Reproductive System, Ovarian Cysts and Tumors

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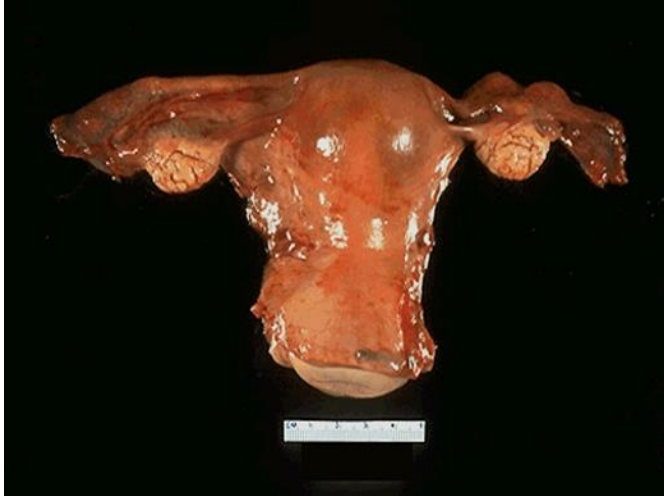
Lecture outlines

Lecture: Ovarian cysts and ovarian tumors.

At the end of this lecture, the students should have a working knowledge of:

- The pathology of the major types of ovarian cysts (follicular and luteal).
- The classification and pathology of common ovarian tumors including surface epithelial, germ cell, stromal and metastatic neoplasms.

Ovarian Cysts and Tumors



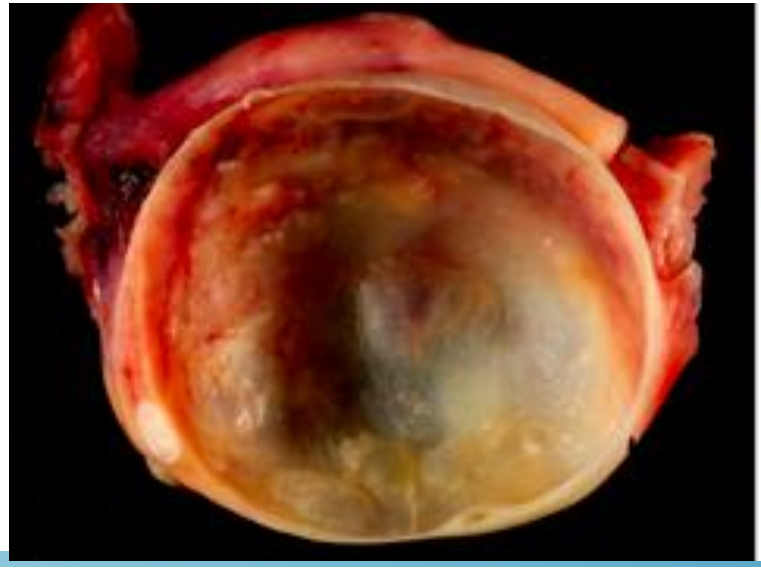
- Non neoplastic cysts are common but they are not serious problems.
- Inflammation of ovaries is rare. It is ususally associated with salpingitis of fallopian tubes (salpingo-oophoritis)
- Frequently, the ovaries are affected by endometriosis.
- The most important medical problems in ovaries are the neoplasms
- Death from ovarian cancers is more common than that of cervix and uterus together because ovarian tumors grow silently and are usually diagnosed late, which make them so dangerous.

Non-Neoplastic Cysts of ovary

Non Neoplastic Cyst are more common than the neoplastic ones. They usually cause no problems. Rarely a non neoplastic cyst can rupture and cause acute pain and intrabdominal hemorrhage. Common

non-neoplastic cysts are as follows:

- **Follicullar cyst**
- **Corpus luteum cyst**
- **Theca lutein cyst**
- **Chocolate cyst /Endometriotic cyst**



Non-Neoplastic Cysts of ovary

Follicullar cyst

- Arise from the ovarian follicles and are due to distension of un-ruptured Graafian follicle.

Corpus luteum cyst

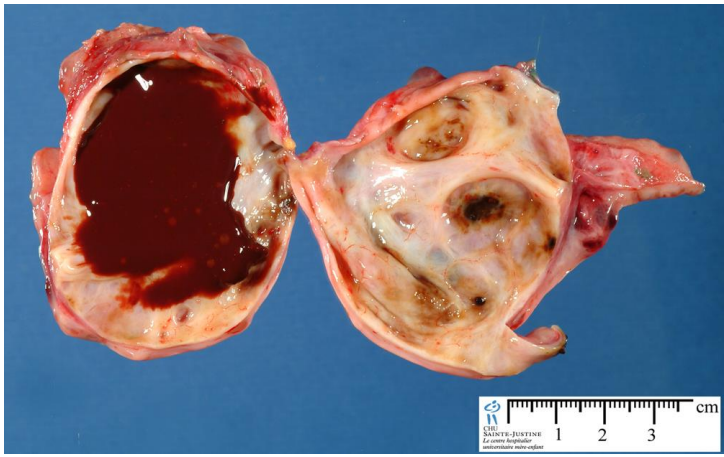
- Results from hemorrhage into a persistent mature corpus luteum.

Theca lutein cyst/ hyperreactio luteinalis

➢ Are thin walled cysts lined by luteinized theca cells. They are associated with high levels of circulating gonadotropins (e.g. pregnancy, hydatidiform mole, etc).

Chocolate cyst /Endometriotic cyst

➢ The ovary is the most frequent site of endometriosis. And chocolate cyst is a blood filled cyst of the ovary. It is due to endometriosis in the ovary with hemorrhage.



Endometriotic cyst

Polycystic ovarian syndrome

- Polycystic ovarian syndrome (formerly called Stein-Leventhal syndrome) is a complex endocrine disorder characterized by hyperandrogenism, menstrual abnormalities, polycystic ovaries, chronic anovulation, and decreased fertility.
- It usually comes to attention after menarche in teenage girls or young adults who present with oligomenorrhea, hirsutism, infertility, and sometimes with obesity.
- The ovaries are usually twice the normal size, graywhite with a smooth outer cortex, and studded with subcortical cysts 0.5 to 1.5 cm in diameter.
- Histologic examination shows a thickened, fibrotic ovarian capsule overlying innumerable cystic follicles lined by granulosa cells with a hyperplastic luteinized theca interna. There is a conspicuous absence of corpora lutea in the ovary

Ovarian Tumors

- One of the leading cause of cancer death in women
- Ovarian cancers grow silently and go undetected in the early stage when it is still curable. Most of the patients already have metastasis at the time of diagnosis.
- The WHO Histological Classification for ovarian tumors divides ovarian neoplasms into **primary and metastatic (secondary).**

