Diagnosis of Testicular Neoplasms: How to Recognize What Matters and Avoid Pitfalls

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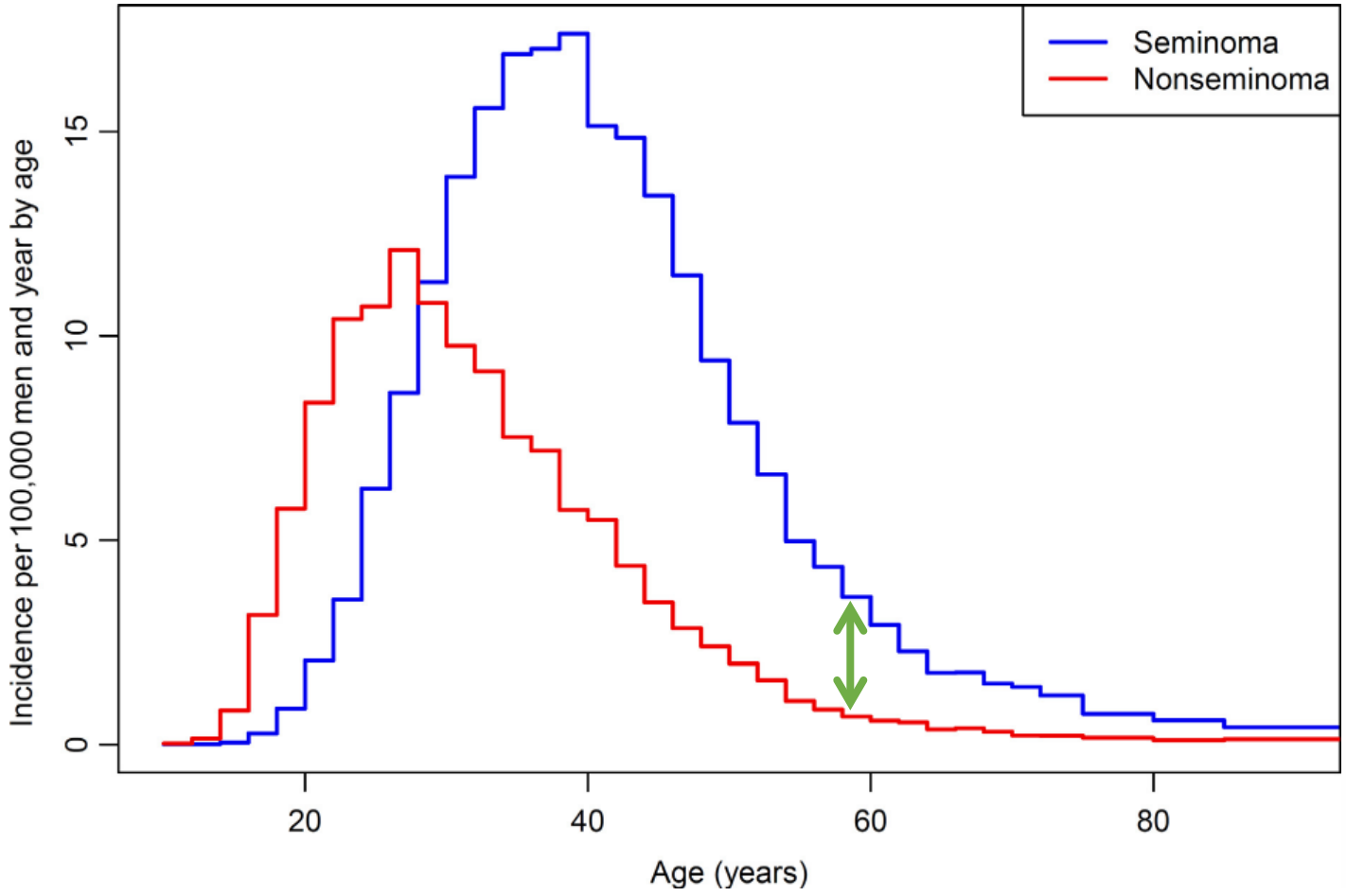
Objectives

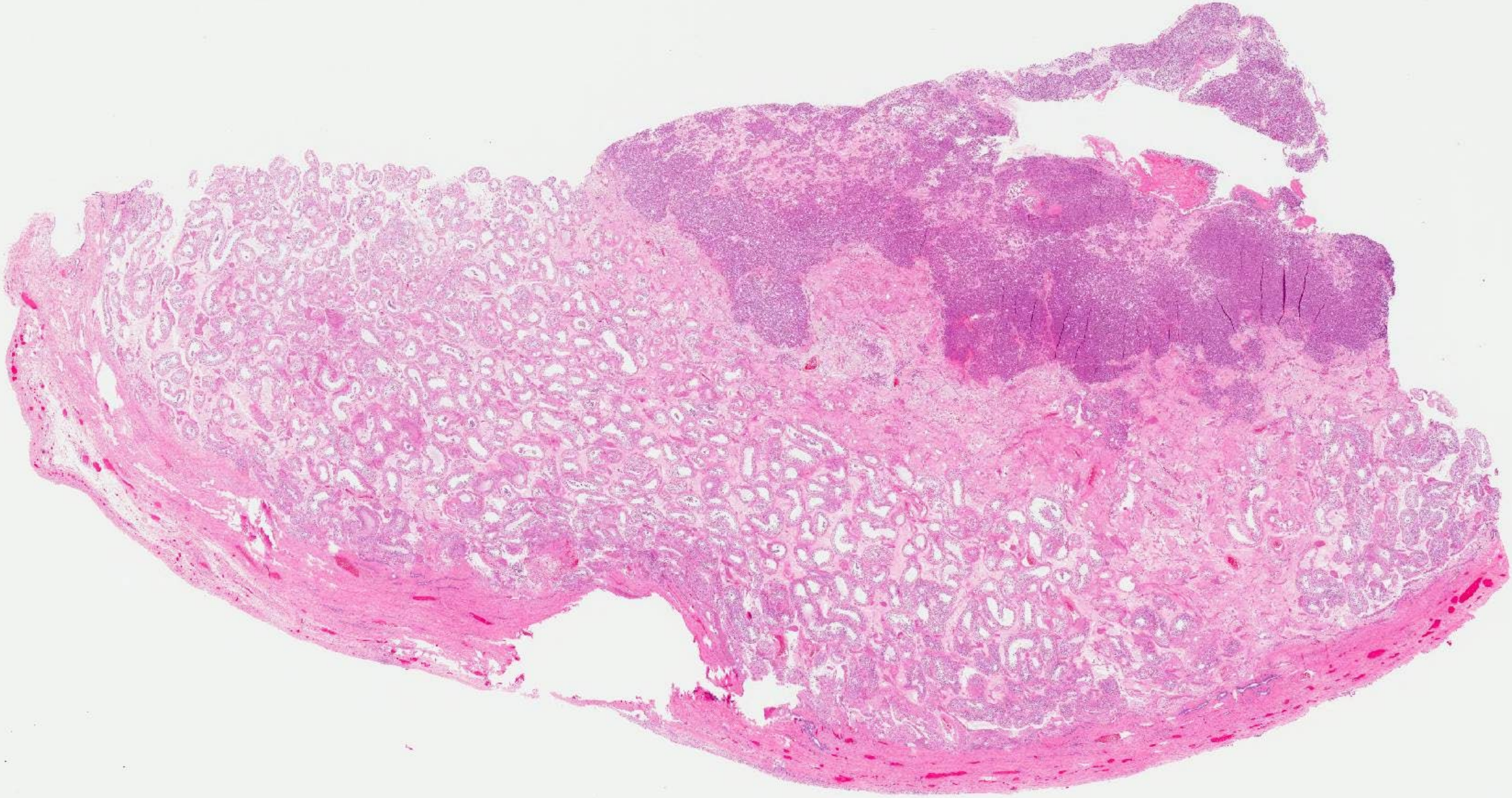
- Case-based discussion of common (and uncommon) pitfalls in testicular pathology
- Approach to resolving the differential diagnosis with morphology and IHC:
  - Germ cell tumors
  - Sex-cord stromal tumors
  - Paratesticular lesions

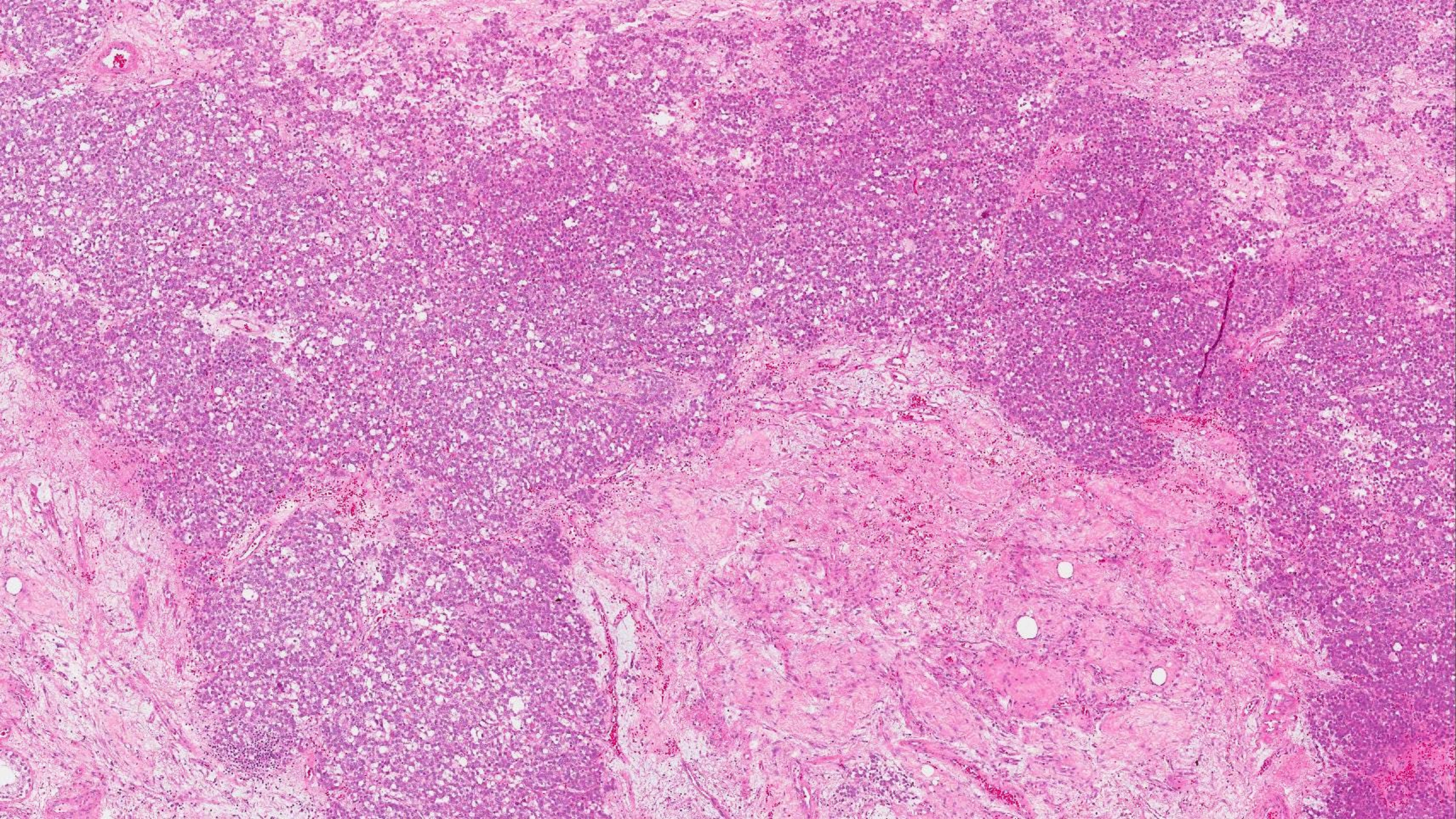
Case 1

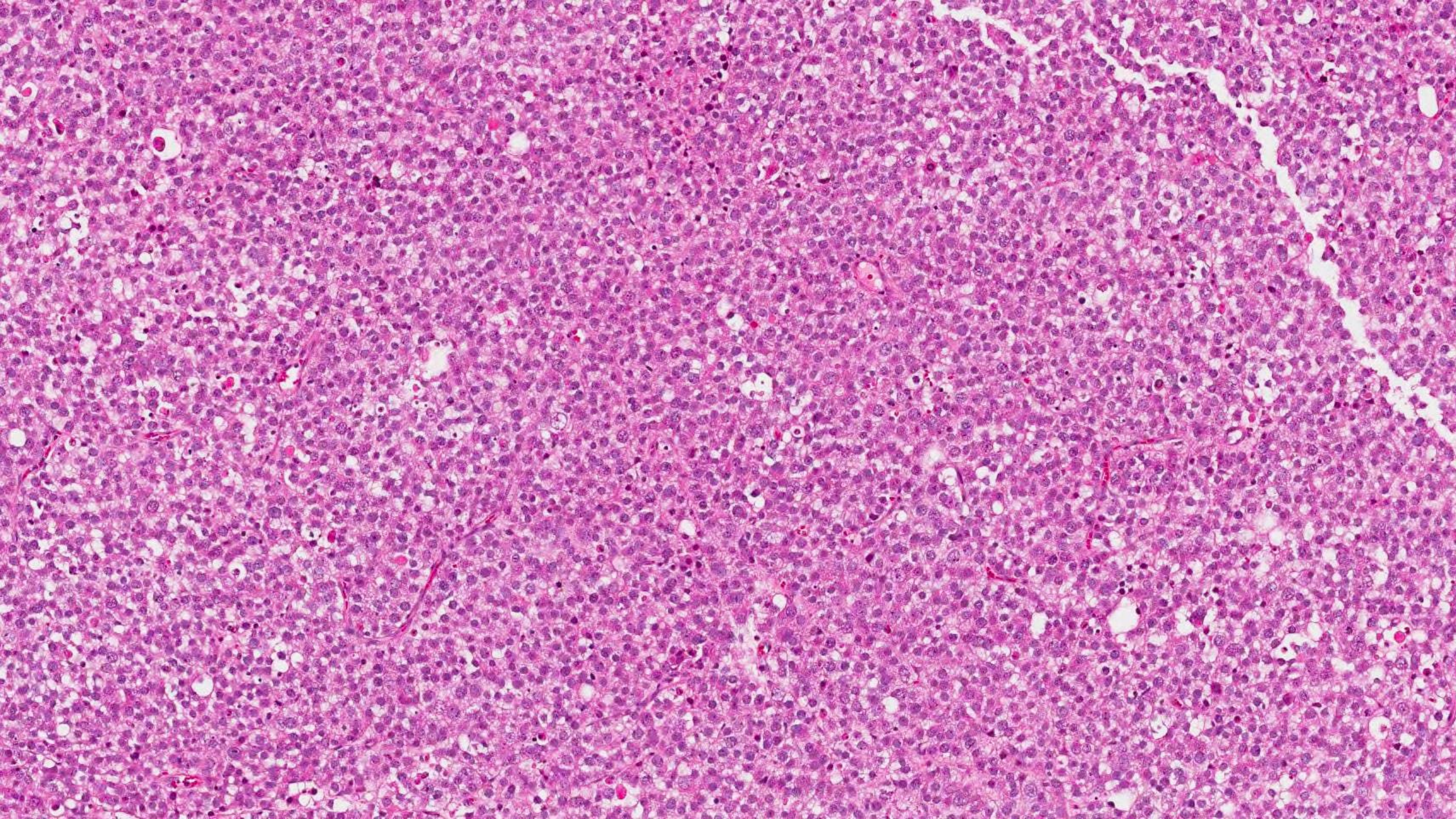
- Testicular mass – 58 year-old man

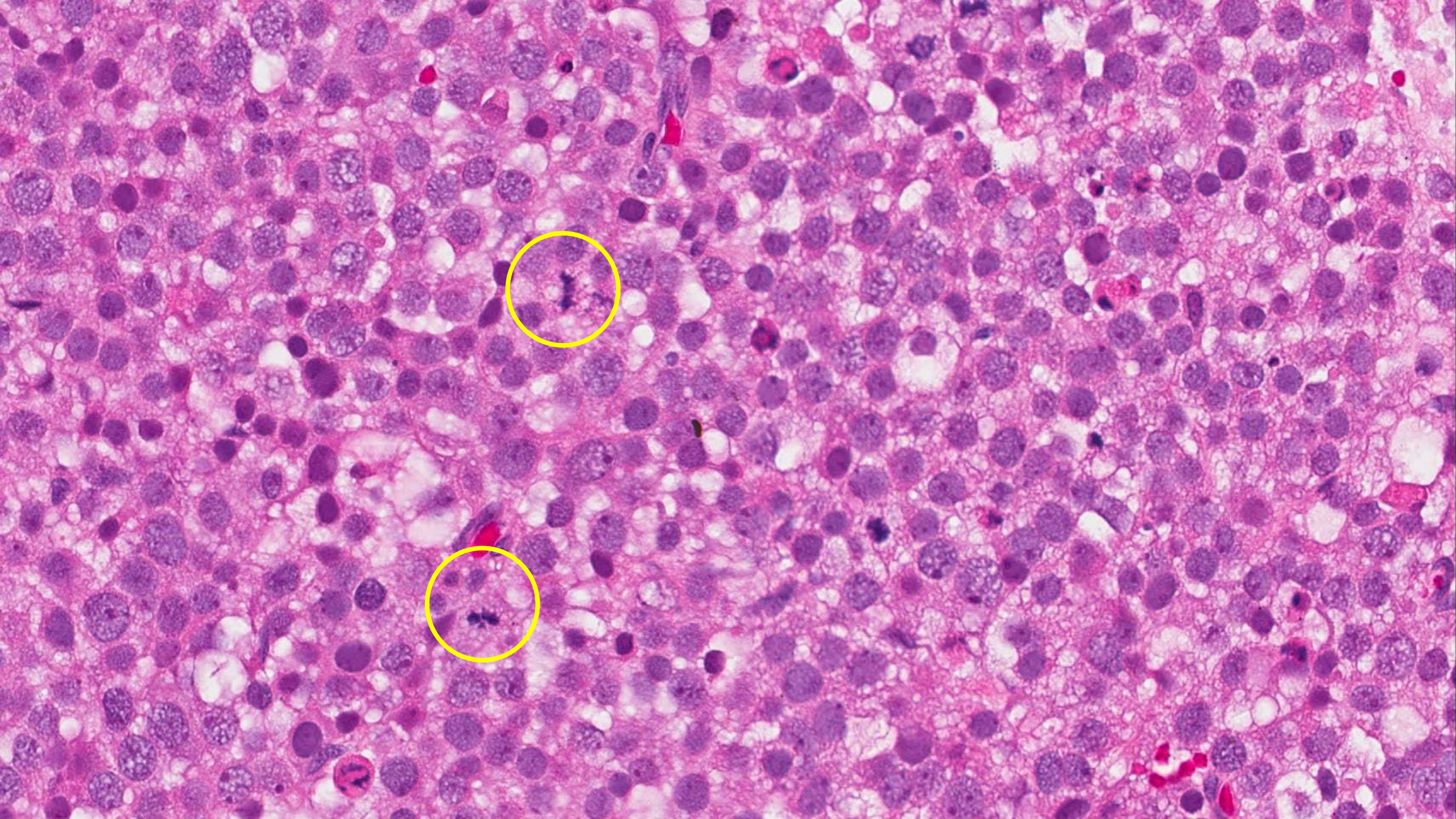


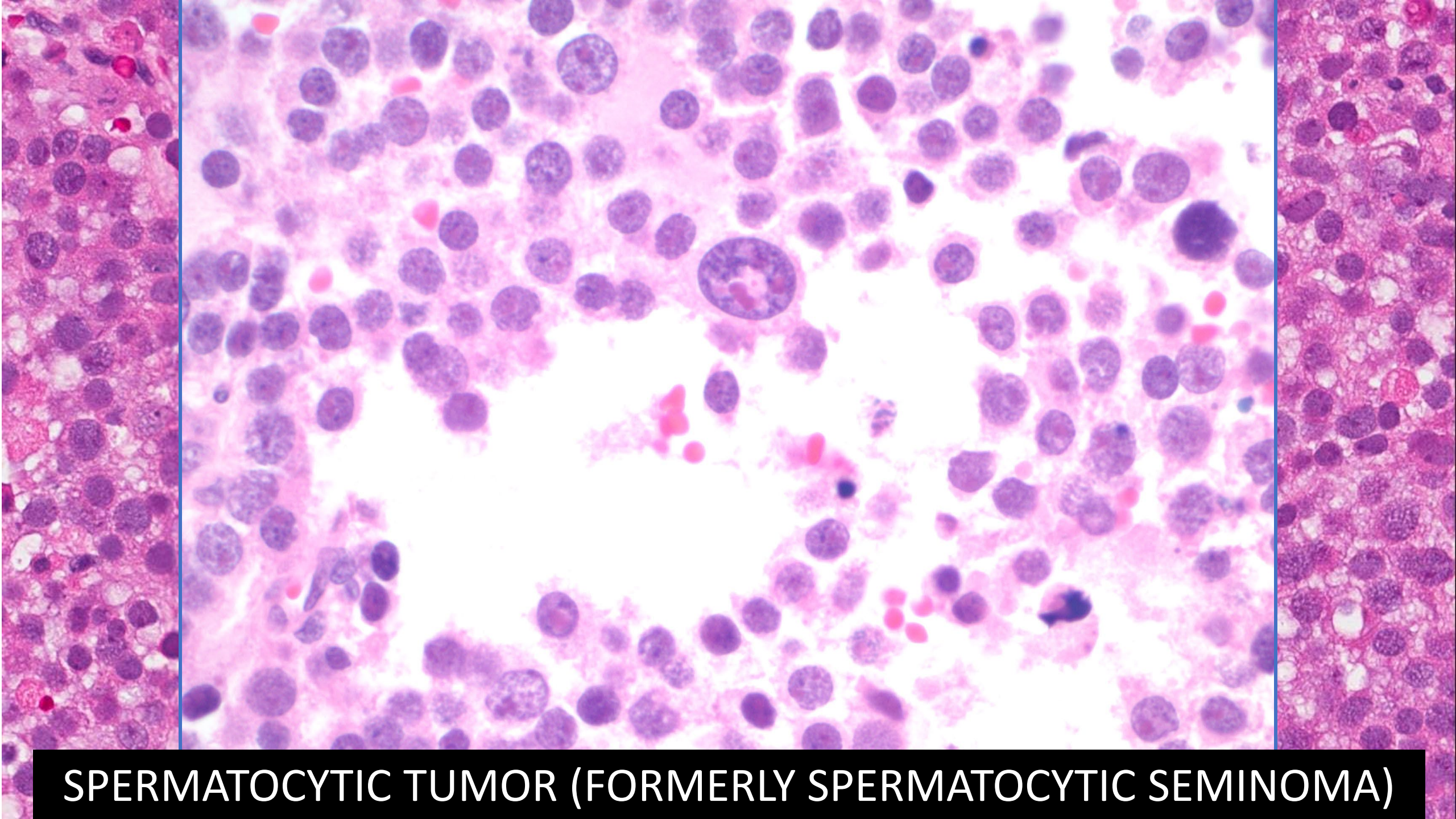
Brandt et al. Andrology, 2019, 7, 408–414



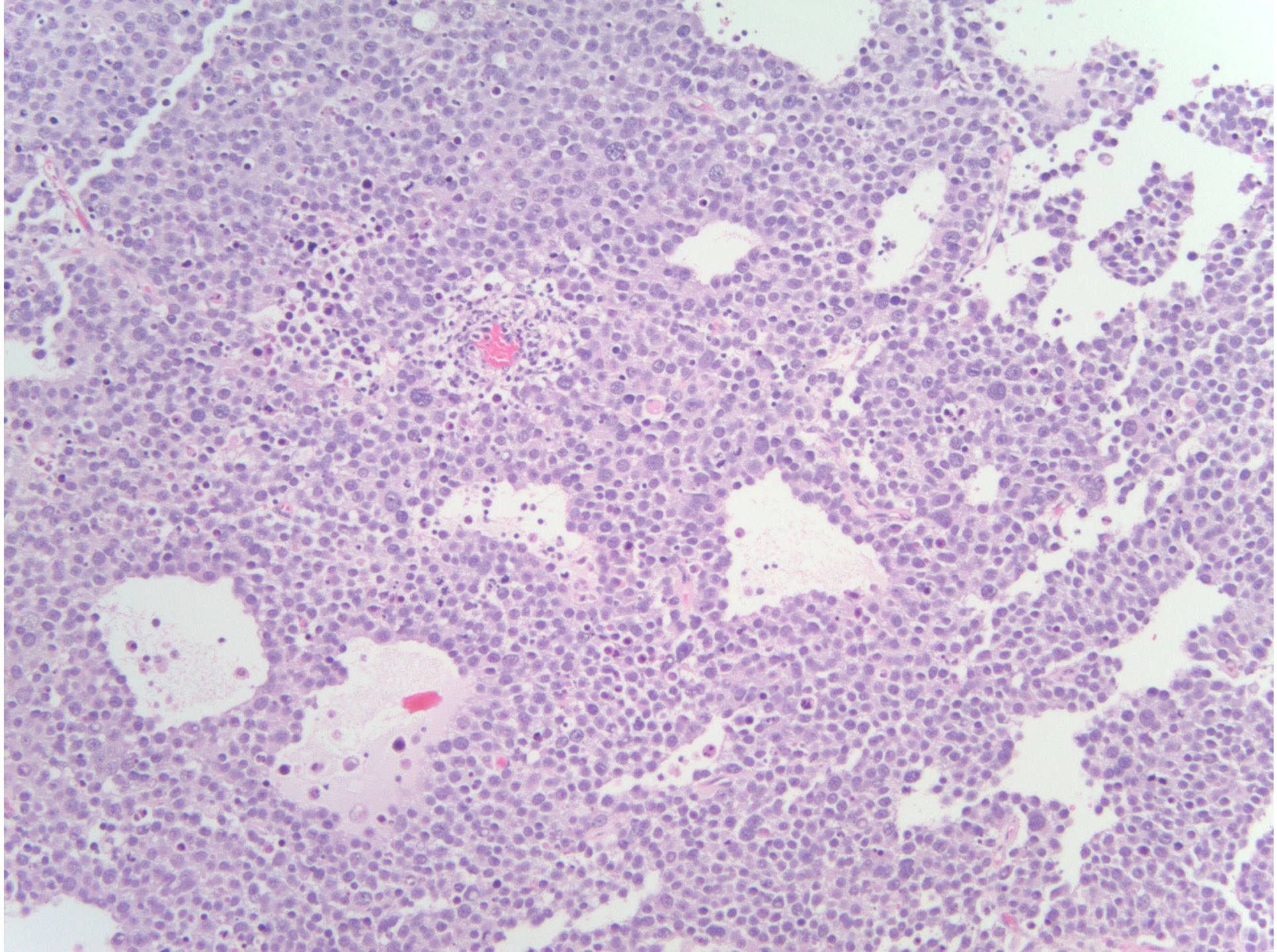




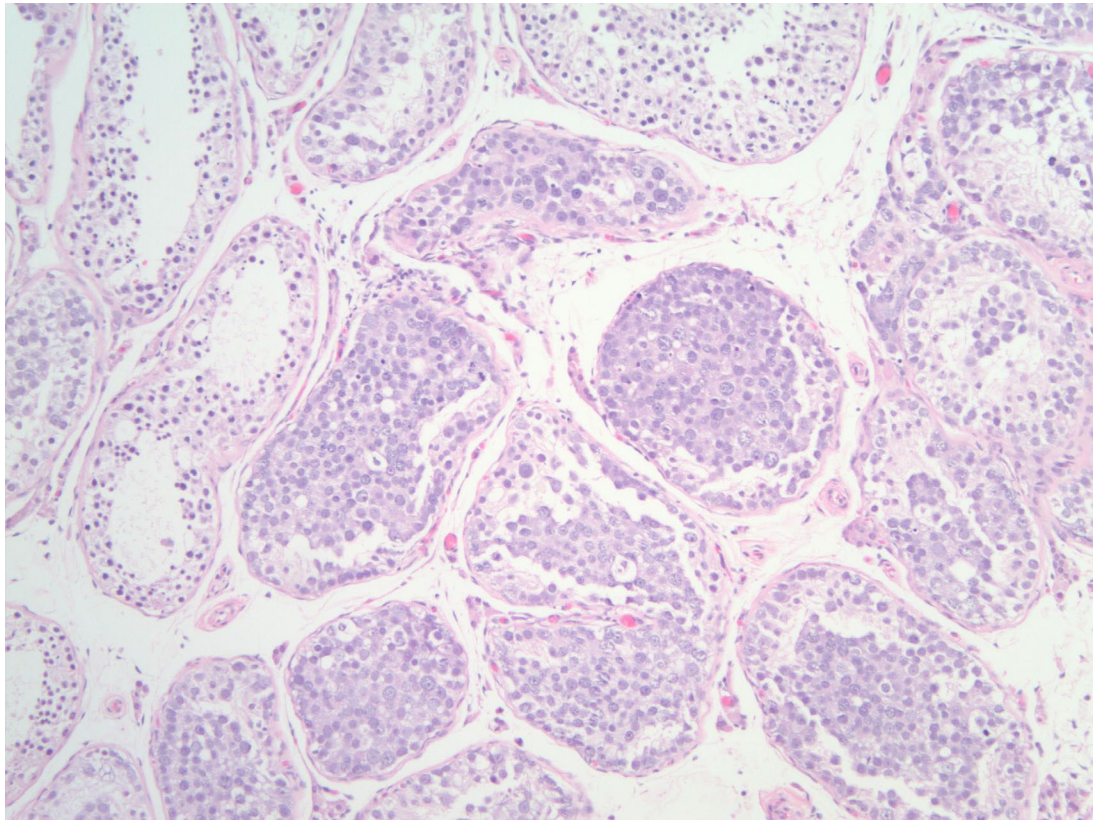


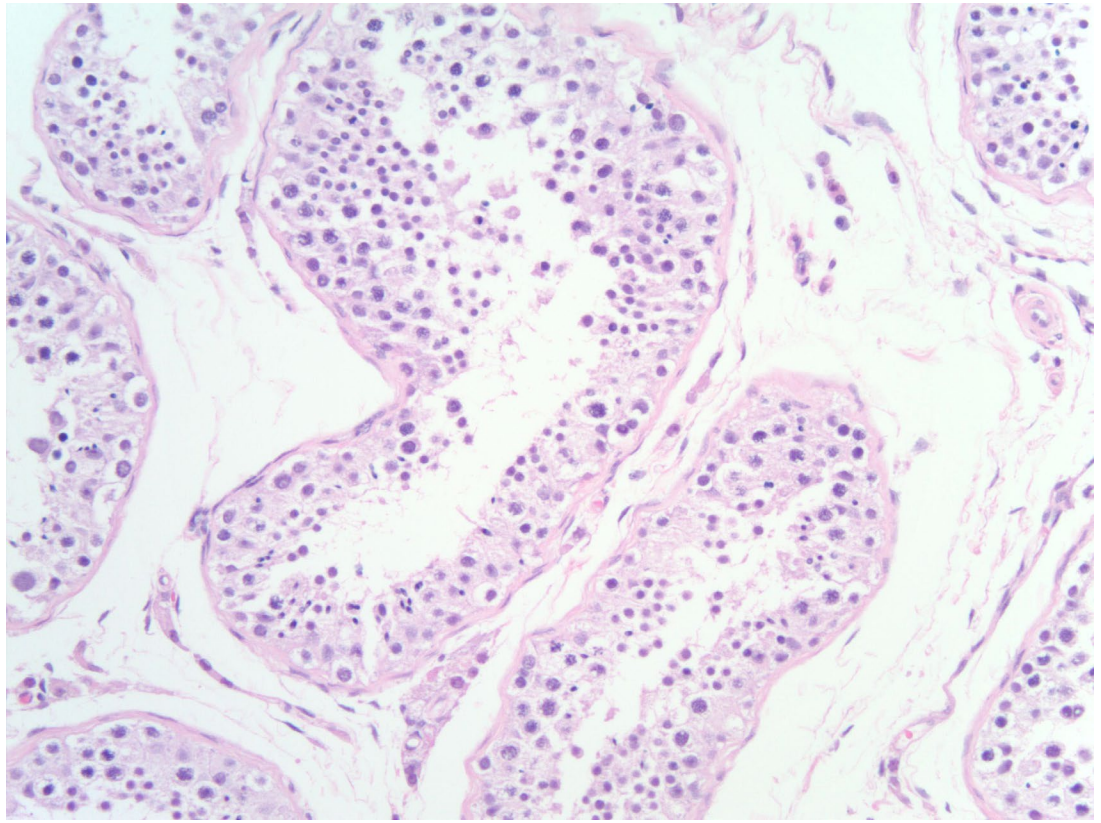


SPERMATOCYTIC TUMOR (FORMERLY SPERMATOCYTIC SEMINOMA)



Adjacent seminiferous tubules

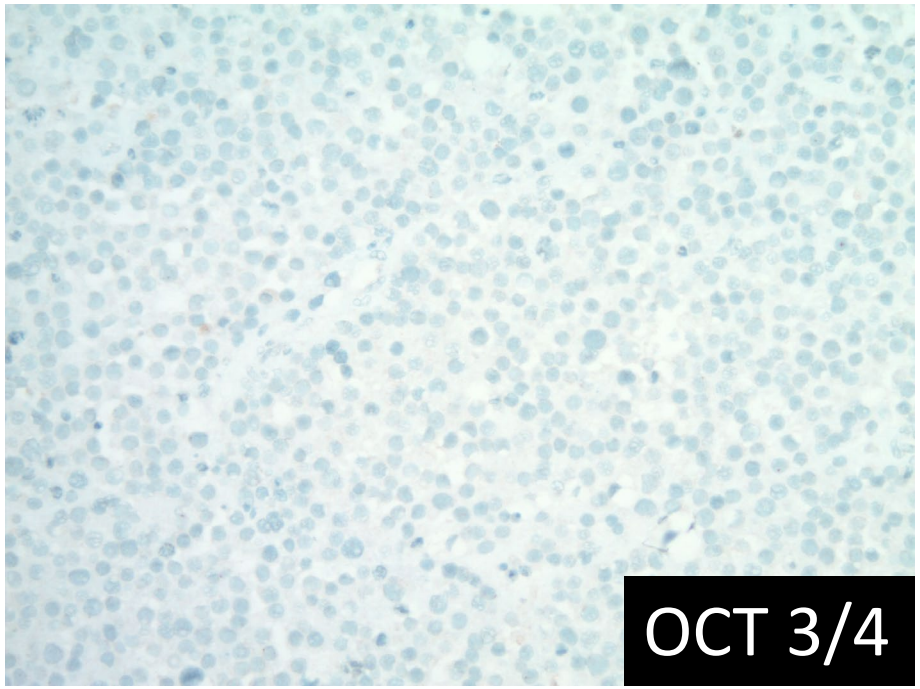




Spermatocytic tumor* – Diagnostic Clues

- Older age than usual GCT patient
  - Mean age 54 years
- Normal serum tumor markers
- Diffuse sheet-like growth
- Tripartite cell population
- Lack of GCNIS

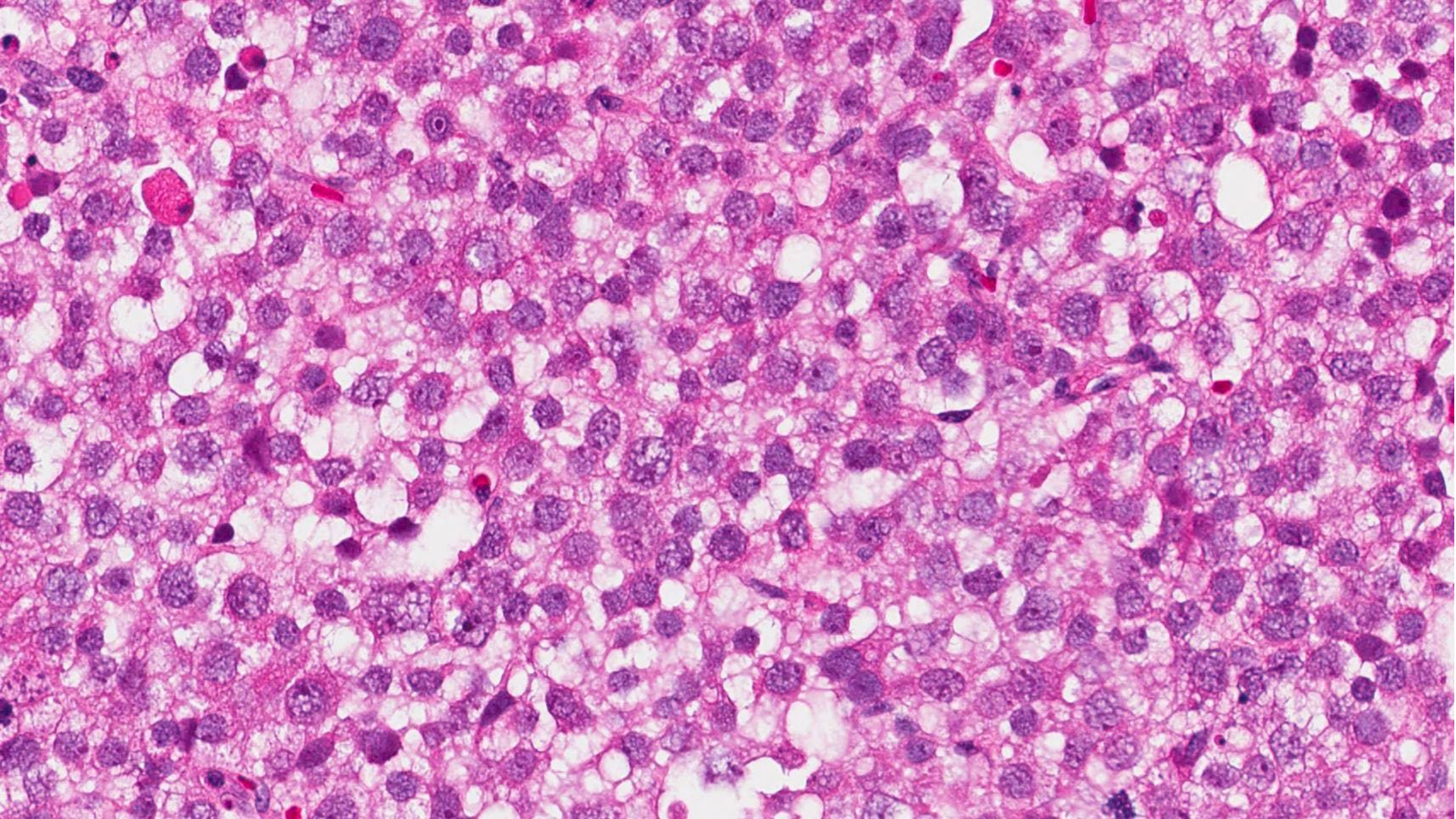
- OCT 3/4 (-), PLAP (-), PAS (-)
- SALL-4 (+), CD117 (+)
- Negative for i(12p)



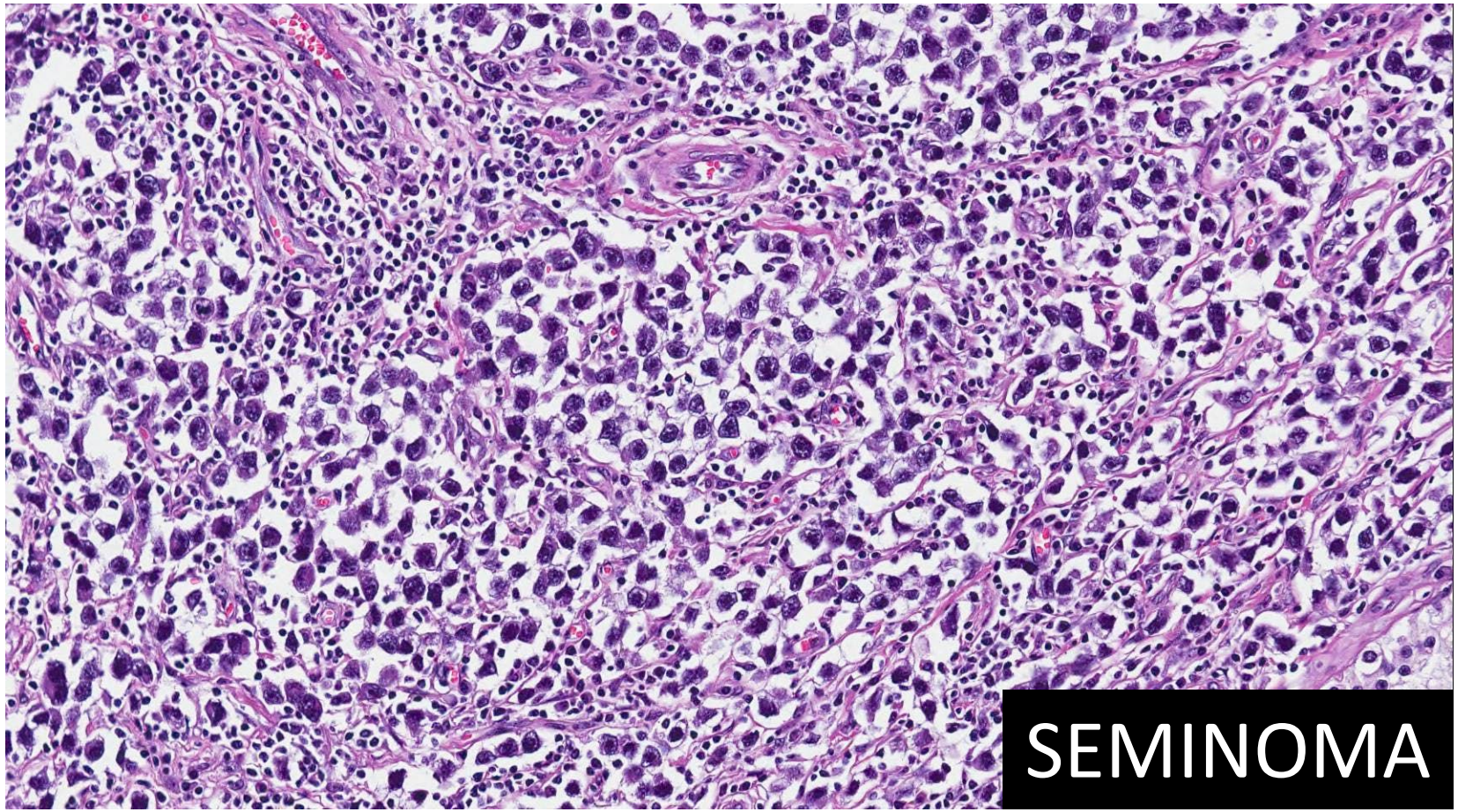
*Formerly Spermatocytic Seminoma

Spermatocytic tumor - Prognosis

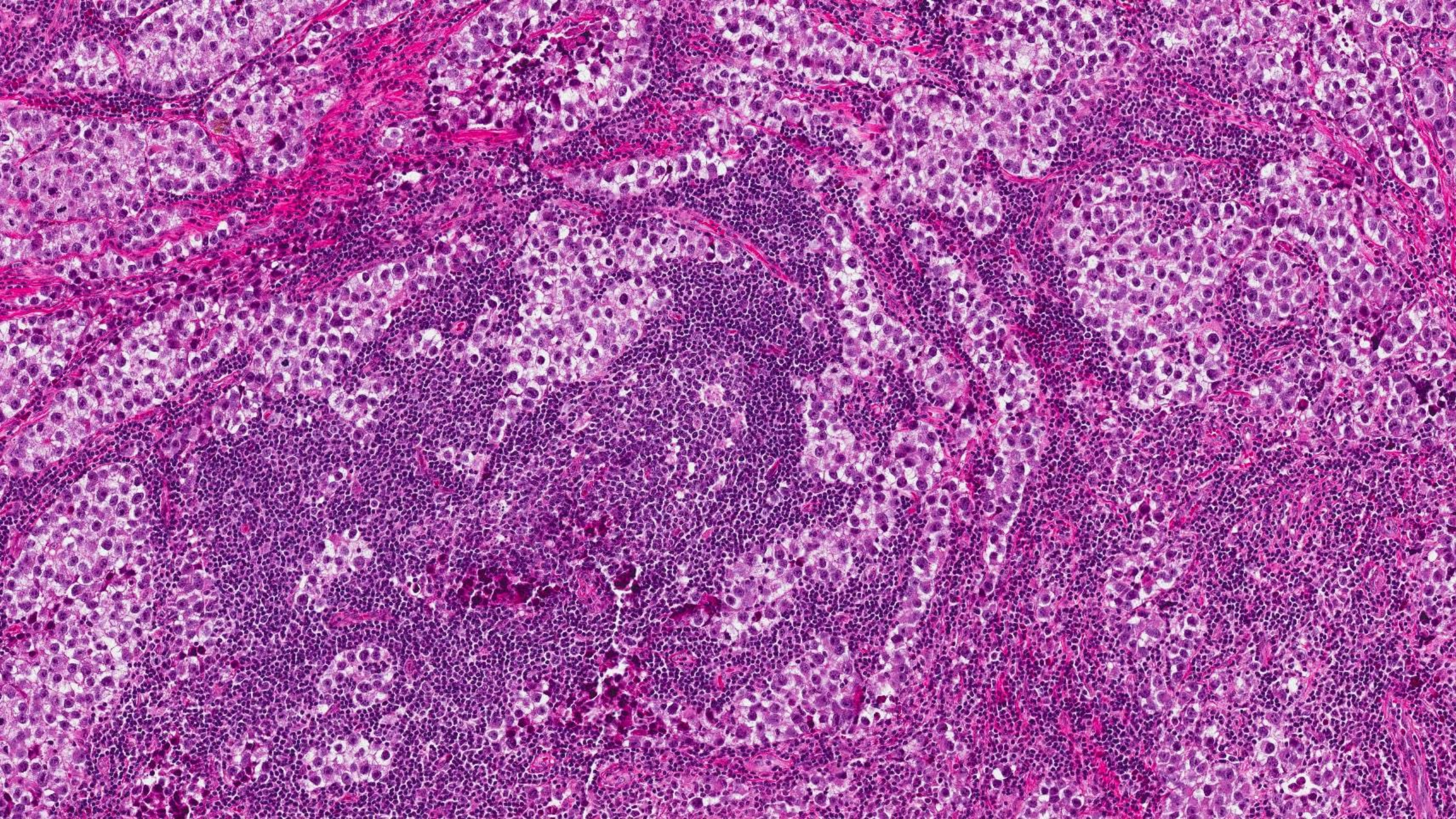
- Excellent prognosis
  - Radical orchiectomy usually curative
  - Rare sarcomatoid features
    - metastases and death of disease
- Rare gain of 12p
  - ?correlation with anaplastic features/aggressive behavior

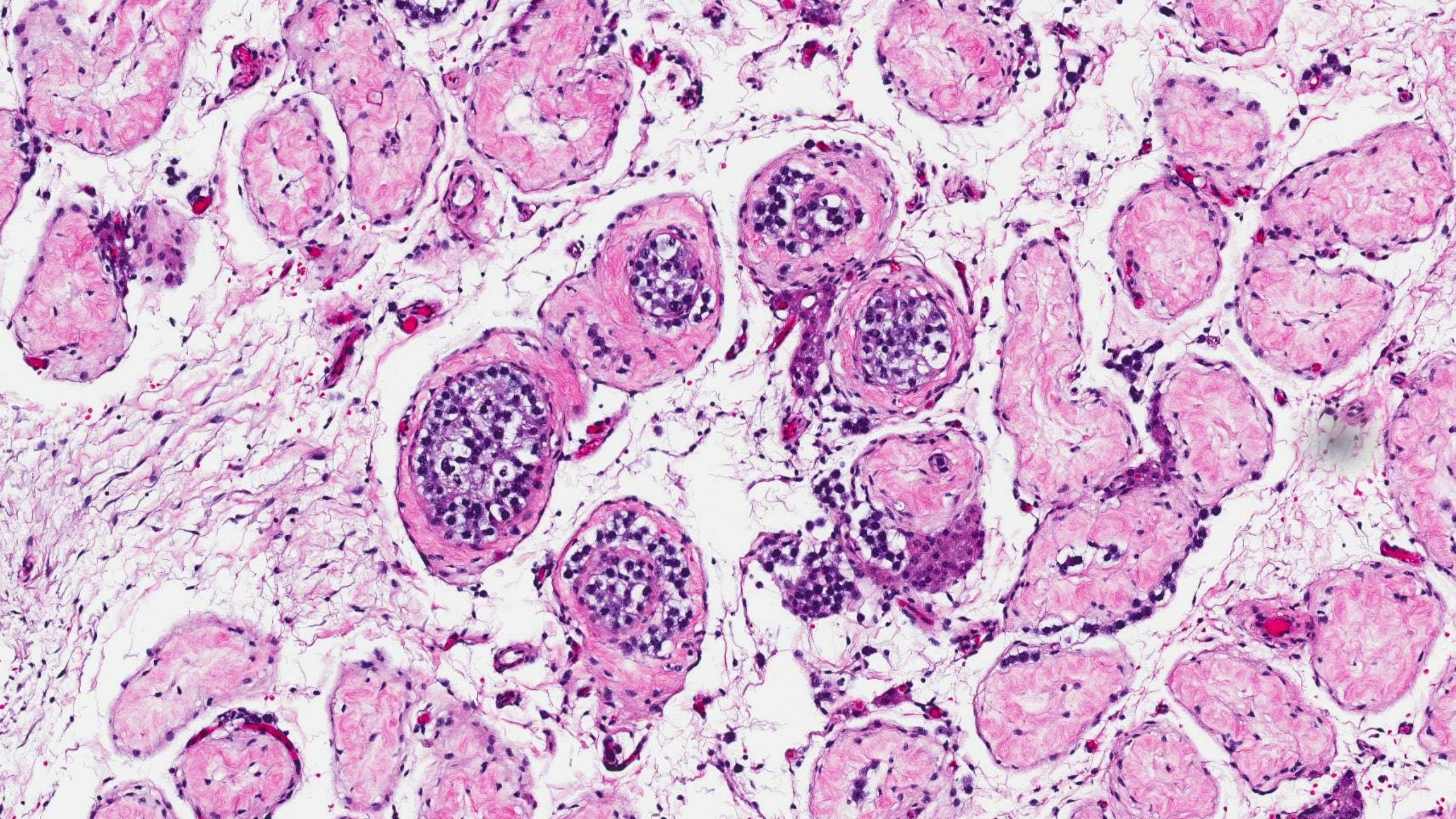


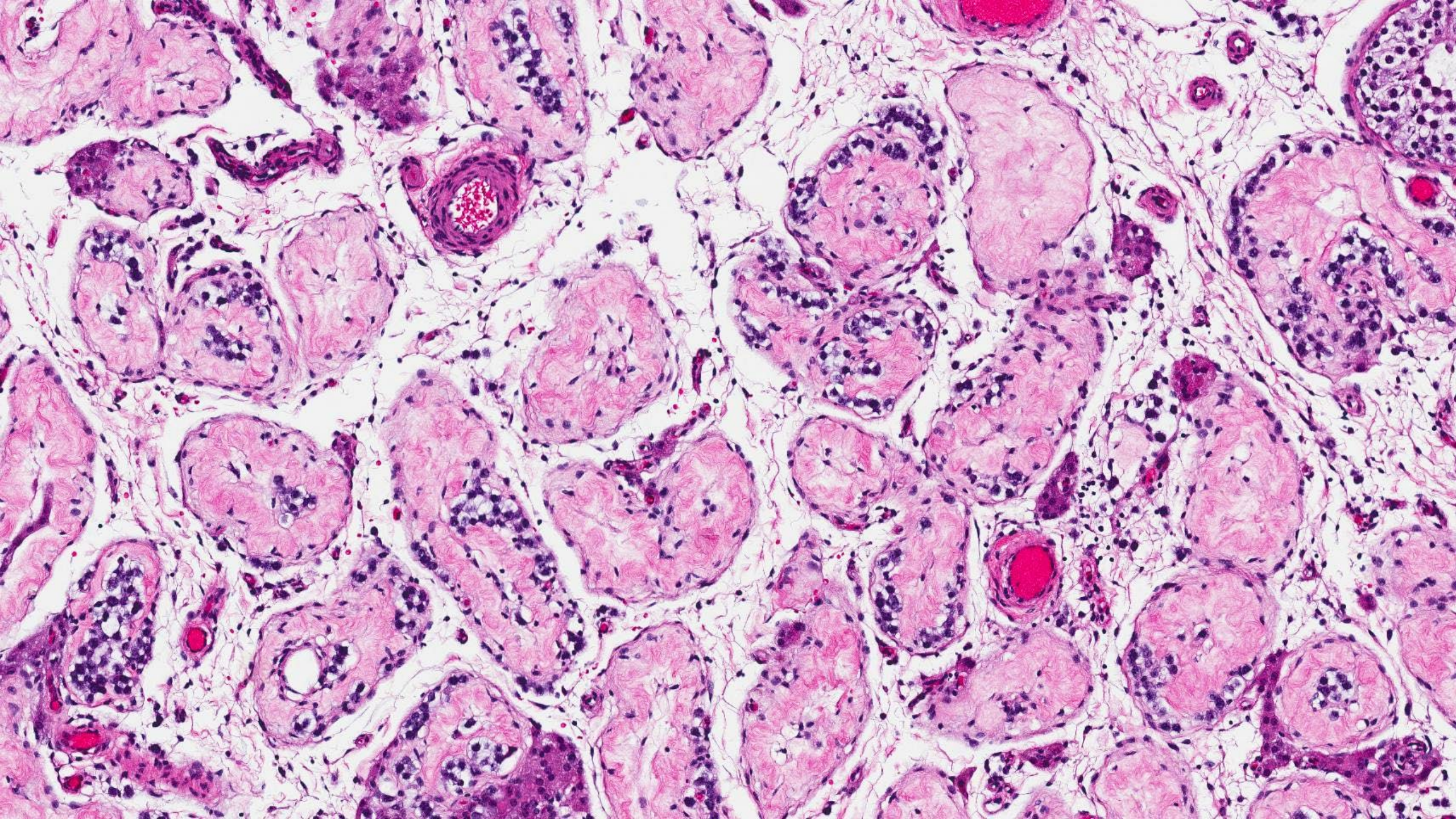
Spermatocytic tumor – differential diagnosis

