Ovaries

Neoplasms of ovaries:

- May be **primary** (Benign or malignant)
  a. Tumours of the ovary may arise from any of the three cell types in the normal ovary:
    i. **Germinal** epithelial layer - 1
      1. Accounts for almost 90% of ovarian cancers, age **>40** years
      2. The protein CA-125, is elevated in the sera of **75% to 90% of women with epithelial ovarian cancer**
        1. Currently, CA-125 measurements are of the greatest value in monitoring response to therapy not for diagnosis since its nonspecific.
        2. CA-125 is **too nonspecific and insensitive** for screening or diagnosis. But **very useful to track known disease** over time.
        3. It often is elevated in a **variety of benign conditions and nonovarian cancers**. Pancreatic carcinoma.
        4. Its usefulness as a screening test in asymptomatic postmenopausal women is limited

    ii. **Germ** cells - 2
      1. The most common ovarian tumour in **young** women; the vast majority are benign.
        1. Predilection to arise in the first 2 decades of life;
        2. Less than 10% of malignant tumours of the ovary.
          1. The younger the person, the greater the likelihood of malignancy (premature = worse prognosis opposite to what was mentioned in the testes)
          2. More than 90% of these germ cell neoplasms are benign mature cystic teratomas
          3. The immature, malignant variant is rare

    iii. **Stromal** cells - 3
      1. Sex cord stromal tumours
      2. Less than 10% of malignant tumours of the ovary. Least common.

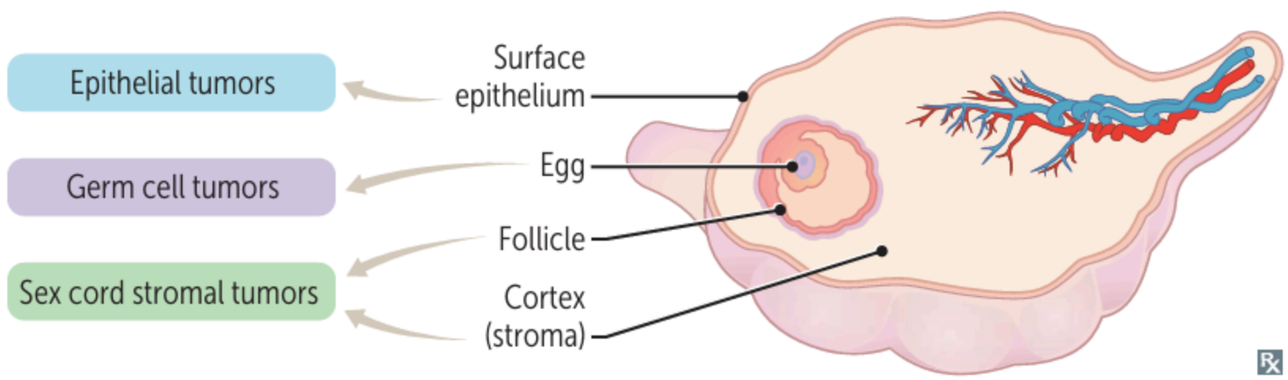
- May be **secondary** (Malignant 2*)
  a. 15% to 30% of women with these ovarian tumours have **concomitant endometrial carcinoma**
  b. Mostly older age
  c. Mostly bilaterally
  d. GI tumours krukenburg, breast, lungs
  e. Anaplastic tumour, cells, cord, glands, dispersed through a fibrous background, cells may be signet ring mucins secreting cells
  f. ↗ ^c17125

Bilateral in cases of:

(1) High grade
(2) Malignant 2*
(3) Metastasis

Tumor Type	Serum Marker
Serous (MC epithelial)	**CA-125**
Mucinous	**CA 19-9**
Endodermal sinus (yolk sac)	**AFP**
Choriocarcinoma	**hCG**
Medullary thyroid	**Calcitonin**

