Female Genital Tract Pathology

LEC 3

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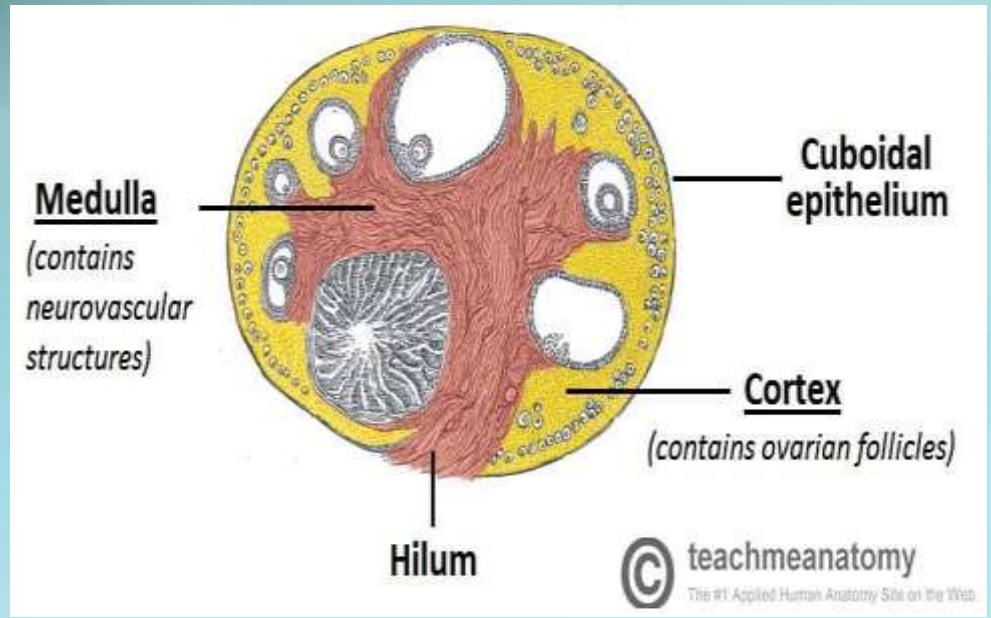
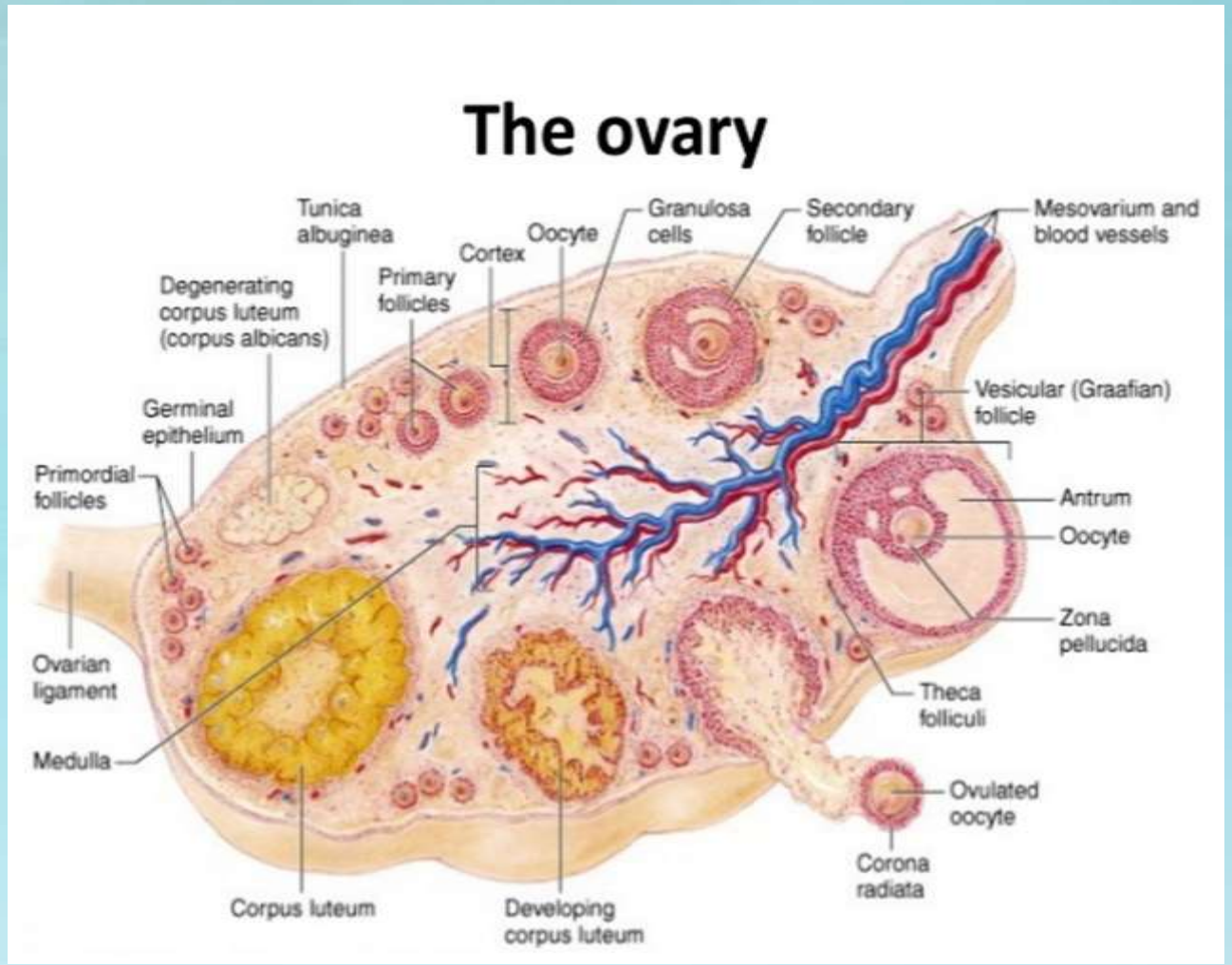
PATHOLOGY OF OVARY





❖ Non neoplastic cysts: Follicular & luteal cysts:

- Common cysts
- Originate either from **unruptured Graafian follicles (follicular cysts)**

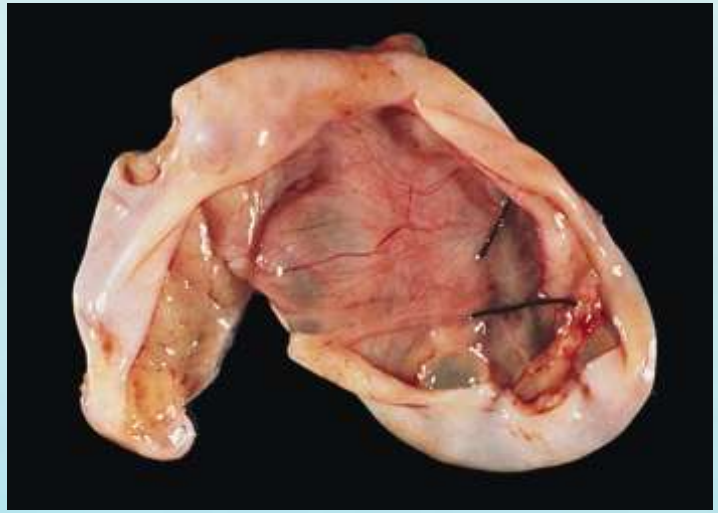
or from follicles that rupture and then immediately seal **(luteal cysts).**

- These cysts often multiple, and develop subjacent to the serosa of the ovary.
- They typically are small (1–1.5 cm in diameter) and are filled with clear serous fluid.

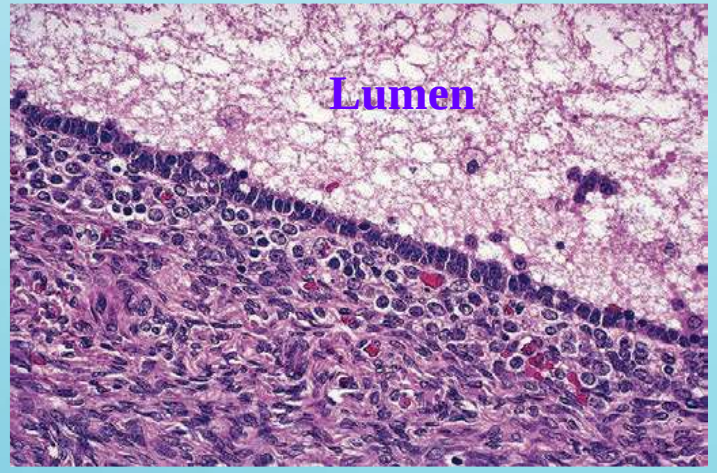
Occasionally, they become sufficiently large (4–5 cm) to produce palpable masses and pelvic pain.

- Majority of cases are asymptomatic but may become twisted & ruptured cause intraperitoneal hemorrhage and acute abdominal pain.

- **Follicular cyst**

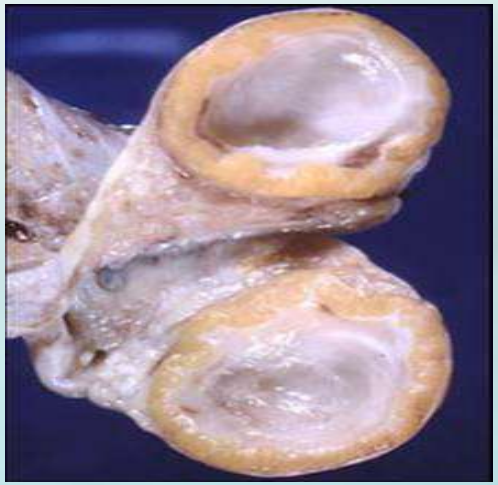


Gross: Thin walled cyst with smooth inner surface and **clear to straw colored fluid contents.**

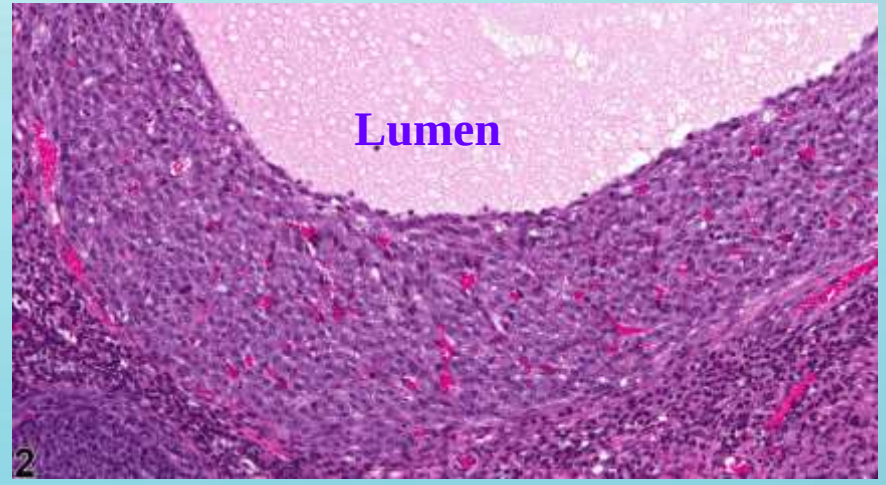


Mic.: Cyst lining is composed of an inner layer of granulosa cells and an outer layer of luteinized theca cells.

