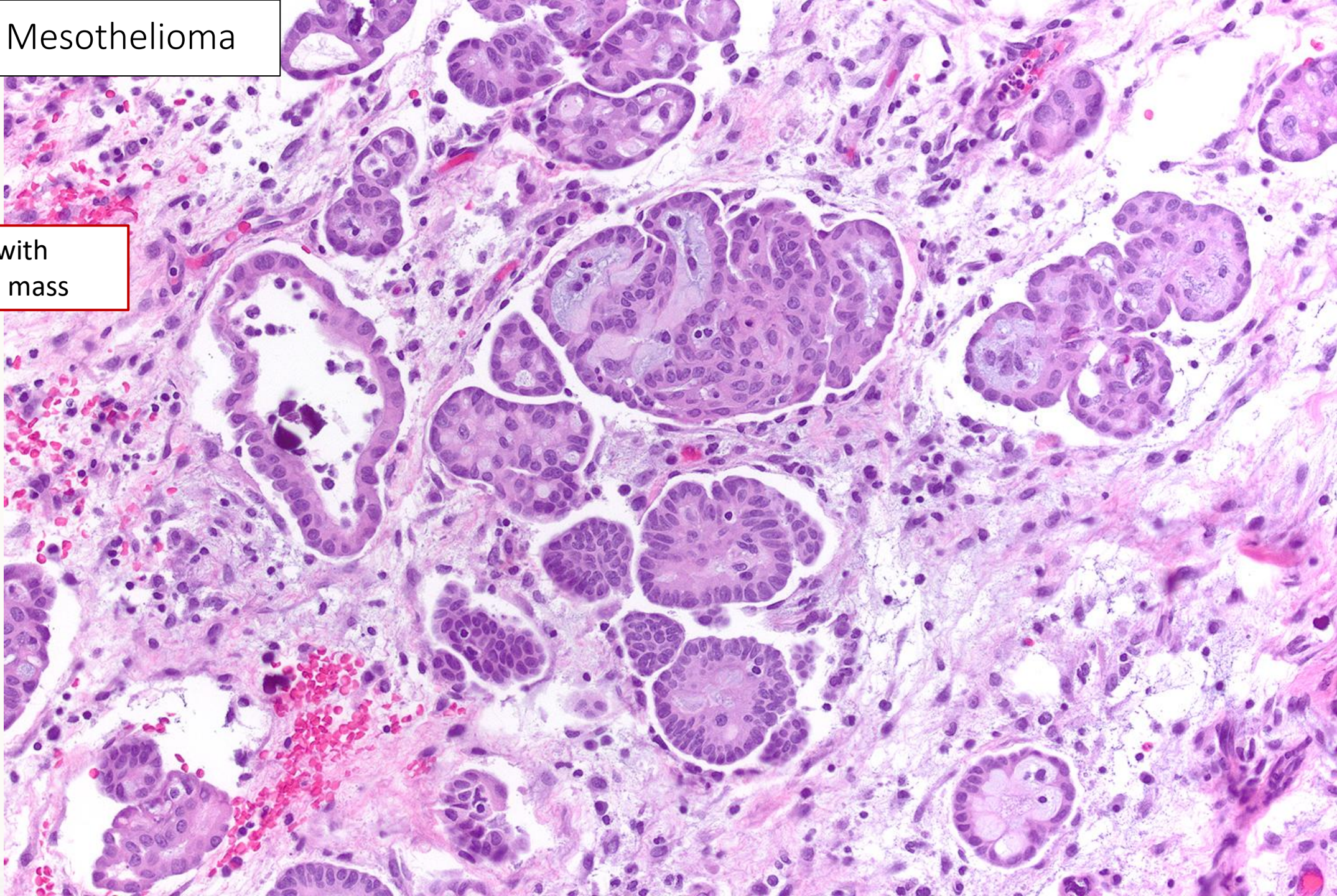
Mimic of LGSC: Mesothelioma

*Rarely presents with
dominant ovarian mass

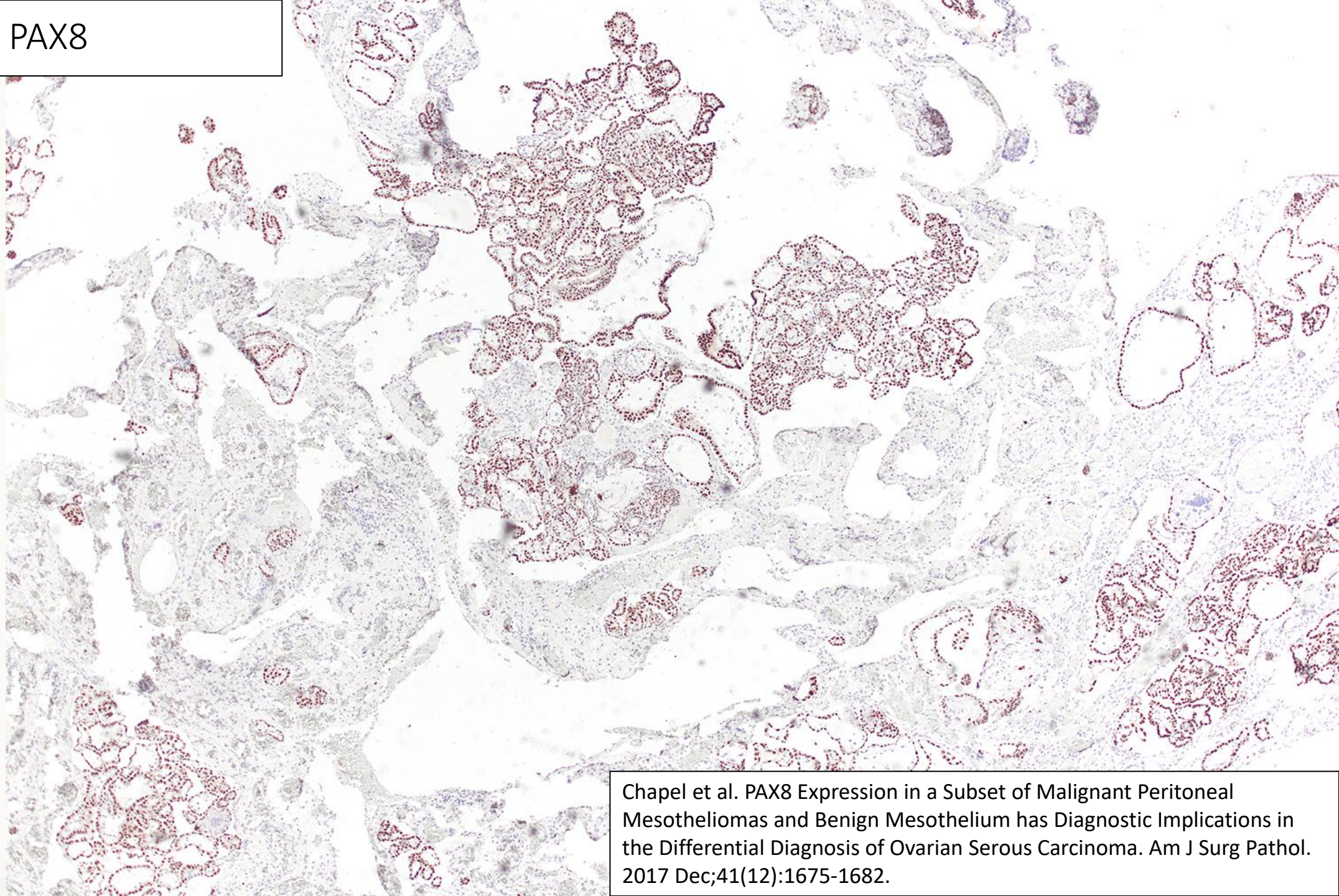


Mimic of LGSC: Mesothelioma

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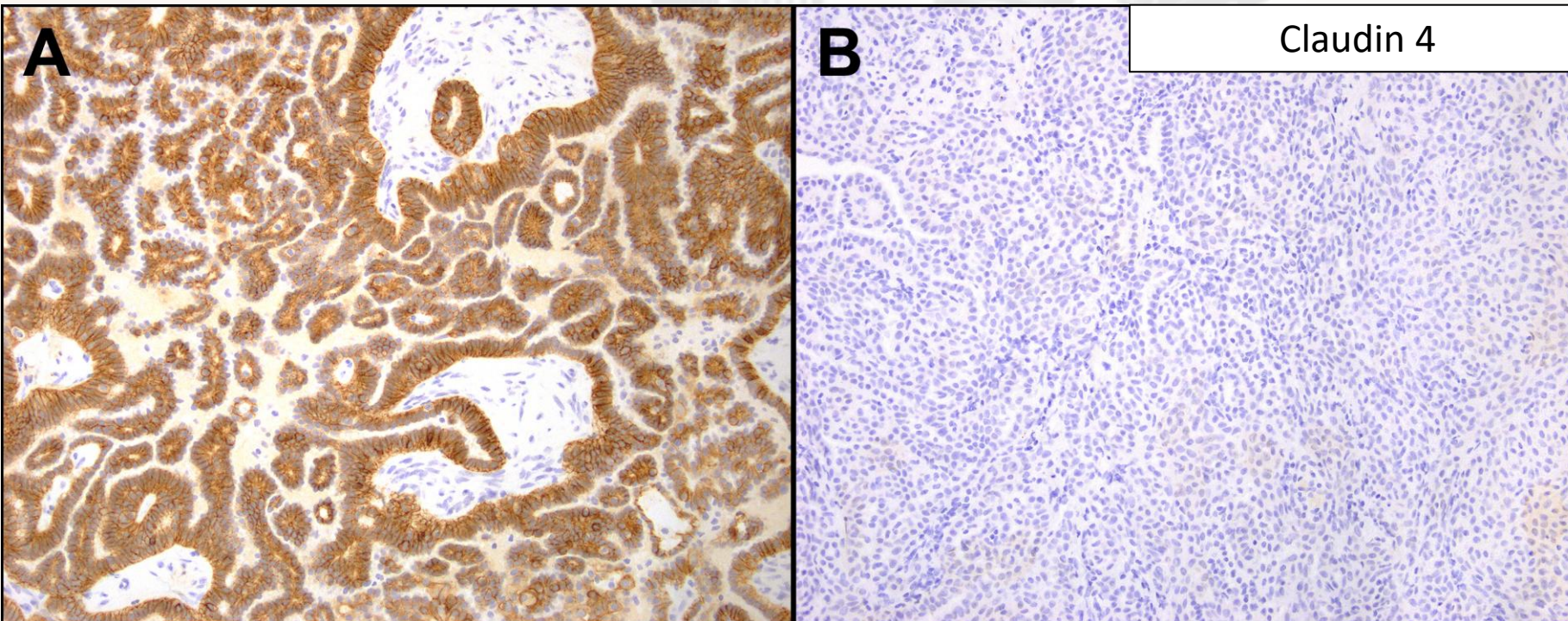


Mesothelioma: PAX8



Chapel et al. PAX8 Expression in a Subset of Malignant Peritoneal