



# PATHOLOGY OF THE FALLOPIAN TUBE AND THE OVARIES

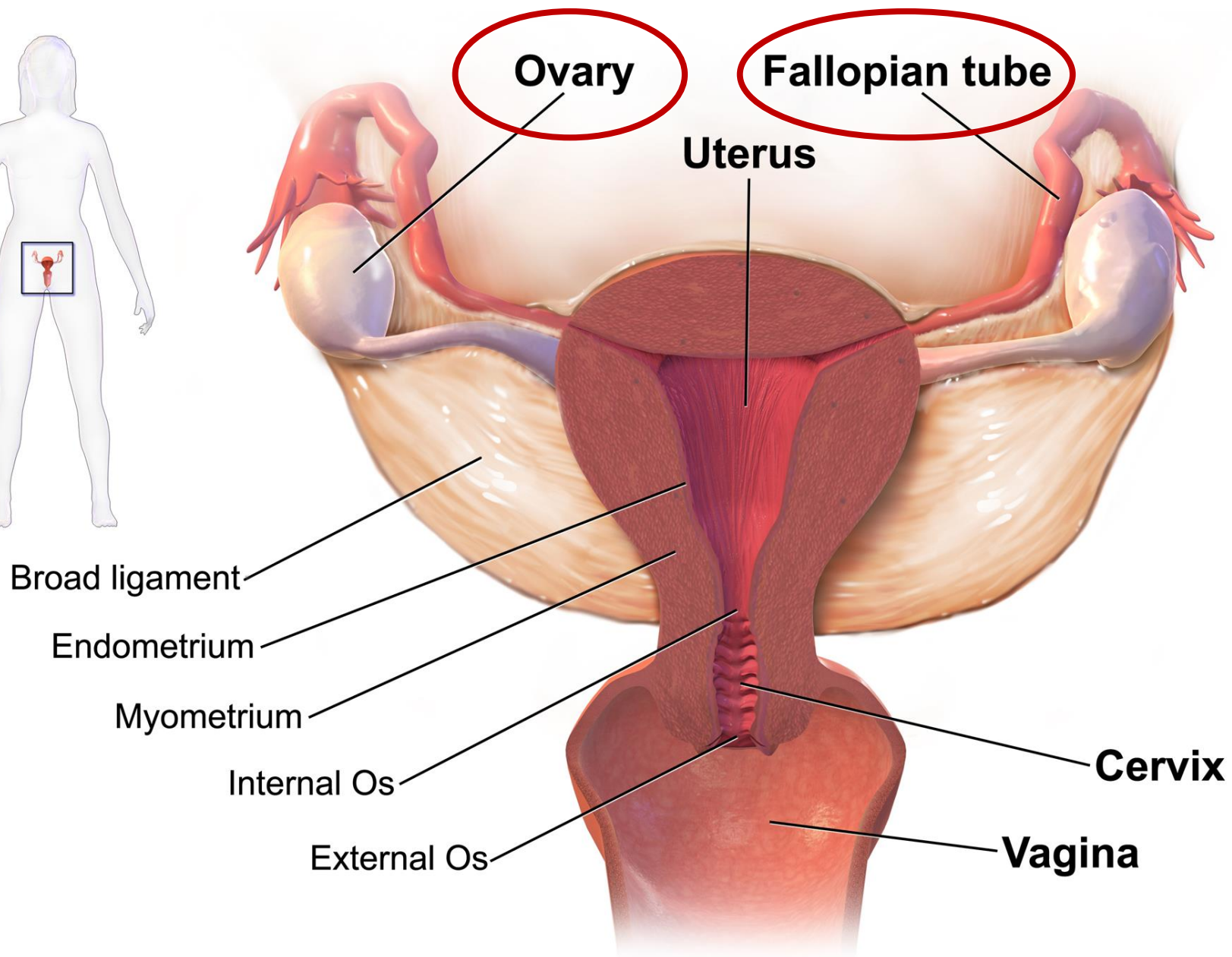
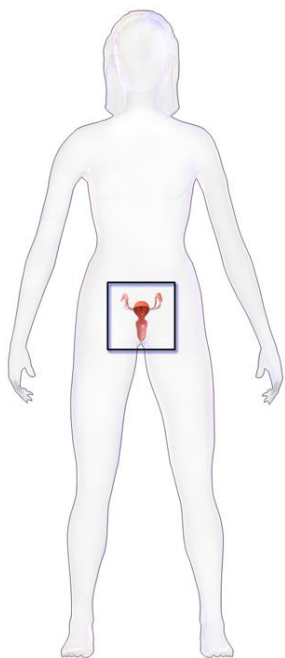
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*250 years of EXCELLENCE  
in medical education,  
research & innovation and  
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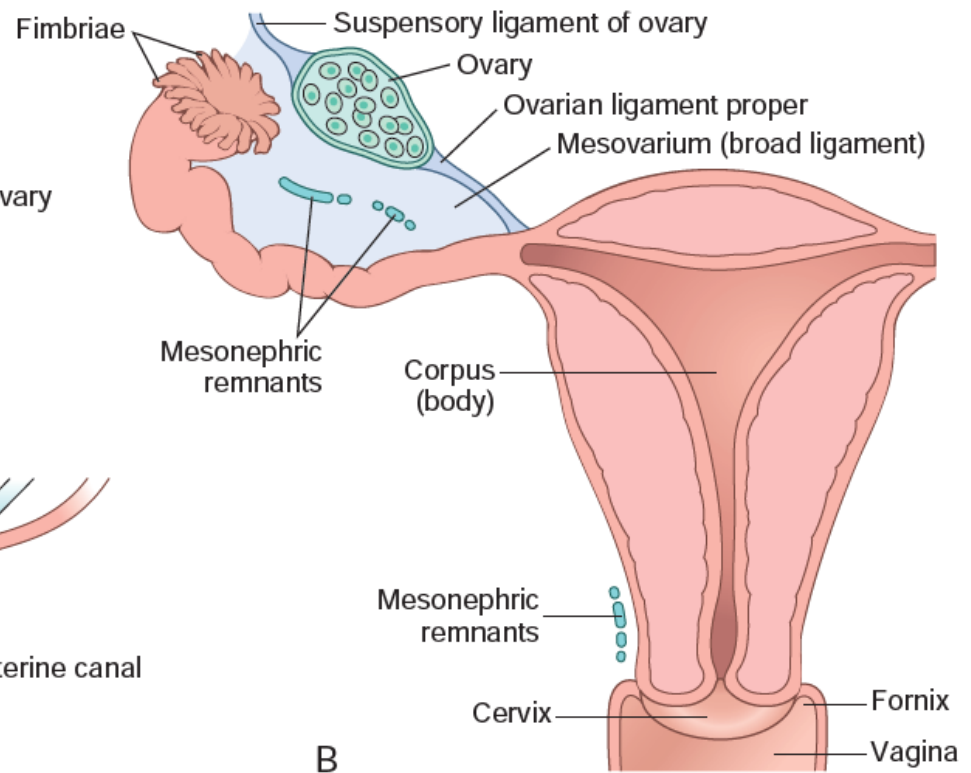
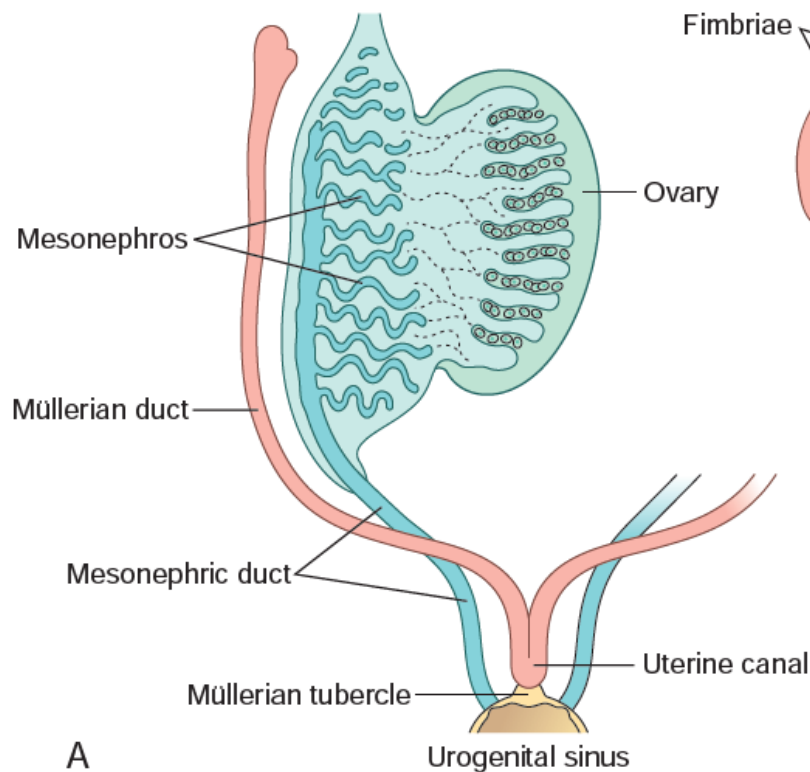


# Hormonal regulation

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- Hypophysis
  - GnRH
- Hypothalamus
  - LH
  - FSH
- Ovarian stroma (theca cells, granulosa cells)
  - Oestrogen
  - Progesteron
  - Inhibin
  - Androgen

# Development and anatomy





# OVARIES - Embriology

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- 4th week of gestation:
  - Primordial germ cells (PGC) in the wall of the yolk sac
- 5-6 weeks of gestation:
  - PGCs migrate into the urogenital ridge
- Later...:
  - The proliferating mesodermal epithelium (PME) of the urogenital ridge forms the epithelium of the gonad
  - In 46 XX, dividing germ cells are incorporated into the PME and eventually the OVARIES develop

# OVARIES

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- Develop mainly from **MESODERM**
  - Surface epithelium
  - Stroma
- Germ cells are of **ENDODERMAL** origin

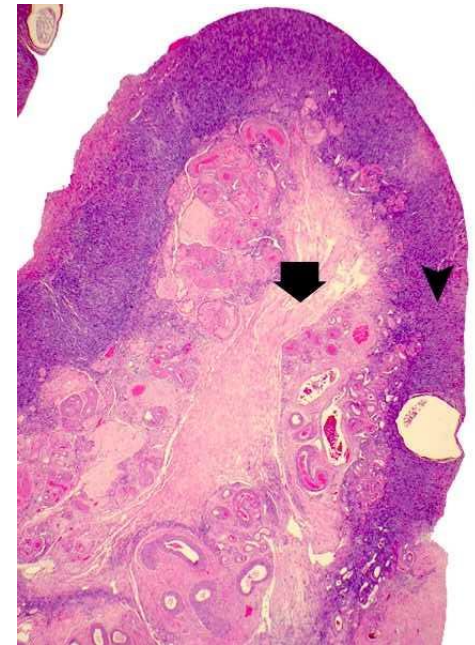
# Related diseases

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- Diseases related to *early developmental failure*: spectrum from lack of ovaries to early menopause
- Extragonadal germ cell tumors are related to the *failure of midline migration of GCs* (retroperitoneum, mediastinum, pineal gland)

# OVARIES - Anatomy

- Size: 4x3x1,5 cm
- Cortex
  - Closely packed plump fibroblasts
  - Follicles and ova
  - Graaf follicles (en route to ovulation)
    - Corpora lutea
    - Corpora albicantia
- Medulla
  - Loosely arranged mesenchymal tissue
  - Hilar cells („ambisexual”, resemble testicular stromal cells). *May give rise to masculinizing tumors.*



# FALLOPIAN TUBE - Embriology

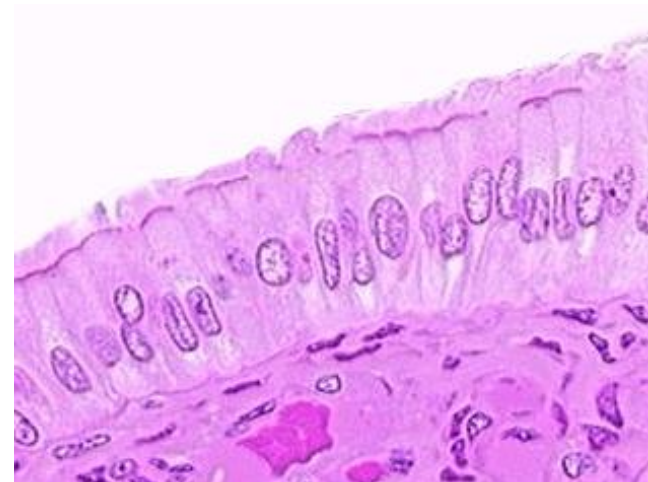
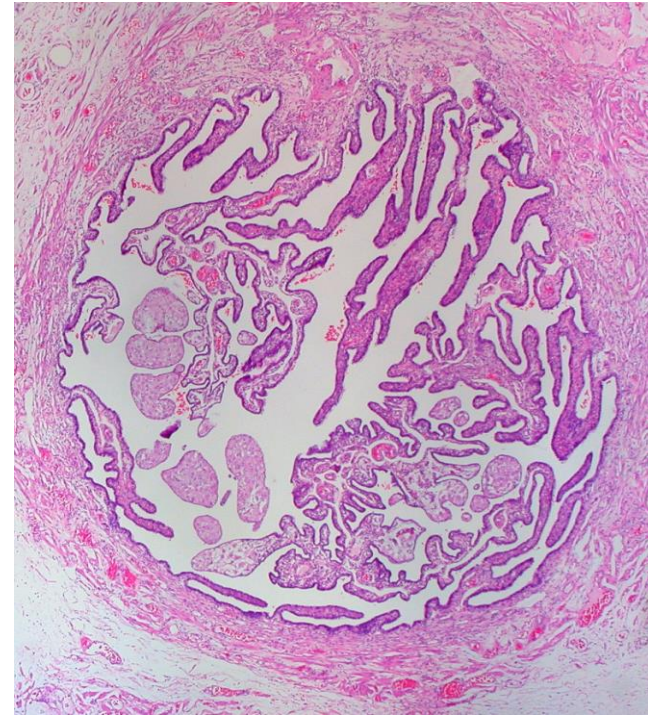
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- 6th week of gestation:
  - **Invagination of the coelomic lining epithelium** creates a groove that
- later will become
  - **Müllerian (paramesonephric) ducts** located high on the dorsal aspect of the coelomic cavity
- Caudal growth and medial fusion
  - Fused ducts become in contact with the urogenital sinus to form the vestibule of external genitalia
- ***Unfused portions become the Fallopian tubes***

# FALLOPIAN TUBE - Anatomy

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- Inner lining is derived from COELOMIC EPITHELIUM
- High, delicate folds of the mucosa --- papillary appearance on cross section
- Three cell types:
  - Ciliated columnar cells
  - Non-ciliated columnar, secretory cells
  - Intercalated cells



# Diseases of the ovaries and fallopian tubes

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## Fallopian tube

- Inflammations
  - Tubo-ovarian abscess
  - Pyosalpinx
- Ectopic pregnancy
- Endometriosis
- Adenocarcinoma

## Ovary

- Cysts
  - Simple
  - Follicular
    - Polycystic ovary
  - Corpus luteum
  - (cystic tumors)
- Endometriosis
- Stromal hyperplasia/hyperthecosis
- Tumors
  - Epithelial
  - Germ cell
  - Stromal
  - Mixed
  - Metastatic



# Clinical/Radiological examination

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- Physical examination (routine gynaecological)
  - Pelvic ultrasound
  - Transvaginal ultrasound
  - Pelvic CT and MRI
- 
- Ascites cytology – tumor cells absent or present

**Table 4. Causes of Palpable Mass on Pelvic Examination That May Be Confused with Ovarian Cancer**

<b>Gynecologic</b>	<b>Nongynecologic</b>
Benign	Benign
Ectopic pregnancy	Appendiceal abscess or mucocele
Endometrioma	Bladder diverticulum
Functional cyst	Diverticular abscess
Leiomyoma	Nerve sheath tumors
Mature teratoma	Paratubal cyst
Mucinous cystadenoma	Pelvic kidney
Serous cystadenoma	Ureteral diverticulum
Tubo-ovarian abscess or hydrosalpinx	Malignant
	Gastrointestinal cancer
	Metastasis
	Retroperitoneal sarcoma

# Laboratory tests

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- CA-125
- HE4 (Human Epididymis secretory protein 4 )
- ROMA (Risk of Ovarian Malignancy Algorithm)  
index = combination of the two above

**TABLE****Tumor markers in ovarian masses**

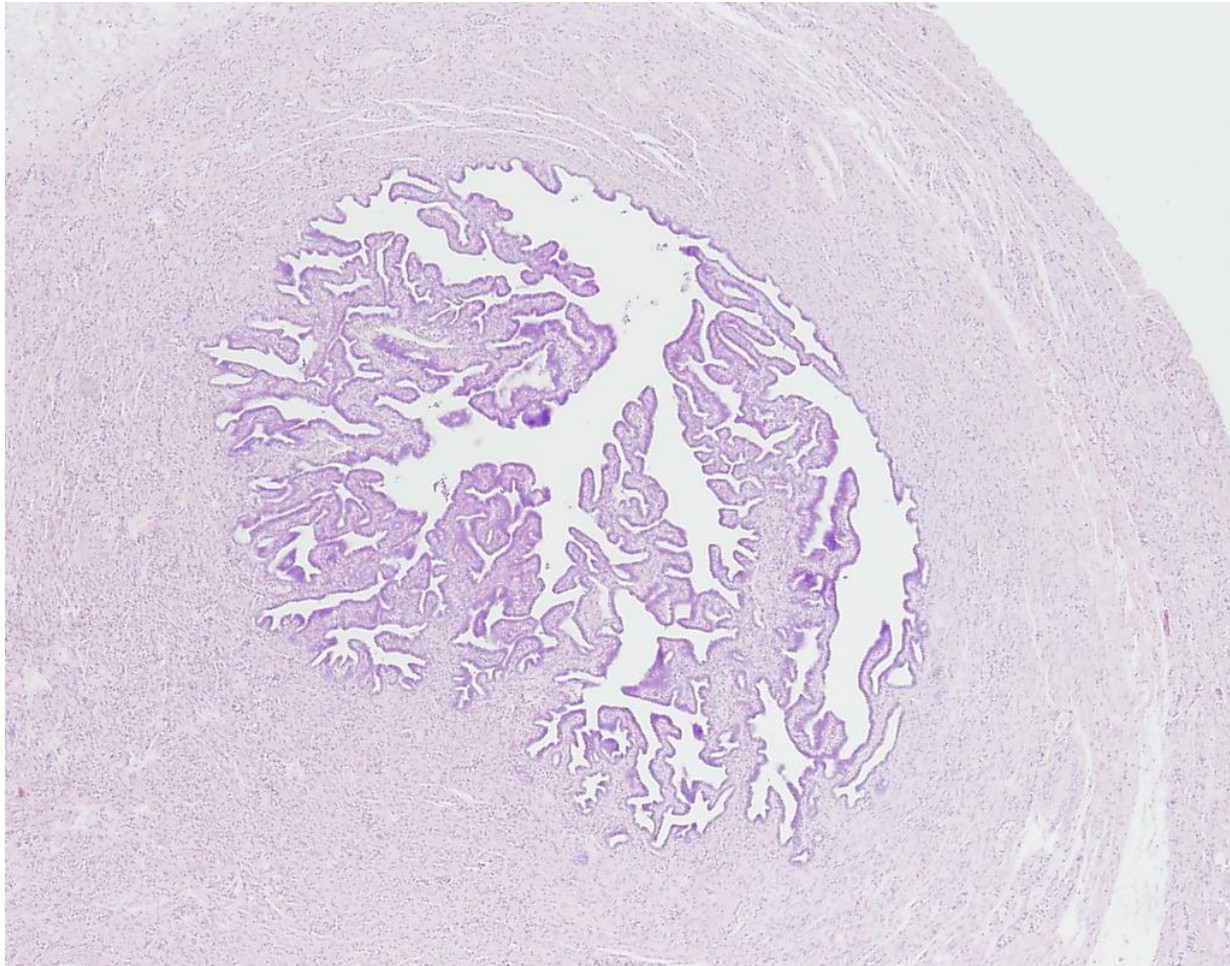
<b>Tumor marker</b>	<b>Ovarian neoplasm</b>
CA-125	Epithelial ovarian cancer
CEA	Mucinous ovarian cancer
HCG	Embryonal carcinoma Choriocarcinoma
Inhibin A or inhibin B	Granulosa cell tumor
Lactate dehydrogenase	Dysgerminoma
$\alpha$ -Fetoprotein	Endodermal sinus tumor Embryonal carcinoma

Abbreviations: CEA, carcinoembryonic antigen; HCG, human chorionic gonadotropin.



# FALLOPIAN TUBE

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# INFLAMMATION

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- Causes
  - *Pyogenic bacteria*
    - Gonococci (60%)
    - Streptococci and Staphylococci (postpartum)
  - *Chlamydia*
  - *Mycoplasma hominis*
  - Coliform bacteria
  - *Mycobacterium tuberculosis* (accompanies tuberculous endometritis)

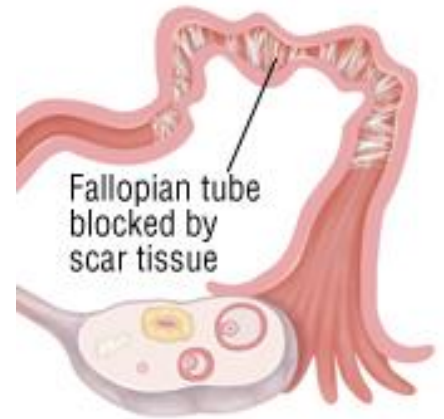
- Symptoms

- Fever
- Pelvic pain
- Pelvic mass

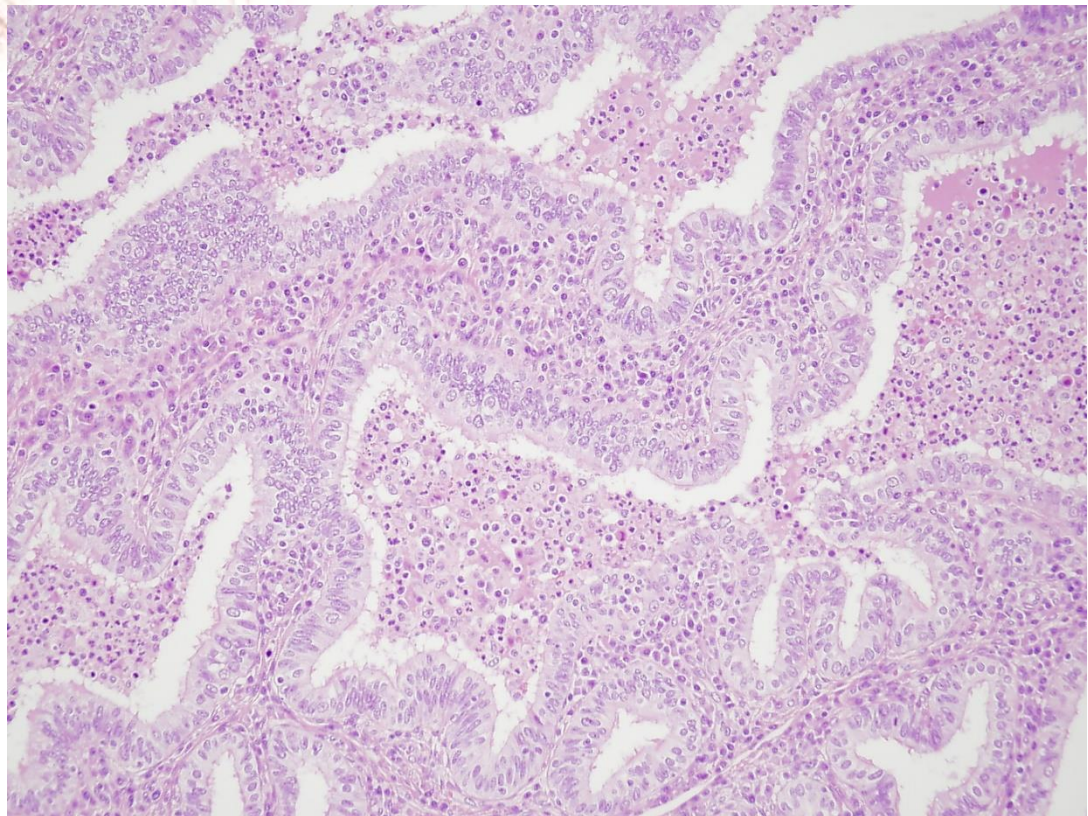
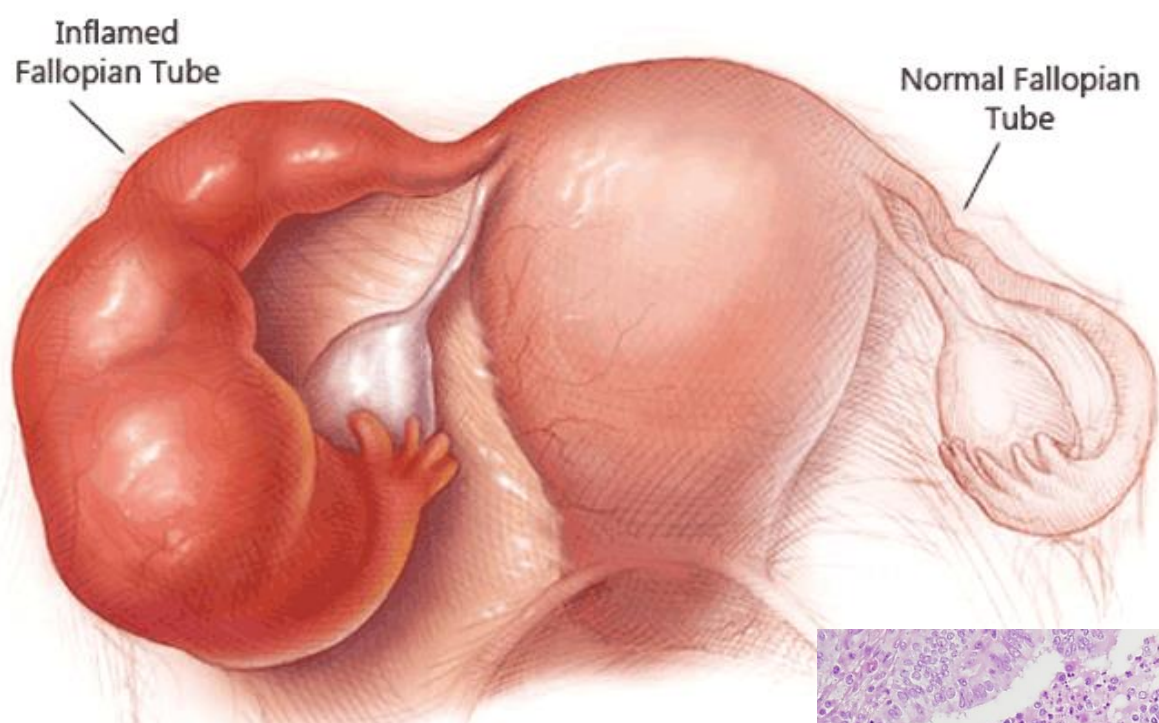