- **Luteal cyst**



Gross: Cyst wall lining appears yellow and convoluted, with **serous or hemorrhagic contents**



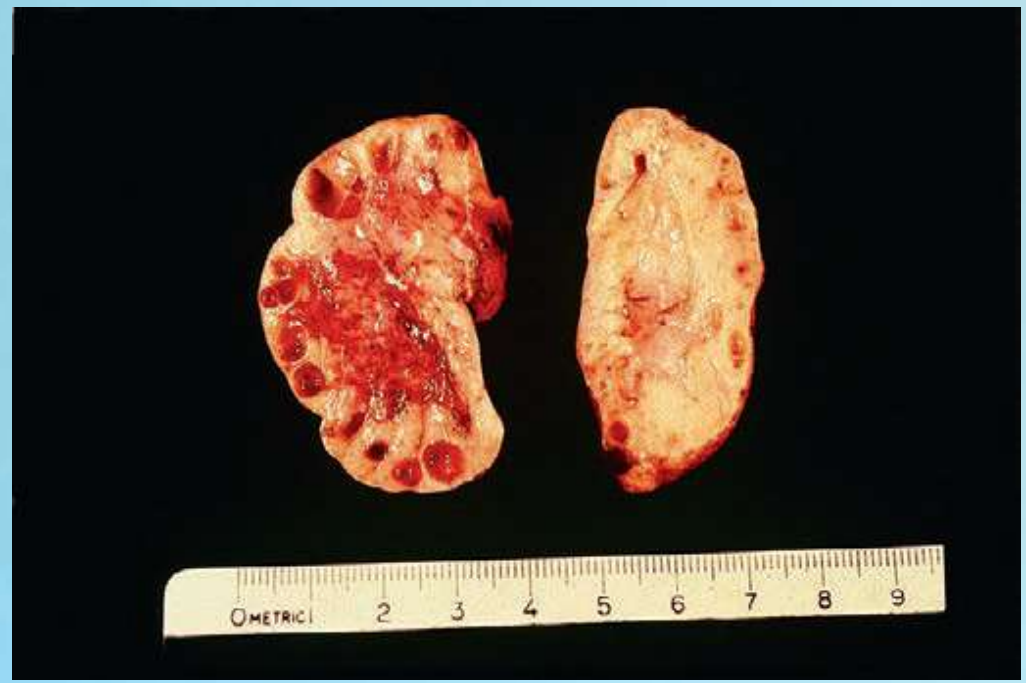
Mic.: Cyst lining with inner several layers of luteinized granulosa cells and outer layer of theca cells.

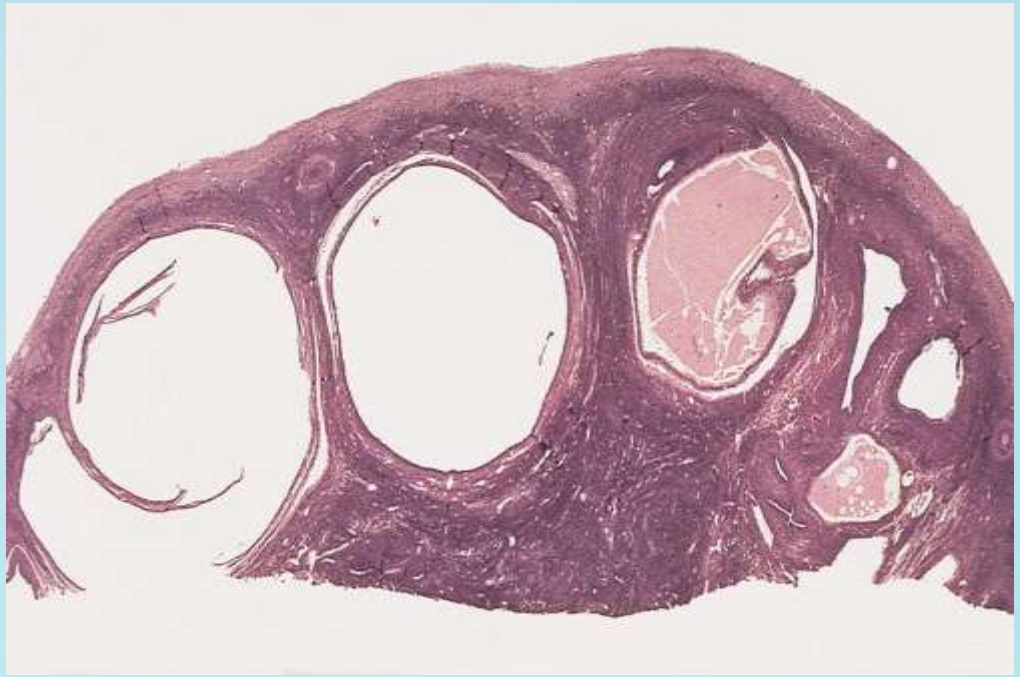
❖ Polycystic ovarian syndrome (PCOS)

- Formerly called (*Stein-Leventhal syndrome*) is **a complex endocrine disorder characterized by:**
  - Hyperandrogenism,
  - Menstrual abnormalities,
  - Polycystic ovaries,
  - Chronic anovulation, and
  - Decreased fertility.
- It affects 6-10% of reproductive age women worldwide.
- **Etiology** of PCOS remains incompletely understood. **It is marked by a dysregulation of enzymes involved in androgen biosynthesis** and **excessive androgen production,** which is considered to be a central feature of this disorder. In addition, women with PCOS show **insulin resistance** and altered adipose tissue metabolism, which contribute to the development of both diabetes and obesity.

- **Clinical manifestations:** oligomenorrhea, hirsutism, acne, androgenic alopecia, infertility, and sometimes with obesity.
- **Risk: high level of estrogen** can cause **endometrial hyperplasia** and **endometrial carcinoma.**

Polycystic ovarian syndrome (PCOS)





Gross:

Enlarged ovaries, with numerous subcortical cysts and covered by thickened fibrosed outer capsule.

Mic.;

Outer cortex is collagenized with several follicle cysts arrayed beneath it.

Tumors of the ovary

- There are numerous types of ovarian tumors. About 80% are benign, and these occur mostly in young women between 20 and 45 years of age. Borderline tumors (tumors of indeterminate malignancy) occur at slightly older ages. Malignant tumors are more common in women between 45 and 65 years of age.
- Ovarian cancer the **fifth** leading cause of cancer death in women.

- **Ovarian tumors Classified to 3 types** depend on type of cells from where the tumors originate.

(1) Surface epithelial tumors
(2) Germ cell tumors.
(3) Sex cord / stromal cells tumors.

- Metastases to the ovary are mostly from primary Mullerian origin (e.g. uterus, fallopian tube, contralateral ovary), or breast and gastrointestinal tract (Krukenberg tumor is the classic metastatic GI cancer causing bilateral ovarian metastases composed of signet-ring cancer cells, usually from the stomach).
- Neoplasms of the **surface epithelial origin account for almost 90%** of ovarian cancers.

Site of origin	Types	Frequency	Age group
Surface epithelial tumors	1.Serous(B,BL,M) 2.Mucinous(B.BL.M) 3.Endometroid 4.Clear cell 5.Brenner	60%-70%	20 years and greater
Germ cell	1.Teratoma (mature and immature) 2.Dysgerminoma(=testicular seminoma) 3. Yolk Sac Tumor 4. Embryonal carcinoma 5.Choriocarcinoma (Non gestational)	15%-20%	0 to 25 years and greater
Sex cord/ stromal tumors	1.Granulosa cell tumors 2.Sertoli-Leydig cell tumors 3.firoma/ thecoma/ Fibrothecoma	5%-10%	All ages
Metastasis	Krukenberg tumors	5%	variable

A. Surface Epithelial Tumors:

They are derived from the müllerian epithelium that covers the surface of the ovary.

- Accounts for most primary ovarian neoplasms, 70% of all ovarian tumors.
- Classified based on histologic type of epithelium **to:**

Serous, mucinous, endometrioid, Brenner tumors and clear cell carcinoma.

- **According to their behavior, each surface epithelial tumor have 3 types**:

Benign lesions are usually cystic (cystadenoma) .

Malignant tumors may also be cystic (cystadenocarcinoma) or solid (carcinoma).

intermediate, borderline category (tumors of **low malignant potential)**.

These are low-grade cancers with limited invasive potential. Thus, they have a better prognosis than the fully malignant ovarian carcinomas.

- **Risk factors:**

1-Nulliparity: There is a higher incidence of carcinoma in unmarried women and married women with low parity.

2-Family history: Up to10% of ovarian cancers are familial; the majority of these hereditary cancers caused by mutations in BRCA1 and BRCA2 genes, these are also associated with hereditary breast cancer. Other molecular changes of ovarian neoplasms include: HER2/NEU & K-RAS proteins over-expression and p53 mutation (which present in about 50% of all ovarian cancers).

1. Serous tumors:

- Are the **most common** of the ovarian epithelial tumors overall, and also make up the greatest fraction of malignant ovarian tumors.
- **About 60% are benign, 15% are borderline, and 25% are malignant.**
- Benign lesions are usually encountered in patients between 30 and 40 years of age, and malignant serous tumors are more commonly seen between 45 and 65 years of age.

