Germ Cell and Sex Cord-Stromal Tumors of the Ovary, an Update

The International Academy of Pathology

Hong Kong Division

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

No conflicts of interest

Germ Cell Tumors, Selected Topics

- Immature Teratoma
- Struma ovarii
  - Cystic
  - Struma carcinoid
  - Tumors

Sex Cord-Stromal Tumors, Selected Topics

Pure stromal tumors

- Microcystic stromal tumor

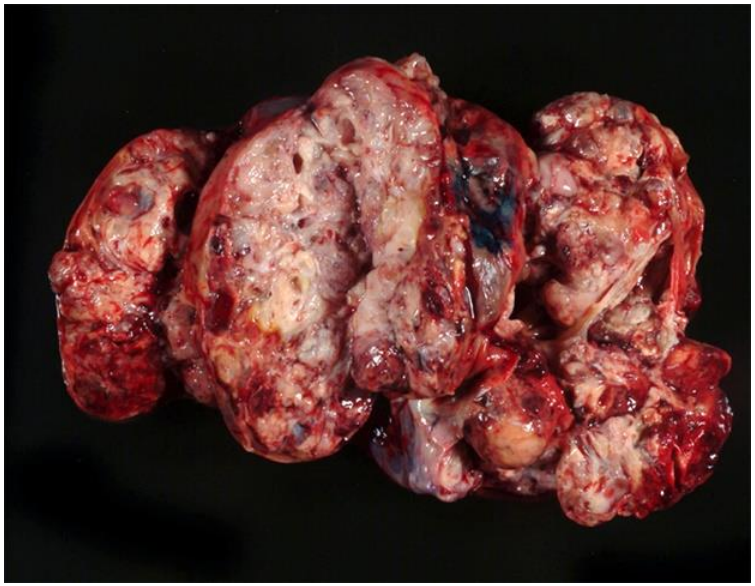
Pure sex cord tumors

- Adult granulosa cell tumor

Mixed sex cord–stromal tumors

- Sertoli-Leydig cell tumor

Immature Teratoma, Relevant Points



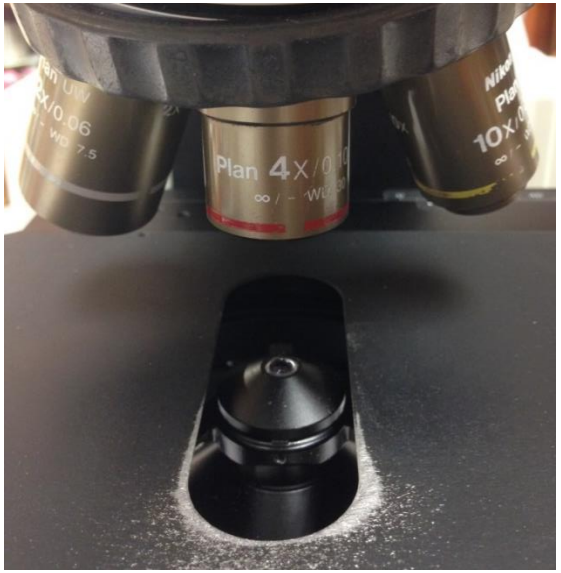
- A synchronous or metachronous mature teratoma can be found in the contralateral ovary
- Unilateral, soft, solid and cystic with hemorrhage and necrosis

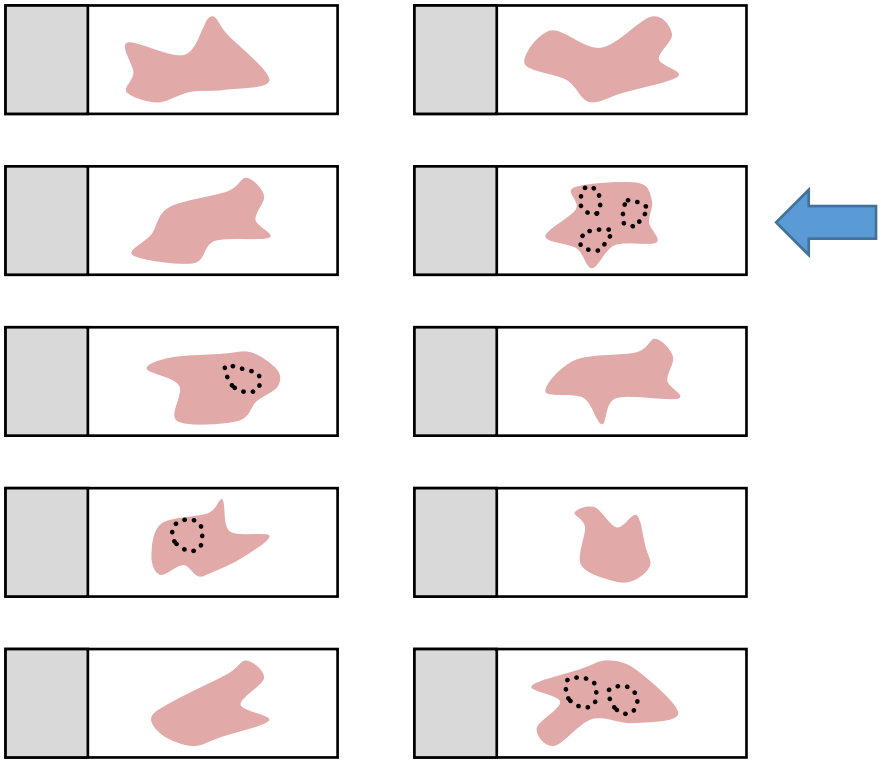
Immature Teratoma, Grading is Based on the Amount of Immature Neuroepithelium

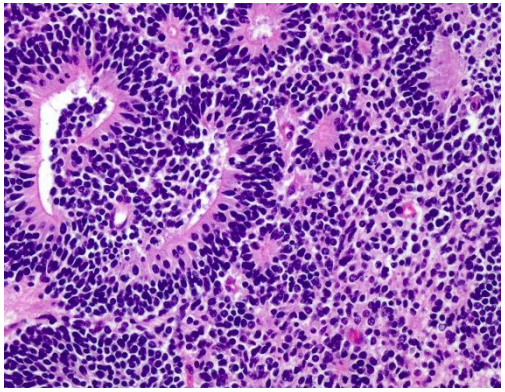
- Low Grade
  - Immature neuroepithelium in any one slide occupies up to one low-power (x 40) microscopic field
- High Grade
  - Immature neuroepithelium in any one slide occupies more than one low-power (x 40) microscopic field

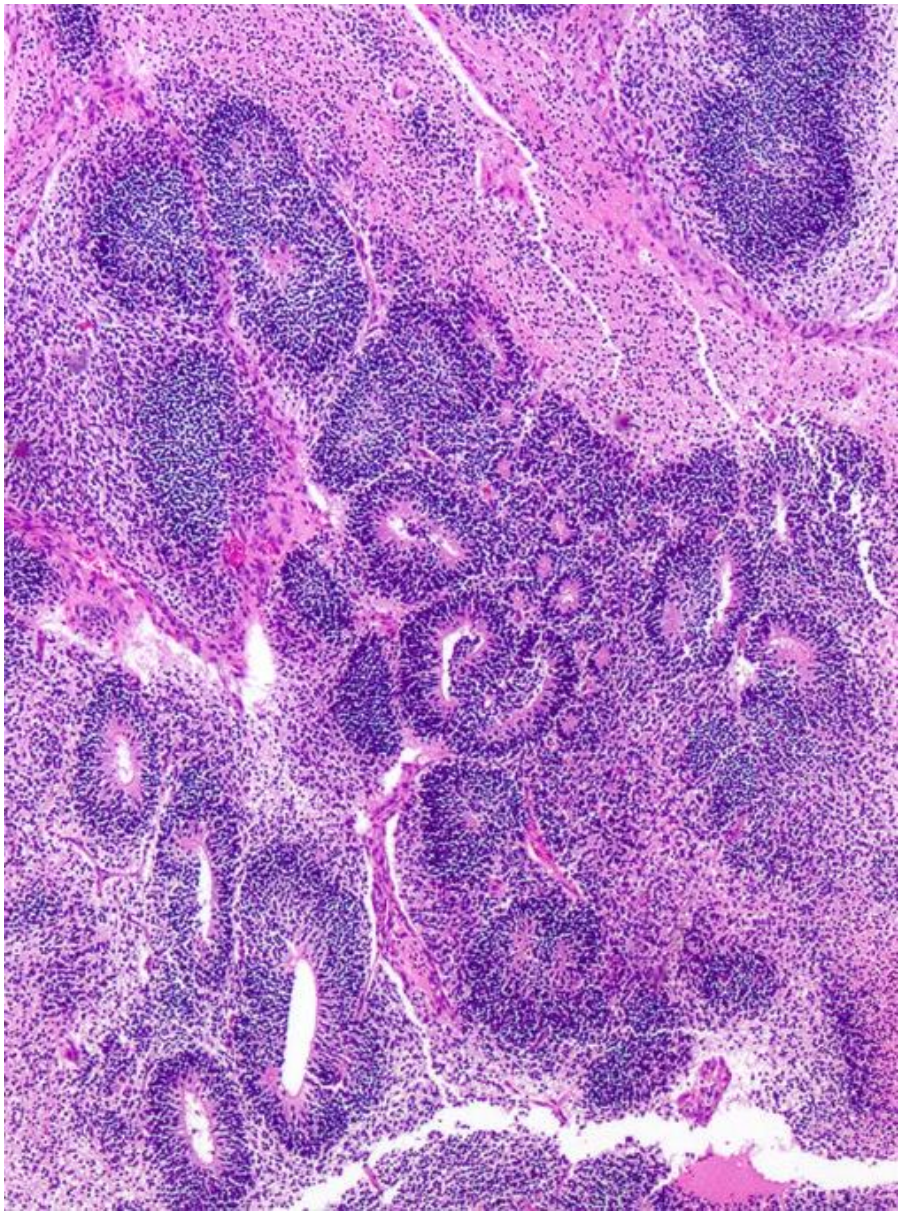
O'Connor and Norris, 1994

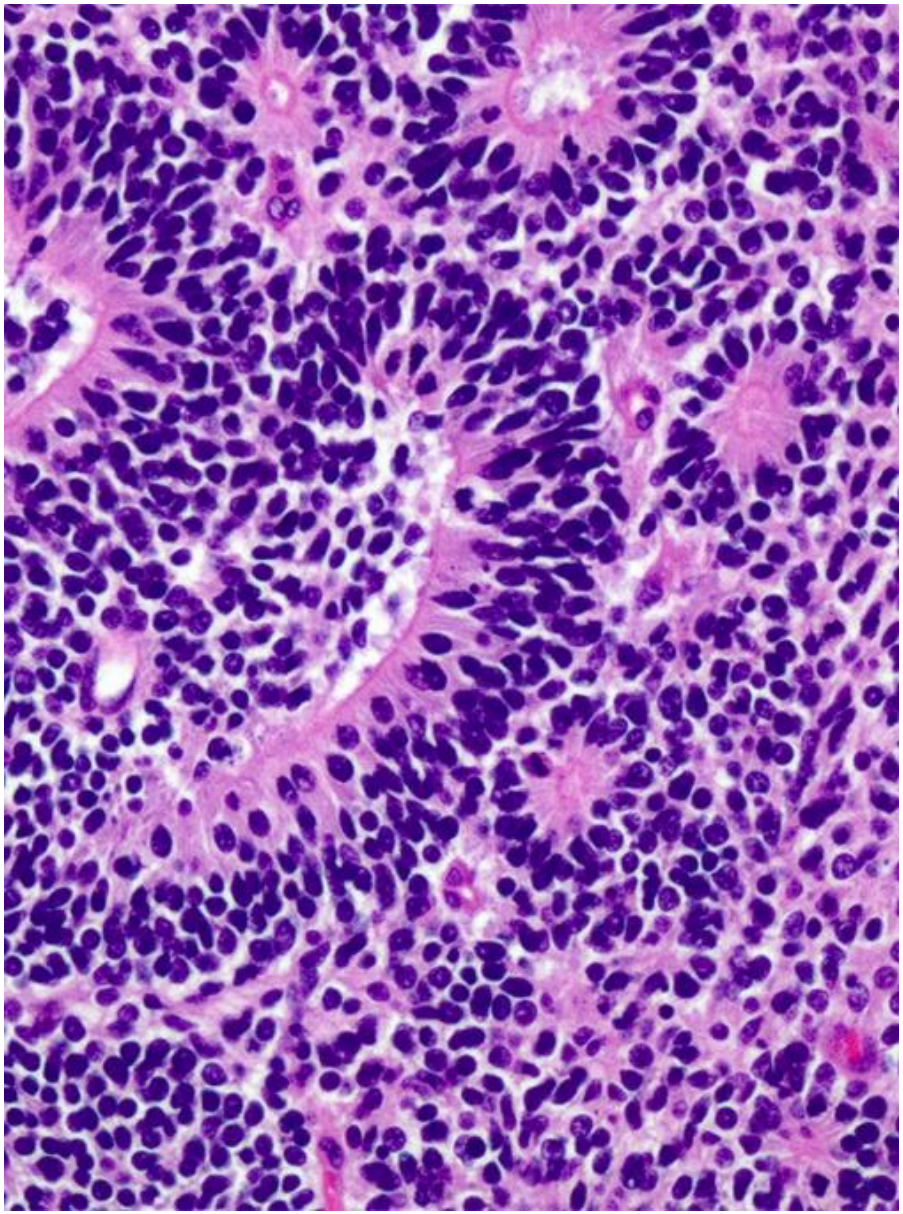

CFI 10X/22


Plan 4X/0

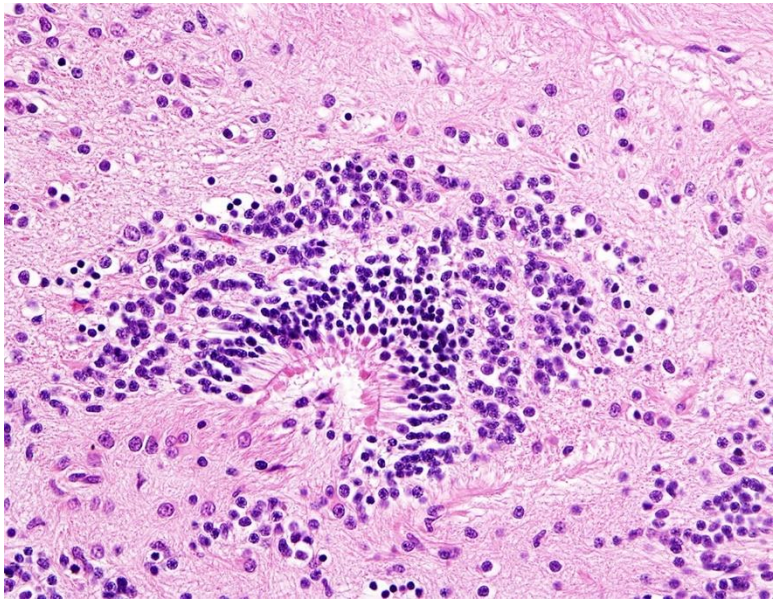


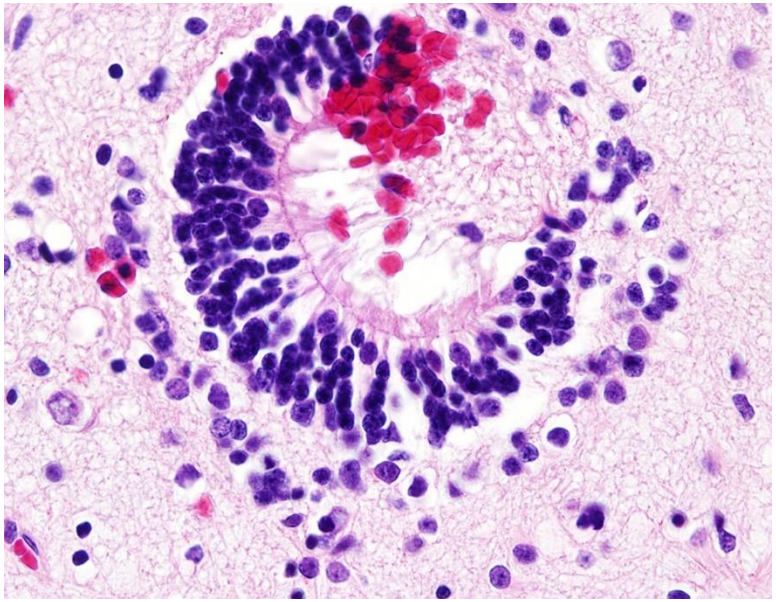




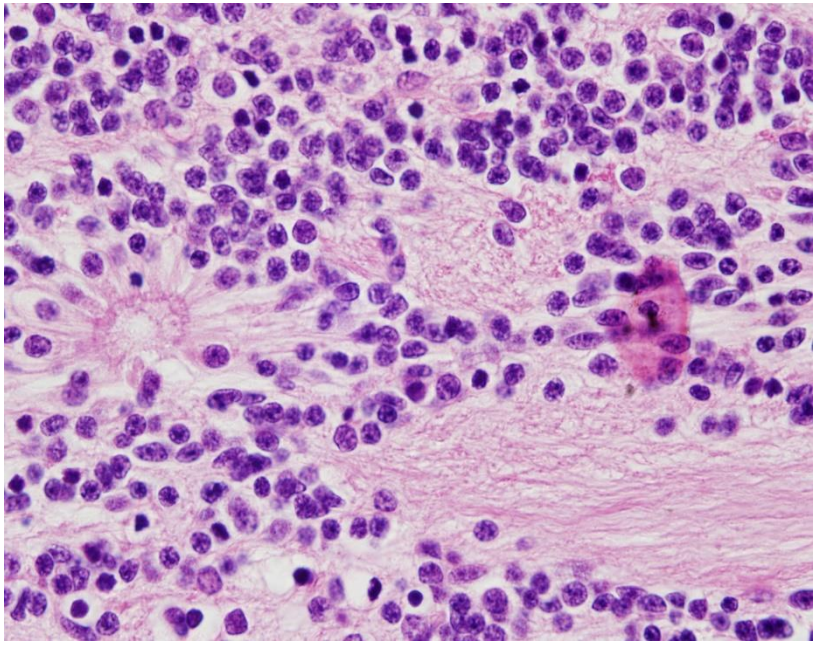


Immature Teratoma, High Grade

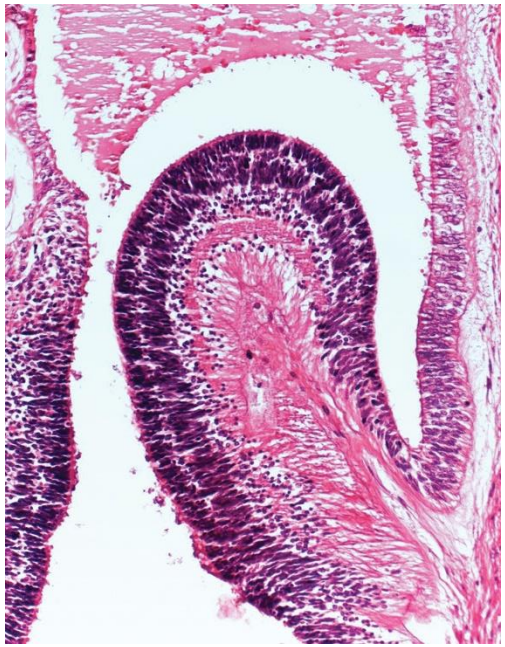




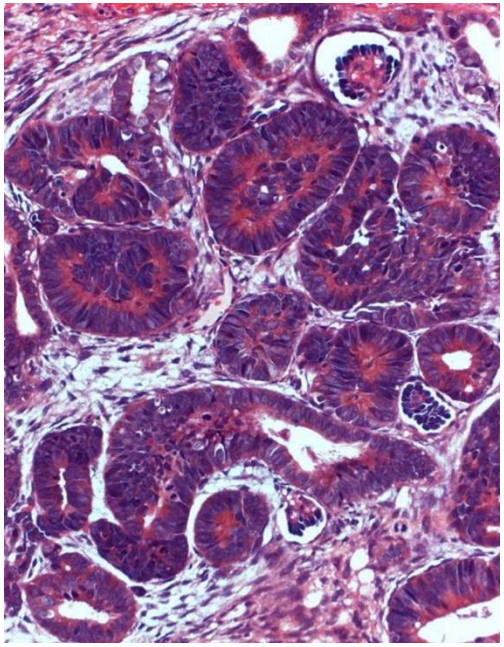
Ependymal tubules



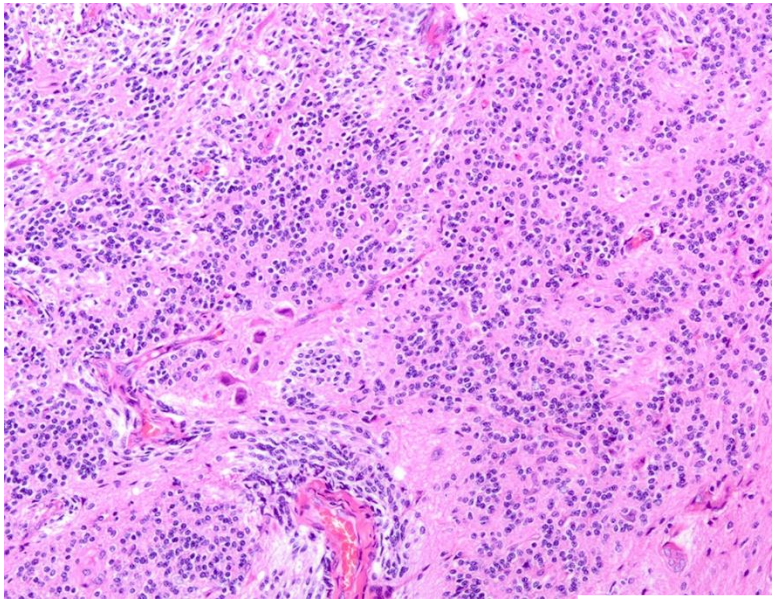
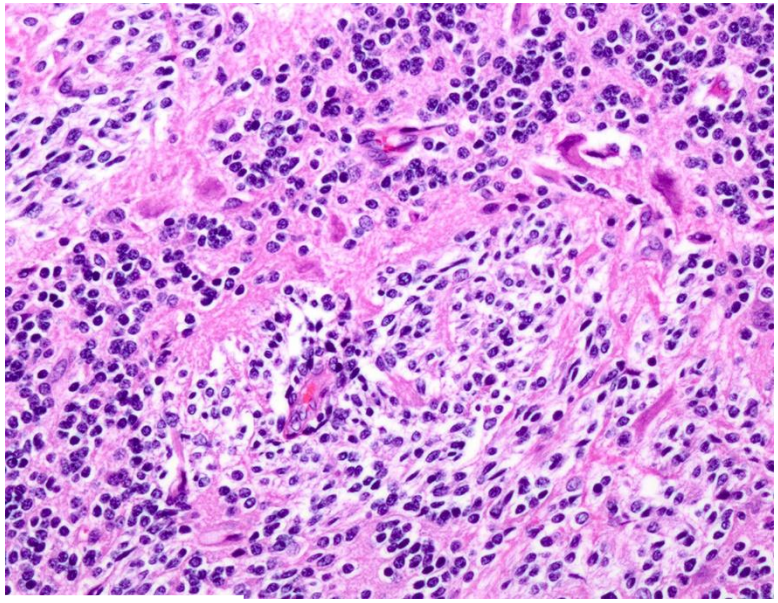
Ependymal tubules



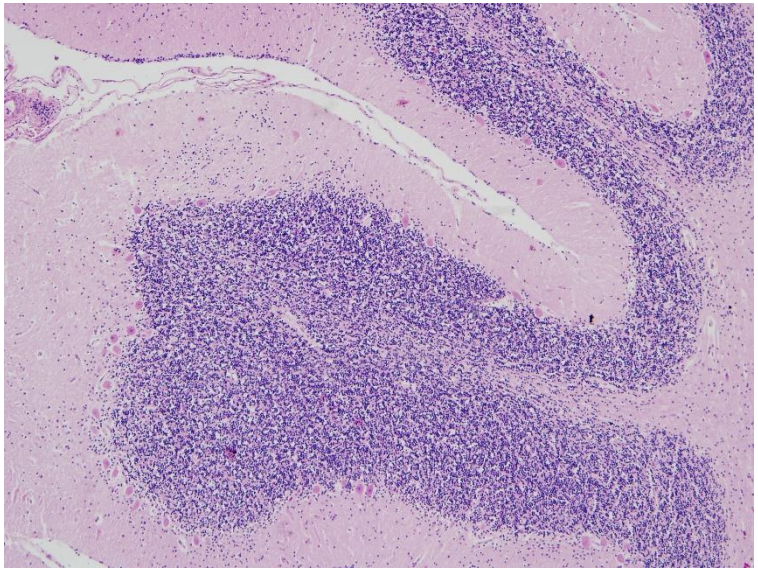
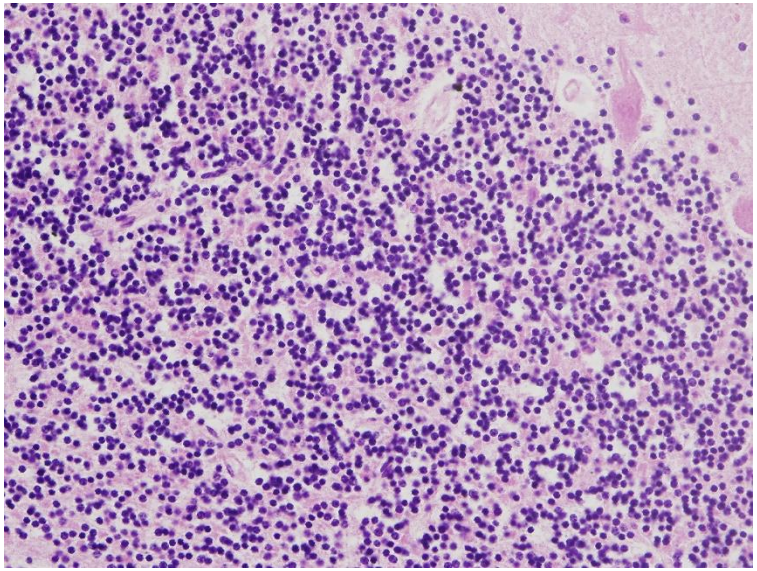
Retina



