

**Advances in Gynecologic Pathology:
Harmonizing Morphologic and Molecular Findings
May 29-30th, 2026 Warsaw, Poland**

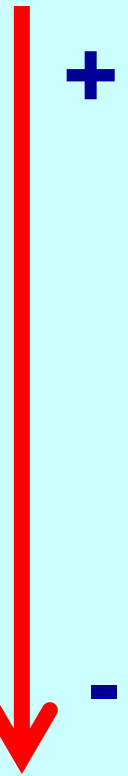
OVARIAN GERM CELL NEOPLASIA

**Esther Oliva
Massachusetts General Hospital
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WHO (2020-2026)

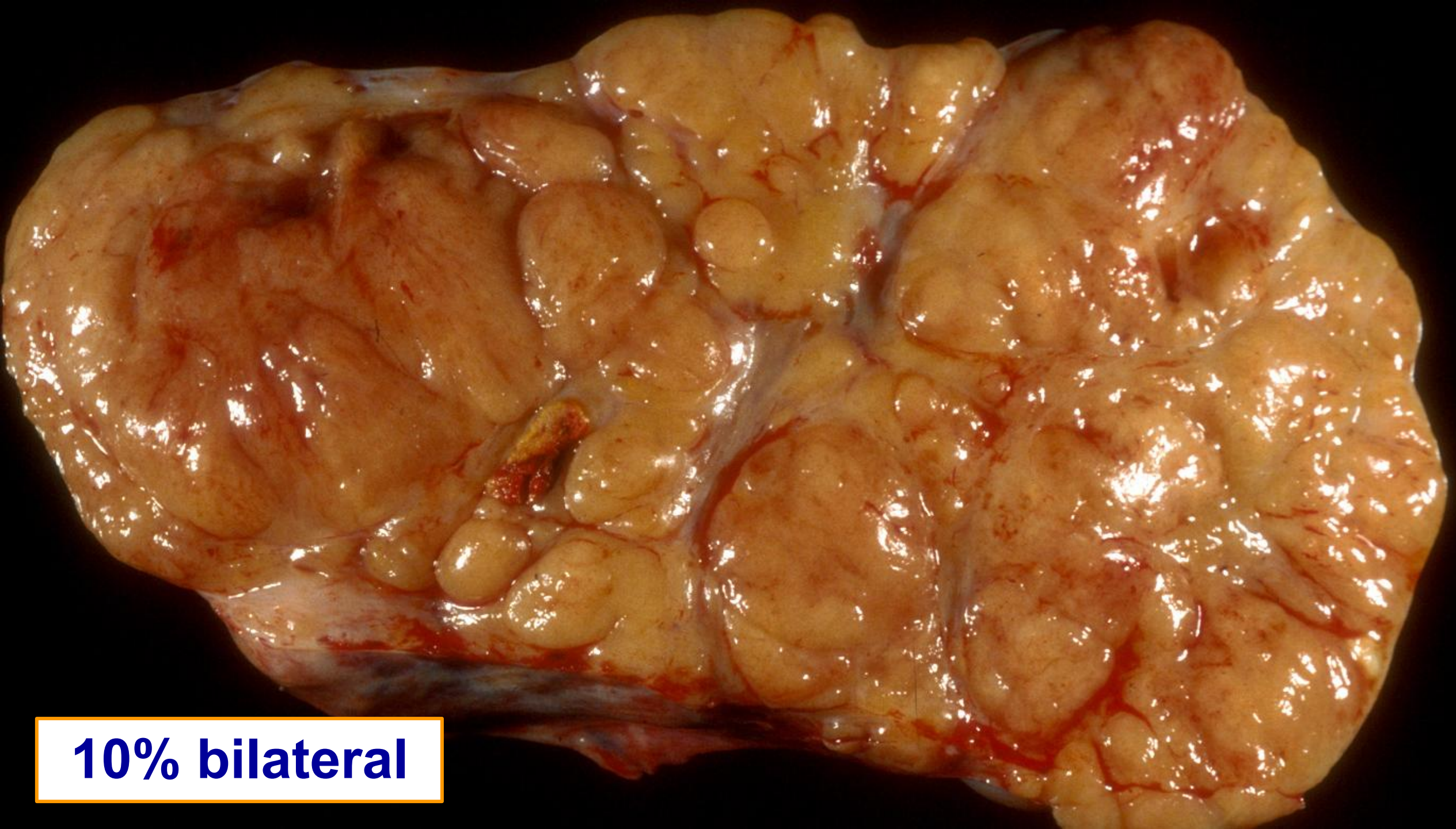
Malignant germ cell tumors:

- **Dysgerminoma**
- **Yolk sac tumor**
- **Immature teratoma**
- **Mixed germ cell tumor**
- **Non-gestational choriocarcinoma**
- **Embryonal carcinoma**

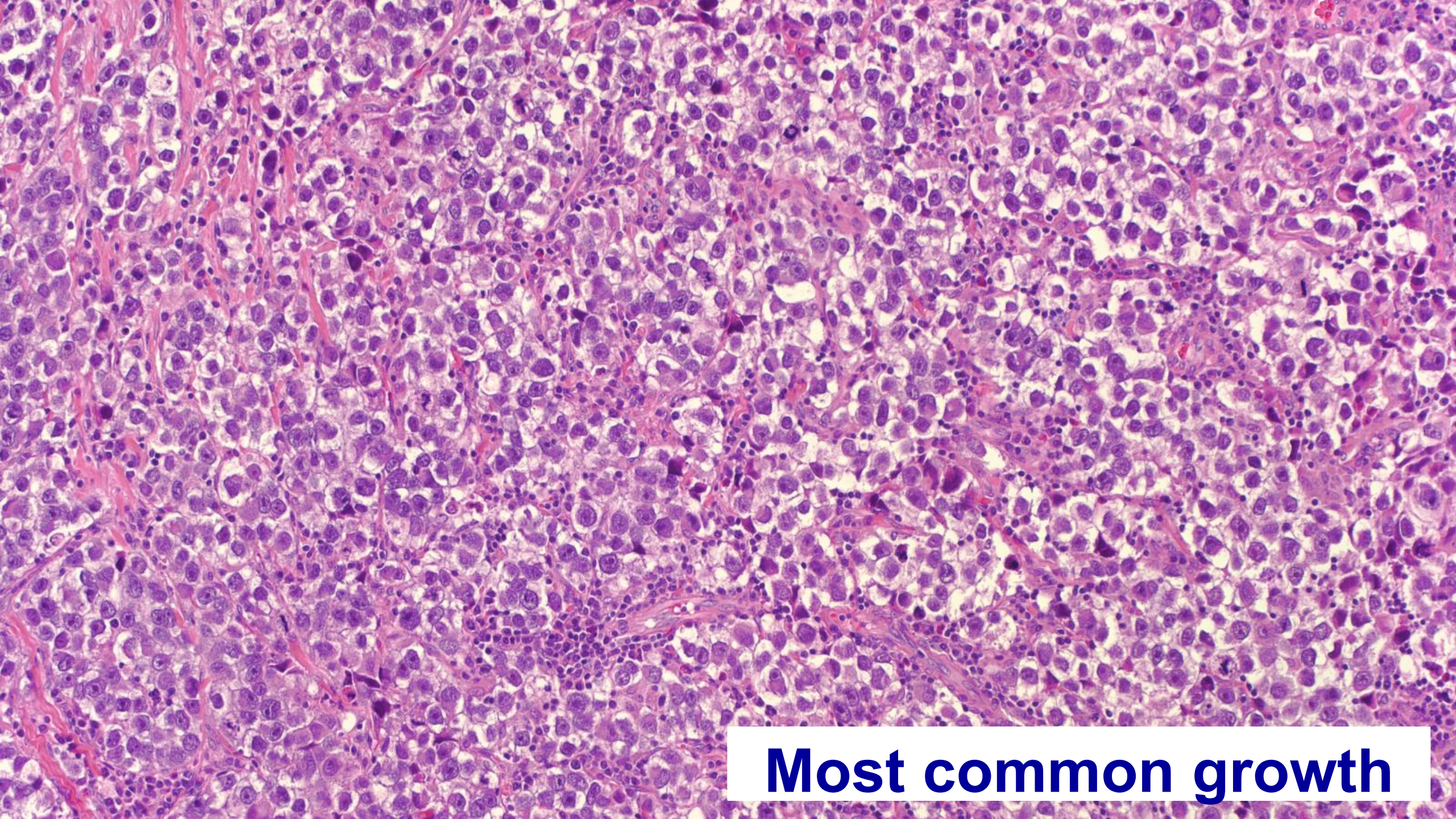


DYSGERMINOMA

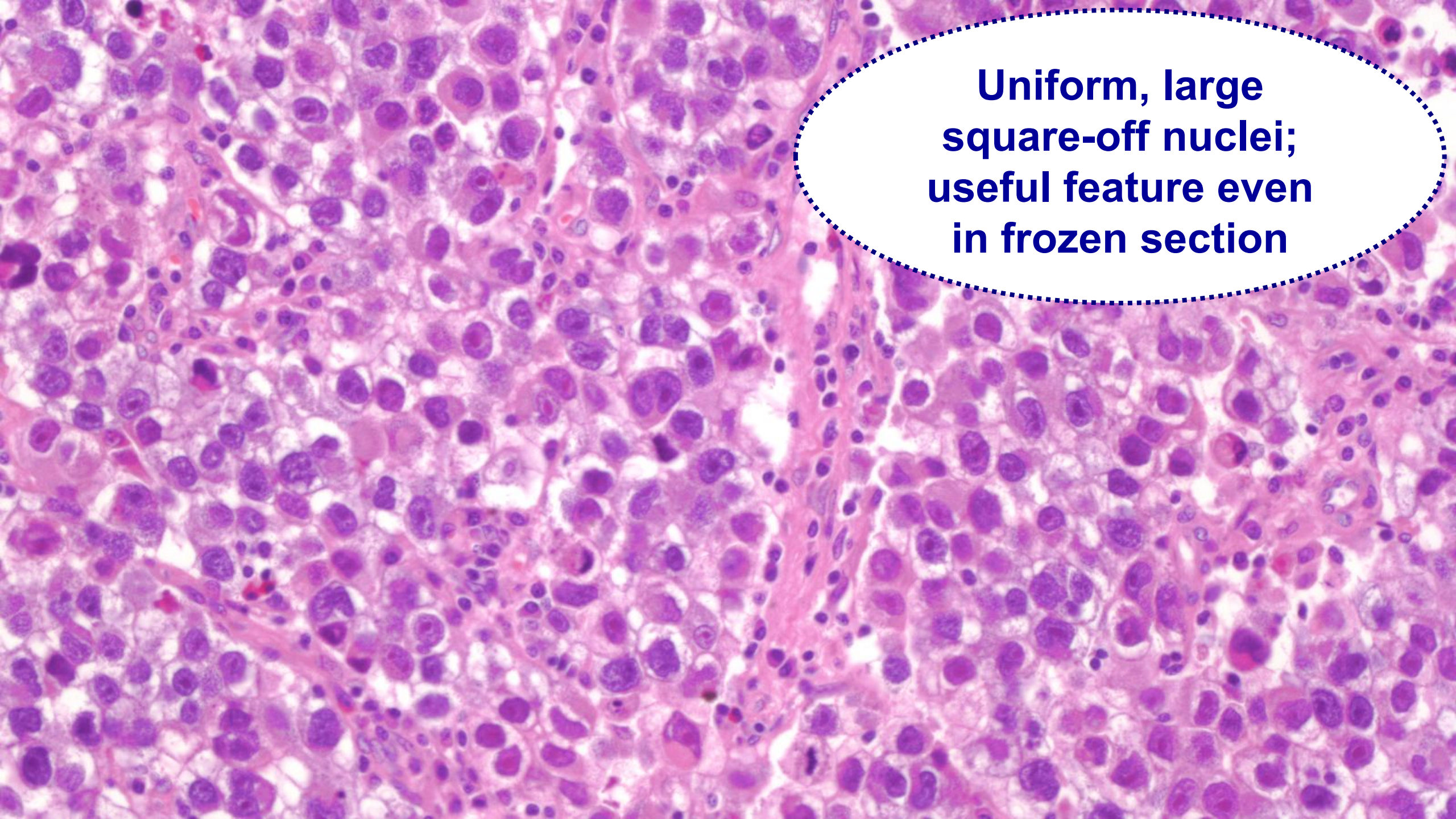
- **~ 50% of ovarian malignant germ cell tumors**
- **Common in adolescents and young adults**
- **~ 20% presentation during pregnancy**
- **Associations:**
 - **Phenotypic women with gonadal dysgenesis or mosaicism (gonadoblastoma)**
 - **↑hCG levels (estrogenic manifestations)**
 - **Paraneoplastic hypercalcemia**



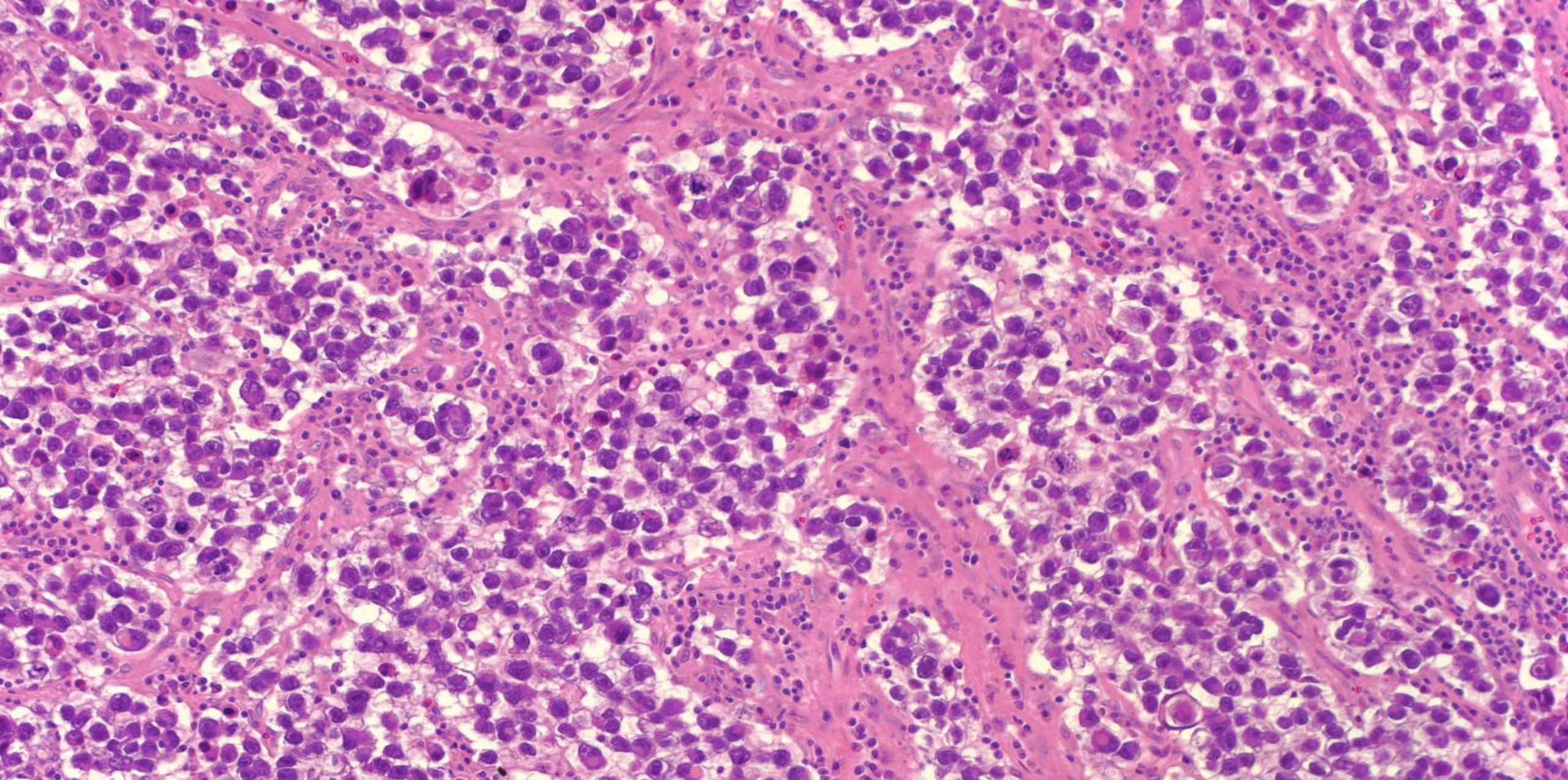
10% bilateral



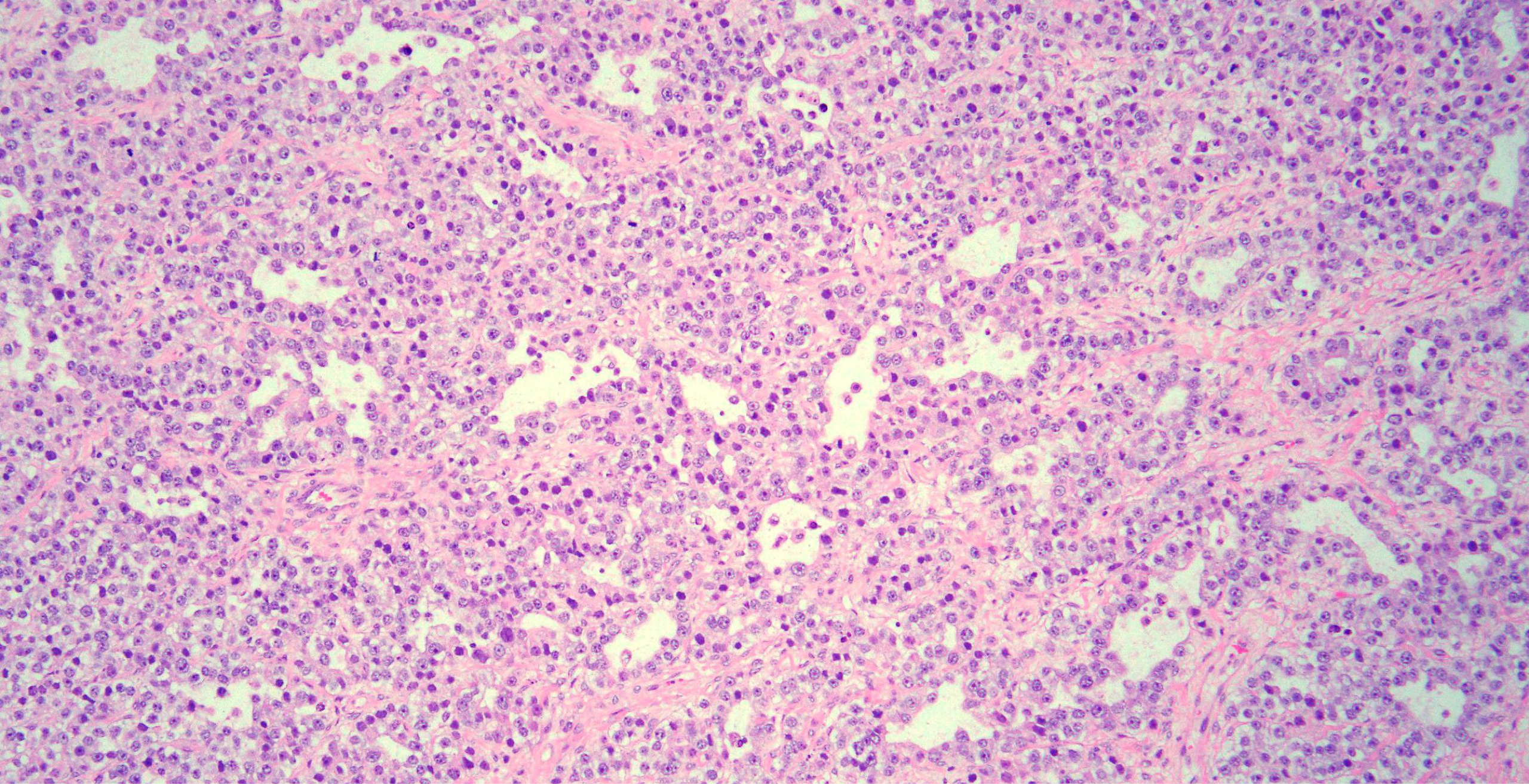
Most common growth

A high-magnification histological micrograph showing a dense population of cells. The cells have large, round to square nuclei with prominent nucleoli, stained dark purple. The cytoplasm and extracellular matrix are stained pink. The overall appearance is characteristic of a malignant neoplasm, such as a carcinoma. A white oval with a black dotted border is overlaid on the right side of the image, containing text.

**Uniform, large
square-off nuclei;
useful feature even
in frozen section**

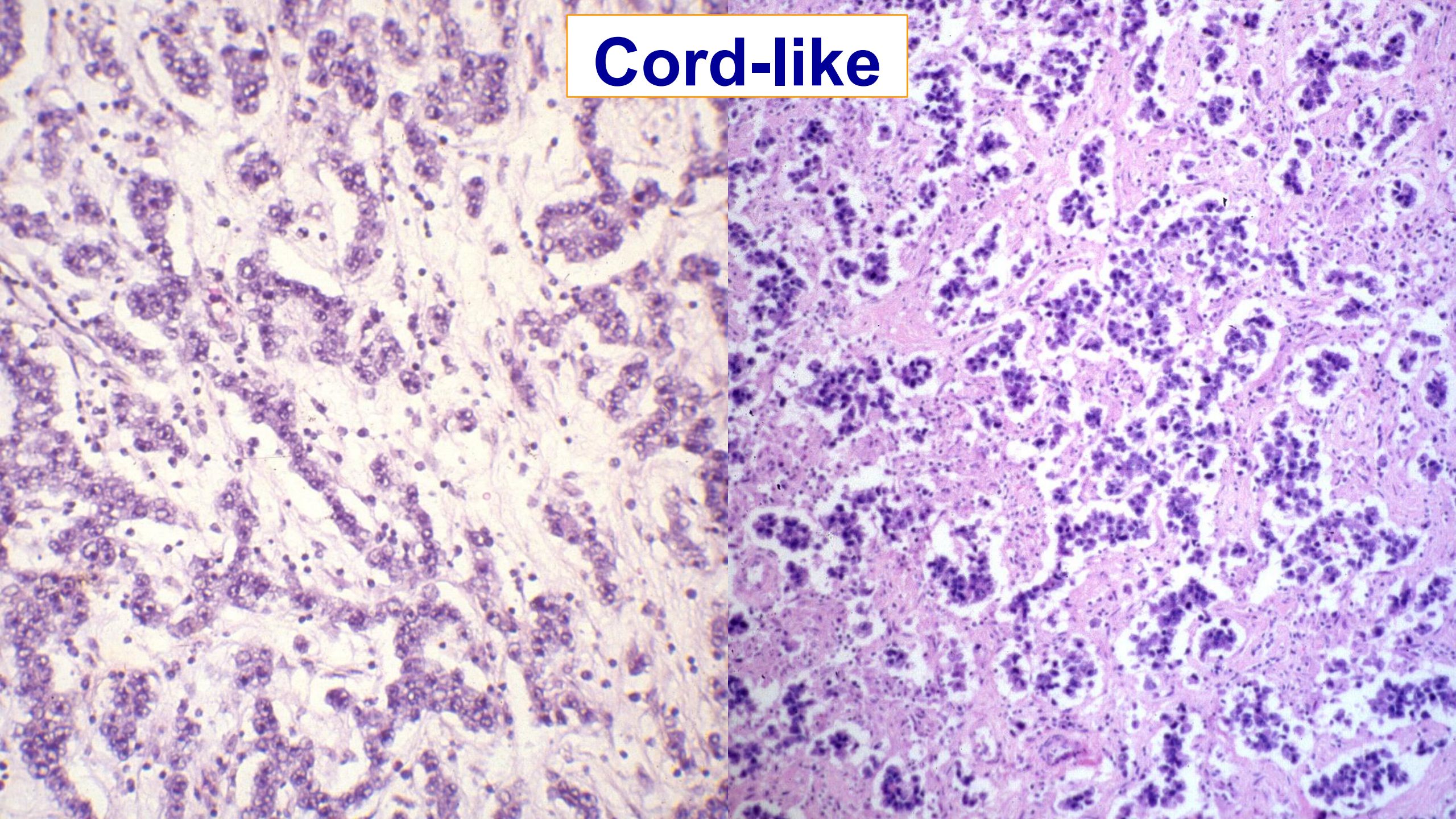


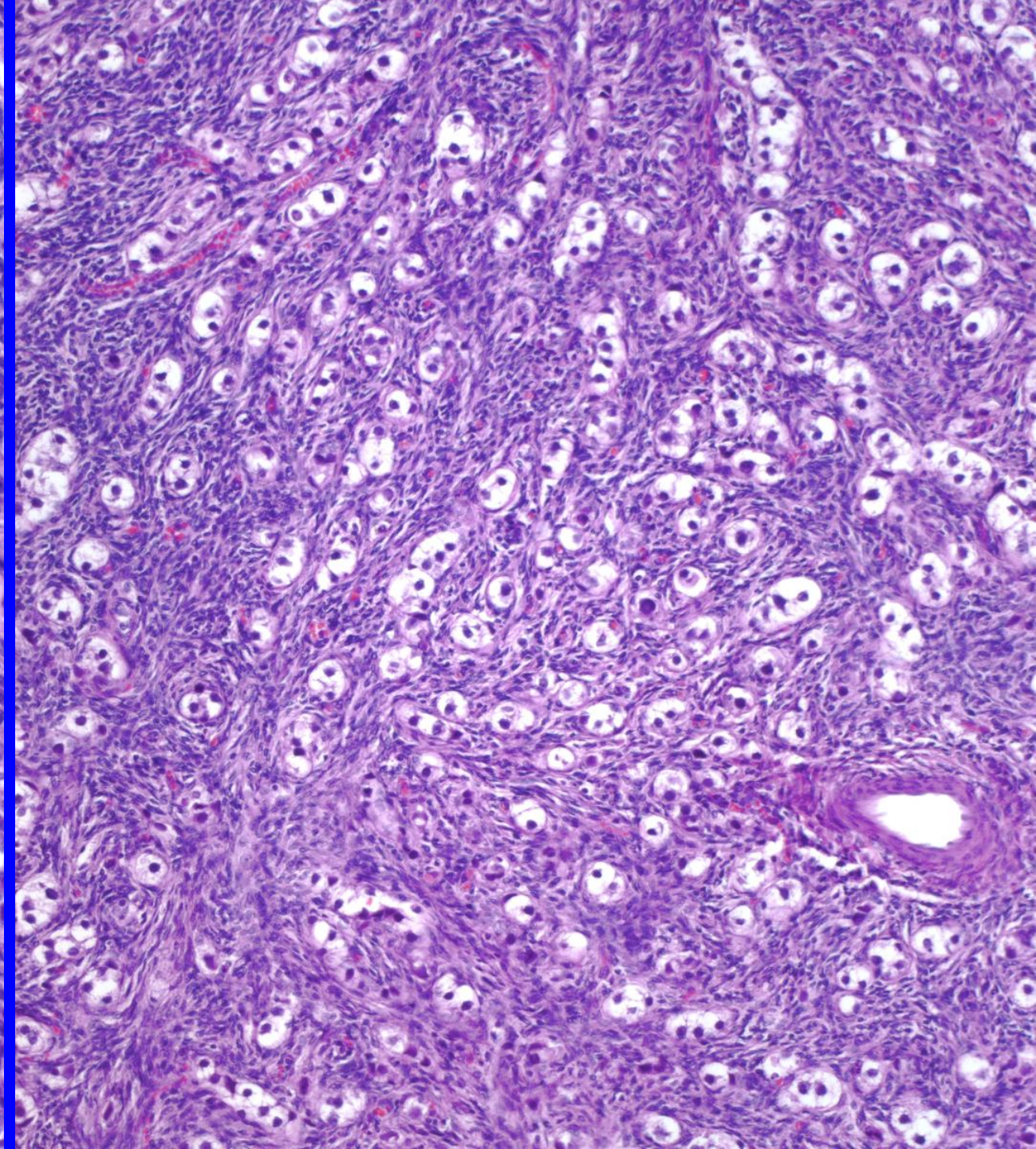
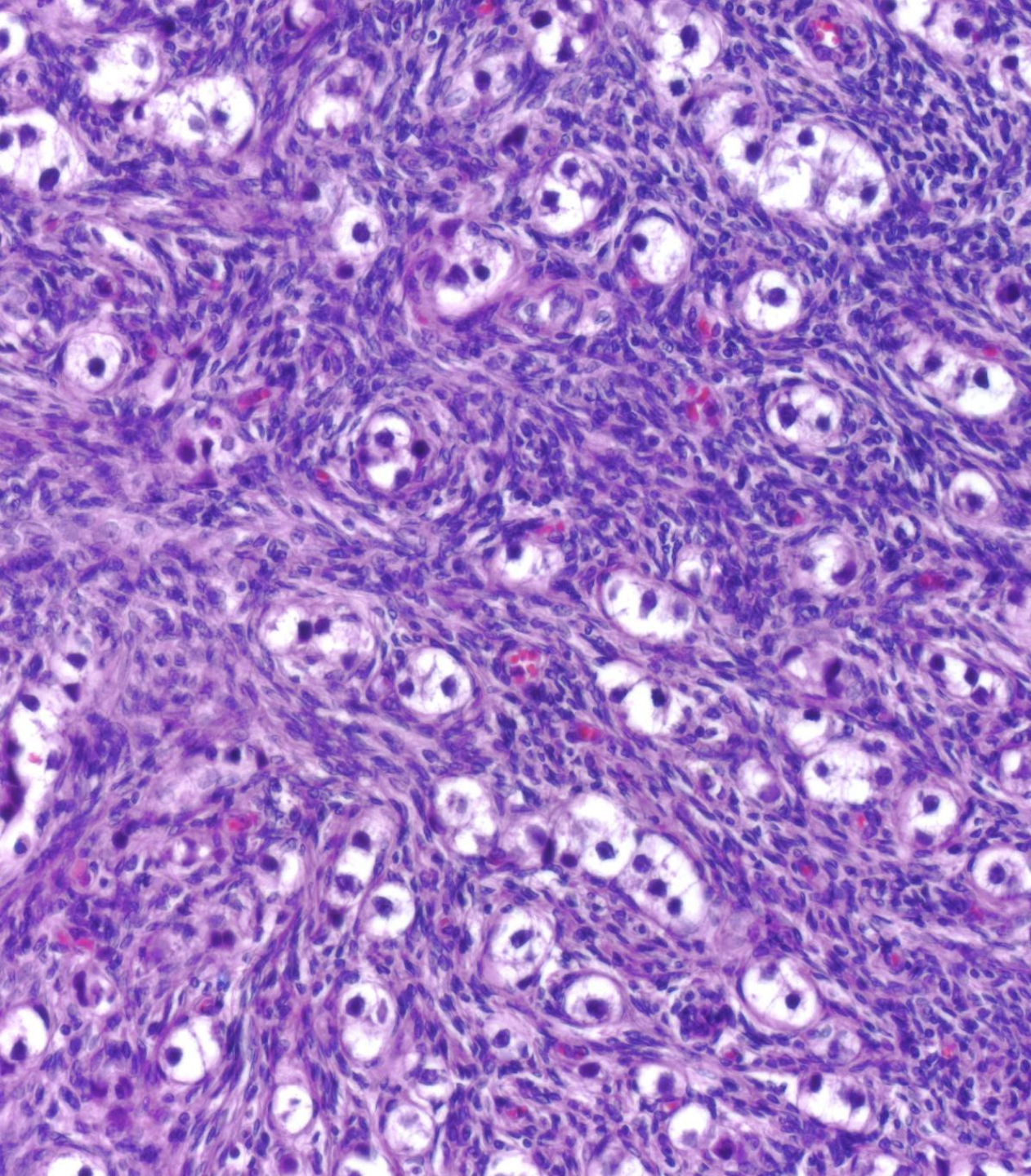
Large aggregates or small nests

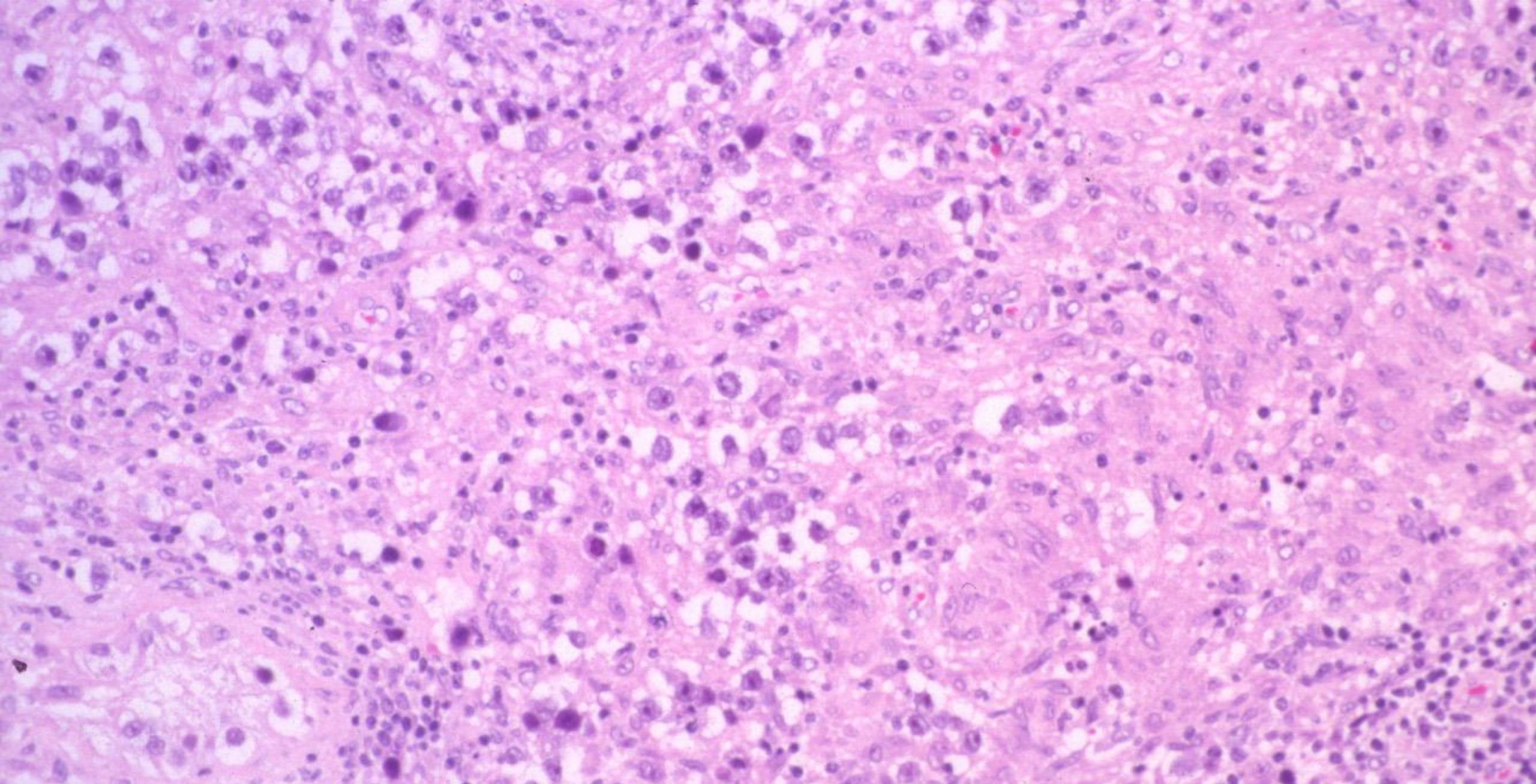


DYSGERMINOMA WITH PSEUDOGLANDS

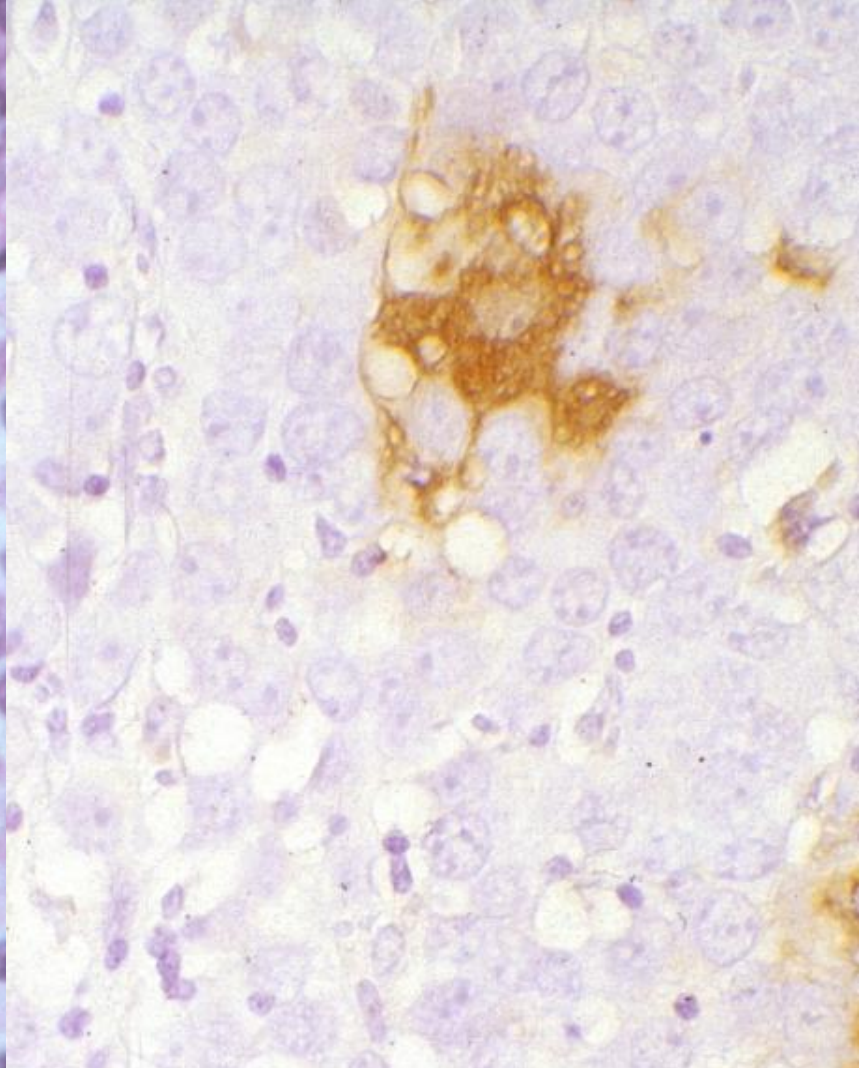
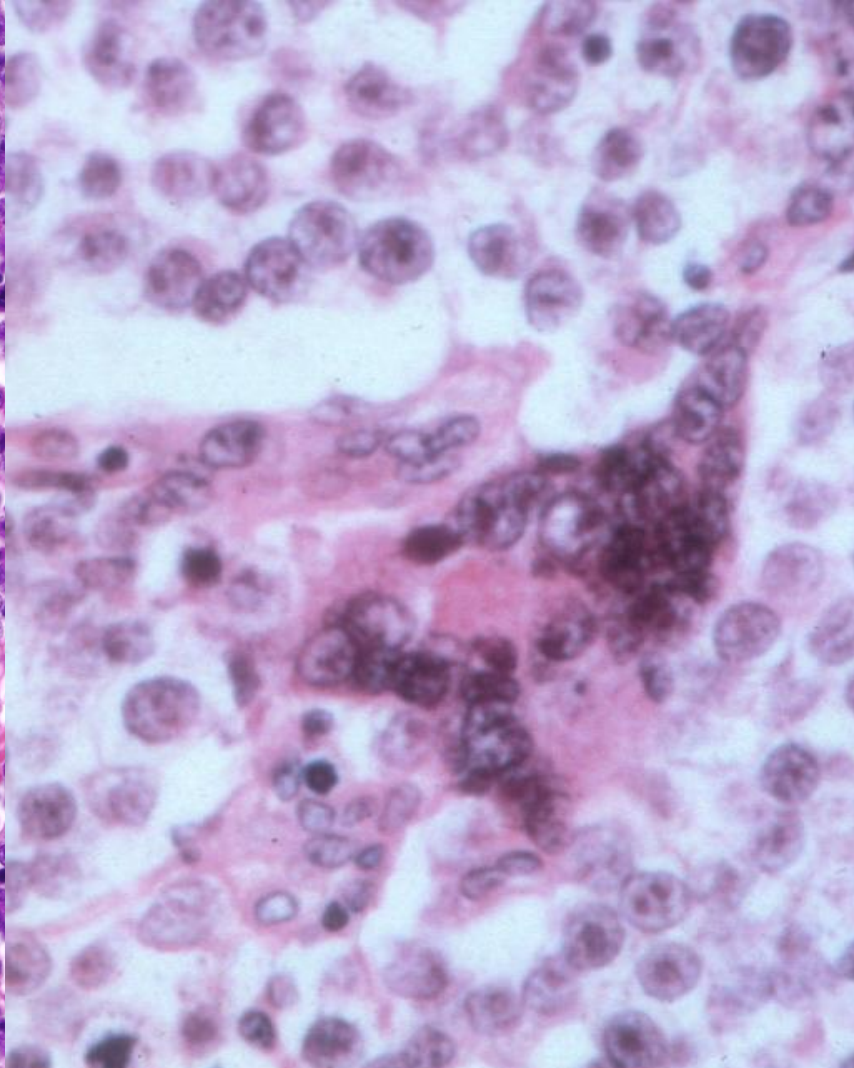
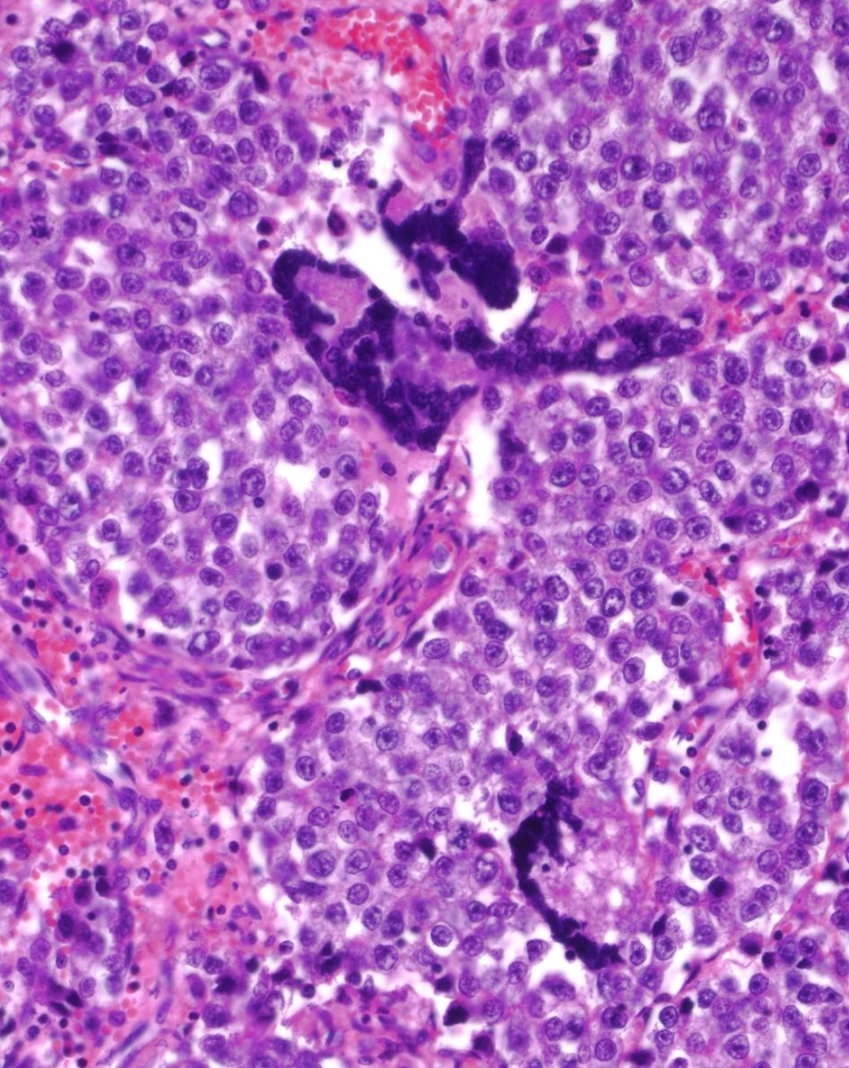
Cord-like