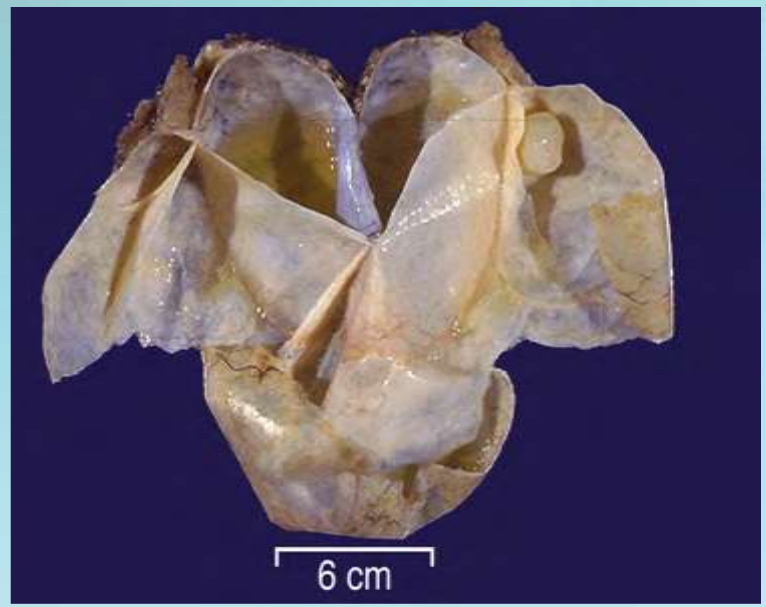
There are two types of serous carcinomas, based on the degree of nuclear atypia, differing mutational profiles, and correlates with patient survival:

- **Low-grade; arise from benign or borderline lesions** and progress slowly to invasive carcinoma. These low-grade tumors are associated with mutations in genes encoding signaling proteins, such as ***KRAS.***
- **High-grade; arise in the fimbriated end of the fallopian tube** via **serous tubal intraepithelial carcinoma,** rather than ovarian coelomic epithelium. ***TP53* mutations.**

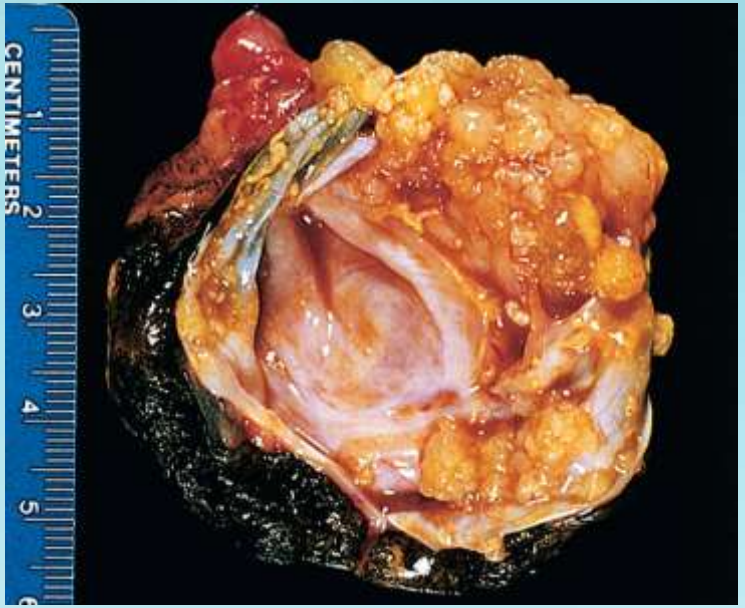
➢ Gross features:

• Most serous tumors are large (up to 30 to 40 cm in diameter), spherical, and cystic masses, filled with a clear serous fluid.

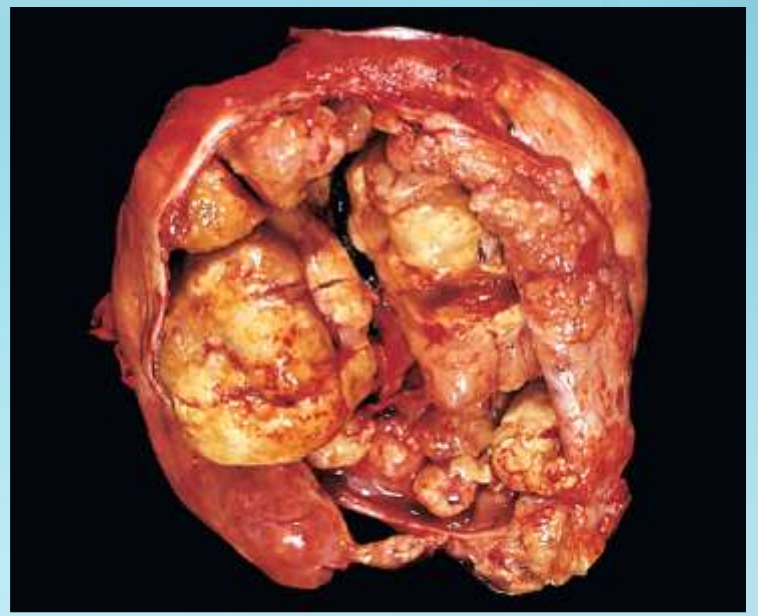
- About **25%** of the benign forms are **bilateral.**
- Benign tumors have a smooth and glistening inner surface; In contrast cystadenocarcinoma have small mural nodularities or papillary projections.
- They are generally unilocular, but larger examples may be multilocular.



Benign serous tumor with smooth and glistening inner surface.

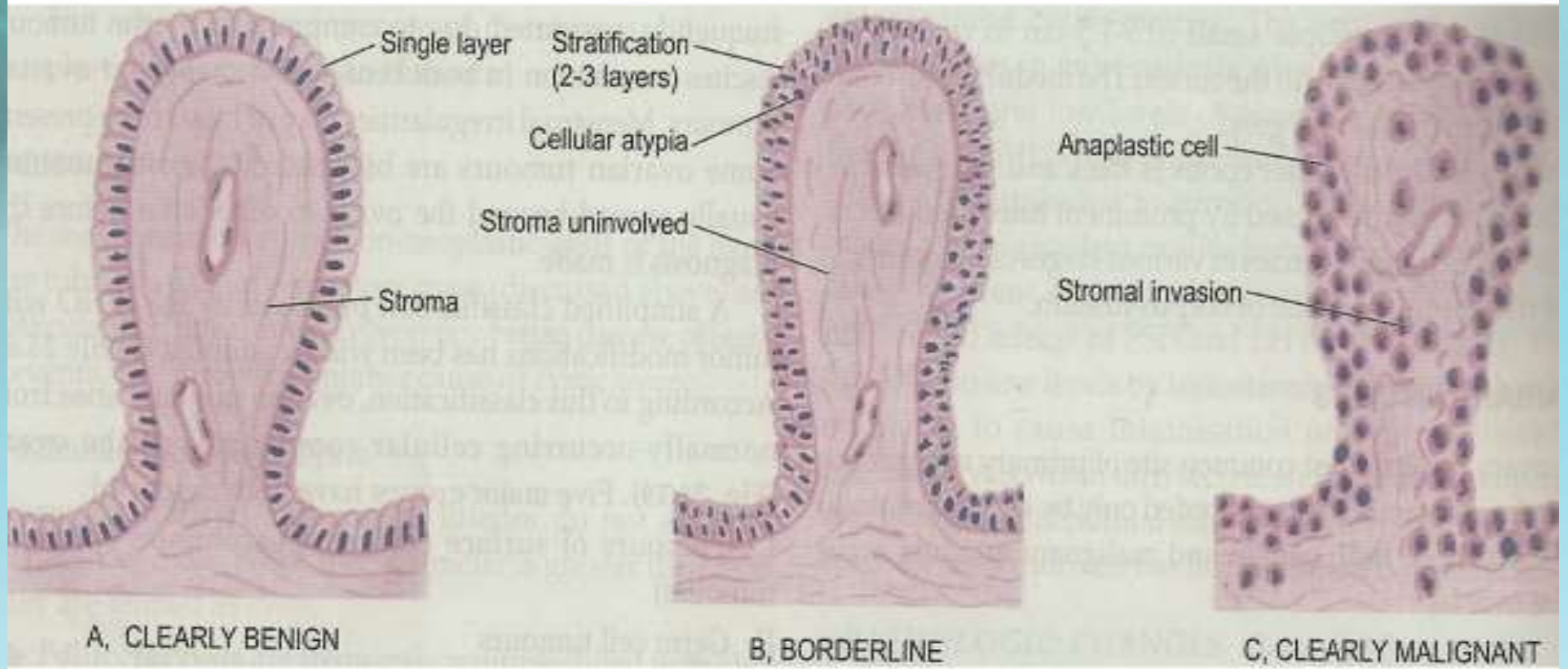


Borderline serous cystadenoma display a cyst cavity lined by delicate papillary tumor growths.



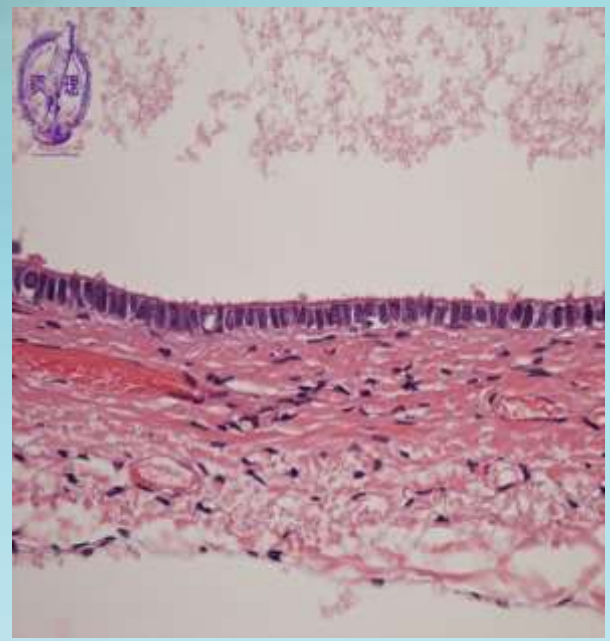
Serous cystadenocarcinoma. The cyst is opened to show a large, bulky tumor mass.