Nephrogenic tubules

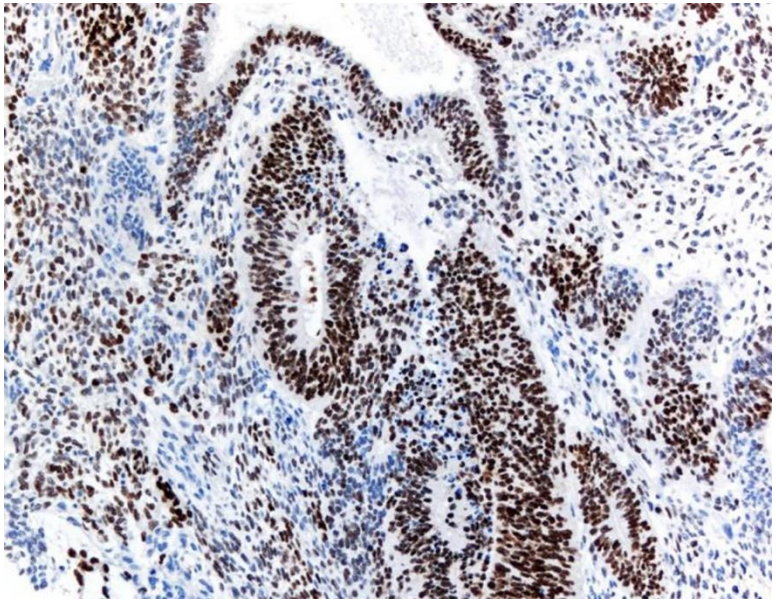



Immature brain

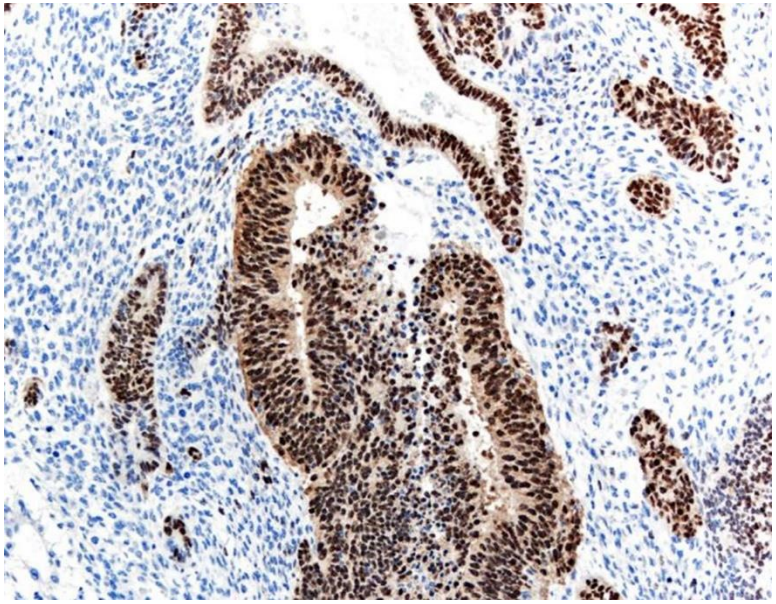



Cerebellum

Immature Cystic Teratoma
IHC to Assist with the Grading



SALL4 +

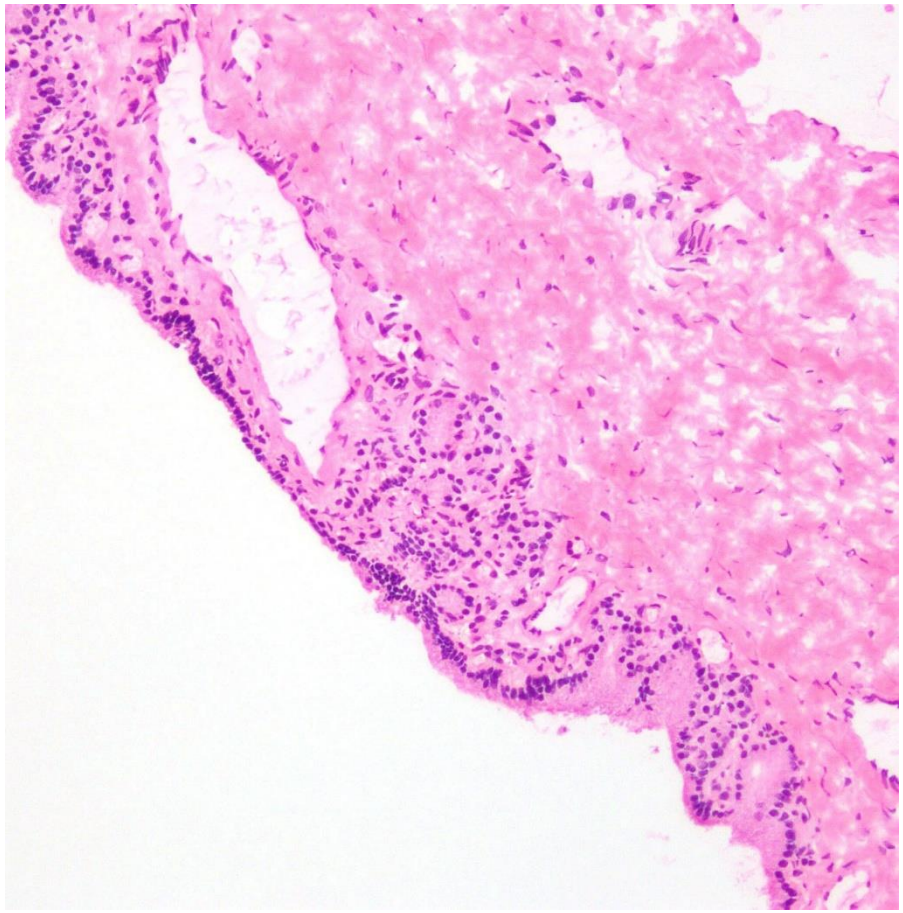


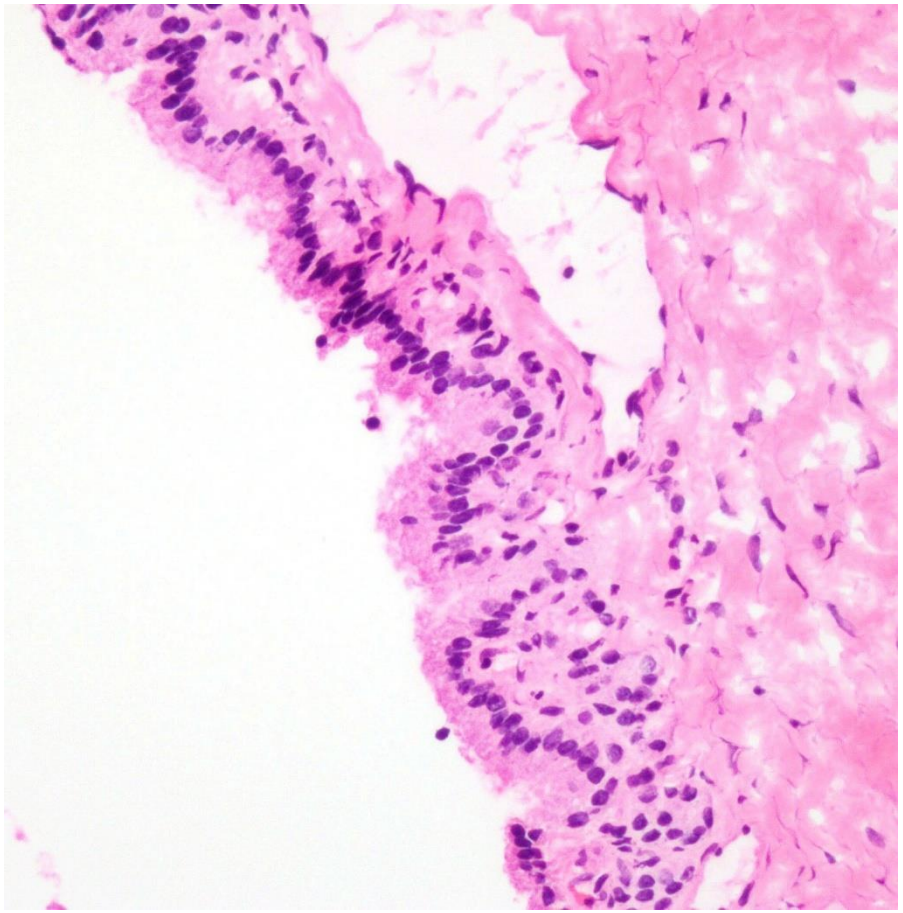
SOX2 +

Courtesy of Dr. Francisco Nogales

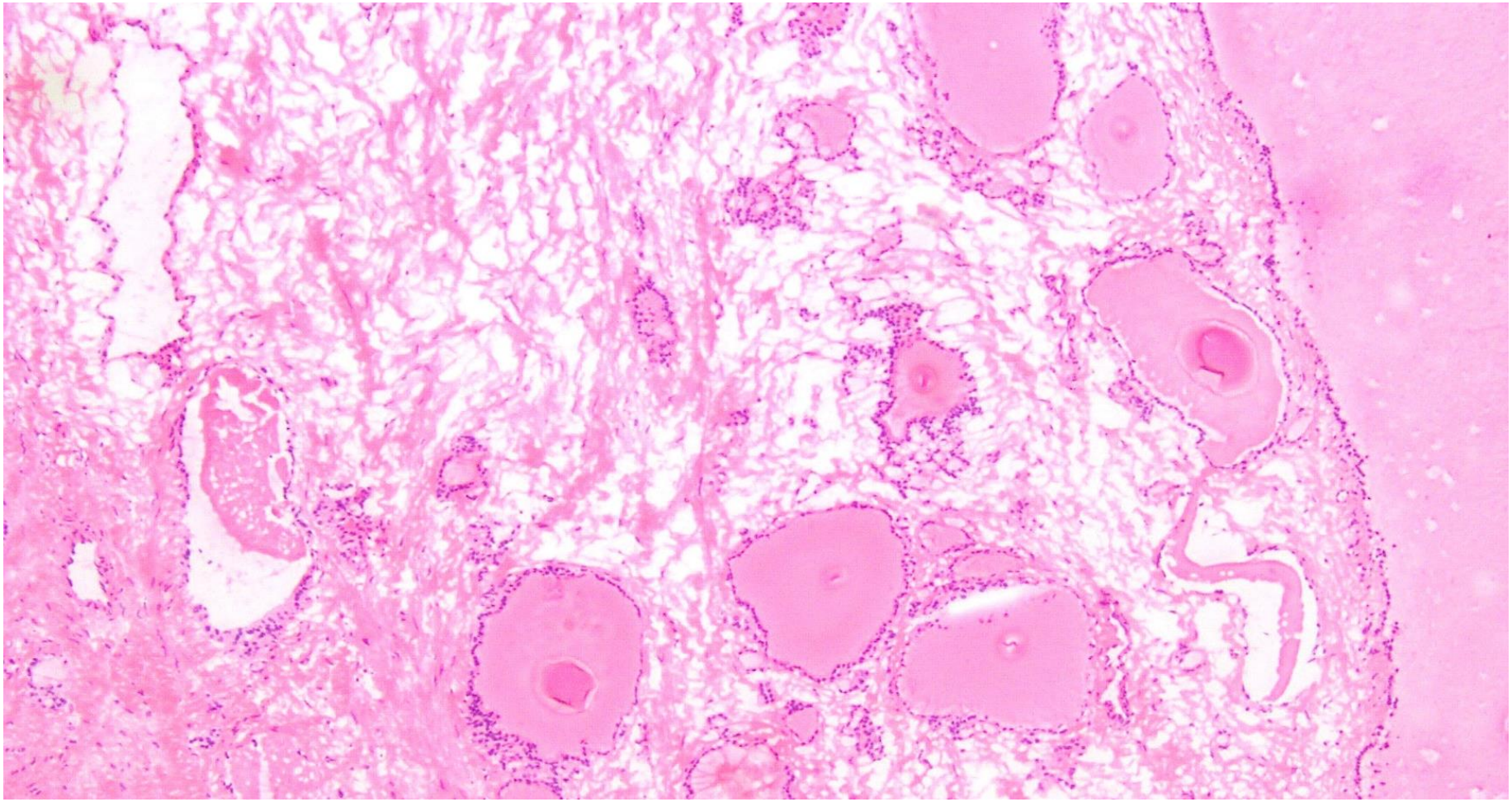
Cystic Struma Ovarii

- Uncommon neoplasm
- It can be under recognized in frozen section
- Patients' age, range 23-83 years (average 46 years)
- Tumors tend to be large
  - Average 13.5 cm (range, 2 to 19 cm)
- Usually, the cyst is multilocular
- The presence of thyroid follicles can be seen just focally