- Consequences/Complications may be

- Pyosalpinx
- Septicaemia
- Tubo-ovarian abscess
- Loss of mucosa with hydrosalpinx
- Higher incidence of ectopic pregnancy
- Infertility (due to adhesions/occlusion of the lumen)







# ECTOPIC PREGNANCY

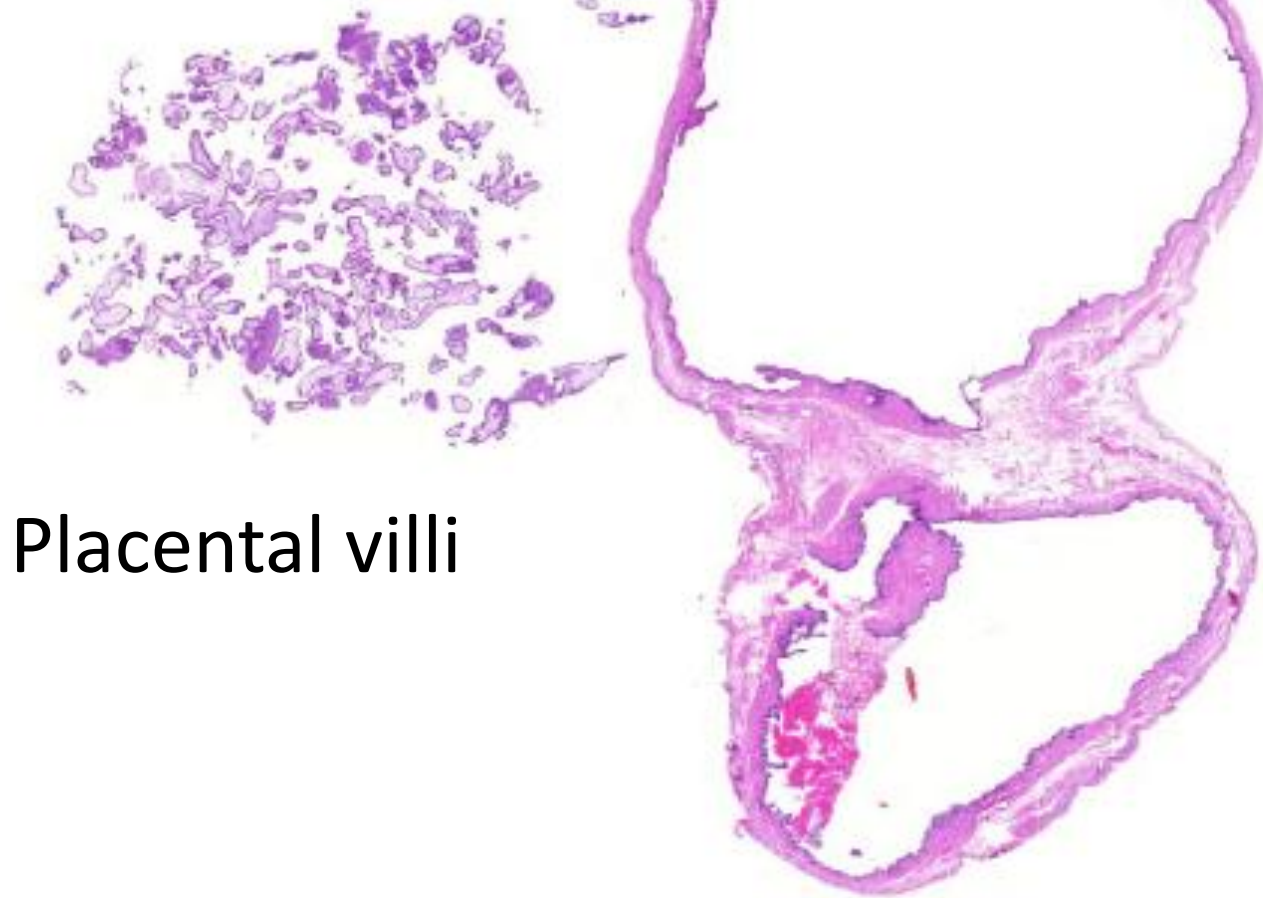
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- Definition: *Pregnancy outside the uterus*
- Fallopian tube is the commonest site
- Lower abdominal pain and abdominal hemorrhage (*hemascos* or *hemoperitoneum*) when it ruptures
- Pregnancy associated changes in the endometrium (so called *Arias-Stella phenomenon*)





Dilated fallopian tube

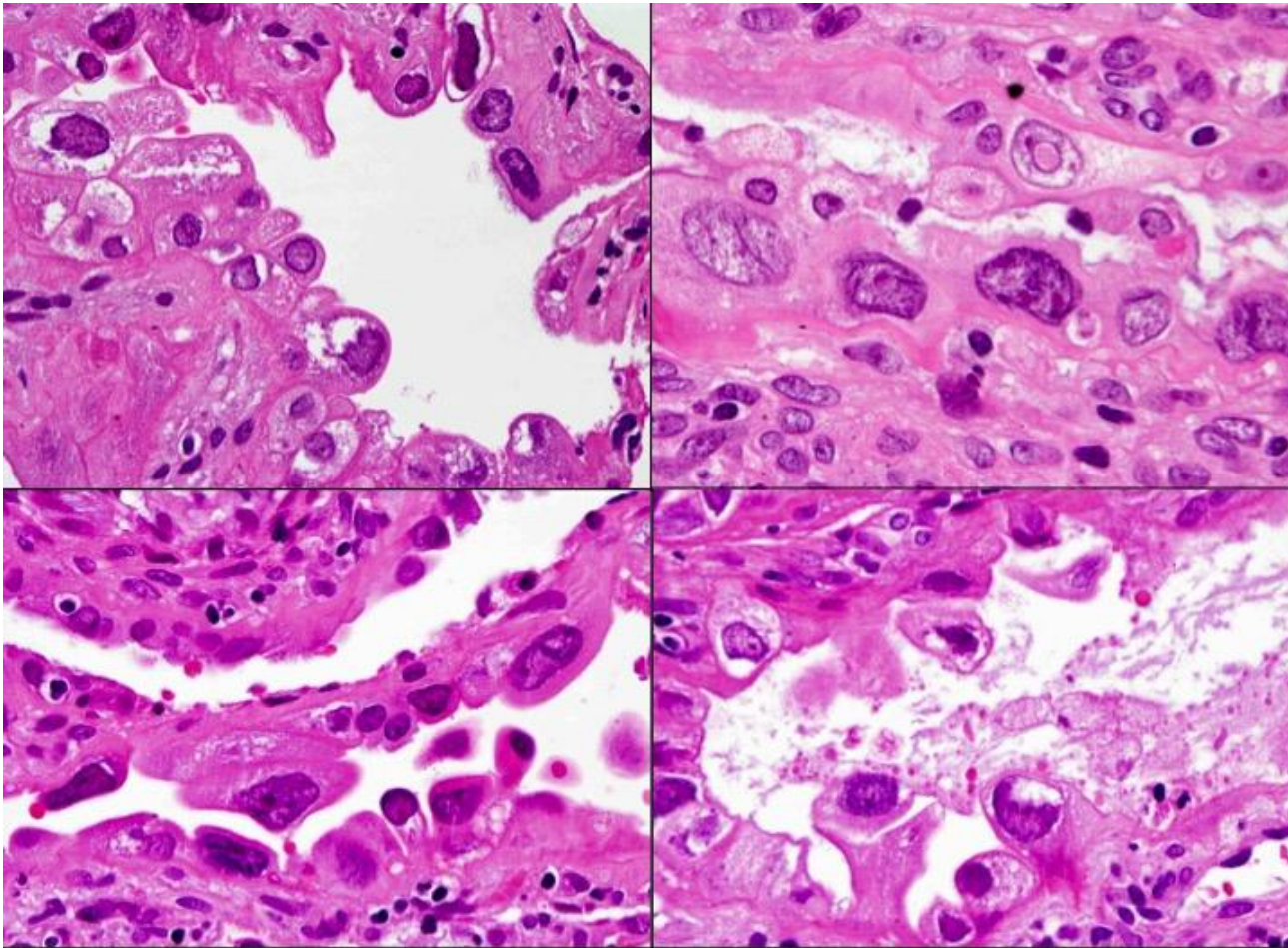


Placental villi

Hemorrhage/blood clot



# Histology of the endometrium: **Arias-Stella reaction**



Hobnail growth pattern as well as nuclei with a vesicular configuration while glands showing no / minimal secretory activity discernible in the combination picture. In the upper right image, monstrous cell pattern with giant, bizarre nuclei with homogenous chromatin containing nuclear pseudoinclusion is visible.

Please examine the nuclear variations from hypertrophied nuclei of ovoid or round shape with granular or vesicular viable chromatin, or hyperchromatic appearance, compact, pyknotic pattern as well as optically clear nuclei / nuclear pseudoinclusions; and cytoplasmic variations changing from abundant either densely eosinophilic or clear and vacuolated cytoplasm.

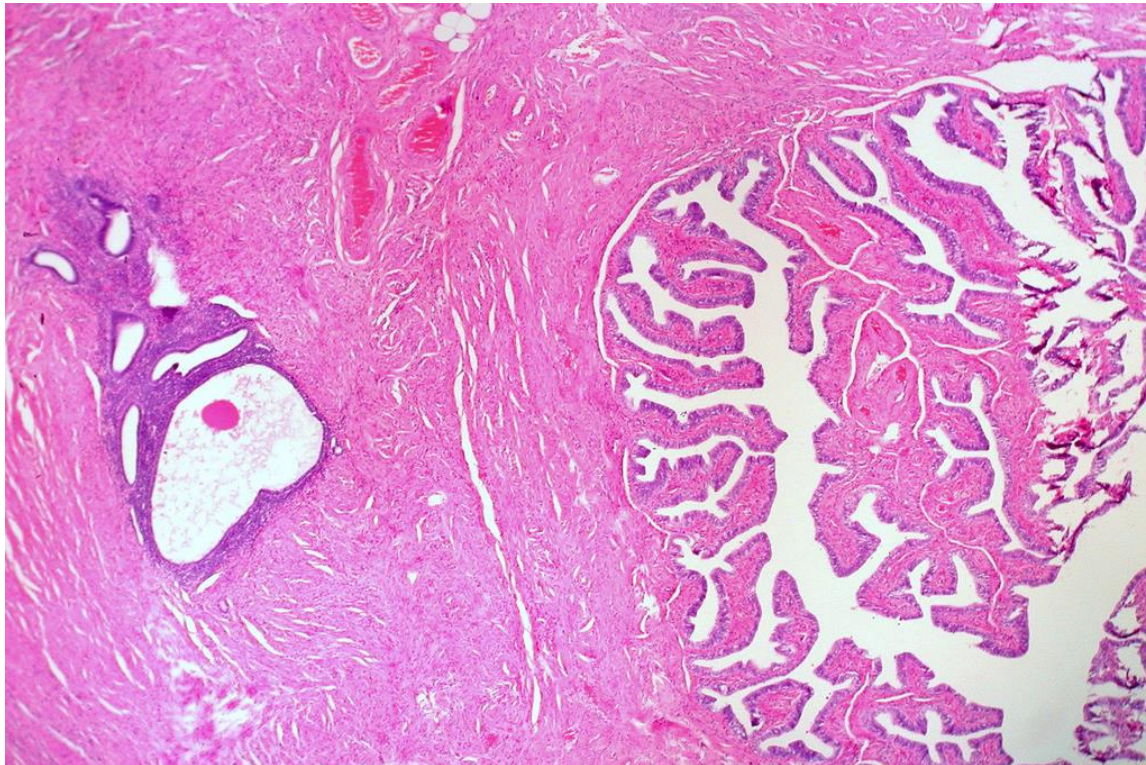
# ENDOMETRIOSIS

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- Definition: **presence of endometrial glands and stroma outside the uterine corpus**
- Endometriosis may involve also
  - Pouch of Douglas
  - Pelvic peritoneum
  - Ovary
  - Serosal surface of the uterus
  - Cervix
  - Vulva
  - Vagina
  - Extra-genital sites: bowel, urinary bladder



- Etiology unknown, but...
  - May be due to **retrograde menstruation**
  - May develop due to **metaplasia** of the mesothelial cells into Müllerian-type epithelium





# **Microscopic diagnostic features of endometriosis**

- 1) Endometrial glands
- 2) Endometrial stroma
- 3) Hemosiderin-laden macrophages

*The presence of minimum 2 features is required to the diagnosis*

# CYSTS, BENIGN TUMORS

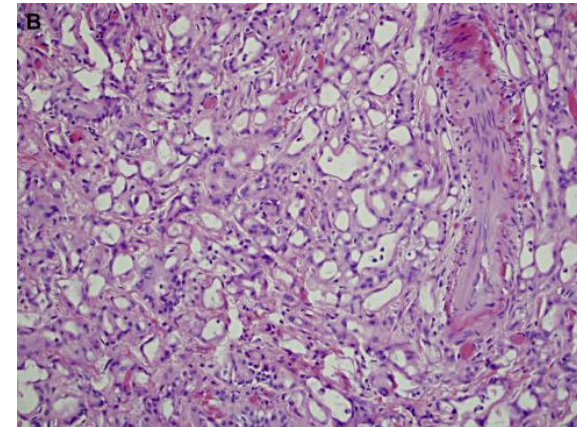
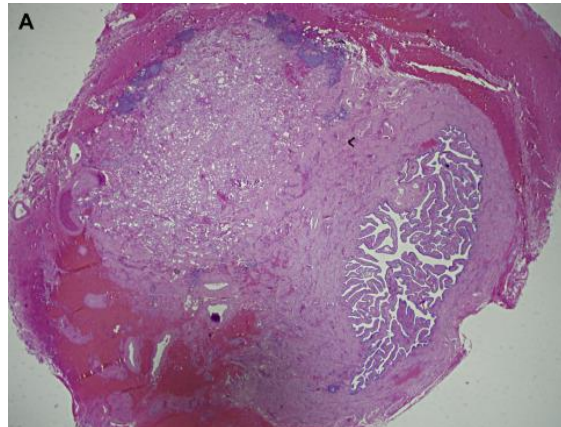
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## CYSTS

- Müllerian duct remnants
- Lining epithelium is serosus (tubal)
  - Paratubal cysts (few mm)
  - Morgagni hydatid (close to the fimbrial end, larger)

## BENIGN TUMORS

- Very rare
  - Adenomatoid tumor

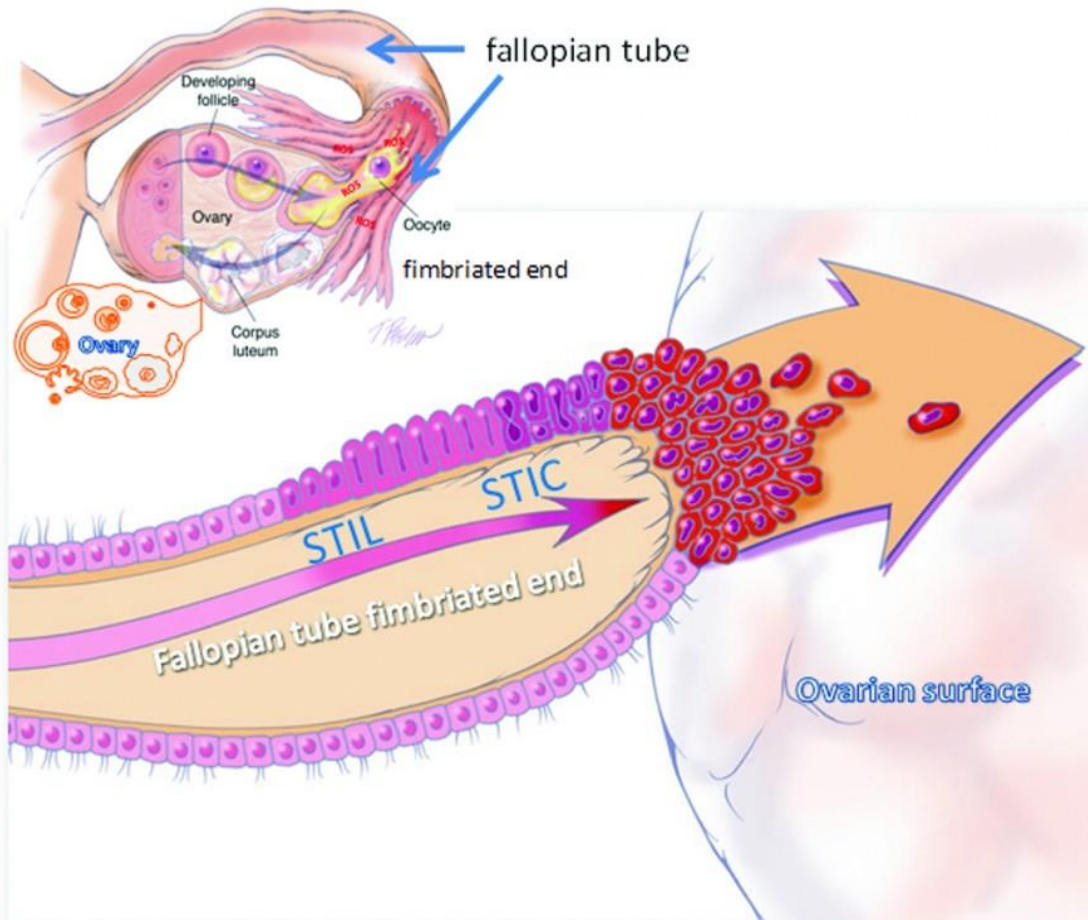


Surgical Pathology 12 (2019) 457–479, Fig. 1.A, B)

# ADENOCARCINOMA

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- Fallopian tubes may be the **site of origin for many of the high-grade serous carcinomas** long thought to arise in the ovary.
- **Precursor: serous tubal intraepithelial carcinoma (STIC)** in the fimbriated ends of Fallopian tubes.
  - mutations in TP53 in more than 90% of cases
  - found frequently in Fallopian tubes removed prophylactically from women who carry mutations in BRCA1 and BRCA2 genes
  - Less common in women with wtBRCA genes but sporadic “ovarian” serous carcinomas probably also originate in the Fallopian tube
  - **Fallopian tube carcinomas frequently involve the ovary, omentum, and peritoneal cavity at presentation (*high grade, advanced stage cancers*).**

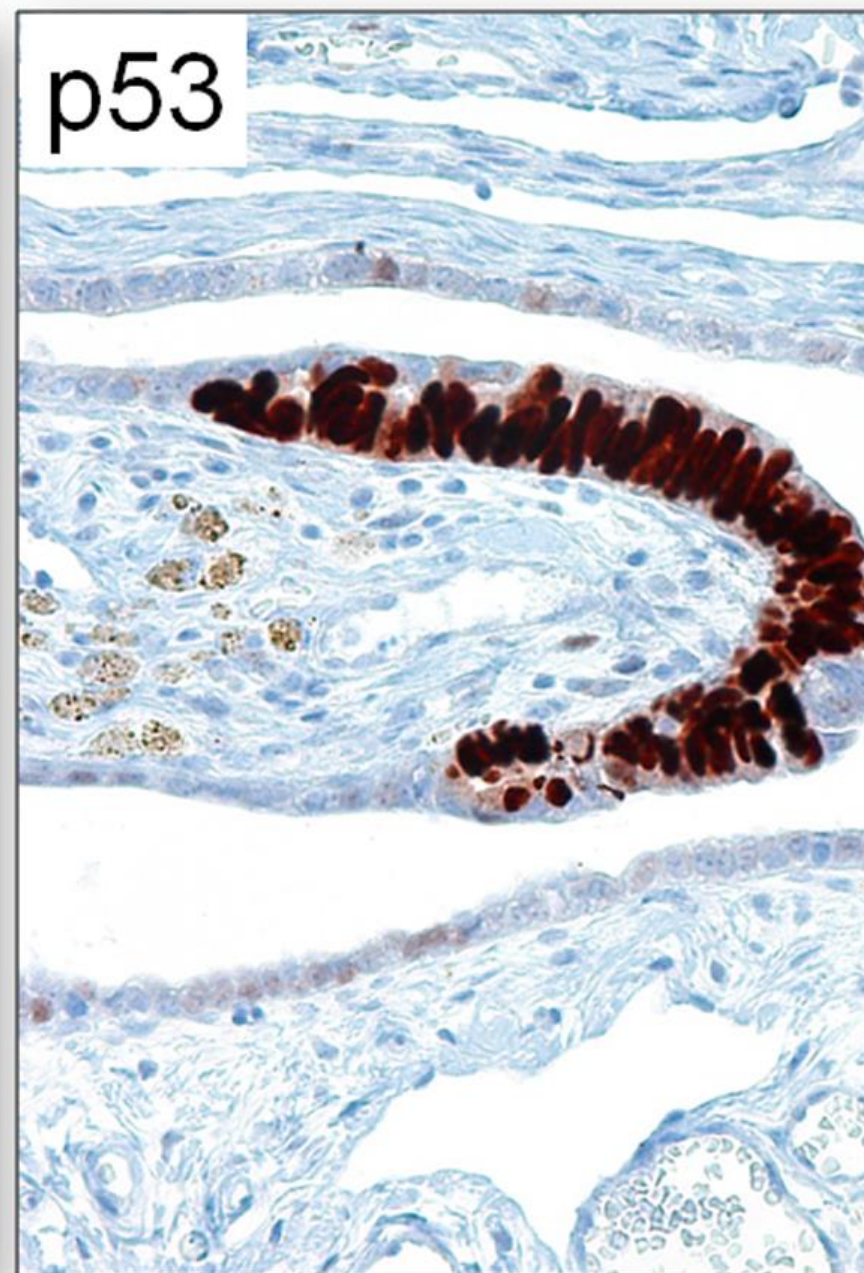
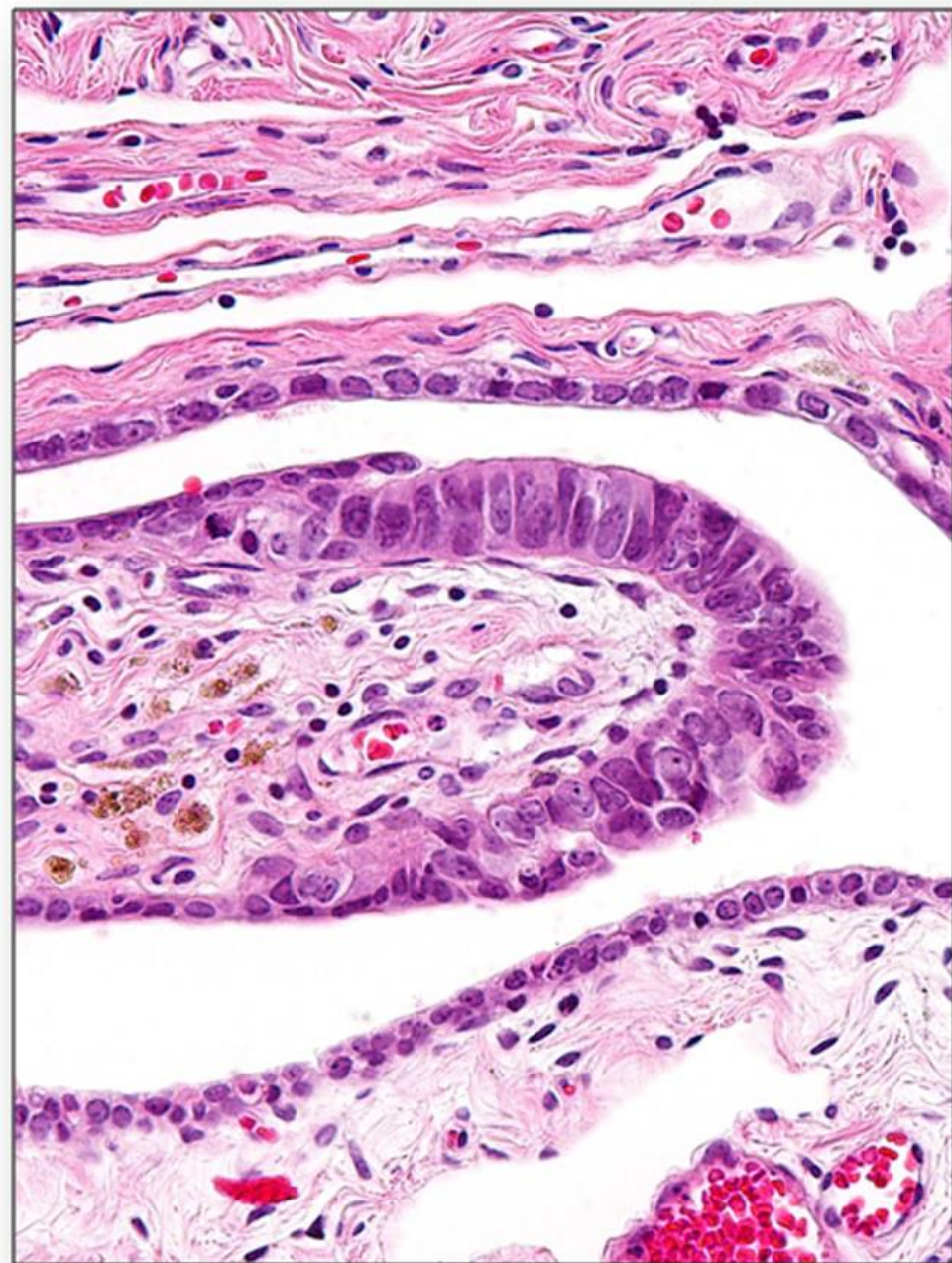


