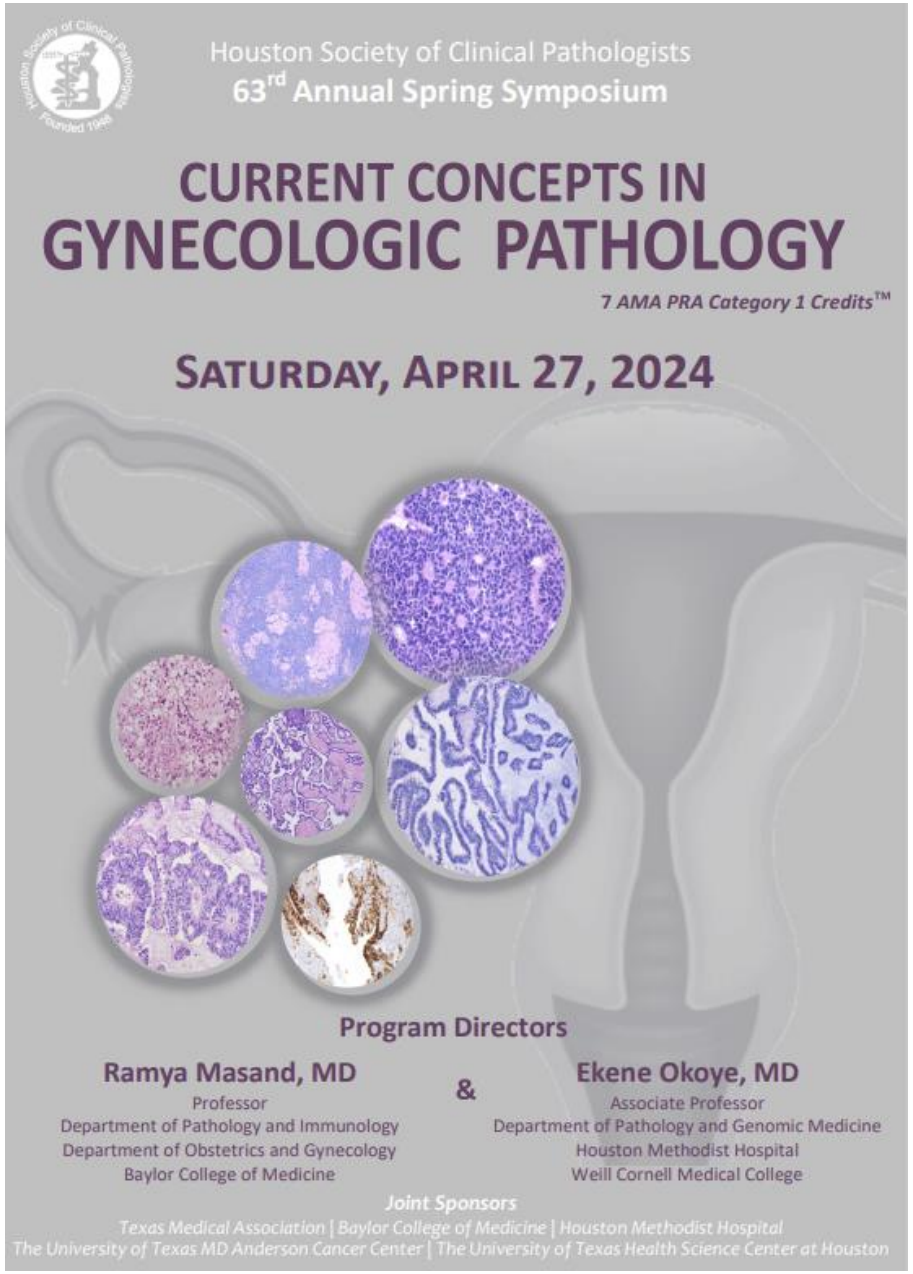
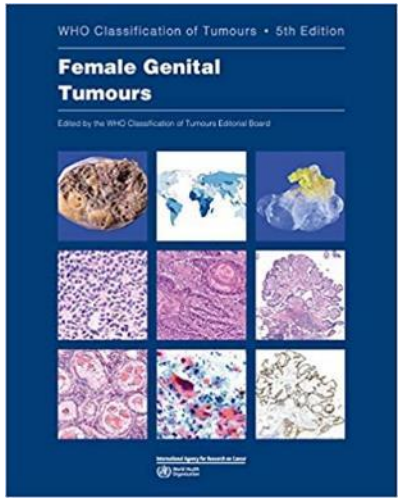


Ovarian Epithelial Tumors in Soundbites

Anaís Malpica, M.D.
Professor
Department of Pathology

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

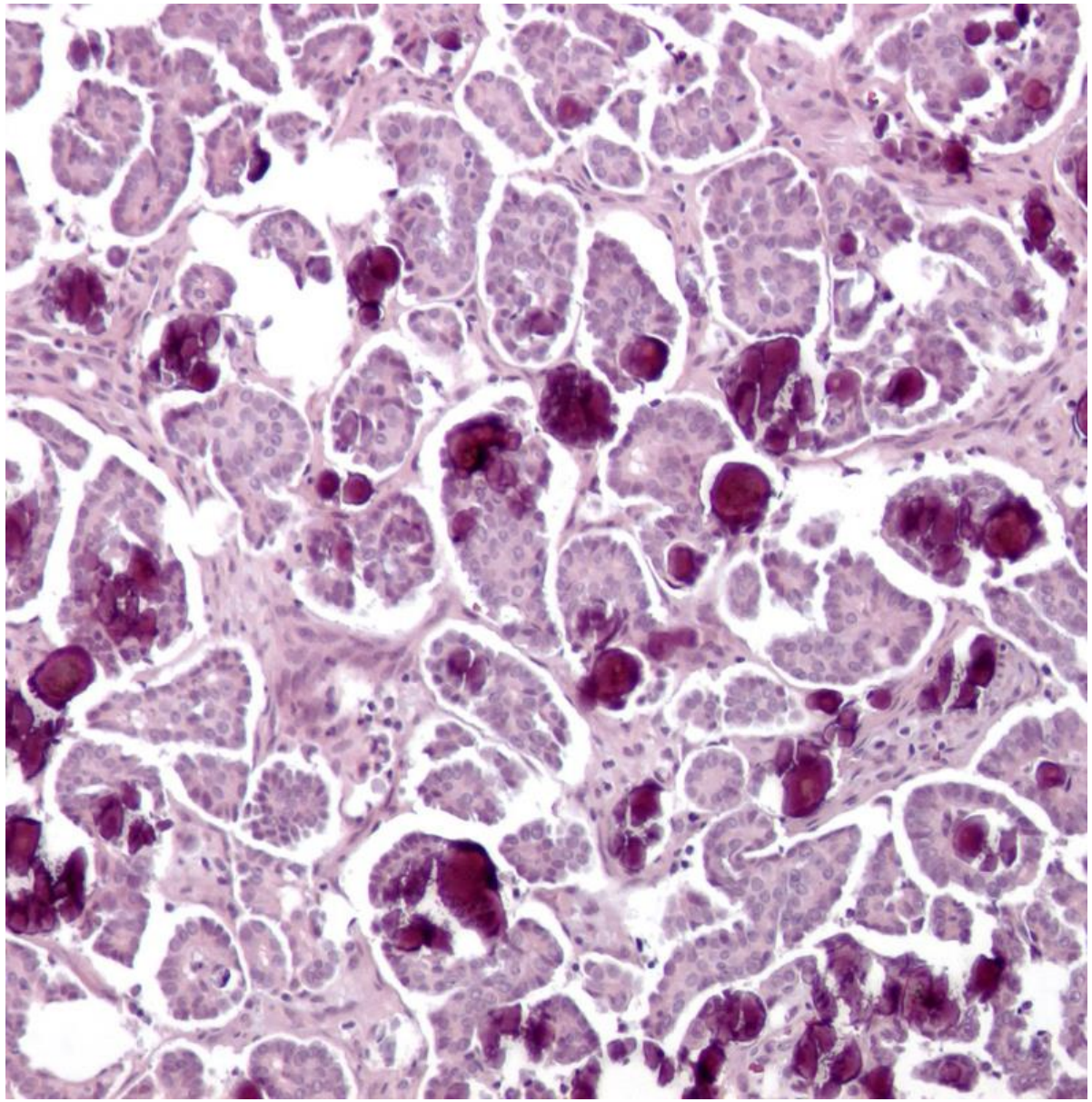


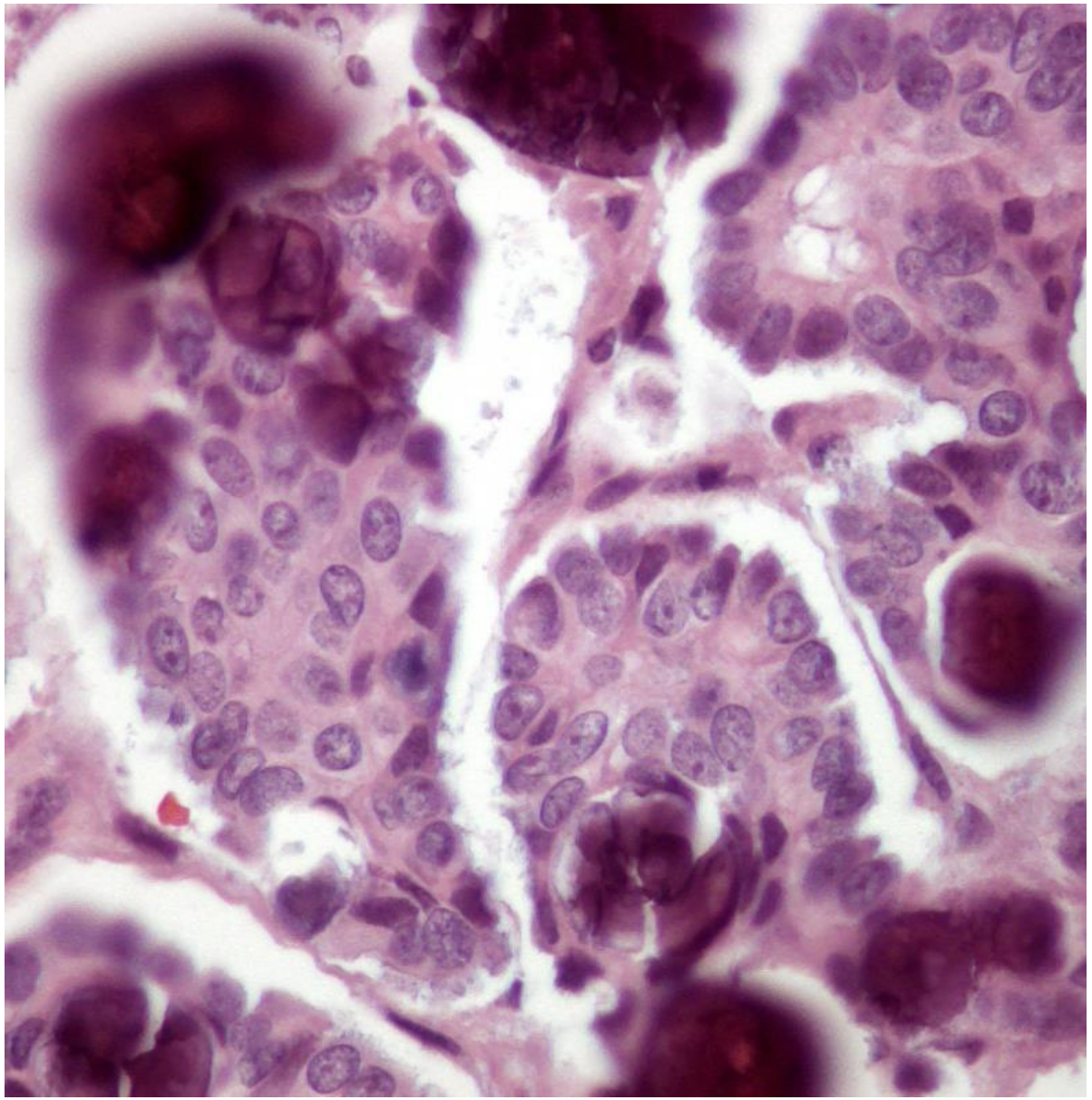
2020

Practical Issues

- Serous Carcinoma
  - Low Grade
  - High Grade
- Mucinous Carcinoma
- Endometrioid Carcinoma
- Clear Cell Carcinoma
- Others:
  - Mesonephric-like Carcinoma
  - Malignant Brenner Tumor

Low-Grade Serous Carcinoma

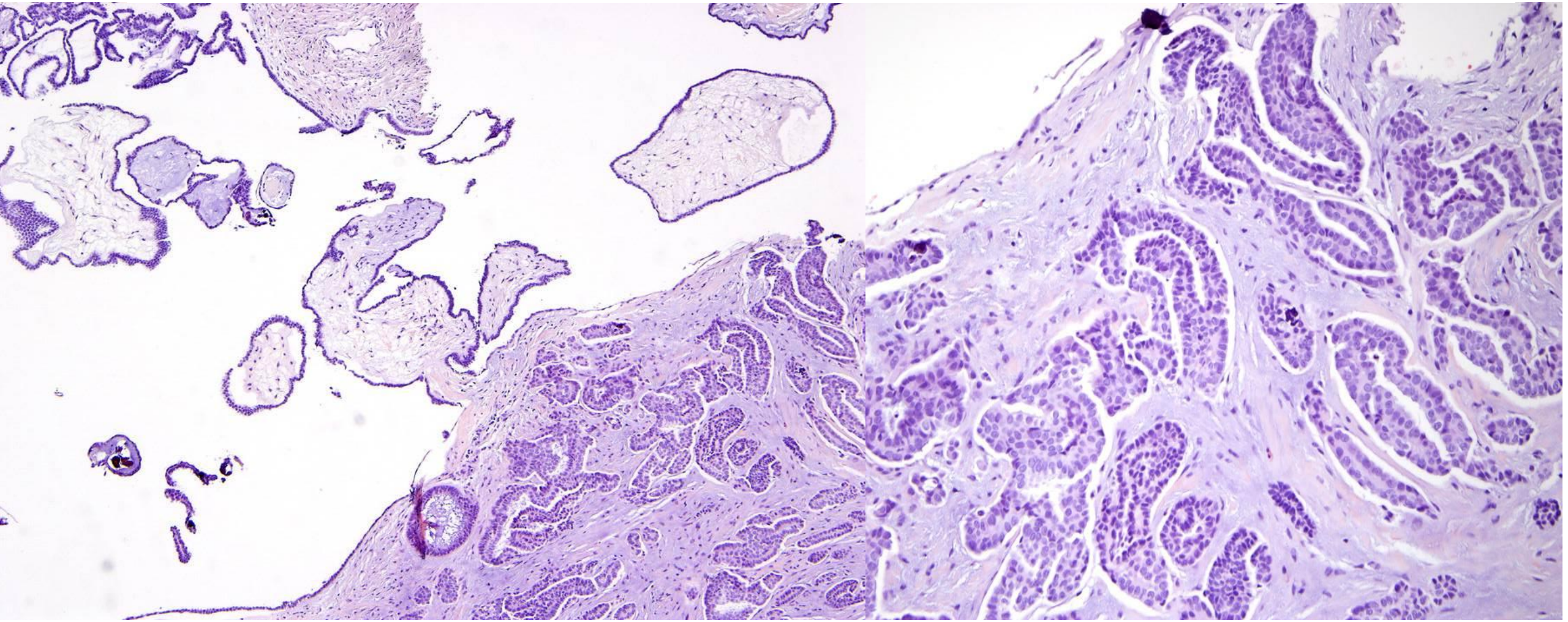




#1. Uniform cells with mild to moderate cytologic atypia

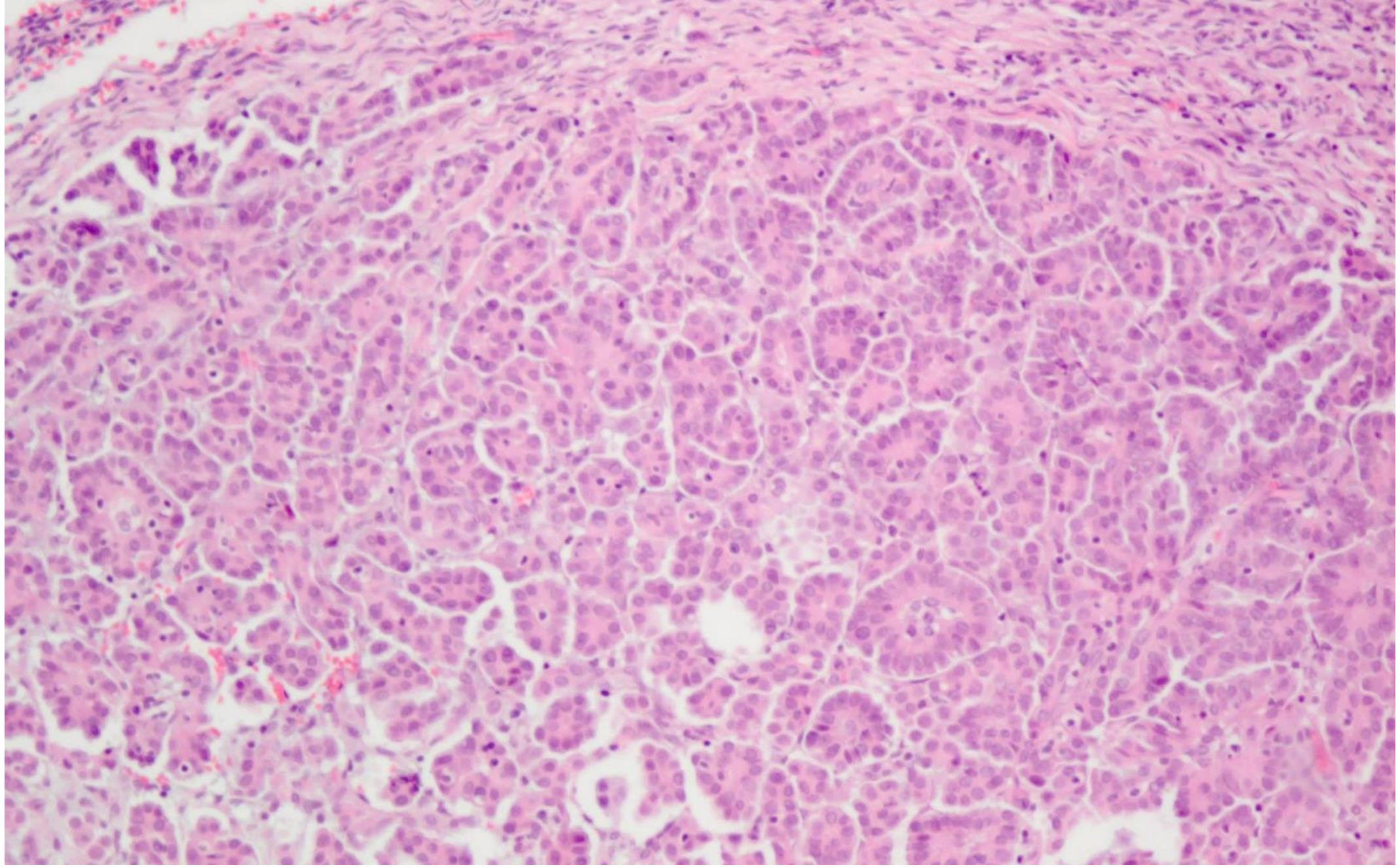
#2. Usually a low mitotic index (≤ 12 mitoses per 10 HPFs)

Microinvasive Low Grade Serous Carcinoma, WHO 2020



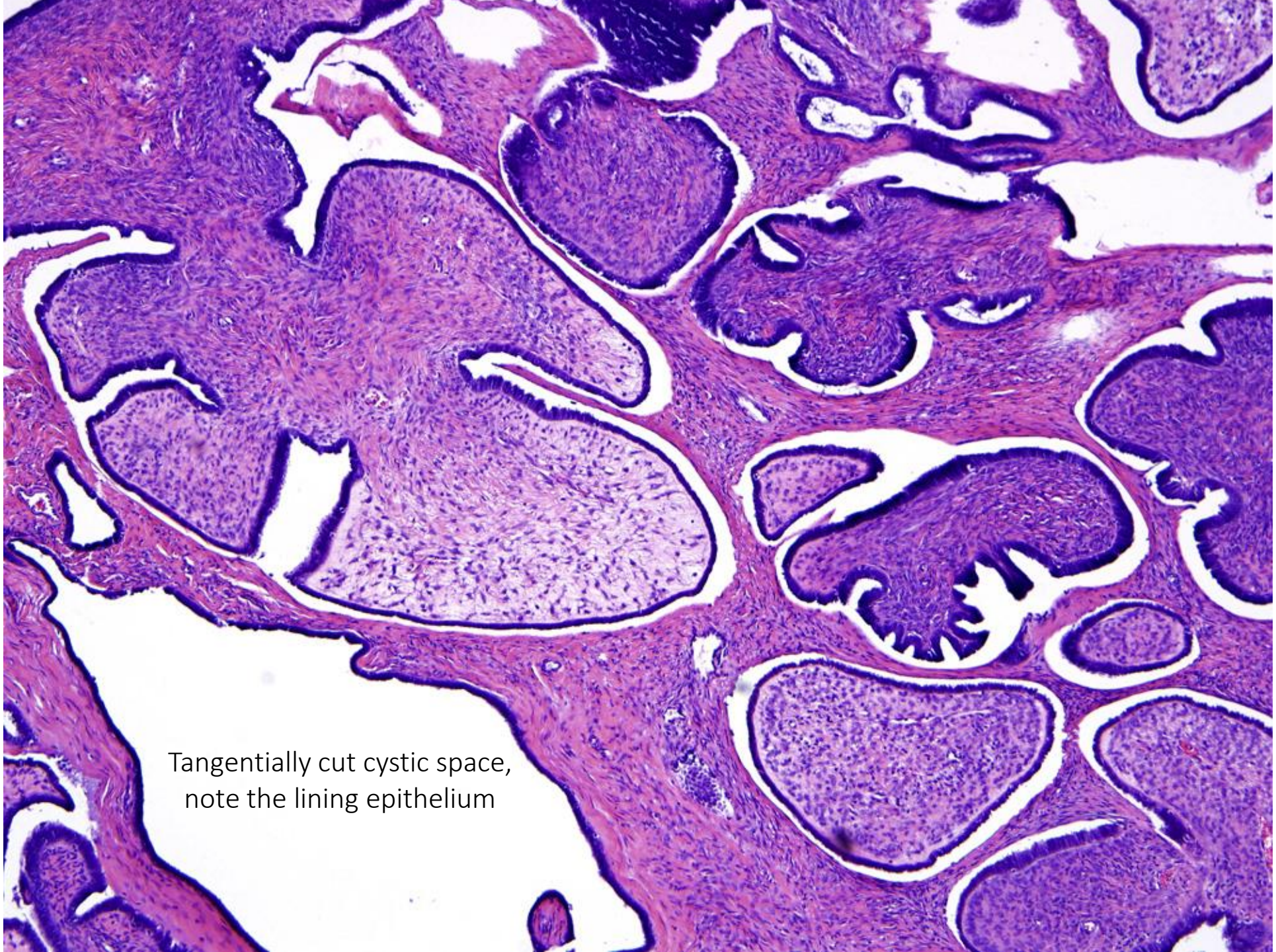
Focus of low-grade serous carcinoma, < 5 mm, desmoplasia

Microinvasive Low Grade Serous Carcinoma, WHO 2020

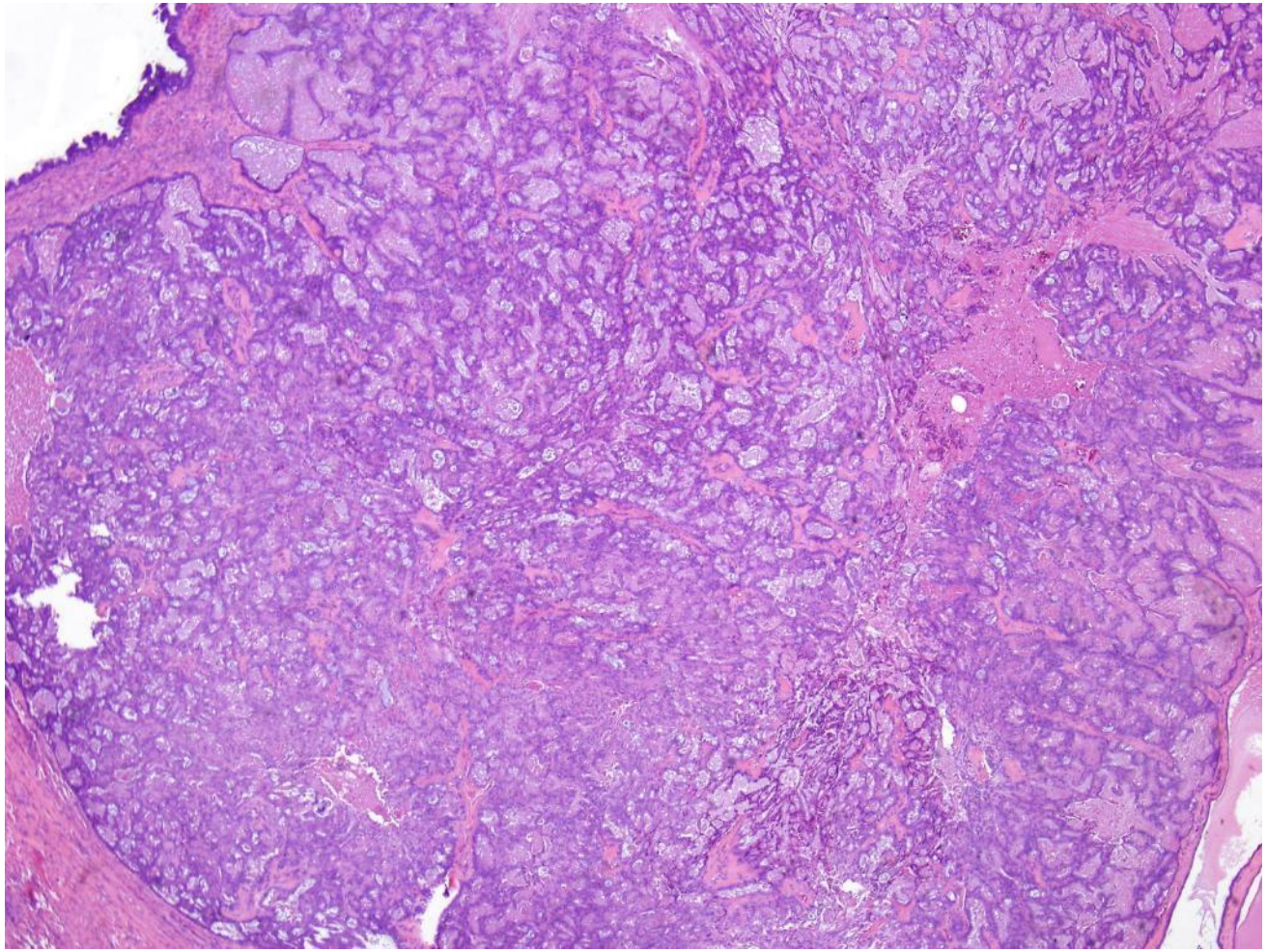


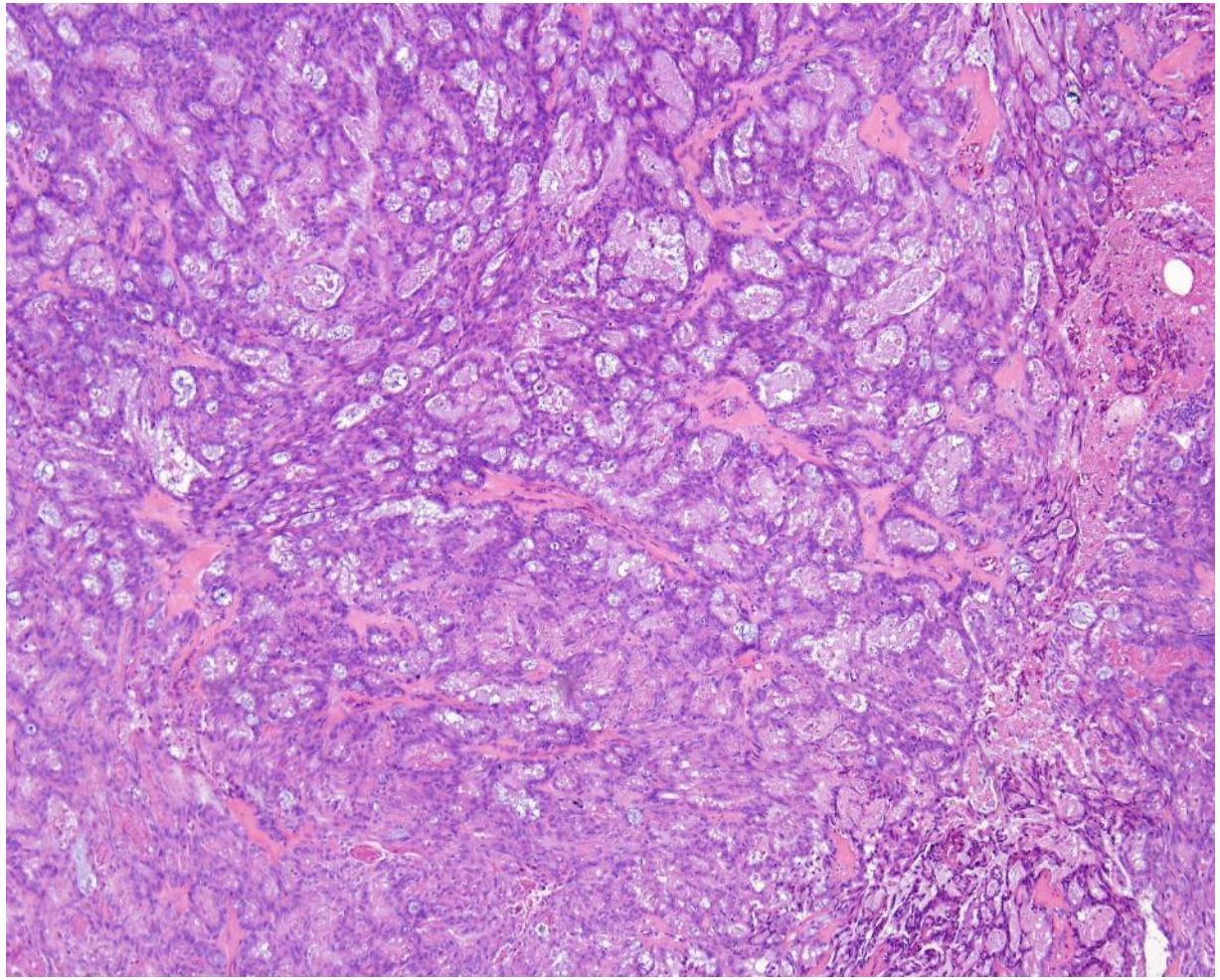
Focus of low-grade serous carcinoma, < 5 mm, marked epithelial proliferation

Low-Grade Serous Carcinoma, Macropapillae

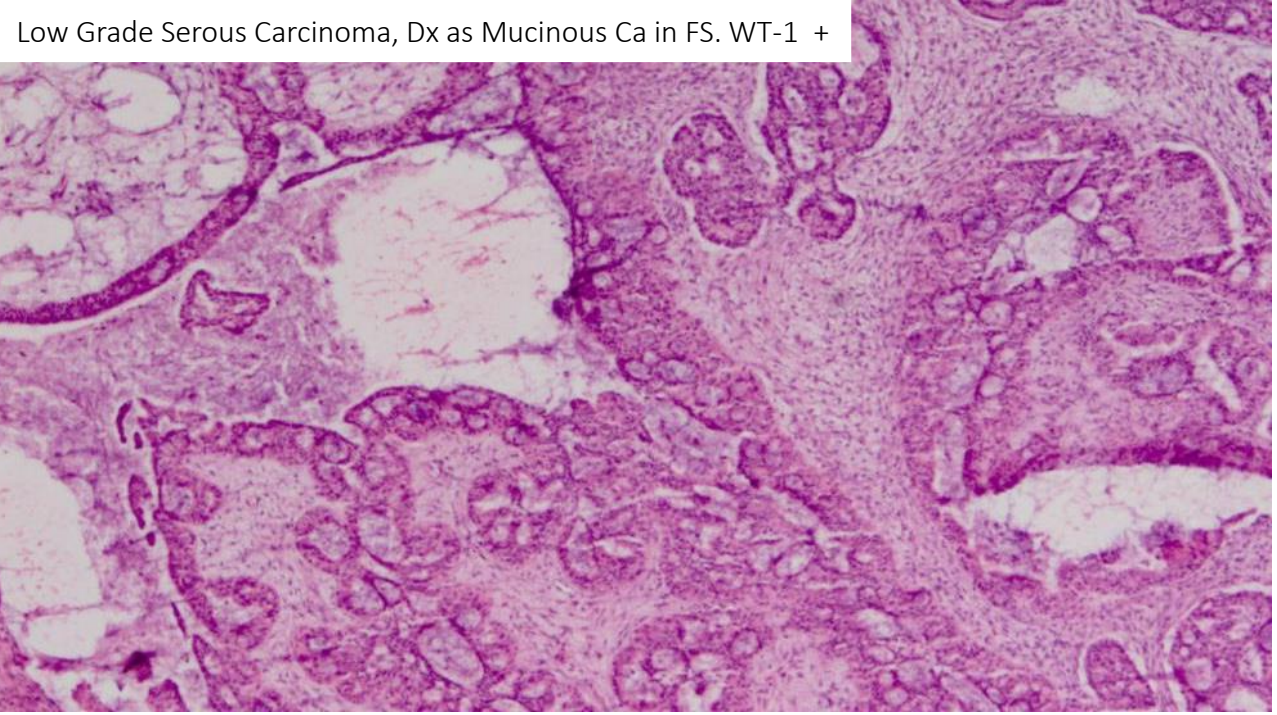


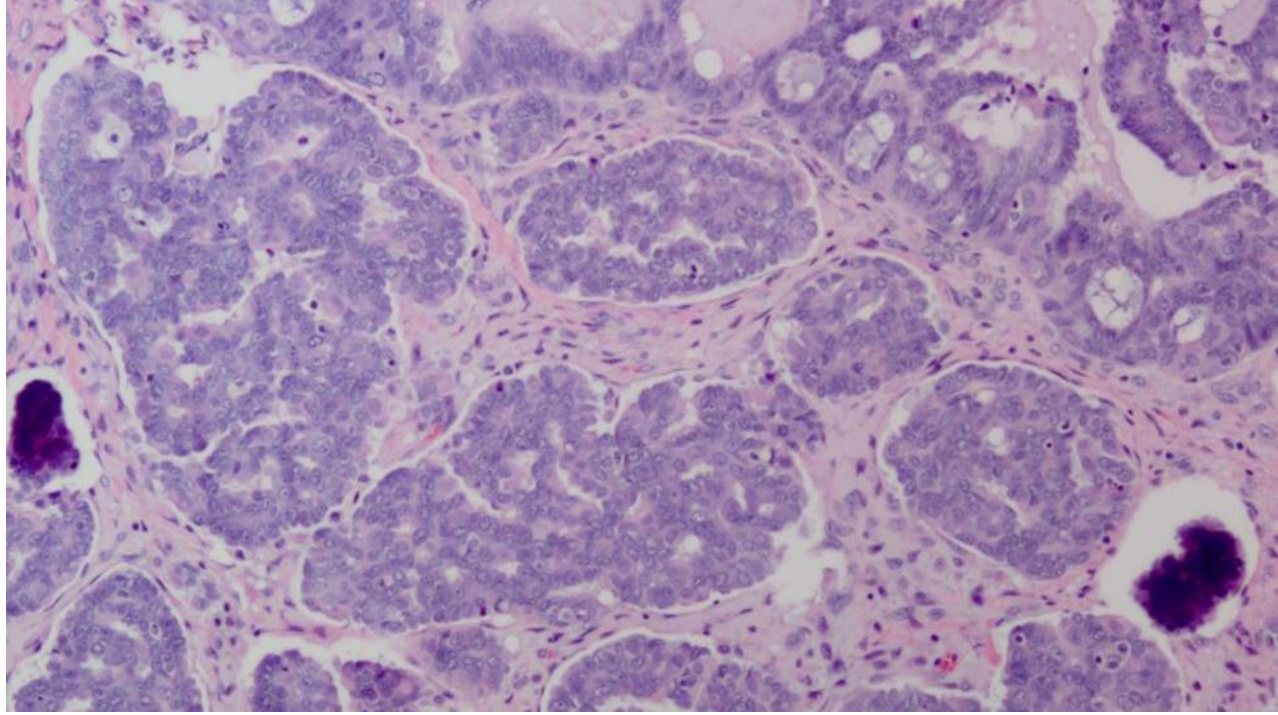
Low-Grade Serous Carcinoma, Massive Epithelial Growth in Cystic Spaces

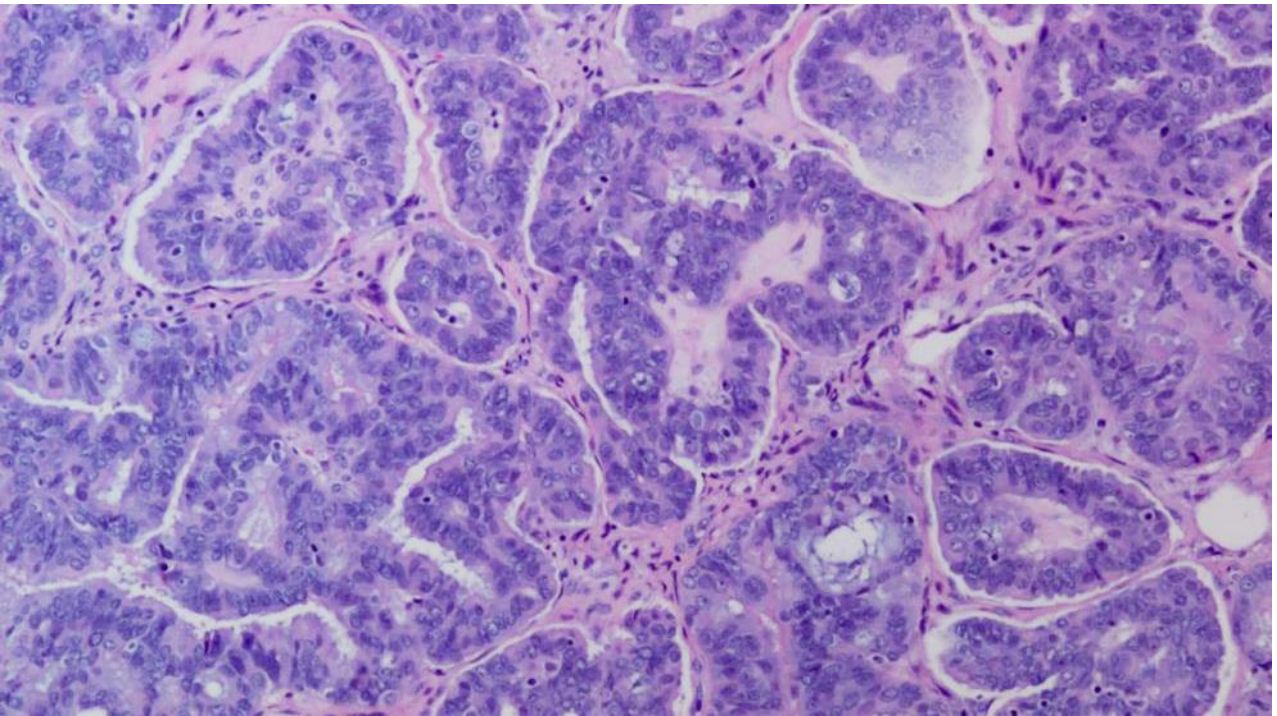


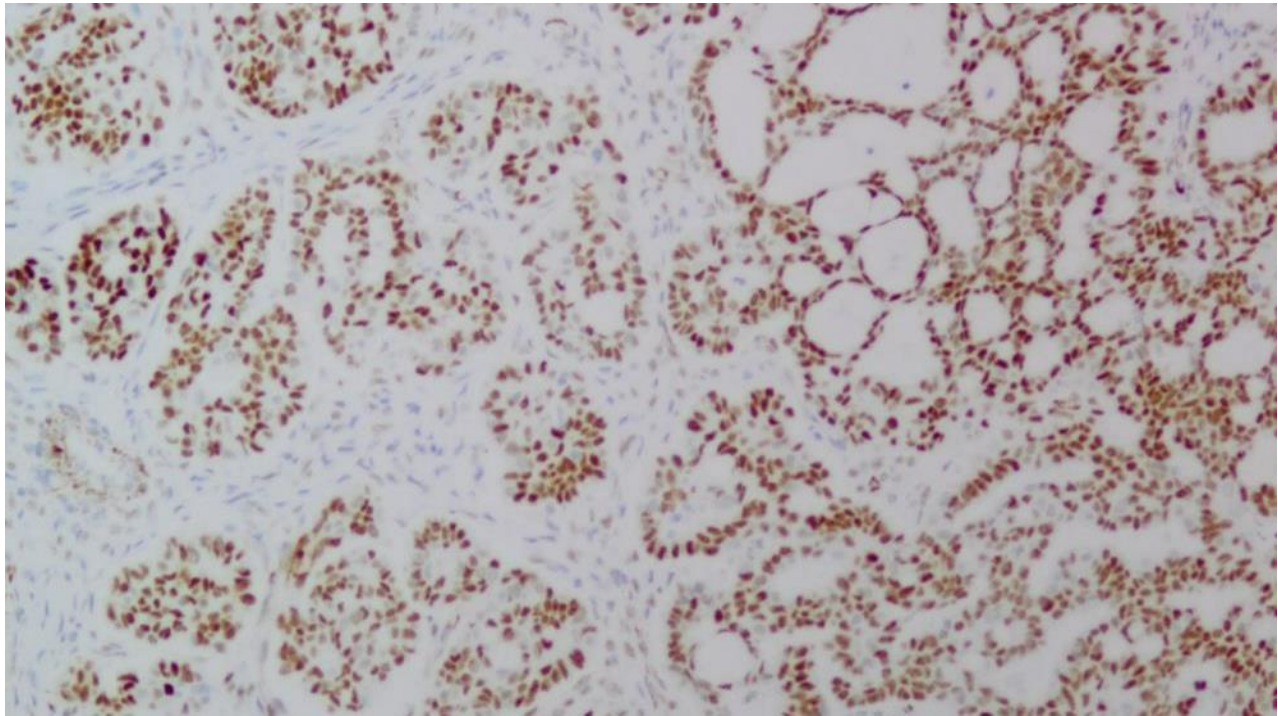


Low Grade Serous Carcinoma, Dx as Mucinous Ca in FS. WT-1 +

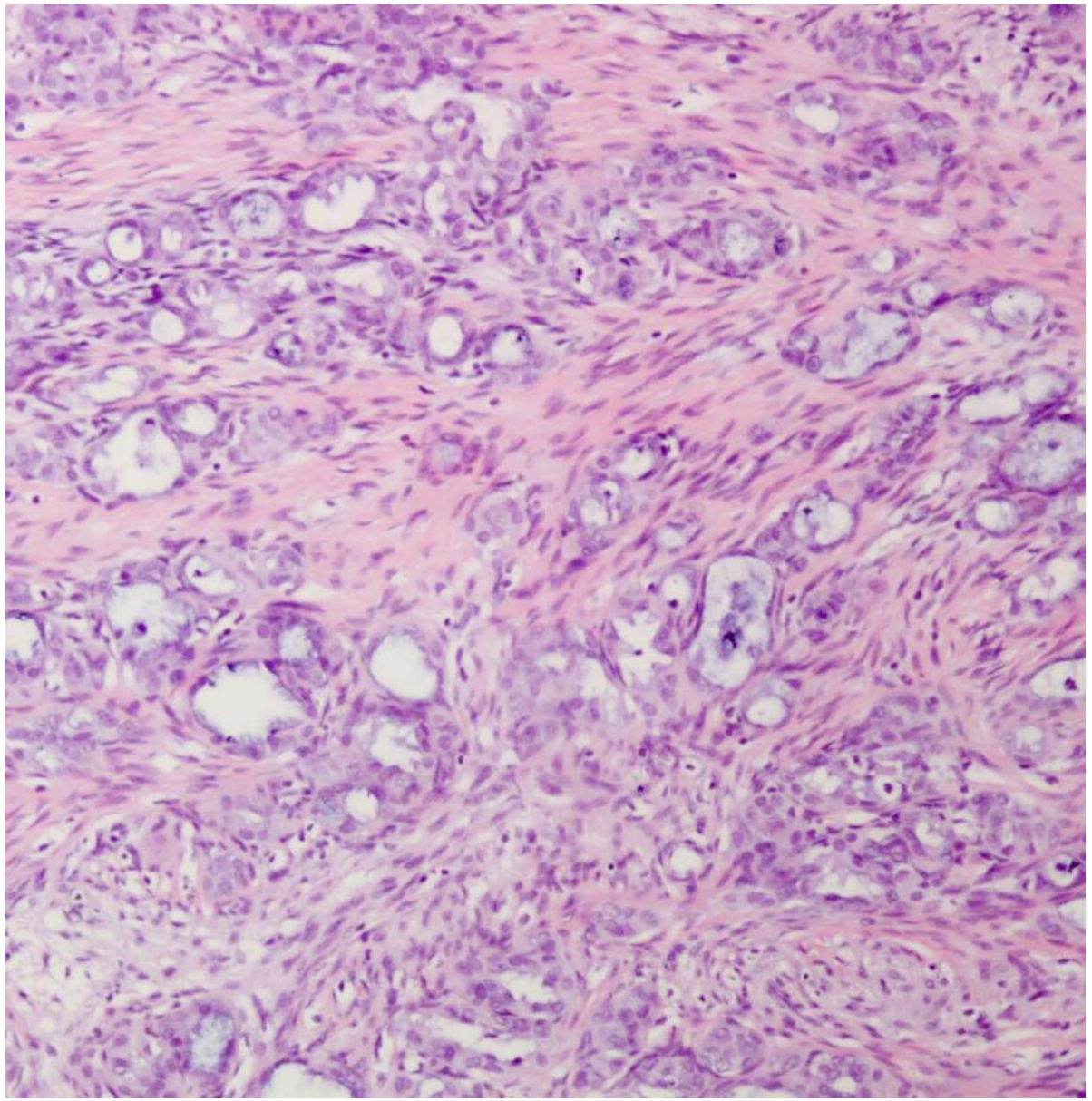




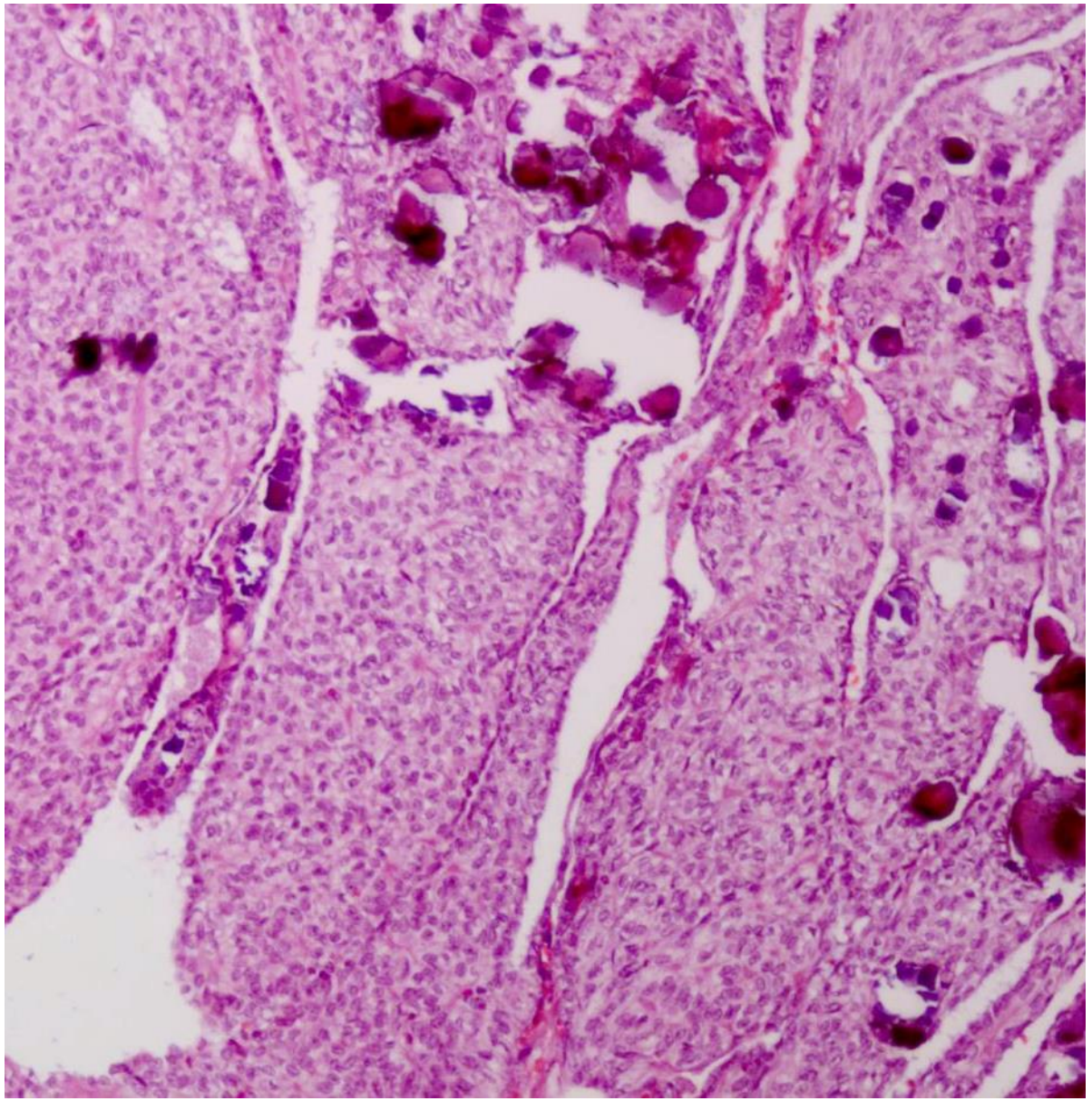


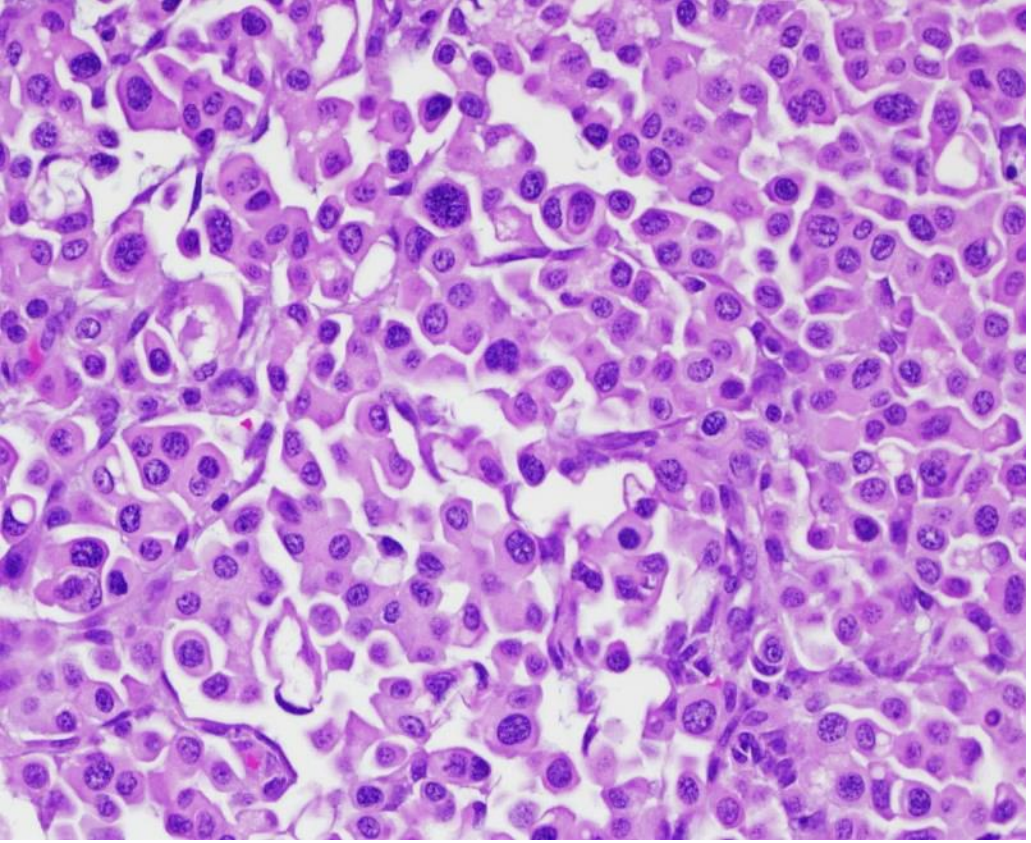


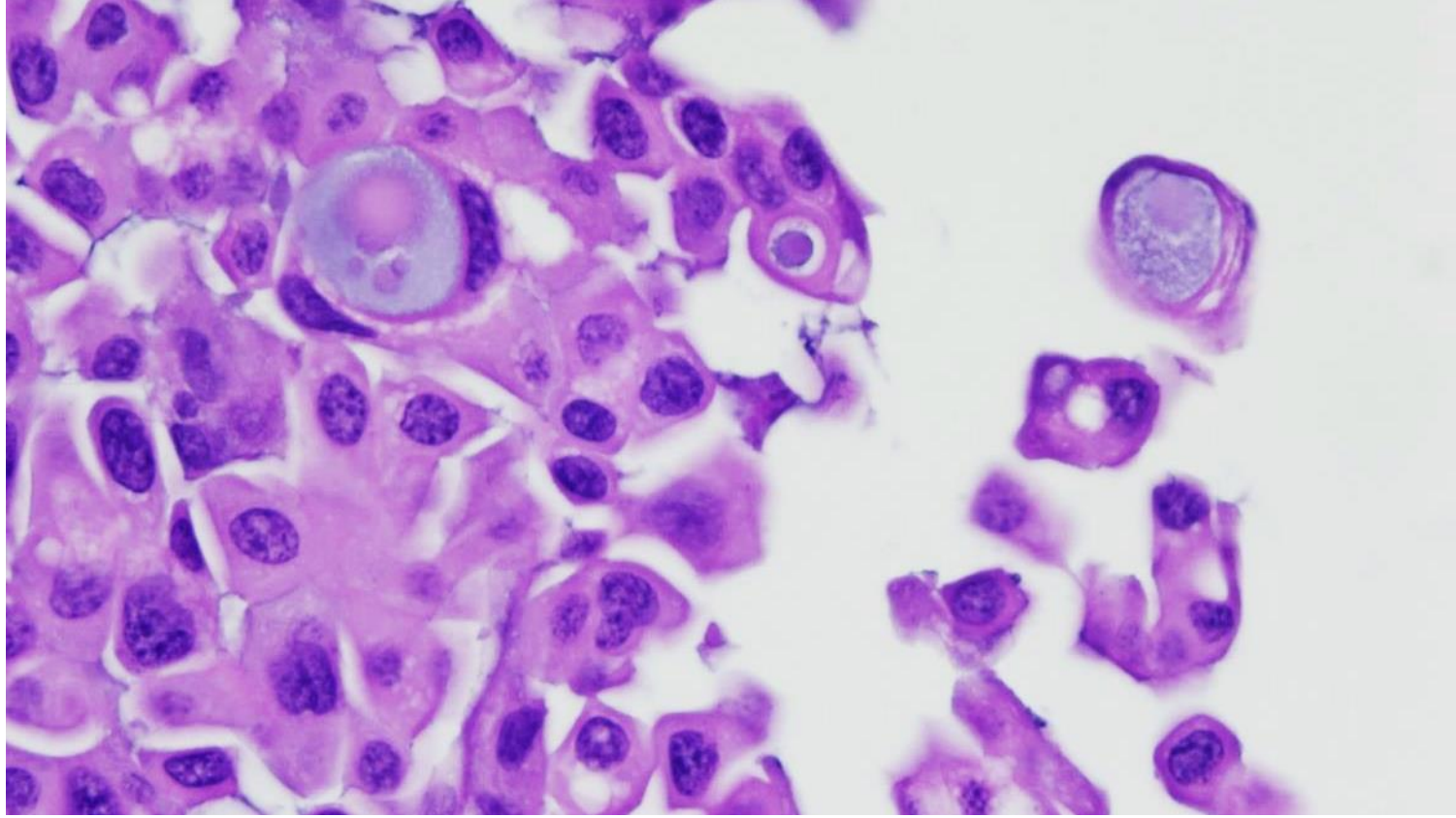
Low Grade Serous Ca, Small Glands and Mucin



