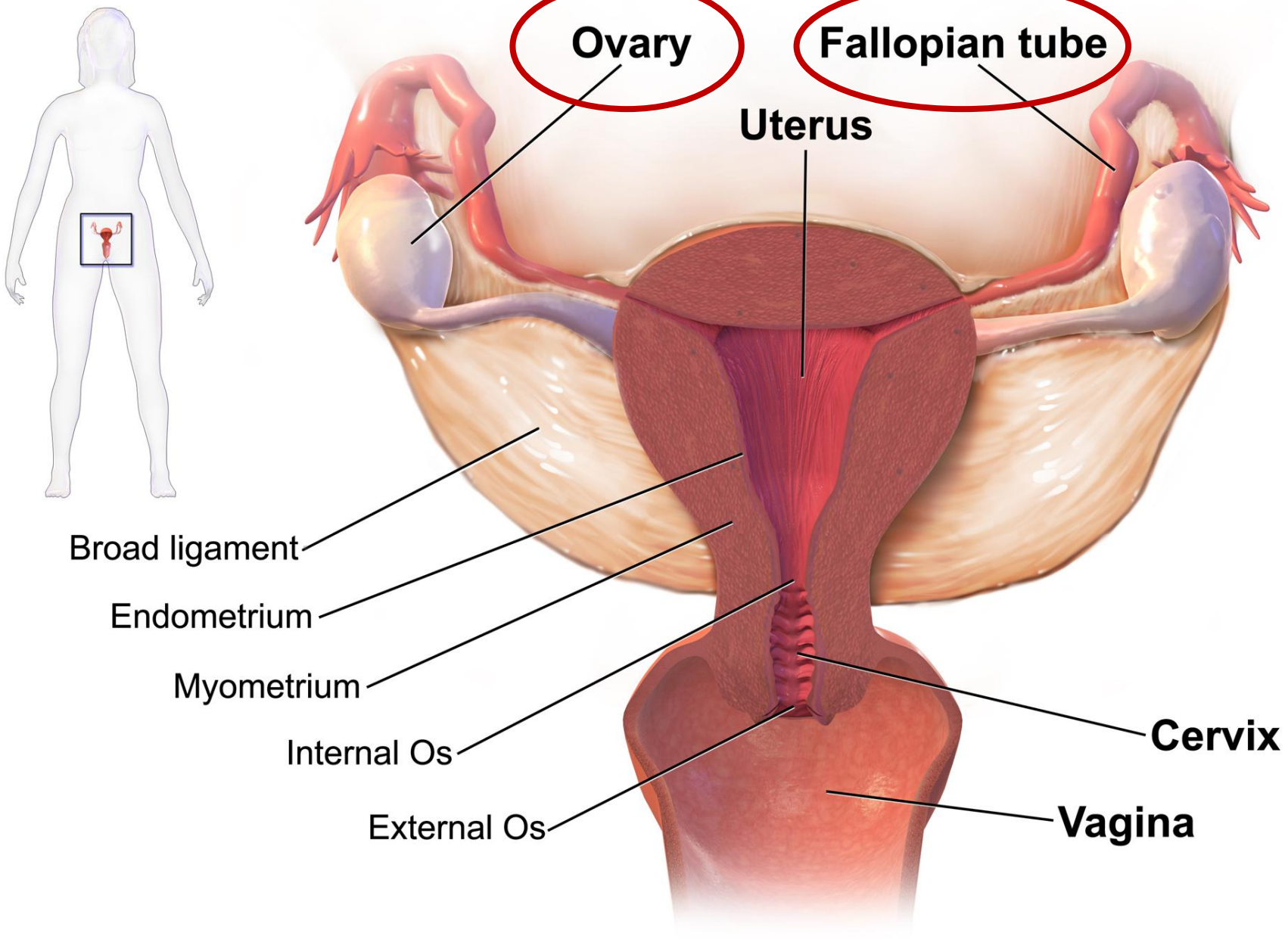
Pathology of the Fallopian tube and the ovaries

Janina Kulka


Ovary
Fallopian tube
Uterus
Broad ligament
Endometrium
Myometrium
Internal Os
External Os
Cervix
Vagina

Hormonal regulation

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

Embriology - OVARIES

- 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

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

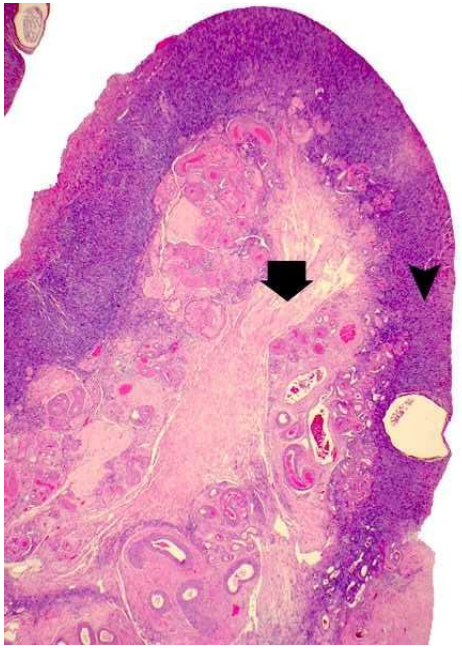
Related diseases

- 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.*



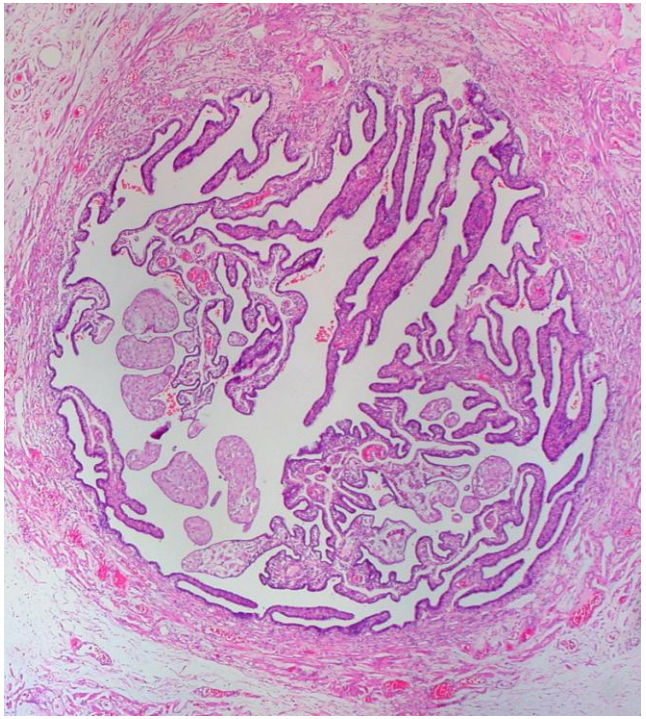
http://www.pathpedia.com/education/eatlas/histology/ovary/Images.aspx?7

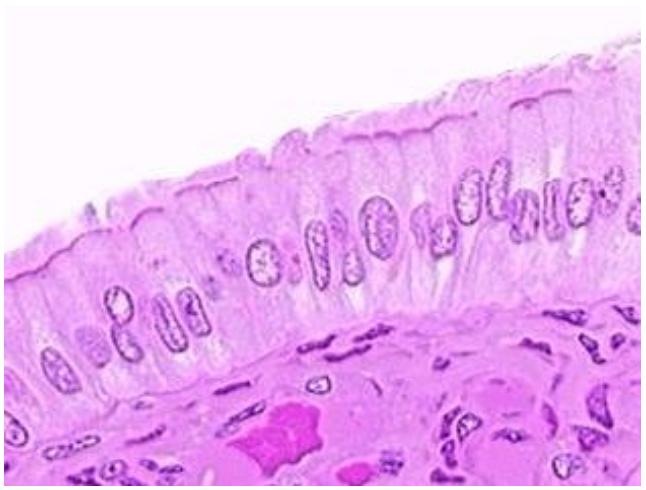
Embriology - FALLOPIAN TUBE

- 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

- 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

Fallopian tube

- Inflammations
  - Tubo-ovarial abscess
- 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

- 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

Gynecologic	Nongynecologic
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

Doubeni CA et al Am Fam Physician. 2016;93(11):937-944

Laboratory tests

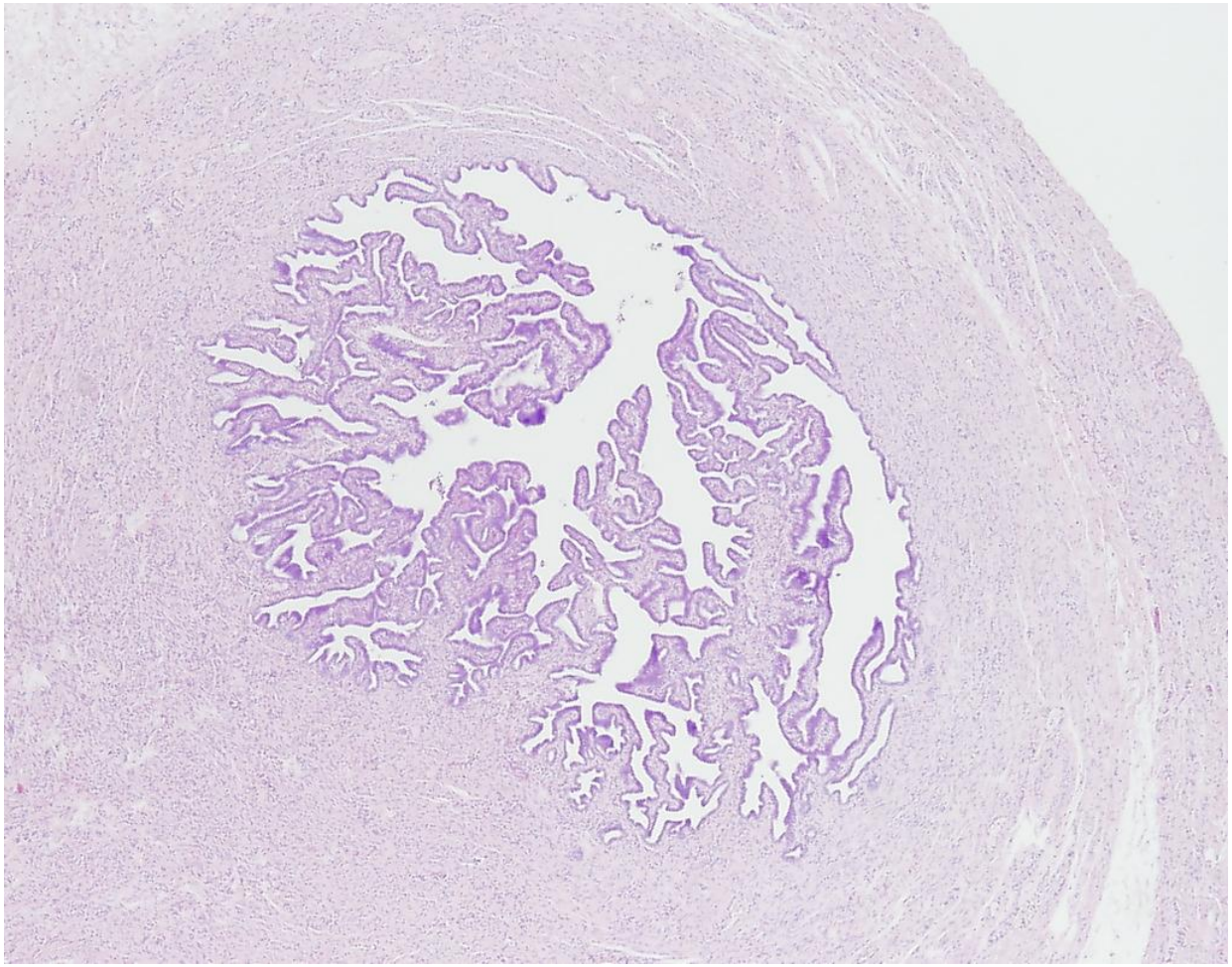
- CA-125
- HE4 (Human Epididymis secretory protein 4)
- ROMA (Risk of Ovarian Malignancy Algorithm) index = combination of the two above

TABLE Tumor markers in ovarian masses

Tumor marker	Ovarian neoplasm
CA-125	Epithelial ovarian cancer
CEA	Mucinous ovarian cancer
HCG	Embryonal carcinoma Choriocarcinoma
Inhibin A or inhibin B	Granulosa cell tumor
Lactate dehydrogenase	Dysgerminoma
α-Fetoprotein	Endodermal sinus tumor Embryonal carcinoma

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

FALLOPIAN TUBE

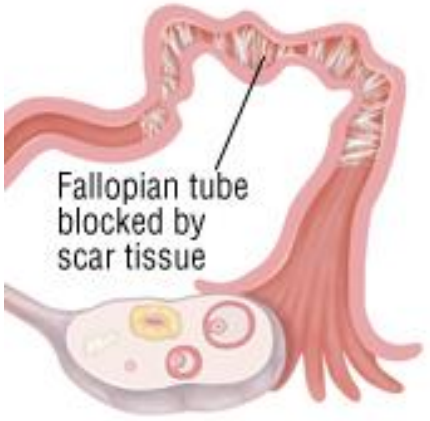


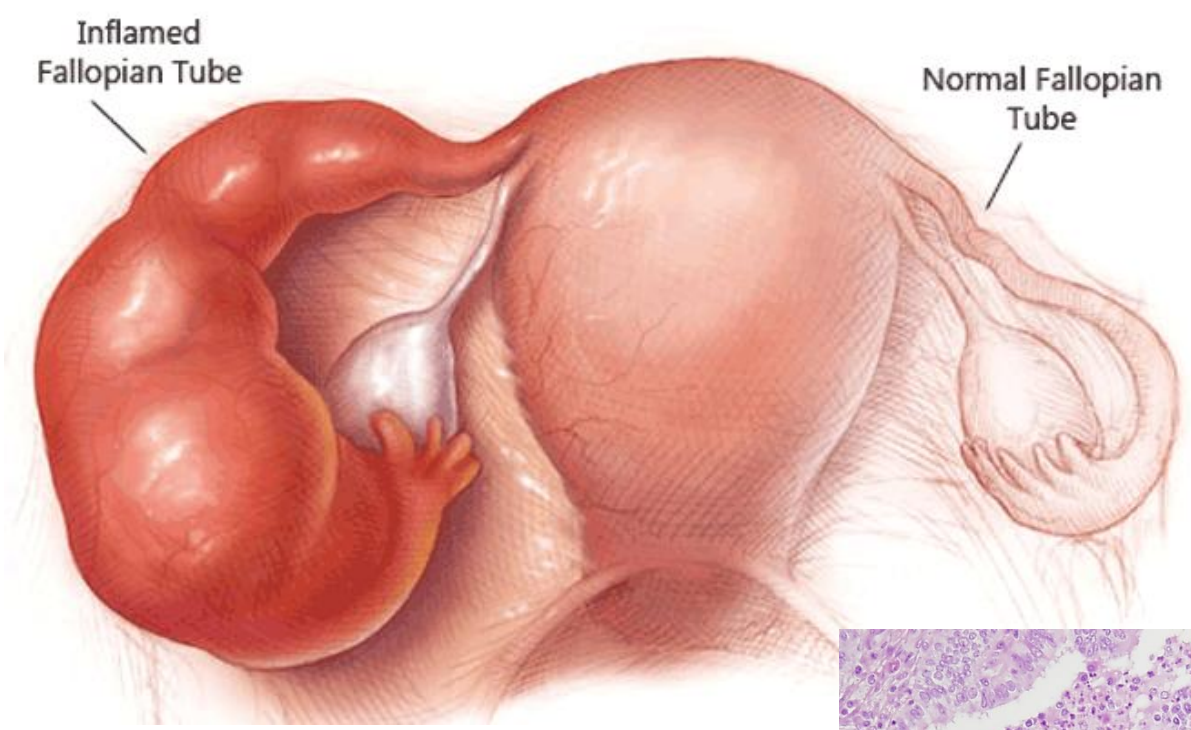
INFLAMMATION

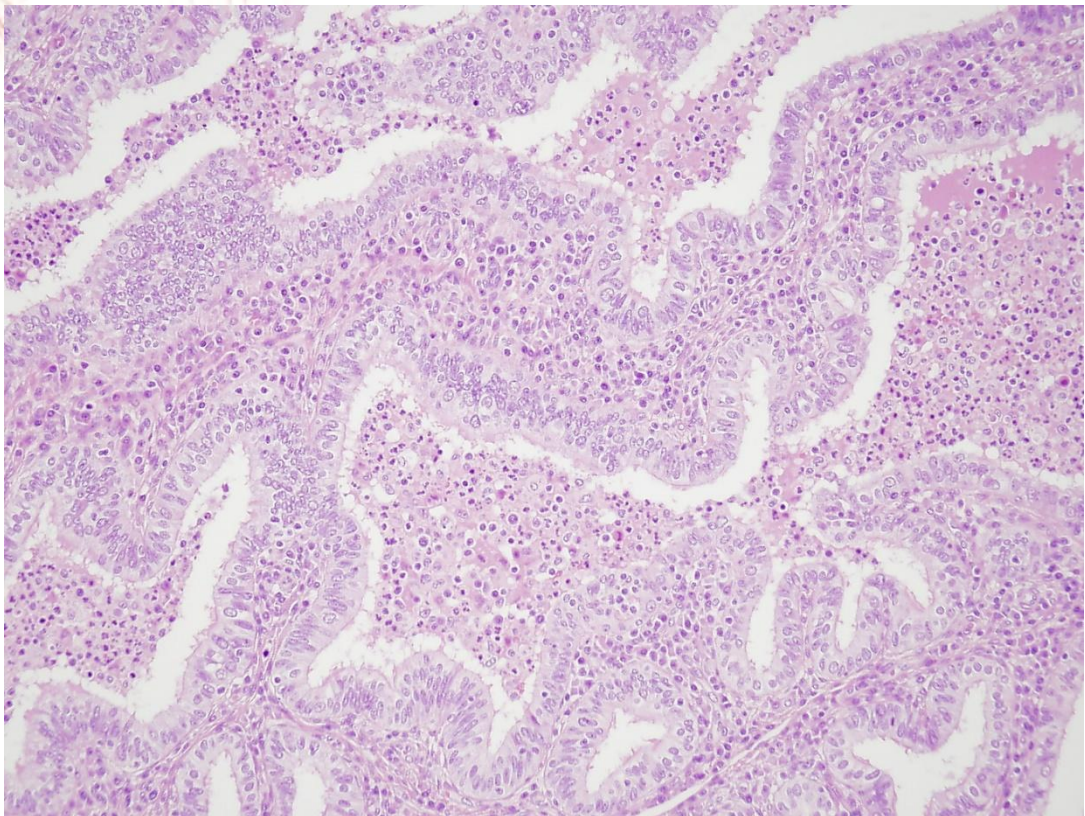
- Causes
  - *Chlamydia*
  - *Mycoplasma hominis*
  - Coliform bacteria
  - gonococci
  - streptococci and staphylococci (postpartum)
  - *Mycobacterium tuberculosis* (accompanies tuberculous endometritis)

- 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)

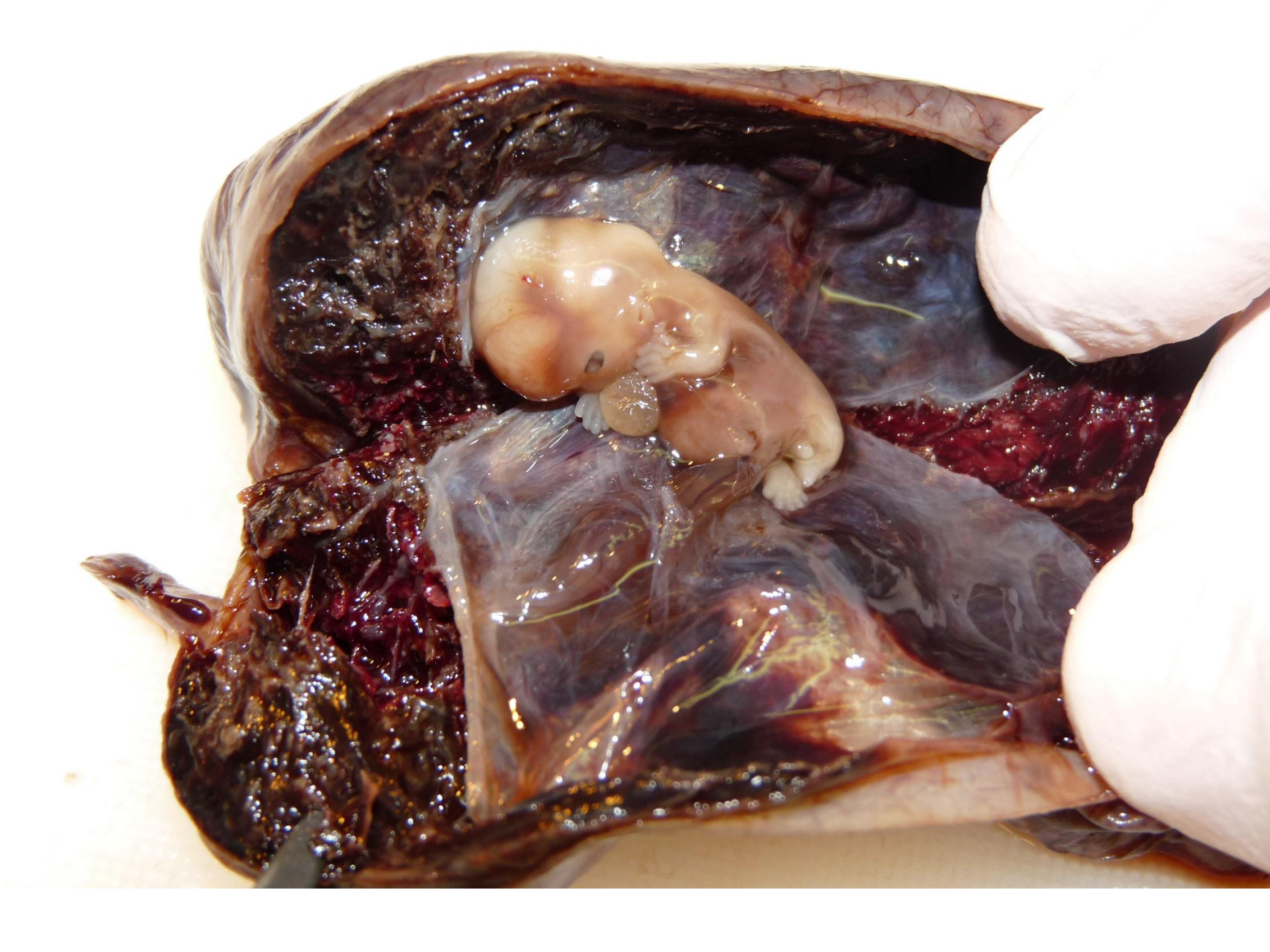



Inflamed
Fallopian Tube
Normal Fallopian
Tube

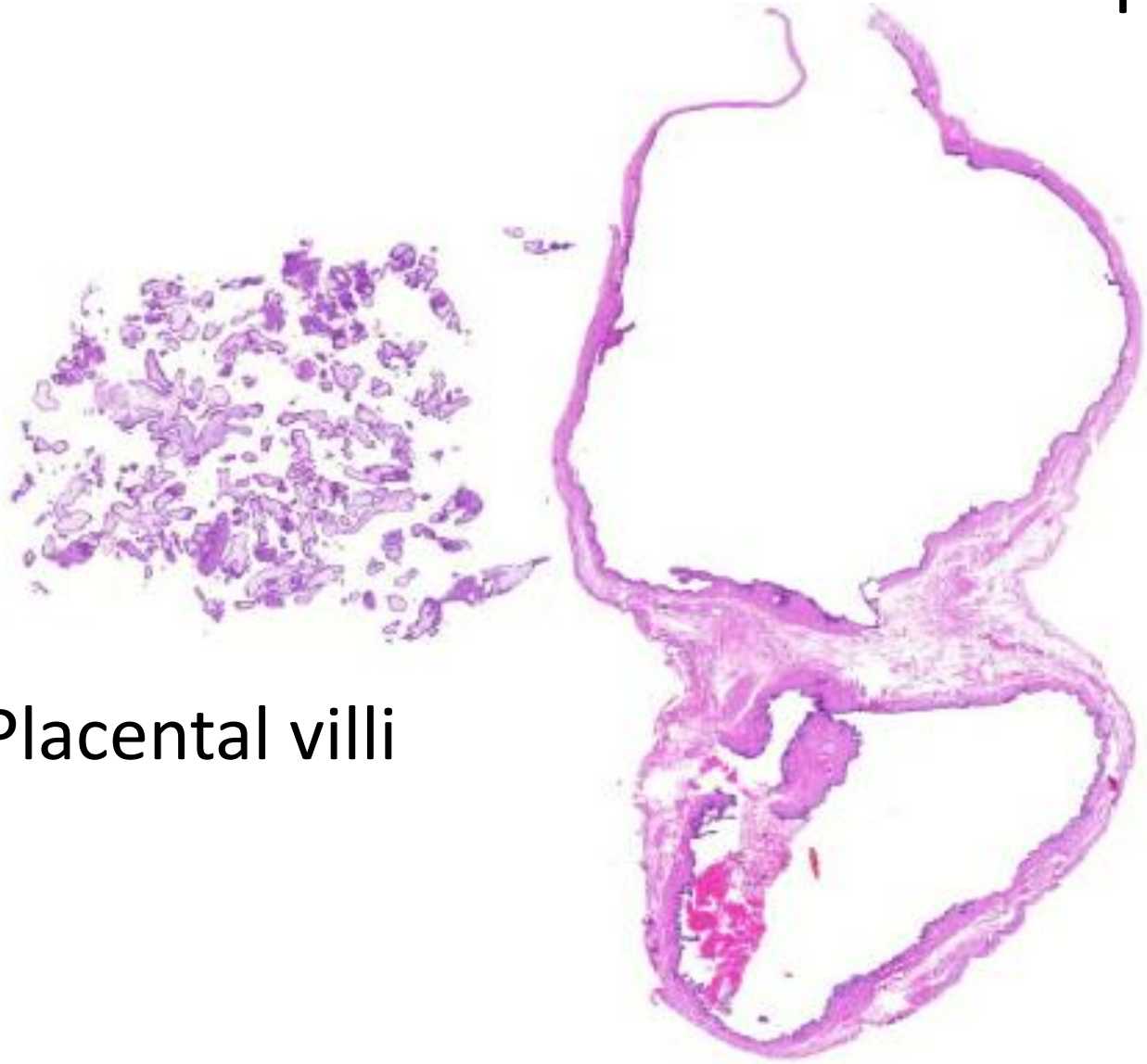


ECTOPIC PREGNANCY

- 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*)