## Diagnostic morphological features of STIC

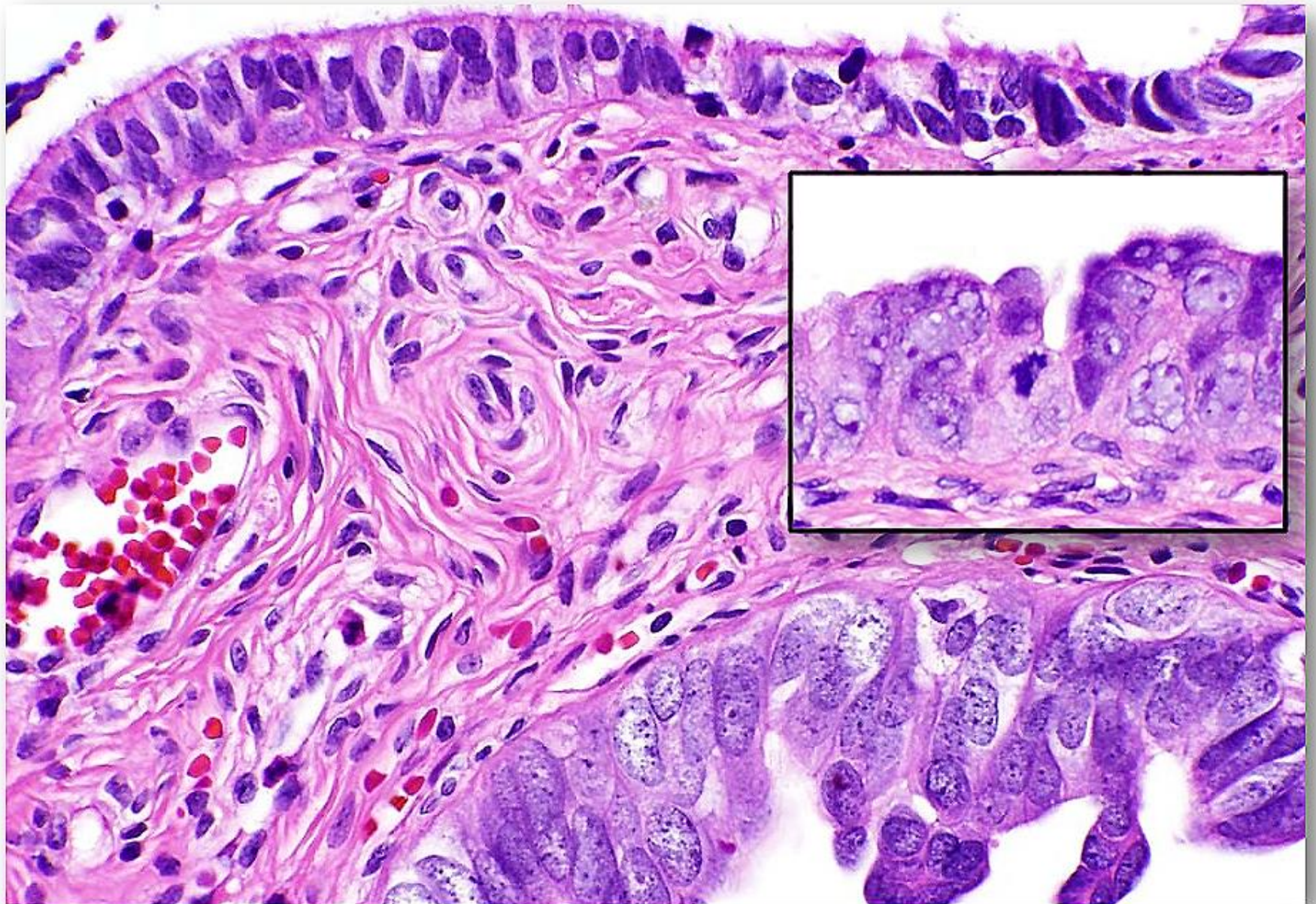
- 1) nuclear enlargement,
- 2) hyperchromasia,
- 3) irregularly distributed chromatin,
- 4) nucleolar prominence,
- 5) mitotic activity,
- 6) apoptosis,
- 7) loss of polarity,
- 8) epithelial tufting.

**Proposed development of ovarian HGSC by direct shedding and implantation of STIC cells from the fimbria onto the ovarian surface.**

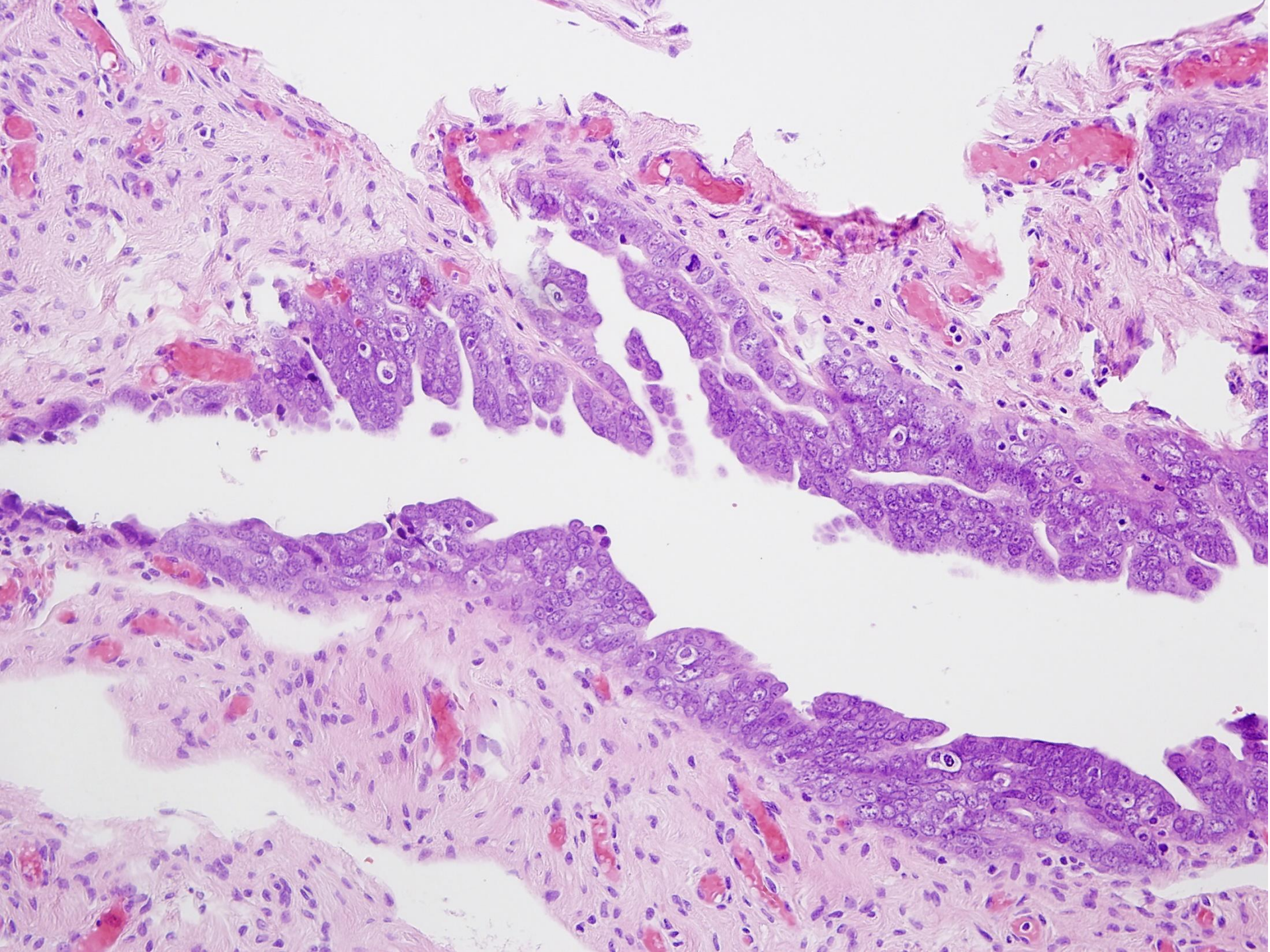




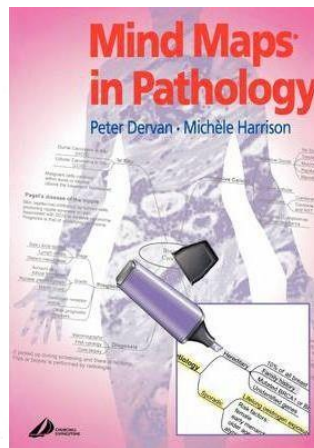












## Uterus and Fallopian Tubes

### Fallopian tubes

Inflammation usually secondary to endometrial infection or an intrauterine device

Acute or chronic - Chlamydia trachomatis

Pyosalpinx - accumulation of pus in lumen of tube

Hydrosalpinx - accumulation of fluid in lumen

Chronic inflammation may lead to loss of tube patency, ectopic pregnancy or secondary infertility

Pregnancy outside uterine cavity

Commonest site is fallopian tube

Increasing incidence - may be related to increasing infection. Most cases no obvious cause

Pain

Haemoperitoneum

Pregnancy associated changes in endometrium in absence of trophoblast or foetus

Fimbrial cysts and paratubal cysts - common, benign

Tumours are rare

Primary adenocarcinoma of fallopian tube - poor prognosis

### Uterus

#### Endometritis

Acute eg. bacterial infections postpartum or after miscarriage, retained products of conception

Chronic - in association with chronic gonorrhoeal pelvic disease, in tuberculosis, intrauterine contraceptive devices, 15% no apparent cause

#### Adenomyosis

Growth of basal layer of endometrium into myometrium

Thickened uterine wall due to reactive myometrial hypertrophy

Clinical features

Menorrhagia

Dysmenorrhoea

Pelvic pain before menstruation

#### Endometriosis

Foci of endometrial glands and stroma in pelvis, peritoneal cavity and about the umbilicus, which undergo cyclical bleeding

Pathogenesis - 3 theories

Metaplastic theory

Regurgitation theory

Vascular or lymphatic dissemination theory

Pathology

Yellow/brown nodules, in ovaries, chocolate cysts

Fibrosis with haemosiderin and ectopic endometrium

Clinical features

Severe dysmenorrhoea

Pelvic pain

Infertility

#### Dysfunctional Uterine Bleeding

Abnormal bleeding in absence of well-defined organic lesion

Failure of ovulation

Inadequate luteal phase

#### Endometrial Hyperplasia

Excess oestrogen

3 types

Simple hyperplasia

Complex hyperplasia

Atypical hyperplasia

Clinical features

Excessive and irregular uterine bleeding

Atypical, associated with a 20 to 25% risk of carcinoma

**OVARY**

# CYSTS

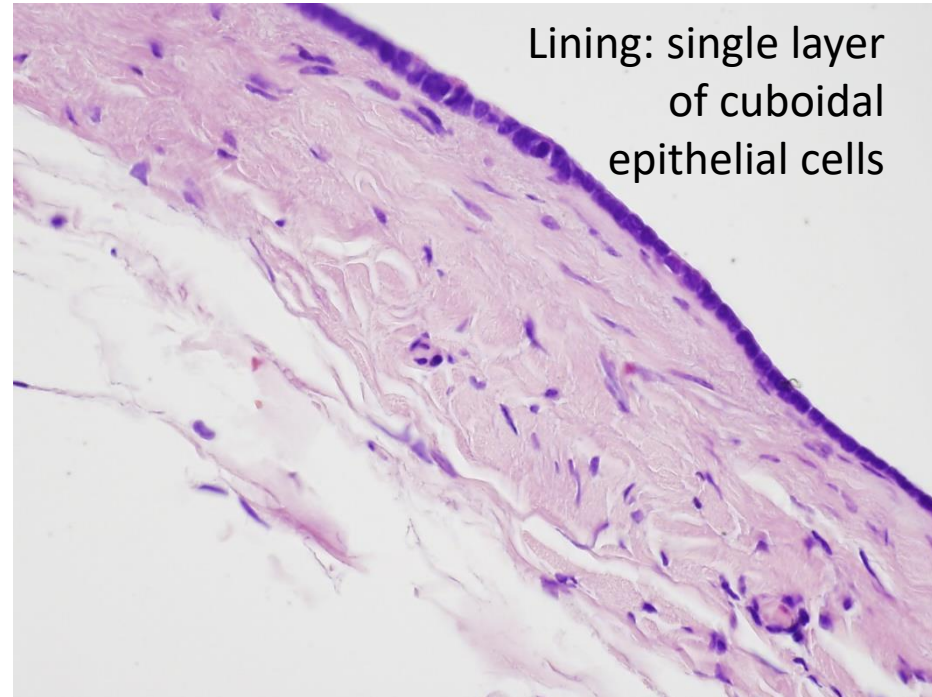
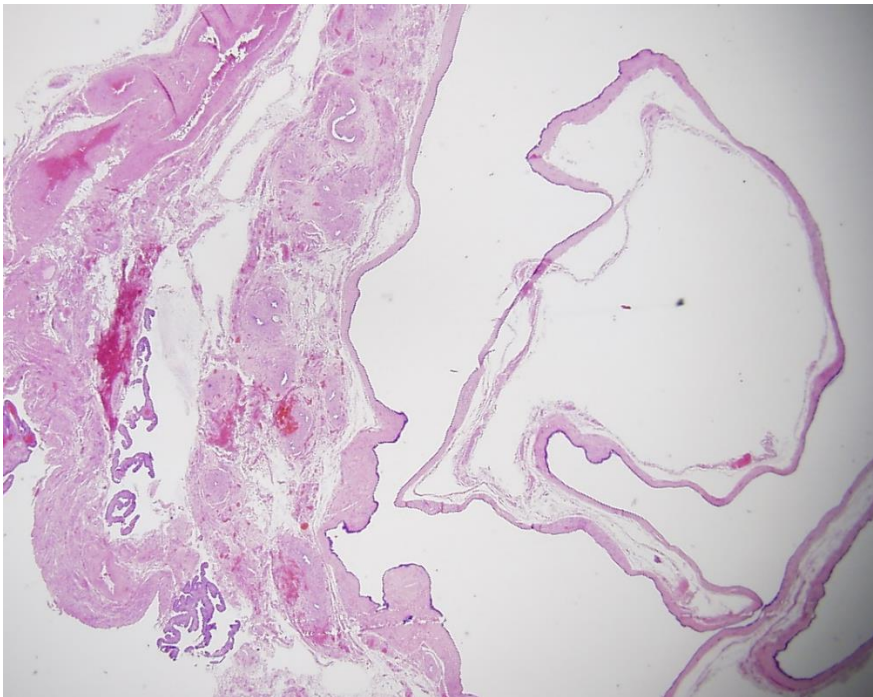
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- Simple
  - Invagination of the surface (coelomic) epithelium
- Follicular
  - Polycystic Ovary (PCO)
    - ANOVULATION, OBESITY, HIRSUTISM, Virilism
    - Ovaries are enlarged and cystic
    - In 3-6% of reproductive age women
    - Oligomenorrhea
    - Disturbed biosynthesis of androgens
    - ***Insulin resistance***
- Corpus luteum cyst
  - May mimic cystic tumor clinically
- Endometrioid
  - So called „chocolate” cyst
- *CYSTIC TUMORS*
  - *Serous*
  - *Mucinous*

# Simple cyst



Smooth  
outer and  
inner surface



Lining: single layer  
of cuboidal  
epithelial cells

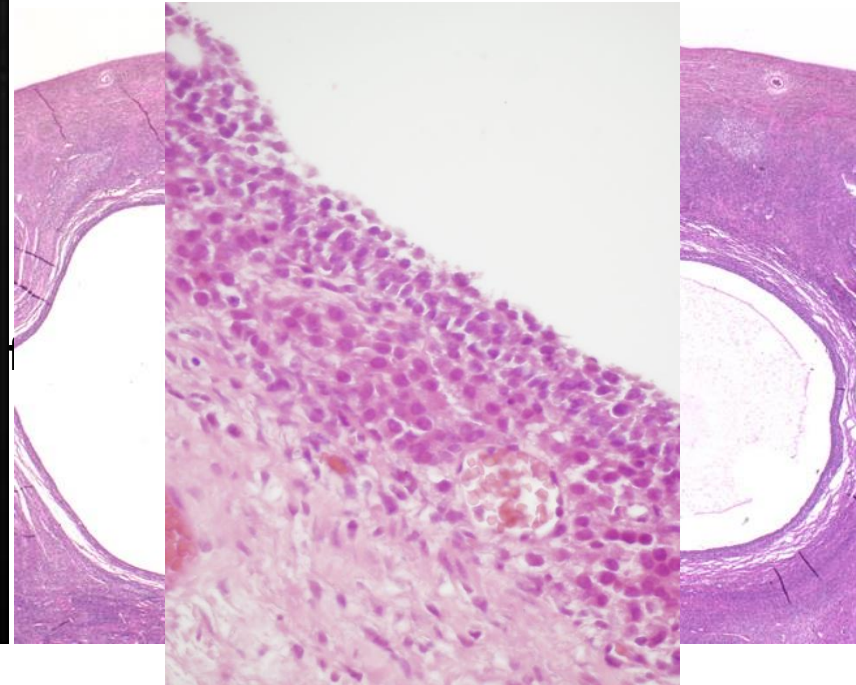


# Follicular cyst

Polycystic ovary syndrome



Multiple cysts in the cortex, inner surface smooth



Lining of cysts: granulosa cells

# Polycystic Ovary - PCO

## Background:

*insulin resistance*

→ hyperinsulinemia

→ decreased hepatic synthesis of steroid hormone binding globulin (SHBG) and insulin-like growth factor-1 (IGF-1)

→ increased level of free androgens and estrogens

→ inhibin production increased

→ inhibit FSH rise

→ follicular development is inadequate

LH levels are high (but lack the characteristic midcycle surge responsible for ovulation) → thecal hypertrophy → increased androgen production by the ovary → aromatase → estrogen levels increase → elevated risk of endometrial hyperplasia and endometrial cancer

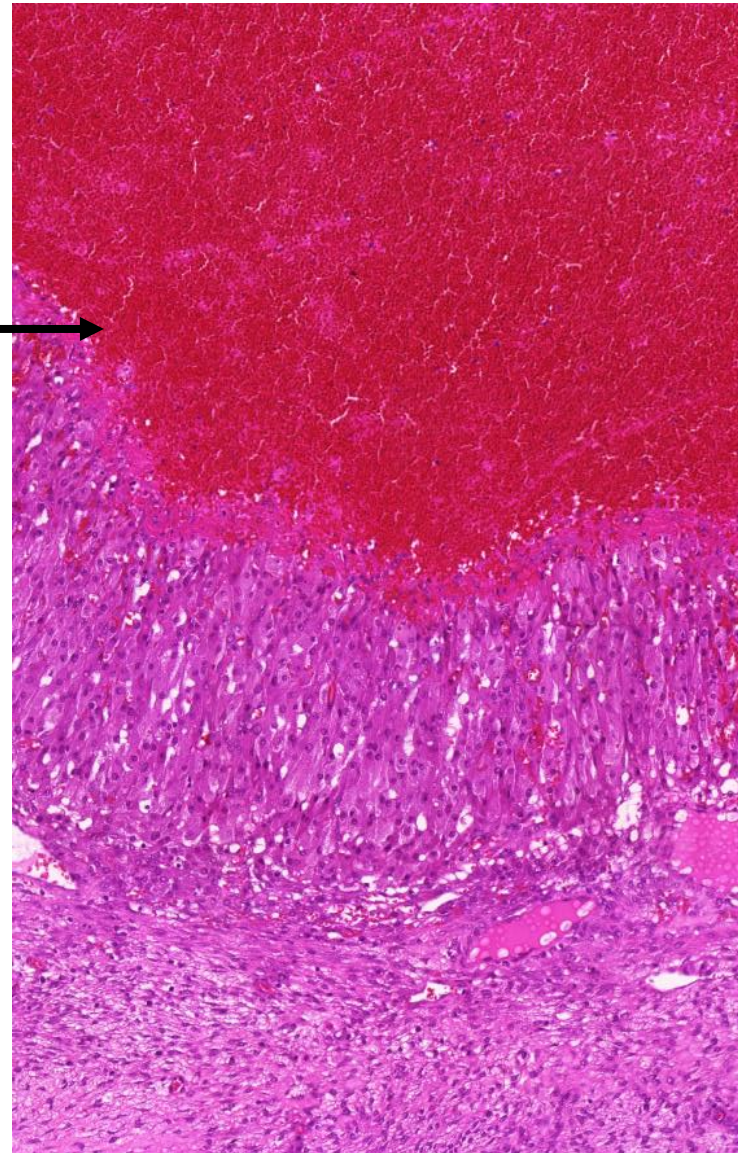
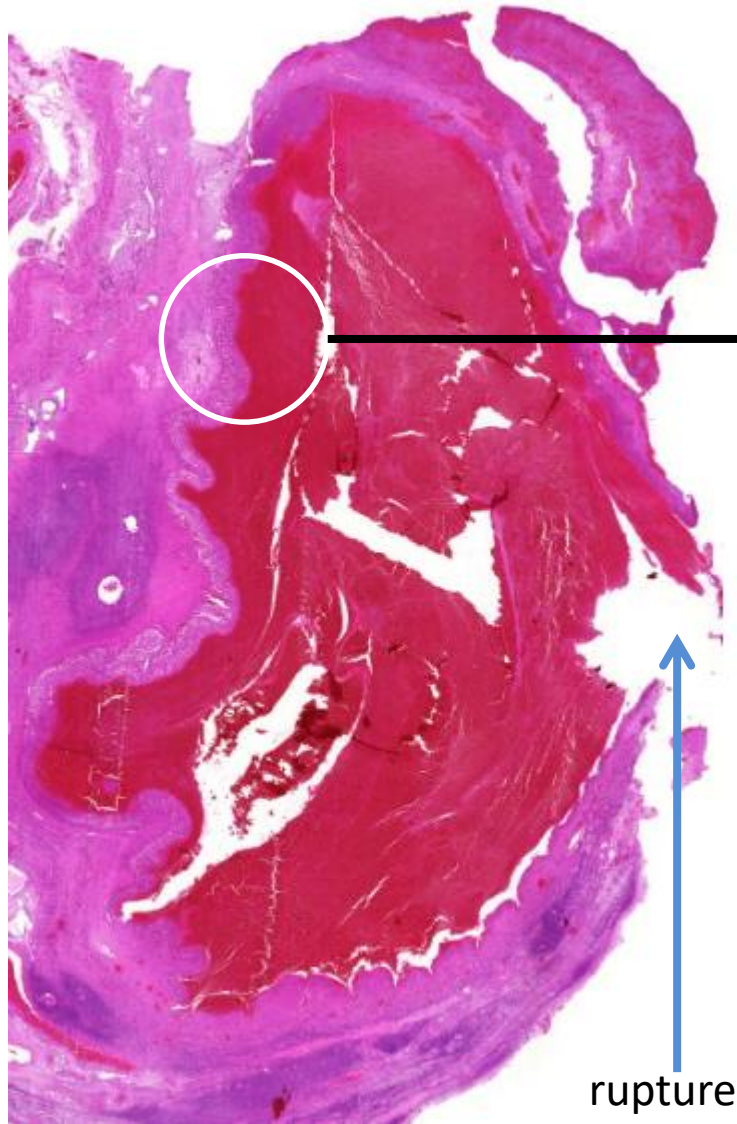
# Corpus luteum cyst