Low Grade Serous Ca, Solid Pattern and Clear Cytoplasm





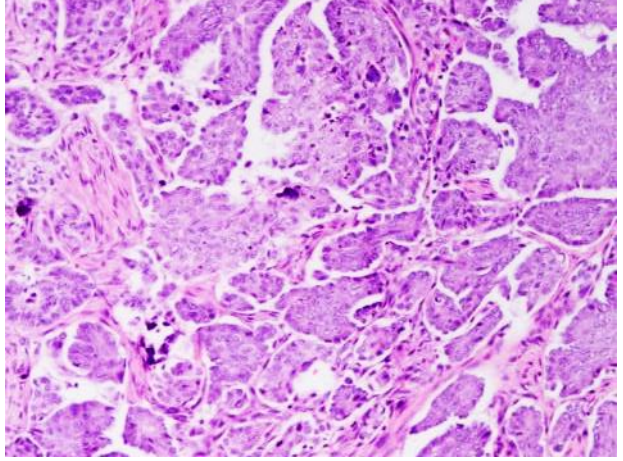


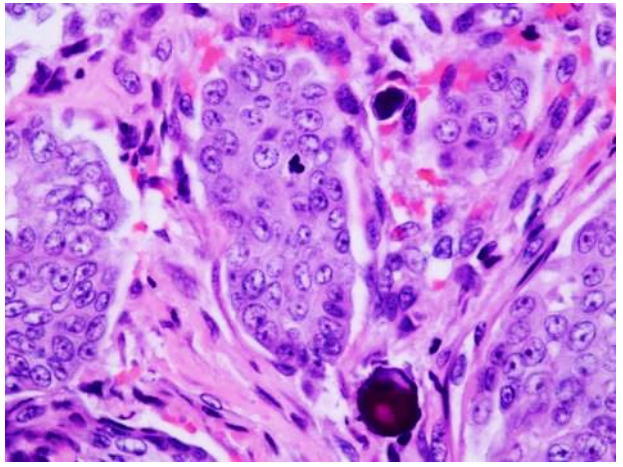
Low-Grade Serous Carcinoma

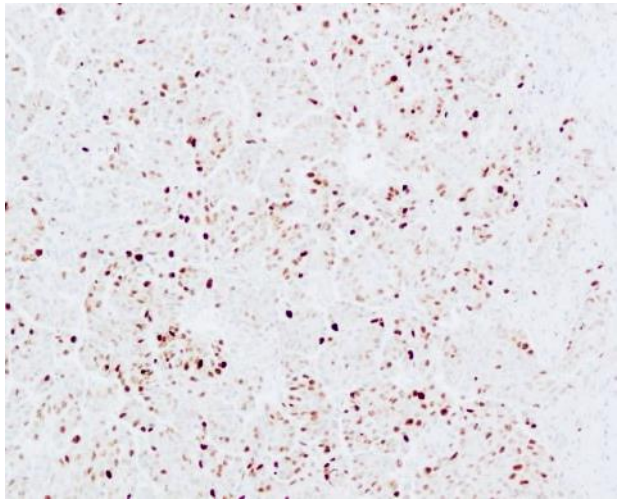
- Polygonal cells with eosinophilic cytoplasm, nuclear pleomorphism and signet-ring cells
- Low mitotic index
- The tumor has a mesothelioma-like appearance
- IHC:
  - Claudin 4, MOC-31, PAX-8, ER, PR, +
  - Calretinin, thrombomodulin, keratin 5/6 , -
  - p53 wild type

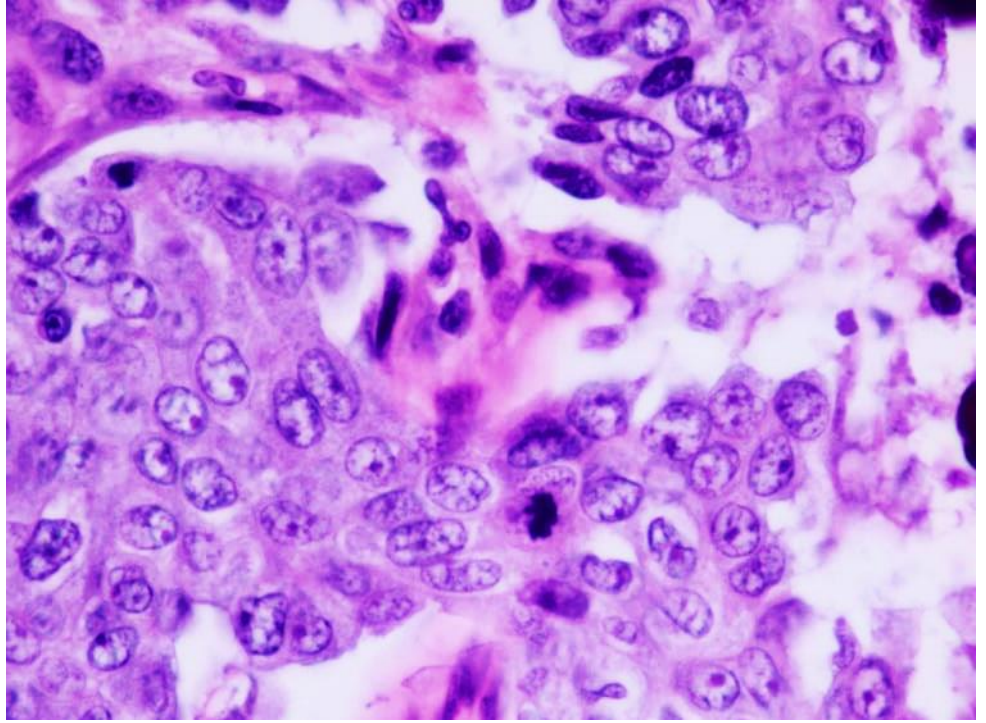
Low-Grade Serous Carcinoma

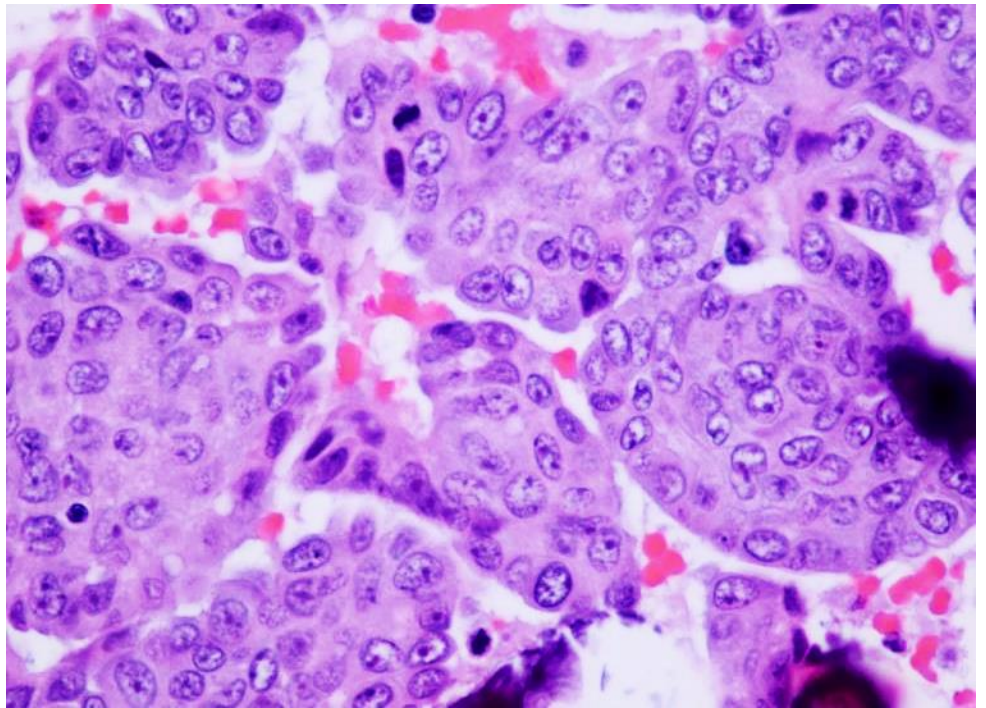
- 20 mitoses per 10 HPFs
- No significant pleomorphism
- p53 wild type

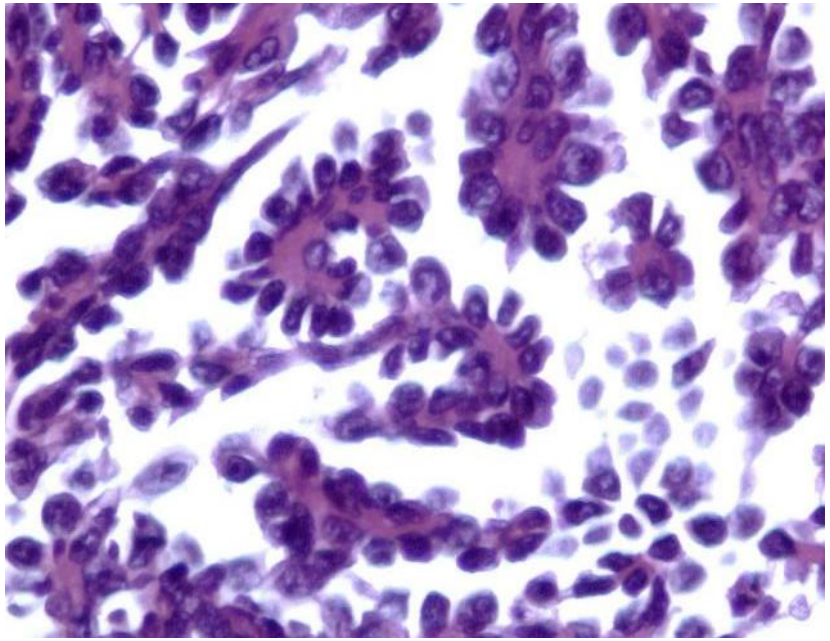


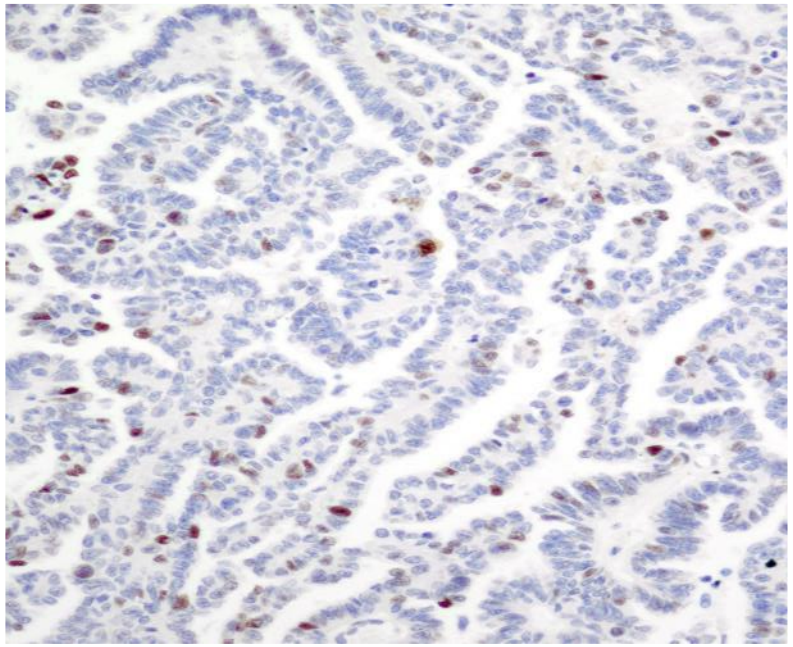


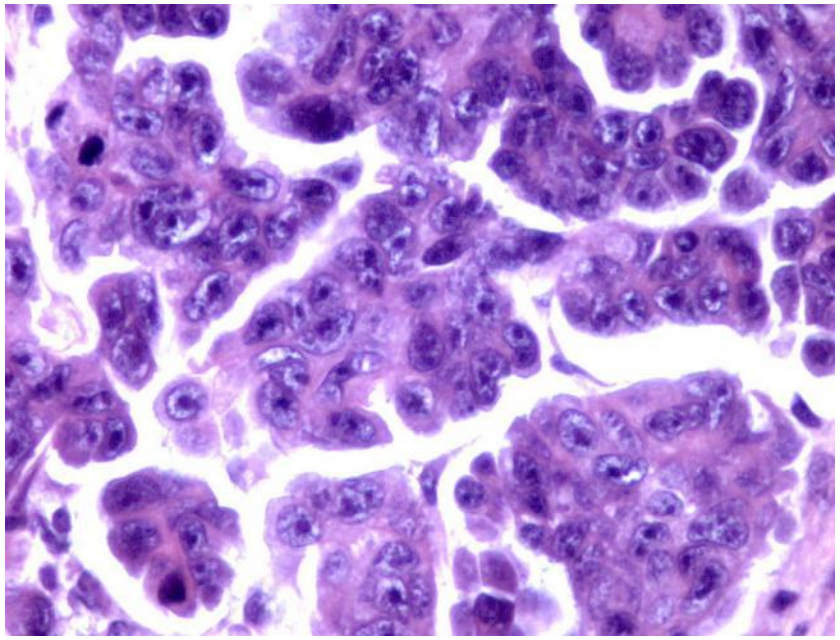


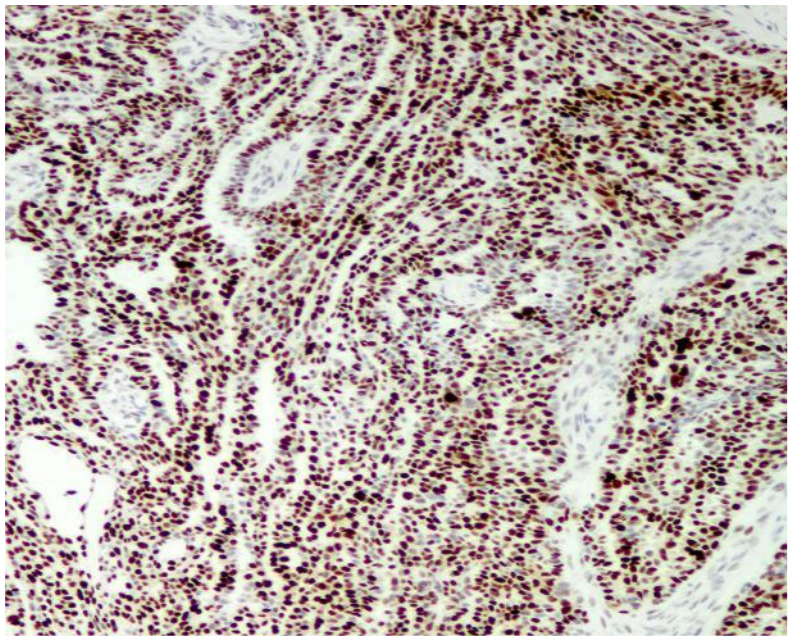












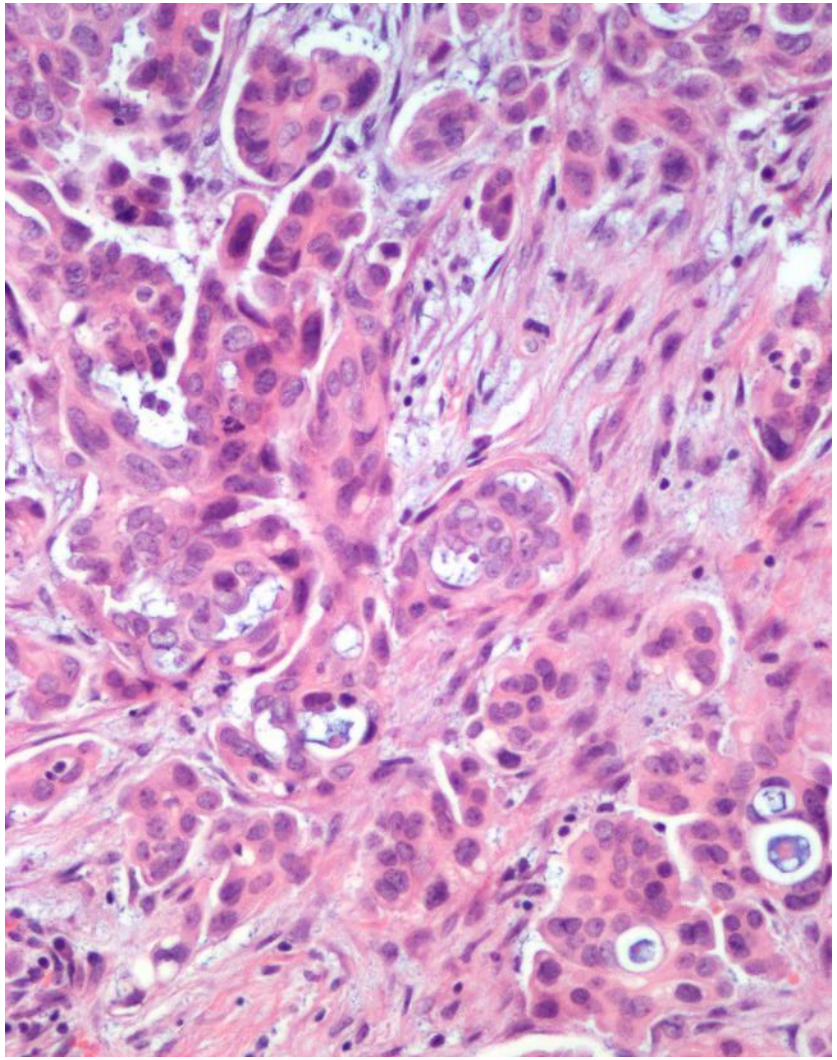
Serous Carcinoma, Tumor Heterogeneity

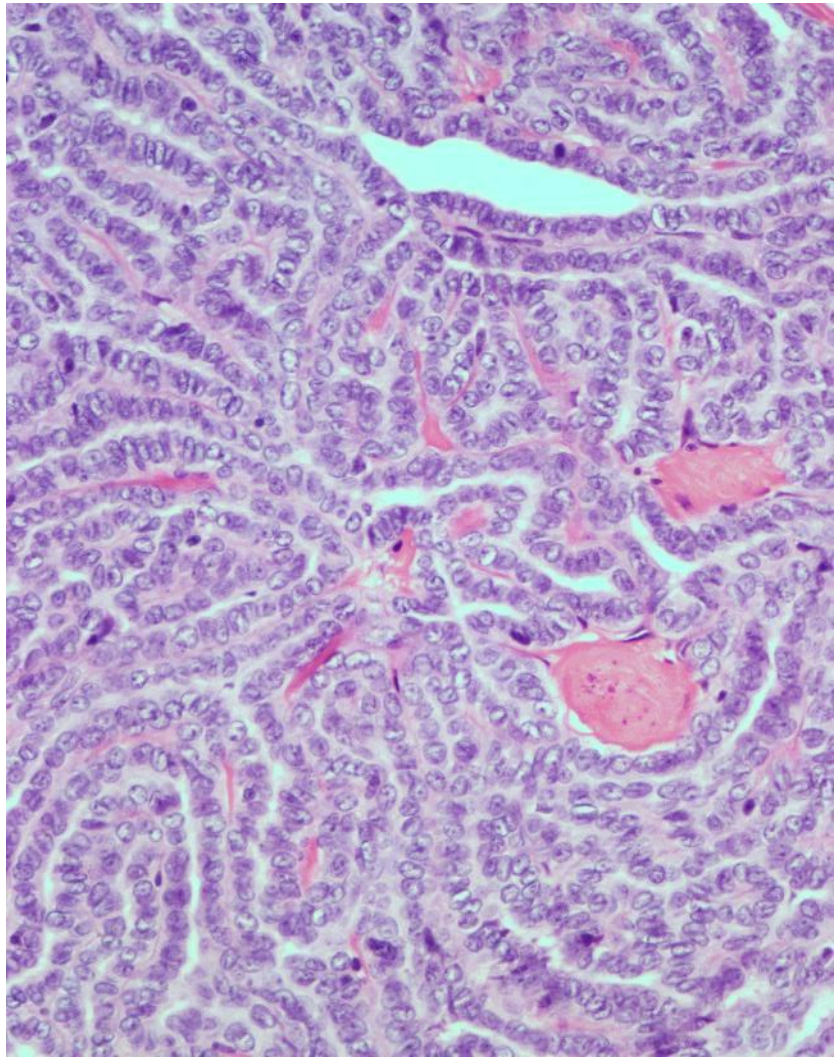
(Low Grade and High Grade)

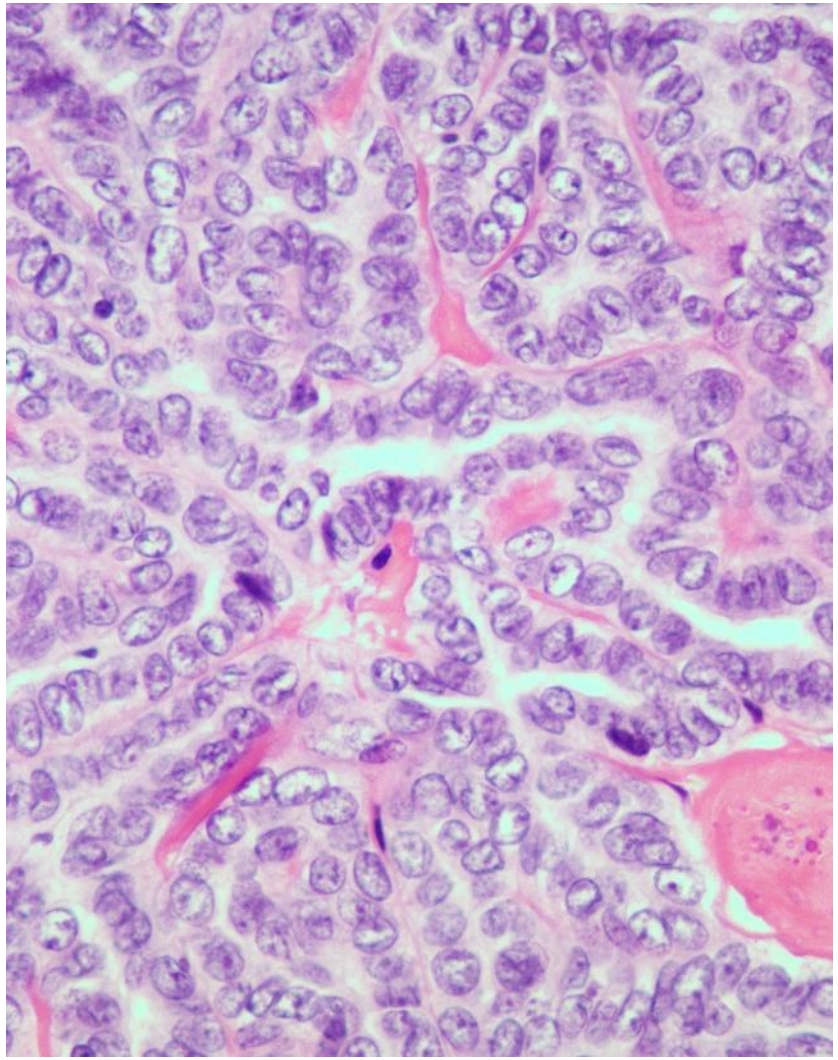
- Uncommon
- Synchronous or metachronous
- A problem when dealing with limited tissue

p53

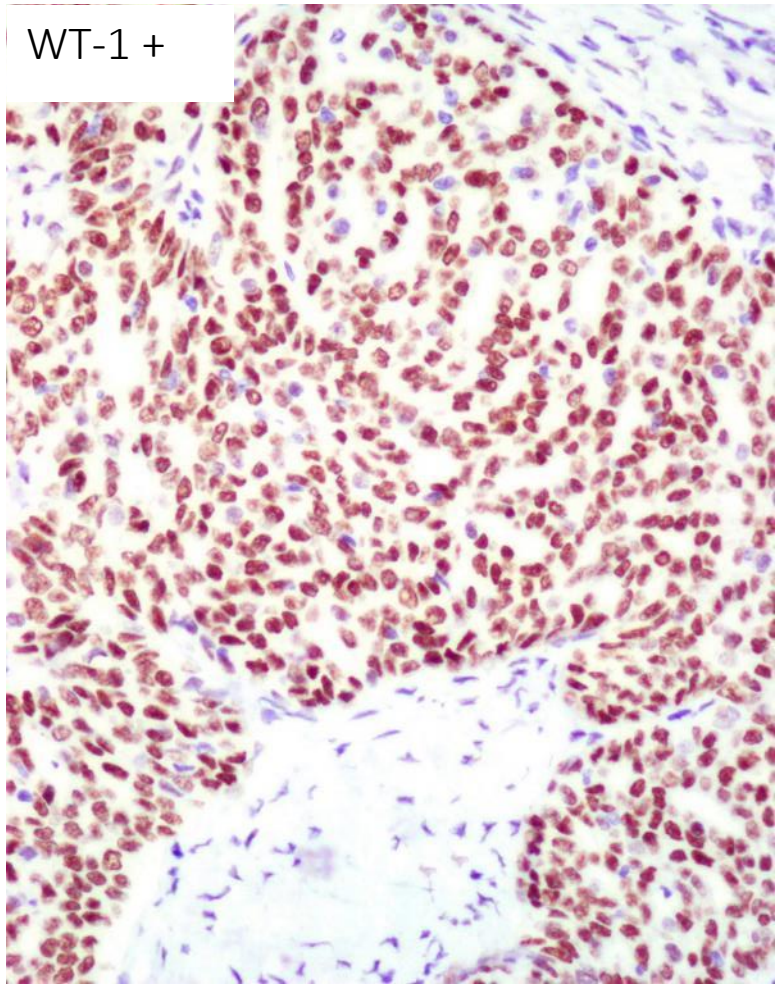
Low Grade Serous Ca vs. Mesonephric-like Ca

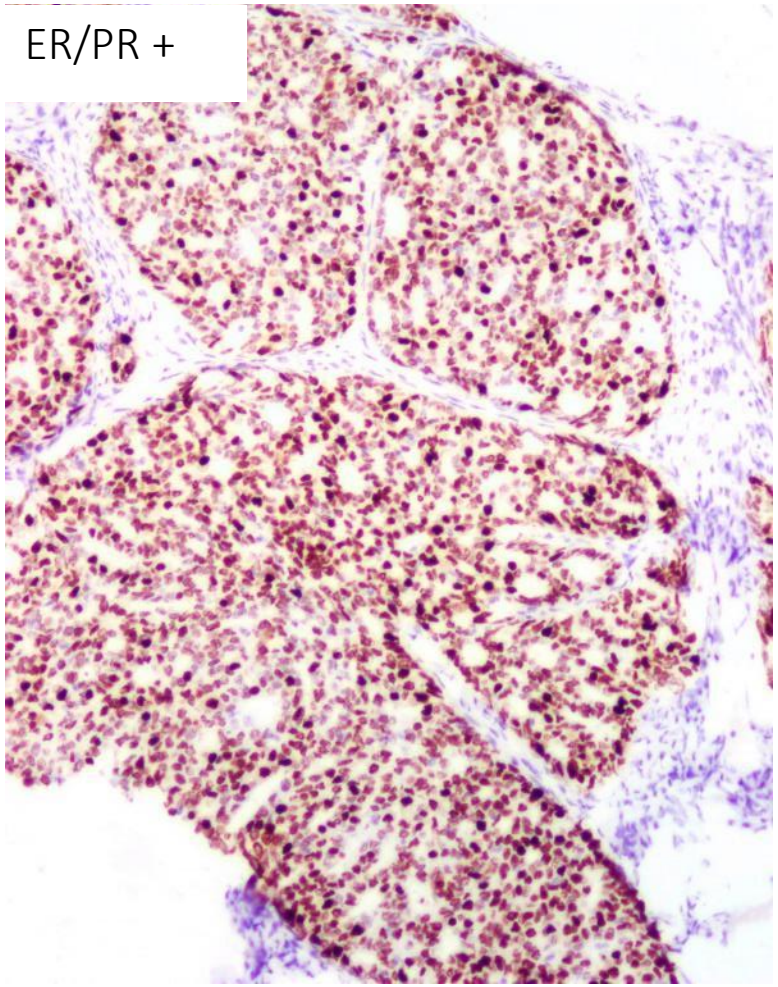


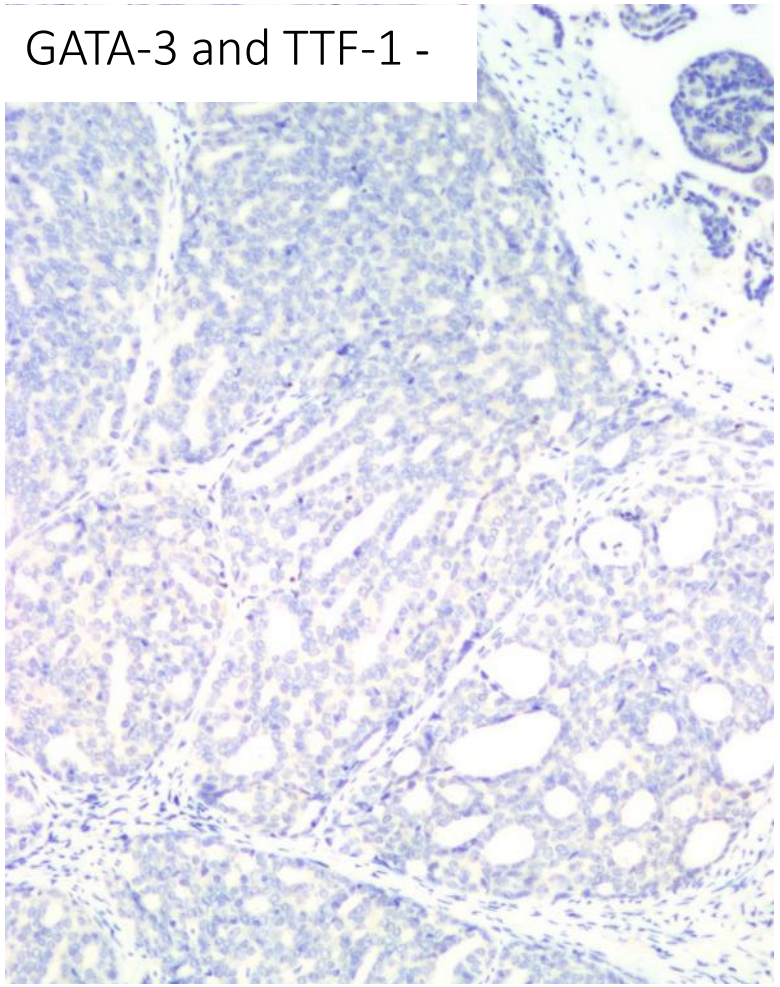




Low Grade Serous Ca vs. Mesonephric-like Ca

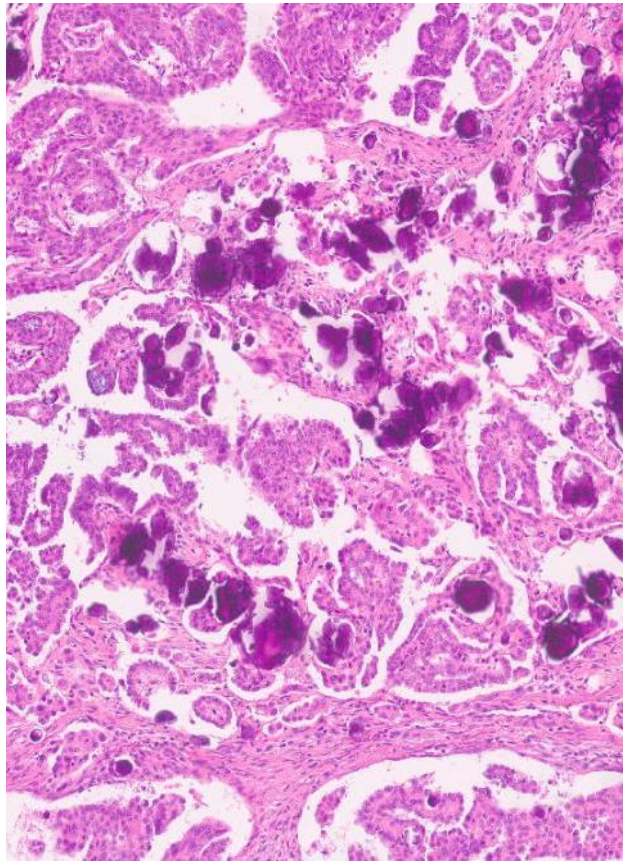
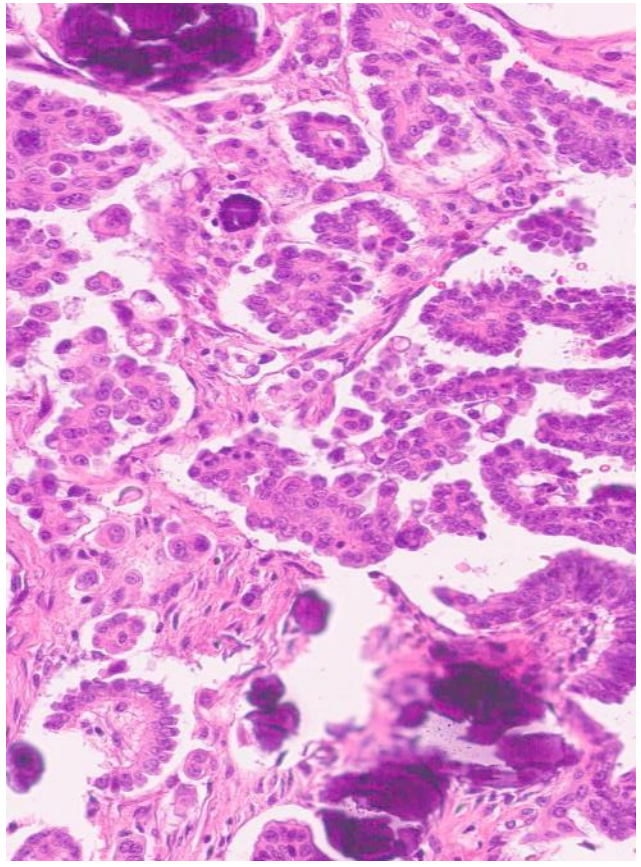
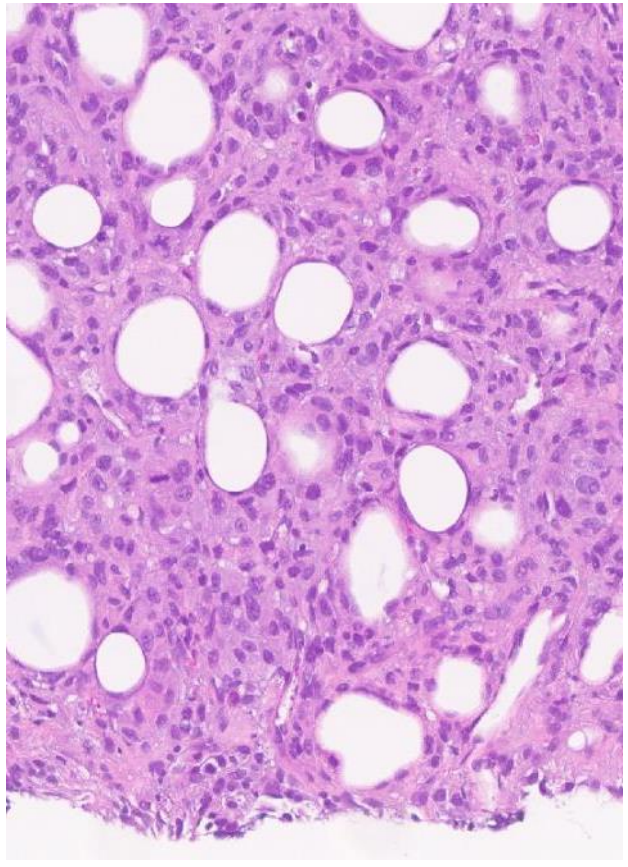
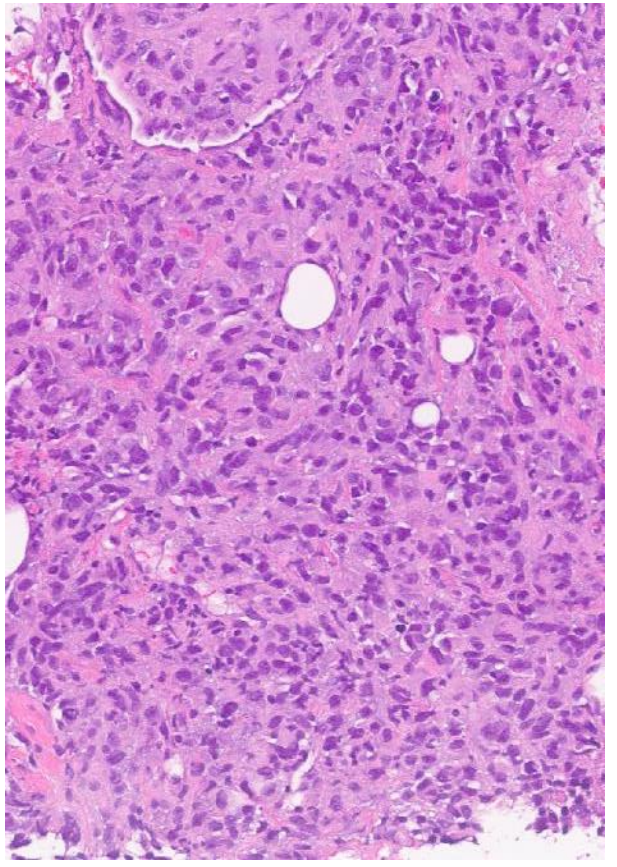




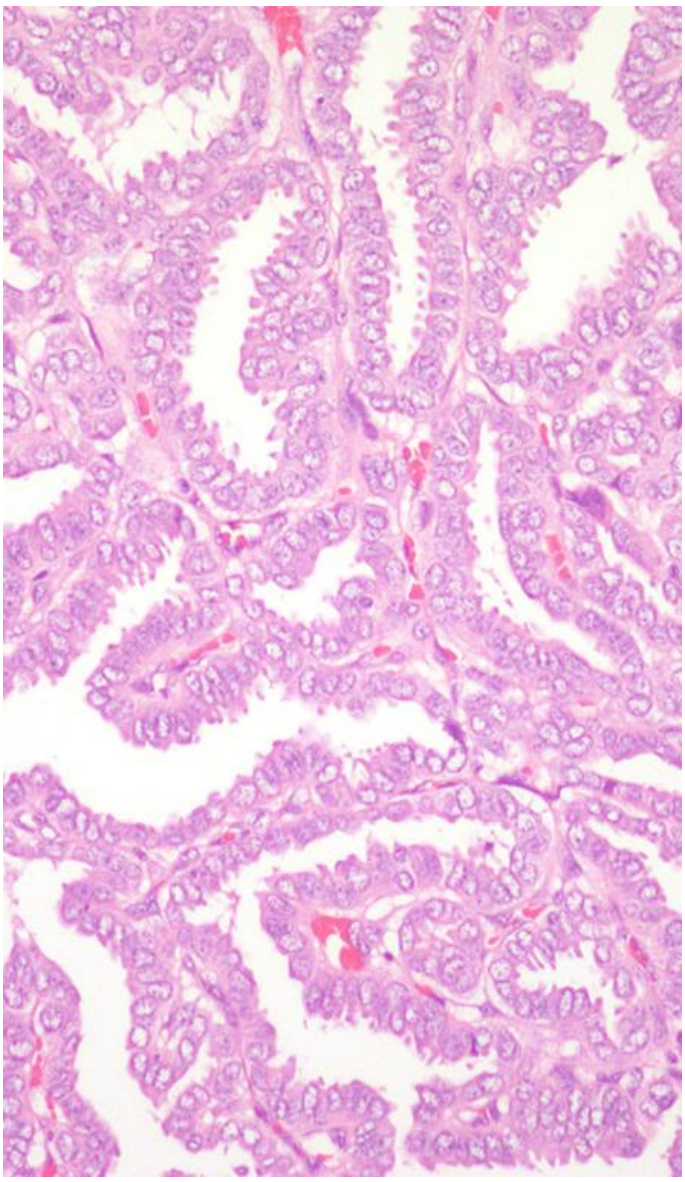


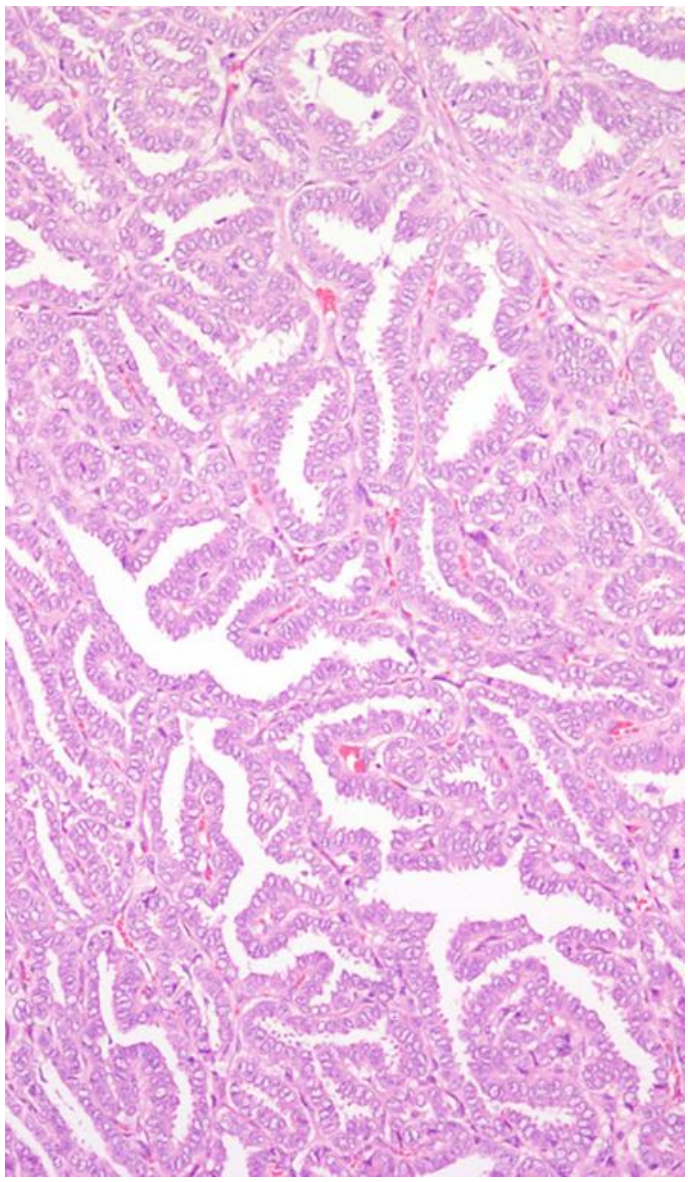
Low Grade Serous Carcinoma, Recurrence

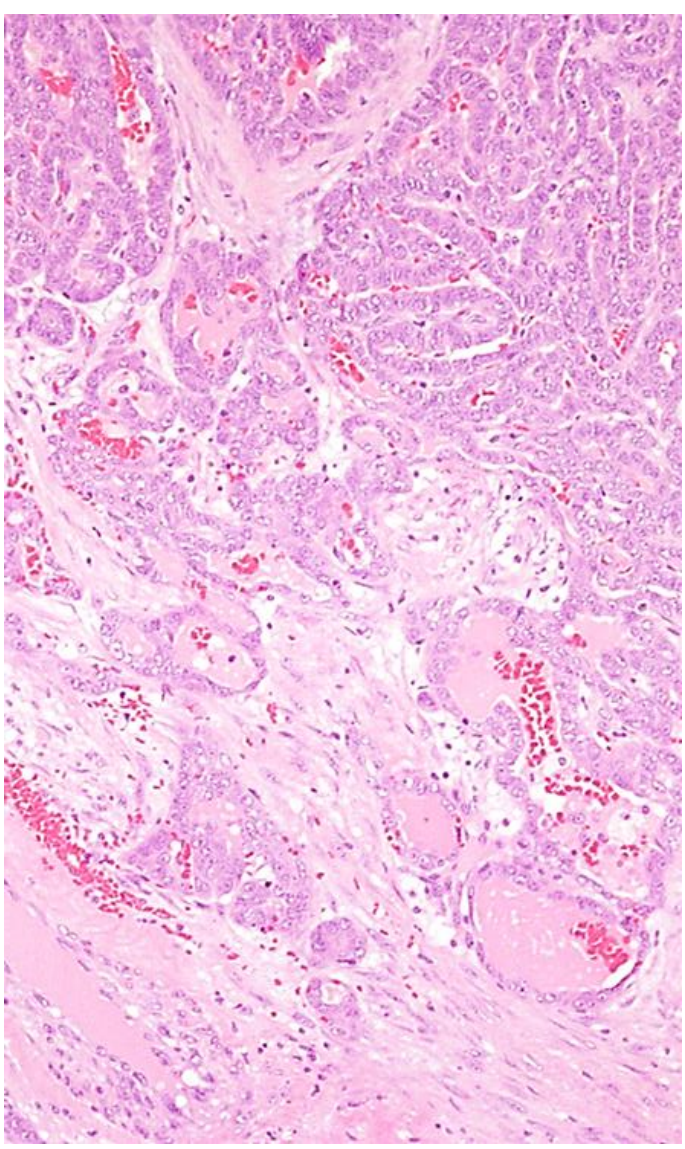
- Usually, as low grade serous carcinoma
- Rare cases as:
  - Sarcomatoid carcinoma, example below (14 years after initial Dx)
  - Undifferentiated carcinoma
  - Mesonephric-like carcinoma
  - Carcinosarcoma

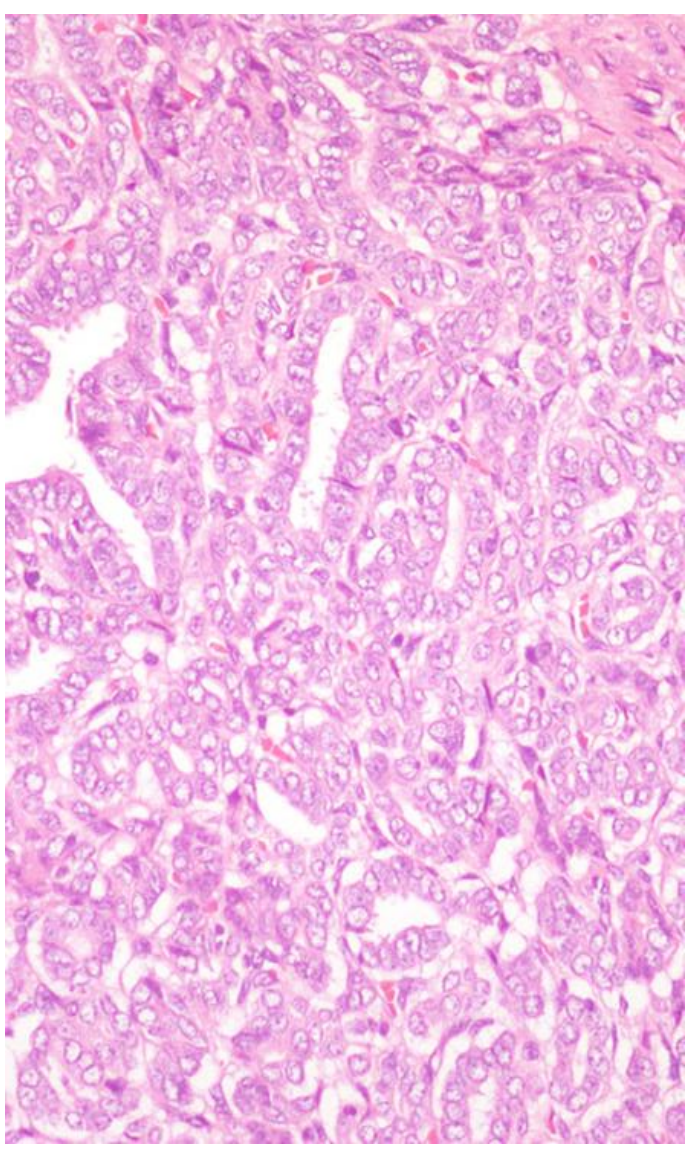





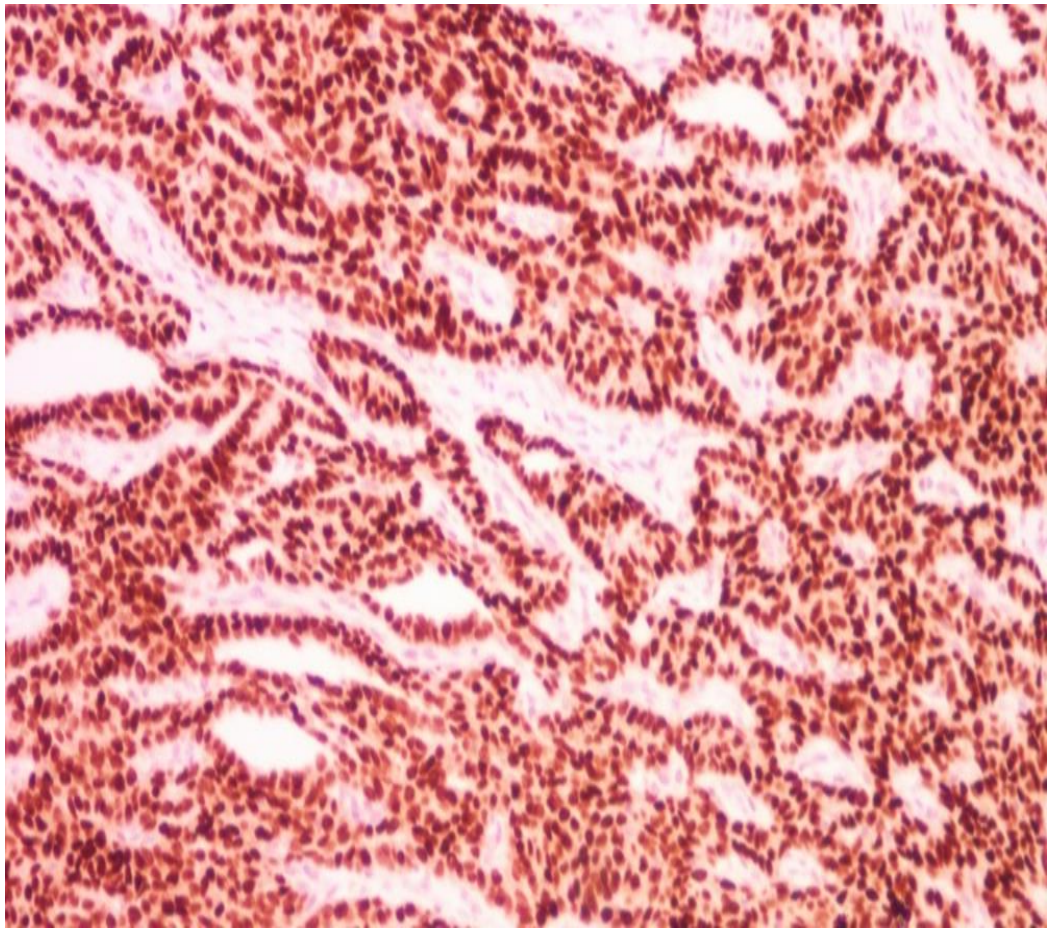
Mesonephric-like Ca after the Dx of LGSCa



