

HISTOLOGIC VARIANTS OF BLADDER CANCER: *DIAGNOSTIC, THERAPEUTIC AND PROGNOSTIC IMPLICATIONS*

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UNUSUAL “EPITHELIAL” NEOPLASMS IN THE BLADDER

- **Primary:** Urothelial carcinoma & its variants, squamous cell carcinoma & adenocarcinoma
- ***Metastatic***
- ***Non-epithelial***

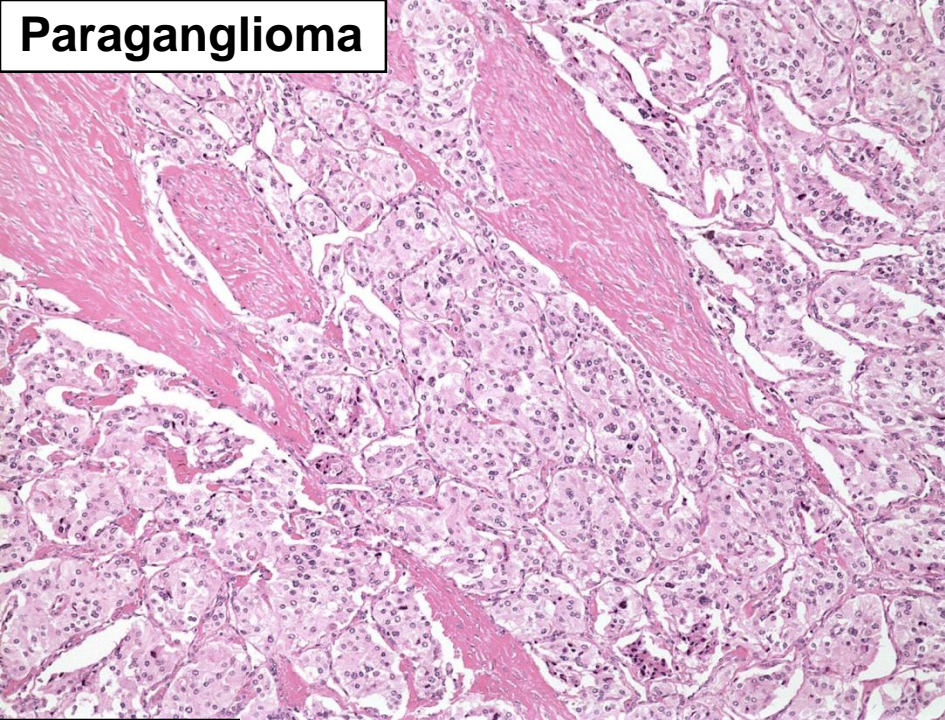
Paraganglioma

PEComa

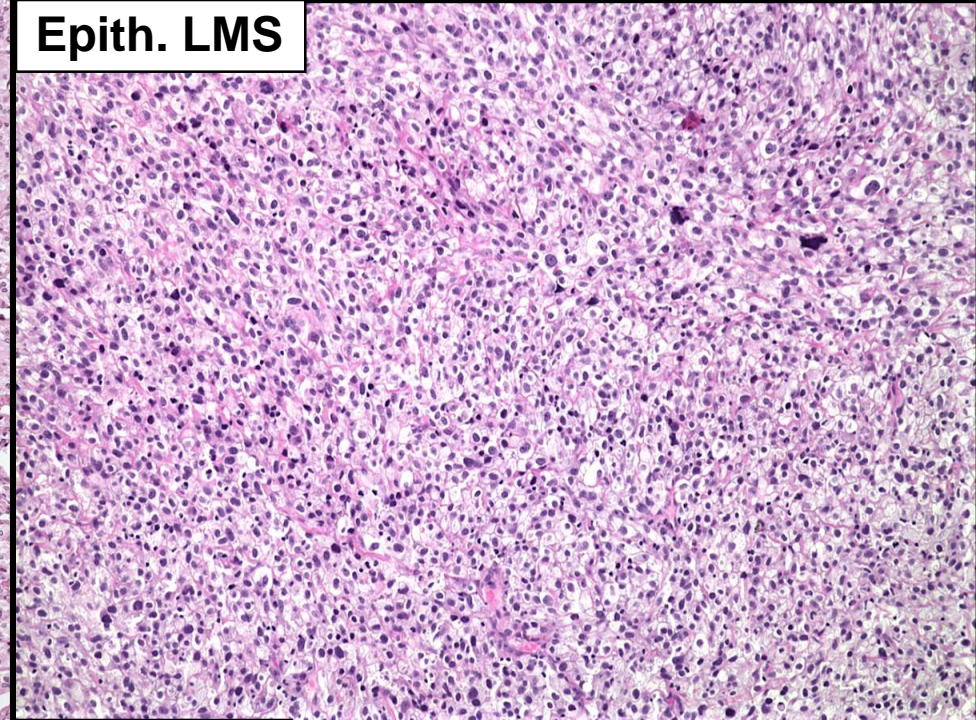
Epith. LMS

Prim. Melanoma

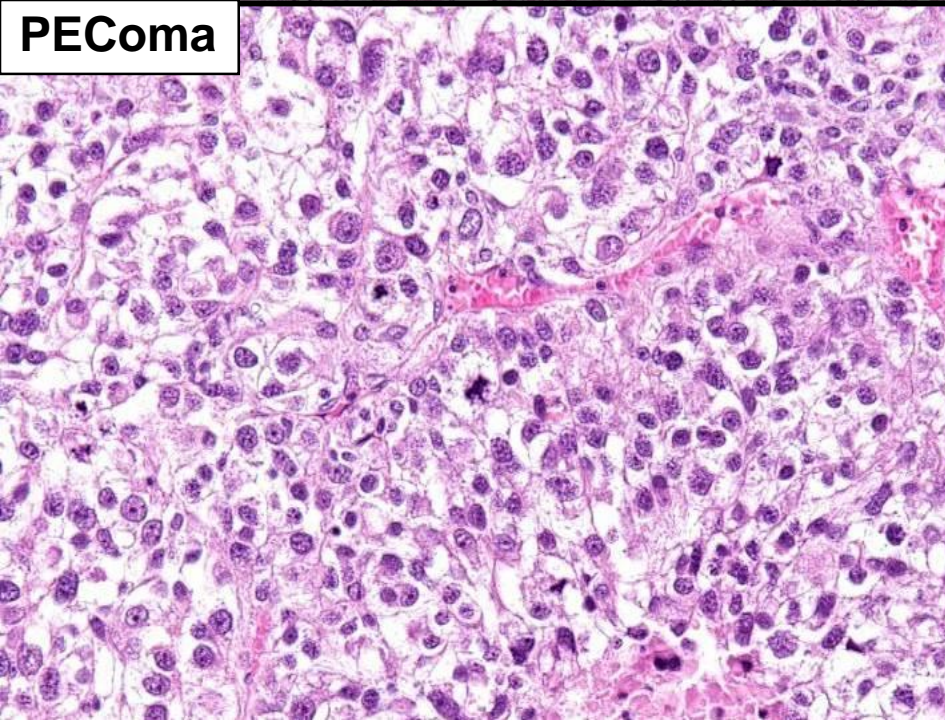
Paraganglioma



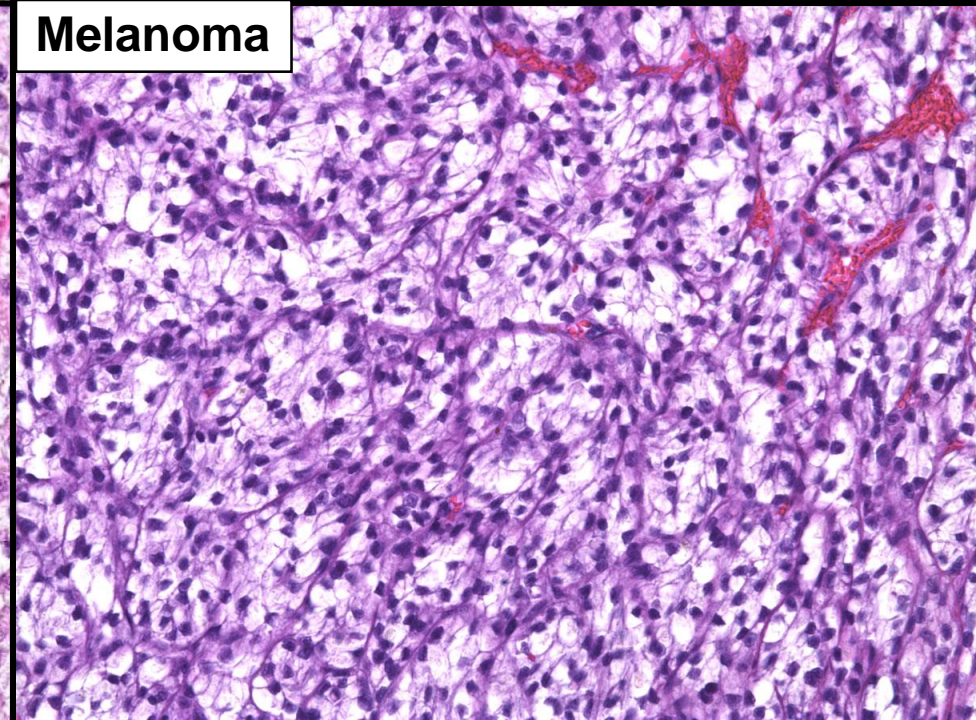
Epith. LMS



PEComa



Melanoma



UROTHELIAL CARCINOMA

(Prim. or Metastatic site)

Challenges:

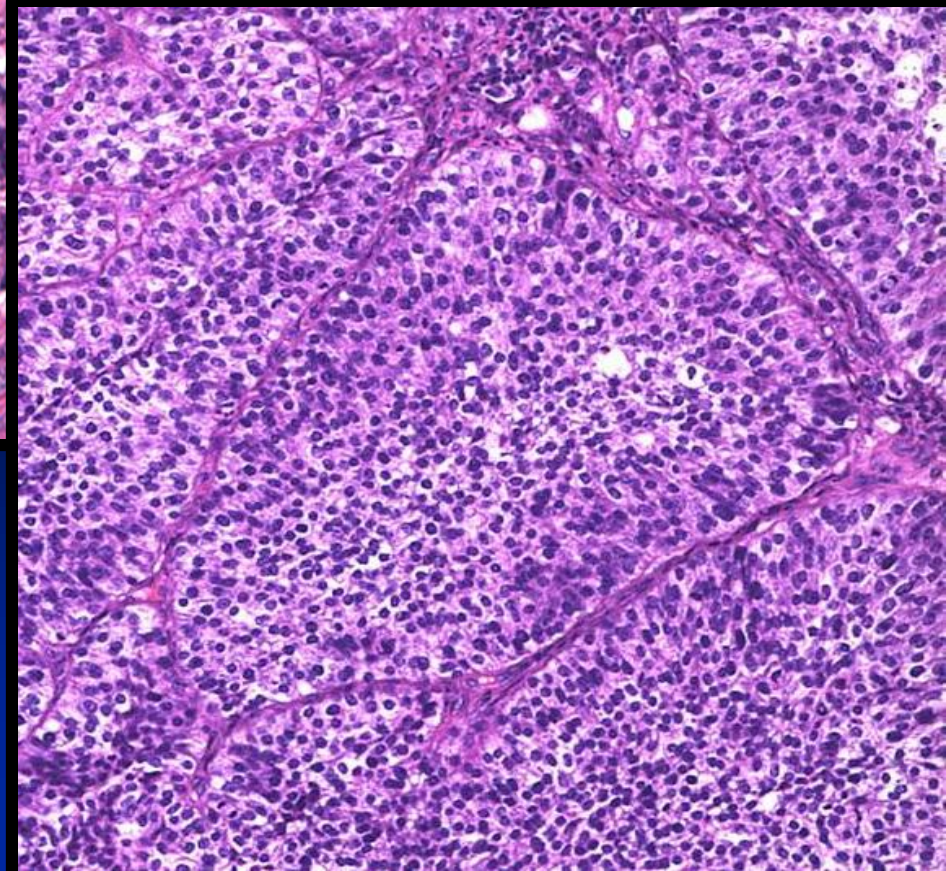
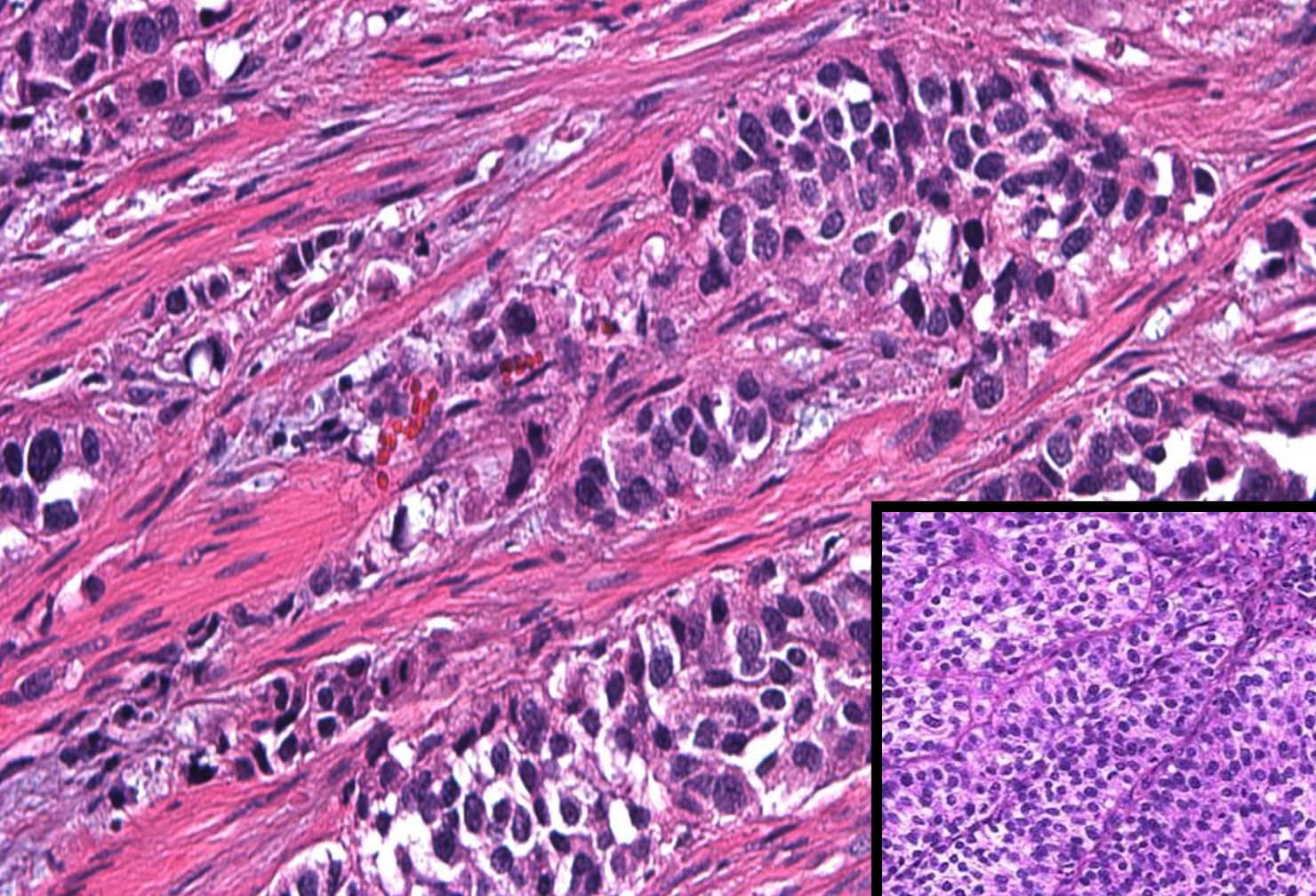
- Poorly differentiated carcinoma
- “Characterless”: solid, nested & trabecular architecture

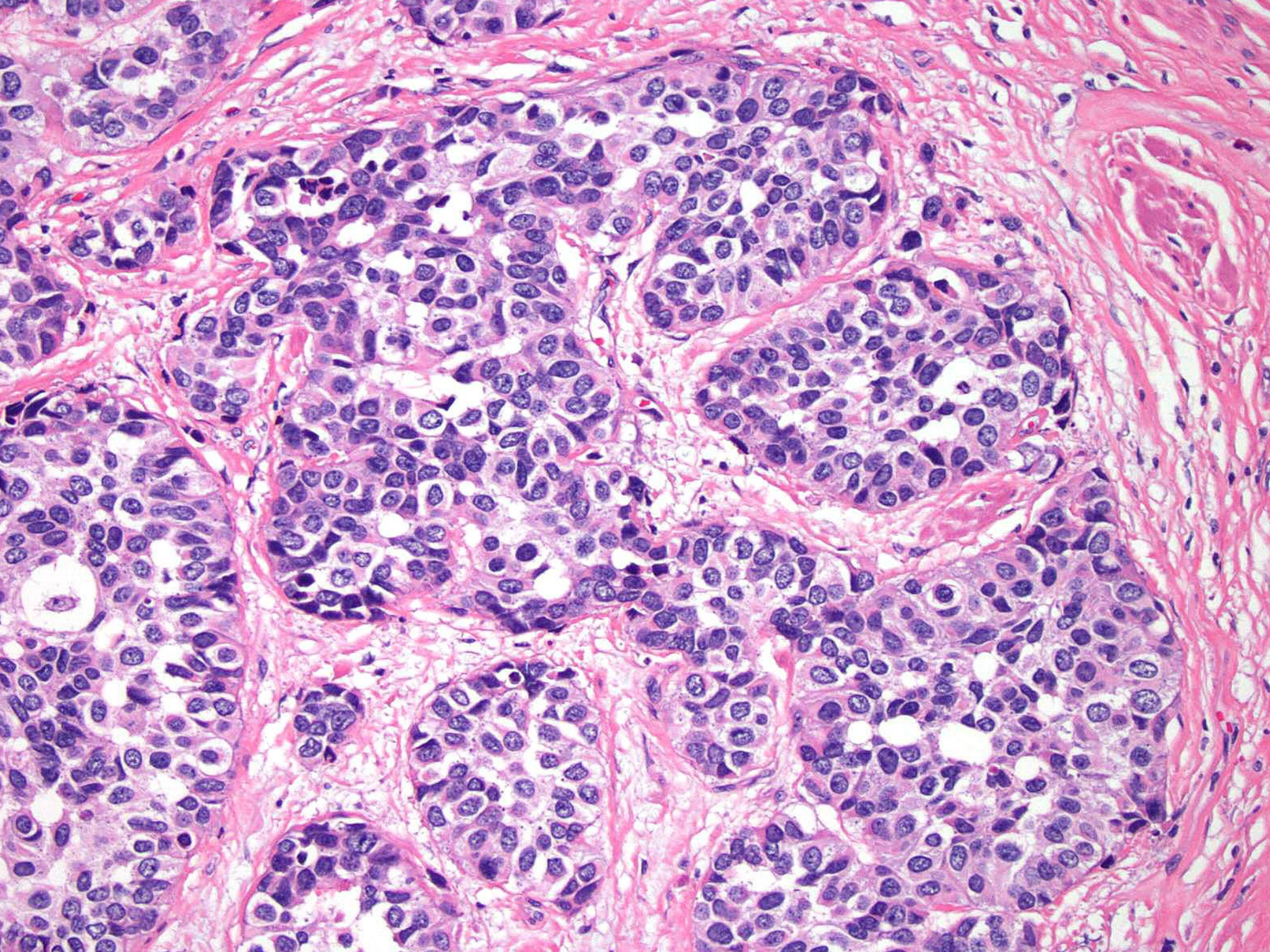
Hallmarks:

- *Frequent squamous and / or glandular diff.*
- *Cells with nuclear grooves*
- *Nuclear atypia obvious +/- anaplasia*

Approach

- *Clinical history (invasive, usually high stage carcinoma)*
- *Compare with primary*
- *Judicious IHC: ? Best markers*





CLASSIFICATION OF INVASIVE BLADDER CA

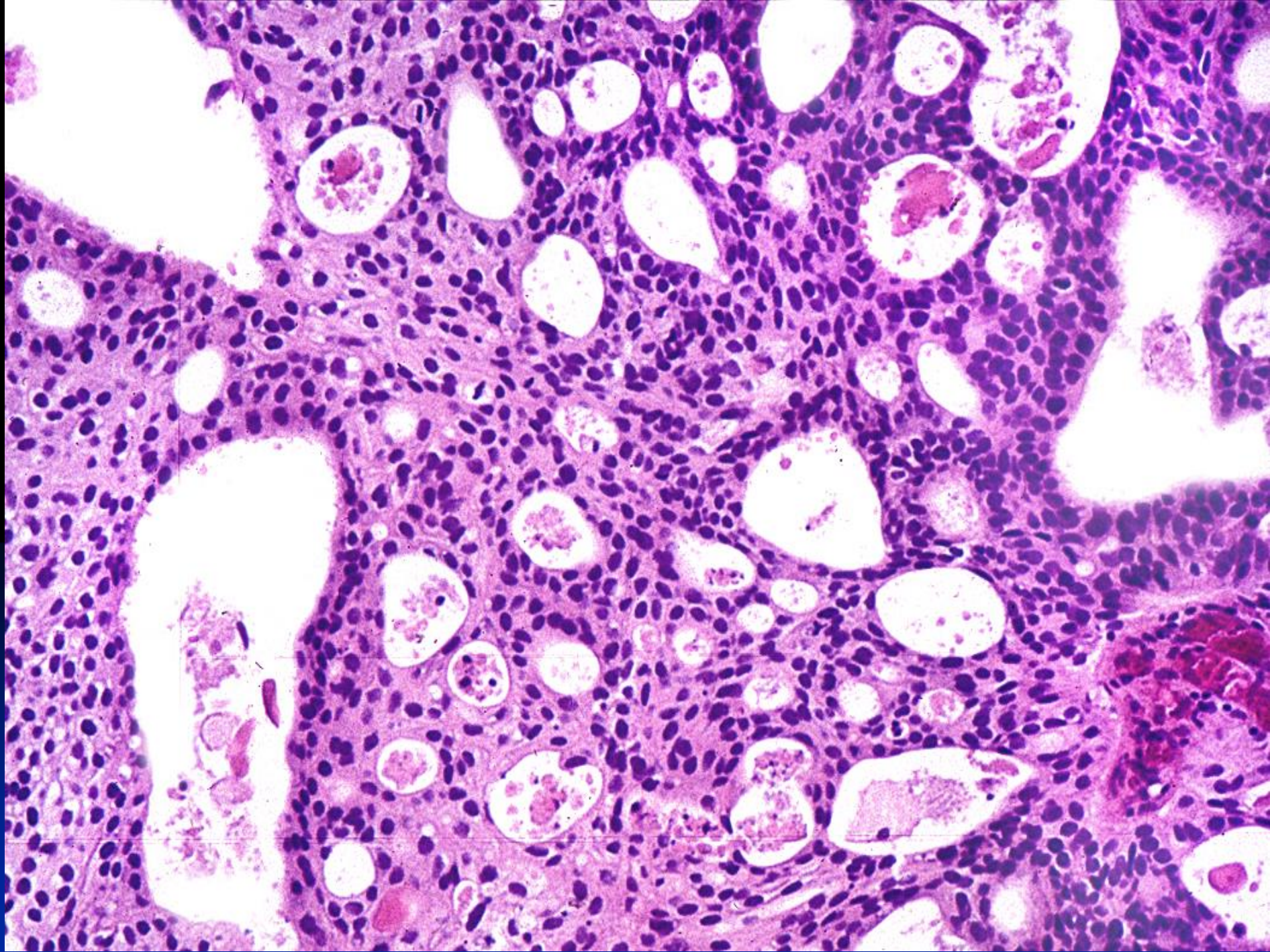
- **Urothelial carcinoma**
- **Squamous cell Ca**
 - *conventional*
 - *verrucous*
 - *basaloid*
- **Adenocarcinoma**
 - *mucosal based*
 - *urachal*
- **Neuroendocrine carcinoma**
 - Small cell
 - Large cell
 - Well differentiated tumor
 - Paraganglioma
- **Variants of urothelial Ca**
 - *nested (incl. large nested)*
 - *microcystic*
 - *micropapillary*
 - *lymphoepithelioma-like*
 - *sarcomatoid*
 - *diffuse/plasmacytoid*
signet ring cell
 - *giant cell*
 - *lipid rich*
 - *clear cell*
 - *undifferentiated*

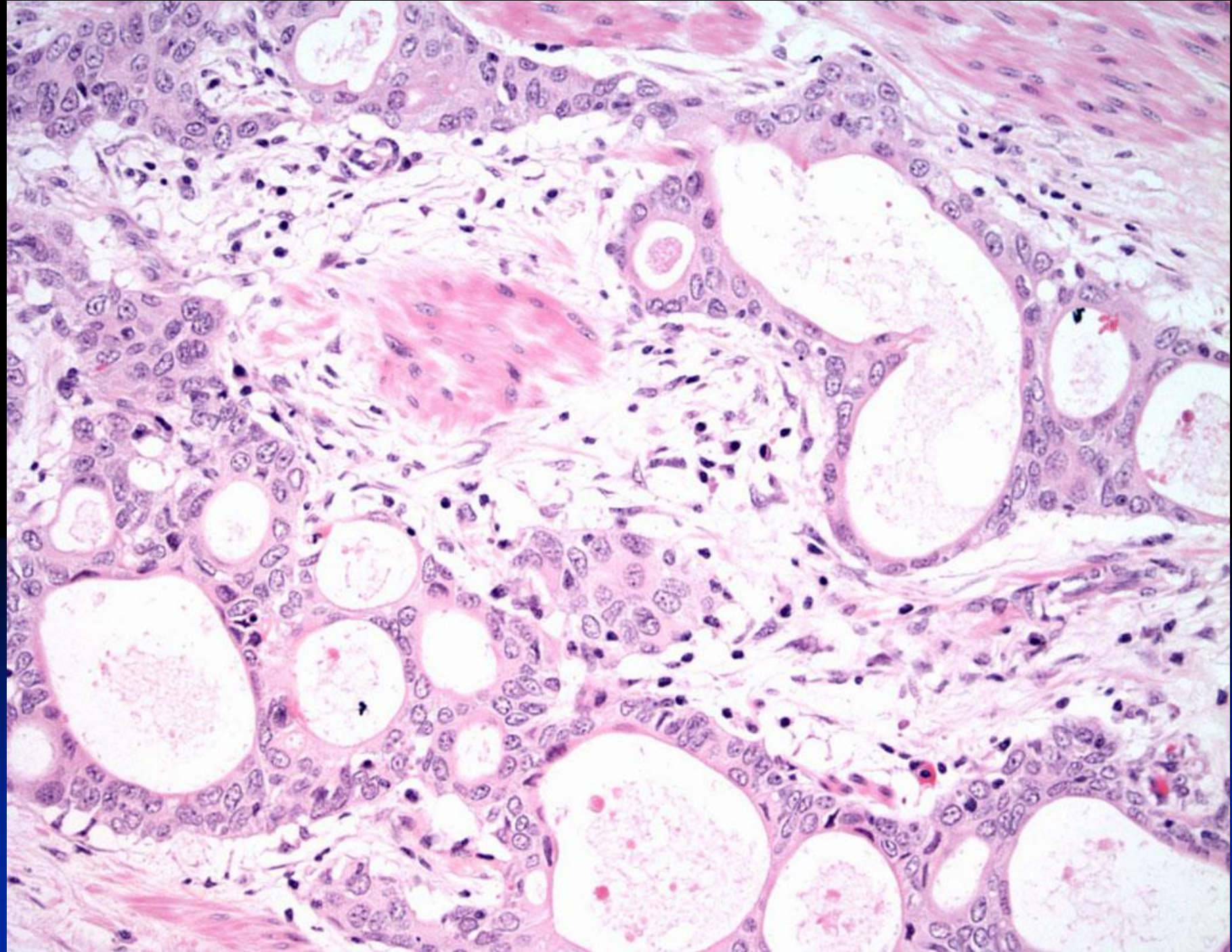
CARCINOMAS OF THE BLADDER WITH GLANDULAR HISTOLOGY

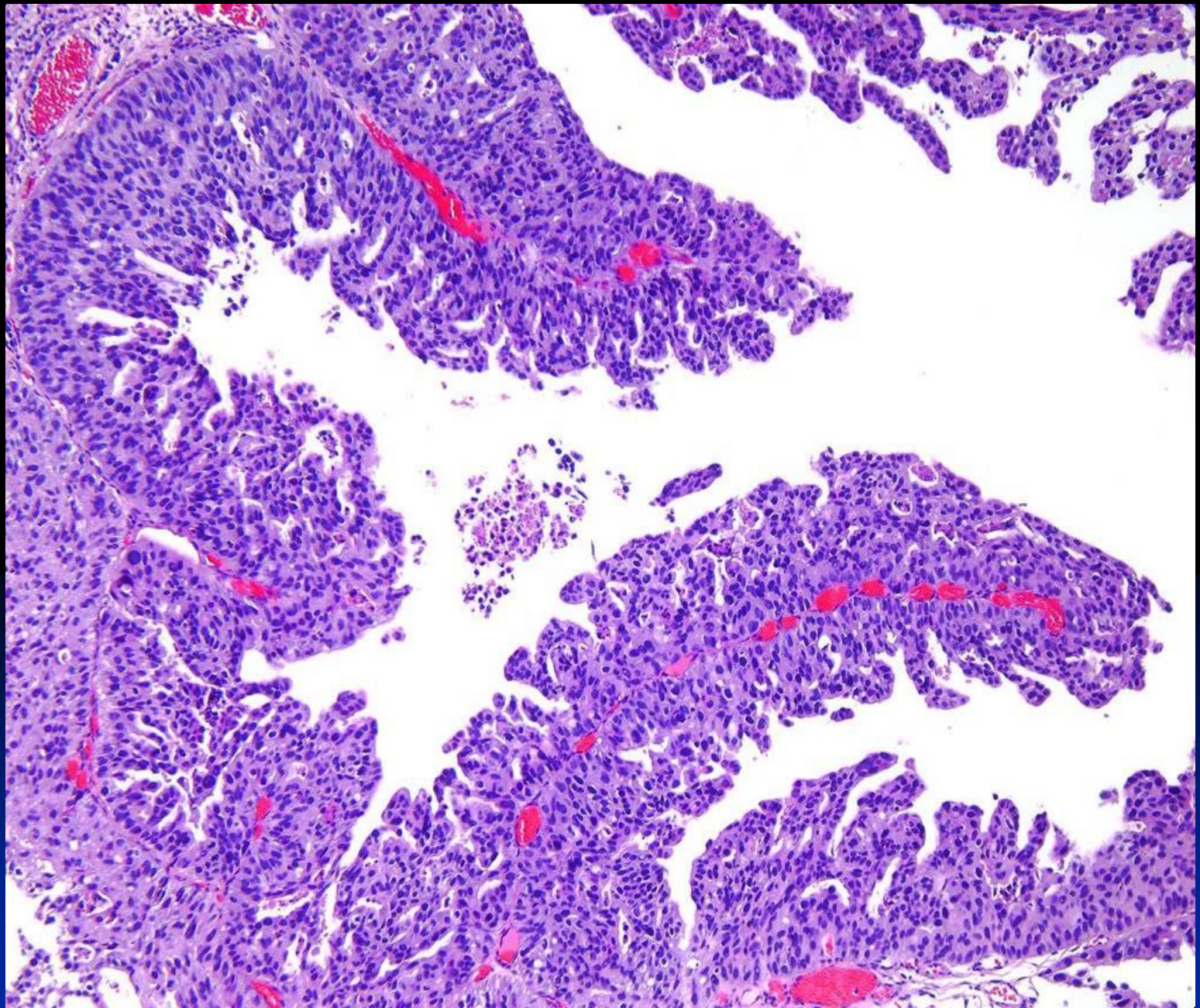
- **Histologic:**
 - **Primary urothelial carcinoma with glandular differentiation – patterns**
 - **Primary adenocarcinoma of urinary bladder – subtypes**
 - **Metastatic adenocarcinoma**

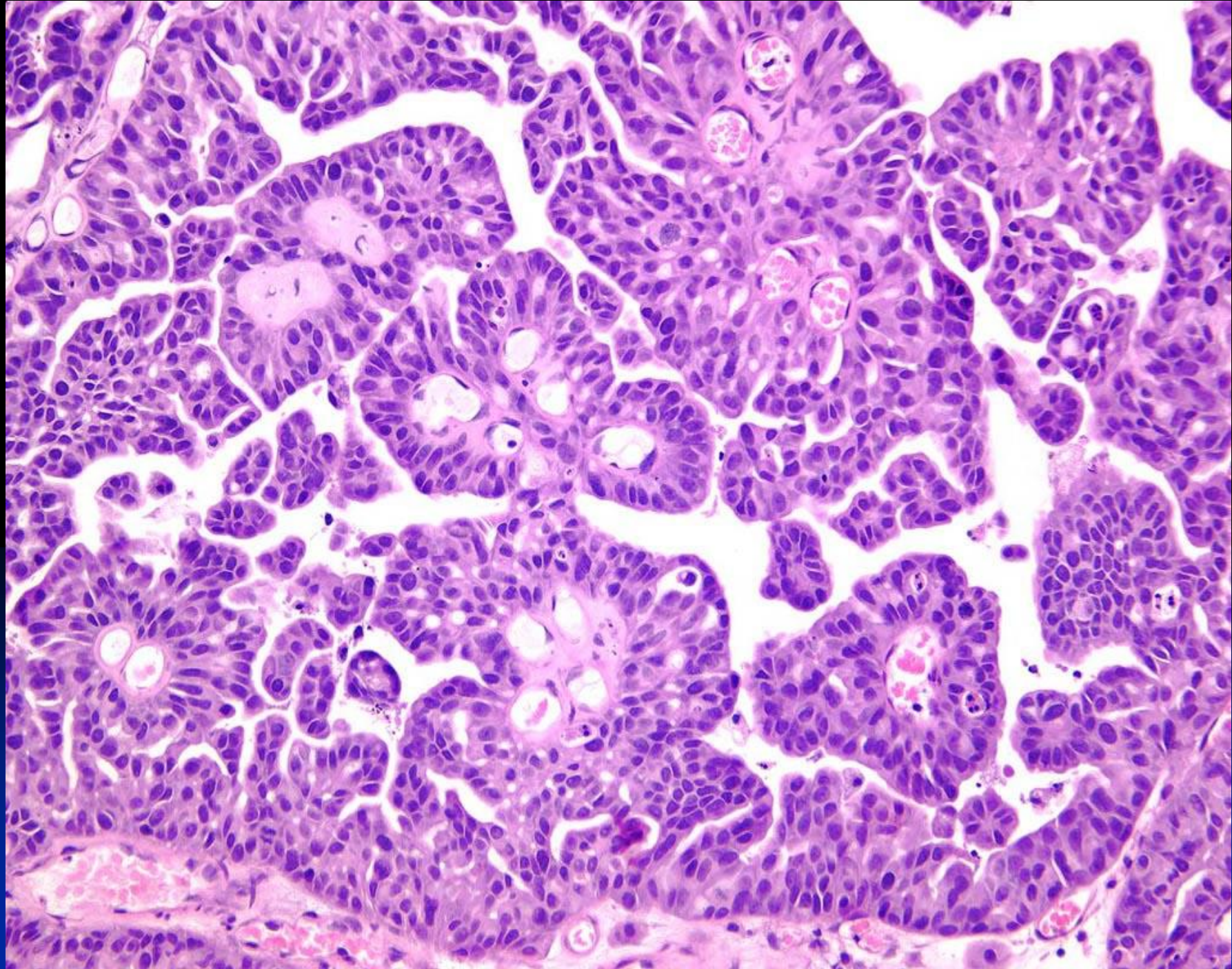
UROTHELIAL CARCINOMA WITH GLANDULAR FEATURES

- **Gland-like lumina (NOS)**
- **Microcystic**
- **Small tubules**
- **With villoglandular features**
- **With specific adenocarcinoma pattern**









PRIMARY ADENOCARCINOMA OF THE BLADDER

Anatomic:

- Urachal
- Bladder mucosa

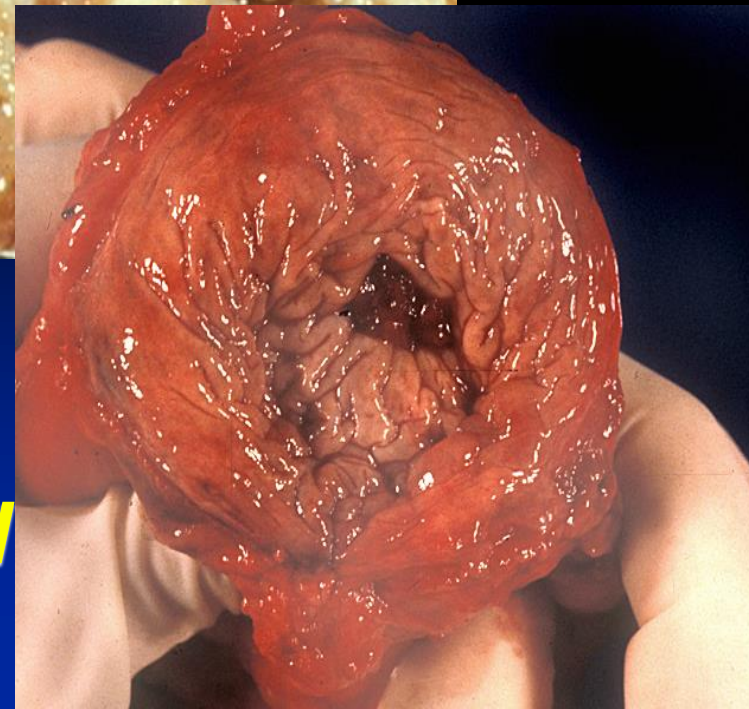
Histology:

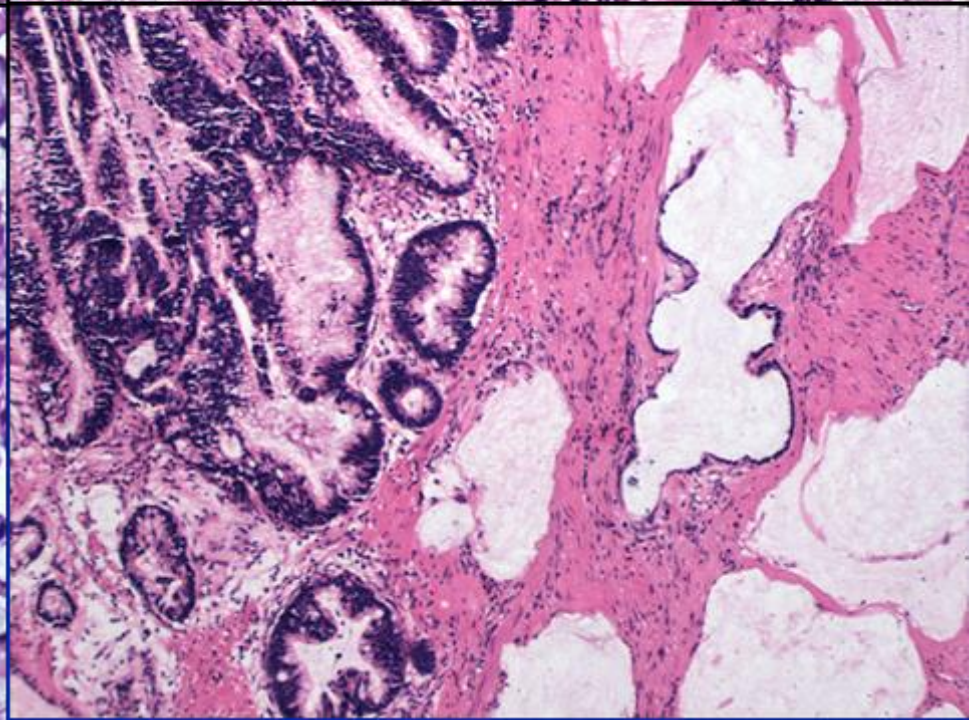
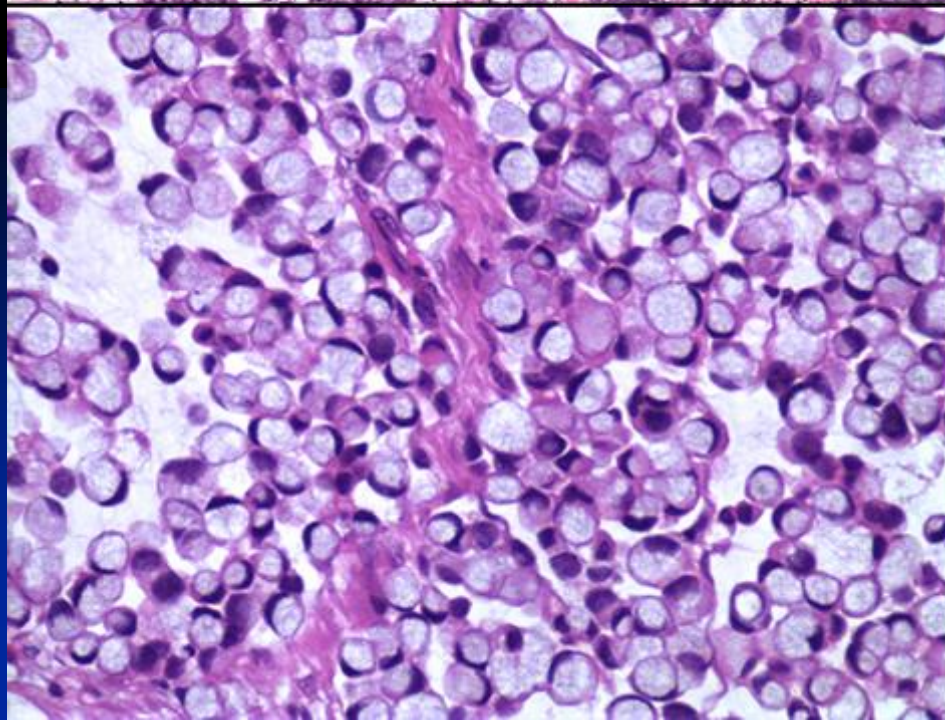
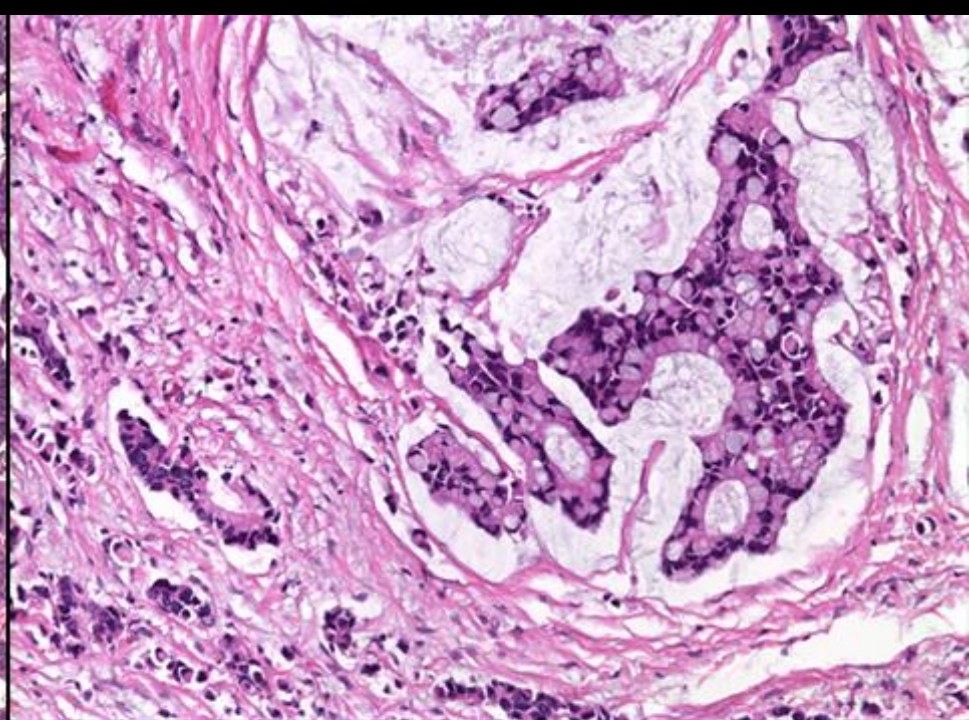
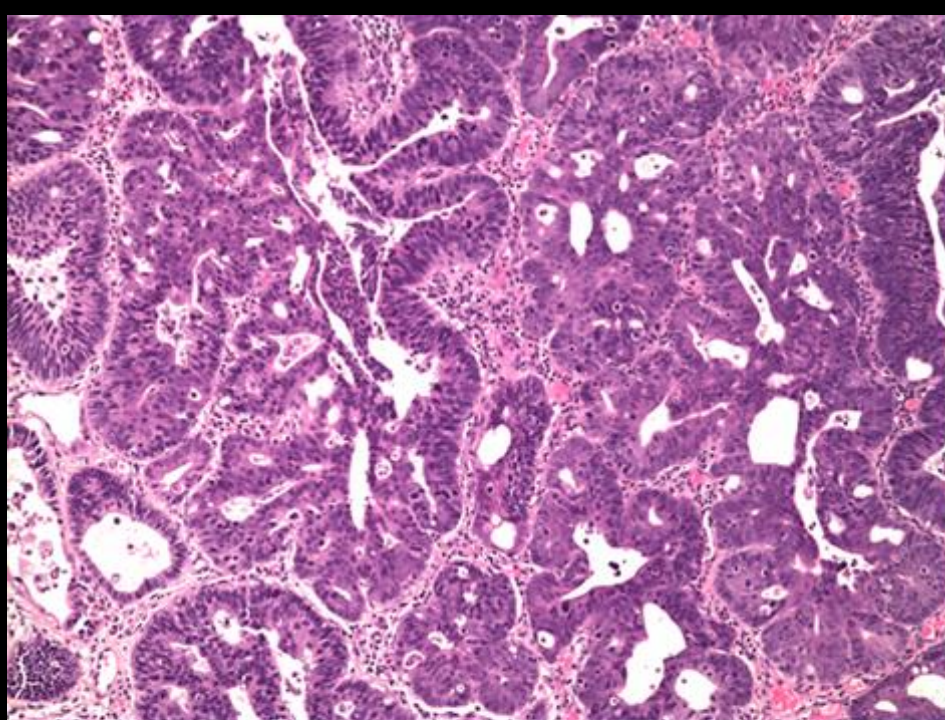
- Adenocarcinoma NOS
- Enteric
- Mucinous
- Signet ring
- Clear cell
- Hepatoid
- Combined (from above)

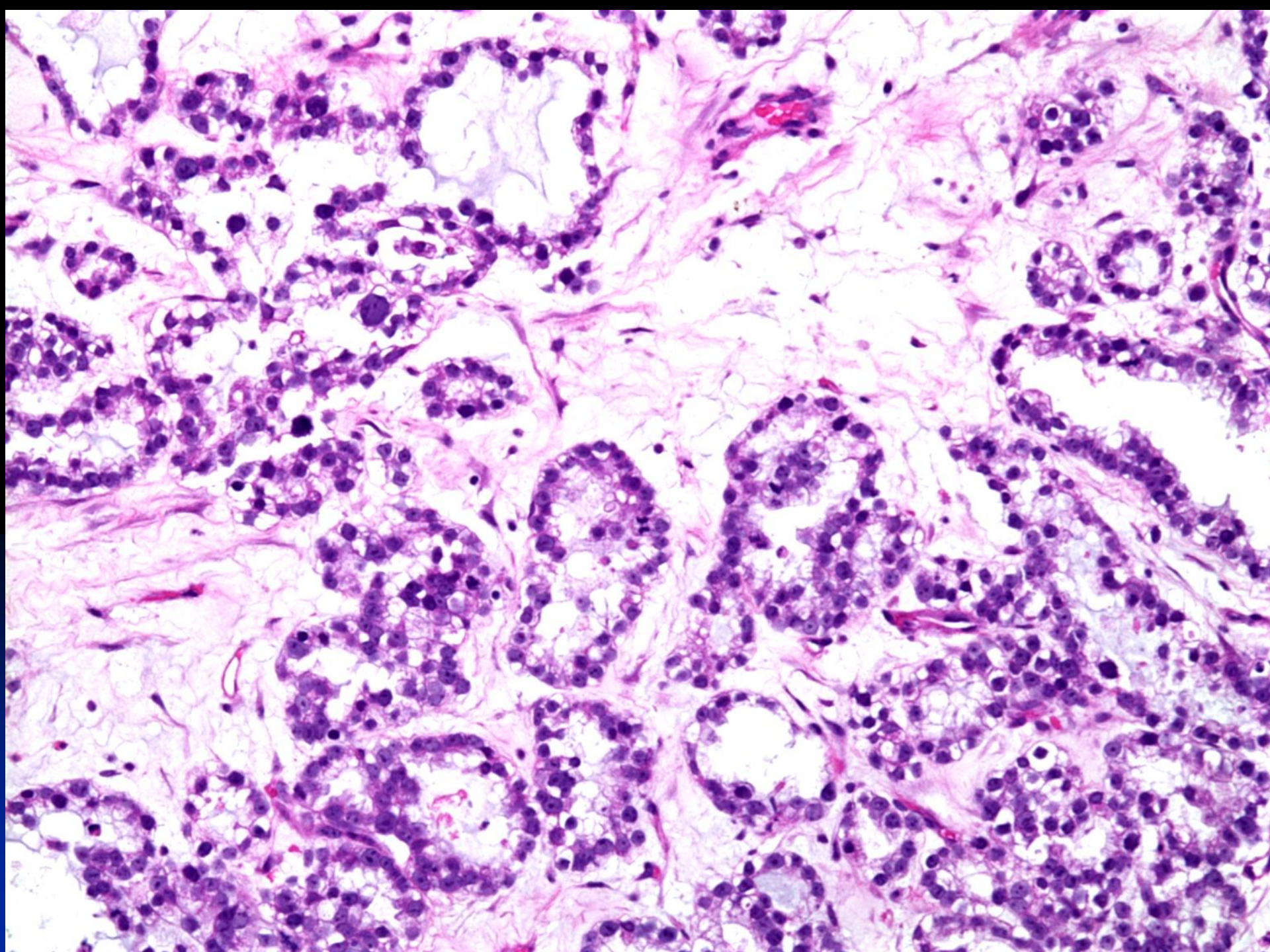


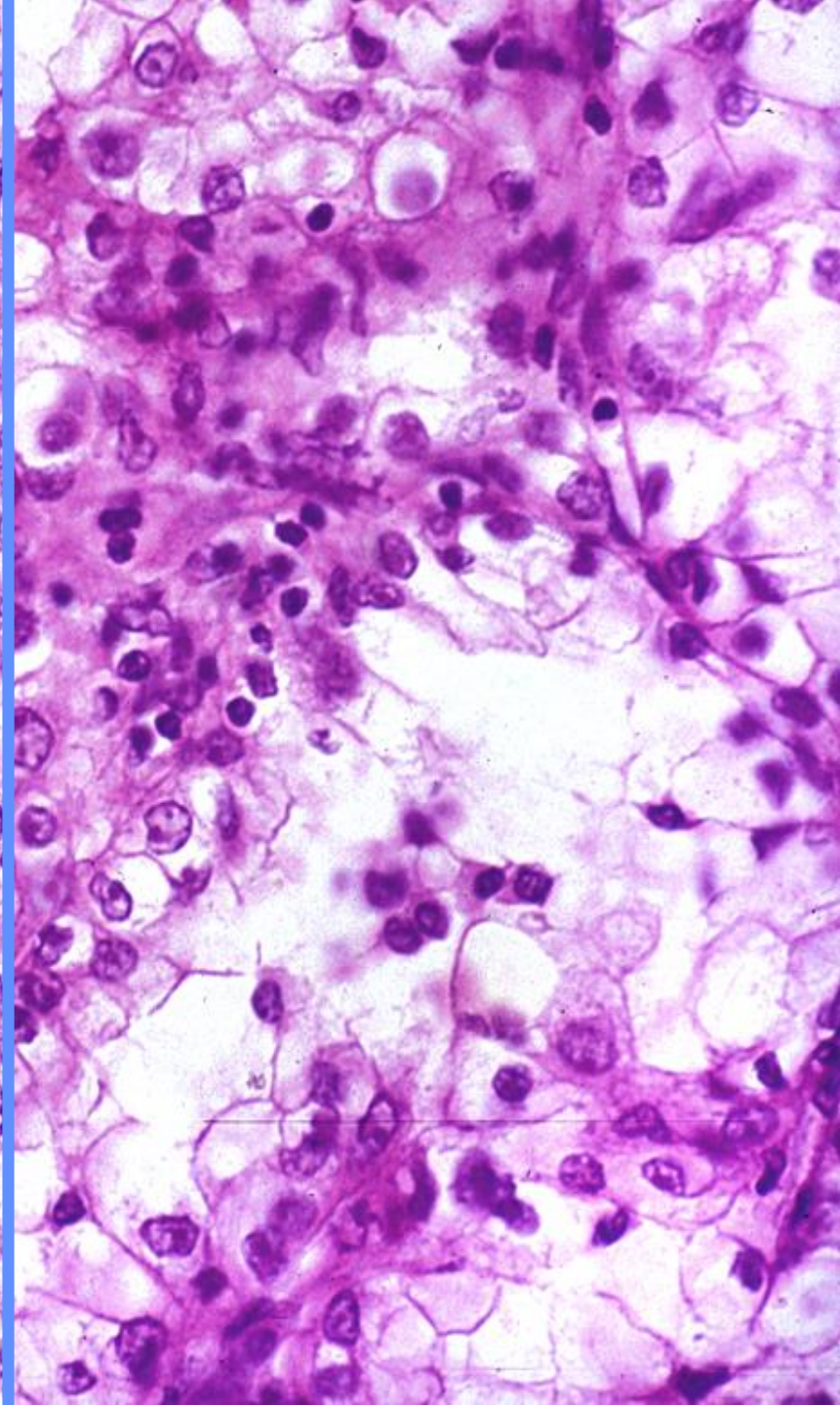
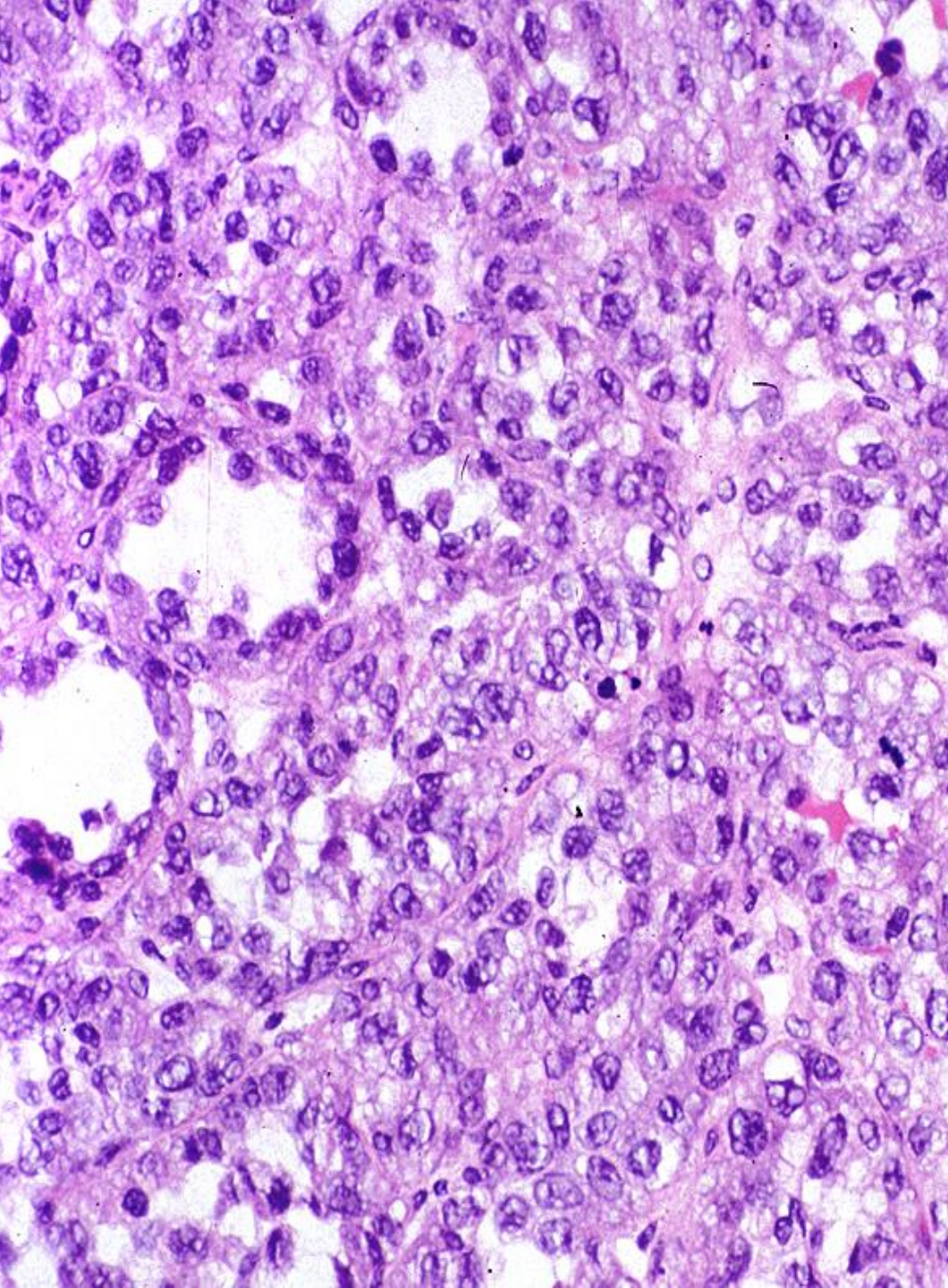
Mucosal based

Urachal









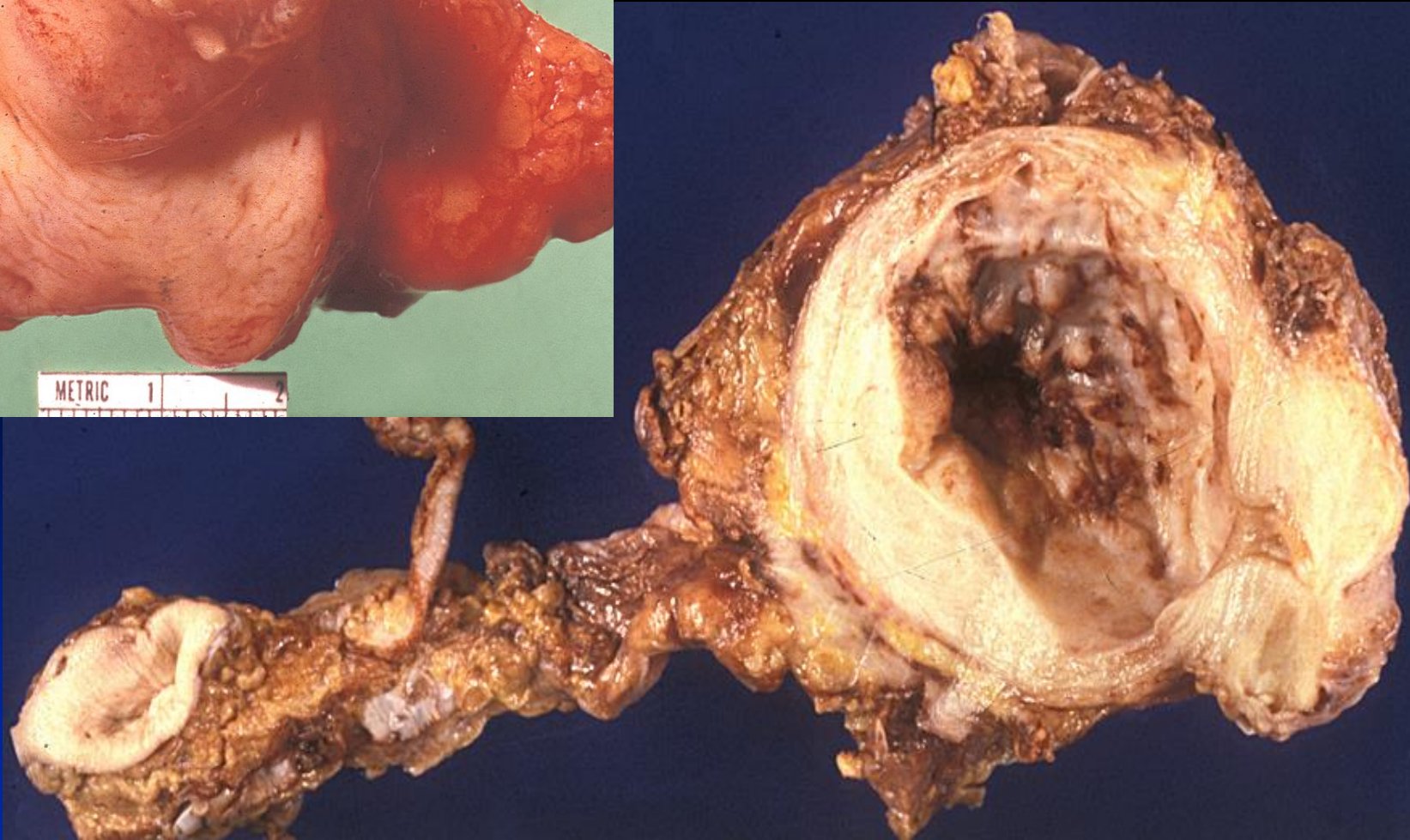
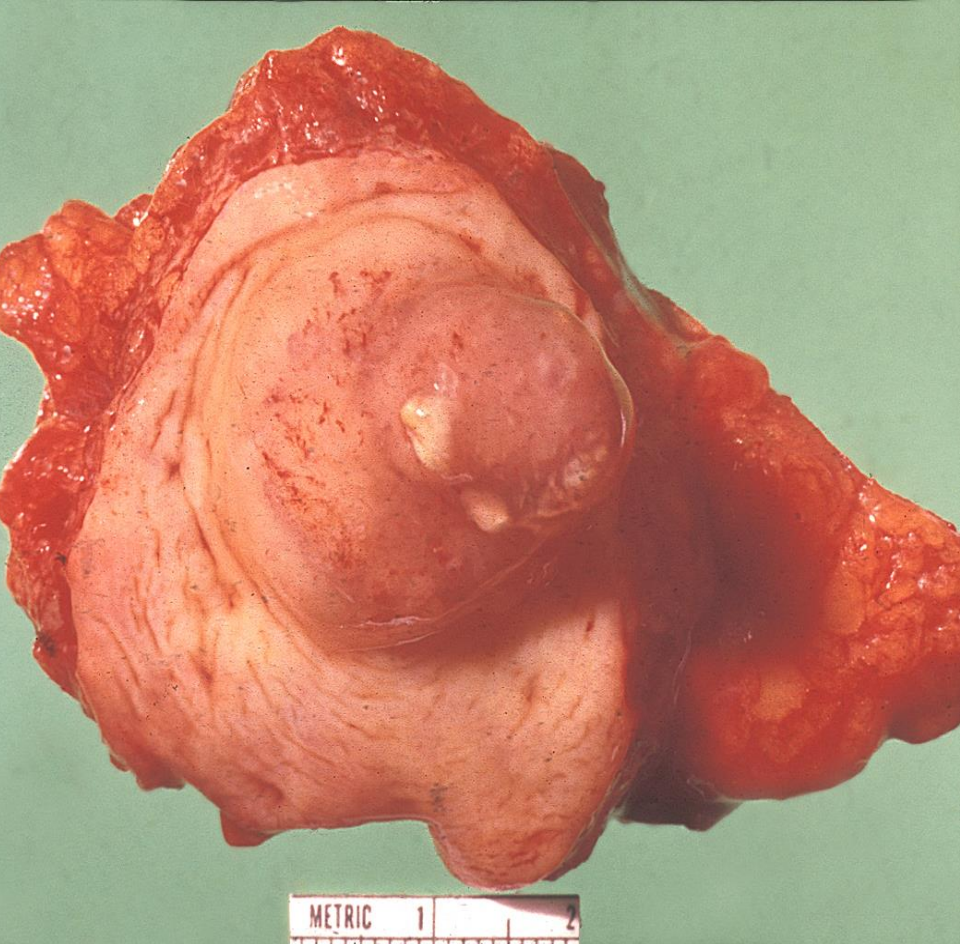
URACHAL CARCINOMA

- Clinicopathologic diagnosis

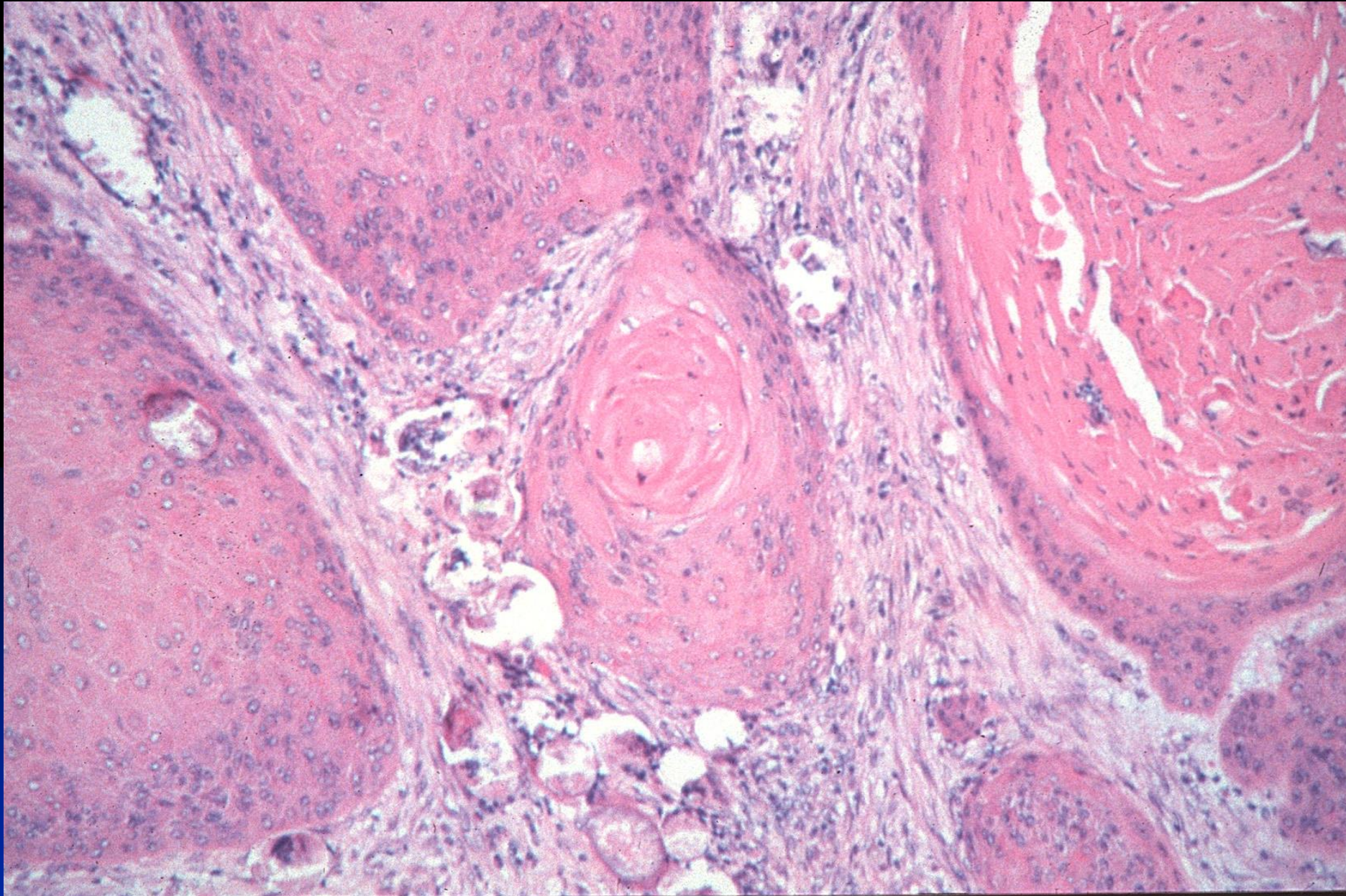
- *Criteria:*

- *Dome or anterior location*
- *Absence of cystitis glandularis or intestinal metaplasia*
- *Absence of primary elsewhere*
- *Epicenter of mass in bladder wall*

