




**pathCast lecture**  
**Intraoperative Approach to Mucinous Lesions Involving the Ovary and Other Diagnostic Challenges**

Bojana Djordjevic

Gynecologic Pathologist, Associate Professor  
 Sunnybrook Health Sciences Centre, Department of Anatomic Pathology  
 University of Toronto, Department of Laboratory Medicine and Pathobiology  
[bojana.djordjevic@sunnybrook.ca](mailto:bojana.djordjevic@sunnybrook.ca)

Laboratory Medicine & Pathobiology  
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## Session Overview

- What to know and do before FS interpretation
- Distinctions most impactful to patient management
- The algorithm
- What to write down as a FS diagnosis
- Case examples
  - special emphasis on mucinous tumors involving the ovary

## Before Frozen Section Interpretation

- Relevant history
  - Patient age
  - Tumor markers – Ca125, CEA, Ca19-9, HCG, AFP, LDH
  - Imaging – RMI score >200 indicates high malignancy risk

Table 2. The risk of malignancy index (RMI) scoring system

Ultrasound features	RMI score	
	RMI 1 score	RMI 2 score
Multilocular cyst	0 = no abnormality	1 = no or one abnormality
Presence of solid areas	1 = one abnormality	4 = two or more abnormalities
Bilaterality of lesions	3 = two or more abnormalities	
Presence of ascites		
Presence of intra-abdominal metastasis		
Premenopausal	1	1
Postmenopausal	3	4
CA125 level	U/mL	U/mL

Example: A postmenopausal woman with a multilocular cyst with solid areas with ascites and a CA125 level of 100 has a RMI 2 score of  $4 \times 4 \times 100 = 1600$ .

SOG/GOC SCC Clinical Practice Guidelines No. 230, July 2009.

## Before Frozen Section Interpretation

- Relevant history
  - Laterality
    - If known bilateral ovarian masses, think:
      - Serous carcinomas and borderline tumors
      - Metastases
    - *Preoperatively unilateral masses may become bilateral eventually!*
  - Previous pathology
  - Previous therapy
  - Intraoperative findings
    - Extraovarian tumor spread

### Before Frozen Section Interpretation

- Gross Assessment
  - Tumor size
  - Tumor surface
    - Tumor excrescences
    - Surface adhesions
  - Tumor integrity
- Sample generously at FS
  - Start with 3 sections, take more if needed

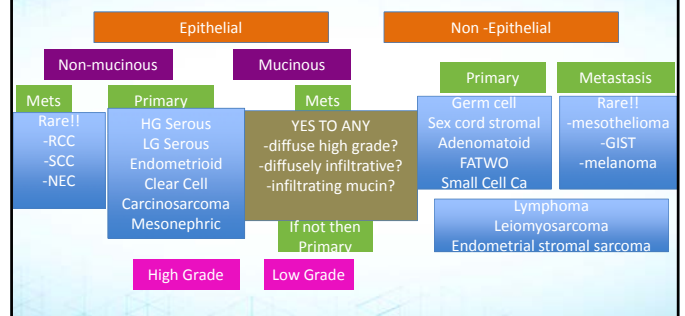
### Distinctions Most Impactful to Patient Management

- TAH BSO with staging including lymph nodes - the default operation for every patient with an ovarian mass
- FS evaluation guides modifications from this standard approach

### Distinctions Most Impactful to Patient Management

- Primary versus metastasis - most relevant with epithelial tumors
  - May stop surgery, opportunity to identify primary source intraoperatively
- Mucinous borderline tumors and carcinomas
  - Should examine abdomen including appendix and pancreatobiliary tree
- Carcinoma versus lymphoma
  - Initiate lymphoma protocol, may stop surgery
- Carcinoma versus germ cell or sex cord stromal tumor
  - Consider USO if young patient, no nodes
- Cystadenoma versus borderline tumor
  - Will not perform staging
- Carcinomas
  - Low grade carcinomas ( esp mucinous, gr 1 endometrioid): may omit lymph node dissection
  - High grade serous: may omit lymph node dissection and place an intraperitoneal catheter

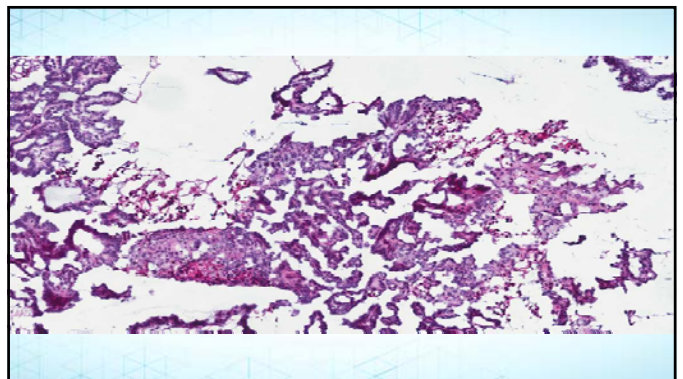
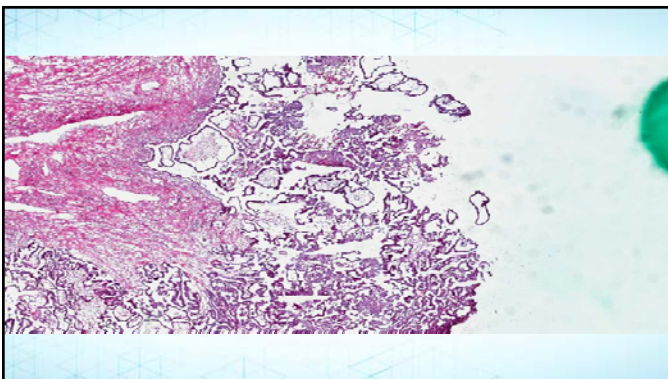
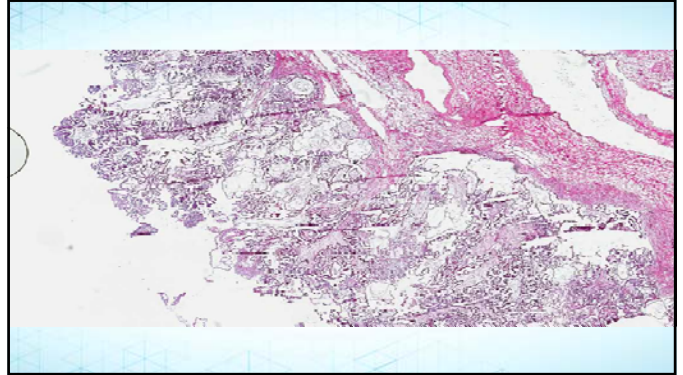
### The Algorithm

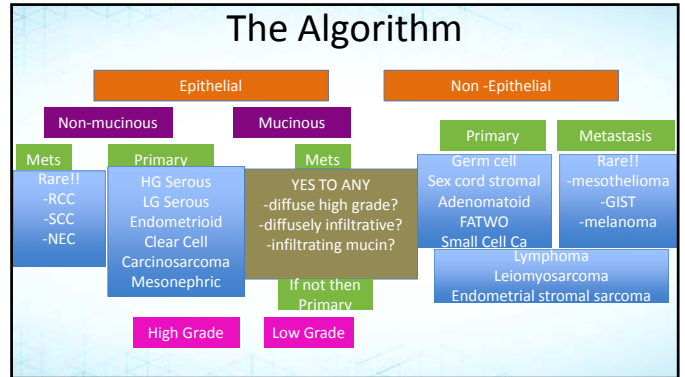
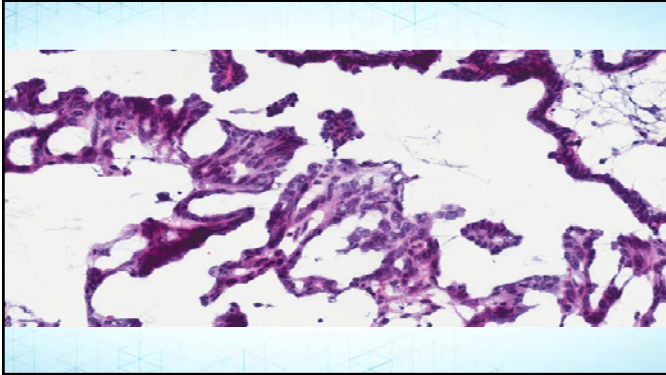




## Case 1

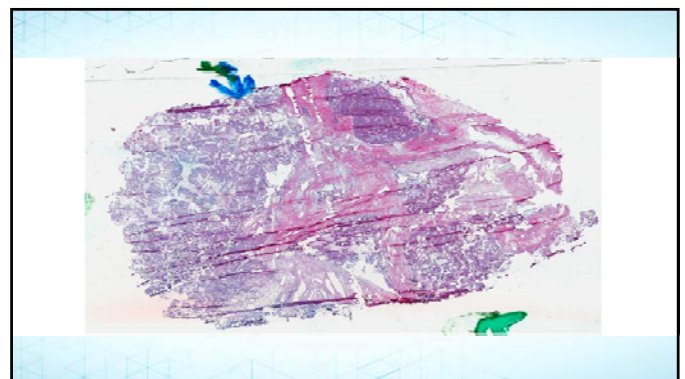
58 yo. 16cm mass. Unilateral.  
Ca 125: 107 U/mL

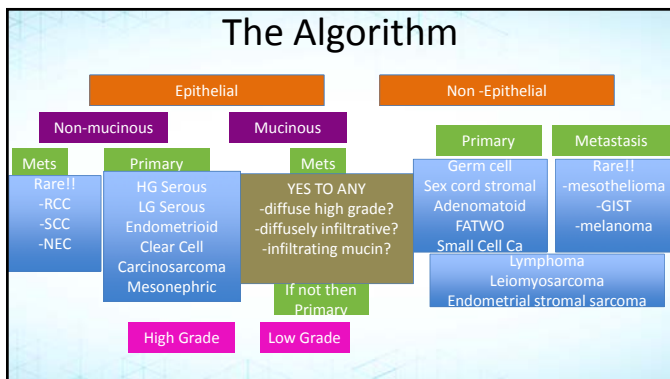
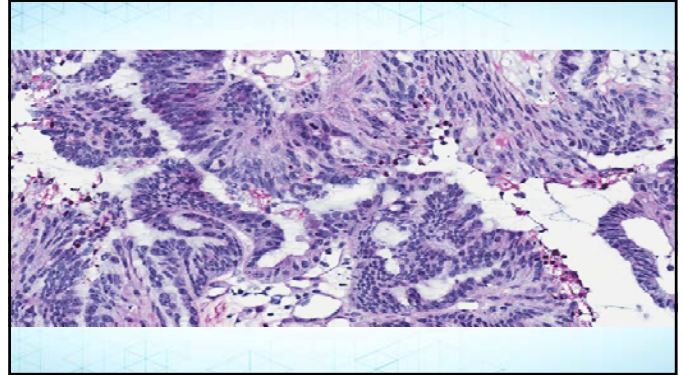
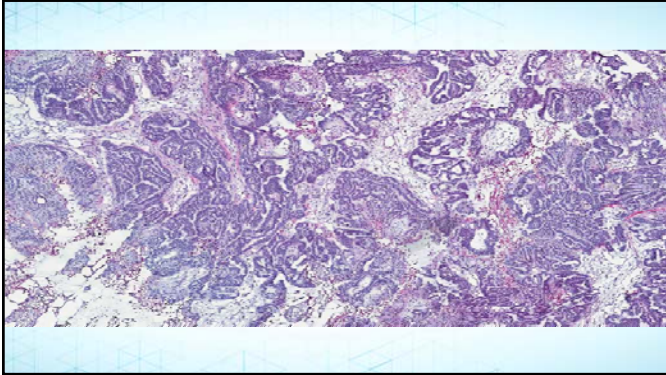




What is your diagnosis?