Germ cells tumour	Stromal cells tumour	Germinal (Epithelial) cells tumour
Dysgerminoma - undifferentiated Malignant. Most common in adolescents. Equivalent to male seminoma but rarer. Sheets of uniform “fried egg” cells D. Tumor markers: hCG, LDH ARE elevated.	Fibroma	Serous
Yolk sac - extra-embryonic structures	Thecoma	Mucinous
Embryonal carcinoma	Granulosa	Endometroid
Choriocarcinoma	Sertoli-Leydig	Clear
Teratoma - somatic structures	Cortical	Transitional
Most of them are unilateral	Steroidal	Brenner tumour



In the germ cell tumour:

- In the testes we said that seminomas and the mix type are the most common.. while here in the ovaries we said its the teratoma
- The younger the person, the greater the likelihood of malignancy (premature = worse prognosis opposite to what was mentioned in the testes)
- In the testes we said that immature or mature does not affect prognosis while in the ovaries it does, where the immature ones are mostly malignant

NOTES:

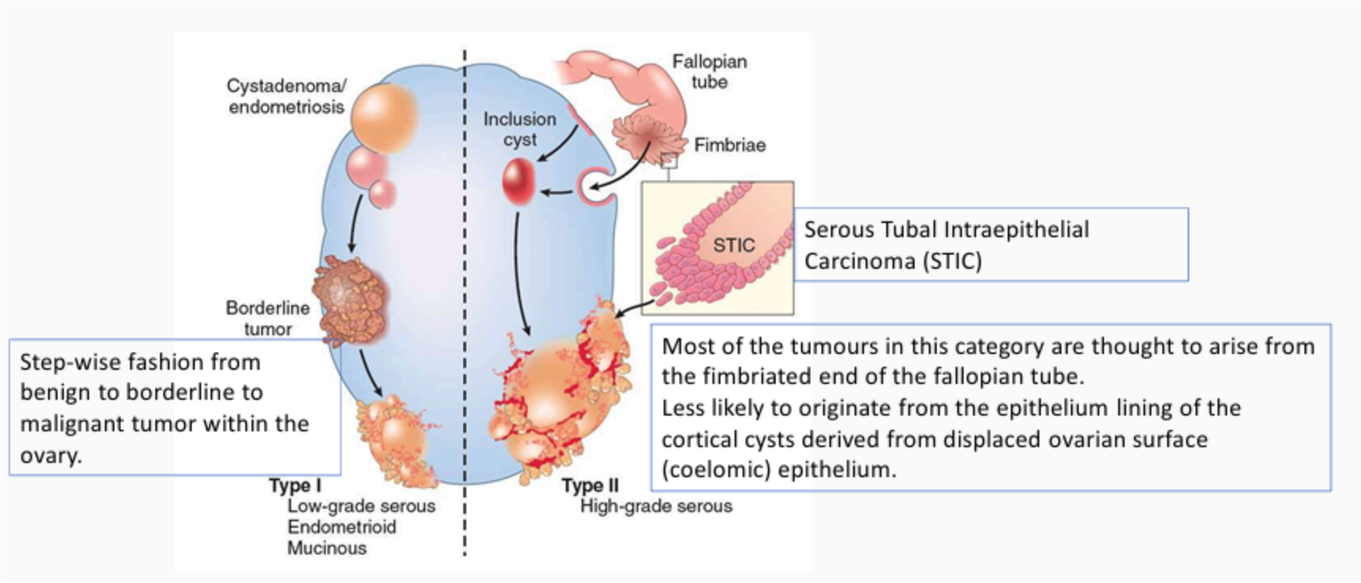
MOST COMMON OVARIAN NEOPLASM IS THE SEROUS CYSTADENOMA
MOST COMMON MALIGNANT OVAIRAN NEOPLASM IS THE SEROUS CARINOMA
MOST COMMON OVARIAN TUMOUR IN YOUNG FEMALES IS THE MATURE BENIGN TERATOMA