Mesotheliomas and Benign Mesothelium has Diagnostic Implications in the Differential Diagnosis of Ovarian Serous Carcinoma. *Am J Surg Pathol*. 2017 Dec;41(12):1675-1682.

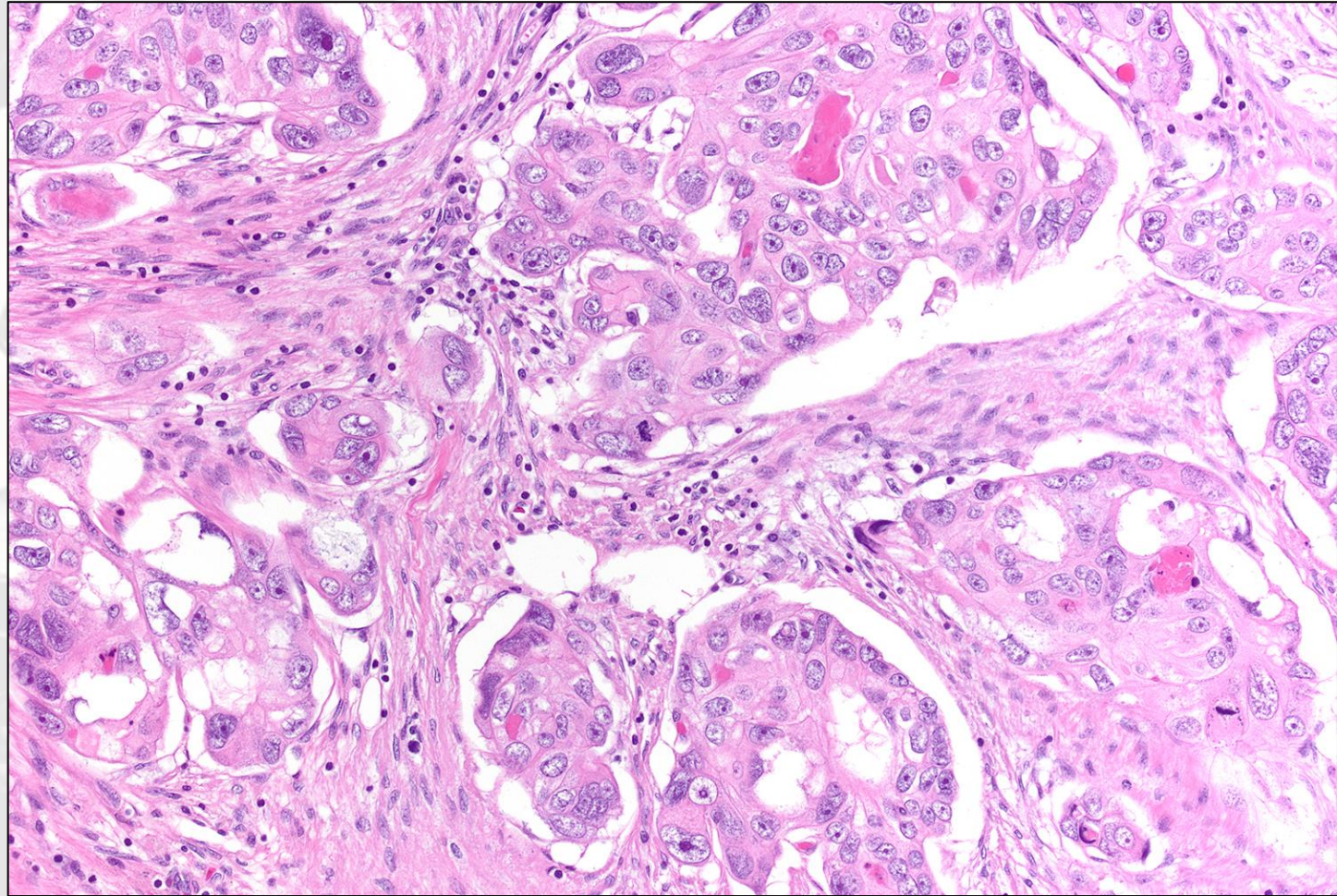
Serous Tumors	Mesothelioma	Overlap
Claudin-4	Calretinin	Pankeratin and keratin 7
ER	Keratin 5/6	WT1
BER-EP4	D240	PAX8
MOC31	BAP1 loss in ~40-60%	