- Single cyst
- Yellowish





# Cystic-hemorrhagic corpus luteum



Luteinized  
theca- and  
granulosa  
cells

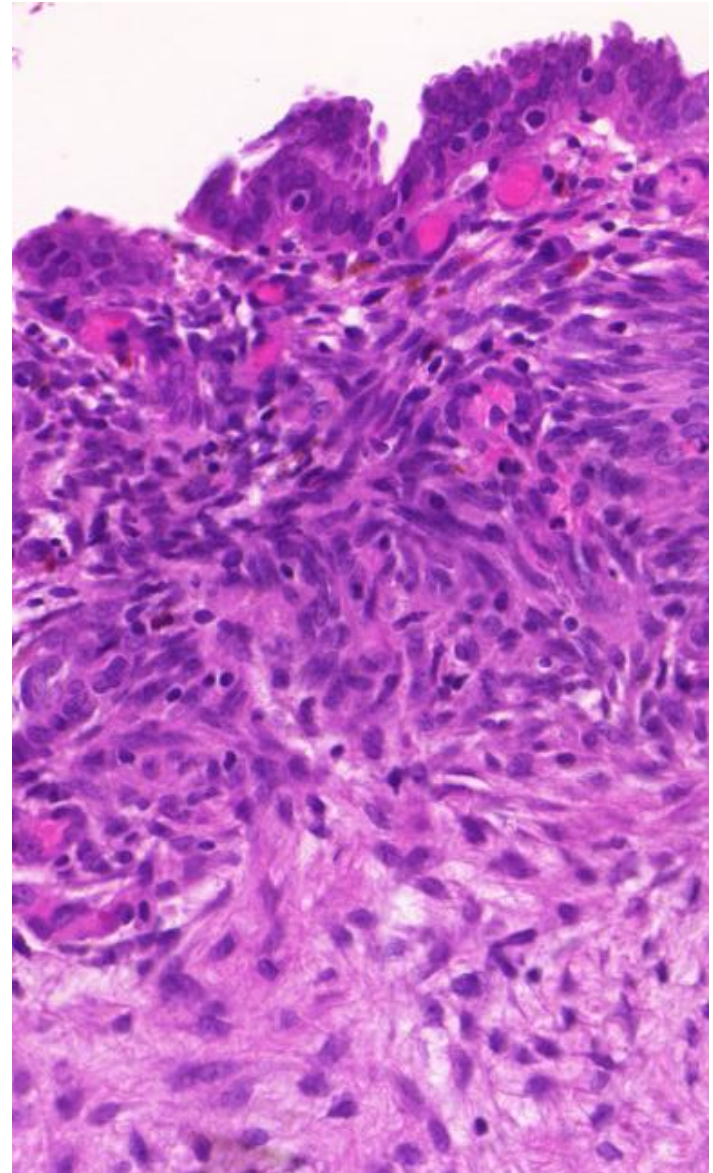


# Endometriosis – endometriotic cyst

Endometrial epithelial lining

Endometrial stroma

Hemosiderin



# Stromal hyperplasia/hyperthecosis

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- Postmenopausal women
- Signs: hyperestrogenism, hyperandrogenism, virilism, obesity, abnormal glucose tolerance test
- enlarged ovaries (up to 7 cm), no cysts
- hypercellular stroma with luteinized stromal cells ( producing androgens)

# Tumors of the ovary

**Benign tumors: 80%**

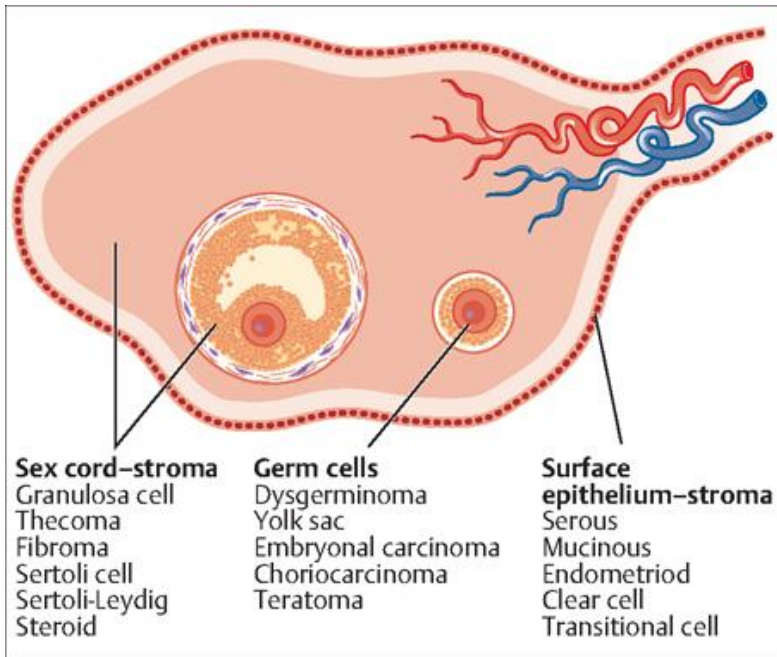
Age 20-45

**Malignant tumors**

Age 45-65

**3% of all cancers in women**

**5th most common cause of cancer death**



Epithelial Tumors 90%

Stromal Tumors 7%

Germ Cell Tumors 3%

# WHO Classification of tumours of the ovary<sup>a,b</sup>

<b>Epithelial tumours</b>		Malignant
<b>Serous tumours</b>		Malignant Brenner tumour
Benign		
Serous cystadenoma	8441/0	
Serous adenofibroma	9014/0	
Serous surface papilloma	8461/0	
Borderline		
Serous borderline tumour /		
Atypical proliferative serous tumour	8442/1	
Serous borderline tumour - micropapillary variant / Non-invasive low-grade serous carcinoma	8460/2*	
Malignant		
Low-grade serous carcinoma	8460/3	
High-grade serous carcinoma	8461/3	
<b>Mucinous tumours</b>		
Benign		
Mucinous cystadenoma	8470/0	
Mucinous adenofibroma	9015/0	
Borderline		
Mucinous borderline tumour / Atypical proliferative mucinous tumour	8472/1	
Malignant		
Mucinous carcinoma	8480/3	
<b>Endometrioid tumours</b>		
Benign		
Endometriotic cyst		
Endometrioid cystadenoma	8380/0	
Endometrioid adenofibroma	8381/0	
Borderline		
Endometrioid borderline tumour / Atypical proliferative endometrioid tumour	8380/1	
Malignant		
Endometrioid carcinoma	8380/3	
<b>Clear cell tumours</b>		
Benign		
Clear cell cystadenoma	8443/0	
Clear cell adenofibroma	8313/0	
Borderline		
Clear cell borderline tumour / Atypical proliferative clear cell tumour	8313/1	
Malignant		
Clear cell carcinoma	8310/3	
<b>Brenner tumours</b>		
Benign		
Brenner tumour	9000/0	
Borderline		
Borderline Brenner tumour / Atypical proliferative Brenner tumour	9000/1	

<b>Germ cell tumours</b>			Wolffian tumour
Dysgerminoma	9060/3		Small cell carcinoma, hypercalcaemic type
Yolk sac tumour	9071/3		Small cell carcinoma, pulmonary type
Embryonal carcinoma	9070/3		Wilms tumour
Non-gestational choriocarcinoma	9100/3		Paraganglioma
Mature teratoma	9080/0		Solid pseudopapillary neoplasm
Immature teratoma	9080/3		
Mixed germ cell tumour	9085/3		
<b>Monodermal teratoma and somatic-type tumours arising from a dermoid cyst</b>			<b>Mesothelial tumours</b>
Struma ovarii, benign	9090/0		Adenomatoid tumour
Struma ovarii, malignant	9090/3		Mesothelioma
Carcinoid	8240/3		
Strumal carcinoid	9091/1		
Mucinous carcinoid	8243/3		
Neuroectodermal-type tumours			
Sebaceous tumours			
Sebaceous adenoma	8410/0		
Sebaceous carcinoma	8410/3		
Other rare monodermal teratomas			
Carcinomas			
Squamous cell carcinoma	8070/3		
Others			
<b>Germ cell - sex cord-stromal tumours</b>			
Gonadoblastoma, including gonadoblastoma with malignant germ cell tumour	9073/1		
Mixed germ cell-sex cord-stromal tumour, unclassified	8594/1*		
<b>Miscellaneous tumours</b>			
Tumours of rete ovarii			
Adenoma of rete ovarii	9110/0		
Adenocarcinoma of rete ovarii	9110/3		

2014



## T - Primary Tumour

### TNM FIGO

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	I Tumour limited to the ovaries
T1a	IA Tumour limited to one ovary (capsule intact) or fallopian tube surface; no malignant cells in ascites or peritoneal washings
T1b	IB Tumour limited to one or both ovaries (capsules intact) or fallopian tubes; no tumour on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
T1c	IC Tumour limited to one or both ovaries or fallopian tubes with any of the following:
T1c1	IC1 Surgical spill
T1c2	IC2 Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface
T1c3	IC3 Malignant cells in ascites or peritoneal washings
T2	II Tumour involves one or both ovaries or fallopian tubes with pelvic extension below pelvic brim or primary peritoneal cancer
T2a	IIA Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
T2b	IIB Extension to other pelvic intraperitoneal
T3	III Tumour involves one or both ovaries or fallopian tubes, and/or or primary peritoneal carcinoma, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
N1	IIIA1 Retroperitoneal lymph node metastasis only
N1a	IIIA1i Lymph node metastasis up to 10 mm in greatest dimension
N1b	IIIA1ii Lymph node metastasis more than 10 mm in greatest dimension
T3a	IIIA2 Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without retroperitoneal lymph node
T3b	IIIB Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension with or without retroperitoneal lymph node metastasis
T3c	IIIC Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without retroperitoneal lymph node metastasis (excludes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)
M1	IV Distant metastasis excluding peritoneal metastasis
M1a	IVA Pleural effusion with positive cytology
M1b	IVB Parenchymal metastasis and metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity)

## N — Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Lymph node metastasis up to 10 mm in greatest dimension
N1b	Lymph node metastasis more than 10 mm in greatest dimension

## M — Distant Metastasis

M0	No distant metastasis
M1	Distant metastasis
M1a	Pleural effusion with positive cytology
M1b	Parenchymal metastasis and metastasis to extra abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity)

### pTNM Pathological Classification

The pT and pN categories correspond to the T and N categories.

pM1 Distant metastasis microscopically confirmed

**Note:** pM0 and pMX are not valid categories.

**pN0** Histological examination of a pelvic lymphadenectomy specimen will ordinarily include 10 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

### Stage Grouping

Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC1	T1c1	N0	M0
Stage IC2	T1c2	N0	M0
Stage IC3	T1c3	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIIA1	T1/T2	N1	M0
Stage IIIA2	T3a	N0/N1	M0
Stage IIIB	T3b	N0/N1	M0
Stage IIIC	T3c	N0/N1	M0
Stage IV	Any T	Any N	M1

**Note:** There is no longer a T2c category.

### References

- American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7th ed. (2011). Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti III eds. Springer: New York
- International Union against Cancer (UICC): TNM Classification of Malignant Tumours, 7th ed. (2009) Sobin LH, Gospodarowicz MK, Wittekind Ch eds. Wiley-Blackwell: Oxford
- A help-desk for specific questions about the TNM classification is available at <http://www.uicc.org>.
- Prat J, FIGO Committee on Gynecologic Oncology (2014). Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet 124:1-5.

## TNM and FIGO Fallopian tube and Ovary

2017

TNM: Tumor – Node – Metastasis  
FIGO: Fédération Internationale  
de Gynecologie et Ostétrique

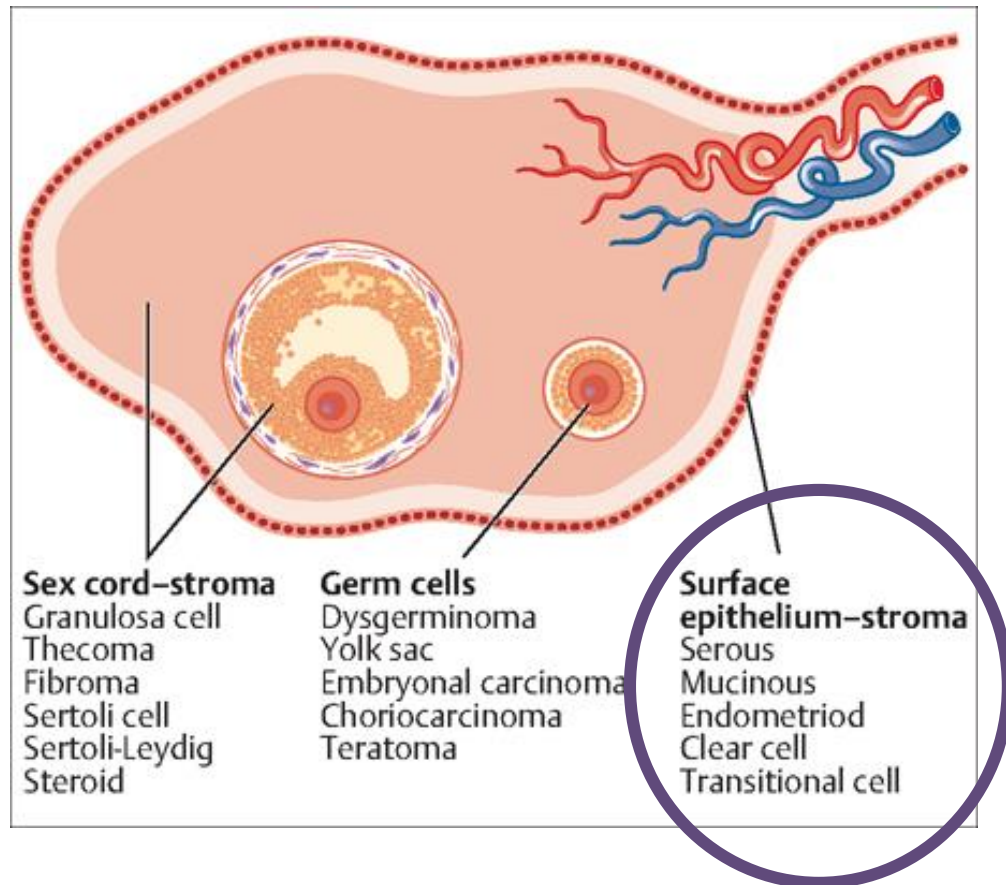


**TABLE 19.3** Frequency of Major Ovarian Tumors

Type	Percentage of Malignant Ovarian Tumors	Percentage That Are Bilateral
Serous	47 %	
Benign (60%)		25 %
Borderline (15%)		30 %
Malignant (25%)		65 %
Mucinous	3 %	
Benign (80%)		5 %
Borderline (10%)		10 %
Malignant (10%)		<5 %
Endometrioid carcinoma	20 %	30 %
Undifferentiated carcinoma	10 %	—
Clear cell carcinoma	6 %	40%
Granulosa cell tumor	5 %	5 %
Teratoma	1 %	
Benign (96%)		15 %
Malignant (4%)		Rare
Metastatic	5 %	>50%
Others	3 %	—

# EPITHELIAL TUMORS

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- **Serous**
  - 25% malignant
  - Bilaterality common
  - Psammoma bodies
- **Mucinous**
  - Majority benign
  - Can be very large
  - Pseudomyxoma peritonei
- **Endometrioid**
  - Majority malignant
  - 15-30% with synchronous endometrial carcinoma
- **Clear cell**
  - Variant of endometrioid diff.
  - „hobnail” cells
- **Transitional cell/Brenner tumor**
  - Mostly benign
  - Wolffian differentiation
- **Seromucinous**
  - Rare
  - Often adjacent to endometriosis
  - Various Müllerian epithel

- **BENIGN**
  - CYSTADENOMA
  - CYSTADENOFIBROMA
  - ADENOFIBROMA
- **BORDERLINE**
  - INCREASED STRUCTURAL COMPLEXITY
  - NO DESTRUCTIVE INFILTRATIVE GROWTH
- **MALIGNANT**
  - HIGHLY COMPLEX STRUCTURE
  - INVASION

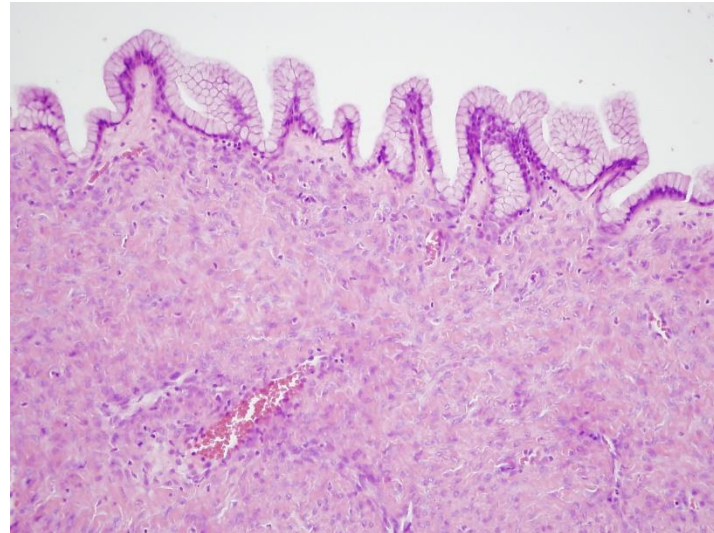
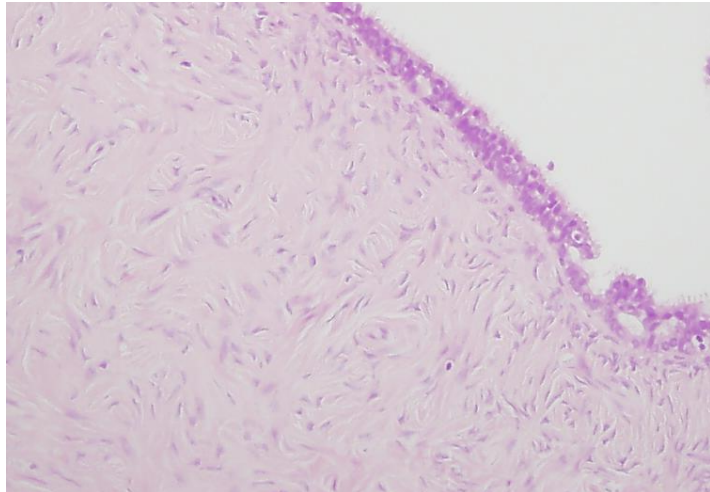
# ***Benign epithelial tumors***

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Serous cystadenoma (25% bilateral)