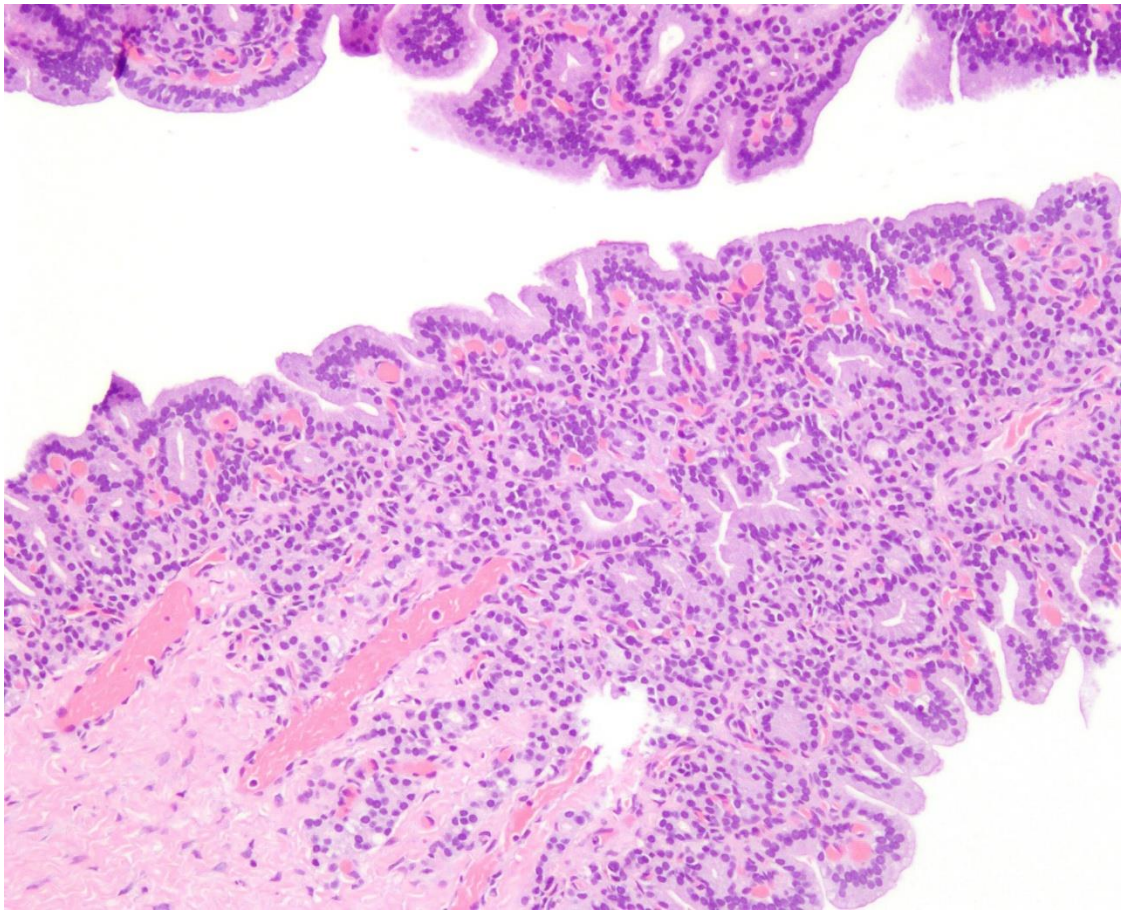


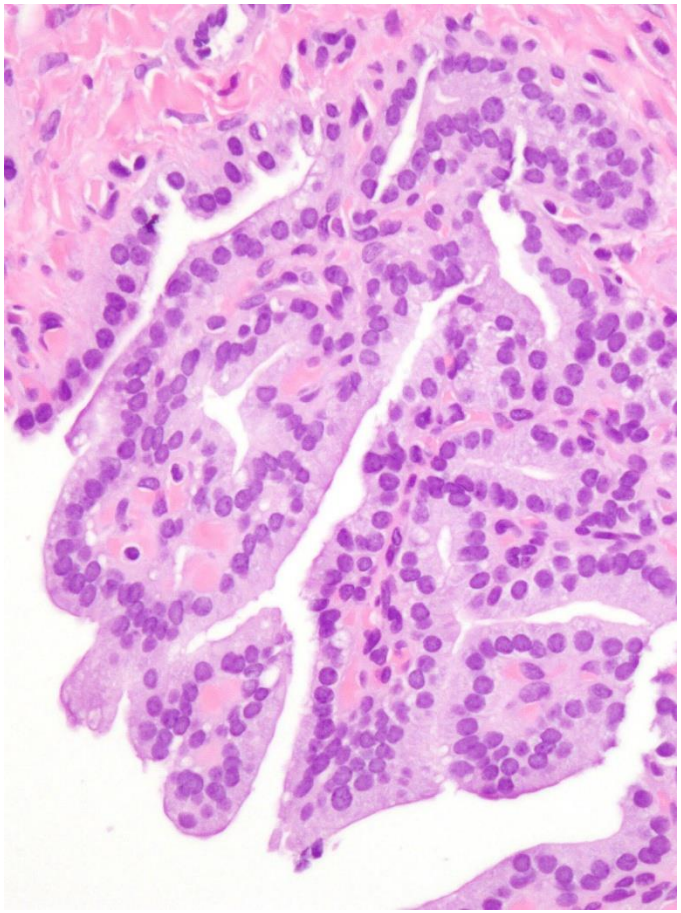


Frozen Section

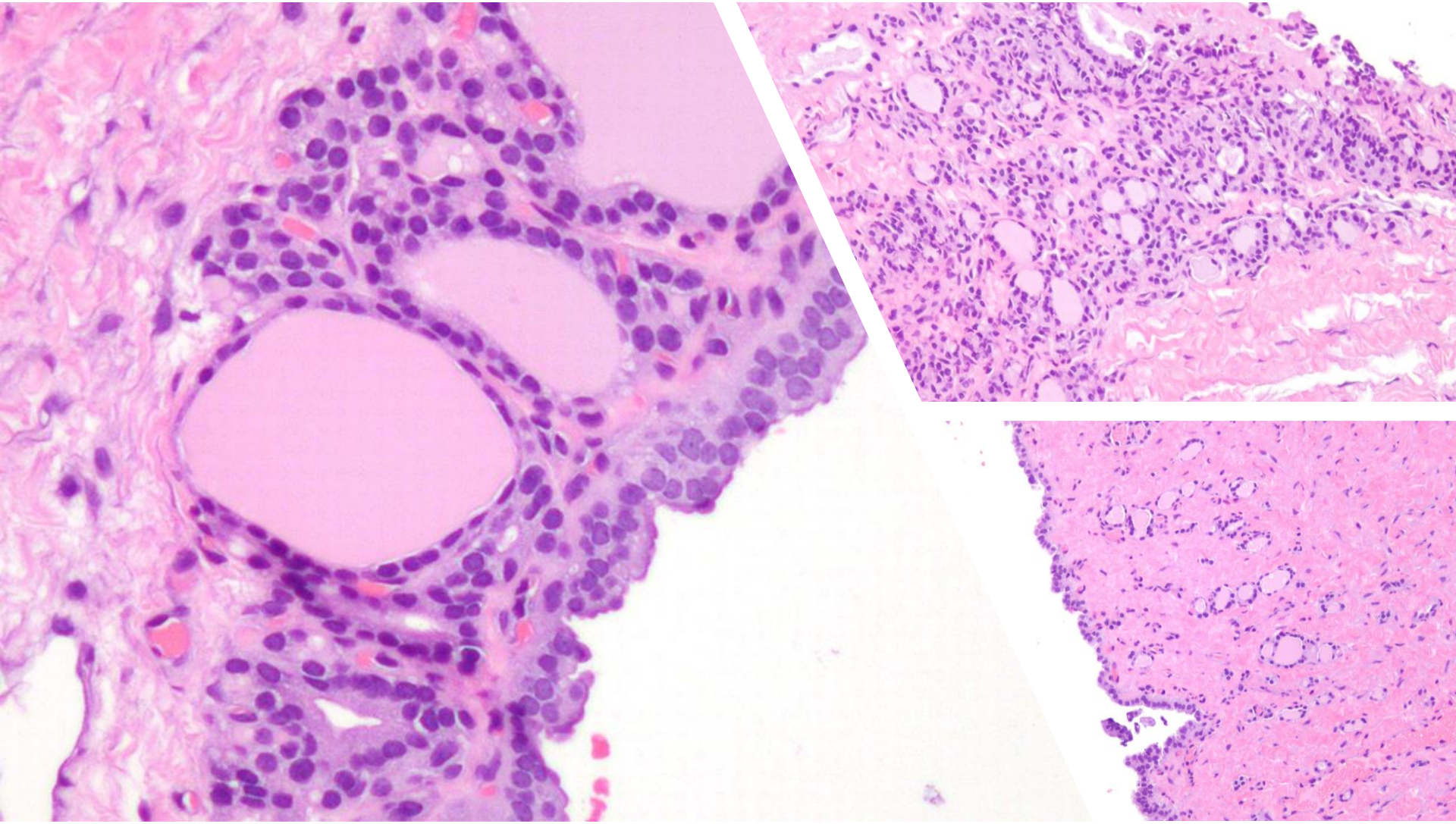


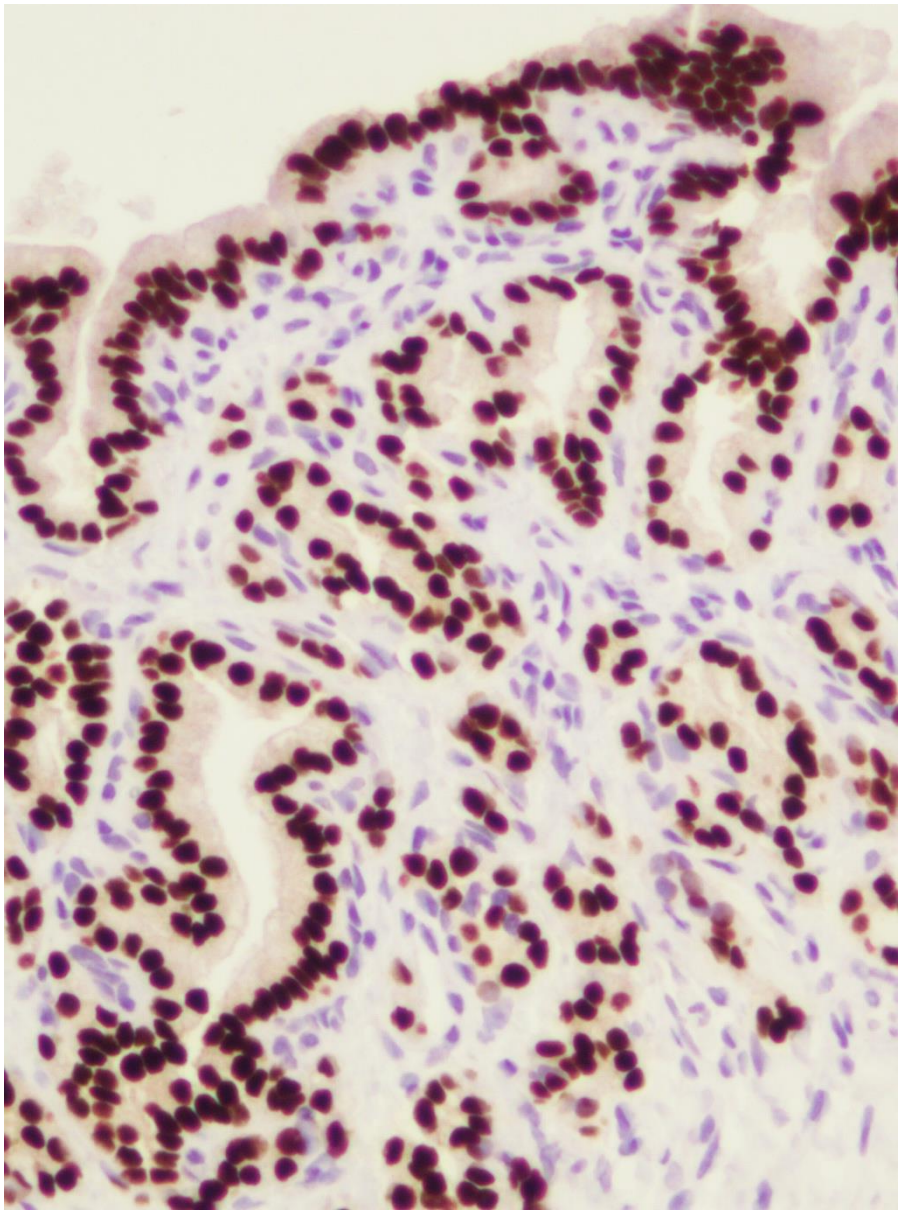
Frozen Section



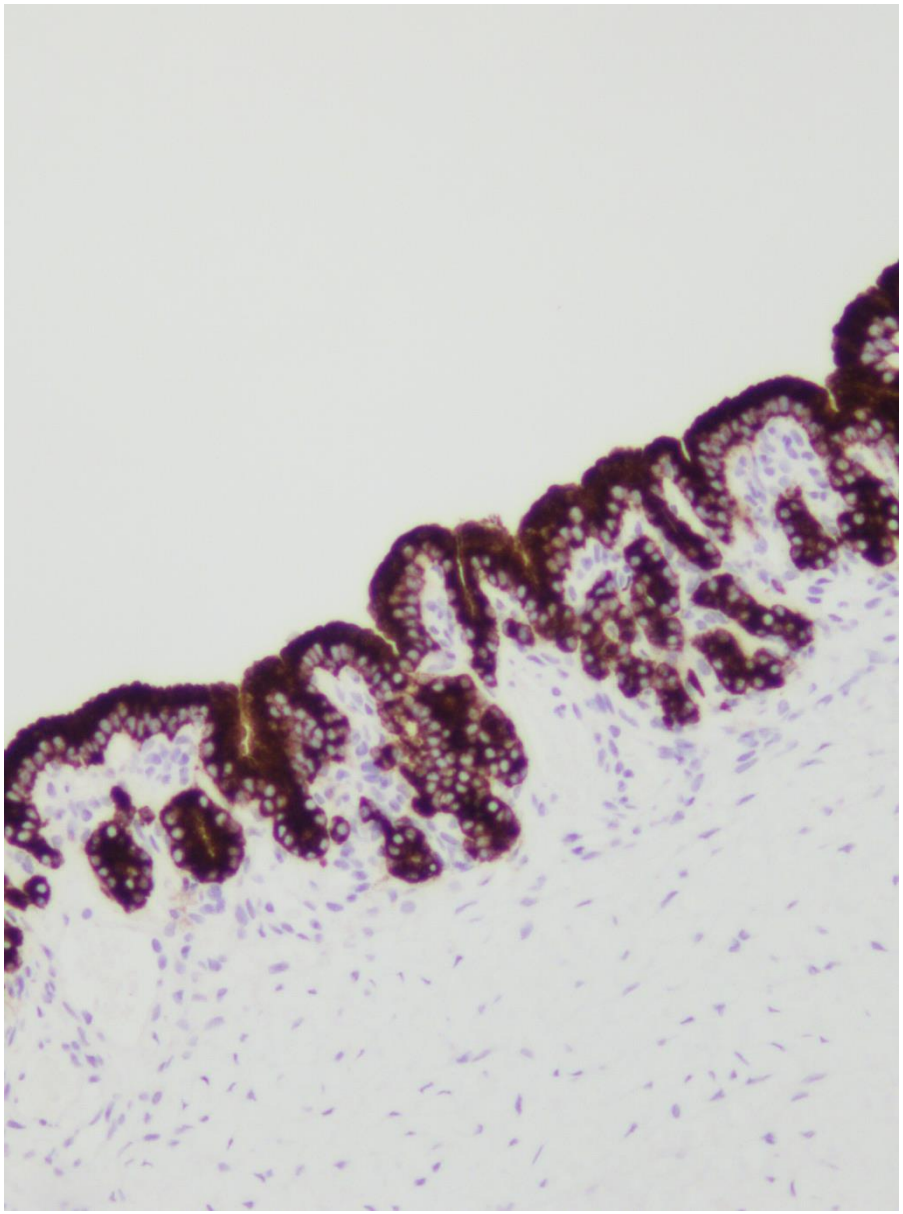


Permanent Sections



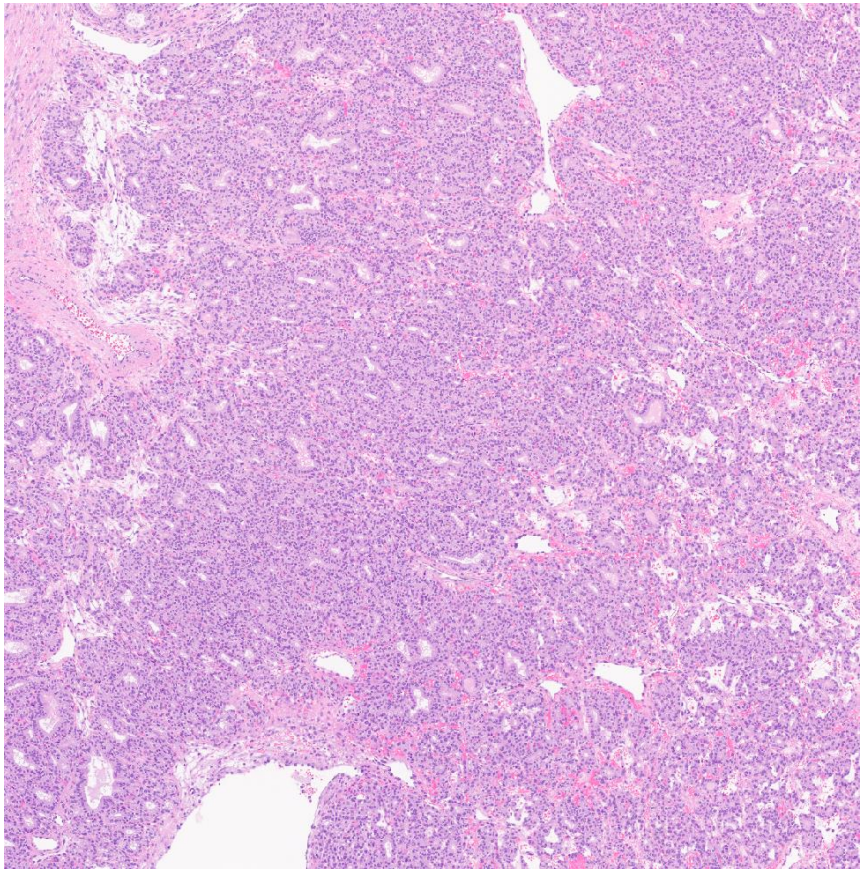


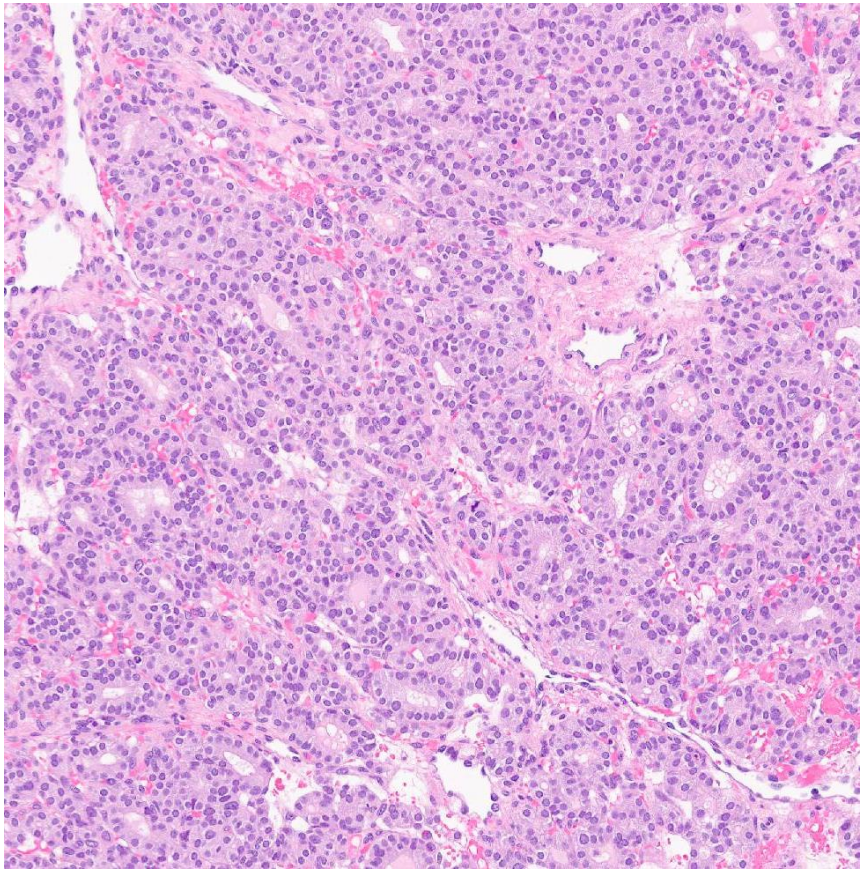
TTF-1 +



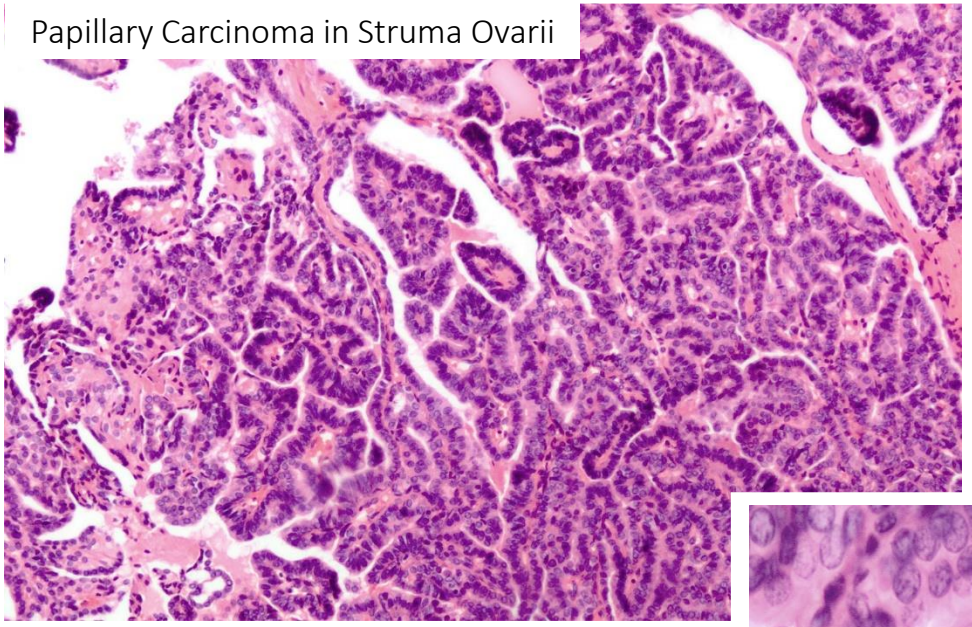
Thyroglobulin +

Adenomatous Hyperplasia in Struma Ovarii





Papillary Carcinoma in Struma Ovarii



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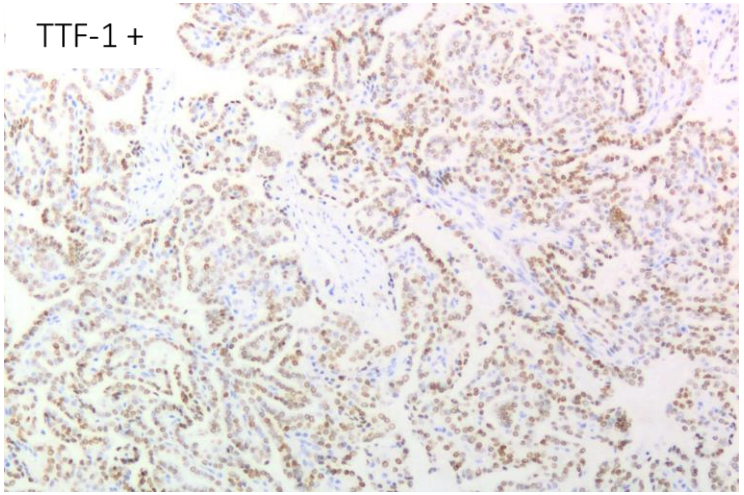
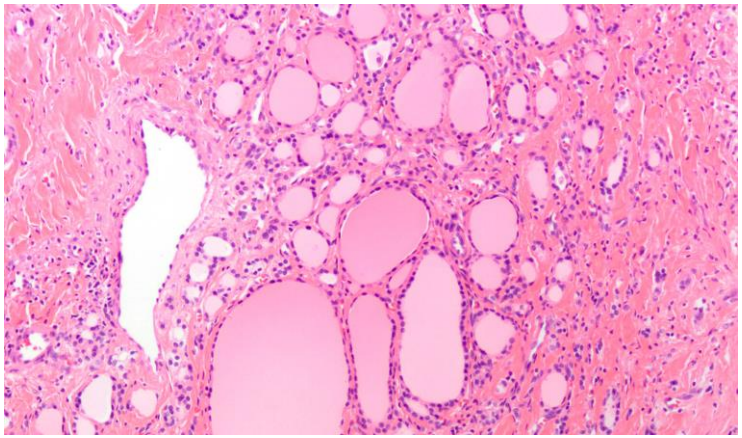
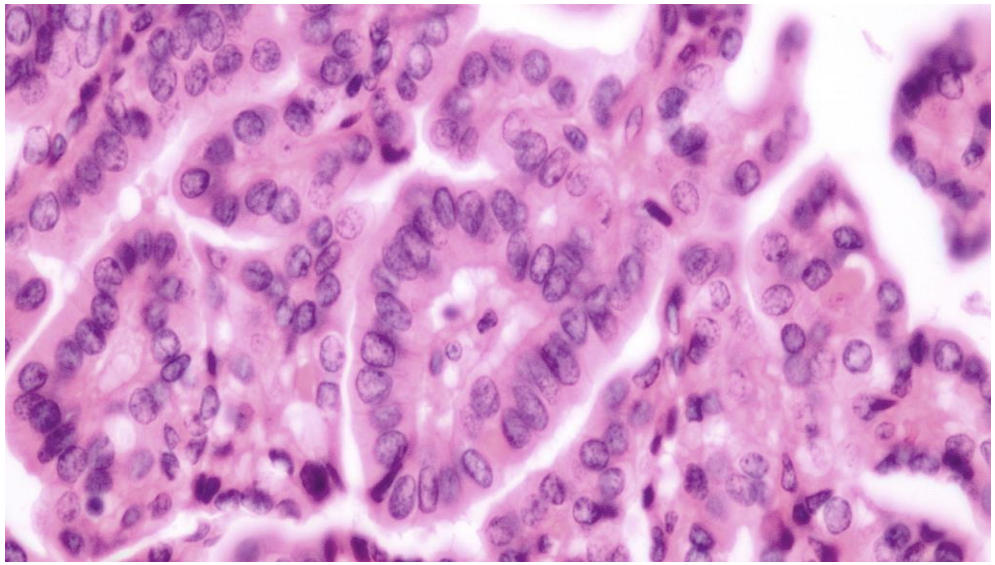
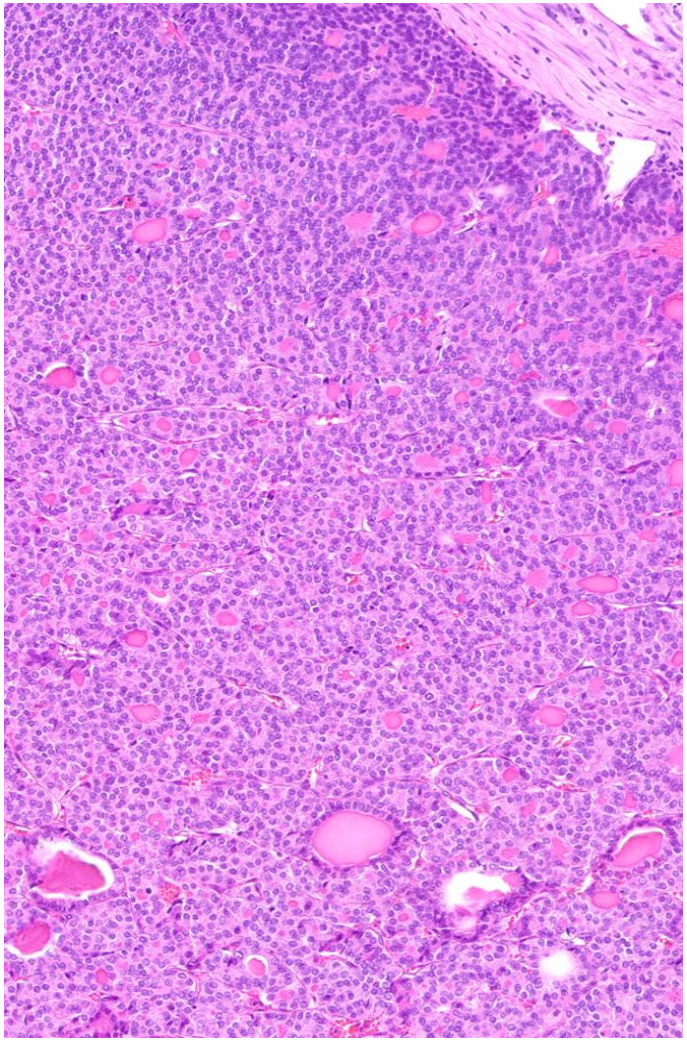
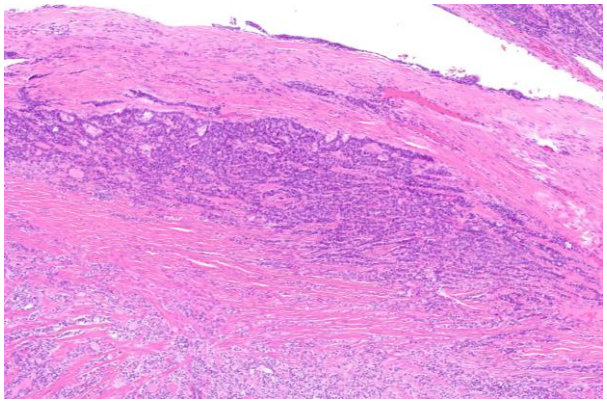


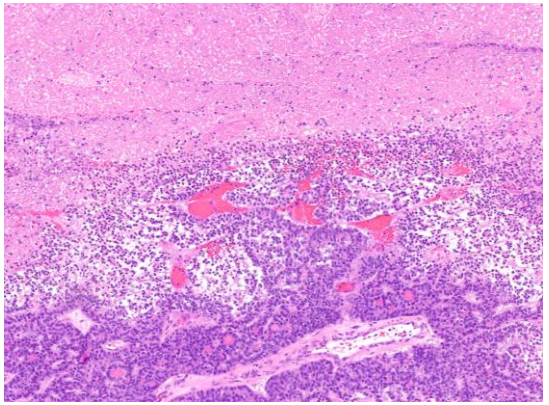


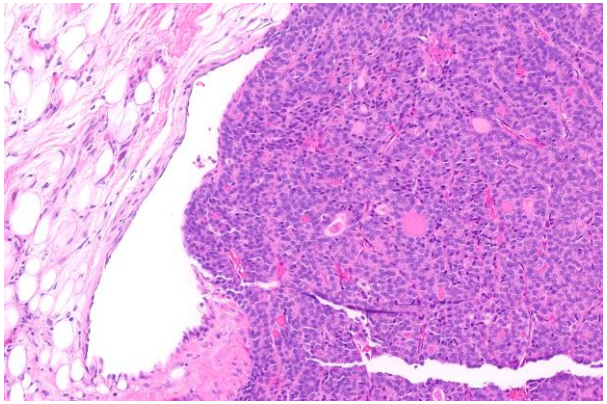


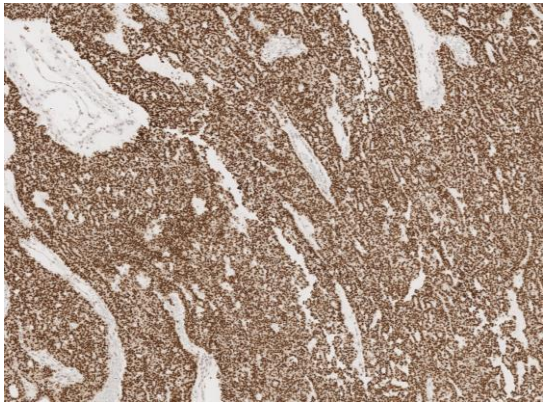
Follicular Carcinoma in Struma Ovarii











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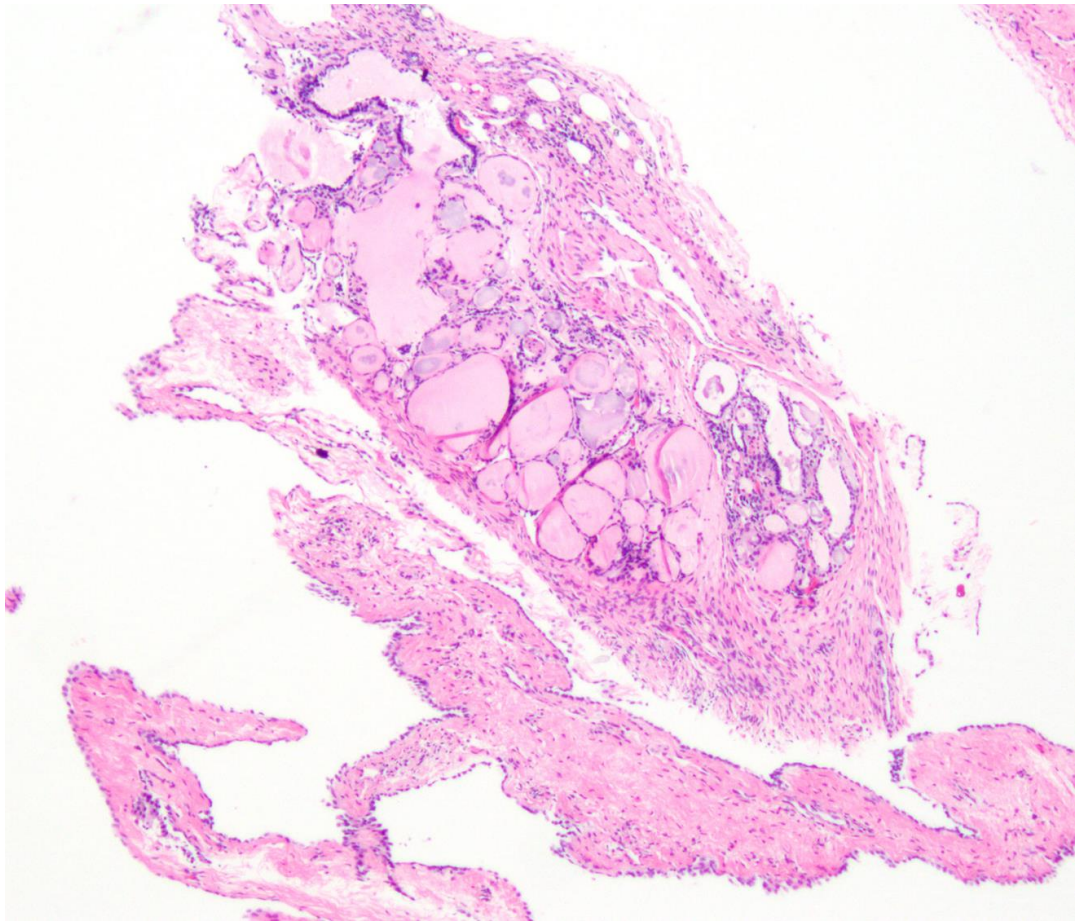
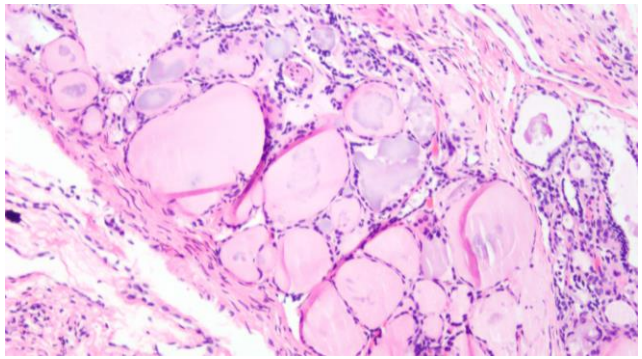
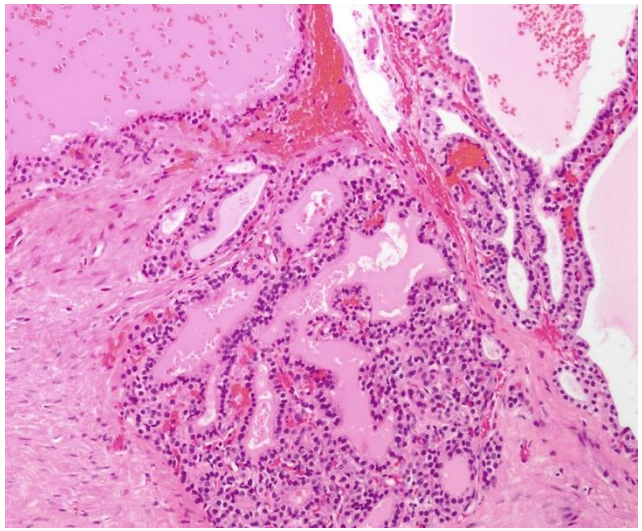
Highly Differentiated Follicular Carcinoma in Right Pelvic Wall Adhesion





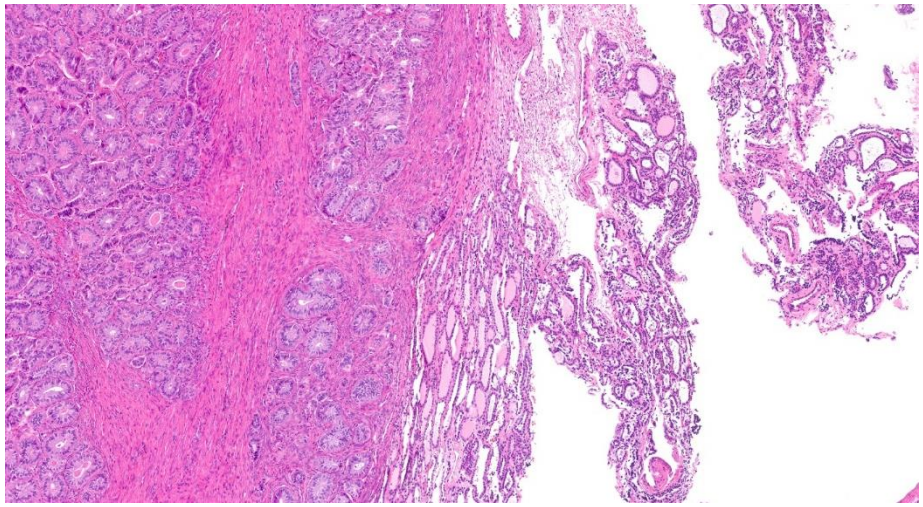


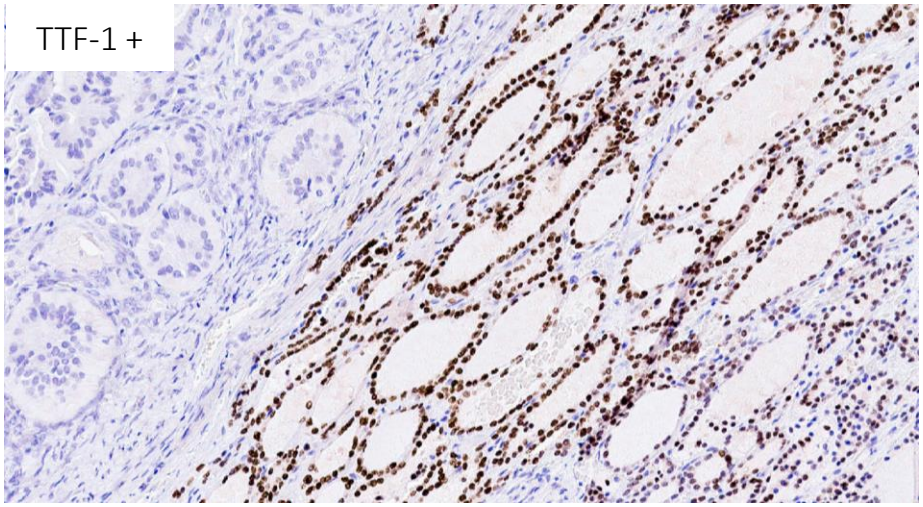
Left ovary, Struma Ovarii, 13 yrs prior

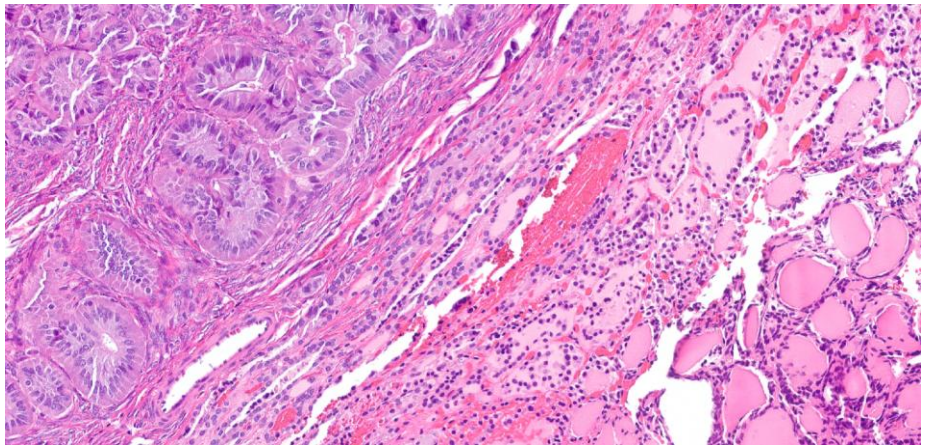
Clinical Behavior

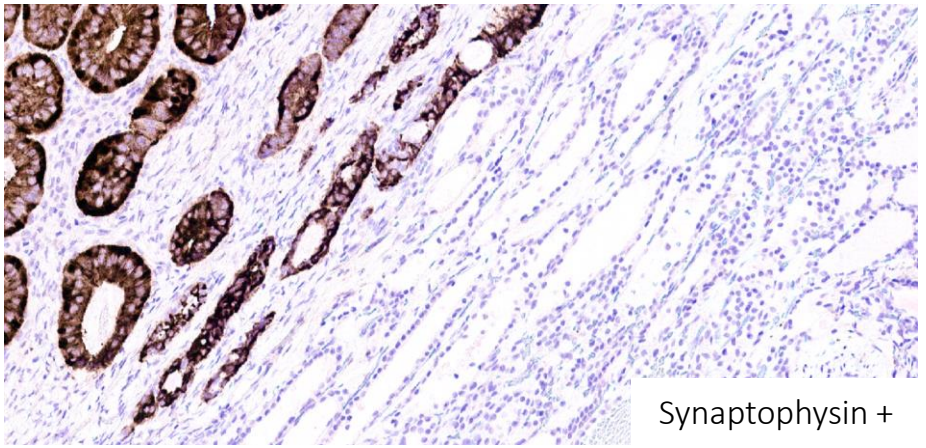
Ca in struma ovarii

- Seen in 5-10% of the cases
- Usually confined to the ovary at presentation
- Papillary > Follicular >>> Poorly differentiated or anaplastic
- Overall survival
  - 5-yr, 91-96%
  - 10-yr, 88-94%
  - 20-yr, 85-88%
- Highly differentiated follicular carcinoma arising from struma ovarii (formerly known as peritoneal strumosis)
  - Bland thyroid tissue in the pelvis or distant mt (liver, bone, lung or heart)
  - Low grade



