Approach to Common Gynecologic Frozen Sections

Elke Jarboe, MD
Associate Professor, Pathology and
Adjunct Associate Professor, Obstetrics and Gynecology
Director, Gynecologic Surgical Pathology

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Outline

- Introduction – what are “common” frozens?
- Endometrial carcinoma – when to freeze and why:
  - Mayo Criteria (and modified Mayo criteria) for endometrial carcinomas
  - Sentinel lymph nodes
- The dreaded ovarian mass frozen:
  - General advice
  - Mucinous carcinoma: metastasis vs primary

What are "common" gyn frozens?

- Uterine tumors:
  - Largely to inform decision making on endometrial cancers – majority are endometrioid type
- Ovarian epithelial tumors:
  - 85% of malignant tumors
  - 35% of benign tumors

Intraoperative evaluation of endometrial carcinoma

When is it necessary?

Intraoperative evaluation of endometrial carcinoma

When is it necessary?
It depends...

Bottom line: The gyn/onc surgeon needs our guidance in deciding whether or not to take lymph nodes

Intraoperative evaluation of endometrial carcinoma

- Lymph node status is the most important prognostic factor
- High incidence of lower extremity lymphedema following pelvic and para-aortic lymphadenectomy (LAD) in patients with gyn tumors
  - 30-40%
  - Up to 60% when combined with radiation therapy
  - Risk correlates with number of lymph nodes removed

Uterine frozens

- A little history:
  - In the “olden days”, we froze endomyometrium with tumor and implemented the Mayo (or modified Mayo) criteria for evaluating them, then lymph nodes were taken or not
  - Also in the “olden days”, some gyn/onc surgeons just took all the lymph nodes irrespective of tumor features
  - Then came along the sentinel lymph node, and we do fewer endomyometrial frozens now…but we still do them

Uterine frozen – Mayo Criteria

- Size
- Histology
- Depth of Invasion

Mariani et al. 2000

Uterine frozen – Mayo Criteria

- Size: ≤ 2cm
- Histology: Endometrioid type, FIGO grade 1 or 2 (risk of spread to lymph nodes <5% in low grade emca)
- Depth of Invasion: ≤ 50%
- If all three criteria met, full LAD can be avoided
- If all three criteria not met, "systematic LAD (SLAD)" performed

Mariani et al. 2000

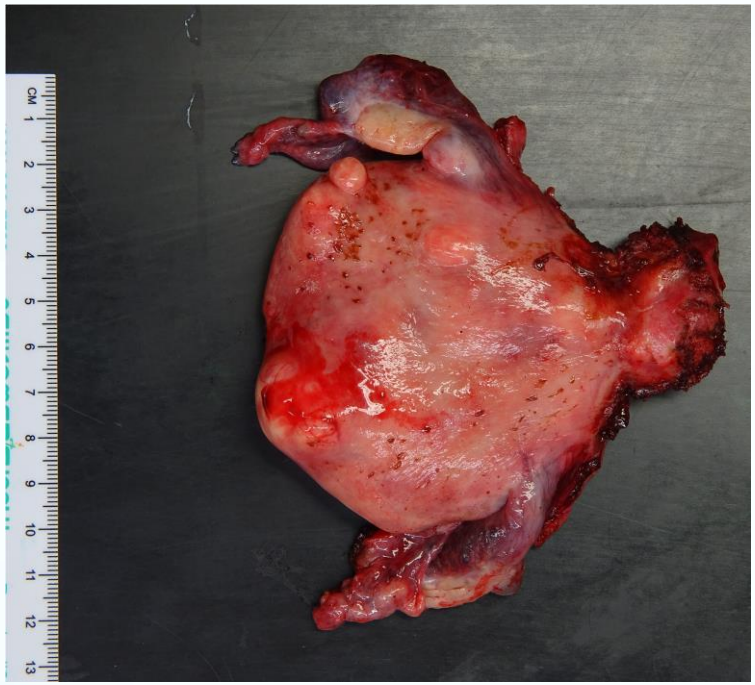
Uterine frozen – Mayo Criteria

- Strict implementation of Mayo Criteria results in 75% of patients requiring SLAD
- 15% rate of lymph node involvement in patients with endometrioid carcinoma
- Size criterion:
  - may not be as useful as an independent predictor of lymph node involvement
  - may result in unnecessary SLAD

Uterine frozen – Modified Mayo Criteria

- Size criterion:
- Histology
- Depth of Invasion

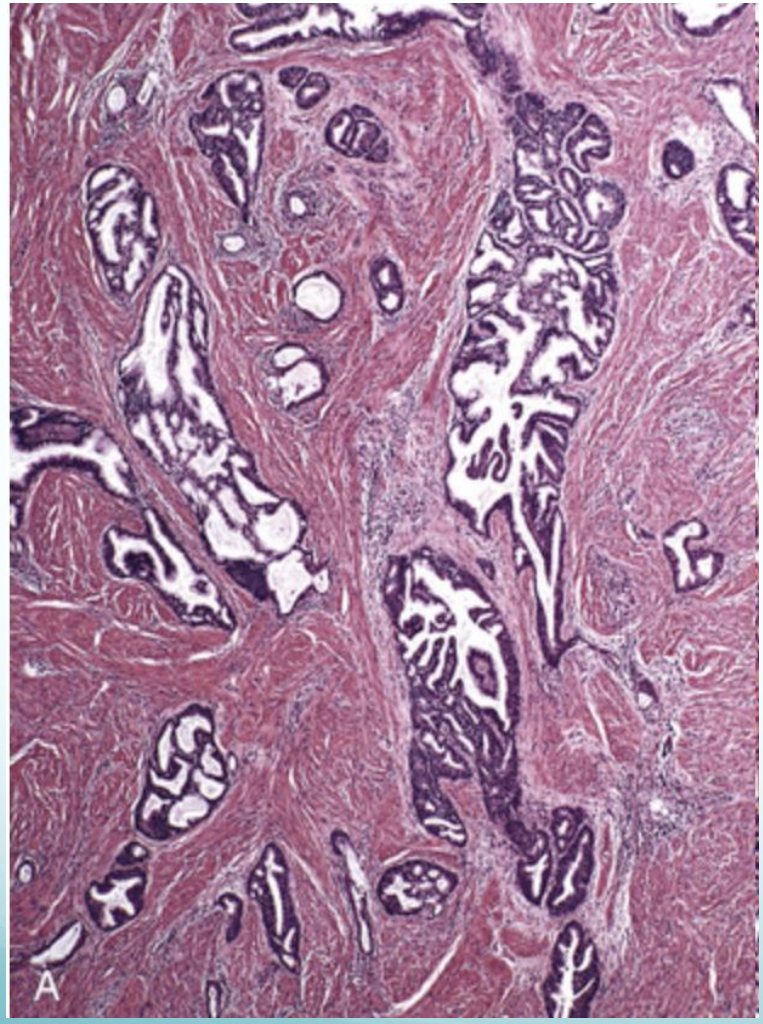
cancer



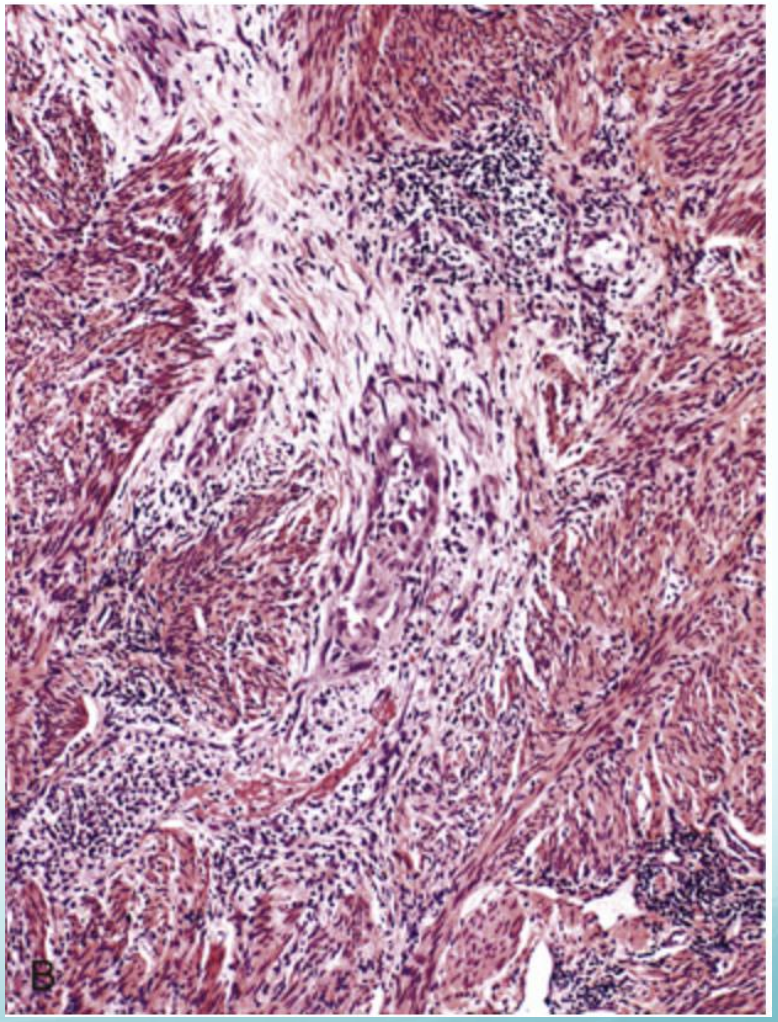
Please open uteri with scissors, not a knife!!!

Uterine frozen for endometrial cancer
Depth of Invasion

Easy on frozen



Really really hard on frozen!



Crum, 2nd Ed

Uterine frozen for endometrial cancer

- What if there is no gross mass? Is a random section useful?

Uterine frozen for endometrial cancer

- What if there is no gross mass? Is a random section useful? **NO. It is not.**

Table 1
Frozen-Section Examination According to Final Diagnosis in Hysterectomy Cases With No Lesion Suspicious for Malignancy Identified on Gross Examination[a]

Frozen-Section Interpretation	Final Diagnosis, No. (%)		
	No Carcinoma (n = 44)	Carcinoma Present (n = 20)	Total No.
No carcinoma	44 (100)	17 (85)	61
Carcinoma present	0	3 (15)	3
Total	44 (100)	20 (100)	64

[a]Sensitivity, 15%; specificity, 100%; and negative predictive value, 72%.

Fadare et al, 2017

Endometrial Sentinel Lymph Node Mapping

- First described in 1996
- Originally implemented as an alternative to complete LAD in low grade low clinical stage endometrial cancer
- Acceptable alternative to complete LAD in both low and high grade clinical Stage I endometrial cancer
  - Full LAD *independent of the effect of adjuvant tx* does not improve survival
  - Similar diagnostic accuracy for identifying nodal metastases

Endometrial Sentinel Lymph Node Mapping

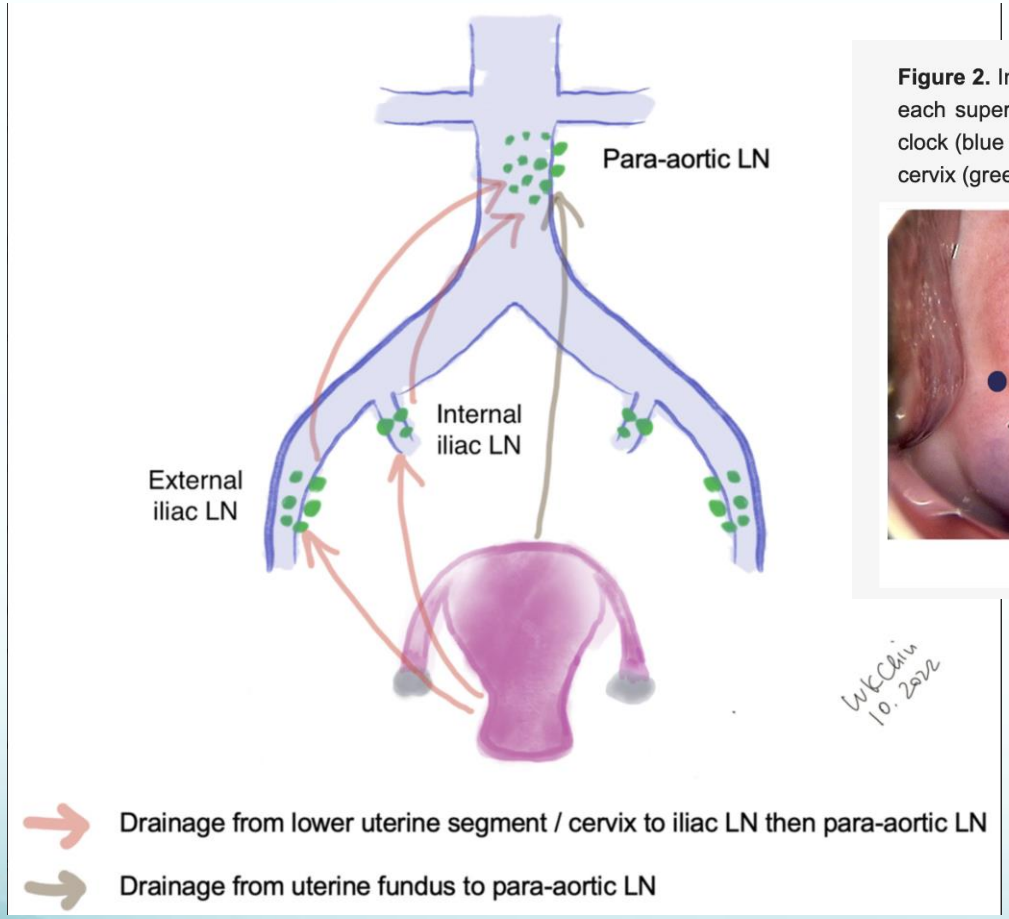
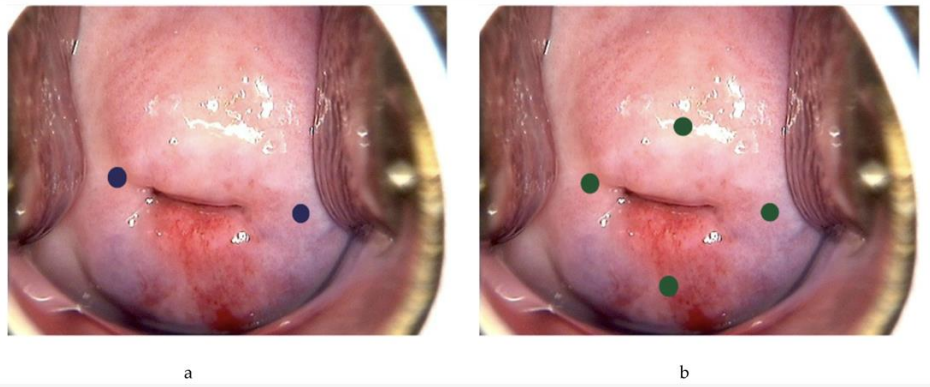


Figure 2. Injection of tracer at the cervix. Using ICG as example, 0.5–1 mL can be injected each superficially (1–3 mm at submucosa) and deeply (1–2 cm at stroma) at 3 and 9 o' clock (blue dots) (**a**), or 0.5 mL each superficially and deeply at 3, 6, 9 and 12 o'clock of the cervix (green dots) (**b**).



Indocyanine green commonly used as the tracer

Chu WK, et al, JCM, 2022

Endometrial Sentinel Lymph Node Mapping

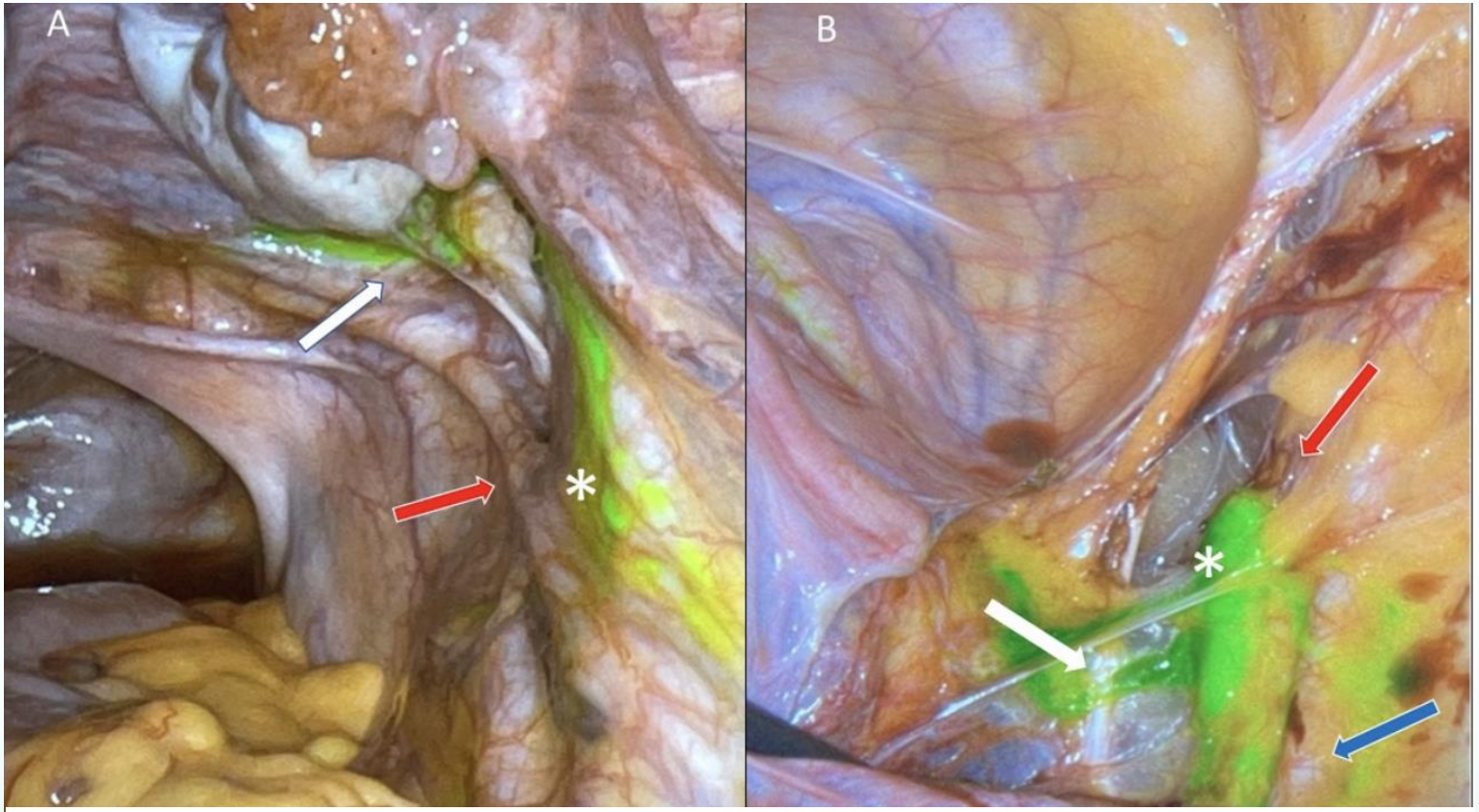


Figure 1. Mapping of a sentinel lymph node using cervical injection of indocyanine green. (**A**) Parametrial lymphatic chains (white arrow) leading to the right external iliac sentinel lymph node (*), while identifying the adjacent structures such as the right ureter (red arrow). (**B**) Right external iliac sentinel lymph node (*) clearly identified after exposing the retroperitoneal space. Important vessels identified in the retroperitoneal space: superior vesicle artery (white arrow), right external iliac vein (red arrow), and right external iliac artery (blue arrow).