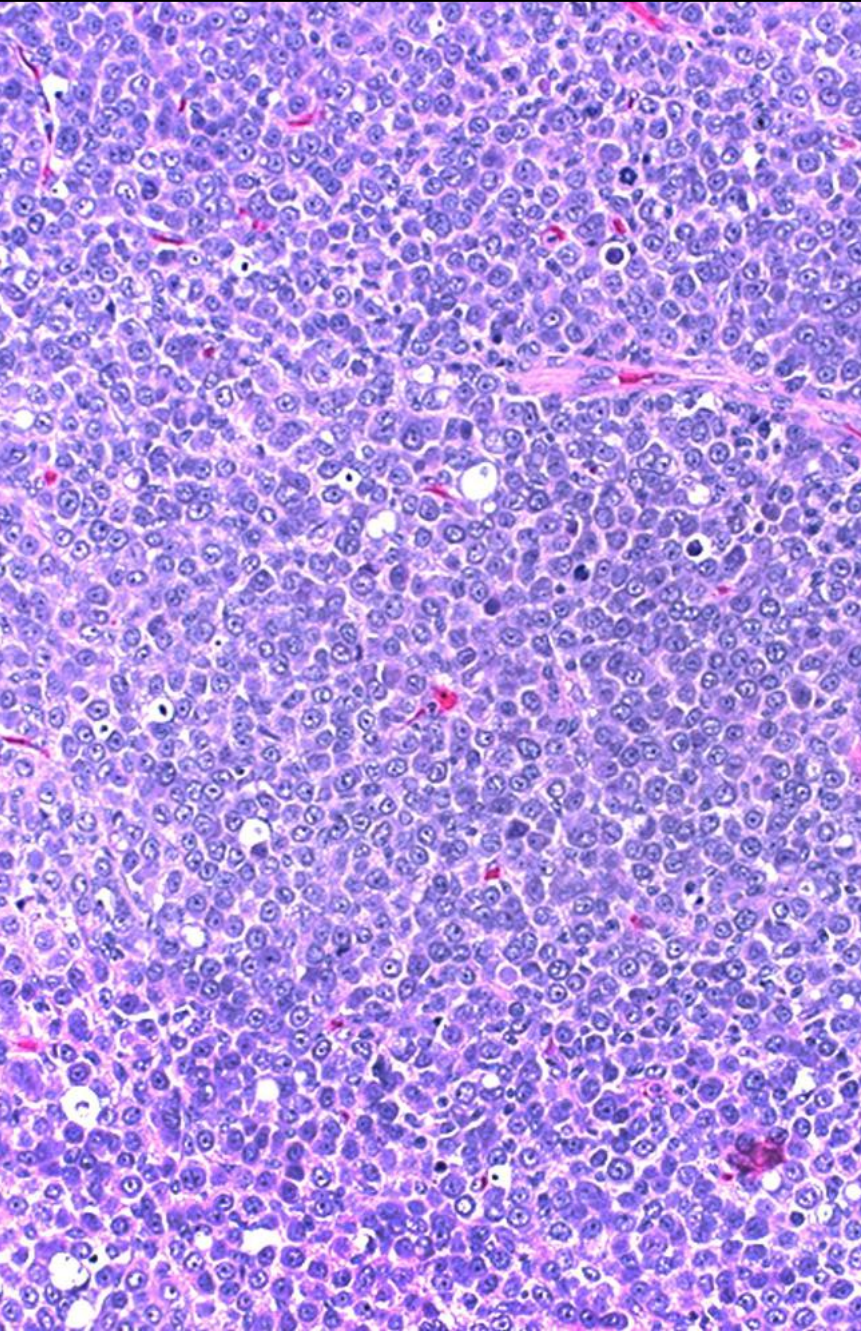
Devins KM et al. *Int J Gynecol Pathol.* 2023;42(2):159-166

High Grade Serous Carcinoma

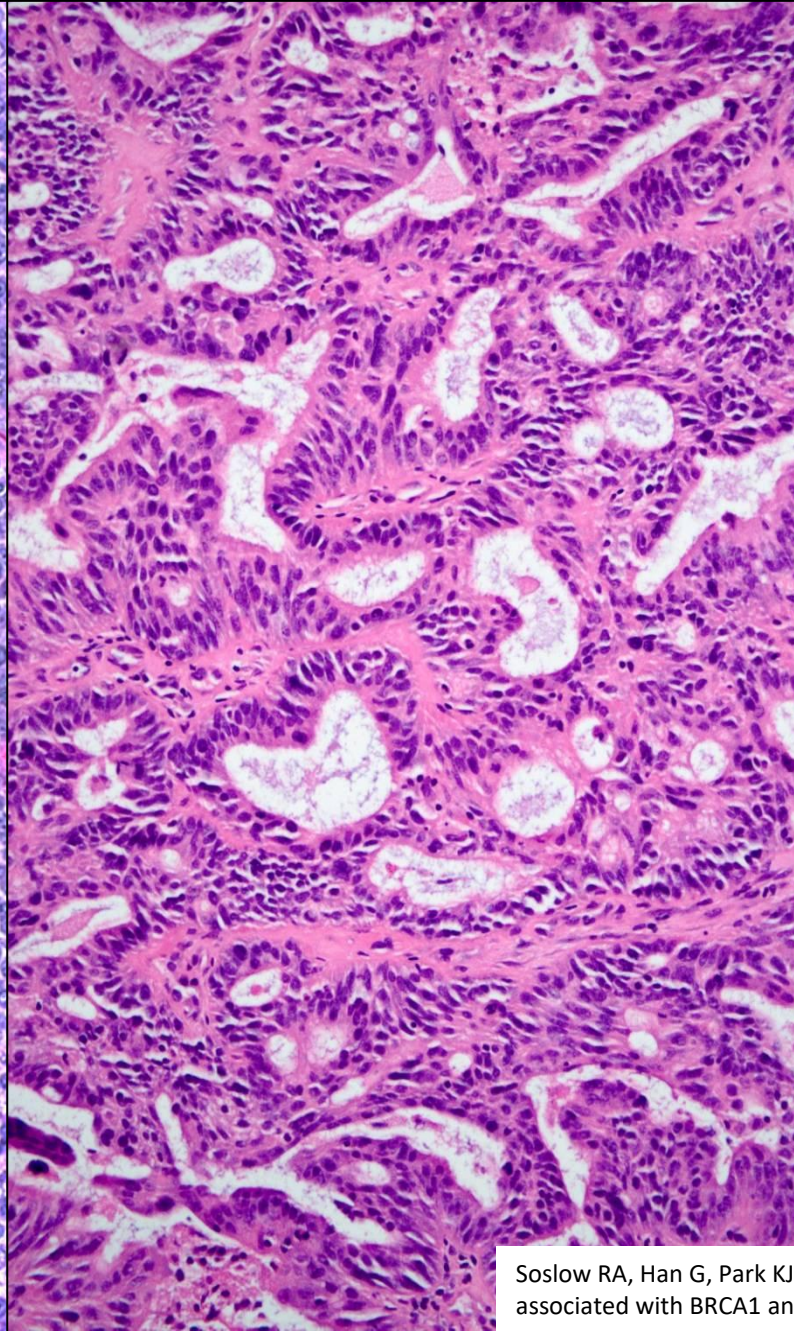
- Diagnosis is usually straightforward
 - Pleomorphism
 - Large irregular nests
 - Solid pattern
 - Glands with “slit-like” spaces
- Troublesome morphologic features
 - “SET” pattern – Solid, pseudoEndometrioid, Transitional-like
 - Vacuolization / microcysts
 - Cytoplasmic clearing
 - Hyaline globules
 - Cyst formation