- A. Malignant neoplasm
- B. Carcinoma
- C. Serous carcinoma
- D. High grade serous carcinoma
- E. Low grade serous carcinoma





### Case 1

FS diagnosis: High grade serous carcinoma

Pitfall:

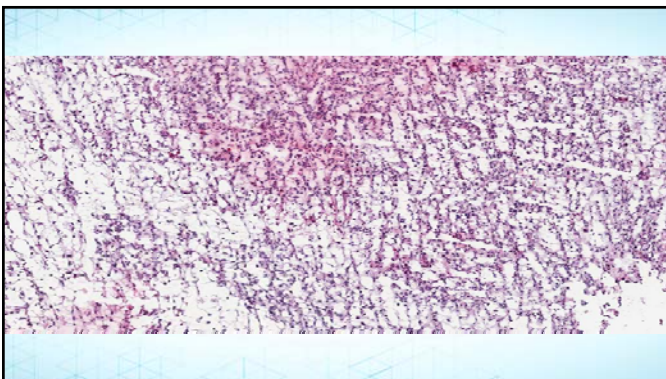
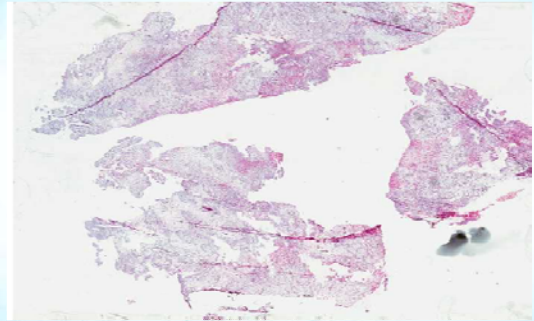
- Focal areas of borderline architecture, resembling serous borderline tumor
- High power examination reveals high grade nuclei

Final diagnosis: High grade serous carcinoma

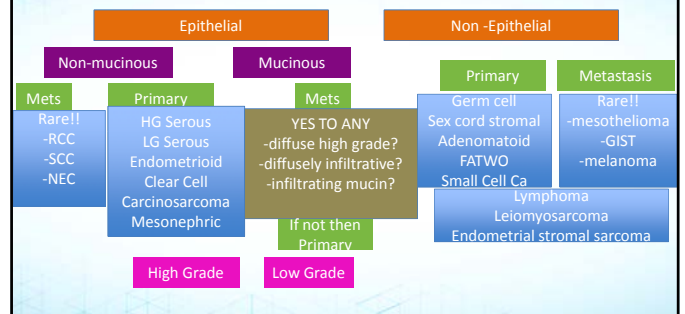
## Case 2

88 yo. 15cm mass. Unilateral. Received in fragments.

Ca 125: 176 (0-35U/mL)  
 Ca19-9: 9 (<35KU/L)  
 CEA: 0.6 (0-4mg/L)

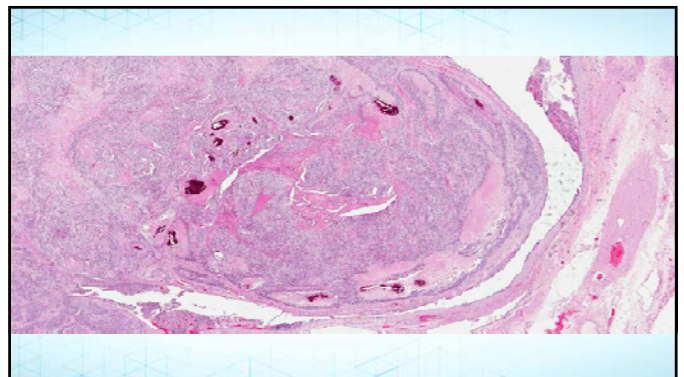
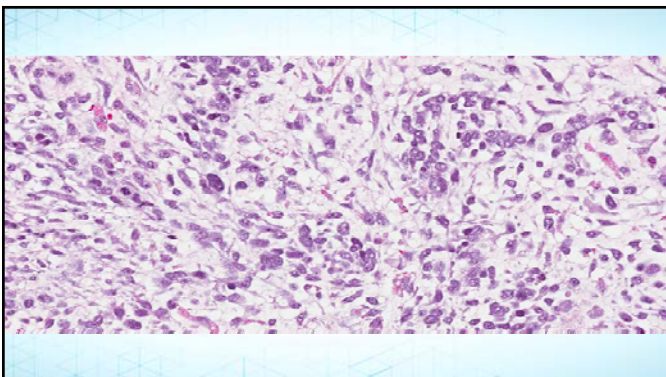
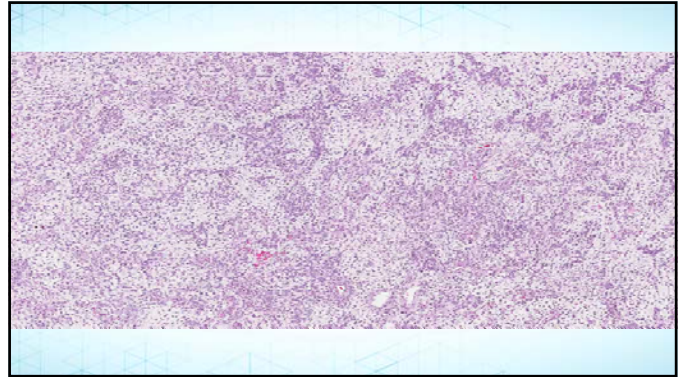


## The Algorithm



What is your diagnosis?

- A. Malignant neoplasm
- B. Carcinoma
- C. Sarcoma
- D. Serous carcinoma
- E. Carcinosarcoma





## Case 2

FS diagnosis: High grade malignant neoplasm

Final diagnosis: Carcinosarcoma with a high grade serous carcinomatous component.

Tumor is a fallopian tube primary.

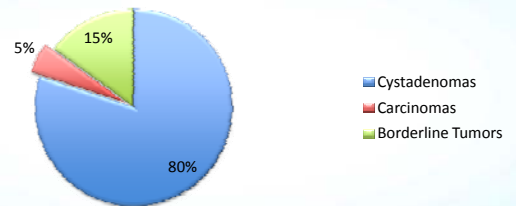
## Cases 3-8

Mucinous tumors involving the ovary

## Mucinous Neoplasms Involving the Ovary

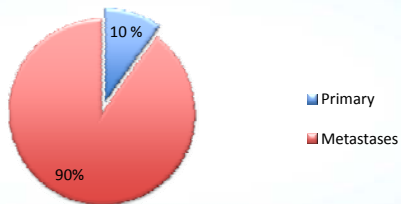
- Key diagnostic challenge
  - Tumors metastatic to the ovary may mimic the full range of morphologies of primary ovarian mucinous lesions

## Primary Ovarian Mucinous Neoplasms



Mucinous carcinoma represents only 5% of all mucinous lesions in the ovary

## Mucinous Carcinomas Involving the Ovary



➔ Mucinous carcinoma in the ovary is a metastasis until proven otherwise!

## Ovary is the Most Common Recipient of Metastases in the Female Genital Tract

- Lower gastrointestinal tract
- Appendix
- Upper gastrointestinal tract
- Pancreas
- Hepatobiliary tree
- Endocervix
- Breast
- Lung

## Primary vs. Metastases: Gross Tumor Features

- Tumor surface
  - Smooth -> favors a primary
  - Multinodular -> favors a metastasis
  - Surface hemorrhage or adhesions-> favors a metastasis

## Primary vs. Metastasis: Gross Tumor Features

- Laterality and Tumor size
  - Bilateral or <10cm, favors metastasis
    - 100% of primary ovarian tumors
    - 77% of metastases to the ovary
  - Bilateral or <13cm, favors metastasis
    - 98% of primary ovarian tumors
    - 82% of metastases to the ovary

Seidman et al. Am J Surg Pathol. 2003.  
Yeimeyanova et al. Am J Surg Pathol. 2008.

	Metastases (n = 21) n (%)	Primary ovarian tumours (n = 20) n (%)	p-value
<b>Ovarian involvement</b>			0.0001
Unilateral	8 (38)	20 (100)	
Bilateral	13 (61)	0	
<b>Ovarian size (cm) (range, median, mean)</b>	4.5-30, 14.3, 17.7	8-50, 20.3, 21.3	0.03
<b>Largest involved ovary size</b>			
< 5cm	1 (5)	0	
Subtotal with UO, OI	1	0	
5-9.9cm	1 (5)	1 (5)	
Subtotal with UO, OI	2	1	
10-12.9cm	2 (10)	0	
Subtotal with UO, OI	2	0	
13-14.9cm	3 (14)	0	
Subtotal with UO, OI	3	0	
15-19.9cm	8 (38)	7 (35)	
Subtotal with UO, OI	8	7	
> 20cm	1 (5)	12 (60)	
Subtotal with UO, OI	1	12	

UO, OI = Unilateral ovarian involvement

Hodgson et al. Canadian Journal of Pathology, 2020.

- Bilateral mucinous tumors are highly likely to be metastases
- Unilateral tumors could easily be metastases also
- Metastatic tumors can be large
  - >15cm - 67%
  - >20cm - 38%
- Impression of unilaterality pre-operatively may change subsequently
- BOTTOM LINE:
  - Do not be biased by unilaterality and large tumor size!

### Primary vs. Metastases: Histological Tumor Features

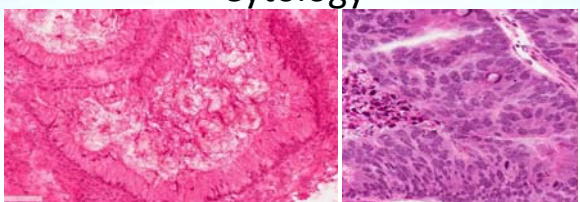
- Findings typically associated with primary mucinous ovarian tumors
  - Mucinous cystadenoma or borderline tumor in the background of mucinous carcinoma
  - Mural nodules
    - Anaplastic carcinoma
    - Sarcoma-like nodule
    - Sarcomatoid nodule
  - Brenner tumor
  - Teratoma
  - Carcinosarcoma
  - Leiomyoma

### Frozen Section Diagnostic Approach to Mucinous Tumors Involving the Ovary

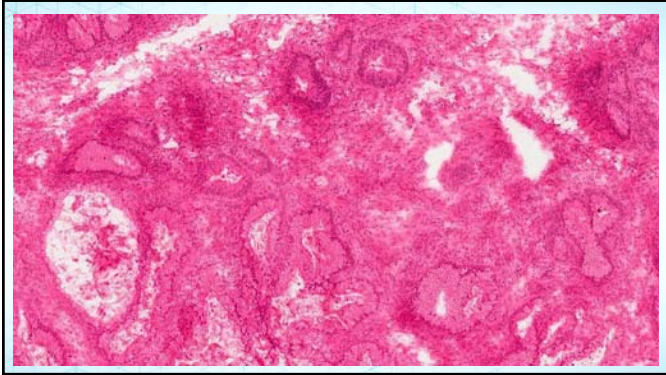
- Any of 3 key histological features:
  - Diffusely high grade cytology
  - Diffusely infiltrative pattern of invasion
  - Stromal infiltrating mucin
 =metastasis

Hodgson et al. Canadian Journal of Pathology, 2020.

