Ovarian Tumors (and adnexa)

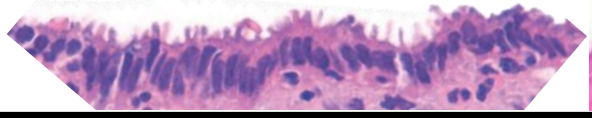
Physiologic/Non-neoplastic Lesions

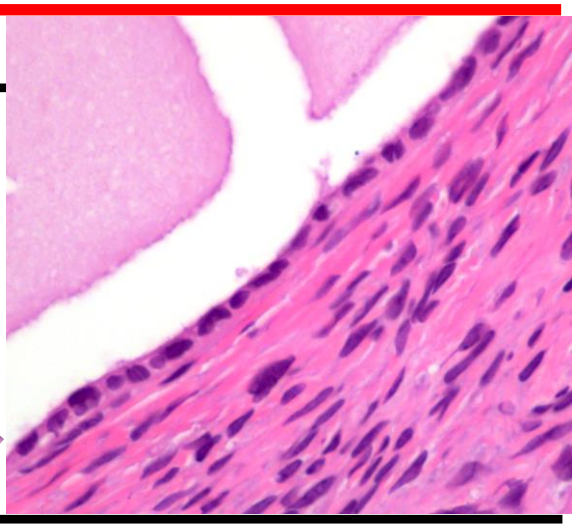
Cortical Inclusion Cyst

Typically lined by, at least focally, **tubal-type epithelium**.
Other areas may have <u>non-specific flattened cuboidal lining</u>.

Common **incidental** finding. Usually in **cortex**.
More common in older women.

By convention, **<1cm**
(If >1cm→ serous cystadenoma)



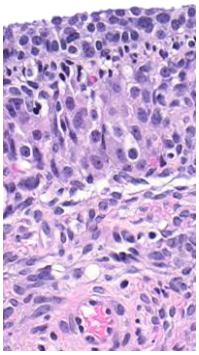


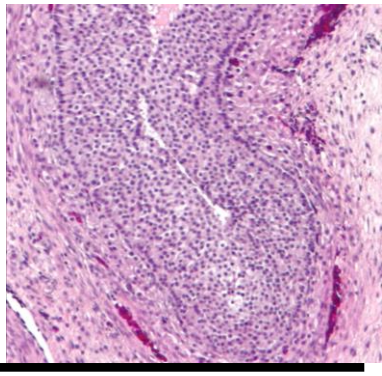
Follicle Cyst

Cyst lined by **uniform granulosa cells**, which are often **luteinized**, with outer theca cells.

Usually ~4cm (almost always <8cm)

Physiologic during reproductive age
Likely due to abnormal pituitary gonadotropin secretion



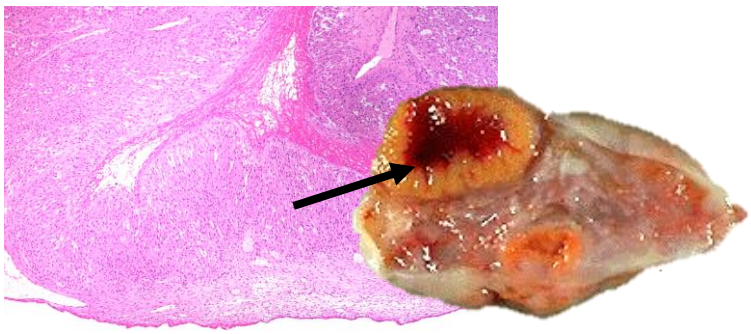


Corpus Luteum Cyst

Undulating, convoluted, thick lining composed of large, luteinized granulosa cells.

Grossly yellow and filled with blood.