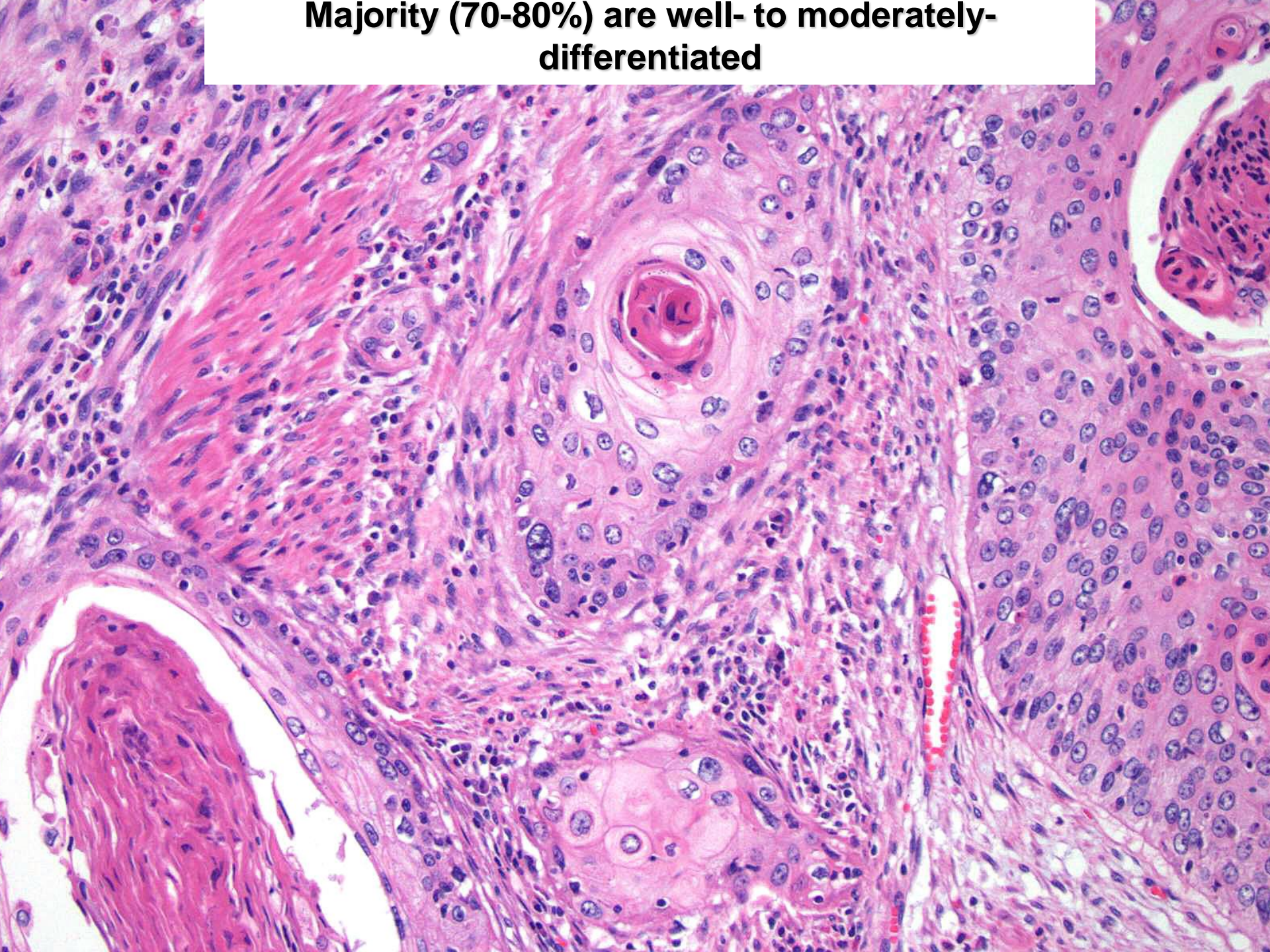
- > 90% are adenocarcinoma



SQUAMOUS CELL CARCINOMA



Majority (70-80%) are well- to moderately-
differentiated



HISTOLOGIC VARIANTS

Morphology not typical of usual or conventional type

Awareness: Diagnostic, prognostic or therapeutic importance

General rules:

- Document in report - facilitates association with histology of metastasis
- “Unusual” histology - rule out metastasis

Histologic Variants of Bladder Cancer

Prognosis:

- **Aggressive**
 - Micropapillary
 - Small cell
 - Sarcomatoid
 - With rhabdoid features
 - Signet ring adenocarcinoma
 - Giant cell carcinoma
- **Favorable**
 - Pure LELC
 - Verrucous Ca
 - Carcinoid tumor

Therapy:

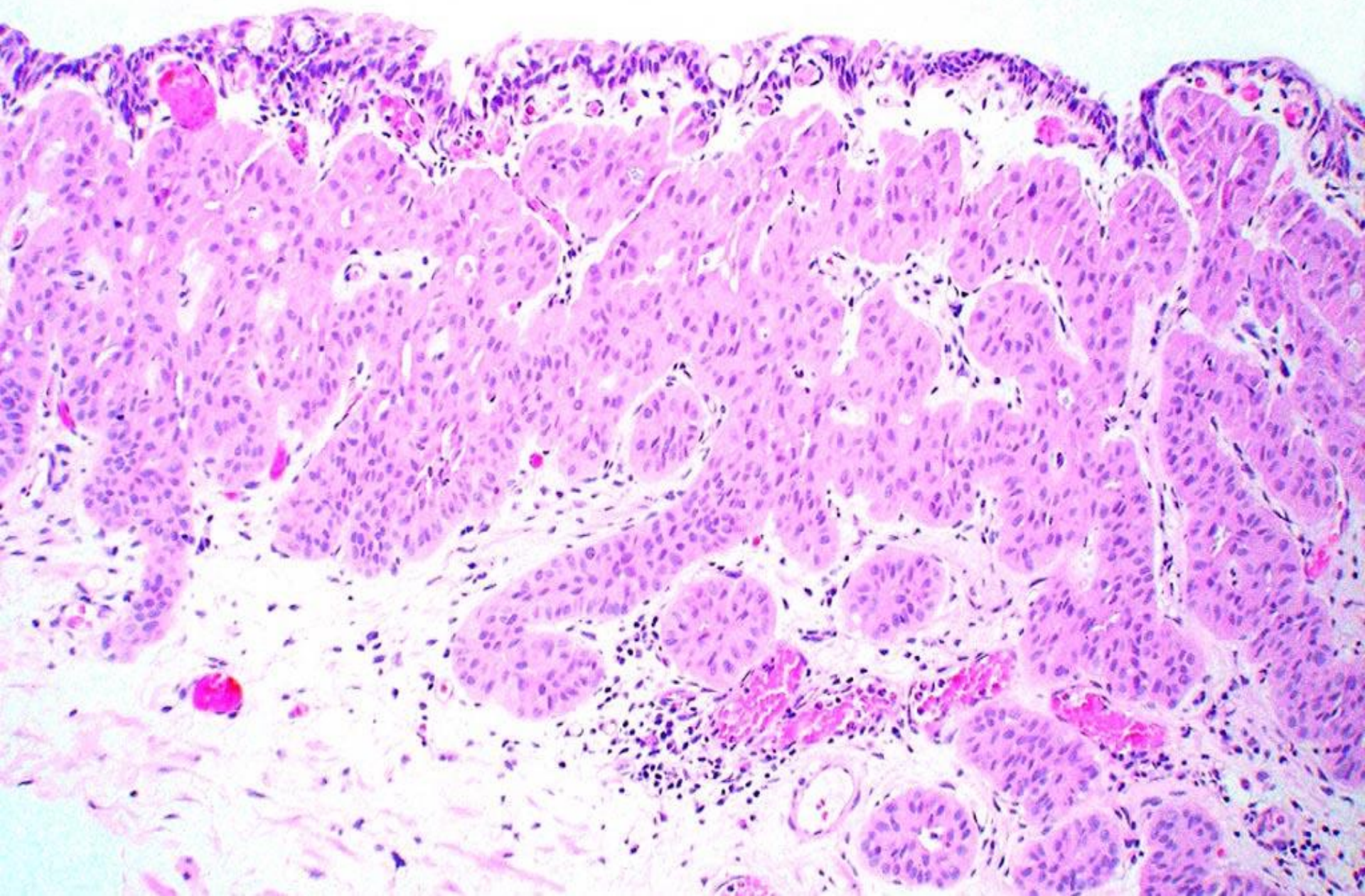
- Sarcomatoid Ca
- Small cell
- Large cell neuroendocrine
- Lymphoepithelioma-like
- Micropapillary

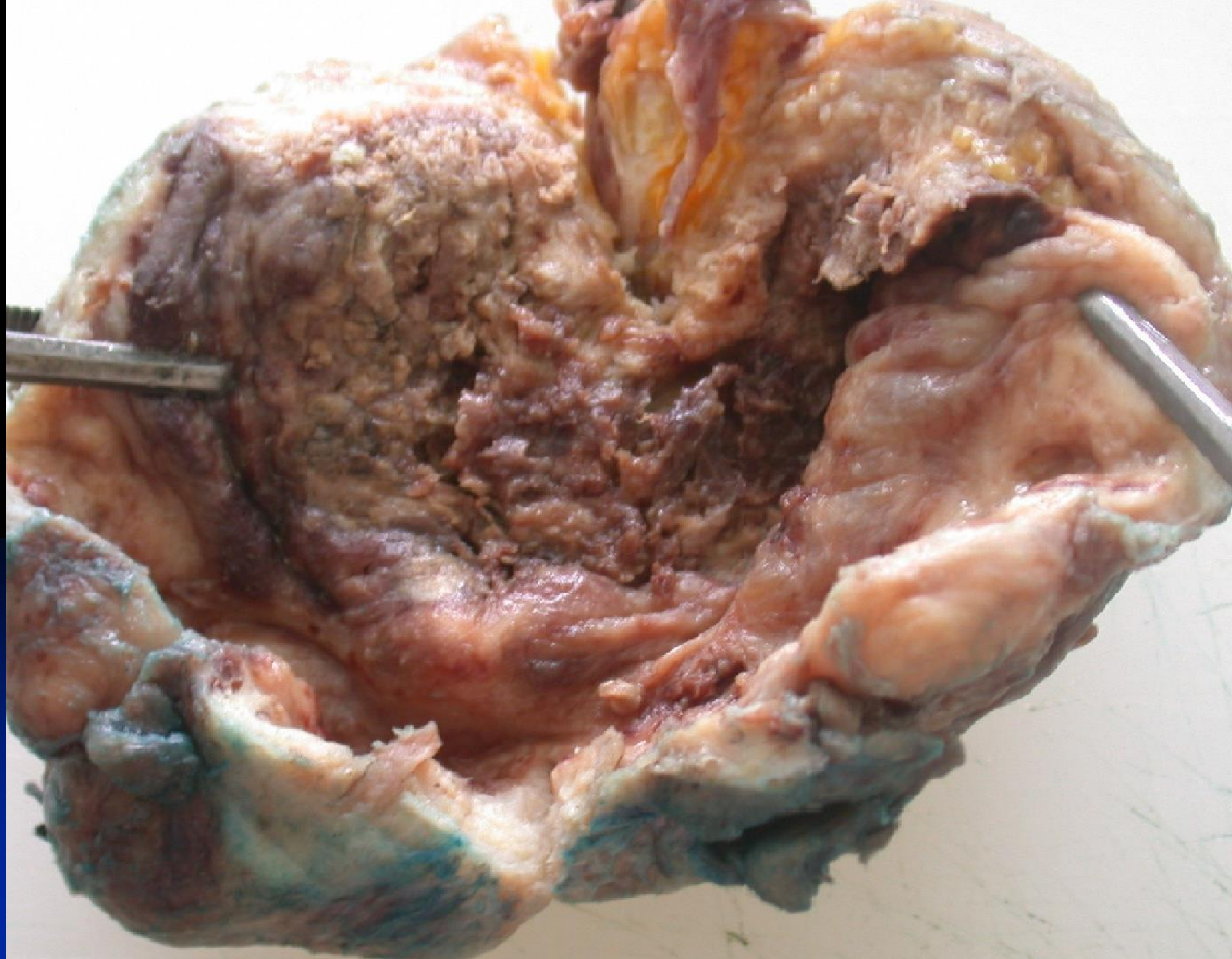
Diagnosis

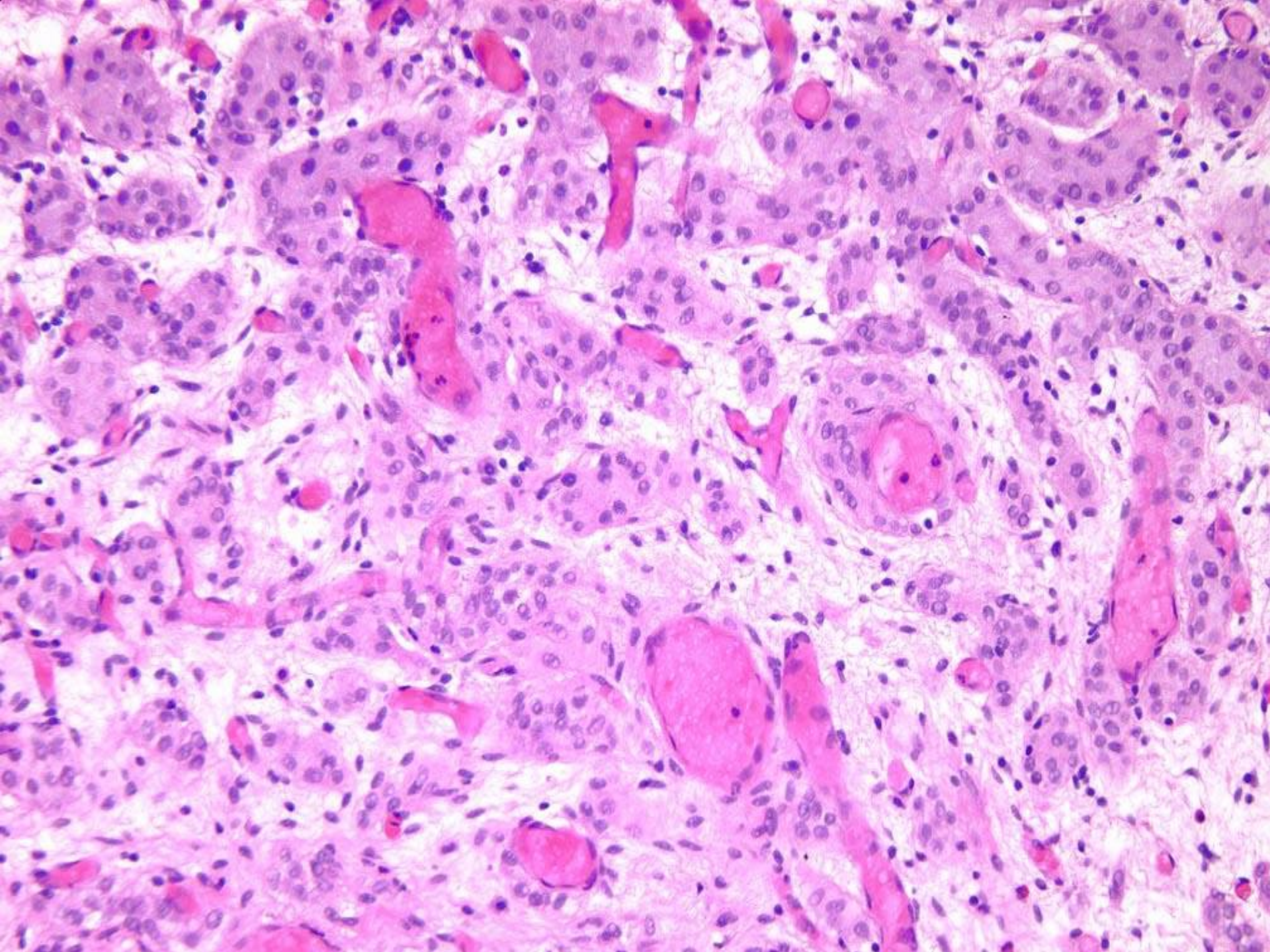
- Nested variant
- UCa with small tubules
- Plasmacytoid UCa
- UCa with clear cell features

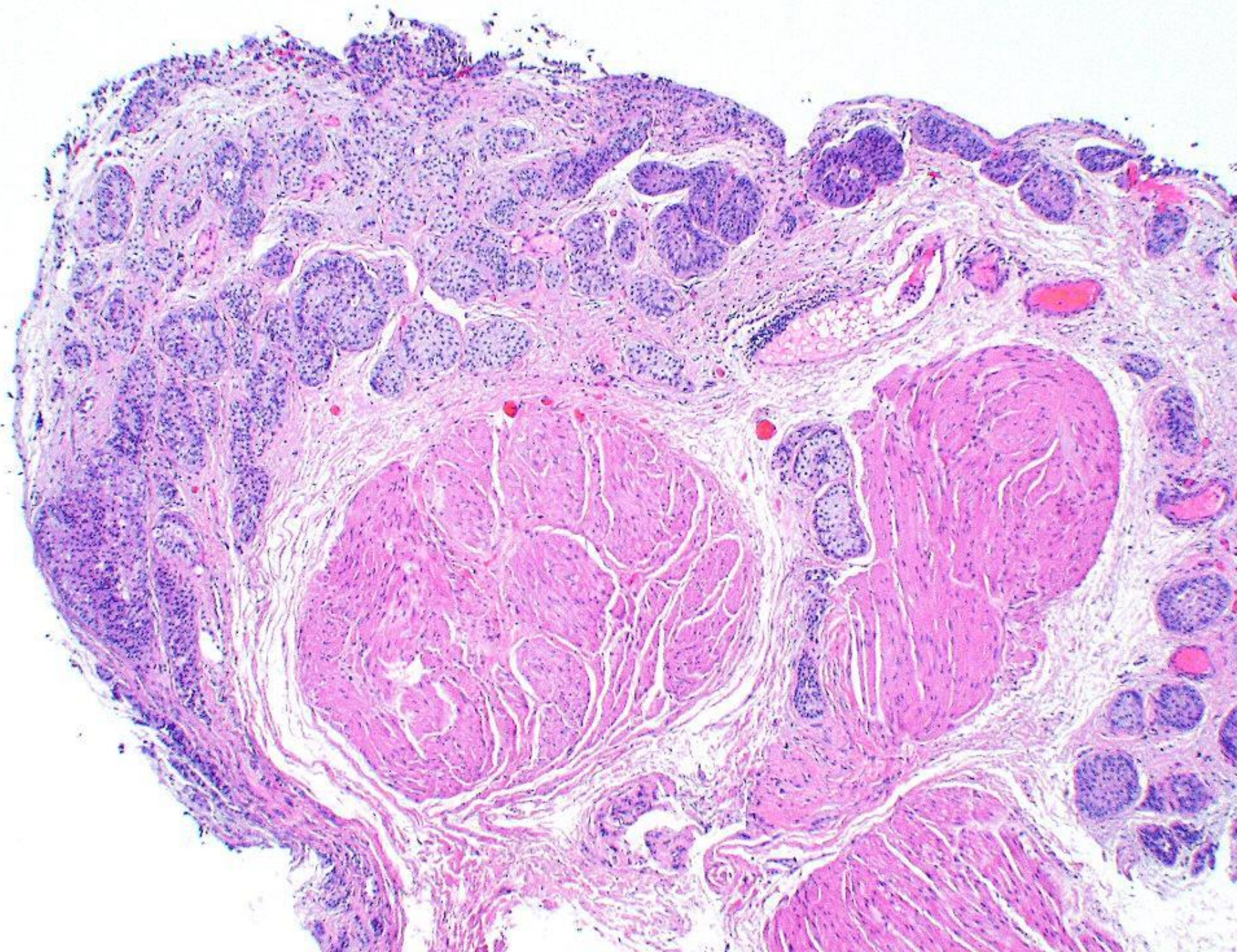
U Ca. WITH DECEPTIVELY BLAND FEATURES

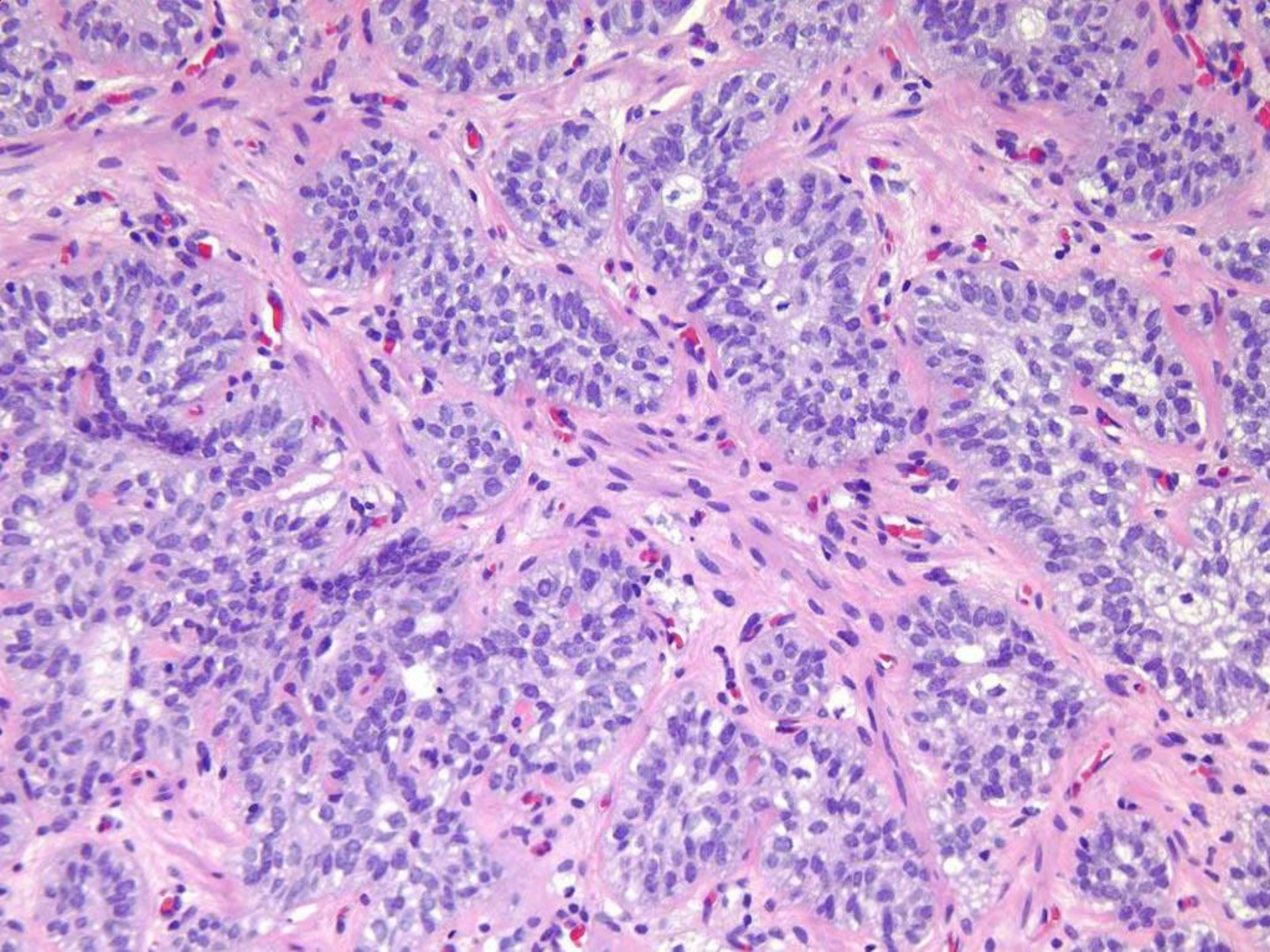
- **Nested variant**
- **U Ca. with small tubules**
- **Microcystic variant**

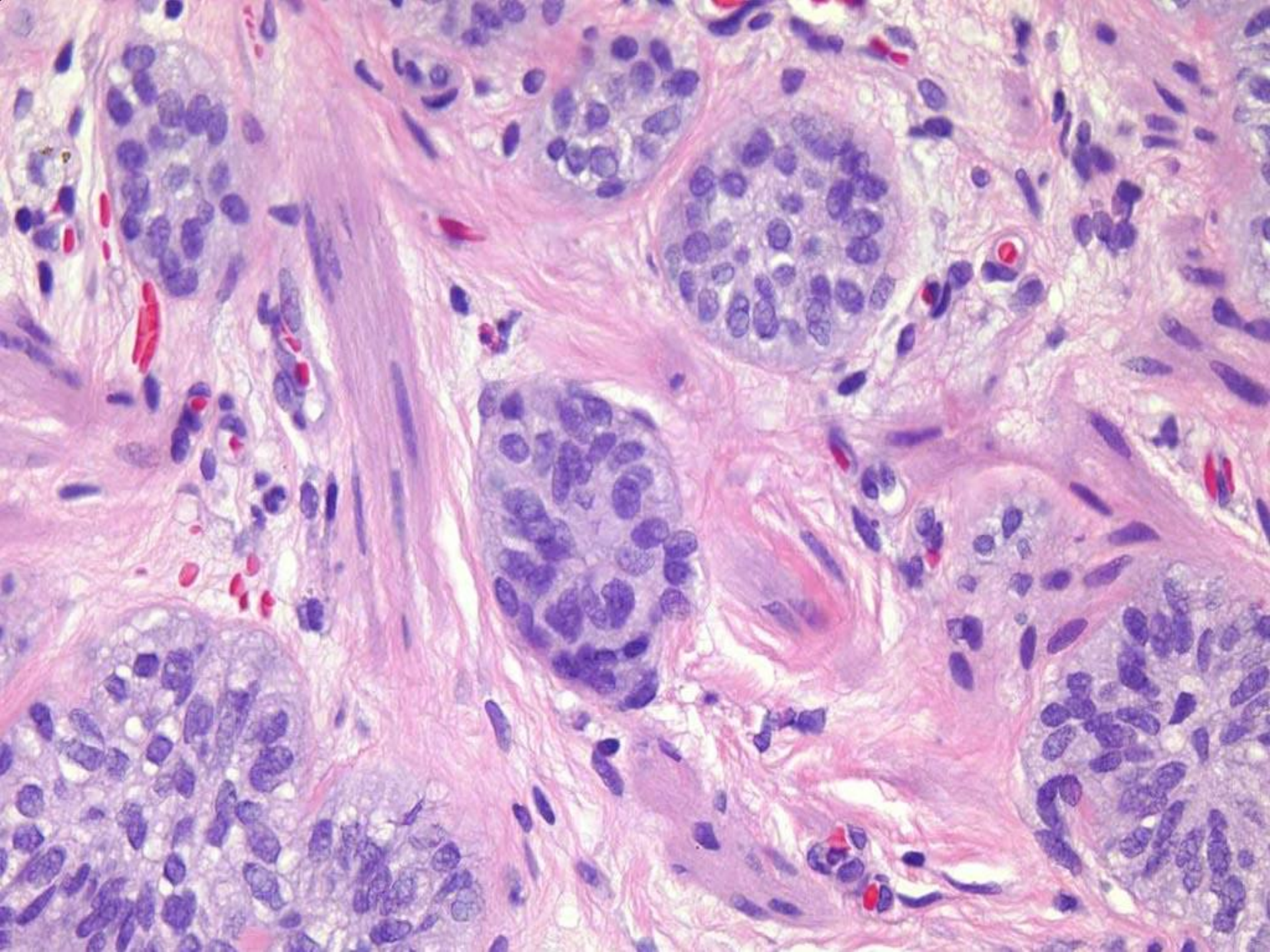


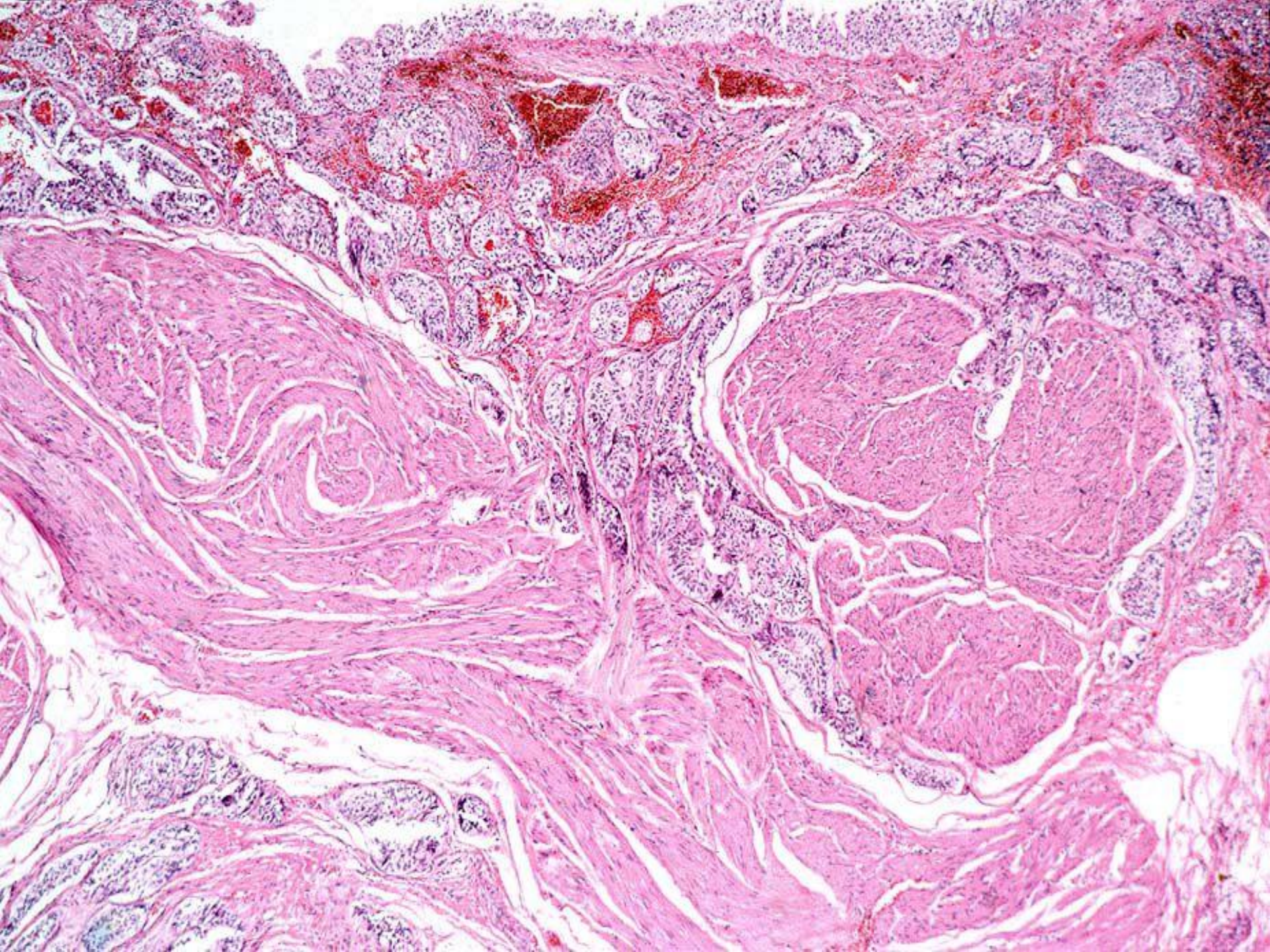


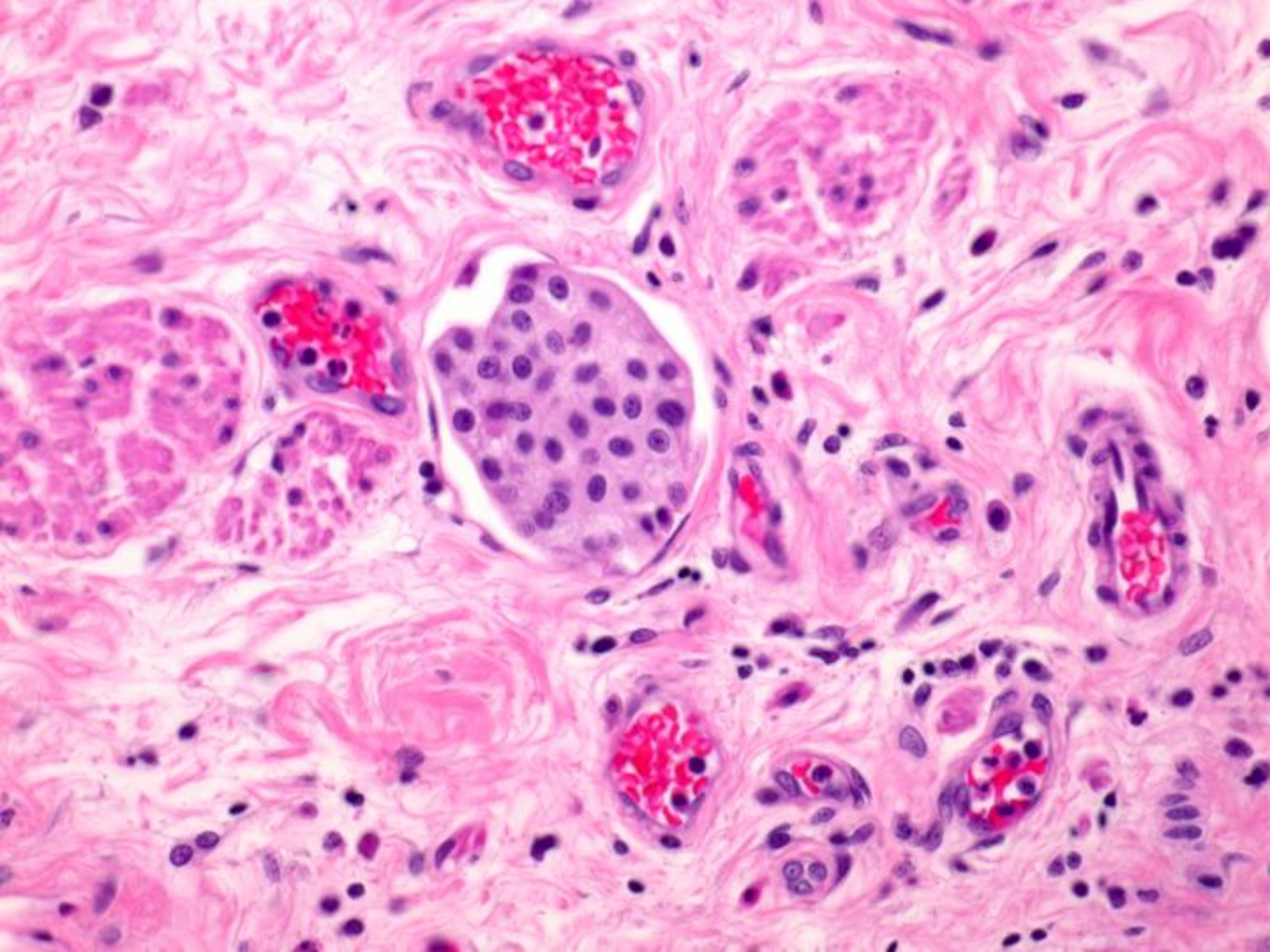


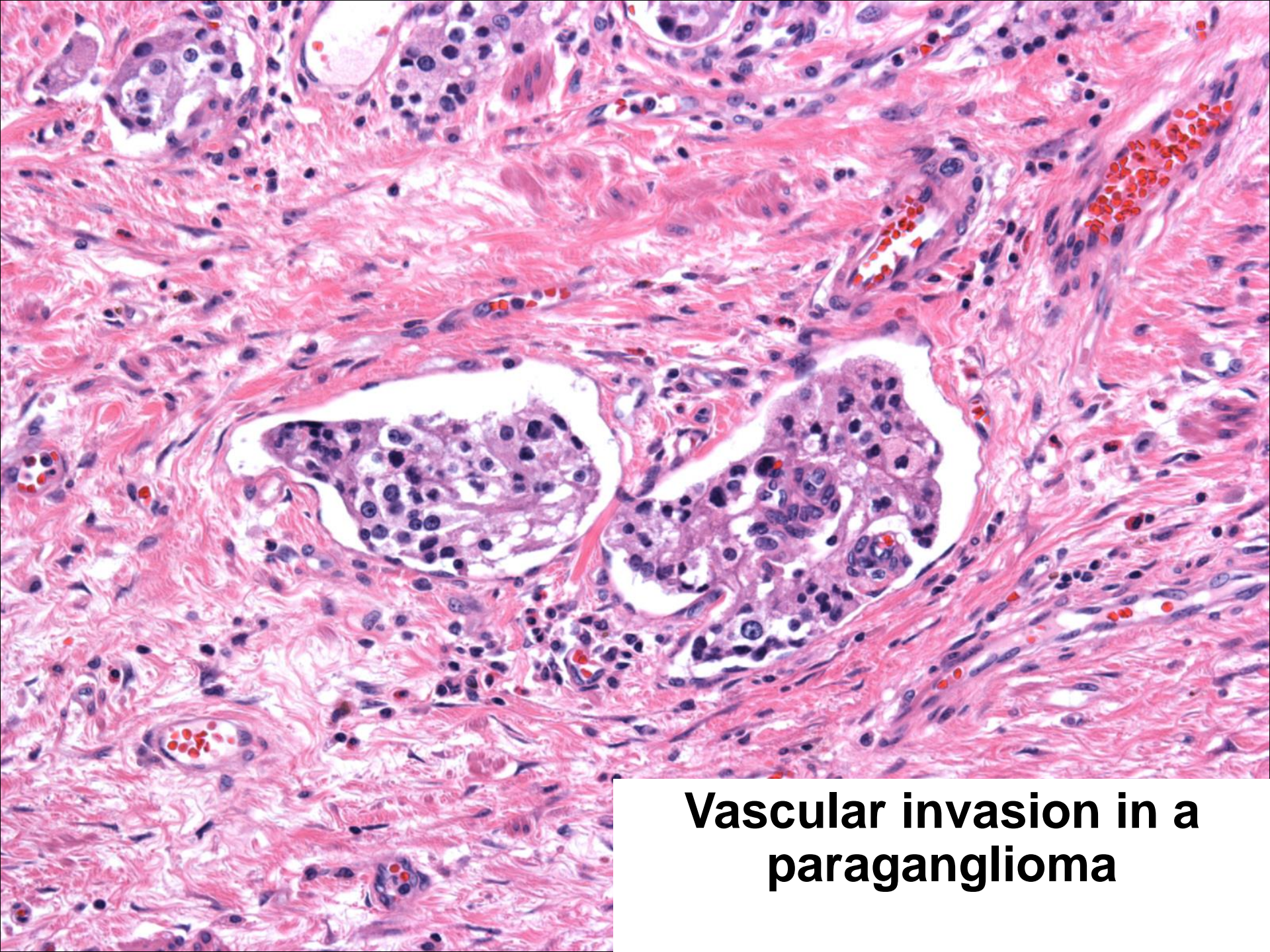




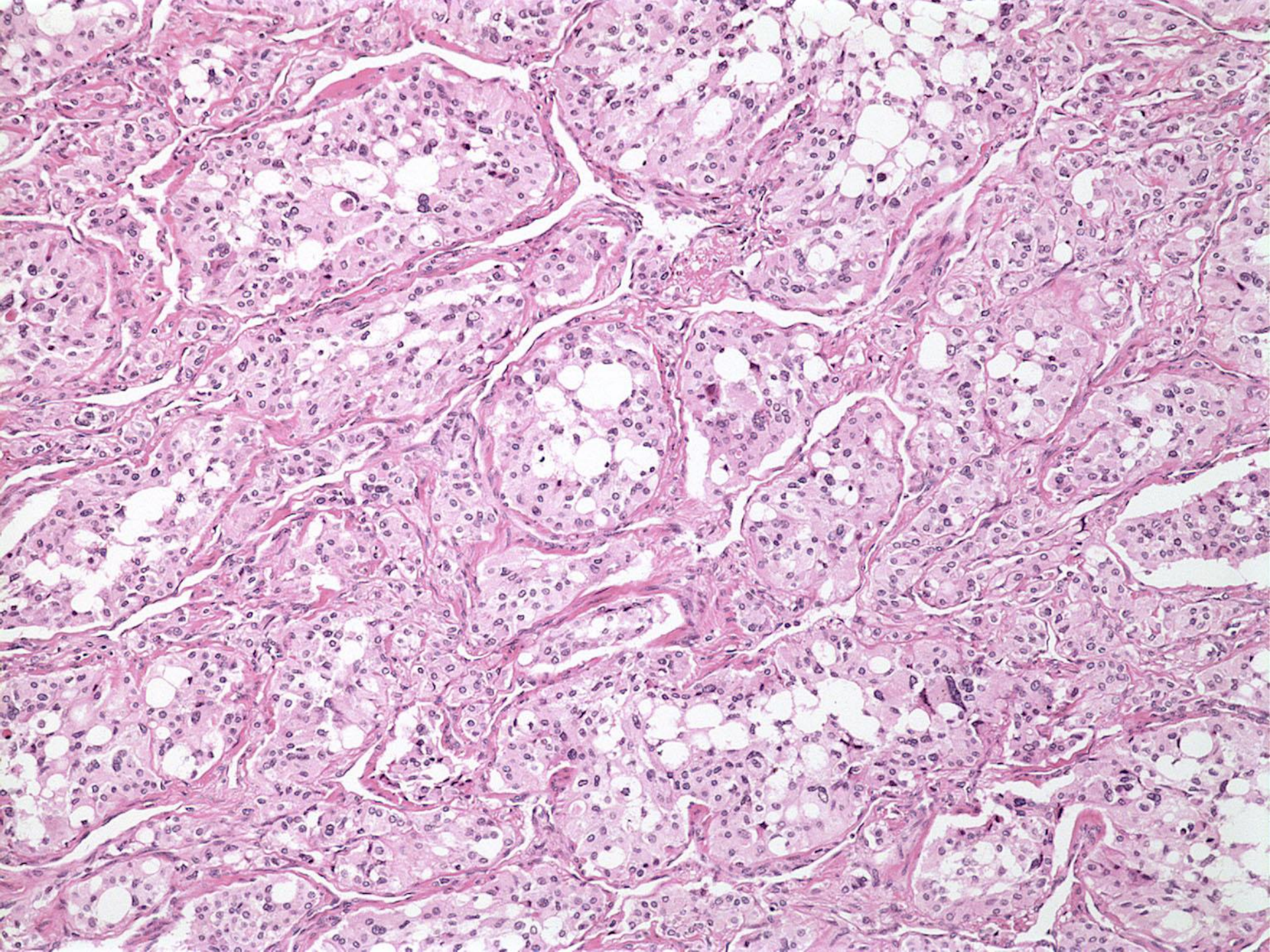


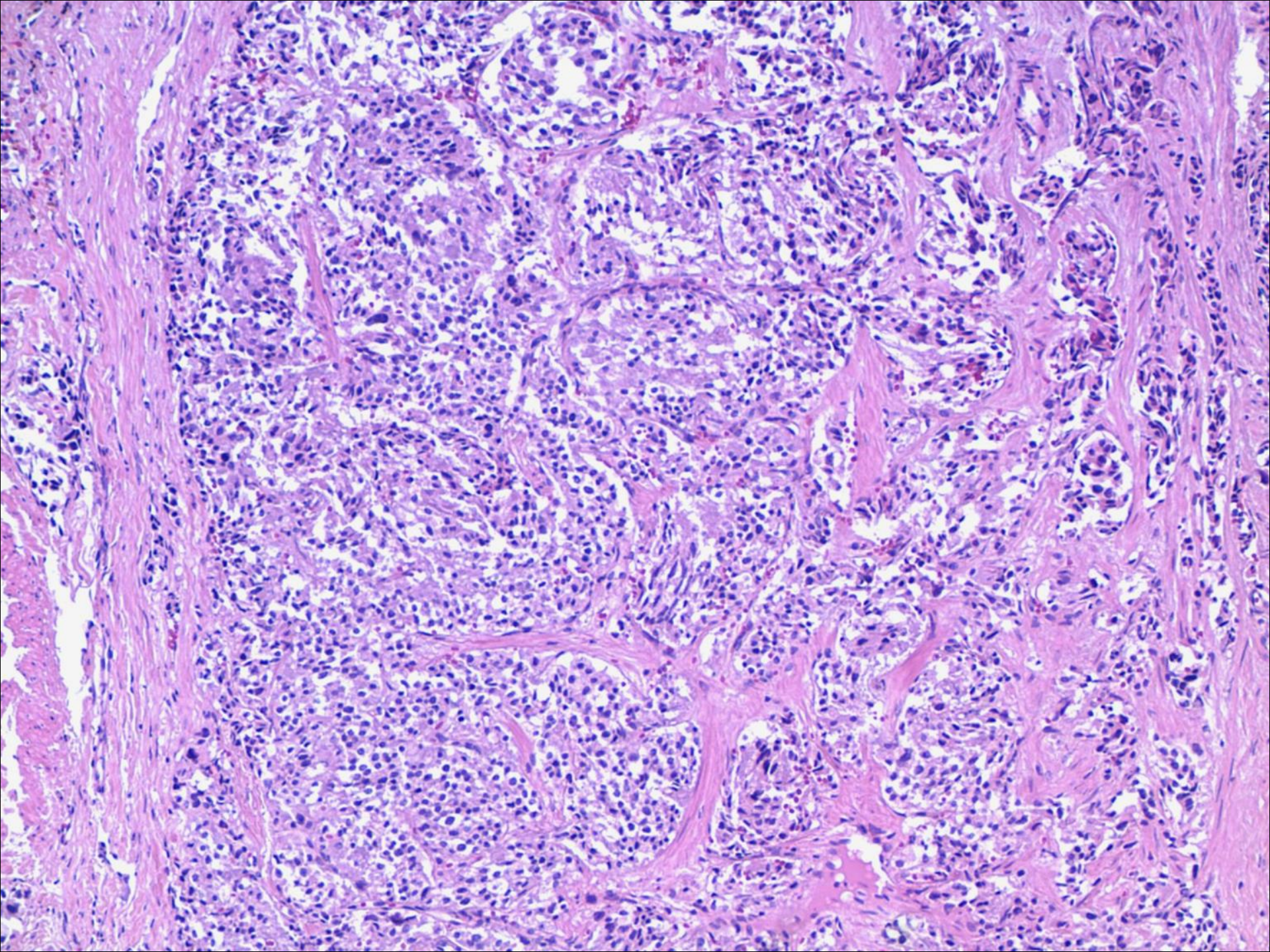


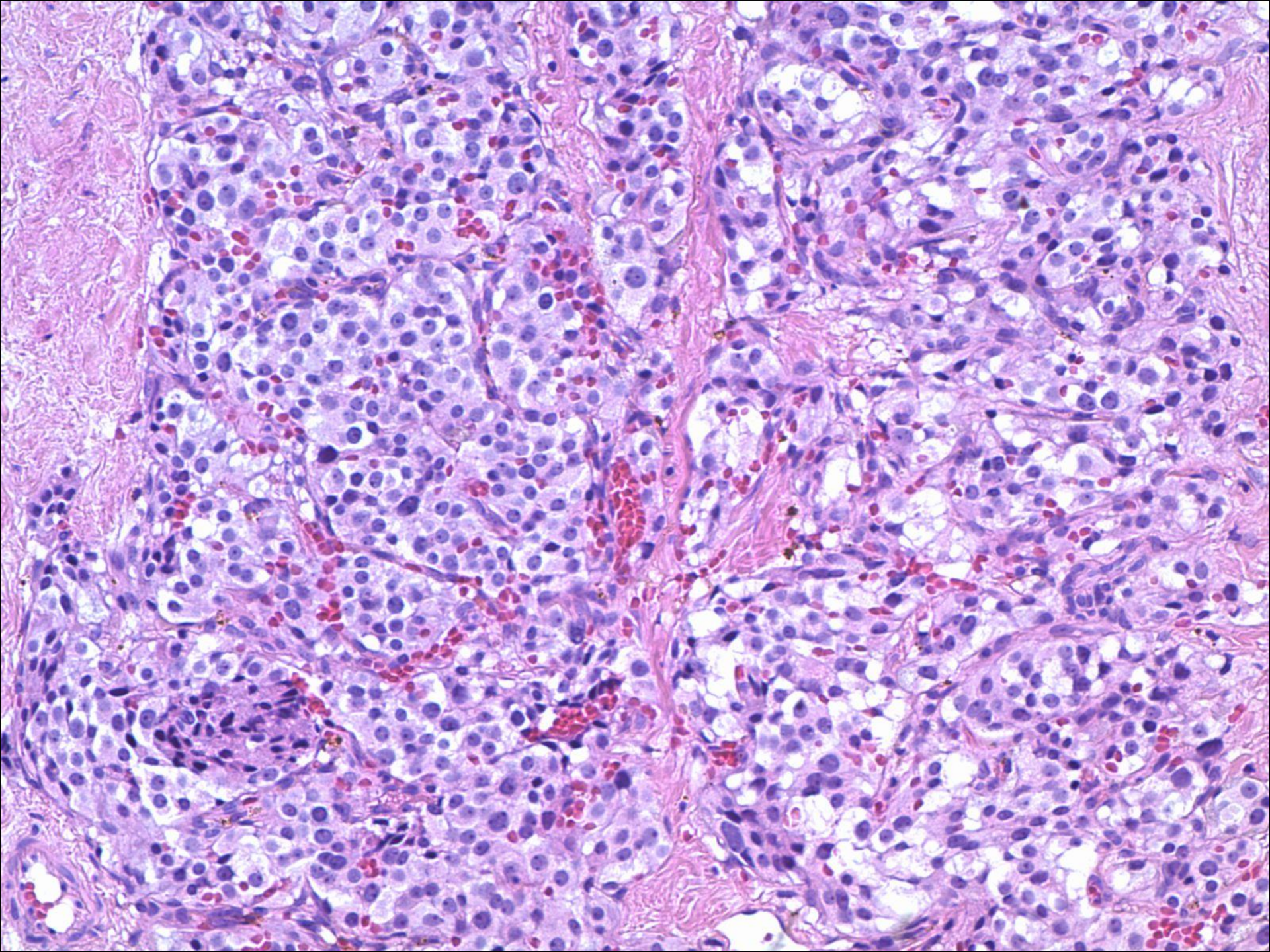




Vascular invasion in a paraganglioma

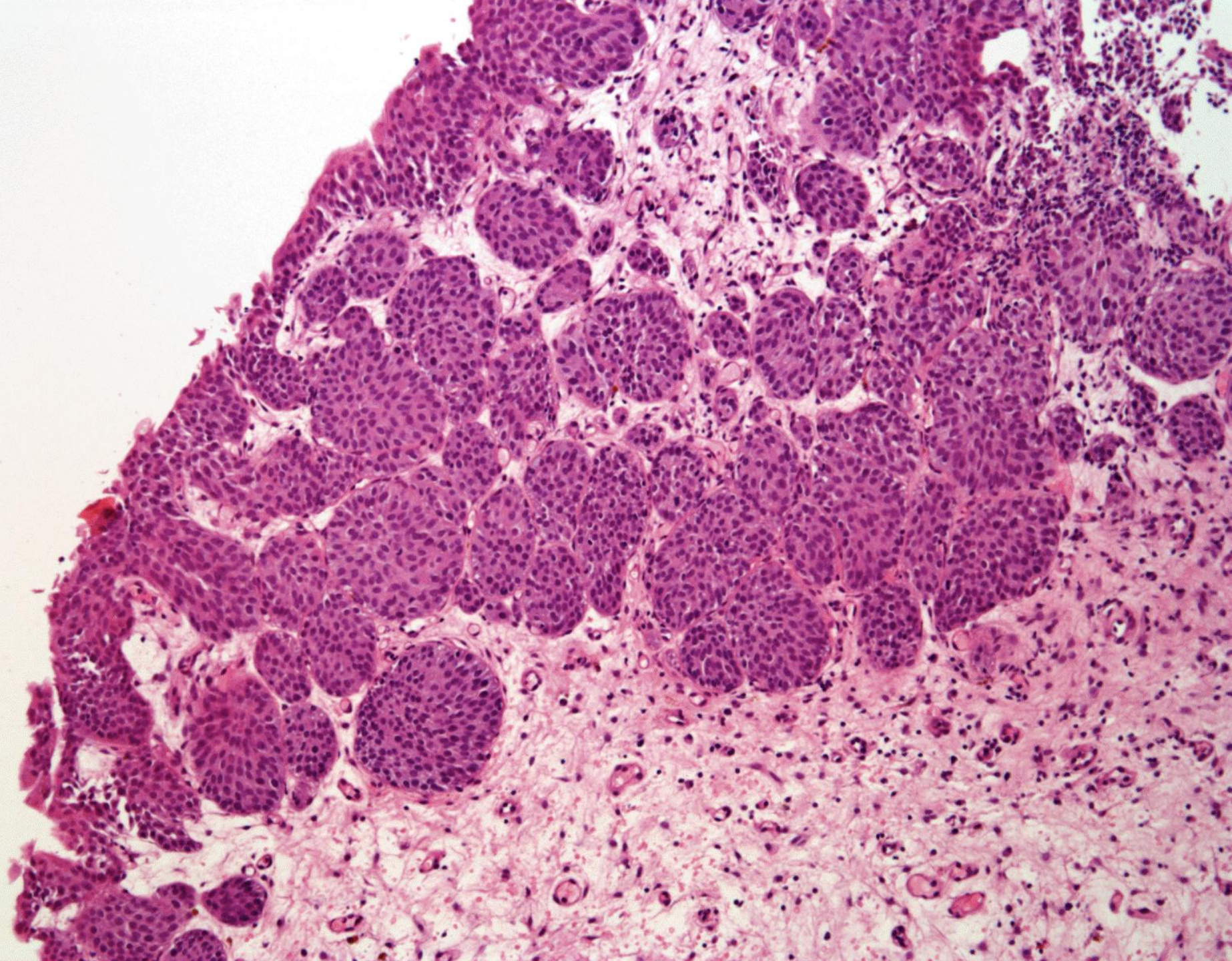


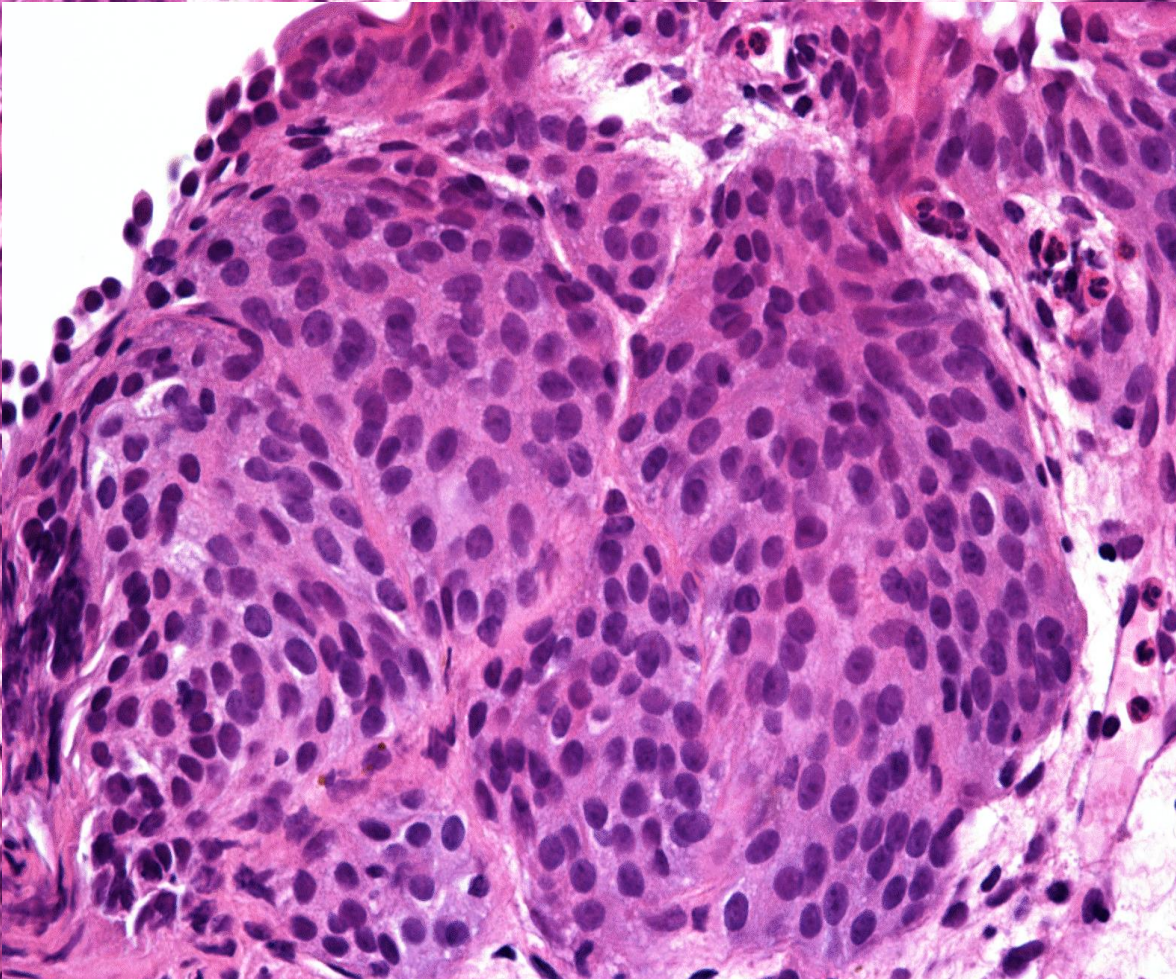
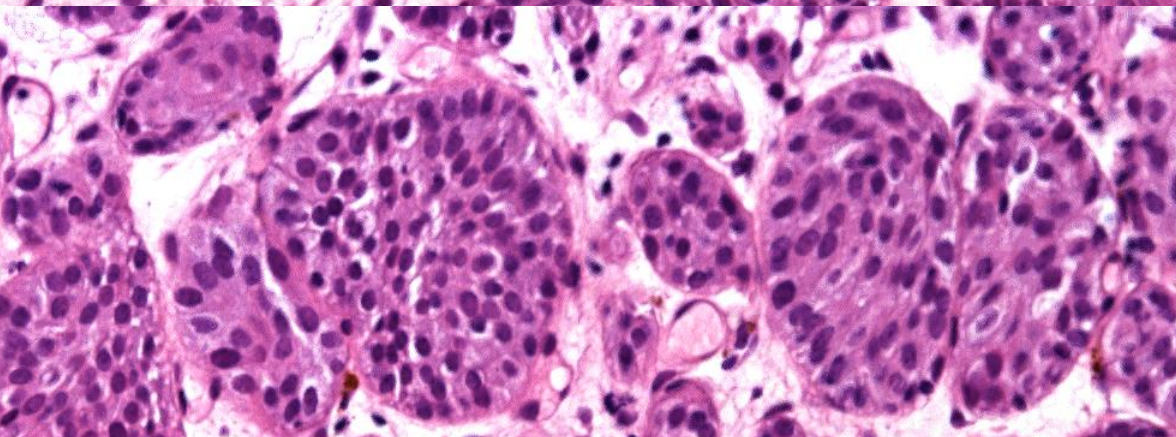
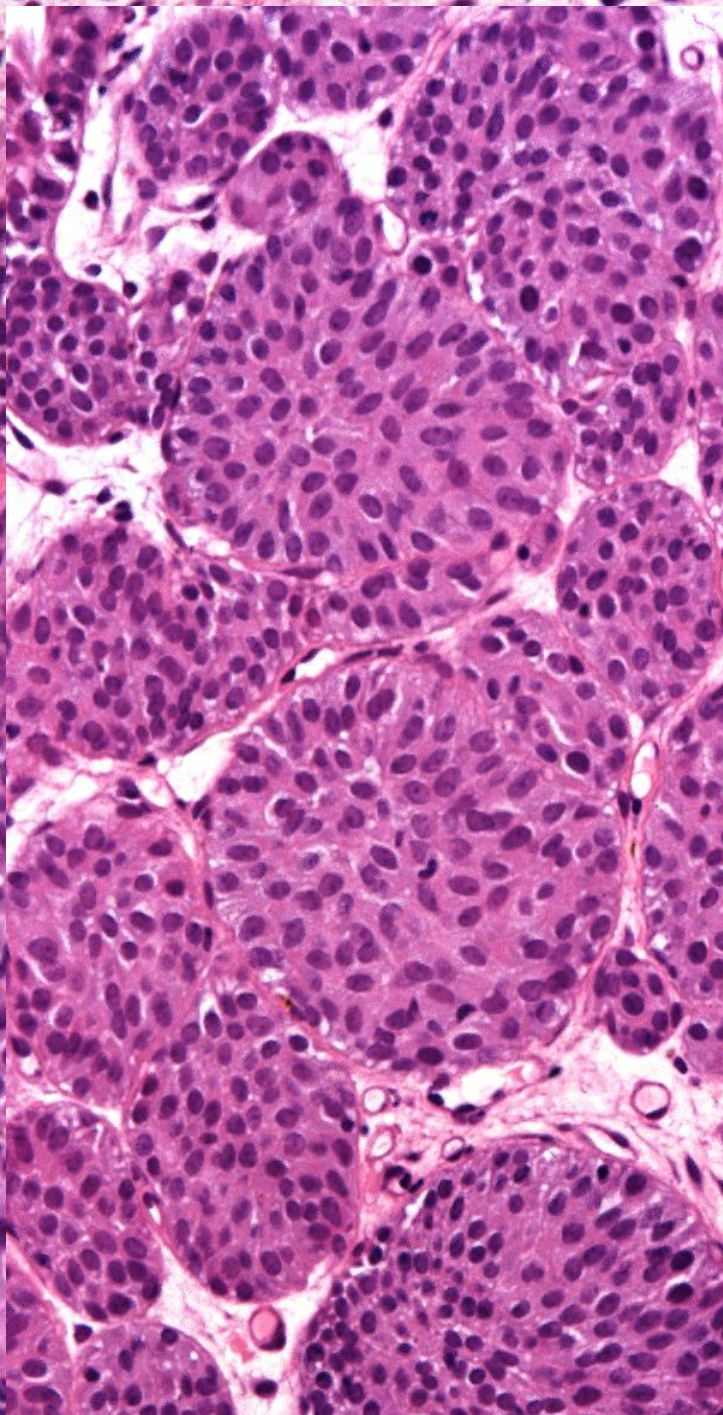




NESTED VARIANT OF U Ca.