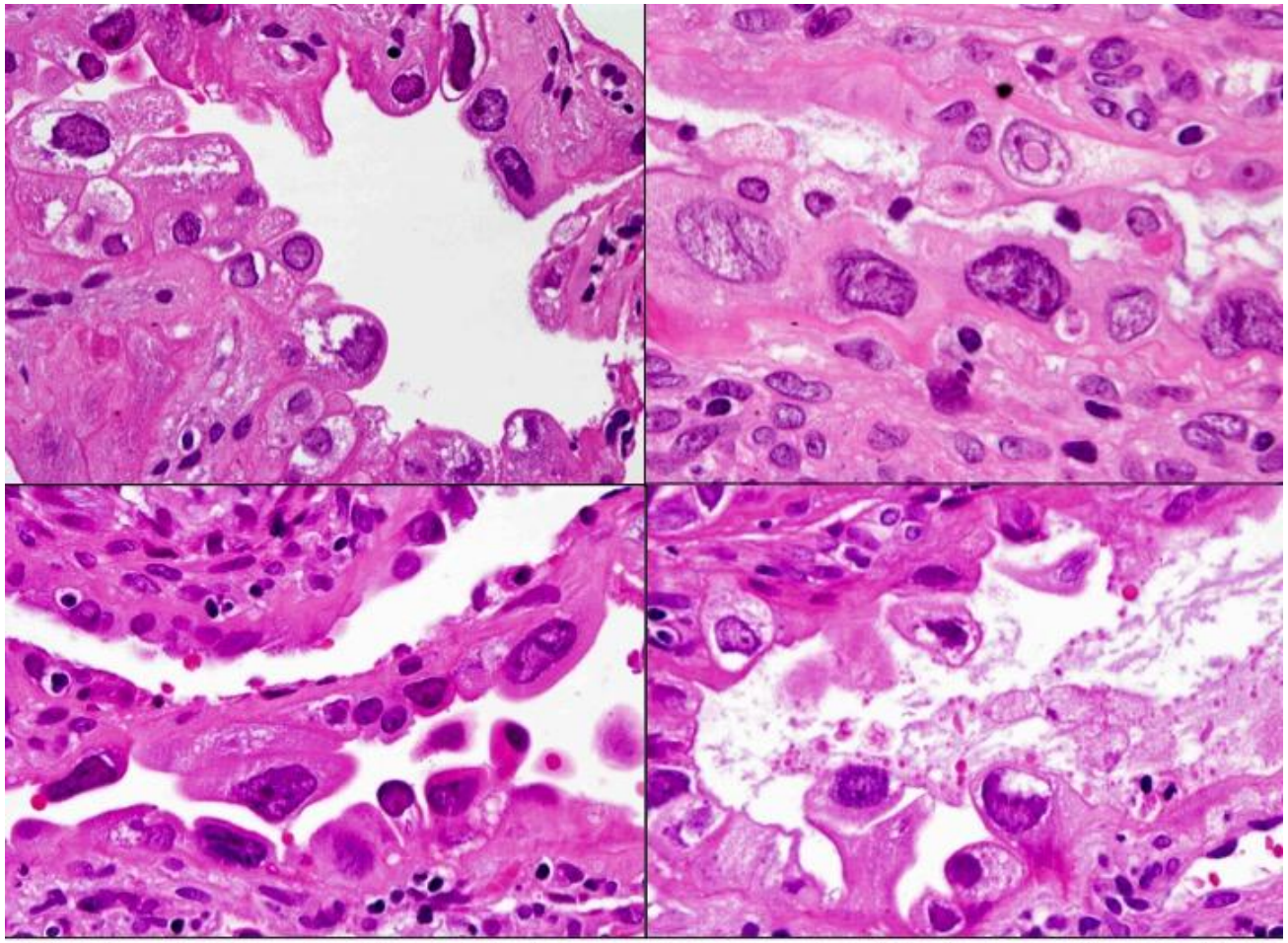
Dilated fallopian tube



Placental villi

Hemorrhage/blod clot

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



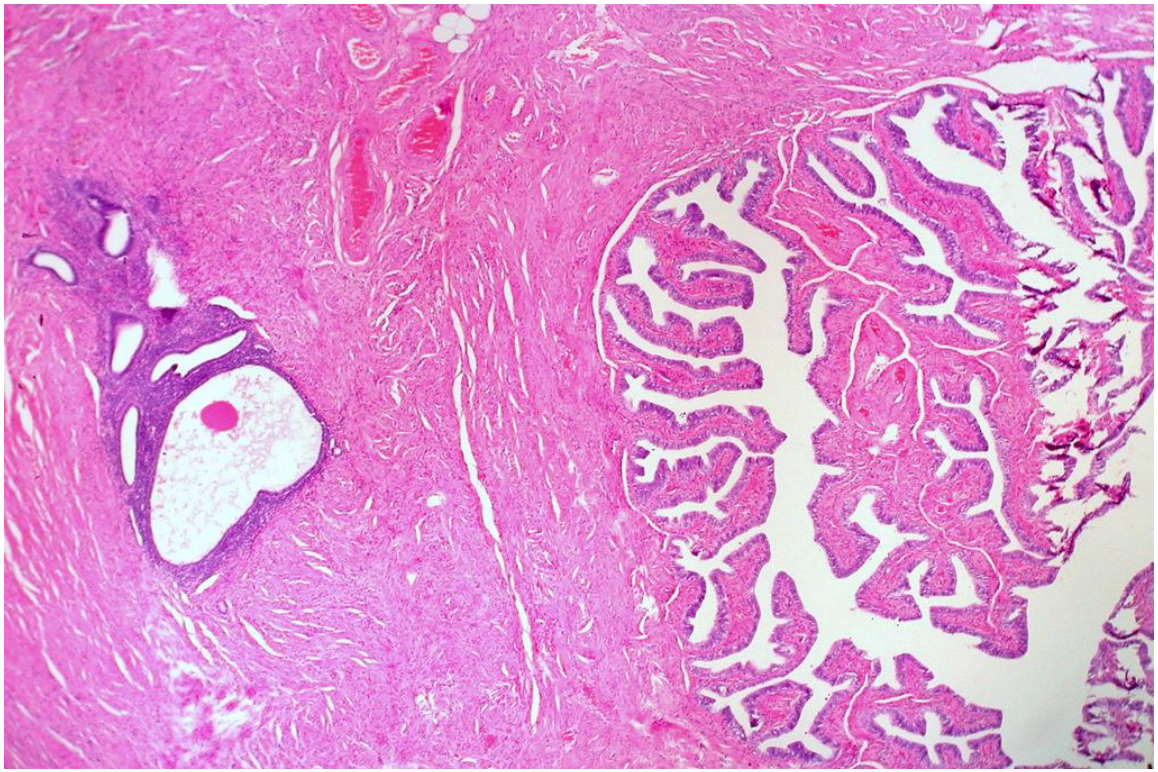
Hobnail growth pattern as well as nuclei with a vesicular configuration while glands showing no / minimal secretory activity discernible in the combination picture. In the upper right image, monstrous cell pattern with giant, bizarre nuclei with homogenous chromatin containing nuclear pseudoinclusion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

http://www.pathologyoutlines.com

ENDOMETRIOSIS

- 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



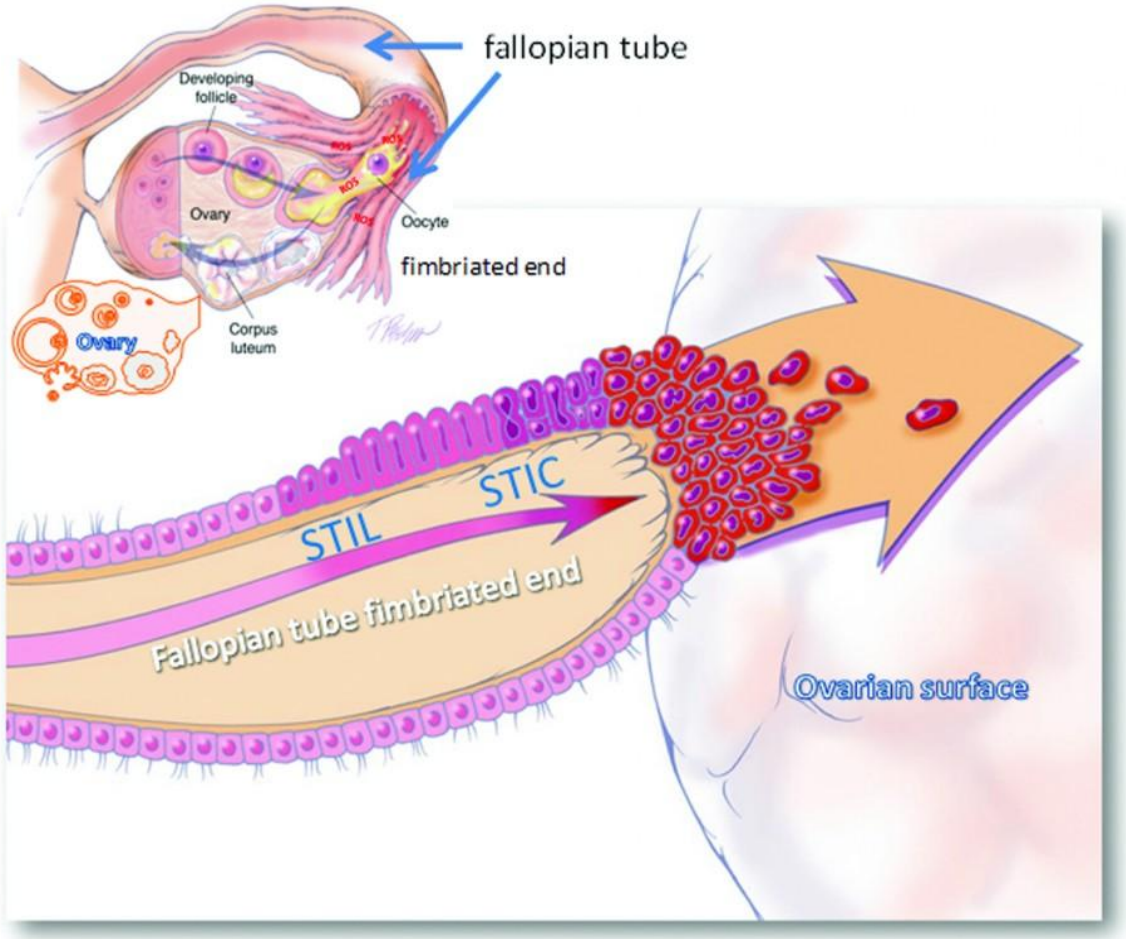
Microscopic diagnostic features of endometriosis

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

The presence of minimum 2 features is required to the diagnosis

ADENOCARCINOMA

- 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*)**.

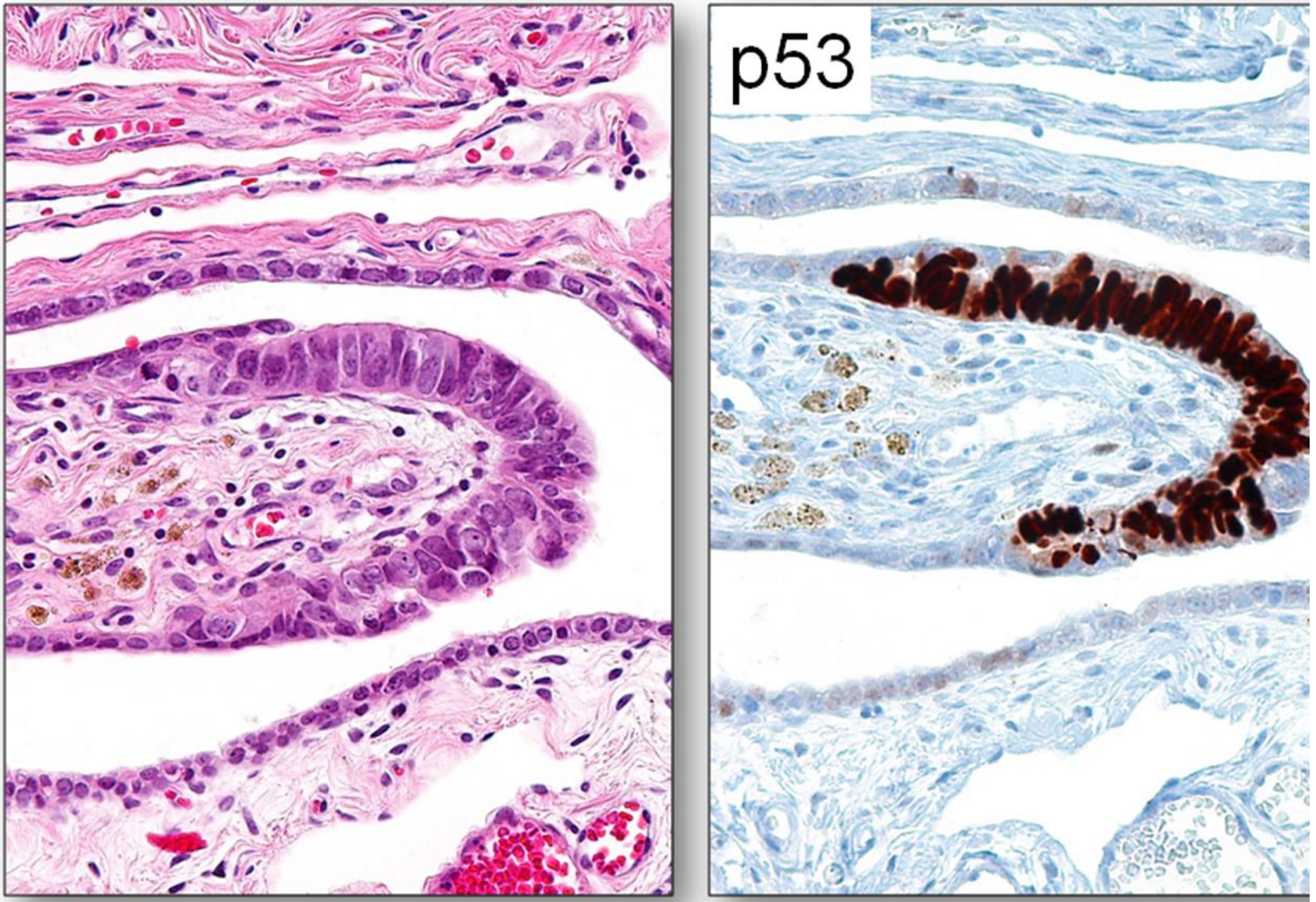


Proposed development of ovarian HGSC by direct shedding and implantation of STIC cells from the fimbria onto the ovarian surface.

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.

http://www.ovariancancerprevention.org



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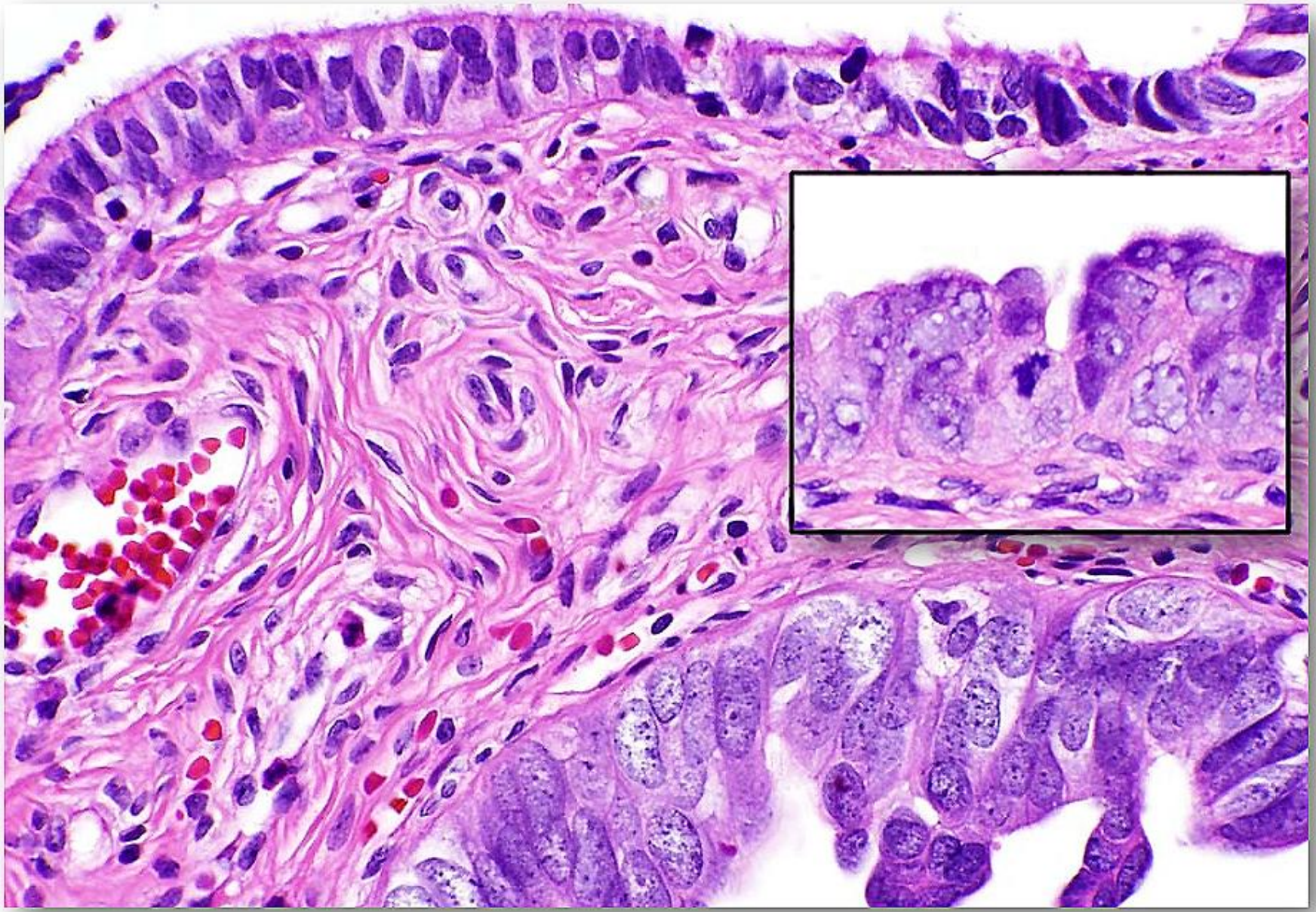