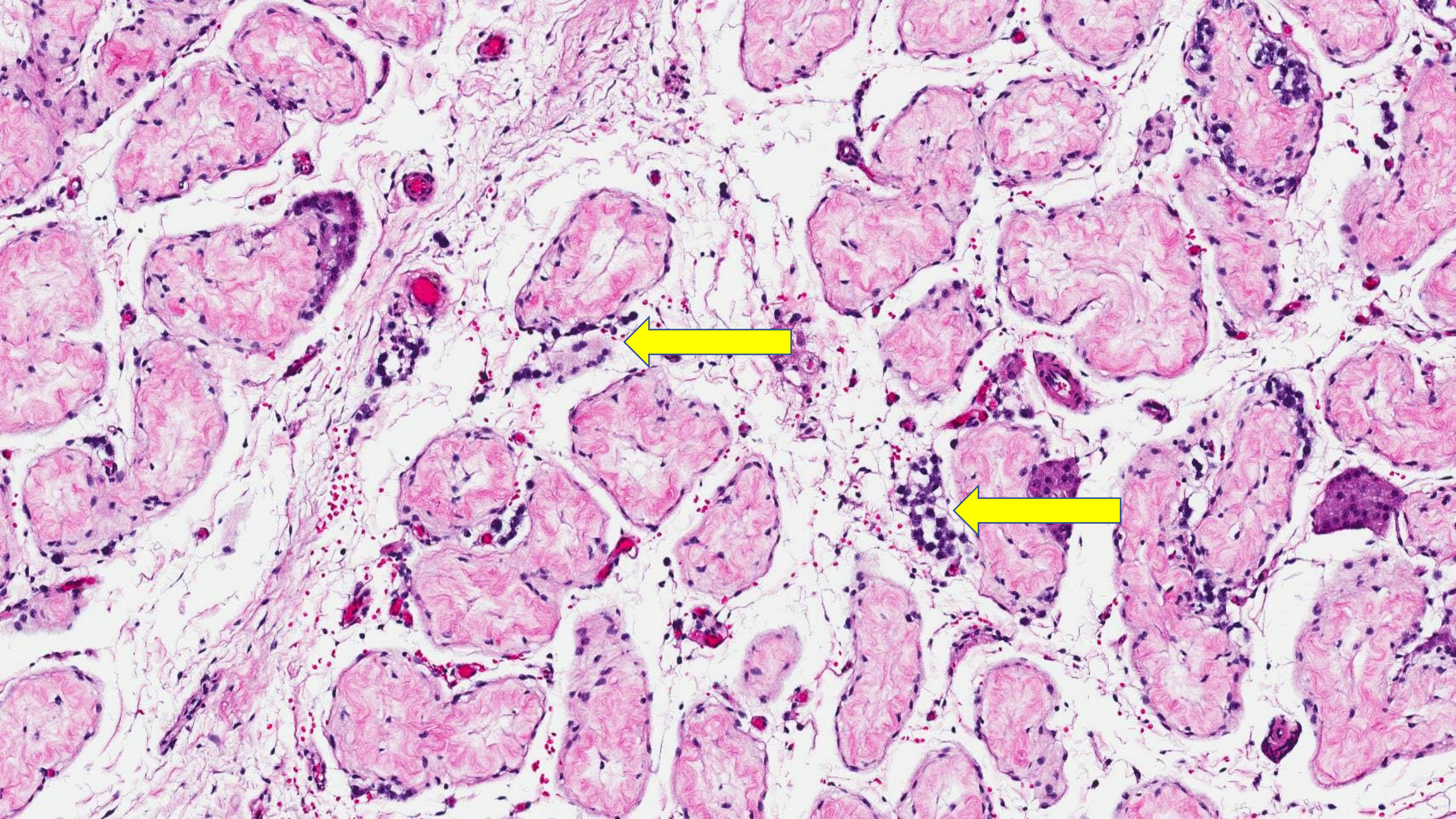


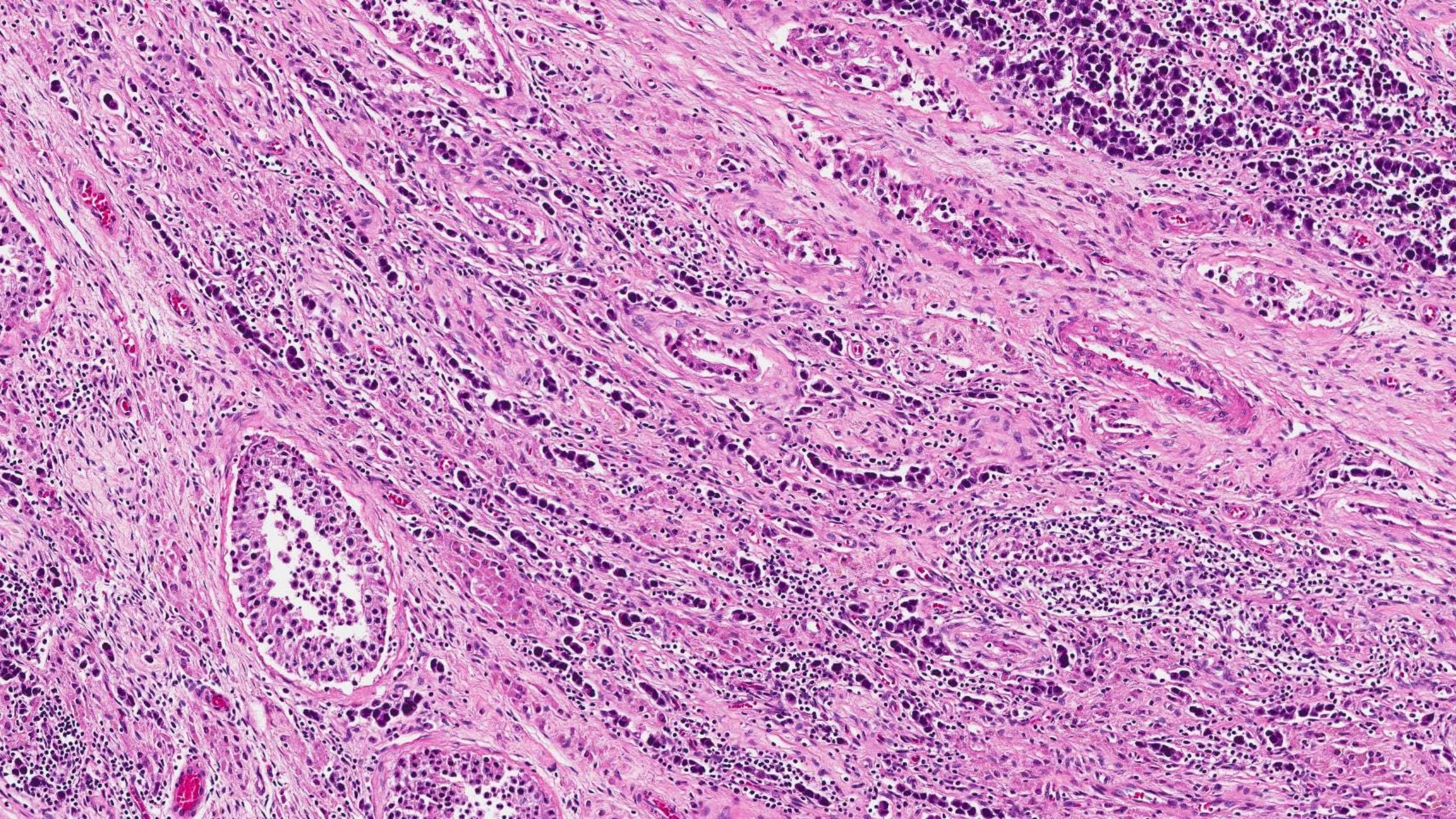
- Seminoma
  - Morphologic differences
  - OCT 3/4 +
  - Beware CD117









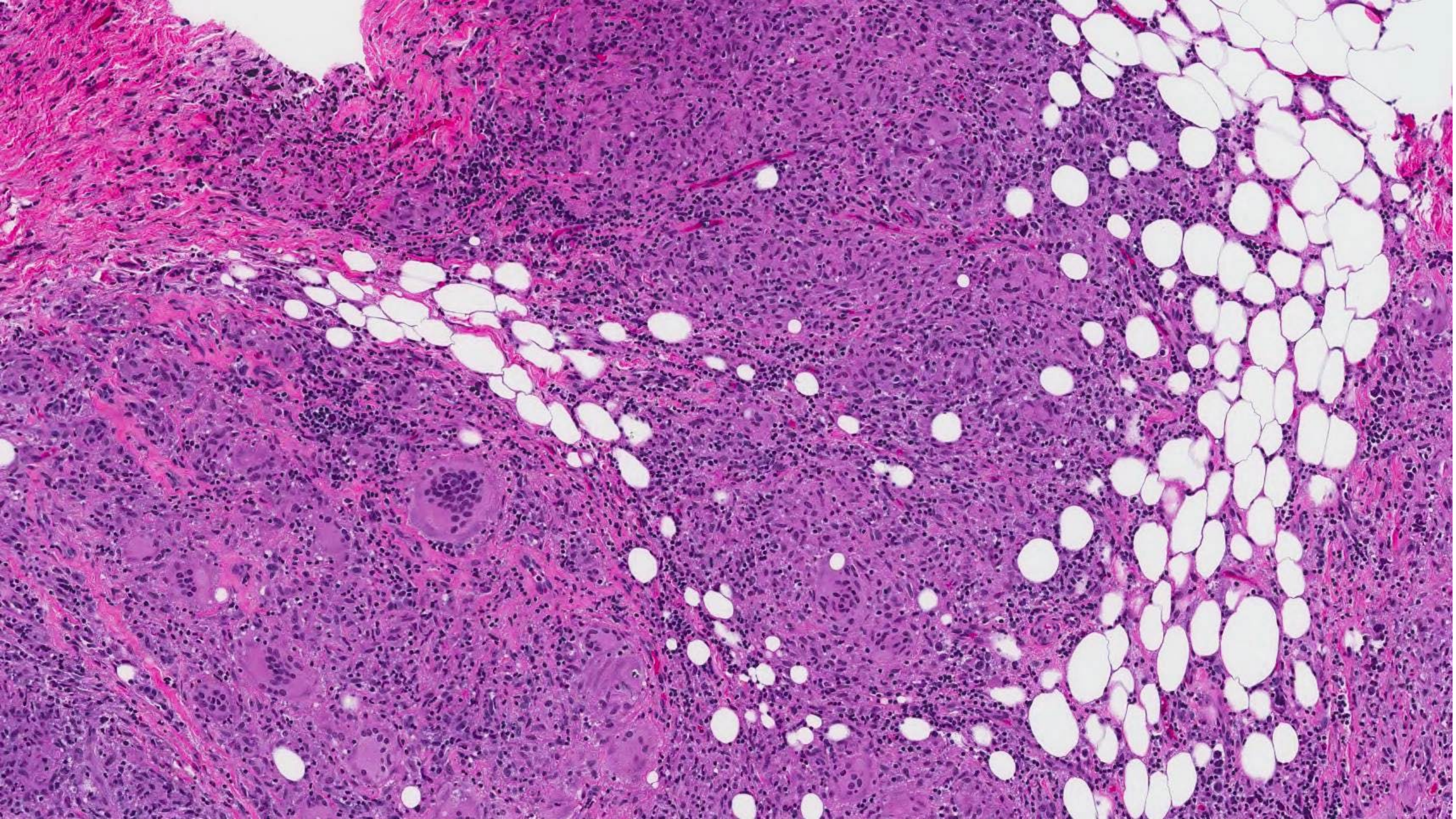


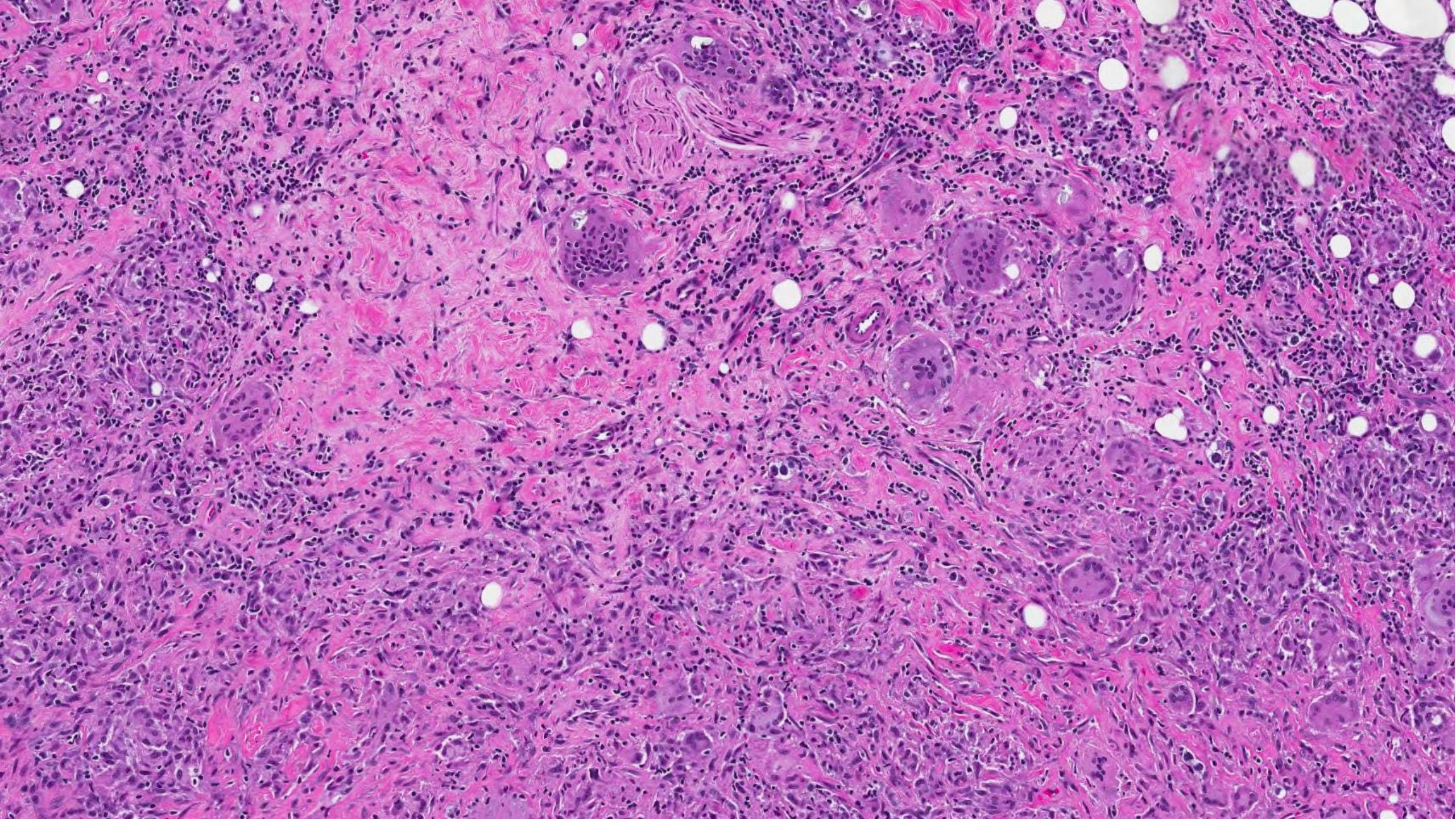
Example case

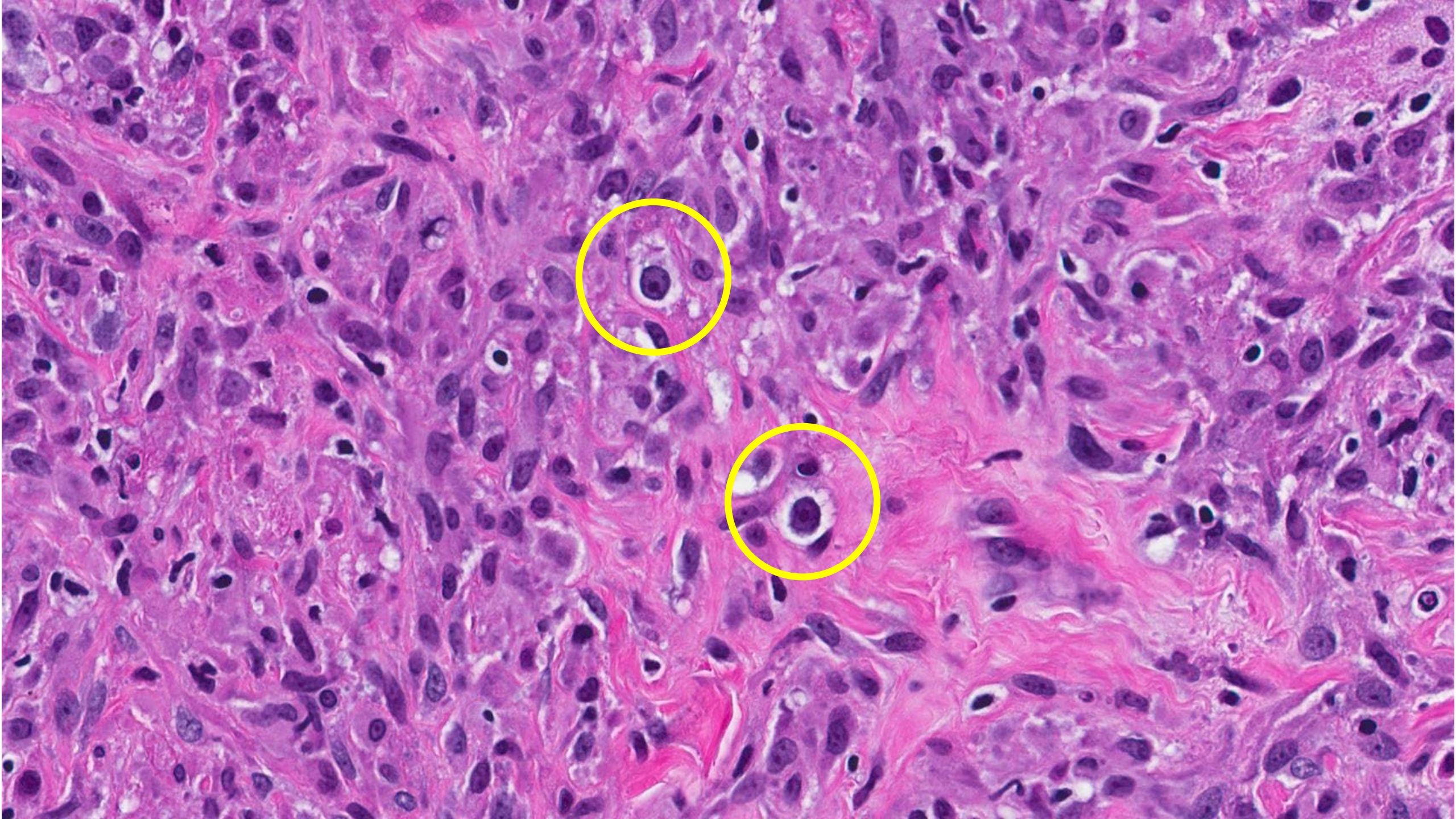
Retroperitoneal mass – 54-year old man

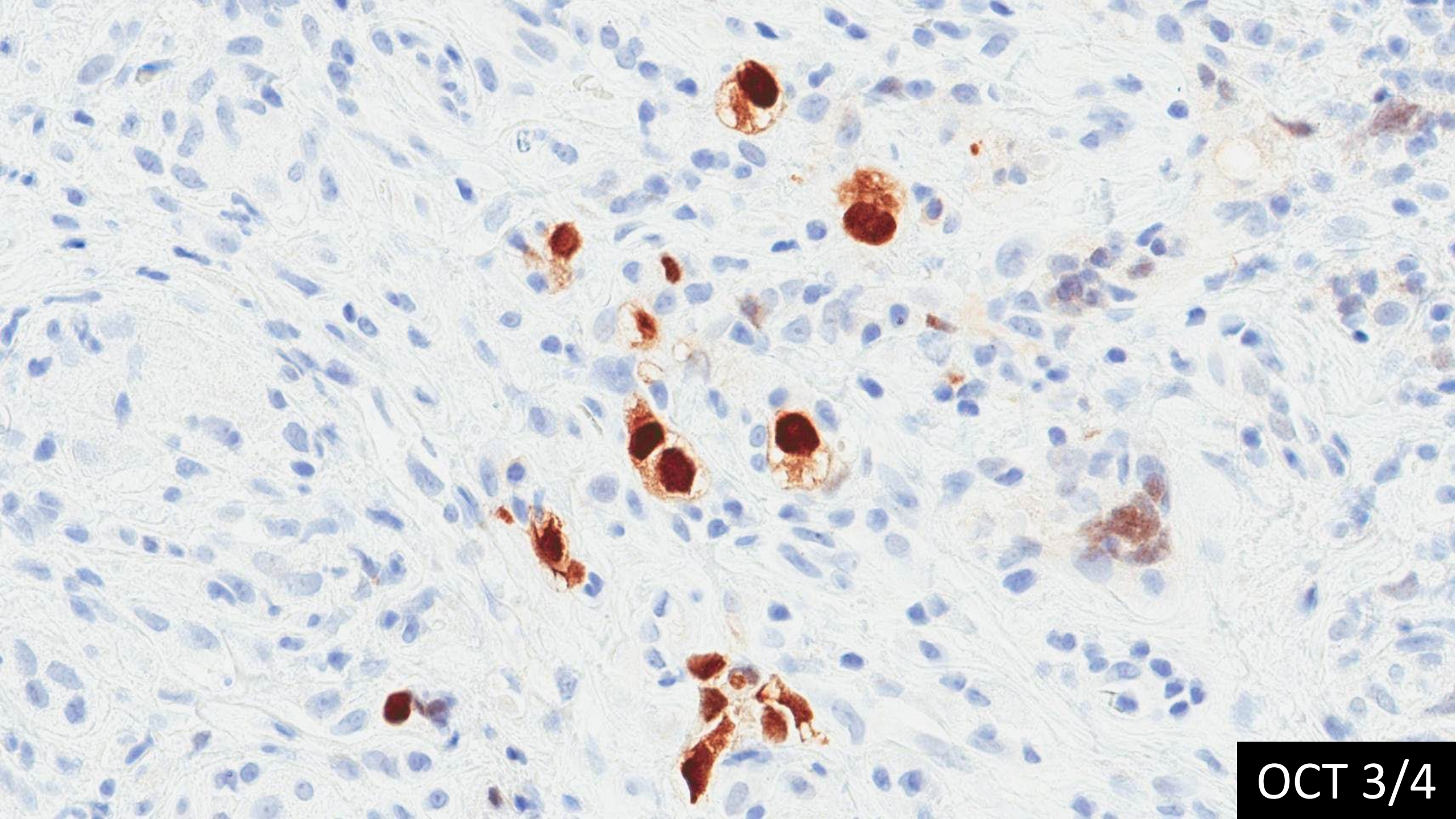
Clinical history

- 54 year-old man
  - Incidentally discovered retroperitoneal mass
- No history of malignancy
- Prior biopsies
  - Chronic inflammation and fibrosis
- Testicular ultrasound
  - Testicular mass
  - Orchiectomy: Testicular parenchymal scar
- Resection of retroperitoneal mass:



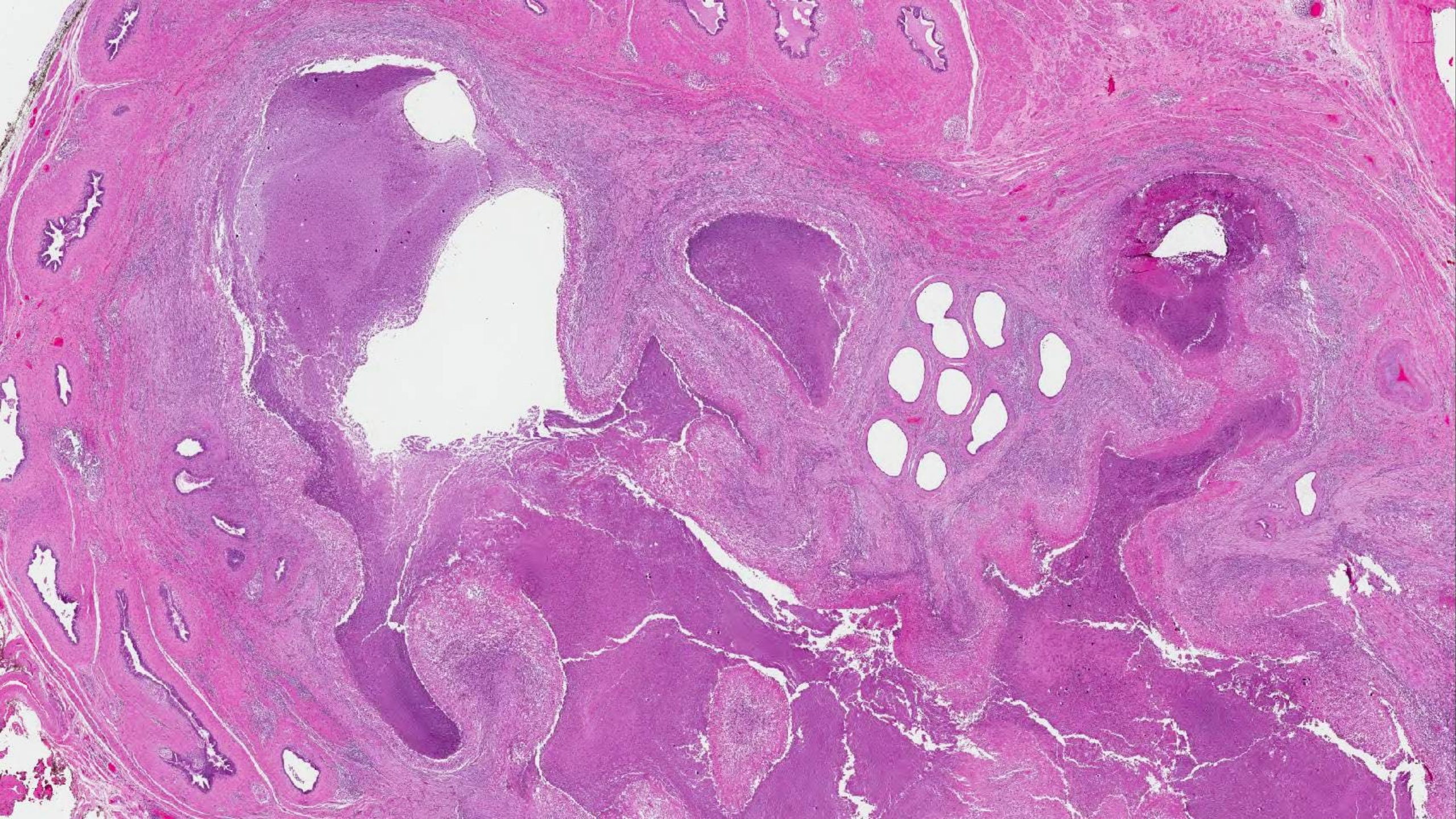


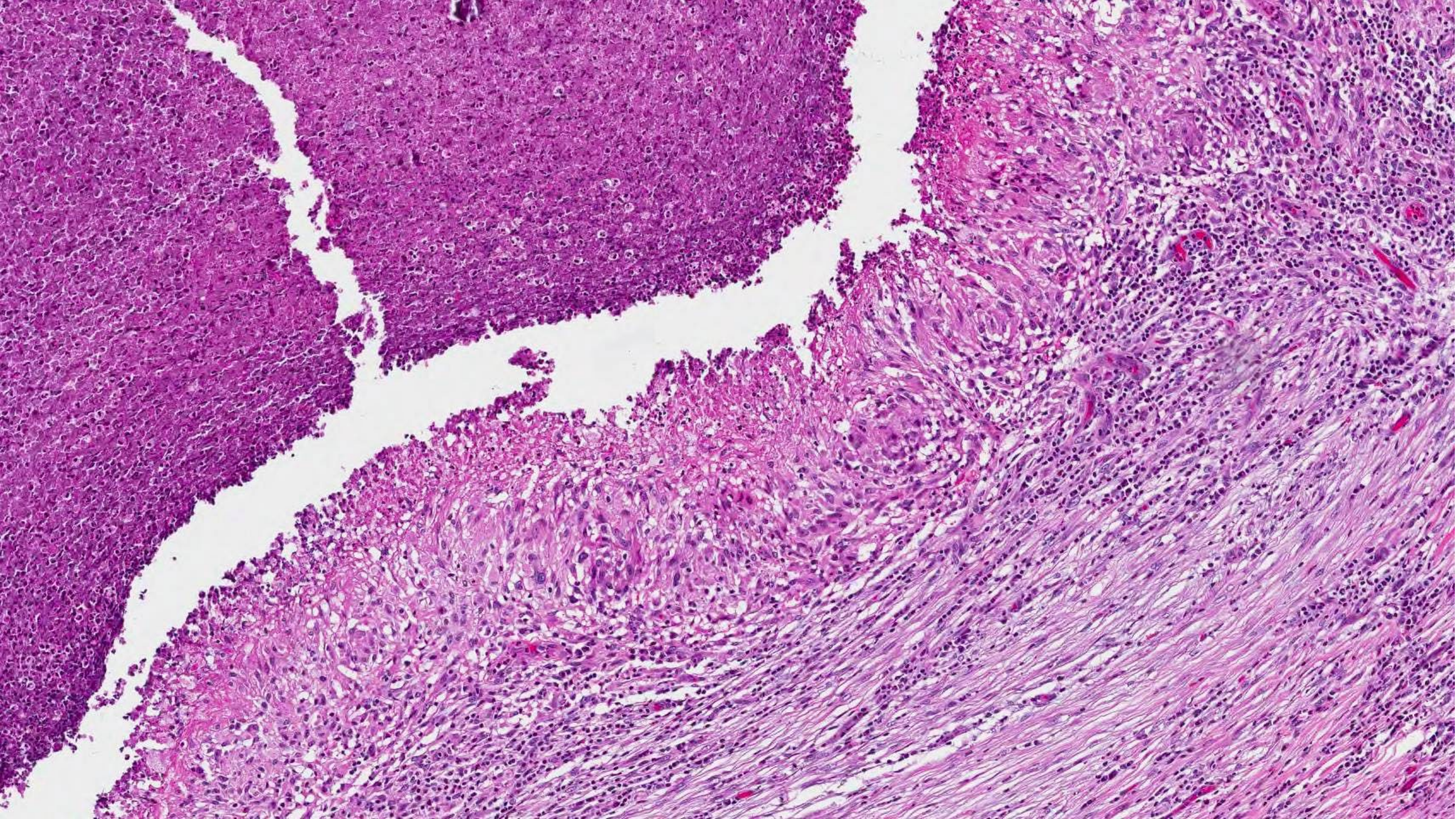


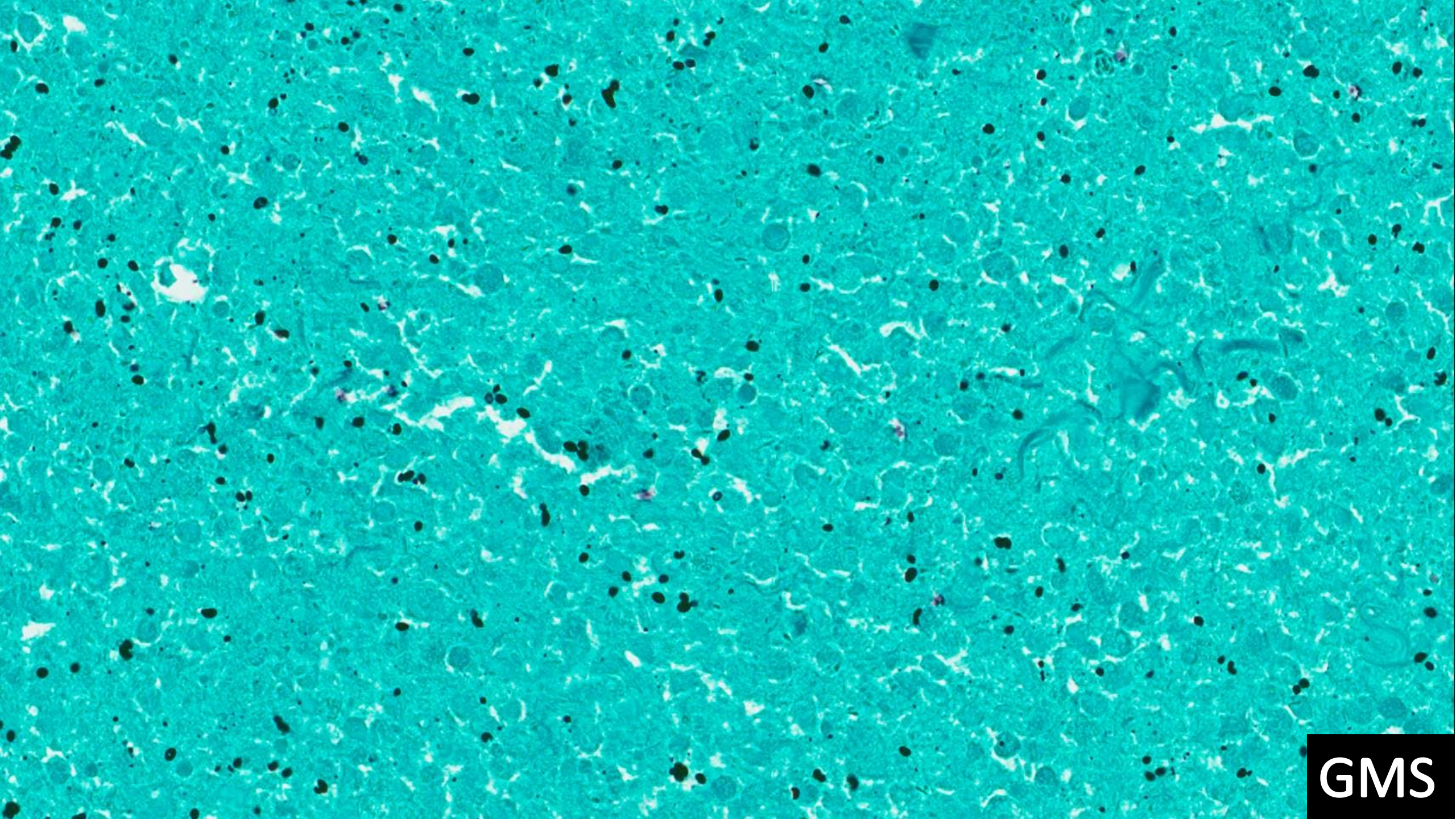

OCT 3/4

Diagnosis: Metastatic seminoma

- Take home points:
  - Testicular scars can represent regressed (“burnt-out”) germ cell tumors
    - Can present with RPLN metastases
  - Seminomas can be obscured by granulomatous inflammation
    - DDX: Infectious granulomas, nonspecific (idiopathic) granulomatous orchitis, sperm granuloma
    - Unsure? Do an OCT3/4






GMS

Localized Histoplasma epididymitis

- Clinically distinct from disseminated Histoplasmosis
  - Patients not systemically ill

- Other causes of infectious granulomatous orchitis:
  - Syphilis
  - Tuberculosis
  - Brucellosis
  - Other fungi

Testicular scars can represent regressed (“burnt-out”) germ cell tumors

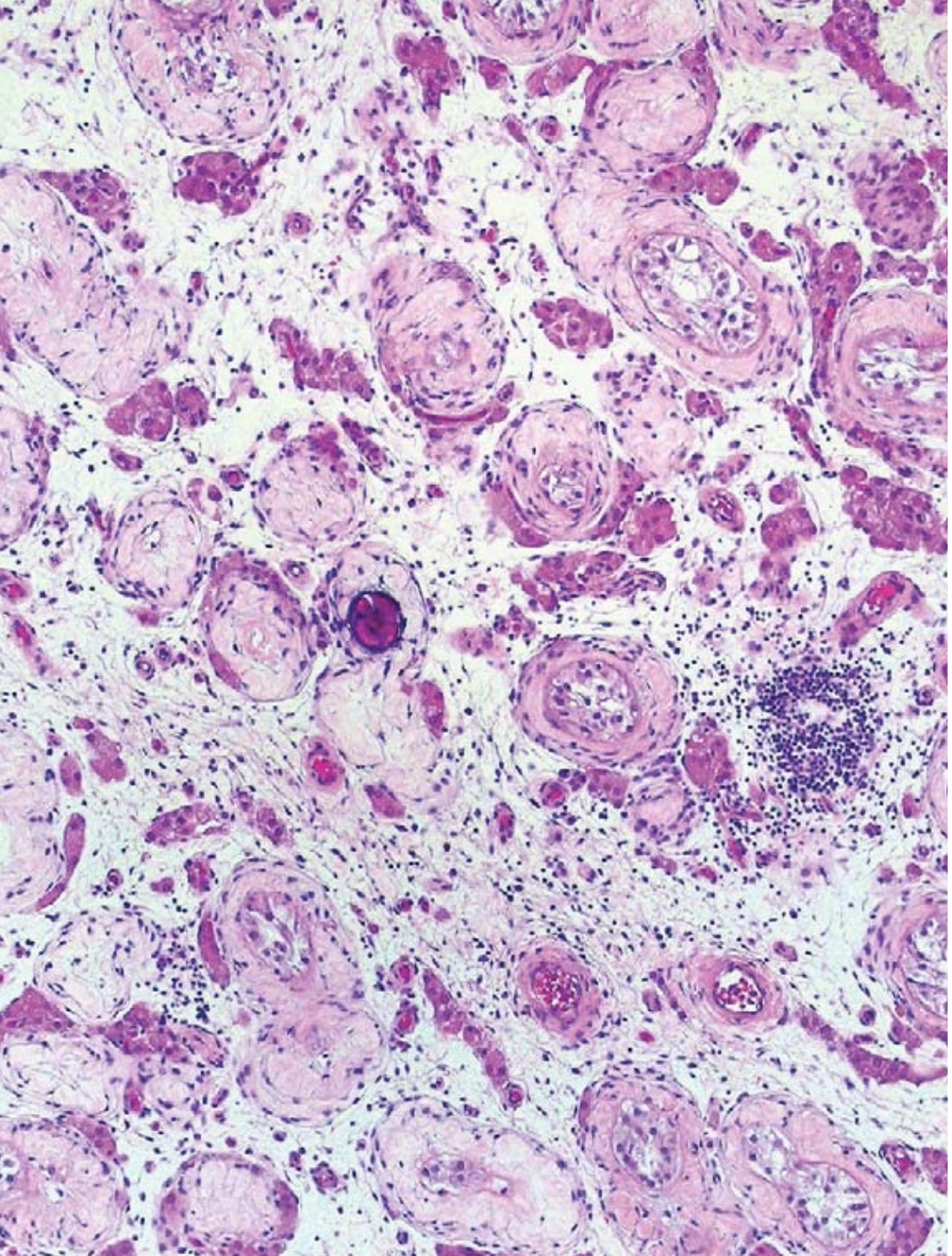
- Are there characteristics of testicular scars that can suggest a regressed germ cell tumor?

Regressed (“burnt-out”) germ cell tumors

- Balzer and Ulbright (*Am J Surg Pathol* 2006;30:858-865)
- 42 cases
  - 100% scar: 26 cases, >50% scar: 16 cases
  - 37 (88%) cases with known metastatic GCT or residual testicular GCT

Regressed ("burnt-out") germ cell tumors (Balzer et al)

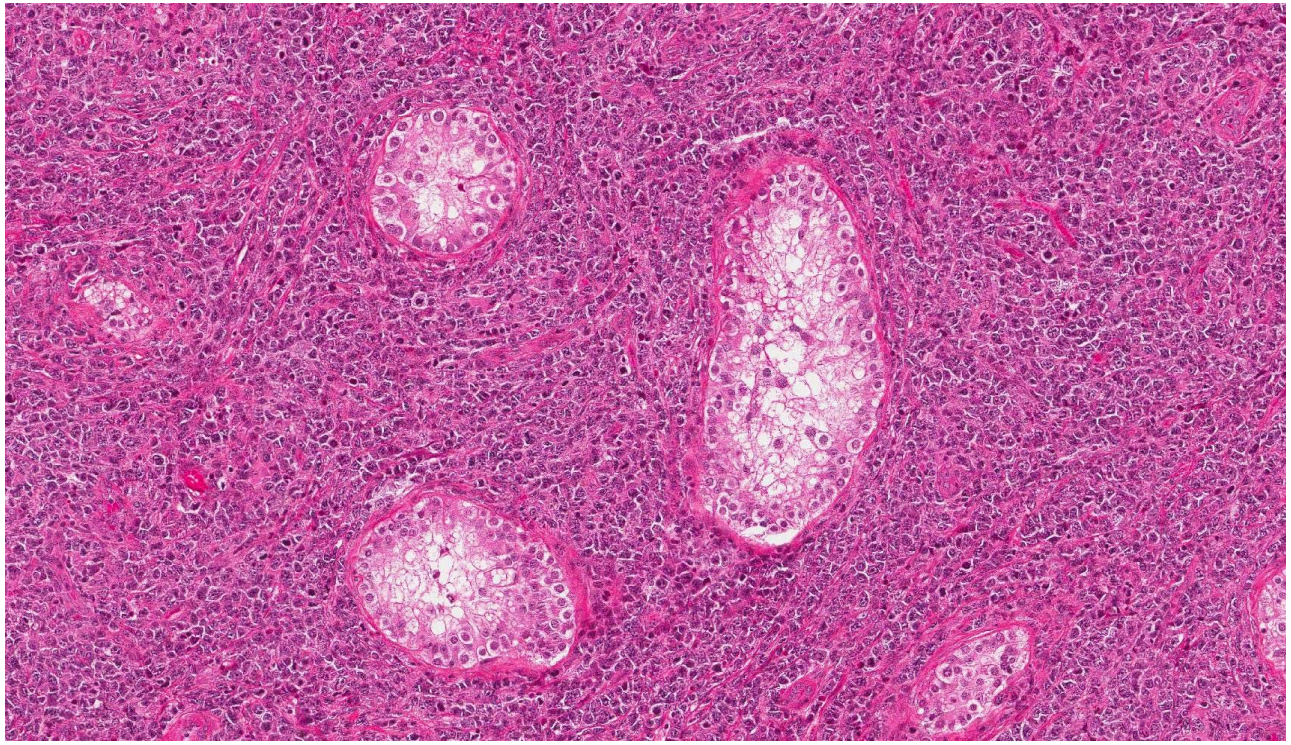
- All cases:
  - Circumscribed to irregular SCAR + widespread atrophy
- Other common features (within scar):
  - Lymphoplasmacytic infiltrate
  - "Ghost" tubules
  - Angiomatous foci
  - Siderophages
  - Coarse intratubular Ca^{2+}
- Common features (surrounding testis)
  - GCNIS
  - Leydig cell prominence
  - Necrosis
  - Tubular microliths
- DDx:
  - Nonspecific atrophy – no distinct scars
  - Scars from other causes – lack associated findings



Balzer and Ulbright

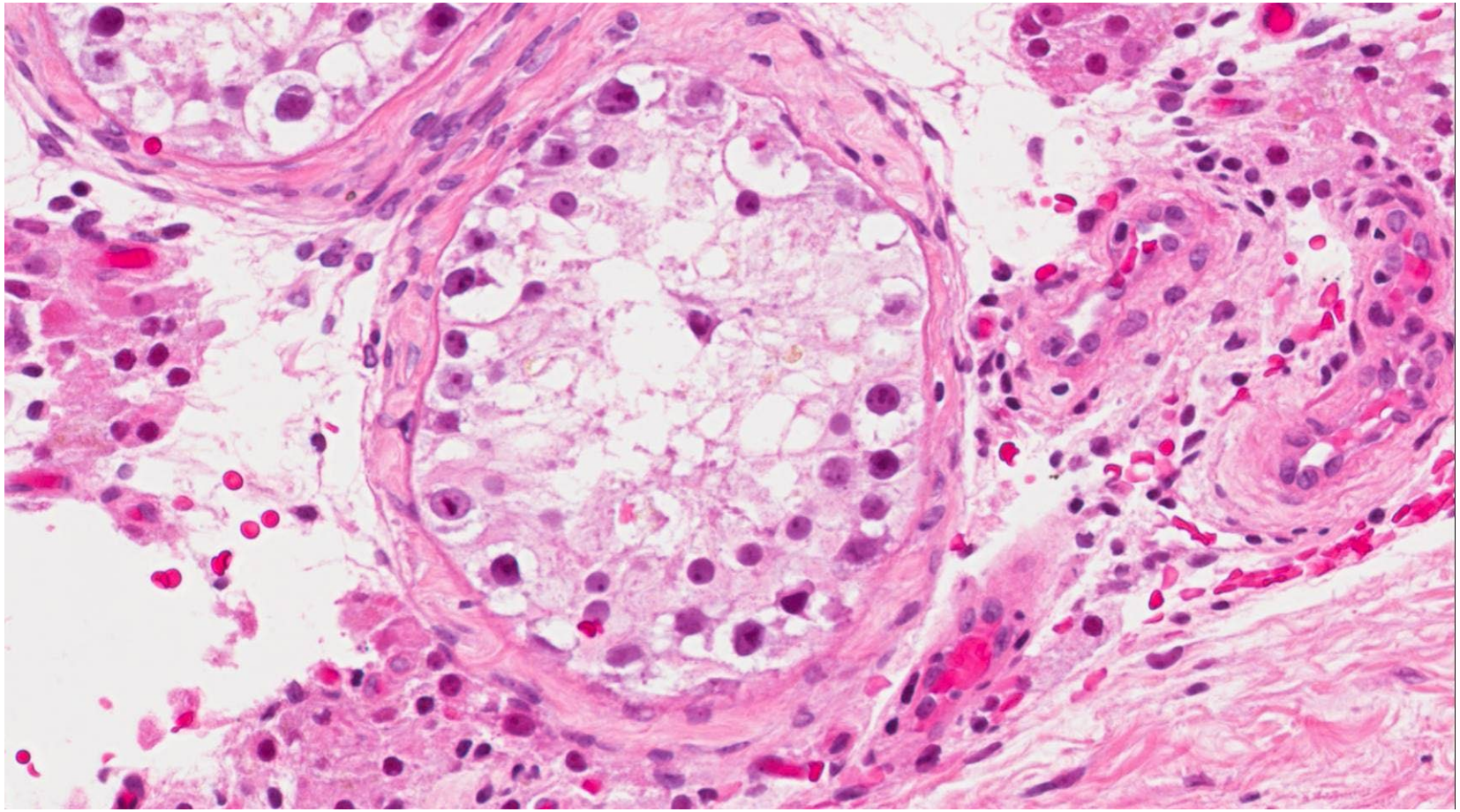
(*Am J Surg Pathol* 2006;30:858-865)

Spermatocytic tumor – differential diagnosis

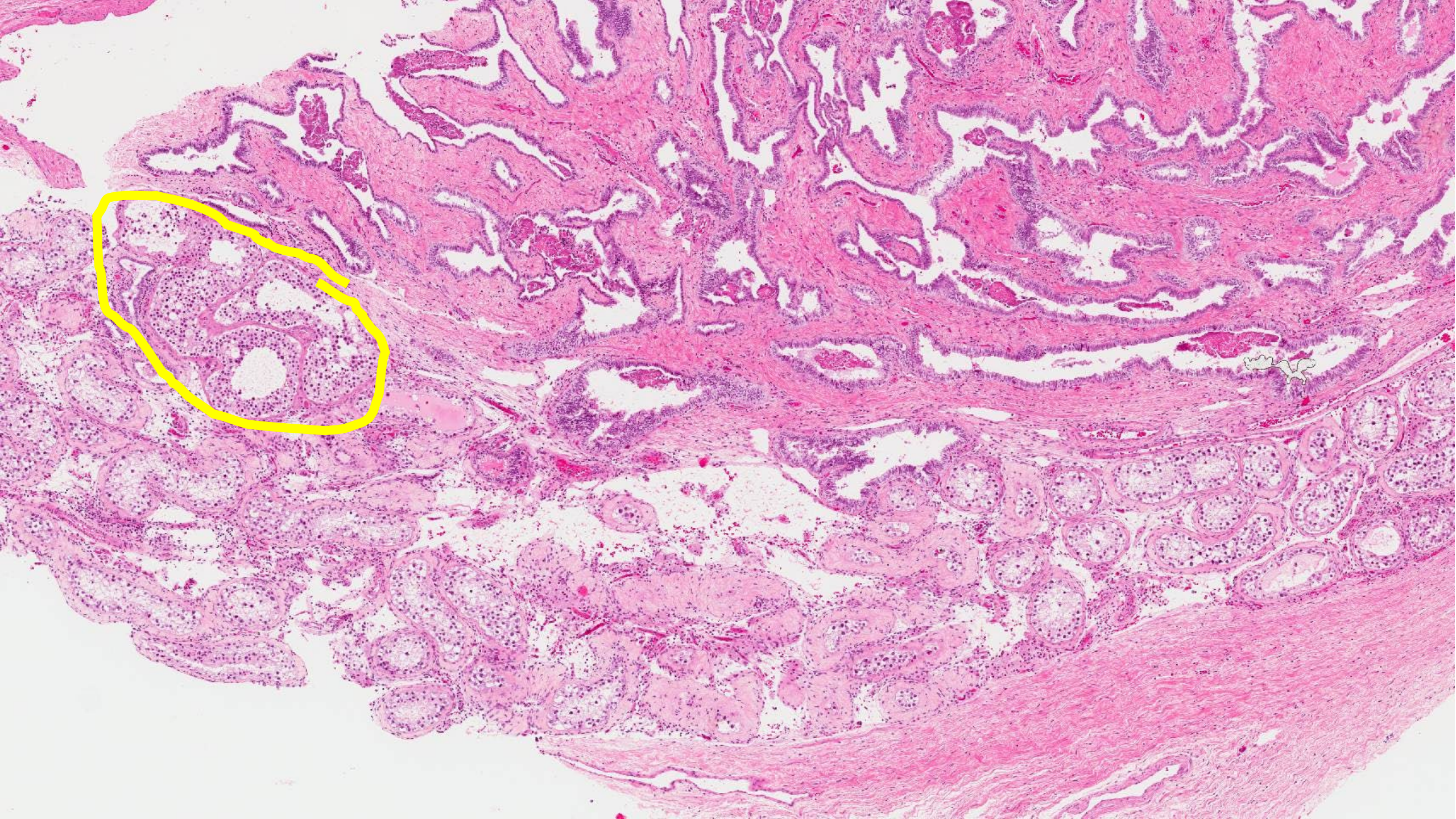


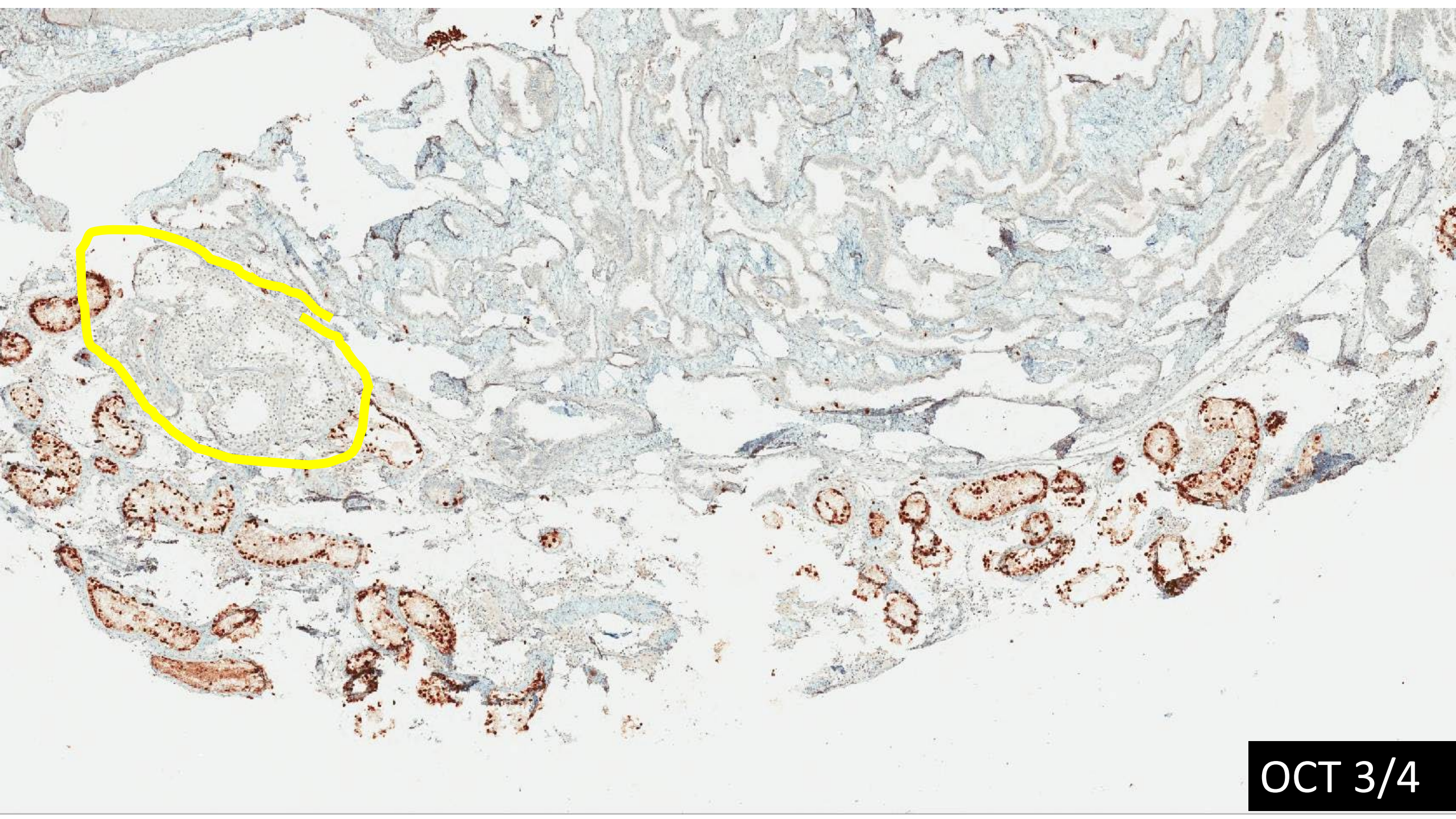
- Hematopoietic neoplasms
  - Lymphoma
    - 1°or 2°
    - Diffuse growth
    - Often bilateral
    - Systemic symptoms
  - Plasmacytoma
  - Leukemic infiltrate
- Distinguish via IHC

