Challenges in Frozen Section Diagnosis of Ovarian Tumors

XXXII International Academy of Pathology Congress

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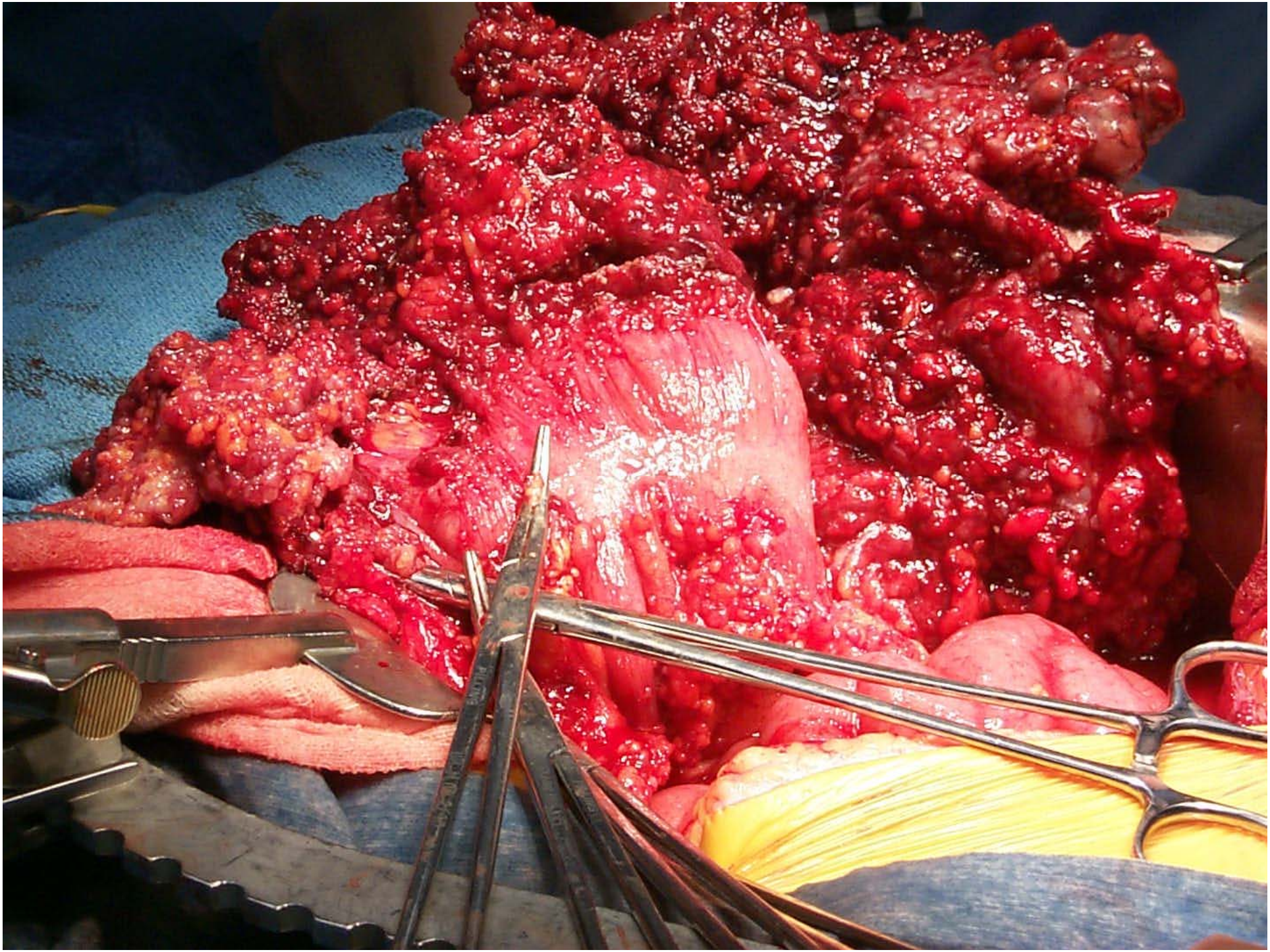
Frozen Section Indication

- Render a diagnosis (in less than 20 minutes) that may need *immediate* further surgical management



Issues to be addressed by frozen section diagnosis (FS)

- Neoplastic vs. non neoplastic lesion
- Benign, borderline or malignant neoplasm
- Primary vs. metastatic tumors
- Histologic type of primary neoplasm: epithelial, germ cell or sex cord/stromal,
- Nature of peritoneal nodules and adhesions

Impact of FS diagnosis

- Benign: No further surgical management
- Borderline tumors:
  - TAH-BSO in postmenopausal + staging
  - Unilateral SO in young patients + staging
- Carcinomas:
  - TAH-BSO + staging/debulking
- Malignant sex-cord stromal tumors and germ cell tumors:
  - Unilateral SO in young patients + staging

- When you are not sure: Do not render a malignant diagnosis (better to under-call)
    - Examine specimen carefully
    - Touch prep can be useful
    - Submit additional sections
    - Get a second opinion
    - Call the surgeon and ask for more history and his/her DDx

FS of Ovarian Lesions: Relevant Clinical Information

- Patient's age
- Relevant clinical/family history
- Prior malignancy
- Serum tumor markers (HCG, AFP, CEA, CA125, CA19.9), hormonal levels (estrogens, androgens)
- Abnormal uterine bleeding
- Imaging studies
- Prior treatment (chemoradiation therapy)

FS of Ovarian Lesions: Gross Examination

- Measure and weight
- Intact or ruptured surface
- Any lesions on external surface (ink)
- Solid vs. cystic lesion
- Unilocular vs. multilocular cysts
- Cyst lining (smooth, irregular, papillary projection)
- Cyst contents: serous, mucinous or keratinaceous
- Selection of areas to sample: Intramural nodules, papillary excrescences, solid component, flat cystic component

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Broad gross differential diagnosis of ovarian lesions

- **“Simple cyst”:**
  - usually benign like follicular cyst and cystadenomas
- **“Complex cyst”:**
  - Non-neoplastic (endometriotic cyst)
  - Benign neoplasm (dermoid cyst)
  - Borderline or malignant tumor (including serous, mucinous, endometrioid and clear neoplasms)
- **Solid tumor:**
  - Benign fibromas, granulosa cell tumor, Brenner tumor
  - Malignant neoplasm
  - Any solid tumor can undergo cystic changes

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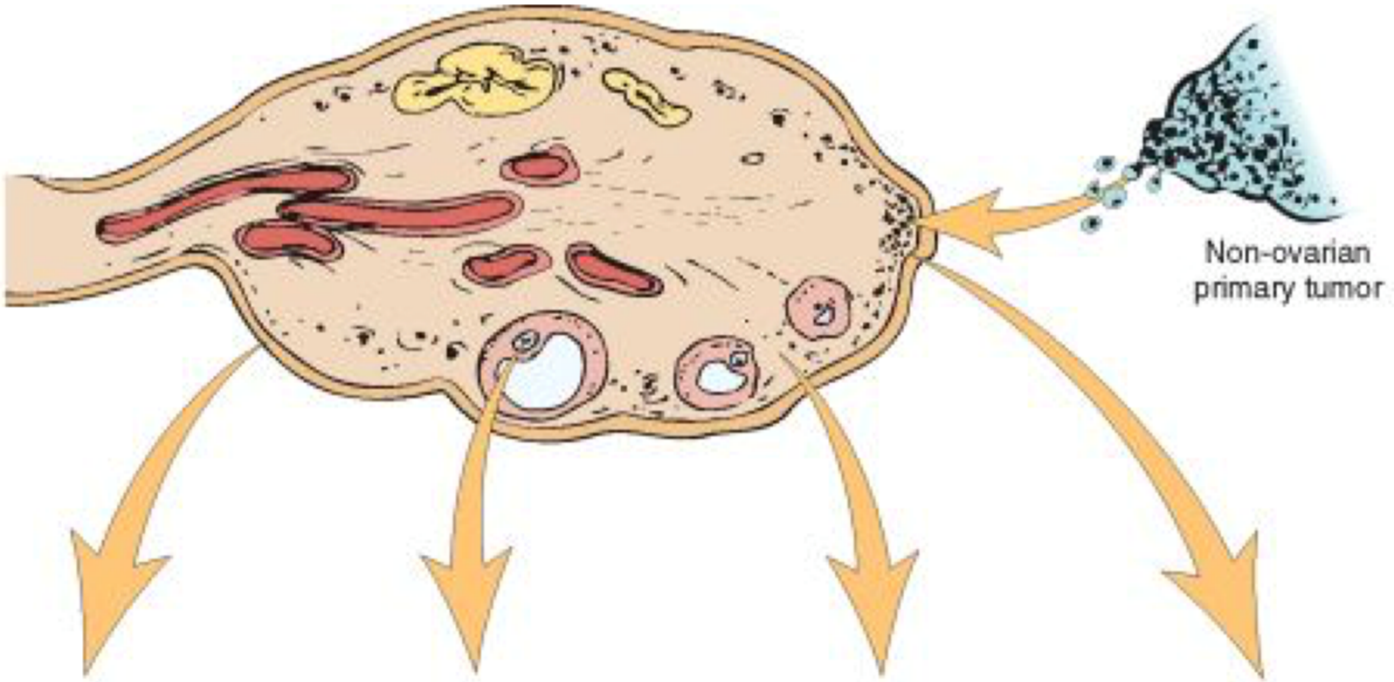

ORIGIN	SURFACE EPITHELIAL CELLS (Surface epithelial–stromal cell tumors)	GERM CELL	SEX CORD–STROMA	METASTASIS TO OVARIES
Overall frequency	65–70%	15–20%	5–10%	5%
Proportion of malignant ovarian tumors	90%	3–5%	2–3%	5%
Age group affected	20+ years	0–25+ years	All ages	Variable
Types	• Serous tumor • Mucinous tumor • Endometrioid tumor • Clear cell tumor • Brenner tumor • Cystadenofibroma	• Teratoma • Dysgerminoma • Endodermal sinus tumor • Choriocarcinoma	• Fibroma • Granulosa–theca cell tumor • Sertoli–Leydig cell tumor	

Intraoperative Frozen Section of Ovarian Tumors: 10 Years Single Institute Experience

Intraoperative frozen section of ovarian tumors, 10 years single institute experience

Objectives: Intraoperative frozen section diagnosis (FSD) is a critical part of the management of ovarian neoplasms. The aim of this study is to evaluate the diagnostic ability of the FSD, the discrepancies between the FSD and the permanent diagnosis (PD), and its clinical implication on the patient's care.

Methods: We retrospectively identified a 10 year cohort of 626 patients with ovarian tumors who underwent surgery with FSD. FSD and PD were divided into three categories (benign, borderline and malignant) and the discrepancies were classified as major and minor. Evaluating pathologists were categorized as gynecological (gyn) or general pathologist. Intra-rater concordance between FSD and PD for he diagnosis of malignancy was assessed with kappa coefficient. Surgical outcomes of the discrepant cases were evaluated.

Results: Of the 618 cases studied, the final diagnosis was 72.7% benign, 8.5% borderline and 18.8% malignant. Major discrepancies are reported in 5.3% (n=33), with mucinous epithelial tumors being the most common type 27.3% (9 of 33). Of the major discrepancies, 18% (6 of 33) were over-diagnosis (5 epithelial and 1 sex cord tumor) and 81% (27 of 33) were under-diagnosis (19 epithelial, 2 sex cord, 2 germ cell and 4 metastasis).

The major discrepancies rate was 5.5% and 5.3% by gyn and general pathologist, respectively (Z-score: 0.12, p = 0.9). Intra-observer Kappa coefficient of concordance was 0.84 & 0.90 for gynecologic and general pathologist, respectively.
The discrepancies had no effect on 30-day postoperative mortality (zero cases). Return to the operating room for completion procedures was indicated in 2 underdiagnosed cases (2/618, 0.3%), however, one patient refused and the other underwent the surgery. Performance of unnecessary procedures was identified in one overdiagnosed case (1/618, 0.2%).

Conclusions: Intraoperative frozen section is an important diagnostic tool for surgical management of ovarian neoplasms. FSD showed the highest sensitivity for benign tumors and highest specificity for malignant ones. However, borderline tumors are difficult to accurately diagnose at frozen section. No significant difference is observed in major discrepancies between gynecological and general pathologist.

Results

618 patients were included:
72.7% benign, 8.5% borderline, 18.8% malignant
FSD diagnostic ability is as follows:

	Benign	**Borderline**	**Malignant**
Sensitivity	98.9%	79.2%	87.0%
Specificity	90.5%	98.2%	99.0%
PPV	96.5%	80.8%	95.3%
NPV	96.8%	98.1%	97.1%

Results

Major discrepancies

5.3%, 33/618 major discrepancies were identified with mucinous epithelial tumor being the most common.

	Epithelial	Sex cord	Germ cell	Mets
overdiagnosis, n=6	5	1	0	0
underdiagnosis, n=27	19	2	2	4

Ovarian Serous Tumors

Ovarian Serous Tumors

- One or multiple cysts filled with clear watery fluid
- ***Benign*** cystadenomas: thin walls with smooth inner lining
- ***Borderline*** tumors: may have subtle areas of soft friable papillary projections
- Extraovarian implants (30%)
- ***Malignant*** tumors: may have solid areas or papillary growth with necrosis


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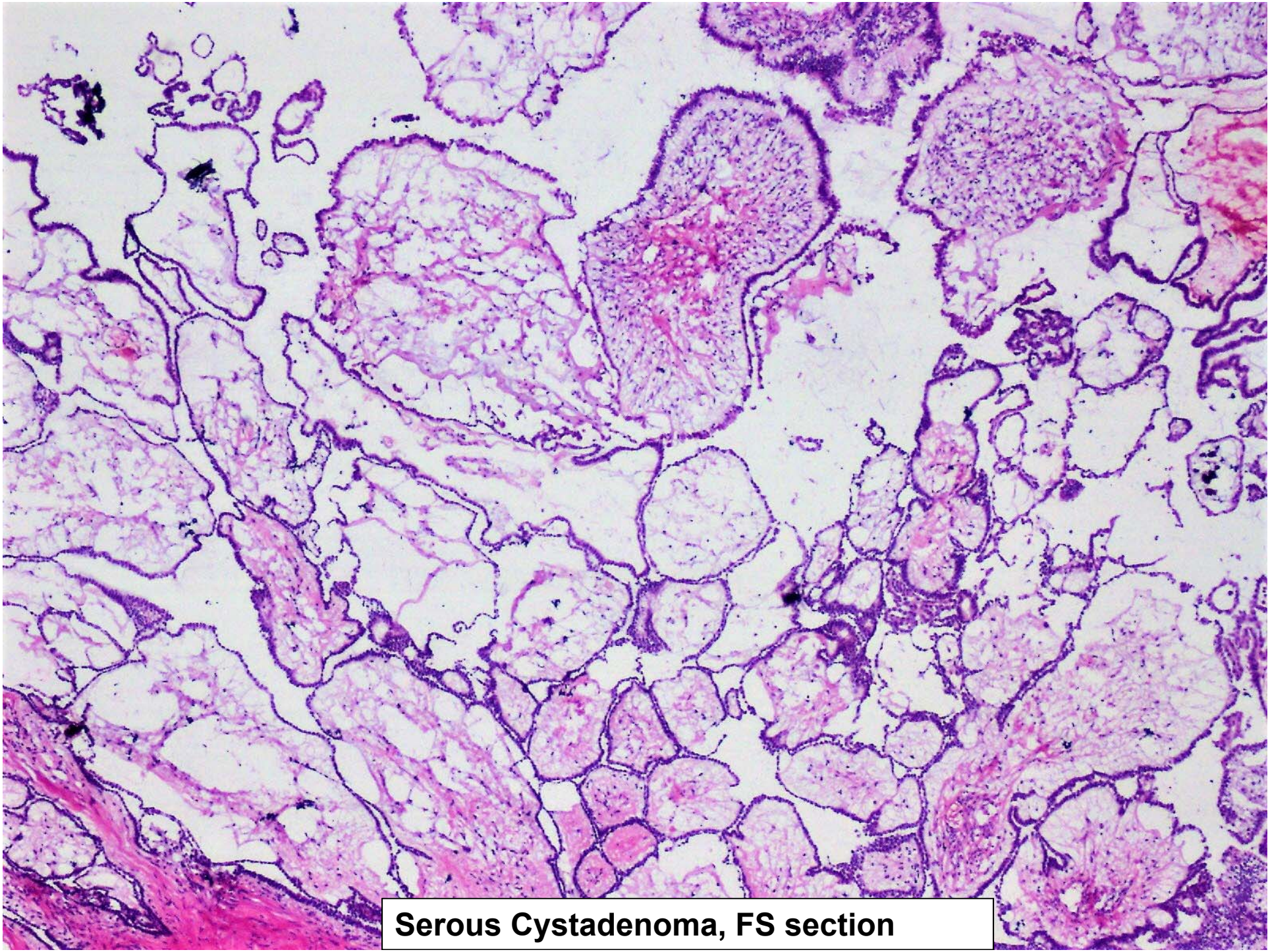
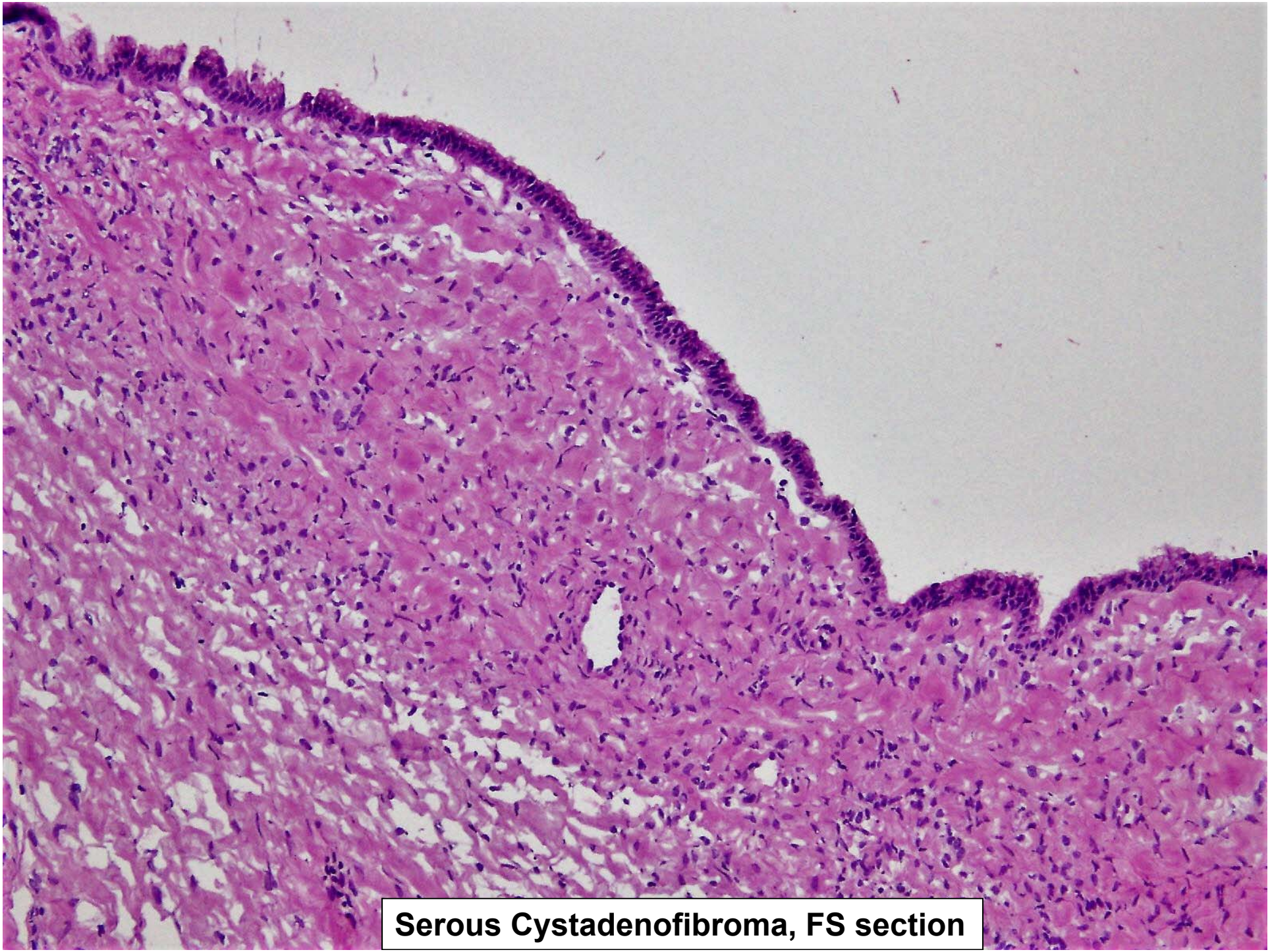
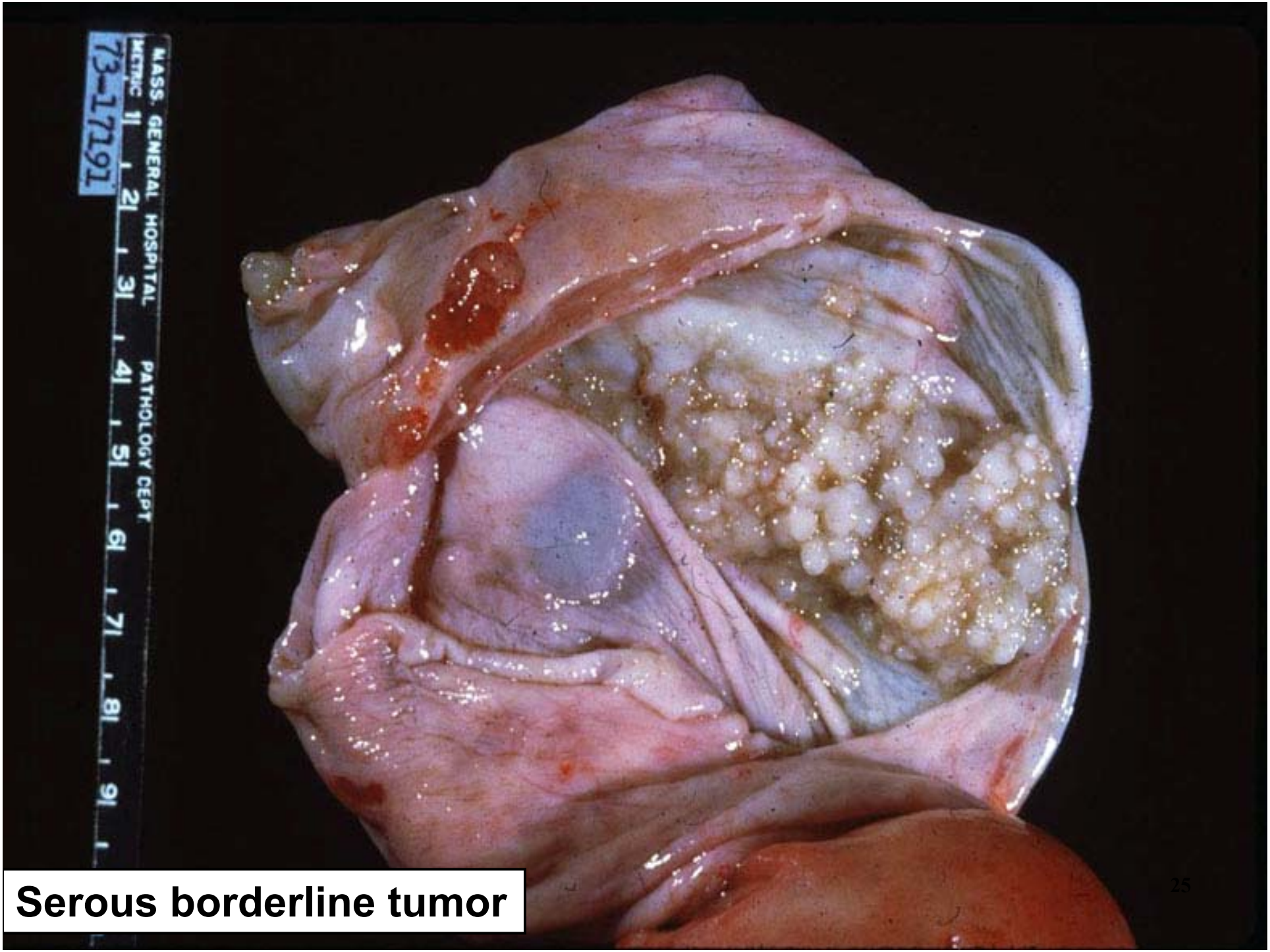