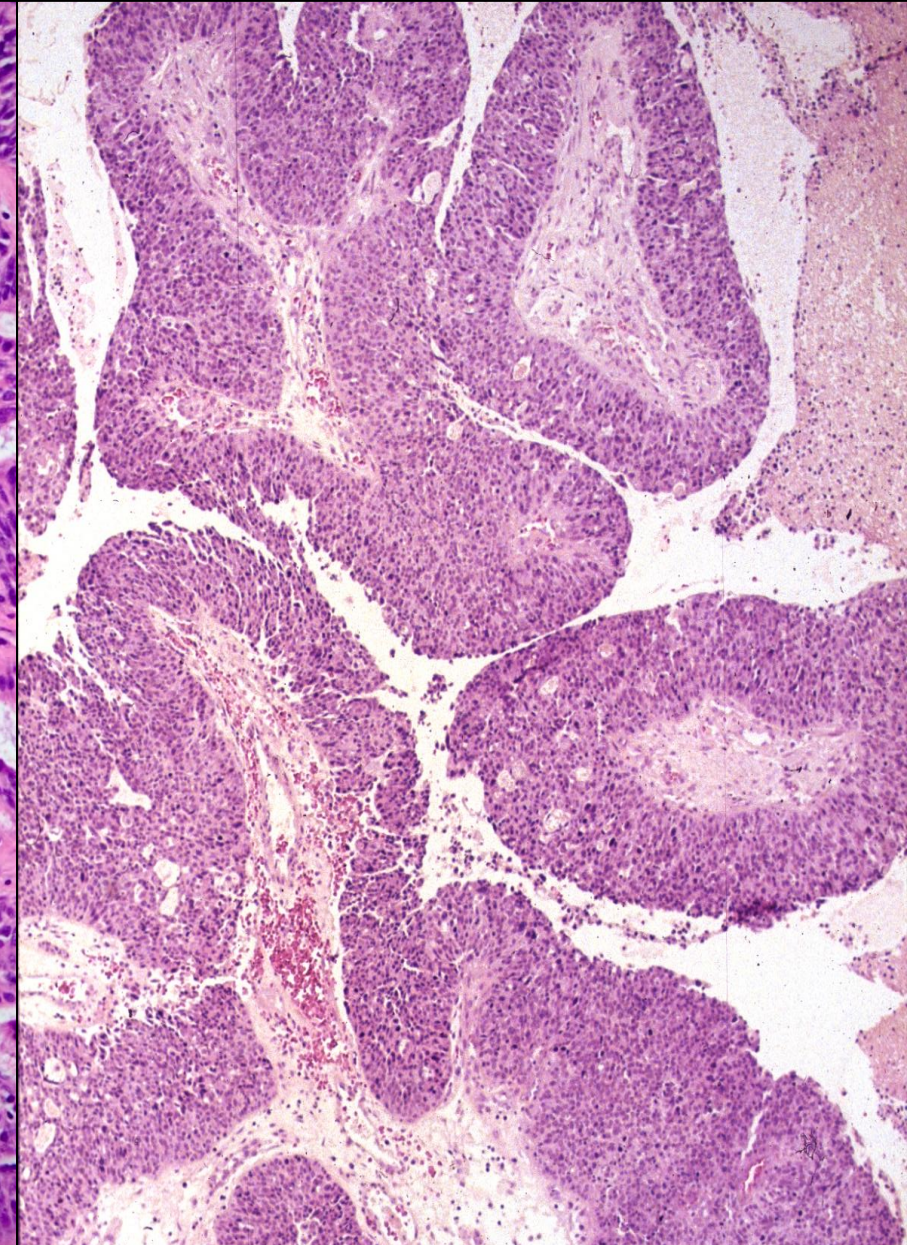
Solid



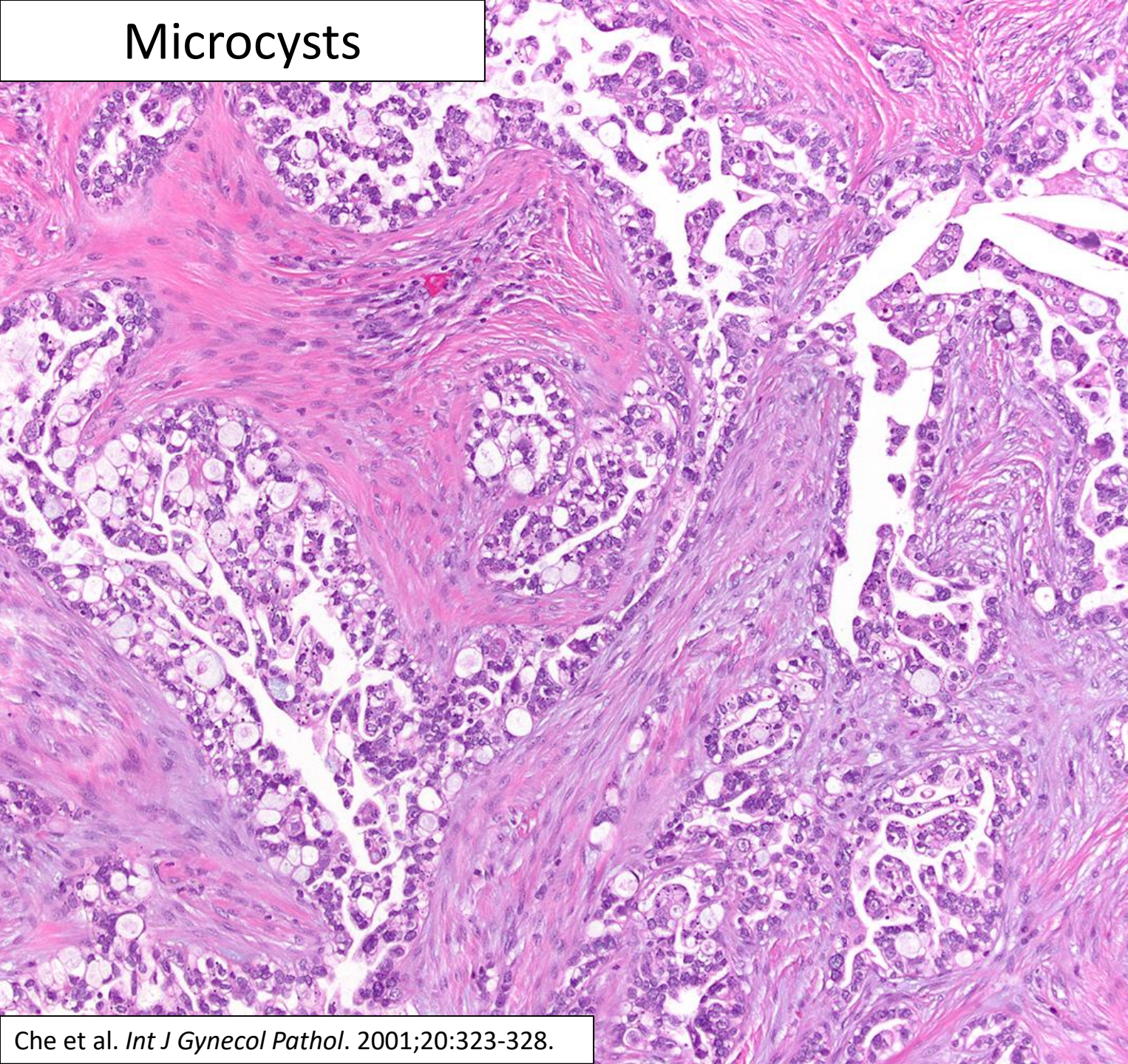
Pseudoendometrioid



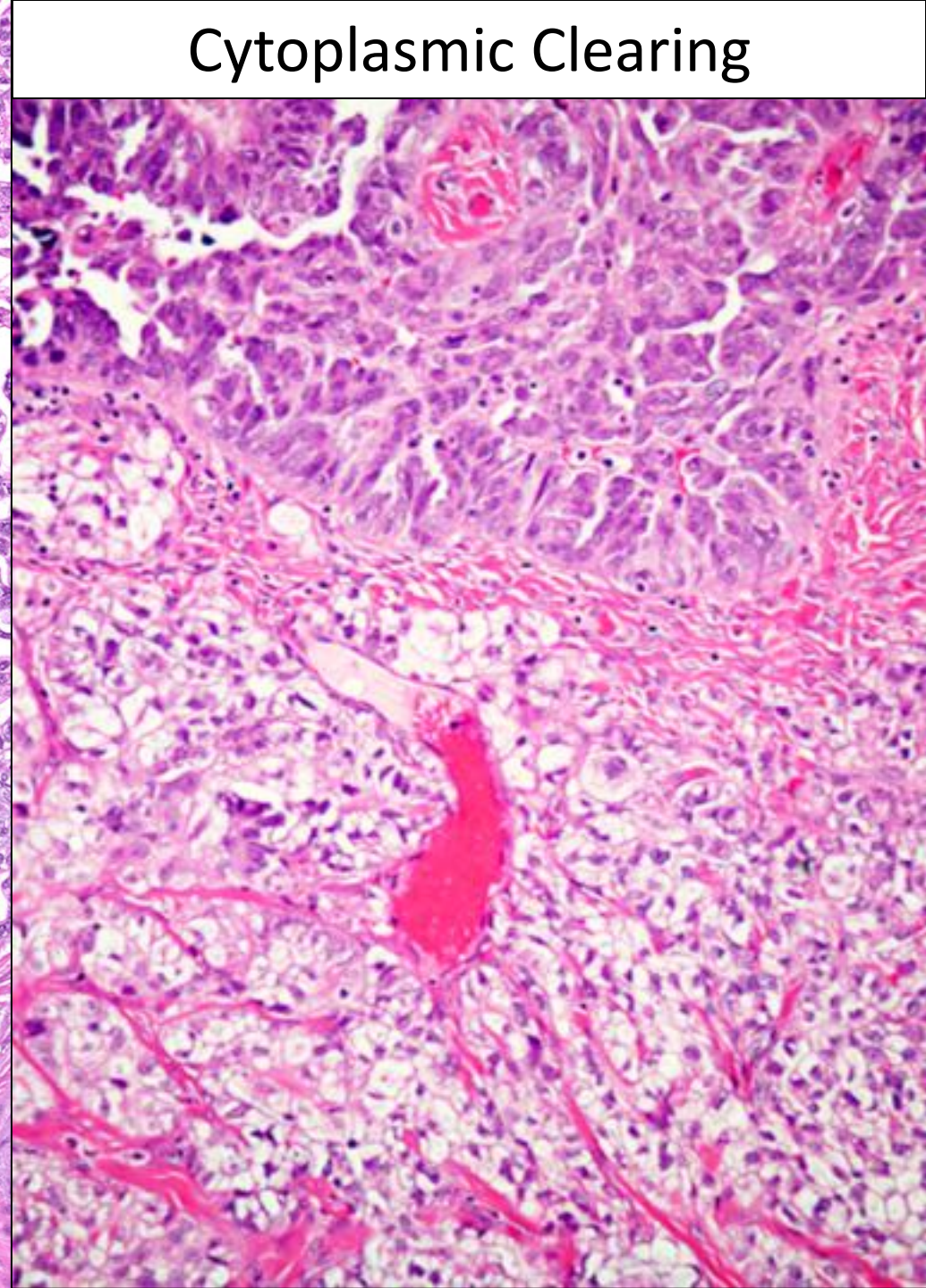
Transitional-like



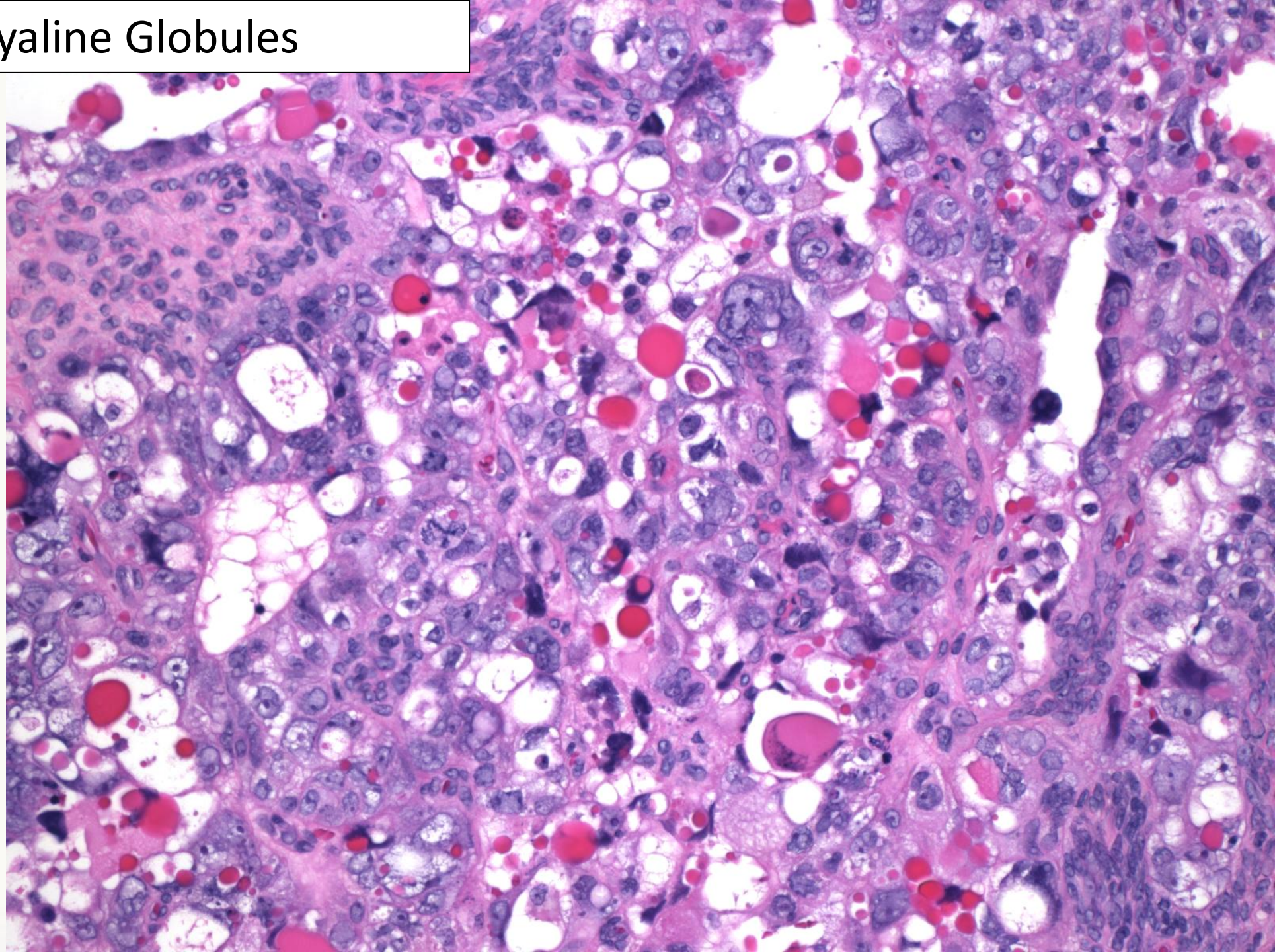
Microcysts



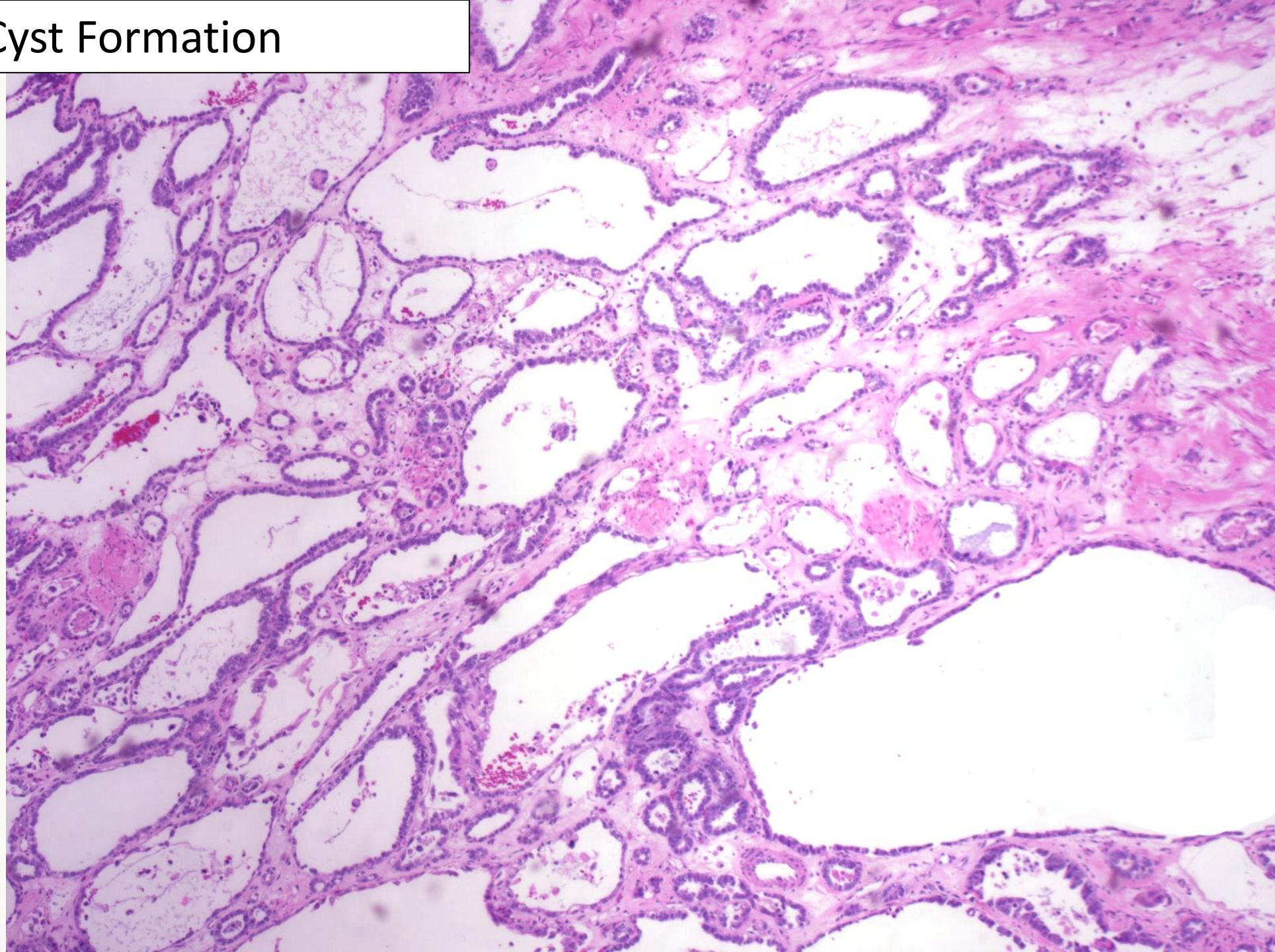
Cytoplasmic Clearing



Hyaline Globules



Cyst Formation



Immunohistochemistry

- Markers of GYN origin

- PAX8+
- SOX17+

- Others

- WT1+