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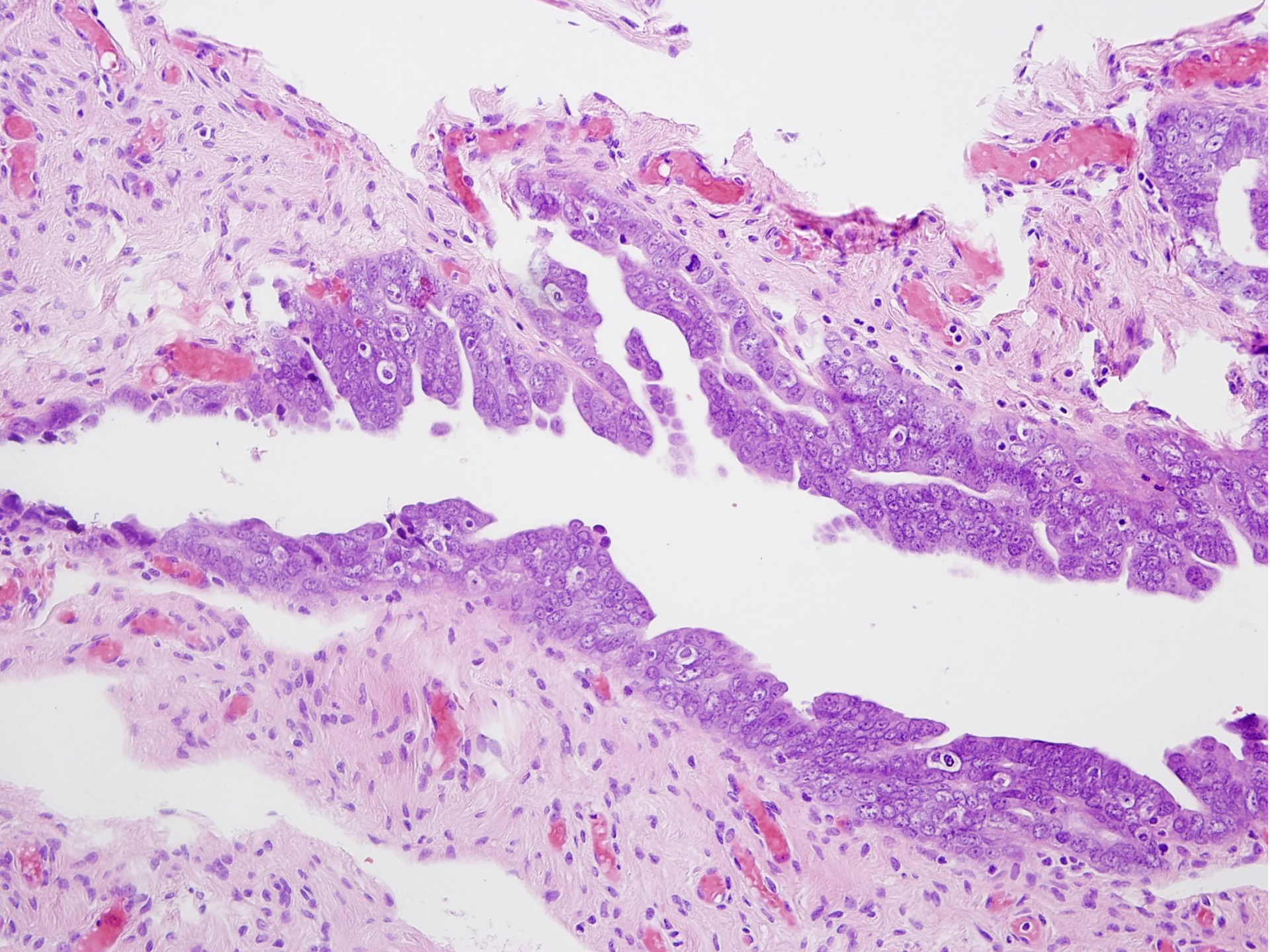
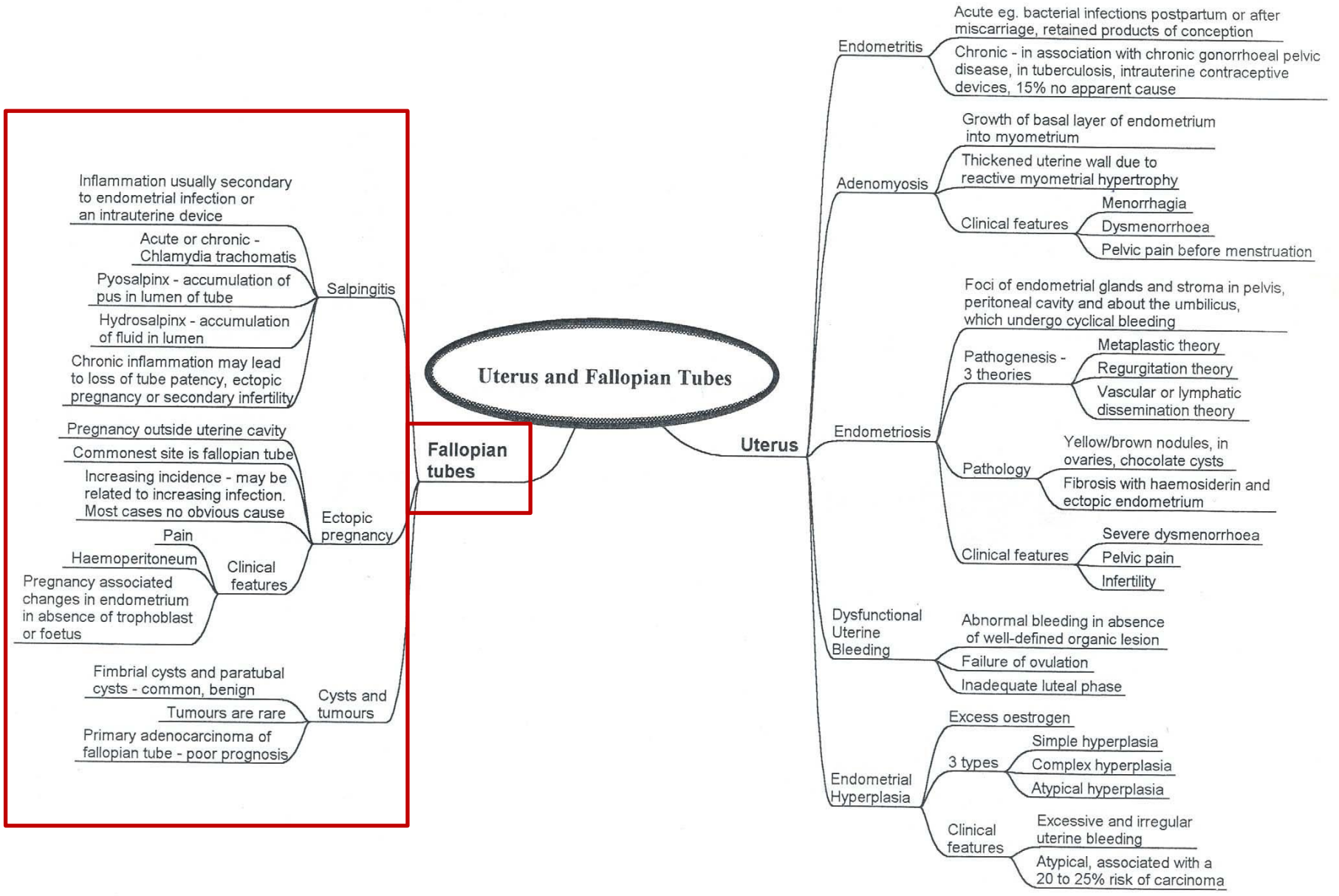



Uterus and Fallopian Tubes
Fallopian tubes
Salpingitis
Inflammation usually secondary to endometrial infection or an intrauterine device
Acute or chronic - Chlamydia trachomatis
Pyosalpinx - accumulation of pus in lumen of tube
Hydrosalpinx - accumulation of fluid in lumen
Chronic inflammation may lead to loss of tube patency, ectopic pregnancy or secondary infertility
Ectopic pregnancy
Pregnancy outside uterine cavity
Commonest site is fallopian tube
Increasing incidence - may be related to increasing infection. Most cases no obvious cause
Clinical features
Pain
Haemoperitoneum
Pregnancy associated changes in endometrium in absence of trophoblast or foetus
Cysts and tumours
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

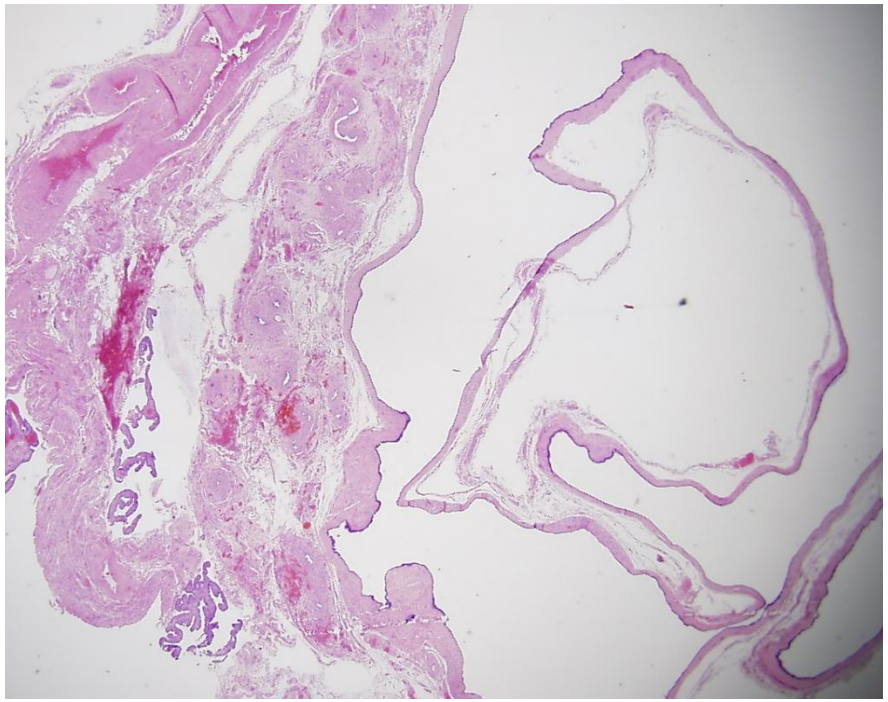
CYSTS

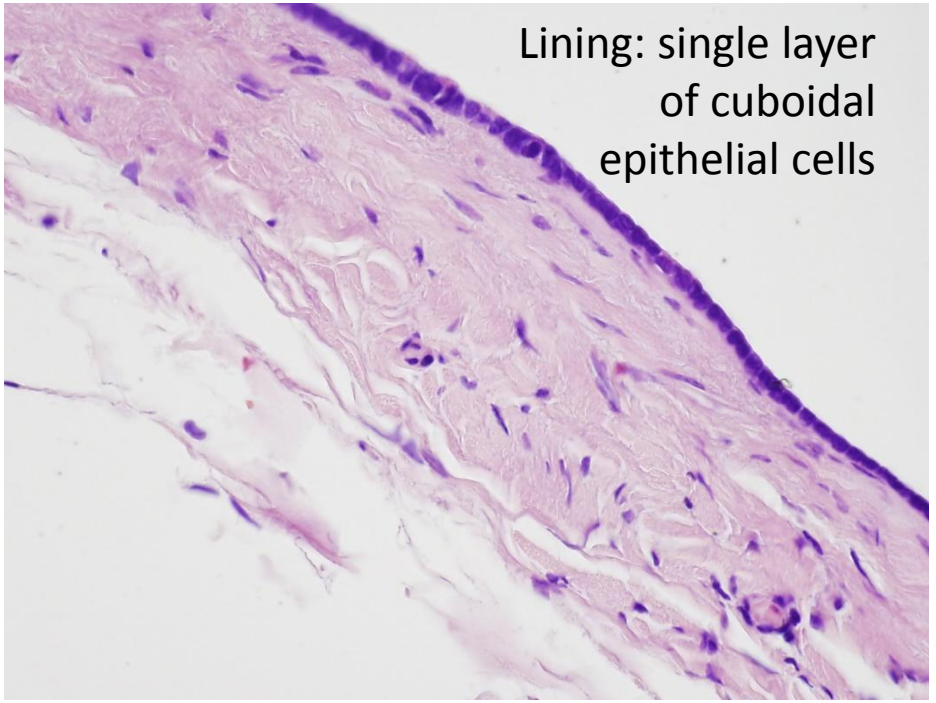
- Simple
  - Invagination of the surface (coelomic) epithelium
- Follicular
  - Polycystic Ovary (PCO)
    - ANOVULATION, OBESITY, HIRSUTISM, Virilism
    - Ovaries are enlarged and cystic
    - In 3-6% of reproductive age women
    - Oligomenorrhea
    - Disturbed biosynthesis of androgens
    - ***Insulin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

- *CYSTIC TUMORS*

Simple cyst

Smooth
outer and
inner surface

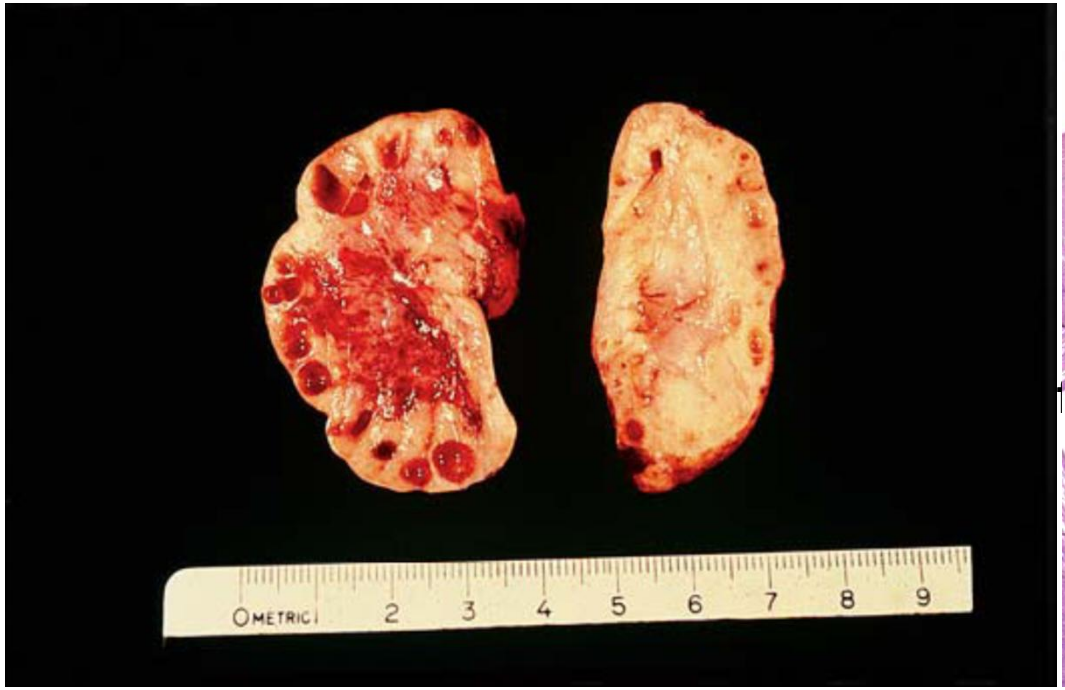




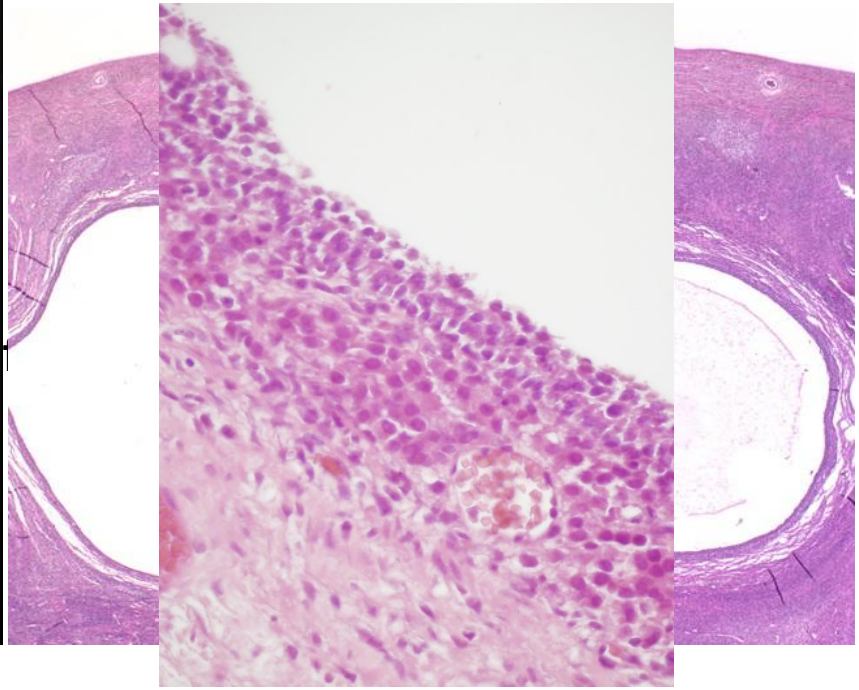
Lining: single layer
of cuboidal
epithelial cells

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

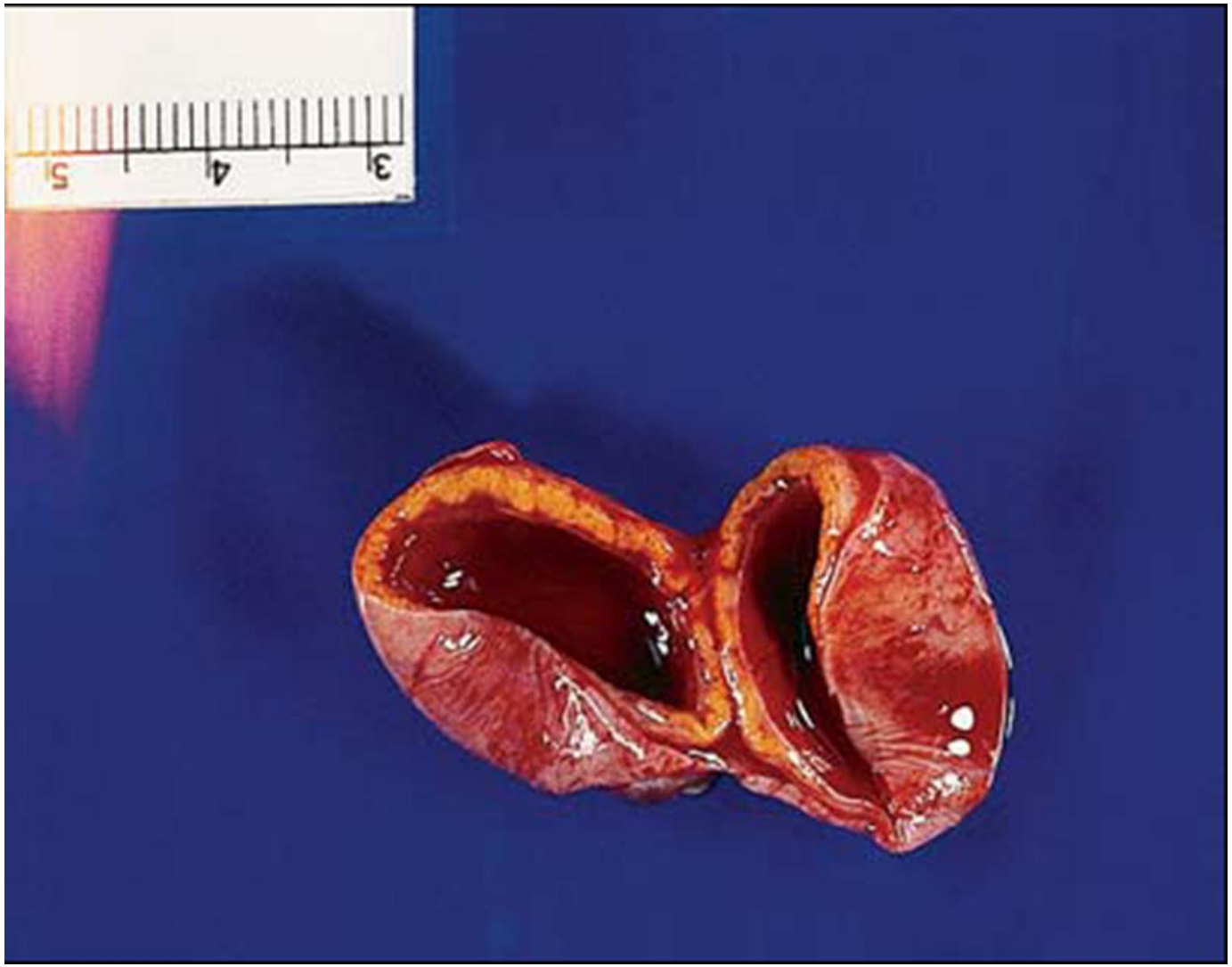
→inhibin production increased

→inhibit FSH rise

→ follicular development is inadequate

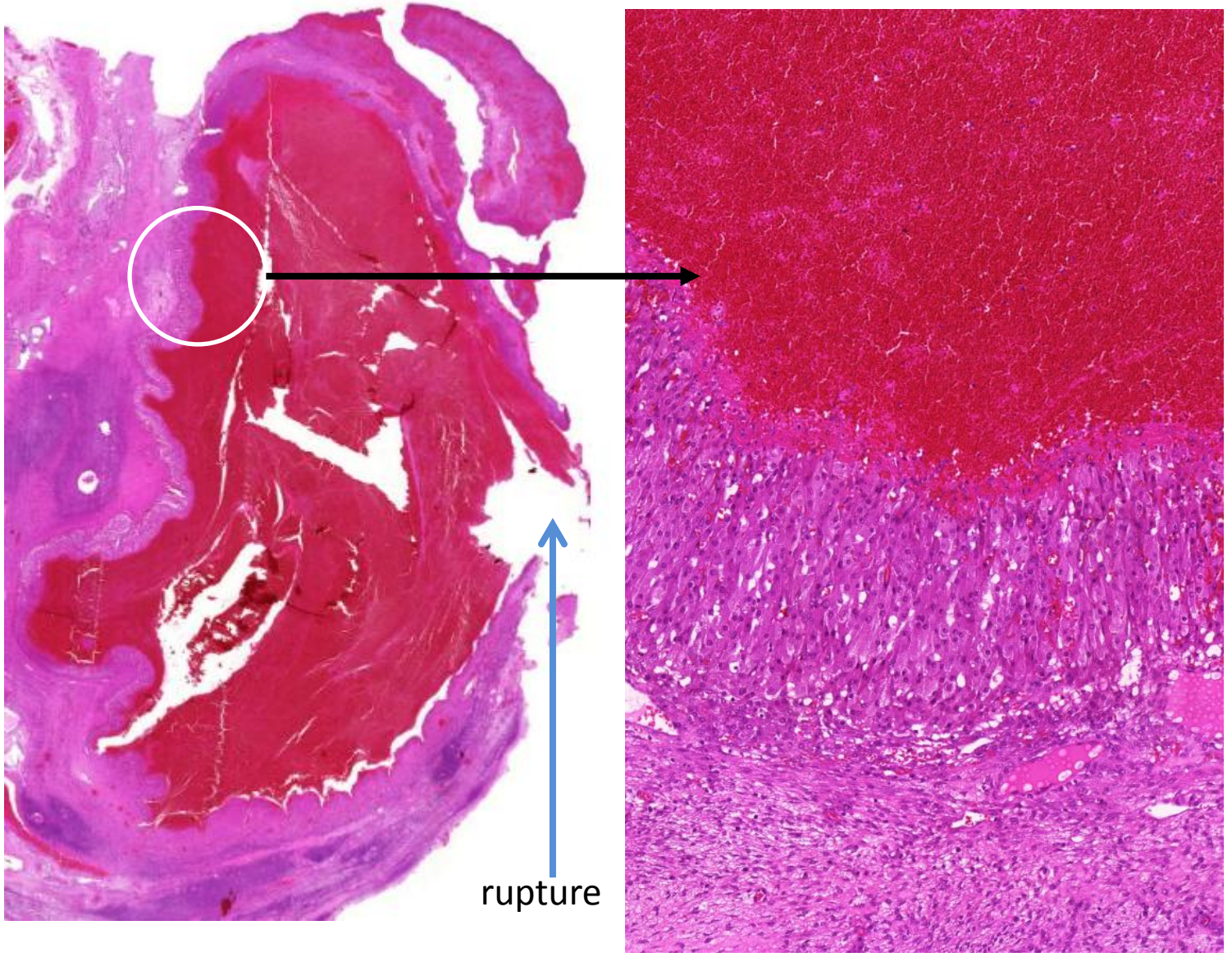
LH levels are high (but lack the characteristic midcycle surge responsible for ovulation)→thecal hypertrophy→increased androgen production by the ovary→aromatase→estrogen levels increase