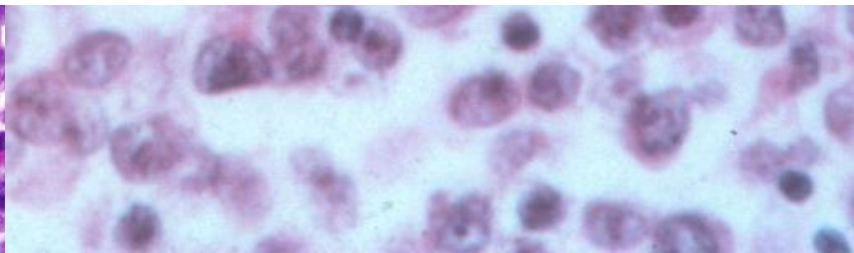
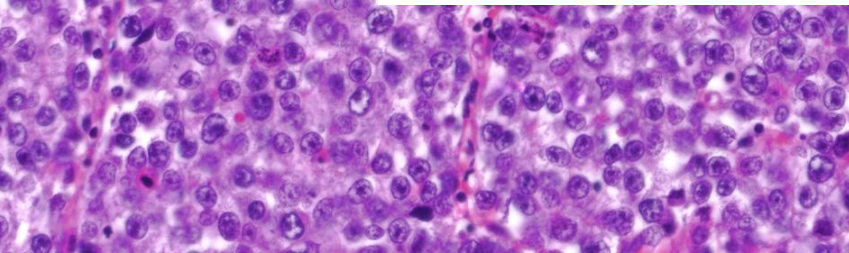




Prominent granulomatous reaction may obscure neoplastic cells

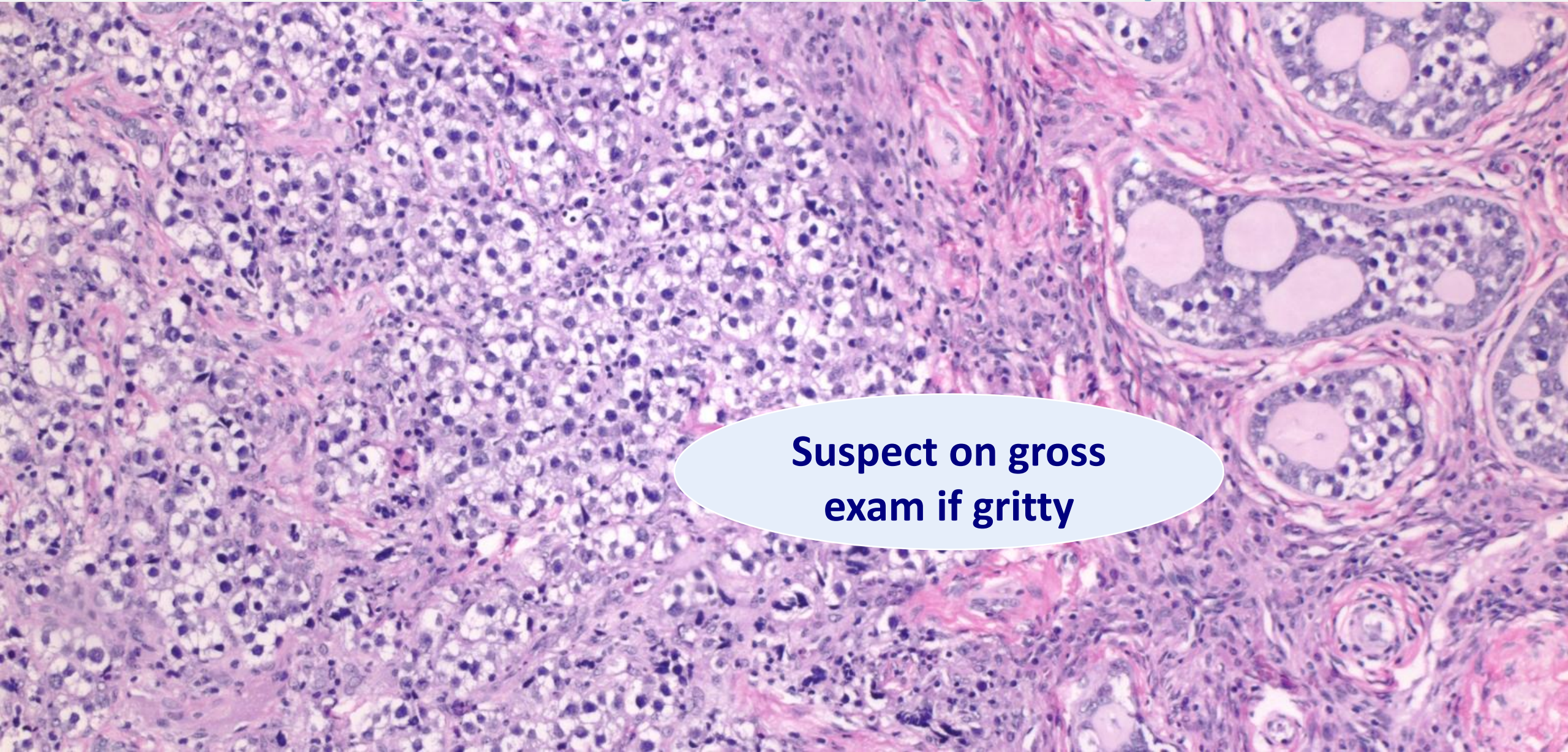


Syncytiotrophoblast cells $\neq$ Choriocarcinoma

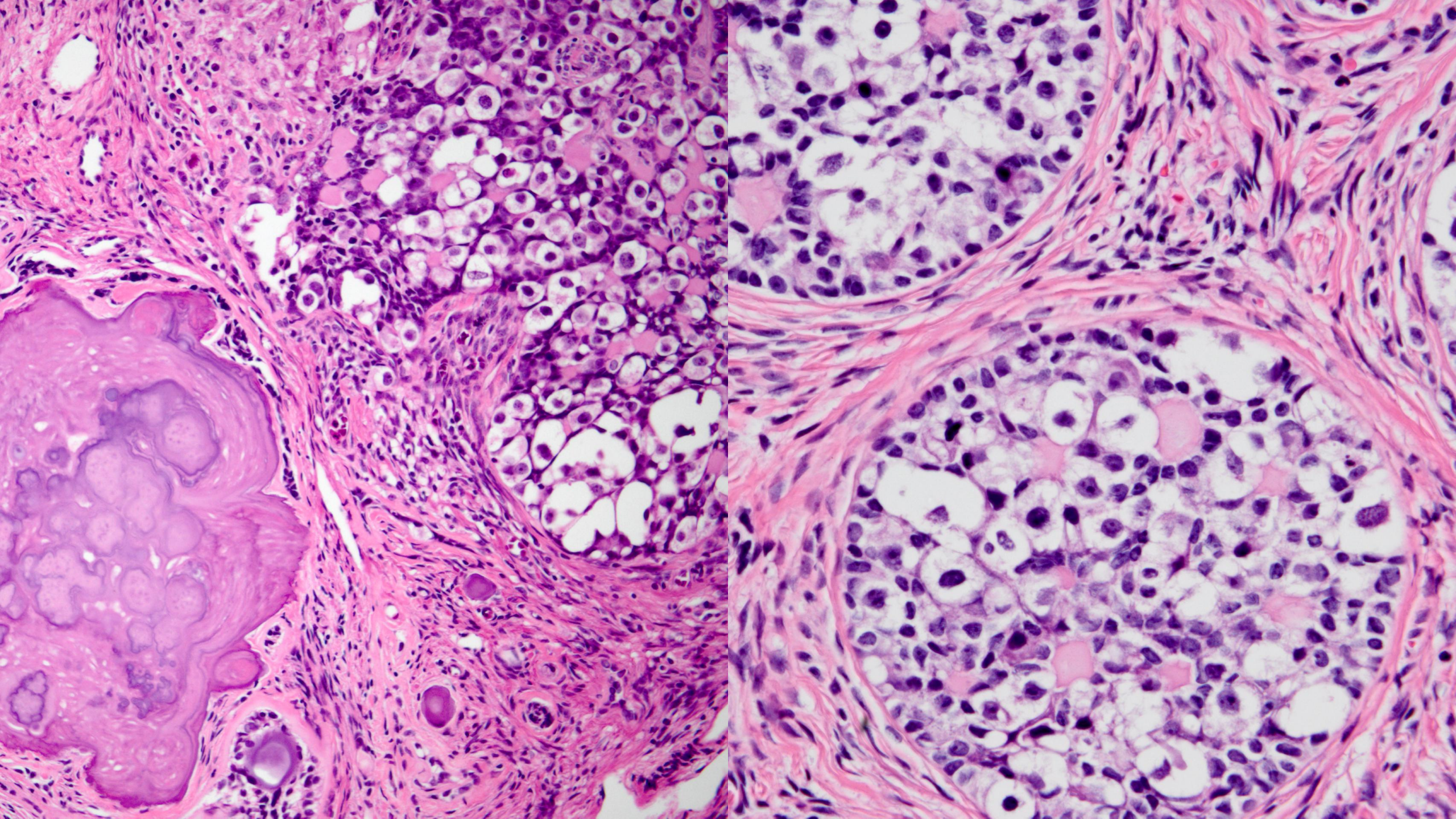


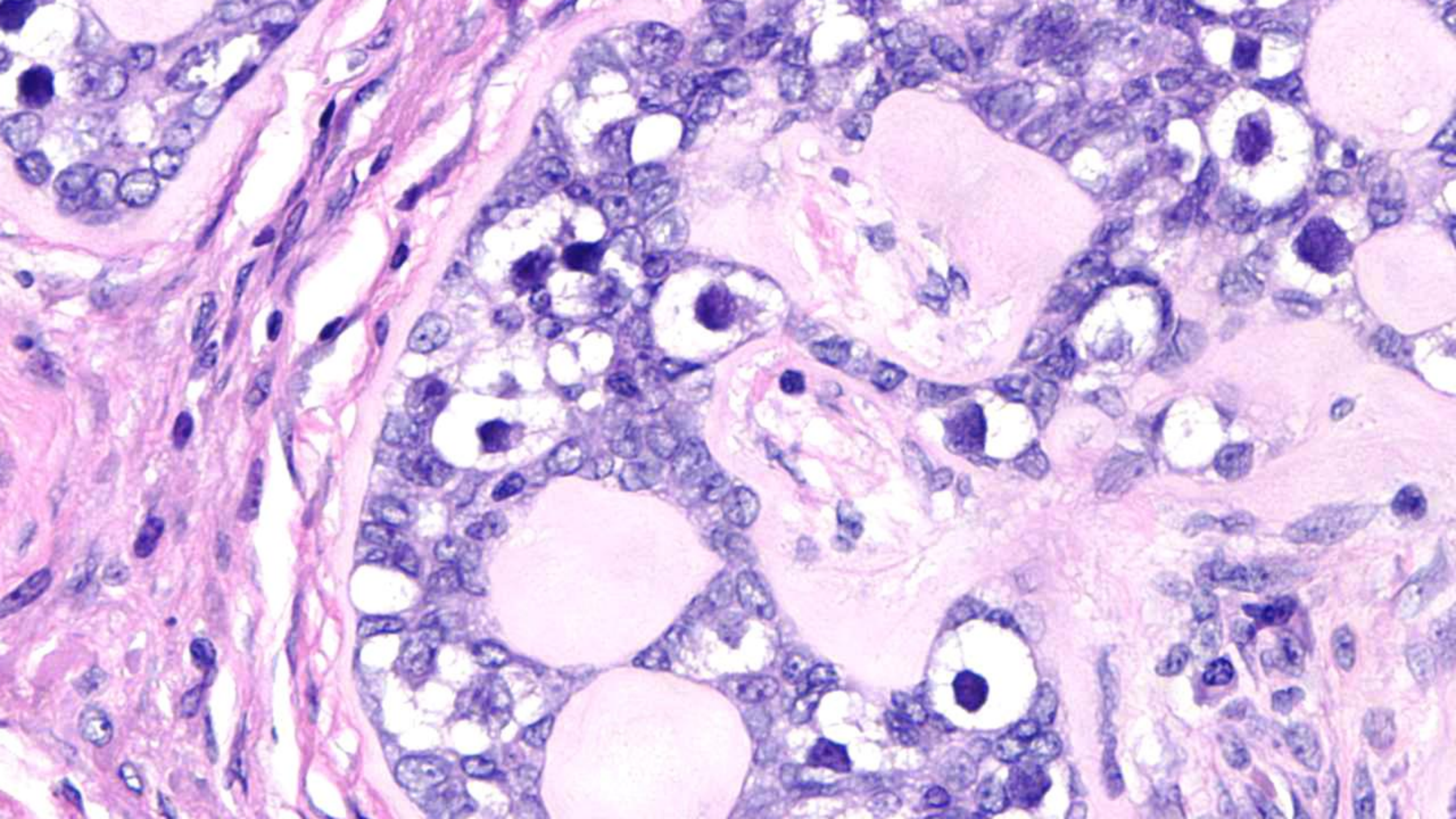
B-hCG

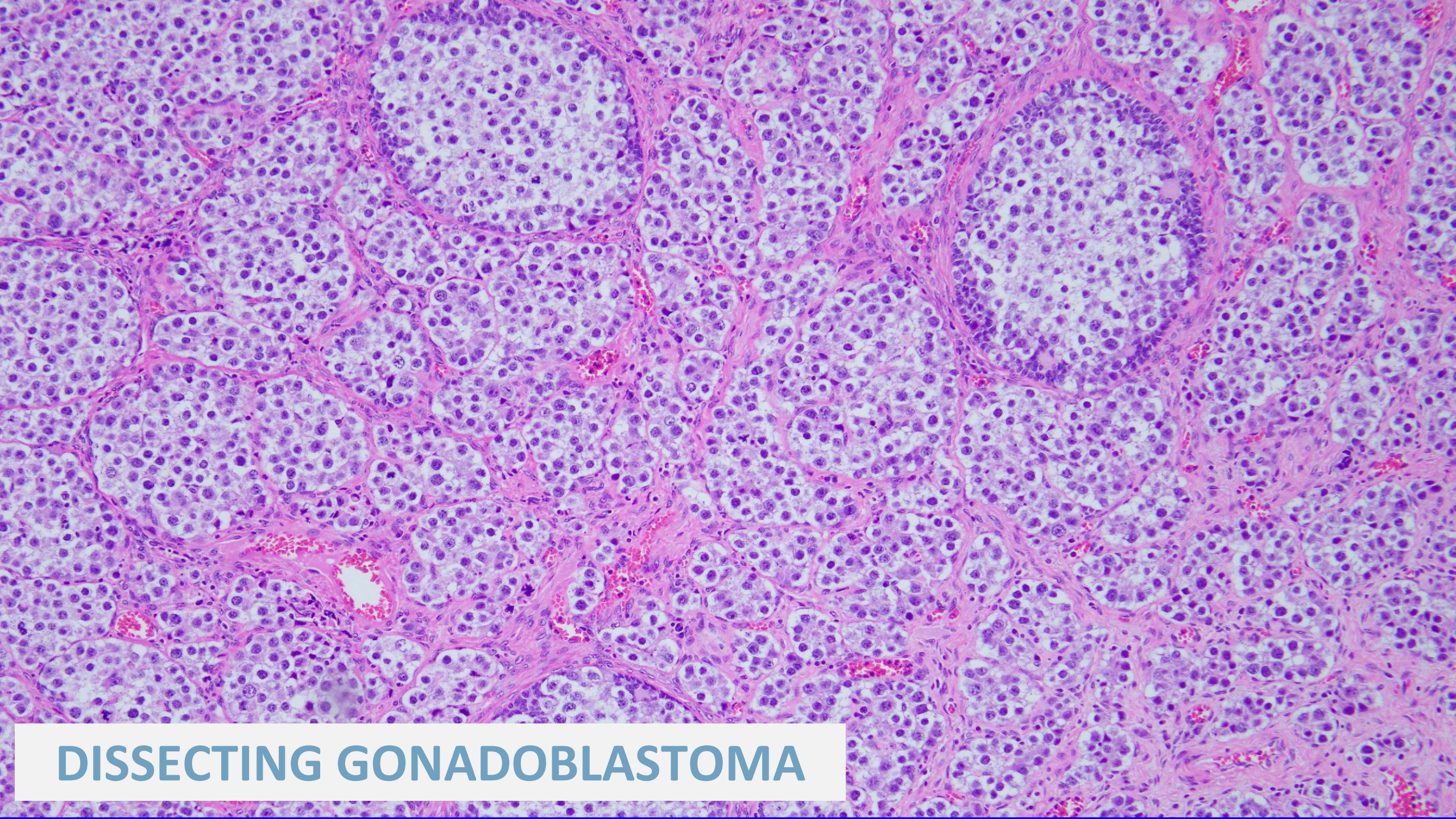
DYSGERMINOMA arising from Gonadoblastoma (Clinically Gonadal Dysgenesis)



**Suspect on gross
exam if gritty**







DISSECTING GONADOBLASTOMA

DYSGERMINOMA

Ancillary Tools

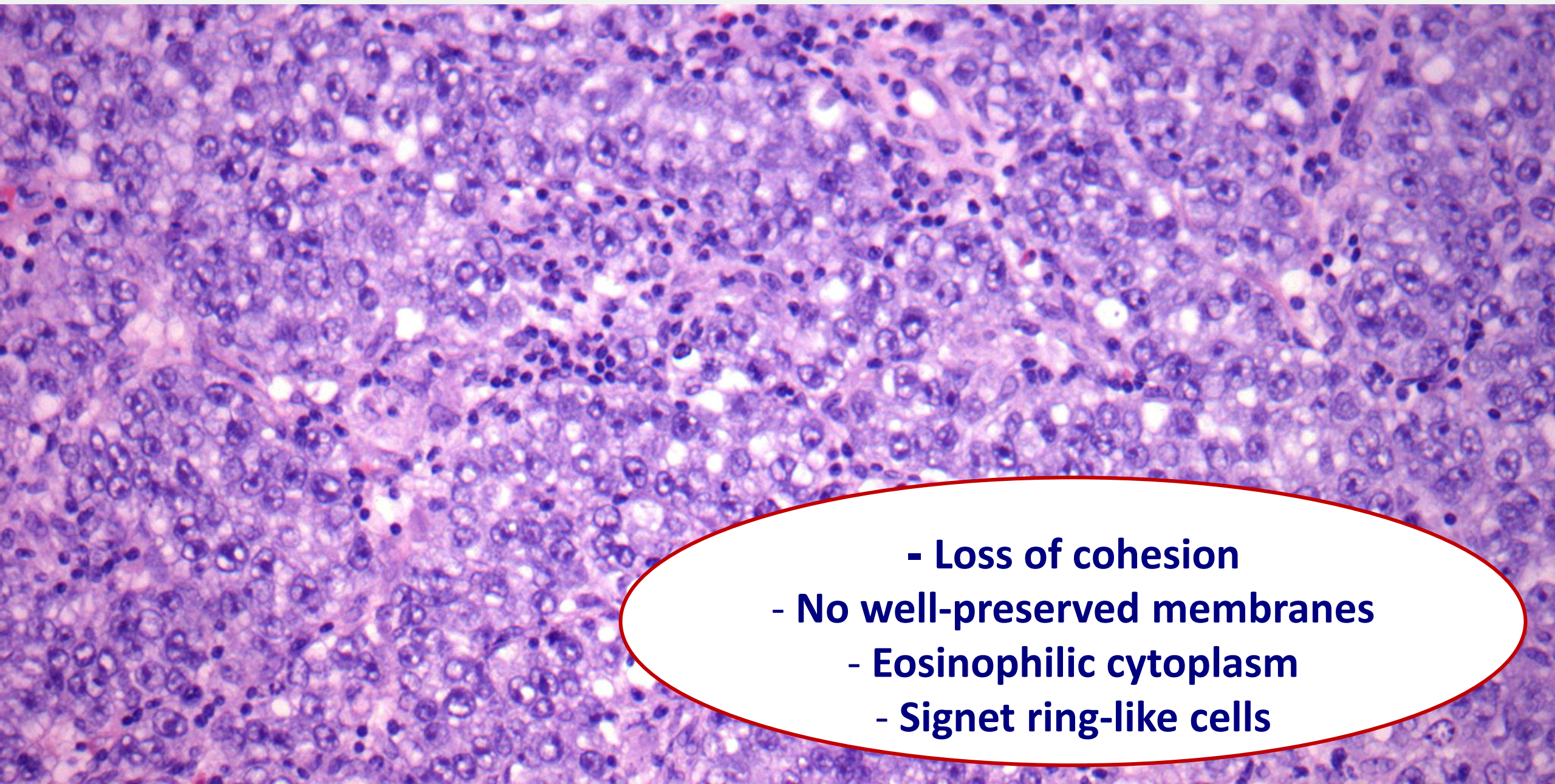
- Immunohistochemistry:
 - OCT3/4, KIT, D2-40, LIN28, and SALL4 positive
 - Cytokeratin may be focally positive
 - EMA, CD30, and Glypican 3 negative
- Molecular:
 - Chromosome 12 abnormalities, typically iso12p or 12p amplification (~80%)
 - *KIT* mutations (exon 17) (~30-50%) and amplification (~30%)

DYSGERMINOMA

Differential Diagnosis

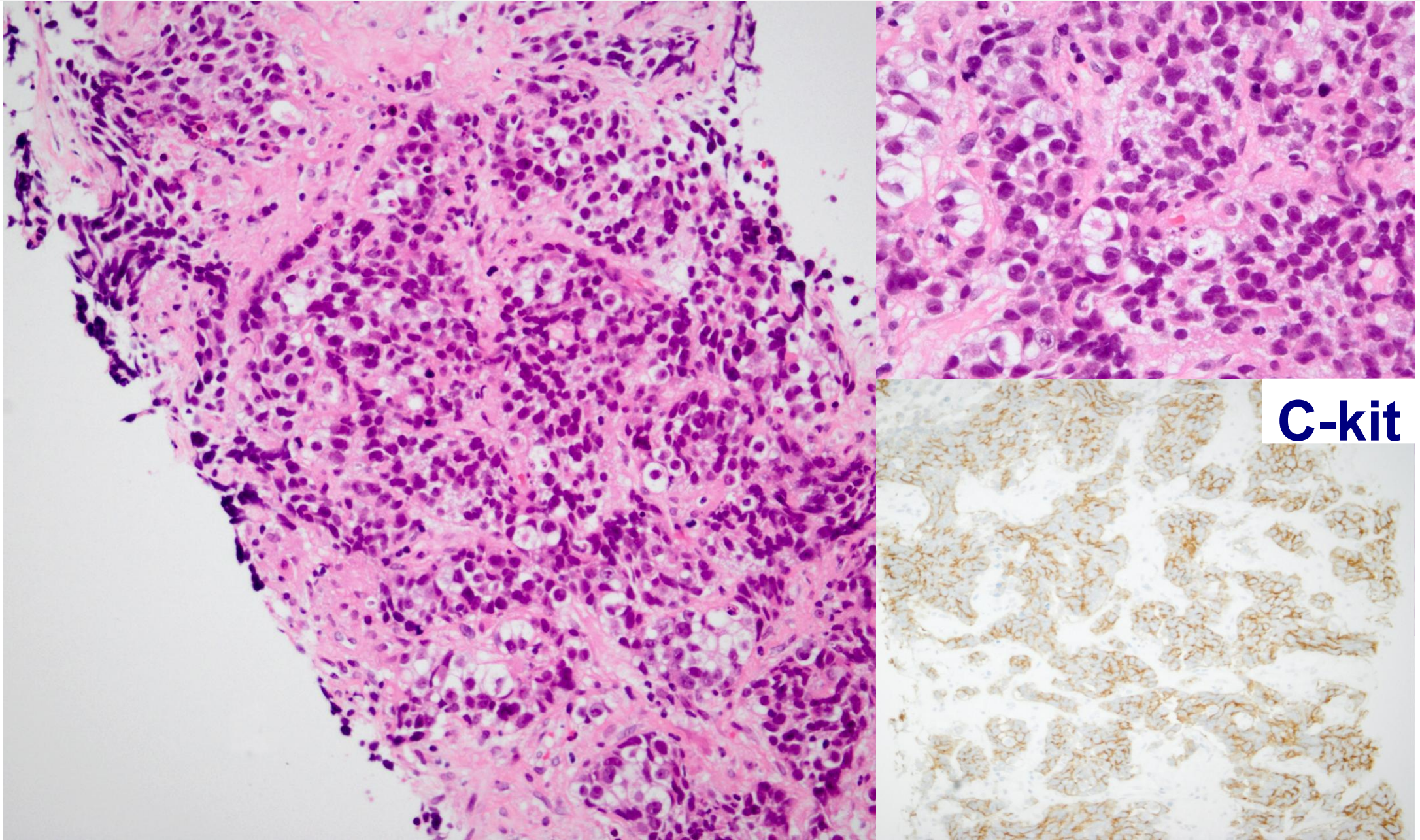
- **Other germ cell tumors with solid growth (YST and EC)**
- **Clear cell carcinoma**
- **Sertoli cell tumor**
- **Undifferentiated carcinoma**
- **Lymphoma (mostly on gross exam)**

DYSGERMINOMA with Suboptimal Fixation



- Loss of cohesion
- No well-preserved membranes
- Eosinophilic cytoplasm
- Signet ring-like cells

DYSGERMINOMA with Marked Crash Artifact



DYSGERMINOMA vs EMBRYONAL CARCINOMA

When:

- **Dense and amphophilic cytoplasm**
 - **Nuclei irregularly shaped and crowded**
 - **No distinct cytoplasmic borders**
 - **If real transformation from dysgerminoma to embryonal carcinoma occur**
-

Favors solid embryonal carcinoma if:

- **Glandular or papillary architecture**
- **AE1/AE3 (diffuse) and CD30 + and c-kit -**

SEMINOMA (microcystic or with scant lymphocytes) vs Solid YST

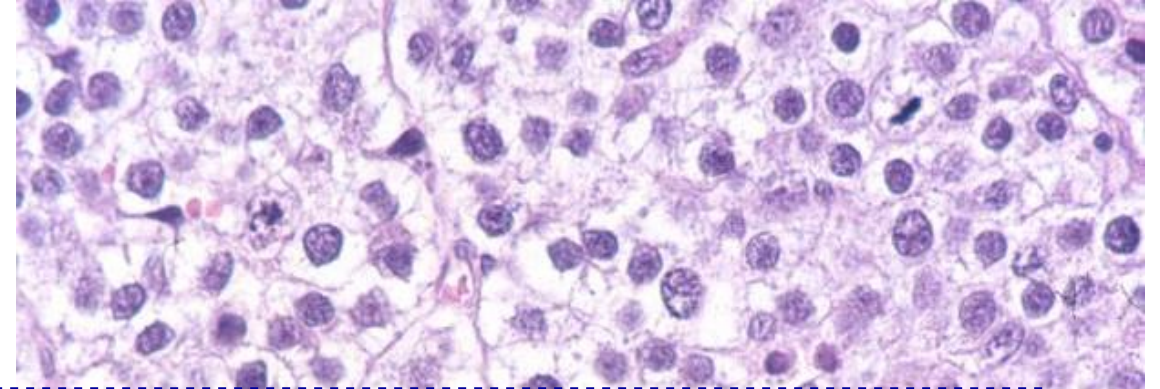
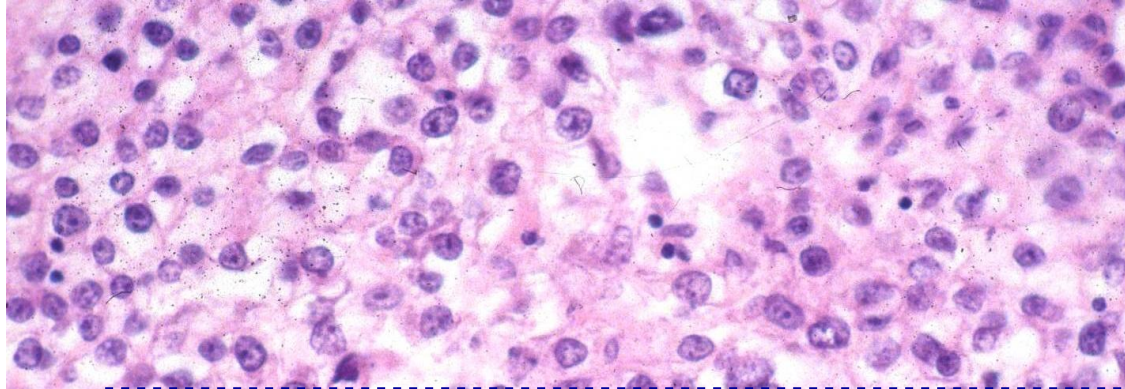
Features favoring YST:

- Clearcut AFP serum elevation**
- Other typical patterns of YST**
- Deposits of extracellular basement membrane**
- No lymphocytes or septae**
- Variable nuclear appearance (shape and size)**
- Intracytoplasmic hyaline globules**

DYSGERMINOMA

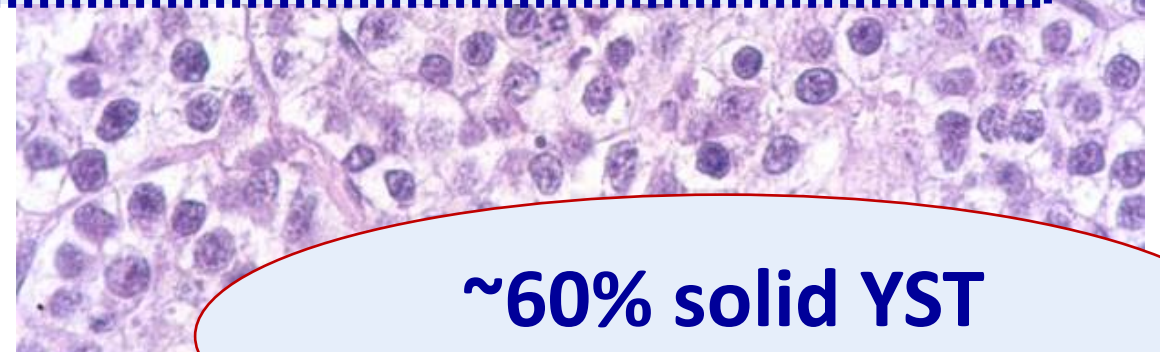
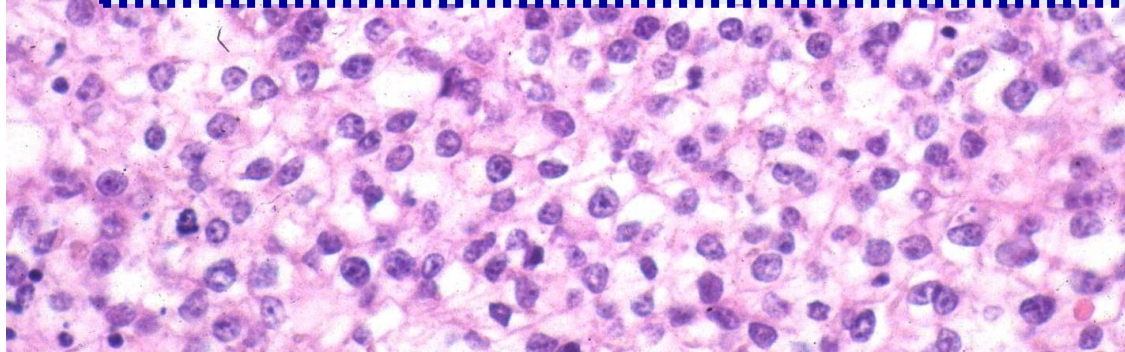
vs

YST



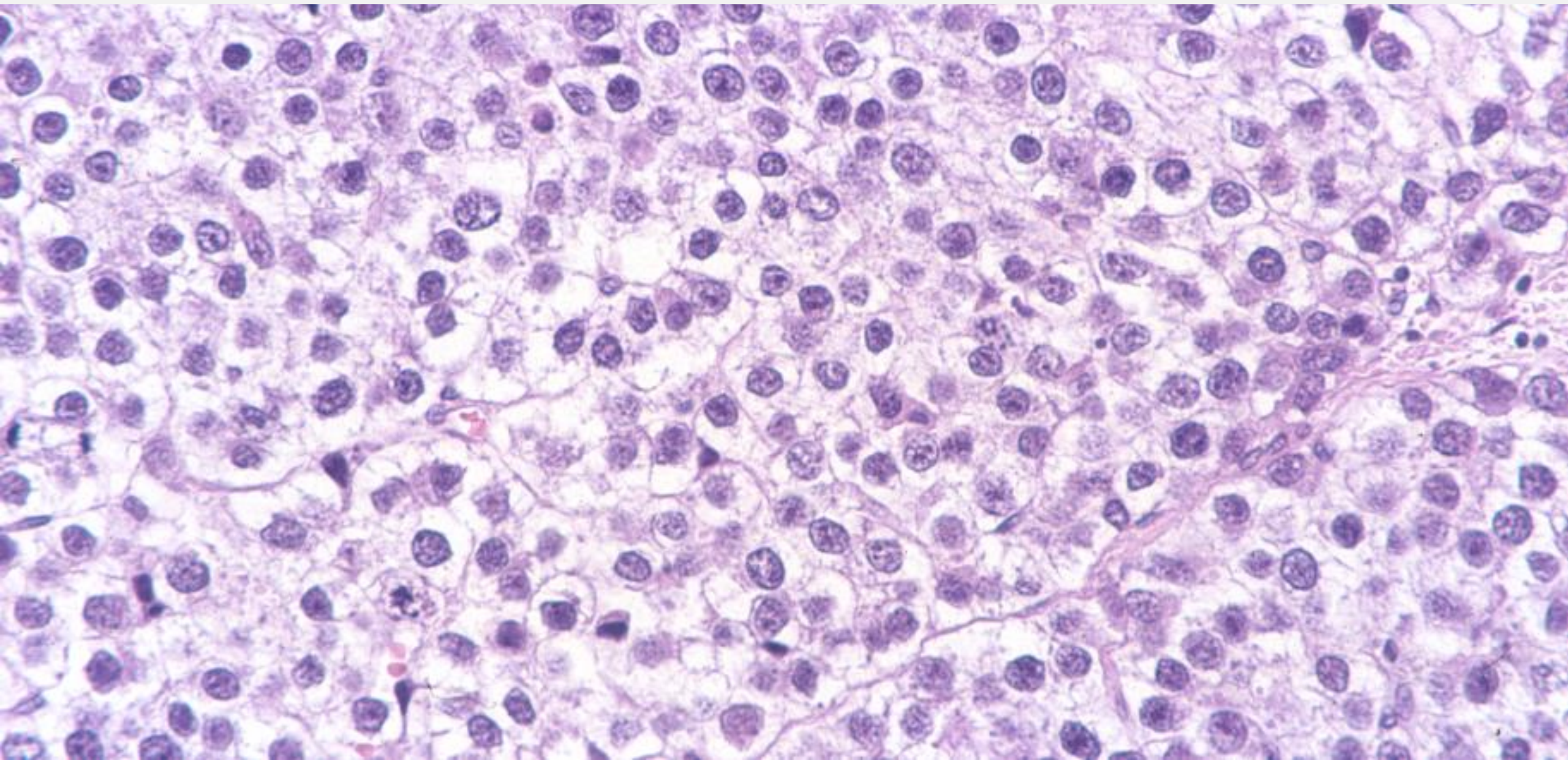
**Dysgerminoma: OCT4, c-kit, D2-40 +
AE1/AE3 -/+, AFP, glypican3 –**