Teratomas	Benign (mature) cystic teratomas	Immature malignant teratomas	Specialized teratomas
Constitute 15% to 20% of ovarian tumours	Mature tissues are derived from all three germ cell layers ectoderm (skin, neural tissue), endoderm (lining of digestive and respiratory tract, organs like liver and pancreas), mesoderm (bone, muscle, connective tissue). Dermoid cyst:- Cysts lined by epidermis On cut section, they often are filled with sebaceous secretion and matted hair Sometimes there is a nodular projection from which teeth protrude Foci of bone and cartilage 90% are unilateral, with the right side more commonly affected May appear with monodermal form with thyroid tissue (struma ovarii)	Found early in life, the mean age at clinical detection being 18 years Age younger than mature teratoma They typically are bulky and appear solid on cut section, and they often contain areas of **necrosis** The distinguishing feature is the presence of immature elements---- primitive neuroepithelial elements "SMALL ROUND CELLS" The prognosis depends on grade and stage just like the serous, while the prognosis of mucinous carcinoma:- Stage rather than histologic type (serous versus mucinous) is the major determinant of outcome.	Rare subtype Composed entirely of specialized tissue The most common example is **struma** ovarii: Composed entirely of mature thyroid tissue--------hyperthyroidism ----- low TSH (negative feedback) Other specialized teratomas include ovarian carcinoid, which in rare instances produces carcinoid syndrome (flushing, diarrhea, wheezing, and heart problems)
Are sufficiently common to merit description	Ovarian masses Incidentally on abdominal radiographs/scans---calcification/toothlike structures May rapture, causes anaphylaxis due to sebum secretions Torsion (in 10%–15% of cases)----acute surgical emergency "May be painful 2˚ to ovarian enlargement or torsion" Rarely, paraneoplastic complication is limbic encephalitis teratomas containing mature neural tissue and often remits with tumour resection, due to auto antibodies -> secondary neurological and psycatric problems Malignant transformation, usually to a squamous cell carcinoma, is seen in about 1% of cases "Teratoma with malignant transformation: non–germ cell tumors may arise in teratoma (e.g. SCC)."		

HY TABLE - OVARIES NEOPLASMS:

Ovaries neoplasms
Nonfunctional, can't produce hormones because M.C cause is epithelial tumours
Most common adnexal mass in females > 55 years old.
Benign neoplasms may be asymptomatic and occasionally incidentally discovered on imaging or during operations
Produce mild symptoms until they reach large sizes. **MAINLY** mass effect. again, as most of them appear from the **epithelial germinal layer** of the ovaries.
Surface Epithelial Tumors: M.C and can be benign or malignant – M.C benign
Since it is most commonly to arise from the epithelium that covers the ovaries then it could be different depends on the type of the cell involved
It can be serous, mucinous, or endometrioid, depending on the type of epithelial lining
Serous tumors are lined by cuboidal cells that resemble surface (or tubal) epithelium -> High-grade tumors -> **Serous** = **Serious**
Mucinous tumors are lined by mucus-secreting cells similar to those of the endocervix -> Low-grade tumors
Endometrioid tumors are lined by glandular cells that resemble endometrial epithelium -> Low-grade tumors
Functioning ovarian tumours (that secrete hormones) often come to attention because of the endocrinopathies they produce. Estrogen or androgen, hairutusim.
Abdominal **pain**
Abdominal **distension**
Urinary frequency or GI symptoms due to **compression** or invasion
So, Present with abdominal distention, bowel obstruction, pleural effusion
Vaginal bleeding

HY TABLE FOR THIS FOLLOWING DRAW:



Notes
High-grade **serous carcinoma** is called *serous* because the **fallopian tube fimbrial epithelium**, where it originates, is **histologically serous epithelium**
The migration of these fimbrial cells will cause an inclusion cyst OR from the ovary surface it self (coelomic, germinal) epithelium but is less likely
The surface (coelomic) epithelium undergoes **Müllerian metaplasia**, giving rise to serous, mucinous, endometrioid, etc
Endometriosis **can form a benign cystic lesion in the ovary** called a **"chocolate cyst"**