Corpus luteum cyst



- Single cyst
- Yellowish

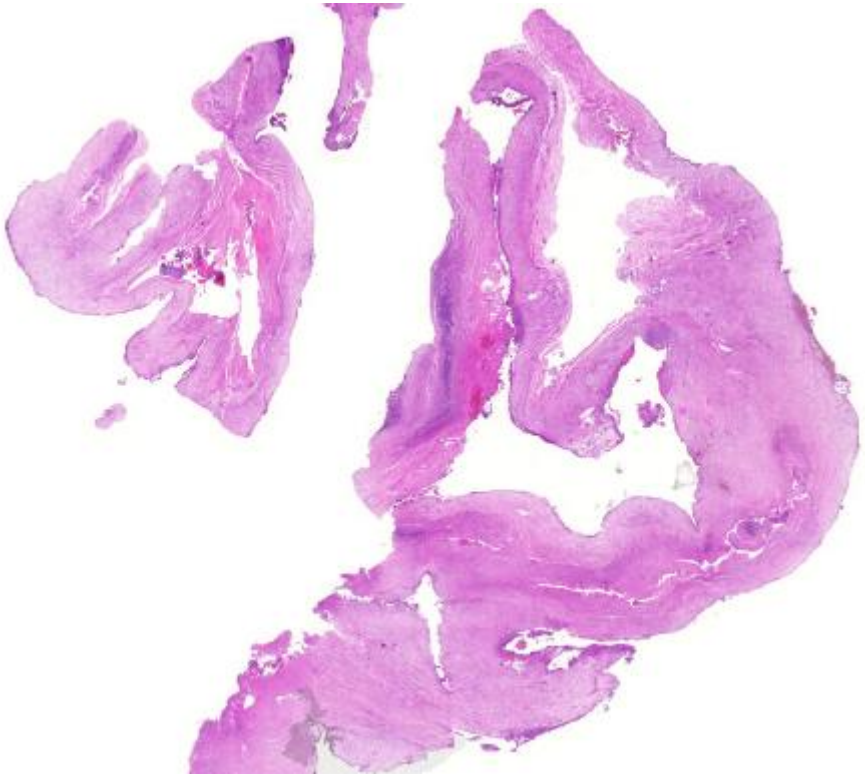
Cystic-hemorrhagic corpus luteum

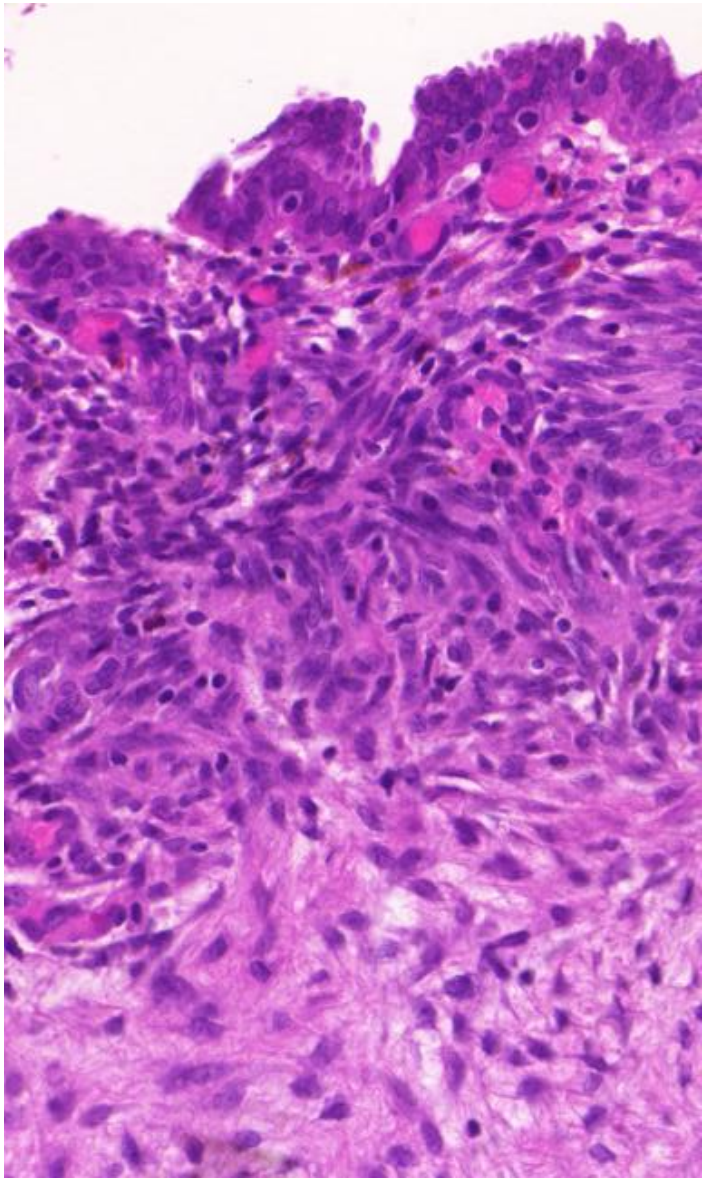


Luteinized theca- and granulosa cells

Endometriosis – endometriotic cyst

Endometrial epithelial lining
Endometrial stroma
Hemosiderin





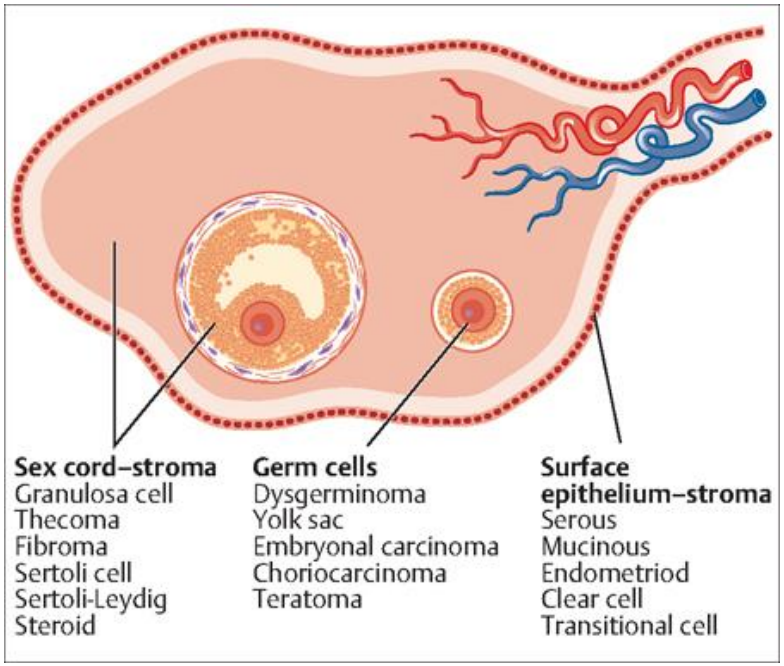
Stromal hyperplasia/hyperthecosis

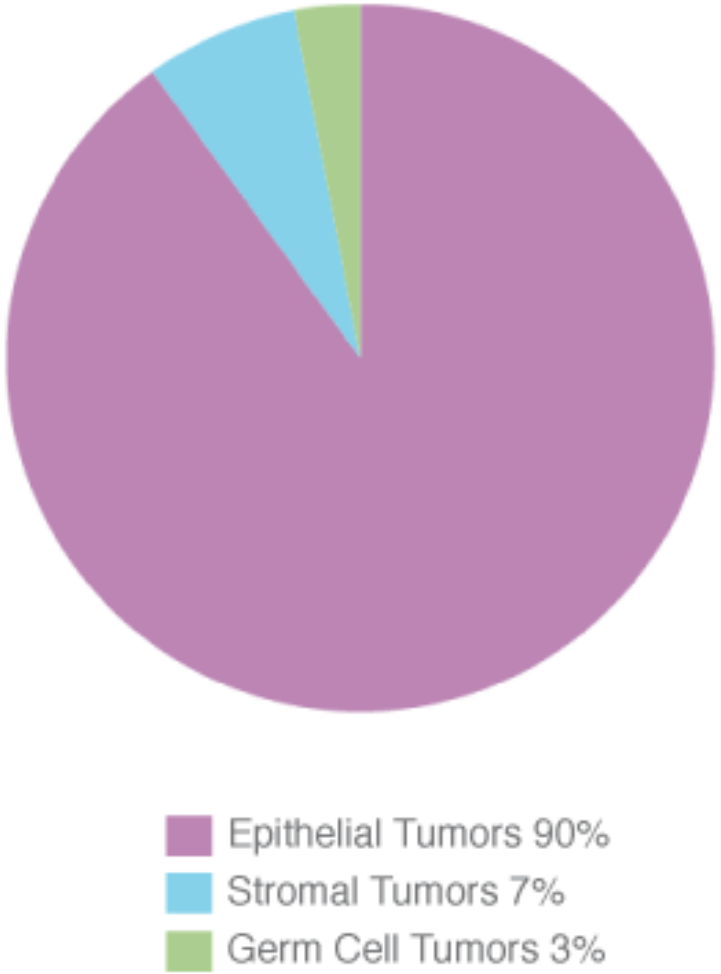
- Postmenopausal women
- Signs: hyperestrogenism, hyperandrogenism, virilism, obesity, abnormal glucose tolerance test
- enlarged ovaries (up to 7 cm), no cysts
- hypercellular stroma with luteinized stromal cells (producing androgens)

Tumors of the ovary

Benign: 80%
Age 20-45

Malignant tumors
Age 45-65
3% of all cancers in women
5th most common cause of cancer death





WHO Classification of tumours of the ovary[a,b]

Epithelial tumours	
Serous tumours	
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
Mucinous tumours	
Benign	
Mucinous cystadenoma	8470/0
Mucinous adenofibroma	9015/0
Borderline	
Mucinous borderline tumour / Atypical proliferative mucinous tumour	8472/1
Malignant	
Mucinous carcinoma	8480/3
Endometrioid tumours	
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
Clear cell tumours	
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
Brenner tumours	
Benign	
Brenner tumour	9000/0
Borderline	
Borderline Brenner tumour / Atypical proliferative Brenner tumour	9000/1
Malignant	
Malignant Brenner tumour	
Seromucinous tumours	
Benign	
Seromucinous cystadenoma	
Seromucinous adenofibroma	
Borderline	
Seromucinous borderline tumour / Atypical proliferative seromucinous tumour	
Malignant	
Seromucinous carcinoma	
Undifferentiated carcinoma	
Mesenchymal tumours	
Low-grade endometrioid stromal sarcoma	
High-grade endometrioid stromal sarcoma	
Mixed epithelial and mesenchymal tumours	
Adenosarcoma	
Carcinosarcoma	
Sex cord-stromal tumours	
Pure stromal tumours	
Fibroma	
Cellular fibroma	
Thecoma	
Luteinized thecoma associated with sclerosing peritonitis	
Fibrosarcoma	
Sclerosing stromal tumour	
Signet-ring stromal tumour	
Microcystic stromal tumour	
Leydig cell tumour	
Steroid cell tumour	
Steroid cell tumour, malignant	
Pure sex cord tumours	
Adult granulosa cell tumour	
Juvenile granulosa cell tumour	
Sertoli cell tumour	
Sex cord tumour with annular tubules	
Mixed sex cord-stromal tumours	
Sertoli-Leydig cell tumours	
Well differentiated	
Moderately differentiated	
With heterologous elements	
Poorly differentiated	
With heterologous elements	
Retiform	
With heterologous elements	
Sex cord-stromal tumours, NOS	

Germ cell tumours	
Dysgerminoma	9060/3
Yolk sac tumour	9071/3
Embryonal carcinoma	9070/3
Non-gestational choriocarcinoma	9100/3
Mature teratoma	9080/0
Immature teratoma	9080/3
Mixed germ cell tumour	9085/3
Monodermal teratoma and somatic-type tumours arising from a dermoid cyst	
Struma ovarii, benign	9090/0
Struma ovarii, malignant	9090/3
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	
Germ cell - sex cord-stromal tumours	
Gonadoblastoma, including gonadoblastoma with malignant germ cell tumour	9073/1
Mixed germ cell-sex cord-stromal tumour, unclassified	8594/1*
Miscellaneous tumours	
Tumours of rete ovarii	
Adenoma of rete ovarii	9110/0
Adenocarcinoma of rete ovarii	9110/3
Wolffian tumour	
Small cell carcinoma, hypercalcaemic type	
Small cell carcinoma, pulmonary type	
Wilms tumour	
Paraganglioma	
Solid pseudopapillary neoplasm	
Mesothelial tumours	
Adenomatoid tumour	
Mesothelioma	
Soft tissue tumours	
Myxoma	
Others	
Tumour-like lesions	
Follicle cyst	
Corpus luteum cyst	
Large solitary luteinized follicle cyst	
Hyperreactio luteinalis	
Pregnancy luteoma	
Stromal hyperplasia	
Stromal hyperthecosis	
Fibromatosis	
Massive oedema	
Leydig cell hyperplasia	
Others	
Lymphoid and myeloid tumours	
Lymphomas	
Plasmacytoma	
Myeloid neoplasms	
Secondary tumours	

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 and/or N1	III	Tumour involves one or both ovaries or fallopian tubes, 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.

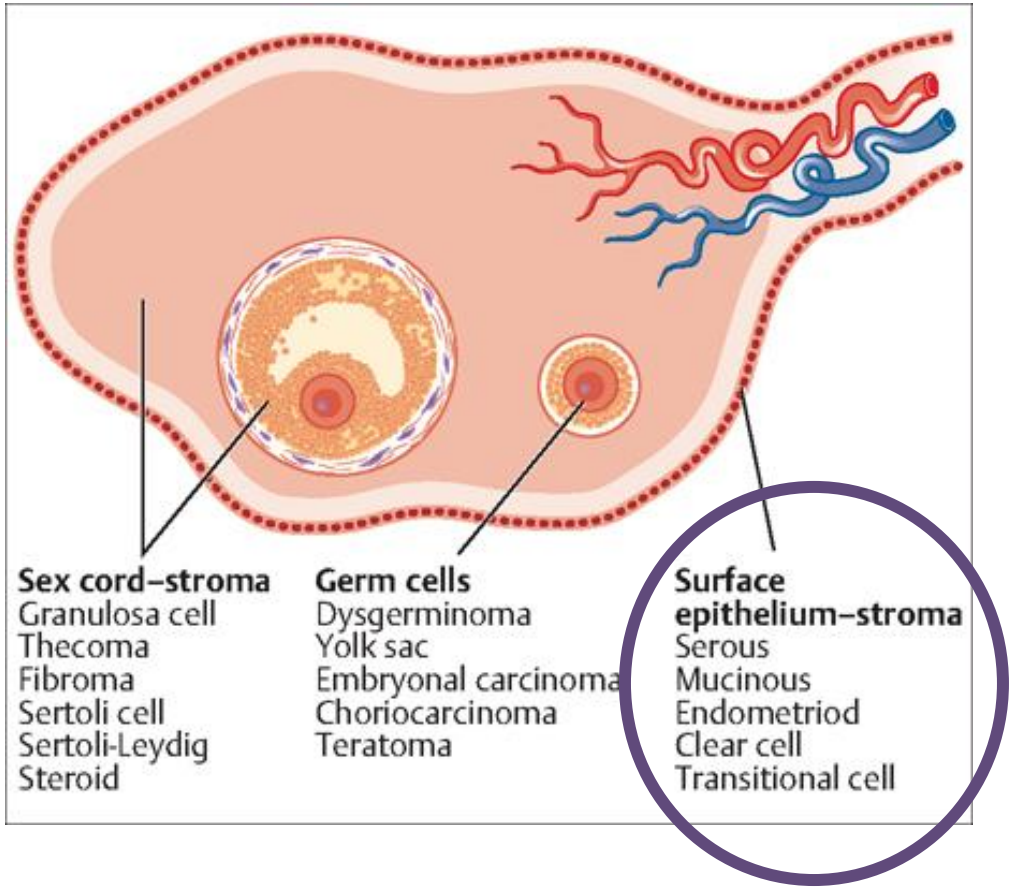
TNM and FIGO
Fallopian tube and Ovary

2017

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

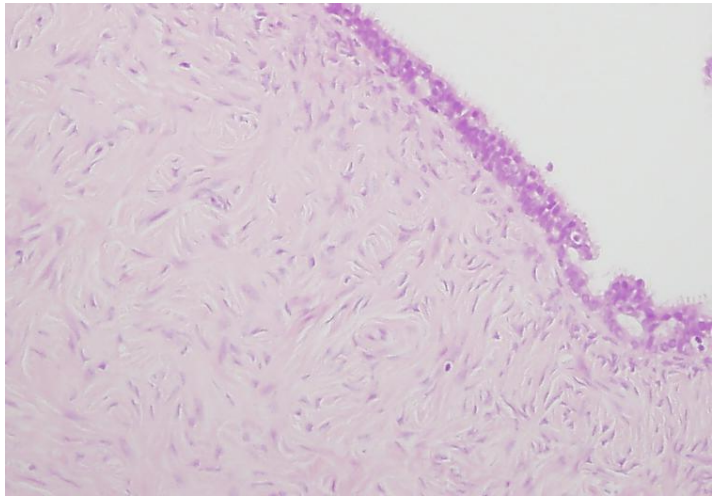


- **Serous**
  - 25% malignant
  - Bilaterality common
  - Psammoma bodies
- **Mucinous**
  - Majority benign
  - Can be very large
  - Pseudomyxoma peritonei
- **Endometrioid**
  - Majority malignant
  - 15-30% with synchronous endometrial carcinoma
- Clear cell
  - Variant of endometrioid diff.
  - „hobnail" cells
- Transitional cell/Brenner tumor
  - Mostly benign
  - Wolffian differentiation

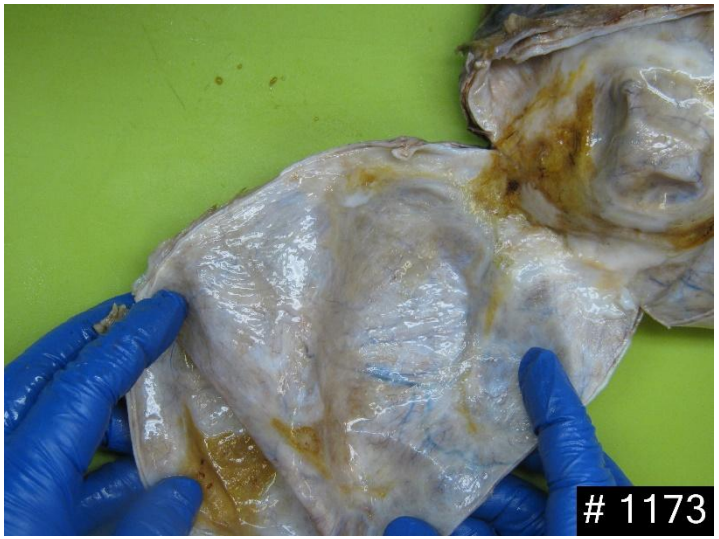
- **BENIGN**
  - **CYSTADENOMA**
  - **CYSTADENOFIBROMA**
  - **ADENOFIBROMA**
- **BORDERLINE**
  - **INCREASED STRUCTURAL COMPLEXITY**
  - **NO DESTRUCTIVE INFILTRATIVE GROWTH**
- **MALIGNANT**
  - **HIGHLY COMPLEX STRUCTURE**
  - **INVASION**

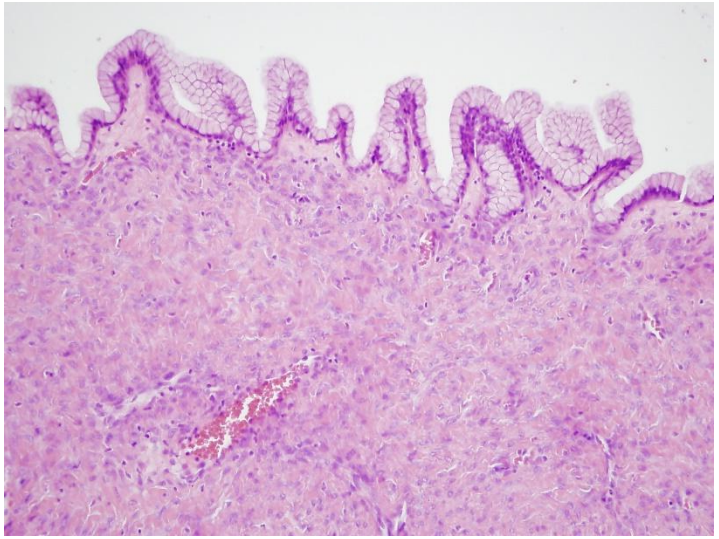
Benign epithelial tumors

Serous cystadenoma (25% bilateral)