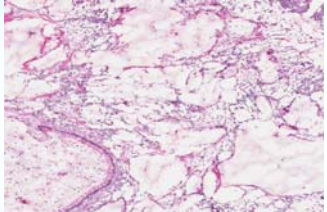
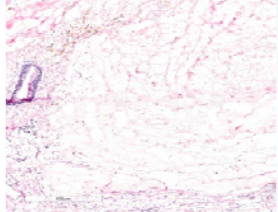
### Cytology



	Colonic Metastases (n = 16)	Appendiceal Metastases (n = 5) [n (%)]	All Metastases (n = 21)	Primary Ovarian (n = 20)	P-value
<b>Cytology</b>					
Low grade or focal high grade	7 (44)	5 (100)	12 (57)	20 (100)	
High grade	9 (56)	0	9 (43)	0	0.001

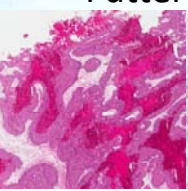
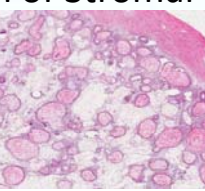
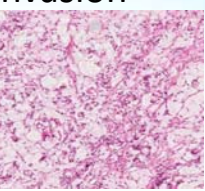


### Stromal Infiltrating Mucin

	Colonic Metastases (n = 16)	Appendiceal Metastases (n = 5) <small>In (9%)</small>	All Metastases (n = 21)	Primary Ovarian (n = 20)	P-value
<b>Stromal infiltrating mucin</b>					
Absent	12 (75)	2 (40)	14 (67)	20 (100)	0.009
Present	4 (25)	3 (60)	7 (33)	0	

### Pattern of Stromal Invasion

	Colonic Metastases (n = 16)	Appendiceal Metastases (n = 5) <small>In (9%)</small>	All Metastases (n = 21)	Primary Ovarian (n = 20)	P-value
<b>Pattern of stromal invasion</b>					
Absent or expansile or focally infiltrative	8 (50)	2 (40)	10 (48)	20 (100)	0.0002
Diffusely infiltrative	8 (50)	3 (60)	11 (52)	0	

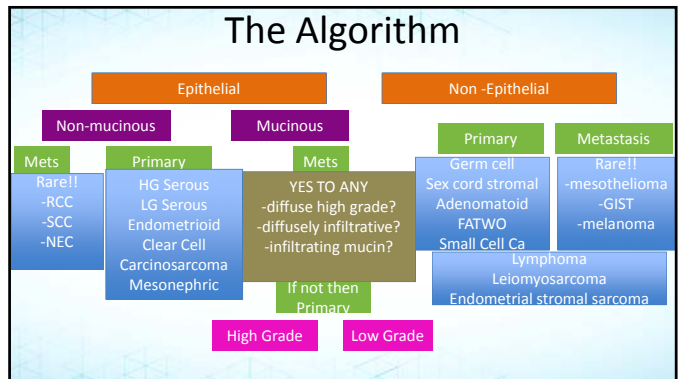
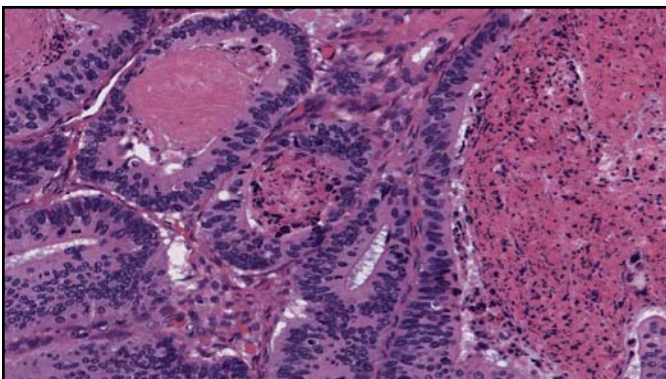
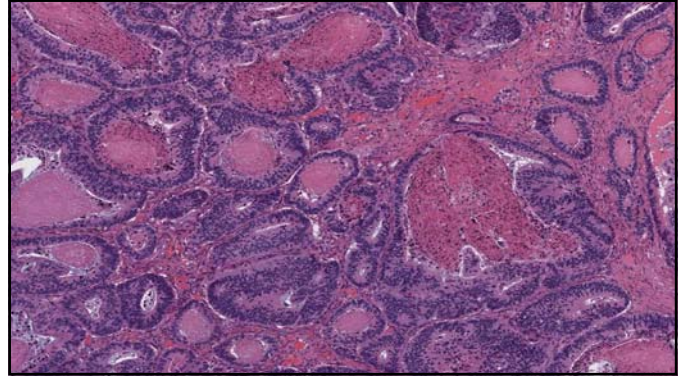
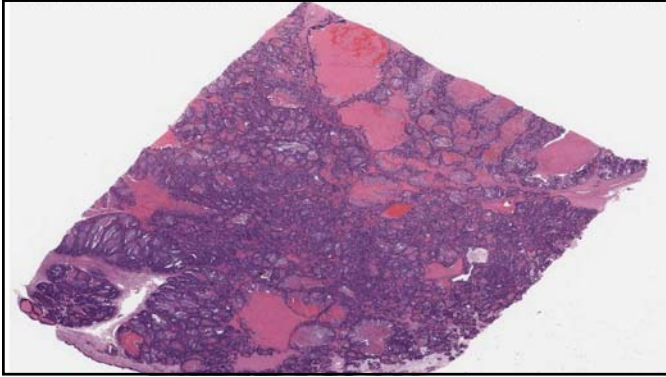
### Case 3

Presenting history:

- 71 year old woman
- 4 years ago T4 carcinoma of the right colon
- Now presents with a right ovarian mass

• Gross examination:

- 10 cm right ovarian mass (unilateral)
- Tan colour with hemorrhagic areas



### What is your diagnosis?

- A. Malignant neoplasm
- B. Carcinoma
- C. Mucinous carcinoma
- D. Mucinous carcinoma, favor colorectal metastasis to ovary

### Case 3

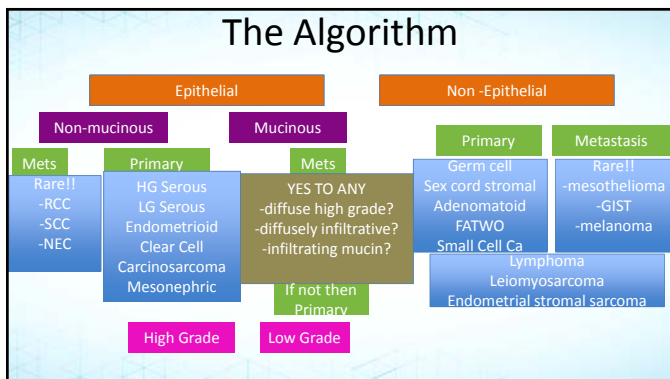
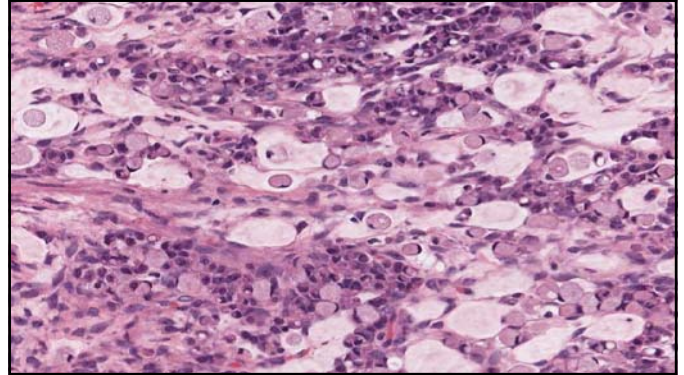
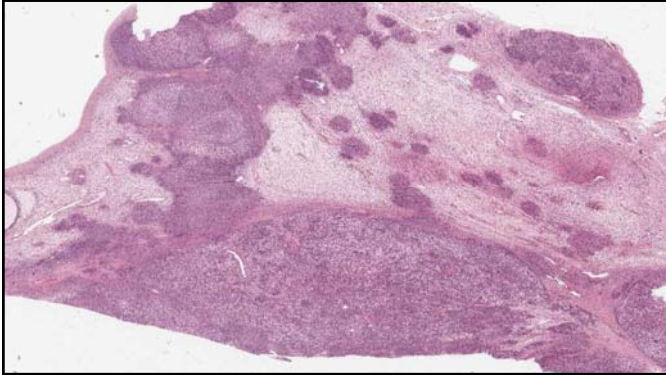
- Diagnosis:
  - Metastatic colon carcinoma to the ovary
- Conclusion:
  - Unilateral mass
  - Size <13cm
  - Morphology strongly suggestive of metastases
    - Dirty necrosis, garland pattern

### Case 4

- Presenting history:
  - 33 year old woman
  - Recent history of miscarriage
  - Enlarging bilateral adnexal masses for past 5 months
  - Virilization

### Case 4

- Gross examination:
  - 15 cm right ovary
  - 15 cm left ovary
  - White, solid multilobular masses
  - Smooth on external surface



### What is your diagnosis?

- A. Malignant neoplasm
- B. Carcinoma
- C. Mucinous carcinoma
- D. Mucinous carcinoma, favor colorectal metastasis to ovary
- E. Signet ring carcinoma metastatic to ovary

## Case 4

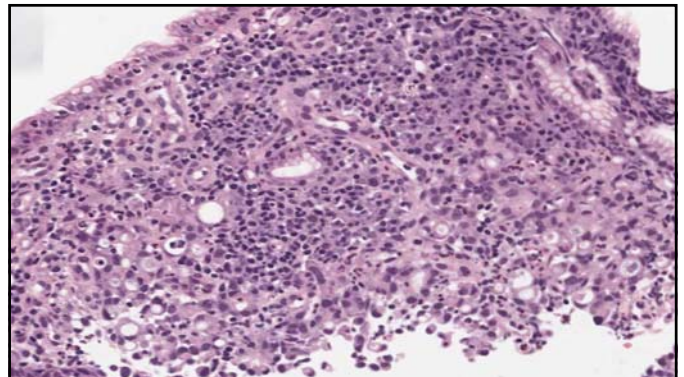
- IHC: CK7, CK20 positive
- Diagnosis:
  - Metastatic adenocarcinoma, diffuse (signet ring type)
  - Krukenberg tumor
- Conclusion:
  - Bilateral masses
  - But large, smooth outer surface
  - Convincing pattern for metastases – diffusely infiltrating signet ring cells
  - Virilization following a recent pregnancy is a clue
    - Has been described in association with metastatic gastric tumors in young patients
    - Poorly understood mechanism. Combination of gastric tumor and HCG stimulus thought to be required to stimulate ovarian androgen production