Supposed to be >3cm to be a "cyst"

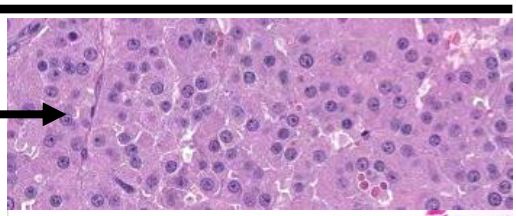


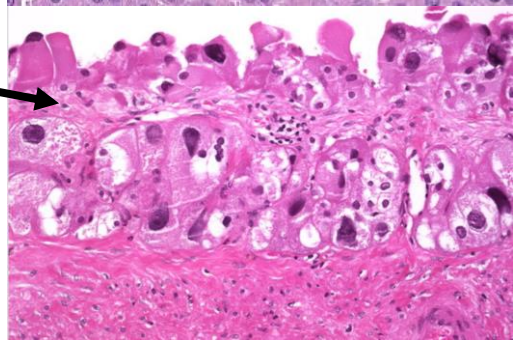
Pregnancy-related lesions

<u>Pregnancy luteoma</u>—Multinodular hyperplastic proliferation of luteinized cells during pregnancy

<u>Large solitary luteinized follicle cyst</u>—large, unilateral, solitary cyst lined by luteinized cells occurring around pregnancy.

<u>Hyperreactio Luteinalis</u>—bilateral ovarian enlargement due to numerous luteinized follicle cysts related to pregnancy. Ovulation induction can result in similar changes (Ovarian hyperstimulation syndrome)





Ovarian Tumors/Neoplasms

Always think Broadly!

Consider the 4 main families of ovarian tumors

Ovarian Tumors

Germ Cell

~10%

- Dysgerminoma
- Choriocarcinoma
- Teratoma
- Yolk Sac
- Embryonal

Sometimes "Mixed"

Epithelial/Surface

~70%

- Brenner
  - Nests of cells resembling Bladder in fibrous stroma
- Serous
  - Cells resembling fallopian tube
  - 2 pathways:
  - 1)Low-grade (KRAS/BRAF mt)
  - 2) High-grade (p53 mt and genetically unstable)
- Mucinous
  - Mucinous epithelium (must consider GI source if carcinoma)
- Endometrioid
  - Resembles endometrial glands
  - Associated with Endometriosis
- Clear Cell
  - Large, clear cells with pleomorphic nuclei
  - Associated with Endometriosis

Sex Cord-Stromal

~15%

Metastasis

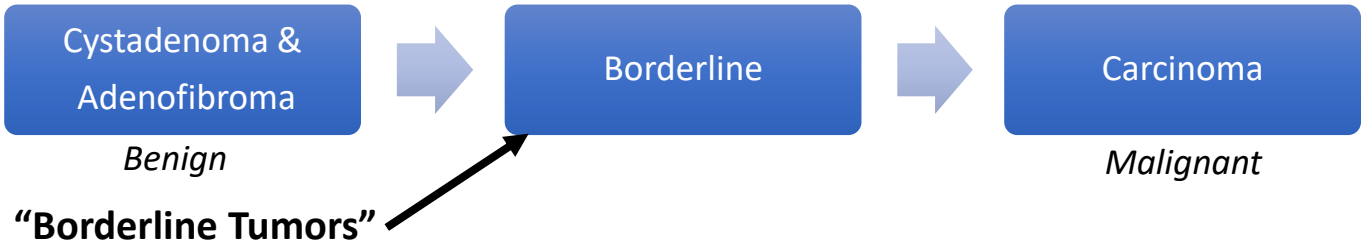
Always a possibility, often from **GI tract**

~5%

Remembering the "pentagons" can help you remember that there are 5 of each

Epithelial/Surface Subclassification:

Three levels of biologic potential



"Borderline Tumors"

aka (older terminology): "Atypical proliferative tumor" or "Low Malignant Potential (LMP)"
Neither clinically benign or malignant: Peritoneal dissemination and recurrence, but rarely death
Neither morphologically benign or malignant: Architectural complexity, but no invasion or high-grade cytology
Serous and seromucinous borderline tumors are morphologically and clinically borderline.
Mucinous, endometrioid, and clear cell borderline tumors are morphologically borderline, but clinically benign.