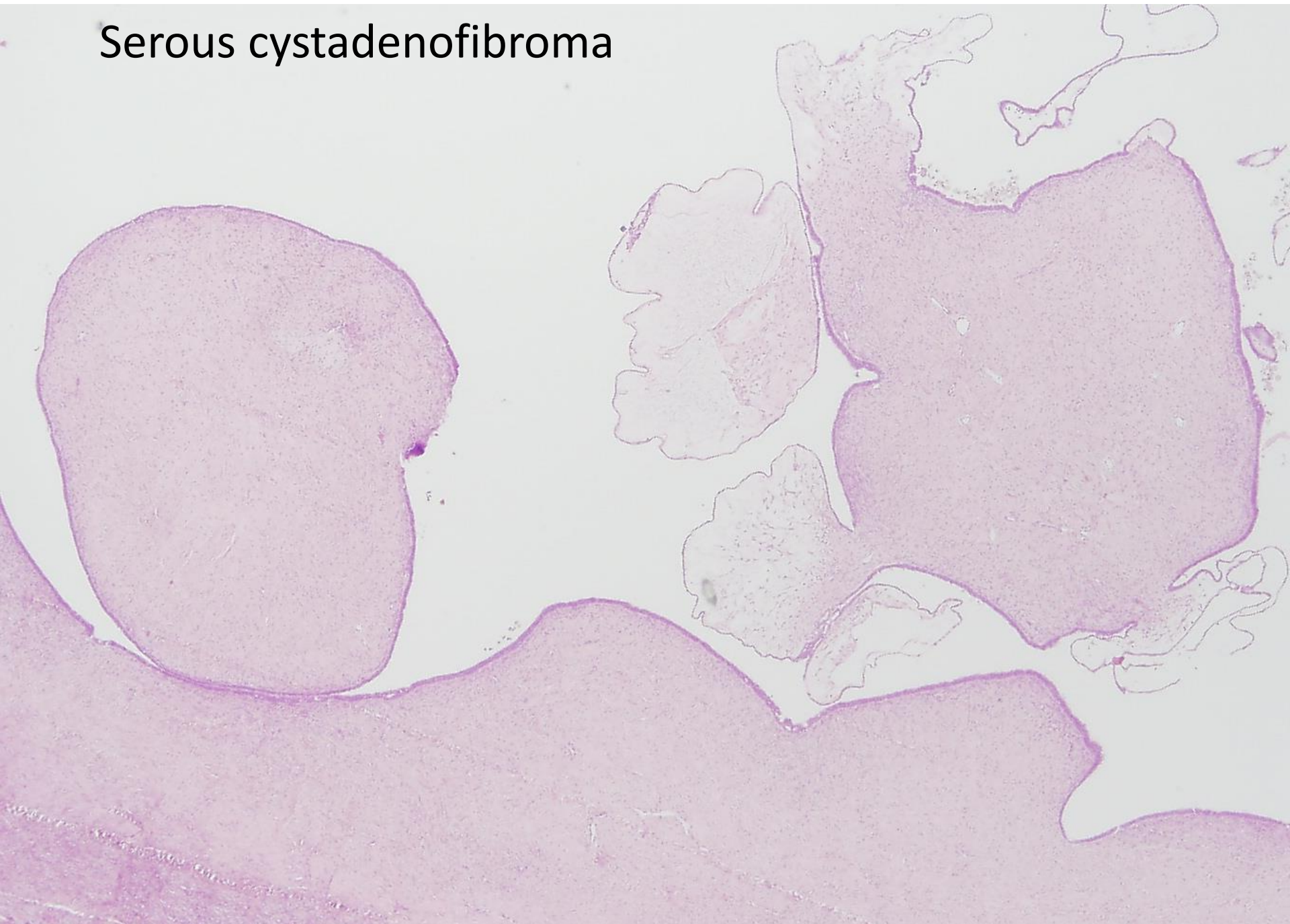


Mucinous cystadenoma



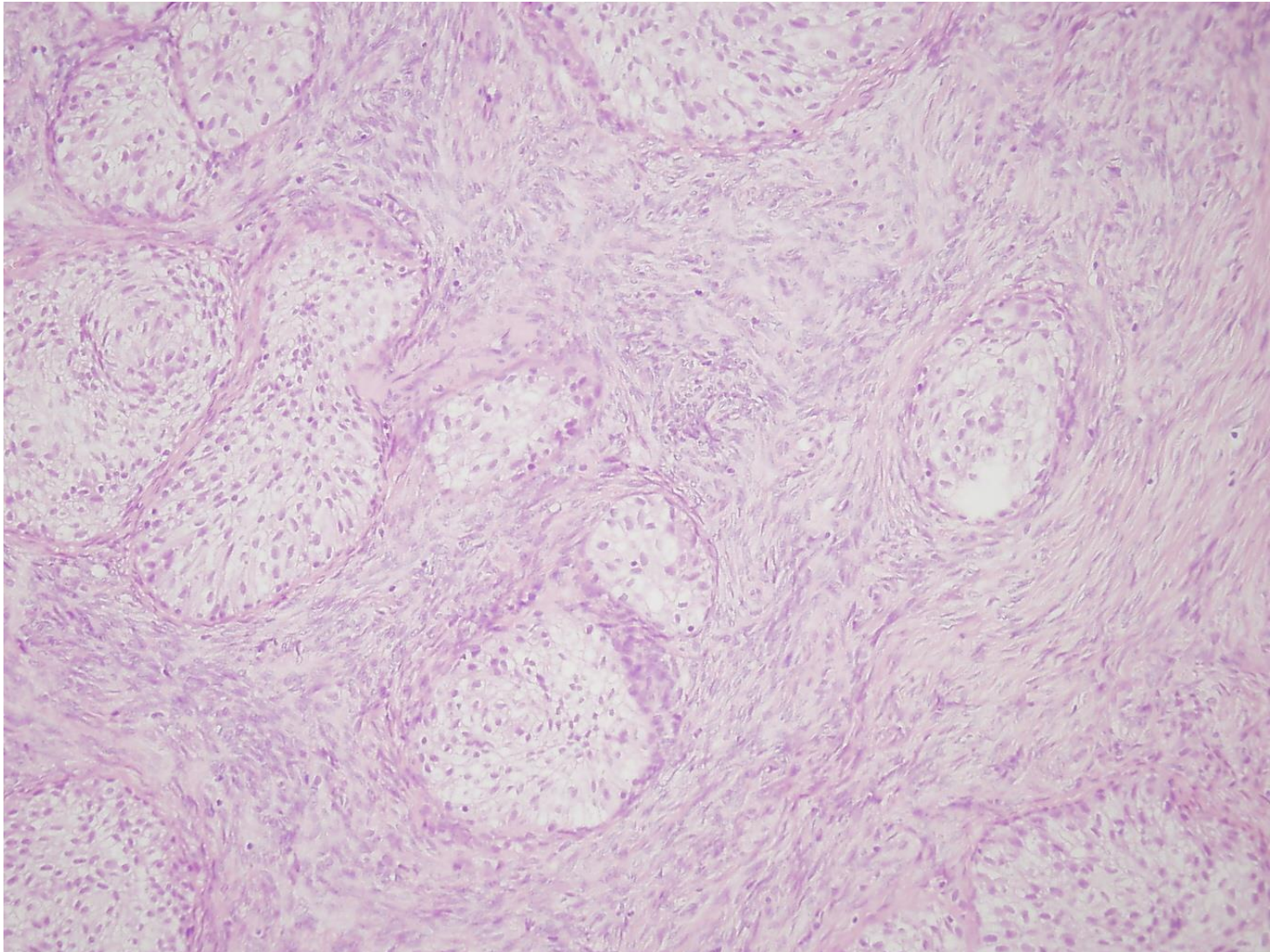


# Serous cystadenofibroma





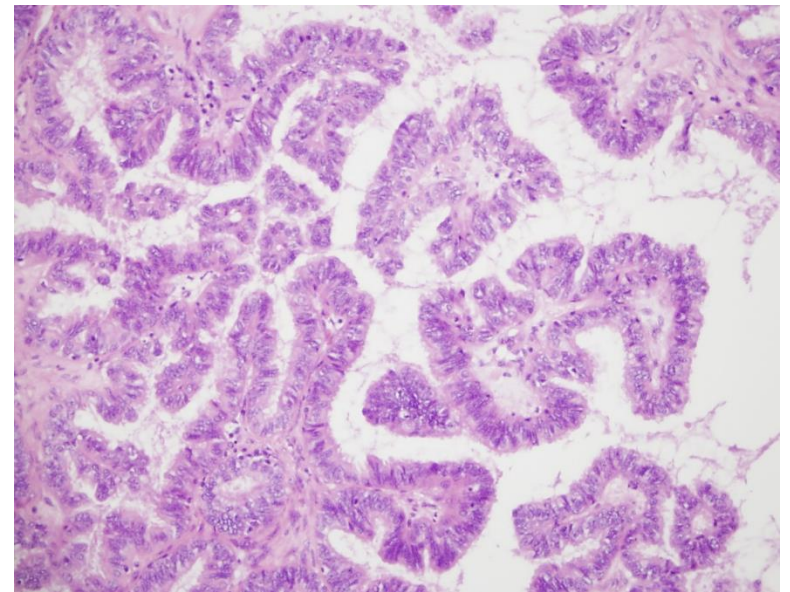
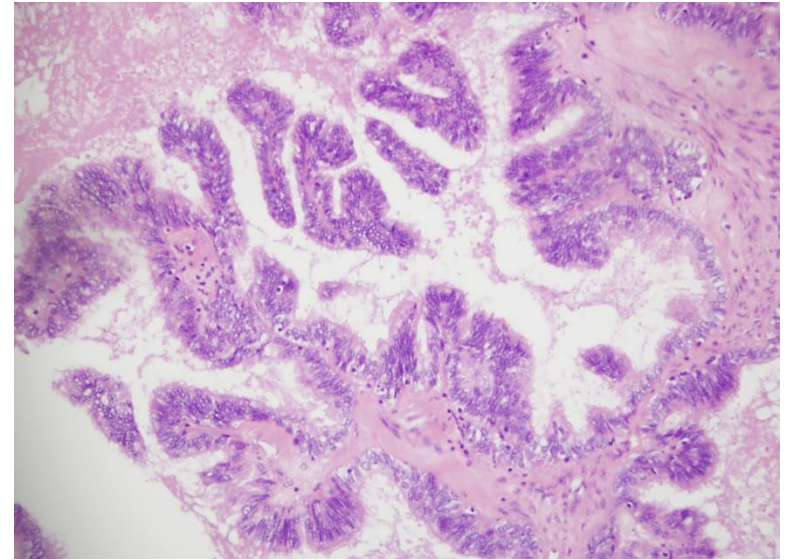
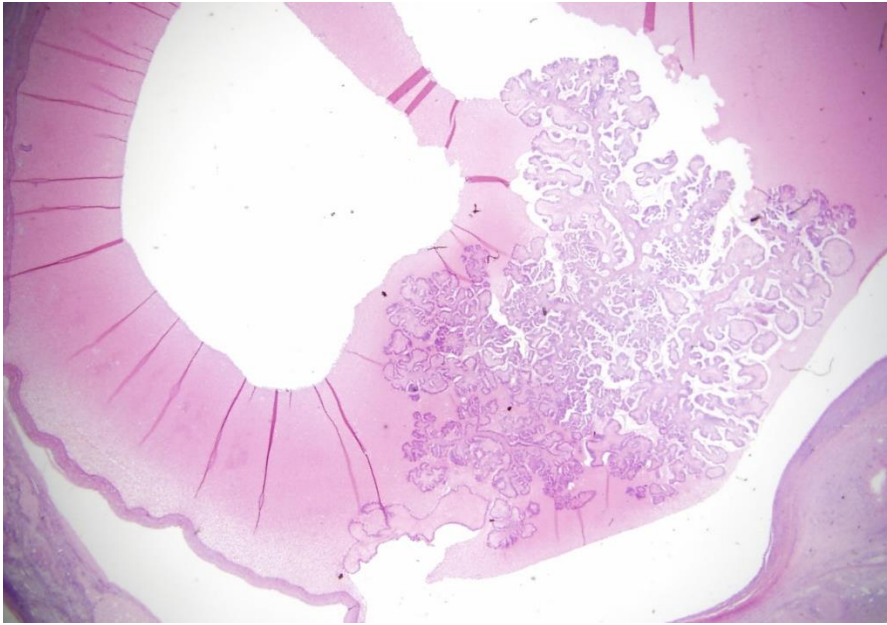
# Brenner tumor



Transitional cell nests in abundant stroma



# Serous *borderline* tumor



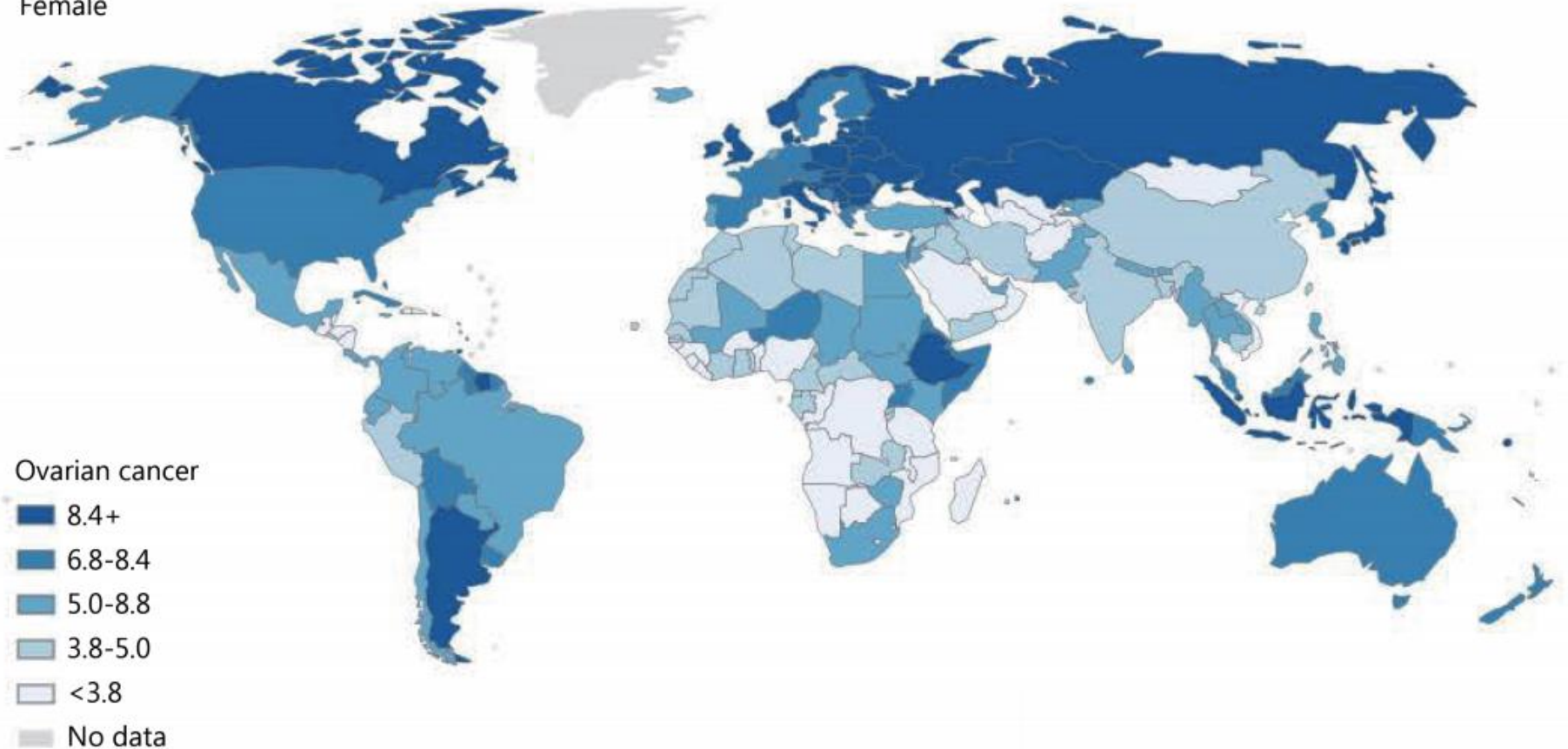
## **Borderline tumor:**

Histological and cytological features of malignancy (complex structure, atypia, mitoses) *BUT* NO INVASION

# Worldwide incidence of *ovarian carcinoma*

Cancer Biol Med Vol 14, No 1 February 2017

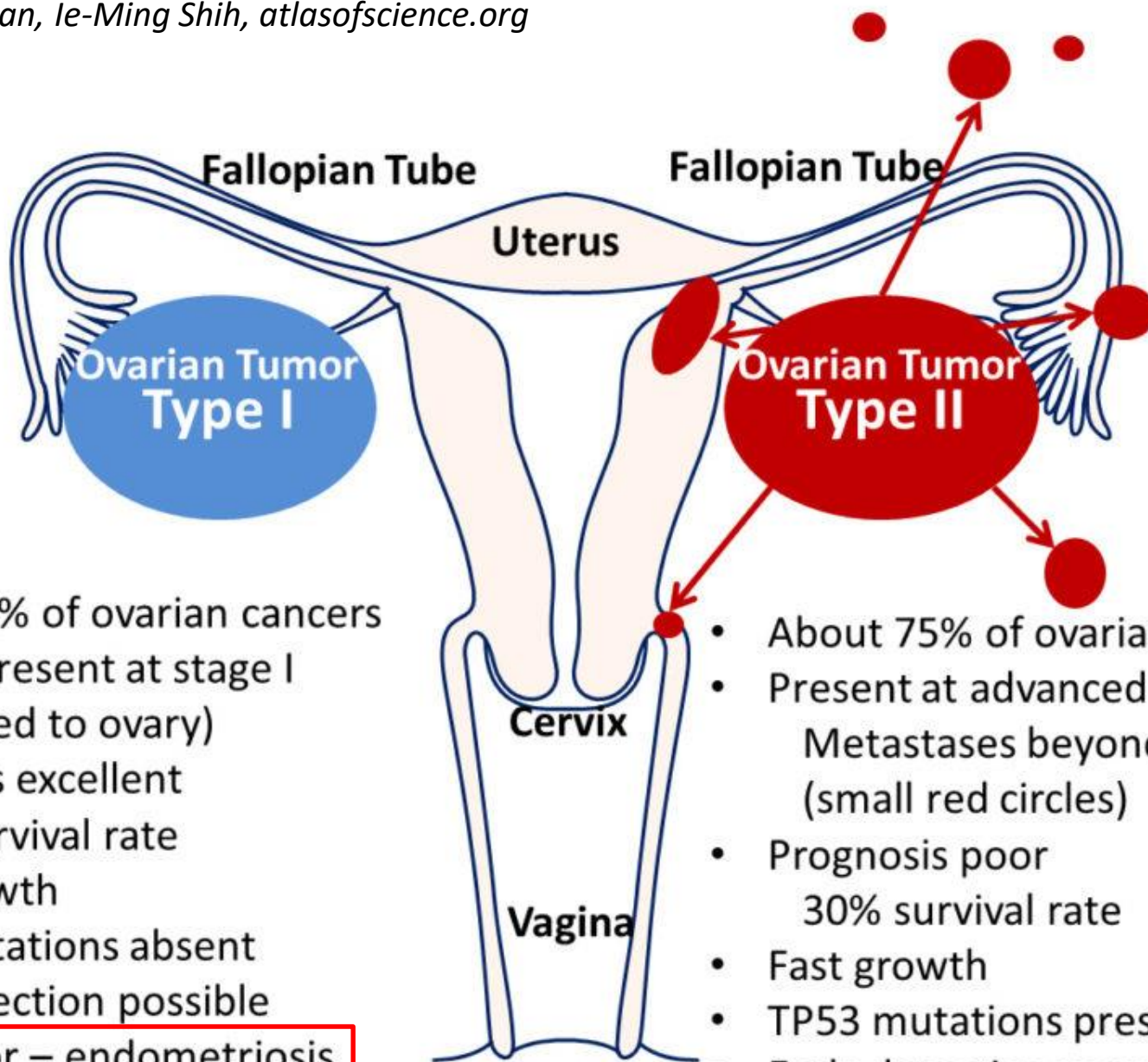
Incidence ASR  
Female



Source: GLOBOCAN 2012 (IARC)

**Figure 1** Ovarian cancer incidence exhibits wide geographic variation.

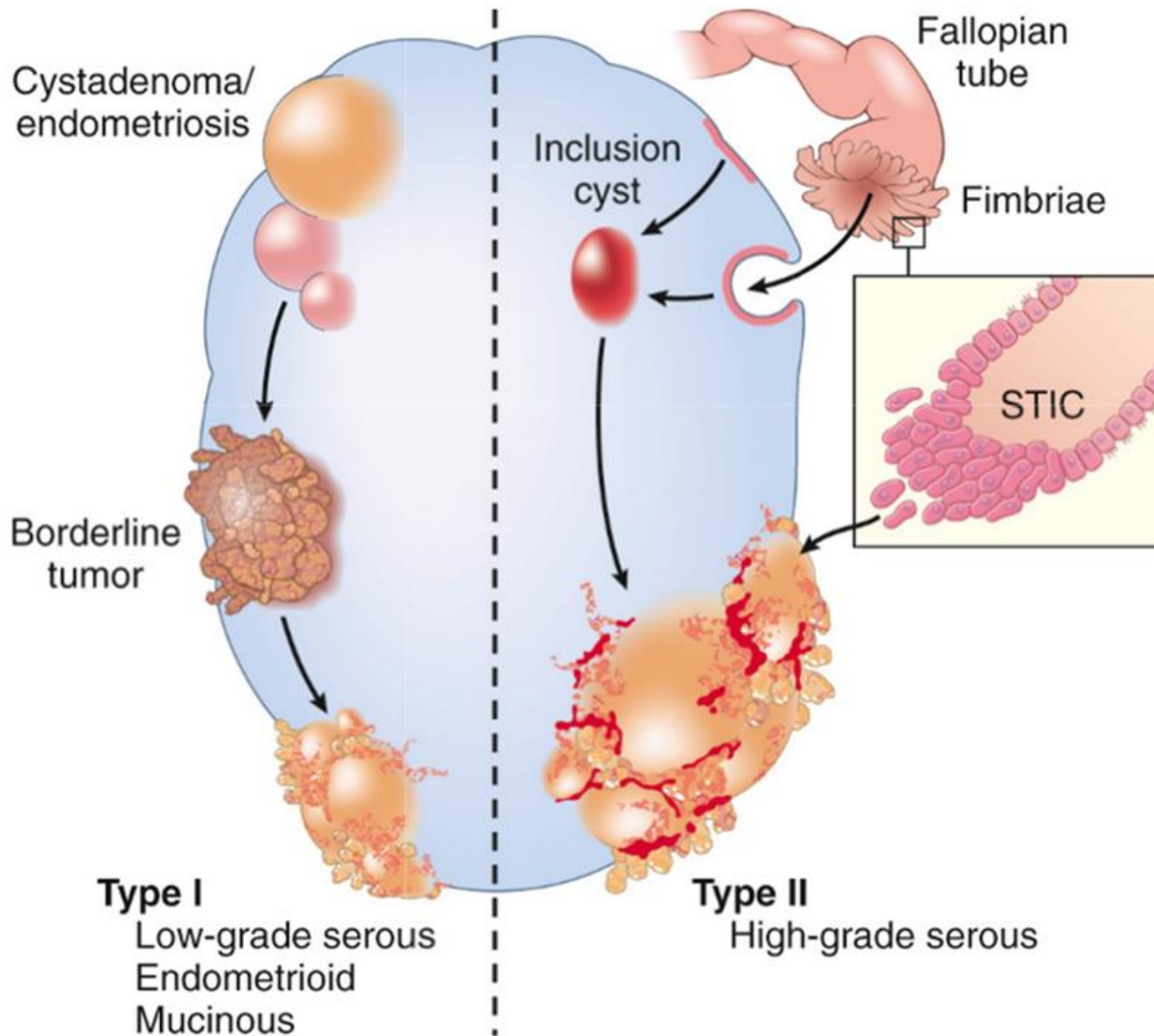




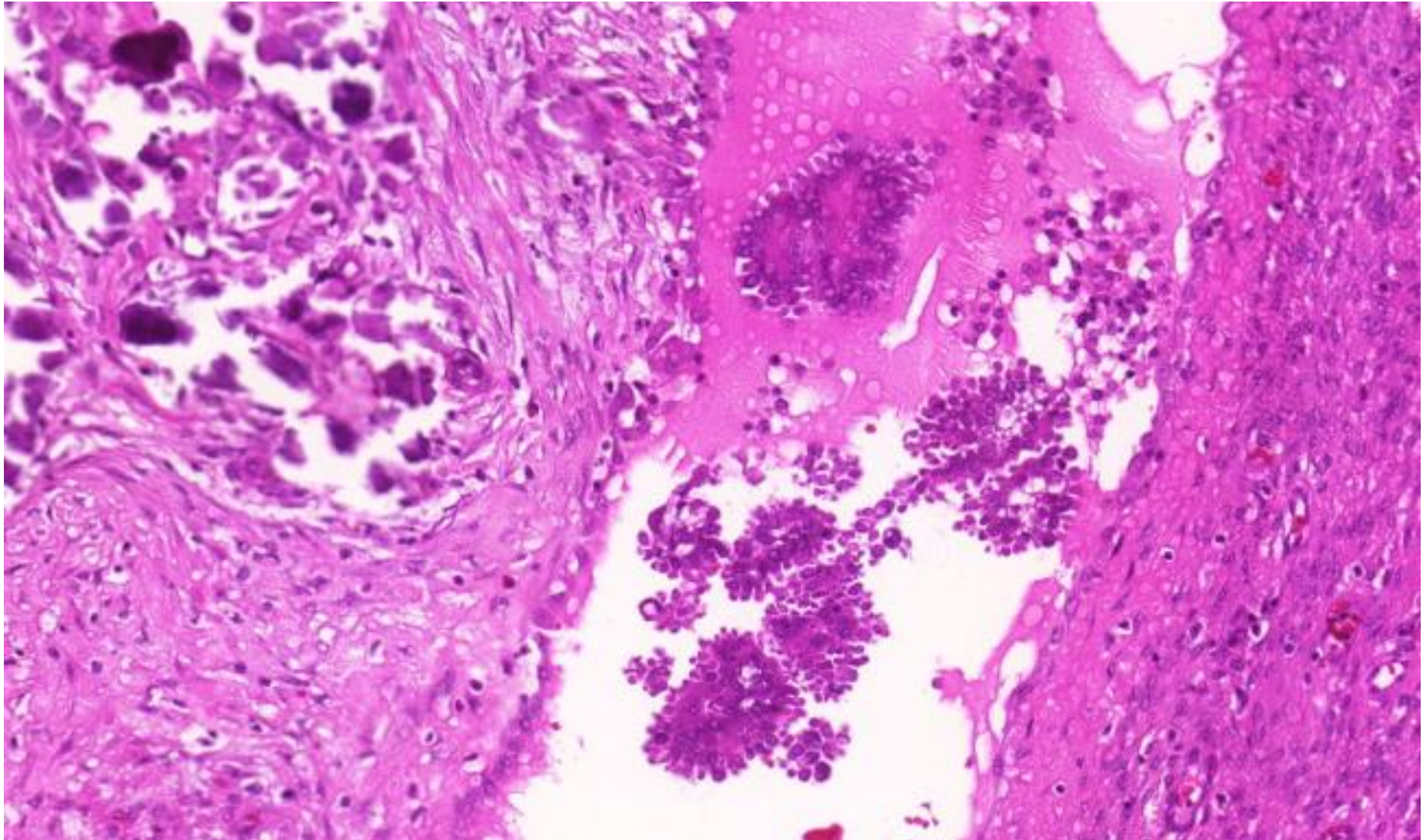
- About 25% of ovarian cancers
- Usually present at stage I (confined to ovary)
- Prognosis excellent  
90% survival rate
- Slow growth
- TP53 mutations absent
- Early detection possible
- Risk factor – endometriosis in some cases

- About 75% of ovarian cancers
- Present at advanced stage  
Metastases beyond ovary (small red circles)
- Prognosis poor  
30% survival rate
- Fast growth
- TP53 mutations present
- Early detection very difficult
- Risk factor – BRCA mutation in some cases (usually inherited)



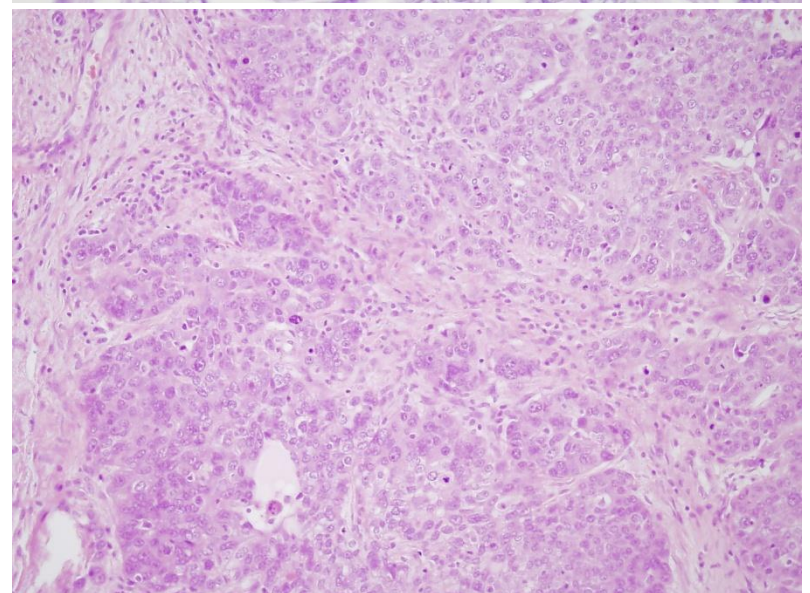
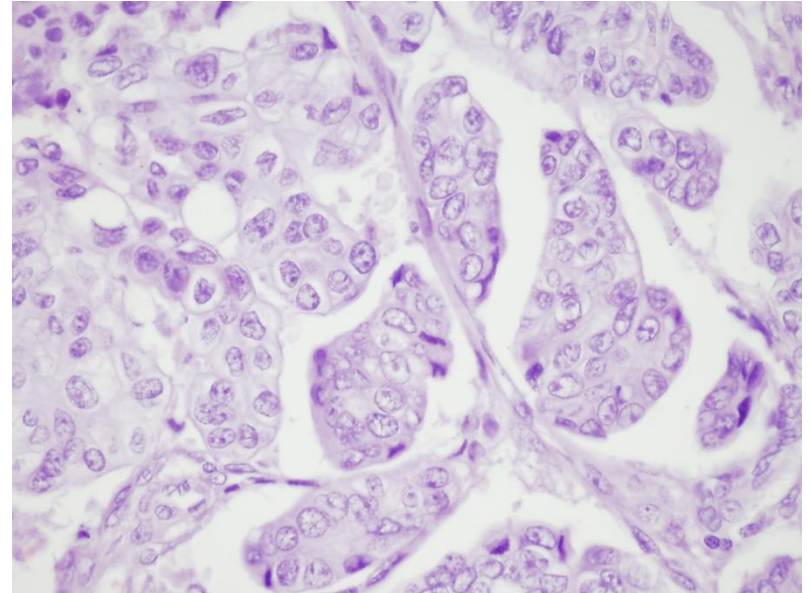