## Case 4

- Additional work up:
  - Antral mass
    - Signet ring adenocarcinoma

## Case 4

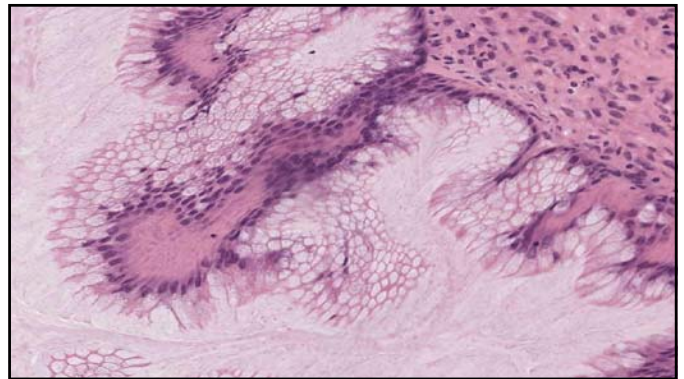
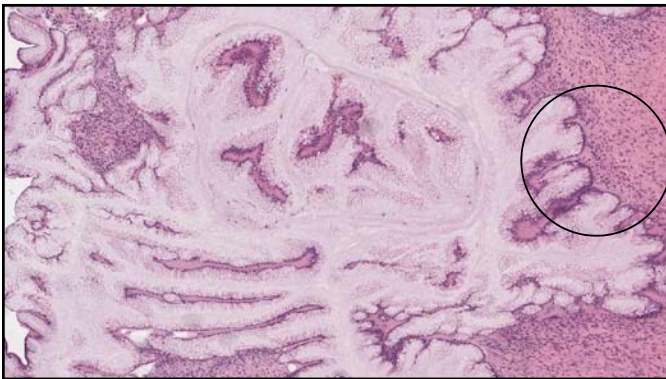
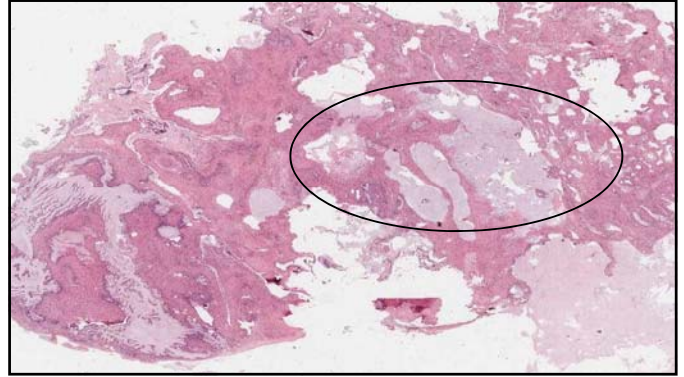
- Additional work up:
  - Antral mass
    - Signet ring adenocarcinoma

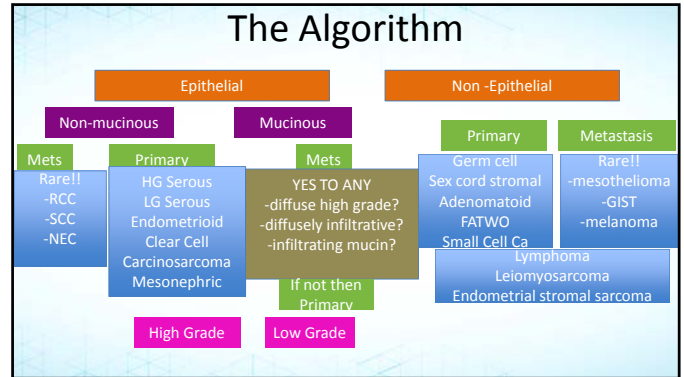
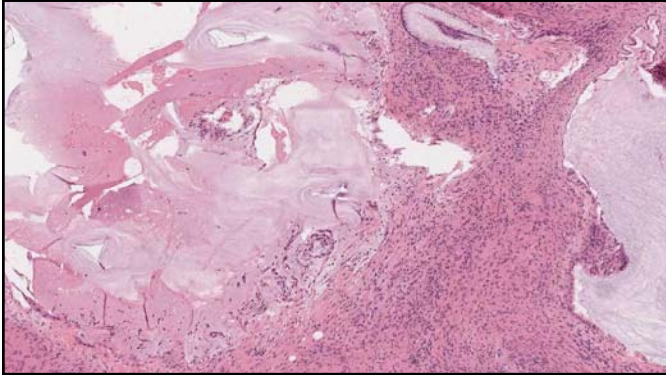




## Case 5

- Presenting history:
  - 52 year old patient with a pelvic mass
- Gross examination:
  - 14 cm left ovarian mass (unilateral)
  - Multiloculated
  - Smooth outer surface





### What is your diagnosis?

- A. Mucinous cystadenoma
- B. Mucinous borderline tumor
- C. Mucinous carcinoma
- D. Mucinous carcinoma, favor metastasis to ovary
- E. Low grade mucinous neoplasm, defer primary site assignment

### Case 5

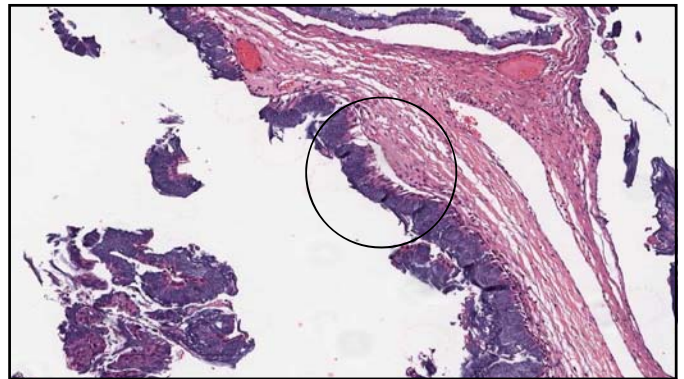
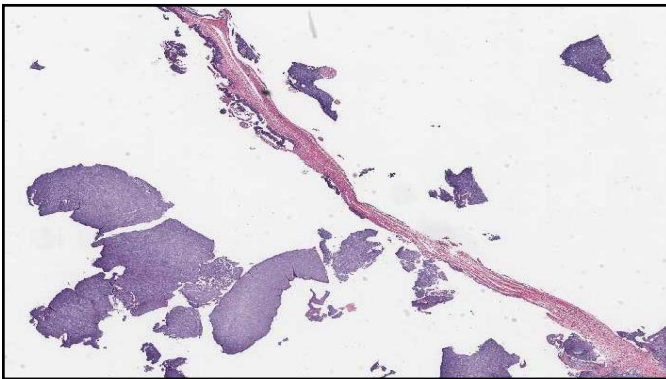
- Additional findings:
  - Dissecting pools of mucin in the omentum as well
  - Operative note indicates mucinous material present in the peritoneum – pseudomyxoma peritonei
    - Surgery stopped - unable to visualize the appendix
- IHC:
  - CK20 diffusely positive
  - CK 7 focally positive
  - CDX2 positive

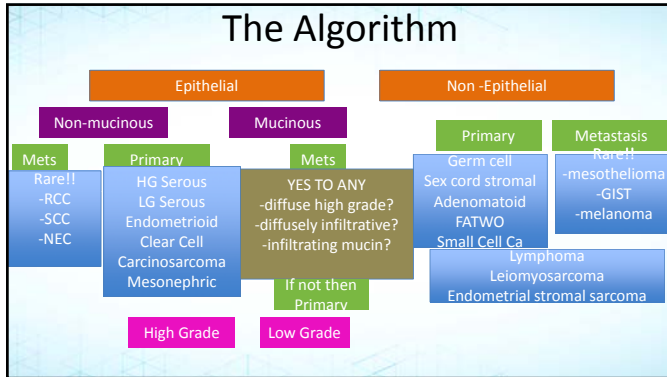
## Case 5

- **Diagnosis:**
  - Invasive low grade mucinous neoplasm
  - Favor metastasis of appendiceal origin
- **Conclusion:**
  - Large unilateral mass, smooth surface
  - Deceptively bland cytologically and architecturally
  - Dissecting mucin in ovarian parenchyma
  - Clinically highly suggestive of metastasis
  - IHC profile does not support an ovarian primary

## Case 6

- **Presenting history:**
  - 57 year old with a pelvic mass
- **Gross examination:**
  - 26cm right ovarian mass (unilateral)
  - Multiloculated cystic
  - Smooth outer surface
- **Intraoperative findings:**
  - No evidence of peritoneal disease





### What is your diagnosis?

- A. Mucinous cystadenoma
- B. Mucinous borderline tumor
- C. Mucinous carcinoma
- D. Mucinous carcinoma, favor metastasis to ovary
- E. Low grade mucinous neoplasm, defer primary site assignment

### Case 6

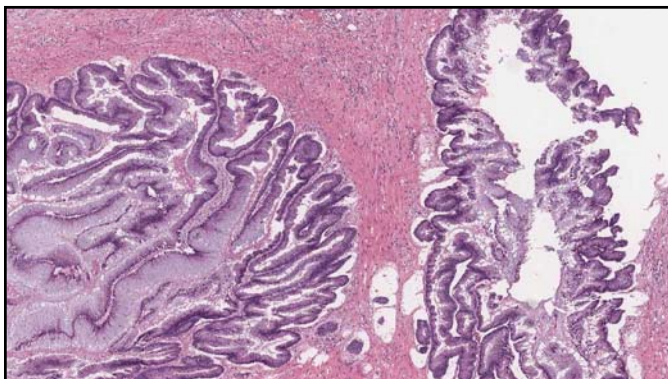
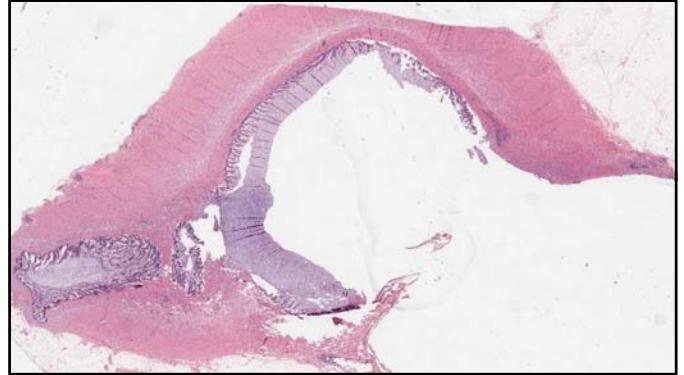
- IHC:
  - CK20 diffusely positive
  - CK7 focally and weakly positive
- Diagnosis:
  - Low grade mucinous neoplasm
  - Favor metastasis
    - Appendix
    - Lower GI tract
    - Upper GI tract
    - Pancreatobiliary system