Tumor Type	Metaplastic Differentiation Into:
Serous cystadenoma	Fallopian tube–like **ciliated columnar** epithelium
Mucinous cystadenoma	Endocervical or **intestinal-type mucinous epithelium**

Notes (continues)
Borderline tumors, intermediate atypia, **no stromal invasion**. Step between benign and malignant.
For type I tumours, *Low-grade serous*, *endometrioid*, *mucinous* cancers. Develop **slowly** from precursors (benign → borderline → malignant).

Lesion Type	Description
STIC (Serous Tubal Intraepithelial Carcinoma)	**Precursor lesion in distal fallopian tube** fimbria (seen especially in BRCA mutation carriers)
Type II Tumors	High-grade serous carcinoma

Benign lesions	Borderline tumours (intermediate)	Malignant tumours
Usually are cystic (`cystadenoma`)	Although the majority of borderline tumours behave in a (`benign`) manner	Maybe cystic (`cystadenocarcinoma`)
May have an accompanying stromal component (`cystadenofibroma`)	They can recur, and some can progress to (`carcinoma`)	Maybe solid (`carcinoma`)

Risk factors for ovarian cancer
Nulliparity: **Never** having given birth to a viable fetus (**parity = 0**), No pregnancy "breaks"
Low parity: Having given birth **once or very few times** (e.g., parity = 1 or 2)
Family history (ovarian ca, breast ca, endometrial ca)
Germline mutations: Around **5**% to 10% of ovarian cancers are **familial**, In breast cancer it has about 90% associated with BRCA familial form. Around **8**% to 10% of ovarian cancers are **sporadic** Most of these are associated with mutations in the BRCA1 or BRCA2 tumour suppressor genes (recall the prostate) The average lifetime risk for ovarian cancer is approximately **50**% in BRCA**1** carriers. The risk in BRCA**2** carriers is somewhat lower (**10-35%**) BRCA are tumour suppressor genes. Mutations in BRCA1 and BRCA2 also are associated with hereditary breast cancer

Risk factors for ovarian cancer
Estrogen-only hormonal therapy **or paraneoplastic syndrome from lung cancer or else where** The main risk factor is prolonged exposure to unopposed estrogen acting on the ovary. I have estrogen that is not neutralized by progesterone**
Early age at menarche "The more **ovulatory cycles** a woman experiences over her lifetime, the **higher her risk of epithelial ovarian cancer**."
Later age of menopause, ↑ Longer reproductive span DESPITE the low level of estrogens
Postmenopausal women: By endometrial hyperplasia at this age Or receiving estrogen therapy Or obese, aromatase estrogen production

Summary of the risk factors:

Risk with advanced age, number of lifetime ovulations (early menarche, late menopause, nulliparity), endometriosis, genetic predisposition (eg, BRCA1/BRCA2 mutations, Lynch syndrome).

Factors that decreases the risk of the ovarian cancer
Parity
Later age at menarche
Earlier age of menopause
Oral contraceptive use. Progastrin only pills.

Summary of the good factors:

Previous pregnancy, history of breastfeeding, OCPs, tubal ligation

---

Serous tumour
The most common of ovarian epithelial tumours overall
Make up the greatest fraction of malignant ovarian tumours. **S**erous carcinoma is the **s**ingle most frequent subtype
Most serous tumours are large and **c**ystic (**s**erous, **c**uboidal cells)
Cystic spaces usually are filled with a clear serous fluid
60% are benign-----30 and 40 years of age.------Serous cystadenoma, adenofibroma and surface papilloma (simple, scattered, has no complexity, lined by single layer of cells) -> 25% bilateral, the serosal covering is smooth and glistening. cystic only Single layer of columnar epithelial cells that line the cysts. No atypia or inavaion. Psammoma bodies are common in the tips of papillae.
15% are borderline------ Serous borderline tumor. (age in between), 40s. Complex architecture:

Serous tumour
Papillary formation.- Solid growth.- Stratification.- Crowding. less cytologic atypia and typically no stromal invasion.
25% are malignant-----45 and 65 years of age----Serous carcinoma -> 66% bilateral, the surface has nodular irregularities. invasion The cells are markedly atypical The papillary formations are usually complex, branched, lined by more than one layer, and multilayered Nests or sheets of malignant cells invade the ovarian stroma Papillary projections are more prominent in malignant tumours SEVER ATYPIA + INVASION -> MALIGNANT LESS ATYPIA + NO INVASION -> BORDER LINE
If a patient presents with an ovarian mass, how do we diagnose it? • If it is mostly cystic, it is likely benign. • If it has both cystic and solid components, it could be any of the three types, so we include benign, borderline and malignant tumors in the differential diagnosis.

Low grade serous tumour	High grade serous tumour
Arise from benign or borderline lesions	Many arise in the fimbriated end of the fallopian tube, from a precursor lesion known as serous tubal intraepithelial carcinoma (STIC)
Progress slowly in a stepwise manner to become invasive carcinoma	Develop rapidly
Mutations in genes encoding signaling proteins: **KRAS and BRAF mutation in 50-60%**, **NRAS** mutation (**KBN**)	**TP53** mutations in nearly all cases (rule) Germline, somatic or promoter hypermethylation (inactivation) of **BRCA1 and BRCA2 in 50%** of cases
May rarely progress to high grade serous carcinoma	

Prognosis of serous carcinoma:

The stage at diagnosis:	The grade of the tumour:	Mutations of the tumour:
The 5-year survival for women with carcinoma confined to one ovary is about 90%	Low-grade serous carcinoma has an excellent prognosis if confined to the ovary	Women with tumours containing BRCA1/2 mutations tend to have a better prognosis than women whose tumours lack these genetic abnormalities
The 5-year survival for women with high stages is less than 40%.	Borderline tumours are associated with nearly 100% survival Borderline tumors may seed the peritoneum----the tumor implants usually are noninvasive---- complications: e.g. **intestinal obstruction**	
Malignant serous tumors spread throughout the peritoneal cavity and to regional lymph nodes, including periaortic lymph nodes but Distant lymphatic and hematogenous metastases are infrequent	The prognosis for patients with high-grade serous carcinoma is poor	