# Low grade serous carcinoma



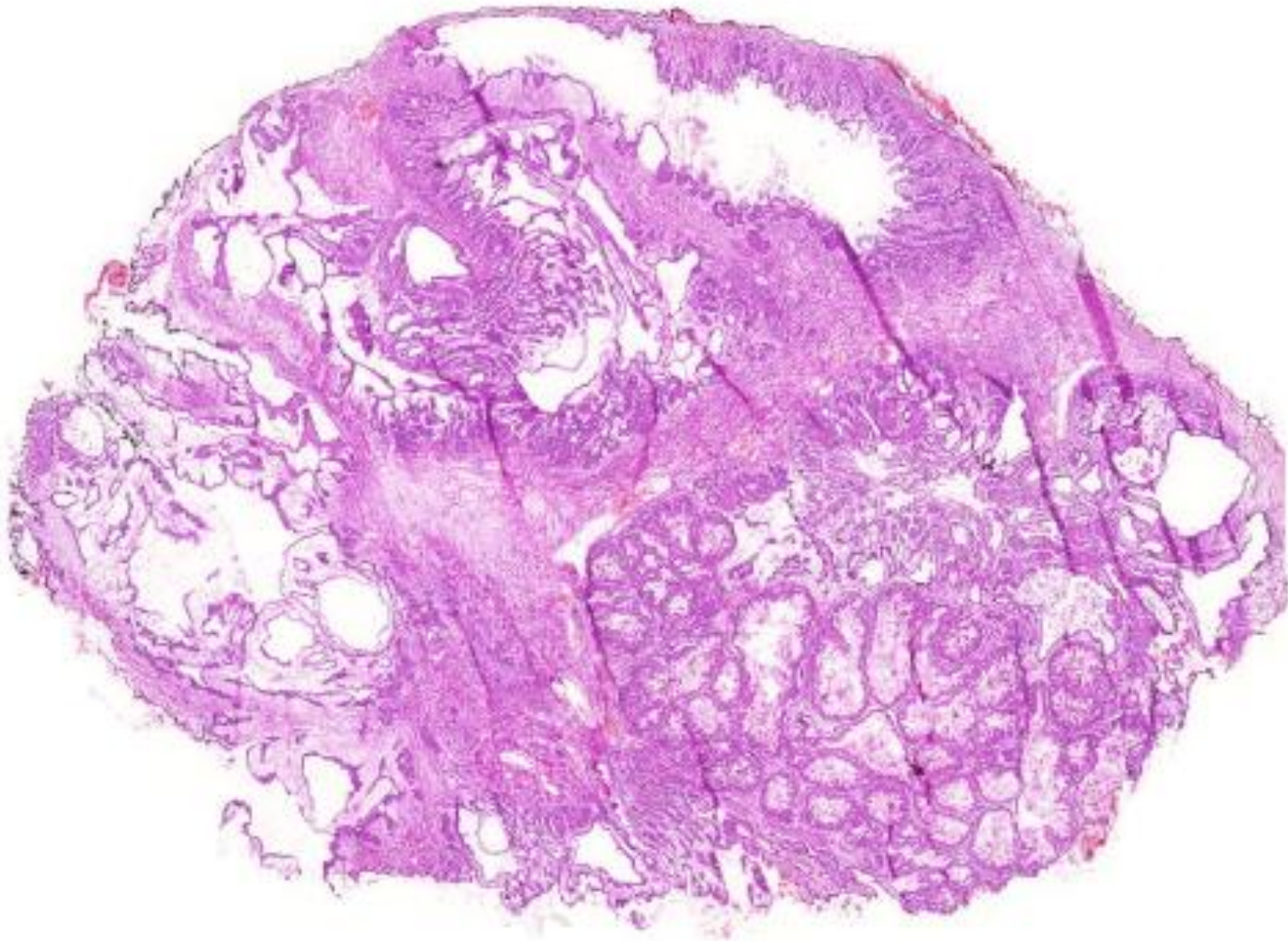


# High grade serous carcinoma





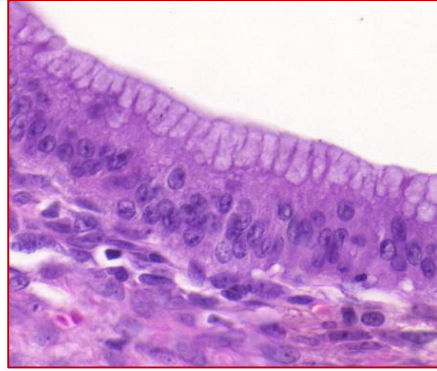
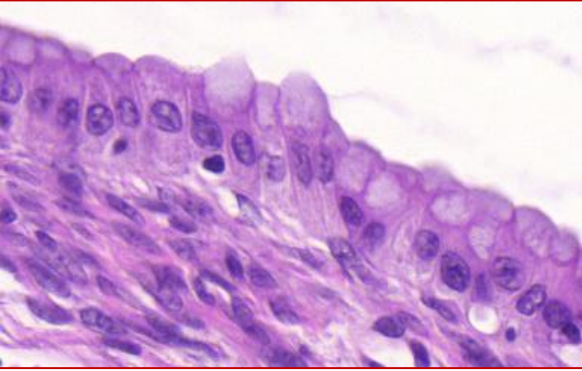
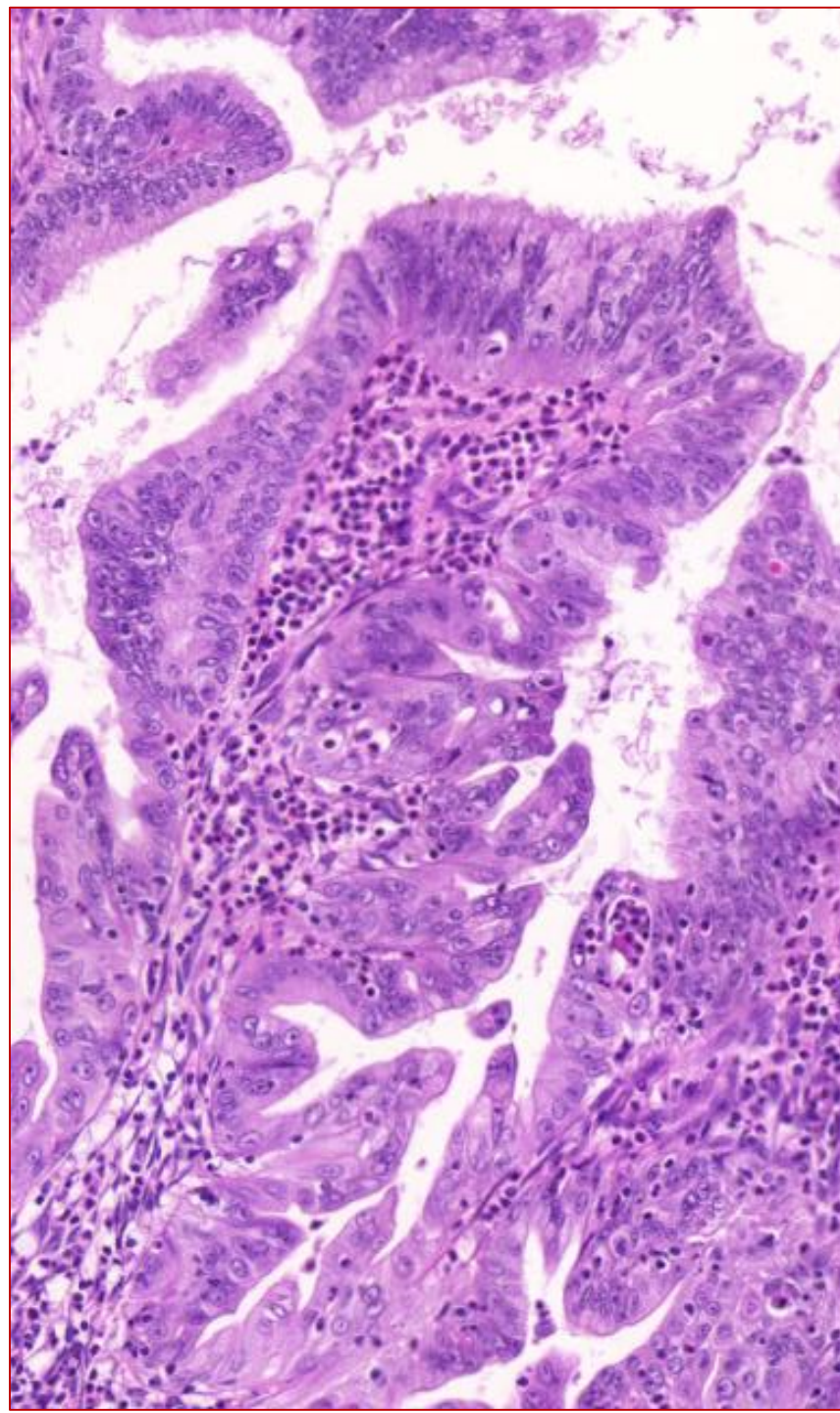
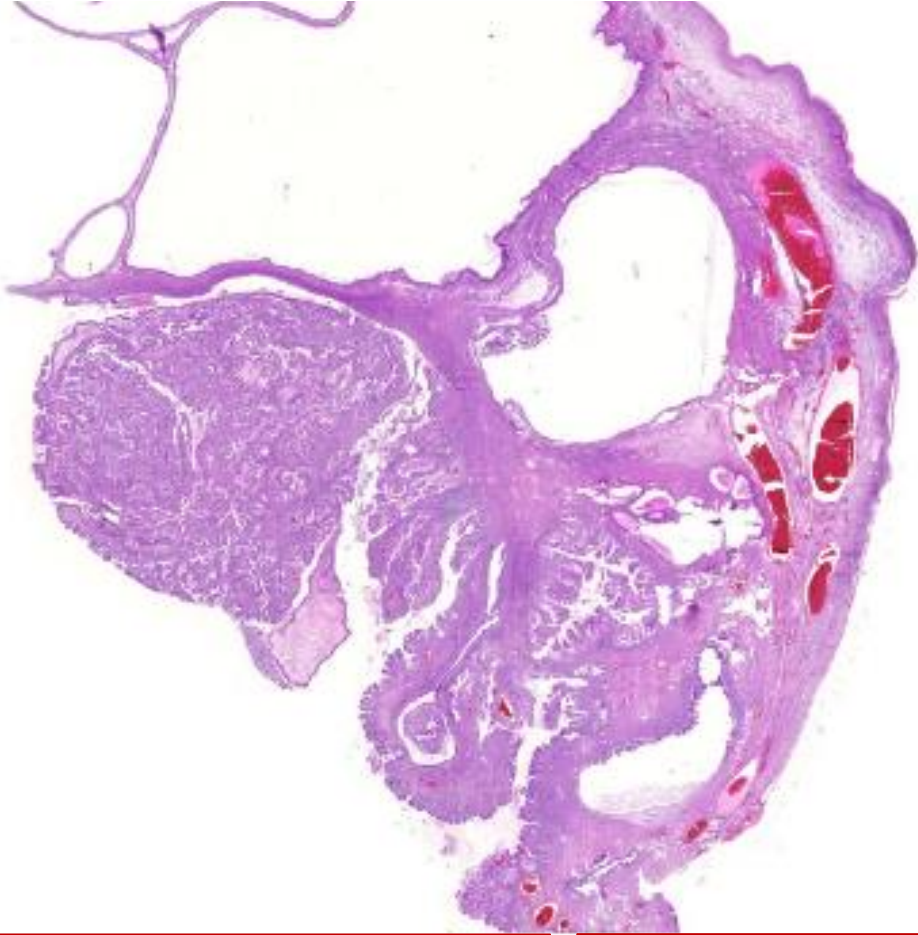
# Frozen section – ovarian cystic tumor



Differential diagnosis: Metastatic mucin-producing adenocarcinoma (e.g. colon adenocarcinoma)



# Mucinous cystadenocarcinoma



# Primary ovarian mucinous adenocarcinoma or metastasis in the ovary?

## Primary

- Unilateral
- Cystic (at least partially)
- Smooth surface
- No history of cancer
- Usually large (>13 cm)

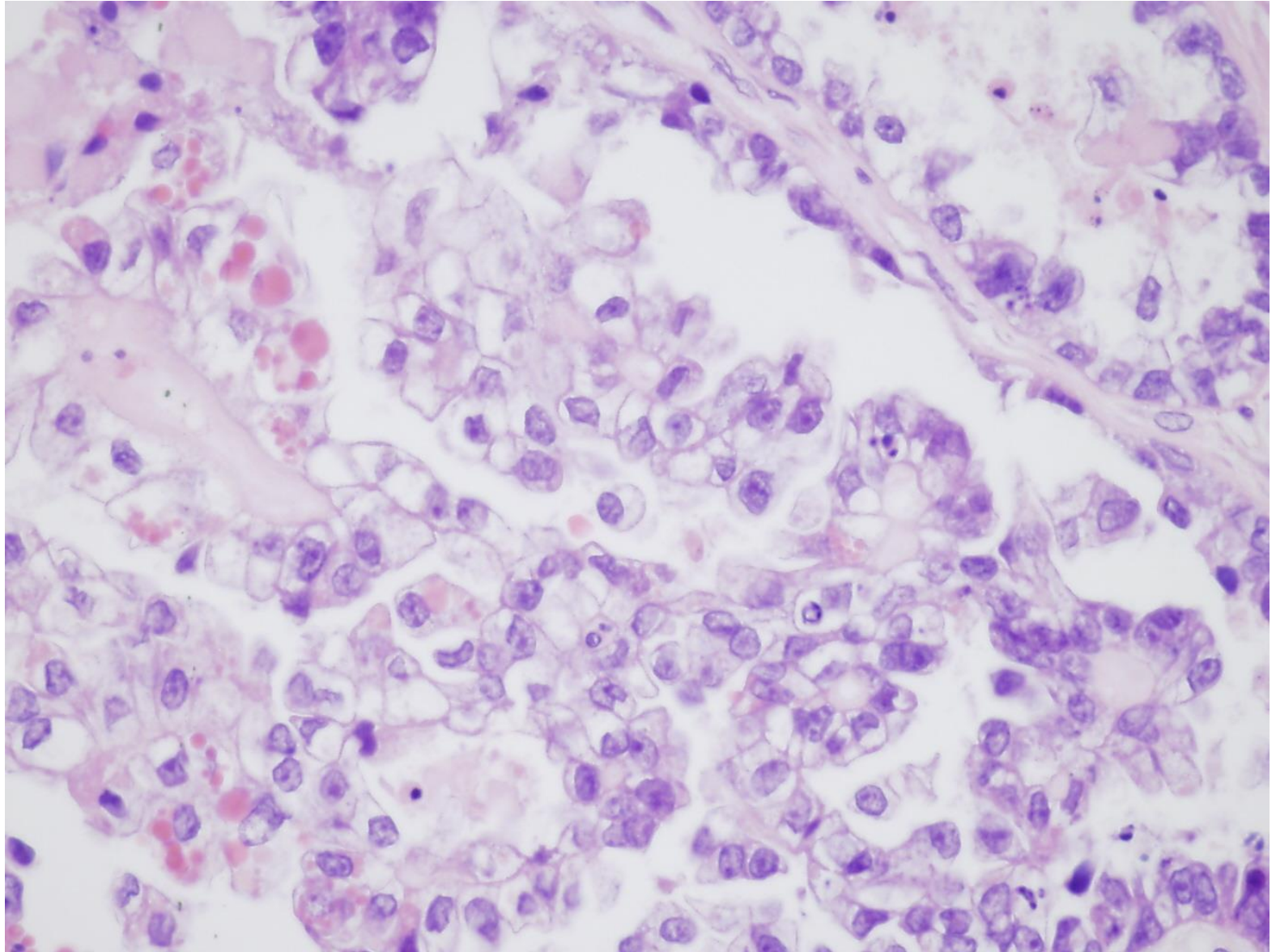
## Metastasis

- Bilateral
- Solid
- Nodular ar surface
- History of cancer
- Usually smaller (<13 cm)

Source of metastases: colon-, appendix-, pancreas-, bile ducts-, stomach-, small intestine-, lung, endocervix (mucinous) adenocarcinomas



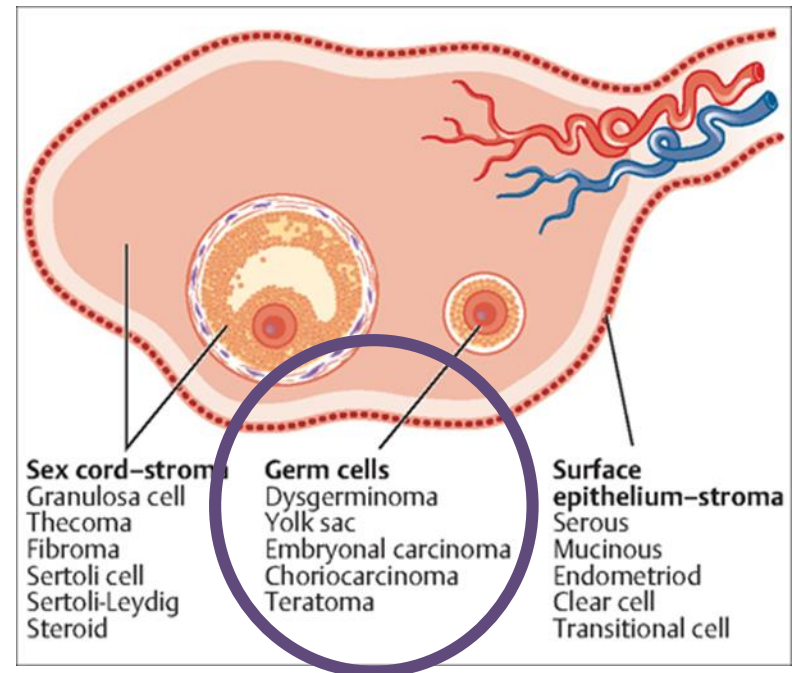
# Clear cell carcinoma



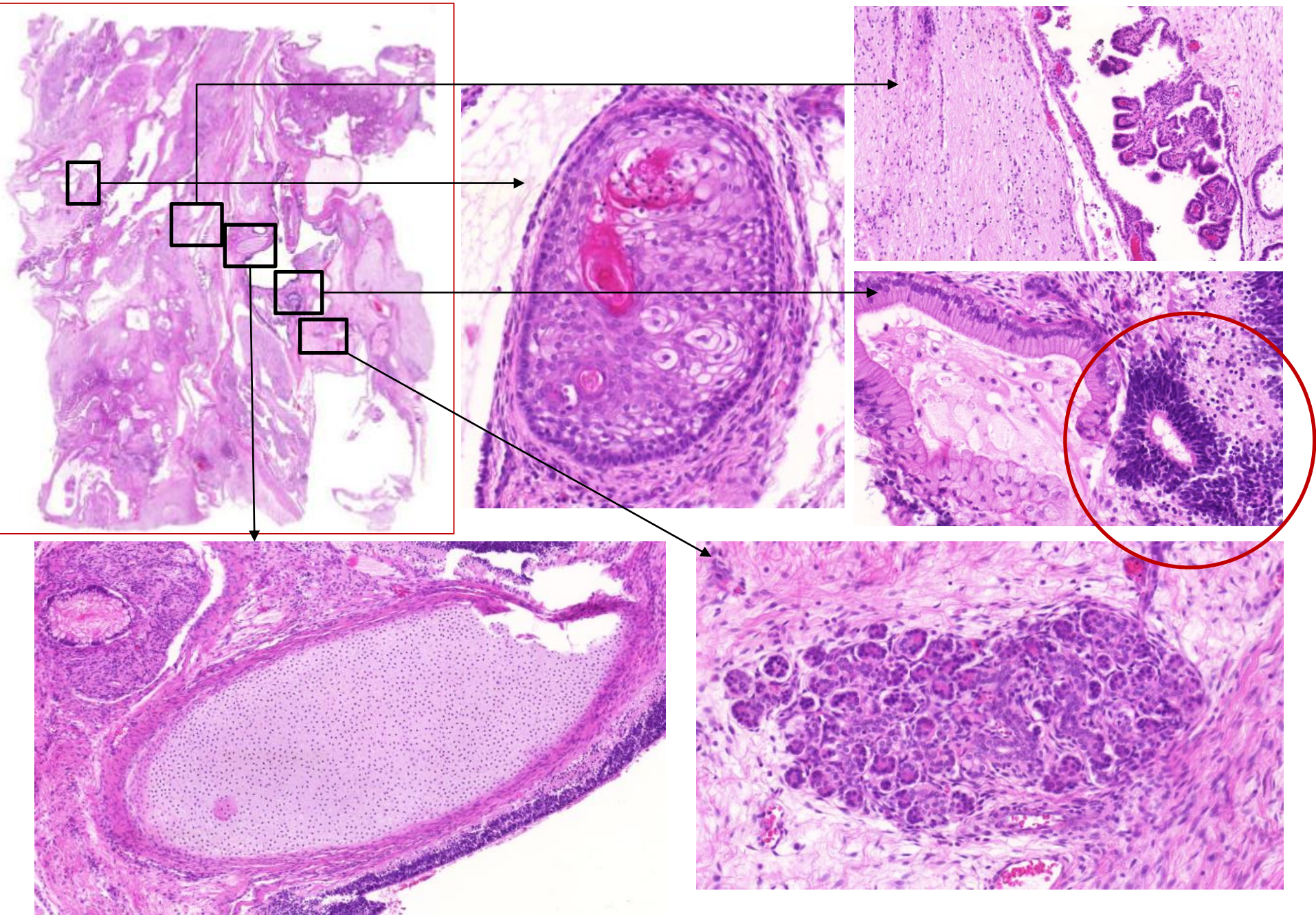
# GERM CELL TUMORS

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- Teratoma
  - *Mature*: most common DERMOID CYST
  - *Immature*: grade is defined according to the proportion of immature neuroepithelial tissue
  - *Monodermal*
- Dysgerminoma
- Embryonal carcinoma
- Yolk sac tumor
- Choriocarcinoma







**Immature teratoma**

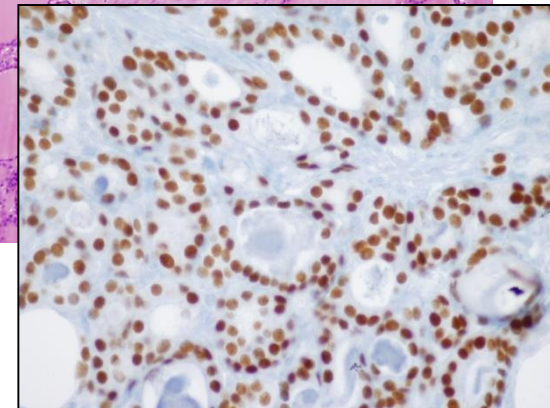
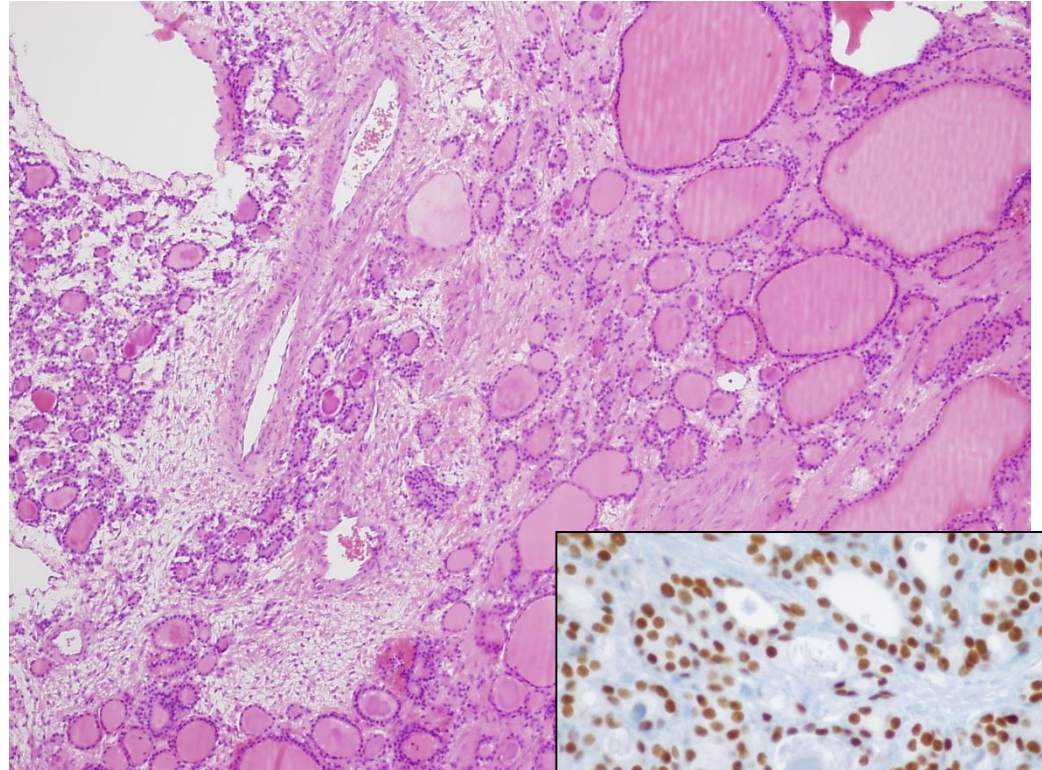
**Table 1.2** Grading of ovarian immature teratomas using a three-tiered grading system compiled from {1382}

Grade	Histological criteria
Grade 1	Tumours with rare foci of immature neuroepithelial tissue that occupy < 1 low power field (40x) in any slide (low-grade).
Grade 2	Tumours with similar elements, occupying 1-3 low power fields (40x) in any slide (high-grade).
Grade 3	Tumours with large amount of immature neuroepithelial tissue occupying > 3 low power fields (40x) in any slide (high-grade).