Serous Cystadenoma, FS section

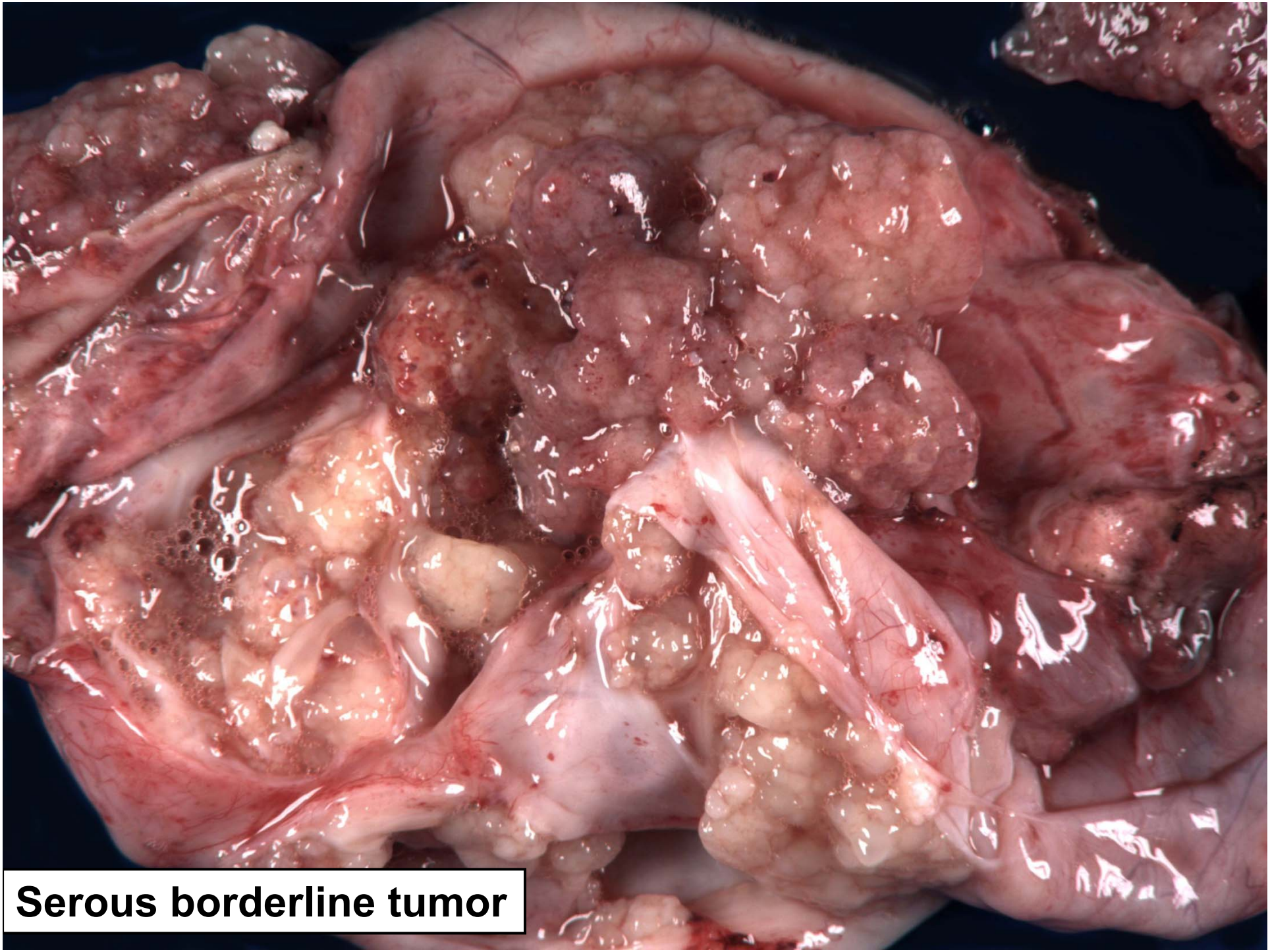

Serous Cystadenofibroma, FS section

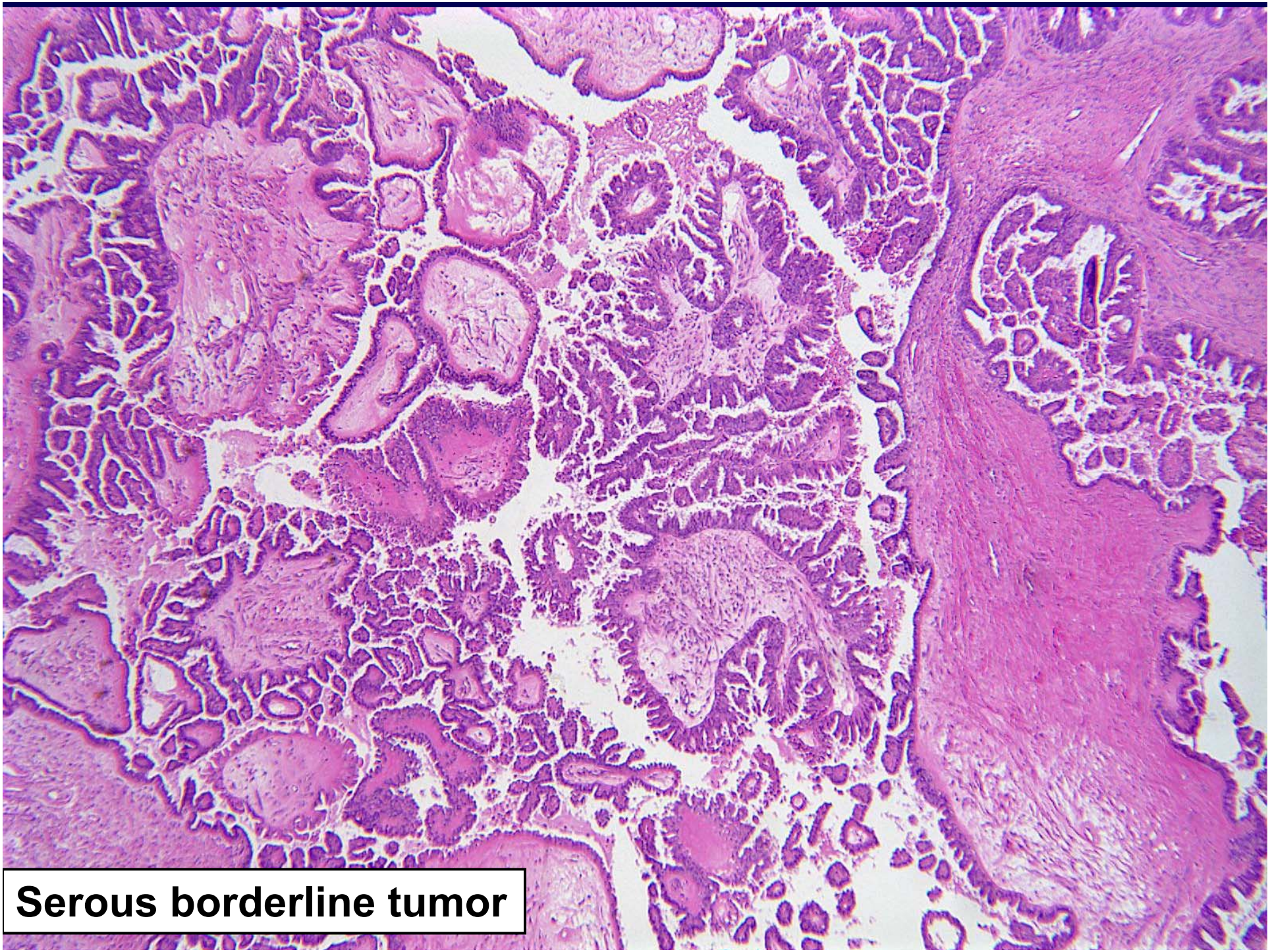
DDx: Ovarian tumors with papillary growth pattern grossly

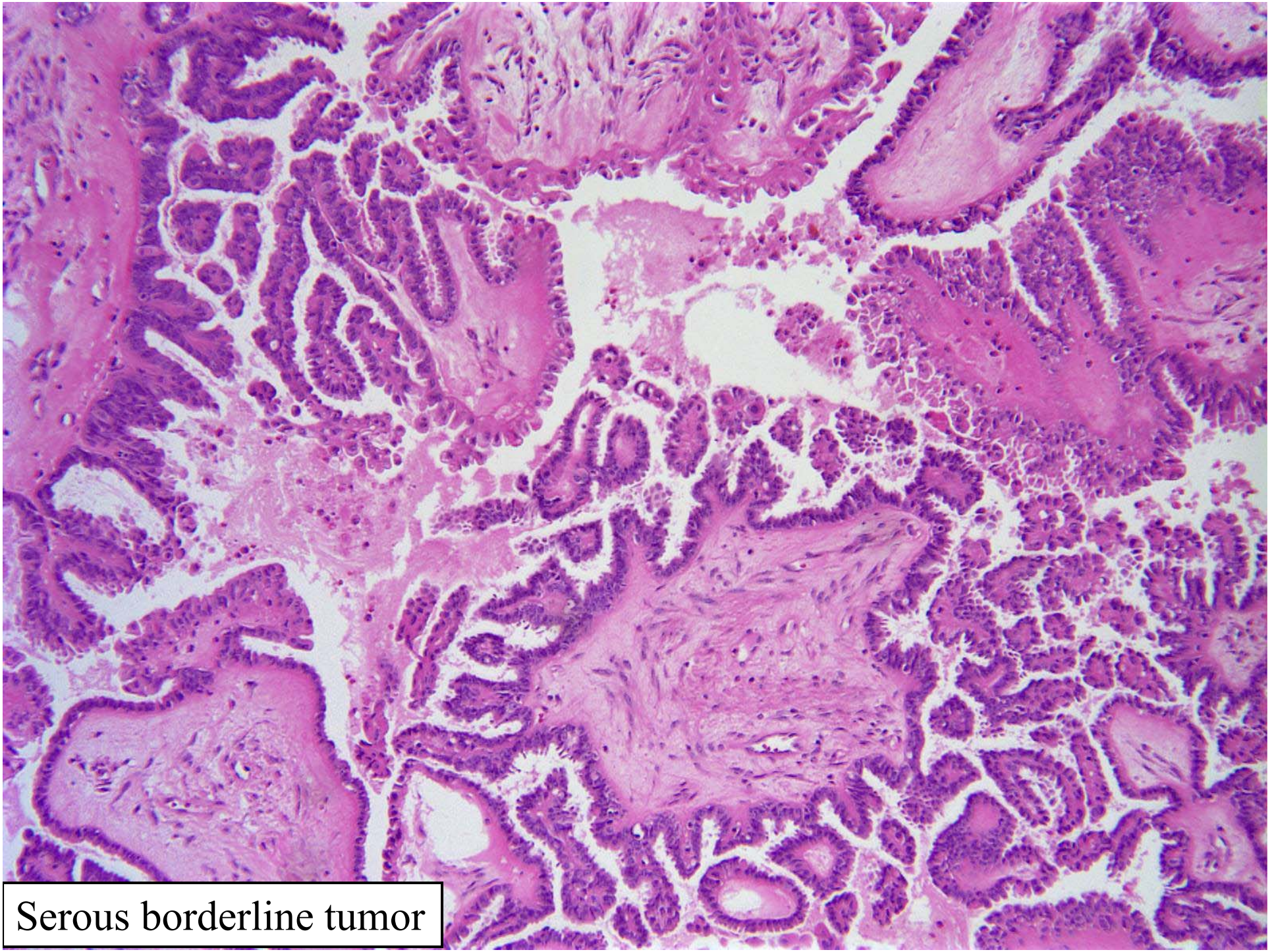
- Benign cystadenofibroma
- Serous borderline tumors
- Seromucinous BLT
- Infrequently mucinous tumor
- Rarely serous carcinomas



Serous borderline tumor


Serous borderline tumor

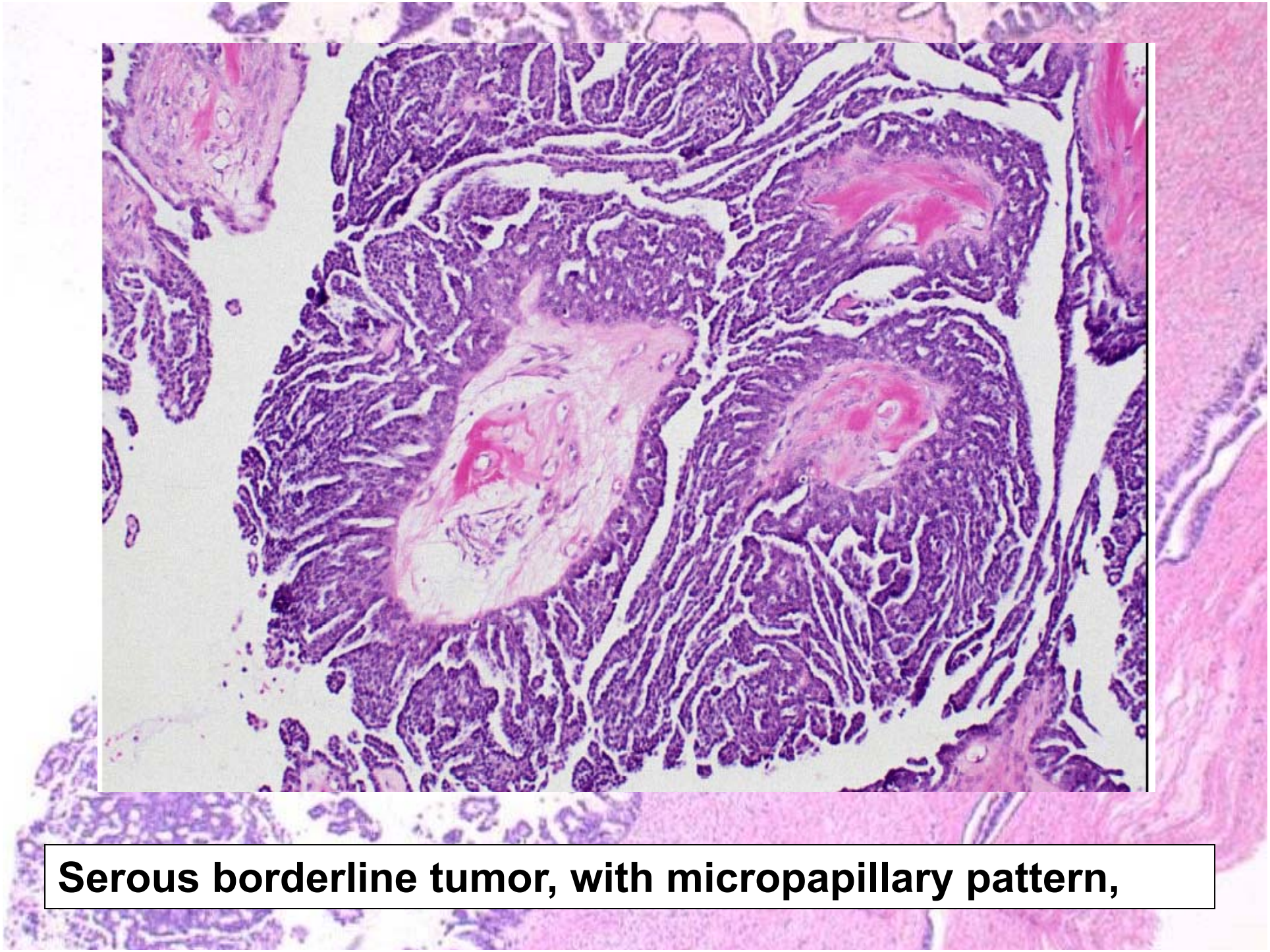

Serous borderline tumor



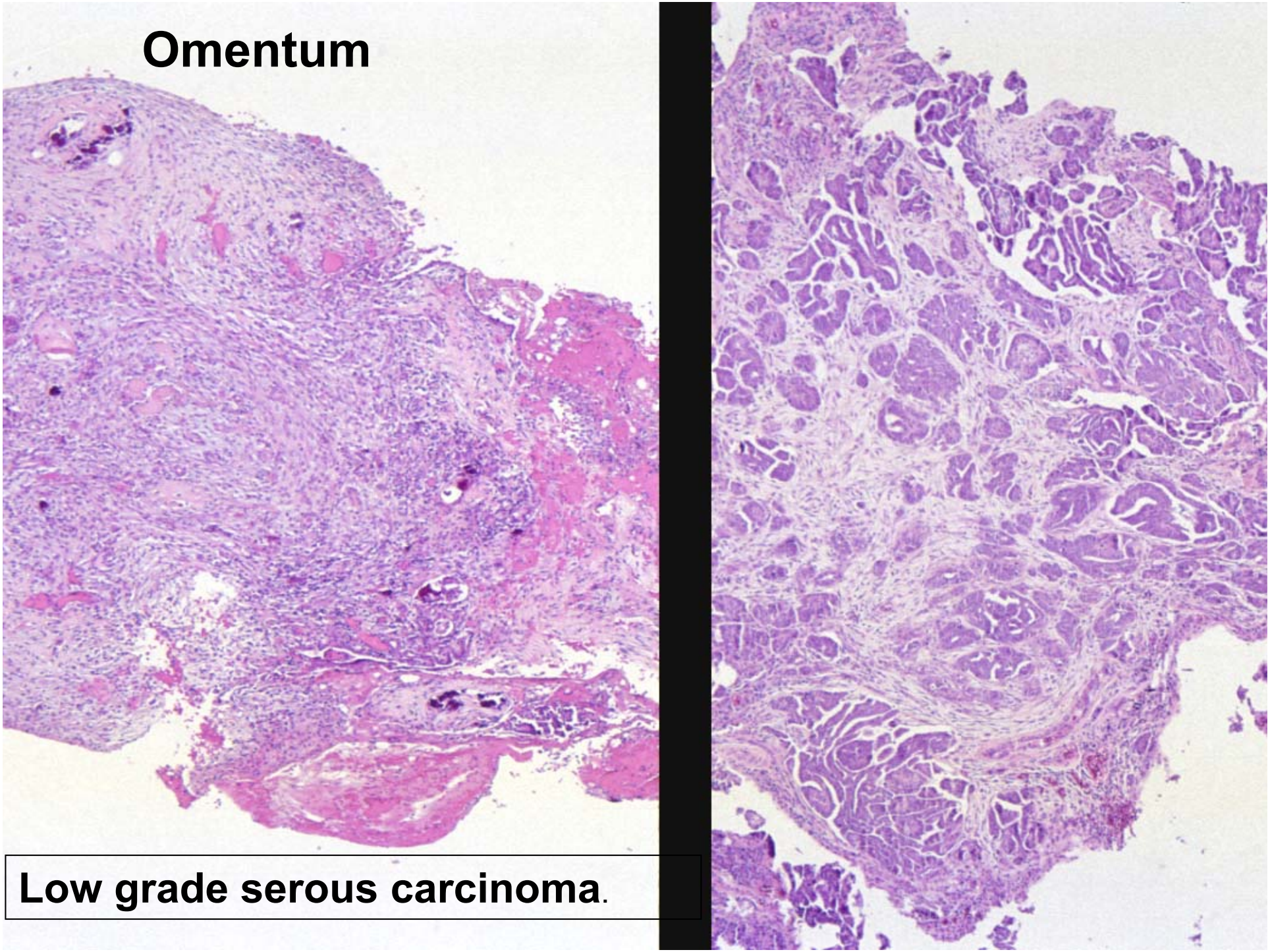
Serous borderline tumor

Case #1

- 42 y/o presents with pelvic mass.
- TAH & BSO performed



Serous borderline tumor, with micropapillary pattern,



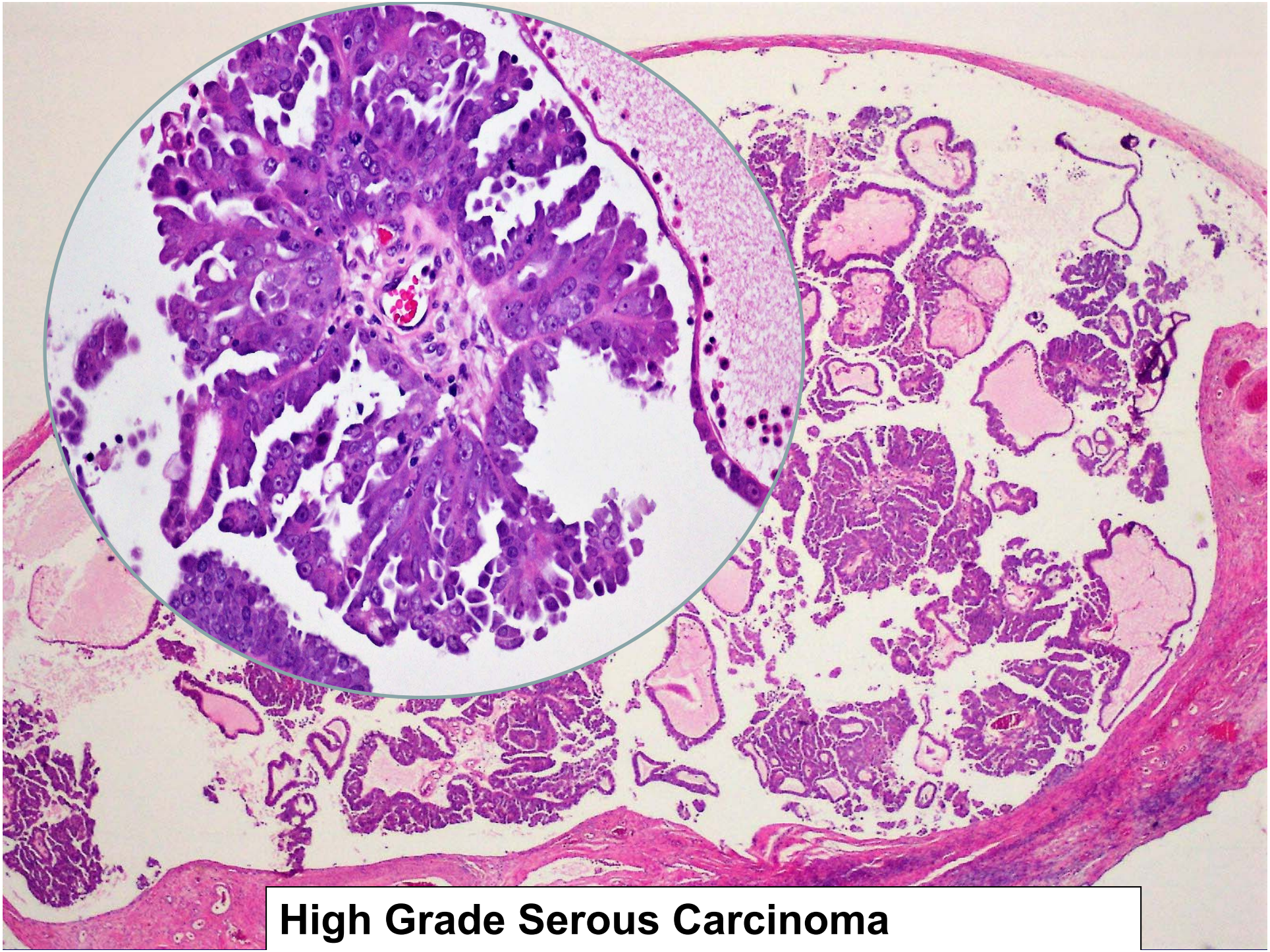
Low grade serous carcinoma.

Summery case #1:

- Serous borderline tumor, with micropapillary pattern,
  - endophytic and exophytic components are seen
  - involving both ovaries.
- Omentum: Low grade serous carcinoma.
- Lymph nodes: negative
- Cytology: positive for serous neoplasm.

