

Ovarian Sex Cord Stromal Tumors

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Objectives

- Recognize the distinguishing features of the most common malignant ovarian sex cord-stromal tumors (SCST)
- Understand the application and interpretation of relevant ancillary studies when available
- Identify tumors that may indicate an underlying genetic syndrome
- Be aware of updates in the classification and understanding of ovarian SCST

Ovarian Sex Cord-Stromal Tumors

Pure Stromal Tumors

- Fibroma
- Thecoma
- Sclerosing Stromal Tumor
- Microcystic Stromal Tumor
- Myxoma
- Signet Ring Stromal Tumor
- Luteinized Thecoma with Sclerosing Peritonitis

Pure Sex Cord Tumors

- Adult Granulosa Cell Tumor
- Juvenile Granulosa Cell Tumor
- Sertoli Cell Tumor
- Sex Cord Tumor with Annular Tubules (SCTAT)

“True” Sex Cord-Stromal Tumors

- Sertoli Leydig Cell Tumor

Others

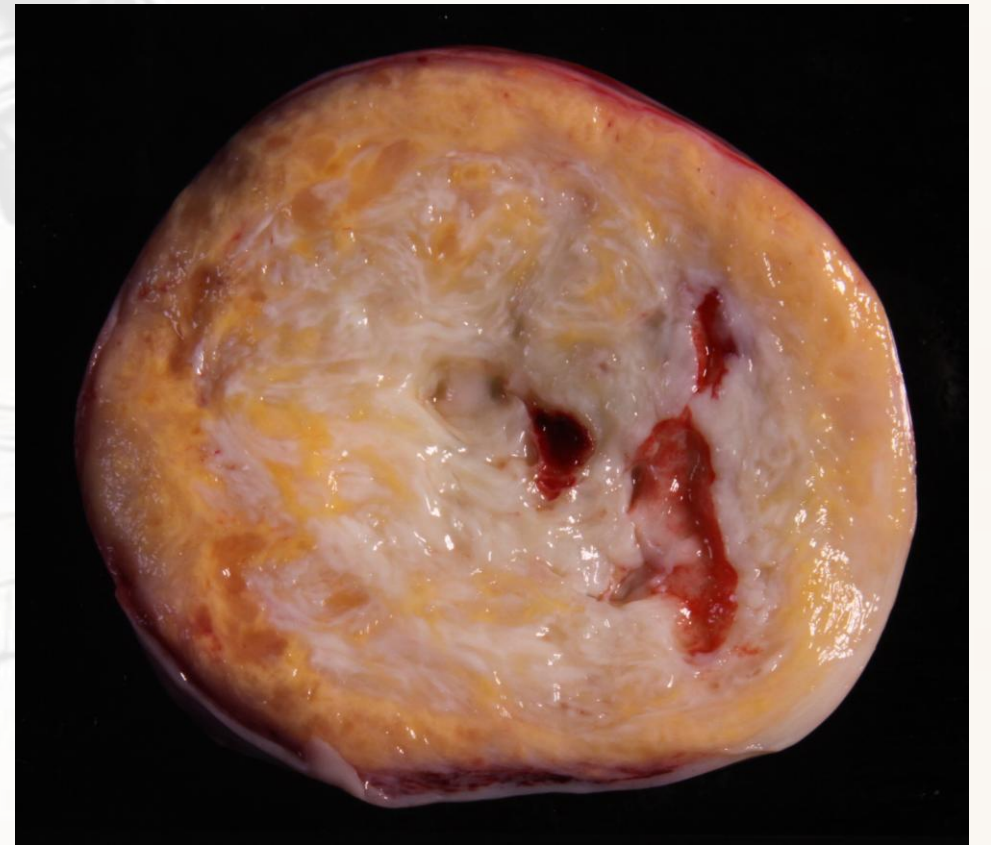
- Mixed SCSTs
 - Gynandroblastoma
- Unclassified SCST

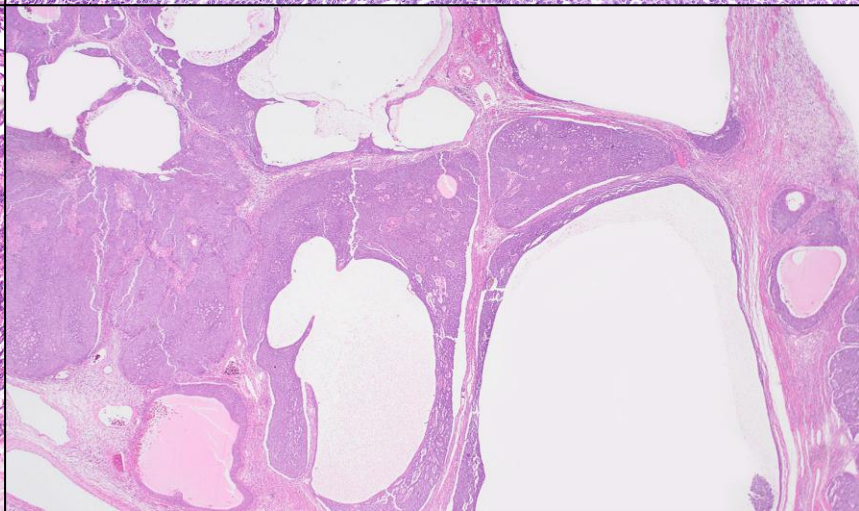
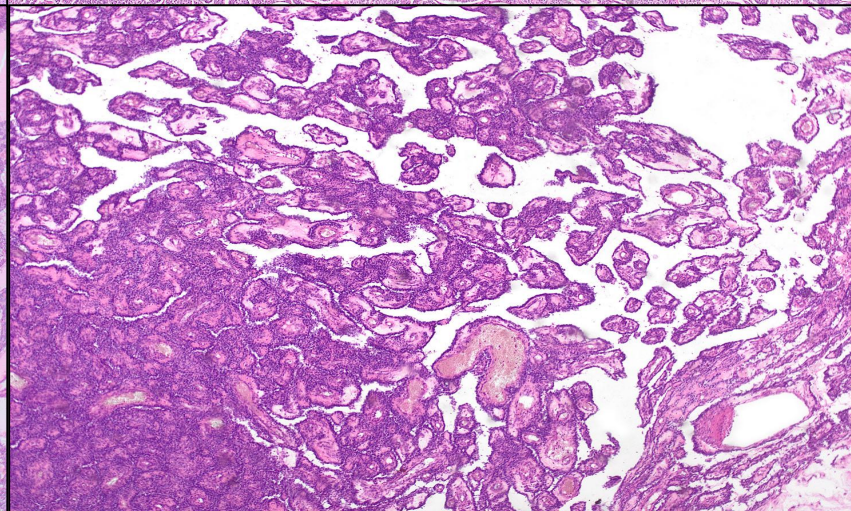
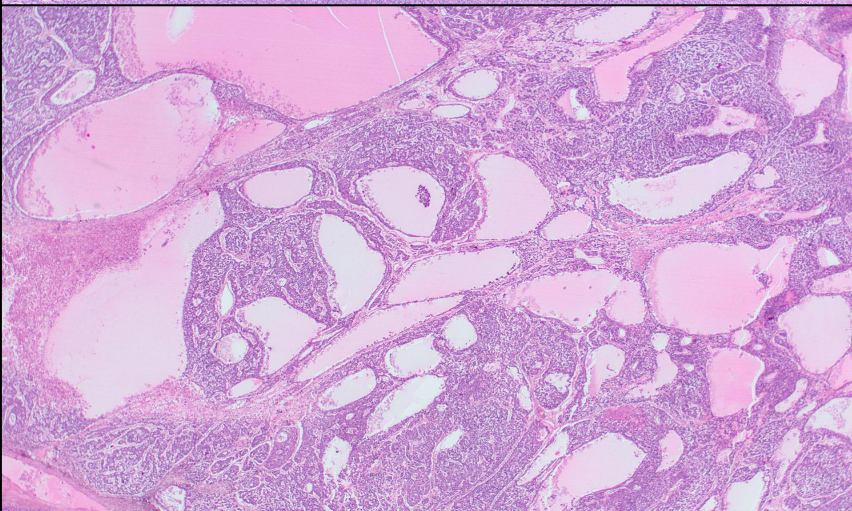
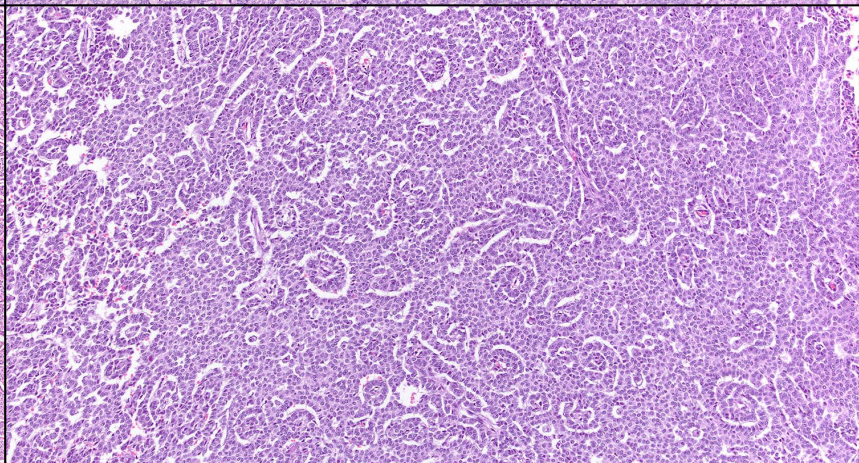
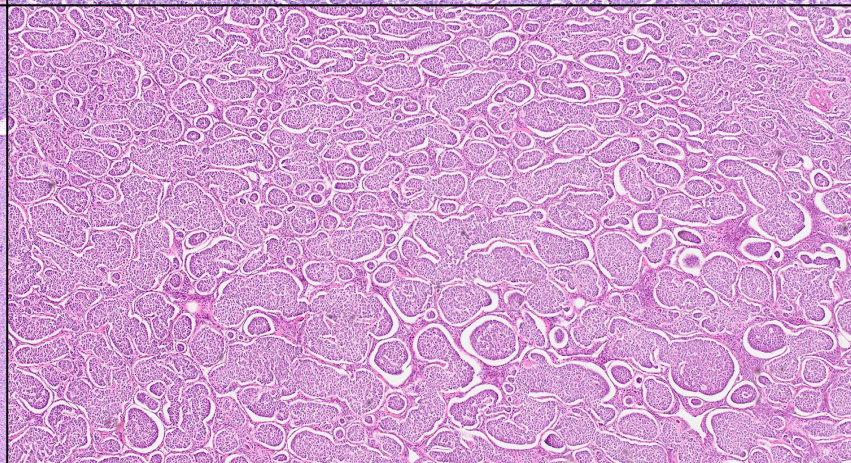
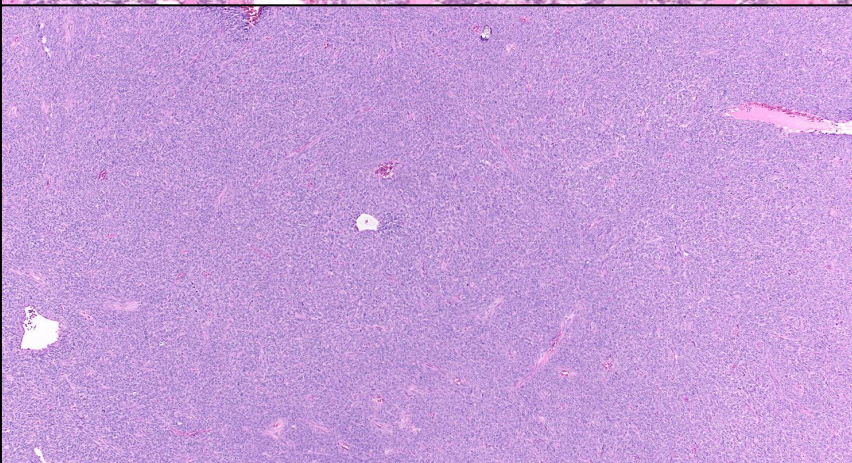
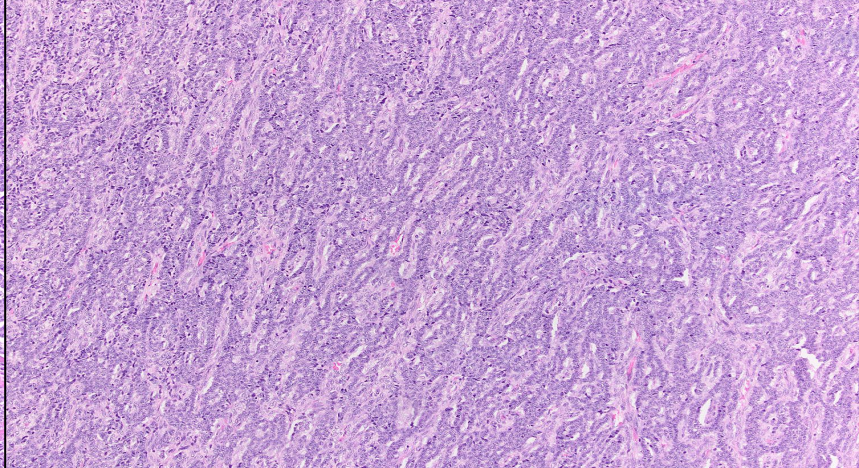
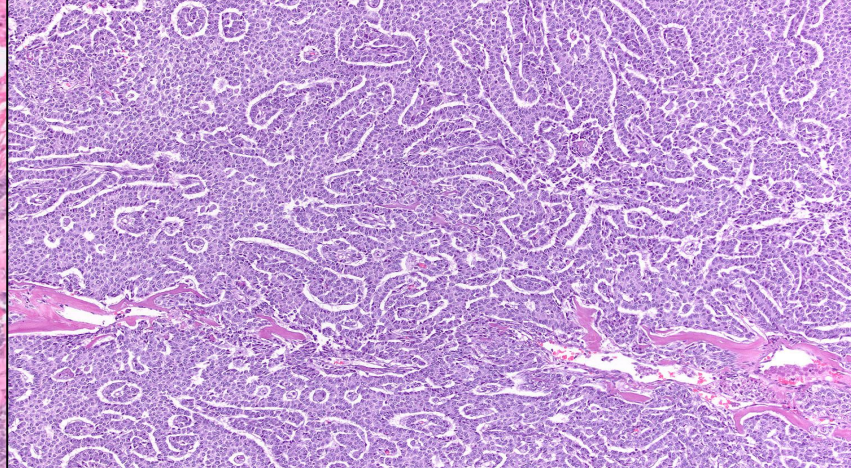
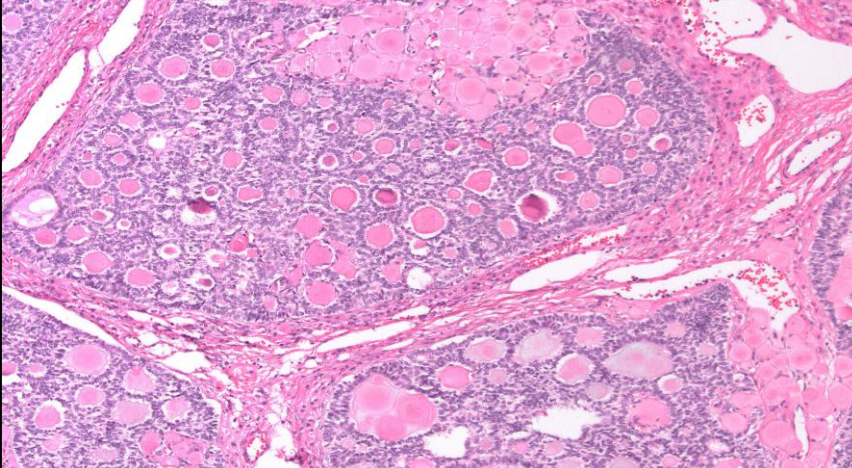
Steroid Cell Tumors

- Stromal Luteoma
- Leydig Cell Tumor
- Steroid cell tumor, NOS

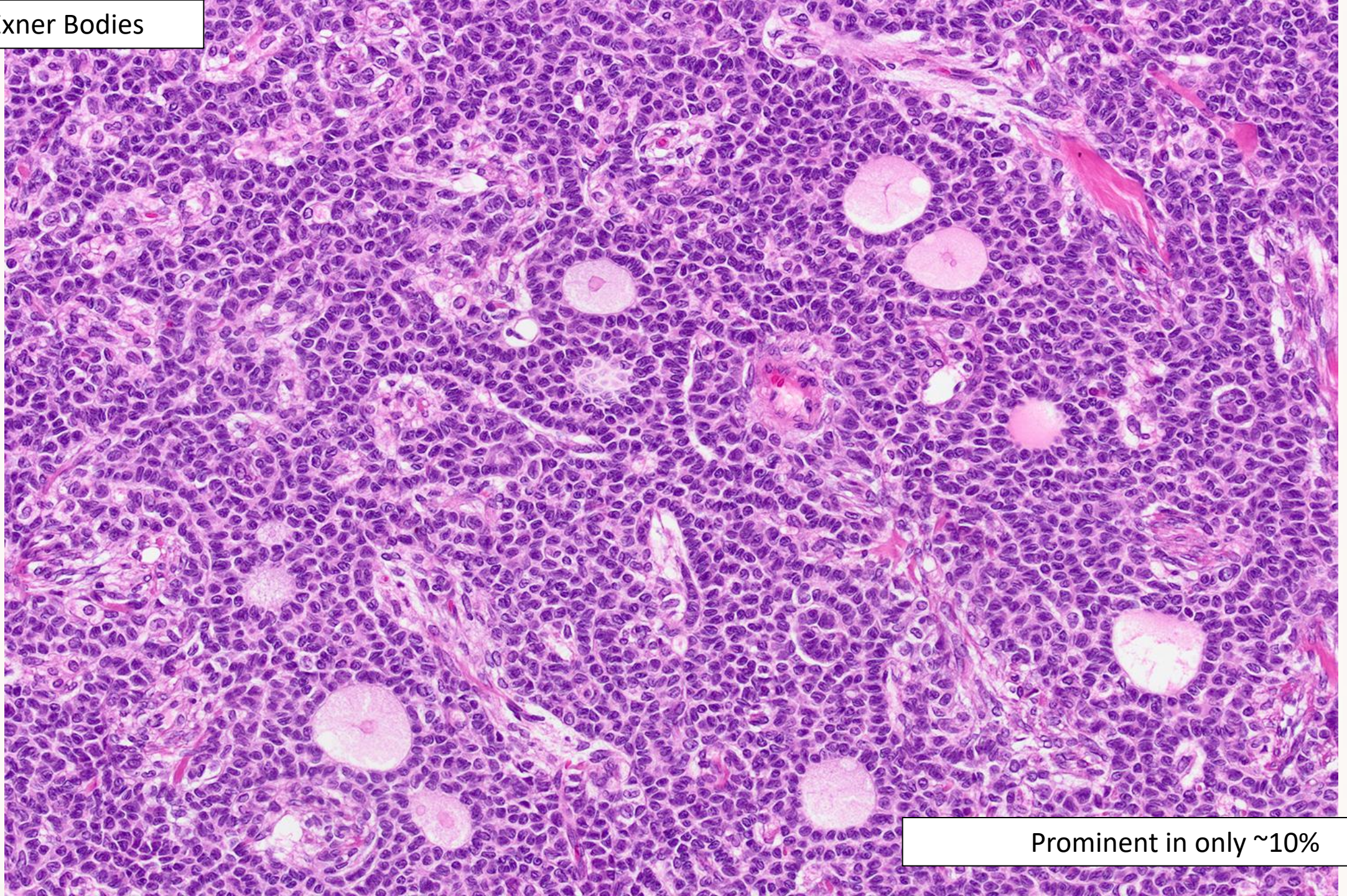
Adult Granulosa Cell Tumor (AGCT)

- Mean age 50s (wide age range)
- Estrogenic manifestations common (rarely androgenic)
 - Abnormal / postmenopausal bleeding
 - Endometrial hyperplasia or carcinoma
- Risk of late recurrence (even 10+ years after diagnosis)
 - Stage most important prognostic factor