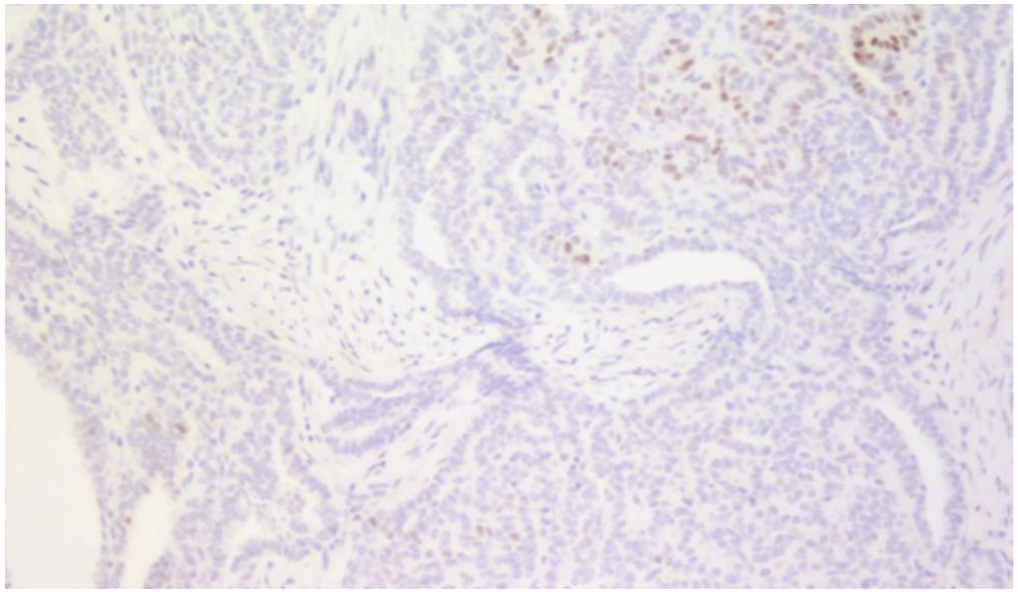




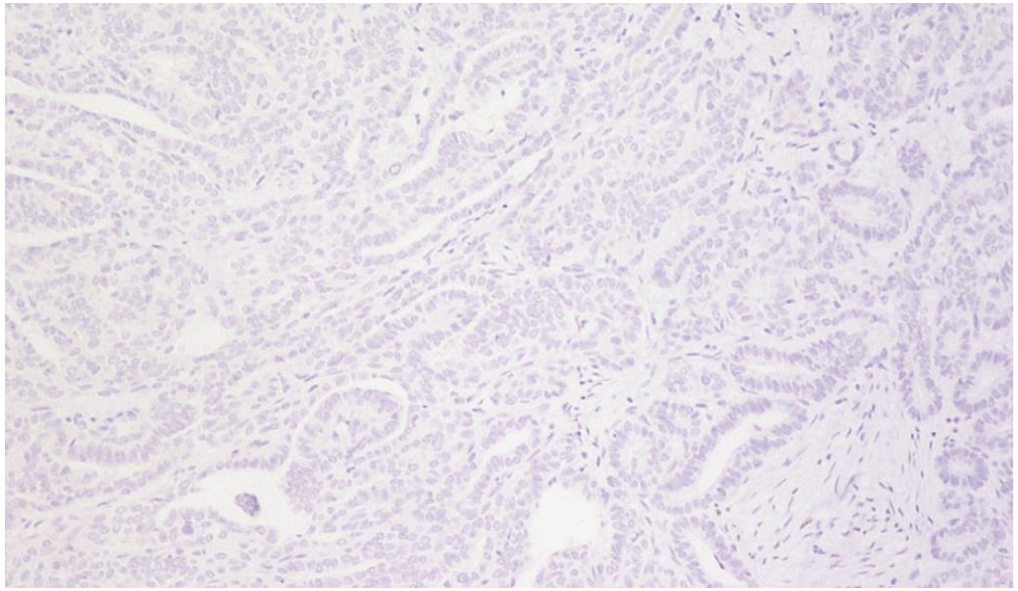




TTF-1+

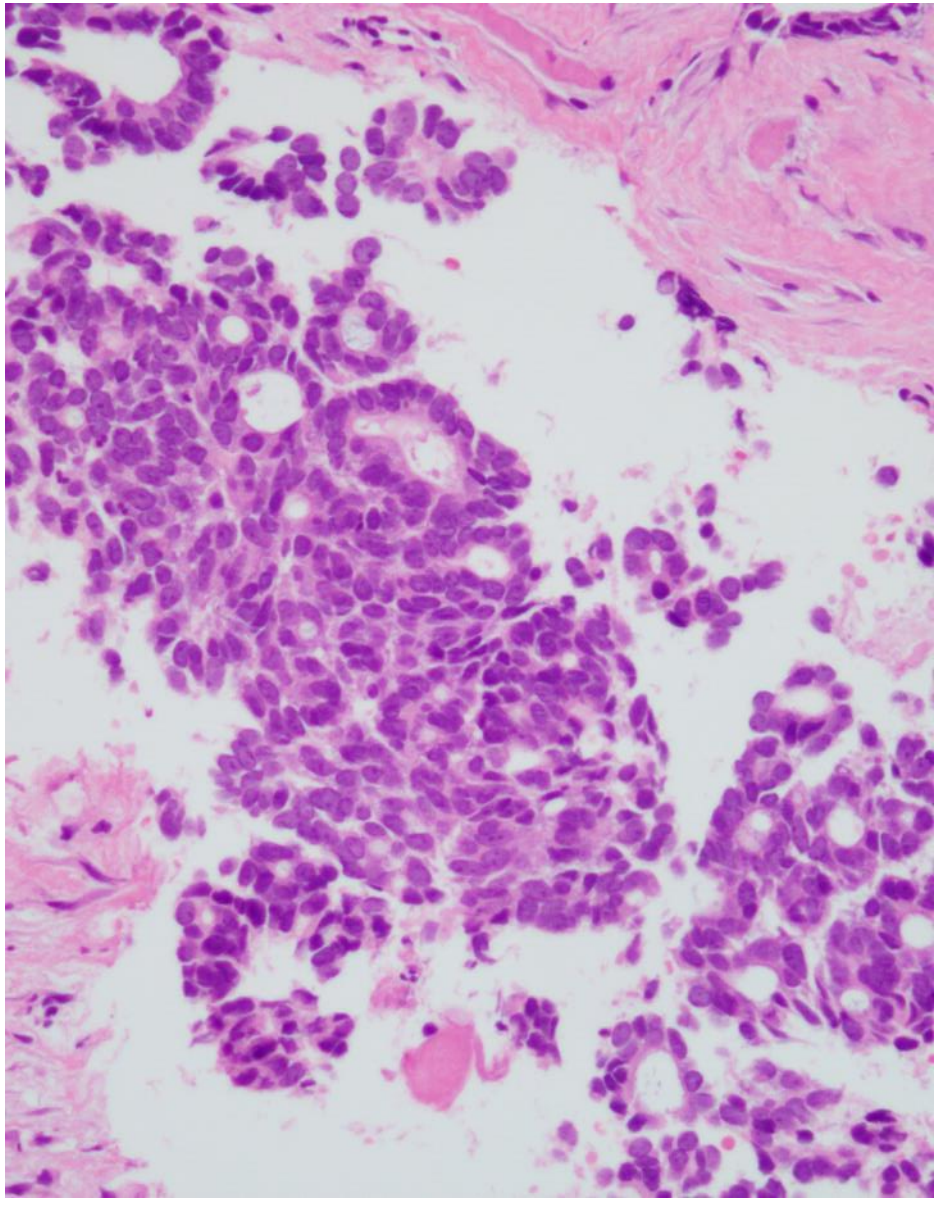


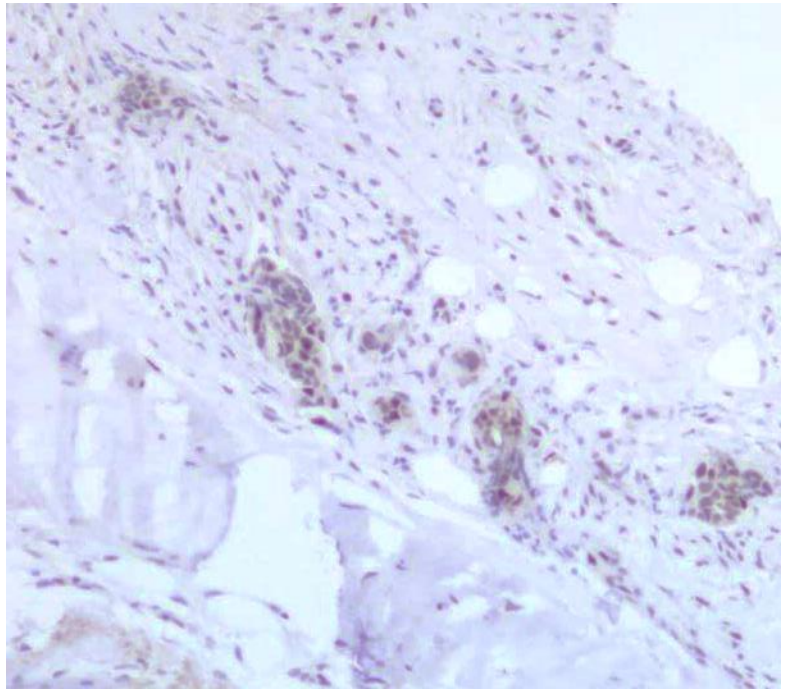
ER/PR rare cells +



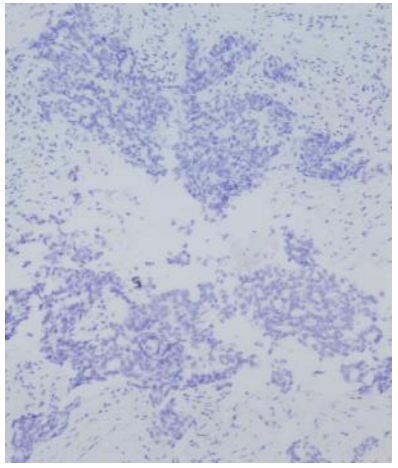
WT-1 -

Mesonephric-like Ca after the Dx of LGSCa, Misinterpreted as High Grade Serous Carcinoma

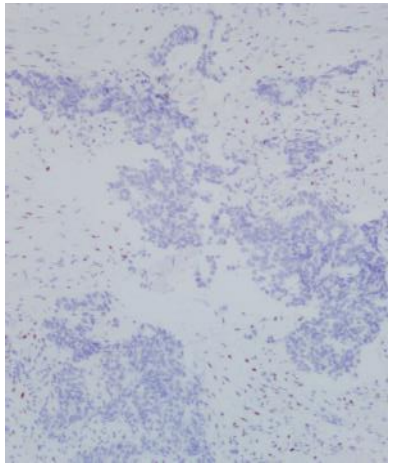




p53, wild type

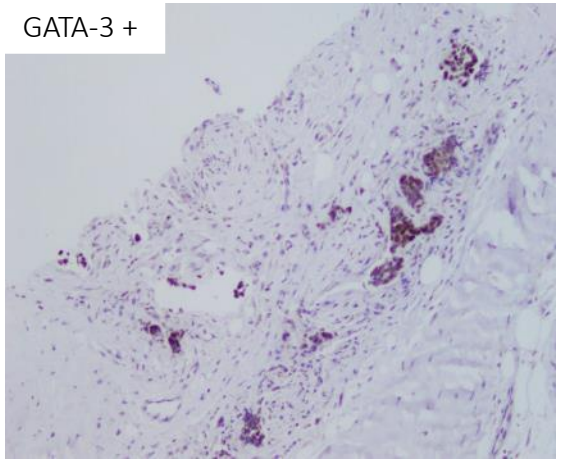


ER, -

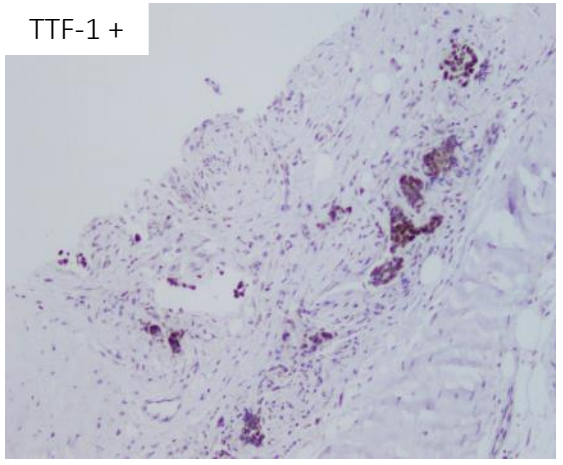


PR, -

GATA-3 +



TTF-1 +



Low Grade Serous Carcinoma, Rare Associations

Ovarian Primary

- Germline mutations:
  - *BRCA1/2*
  - *MUTYH*
  - *BAP1*
  - *RB1*
  - *CHEK2*
  - *APC*
  - *FANCA*
- Rubinstein-Taybi syndrome

Peritoneal Primary

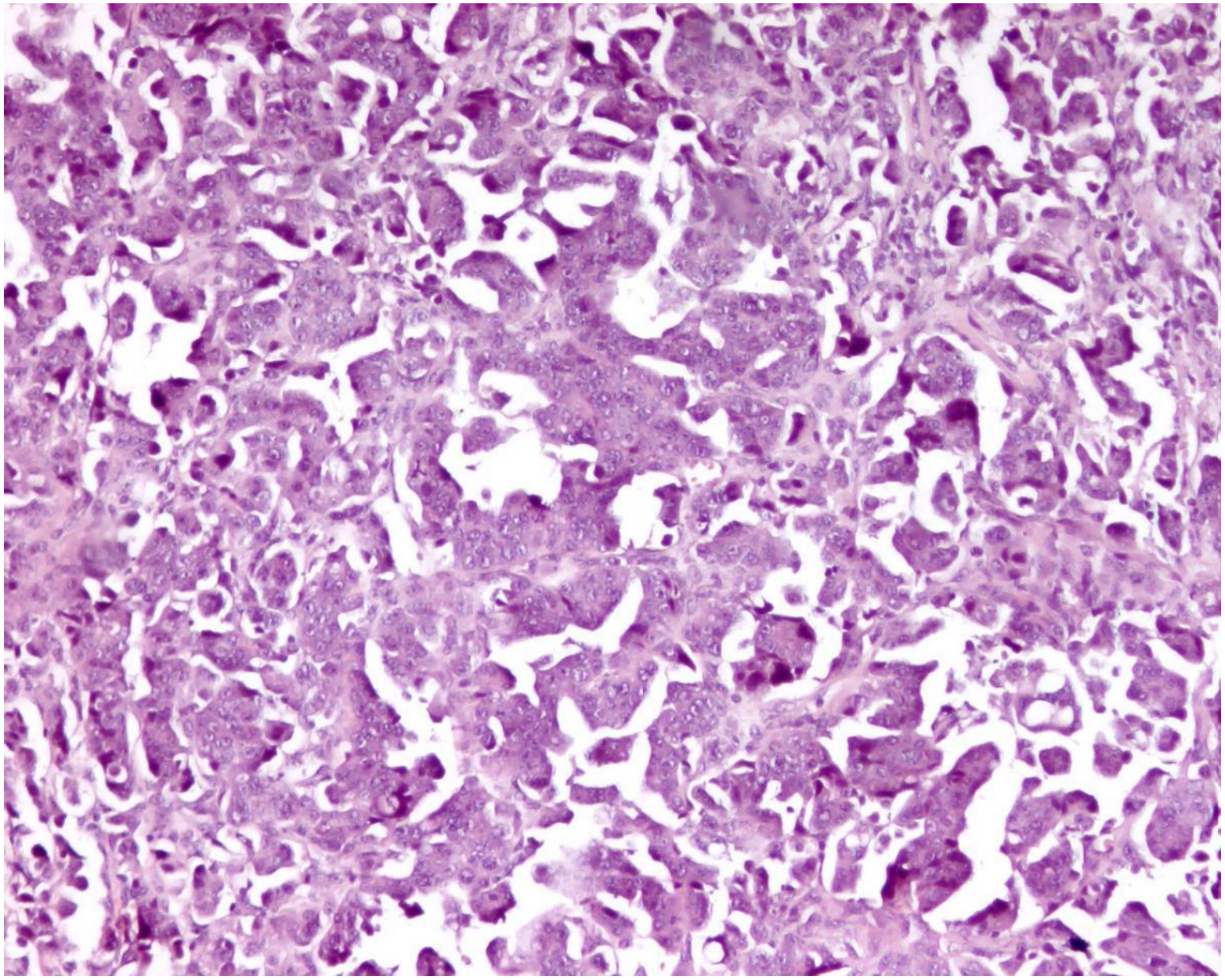
- *BRCA1* mutation
- Lynch syndrome
- *PALB2* mutation

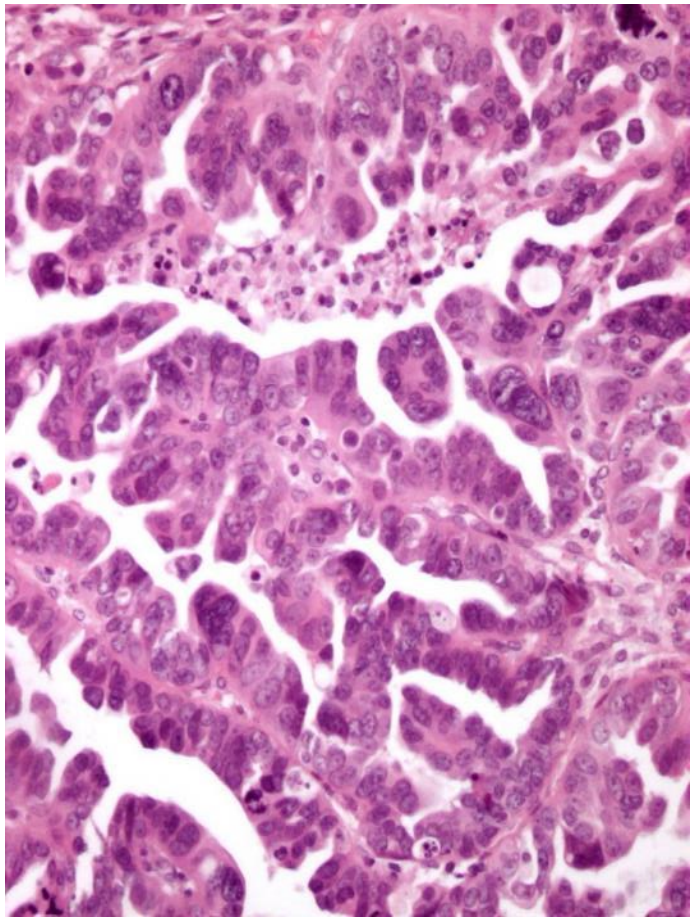
Low-Grade Serous Carcinoma, Molecular Findings

- MAPK pathway mutations in ≈ 60% of the cases:
  - *KRAS* (19%-40%), *NRAS* (9-26%), and *BRAF* (2%-16%)
    - Rare*, HRAS, NF1, NF2, MAP3K1, and ERBB2*
- Other mutations*: USP9X, E1F1AX, MACF1, ARID1A, DOT1L, ASH1L, UBR5, PIK3CA, FFAR1,* and *DNM3*

*potential use of mTOR inhibitors

High Grade Serous Carcinoma



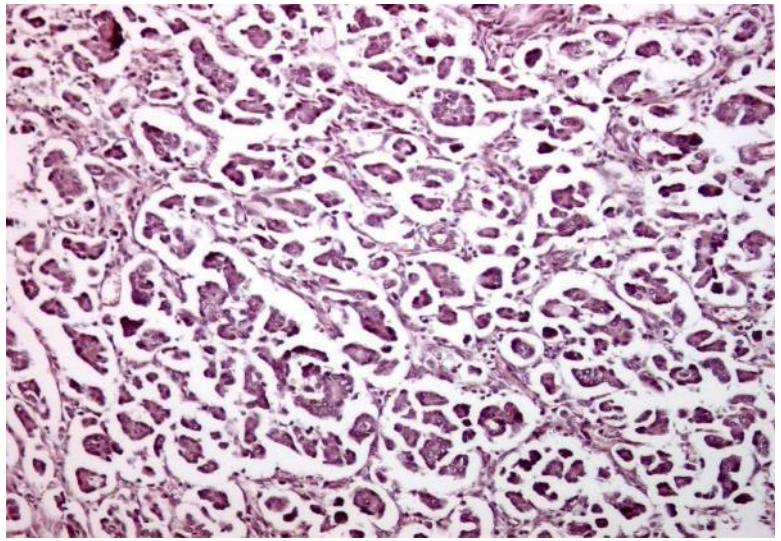


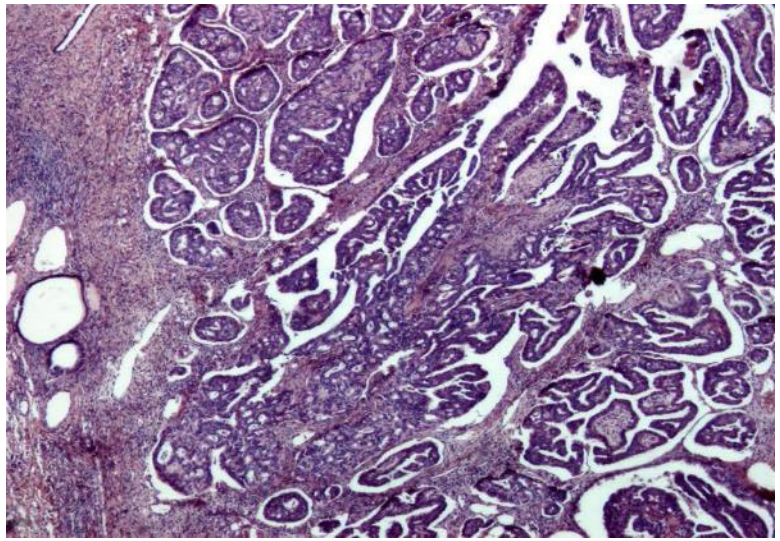
Pleomorphic cells with marked nuclear atypia (≥3:1 variation in size and shape)
High mitotic index (>12 mitoses per 10 HPFs)

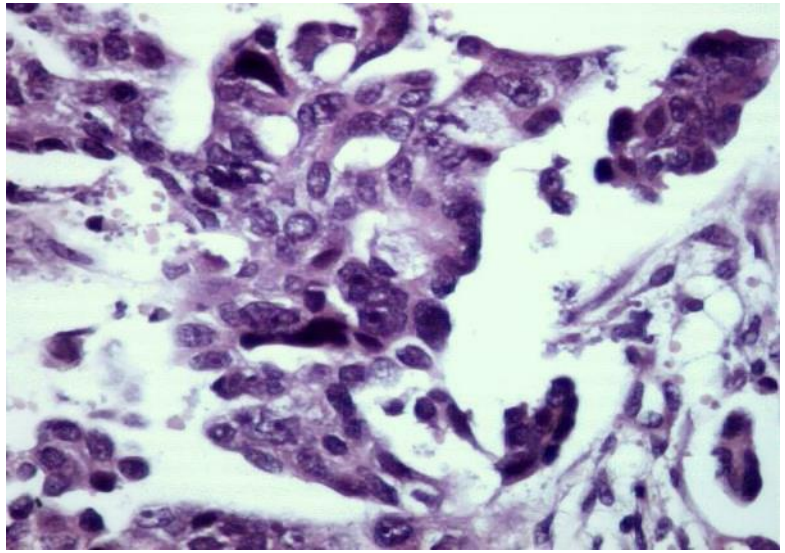
High Grade Serous Ca, Issues

- Using the architecture and not paying attention to the cytology to assign the grade
- Tumor heterogeneity
- A wide variety of patterns and appearances
- Recurrence has a different histotype
  - Carcinosarcoma -–undersampling vs. lack of recognition vs. dedifferentiation
  - Sarcoma –undersampling vs. lack of recognition vs. dedifferentiation
  - Neuroendocrine Ca – lack of recognition

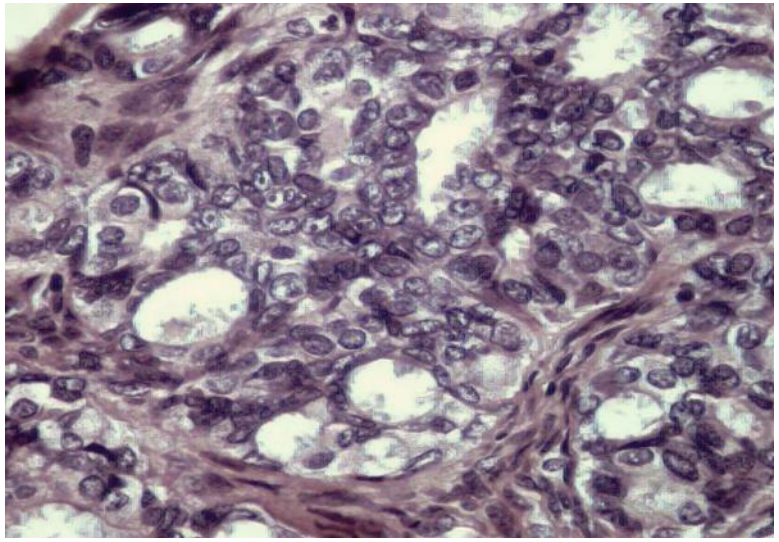
Pathologist does not follow diagnostic criteria





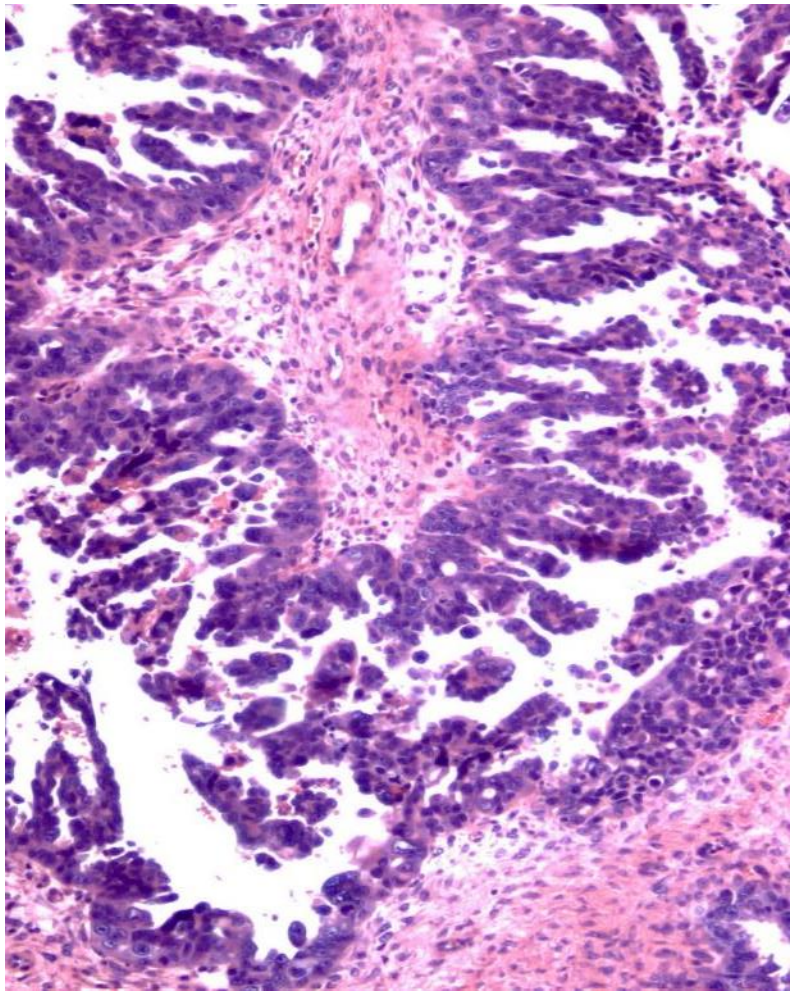


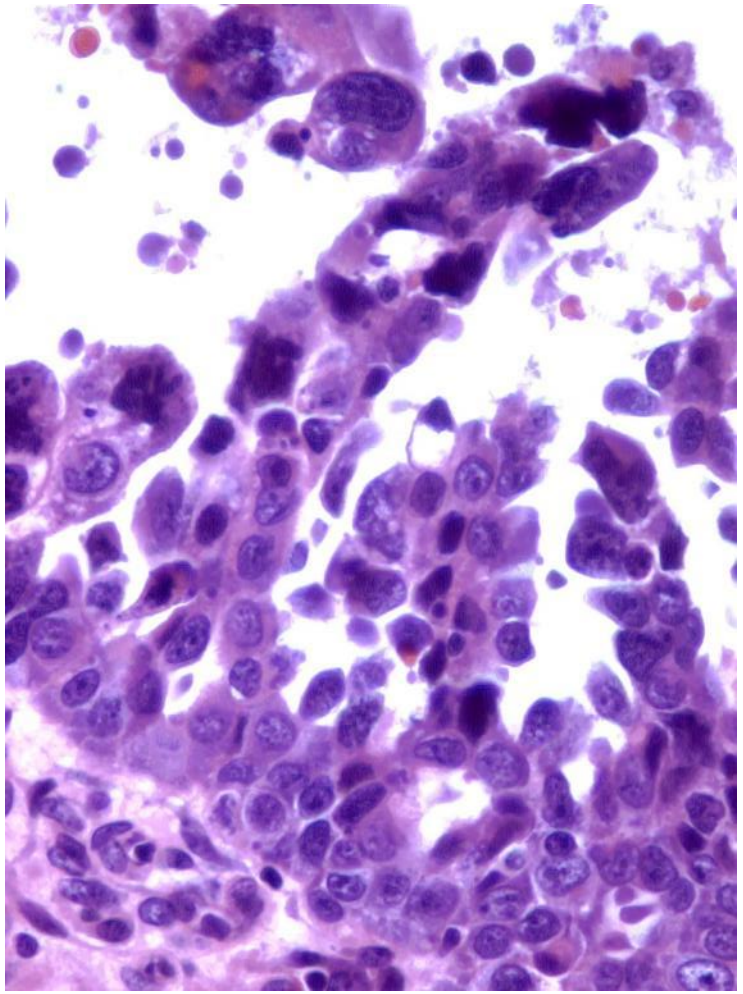
High grade serous Ca, interpreted as low grade

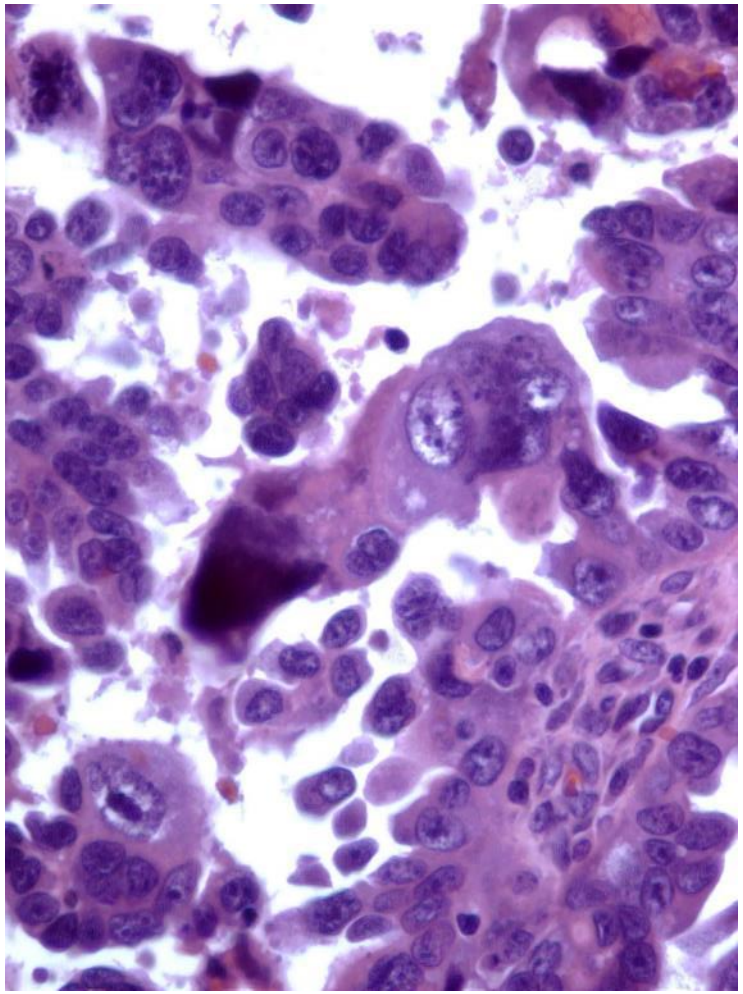


Low grade serous Ca, interpreted as high grade

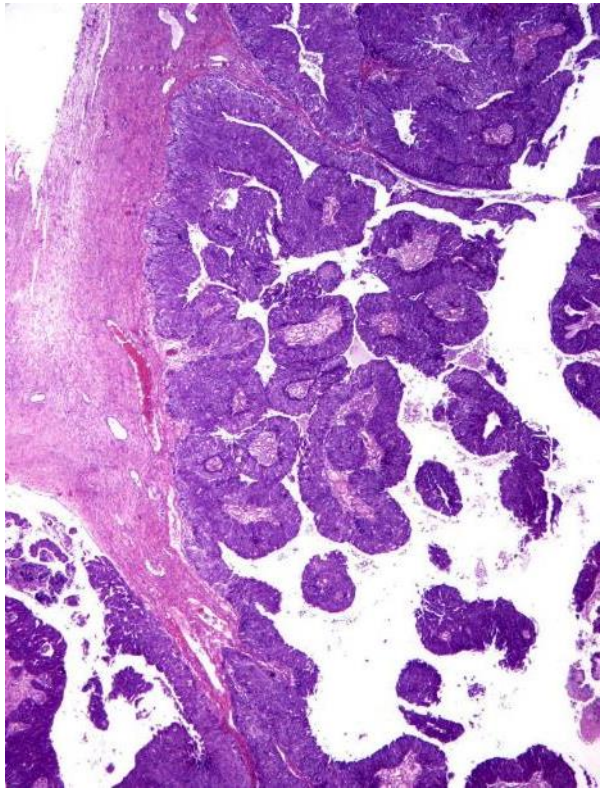
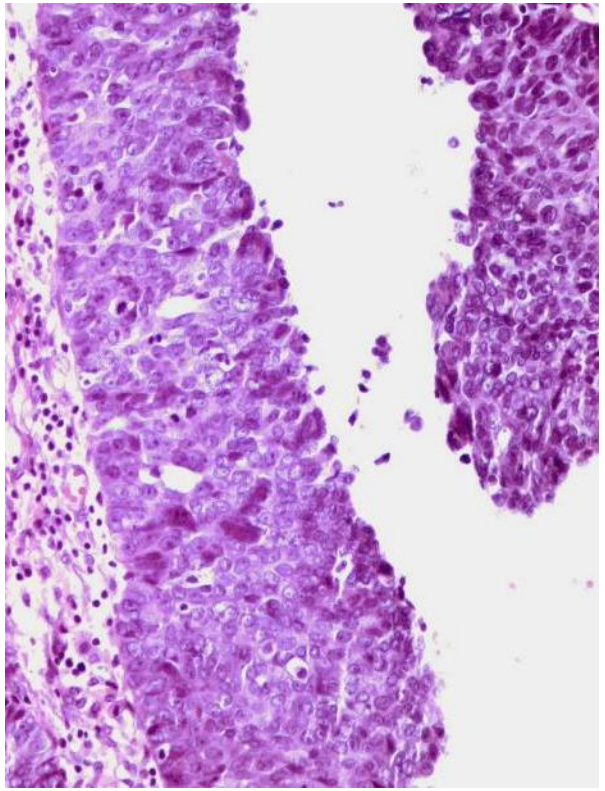
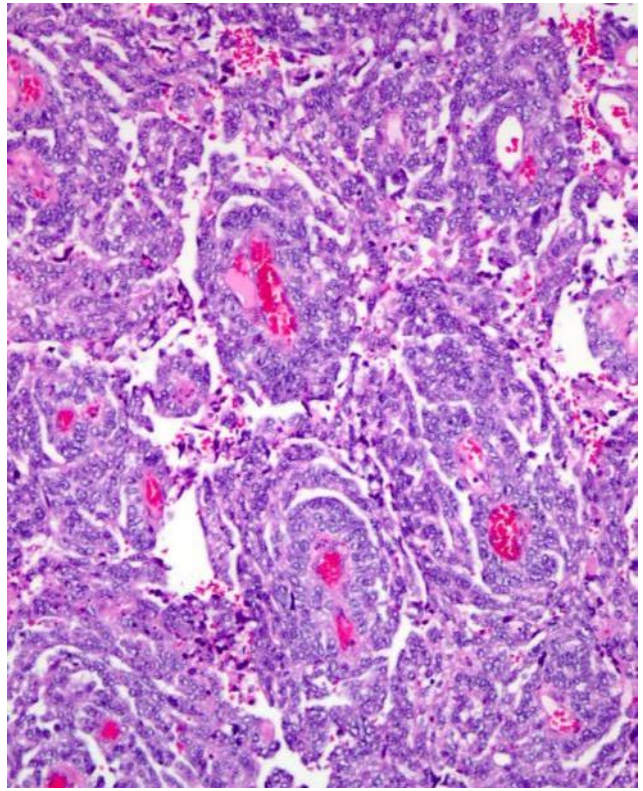
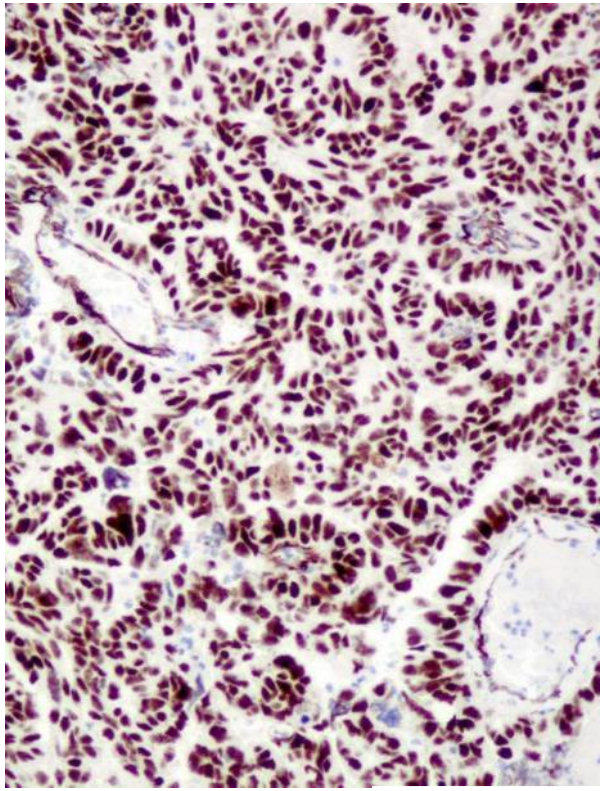
High Grade Serous Ca, Papillary Pattern, Mimicking a Serous Borderline Tumor with a MP







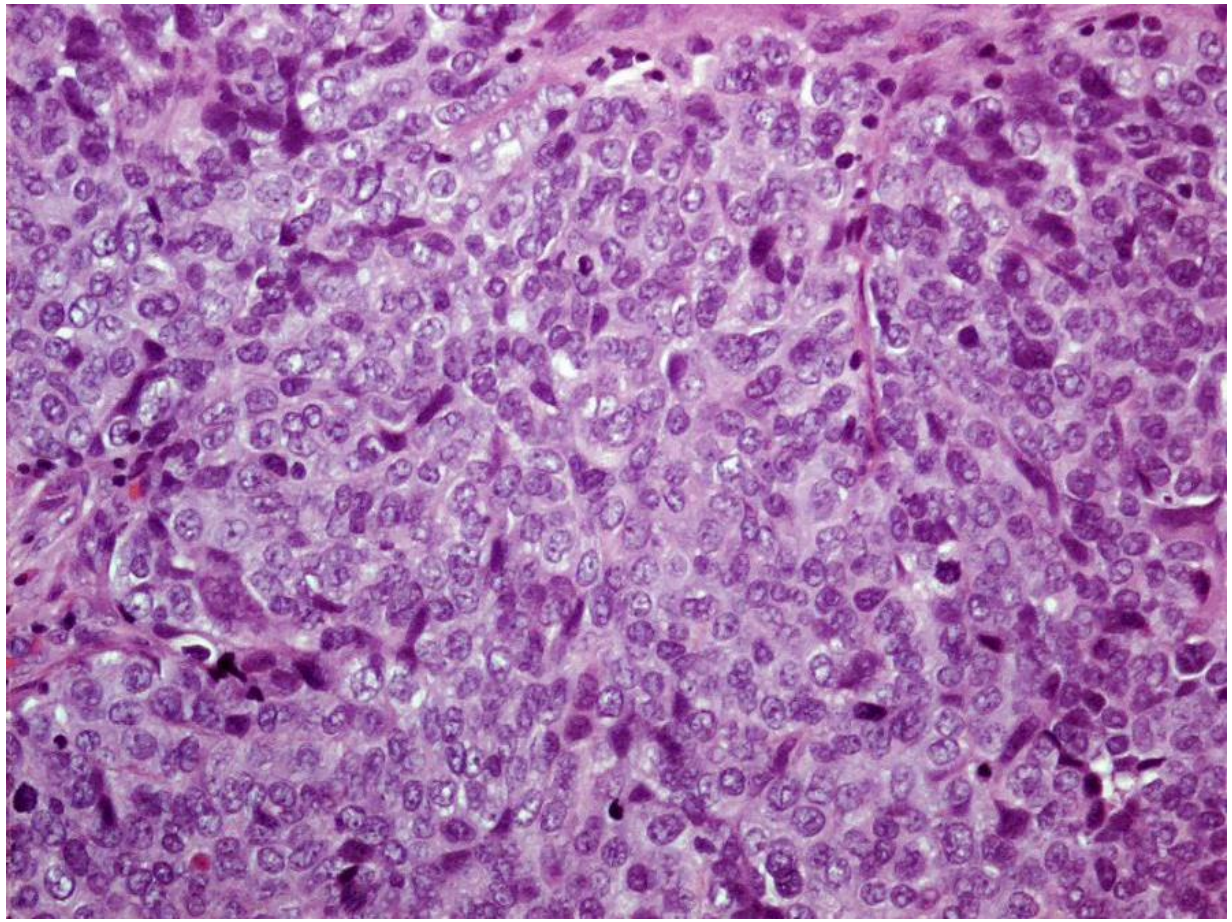
High Grade Serous Ca, Broad Base Papillae (TCC Pattern) and Papillae with Prominent Vessels