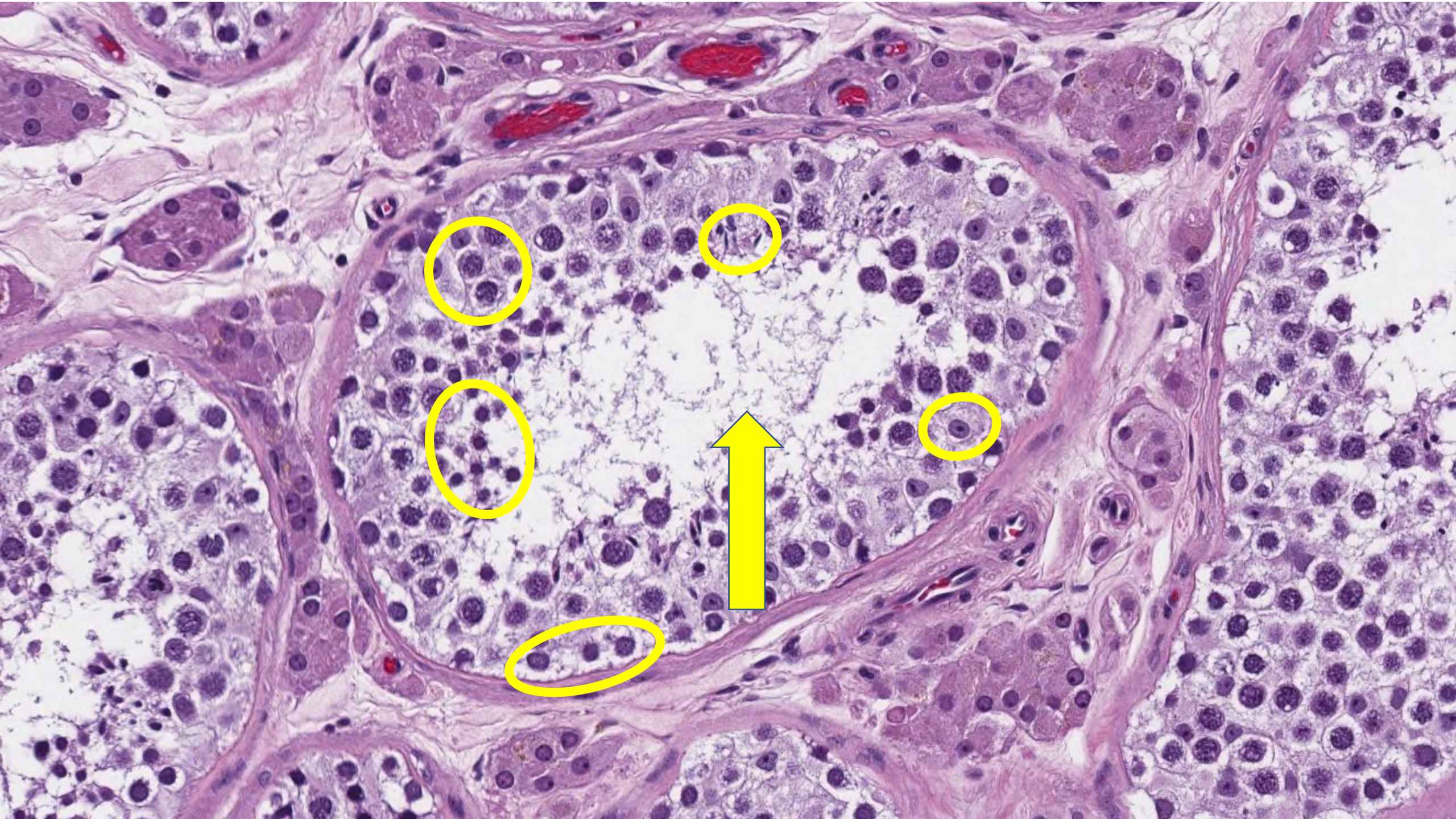
Germ cell neoplasia in situ (GCNIS)*

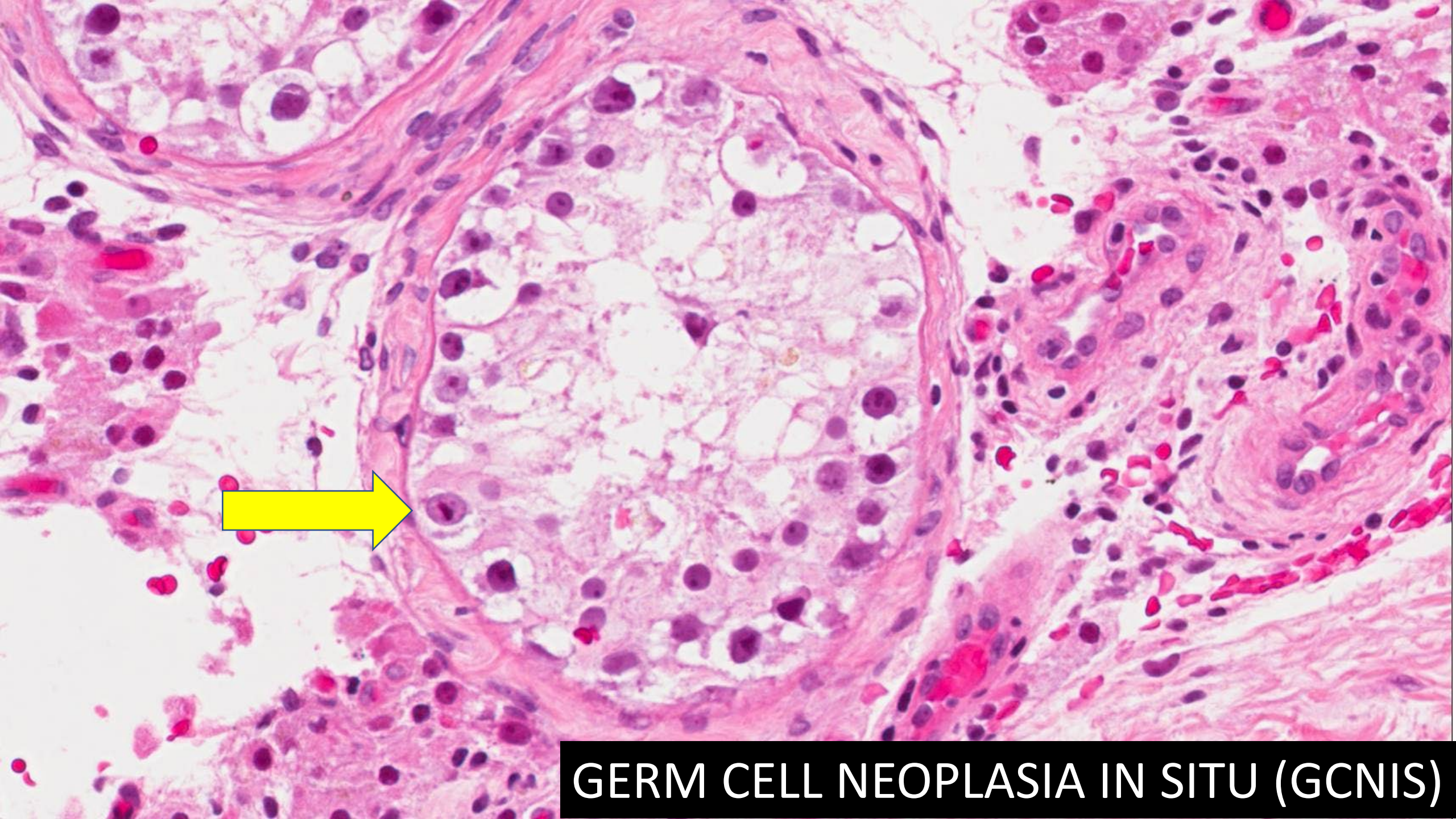


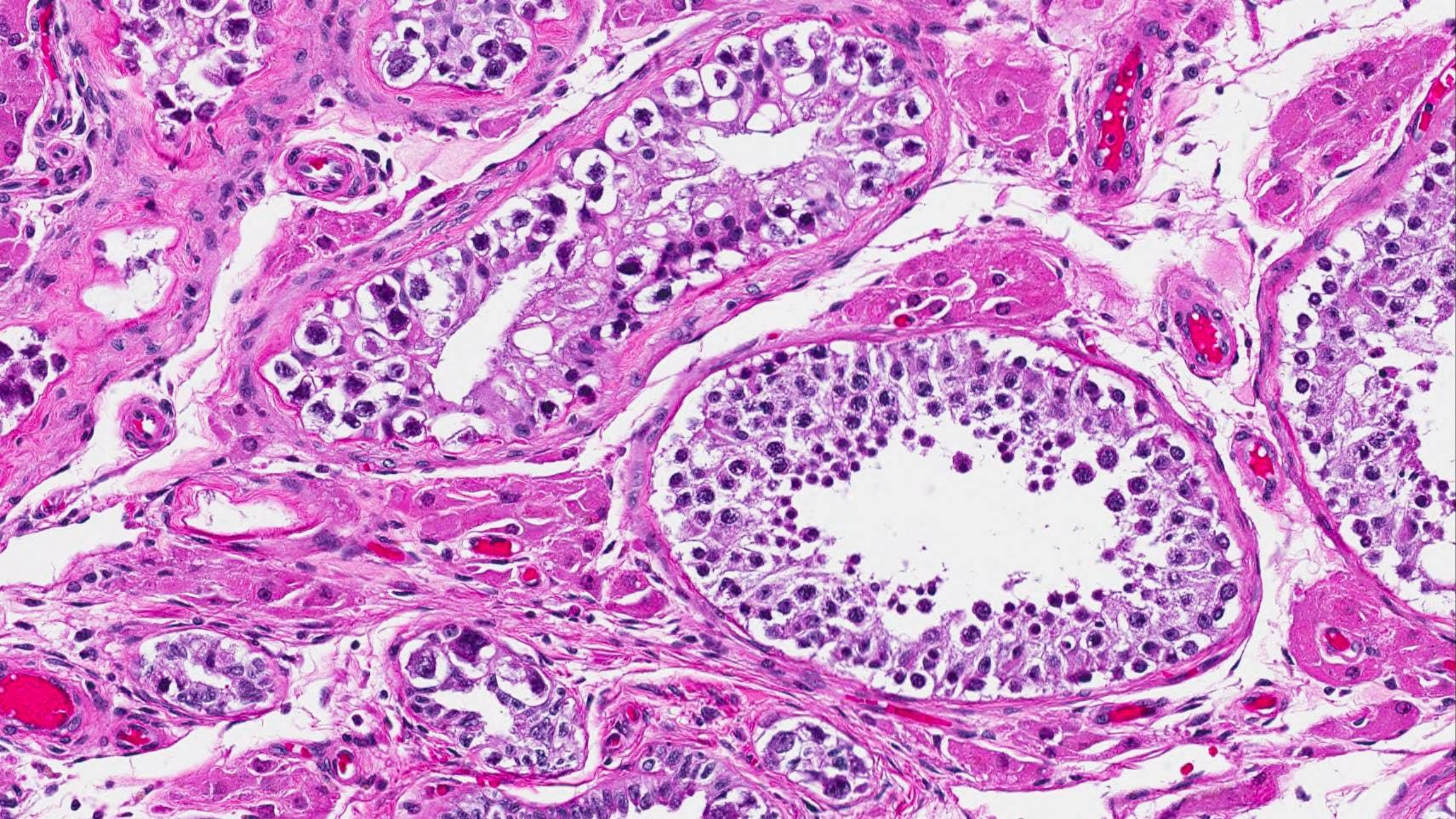
*Formerly intratubular germ cell neoplasia (ITGCN)

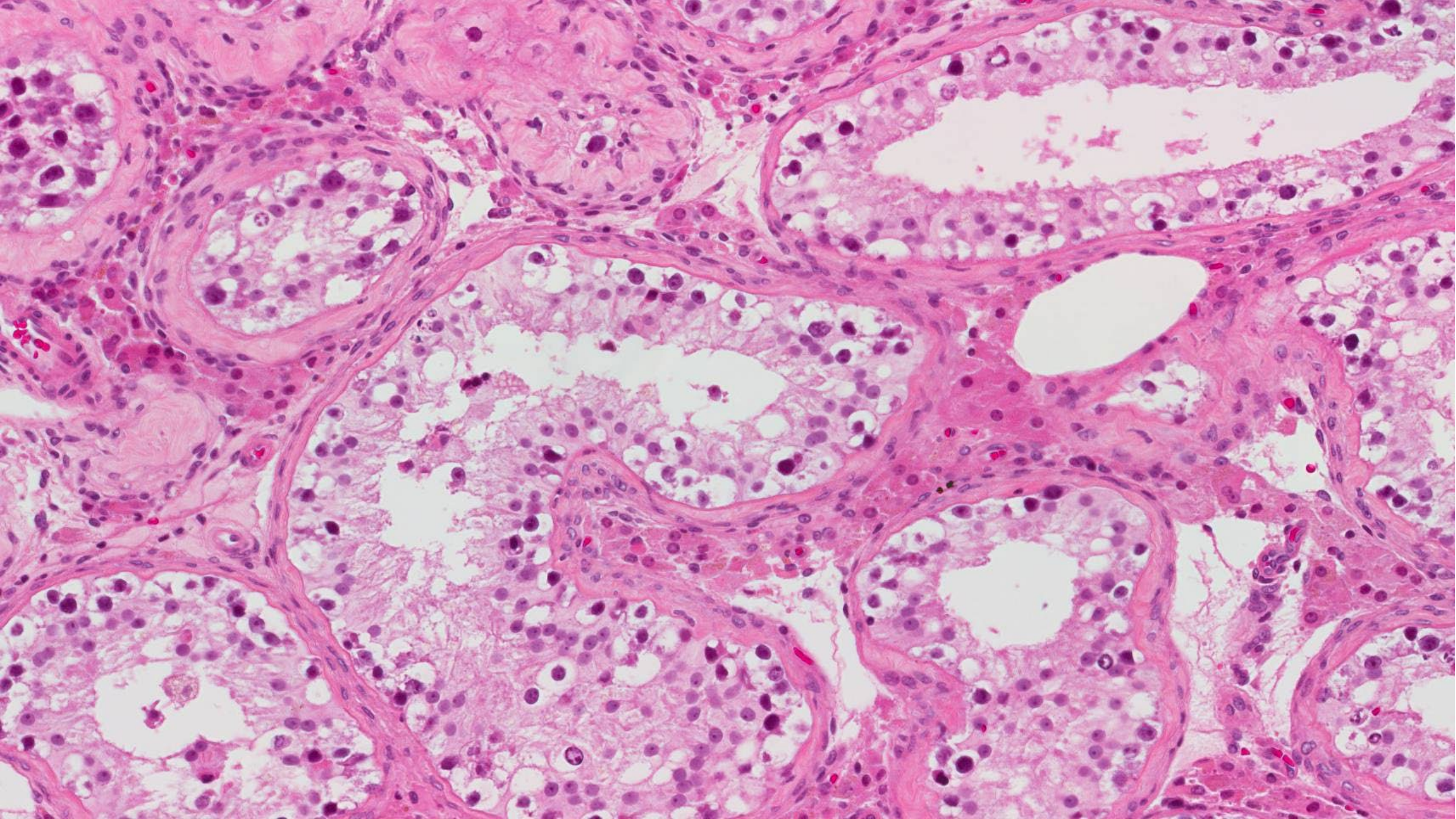


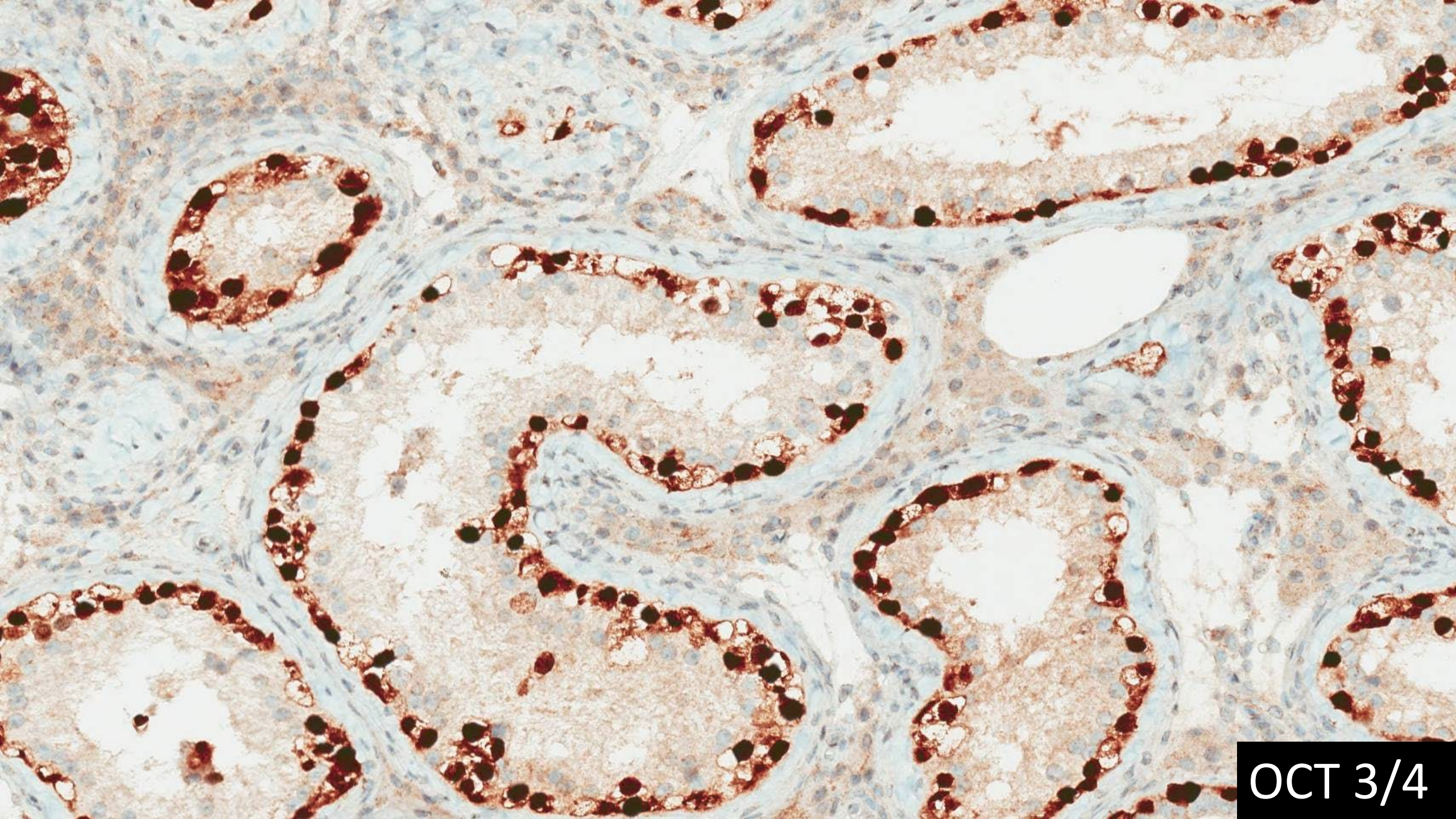

OCT 3/4




GERM CELL NEOPLASIA IN SITU (GCNIS)



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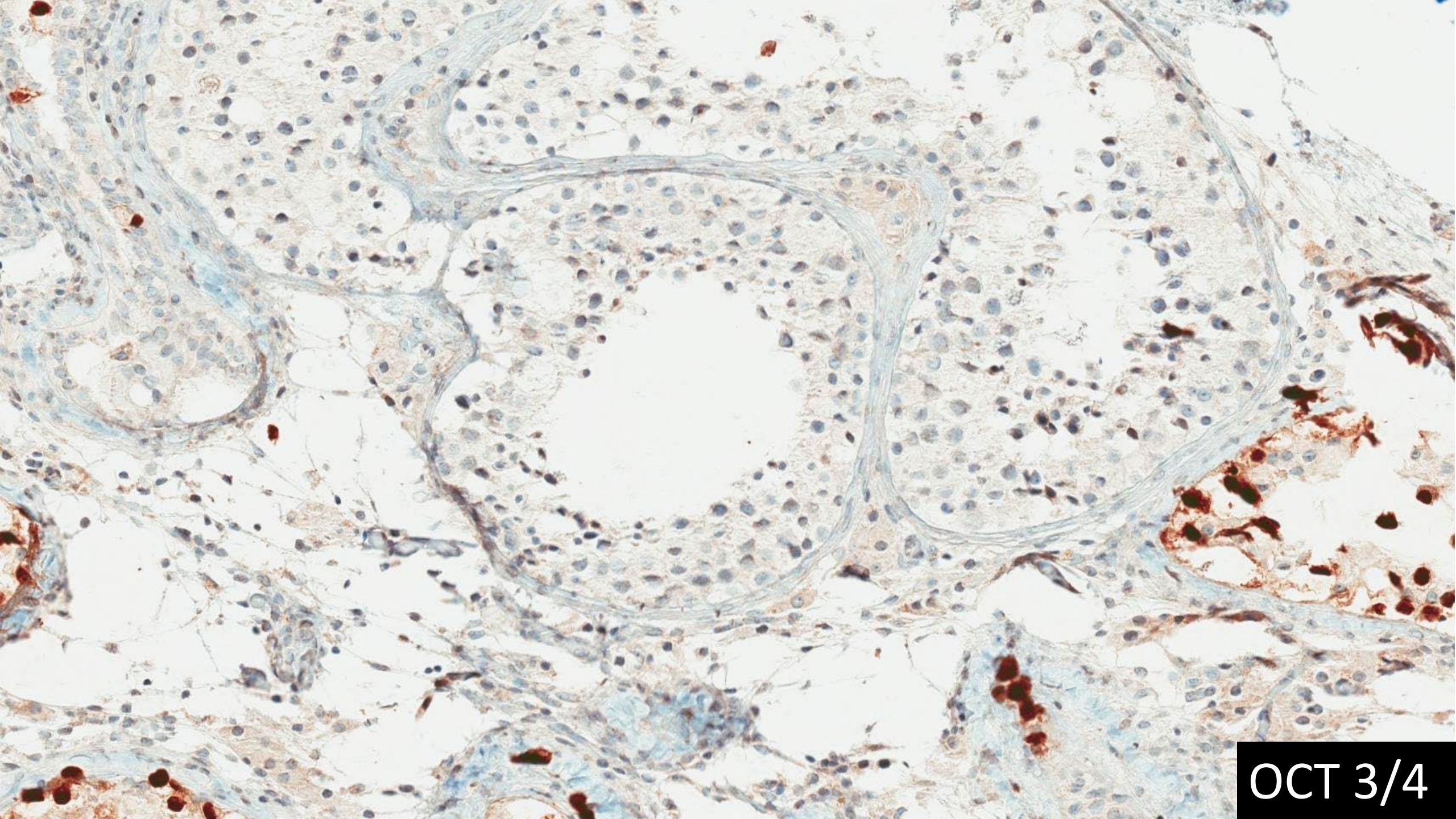
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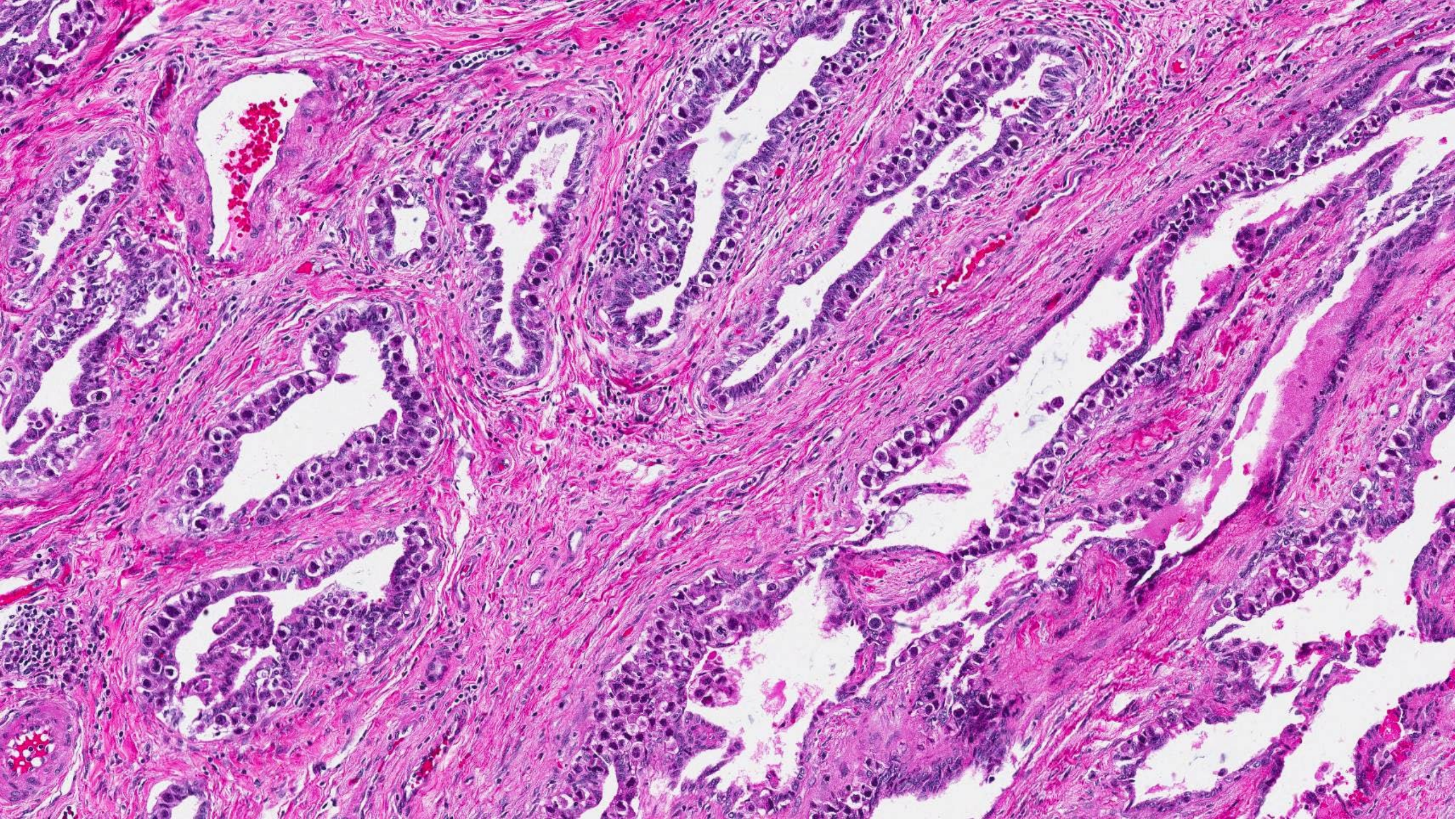
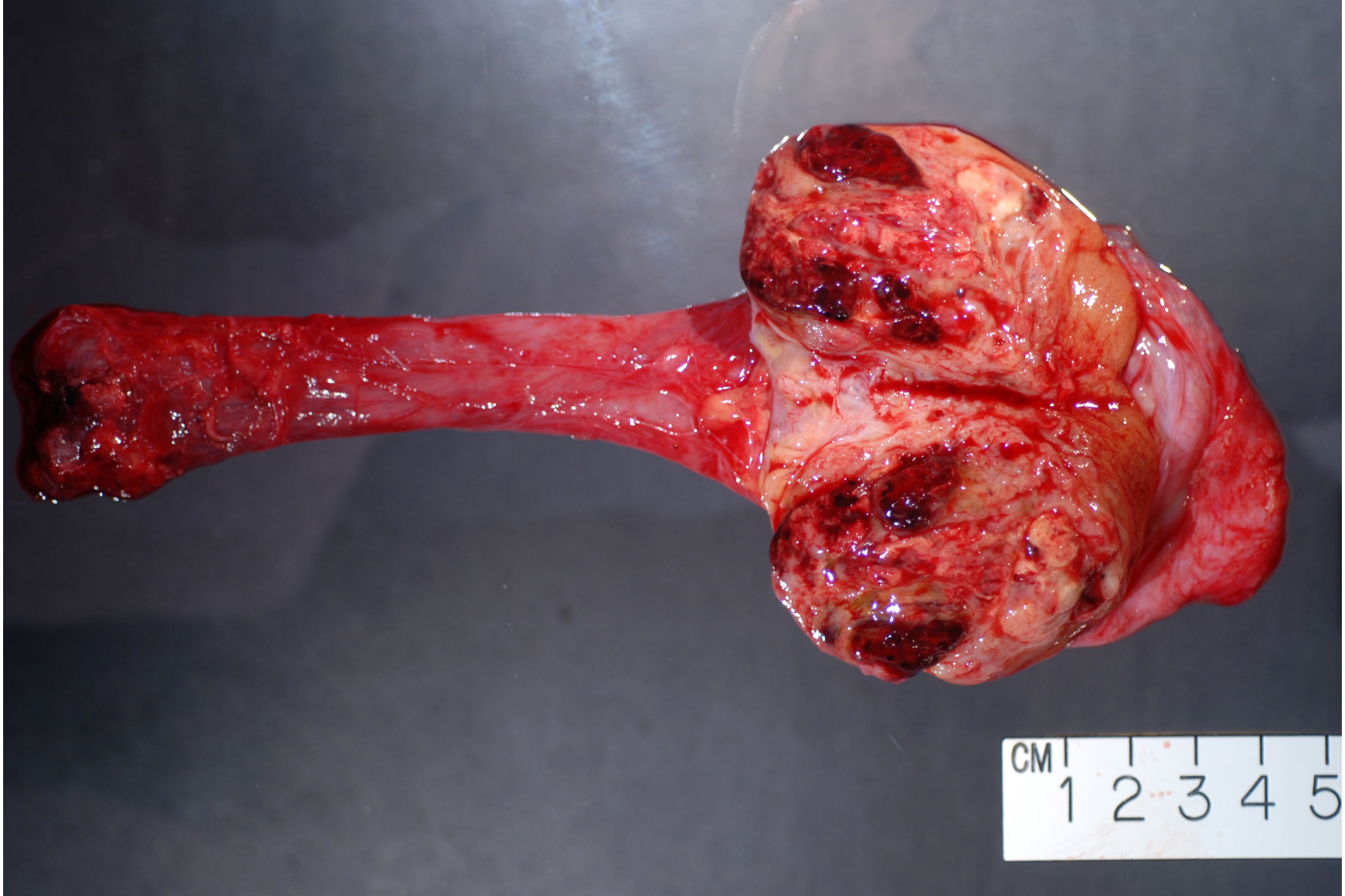
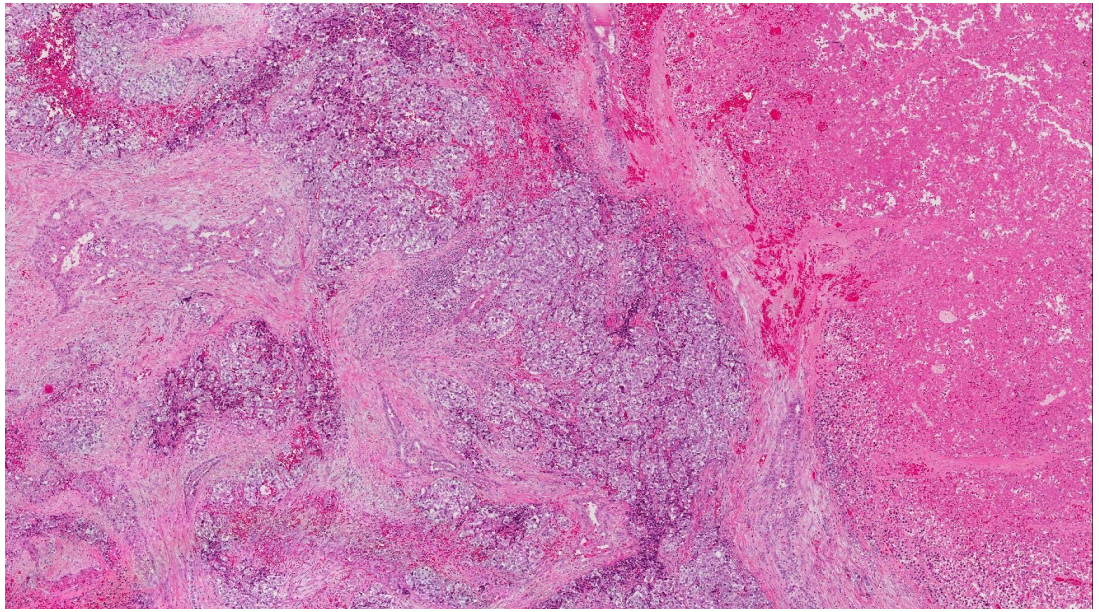


Case 2

Testicular mass – 25-year old man

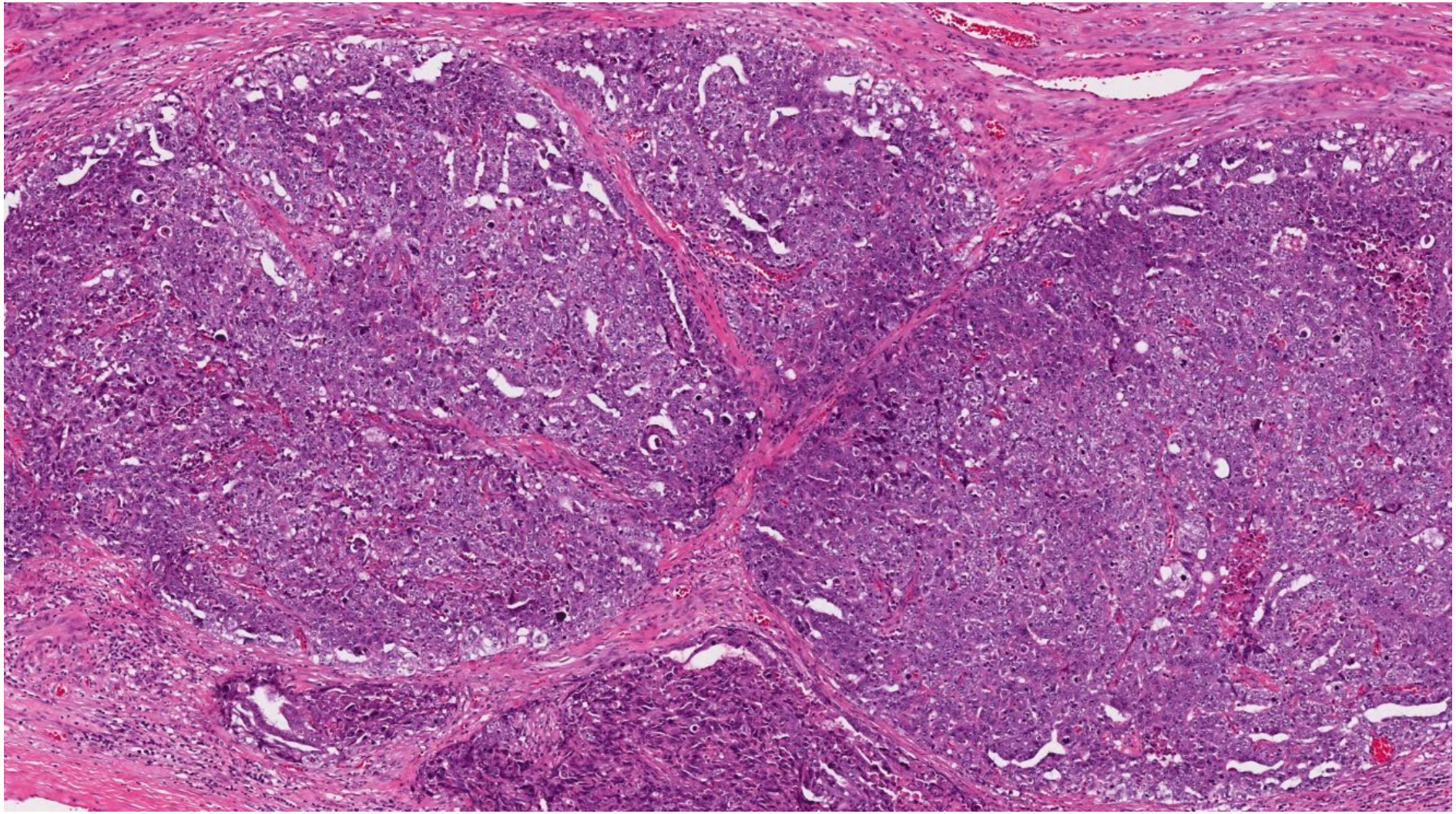

CM
1 2 3 4 5

Considerations in mixed germ cell tumors

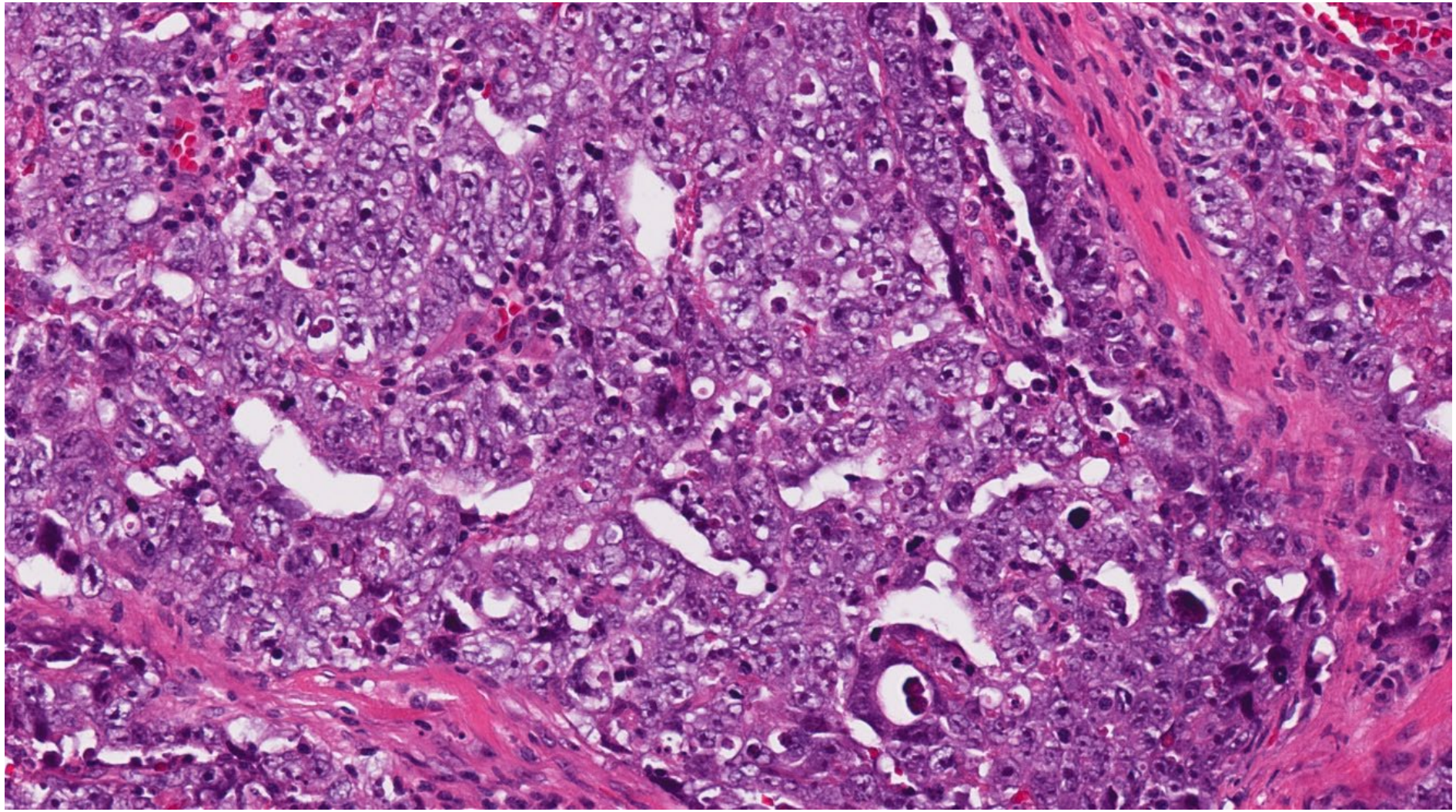


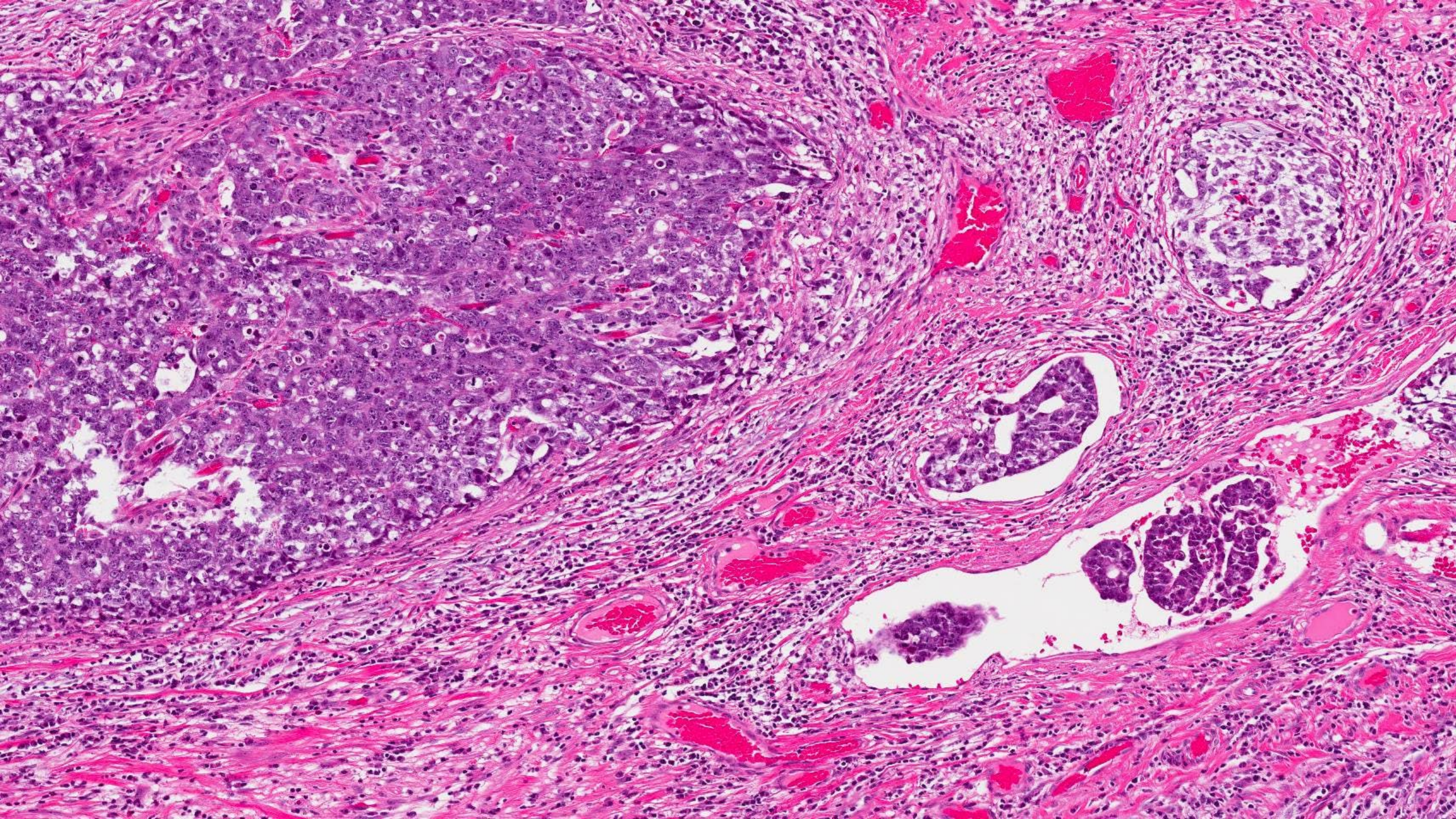
- Importance of classifying GCT components and proportions
  - Influences prognosis
  - Patterns of metastasis (e.g. lung, liver, and bone in chorio)
  - Treatment (seminomatous vs nonseminomatous)
- Gross examination – tumor heterogeneity
  - Sample necrotic and hemorrhagic areas
  - At least 1 section per cm

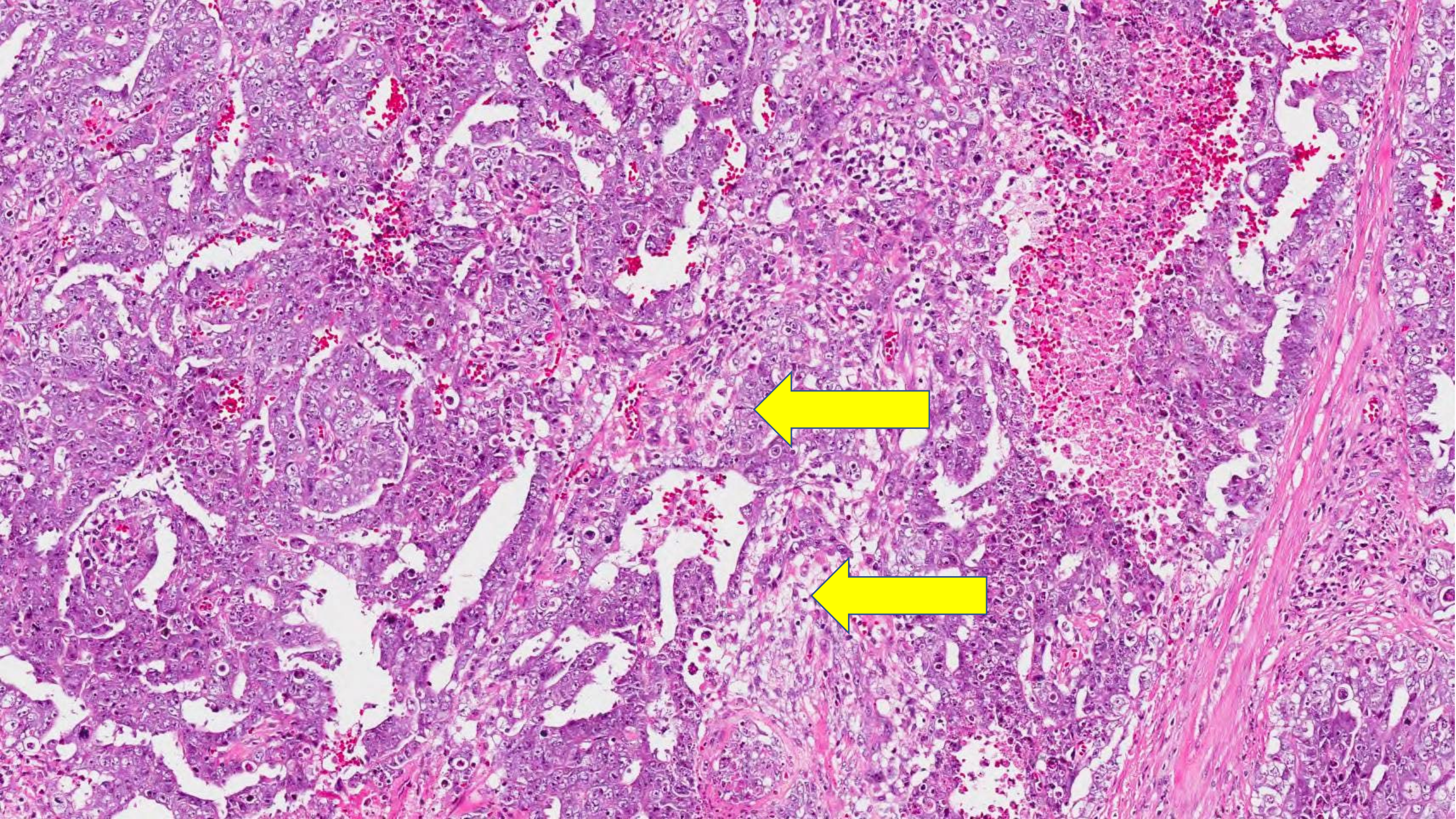
Embryonal Carcinoma

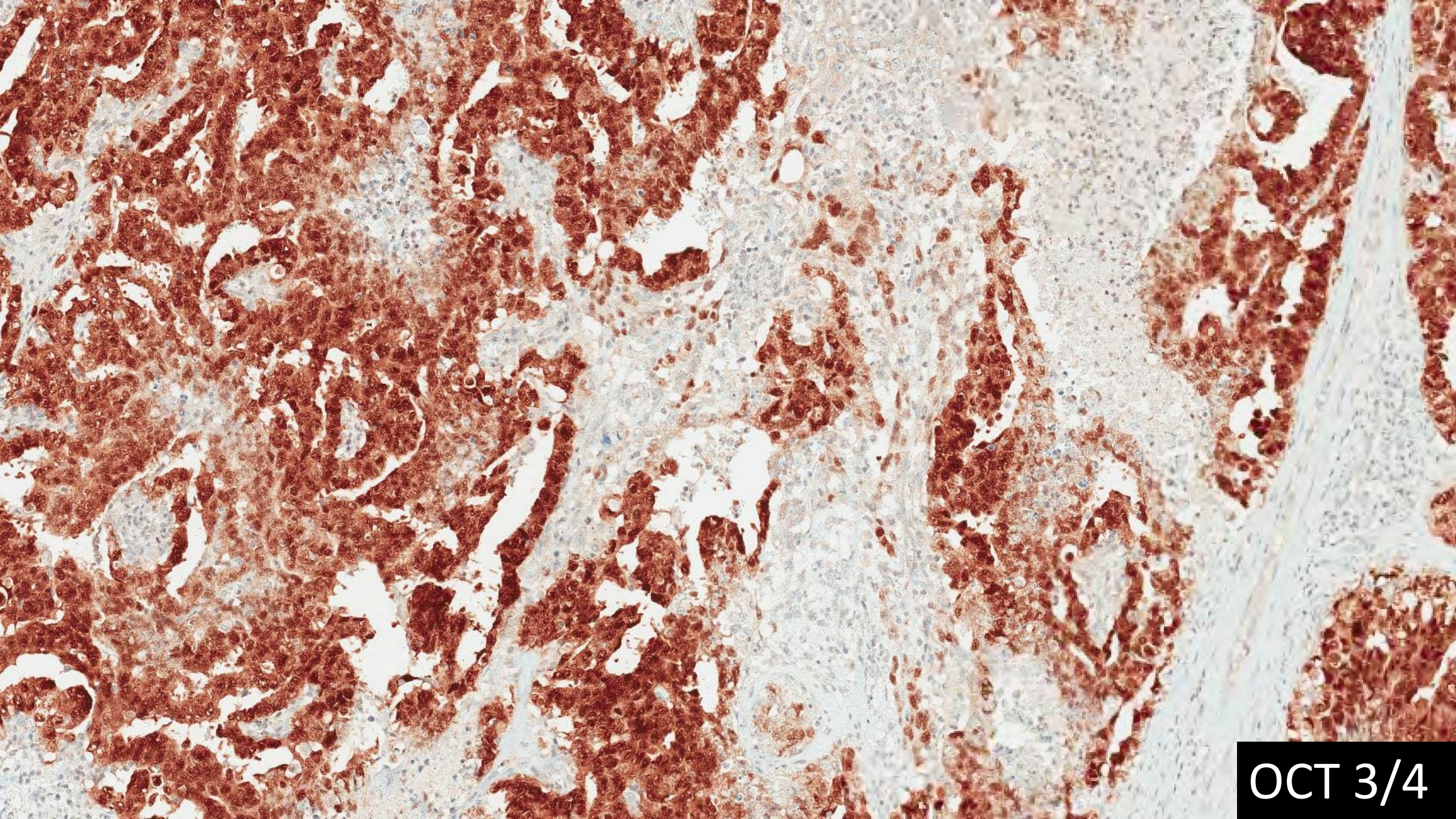


Embryonal Carcinoma





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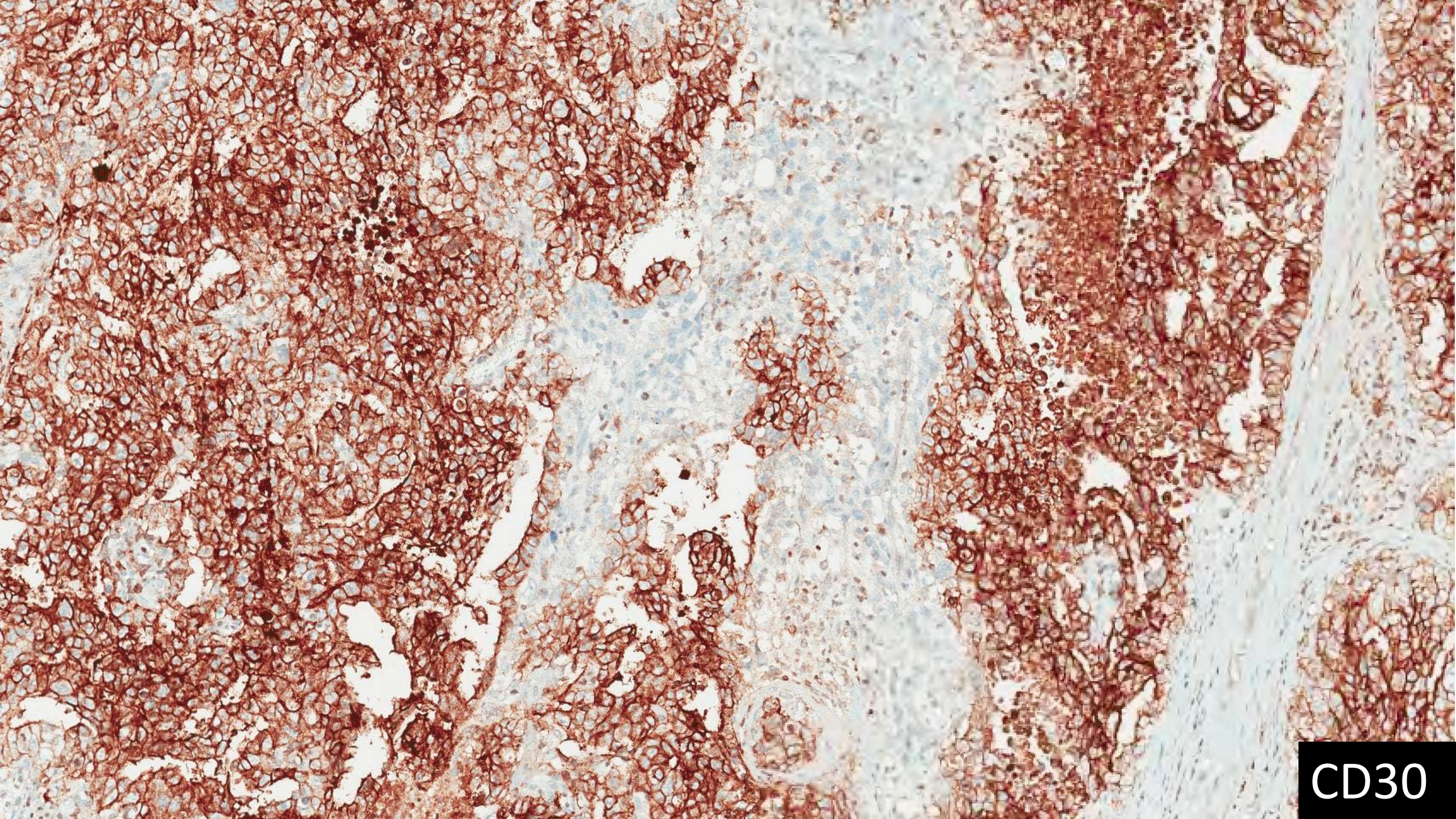
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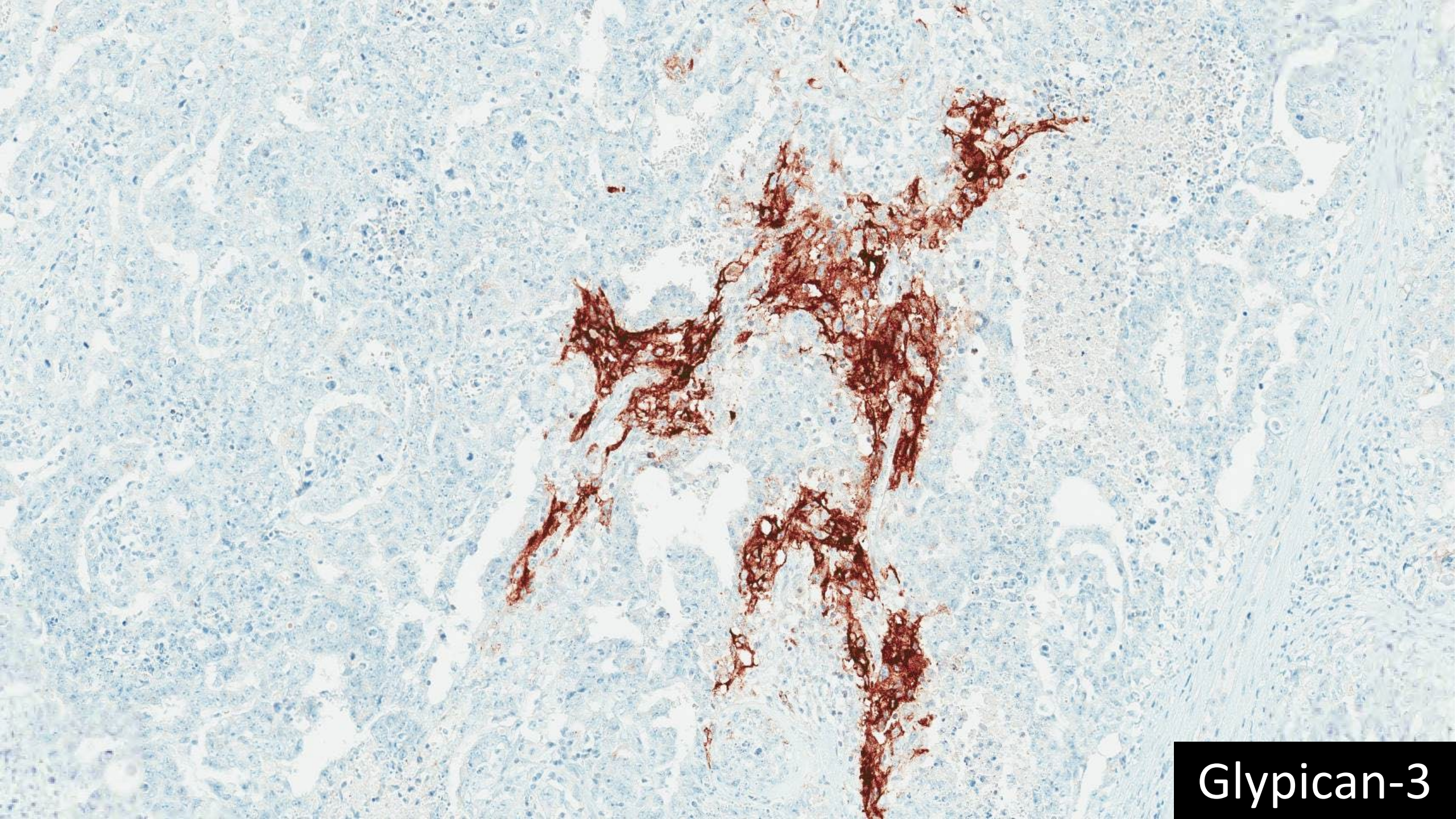
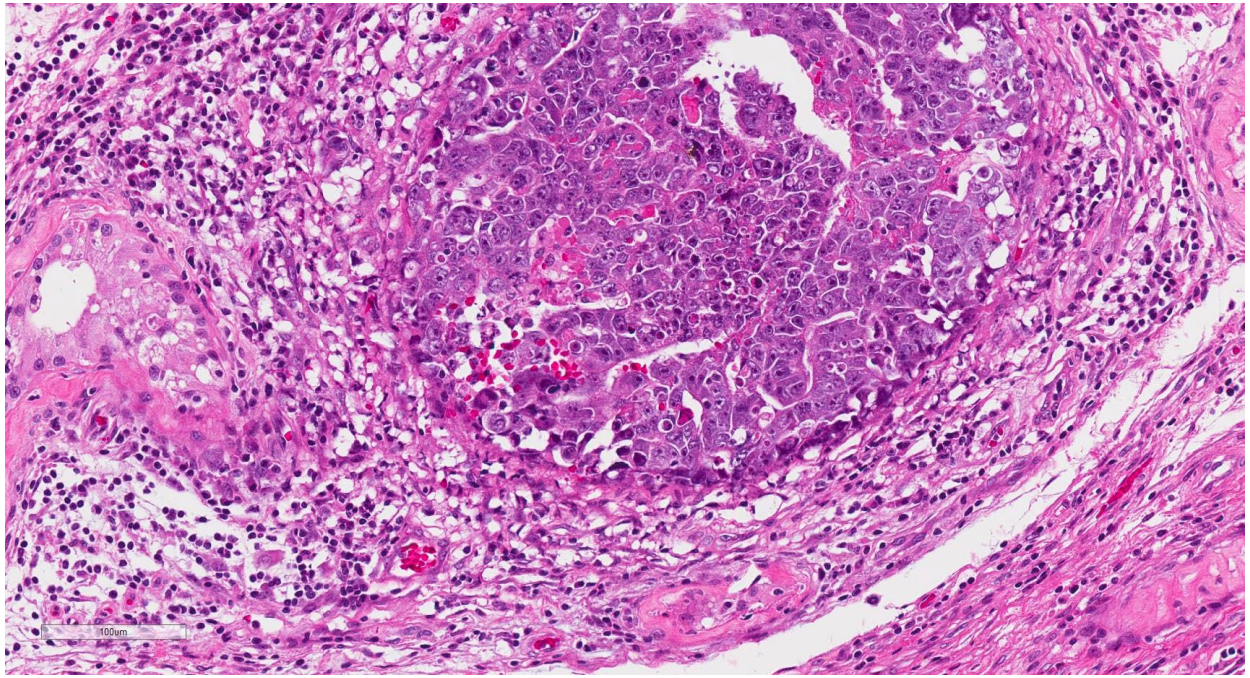
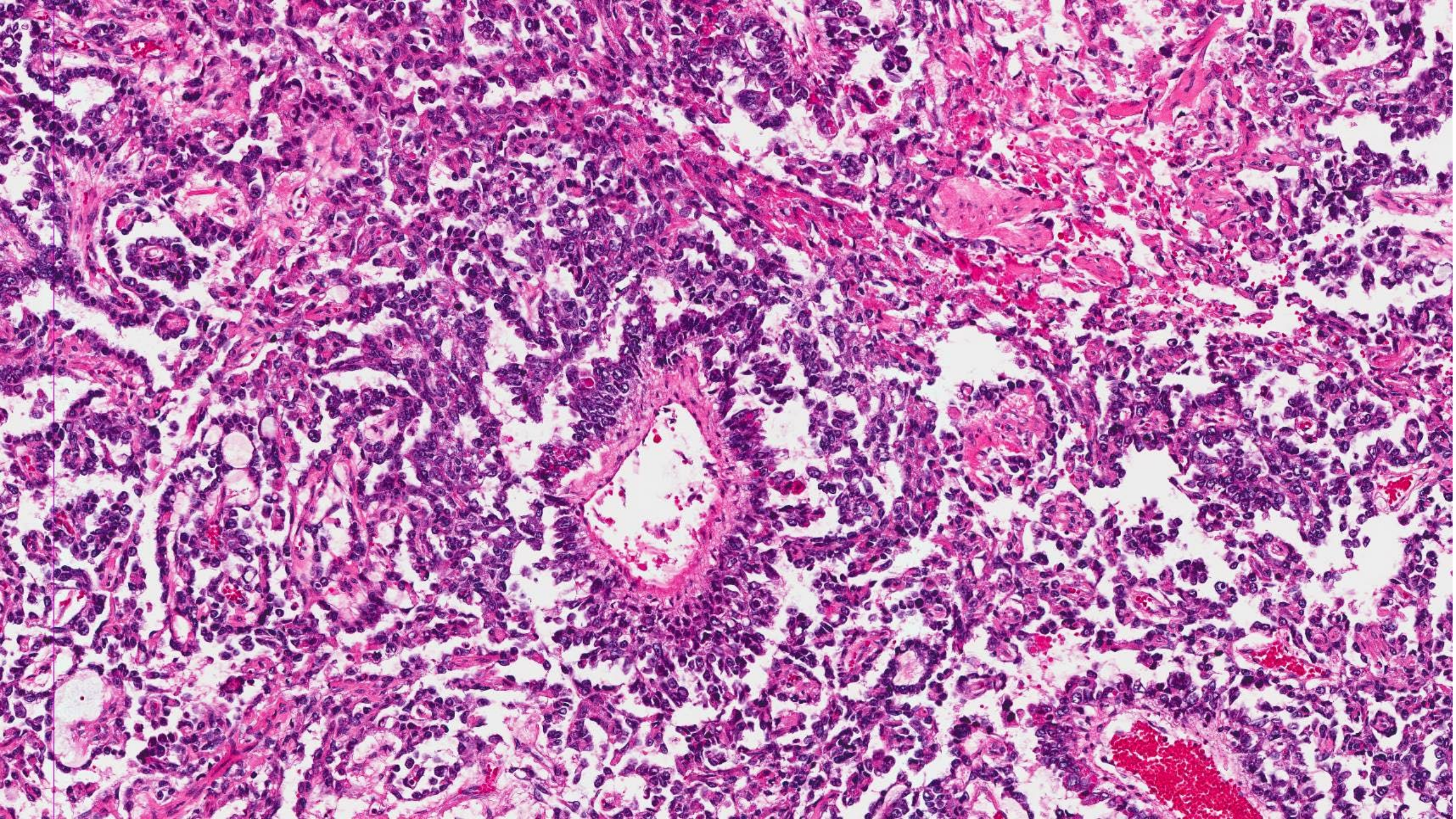
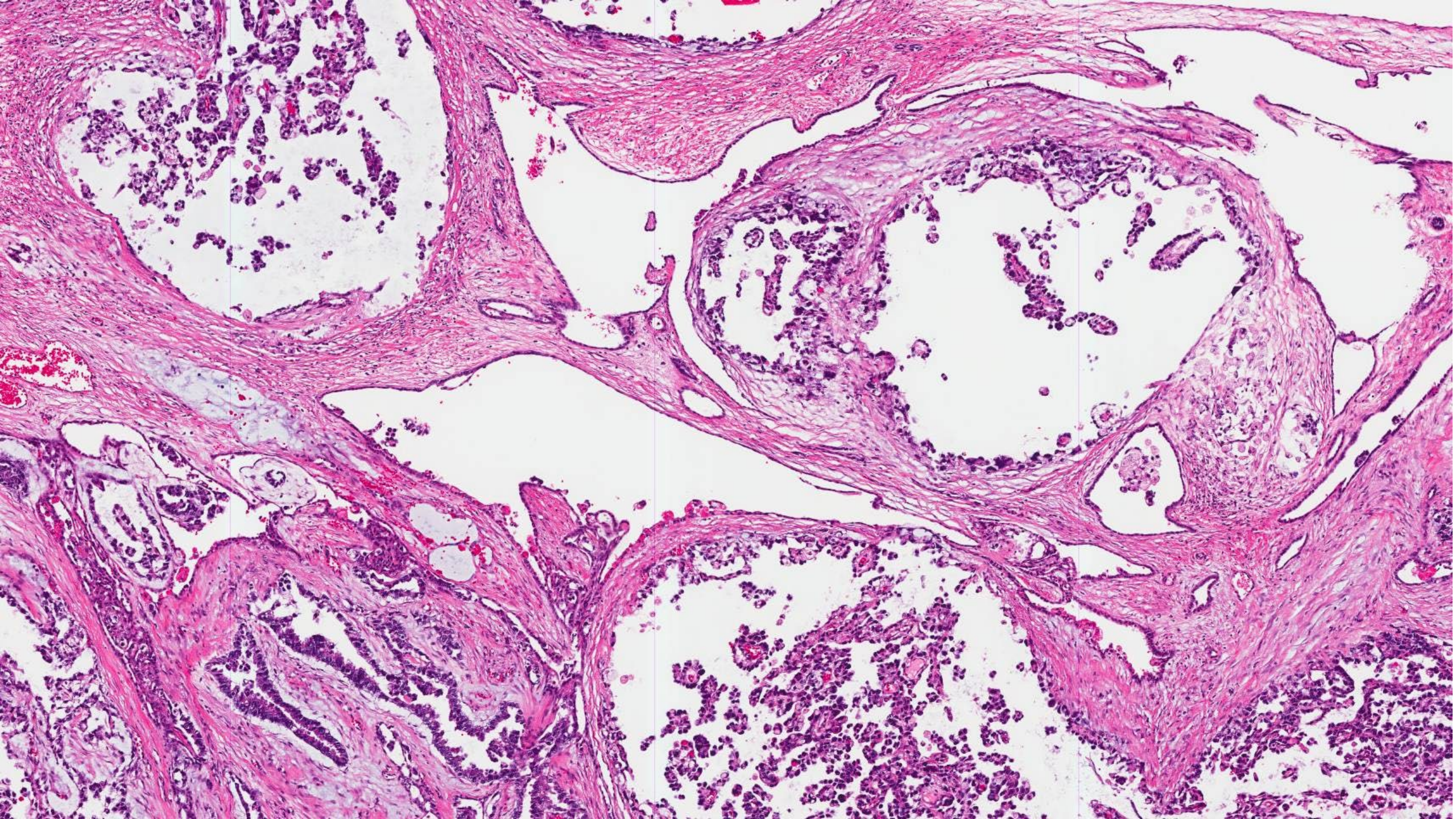