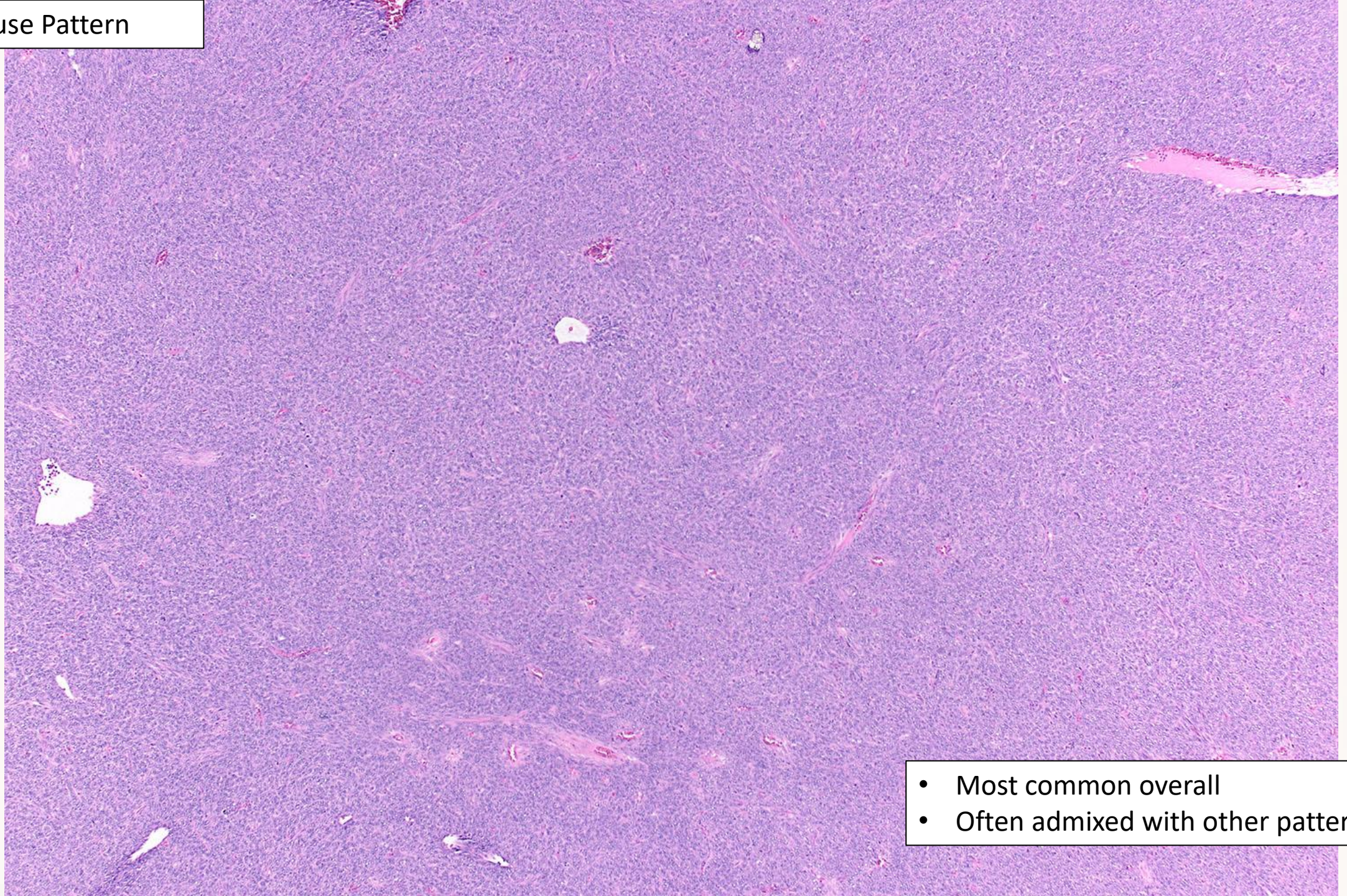


Call-Exner Bodies



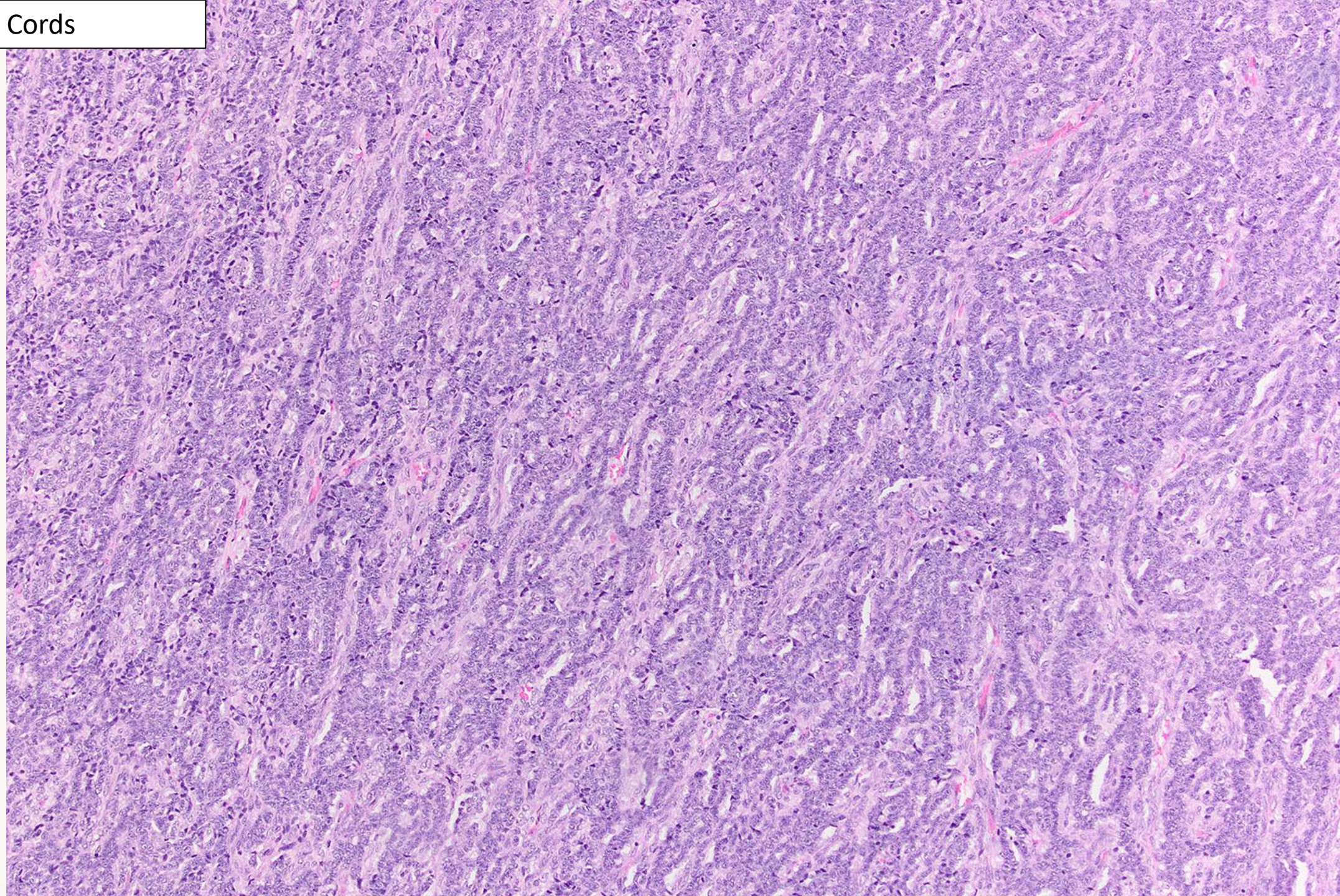
Prominent in only ~10%

Diffuse Pattern

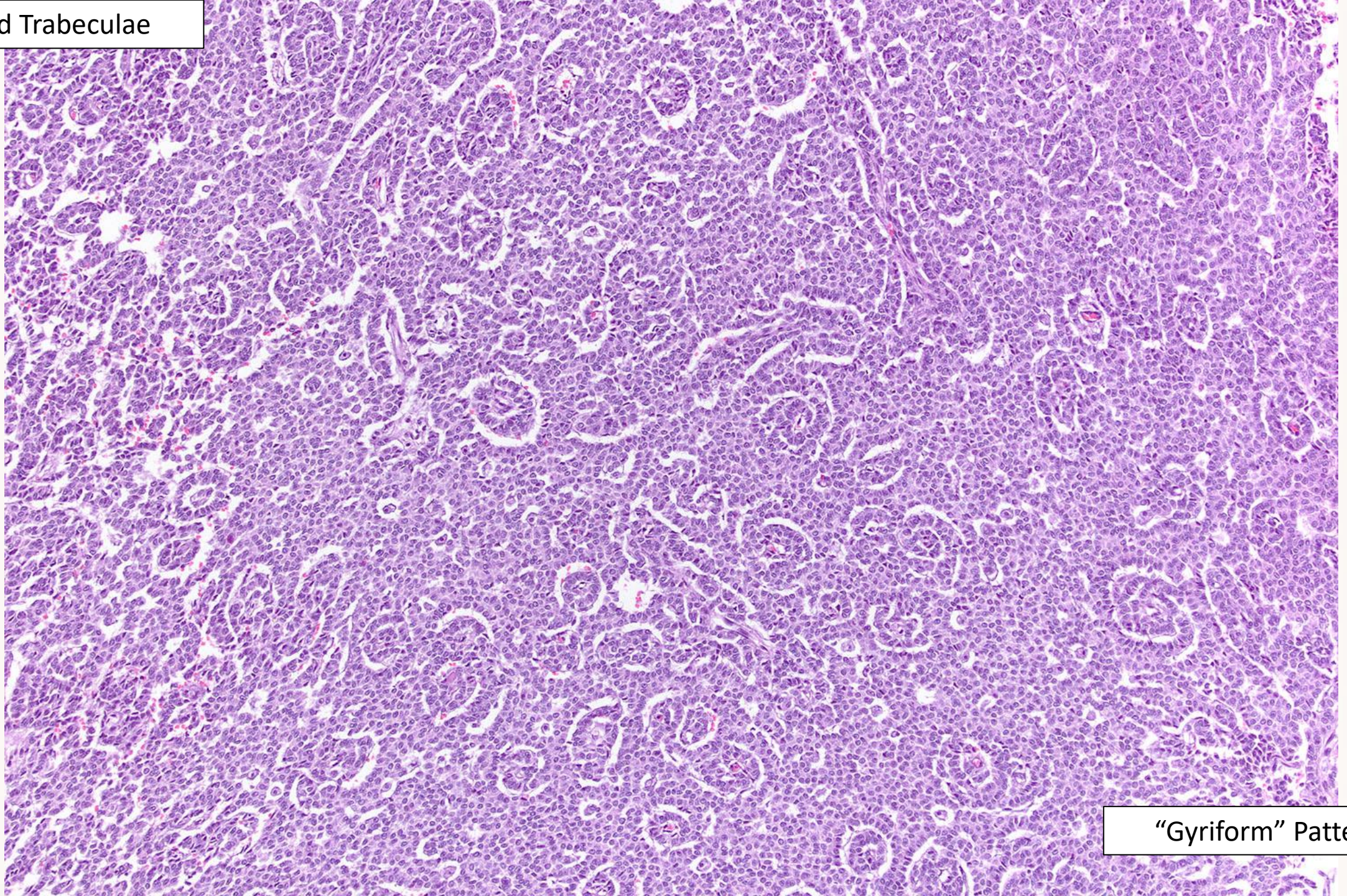


- Most common overall
- Often admixed with other patterns

Cords

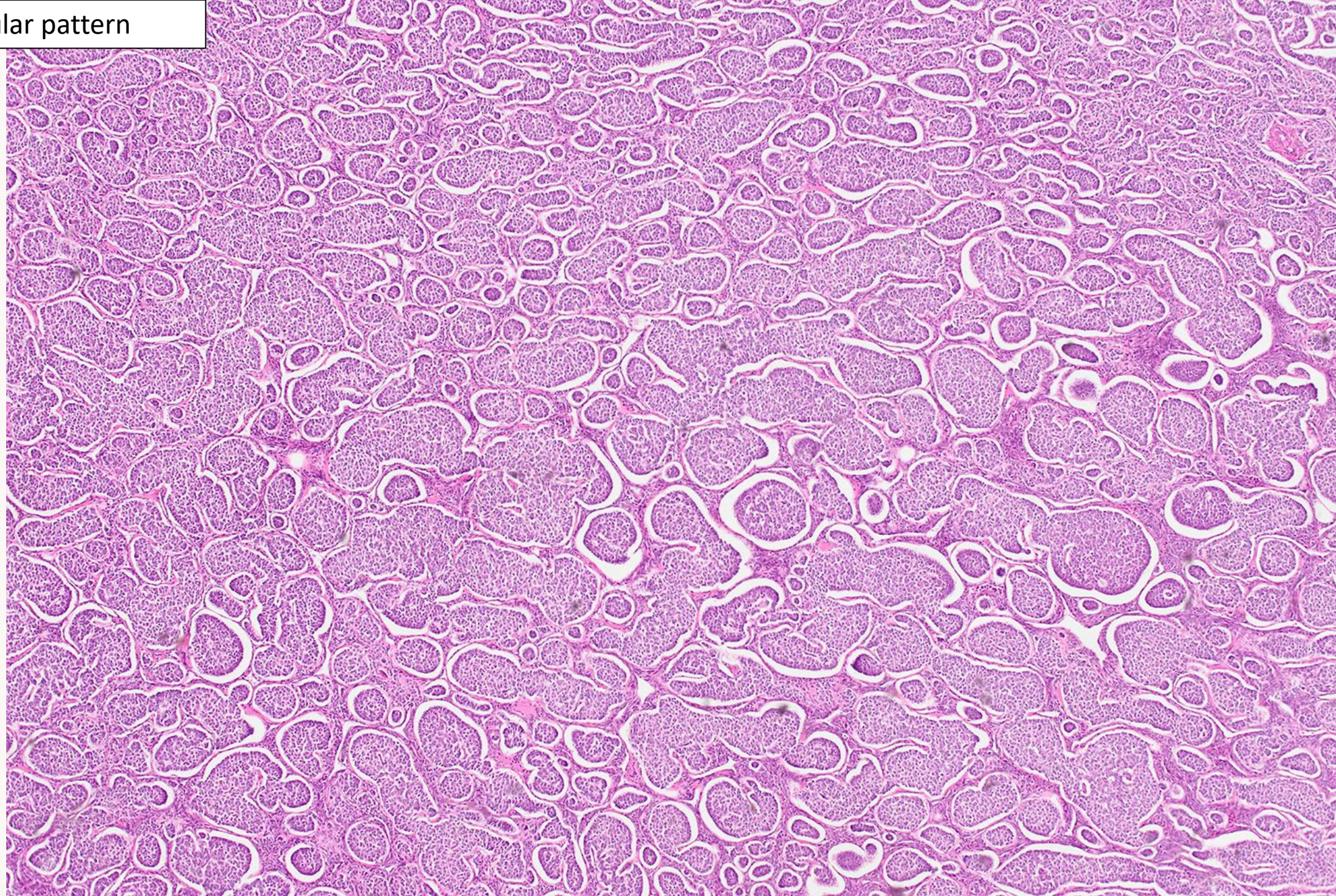


Packed Trabeculae

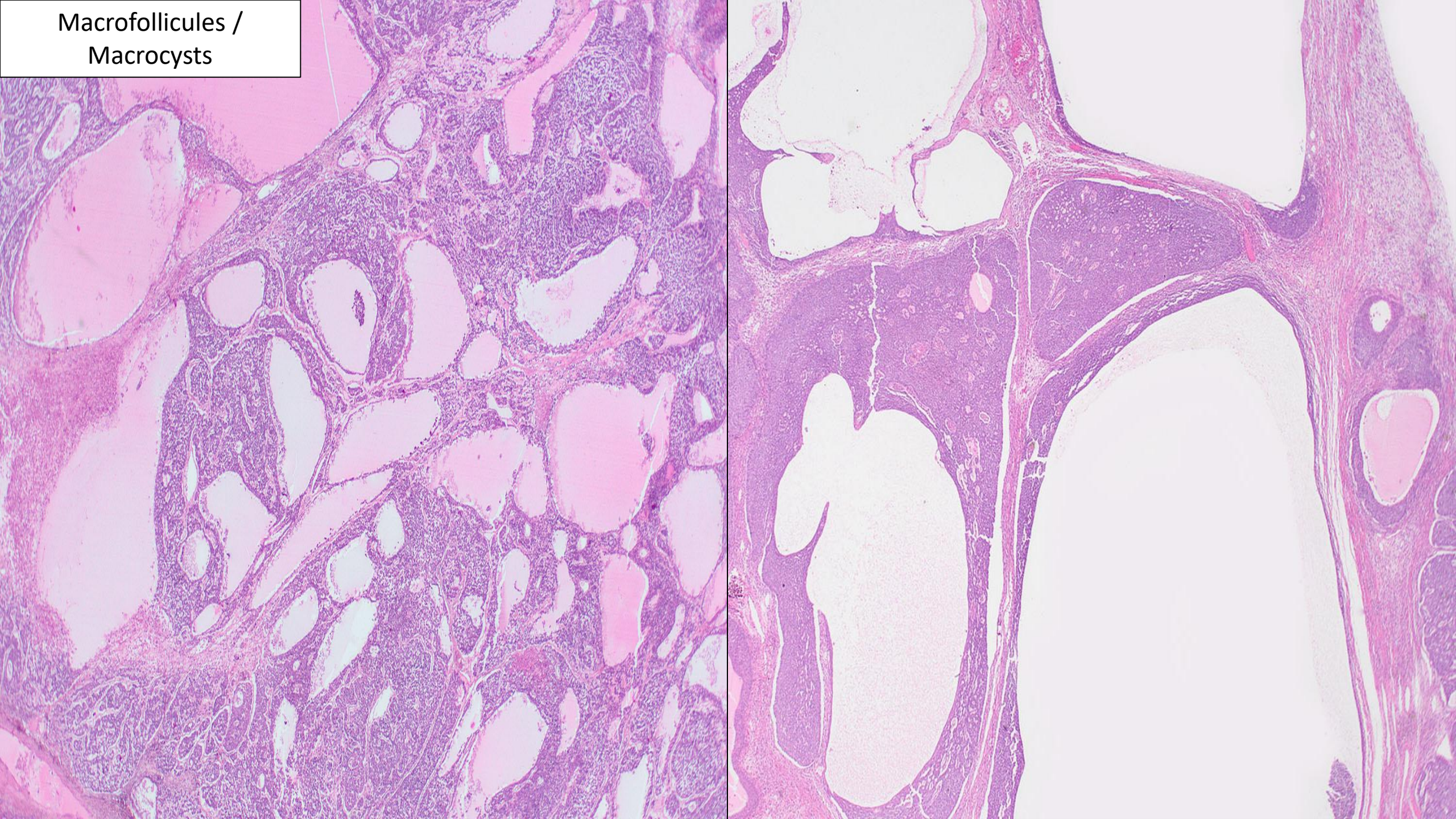


"Gyriform" Pattern

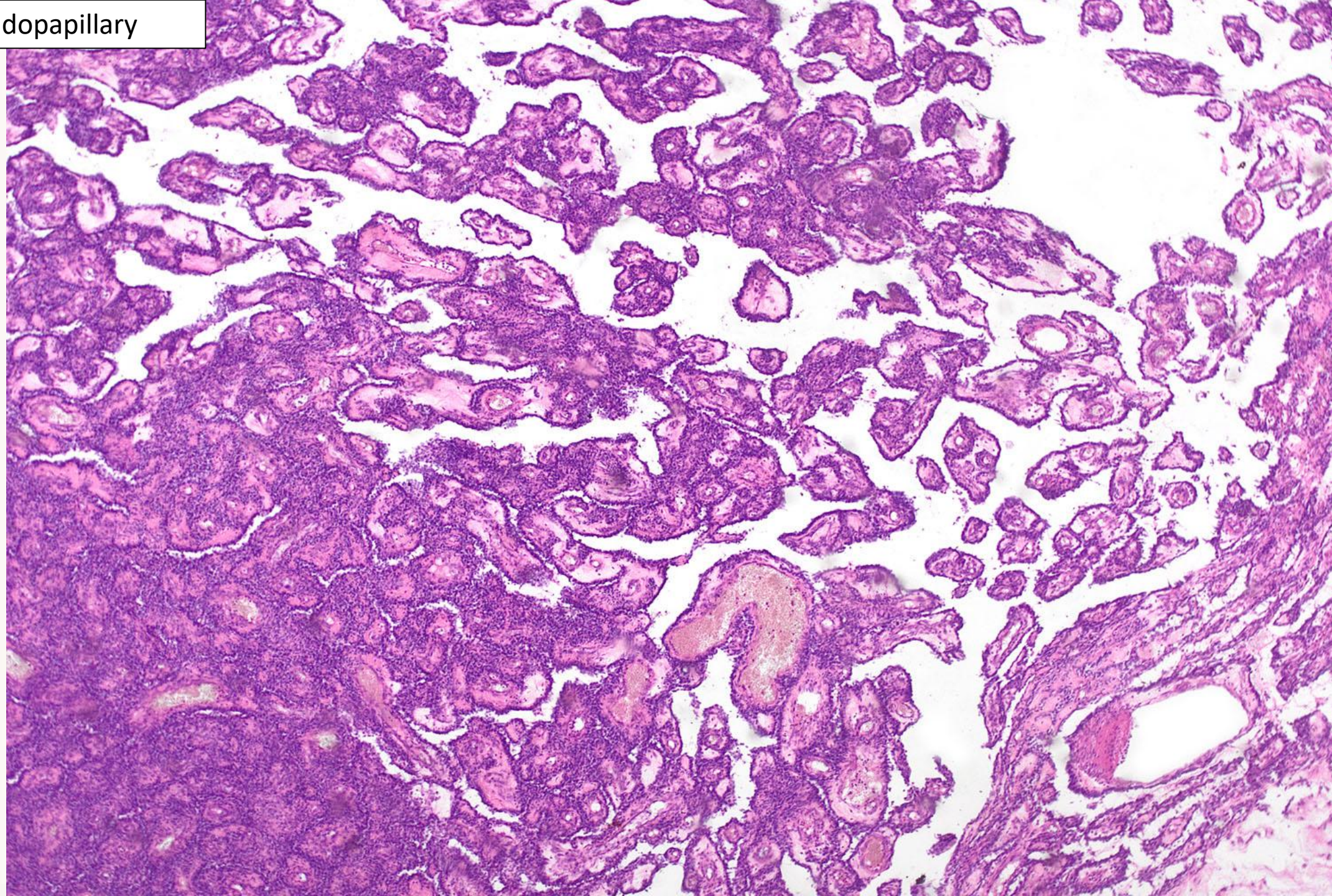
Insular pattern



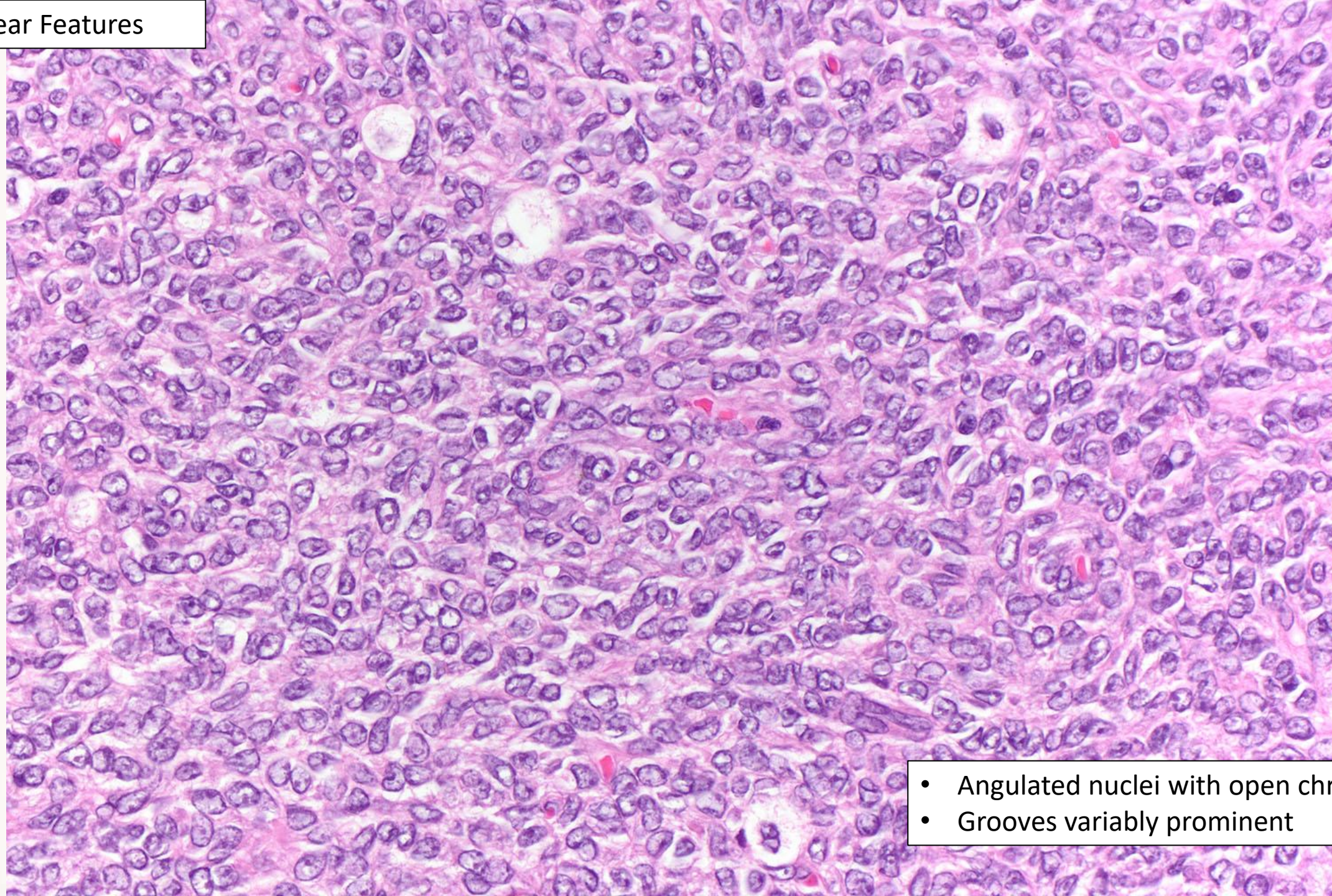
Macrofollicles /
Macrocysts



Pseudopapillary

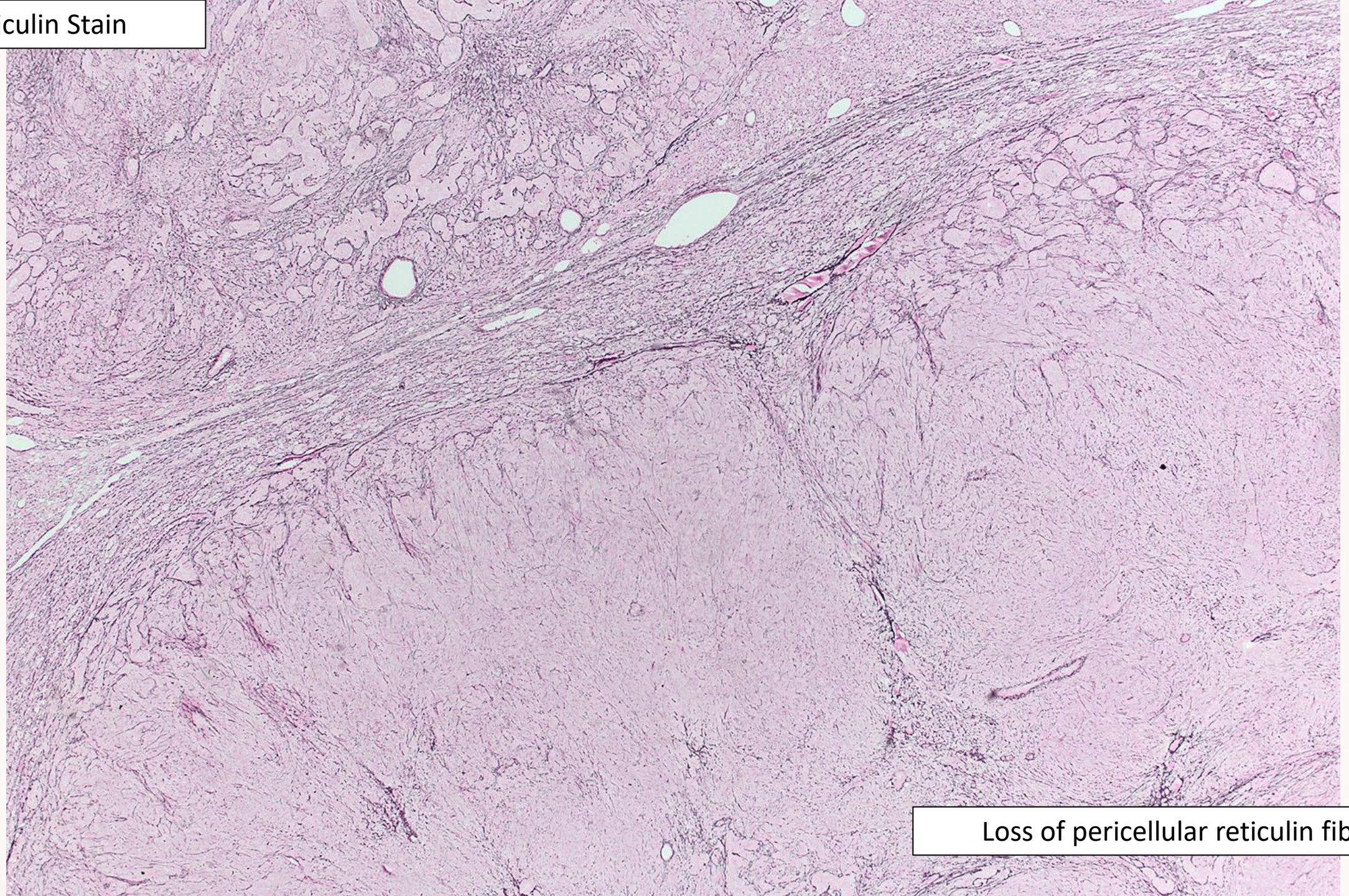


Nuclear Features



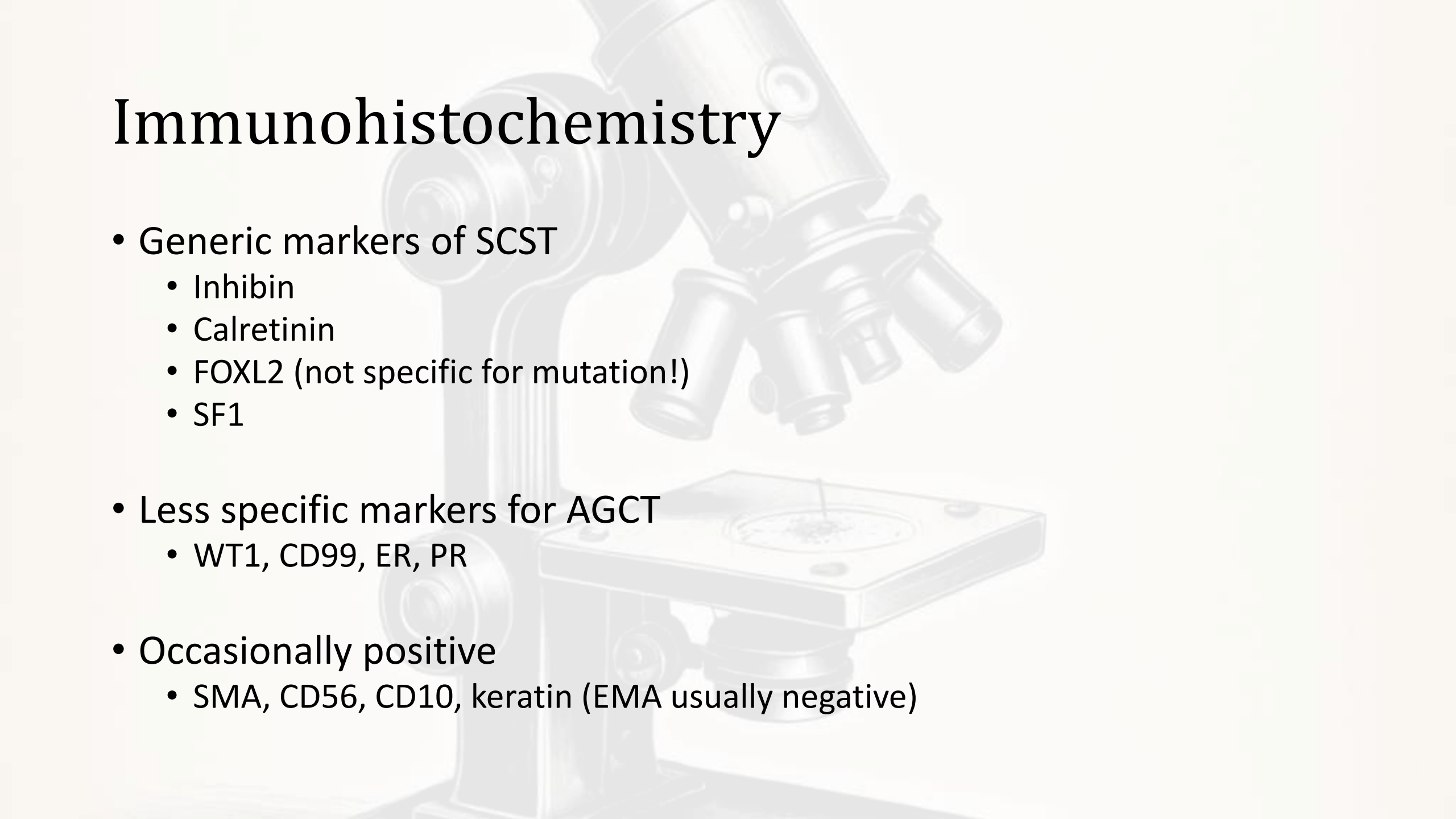
- Angulated nuclei with open chromatin
- Grooves variably prominent

Reticulin Stain



Loss of pericellular reticulin fibers

Immunohistochemistry



- Generic markers of SCST
 - Inhibin
 - Calretinin
 - FOXL2 (not specific for mutation!)
 - SF1
- Less specific markers for AGCT
 - WT1, CD99, ER, PR
- Occasionally positive
 - SMA, CD56, CD10, keratin (EMA usually negative)

FOXL2 Mutations

- c.402 (C > G) in up to 95% of AGCTs
- Does lack of *FOXL2* mutation rule out AGCT?
 - If other features support are supportive -> diagnose AGCT
 - Rare alternate *FOXL2* mutations (c.398C>T)
 - Rare tumors have alternate driver mutations (*FGFR1*)
 - *FOXL2* less frequent in certain subtypes
 - Cellularity of granulosa component may impact detection

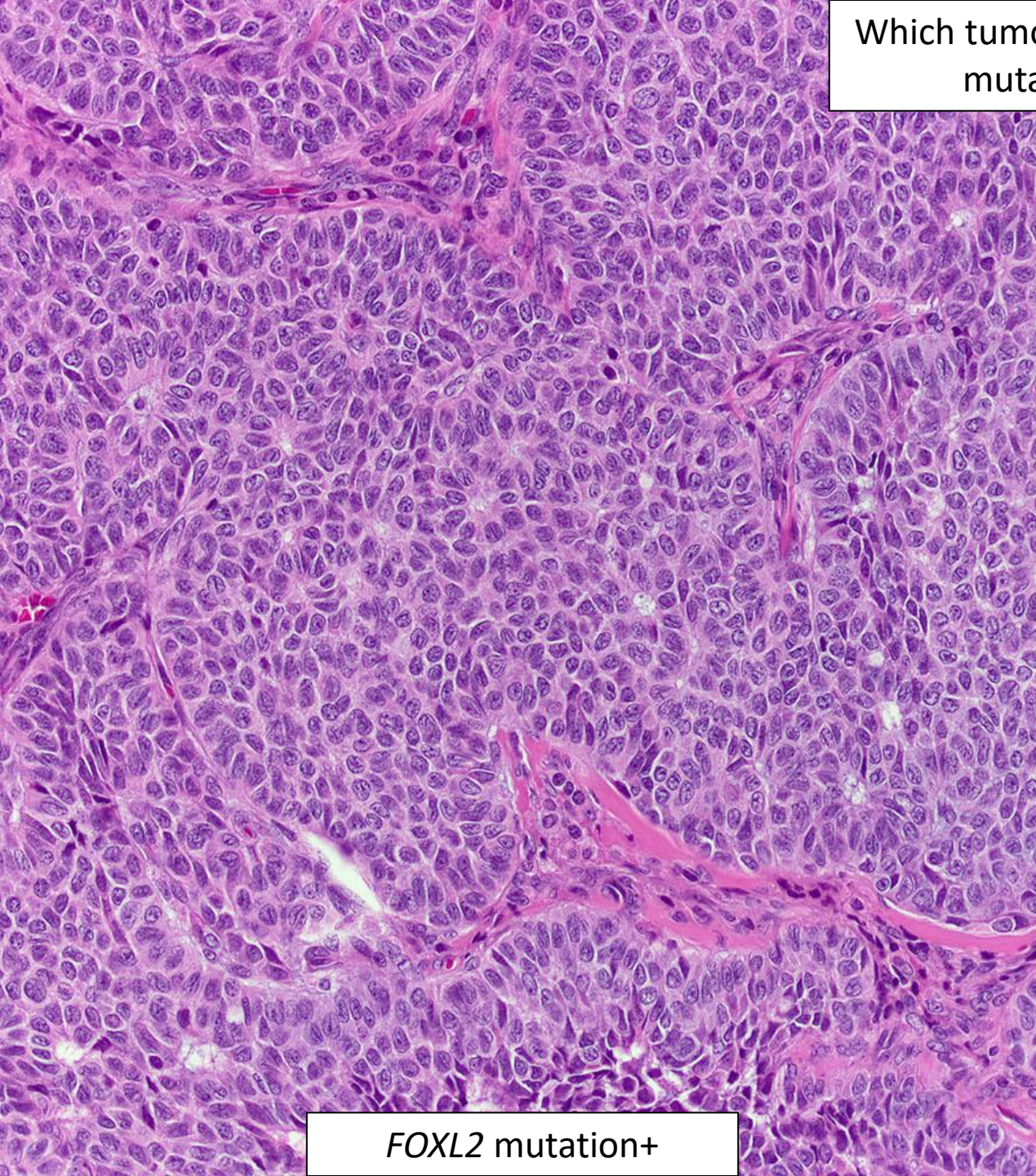
Kolin DL, Mata DA, Lin DI, Ellenson LH, Momeni-Boroujeni A. FGFR1 Mutations Are Rare Alternate Oncogenic Drivers in FOXL2 - Wildtype Adult Granulosa Cell Tumors of the Ovary. Am J Surg Pathol. 2025 Dec 1;49(12):1245-1250.

Nagy A, et al. Novel FOXL2 Mutation in an Ovarian Adult Granulosa Cell Tumor: Report of a Case With Diagnostic and Clinicopathologic Implications. Int J Gynecol Pathol. 2024 Nov 1;43(6):631-636.

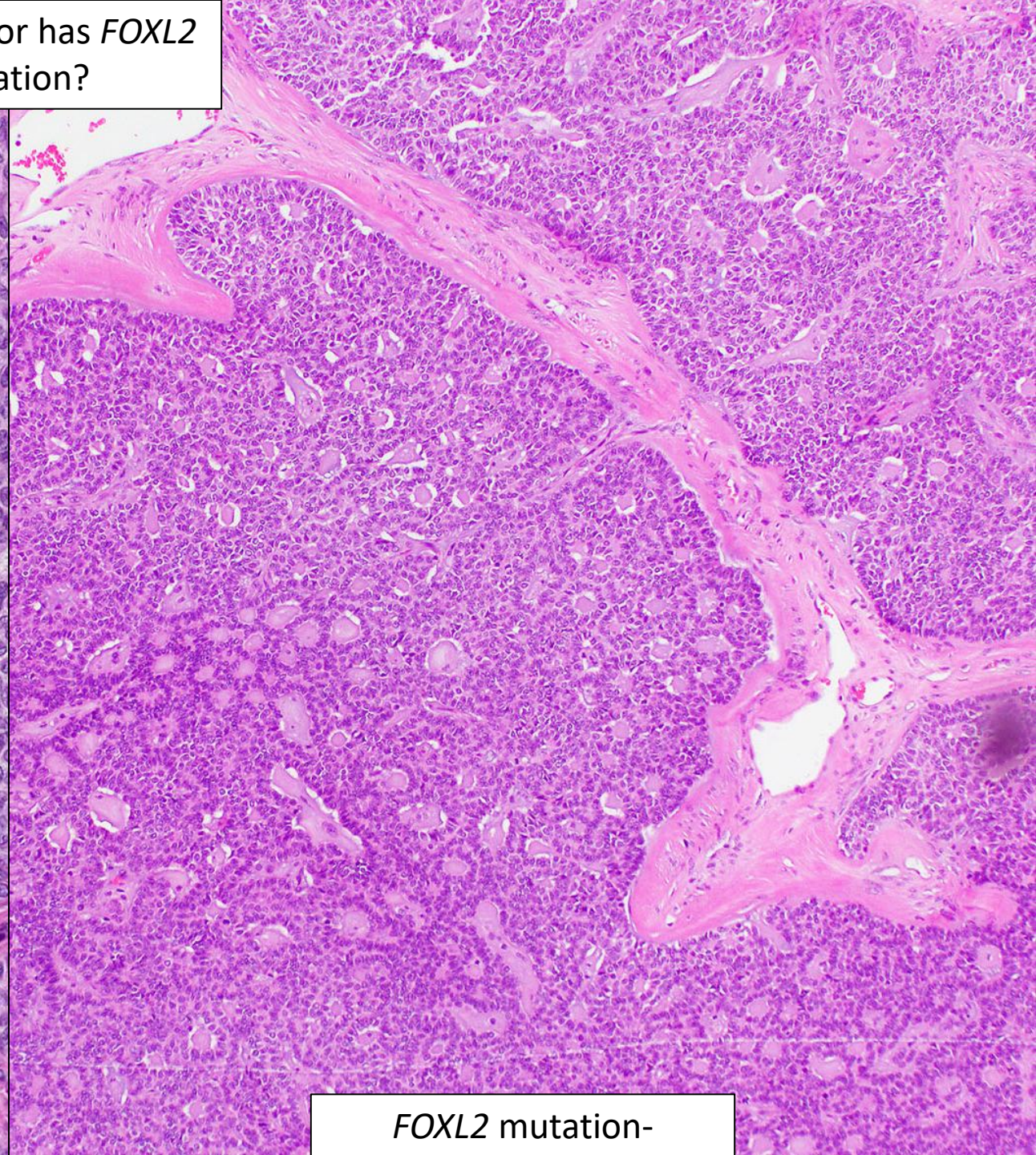
Shah S, et al. Mutation of FOXL2 in granulosa-cell tumors of the ovary. N Engl J Med. 2009 Jun 25;360(26):2719-29.

Michálková R, et al. The Molecular Landscape of 227 Adult Granulosa Cell Tumors of the Ovary: Insights into the Progression from Primary to Recurrence. Lab Invest. 2025 Mar;105(3):102201.

Which tumor has *FOXL2* mutation?



FOXL2 mutation+



FOXL2 mutation-

FOXL2 Mutations

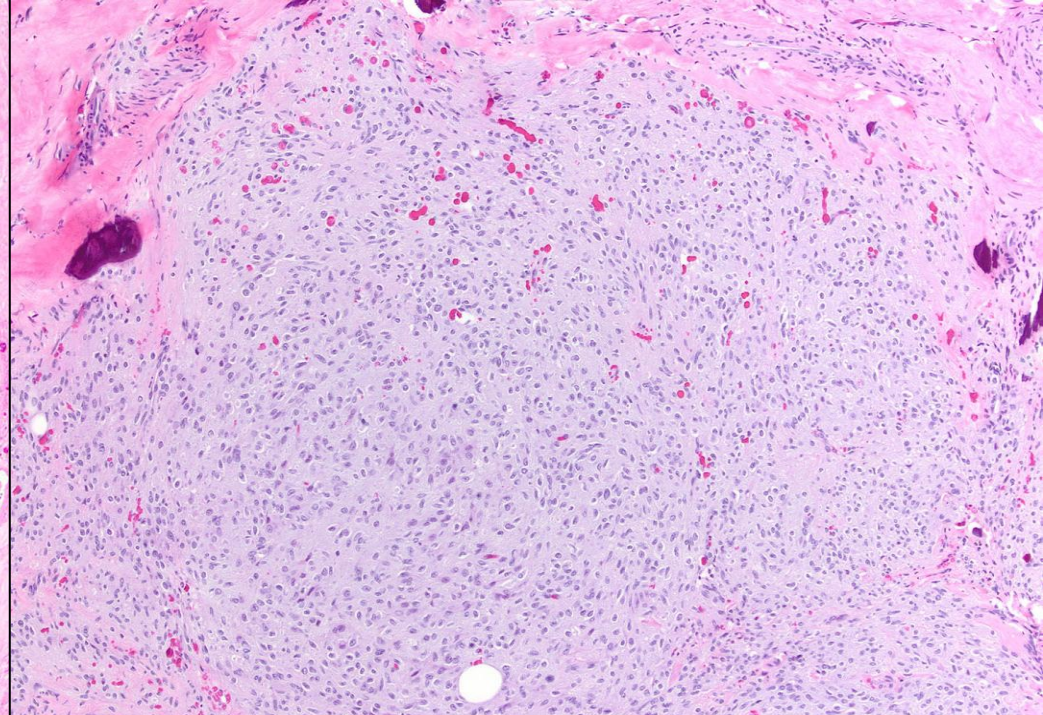
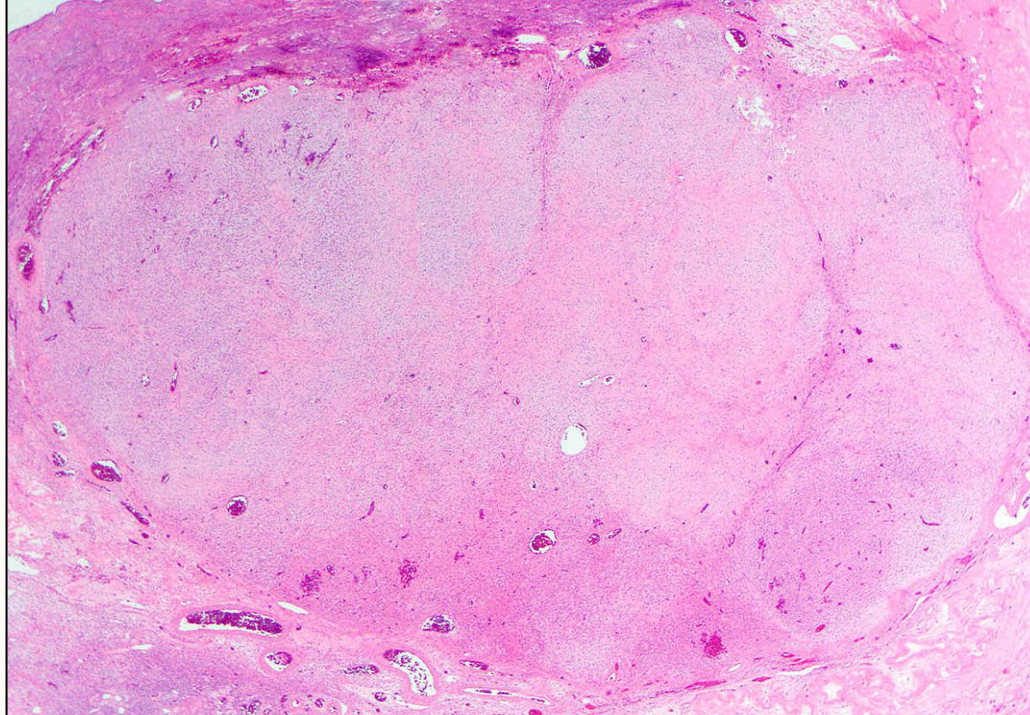
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 - *FOXL2* less frequent in certain subtypes
 - Cellularity of granulosa component may impact detection
- Is *FOXL2* mutation specific for AGCT?
 - Rare reports of “thecomas,” SLCT, and JGCT with *FOXL2* mutations
 - At least one report of “thecoma” recurring as tumor with classic AGCT features
 - Identical *FOXL2* mutations found in both primary and recurrent tumors

Nagy A, et al. Novel *FOXL2* Mutation in an Ovarian Adult Granulosa Cell Tumor: Report of a Case With Diagnostic and Clinicopathologic Implications. *Int J Gynecol Pathol*. 2024 Nov 1;43(6):631-636.

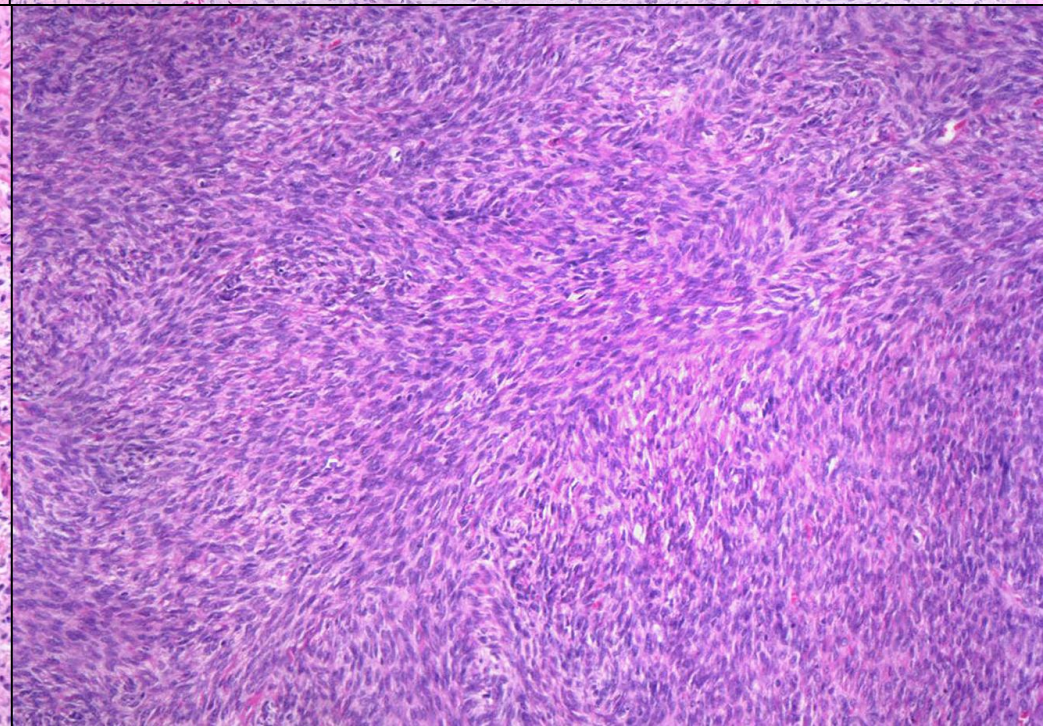
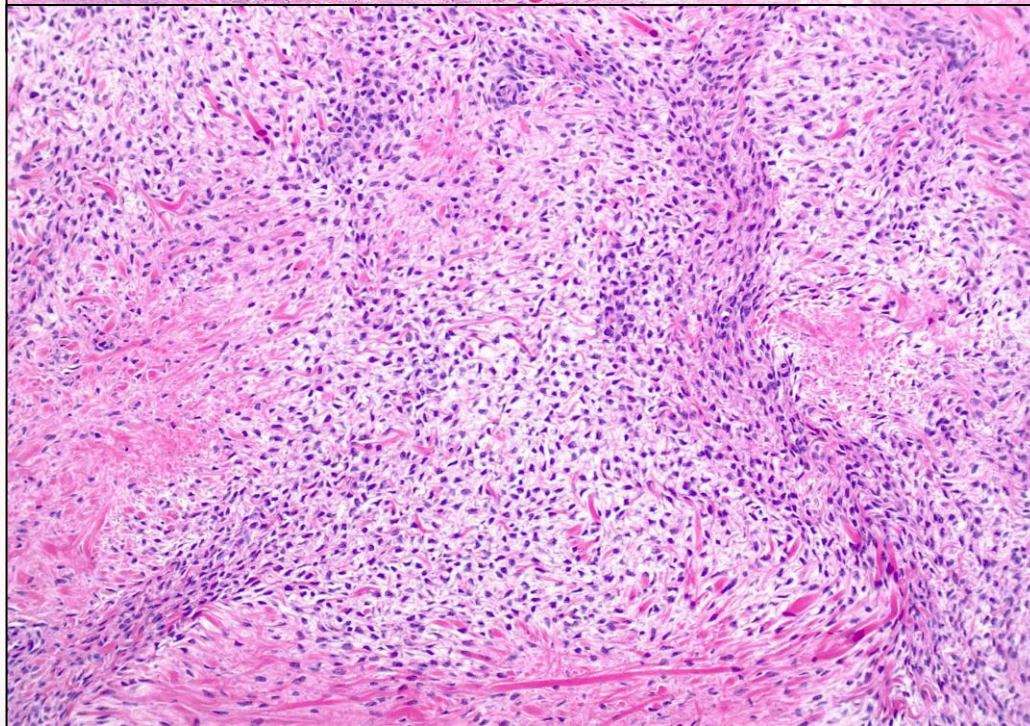
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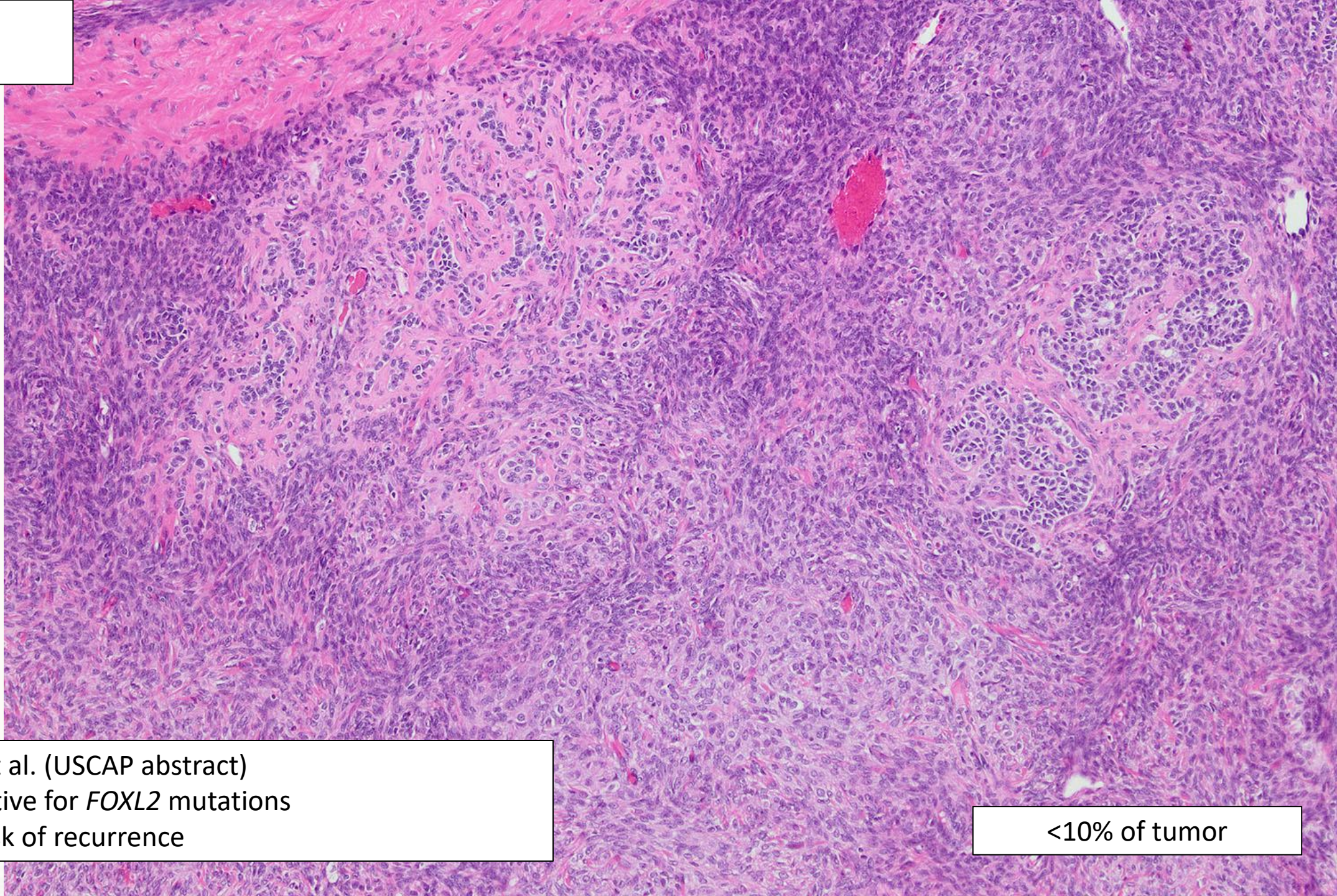
Thecoma