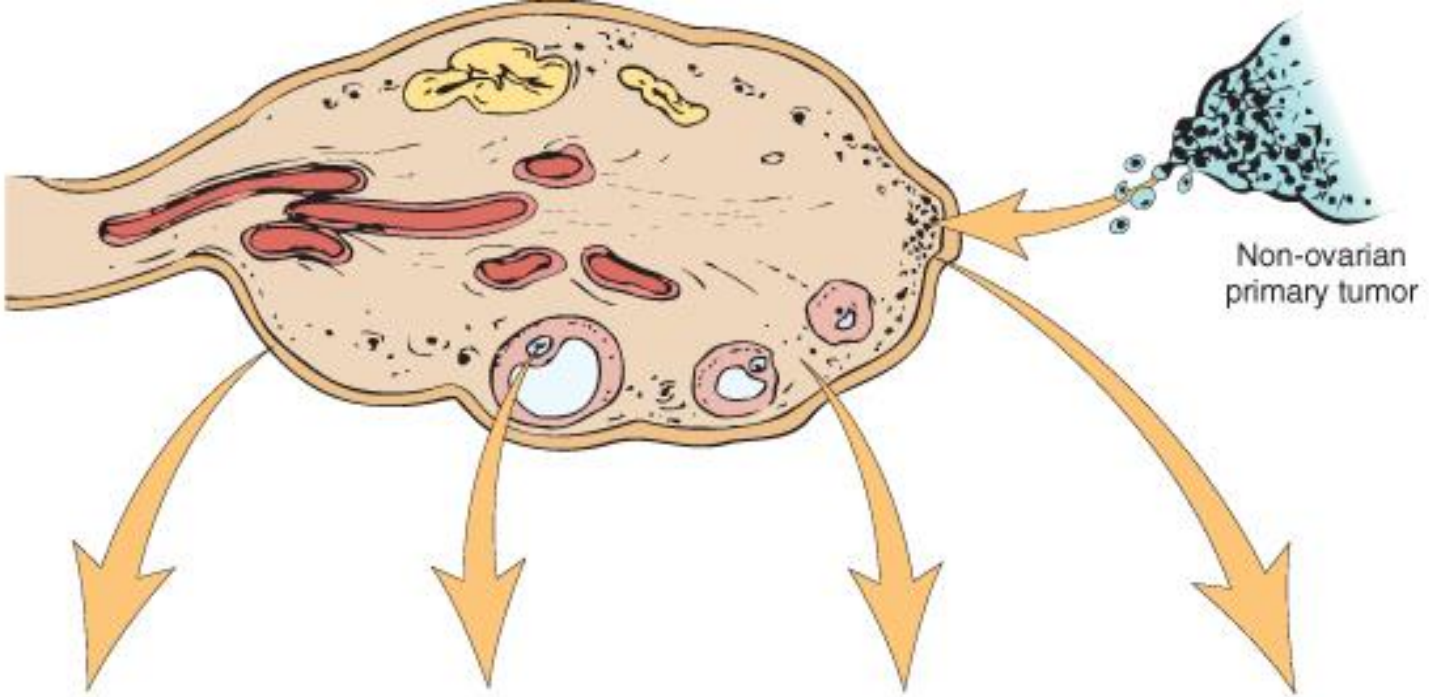
Ovarian Tumors classification

A. PRIMARY TUMORS: There are **three main primary types** of ovarian tumors based on the origin of the tumor cell. They are:

1. **Surface epithelial ovarian tumors (65%):** derived from the cells on the surface of the ovary. This is the most common form of primary ovarian cancer and occurs in adults.
2. **Germ cell tumors (15%):** derived from the from the ovarian follicles. This occurs mainly in children, teens and young women. They are less common as compared to epithelial ovarian tumors.
3. **Sex cord stromal tumors (10%):** derived from the ovarian stroma. Uncommon and this class of tumors often produces steroid hormones.

These 3 main types are further divided into many subtypes (see later).

B. METASTATIC/SECONDARY TUMORS (5%): Cancers from other organs can also spread to the ovaries



ORIGIN	SURFACE EPITHELIAL CELLS (Surface epithelial–stromal cell tumors)	GERM CELL	SEX CORD–STROMA	METASTASIS TO OVARIES
Overall frequency	65%-70%	15%-20%	5%-10%	5%
Proportion of malignant ovarian tumors	90%	3%-5%	2%-3%	5%
Age group affected	20+ years	0-25+ years	All ages	Variable
Types	• Serous tumor • Mucinous tumor • Endometrioid tumor • Clear cell tumor • Brenner tumor • Cystadenofibroma	• Teratoma • Dysgerminoma • Endodermal sinus tumor • Choriocarcinoma	• Fibroma • Granulosa–theca cell tumor • Sertoli–Leydig cell tumor	

Various ovarian neoplasms and their frequency and age distribution.

Simplified classification of primary ovarian tumors

SURFACE EPITHELIAL TUMORS

Serous tumors:
•Benign (cystadenoma)
•Borderline tumors (serous borderline tumor)
•Malignant (serous adenocarcinoma)

Mucinous tumors:
•Benign (cystadenoma)
•Borderline tumors (mucinous borderline tumor)
•Malignant (mucinous adenocarcinoma)

Endometrioid tumors:
•Benign (cystadenoma)
•Borderline tumors (endometrioid borderline tumor)
•Malignant (endometrioid adenocarcinoma)

Clear cell tumors:
•Benign
•Borderline tumors
•Malignant (clear cell adenocarcinoma)

Transitional cell tumors:
•Brenner tumor
•Brenner tumor of borderline malignancy
•Malignant Brenner tumor
•Transitional cell carcinoma (non-Brenner type)

Others

SEX CORD STROMAL TUMORS

Almost always Benign
- **Fibromas/ Fibrothecomas /Thecomas**

With Malignant Potential
- **Granulosa cell tumors**
- **Sertoli-Leydig cell tumors**

Others

GERM CELL TUMORS

•Teratoma:
- Immature (malignant)
- Mature (benign)
  - Solid
  - Cystic (dermoid cyst)
- Monodermal (e.g., struma ovarii, carcinoid)

•Dysgerminoma
•Yolk sac tumor (endodermal sinus tumor)
•Choriocarcinoma
•Embryonal carcinoma
•Mixed germ cell tumors

NOTE: all ovarian GCTs are considered as malignant except mature teratoma

Surface Epithelial Ovarian Tumors

Surface Epithelial Ovarian Tumors

- Neoplasms of surface epithelium account for majority of all primary ovarian tumors.
- Are 65 – 70 % of overall tumors
- They account for 90 % of malignant tumors in the ovary
- Age 20+

- The majority of ovarian tumors arise from the fallopian tube or epithelial cysts in the cortex of the ovary . S
- tudies have shown that many of the tumors thought to arise from the coelomic epithelium that covers the surface of the ovary are now thought to arise from the fimbriated end of the fallopian tube .
- The epithelium lining the cortical cysts may be derived from displaced ovarian surface epithelium or the lining of fallopian tube. These can become metaplastic or undergo neoplastic transformation to give rise to a number of different epithelial tumors.

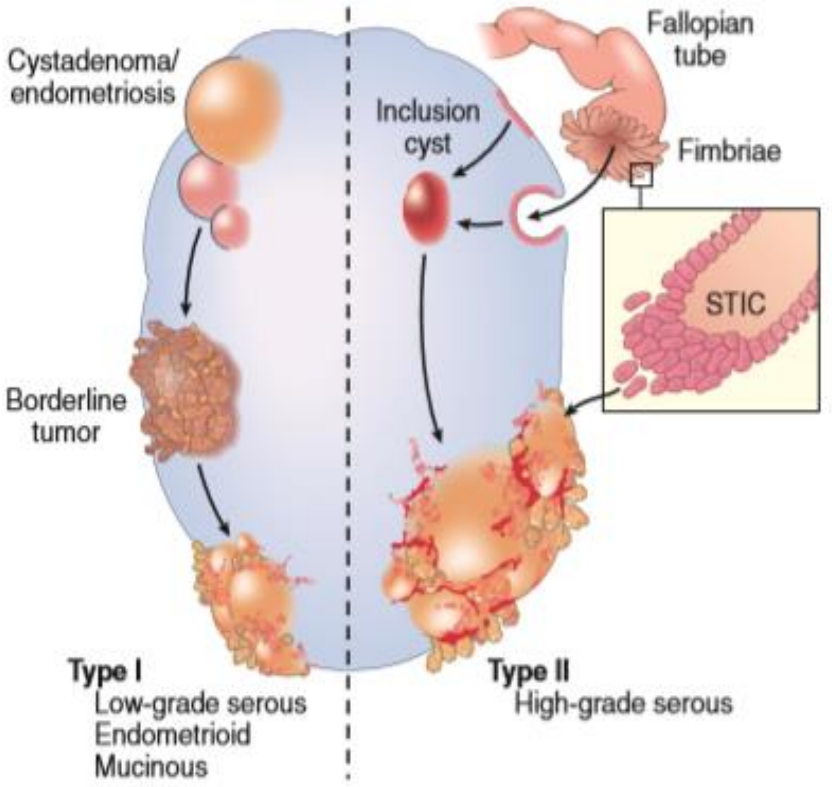


Fig. 19.15 Derivation, of various ovarian neoplasms. Type I tumors progress from benign tumors through borderline tumors that may give rise to a low-grade carcinoma. Type II tumors arise from inclusions cysts/fallopian tube epithelium via intraepithelial precursors that are often not identified. They demonstrate high-grade features and are most commonly of serous histology. STIC, serous tubal intraepithelial carcinoma.

- Important risk factors for ovarian cancer include:

nulliparity, family history, and germline mutations in certain tumor suppressor genes.

* Of interest, prolonged use of oral contraceptives reduces the risk.