Diagrammatic representation of aggressiveness

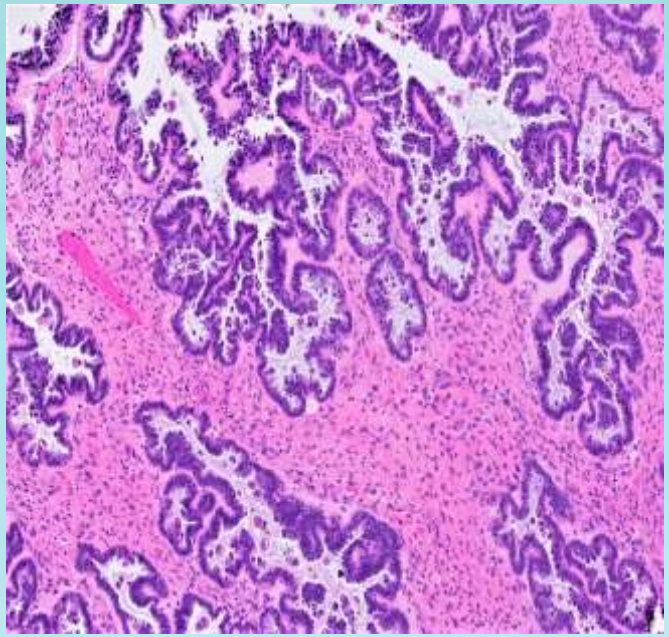


Microscopic features:

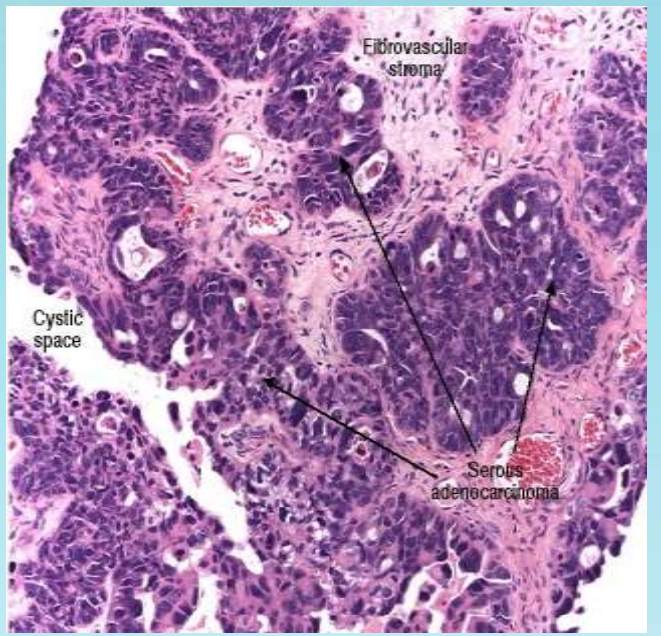
- **The benign tumors** show a single layer of ciliated tall columnar epithelium that lines the cyst.
- **Borderline tumors** show milder cytological atypia and typically shows no stromal invasion.
- **In carcinoma**, the lining cells display malignant features with invasion of the stroma and papillary formations are complex and multilayered.
- Psammoma bodies (rounded laminated calcified structures) are common in the tip of the papillae.



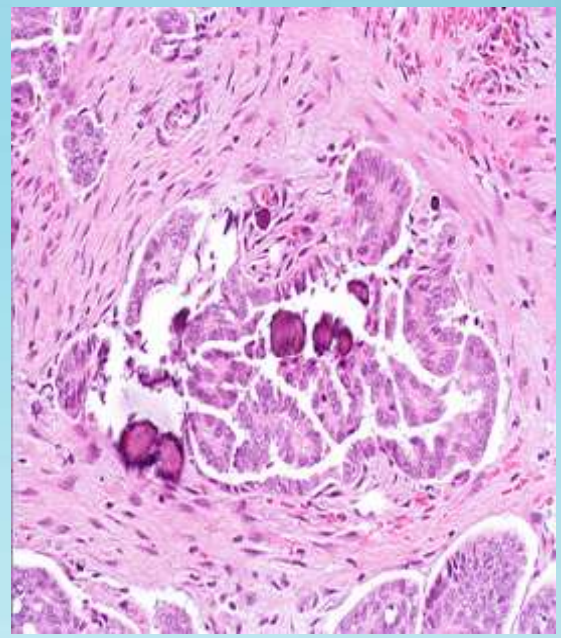
Benign (serous cystadenoma)



Borderline serous tumor



Serous cystadenocarcinoma



Psammoma bodies

➢ Prognosis:

- In general, malignant serous tumors spread throughout the peritoneal cavity and to regional lymph nodes, including periaortic lymph nodes; distant lymphatic and hematogenous metastases are infrequent.
- The prognosis for the clearly invasive serous cystadenocarcinoma is poor and depends on the stage of the disease at the time of diagnosis.
- Prognosis of the borderline tumors is much better.
- Women **with** tumors containing **BRCA1/2 mutations** tend to have a **better prognosis** than women whose tumors lack these genetic abnormalities.

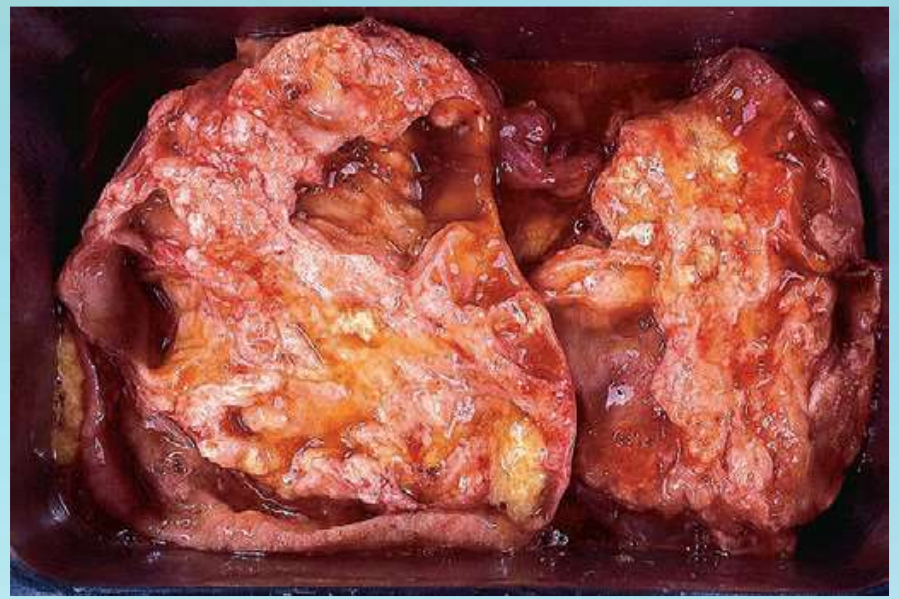
2. Mucinous Tumors:

- Differ from serous tumors essentially in the epithelium, which is of mucin-secreting cells and mucinous tumors are considerably **less likely to be malignant.**
- Overall, only **10% of mucinous tumors are malignant; another 10% are borderline, and 80% are benign.**
- These tumors occur in women in the same age range as those with serous tumors.

➢ Gross features :

- Large, multiloculated cystic masses, filled with sticky gelatinous fluid rich in glycoproteins
- **Serosal penetration and solid areas of growth are suggestive of malignancy.**
- Compared with serous tumors, mucinous tumors are much less likely to be bilateral (5%).

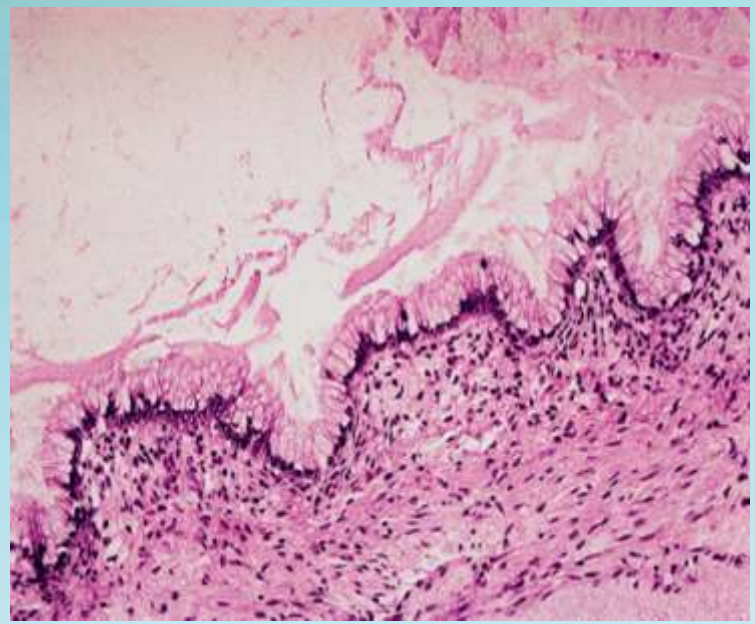
Mucinous cystadenoma, displaying **multicystic appearance and delicate septa.** Note the presence of glistening mucin within the cysts.



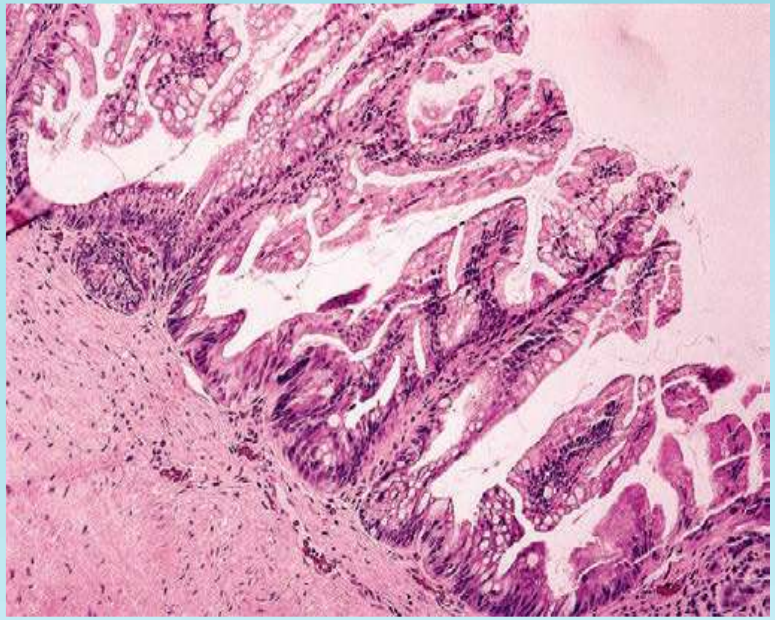
Mucinous Cystadenocarcinoma.
The neoplasm is **predominantly solid,** but some mucin-containing cystic spaces can still be appreciated.