Fibroma



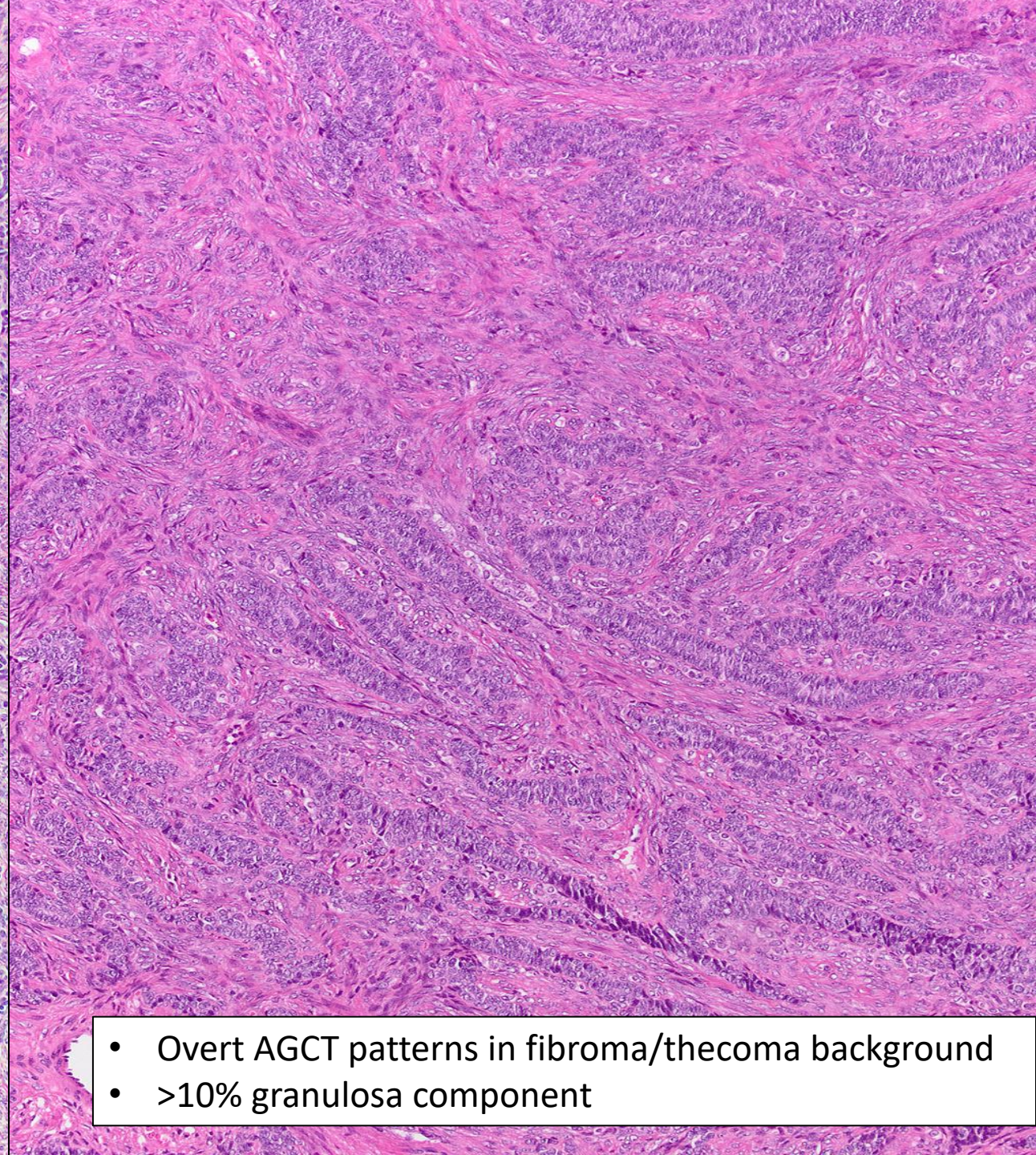
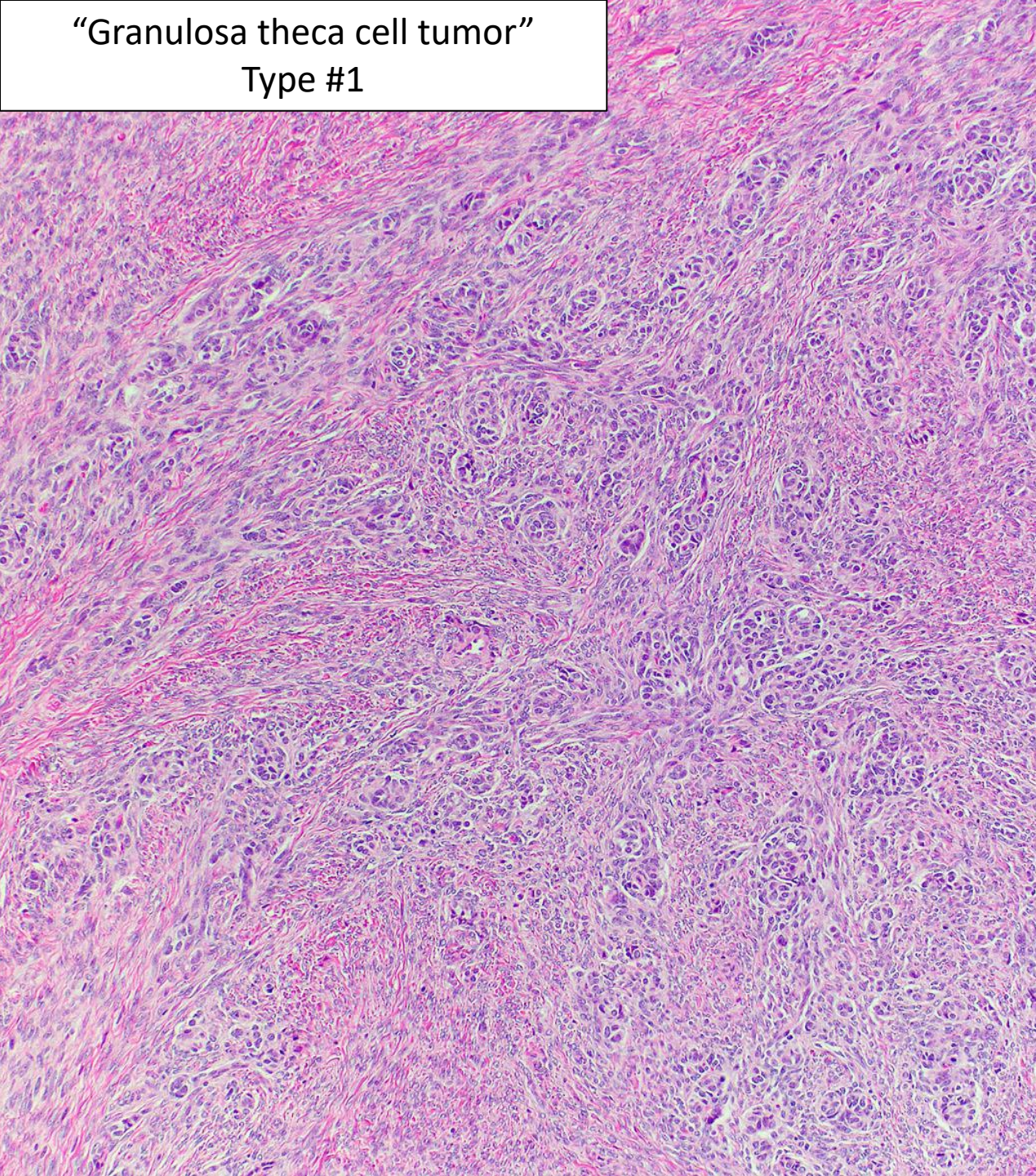
Minor Sex Cord Elements



- Siatecka et al. (USCAP abstract)
 - Negative for *FOXL2* mutations
 - No risk of recurrence

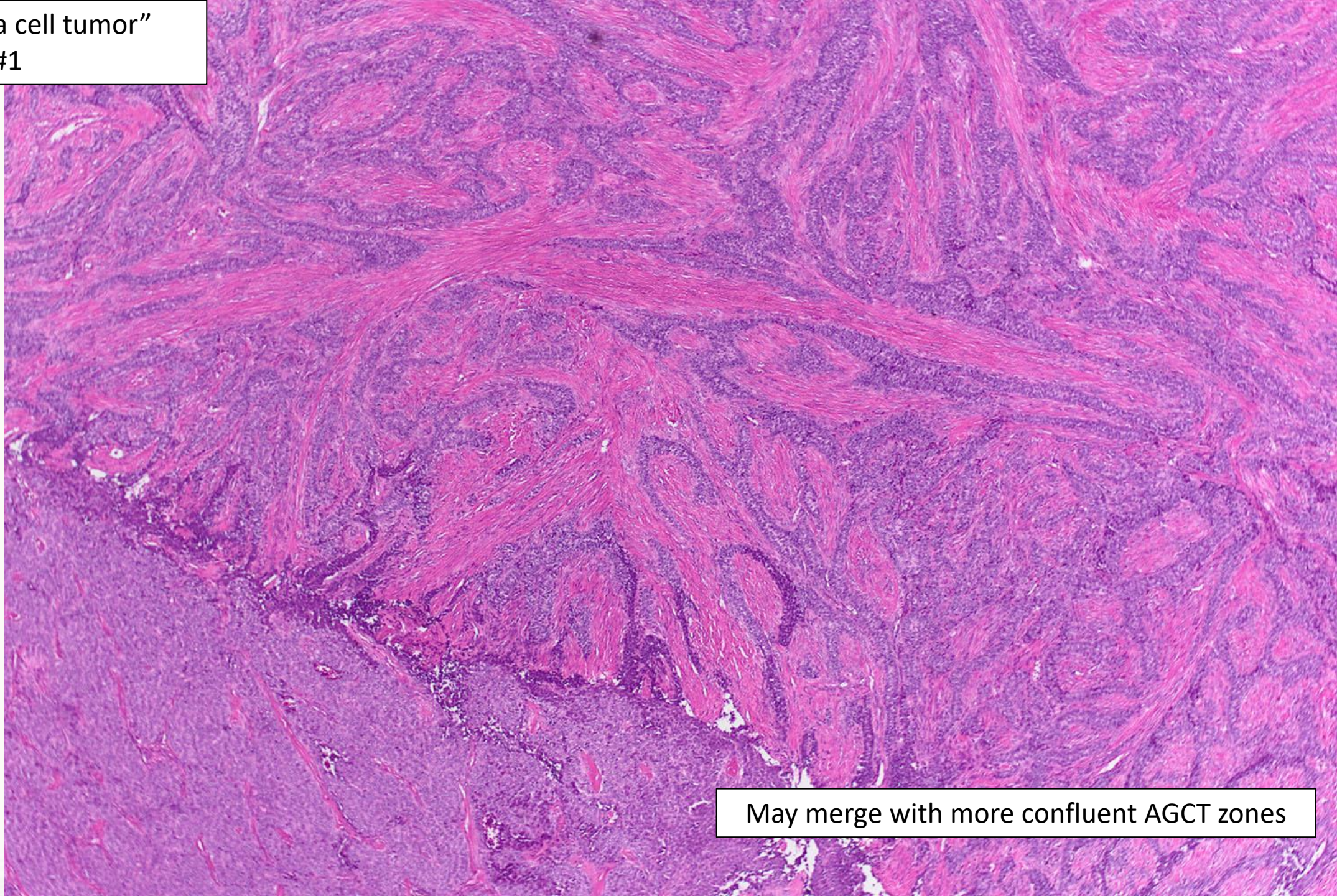
<10% of tumor

“Granulosa theca cell tumor”
Type #1



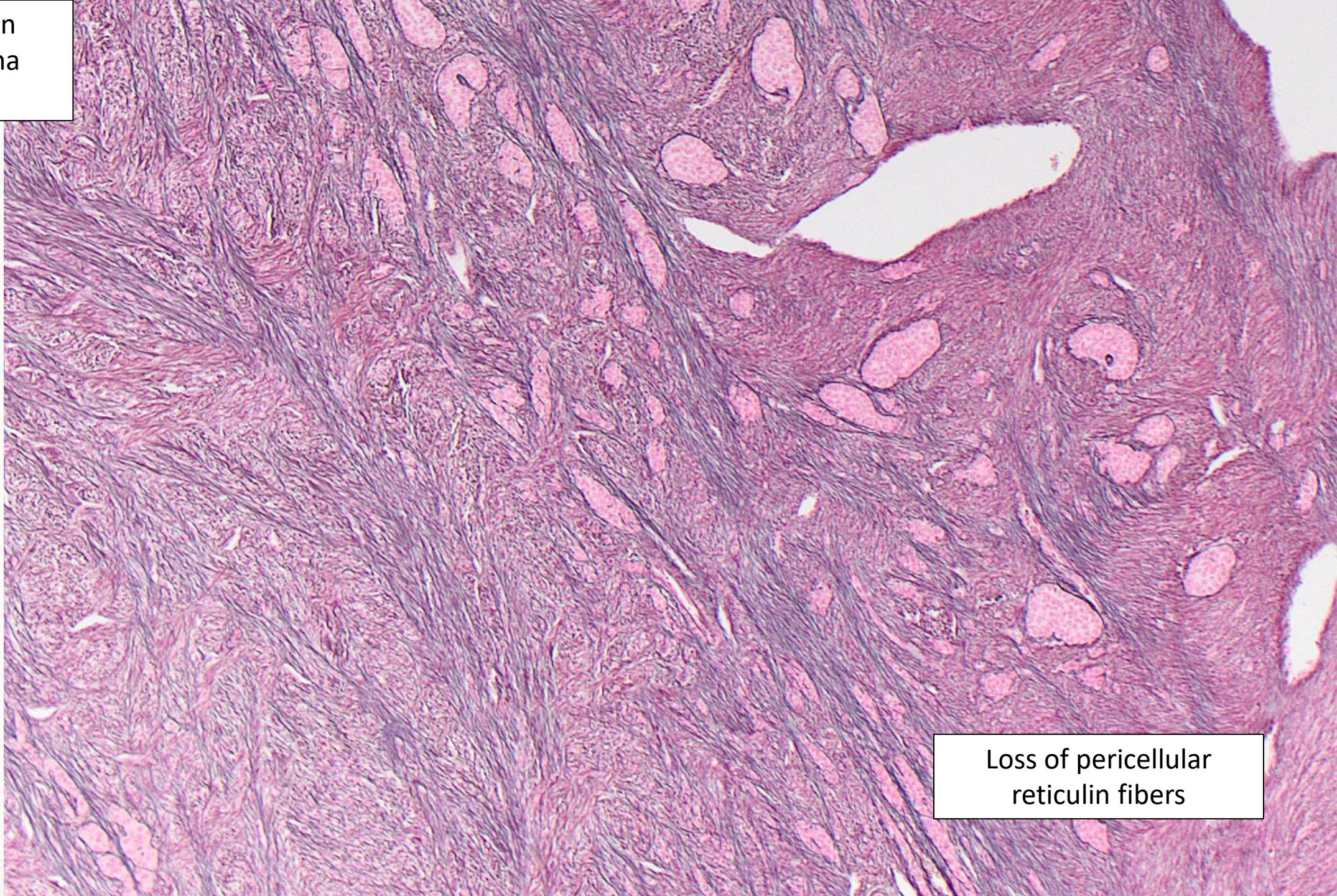
- Overt AGCT patterns in fibroma/thecoma background
- >10% granulosa component

“Granulosa theca cell tumor”
Type #1



May merge with more confluent AGCT zones

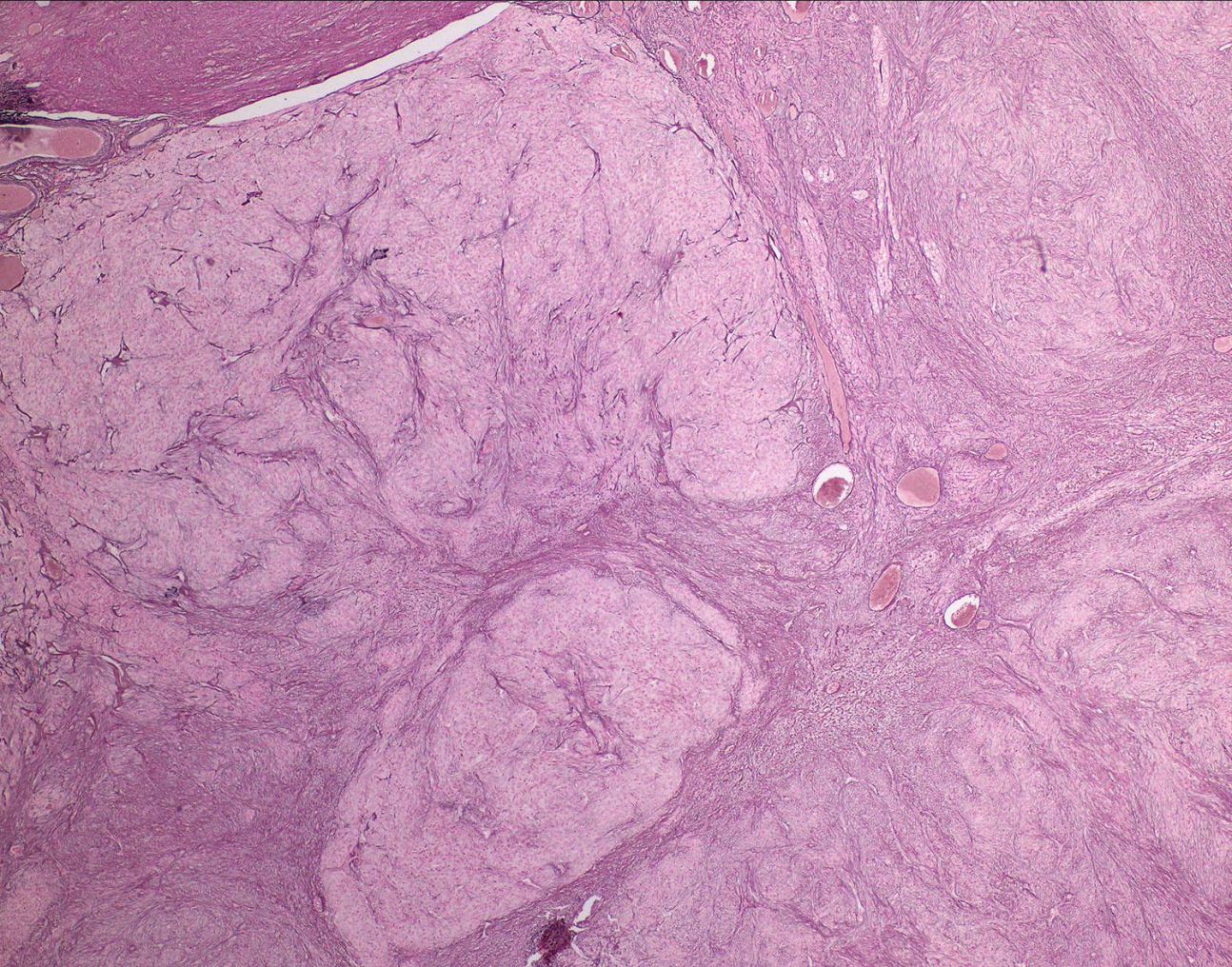
Granulosa Cells in
Fibroma/Thecoma
Background



Loss of pericellular
reticulin fibers

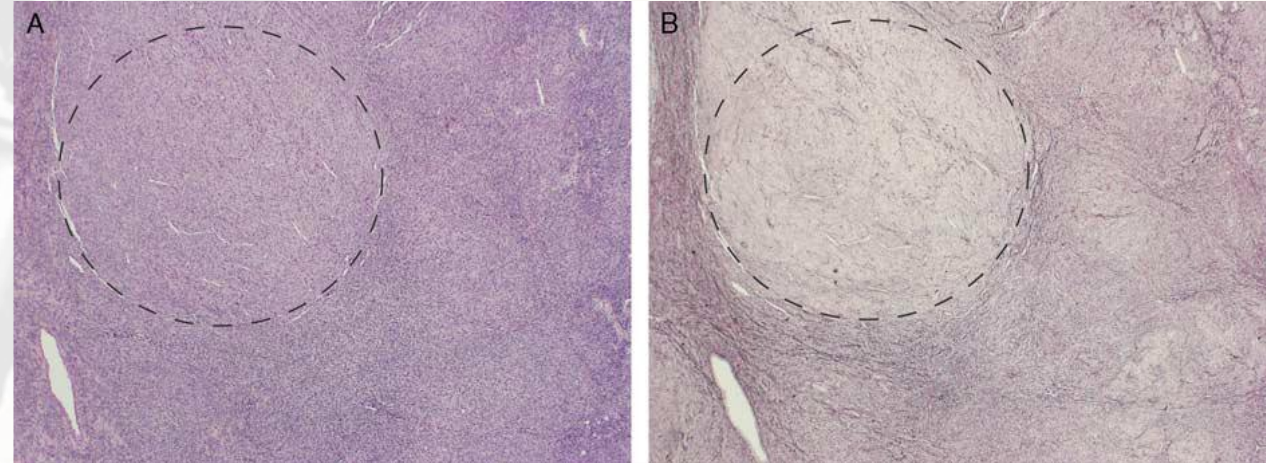
“Granulosa theca cell tumor”
Type #2

- Cellular rounded epithelioid aggregates of granulosa cells in a fibroma/thecoma background
- Loss of reticulin fibers in these aggregates



FOXL2 in AGCT with Fibroma/Thecoma Background

- Nolan et al.
 - *FOXL2* mutations in 6/12 (50%)



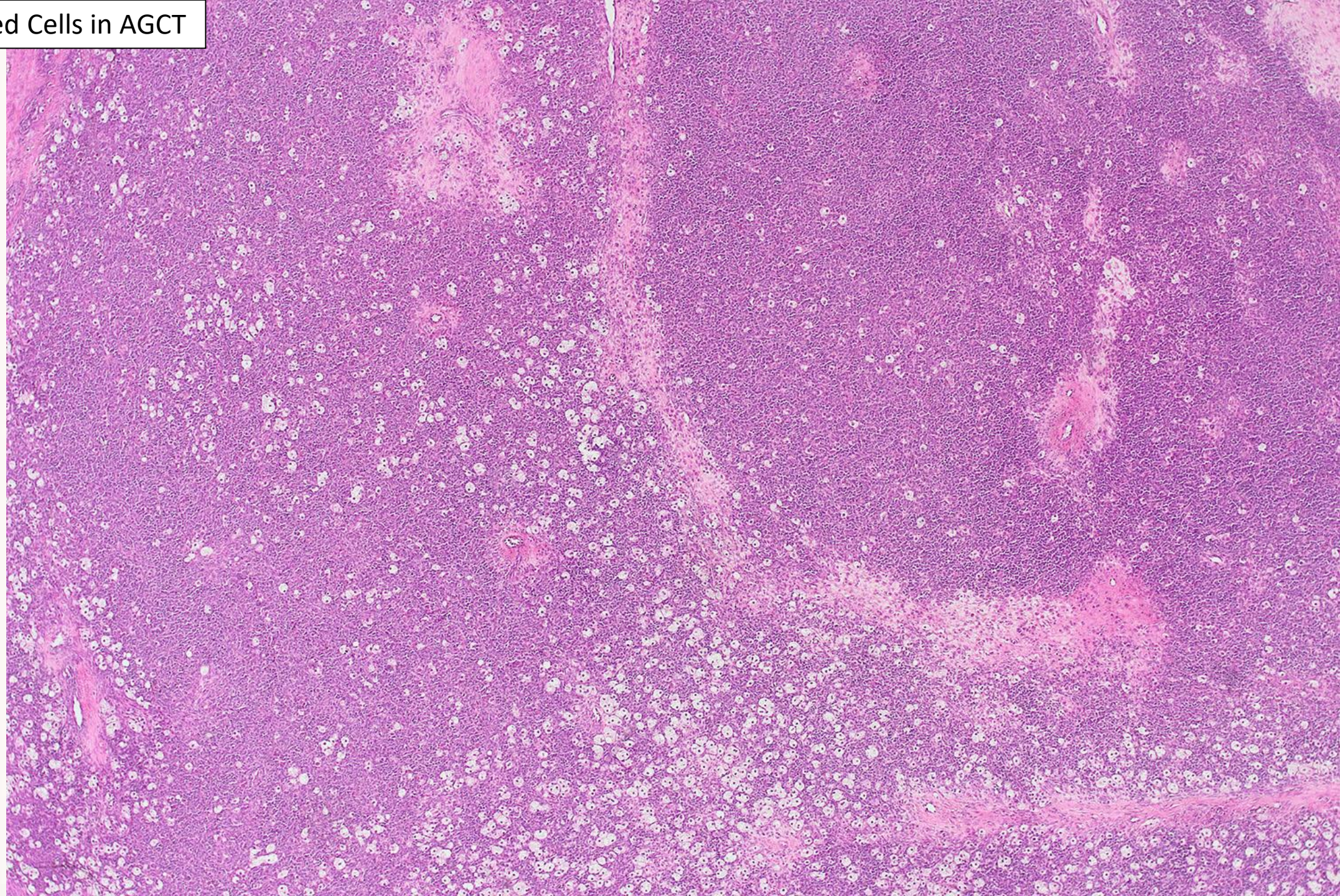
4/4 Tumors with cellular aggregates in a fibroma/thecoma background

- Mutation present in both granulosa and background fibroma/thecoma
- Rough correlation with % granulosa cells and mutation status
 - None of the tumors with <30% granulosa cells had *FOXL2* mutations

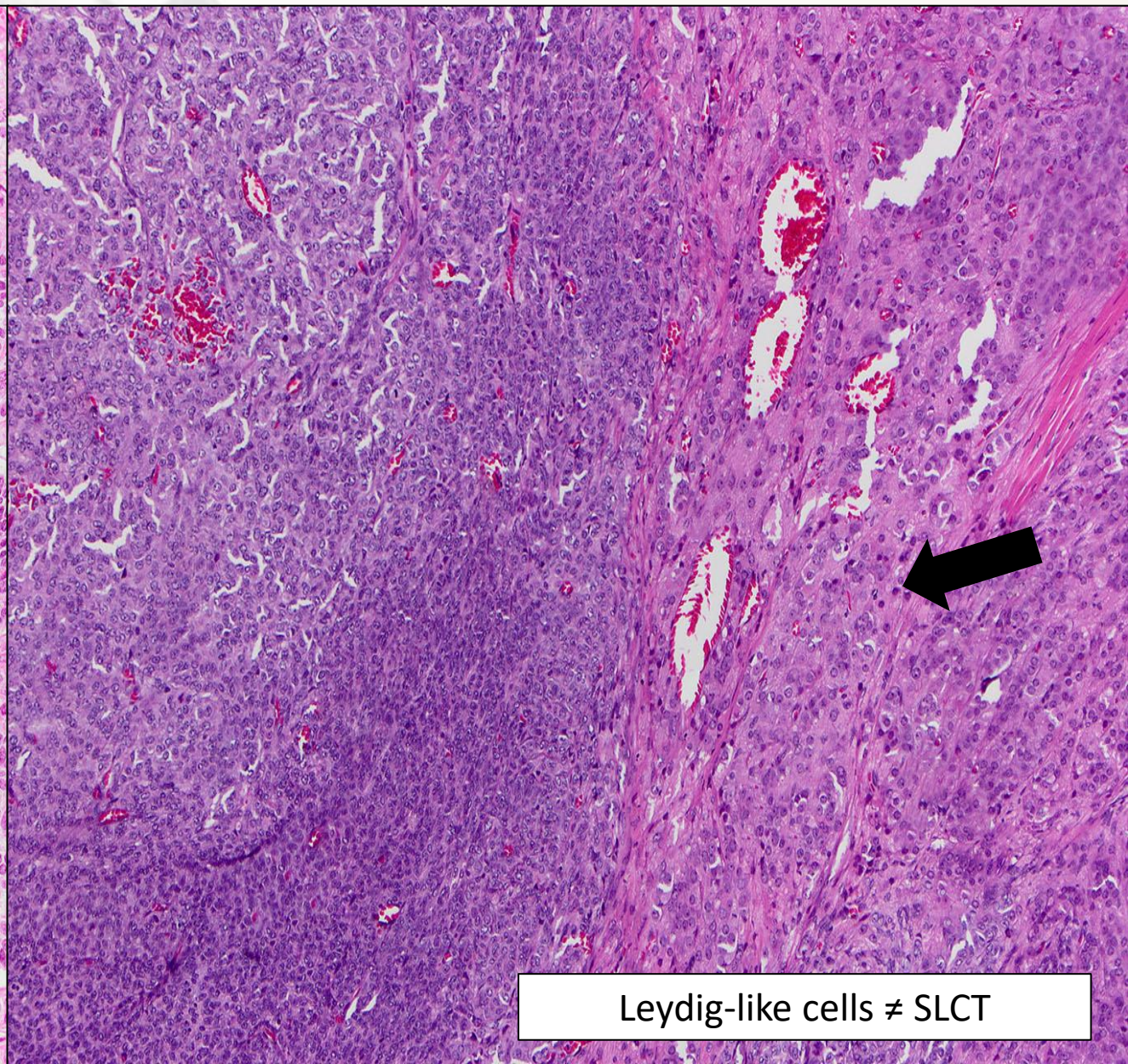
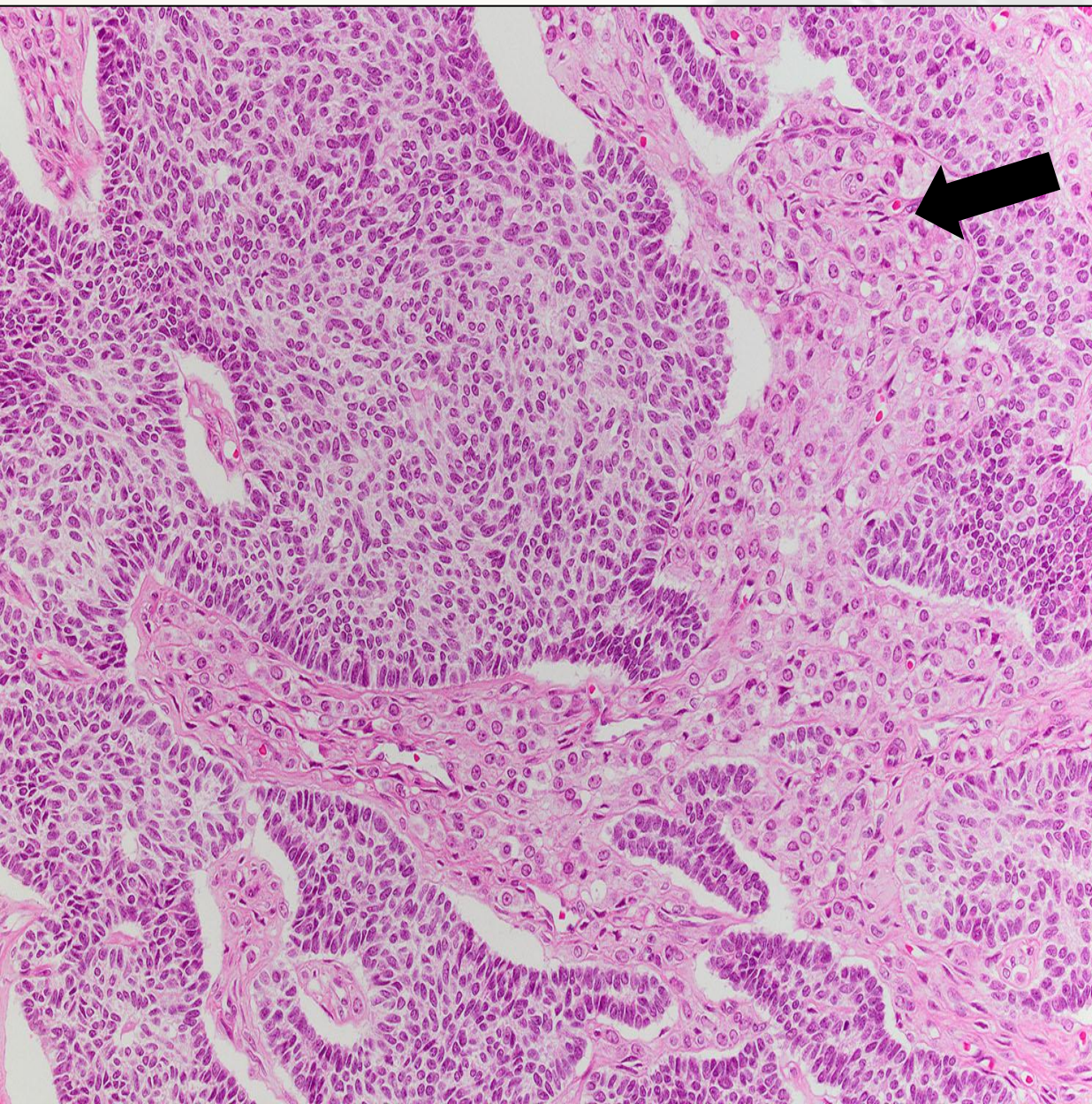
AGCT with Fibroma/Thecoma Background

- Outcomes difficult to assess
 - Rare tumors
 - Long follow-up required
 - Many studies of recurrent AGCT do not document fibroma/thecoma component in primary tumor
- Does *FOXL2* status impact diagnosis/outcome?
 - Most but not all recurrent AGCTs harbor *FOXL2* mutations
 - Unclear impact specifically in tumors with fibroma/thecoma background
- Practical recommendations
 - If a tumor shows >10% overt sex cord component: AGCT
 - If unsure, reticulin stain may be helpful
 - Loss in morphologically suspicious areas: AGCT
 - Individual cell pattern: Thecoma/Fibroma
 - Role of *FOXL2* testing?
 - If mutation positive: AGCT
 - If mutation negative: Does not rule out AGCT