- **Diagnostic importance**
- Significant pitfall in limited biopsies
- *Differential diagnosis*
 - Von Brunn's nests
 - Post treatment pseudocarcinomatous hyperplasia
 - Paraganglioma
 - Nephrogenic adenoma
 - Metastatic prostate carcinoma
 - Carcinoid tumor

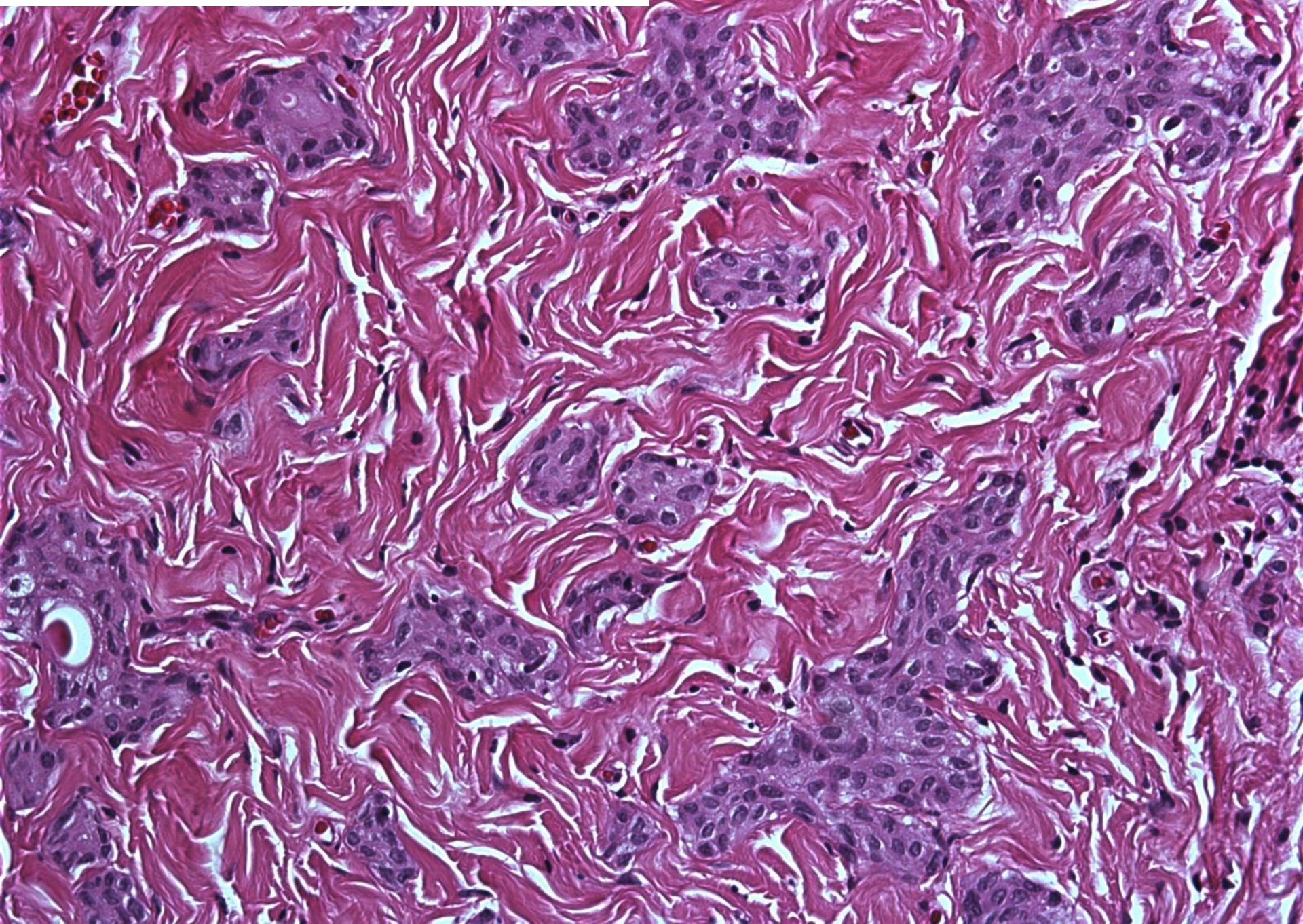


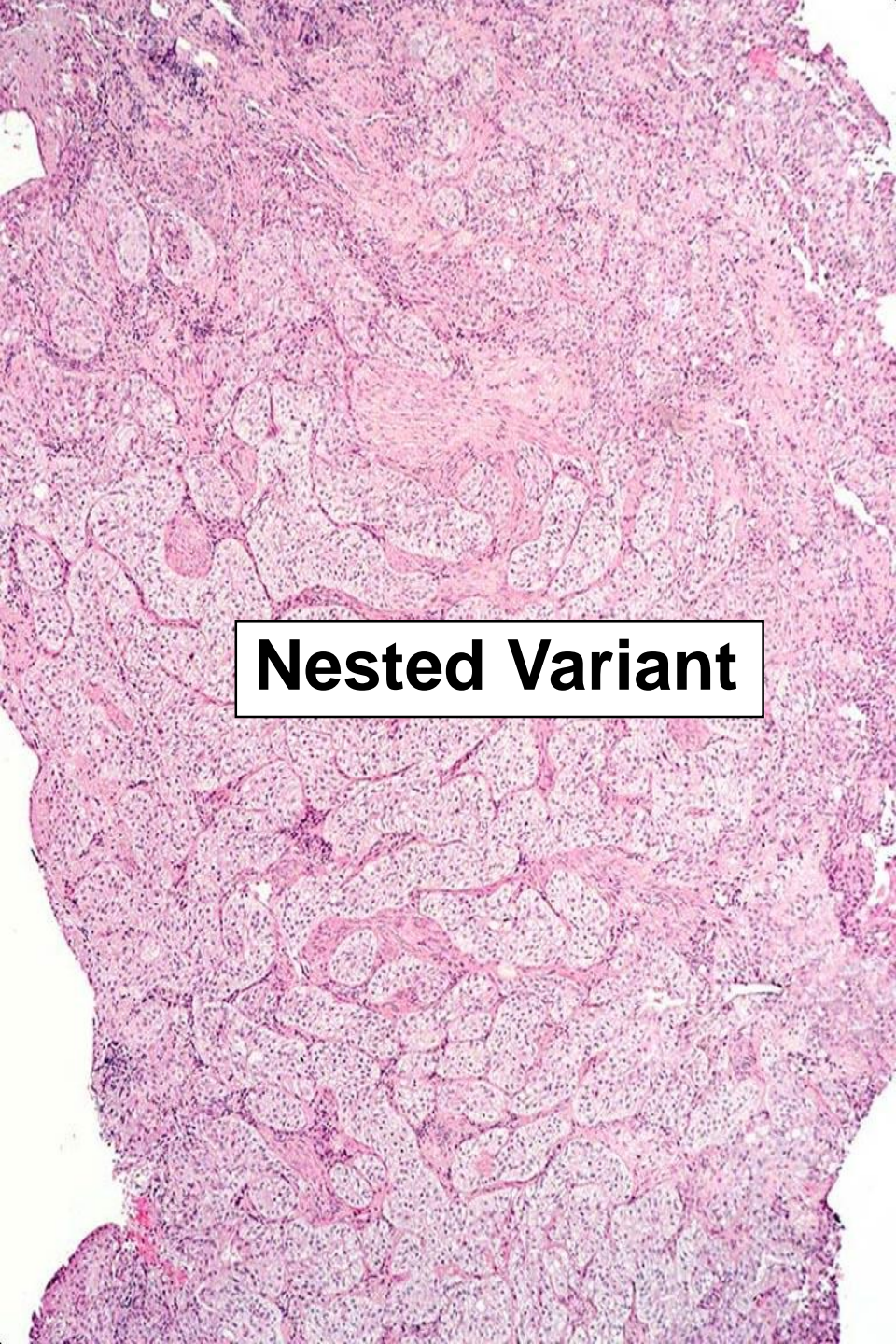


FLORID VON BRUNNS NESTS



FLORID VON BRUNNS NESTS

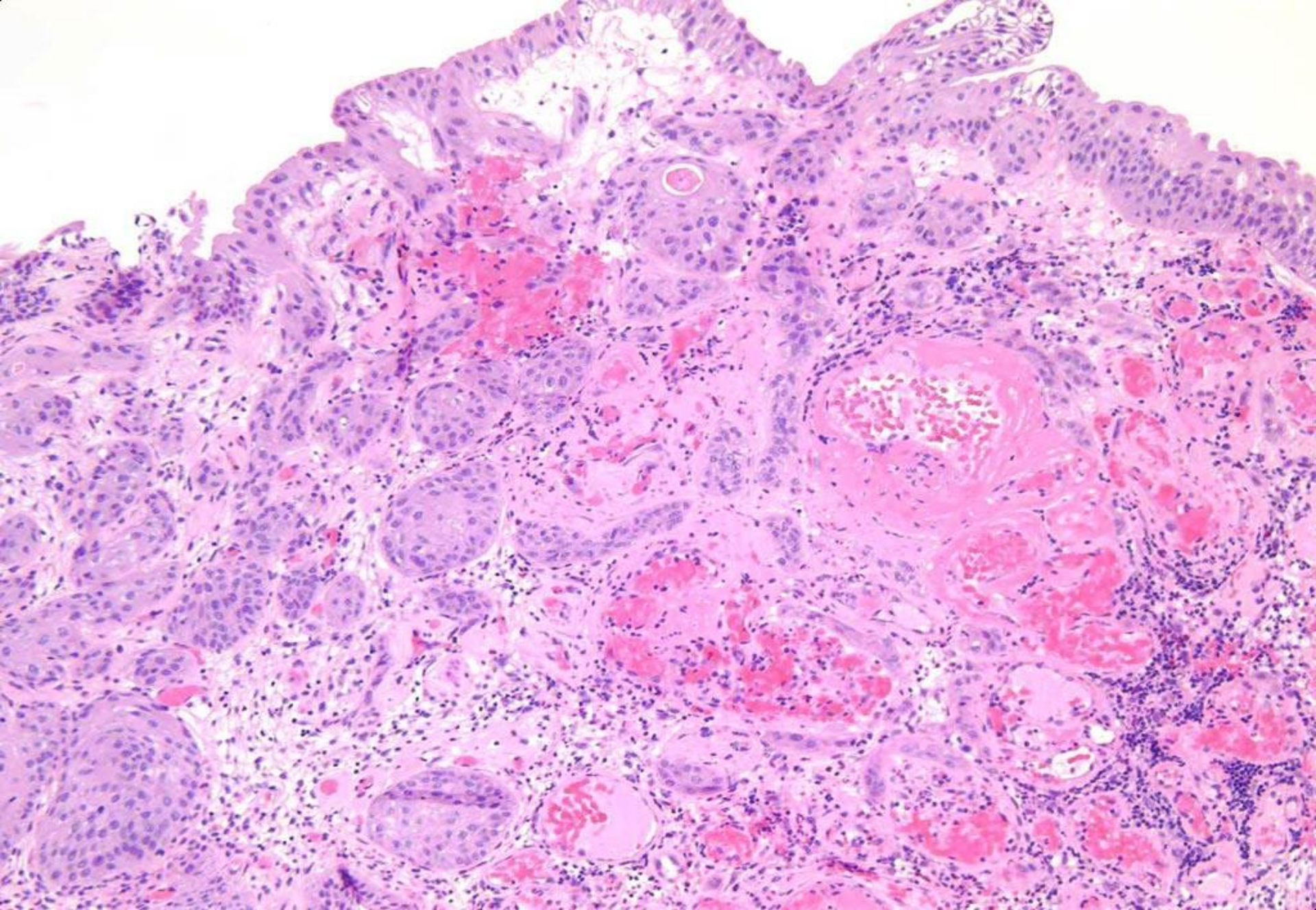




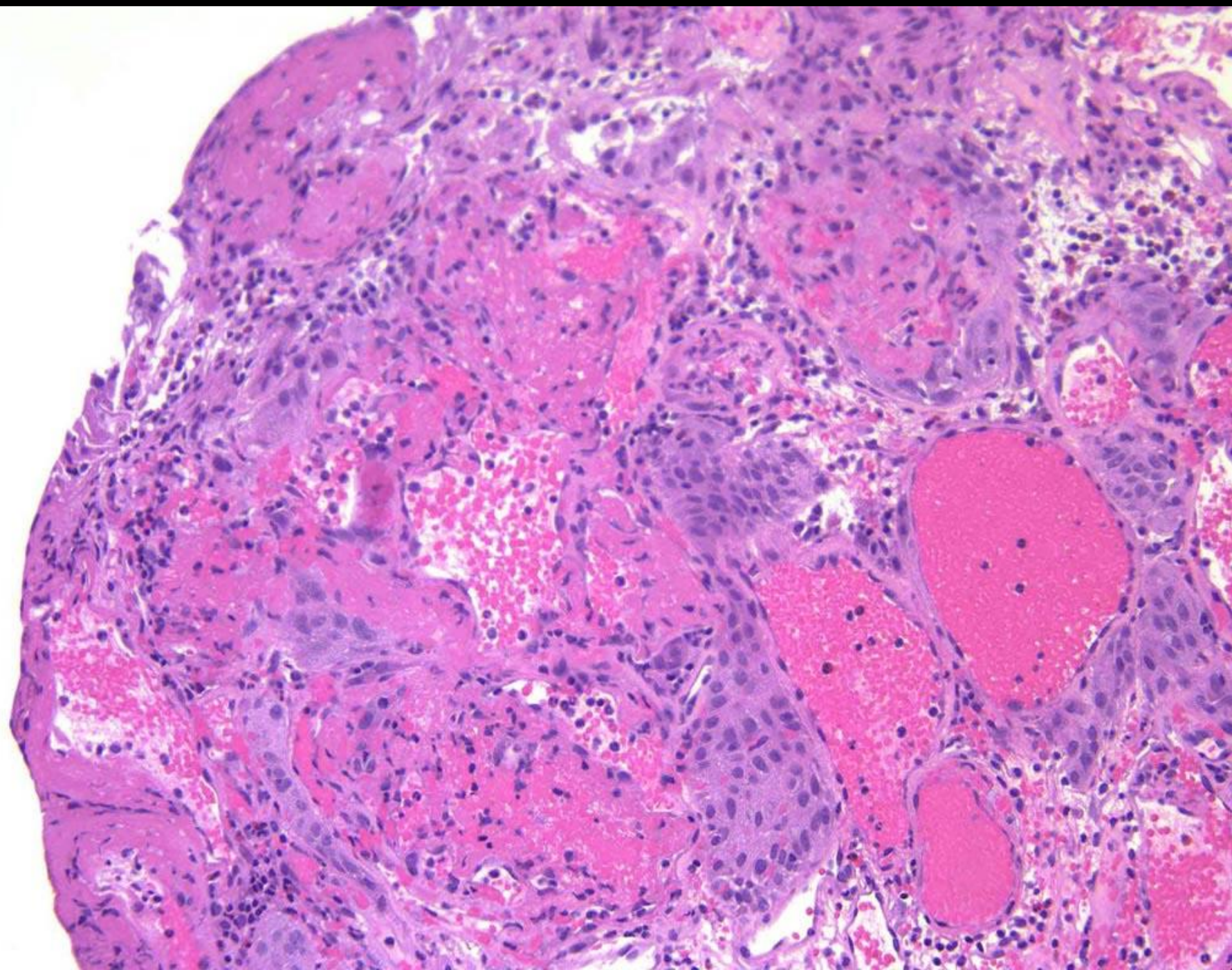
Nested Variant

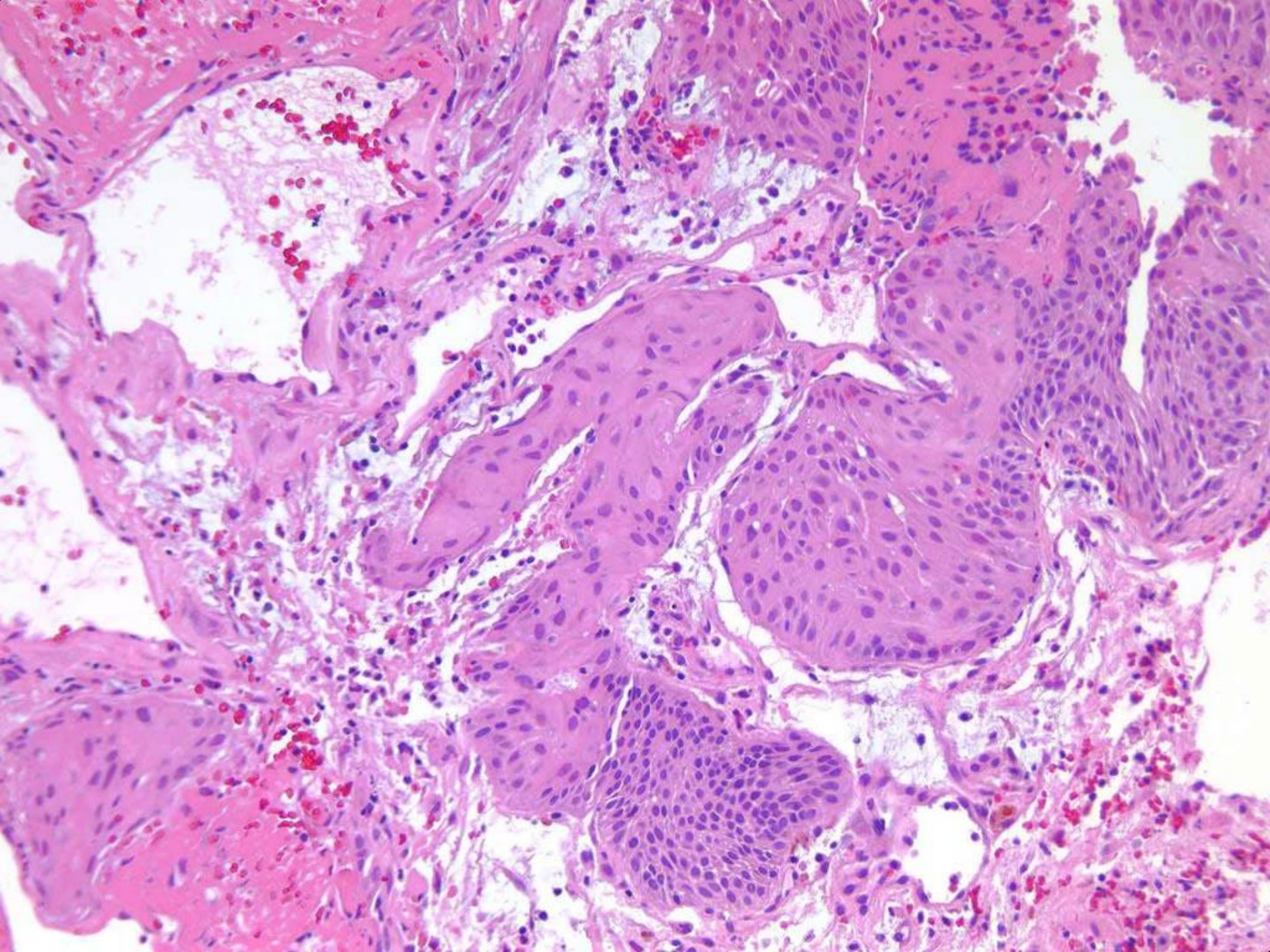


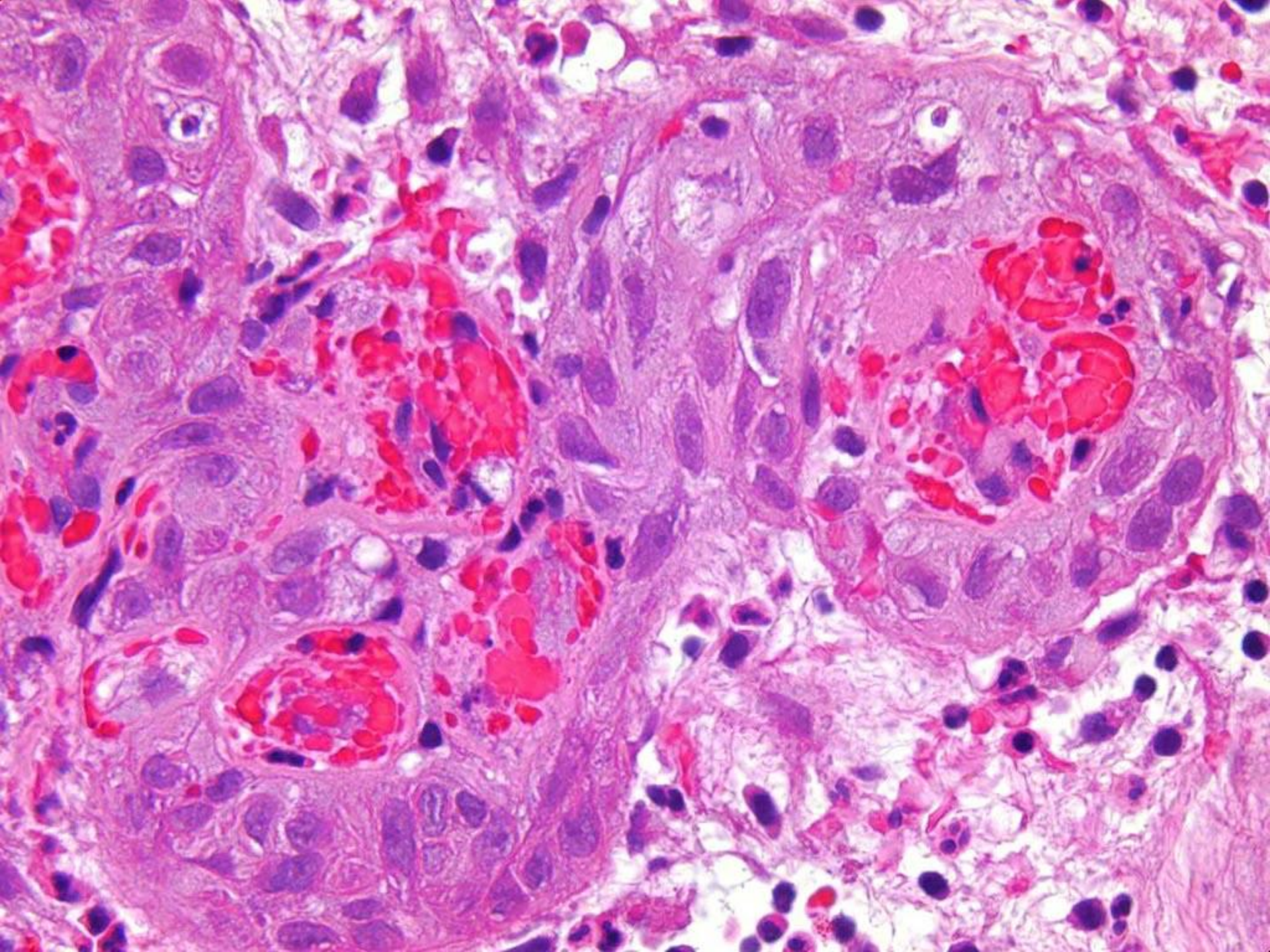
Von Brunn's nests

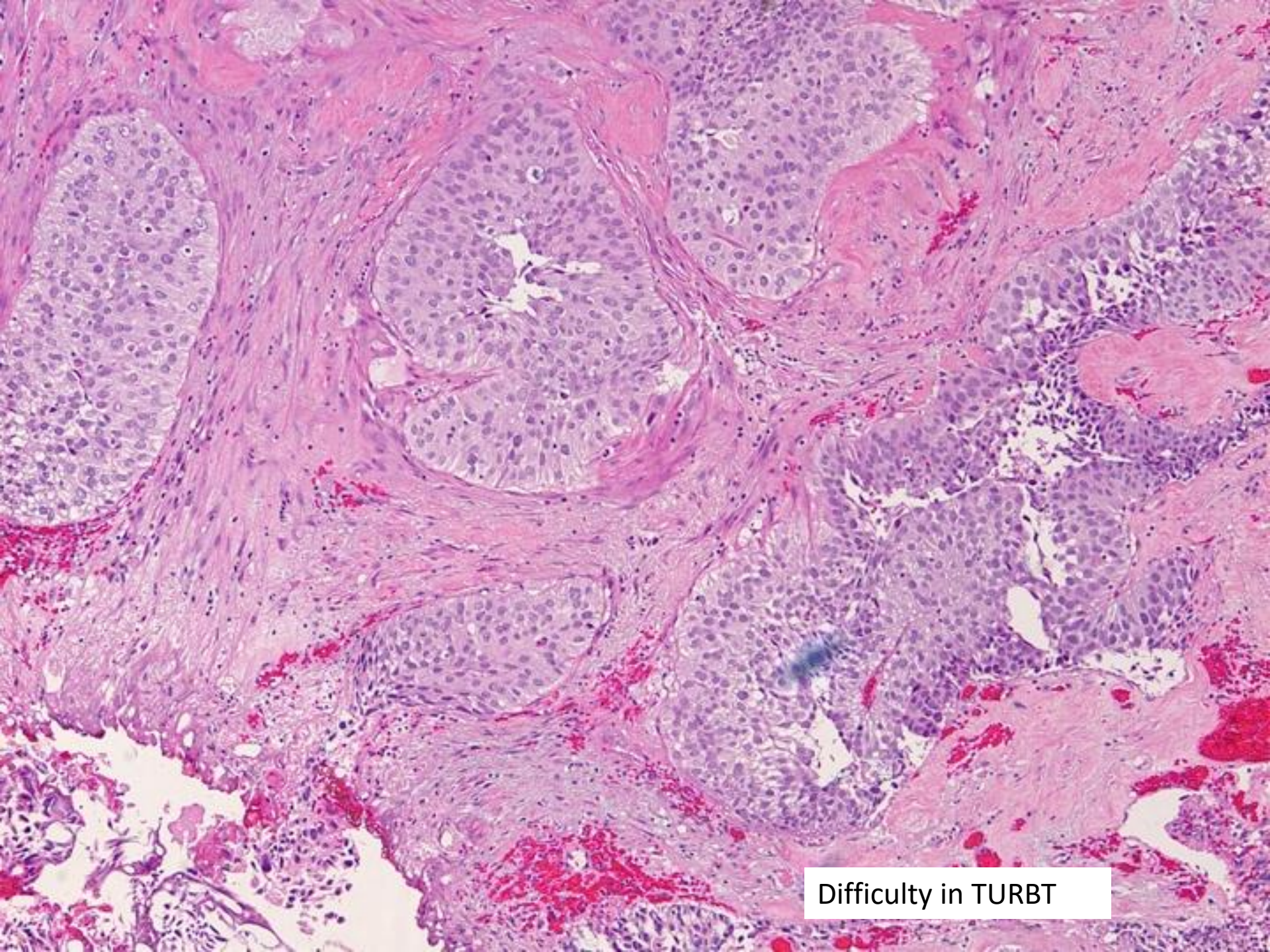


POST TREATMENT PSEUDOCARCINOMATOUS HYPERPLASIA





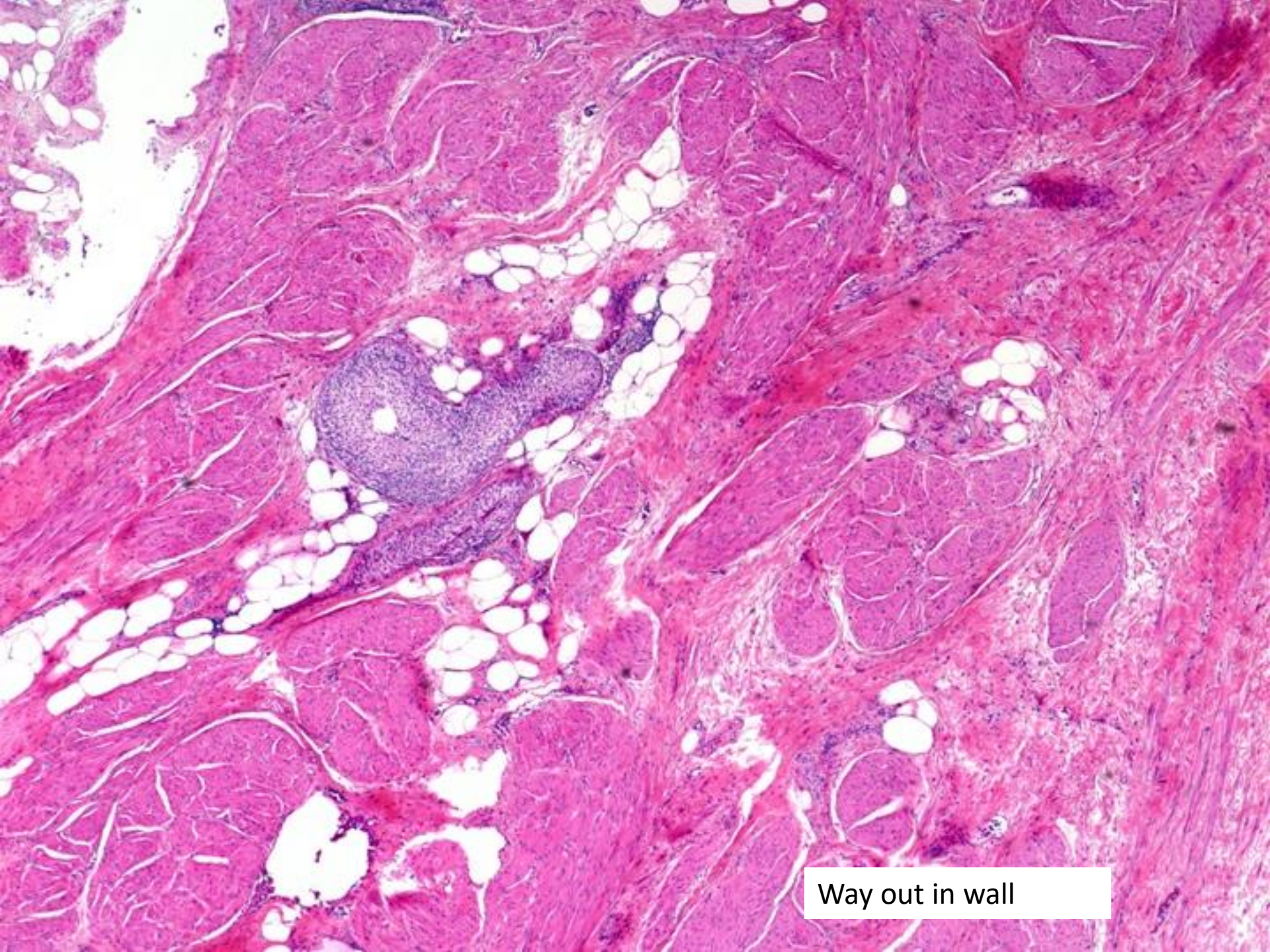




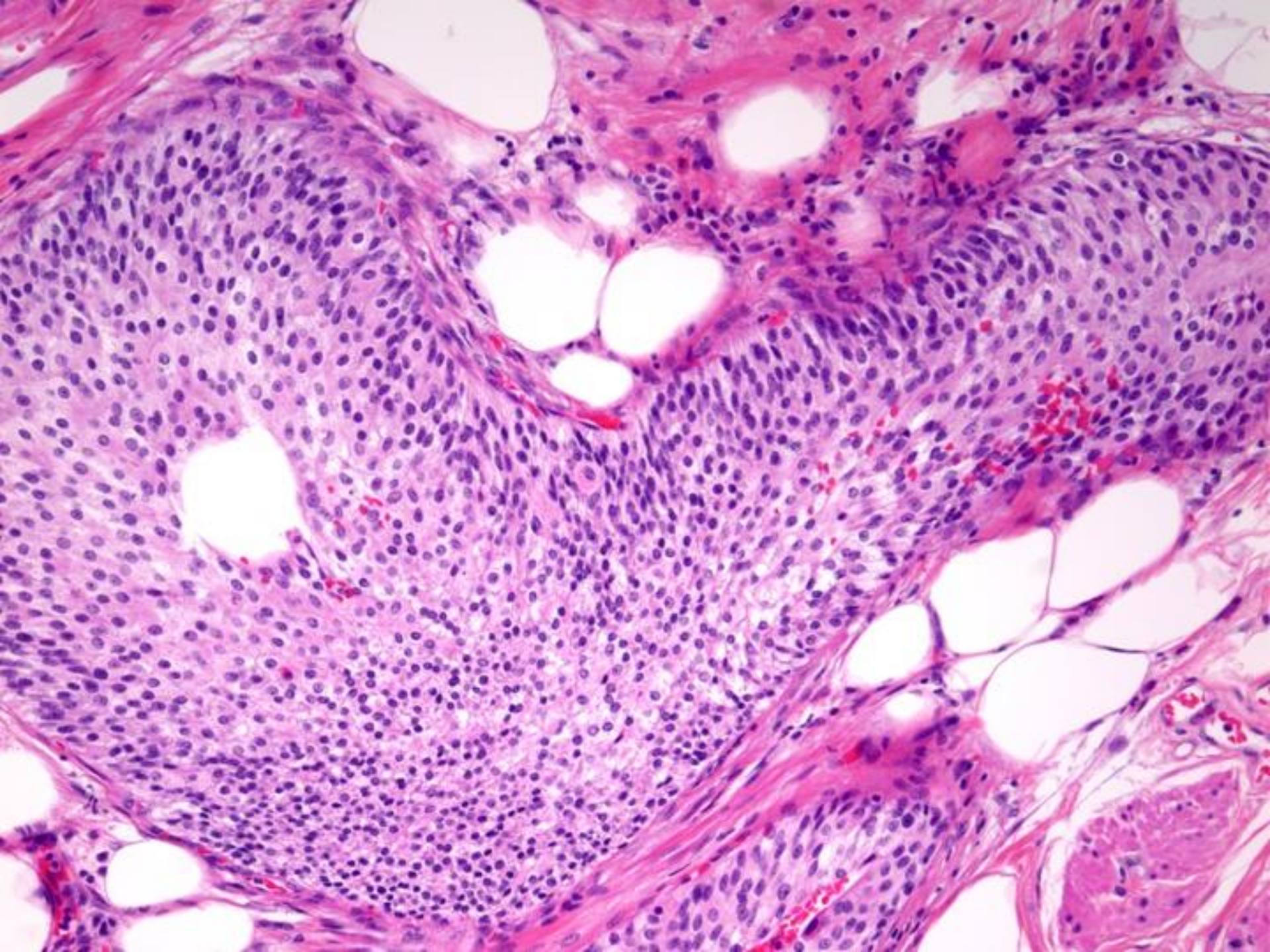
Difficulty in TURBT

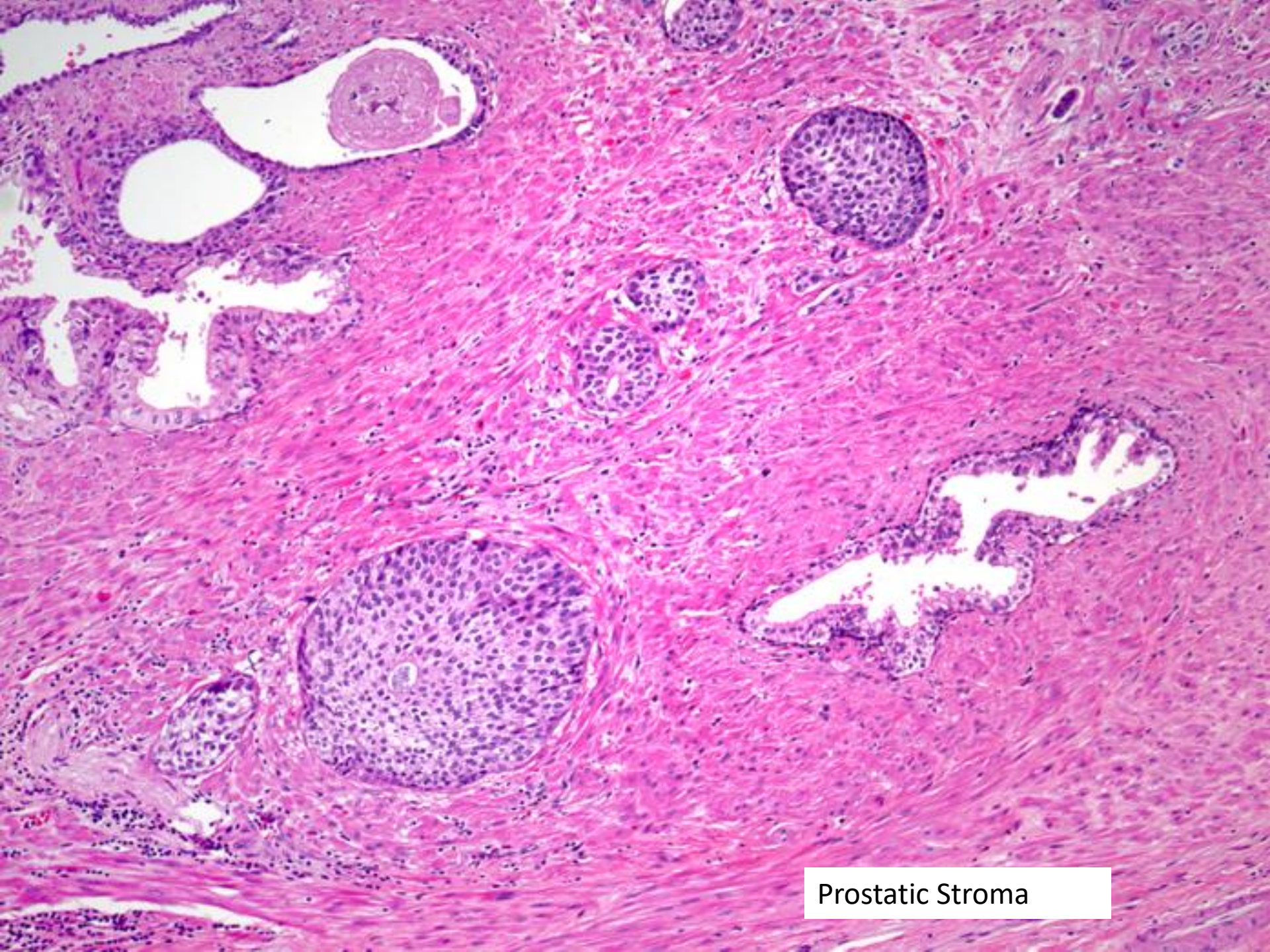


Bland Cytology



Way out in wall





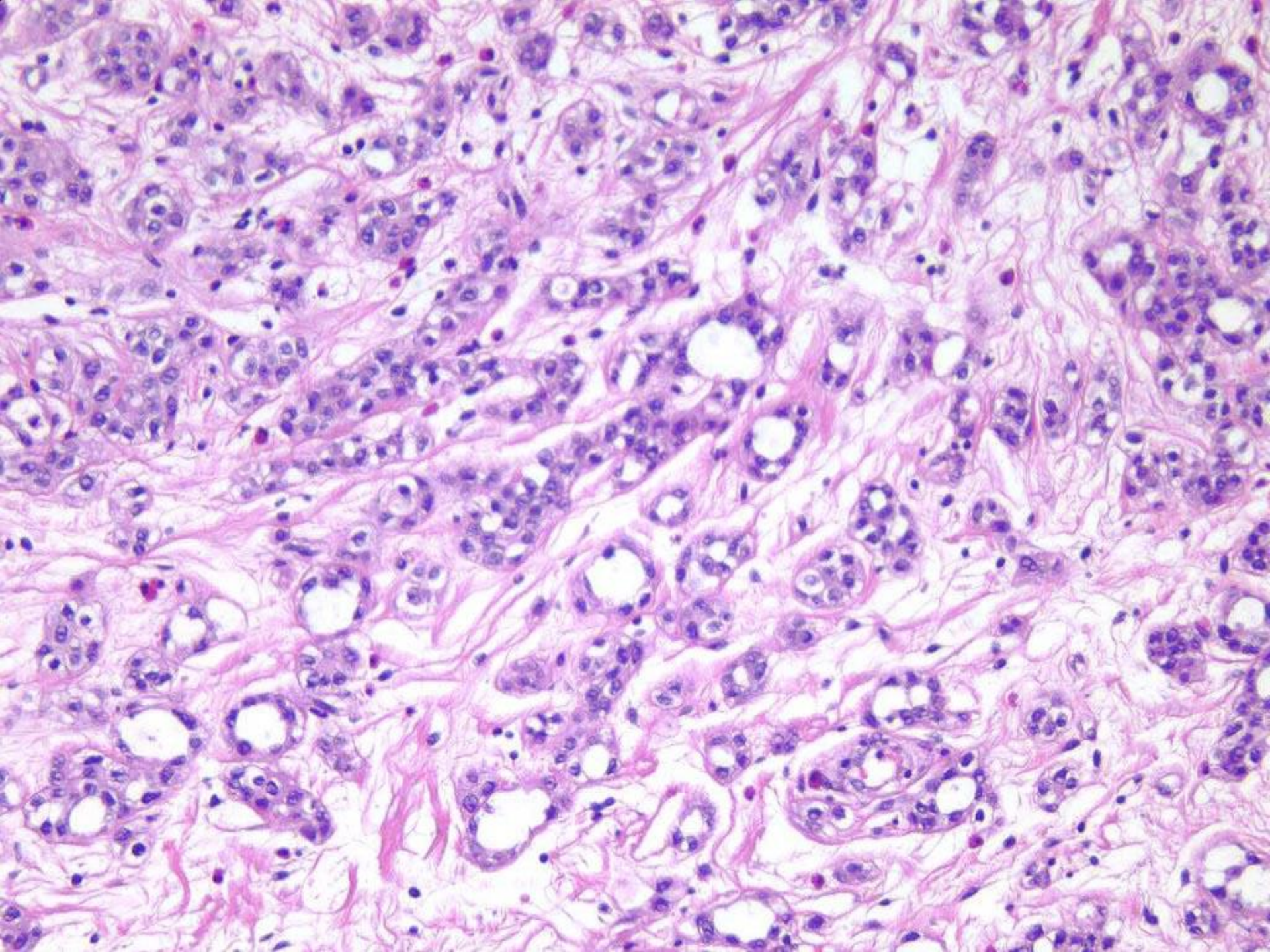
Prostatic Stroma

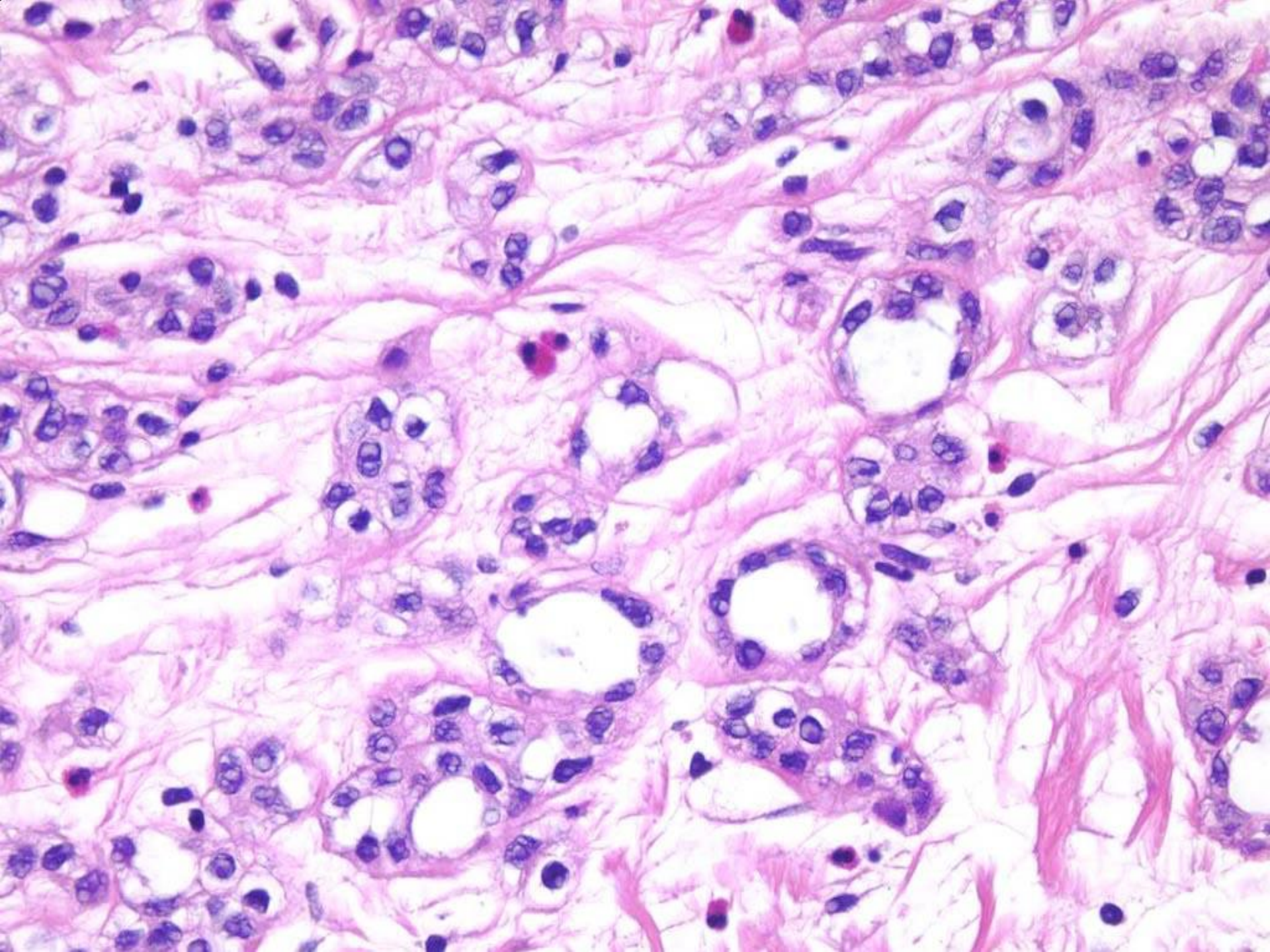
NESTED VARIANT OF U Ca.

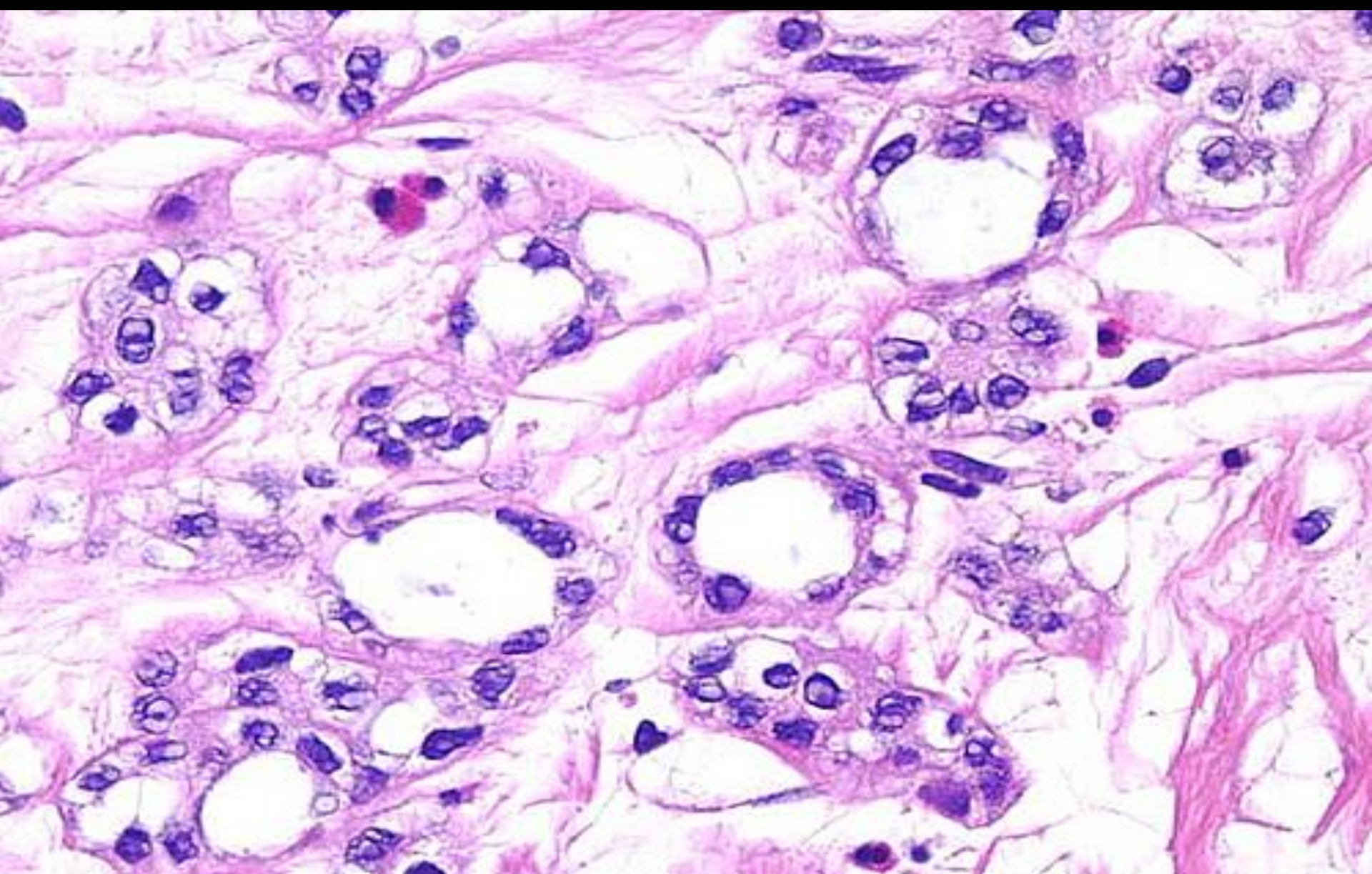
- **Prognostic significance**
 - Small number of cases, variable follow up
 - Aggressive clinical course in spite of low histologic grade
 - Distinct capability of progression with metastasis and death

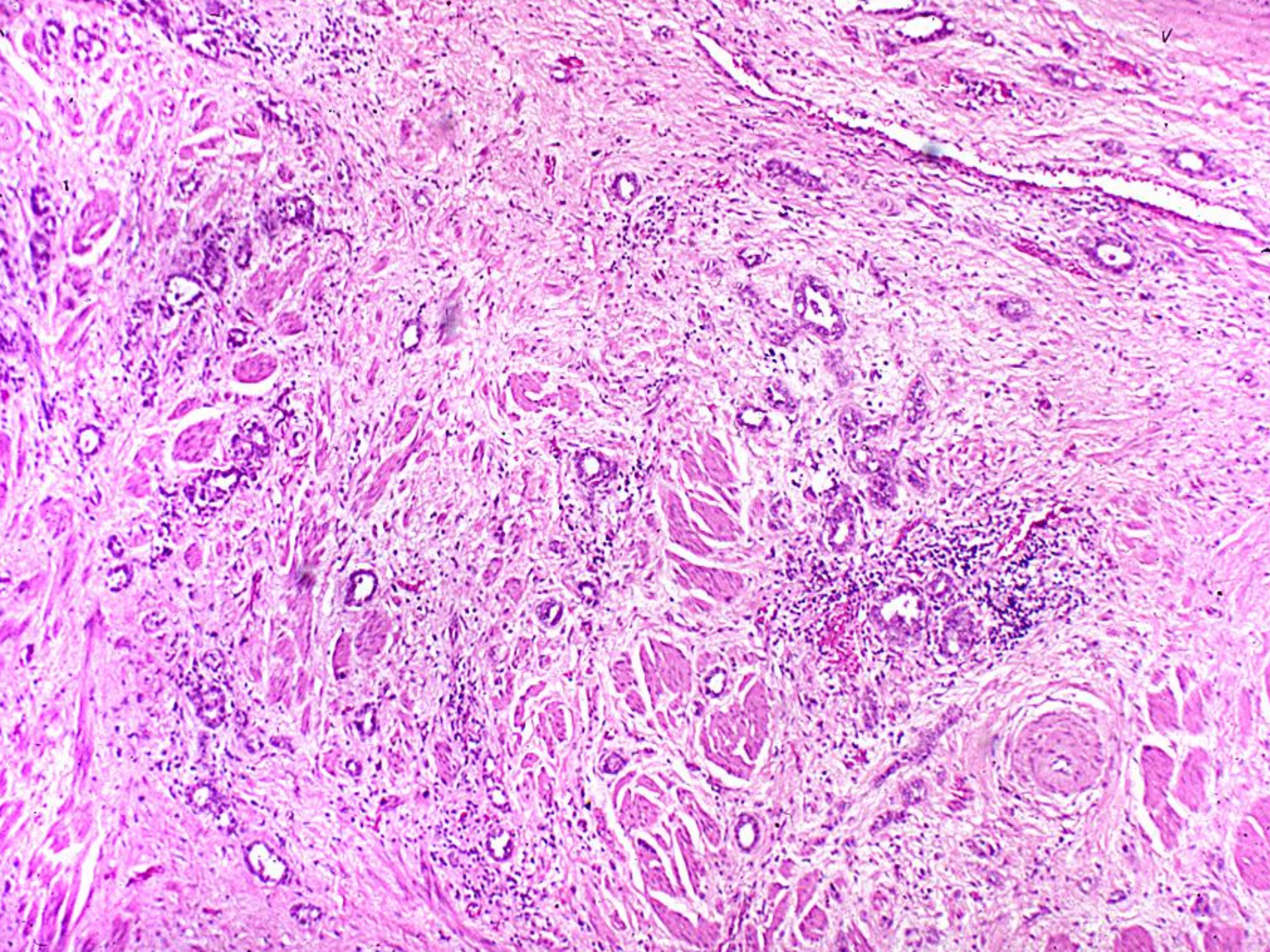
UROTHELIAL Ca. WITH SMALL TUBULES

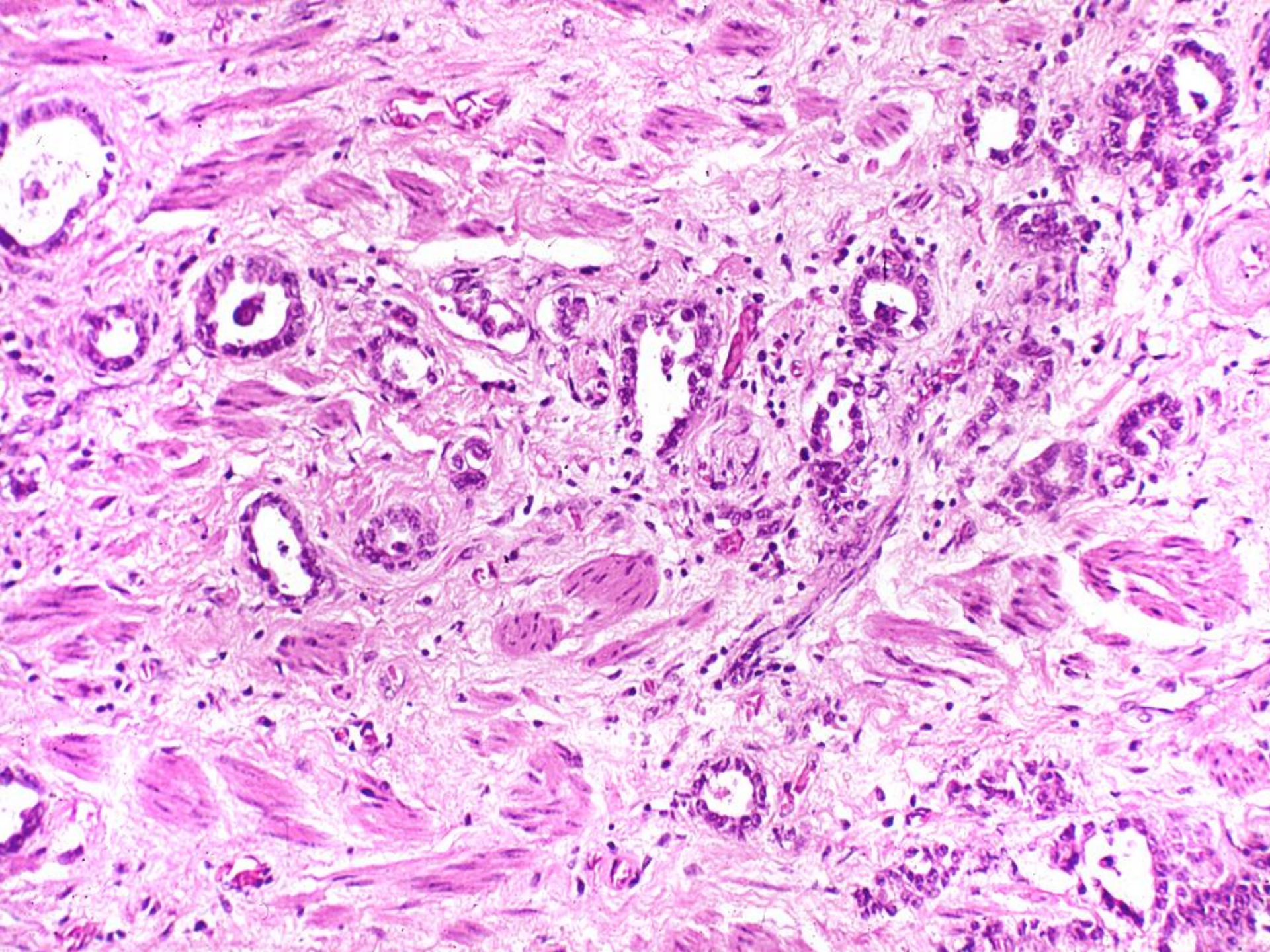
- Frequently admixed with nested variant
- **Differential diagnosis**
 - *nephrogenic adenoma*
 - *prostatic carcinoma*
- **Prognostic significance**
 - *unclear (stage of disease)*

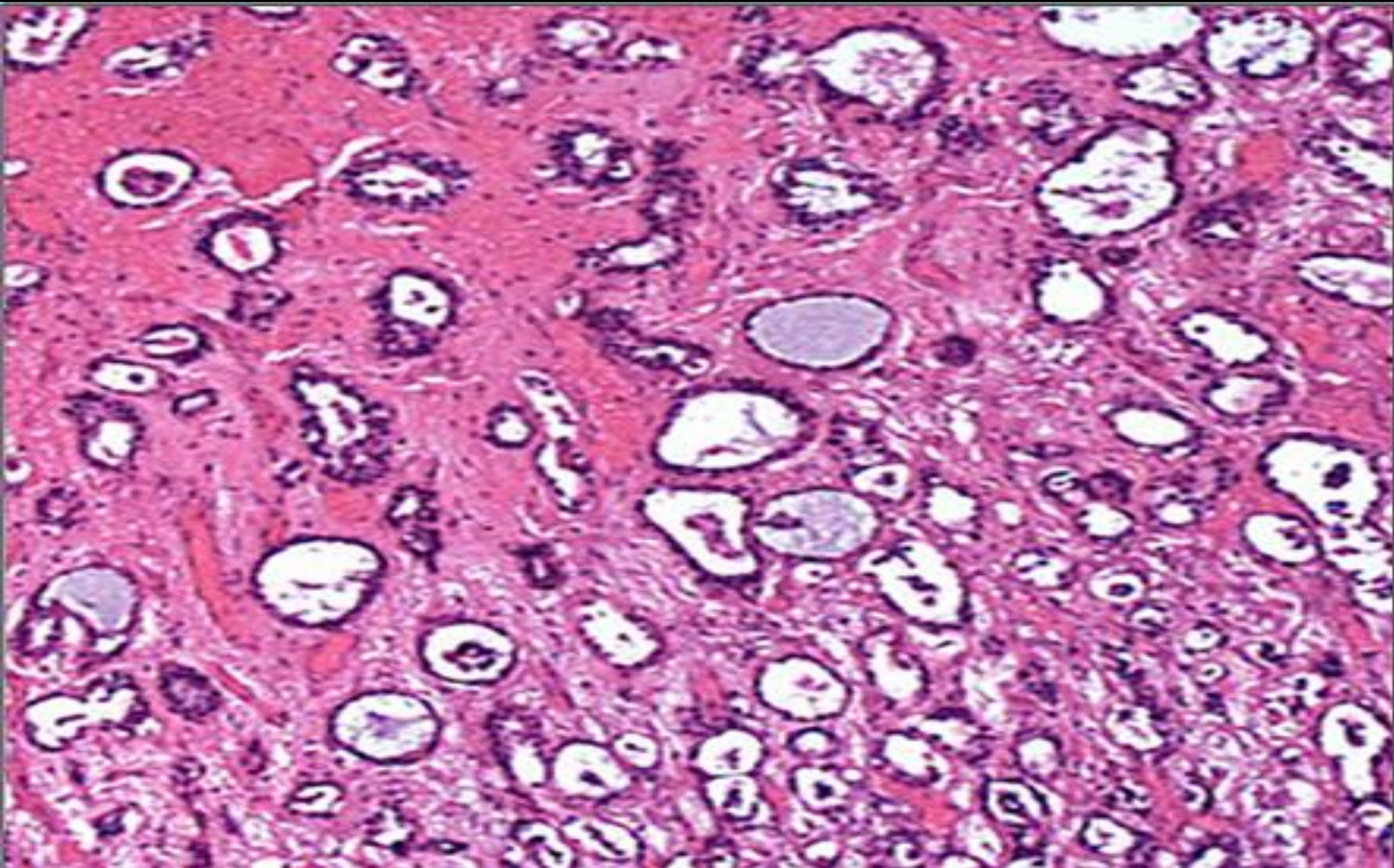


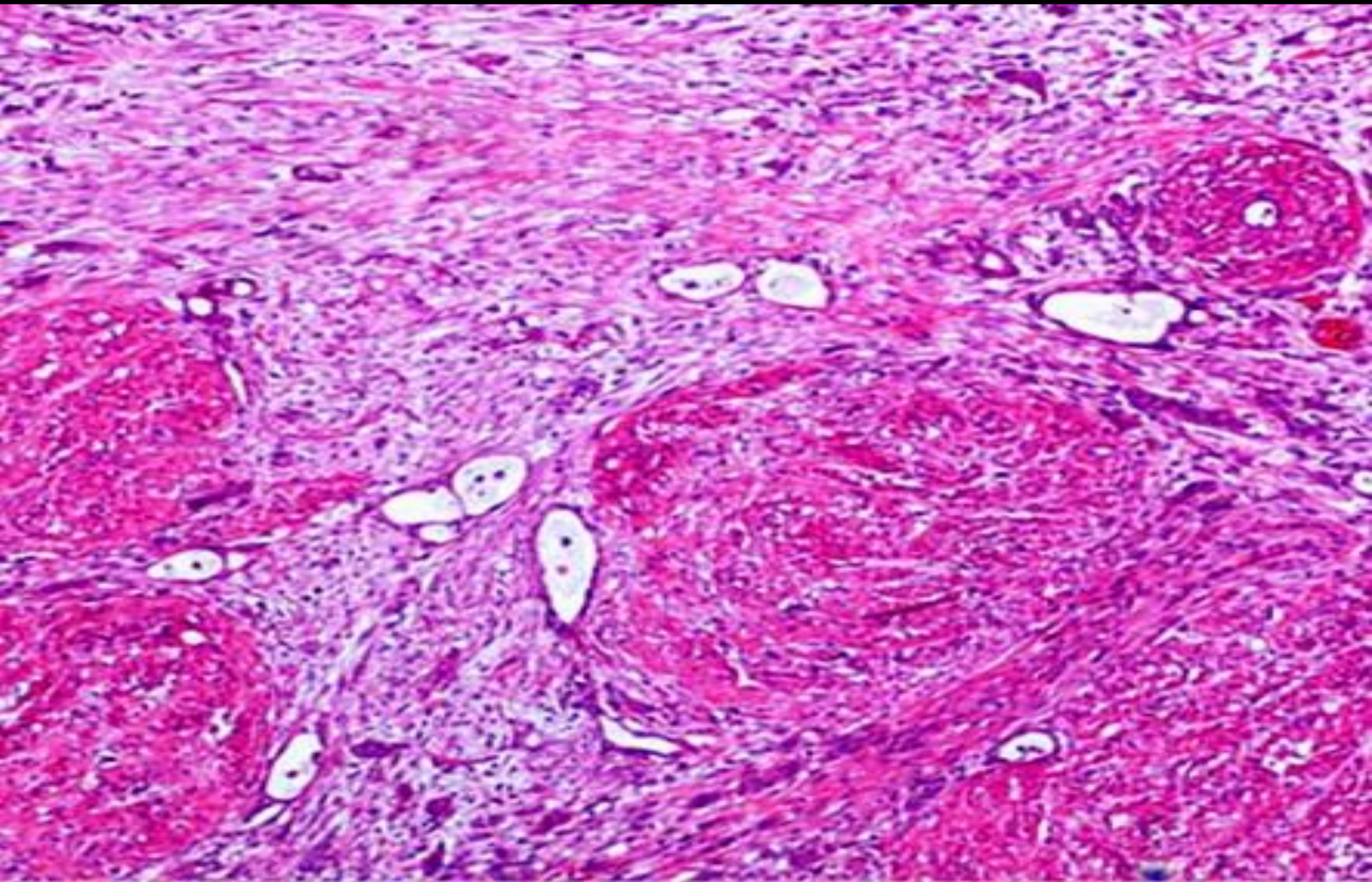


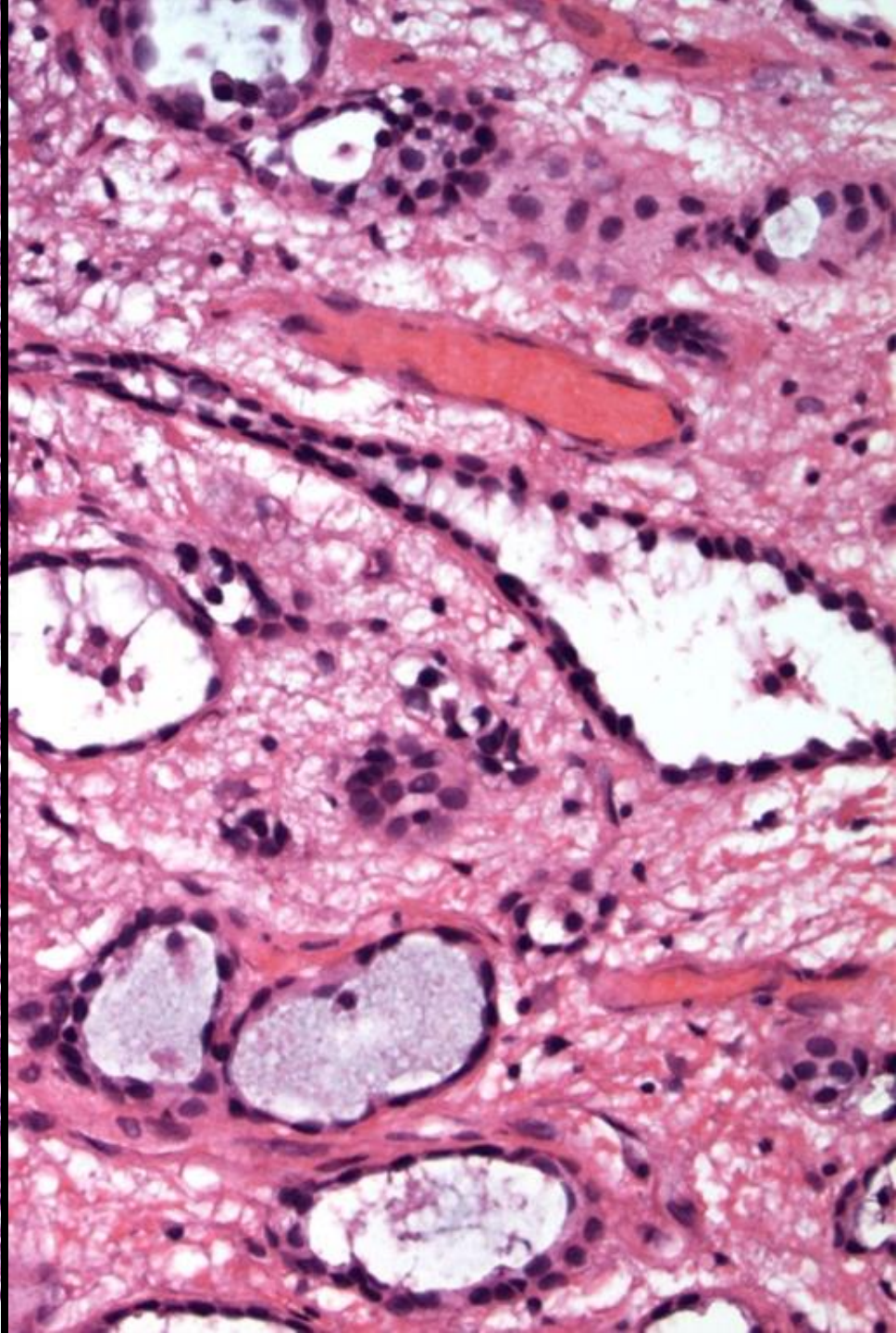
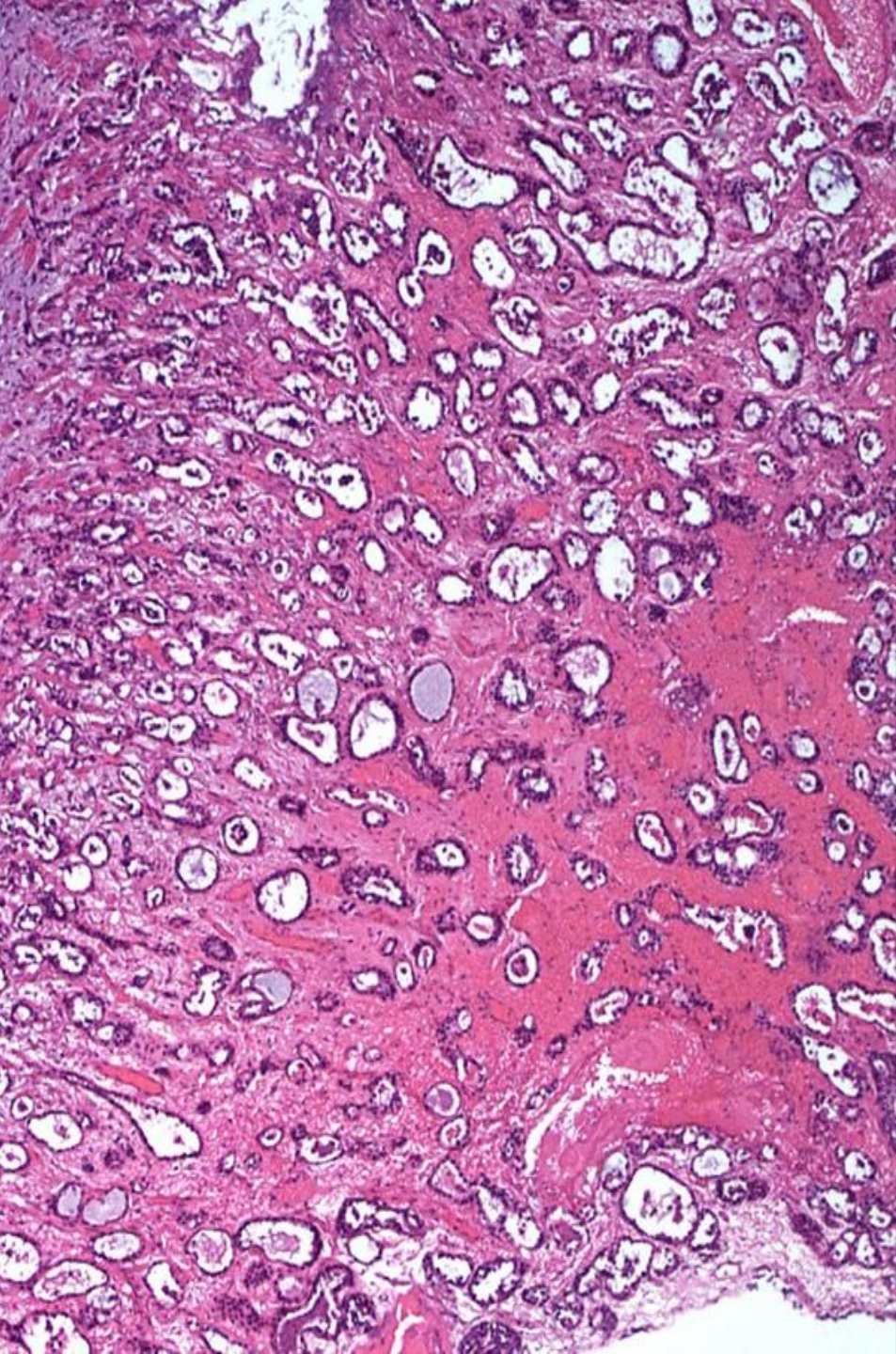


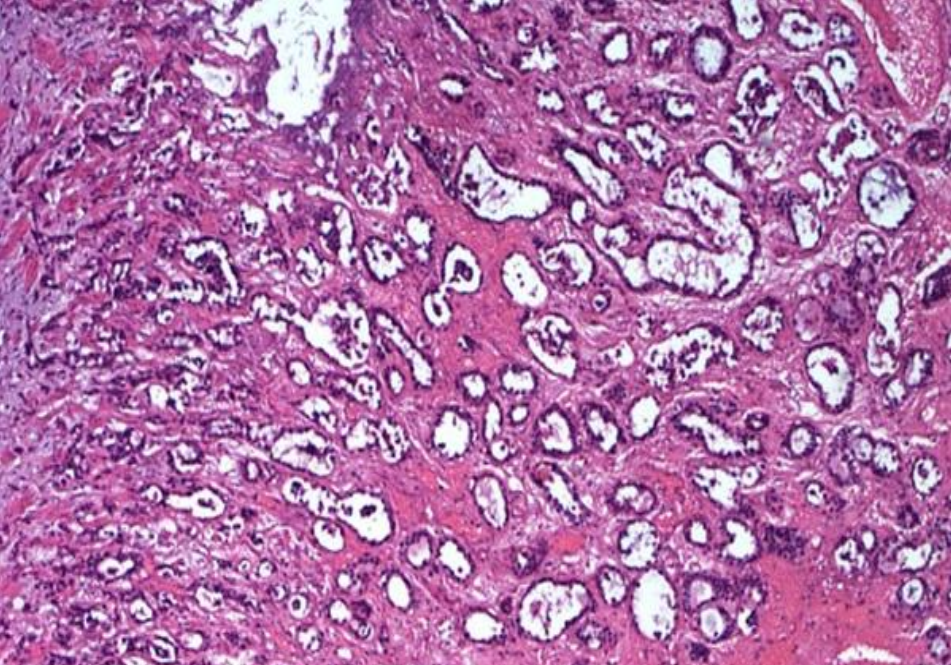




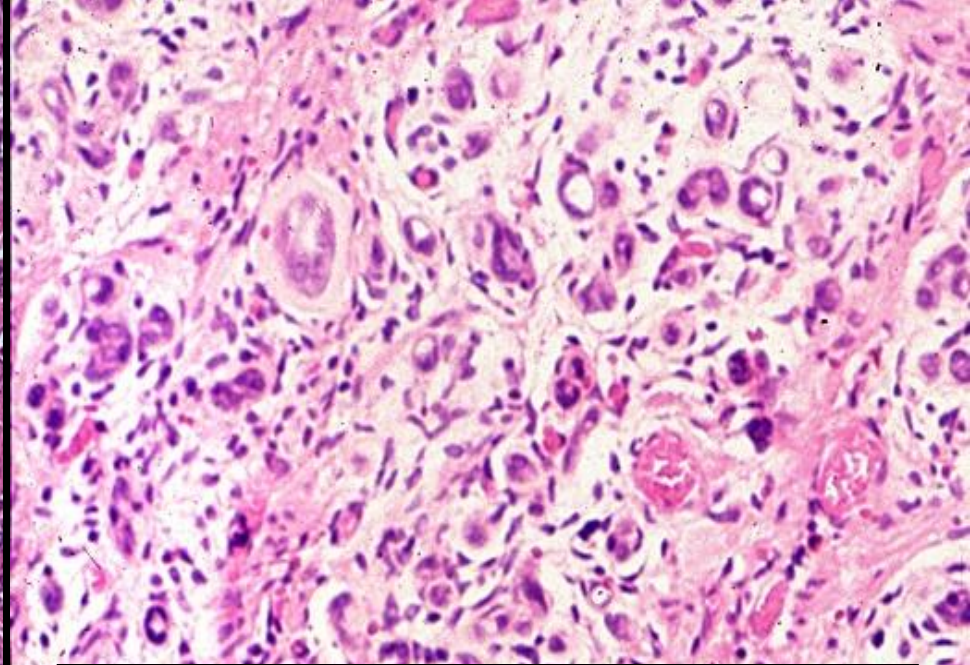
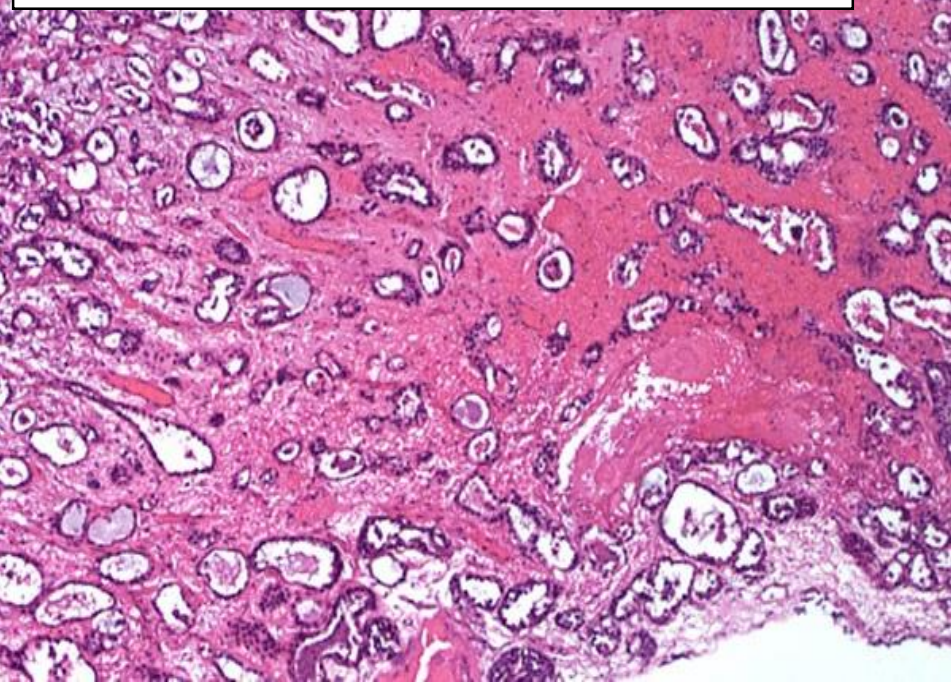