Mucinous tumours	Serous tumours	Endometrioid Tumors	Brenner tumour
The neoplastic epithelium consists of mucin-secreting cells	Most common form of epithelial tumours and malignant tumour The neoplastic epithelium consists of serous-secreting cells	They sometimes develop in association with endometriosis (15%)	Uncommon The surface epithelium OR Urogenital epithelium trapped within the germinal ridge (bladderlike)
Mucinous tumours are considerably less likely to be malignant	Serous tumours are considerably more likely to be malignant	Endometrioid tumours are most commonly malignant	Most are benign (smooth and encapsulated)
80% benign; mucinous cystadenoma and adenofibroma	60% benign; serous cystadenoma and adenofibroma, or papilloma type	Benign: Endometrioid cystadenoma and adenofibroma (rare)	Benign M/C
10% borderline; mucinous borderline tumor	15% borderline; serous borderline tumor	Borderline: Endometrioid borderline tumor	Borderline tumours have been described
10% malignant; mucinous carcinoma	25% malignant; serous carcinoma	Malignant: Endometrioid carcinoma (m.c)	Malignant tumours have been described
Cystic or solid mass (like serous tumours)	Cystic or solid mass (like mucinous tumours)	Solid or cystic	Solid
Mucinous cyst contents (mucin)	Serous cyst contents (serous)	Distinguished by the formation of tubular glands (similar to endometrium)	Abundant stroma Nests of transitional-type epithelium resembling that of the urinary tract
More likely to be larger and multicystic	Large cysts		
Much **less** likely to be bilateral Usually unilateral	**Depends**: Benign: 25% bilateral Malignant: 66% bilateral Since they are more likely to be malignant so that means they are often bilateral	They are bilateral in about **30%** of cases	Usually unilateral
Serosal penetration and solid areas of growth are suggestive of malignancy	-		
Mucin-producing epithelial cells line the cysts	Serous-producing epithelial cells line the cysts		
Malignant histology: Cytologic atypia Solid/papillary areas of growth Piling up (stratification) of lining cells Stromal invasion	Malignant histology: The cells are markedly atypical The papillary formations are usually complex and multilayered Nests or sheets of malignant cells invade the ovarian stroma Papillary projections are more prominent in malignant tumours		
Ruptured ovarian mucinous tumours May seed the peritoneum These deposits **rarely** regress spontaneously Pseudomyxoma Peritonei (omental caking): Stable implantation of mucinous tumour cells in the peritoneum with production of copious amounts of mucin --- Adhesions and GI obstructions	Borderline tumors may seed the peritoneum----the tumor implants usually are noninvasive---- complications: e.g. **intestinal obstruction** Malignant serous tumors spread throughout the peritoneal cavity and to regional lymph nodes, including periaortic lymph nodes but Distant lymphatic and hematogenous metastases are infrequent		

Mucinous tumours	Serous tumours	Endometrioid Tumors	Brenner tumour
DDx: Metastatic spread of tumours originating from the gastrointestinal tract, primarily the appendix (more common than ovarian origin)			
Krukenberg tumour: Metastatic mucinous adenocarcinoma from a gastrointestinal tract primary (most commonly from gastric cancer, even if the stomach is removed, may be recurrance) -> Bilateral ovarian masses.		15% to 30% of women with these ovarian tumours have concomitant endometrial carcinoma	
Mutations in **KRAS** are detected in approximately **50%** of ovarian mucinous carcinomas This does not help distinguish them from metastatic GI tumours, which also have a high frequency of KRAS mutations	Low grade serous: Mutations in genes encoding signaling proteins: **KRAS and BRAF mutation in 50-60%**, **NRAS** mutation (**KBN**) High grade serous: **TP53** mutations in nearly all cases Germline, somatic or promoter hypermethylation (inactivation) of **BRCA1 and BRCA2 in 50%** of cases	**CTNNB1** (**53%**)--- WNT/beta catenin **KRAS** (**33%**)	
Prognosis of mucinous carcinoma:- Stage rather than histologic type (serous versus mucinous) is the major determinant of outcome. They usually say that mucinous is better than serous but we depends on the staging and grading process	↗ Prognosis of serous carcinoma		

Malignant ovarian neoplasms		
Histologic type	**Diagnosis**	**Key features**
Epithelial	**Serous cystadenocarcinoma**	• Most common ovarian cancer • Often bilateral • Histology: psammoma bodies
	Mucinous cystadenocarcinoma	• Pseudomyxoma peritonei • Mucin-producing epithelial cells
Germ cell	**Dysgerminoma**	• Adolescents • ↑ β-hCG, ↑ LDH • Histology: "fried-egg" cells
	Endodermal sinus (yolk sac)	• ↑ AFP • Aggressive • Schiller-Duval bodies resembling glomeruli
Stroma (sex cord)	**Granulosa cell tumor**	• ↑ Estrogen (eg, endometrial hyperplasia, postmenopausal bleeding) • ↑ Inhibin • Histology: Call-Exner bodies, coffee-bean nuclei
	Sertoli-Leydig cell tumor	• ↑ Androgens (eg, hirsutism, clitoromegaly)
AFP = alpha-fetoprotein; **LDH** = lactate dehydrogenase.		