- Keratin 7+
- ER (80%)
- p53 mutant pattern

- Vs. Mesothelioma

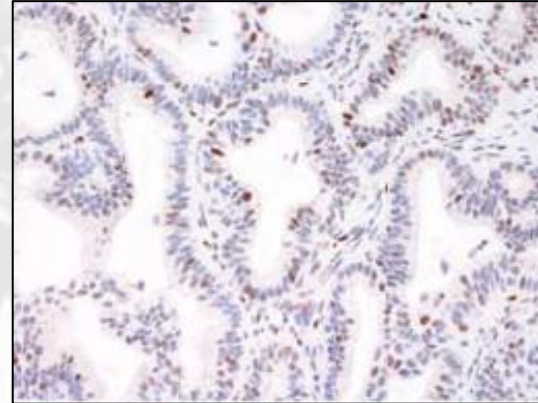
- Claudin-4+**
- BER-EP4+ / MOC31+
- Less reliable: Calretinin, keratin 5/6, D2-40, PAX8/SOX17, BAP1

- Vs. Breast Carcinoma

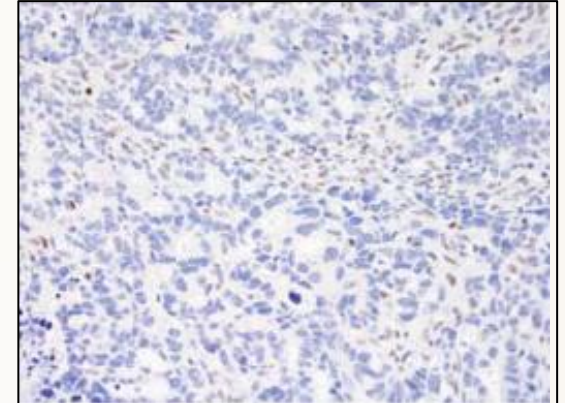
- GATA3 (may show aberrant expression in small % HGSC)
- Mammaglobin-
- GCDFP-15-
- TRPS1 not reliable

p53 Immunohistochemistry