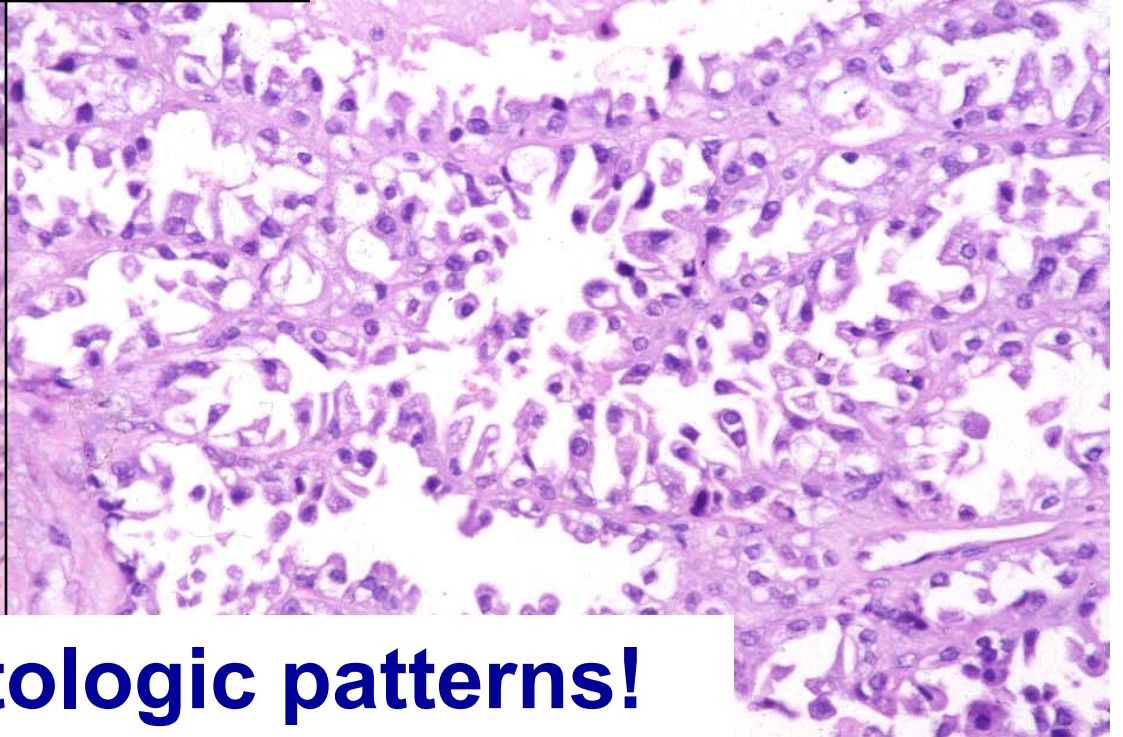
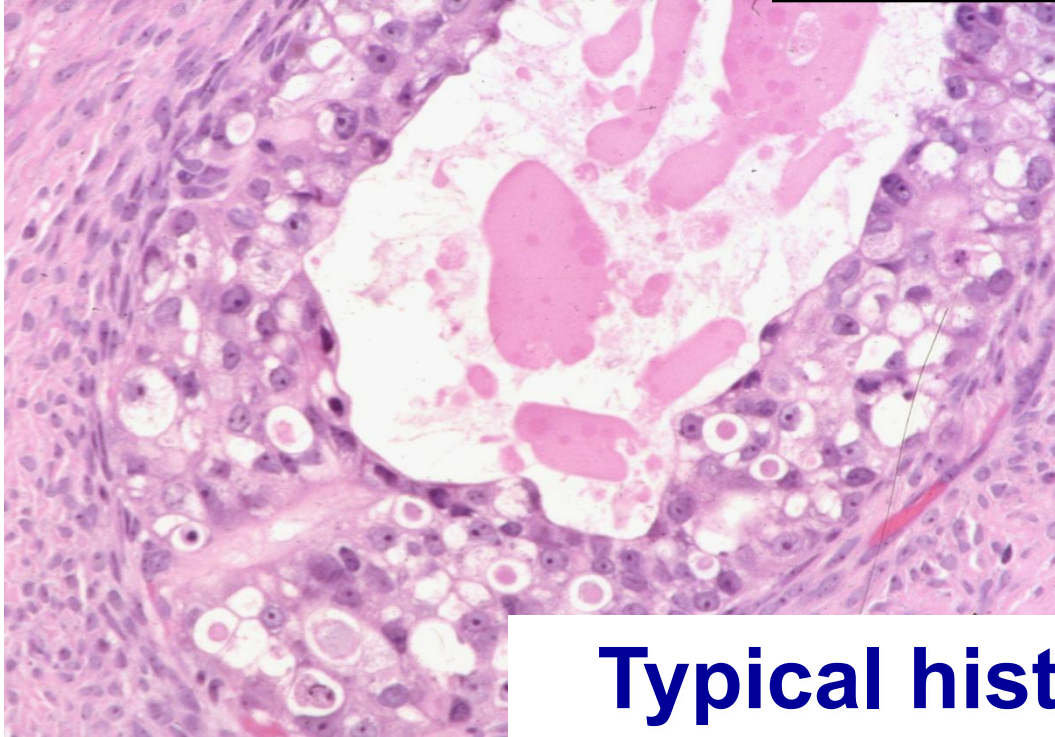
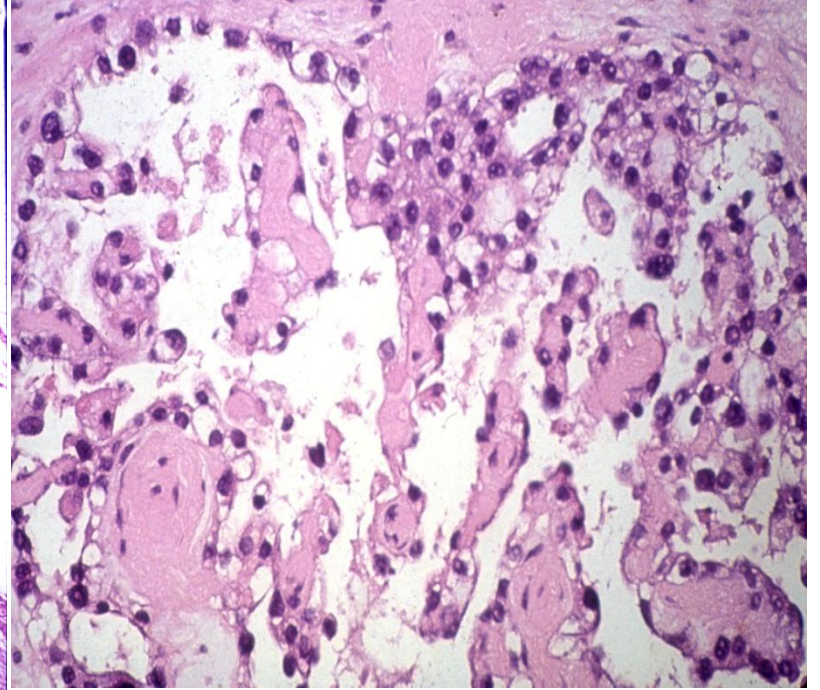
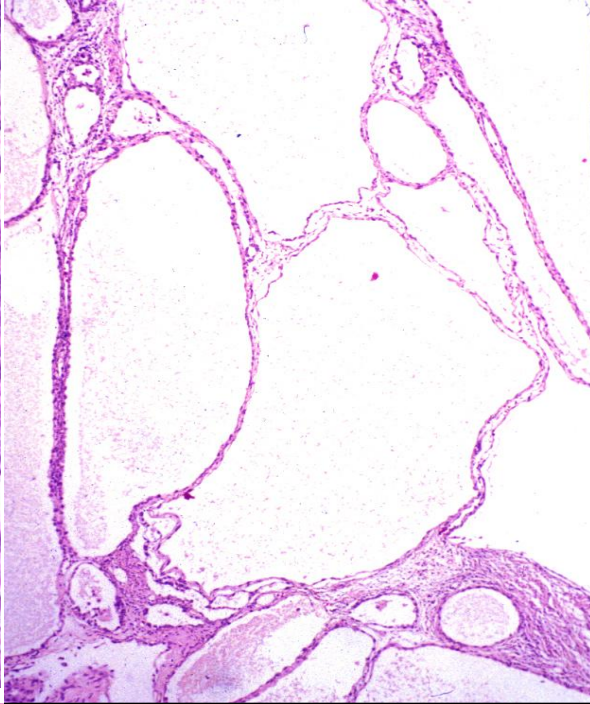
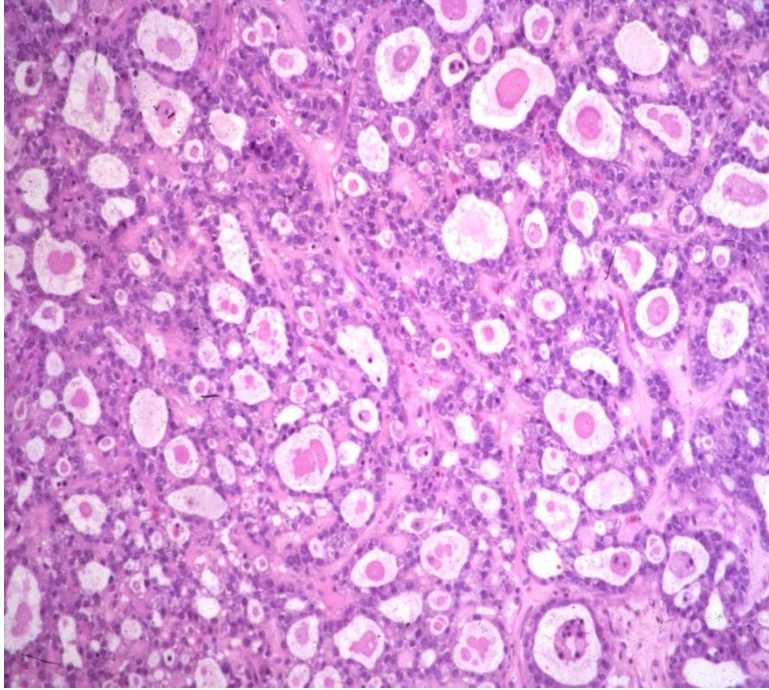
**YST: OCT4, c-kit , D2-40 –
AE1/AE3, GATA3 (90%), AFP (focal), and glypican3 +**



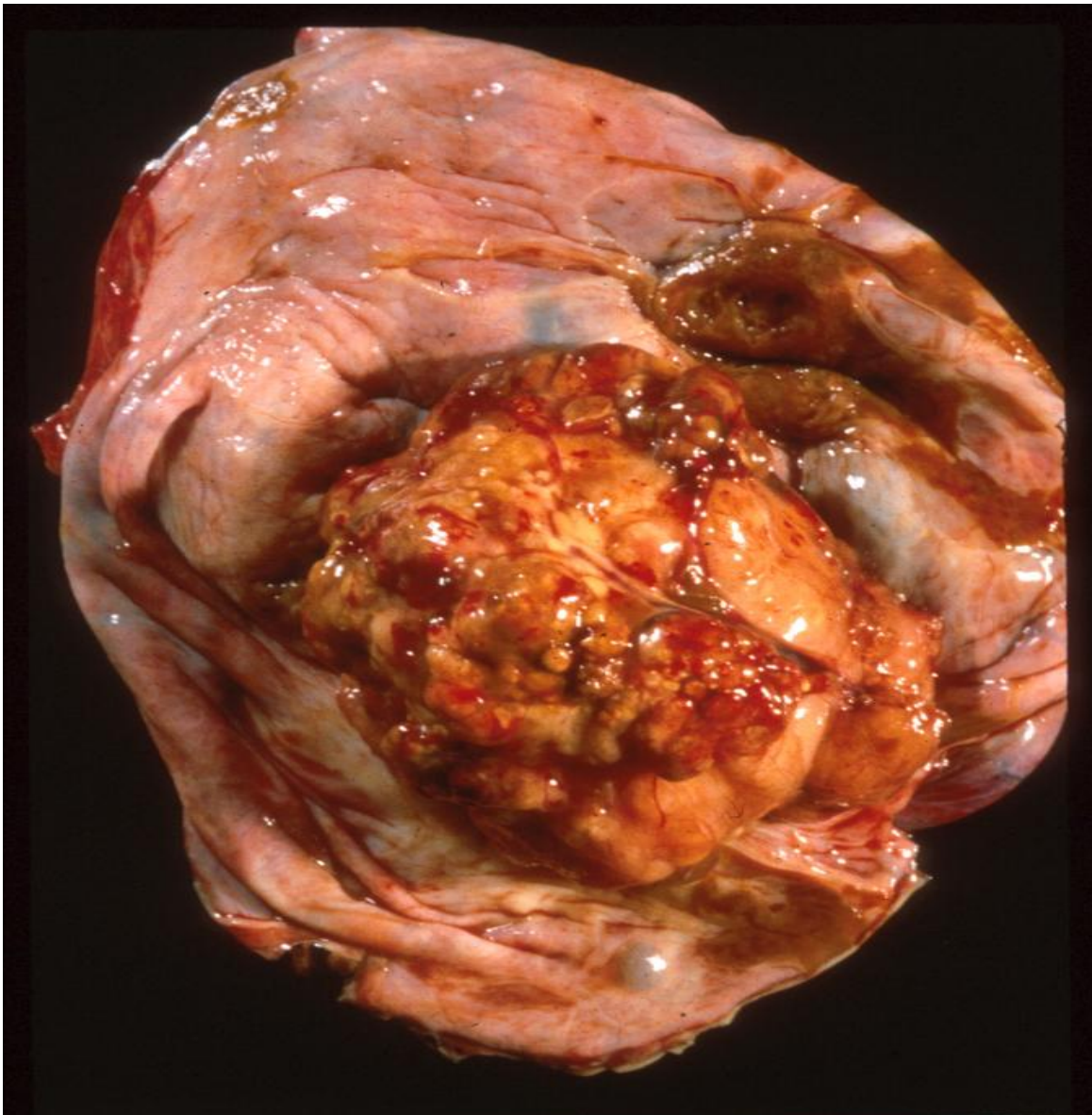
**~60% solid YST
express c-kit!**

DYSGERMINOMA mimicking CCC

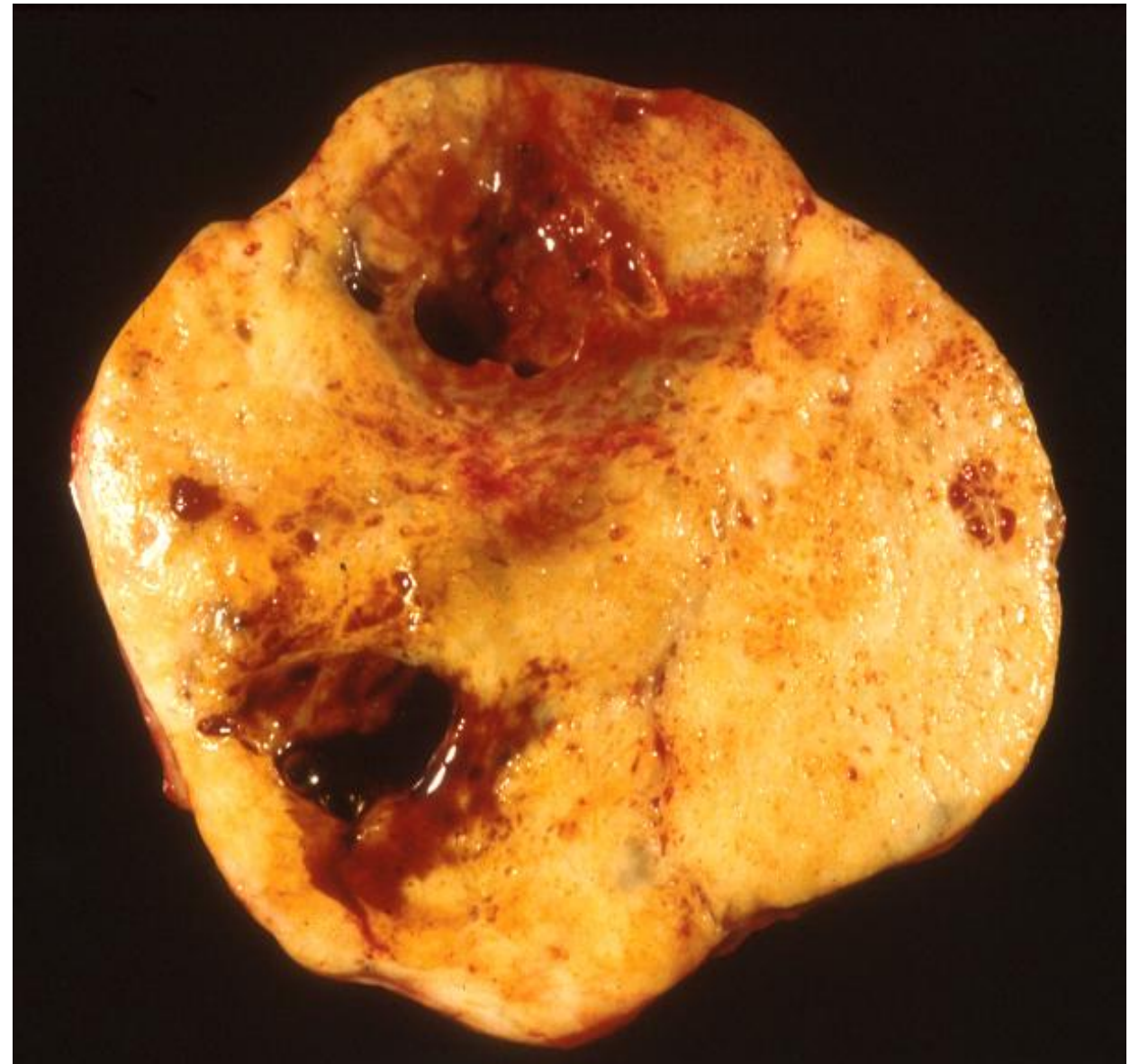




Typical histologic patterns!



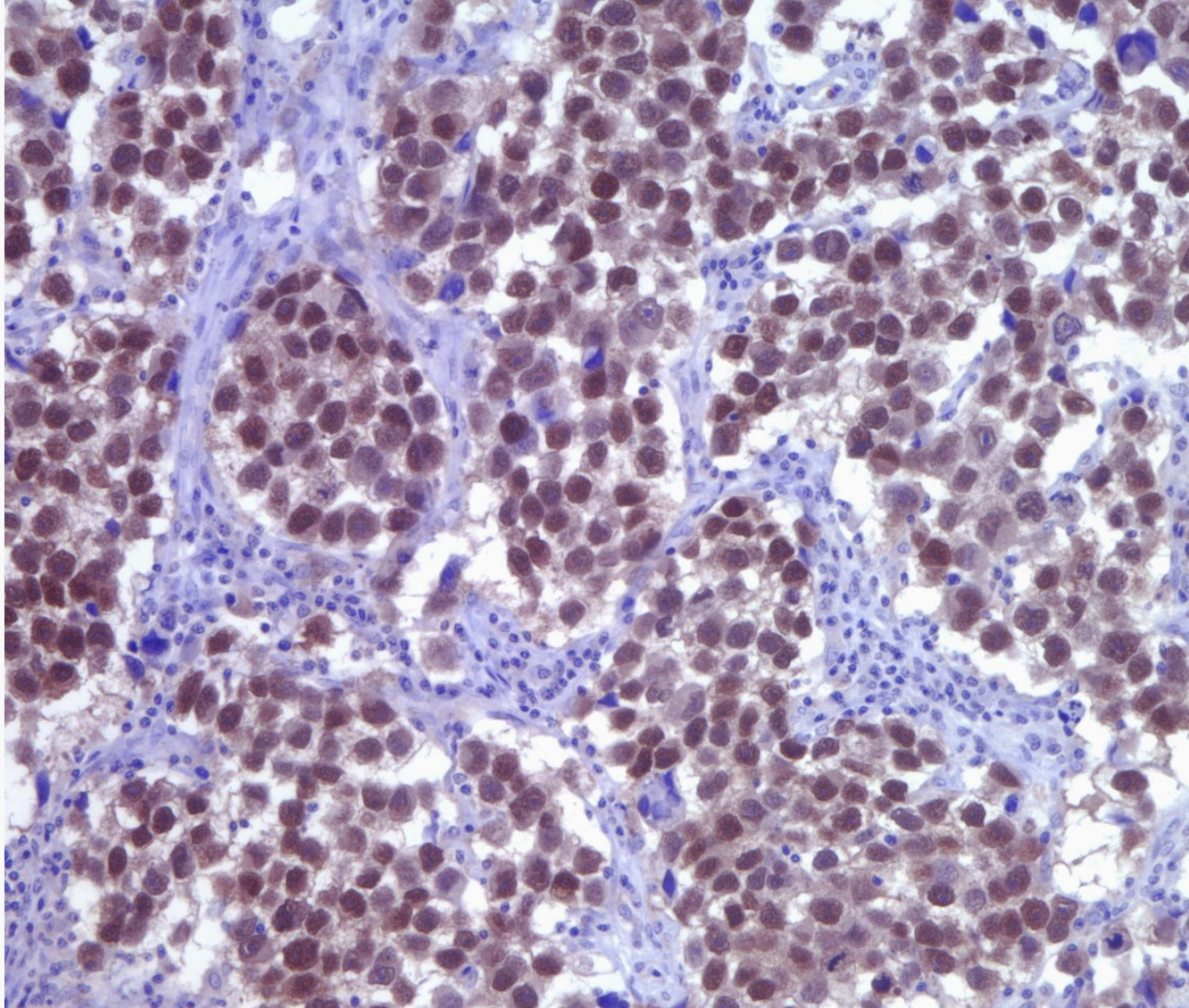
Background of Endometriosis



Background of Adenofibroma

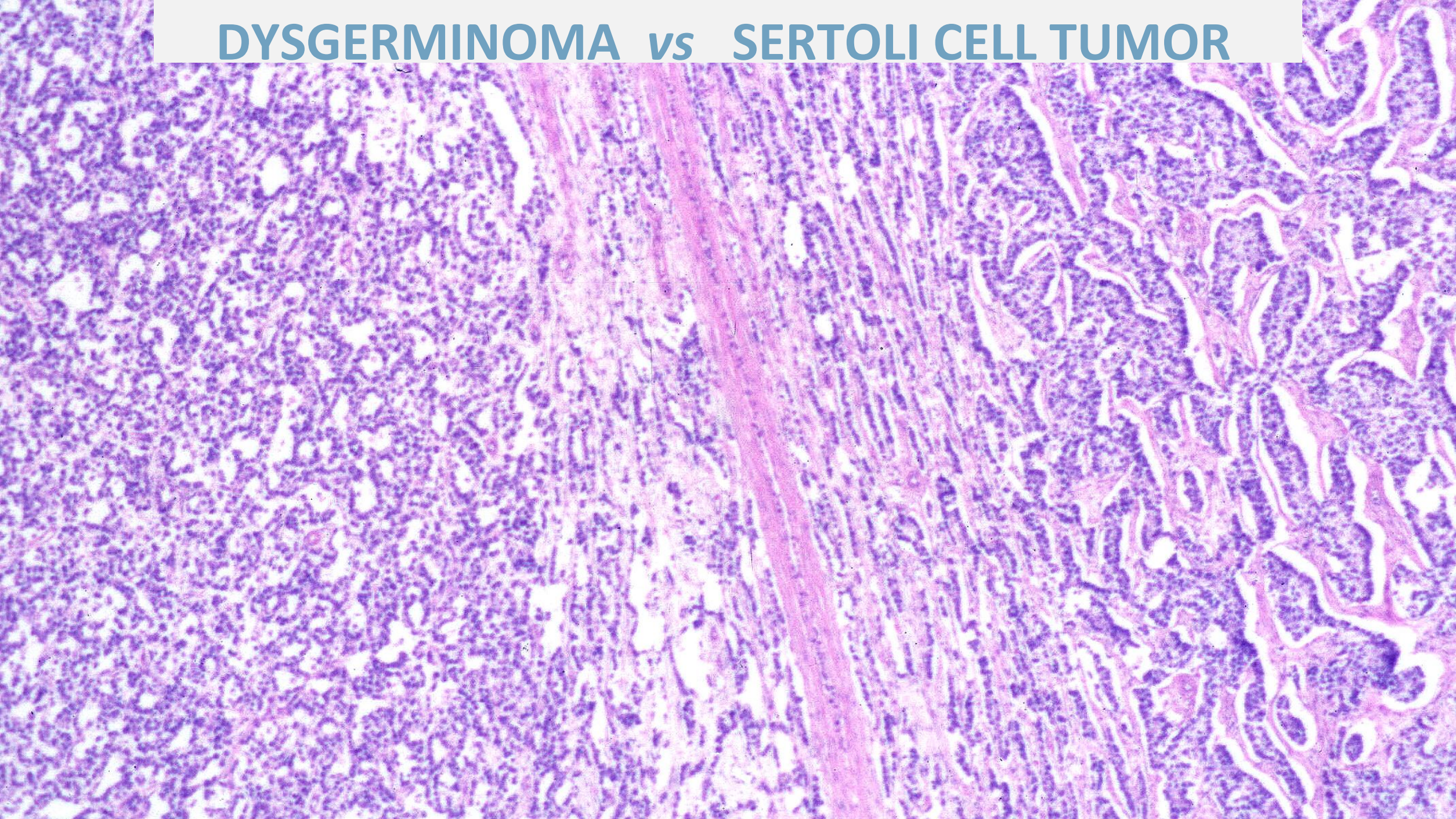
	CCC	DYS
CK7	+	-
EMA	+	-
CA-125	+	-
Leu-M1	+	-
PAX8/SOX17	+	-
Racemase/Napsin	+	-
AFP	-/+	-/+
PLAP	-	+
c-kit	-	+
OCT4	4/14 + (focal)	+(diffuse)
D2-40	-	+
SALL4	-	+

OCT3/4 CAVETAS



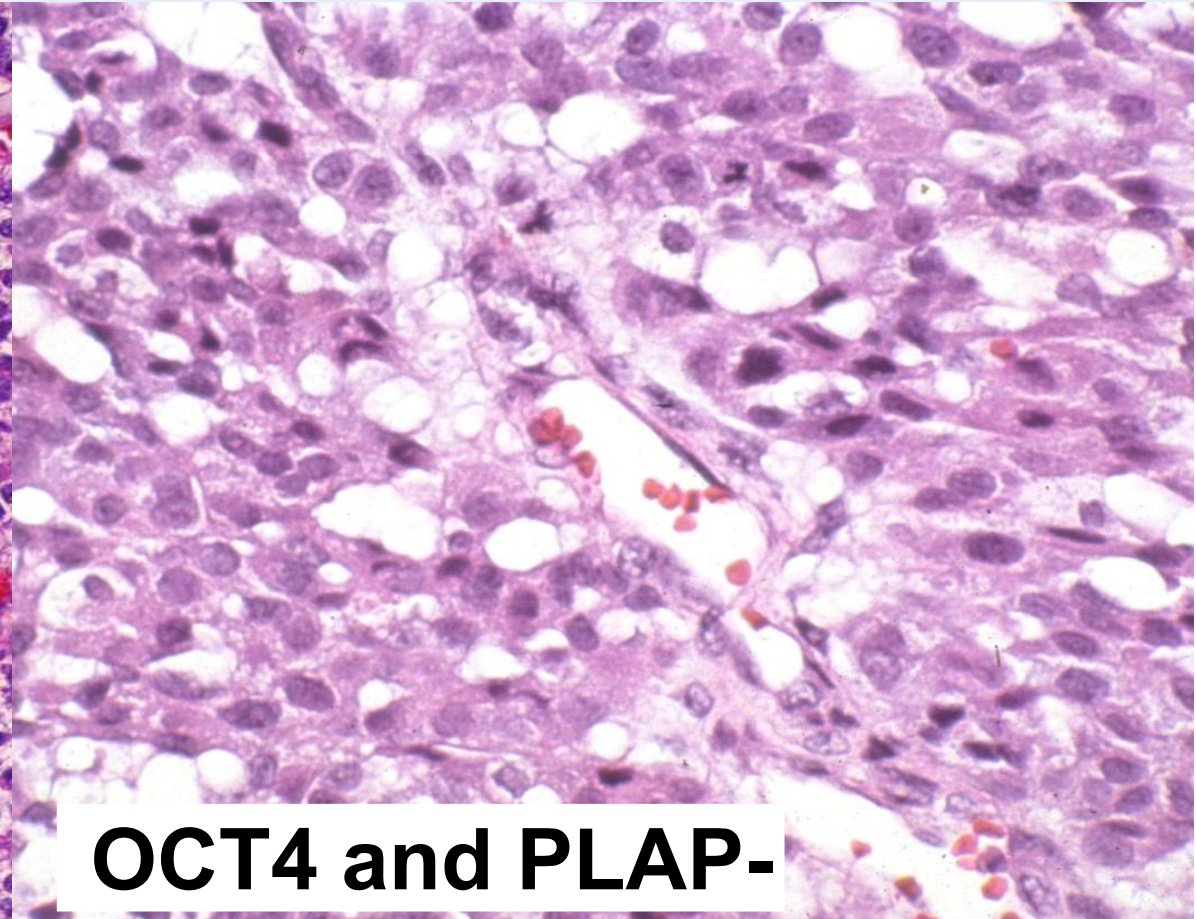
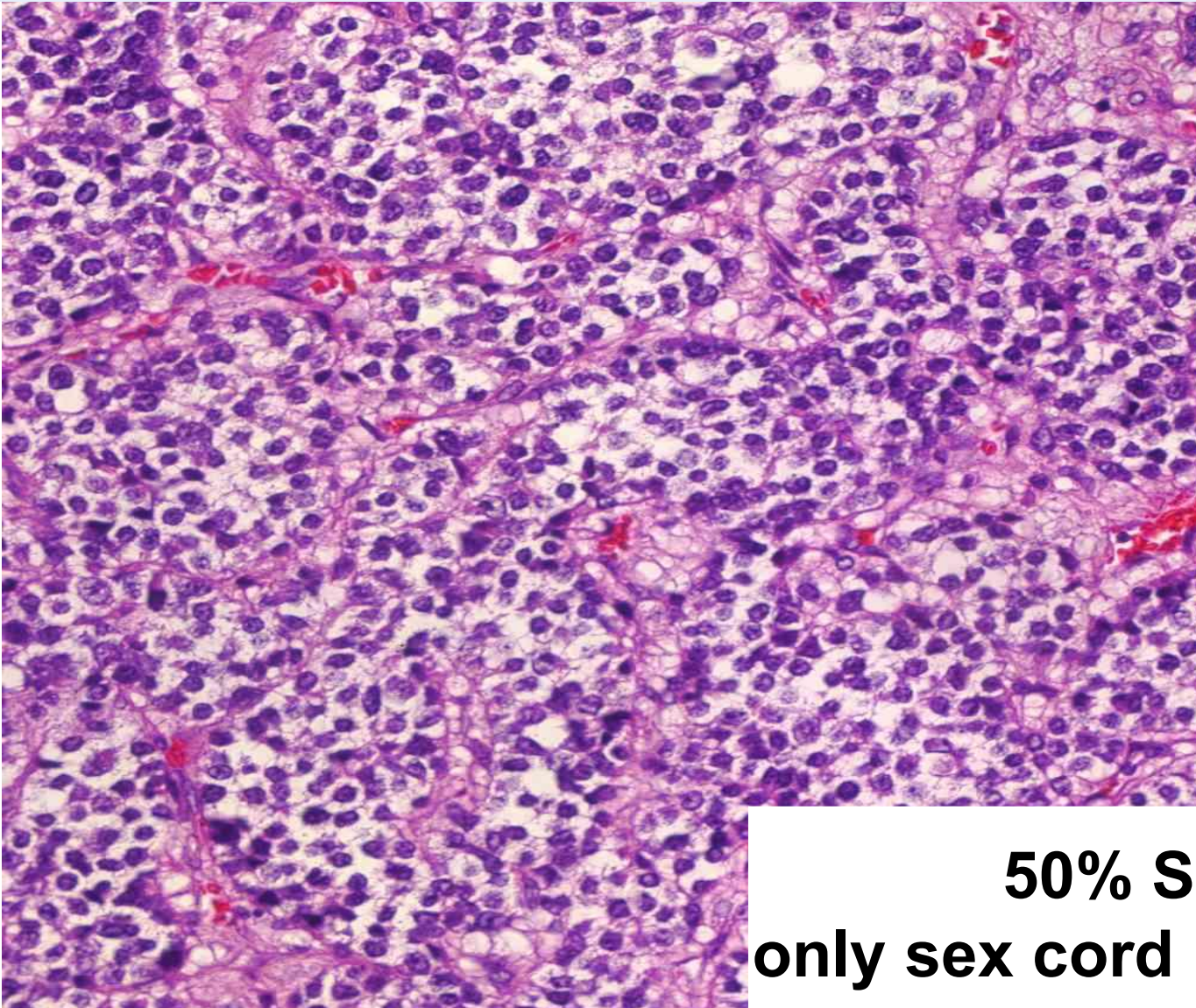
- It can be detected in Clear Cell Ca, although expression is focal in contrast to diffuse staining in Dysgerminoma
- It does not distinguish Dysgerminoma from Embryonal Ca, although the latter is exceedingly rare in the ovary (but not in the testis!)

DYSGERMINOMA vs SERTOLI CELL TUMOR



SERTOLI CELL TUMOR vs DYSGERMINOMA

Smaller nuclei/nucleoli and fewer mitoses in SCT



OCT4 and PLAP-

**50% SCT inhibin-, thus if using
only sex cord markers use also SF1 +/- FOXL-2**

POTENTIAL FROZEN SECTION ISSUES

Dysgerminoma vs lymphoma

- **Similarities:** Homogeneous, solid, white to tan cut surface
Background lymphocytes
Large nuclei
- **Differences:** Thickening of the fallopian tube (lymphoma)
Fibrous septae and squared-off nuclei (dysgerminoma)

DDX: Typically large cell anaplastic lymphoma (ALK+)

YOLK SAC TUMOR

- ~20% of all malignant germ cell tumors
- Most common malignant germ cell tumor in children and young adults
- ~65% extraovarian spread at time of diagnosis
- Associations:
 - With surface epithelial tumors (endometrioid, serous, and mucinous) in older women
 - ↑ AFP levels

Yolk Sac Tumor of the Ovary

A Report of 150 Cases and Review of the Literature

Robert H. Young, MD, FRCPath, Adele Wong, MB, FRCPath,† and Jennifer N. Stall, MD‡*