Glypican-3

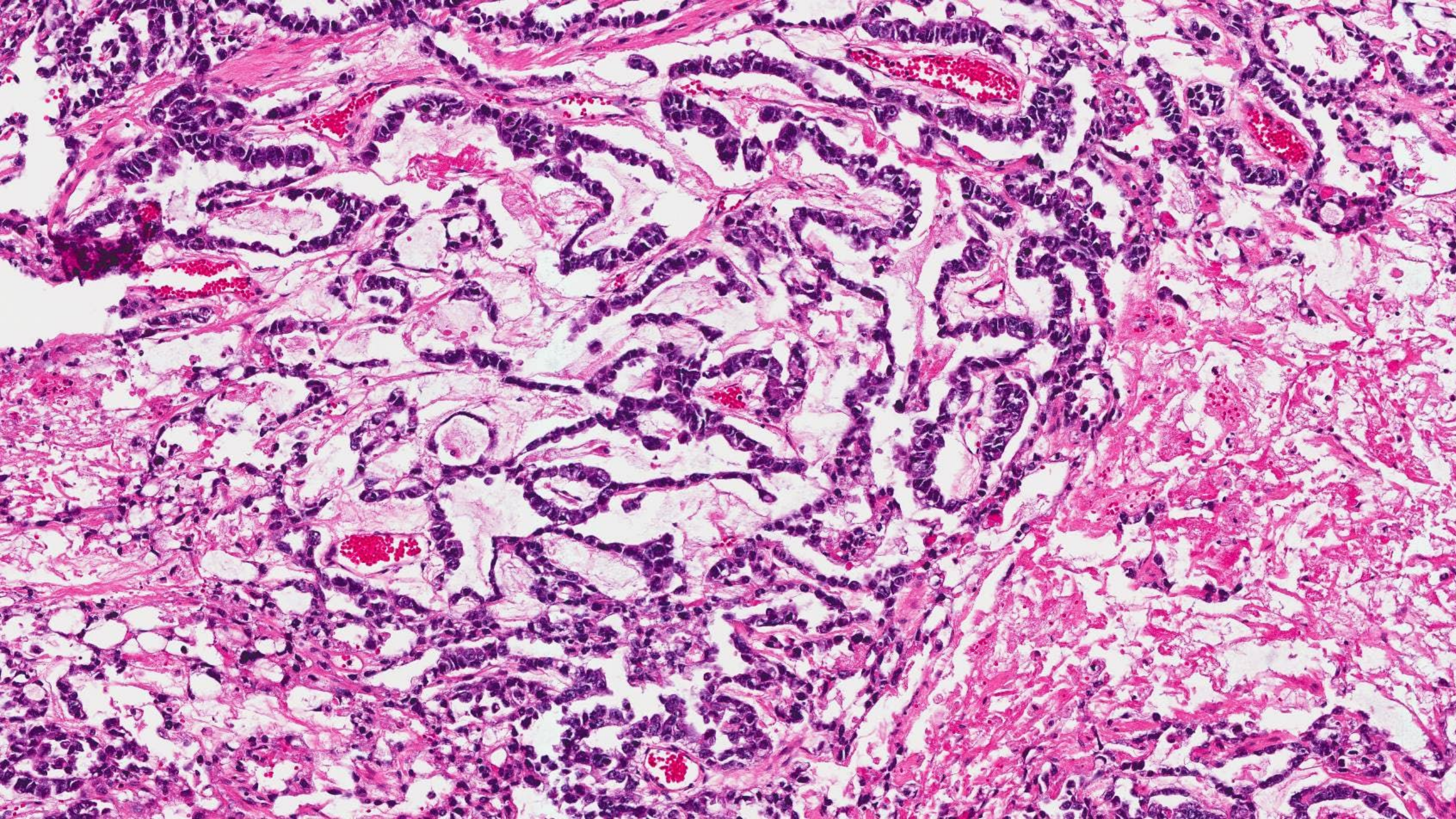
Architectural variety in GCT components

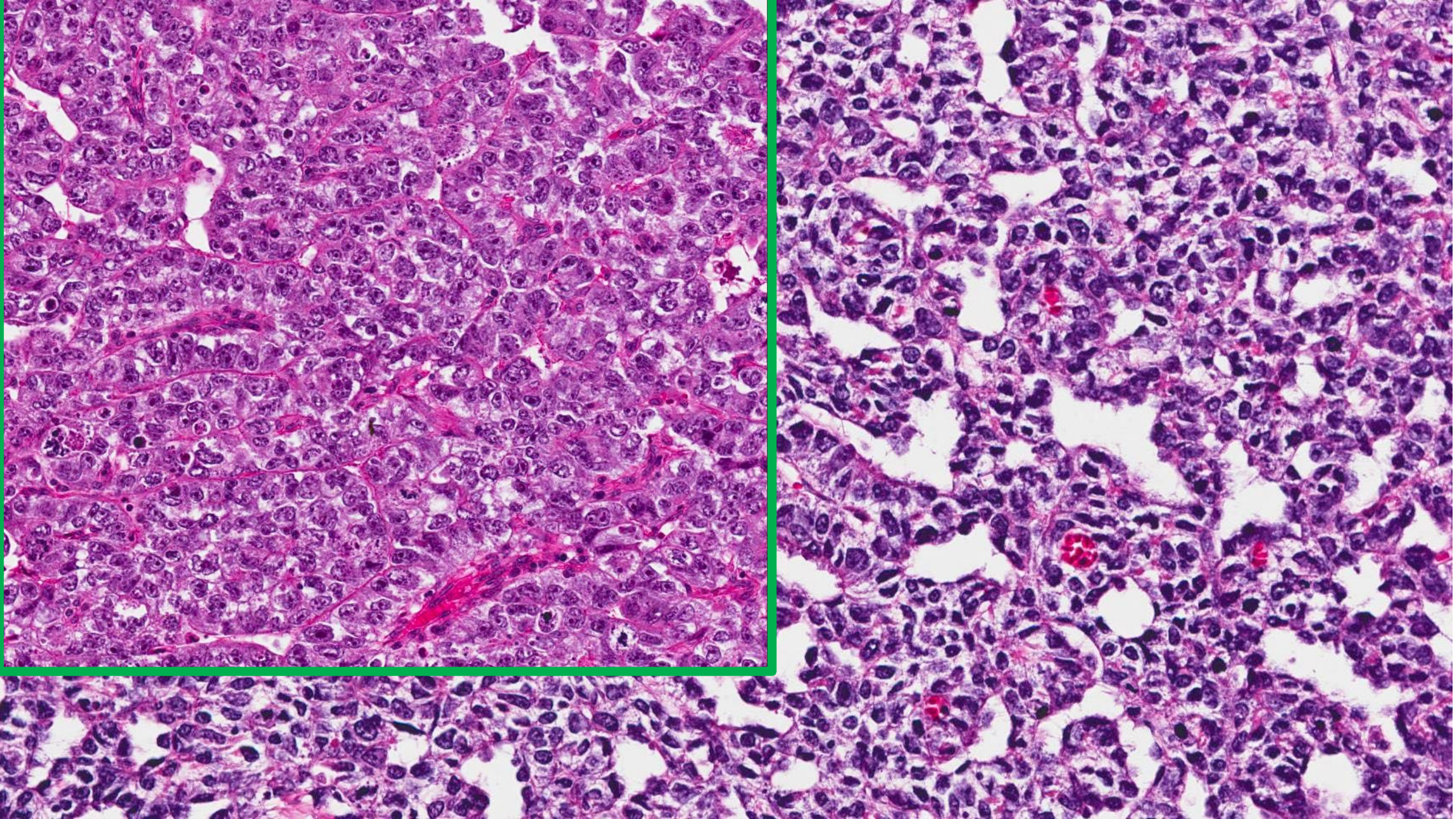


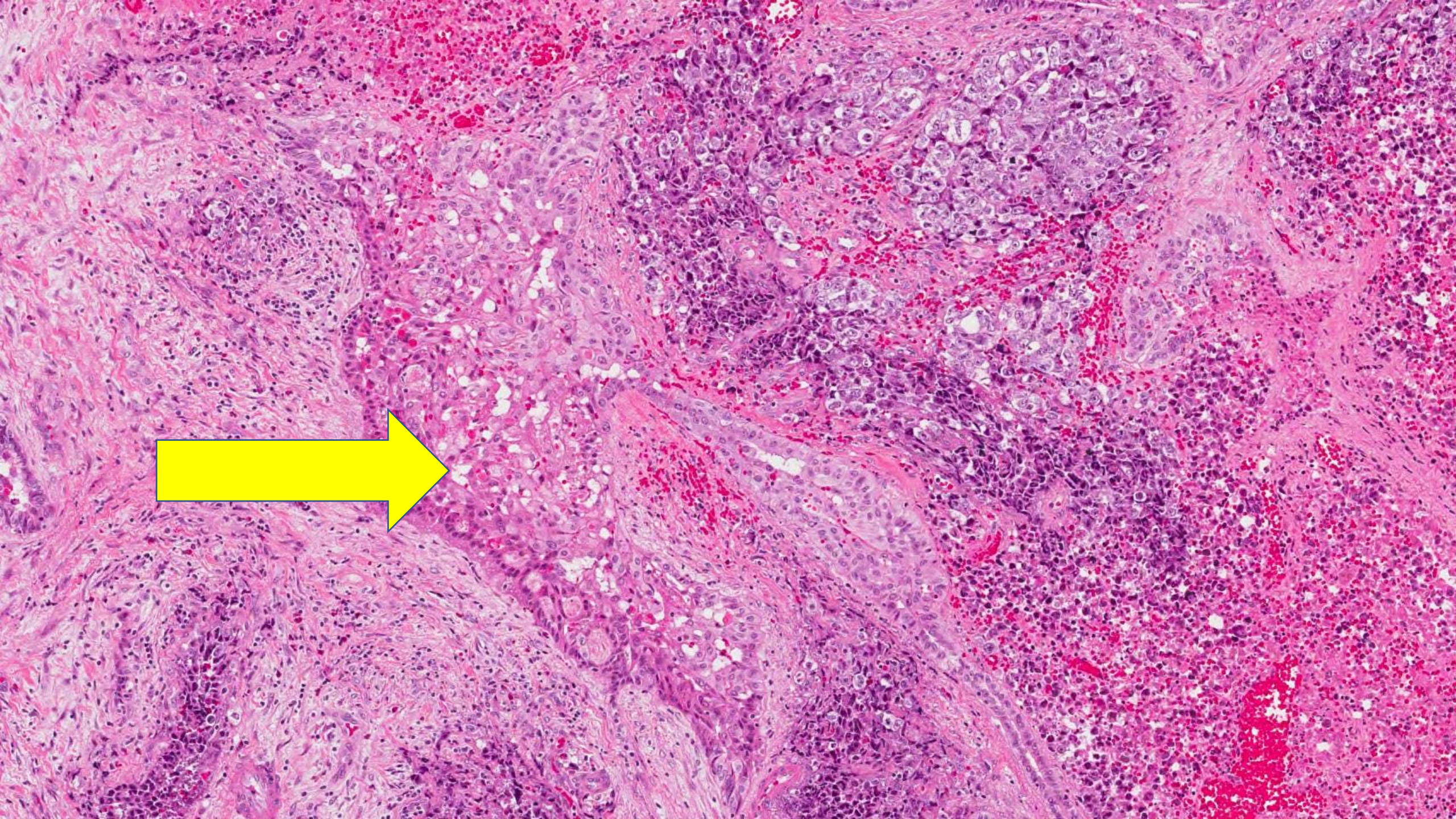
- Embryonal carcinoma
  - Solid
  - Glandular
  - Papillary
- Yolk sac tumor
  - Microcystic (reticular)
  - Endodermal sinus
  - Solid
  - Papillary
  - Polyvesicular vitelline
  - Glandular
  - Parietal
  - Endometrioid
  - Hepatoid
  - Spindled

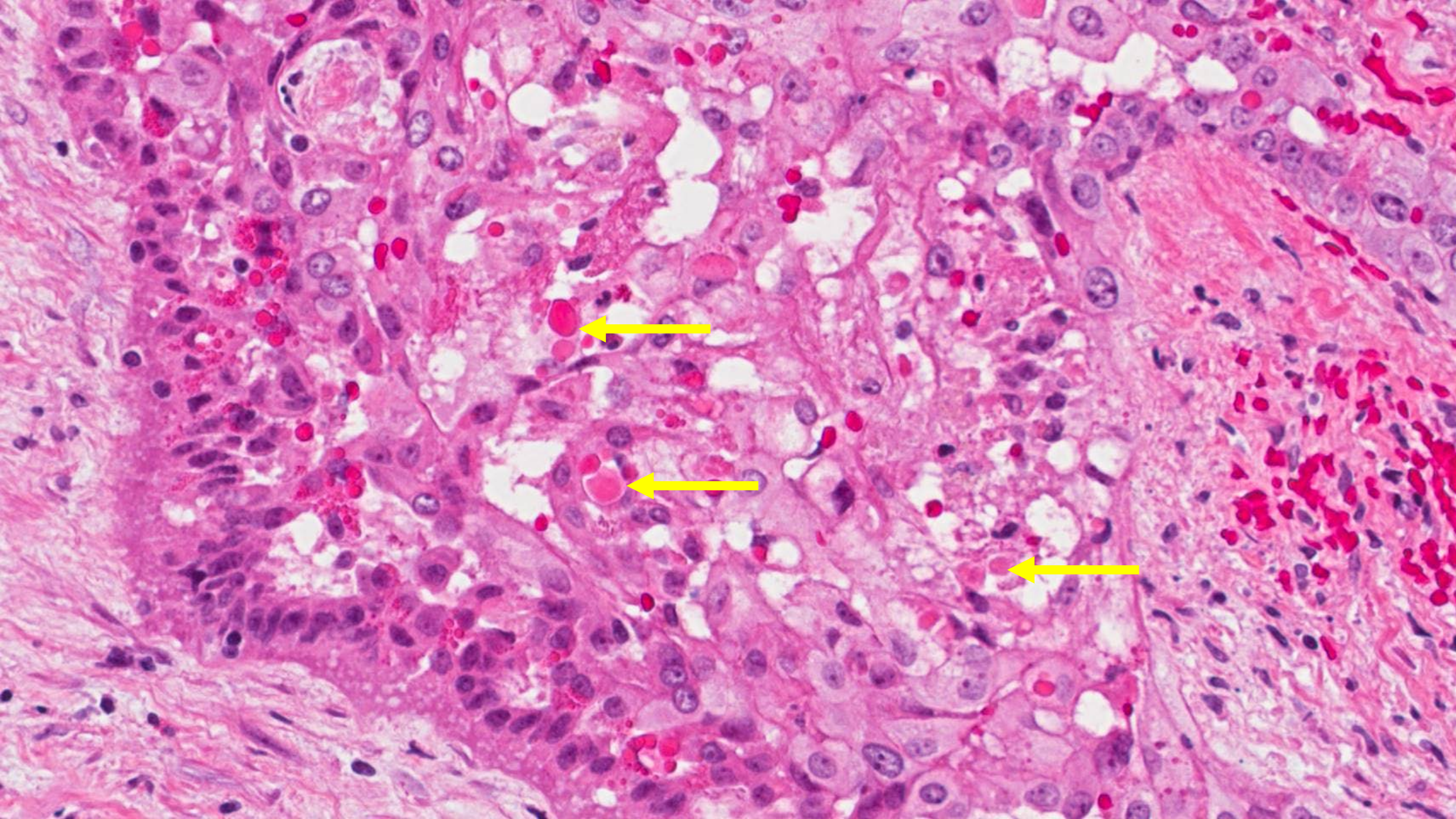


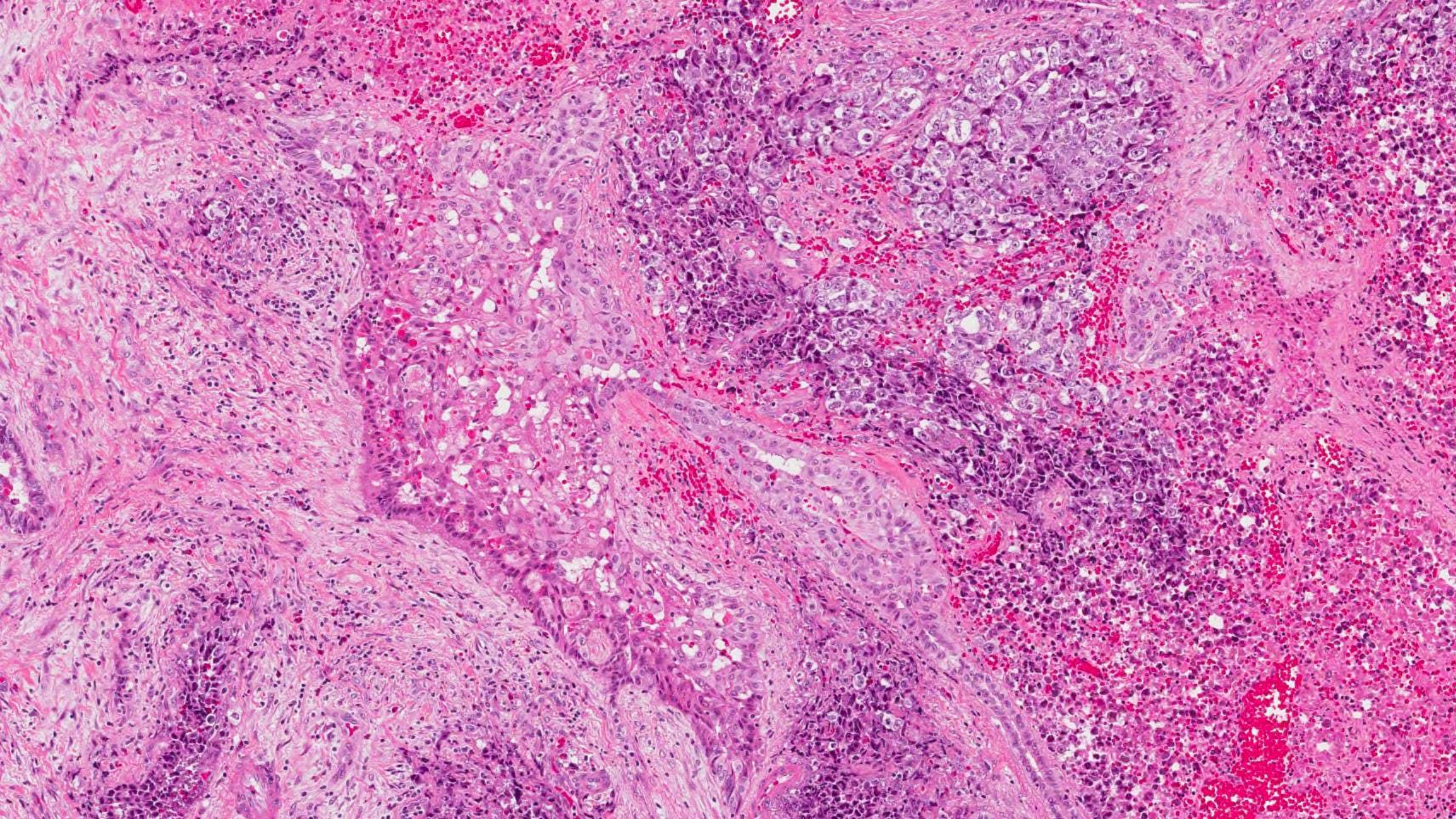


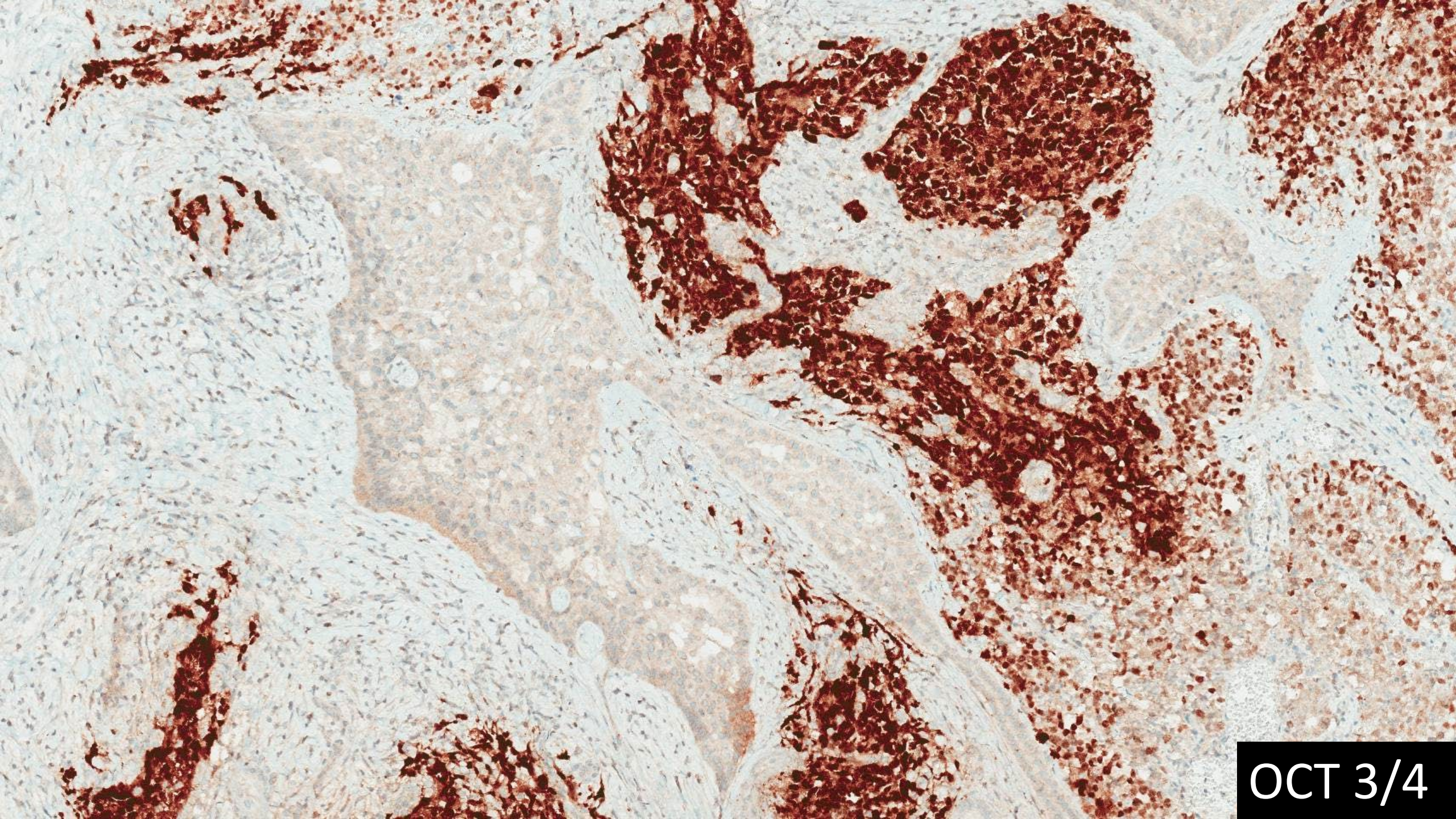


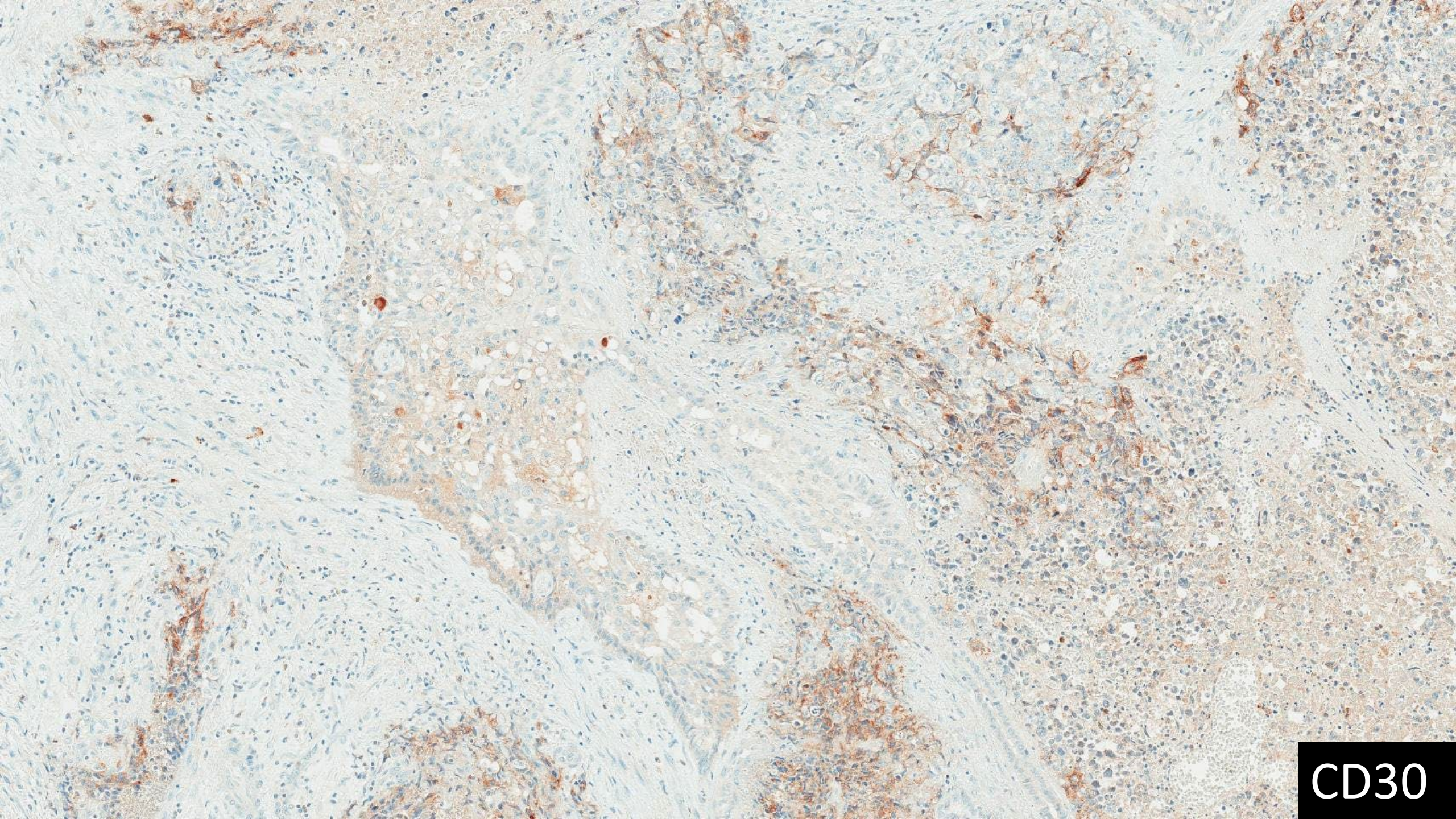


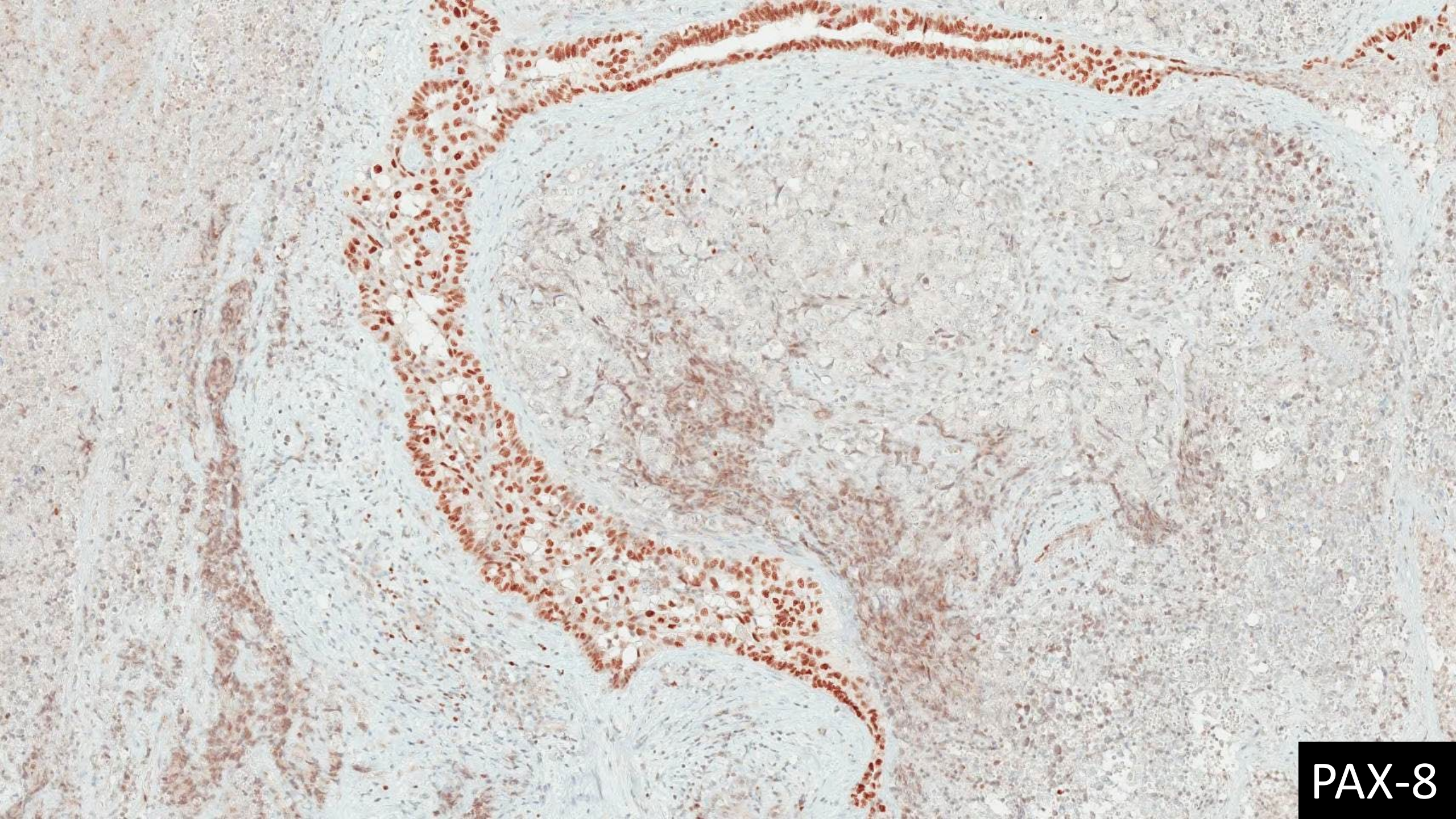







OCT 3/4

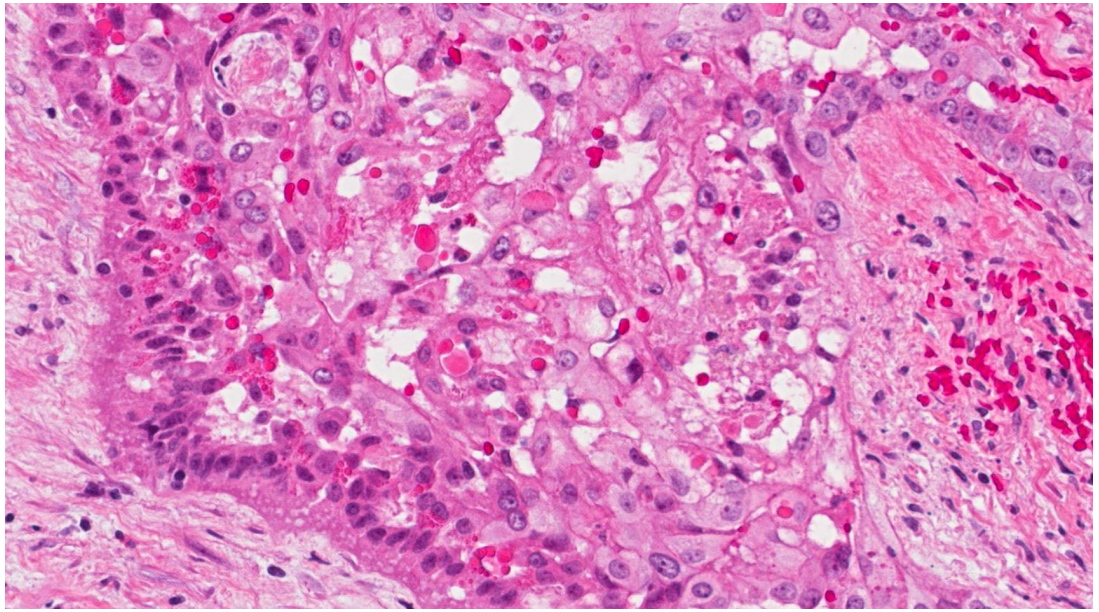

CD30


PAX-8

Rete testis hyperplasia

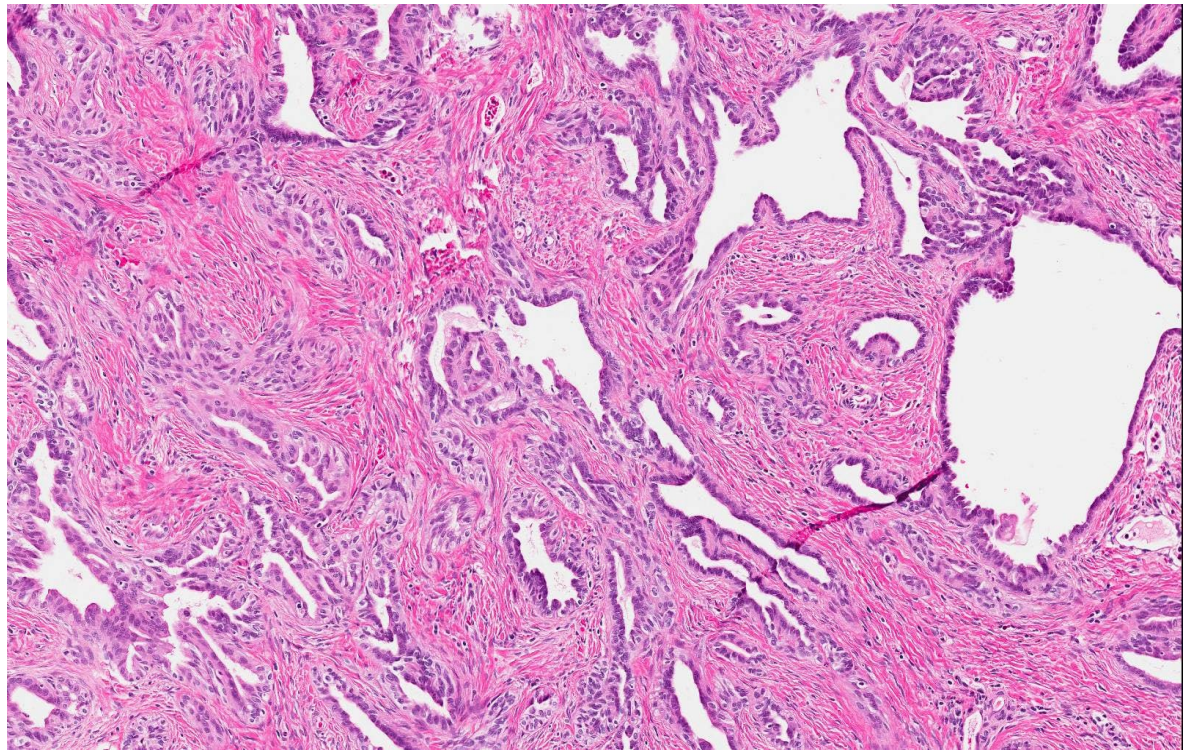
- Mimics yolk sac tumor: Hyaline globules + microcystic pattern
  - Seen with invasion of rete testis
  - Retains low power rete architecture
  - Hyaline globules:
    - AFP-
    - Variable + for albumin, α-1-antitrypsin, transferrin, α-lactalbumin
- Ulbright and Gersell *Am J Surg Pathol* (1991): 15(1):66-74.
  - 27 cases from 48 specimens
    - Hyperplasia and/or hyaline globules in MGCT, seminoma, other
    - Neither finding in nonneoplastic testis
  - No adverse outcomes

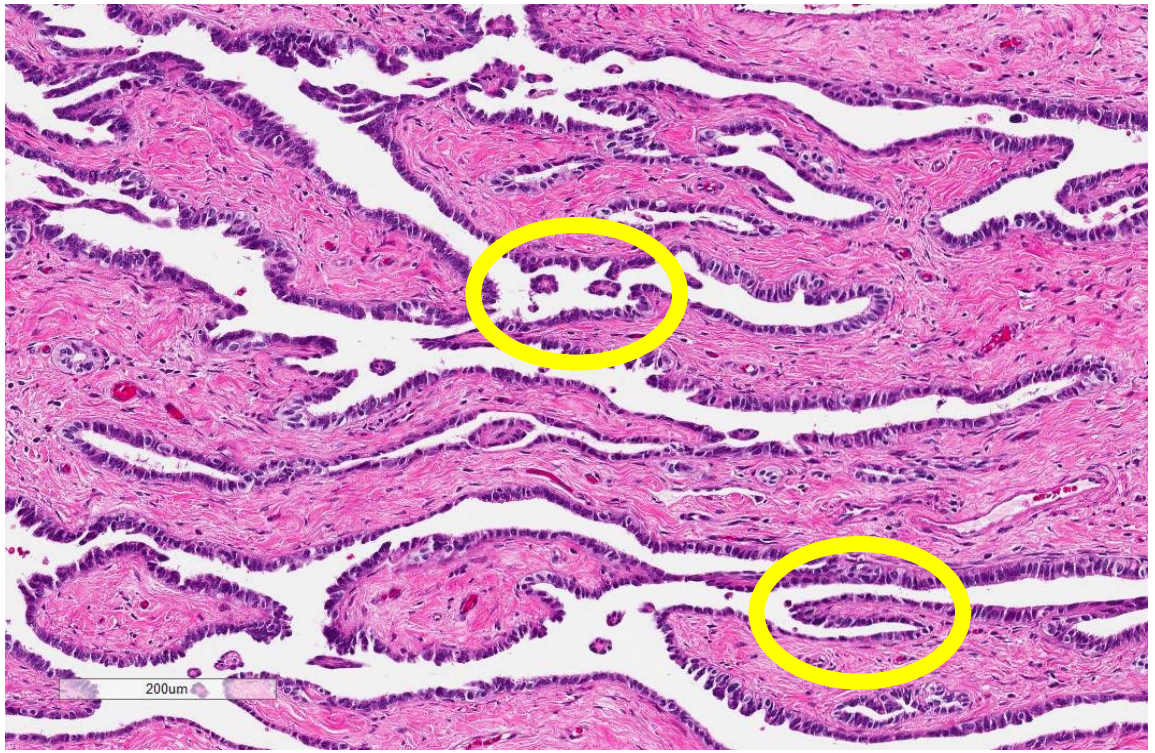
Rete testis hyperplasia



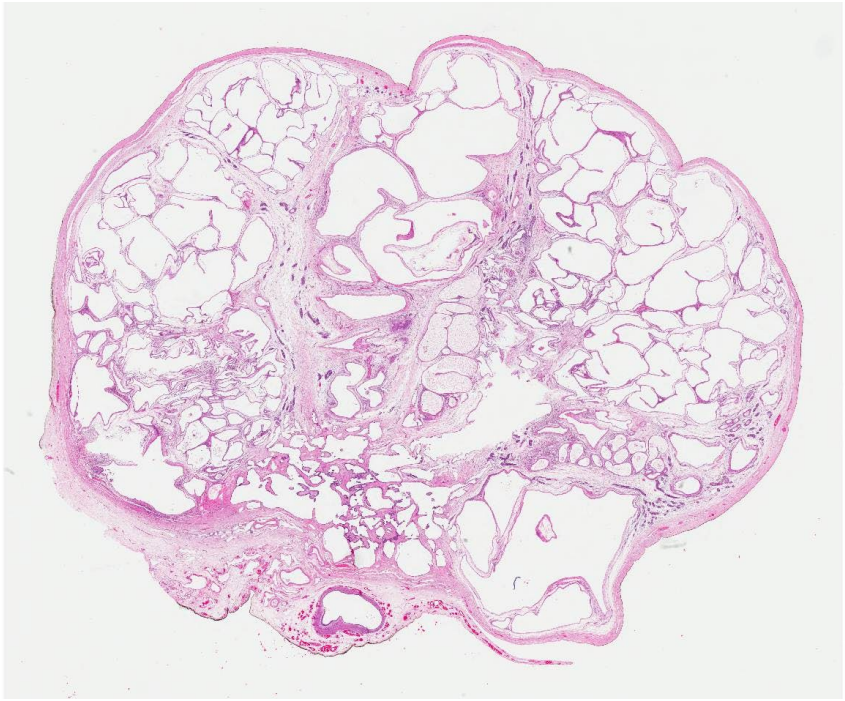
- Differential diagnosis
  - Yolk sac tumor
  - Rete testis adenocarcinoma
  - Cystic dysplasia of the rete testis

Structure of rete testis

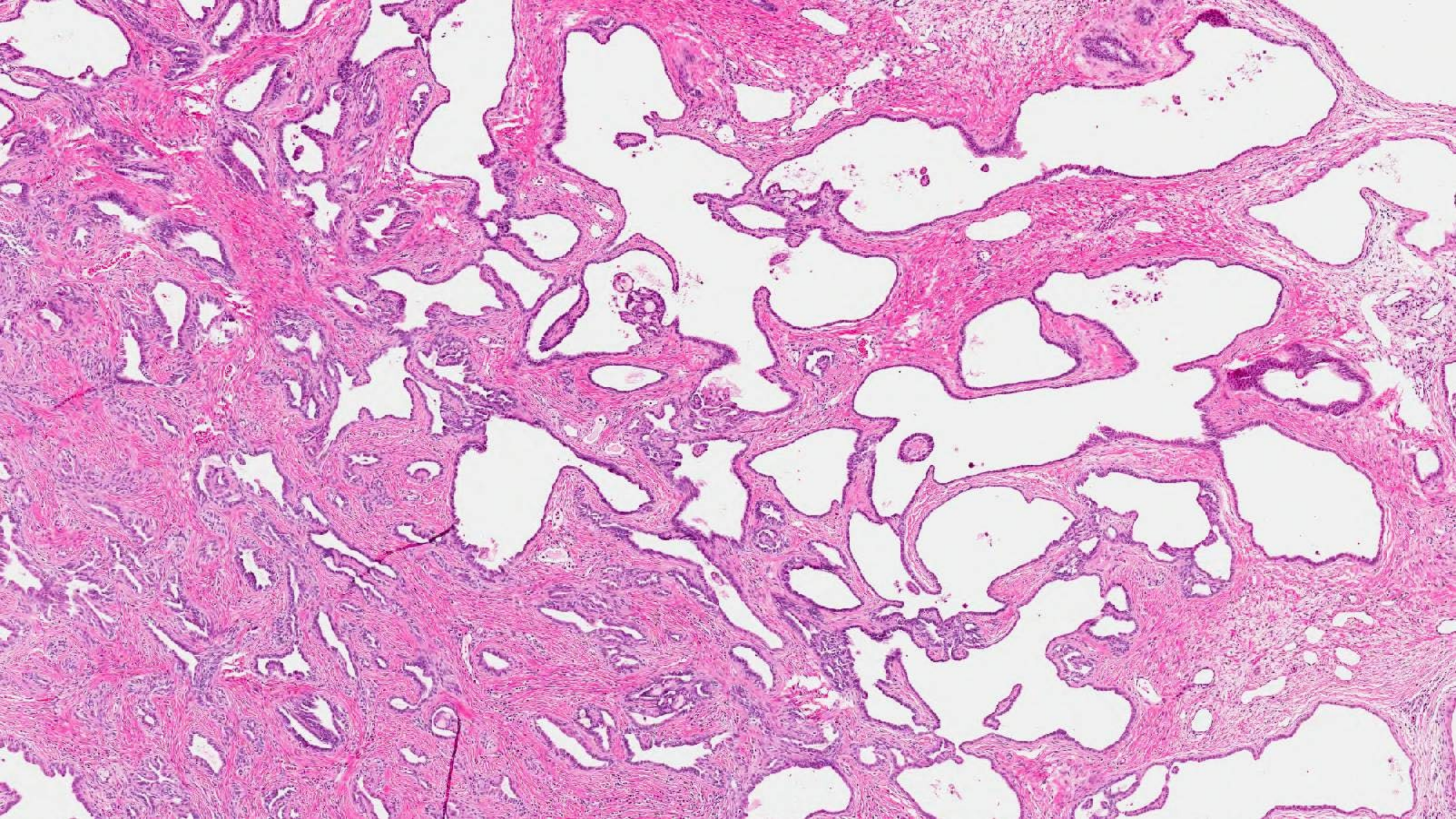


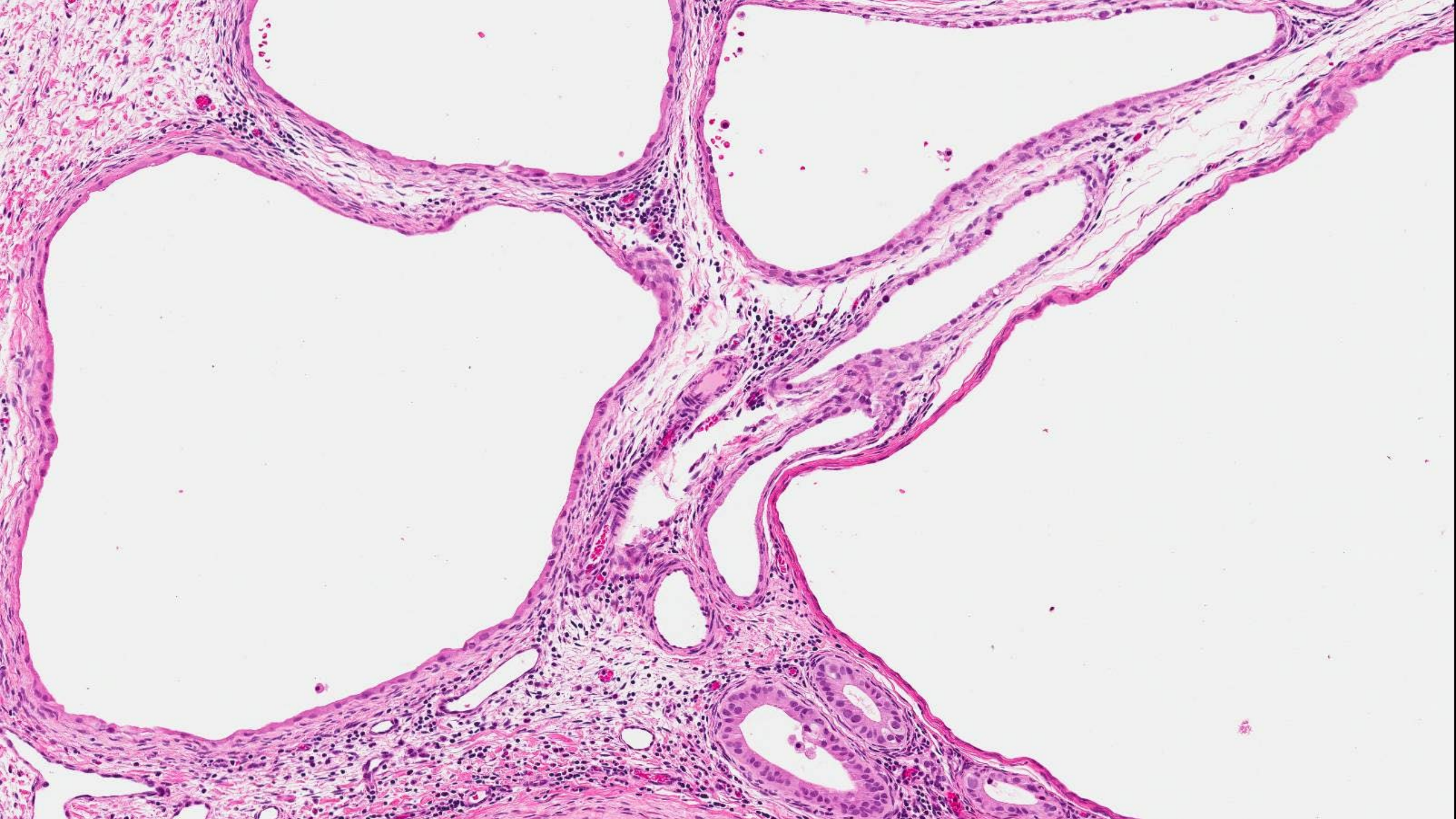


Cystic dysplasia of the rete testis

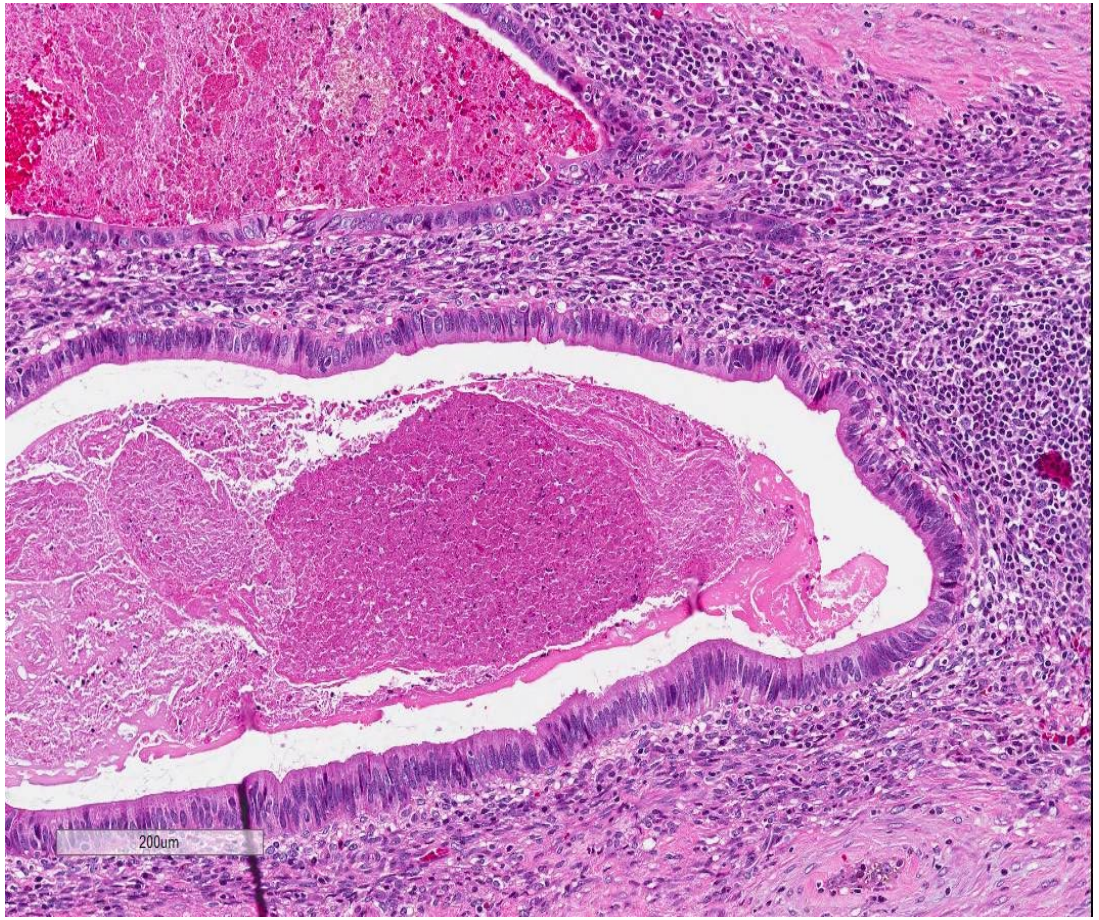


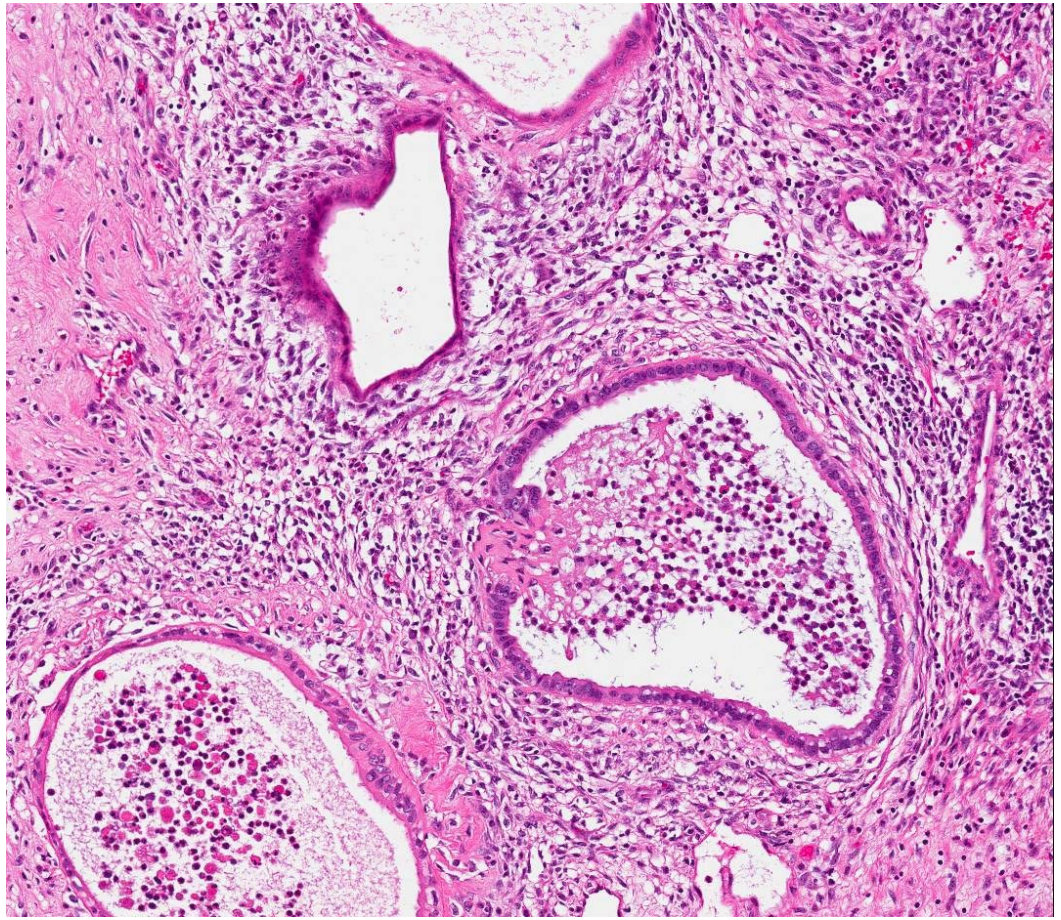
- Presents in infancy to adolescence (mean 5 yrs)
- Usually unilateral
- Scrotal swelling or testicular mass
  - Can mimic a cystic neoplasm on ultrasound
- Associated with other GU anomalies (e.g. ipsilateral renal agenesis, urethral strictures, cryptorchidism)