Salman L, et al, Curr Oncol, 2022

Endometrial Sentinel Lymph Node Mapping

- Other advantages over LAD besides preventing lower extremity lymphedema:
  - Decreased blood loss
  - Decreased surgery time (by up to 90 minutes)
  - Decreased risk of vascular and nerve injury

Salman L, et al, 2022

Endometrial Sentinel Lymph Node Mapping: Different groups, different guidelines

TABLE 1 Summary of results

Parameter	NCCN	SGO	ESGO	BGCS	JSGO
Indications					
Stages I–II (uterine confined) (low/intermediate risk)	May be considered	Can be performed	Can be considered	Can be considered	An option. Omission of full LAD is suggested
High grade (grade 3, clear cell/serous/carcinosarcoma) (intermediate–high/high risk)	Potential alternative to full LAD	Feasible with completion of full LAD + para-aortic assessment	Acceptable alternative to full LAD in stages I–II	Can be considered	Not mentioned

- General consensus that SLN mapping is appropriate in the context of low-risk endometrial cancer
- Less unified, less enthusiastic support for high-risk endometrial cancers

Dick A, et al, 2022

“There is a lot of controversy”

- The gyn/onc surgeon ultimately has 4 choices:
  - Take no lymph nodes
  - Take all the lymph nodes
  - Take sentinel lymph nodes
  - Do SLAD depending on Mayo criteria

Uterine frozen – what do WE do at the University of Utah/Huntsman Cancer Hospital

- For all endometrial carcinoma/carcinosarcoma:
  - Try for the sentinel lymph nodes; if they don't map, then:
    - Perform endomyometrial frozen and implement Mayo (or modified Mayo) criteria, then do or don't do SLAD
    - Other institutions may automatically do LAD when sentinel lymph nodes do not map, but we do not.

Uterine frozen – what do WE do at the University of Utah/Huntsman Cancer Hospital

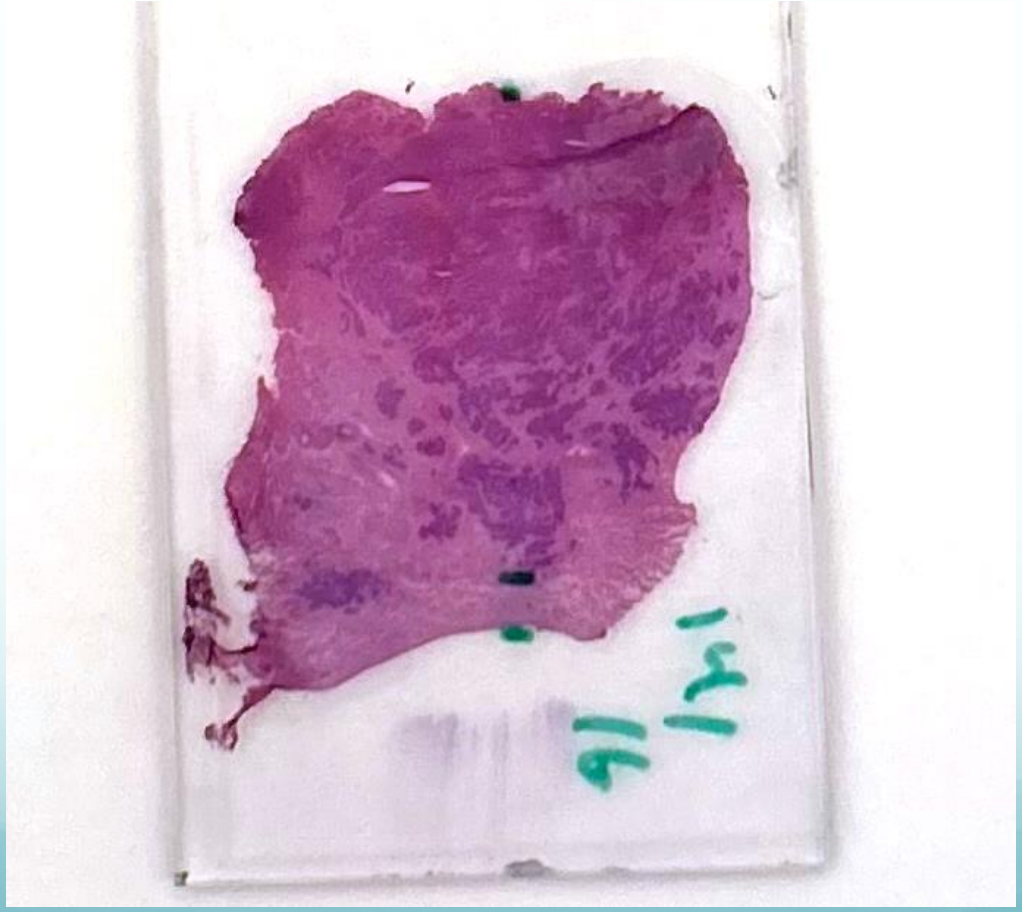
- For EIN/atypical hyperplasia (depending on many factors):
  - Sentinel lymph nodes may be procured; if they don't map, then:
    - Intra-op eval of endometrium may be requested, then do or don't do SLAD
    - Intra-op eval of endometrium may *not* be requested, and no nodes taken

Uterine frozen – what do WE do at the University of Utah/Huntsman Cancer Hospital

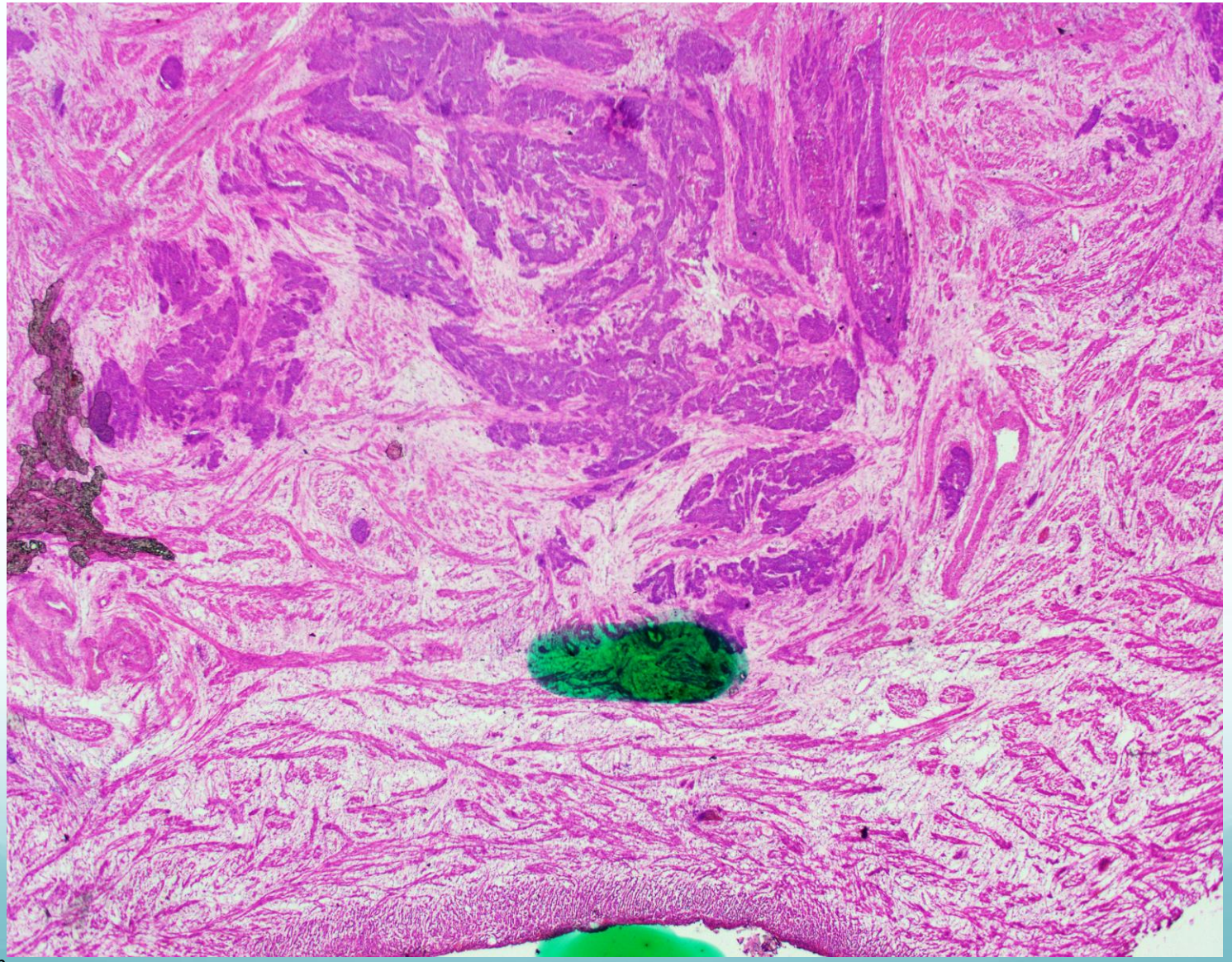
- 63 year-old with post-menopausal bleeding:
  - Endometrial biopsy revealed FIGO grade I endometrioid type endometrial carcinoma
  - Referred for TAH-BSO, sentinel LND
  - Left sentinel lymph node mapped
  - Right sentinel lymph node did not map: Decision was made to proceed with endomyometrial frozen section for Mayo criteria evaluation

63 year-old with post-menopausal bleeding

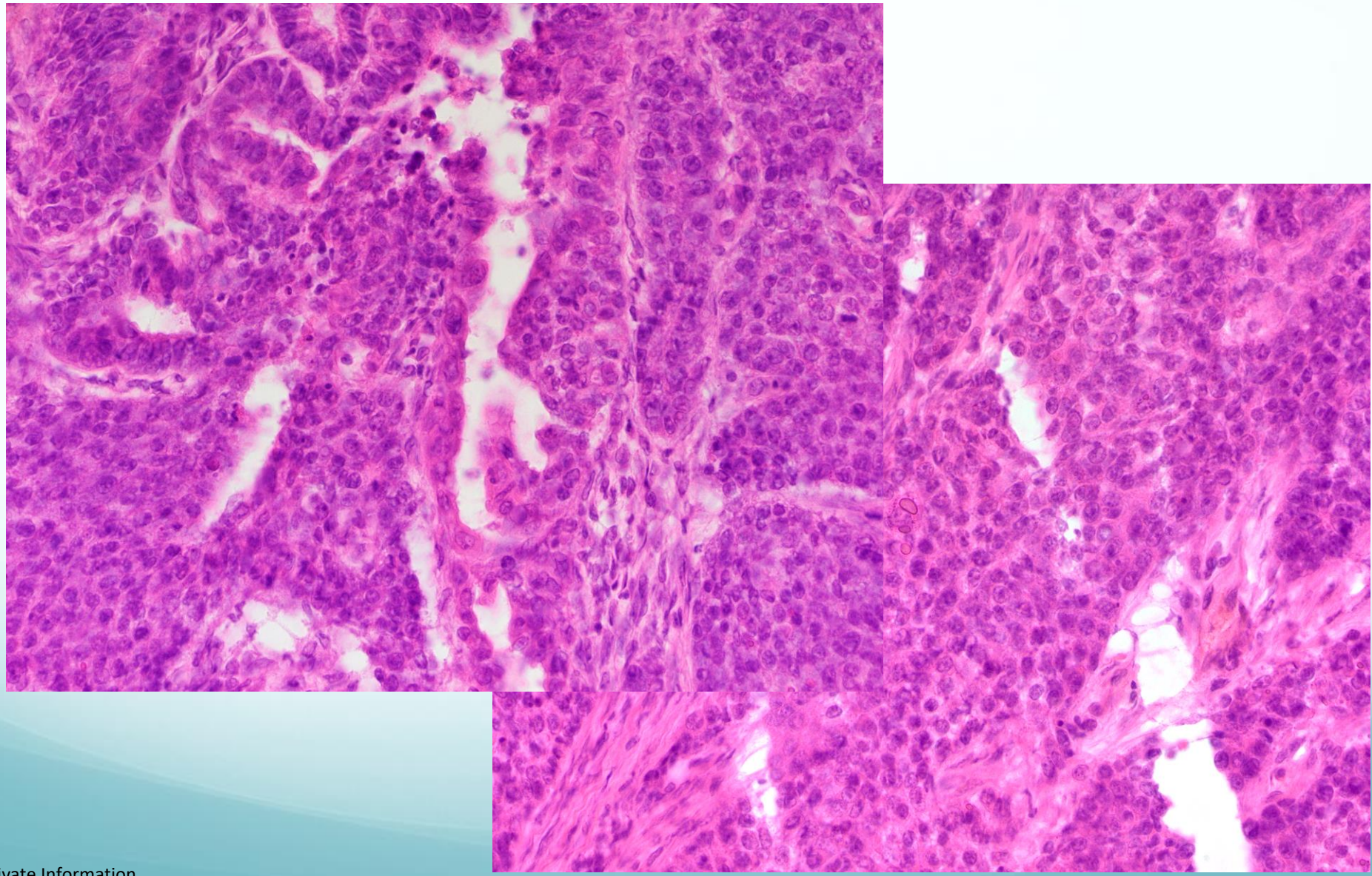
- Uterus was opened, revealing 4 cm tumor with grossly obvious deep myometrial invasion; representative frozen section was taken:



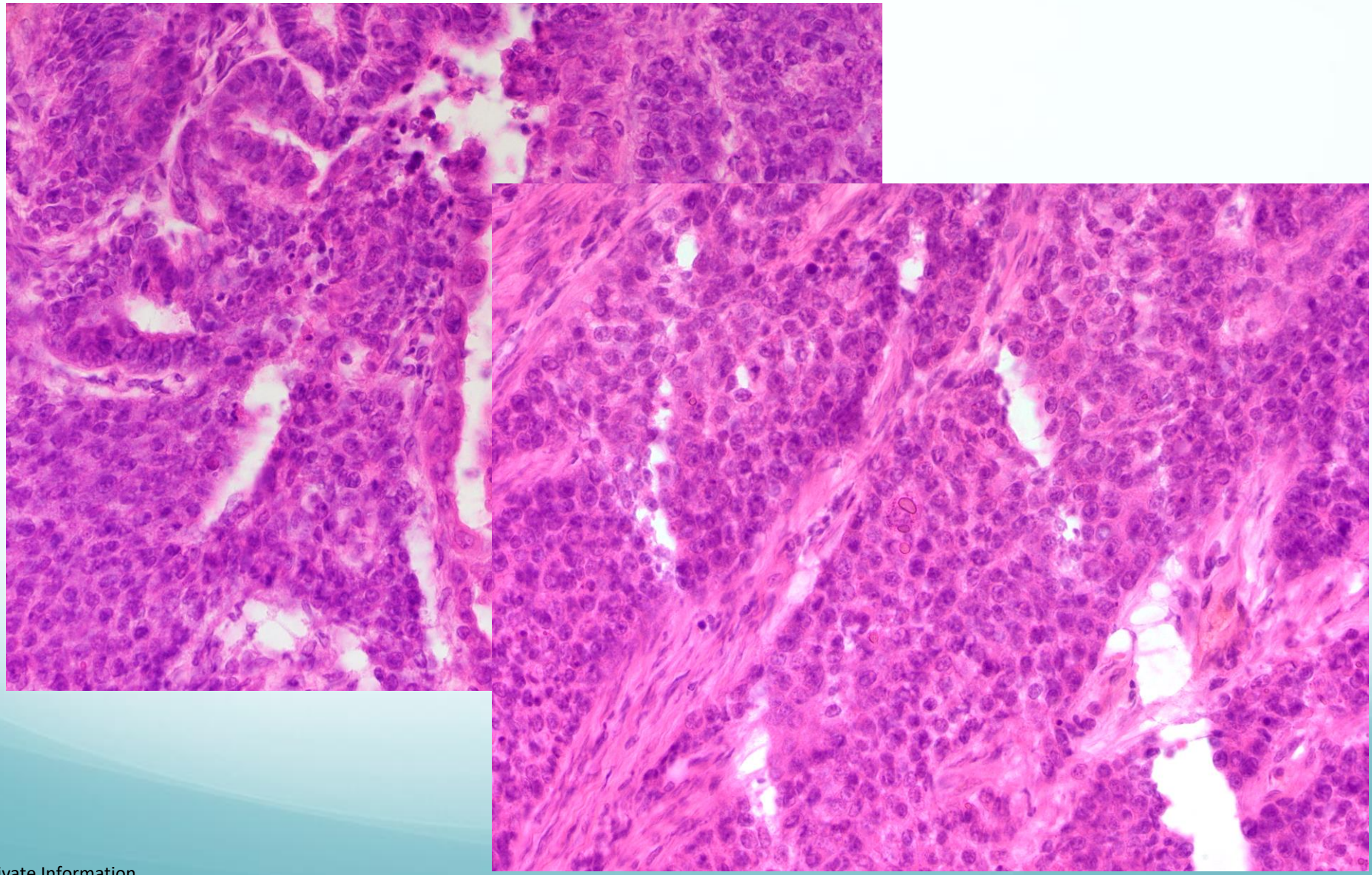
63 year-old with post-menopausal bleeding



63 year-old with post-menopausal bleeding



63 year-old with post-menopausal bleeding



63 year-old with post-menopausal bleeding

- Frozen diagnosis: " FIGO 3 endometrioid carcinoma, deeply invasive greater than 50%"
  - Right complete LAD was performed

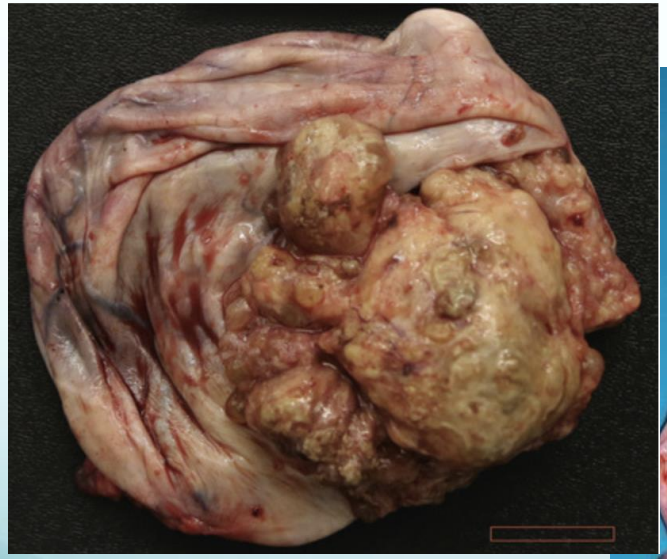
- Final diagnosis:
  - "Endometrial carcinoma, endometrioid type, FIGO grade 3, with invasion through approximately 90% of the myometrial thickness"
  - Left sentinel lymph node and right complete lymph nodes were negative.