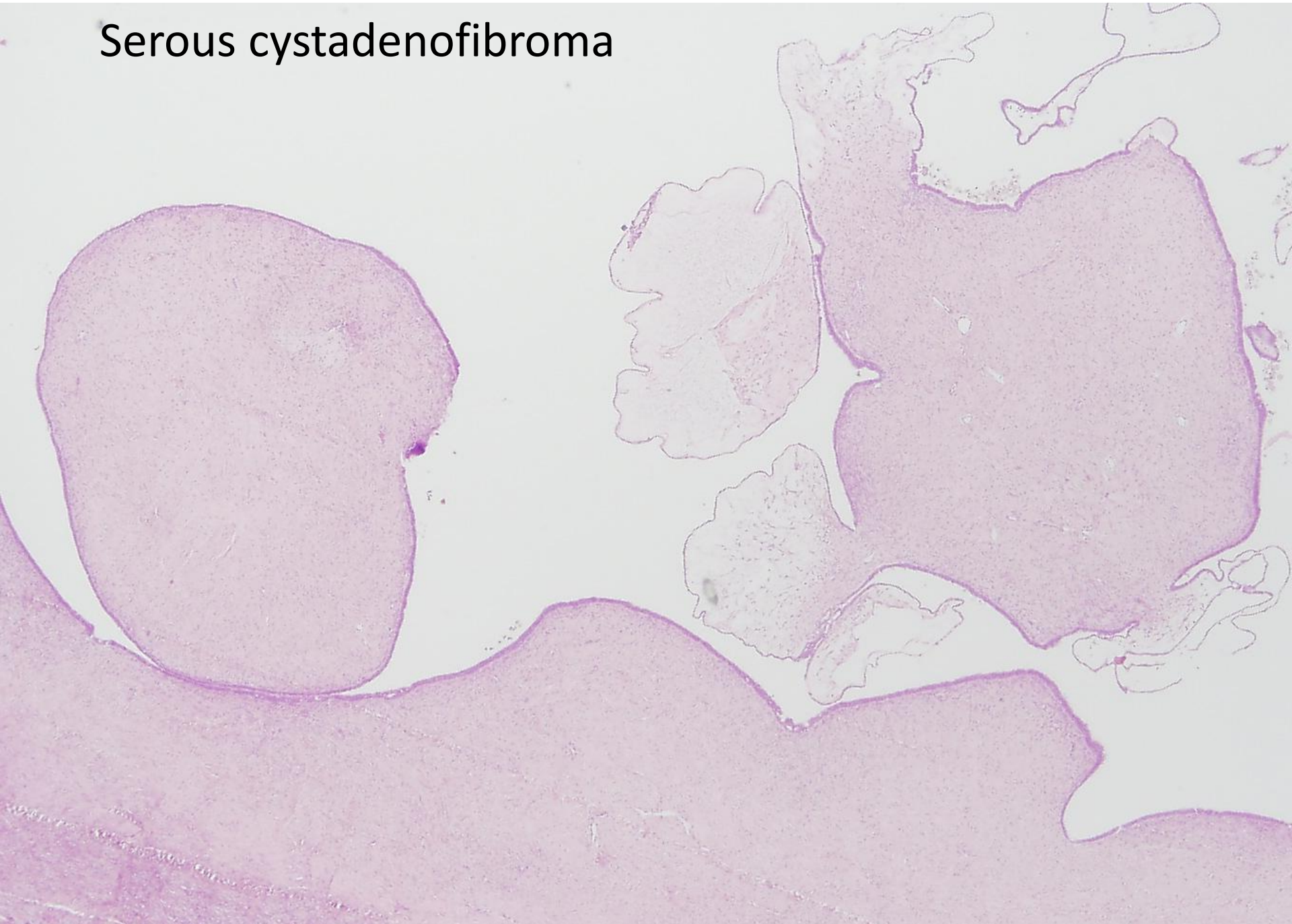


Mucinous cystadenoma

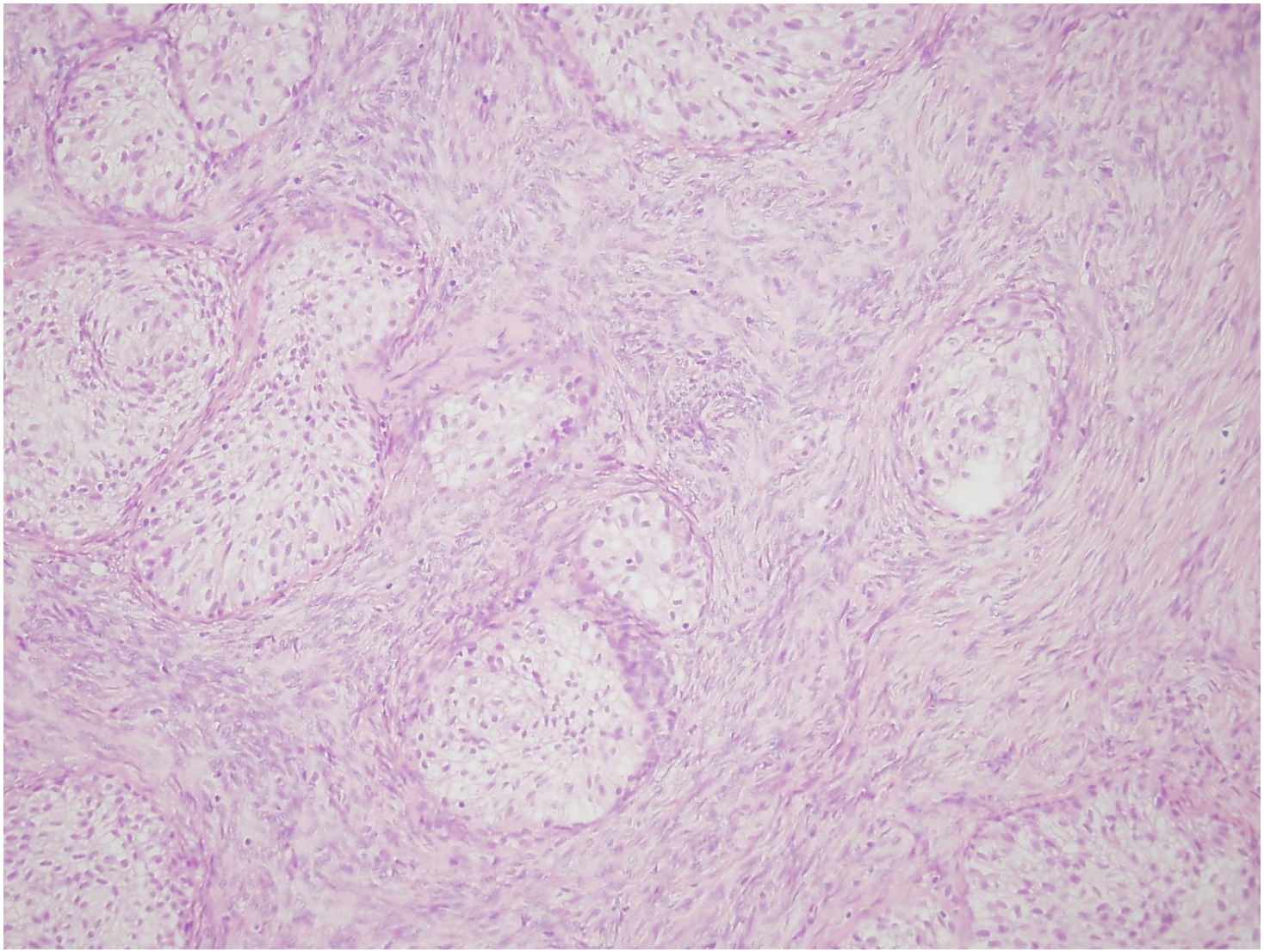




Serous cystadenofibroma

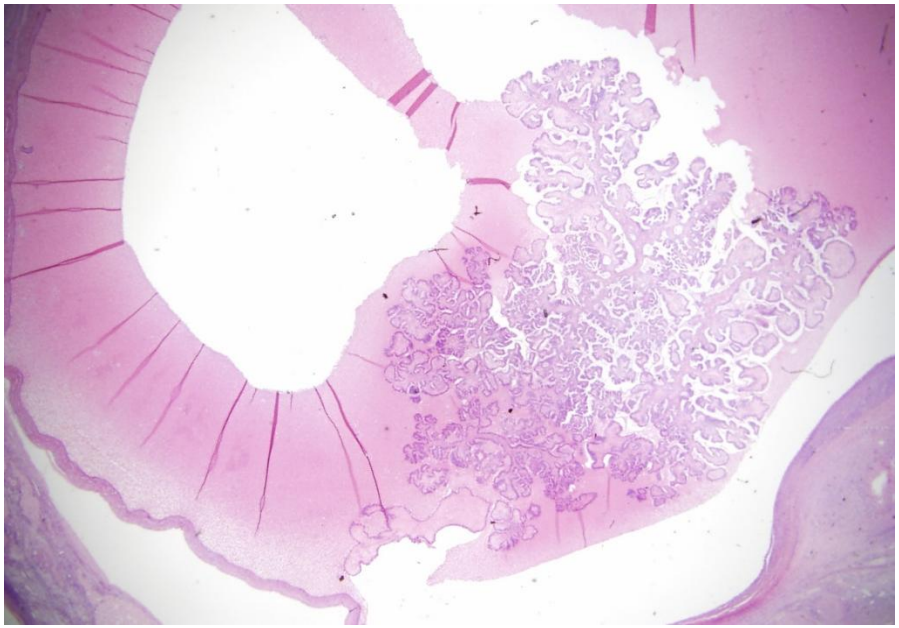


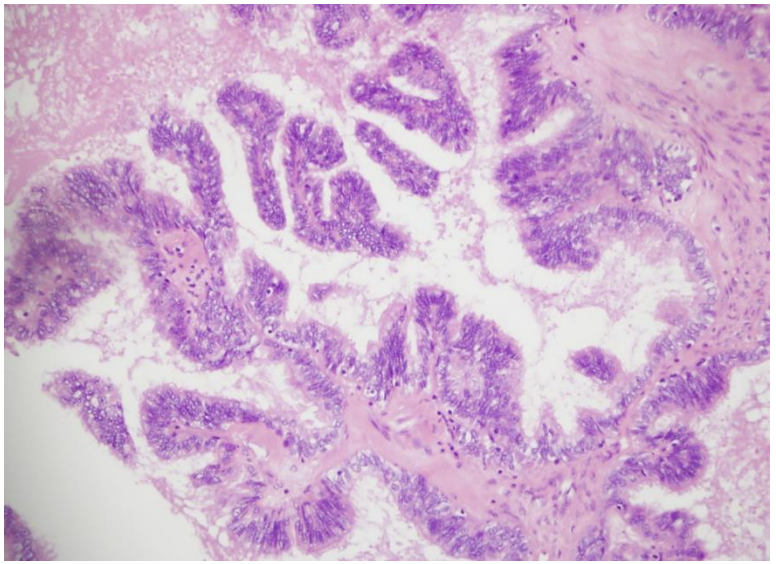
Brenner tumor

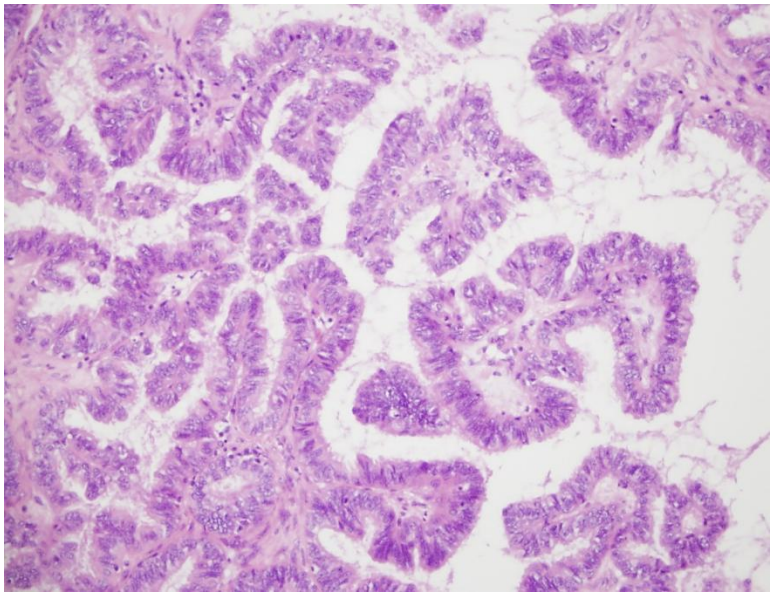


Transitional cell nests in abundant stroma

Serous ***borderline*** tumor





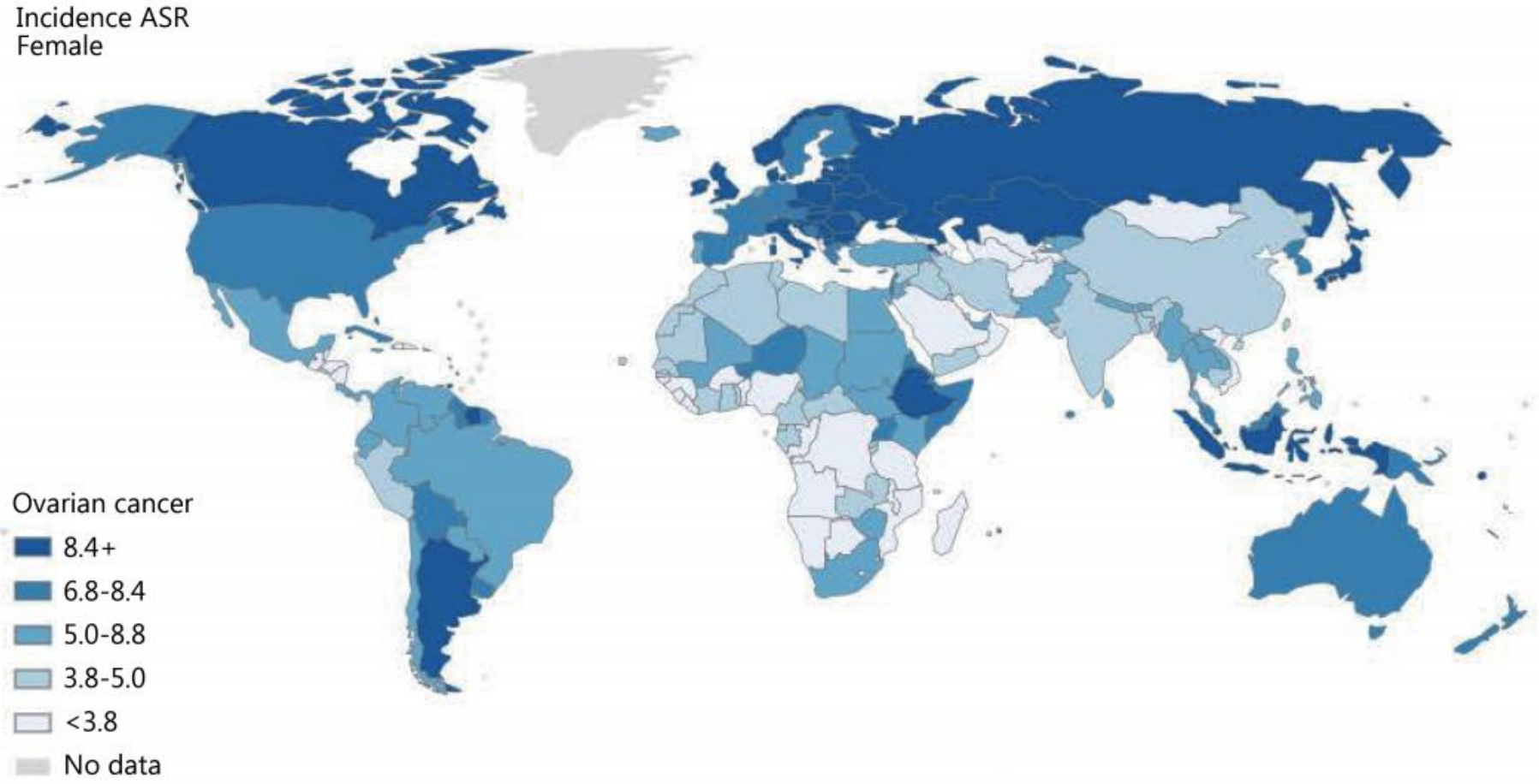


<u>Borderline tumor:</u>

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

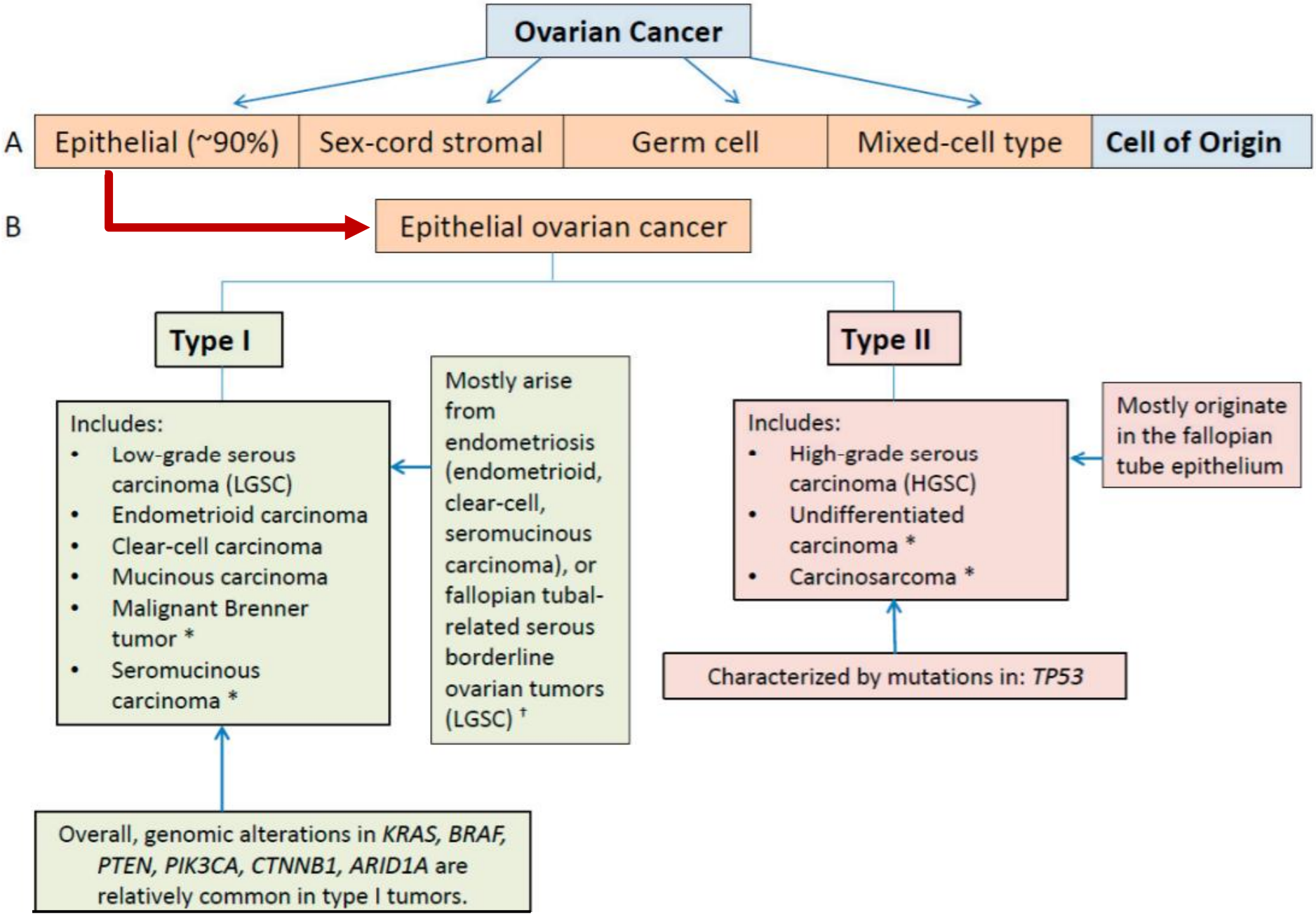
Worldwide incidence of ***ovarian carcinoma***

Cancer Biol Med Vol 14, No 1 February 2017



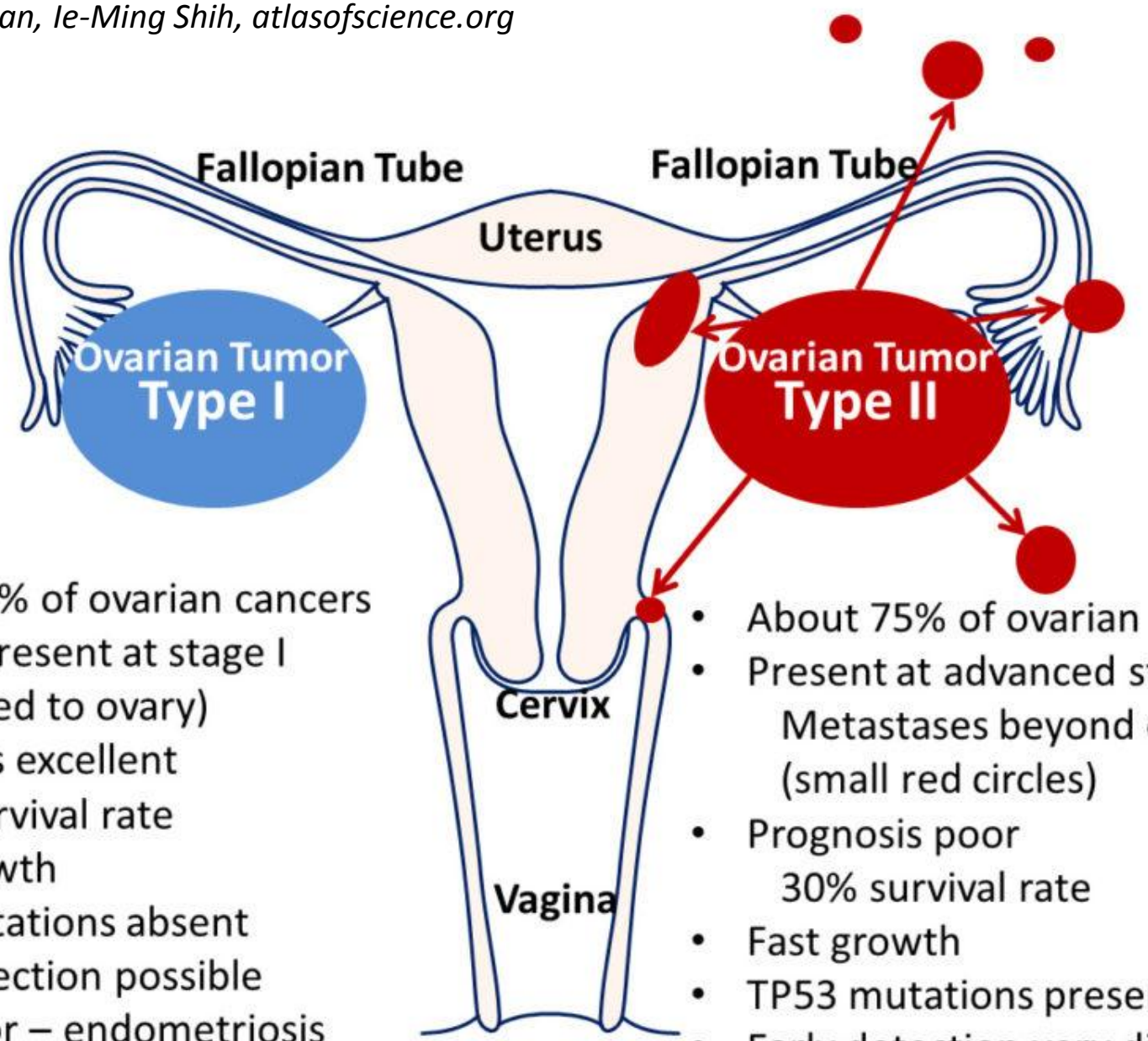
Source: GLOBOCAN 2012 (IARC)

Figure 1 Ovarian cancer incidence exhibits wide geographic variation.



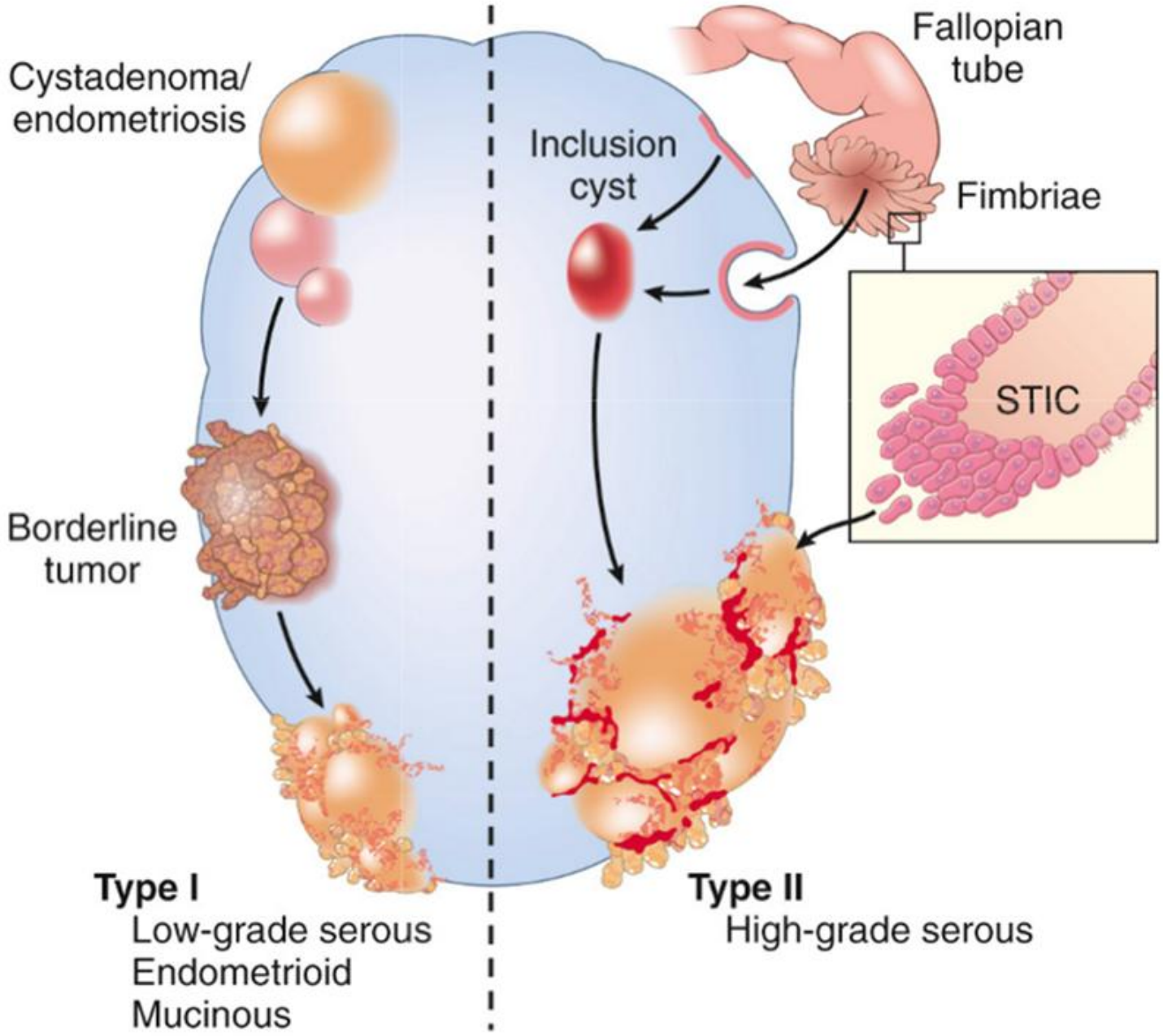
Veronica Rojas et al. Int. J. Mol. Sci. 2016, 17, 2113.