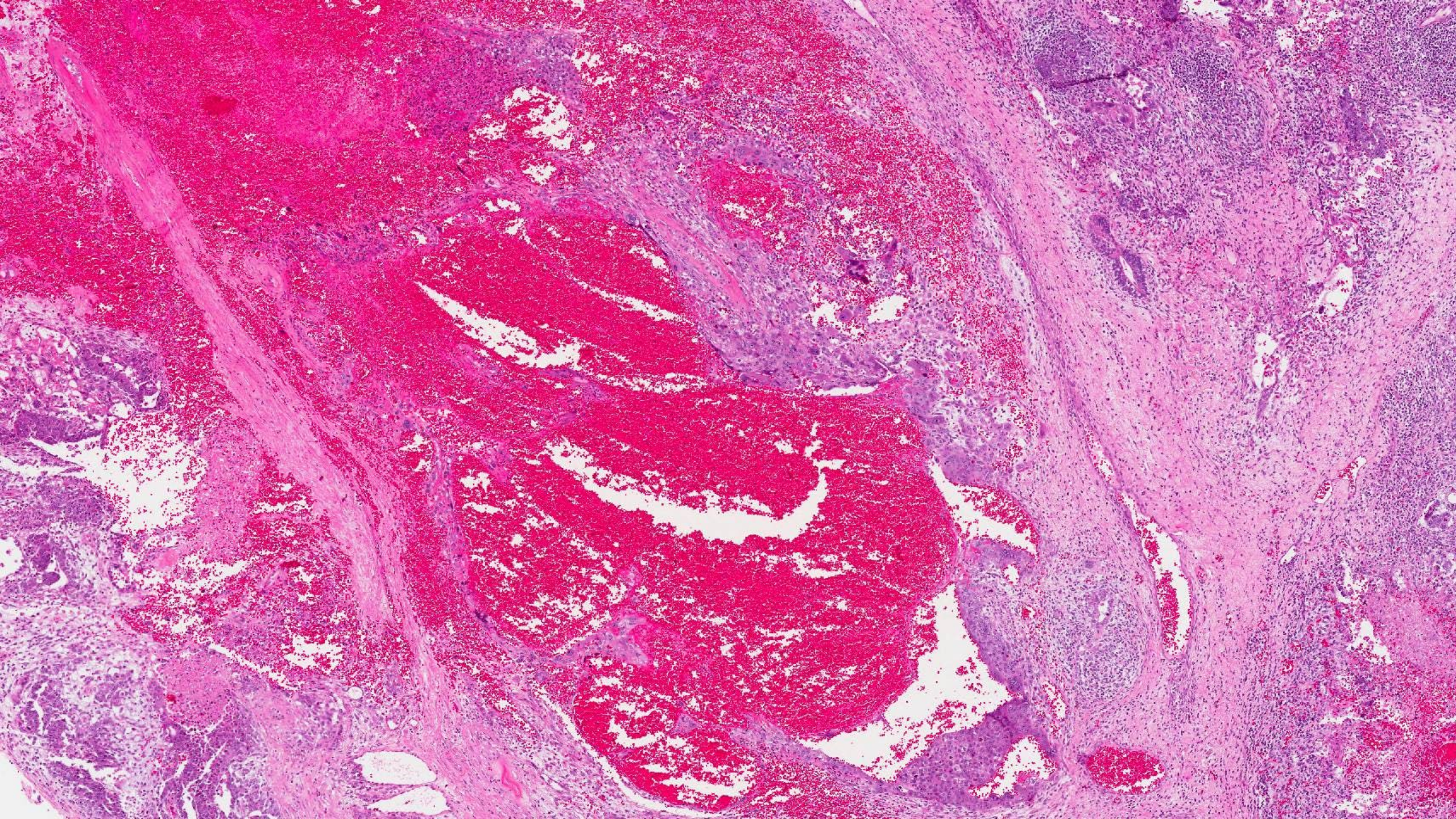


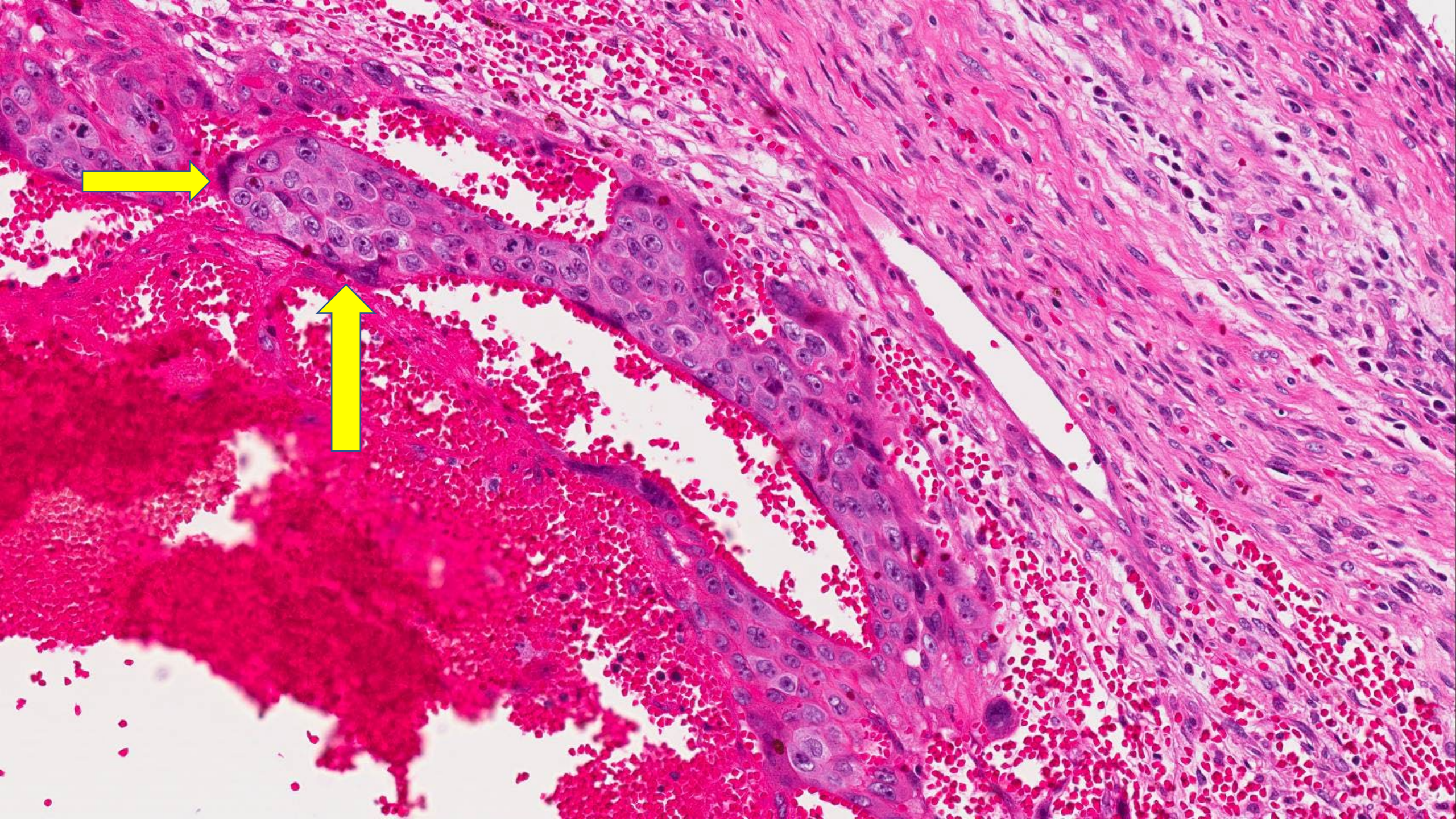


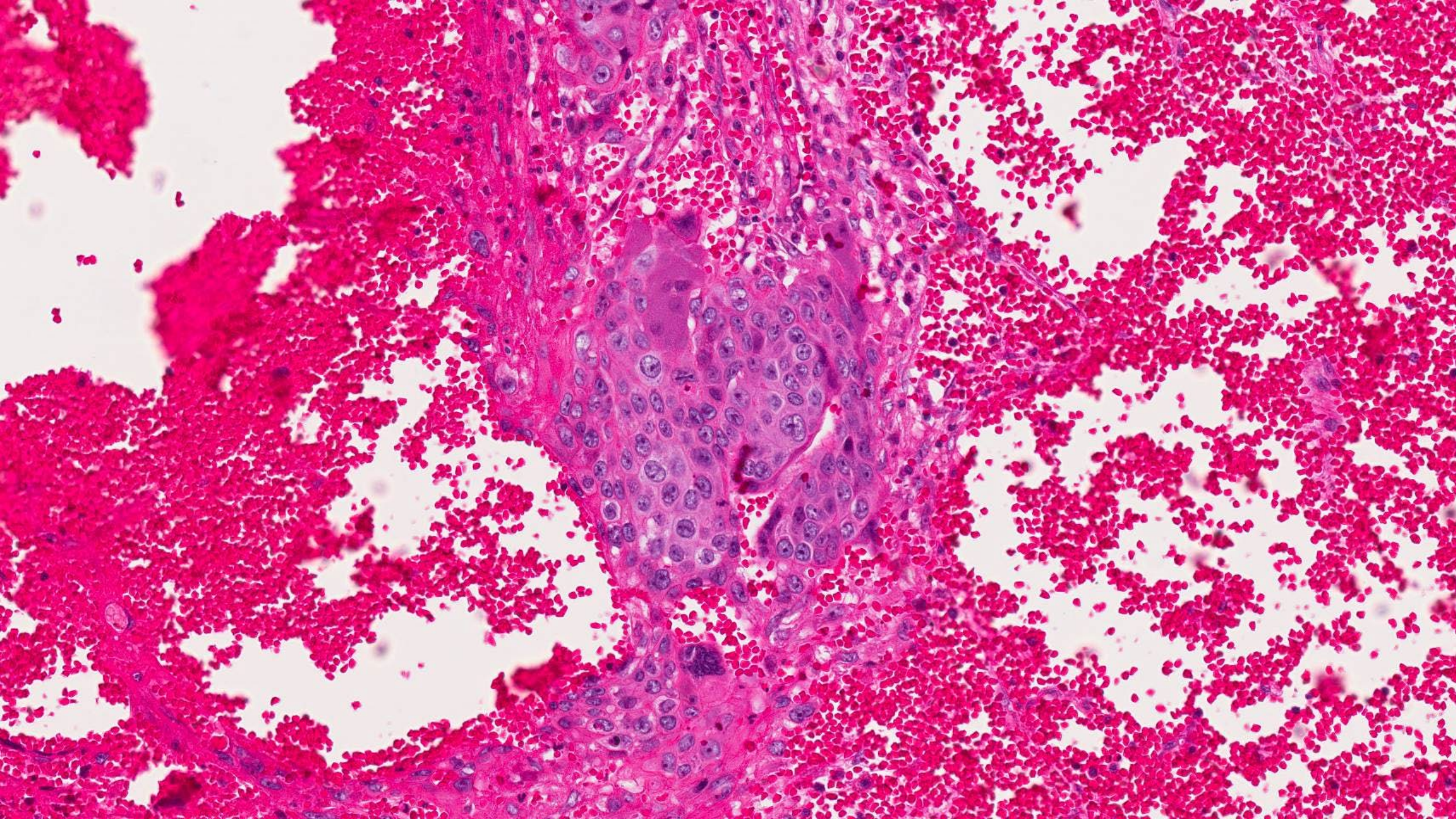
Teratoma (including mesenchyme)

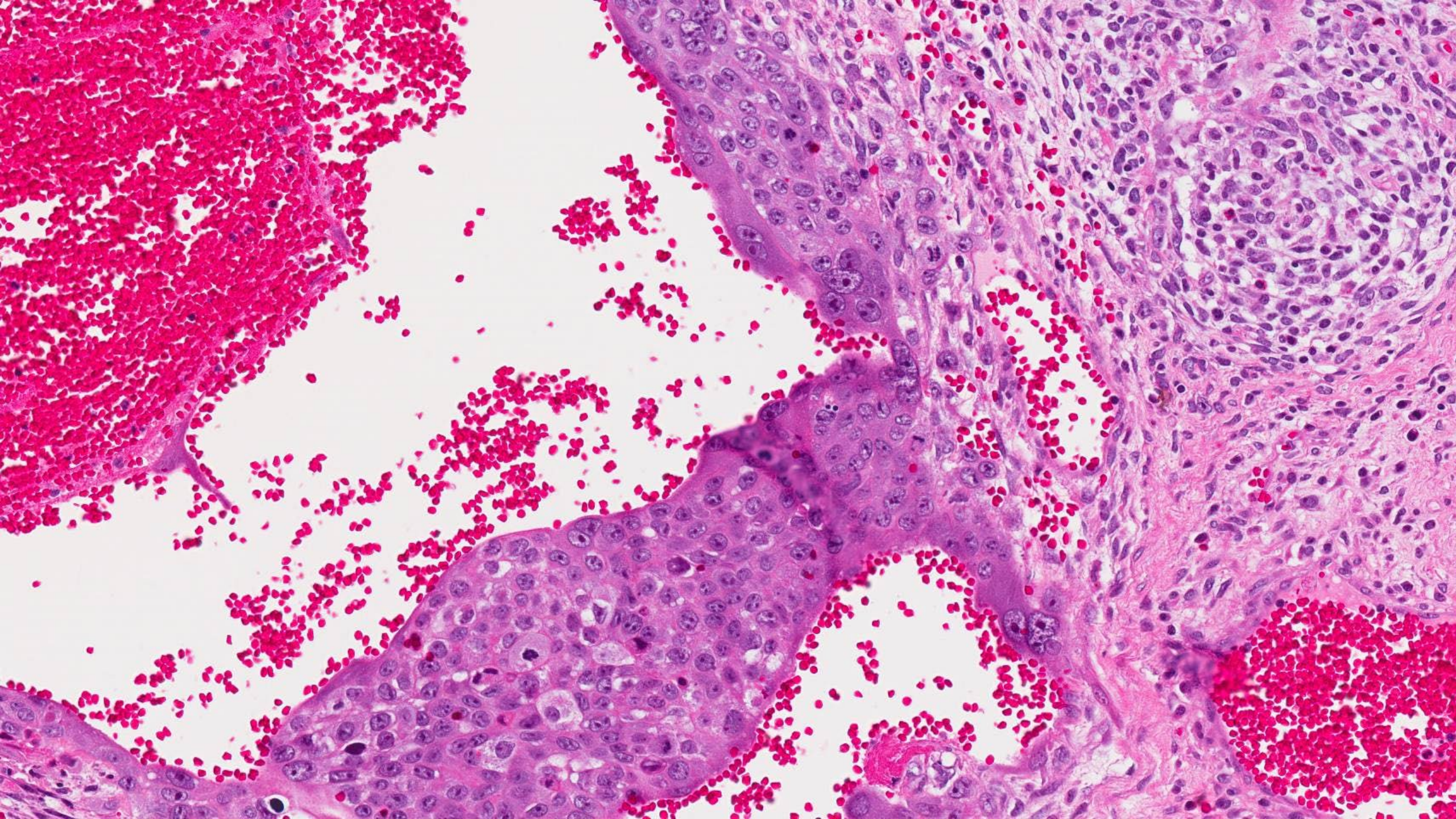










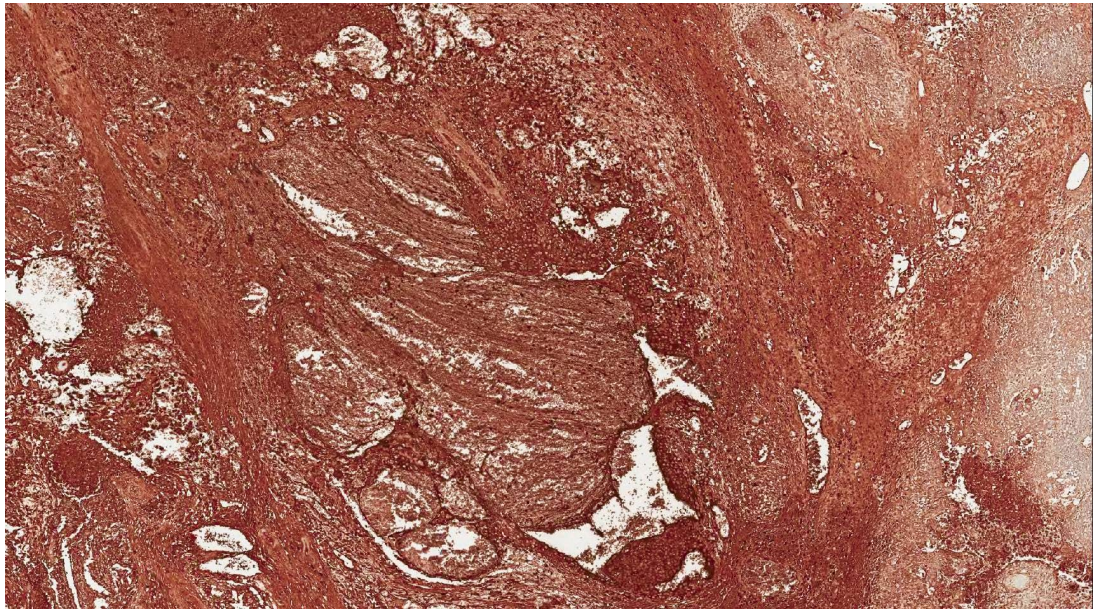


Testicular choriocarcinoma

- Usually requires biphasic tumor:
  - Syncytiotrophoblast+cytotrophoblast*
  - Villous configuration
  - Hemorrhage+necrosis
- Very high serum HCG (>100,000 mIU/mL)
- Early hematogenous mets to brain, lung, liver

*exception: monophasic CC composed of cytotrophoblast only (rare, post-chemo)

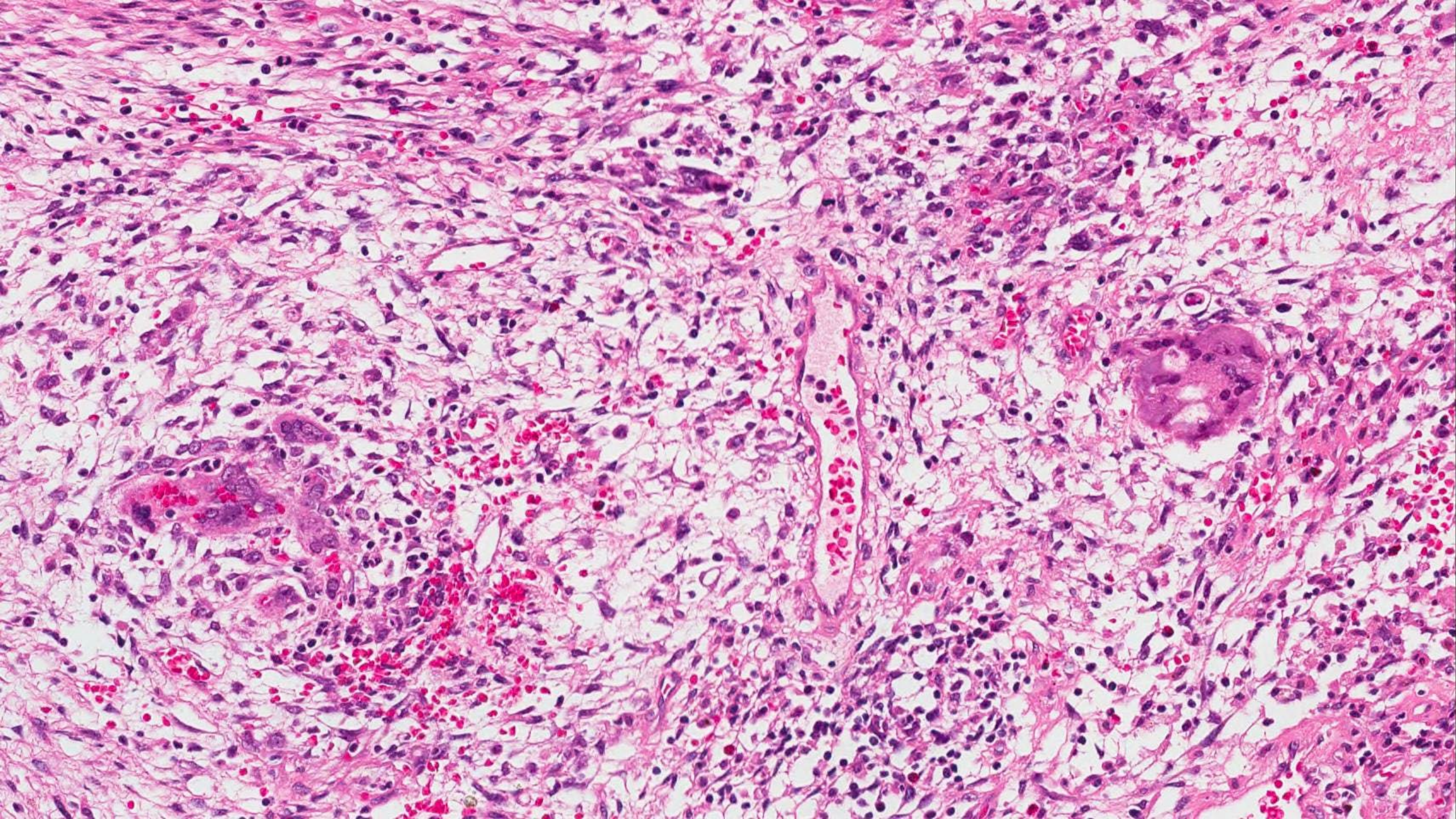
HCG immunohistochemistry - problematic

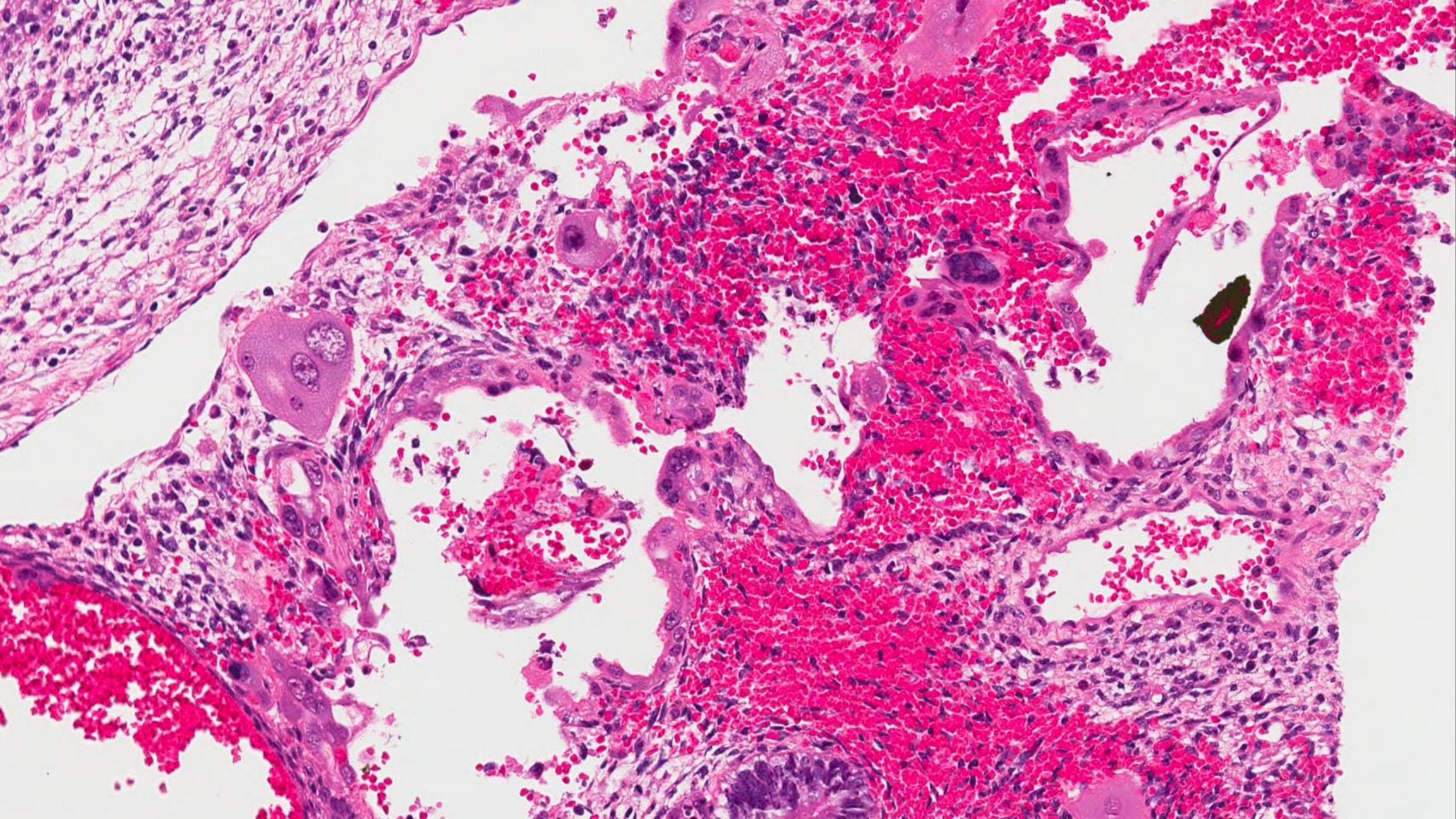


- Diffuse non-specific staining
- Embryonal CA can express HCG
- Any GCT can have syncytiotrophoblast (HCG+)

Differential diagnosis – Choriocarcinoma

- Syncytiotrophoblast in other germ cell components
- Seminoma
- Cystic trophoblastic tumor (CTT)
- Other trophoblastic neoplasms (intermediate trophoblast tumors)

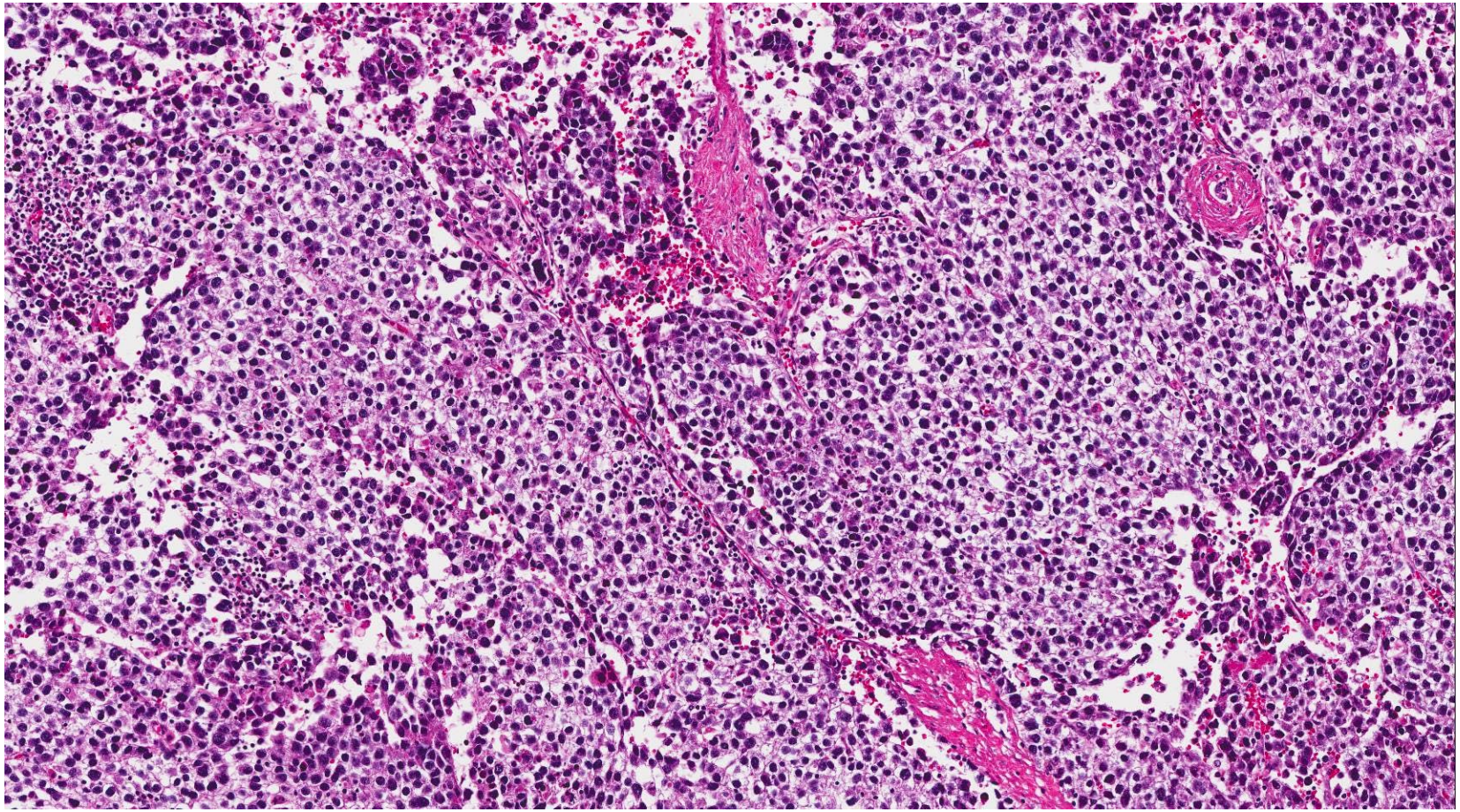


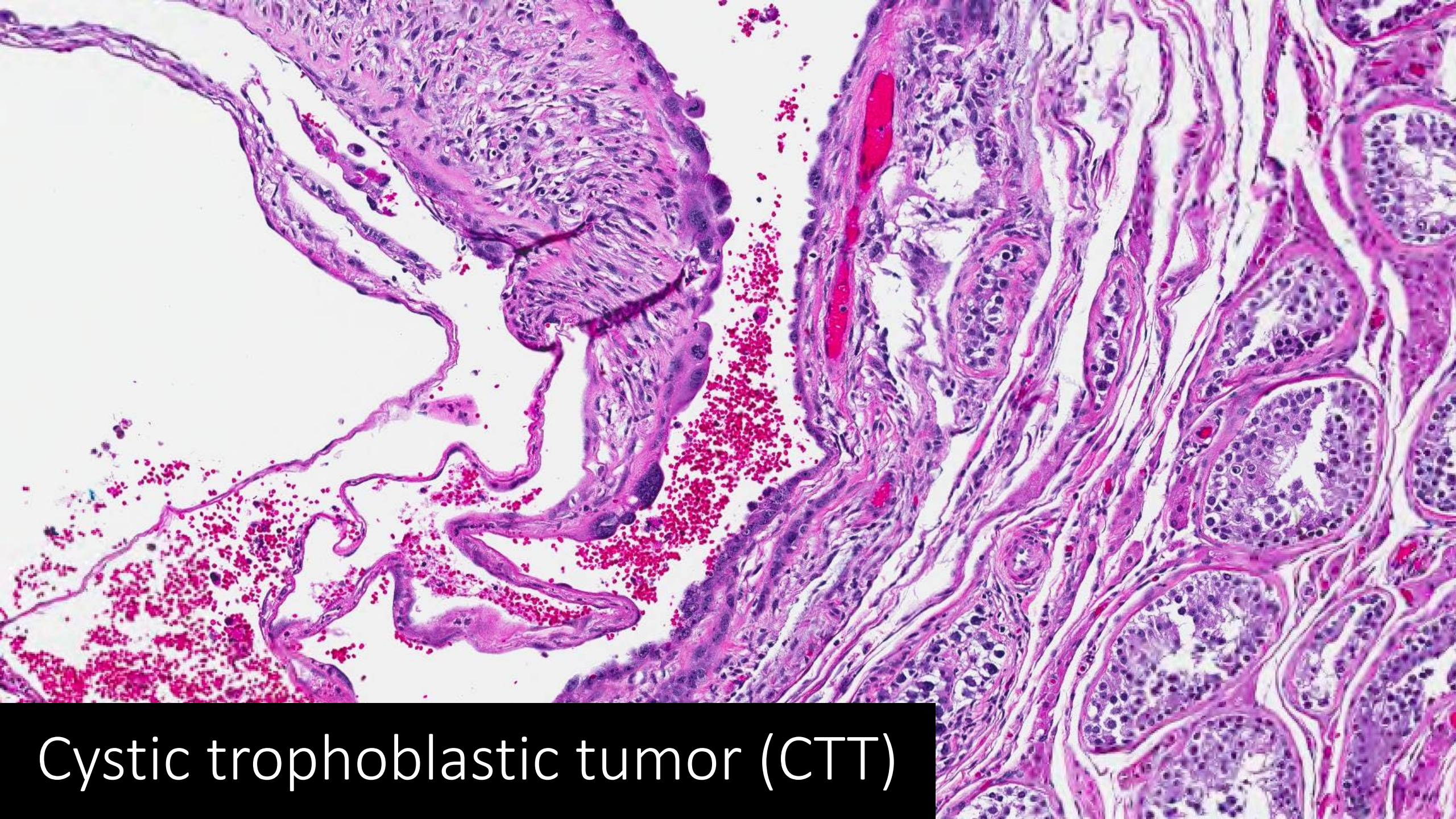


Syncytiotrophoblast in MGCT

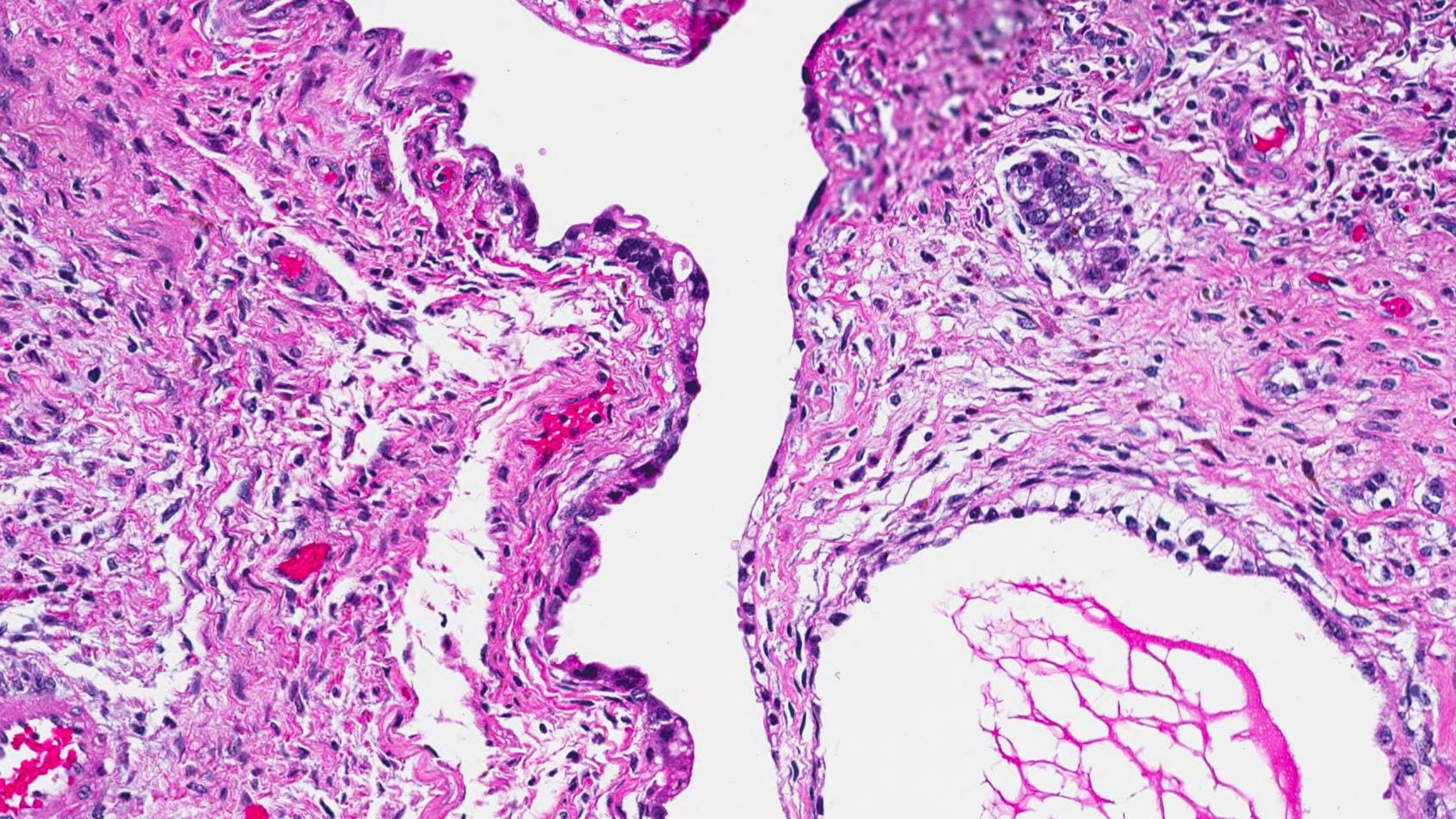
- NOT choriocarcinoma
- Elevated serum HCG, but lower than in choriocarcinoma (HCG <500 vs >100,000s mIU/mL)
- Reported in seminoma, embryonal carcinoma, yolk sac tumor

Seminoma mimicking choriocarcinoma



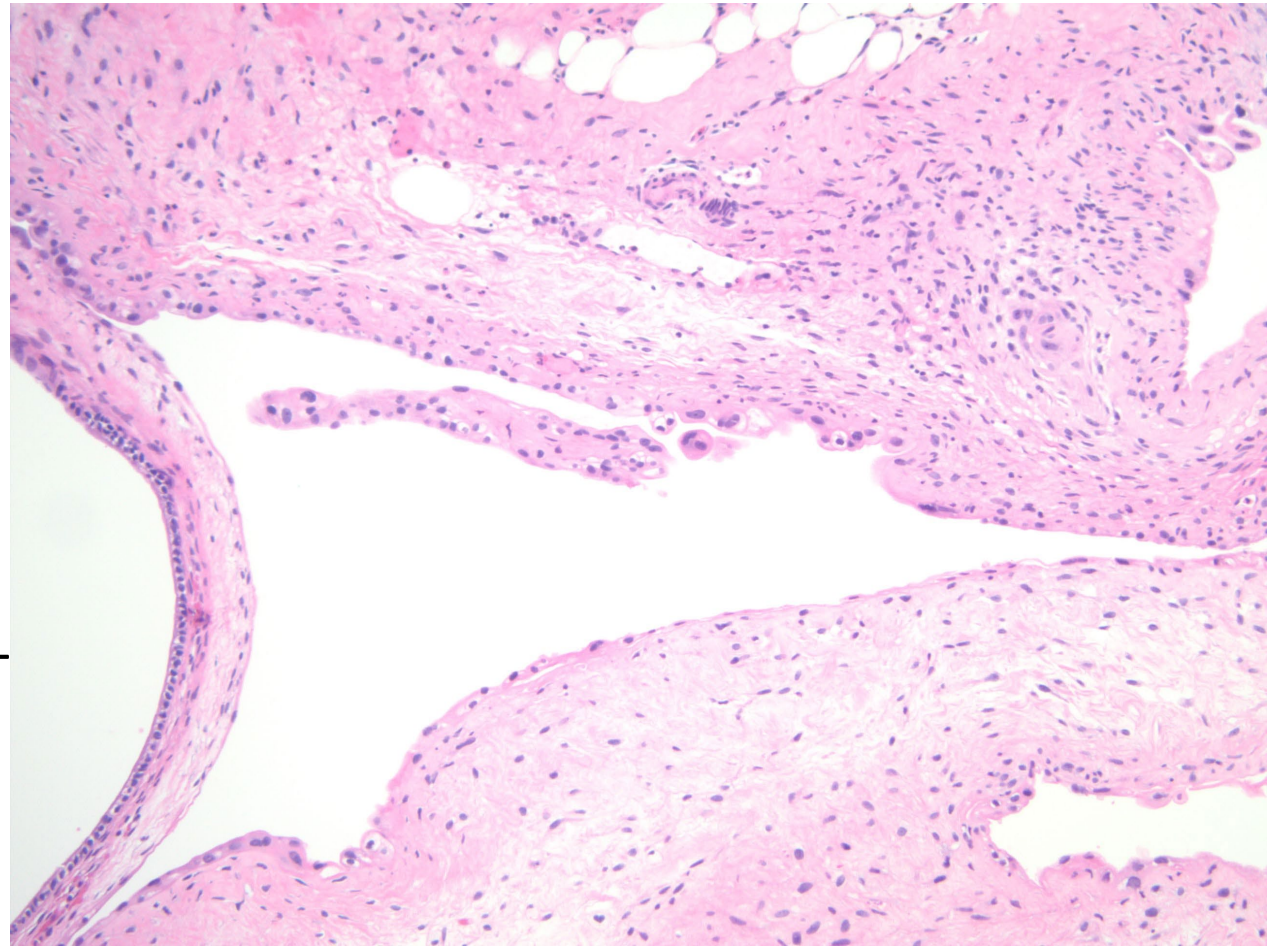


Cystic trophoblastic tumor (CTT)



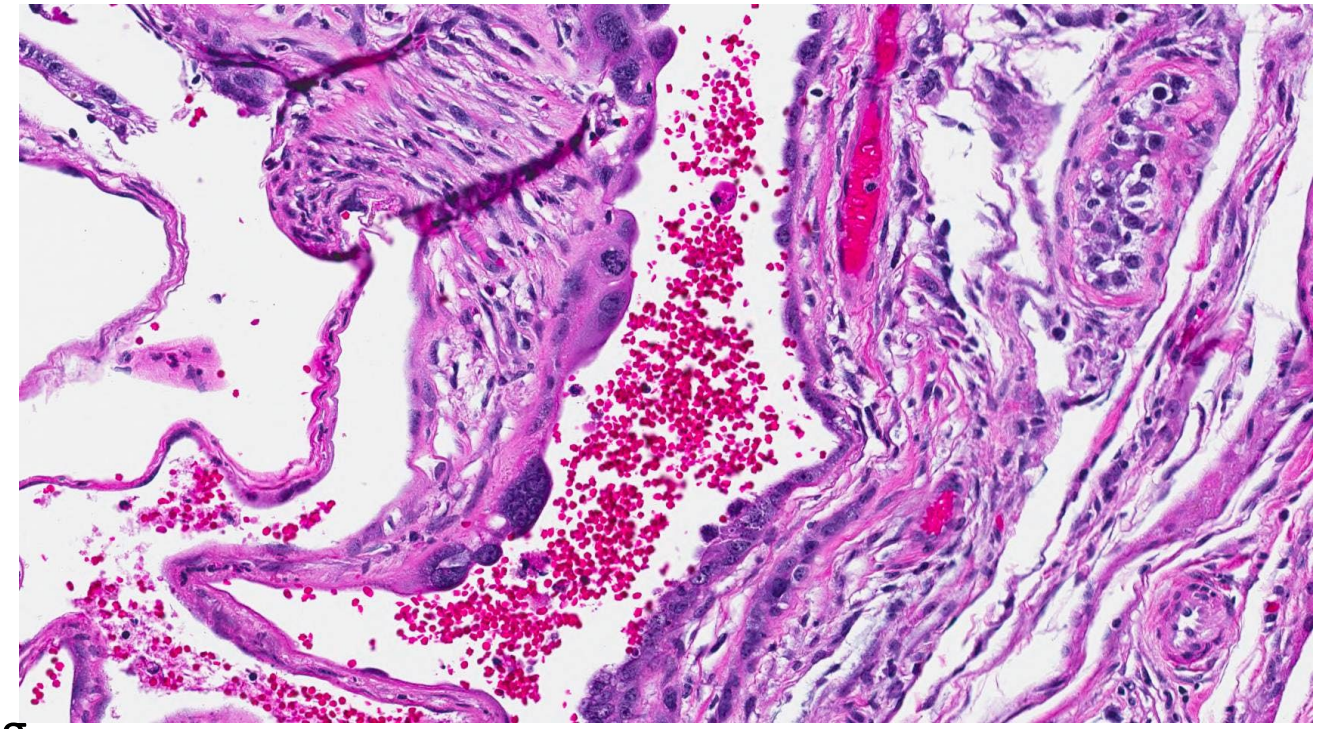
Cystic trophoblastic tumor (CTT)

- Originally described in post-chemotherapy RPLND specimens
  - Ulbright et al *Am J Surg Pathol* 2004;28:1212–1216
  - 17 patients S/P chemo for testicular GCT
  - Only viable components: teratoma and cystic trophoblastic tumor
  - Normal to slightly elevated HCG (1.6–165 mIU/mL, median, 8.0 mIU/mL)
  - Cystic – single layer of trophoblast
  - Nonaggressive behavior



Cystic trophoblastic tumor (CTT)

- Also described in primary testis tumors
- Gondim et al *Am J Surg Pathol* 2017;41:788–794
  - 17 cases in primary testicular GCT
  - CTT was minor component (1-10%)
  - Associated with
    - Teratoma (14 cases)
    - Embryonal CA (7 cases)
    - YST (7 cases)
    - Seminoma (1 case)
    - Chroriocarcinoma (1 case)
  - Etiology - ?regressed or transforming choriocarcinoma



Other trophoblastic tumors in testicular GCT

- Tumors of intermediate trophoblast
- Epithelioid trophoblastic tumor (ETT)
- Placental site trophoblastic tumor (PSTT)
- Unclassified trophoblastic tumor (UTT)

- Idrees et al *Am J Surg Pathol* 2015;39:1468–1478
- 8 cases of non-chorio trophoblastic tumors:
  - 5 arose in testis; 3 in mets after chemo

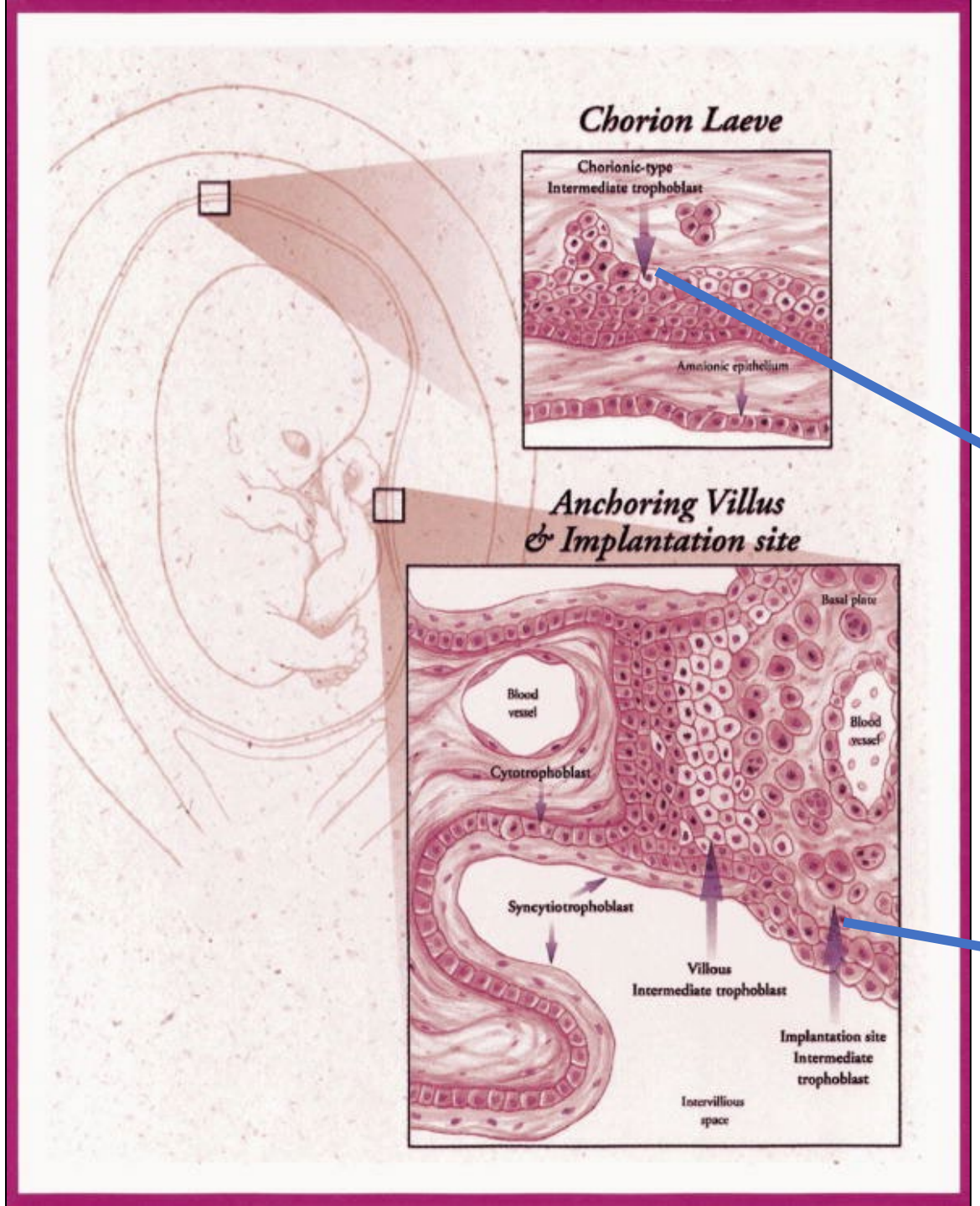


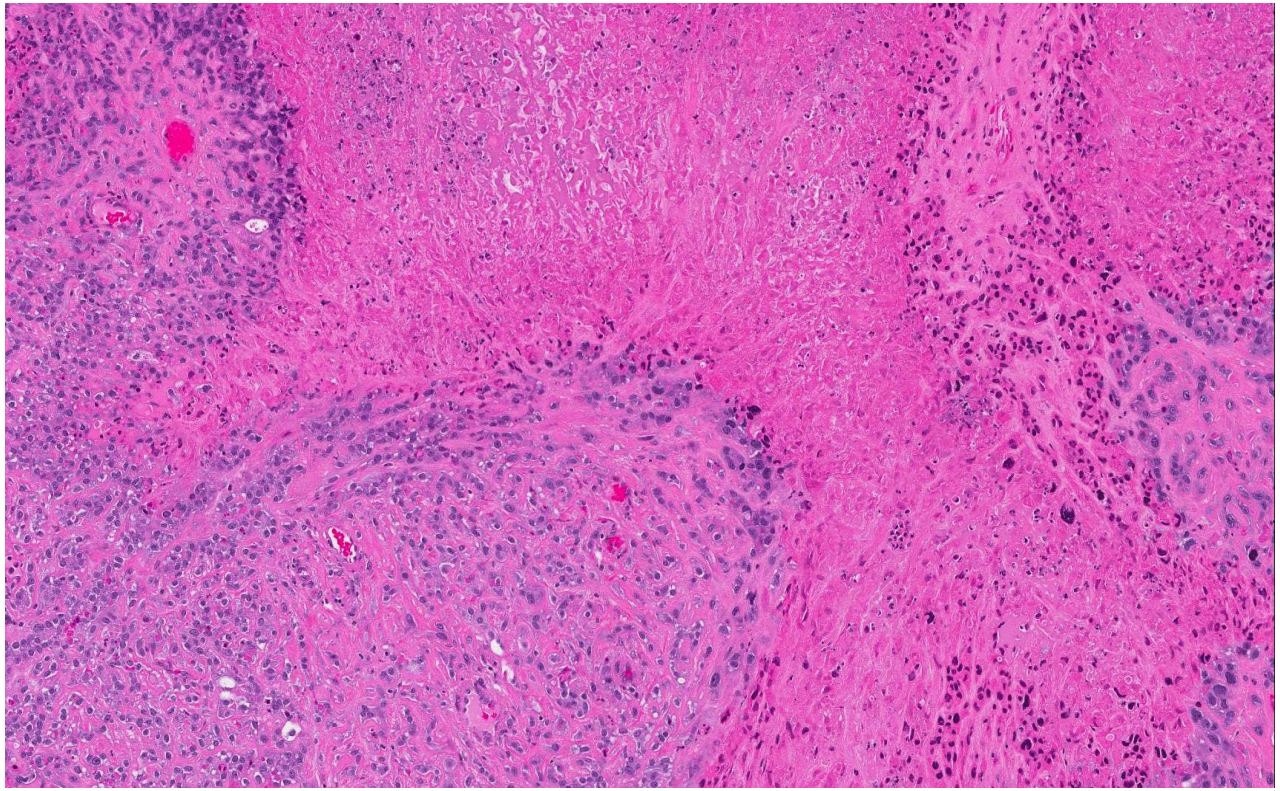
FIG. 1. A schematic representation of the trophoblastic subpopulations in the placenta and fetal membranes. Reprinted with permission from Shih IM, Seidman JD, Kurman RJ. Placental site nodule and characterization of distinctive types of intermediate trophoblast. Hum Pathol 1999;30:687-94.