Am J Surg Pathol 2021

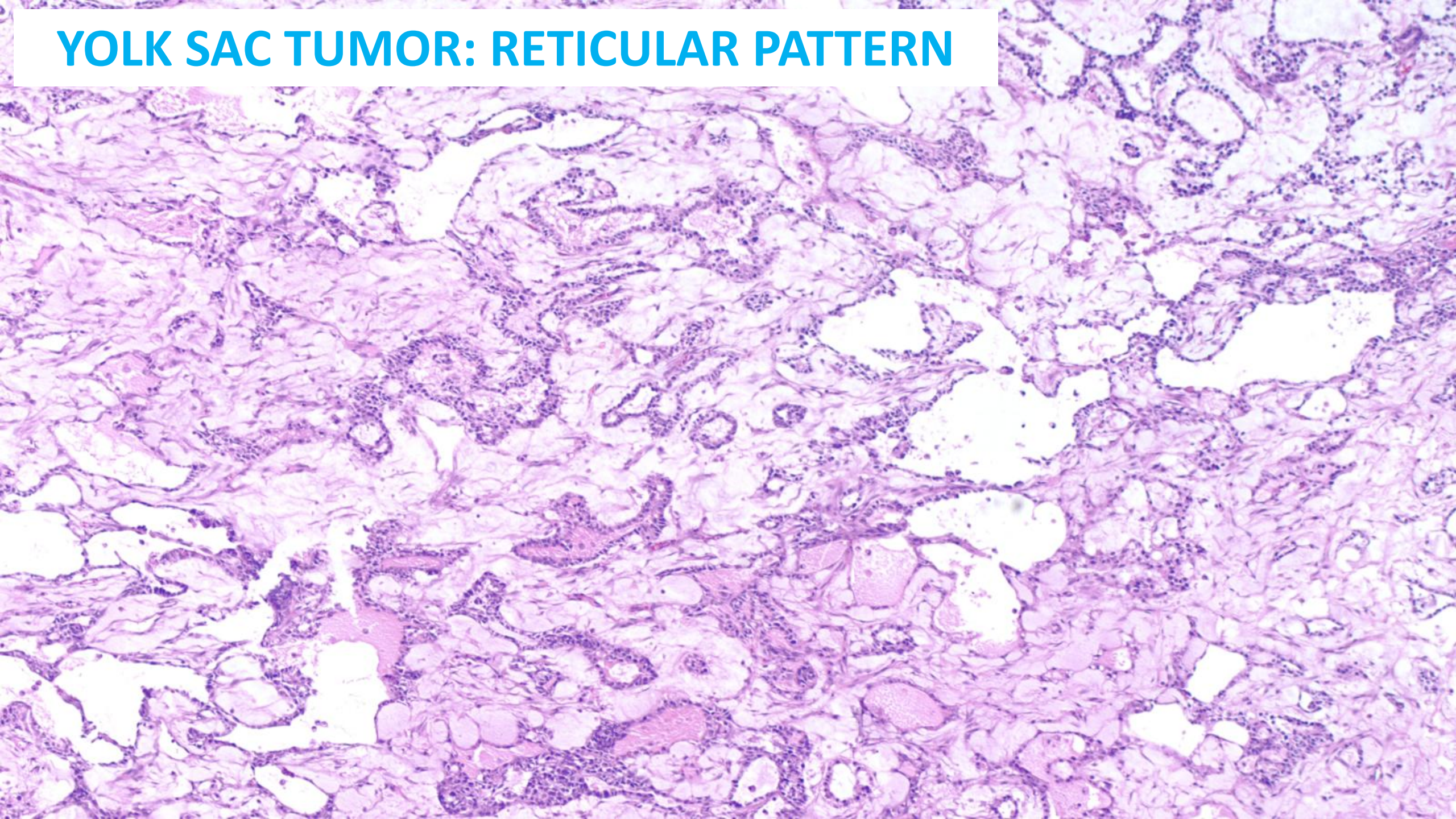
YOLK SAC TUMOR



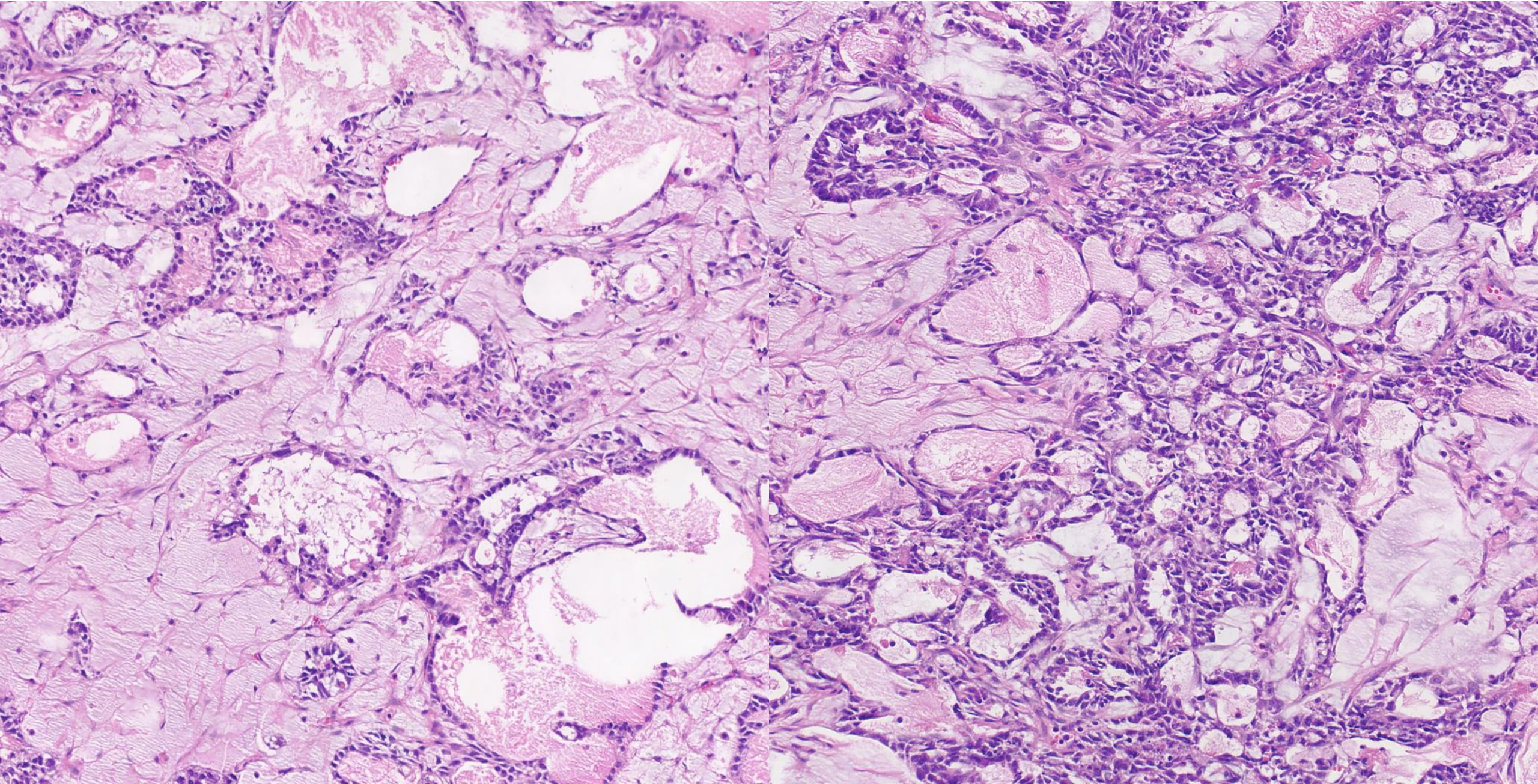
**Solid and cystic
~60%**

Multicystic ~ 25%
Solid ~20%

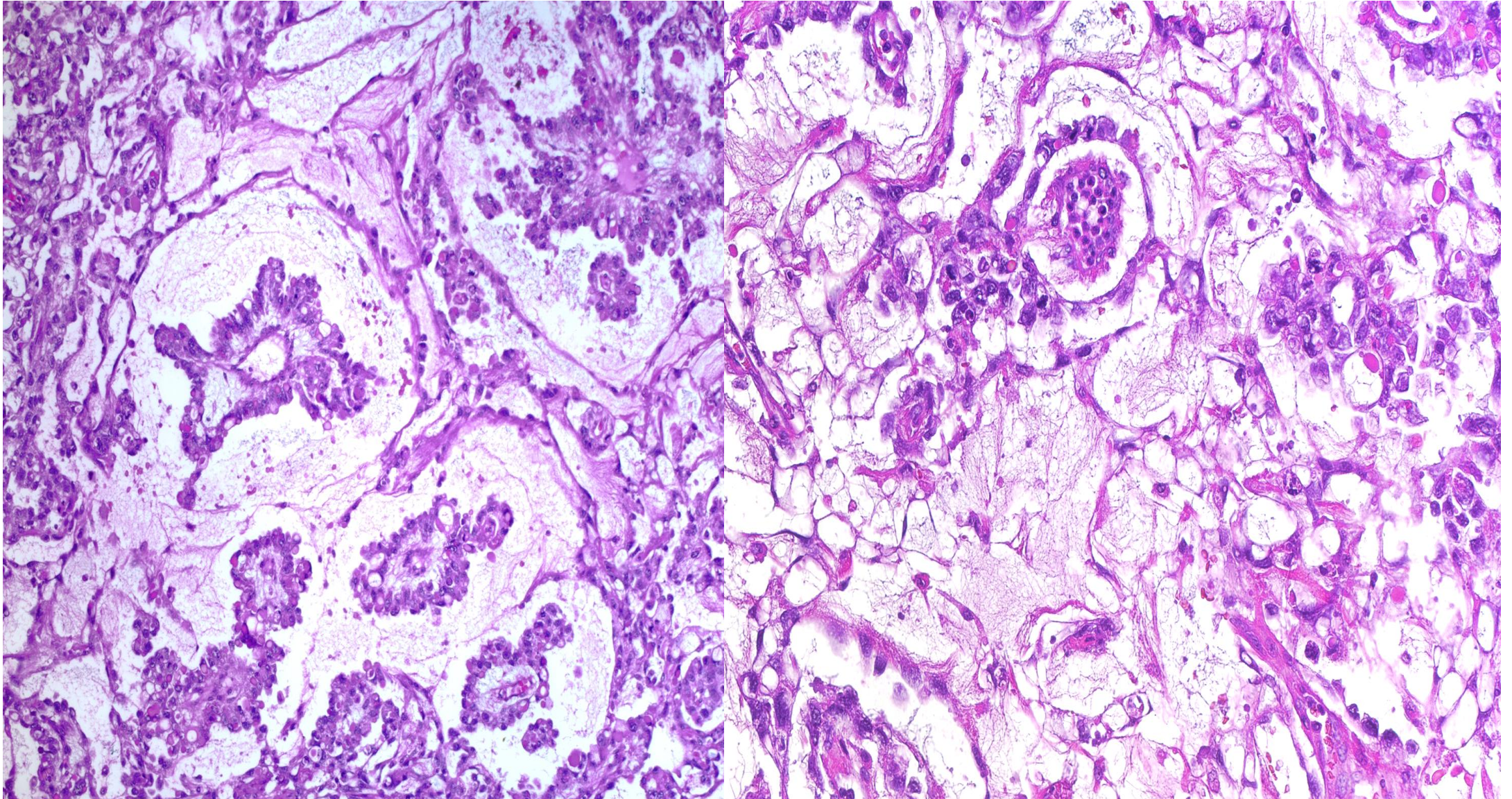
YOLK SAC TUMOR: RETICULAR PATTERN



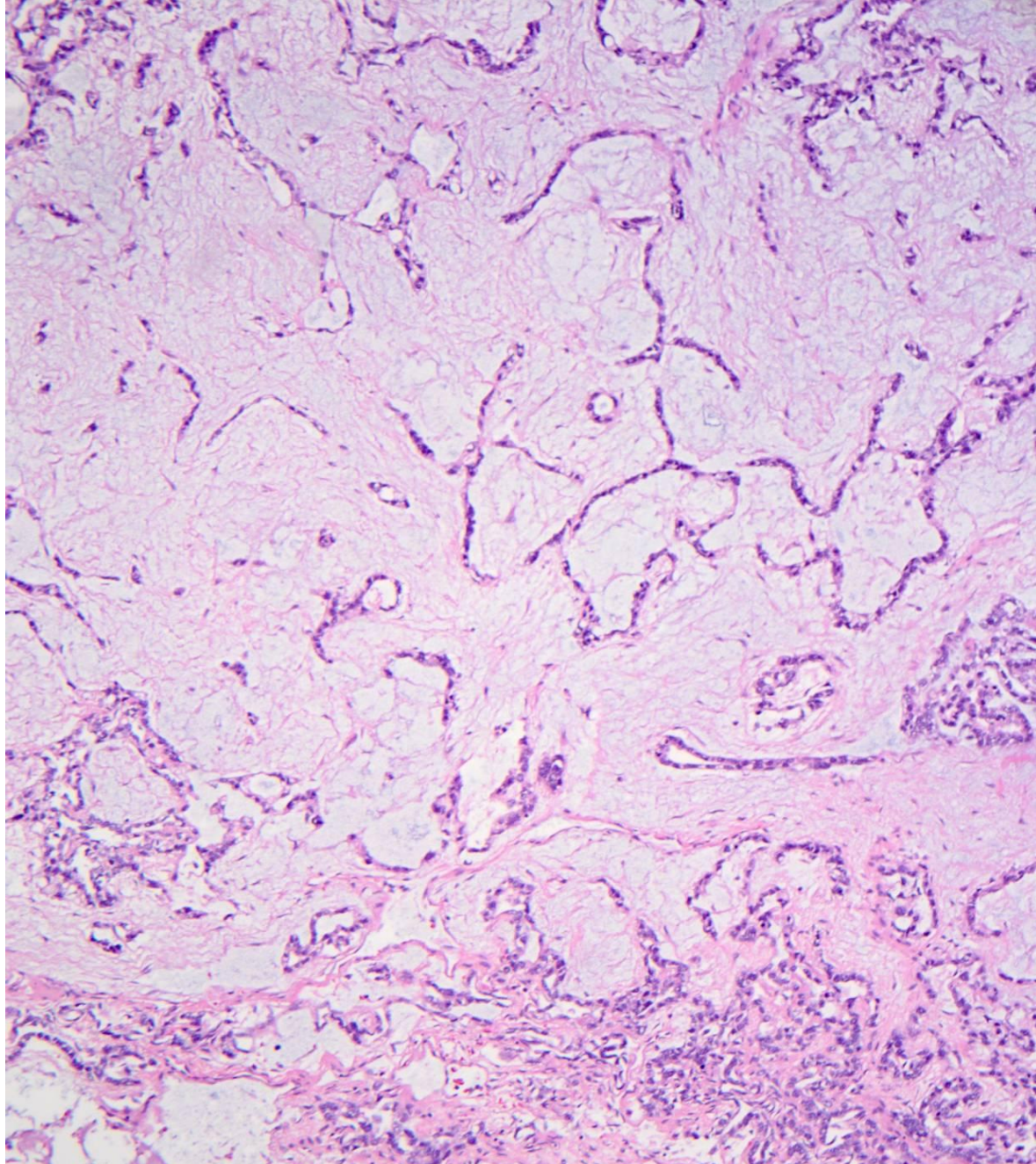
RETICULAR-MICROCYSTIC PATTERNS- most common



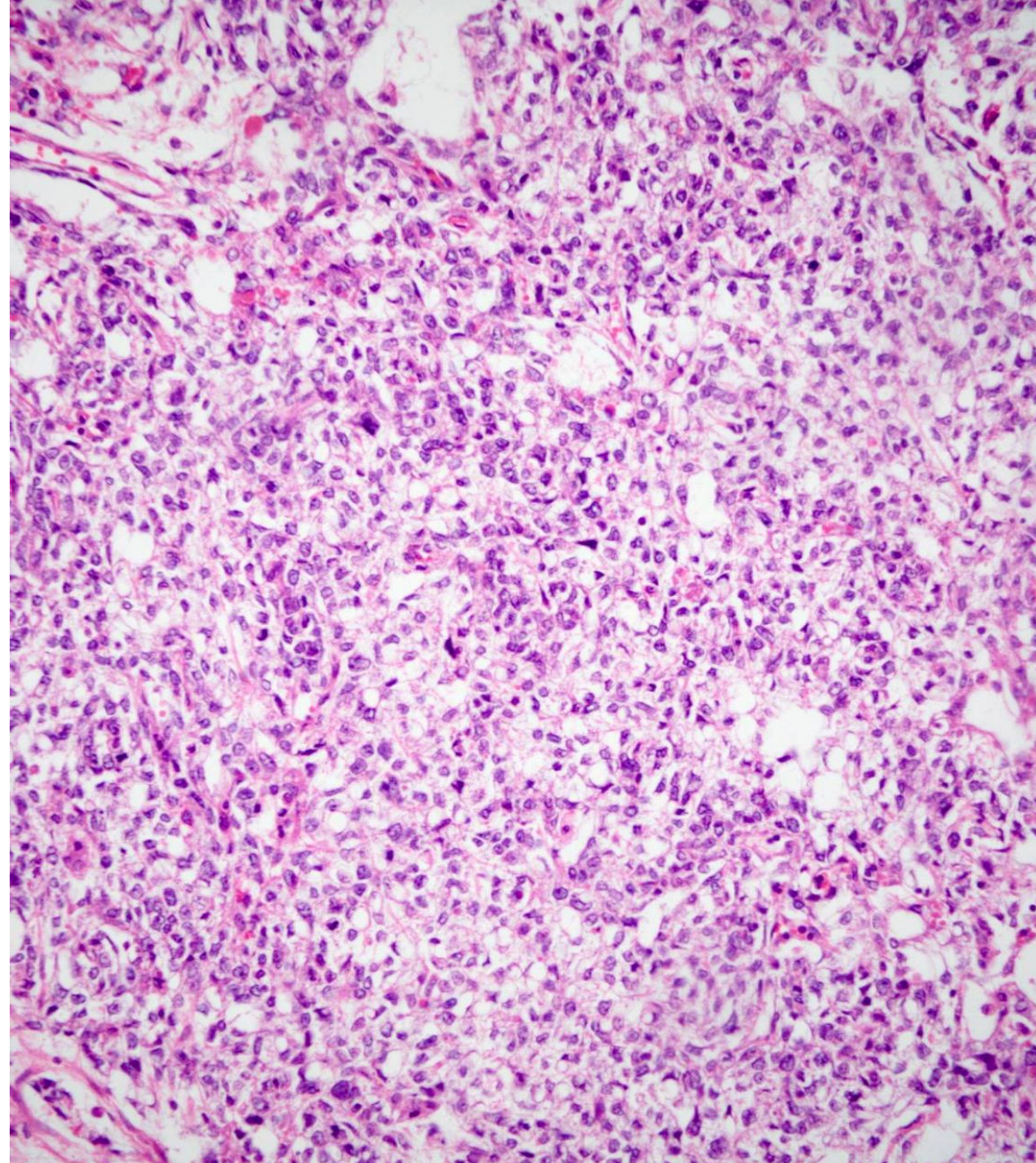
Endodermal Sinus with Schiller-Duval bodies



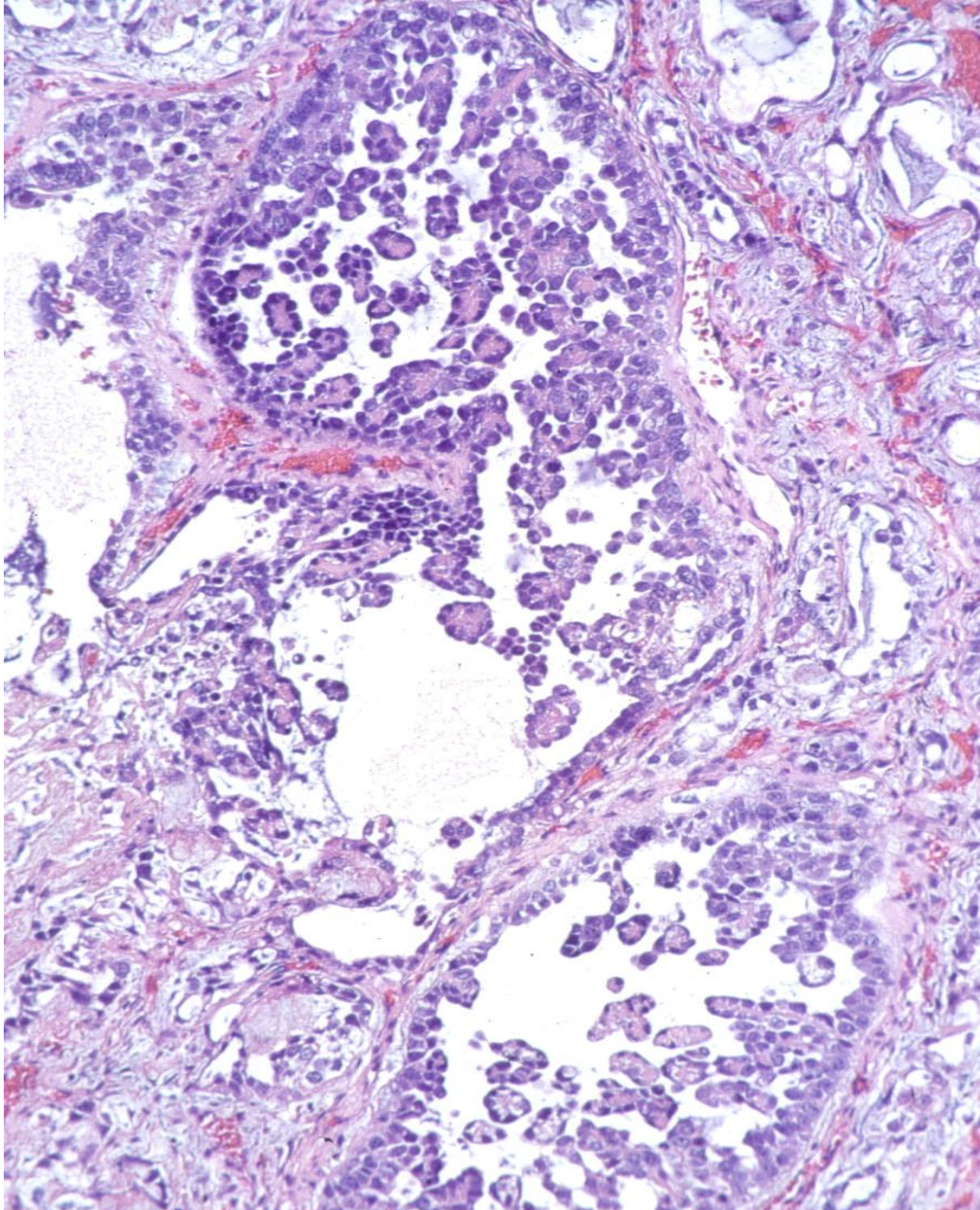
Present in only 1/3 of YSTs



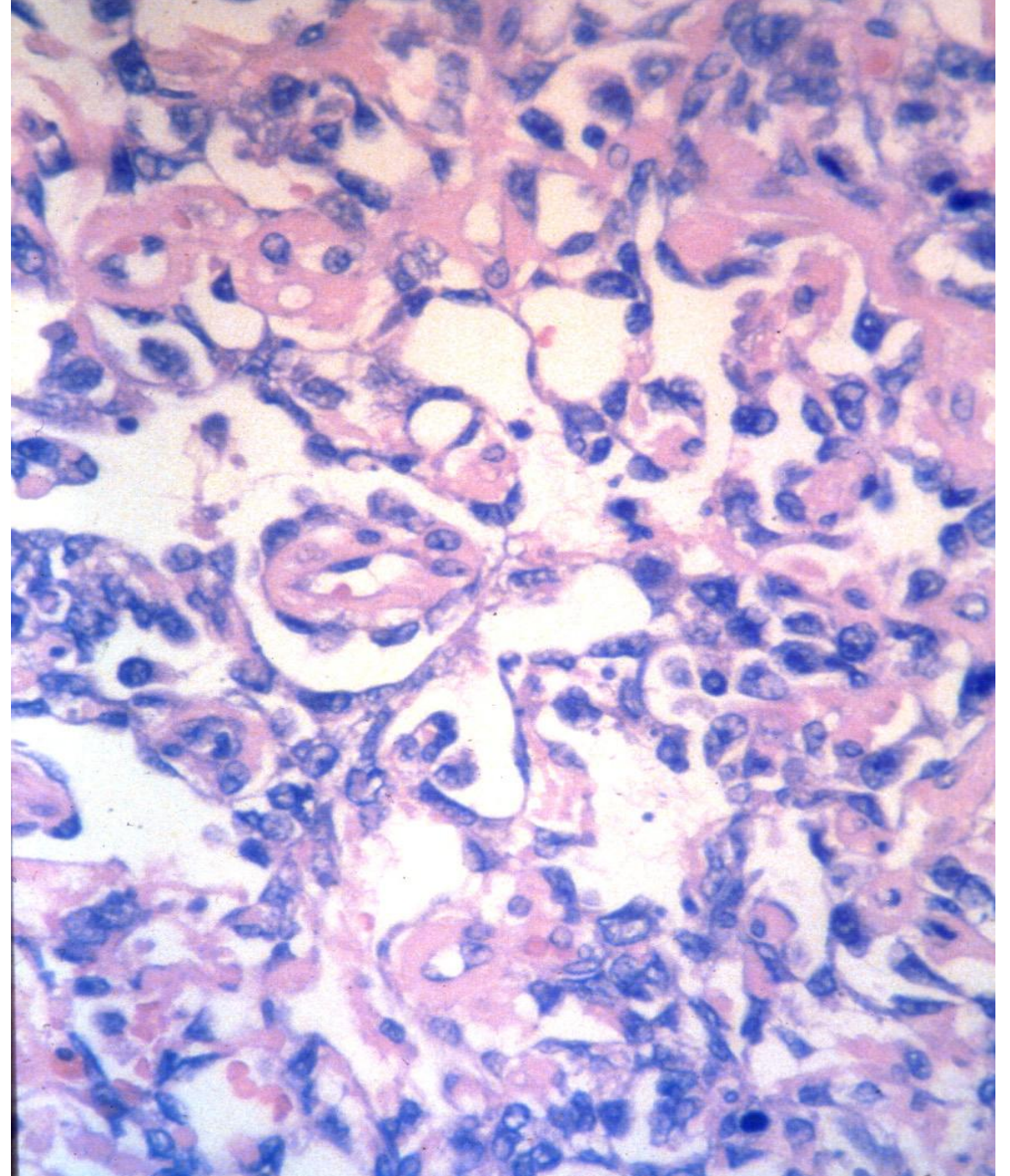
FESTON



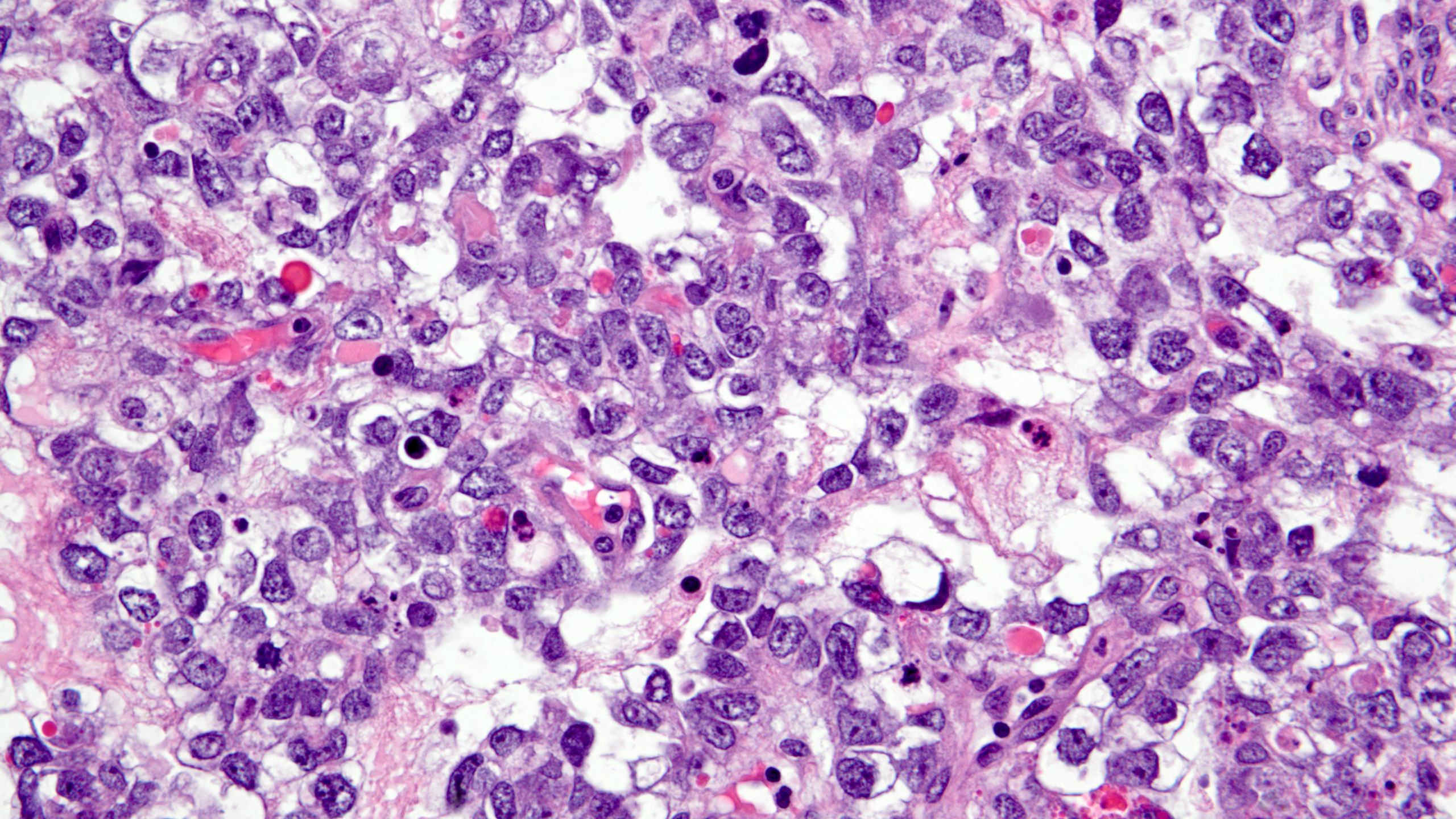
SOLID



Papillary, NOS



Parietal



YOLK SAC TUMOR

Immunohistochemical profile:

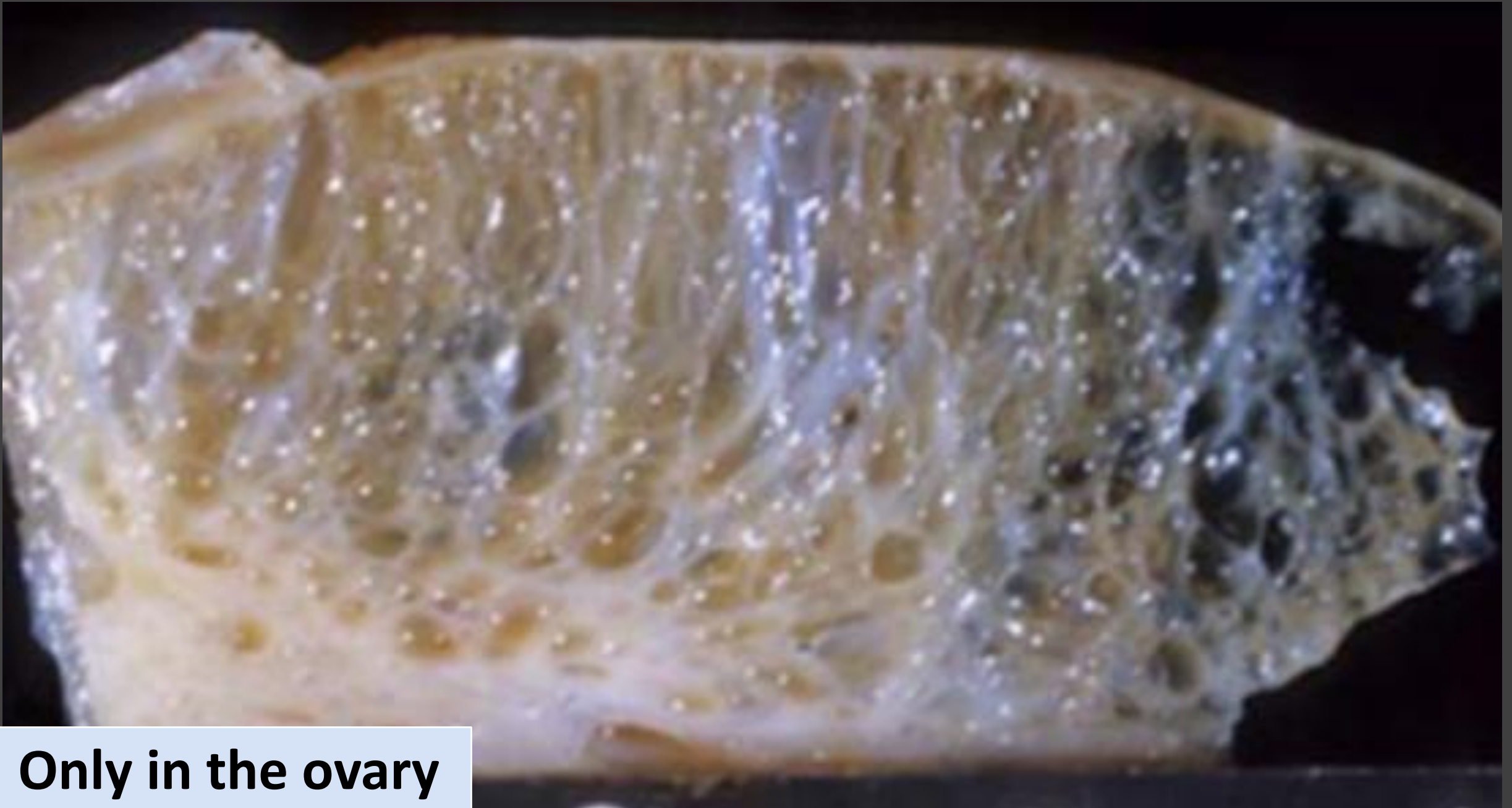
- SALL4, Glypican3, LIN28, AFP (often focal and weak)

Molecular profile:

- Chromosome 12 abnormalities, most commonly isochromosome 12p

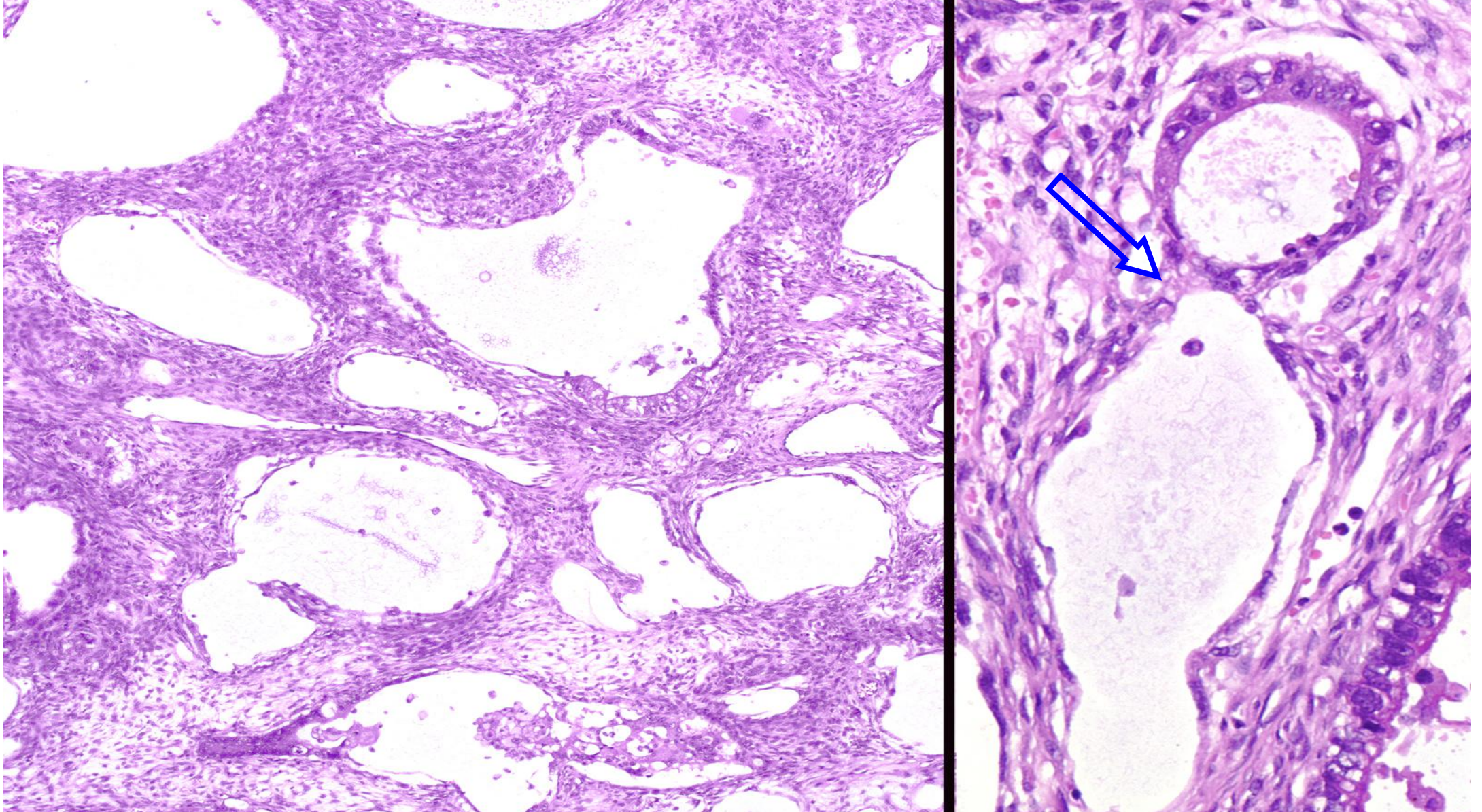
YOLK SAC TUMOR: Variants

- Polyvesicular vitelline
- Hepatoid
- Glandular
 - Intestinal (CDX2 positive)
 - Endometrioid



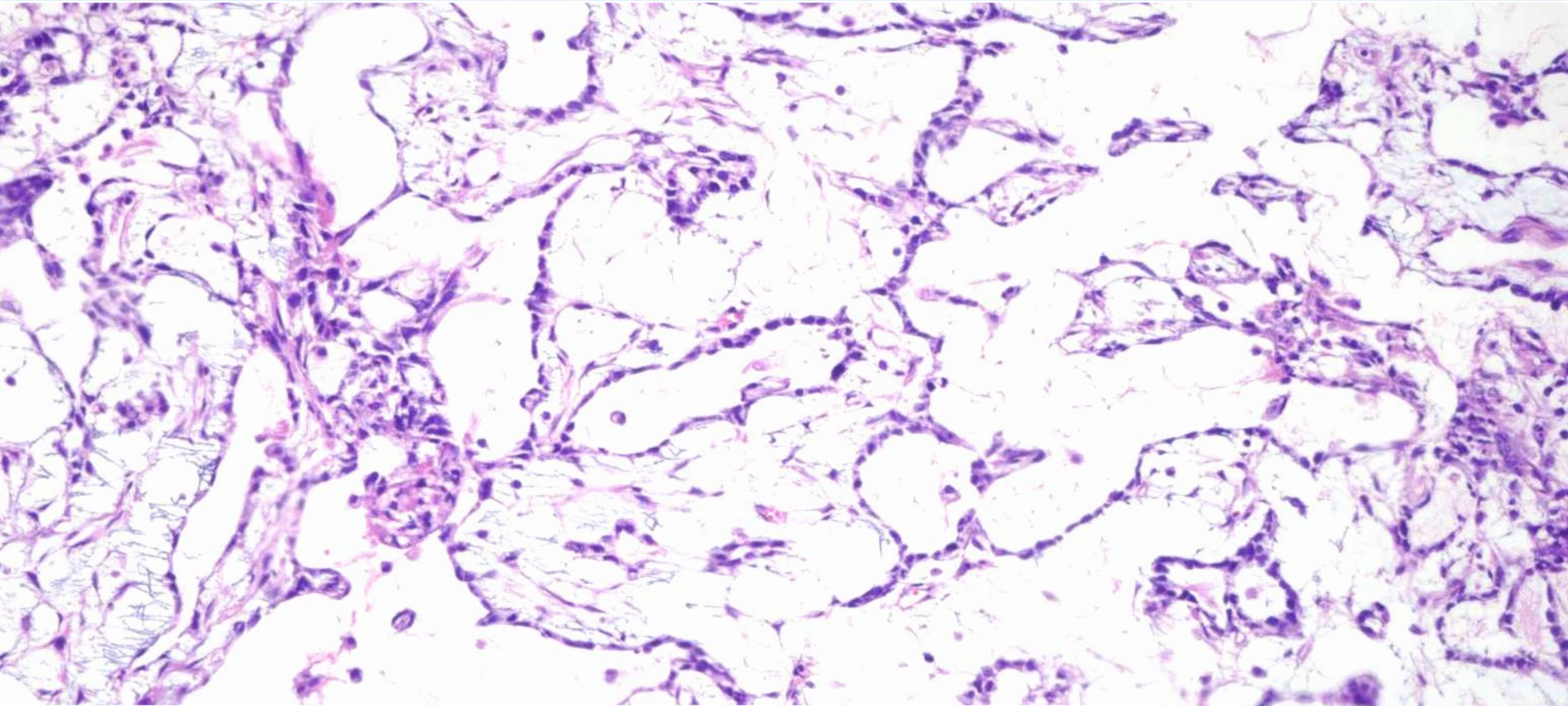
Only in the ovary

POLYVESICULAR VITELLINE VARIANT



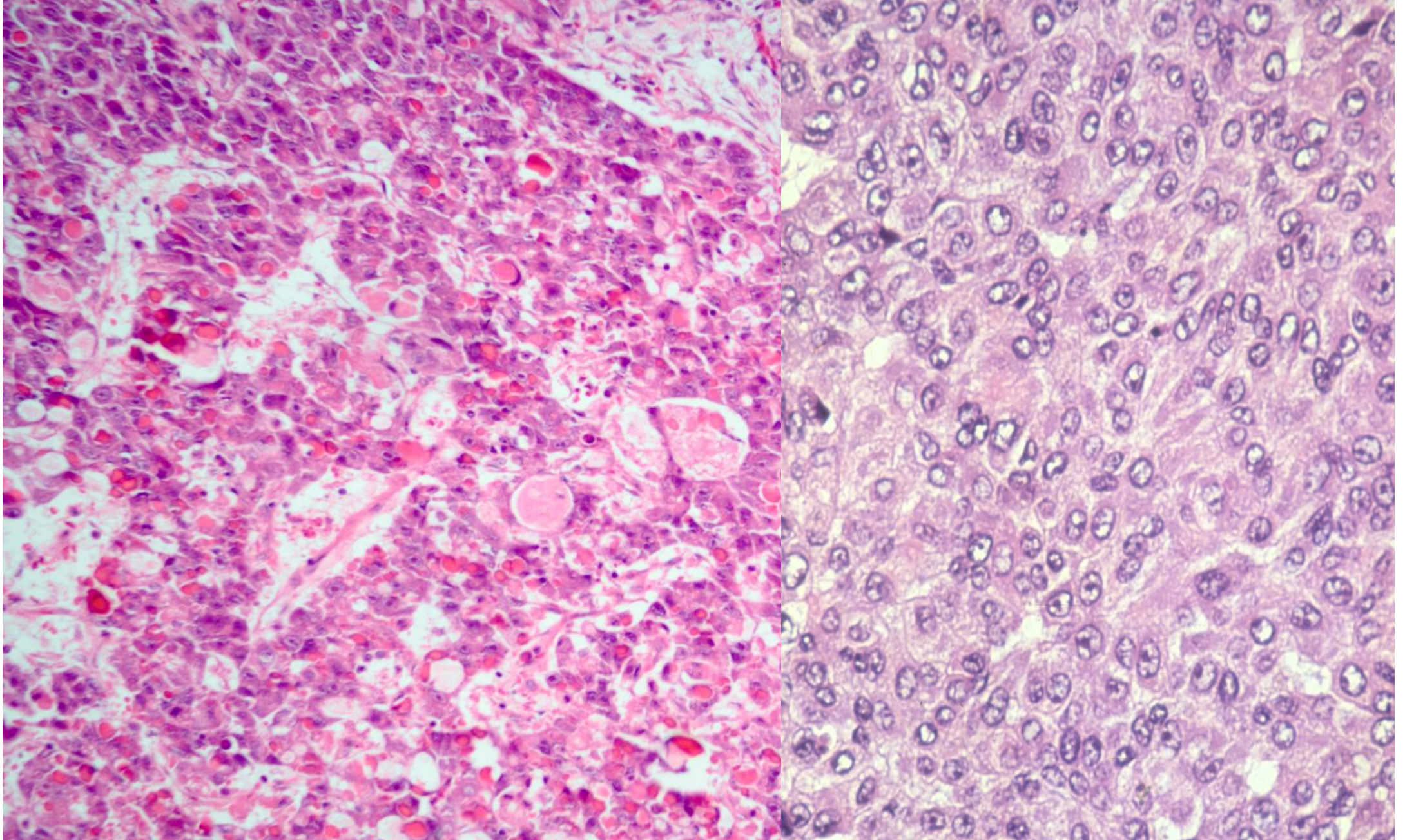
May be associated with hepatoid or glandular diff

YOLK SAC TUMOR, POLYVESICULAR VITELINE

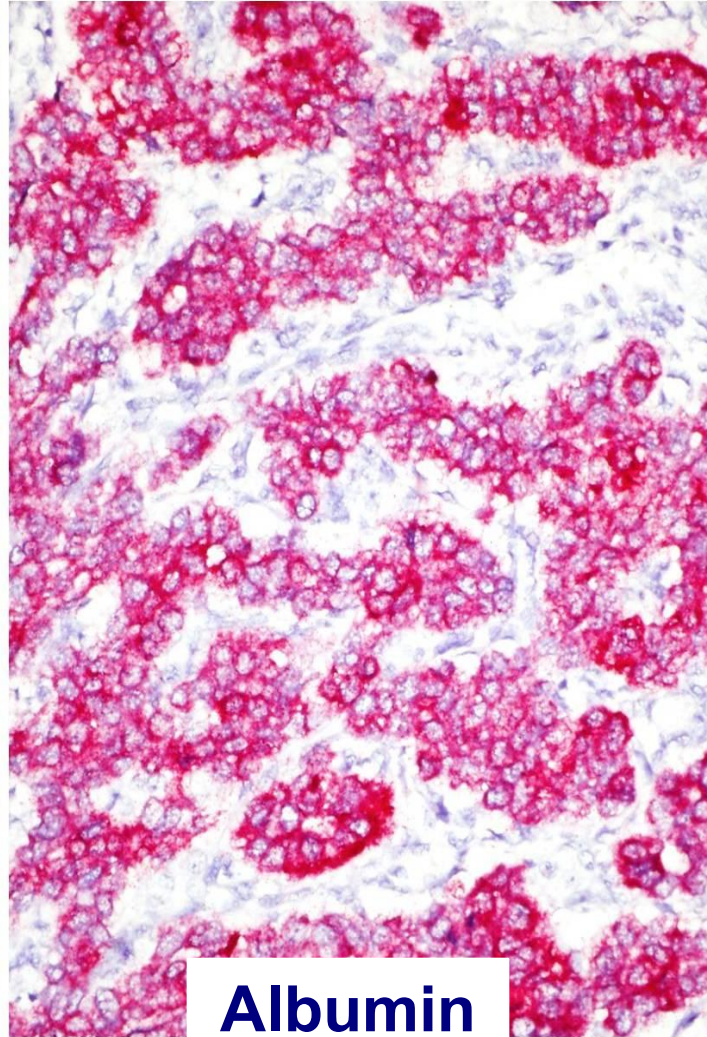
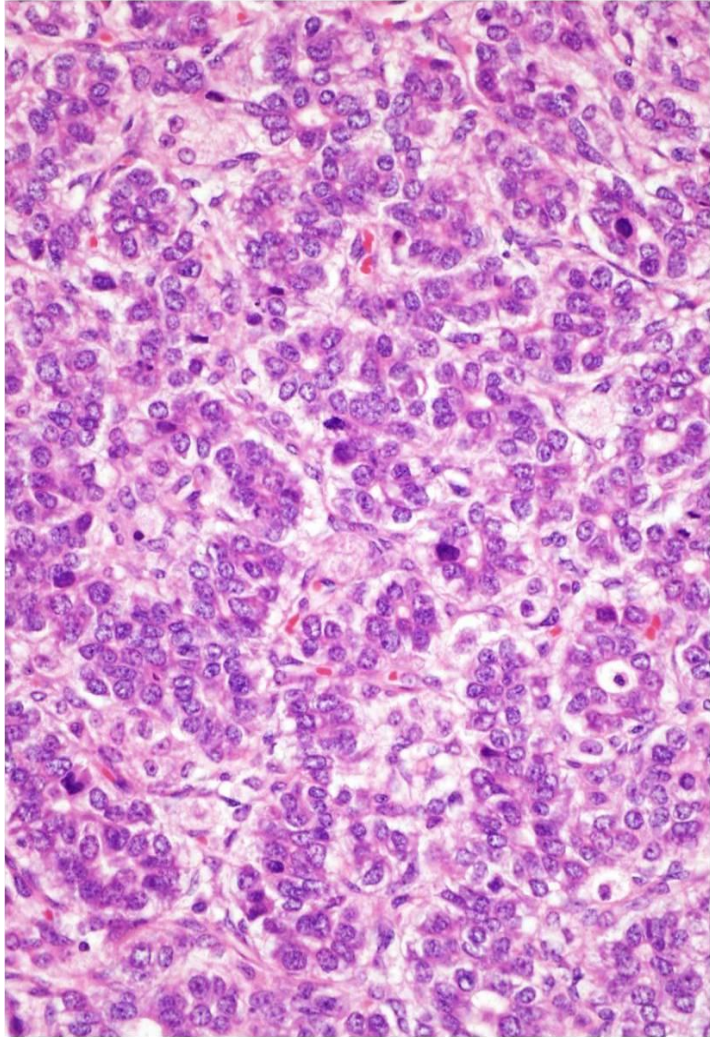