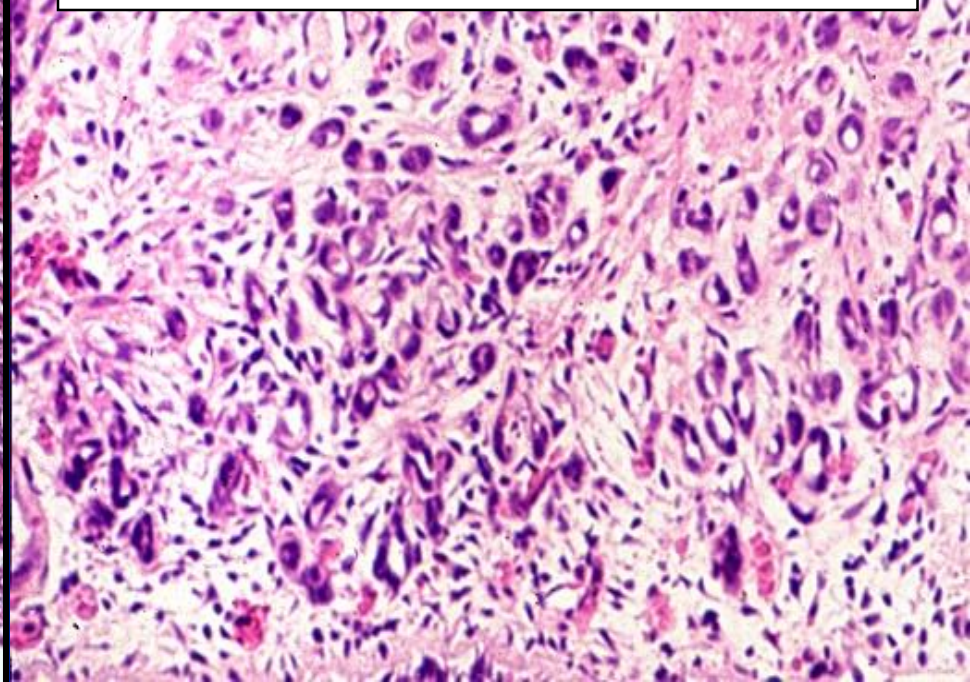


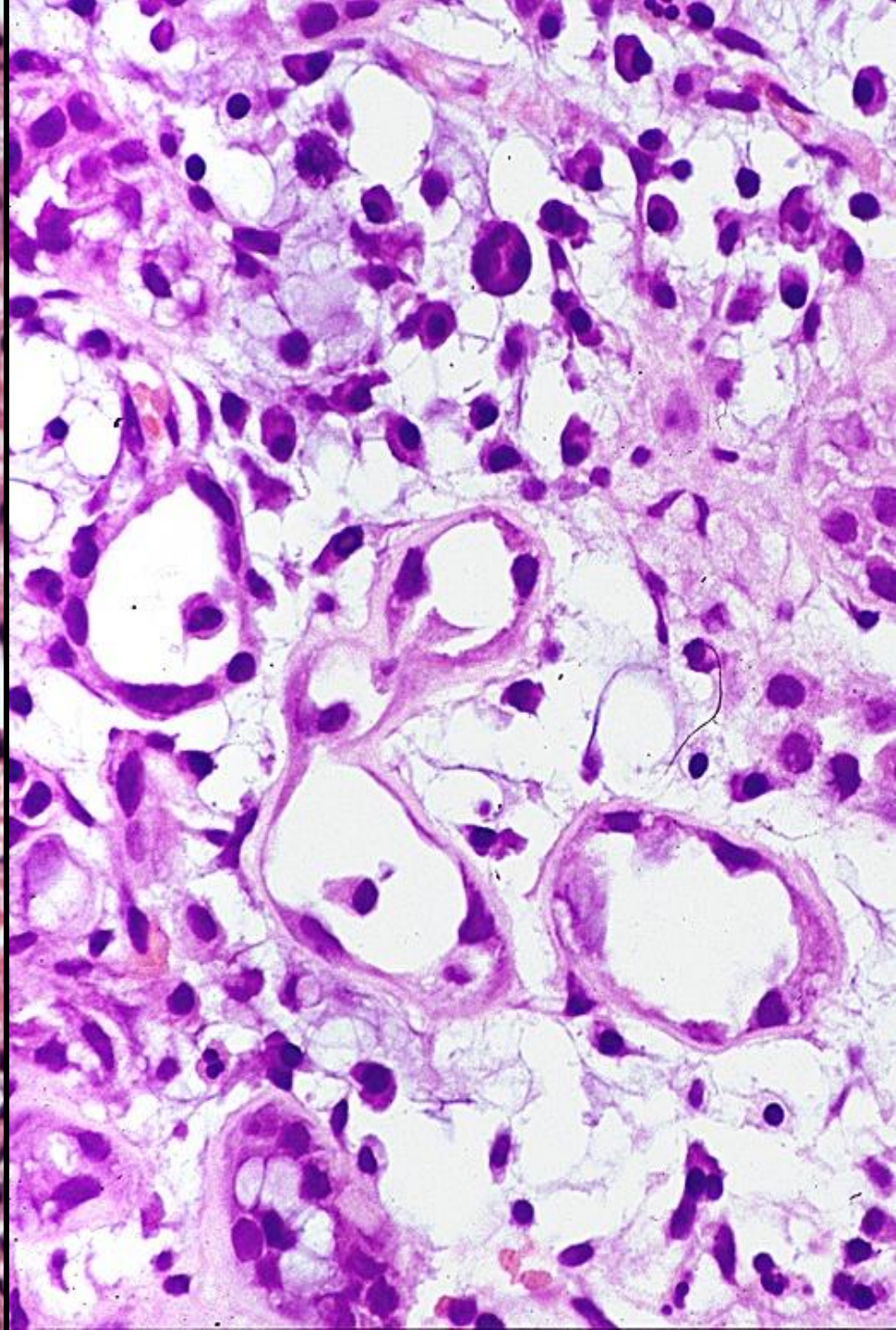
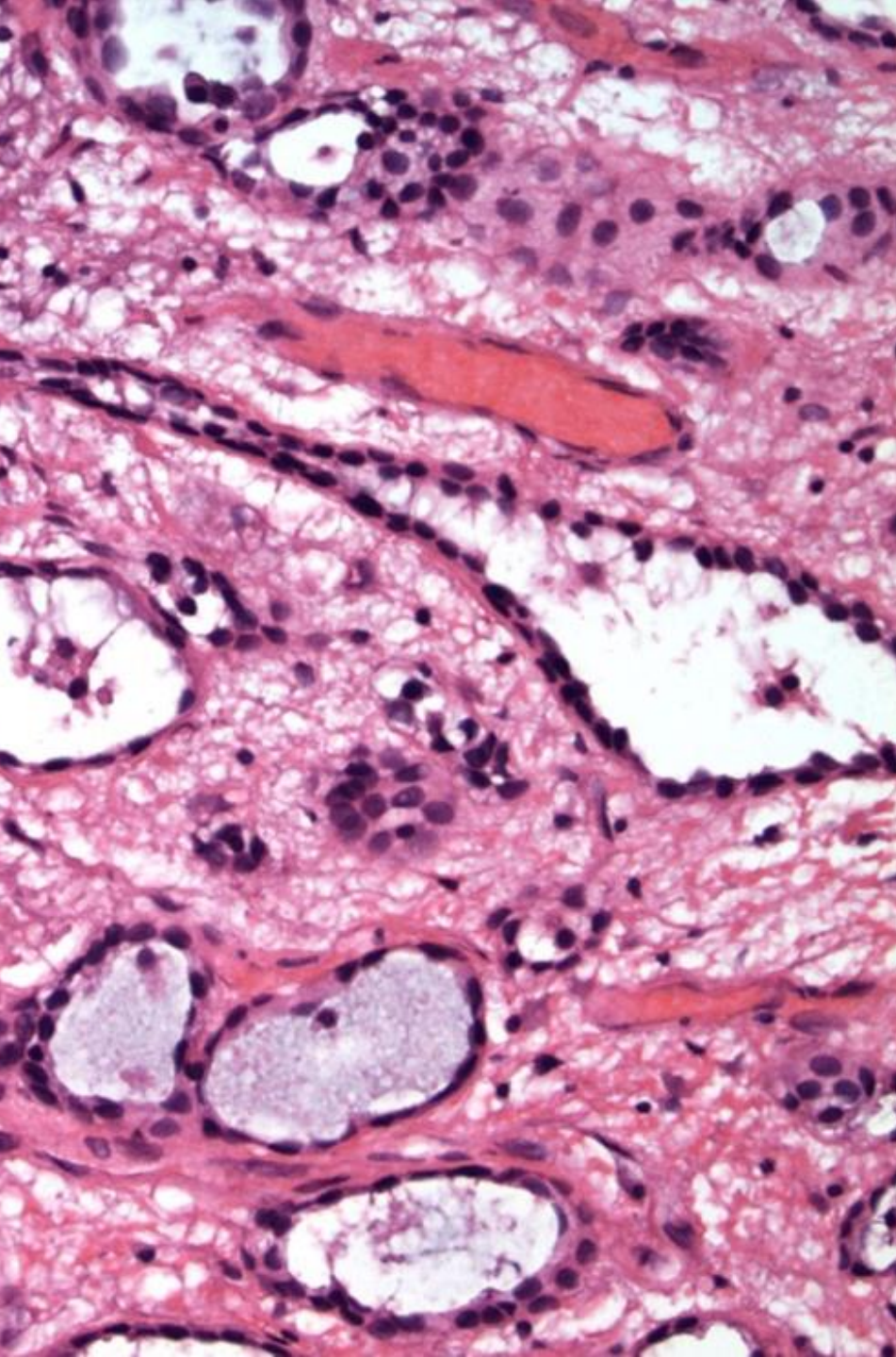


U Ca. with small tubules



Nephrogenic Adenoma





UROTHELIAL Ca. WITH MICROCYSTIC PATTERN

- **Histologic features**

- Widespread cystic change within nests of U Ca. (urothelial lining) or U Ca. with glandular differentiation (columnar lining); or flattened lining
- Cysts oval to round, 1-2 mm, \pm secretions
- Cytologically bland by definition

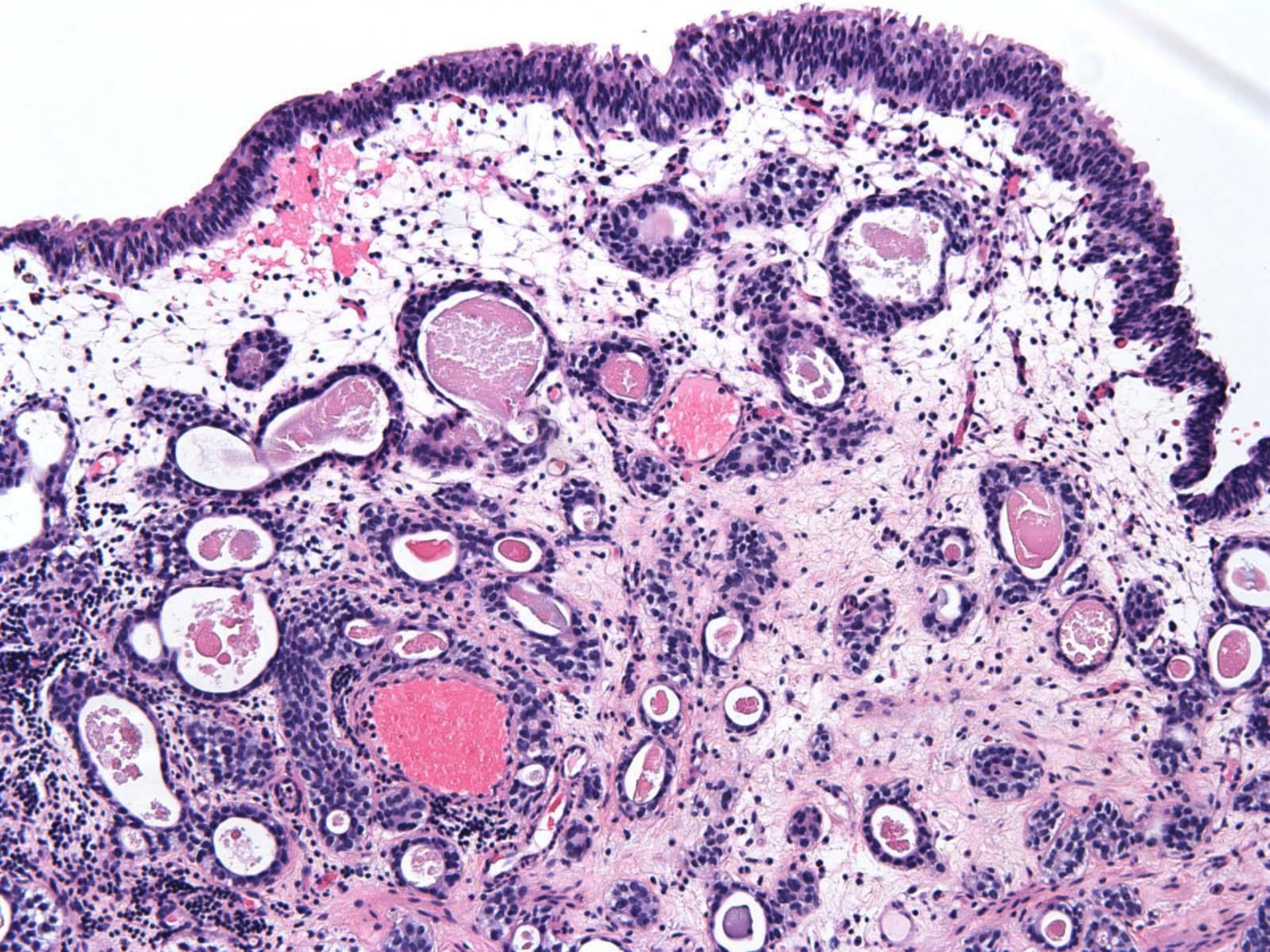
Cancer: *marked variation in size*

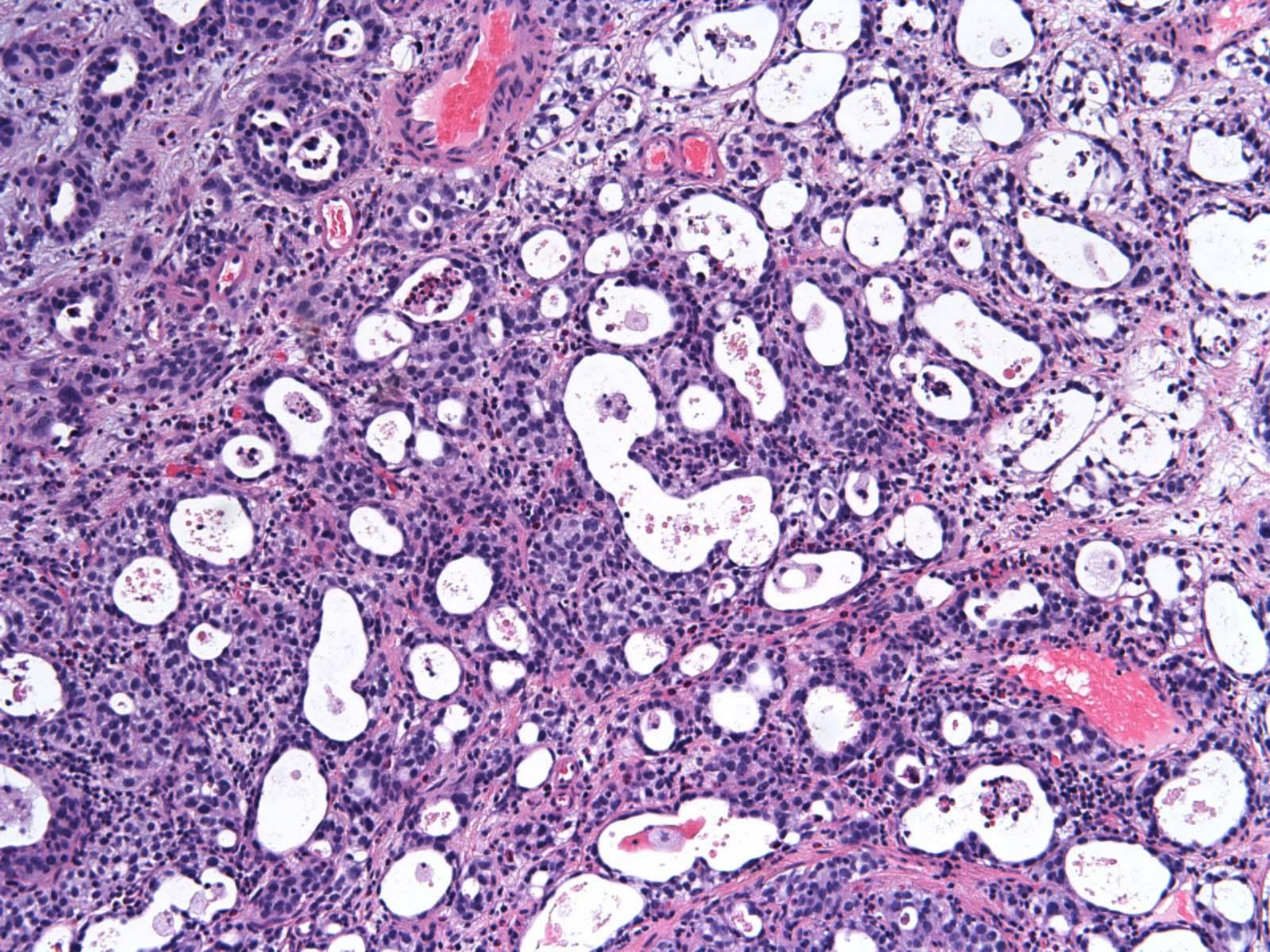
architectural complexity

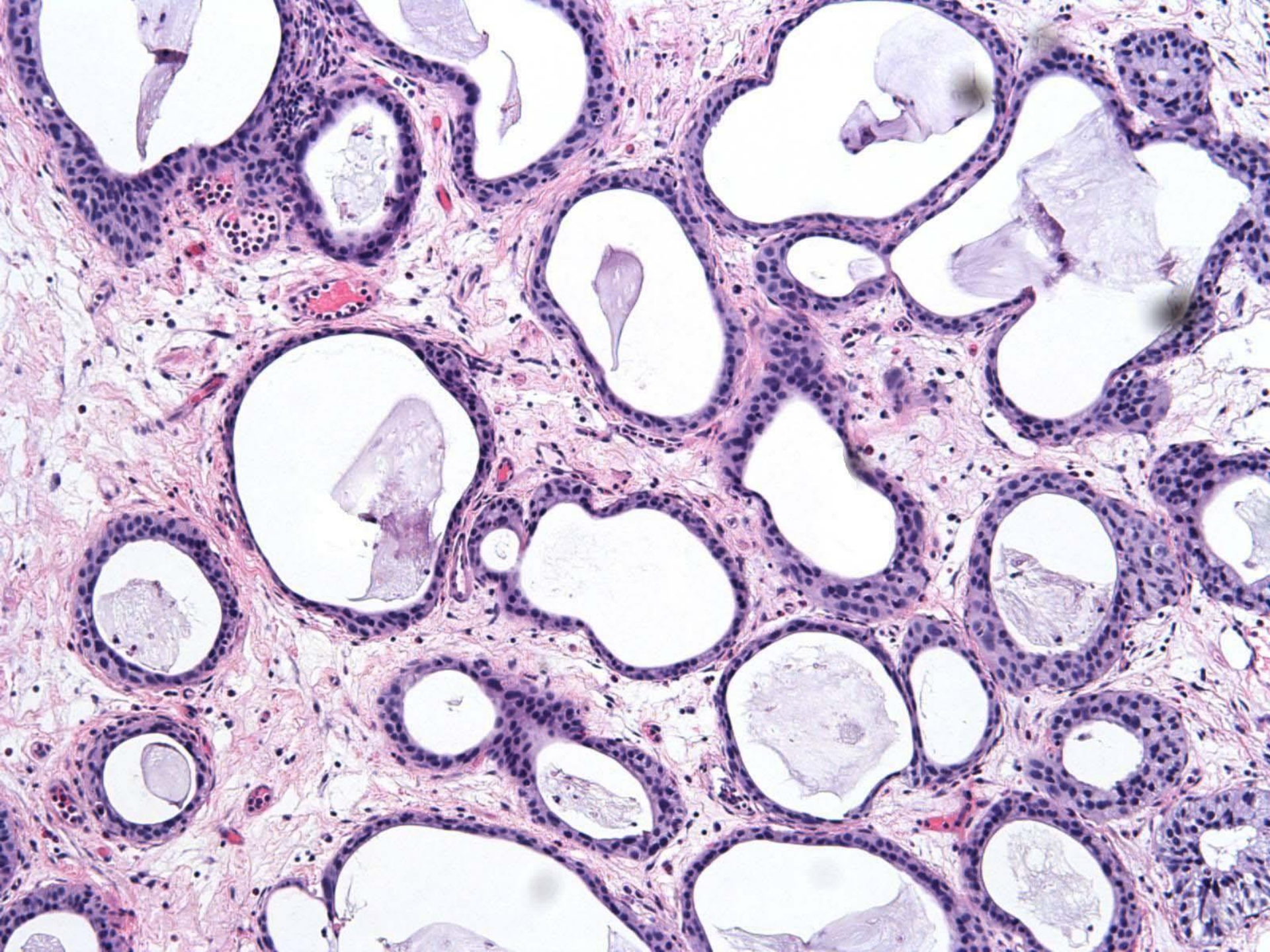
haphazard growth

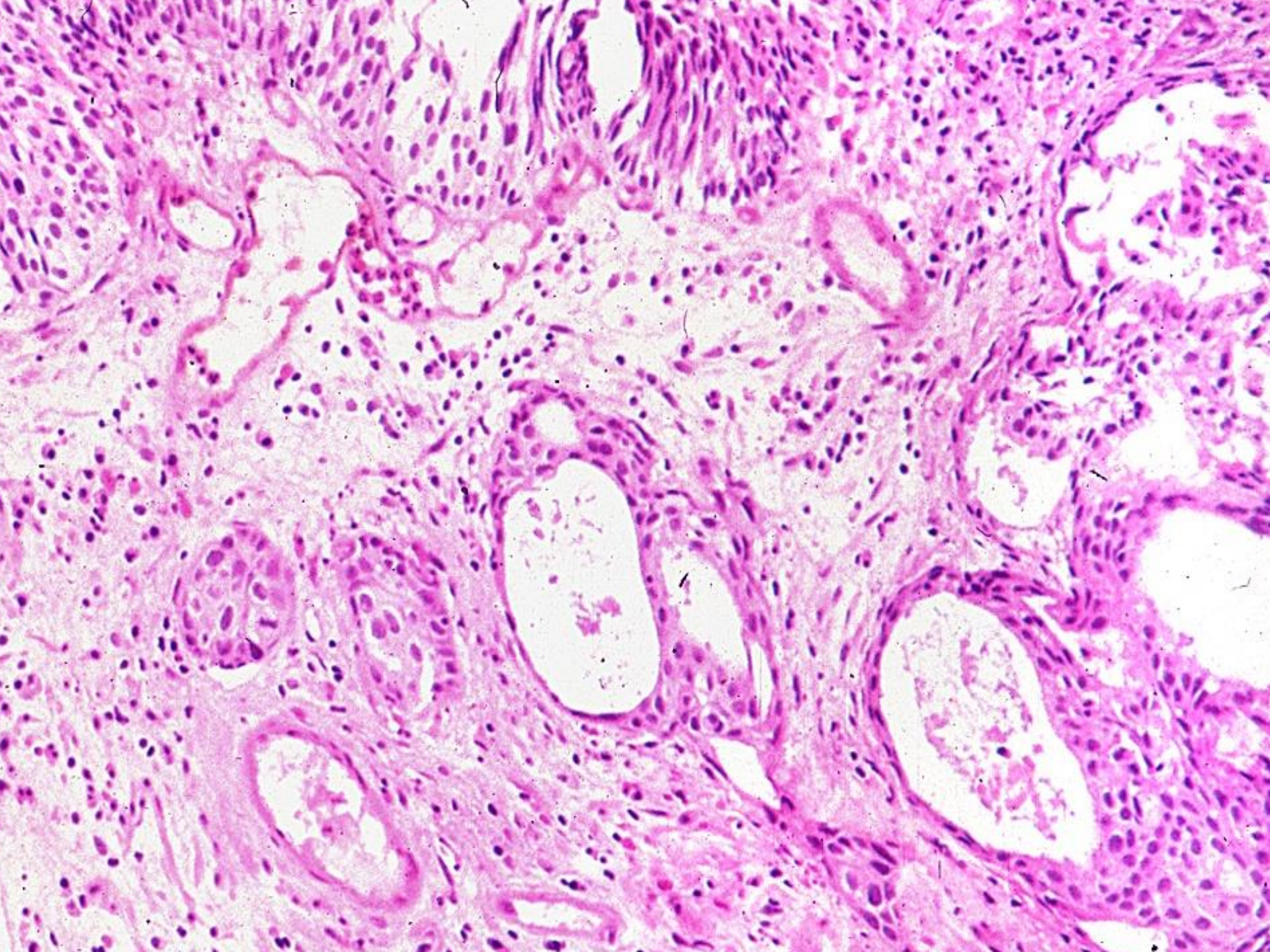
desmoplasia or myxoid reaction

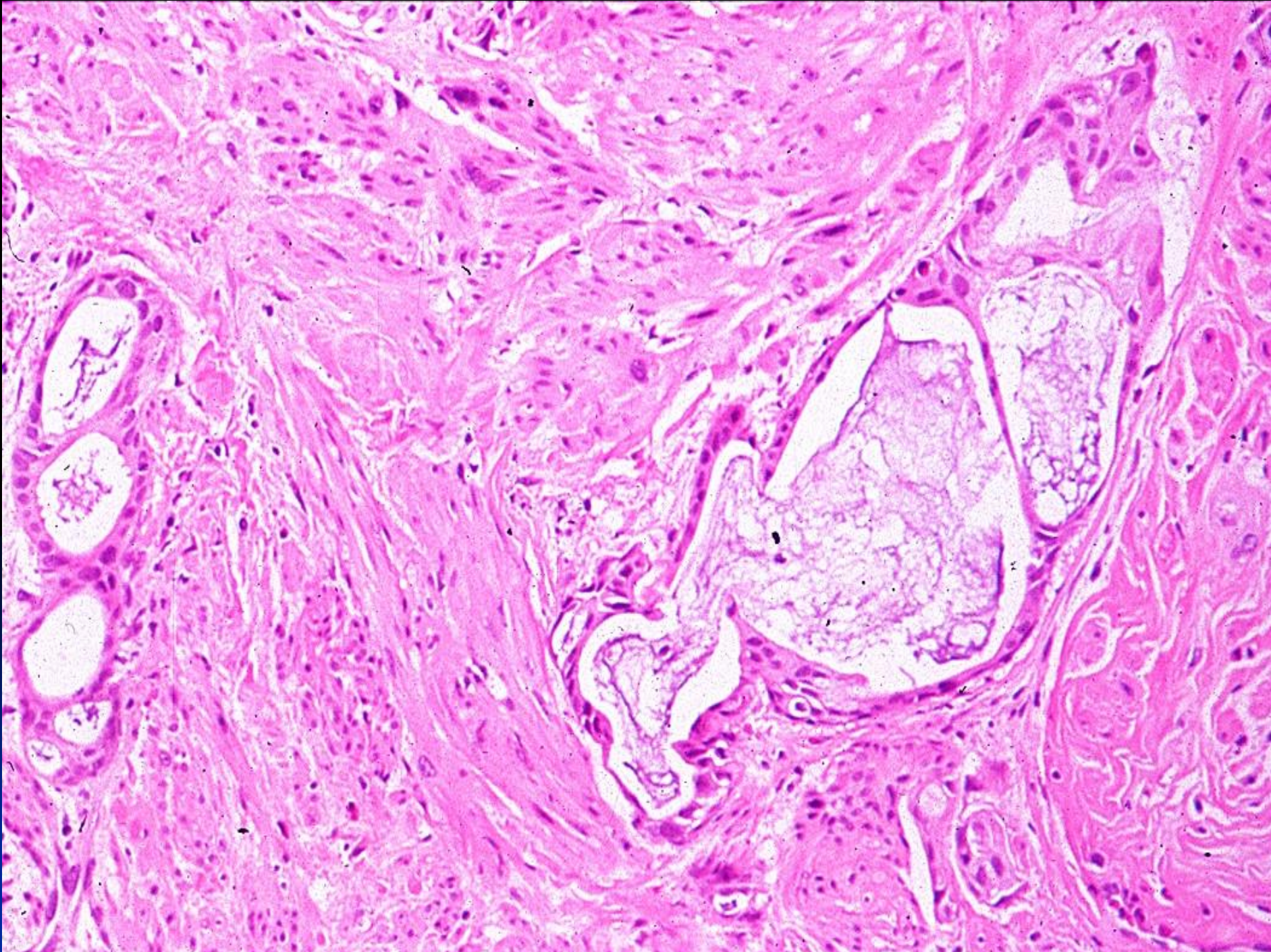
muscularis propria invasion

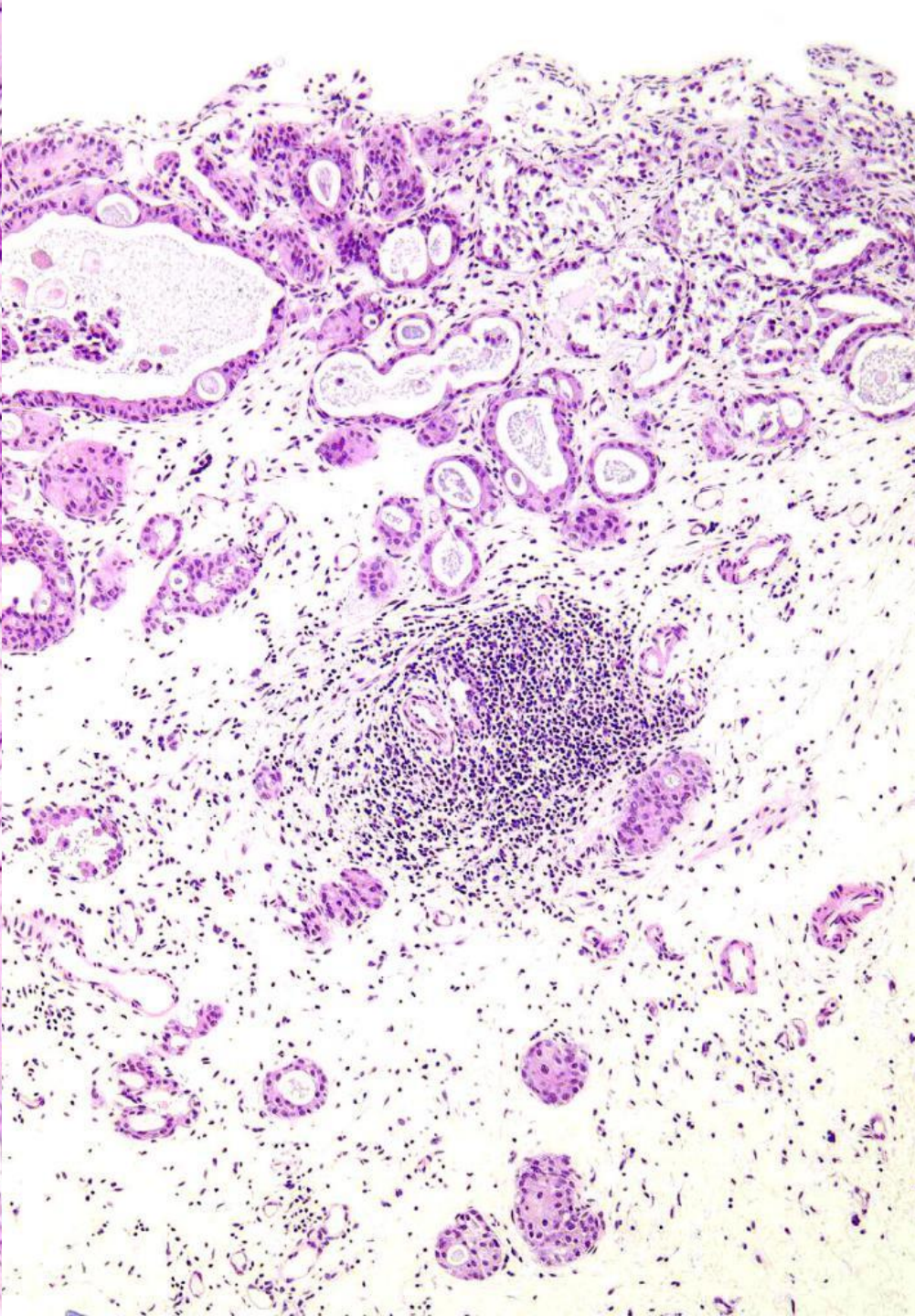
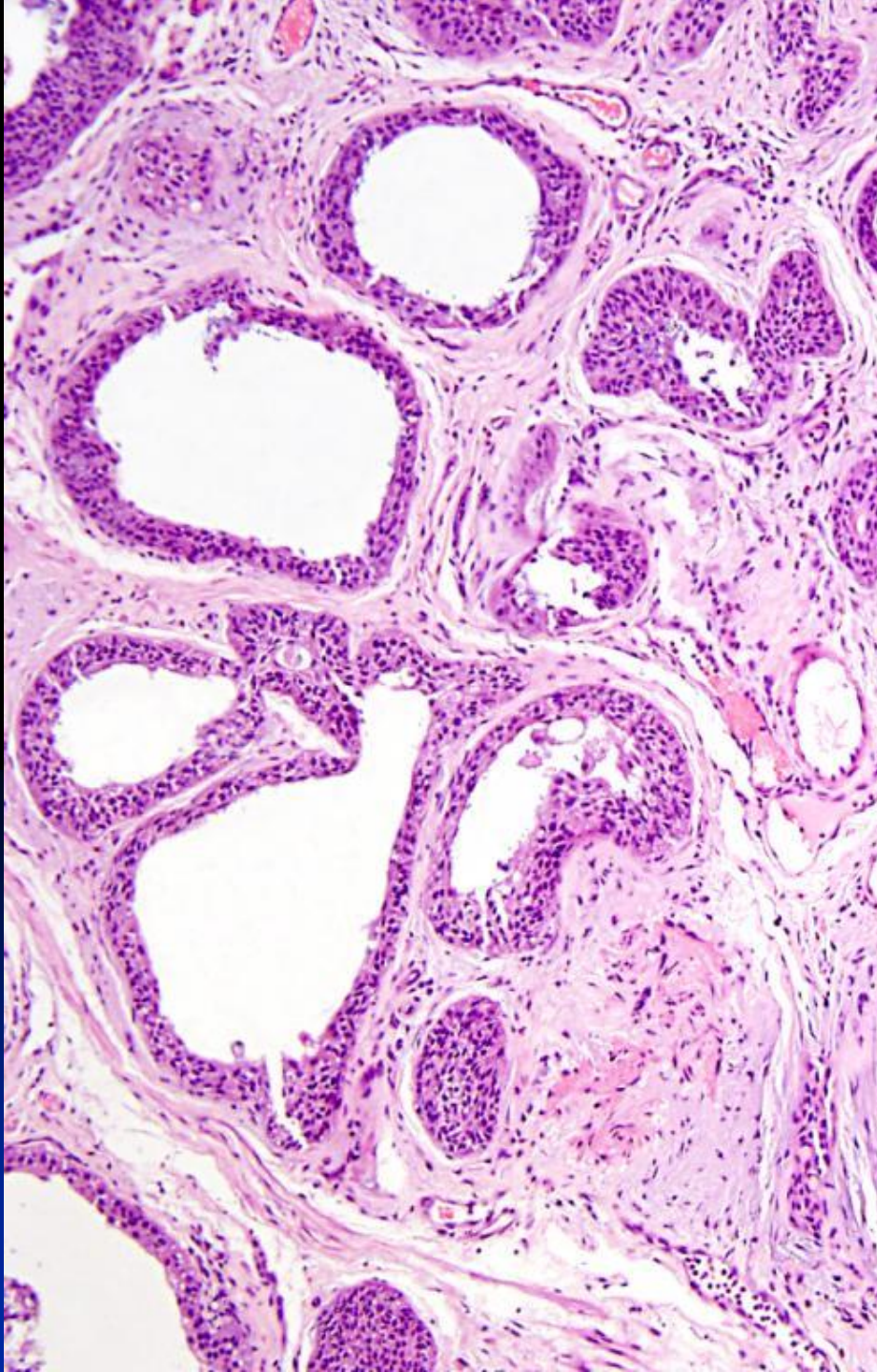


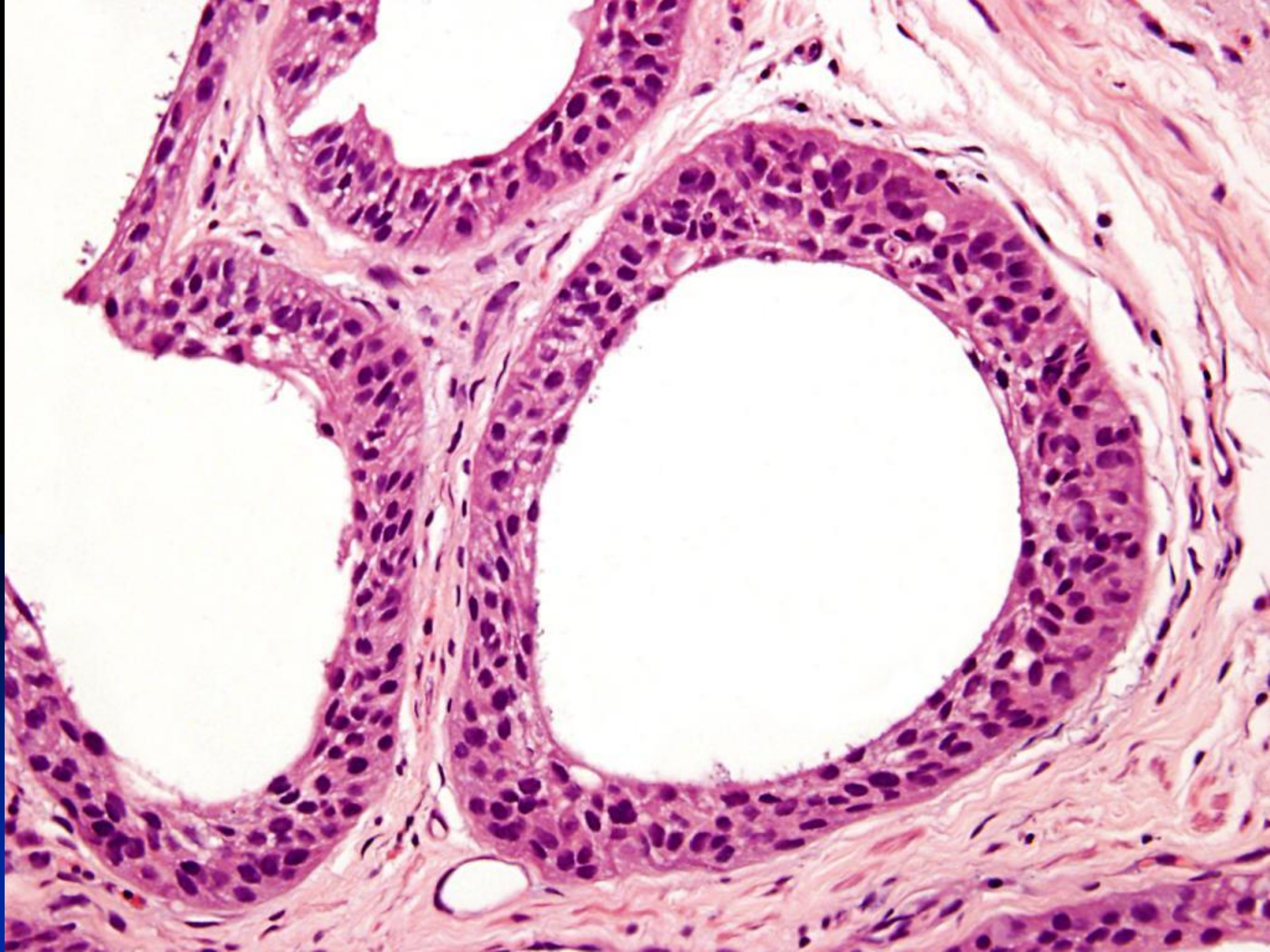






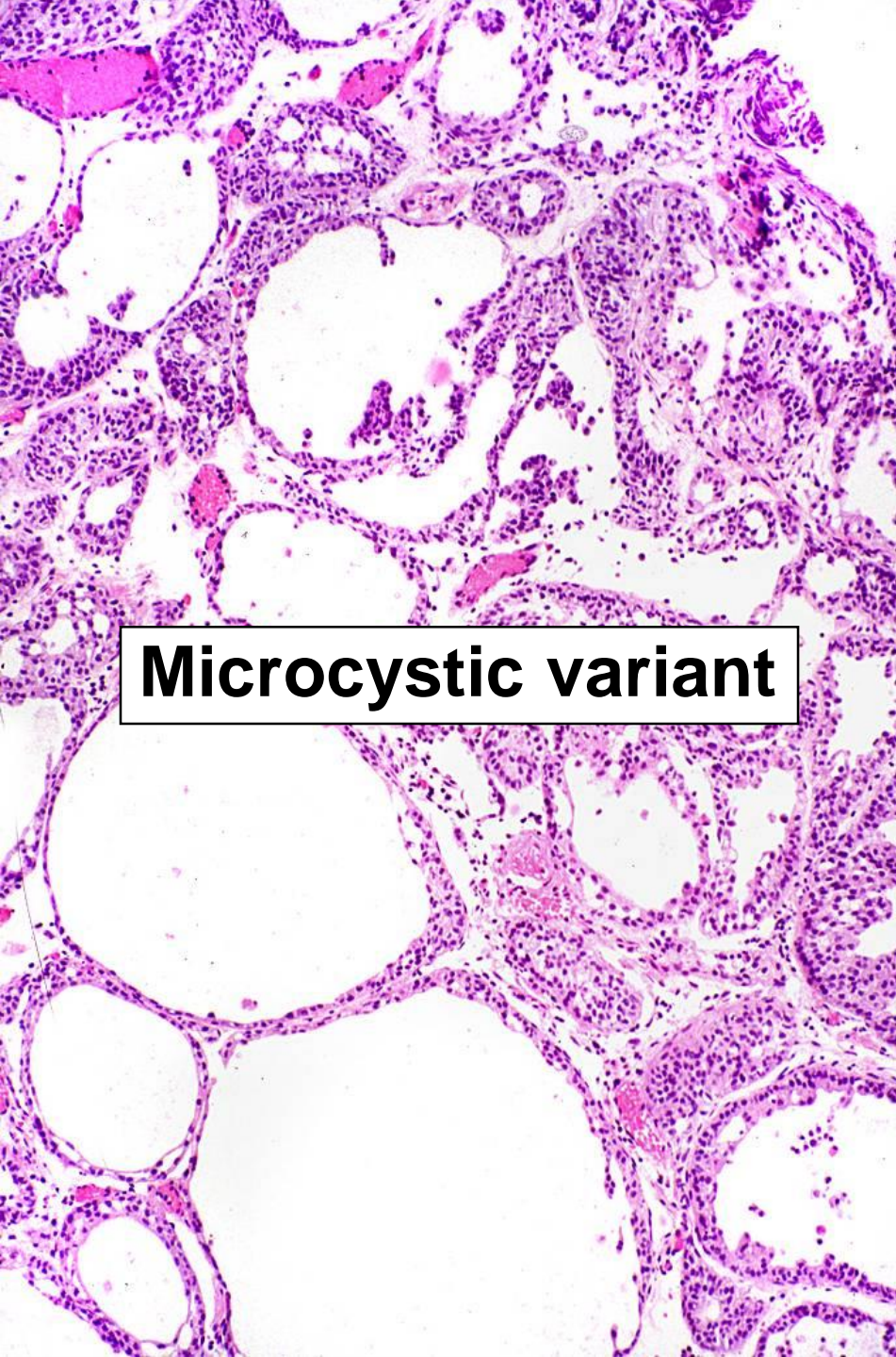




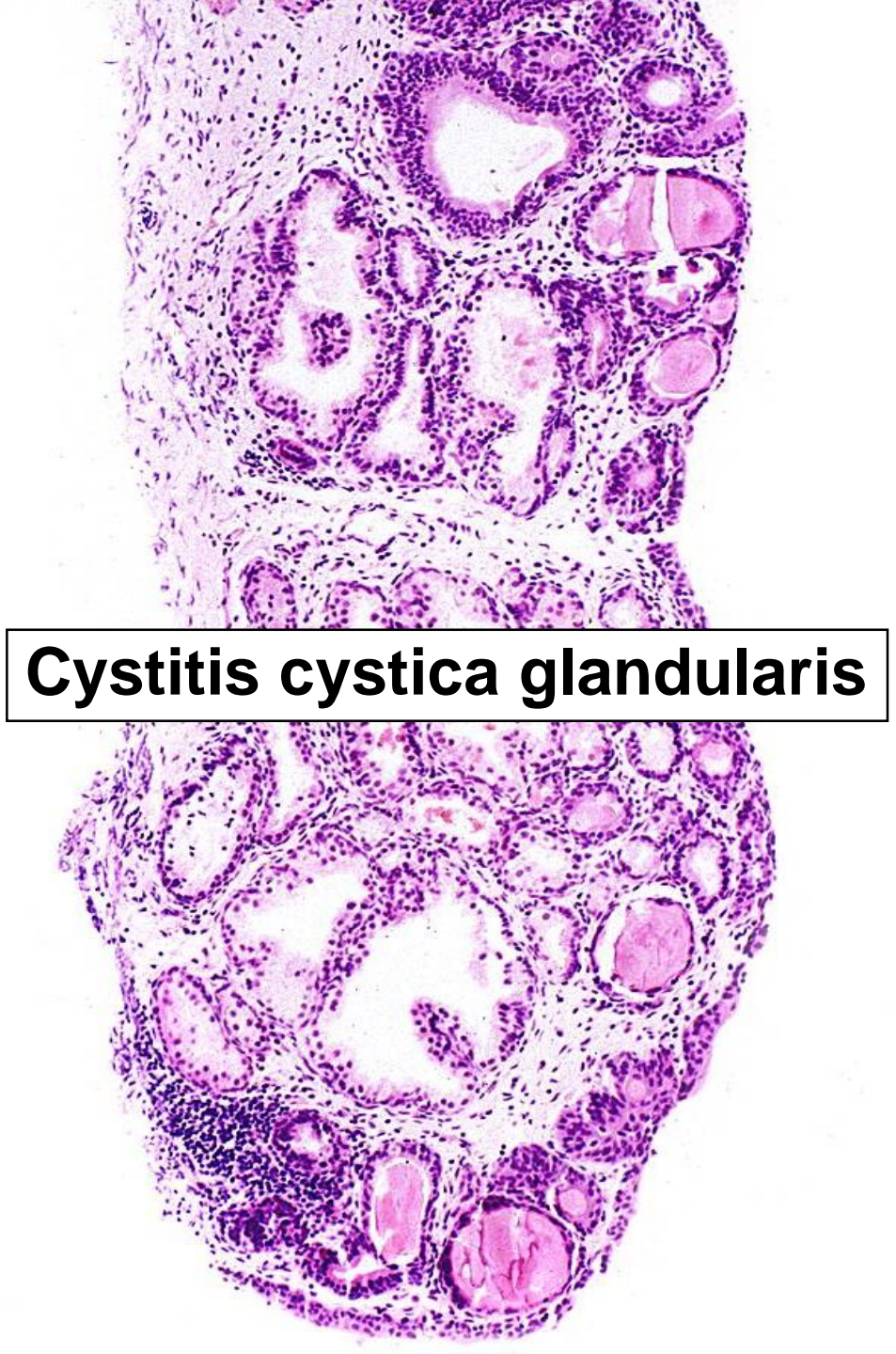


UROTHELIAL Ca. WITH MICROCYSTIC PATTERN

- **Diagnostic Significance: Pitfall**
- **Differential diagnosis**
 - *cystitis cystica / glandularis*
 - *adenocarcinoma*

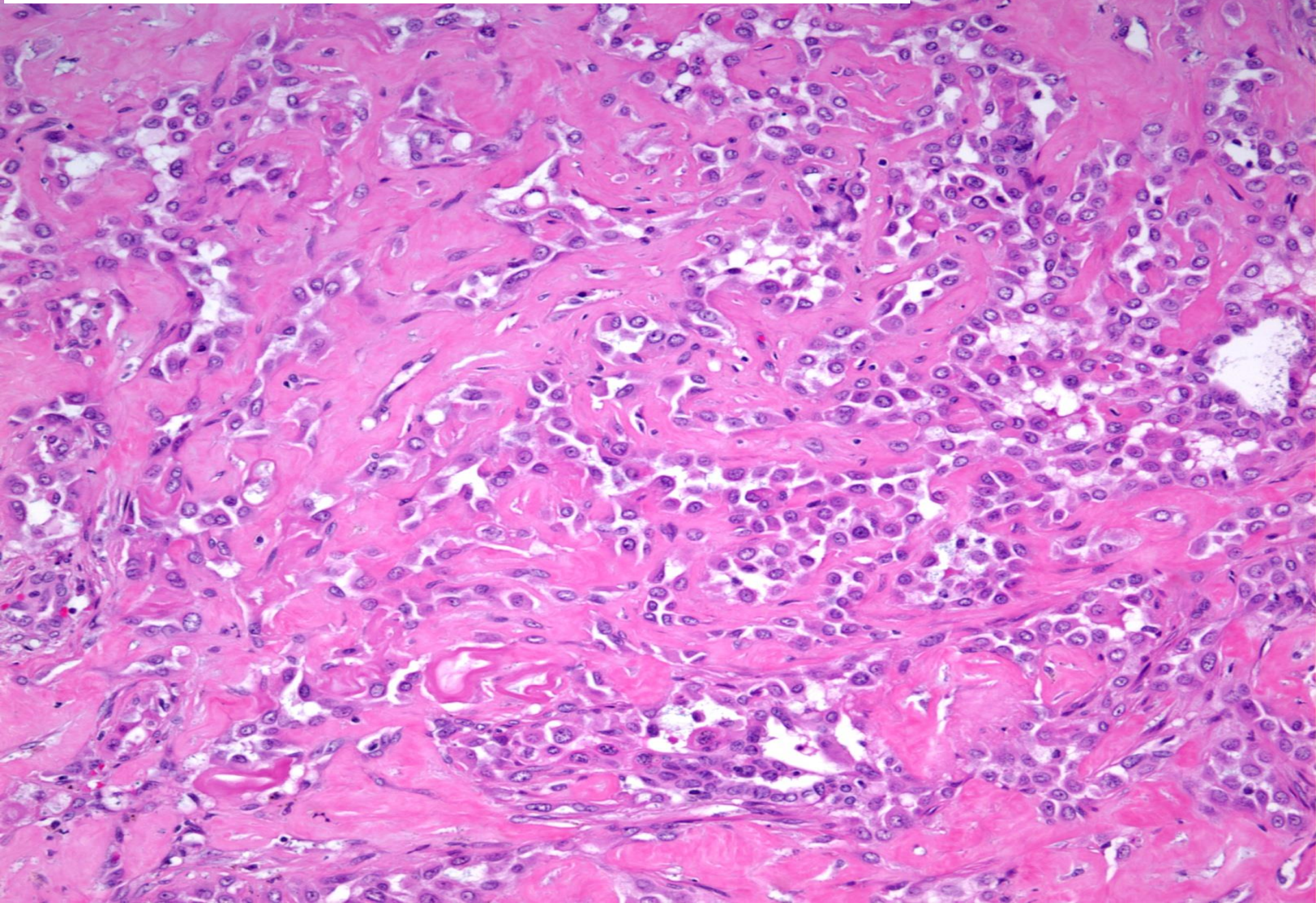


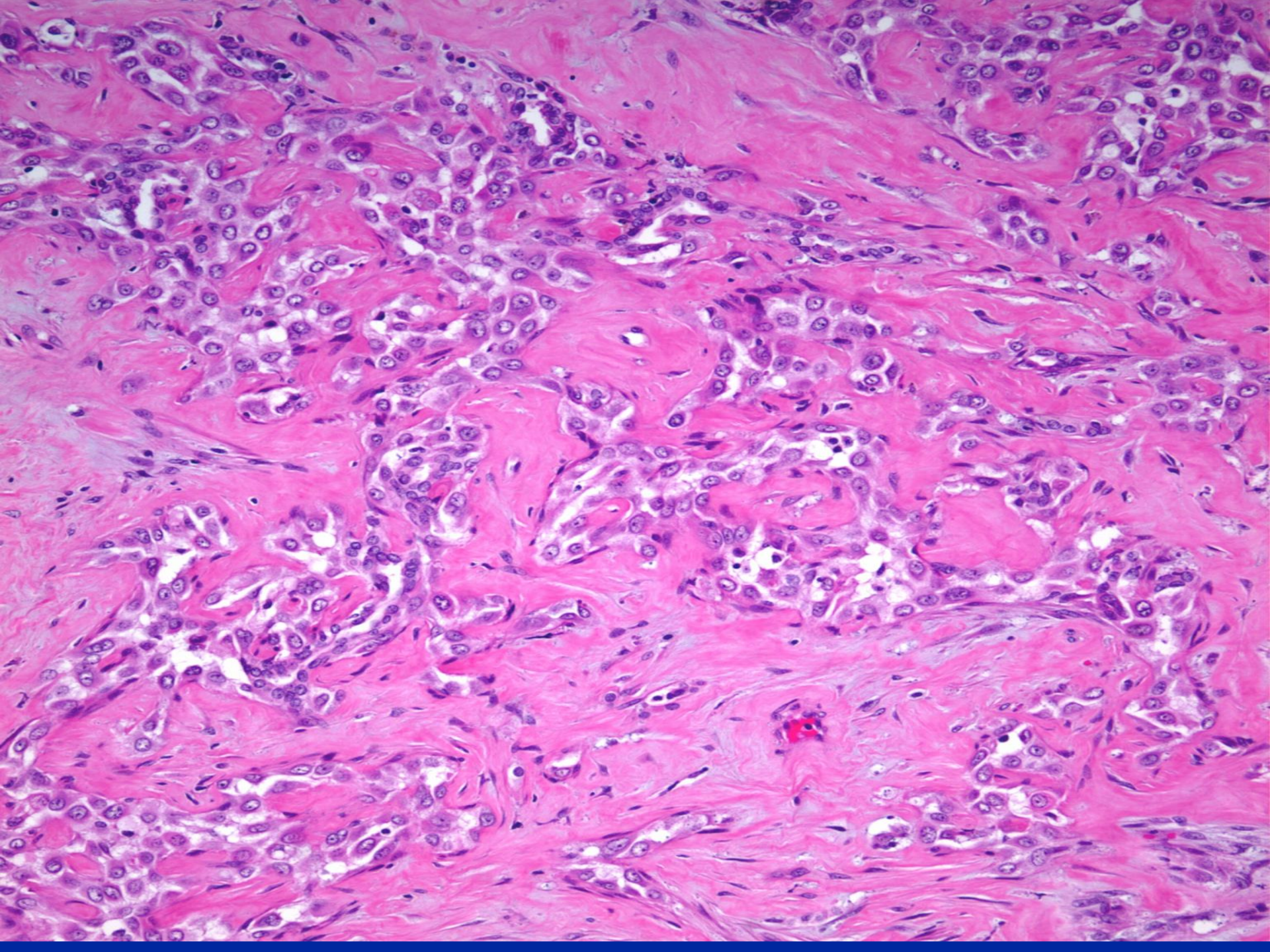
Microcystic variant

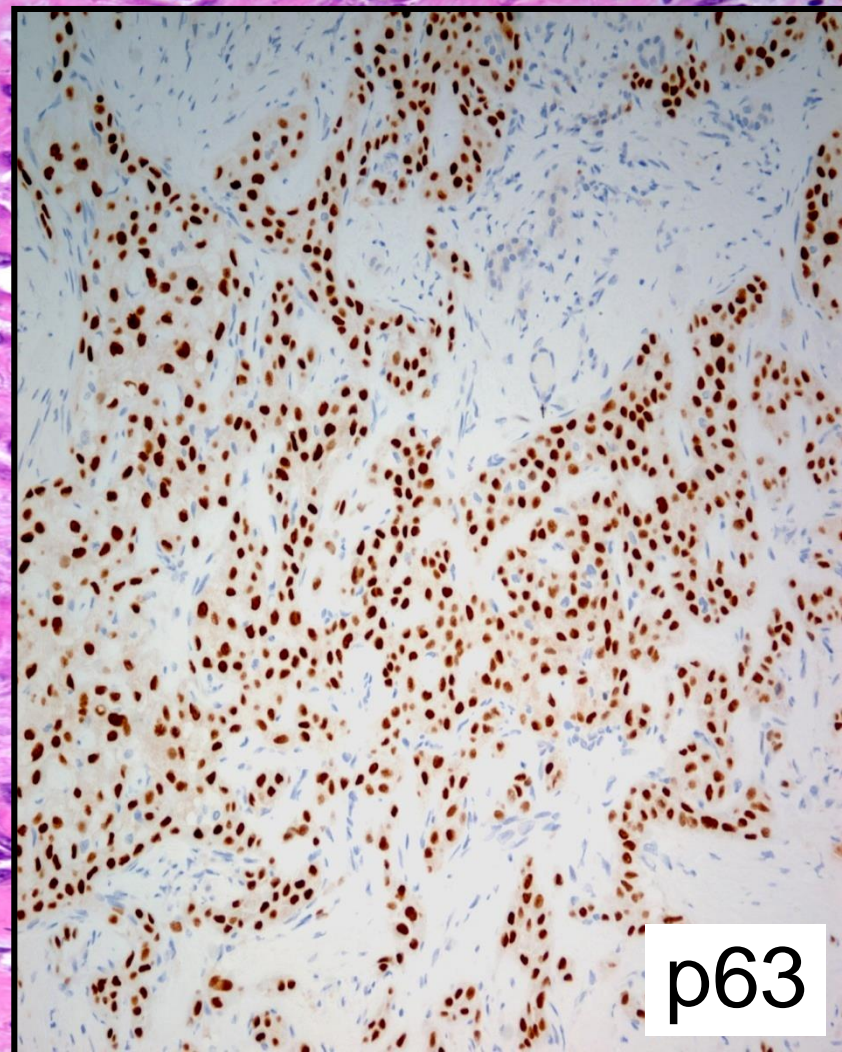
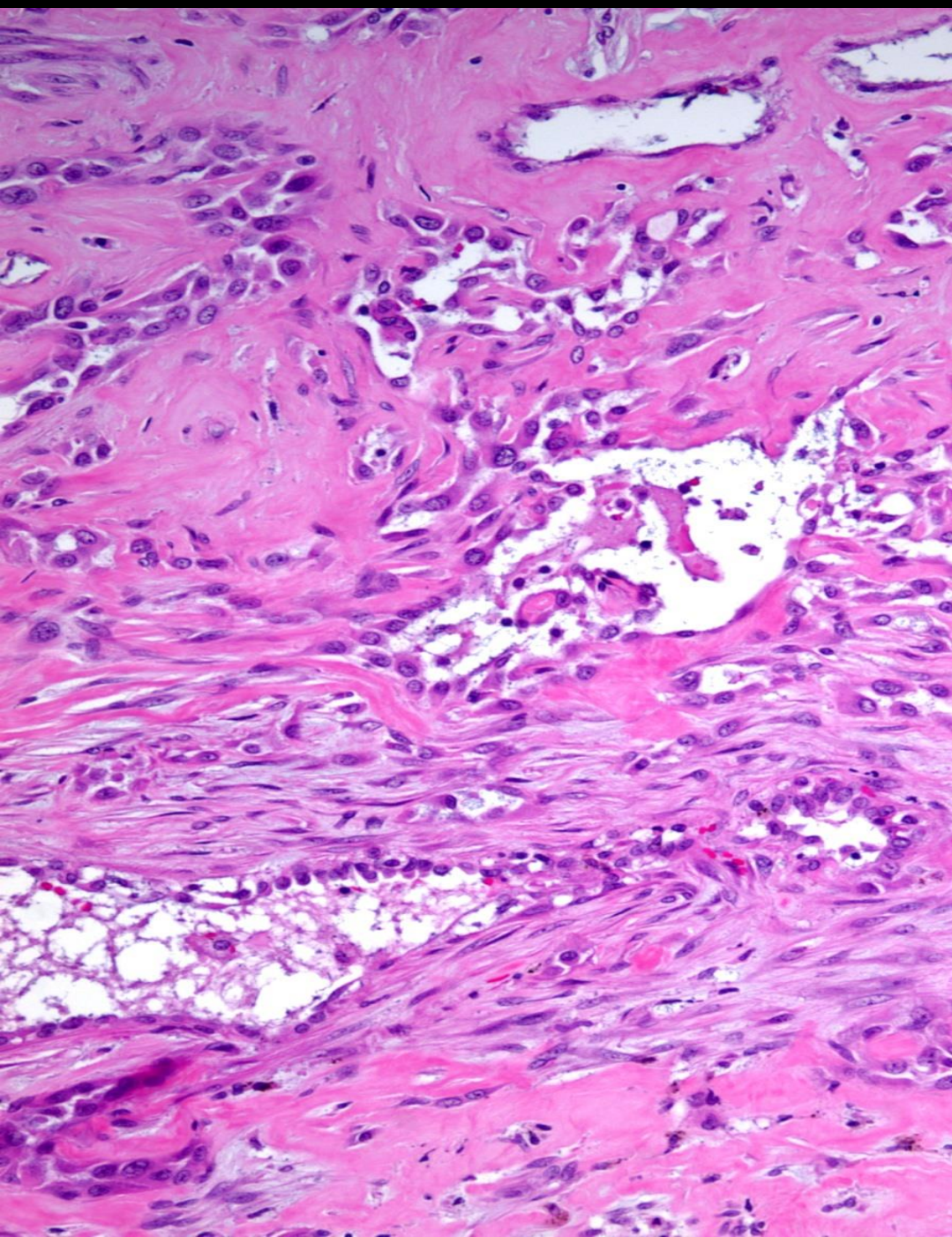


Cystitis cystica glandularis

Pseudoangiosarcomatous U Ca

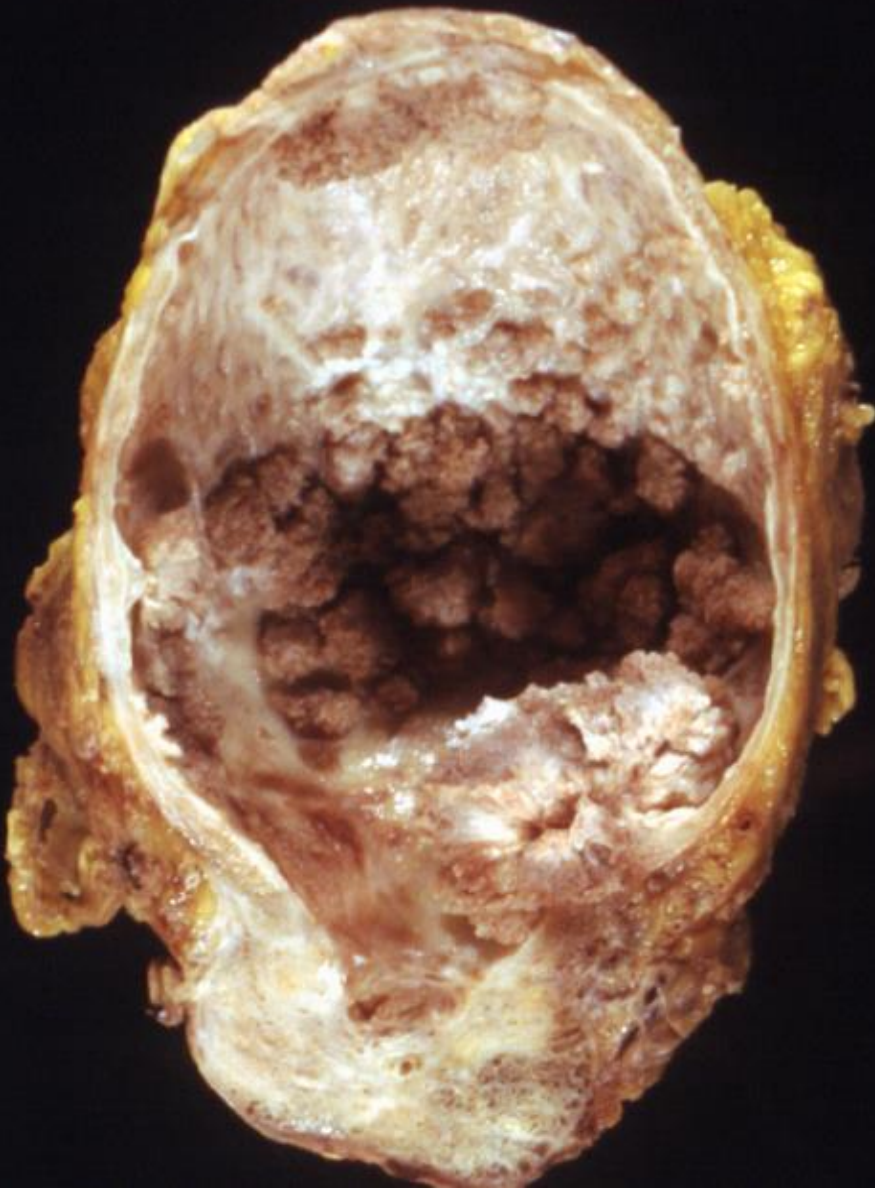






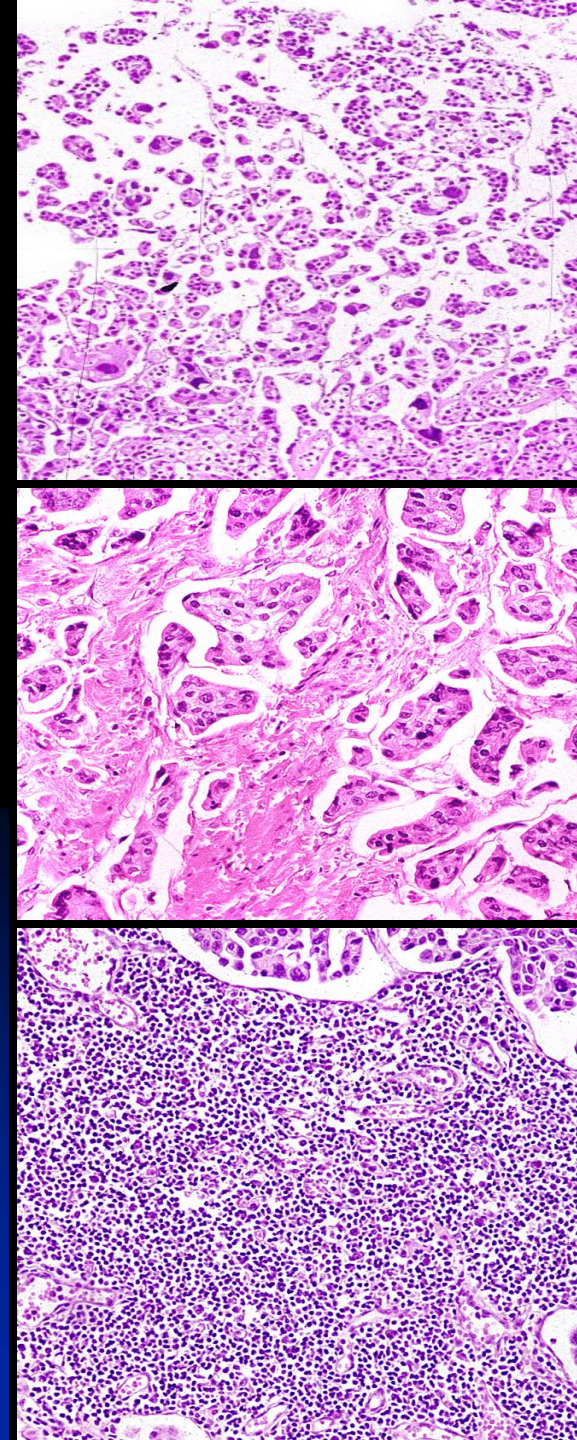
p63

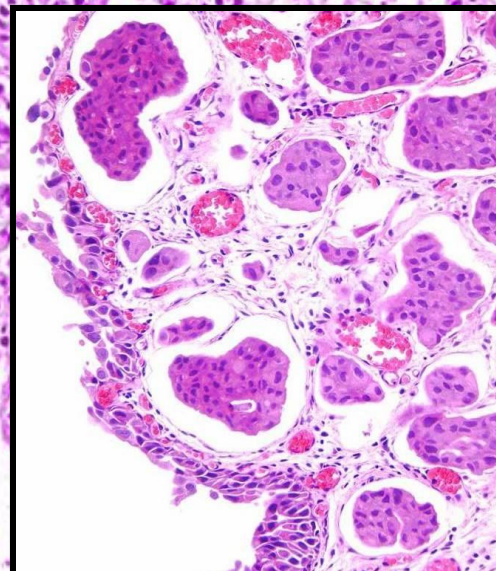
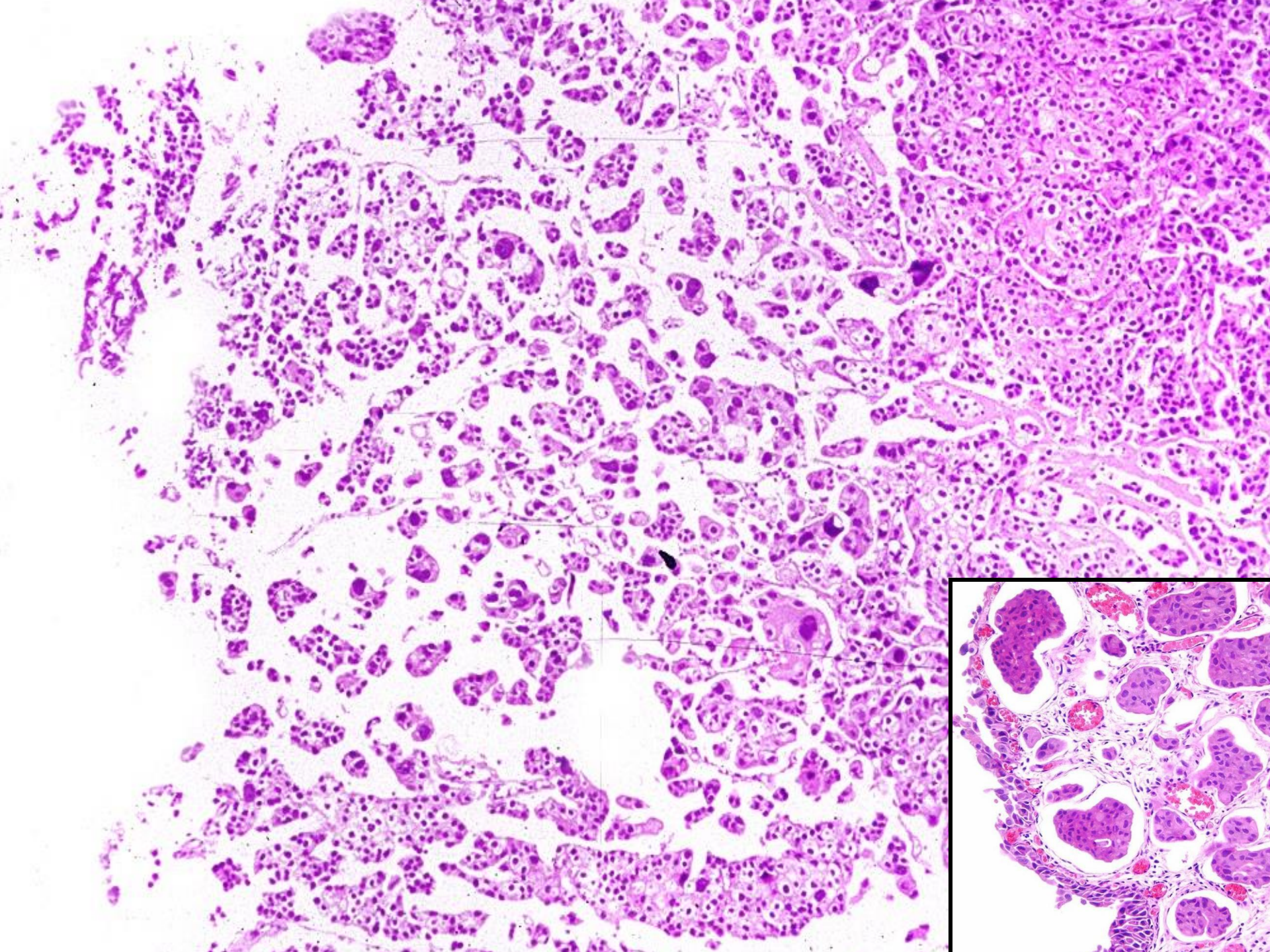
MICROPAPILLARY UROTHELIAL CARCINOMA