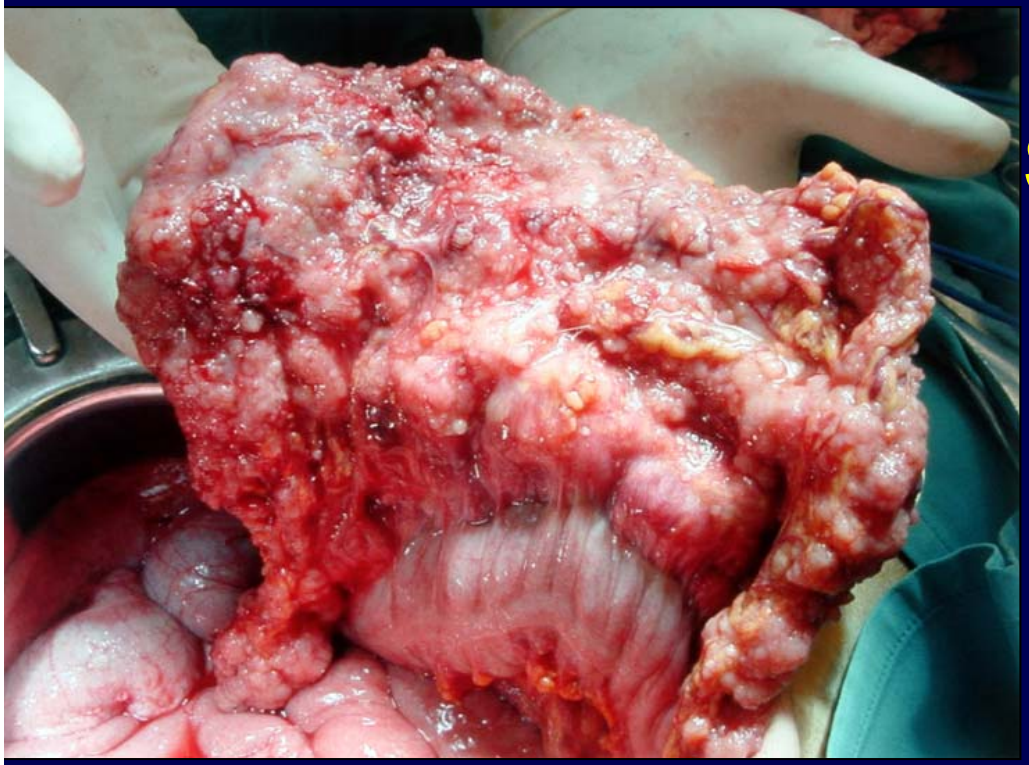
Case# 2

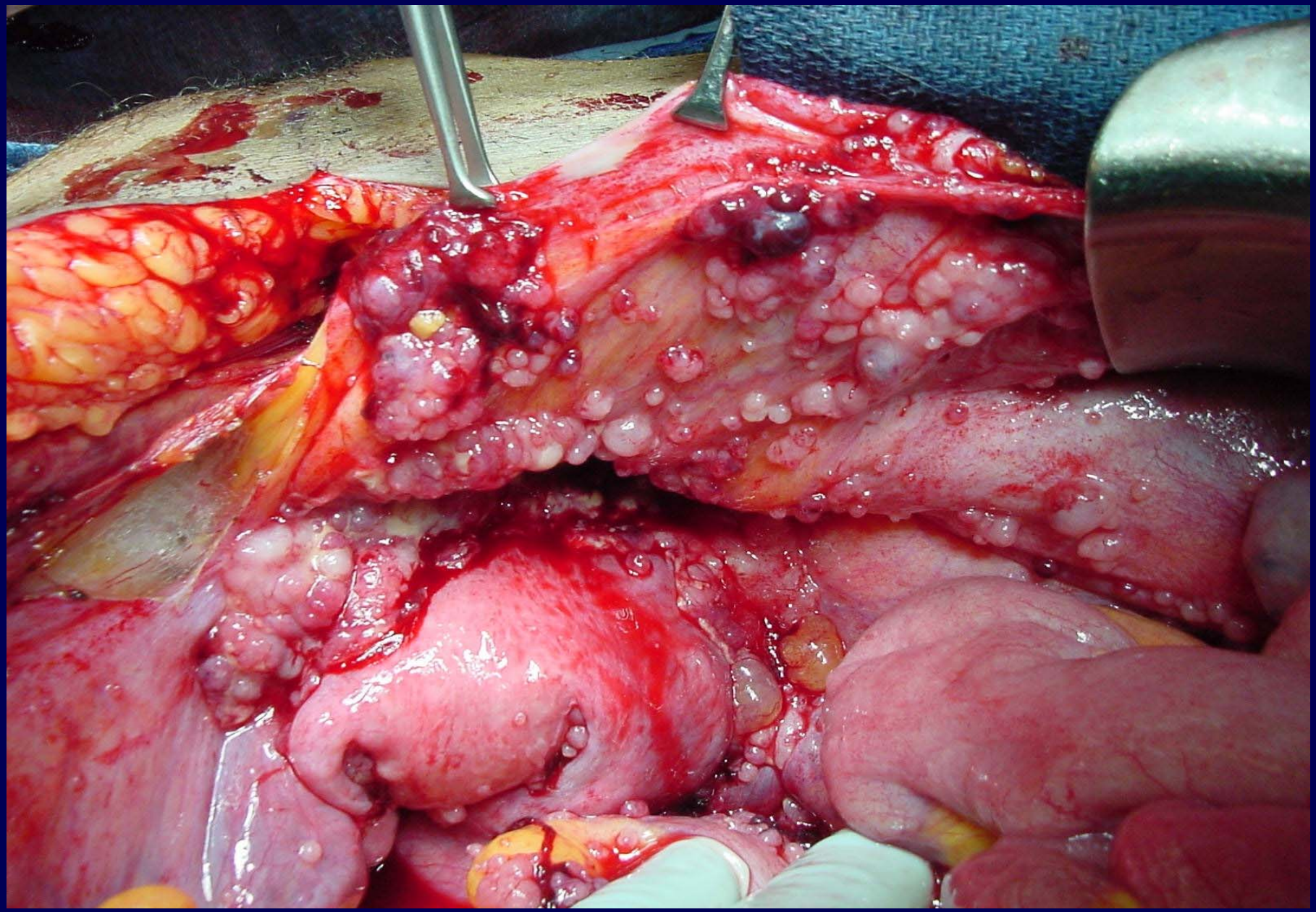
60 y/o , 2 cm ovarian mass

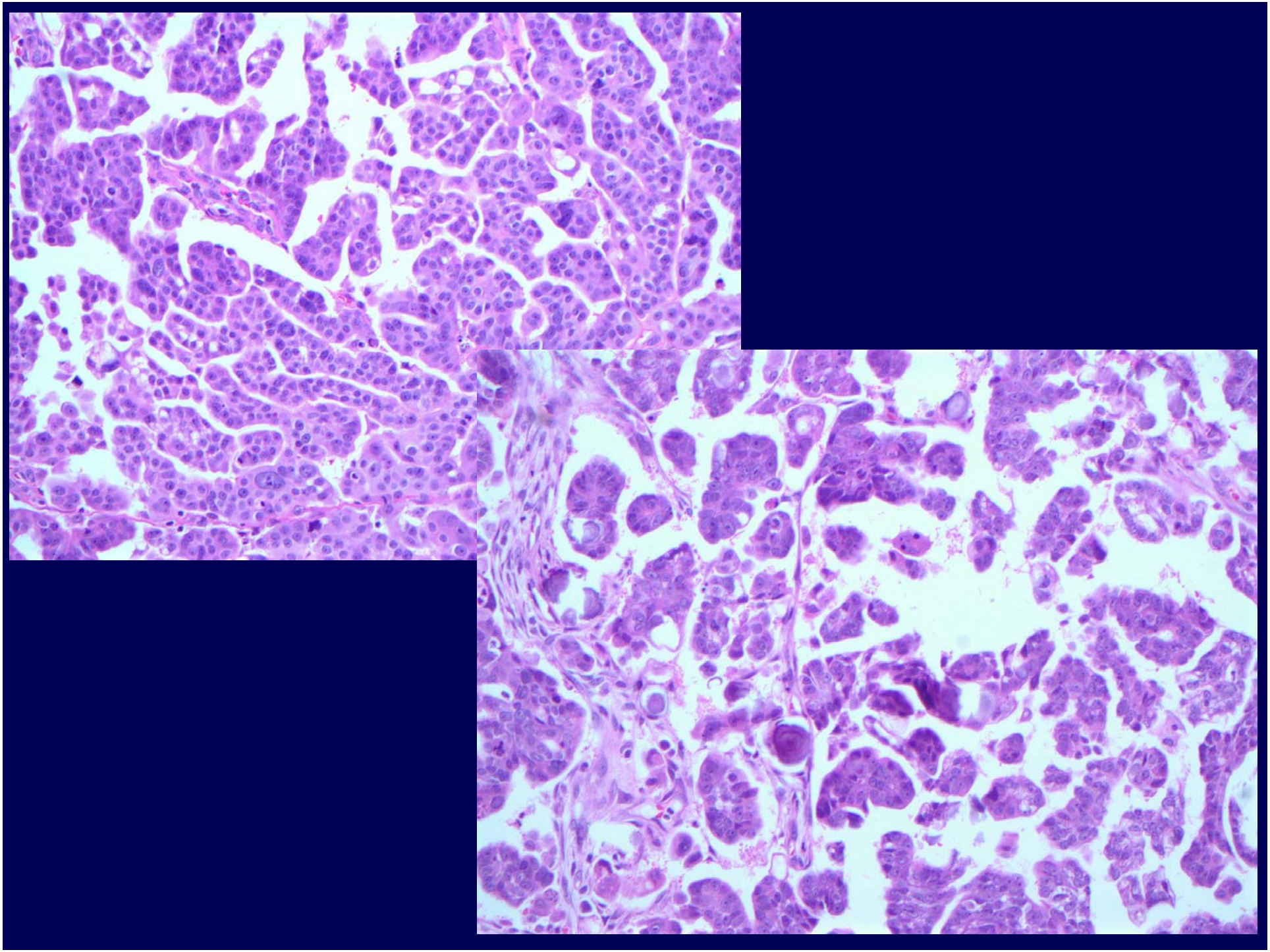


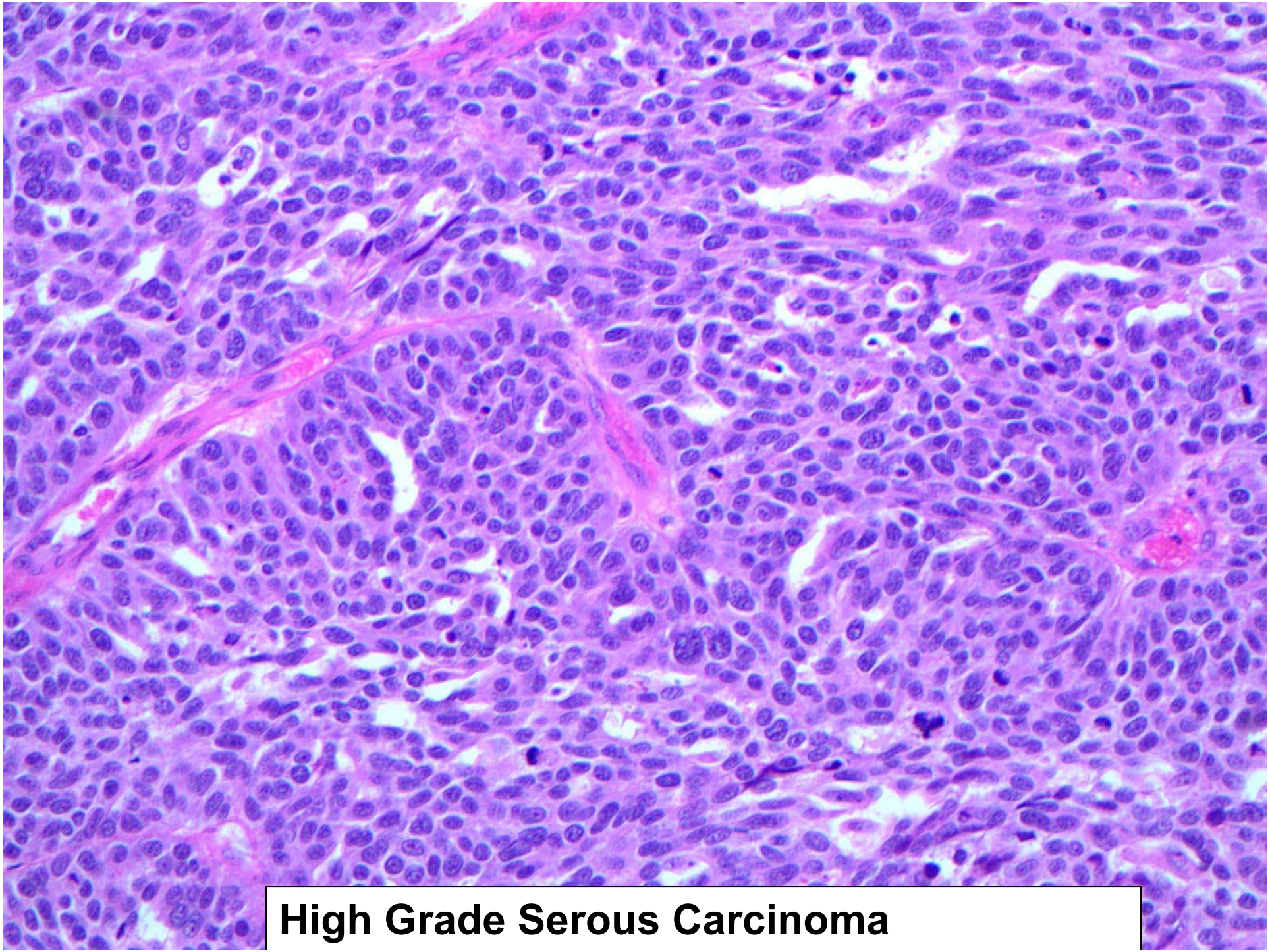
High Grade Serous Carcinoma

High Grade Serous carcinoma









High Grade Serous Carcinoma

Ovarian Mucinous Tumors

Ovarian Mucinous Tumors

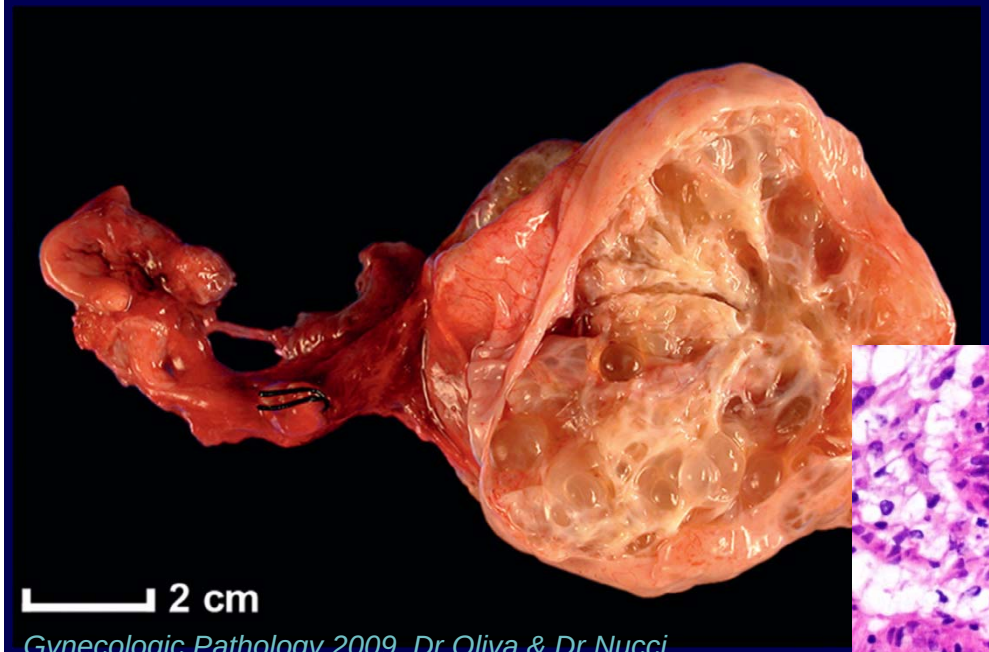
- Usually unilateral (>95%) and large in size
- Multiloculated cysts filled by thick gelatinous fluid
- ***Benign*** cystadenomas: thin walls with smooth inner lining
- ***Borderline*** tumors: may have subtle areas of papillary projections
- ***Malignant*** tumors: may have solid areas and necrosis

Ovarian Mucinous Tumors

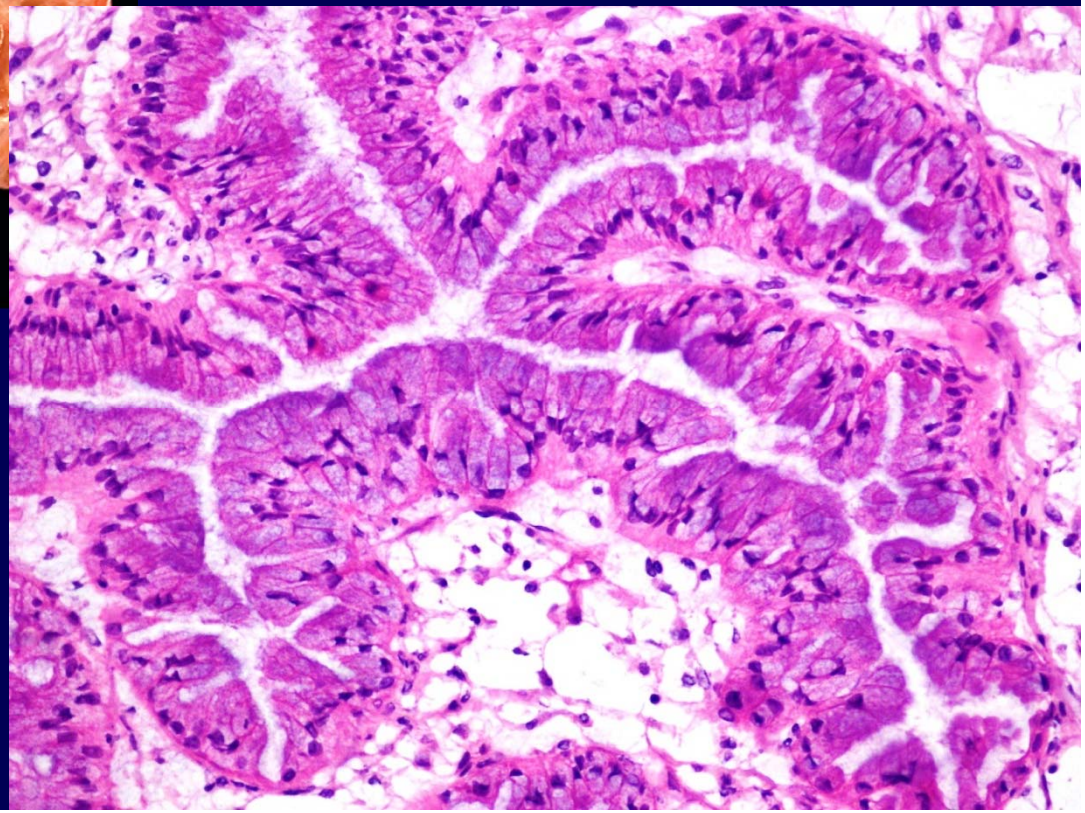
- Surface involvement is not common (think of metastatic tumor)

- Extensive sampling is required (may vary histologically within the tumor)
  - spectrum of morphologic changes: benign, BLT and malignancy.

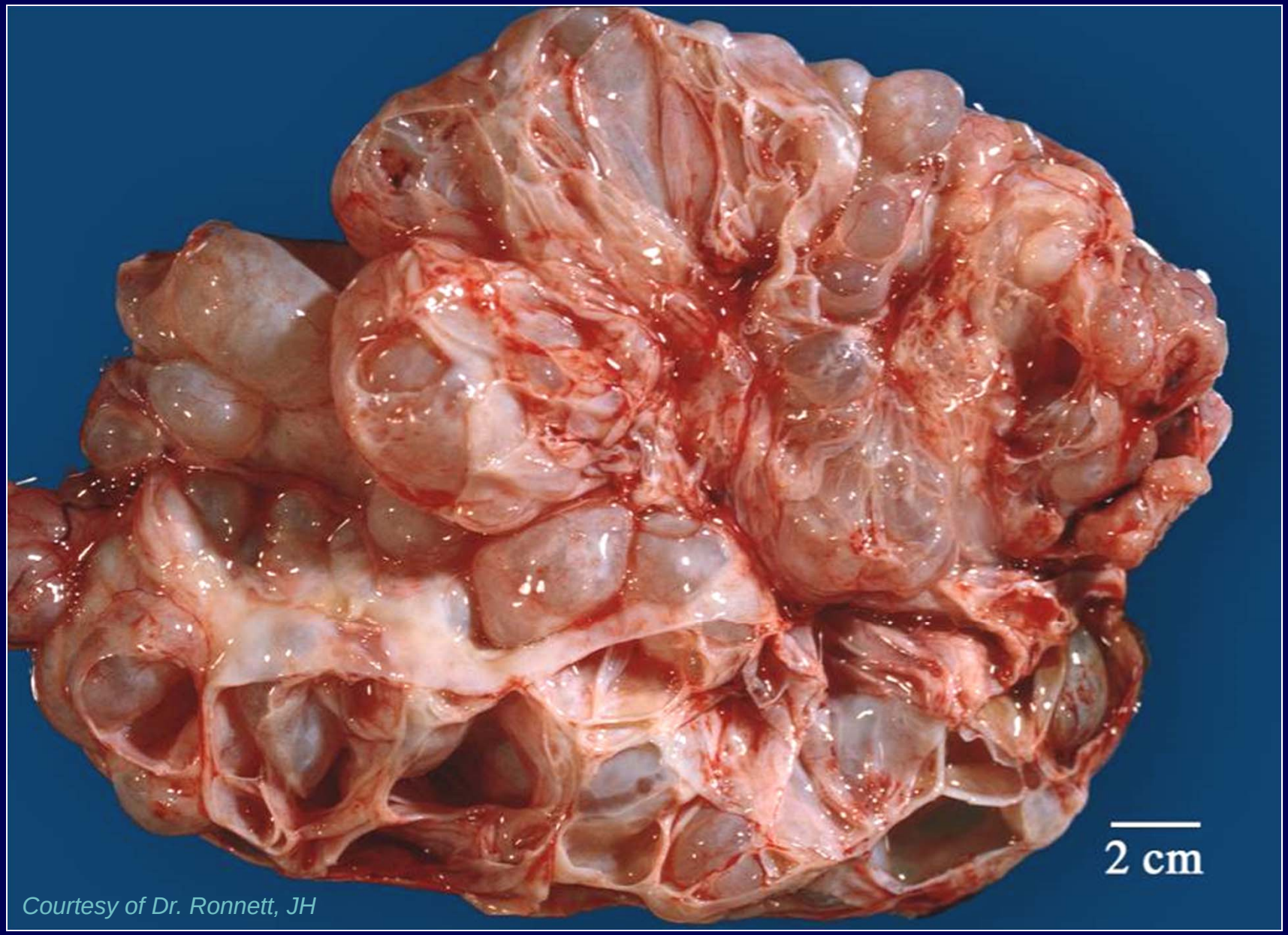
Mucinous Cystadenoma



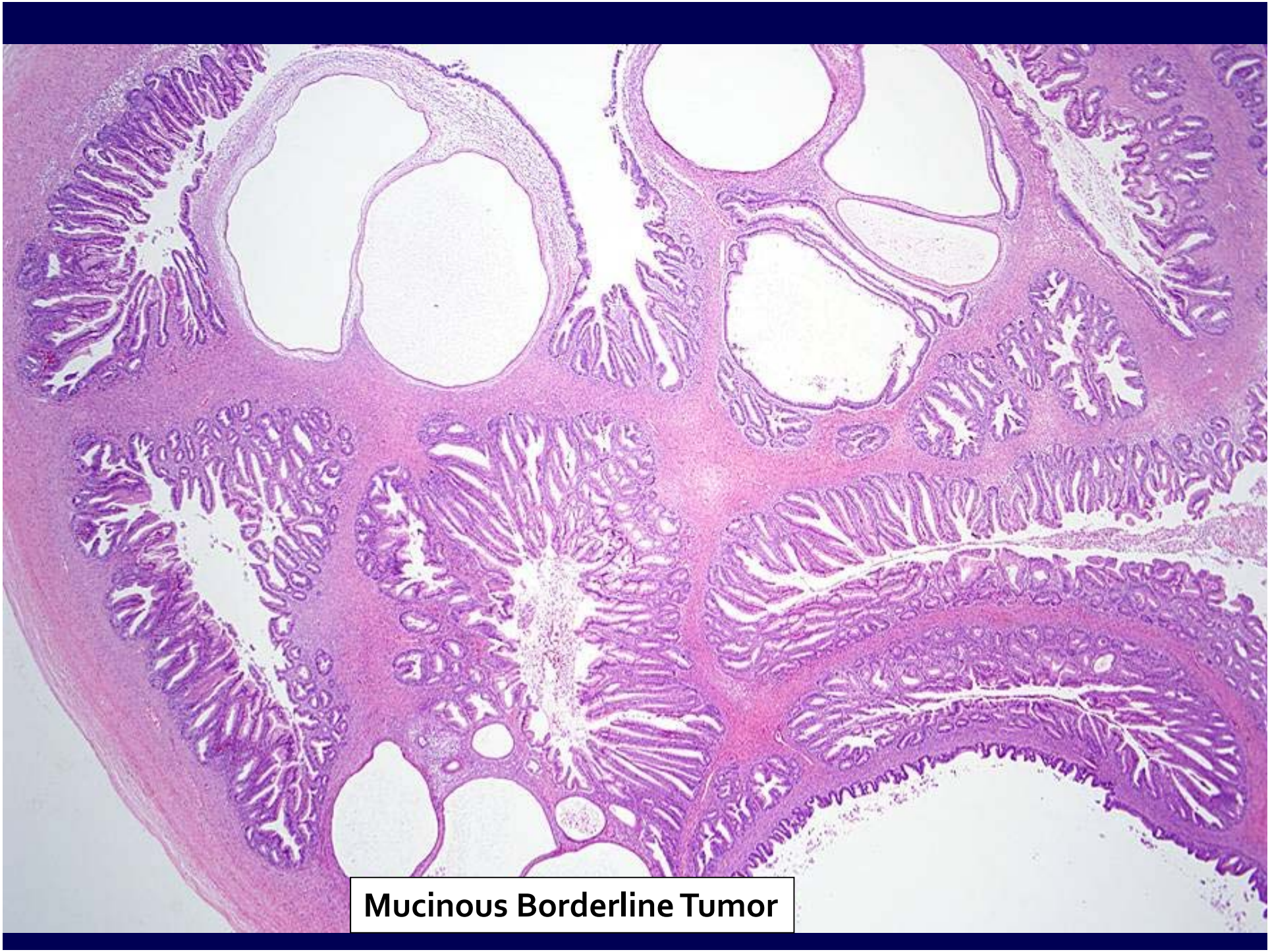
Gynecologic Pathology 2009, Dr Oliva & Dr Nucci