➢ Microscopical features:

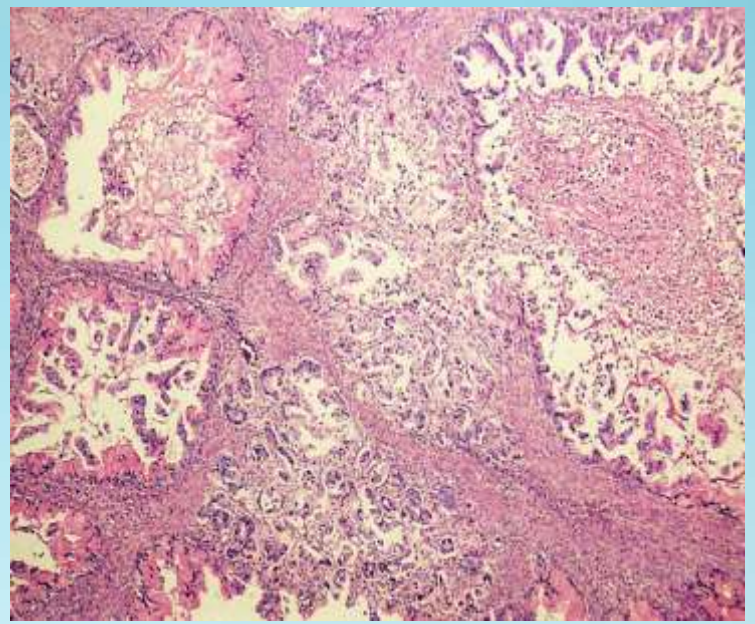
- Benign mucinous tumors are characterized by a lining of tall, columnar epithelial cells with apical mucin that lack cilia.
- Borderline mucinous tumors are distinguished from cystadenomas by epithelial stratification, tufting, and/or papillary growth, with mild atypia, and no stromal invasion.
- In carcinoma: there is stratification of lining cells, cytologic atypia, and stromal invasion.
- **Mucinous tumors are classified according to the type of the mucin-producing epithelial cells into: 2 histological types * Endocervical type. * Intestinal type**



Benign (mucinous cystadenoma)



Borderline mucinous tumor

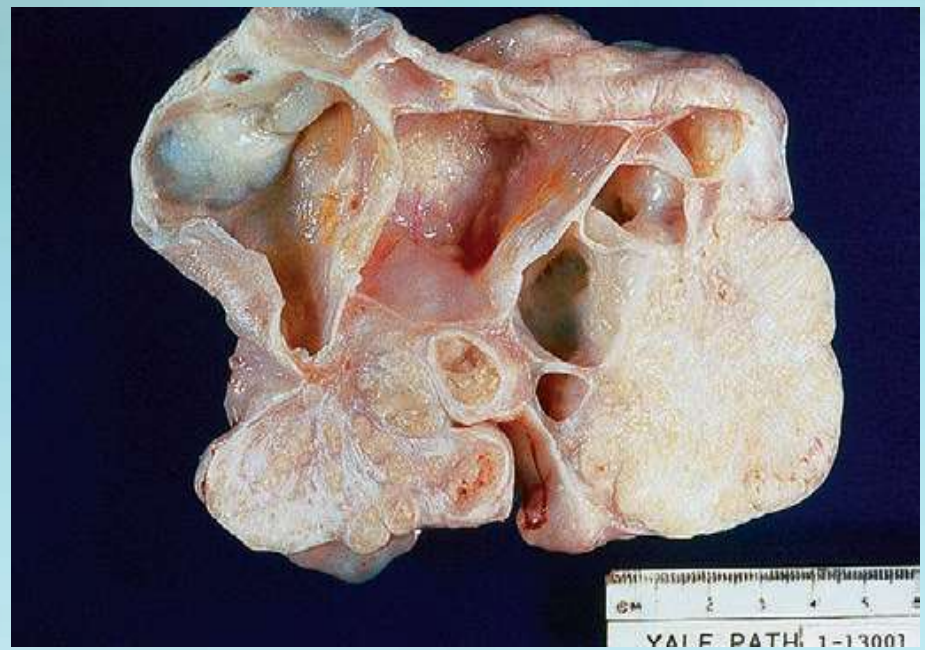


Mucinous cystadenocarcinoma

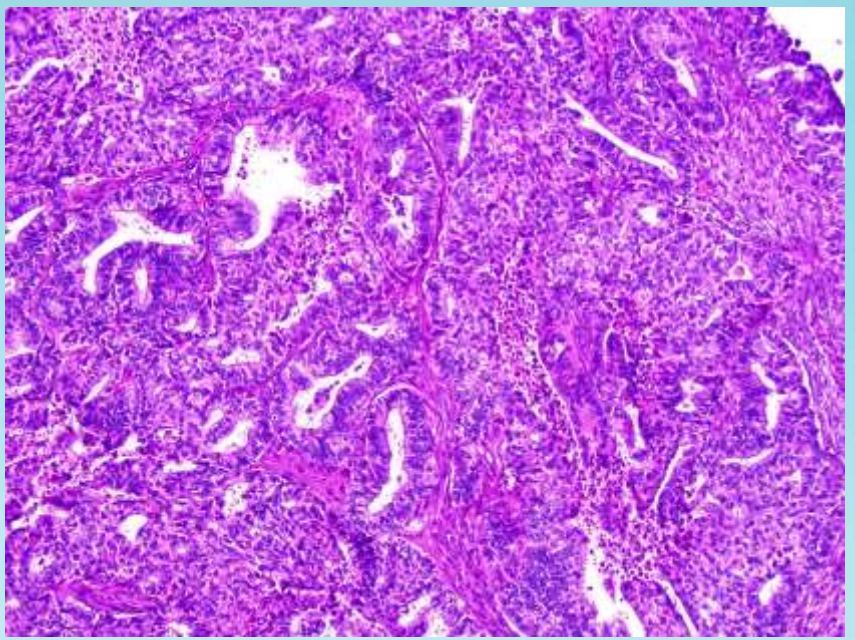
- **Rupture of mucinous tumors** may result in mucinous deposits in the peritoneum but typically do not result in the malignant growth referred to as **pseudomyxoma peritonei** (peritoneal cavity filled with mucinous material similar to cystic contents
- The vast majority if not all cases of the latter are caused by **metastasis** from the GIT, primarily the appendix.
- Metastasis of mucinous tumor of the gastrointestinal tract to the ovaries (**Krukenberg tumor**) may also **mimic an ovarian primary tumor.**
- Compared with serous tumors, mucinous tumors are much less likely to be bilateral (5%). This feature is sometimes useful in differentiating mucinous tumors of the ovary from metastatic mucinous adenocarcinoma from a gastrointestinal tract primary (the so-called "**Krukenberg tumor**"), which more often produces bilateral ovarian masses.
- Mutations in ***KRAS*** are detected in approximately **50% of ovarian mucinous carcinomas**, however this does not help distinguish them from metastatic GI tumors, which also have a high frequency of *KRAS* mutations.
- **The prognosis** of mucinous cystadenocarcinoma is somewhat better than that of the serous counterpart, but the **stage** rather than the histologic type (serous versus mucinous) is the major determinant of prognosis.

3. Endometrioid Tumors:

- May be solid or cystic, sometimes they develop as a mass projecting from the wall of an endometriotic cyst.
- They **are usually malignant**, although benign and borderline forms also exist.
- **Mic.:** formation of tubular glands similar to those of the endometrial adenocarcinoma.
- They are bilateral in about 30% of cases and 15-30% have a concomitant endometrial carcinoma.
- Similar to endometrial cancer (endometrioid carcinoma) have mutations in PTEN suppressor gene.



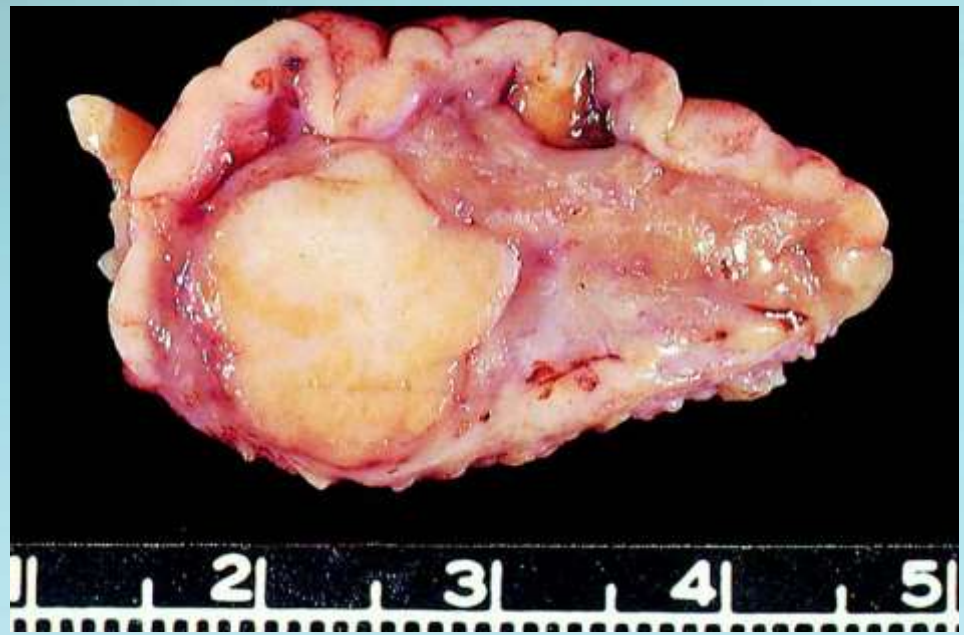
Gross: presence of both solid and cystic areas



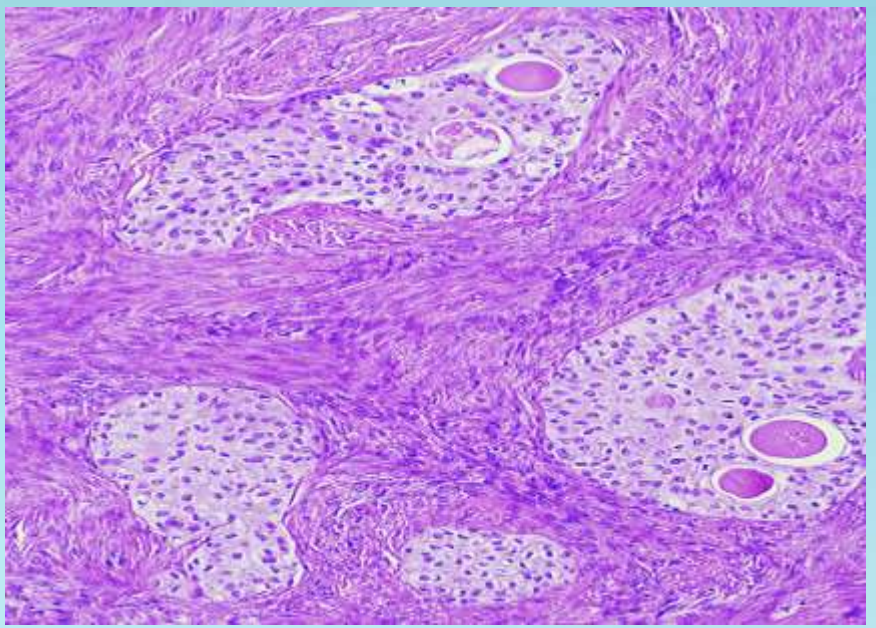
Microscopic: Tubular glands resemble those of typical endometrial adenocarcinoma.