- **Monodermal teratoma**

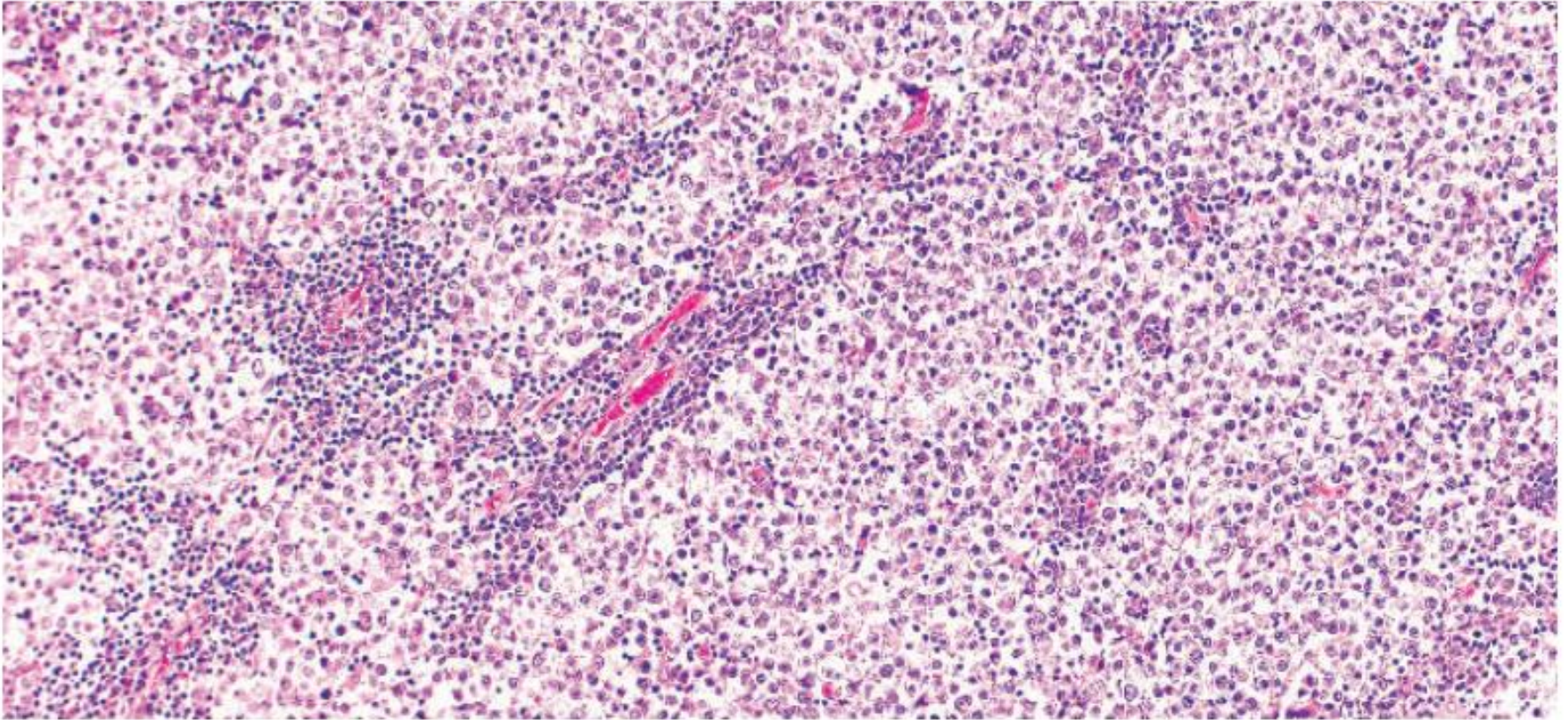
- Struma ovarii →
- Carcinoid ovarii



TTF-1 immunohistochemical reaction



# Dysgerminoma



**Fig. 1.53** Dysgerminoma. Nests and sheets of dysgerminoma cells are separated by fibrous septa containing lymphocytes  
World Health Organization Classification of Tumours, 2014

More common in Gonadal dysgenesis syndromes

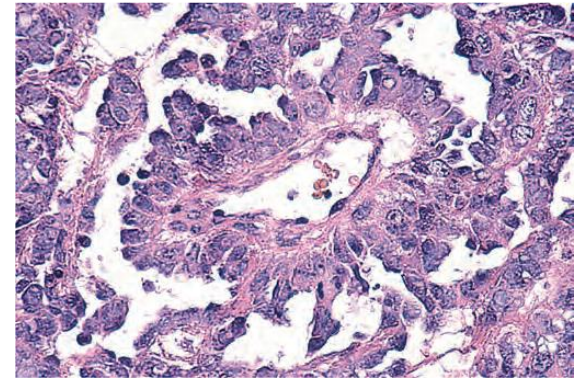
Mainly young adults

Unilateral, solid, malignant tumor. In early stage, almost 100% cure



- **Yolk sac tumor**

- Young girls
- Unilateral
- Alfa-foetoprotein (AFP)
- Histological hallmark: Schiller-Duval body



Robbins and Cotran, Pathologic Basis of Disease, 9. kiadás, Fig. 22-42

- **Non-gestational choriocarcinoma**

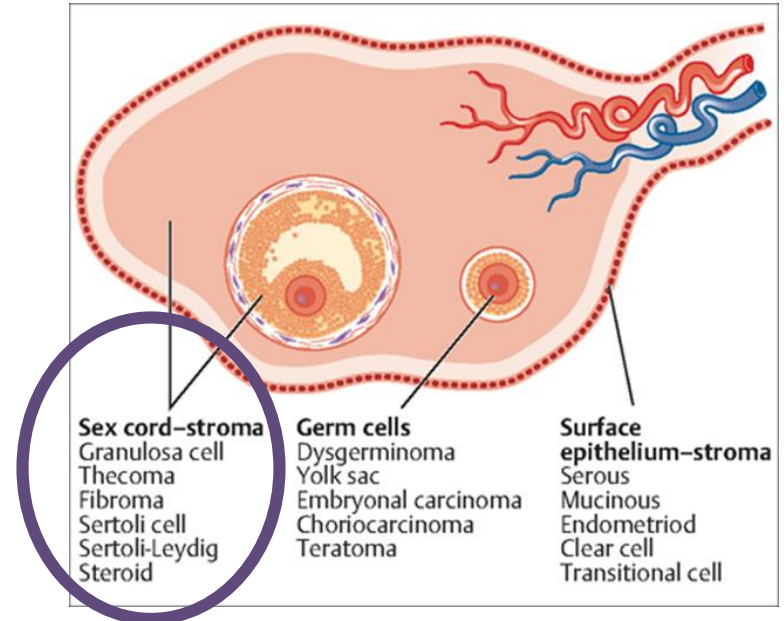
- Aggressive
- Widespread hematological metastases
- Human choriogonadotropin (HCG)
- Resistent to therapy

- **Others**

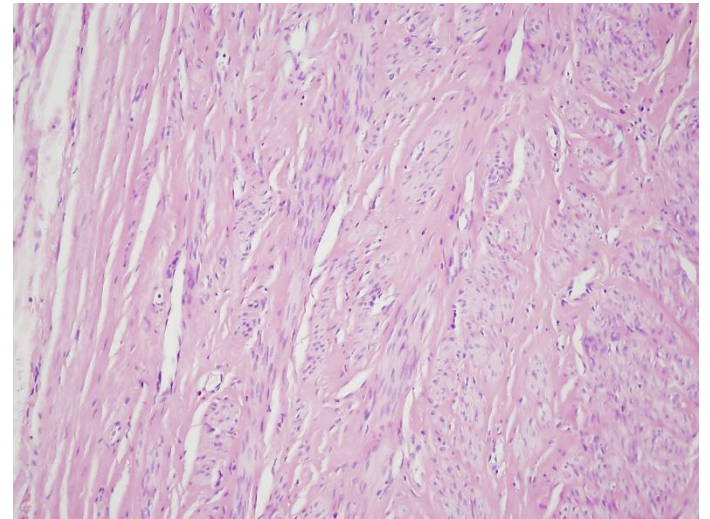
- Embryonal carcinoma
- Polyembrioma
- Mixed germ cell tumors

# SEX-CORD/STROMAL TUMORS

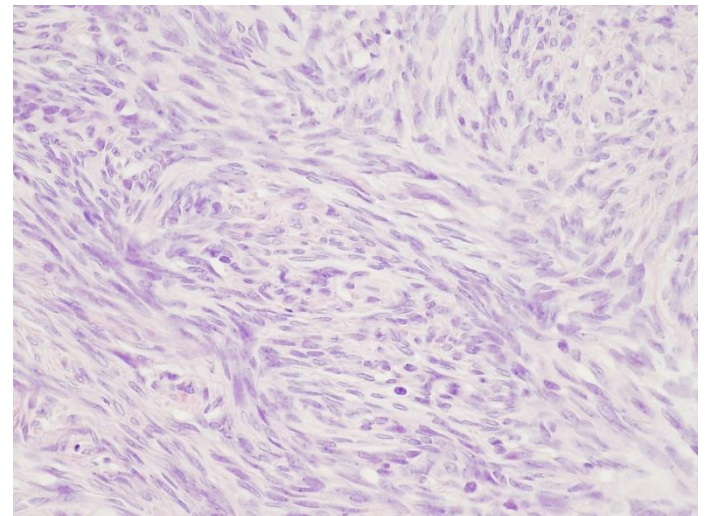
- Fibroma
- Thecoma
- Theco-fibroma
- Granulosa cell tumors
  - Juvenile granulosa cell tumors
- Sertoli cell tumors
- Leydig cell tumors



**Fibroma**



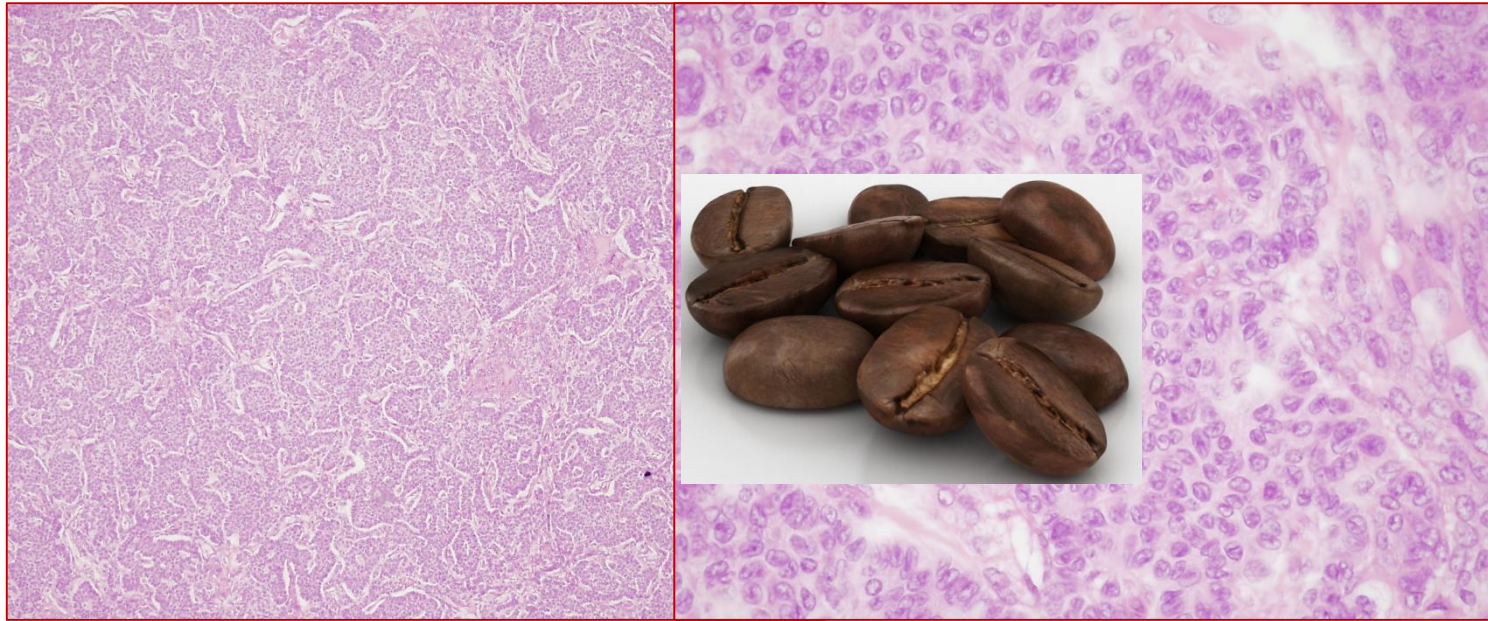
**Thecofibroma**



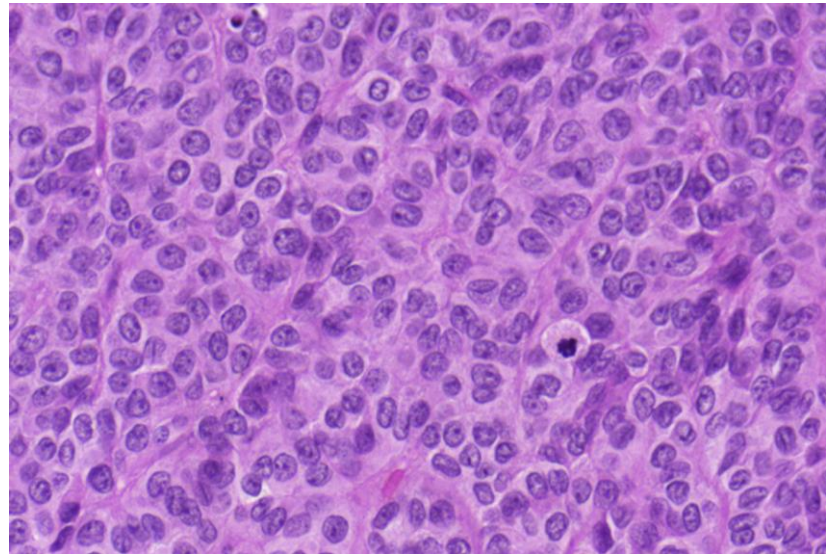
**Meigs syndrome: Associated hydrothorax**