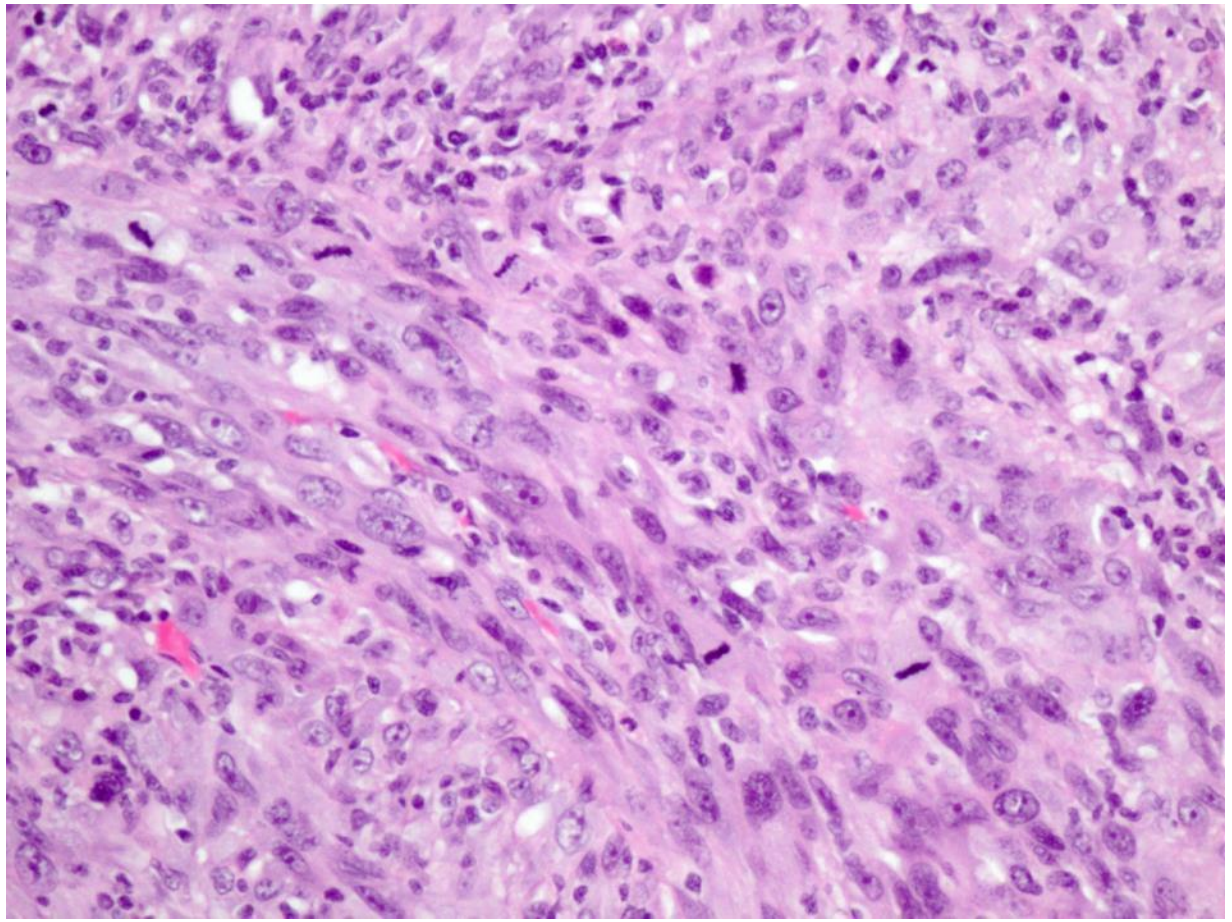
WT-1+

High Grade Serous Ca

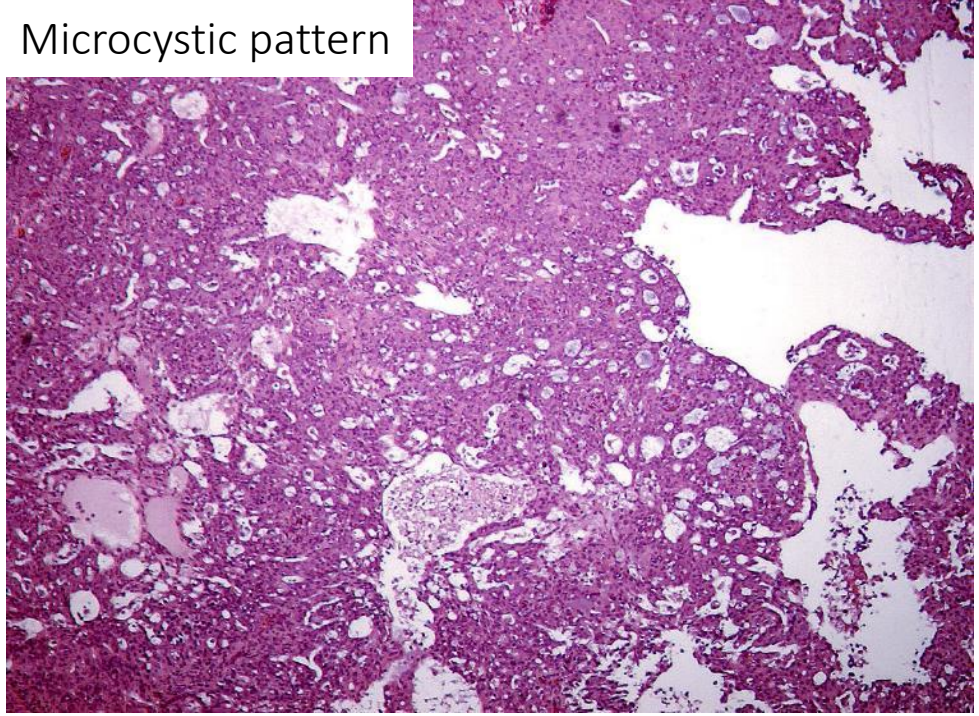
Solid pattern



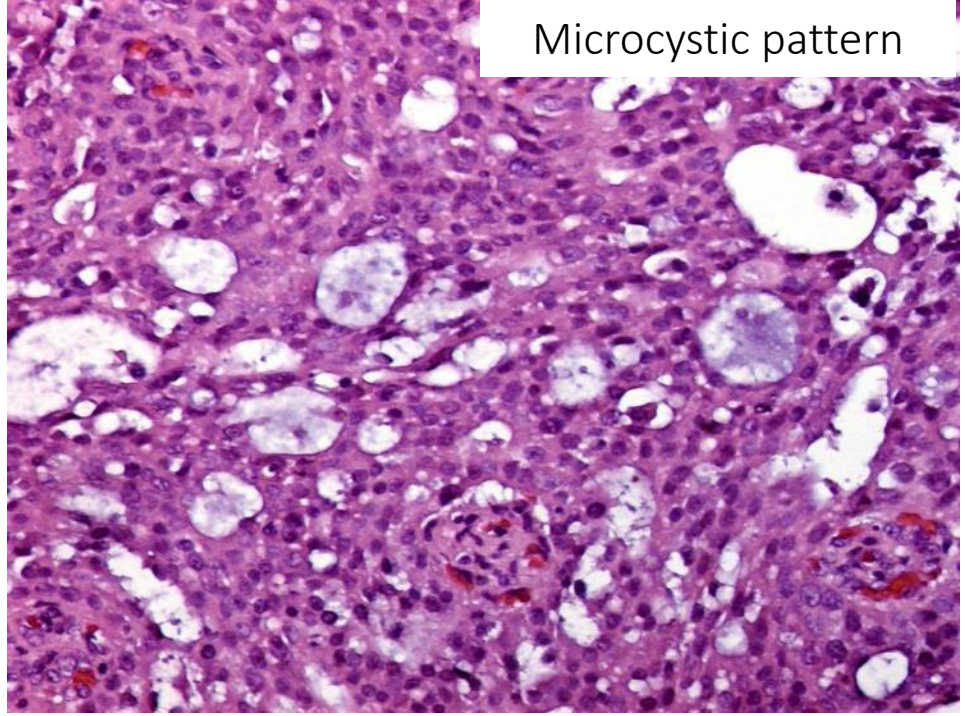
Spindle cells



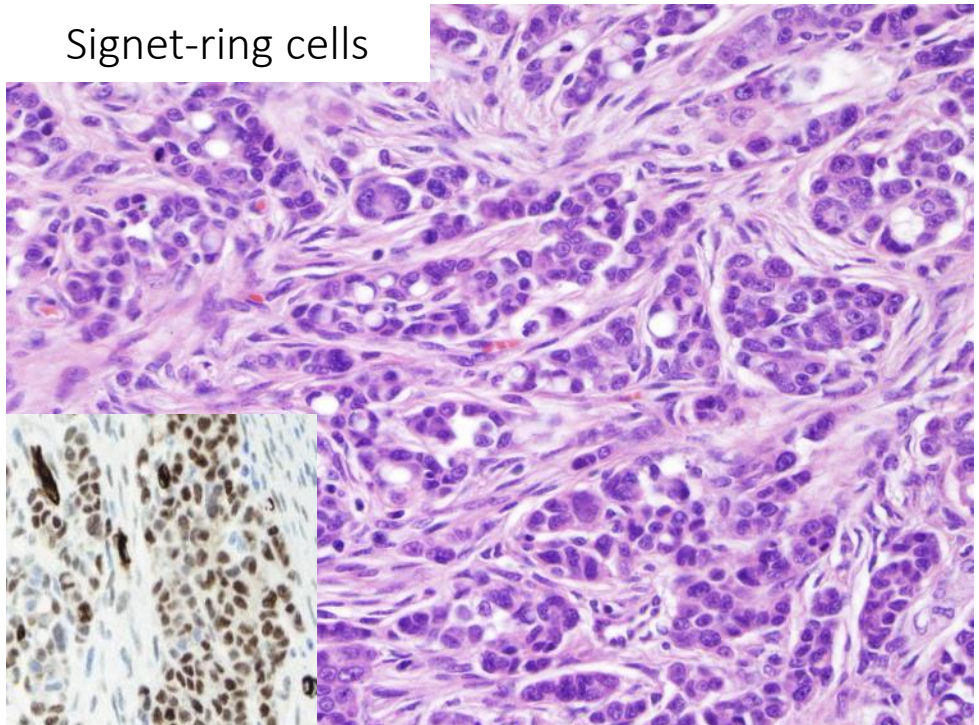
Microcystic pattern



Microcystic pattern

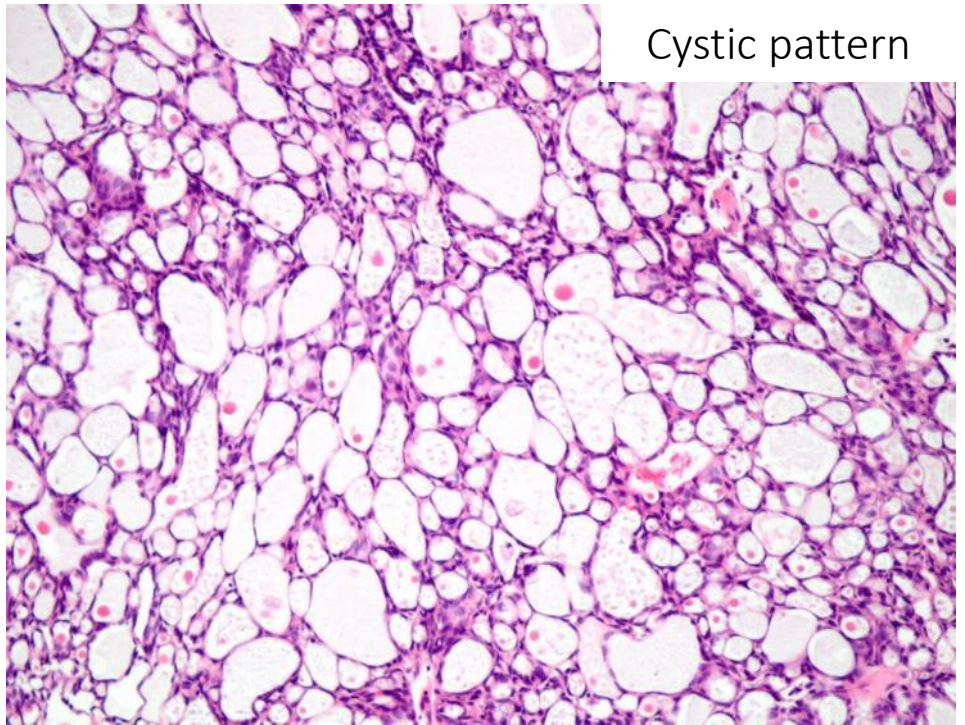


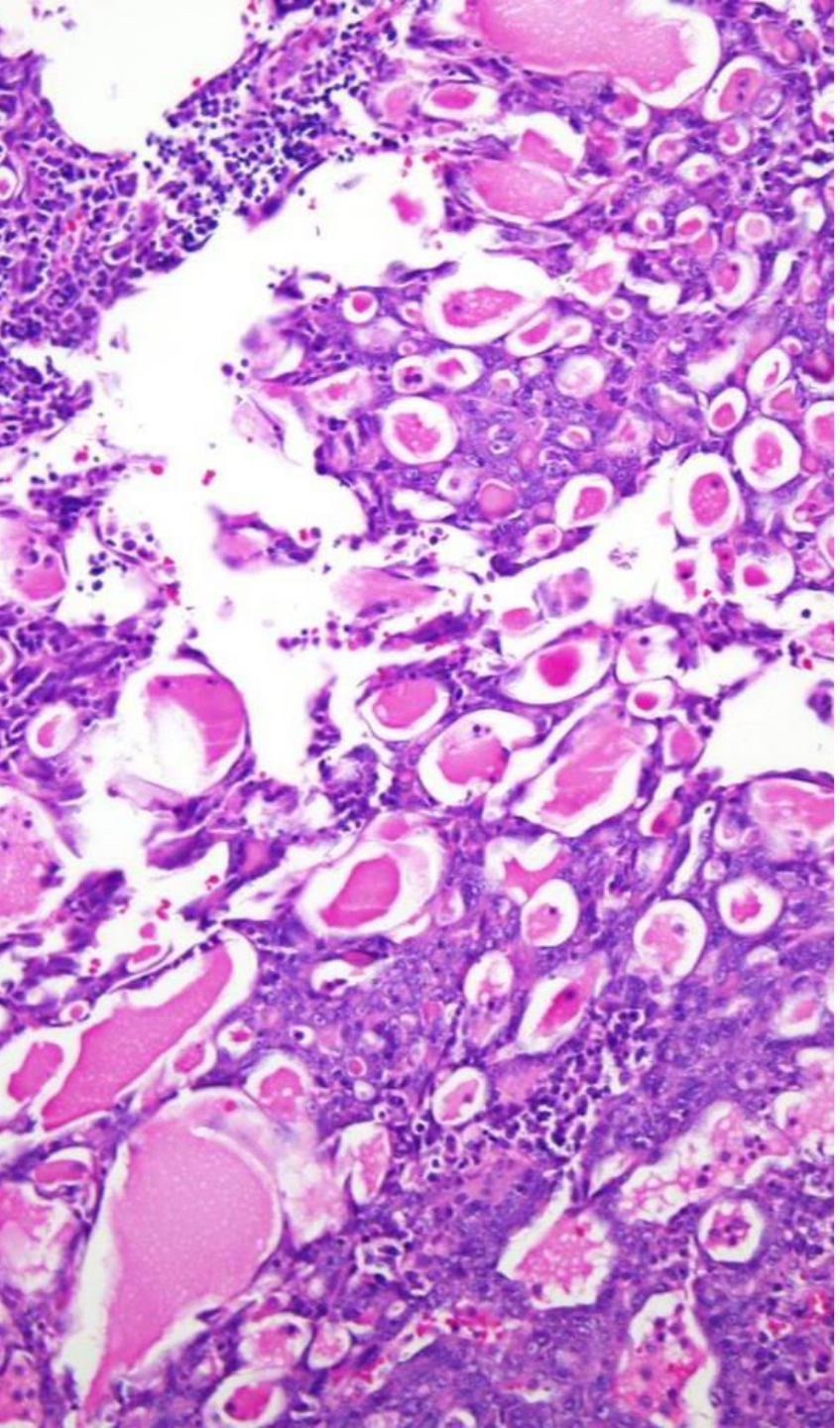
Signet-ring cells

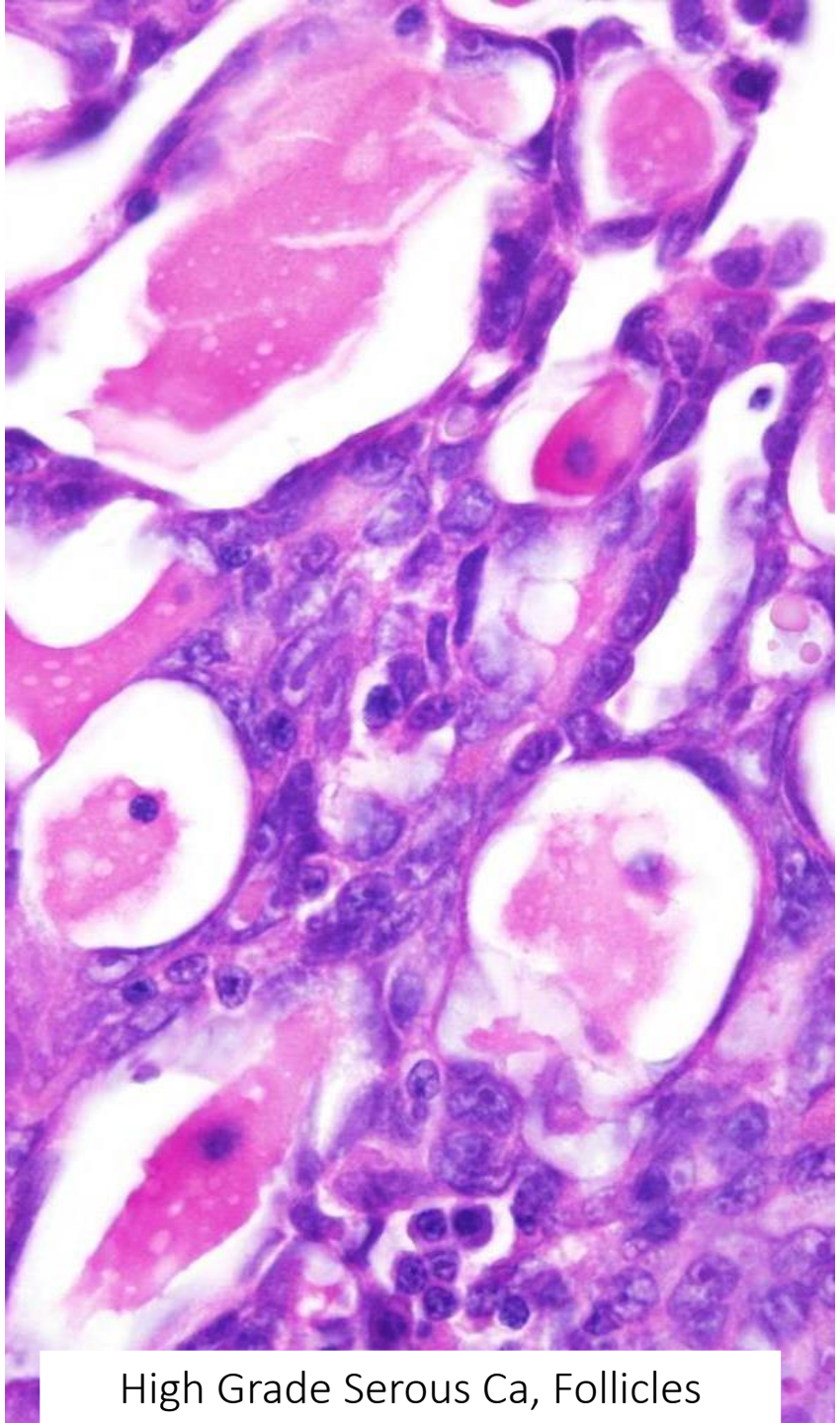


WT-1+

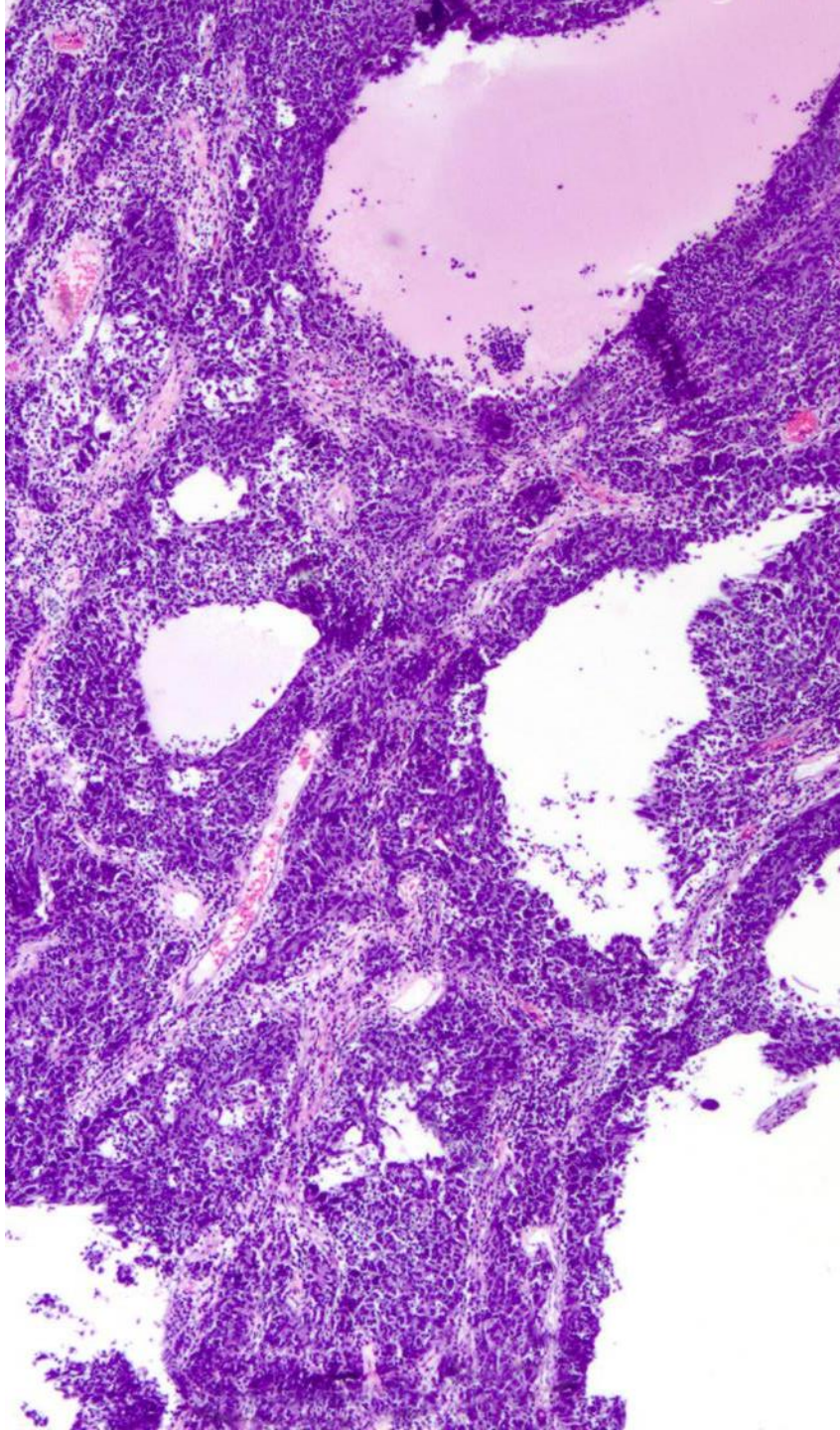
Cystic pattern



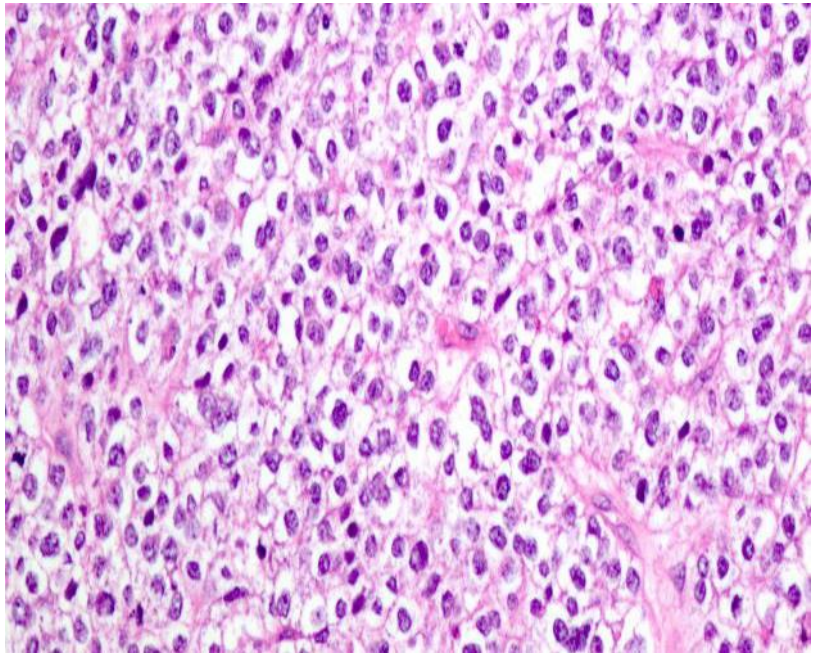


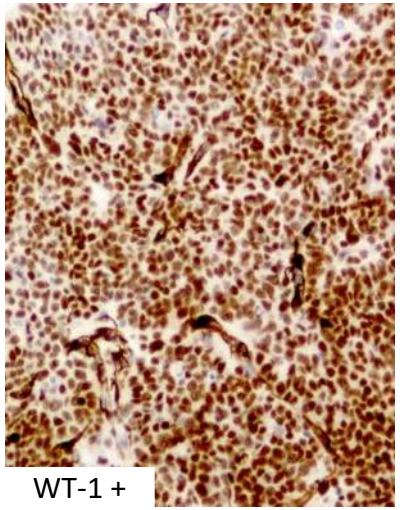


High Grade Serous Ca, Follicles

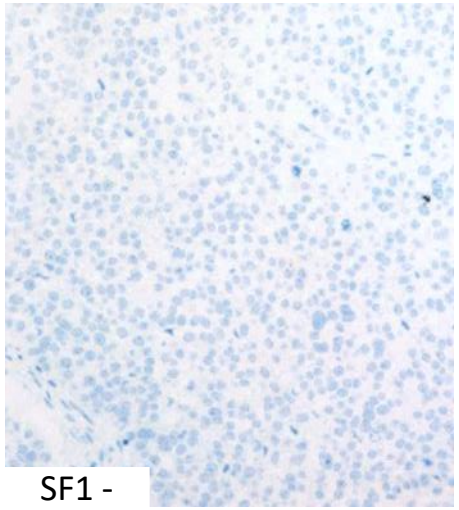


High Grade Serous Ca

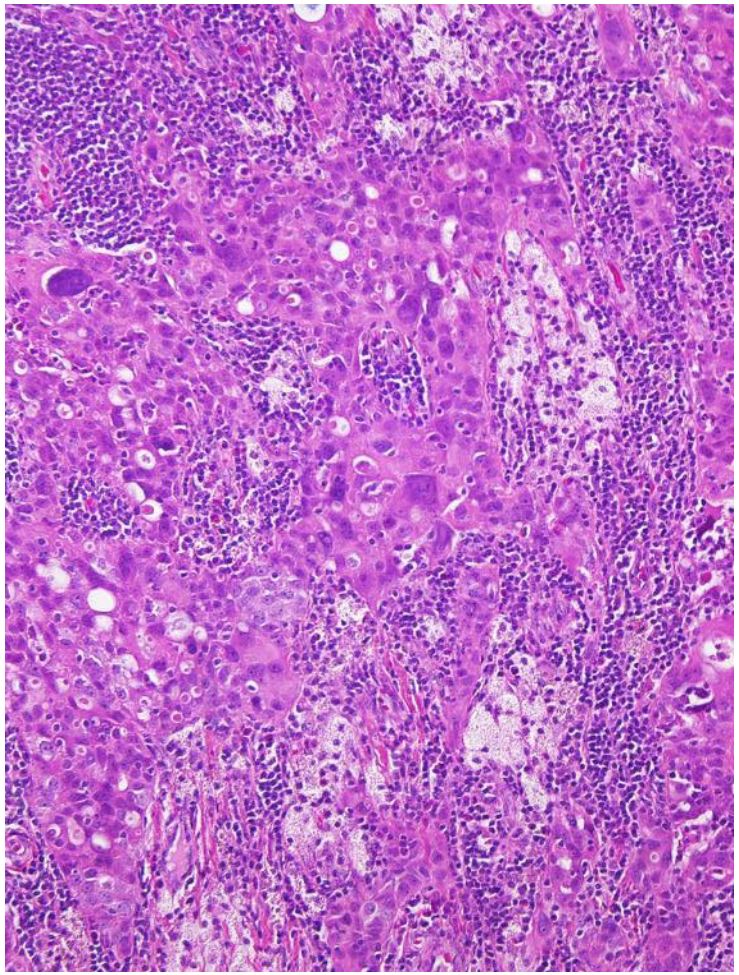




WT-1 +

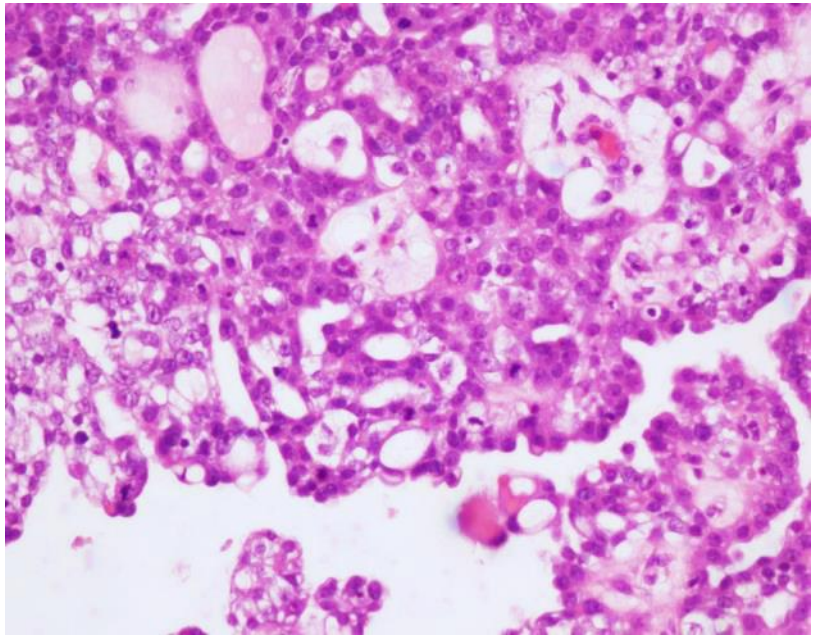


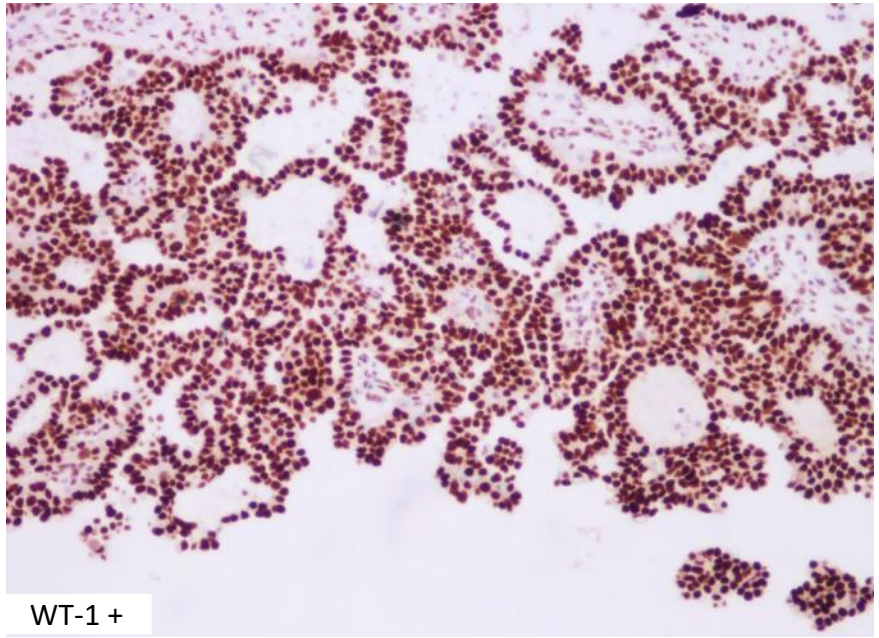
SF1 -



Adenosquamoid appearance

Clear cells





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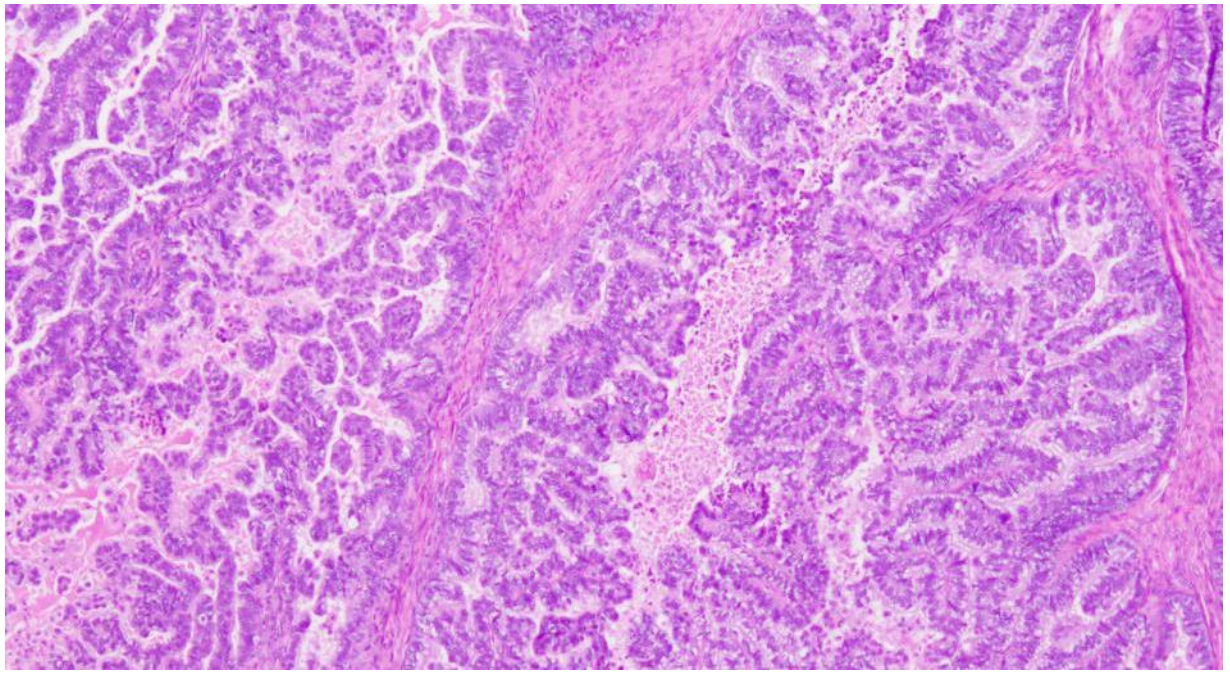
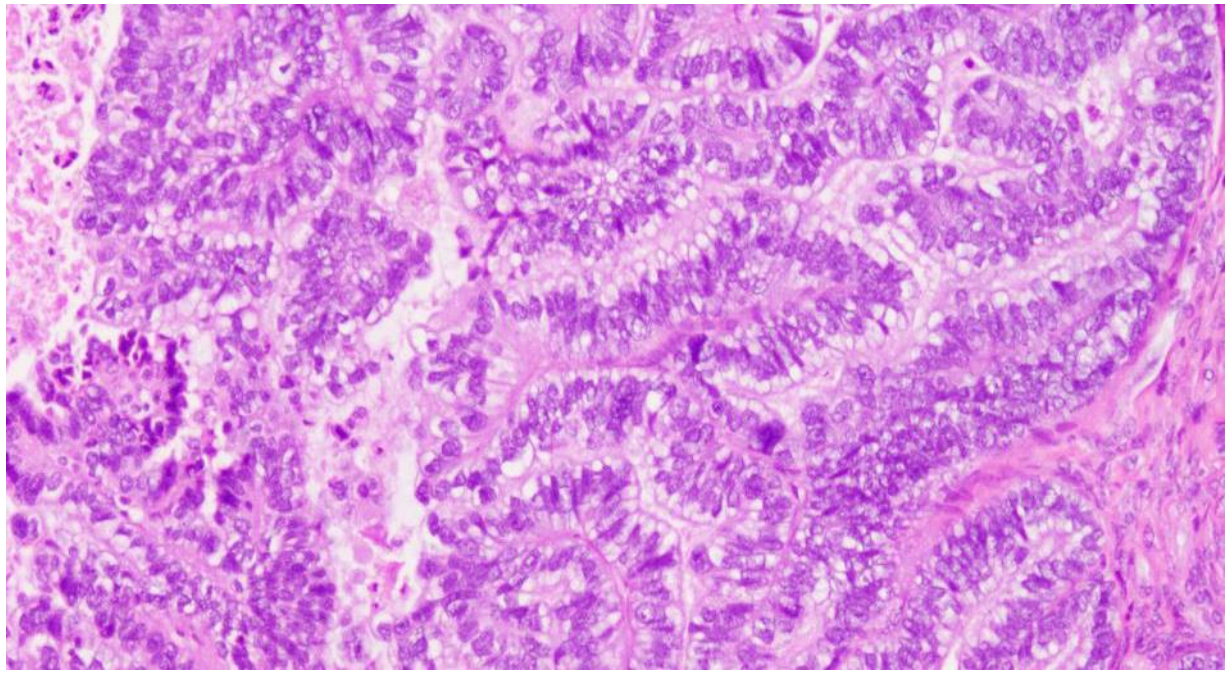
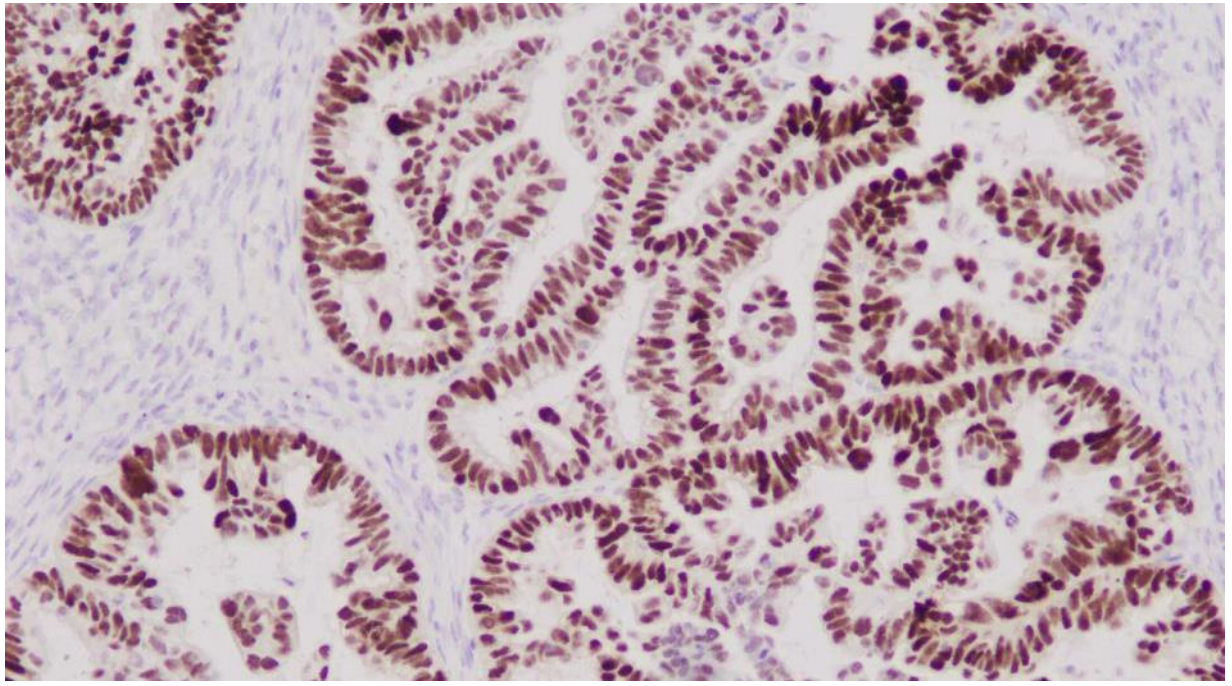
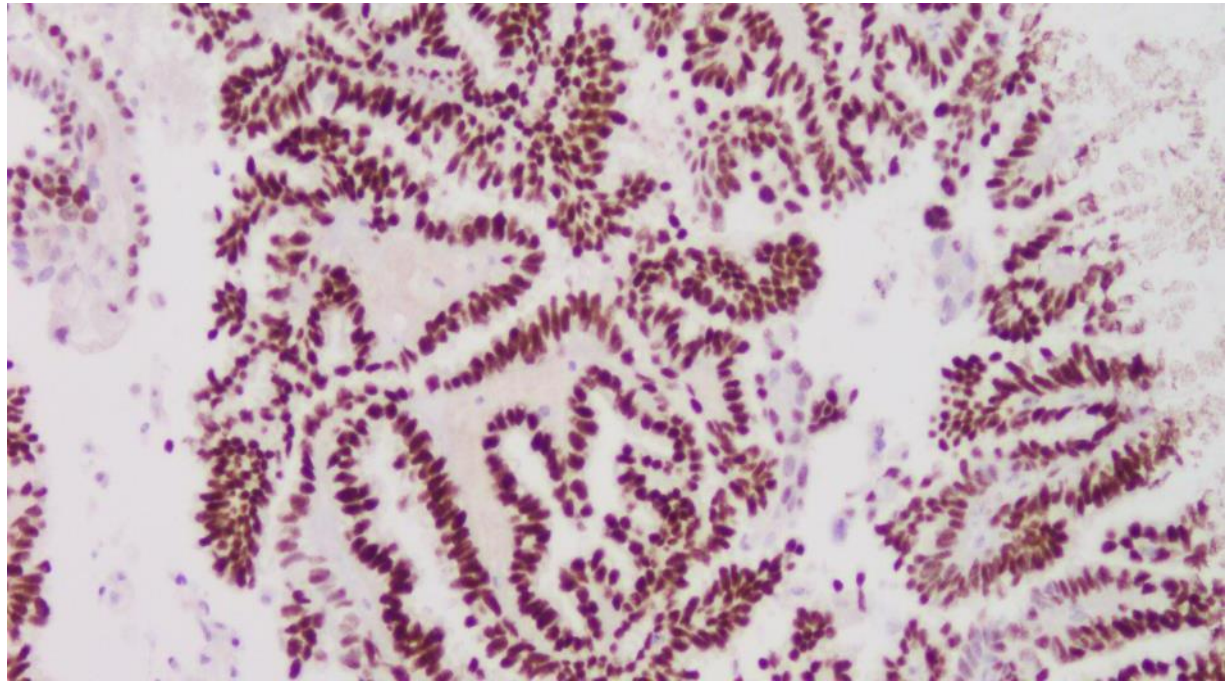




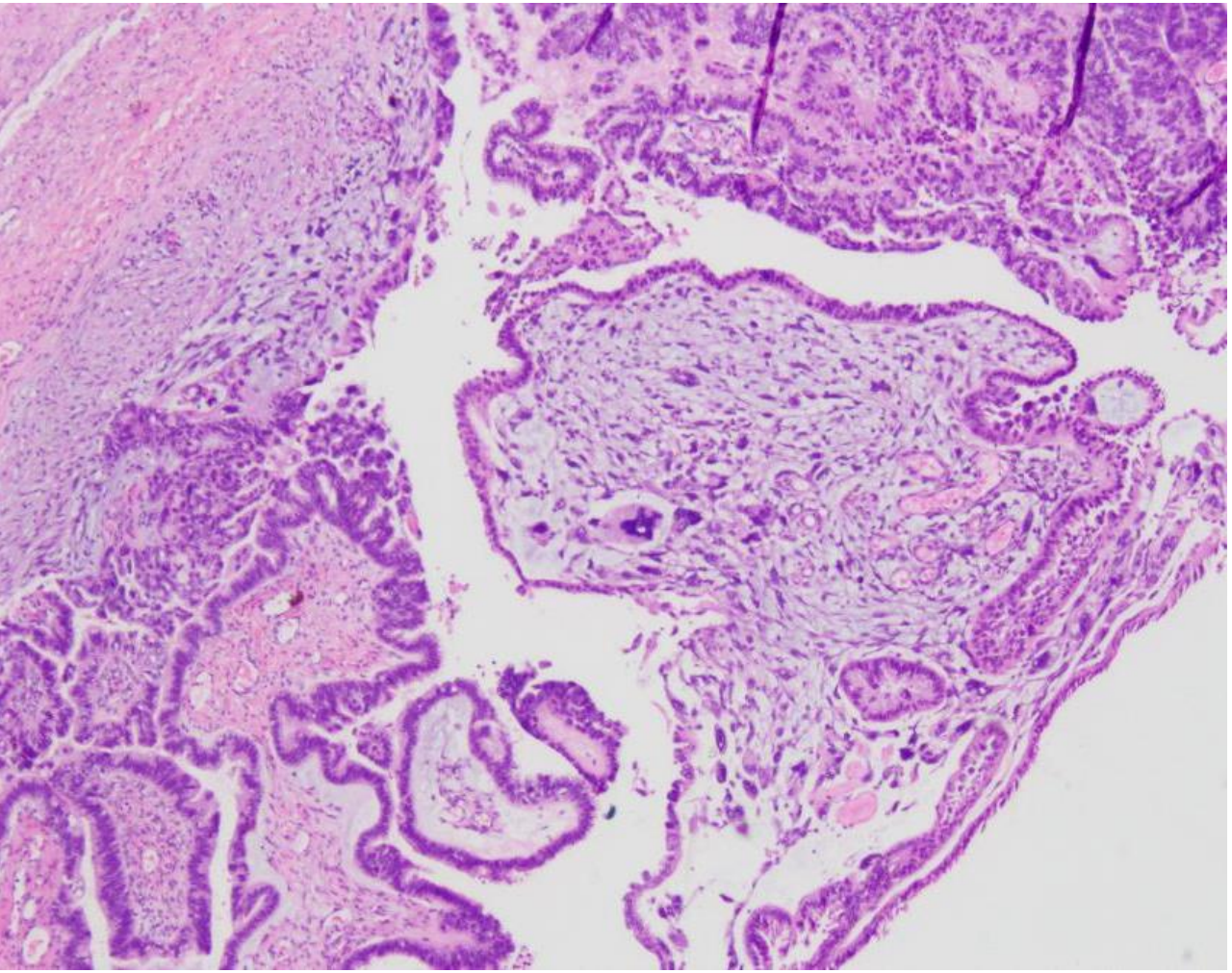


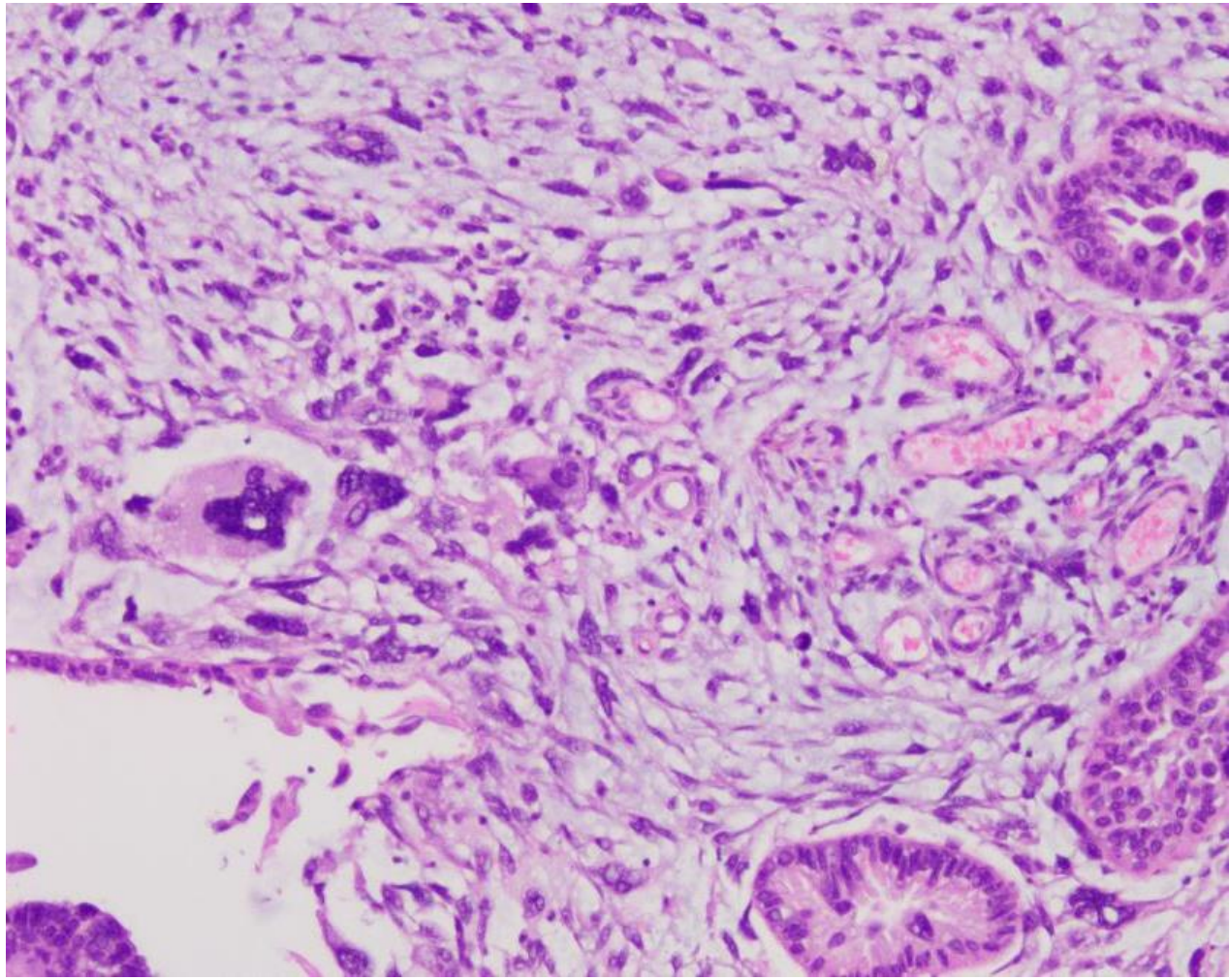
PAX-8 +



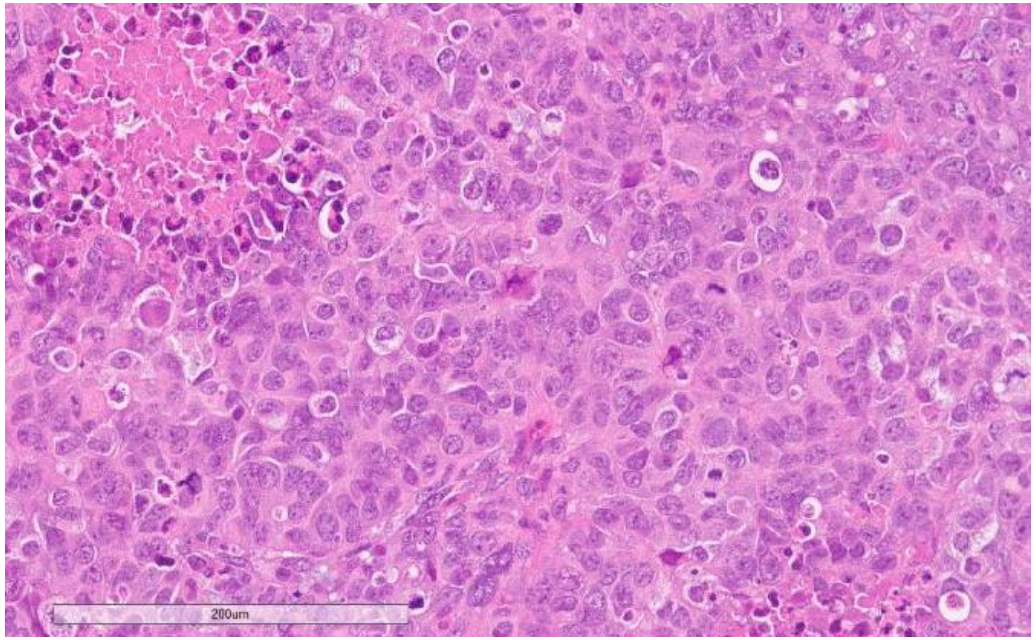
WT-1 +

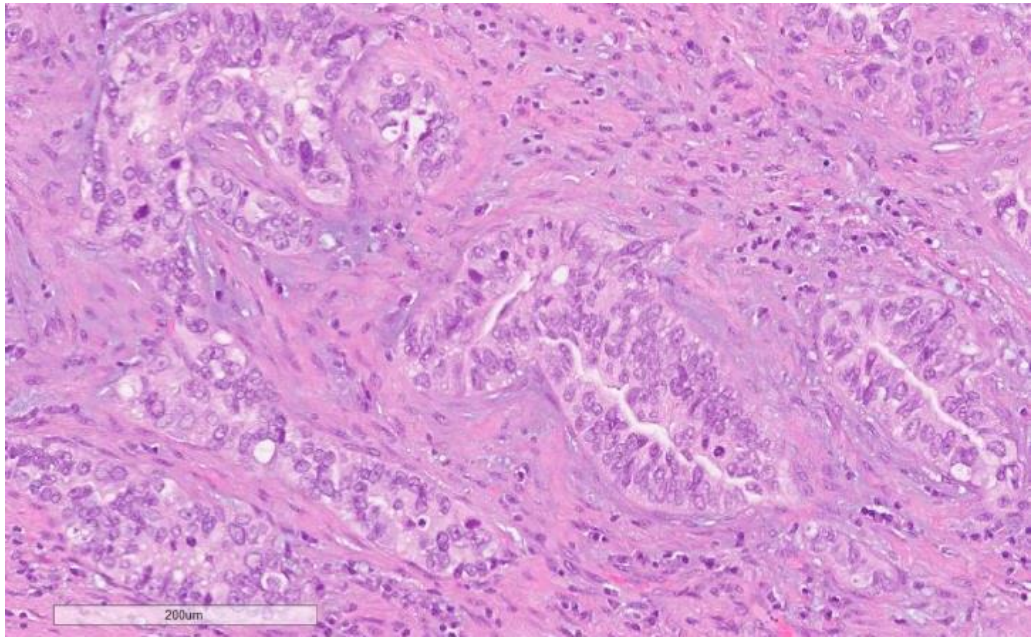
Carcinosarcoma, Initially Interpreted as HGSCa