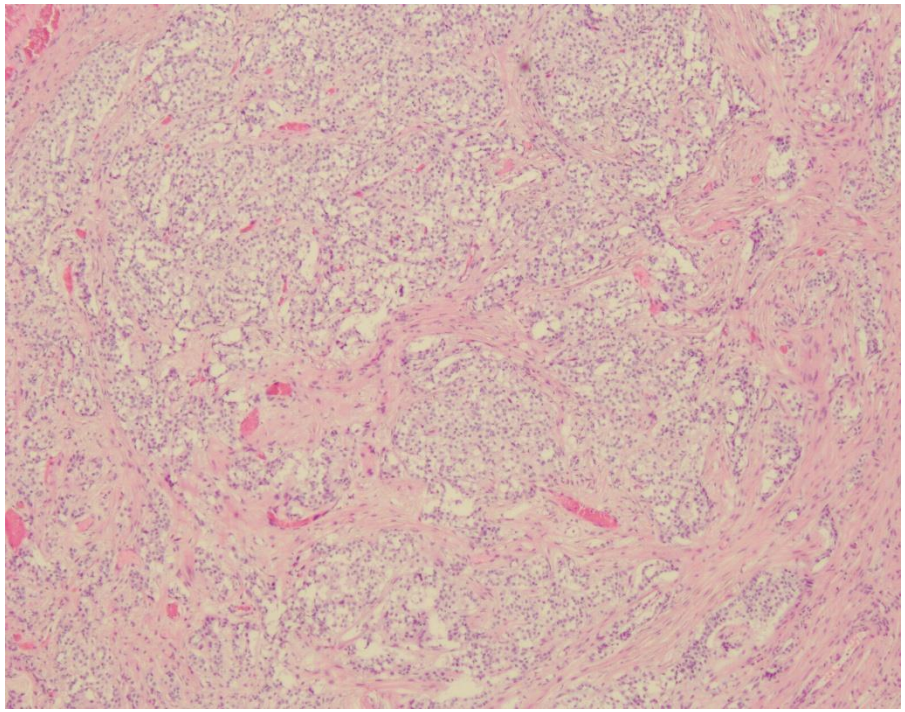


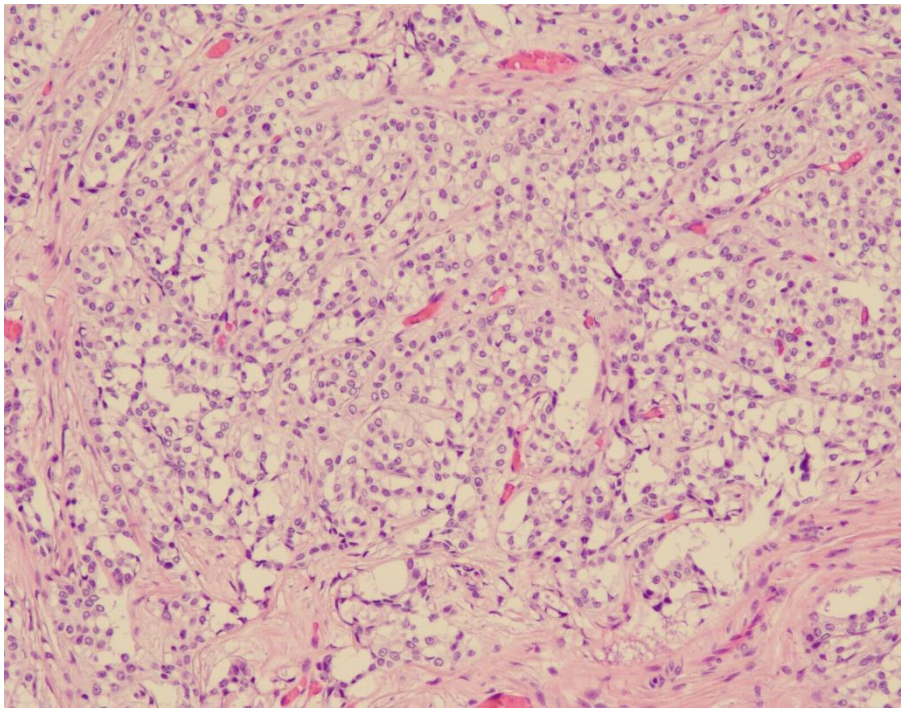


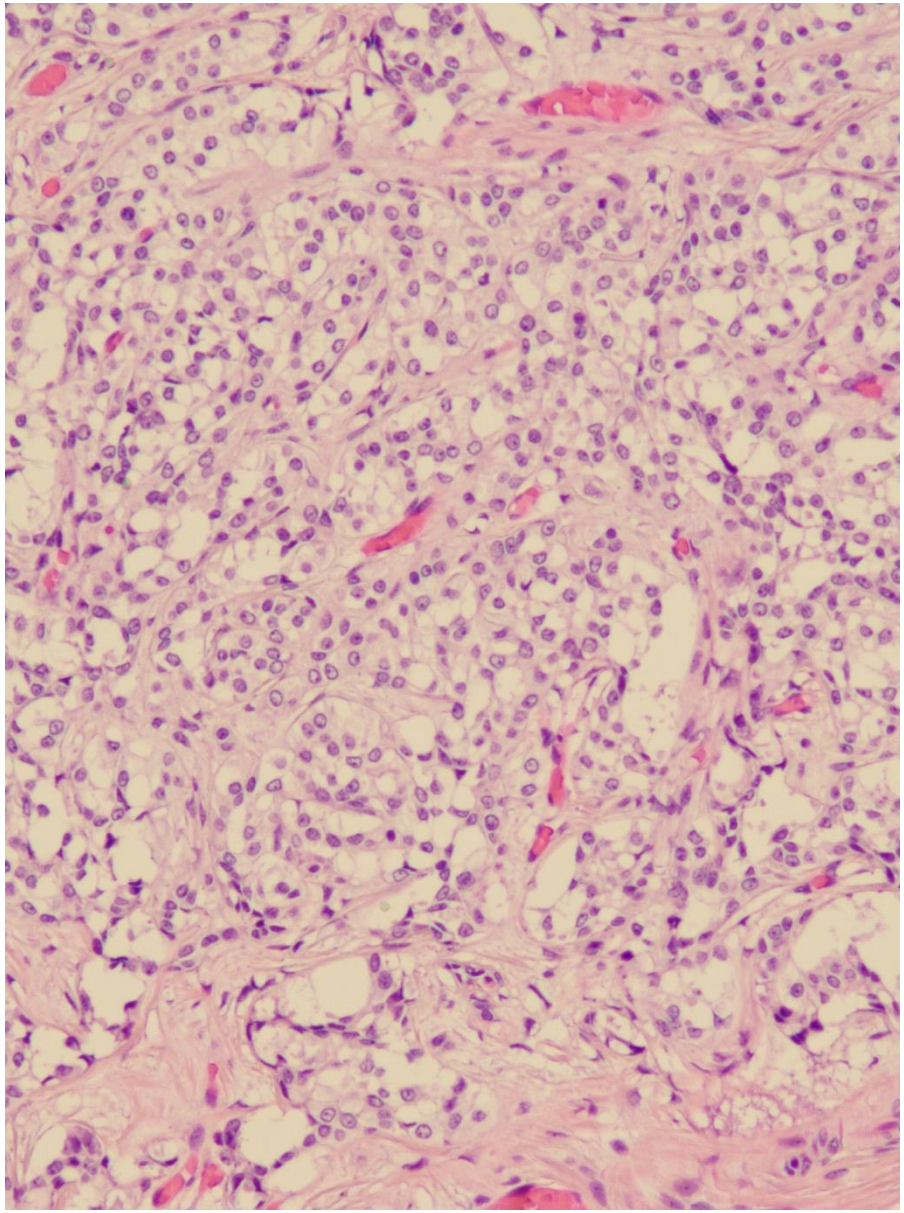


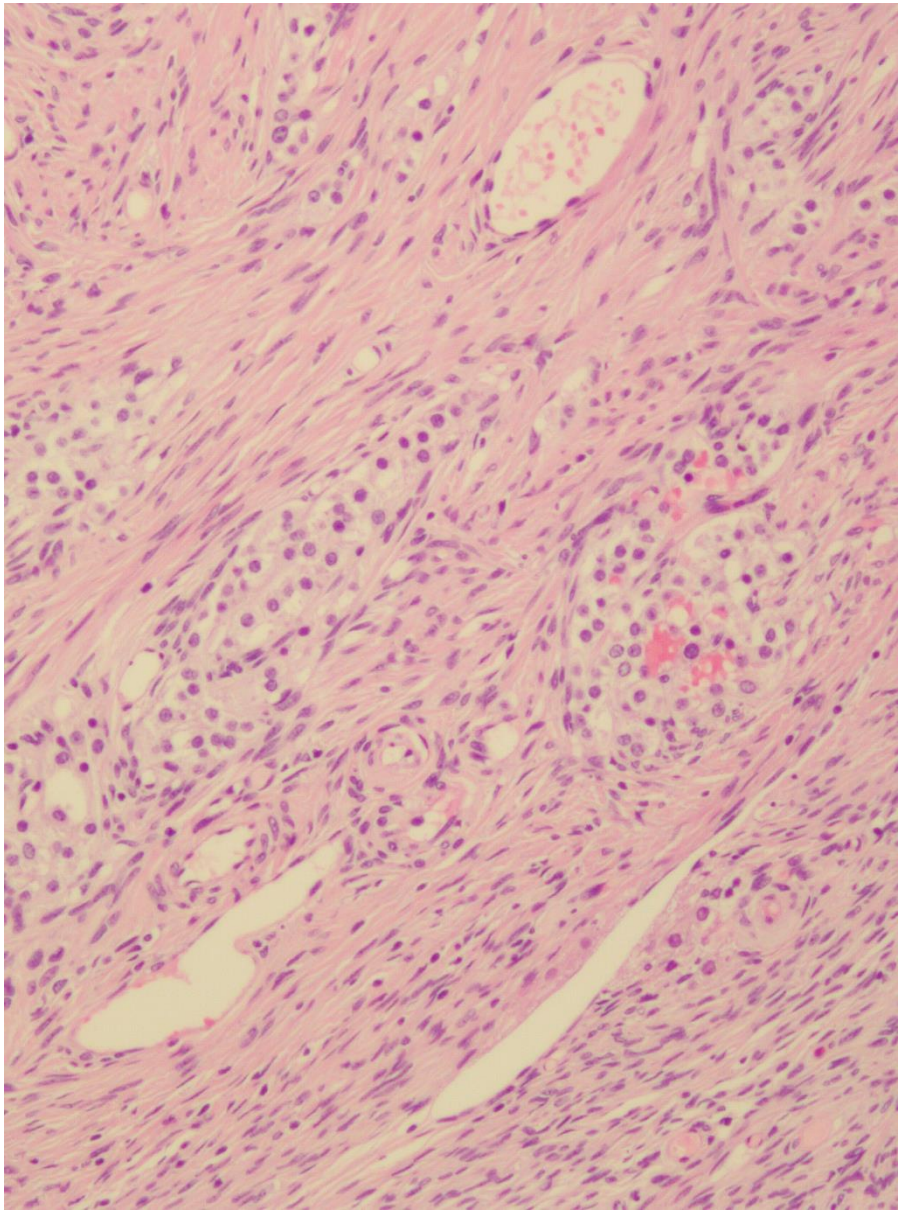
Struma Carcinoid

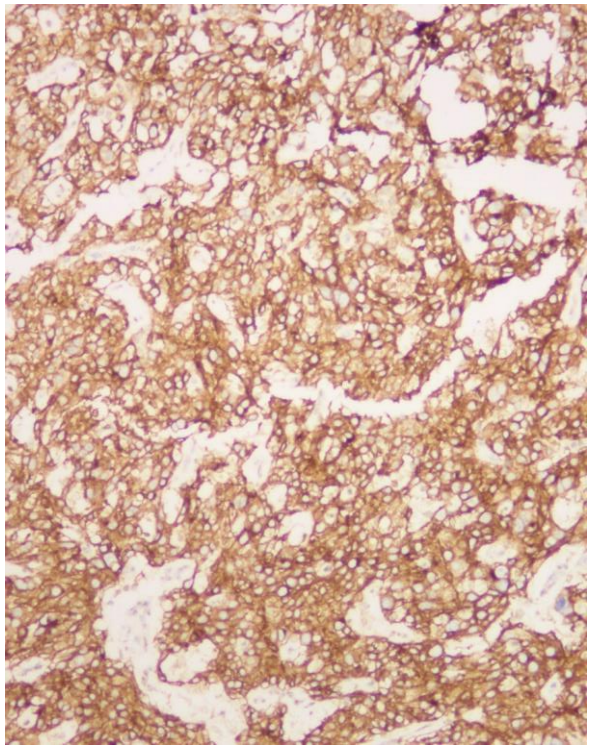
Microcystic Stromal Tumor



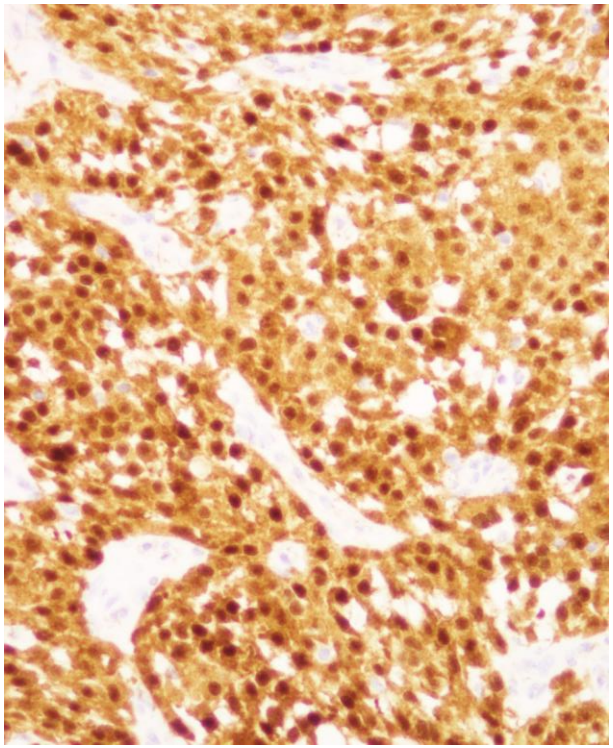




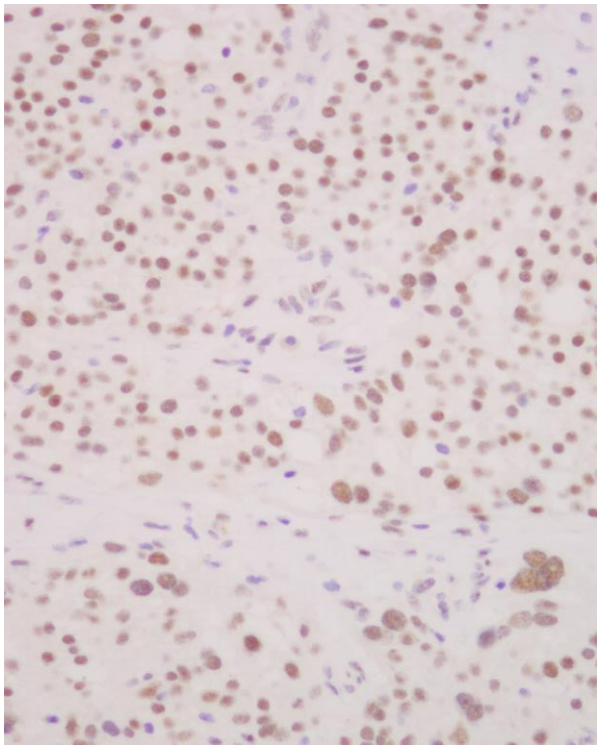




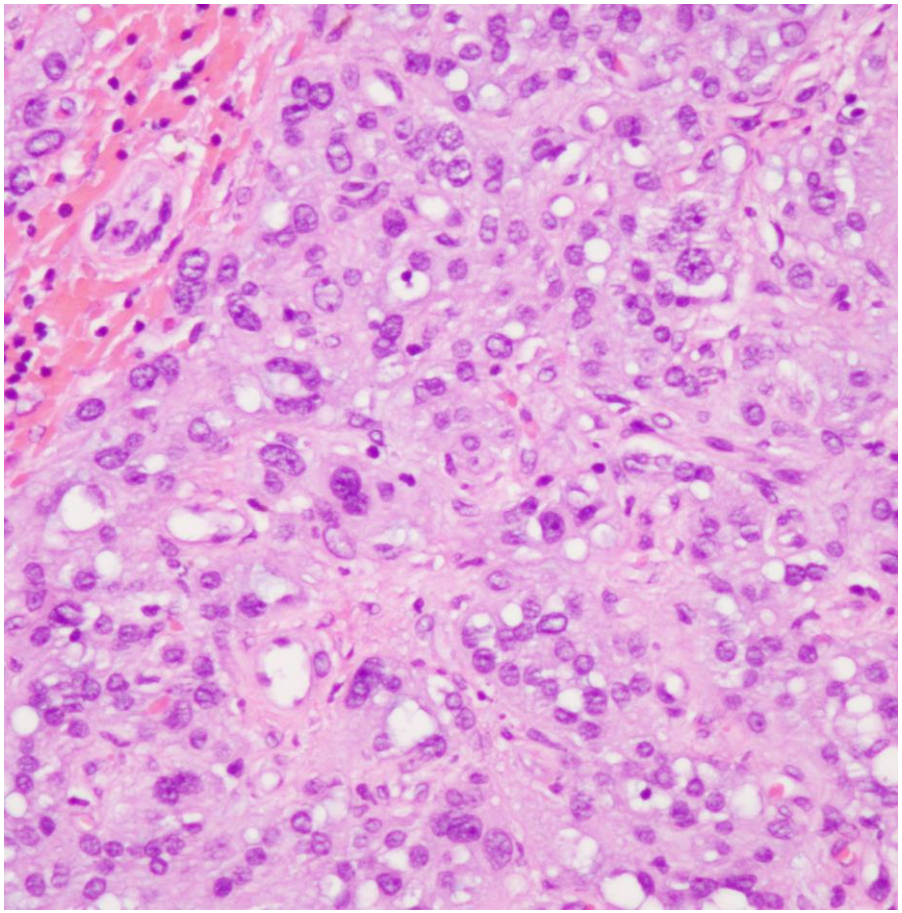
CD10 +

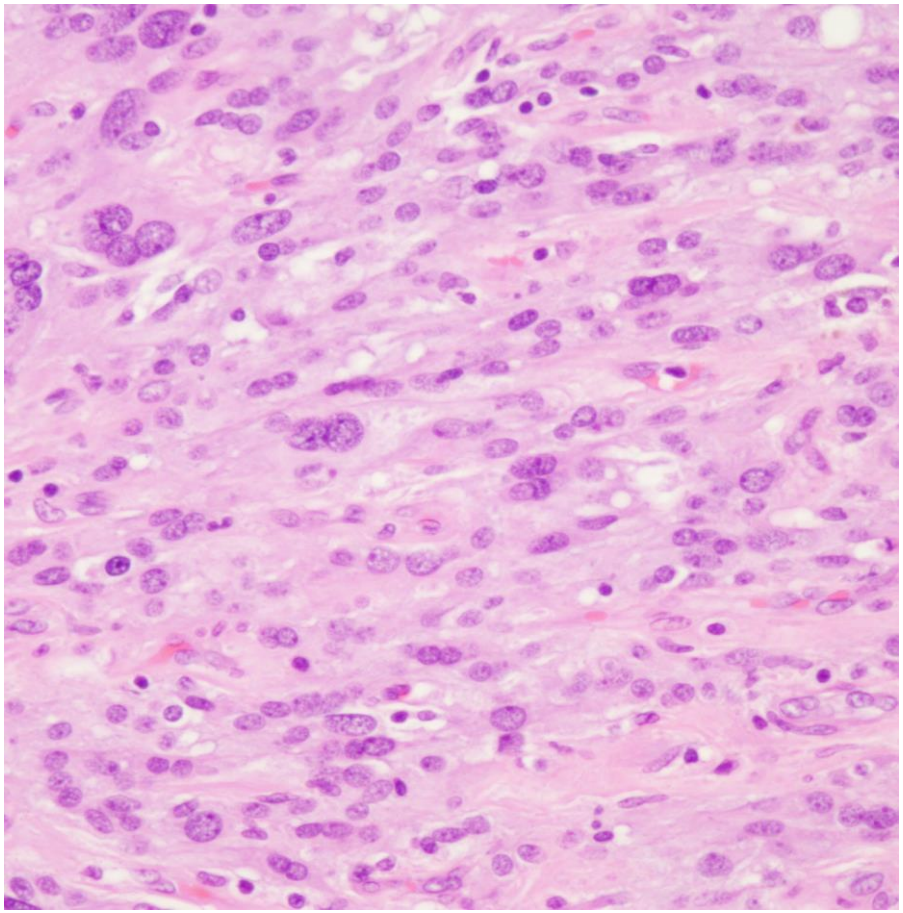


B-catenin +

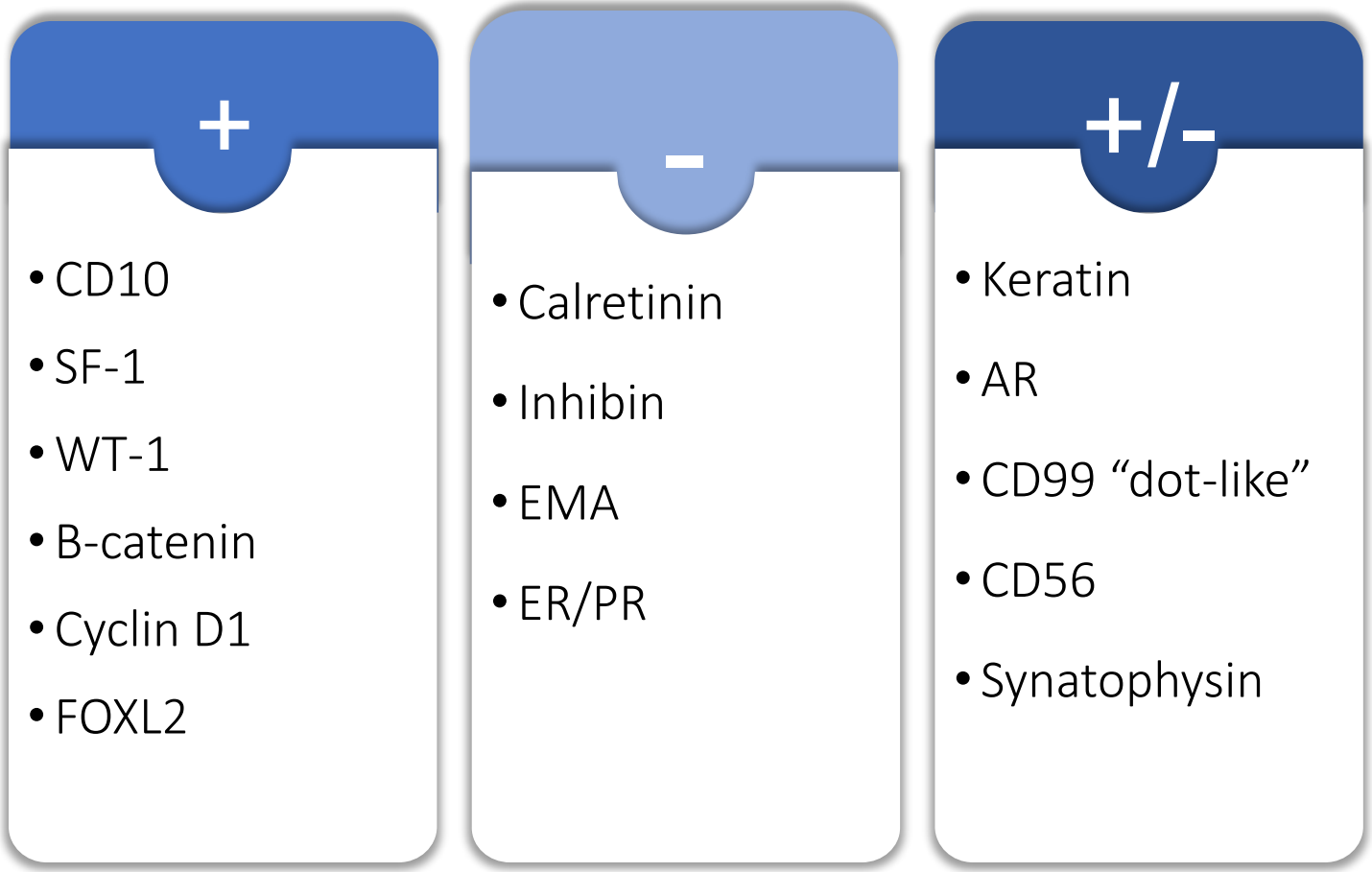


SF-1 +





Microcystic Stromal Tumor, IHC

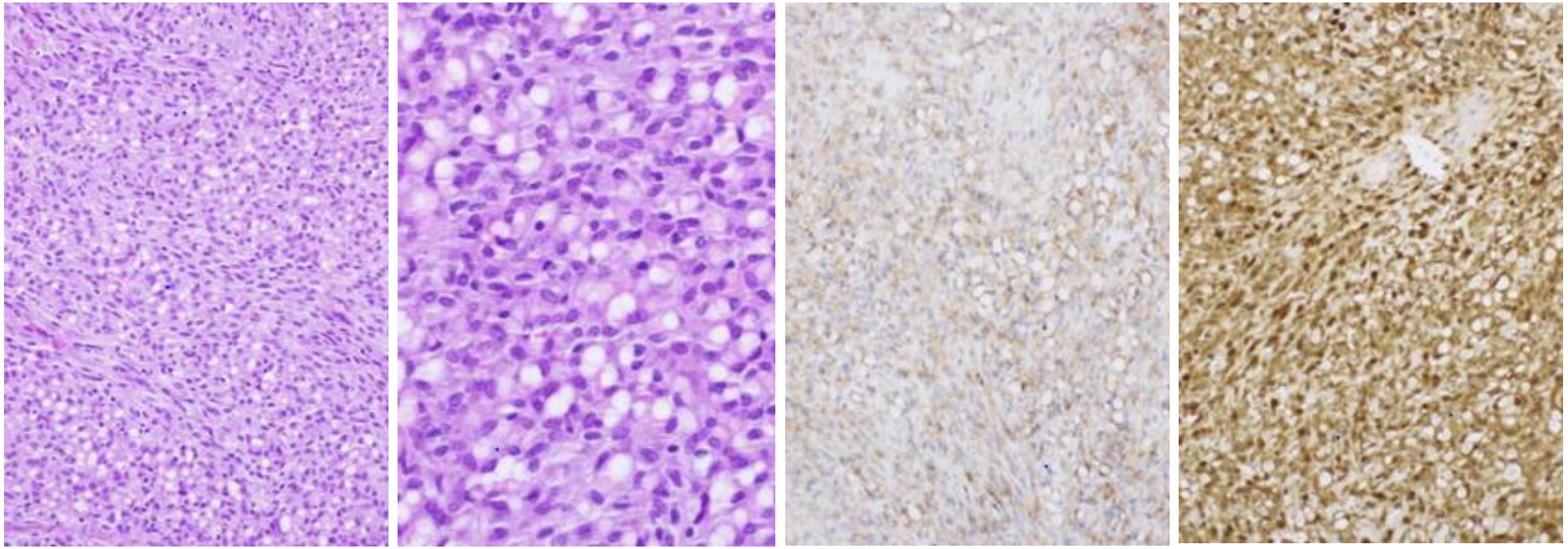


Differential Diagnosis

- Sex-cord stromal tumors
  - Thecoma
  - Steroid cell tumor
  - Sclerosing stromal tumor
  - Juvenile granulosa cell tumor
  - Adult granulosa cell tumor luteinized

Inhibin and/or calretinin +

Differential Diagnosis: Signet Ring Stromal Tumor



B-catenin, -

Calretin, +

Tchrakian N, et al, 2022

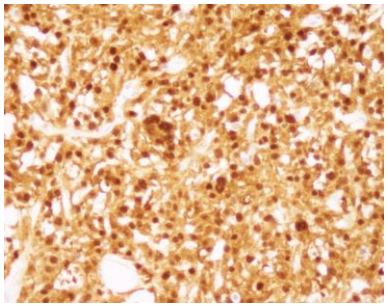
Microcystic Stromal Tumor

Mutually exclusive mutations

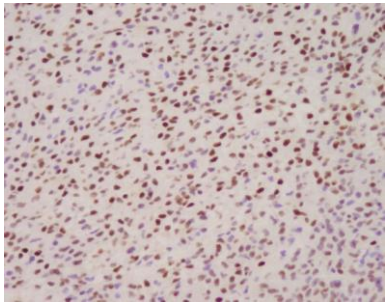
CTNNB1 mutation

APC mutation

Almost all cases



B-catenin +



Cyclin-D1 +

Part of the FAP (familial adenomatous polyposis) phenotype, potential sentinel neoplasm for the dx of FAP

Microcystic Stromal Tumor

- Behavior
  - Most cases, benign
    - Limited experience
  - One case presented with a minute focus (2 mm) of metastatic focus in the omentum
  - Two cases with recurrences
    - Both initially treated with cystectomies
      - Recurrences in 4 yrs and 9 yrs, respectively
      - Both with recurrences in the ovary, omentum, and pelvis

Adult Type, Granulosa Cell Tumor

When does it trigger questions ?

- Incidental finding
- Frozen Section
- Unilocular cyst
- Prominent fibromatous background
- Solid/diffuse pattern
- Papillary areas
- Prominent luteinization
- Bizarre cells

Adult Type, Granulosa Cell Tumor

When does it trigger questions ?