**Granulosa cell  
tumor**

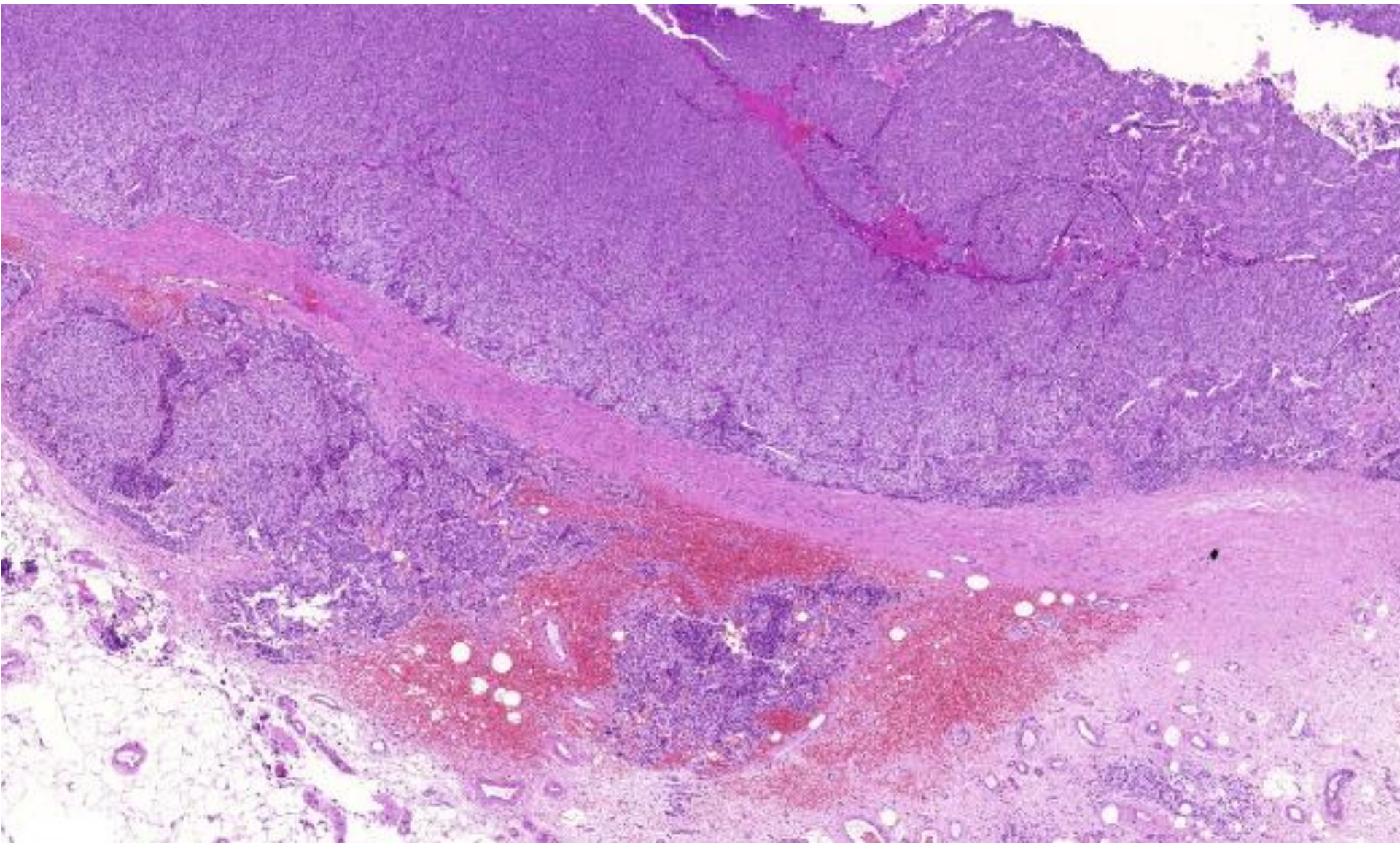


**Sertoli cell  
tumor**



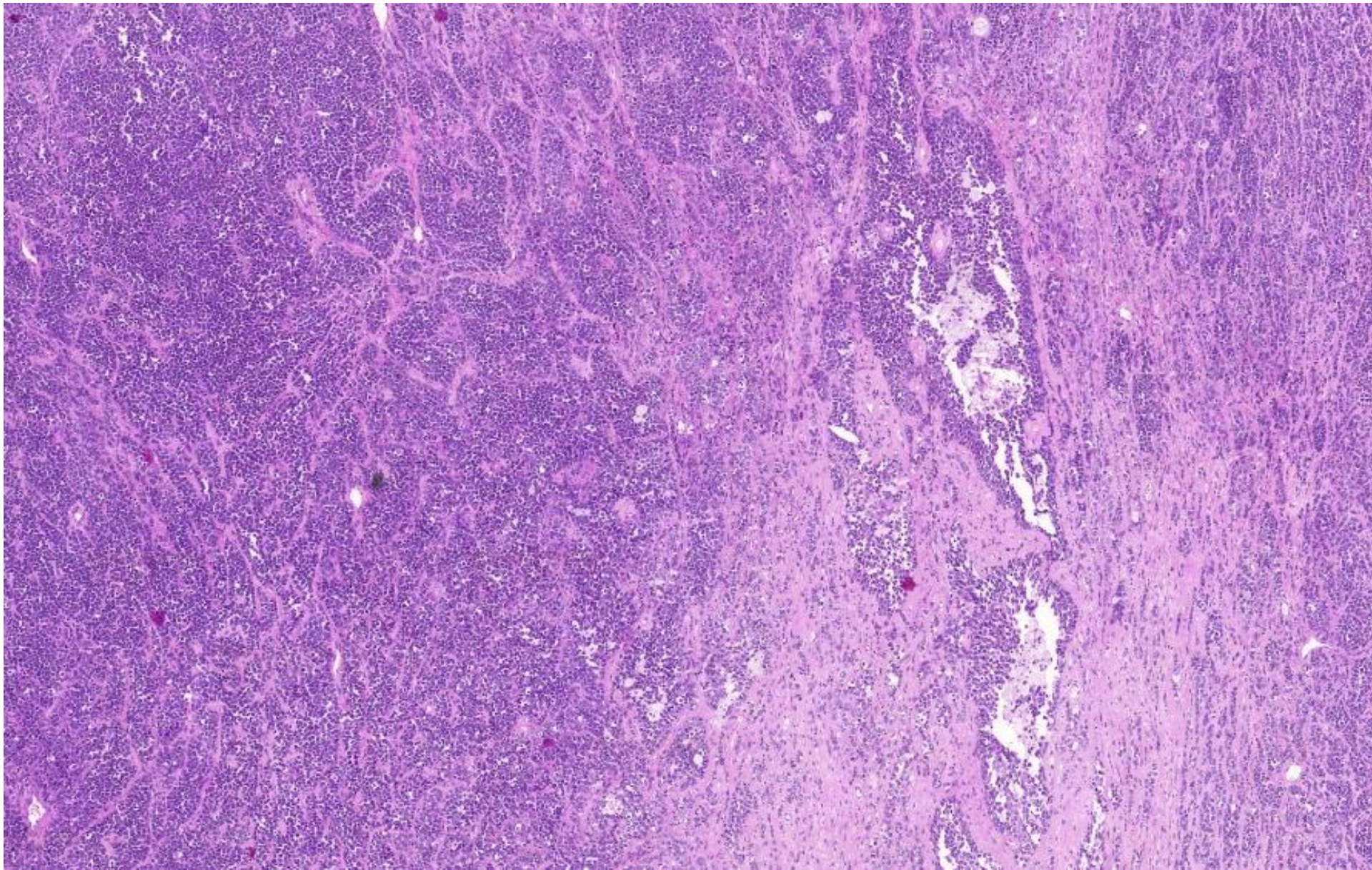


# Malignant Sertoli cell tumor



# **MISCELLANEOUS TUMORS**





Small cell hypercalcaemic tumor diagnosed in a pregnant young woman

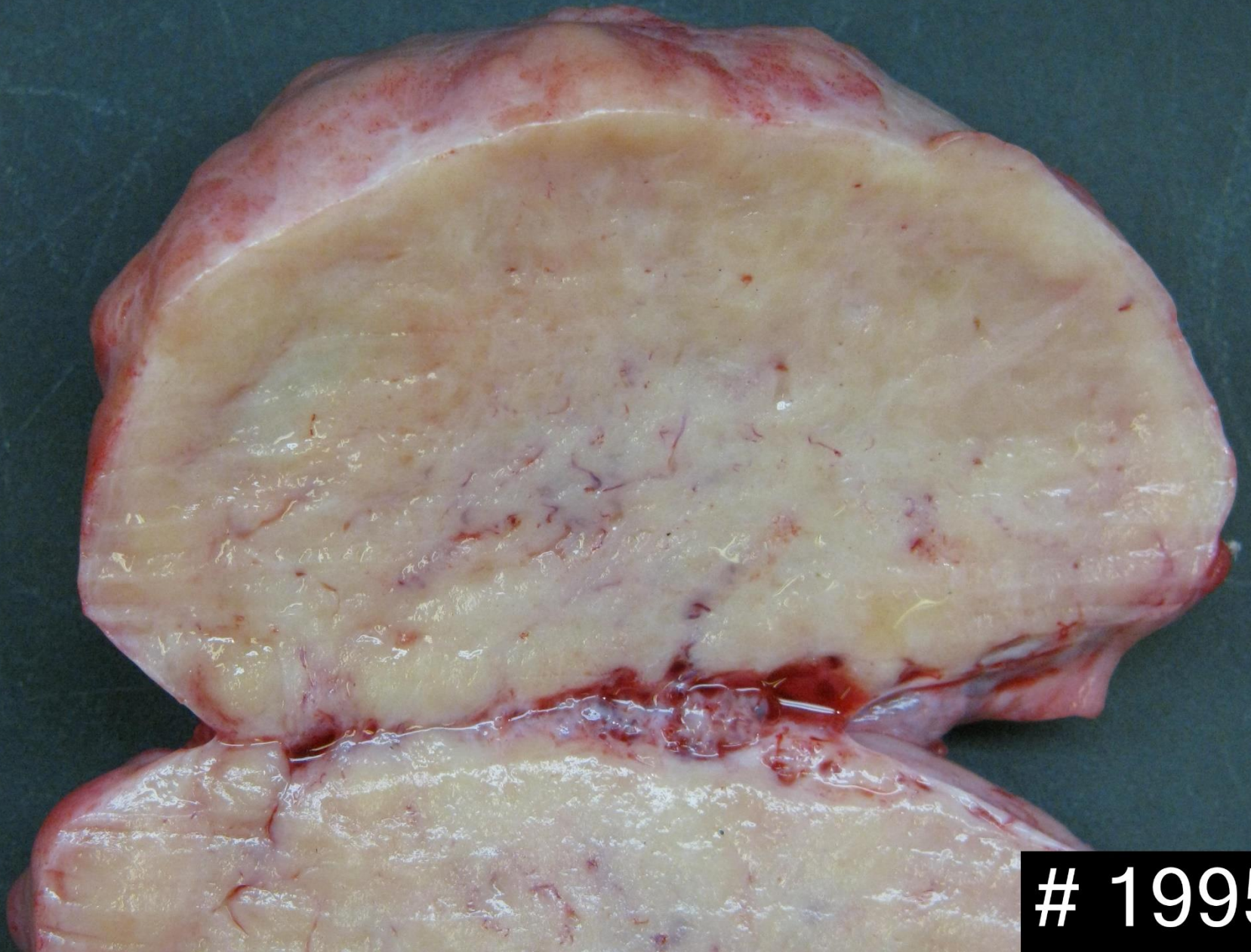


# METASTATIC TUMORS

5% of all malignant ovarian tumors  
>50% bilateral

Mostly from GI tract, breast, lung

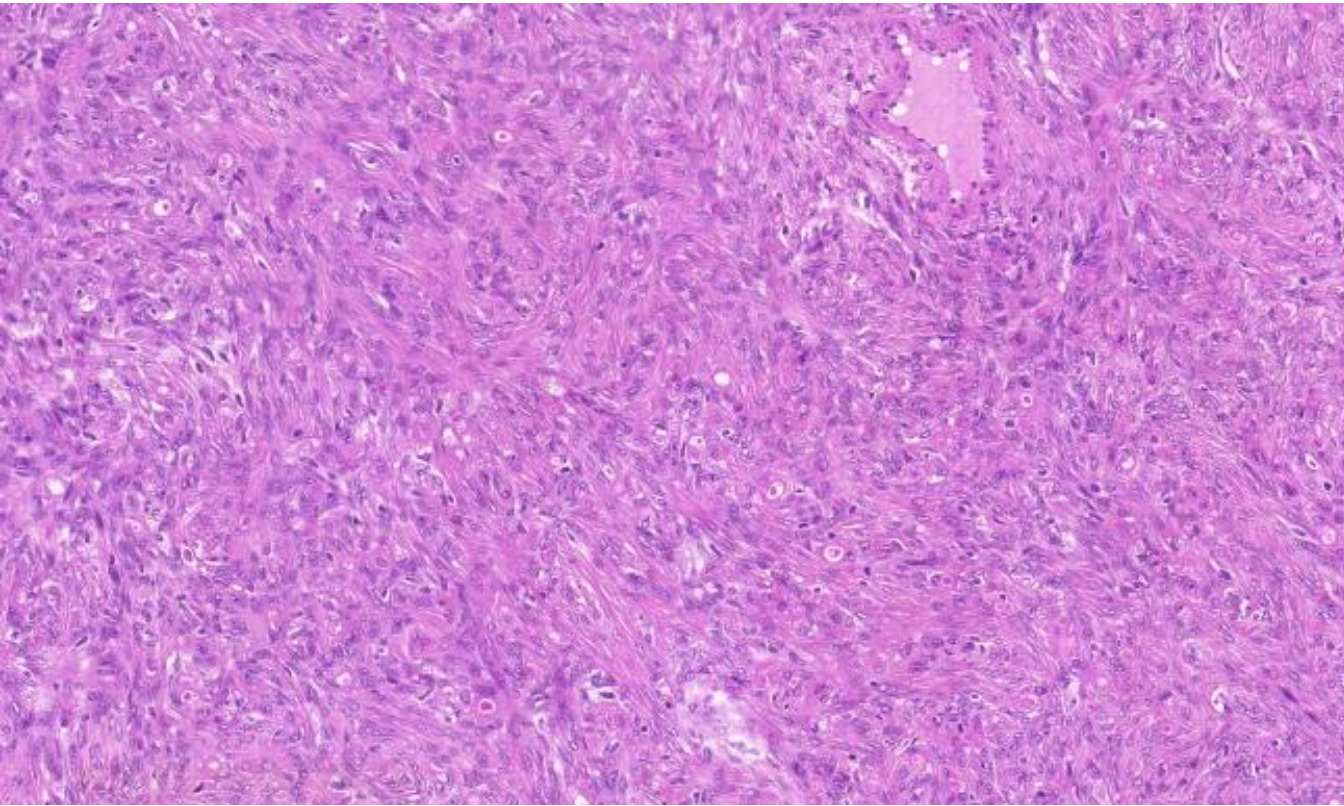
**Mucinous adenocarcinoma metastasis to the ovaries: *Krukenberg tumor***



# 1995



45 y, pelvic mass, clinically benign



# Metastatic spread of ovarian primary cancers

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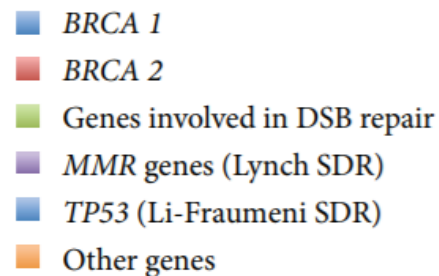
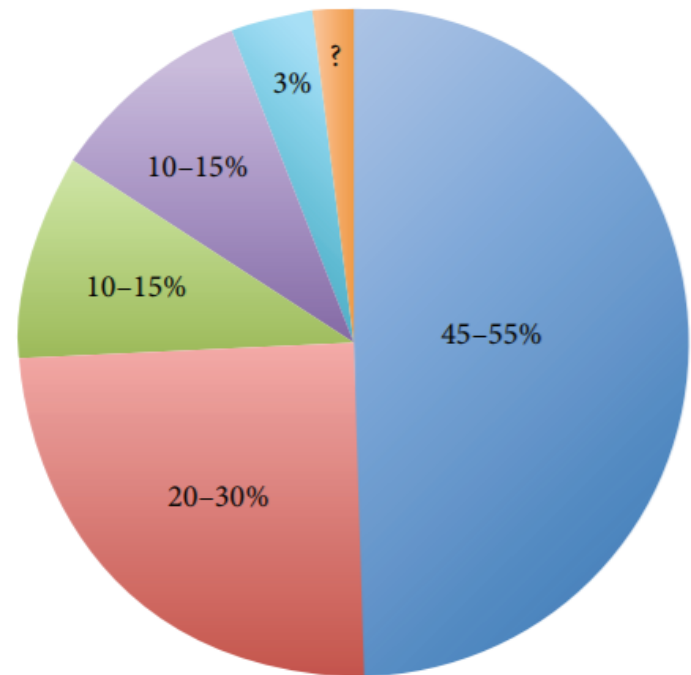
- Peritoneal surface
  - Ascites
  - Carcinosis peritonei
  - „Pseudomyxoma” peritonei
- Opposite ovary
- Distant lymph nodes
- Liver
- Spleen
- *Sister Mary Joseph nodule*



# Genetics and ovarian cancer

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- **Hereditary OC**  
syndromes/germline  
mutations





**Table 2. Genetic Syndromes with Increased Risk of Ovarian Cancer**

<i>Syndrome</i>	<i>Gene mutations</i>	<i>Features/epidemiology</i>	<i>Lifetime ovarian cancer risk</i>
Hereditary breast and ovarian cancer syndrome	<i>BRCA1</i> and <i>BRCA2</i> tumor suppressors, possibly others	10 times more common in Ashkenazi Jews; associated with breast, <u>ovarian, fallopian tube, peritoneal</u> , and pancreatic cancers	<i>BRCA1</i> : 25% to 65% <i>BRCA2</i> : 10% to 30%
Hereditary nonpolyposis colorectal cancer (Lynch syndrome)	<i>MLH1</i> , <i>MLH3</i> , <i>MSH2</i> , <i>MSH6</i> , <i>TGFBR2</i> , <i>PMS1</i> , and <i>PMS2</i>	Increased risk of colon cancer, as well as endometrial and <u>ovarian cancers</u>	10%
<i>MUTYH</i> -associated polyposis	<i>MUTYH</i>	Polyps in the colon and small intestine; increased risk of colon and other cancers, including <u>ovarian</u> and bladder cancers	No good data available
Peutz-Jeghers syndrome	<i>STK11</i>	Polyps in the stomach and intestine in teenagers; increased risk of esophageal, stomach, small intestine, and colon cancers, as well as <u>epithelial ovarian cancer and stromal tumors</u> (sex cord tumor with annular tubules)	No good data available
<i>PTEN</i> hamartoma tumor syndrome	<i>PTEN</i>	Increased risk of thyroid disorders and thyroid, breast, and <u>ovarian cancers</u>	No good data available

Information from references 10, 11, 13, and 14.

# Type I (low grade) ovarian cancers

**Table 1.** Type I ovarian cancers: Frequencies of selected potentially pathogenic genomic alterations.

Gene Alterations	Low-Grade Serous Cancer	Ovarian Clear Cell Carcinoma	Endometrioid	Mucinous
Mutations				
<i>BRAF</i>	33% <sup>a</sup> ; 38% <sup>b</sup> ; 16% <sup>c</sup>	0% <sup>e</sup> ; 1% <sup>f</sup>	24% <sup>a</sup>	0% <sup>k</sup> ; 23% <sup>l</sup> ; 5% <sup>m</sup> ;
<i>KRAS</i>	19% <sup>b</sup> ; 35% <sup>a</sup> ; 21% <sup>c</sup>	<1% <sup>a</sup> ; 7% <sup>f</sup>	<1% <sup>a</sup>	50% <sup>k</sup> ; 68% <sup>n</sup> ; 65% <sup>m</sup>
<i>PIK3CA</i>	11% <sup>b</sup>	25% <sup>e</sup> ; 33% <sup>f</sup>	12% <sup>e</sup>	14% <sup>m</sup>
<i>PTEN</i>	20% <sup>d</sup>	0% <sup>e</sup> ; 5% <sup>f</sup>	14% <sup>j</sup> ; 31% <sup>e</sup>	3% <sup>m</sup>
<i>ARID1A</i>	–	46% <sup>g</sup> ; 57% <sup>h</sup>	30% <sup>g</sup>	9% <sup>l</sup>
<i>CTNNB1</i>	–	0% <sup>e</sup> ; 3% <sup>f</sup>	23% <sup>e</sup> ; 24% <sup>j</sup>	5% <sup>m</sup>
<i>CDKN2A</i>	–	–	–	19% <sup>m</sup>
<i>TP53</i>	–	–	–	57% <sup>m</sup> ; 52% <sup>l</sup>
Copy number alterations				
<i>ERBB2</i> (HER2; gain)	–	14% <sup>i</sup>	–	12% <sup>m</sup> ; 19% <sup>o</sup>

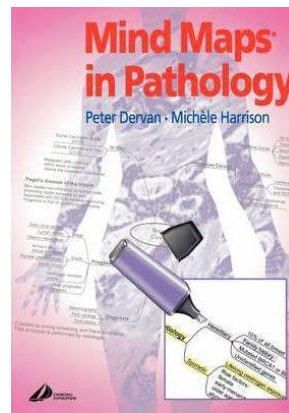
<sup>a</sup> Singer et al. [29]; <sup>b</sup> Jones et al. [20]; <sup>c</sup> Hunter et al. [32]; <sup>d</sup> Landen, et al. [23]; <sup>e</sup> Willner et al. [25]; <sup>f</sup> Kuo et al. [24]; <sup>g</sup> Wiegand et al. [27]; <sup>h</sup> Jones et al. [26]; <sup>i</sup> Tan et al. [22]; <sup>j</sup> Catasus et al. [34]; <sup>k</sup> Gemignani et al. [30]; <sup>l</sup> Ryland et al. [35]; <sup>m</sup> Mackenzie et al. [36]; <sup>n</sup> Cuatrecasa et al. [31]; and <sup>o</sup> Angelesio et al. [37]; HER2: human epidermal growth factor receptor 2; – Dashed lines indicate that data are unavailable or not included.

# Type II (high grade) ovarian cancers

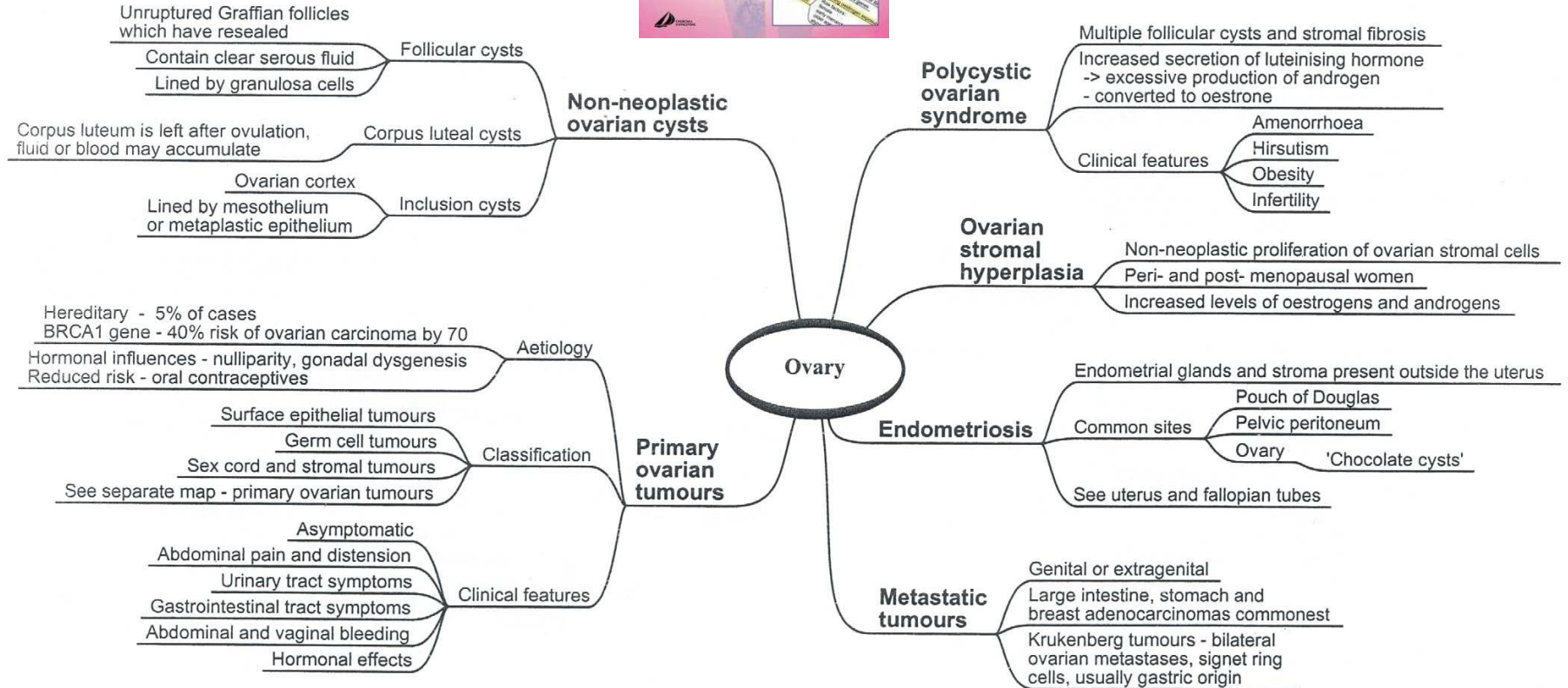
Gene	Frequency of Mutations	Frequency of Copy Number Alterations <sup>b</sup>
<i>TP53</i>	96%	0.9%
<i>BRCA1</i> <sup>c</sup>	12%	0.6%
<i>BRCA2</i>	11%	2%
<i>MYC</i>	0%	31%
<i>MECOM</i>	0.6%	22%
<i>CCNE1</i>	0%	20%
<i>PRKCI</i>	0.6%	19%
<i>EIF5A2</i>	0%	18%
<i>PIK3CA</i>	0.6%	17%
<i>NOTCH3</i>	0.9%	11%
<i>KRAS</i>	0.6%	11%
<i>RAB25</i>	0%	7%
<i>AKT2</i>	0%	6%
<i>AURKA</i>	0%	3%
<i>PIK3R1</i>	0.3%	2% <sup>d</sup>
<i>AKT1</i>	0%	3%
<i>ERBB2</i>	0.9%	2%
<i>KIT</i>	2%	1%
<i>FGF1</i>	0%	1%
<i>EGFR</i>	2%	0.4%
<i>BRAF</i>	0.6%	5%
<i>PTEN</i>	0.6%	6% <sup>d</sup>
<i>RB1</i>	2%	7% <sup>d</sup>
<i>NF1</i>	4%	6% <sup>d</sup>
<i>ETV4</i>	0%	0.5%
<i>FOXM1</i>	0%	5%
<i>LSR</i>	0%	8%
<i>CD9</i>	0.3%	6%
<i>RAB11FIP4</i>	0%	3% <sup>d</sup>
<i>FGFRL1</i>	0%	3%

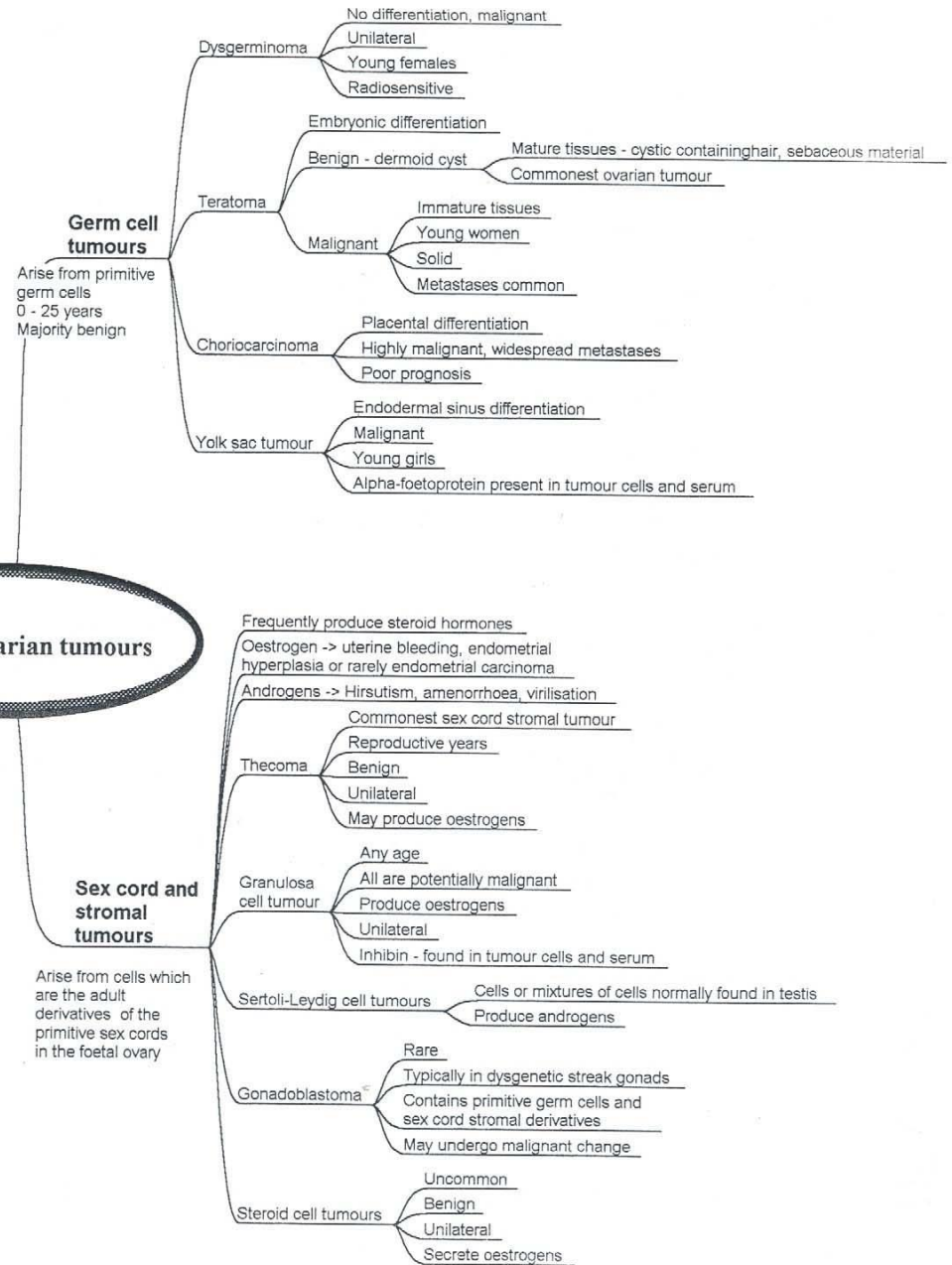
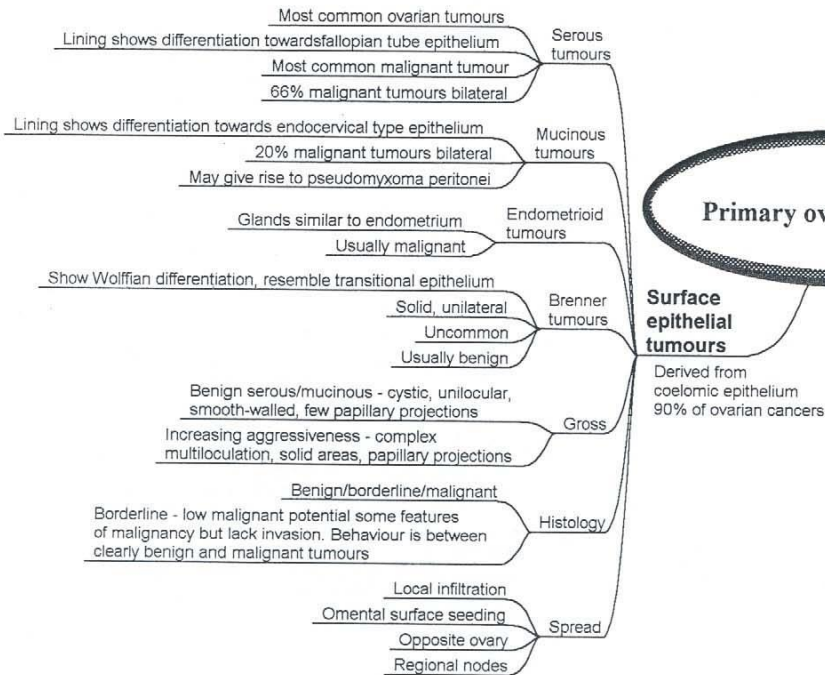
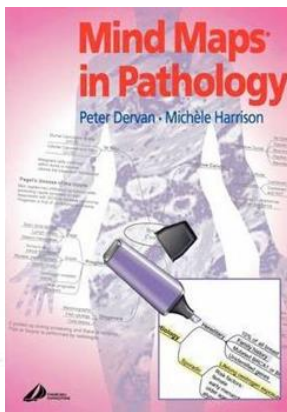
<sup>a</sup> The Cancer Genome Atlas Research Network [16]; <sup>b</sup> Other genes with copy number alterations exceeding a frequency of 15% include *NDRG1*, *EPPK1*, *PLEC*, *RECQL4*, *PTK2*, *EXT1*, and *RAD21*; <sup>c</sup> Promoter hypermethylation is also present in 12% of *BRCA1*; and <sup>d</sup> Represented by all or mostly all copy number deletions.





## SYSTEMATIC PATHOLOGY





#1

DEADLIEST GYNECOLOGIC CANCER



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