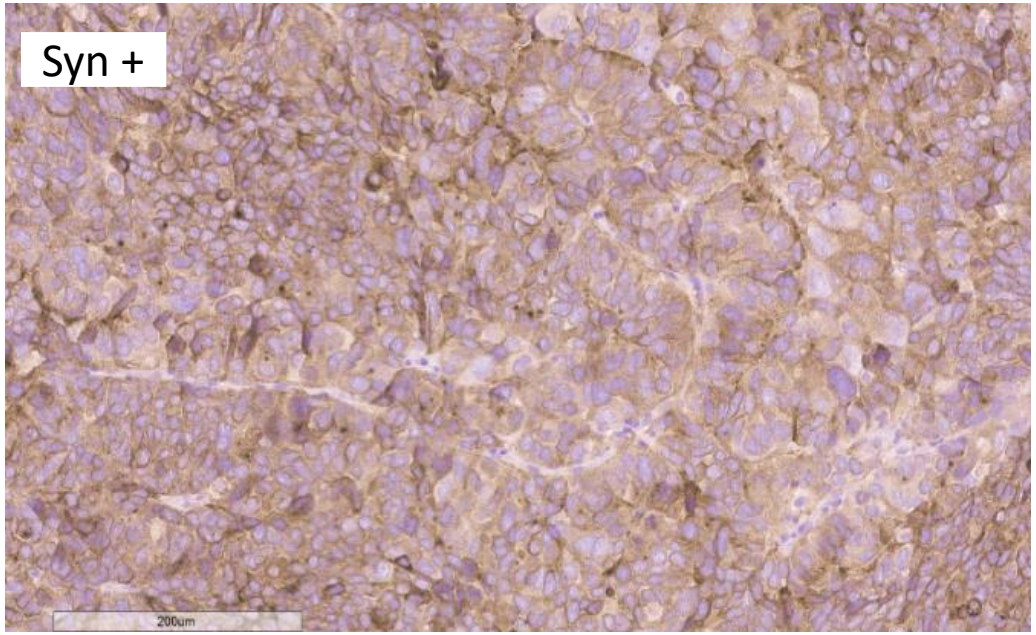


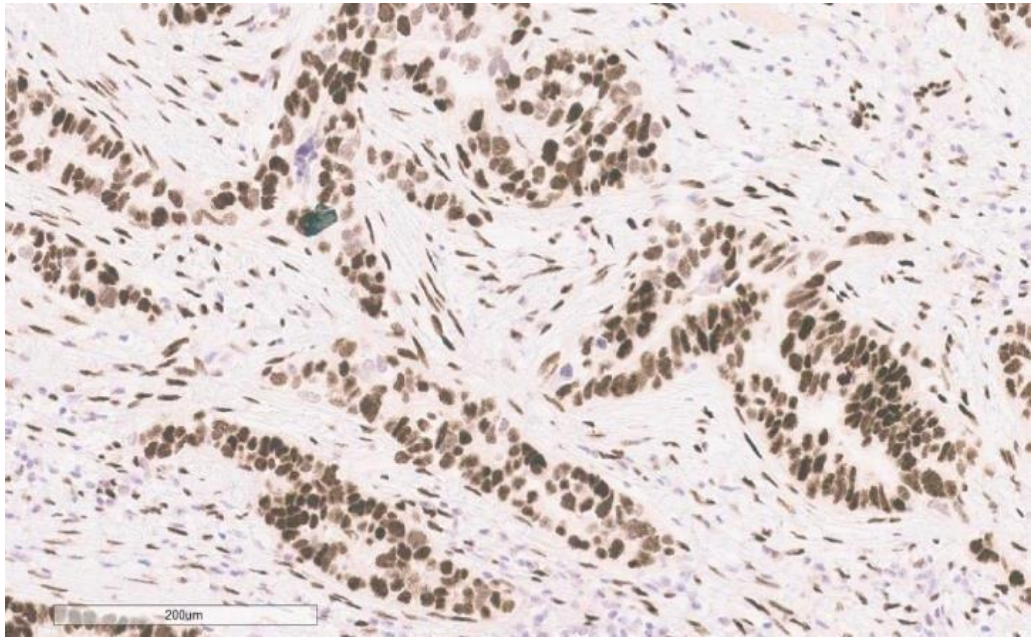


Mixed Ca, Neuroendocrine Ca and HGSCa, Initially Interpreted as HGSCa

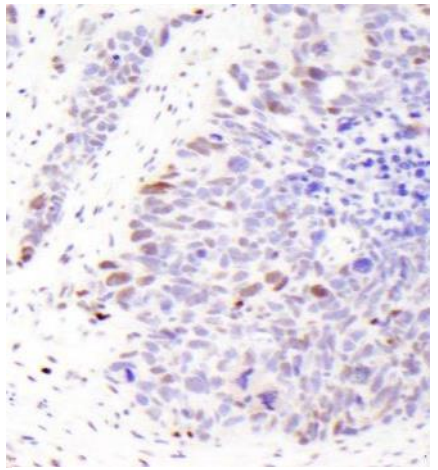




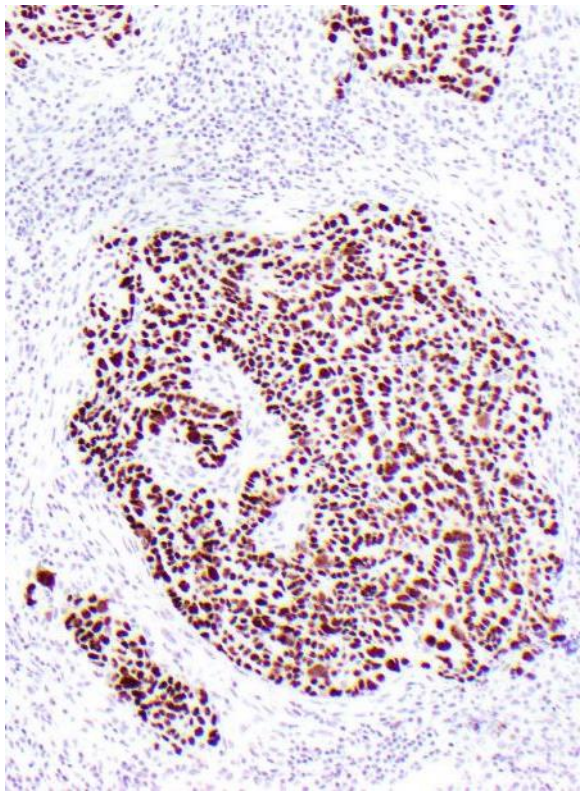


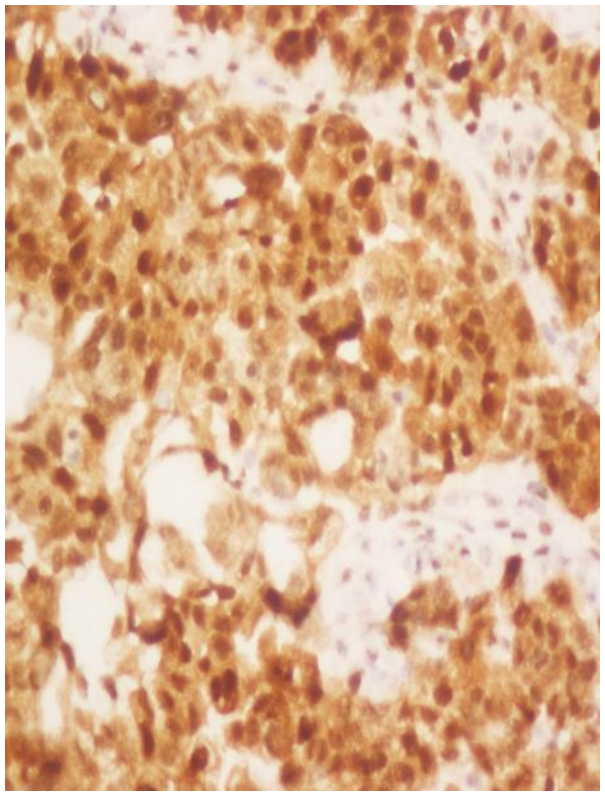


Extrauterine High Grade Serous Carcinoma: p53

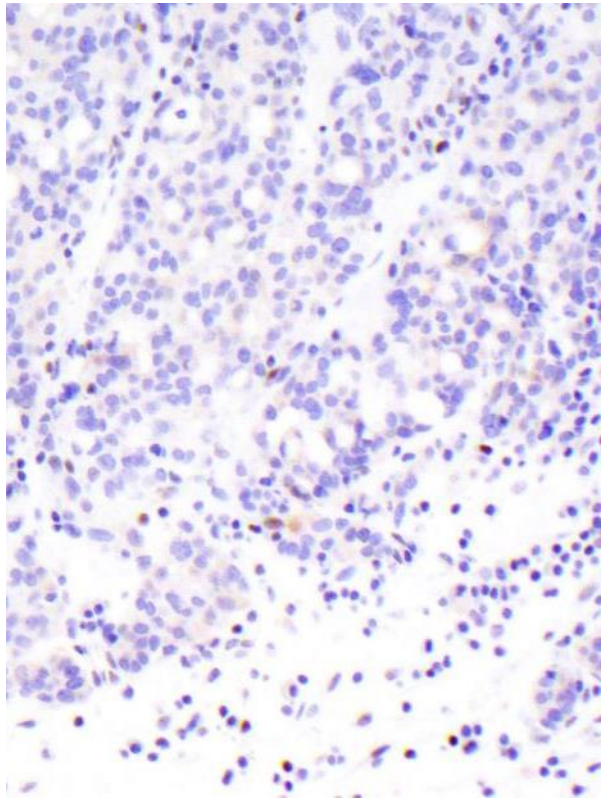


Wild-type, < 10% of cases

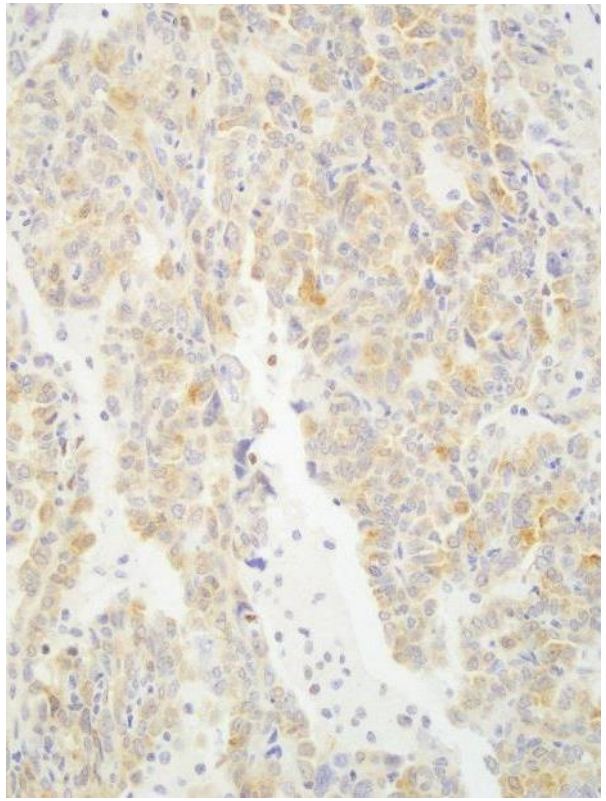




Nuclear overexpression, without or with cytoplasmic staining



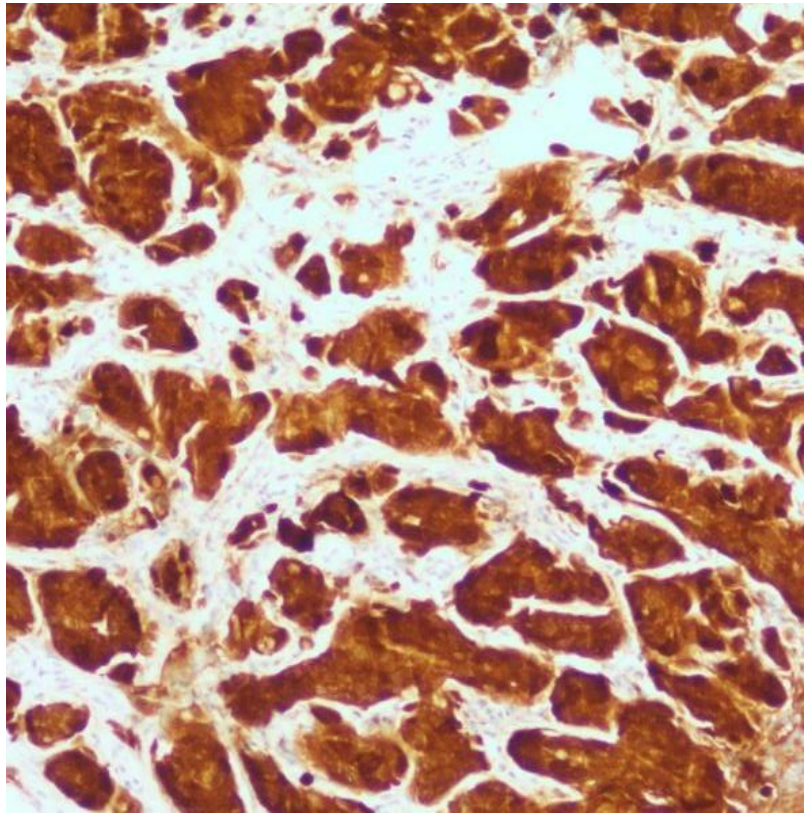
Null phenotype

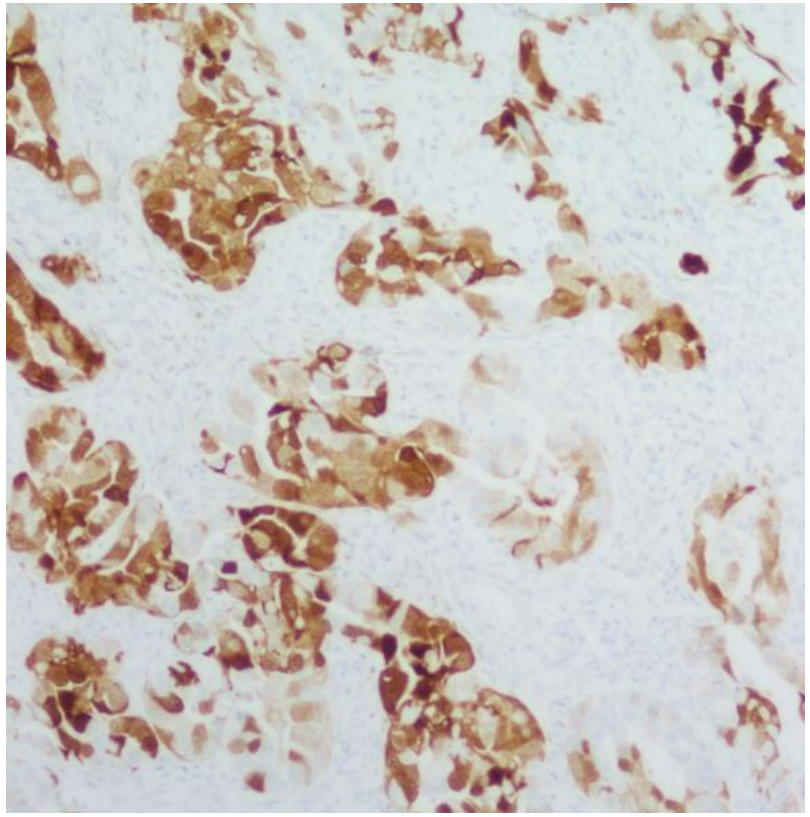


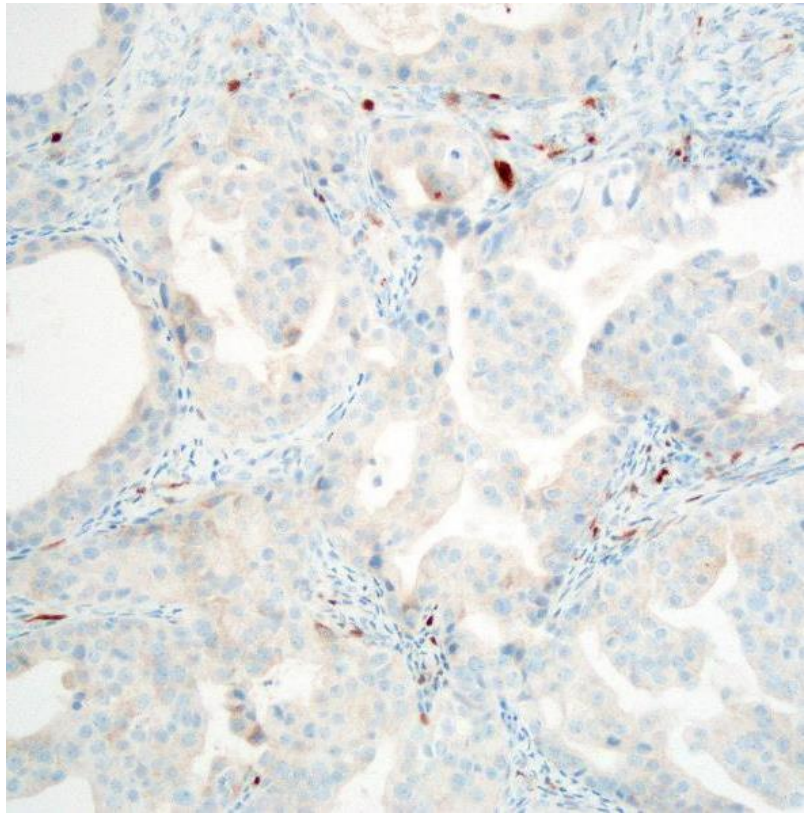
Cytoplasmic overexpression

Extrauterine High Grade Serous Carcinoma: p16

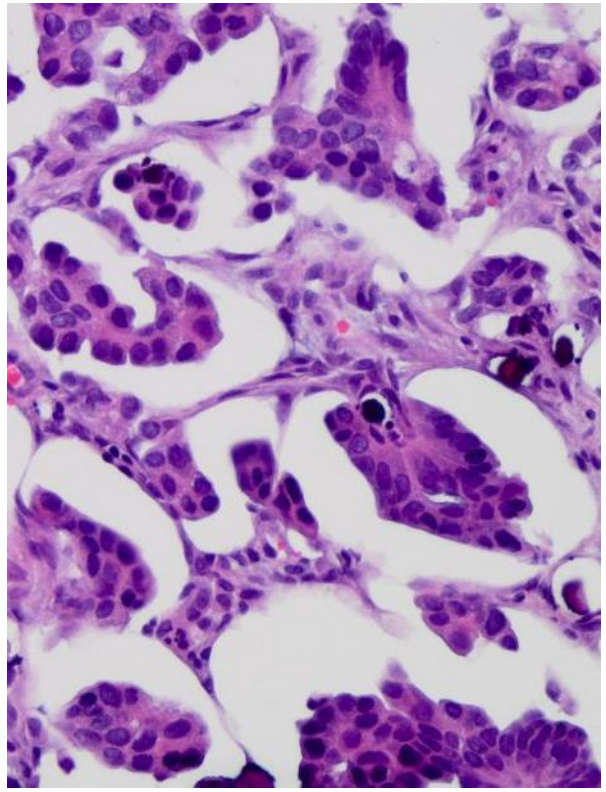
- p16 expression is variable: block, patchy or absent

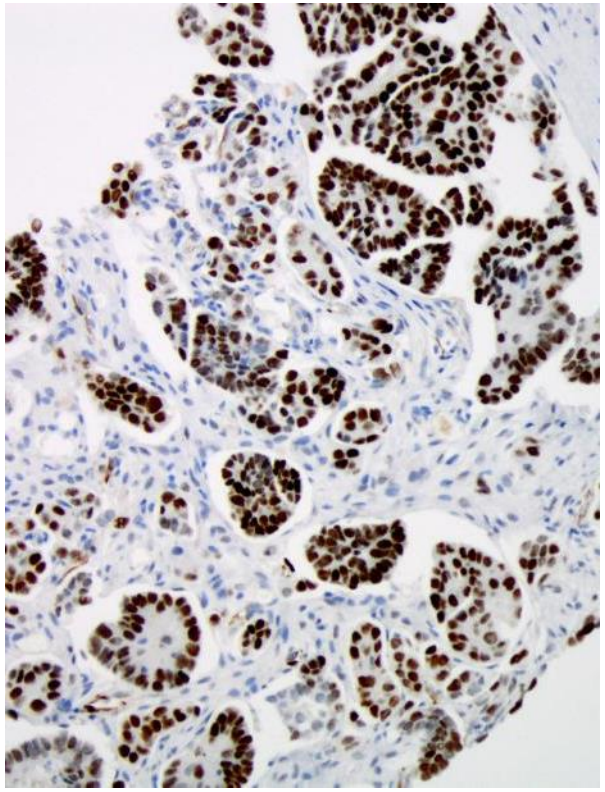




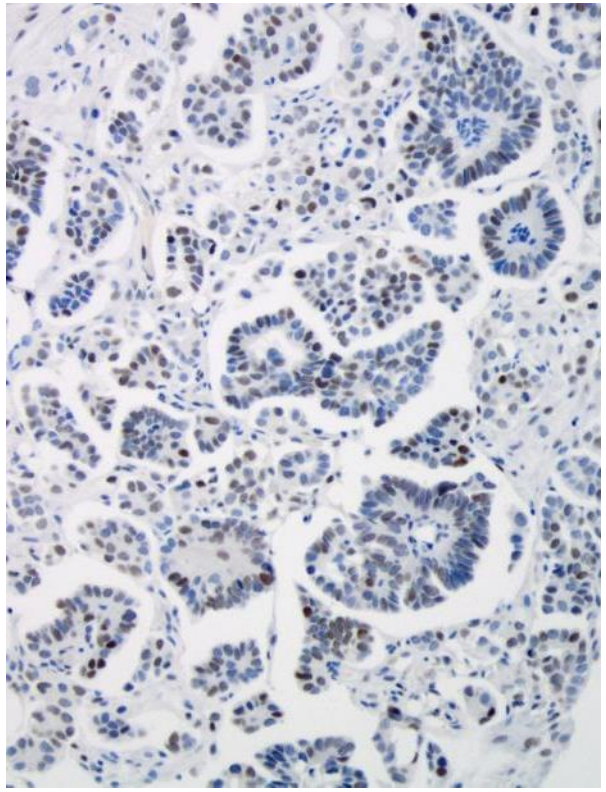


Low Grade Serous Carcinoma: p16, block expression ≈ 7% of cases

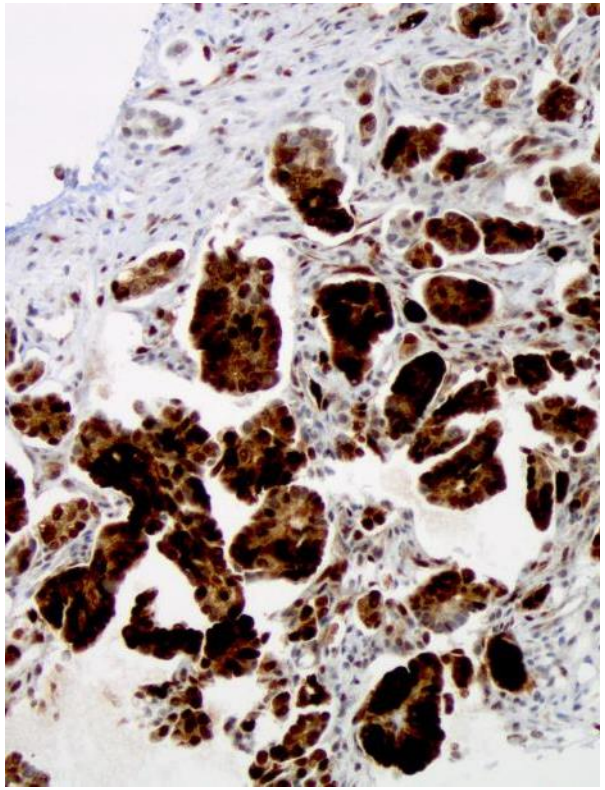




WT-1



p53



p16

Assessment of Folate Receptor Alpha/Folate Receptor 1 Protein (FRα/FOLR1) by IHC

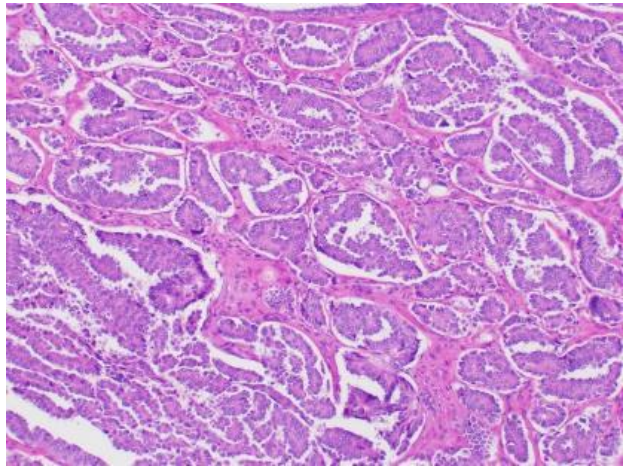
Why?

- To justify the use of mirvetuximab soravtansine (Elahere™)
  - Antibody-drug conjugate (ADC), comprised of a FRα directed antibody conjugated to a microtubule inhibitor
    - Arrests cell cycle and causes apoptotic cell death
  - November 2022, it received accelerated approval by the USA FDA
    - Treatment of adult patients with FRα positive, platinum-resistant ovarian, fallopian tube or peritoneal cancer who have received 1-3 prior systemic treatment regimens

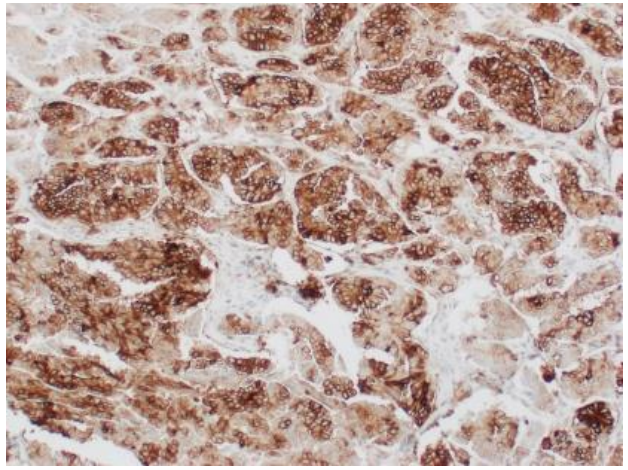
Assessment of Folate Receptor Alpha/Folate Receptor 1 protein (FRα/FOLR1) by IHC

USA FDA approved Ventana FOLR1 RxDx Assay

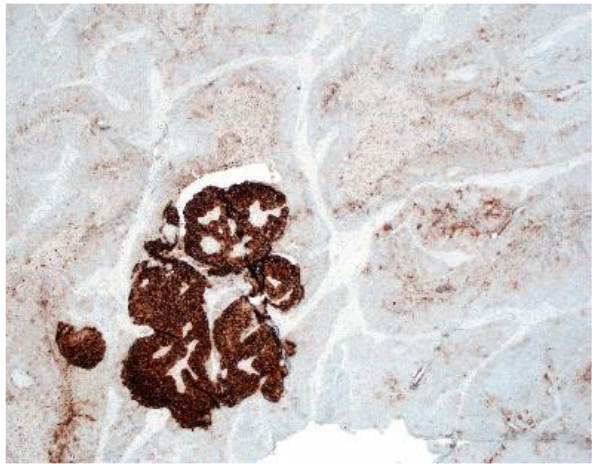
≥ 75% of cells with moderate and/or strong membranous staining



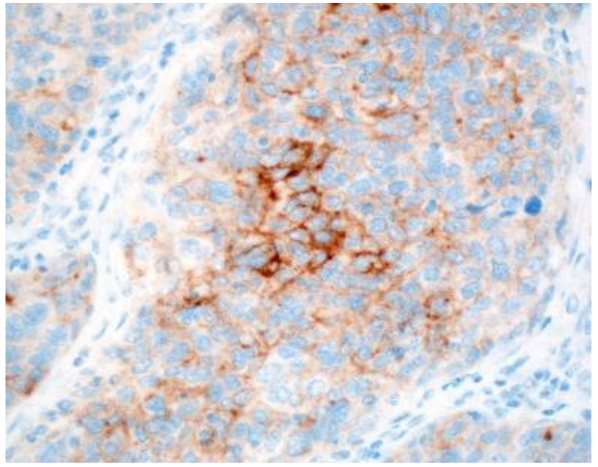
Low grade serous carcinoma



Moderate and strong membranous staining



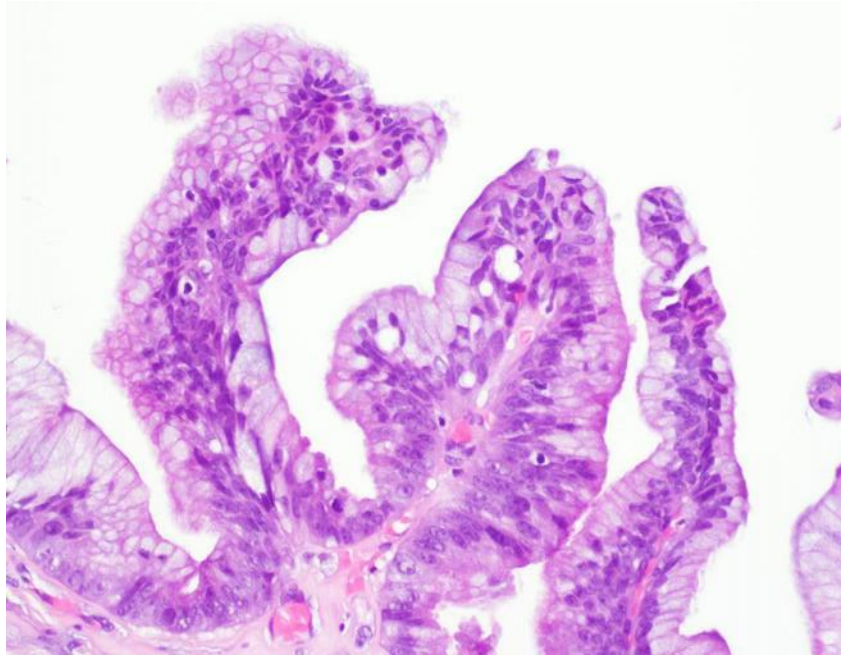
Variable staining in <75% of cells



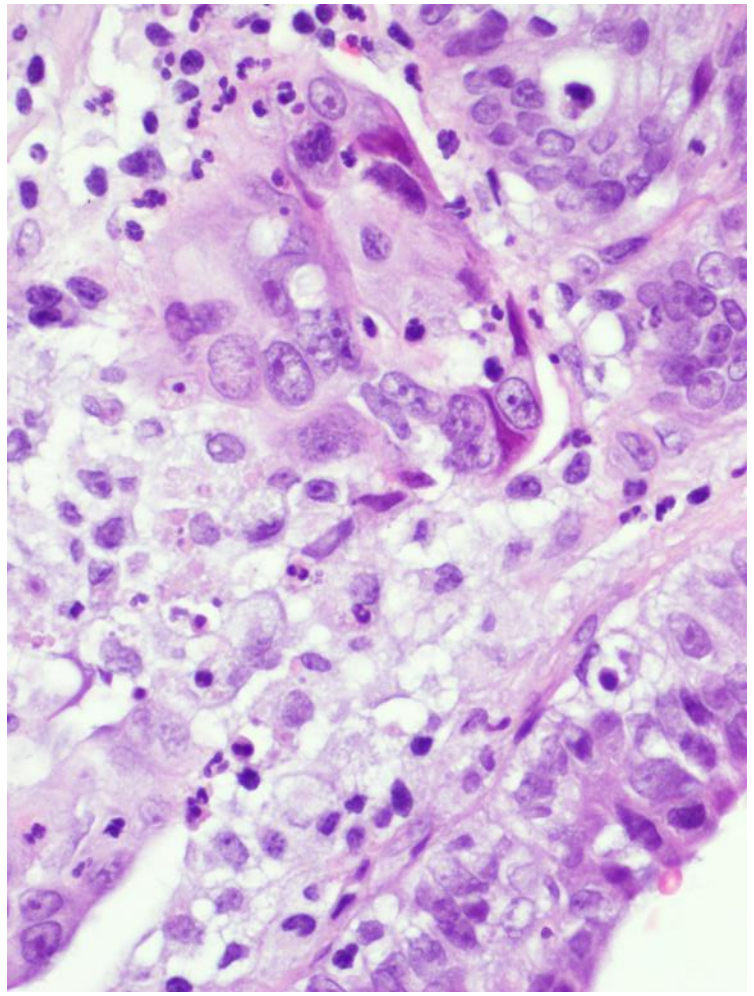
Cytoplasmic staining

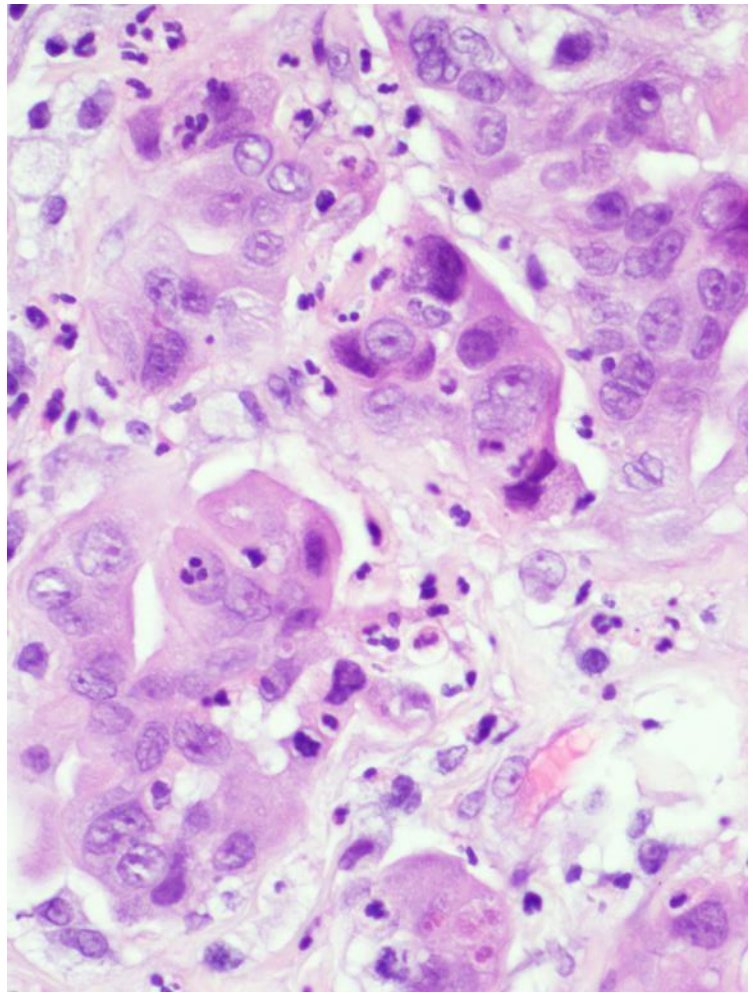
Irrelevant findings

Microinvasive Mucinous Carcinoma



Borderline Mucinous Tumor





- Focus of invasion into the stroma < 5mm in greatest linear extent
- Marked cytologic atypia within the invasive

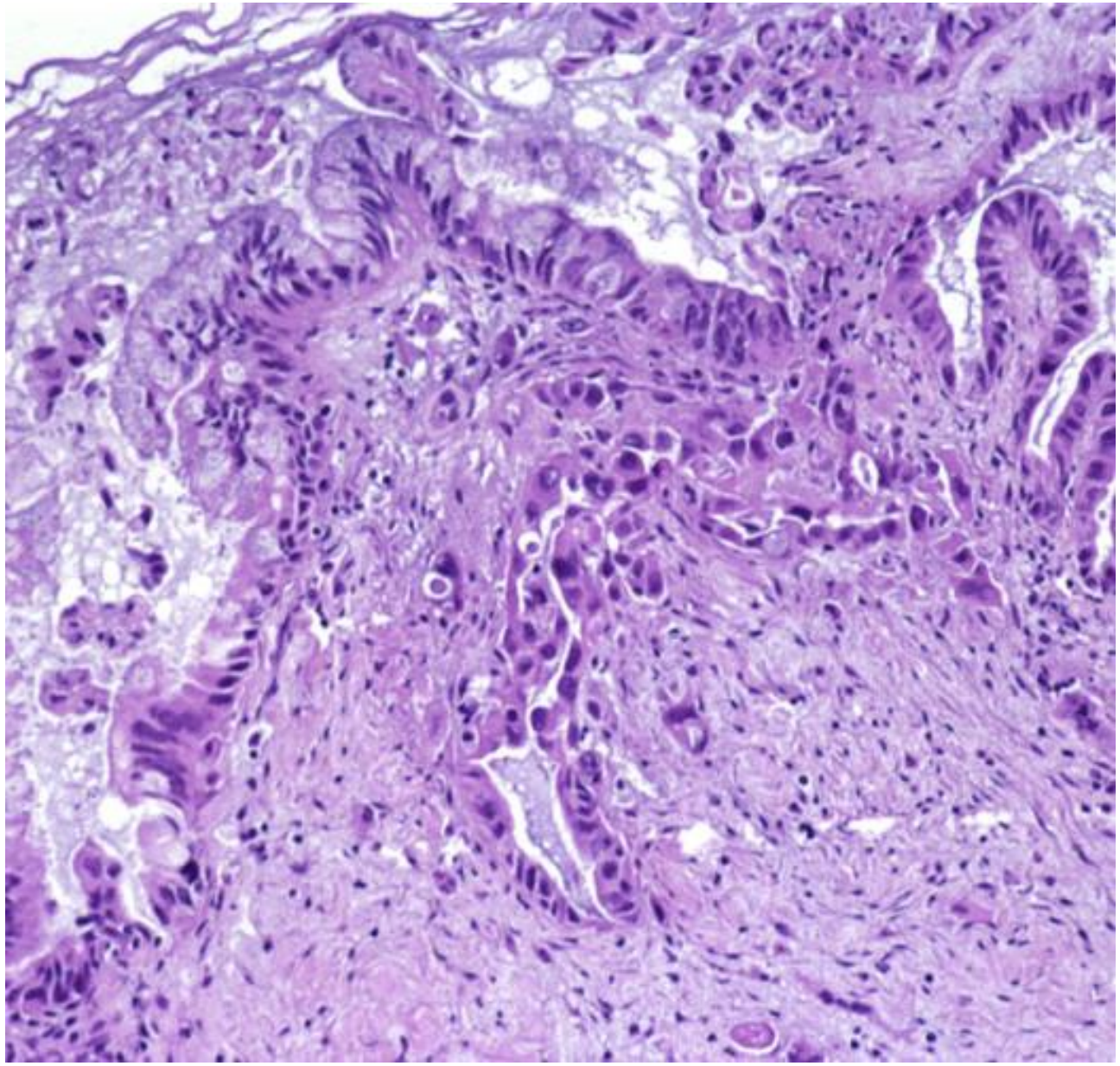
Microinvasive Mucinous Carcinoma

- Experience is limited
- Rare cases have been reported with recurrences and death

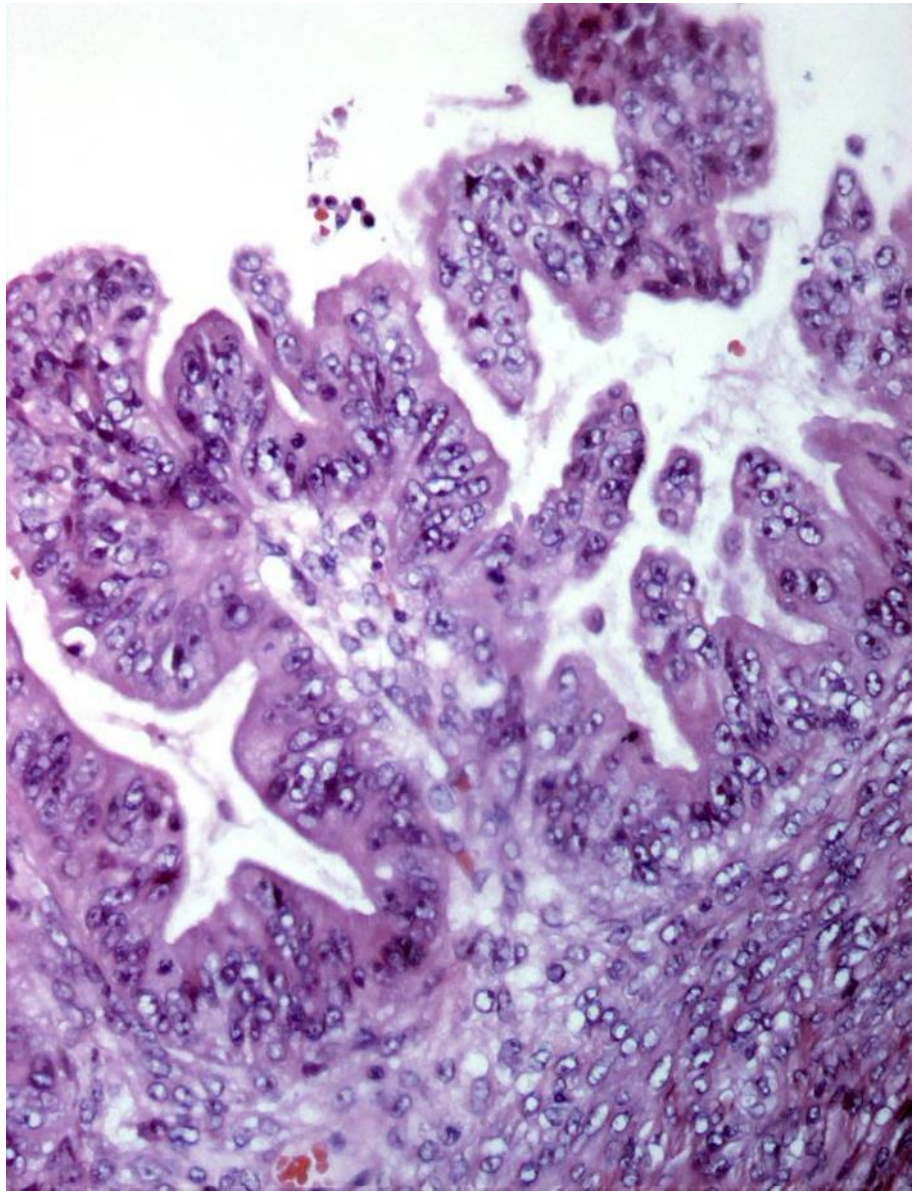
Nomura K, Aizawa S. Cancer 2000
Khunamornpong S. et al. Int J Gynecol Path 2011
WHO 2014 and 2020

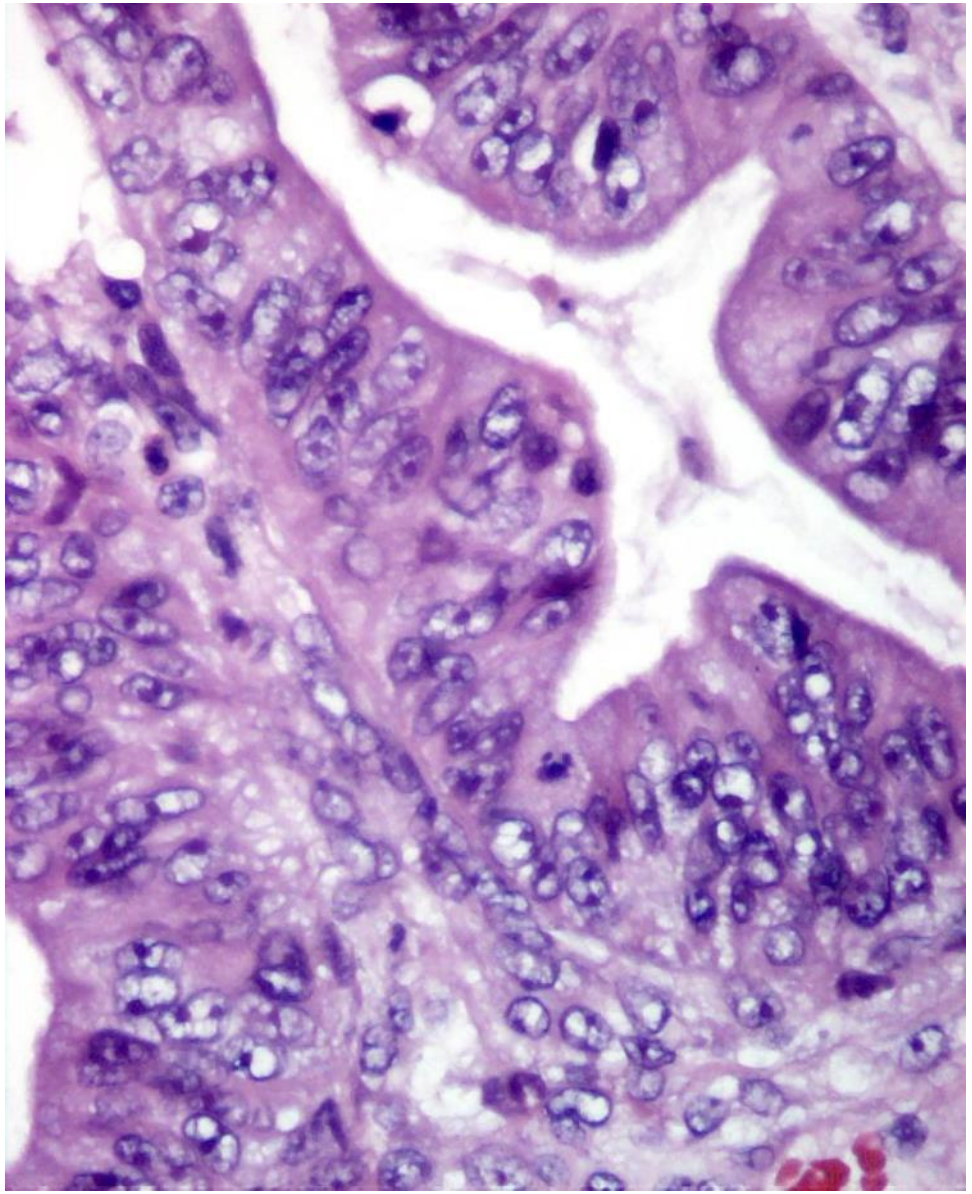
Mucinous Borderline Tumor with Microinvasion

- Focus of invasion into the stroma < 5 mm in greatest linear extent
- Mild to moderate cytologic atypia within the invasive focus



Mucinous Intraepithelial Carcinoma, Marked Atypia of the Epithelium

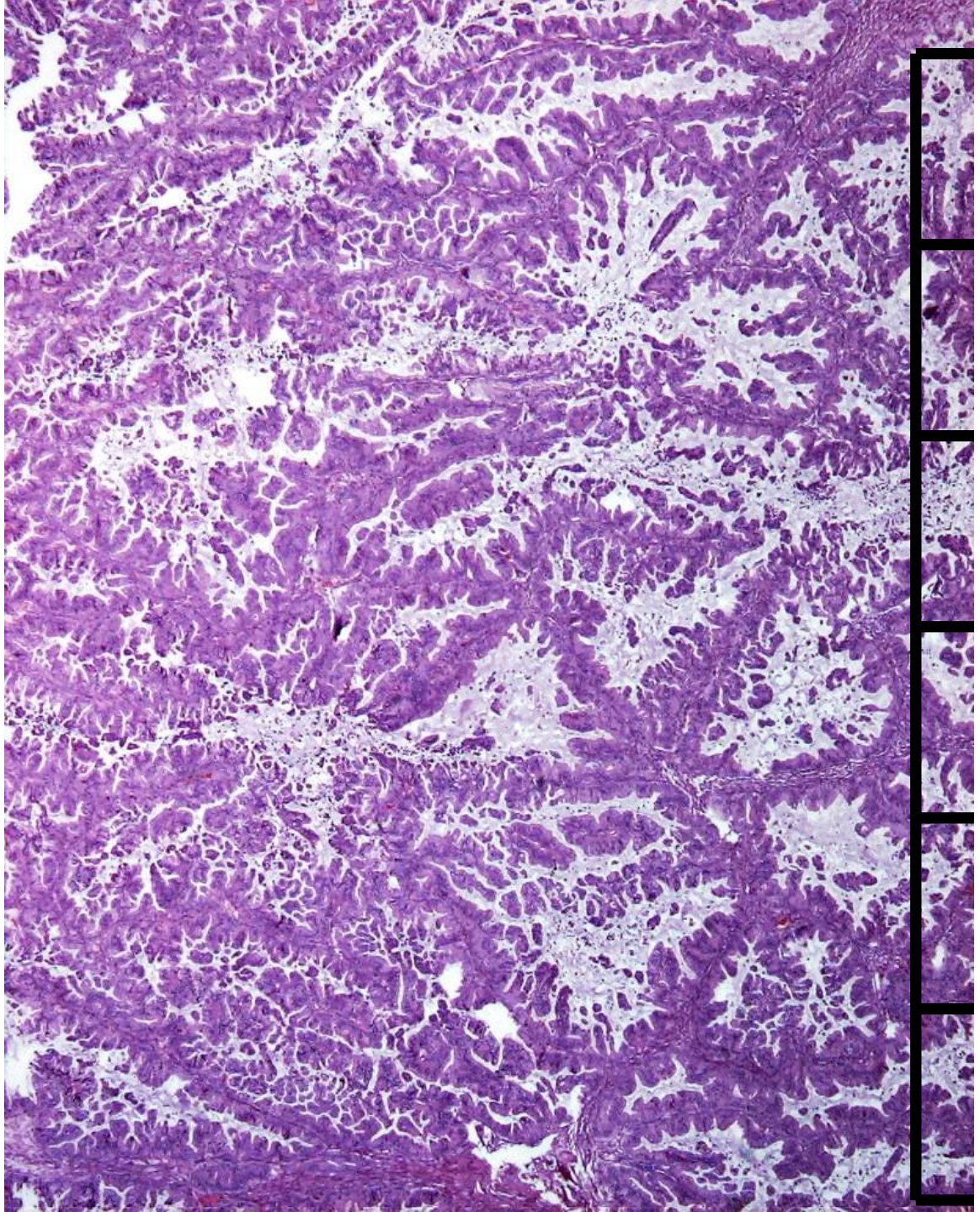




Invasive Mucinous Carcinoma

Expansile/confluent type

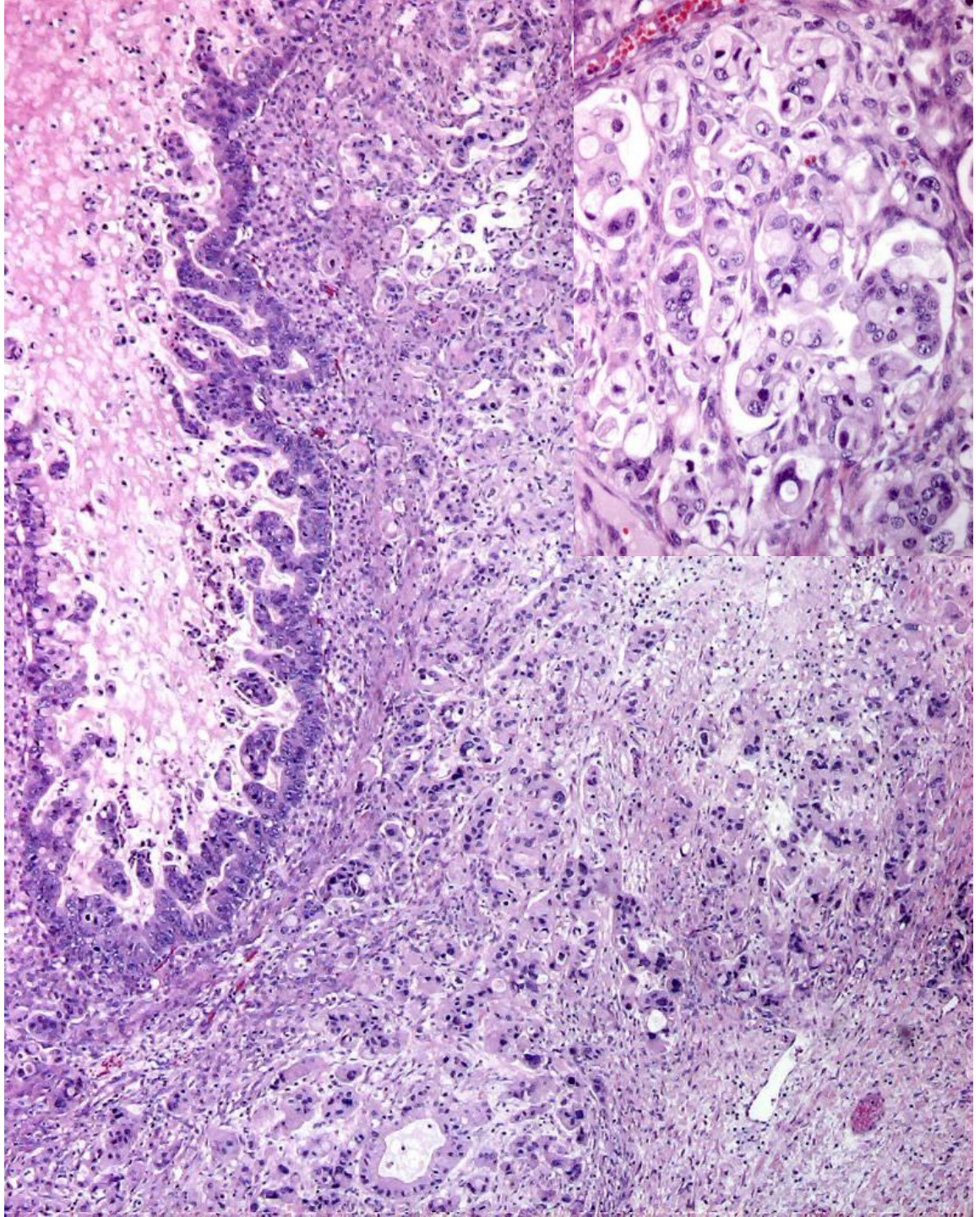
- confluent glandular pattern
- uninterrupted by normal ovarian stroma
- measuring at least 5 mm in linear extent



Invasive Mucinous Carcinoma

Infiltrative type

- Small glands, nests of cells or individual cells infiltrating the stroma in an area measuring at least 5 mm in linear extent



Mucinous Carcinoma

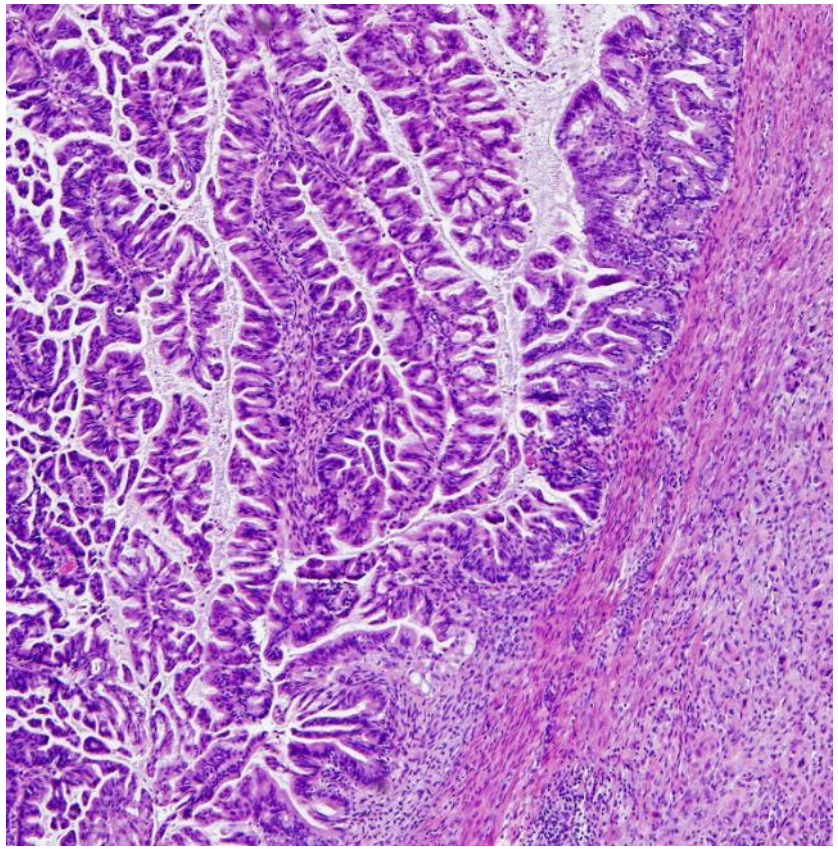
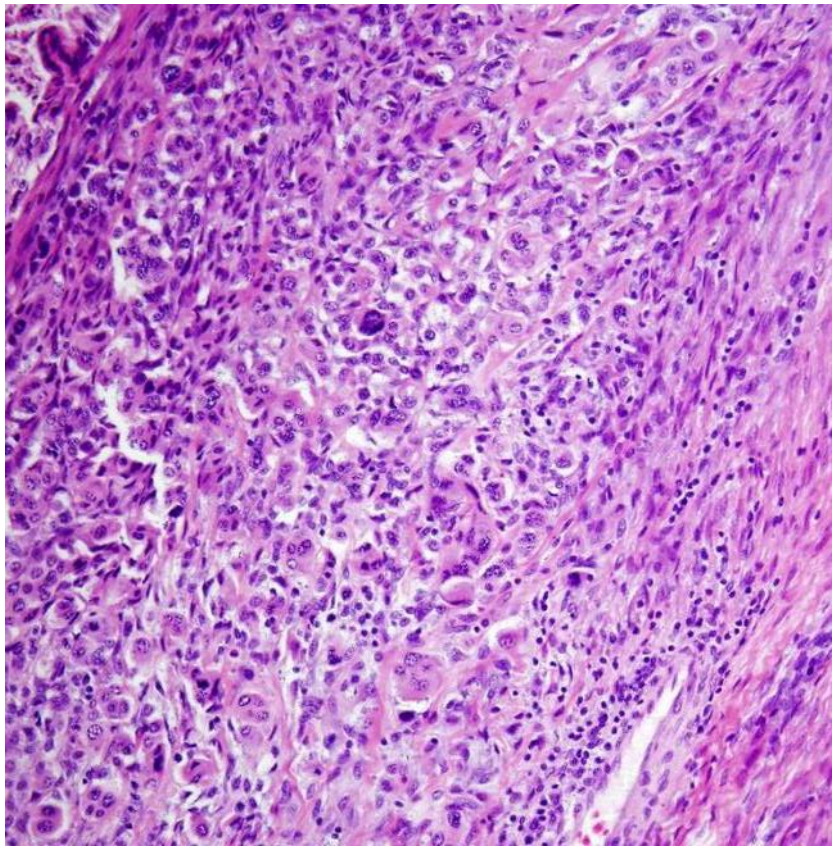
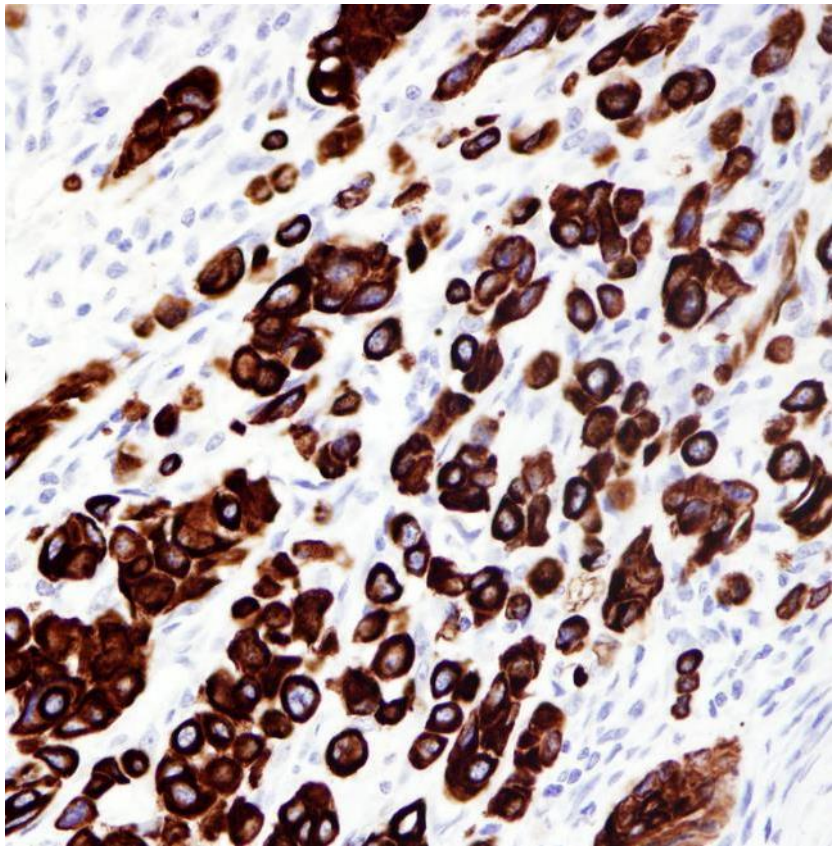
- Intraepithelial Carcinoma
  - Stage I disease, recurrence rate 5%
- Invasive Carcinoma
  - Stage I disease , 5-year survival 91%
  - Advanced stage disease, all patients die of disease
  - Expansile pattern more common than the infiltrative pattern
    - Recurrences in stage I tumors with an expansile pattern tend to be seen in the pelvis
  - Infiltrative invasion appears to be more aggressive than the expansile type

Riopel MA, et al., 1999
Lee KR and Scully R, 2000
Rodriguez IM and Prat J, 2002
Gouy S, et al., 2018

Molecular Alterations in Ovarian Mucinous Carcinoma

Molecular Alteration	Ovarian Mucinous Carcinoma
MSI-H	22%
KRAS mutation	43%
BRAF mutation	0%
HER2 amplification	18%
APC or CTNNB1 mutations	9%
TP53 mutations	26%