ETT

PSTT

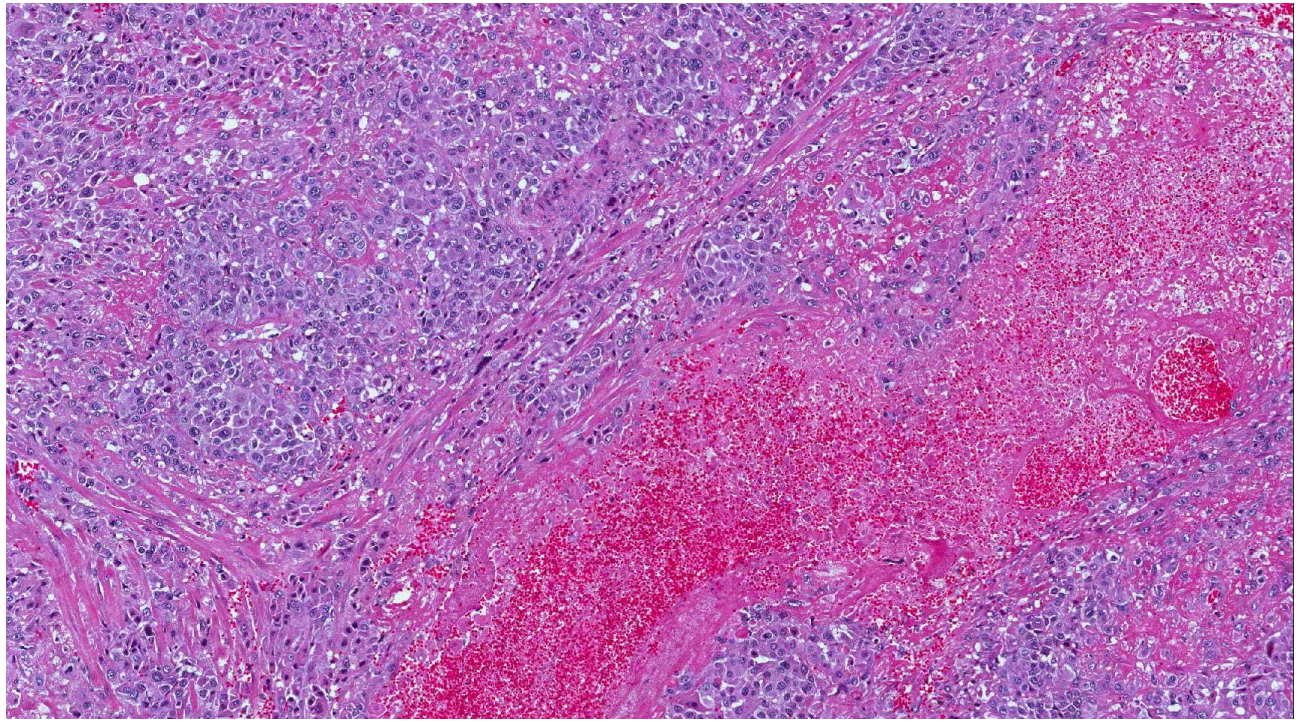
Epithelioid trophoblastic tumor (ETT)

- Tumor of chorionic- type intermediate trophoblast
- Epithelioid/squamoid cells in cords and nests
- Geographic necrosis
- Mimics squamous cell CA
  - Also p63+
- Low-level serum hCG elevation
- Usually indolent, but difficult to treat if metastasizes



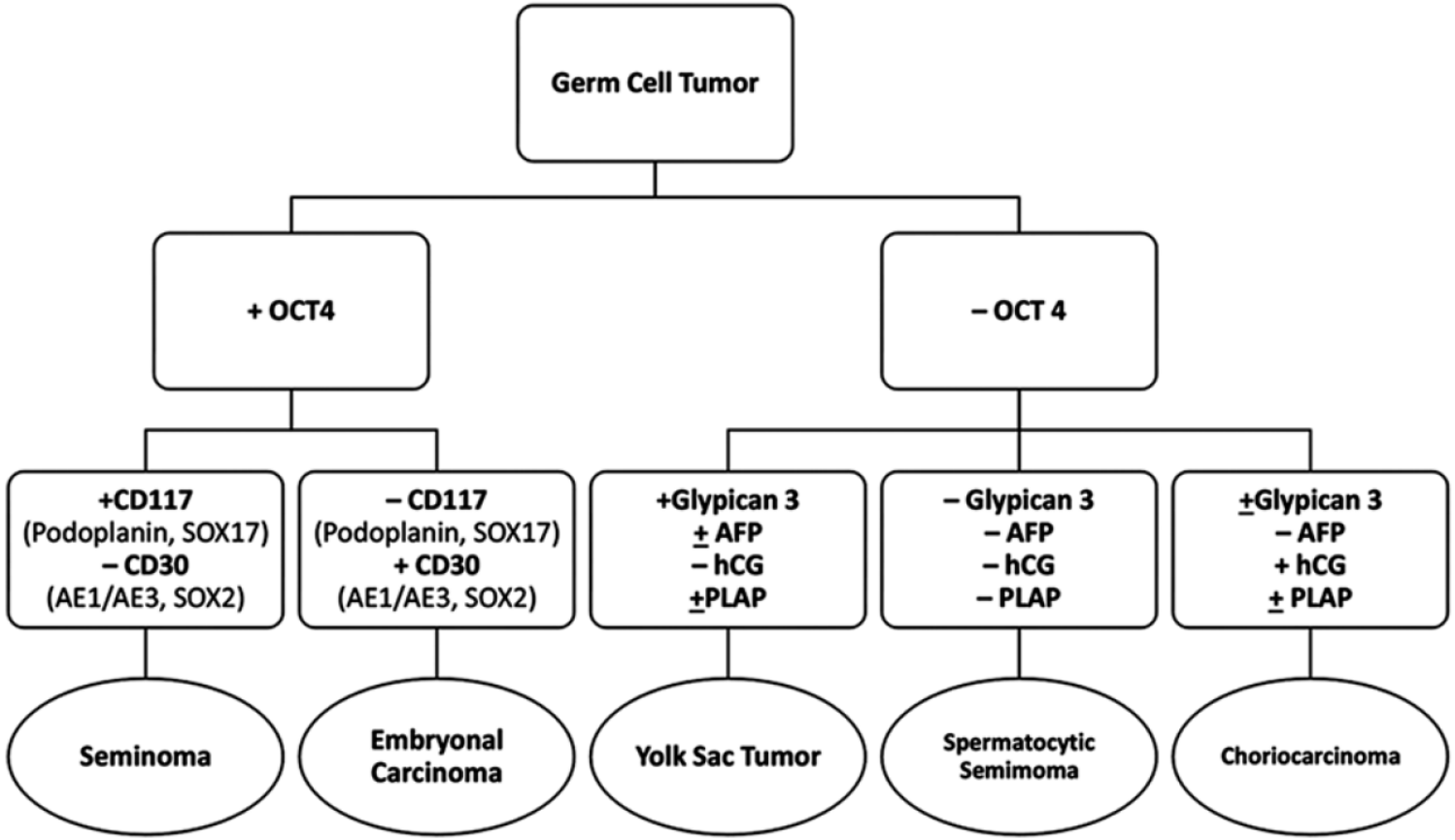
Placental site trophoblastic tumor (PSTT)

- Tumor of implantation site intermediate trophoblast
- Diffusely infiltrative
- Vascular invasion
- Fibrinoid material
- p63-
- Low-level serum hCG elevation
- Usually indolent, but difficult to treat if metastasizes



Helpful IHC – mixed germ cell tumors

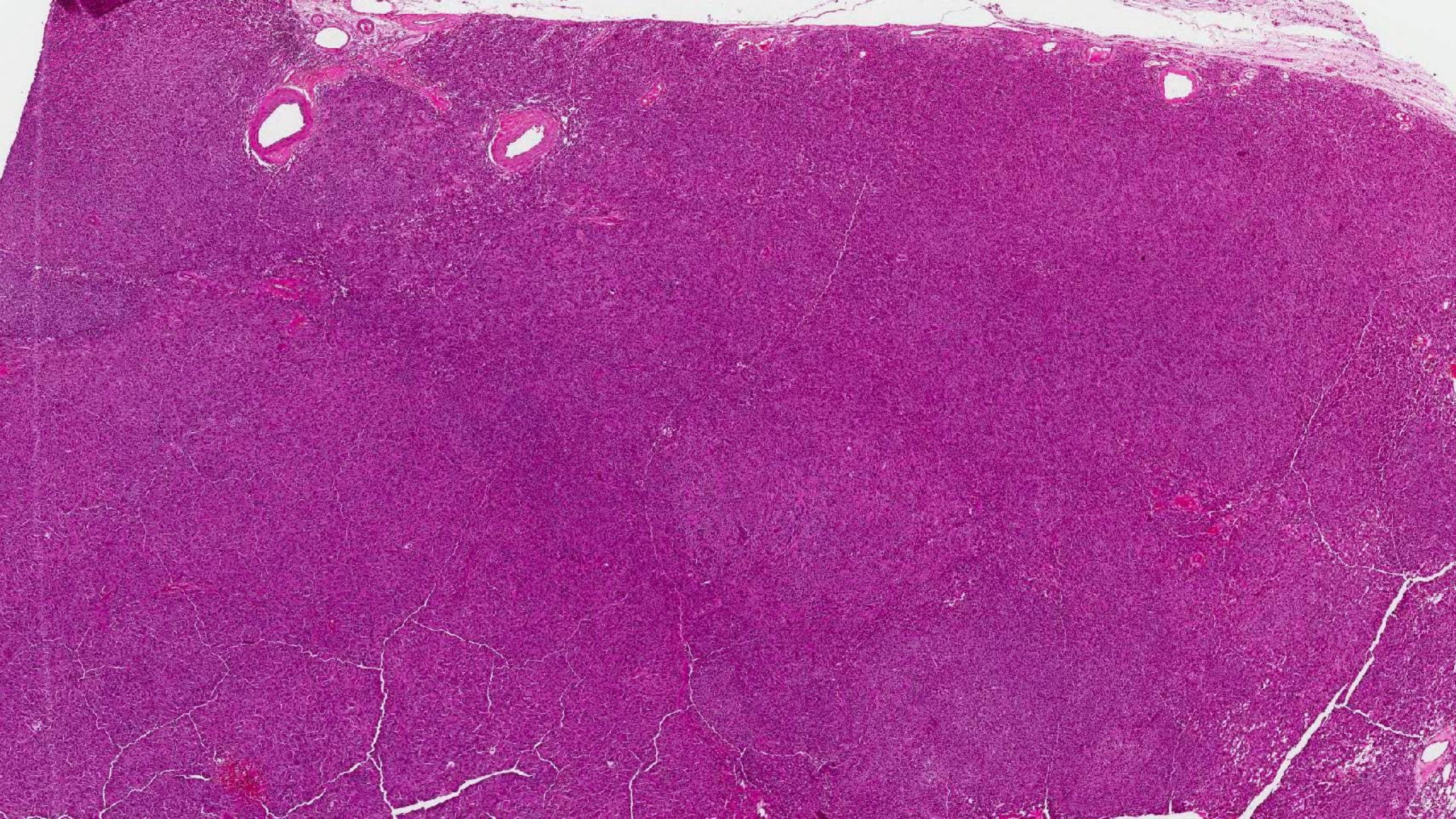
TABLE 1. Useful Algorithm for the Distinction Between Various Types of Germ Cell Tumors - Alternative Stains in Parentheses

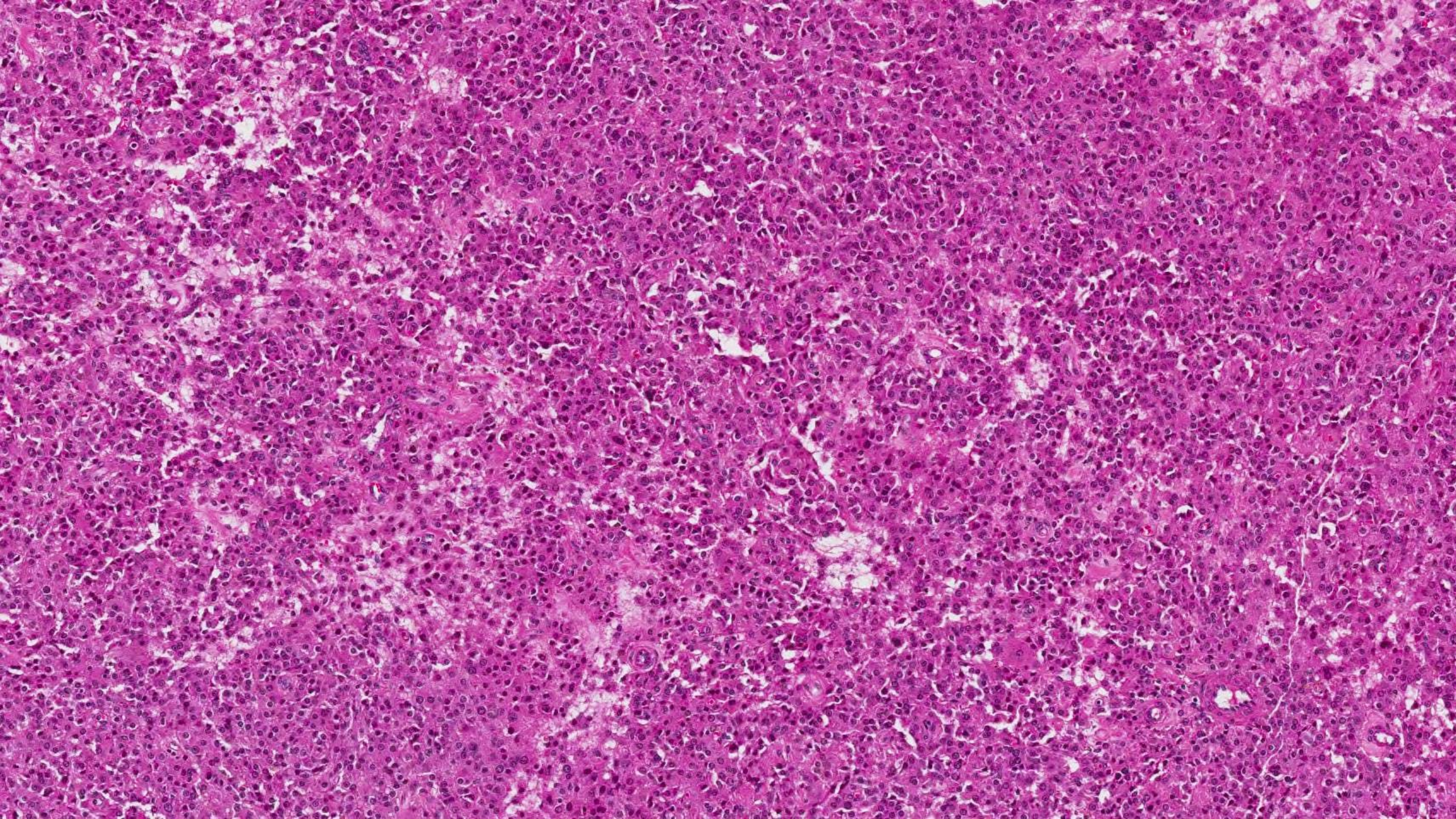


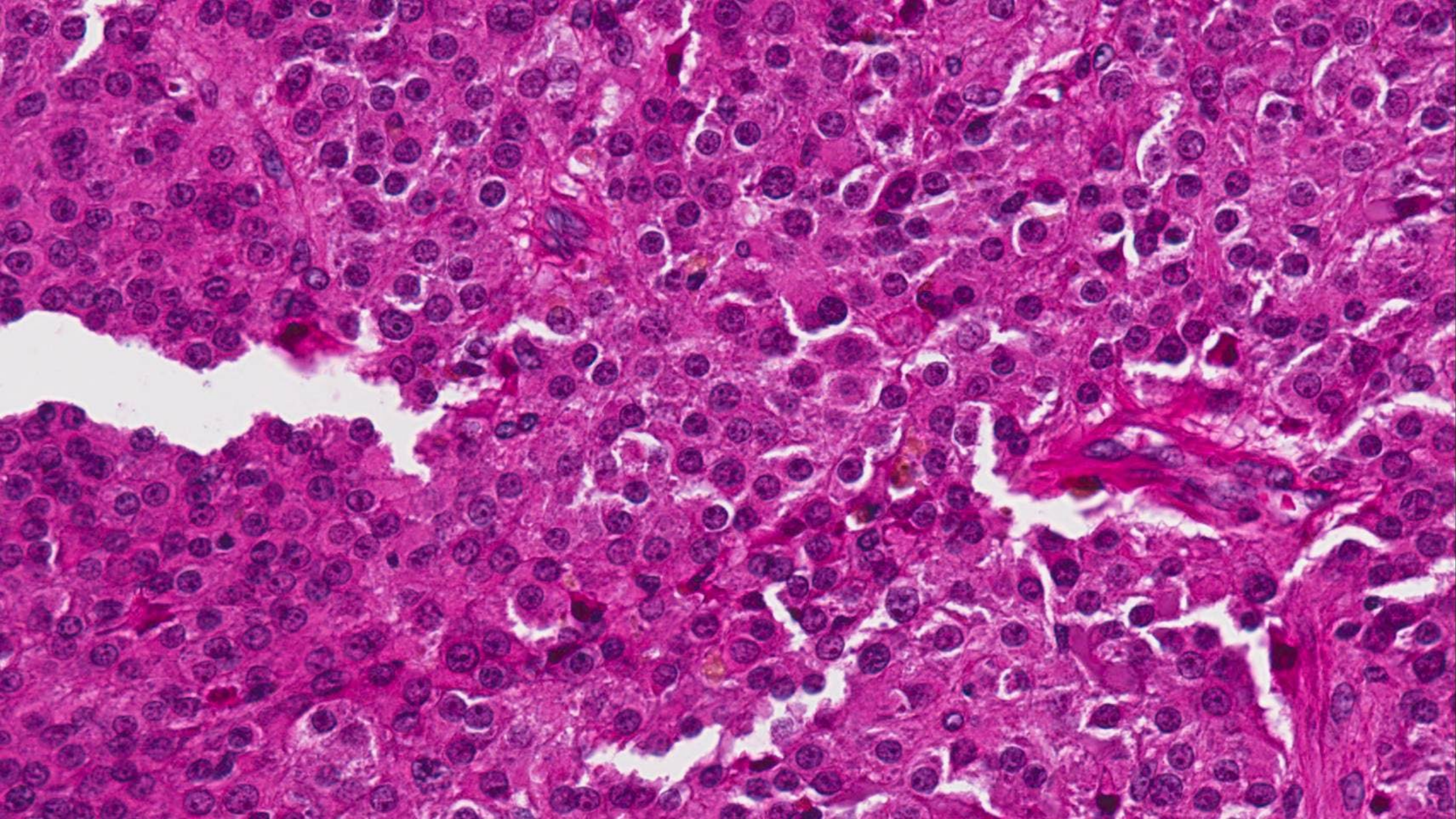
Ulbright et al *Am J Surg Pathol* 2014;38:e50-e59

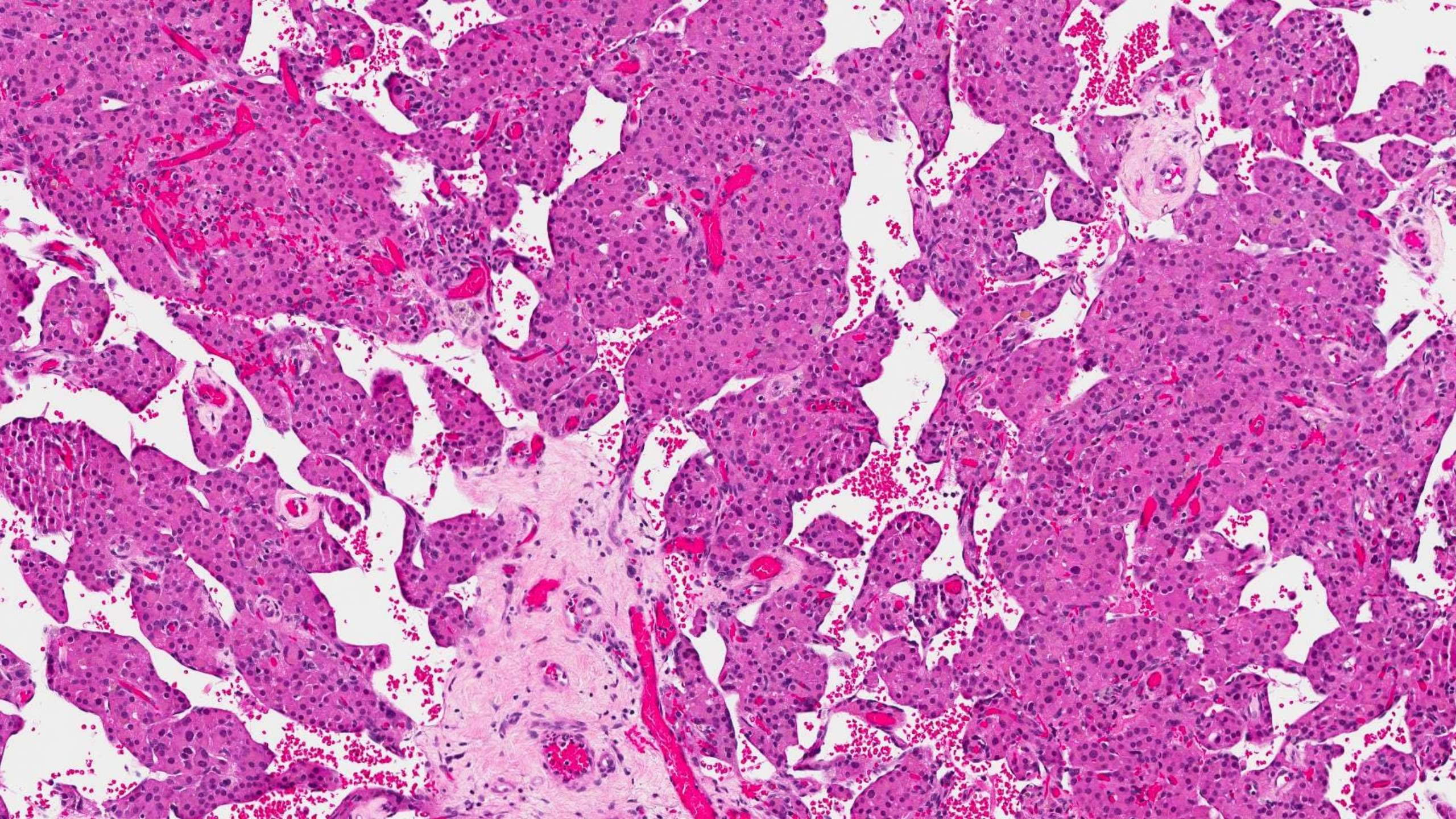
Case 3

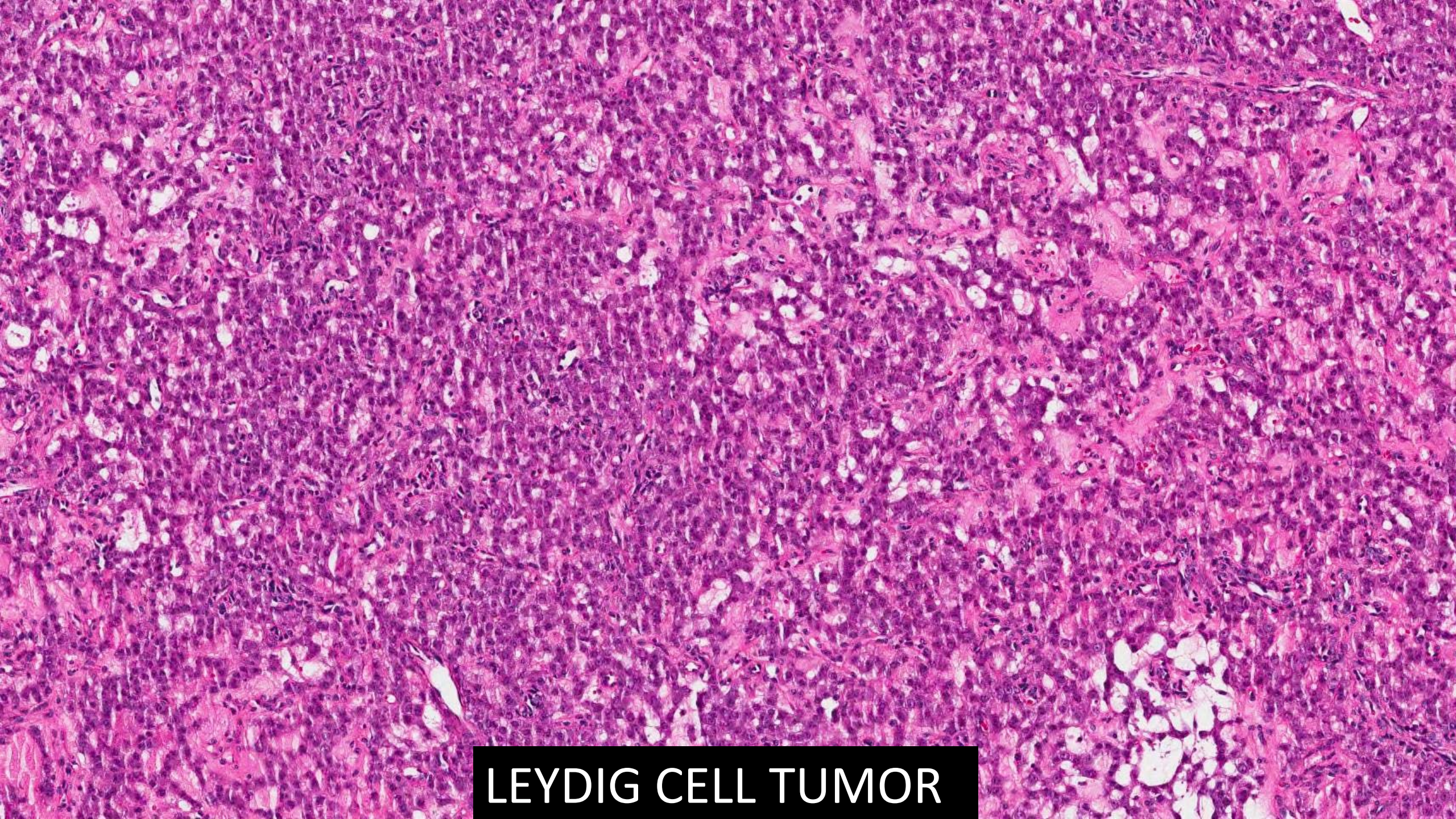
29 year-old man – testicular mass



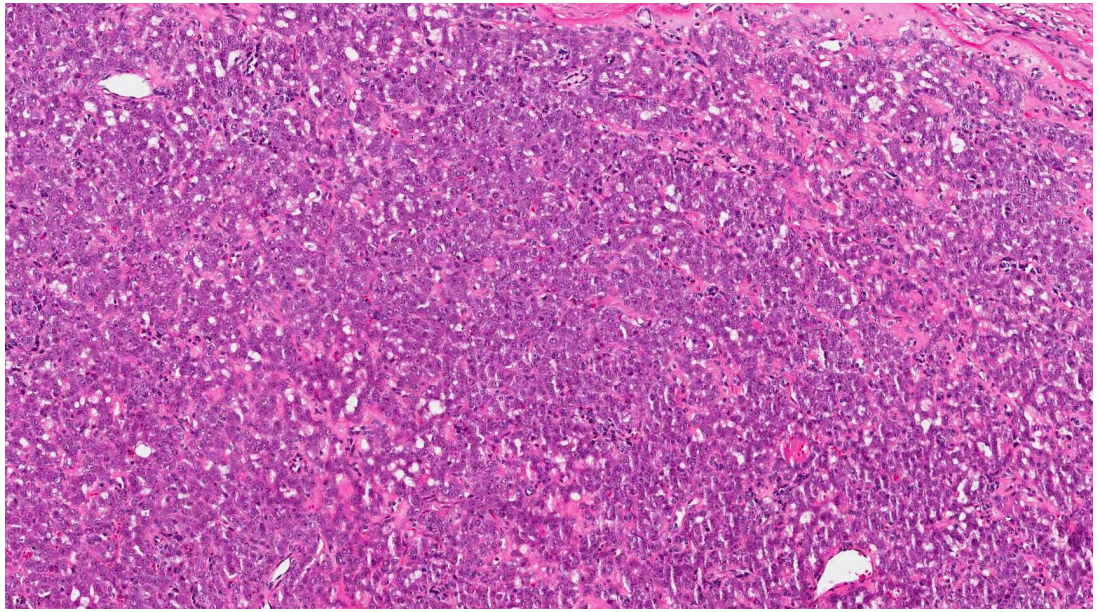


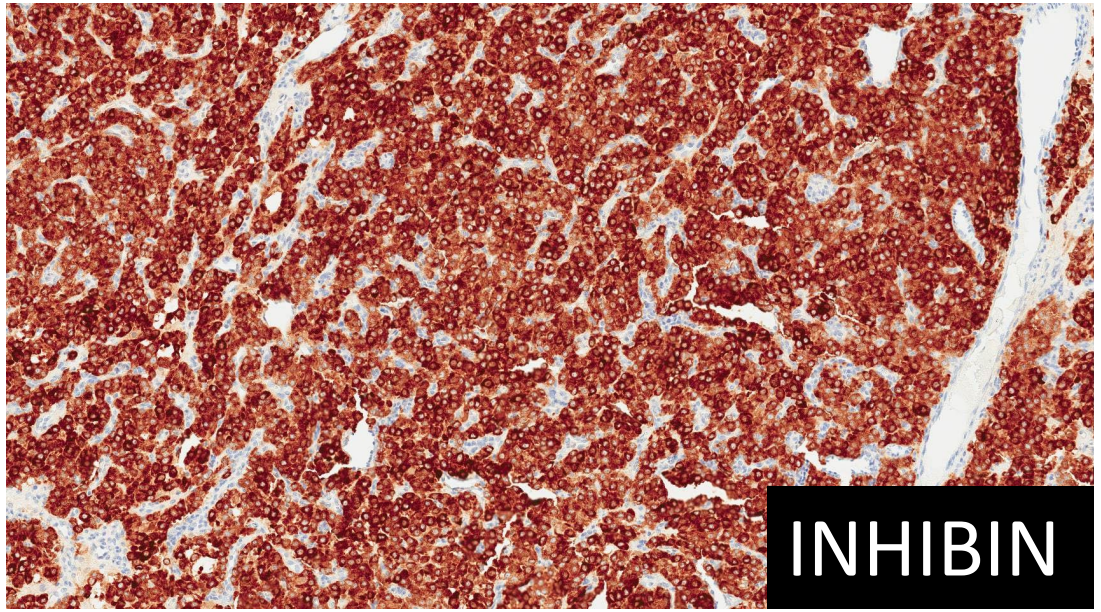





LEYDIG CELL TUMOR

Leydig cell tumor - IHC

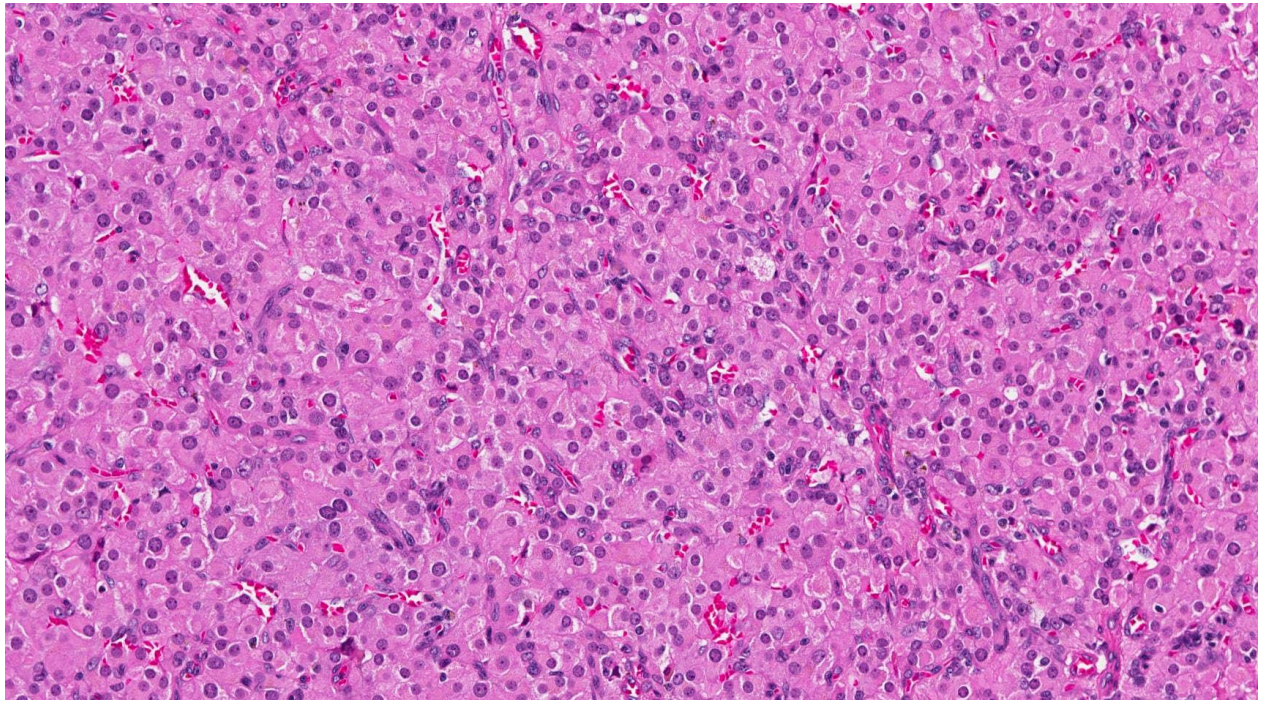




OTHER POSITIVE STAINS:
CALRETININ, CD99, SF-1

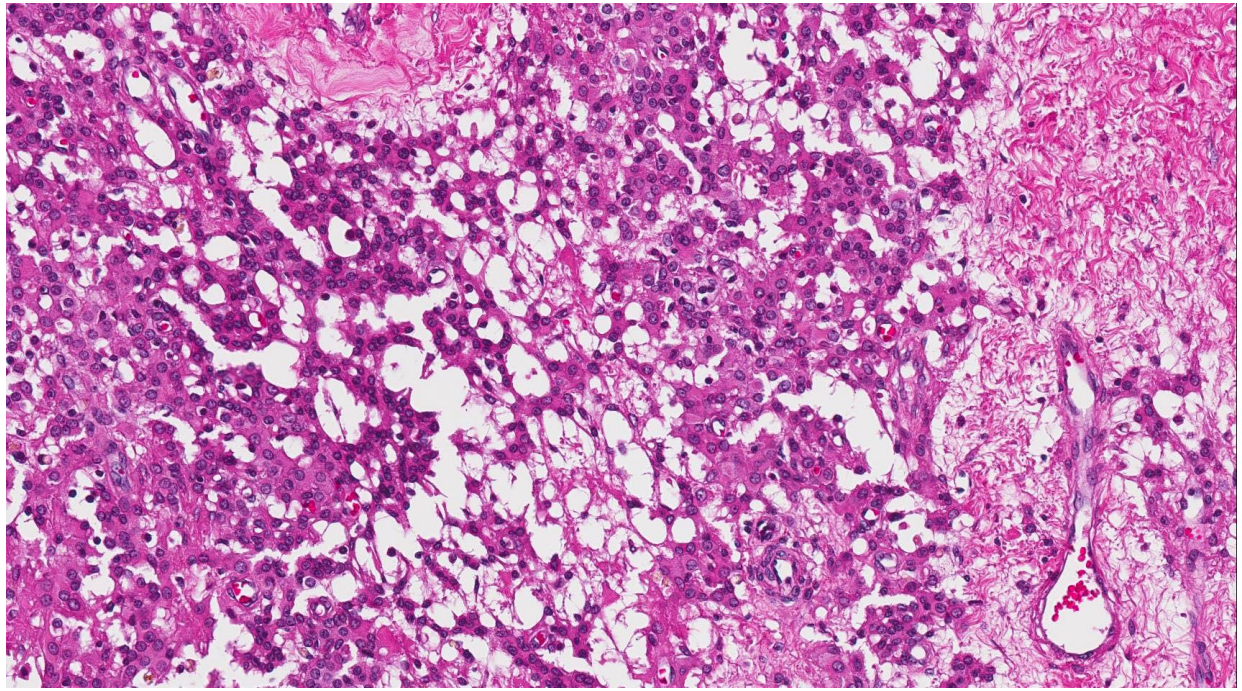
Leydig cell tumor

- Most common sex cord-stromal tumor of the testis (1-3% of testicular tumors
  - Peak ages 5-10 yrs and 30-35 yrs
- Hormonal manifestations (10-20%)
  - Decreased libido
  - Gynecomastia
  - Precocious puberty



Leydig cell tumor

- Varied architectural patterns: diffuse, insular, tubular, ribbon-like, pseudofollicular
- Rare features: adipose metaplasia, microcystic change, rhabdoid features
- Cytoplasmic lipofuscin and Reinke crystals
- Bilaterality RARE

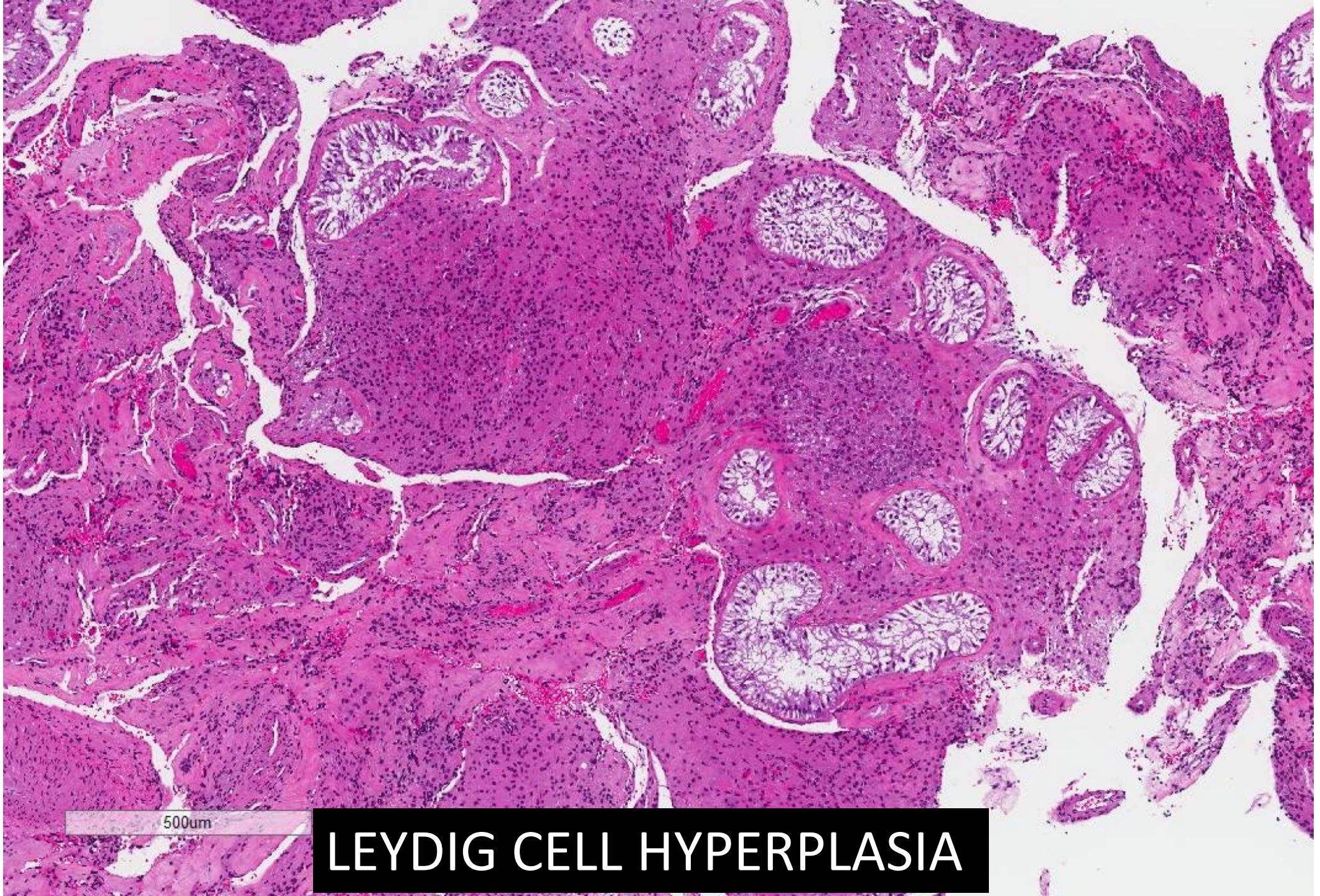


Leydig cell tumor – prediction of behavior

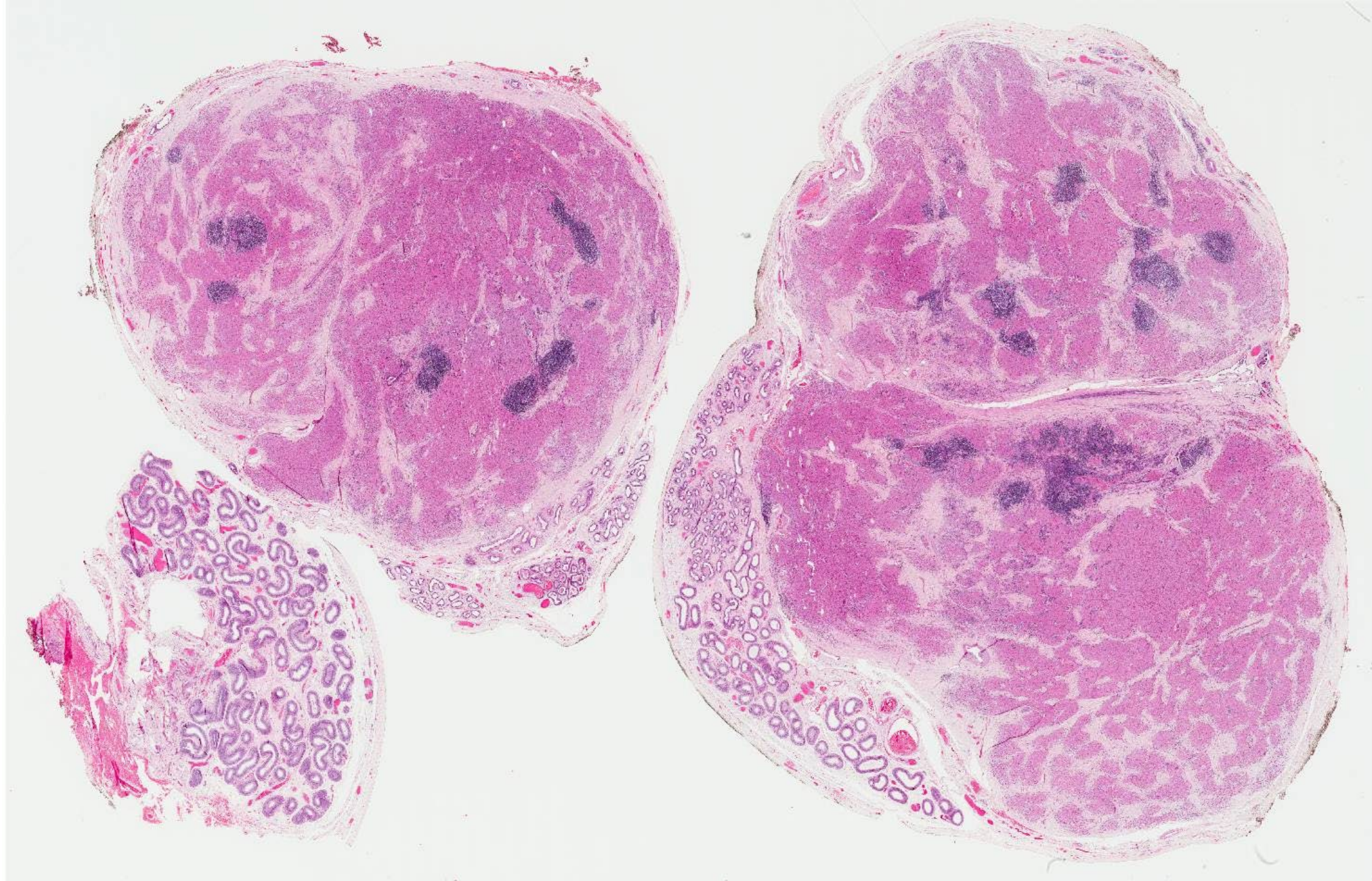
- <10% of Leydig cell tumors are malignant
  - Leydig cell tumor Scaled Score (LeSS) – Collechia et al (2021) Histopathology 78, 290–299
  - 51 cases (37 benign, 14 malignant)
  - Score based on 6 parameters:
    - Tumor size
    - Infiltrative margins
    - Necrosis
    - Mitotic rate
    - Nuclear atypia
  - Preliminary – needs to be further validated
  - FH-deficient examples

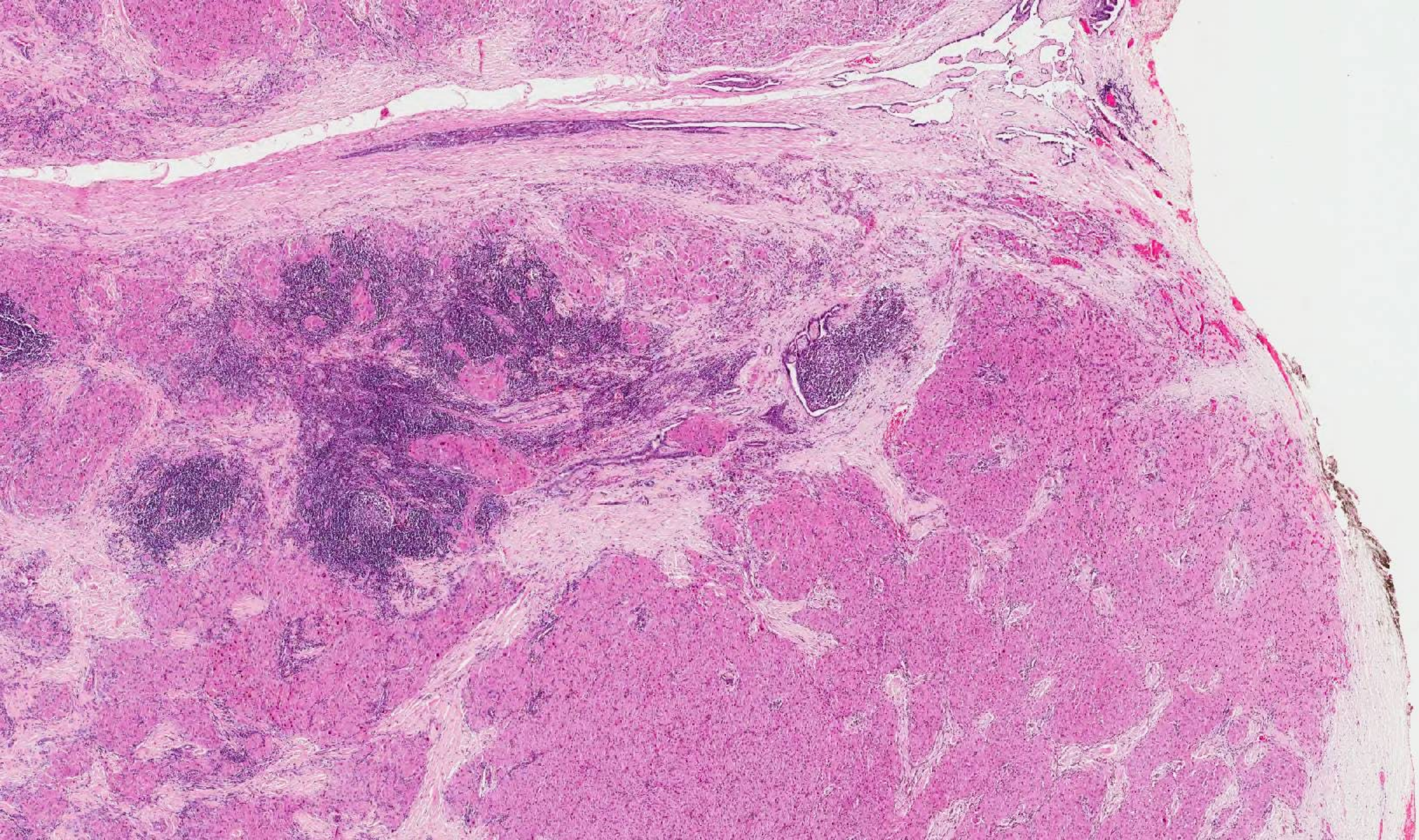
Leydig cell tumor – differential diagnosis

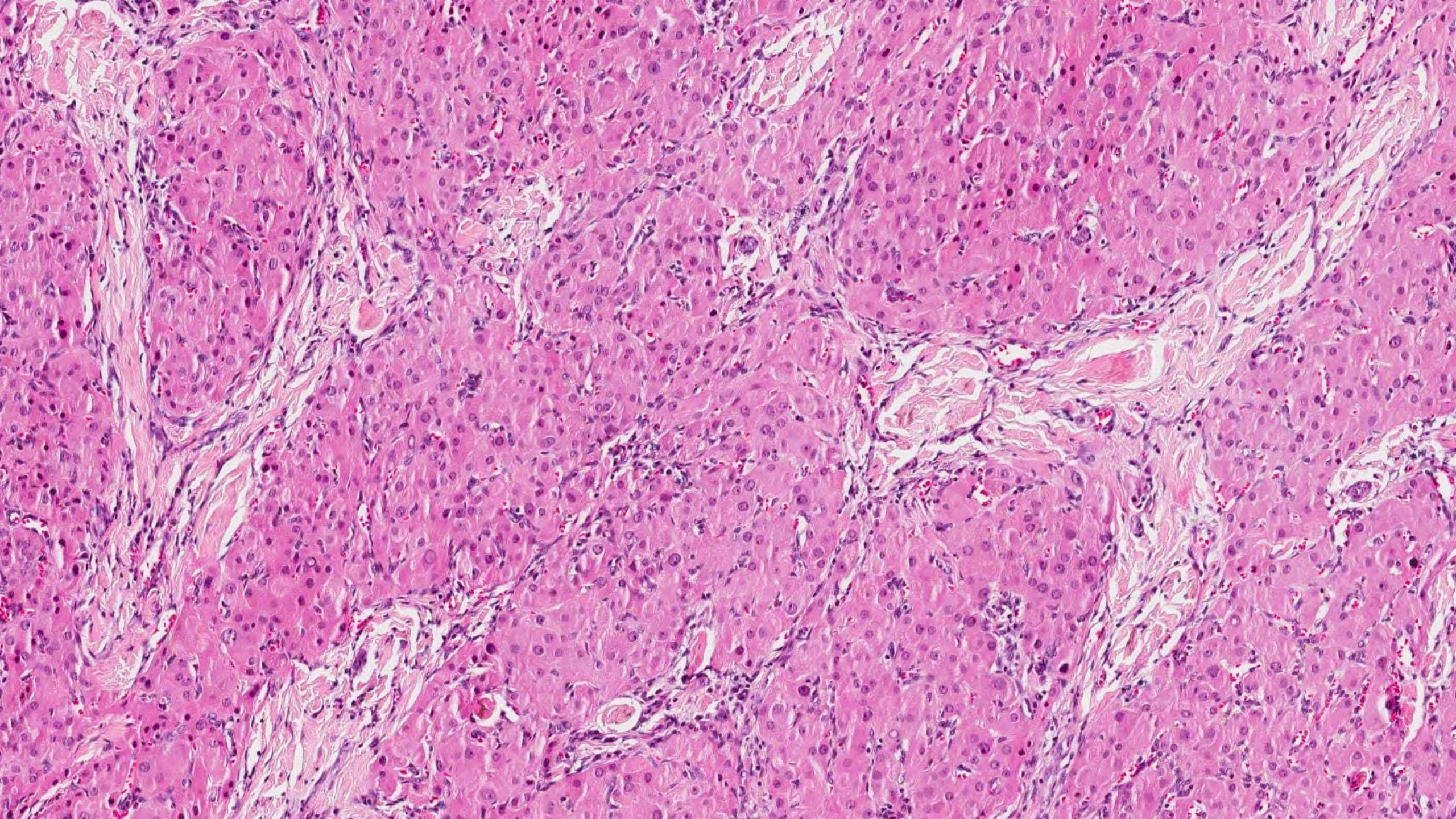
- Leydig cell hyperplasia
- Testicular tumor of the adrenogenital syndrome (TTAG)
- Histiocytic proliferations