Tubules

High mitotic index

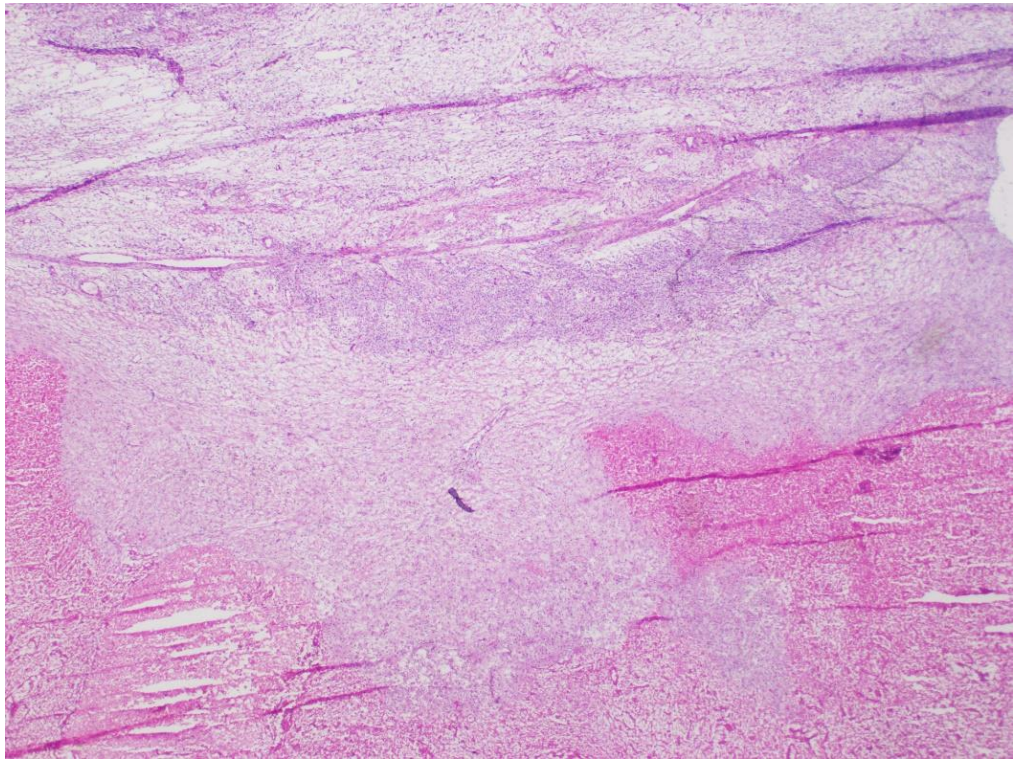
Mixed with juvenile granulosa cell tumor

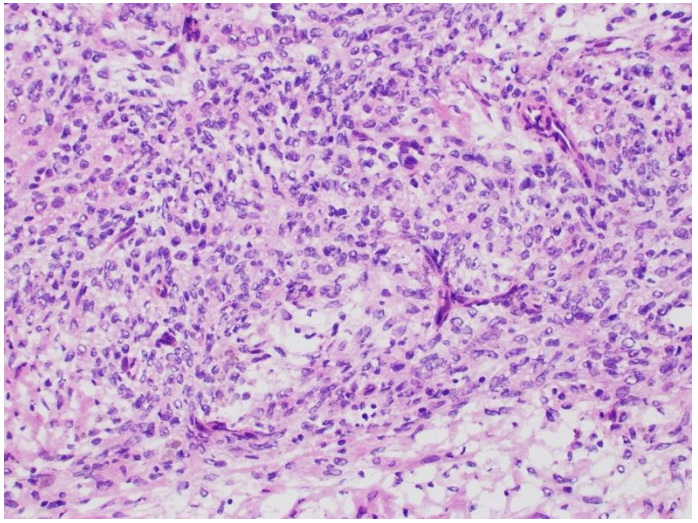
IHC problems

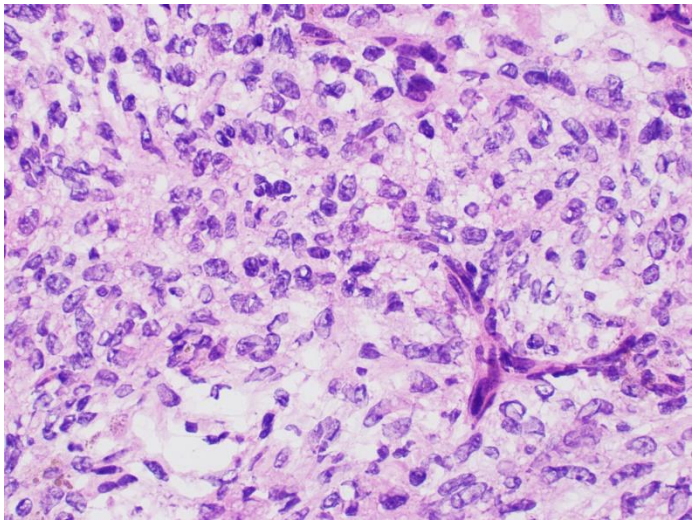
Not to overcall extraovarian small deposits of granulosa cells

Adult Type, Granulosa Cell Tumor

- Tumor incidentally found in a 4 cm ovary
- 49 yo pt underwent TAHBSO for atypical endometrial hyperplasia

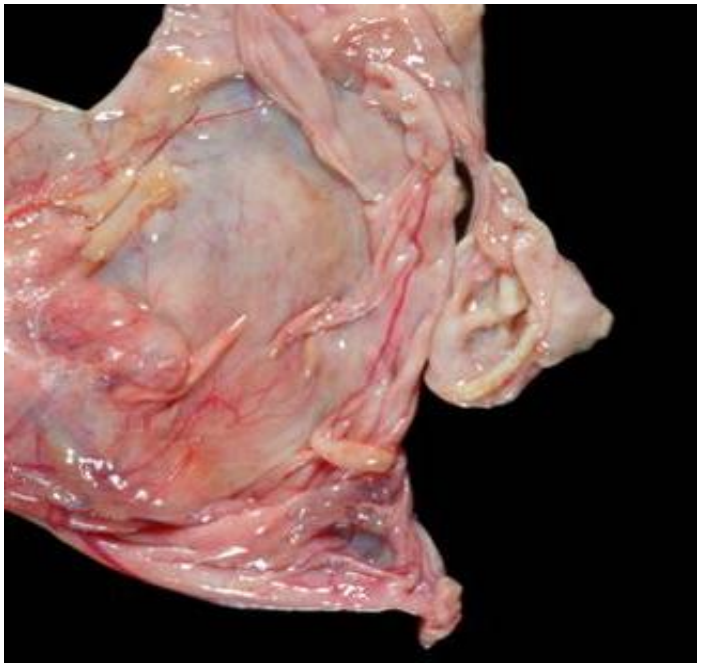


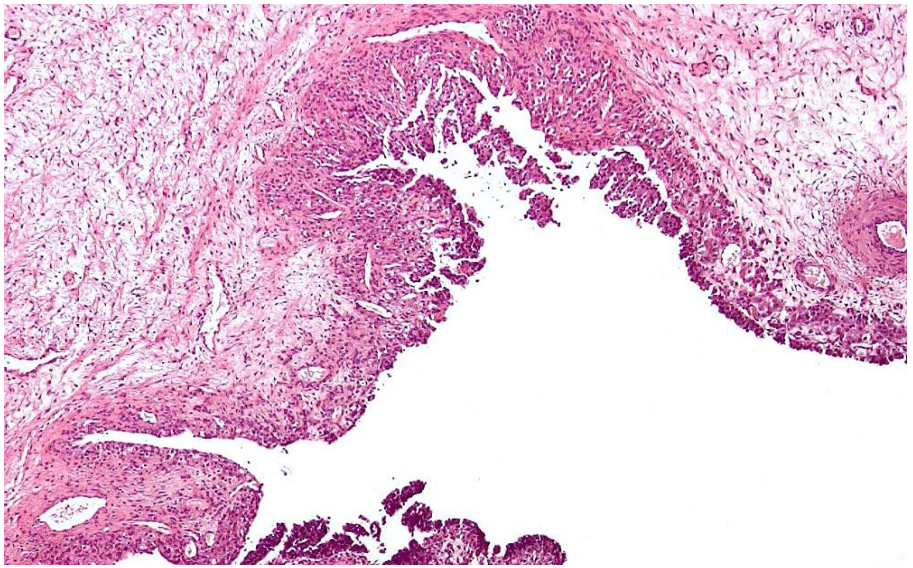


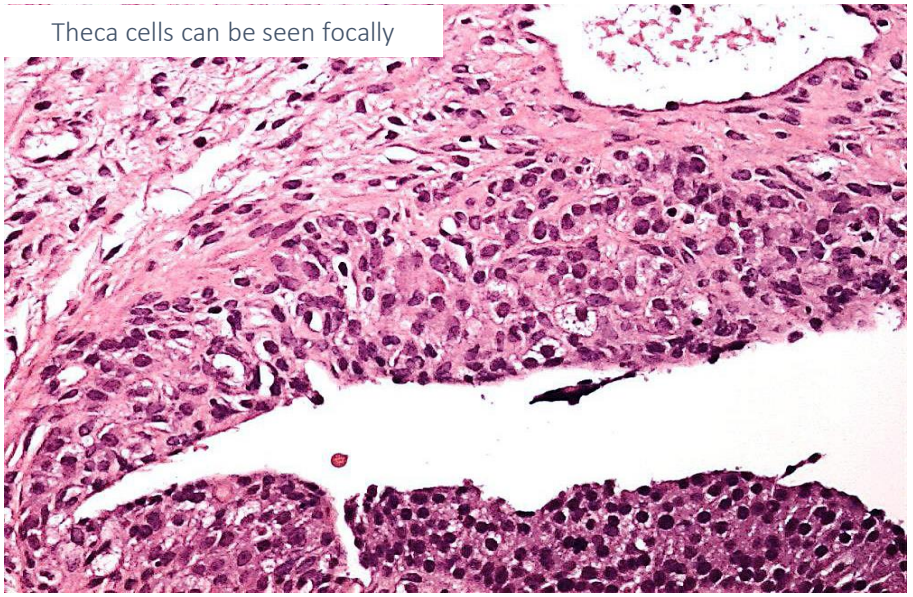


Adult Type, Granulosa Cell Tumor, Frozen Section rim of tumor can be overlooked because of the hemorrhage

Adult Granulosa Cell Tumor, Unilocular Cyst



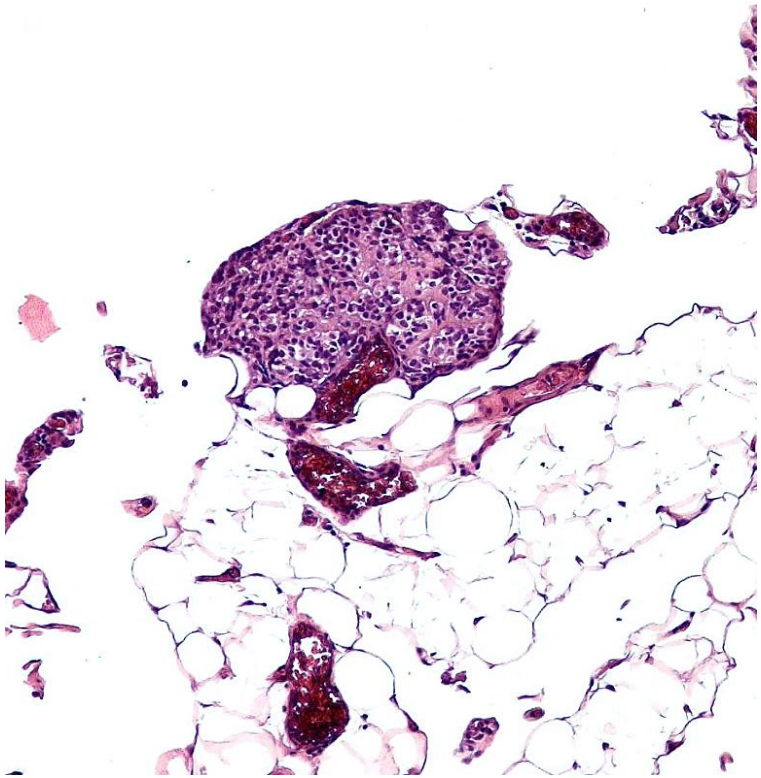


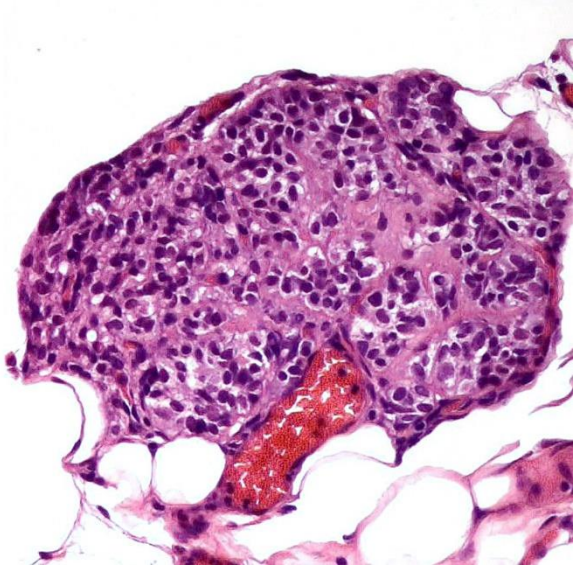


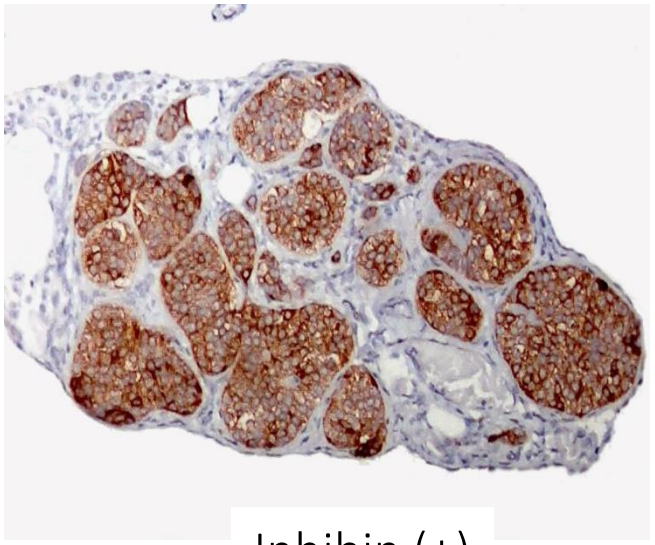
Theca cells can be seen focally

Initial Frozen Section Impression: Large Follicular Cyst vs. Unilocular, Cystic, Adult Type, Granulosa Cell Tumor

→ Staging

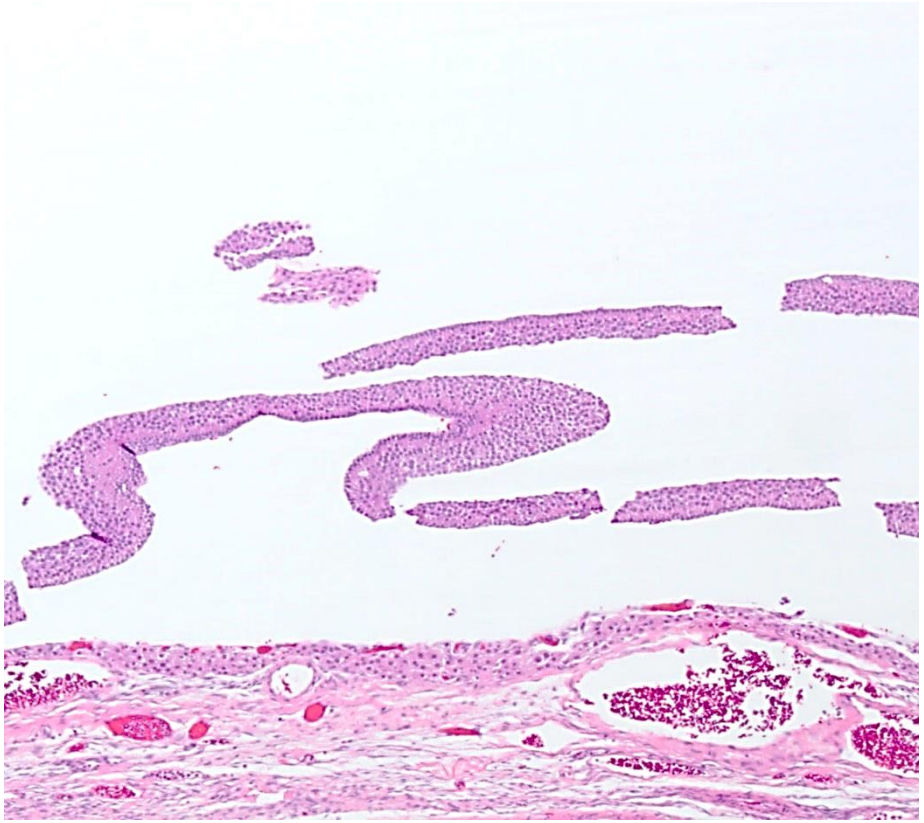


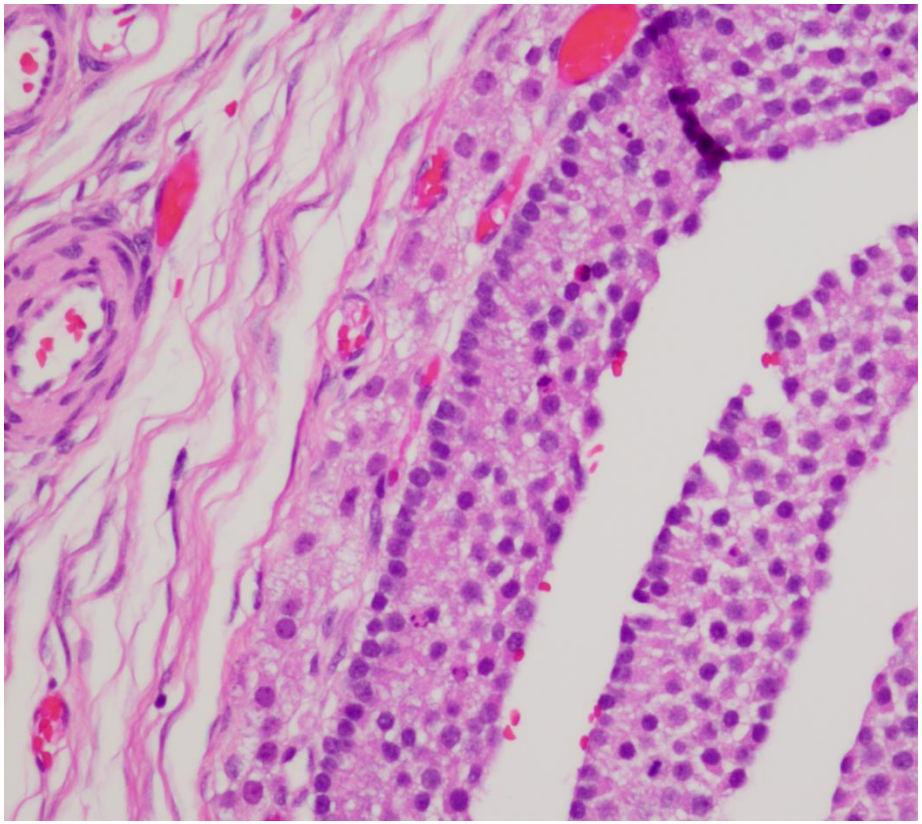




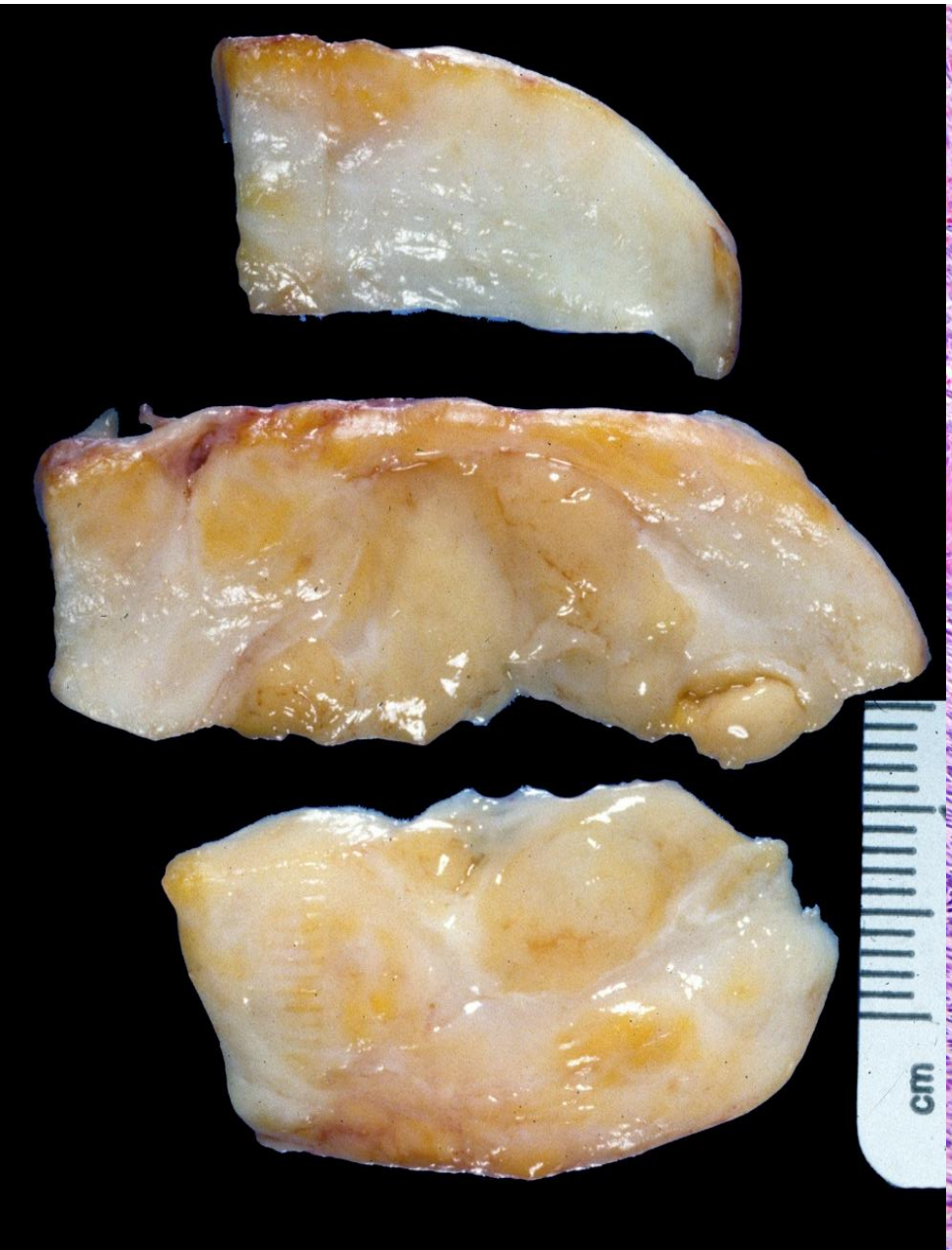
Inhibin (+)

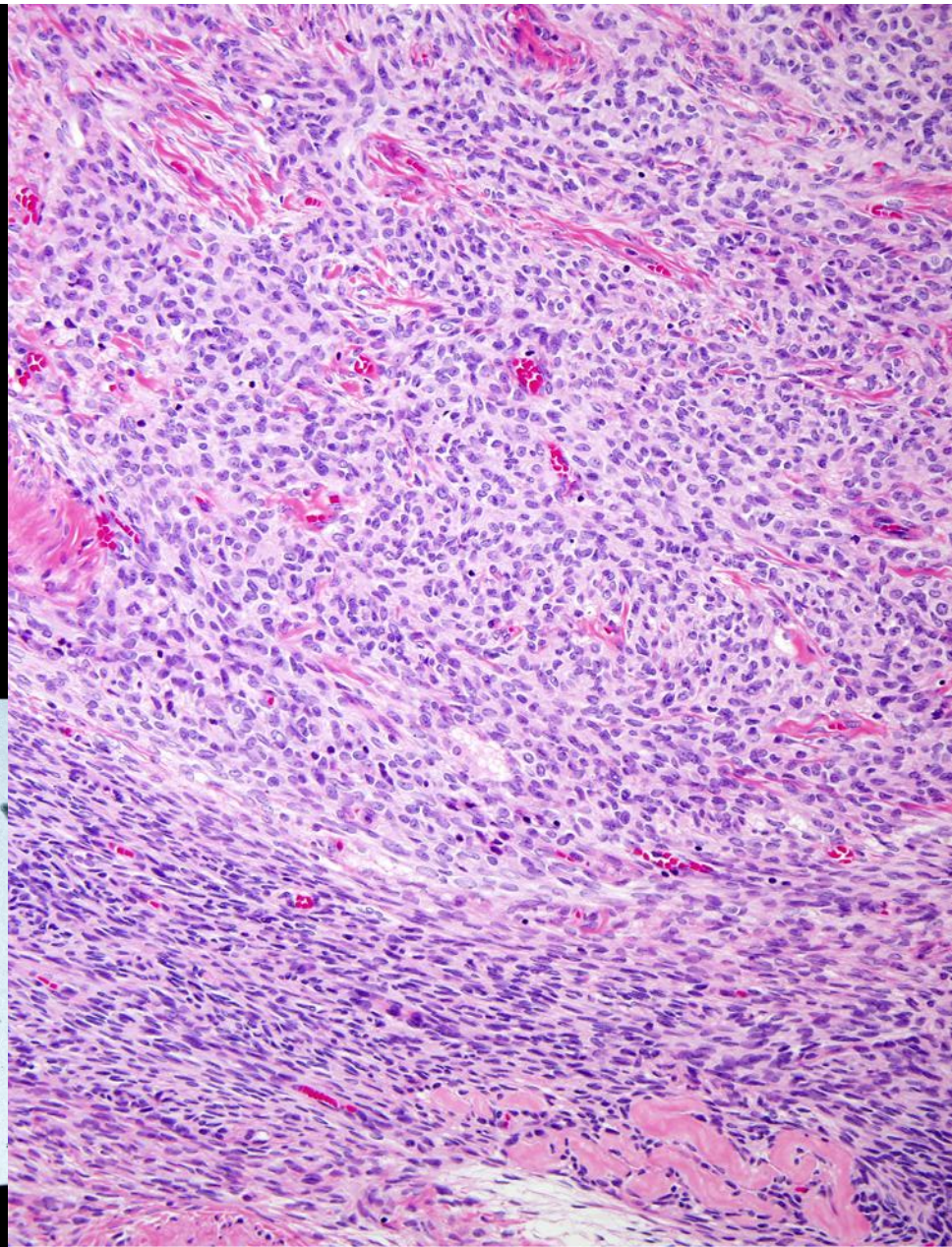
Solitary Follicular Cyst, Usually < 8 cm
Except during pregnancy or puerperium



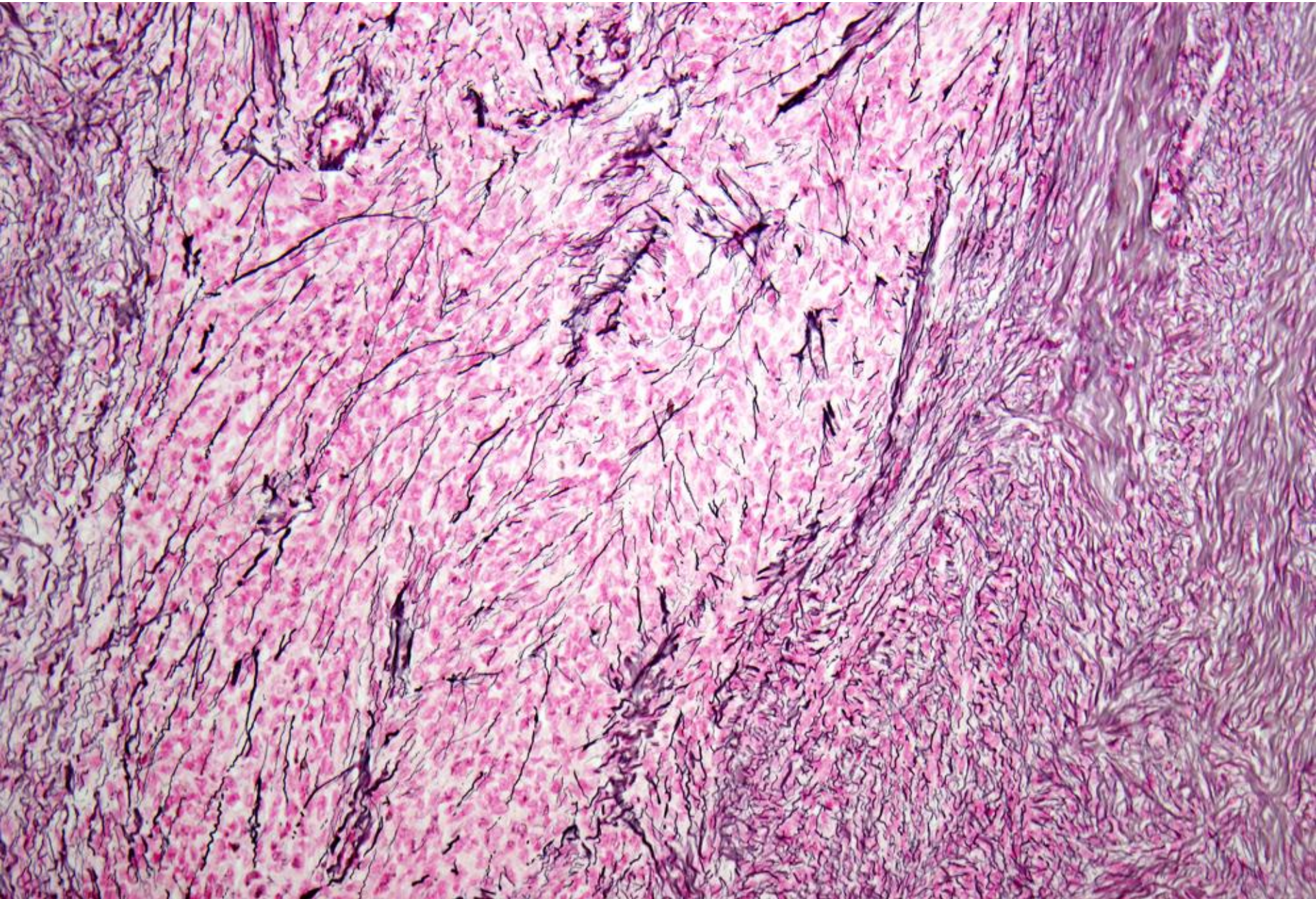


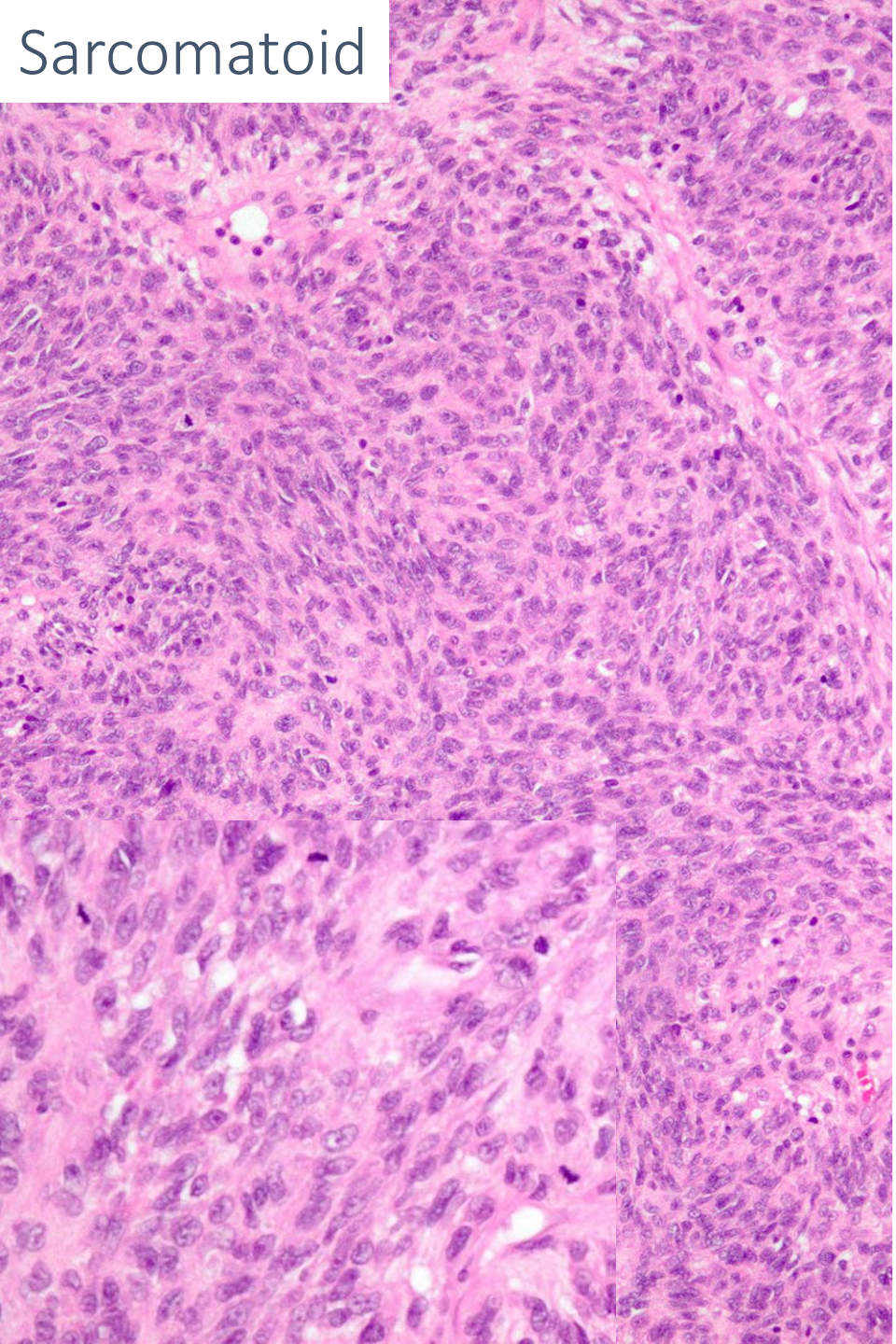
Adult Granulosa Cell Tumor, Solid Pattern with a Prominent Fibromatous Background