*Around 5% to 10% of ovarian cancers are familial, and most of these are associated with mutations in the BRCA1 or BRCA2 tumor suppressor genes. mutations in BRCA1 and BRCA2 also are associated with hereditary breast cancer.

* The average lifetime risk for ovarian cancer is approximately 30% in BRCA1 carriers; the risk in BRCA2 carriers is somewhat lower.

Surface Epithelial Ovarian Tumors

The subtypes of the surface epithelial tumors are:

- **Serous Tumors**
- **Mucinous Tumors**
- **Endometrioid Tumors**
- **Clear cell Tumors**
- **Transitional/Brenner cell Tumors**
- **Others**

All surface epithelial tumors are further divided into:

i. **Benign:** They do not spread and invade other tissues.

ii. **Malignant:** are carcinomas and have potential to metastasize beyond the ovary.

iii. **Borderline/ intermediate/ tumors of low malignant potential**: this is a gray zone. They are 'semi-malignant'. These appear to be low grade cancers with limited invasive potential. They have better prognosis than malignant. These tumors may seed or implant into the peritoneum.

Simplified classification of primary ovarian tumors

SURFACE EPITHELIAL TUMORS

A. Serous tumors:
- Benign (cystadenoma) /(cystadenofibroma)
- Borderline tumors (serous borderline tumor)
- Malignant (serous adenocarcinoma)

B. Mucinous tumors, endocervical-like and intestinal type:
- Benign (cystadenoma)
- Borderline tumors (mucinous borderline tumor)
- Malignant (mucinous adenocarcinoma

C. Endometrioid tumors:
- Benign (cystadenoma)
- Borderline tumors (endometrioid borderline tumor)
- Malignant (endometrioid adenocarcinoma)

D. Clear cell tumors:
- Benign
- Borderline tumors
- Malignant (clear cell adenocarcinoma)

E. Transitional cell tumors:
- Brenner tumor
- Brenner tumor of borderline malignancy
- Malignant Brenner tumor
- Transitional cell carcinoma (non-Brenner type)

F. Others

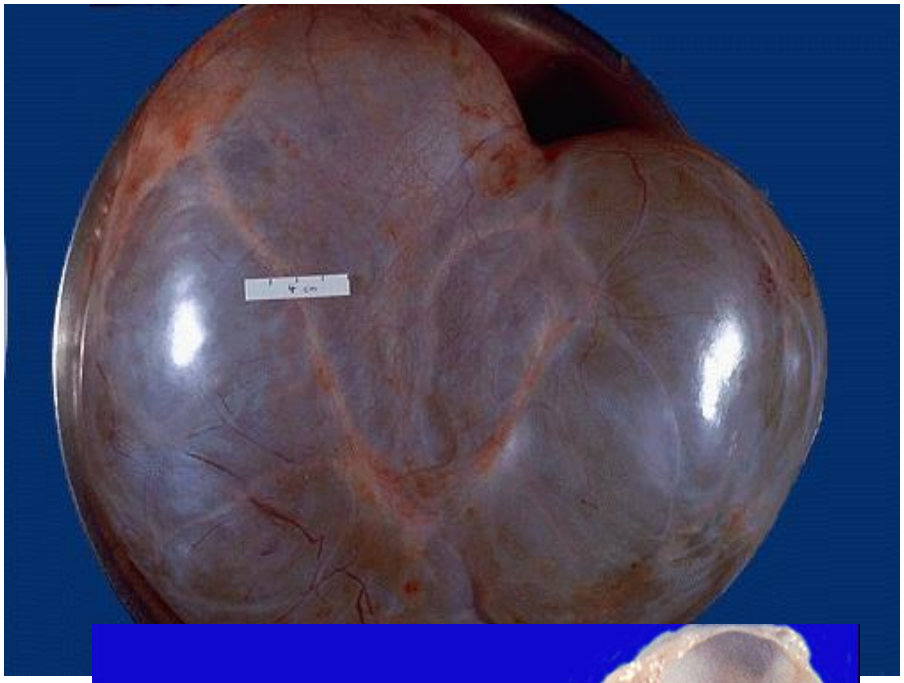
Serous tumors

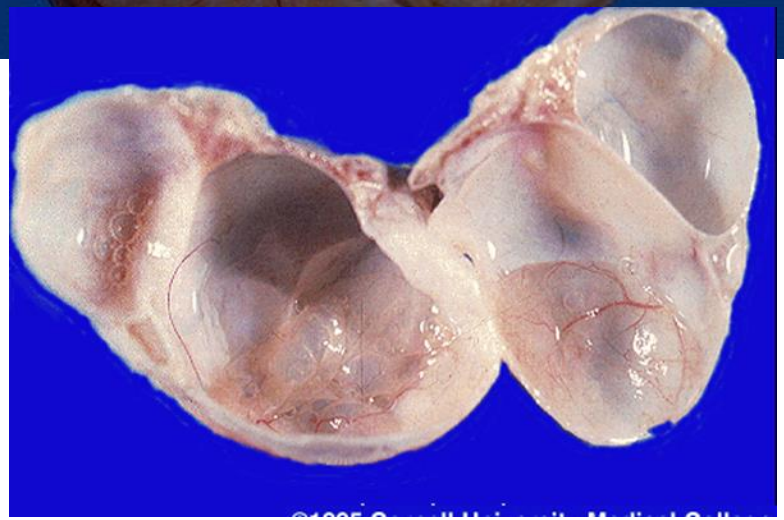
- Serous tumors are the most common of the ovarian epithelial tumors overall, and also make up the greatest fraction of malignant ovarian tumors.
- About 60% are benign, 15% are borderline, and 25% are malignant.
- Benign lesions are usually encountered in patients between 30 and 40 years of age, and malignant serous tumors are more commonly seen between 45 and 65 years of age.
- There are two types of serous carcinomas, low-grade and high-grade. The former arise from benign or borderline lesions and progress slowly in a stepwise manner to become invasive carcinoma. These low-grade tumors are associated with mutations in genes encoding signaling proteins, such as KRAS, a member of the RAS gene family.
- The high-grade serous tumors develop rapidly. many of these high-grade lesions arise in the fimbriated end of the fallopian tube via serous tubal intraepithelial carcinoma, rather than ovarian coelomic epithelium.
- TP53 mutations in high-grade serous cancers, being present in over 95% of cases.
- Other frequently mutated genes include the tumor suppressors NF1 and RB, as well as BRCA1 and BRCA2 in familial ovarian cancers.

Serous tumor, morphology

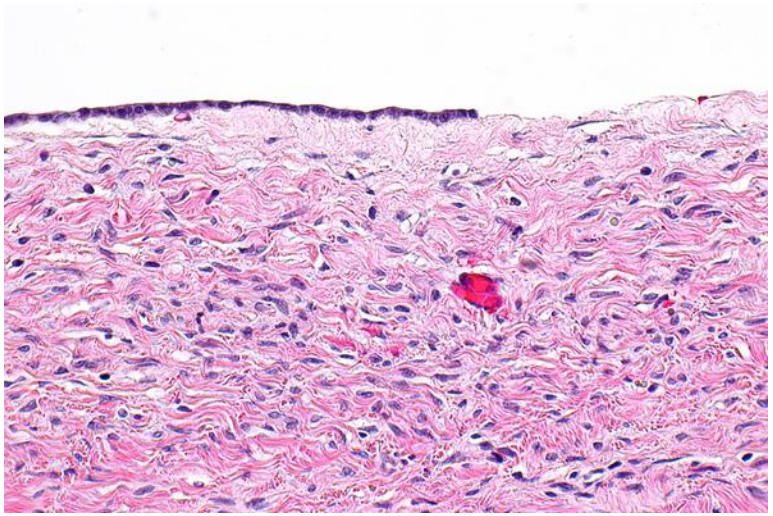
- **Gross**:
- Most serous tumors are large, spherical to ovoid, cystic structures up to 30 to 40 cm in diameter.
- About 25% of the benign tumors are bilateral.
- In the benign tumors, the serosal covering is smooth and glistening. By contrast, the surface of adenocarcinomas often has nodular irregularities representing areas in which the tumor has invaded the serosa.
- On cut section, small cystic tumors may have a single cavity, but larger ones frequently are divided by multiple septa into multiloculated masses. The cystic spaces usually are filled with a clear serous fluid. Protruding into the cystic cavities are papillary projections, which are more prominent in malignant tumors