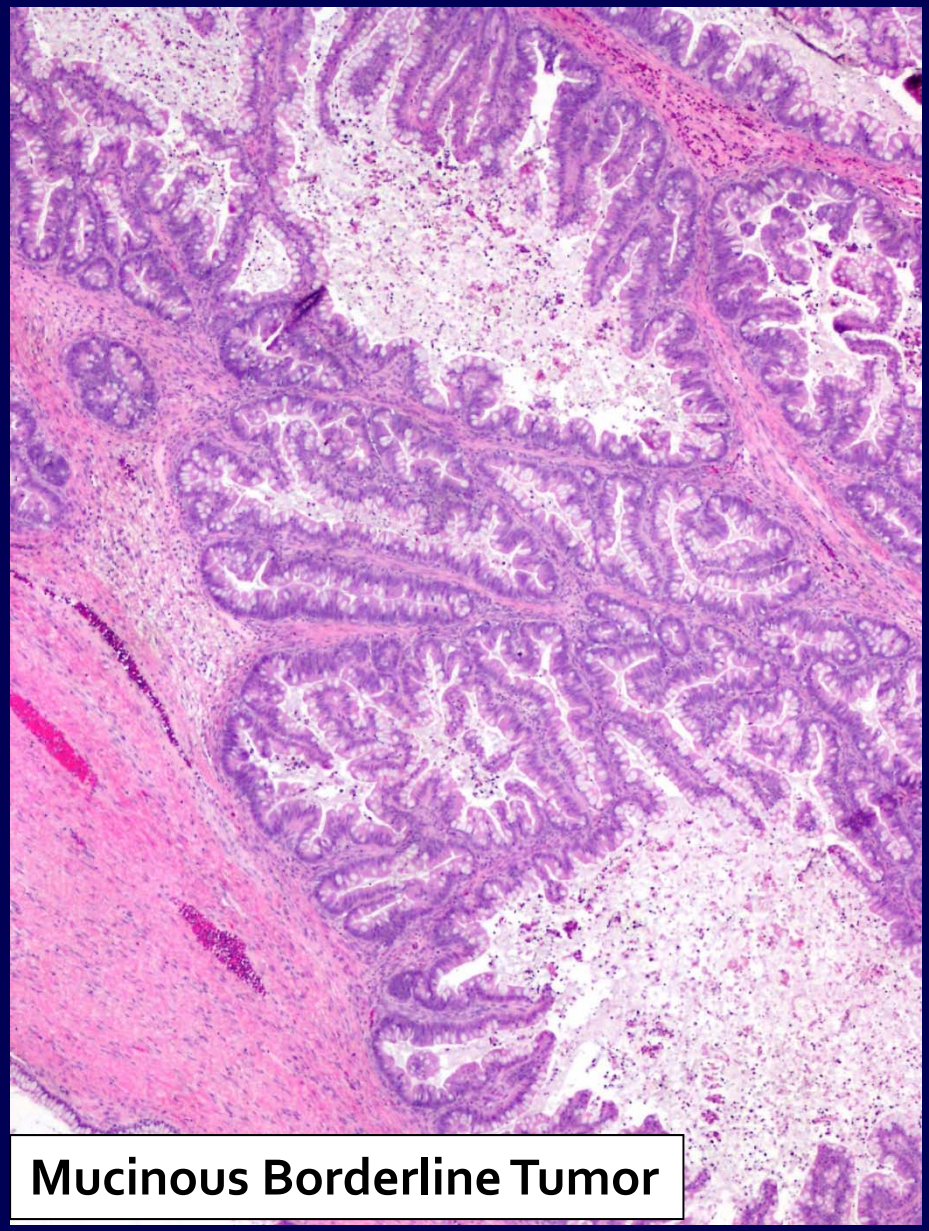


Mucinous Borderline Tumor

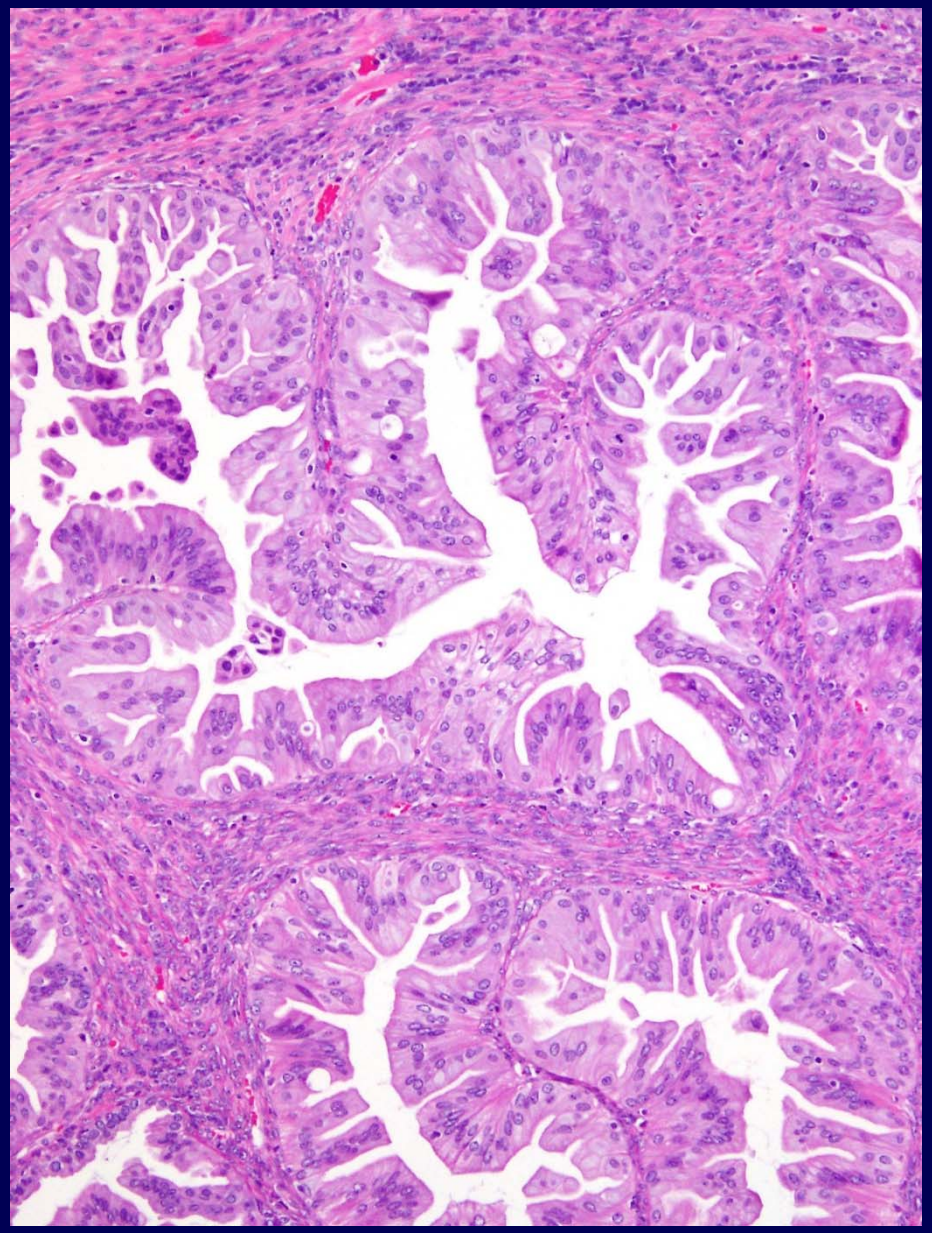


Courtesy of Dr. Ronnett, JH


Mucinous Borderline Tumor

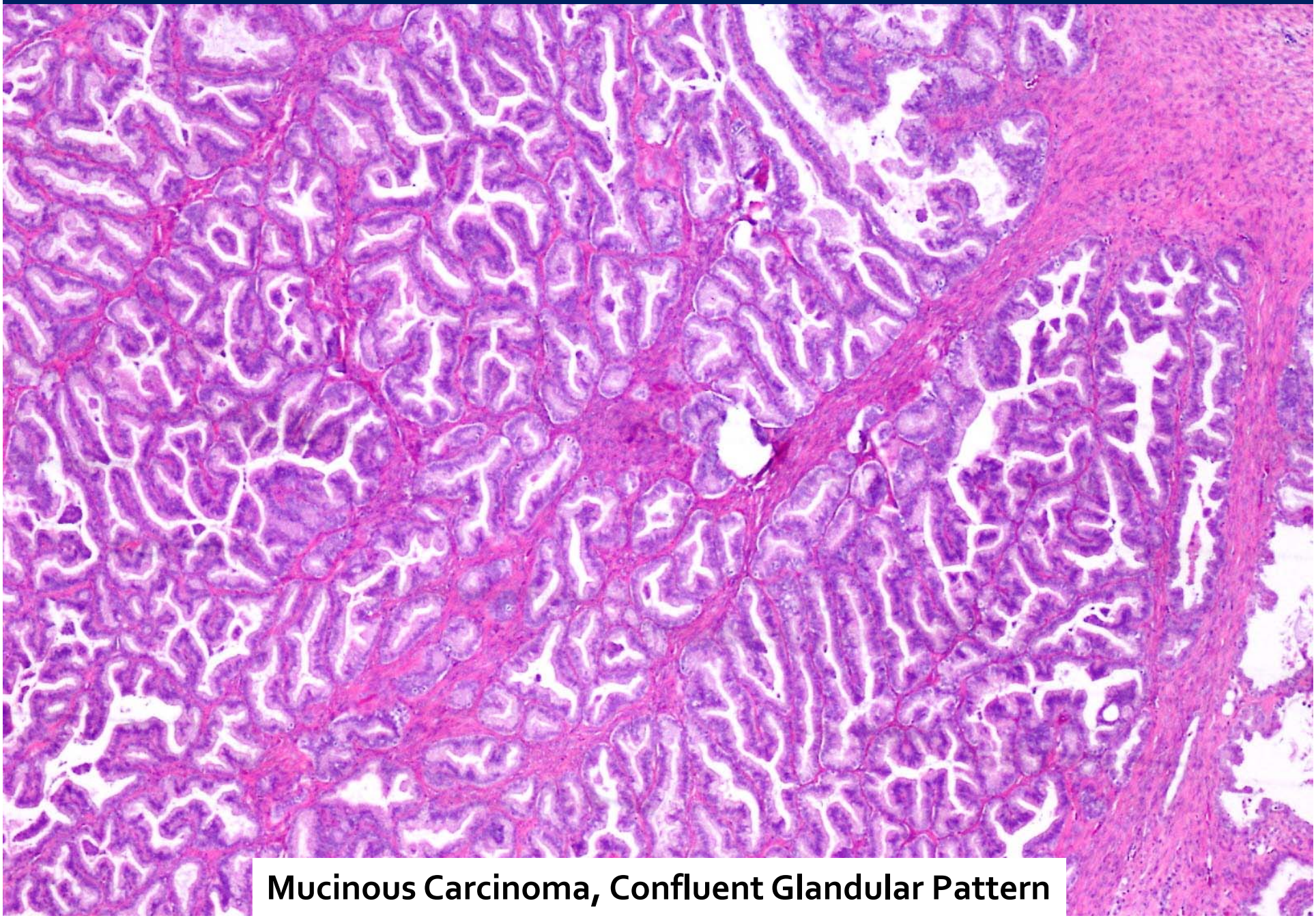


Mucinous Borderline Tumor



Complex Papillary Architecture Favor
Ovarian Primary Tumor

Expansile Pattern of Invasion Favors Ovarian ***Primary*** Tumor

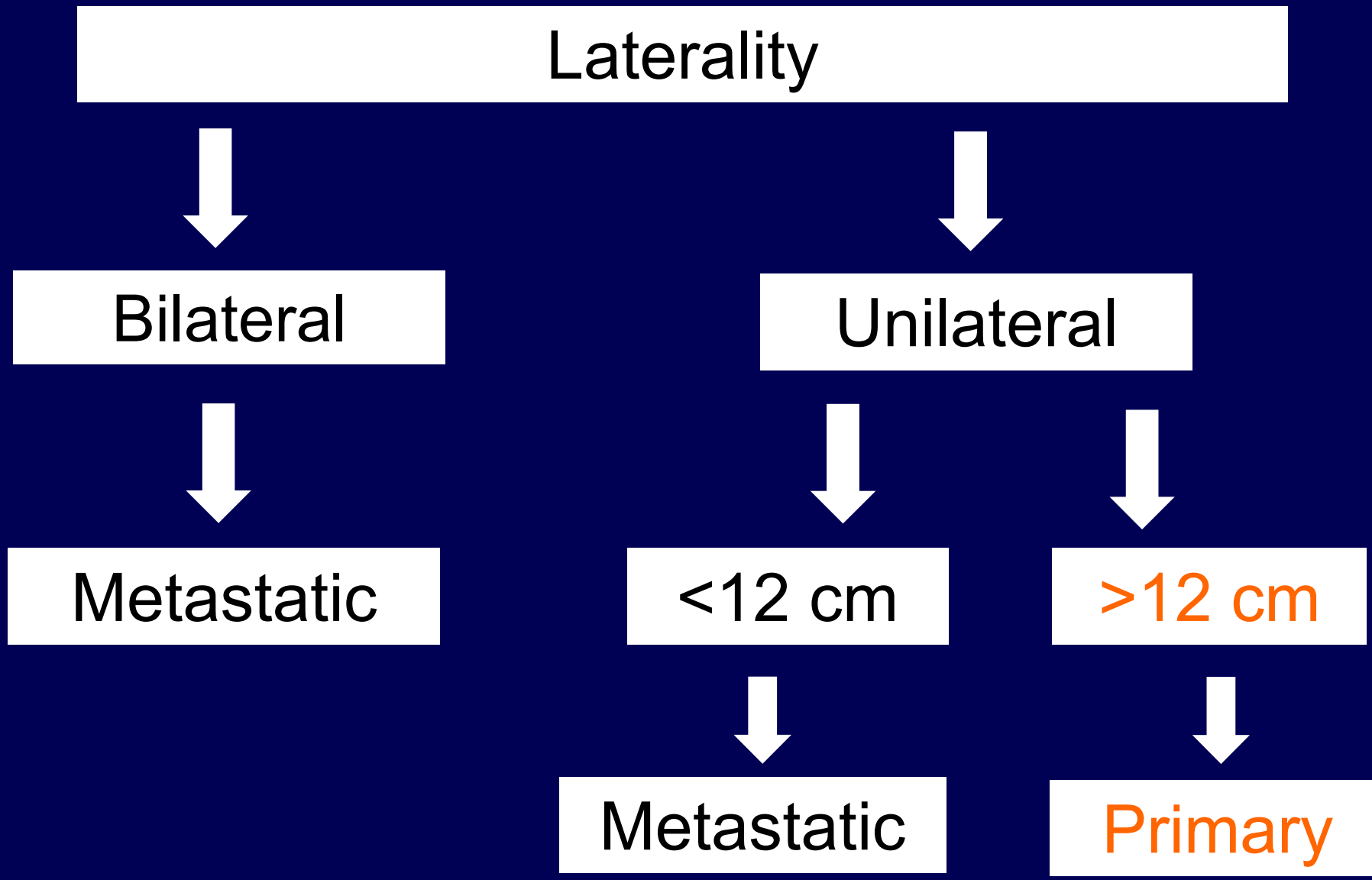


Mucinous Carcinoma, Confluent Glandular Pattern

Metastatic Tumors that Mimic Primary Ovarian mucinous Tumors

- Colorectal adenocarcinoma
- Appendiceal adenocarcinoma
- Pancreaticobiliary adenocarcinomas
- Gallbladder adenocarcinoma
- Gastric adenocarcinoma
- Endocervical adenocarcinoma
- Pulmonary adenocarcinoma

Primary vs. Metastatic Mucinous Tumor



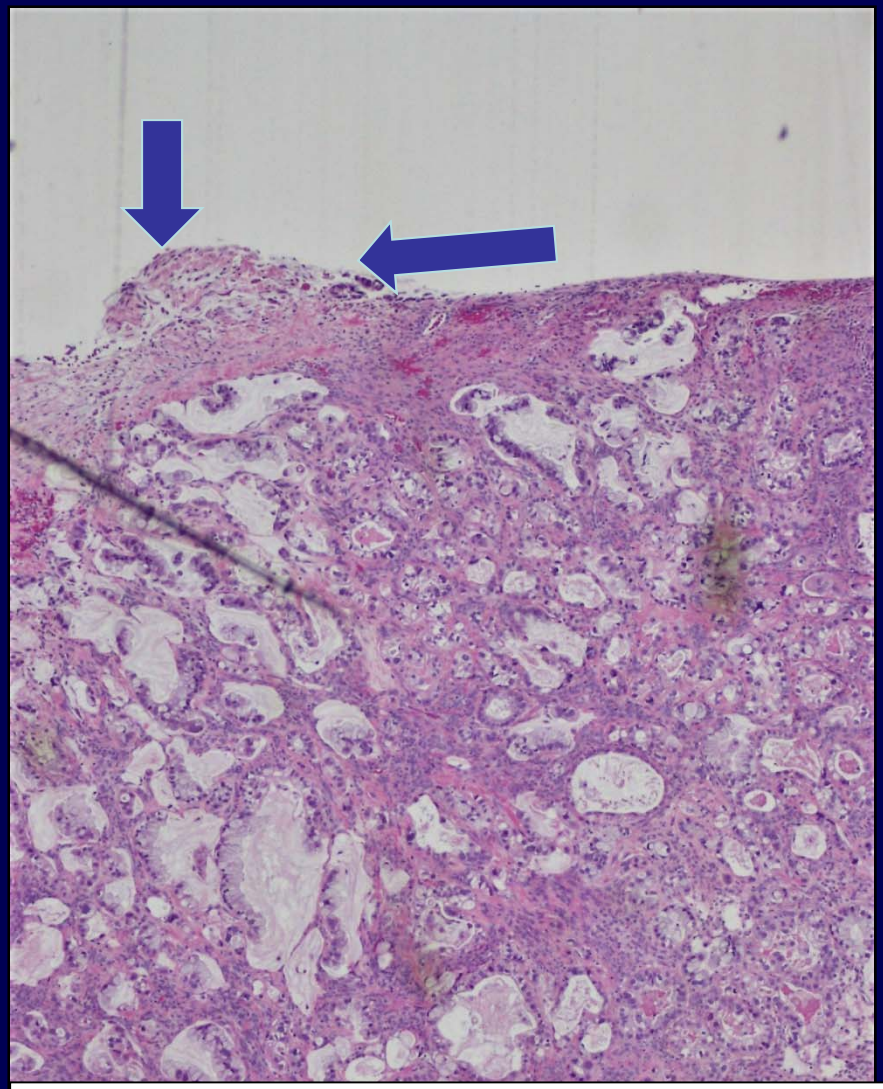
Bilateral Ovarian Involvement by Metastatic Mucinous Carcinoma

Secondary/metastatic vs. Primary Mucinous Tumor

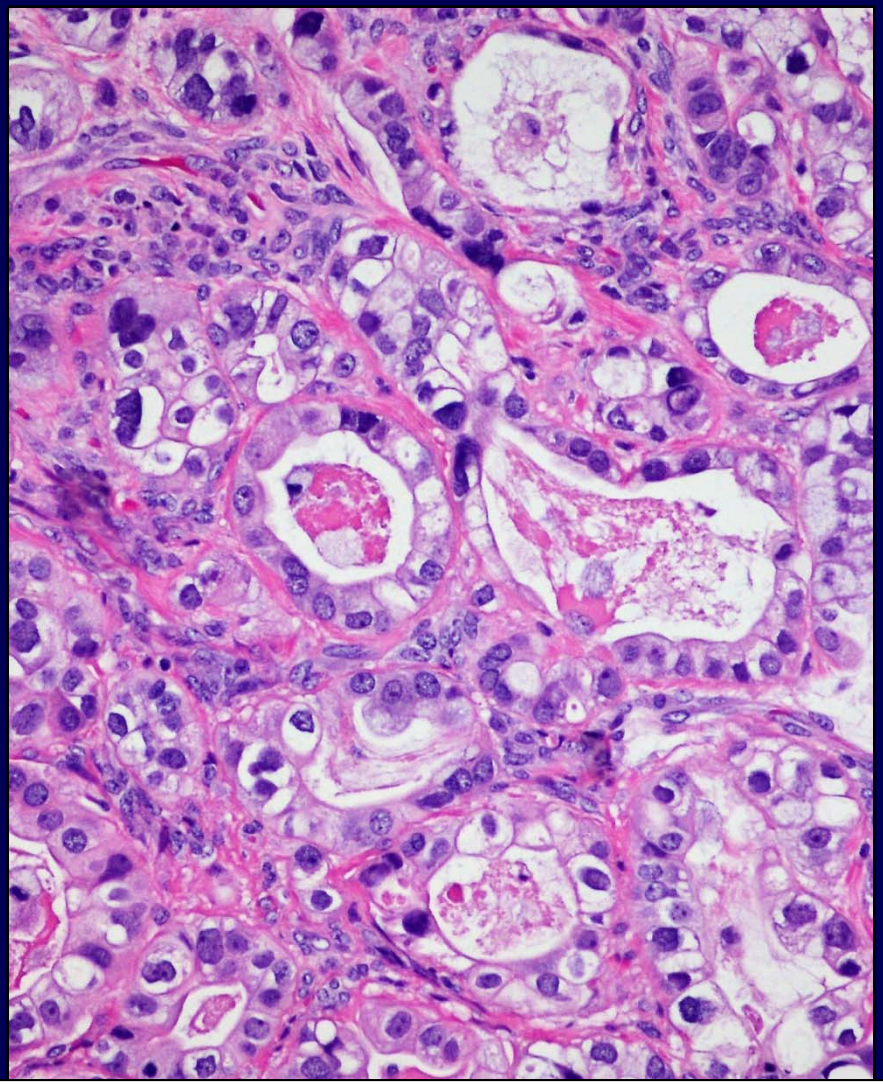
	Primary Ovarian Tumor	Secondary/Metastatic Tumor
Laterality	Unilateral (>95%)	Bilateral (> 65%)
Size	Large (>12-15 cm), mean 21 cm	Often smaller (<12 cm) but can be large
Gross features	Multicystic and/or solid without parenchymal nodules	Often ***nodular*** with surface involvement. Can be cystic with smooth outer surface
Microscopic features	Well-diff., mostly confluent pattern of invasion	Destructive Stromal Invasive Pattern
extraovarian tumor	Typically stage I	Often extraovarian tumor

Surface involvement, destructive growth pattern and marked atypia ~ metastasis

Courtesy of Dr. Ronnett, JH



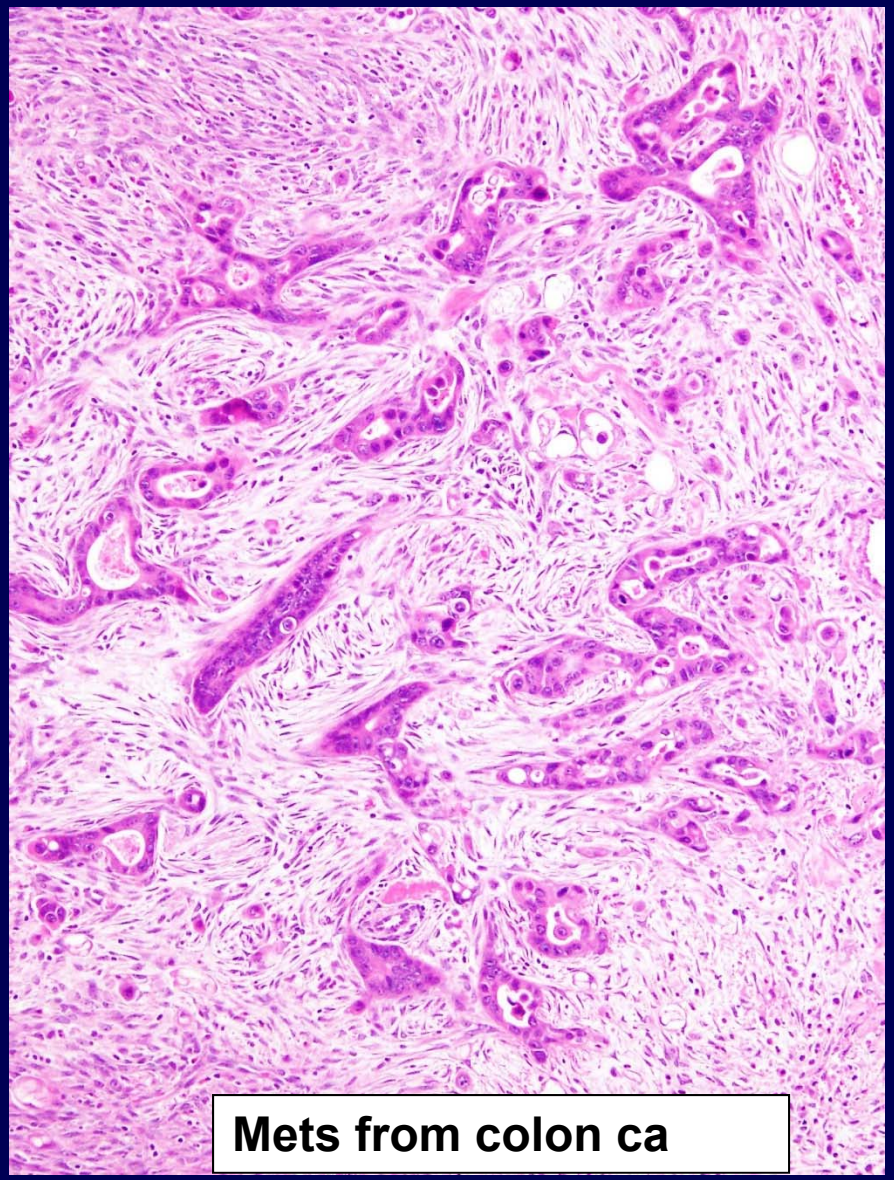
Met from Gallbladder ca , FS section



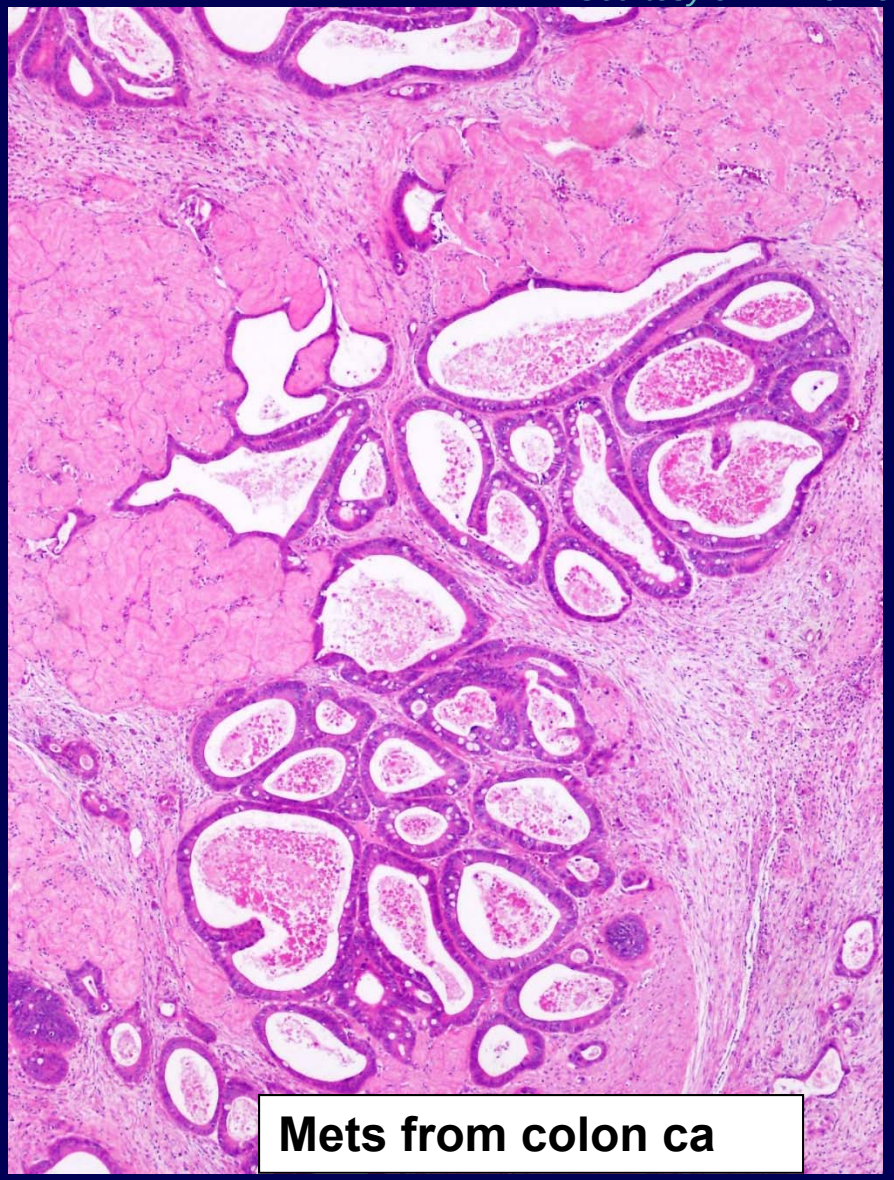
Met from Gallbladder ca , Per. section

Angulated glands, severe desmoplastic reaction and dissecting the corpora albicantia ~ mets