Take home points

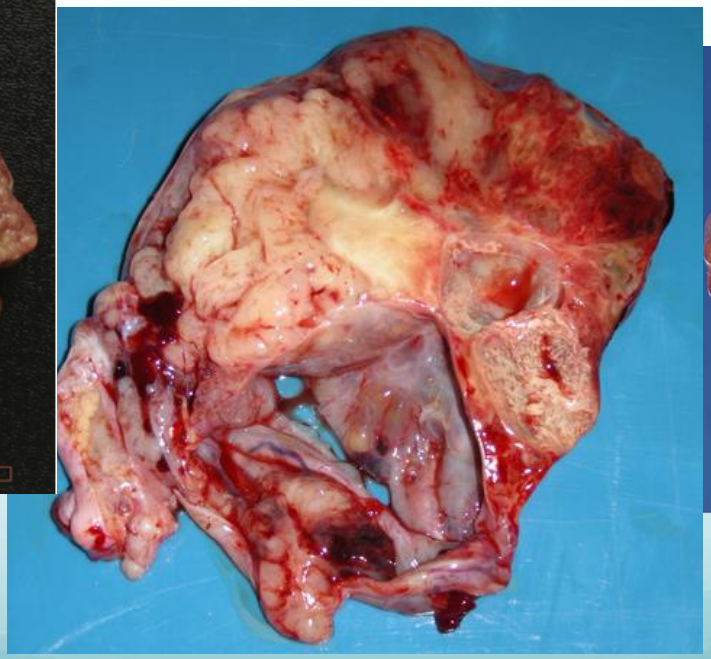
- Intraoperative management planning for endometrial cancer is nuanced and rapidly evolving:
  - For now, we need to be prepared to evaluate “old school” endomyometrial frozen sections.
  - As clinical data continue to emerge, our individual practices will continue to change.

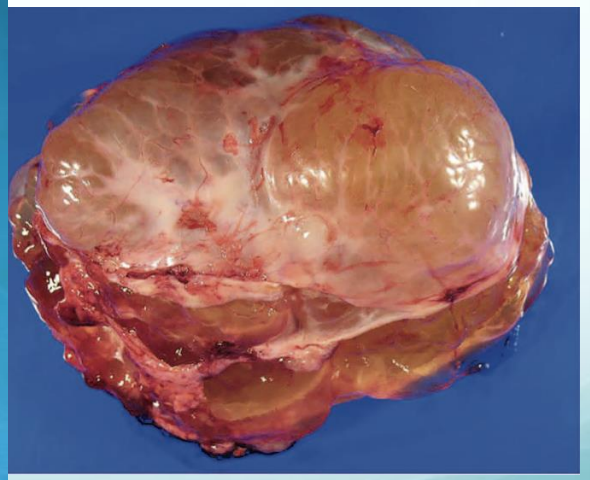
The dreaded ovarian mass frozen

Why do we fear them?



Crum, 3rd Ed



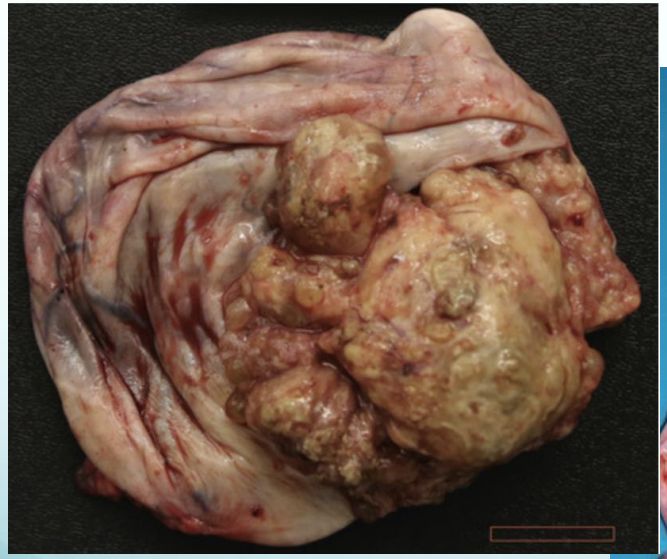


Buza, et al, Arch Pathol Lab Med, 2019

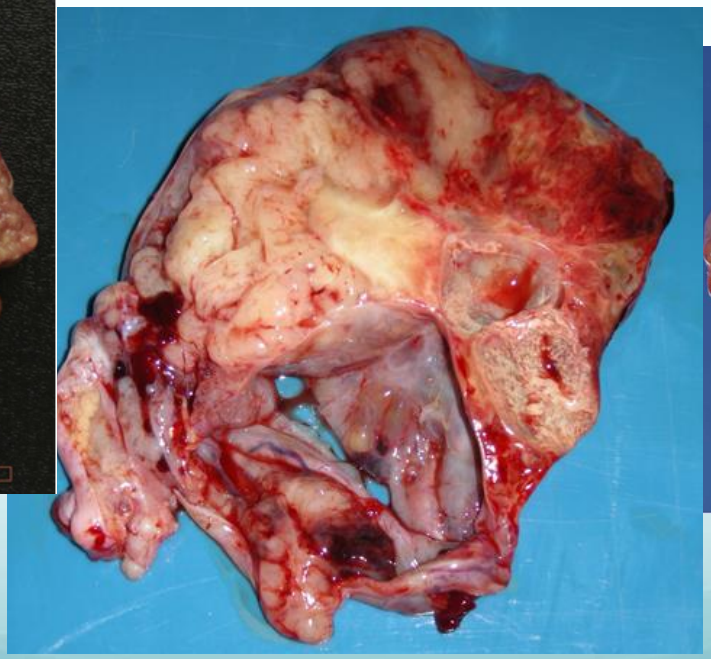
The dreaded ovarian mass frozen

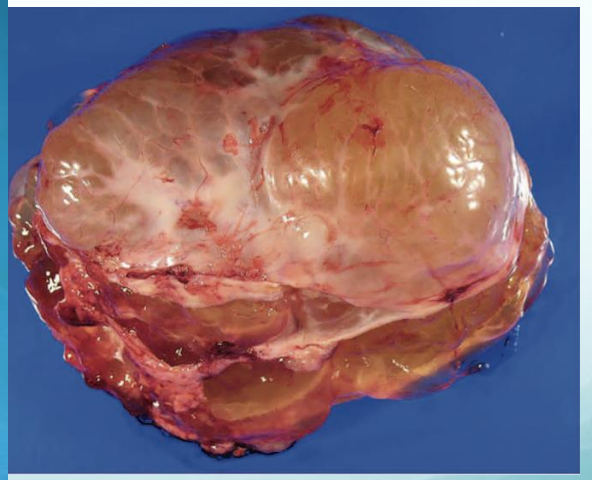
Why do we fear them?

Because they are hard!



Crum, 3rd Ed





Buza, et al, Arch Pathol Lab Med, 2019

The dreaded ovarian mass frozen

However, we are actually pretty good at them (except for borderline tumors)

Accuracy of frozen section dx (%) relative to final

	Benign	Borderline	Malignant
Sensitivity	93-98	61-84	84-98
PPV	92	62-65	98-100

Table 26-8 from Diagnostic Gynecologic and Obstetric Pathology, Crum, Nucci, Lee, 2nd Ed

The biggest source of discrepancy between the frozen interpretation and the final diagnosis: **Sampling error**

The dreaded ovarian mass frozen

Why else do we fear them?

The dreaded ovarian mass frozen

Why else do we fear them?

Because a lot is riding on our diagnosis!

The dreaded ovarian mass frozen

- Patients with adnexal masses rarely have conclusive pre-operative diagnosis
  - Imaging studies and serum markers are neither sensitive nor specific
  - Difficult to access tissue for biopsy/FNA
- Intraoperative evaluation by frozen section is **critical** in guiding the surgeon's next step

The dreaded ovarian mass frozen

- What does the gyn surgeon want from us, and what will they do with the information?

The dreaded ovarian mass frozen

- What does the gyn surgeon want from us?
  - Benign or malignant? Or borderline?

The dreaded ovarian mass frozen

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NCCN Guidelines Version 1.2024
Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer

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WHO HISTOLOGIC CLASSIFICATION[1,2]

Sex Cord-Stromal Tumors: Pure Sex Cord Tumors	
• Adult granulosa cell tumor of the ovary	3
• Granulosa cell tumor, juvenile	1
• Sertoli cell tumor NOS	1
• Sex cord tumor with annular tubules	1
Sex Cord-Stromal Tumors: Pure Stromal Tumors	
• Fibroma NOS	0
▸ Cellular fibroma	1
• Thecoma NOS	0
• Thecoma, luteinized	0

Mixed Sex Cord-Stromal Tumors	
• Sertoli-Leydig cell tumor NOS	1
▸ Sertoli-Leydig cell tumor, well differentiated	0
▸ Sertoli-Leydig cell tumor, moderately differentiated	1
▸ Sertoli-Leydig cell tumor, poorly differentiated	3
▸ Sertoli-Leydig cell tumor, retiform	1
• Sex cord tumor NOS	1

[1] Reproduced with permission from Adhikari J, Hassell LA. World Health Organization Classification of Female Genital Tumours, 5th edition. IARC, 2020.

[2] Behavior is coded 0 for benign tumors; 1 for unspecified, borderline, or uncertain behavior; 2 for carcinoma in situ and grade III intraepithelial neoplasia; 3 for malignant tumors, primary site.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

The dreaded ovarian mass frozen

- What does the gyn surgeon want from us?
  - Benign or malignant? Or borderline?
  - If malignant, primary tubo-ovarian or metastatic?
    - Metastatic carcinoma accounts for up to 15% of ovarian malignancies

The dreaded ovarian mass frozen

- What does the gyn surgeon want from us?
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  - If metastatic, gyn primary or non-gyn?

The dreaded ovarian mass frozen

- What does the gyn surgeon want from us?
  - Benign or malignant? Or borderline?
  - If malignant, primary tubo-ovarian or metastatic?
    - Metastatic carcinoma accounts for up to 15% of ovarian malignancies
  - If metastatic, gyn primary or non-gyn?

Don't be afraid to chat to your surgeon about your observations/diagnostic dilemmas – even if you can't be conclusive

The dreaded ovarian mass frozen
What will the surgeon do next?

- Benign:
  - Cystectomy
  - Adnexectomy
- Borderline:
  - Options…
- Malignant, primary tubo-ovarian:
  - Comprehensive staging/debulking with omentectomy for epithelial tumors)
- Malignant, metastasis from other primary gyn site:
  - Comprehensive staging, sometimes without omentectomy
- Malignant, metastasis from non-gyn primary:
  - Something different

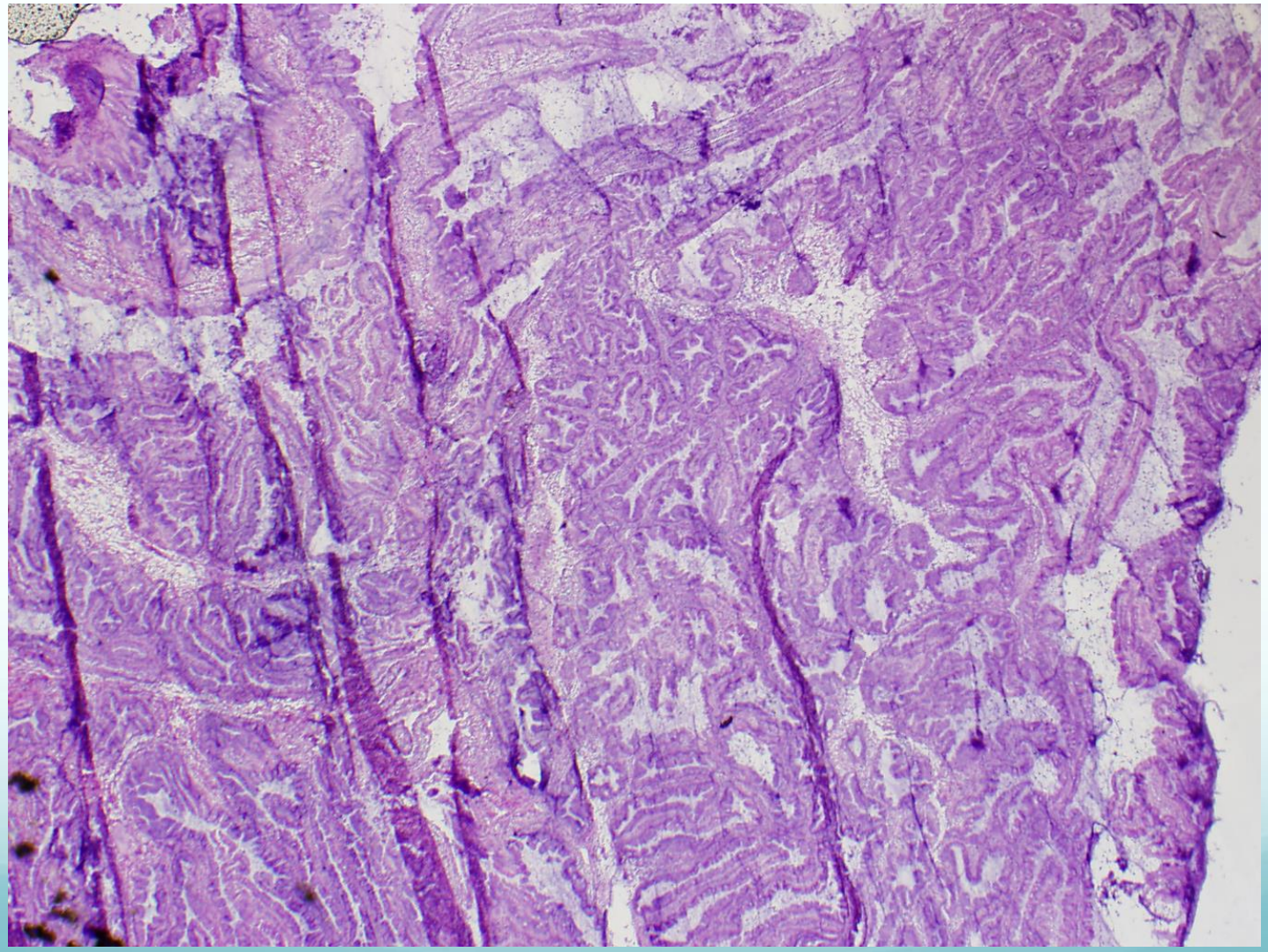
The dreaded ovarian mass frozen
What will the surgeon do next?