Kelemen LE, Köbel M, 2011

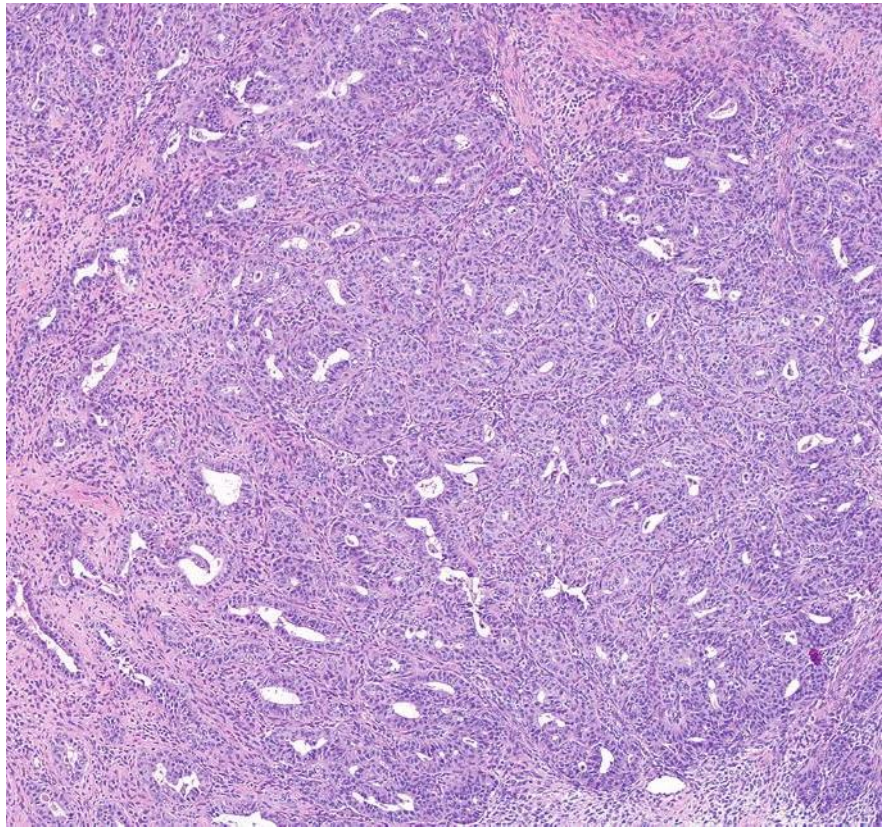




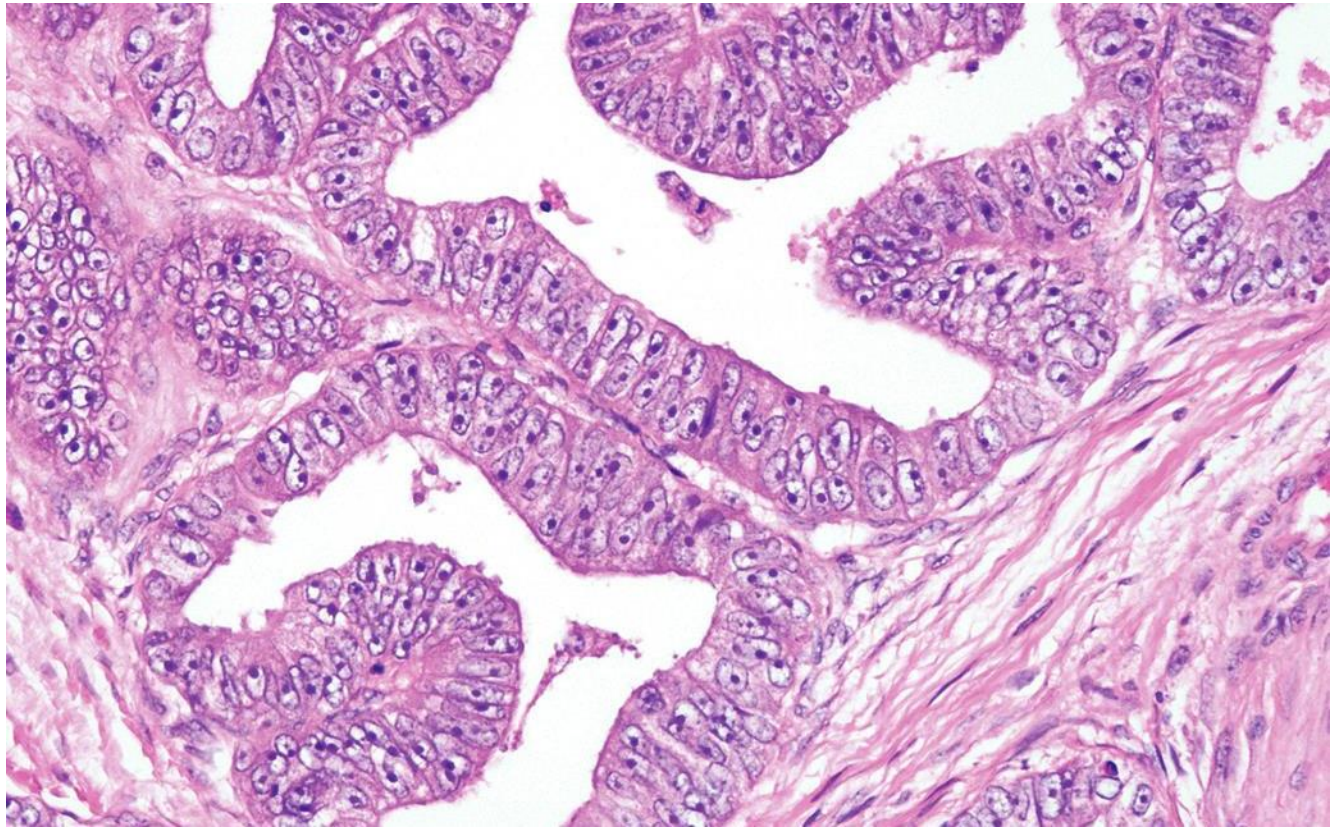
Anaplastic Carcinoma

- Keratin is useful to assess the extent of the tumor or if spindle cells are present
- Pts who present with stage 1A disease tend to have a favorable outcome

Endometrioid Borderline Tumor

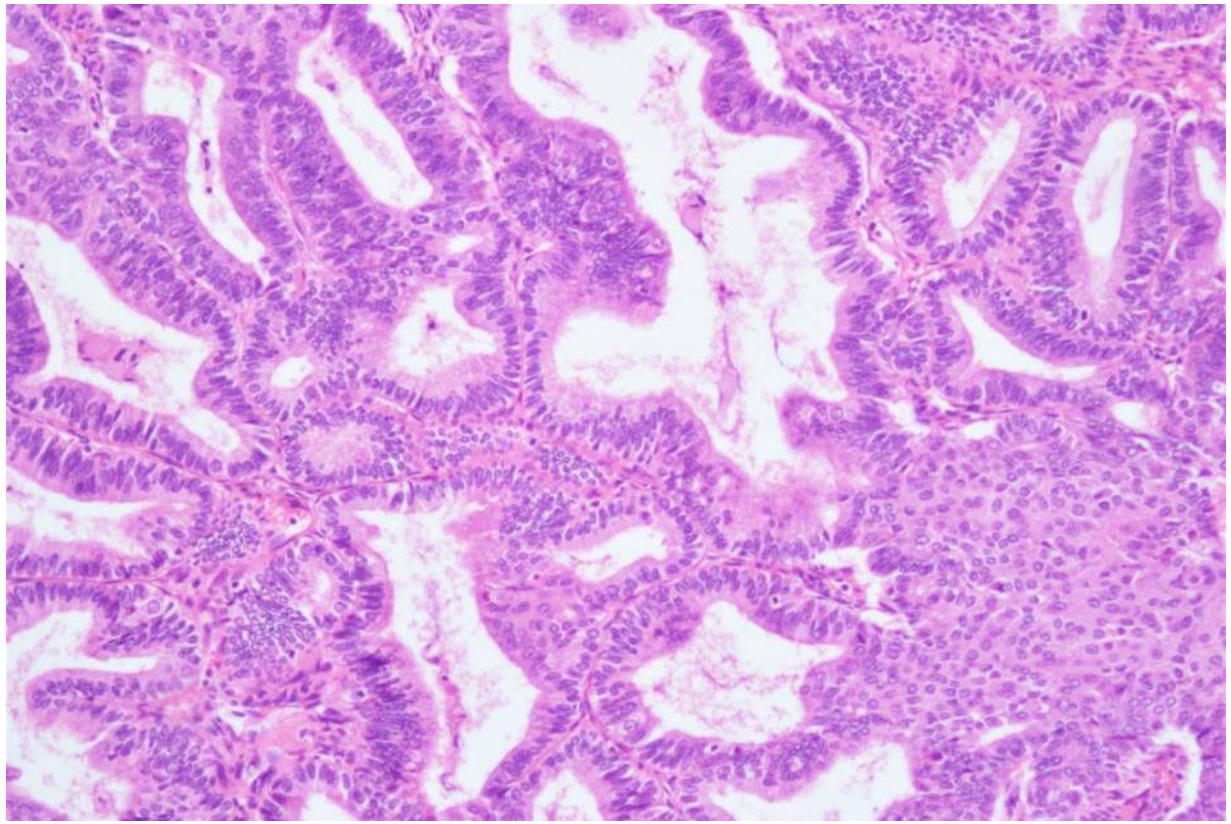
- Microinvasion: confluent glandular proliferation < 5 mm in linear extent
- Intraepithelial carcinoma: marked cytologic atypia



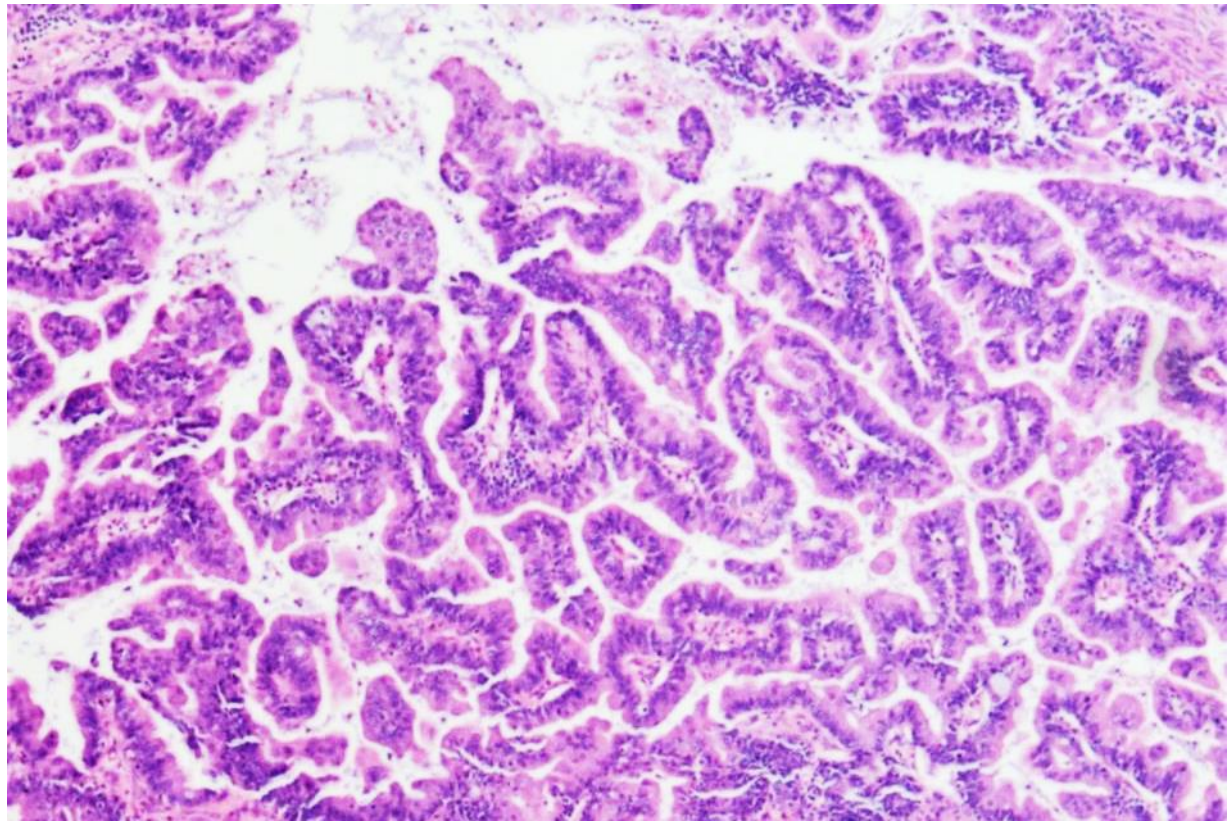


Endometrioid Carcinoma

Back-to-back glandular proliferation > 5mm

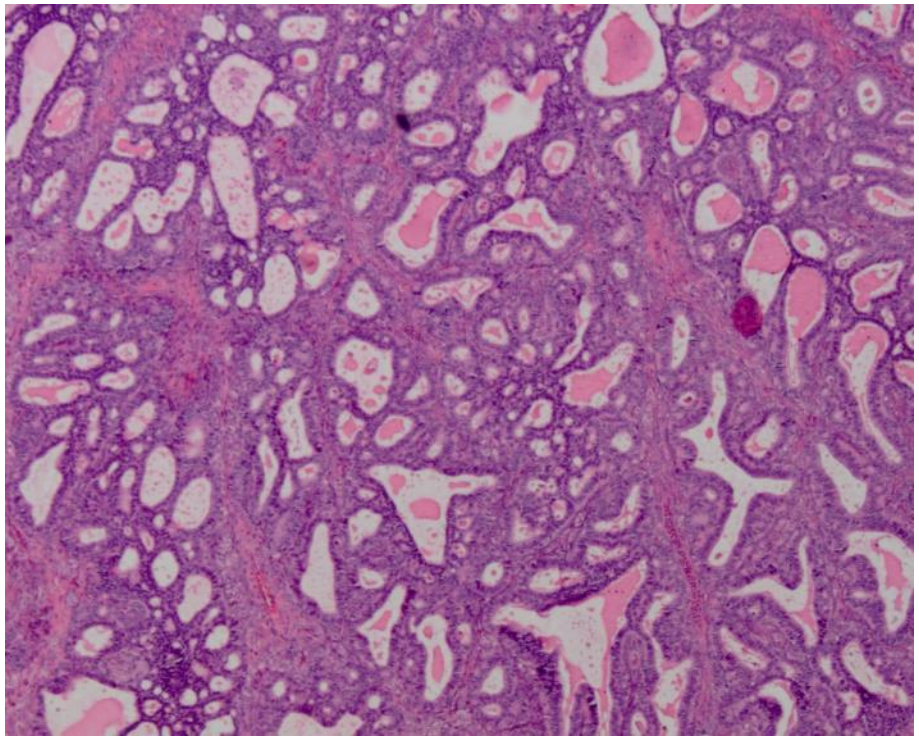


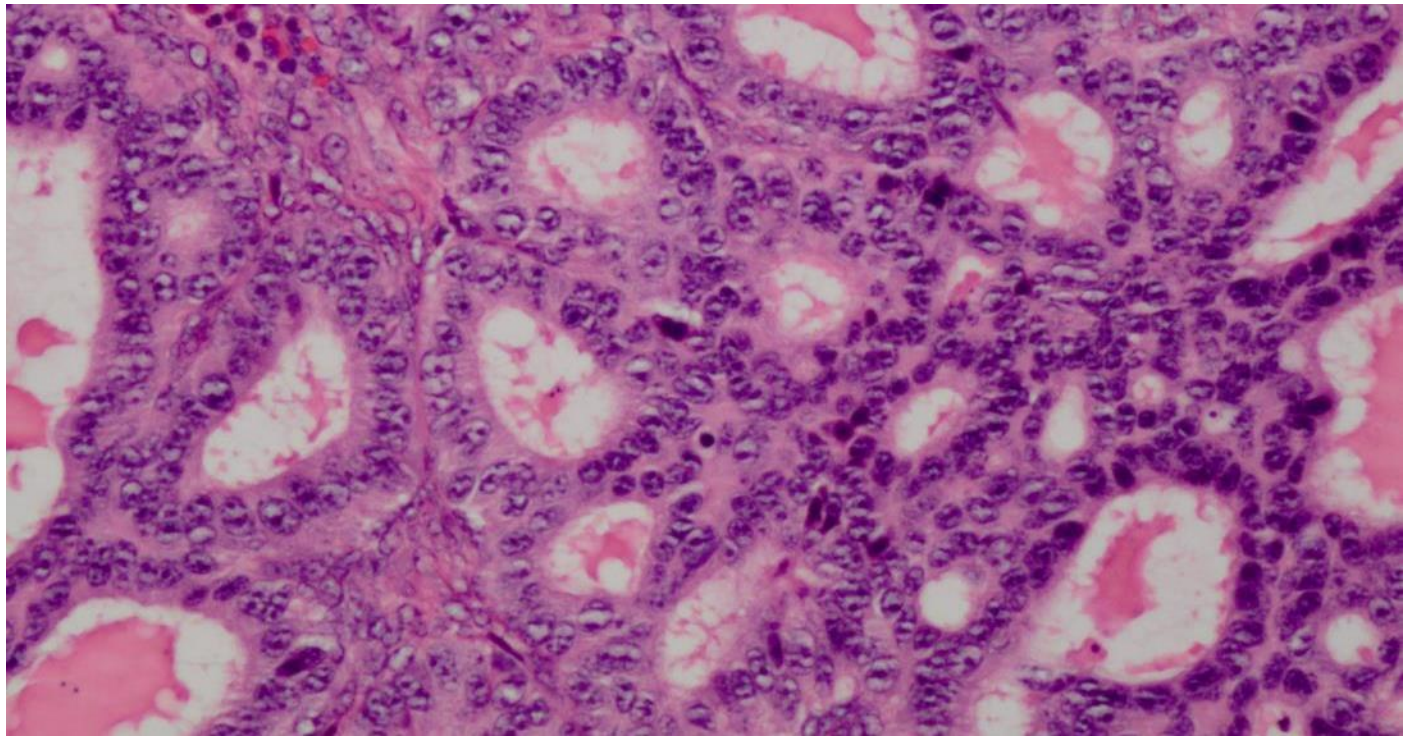
Intracystic complex papillary growth



Endometrioid Carcinoma

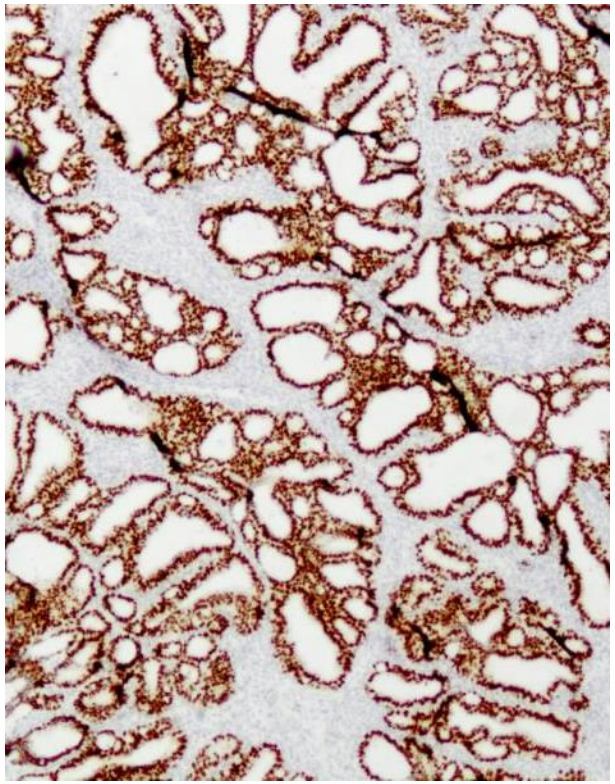
- Confounding histological features:
  - Nuclear disorganization, to exclude high-grade serous carcinoma
    (WT-1, p53, and p16)
  - Eosinophilic luminal contents, to exclude mesonephric-like carcinoma (ER, PR, GATA-3, and TTF-1)



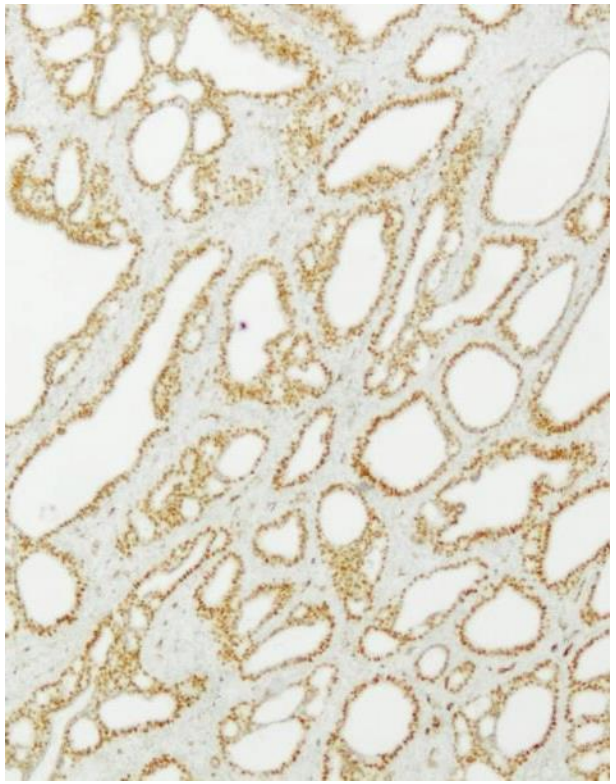


Endometrioid Carcinoma

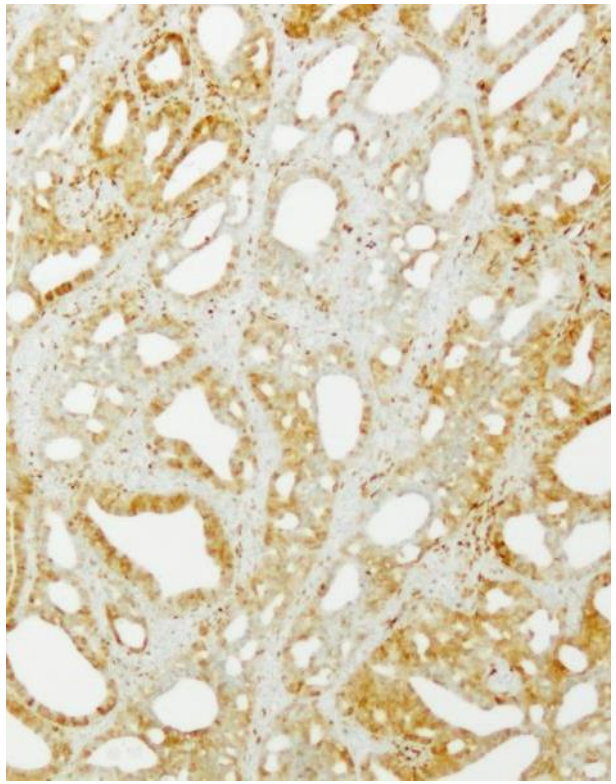
- IHC confounding findings: CDX2+ and WT-1+



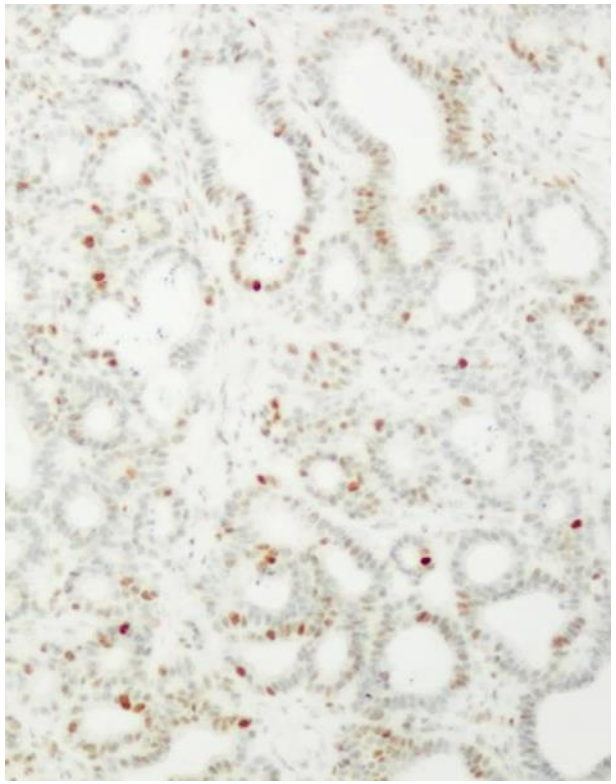
CDX-2+



WT-1+

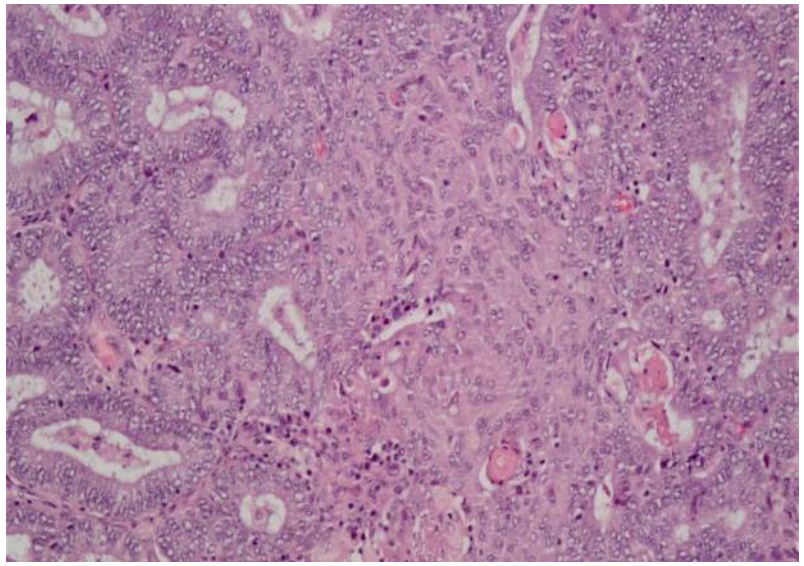


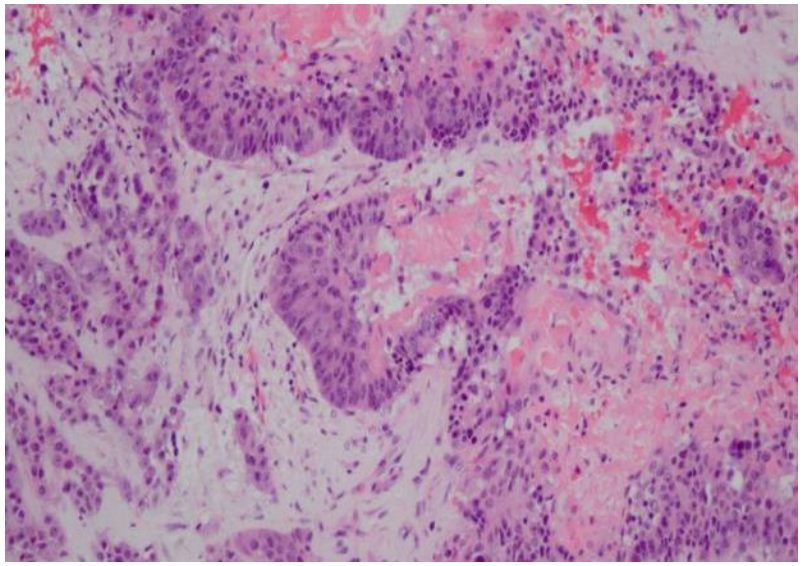
p16 patchy

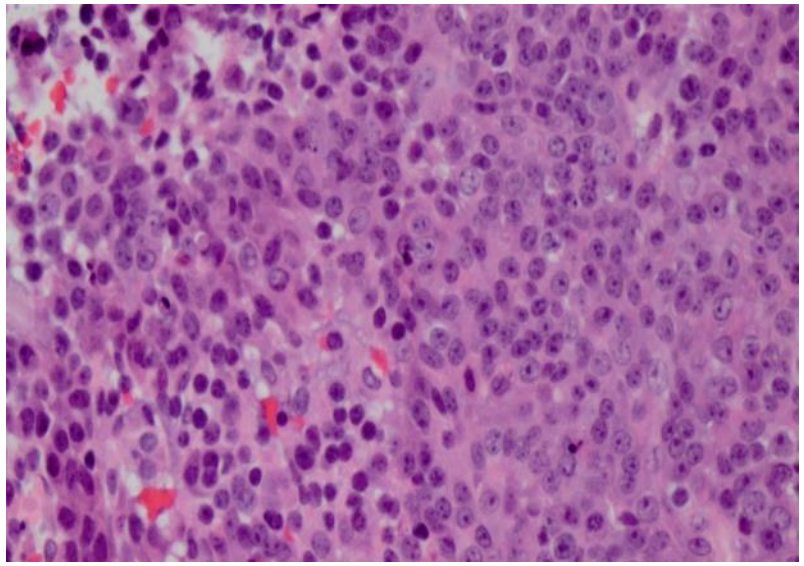


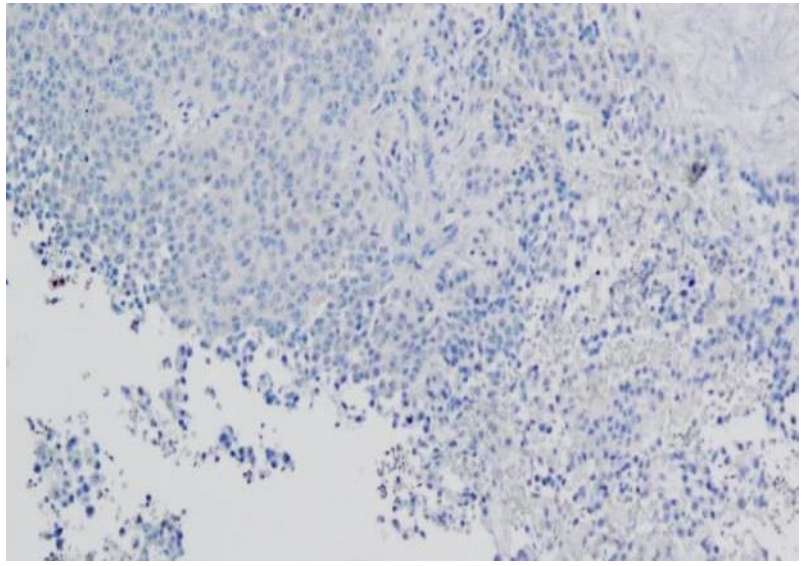
p53 wild type

Endometrioid and Undifferentiated Carcinoma (Dedifferentiated Carcinoma)

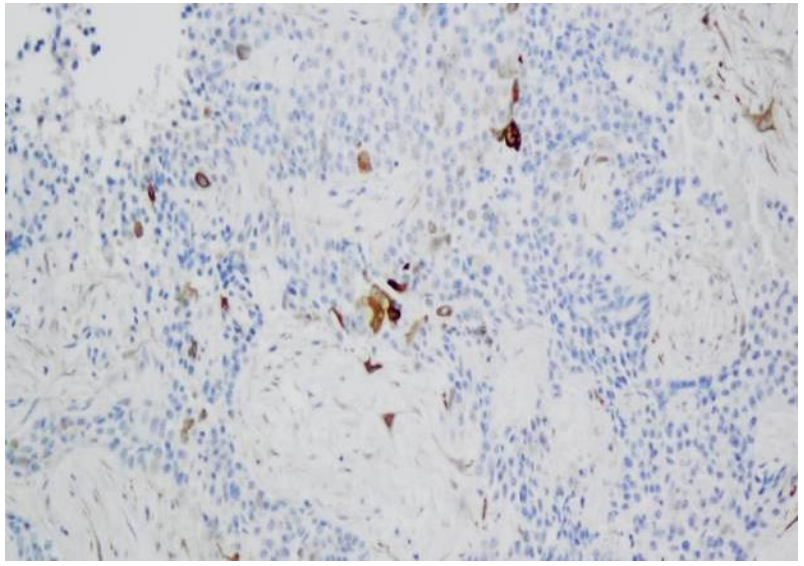




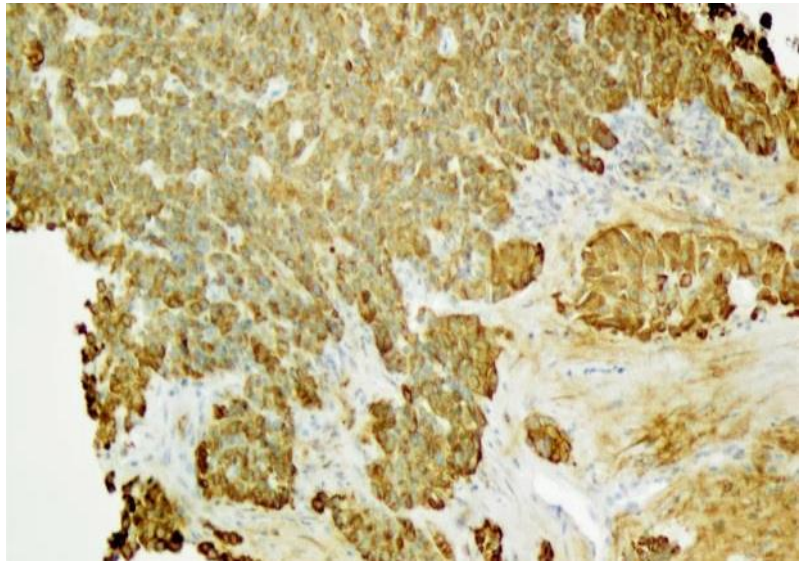




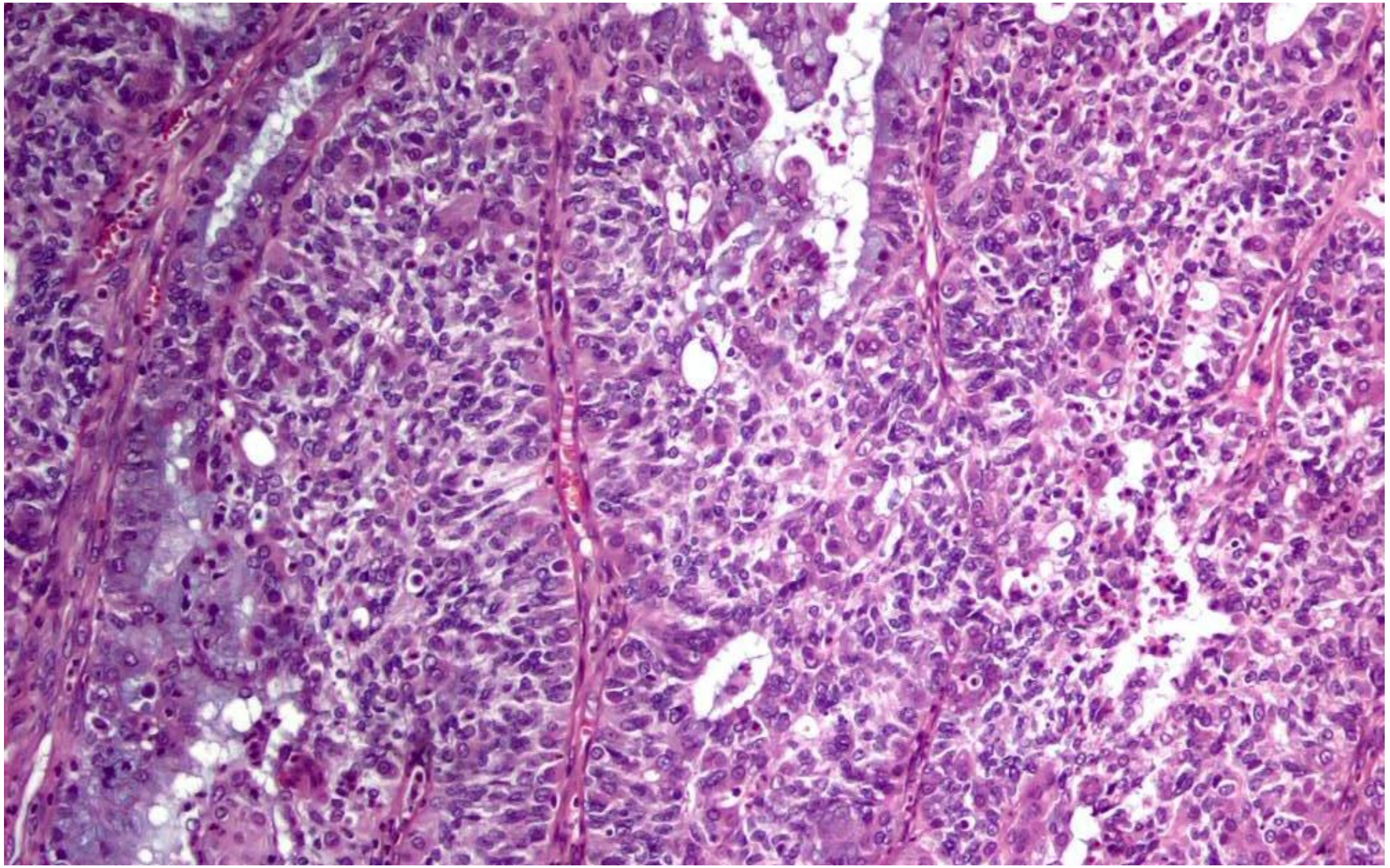
PAX-8 -



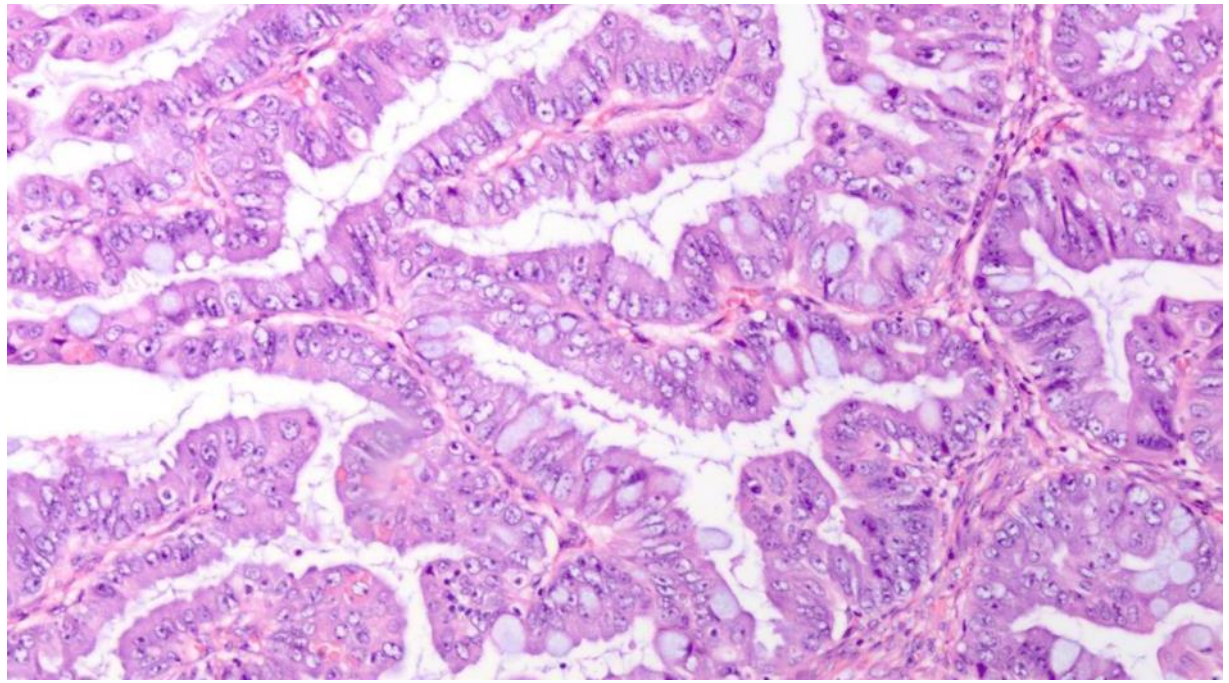
Ker 7 rare cells +

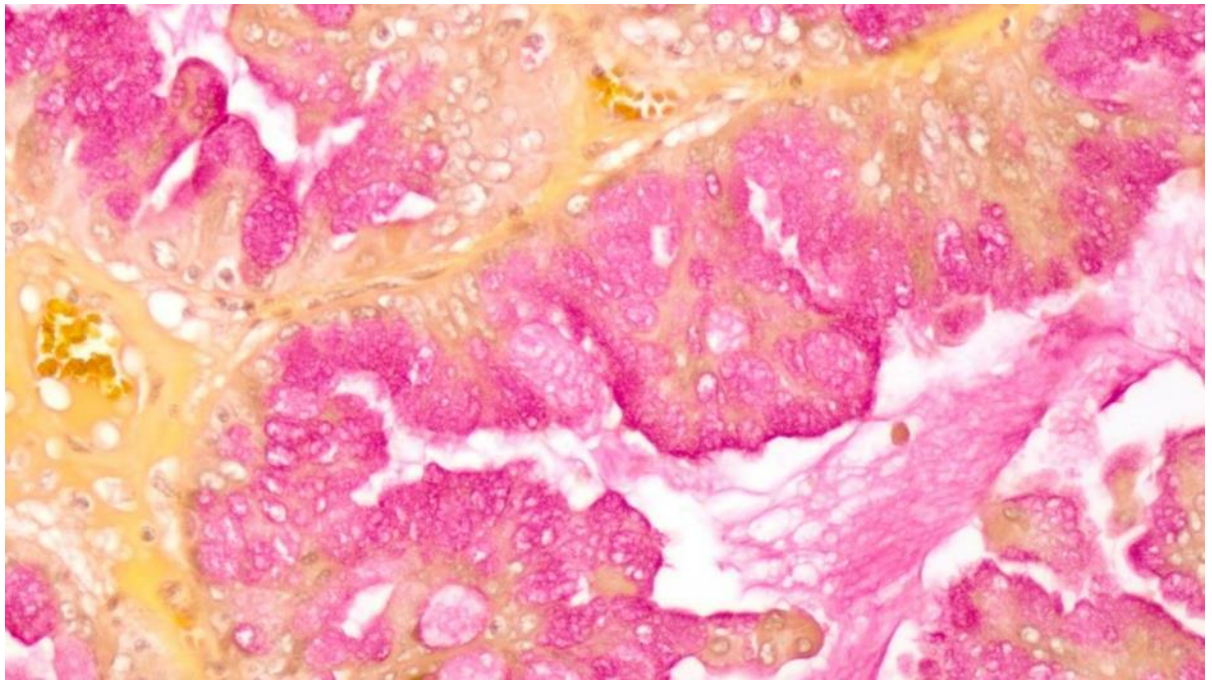


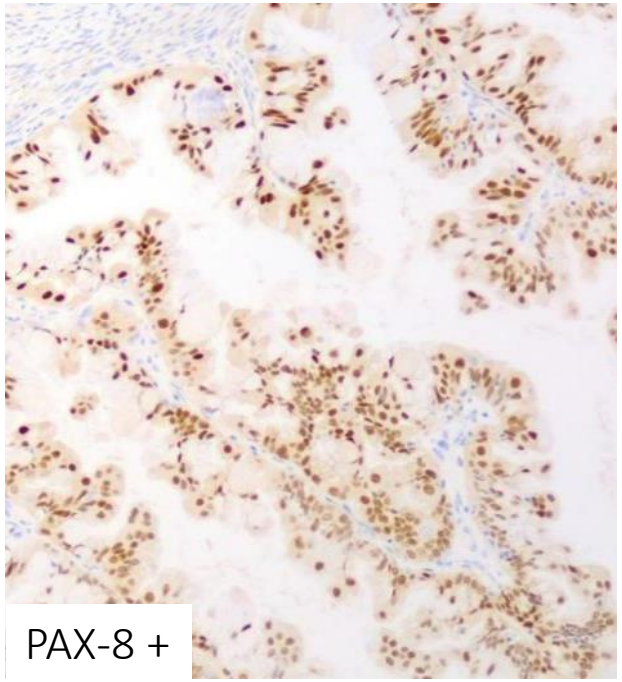
Ker 18 +



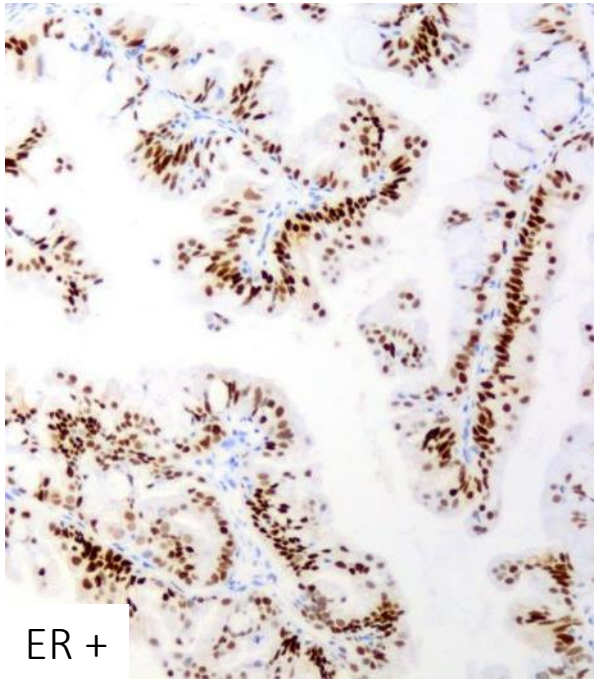
Endometrioid Carcinoma with Mucinous Metaplasia



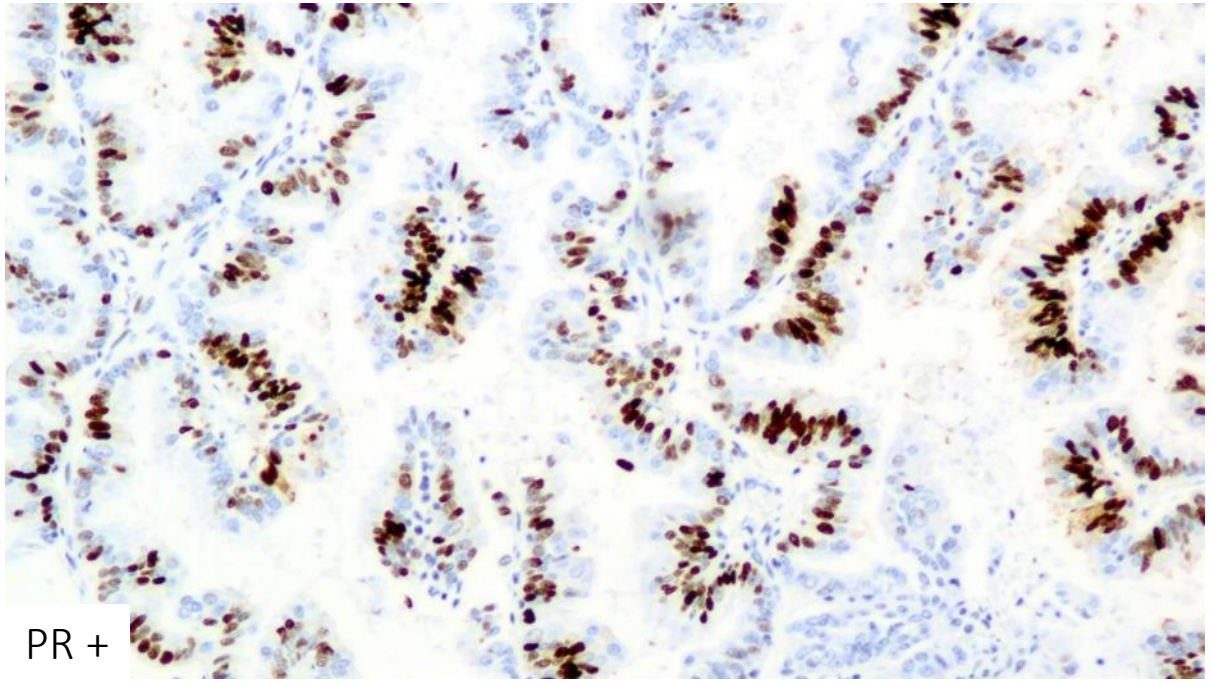




PAX-8 +

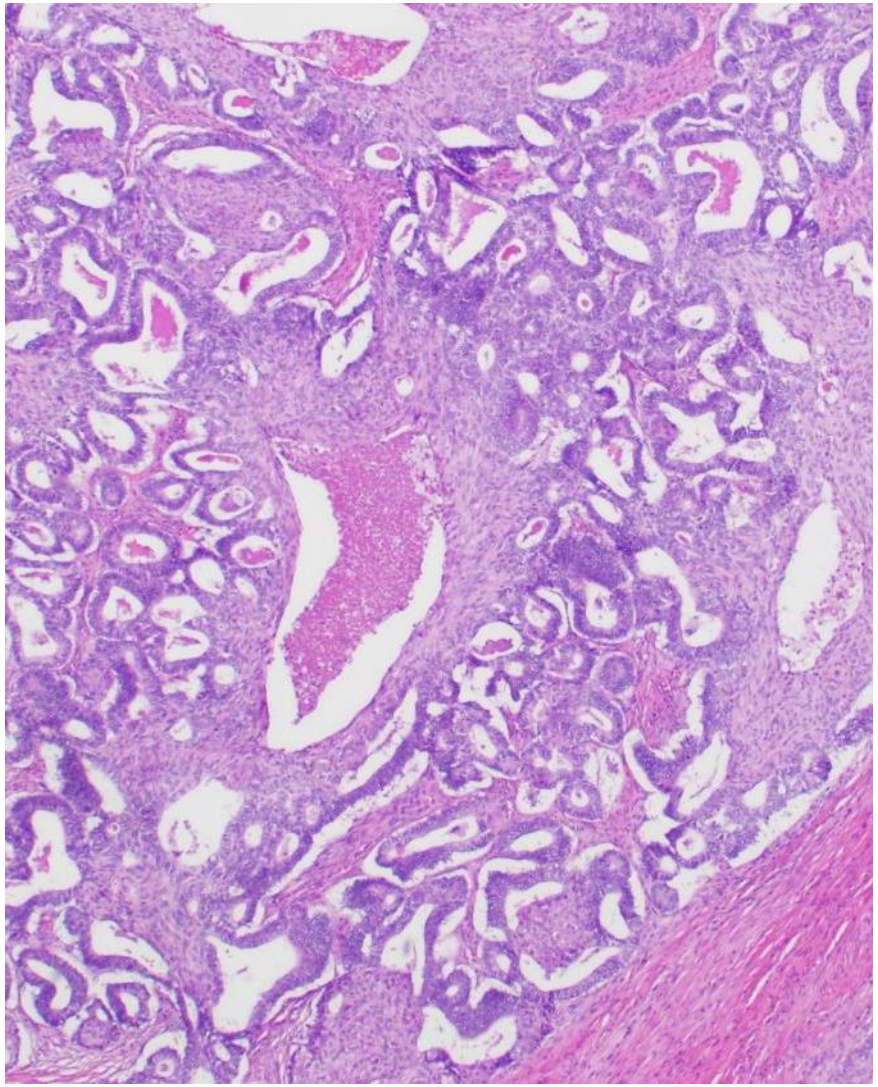


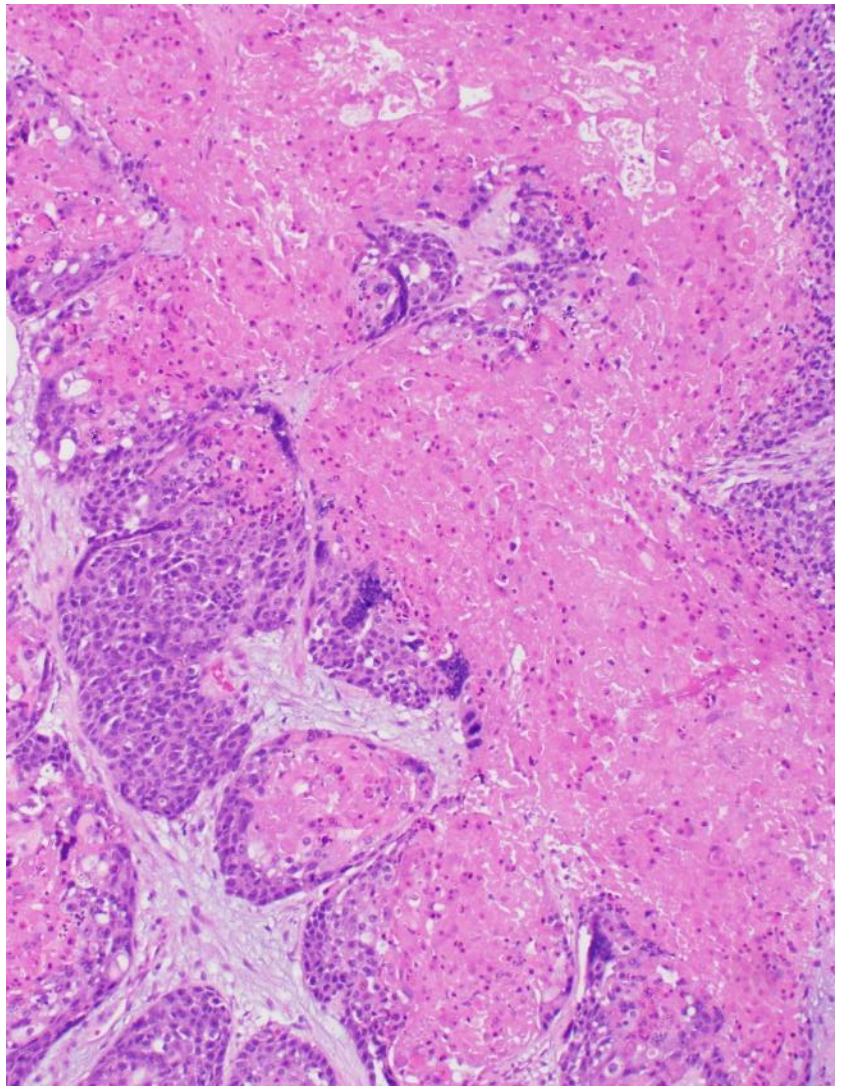
ER +

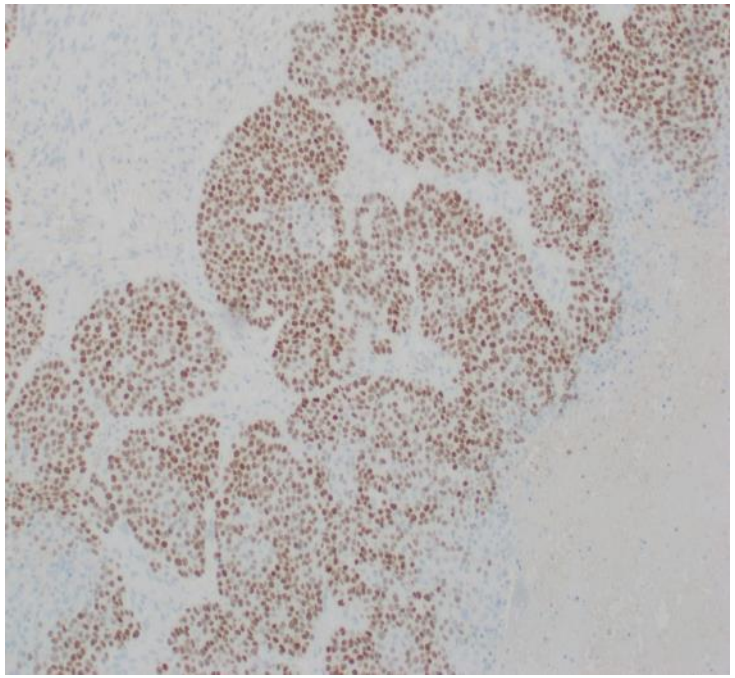


PR +

Endometrioid Ca and Poorly Differentiate Squamous Ca







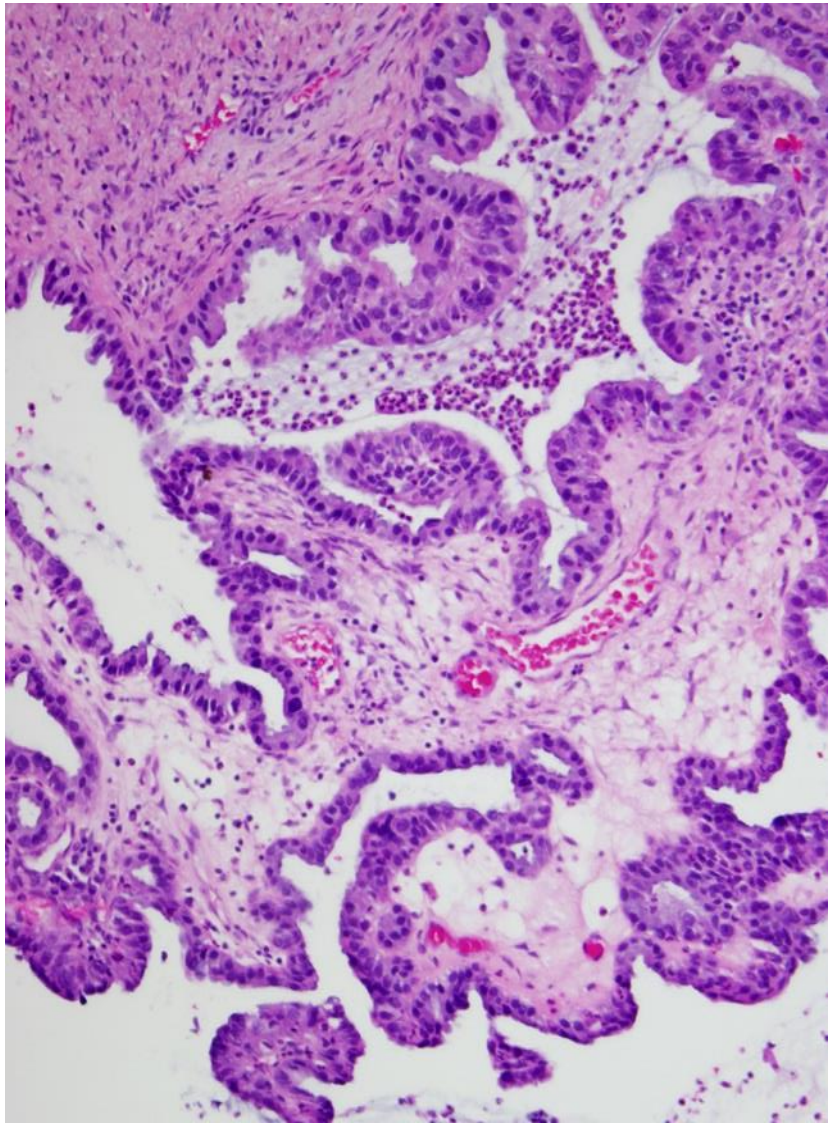
p40 and p63 positive

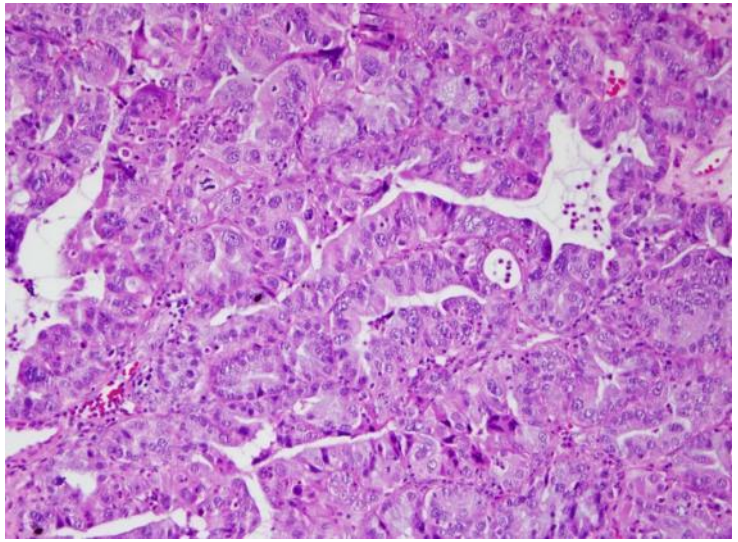
Endometrioid Carcinoma of Ovary

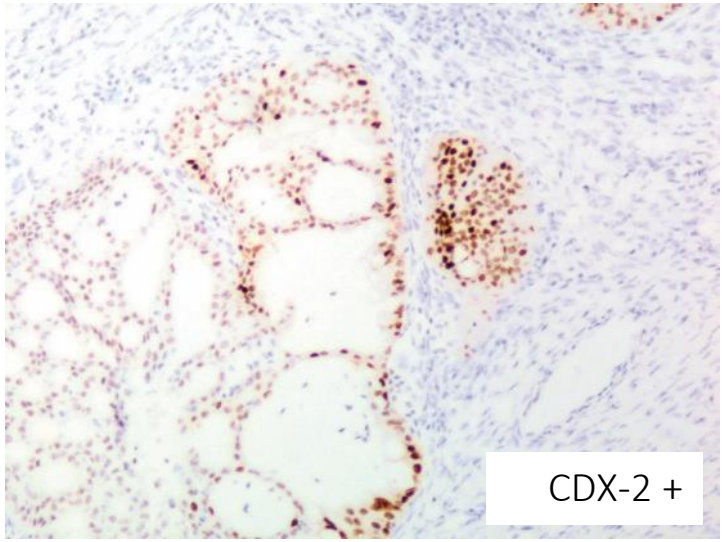
Molecular Subtype	Percentage
No specific molecular profile	69-73%
Hypermutated due to mismatch repair deficiency	13%
TP53 mutated	9-13%
Ultramutated due to *POLE* mutations	5%