Courtesy of Dr. Ronnett,



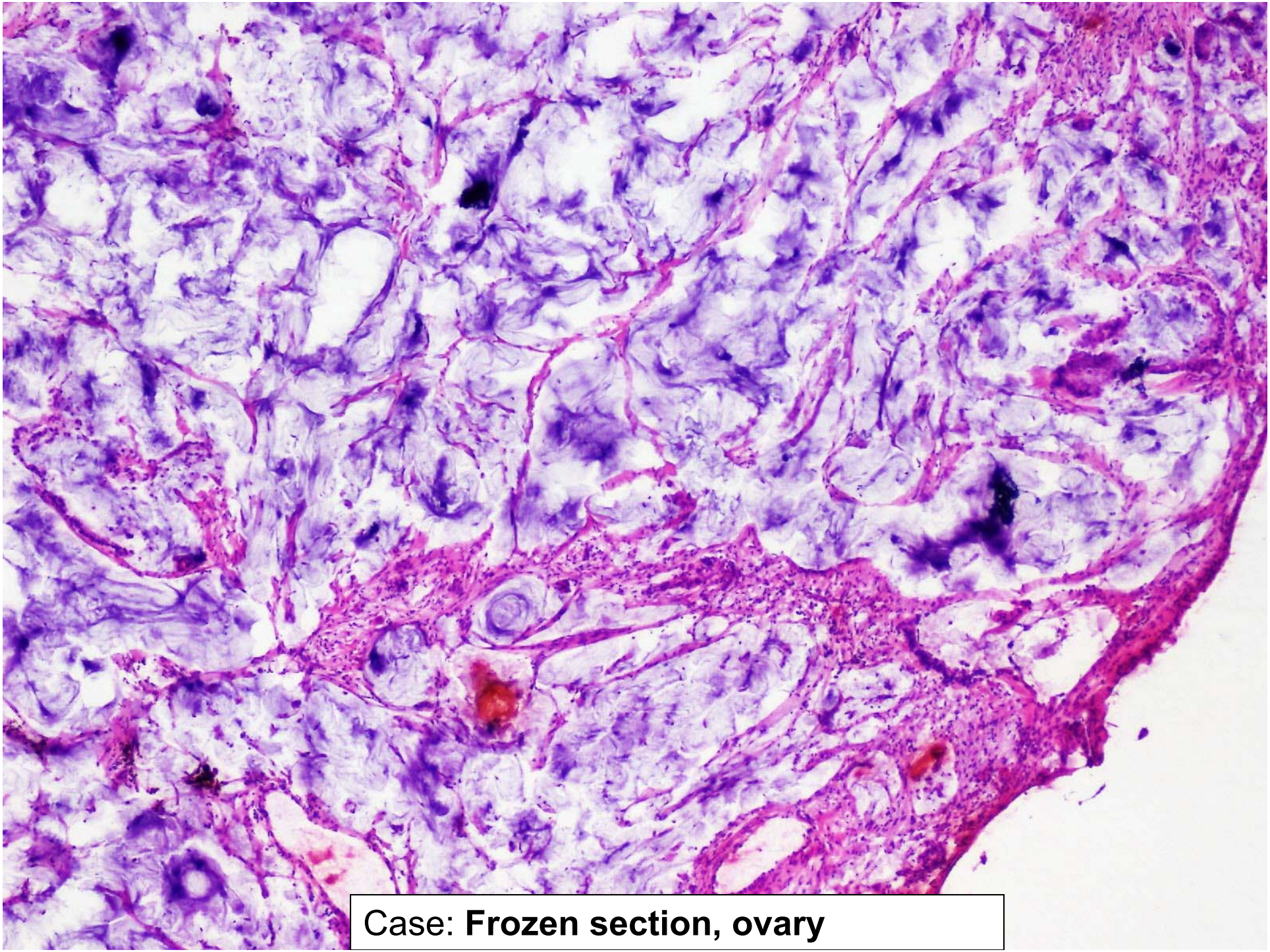
Mets from colon ca

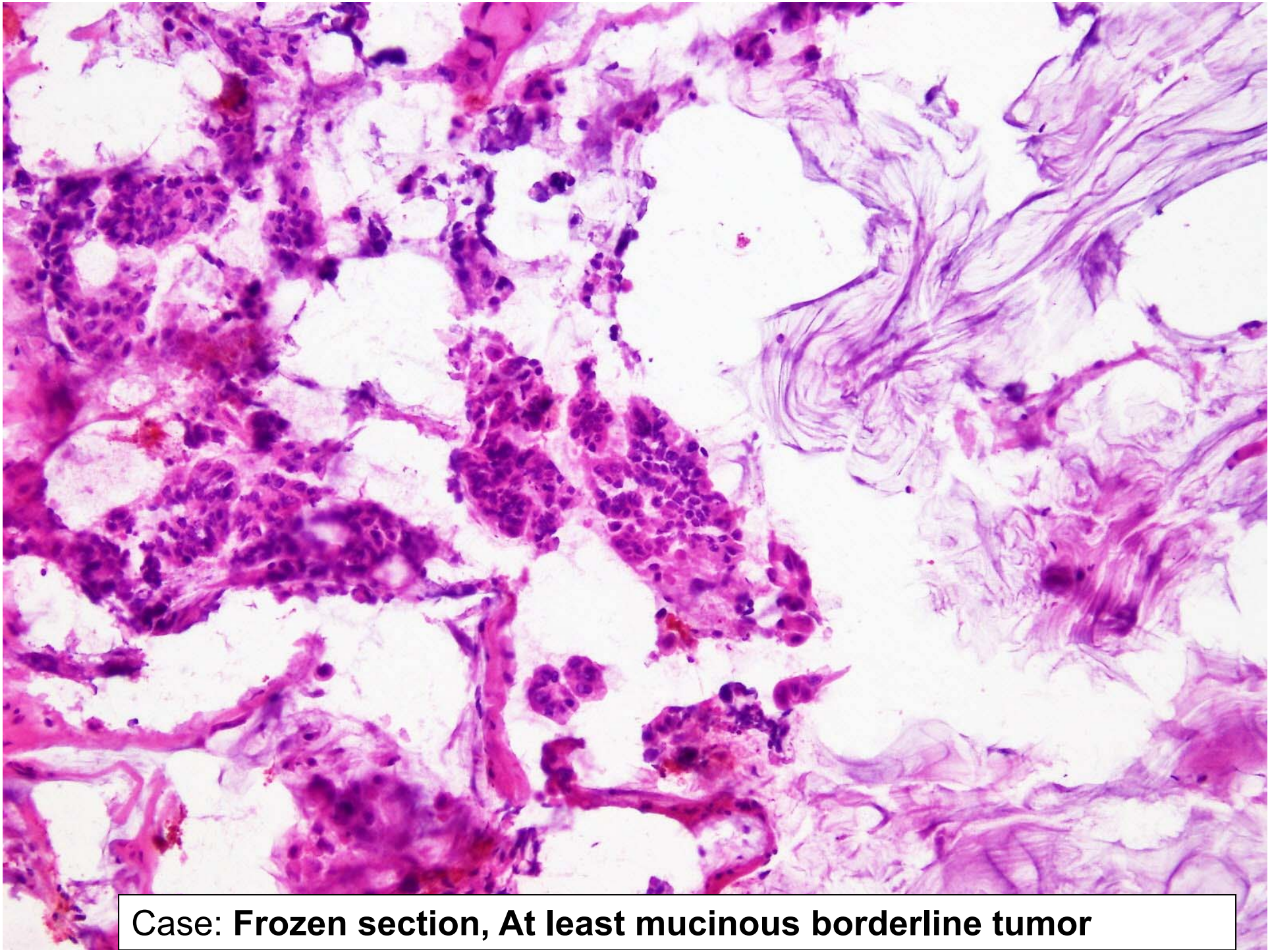


Mets from colon ca

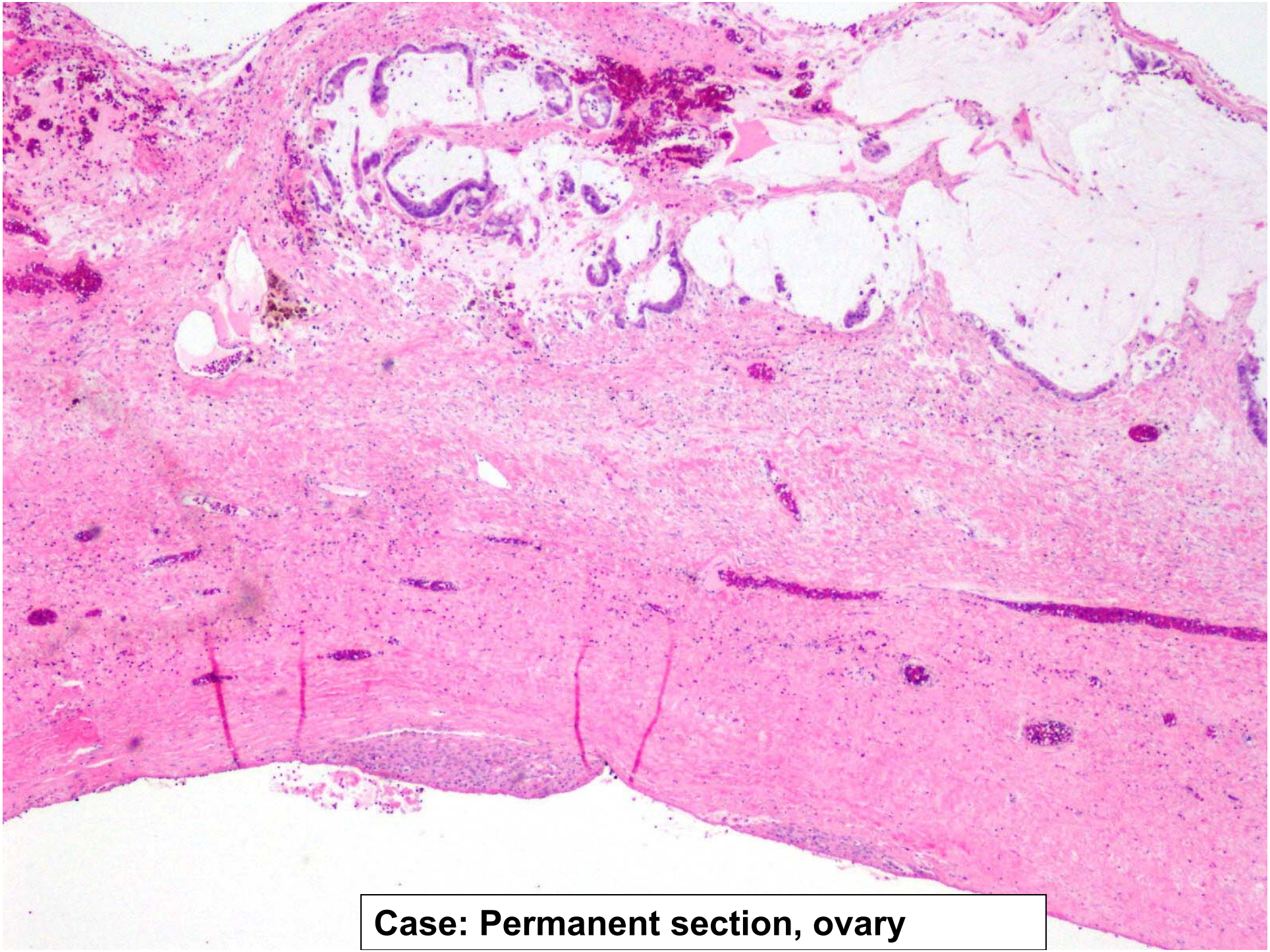
Case #3

- 44 year-old female
- Left ovary measures 3.5 x 3 x 1 with cystic mucinous cut surfaces
- Right ovary measures 3 x 2.5 x 1.5 with cystic mucinous cut surfaces

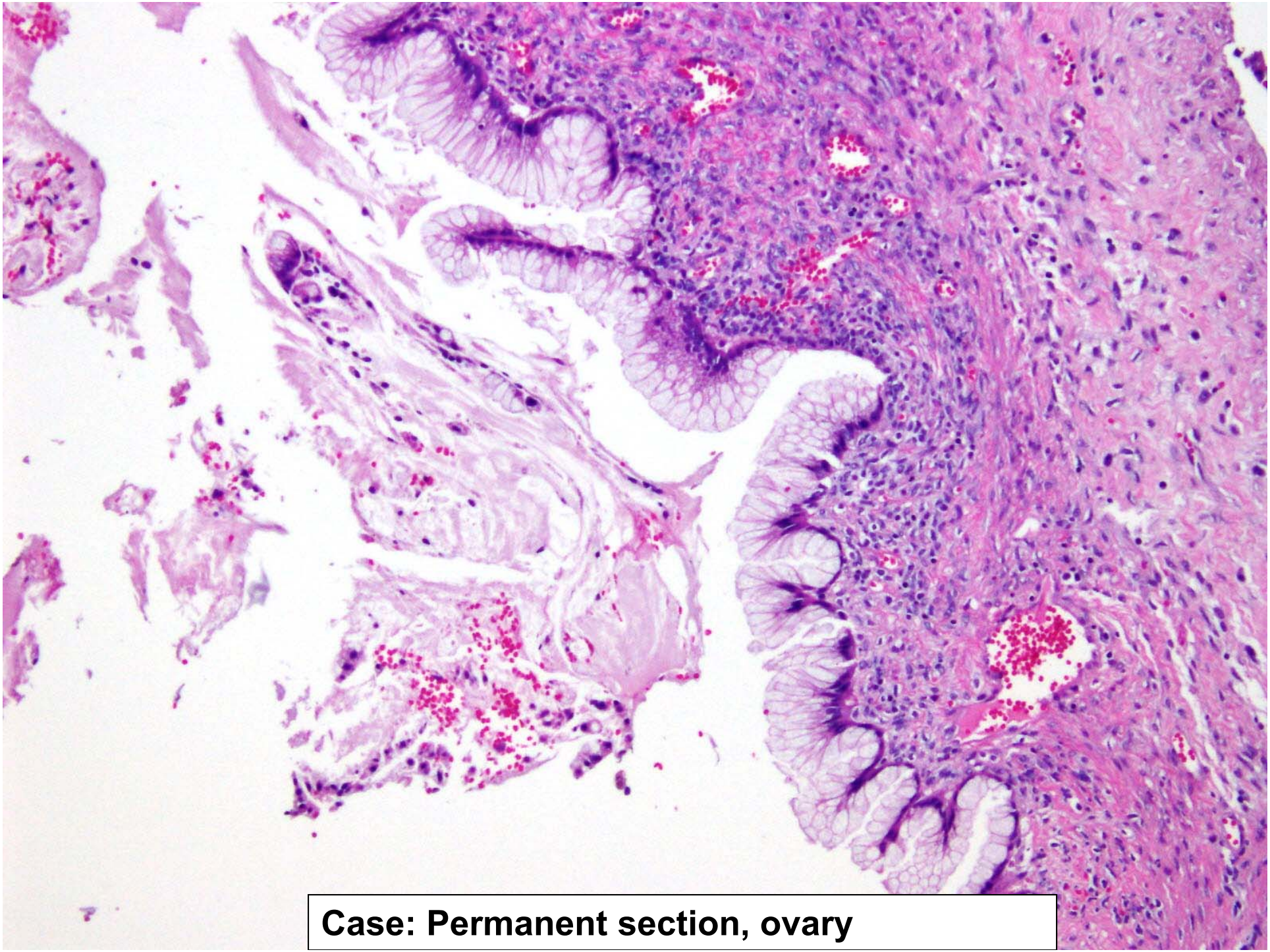

Case: **Frozen section, ovary**



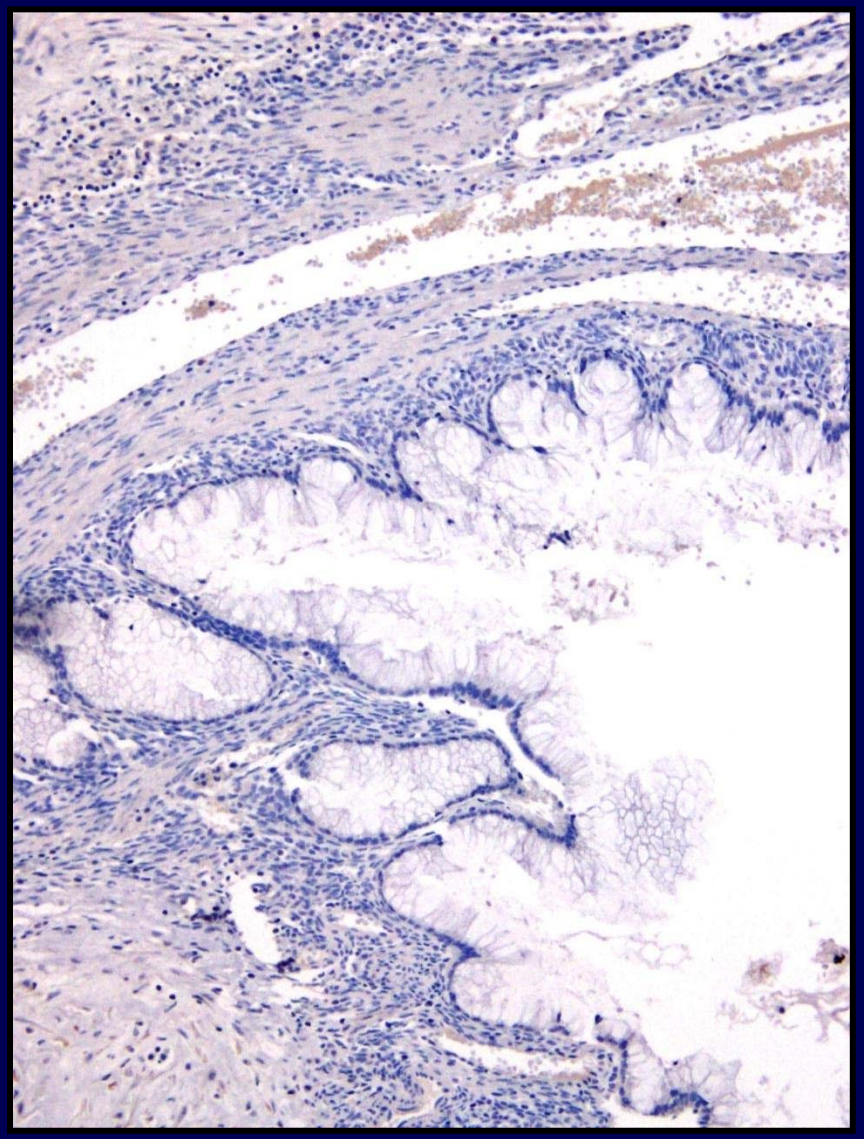
Case: **Frozen section, At least mucinous borderline tumor**



Case: Permanent section, ovary



Case: Permanent section, ovary



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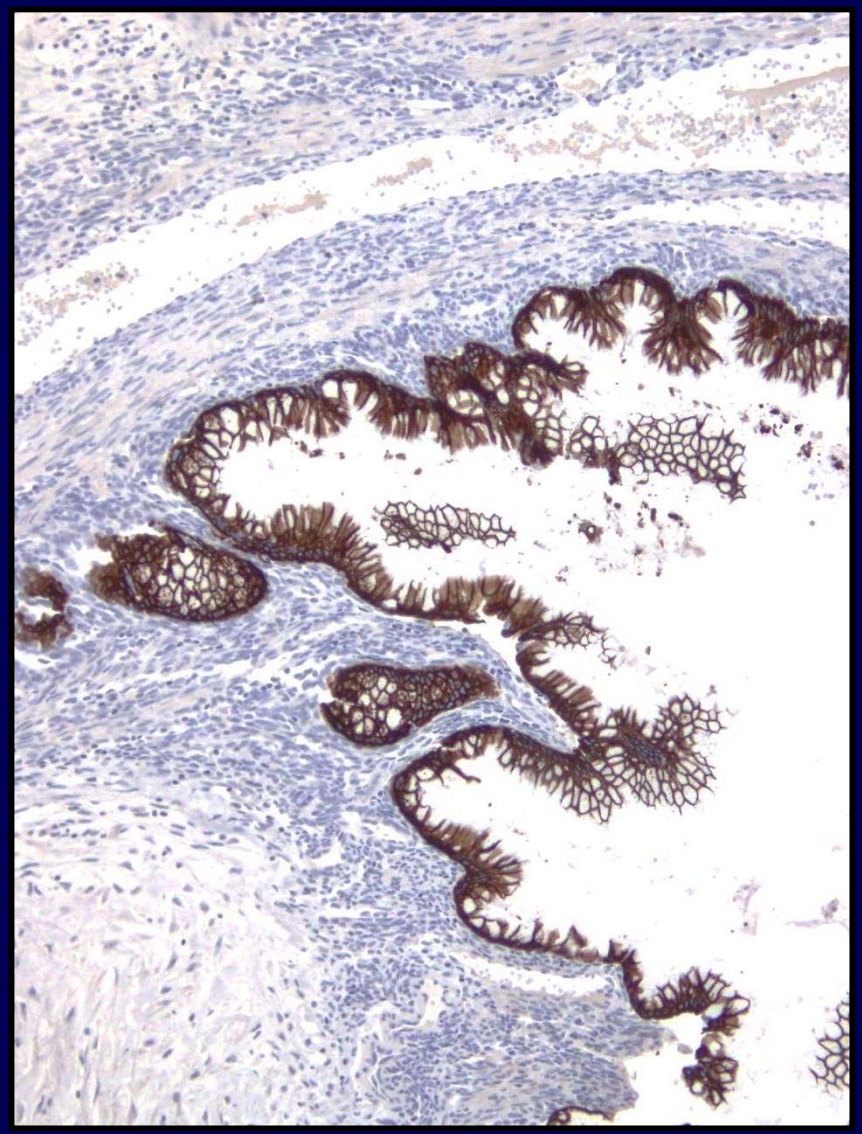

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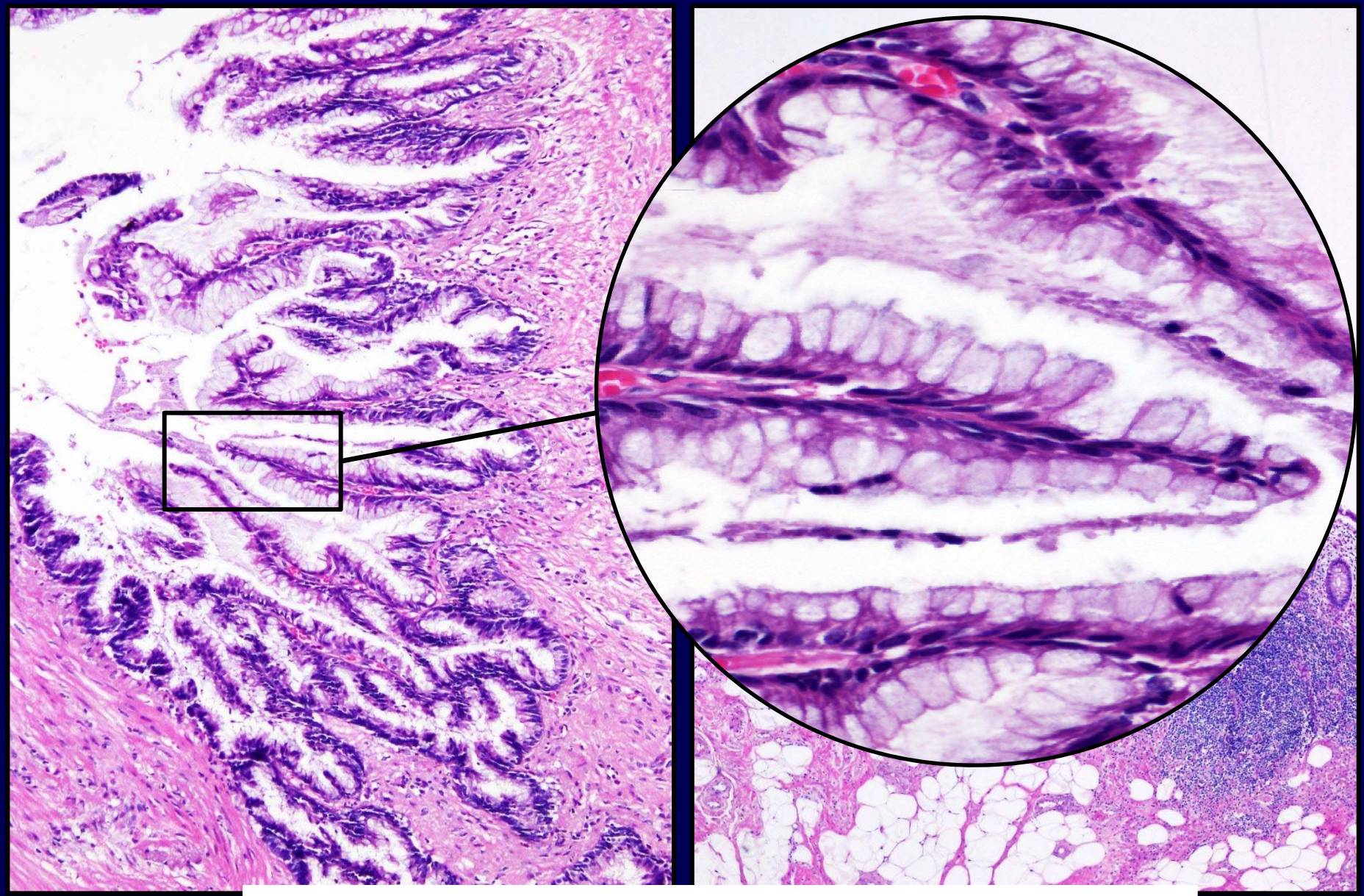
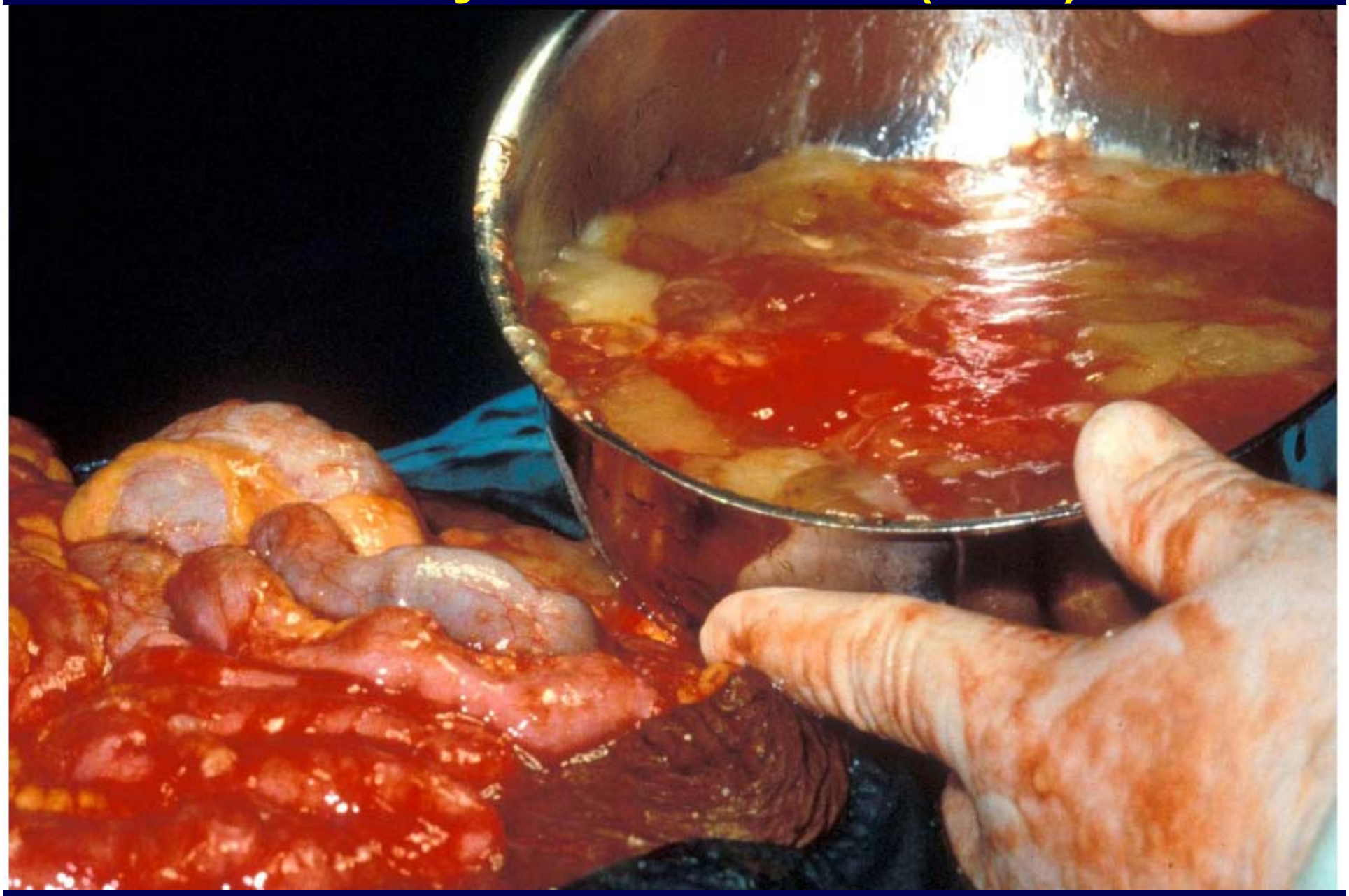
Summery Case #3