Robert J. Kurman, Ie-Ming Shih, atlasofscience.org

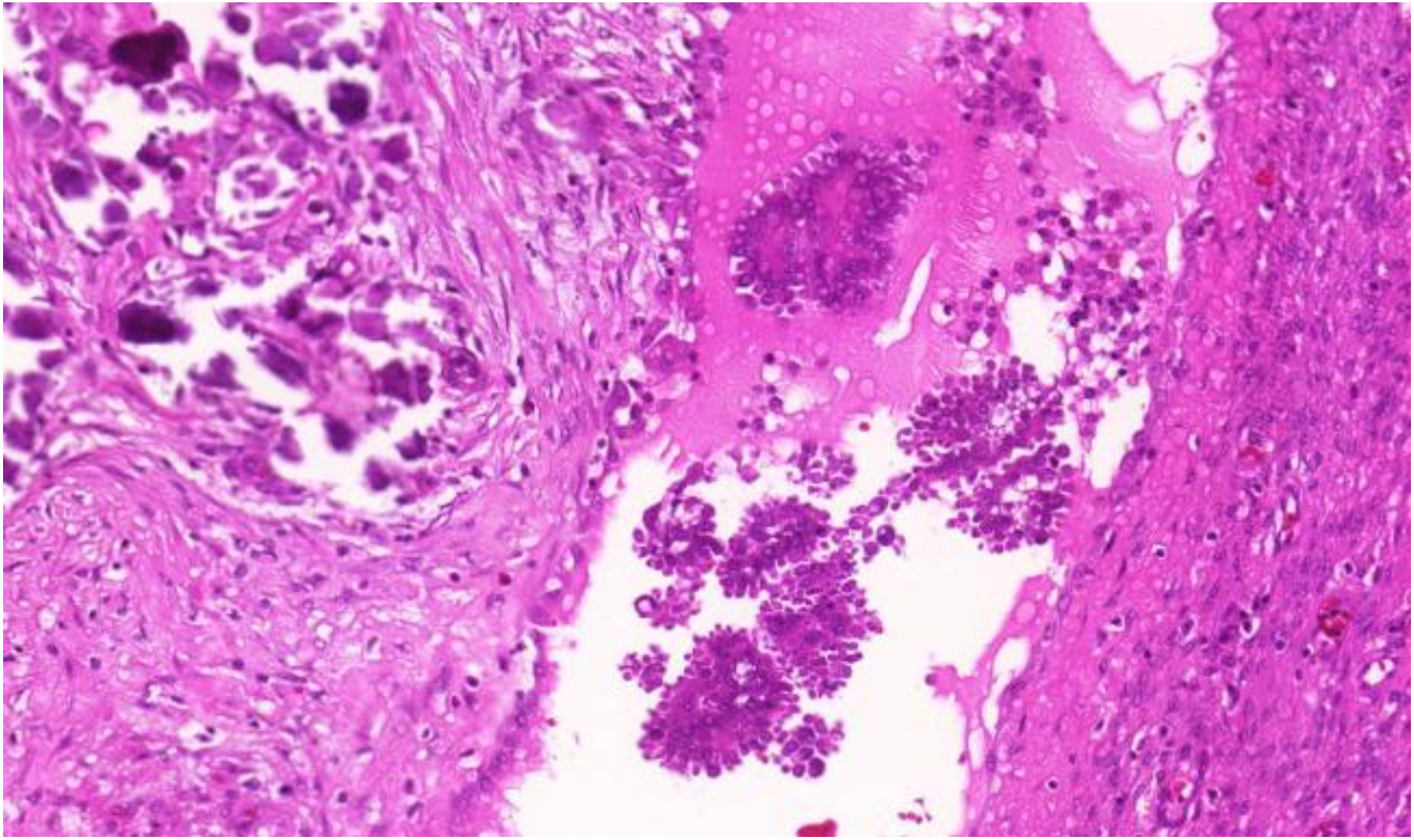


- About 25% of ovarian cancers
- Usually present at stage I
  (confined to ovary)
- Prognosis excellent
  90% survival rate
- Slow growth
- TP53 mutations absent
- Early detection possible
- Risk factor – endometriosis
  in some cases

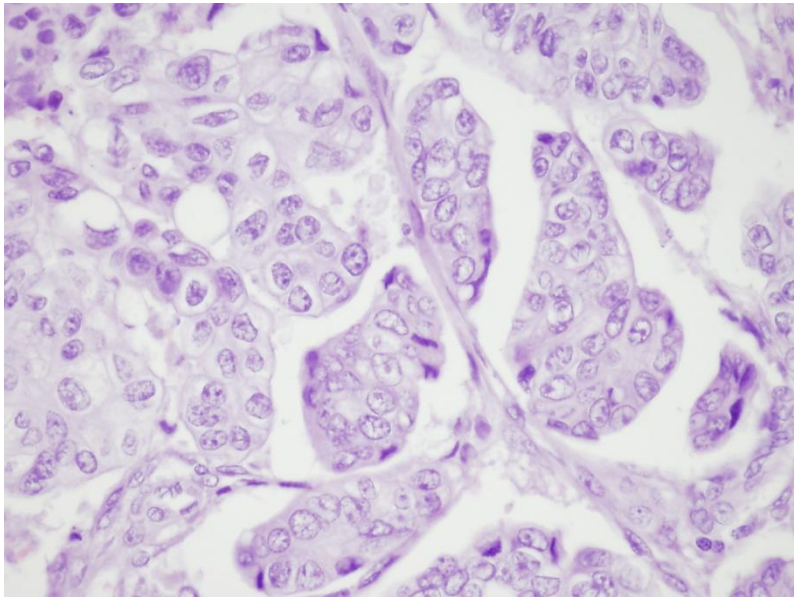
- About 75% of ovarian cancers
- Present at advanced stage
  Metastases beyond ovary
  (small red circles)
- Prognosis poor
  30% survival rate
- Fast growth
- TP53 mutations present
- Early detection very difficult
- Risk factor – BRCA mutation
  in some cases (usually inherited)

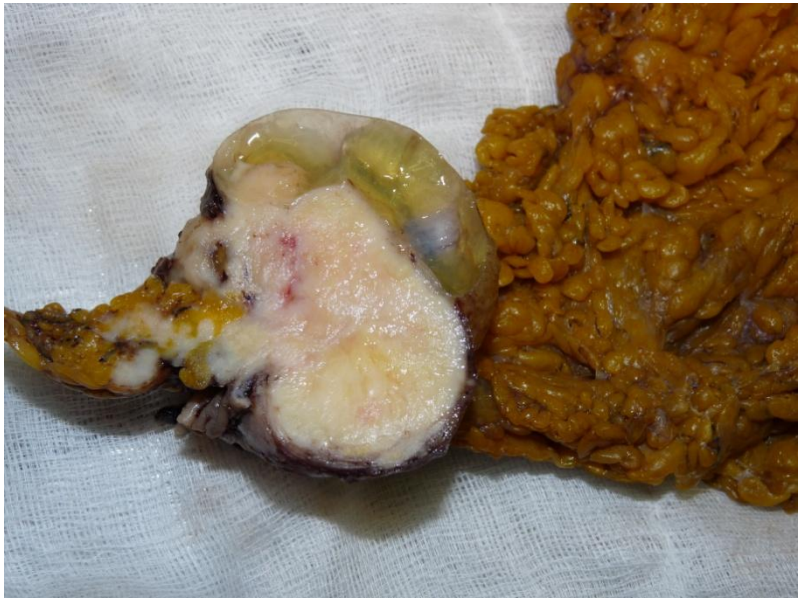

Cystadenoma/
endometriosis
Inclusion
cyst
Fallopian
tube
Fimbriae
STIC
Borderline
tumor
Type I
Low-grade serous
Endometrioid
Mucinous
Type II
High-grade serous

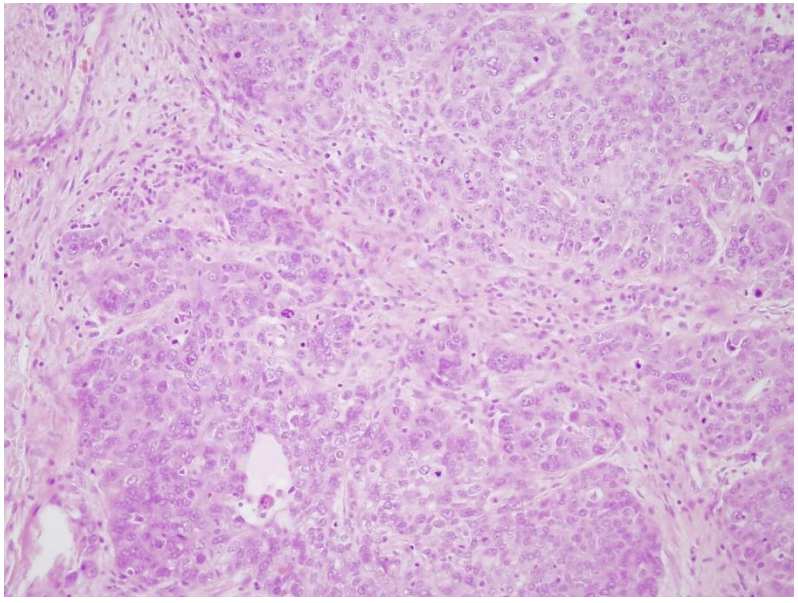
Low grade serous carcinoma



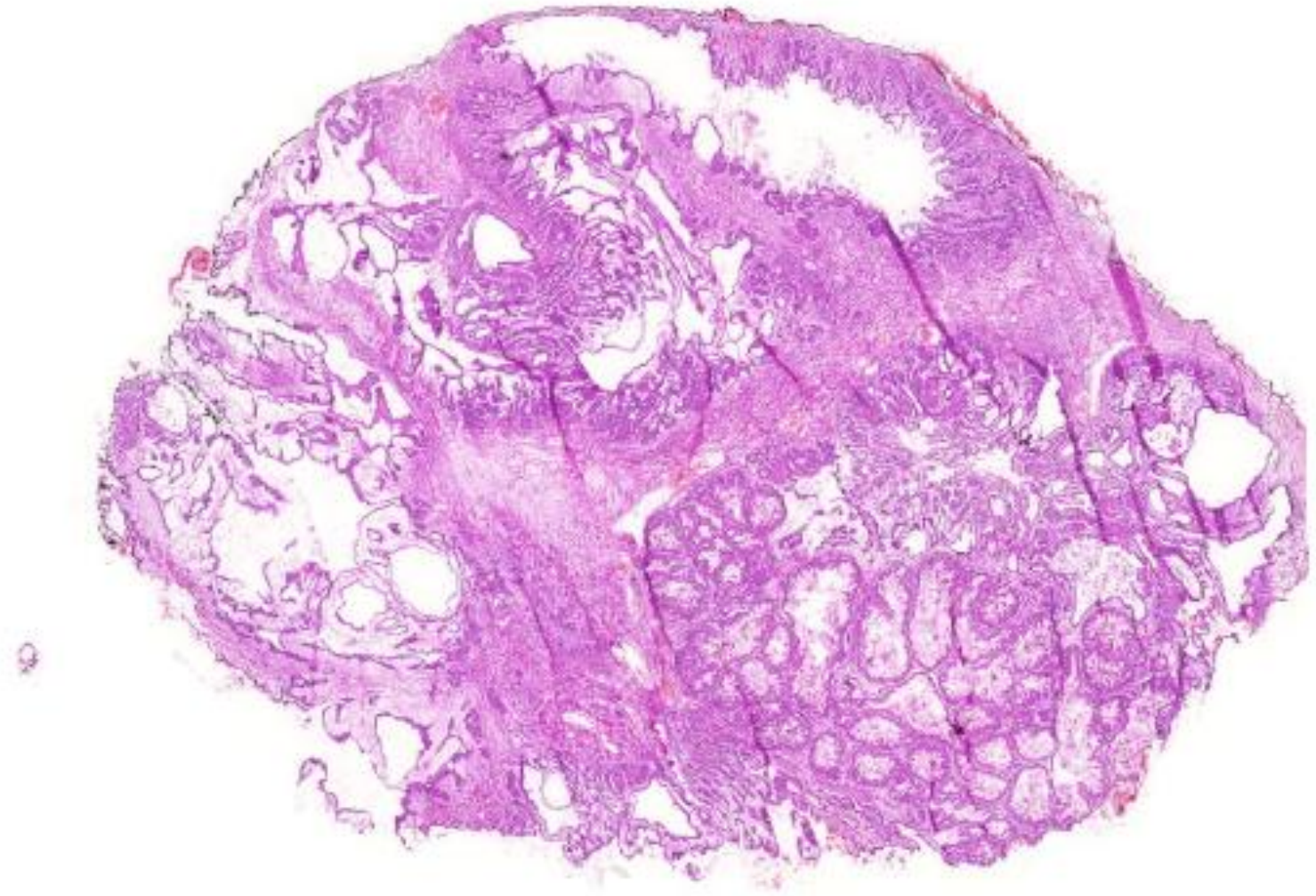
High grade serous carcinoma





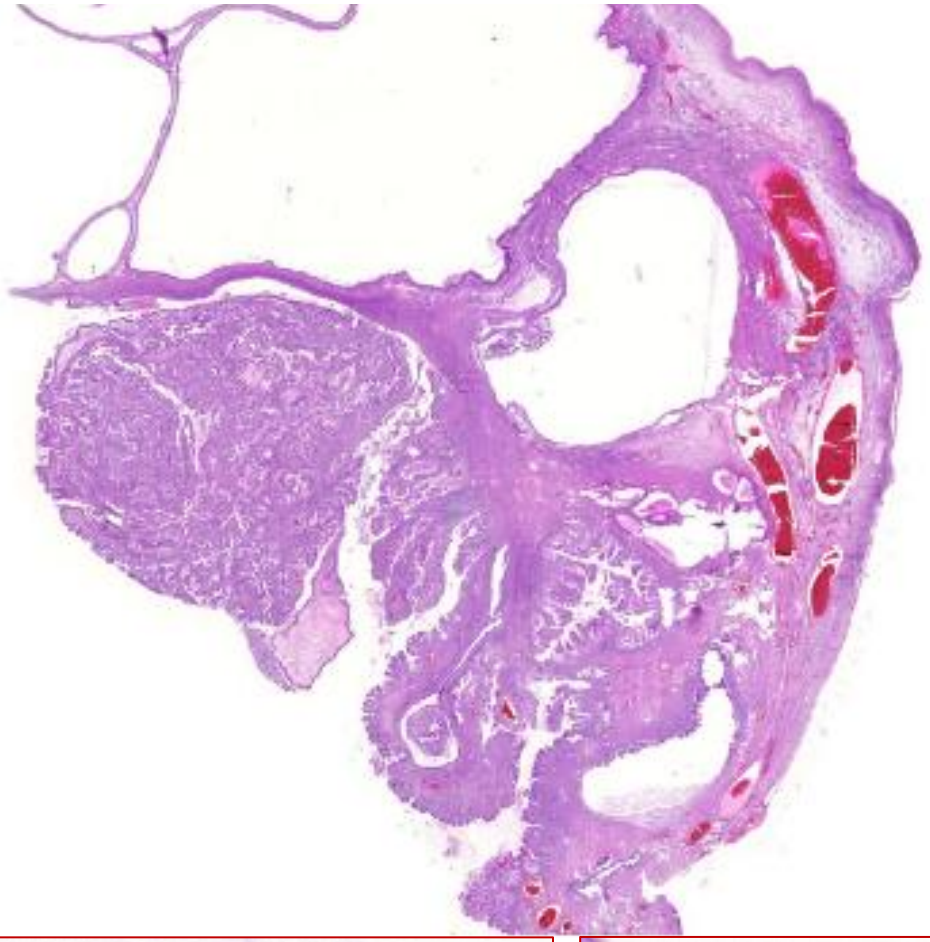


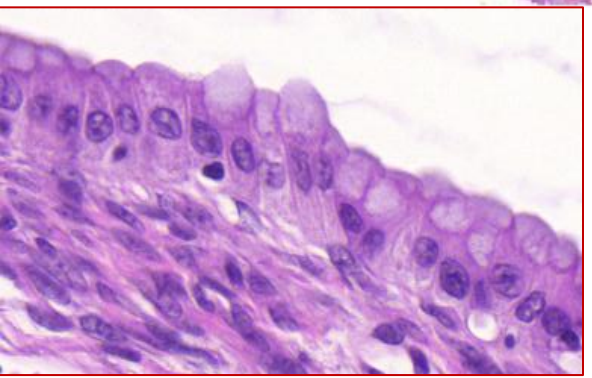
Frozen section – ovarian cystic tumor

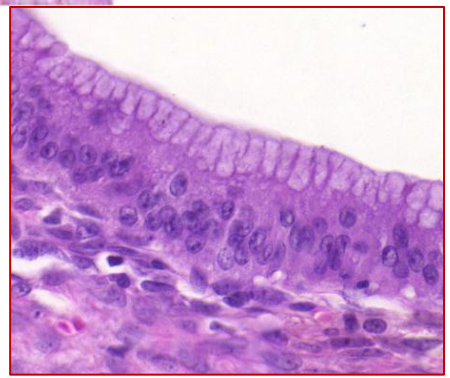


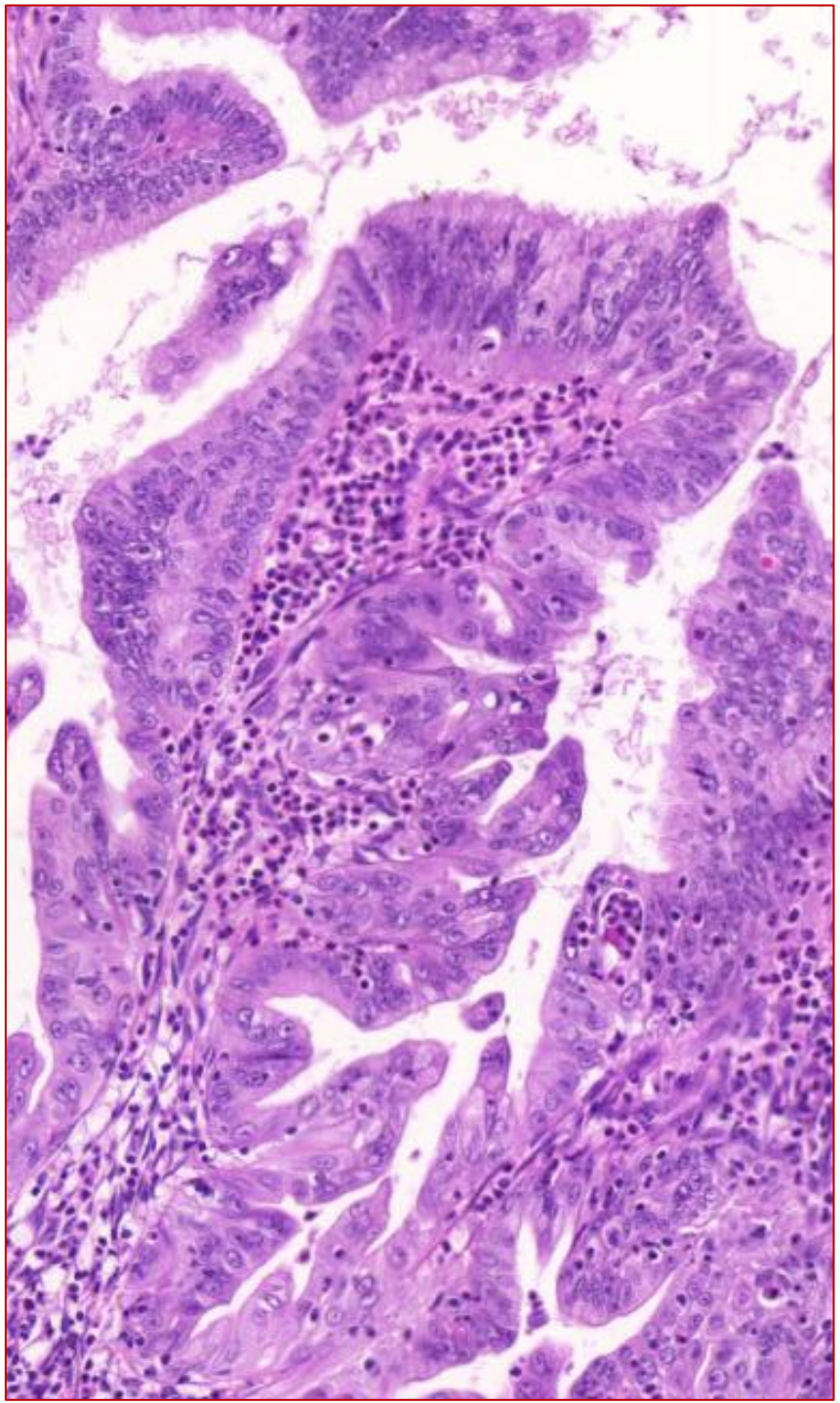
Differential diagnosis: Metastatic mucin-producing adenocarcinoma (e.g. colon adenocarcinoma)