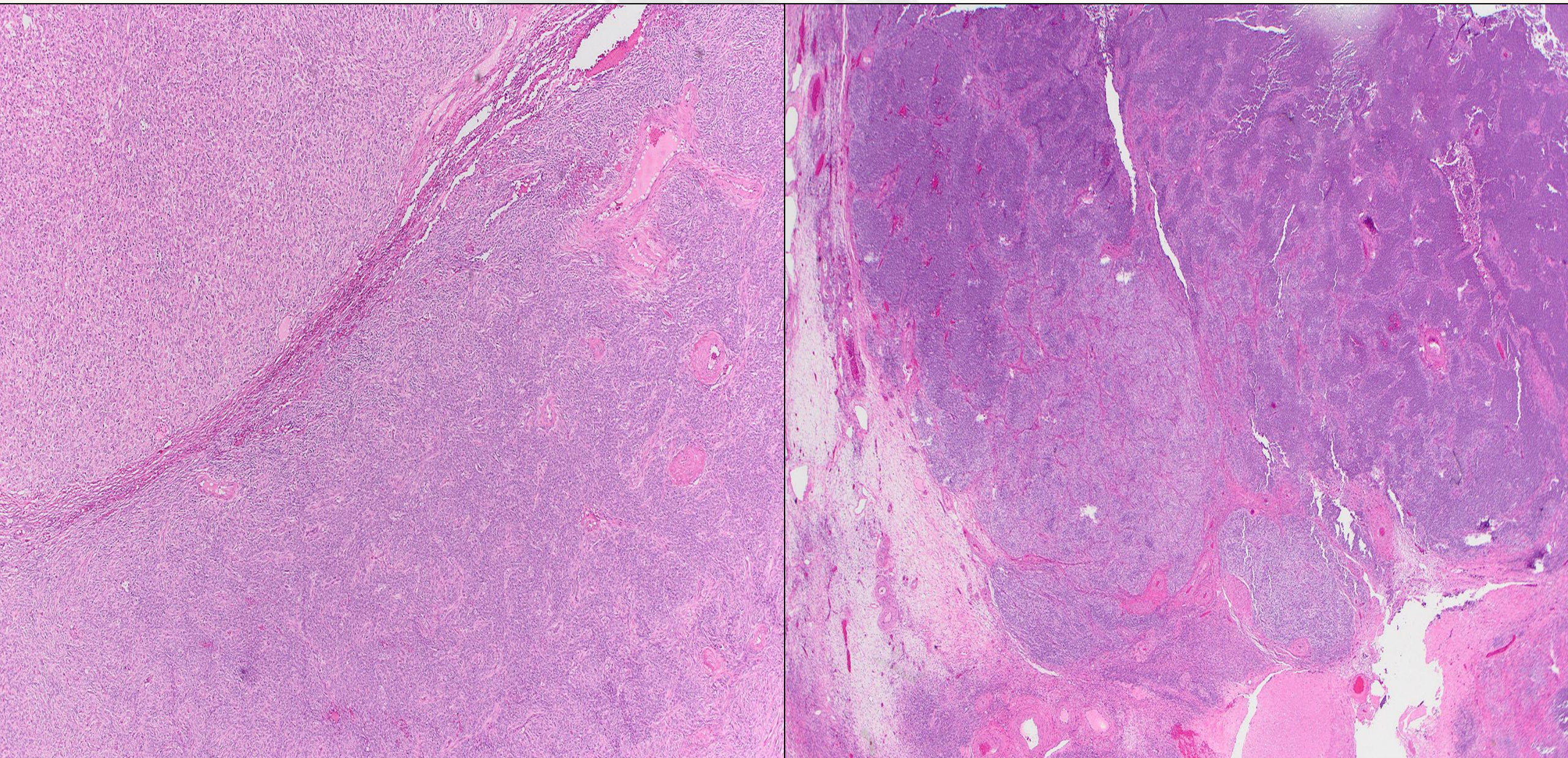
Luteinized Cells in AGCT



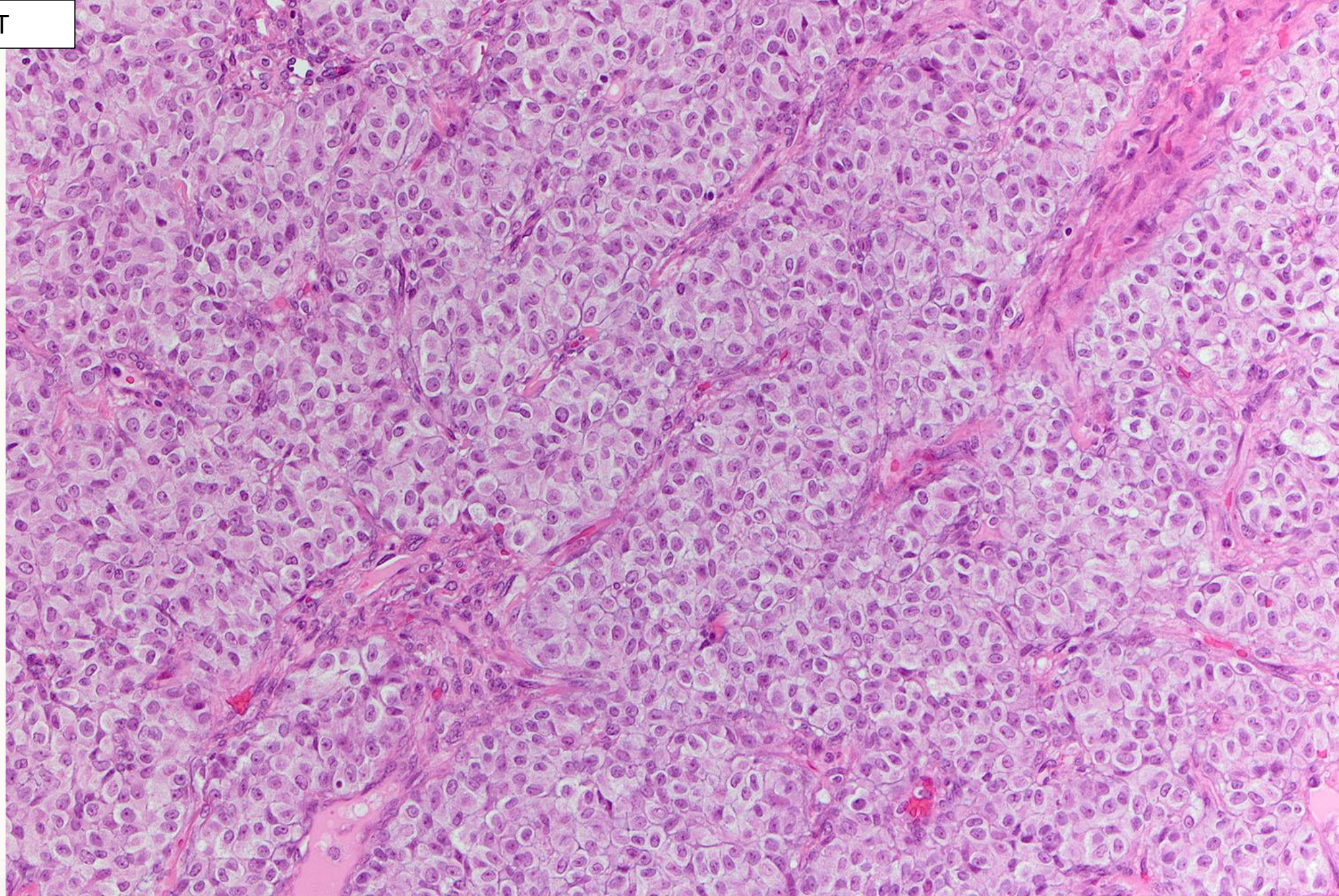
Luteinized Cells in AGCT



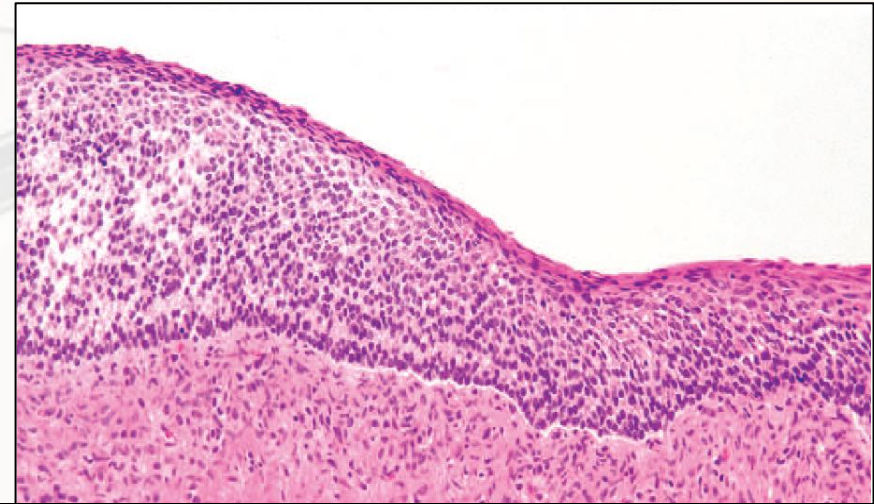
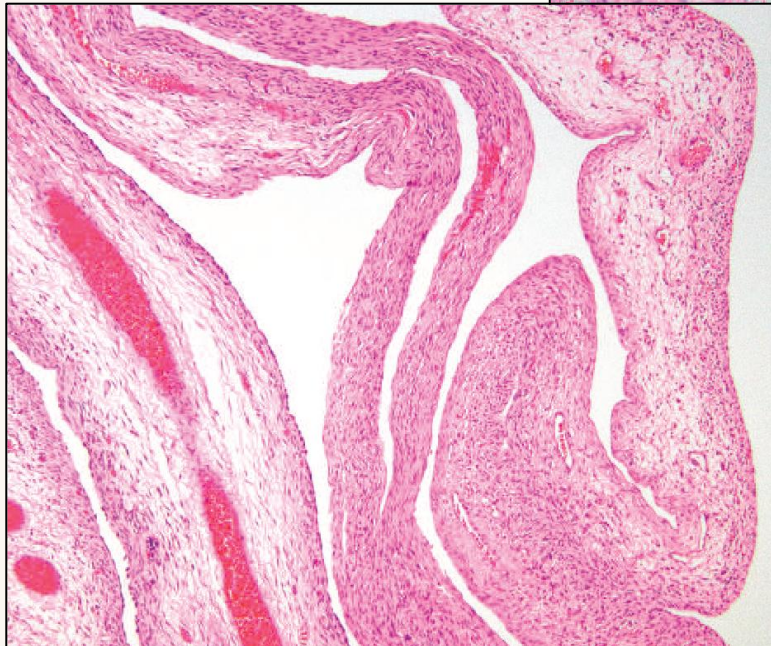
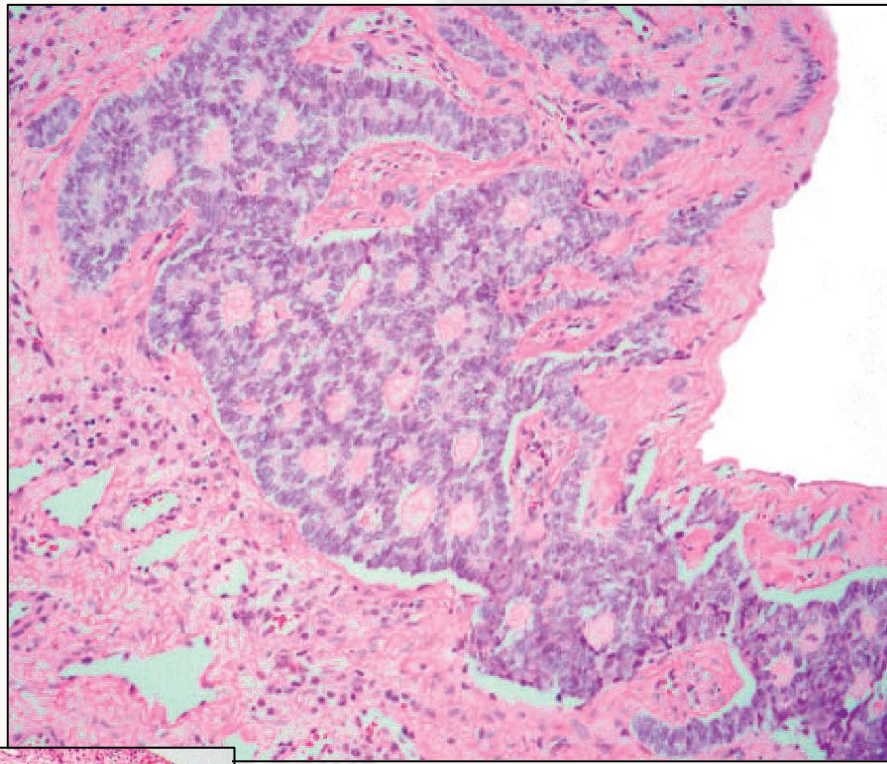
Leydig-like cells $\neq$ SLCT



Luteinized AGCT



Cystic AGCT

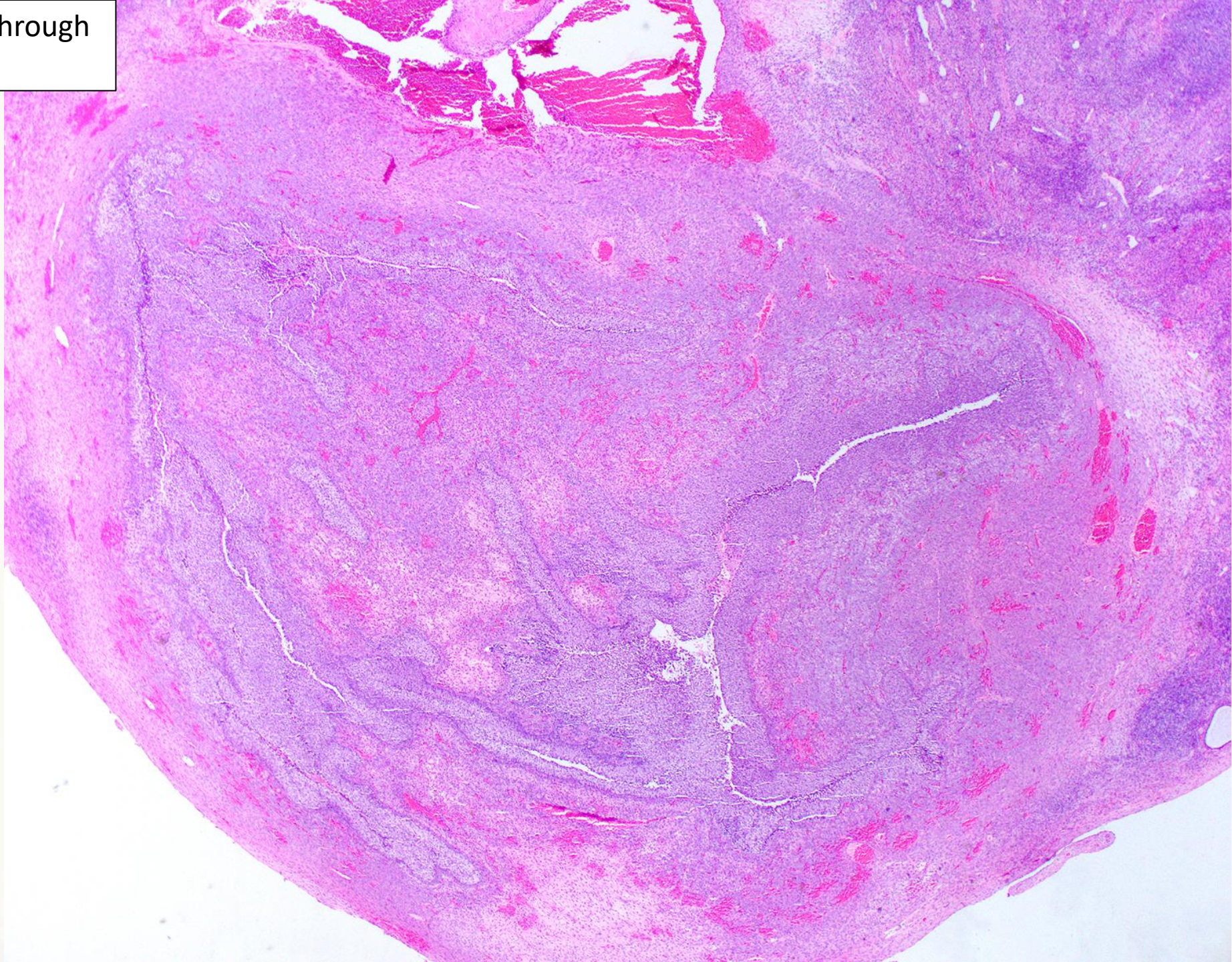


Cystic AGCT vs. Follicle Cyst

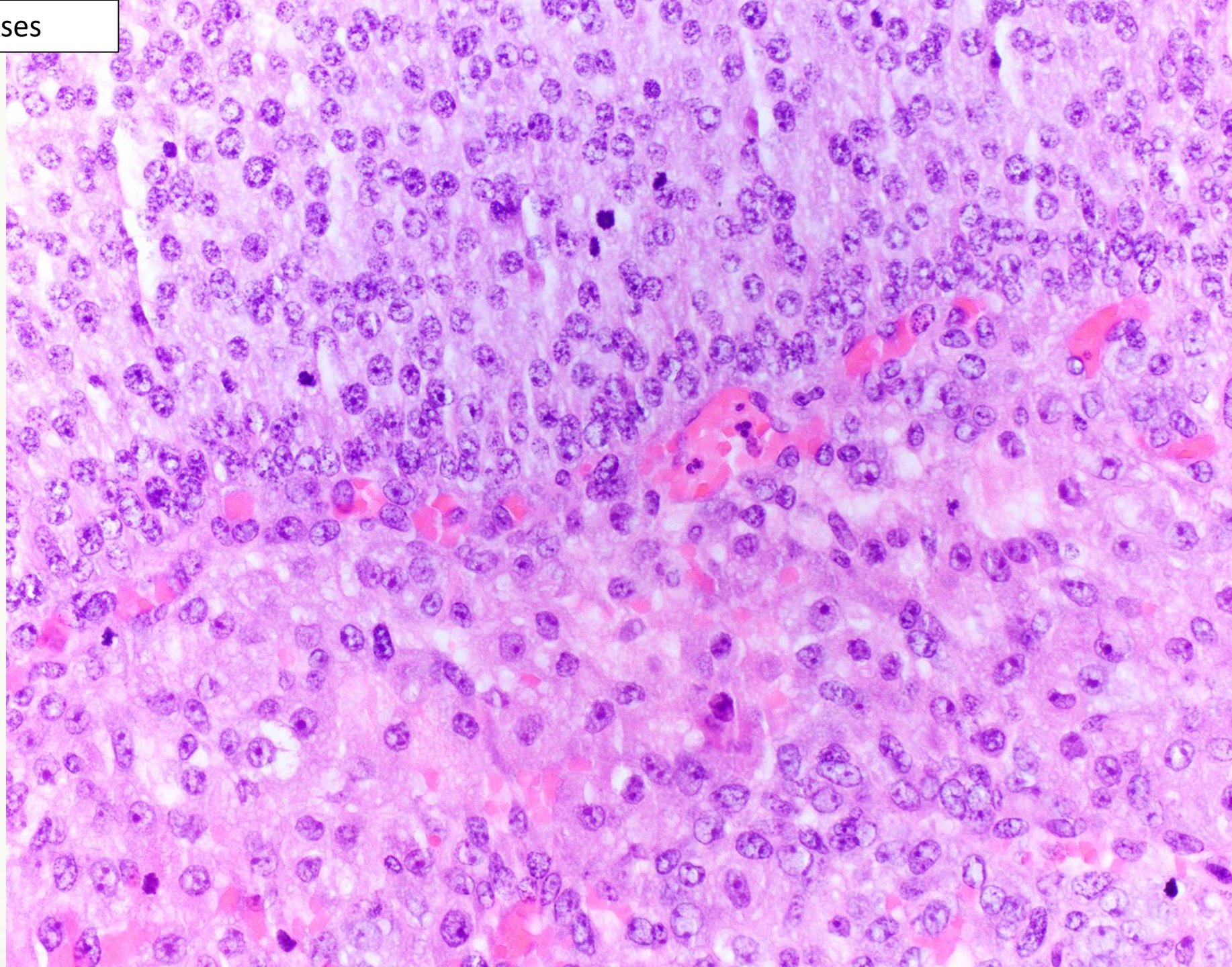
Feature	Follicle Cyst	Cystic AGCT
Age	Premenopausal	Pre- or post-menopausal
Size	Typically < 8 cm	Usually > 8 cm
Cut Surface	Unilocular, no solid areas	Unilocular or multilocular, may have solid nodules in wall
Architecture	Flat lining, no papillary projections	Cords, trabeculae, Call-Exner bodies, or solid nests invading into surrounding stroma
Number of Cell Layers	3 – 10 (avg. 6)	5-45 (avg. 22)
Mitotic Index	1 – 34 / 10 HPF	1 – 20 / 10 HPF
<i>FOXL2</i>	Wild-type	Mutations in at least 25%

****Presence of theca cell layer does not help****

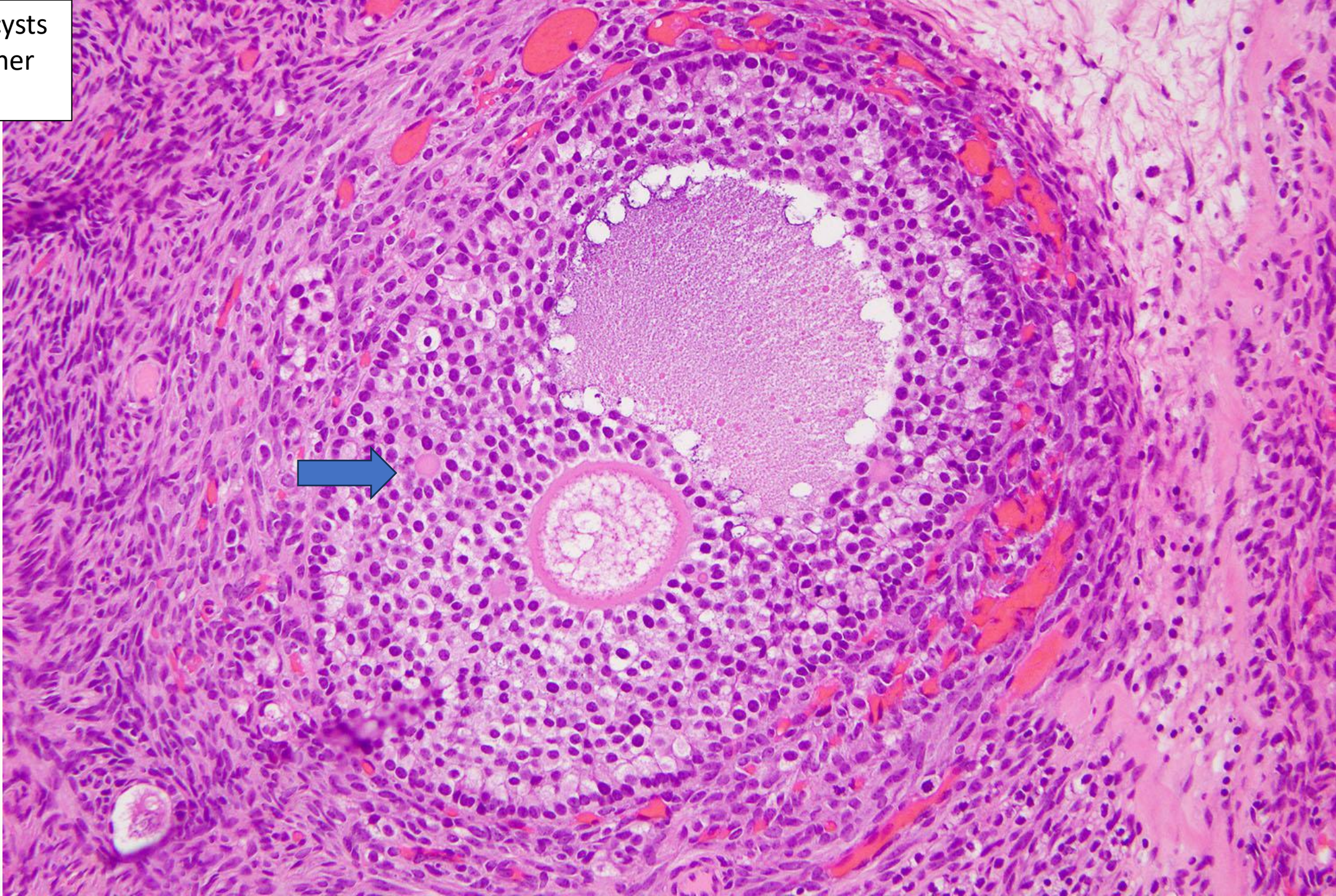
Tangential Cut Through
Follicle



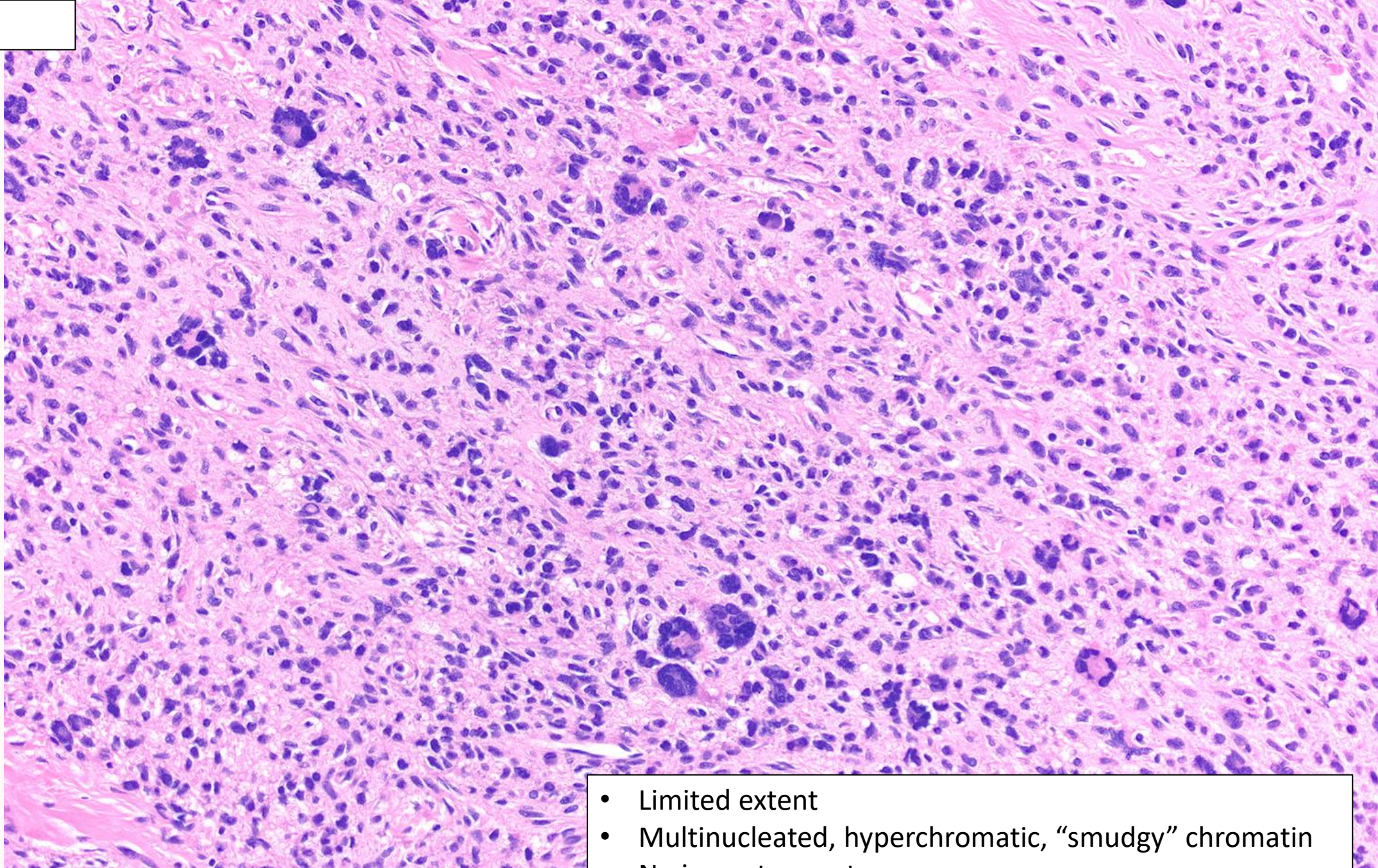
Follicle Mitoses



Follicle with Microcysts
Mimicking Call-Exner
Bodies

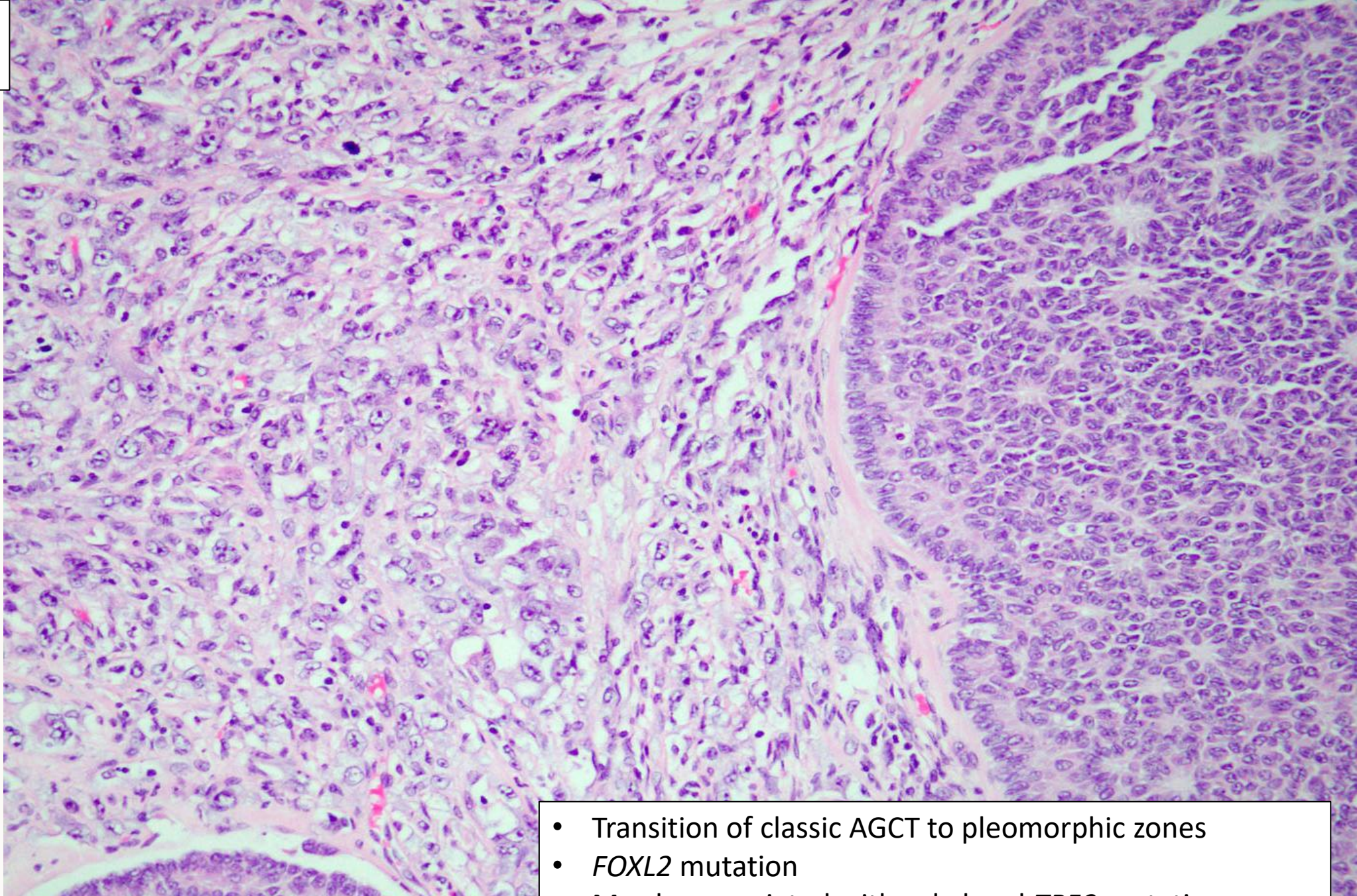


Bizarre Nuclei



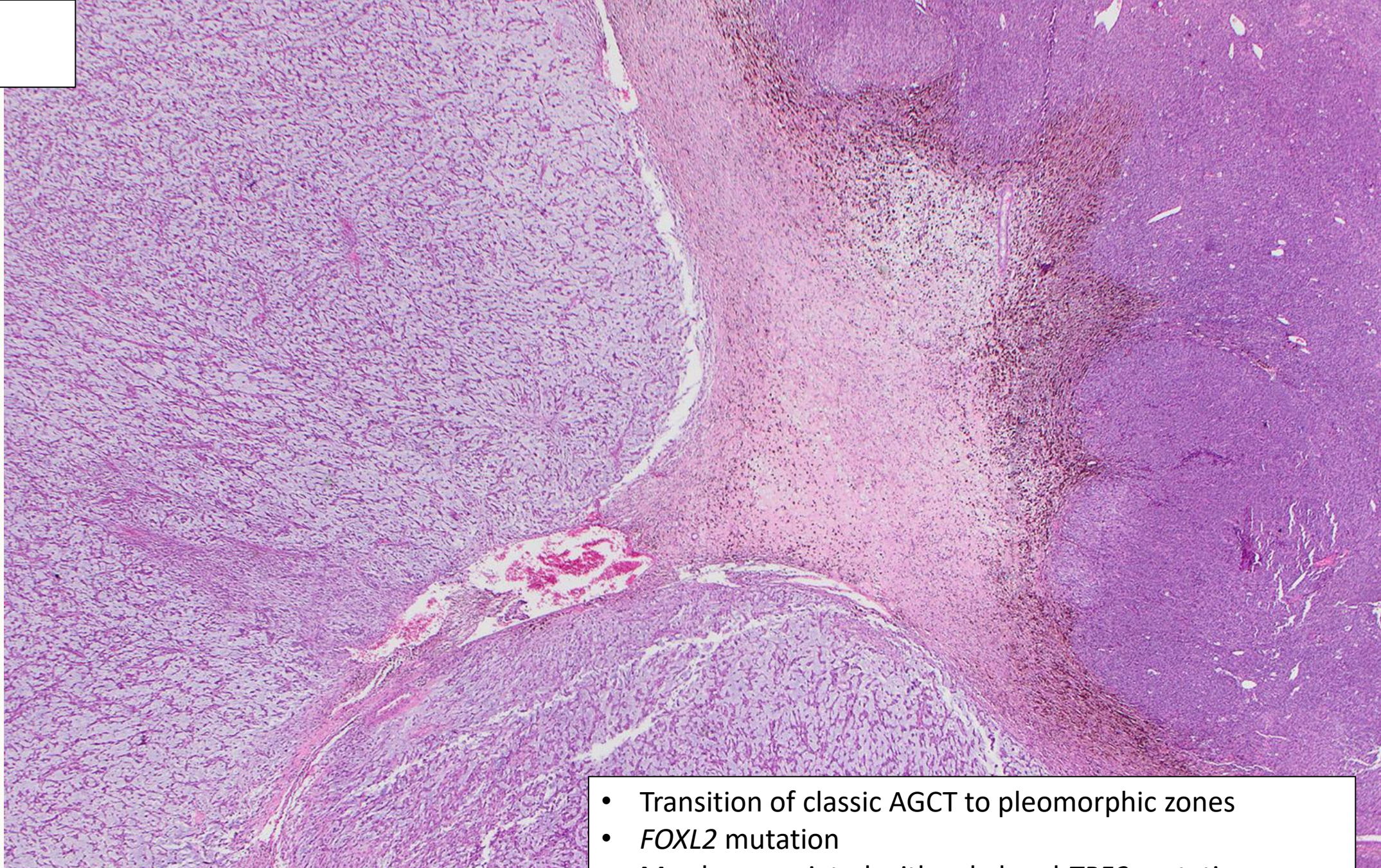
- Limited extent
- Multinucleated, hyperchromatic, "smudgy" chromatin
- No impact on outcome

High-Grade Transformation



- Transition of classic AGCT to pleomorphic zones
- *FOXL2* mutation
- May be associated with subclonal *TP53* mutation

High-Grade Transformation



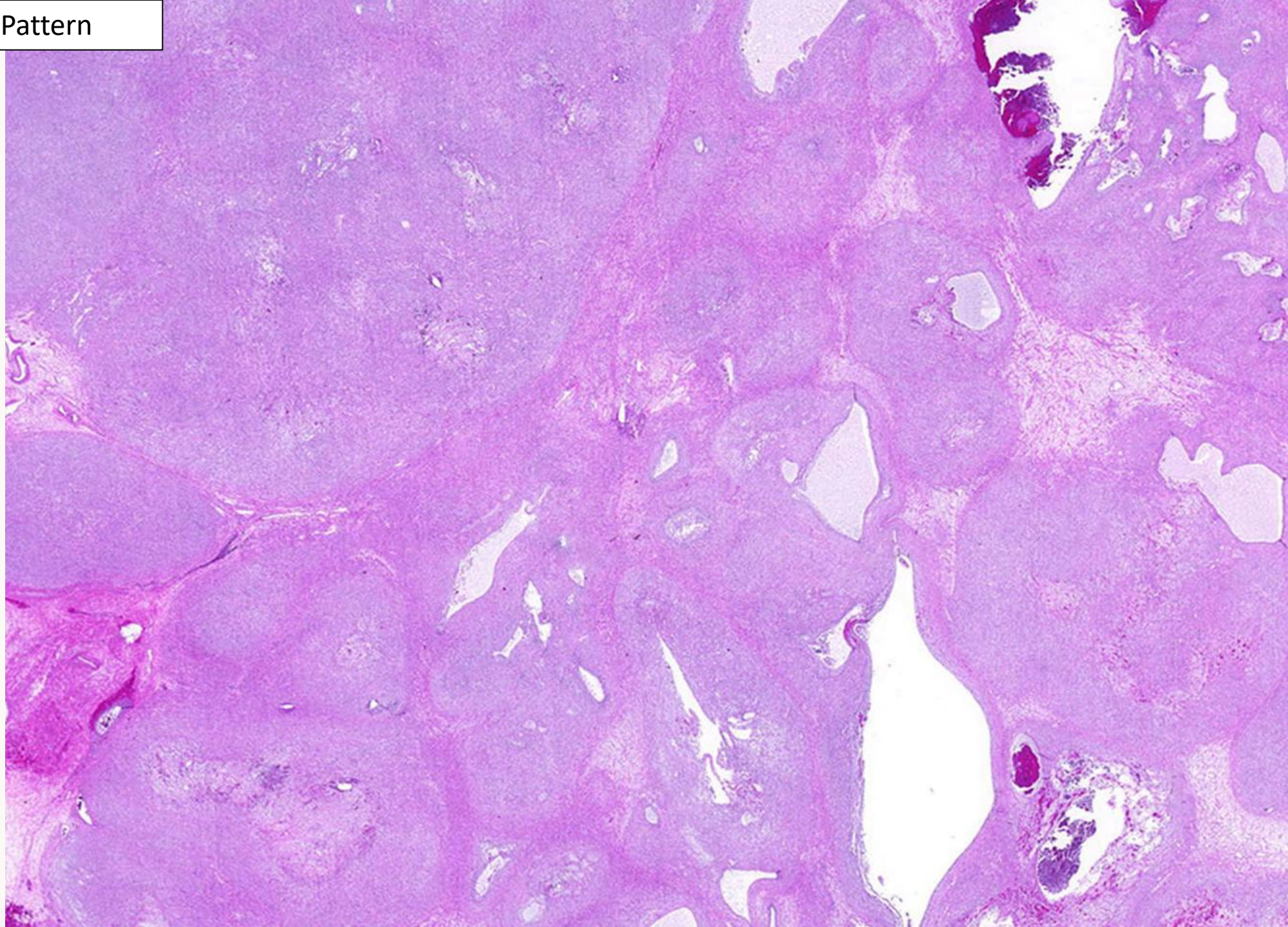
- Transition of classic AGCT to pleomorphic zones
- *FOXL2* mutation
- May be associated with subclonal *TP53* mutation