### Case 6

- Conclusion:
  - Large unilateral mass, smooth surface
  - Deceptively bland cytologically and architecturally
  - IHC profile does not support an ovarian primary
  - Although no clinical signs of an extraovarian primary, case is highly suspicious
    - Called the clinician

## Case 6

- Case follow-up:
  - Tumor in distal appendix identified at second surgery
- Diagnosis:
  - Low grade mucinous adenocarcinoma

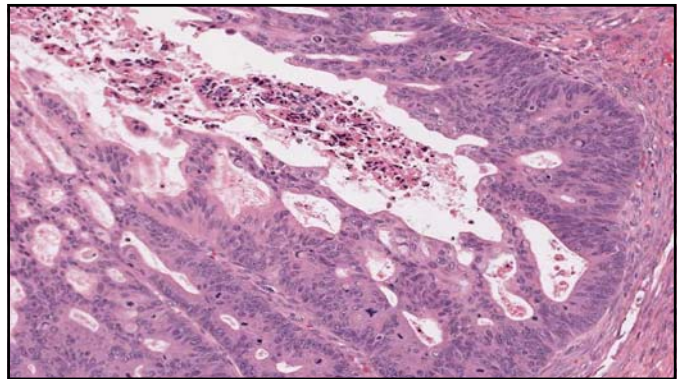
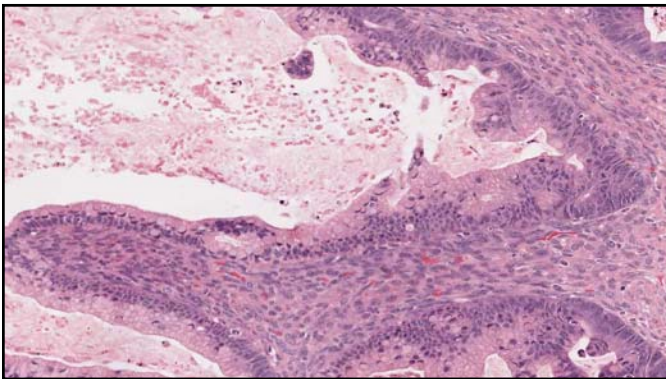
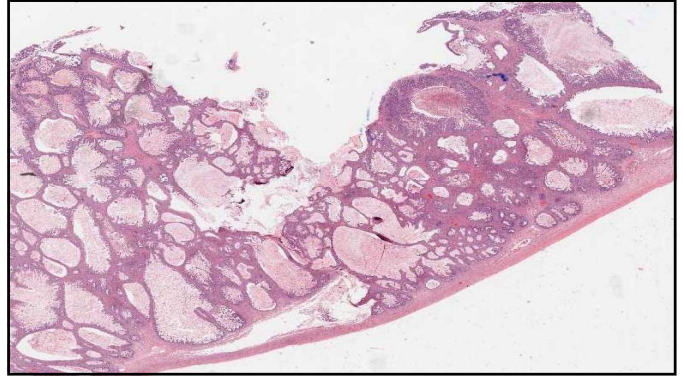


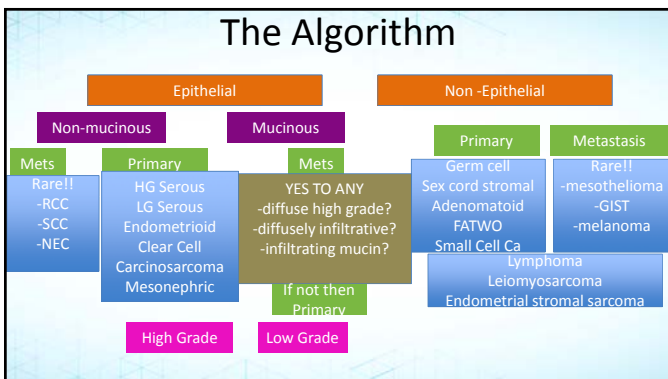
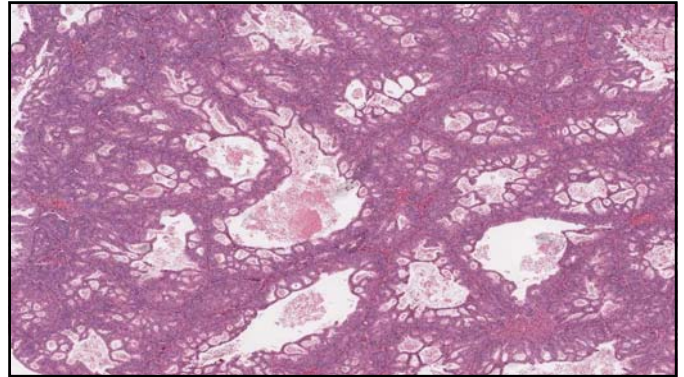
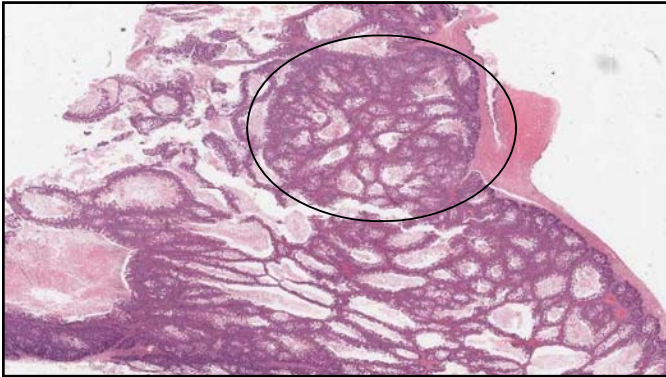
## Case 6

- Important caveat:
  - Ovarian mucinous tumor associated with an ovarian dermoid cyst is an important consideration in the differential diagnosis
  - The tumor would have an identical appearance and IHC profile of an appendiceal primary

## Case 7

- Presenting history:
  - 58year old female with a pelvic mass
- Gross examination:
  - 15cm mass (unilateral)
  - Multiloculated solid and cystic
  - Smooth outer surface





### What is your diagnosis?

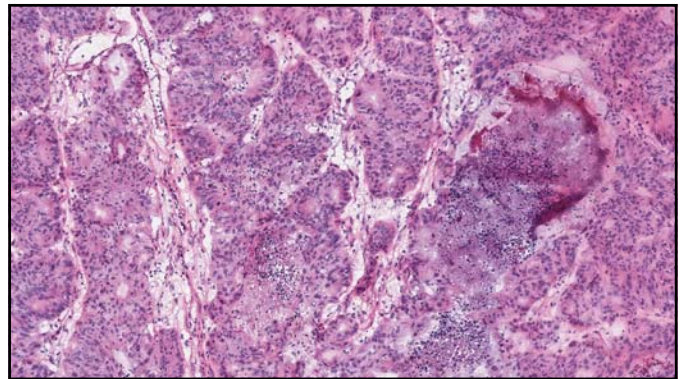
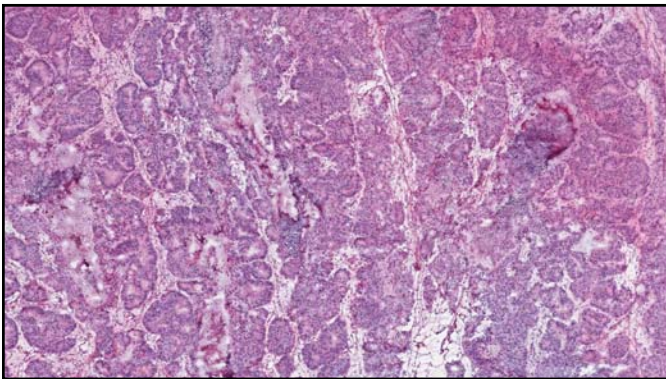
- A. Mucinous cystadenoma
- B. Mucinous borderline tumor
- C. Mucinous carcinoma
- D. Mucinous carcinoma, favor metastasis to ovary
- E. Low grade mucinous neoplasm, defer primary site assignment

### Case 7

- IHC: CK7, CK20 (patchy) and Pax 8 positive
- Diagnosis:
  - Primary ovarian mucinous adenocarcinoma
- Conclusion:
  - Unilateral large mass
  - Carcinoma arises in a background of mucinous borderline tumor with intraepithelial carcinoma
  - IHC supports a primary ovarian neoplasm

### Case 8

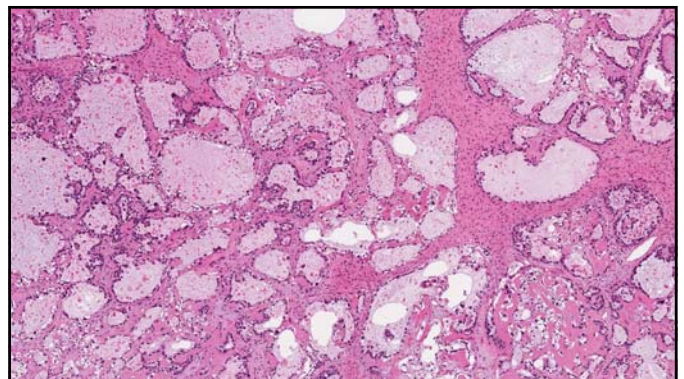
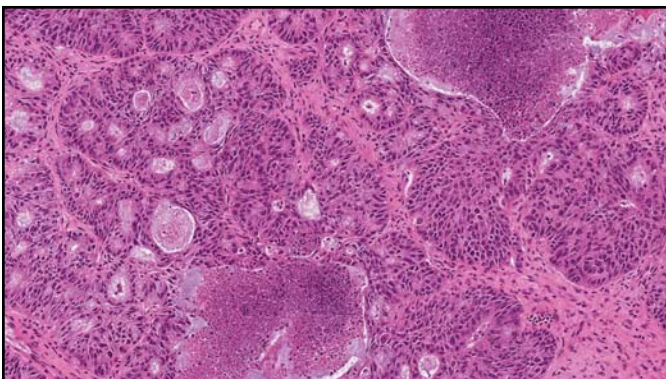
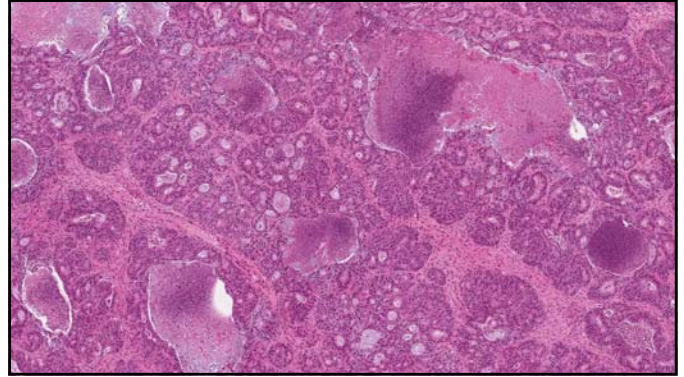
- Presenting history:
  - 50 year old female with bilateral pelvic masses
  - History of pT3N1 colorectal carcinoma treated with surgery and chemotherapy
  - Ca125: 208U/mL; Ca19.9kU/L: 396ug/L
- Gross examination:
  - 13 cm ovary (received for FS), 5.5cm contralateral ovary (received for PS)
  - Multiloculated solid and cystic
  - Smooth outer surface