- Dx: Appendiceal mucinous adenocarcinoma, well differentiated with bilateral ovarian involvement

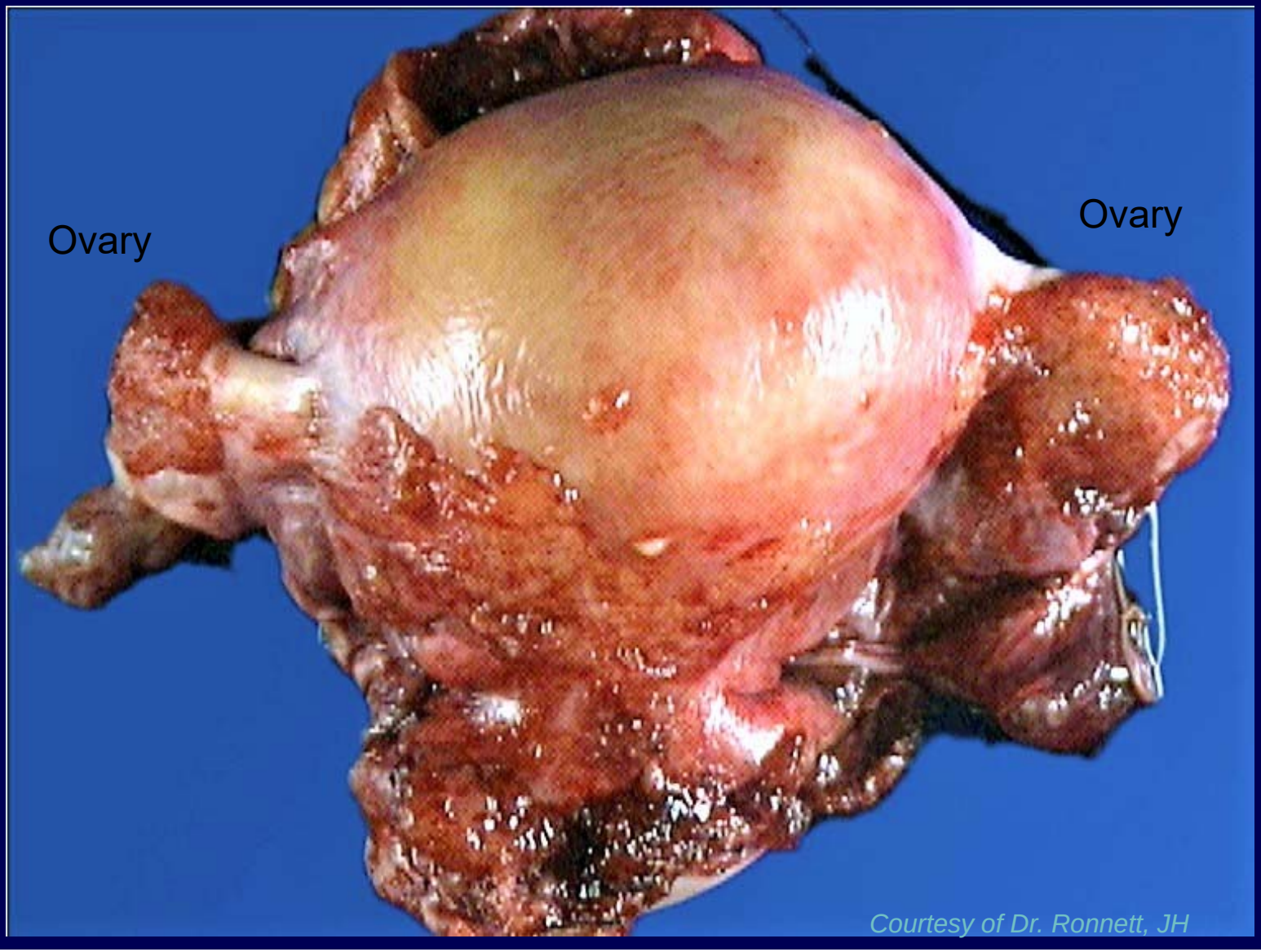


Appendiceal mucinous adenocarcinoma, well differentiated

Pseudomyxoma Peritonii (PMP)



Bilateral Secondary Involvement of Ovaries by PMP

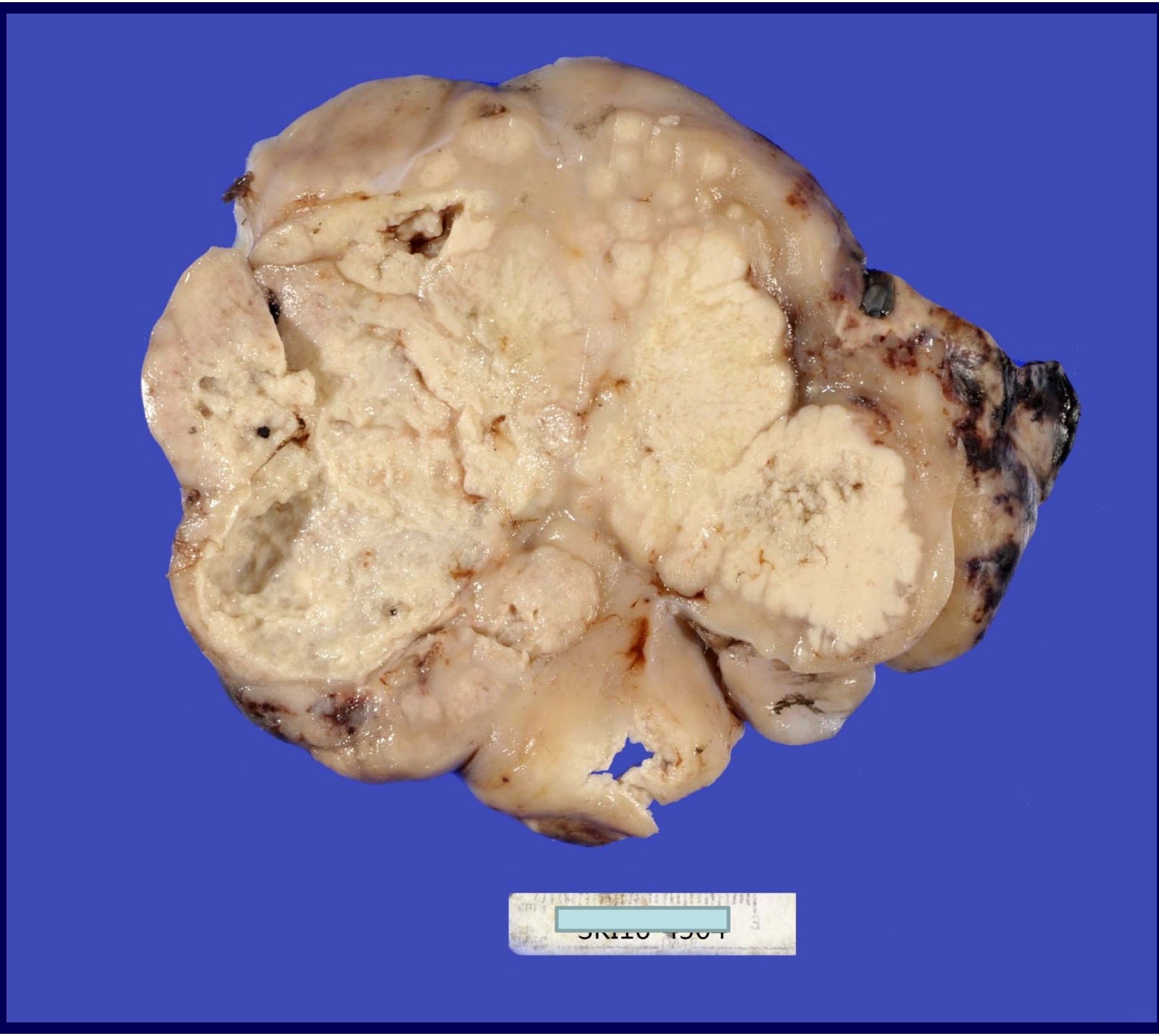


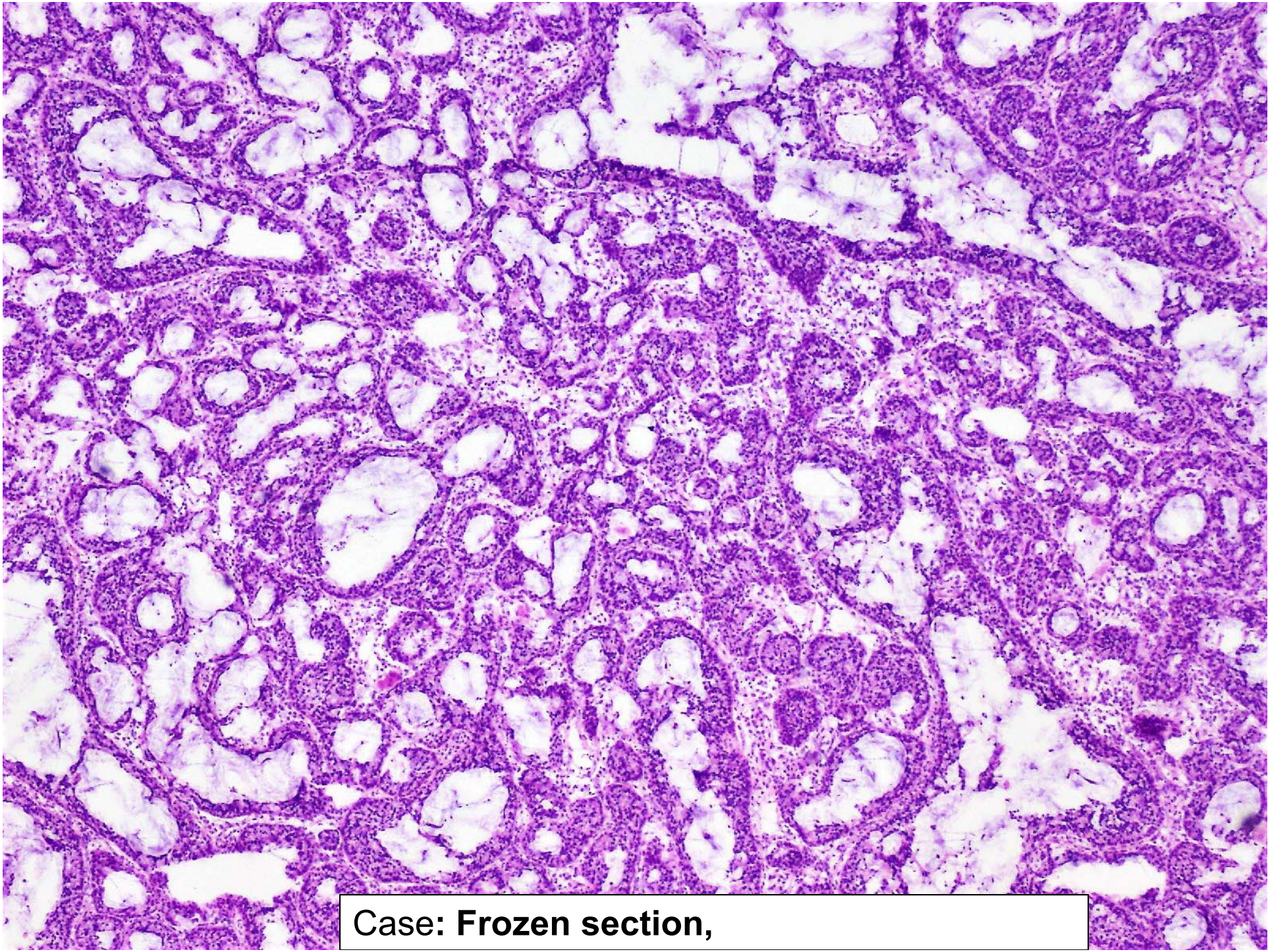
Ovarian Tumor in PMP vs. Primary MBLT

	Ovarian tumor in PMP	Primary MBLT
Size	Mean size=14 cm	Mean size=22 cm
Laterality	Bilateral (80%)	Unilateral (100%)
Location	Surface, superficial cortex, stroma	Mostly within stroma
Pseudomyxoma Ovarii	Often prominent	Usually absent or limited
Epithelium	Scant	abundant
Associated appendiceal mucinous tumor	Virtually all cases	None

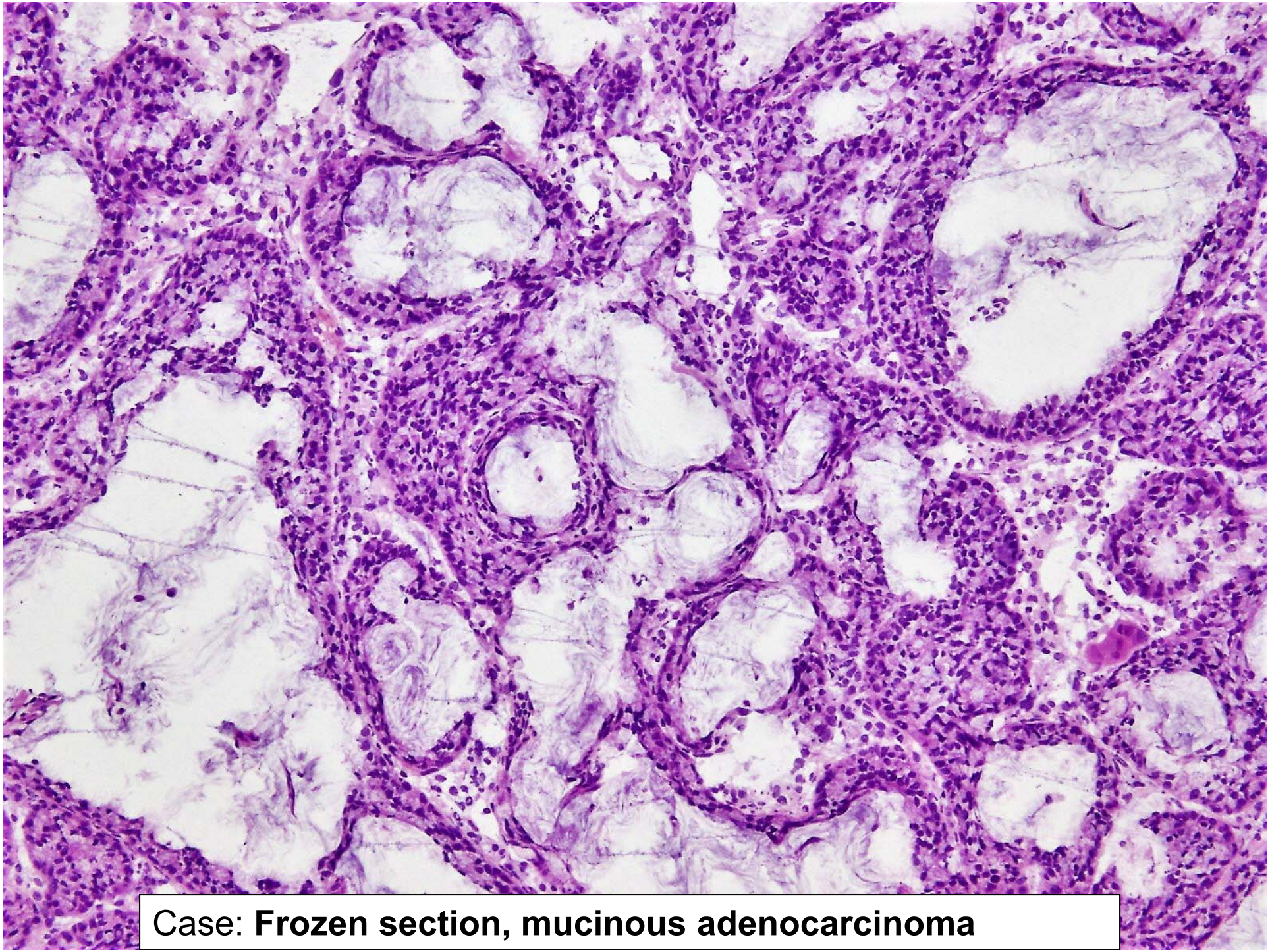
Case #4

- 45 year-old female
- Right ovarian mass 26 x 20 x 12 cm with numerus white nodules
- Left ovary 3 x 2 1.5 cm