Juvenile Granulosa Cell Tumor (JGCT)

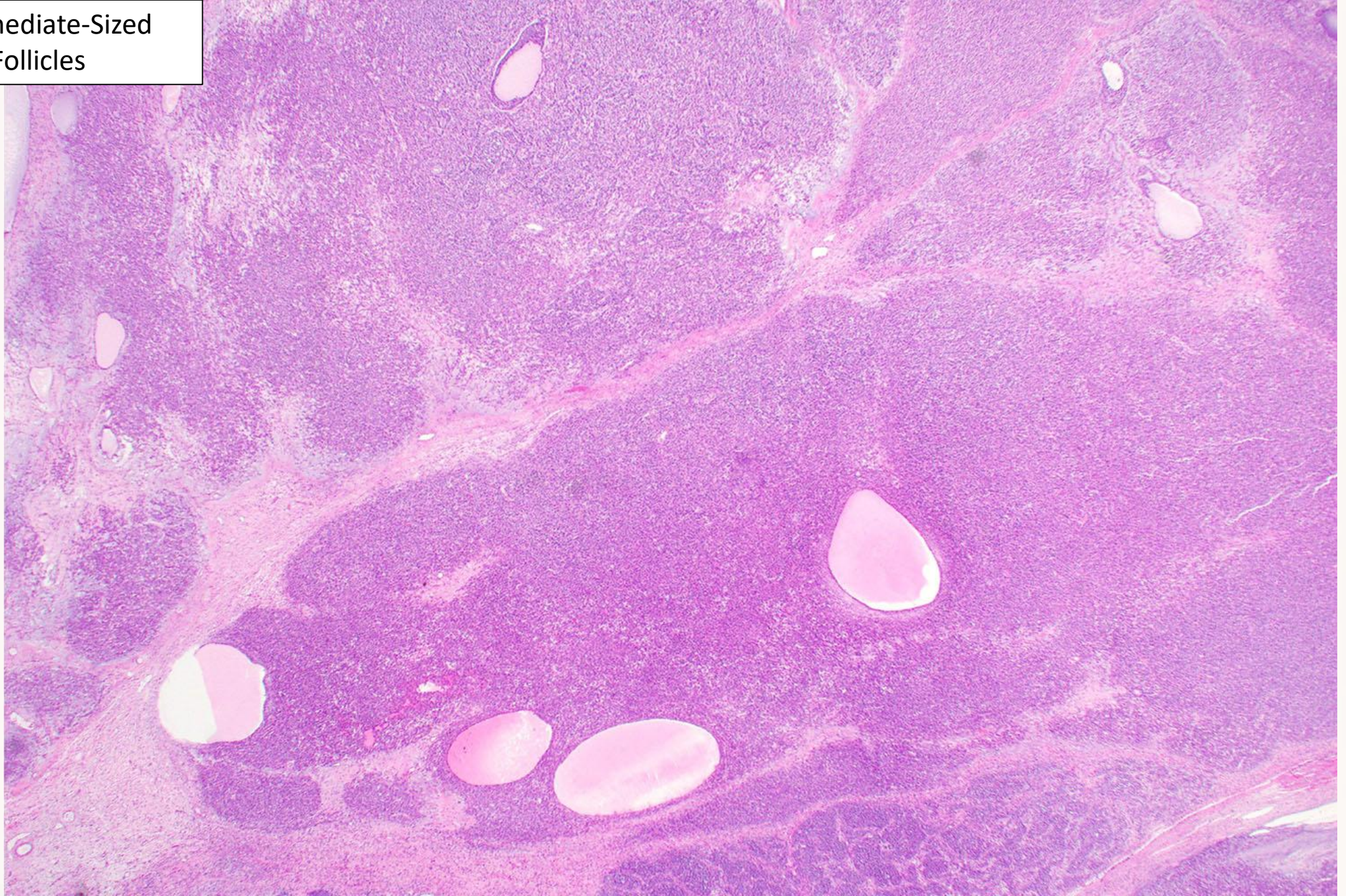
- Mean age 13
- Estrogenic manifestations common (rarely androgenic)
 - Isosexual pseudoprecocity in premenopausal patients
- May present with rupture and hemoperitoneum
- Stage most important prognostic factor
 - Unlike AGCT, when JGCT recurs it is usually in the first 2 years
 - >95% survival if confined to ovary without rupture

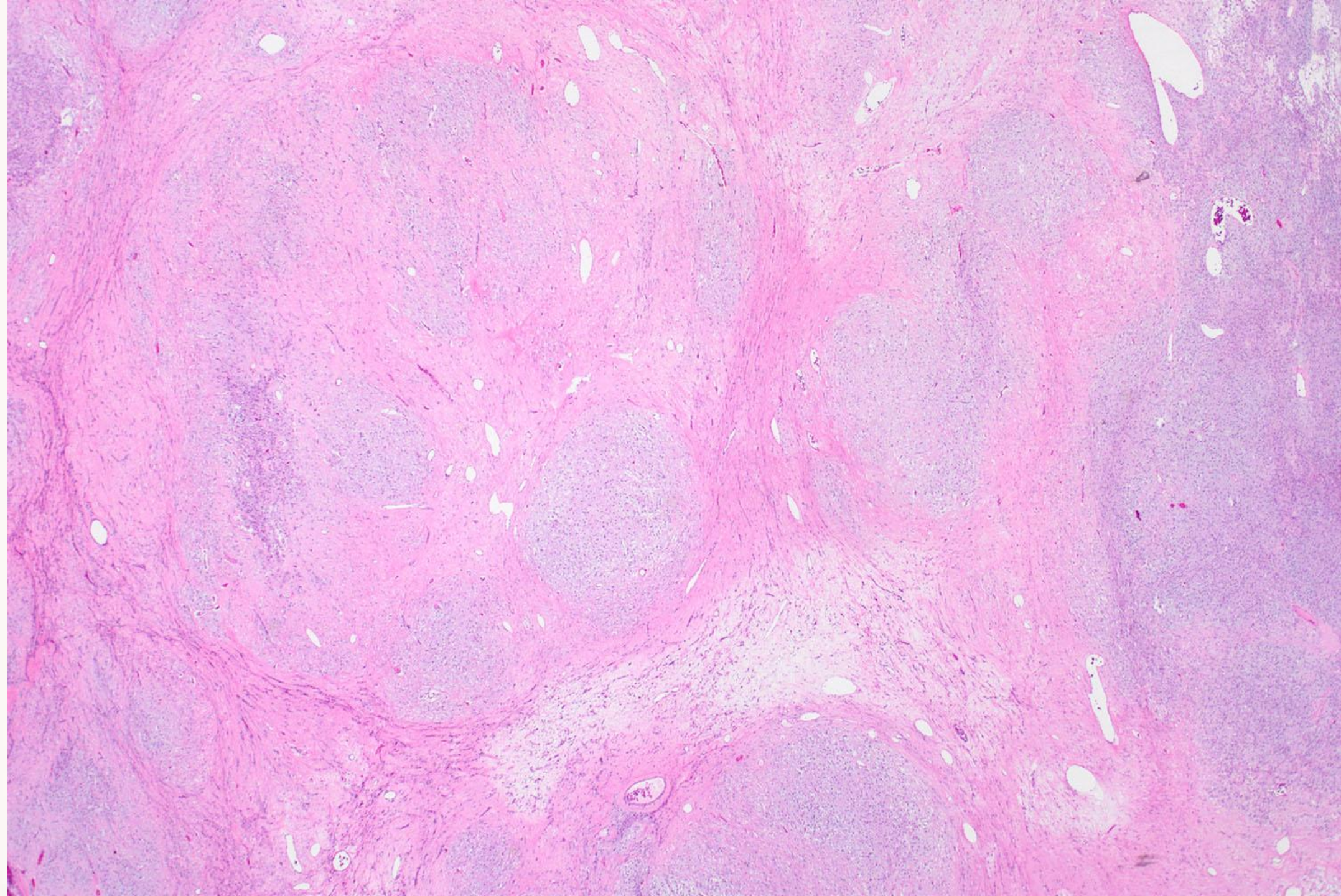


Nodular Pattern

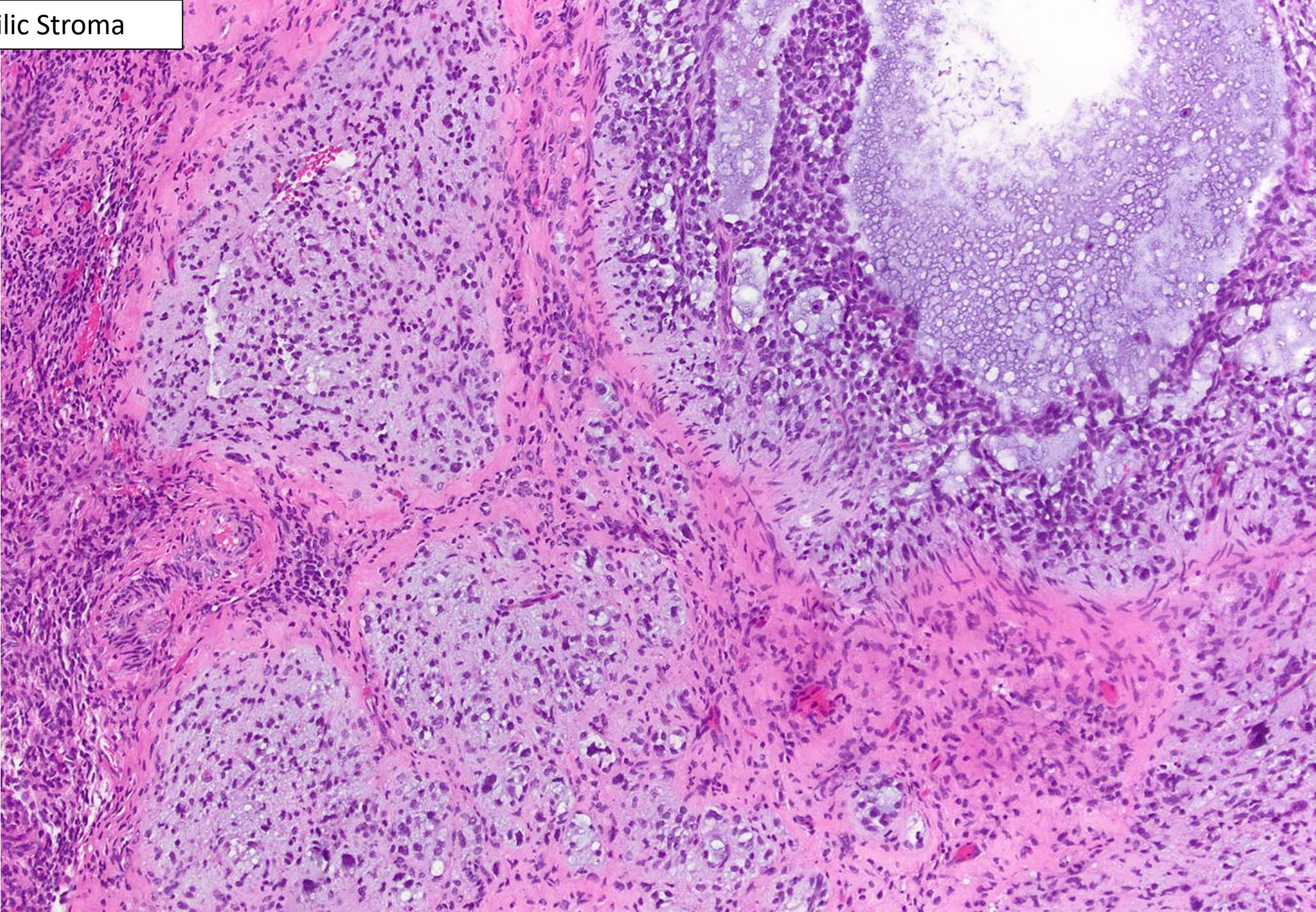


Intermediate-Sized
Follicles

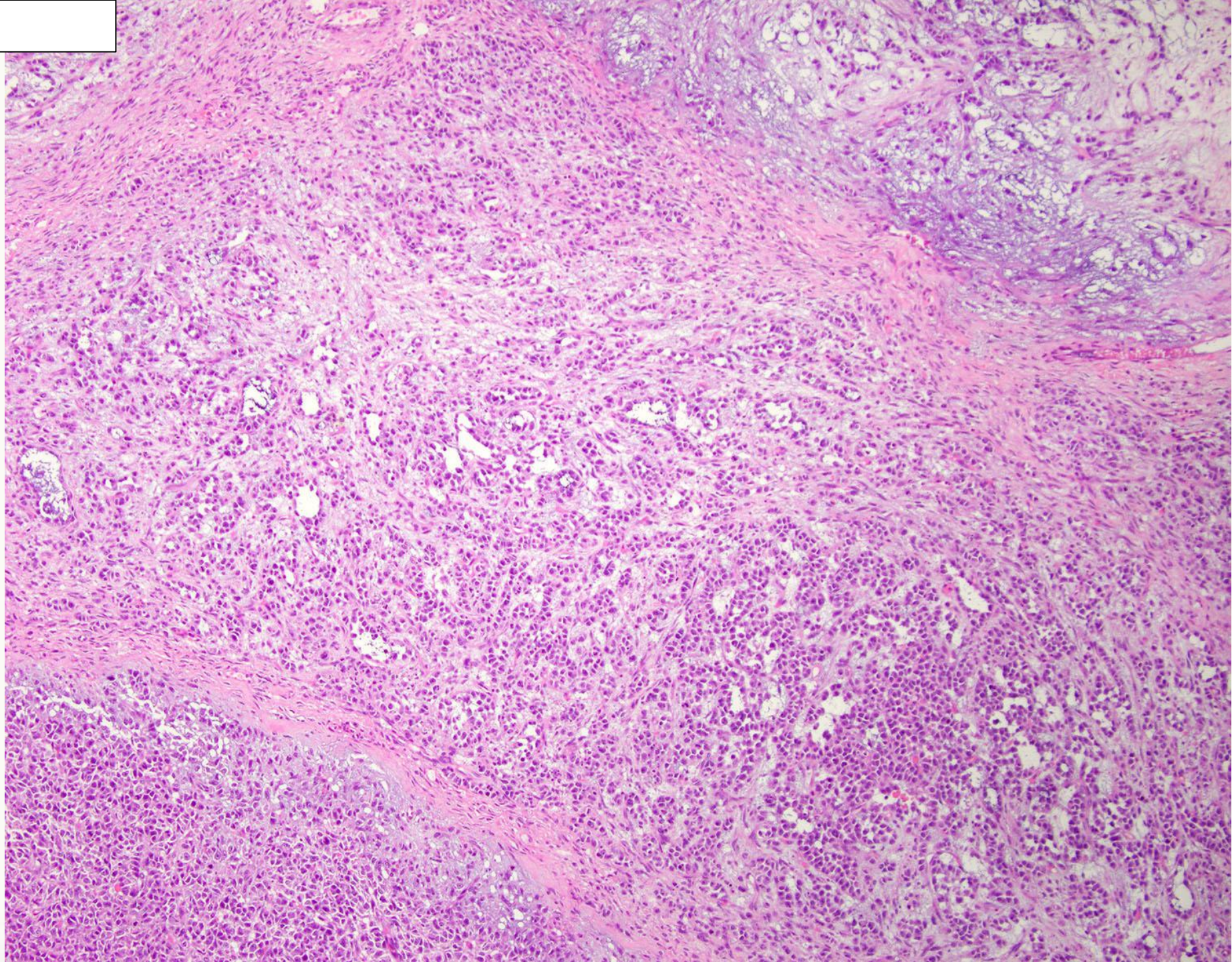




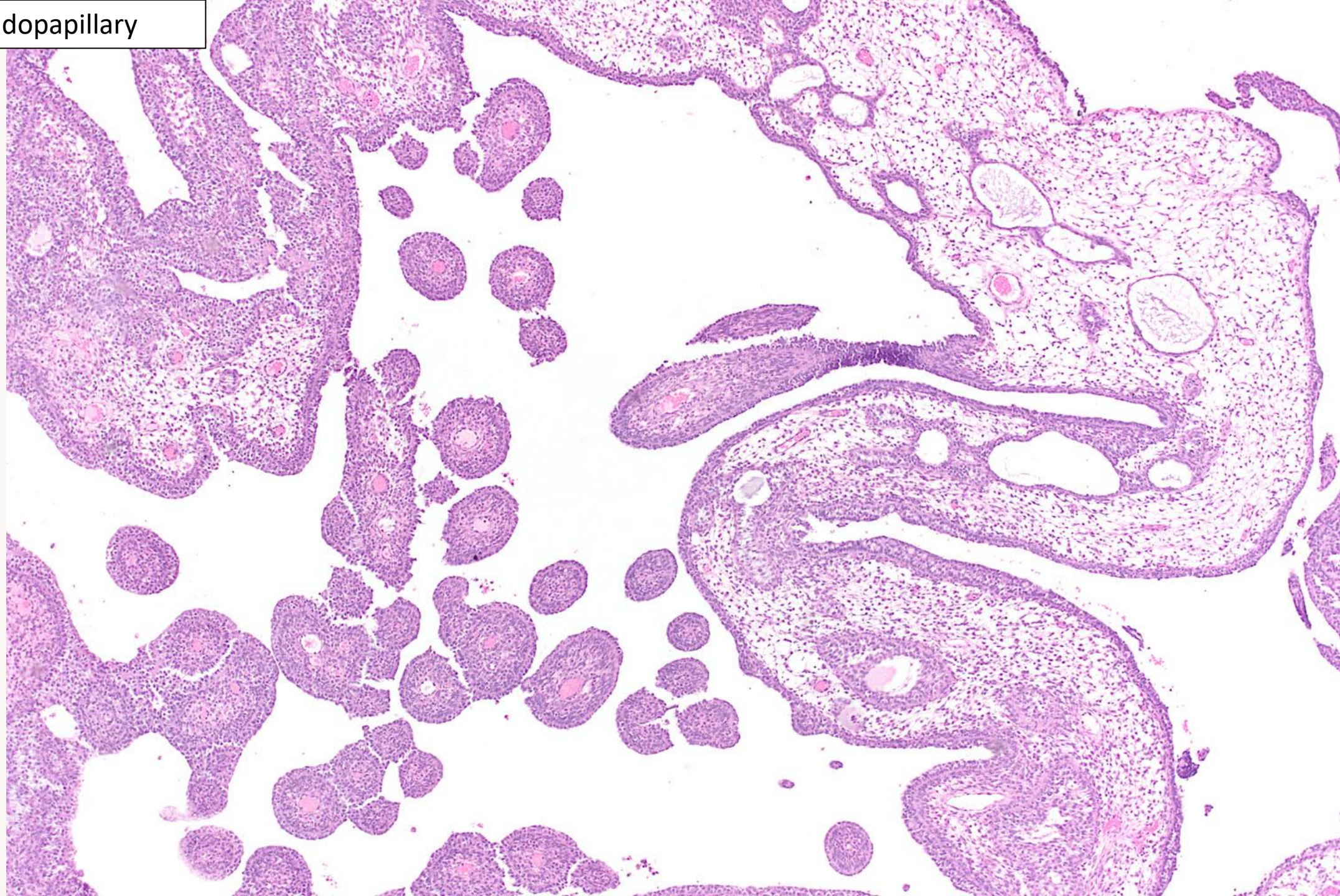
Basophilic Stroma



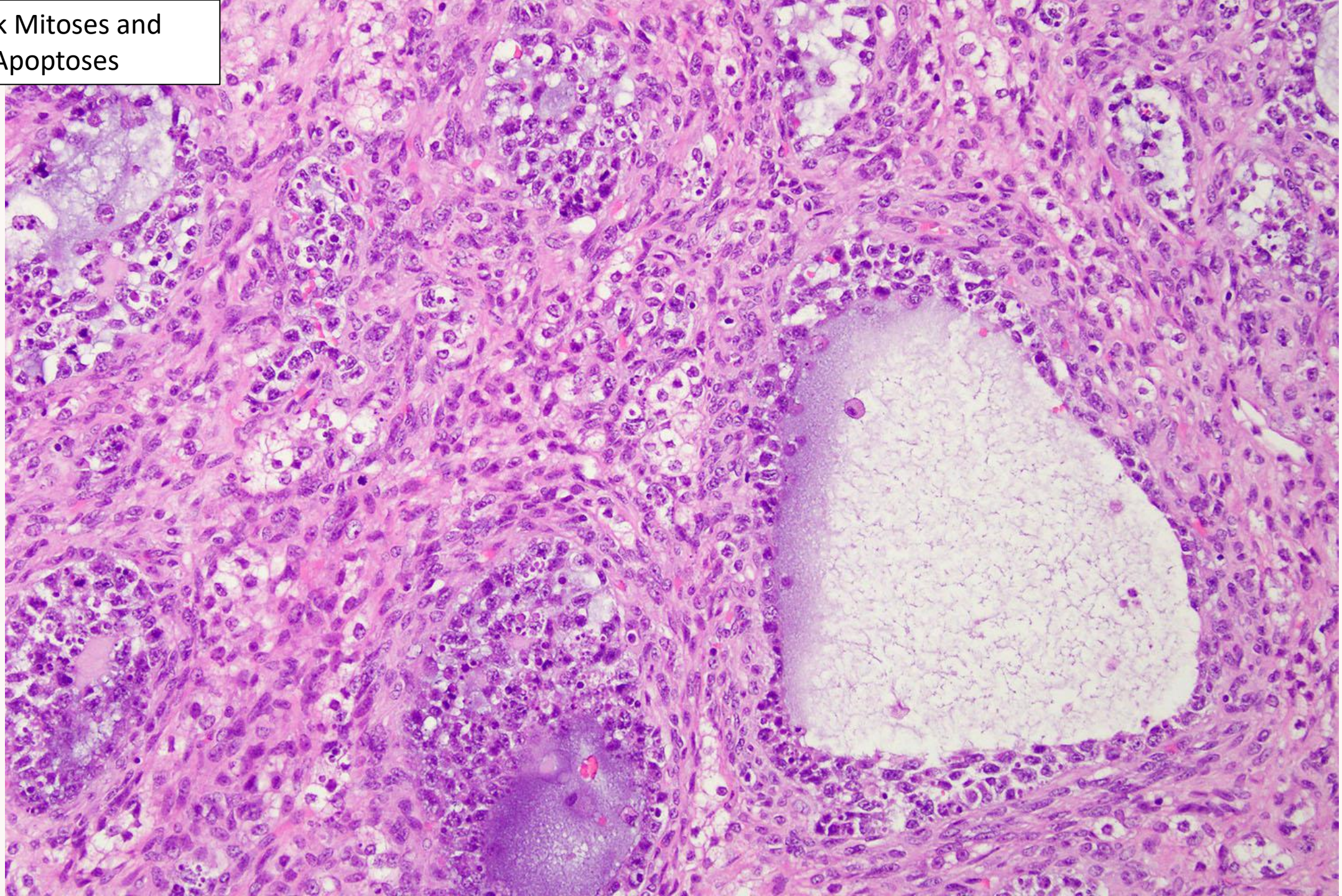
Cords



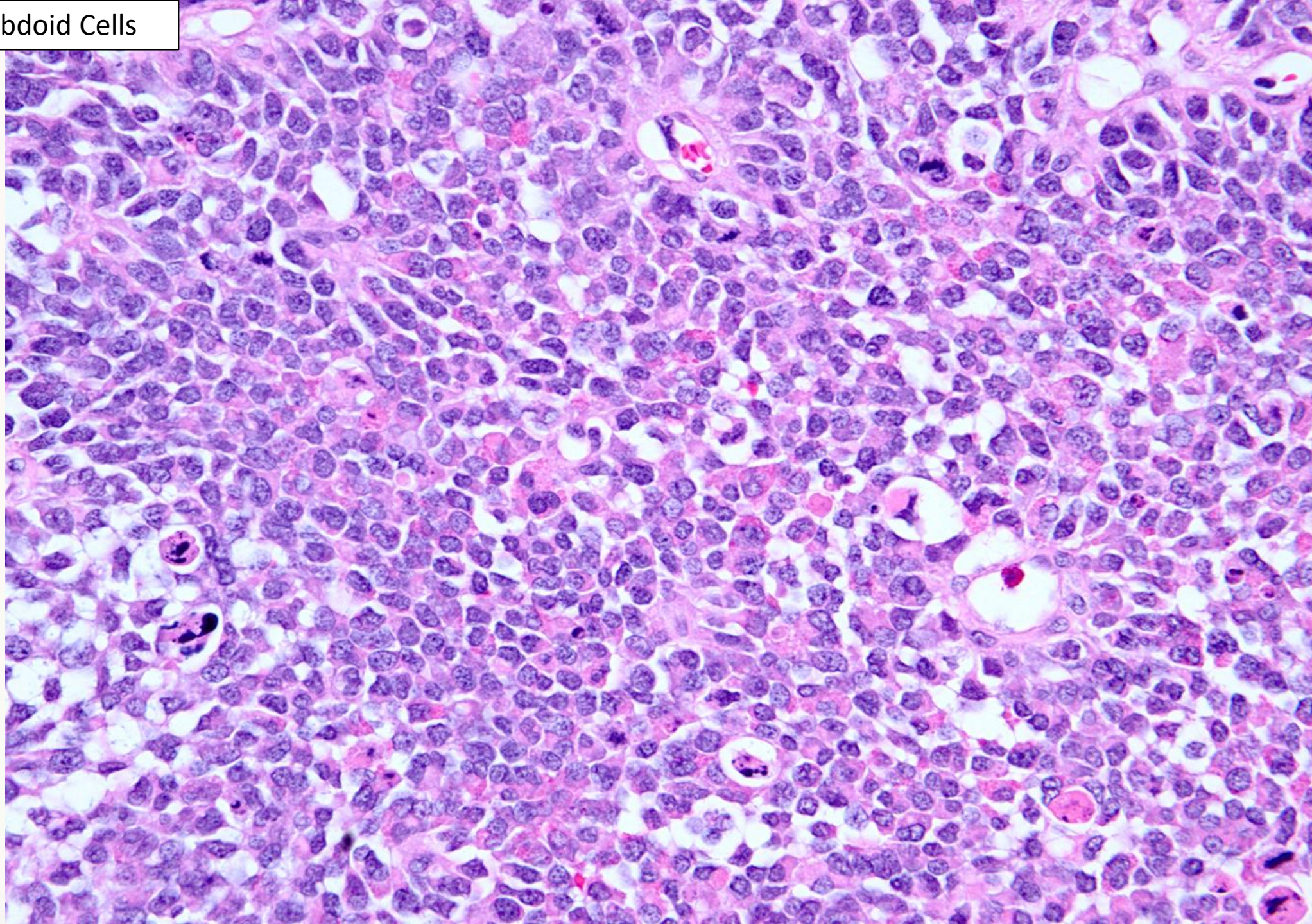
Pseudopapillary



Brisk Mitoses and
Apoptoses



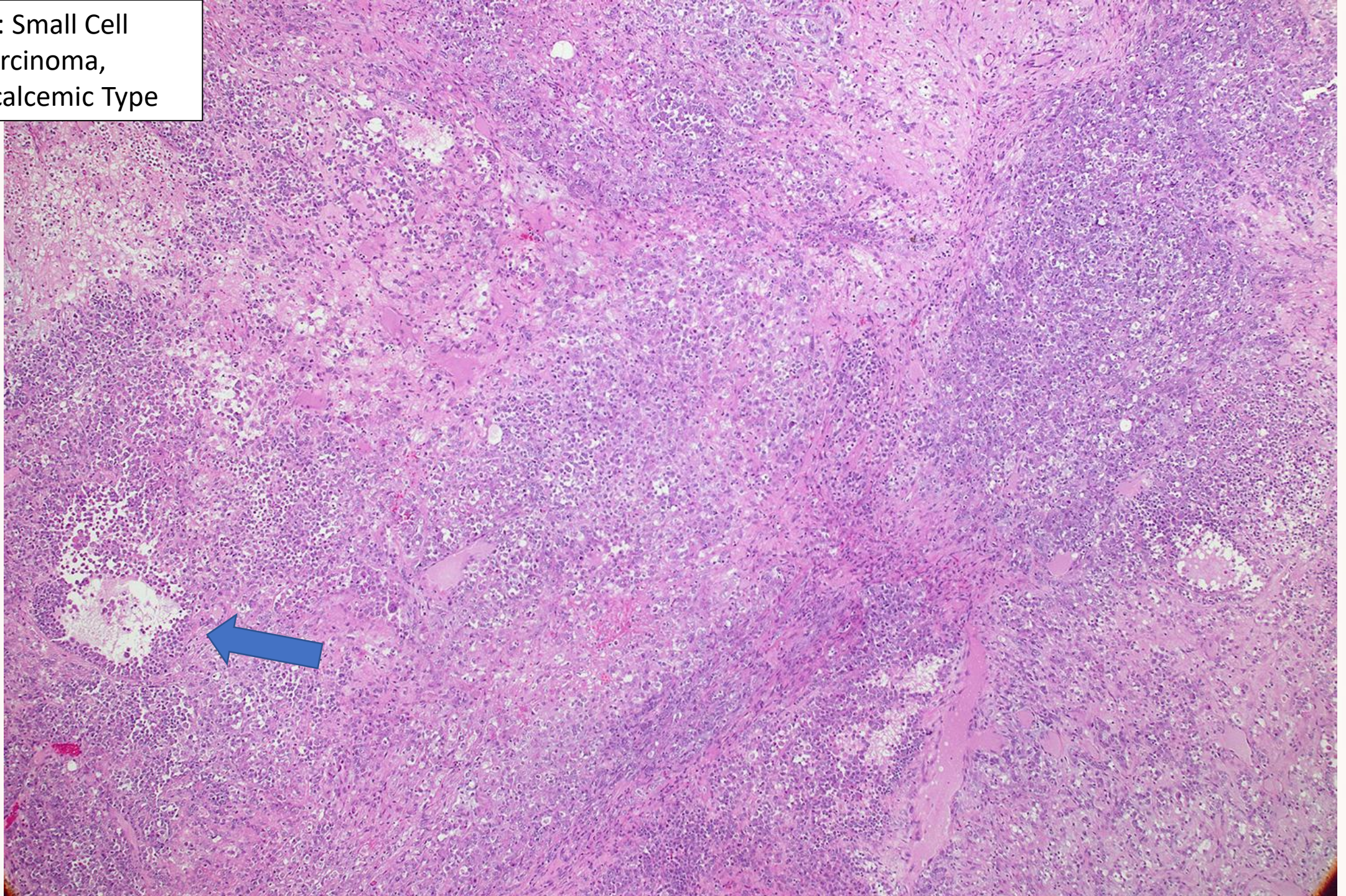
Focal Rhabdoid Cells



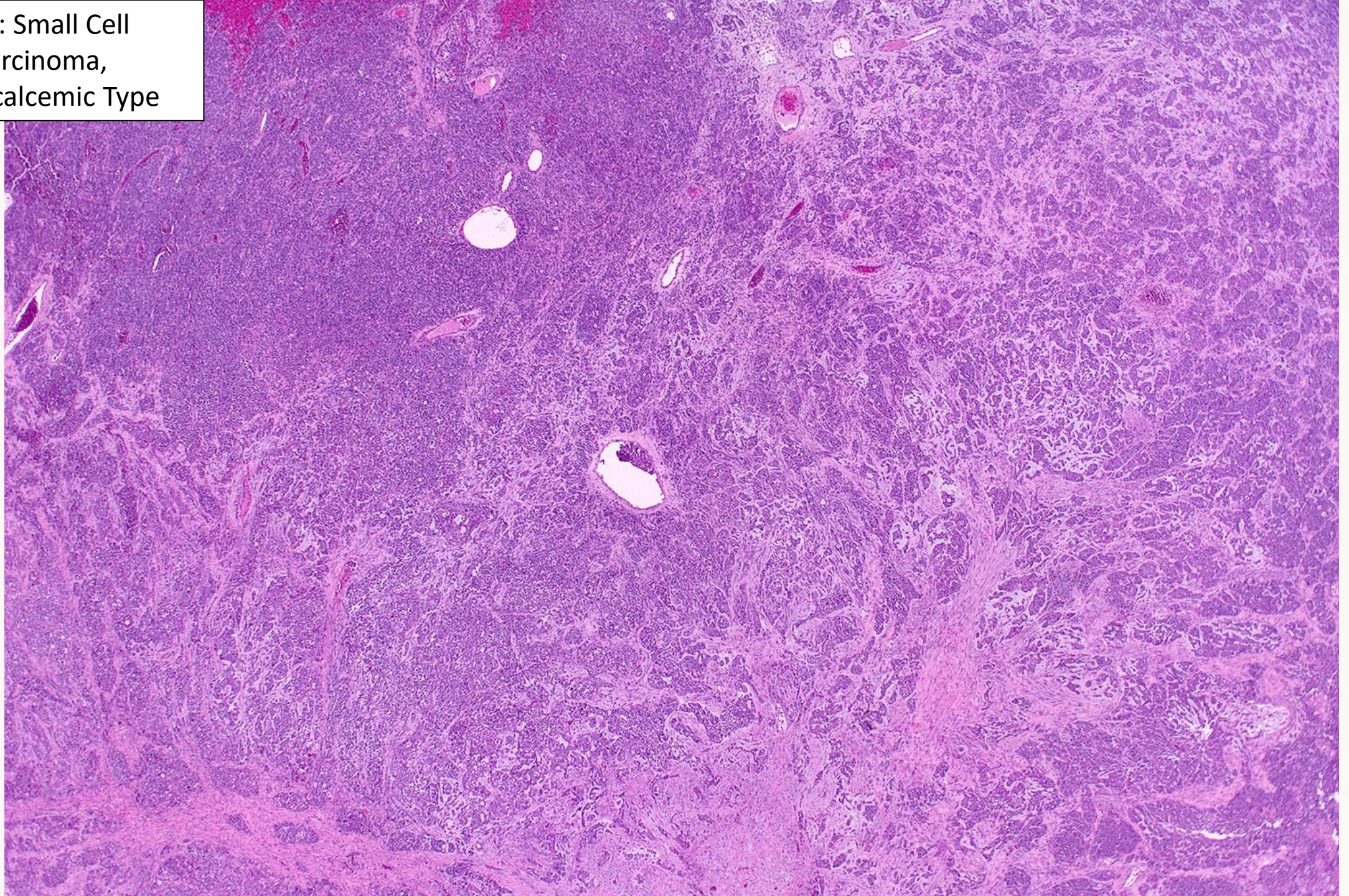
Juvenile Granulosa Cell Tumor

Feature	AGCT	JGCT
Age	Avg. 50s but may occur at any age	Avg. 13 but may occur at any age
Low power impression	Relatively “blue” appearance	Relatively “pink” appearance
Cytoplasm	Scant, amphophilic	Moderate to abundant, pink or occasionally clear
Follicles	Microfollicles (Call-Exner bodies) or occasionally macrofollicles	Variably sized and shaped, no Call-Exner bodies
Nuclei	Angled, prominent grooves	Round to ovoid, open chromatin or hyperchromatic, grooves not prominent
Mitotic index	Variable	Often brisk with frequent apoptoses
Mutational Profile	Frequent <i>FOXL2</i>	<i>AKT1</i> , activating <i>GNAS</i> , occasional <i>DICER1</i> , lack <i>FOXL2</i>

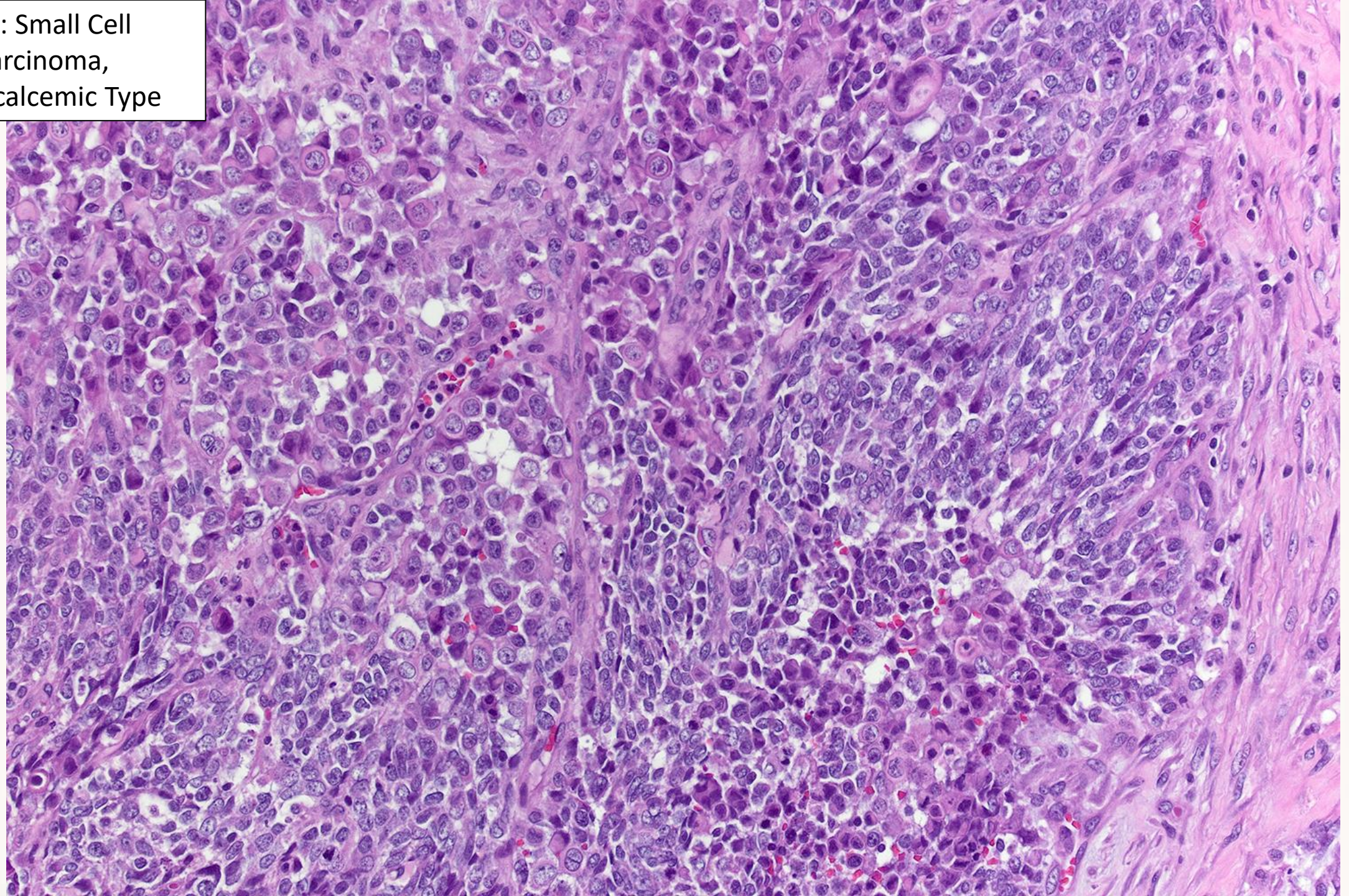
DDx: Small Cell
Carcinoma,
Hypercalcemic Type