Given the differences in outcome between borderline and carcinoma, these tumors must be well sampled (>1 section / cm) to appropriately exclude a carcinomatous component.

Distribution of each Epithelium type by biologic potential:

	Serous	Mucinous	Endometrioid	Clear Cell	Brenner/ Transitional	Seromucinous
Benign	50%	80%	5%	<1%	99%	<1%
Borderline	15%	15%	20%	<1%	<1%	99%
Carcinoma	35%	5%	75%	99%	<1%	N/A

Histologically exists, **but** likely not a true histomolecular entity that will eventually disappear as likely composed of serous and endometrioid tumors

Common *mixtures* of Epithelial tumors:

- Brenner + Mucinous Cystadenoma or Borderline
- Serous + Seromucinous Borderline
- Endometrioid + Clear Cell Carcinoma

Carcinoma	PAX8	WT1	p53 mutant	Napsin A	PR
High-grade Serous	95%	**95%**	**>95%**	1%	40%
Low-grade Serous	95%	**99%**	0%	0%	60%
Endometrioid	80%	10%	15%	5%	**80%**
Clear cell	95%	1%	10%	**95%**	5%
Mucinous	40%	0%	60%	0%	0%

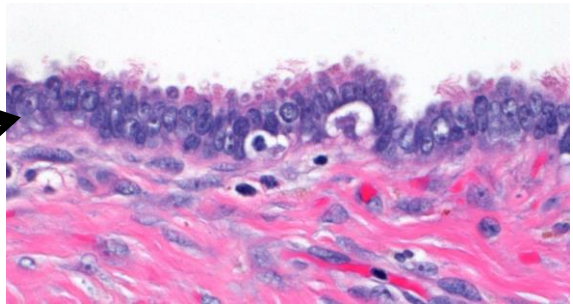
Adapted from WHO Classification of Tumors: Female Genital Tumors. 5th ed.

Epithelial/Surface

Serous

Fallopian Tube-like *Thought to arise from either tubal metaplasia of cortical inclusion cysts (likely derived from surface mesothelium) or tubal implant*

Serous Cystadenoma/Adenofibroma

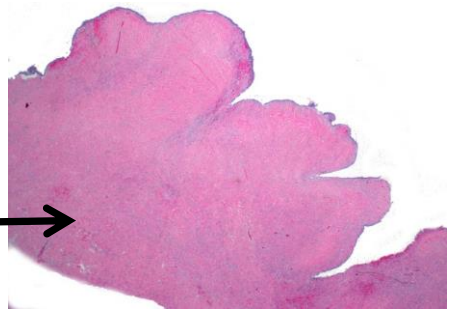


Benign. Often incidental and asymptomatic in reproductive age.

Epithelium resembles **fallopian tube**

- Cuboidal to columnar cells; Simple architecture
- **Ciliated**
- Sometimes stratified; No hierarchical branching

Can be cystic → **Serous cystadenoma**
>1 cm in size (if < 1cm considered a cortical inclusion cyst)

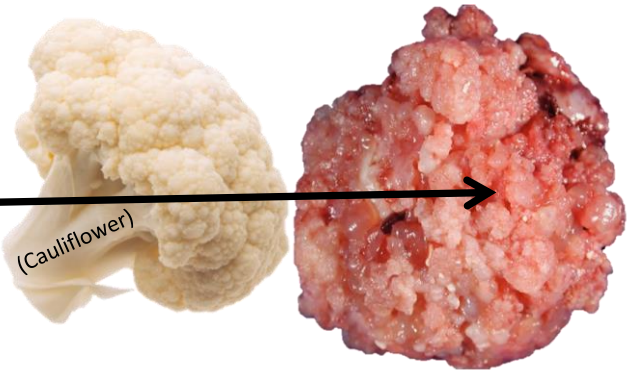


Can have a prominent exophytic fibrous component → **Serous adenofibroma**

Can have BOTH → **Serous cystadenofibroma**

Molecular: Typically **polyclonal** (not neoplasms→ hyperplastic expansion of epithelial inclusions)