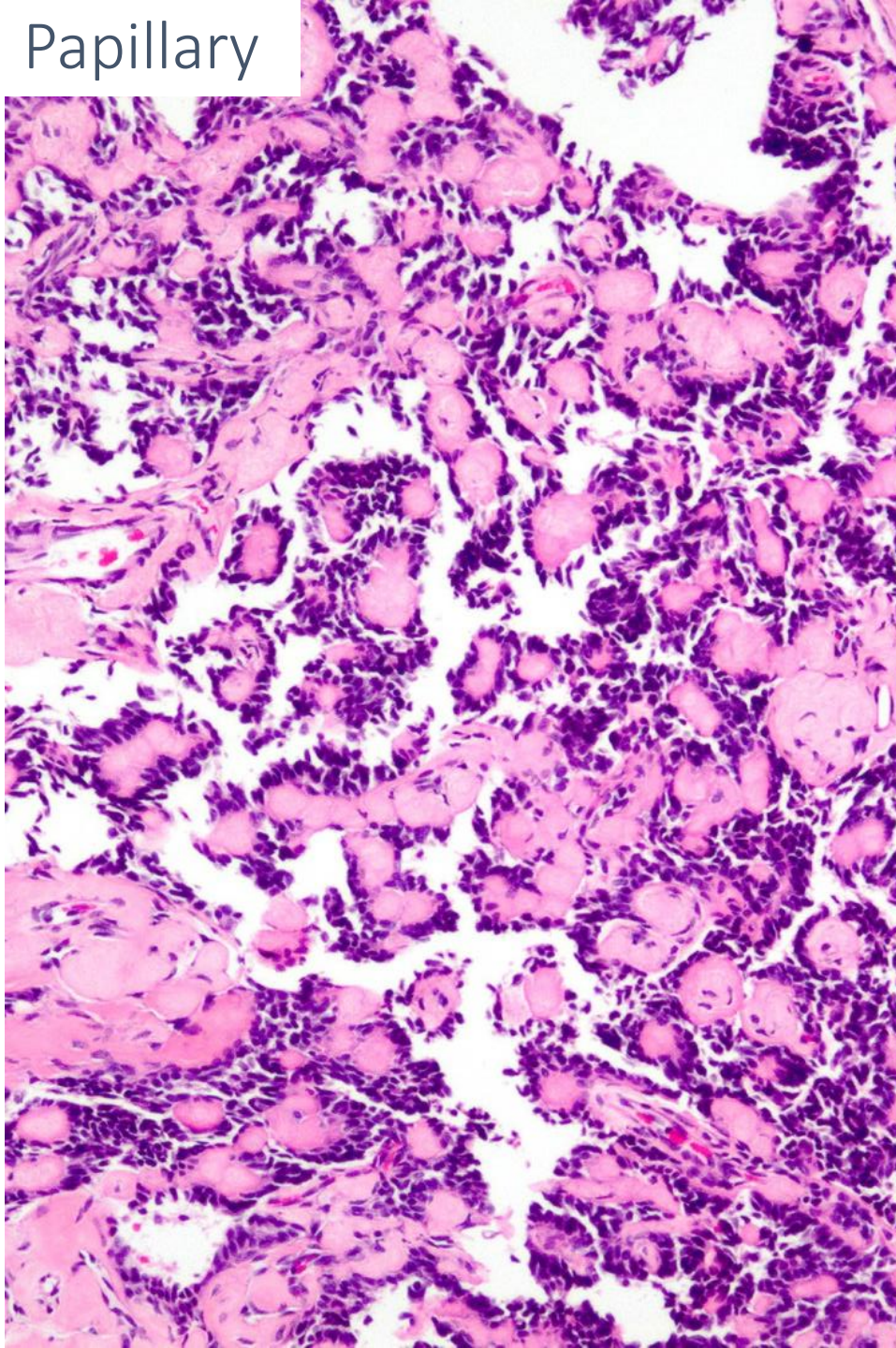




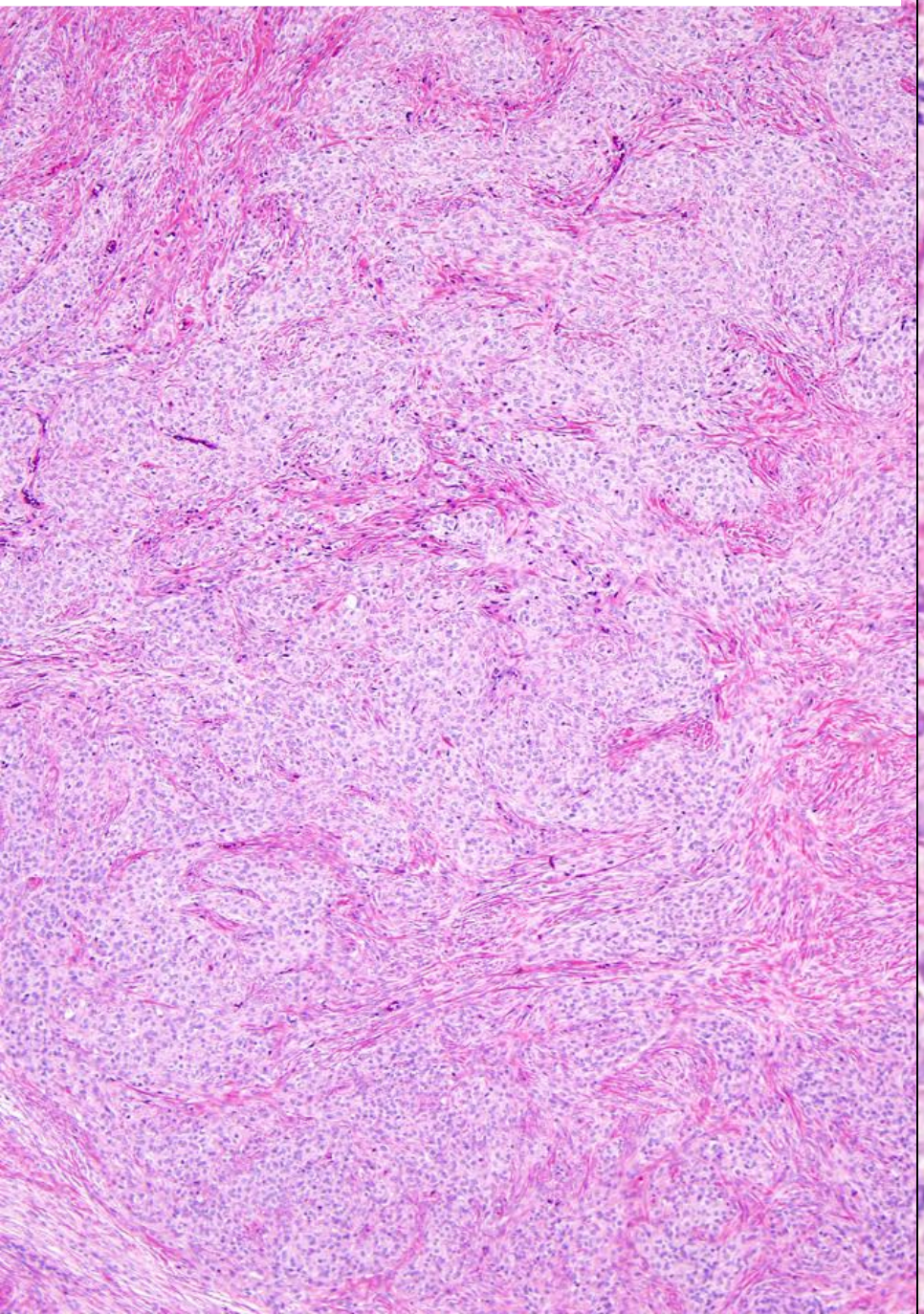
Reticulin fibers around groups of granulosa cells

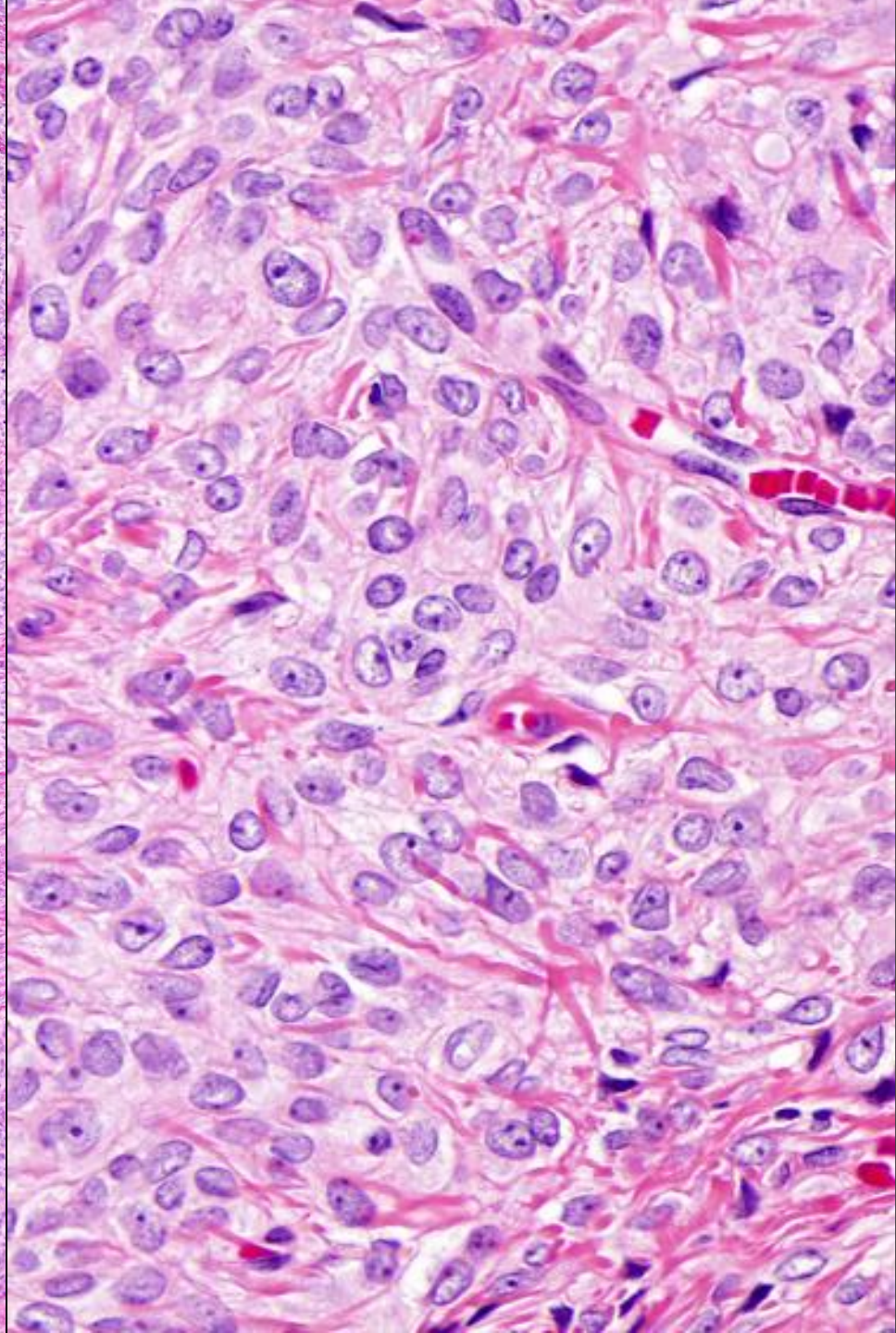



Sarcomatoid

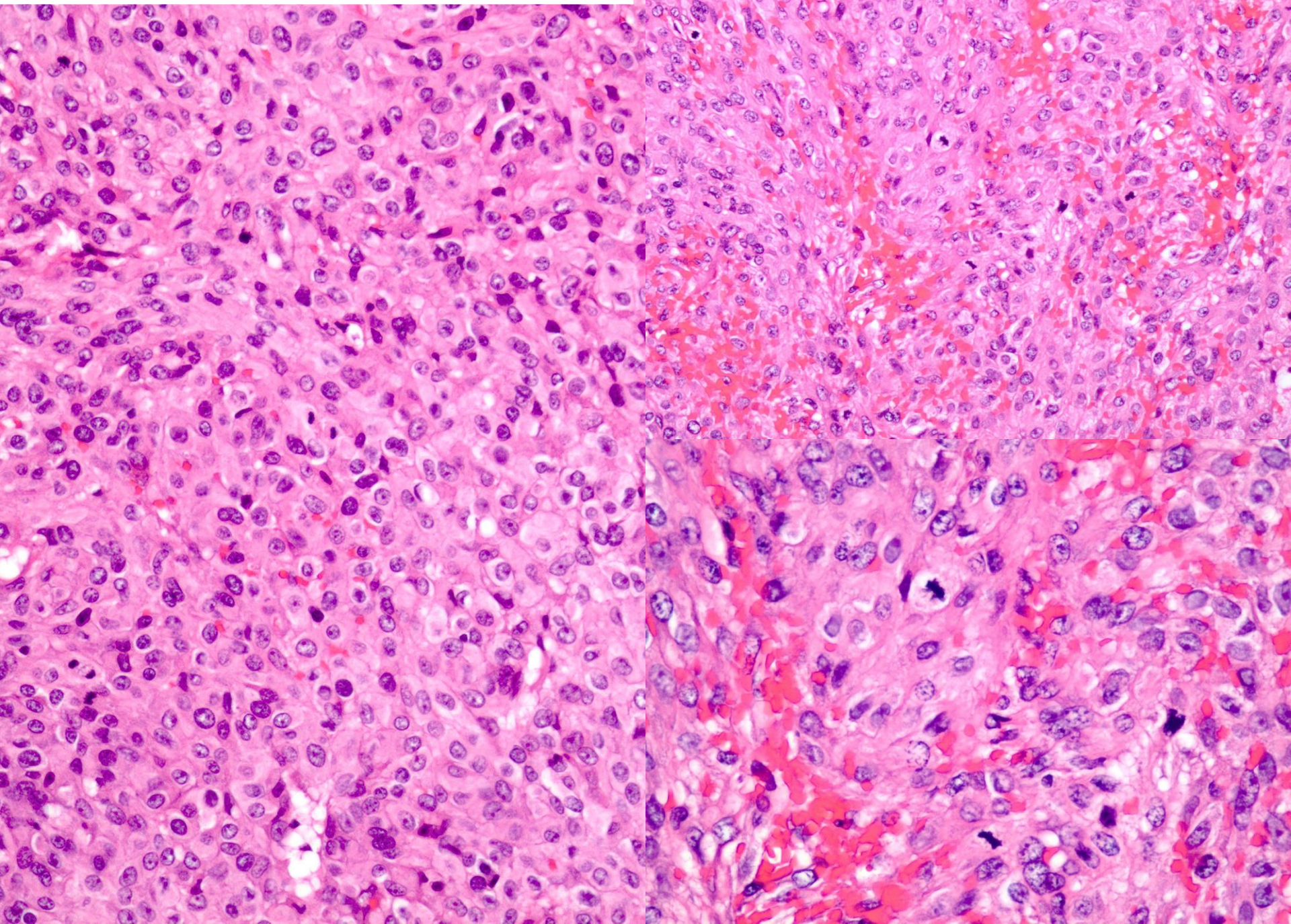

Papillary

AGCT, luteinized





AGCT, luteinized and with numerous mitoses

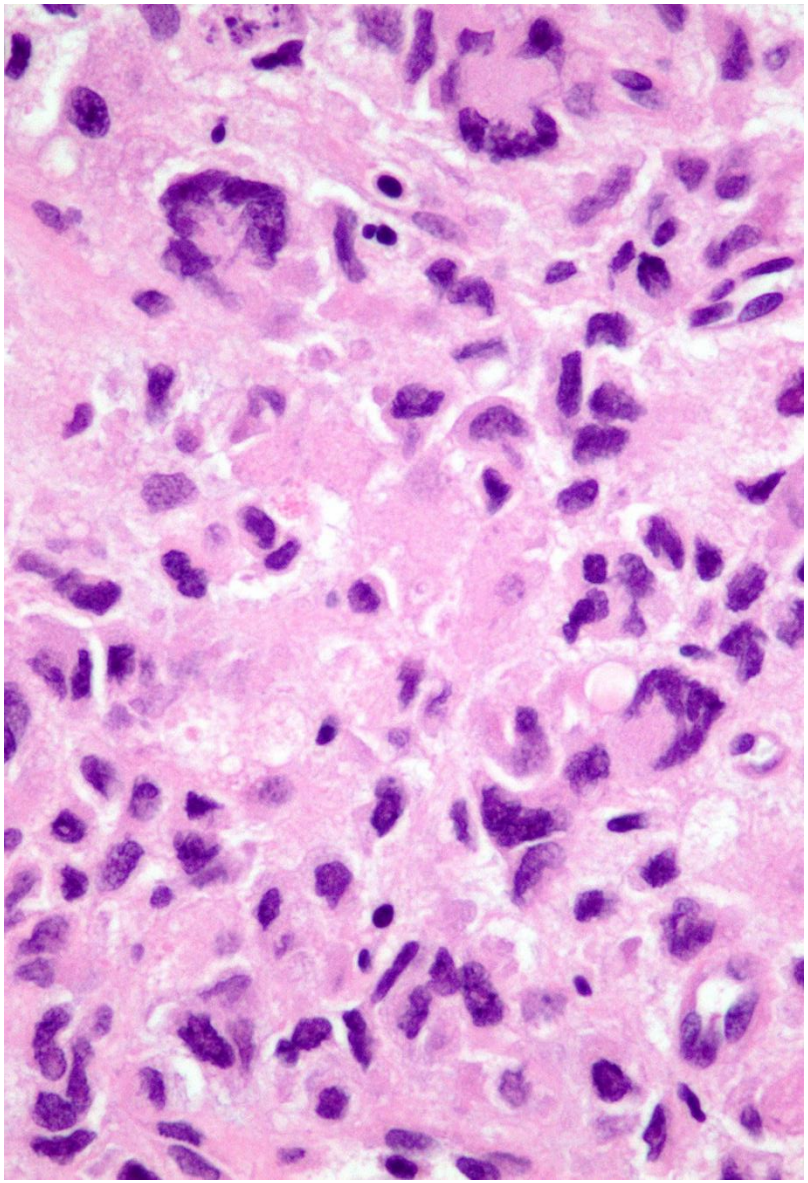


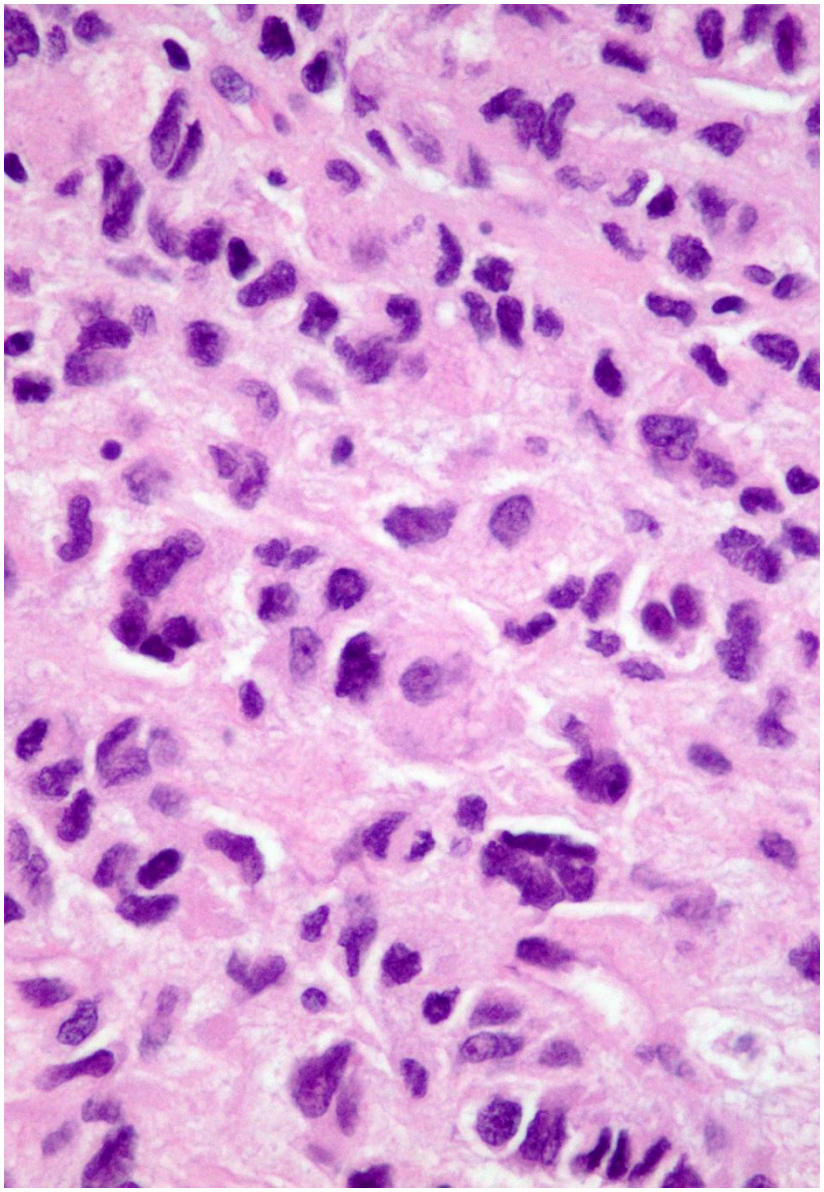
Pts asking for the mitotic index of the tumor

FIGO Stage I tumors ≥10 mitoses/10 HPFs, worse survival

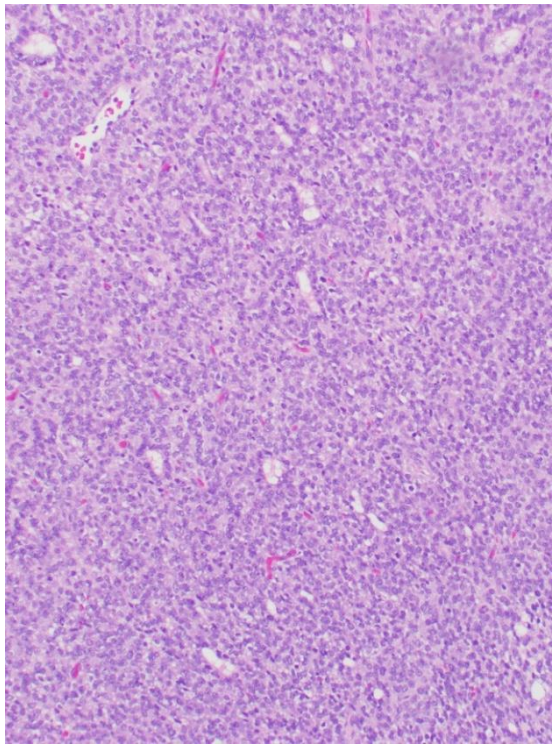
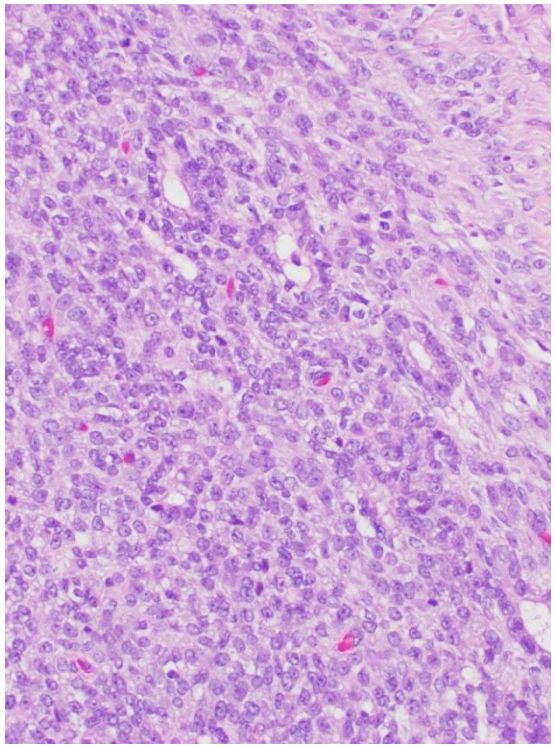
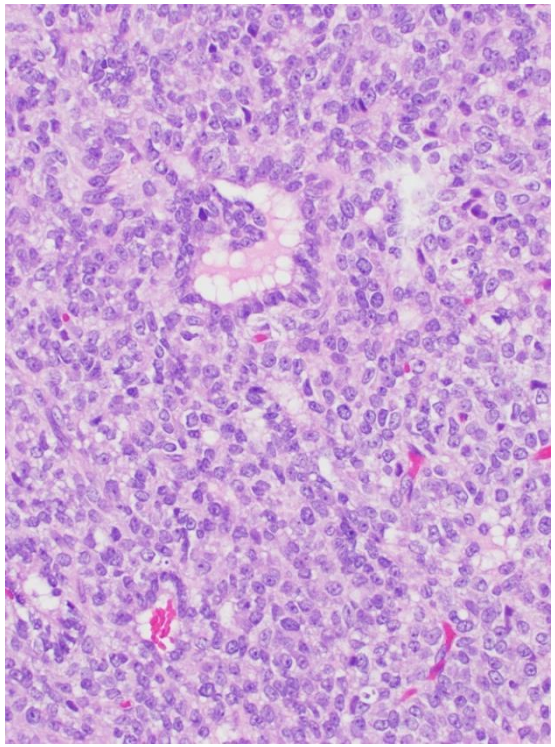
Malmström H, et al. 1994