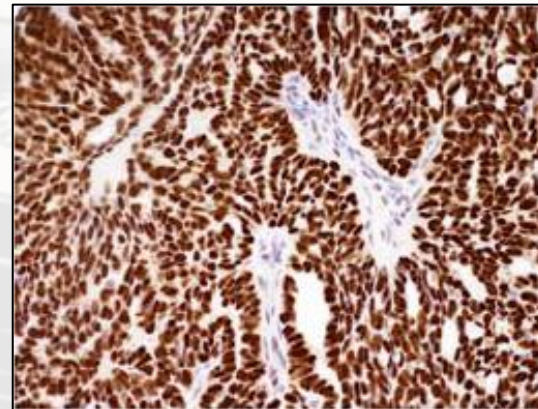
- Mutant pattern in >95% of HGSC



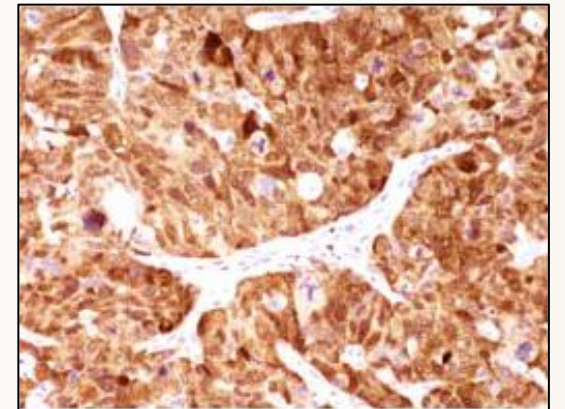
Wild-type



Null



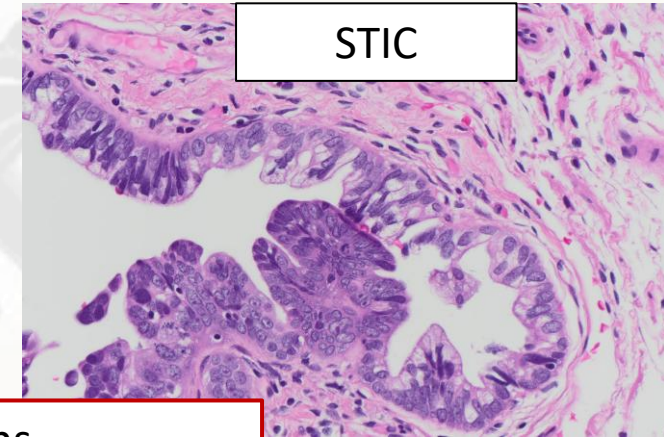
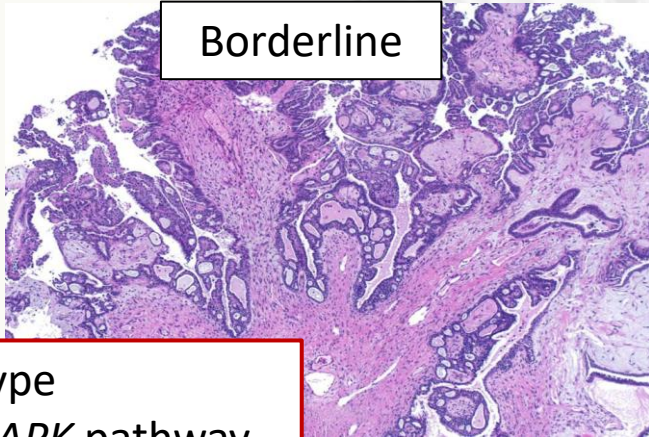
Overexpression



Cytoplasmic

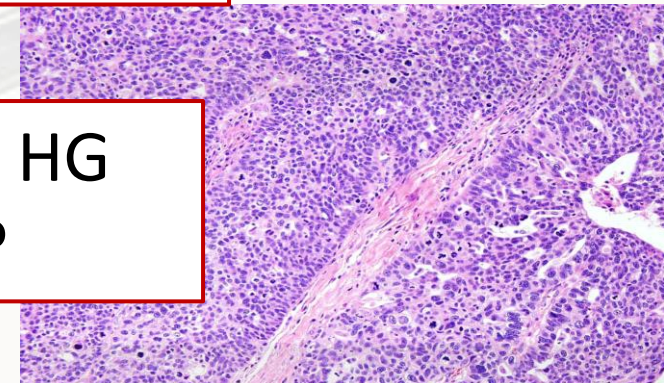
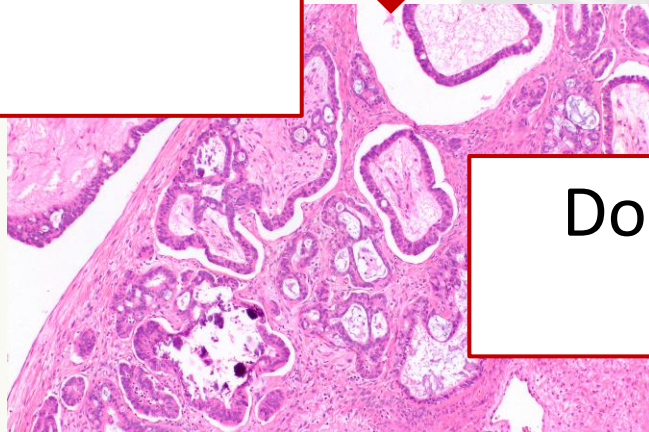
- p53 wild-type by IHC in ~4% of HGSC
- Still harbor *TP53* mutations by sequencing