4. Brenner Tumor:

- An uncommon, solid, usually unilateral ovarian tumor
- **Mic.:** Consisting of an abundant stroma containing nests of transitional epithelium resembling that of the urinary tract.
- Although most are benign, both malignant and borderline tumors have been described.



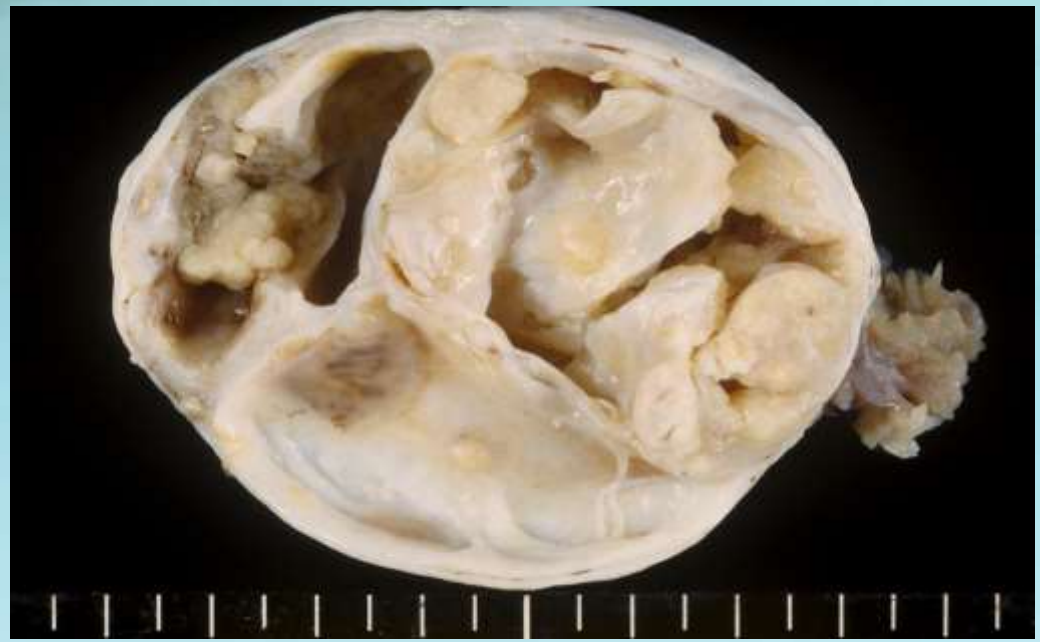
Gross: Smoothly encapsulated and gray-white



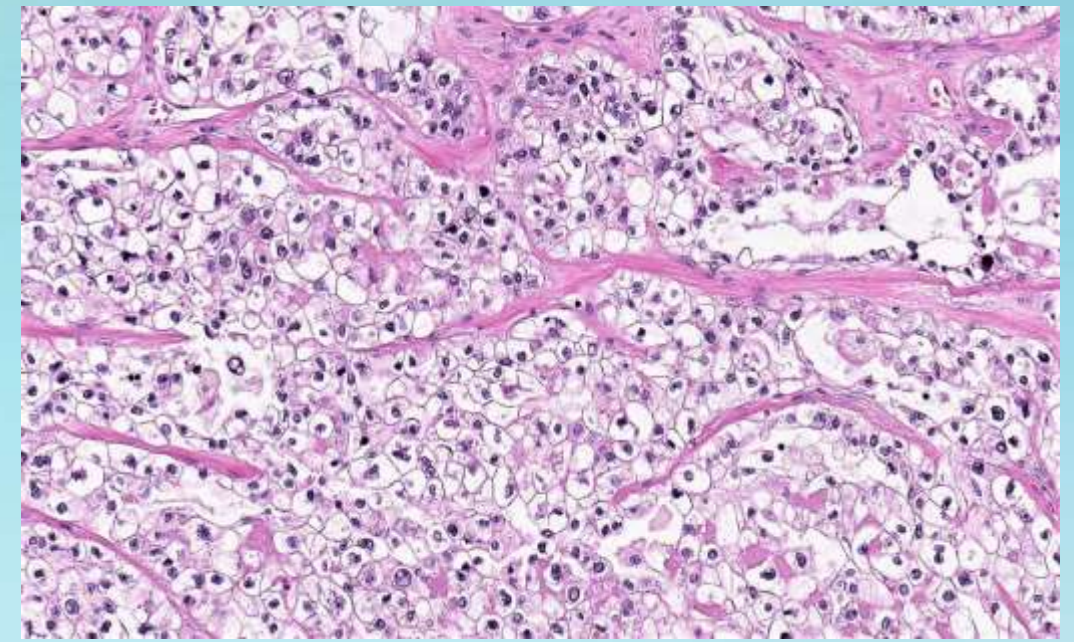
Microscopically: Nests of transitional cells, some containing cysts, lie in a fibromatous stroma.

5. Clear cell carcinoma:

- These are uncommon and aggressive tumors.
- Can be predominantly solid or cystic.
- **Mic.:** Composed of large epithelial cells with abundant clear cytoplasm.
- In the solid neoplasms, the clear cells are arranged in sheets or tubules, while in the cystic variety, the neoplastic cells line the spaces.



Gross: can present in solid and or cystic pattern.



Microscopically: large epithelial cells with abundant clear cytoplasm.

B. Germ Cell Tumors

- Germ cell tumors constitute 15% to 20% of all ovarian tumors and include **multiple subtypes:**

1-Dysgerminoma: these usually presents within 10 to 30 years of age. Their microscopic picture is analogous to testicular seminoma.

2. Yolk sac tumor & Embryonal carcinoma: are similar to their testicular counterparts.

3. Choriocarcinoma: presents within the first three decades of life. They are pathologically identical to placental choriocarcinoma.

4. Teratomas:

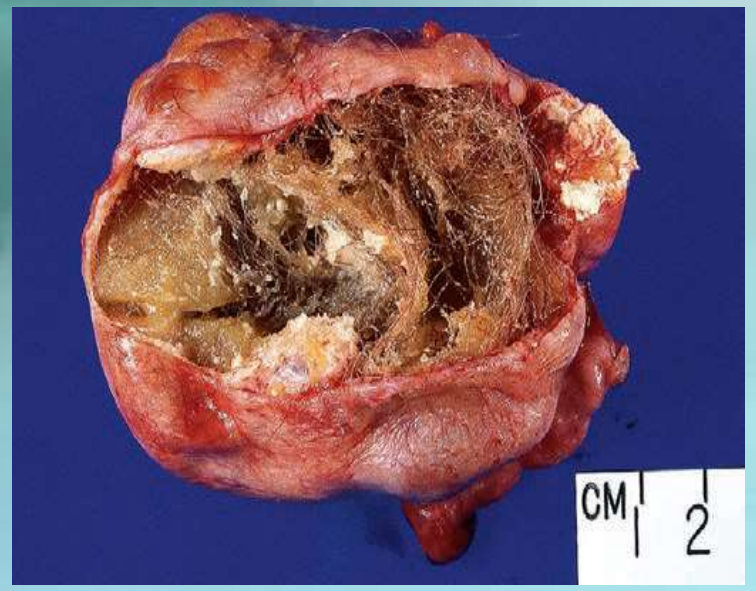
- Constitute up to 20% of ovarian tumors and arise in the first two decades of life; the **younger** the person, the **greater** is the likelihood of **malignancy.**
- However, more than 90% of these germ-cell neoplasms are benign mature cystic teratomas.

➢ **Benign (Mature) Cystic Teratomas**

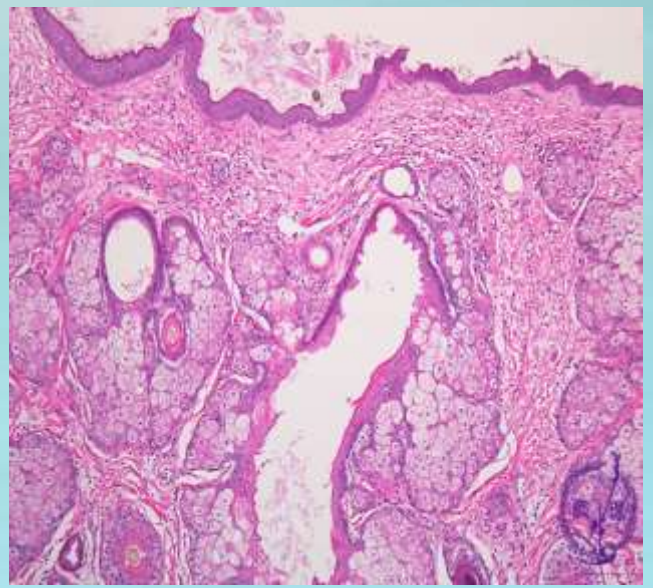
- Are characterized by differentiation of totipotential germ cells into mature tissues representing all three germ cell layers: ectoderm, endoderm, and mesoderm.
- Usually there is the formation of a cyst lined by recognizable epidermis with adnexal appendages **(dermoid cysts).**
- On opening, they are often filled with sebaceous secretion and hair. Sometimes there is a nodular projection from which teeth protrude. Occasionally, foci of bone and cartilage, nests of bronchial or GIT epithelium, and other recognizable lines of development are also present.
- **Complications of mature teratoma:**

1. **Malignant transformation** in 1% of cases (squamous cell carcinoma).
2. Prone to **torsion** in 10%-15% (acute surgical emergency).
3. For unknown reason produce **infertility.**