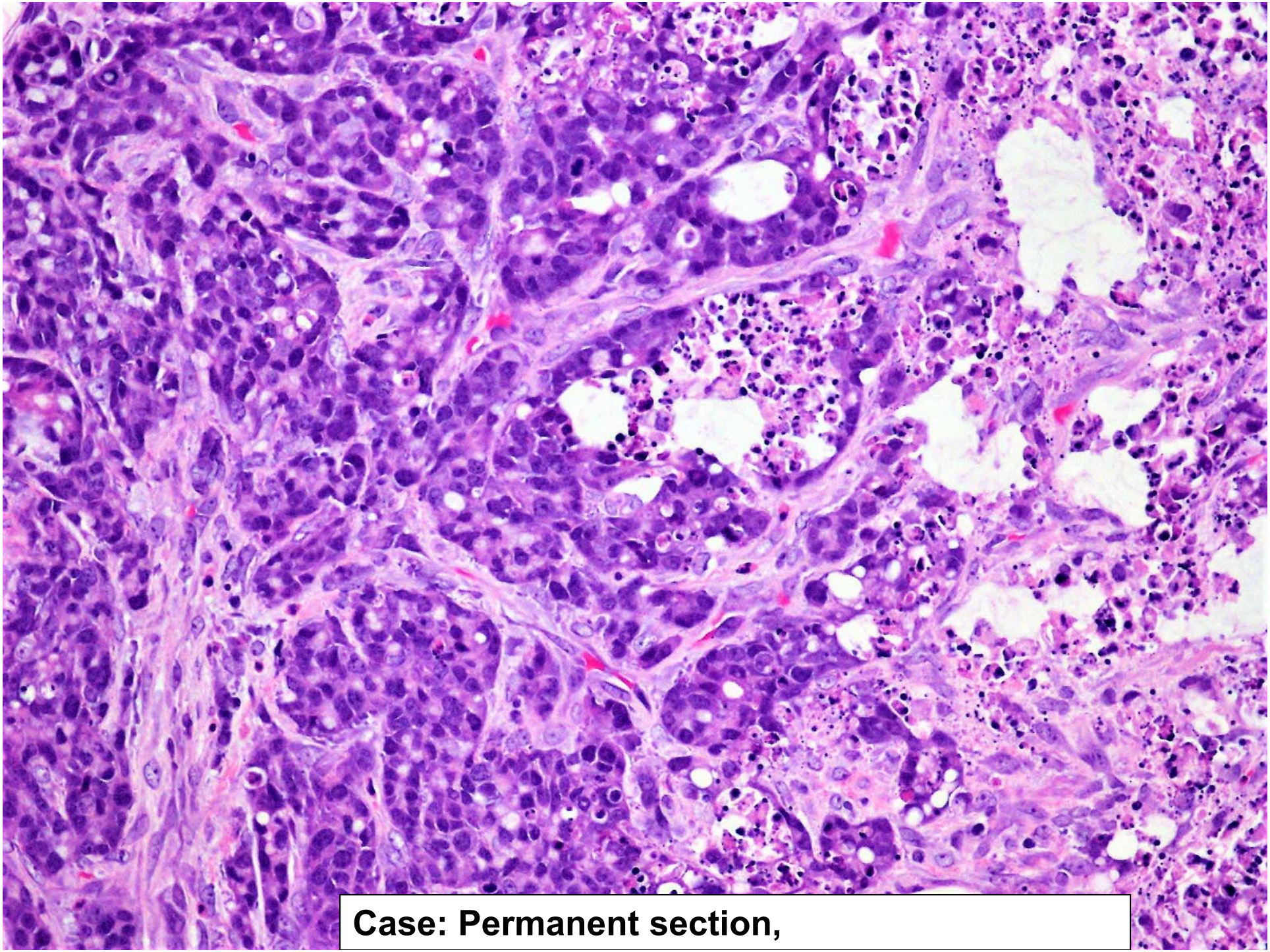


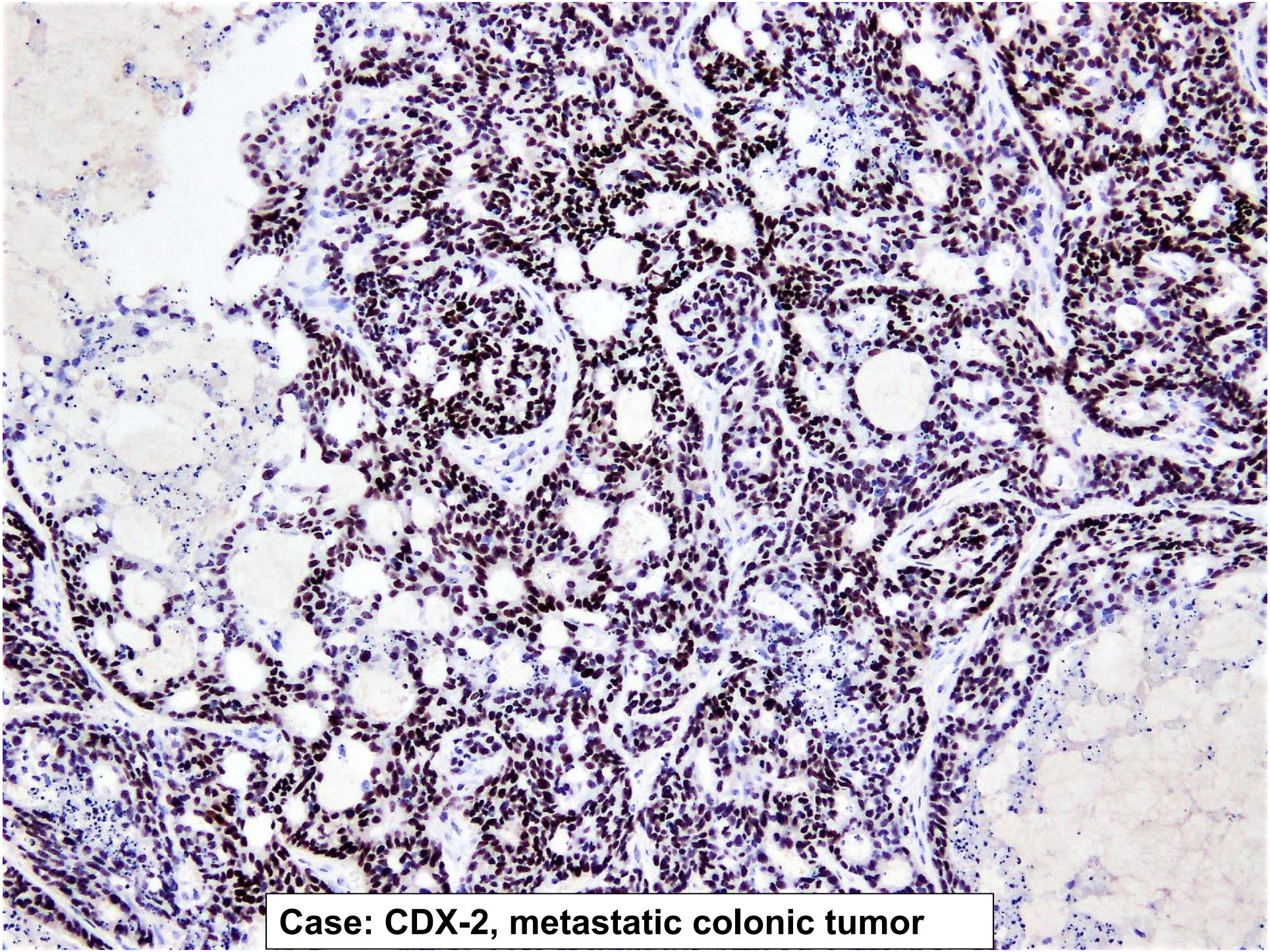


Case: **Frozen section,**



Case: **Frozen section, mucinous adenocarcinoma**


Case: Permanent section,

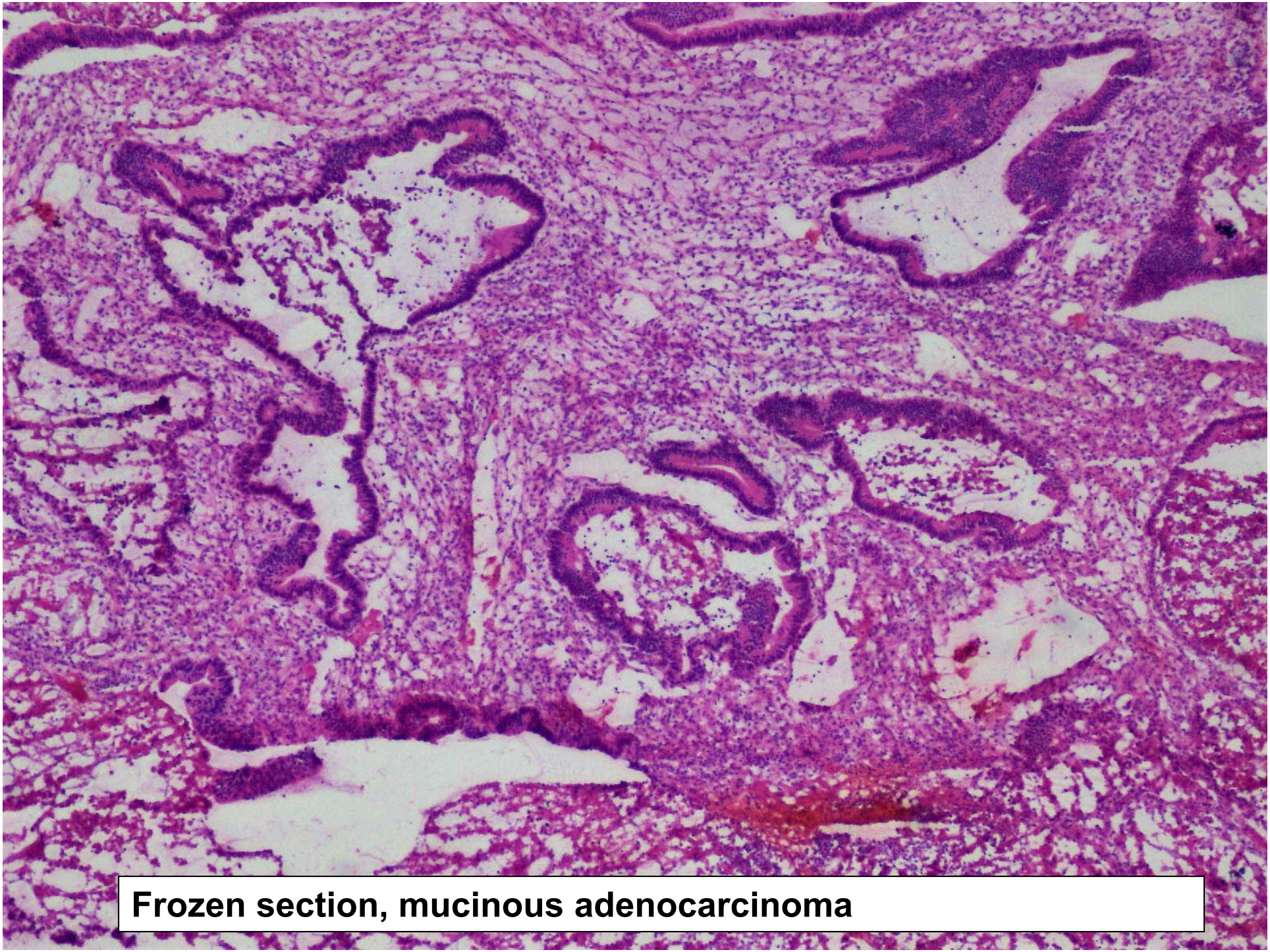

Case: CDX-2, metastatic colonic tumor

Summery Case # 4

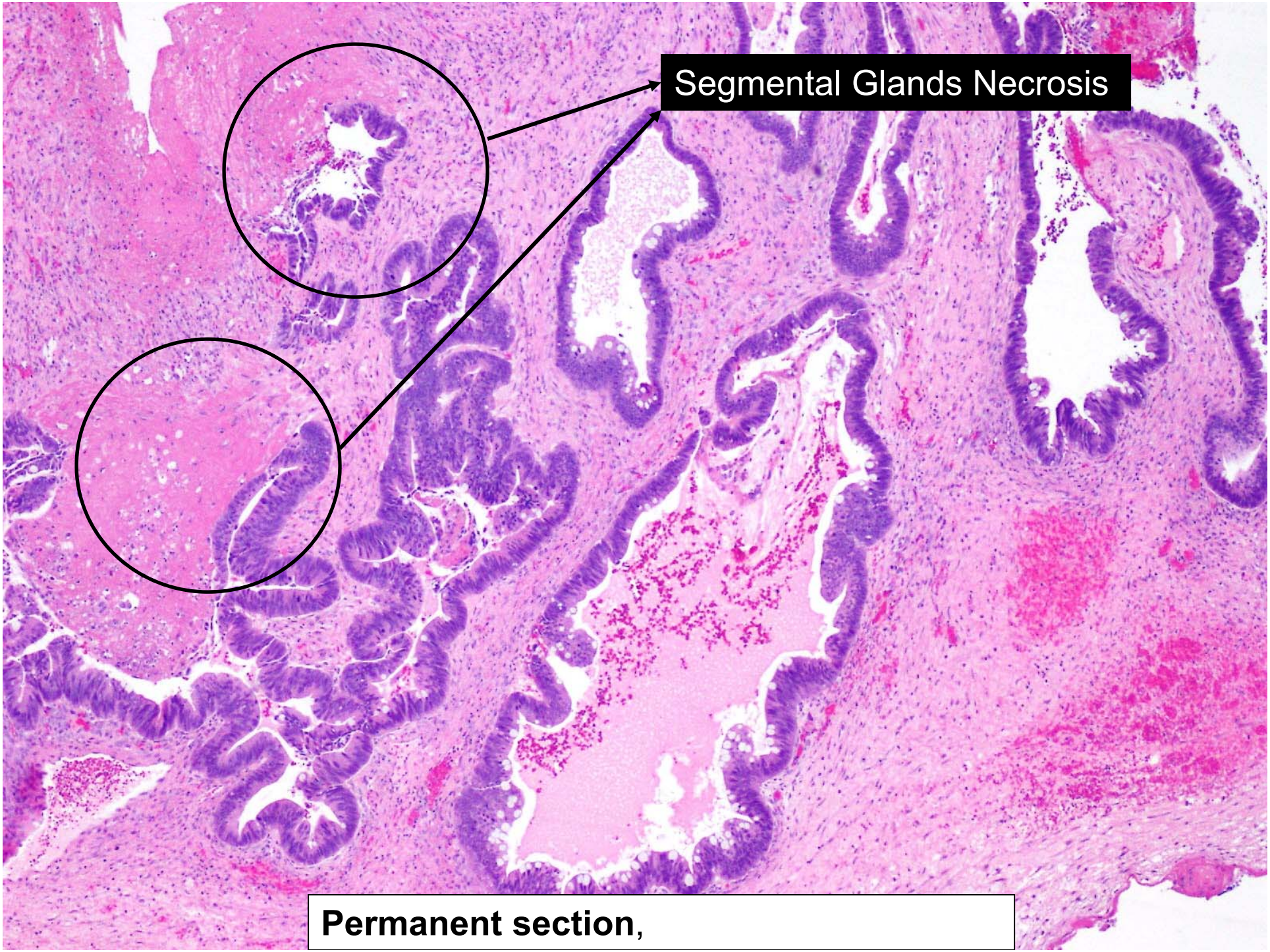
- Not all large unilateral tumors are ovarian primary tumor (but most yes)
- Multinodular and destructive growth pattern with extensive necrosis are clues of metastatic GI tumor
- IHC can help

Case # 5

- 45 years old with bilateral adnexal mass measuring 7 cm and 9 cm respectively

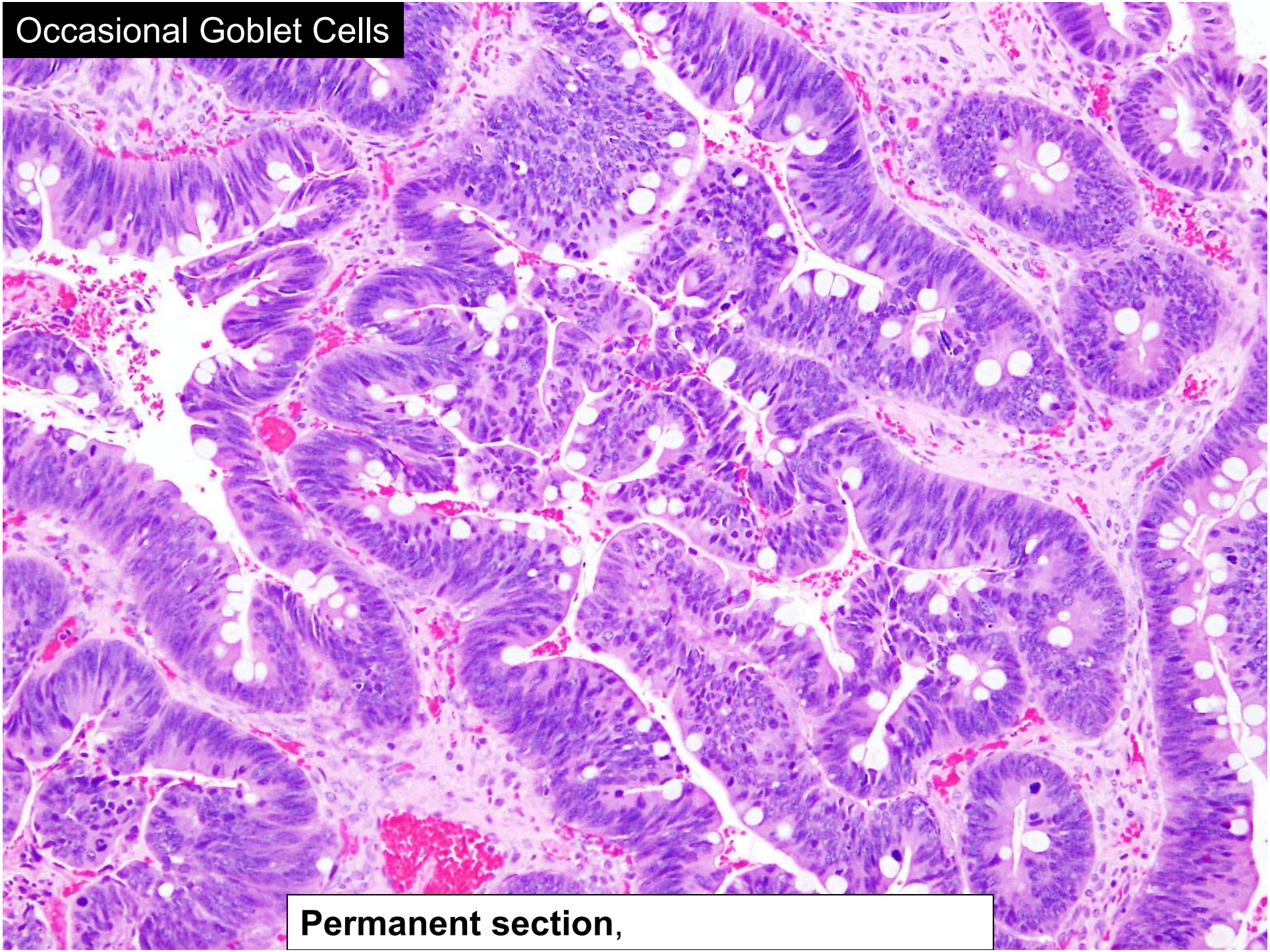


Frozen section, mucinous adenocarcinoma

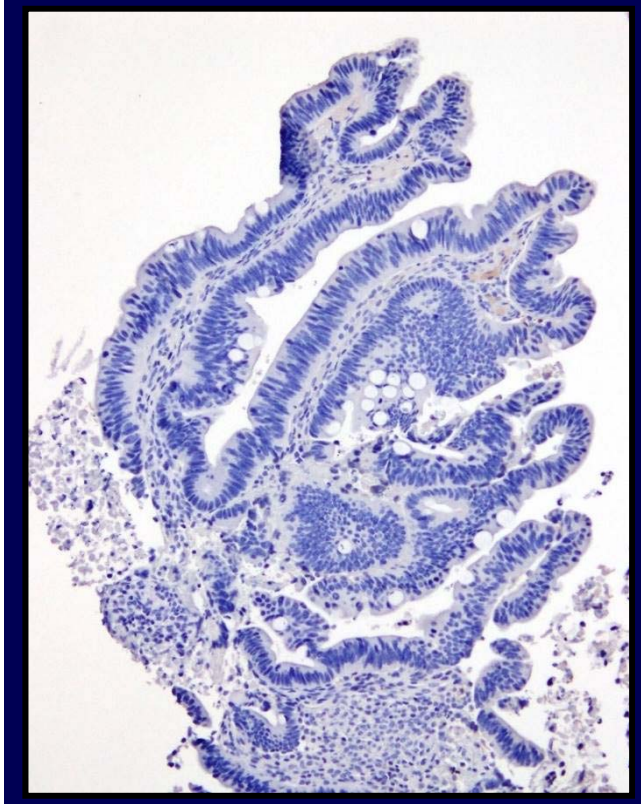


Permanent section,

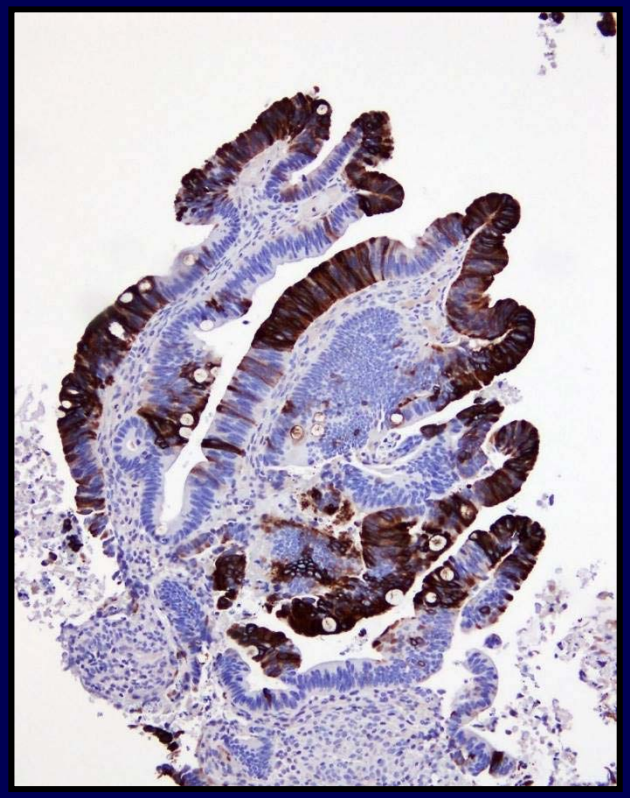
Occasional Goblet Cells



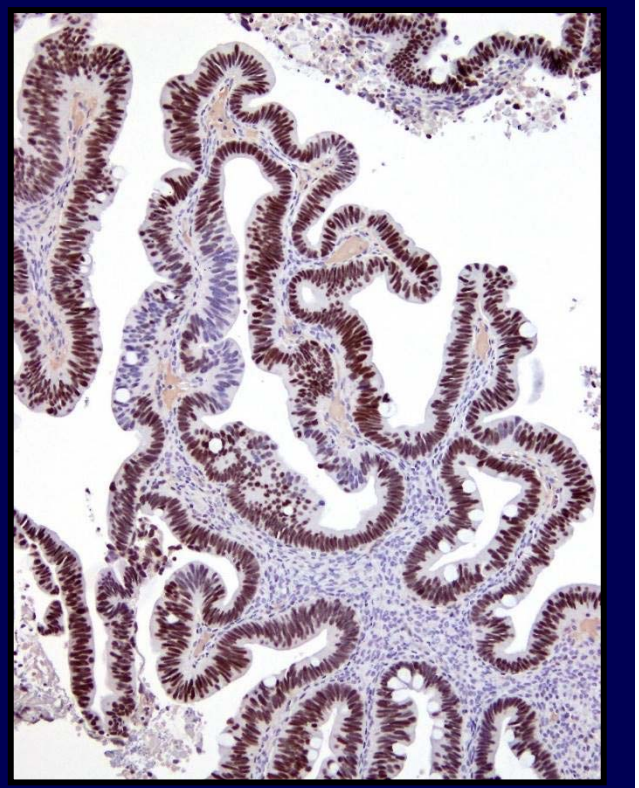
Permanent section,



CK-7



CK-20



CDX-2

Metastatic adenocarcinoma from colon

Summery Case # 5

- Not all well-differentiated tumors are ovarian primary tumors
- Bilaterally and IHC are good clues to trigger further clinical investigation of GI primary tumor
- Occasional goblet cells and segmental glands necrosis favor colonic mets
- The patient was found to have a mass in the colon

Ovarian Endometrioid Neoplasms

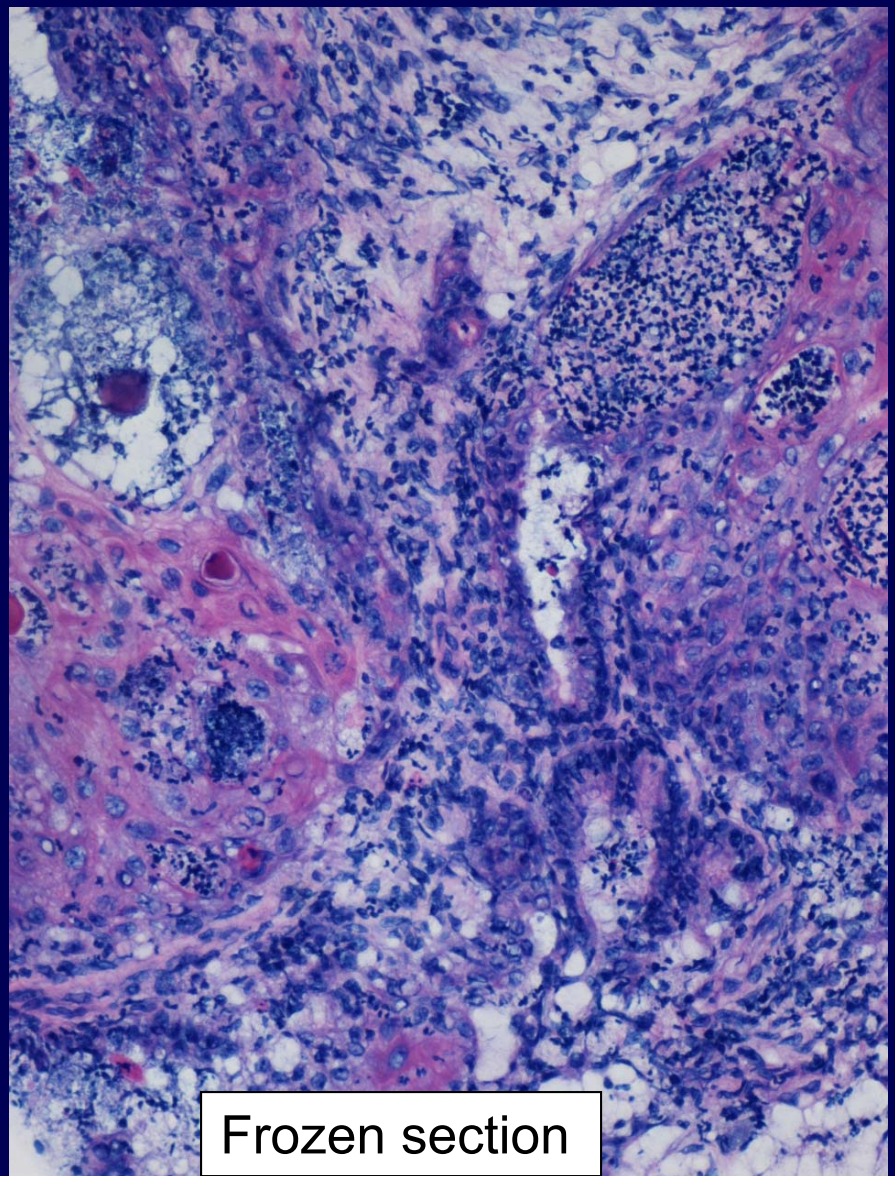
Gross Examination: Ovarian Endometrioid Neoplasms

- Bilateral in 40% of the cases
- Mixture of solid and cystic areas
- Cysts may filled with bloody or mucinous fluid
- Associated with endometriosis in 20% of cases

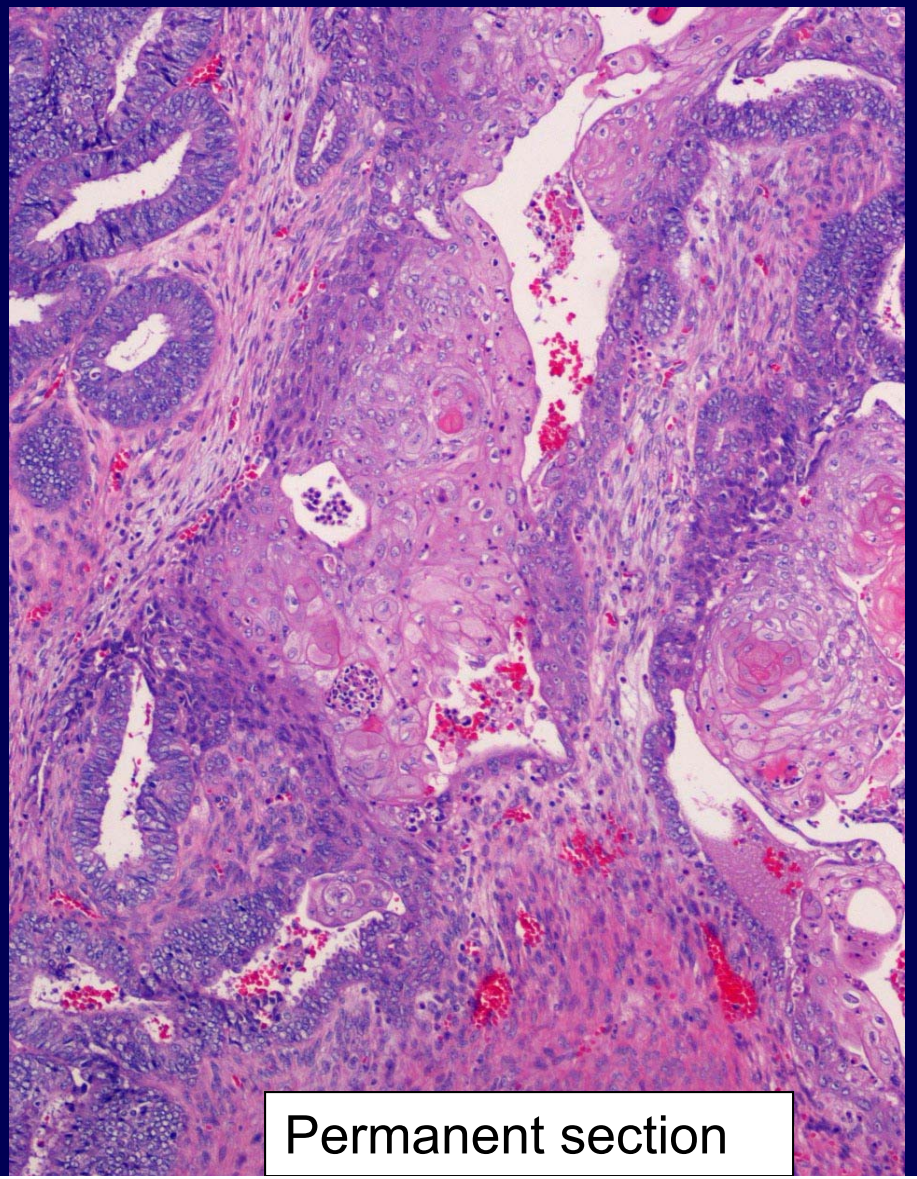
Features that Favor Primary Endometrioid Ovarian Tumor

- Endometriosis
- Variable histology
- Squamous metaplasia
- Adenofibroma component
- Sex-cord like areas