Serous cystadenoma





single layer of columnar epithelial cells that line the cyst or cysts. The cells often are ciliated. Psammoma bodies (concentrically laminated calcified concretions) are commo



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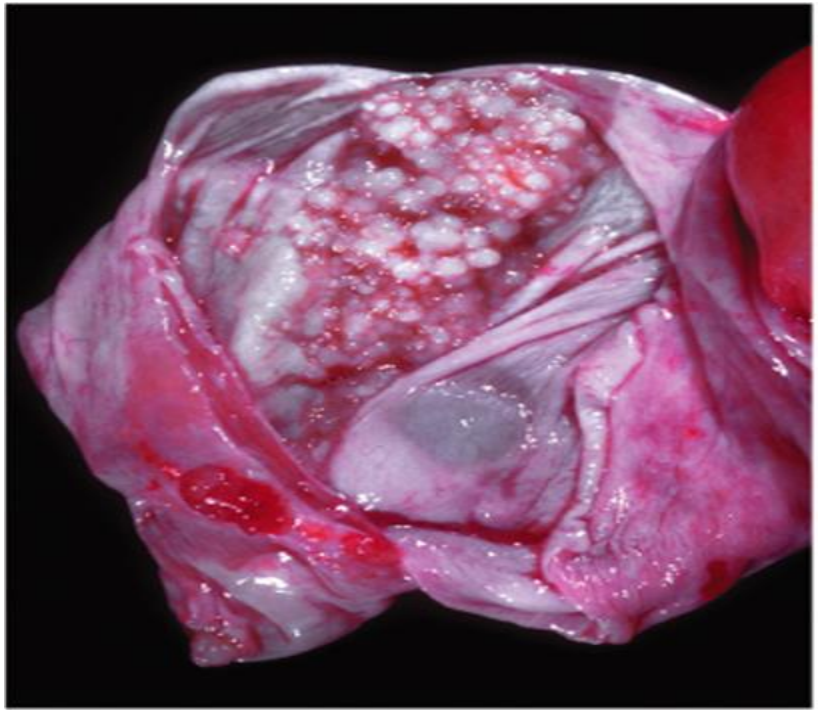
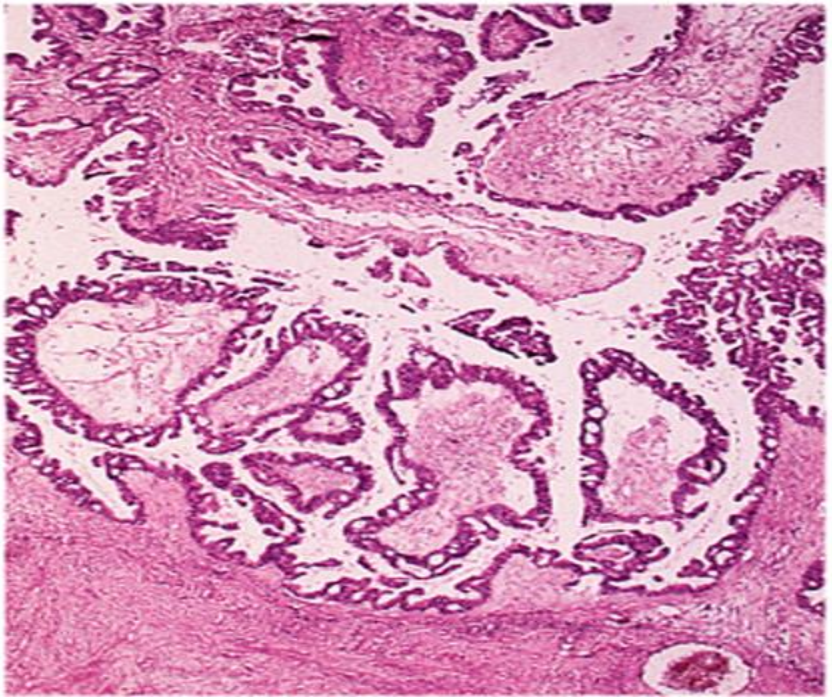
Borderline serous tumor

borderline tumors, which exhibit cytologic atypia and typically no stromal invasion

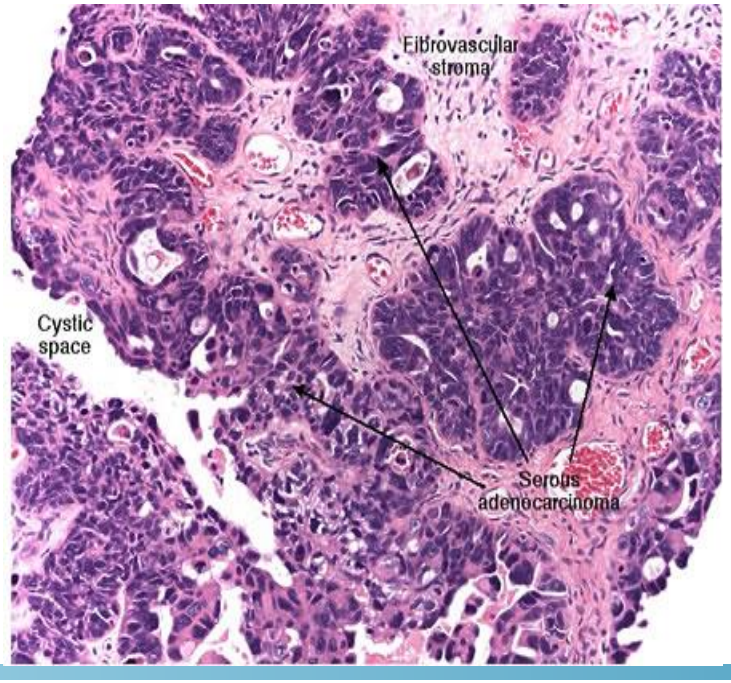




"Ovarian Cancer - A Clinical and Translational Update", book edited by Iván Díaz-Padilla, ISBN 978-953-51-1030-9, Published: February 27, 2013 under CC BY 3.0 license. © The Author(s). **Borderline Epithelial Tumors of the Ovary** By Gennaro Cormio, Vera Loizzi, Maddalena Falagario, Doriana Scardigno, Donatella Latorre and Luigi E. Selvaggi DOI:http://dx.doi.org/10.5772/54828

Serous cystadenocarcinoma, ovary

In high-grade carcinoma the cells are markedly atypical, the papillary formations are usually complex and multilayered, and by definition nests or sheets of malignant cells invade the ovarian stroma.



Ed Uthman, MD.
http://web2.airmail.net/uthman/specimens/images/ovary_serous_ca.html

imgbuddy.com
http://missinglink.ucsf.edu/lm/IDS_107_ovary_uterus_kidney/assets/Slide340OACAhp_small.jpg