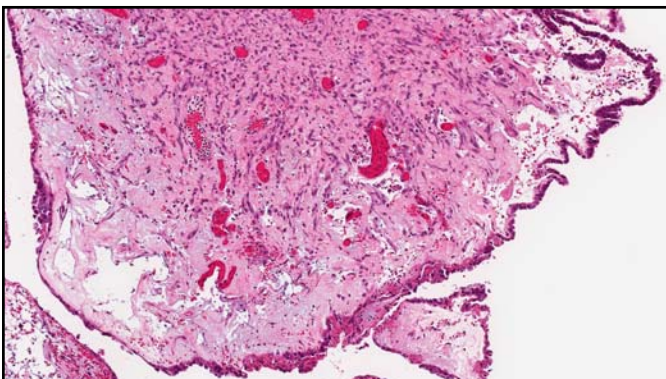
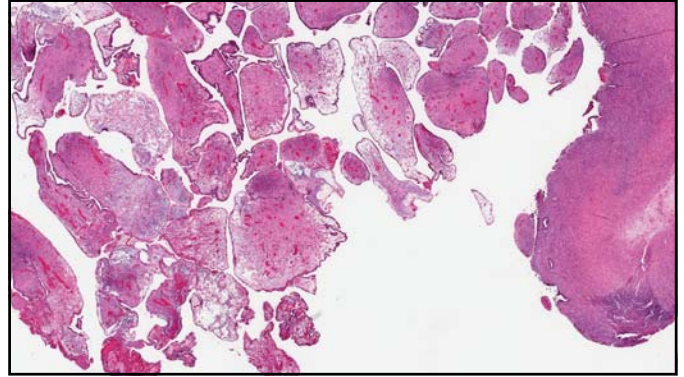
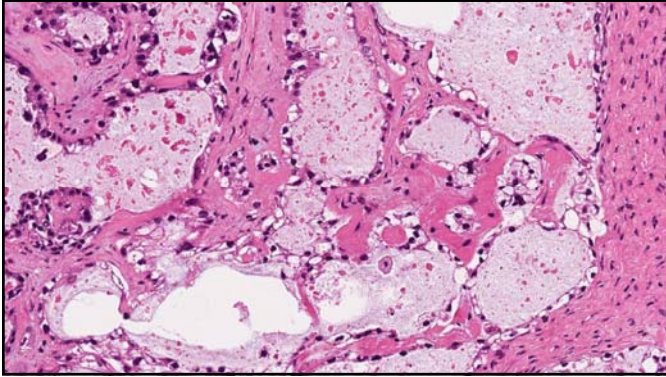




What is your diagnosis?

- A. Primary endometrioid carcinoma
- B. Colorectal carcinoma metastatic to ovary
- C. Primary ovarian mucinous carcinoma
- D. Primary ovarian mucinous borderline tumor



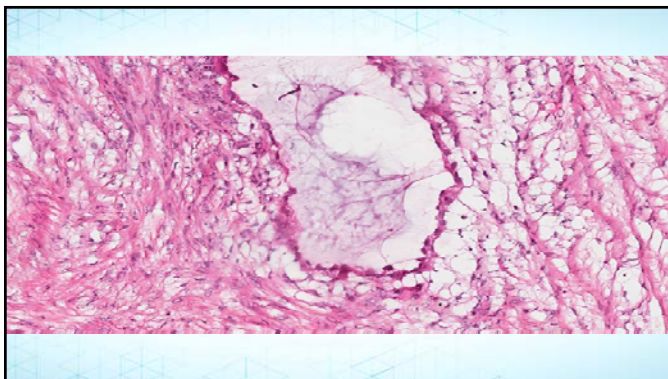
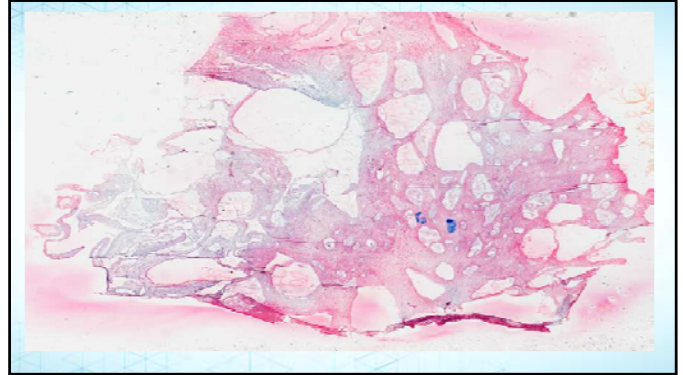


## Case 8

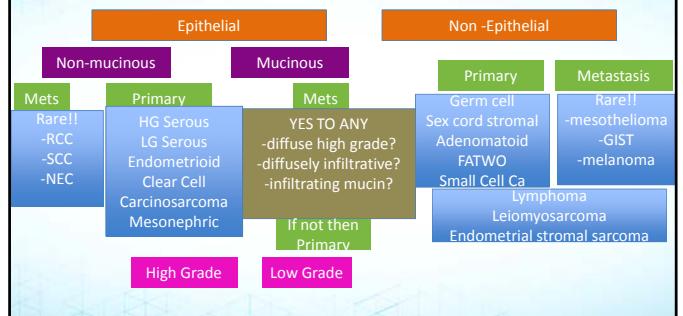
- IHC: 13cm mass CK7 and Pax 8 strongly positive, CK20 negative
- Diagnosis:
  - 13cm mass: primary ovarian endometrioid and clear cell carcinoma
  - 5.5cm mass: primary ovarian seromucinous borderline tumor
  - Both tumors had intact expression of MMR IHC
- Conclusion:
  - Highly unusual case!
  - Previous cancer history a major bias
  - Pitfall: Endometrioid carcinoma with mucinous differentiation can resemble a colorectal metastasis on frozen section
  - Patient referred for genetic counselling

### Case 9

58 yo. 17cm mass. Unilateral. Smooth outer surface.  
Ca125: 46 (0-35 U/mL)

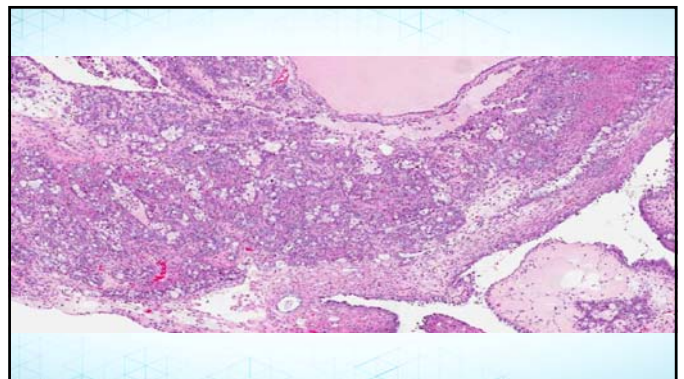
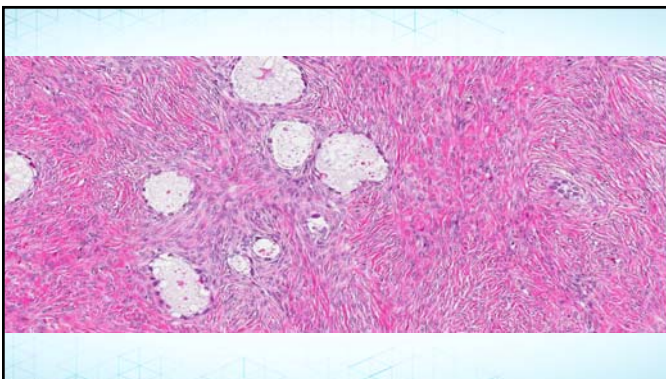
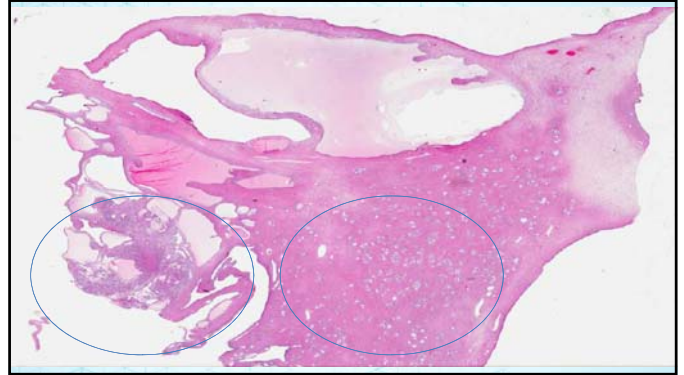


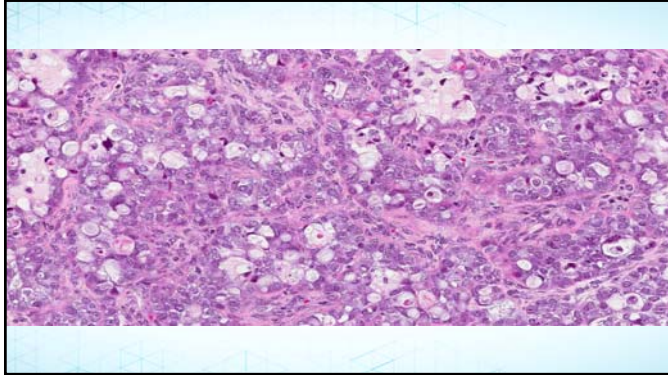
### The Algorithm



What is your diagnosis?