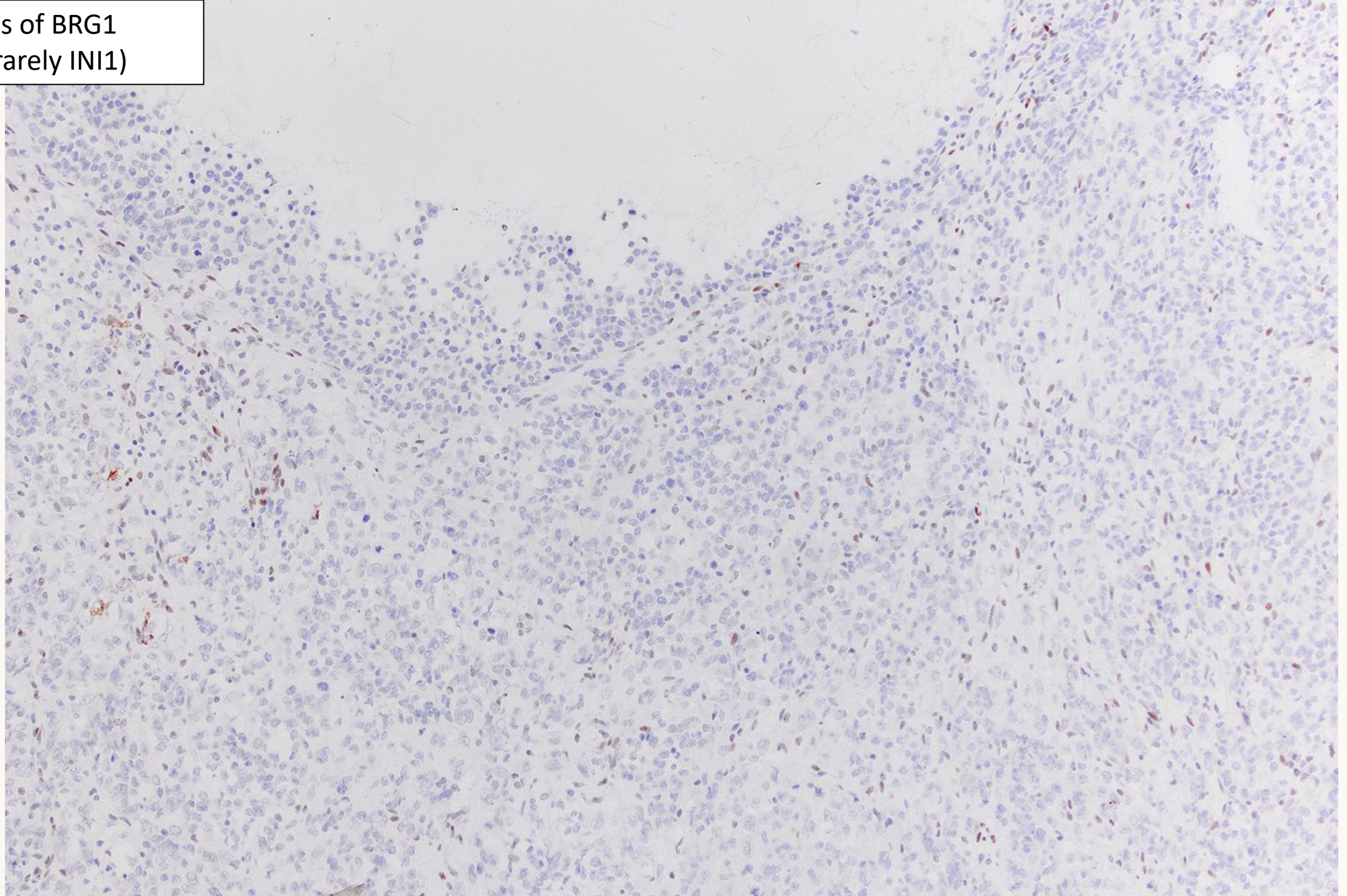
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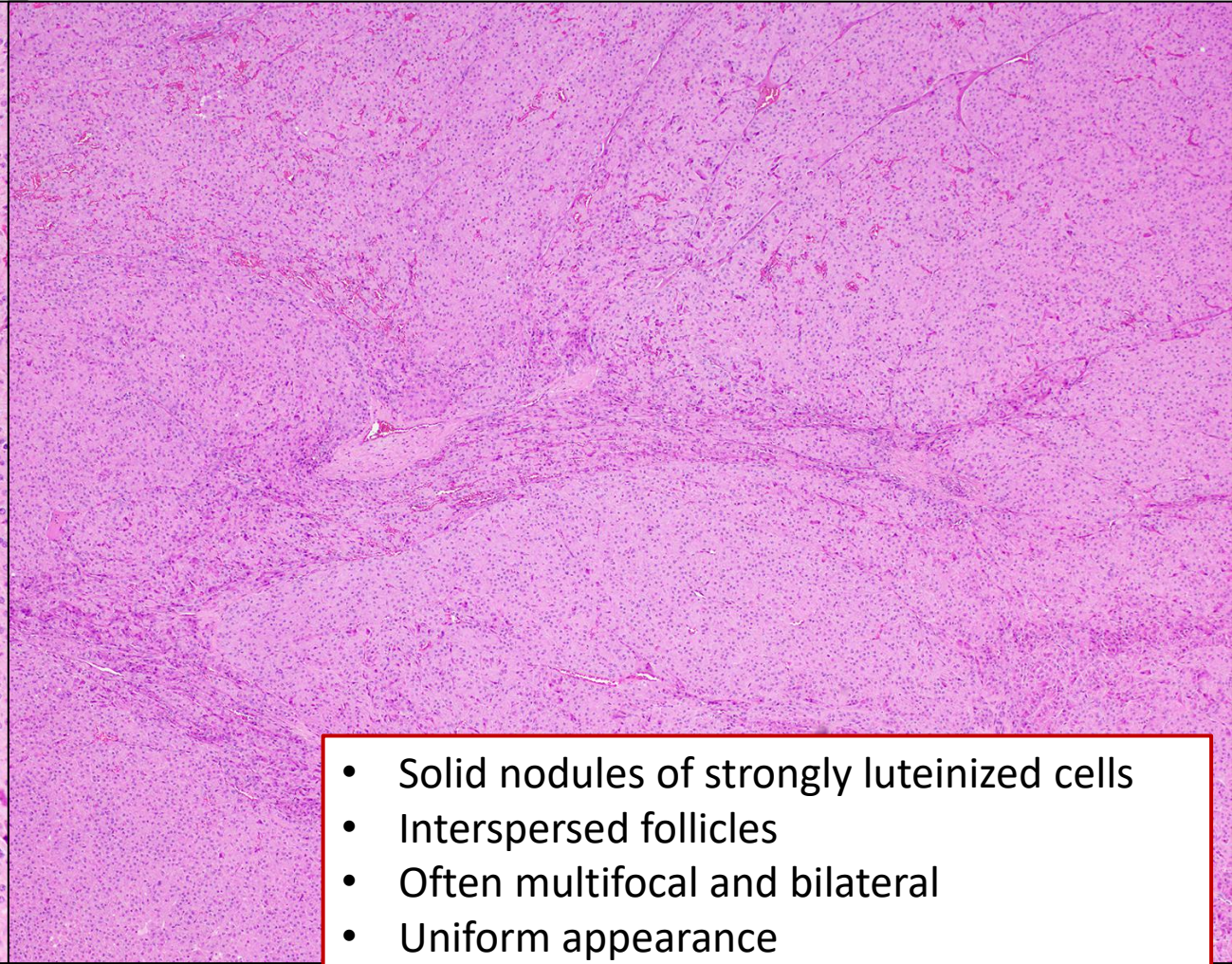
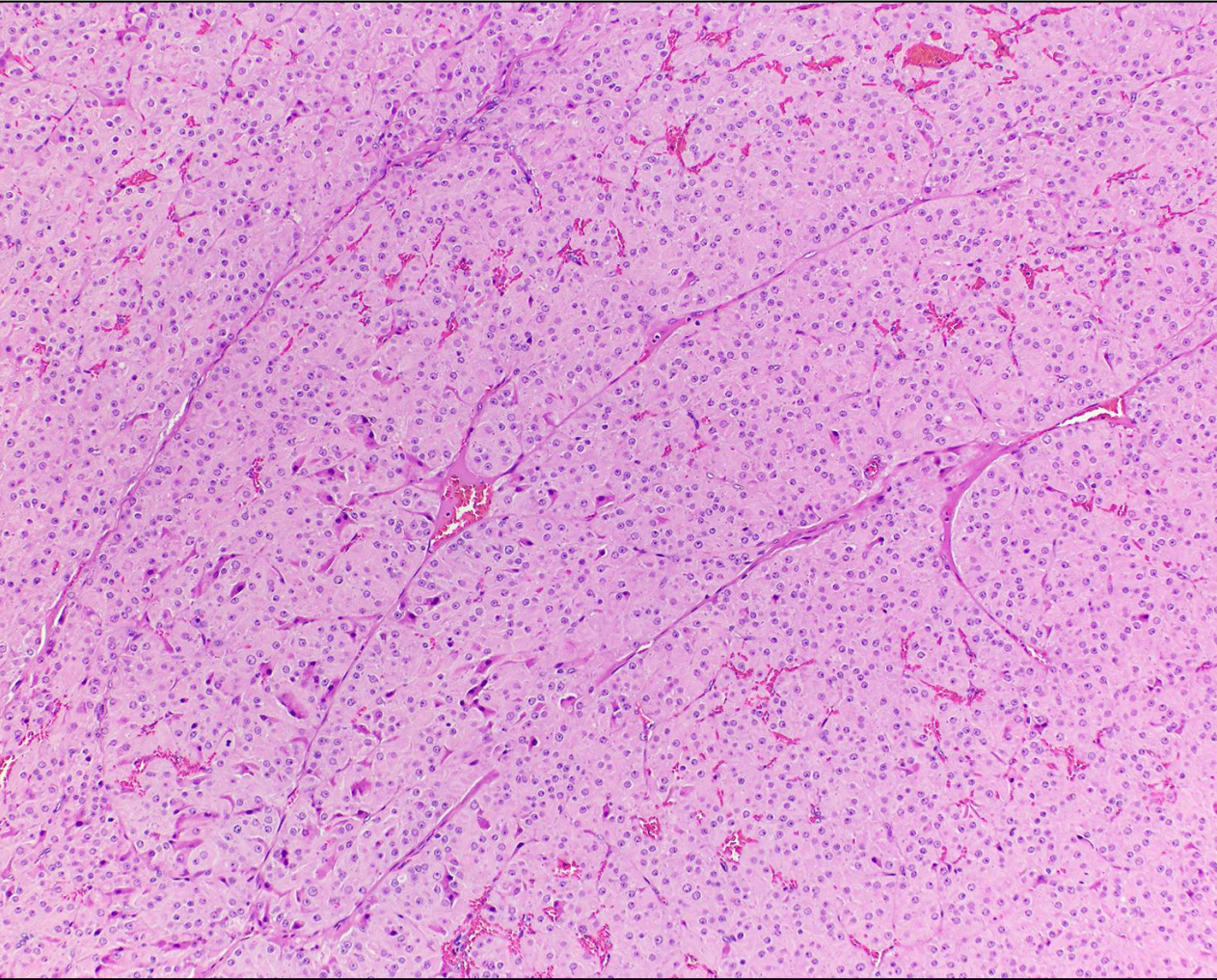
DDx: Small Cell
Carcinoma,
Hypercalcemic Type



Loss of BRG1
(or rarely INI1)

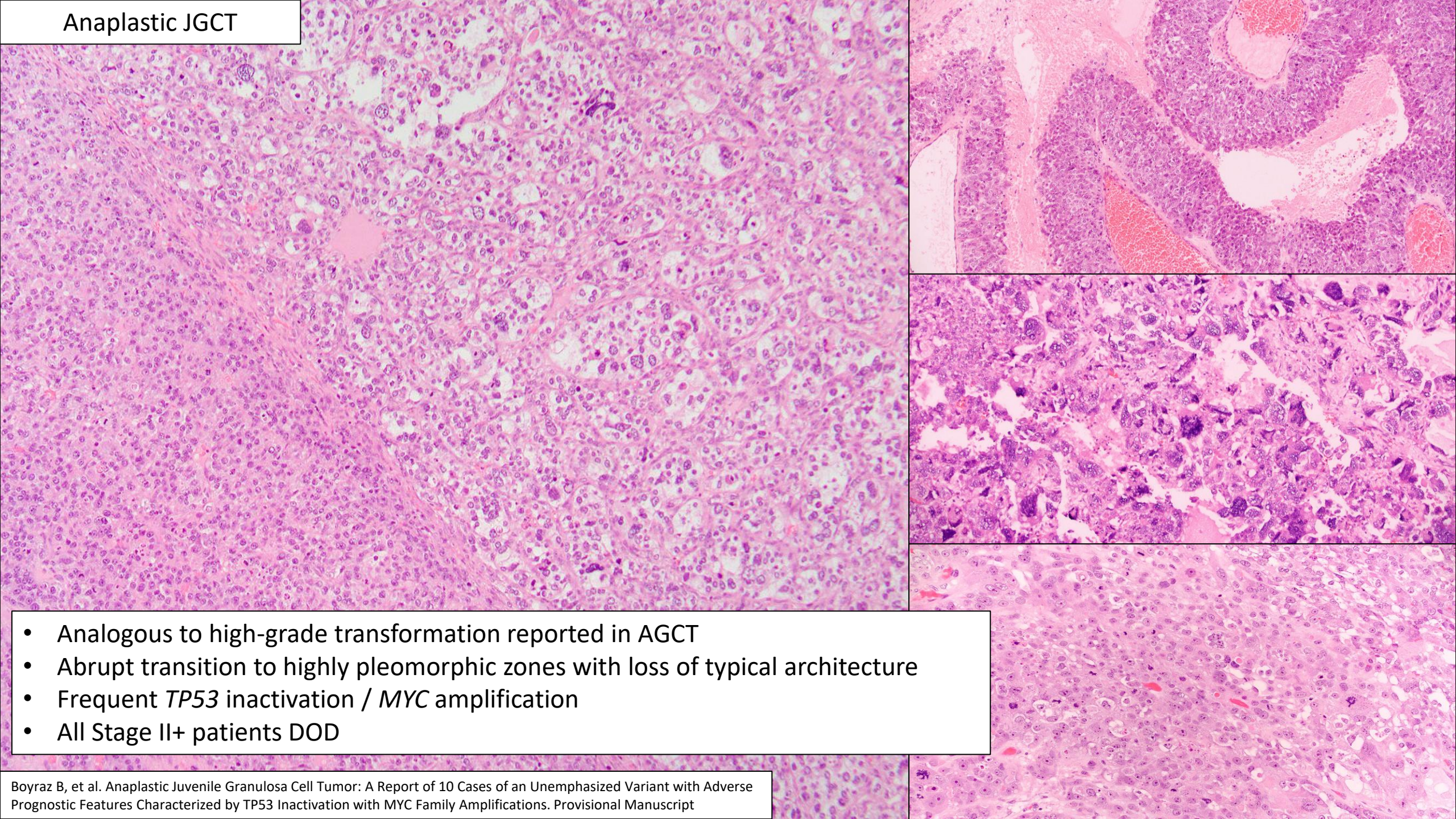


Pregnancy Luteoma



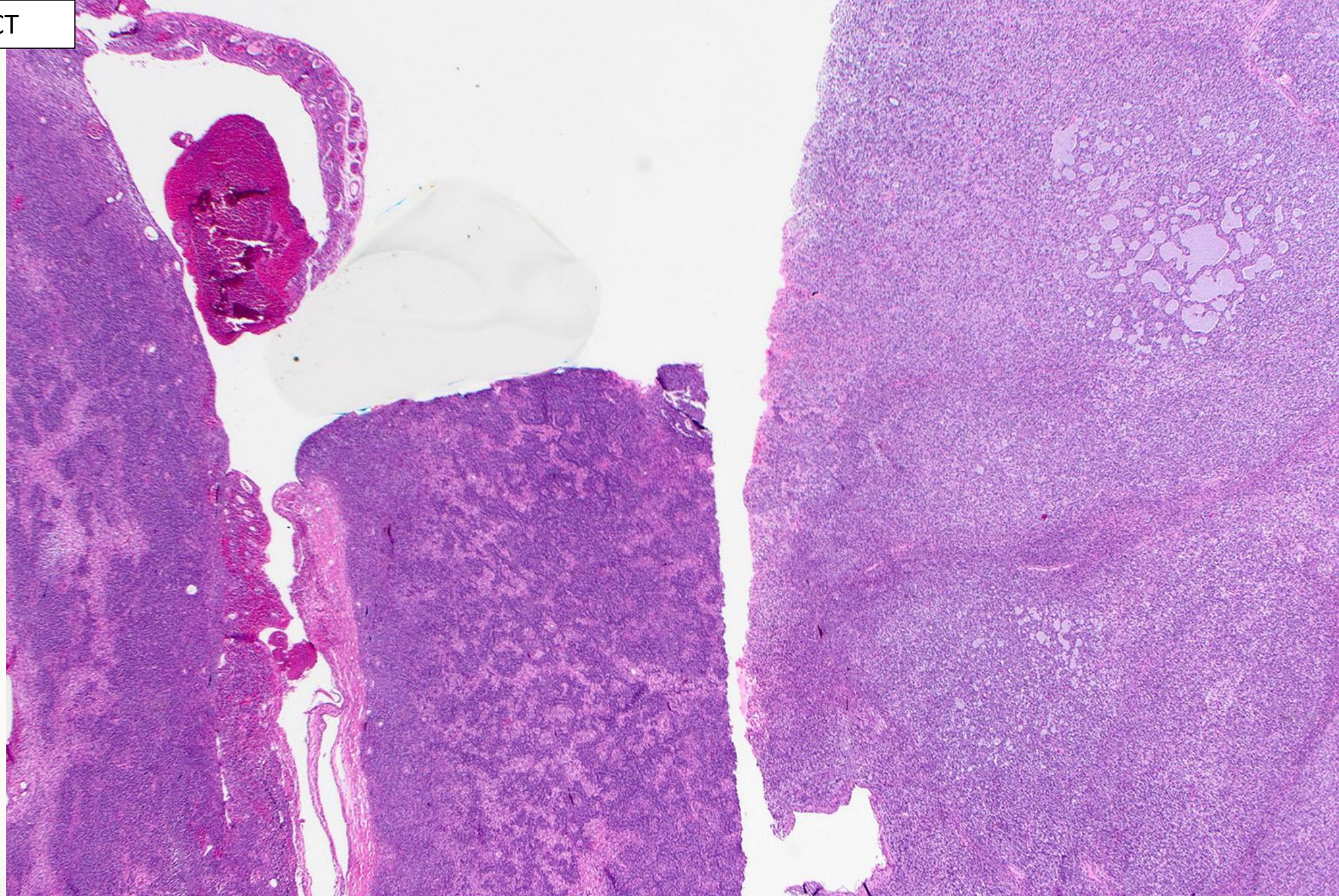
- Solid nodules of strongly luteinized cells
- Interspersed follicles
- Often multifocal and bilateral
- Uniform appearance
- More abundant cytoplasm
- Mitoses usually rare
- Lack basophilic stroma, cords, trabeculae

Anaplastic JGCT



- Analogous to high-grade transformation reported in AGCT
- Abrupt transition to highly pleomorphic zones with loss of typical architecture
- Frequent *TP53* inactivation / *MYC* amplification
- All Stage II+ patients DOD

Mixed AGCT/JGCT



Sertoli-Leydig Cell Tumor (SLCT)

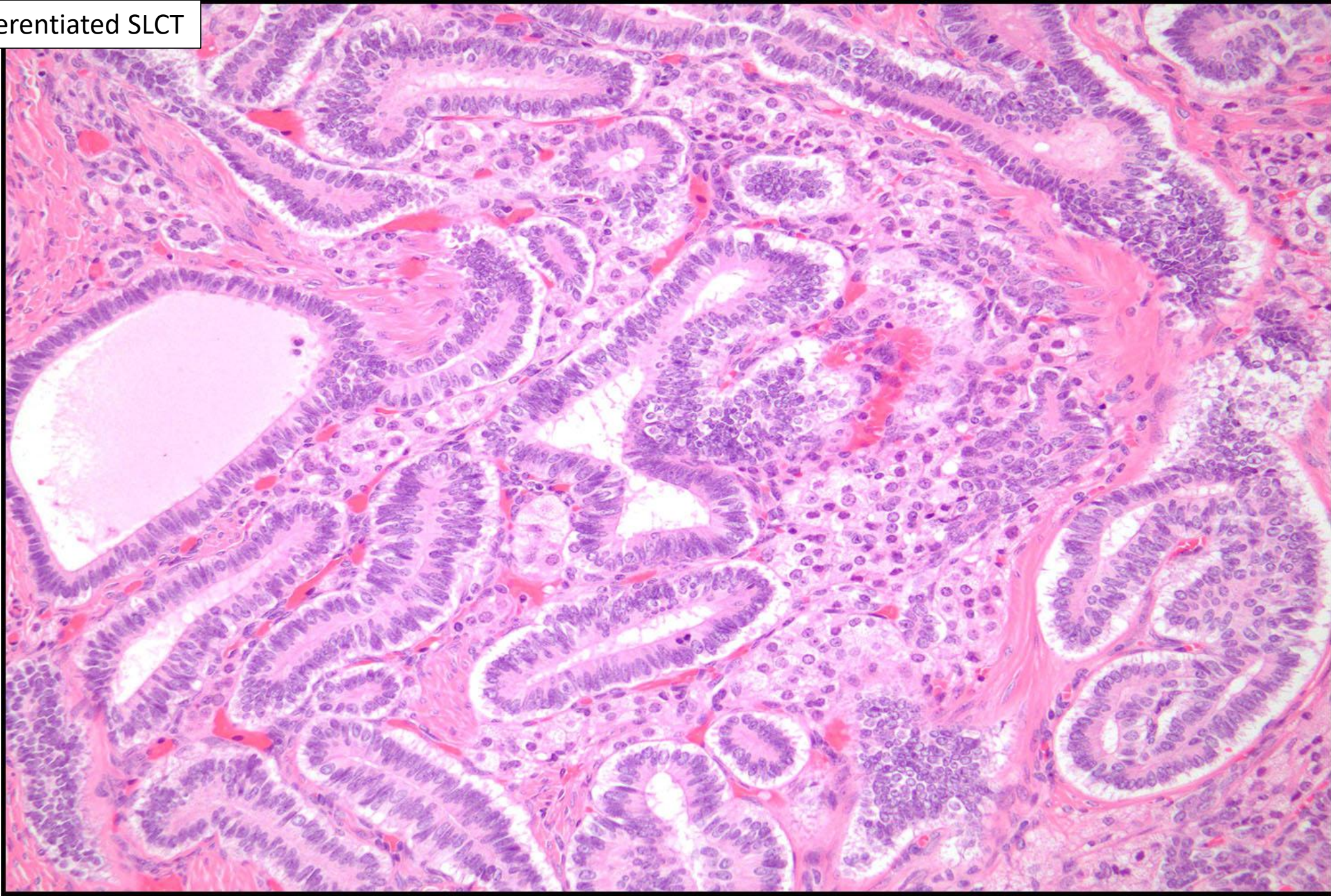
Well-Differentiated

- Mean age 30s
- Rare
- Benign
- Well-formed tubules
- Clusters of Leydig cells
- No mutations found

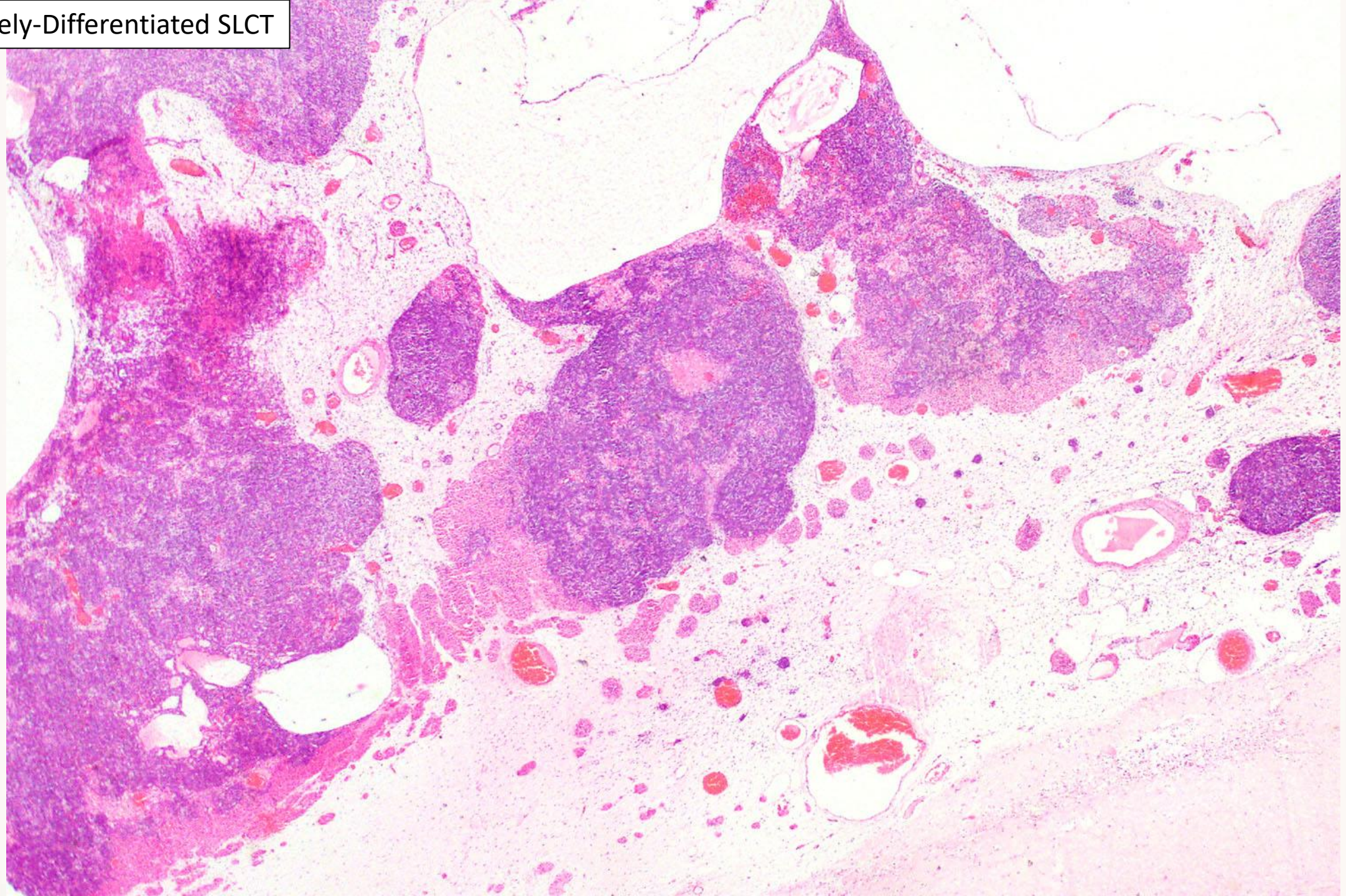
Moderately and Poorly-Differentiated

- Mean age 20s
- Uncommon
- May recur or metastasize
- Sheets and aggregates of darkly-staining immature Sertoli cells
- Variable Leydig cell component
- Frequent *DICER1* mutations