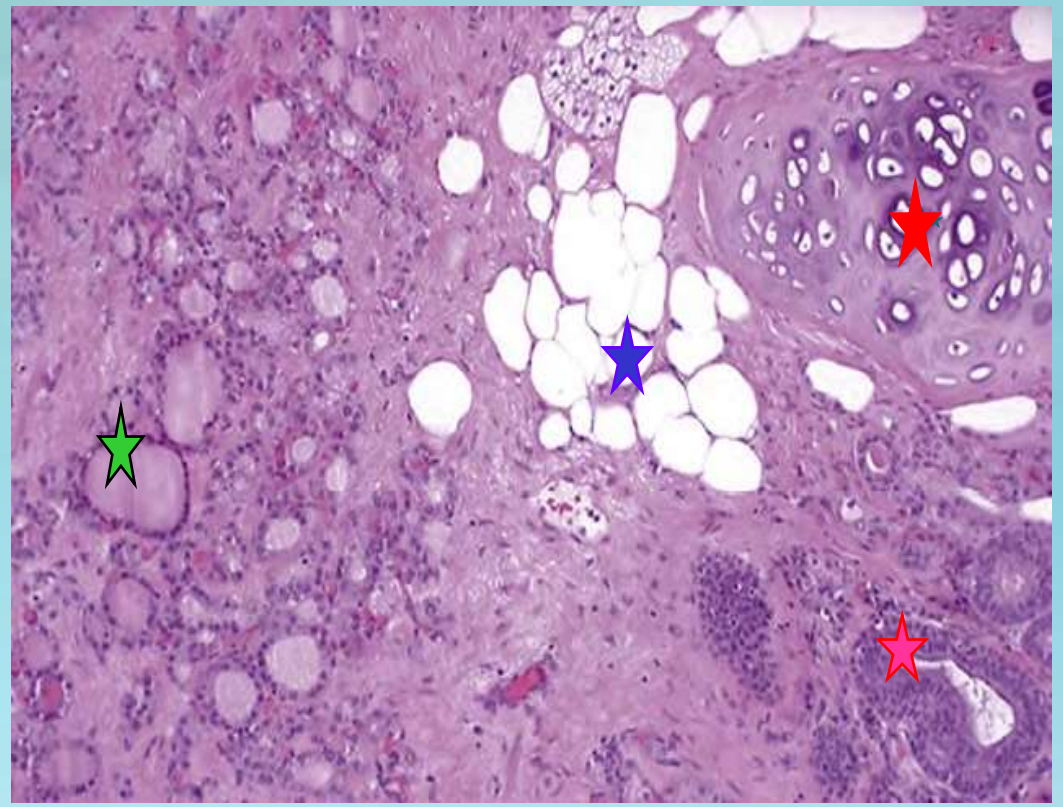
Benign (Mature) Cystic Teratomas



Gross: Unilocular cyst containing hair and sebaceous material. Often a **solid nodule** within the wall which may contain **teeth, bone or calcifications.**



Mic.: cyst wall **stratified squamous epithelium** and underlying **sebaceous, sweat glands and other adnexa.** other structures like thyroid tissue, cartilage bone may be seen.



The benign teratoma shown here contains cartilage, adipose tissue, intestinal glands and numerous **thyroid follicles.**

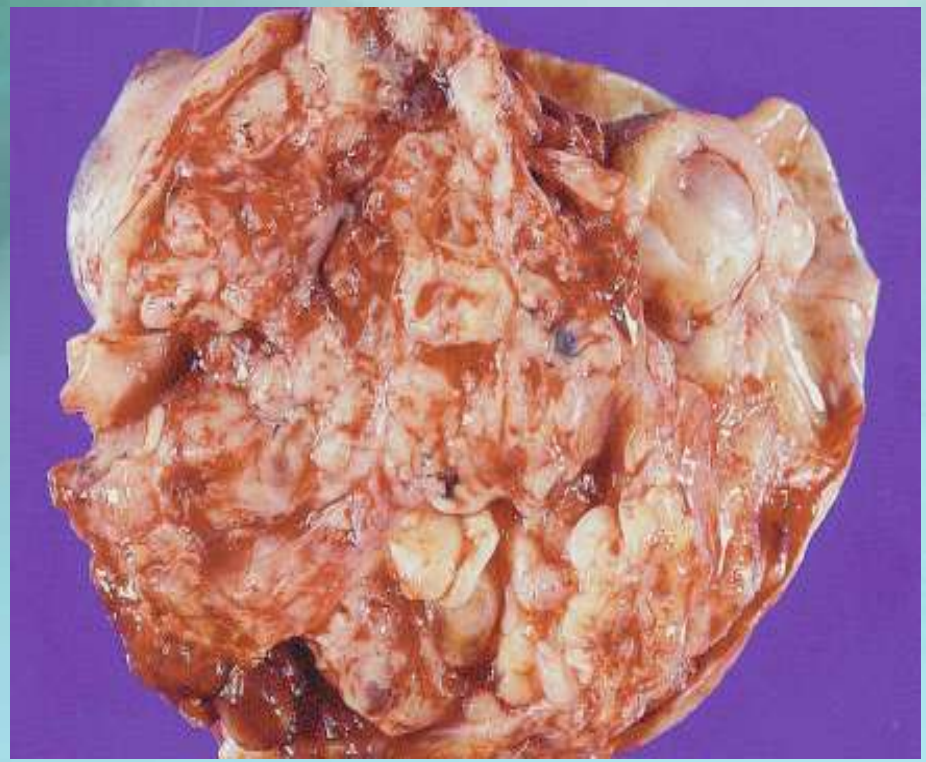
➢ Immature Malignant Teratomas:

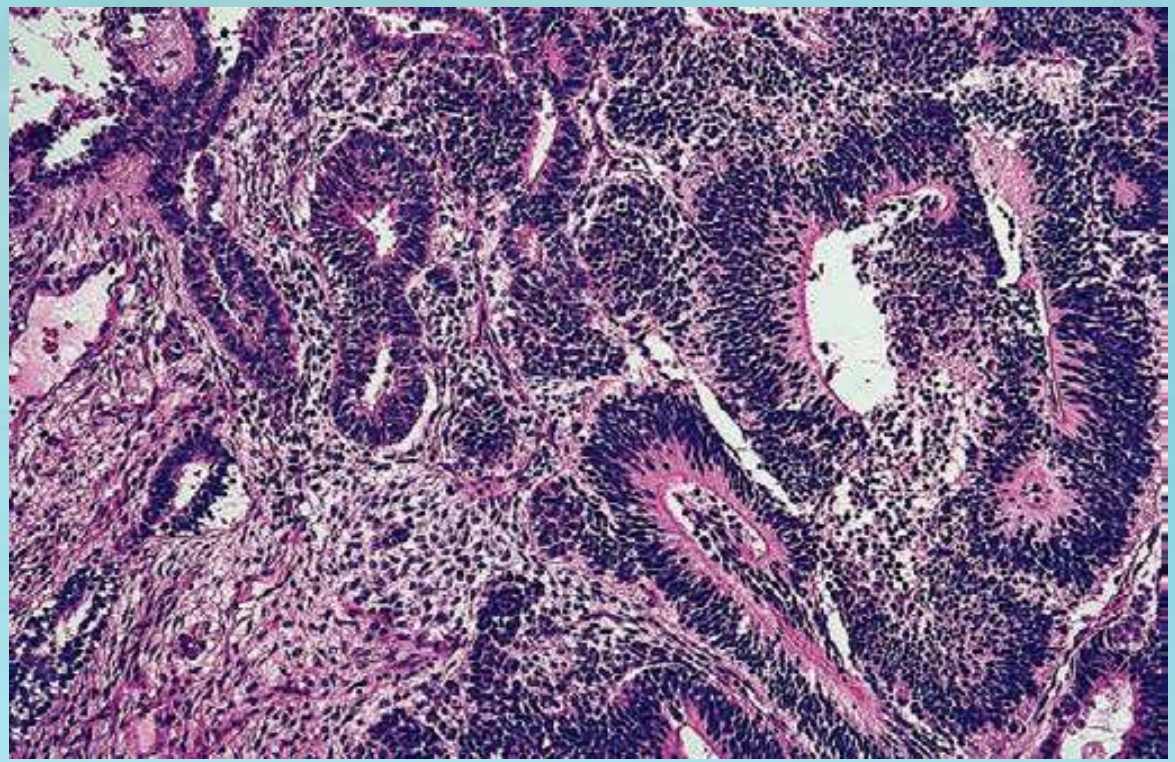
- Are found **early in life**, the mean age at clinical detection being **18 years.**
- **Differ from mature cystic teratomas by:**

1. Often bulky, solid or semisolid on transaction,
2. Areas of necrosis
3. Uncommonly contain foci of sebaceous secretion, hair like mature teratoma.

- Microscopically, the distinguishing feature is a variety of **immature tissues** such as cartilage, bone, muscle, nerve, and other structures. Particularly **worrying are foci of neuroepithelial differentiation**, because most of these are aggressive and metastasize widely.

Immature Malignant Teratomas:





Gross: solid with multiple minute cysts.

Mic.: Composed of embryonal (immature) as well as variable amounts of mature tissues derived from all the three germ cell layers. The most frequently seen tissues are neuroectodermal tubules and rosettes lined by mitotically-active hyperchromatic cells.

➢ Specialized Teratomas (Monodermal Teratomas)

- Most commonly **struma ovarii** (composed entirely of mature thyroid tissue which may actually produce hyperthyroidism) and ovarian **carcinoid** (presumably arises from intestinal tissue found in teratomas; can also be functional and cause carcinoid syndrome
- These tumors appear as small, solid, unilateral brown ovarian masses.