- Borderline epithelial tumors – surgical options:
  - Comprehensive staging
  - Conservative, fertility sparing options:
    - Unilateral salpingo-oophorectomy with limited staging
    - Cystectomy

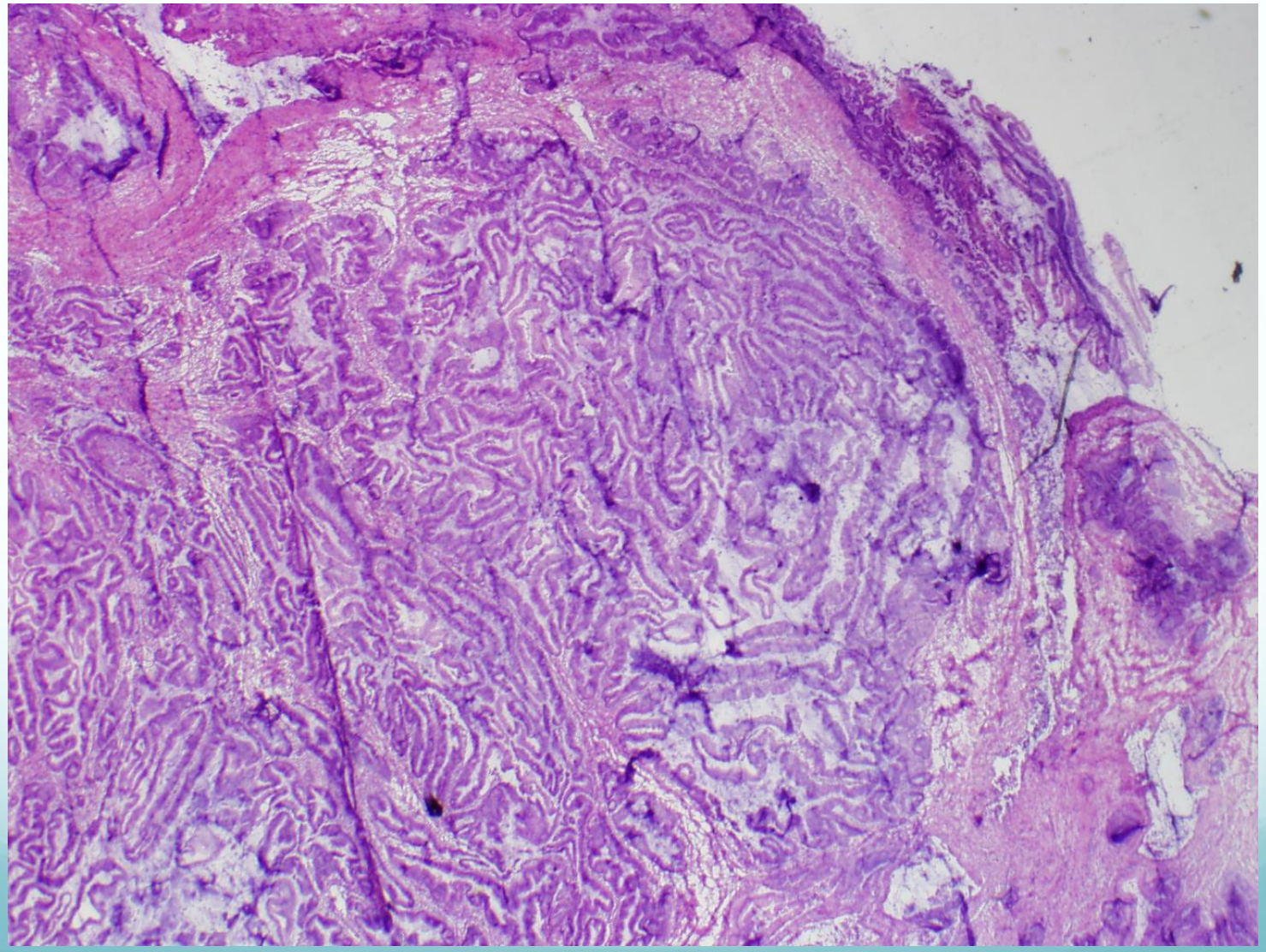
The dreaded ovarian mass frozen
What will the surgeon do next?

- When “borderline vs. malignant” can’t be conclusively answered…
  - Consider asking the surgeon if there are extraovarian masses that can be sampled
  - It is ok to say “at least borderline, defer to permanents”
  - Don’t push it all the way to cancer if conclusive features aren’t present

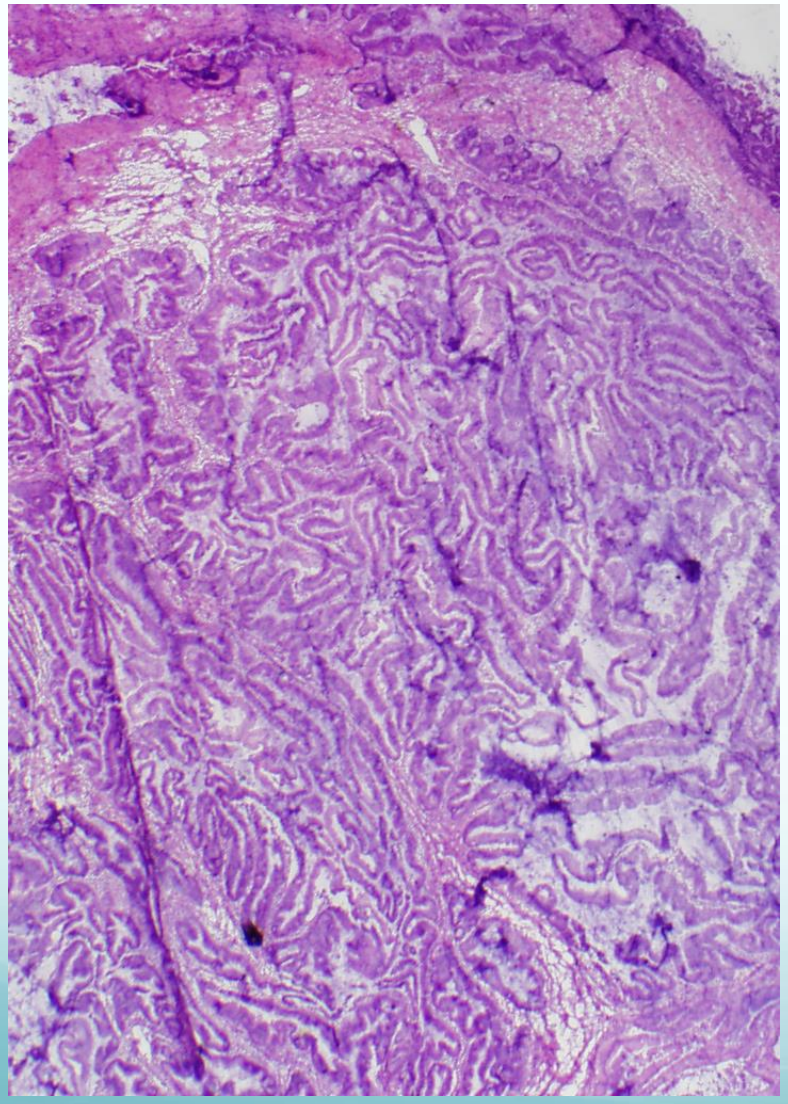
45 y/o, unilateral 28 cm multiloculated cystic ovarian mass

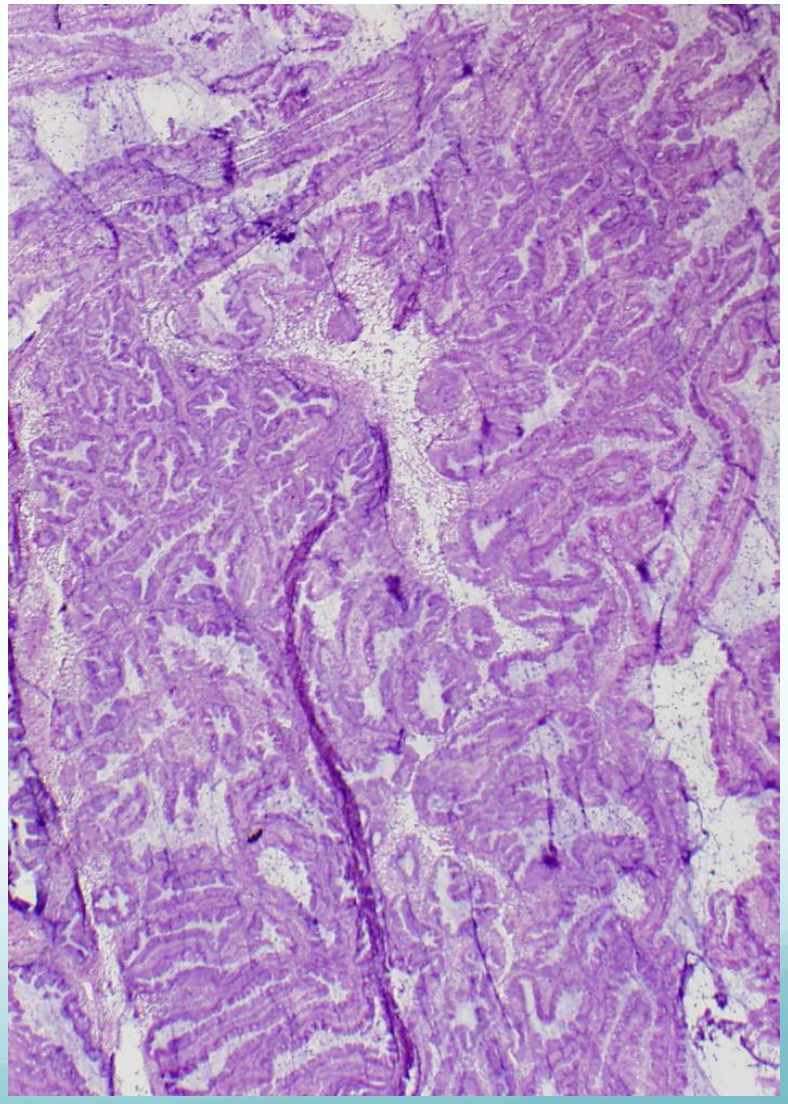


45 y/o, unilateral 28 cm multiloculated cystic ovarian mass

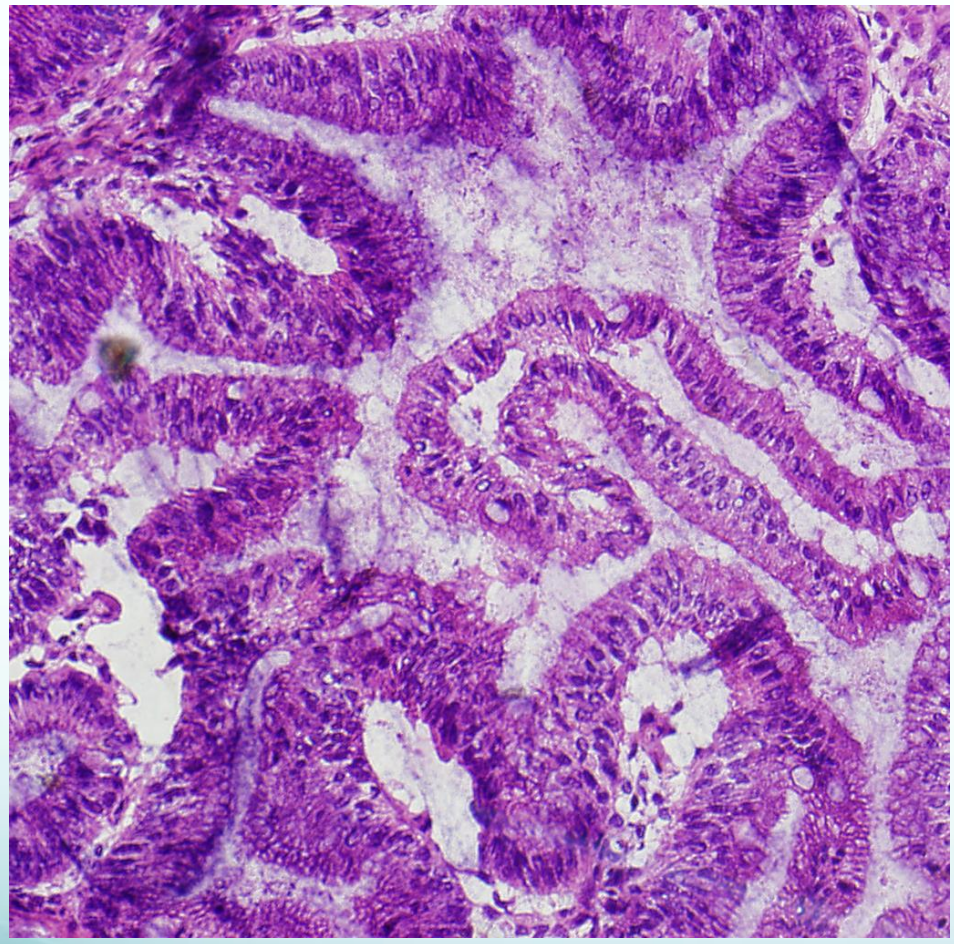


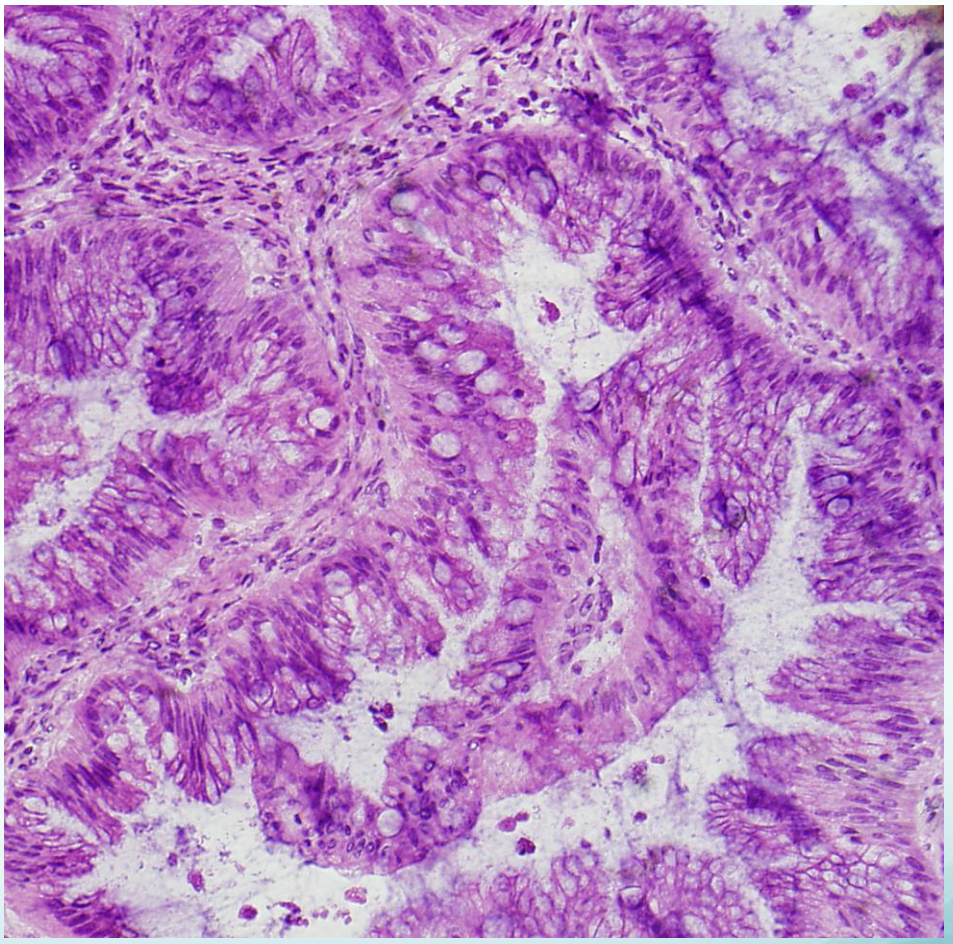
45 y/o, unilateral 28 cm multiloculated cystic ovarian mass





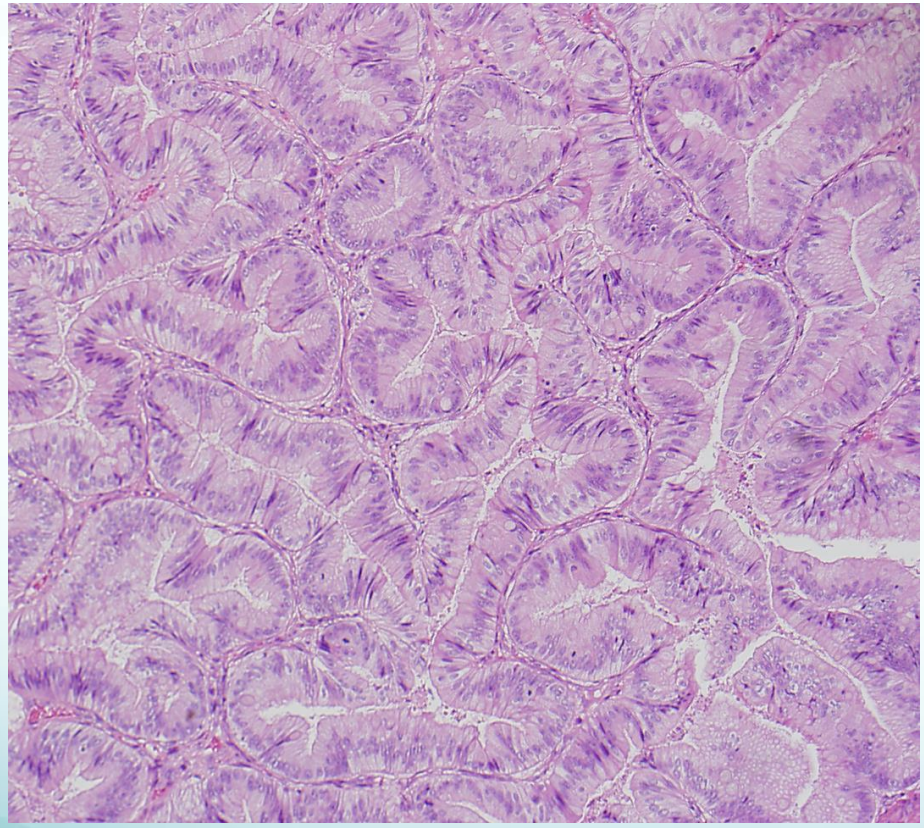
Frozen Dx: “At least mucinous borderline tumor, defer to permanents”