May be associated with a typical YST or rarely MCT

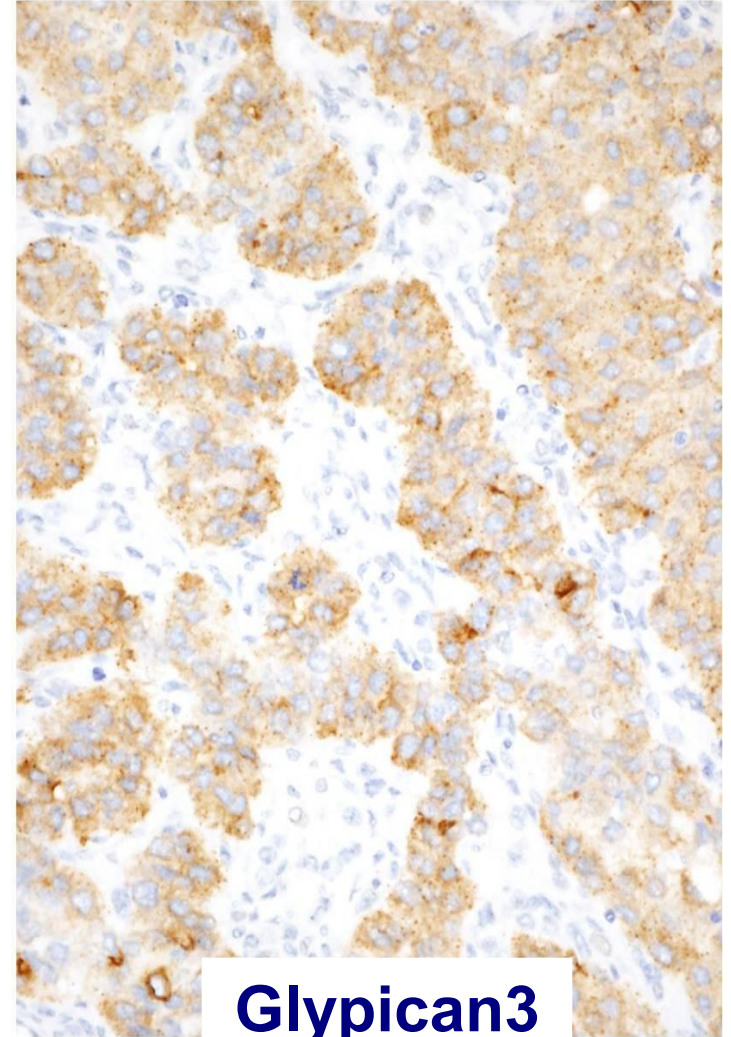
HEPATOID YOLK SAC TUMOR



HEPATOID YST



Albumin



Glypican3

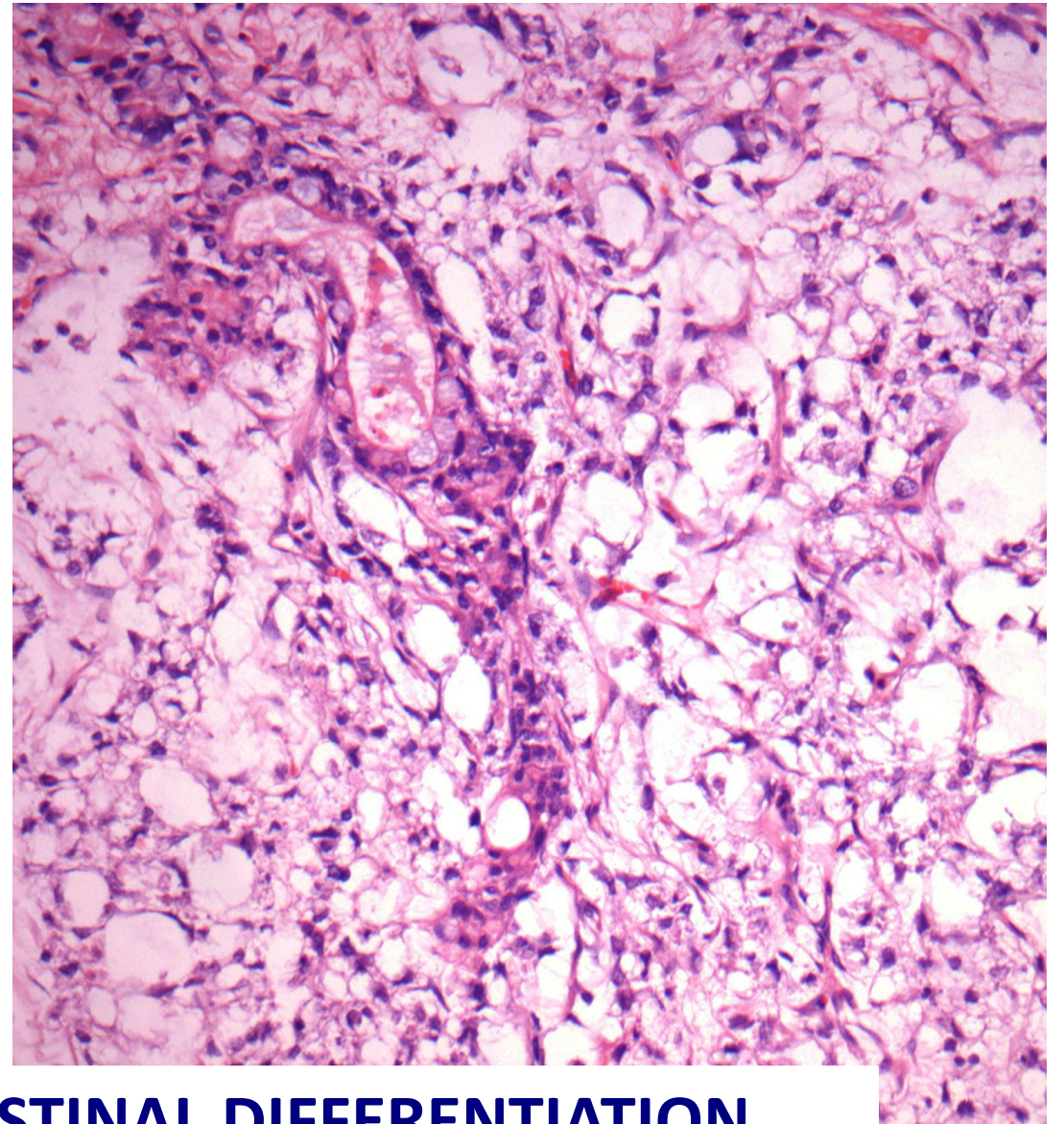
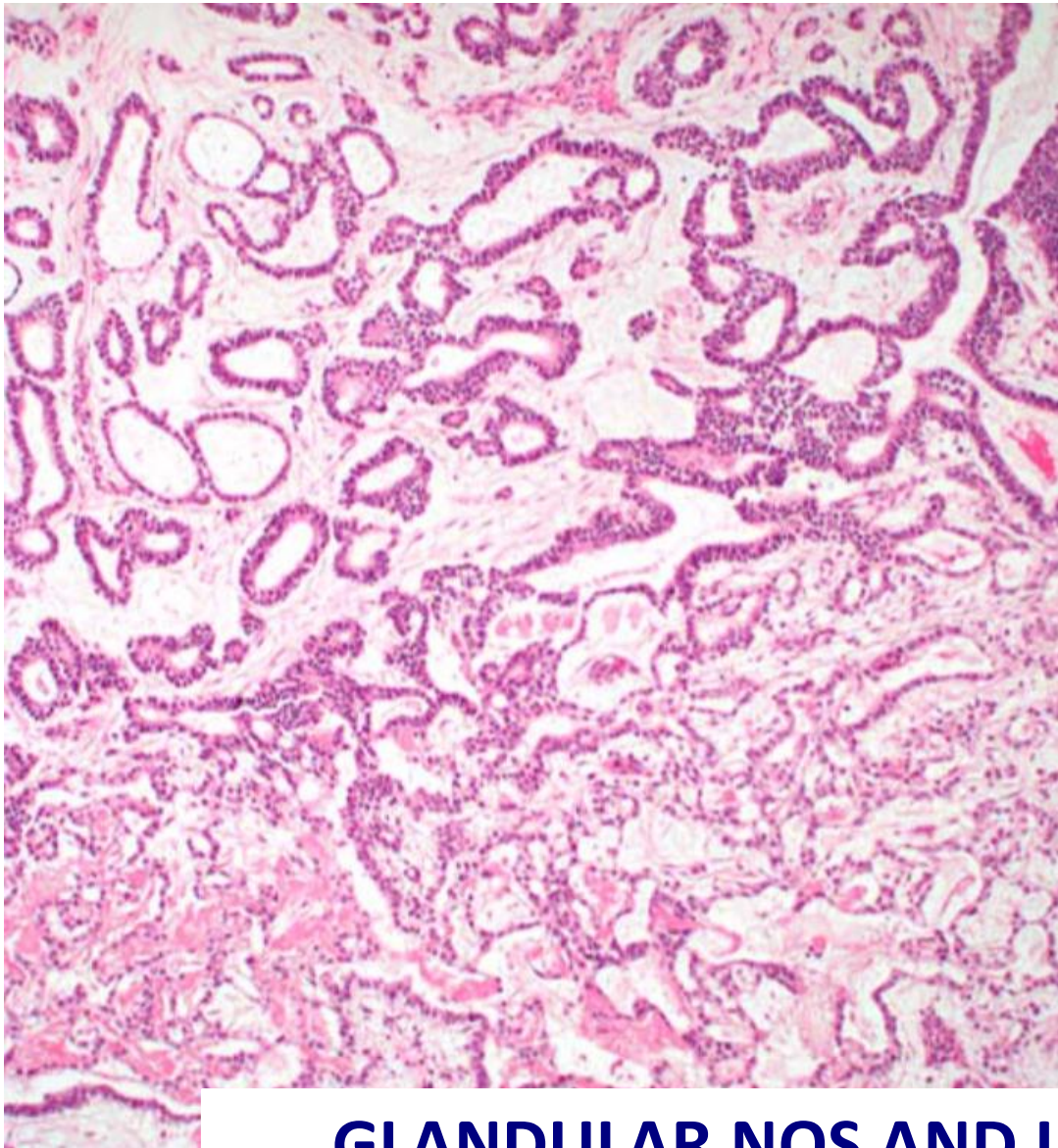
- Albumin, AFP, and Gly3 appear relatively sensitive markers for hepatoid differentiation in the appropriate morphologic context
- Glypican 3 not specific marker of hepatoid differentiation in gyn tract

Malignant Gonadal Germ Cell Tumors (Other Than Pure Germinoma) in Patients With Disorders of Sex Development

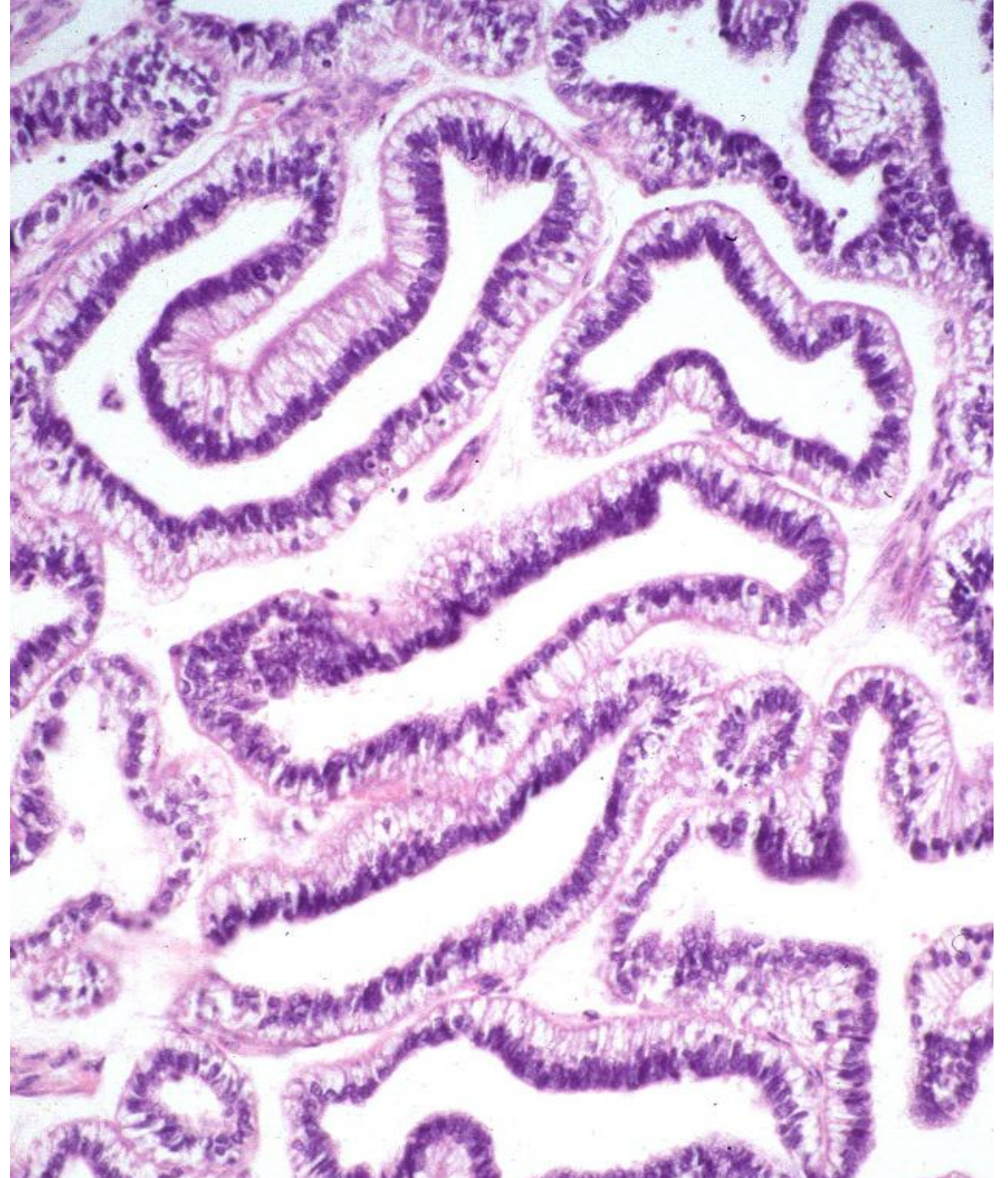
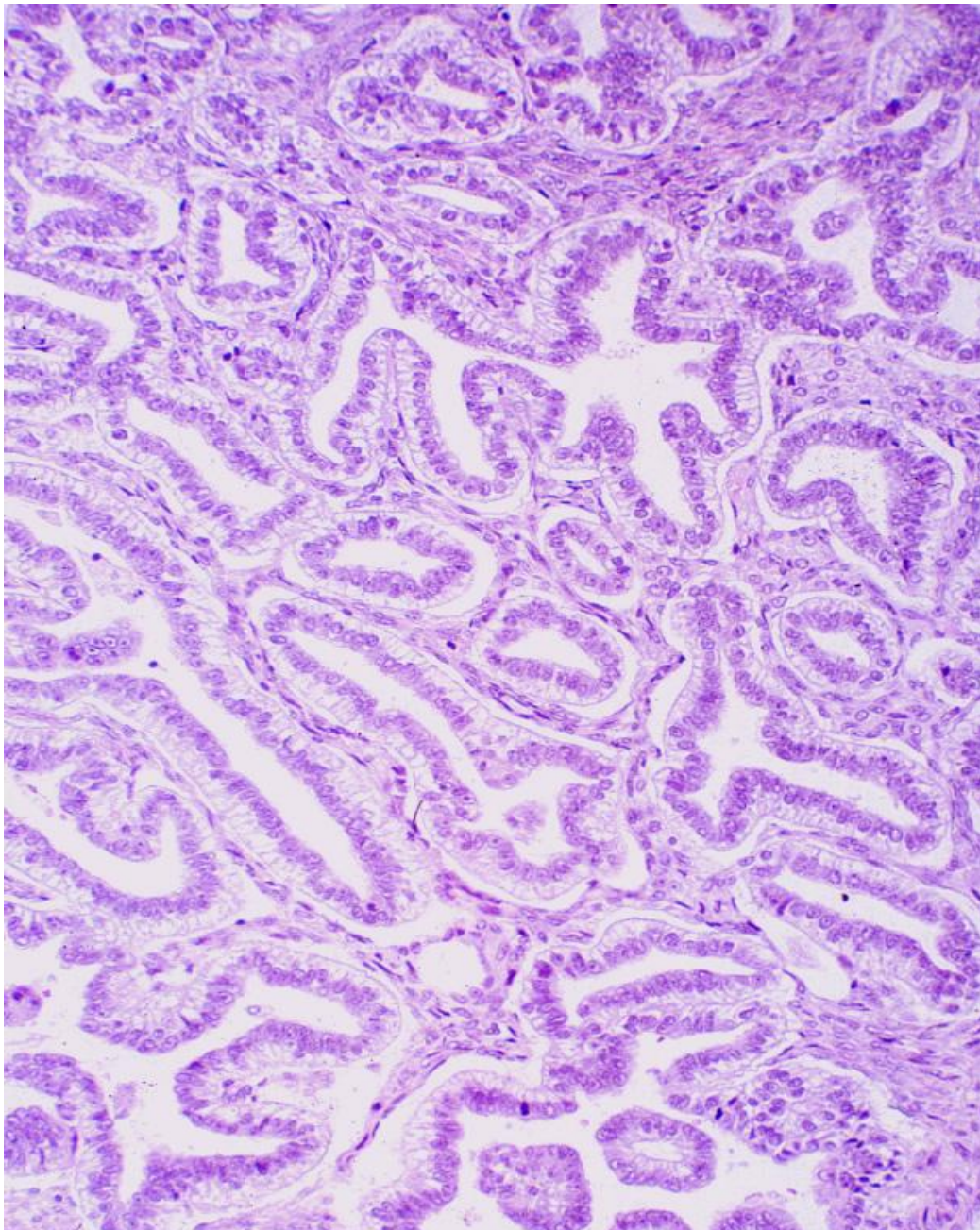
A Report of 21 Cases Based Largely on the Collection of Dr Robert E. Scully, Illustrating a High Frequency of Yolk Sac Tumor With Prominent Hepatoid and Glandular Features

Sheila E. Segura, MD, Robert H. Young, MD,† Esther Oliva, MD,† and Thomas M. Ulbright, MD**

- 20 phenotypic females with ambiguous genitalia/virilization and primary amenorrhea
- 46,XY (10/12; 83%) most common peripheral karyotype
- Gonadoblastoma, classic (70%), dissecting (5%), or combined (25%), identified in all but one
- Malignant germ cell tumors typically mixed except for 5 YSTs and 1 expansile gonadoblastoma with syncytiotrophoblast cells
- YST most common component if mixed (10) followed by germinoma (9), embryonal carcinoma (5), choriocarcinoma (4), immature teratoma (3), and teratoma (2)
- High frequency of YST with glandular (especially cystic) and hepatoid morphologies



GLANDULAR NOS AND INTESTINAL DIFFERENTIATION

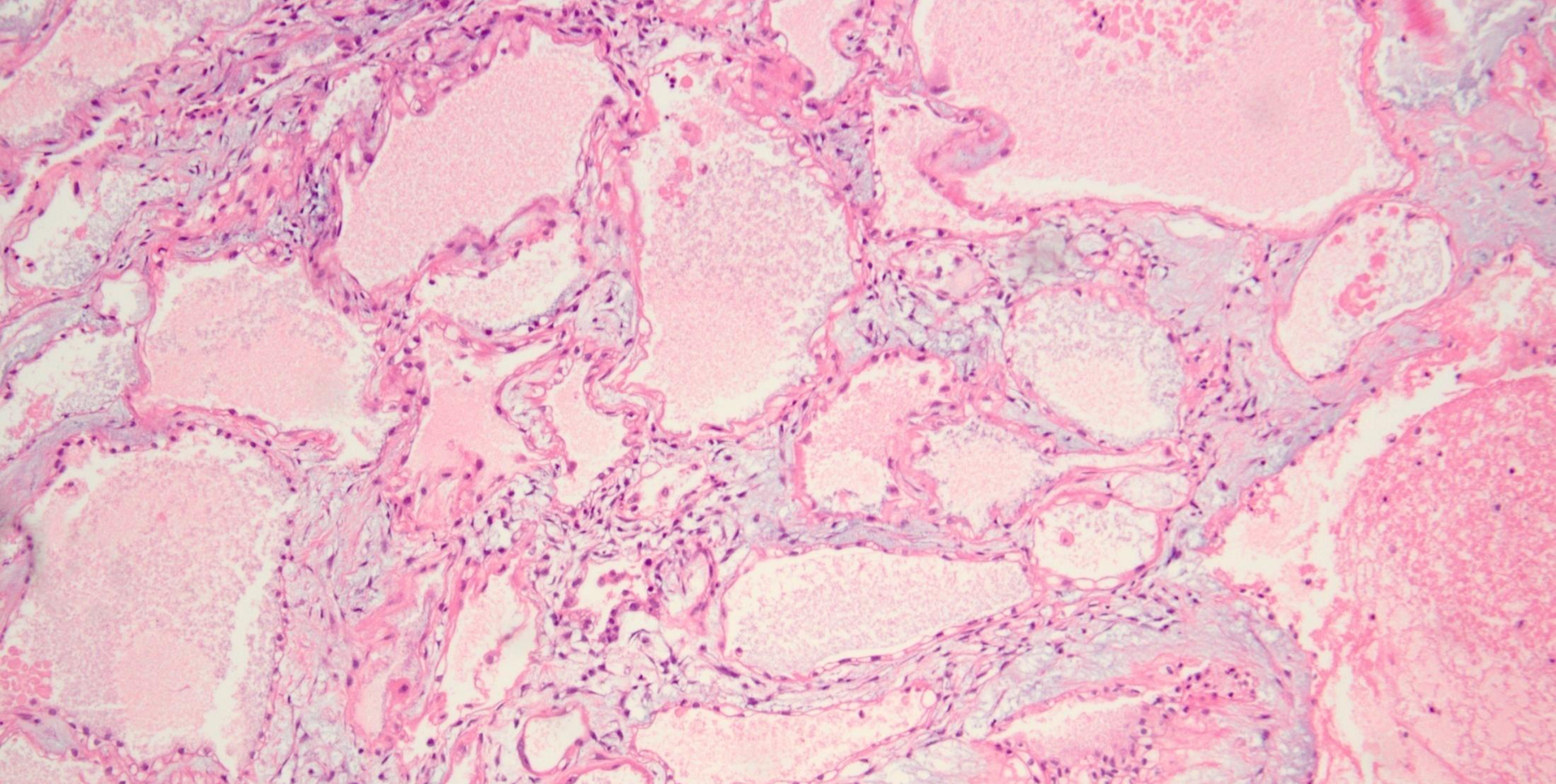


Endometrioid Yolk Sac Tumor

YOLK SAC TUMOR:

Differential Diagnosis

- **Clear cell carcinoma**
- **Endometrioid adenocarcinoma**
- **Sertoli-Leydig cell tumor**
- **Juvenile granulosa cell tumor**
- **Adenomatoid tumor**
- **Hepatocellular carcinoma**
- **Metastatic hepatocellular carcinoma**



Clear Cell Carcinoma mimicking Yolk Sac Tumor

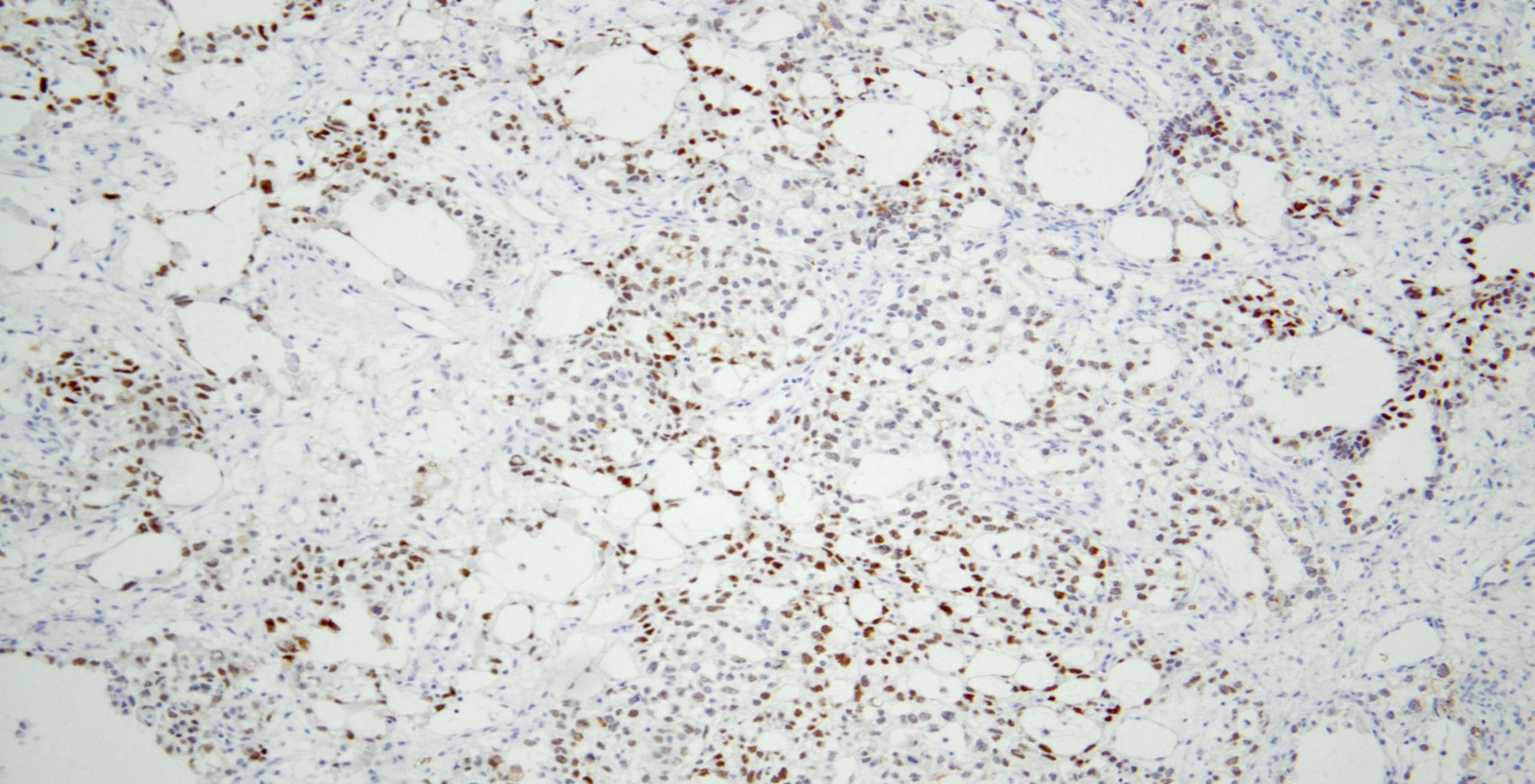
CCC**YST**

Age	>30	<30
Paraneoplastic Synd	+	-
↑ α-fetoprotein	-	+
Clear cells	+	+
Oxyphilic cells (Hepatoid)	+ (Oxyphilic)	+
Hobnail cells	+	-
Hyaline Globules	25%	+
Myxomatous background	-	+
Adenofibromatous backg	+	-
Endometriosis	+	-

Glypican-3 expression in primary/recurrent ovarian carcinomas

Stadlmann S et al. Int J Gynecol Pathol 2007;26:341

- **255 serous, 38 endometrioid, and 15 clear-cell carcinomas**
- **Expressed in 18% of ovarian carcinomas**
- **Strongly associated with clear-cell type**



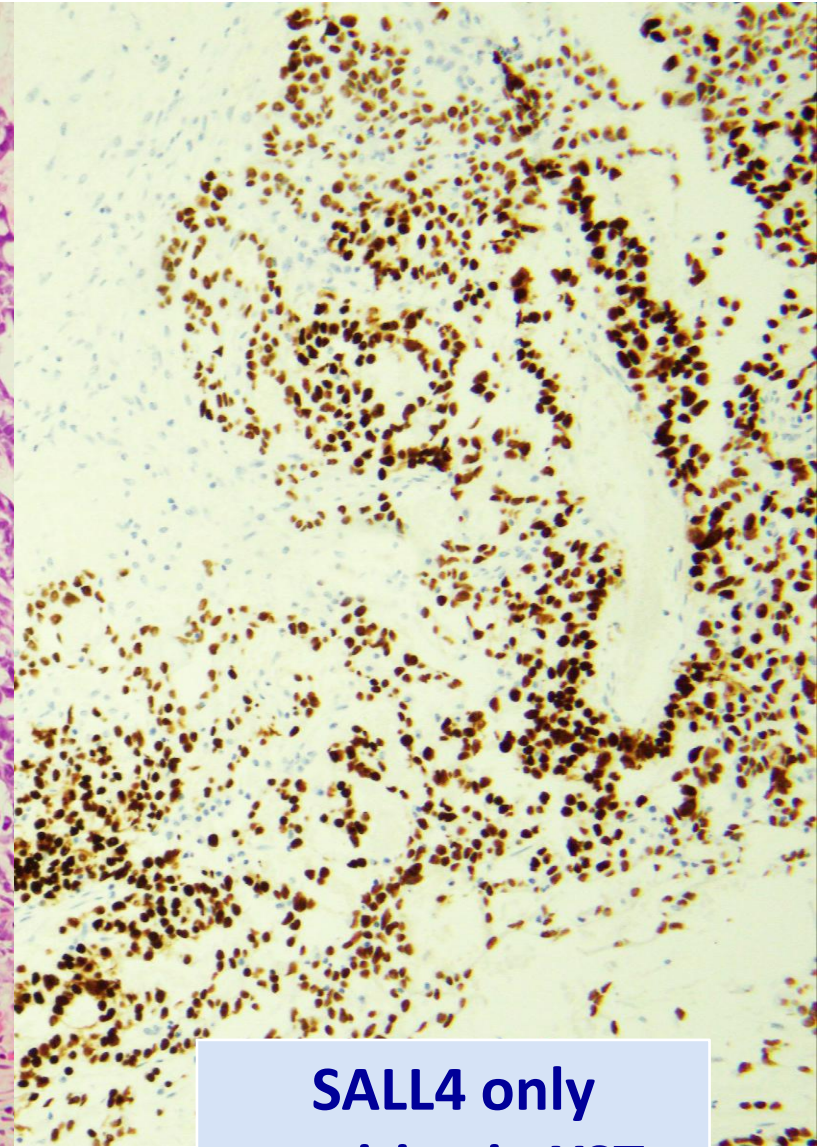
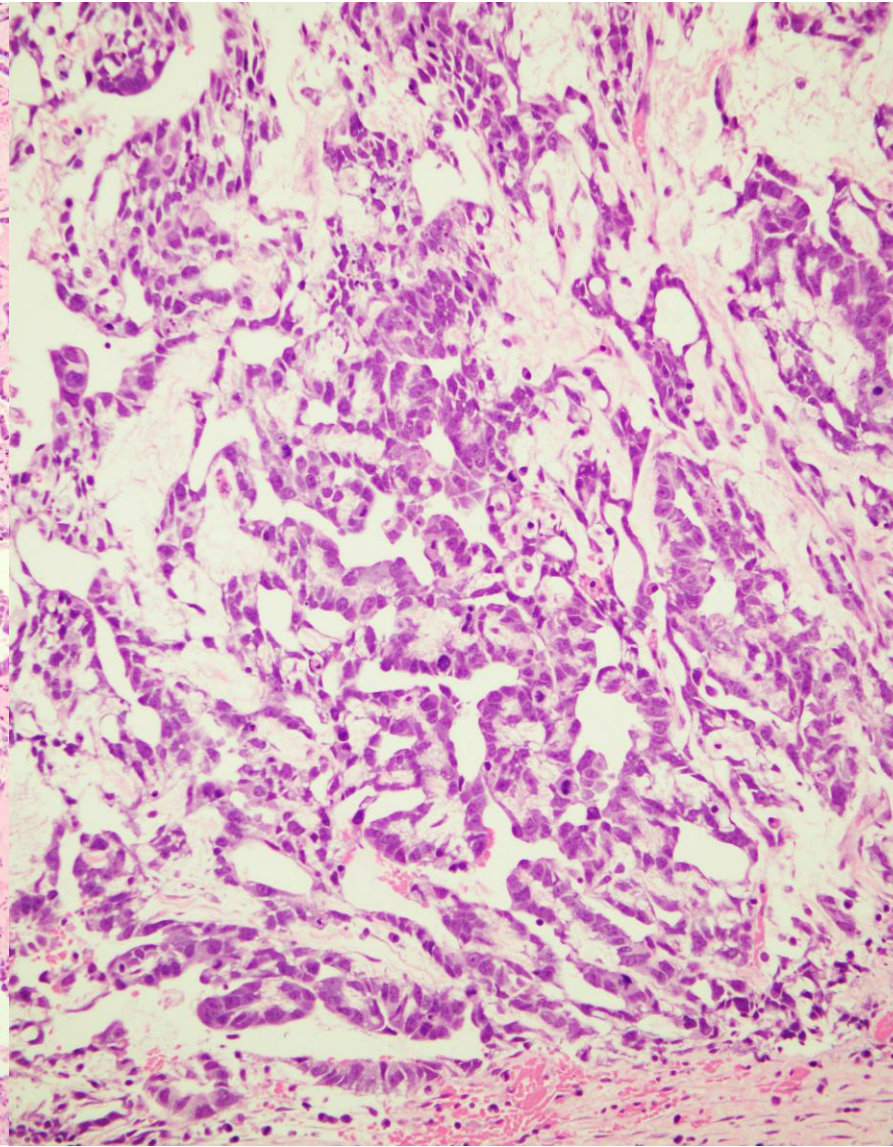
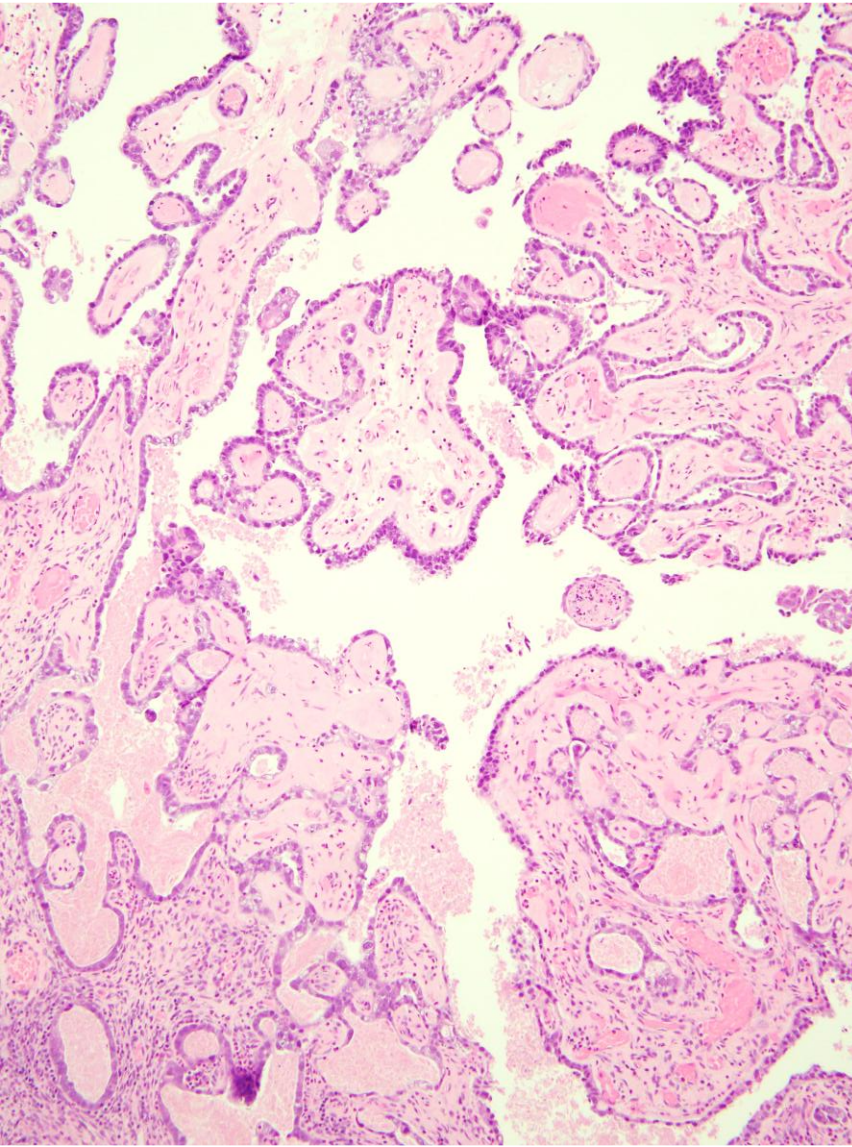
YST: HNF-1 β +, but napsin and racemase– (limited)

Ovarian Endometrioid Tumors with Yolk Sac Tumor Component, an Unusual Form of Ovarian Neoplasm: Analysis of Six Cases

Nogales FF et al, Am J Surg Pathol 1996

- **Peri- or postmenopausal women**
- **Substantial AFP elevation**
- **Frequent benign endometrioid tumors in ipsilateral or opposite ovary**
- **Frequently high stage**
- **Poor prognosis (poor response to chemotherapy)**

CLEAR CELL CARCINOMA AND SOMATIC YOLK SAC TUMOR



**SALL4 only
positive in YST**

Malignant tumours of the uterus and ovaries with Mullerian and germ cell or trophoblastic components have a somatic origin and are characterised by genomic instability*

Andres M Acosta,¹  Lynette M Sholl,² Paola D Cin,³ Brooke E Howitt,⁴ Christopher N Otis⁵ & Marisa R Nucci¹

¹*Women's and Perinatal Pathology, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School,* ²*Molecular Pathology, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School,*

³*Cytogenetics, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA,*

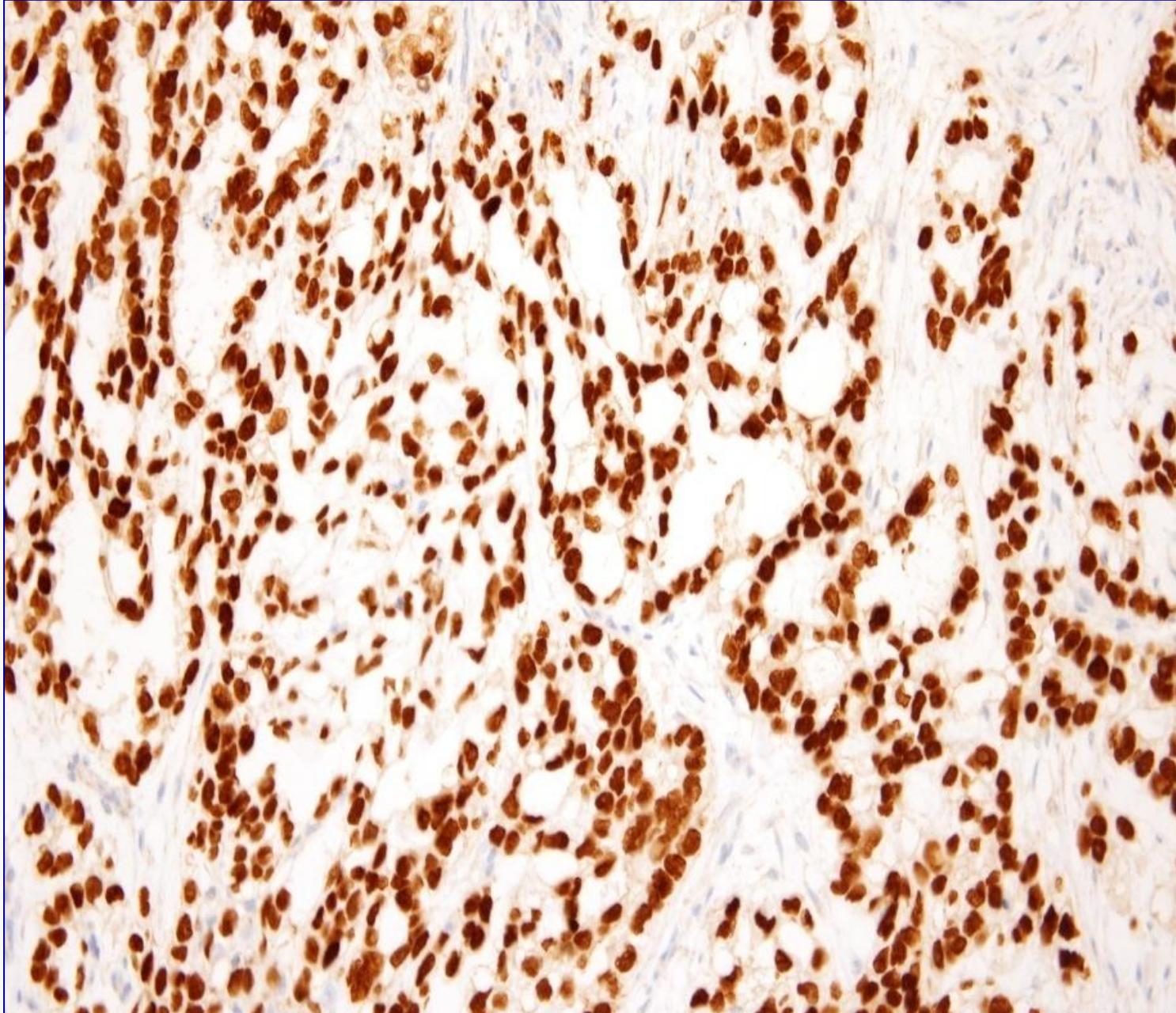
⁴*Department of Pathology, Stanford Medical Center, Stanford University, Palo Alto, CA, and* ⁵*Department of Pathology, University of Massachusetts Medical School–Baystate, Springfield, MA, USA*

YST

EC

- **CK7** - +
- **EMA** - +
- **Glypican 3** + +/-
- **SALL4** + - (exceptions)
- **PAX8** - (25% +) +

Y O L K S A C T U M O R



SALL4 more sensitive than AFP and Glypican 3 to separate YST from EEC and CCC.....