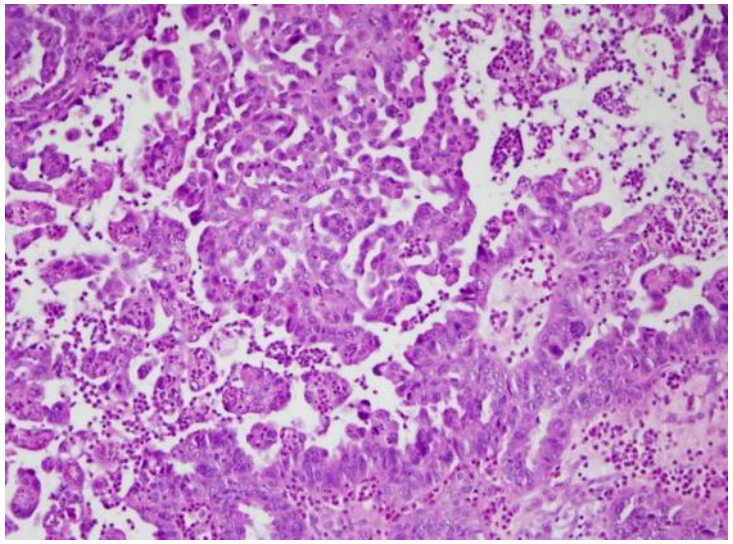
Mutation	Percentage
CTNNB1	53%
PIK3CA	40%
KRAS	33%
ARID1A	30%
PTEN	17%

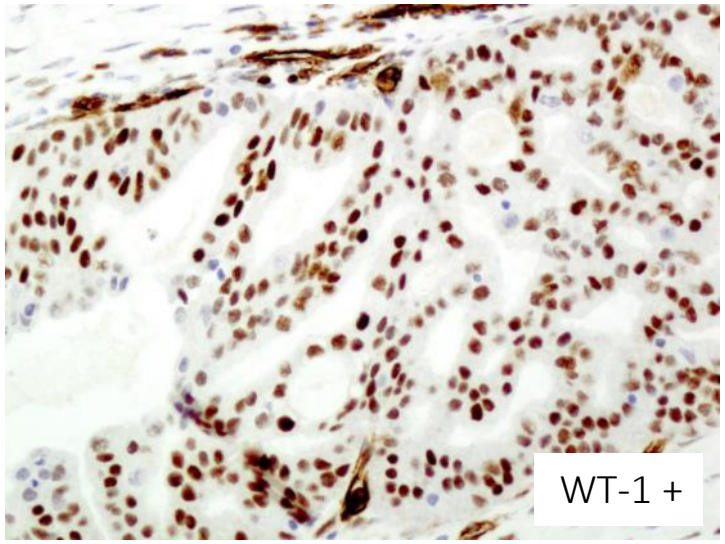
Seromucinous Carcinoma Arising in a Seromucinous Borderline Exists, but It Is a Rare Tumor



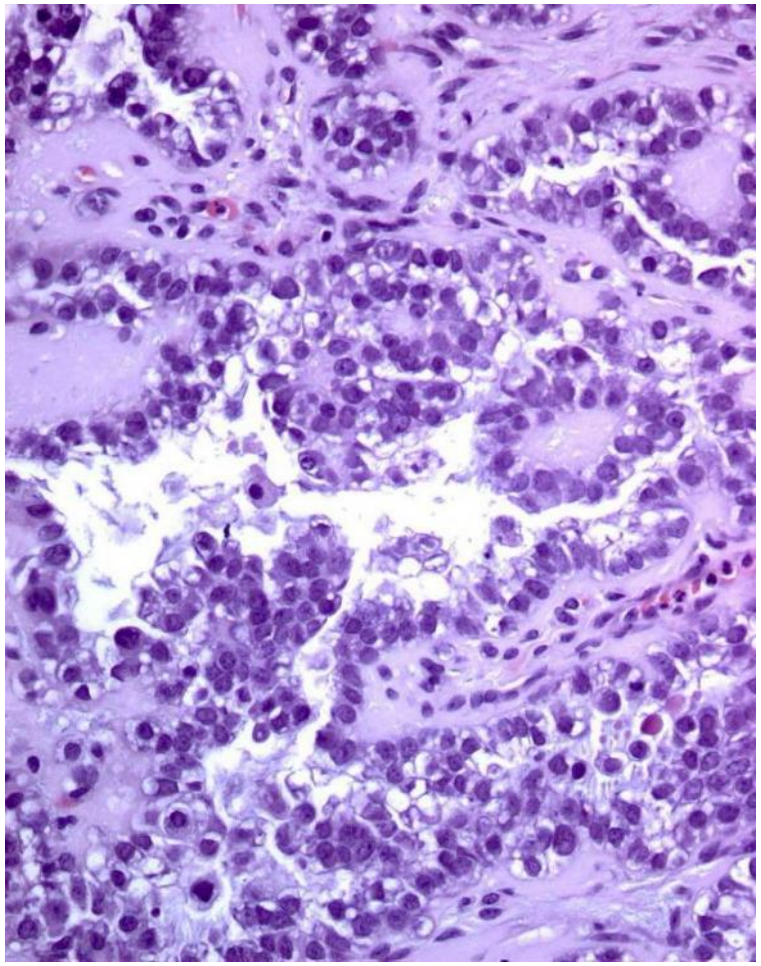


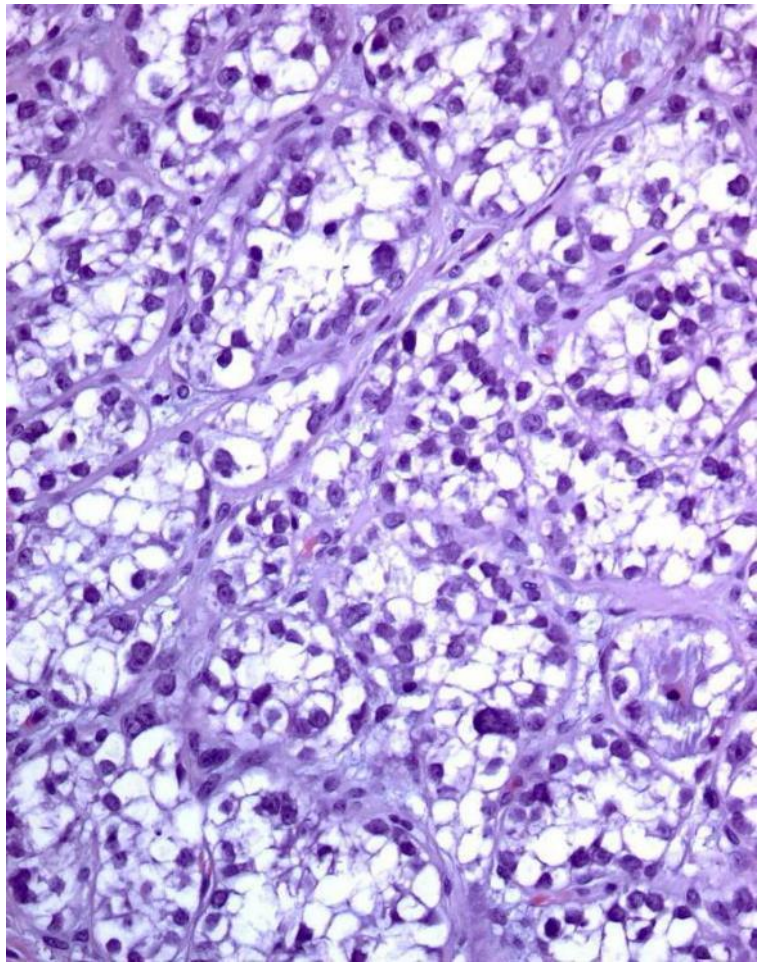


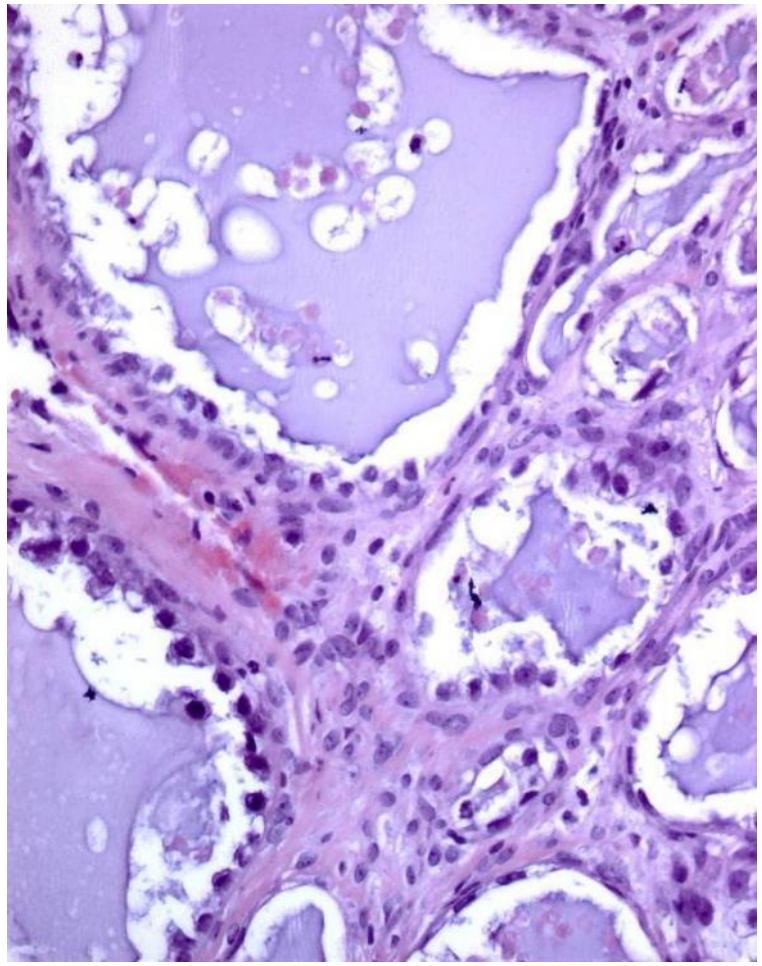


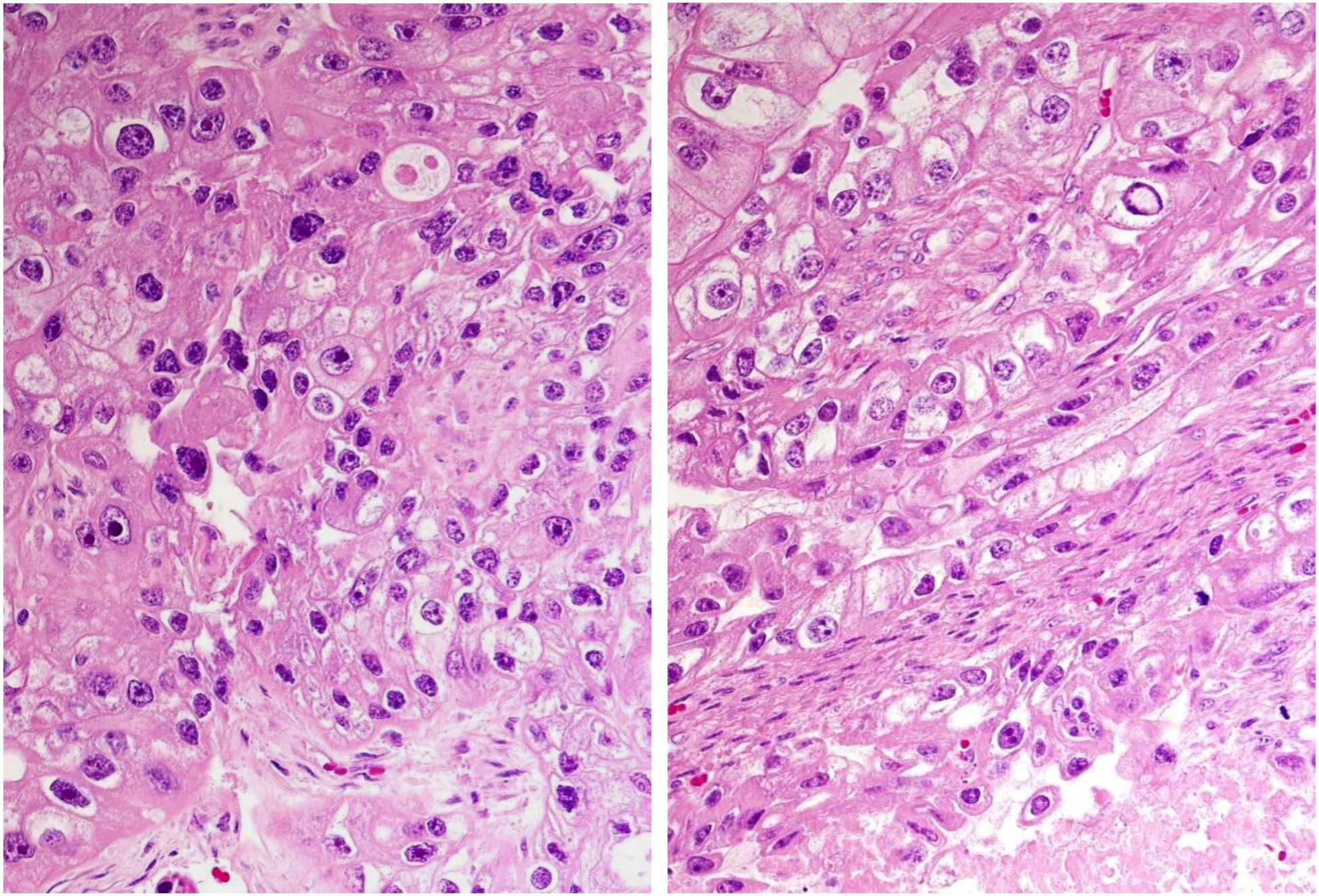


Clear Cell Carcinoma



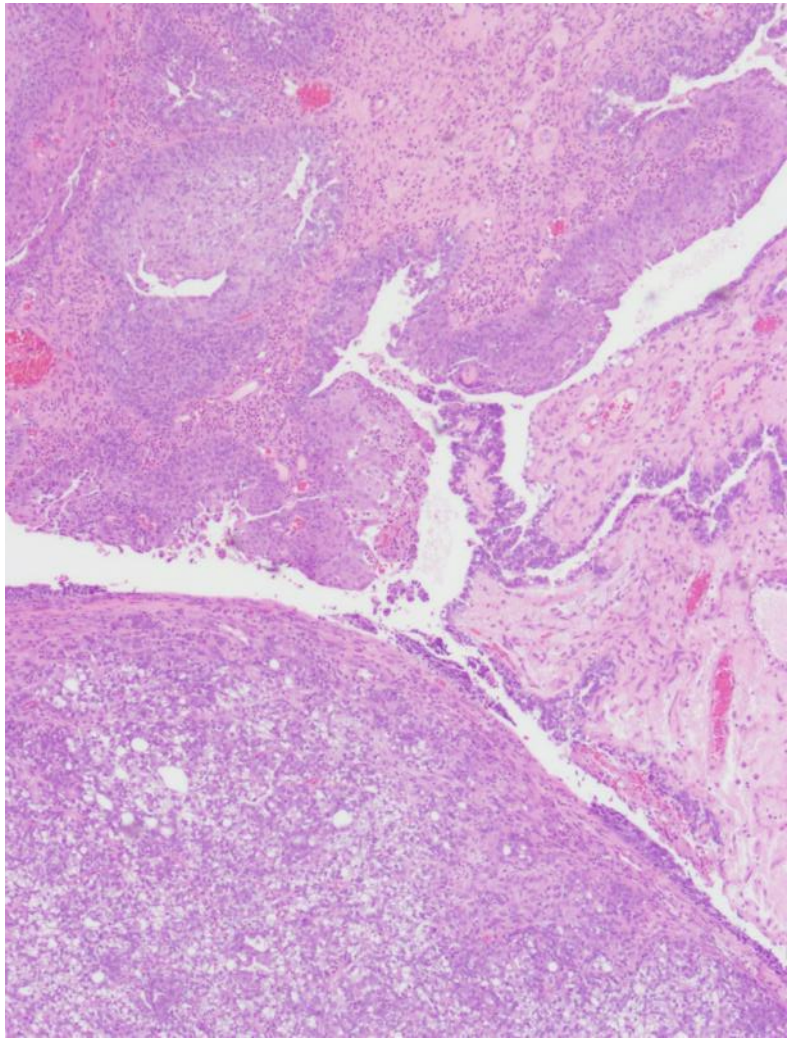


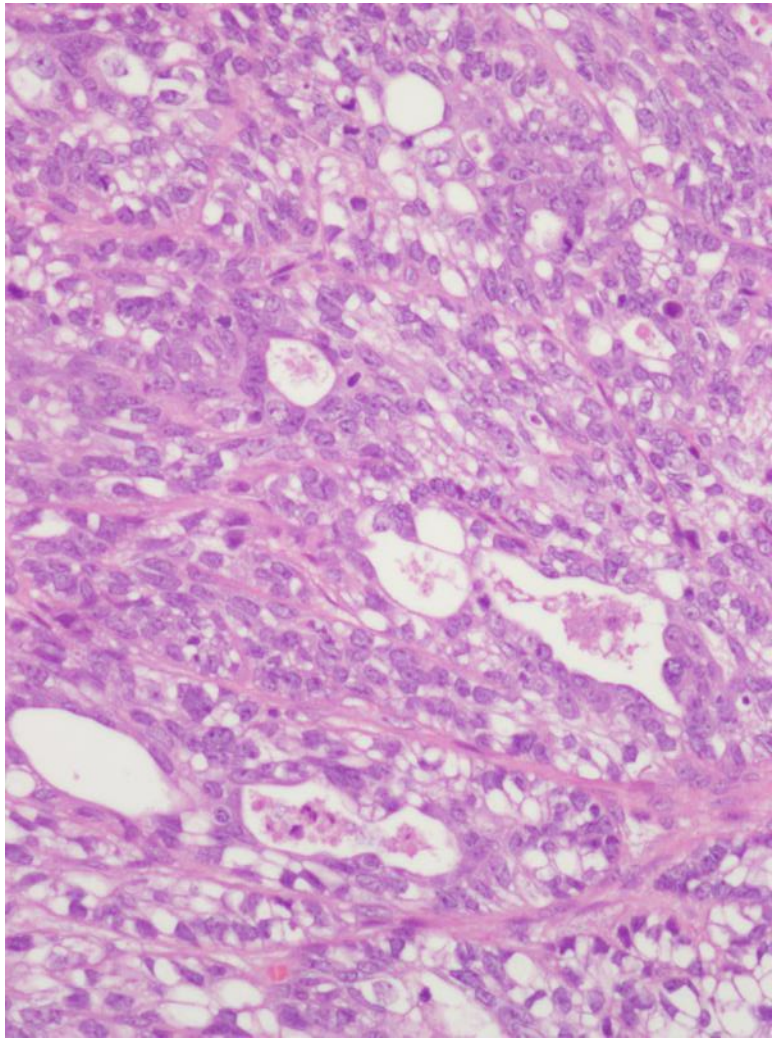


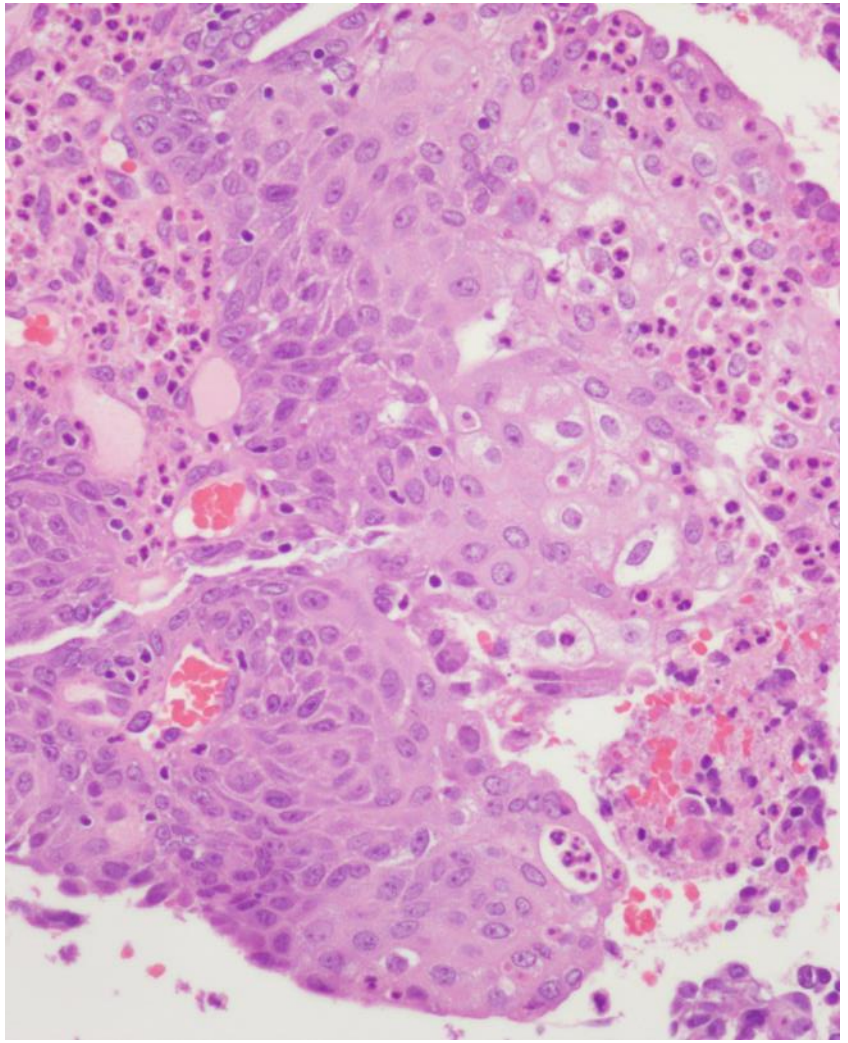


Discrepancy between the degree of atypia and the mitotic index

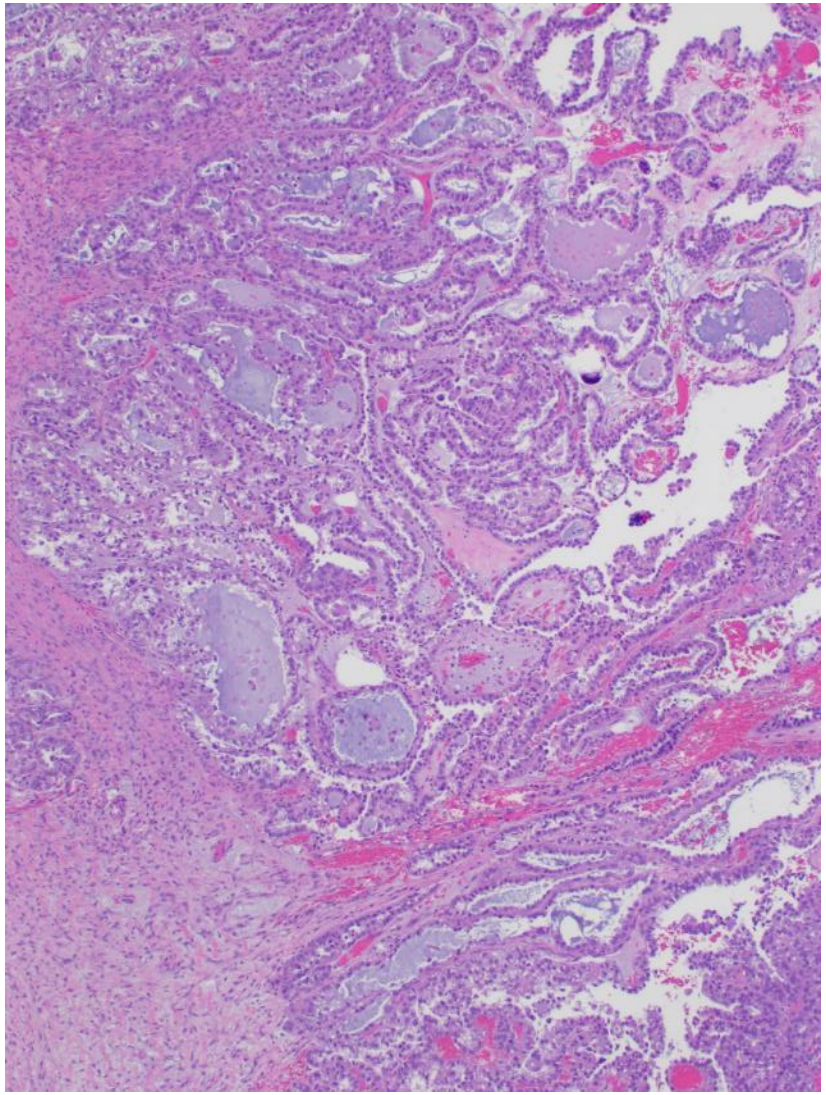
Clear Cell Carcinoma with Squamous Differentiation



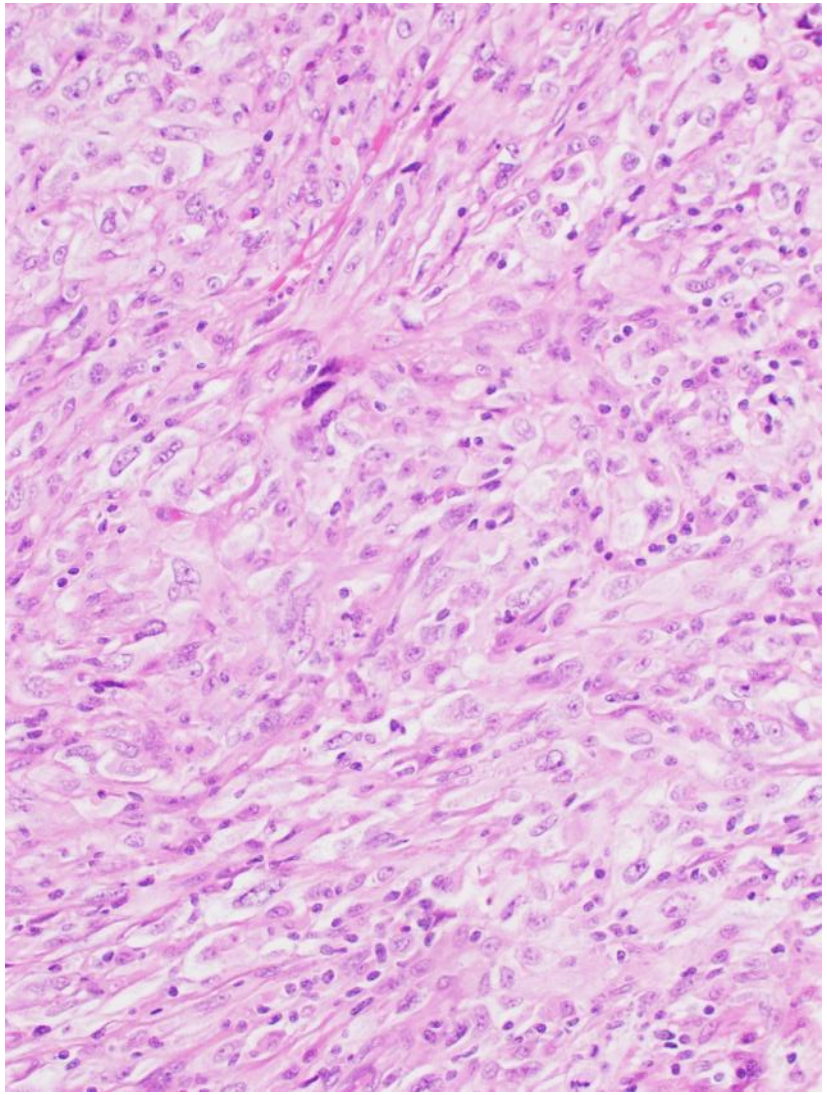


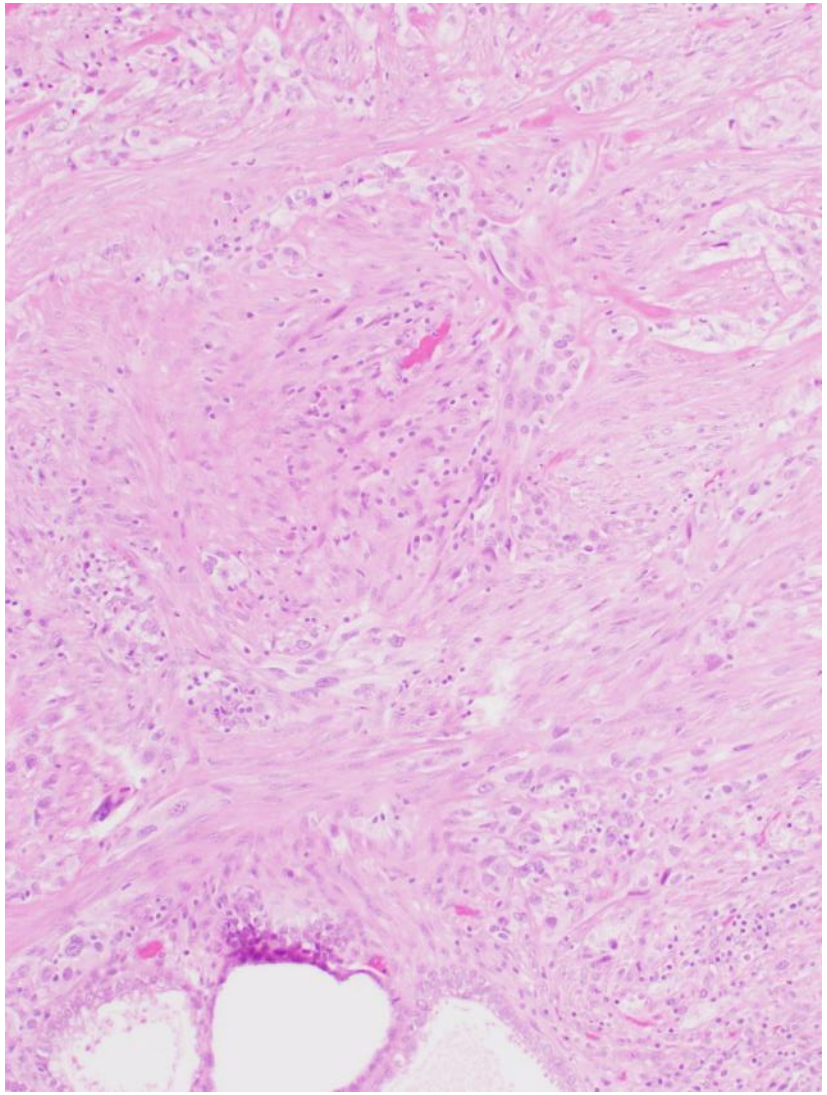


Abundant mucinous material

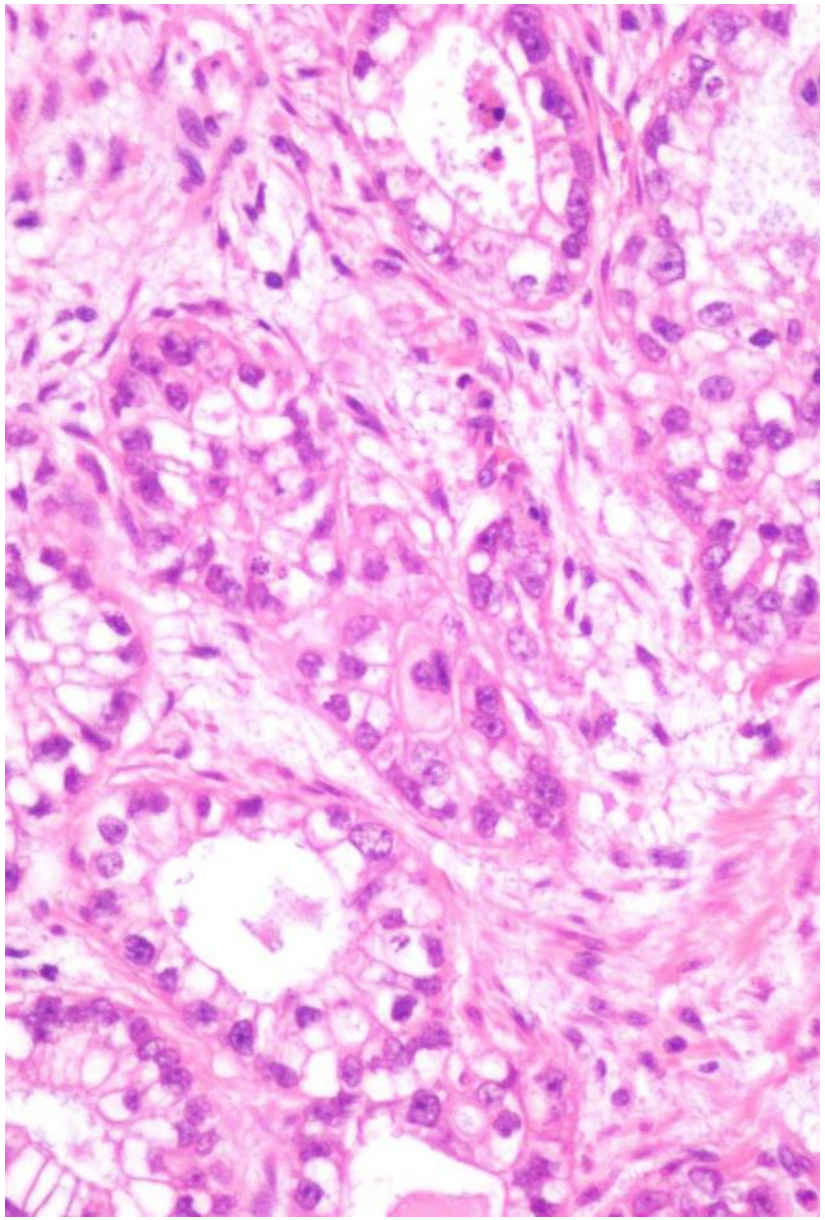


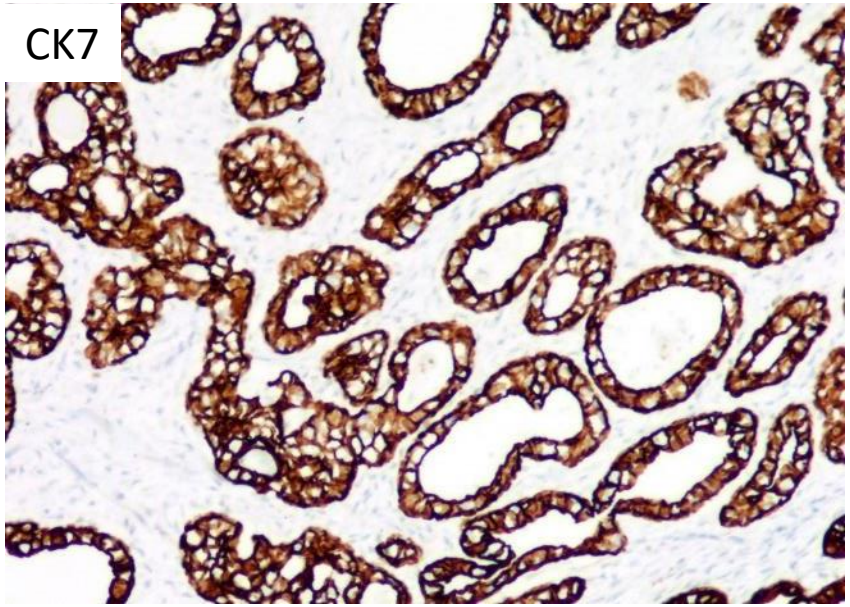
Sarcomatoid features

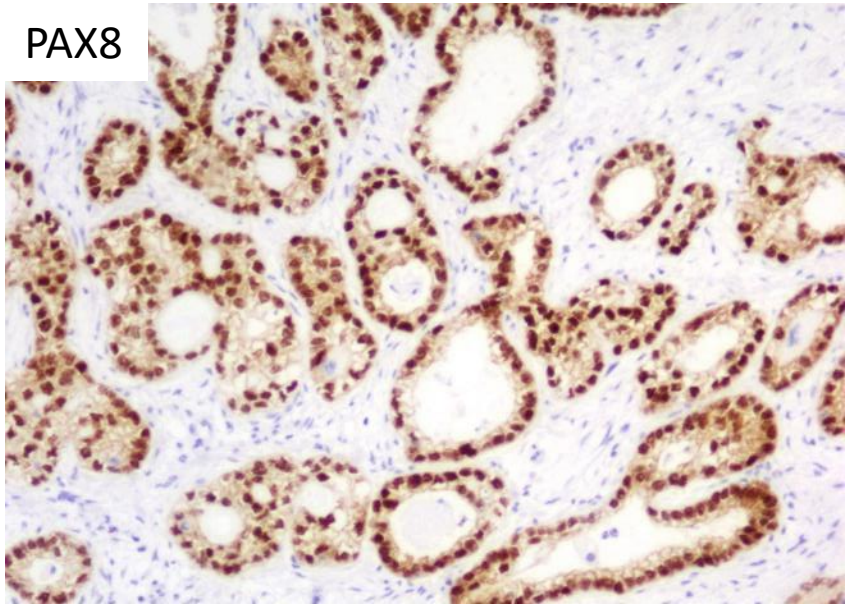


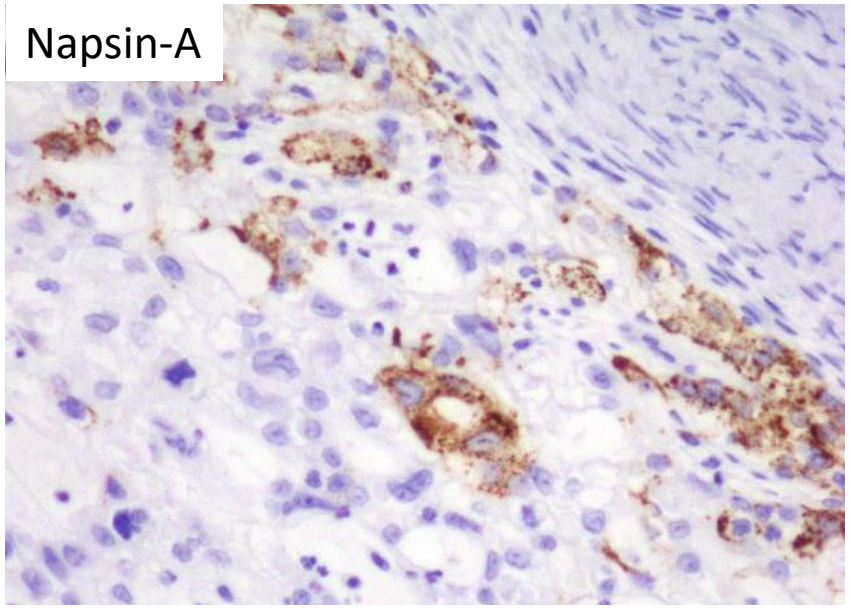


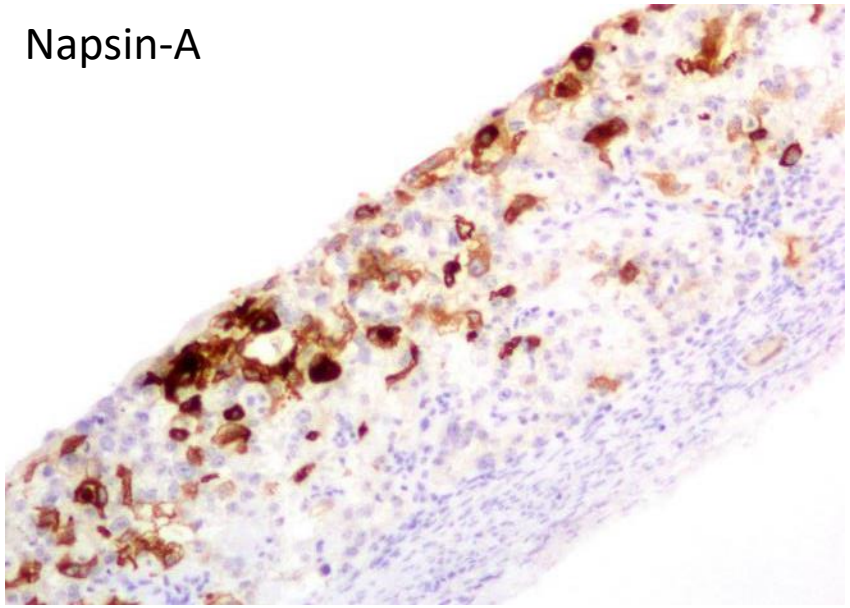
Clear Cell Carcinoma and Yolk Sac Tumor



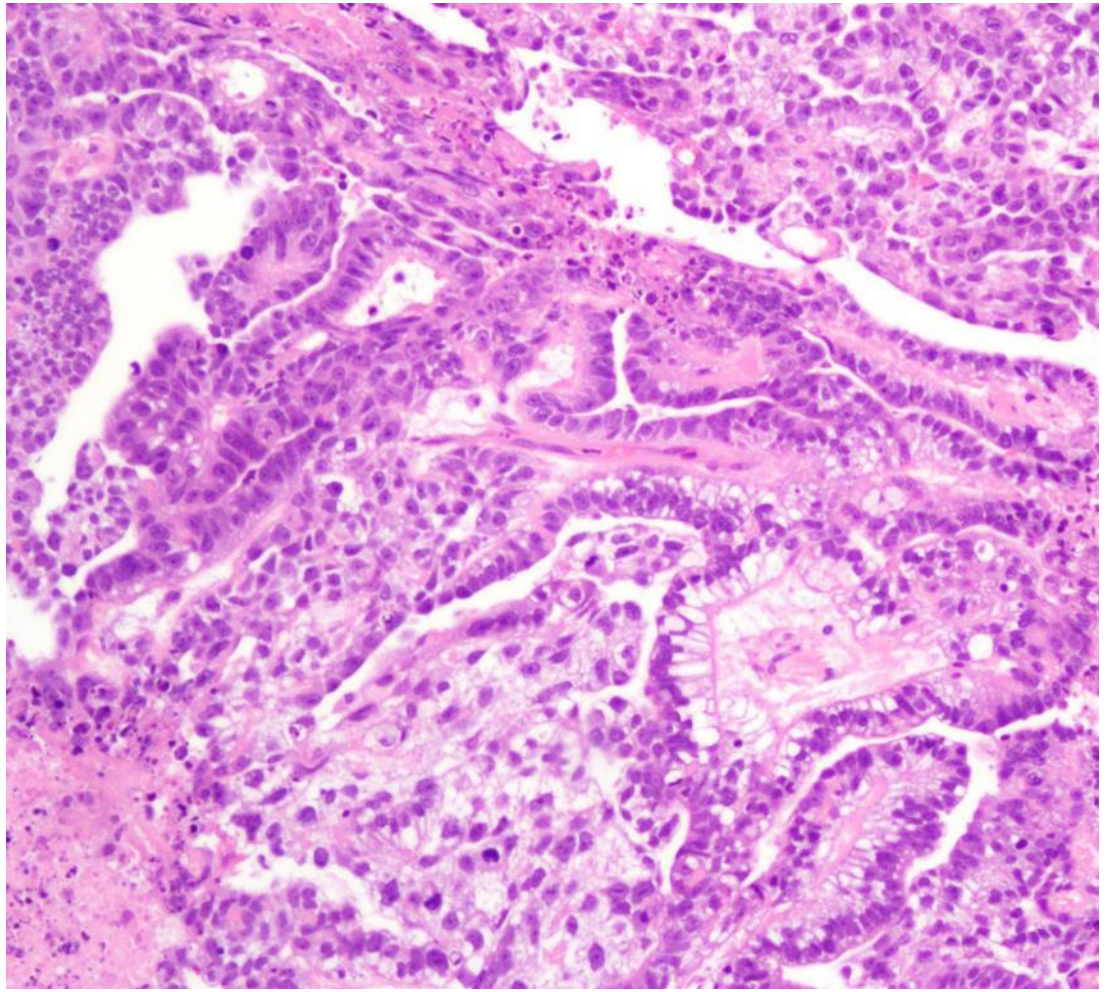


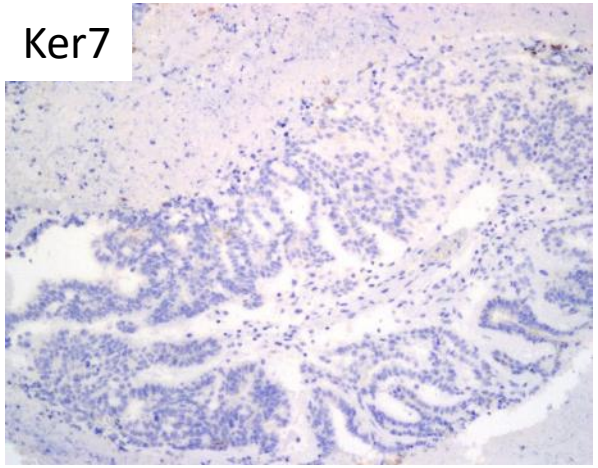


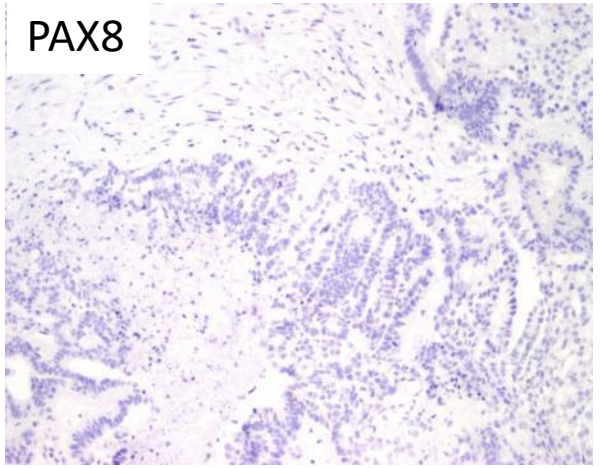


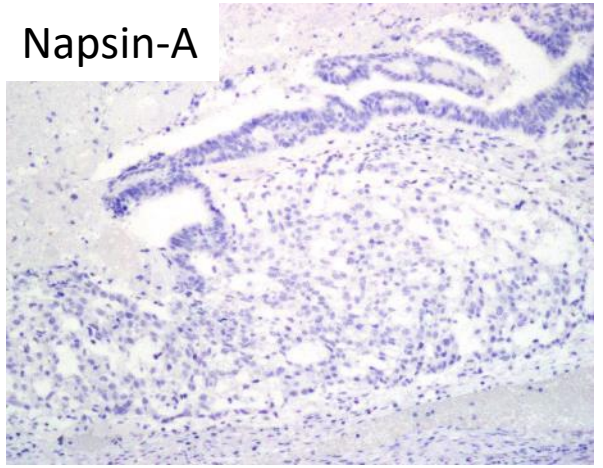


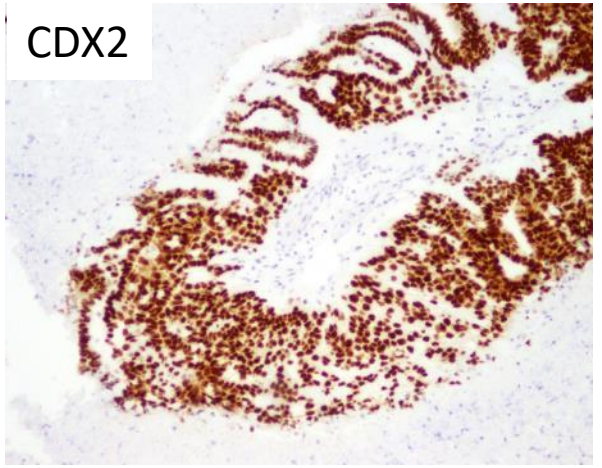
Clear Cell Carcinoma and Yolk Sac Tumor

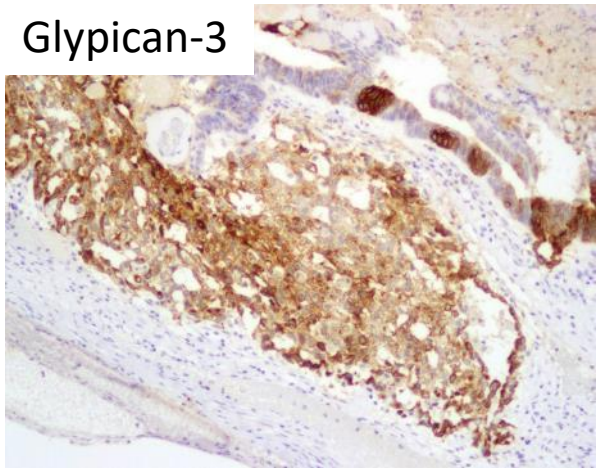


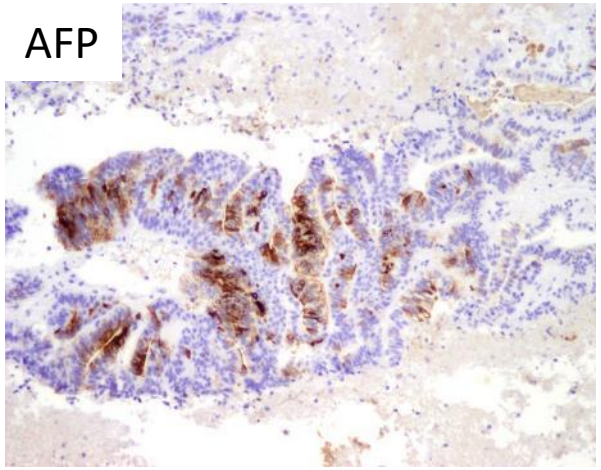












Clear Cell Carcinoma

Molecular classes, in descending order :