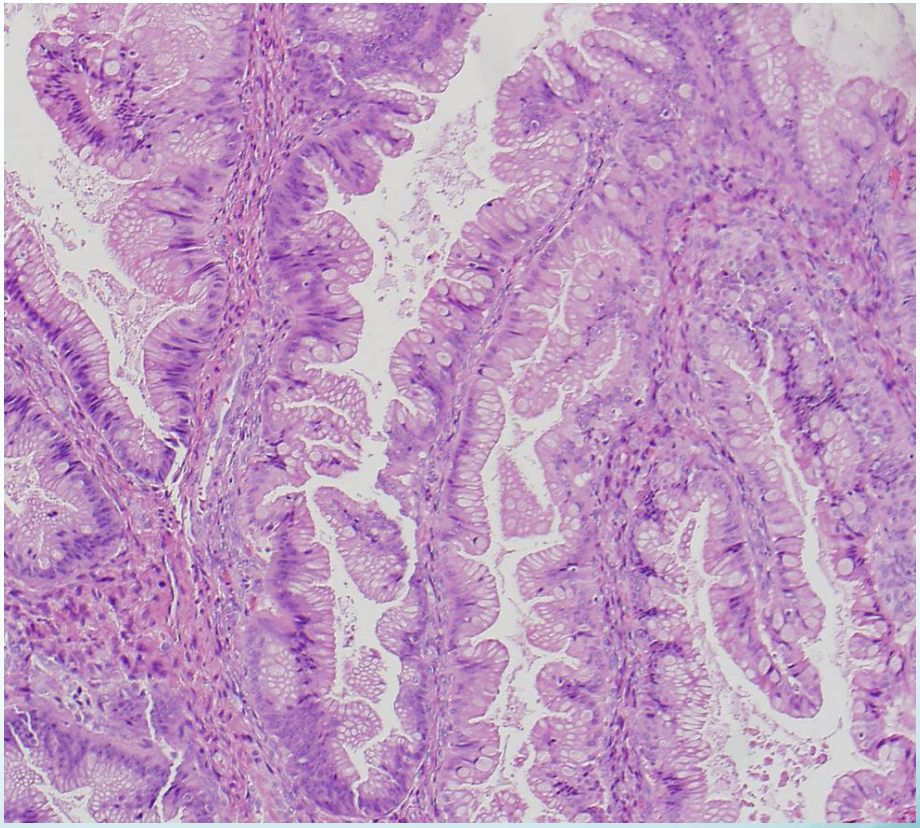




Patient underwent complete staging…

Final Dx: “Mucinous carcinoma arising in a background of mucinous borderline tumor”





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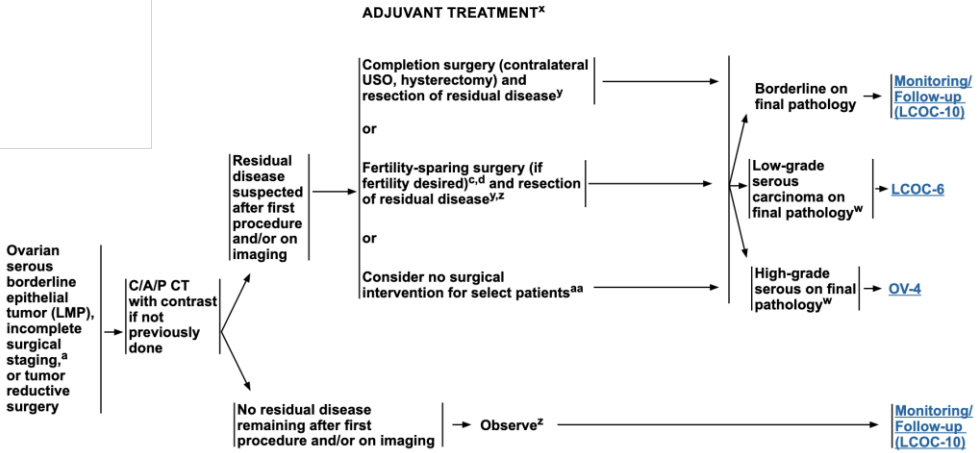
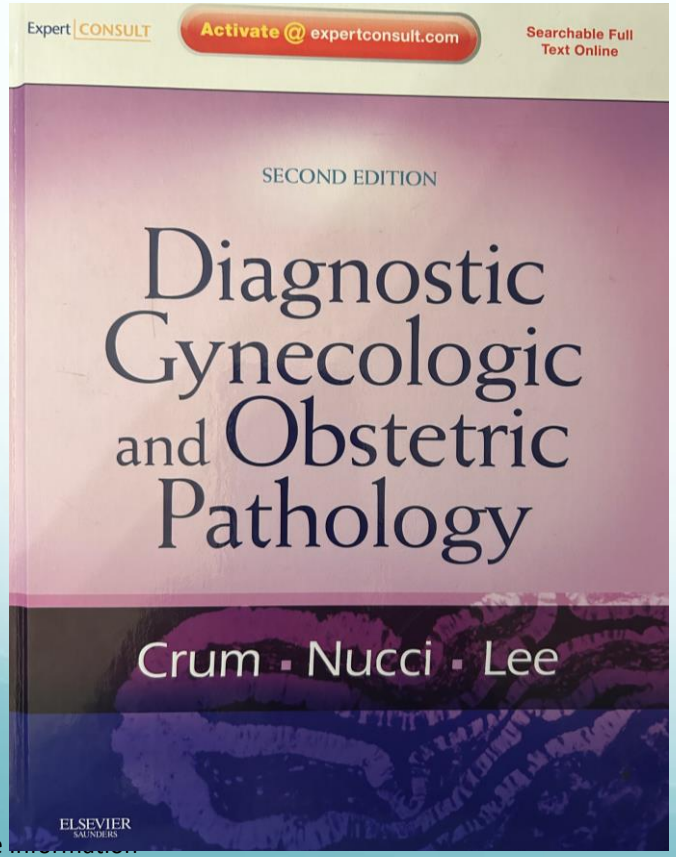


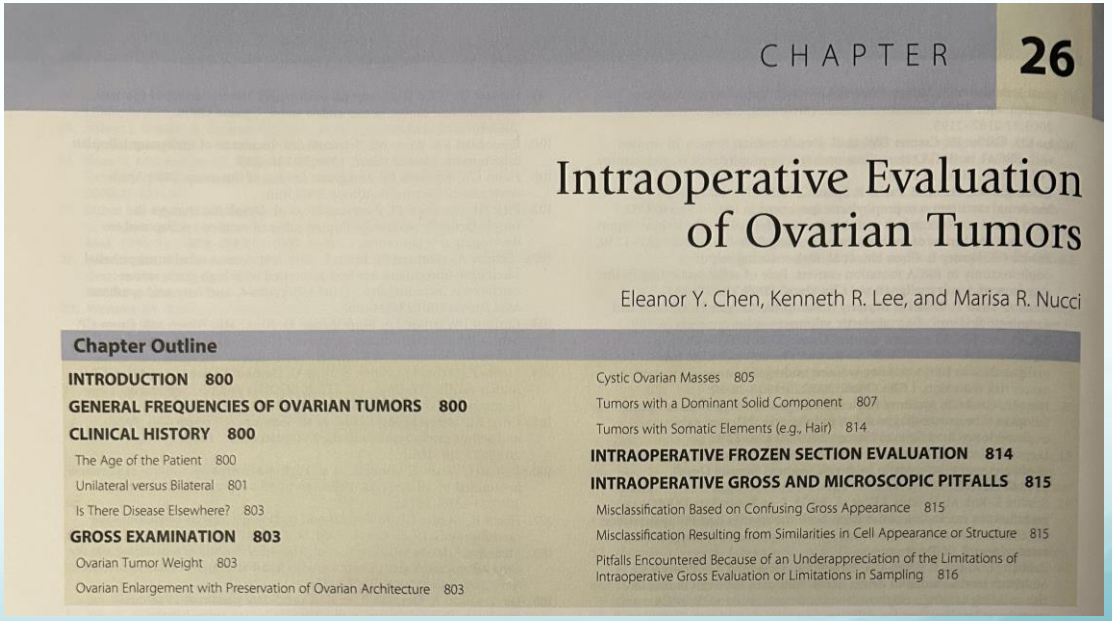
[a] WHO Histologic Classification (OV-E).
[c] Principles of Surgery (OV-A).
[d] Principles of Pathology (OV-B).
[w] Chemotherapy (IV or IP) has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[x] Standard recommendation includes a patient evaluation by a gynecologic oncologist.
[y] For pathologically proven ovarian borderline epithelial tumors, lymph node evaluation may be considered on a case-by-case basis.
[z] In patients who underwent USO, consider completion surgery (eg, contralateral USO, hysterectomy) after completion of childbearing (category 2B).
[aa] If patient is medically unfit, or for those with unresectable residual disease.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

The dreaded ovarian mass frozen

- Where to start:
  - General knowledge of ovarian tumor frequencies based on age, unilaterality/bilaterality





CHAPTER 26

Intraoperative Evaluation of Ovarian Tumors

Eleanor Y. Chen, Kenneth R. Lee, and Marisa R. Nucci

Chapter Outline

The dreaded ovarian mass frozen

- Where to start:
  - General knowledge of ovarian tumor frequencies based on age, unilaterality/bilaterality
  - Clinical/radiologic history:
    - Prior malignancy
    - Imaging findings – tumor distribution
  - Gross exam
  - Good old-fashioned morphology

The dreaded ovarian mass frozen – gross exam

- Remember – sampling errors are the biggest source of diagnostic error, and the gross exam is your guide to avoiding them!

The dreaded ovarian mass frozen – gross exam

- Remember – sampling errors are the biggest source of diagnostic error, and the gross exam is your guide to avoiding them!
  - The most important gross parameters are size, laterality (uni- vs. bi-), and cut surface
  - Measure, weigh, carefully examine the surface
  - Photograph if time permits
  - Ink along any sectioning margin before opening

The dreaded ovarian mass frozen – gross exam

- Some things to consider before opening:
  - Look at the surface – involvement by tumor means it's probably not benign
  - The larger the tumor, the more likely we are to get the frozen diagnosis wrong:
    - Take more sections if you are unsure, especially for mucinous neoplasms
  - Bilaterality is common in serous tumors, rare in primary ovarian mucinous tumors (except for endometriosis-associated mucinous tumors)

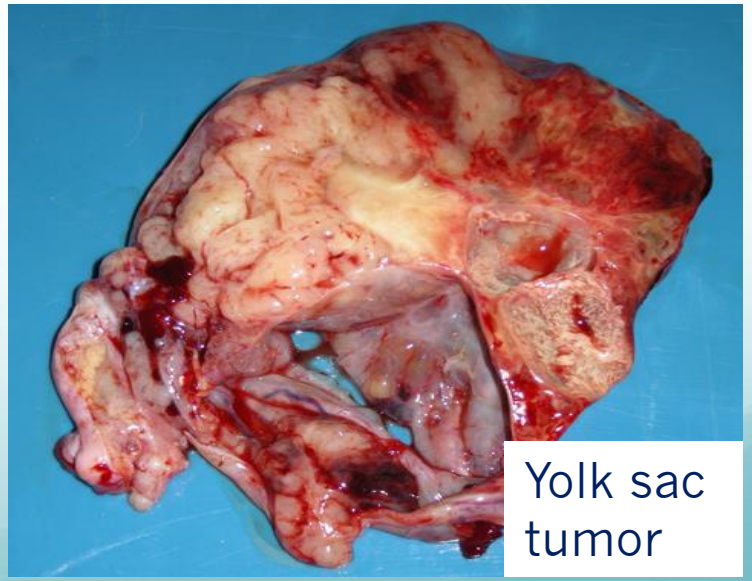
The dreaded ovarian mass frozen – gross exam

- After opening:
  - Appearance of the cut surface:
    - Solid or cystic or both?
    - Are there papillary projections in the cysts?
    - Are the solid parts (including the papillary projections) firm or friable? Uniform or heterogenous? Hemorrhagic? Necrotic?

The dreaded ovarian mass frozen – gross exam

- Some things to consider after opening:
  - Solid and solid+cystic tumors with soft/friable/hemorrhagic areas are usually malignant:
    - Older women: epithelial malignancies
    - Younger women: malignant germ cell tumors

High grade serous carcinoma



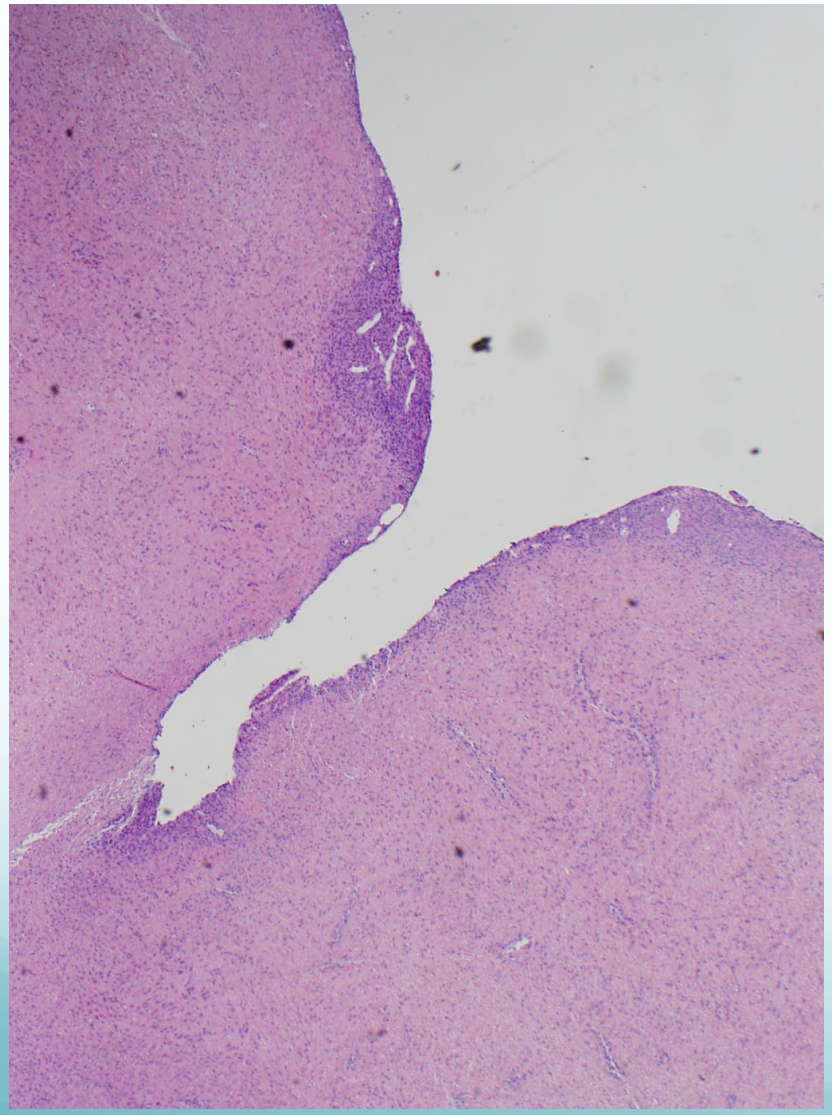
Yolk sac tumor

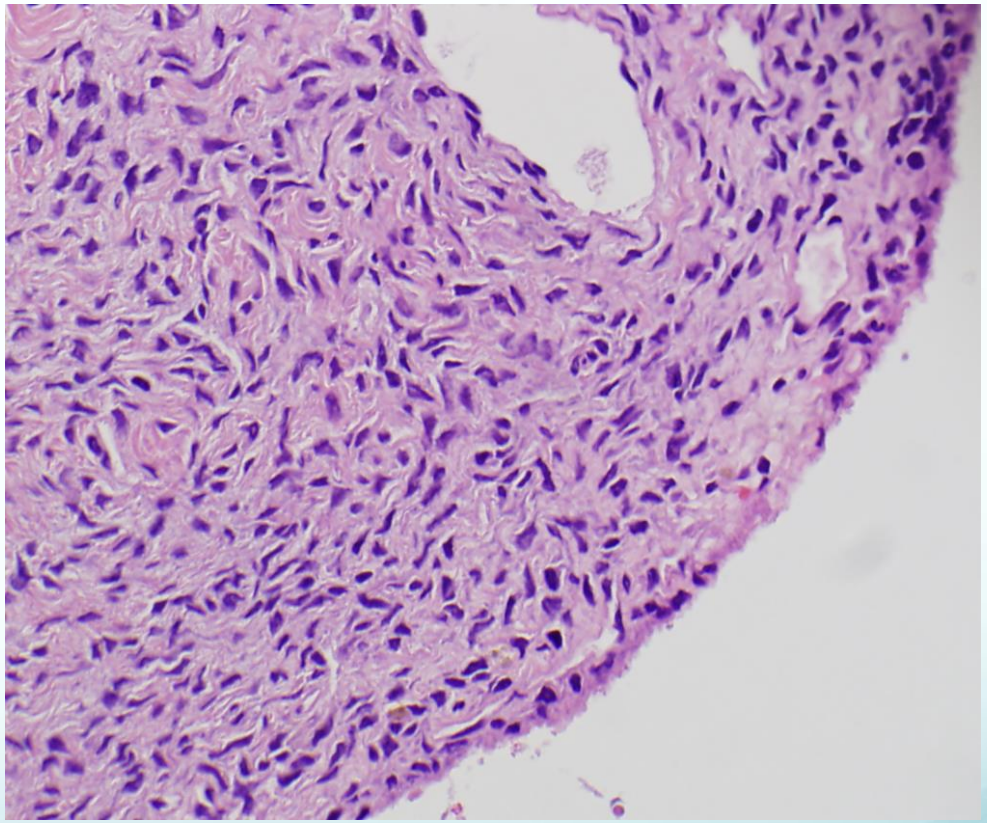
Buza, et al, Arch Pathol Lab Med, 2019

The dreaded ovarian mass frozen – gross exam

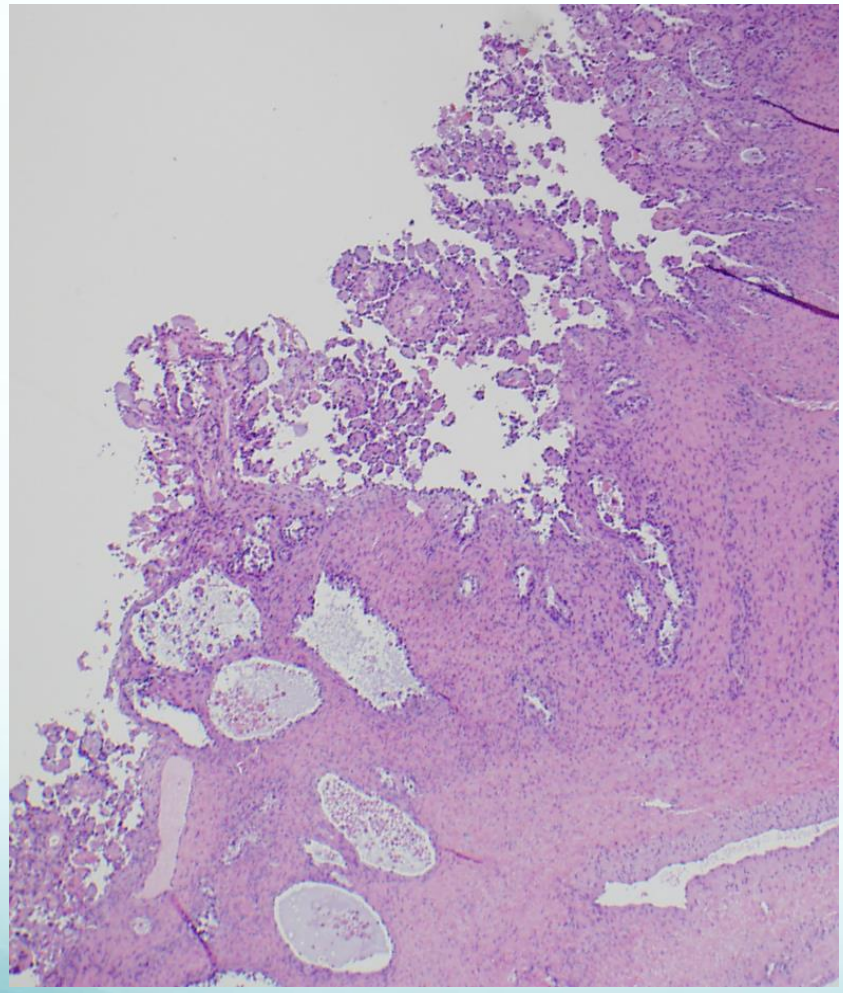
- Some things to consider after opening:
  - Solid+cystic tumors with firm areas are usually benign:
    - Benign Brenner tumors
    - Adenofibromas
  - Remember that endometriomas can grow cancers – have a good look at the lining of a ”chocolate cyst” for irregularity, thickening, solid nodule