- A. Benign ovarian tissue
- B. Benign neoplasm
- C. Serous cystadenofibroma
- D. Clear cell adenofibroma
- E. Clear cell carcinoma





## Case 9

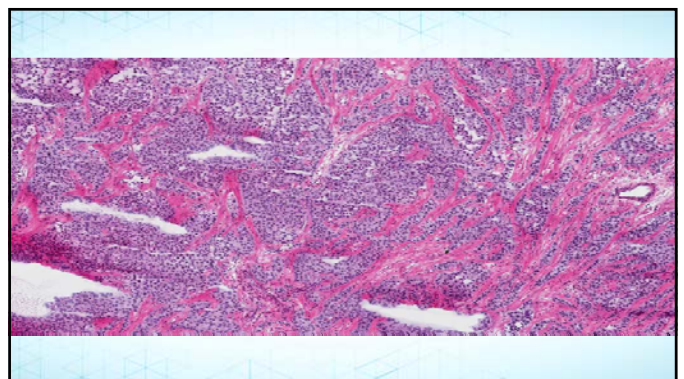
FS diagnosis: Benign neoplasm

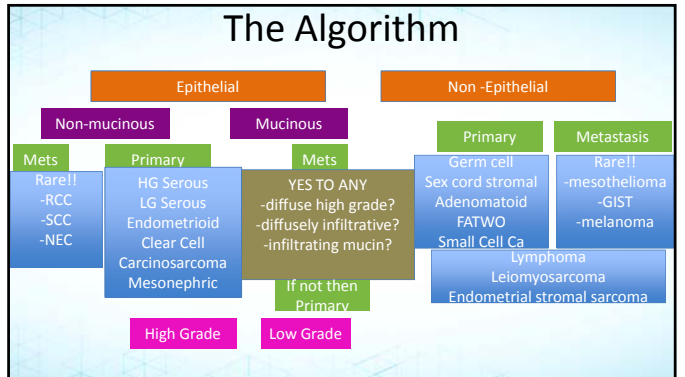
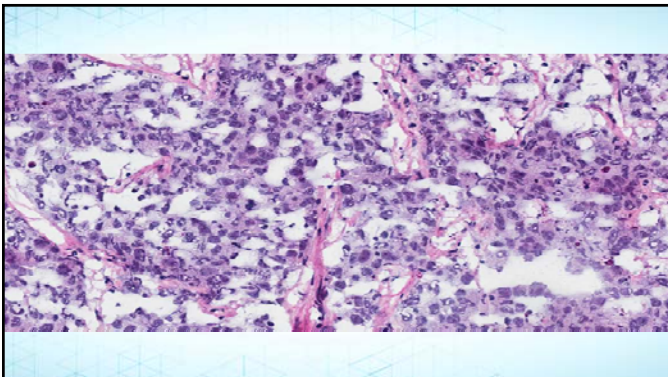
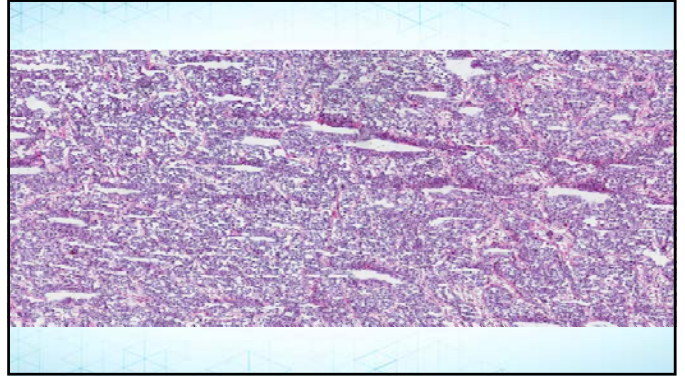
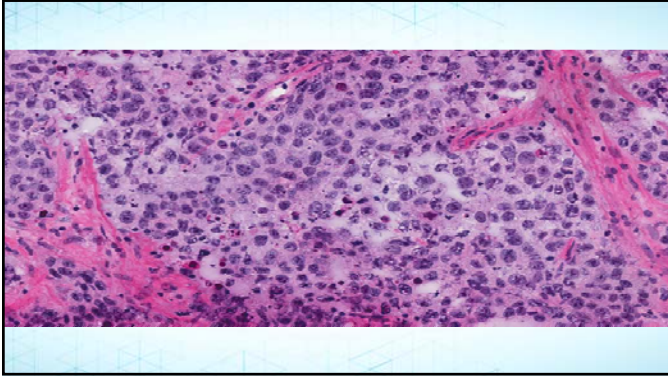
Final diagnosis: Clear cell carcinoma arising in adenofibromatous background

## Case 10

19 yo. 13cm tumor with smooth surface. Unilateral.

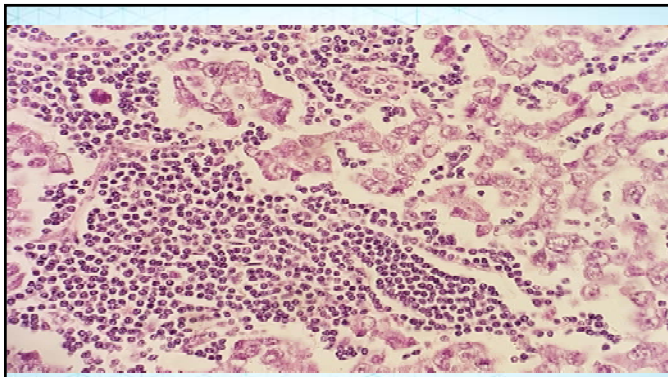
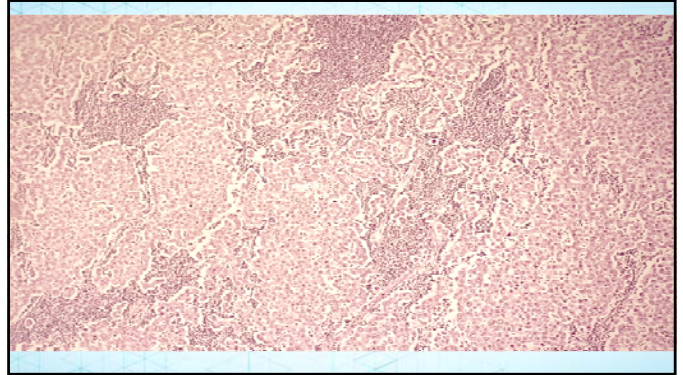
Ca 125: 127 (0-35 U/mL)  
AFP: 2 (0-10ug/L)  
LDH: 398 (100-250 U/L)  
HCG: 0





What is your diagnosis?

- A. Malignant neoplasm
- B. Malignant epithelial neoplasm
- C. Malignant spindle cell neoplasm
- D. Sex cord stromal tumor
- E. Dysgerminoma
- F. Granulosa cell tumor

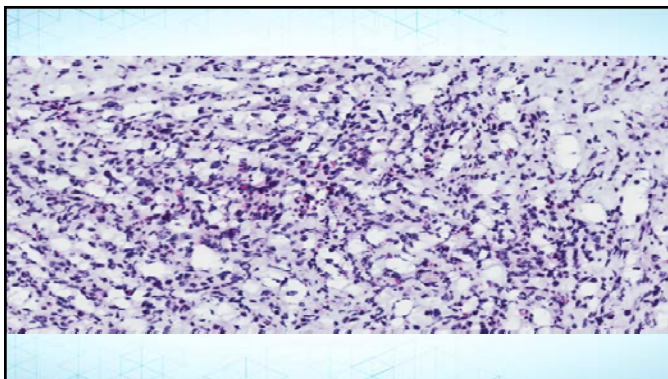
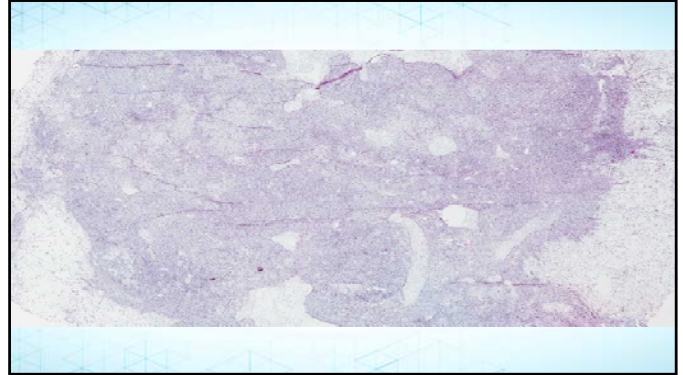


## Case 10

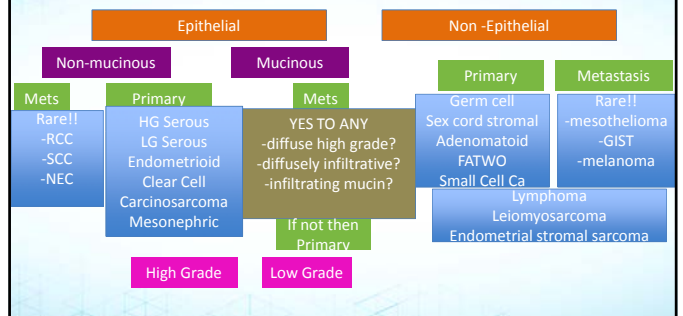
Frozen section diagnosis: Favor dysgerminoma  
Final diagnosis: Dysgerminoma.  
USO performed.

### Case 11

54yo. 10.5cm tumor with adhesions. Unilateral. No markers available.



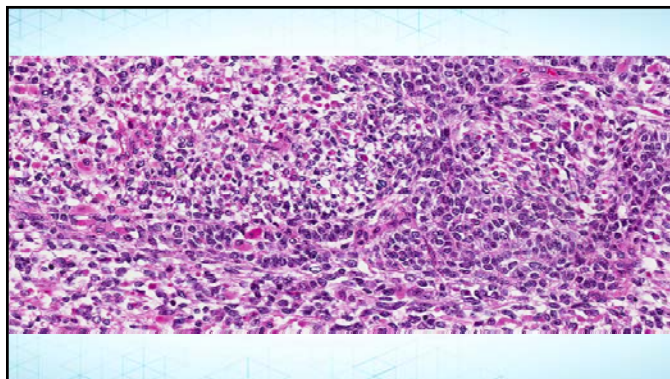
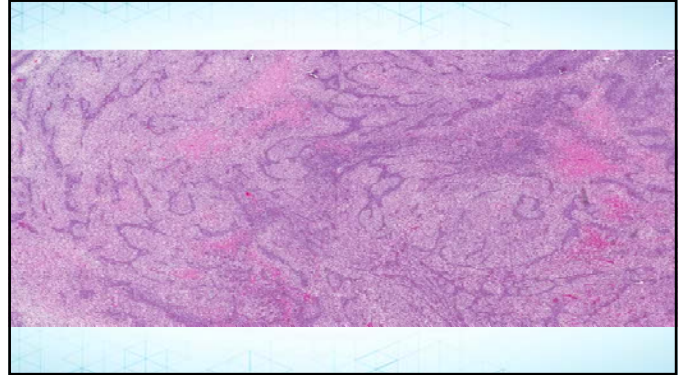
### The Algorithm





What is your diagnosis?