Serous tumors prognosis

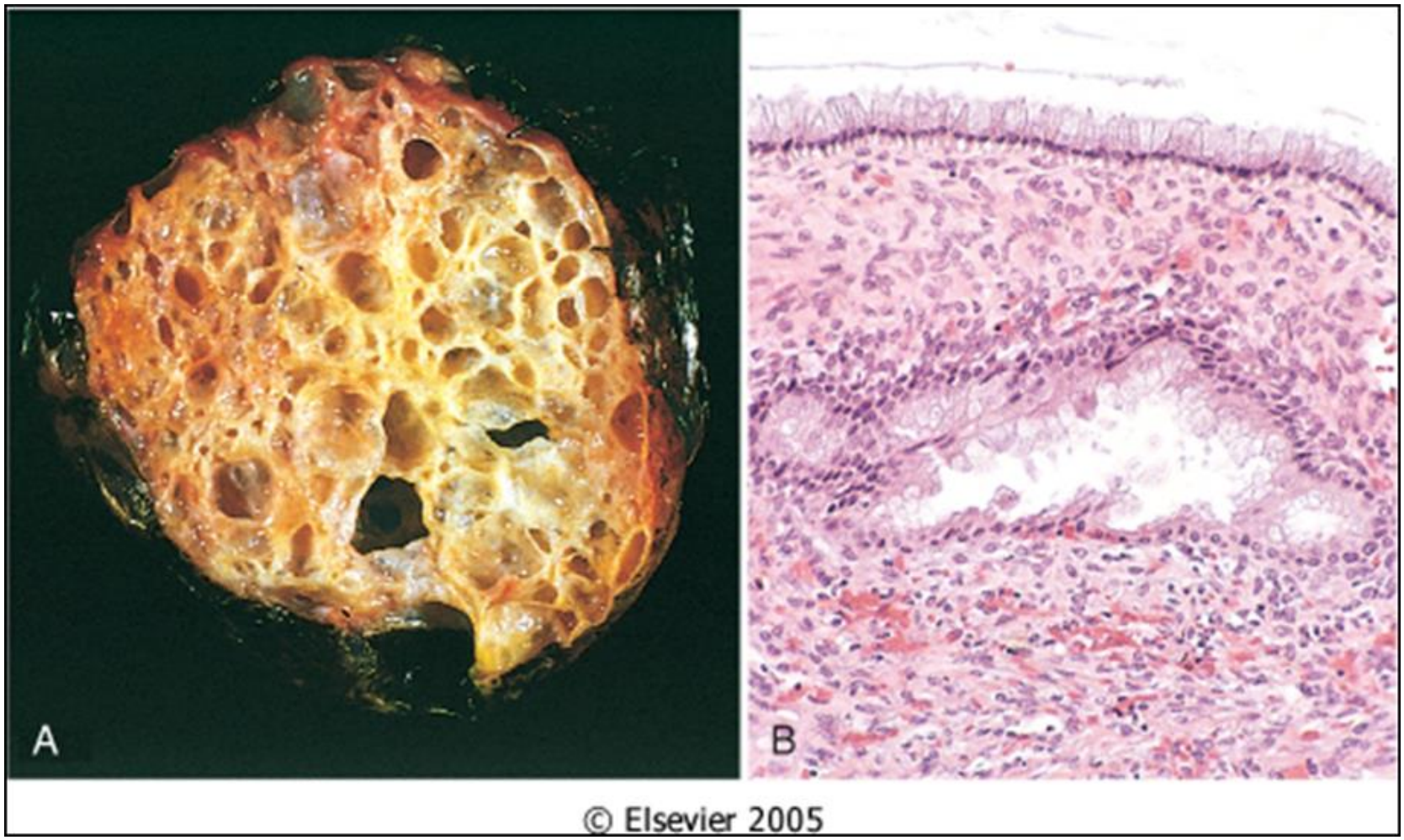
- In general, malignant serous tumors spread throughout the peritoneal cavity and to regional lymph nodes, including periaortic lymph nodes; distant lymphatic and hematogenous metastases are infrequent.
- The prognosis for patients with high-grade serous carcinoma is poor, even after surgery and chemotherapy, and depends heavily on the stage of the disease at diagnosis..

Mucinous Tumors

- Mucinous tumors form about 25% of all ovarian neoplasms. The tumor cells are mucin-producing cells (which are either endocervical type or intestinal type cells).
- Less likely to be malignant
- 80% are benign
- 10% are borderline
- 10% malignant
- Bilaterality is uncommon.
- Mucinous tumors can be very large.
- They are typically cystic and multilocular and filled with thick sticky, viscous mucoid fluid.

- Mucin-producing epithelial cells line the cyst
- Malignant tumors are characterized by solid areas of growth, piling up (stratification) of lining cells, cytologic atypia, and stromal invasion.
- Compared with serous tumors, mucinous tumors are much less likely to be bilateral. 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.

Mucinous cystadenoma with multicystic cut section and glistening mucoid material; in it.
B. the cyst is lined by columnar epithelium (mucin producing)



Other surface epithelial tumors

ENDOMETRIOID TUMORS

- They have tubular gland that resemble the endometrium so the name endometrioid (endometrium-like) .
- Endometrioid tumors form 10 to 20% of all ovarian tumors.
- Most of the endometrioid tumors are malignant (carcinomas).
- Some endometrioid tumors are accompanied by an endometrial carcinoma in the uterus and / or endometriosis in the ovaries

TRANSITIONAL CELL/ BRENNER TUMOR

- Tumor cell are transitional cell type
- Most are benign

Germ Cell Tumors

Classification of Ovarian Germ Cell Tumors (GCT)

GERM CELL TUMORS

- **Teratoma:**
  - Immature
  - Mature (benign)
    - Solid
    - Cystic (dermoid cyst)
    - Monodermal (e.g., struma ovarii, carcinoid)
- **Dysgerminoma**
- **Yolk sac tumor (endodermal sinus tumor)**
- **Choriocarcinoma**
- **Embryonal carcinoma**
- **Mixed germ cell tumors: mixture** of germ cell tumors occurring together in one tumor mass

NOTE: all ovarian GCTs are considered malignant except mature teratoma.

Germ Cell Tumors:
Teratoma

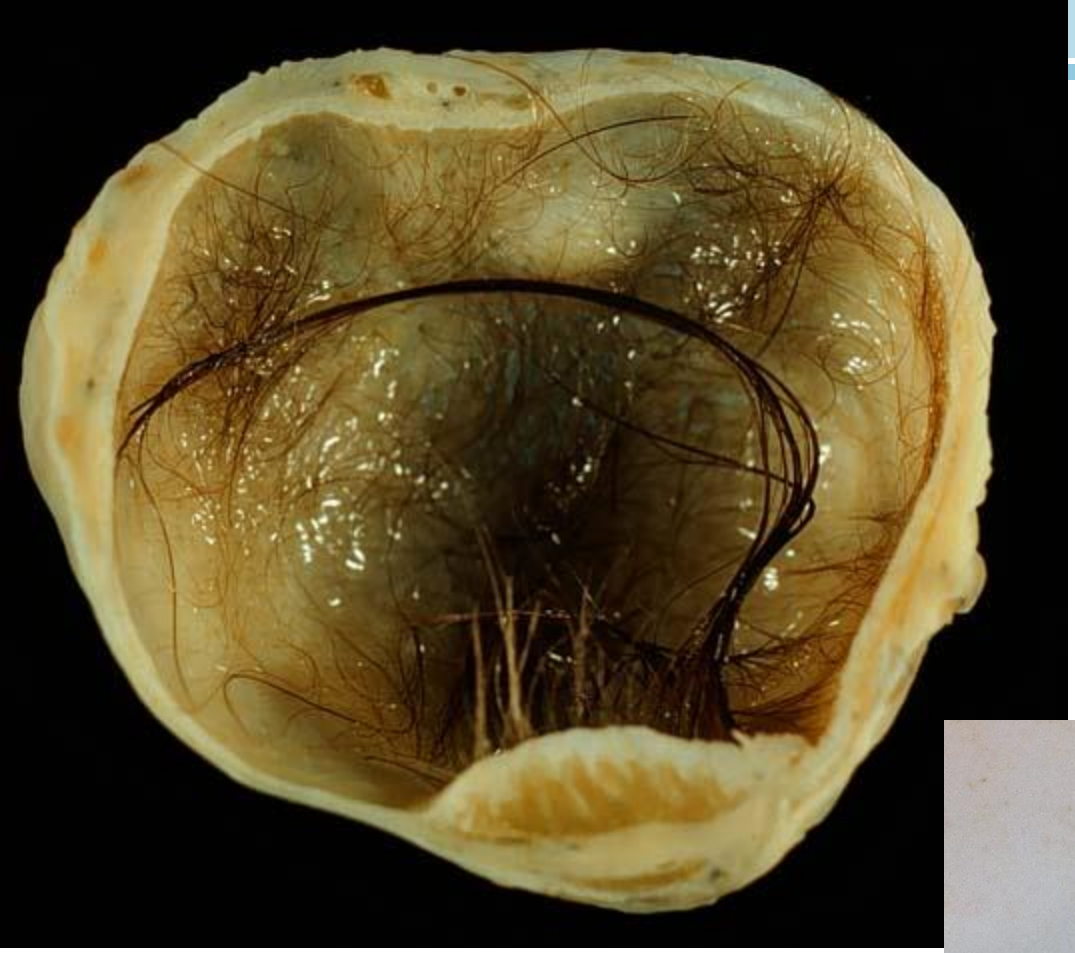
- Teratomas constitute 15% to 20% of ovarian tumors.
- A distressing feature of these germ cell tumors is their predilection to arise in the first 2 decades of life; to make matters worse, the younger the person, the greater the likelihood of malignancy.
- More than 90% of these germ cell neoplasms, however, are benign mature cystic teratomas; the immature, malignant variant is rare.