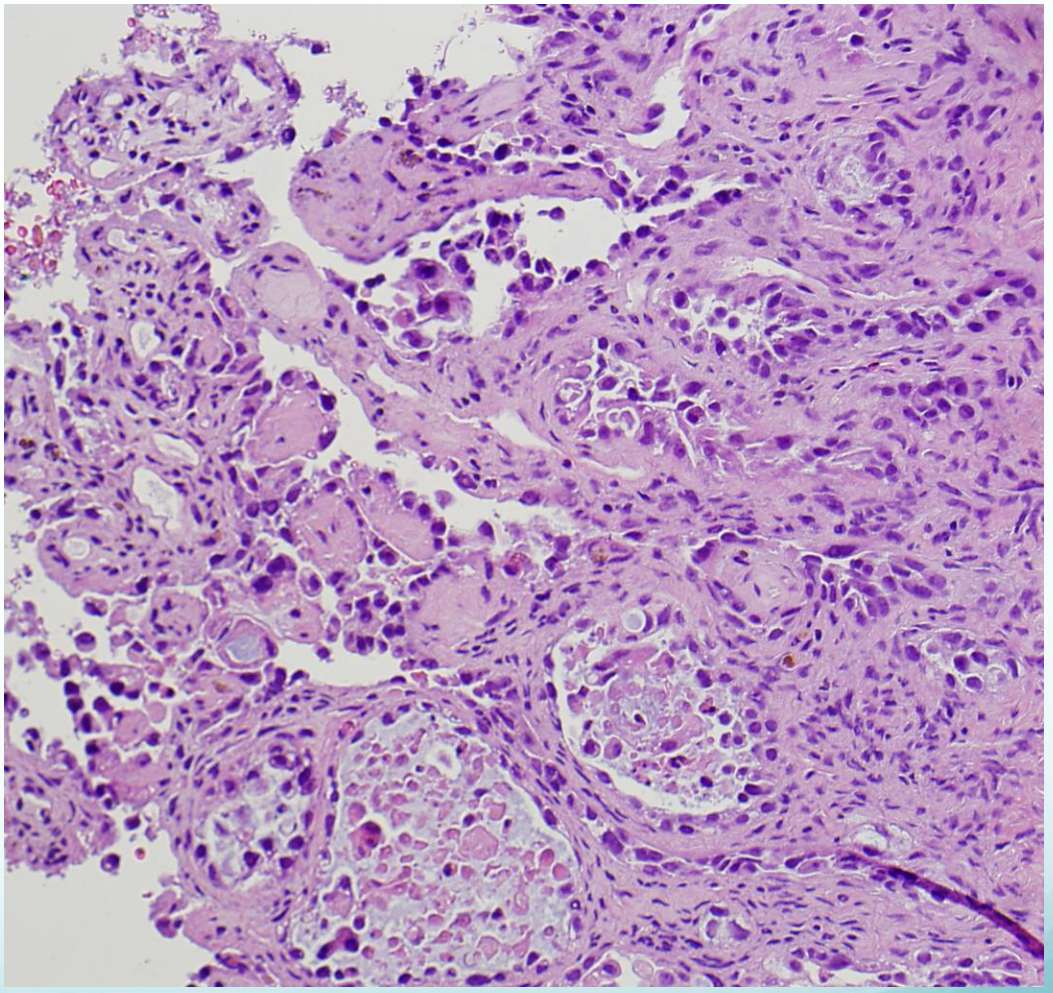
A largely innocent-looking chocolate cyst, called endometrioma on frozen





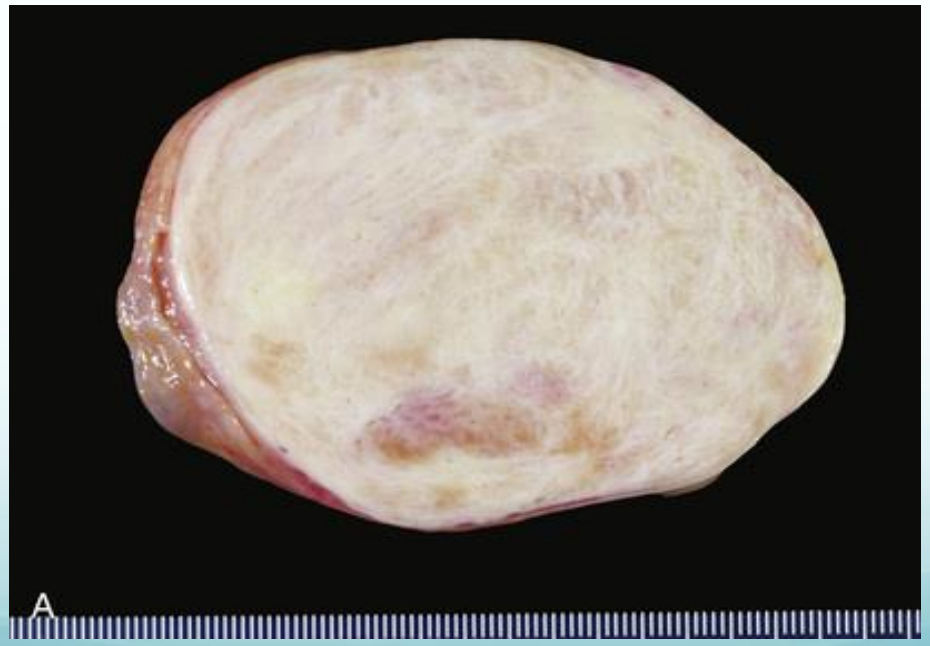
Final diagnosis: clear cell carcinoma





The dreaded ovarian mass frozen – gross exam

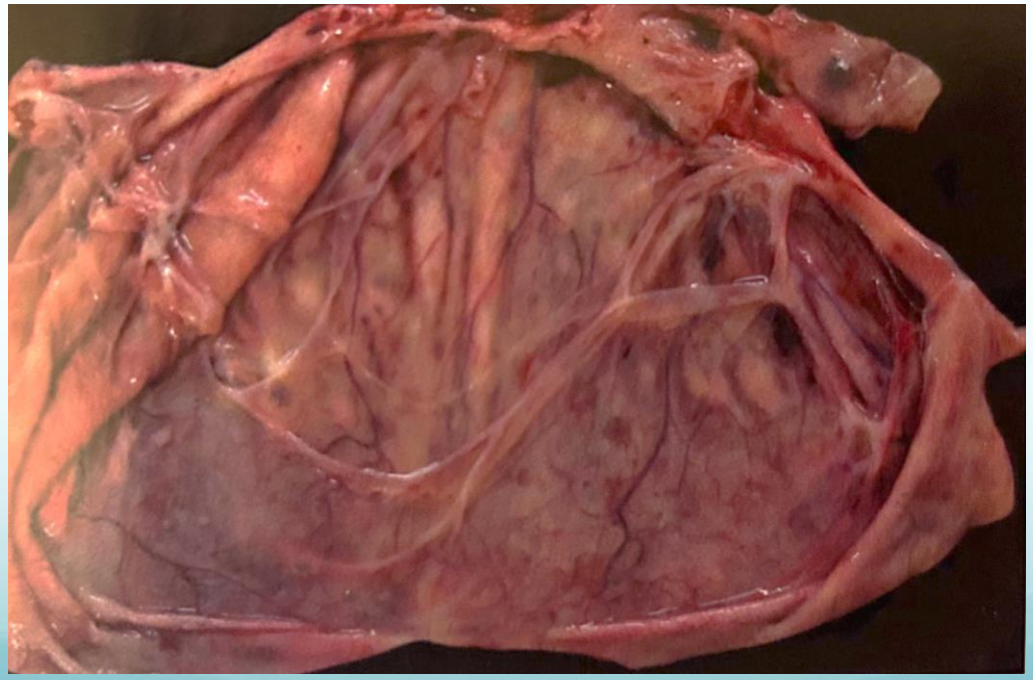
- A few more general comments:
  - Most solid, firm, white tumors are benign:
    - Cytologically bland-appearing spindle cell proliferation ("I think it's a fibroma, but it could be a periovarian leiomyoma")



Crum, 2nd Ed

The dreaded ovarian mass frozen – gross exam

- A few more general comments:
  - Entirely cystic with smooth lining, usually benign
  - You do not have to freeze a thin-walled unilocular cyst from a patient of any age – it's benign!



Crum, 2nd Ed

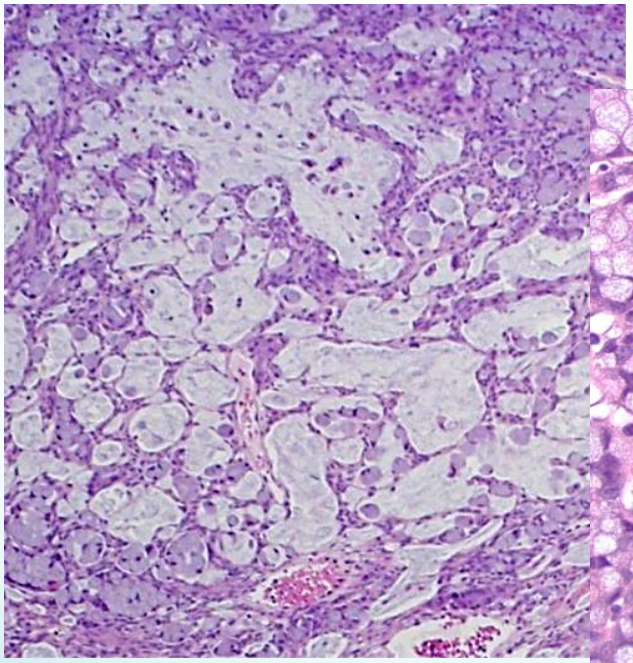
The most dreaded ovarian mass frozen of all: Mucinous neoplasms - primary ovary vs metastasis

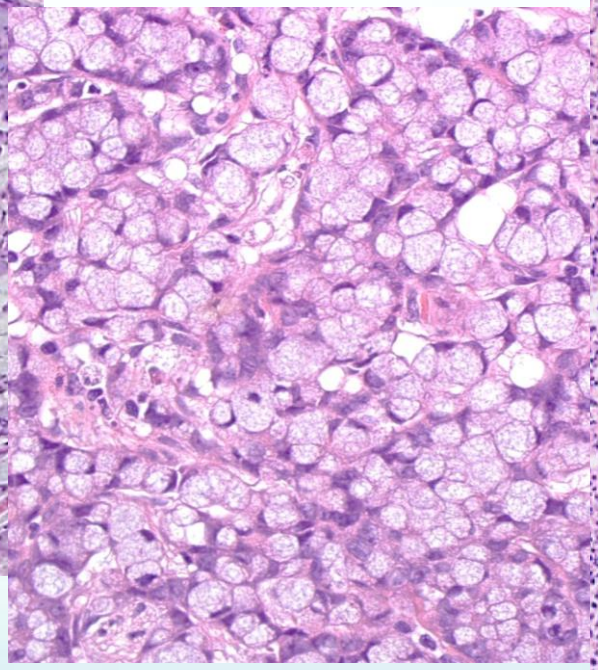
Intraoperative evaluation of mucinous neoplasm – gross exam

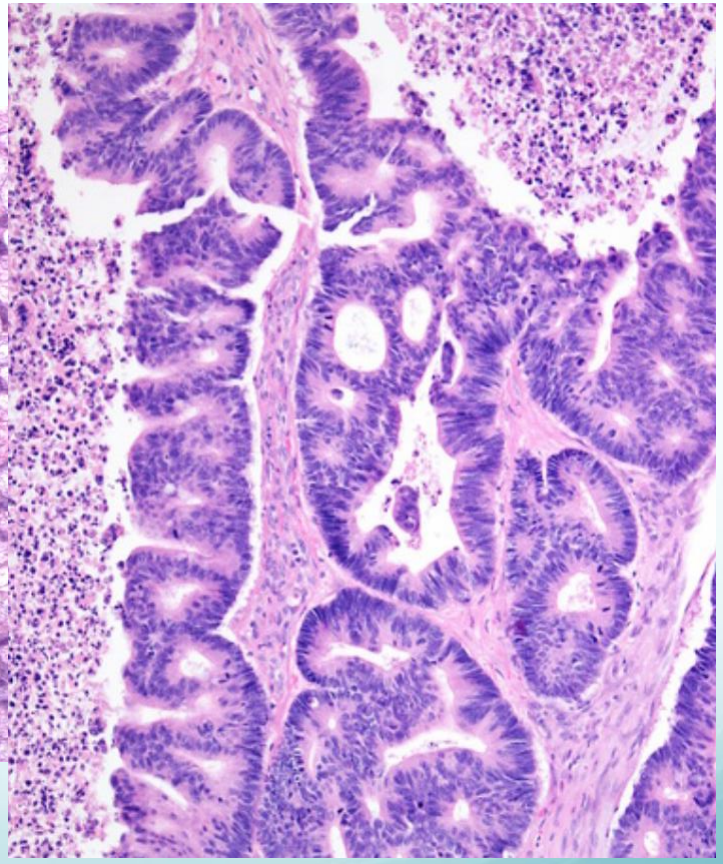
- Primary ovary:
  - Unilateral
  - Large (~22 cm)
  - No surface involvement
  - Stage I
- Metastatic to ovary:
  - Often bilateral
  - Usually “smaller” (16 cm on average)
  - Ovarian surface involvement
  - Extra-ovarian tumor (peritoneum, omentum) is common
  - Pseudomyxoma peritoneii

Intraoperative evaluation of mucinous neoplasm - histology

Classic patterns implicating metastasis:







Intraoperative evaluation of mucinous neoplasm

- Also remember: some mets can look dead bland!
  - Low-grade mucinous neoplasms from the appendix
  - Pancreatic ductal adenocarcinoma
- Also remember: ”GI-looking” mucinous adenocarcinomas may arise in ovarian teratomas

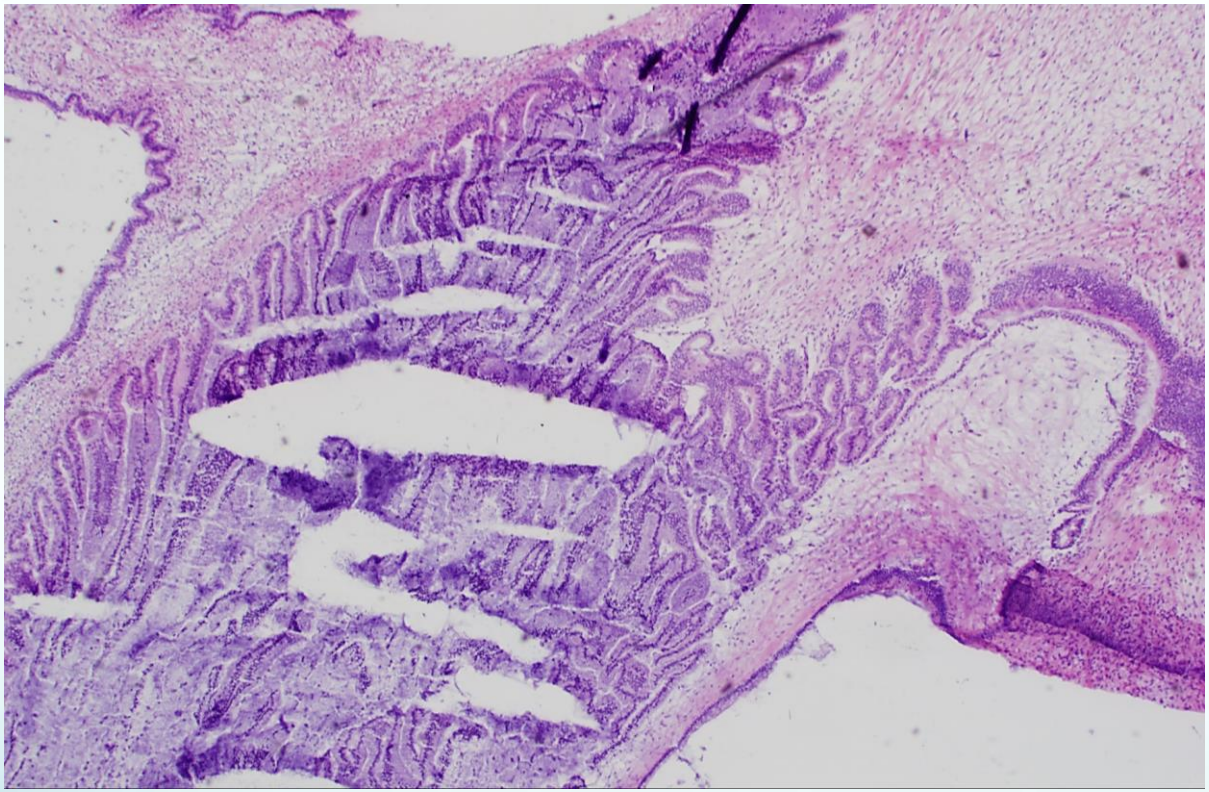
Intraoperative evaluation of mucinous neoplasm - histology

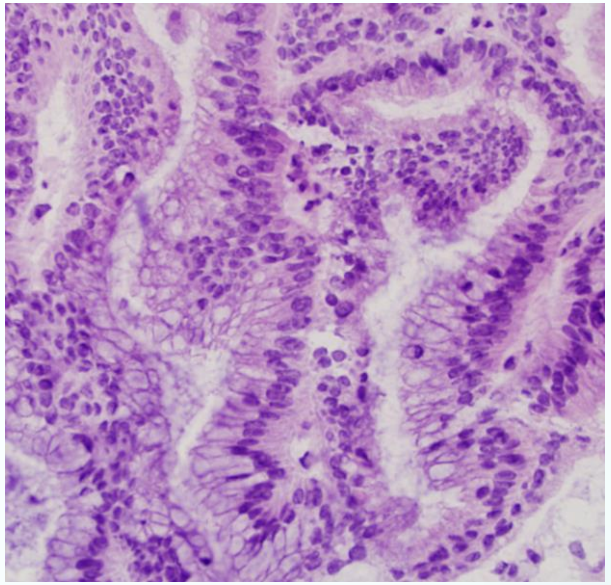
- Other microscopic features STRONGLY suggesting metastasis:
  - An infiltrative pattern of invasion
  - Single-cell infiltration
  - Lymphovascular space invasion
- Microscopic features favoring an ovarian primary:
  - Expansile pattern of invasion
  - Squamous differentiation (endometrioid aca)
  - Associated endometriosis

Intraoperative evaluation of mucinous neoplasm

- **If it's mucinous carcinoma, it's a met until proven otherwise**
  - ~80% of mucinous carcinoma involving the ovary are metastasis from other sites:
    - GI tract, pancreas, cervix, endometrium, breast
- Even if it falls short of carcinoma, still be suspicious (**know the clinical history**, ask questions)
  - Ask them "What about her other ovary? How does the appendix look? Is there tumor elsewhere?"
  - "If this is indeed a primary ovarian neoplasm, then it's a…" borderline tumor, cystadenoma, etc.