Mucinous cystadenocarcinoma

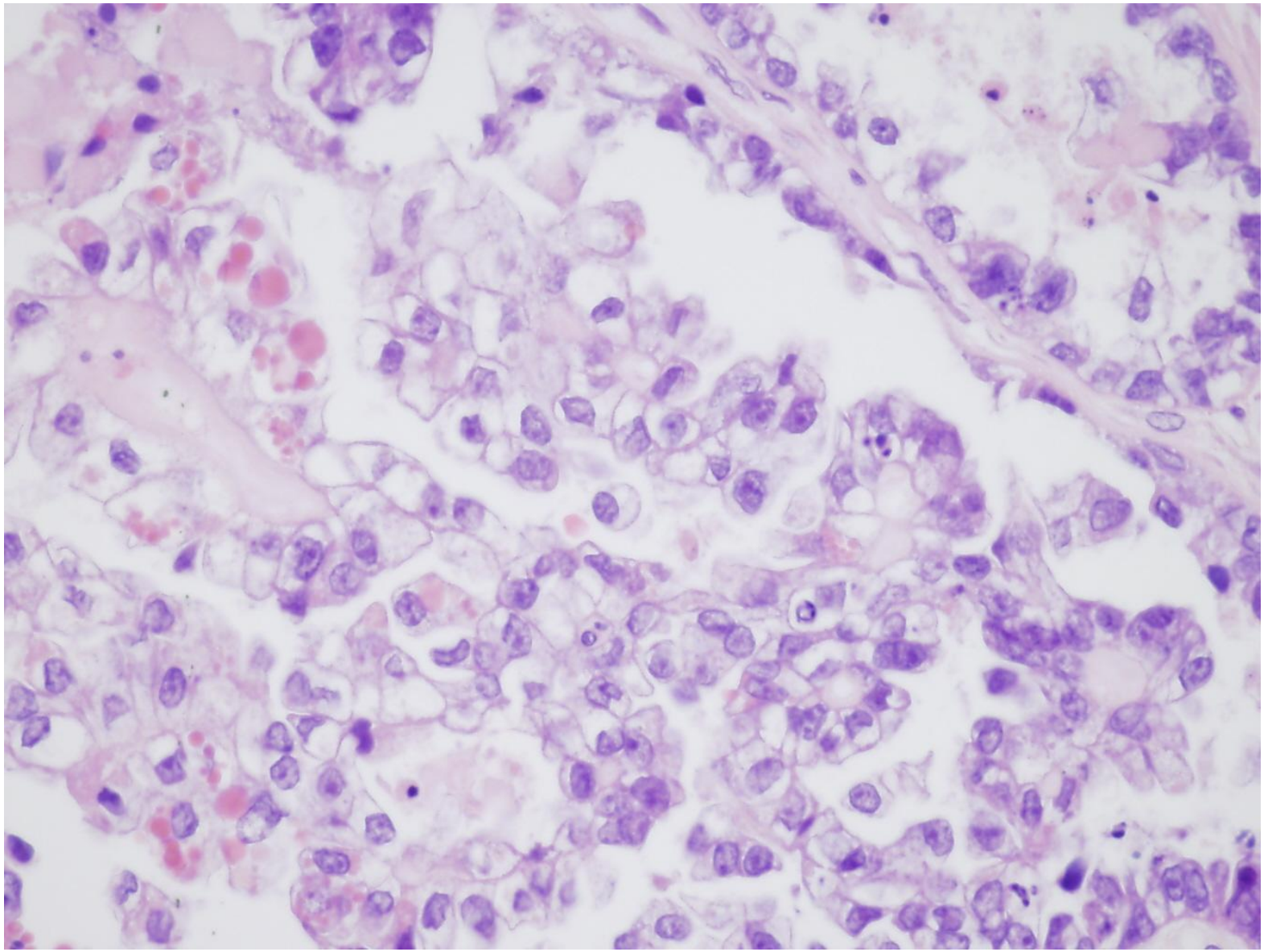






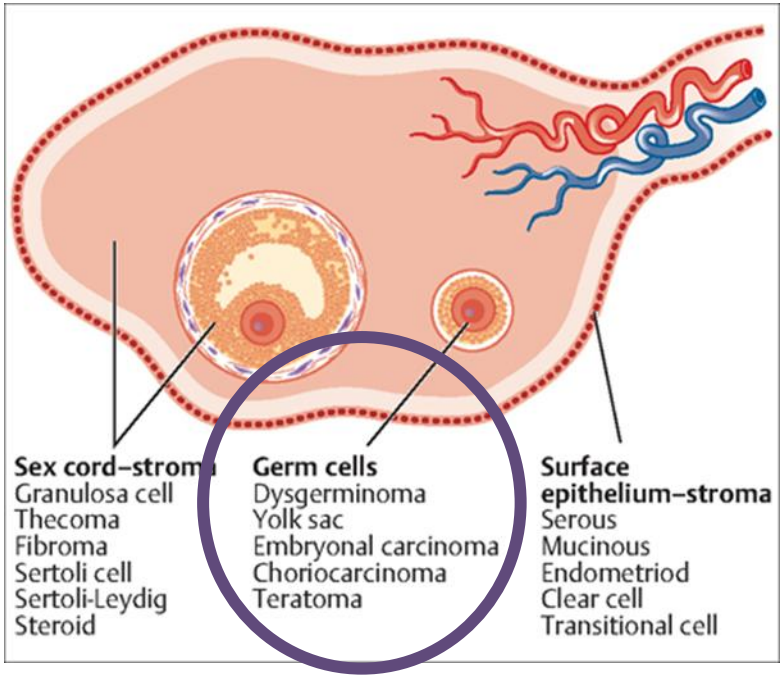


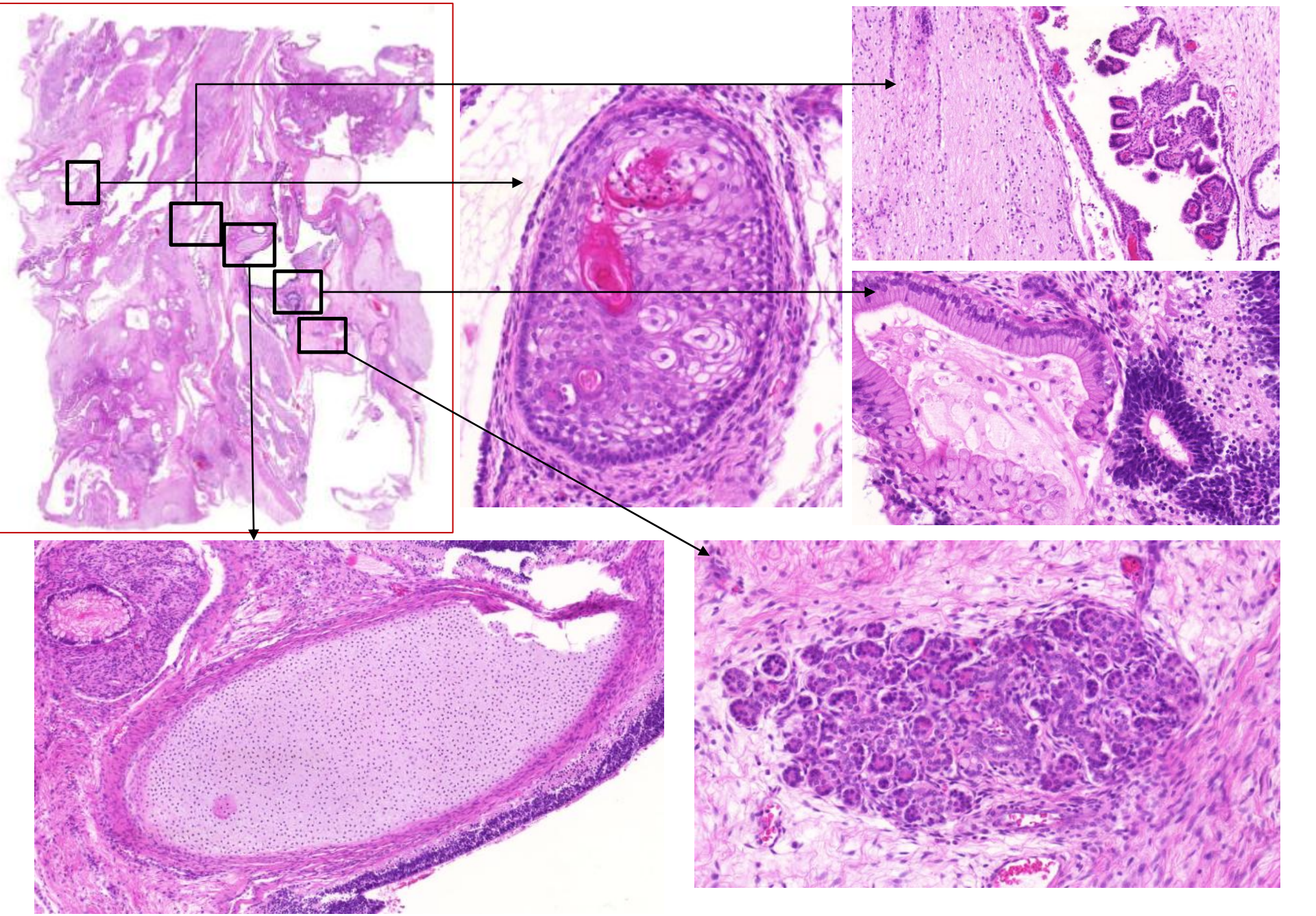
Clear cell carcinoma



GERM CELL TUMORS

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





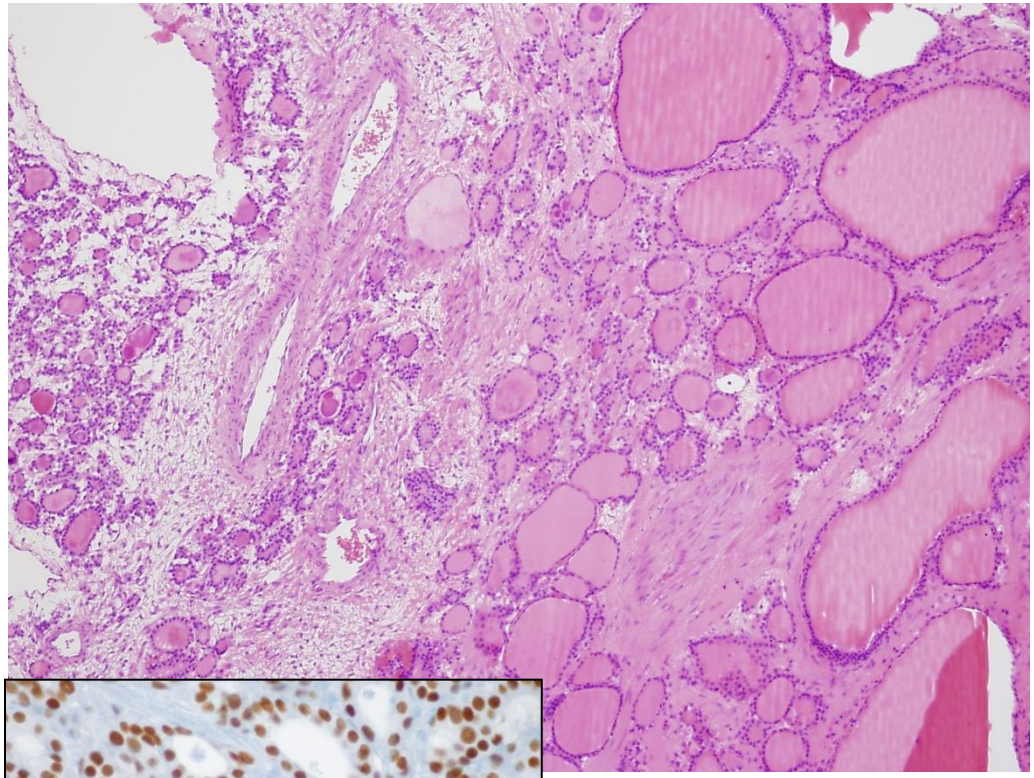
Immature teratoma

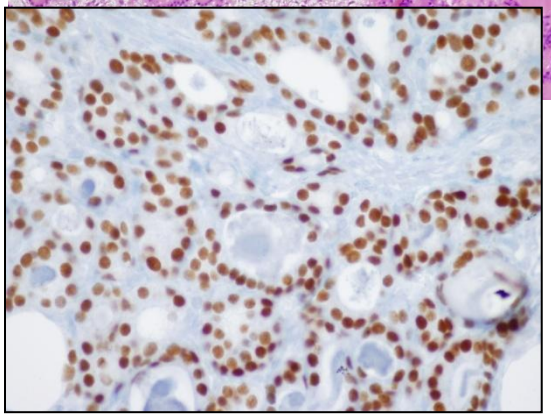
Table 1.2 Grading of ovarian immature teratomas using a three-tiered grading system compiled from {1382}

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).

World Health Organization Classifi cation of Tumours, 2014

- **Monodermal teratoma**
  - Struma ovarii
  - Carcinoid ovarii





TTF-1 immunohistochemical reaction

Dysgerminoma

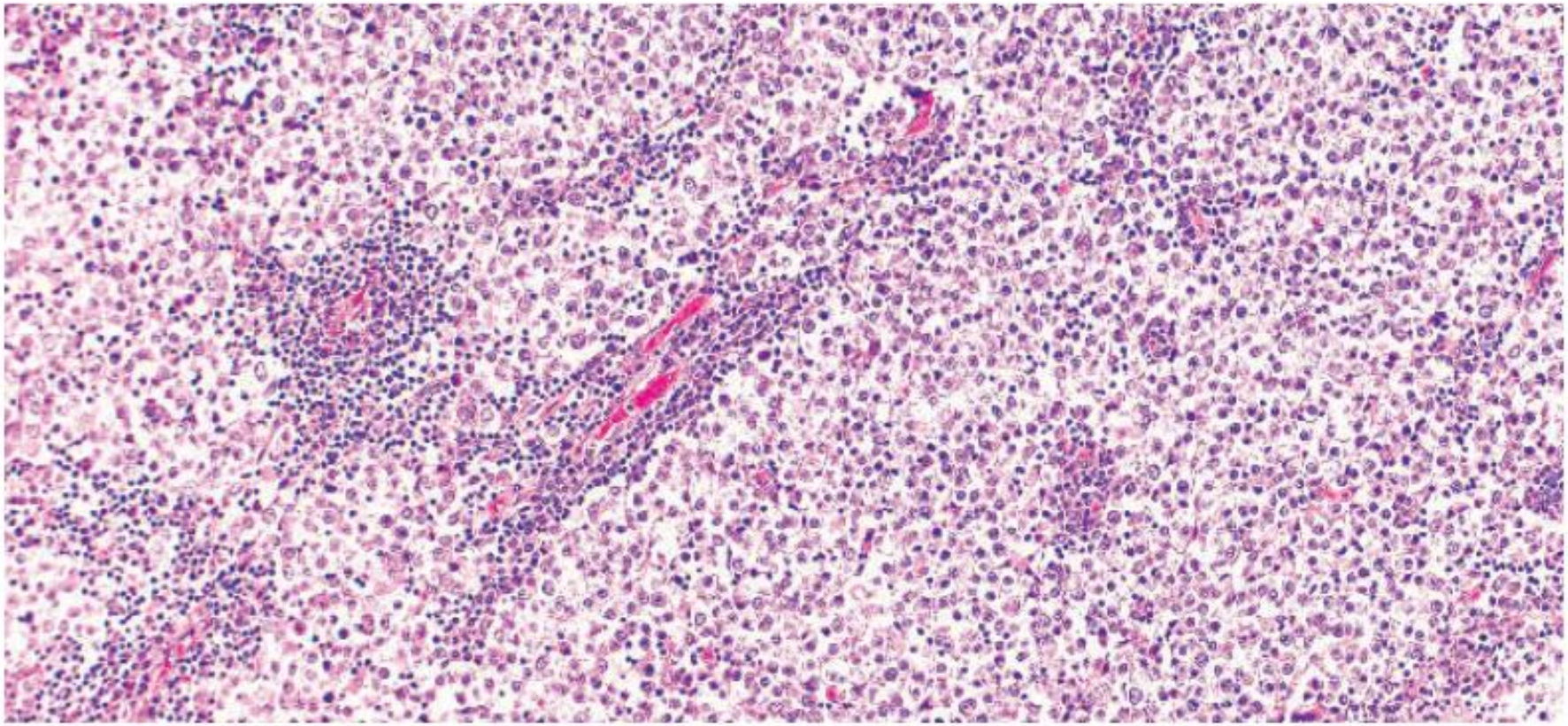


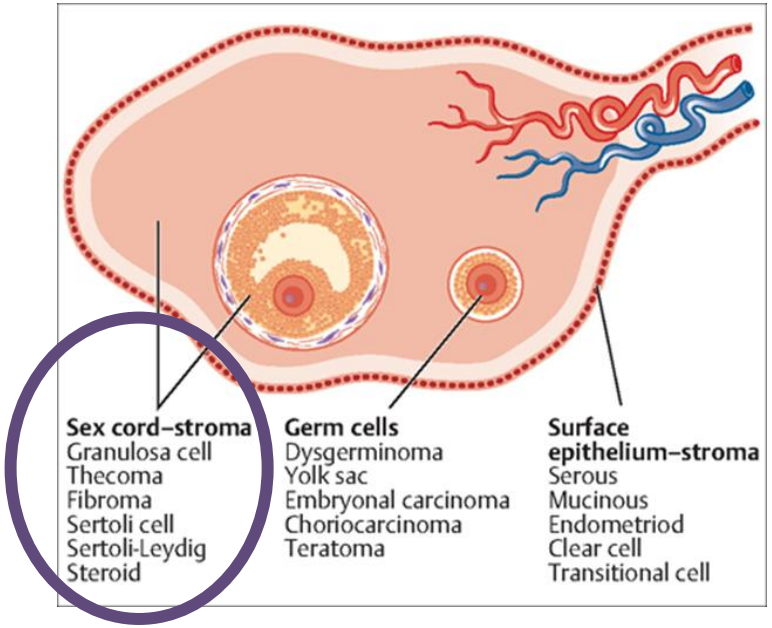
Fig. 1.53 Dysgerminoma. Nests and sheets of dysgerminoma cells are separated by fibrous septa containing lymphocytes

World Health Organization Classifi cation of Tumours, 2014

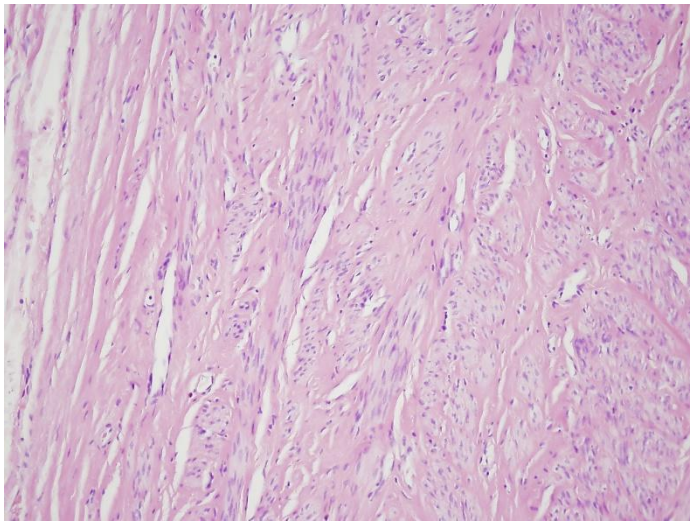
- Embryonal carcinoma
- Yolk sac tumor
- Non-gestational choriocarcinoma

SEX-CORD/STROMAL TUMORS

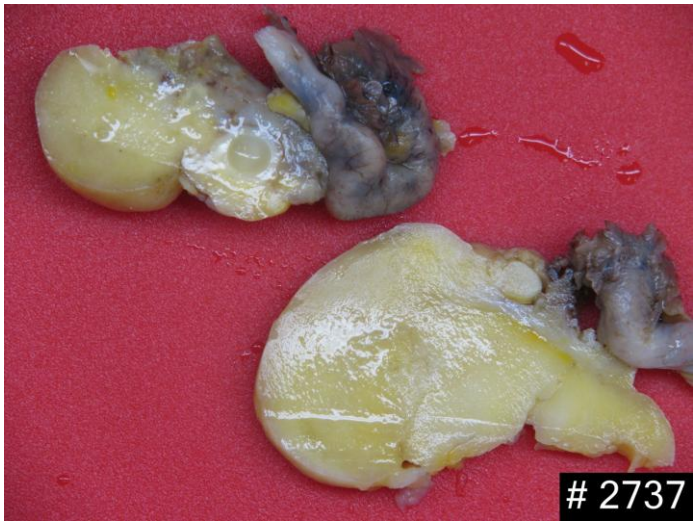
- Fibroma
- Thecoma
- Theco-fibroma
- Granulosa cell tumors
  - Juvenile granulosa cell tumors
- Sertoli cell tumors
- Leydig cell tumors