Mature cystic teratoma

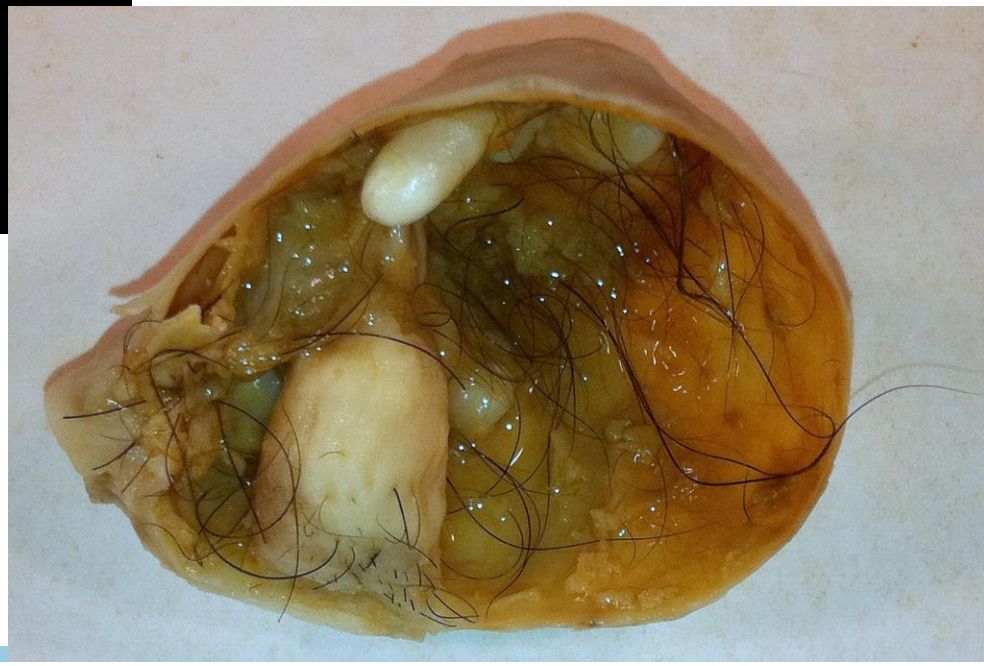
- Is the most common ovarian germ cell tumor and the most common type of ovarian teratoma
- It is a benign neoplasm that typically occurs during reproductive years composed of mature elements of the ectoderm, endoderm and mesoderm
- It is a cystic tumor, filled with sebaceous material and hair and occasionally teeth.
- Histology: skin, hair, sebaceous glands, and mature neural tissue predominate; cartilage, bone, respiratory and intestinal epithelium are common.
- Complications include torsion, rupture, infection etc.

Benign (mature) cystic teratomas

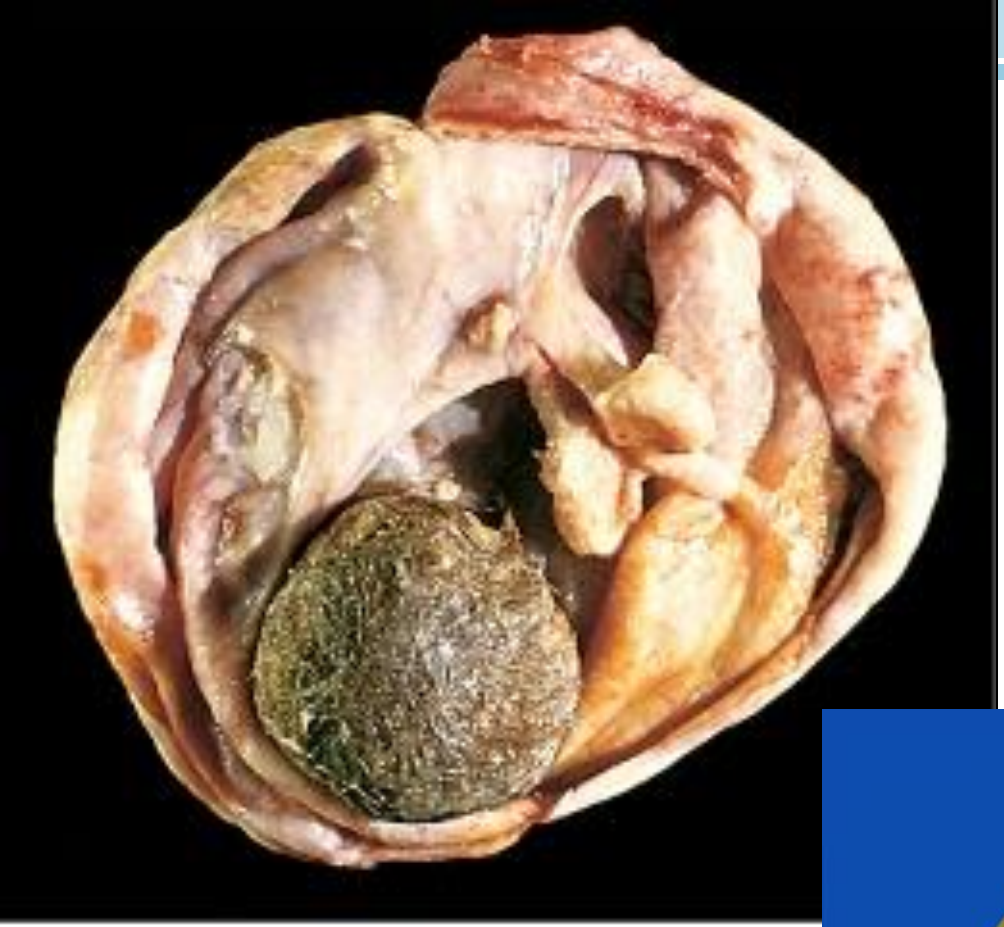
- are marked by the presence of mature tissues derived from all three germ cell layers: ectoderm, endoderm, and mesoderm.
- Usually these tumors contain cysts lined by epidermis with adnexal appendages—hence the common designation dermoid cysts.
- Most are discovered in young women as ovarian masses or are found incidentally on abdominal radiographs or scans because they contain foci of calcification produced by toothlike structures contained within the tumor.
- About 90% are unilateral
- On cut section, they often are filled with sebaceous secretion and matted hair that, when removed, reveal a hair-bearing epidermal lining .
- Sometimes there is a nodular projection from which teeth protrude. Occasionally, foci of bone and cartilage, nests of bronchial or gastrointestinal epithelium, or other tissues are present.
- For unknown reasons, these neoplasms sometimes produce infertility and are prone to undergo torsion (in 10%–15% of cases), which constitutes an acute surgical emergency.
- Malignant transformation, usually to a squamous cell carcinoma, is seen in about 1% of cases.



"Mature cystic teratoma of ovary" by Photograph by Ed Uthman, MD. - http://web2.airmail.net/uthman/specimens/index.html. Licensed under Public Domain via Wikimedia Commons - http://commons.wikimedia.org/wiki/File:Mature_cystic_teratoma_of_ovary.jpg#/media/File:Mature_cystic_teratoma_of_ovary.jpg