63 y/o, bilateral large multicystic ovarian masses, one sent for frozen section



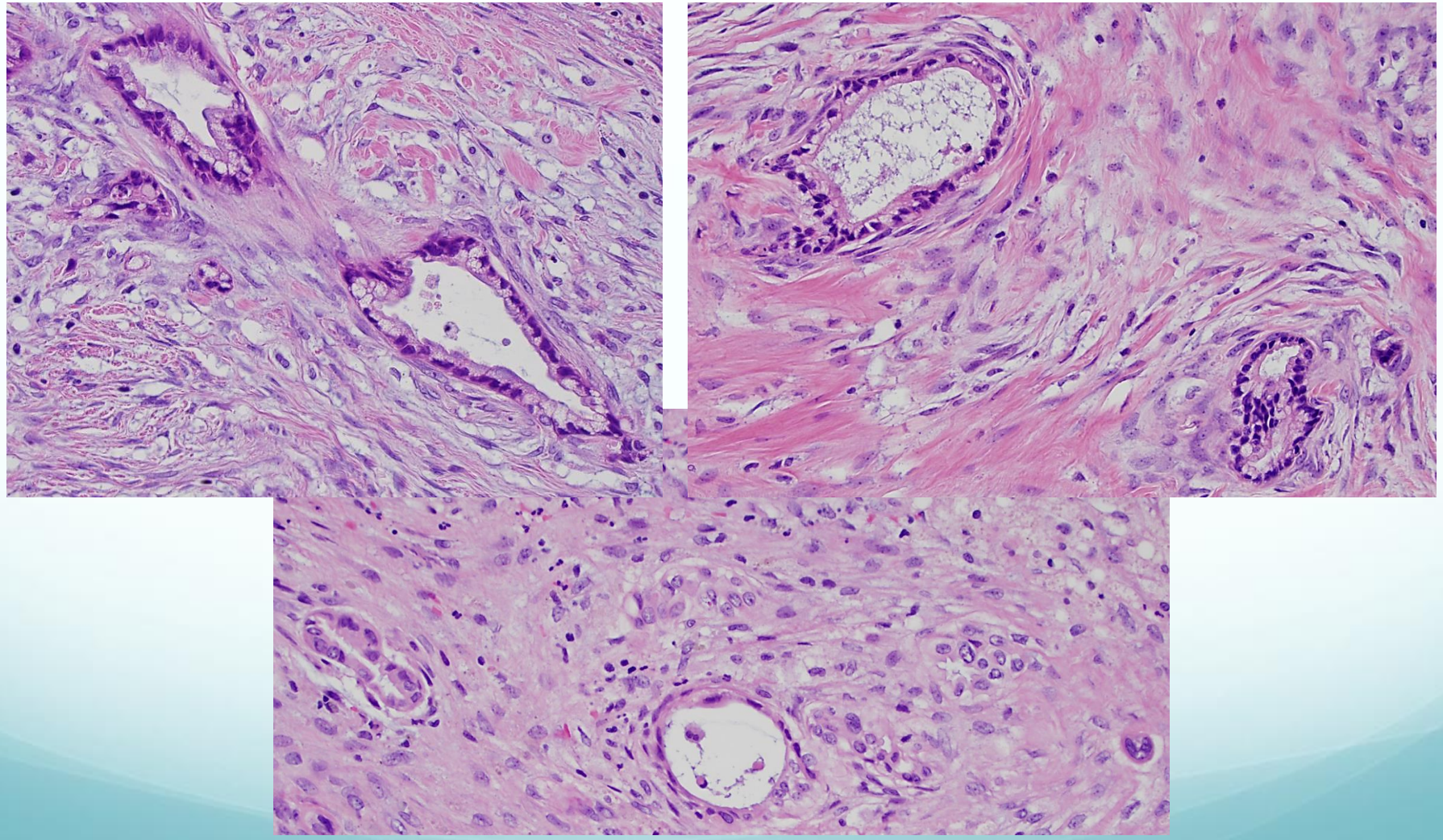


- Frozen dx: “mucinous borderline tumor”
- Staging performed

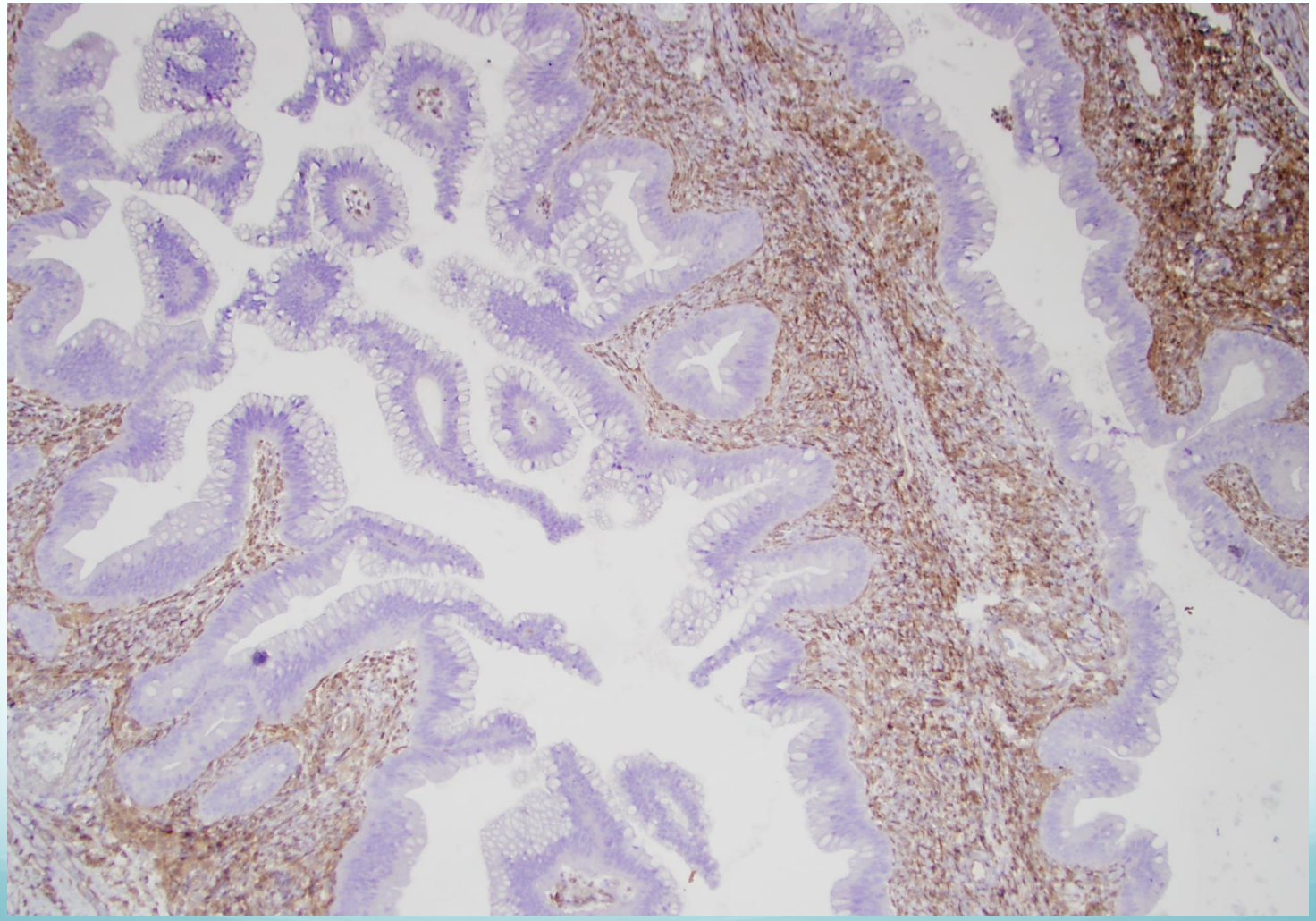
63 y/o, bilateral ovarian masses

- The pathologist was unaware that the patient had history of 5 cm pancreas head mass; prior FNA at outside institution was “inconclusive”

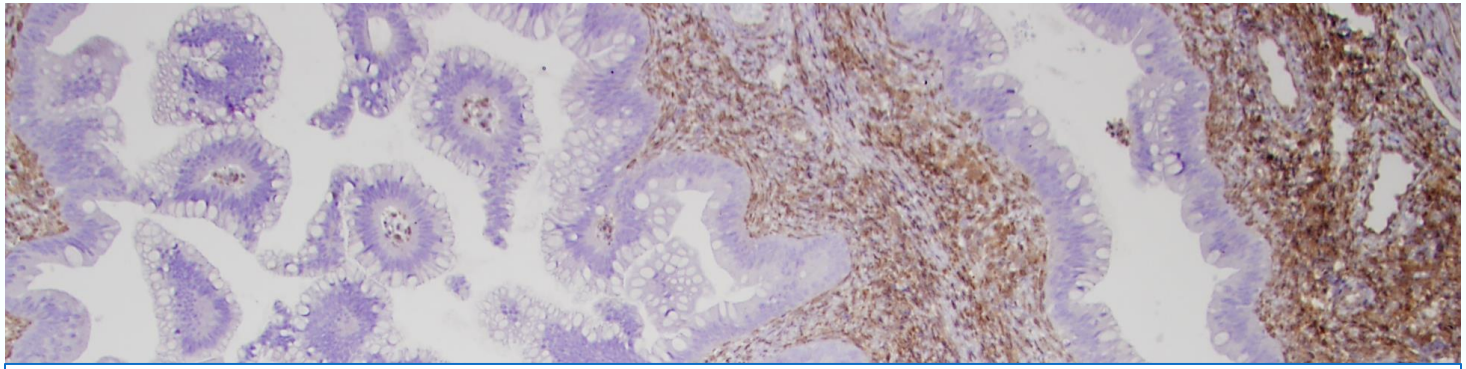
63 y/o, bilateral ovarian masses
Permanent sections



63 y/o, bilateral ovarian masses SMAD4



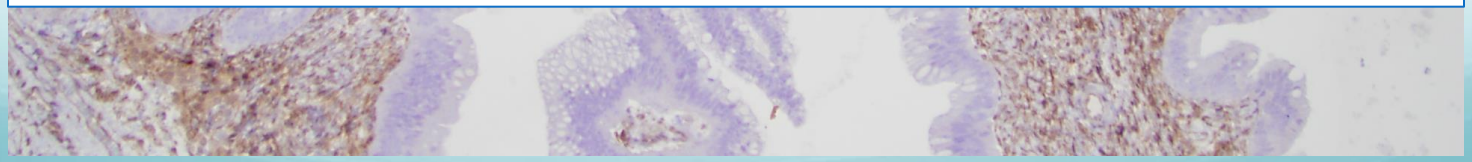
63 y/o, bilateral ovarian masses SMAD4



Final Diagnosis:

Mucinous adenocarcinoma, favor metastasis from a likely pancreatic primary

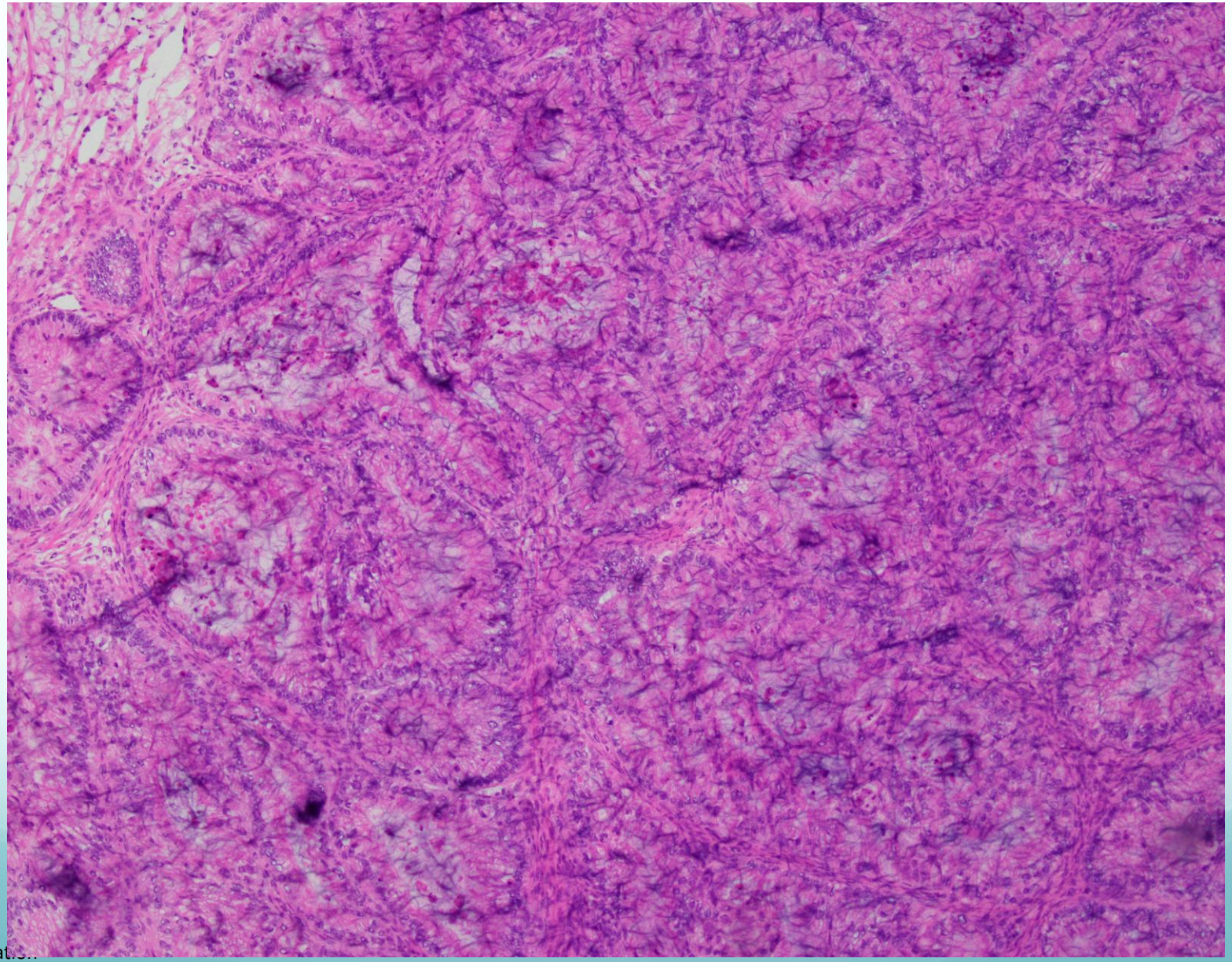
Patient was subsequently diagnosed with pancreatic ductal adenocarcinoma