AGCT, bizarre cells

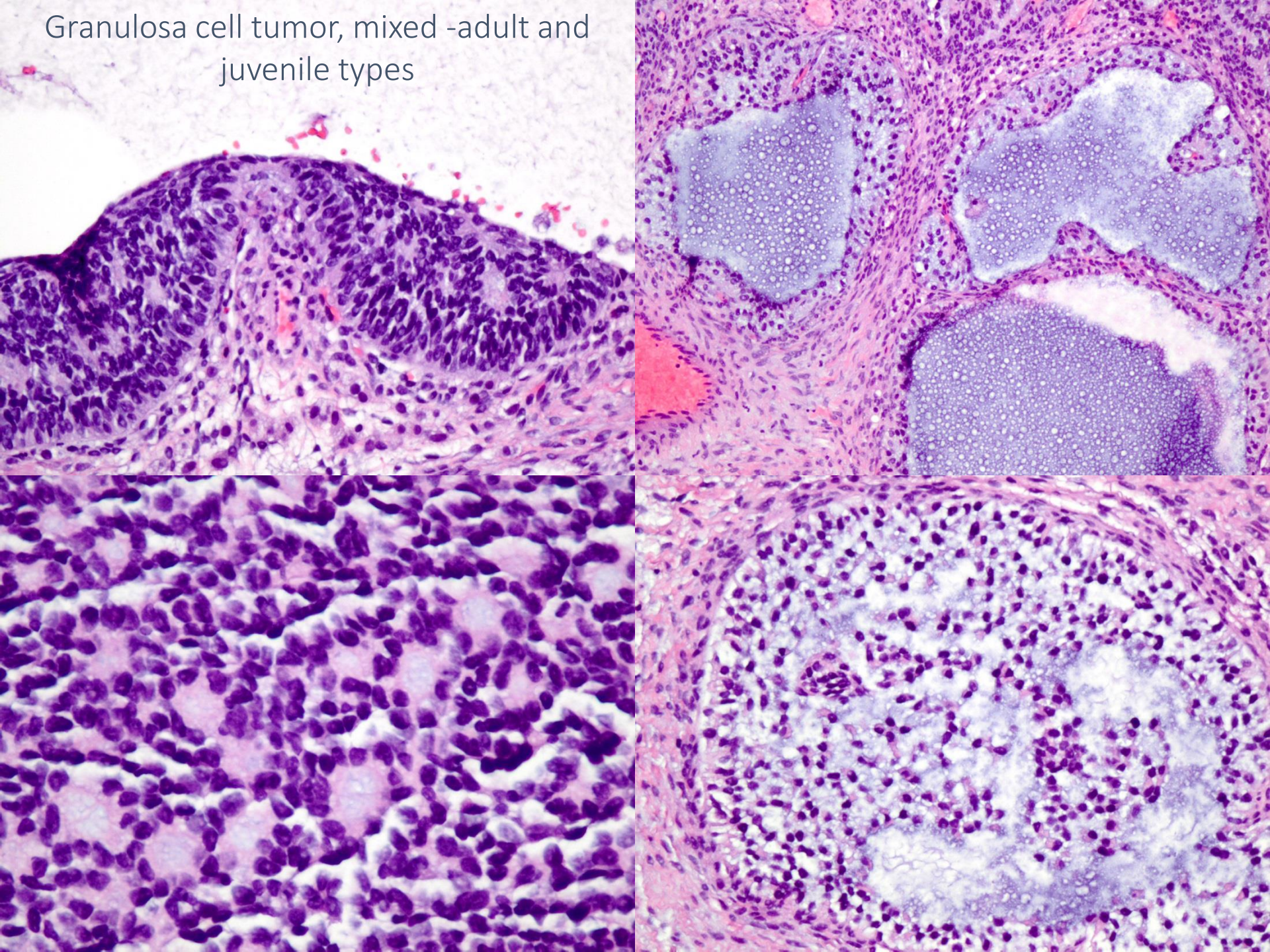


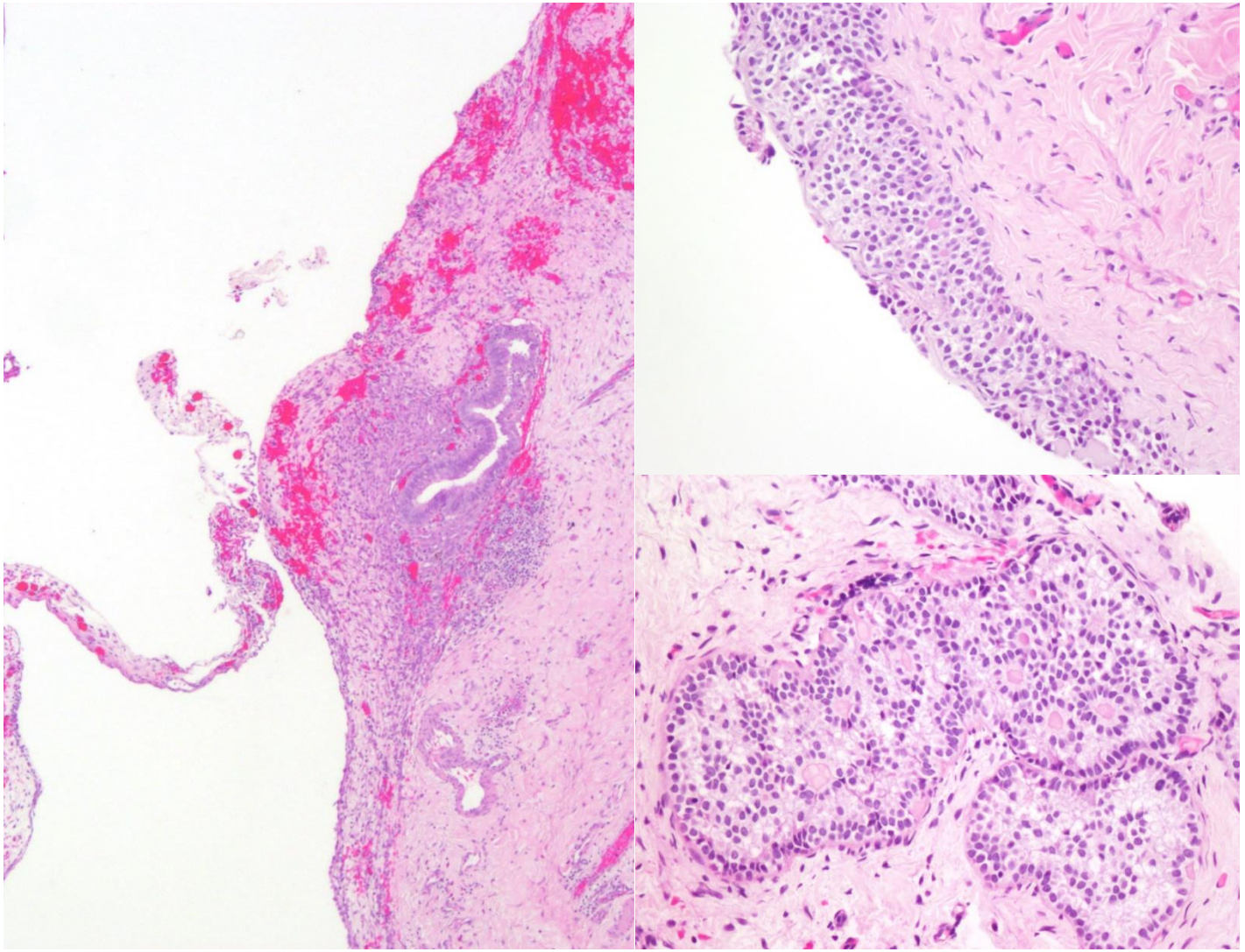


AGCT, Tubules

Granulosa cell tumor, mixed -adult and juvenile types



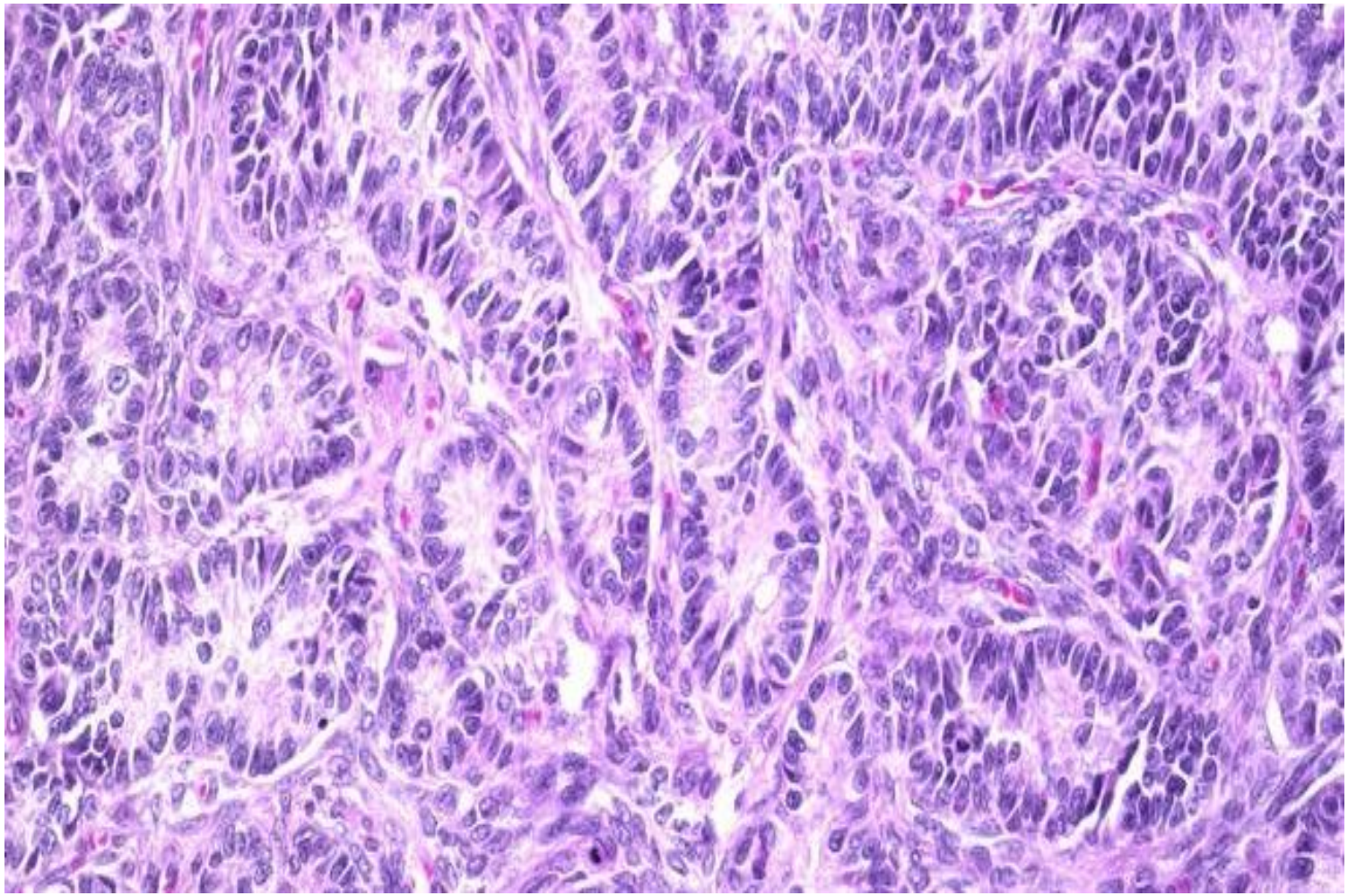


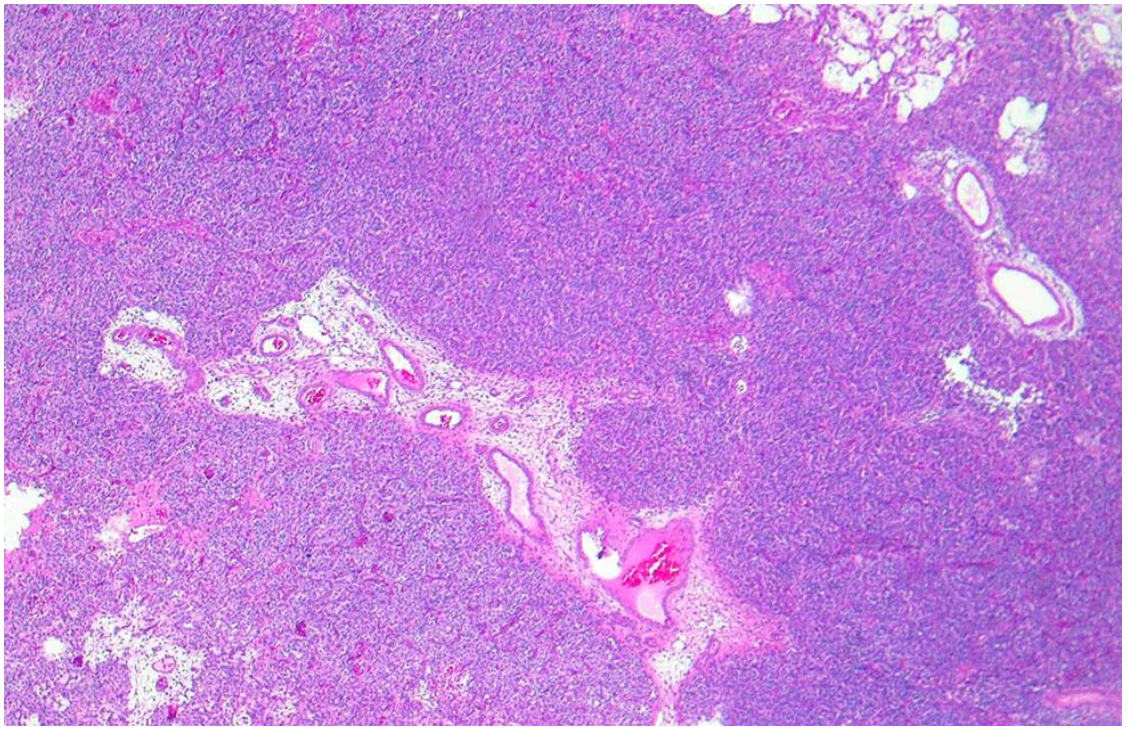
Granulosa cell proliferation associated with endometriosis

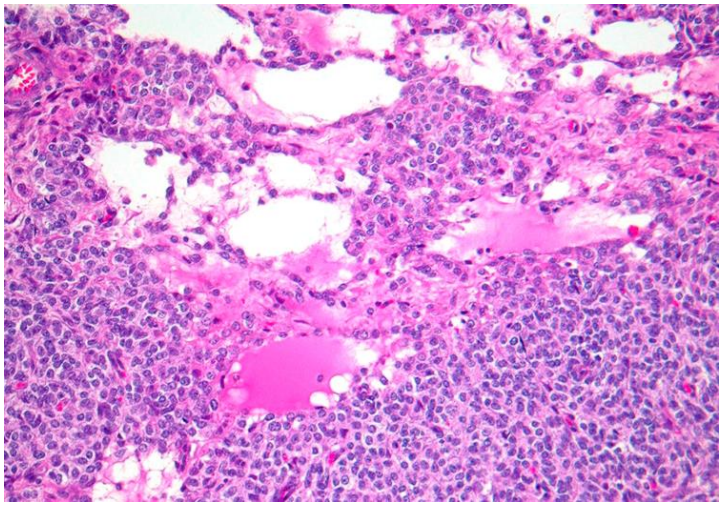
How do we solve cases that represent a diagnostic challenge?

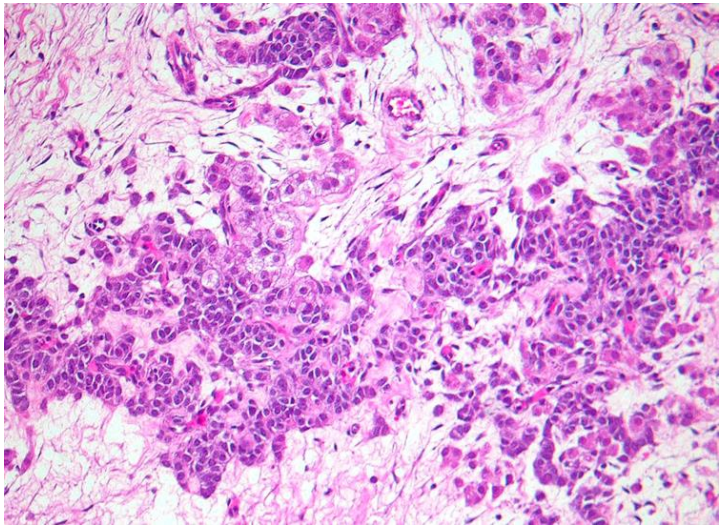
- The most reliable test is
  - *FOXL2* mutation analysis to confirm the diagnosis of adult type, granulosa cell tumor
    - *FOXL2* somatic mutation is seen in most AGCTs
    - *FOXL2* mutation can be seen in small proportion of
      - Juvenile granulosa cell tumors
      - Thecomas
      - Sertoli-Leydig cell tumors

Well Differentiated Sertoli-Leydig Cell Tumor (10%)



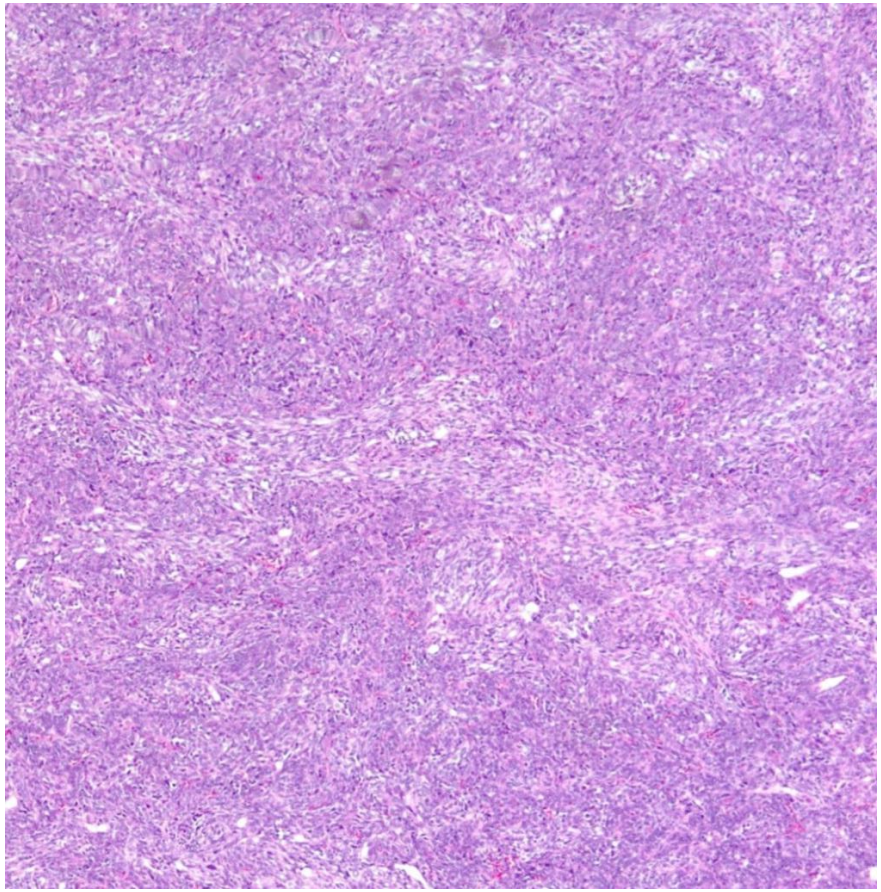


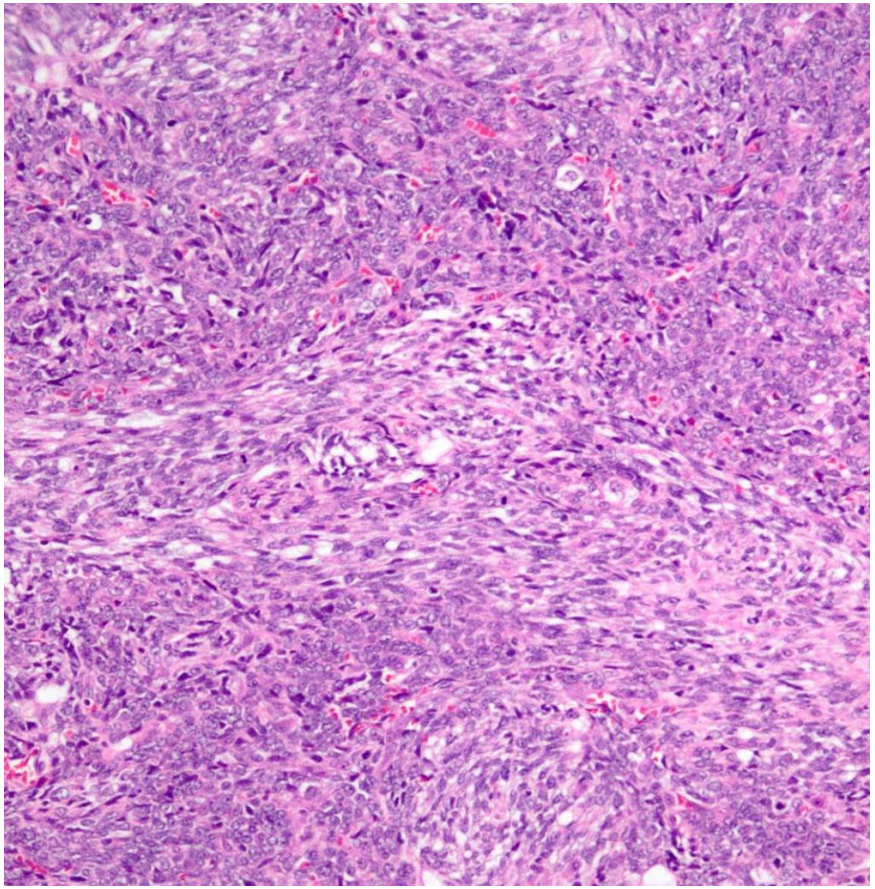




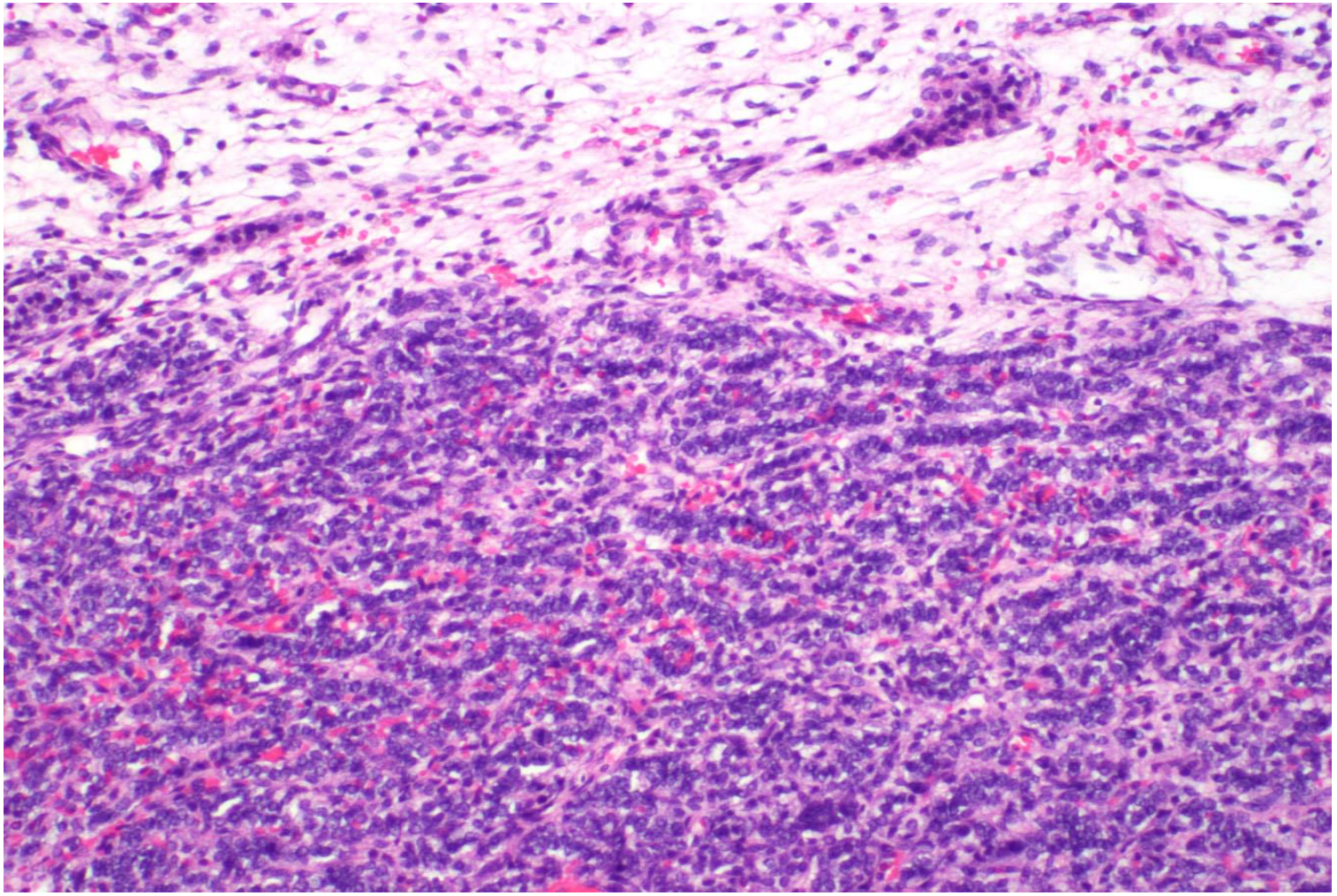
Moderately Differentiated
Sertoli-Leydig Cell Tumor (50%)

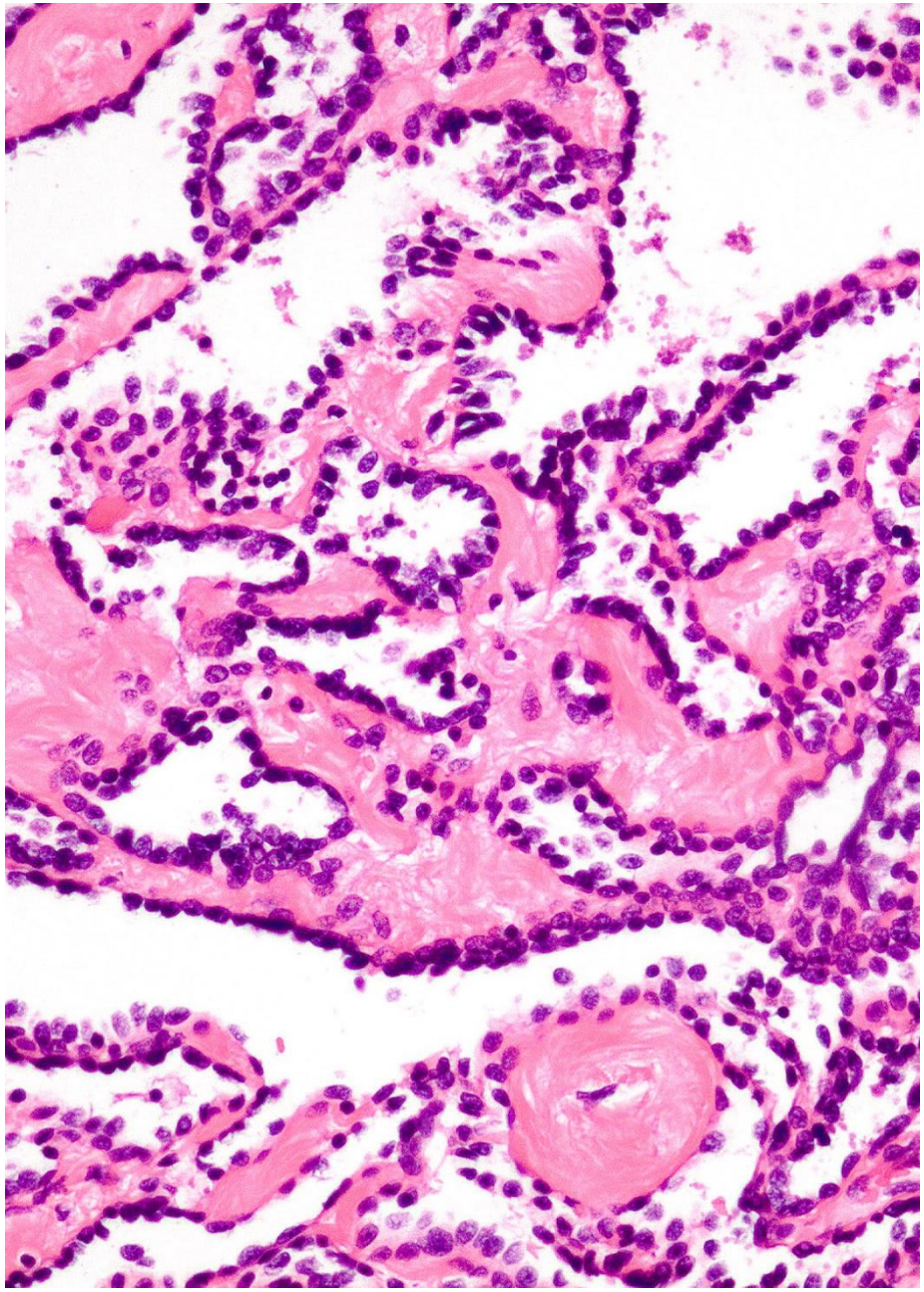
Poorly Differentiated Sertoli-Leydig Cell Tumor (≈40%)

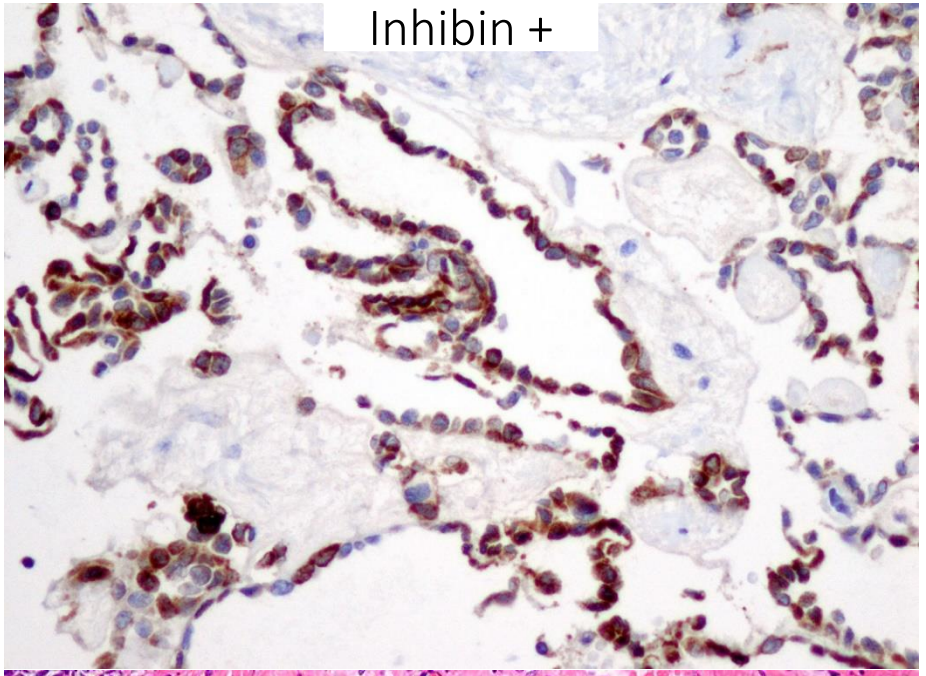




Poorly Differentiated Sertoli Leydig Cell Tumor,
Sertoli Cords and Leydig Cells better seen at the periphery of the tumor