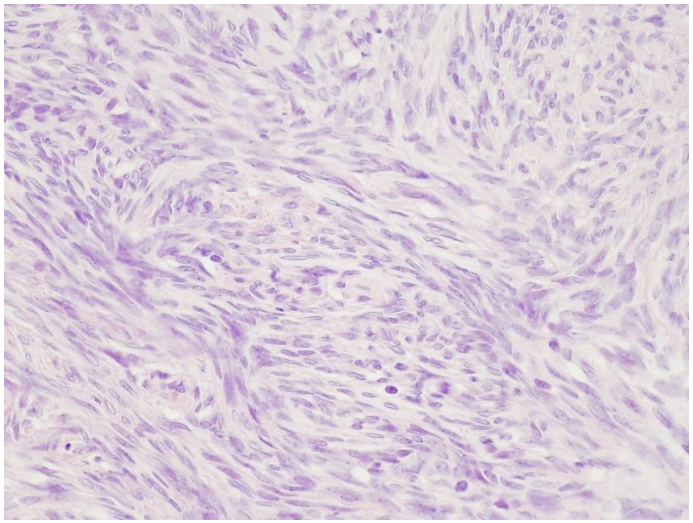


Fibroma



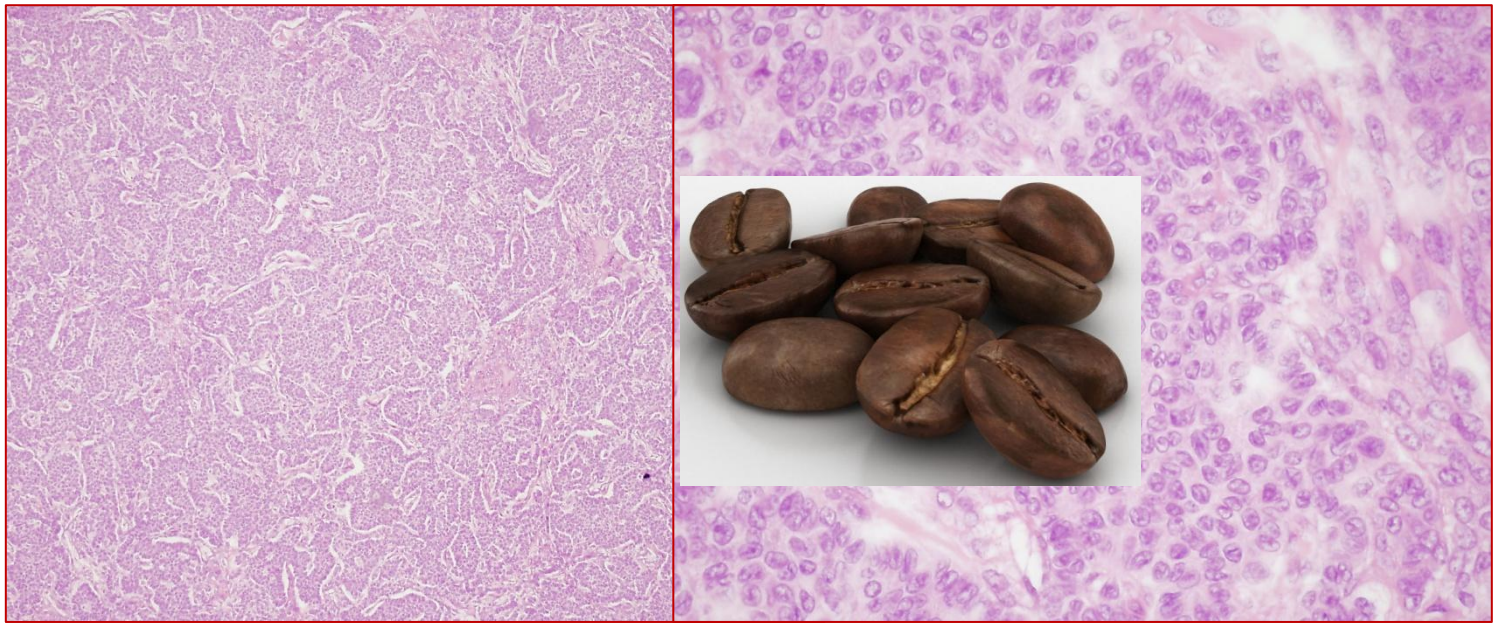
Thecofibroma



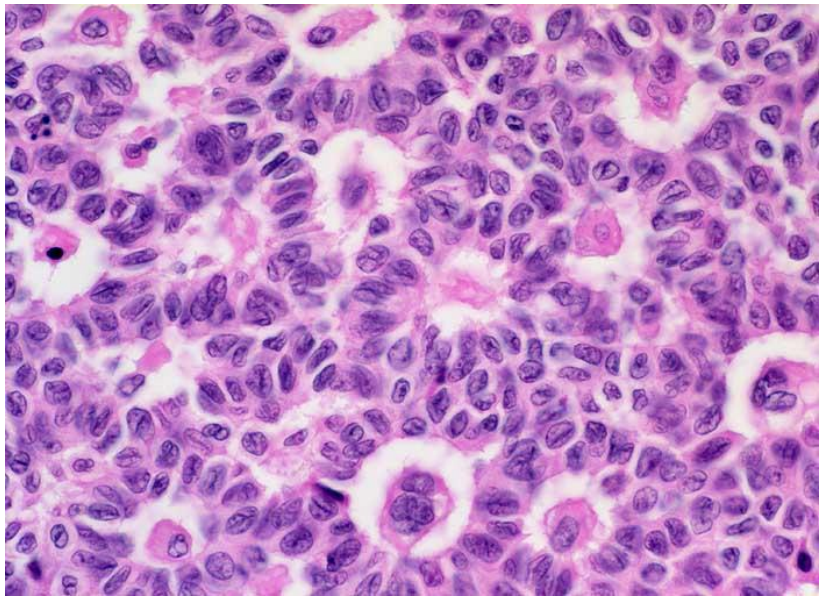


Meigs syndrome: Associated hydrothorax

Granulosa cell tumor

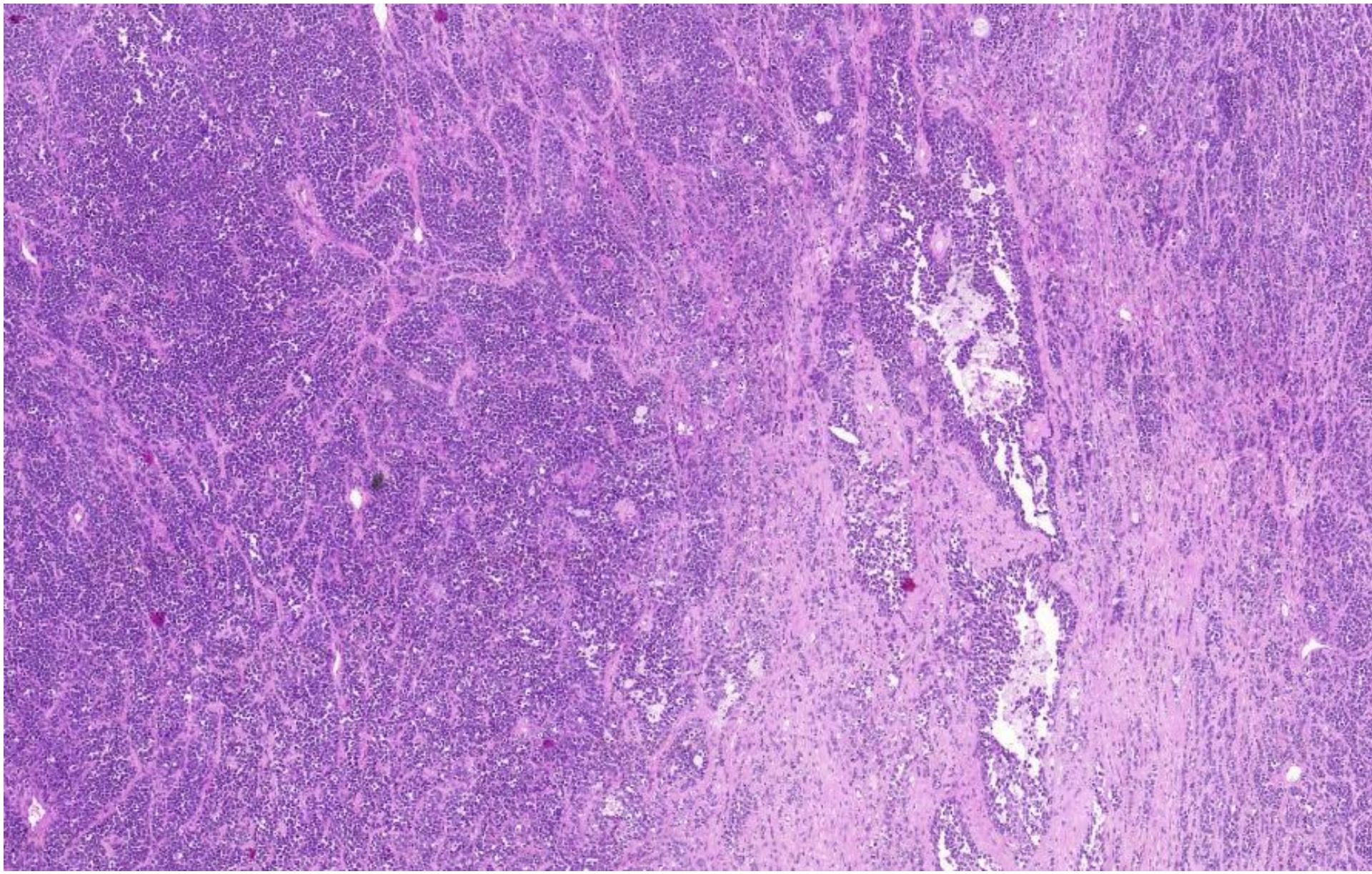


Call-Exner bodies



http://upload.medbullets.com/topic/116039/images

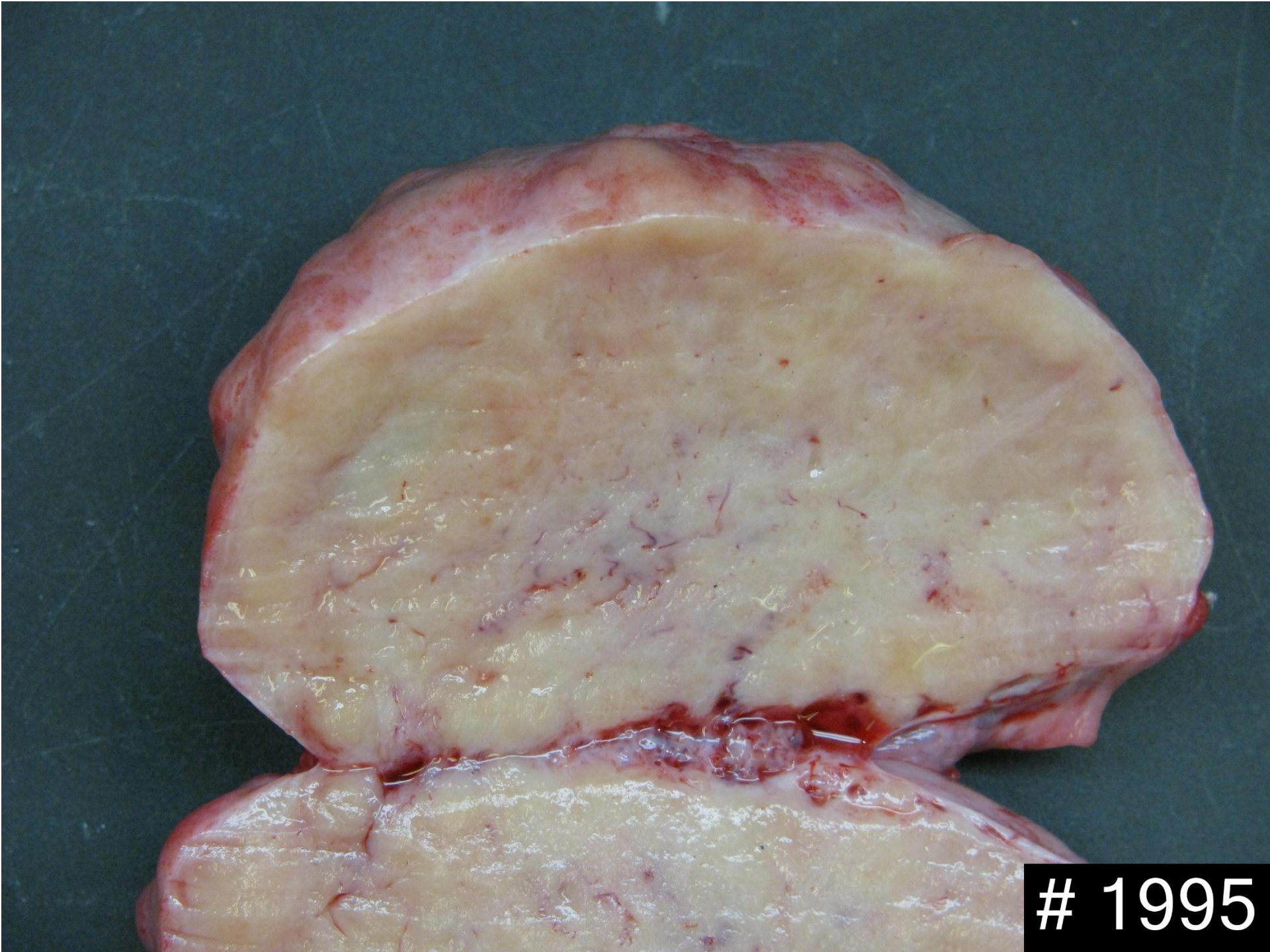
MISCELLANEOUS TUMORS



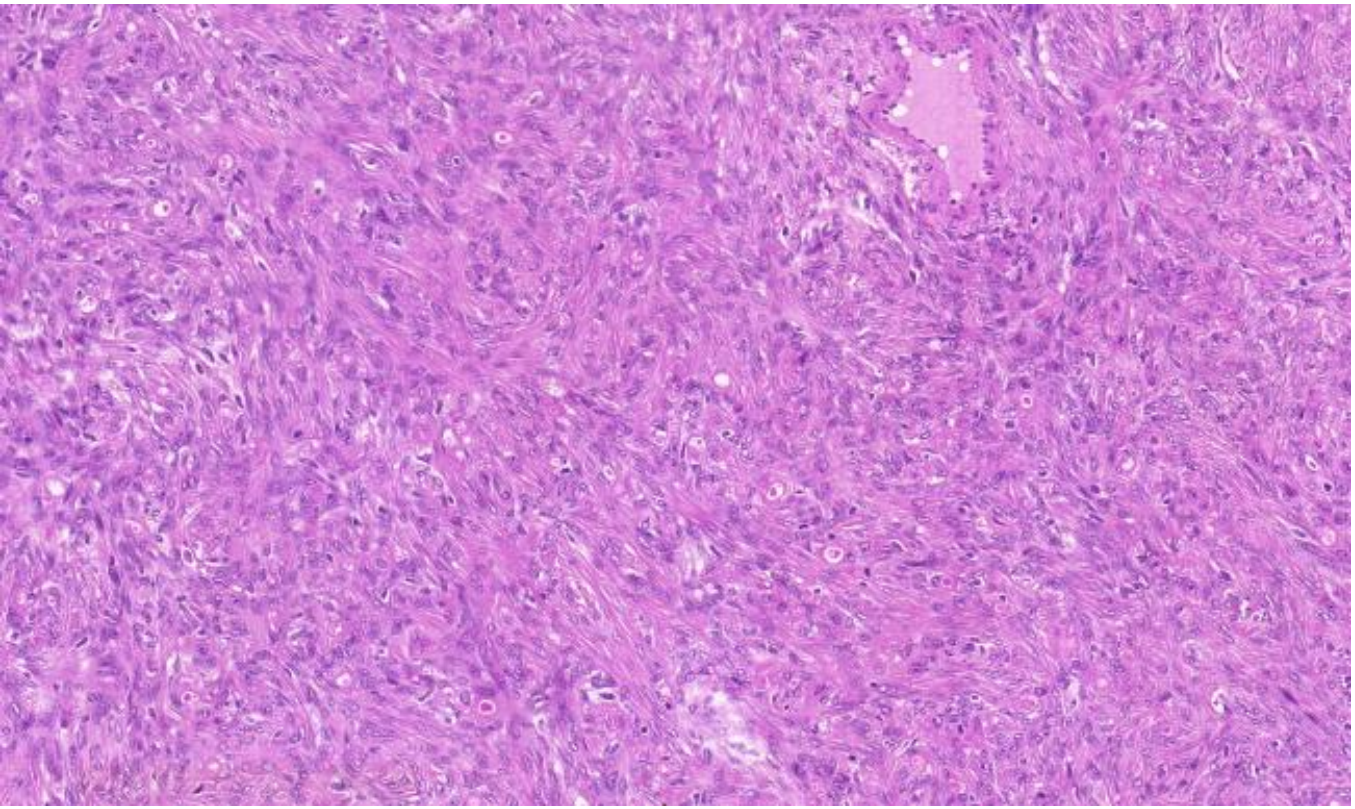
Small cell hypercalcaemic tumor diagnosed in a pregnant young woman

METASTATIC TUMORS

5% of all malignant ovarian tumors
>50% bilateral
Mostly from GI tract, breast, lung
Mucinous adenocarcinoma metastasis to the ovaries: *Krukenberg tumor*

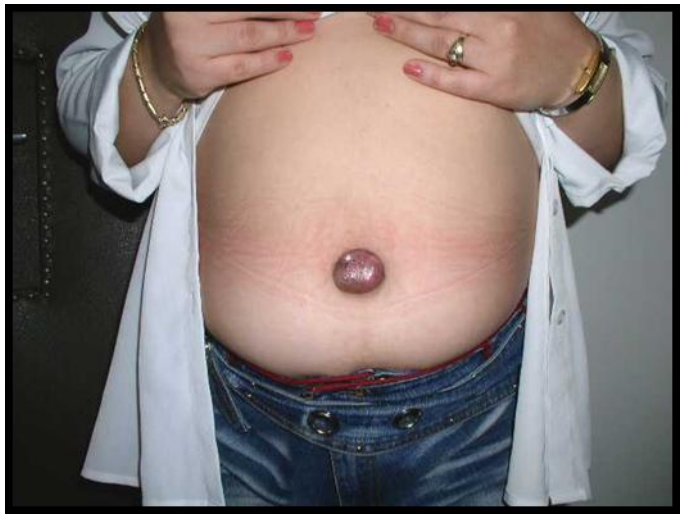

1995

45 y, pelvic mass, clinically benign



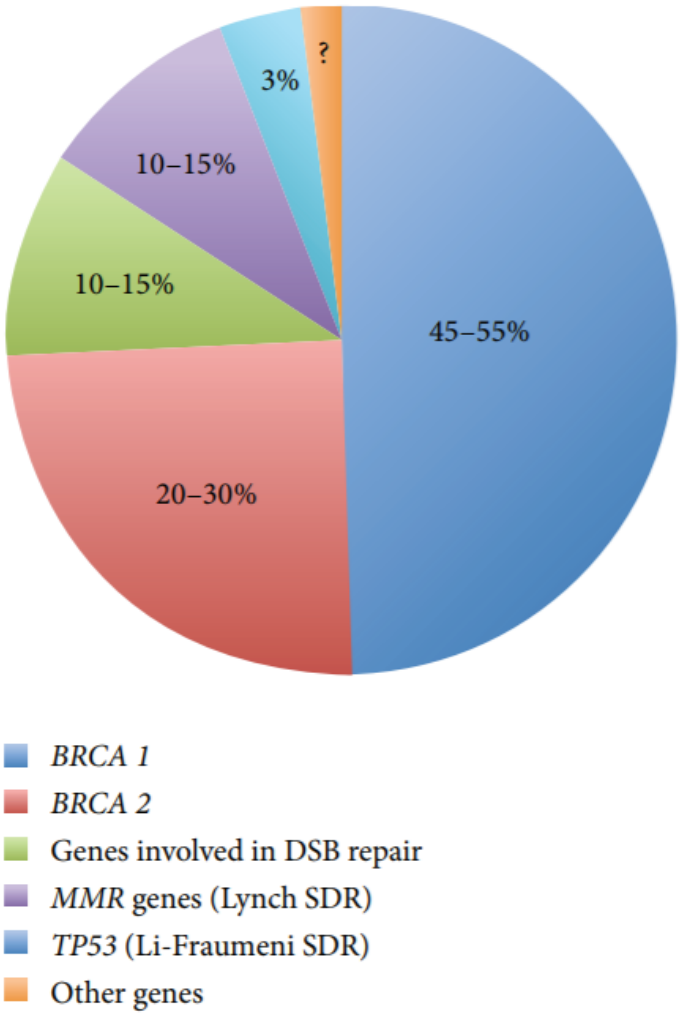
Metastatic spread of ovarian primary cancers

- Peritoneal surface
  - Ascites
- Opposite ovary
- Distant lymph nodes
- Liver
- Spleen and
- *Sister Mary Joseph nodule*



Genetics and ovarian cancer

- **Hereditary** OC syndromes/germline mutations



Angela Toss et al. BioMed Research International Volume 2015, Article ID 341723

Table 2. Genetic Syndromes with Increased Risk of Ovarian Cancer

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

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

Doubeni CA et al Am Fam Physician. 2016;93(11):937-944

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		
BRAF	33% [a]; 38% [b]; 16% [c]	0% [e]; 1% [f]	24% [a]	0% [k]; 23% [l]; 5% [m];
KRAS	19% [b]; 35% [a]; 21% [c]	<1% [a]; 7% [f]	<1% [a]	50% [k]; 68% [n]; 65% [m]
PIK3CA	11% [b]	25% [e]; 33% [f]	12% [e]	14% [m]
PTEN	20% [d]	0% [e]; 5% [f]	14% [j]; 31% [e]	3% [m]
ARID1A	–	46% [g]; 57% [h]	30% [g]	9% [l]
CTNNB1	–	0% [e]; 3% [f]	23% [e]; 24% [j]	5% [m]
CDKN2A	–	–	–	19% [m]
TP53	–	–	–	57% [m]; 52% [l]
		Copy number alterations		
ERBB2 (HER2; gain)	–	14% [i]	–	12% [m]; 19% [o]

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

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Type II (high grade) ovarian cancers

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

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

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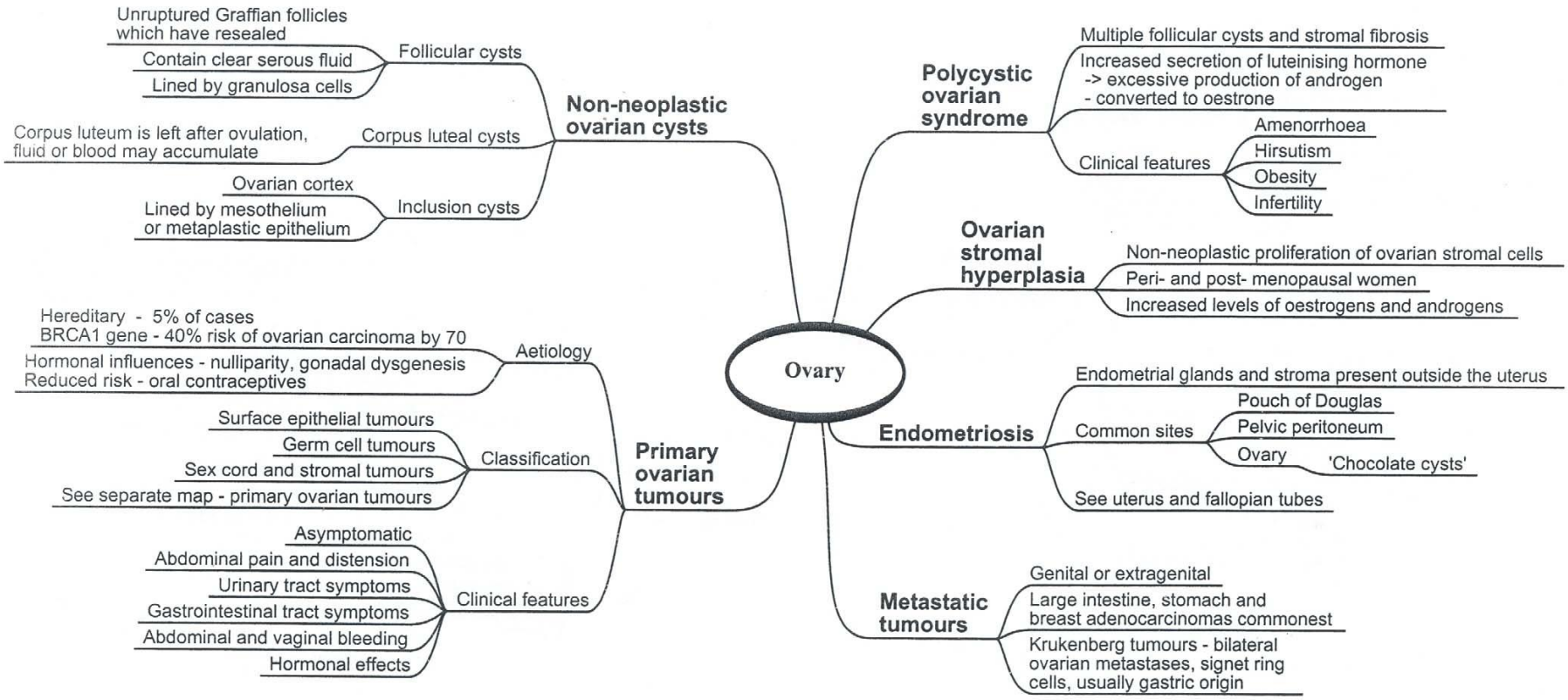
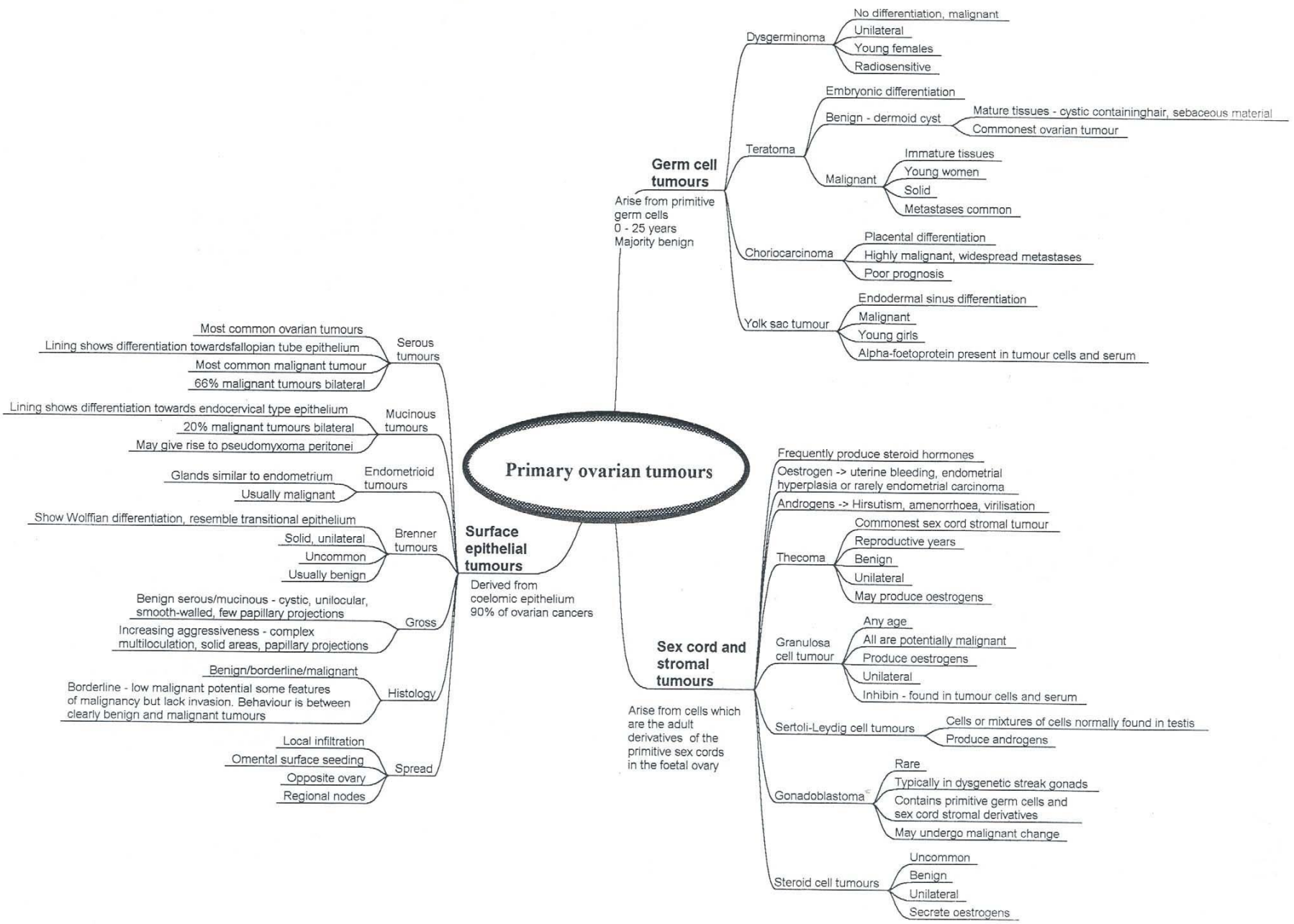

Ovary
Non-neoplastic ovarian cysts
Follicular cysts
Unruptured Graffian follicles which have resealed
Contain clear serous fluid
Lined by granulosa cells
Corpus luteal cysts
Corpus luteum is left after ovulation, fluid or blood may accumulate
Inclusion cysts
Ovarian cortex
Lined by mesothelium or metaplastic epithelium
Polycystic ovarian syndrome
Multiple follicular cysts and stromal fibrosis
Increased secretion of luteinising hormone -> excessive production of androgen - converted to oestrone
Clinical features
Amenorrhoea
Hirsutism
Obesity
Infertility
Ovarian stromal hyperplasia
Non-neoplastic proliferation of ovarian stromal cells
Peri- and post- menopausal women
Increased levels of oestrogens and androgens
Endometriosis
Endometrial glands and stroma present outside the uterus
Common sites
Pouch of Douglas
Pelvic peritoneum
Ovary
'Chocolate cysts'
See uterus and fallopian tubes
Metastatic tumours
Genital or extragenital
Large intestine, stomach and breast adenocarcinomas commonest
Krukenberg tumours - bilateral ovarian metastases, signet ring cells, usually gastric origin
Primary ovarian tumours
Aetiology
Hereditary - 5% of cases
BRCA1 gene - 40% risk of ovarian carcinoma by 70
Hormonal influences - nulliparity, gonadal dysgenesis
Reduced risk - oral contraceptives
Classification
Surface epithelial tumours
Germ cell tumours
Sex cord and stromal tumours
See separate map - primary ovarian tumours
Clinical features
Asymptomatic
Abdominal pain and distension
Urinary tract symptoms
Gastrointestinal tract symptoms
Abdominal and vaginal bleeding
Hormonal effects


Primary ovarian tumours
Germ cell tumours
Arise from primitive germ cells
0 - 25 years
Majority benign
Dysgerminoma
No differentiation, malignant
Unilateral
Young females
Radiosensitive
Teratoma
Embryonic differentiation
Benign - dermoid cyst
Mature tissues - cystic containinghair, sebaceous material
Commonest ovarian tumour
Malignant
Immature tissues
Young women
Solid
Metastases common
Choriocarcinoma
Placental differentiation
Highly malignant, widespread metastases
Poor prognosis
Yolk sac tumour
Endodermal sinus differentiation
Malignant
Young girls
Alpha-foetoprotein present in tumour cells and serum
Surface epithelial tumours
Derived from coelomic epithelium
90% of ovarian cancers
Serous tumours
Most common ovarian tumours
Lining shows differentiation towardsfallopian tube epithelium
Most common malignant tumour
66% malignant tumours bilateral
Mucinous tumours
Lining shows differentiation towards endocervical type epithelium
20% malignant tumours bilateral
May give rise to pseudomyxoma peritonei
Endometrioid tumours
Glands similar to endometrium
Usually malignant
Brenner tumours
Show Wolffian differentiation, resemble transitional epithelium
Solid, unilateral
Uncommon
Usually benign
Gross
Benign serous/mucinous - cystic, unilocular, smooth-walled, few papillary projections
Increasing aggressiveness - complex multiloculation, solid areas, papillary projections
Histology
Benign/borderline/malignant
Borderline - low malignant potential some features of malignancy but lack invasion. Behaviour is between clearly benign and malignant tumours
Spread
Local infiltration
Omental surface seeding
Opposite ovary
Regional nodes
Sex cord and stromal tumours
Arise from cells which are the adult derivatives of the primitive sex cords in the foetal ovary
Frequently produce steroid hormones
Oestrogen -> uterine bleeding, endometrial hyperplasia or rarely endometrial carcinoma
Androgens -> Hirsutism, amenorrhoea, virilisation
Thecoma
Commonest sex cord stromal tumour
Reproductive years
Benign
Unilateral
May produce oestrogens
Granulosa cell tumour
Any age
All are potentially malignant
Produce oestrogens
Unilateral
Inhibin - found in tumour cells and serum
Sertoli-Leydig cell tumours
Cells or mixtures of cells normally found in testis
Produce androgens
Gonadoblastoma
Rare
Typically in dysgenetic streak gonads
Contains primitive germ cells and sex cord stromal derivatives
May undergo malignant change
Steroid cell tumours
Uncommon
Benign
Unilateral
Secrete oestrogens

#1

DEADLIEST GYNECOLOGIC CANCER