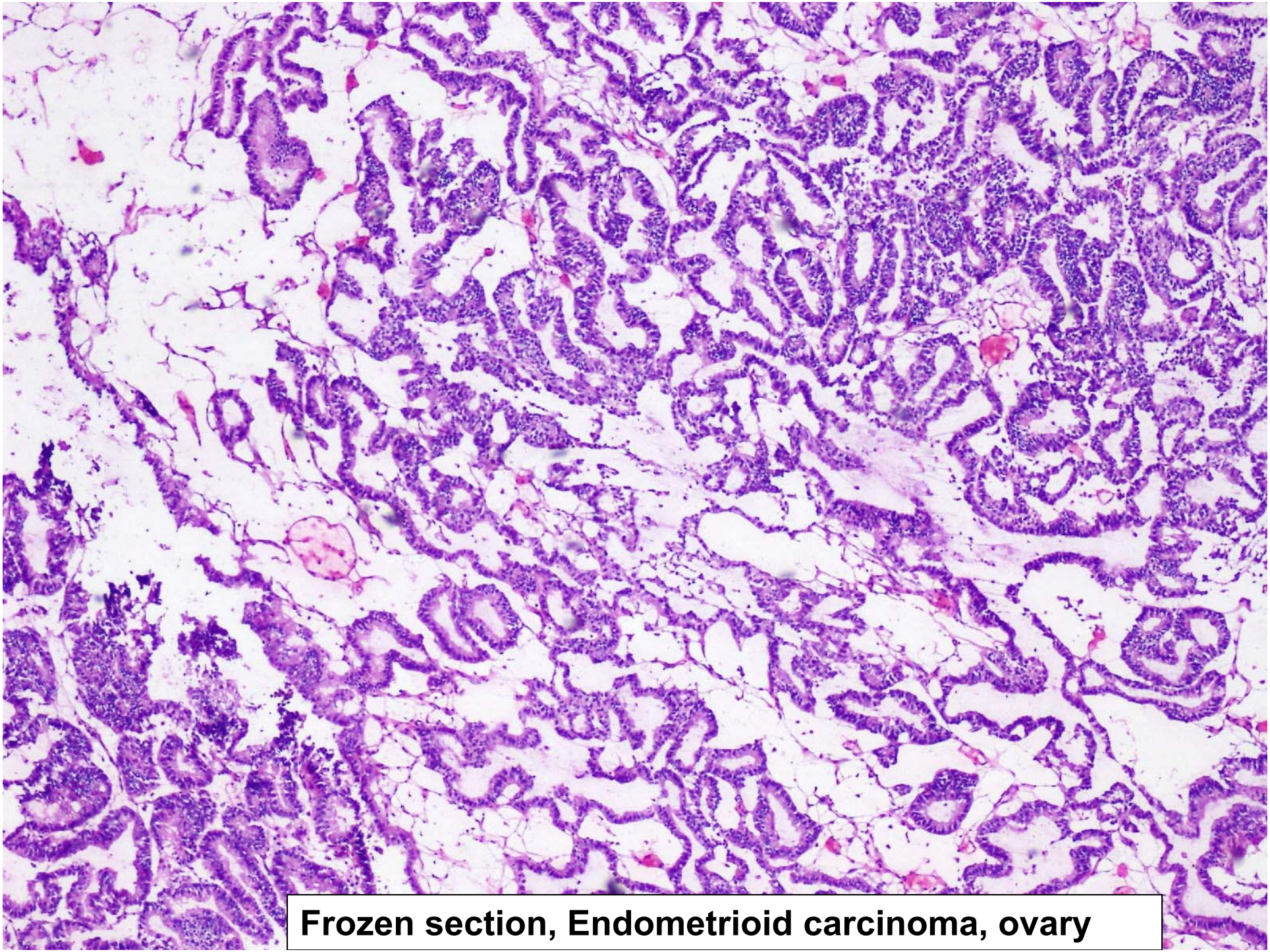
Endometrioid Ovarian Tumor



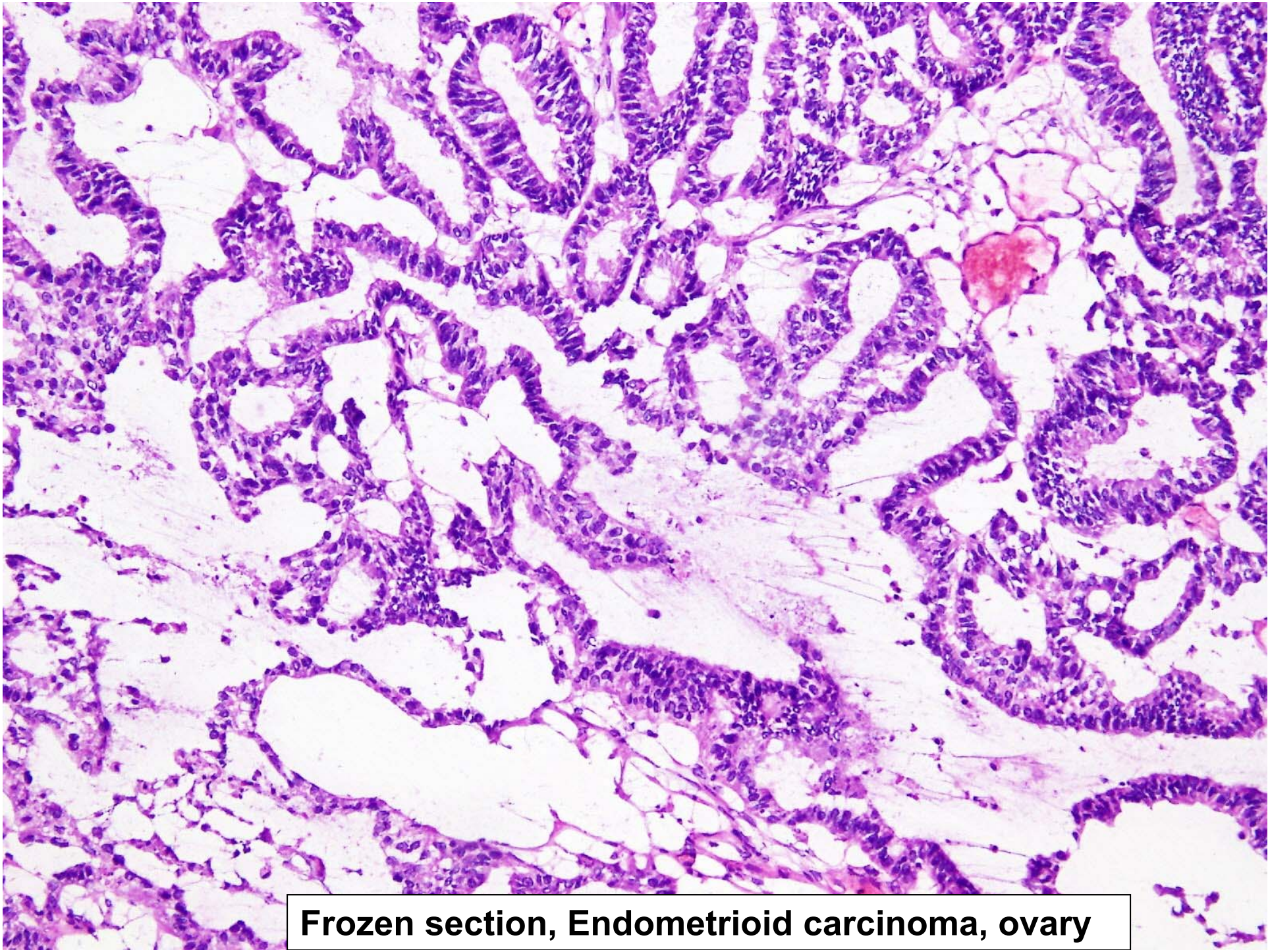
Frozen section



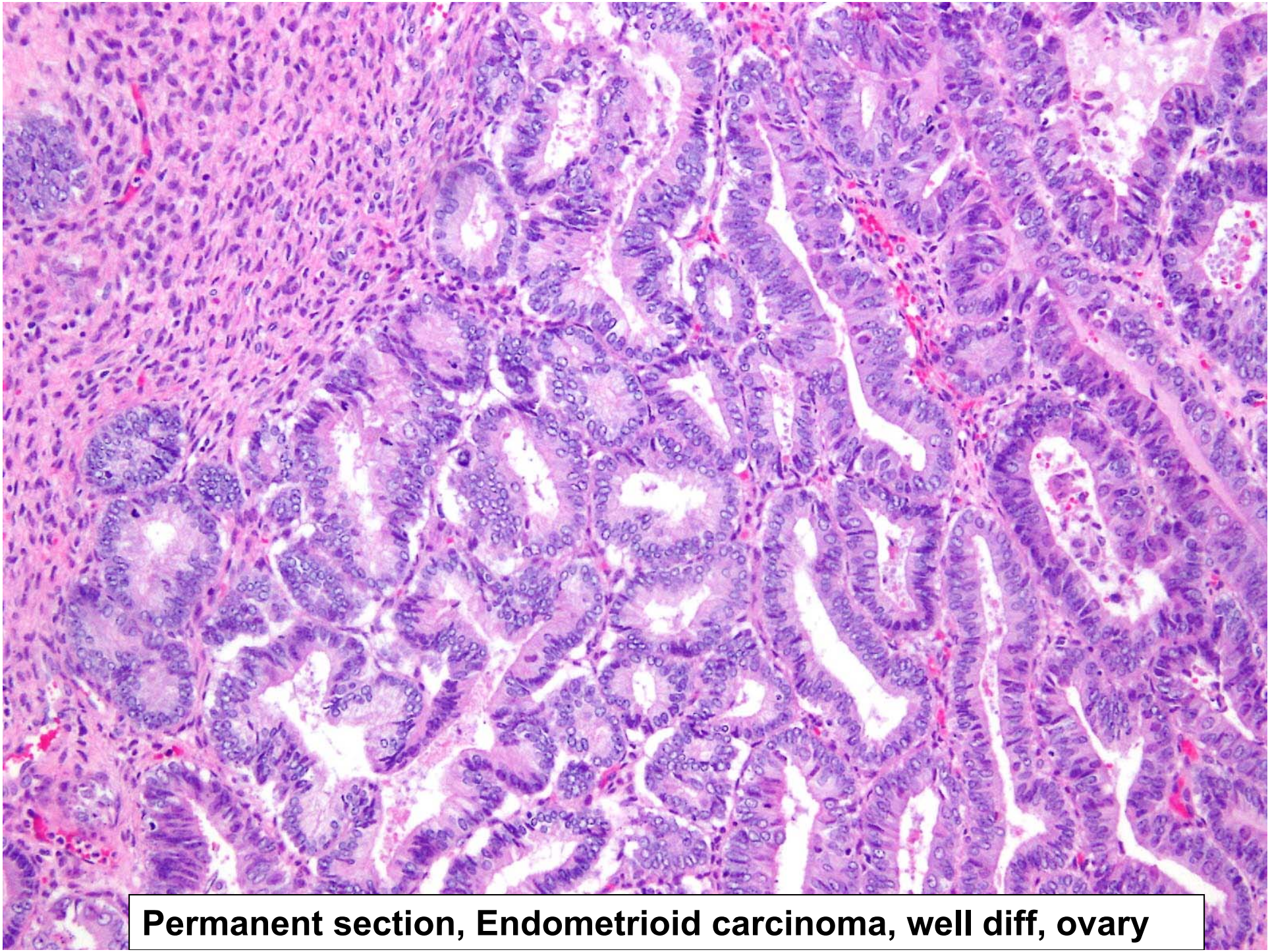
Permanent section



Frozen section, Endometrioid carcinoma, ovary



Frozen section, Endometrioid carcinoma, ovary



Permanent section, Endometrioid carcinoma, well diff, ovary

DD of Ovarian Tumors with Solid growth pattern

- Clear cell carcinoma
- Granulosa cell tumor
- Fibroma
- Thecoma
- Fibrothecoma
- Metastatic carcinoma

Ovarian Clear Cell Carcinoma

Ovarian Clear Cell Carcinoma

- *Most common cause for error* at frozen section & permanent section in gynecologic pathology
- Almost always unilateral (>95%)

Ovarian Clear Cell Carcinoma

- Associated with endometriosis – ovarian and/or pelvic
- Increased risk thromboembolism (x2.5)
- Often low mitotic index
- May not show marked nuclear atypia
- May not have clear cells
- Lots of other tumors have clear changes

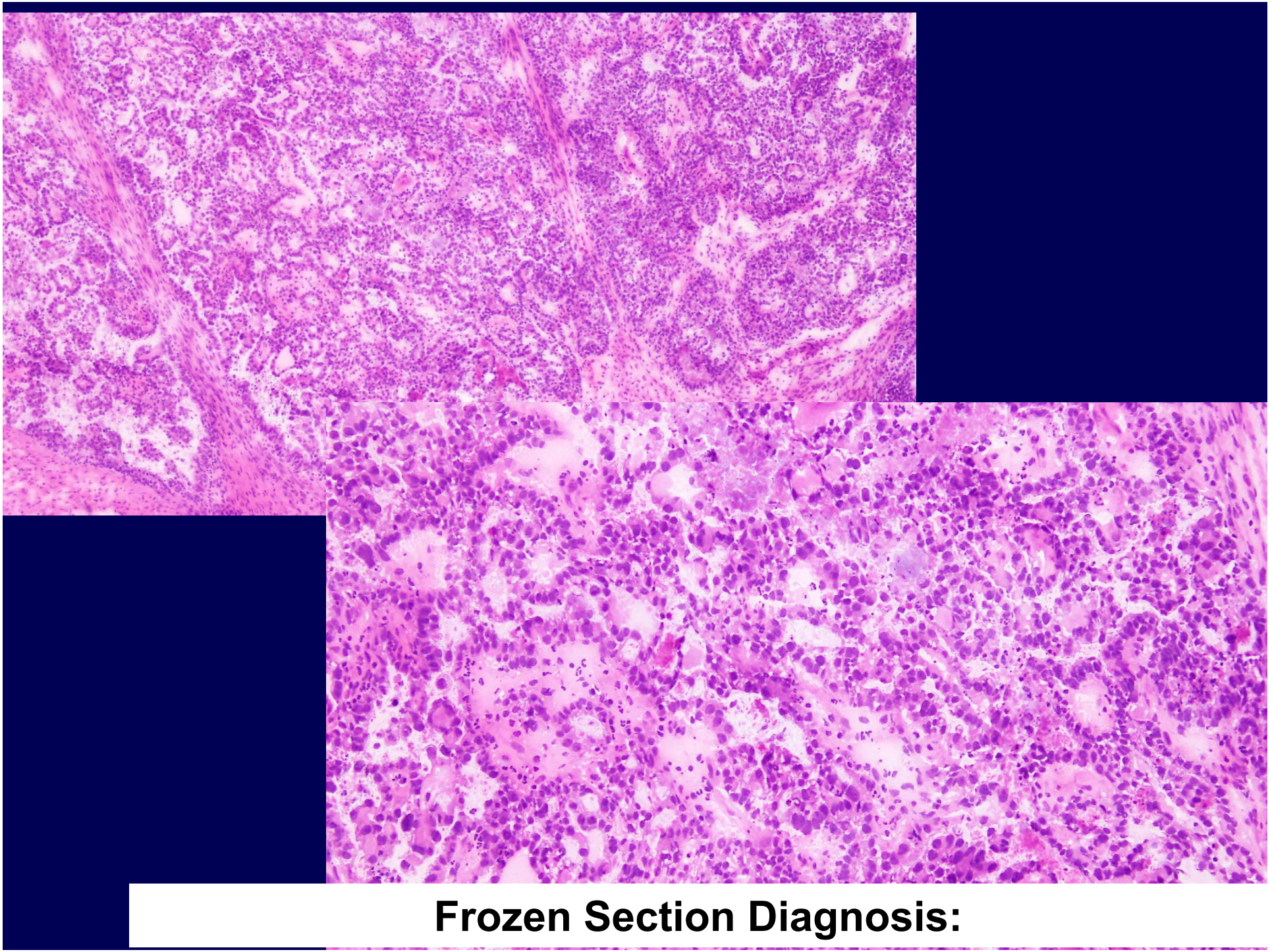
Ovarian Clear Cell Carcinoma

- Papillary
- Tubulocystic (or glandular)
- Cystic
- Solid
- Often prominent hyalinized stroma
- Fibromatous, fibroblastic, edematous stroma

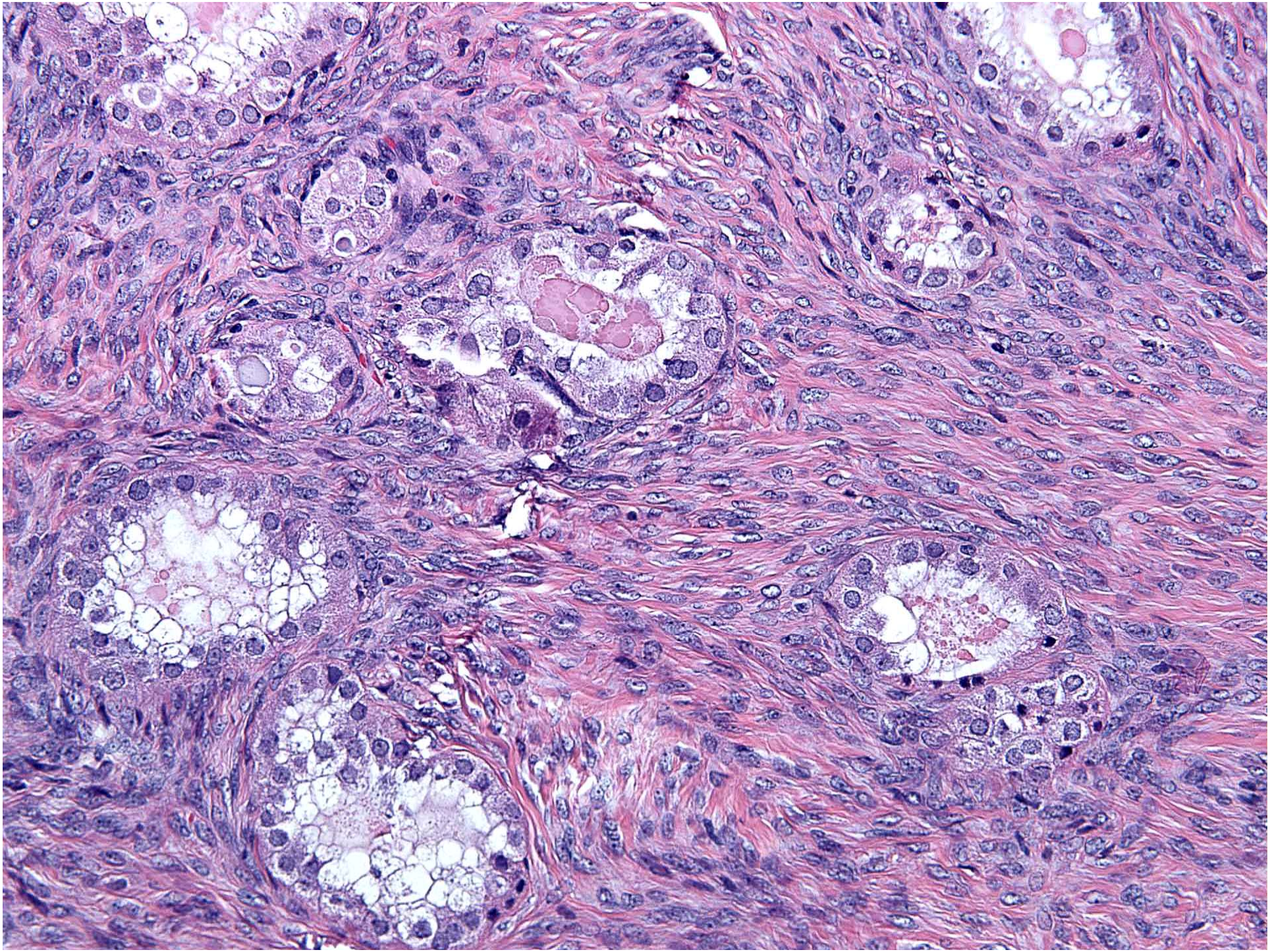
Case # 6

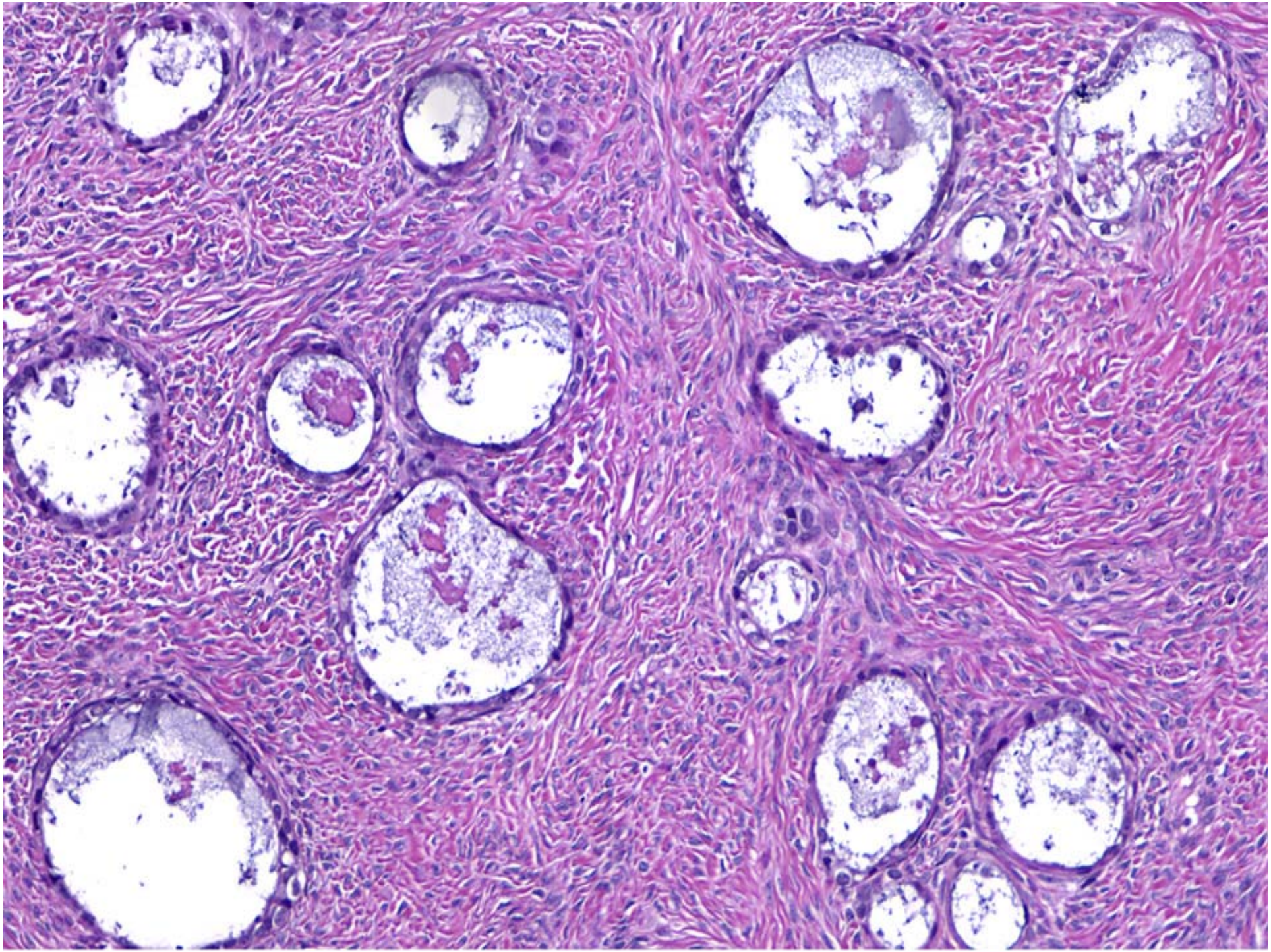
- 50 year old woman with right adnexal mass:
  - 15 x 8 x 6 cm, partially cystic, filled with bloody fluid
  - The right fallopian tube was unremarkable

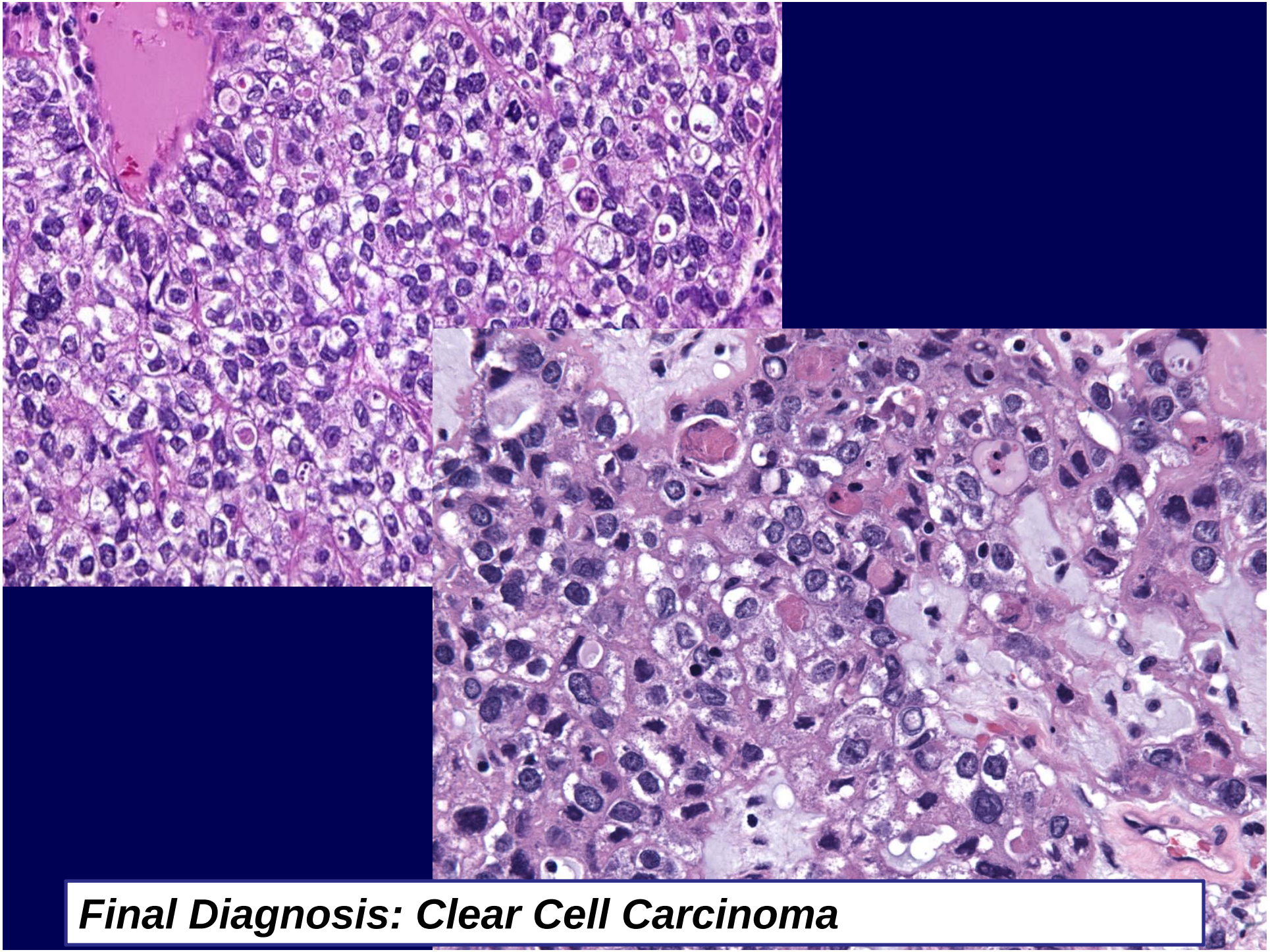
Gynecologic Pathology 2009, Dr Oliva & Dr Nucci



Frozen Section Diagnosis:







Final Diagnosis: Clear Cell Carcinoma

Frozen sections of ovarian lesions: Discrepant diagnosis

- Inadequate Sampling
- Suboptimal quality of the FS
- Misinterpretation by pathologist
- The discrepancy rate (1.1% to 3.8%)

Frozen sections of ovarian lesions: Discrepant diagnosis

- Most common mistakes
  - Mucinous tumors-undercall
  - Met vs. primary
- Predictive factors:
  - Histology Type (mucinous)
  - Tumor size (<10cm)
  - The BLT component (<10%)
  - Pathologist's experience
  - Tendency to undercall borderlines

Thank you