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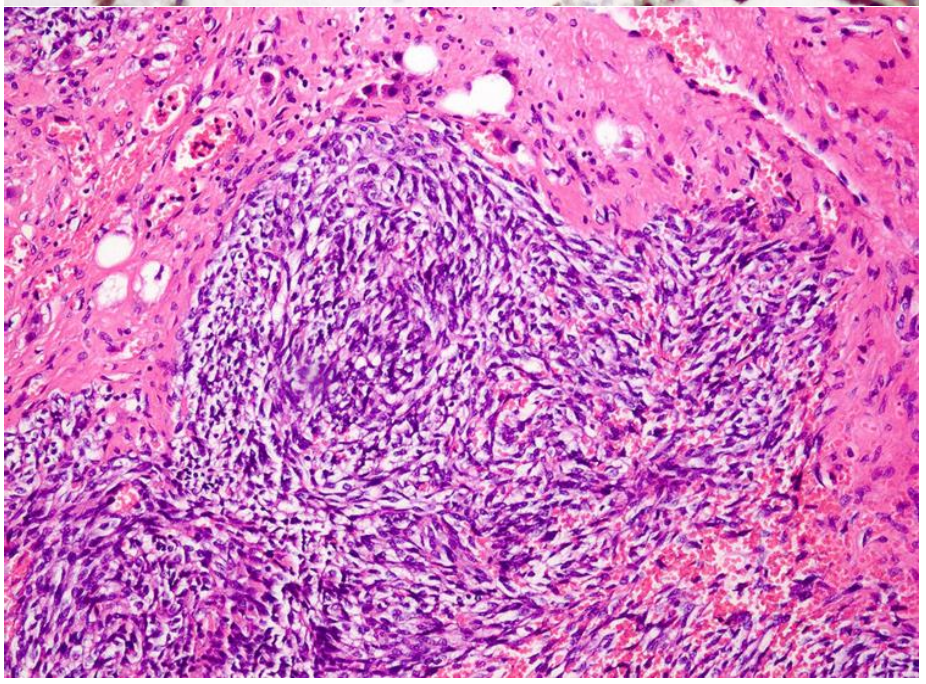
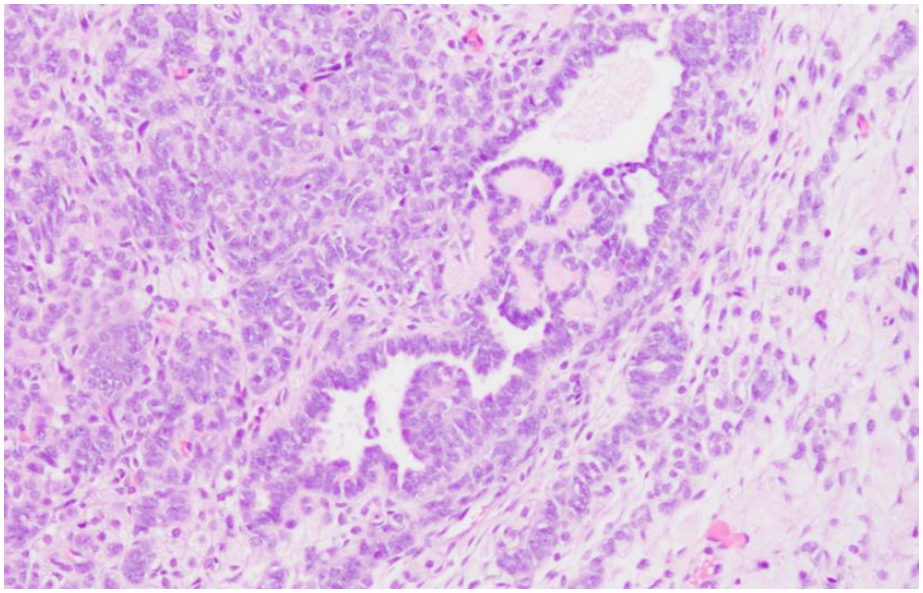
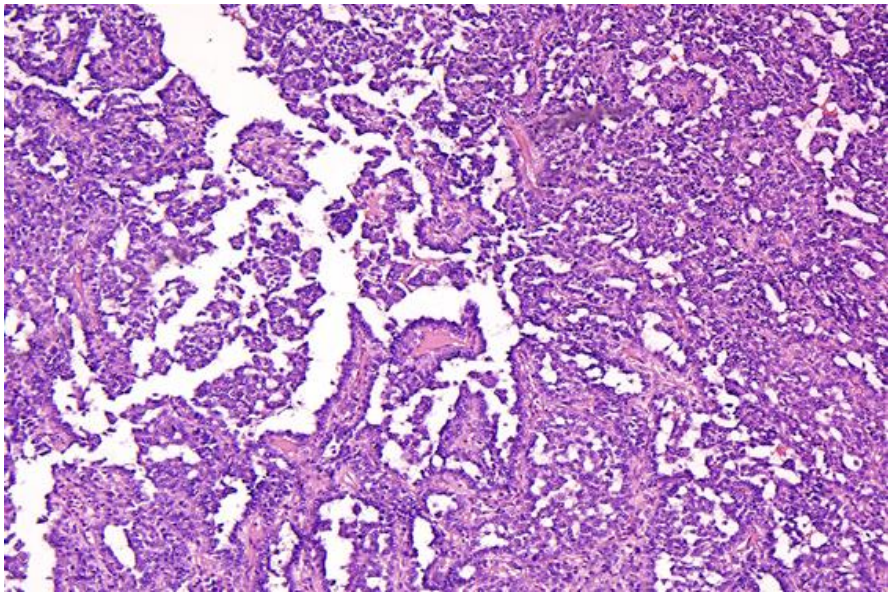
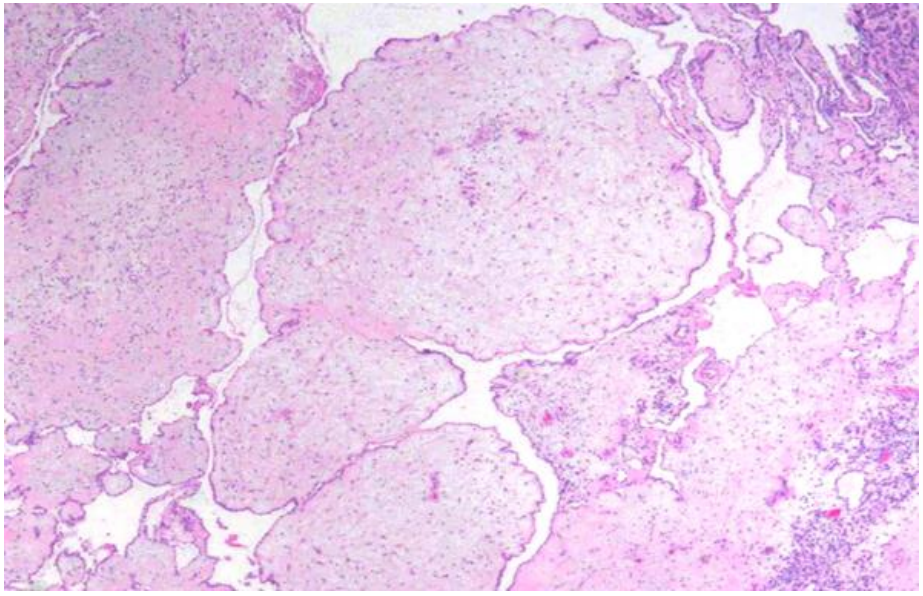
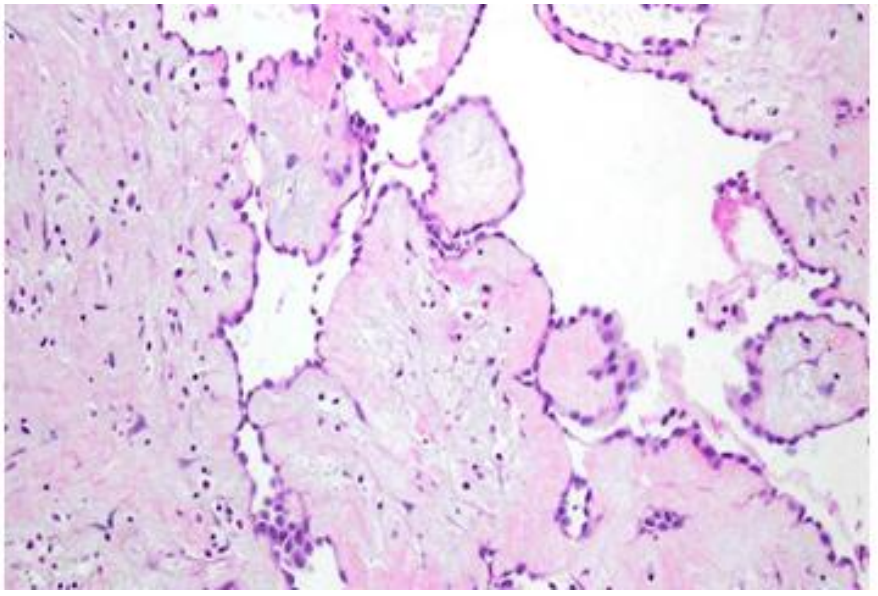


Retiform Pattern

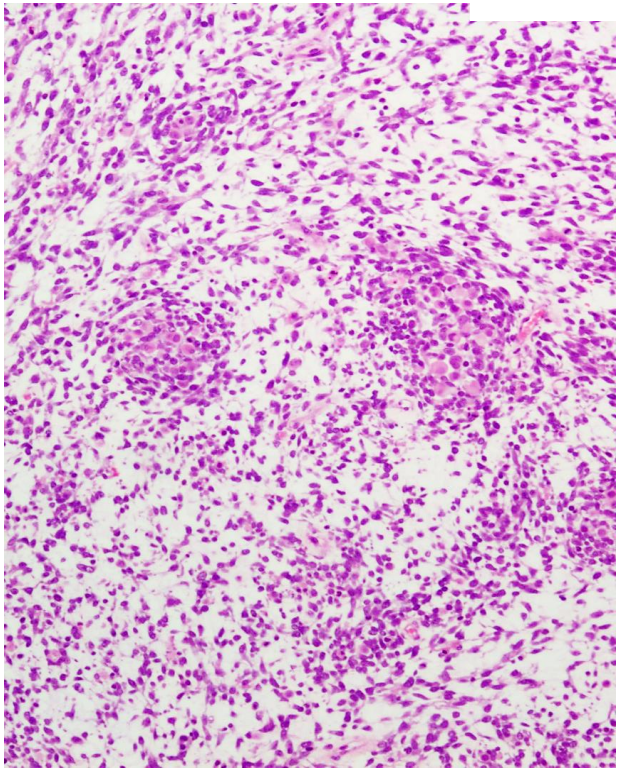


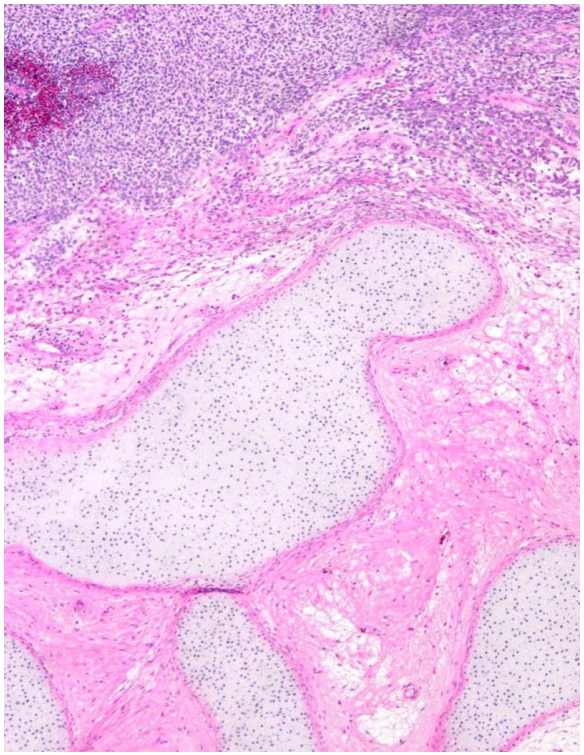


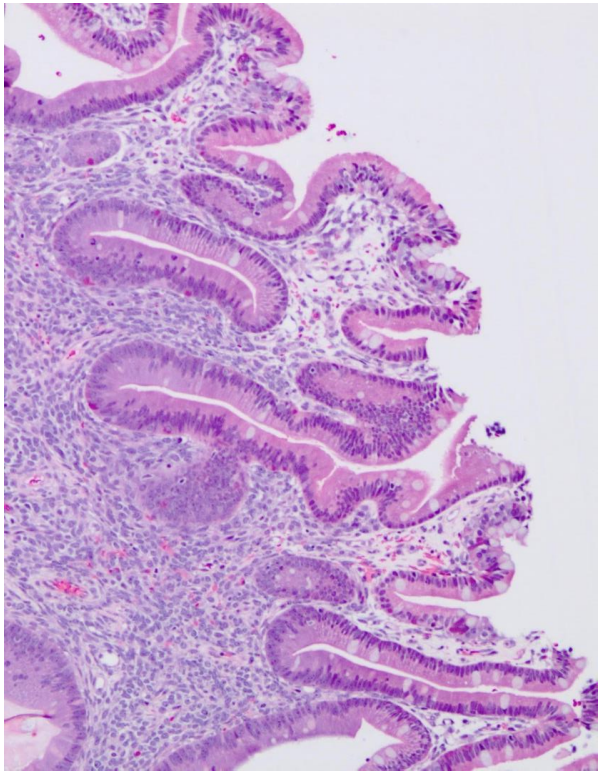




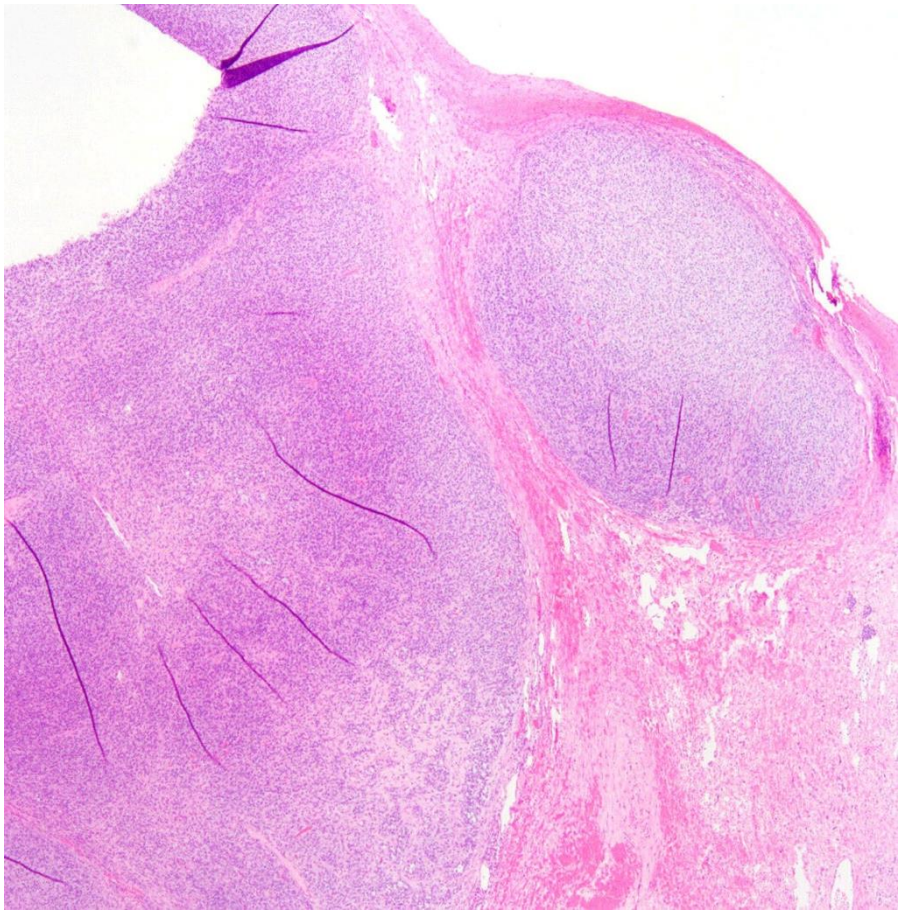
Heterologous Component

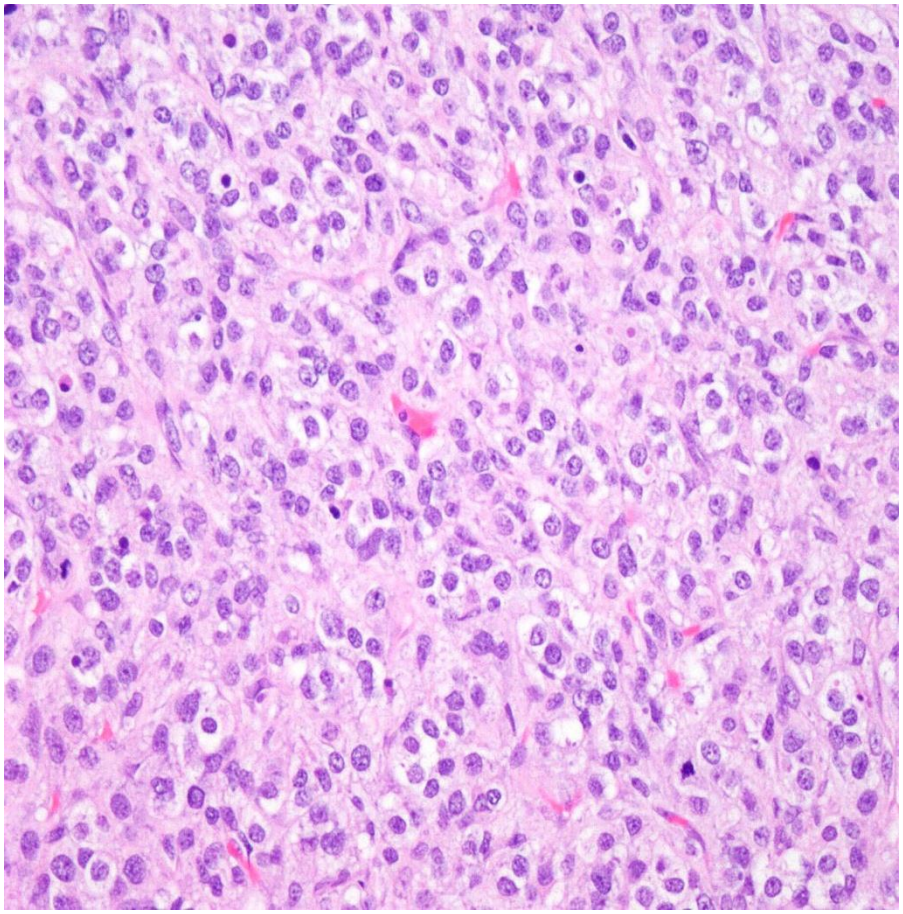




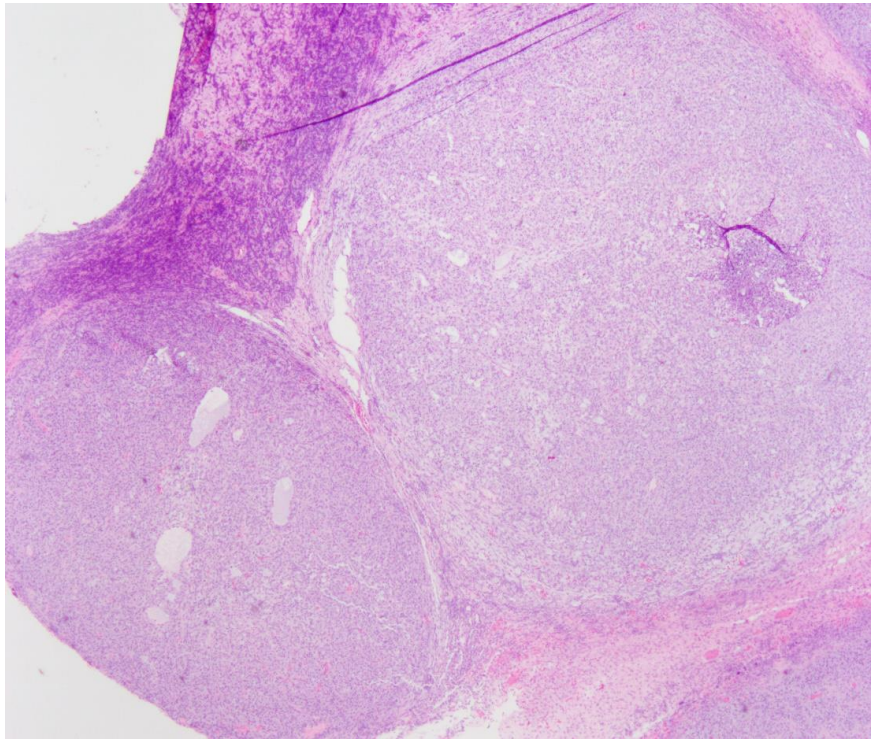


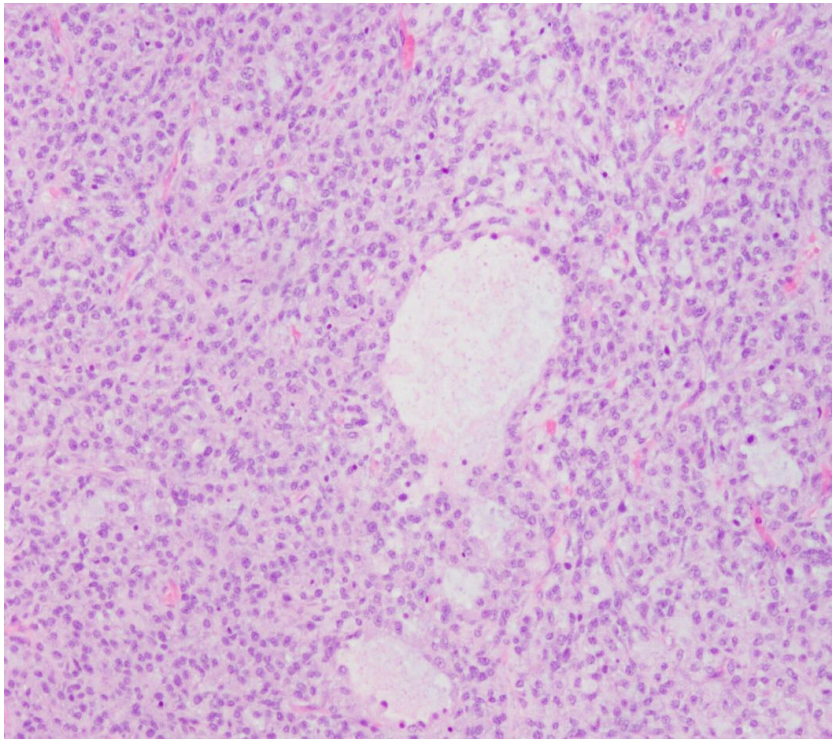
Associated Juvenile Granulosa Cell Tumor





Associated Juvenile Granulosa Cell Tumor





Nomenclature Issue: Gynandroblastoma vs. Sertoli-Leydig Cell Tumor with Areas of Juvenile Granulosa Cell-Like Tumor vs Sertoli-Leydig Cell Tumor and Juvenile Granulosa Cell Tumor, both components share the same *DICER1* mutation

Sertoli-Leydig Cell Tumor

- Ovarian Sertoli-Leydig cell tumors, *DICER1* mutations
  - Sporadic
    - 20-44% of the cases
  - Germline pathogenic or likely pathogenic
    - 50-60% of the cases

- Once the Dx of Sertoli Leydig cell tumor is made
  - Genetic counseling and germline DICER1 testing
    - Among individuals with Sertoli Leydig cell tumor and pathogenic *DICER1* mutations
      - the risk of developing another neoplasm is 36.2% at 10 years

Tumor site	*DICER1*-related tumor
Lungs	Pleuropulmonary blastoma
	Well-differentiated fetal adenocarcinoma of the lung
Urinary system	Wilms tumor
	Cystic nephroma
	Anaplastic sarcoma of the kidney
	Bladder embryonal rhabdomyosarcoma
Female reproductive system	Ovarian Sertoli-Leydig cell tumor
	Cervical embryonal rhabdomyosarcomas
	Ovarian sex cord-stromal tumors (apart from Sertoli-Leydig cell tumor)
	Gynandroblastoma
Male reproductive system	Pediatric paratesticular sarcoma
CNS/head and neck	Pituitary blastoma
	Pineoblastoma
	Primary central nervous system sarcoma
	Ciliary body medulloepithelioma
	Nasal chondromesenchymal hamartoma
	Embryonal tumor with multilayered rosettes
Thyroid	Papillary carcinoma
	Follicular carcinoma
	Poorly differentiated thyroid cancer
	Thyroblastoma
Gastrointestinal	Juvenile intestinal hamartomatous polyp
Others	Pleuropulmonary blastoma-like peritoneal sarcoma
	Presacral malignant teratoid tumor

Review Article

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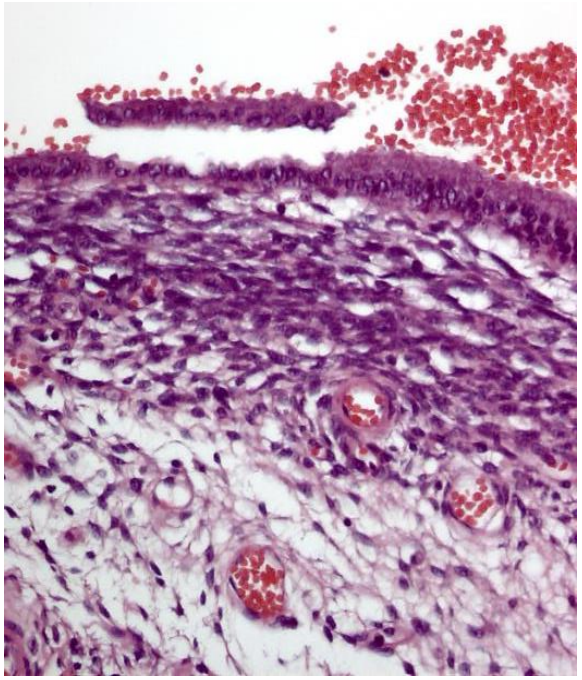
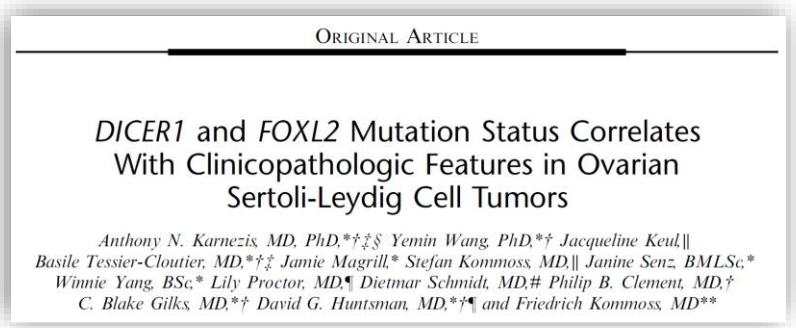
The Histological Spectrum of DICER1-Associated Neoplasms

Alessia Capozzi[1*], Floor A. Jansen[2*], Stephanie E. Smetsers[2], Jette J. Bakhuizen[3], Laura S. Hiemcke-Jiwa[2,4], Mariëtte E. G. Kranendonk[2], Uta Flucke[2], Rita Alaggio[5], and Ronald R. de Krijger[2,4]





ORIGINAL ARTICLE

DICER1 and *FOXL2* Mutation Status Correlates With Clinicopathologic Features in Ovarian Sertoli-Leydig Cell Tumors

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DICER1 mutant	*FOXL2* mutant	*DICER1/FOXL2* wild type
Younger pts	Post-menopausal	Intermediate age
↑ Androgenic manifestations	Abnormal bleeding	Androgenic manifestations may be seen
Moderately/poorly differentiated	Moderately/poorly differentiated	Well differentiated
Retiform or heterologous elements	No retiform or heterologous elements	No retiform or heterologous elements

Twilight Epiphany

Live Oak Friends Meeting House

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