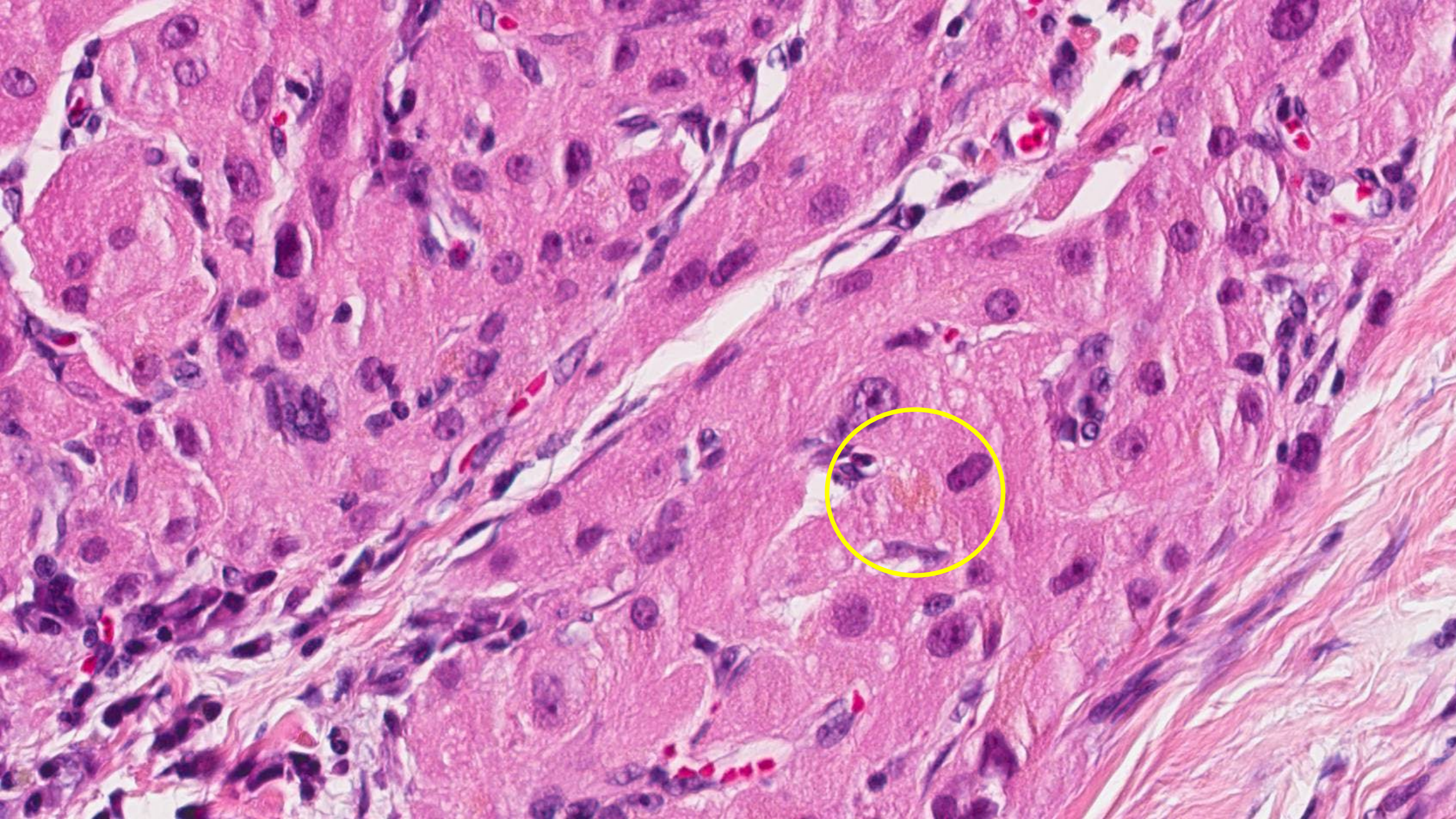


LEYDIG CELL HYPERPLASIA



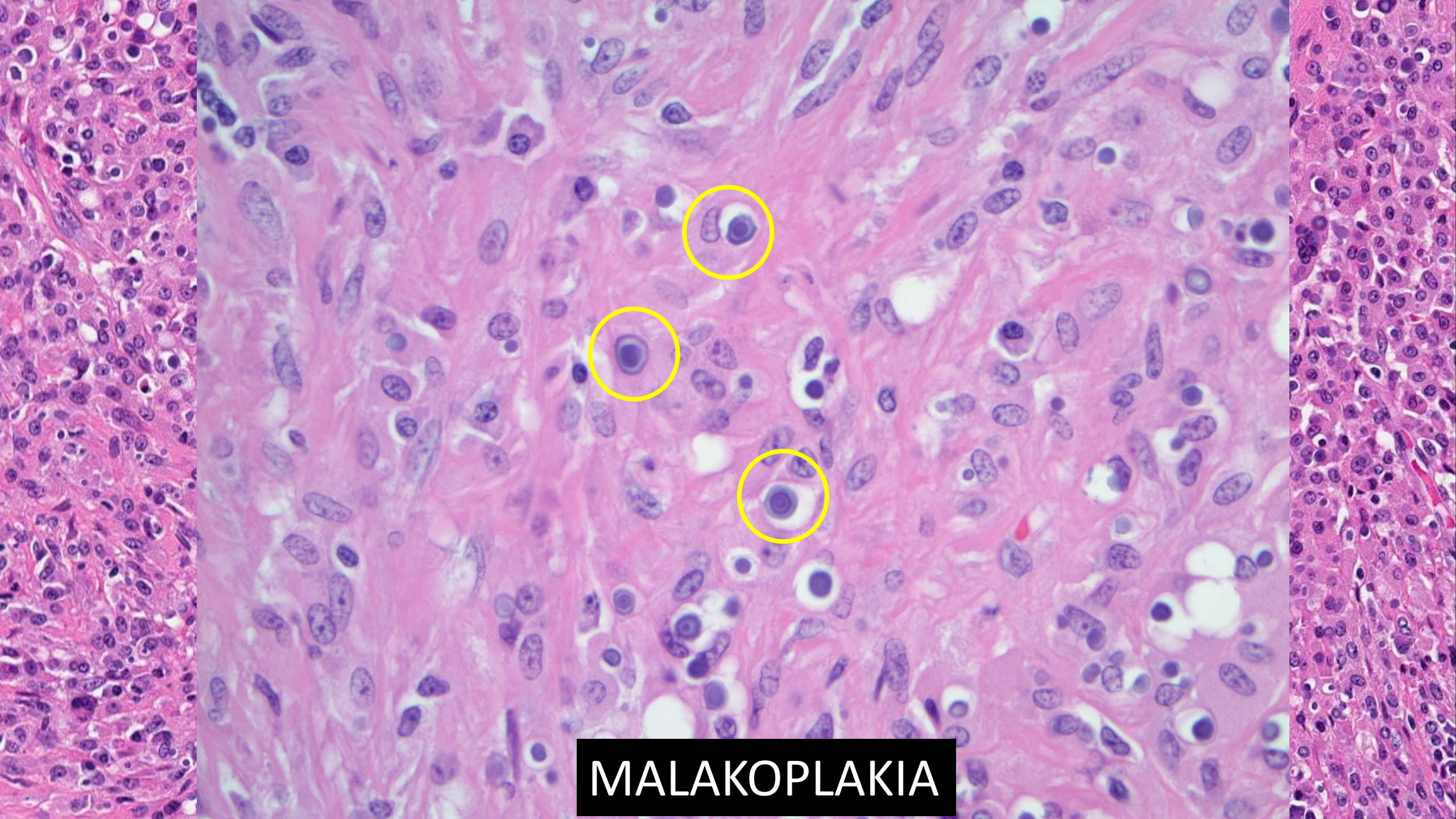


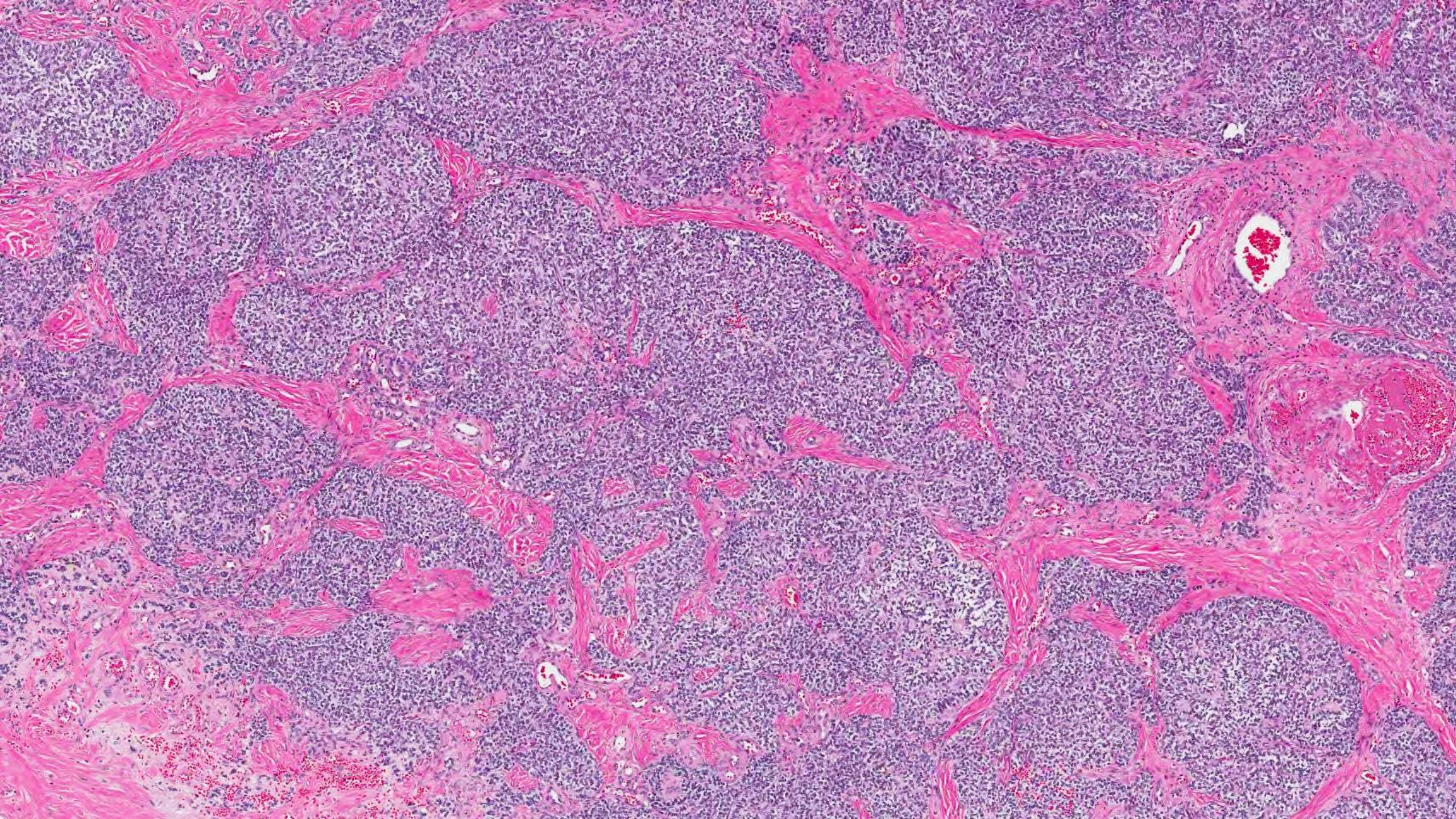


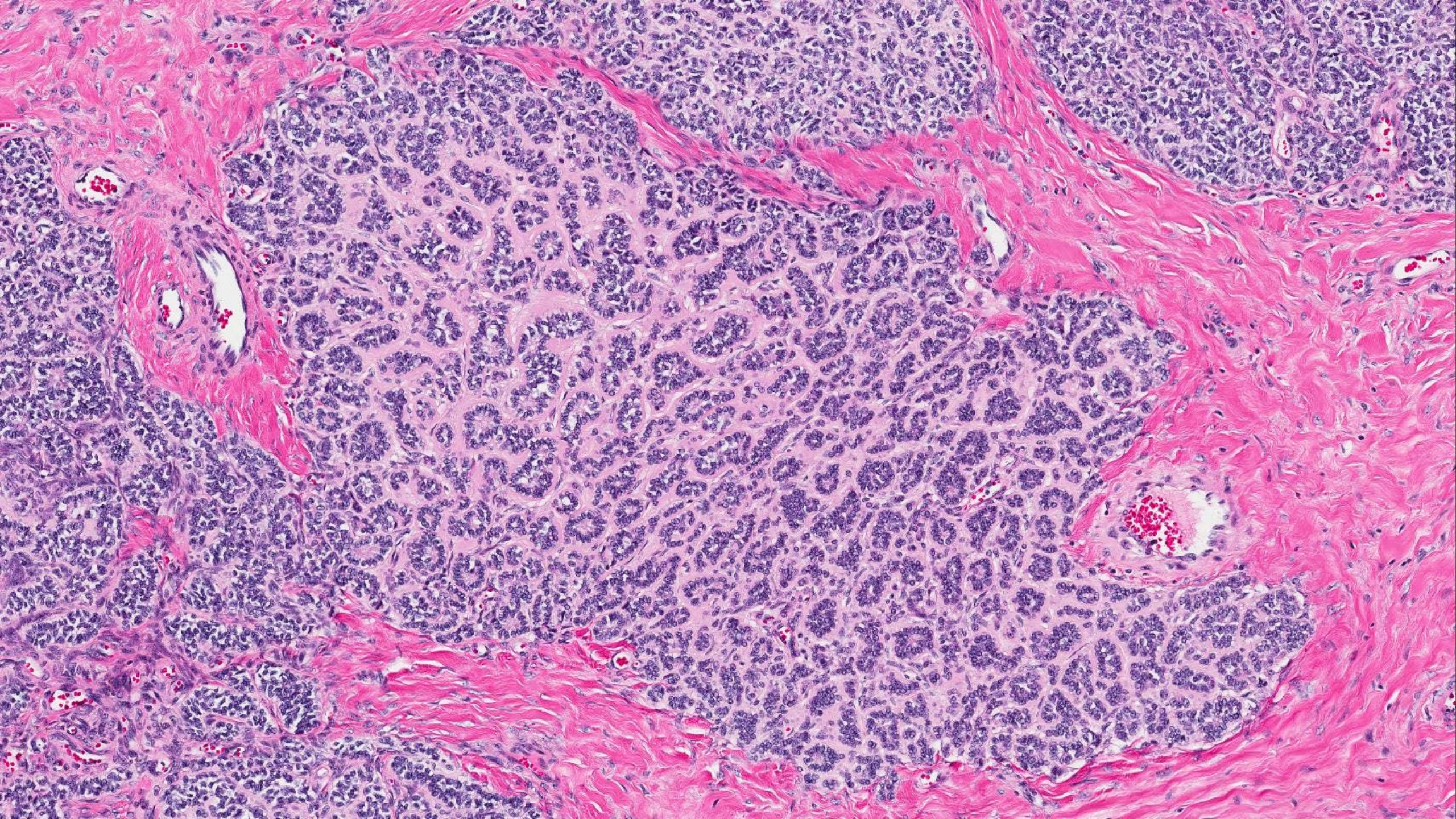


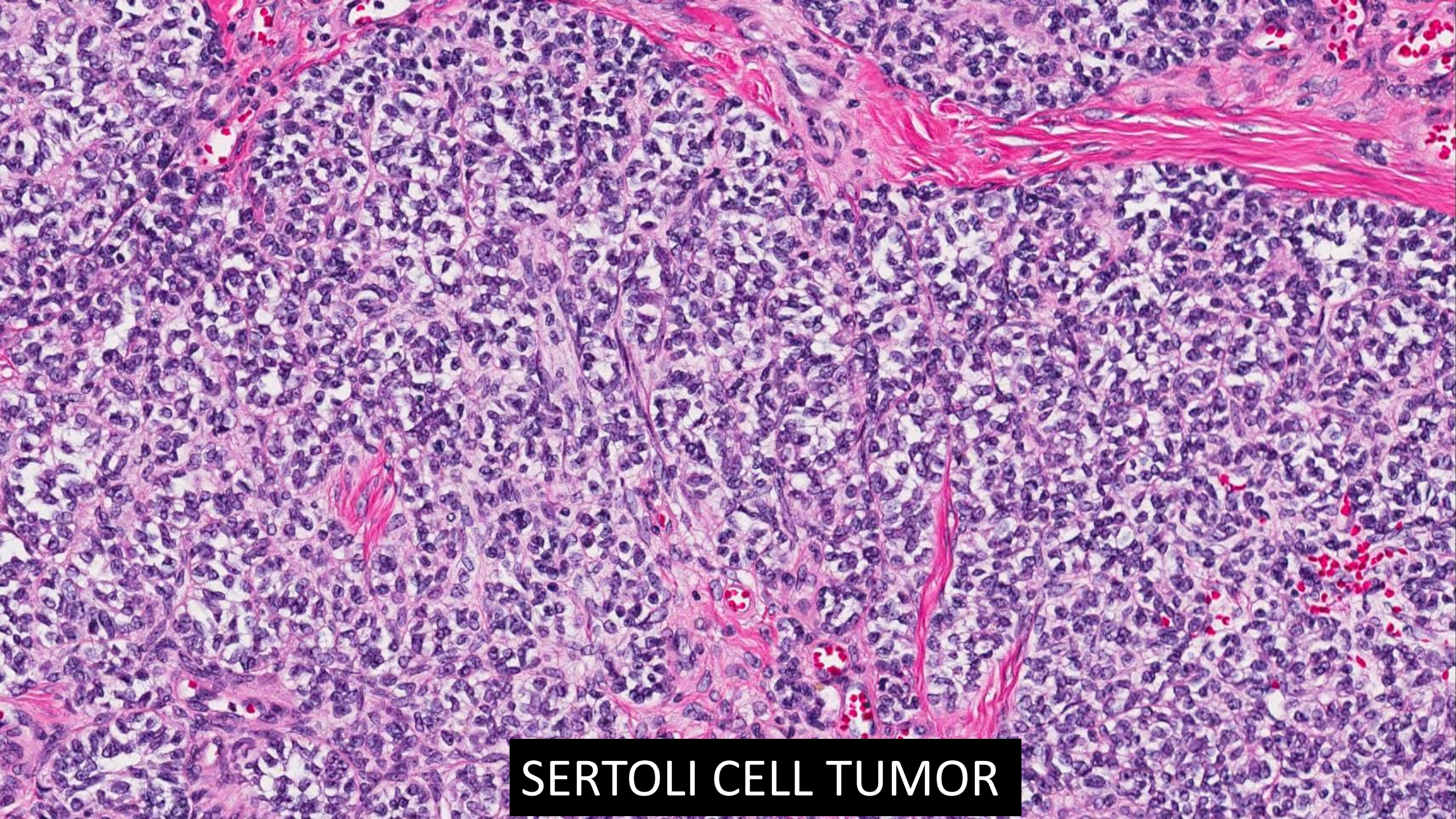
Testicular tumor of the adrenogenital syndrome (TTAG)

- History of congenital adrenal hyperplasia – cells with adrenal phenotype
- Mean age 22 years
- 83% bilateral
- Hilar location
- Treated with high-dose corticosteroids


MALAKOPLAKIA






SERTOLI CELL TUMOR

Sertoli cell tumor

- Less common than Leydig cell tumor
- Mean age 45 years
- Not usually hormonally active
- Predominantly tubular; can have solid, microcystic, or spindled patterns
- Bland cytology; uniform cuboidal to columnar cells
  - Can have cytoplasmic clearing and nests separated by fibrous septa with lymphocytes (like seminoma)

Sertoli Cell Tumor

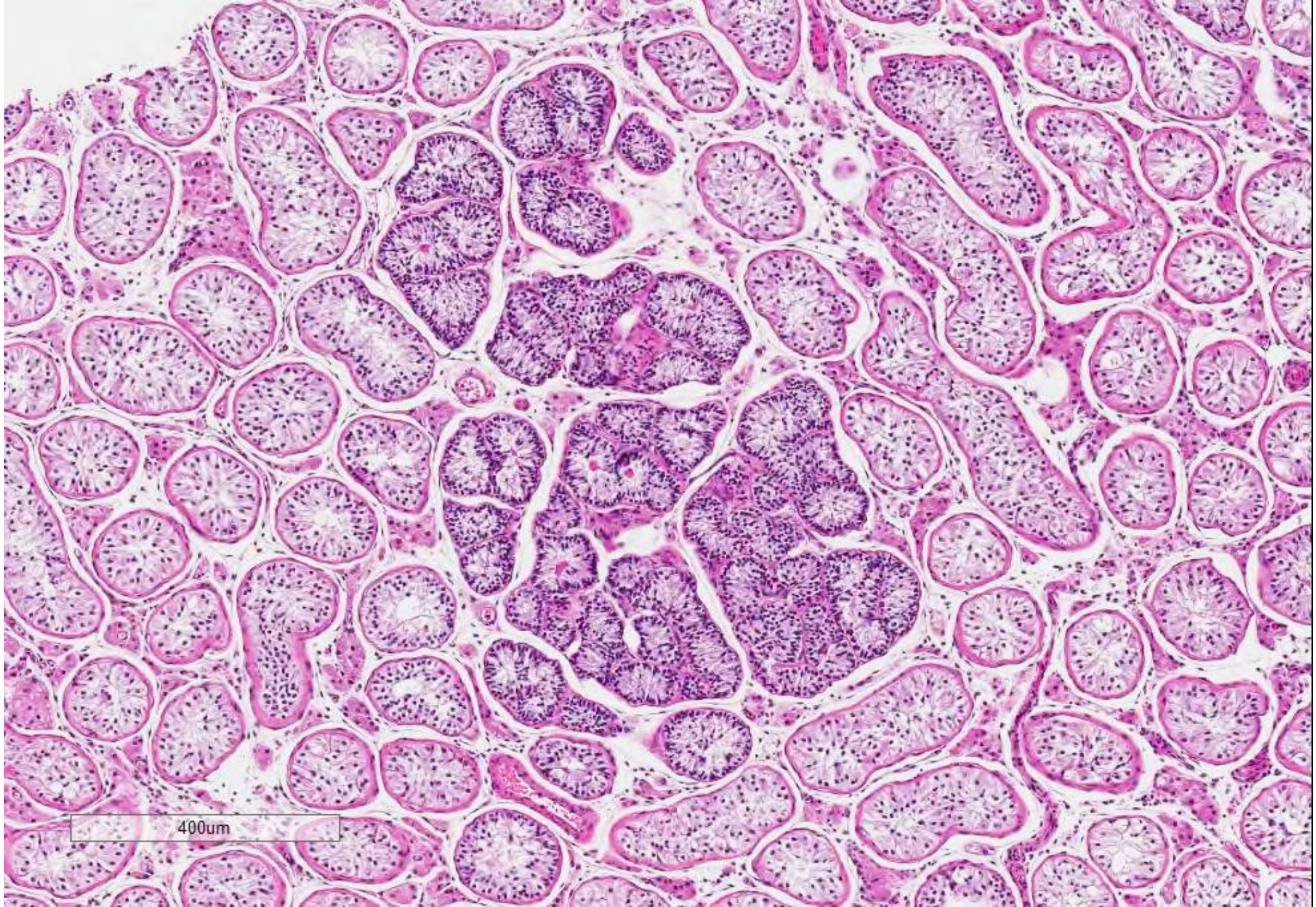
- Immunohistochemistry:
  - Positive for sex cord markers: SF-1, Inhibin, Calretinin, CD99
  - Positive for keratins
  - Negative for SALL-4, OCT3/4, PLAP, D2-40

Sertoli Cell Tumor

- Prognosis:
  - Same approach/challenges as in Leydig cell tumor
    - 10% malignant, but only definitive criterion is metastasis
    - Features associated with adverse outcomes:
      - Large size (> 5 cm)
      - Necrosis
      - Lymphovascular invasion
      - Extratesticular extension
      - Increased mitotic rate (>5/10HPF)
      - Marked nuclear pleomorphism
    - Poor response to chemotherapy

Sertoli cell tumor – differential diagnosis

- Seminoma
- Pick adenoma (Sertoli cell nodule)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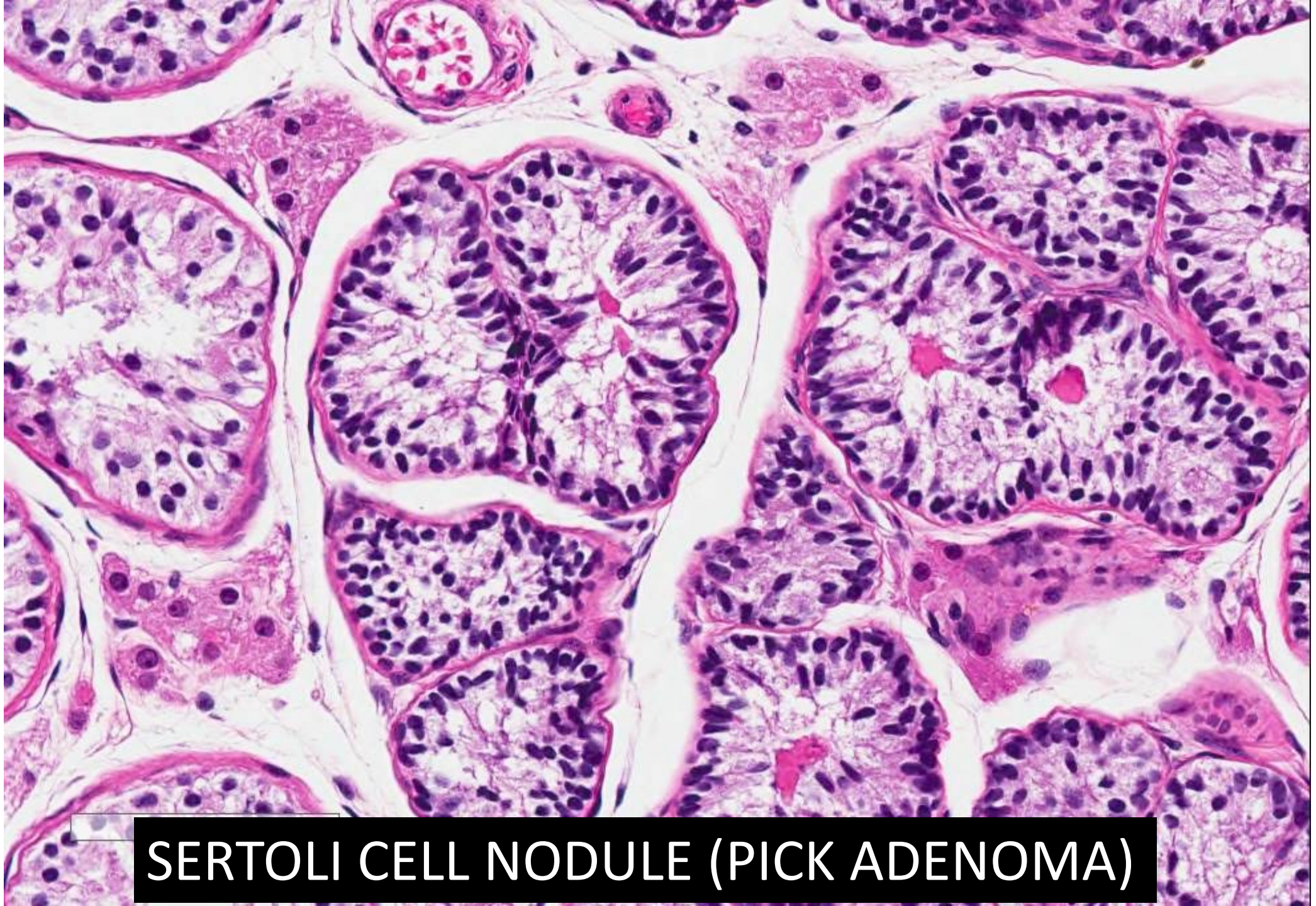
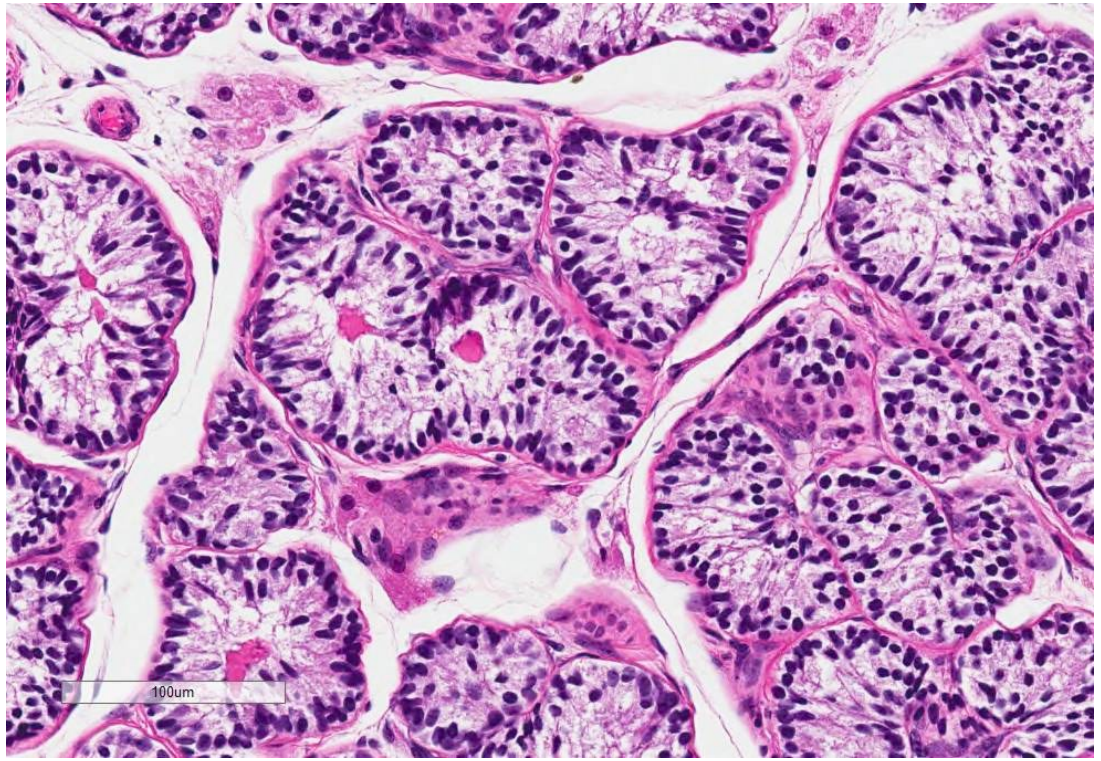


SERTOLI CELL NODULE (PICK ADENOMA)

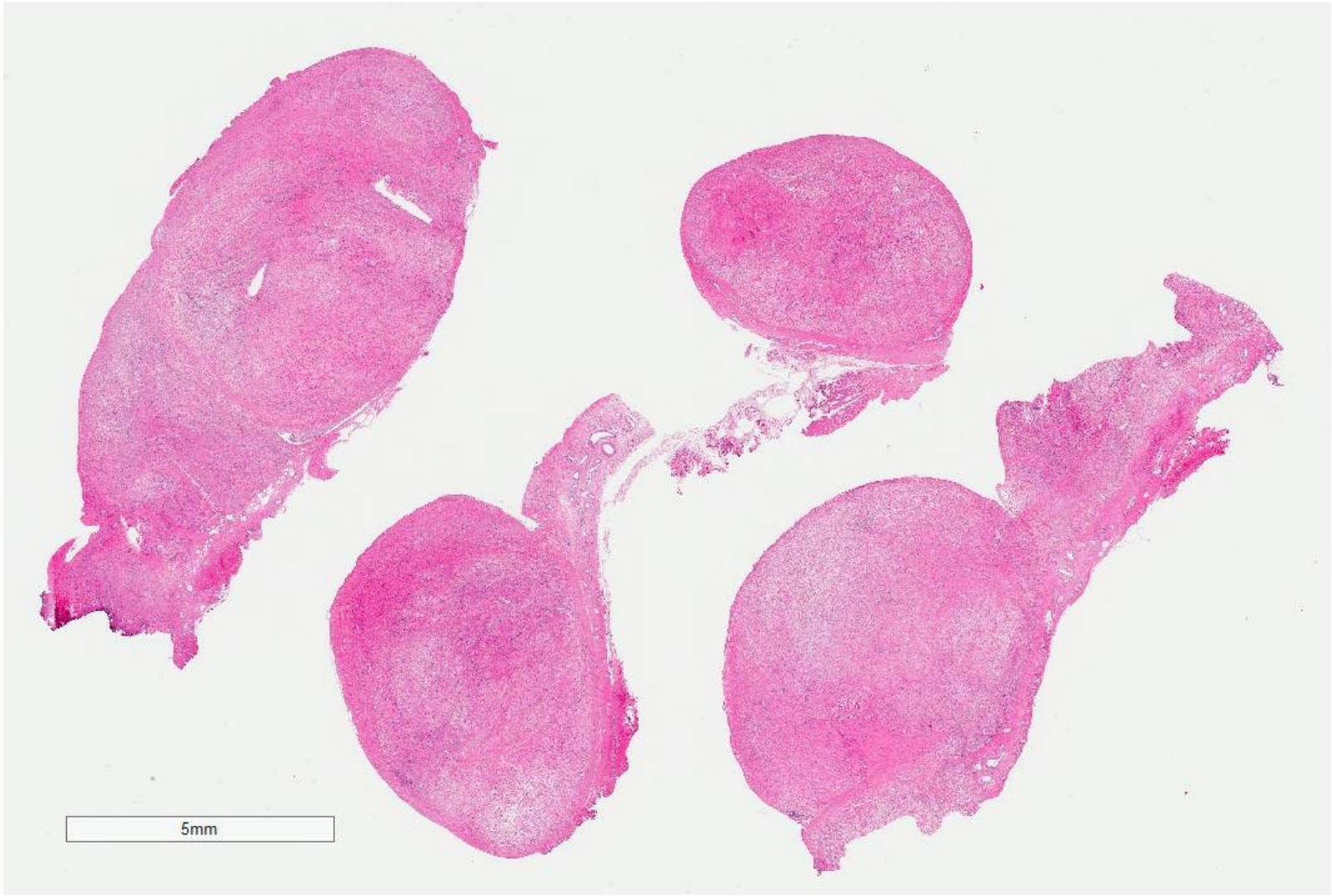
Sertoli Cell Nodule (Pick adenoma)

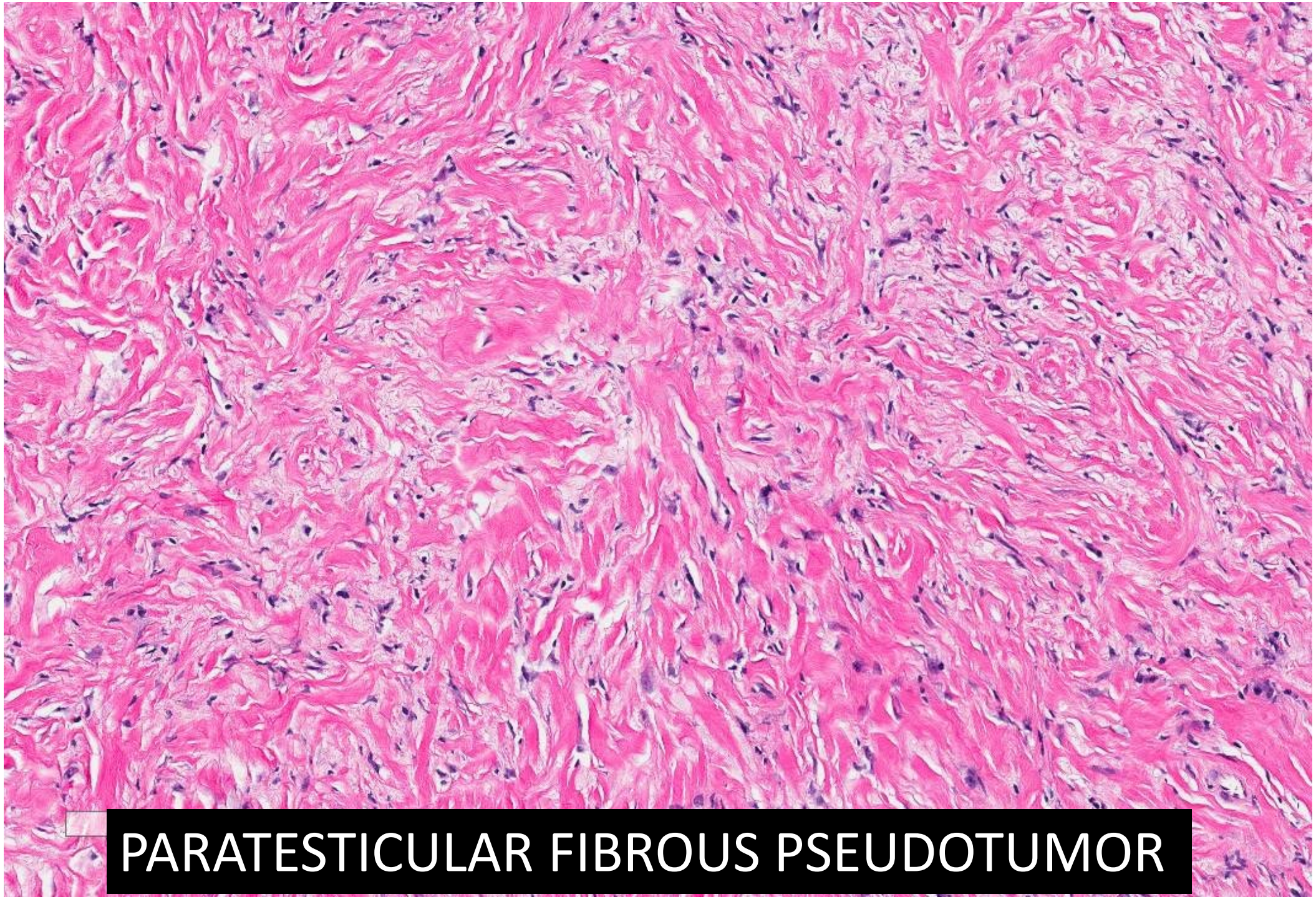
- Cryptorchid testes
- Immature Sertoli cells with eosinophilic material
- Benign behavior
- Occasionally detectable as a mass



Considerations in paratesticular pathology

Paratesticular mass 25 year-old

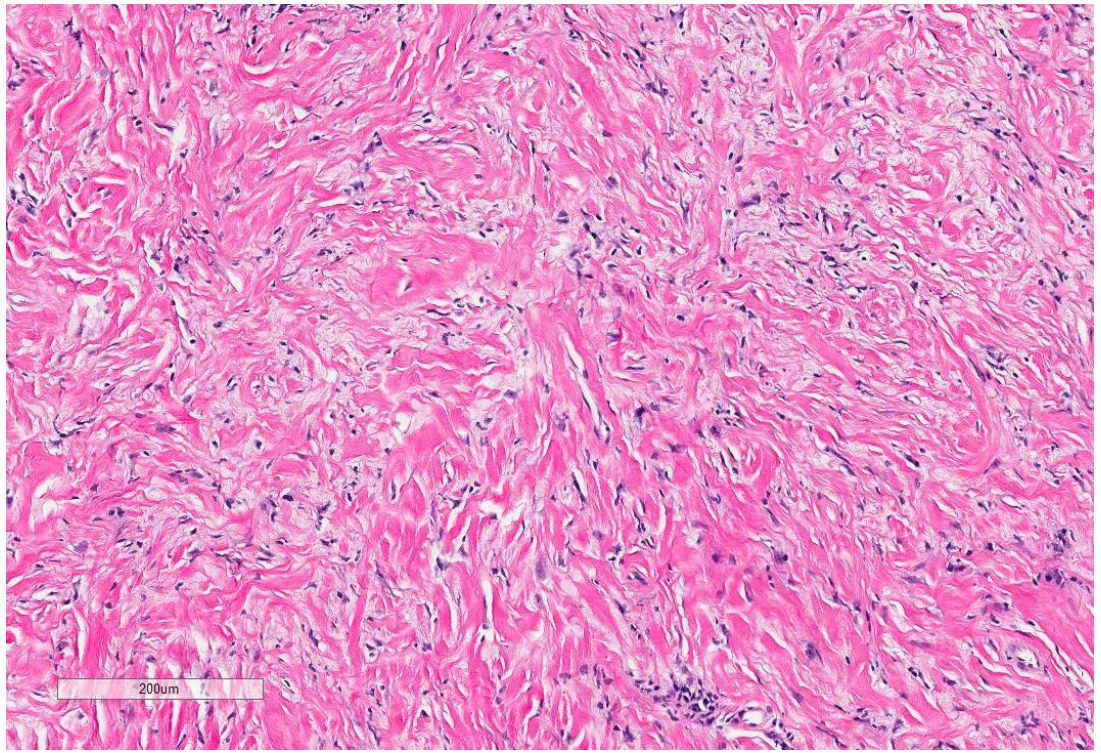


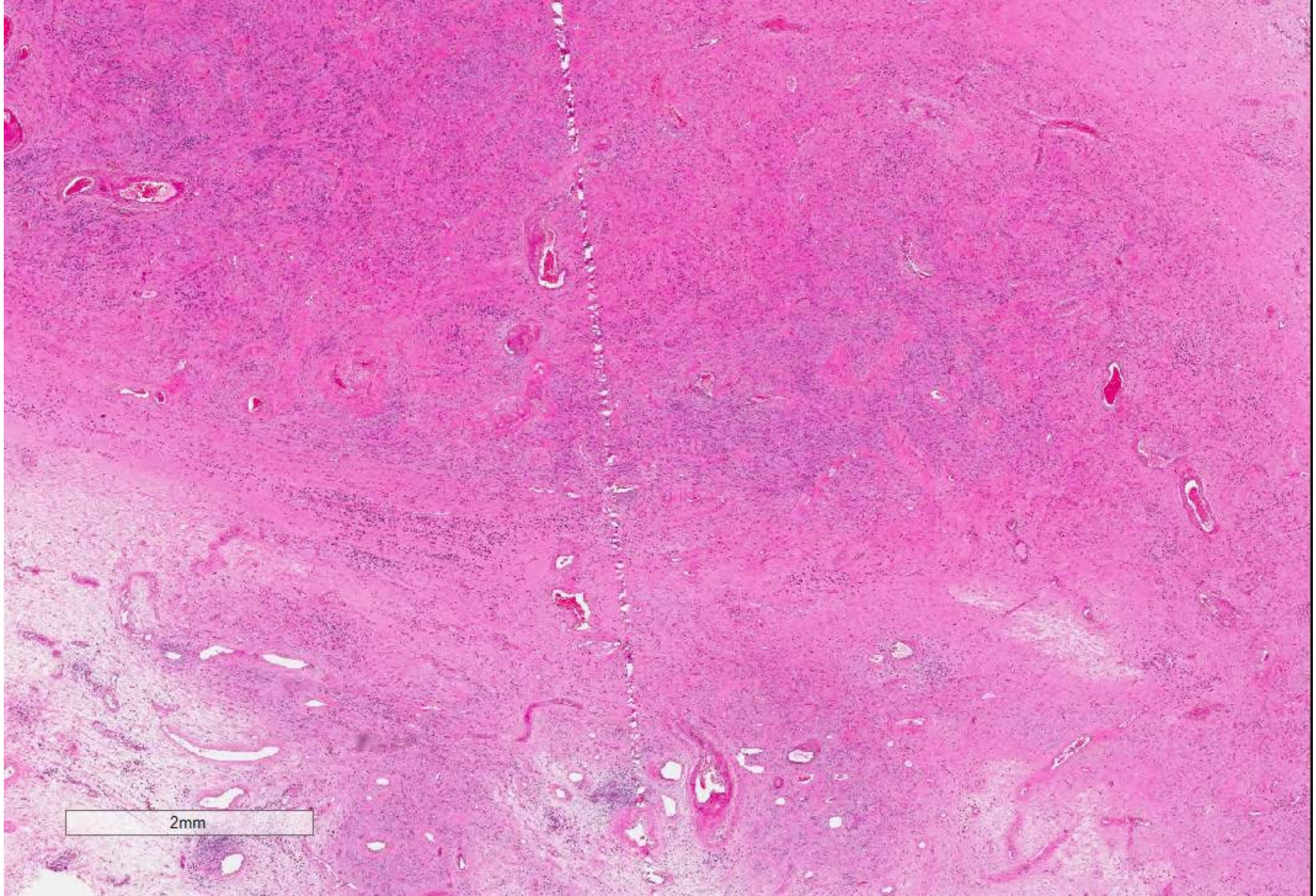


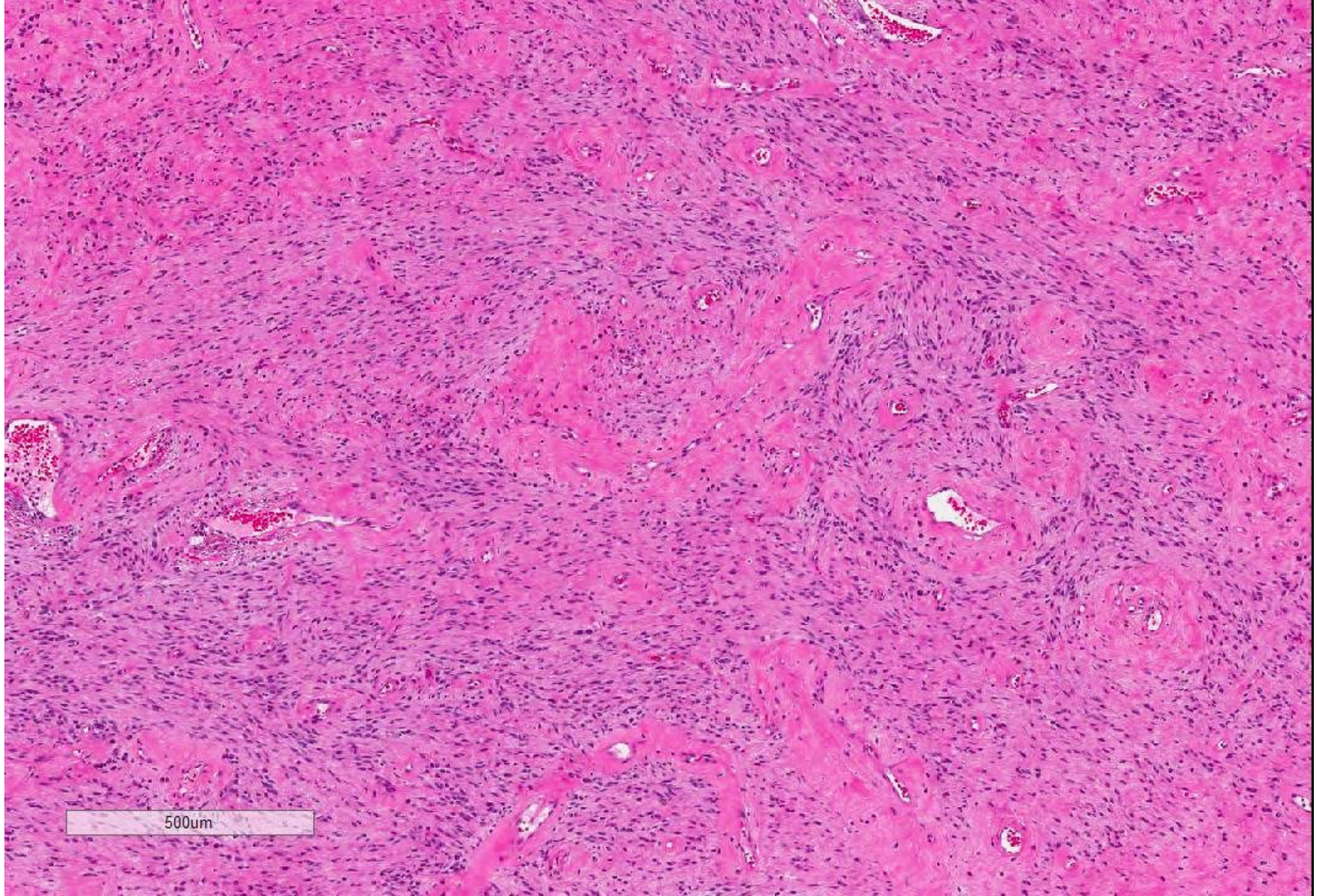
PARATESTICULAR FIBROUS PSEUDOTUMOR

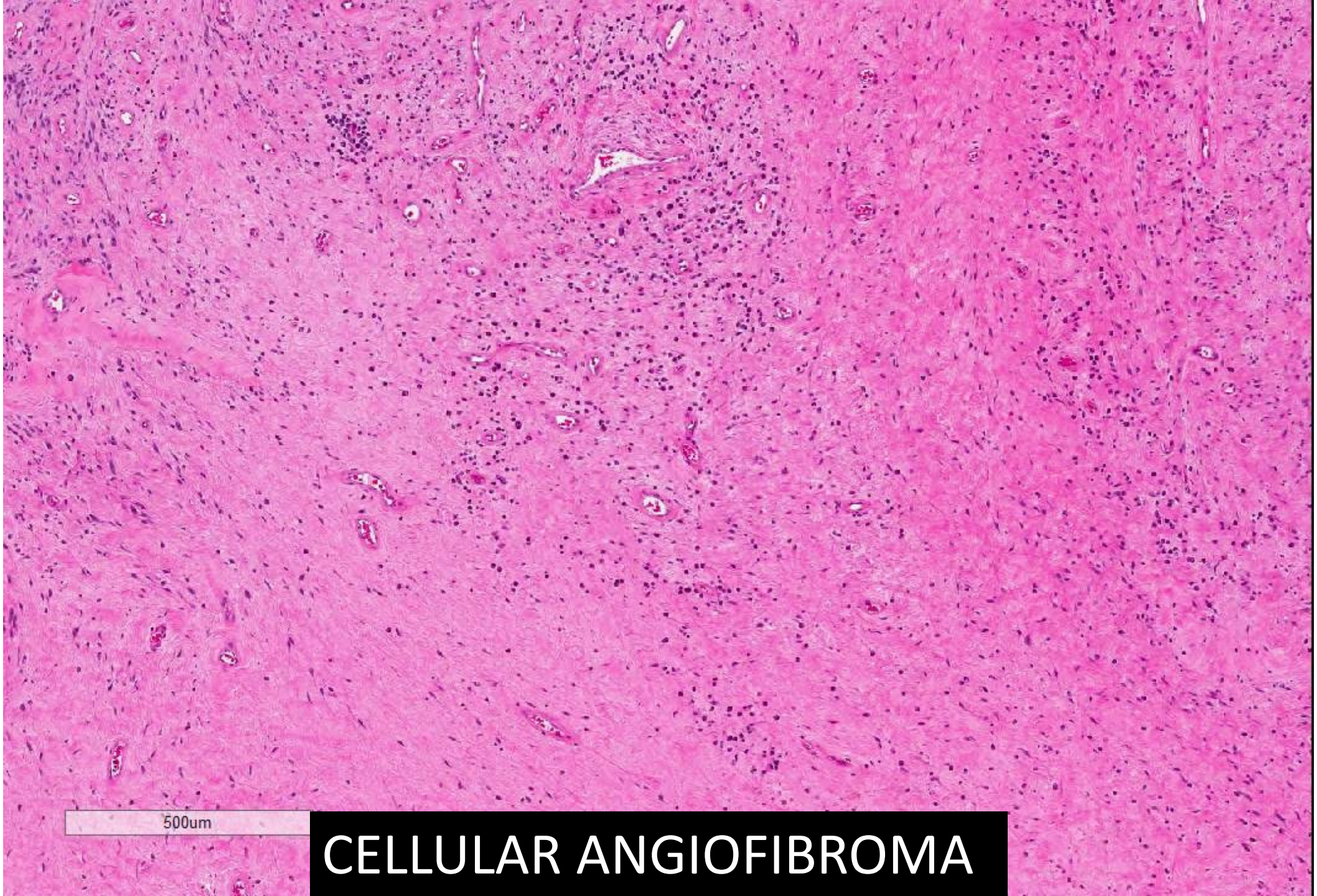
Paratesticular fibrous pseudotumor

- Miyamoto et al *Am J Surg Pathol* 2010;34:569–574
- Mean age 42 years
- Presentation with scrotal mass +/- hydrocele
- Dense sclerosis, inflammatory cells, “tissue-culture” spindle cells, capillaries
- Benign behavior
- IgG4-related disease?