LG vs. HG Serous Carcinoma



- *TP53* wild-type
- Frequent *MAPK* pathway mutations
 - *BRAF*
 - *KRAS*
 - *NRAS*

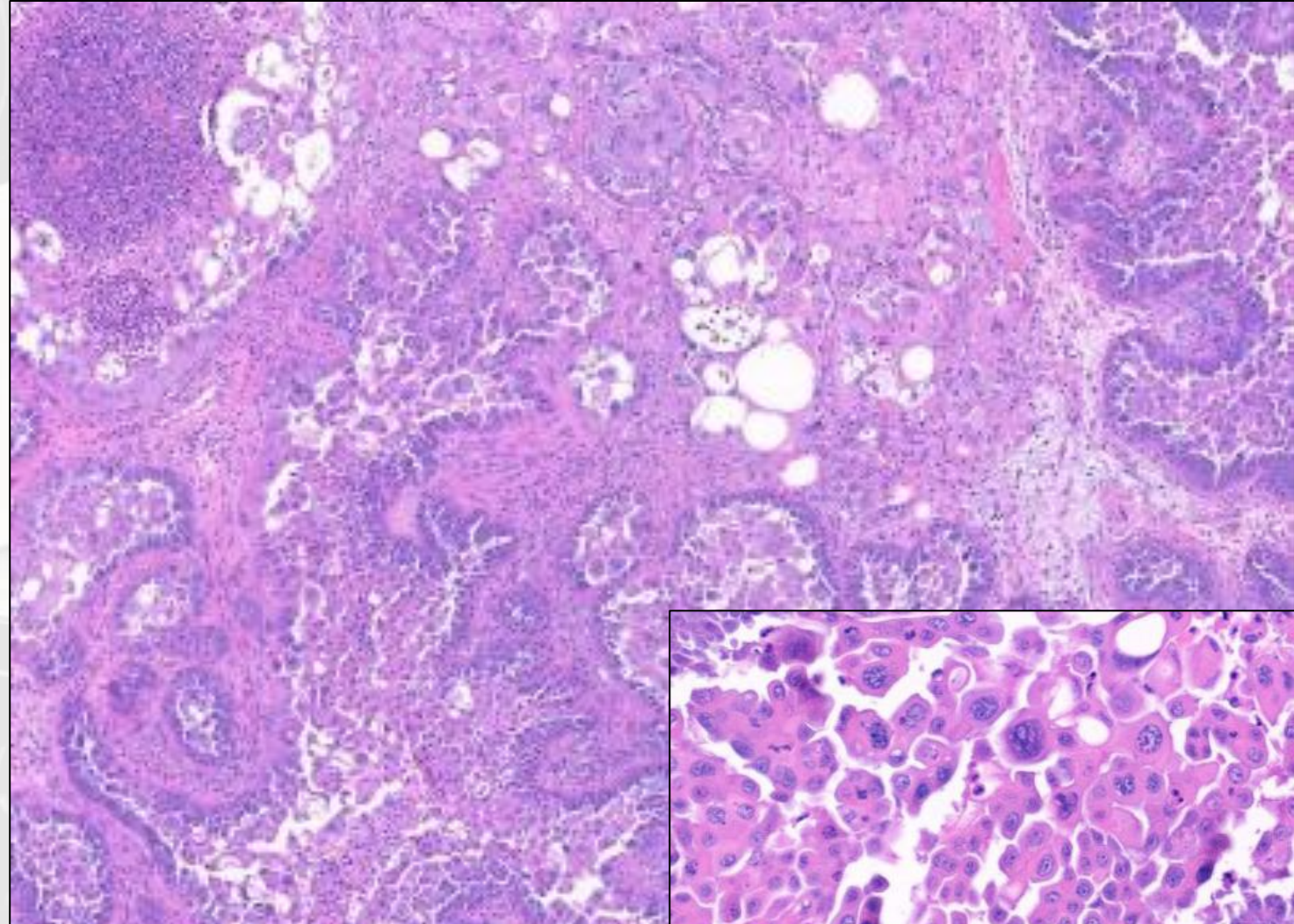
- *TP53* mutations
- Frequent deficiency in homologous recombination repair



Does borderline or LG -> HG transformation exist?

High-Grade Anaplastic Transformation of SBT

- Abrupt transition of SBT -> pleomorphic epithelioid cells with abundant cytoplasm
- Loss of ER, WT1, p16
- p53 WT
- *BRAF*, *TERT* promoter mutations
- Dismal prognosis