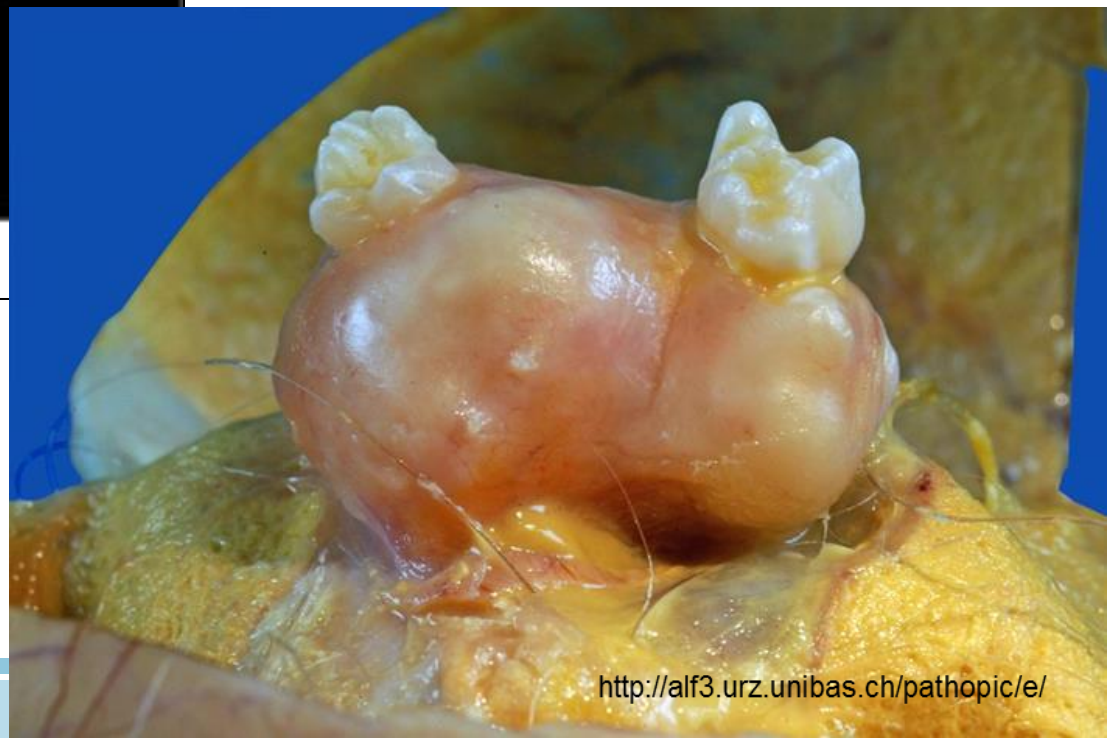


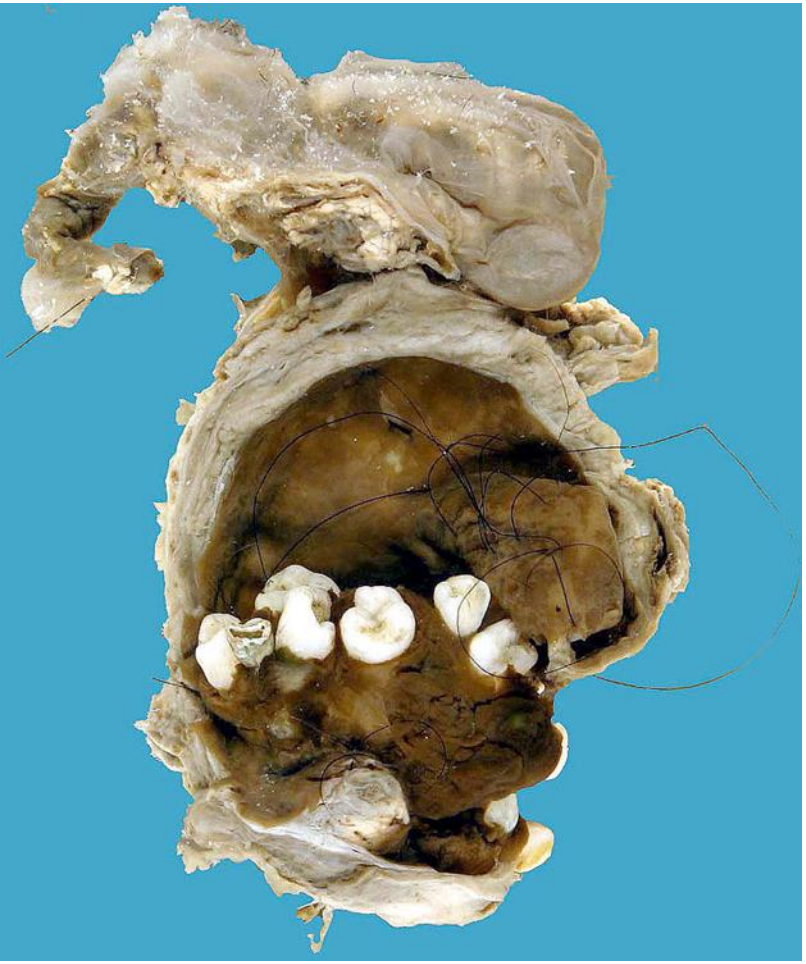
http://commons.wikimedia.org/wiki/File:Mature_Cystic_Teratoma_of_the_Ovary_%285560431170%29.jpg

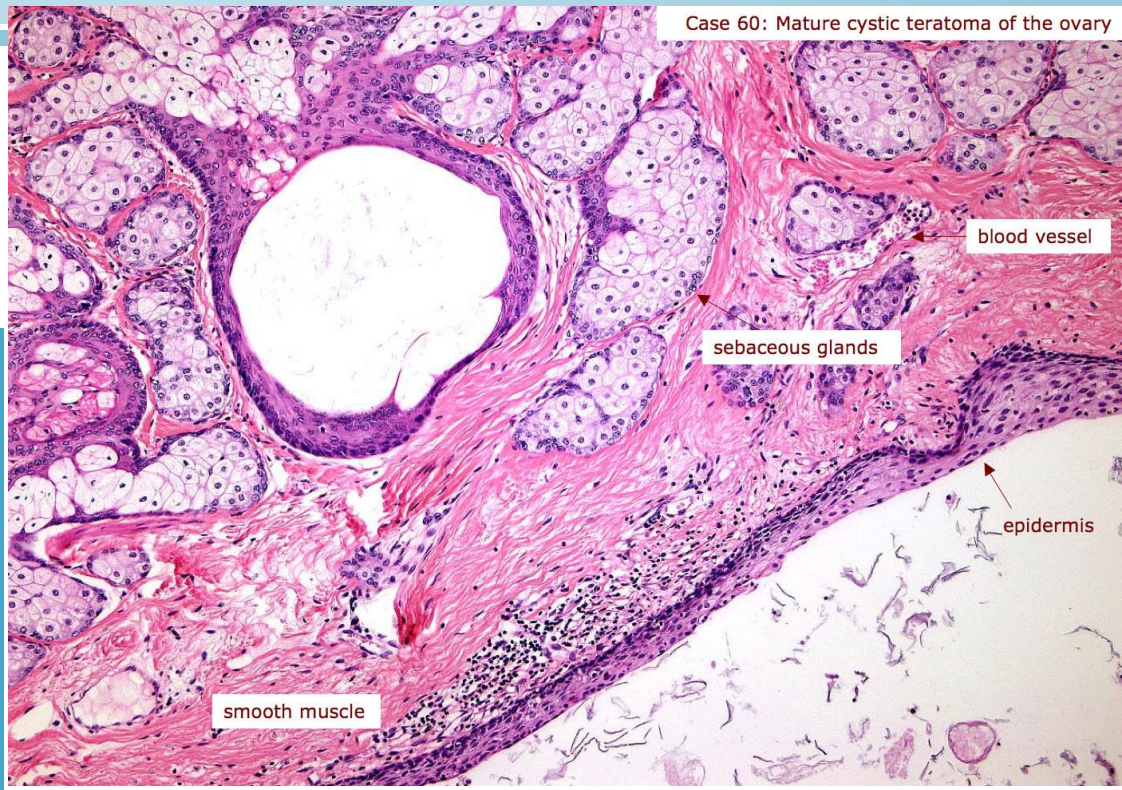


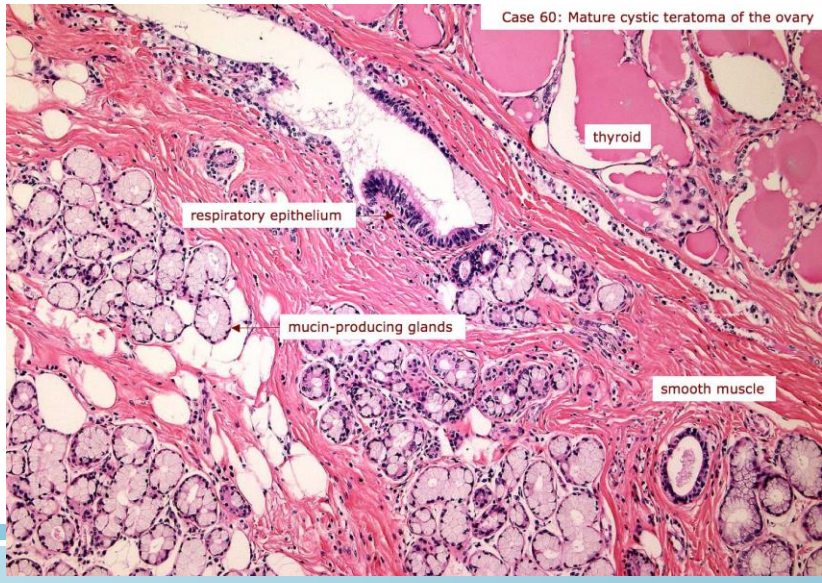
Opened mature cystic teratoma (dermoid cyst) of the ovary. Hair ball is present.