40 y/o bilateral ovarian masses

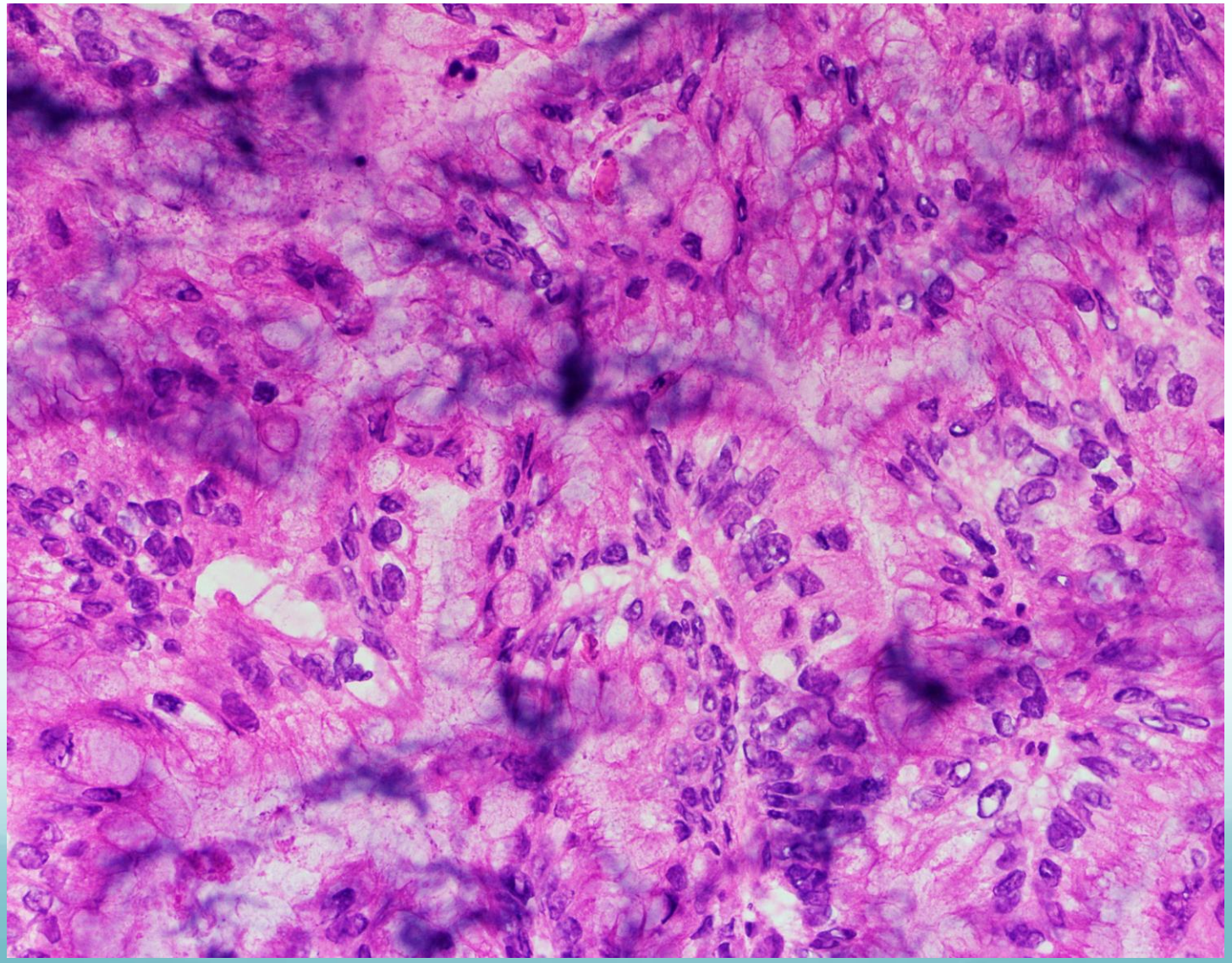
- Right tube and ovary sent for frozen:

40 y/o bilateral ovarian masses



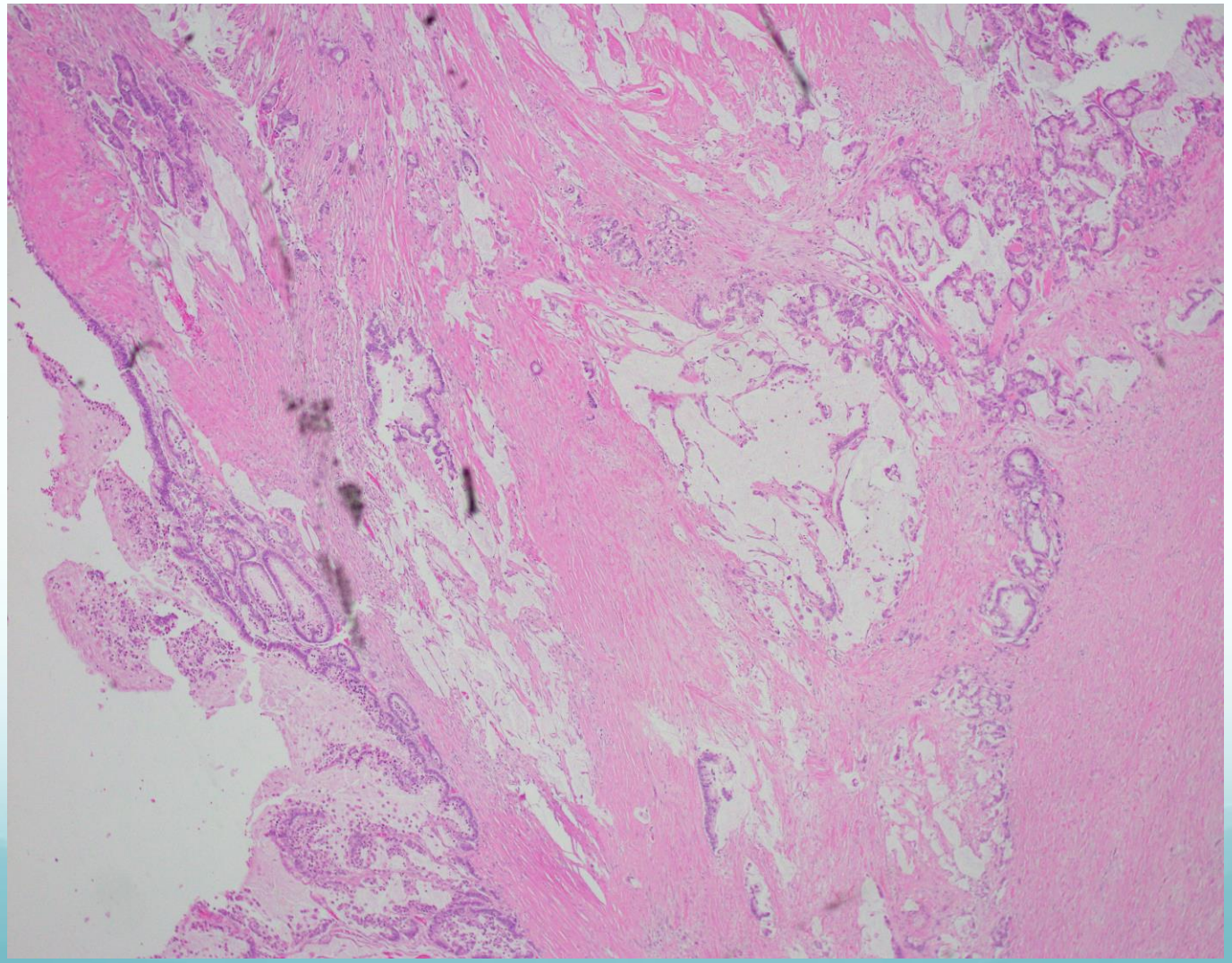
40 y/o bilateral ovarian masses

- Frozen diagnosis: “Mucinous adenocarcinoma”



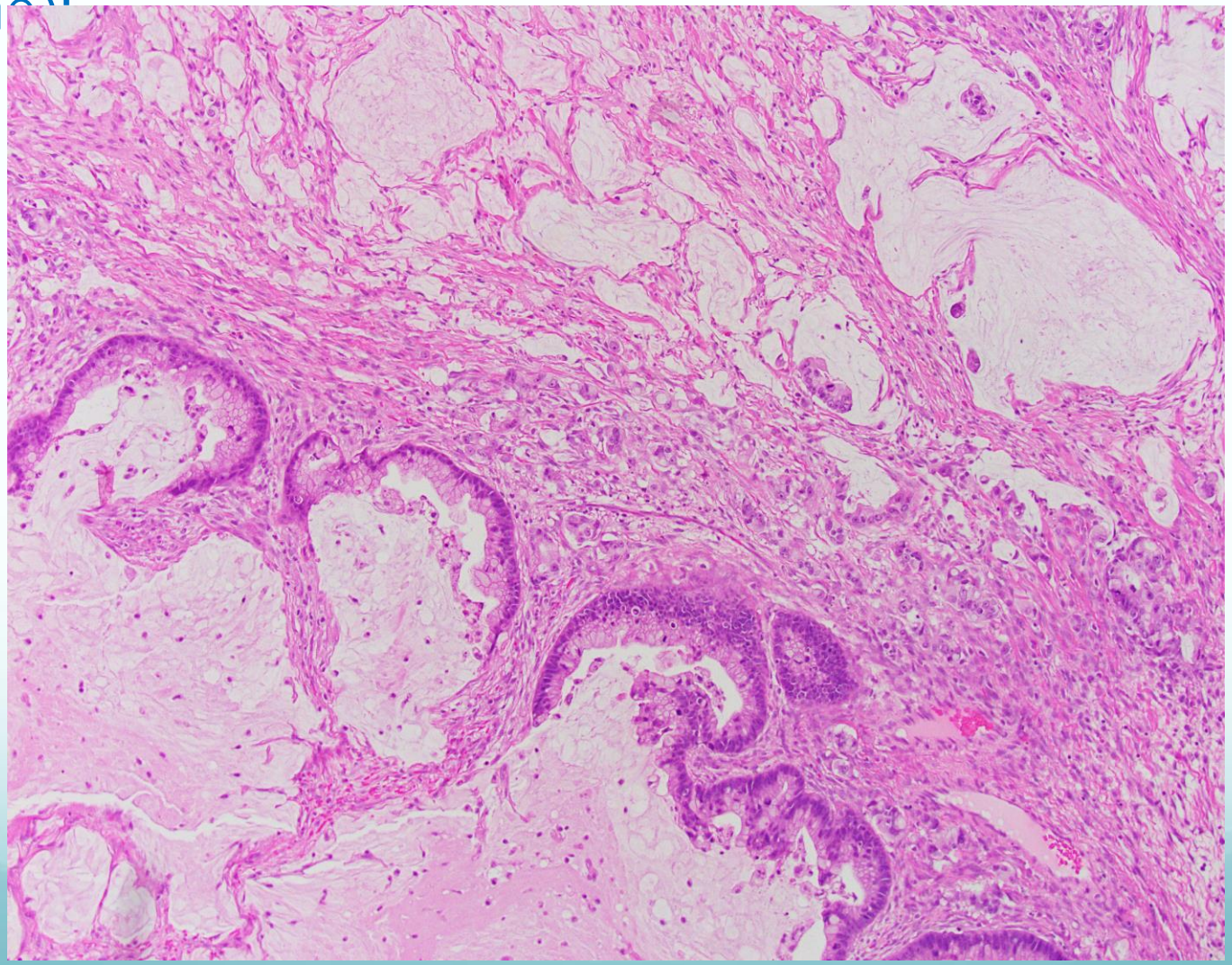
40 y/o bilateral ovarian masses

- Based on this, appendix was removed for permanent:



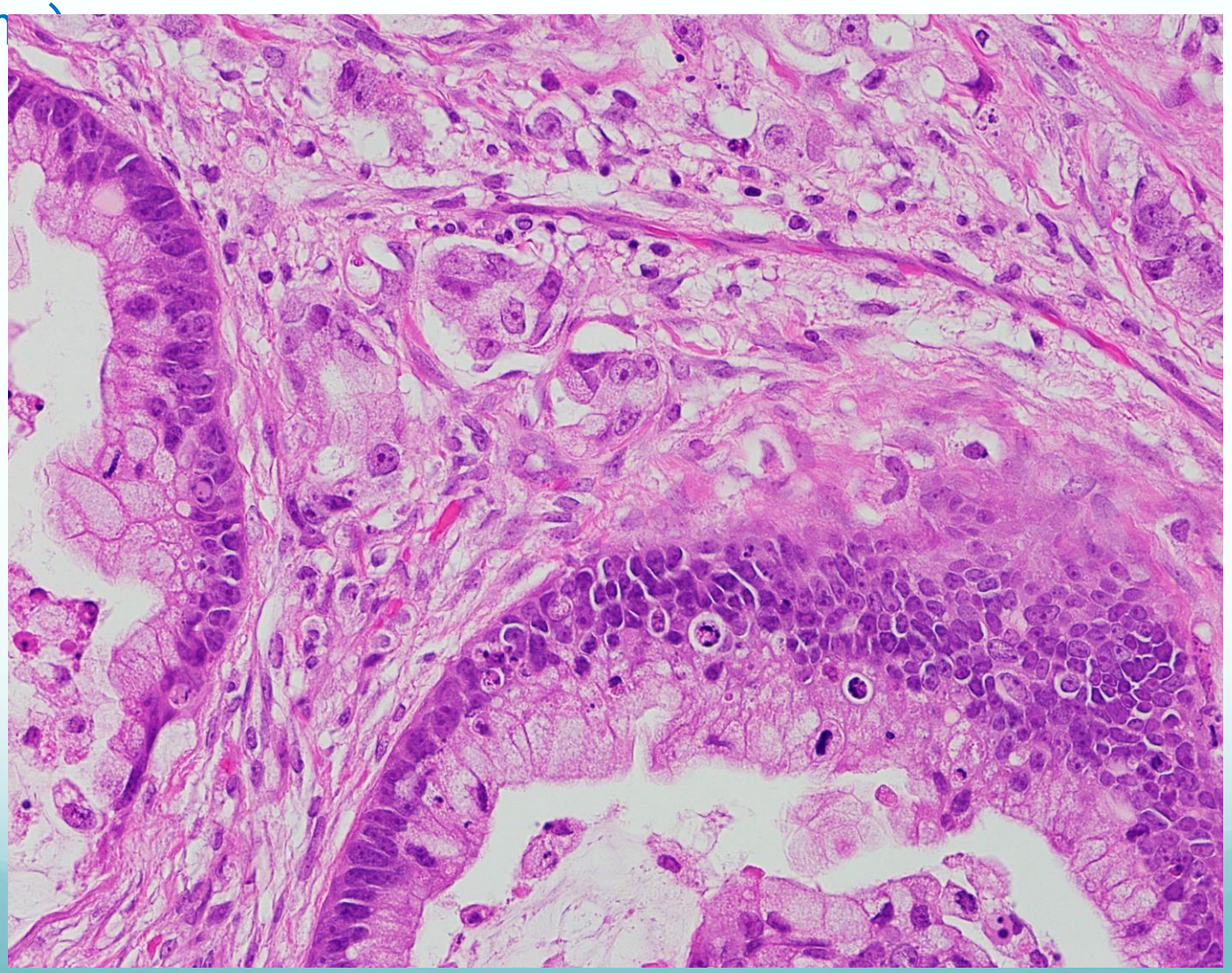
40 y/o bilateral ovarian masses

- Permanents of right ovary (left ovary showed the same):



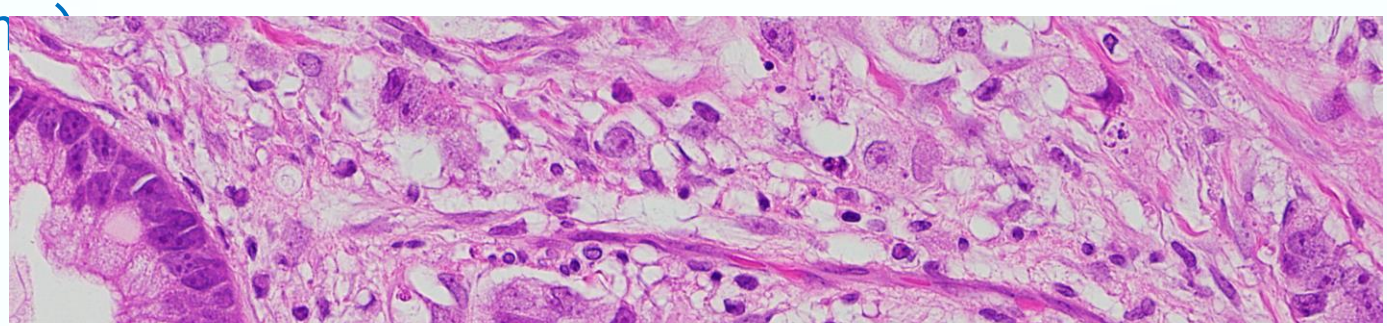
40 y/o bilateral ovarian masses

- Permanents of right ovary (left ovary showed the sam



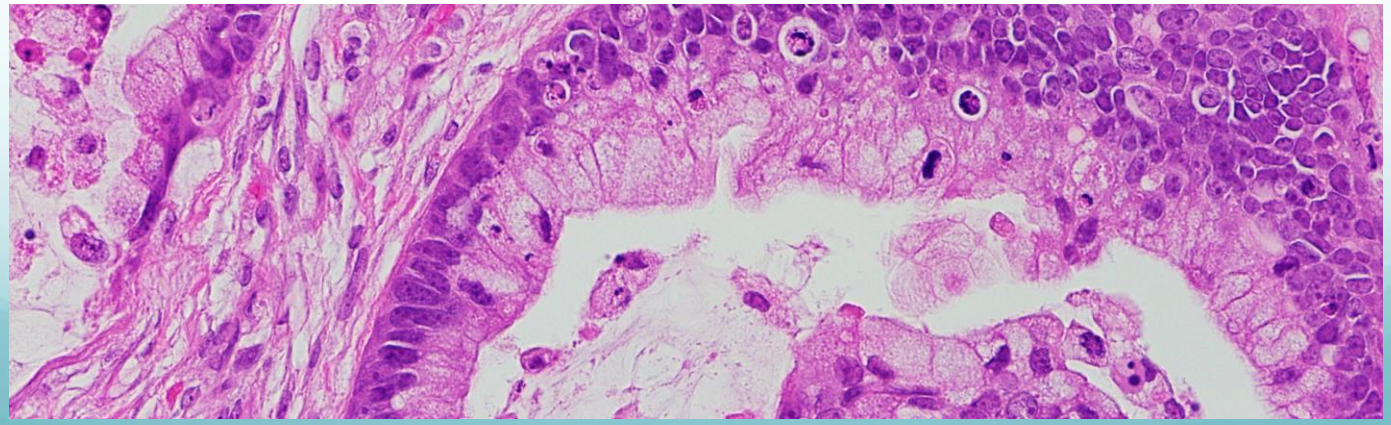
40 y/o bilateral ovarian masses

- Permanents of right ovary (left ovary showed the sam



Final Diagnosis:

Appendiceal mucinous adenocarcinoma
Tumor was present in bilateral ovaries and omentum



Take home points

- Arm yourself with knowledge of clinical history and imaging before walking into the gross room
- Mucinous carcinoma in an ovary is a met until proven otherwise
  - Share your skepticism with the surgeon, ask the right questions

Thank you, and Good luck!