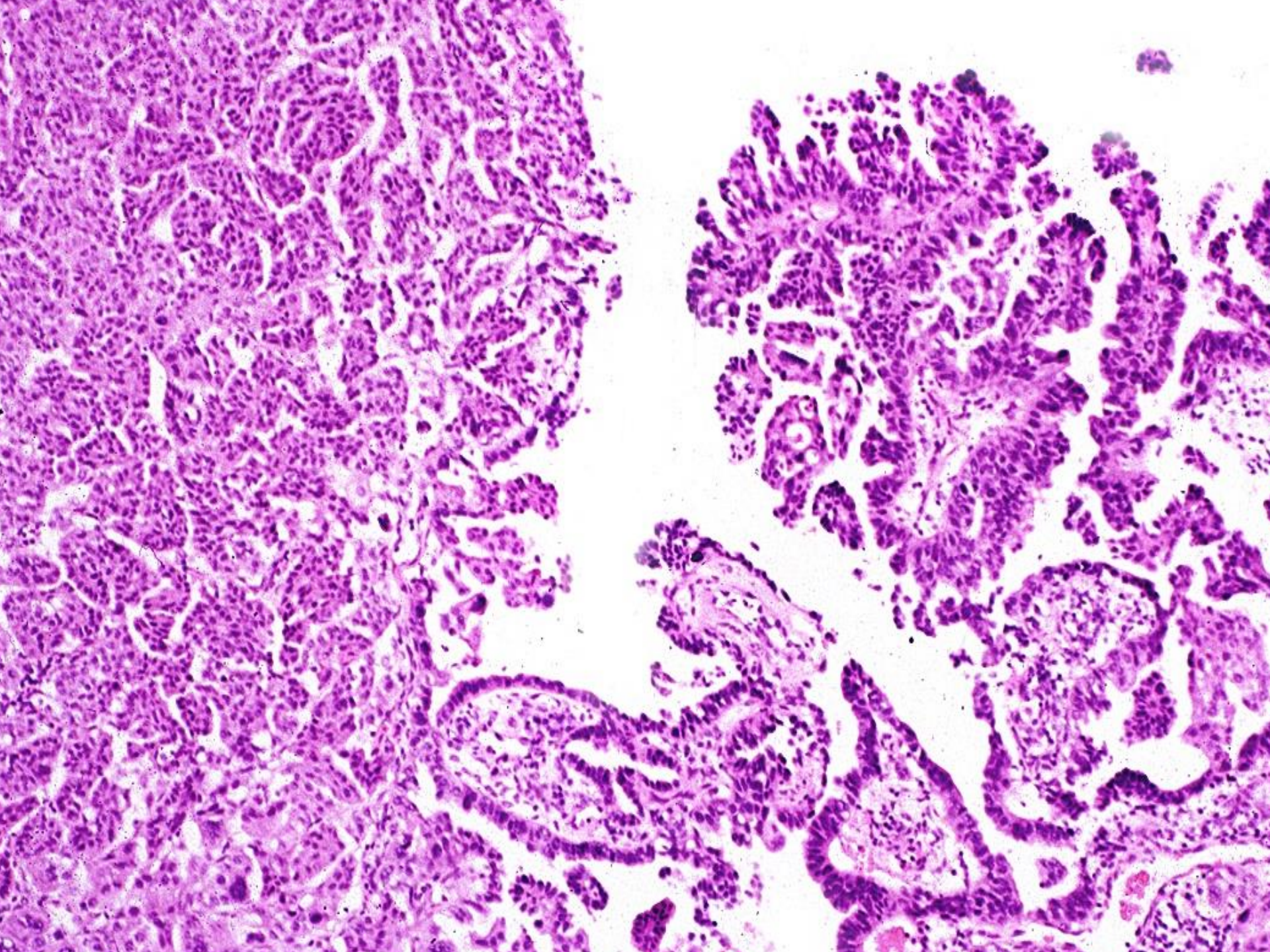


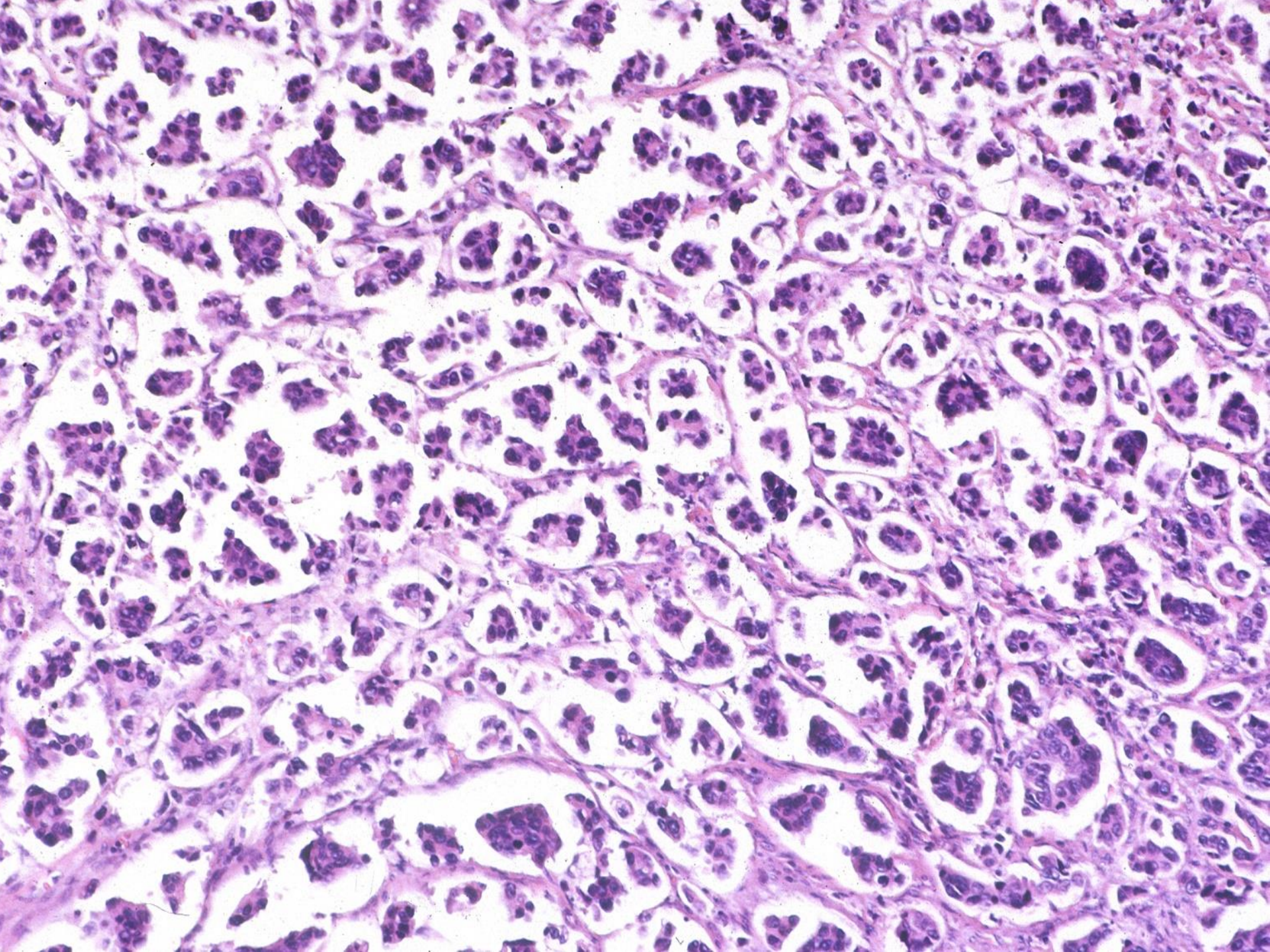
MICROPAPILLARY U Ca.

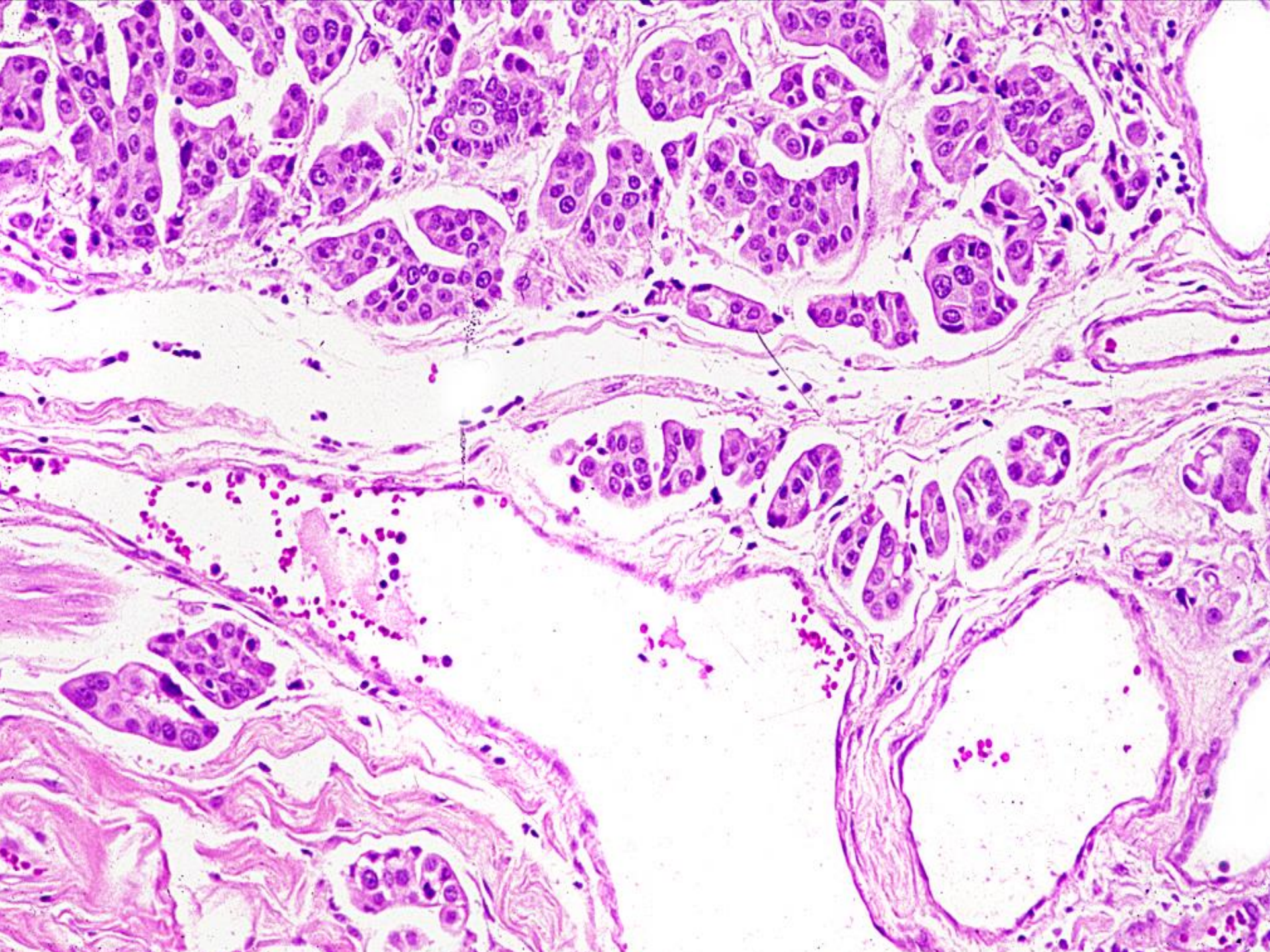
- **Histology:** Reminiscent of ovarian papillary serous tumors
 - **Surface:** Slender, delicate, filiform processes, glomeruloid structures
 - **Invasive:** Small tight nests/balls in lacunae mimic vascular invasion
 - **Metastasis:** Micropapillary histology retained
- **Pattern may be focal, extensive or exclusive**











MICROPAPILLARY U Ca.

- **Prognostic significance**

- Most commonly high-stage with U Ca.
frequent vascular invasion
- Metastasis frequently contain
predominant micropapillary histology
- *Aggressive variant of U Ca.*
 - **5- and 10- year survival:** 51% and 24%
compared to 58% and 50% for invasive U Ca
(> pT2,N0)

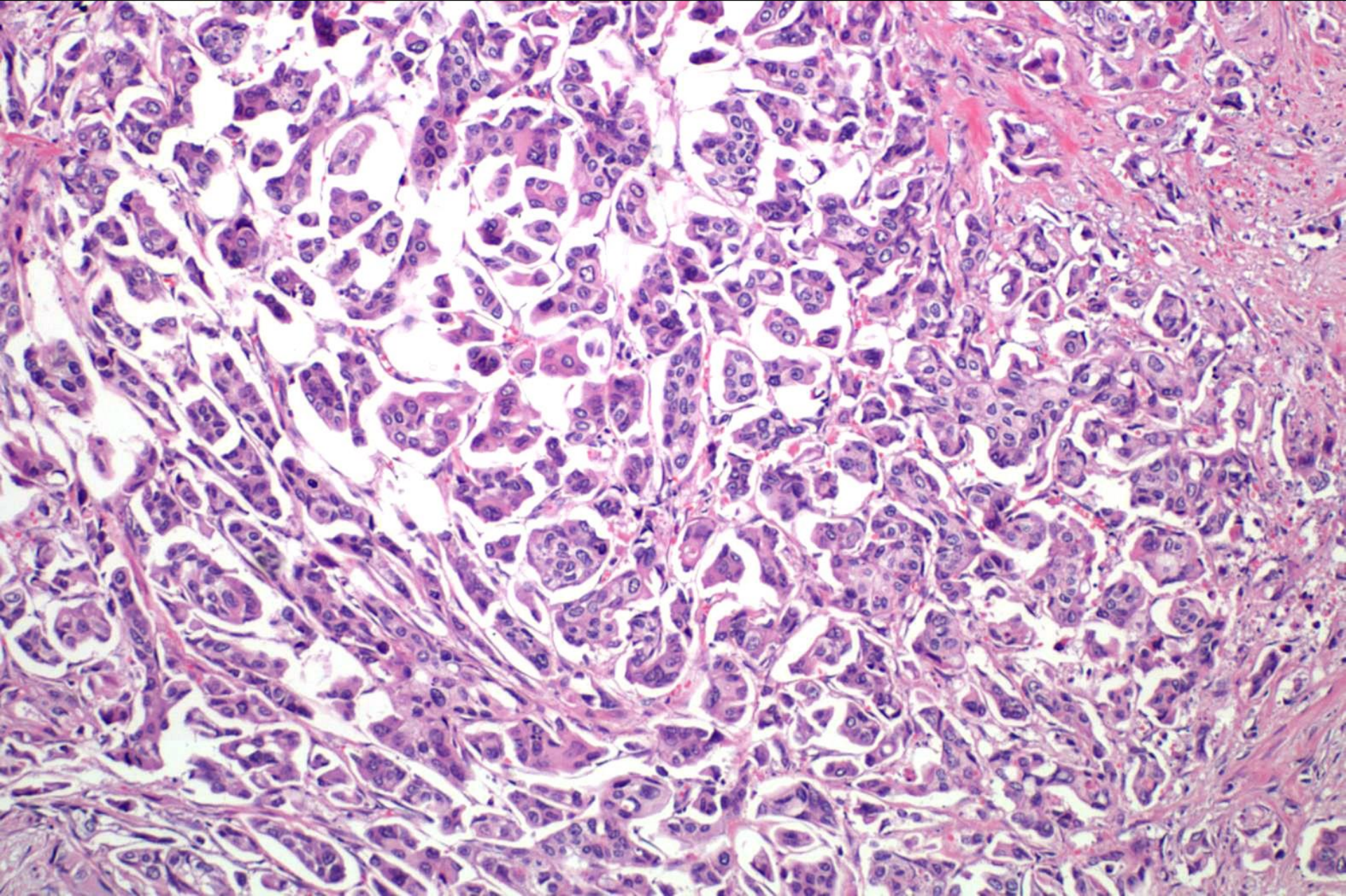
MICROPAPILLARY U Ca.

- **Dx tic & Prognostic significance**
 - Patients with unknown primary - *consider MP U Ca. in males and in females with normal gyn. tract – along with lung, breast, pancreas & salivary gland Ca.*
 - MP U Ca. in superficial biopsy without m. propria - *suggest rebiopsy*
 - pTa/pT1- poor response to immunotherapy
 - *? Early cystectomy for pTa/pT1 tumors*

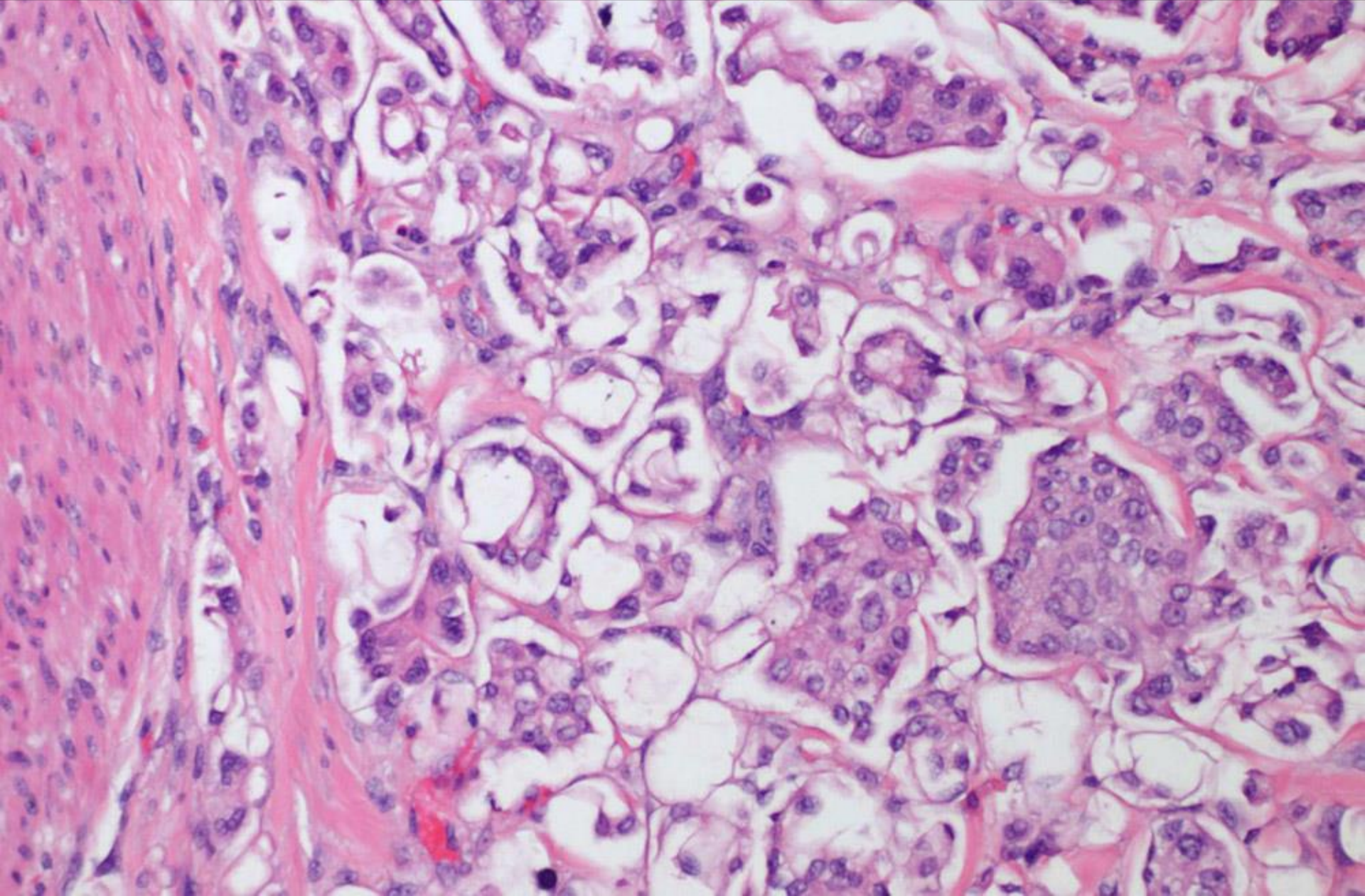
Whats new in Micropapillary UCa

- Distinctive molecular features: ERBB2 mutations and amplifications
- pT1 lesions: early surgery & poor response to intravesical therapy
- Refined criteria for increased diagnostic reproducibly

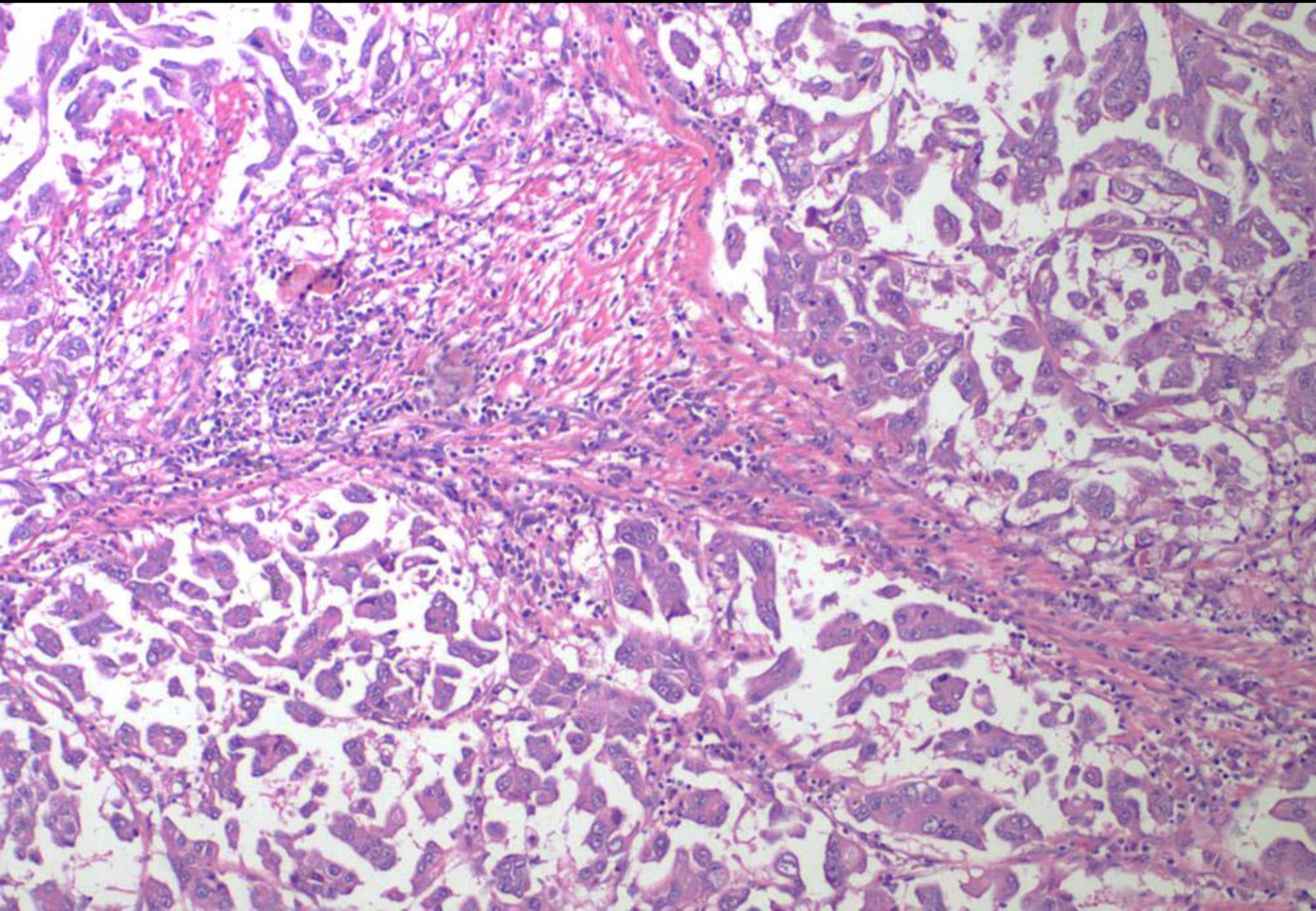
“Classic MP”: Multiple Nests in Same Lacunar Space



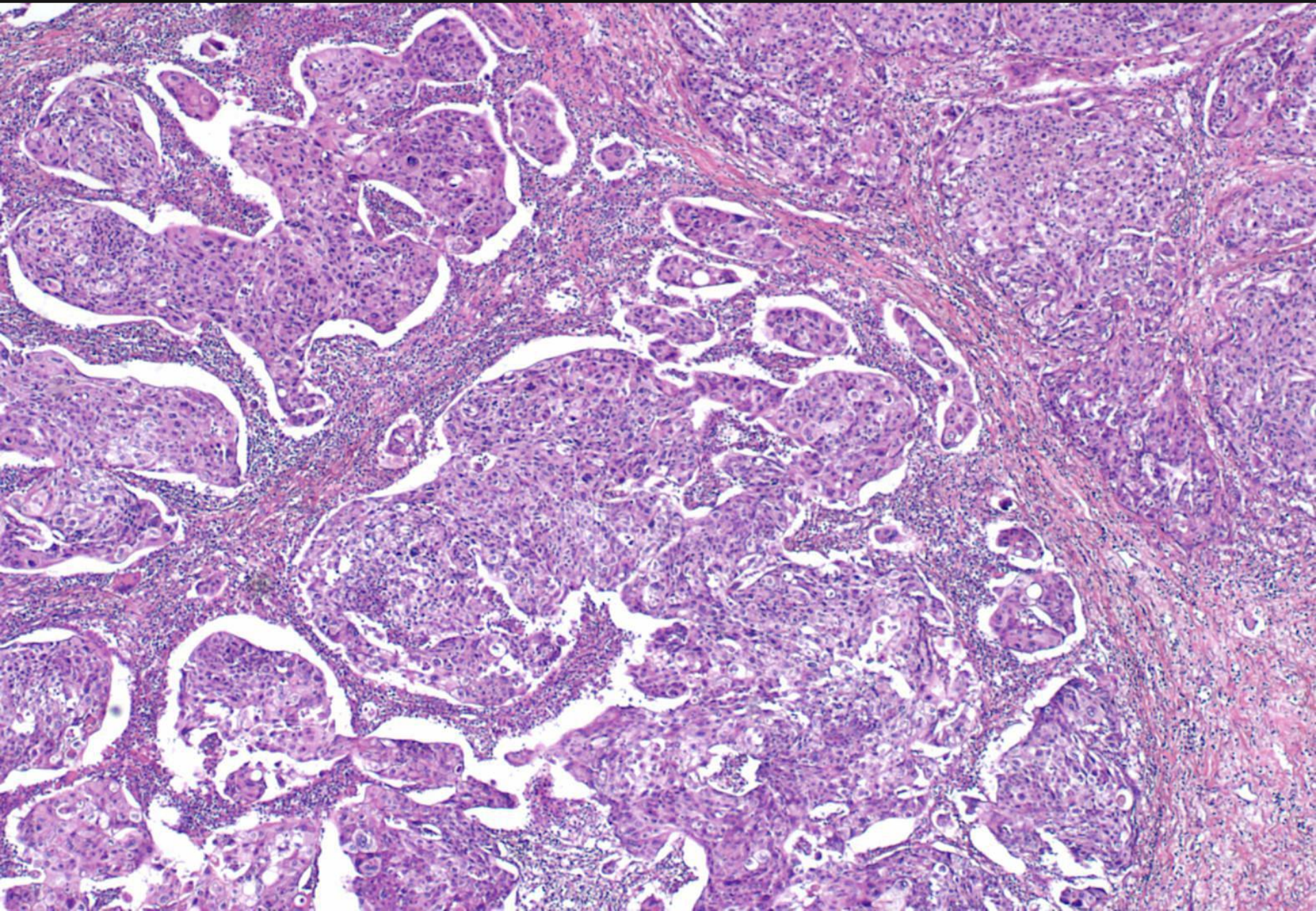
“Classic MP”
Epithelial Ring Forms and Back-to-Back Lacunae



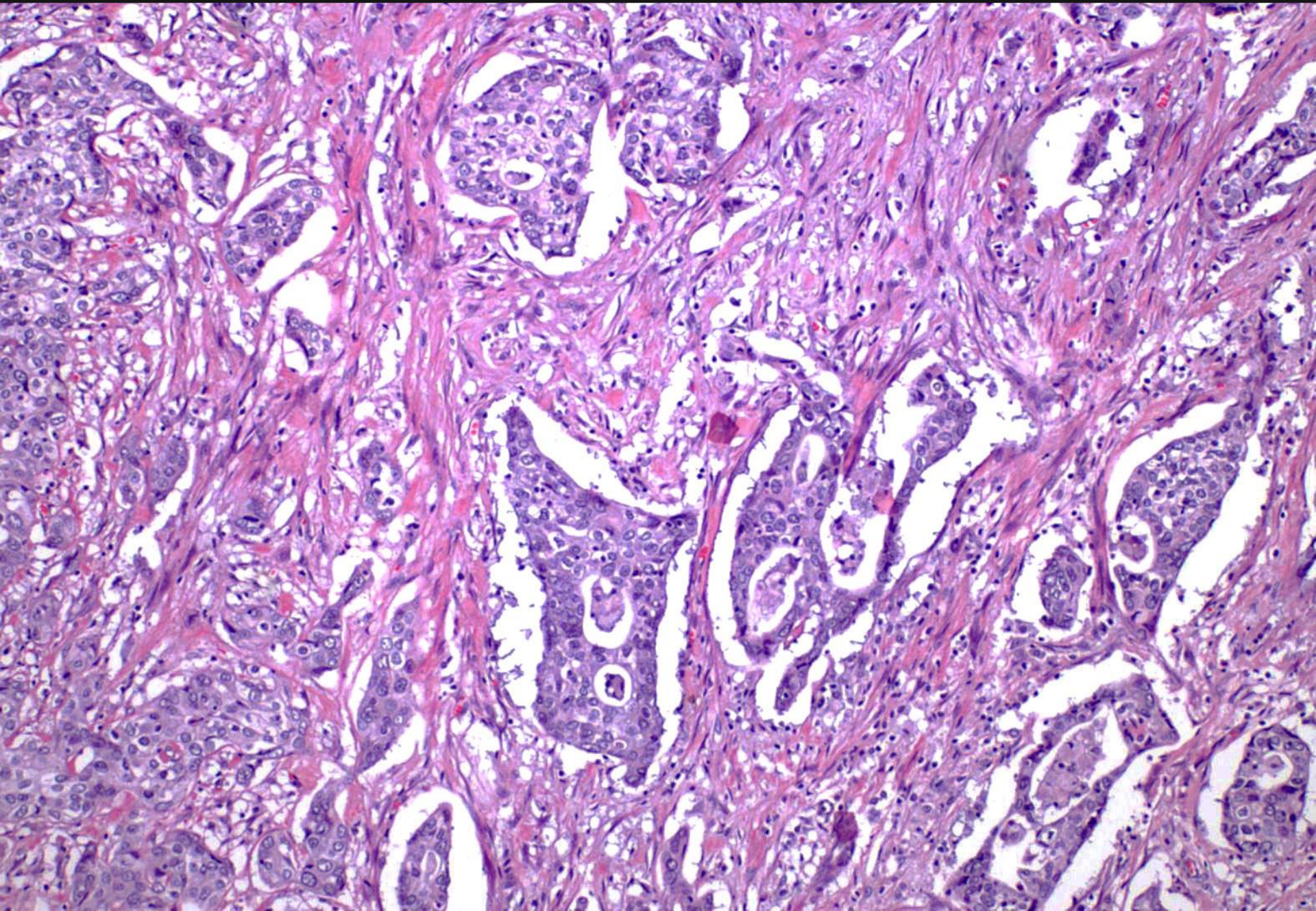
“Classic MP”



NOT Micropapillary

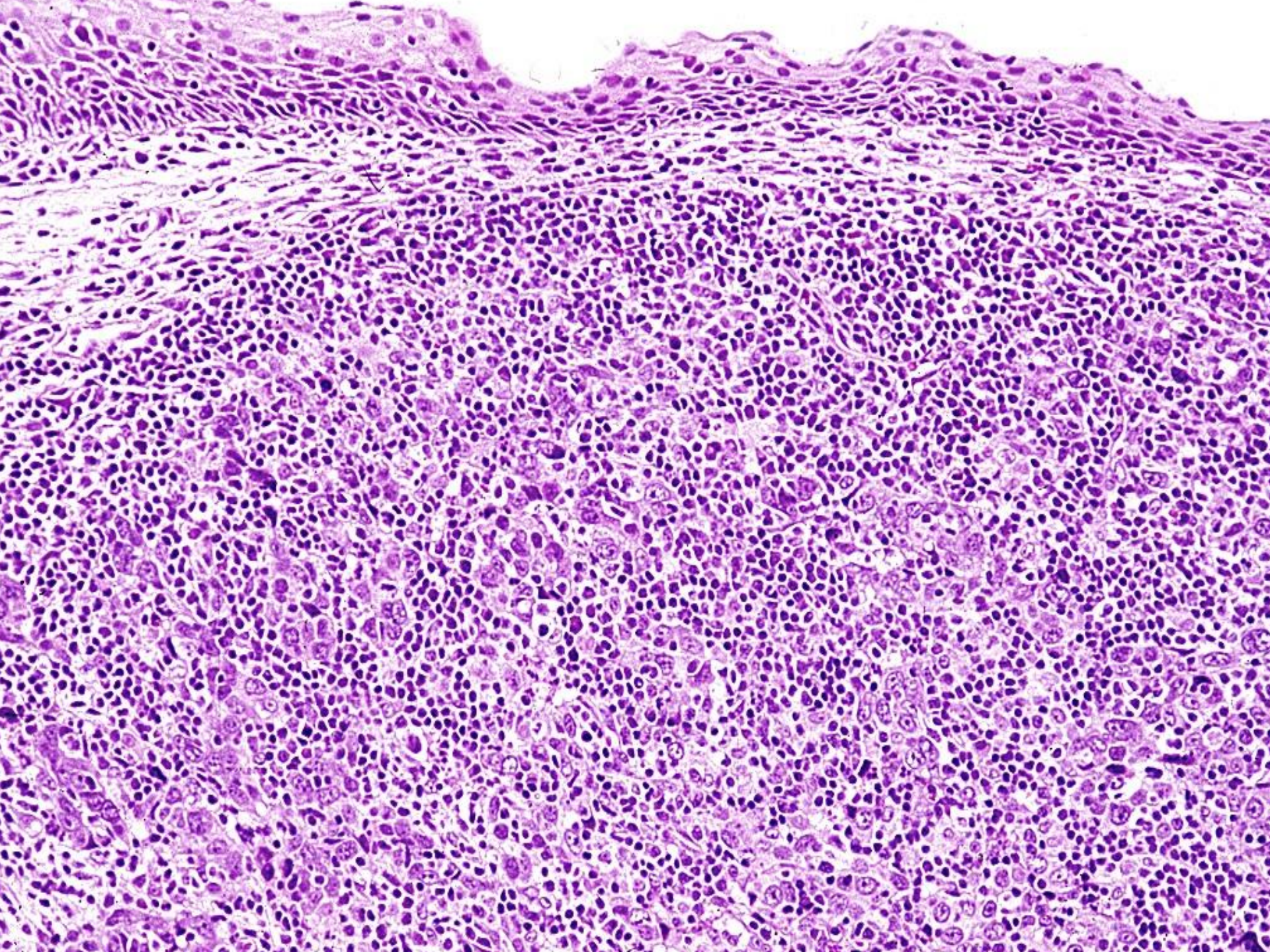


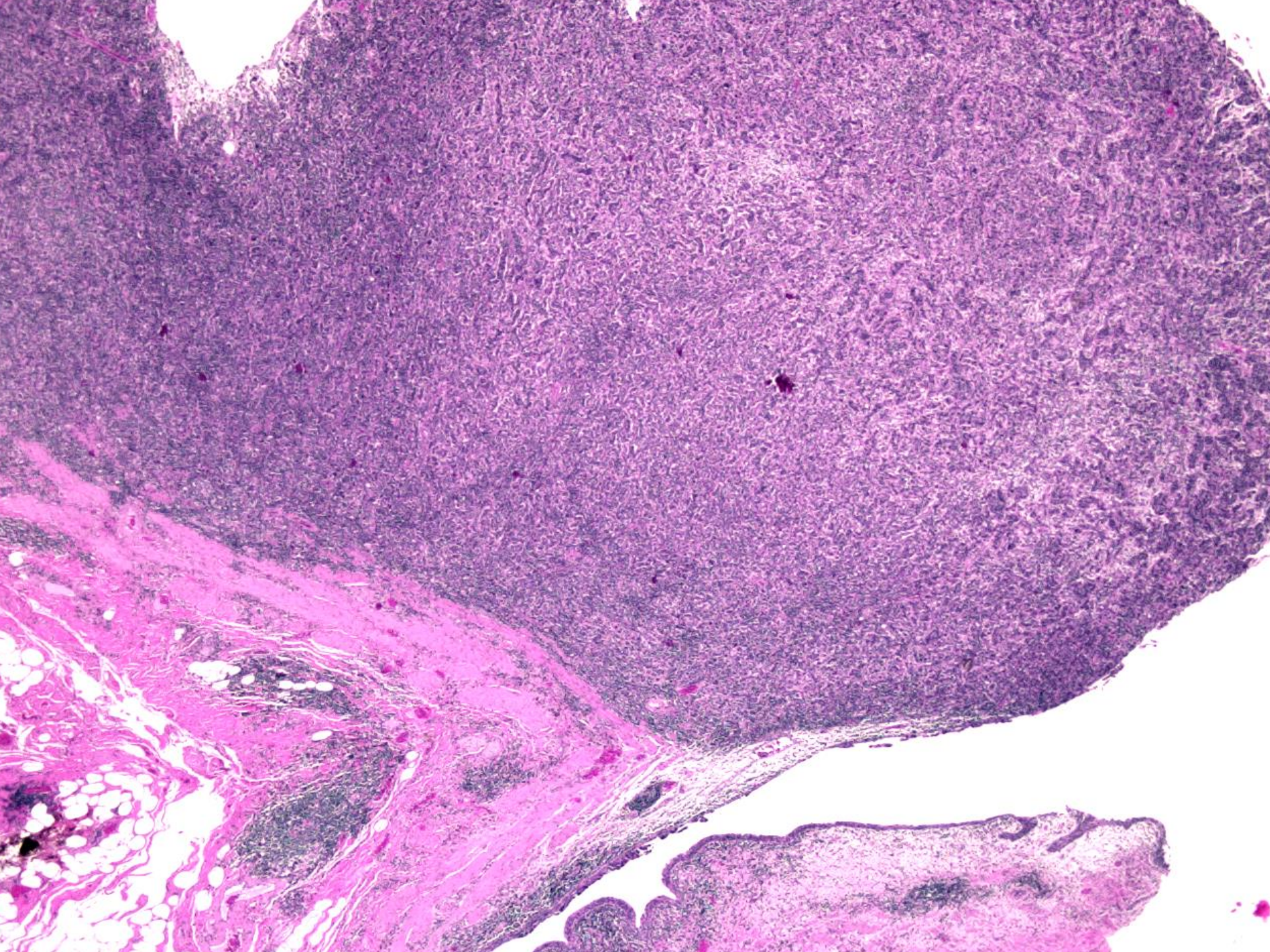
NOT Micropapillary

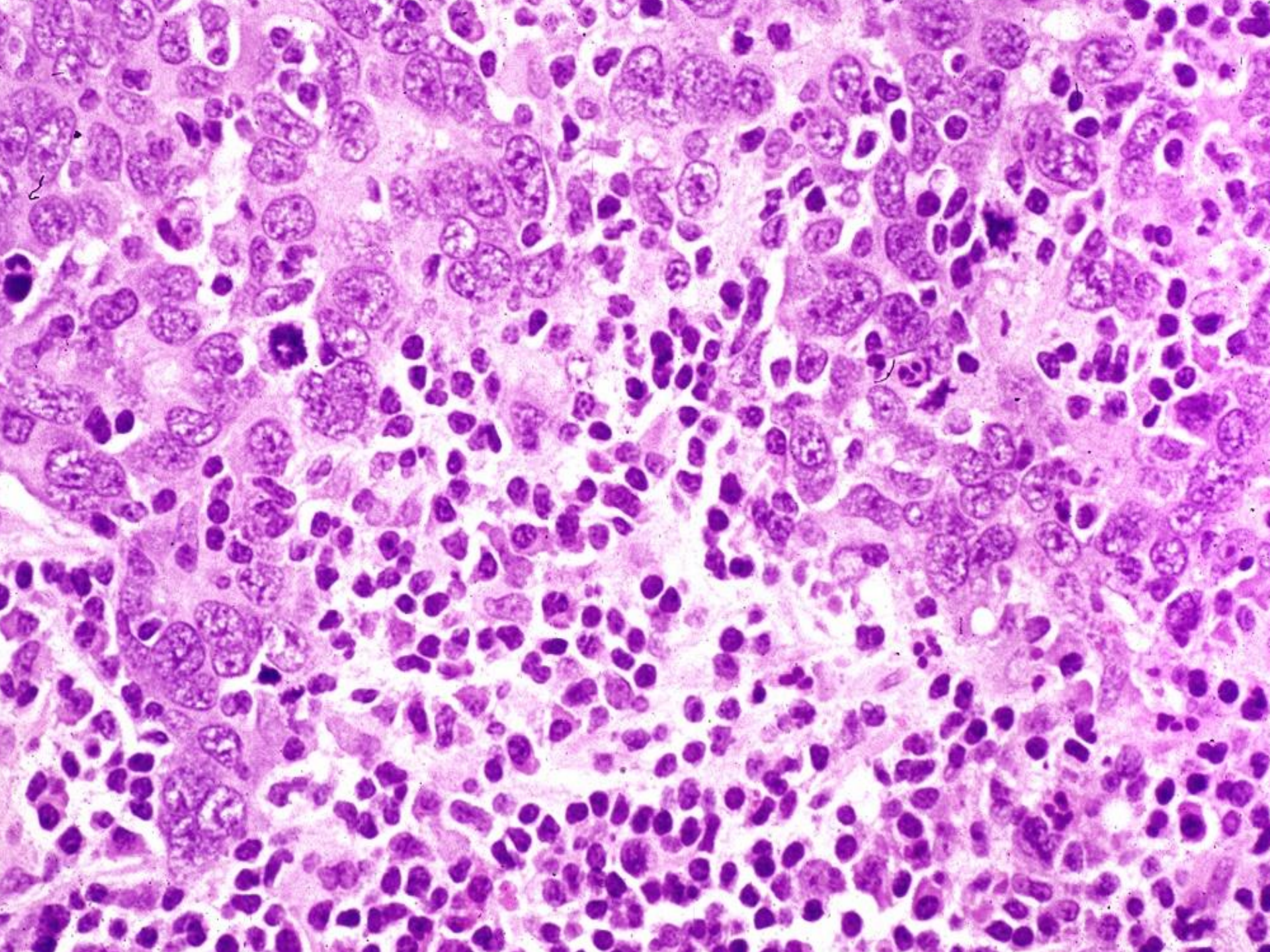


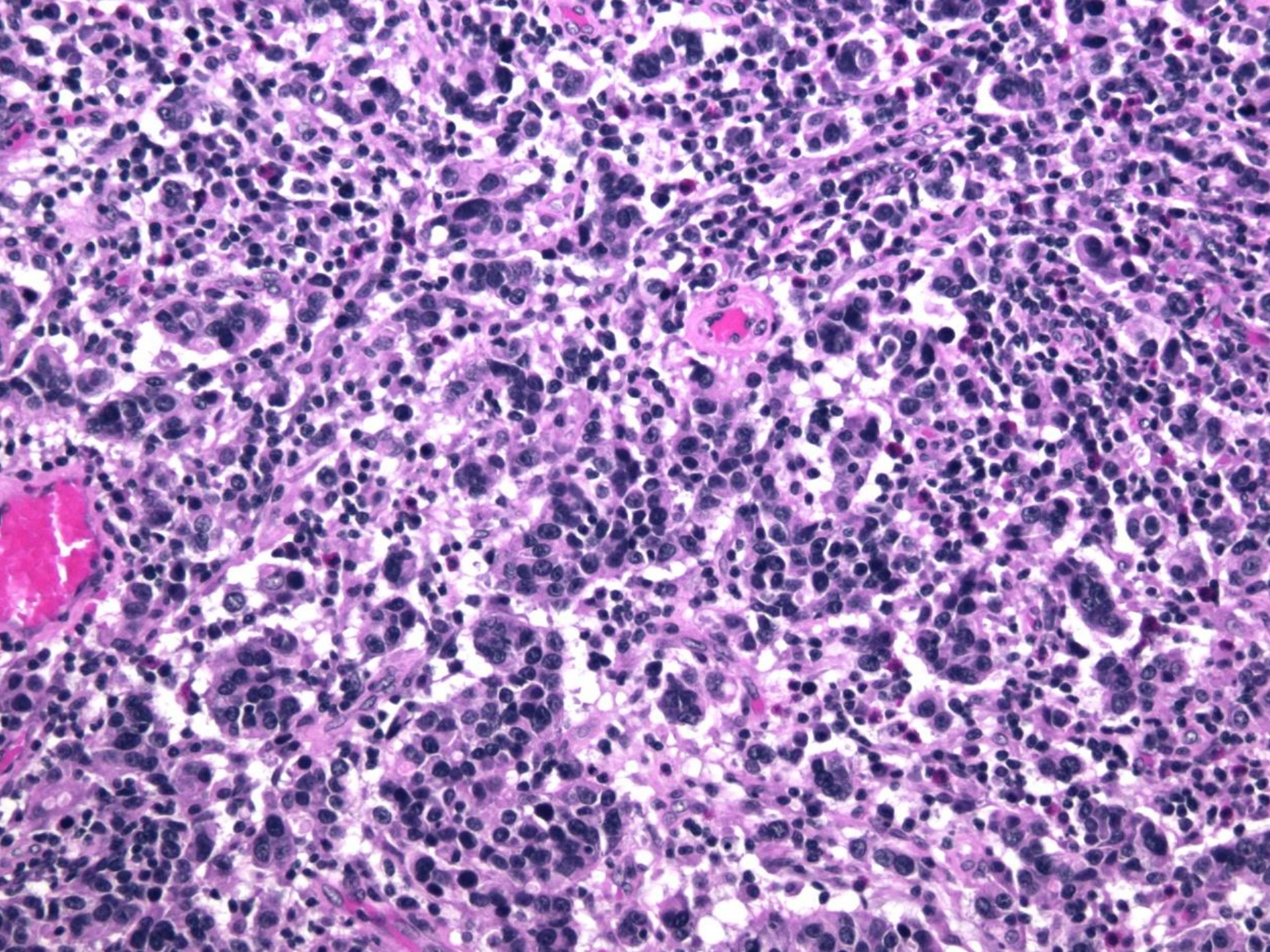
LYMPHOEPITHELIOMA-LIKE CARCINOMA OF THE BLADDER

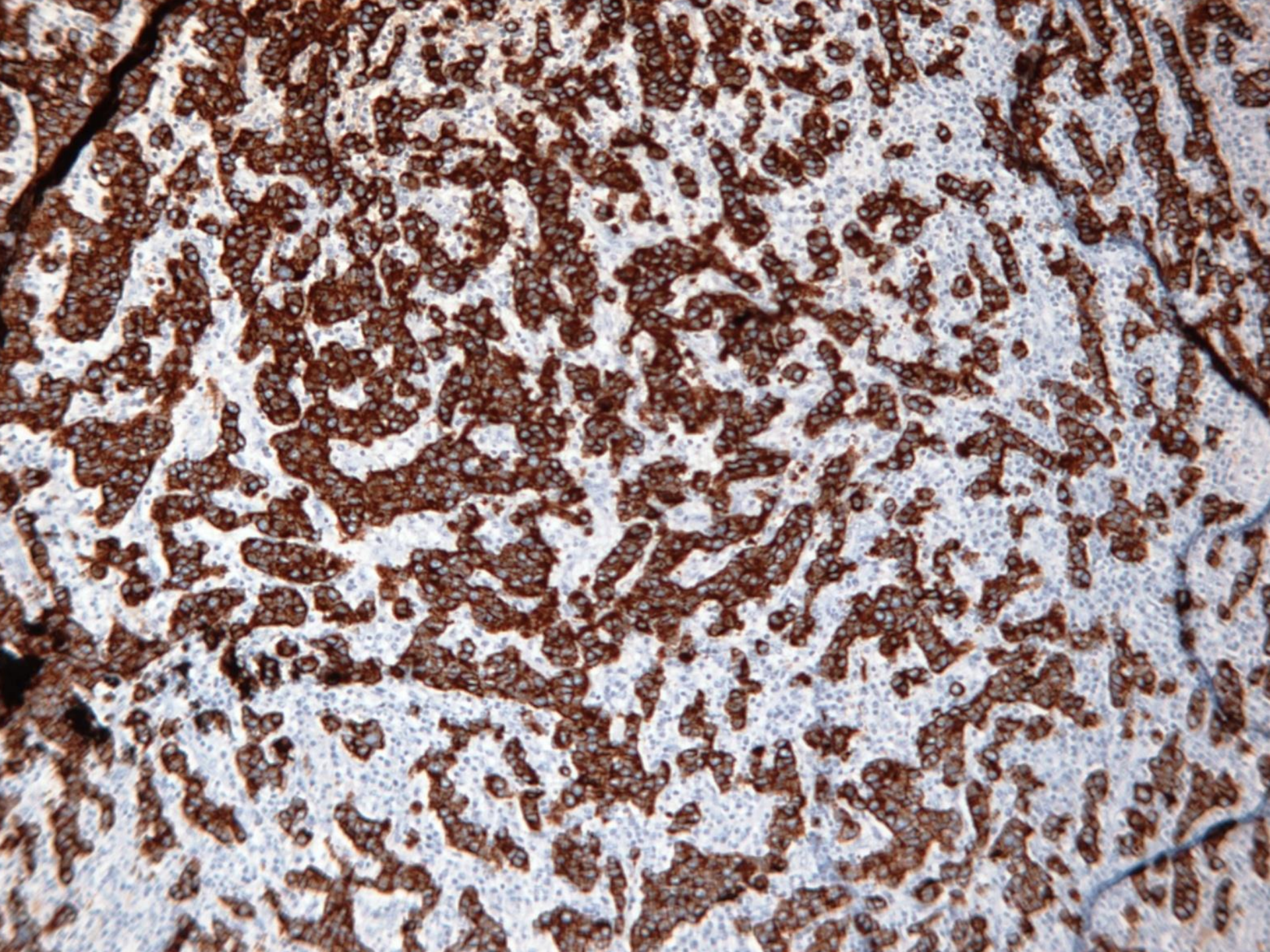
- Indistinguishable from nasopharyngeal counterpart
- Pure, predominant or focal
- Large cells arranged in syncytia, vesicular nuclei, prominent nucleoli
- Lymphoid infiltrate (predominantly T cell) - sine qua non
- Tendency for m. propria invasion (80% cases)
- No association with EBV

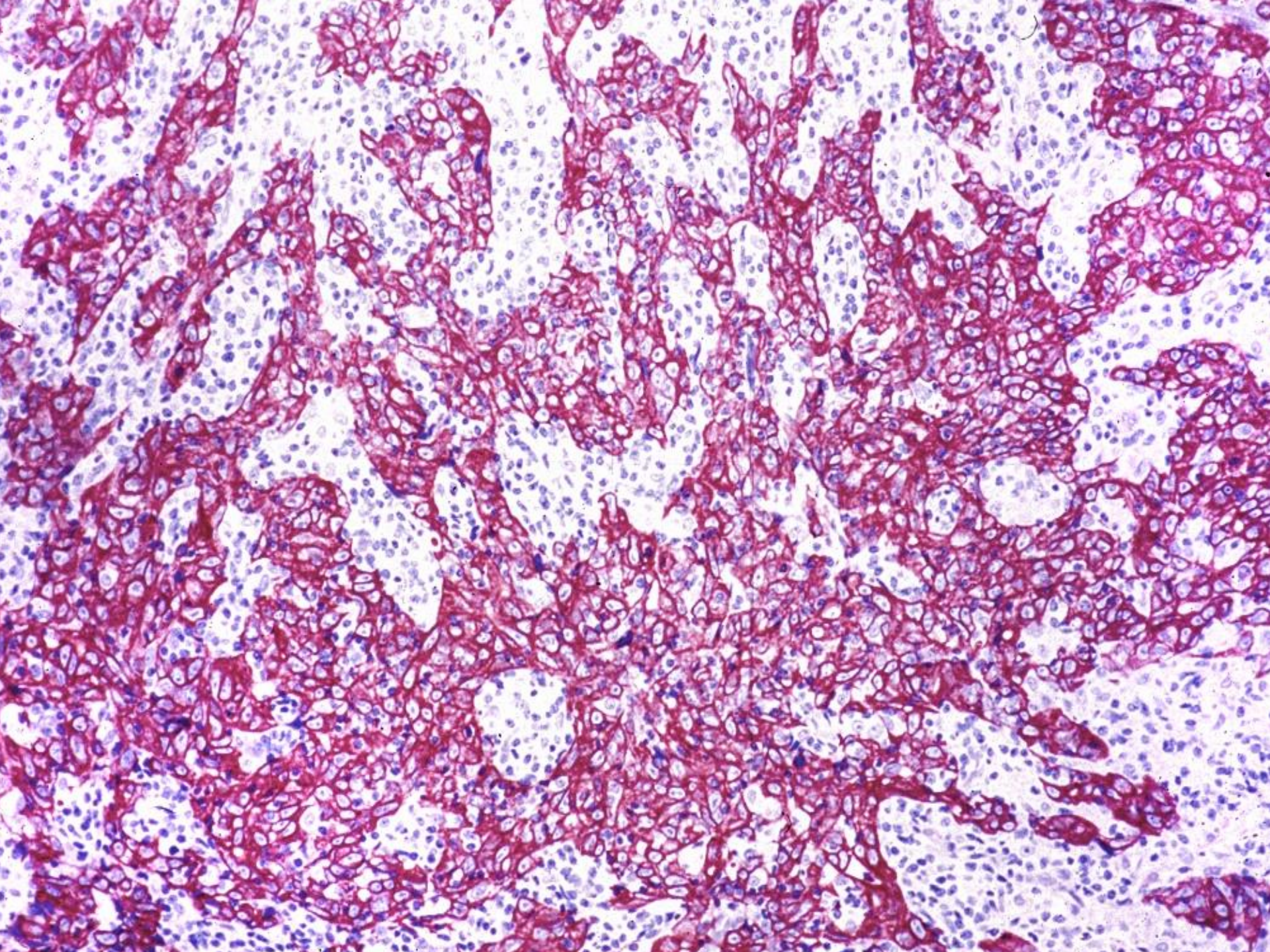






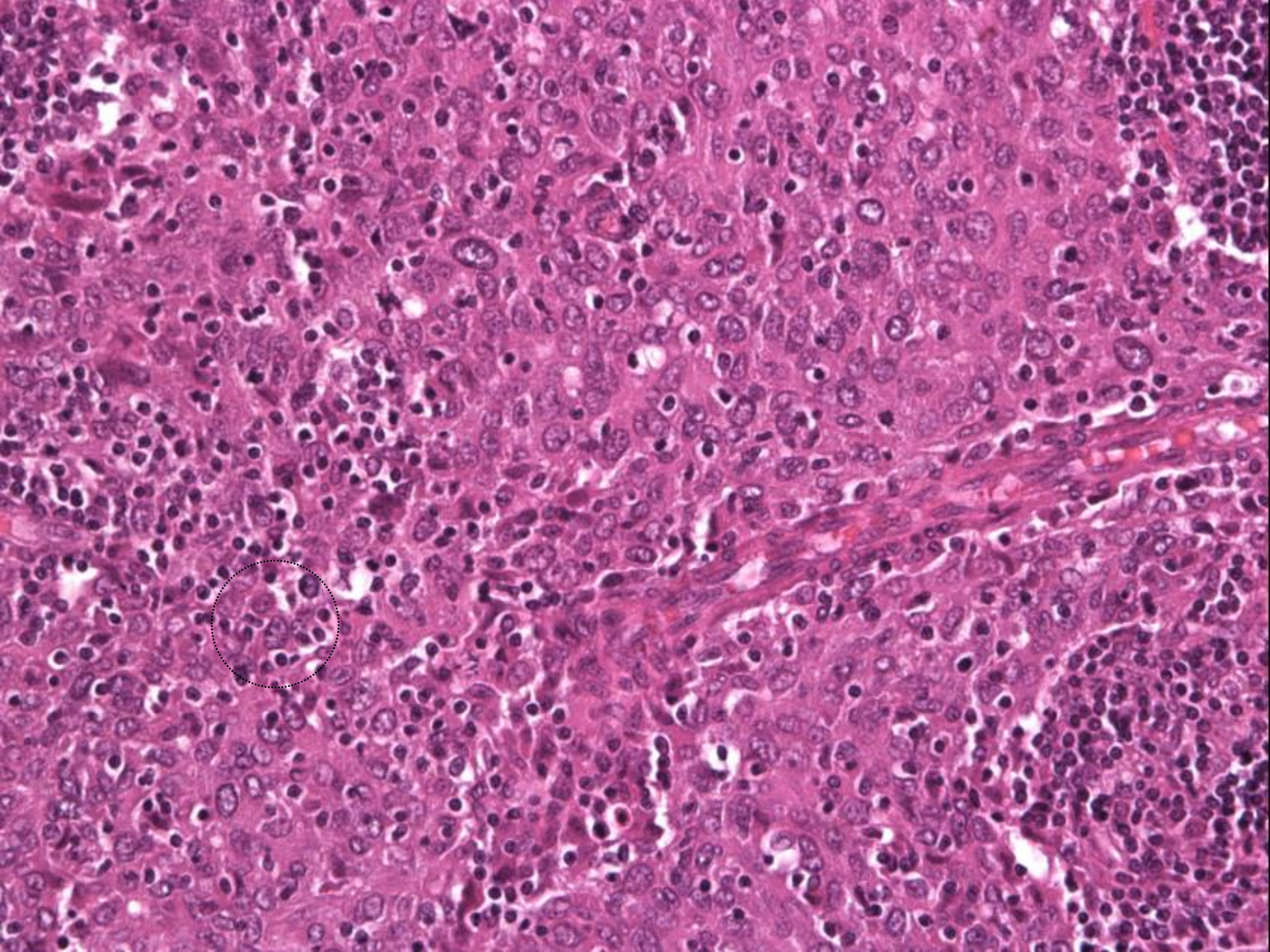


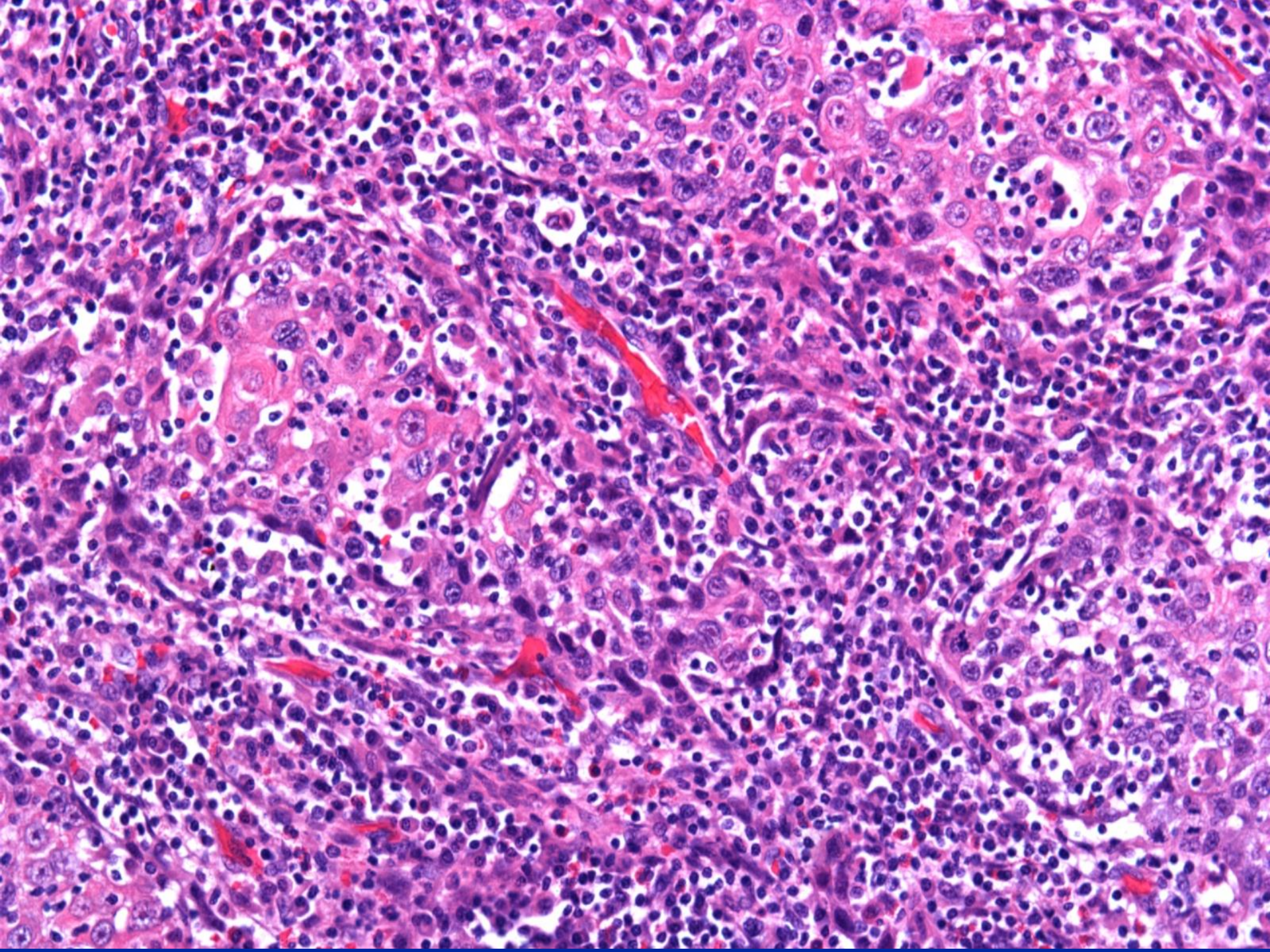




LYMPHOEPITHELIOMA-LIKE CARCINOMA OF THE BLADDER

- **Diagnostic significance**
 - Malignant lymphoma
 - U Ca. with prominent lymphoid infiltrate
 - Chronic cystitis (crushed/limited samples)





LYMPHOEPITHELIOMA-LIKE CARCINOMA OF THE BLADDER

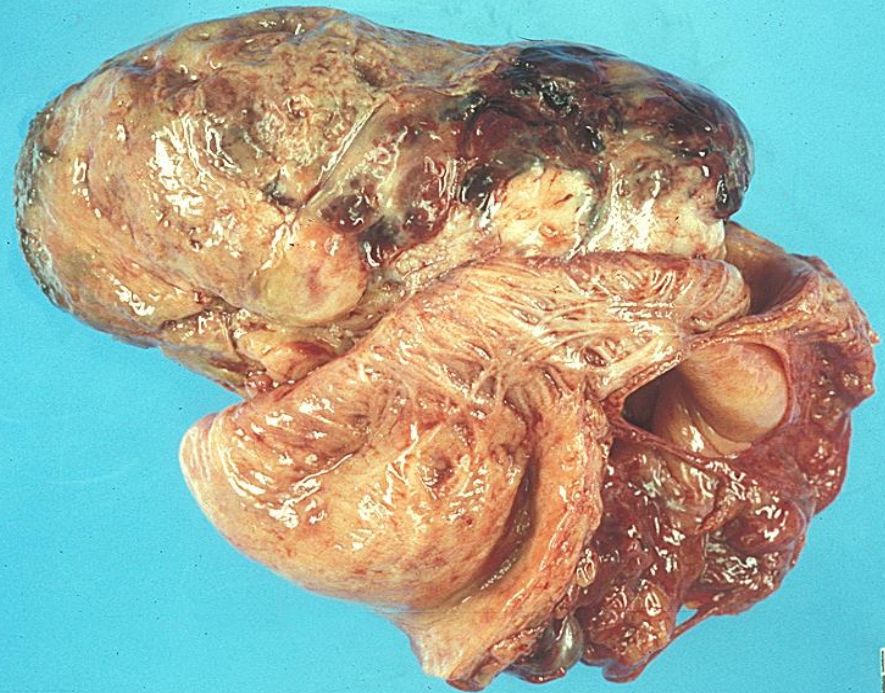
- **Prognostic significance**
 - Majority of tumors: high stage - pT2 or higher
 - Pure and predominant LELC: Better survival : ? host response - few studies
 - Focal LELC: like conventional U Ca. of similar stage