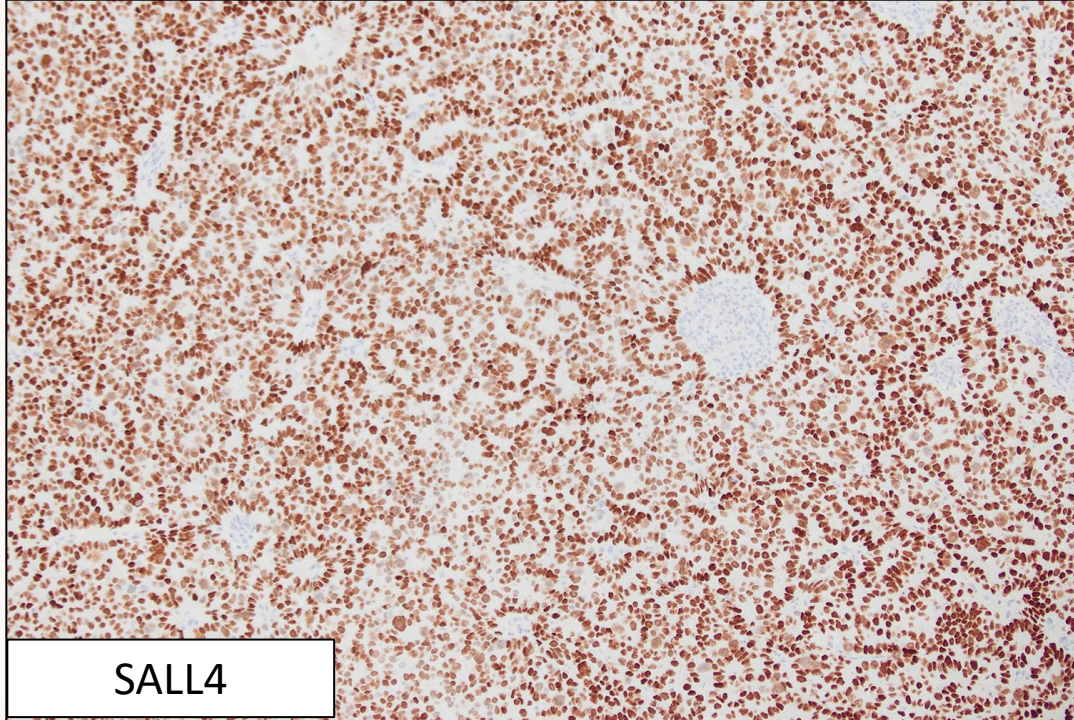
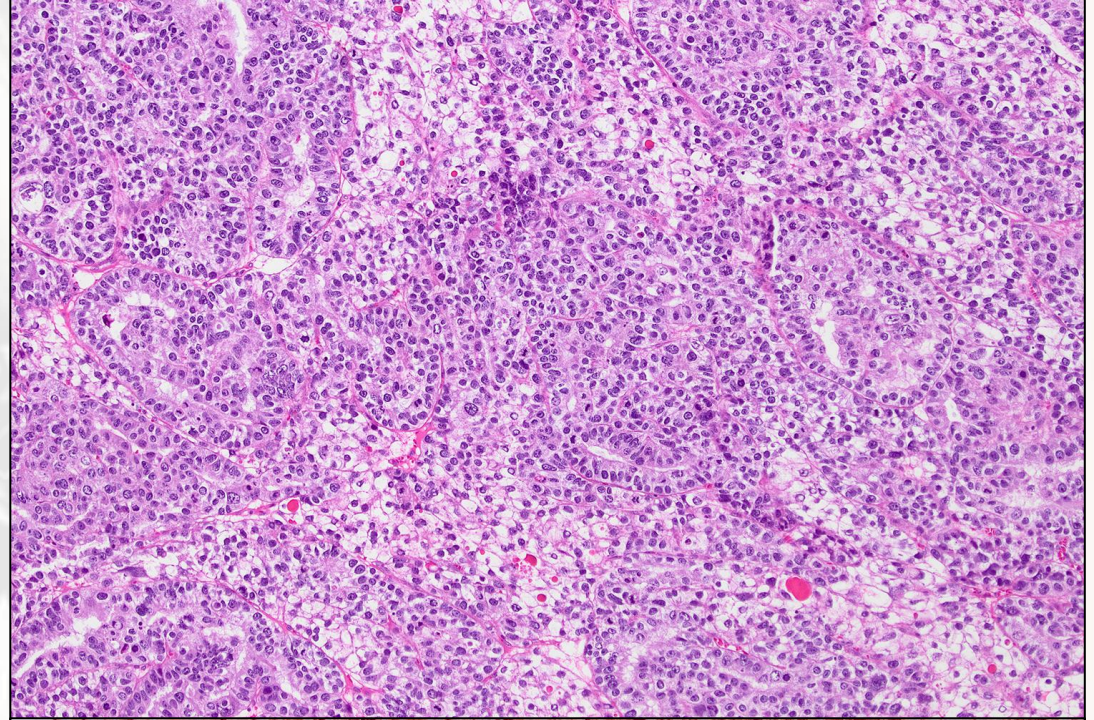
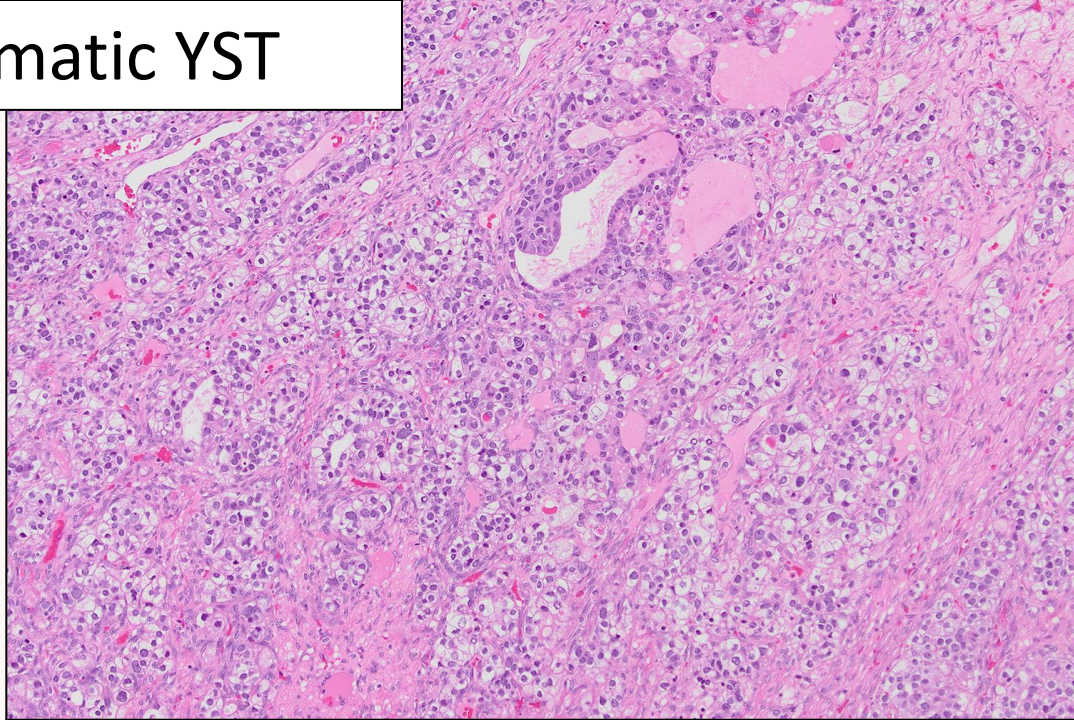


Zhang X, Devereaux KA, Ryan E, Fei F, Kunder CA, Longacre TA. High-grade Anaplastic Transformation of Ovarian Serous Borderline Tumor: A Distinctive Morphology With Abundant Dense Eosinophilic Cytoplasm and Dismal Prognosis. Am J Surg Pathol. 2024 Nov 1;48(11):1395-1407.

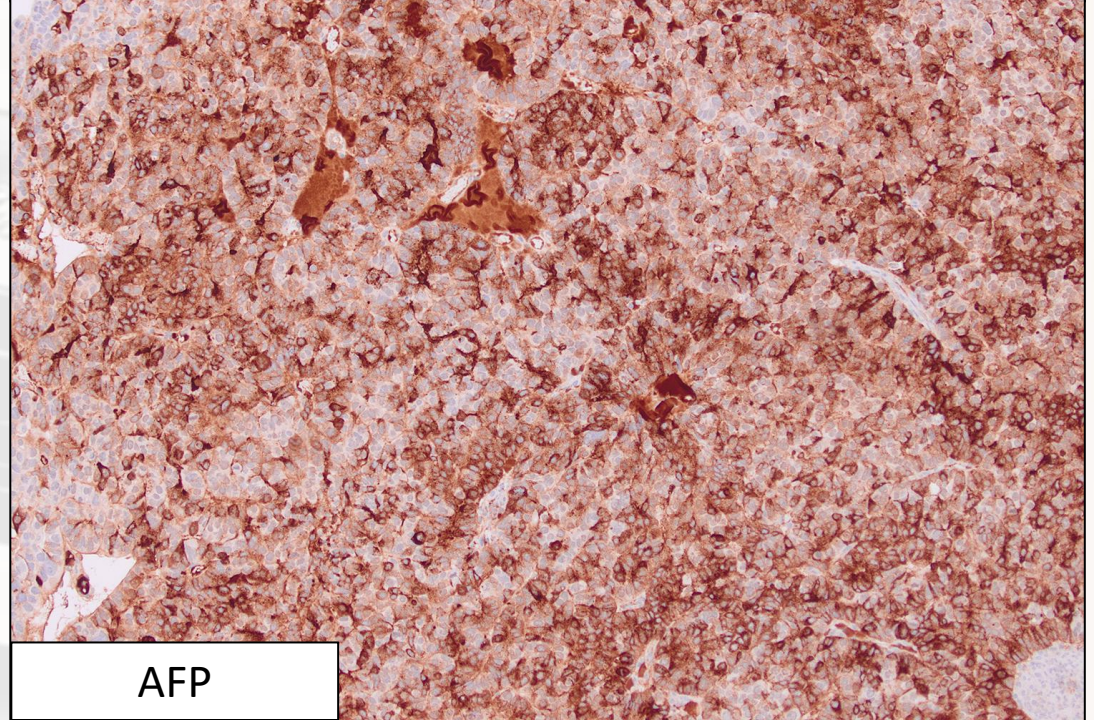
“Somatic Yolk Sac” Tumor

- Form of primitive “retro-differentiation” rarely seen in association with carcinomas
- Often postmenopausal patients
- Serum AFP may be elevated
- Primitive glands with subnuclear vacuoles
- Reticular/microcystic patterns
- Schiller-Duval Bodies
- Hyaline globules
- Mitoses typically numerous (>15 / 10 HPF)
- Variably positive for SALL4, Glypican-3, AFP

Somatic YST



SALL4



AFP

Summary

- Low-grade and high-grade serous carcinoma are distinct neoplasms with divergent molecular pathways
 - p53 immunohistochemistry
- Differentiating implants vs. metastatic serous tumors based entirely on morphology
- Upcoming WHO 6th edition – no longer using the term “microinvasion” in serous borderline tumors
- Mesothelial proliferations may mimic serous neoplasia