C. Sex cord – Stromal Tumors

- These tumors originate from ovarian stroma, which include:

1-Granulosa cell tumors
2-Fibromas
3-Fibrothecomas
4-Thecomas
5-Sertoli-Leydig cell tumors

➢ **Fibromas, Thecomas and Fibrothecomas** (4% of all ovarian tumours)

• **Fibromas**: comprising fibroblasts; **Thecomas**: plump spindle cells with lipid droplets; **Fibrothecomas**: mixture of both cells

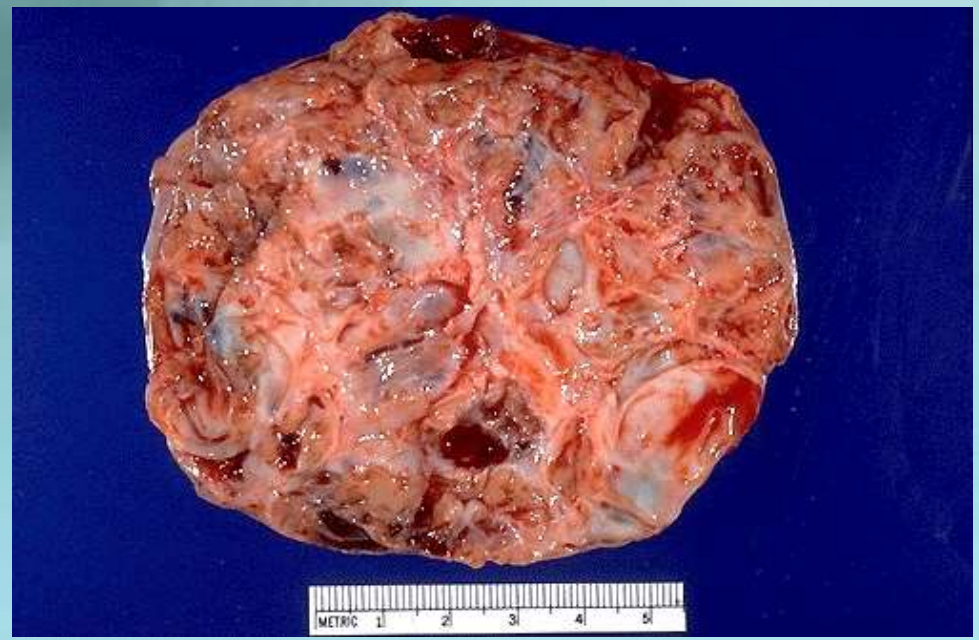
➢ **Sertoli–Leydig Cell Tumors (Androblastomas)**

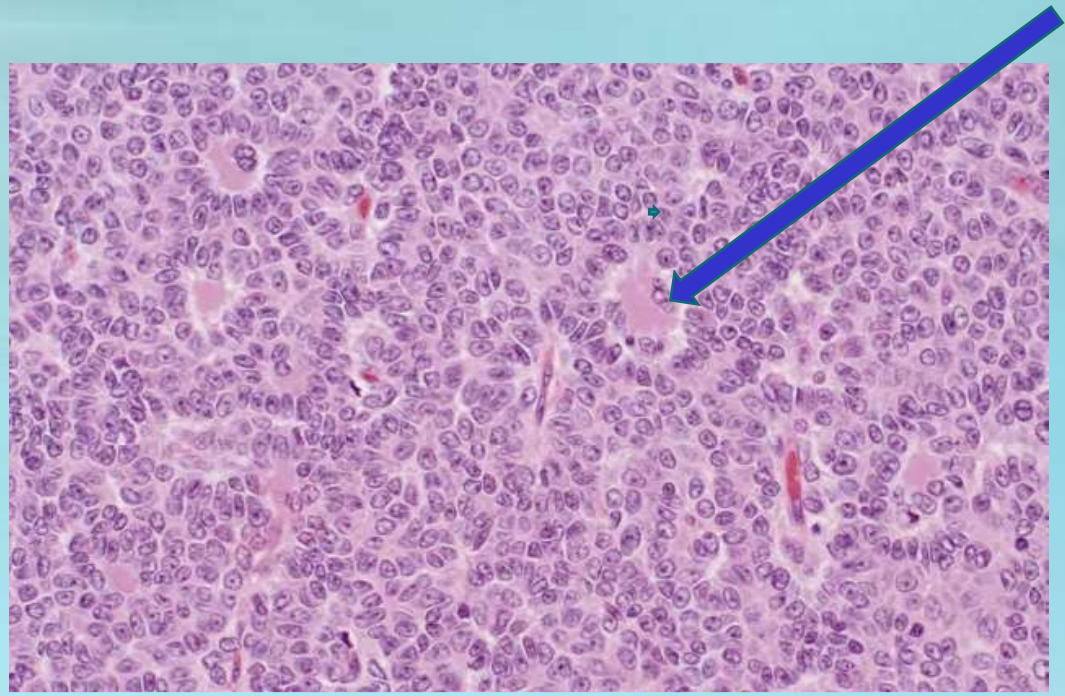
- Sertoli–Leydig cell tumors (androblastomas) recapitulate the cells of the testes and commonly produce androgen that cause masculinization and defeminization. They are usually unilateral and consist of tubules composed of Sertoli cells and/or Leydig cells interspersed with stroma.

➢ Granulosa cell tumors:

- Account for about **5%** of all ovarian tumors.
- Composed of cells that resemble granulosa cells of a developing ovarian follicle.
- They are divided into **adult and juvenile** granulosa cell tumors,
- Approximately two-thirds occur in postmenopausal women.
- Secrete large amounts of estrogen (resulting in precocious puberty in prepubertal girls or associated with proliferative breast disease, endometrial hyperplasia and endometrial carcinoma in adult women).
- Occasionally, granulosa cell tumors produce androgens, masculinizing the patient.

Granulosa cell tumors:





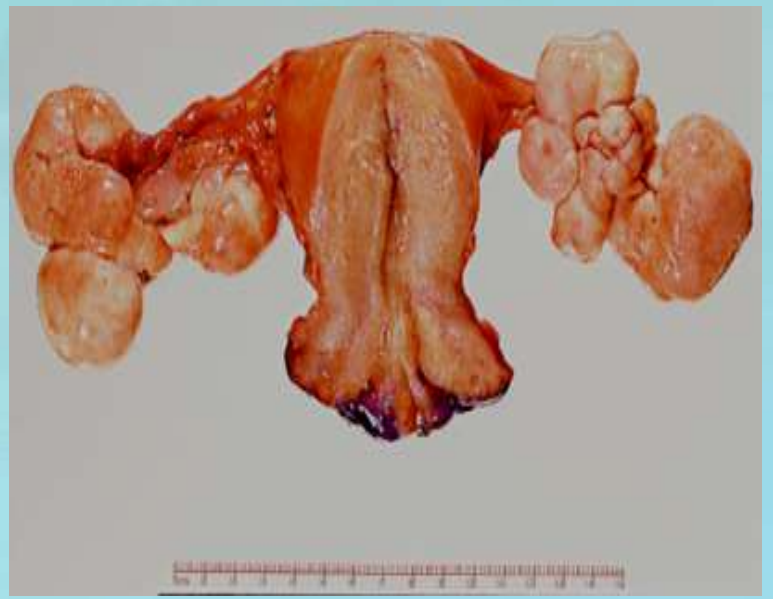
Gross: Usually **unilateral, large,** solid and cystic mass, yellowish if they are hormonally active, due to intracellular lipids.

Mic.: Composed of cords, sheets or strands of small cuboidal to polygonal cells with grooves or folds in the nuclei **(coffee bean appearance).** There are characteristic small gland-like structures with central acidophilic material, resembling immature follicles called **Call-Exner bodies.**

❖ Metastases to ovary

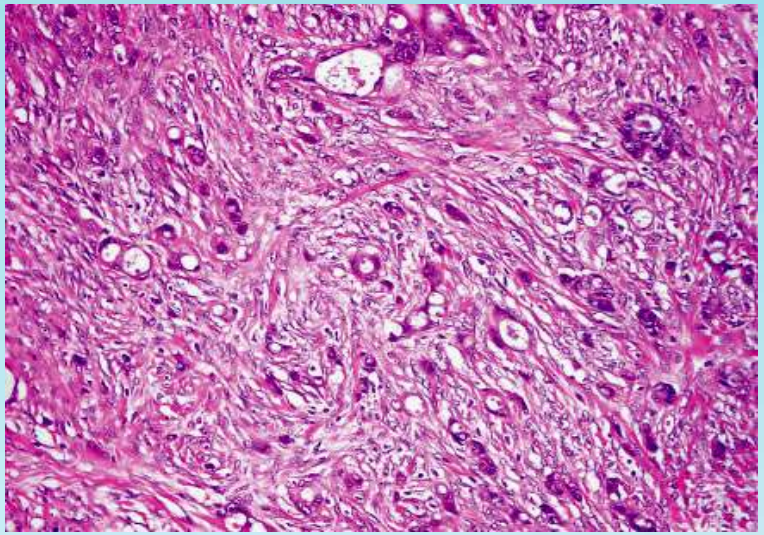
- Are usually occur in older ages.
- In most instances both ovaries are involved.
- **Grossly:** there are **solid gray-white masses** as large as 20cm in diameter. (ovary with multiple white nodules)
- **Microscopically:** There are **malignant tumor cells arranged in cords or glands, and dispersed through a usually prominent fibroblastic background.**
- Primaries include **GIT, breast, and lung & endometrium**.
- When the infiltration is by mucin-containing signet ring cells the term **Krukenberg tumor** is applied, this is usually bilateral and nearly always of metastatic origin.

Krukenberg tumor



Gross:

bilateral involvement with multinodular outer appearance.



Mic.:

Numerous signet ring cells are present **in a highly fibrous stroma,** either individually or in small nests.

➢ Clinical Correlations of ovarian cancers:

- Most ovarian neoplasms produce **no symptoms or signs** until they are well advanced.
- Indeed, about a third of all ovarian neoplasms are discovered incidentally on routine gynecologic examination or incidental imaging or during surgery.
- The clinical presentation of all ovarian tumors is remarkably similar, except for the functioning neoplasms that have hormonal effects.
- When they become large enough they cause local pressure symptoms (e.g., pain, GIT complaints, and urinary frequency).
- Smaller masses, particularly dermoid cysts, sometimes become twisted on their pedicles (torsion), producing severe abdominal pain mimicking an acute abdomen.

- Fibromas and malignant serous tumors often cause ascites, the latter resulting from metastatic seeding of the peritoneal cavity, so that tumor cells can be identified in the ascitic fluid.
- Mucinous carcinoma may fill the abdomen with gelatinous mass (**pseudomyxoma peritonei**).
- Functioning ovarian tumors induce endocrinopathies.
- **Tumor markers:** elevations of the protein CA-125 have been reported in 75% to 90% of women with epithelial ovarian cancer. However, CA-125 measurements are of greatest value in **monitoring response to therapy.**
- Elevated tissue and serum levels of **inhibin**, a product of granulosa cells, are associated with granulosa cell tumors; Detection and measurement of inhibin is useful in diagnosing granulosa and other sex cord–stromal tumors

THANK YOU