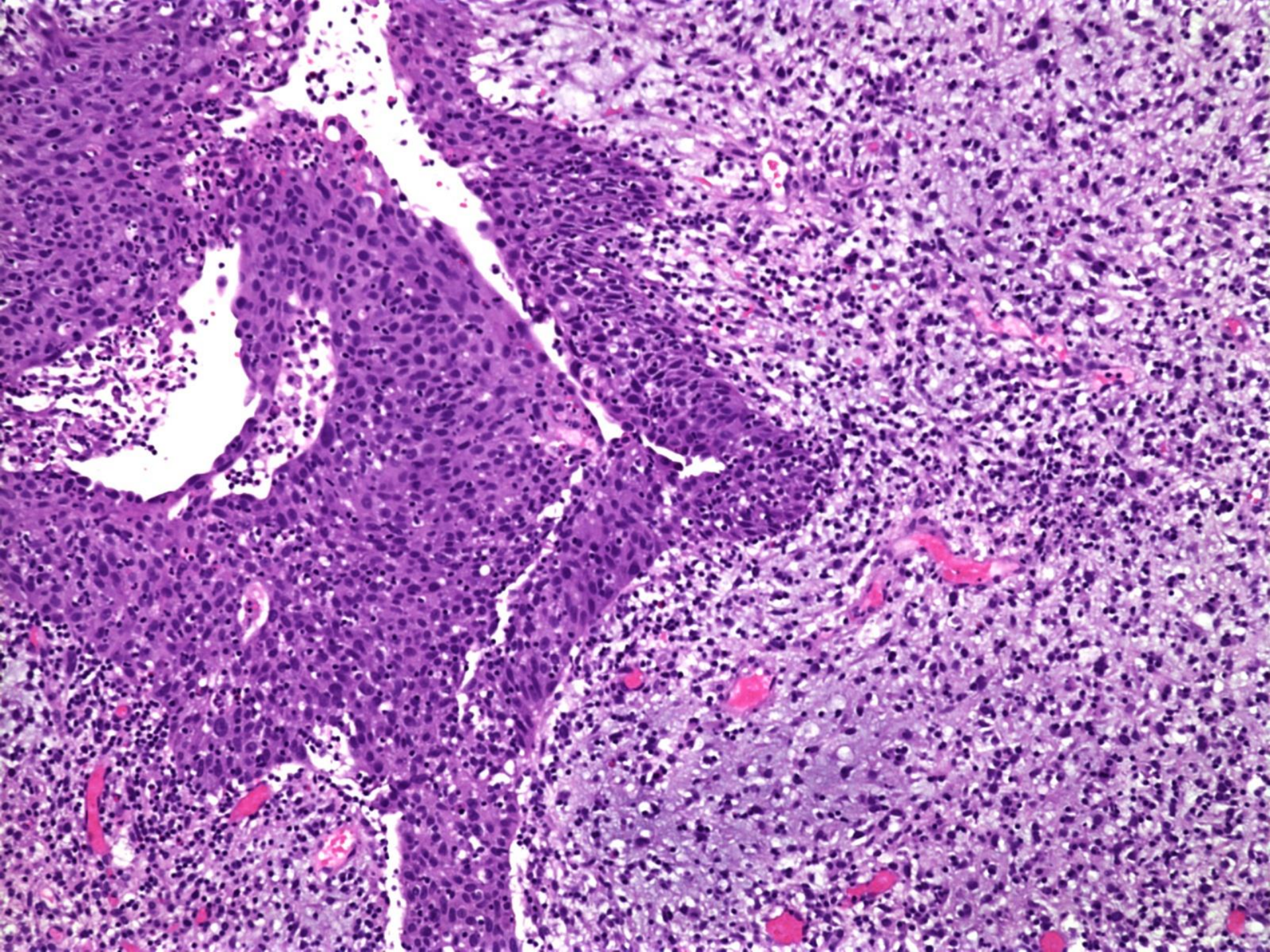
LYMPHOEPITHELIOMA-LIKE CARCINOMA OF THE BLADDER

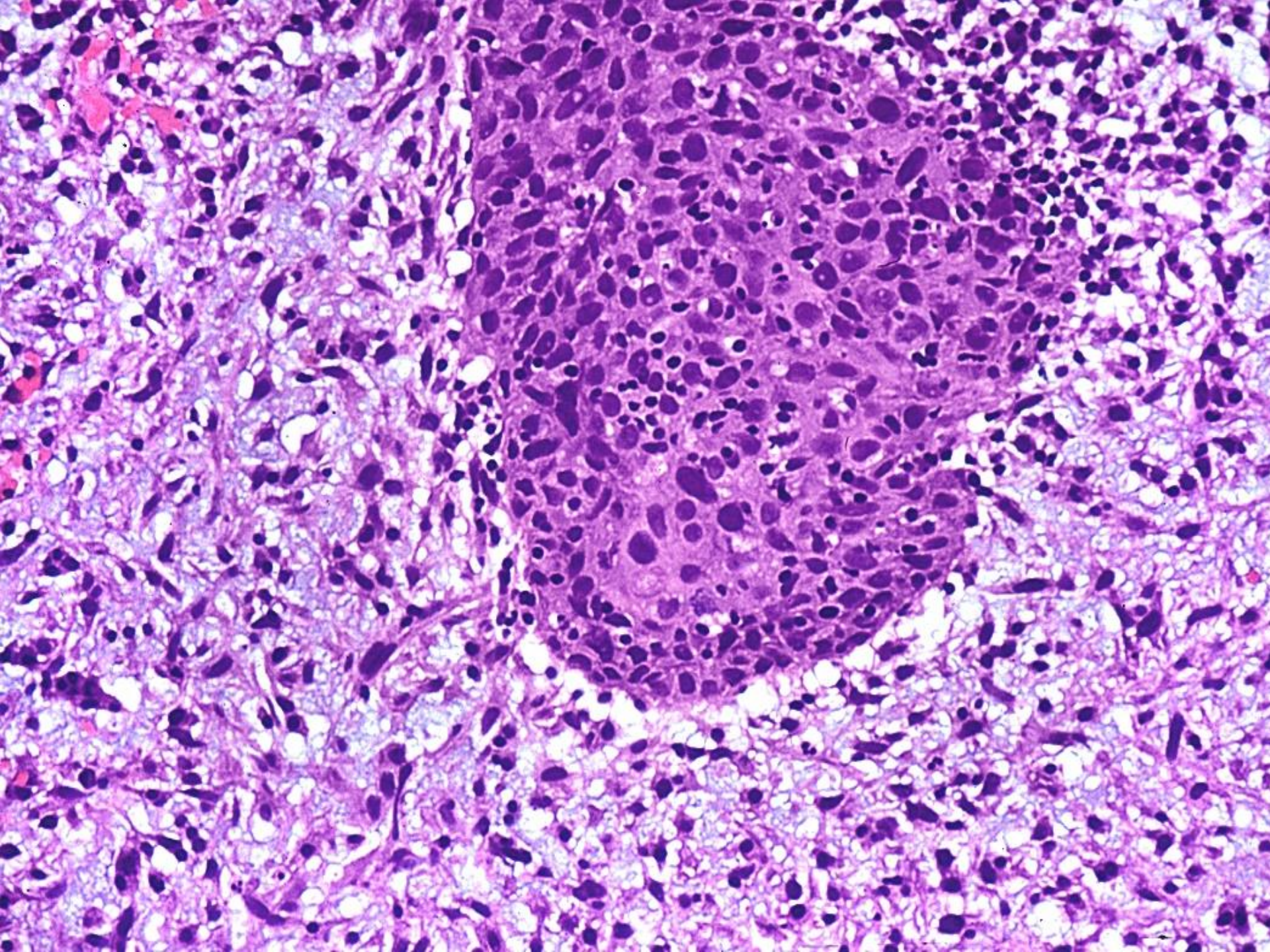
- **Therapeutic significance**
 - **Pure LELC:** Cisplatin-based chemotherapy : potential to salvage bladder function
 - *The diagnosis of pure LELC should be made after examination of entirely resected tumor in a TURBT*

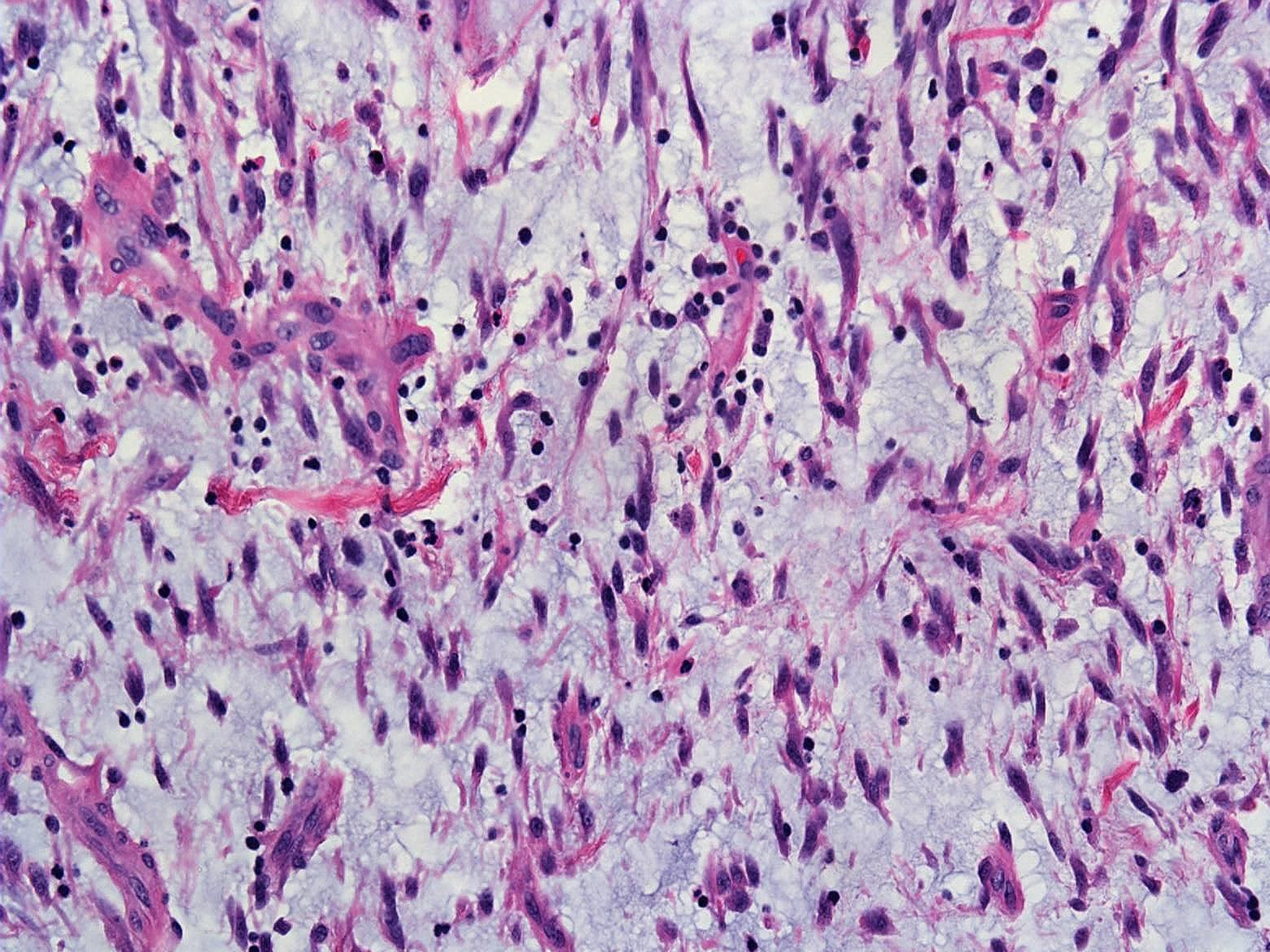
SARCOMATOID U Ca.

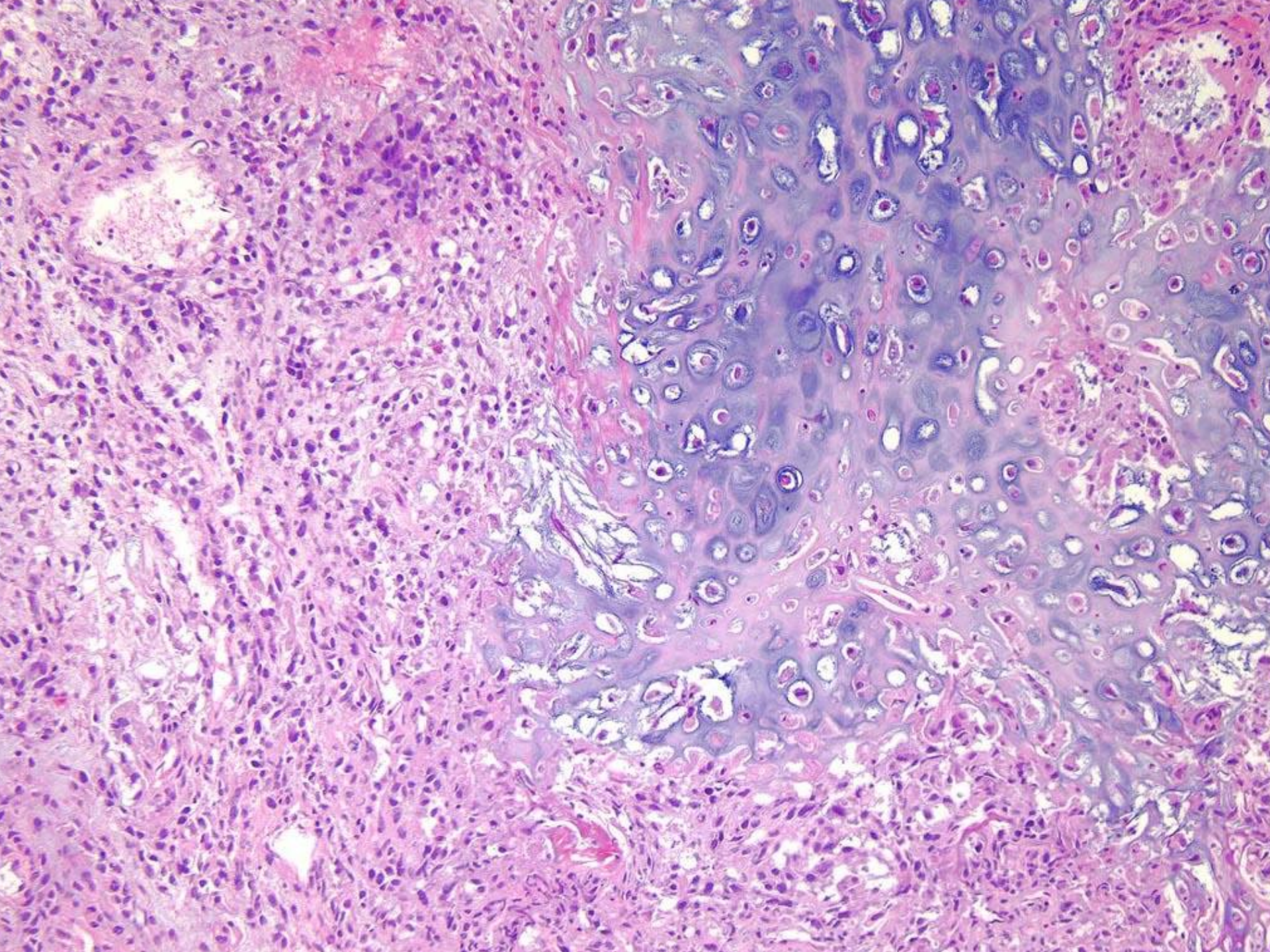
- **Biphasic histology**
 - **Sarcomatoid component**
 - High grade sarcoma, NOS
 - Heterologous differentiation: osteo, chondro, rhabdo, lipo & angiosarcoma
 - **Poorly differentiated carcinoma**
 - Urothelial carcinoma
 - Squamous, adeno- or small cell ca.
 - Mixed histology









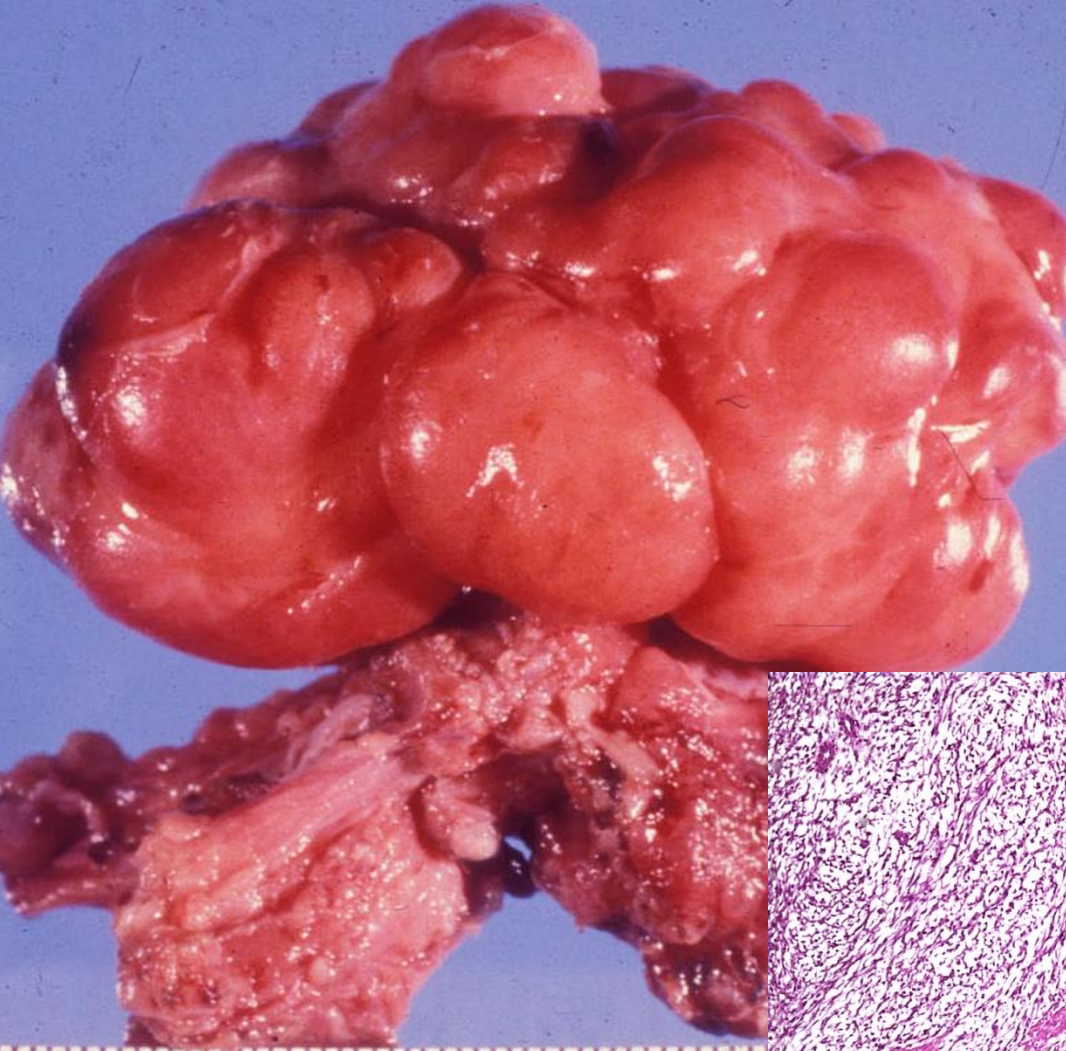


SARCOMATOID U Ca.

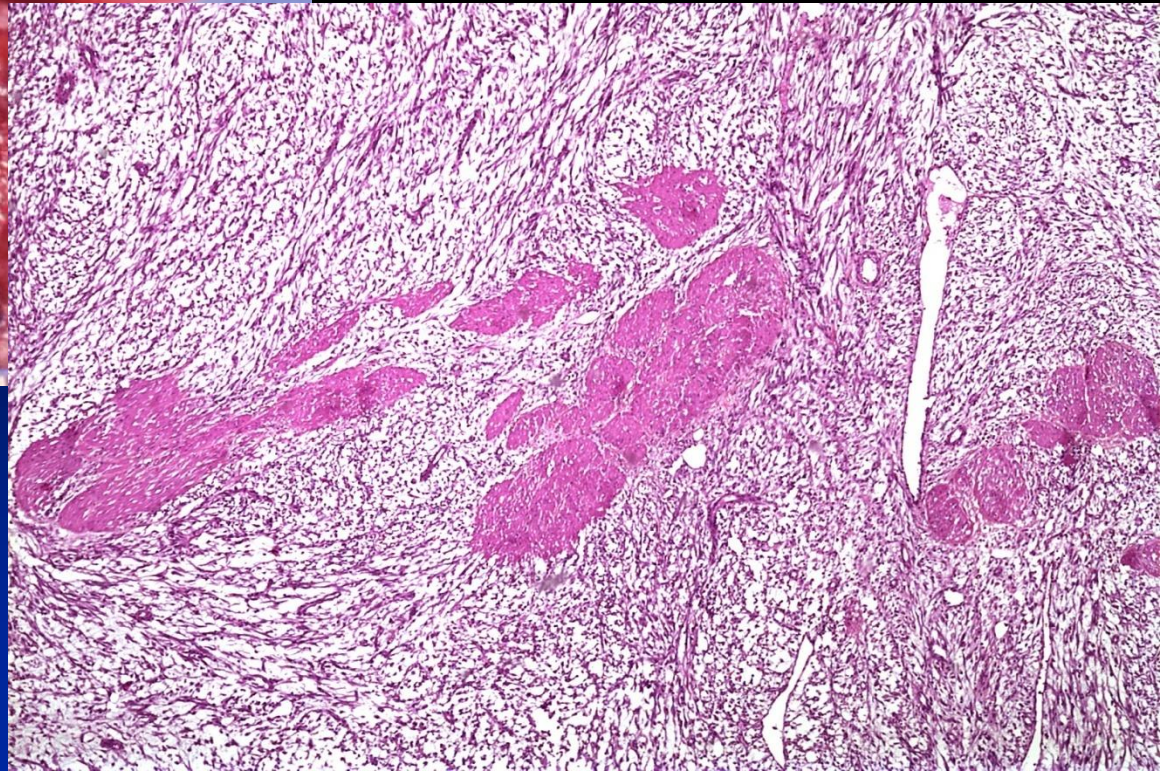
- **Prognostic significance**
 - Invariably presents at high stage
 - Crude 1- and 2-year survival 50% and 25%
 - No apparent difference in outcome if heterologous elements present
- **Therapeutic significance**
 - Different from carcinoma - many institutions

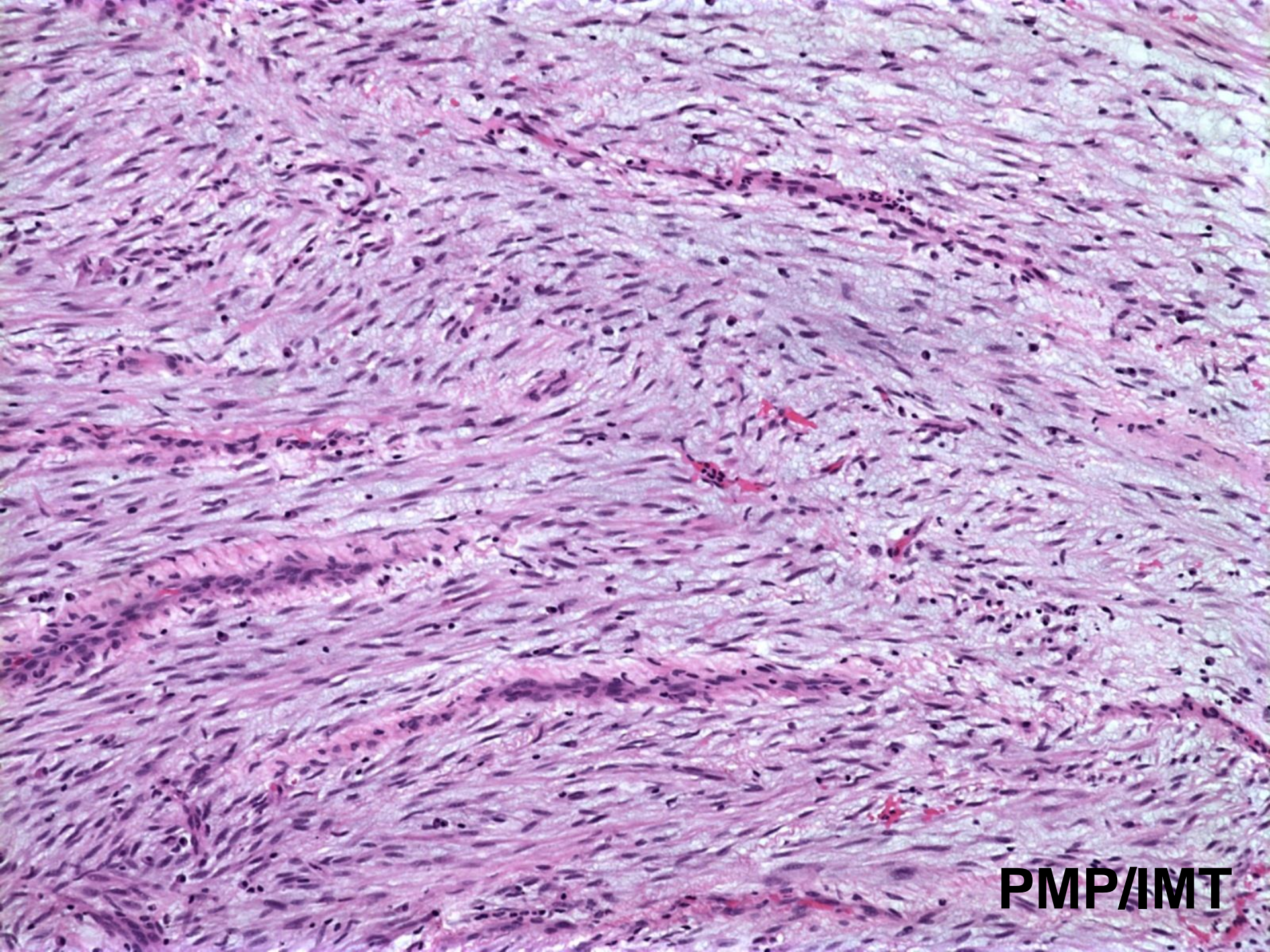
SARCOMATOID U Ca.

- Differential diagnosis
 - Benign
 - *Pseudosarcomatous myofibroblastic proliferation (post-operative spindle cell nodule & pseudotumor)*
 - Carcinoma
 - *UCa. with pseudosarcomatous stroma*
 - *UCa. with osseous/chondroid metaplasia*
 - Sarcoma
 - *Leiomyosarcoma and others*

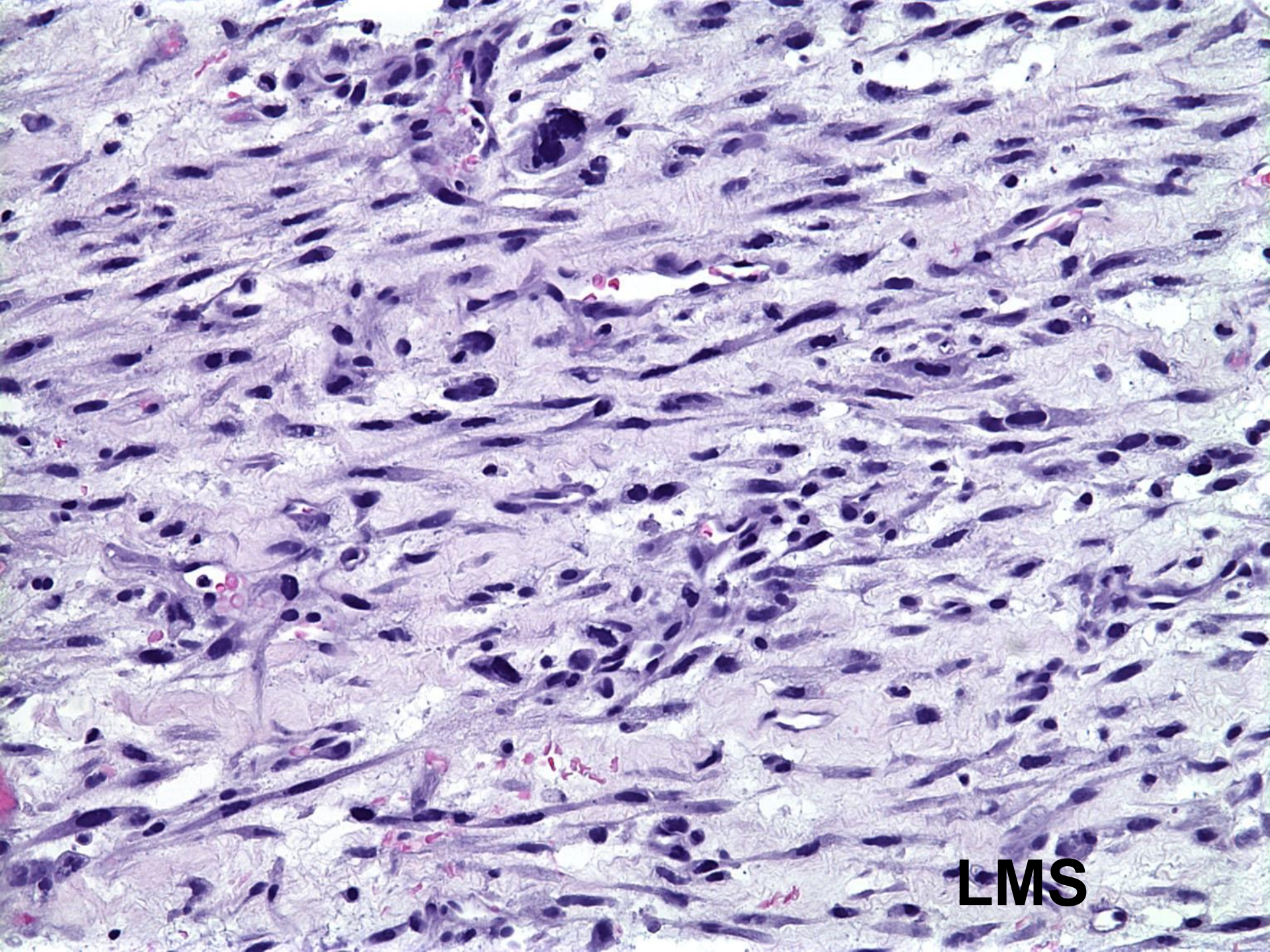


**Pseudosarcomatous
myofibroblastic
proliferation /
pseudotumor / IMT**



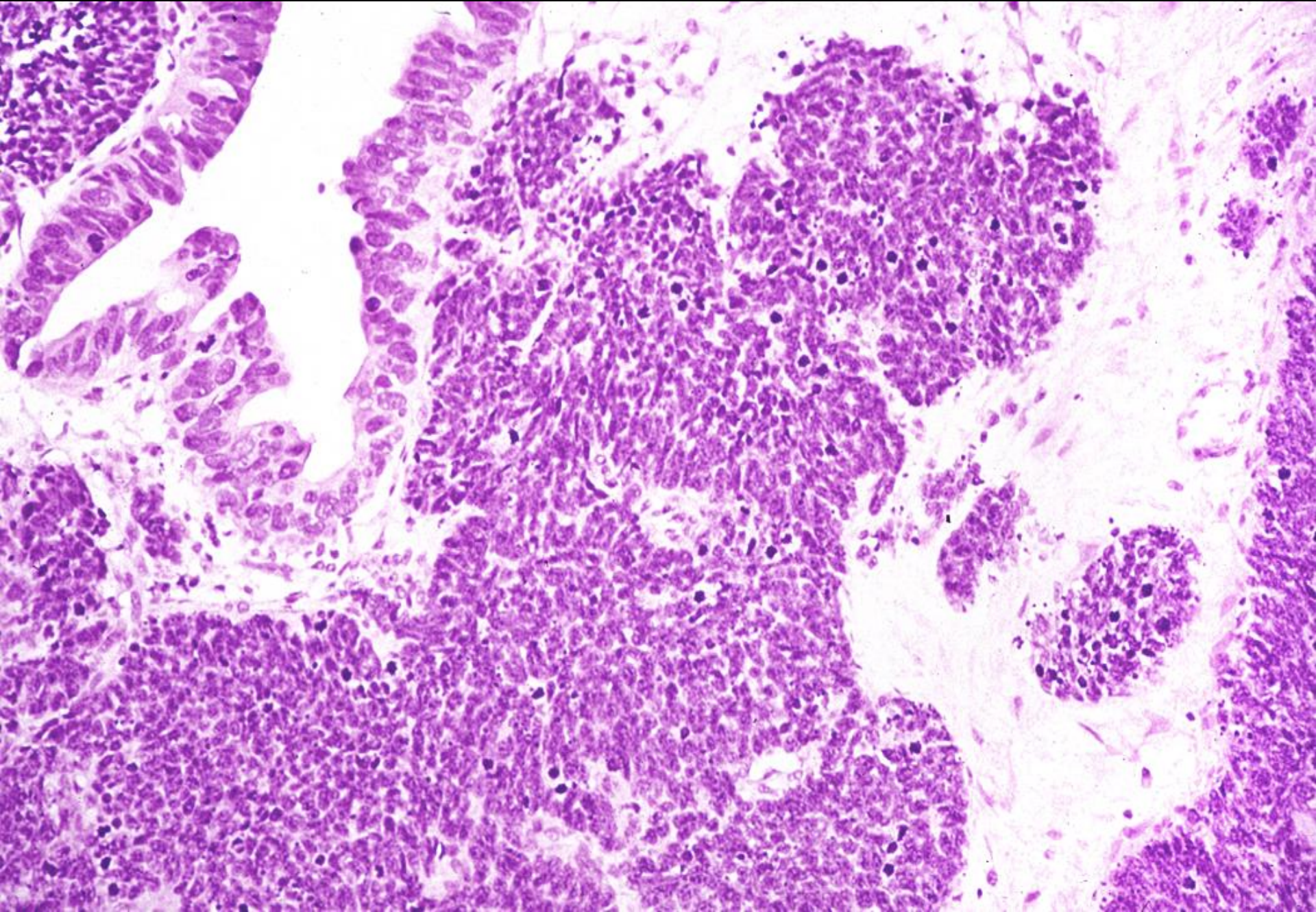


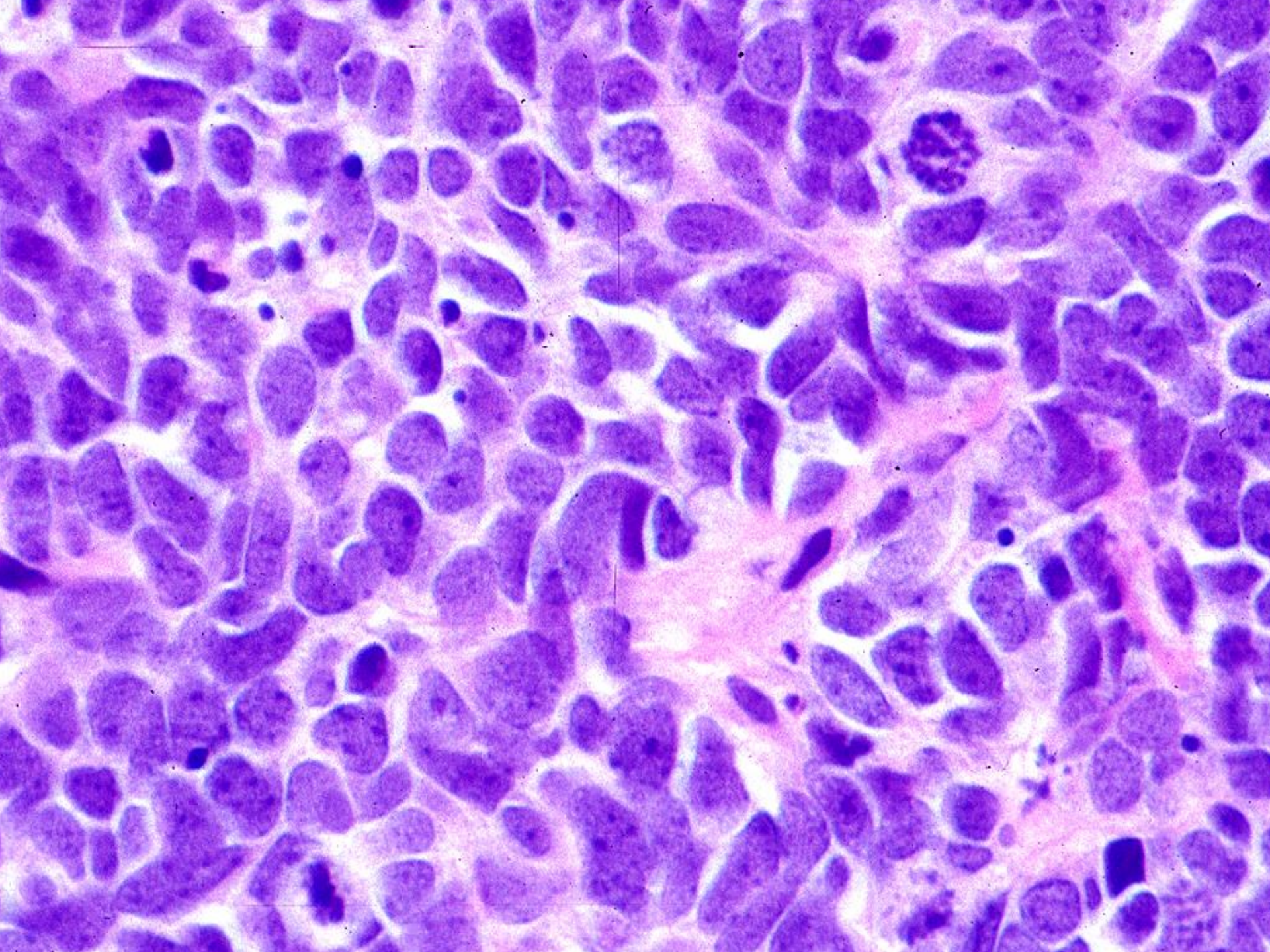
PMP/IMT

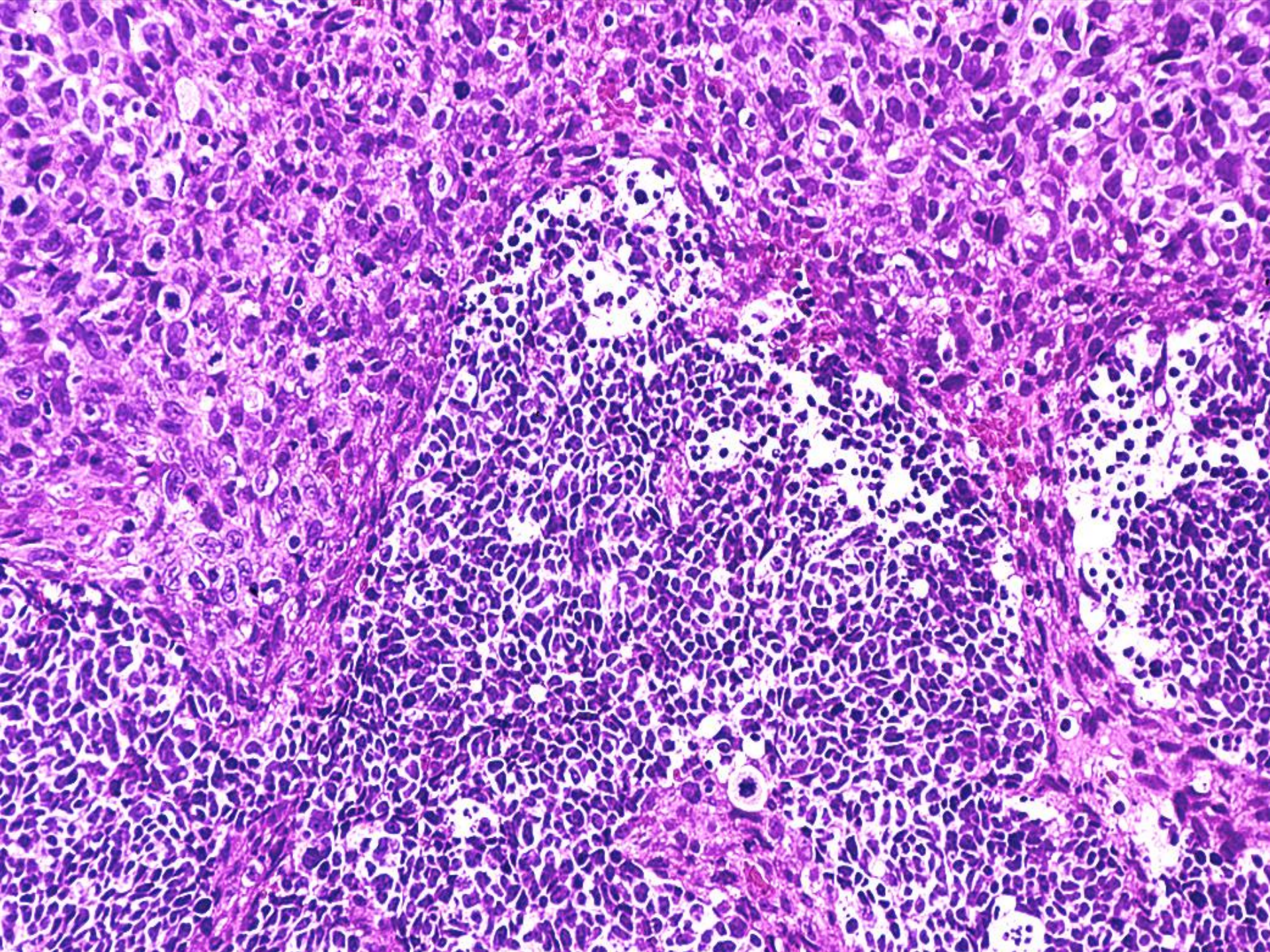


LMS

SMALL CELL CARCINOMA OF THE BLADDER







SMALL CELL CARCINOMA

- **Differential diagnosis**
 - Inflammation (scant/crushed specimens)
 - Malignant lymphoma
 - High-grade (poorly differentiated) U Ca.
 - Alveolar rhabdomyosarcoma (RMS)
 - Metastasis
 - Lung
 - Prostate

SMALL CELL CARCINOMA

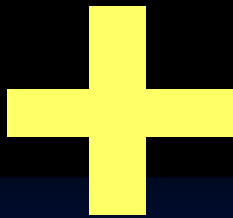
- **Prognostic significance**
 - Present as high-stage tumors (94%)
 - 25% present with metastasis, 67% develop them
 - Poor prognosis in pts without chemotherapy compared to U Ca. patients - mean survival 6-35 months
- **Therapeutic significance**
 - Pre-chemo era: 10% 2-year survival
 - Post-chemo era (cisplatin & etoposide): Longer survival, especially for low-stage tumors → 8-40% 5-year survival
 - Outcome depends on response to chemotherapy

SMALL CELL CARCINOMA

Therapeutic approach

- No formal studies

Chemotherapy



Surgery+/- radiation



- Small cell carcinoma component
- Systemic control

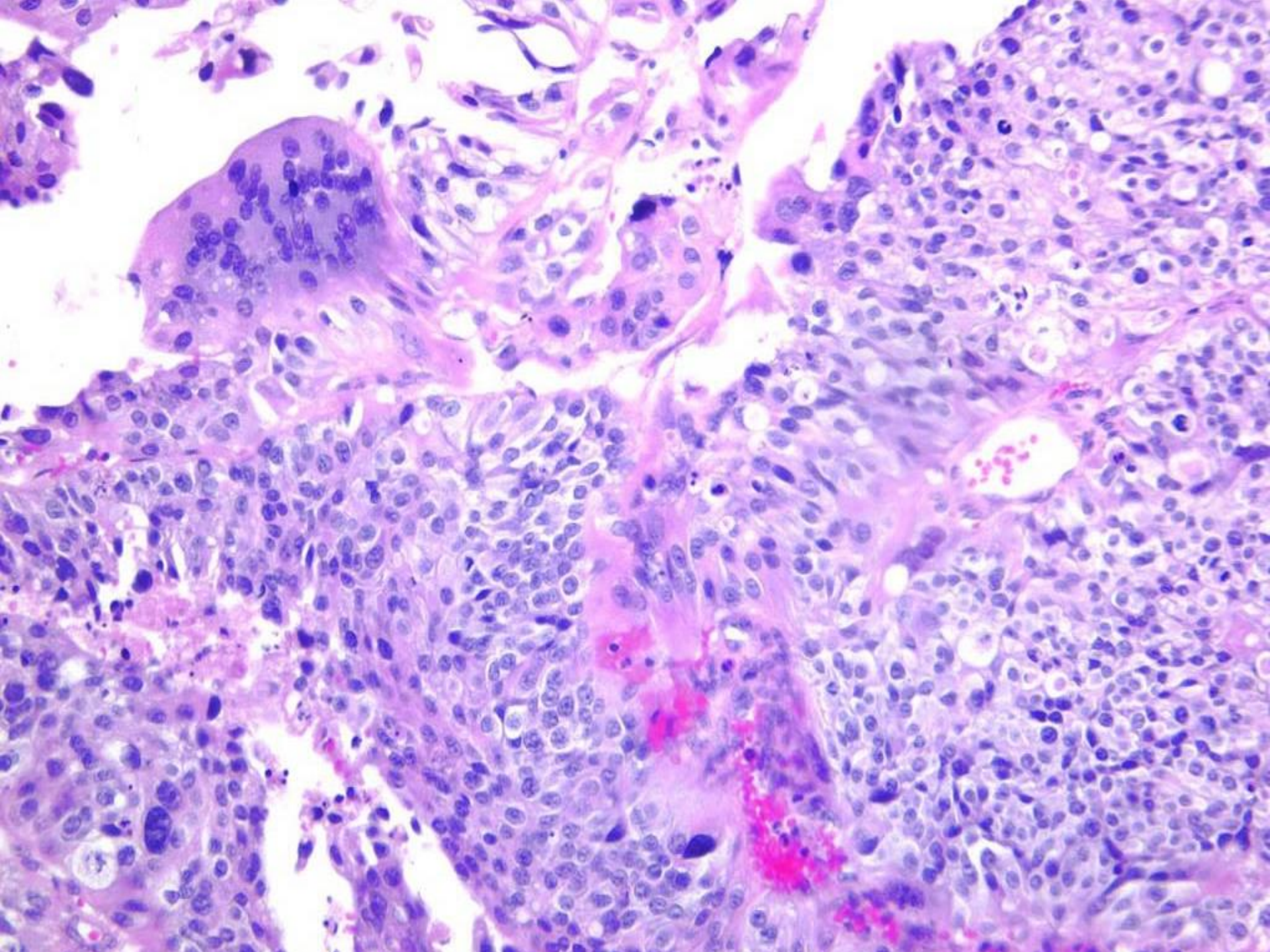


- Sq/U Ca./glandular component
- Aggressive local control

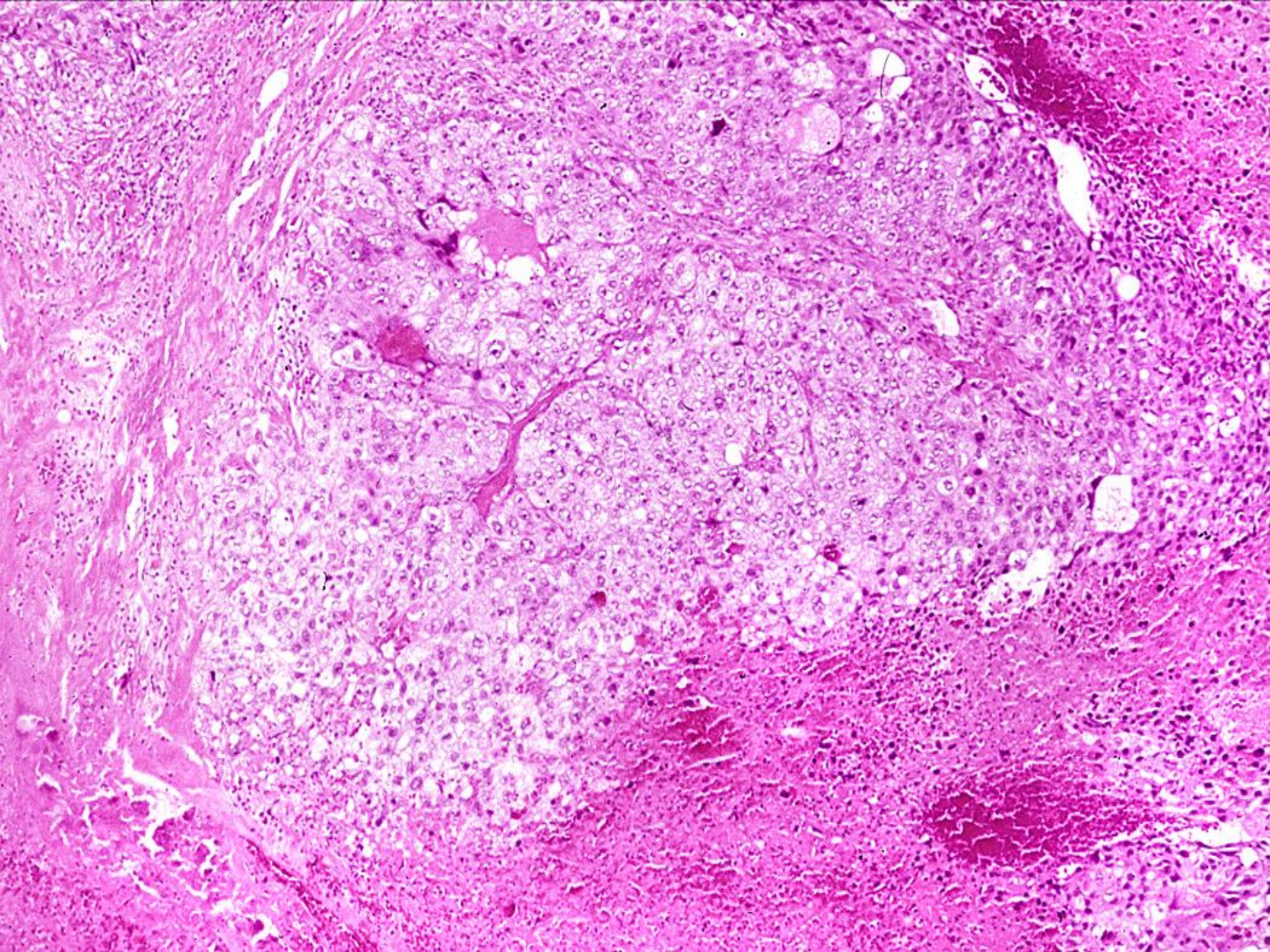
U Ca. WITH TROPHOBLASTIC DIFFERENTIATION

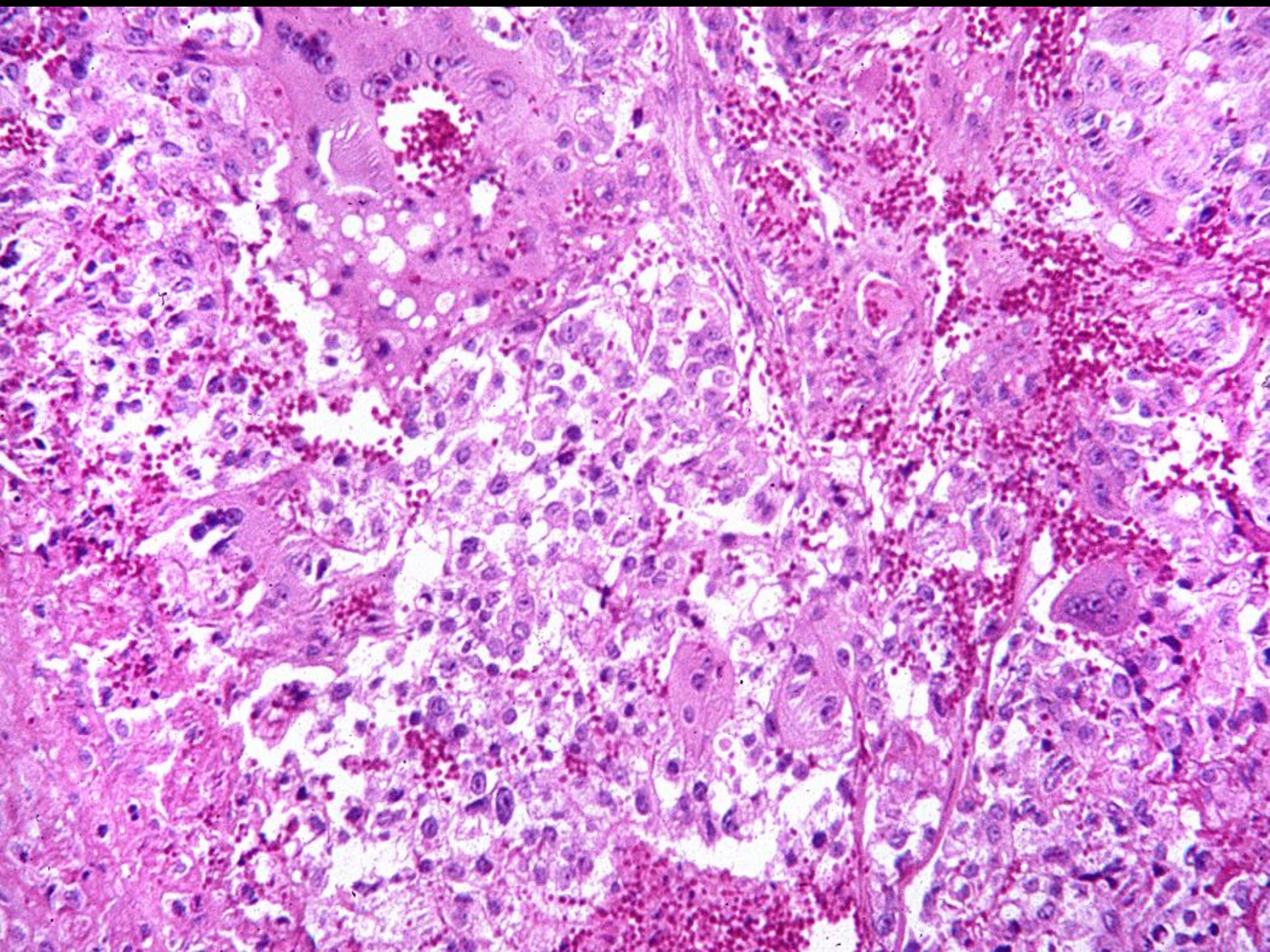
- **High-grade U Ca. with HCG immunoreactivity**
- **High-grade U Ca. with syncytiotrophoblastic giant cells**
- **High-grade U Ca. with choriocarcinoma**
- **Pure choriocarcinoma**

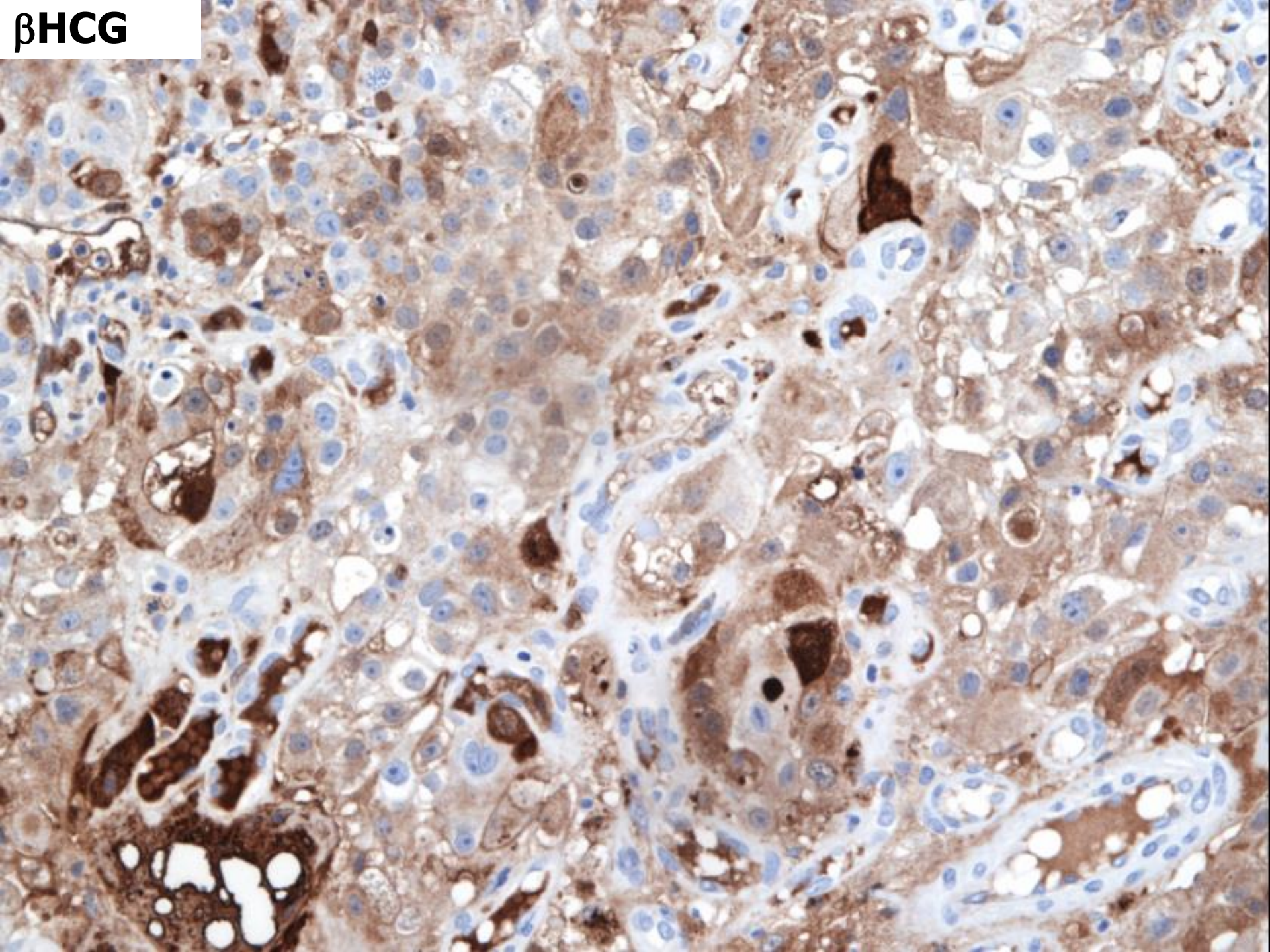
Metaplastic theory suggests a sequence









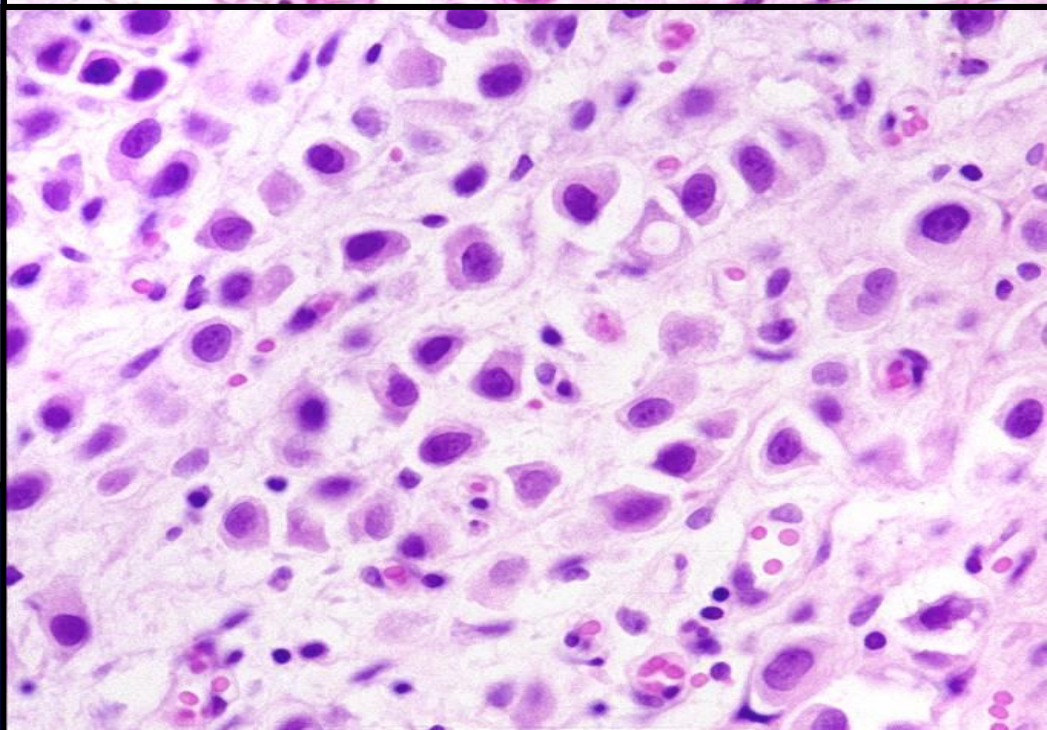
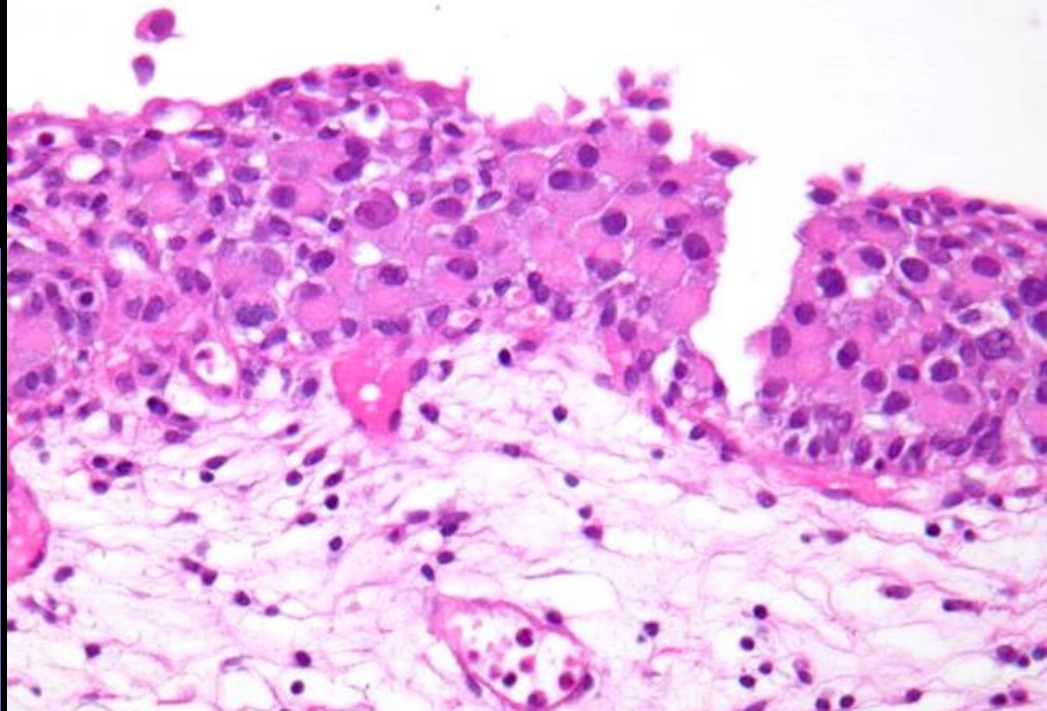


U Ca. WITH TROPHOBLASTIC DIFFERENTIATION

- **U Ca. with HCG positivity or syncytiotrophoblasts**
 - Poor prognosis (assoc. with high-grade U Ca.)
 - Resistance to radiotherapy
 - Serum levels correlate with response to chemotherapy
- **U Ca. with choriocarcinoma**
 - Rare, use strict criteria
 - Poor prognosis (all cases with 1 year follow-up - DOD)
 - Poor response to chemotherapy or radiotherapy

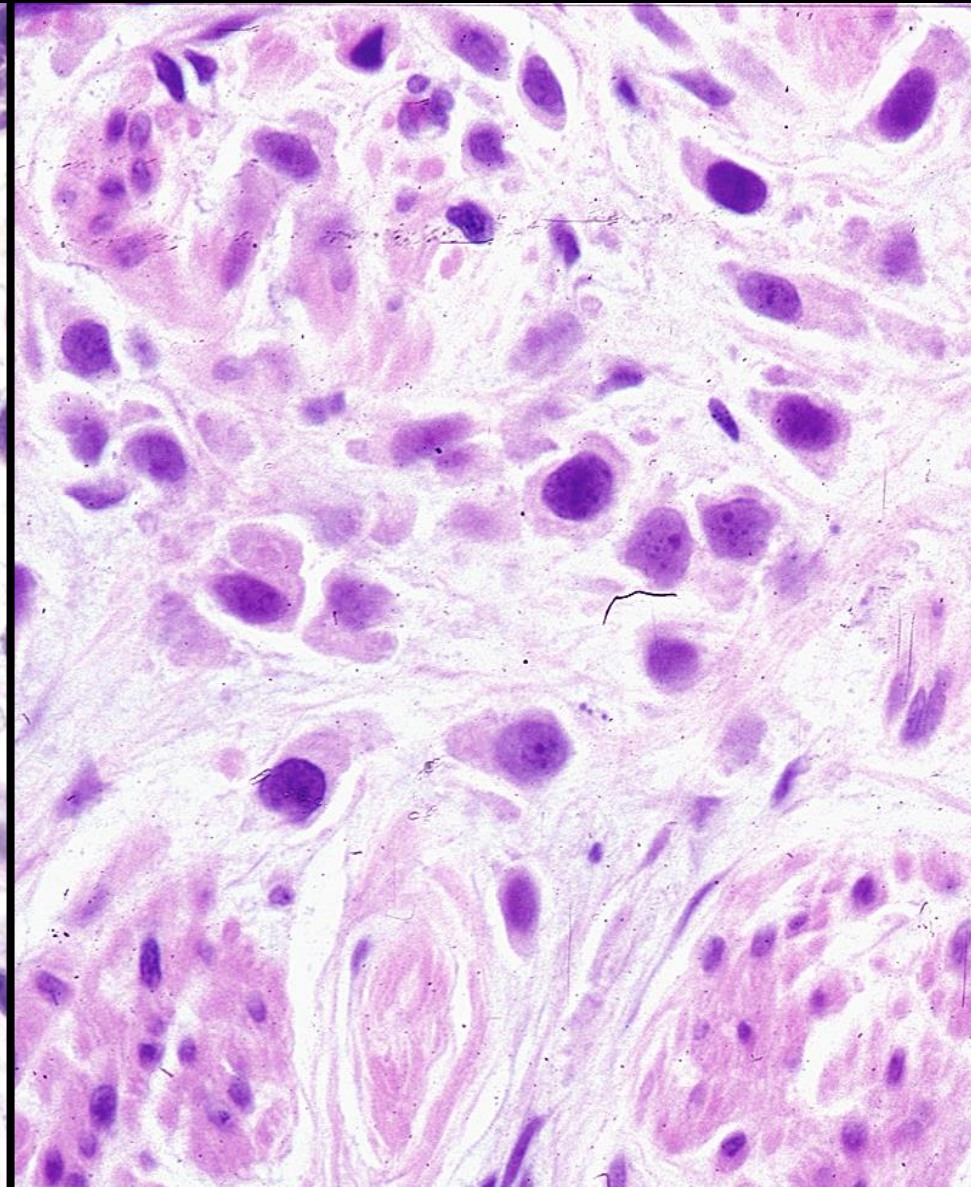
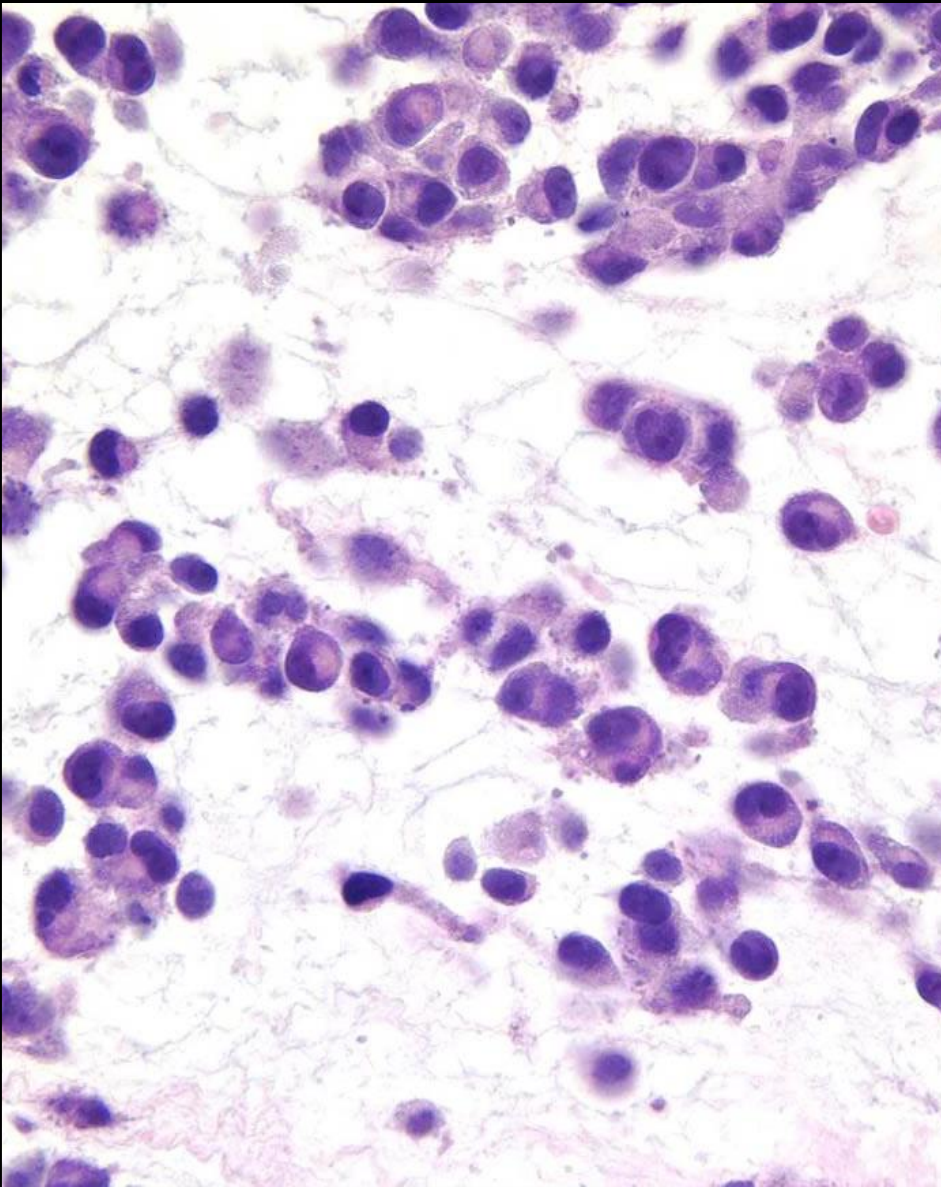
HISTOLOGIC VARIANTS OF U Ca.