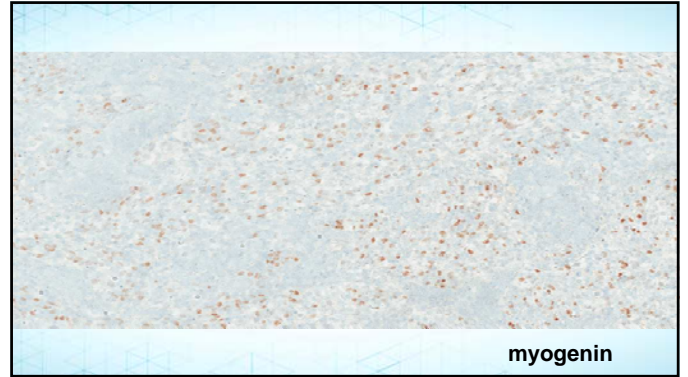
- A. Malignant neoplasm
- B. Malignant epithelial neoplasm
- C. Malignant spindle cell neoplasm
- D. Malignant sex cord stromal tumor



### Case 10

FS diagnosis: Malignant spindle cell neoplasm

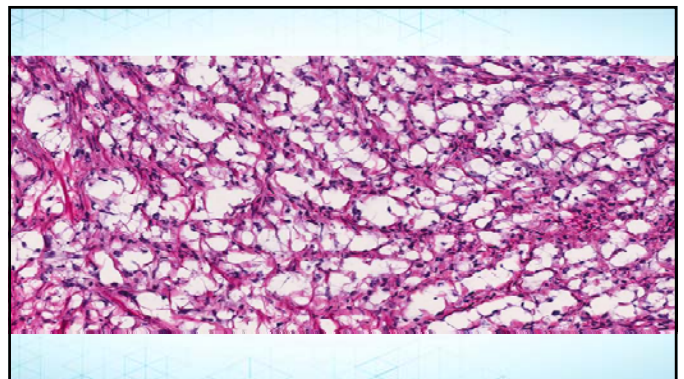
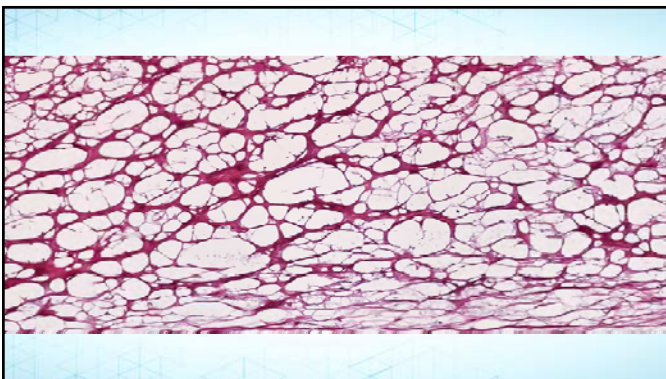
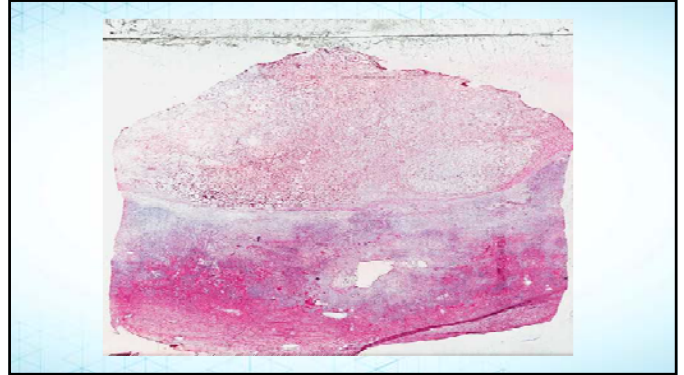
Final diagnosis: Sertoli Leydig cell tumor with sarcomatous components.

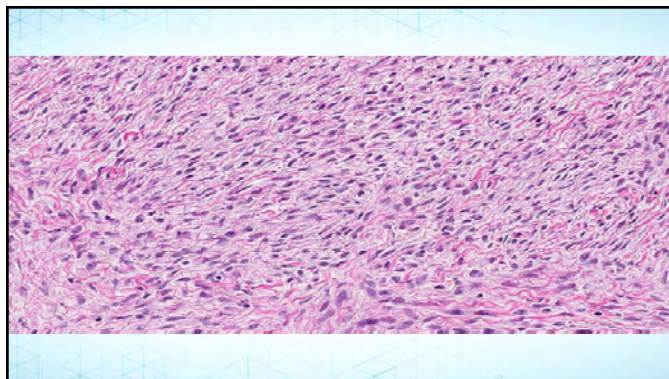
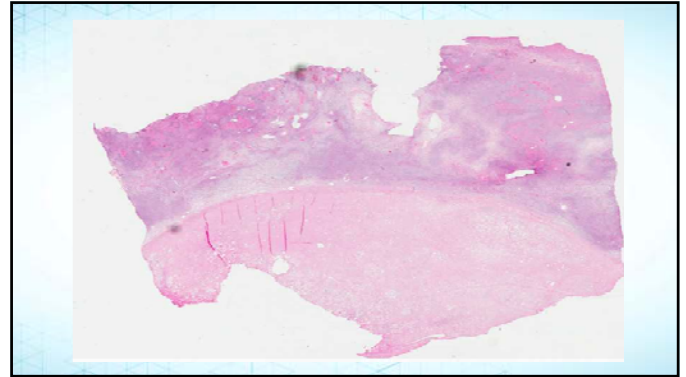
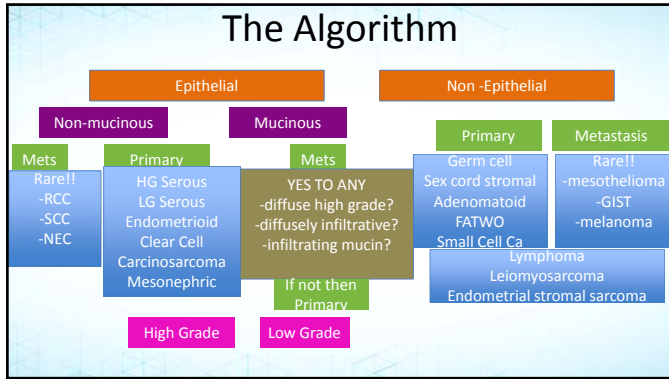


## Case 11

56 yo, 13 cm mass. Smooth outer surface. Unilateral. No markers available.

Hemorrhagic center with a dense white rim.





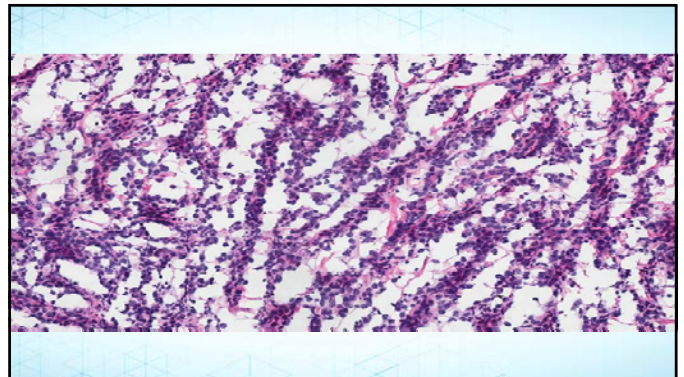
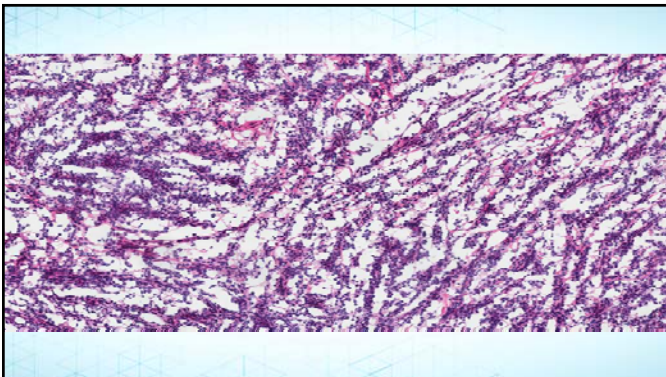
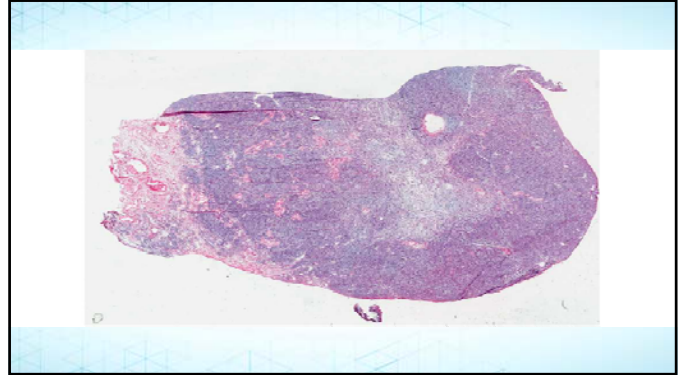
### Case 11

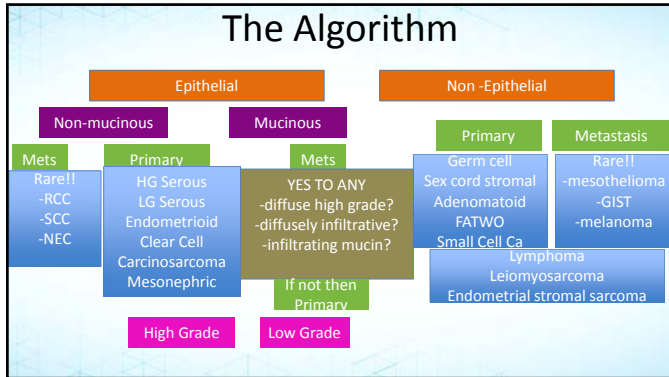
FS diagnosis: Low grade sex cord stromal tumor with extensive degenerative change.

Final diagnosis: Fibroma with extensive degenerative changes.

## Case 12

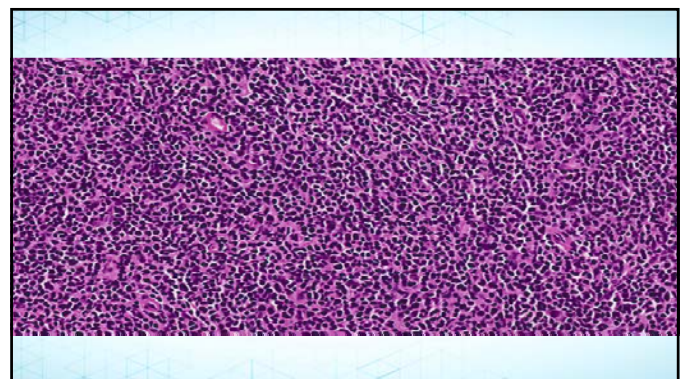
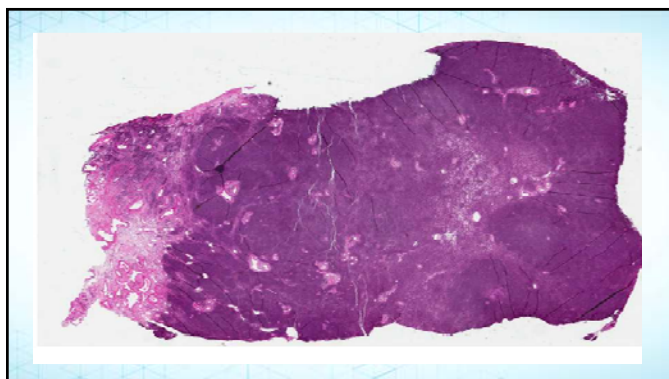
64 yo. 4.2cm tumor with smooth surface.





### What is your diagnosis?

- A. Malignant neoplasm
- B. Malignant epithelial neoplasm
- C. Malignant spindle cell neoplasm
- D. Malignant sex cord stromal tumor



## Case 12

FS diagnosis: Granulosa cell tumor.

Final diagnosis: Follicular lymphoma.

Pitfall #1: No nesting, no grooves. Cannot call anything epithelioid.

Pitfall #2: Lymphomas and mesotheliomas may be associated with an elevated Ca125.

## Session Overview

- What to know and do before FS interpretation
- Distinctions most impactful to patient management
- The algorithm
- Case examples
- What to write down as a FS diagnosis

*Success consists of going from failure to failure without loss of enthusiasm.*

*If you are going through hell, keep going.*

*Success is not final, failure is not fatal: it is the courage to continue that counts.*



Thank you



**Sunnybrook**  
RESEARCH SCIENCES CENTRE  
UNIVERSITY OF TORONTO  
MCCST