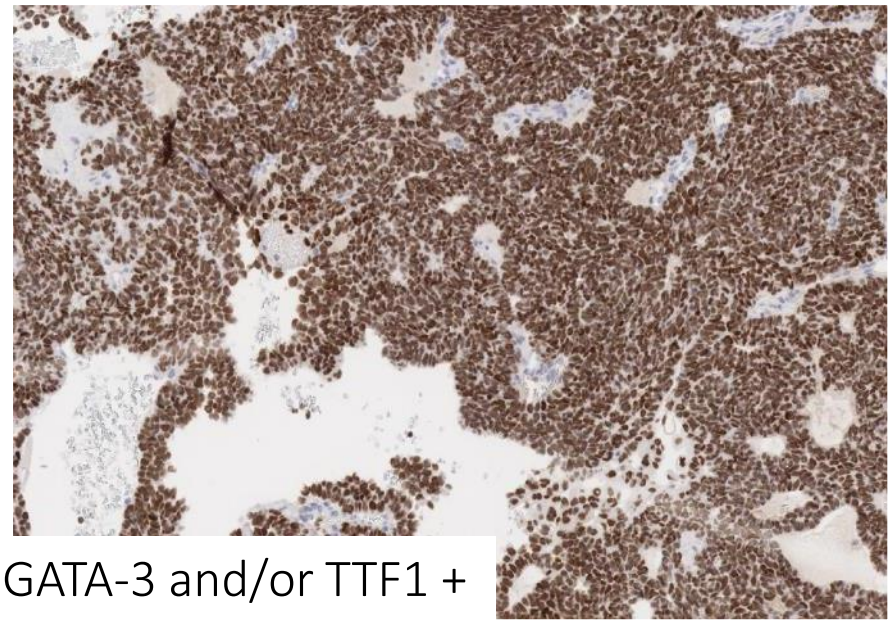
- No specific molecular profile
- *TP53*
- MMRd
- *POLE* mut

Most common mutations:

- *ARID1A*, 51%
- *PIK3CA, 47%*
- *TERT* promoter, 27%
- *KRAS*, 18%

- *TP53*, 12%
- ATM, 10%
- *PTEN*, 6%
- *POLE*, 4%

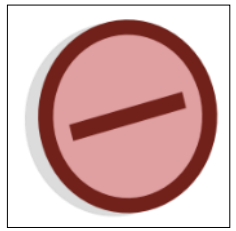
Mesonephric-like Ca



GATA-3 and/or TTF1 +

Mesonephric-like Ca IHC

- CK7
- PAX-8
- TTF-1
- GATA-3
- CD10 (luminal)

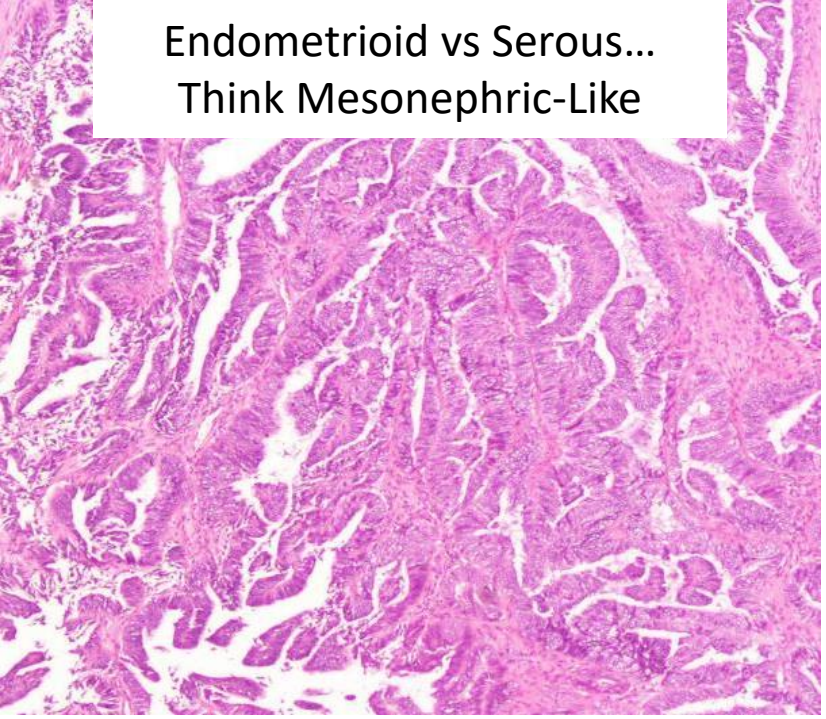
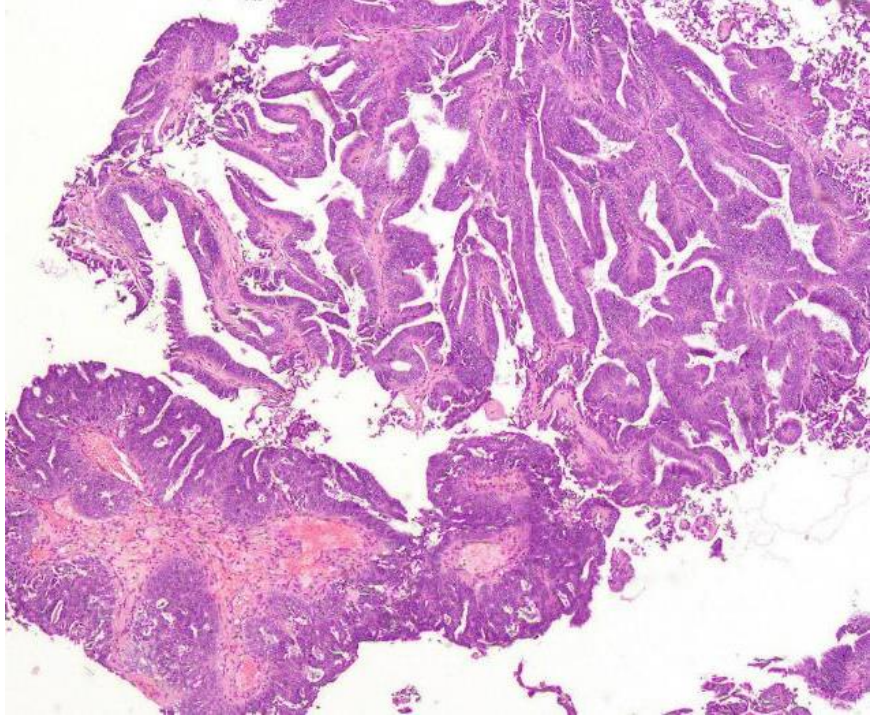
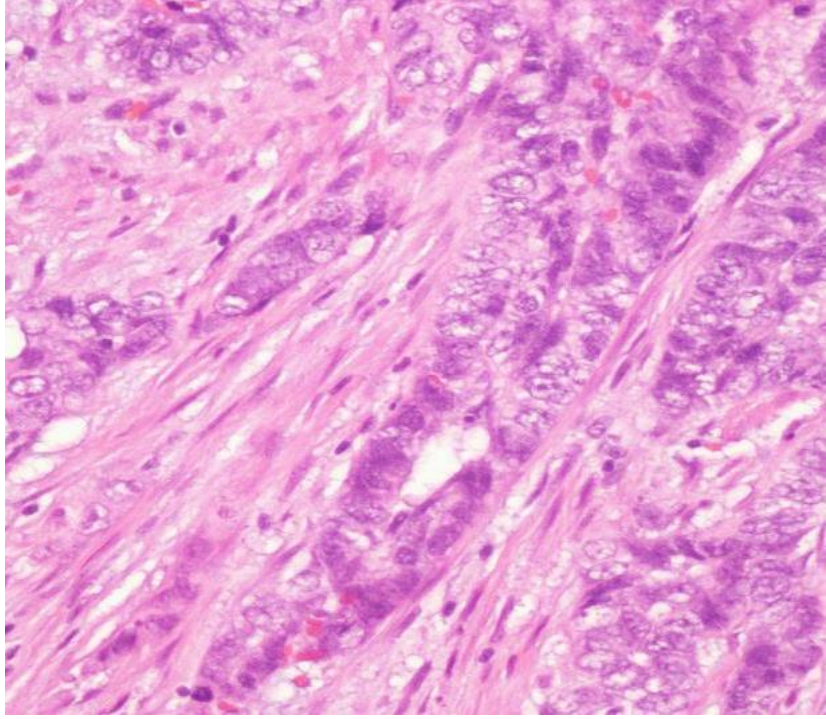
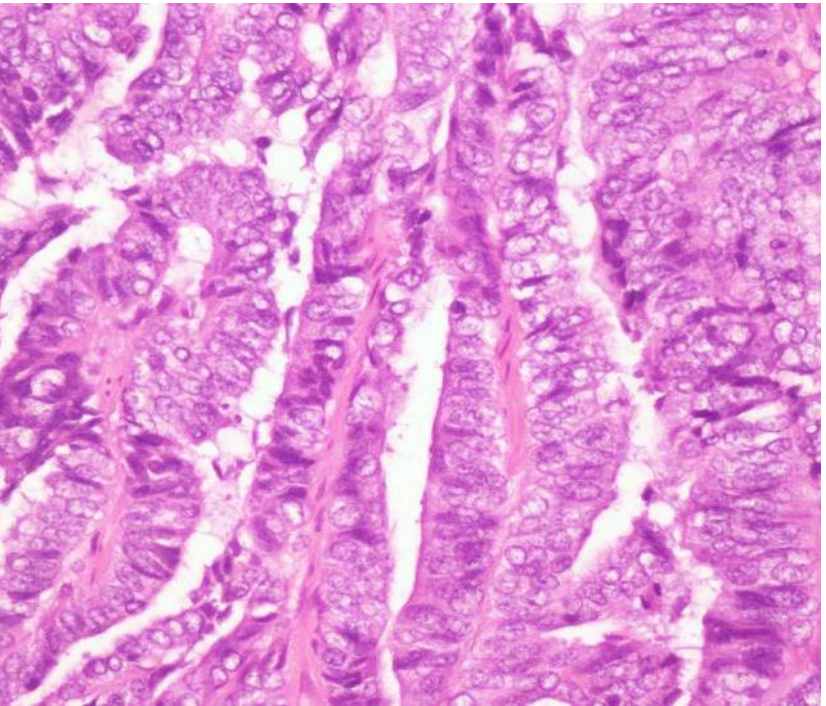
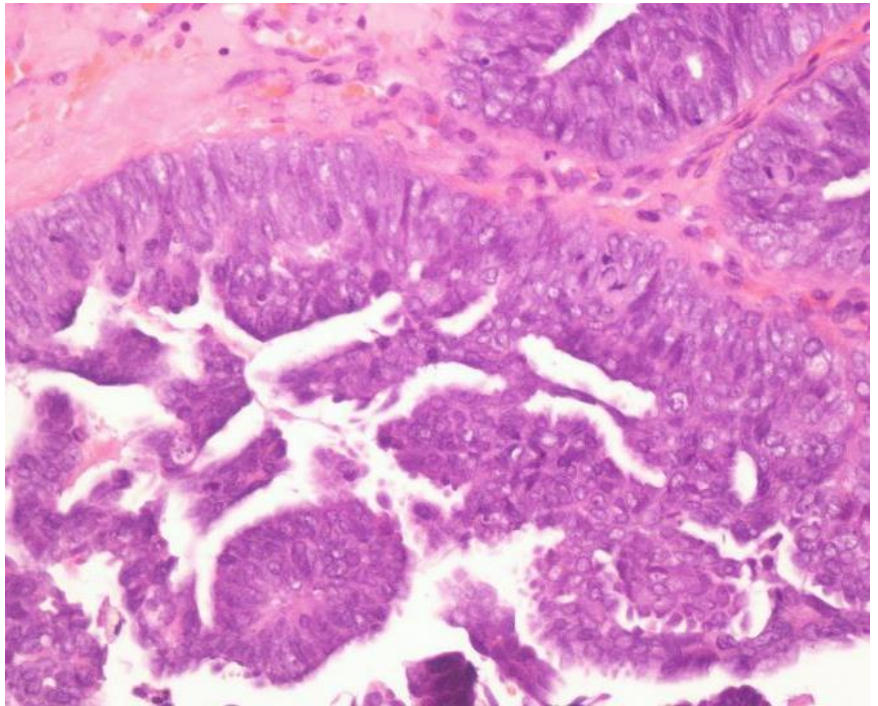
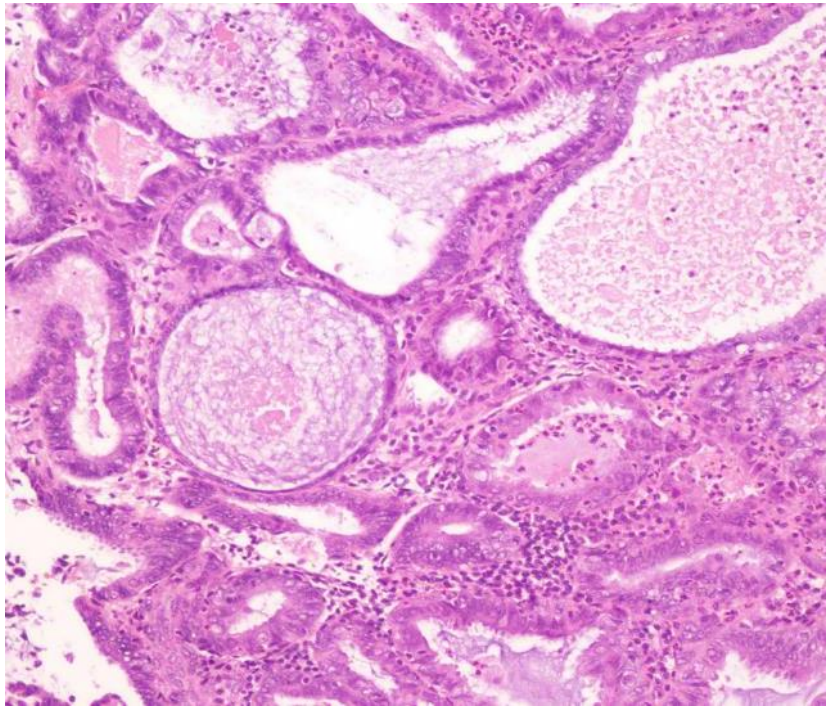


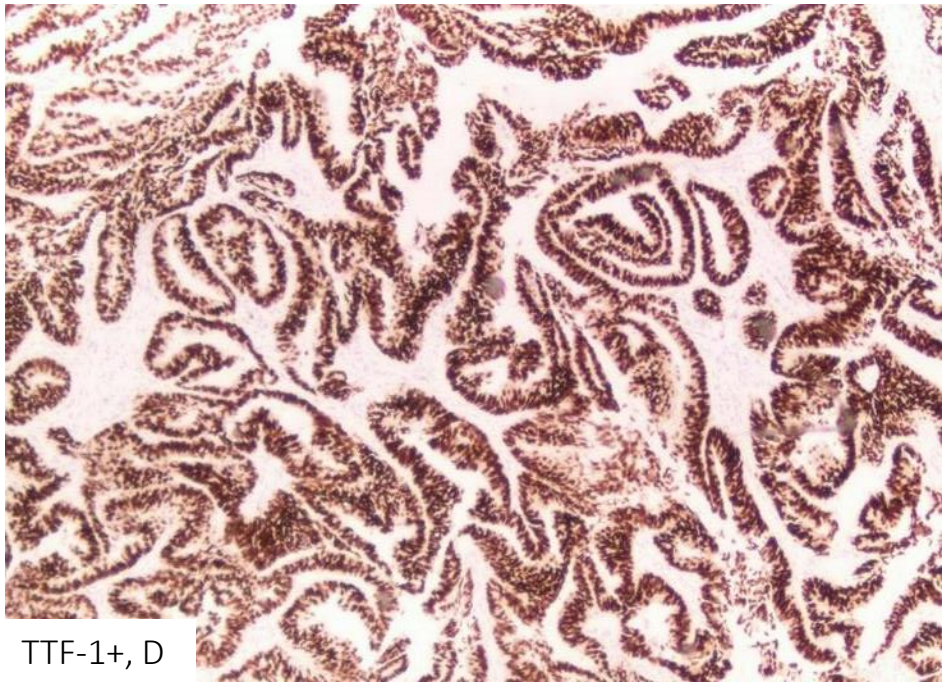
- ER
- PR

p53 wild type, HNF1B can be diffusely +

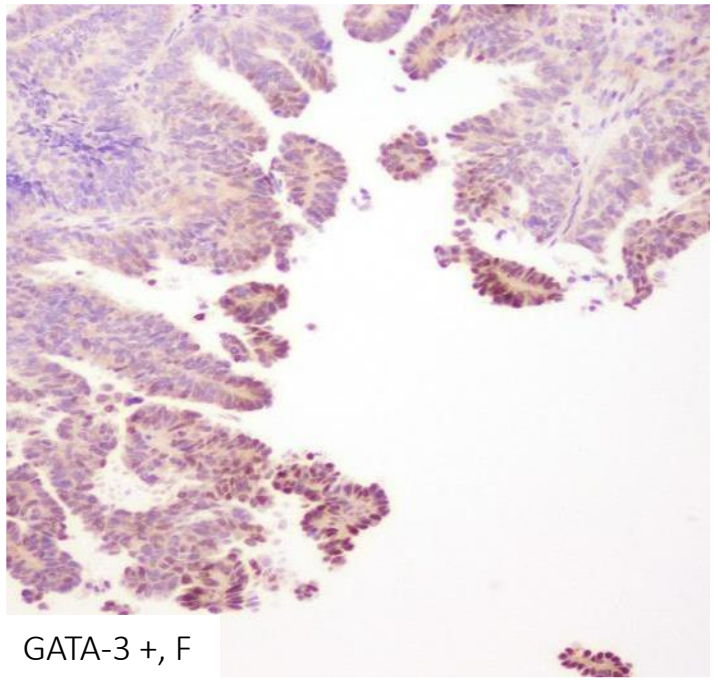
Napsin A and AMACR can be +, but only focally ≤ 5% of cells

Endometrioid vs Serous…
Think Mesonephric-Like

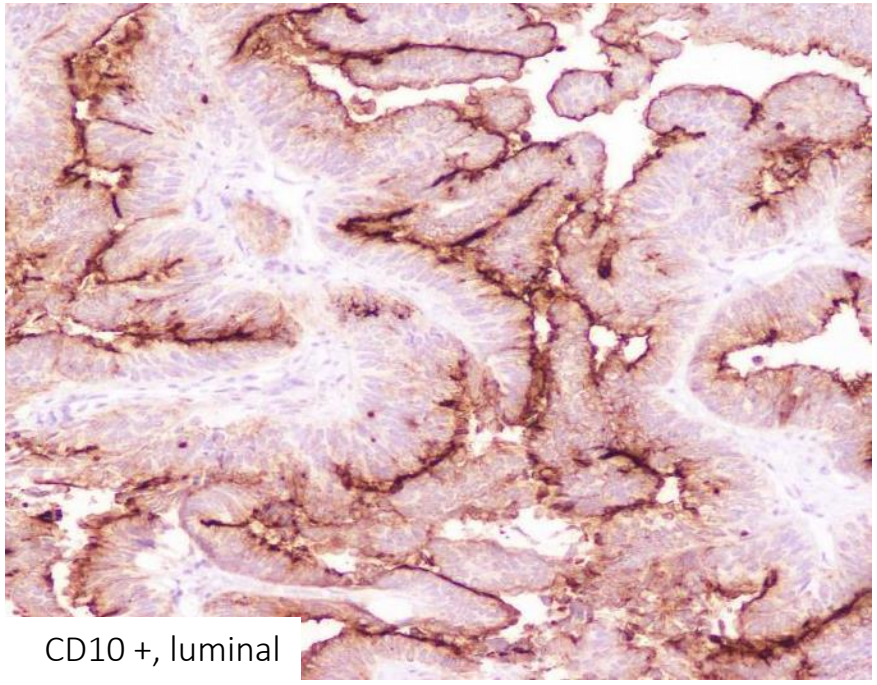









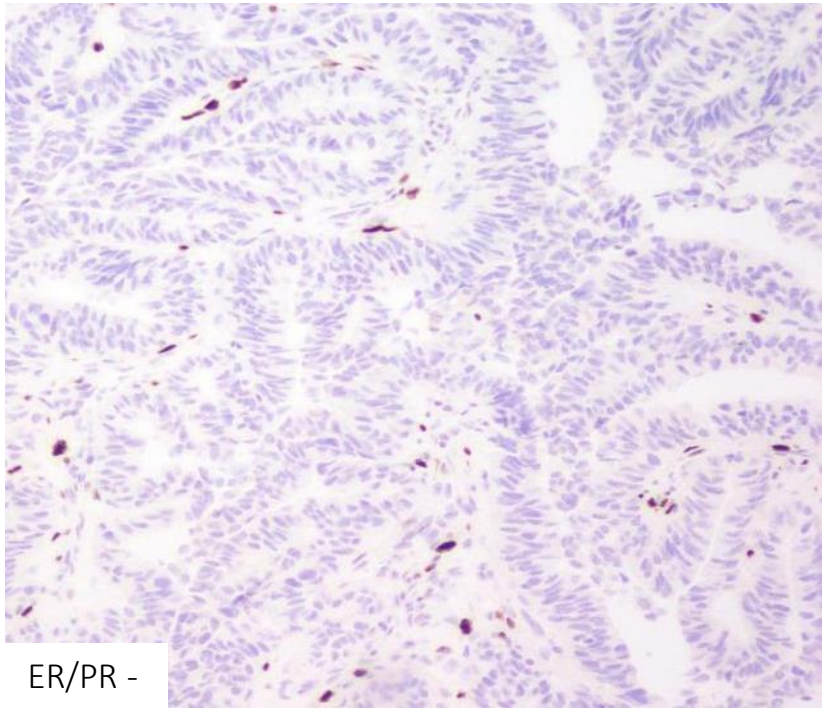
TTF-1+, D



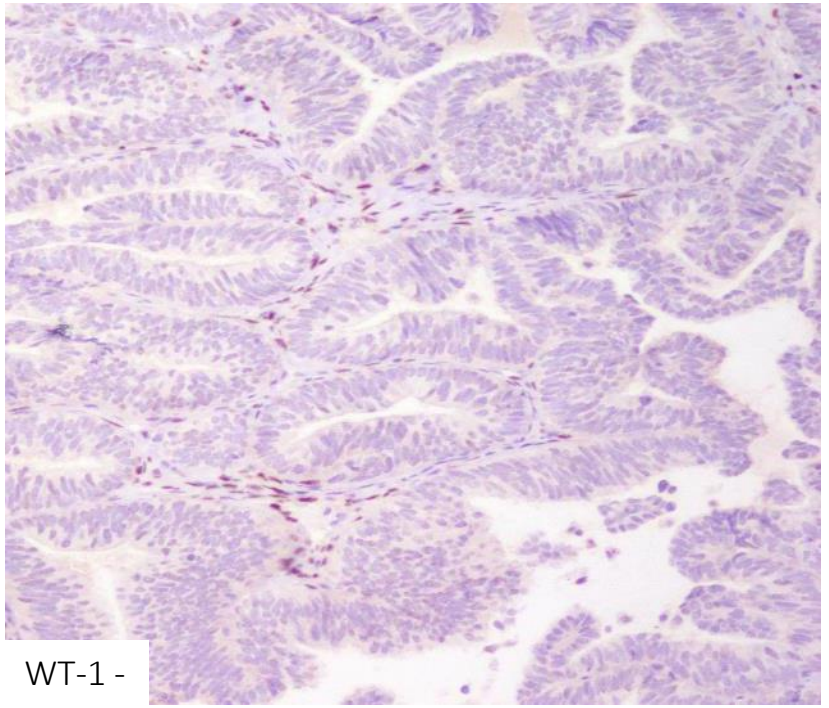
GATA-3 +, F



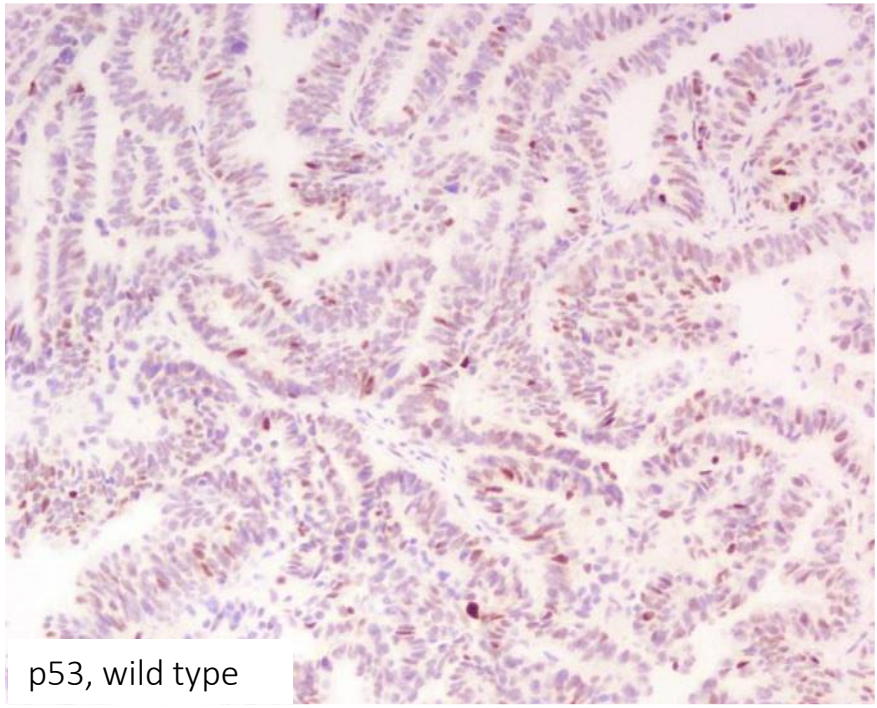
CD10 +, luminal



ER/PR -



WT-1 -



p53, wild type

ORIGINAL ARTICLE

Extrauterine Mesonephric-like Carcinoma

A Comprehensive Single Institution Study of 33 Cases

Elizabeth D. Euscher, MD, Mario L. Marques-Piubelli, MD,* Preetha Ramalingam, MD,* Ignacio Wistuba, MD,* Barrett C. Lawson, MD,* Michael Frumovitz, MD,† and Anais Malpica, MD**

(*Am J Surg Pathol* 2023;00:000–000)

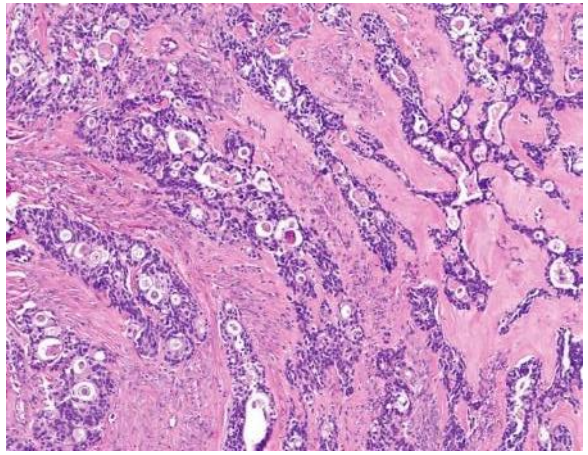
Pts' age: 37-74 yrs (median, 59 yrs)
Advanced stage disease (FIGO III/IV), 13
Sarcomatous differentiation, 2
Associations:
- endometriosis (63%)
- borderline tumor (21%)
- part of a mixed Ca (42%)

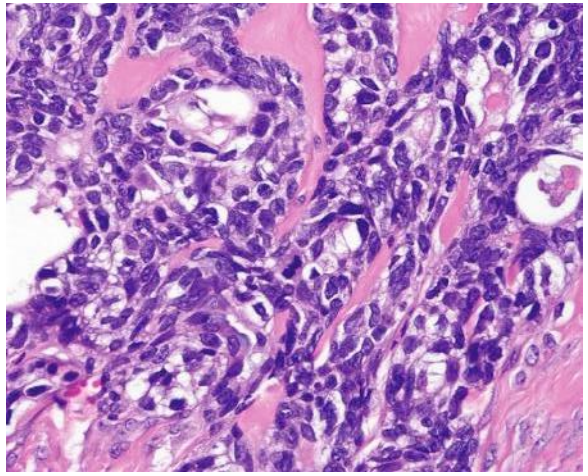
Misclassified, 42%
Molecular Findings: *Kras>>>>Tp53, SPOP, PIK3CA*
Metastasis: liver, lung, peritoneum
More aggressive than low grade endometrioid Ca

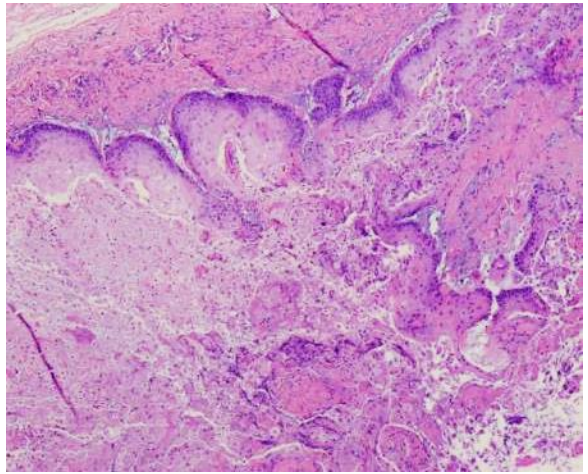
Malignant Brenner Tumor

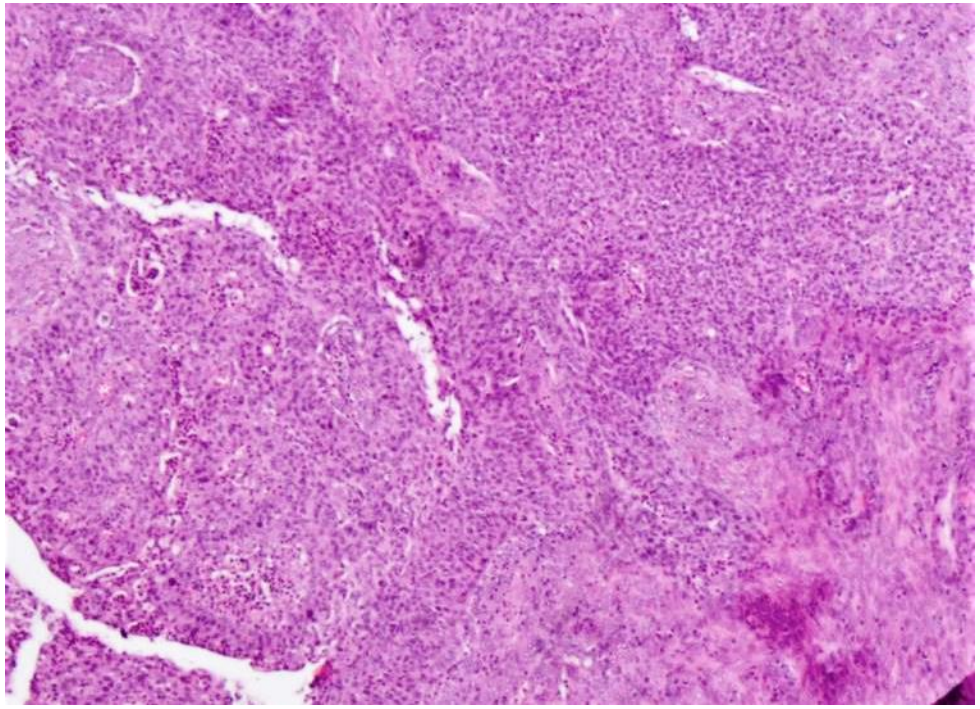
Molecular Findings

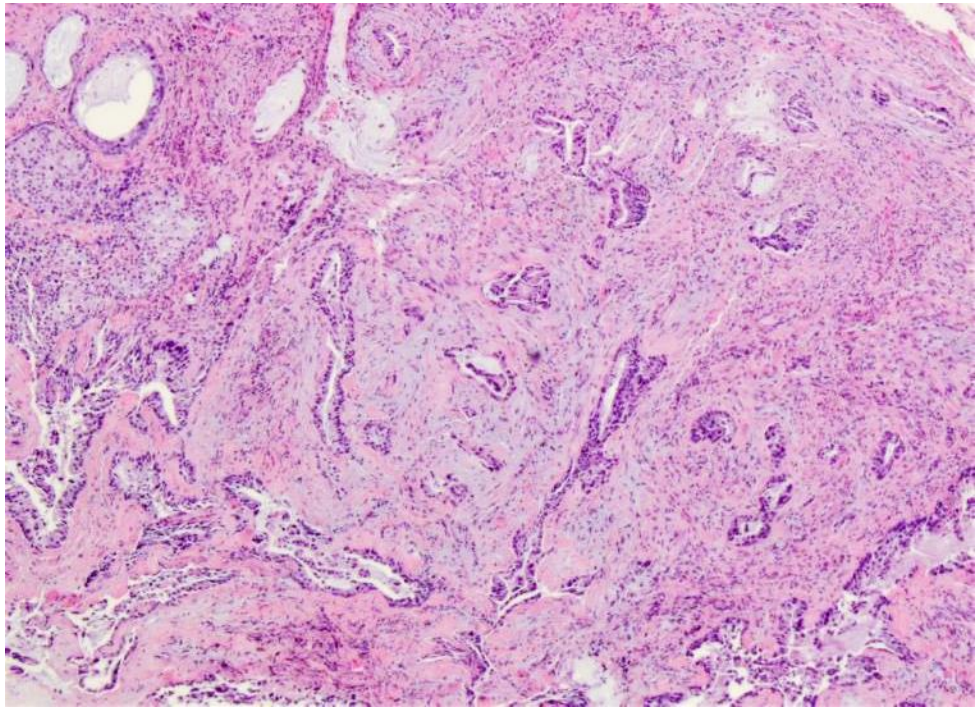
- *PIK3CA* mutations
- *MDM2* amplification



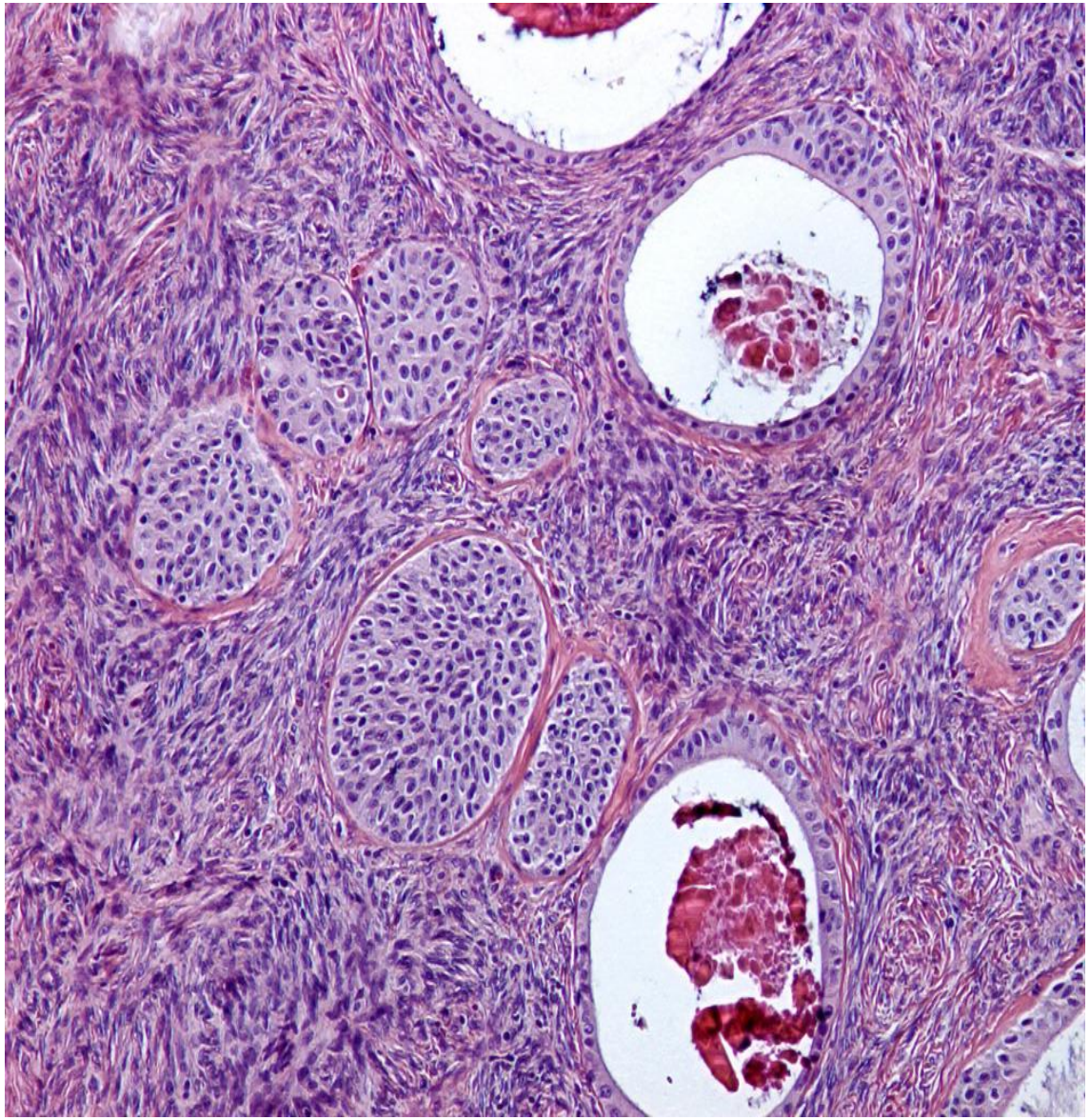




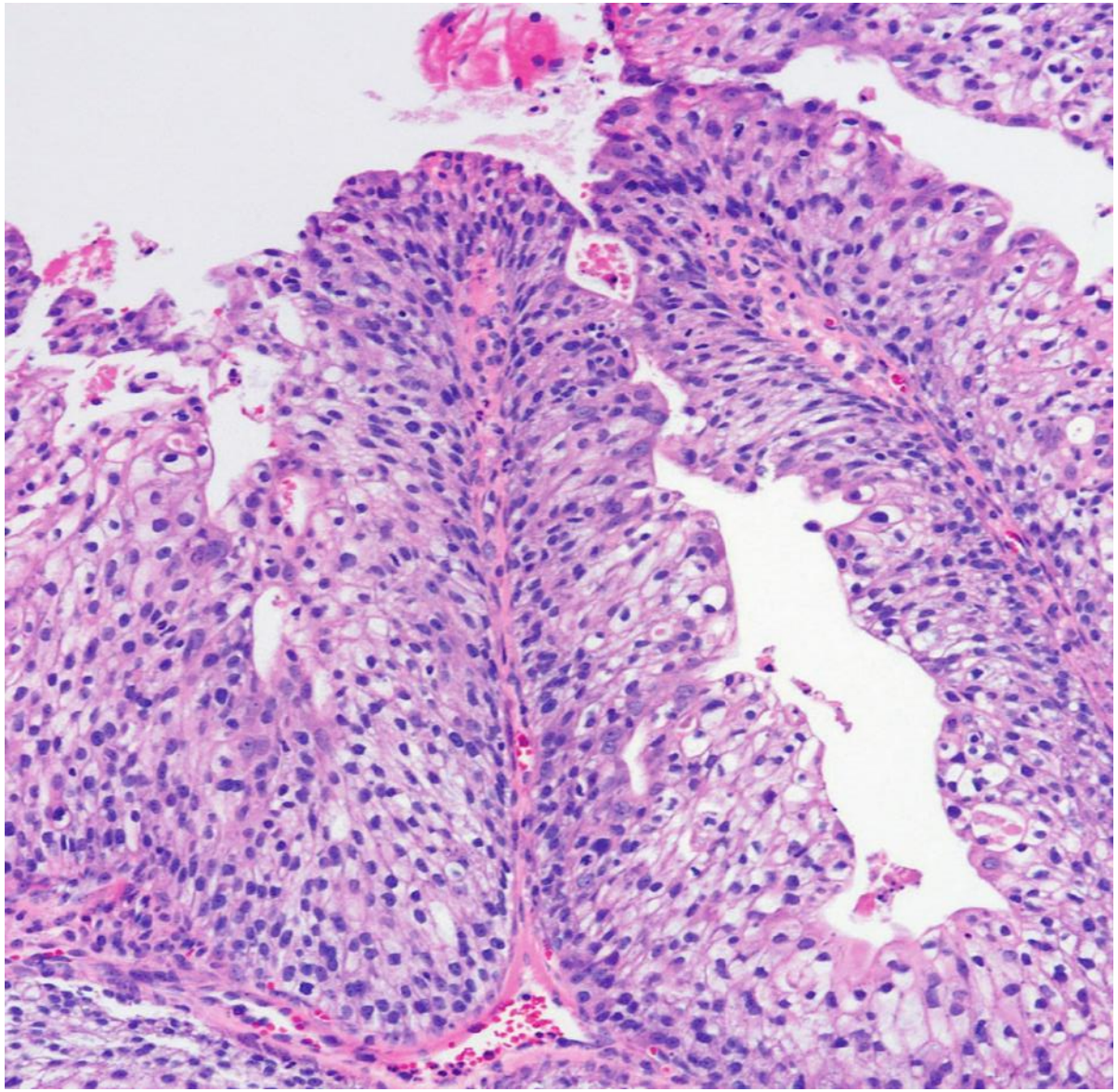




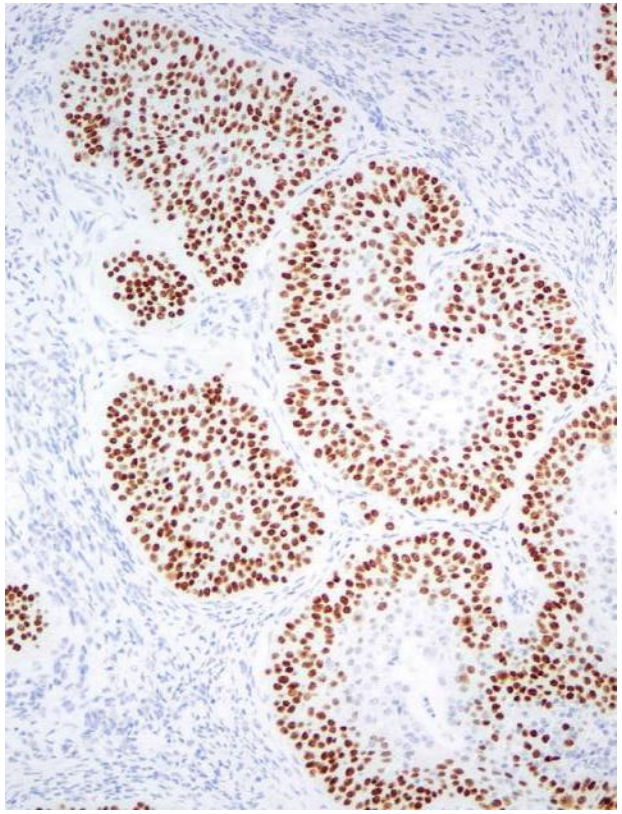
Brenner Tumor



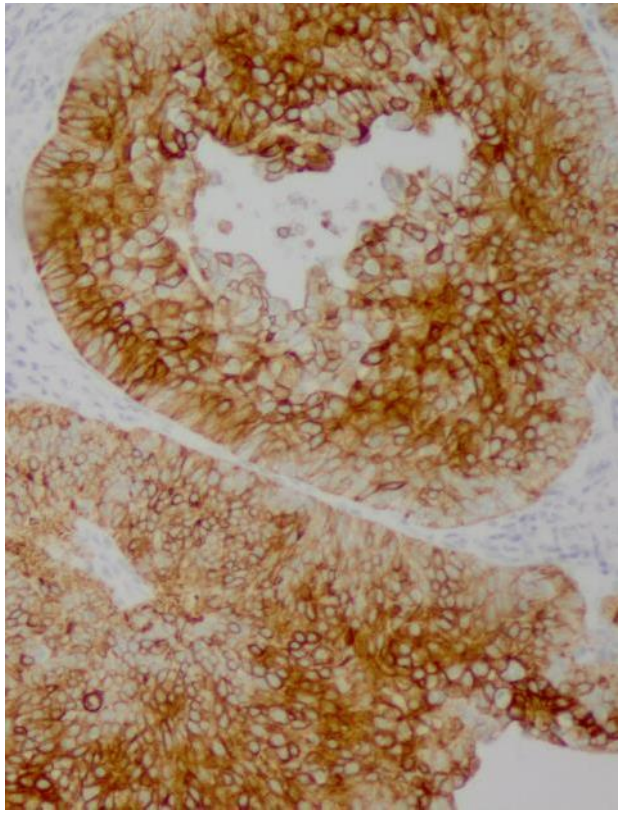
Borderline Brenner Tumor



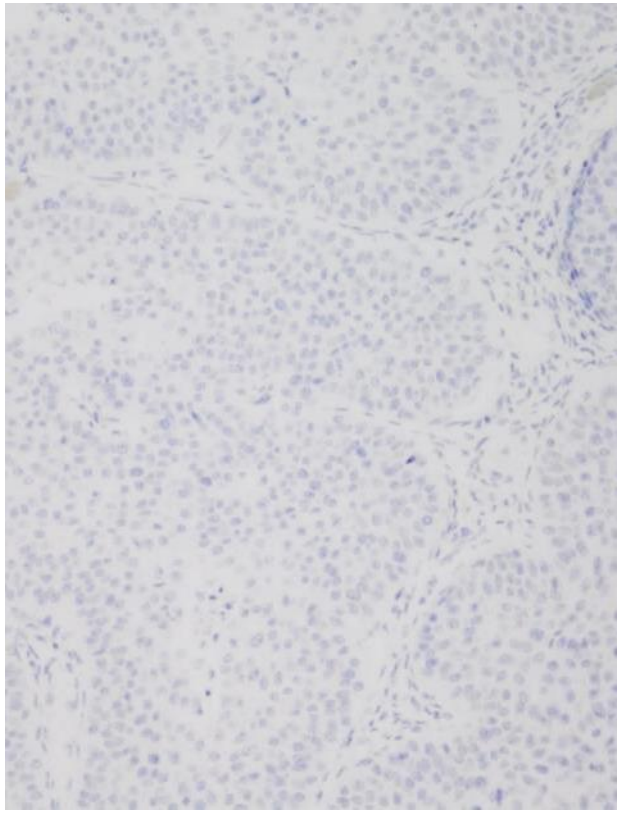
Malignant Brenner Tumor



p63 +



Ker 7 +



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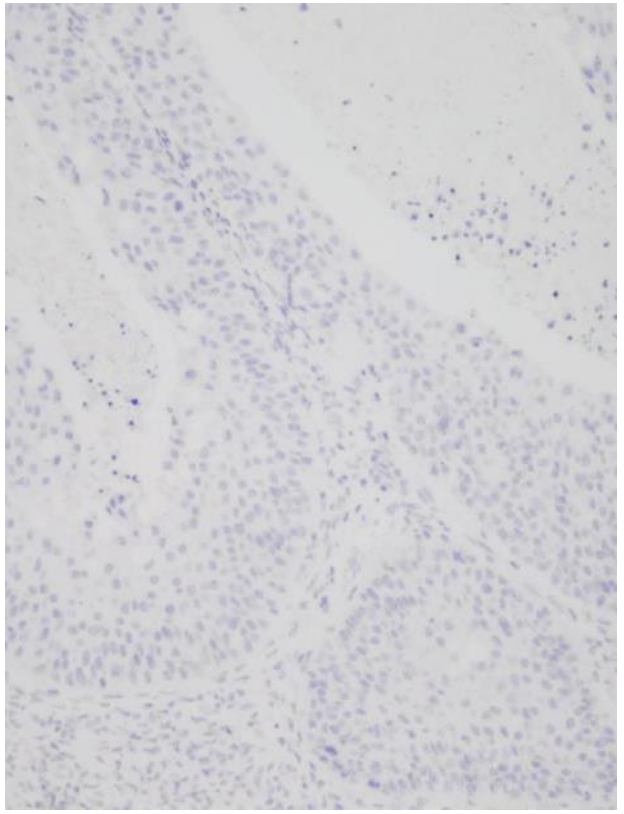
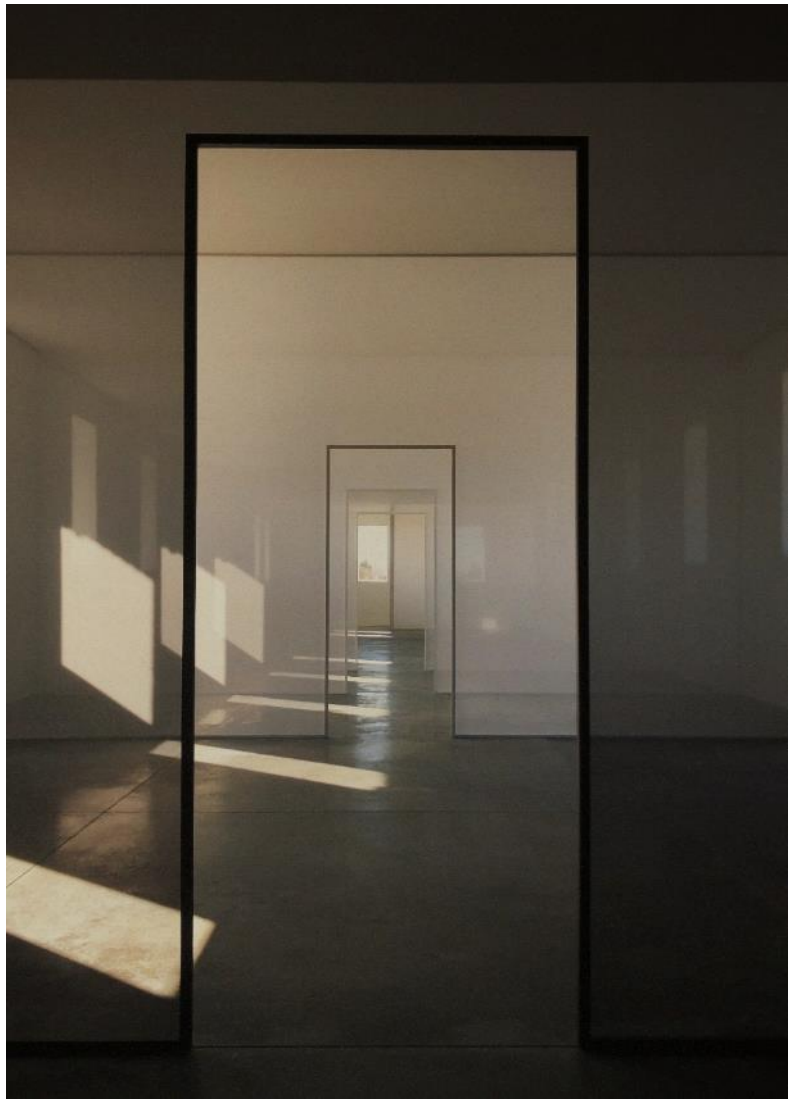


WT-1 -

West Texas is About the Light

A view from Fort Davis

Marfa



Installation by Robert Irwin, from the West Coast Light and Space Movement