2mm

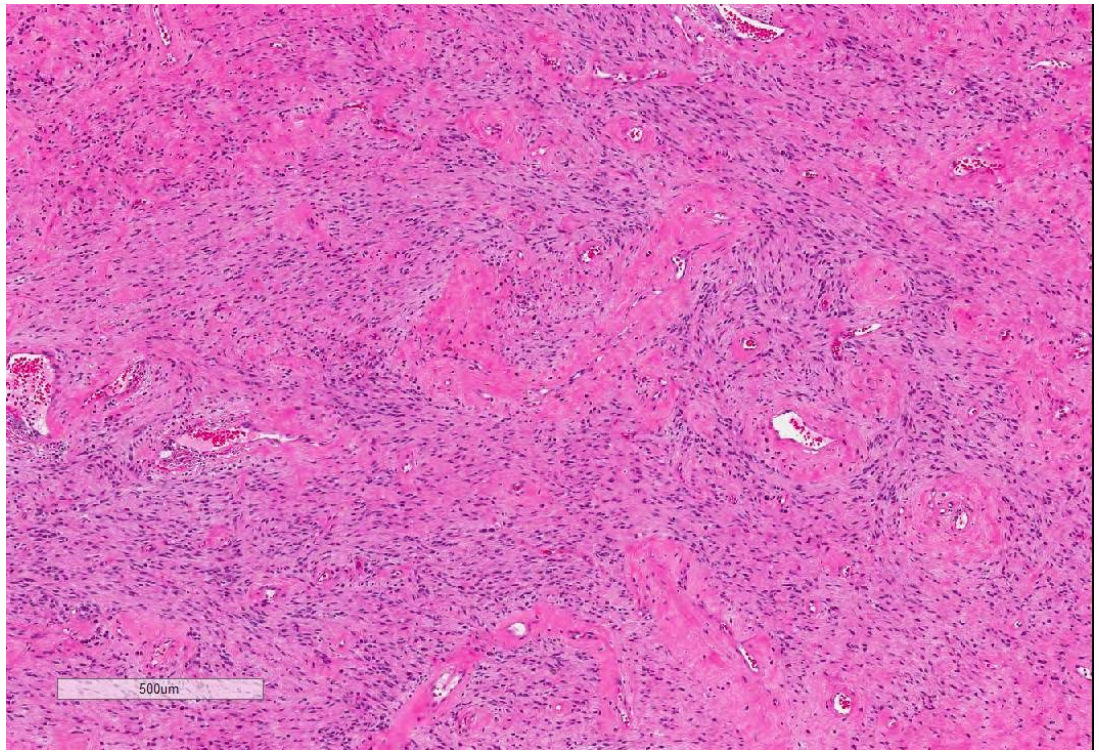

500um

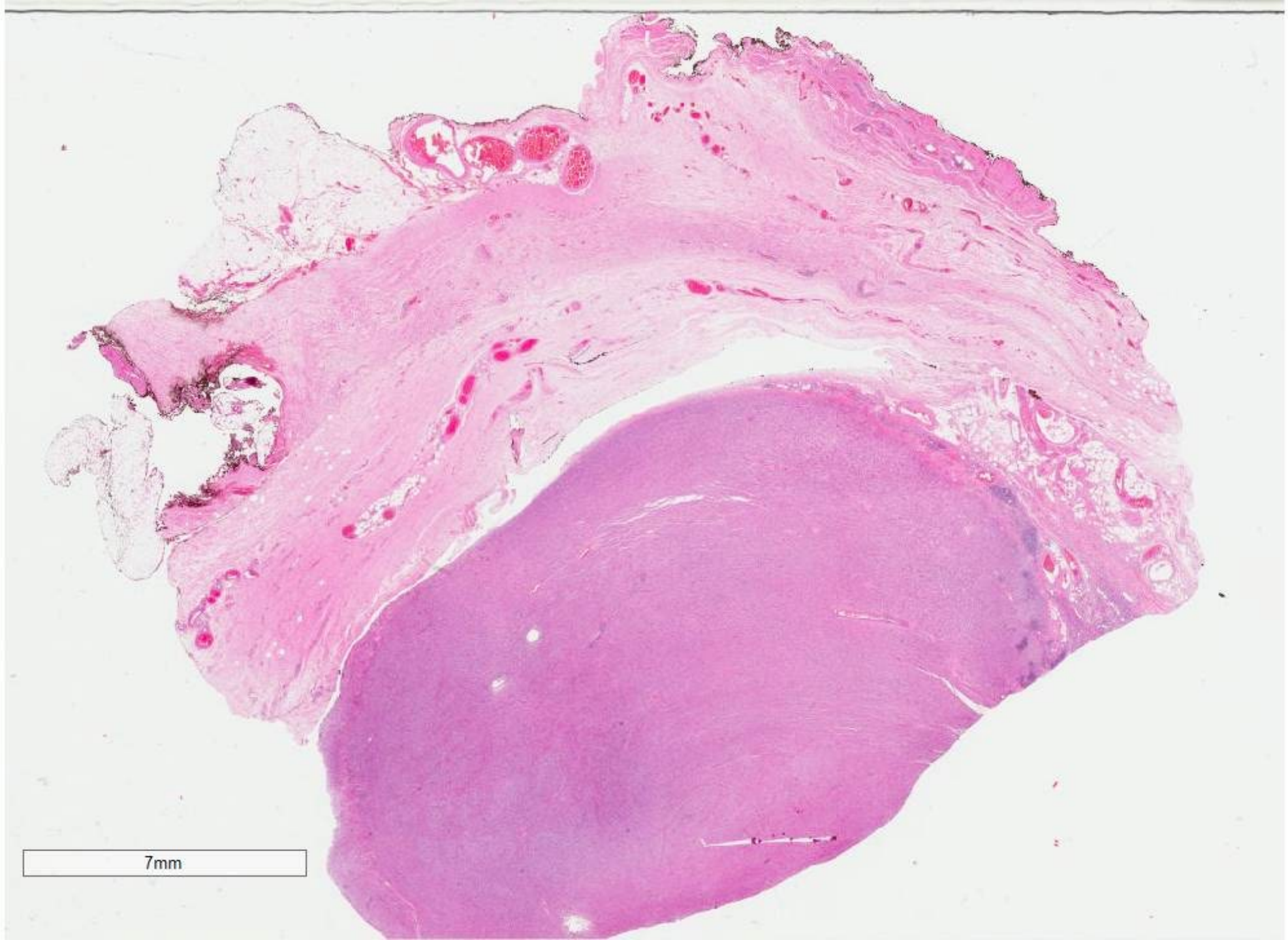


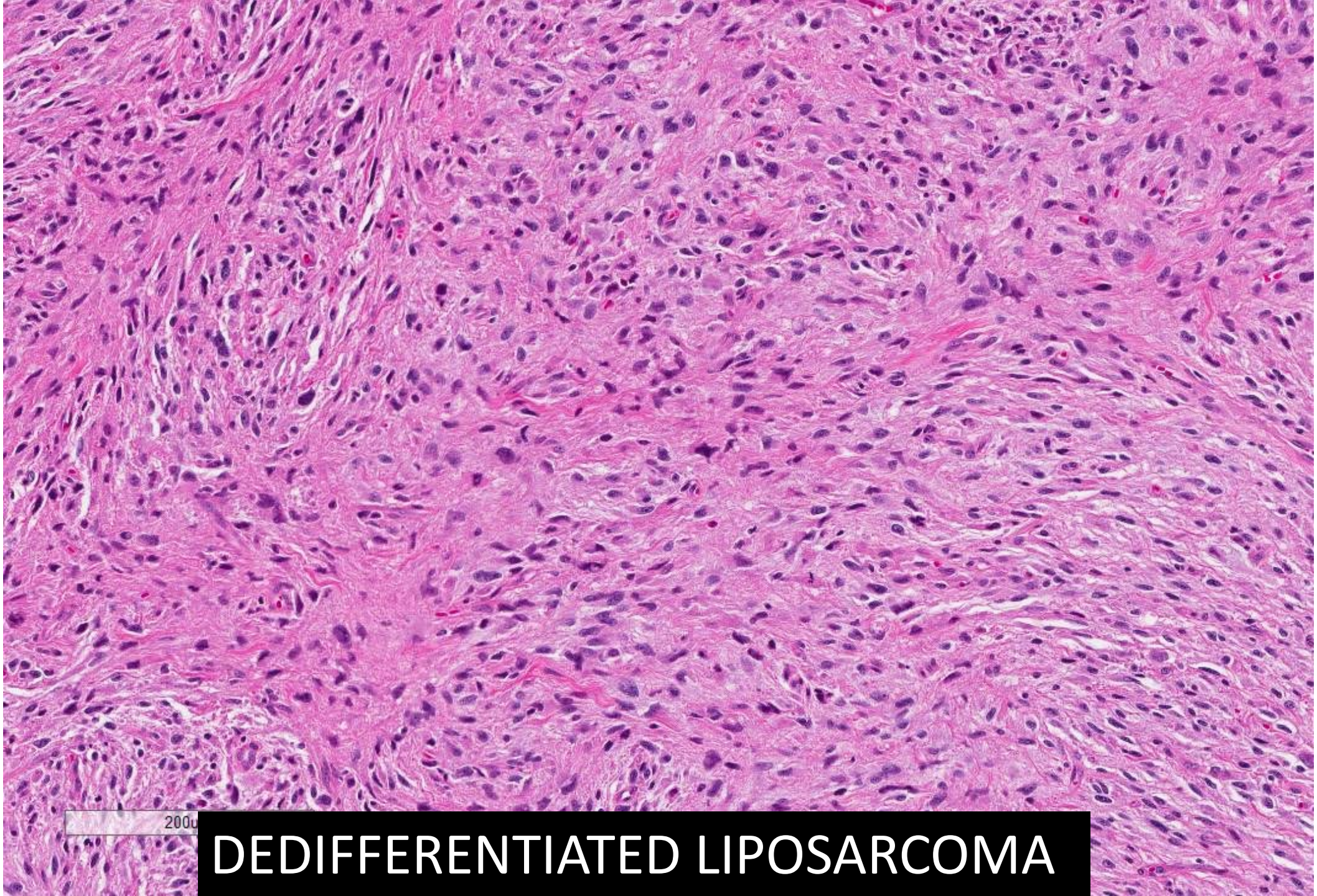
CELLULAR ANGIOFIBROMA

Cellular angiofibroma

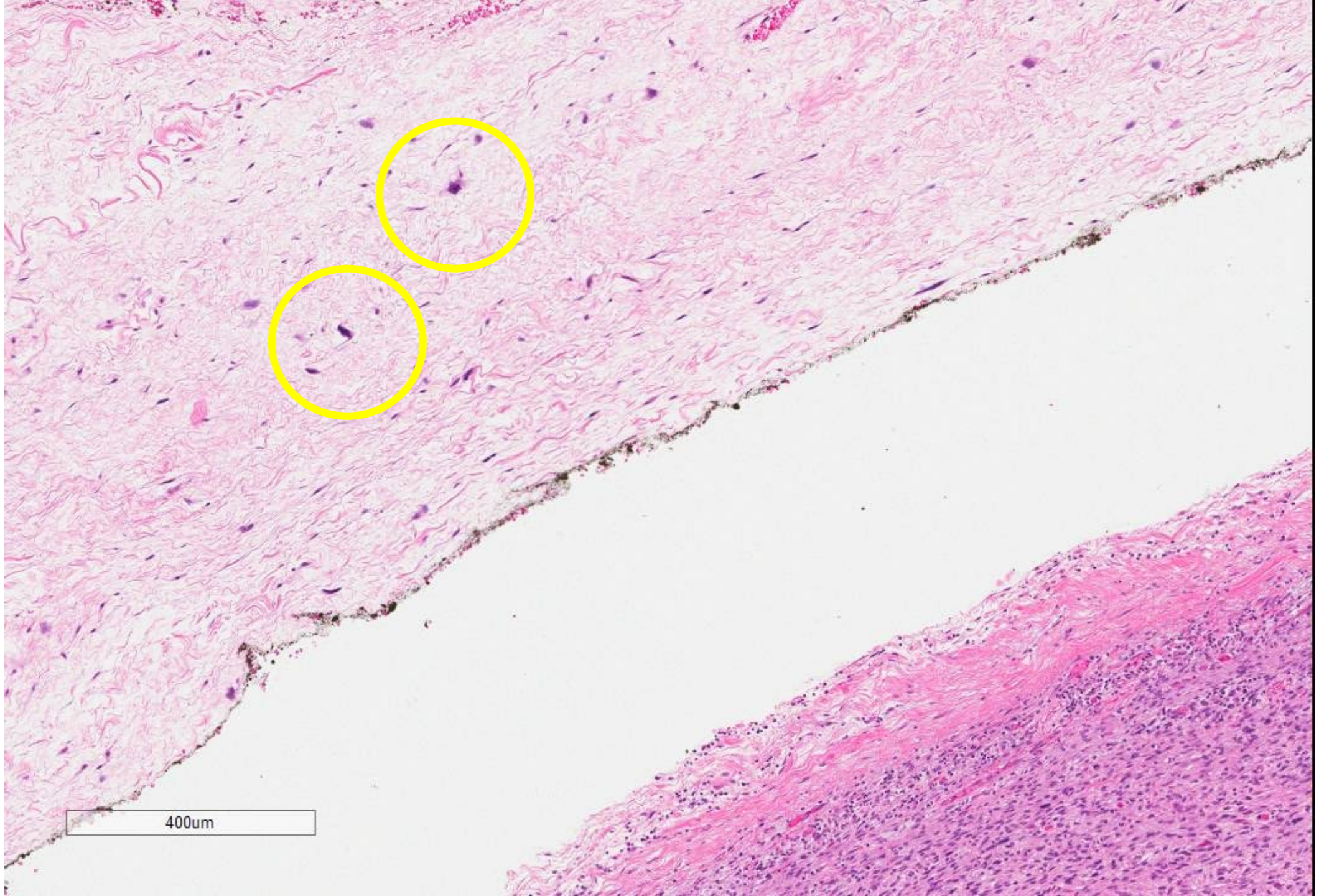
- Mean age 60 years
- Circumscribed
- Superficially located
- Zonal cellularity
- Hyalinized vessels
- DDx: Aggressive angiomyxoma



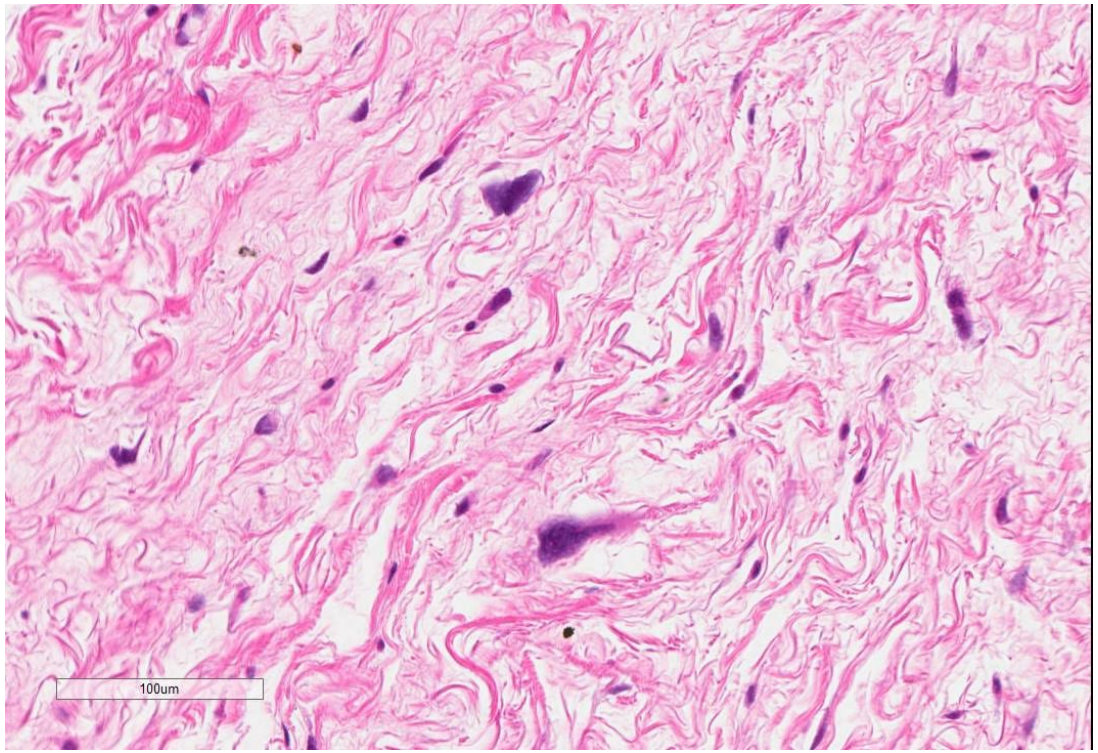

7mm

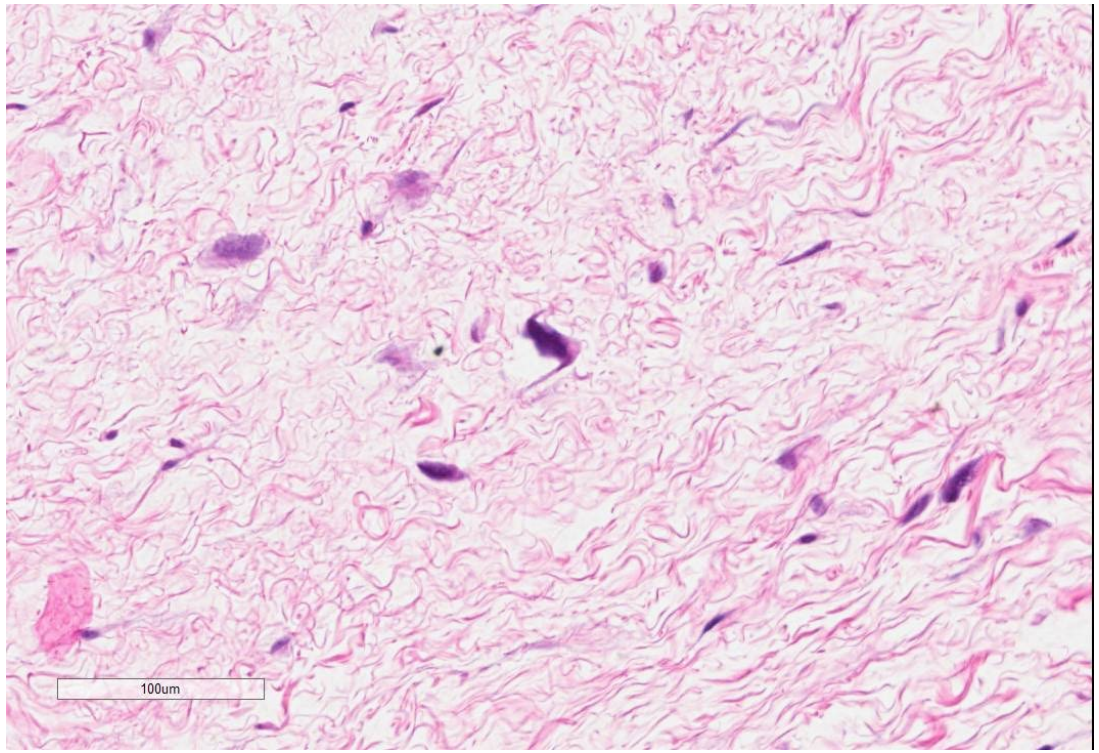


DEDIFFERENTIATED LIPOSARCOMA


400um

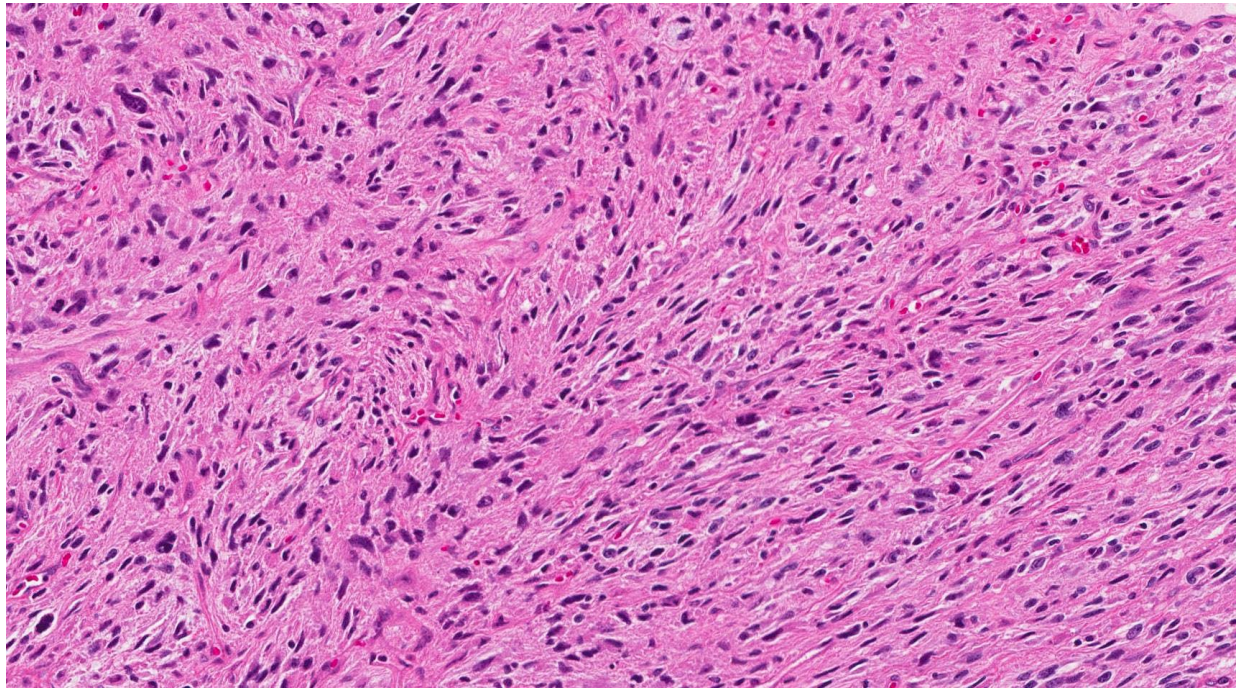
Well-differentiated areas

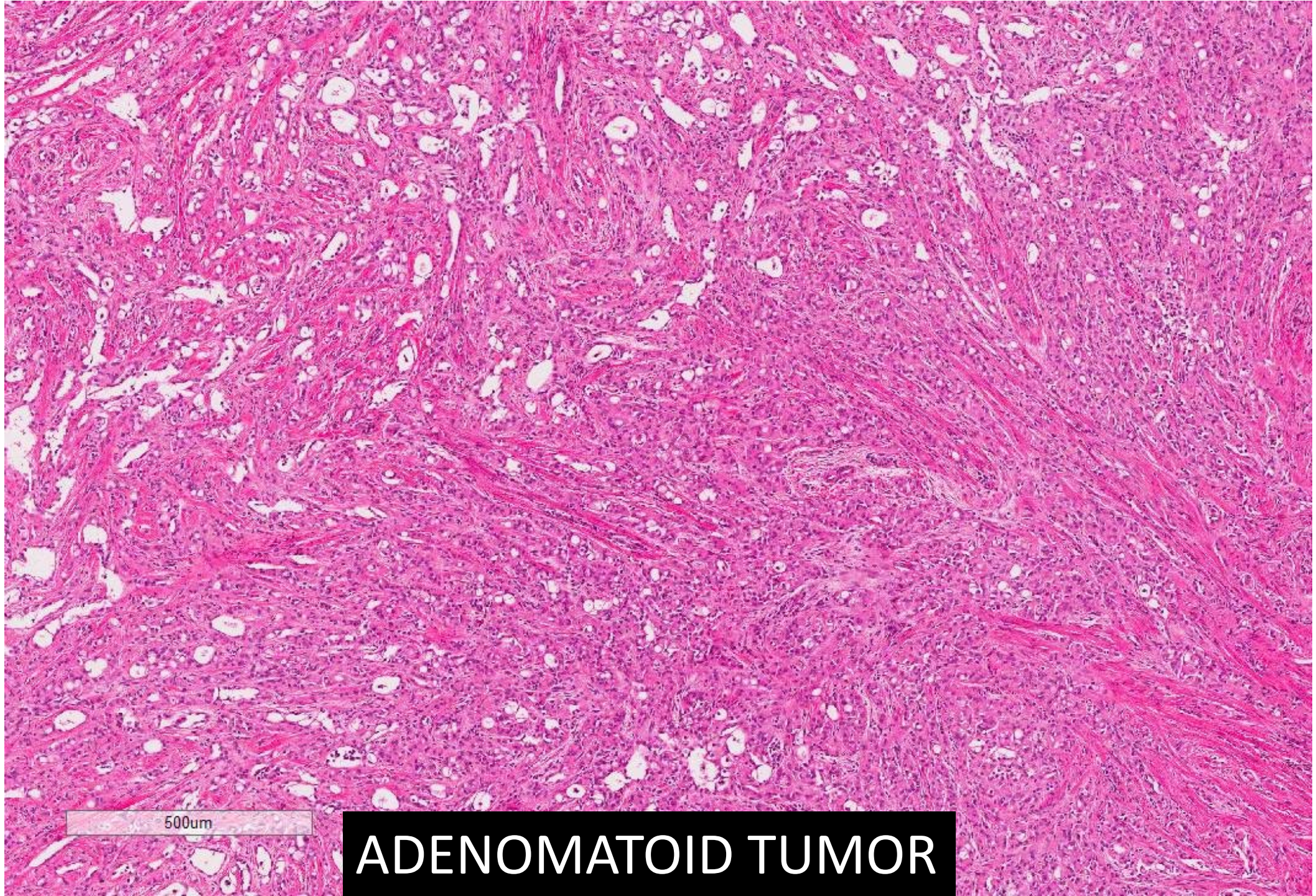




Liposarcoma

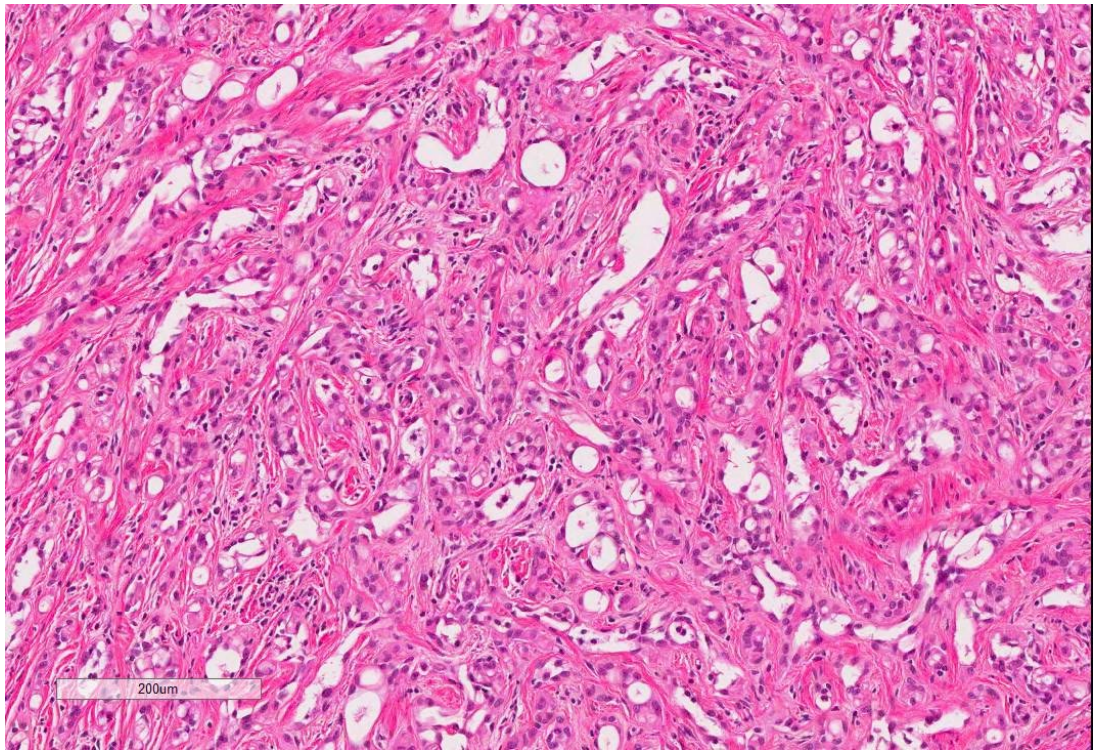
- Most common paratesticular sarcoma
- Mean age 63 years
- Diagnostic key: Large atypical cells with hyperchromatic, irregular nuclei
- Poor prognosis with dedifferentiation
- Confirmation: FISH for MDM2 amplification

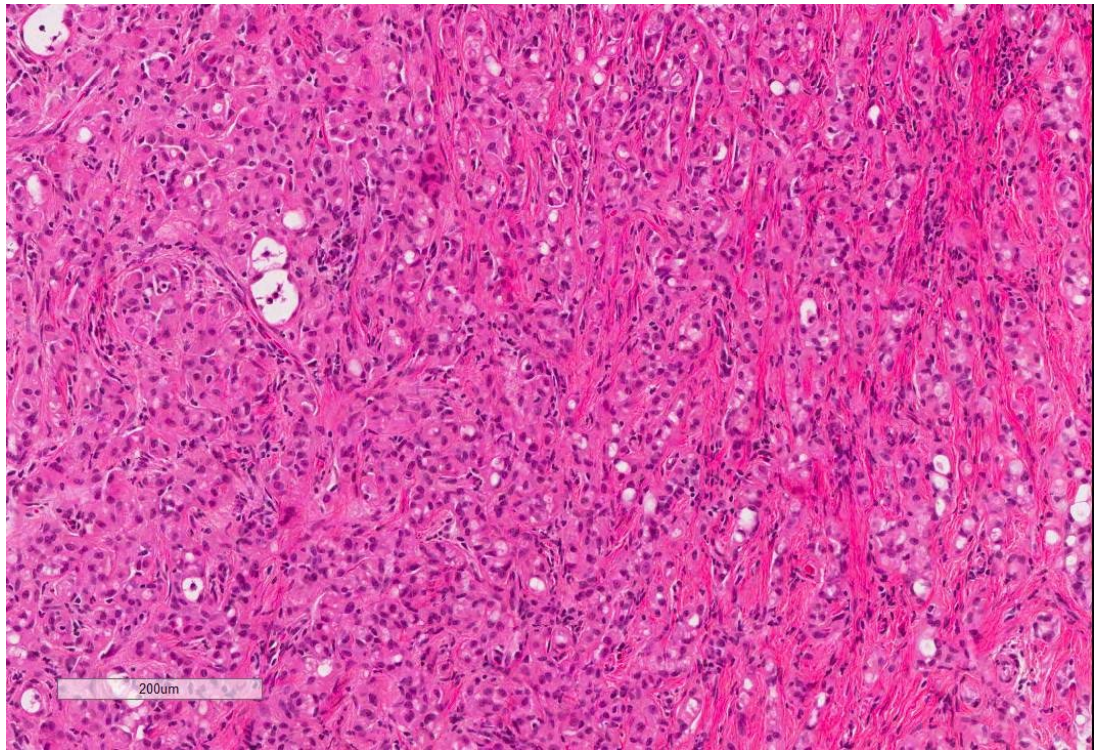




ADENOMATOID TUMOR

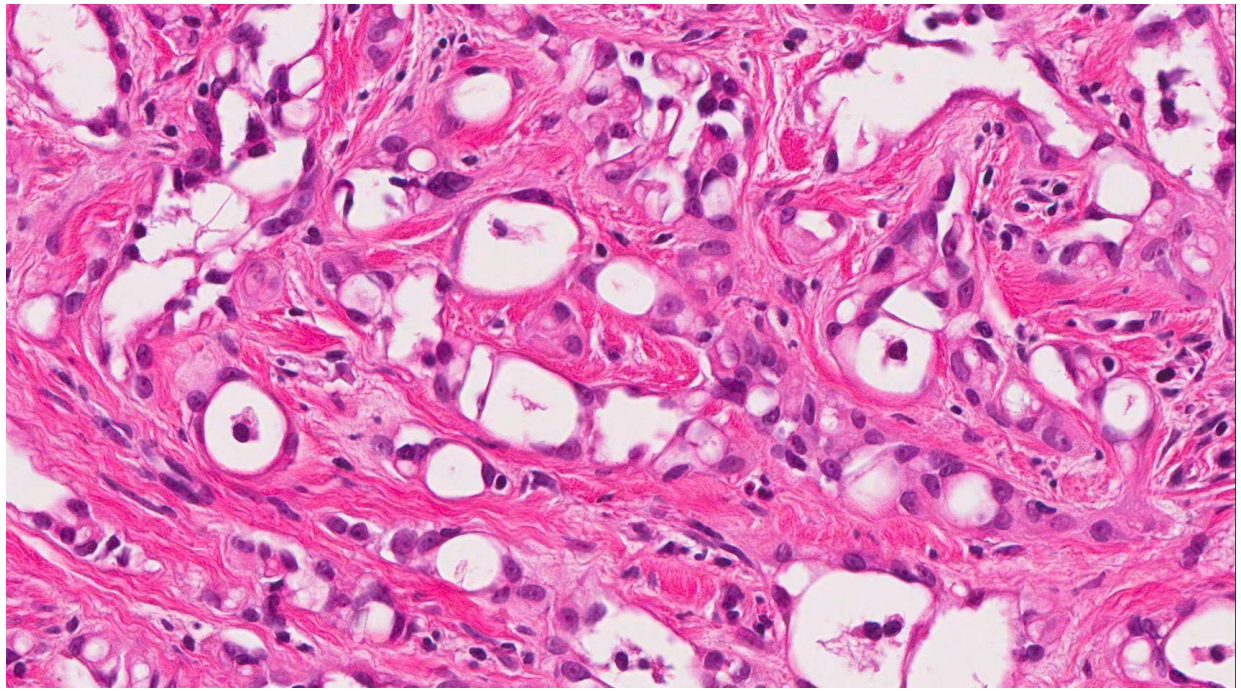
Adenomatoid tumor

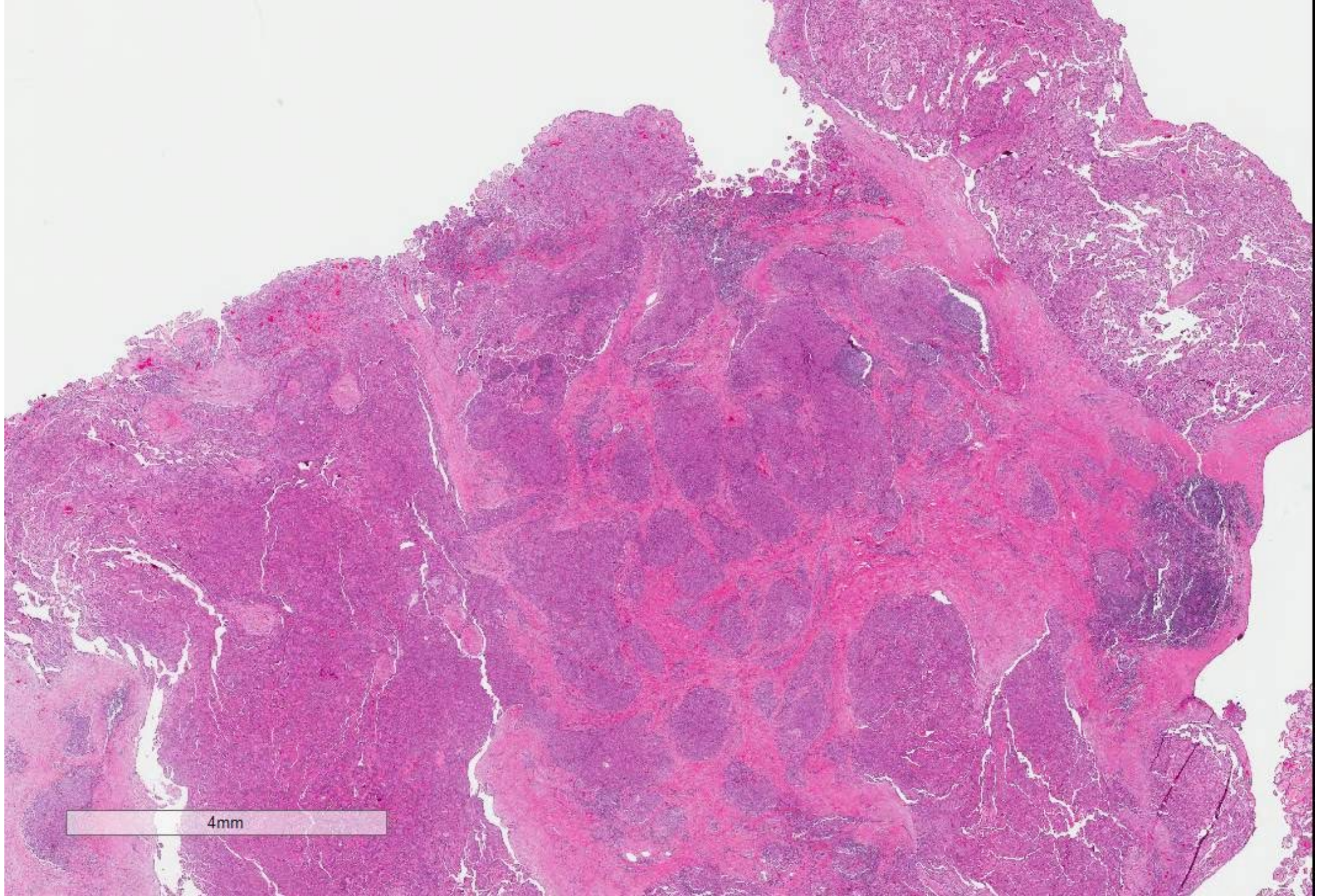


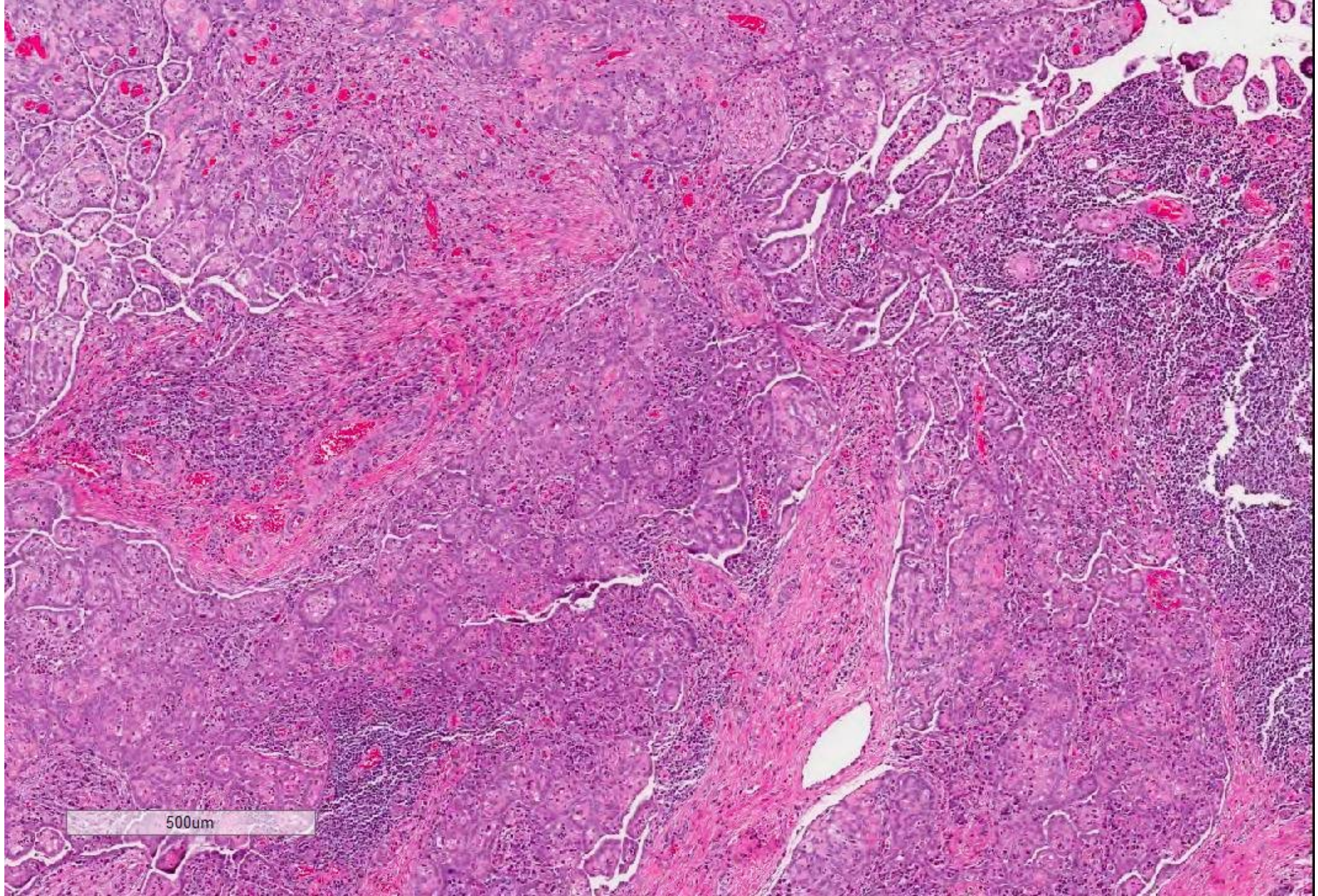


Adenomatoid tumor

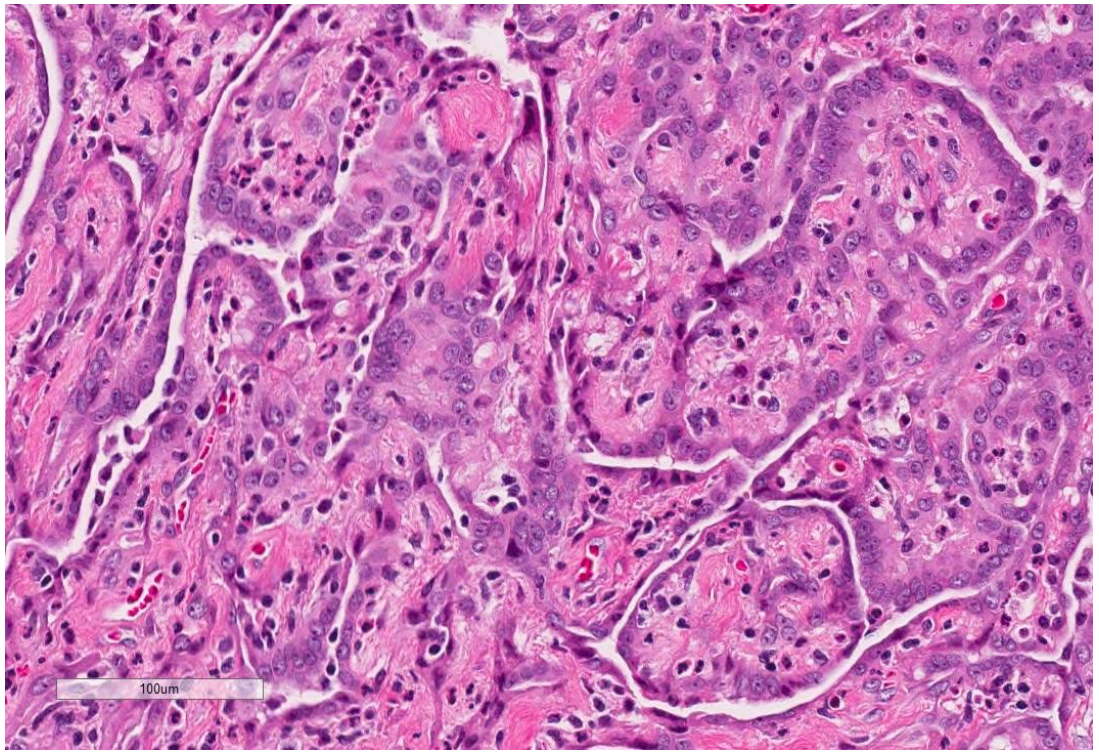
- Benign mesothelial tumor
- Testicular adnexal/epididymal mass
- Positive for mesothelial markers
- DDX: Mesothelioma, sarcomas, carcinomas, GCTs

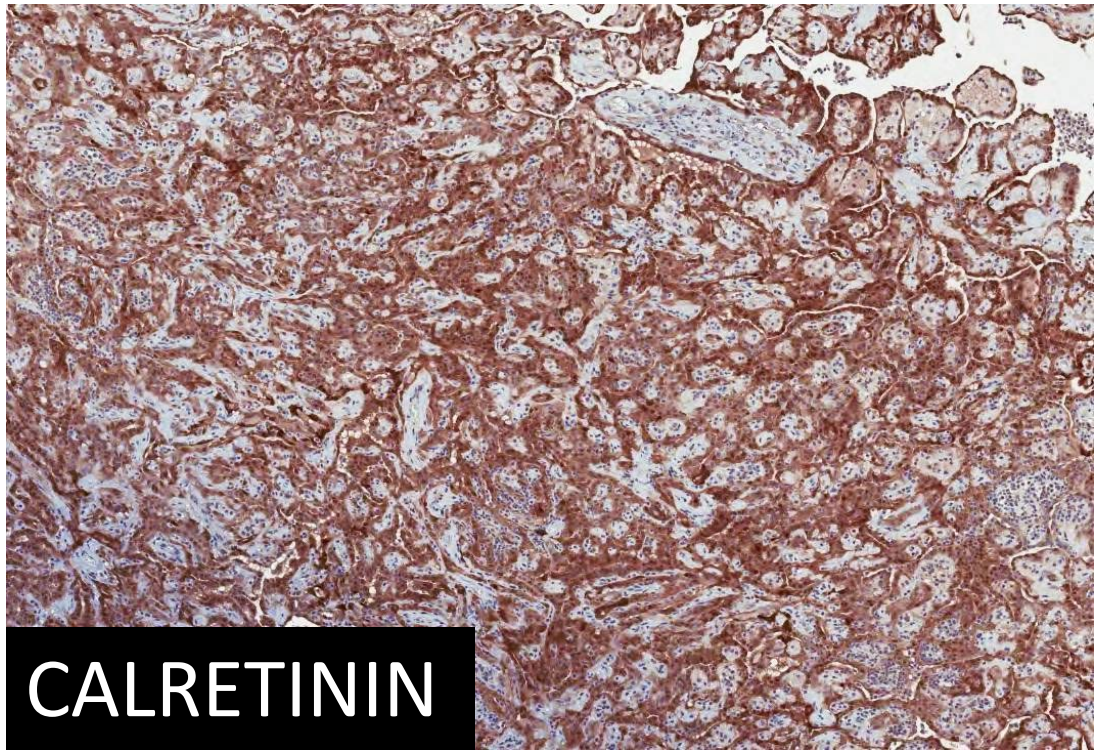



4mm


500um

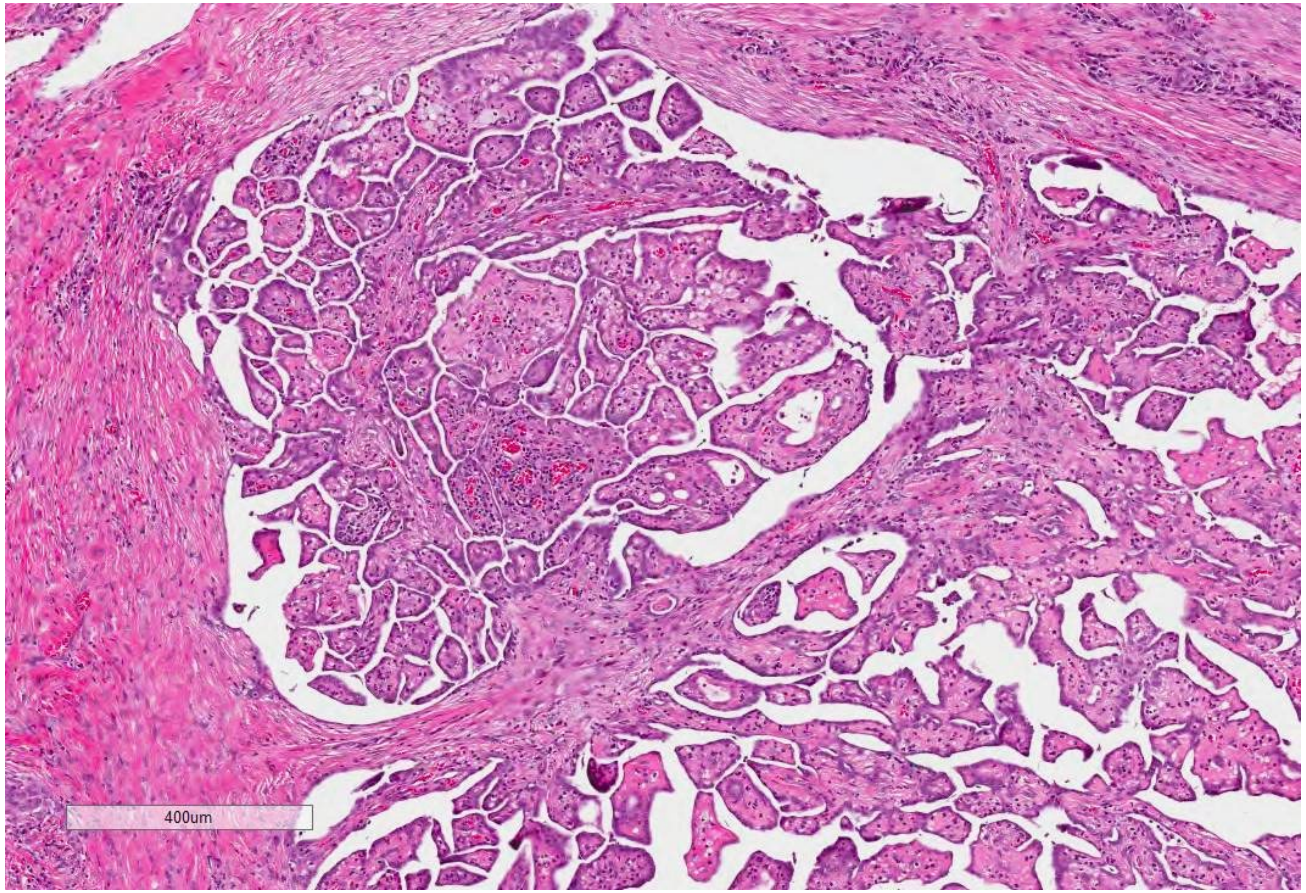
Paratesticular mesothelioma



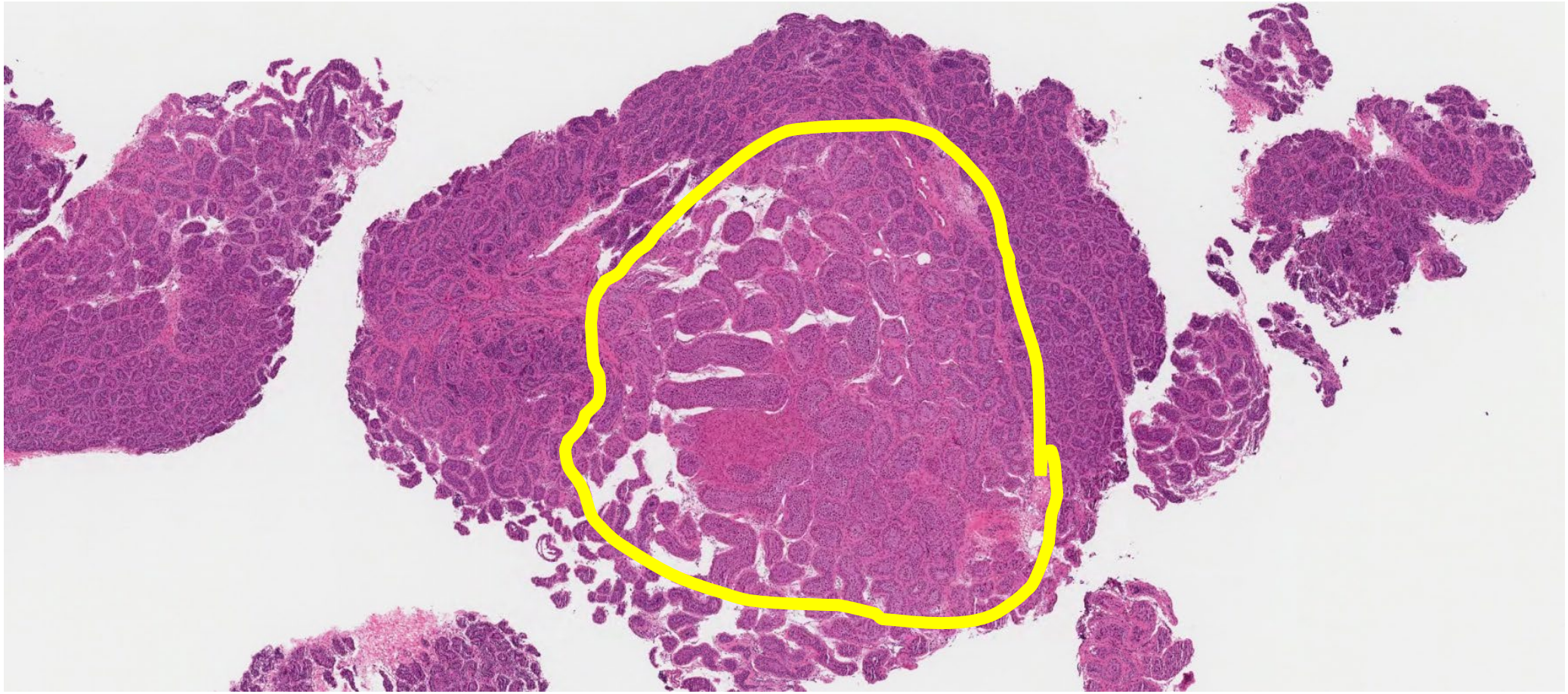


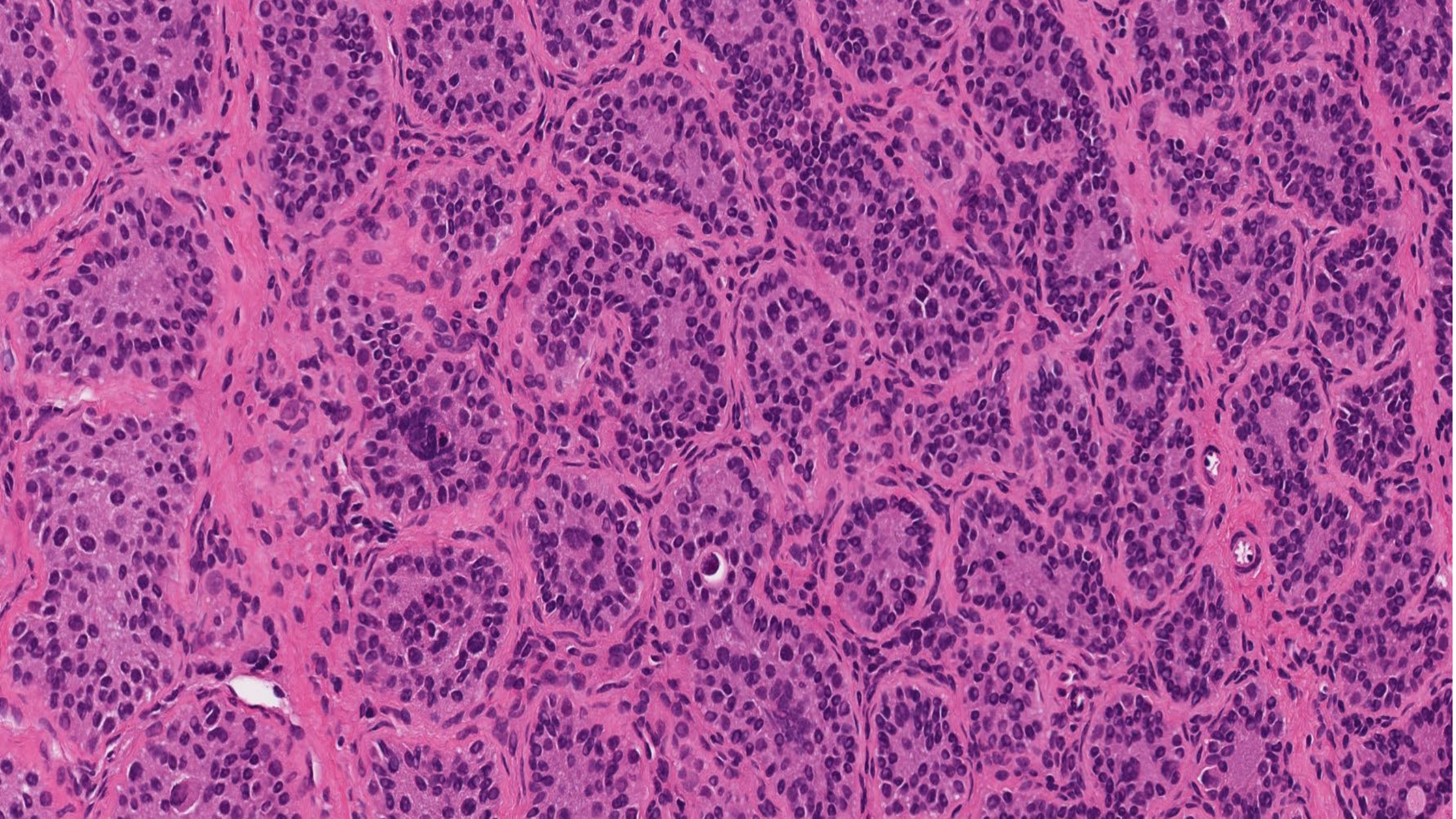
Paratesticular mesothelioma

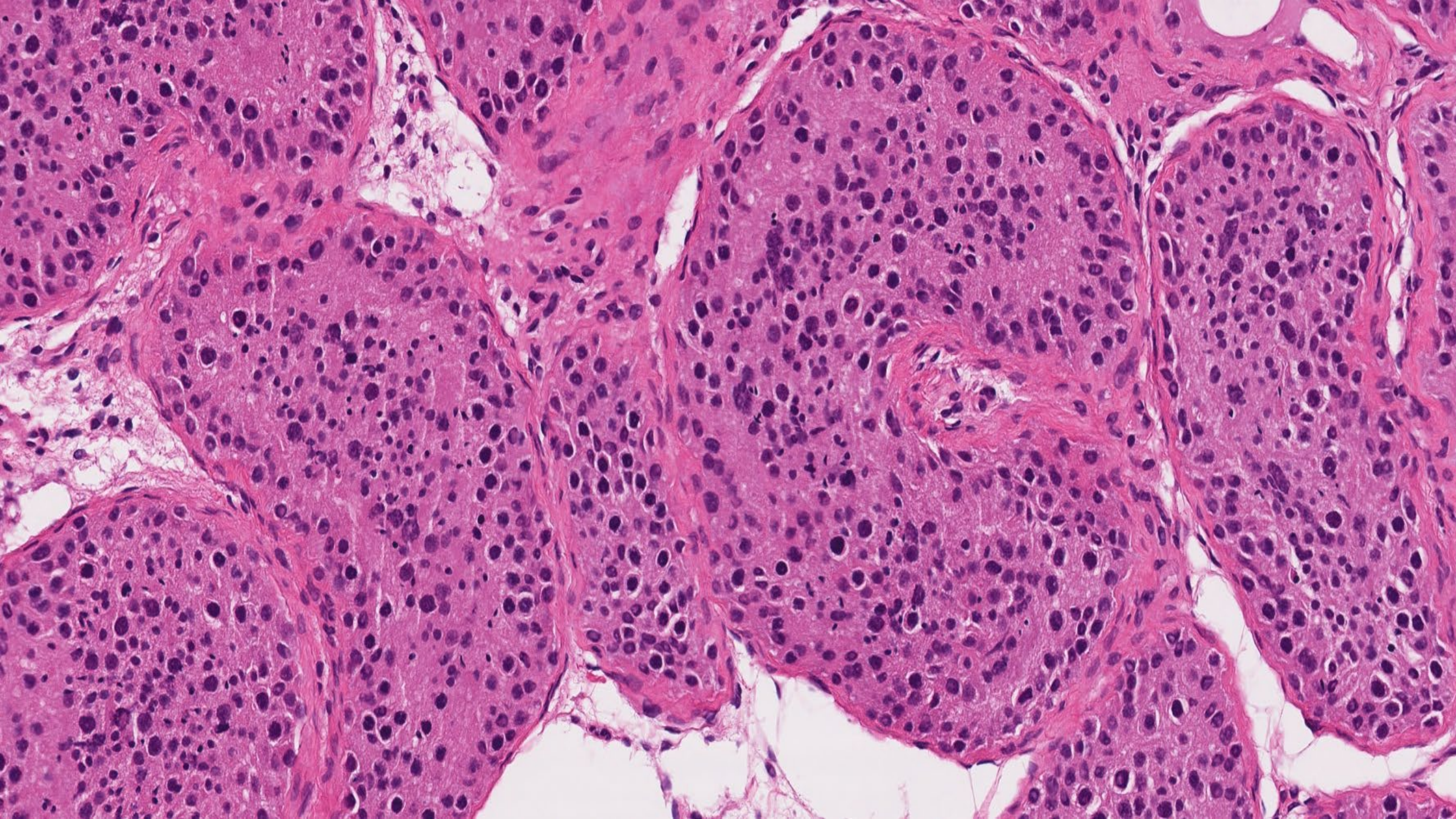
- Second most common paratesticular malignancy (after sarcomas)
- Mean age: 54 years
- Invasive growth
- Pure epithelial>biphasic
- Sarcomatoid and desmoplastic rare
- DDx: Rete testis adenoCA, Mullerian-type adenoCA



Bonus case – extra credit!
Testicular biopsy – 5 yo







Nodular maturation of the testis

- 8 cases
- Mean age = 7.9 y
- All had US abnormalities
- 3 with palpable enlargement/mass
- No gross abnormalities
- Mature seminiferous tubules
- Am J Surg Pathol 2022;46:220–225

THANK YOU!