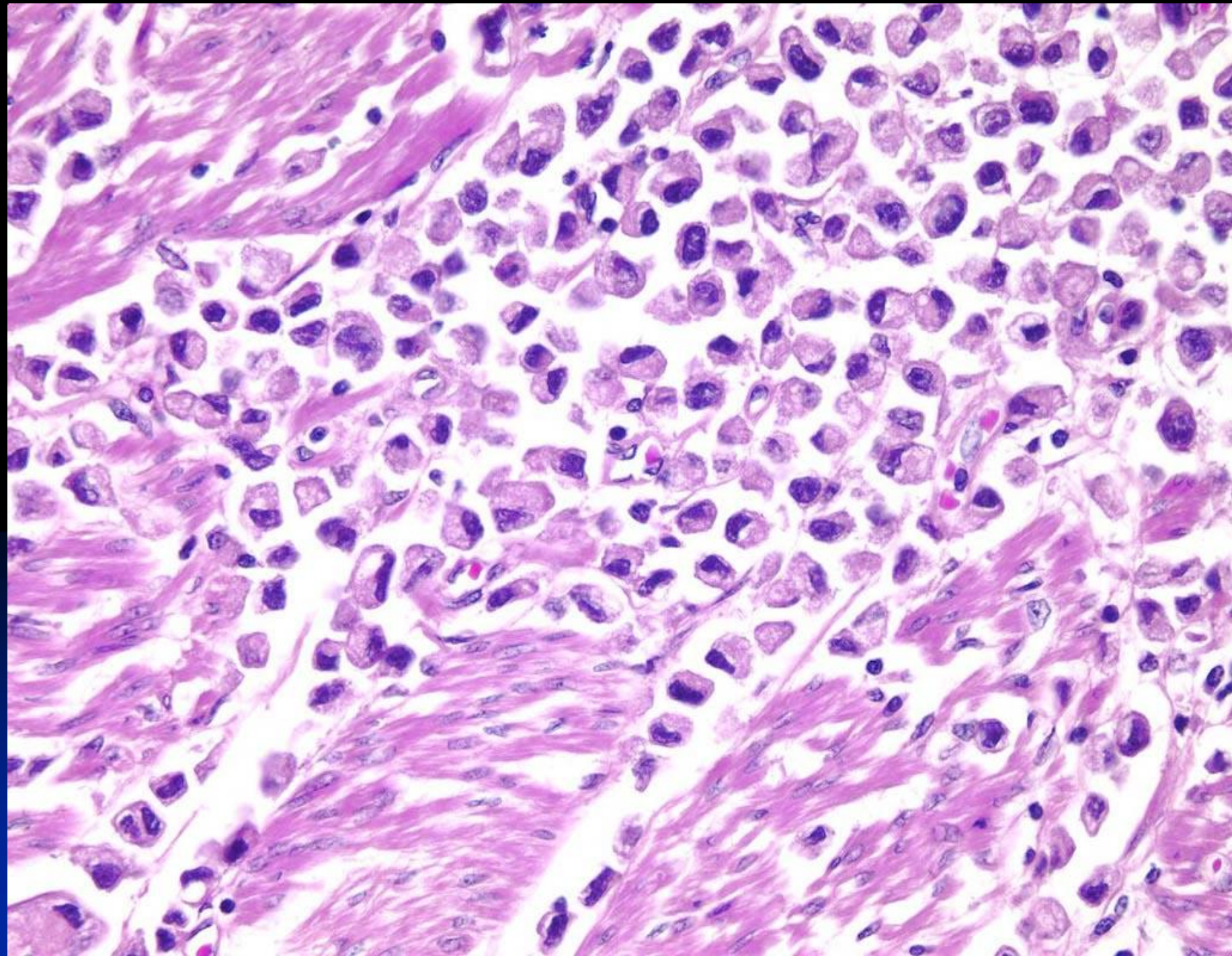
- **Unusual cytoplasmic features**
 - Plasmacytoid
 - Rhabdoid
 - Clear cells
 - Lipid-rich

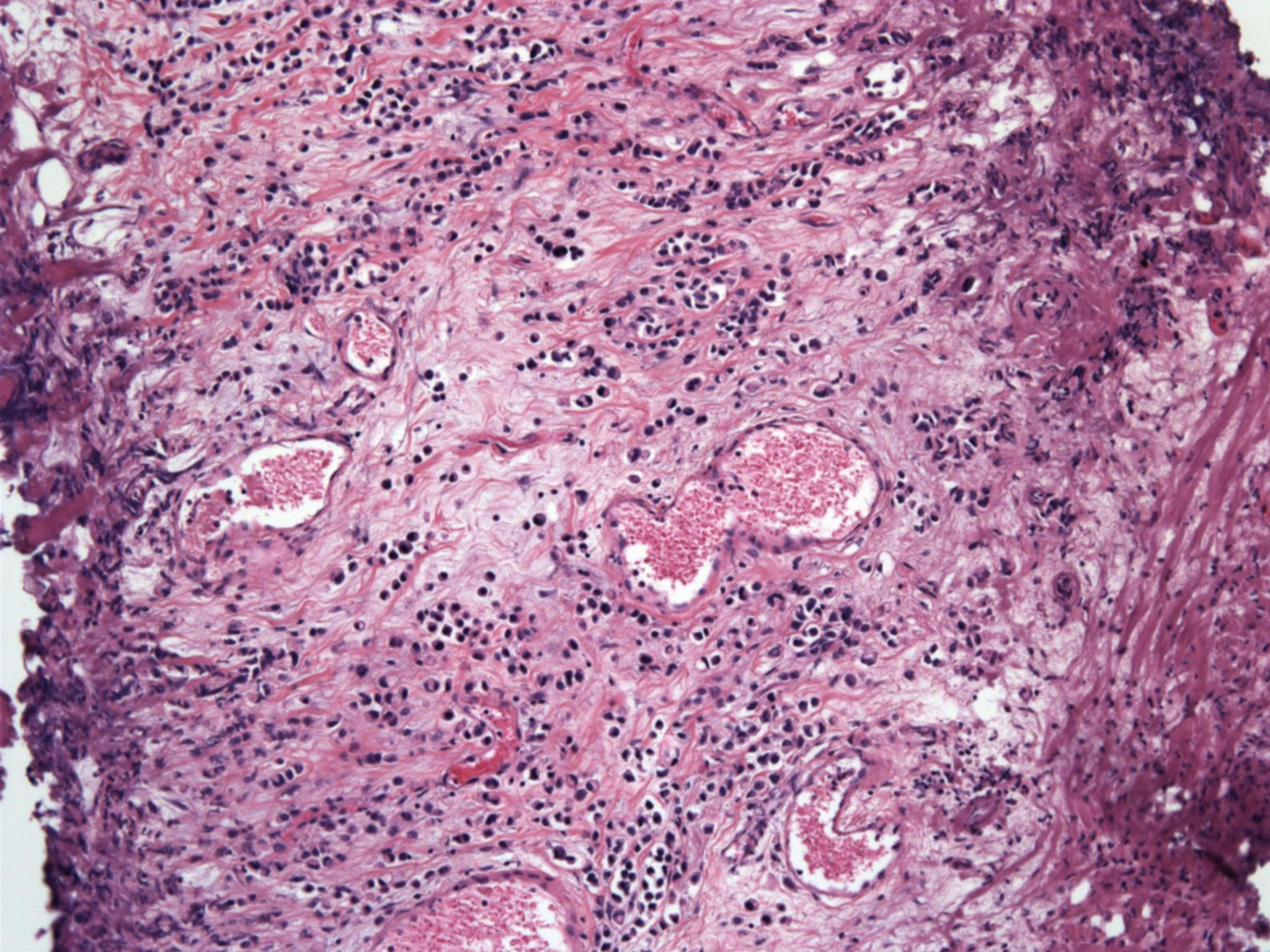


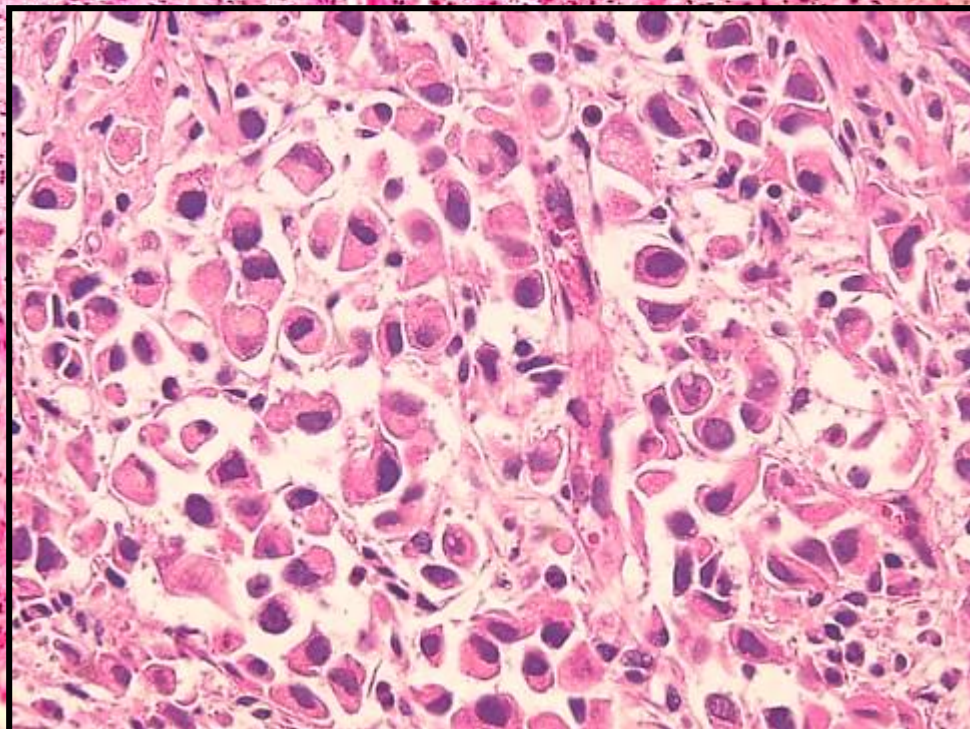
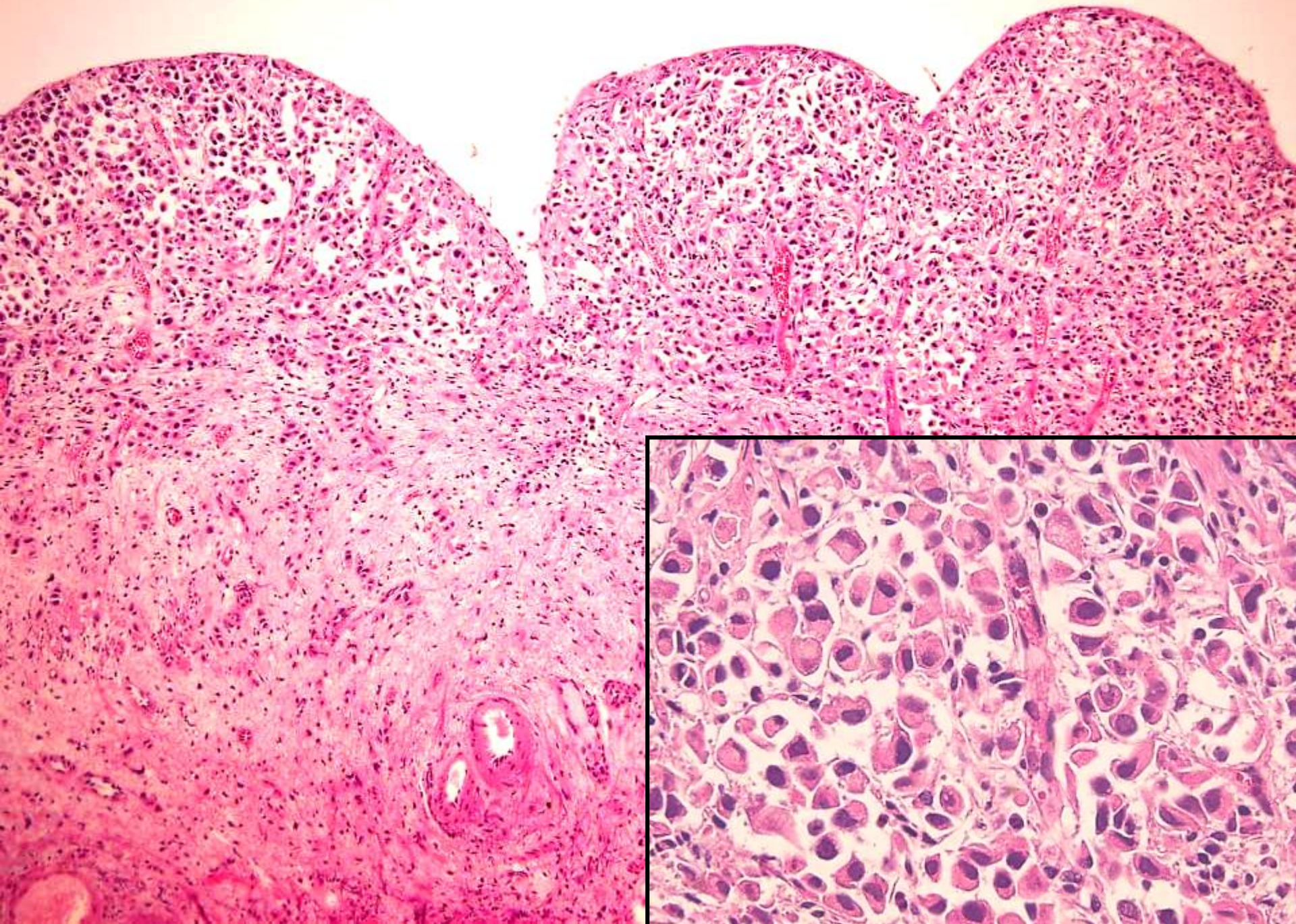
Plasmacytoid Urothelial Carcinoma

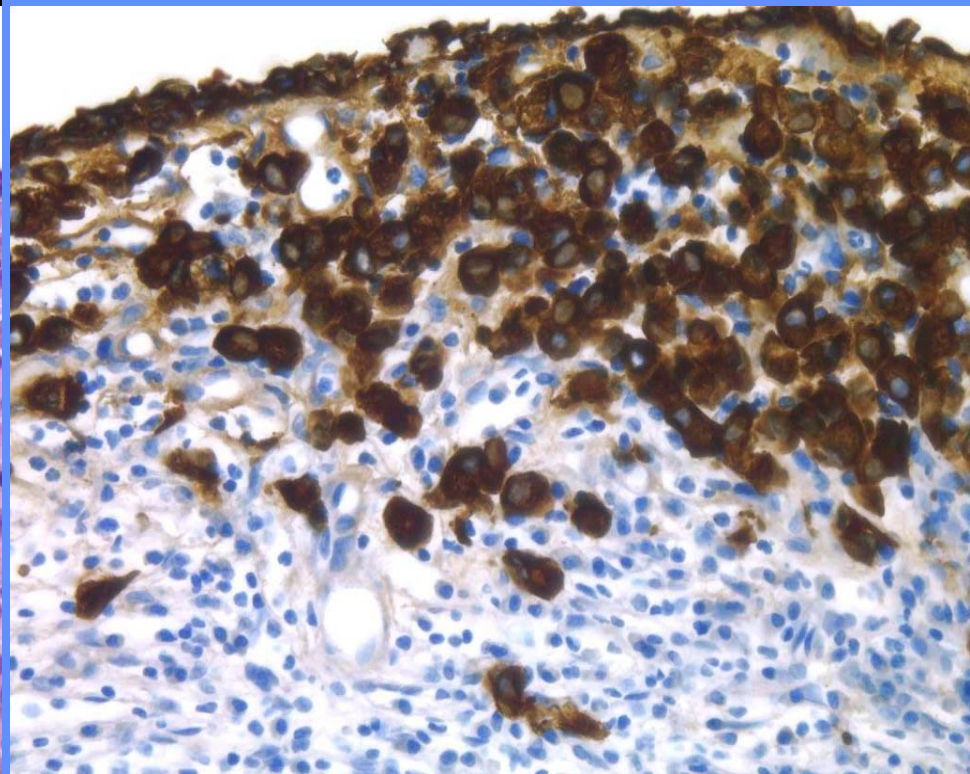
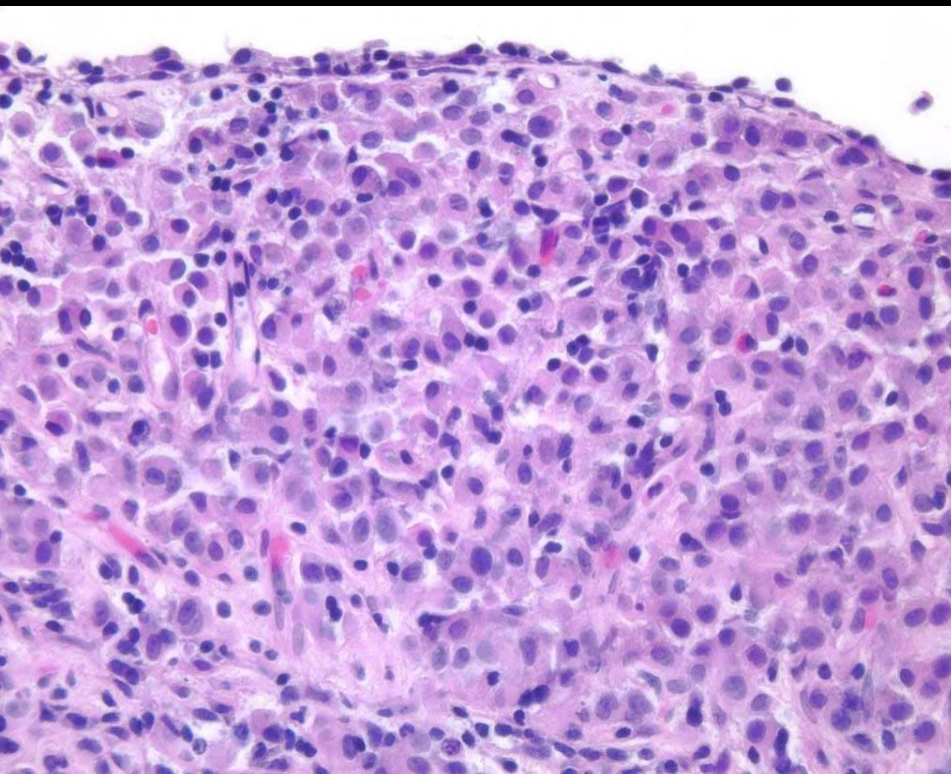
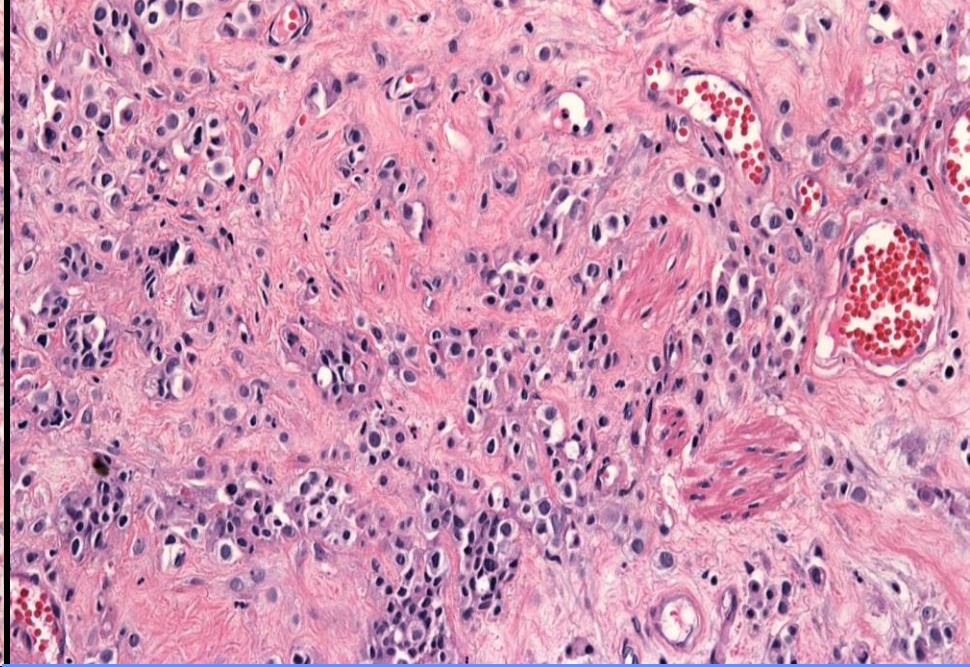
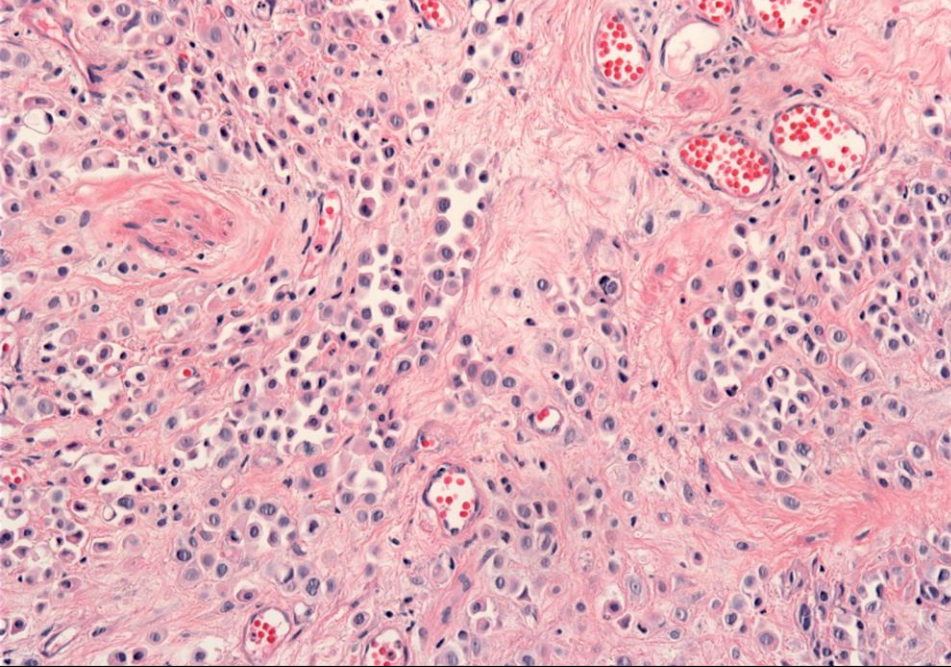
Plasmacytoid UCa now includes signet ring cell carcinoma without extracellular mucin





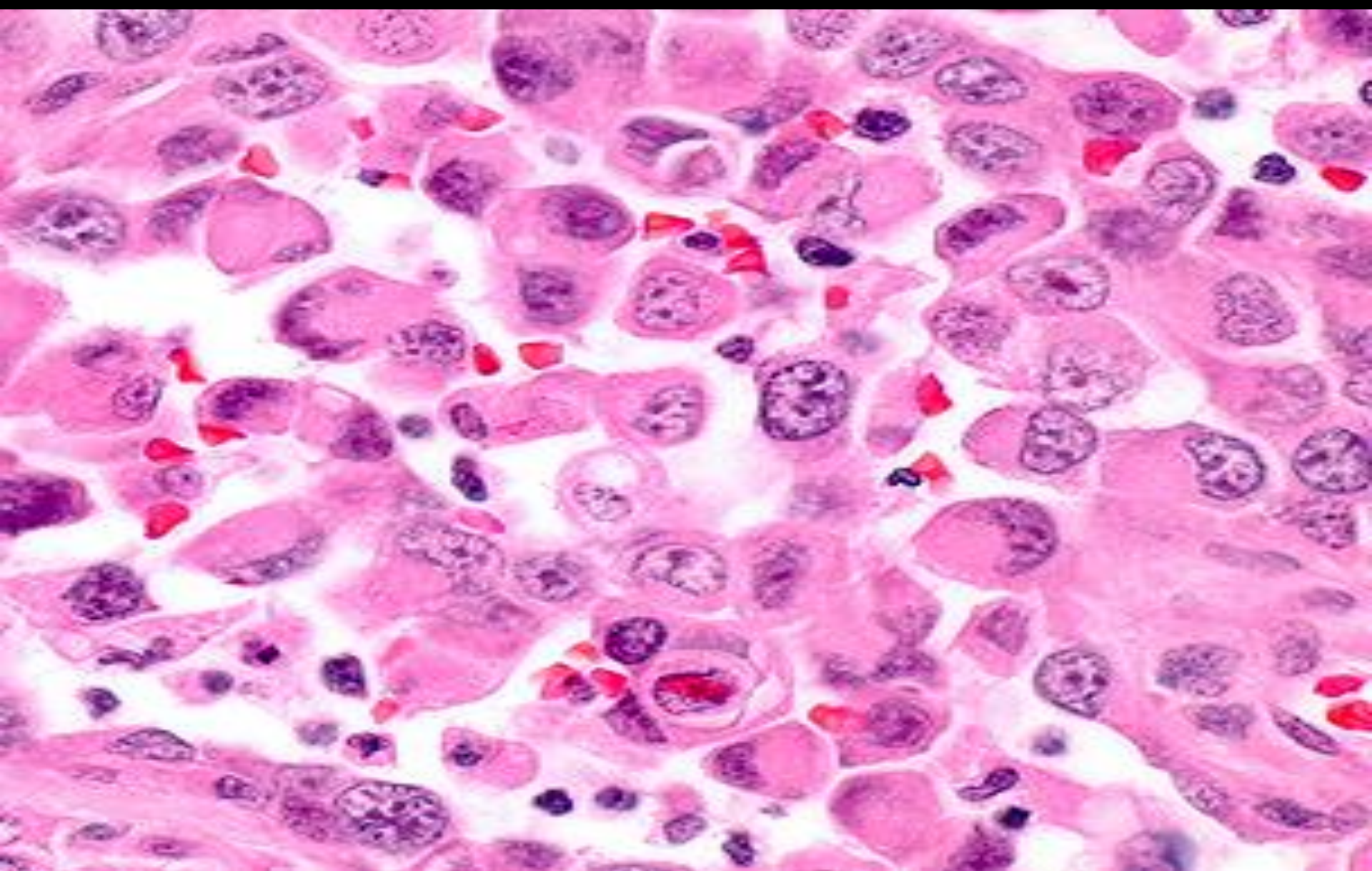


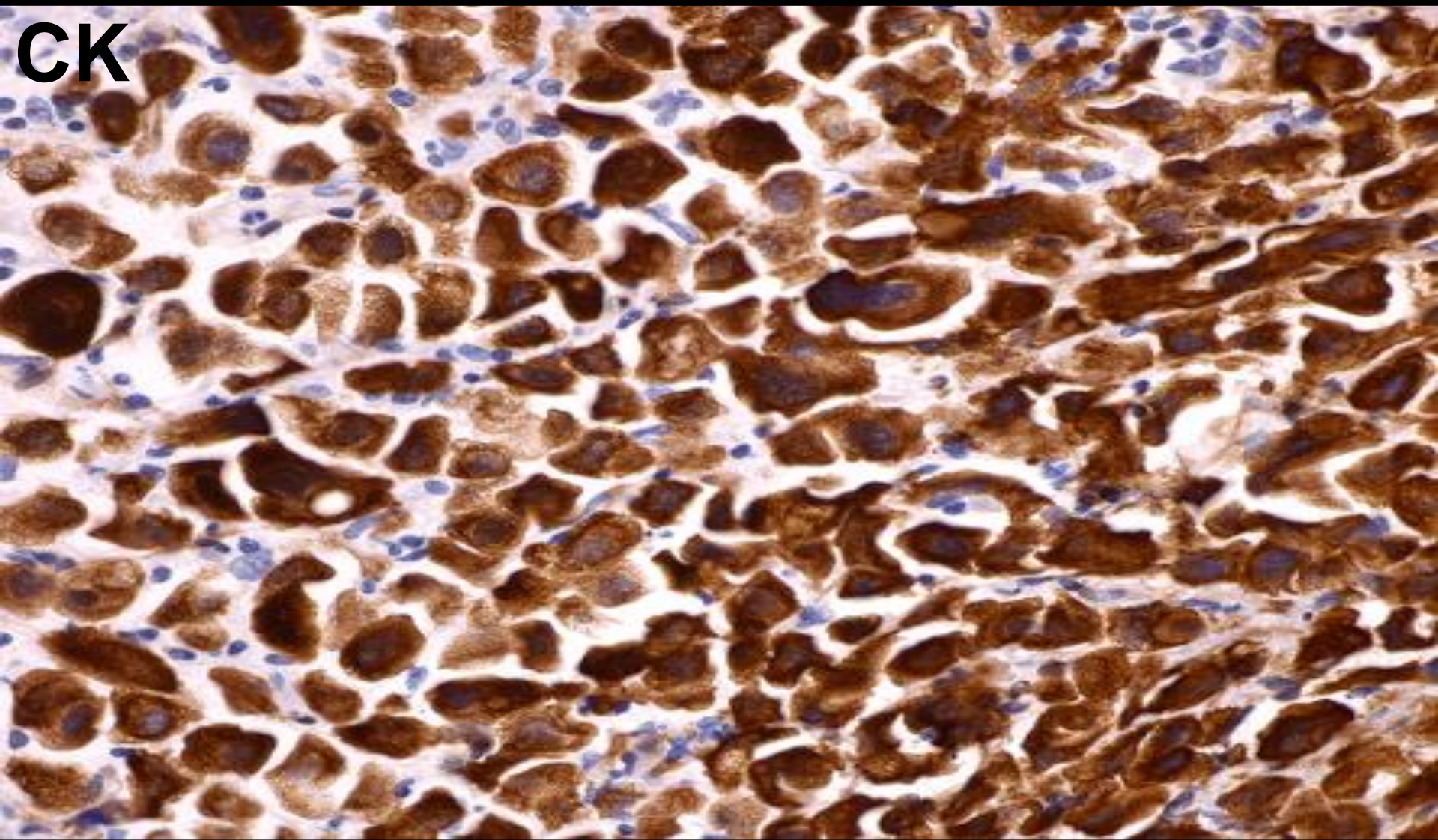


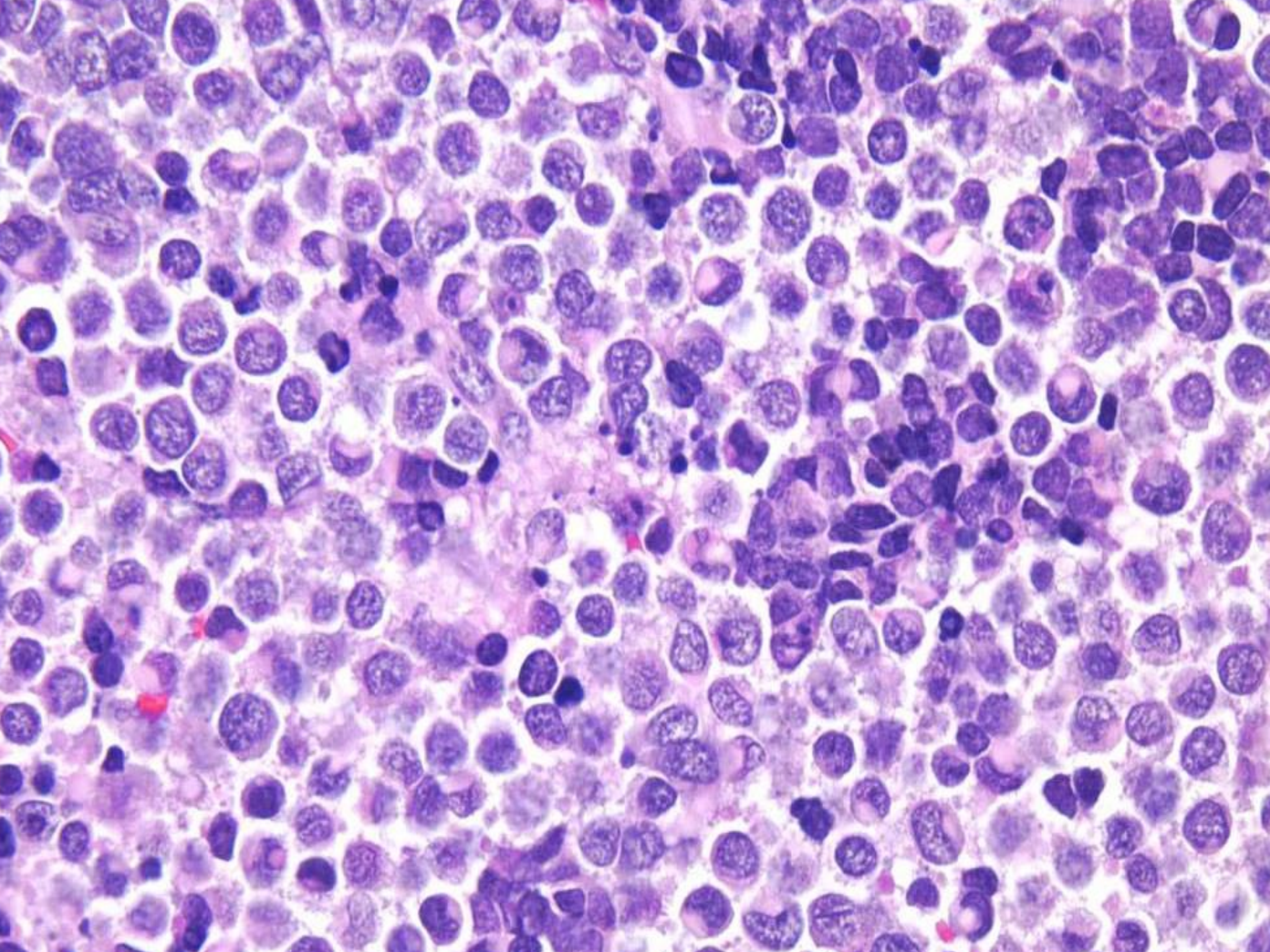


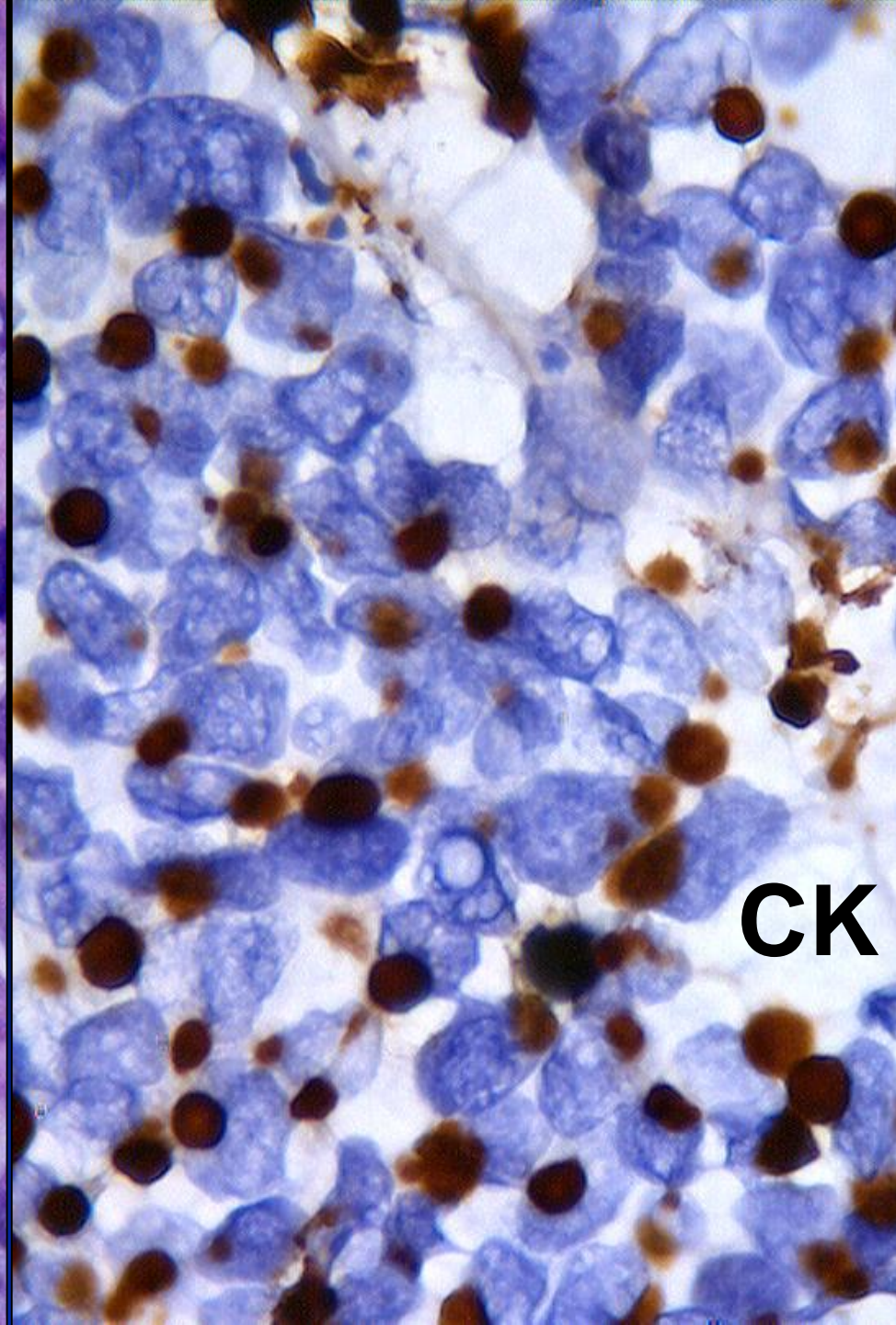
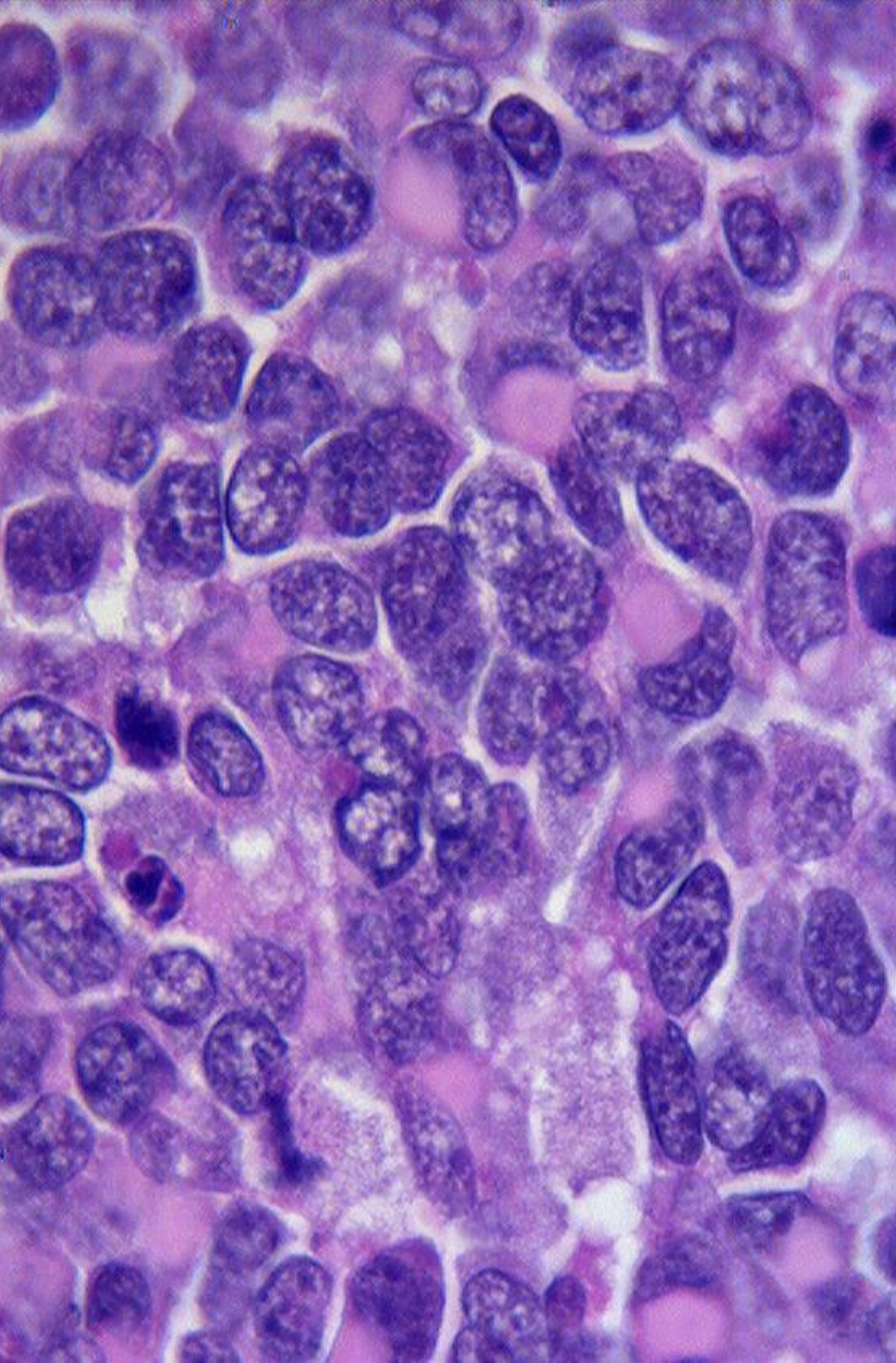
U Ca. WITH RHABDOID FEATURES

- Large discohesive cells with vesicular nuclei, +/- prominent nucleoli, +/- inclusions
- Poor prognosis
- **Differential diagnosis**
 - *pure malignant rhabdoid tumor (INI 1+)*
 - *Other undifferentiated malignancies (e.g. melanoma)*





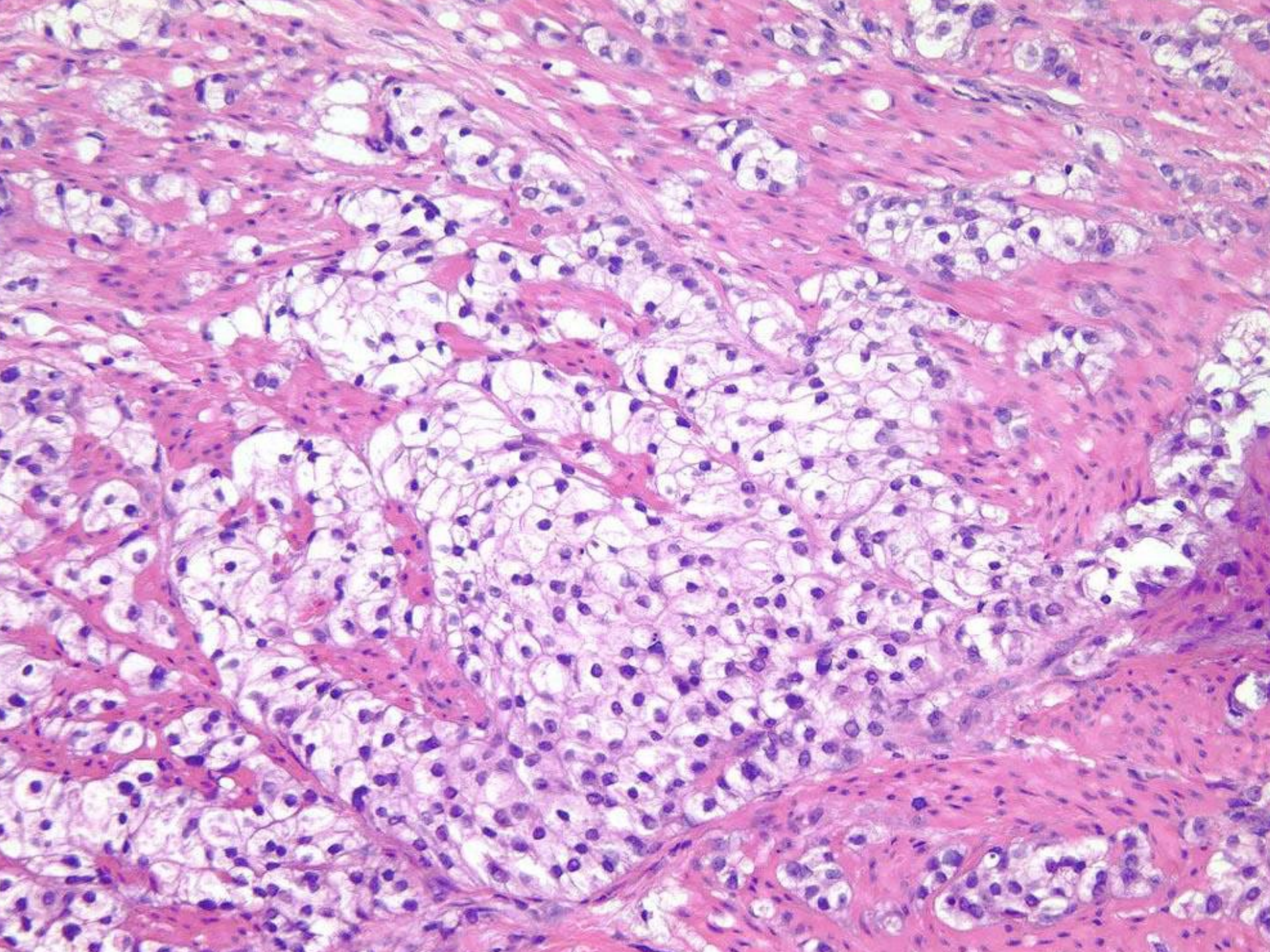


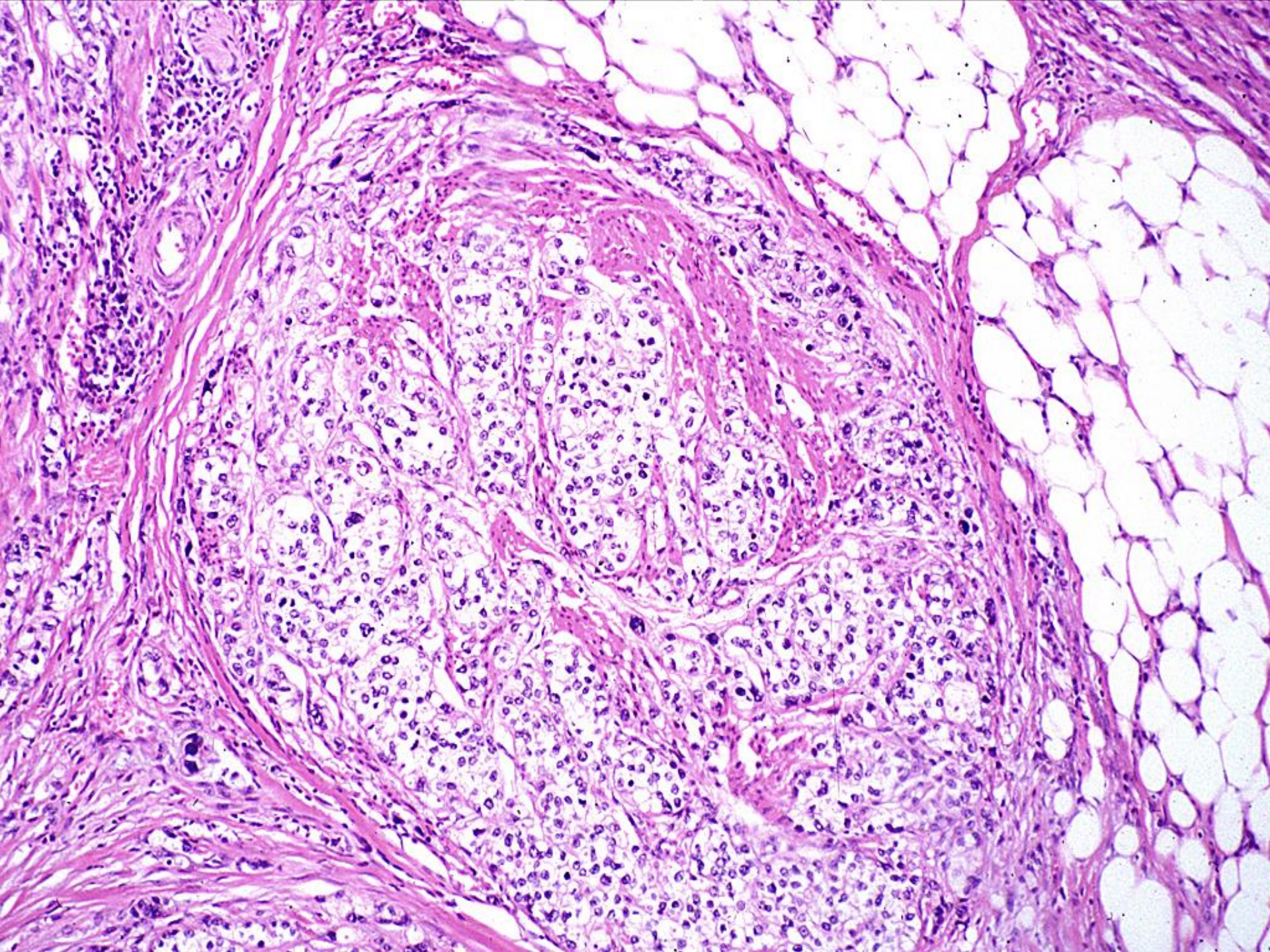


CK

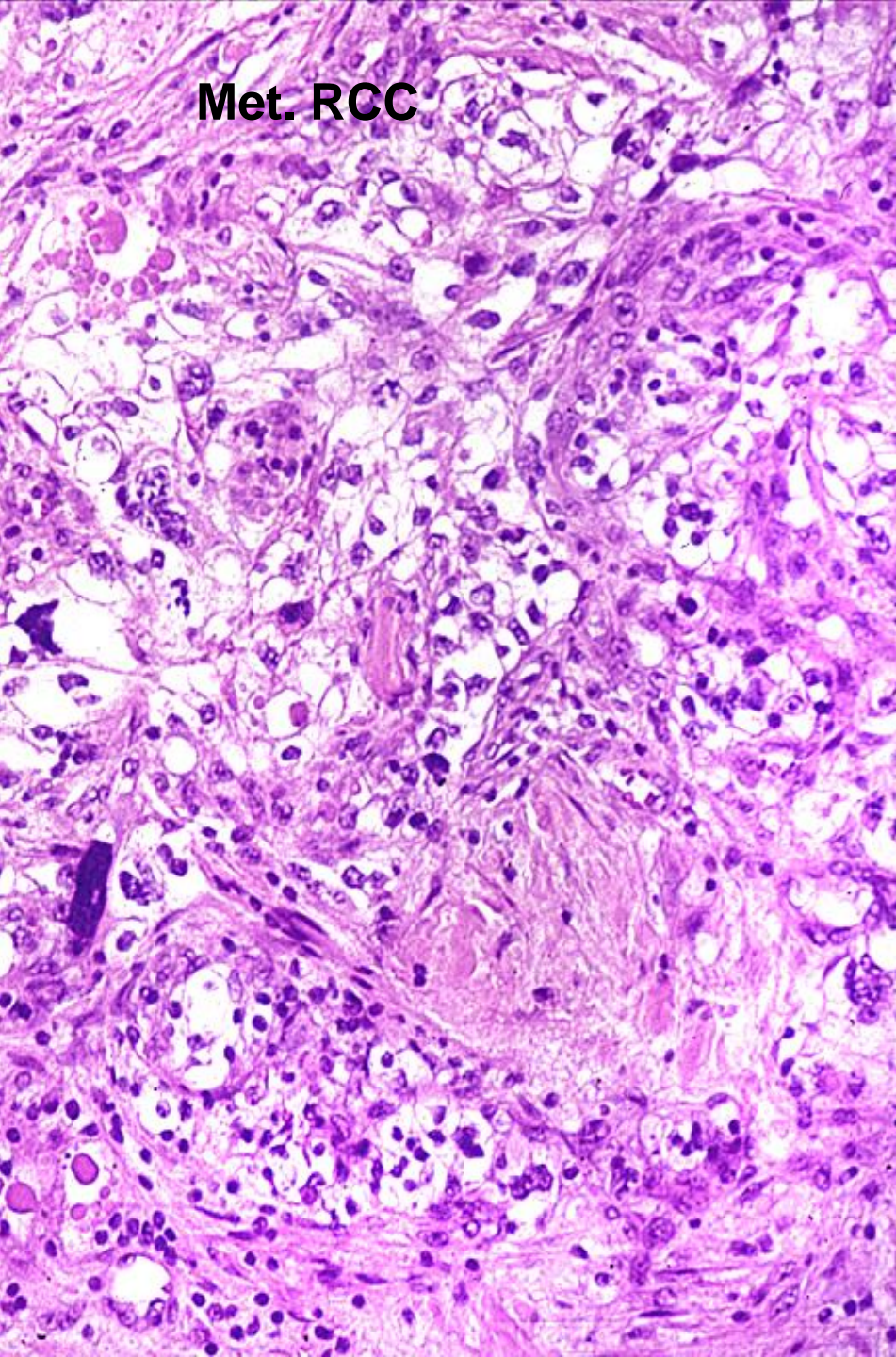
U Ca. WITH CLEAR CELLS

- U Ca. rich in glycogen
- **Differential diagnosis**
 - *Clear cell carcinoma of bladder/urethra*
 - *Metastatic renal cell carcinoma*
 - *Metastatic prostate cancer*
 - *Extension/metastasis from gynecologic primary*

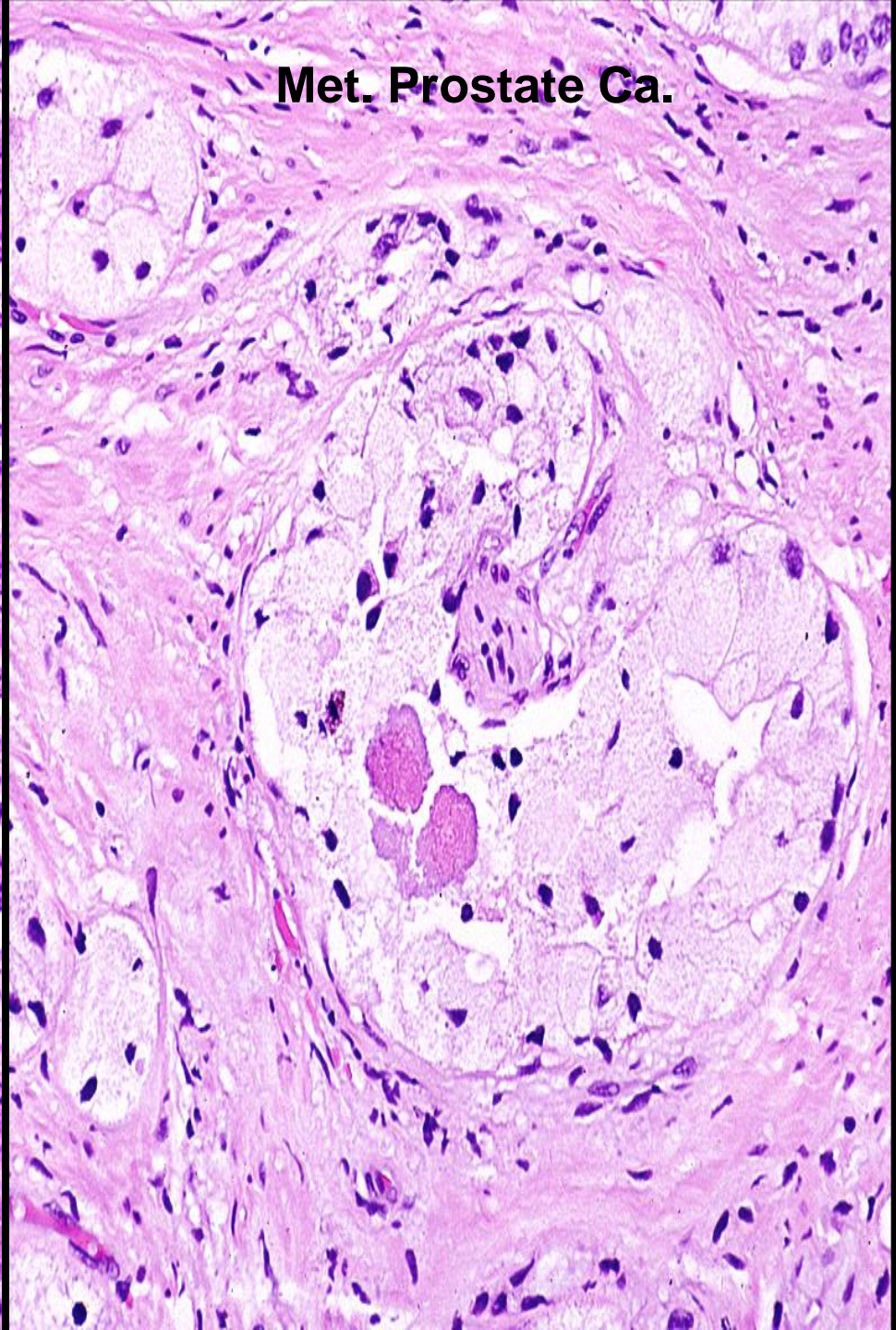




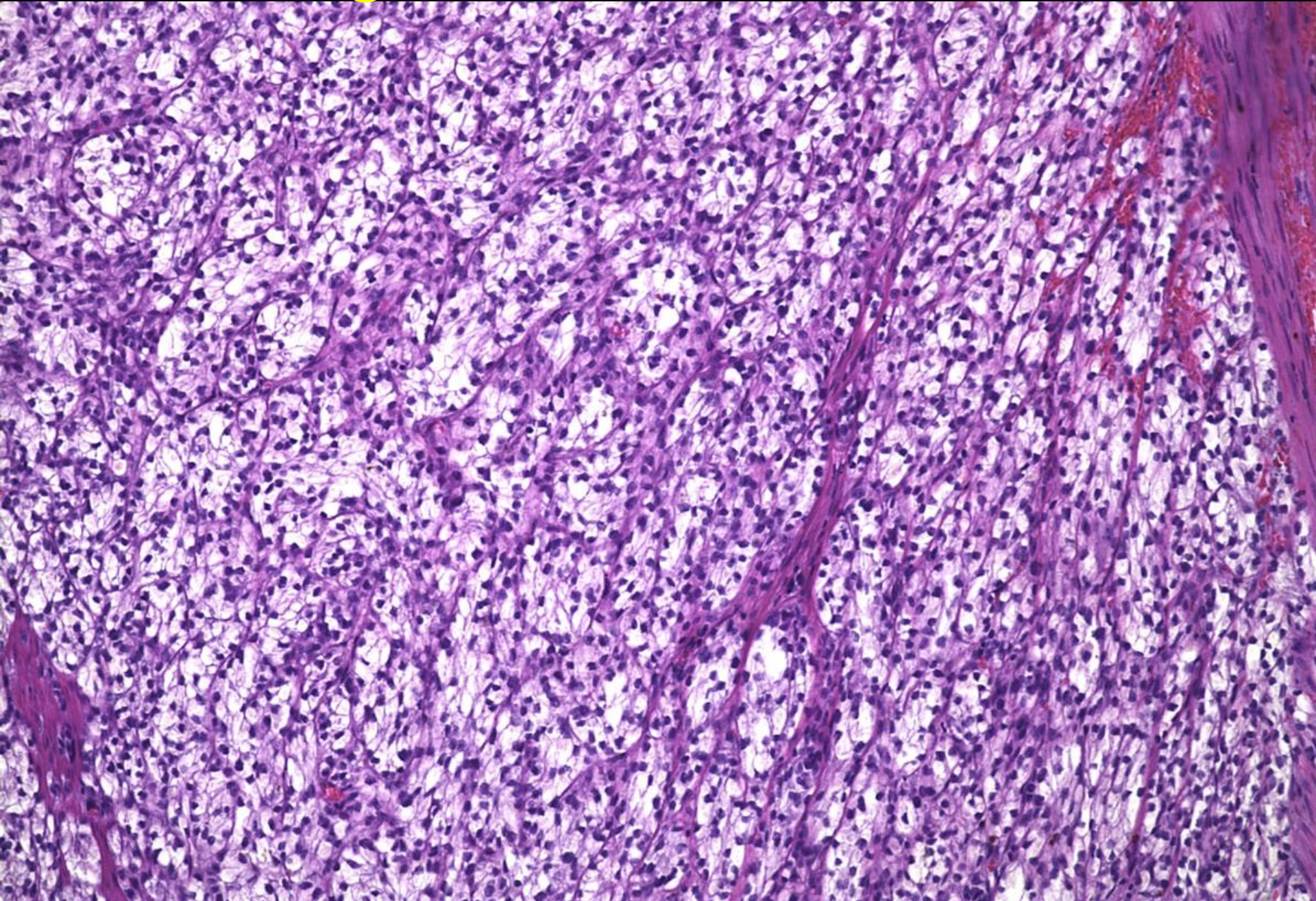
Met. RCC



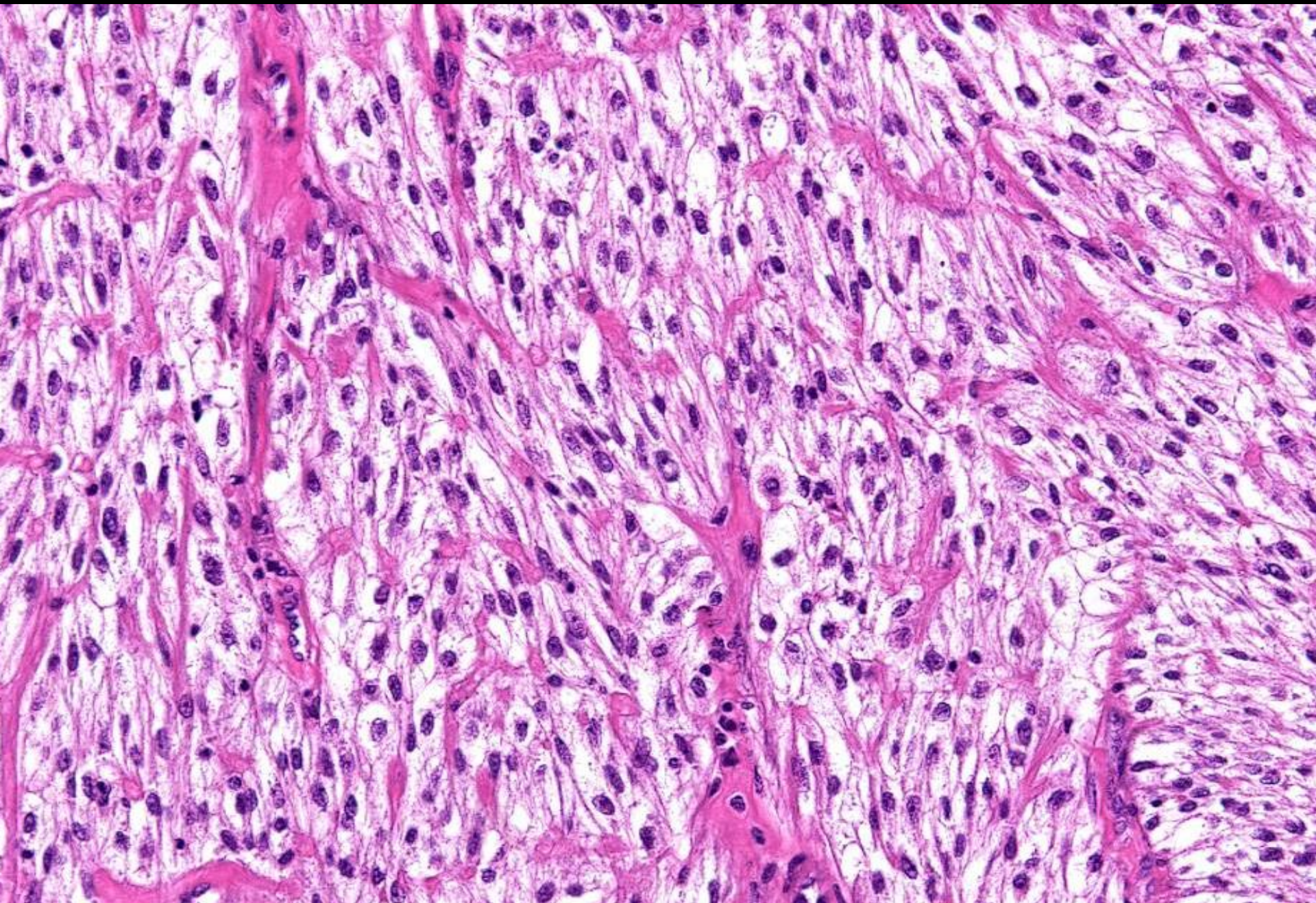
Met. Prostate Ca.