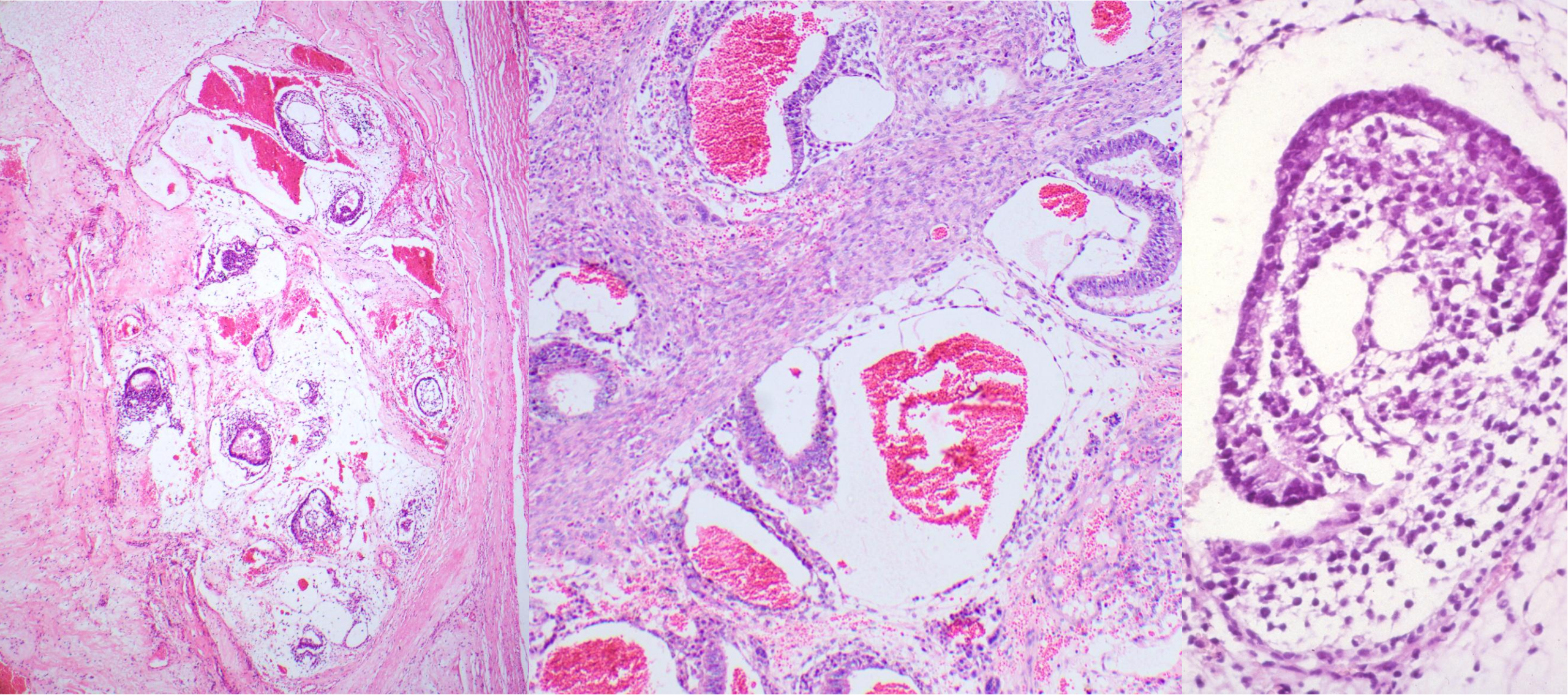
SALL4

Expressed in many high-grade tumors
most frequently undifferentiated/ dedifferentiated
carcinomas (12/30), serous (7/22) and endometrioid
carcinomas (5/26), and carcinosarcomas (both
components)

Expressed in DICER1 related sarcomas

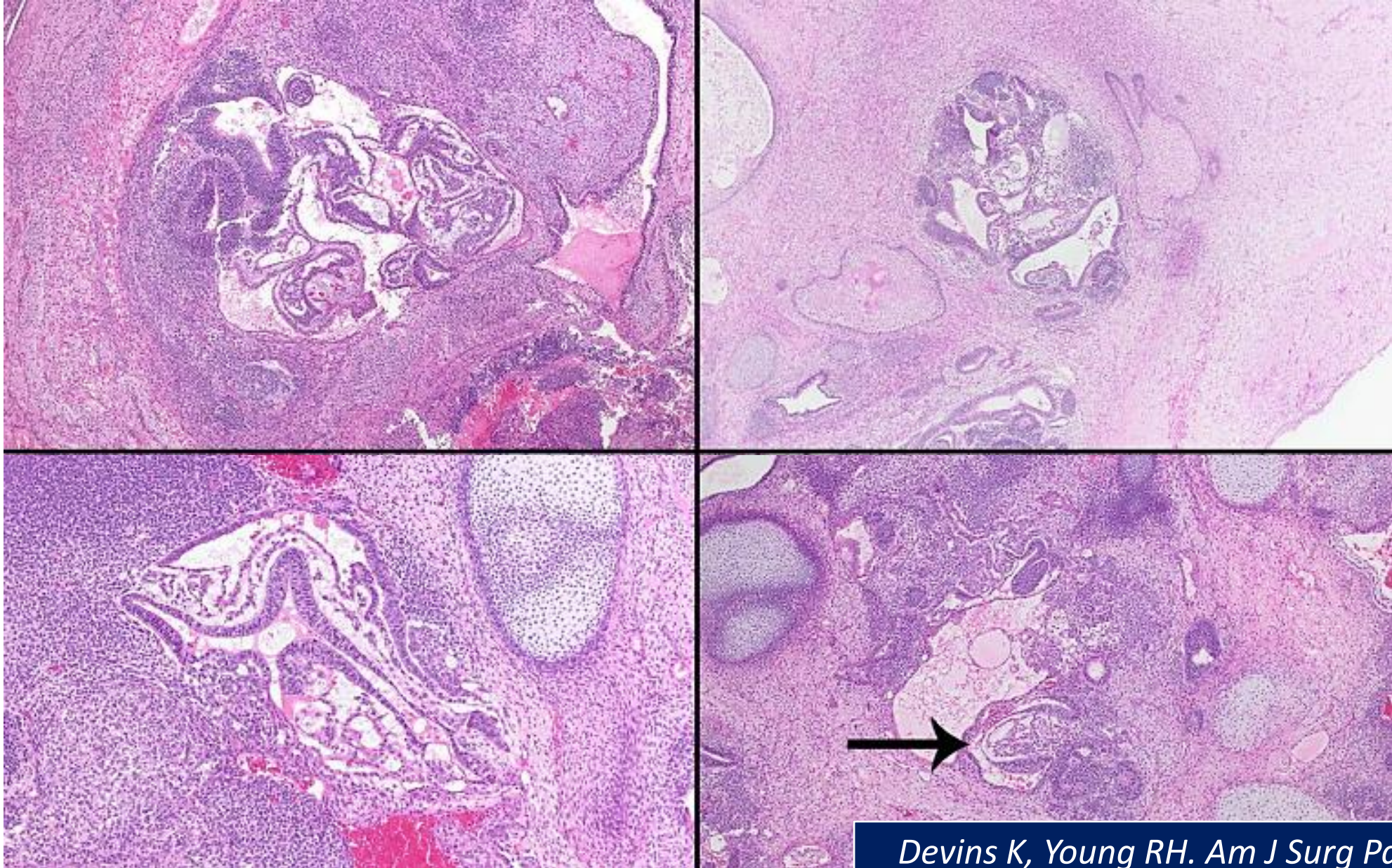
Int J Gynecol Pathol 2023;42:443-450
Hum Pathol 2022;123:46-58

POLYEMBRYOMA



ORIGIN: Most immature form of immature teratoma (as embryoid body recapitulates embryonic life days 13 to 18 of gestation) or mixed germ cell tumor?

POLYEMBRYOMA BACKGROUND/REMNANTS



Malignant Mixed Germ Cell Tumors of the Ovary

An Analysis of 100 Cases Emphasizing the Frequency and Interrelationships of Their Tumor Types

Nida S. Safdar, MD, Jennifer N. Stall, MD, and Robert H. Young, MD

Most common tumor type was yolk sac tumor (91%), followed by dysgerminoma (61%), immature teratoma (58%), embryonal carcinoma (38%), and choriocarcinoma (11%)

Admixture of:

- 
- **Dysgerminoma and yolk sac tumor (25%); 2 components often being sharply demarcated**
 - **Immature Teratoma and yolk sac tumor (20%)**
 - **Yolk sac tumor and embryonal carcinoma +/-immature teratoma (16%)**

Pure embryonal carcinoma or choriocarcinoma are rare!

COMMON MARKERS IN GERM CELL TUMORS

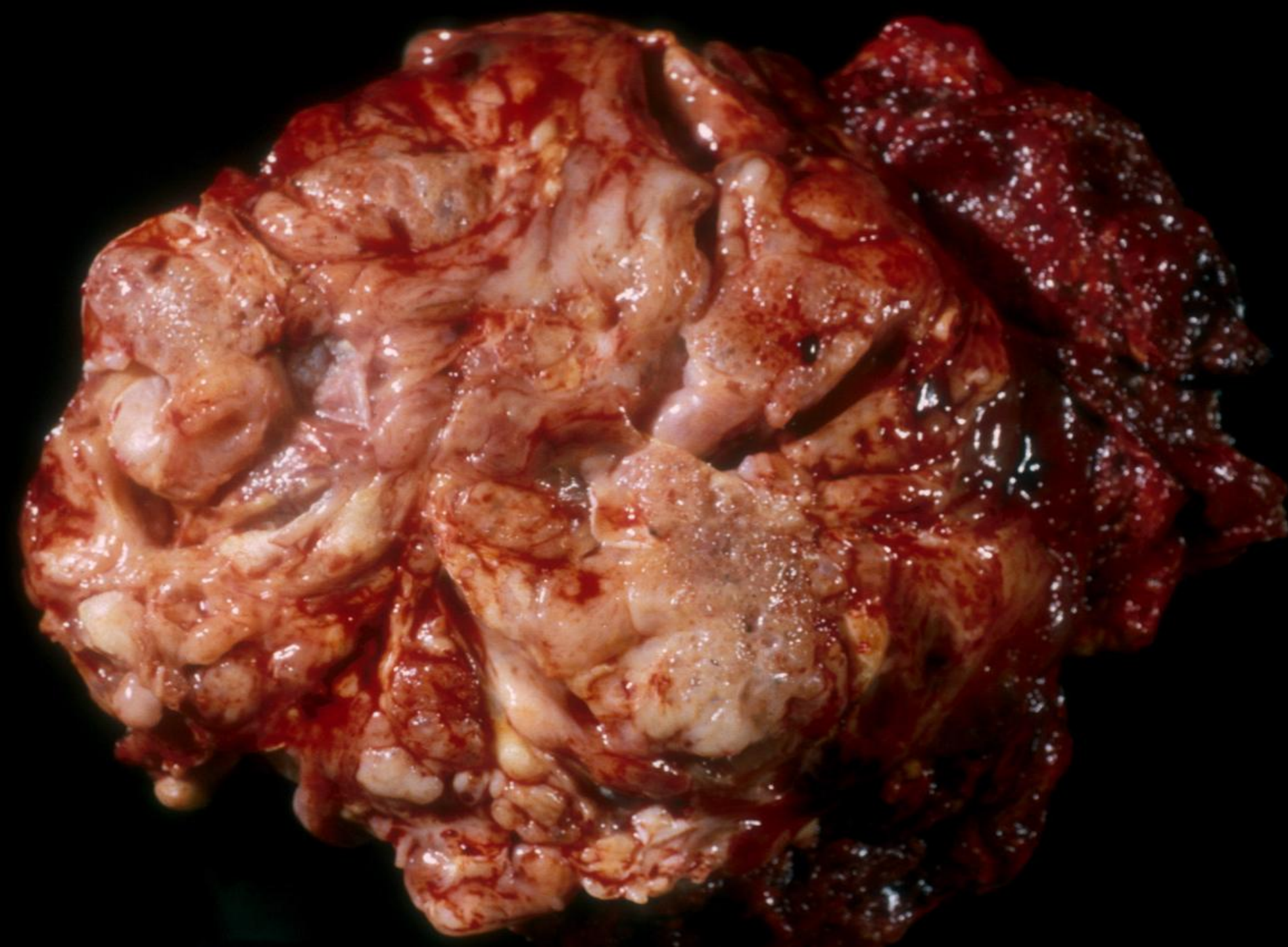
	<u>Dysgerminoma</u>	<u>EC</u>	<u>YST</u>
AE1/3	Variable	+	+
PLAP	+	+	+
OCT4	+	+	-
c-Kit	+	-	Variable
D2-40	+	-/+	-
Glypican 3	-	Variable	+
CD30	-	+	-
SALL4	+	+	+
AFP	-	Variable	Variable

TERATOMAS: Classification

- **Immature teratoma**
- **Mature teratoma, solid**
- **Mature teratoma, cystic**
 - **With secondary malignancy**
- **Monodermal teratomas**
 - **Struma ovarii**
 - **Carcinoid tumors**
 - **Neuroectodermal tumors**
 - **Others**

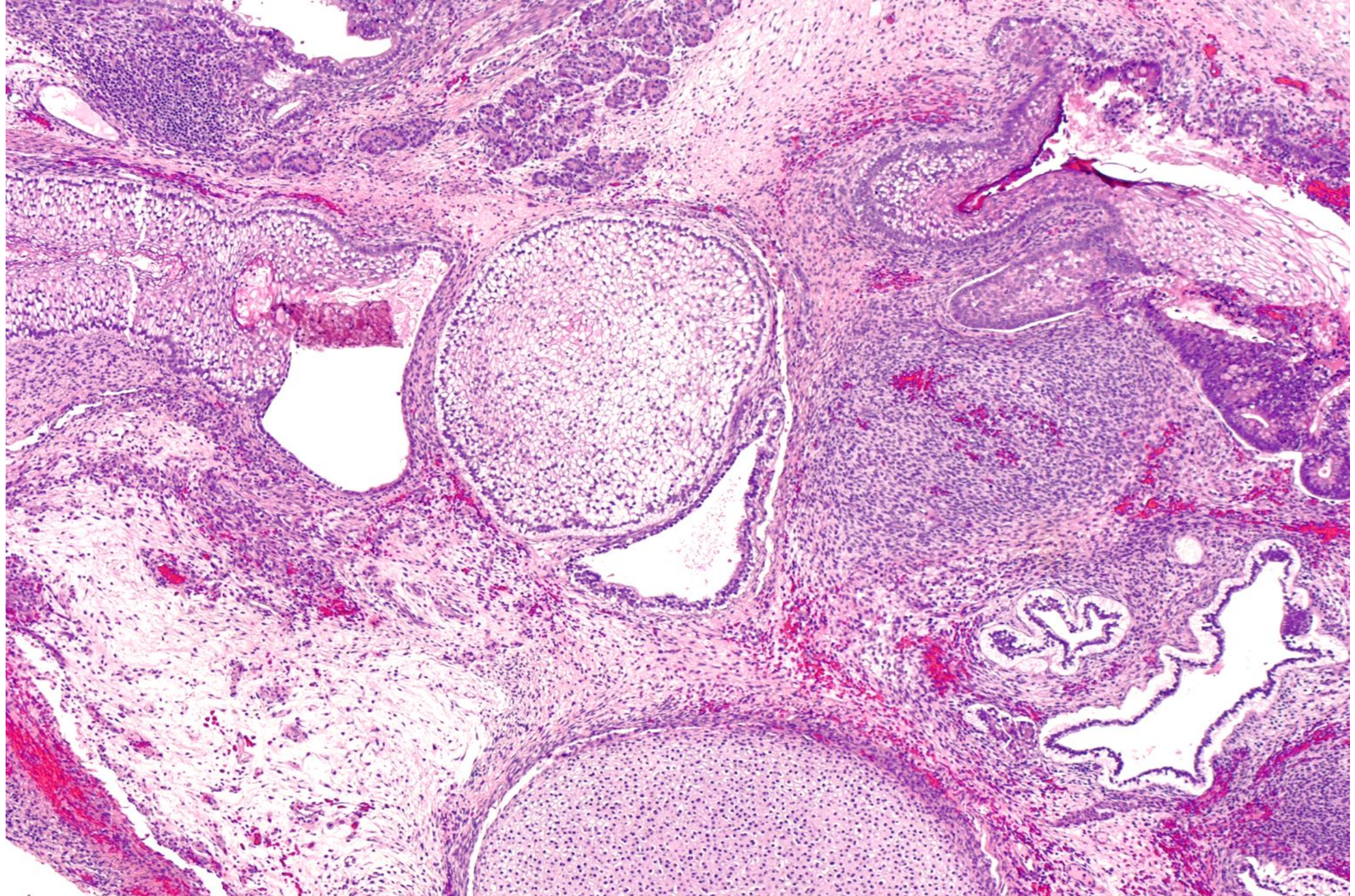
IMMATURE TERATOMA

- **< 20% of primitive germ cell tumors**
- **Only ~ 3% of all teratomas**
- **↑ AFP levels (< YSTs) and CA-125**
- **Relationship with dermoid cysts:**
 - **may coexist in same ovary (26%)**
 - **may coexist in contralateral ovary (10%)**
 - **ipsilateral dermoid cyst priorly resected: in such patients increased risk of IT if dermoid bilateral, multiple, or ruptured**



IMMATURE TERATOMA

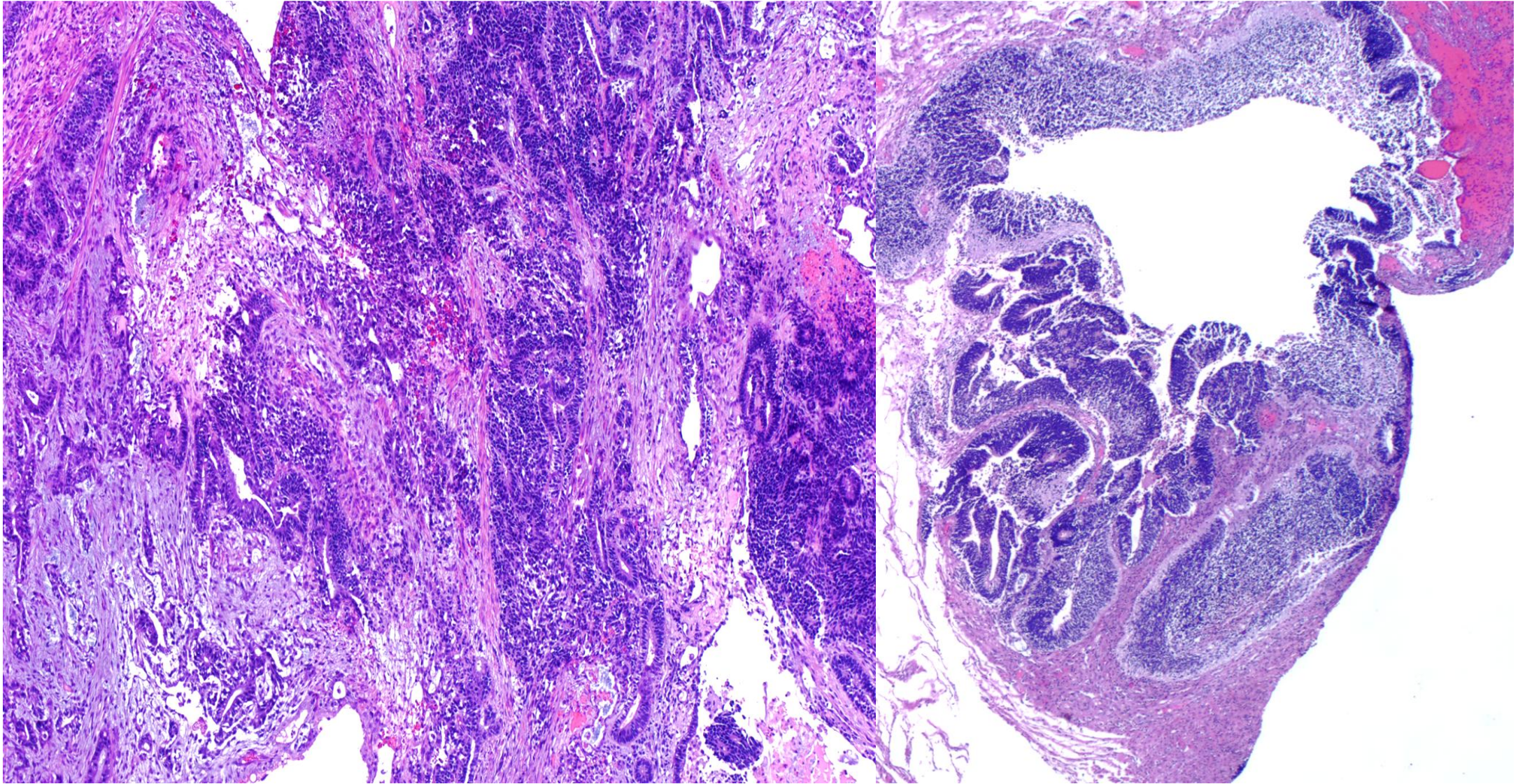
**A mature
cystic
component
seen in ~25%**



IMMATURE TERATOMA

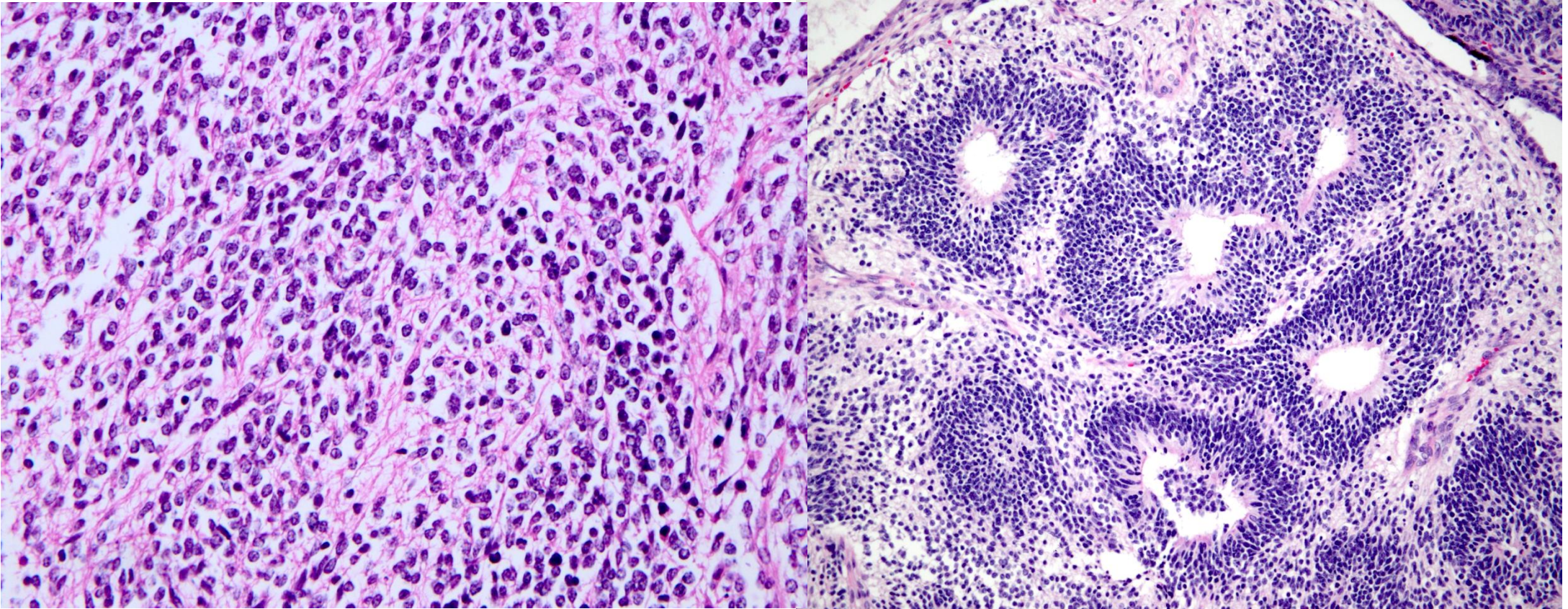
- Tissues from all 3 germ cell layers
- Variable admixture of mature and immature tissues, latter resembling normal embryo
- Presence of immature tissue establishes diagnosis of immature teratoma
- Most common immature element is neuroepithelium, with other common immature elements including immature epithelium or cartilage

IMMATURE TERATOMA: GRADING



Immaturity = Amount of immature neural tissue

IMMATURE TERATOMA: GRADING



**Cellular foci of mitotically
active glia**

**Neuroepithelial rosettes
and tubules**

**... foci resembling glioblastoma or neuroblastoma, but not
overt overgrowth**

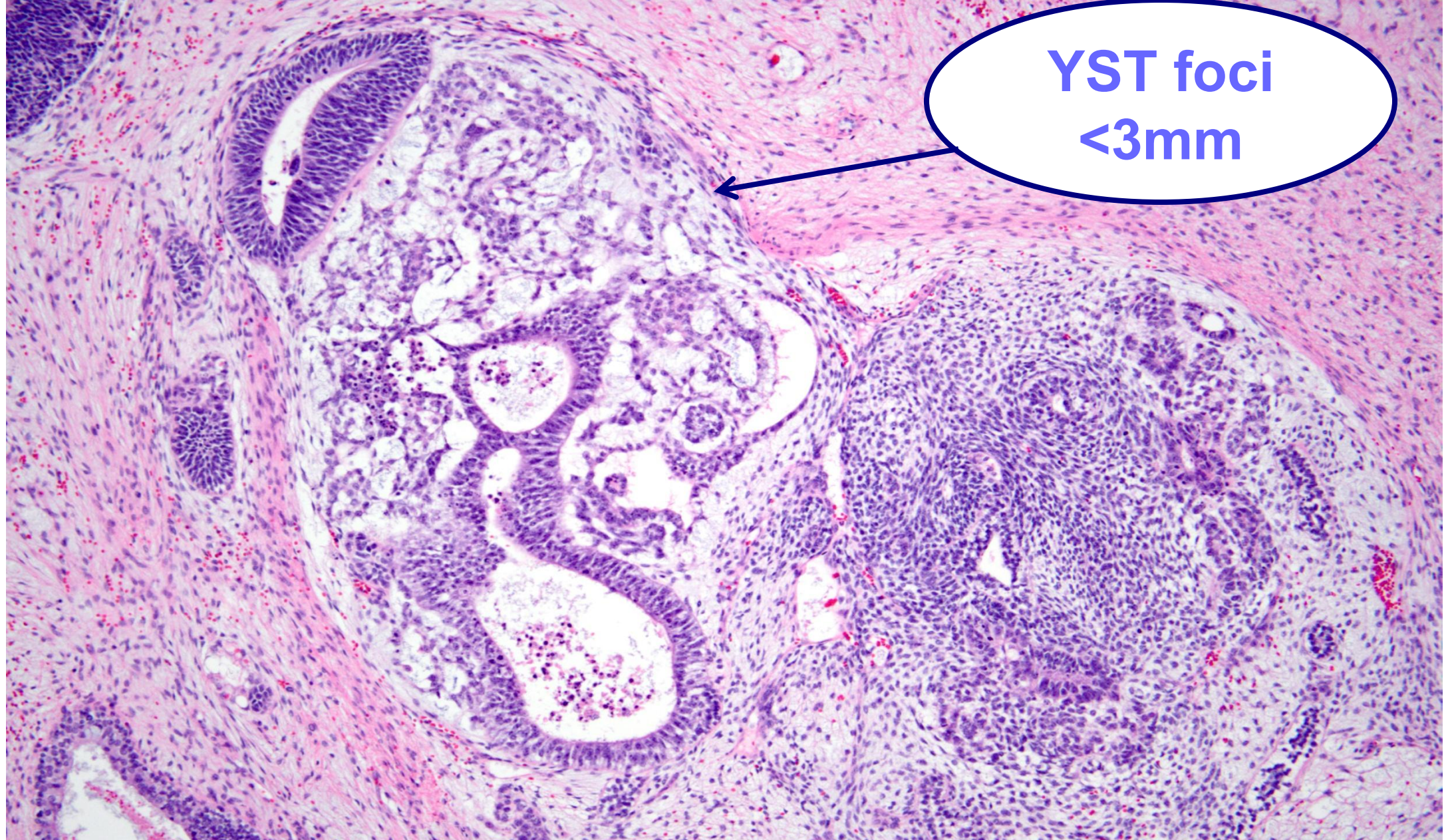
IMMATURE TERATOMA

Grading System

- Amount of immature neuroectodermal tissue
 - GRADE 1: < 1 low-power-field in any one slide
 - GRADE 2: Between 1 and 3 low-power-fields in any one slide
 - GRADE 3: > 3 low-power-fields in any slide
- More recently divided in two-grade system that correlates with prognosis (grade I and II-III)

**EXTENSIVE SAMPLING
IMPORTANT TO IDENTIFY
IMMATURE NEURAL TISSUE**

Typically gross appearance
correlates with teratoma
subtype



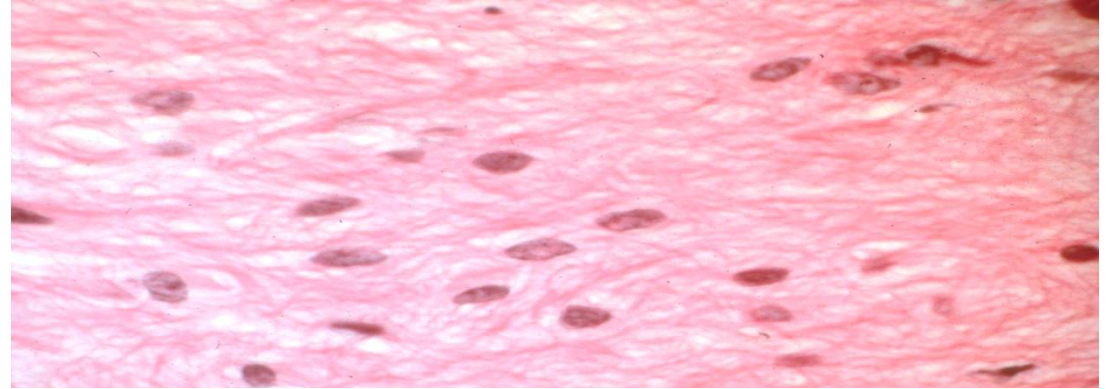
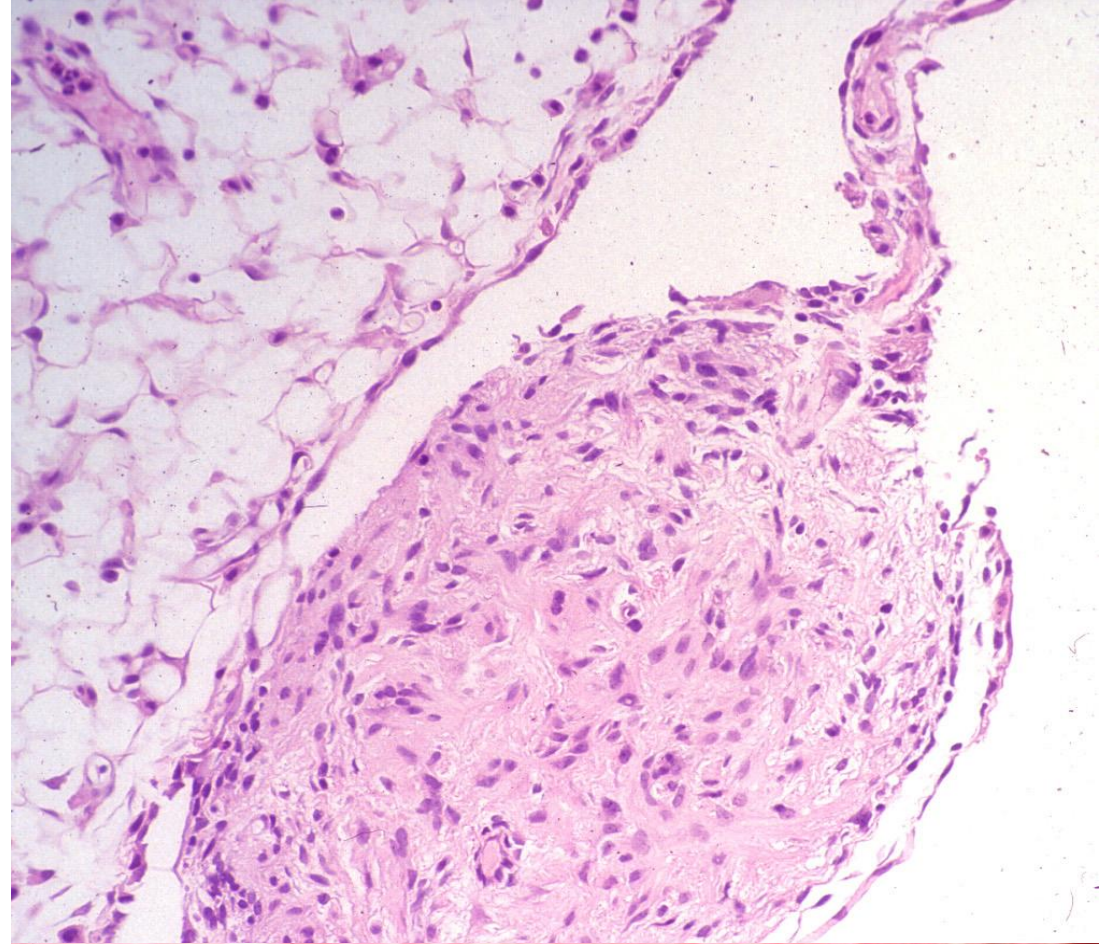
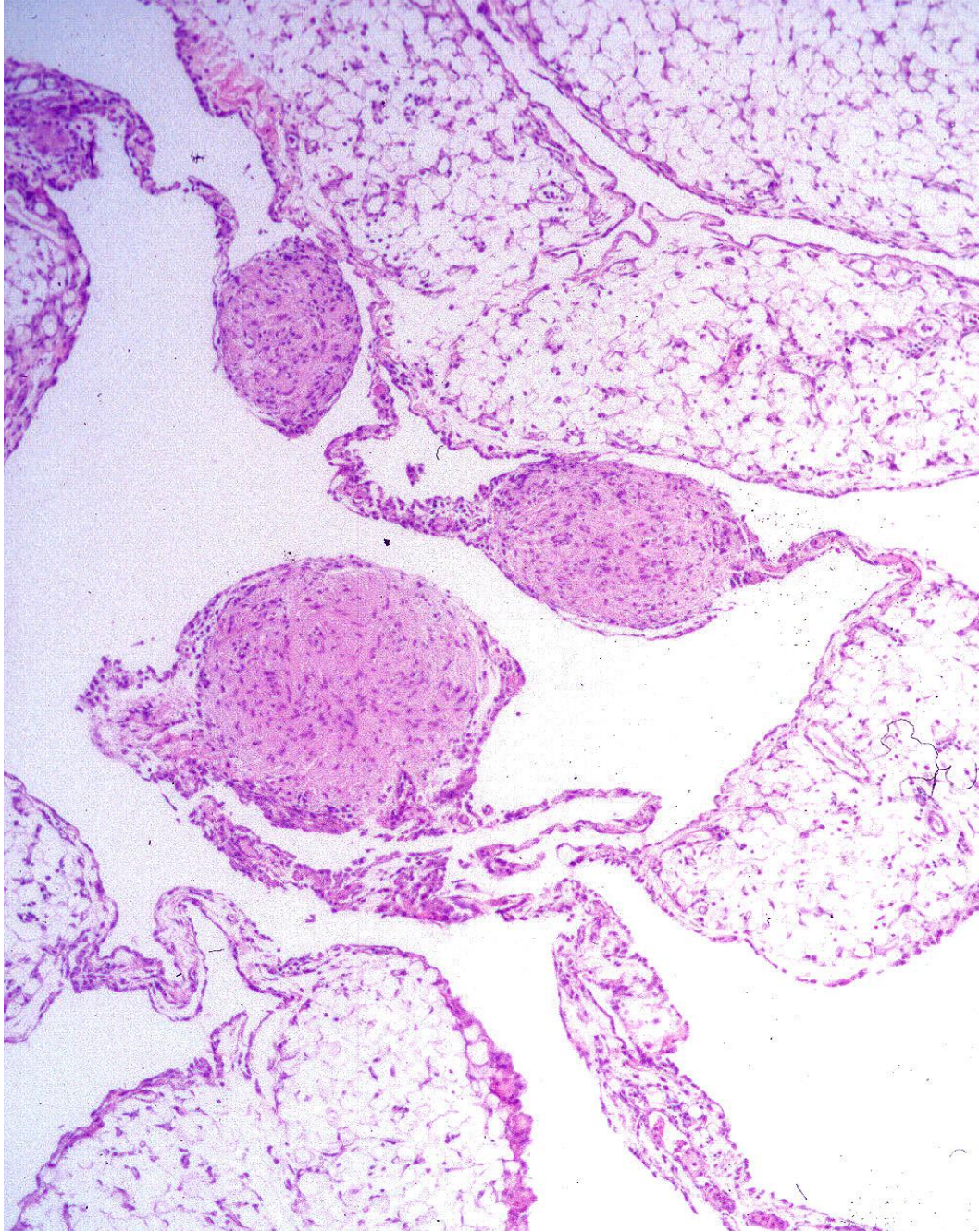
IMMATURE TERATOMA: Associated Findings

IMMATURE TERATOMA

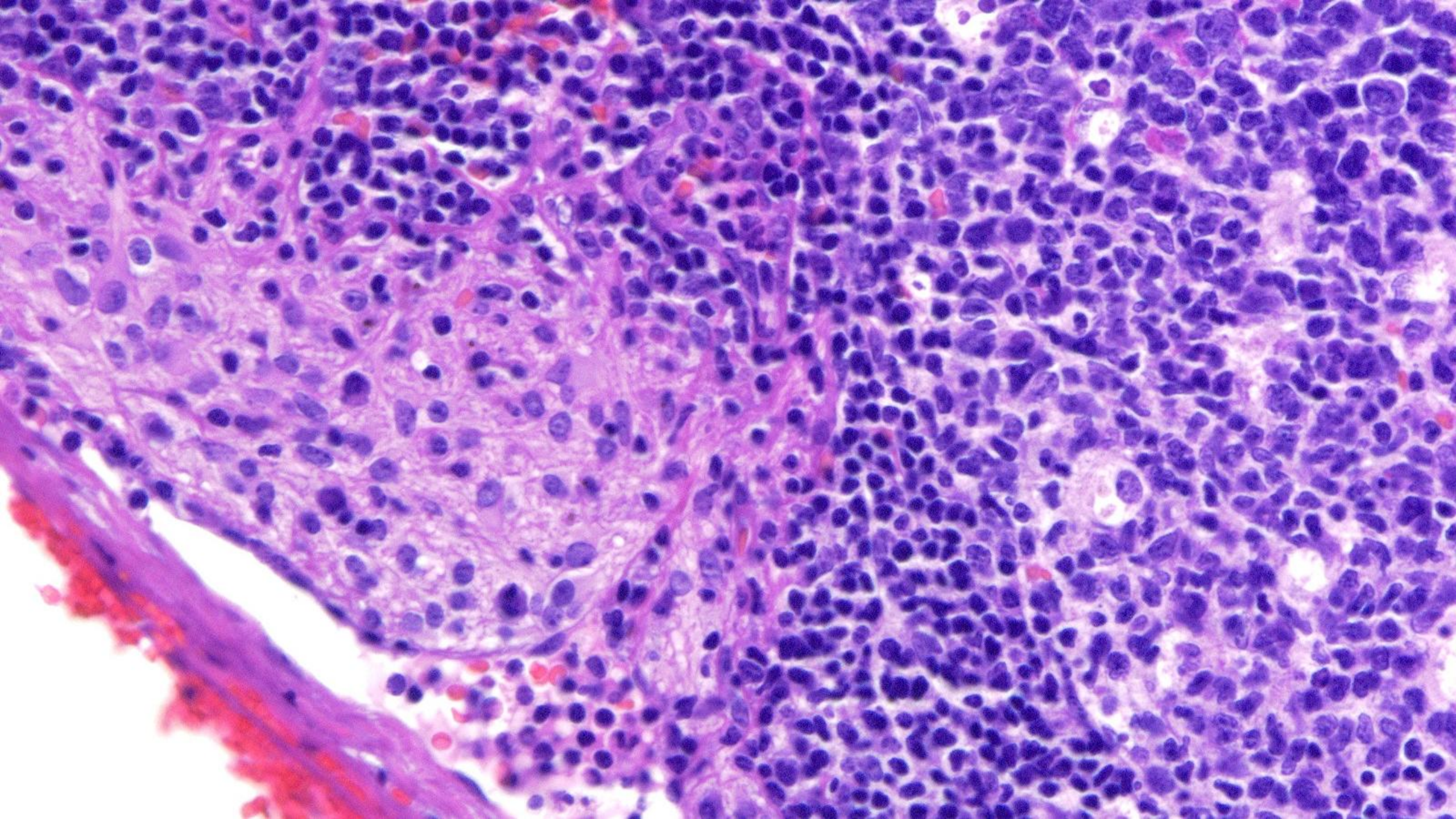
Associated Findings

Peritoneal Gliomatosis:

- Exclusively or predominantly mature glial tissue
- May also be seen in omentum and lymph nodes
- Sometimes intimately associated with endometriosis
- Two theories to explain its origin:
 - A) Secondary to rupture of teratoma
 - B) Metaplasia from submesothelial cells in response to unknown stimuli



Mature glial implants do not affect prognosis

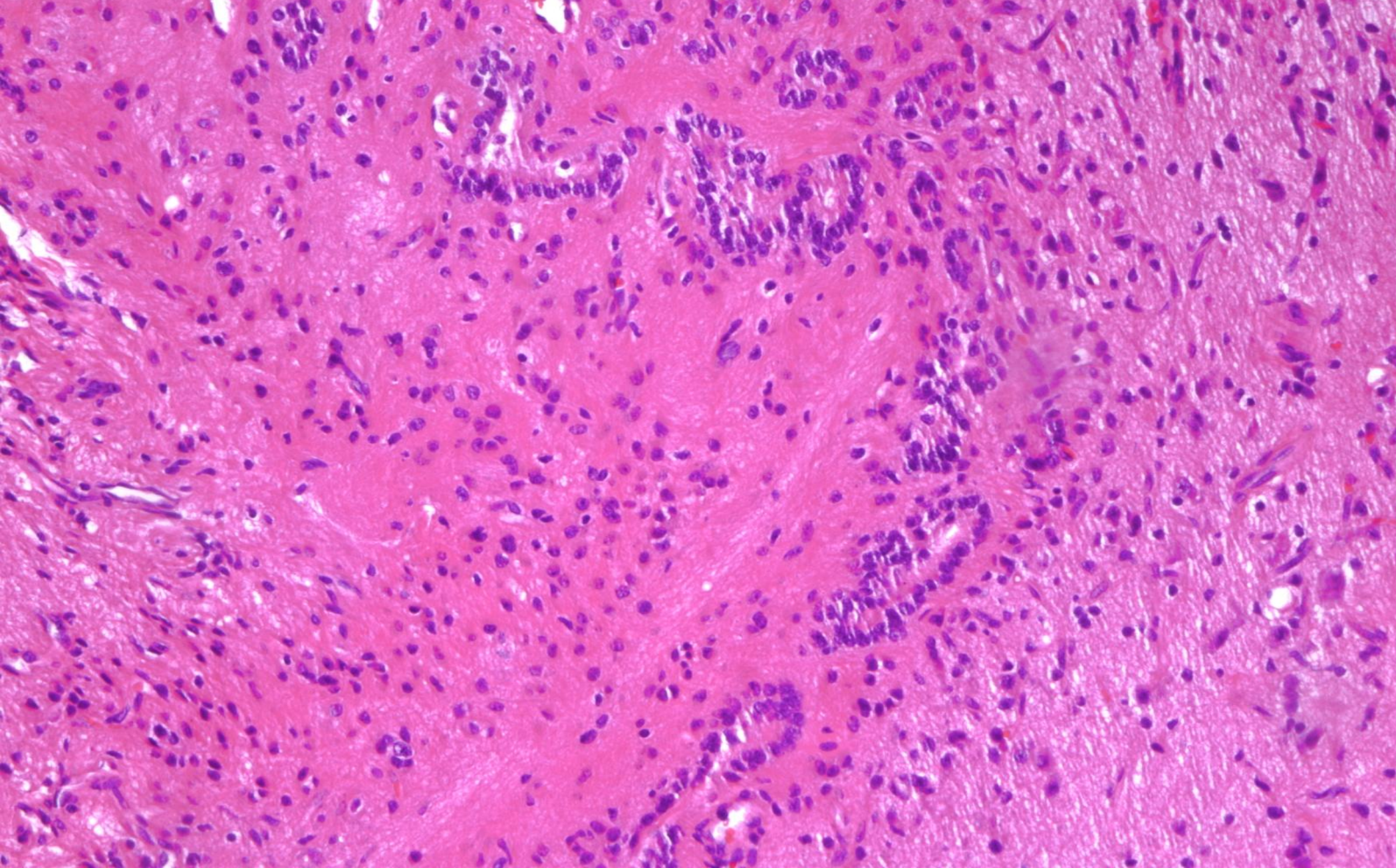


IMMATURE TERATOMA

Differential Diagnosis

- Mature solid teratoma
- Mature cystic teratoma with microscopic immature foci
- Yolk sac tumor (if ↑AFP or predominance of endodermal elements)
- Sertoli-Leydig cell tumor –heterologous (no neural tissue)
- Carcinosarcoma (neural tissue exceptional in contrast to IT)
- Neuroectodermal tumor (if predominance of neural tissue in IT)

MCT with IMMATURE NEURAL ELEMENTS



**TYPICAL
GROSS!!**

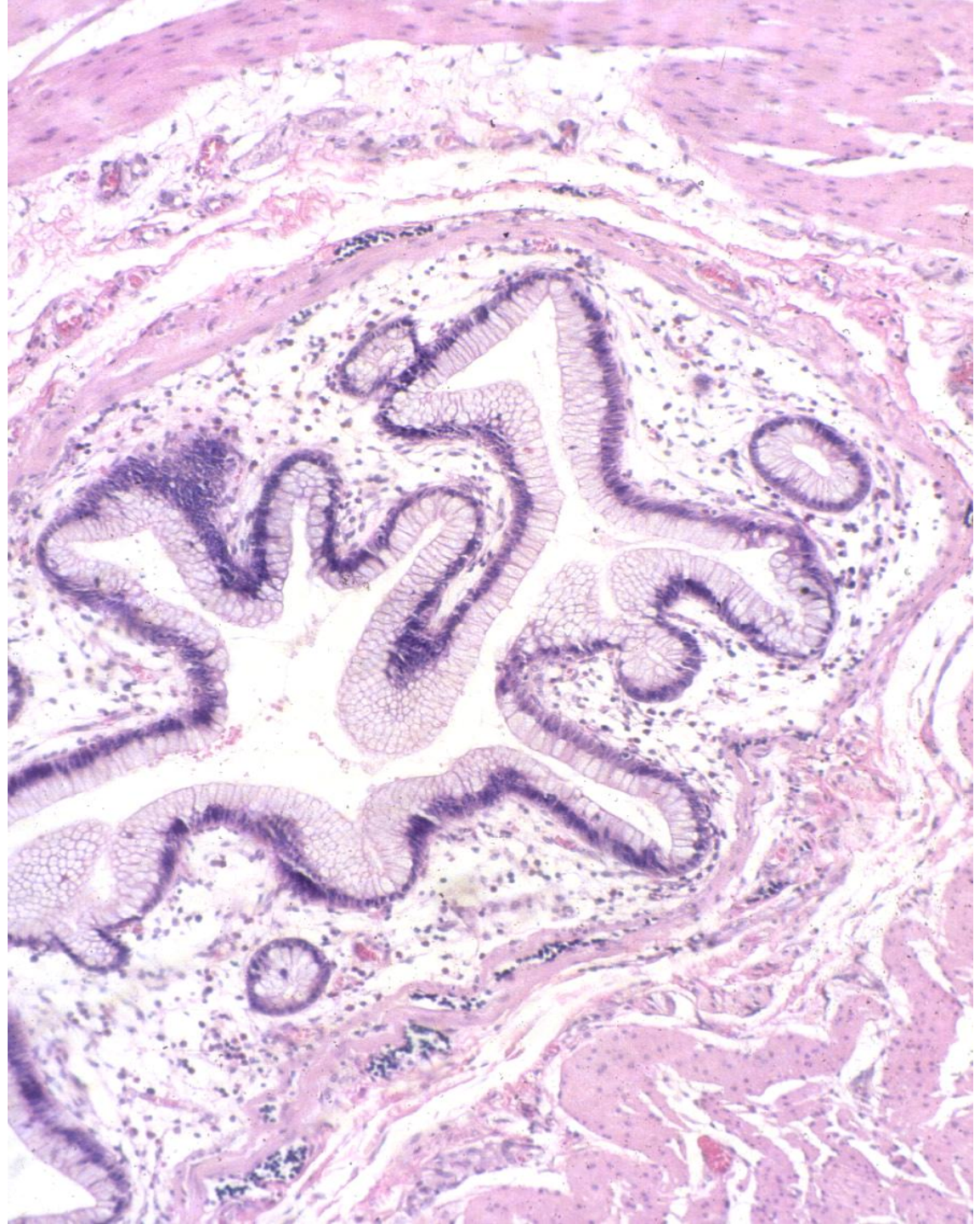
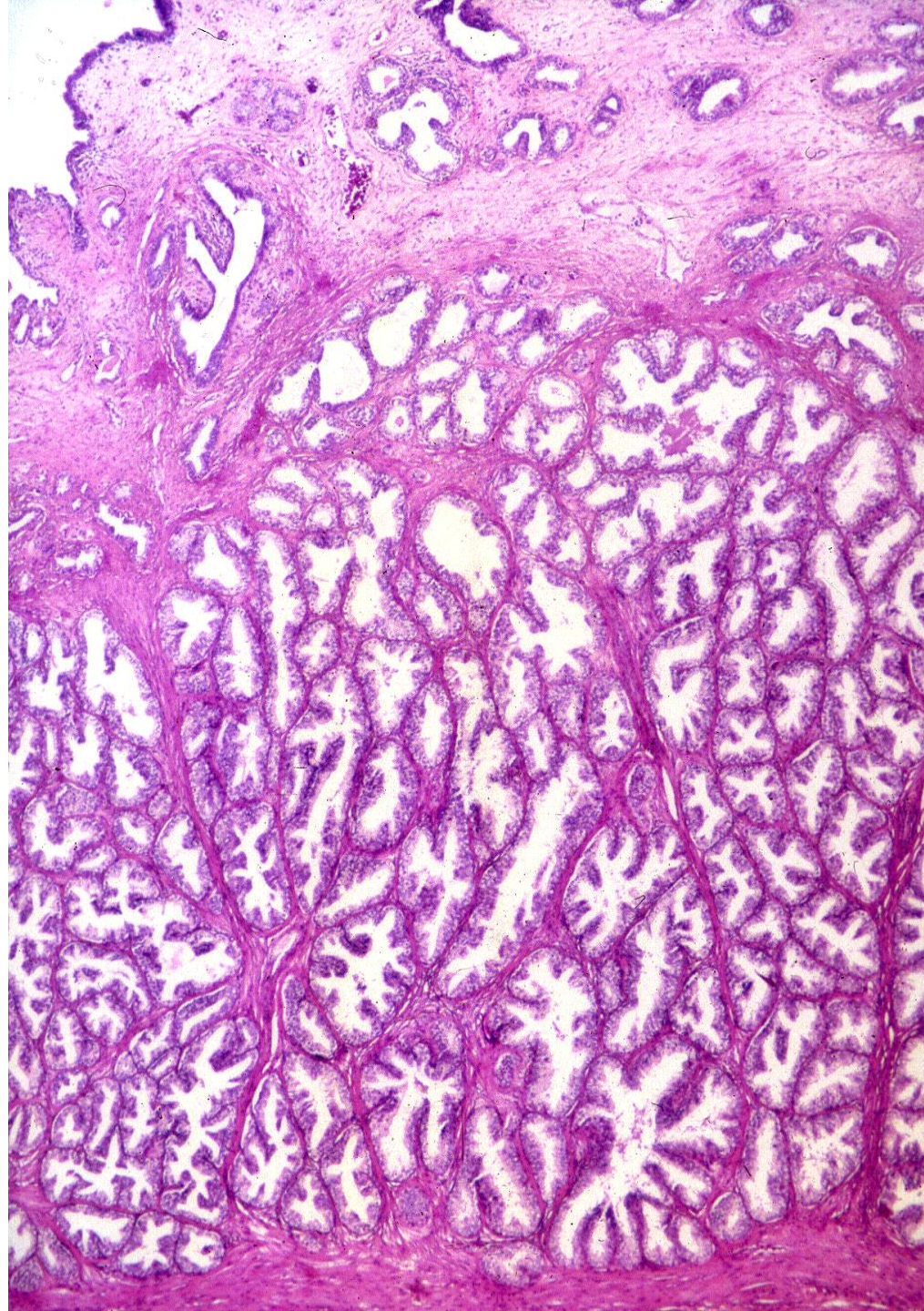
**No
prognostic
significance**

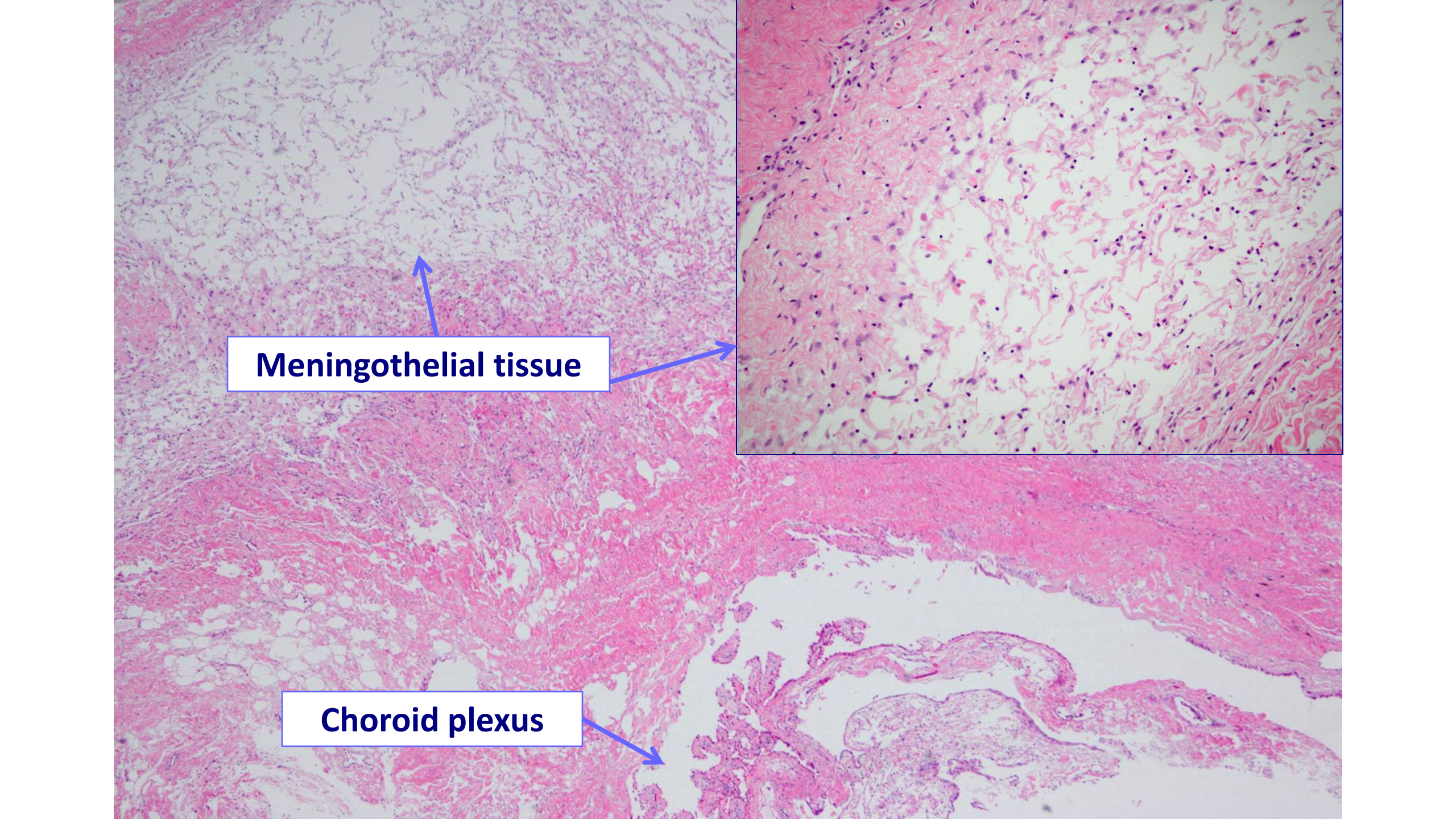
MATURE CYSTIC TERATOMA (DERMOID CYST)

- **60% of all benign ovarian tumors**
- **Mature tissues from all three embryonic layers, recapitulating normal organs**
- **Mostly asymptomatic**
- **Associations:**
 - **Rupture, infarction, hemoperitoneum, infection, autoimplantation**
 - **Paraneoplastic disorders: exercise-induced urticarial vasculitis, hemolytic anemia, polyarthrititis, NMDAR encephalitis (anti-N-methyl aspartate)**



~15% bilateral; CYSTIC; 6-8 cm (smaller than IT)

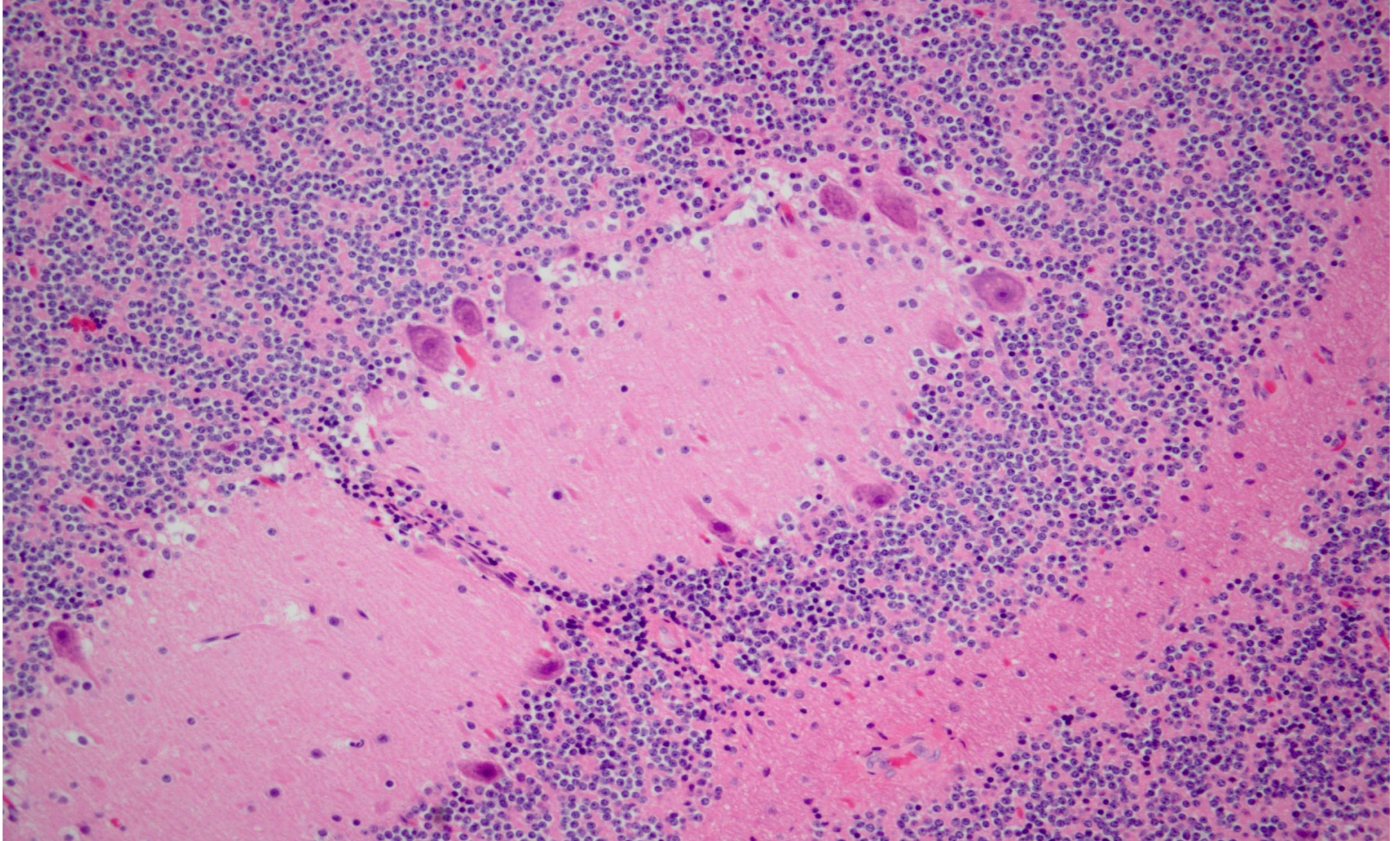




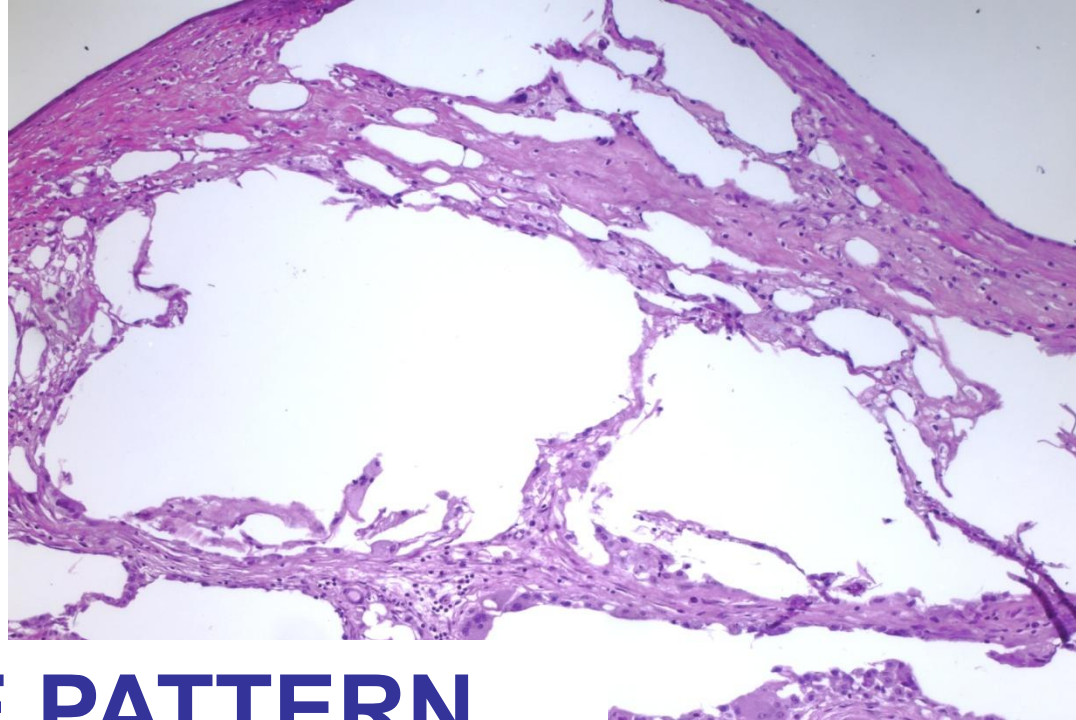
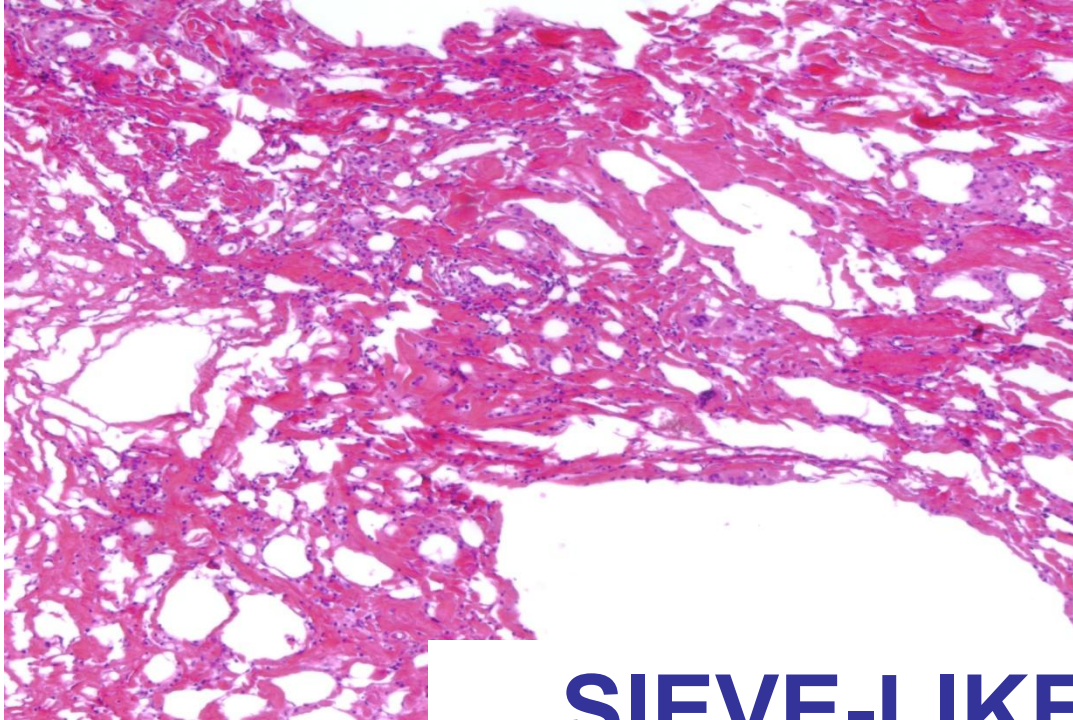
Meningoethelial tissue

This histological image shows a section of the choroid plexus. The upper portion is composed of meningotheelial tissue, which is a layer of cells derived from the meninges. The lower portion shows the choroid plexus itself, characterized by its highly vascularized and convoluted structure. A blue arrow points from the text label to the meningotheelial tissue, and another blue arrow points from the text label to the choroid plexus. An inset in the top right corner provides a higher magnification view of the meningotheelial tissue, showing its cellular details and the underlying choroid plexus.

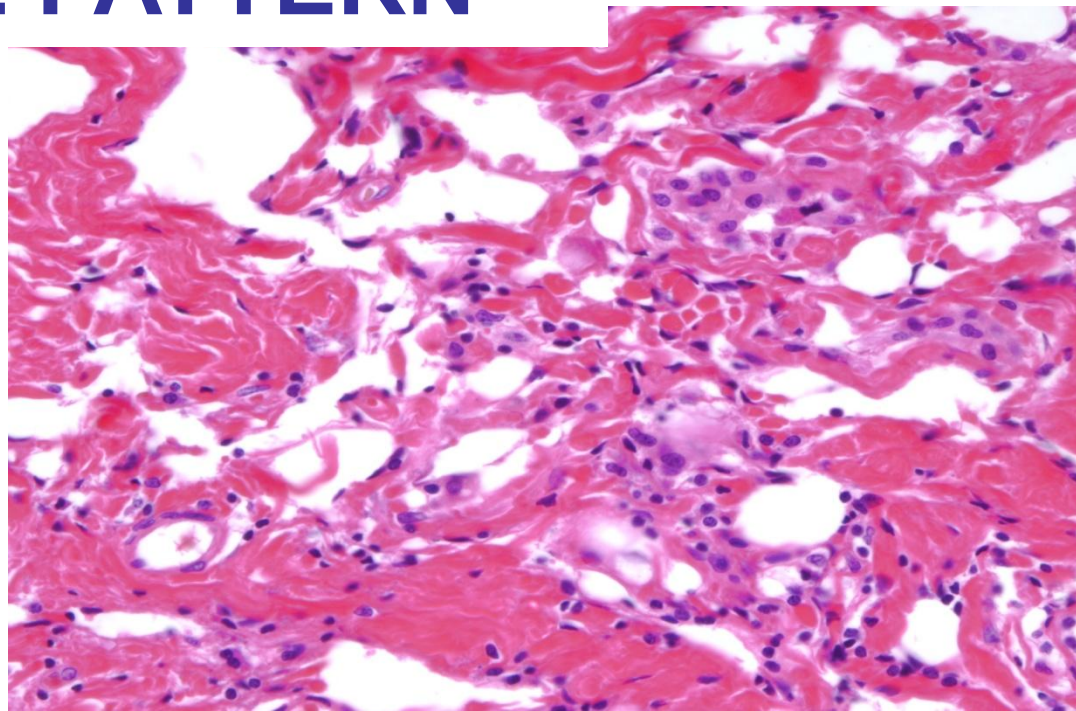
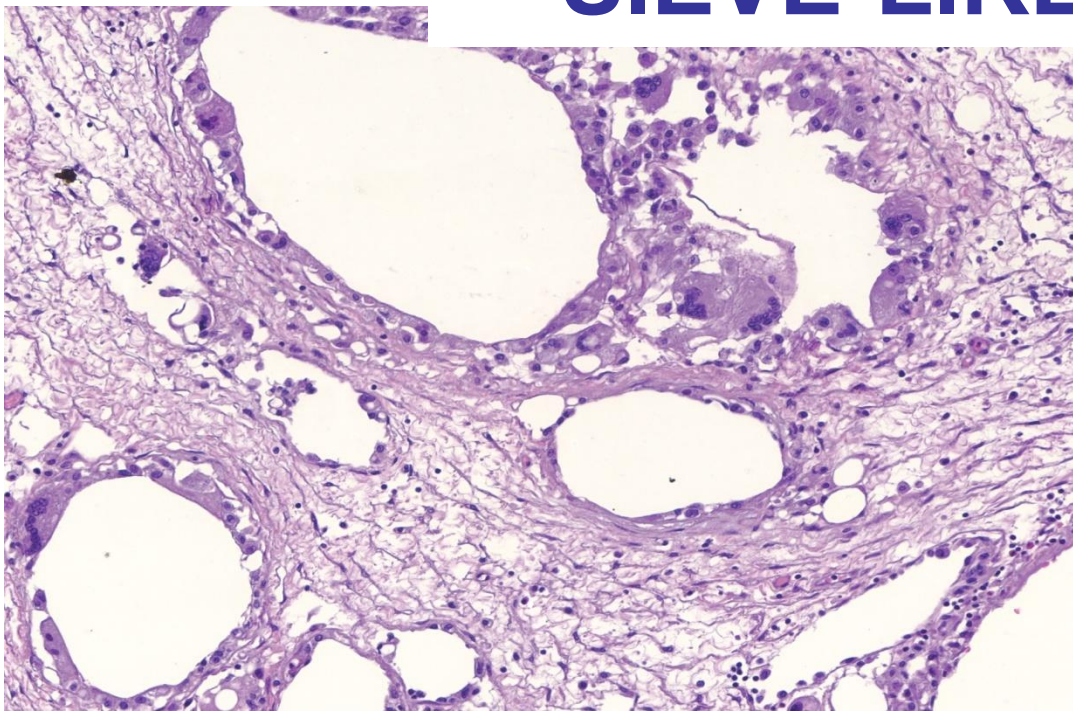
Choroid plexus



CEREBELLUM: Organized architecture



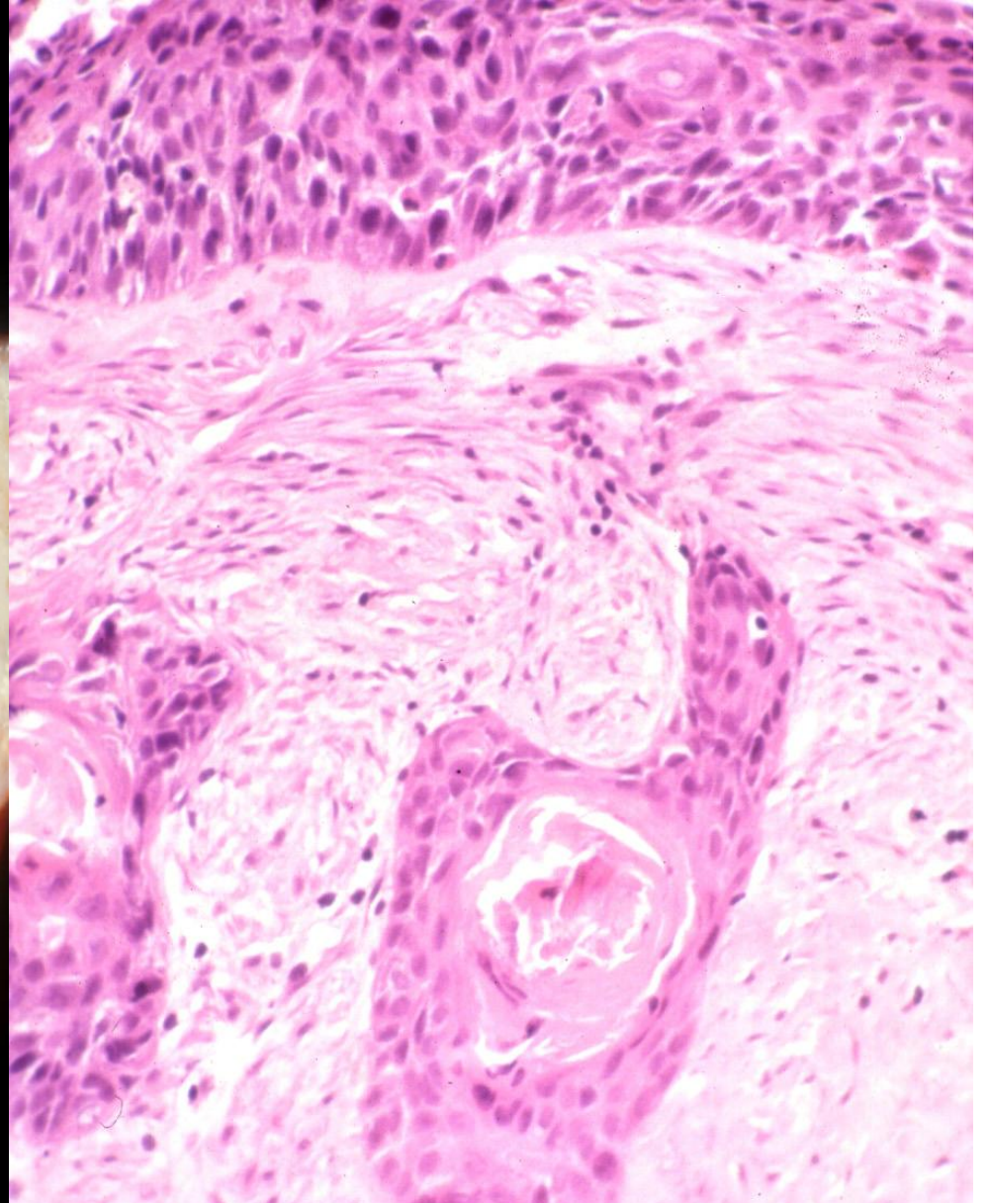
SIEVE-LIKE PATTERN



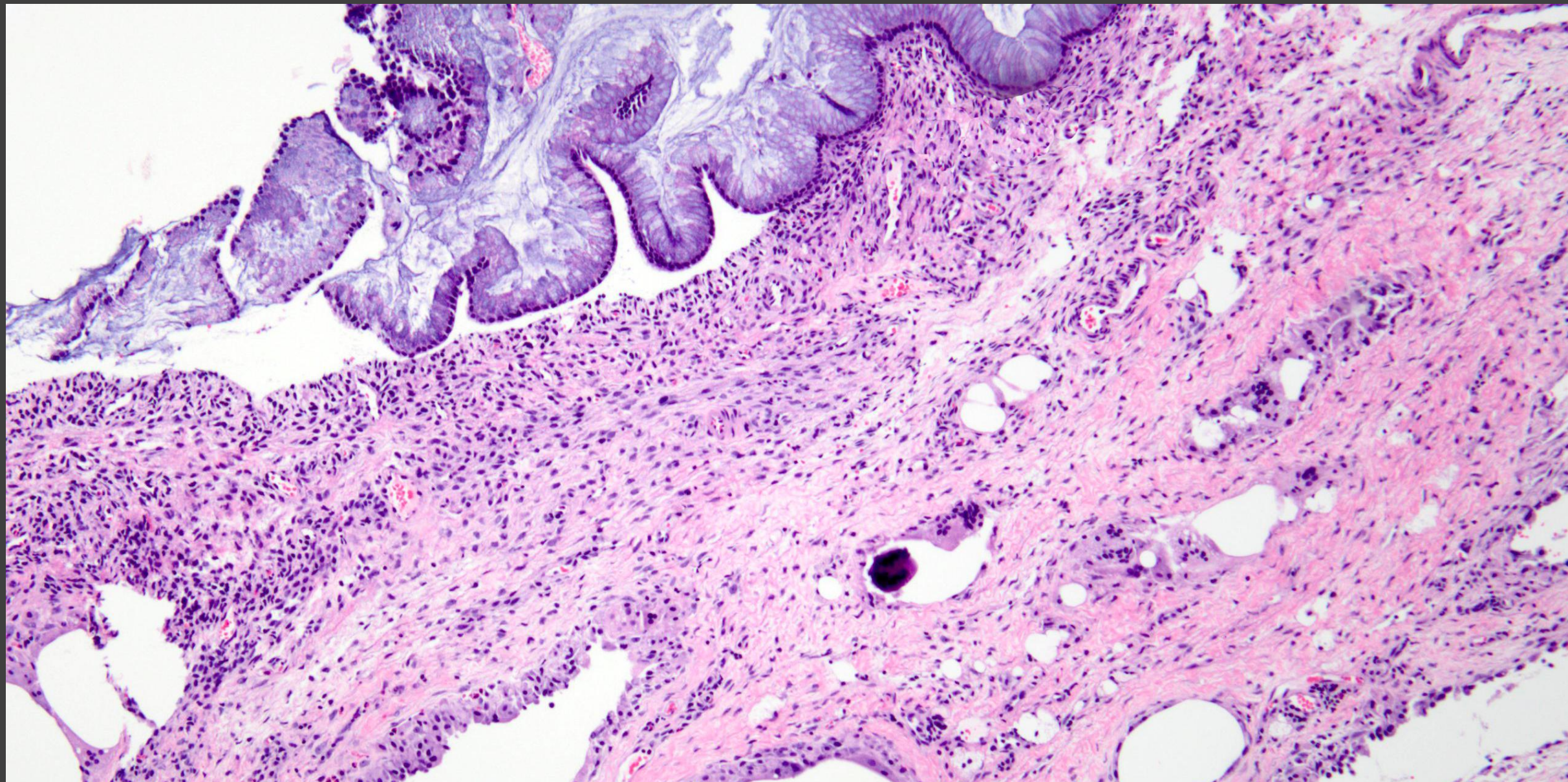
MATURE CYSTIC TERATOMA (DERMOID CYST)

Associated findings:

- **Granulomatous peritonitis**
- **Melanosis peritonei**
- **Secondary malignancy (in up to 1.5%)**



Squamous cell carcinoma most common malignancy
Sample any solid/fleshy nodule in the cyst wall!