Robbins & Cotran Pathologic Basis of Disease







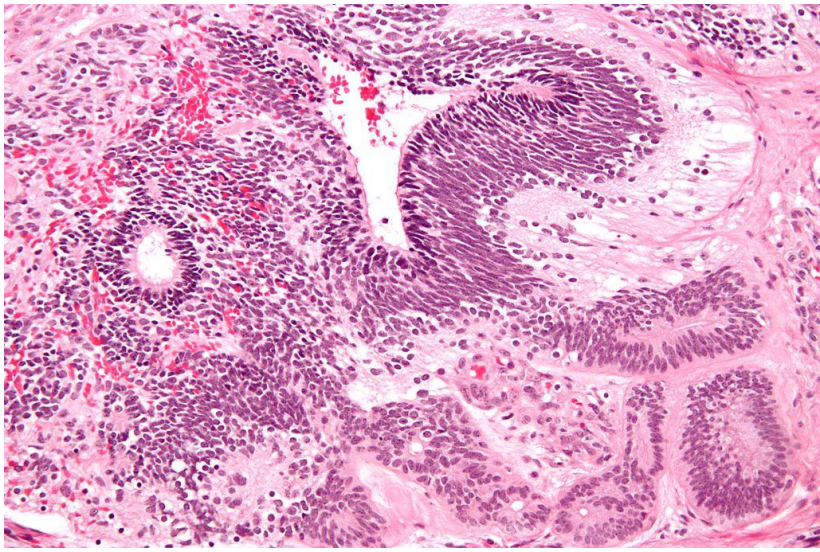


https://secure.health.utas.edu.au/intranet/cds/pathprac/Files/Cases/Female/Case60/Case60.htm

Germ Cell Tumors:
Teratoma

Immature teratoma

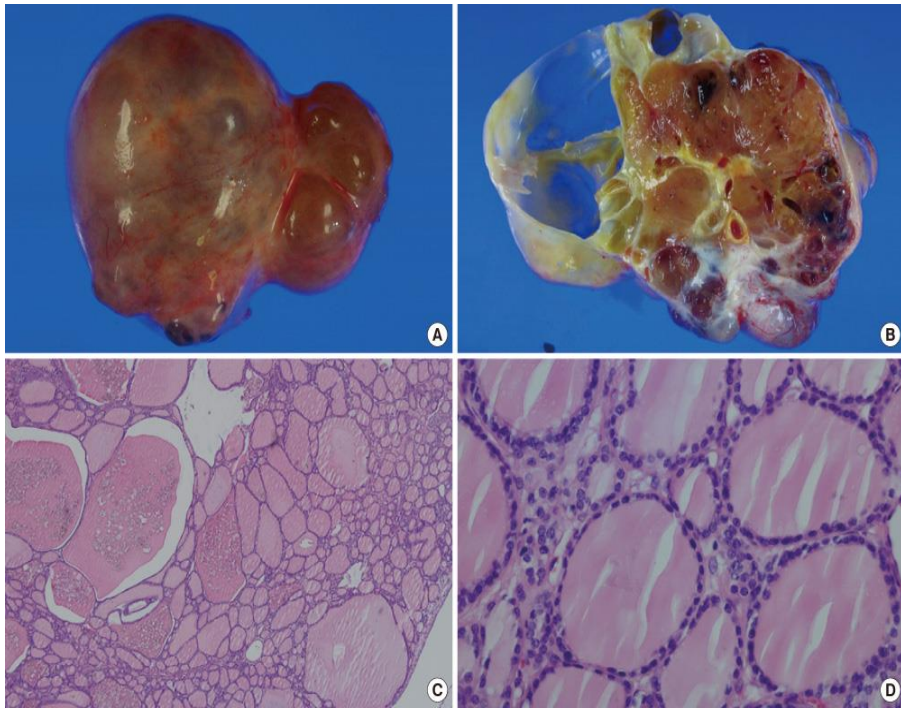
- Are found early in life, the mean age at clinical detection being 18 years.
- They typically are bulky and appear solid on cut section, and they often contain areas of necrosis; uncommonly, cystic foci are present that contain sebaceous secretion, hair, and other features similar to those of mature teratomas.
- On microscopic examination, the distinguishing feature is the presence of immature elements or minimally differentiated cartilage, bone, muscle, nerve, or other tissues.
- As with other tumors, the prognosis depends on grade and stage



Germ Cell Tumors: Teratoma

Specialized teratoma

- A rare subtype of teratoma is composed entirely of specialized tissue. The most common example is struma ovarii. which is composed entirely of mature thyroid tissue that may actually produce hyperthyroidism. These tumors appear as small, solid, unilateral brown ovarian masses.
- Other specialized teratomas include ovarian carcinoid, which in rare instances produces carcinoid syndrome.



A Case of Bilateral Struma Ovarii Combined with Subclinical Hyperthyroidism
Endocrinol Metab. 2012 Mar;27(1):72-76. Korean. http://dx.doi.org/10.3803/EnM.2012.27.1.72

Table 19.4 Salient Features of Ovarian Germ Cell and Sex Cord Neoplasms

Neoplasm	Peak Incidence	Usual Location	Morphologic Features	Behavior
Germ Cell Origin				
Dysgerminoma	Second to third decade of life Occur with gonadal dysgenesis	Unilateral in 80%–90%	Counterpart of testicular seminoma Sheets or cords of large clear cells Stroma may contain lymphocytes and occasional granulomas	All malignant but only one-third metastasize; all radiosensitive; 80% cure rate
Choriocarcinoma	First 3 decades of life	Unilateral	Identical to placental tumor Two types of epithelial cells: cytotrophoblast and syncytiotrophoblast	Metastasizes early and widely Primary focus may degenerate, leaving only metastases Resistant to chemotherapy
Sex Cord Tumors				
Granulosa-theca cell	Most postmenopausal, but may occur at any age	Unilateral	Composed of mixture of cuboidal granulosa cells and spindled or plump lipid-laden theca cells Granulosa elements may recapitulate ovarian follicle as Call-Exner bodies	May elaborate large amounts of estrogen Granulosa element may be malignant (5%–25%)
Thecoma-fibroma	Any age	Unilateral	Yellow (lipid-laden) plump thecal cells	Most hormonally inactive About 40% produce ascites and hydrothorax (Meigs syndrome) Rarely malignant
Sertoli-Leydig cell	All ages	Unilateral	Recapitulates development of testis with tubules or cords and plump pink Sertoli cells	Many masculinizing or defeminizing Rarely malignant
Metastases to Ovary				
	Older ages	Mostly bilateral	Anaplastic tumor cells, cords, glands, dispersed through fibrous background Cells may be "signet ring" mucin-secreting	Primaries are gastrointestinal tract (Krukenberg tumors), breast, and lung

Summary

- Tumors may arise from epithelium, sex cord–stromal cells, or germ cells.
- Epithelial tumors are the most common malignant ovarian tumors and are more common in women older than 40 years of age.
- The major types of epithelial tumors are serous, mucinous, and endometrioid. Each has a benign, malignant, and borderline (low malignant potential) counterpart.
- Sex cord–stromal tumors may display differentiation toward granulosa, Sertoli, Leydig, or ovarian stromal cell type. Depending on differentiation, they may produce estrogens or androgens.
- Germ cell tumors (mostly cystic teratomas) are the most common ovarian tumor in young women; a majority are benign.
- Germ cell tumors may differentiate toward oogonia (dysgerminoma), primitive embryonal tissue (embryonal), yolk sac (endodermal sinus tumor), placental tissue (choriocarcinoma), or multiple fetal tissues (teratoma).

Reference

- Robbins basic pathology 10th edition