Prim. Malignant Melanoma invol. bladder

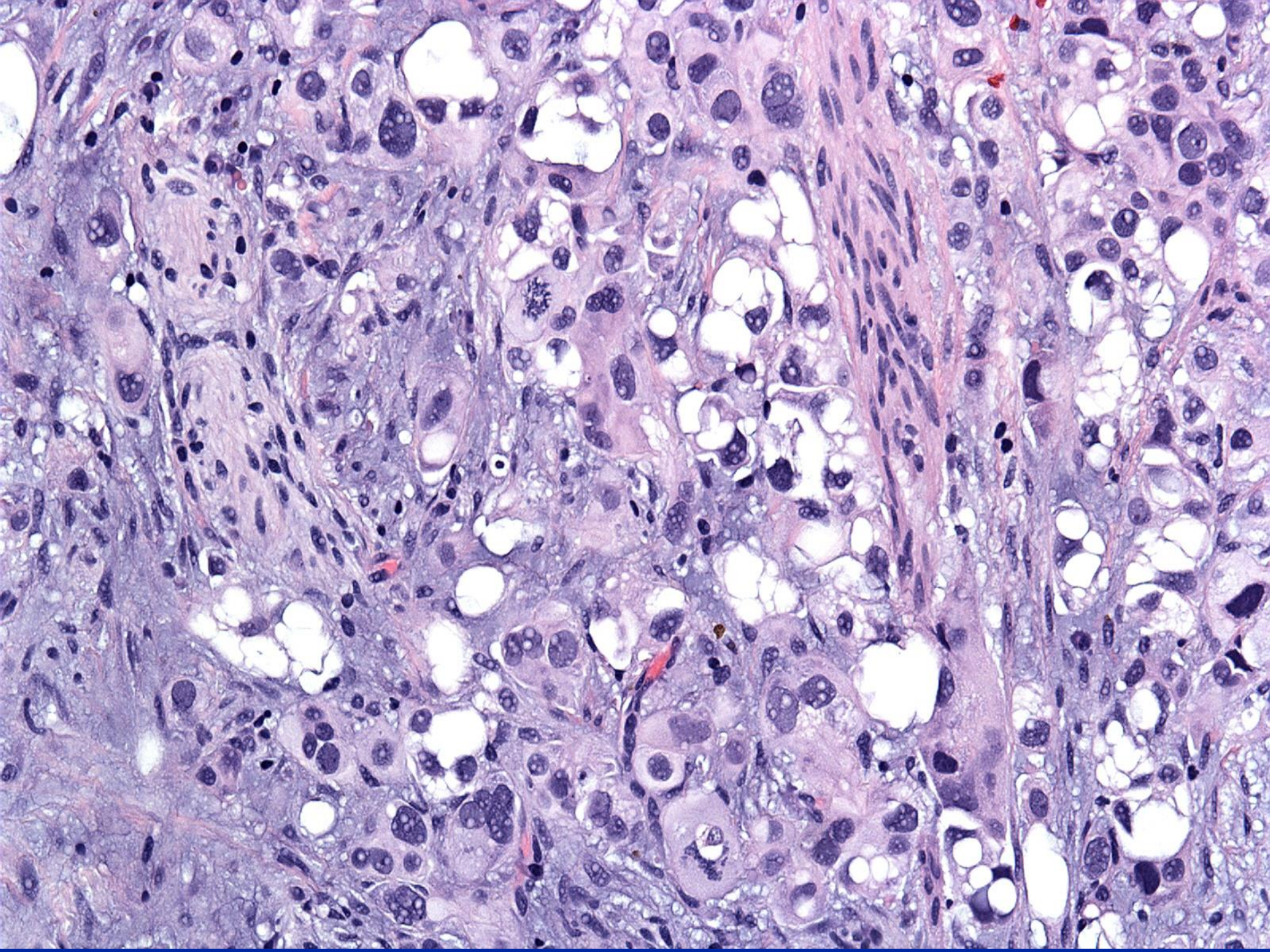


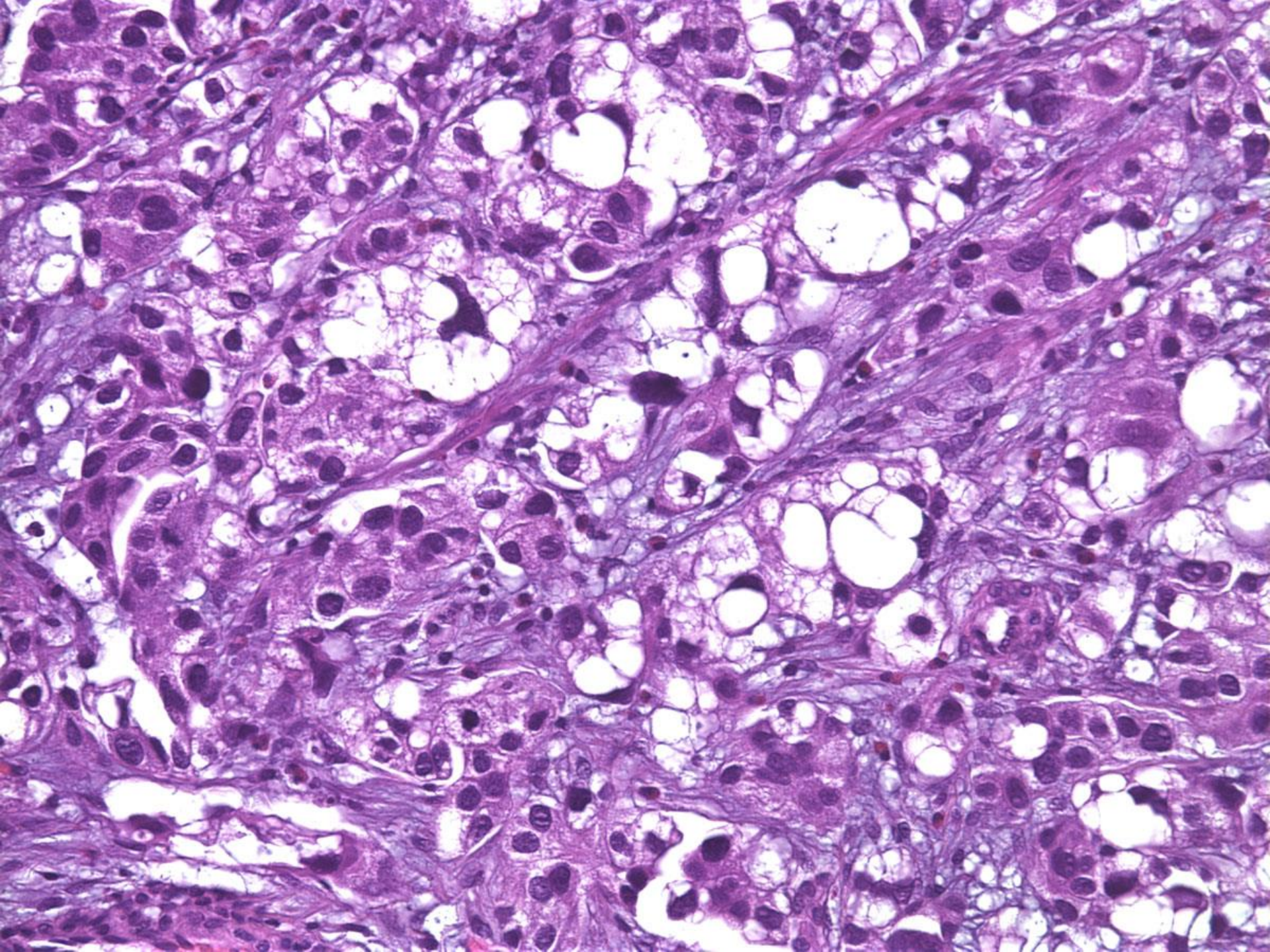
PEComa

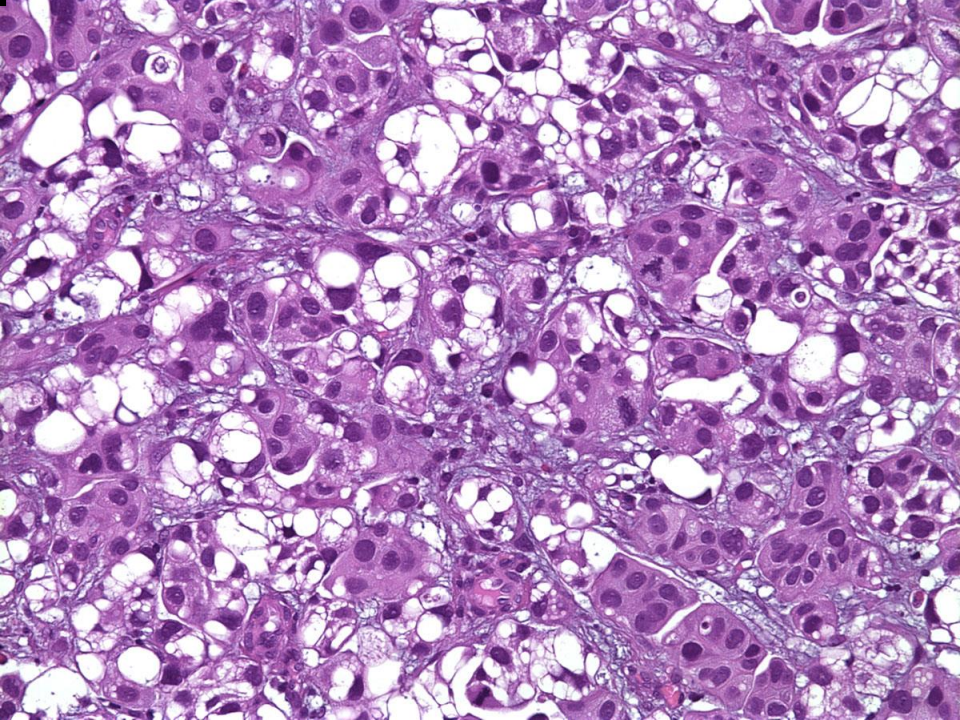
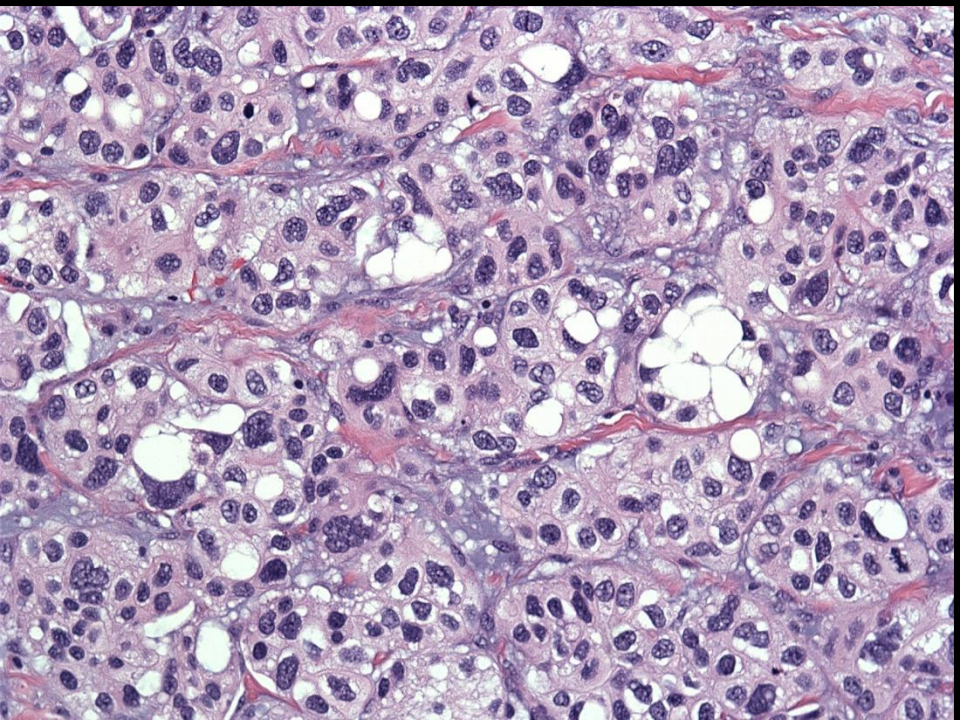
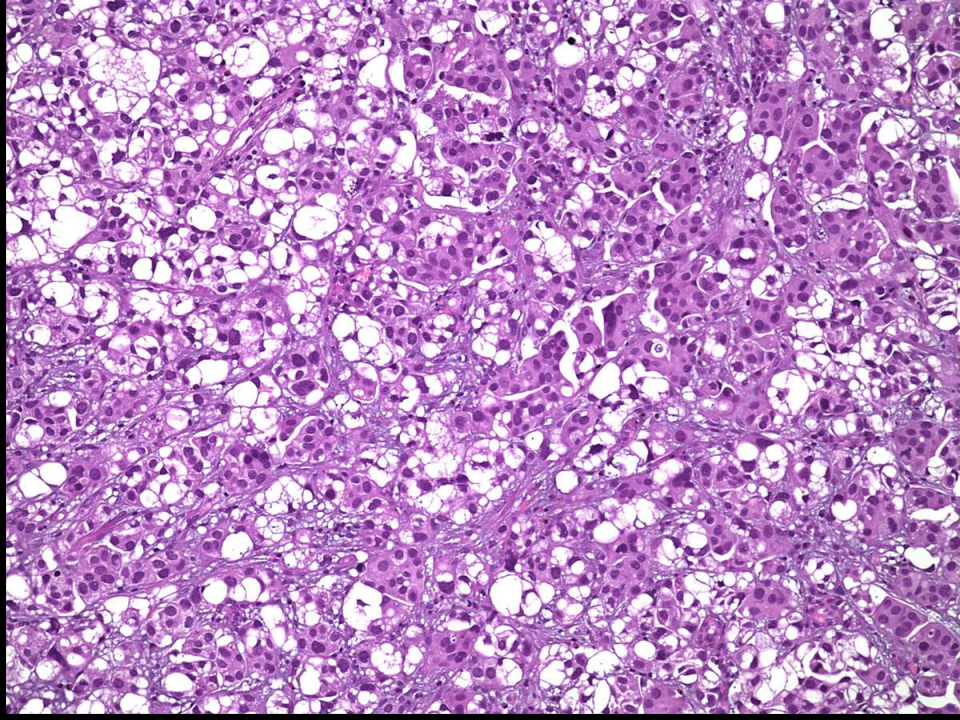
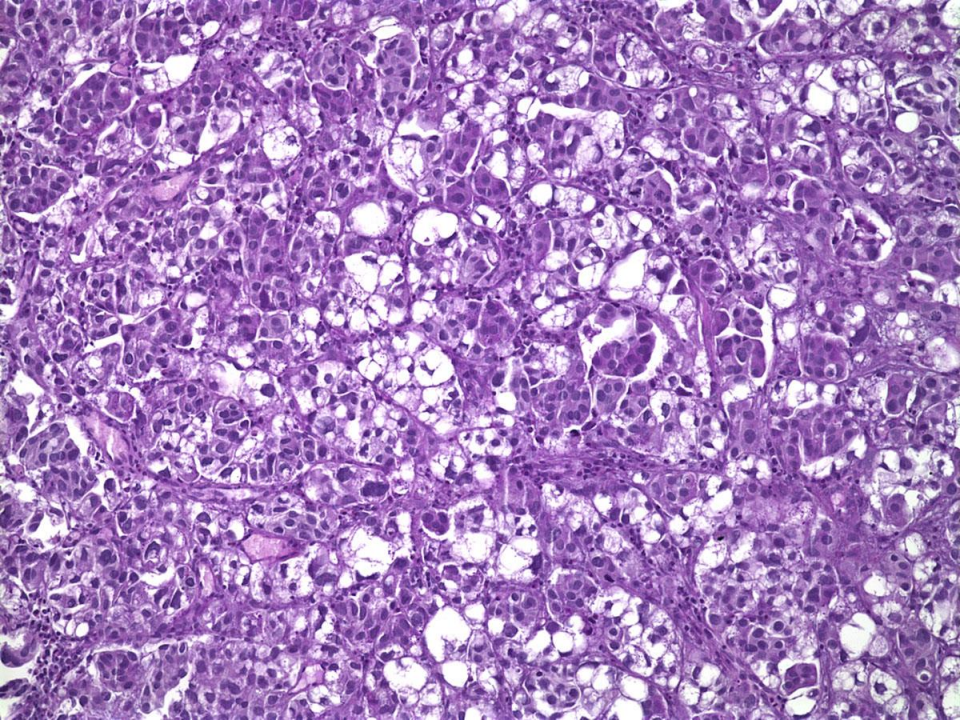


UROTHELIAL CARCINOMA WITH LIPID

- Usually focal in invasive U Ca. : 10-50% of tumor
- **Differential Diagnosis**
 - *signet ring cell component*
 - *liposarcomatous heterologous component*
- No known clinical significance

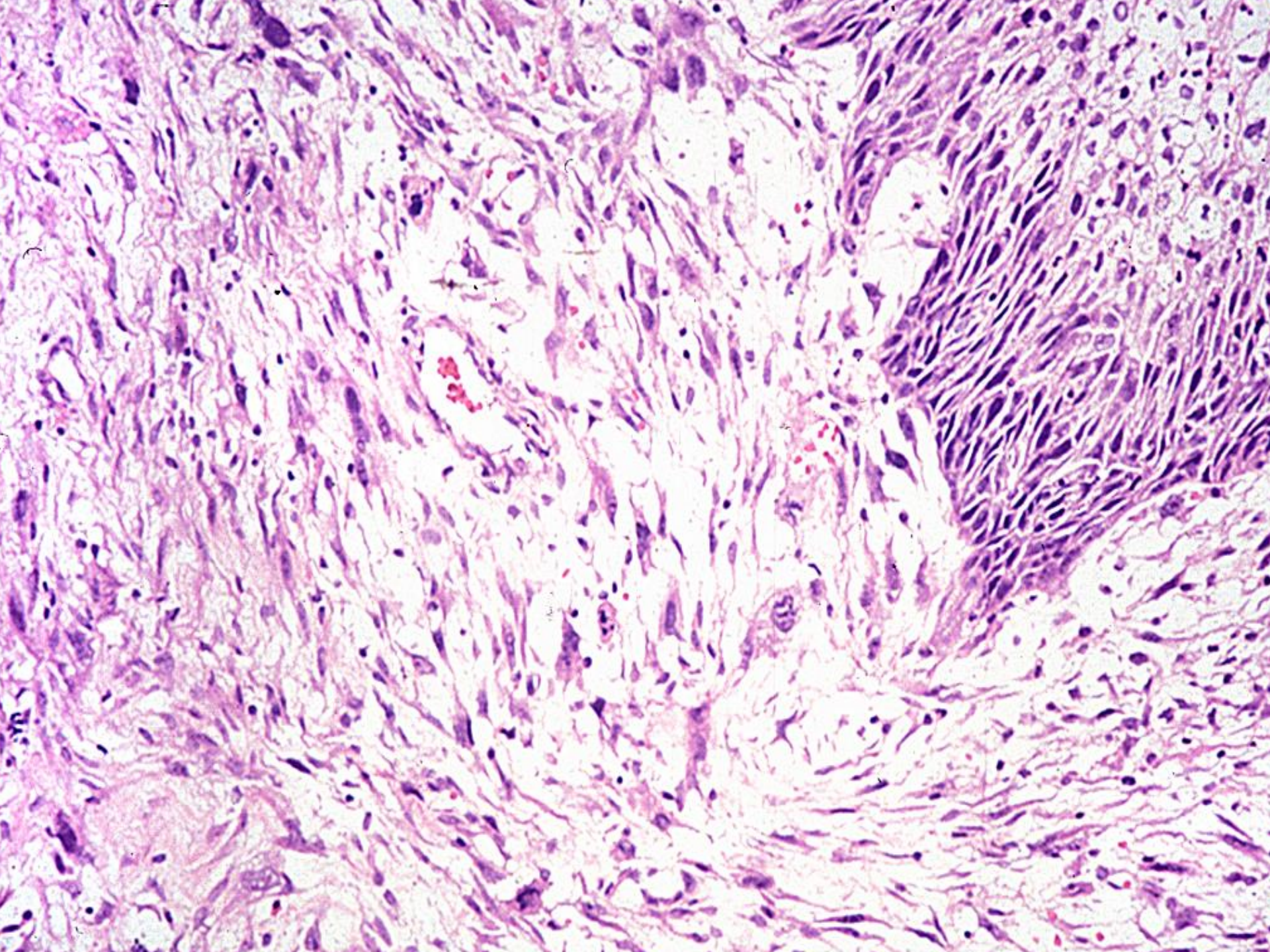


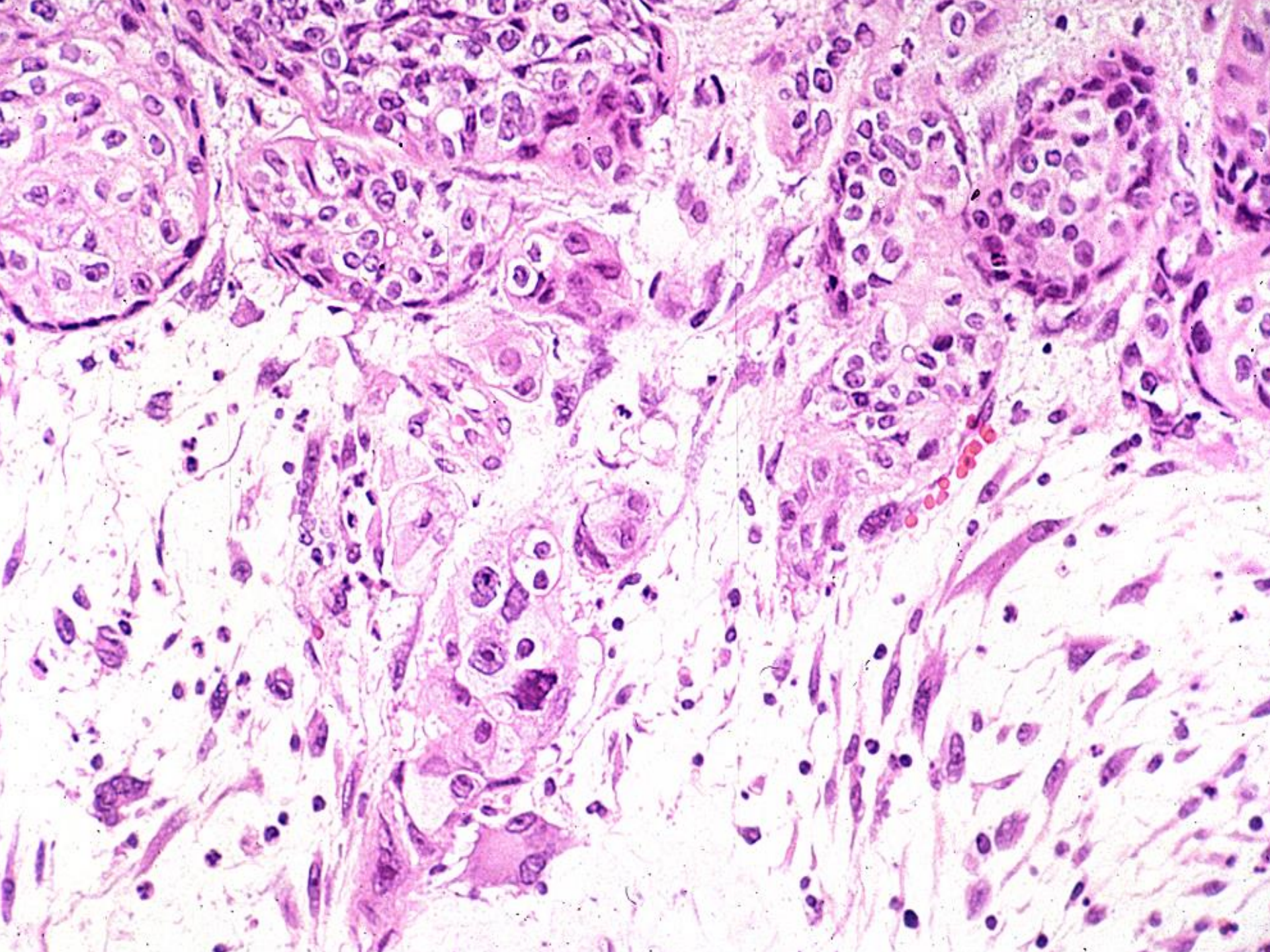


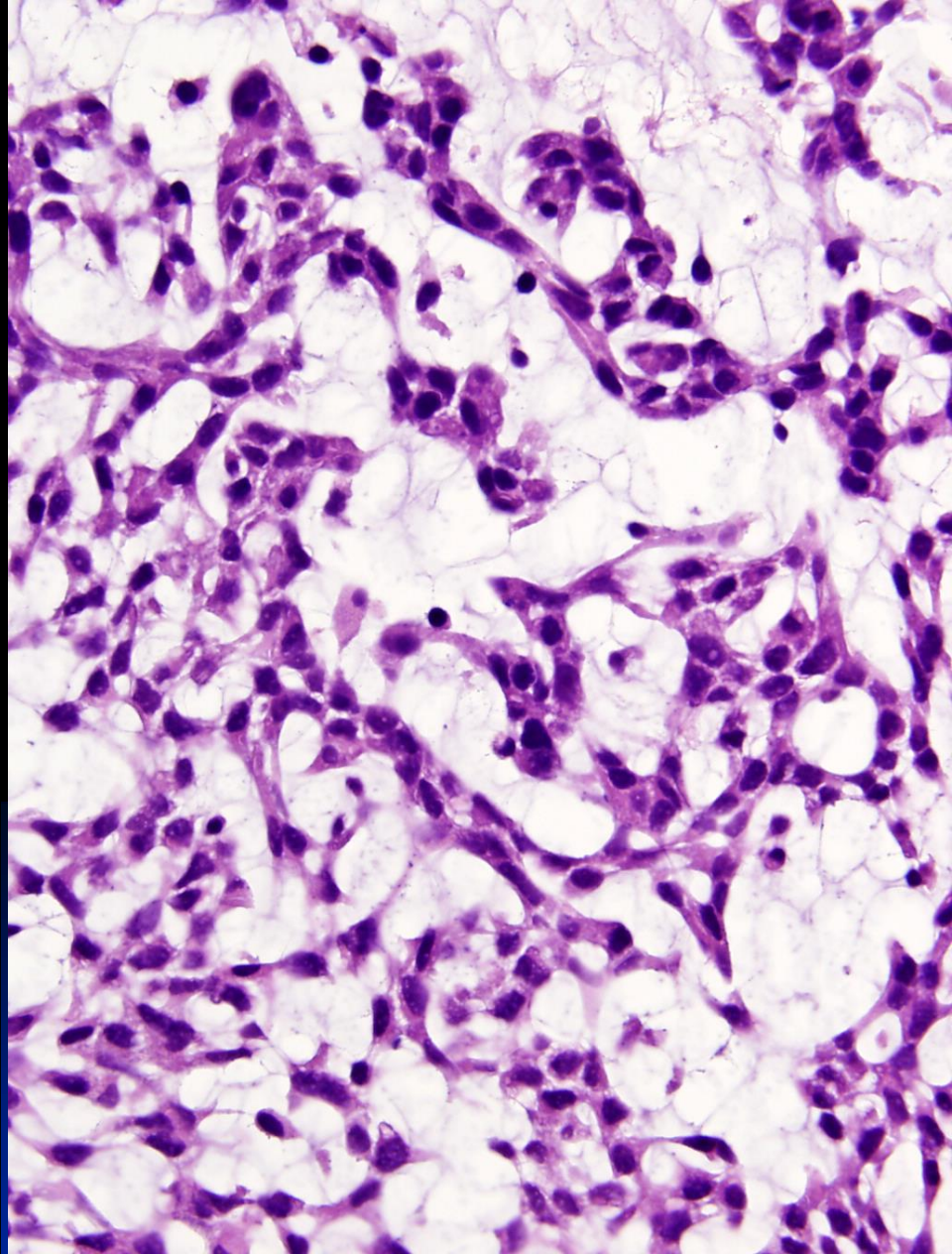
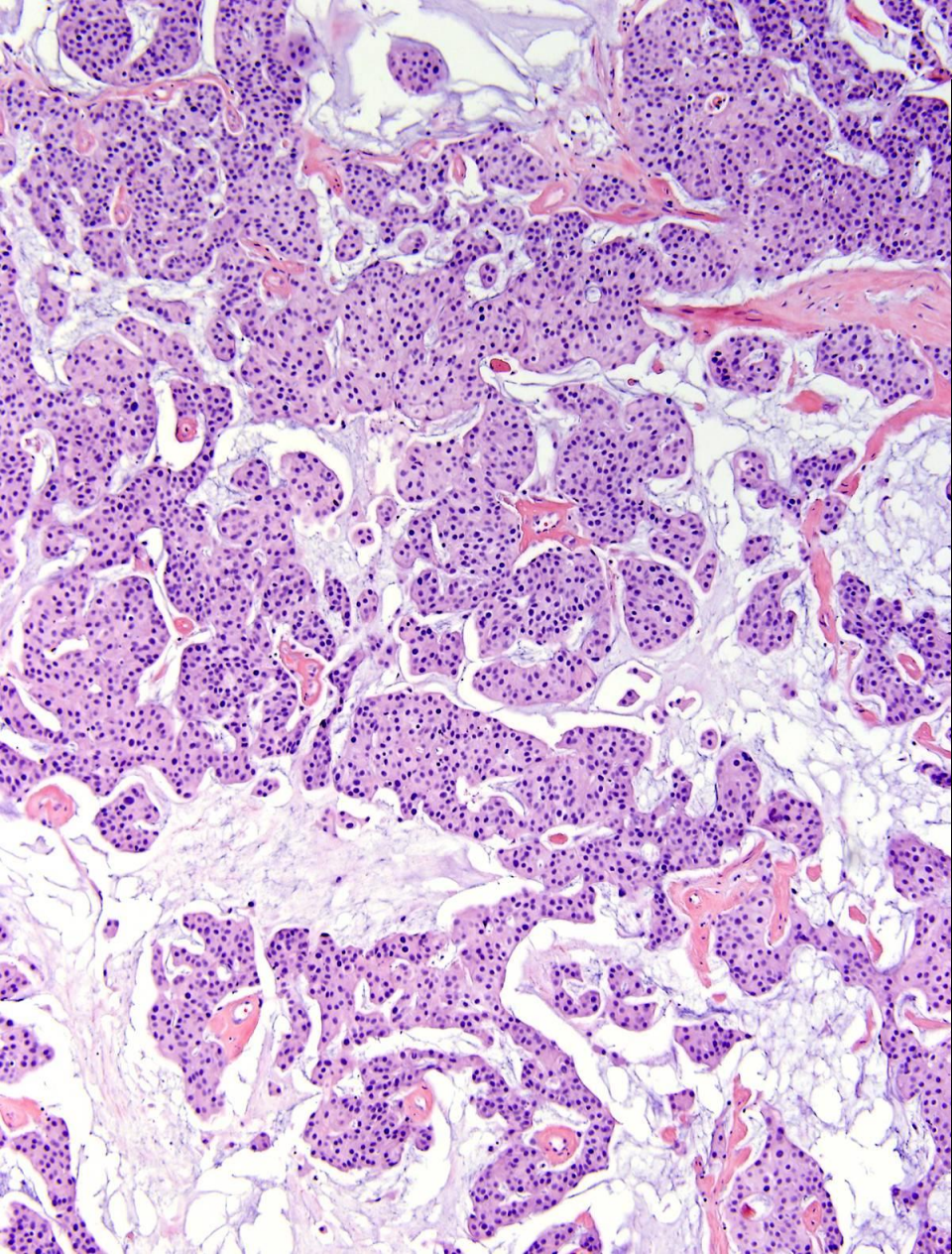


U Ca. WITH UNUSUAL STROMAL REACTIONS

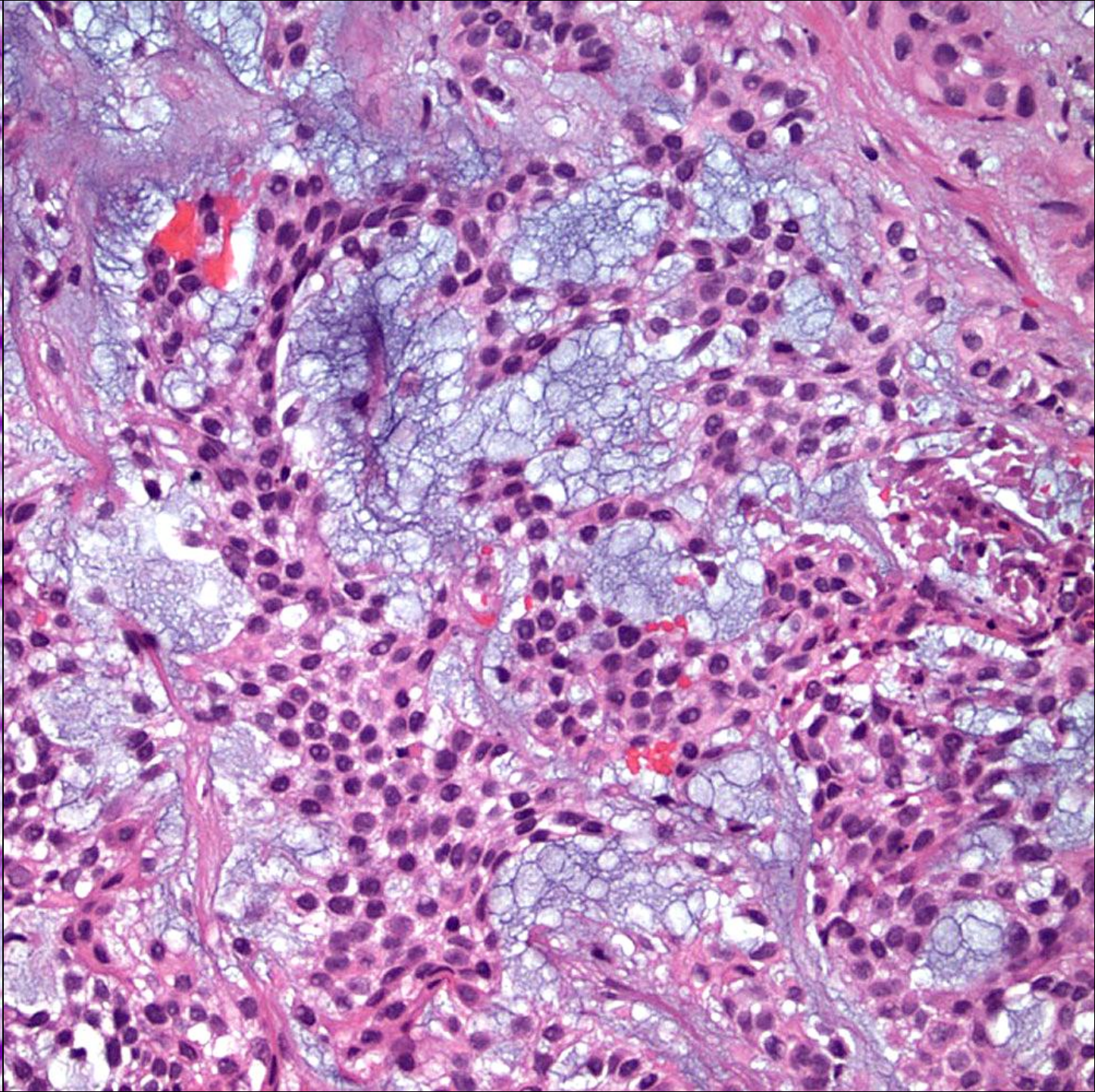
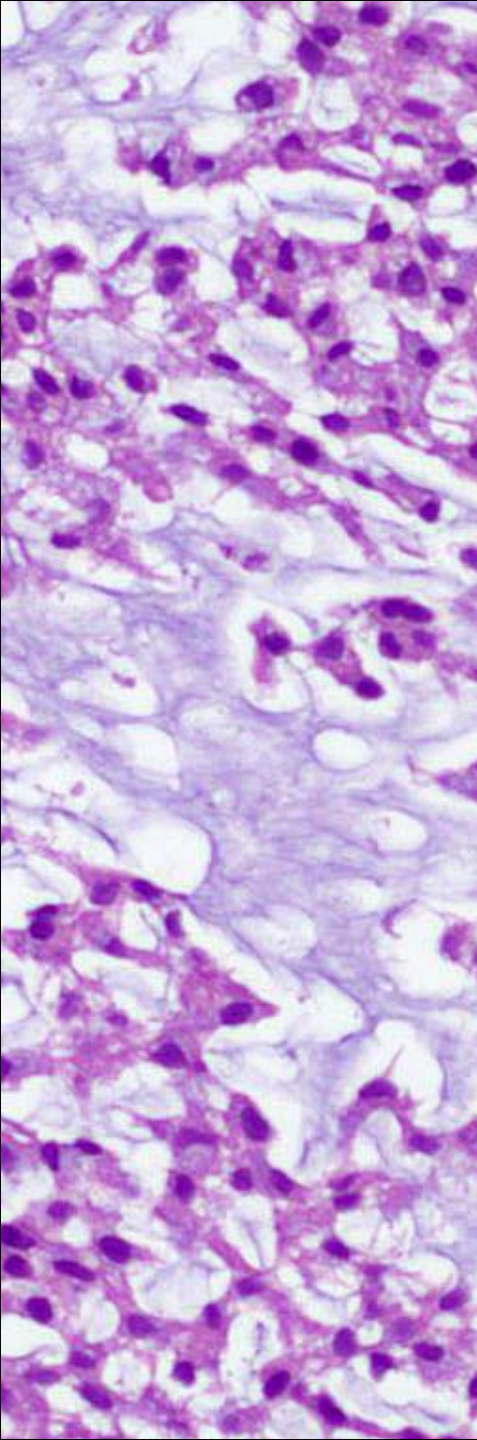
- **Pseudosarcomatous stroma**
- **Myxoid stroma**
- **Chondroid/osseous metaplasia**
- **Osteoclast-like giant cells**

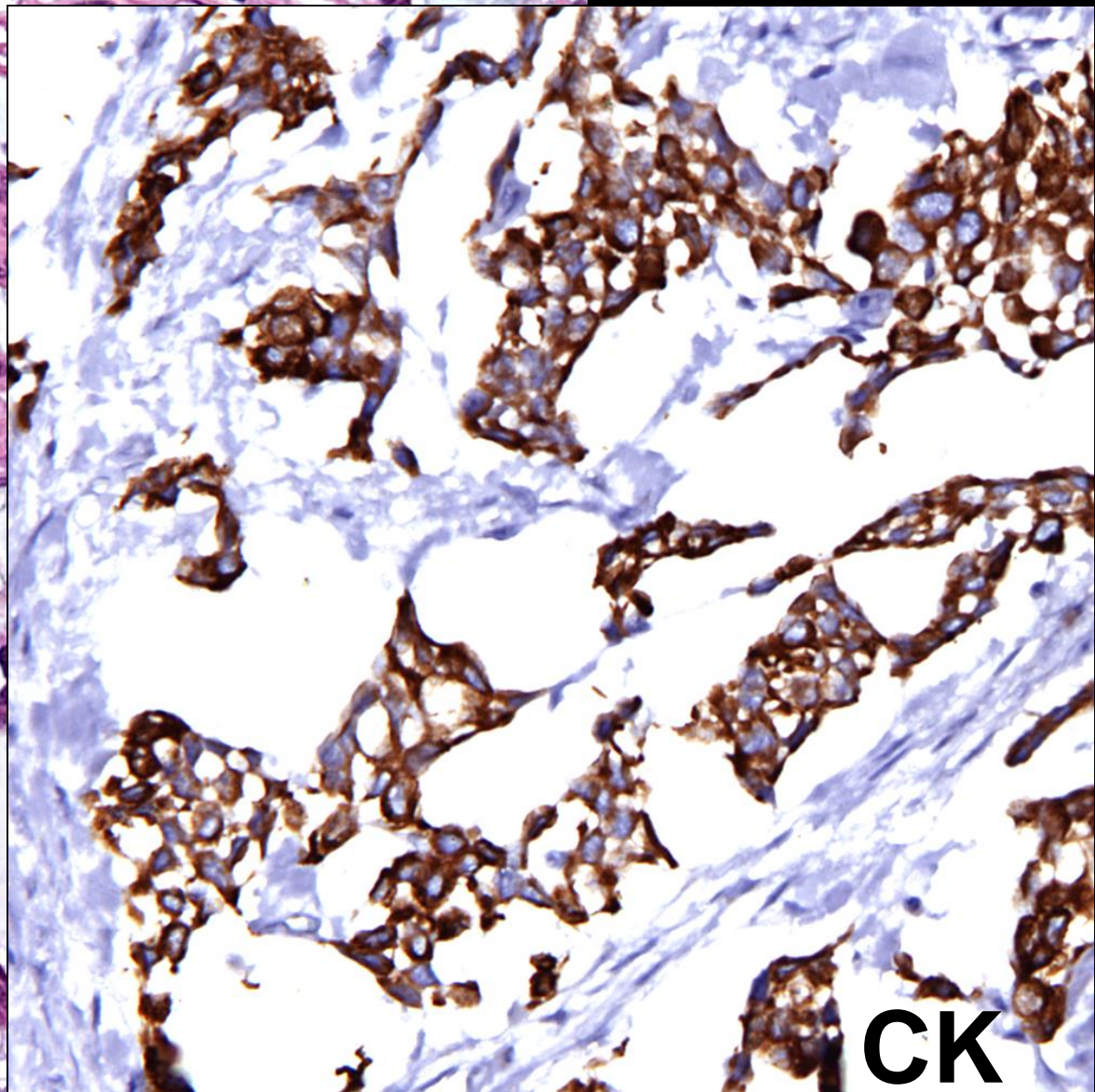
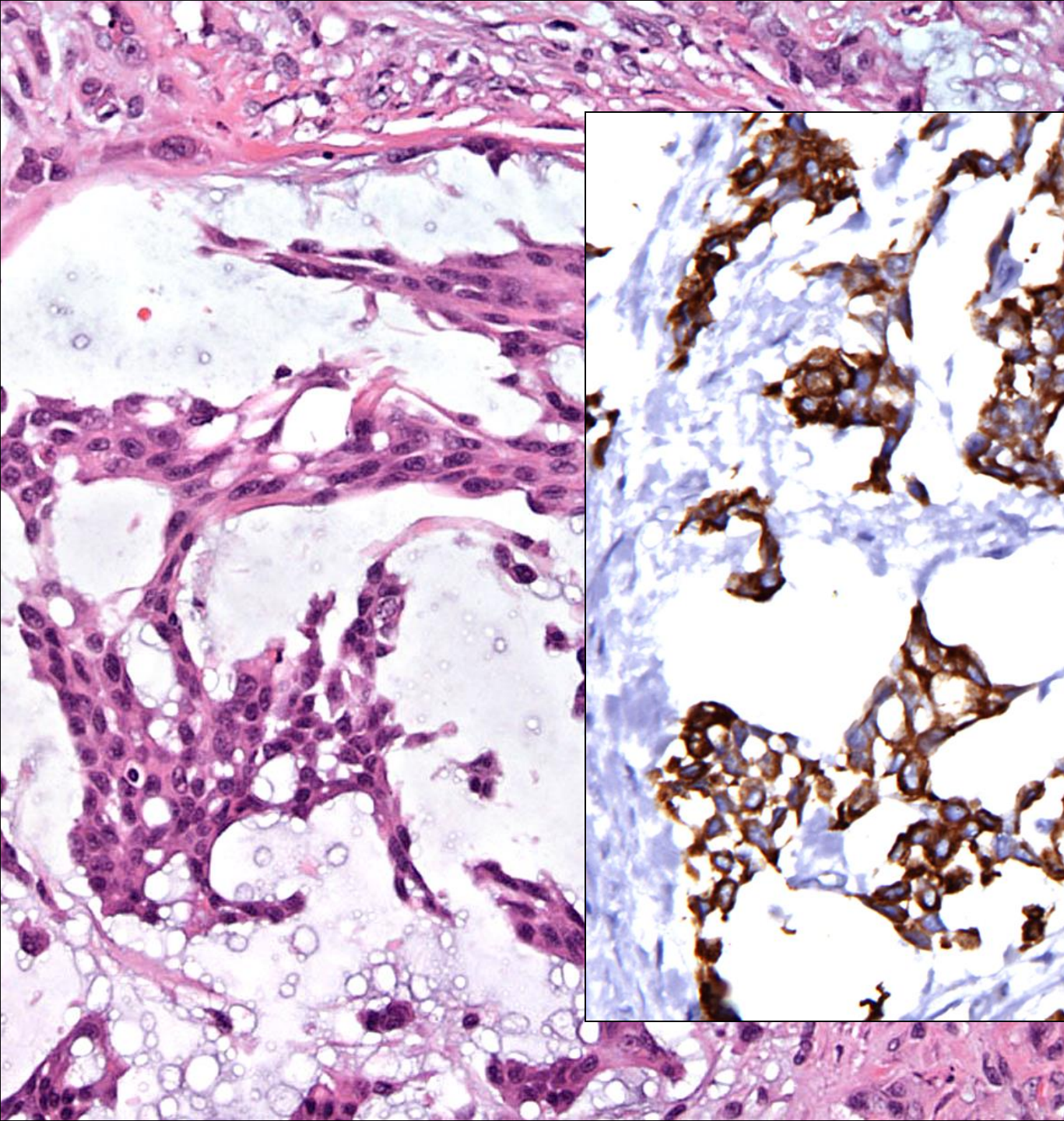






**UROTHELIAL CARCINOMA WITH MYXIOD STROMA :
“CHORDOID VARIANT”**





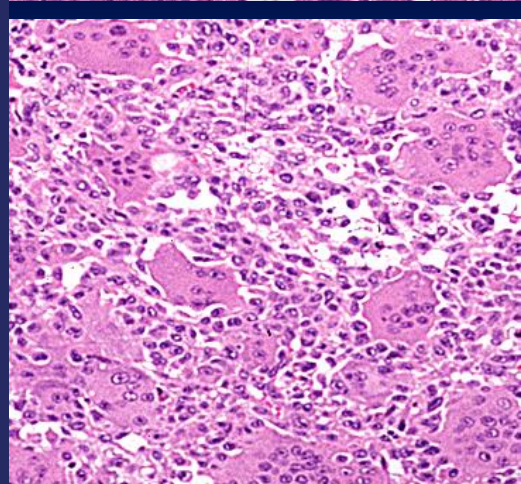
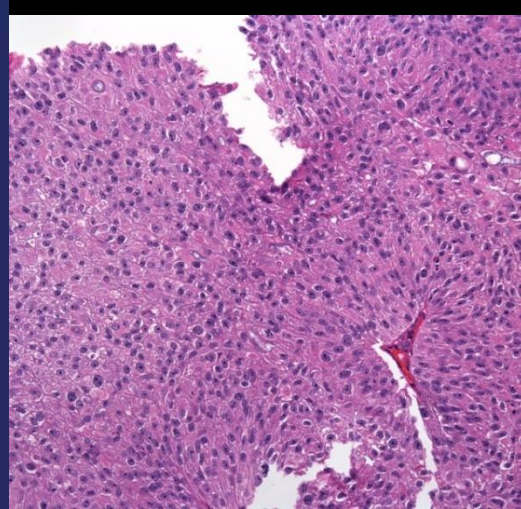
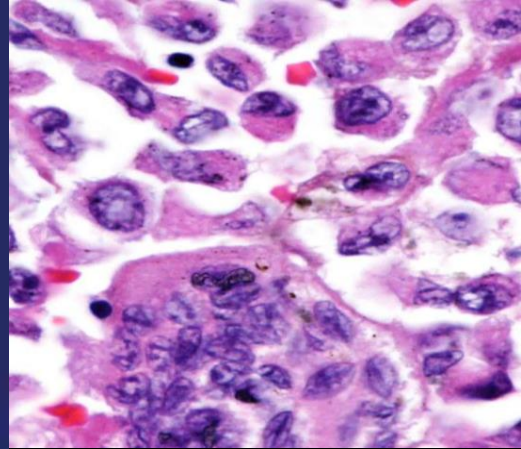
CK

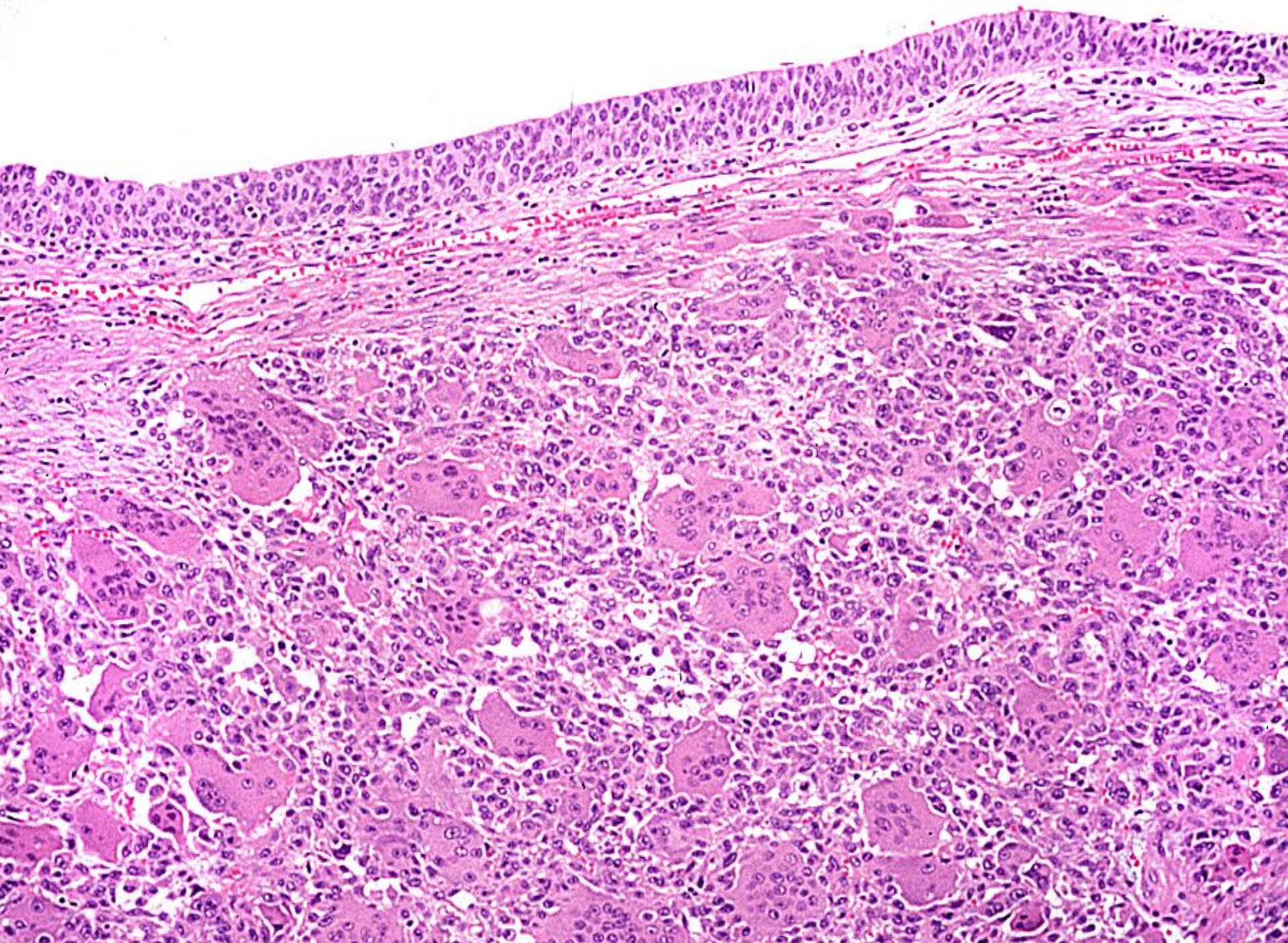
OSTEOCLAST-RICH UNDIFFERENTIATED CARCINOMA

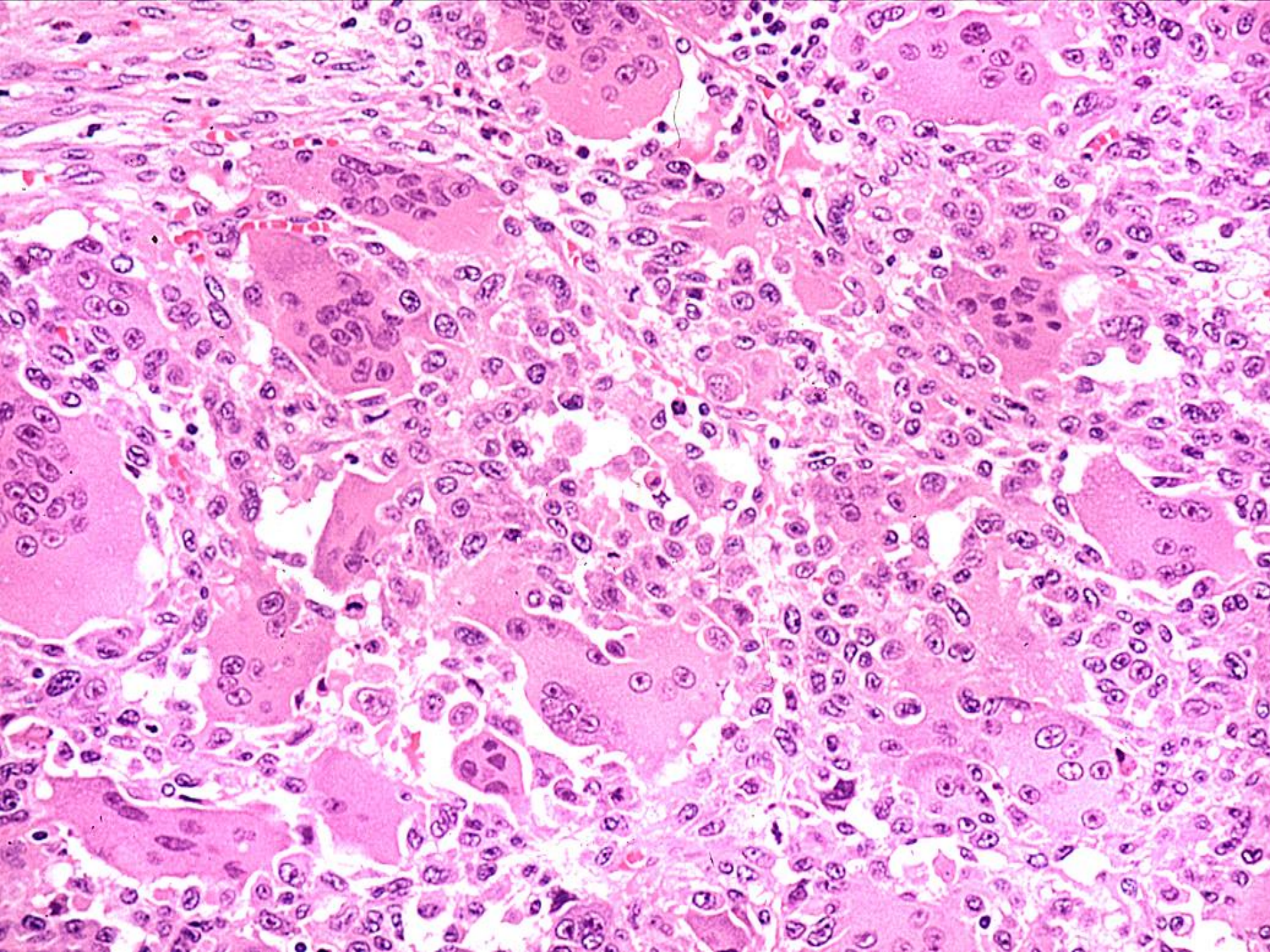
High stage tumors with variable admixtures of:

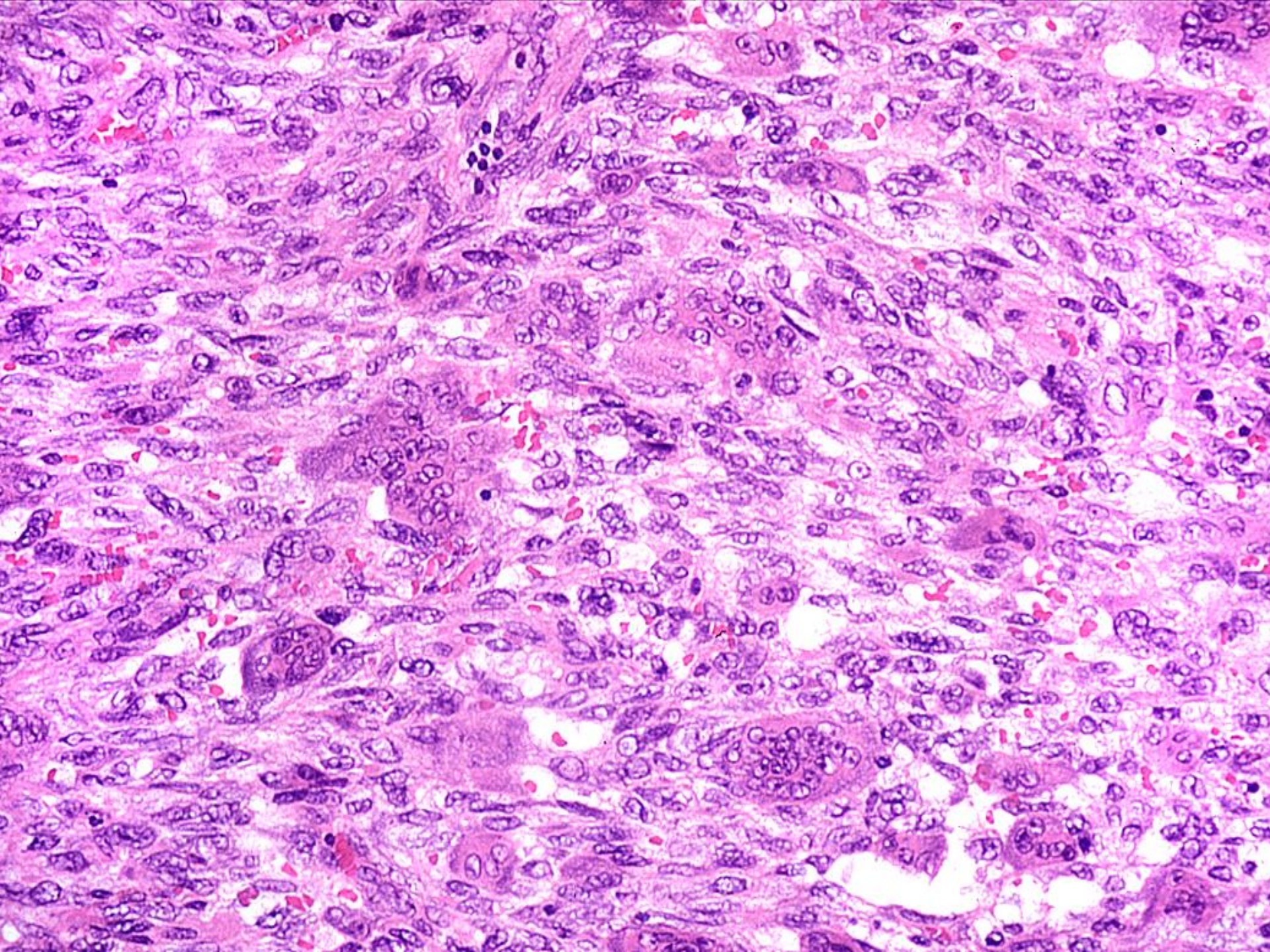
- Osteoclast - like giant cells (*often predominant*)
(CD68, CD51, CD54 +)
- Undifferentiated mononuclear cells
(frequently + for epithelial markers)
- Recognizable urothelial carcinoma
(CIS, papillary or invasive)
- May have blood filled spaces reminiscent of ABC

Most patients have metastasis or die of disease



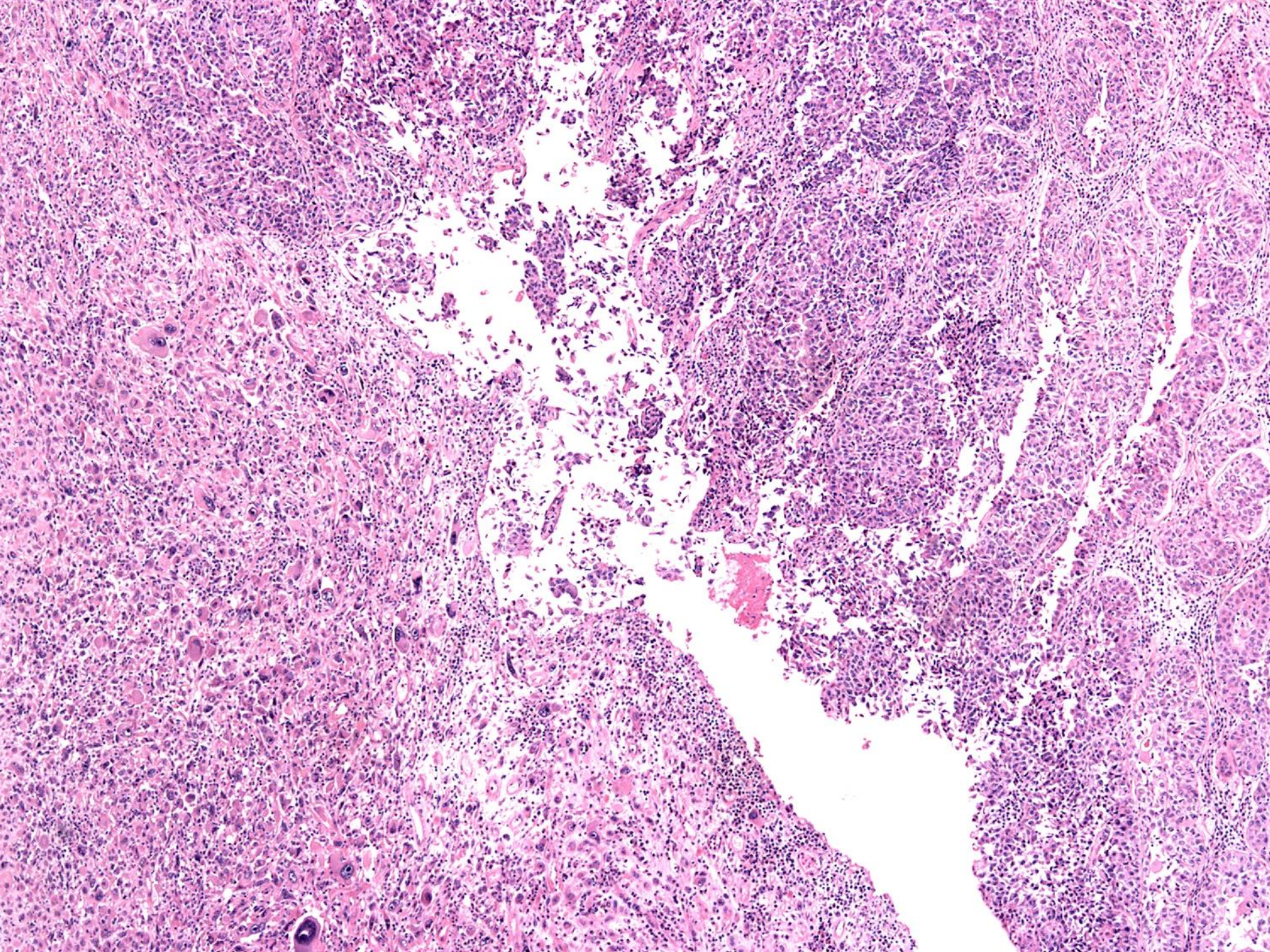


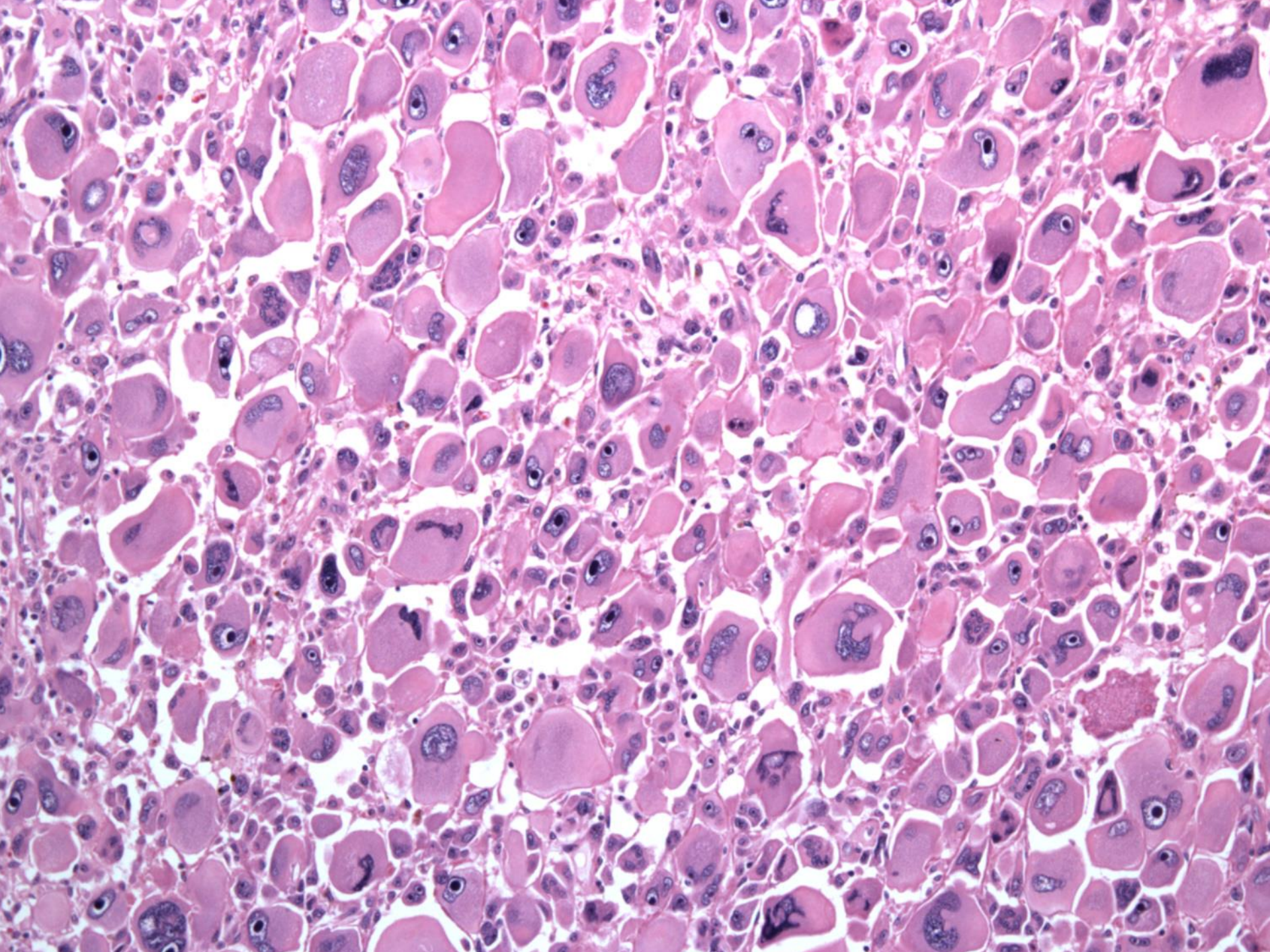


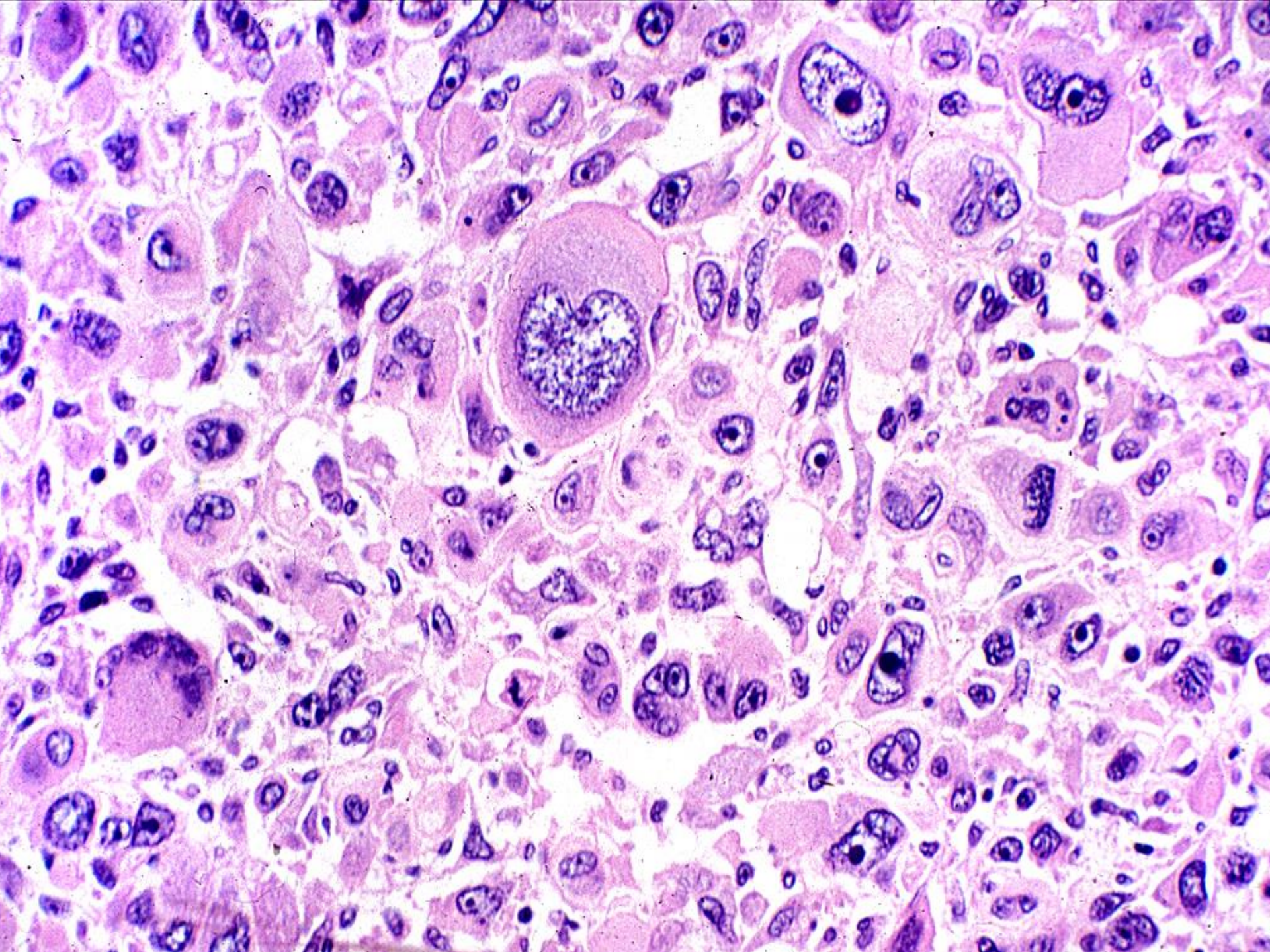


GIANT CELL CARCINOMA

- Large anaplastic, pleomorphic cells
 - Prognostic significance: poor outcome (few cases)







MORPHOLOGIC DIVERSITY OF U Ca

- U Ca. may show myriad patterns and divergent differentiation
 - Wide range demonstrates the totipotentiality of the bladder mucosal lining
 - Awareness of the histologic spectrum
 - Diagnostic
 - Prognostic
 - Therapeutic
- RELEVANCE**

Histologic Variants of Bladder Cancer

- It remains unclear what percentage of variant form impacts survival in most cases
- Hence the percentage of variant component required to make a diagnosis of a particular variant is not defined
- When mixed with conventional or other variants of U Ca, the relative percentages of the different histologies must be specified
 - e.g. *“U Ca with micropapillary histology (40%), conventional U Ca histology (50%) and with squamous differentiation (10%)”*

The treatment algorithm for based on variant histology

- **Variant histology appears to inherently define “high risk” bladder cancer in both nonmuscle invasive & muscle invasive**
- **pT1 disease - consider early cystectomy for some**
- **pT2-4 - consider neo-adjuvant chemotherapy for some**

Thank you!!!