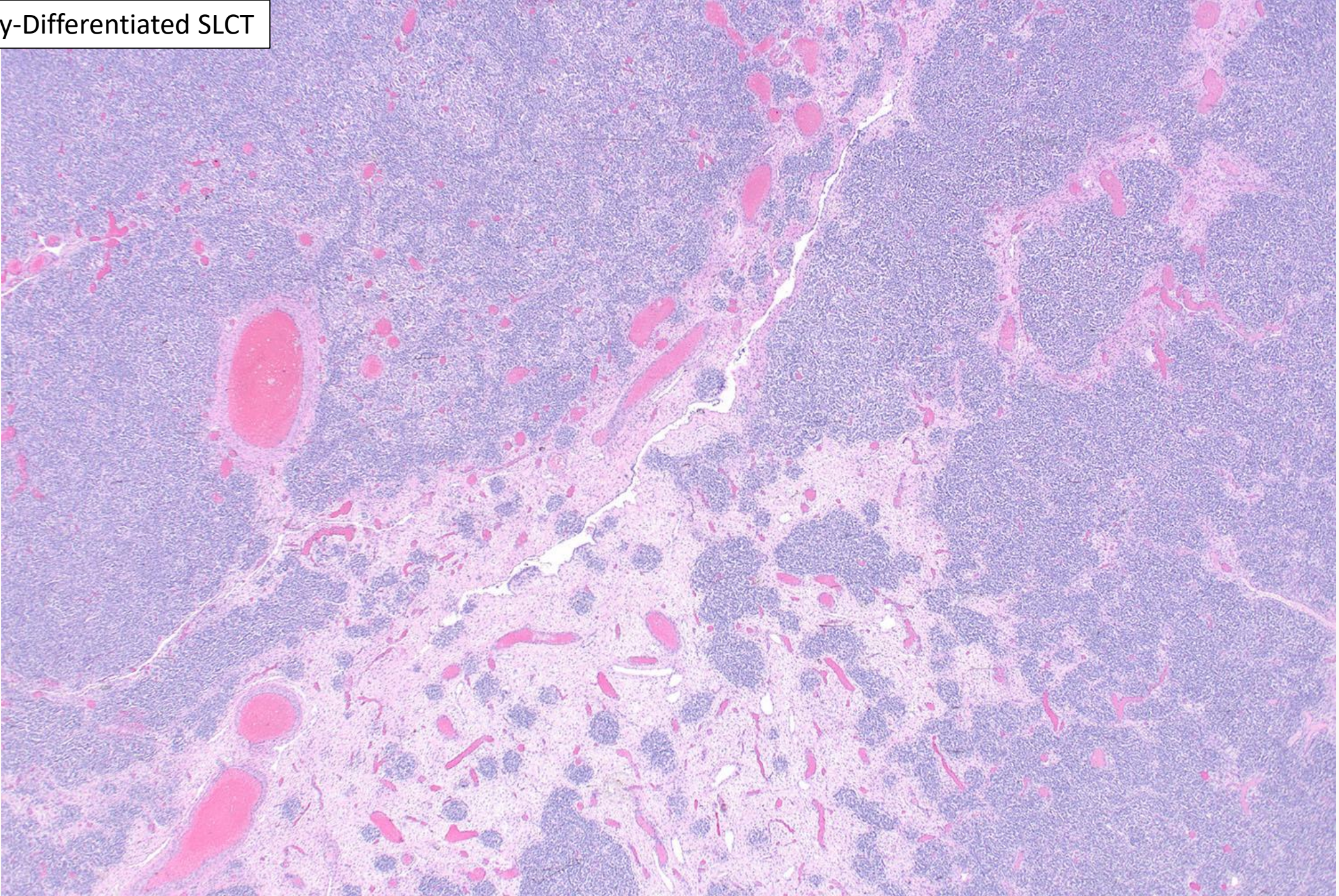
Well-Differentiated SLCT



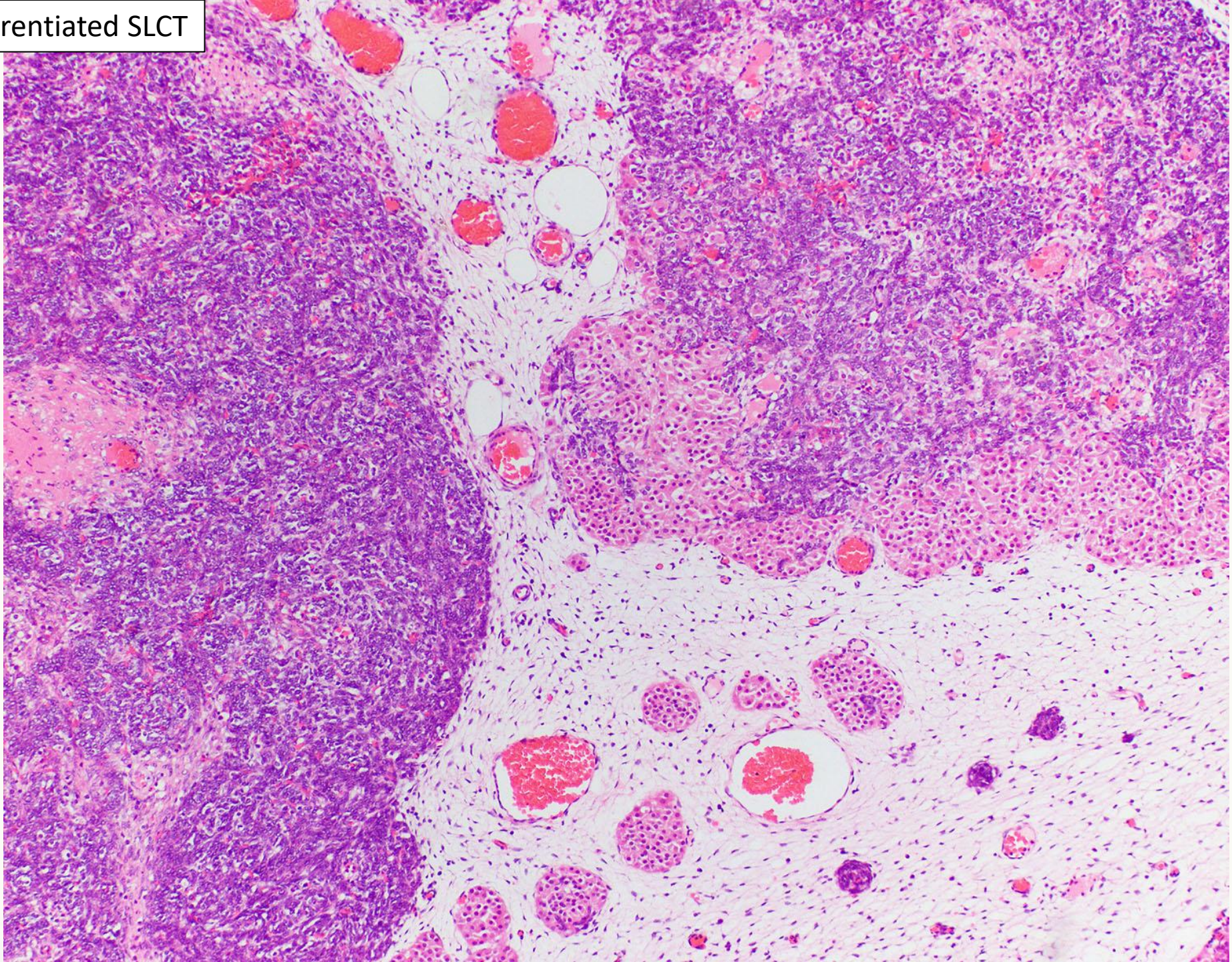
Moderately-Differentiated SLCT



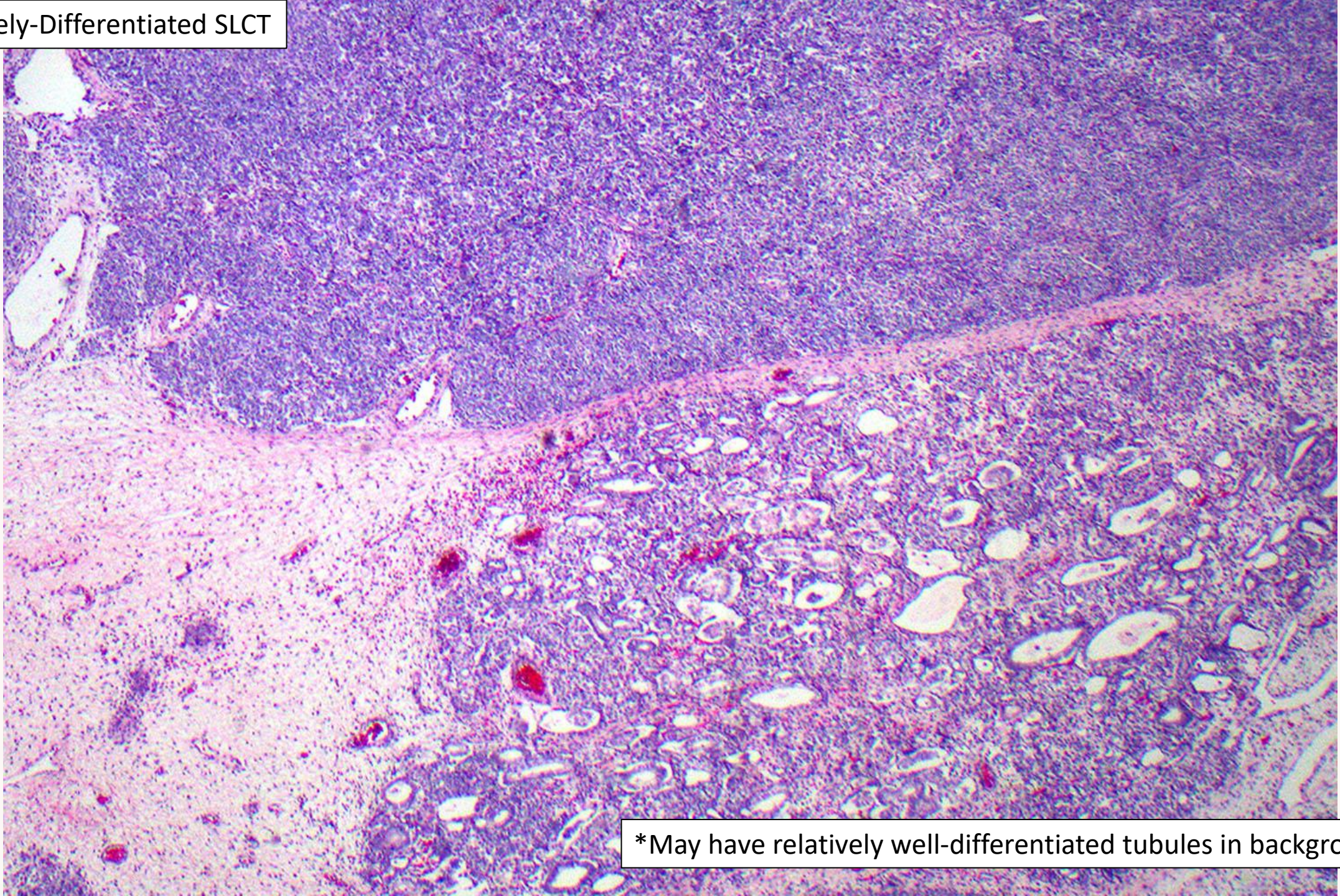
Moderately-Differentiated SLCT



Moderately-Differentiated SLCT

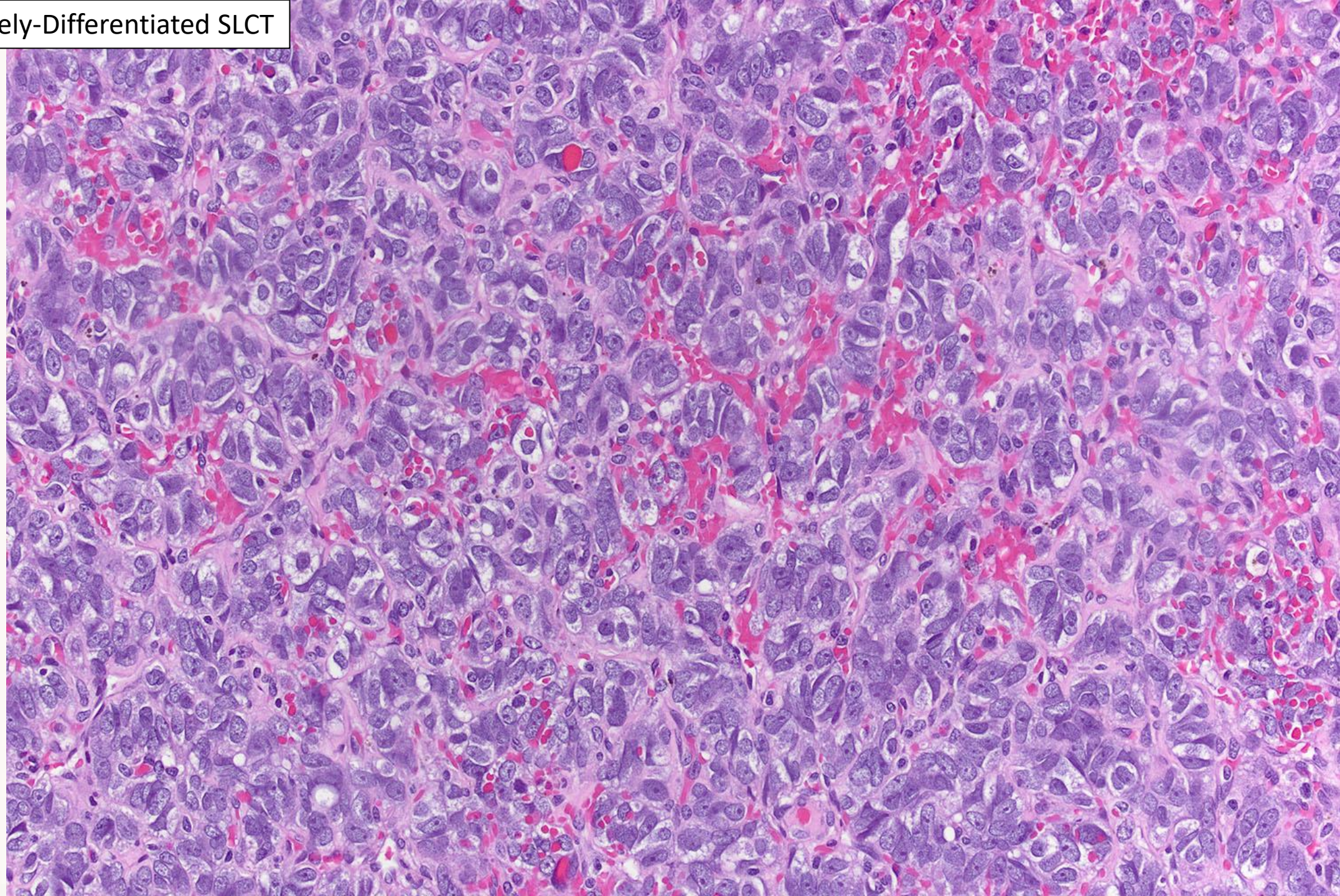


Moderately-Differentiated SLCT

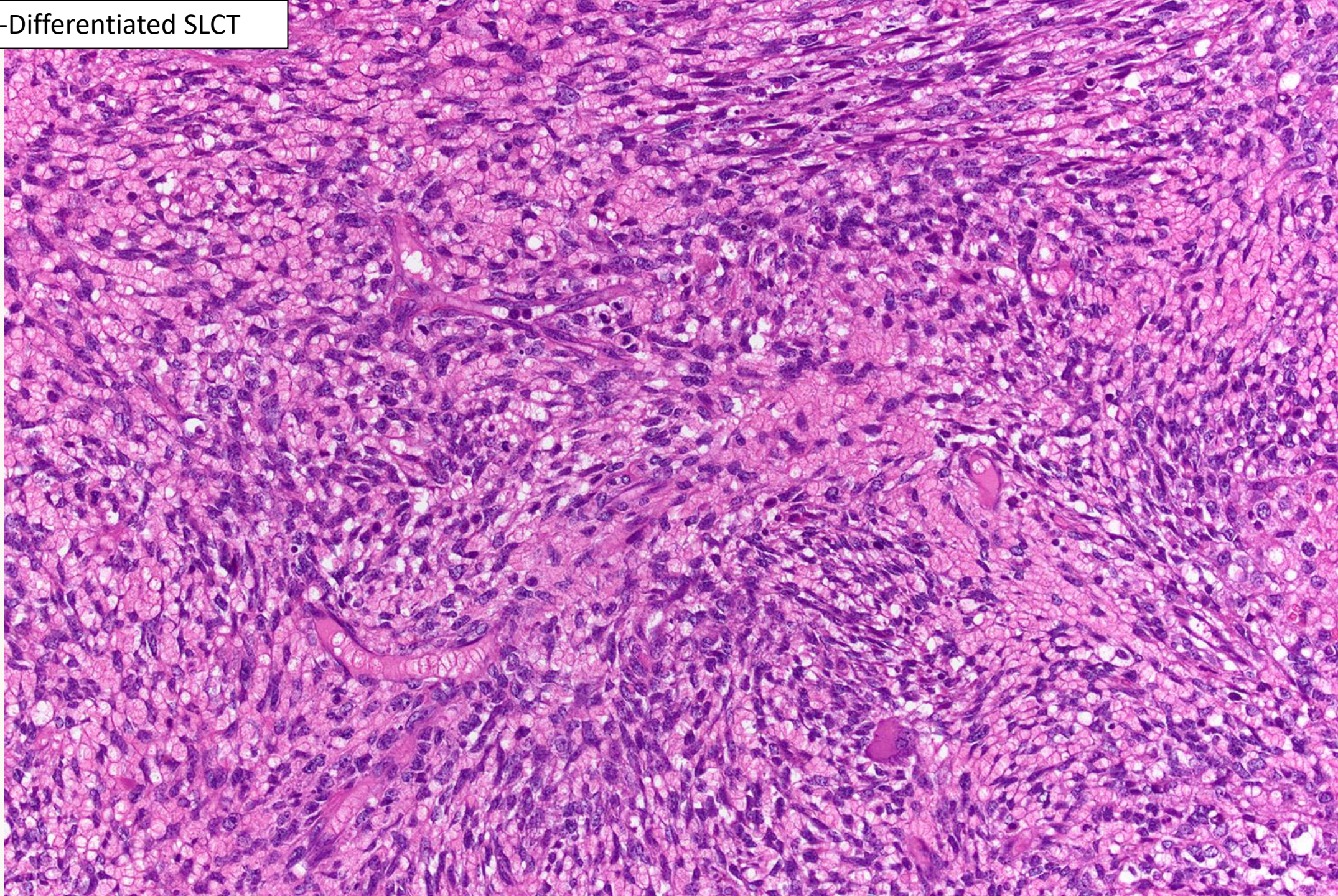


*May have relatively well-differentiated tubules in background

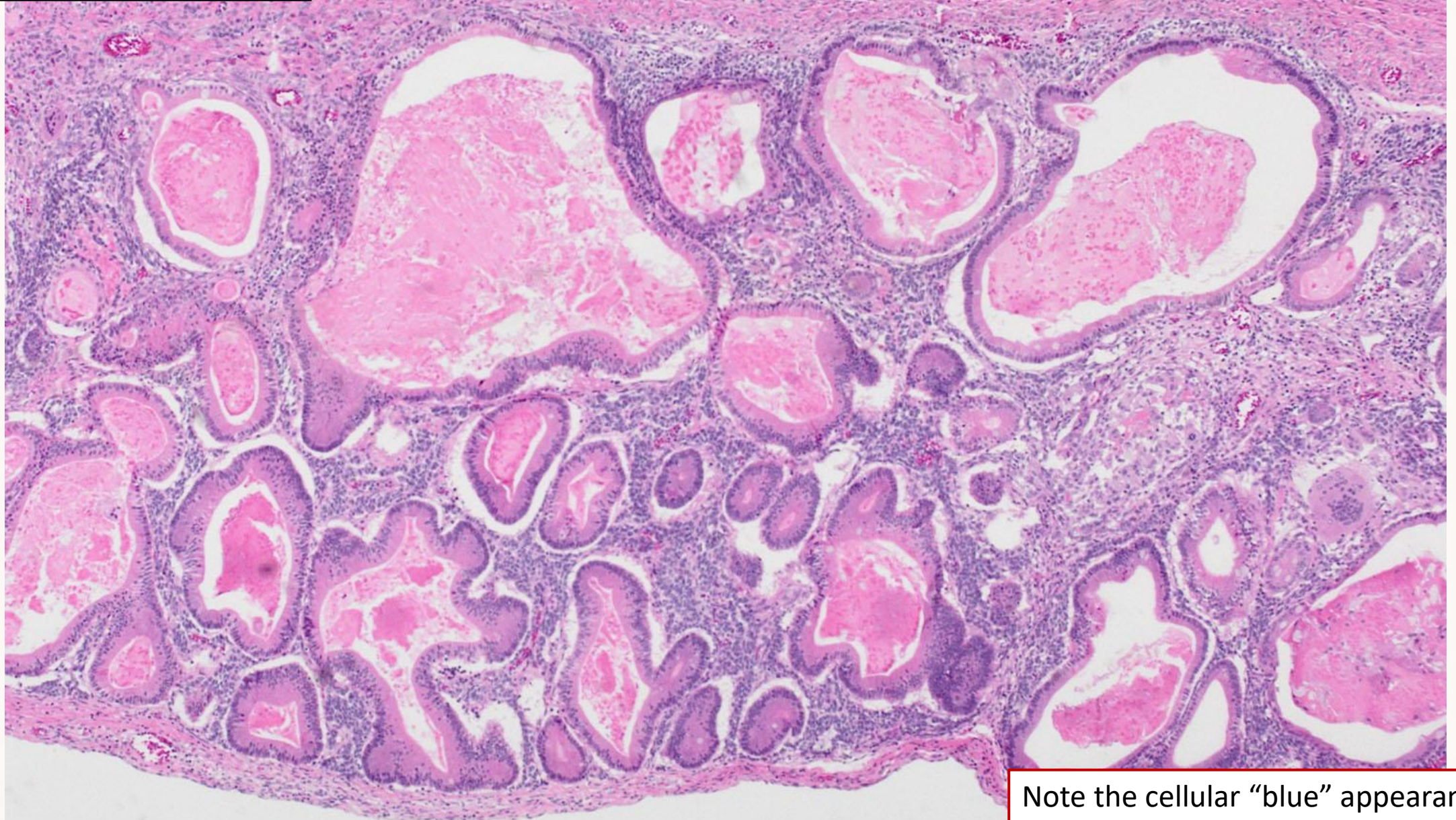
Moderately-Differentiated SLCT



Poorly-Differentiated SLCT

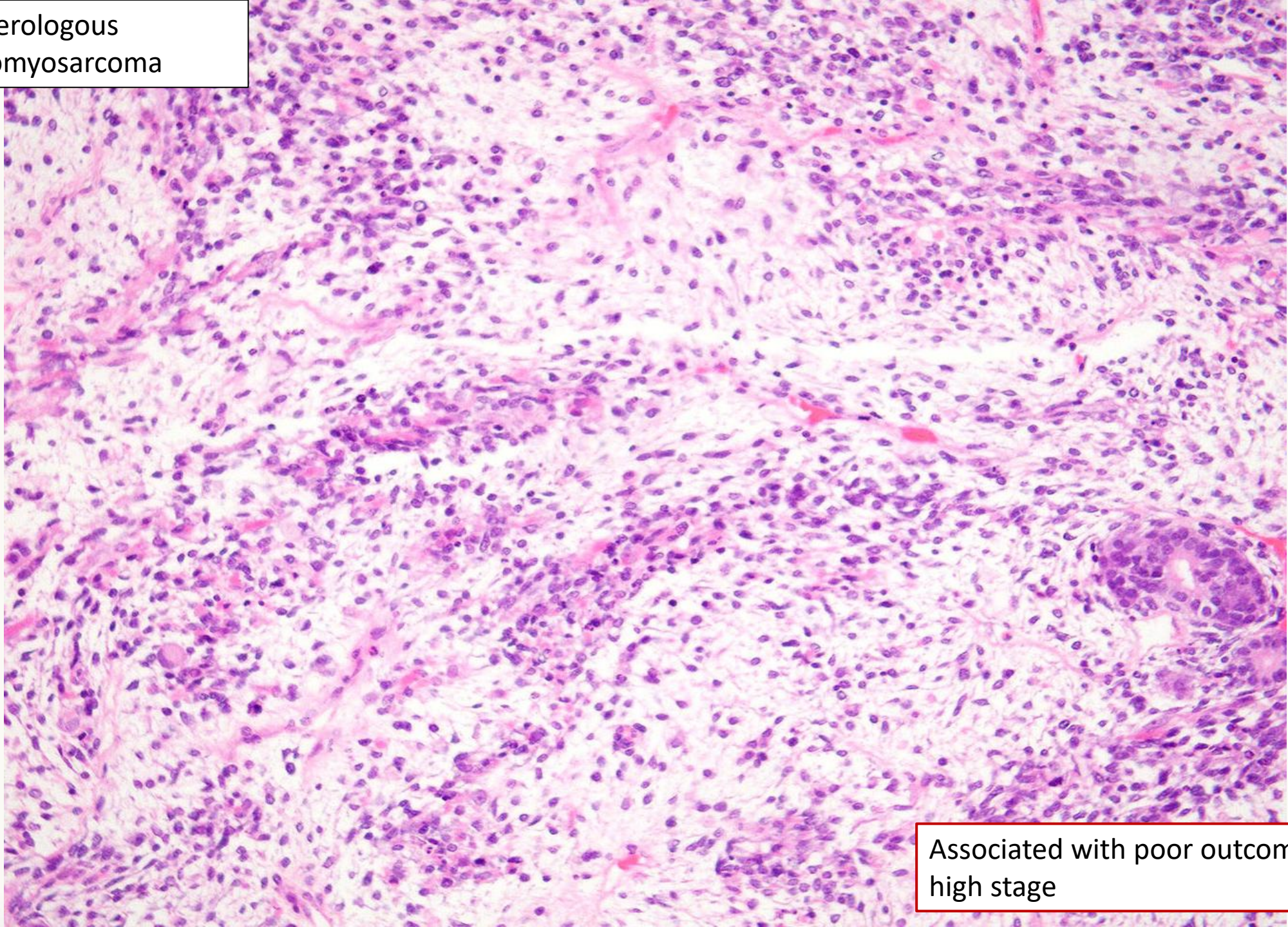


Heterologous Intestinal-Type Glands



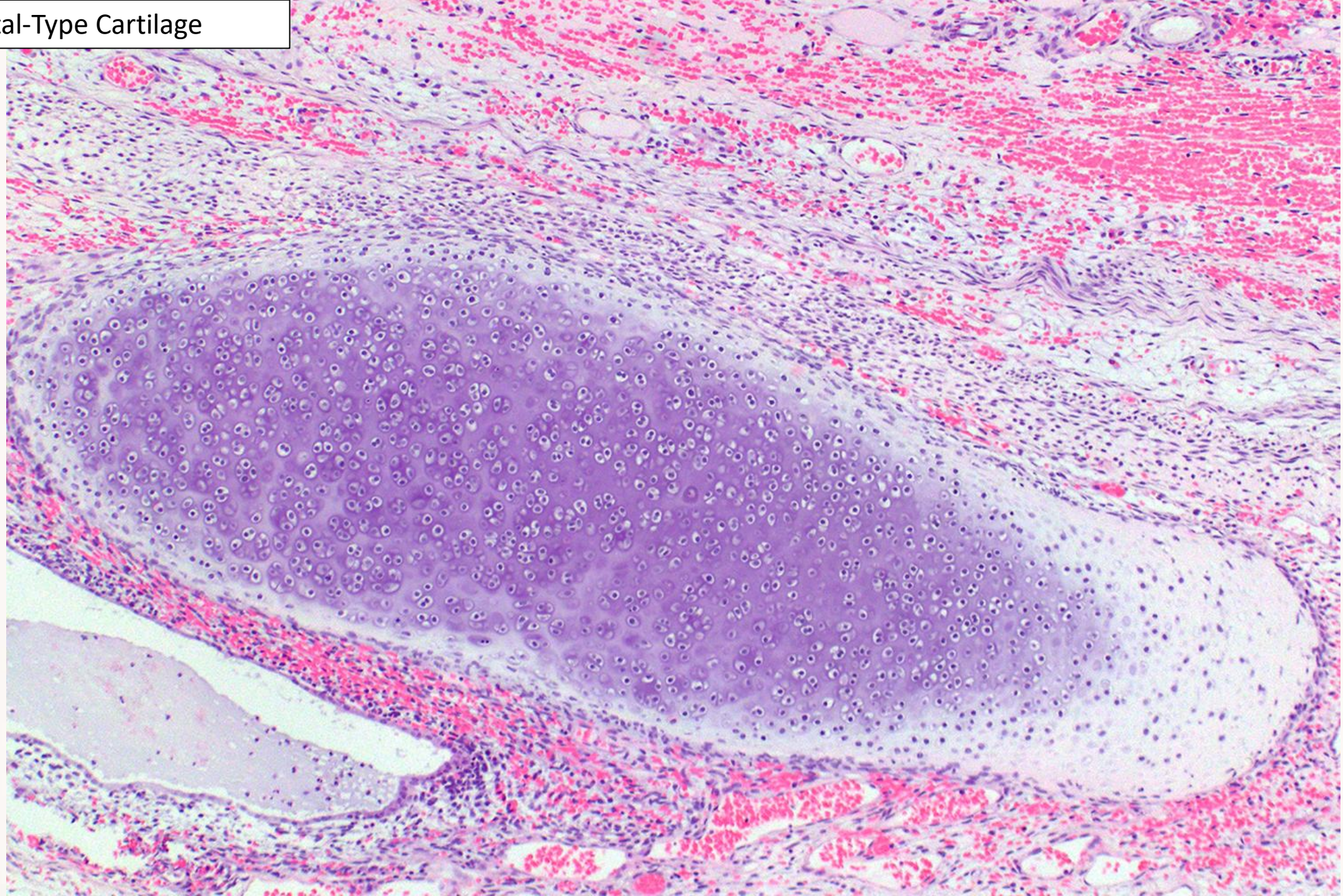
Note the cellular "blue" appearance of Sertoli cells between the glands

Heterologous
Rhabdomyosarcoma

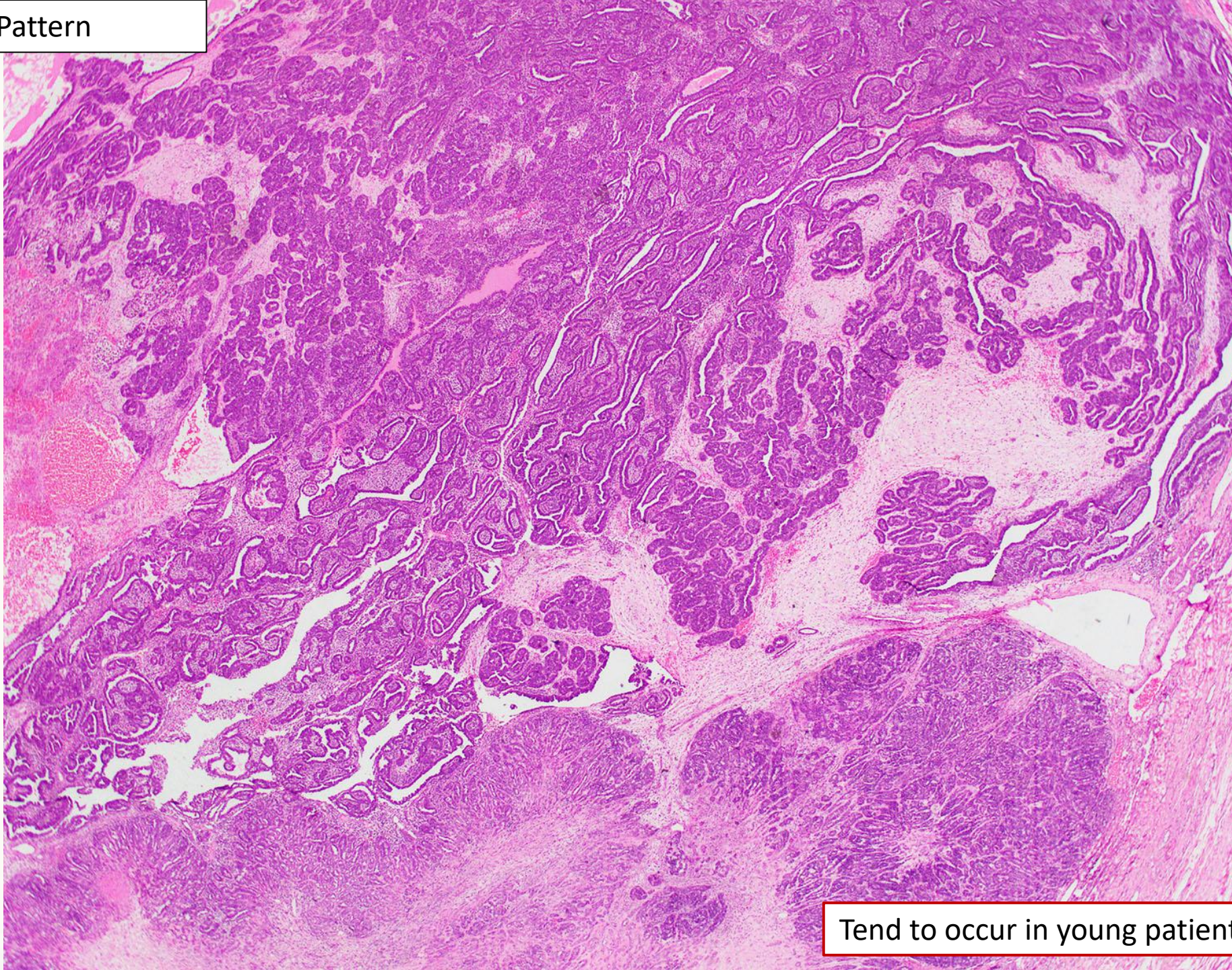


Associated with poor outcome when
high stage

Fetal-Type Cartilage

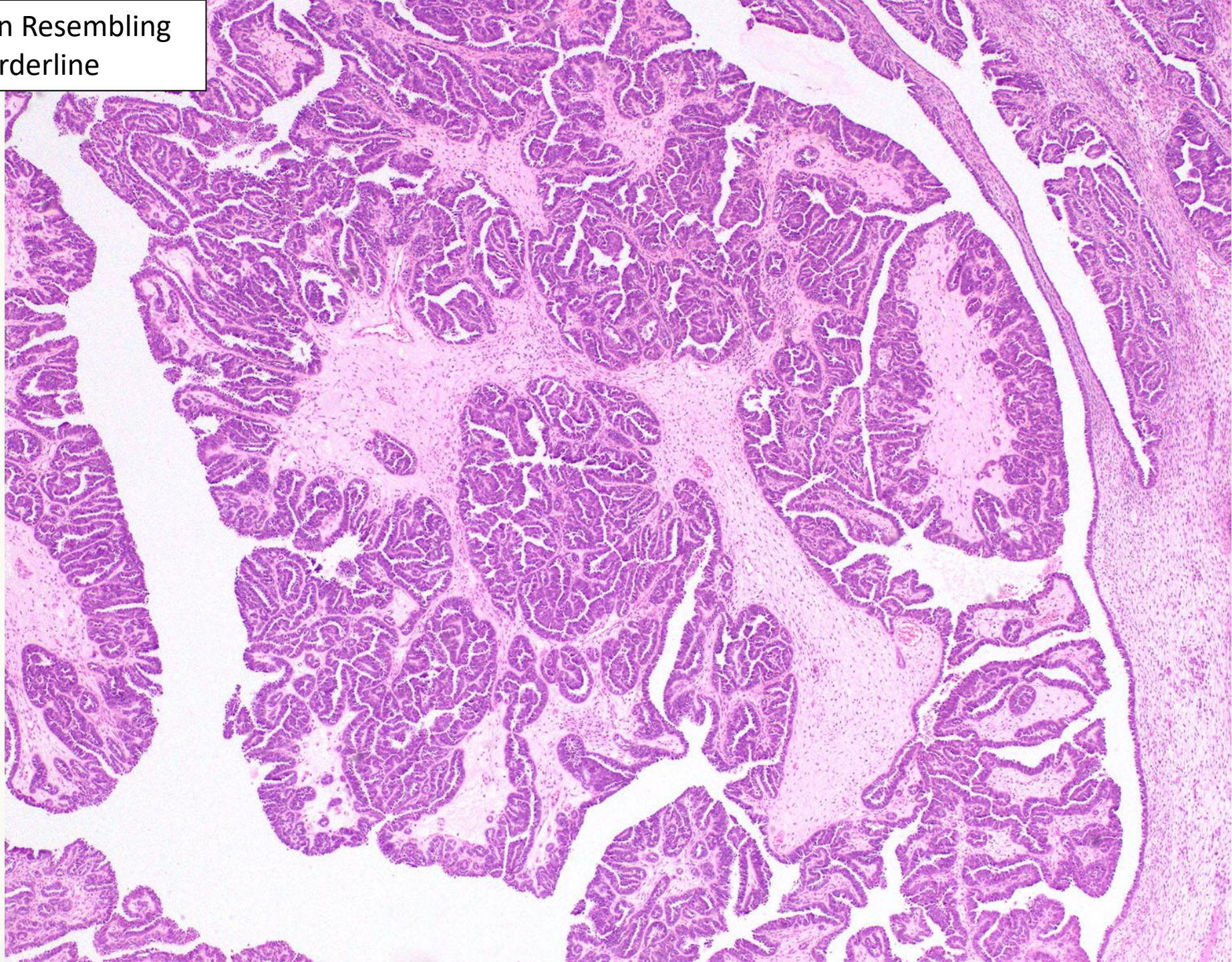


Retiform Pattern



Tend to occur in young patients (mean age 16)

Retiform Pattern Resembling
Serous Borderline



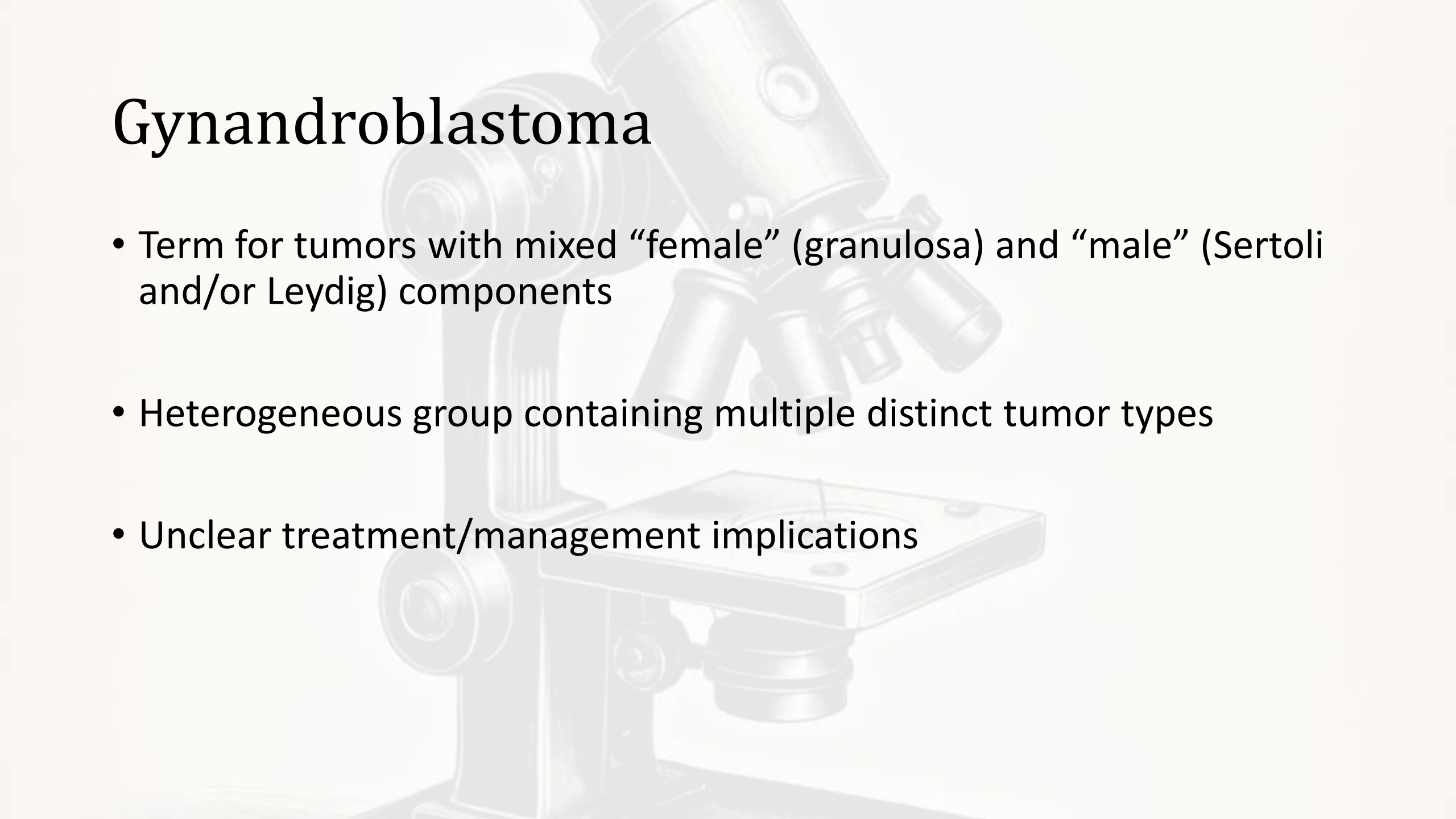
DICER1 Mutations

- Present in vast majority of intermediate and poorly-differentiated SLCT
- Some patients may have germline mutation and *DICER1* tumor predisposition syndrome
 - Pleuropulmonary blastoma
 - Thyroid manifestations (multinodular goiter and thyroid carcinomas)
 - Embryonal rhabdomyosarcoma of uterine cervix
 - Wilms tumor
 - Cystic nephroma
 - Pituitary blastoma
 - Nasal chondromesenchymal hamartoma

Unifying Morphologic Features

- Clusters of primitive cells
- Variable rhabdomyosarcomatous differentiation
- Fetal-type cartilage
- Entrapped or primitive glandular epithelium

Gynandroblastoma



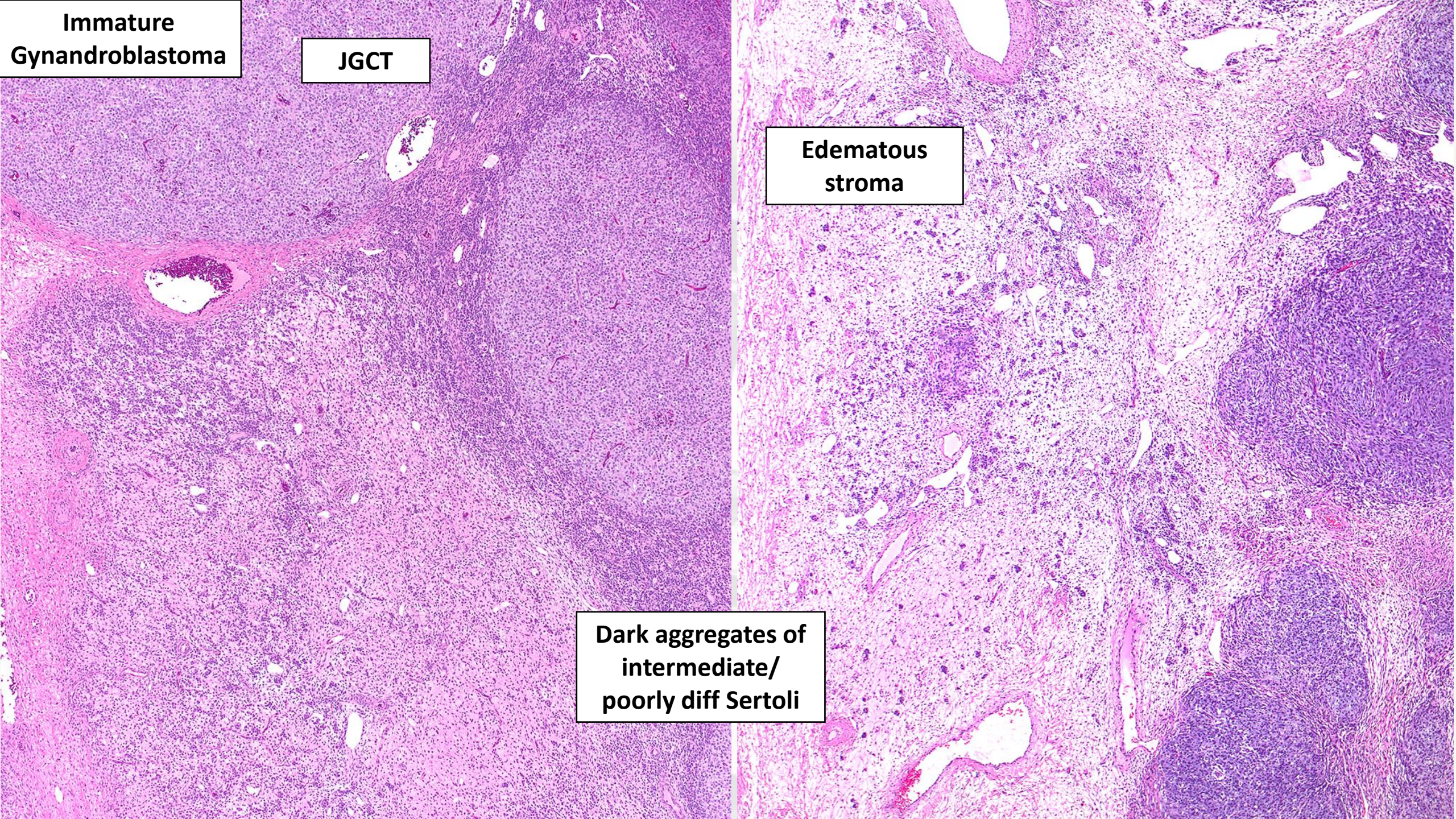
- Term for tumors with mixed “female” (granulosa) and “male” (Sertoli and/or Leydig) components
- Heterogeneous group containing multiple distinct tumor types
- Unclear treatment/management implications