Mucinous cystic tumor arising in MCT

MONODERMAL TERATOMAS

Struma ovarii

- Variant: with malignant tumor

Carcinoids

- Insular
- Trabecular
- Mucinous
- Strumal carcinoid

Neuroectodermal tumors –**EMBRYONIC-TYPE**- New terminology

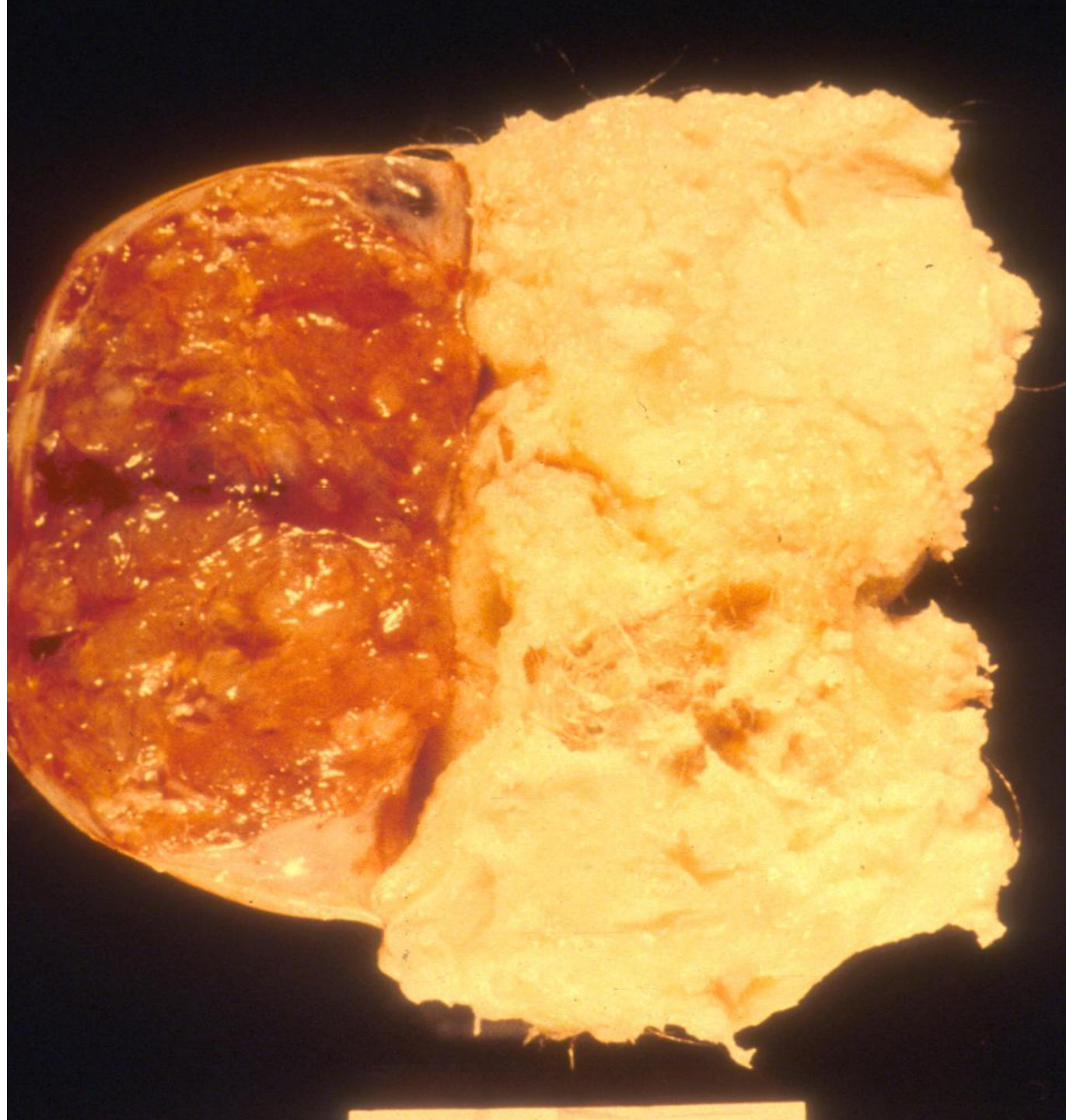
Sebaceous tumors

Others

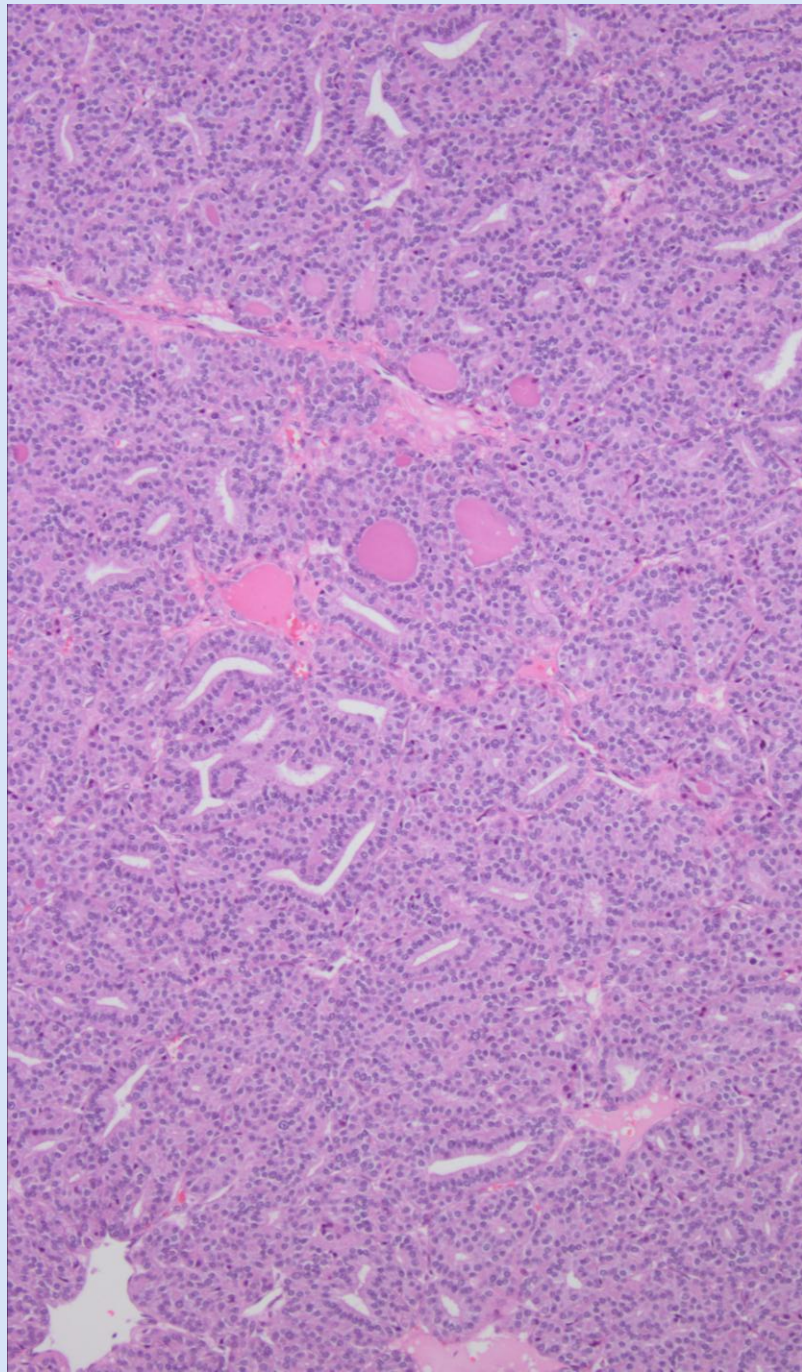
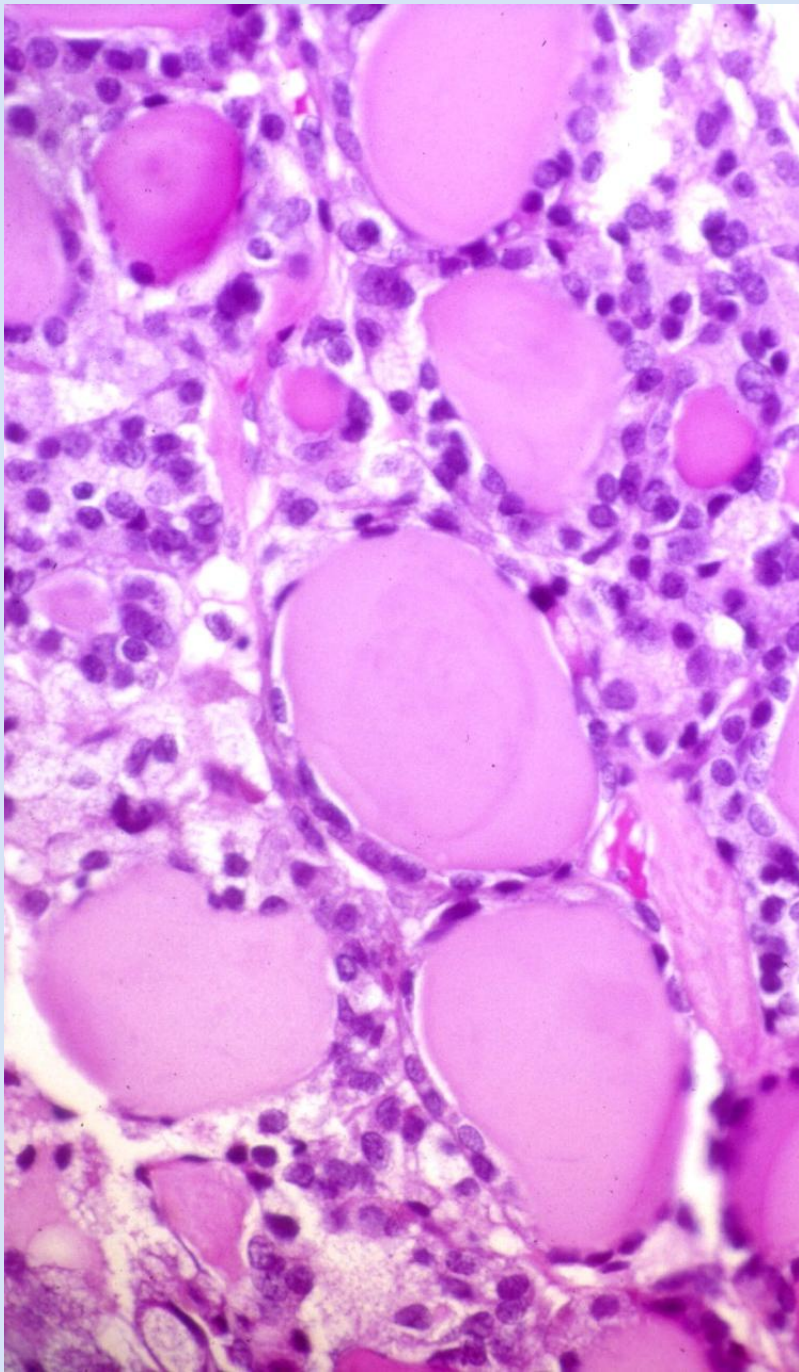
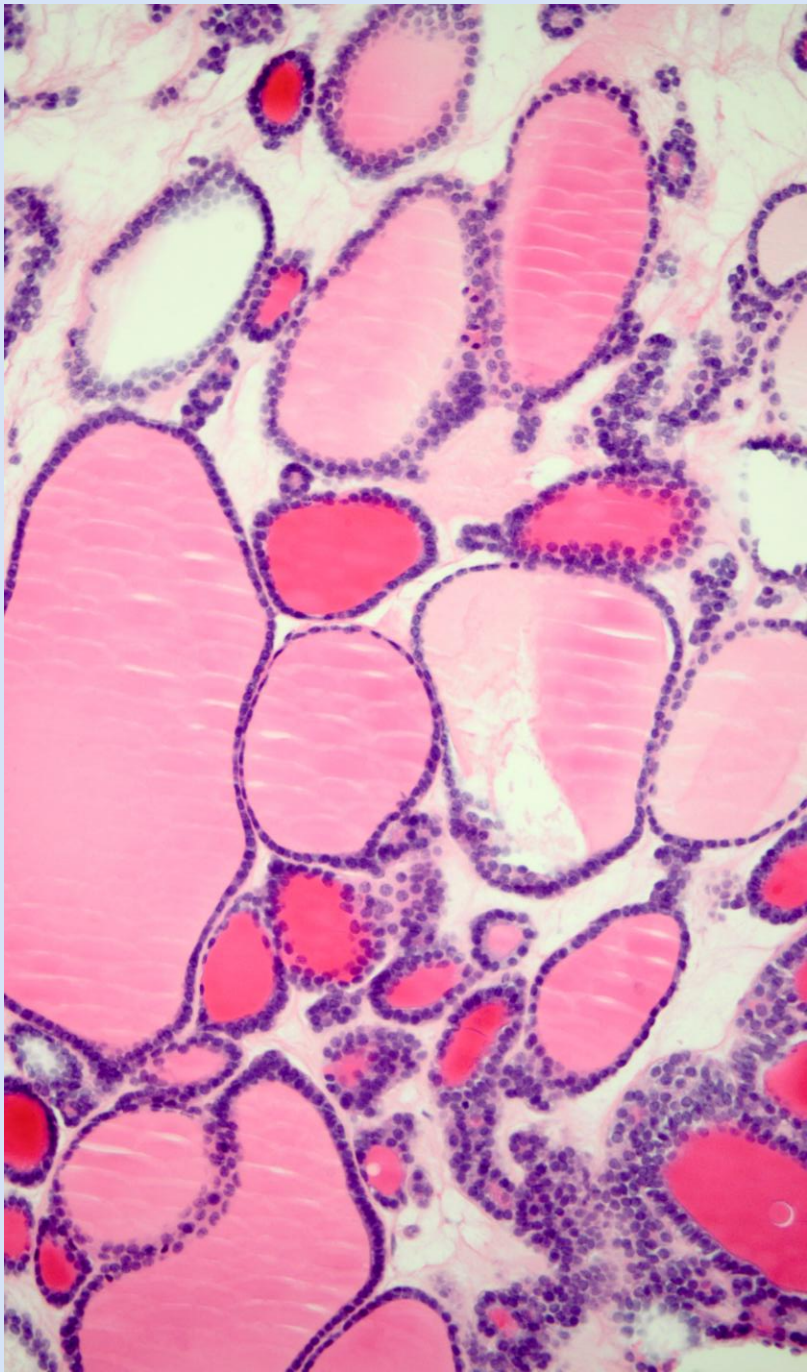
STRUMA OVARII



- Most common monodermal teratoma
- Exclusive or predominant component on gross exam
- Pure or associated with dermoid cyst, carcinoid, cystadenoma, Brenner T
- Peak frequency fifth decade
- Ascites in 1/3 (Meigs'-like syndrome)
- Rarely hyperthyroidism
- Malignant change rare



**Struma ovarii
associated with
dermoid cyst**

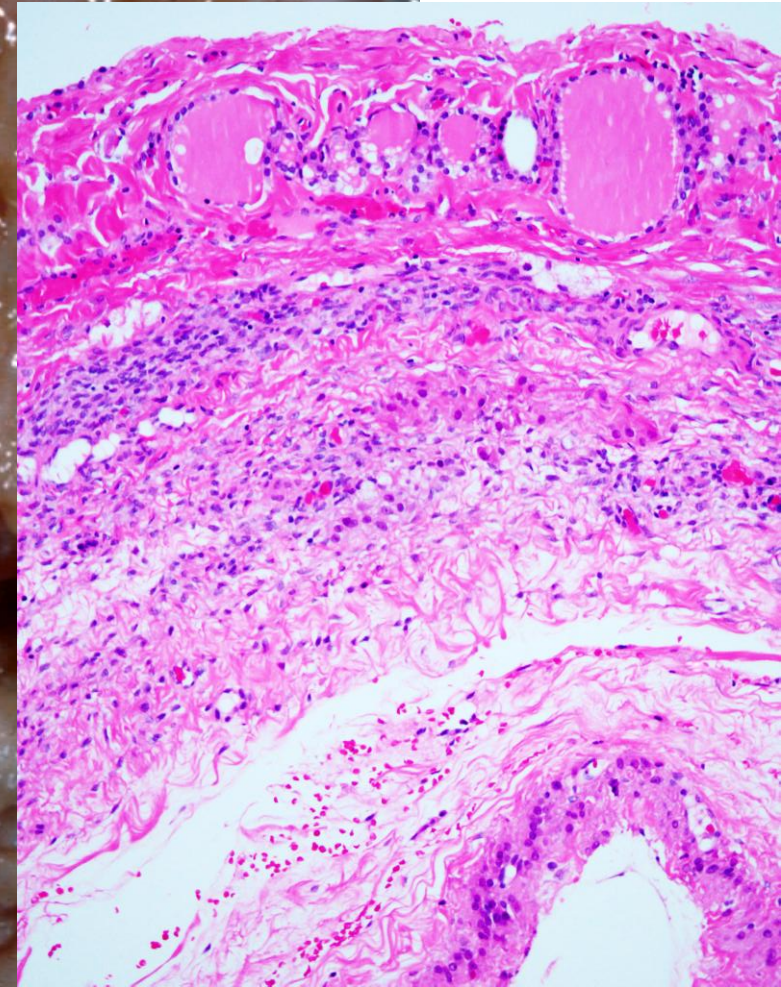
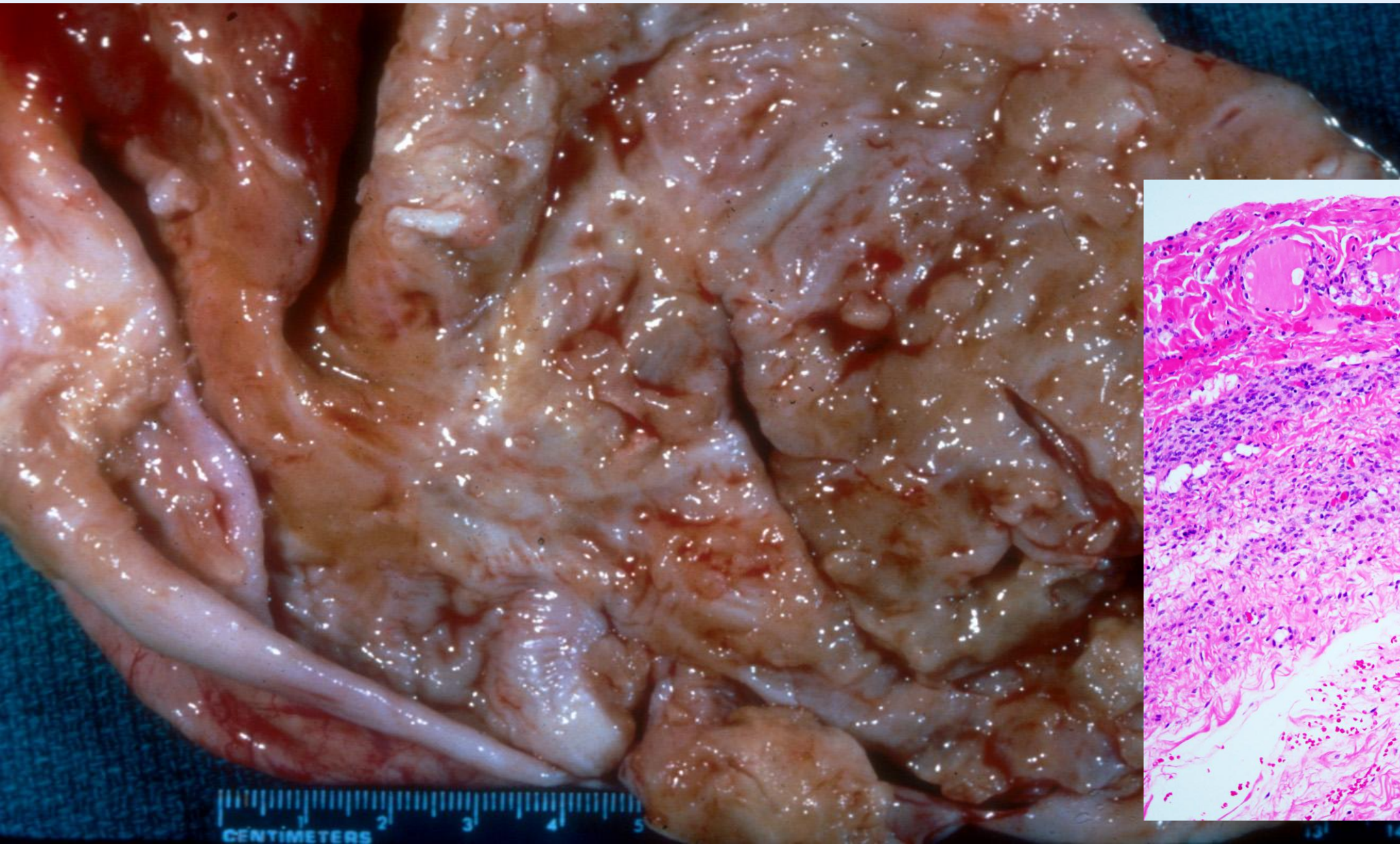


STRUMA OVARIII

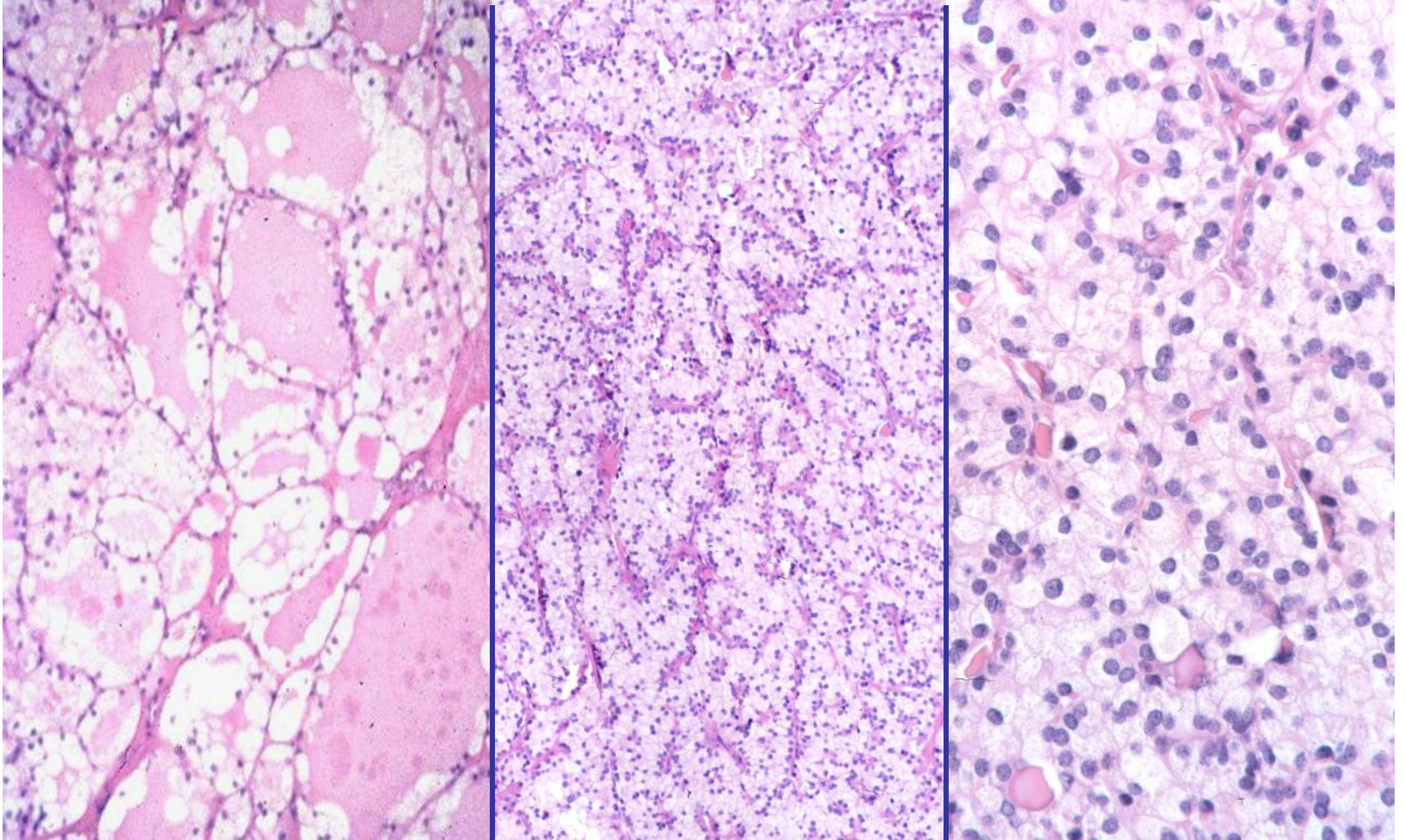
Problems in diagnosis when:

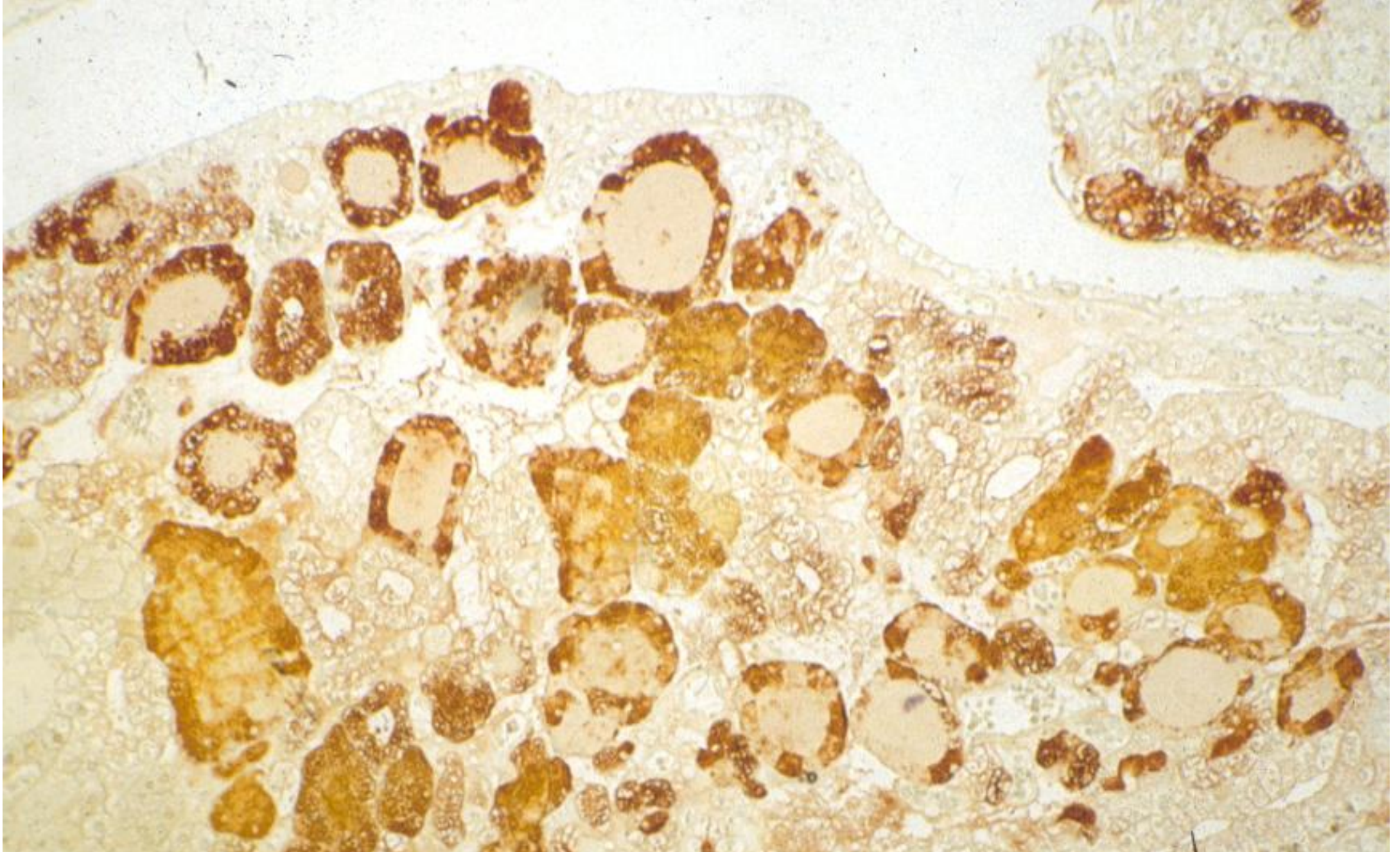
- **Predominantly solid** --- sex cord tumor
--- carcinoma
- **Prominent stroma** --- adenofibroma
- **Only oxyphilic cells** --- sertoli cell tumor
--- steroid cell tumor
- **Predominantly cystic** --- cystadenoma
- **Only clear cells** --- clear cell ca

CYSTIC STRUMA



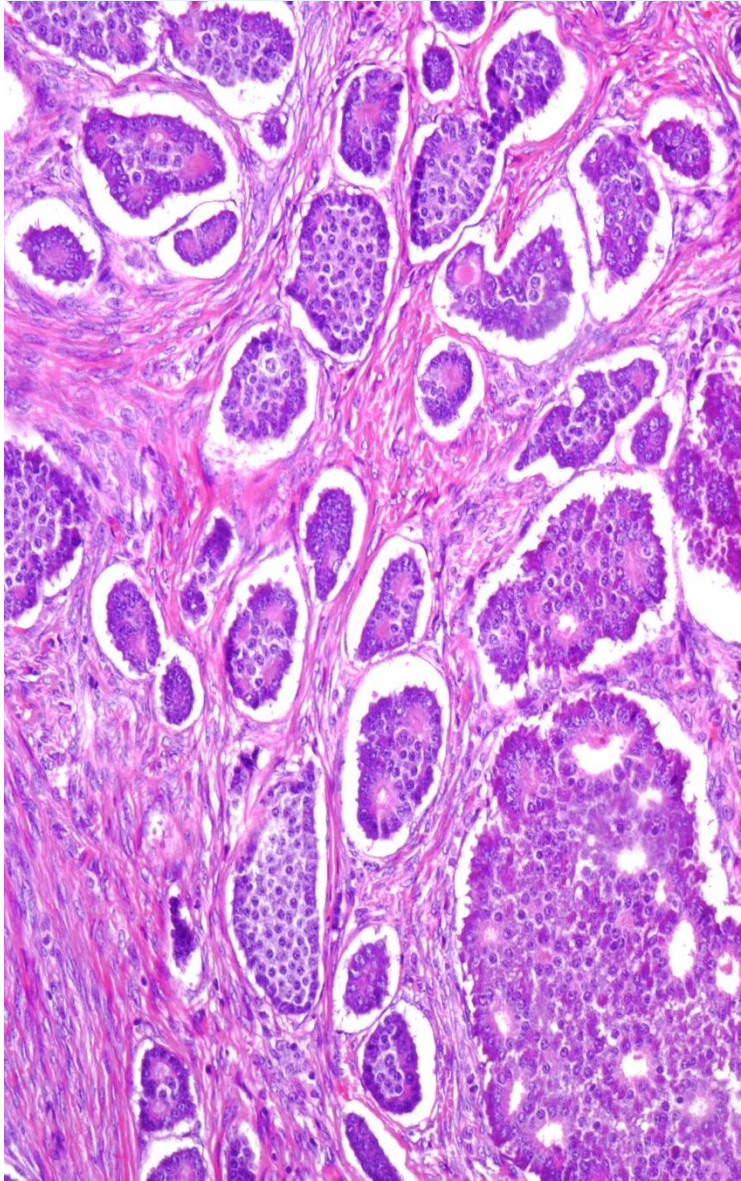
CLEAR CELL STRUMA



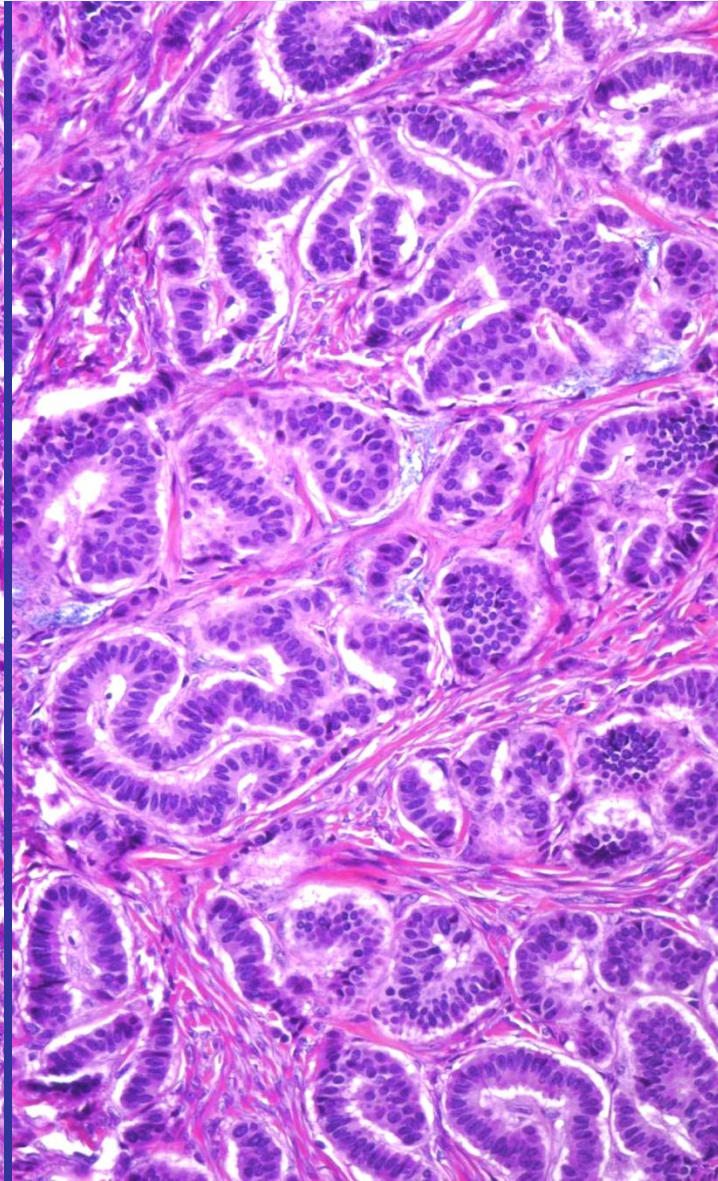


Thyroglobulin or TTF1. Do not use PAX8

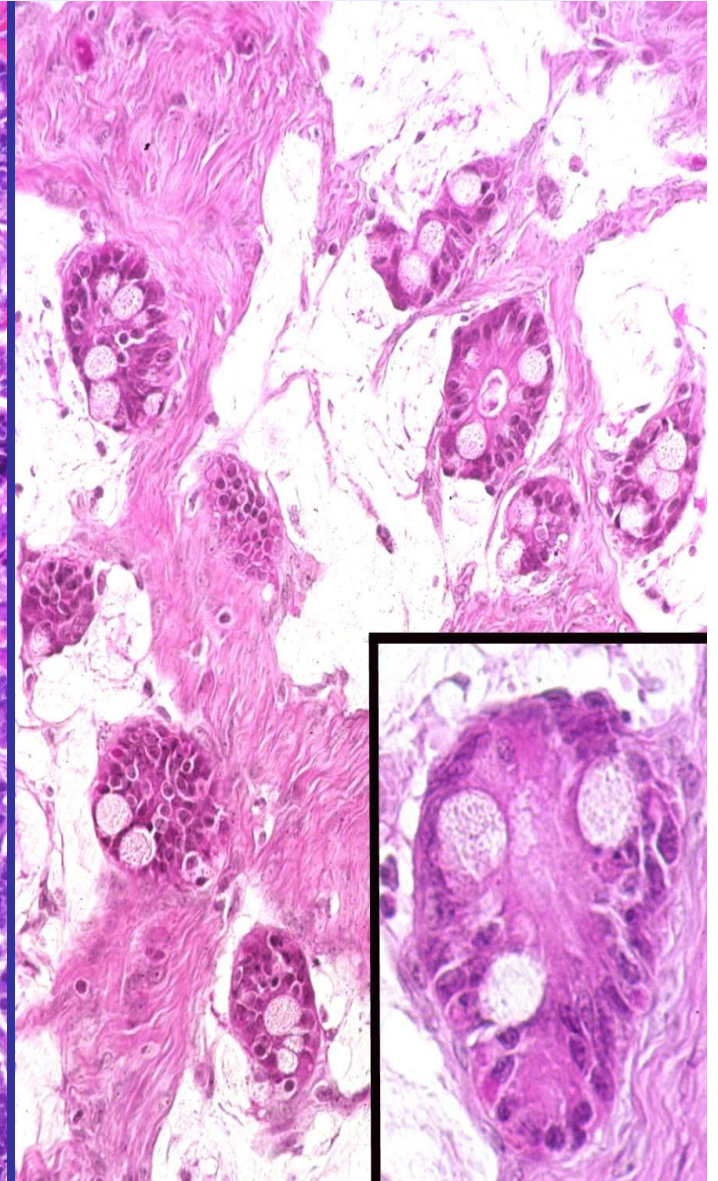
CARCINOIDS



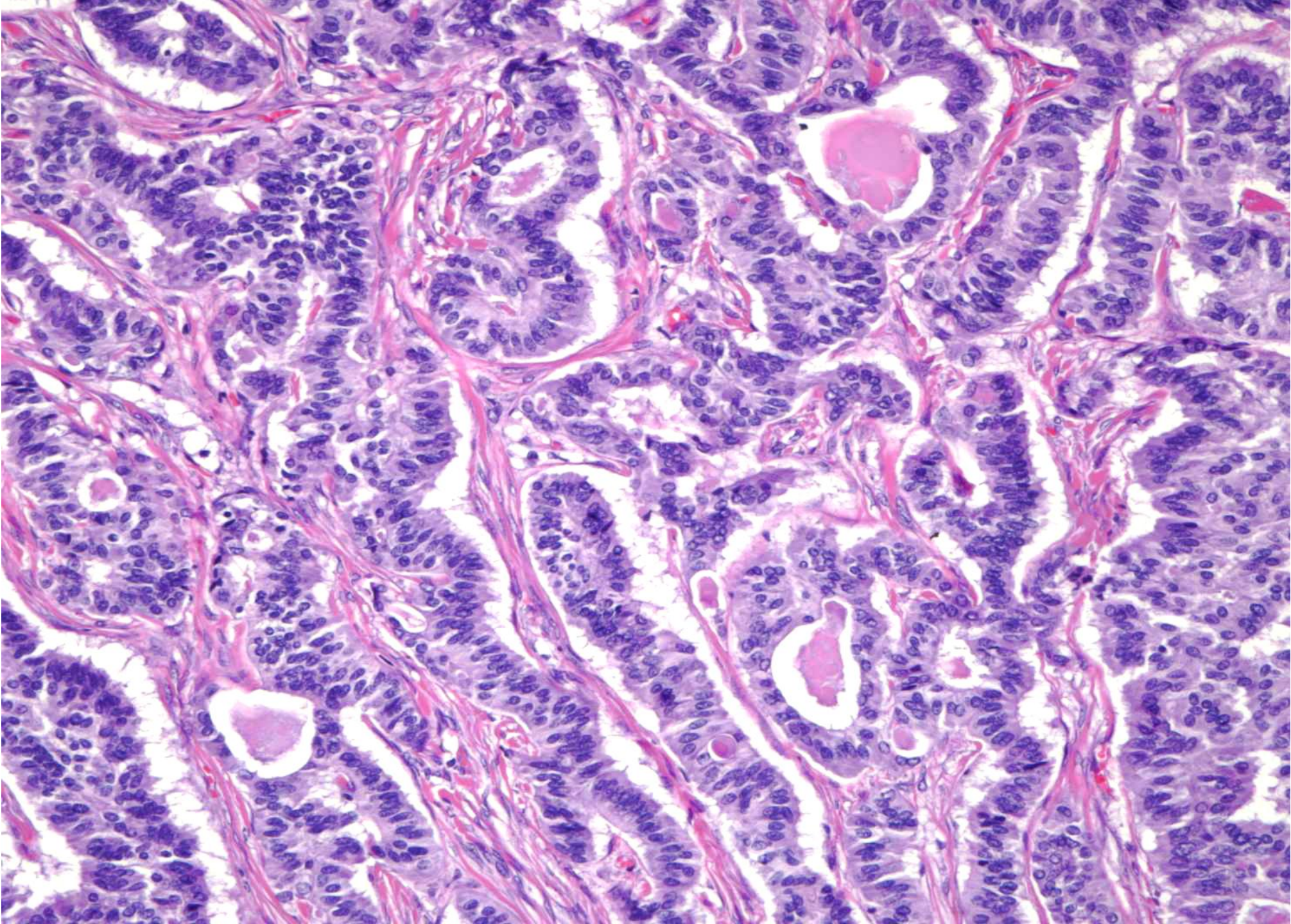
Insular



Trabecular



Mucinous



**STRUMAL
CARCINOID**



Thank you !!!!

GERM CELL TUMOR MARKERS

- PLAP, HCG, AFP, AE1/AE3

- New markers:

SALL4: Expressed in *all* germ cell tumors

OCT4 and NANOG: Only in dysgerminoma and EC

D2-40: Dysgerminoma

c-kit: More common in dysgerminoma, may be seen in EC, and YST

CD30: More common in EC but rarely in dysgerminoma

Glypican-3: Typically in YST, but can be seen in choriocarcinoma and EC

SOX2: Only positive in EC and teratoma

SOX17: Expressed in dysgerminoma and may be seen in YST

CDX2 IS NOT USEFUL IN THE DIFFERENTIAL DIAGNOSIS OF PRIMARY *vs* METASTATIC CARCINOID TO THE OVARY

Rabban JT et al, Int J Gynecol Pathol 2008

- **Most metastatic carcinoid to the ovary are of insular type**
- **Even though CDX2 is marker of intestinal differentiation, is equally expressed in primary and metastatic carcinoids (mainly insular and mucinous types)**
- **Primary carcinoids are CK7/CK20 and TTF1 negative (except mucinous subtype CK20+); thus, these panel of antibodies is not helpful in determining origin**