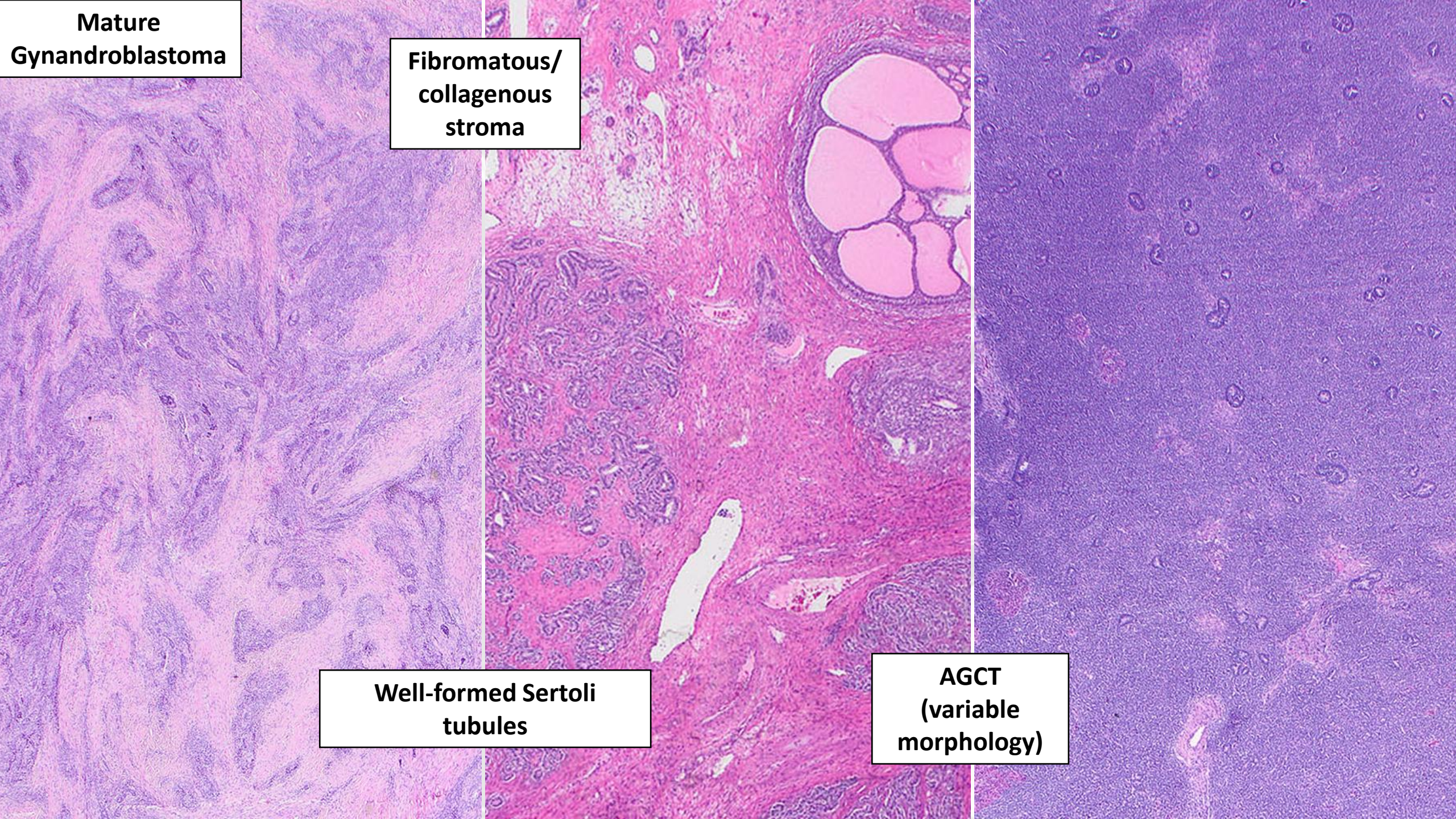
**Immature
Gynandroblastoma**

JGCT

**Edematous
stroma**

**Dark aggregates of
intermediate/
poorly diff Sertoli**





**Mature
Gynandroblastoma**

**Fibromatous/
collagenous
stroma**

**Well-formed Sertoli
tubules**

**AGCT
(variable
morphology)**

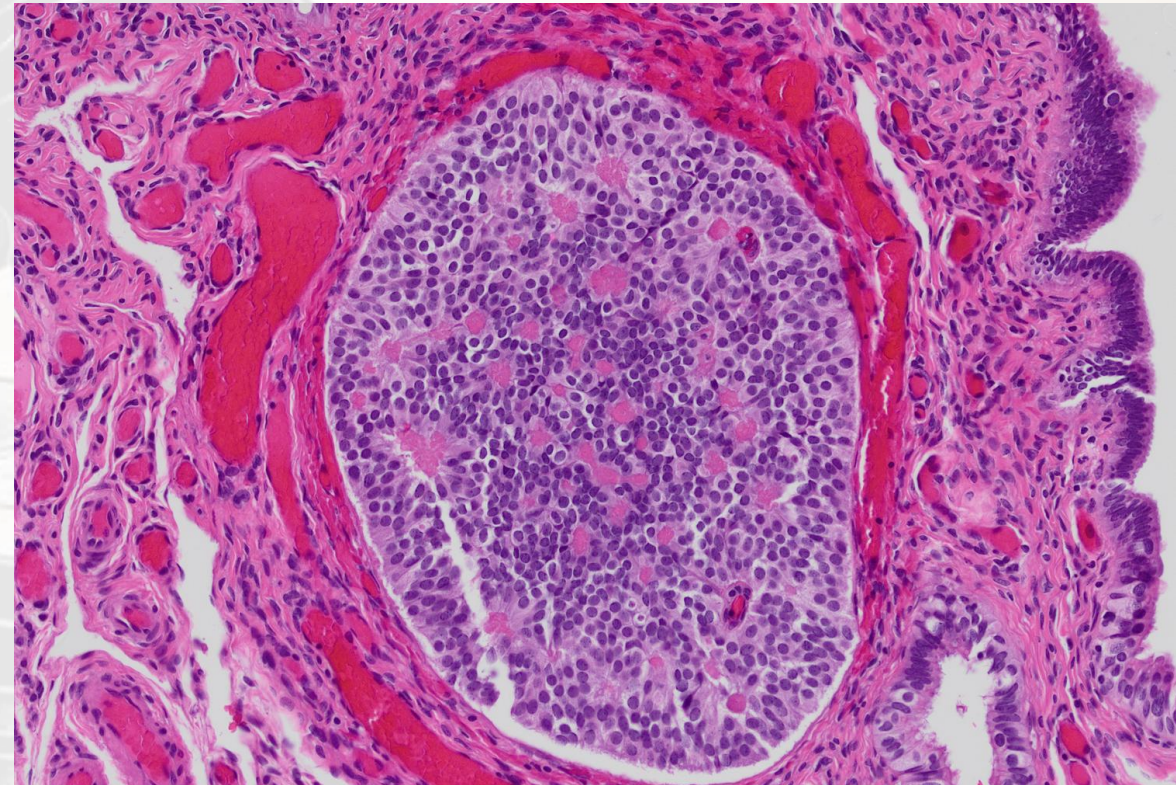
Feature	Immature Gynandroblastoma	Mature Gynandroblastoma
Median Age (p=<0.0001)	17 (11-30) years	51 (15-83) years
Hormonal Manifestations	May be estrogenic or androgenic	
Sertoli Component	Aggregates of dark, poorly formed Sertoli tubules; may have minor areas of well-formed tubules	Well-formed Sertoli tubules only
Granulosa Component	Usually Juvenile	Usually Adult
Stroma	Edematous	Collagenous/Fibromatous
Heterologous Elements	Occasional	Absent
Pathogenic Gene Variants	<i>DICER1</i> or <i>IDH1</i> <i>FOXL2</i> and <i>FGFR1</i> wild-type	Occasional <i>FOXL2</i> or <i>FGFR1</i> Usually <i>DICER1</i> , <i>IDH1</i> , <i>FOXL2</i> , <i>FGFR1</i> wild-type
Syndromic Association	DICER1 syndrome Ollier syndrome	Absent



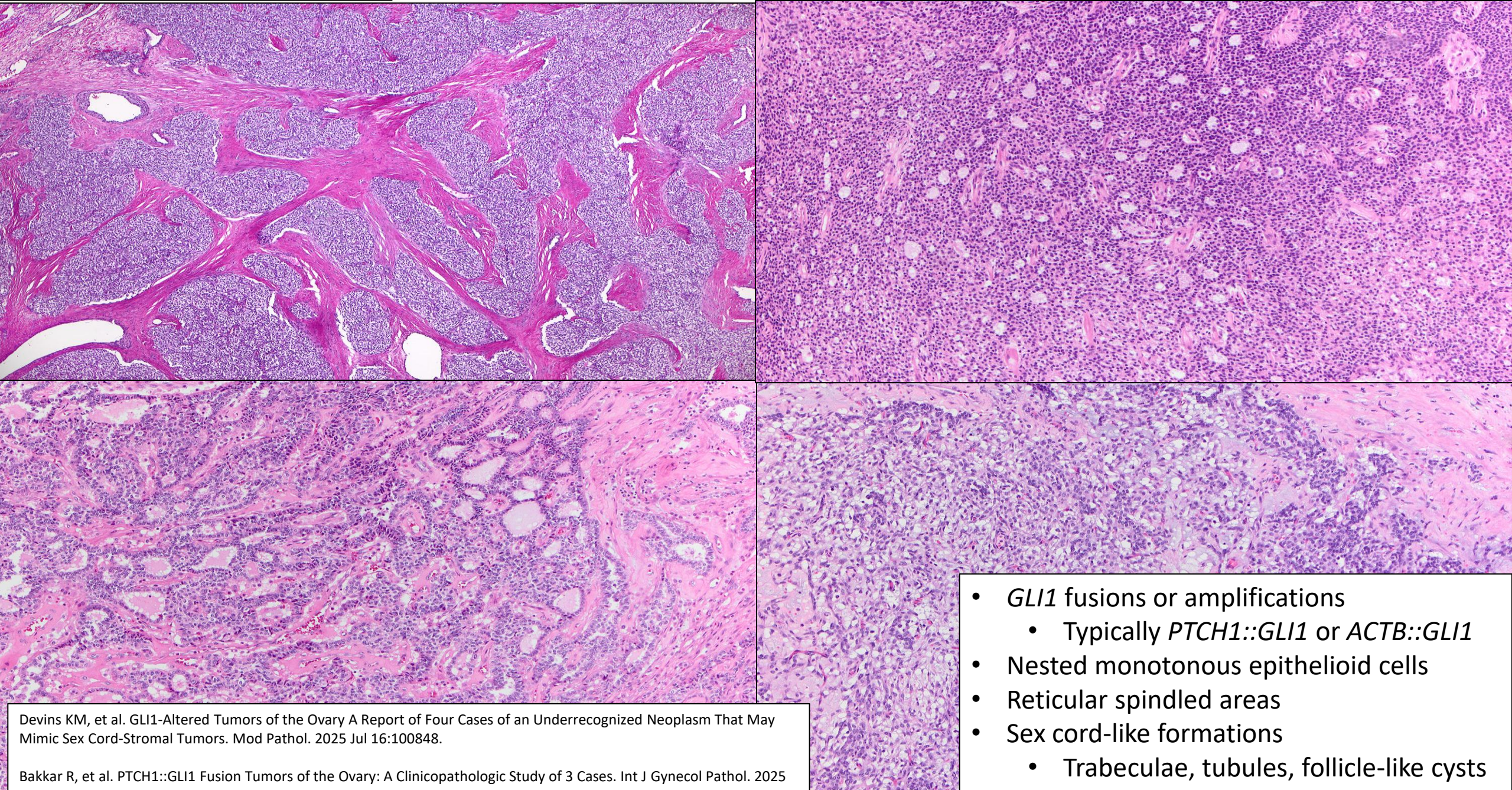
Tumors/Processes Resembling SCST

Microscopic Sex Cord Proliferations

- May occur in peritoneum, fallopian tube, or ovary
- Nonspecific appearance
 - Sertoli
 - SCTAT
 - Granulosa
- May be associated with endometriosis or inflammation
- Benign
- May mimic syndromic SCTAT



GLI1-Altered Tumors

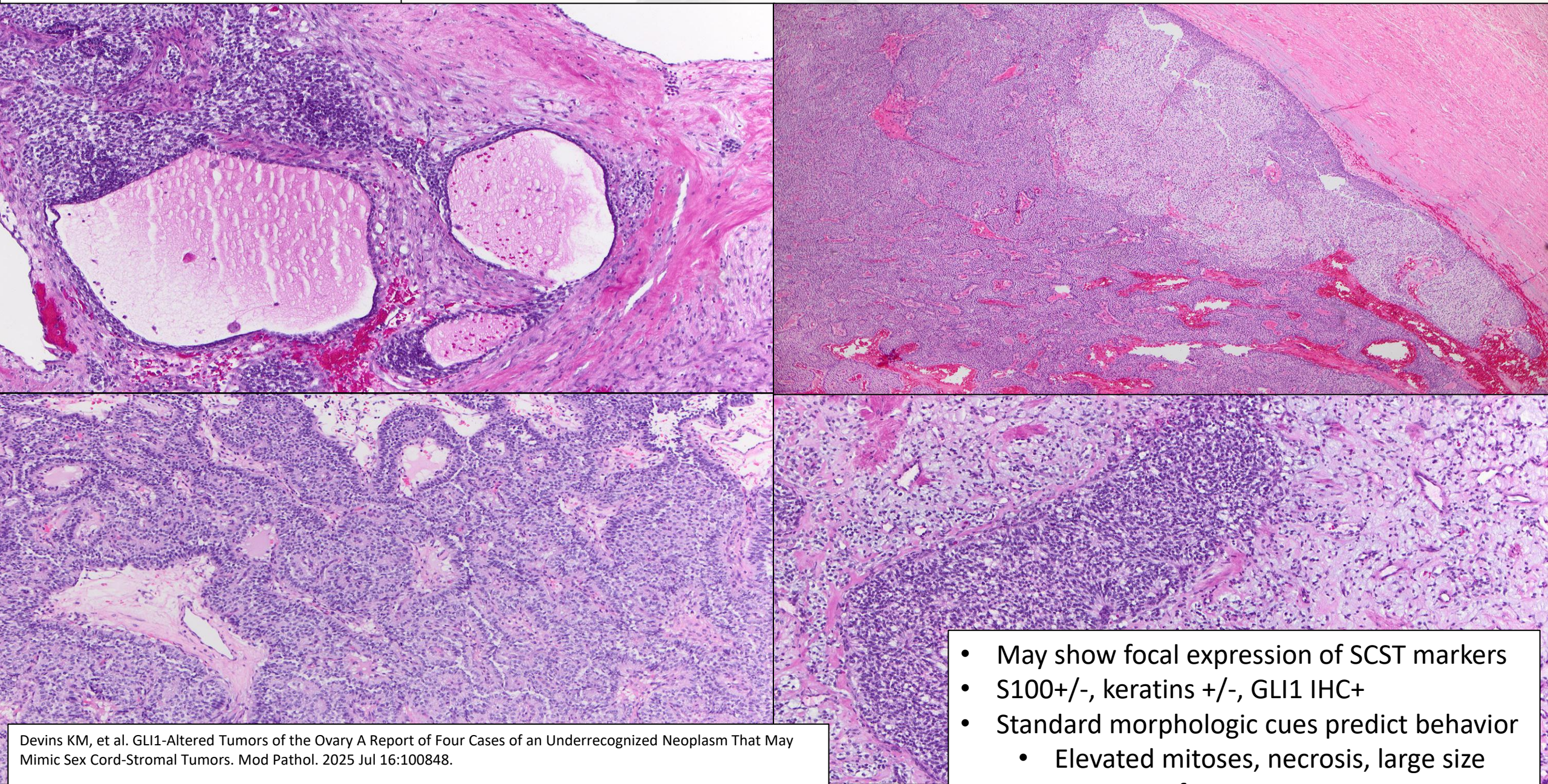


- *GLI1* fusions or amplifications
 - Typically *PTCH1::GLI1* or *ACTB::GLI1*
- Nested monotonous epithelioid cells
- Reticular spindled areas
- Sex cord-like formations
 - Trabeculae, tubules, follicle-like cysts

Devins KM, et al. GLI1-Altered Tumors of the Ovary A Report of Four Cases of an Underrecognized Neoplasm That May Mimic Sex Cord-Stromal Tumors. Mod Pathol. 2025 Jul 16:100848.

Bakkar R, et al. PTCH1::GLI1 Fusion Tumors of the Ovary: A Clinicopathologic Study of 3 Cases. Int J Gynecol Pathol. 2025

GLI1-Altered Tumors



- May show focal expression of SCST markers
- S100+/-, keratins +/-, GLI1 IHC+
- Standard morphologic cues predict behavior
 - Elevated mitoses, necrosis, large size
- Some reports of response to TKIs

Devins KM, et al. GLI1-Altered Tumors of the Ovary A Report of Four Cases of an Underrecognized Neoplasm That May Mimic Sex Cord-Stromal Tumors. Mod Pathol. 2025 Jul 16:100848.

Bakkar R, et al. PTCH1::GLI1 Fusion Tumors of the Ovary: A Clinicopathologic Study of 3 Cases. Int J Gynecol Pathol. 2025

Endometrioid Adenocarcinomas with Sex Cord-Like Features

C

Trabeculae

AGCT-like

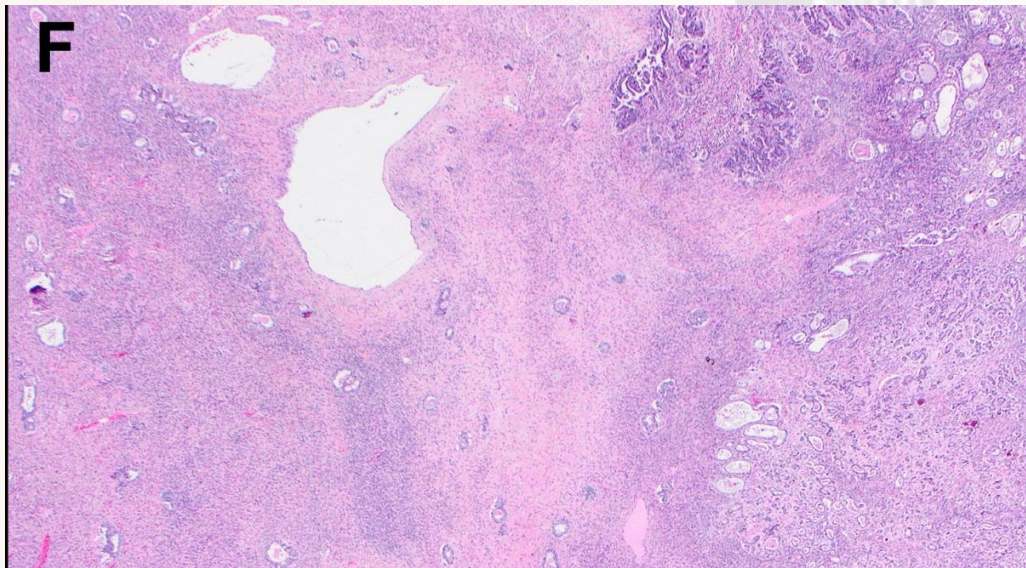
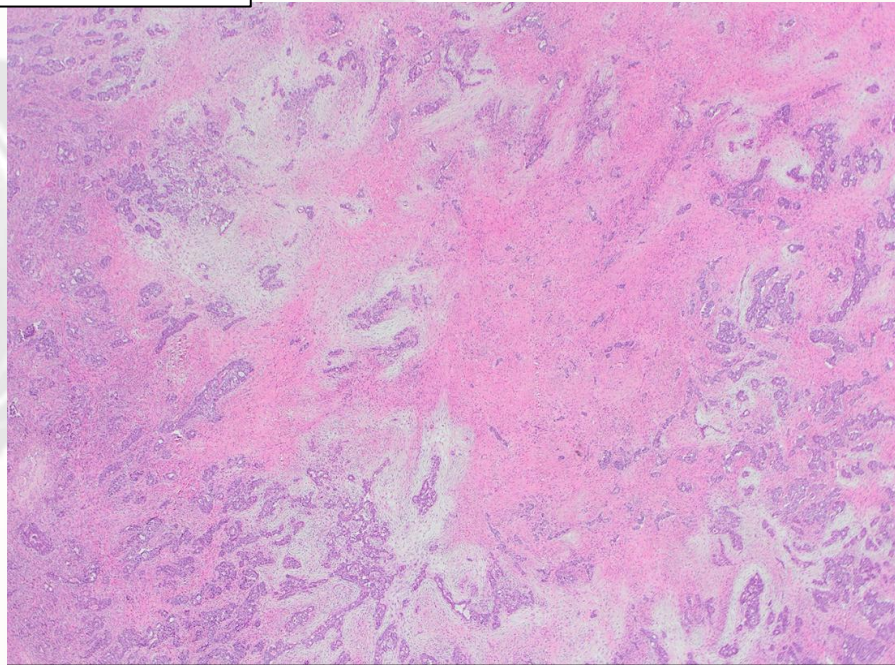
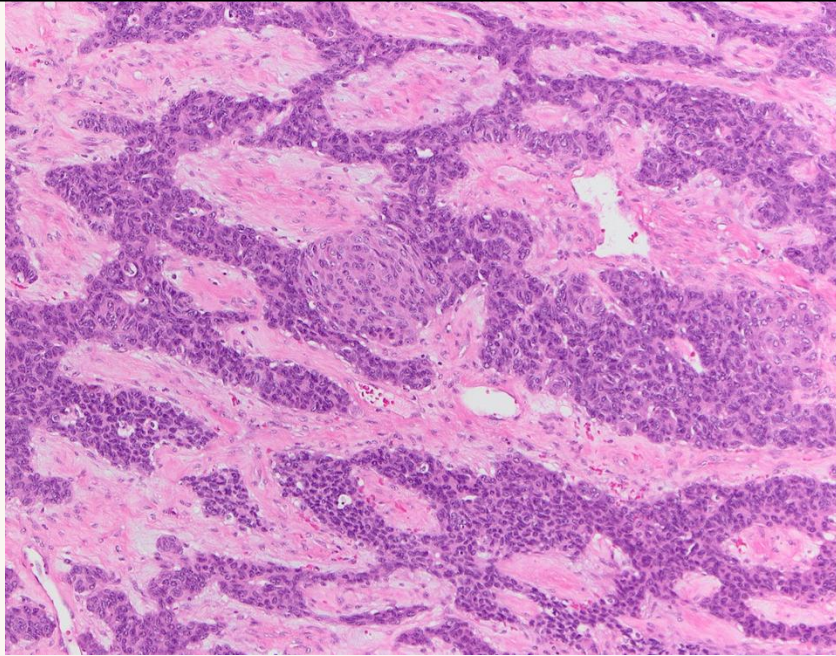
Spindled Cells

Tubular Glands

Ependymoma-like

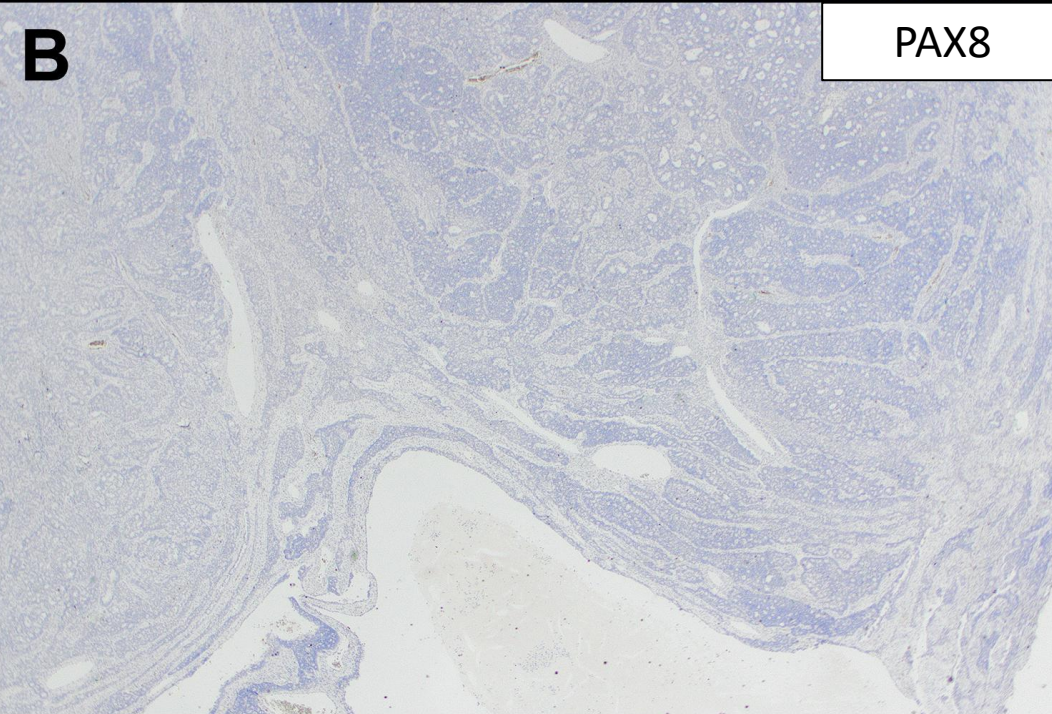
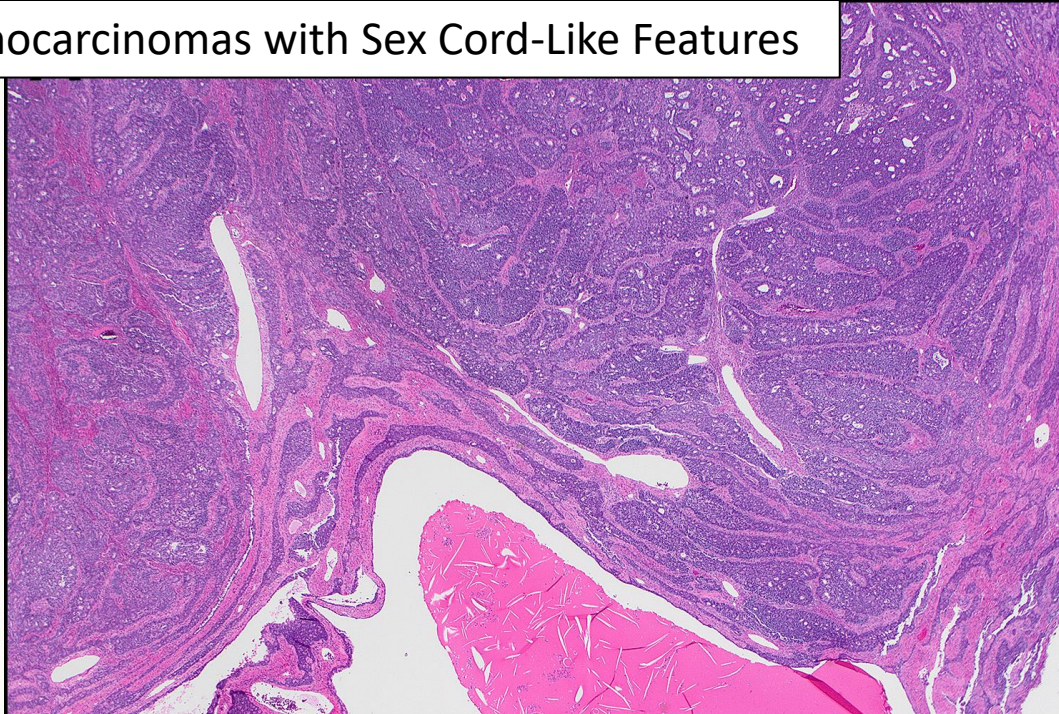
Lengyel K, Musick A, Fisch AS, Lin LH, Turashvili G, Young RH, Oliva E, Devins KM. Adnexal Endometrioid Carcinomas With Sex Cord-Like Morphology are Frequently PAX8-Negative, SOX17-Positive, and Enriched for CTNNB1 Alterations. *Am J Surg Pathol*. 2026 Mar 11. doi: 10.1097

Endometrioid Adenocarcinomas with Sex Cord-Like Features



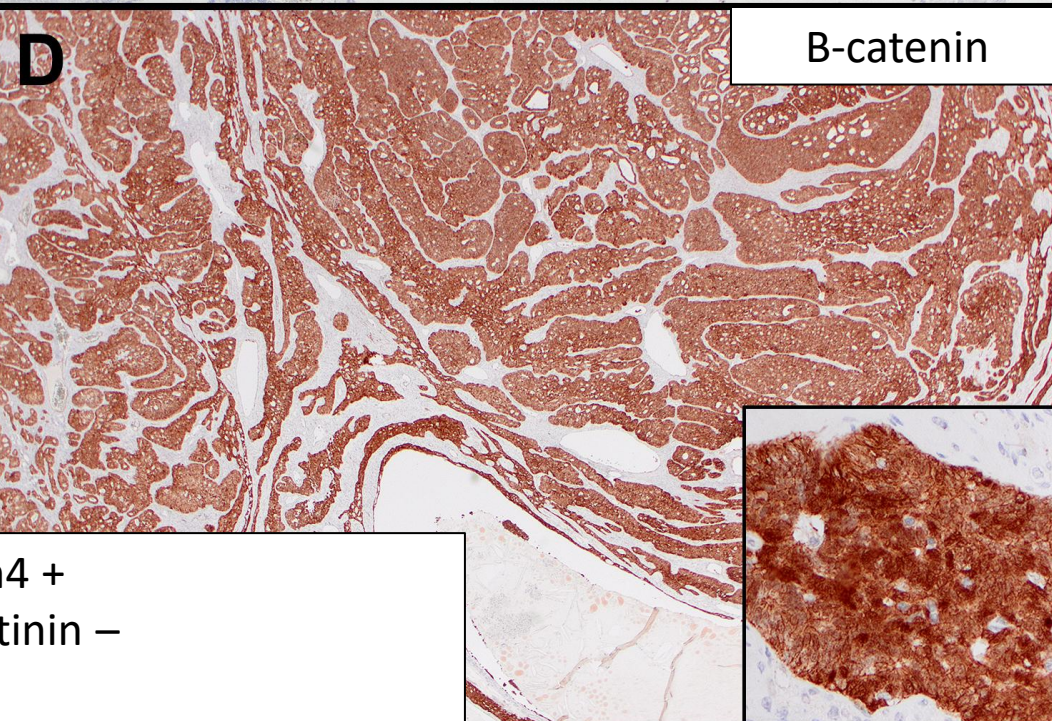
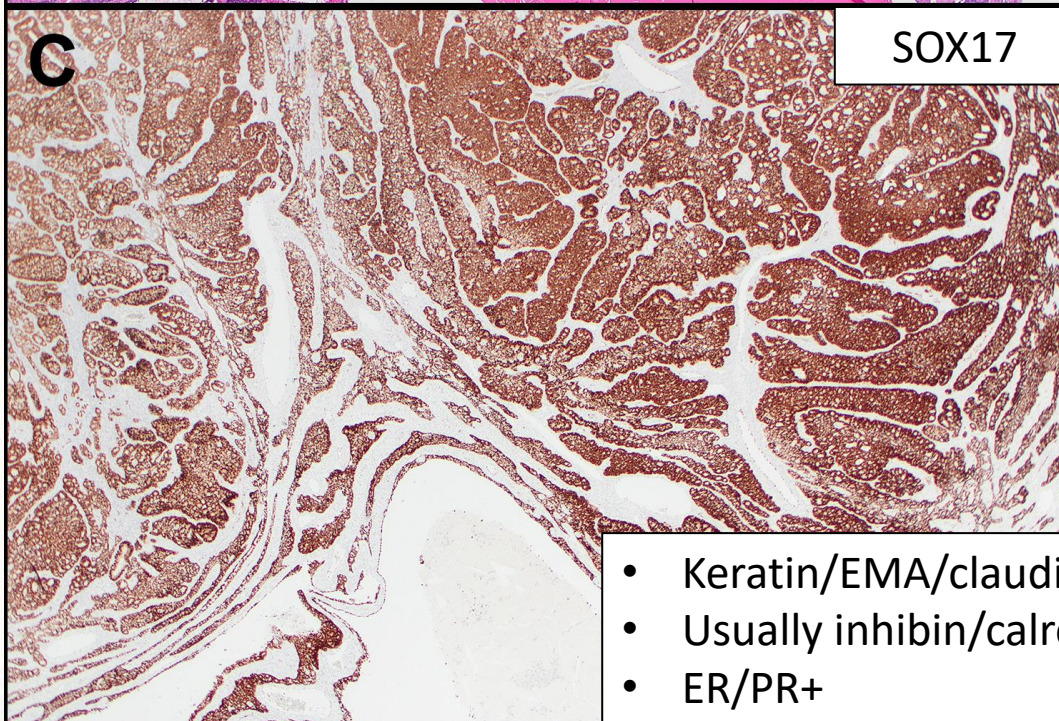
- May see overt endometrioid features
 - Conventional glands
 - Squamous differentiation
 - Endometriosis
- Fibromatous stroma
- Frequent background adenofibroma

Endometrioid Adenocarcinomas with Sex Cord-Like Features



B

PAX8

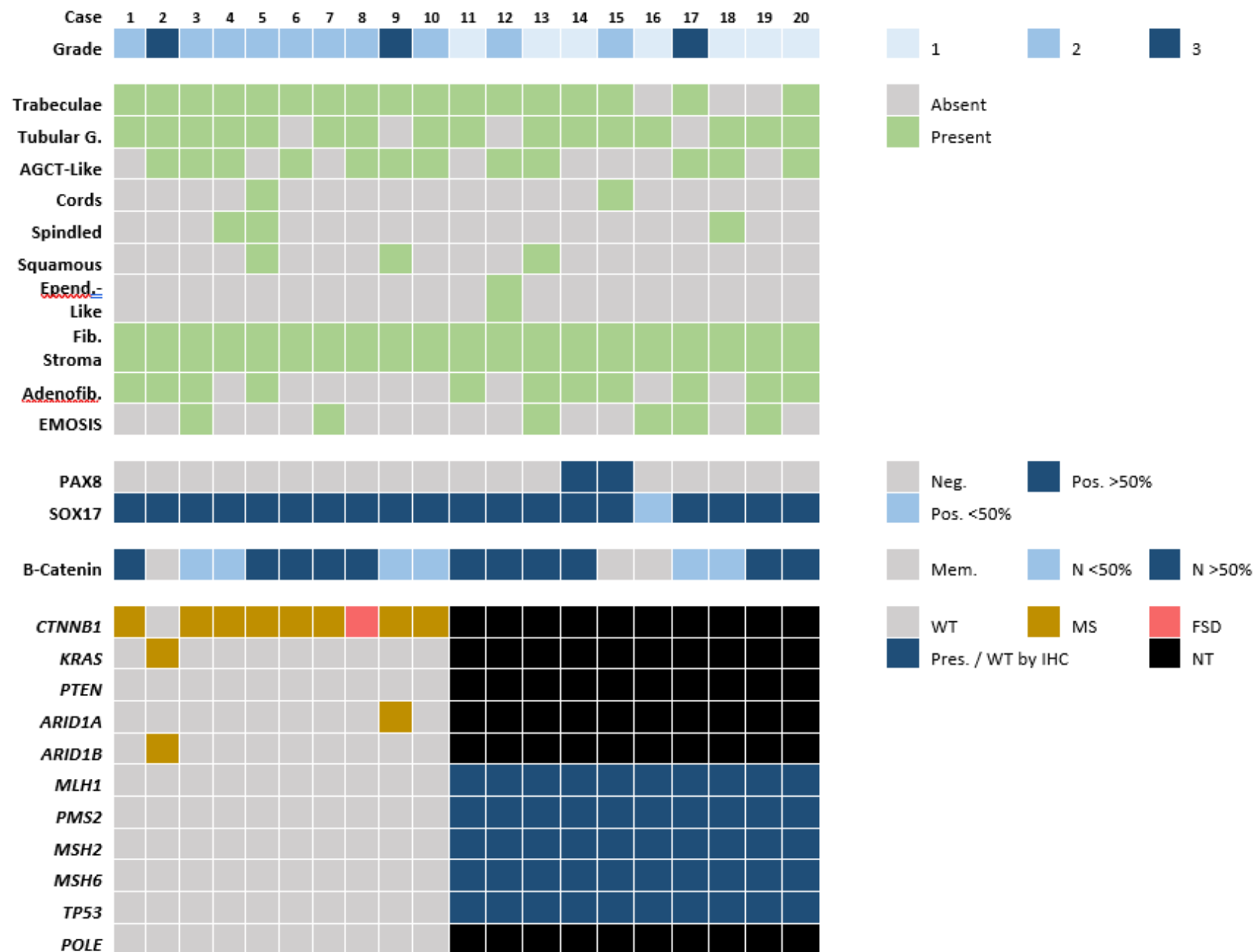


D

B-catenin

SOX17

- Keratin/EMA/claudin4 +
- Usually inhibin/calretinin –
- ER/PR+



G. = Glands, AGCT = adult granulosa cell tumor, Epend. = ependymoma, Fib. = fibromatous, Adenofib. = adenofibroma,

Summary

- Adult and juvenile granulosa cell tumors are diagnosed primarily on morphology
 - Reticulin stains and *FOXL2* mutation analysis useful in select cases
- Most moderately/poorly-differentiated Sertoli-Leydig Cell tumors have *DICER1* alterations
- Gynandroblastomas can be divided into two groups based on degree of differentiation of Sertoli component
- Mimics of sex cord-stromal tumors:
 - Tangentially cut/collapsed follicles
 - Microscopic sex cord proliferations
 - GLI1 tumors
 - Endometrioid carcinomas with sex cord-like morphology