Serous Borderline Tumor

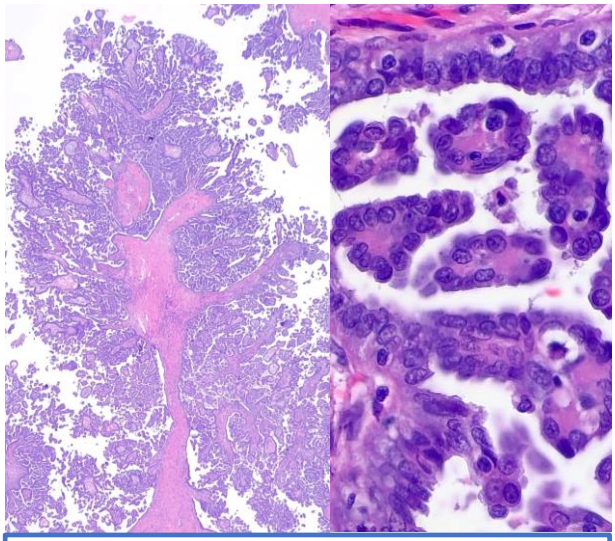


Typically middle-aged women (median 50)

Grossly, cystic with a papillary proliferation that resemble **cauliflower;** Often bilateral

Non-invasive tumors with greater epithelial proliferation and atypia

- **Hierarchical branching**: papillae branch into progressively smaller papillae (like a tree)
- **Epithelial tufting** of columnar to cuboidal cells
- Minimal to moderate cytologic atypia



Proliferative area must be >10% of epithelial volume → otherwise call it "Serous cystadenoma/fibroma with focal epithelial proliferation"

Molecular: KRAS and BRAF most common

IHC: Express ER, PR, PAX8, WT-1;
p53 wild-type; P16 non-diffuse

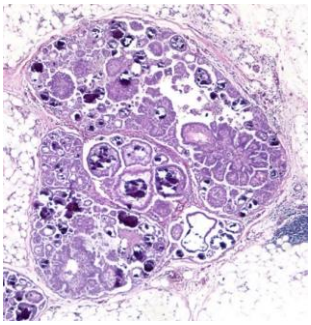
Can spread to peritoneum through "**implants**"

Prognosis depends on stage:

- If limited to ovary→ very good prognosis
- If peritoneal implants→ risk of recurrence and potentially progression to low-grade serous carcinoma

Can progress to low-grade serous carcinoma→ so must be sampled well!

Implants: *Extraovarian spread of a Serous Borderline Tumor*



Often in omentum/peritoneum.
No destructive invasion or high-grade cytology.

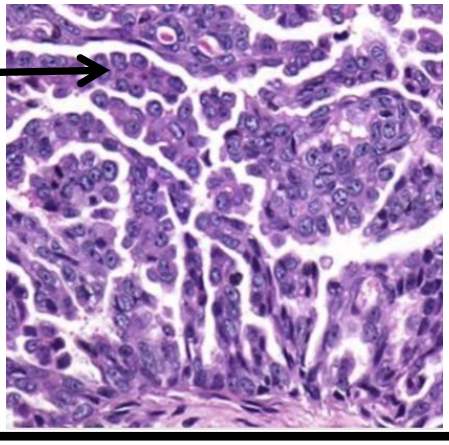
Can have desmoplasia ("reactive" fasciitis-like)→ *"desmoplastic implant"*
These are mostly reactive fibrous tissue with scant admixed epithelium tacked onto the peritoneal surface

Is there fat or muscle invasion? Are there small, solid nests of cells surrounded by a cleft-like space, micropapillae, and/or cribriform growth? If so→ low-grade serous carcinoma (formerly called invasive implants)

Diffuse high-grade cytology→ High-grade serous carcinoma

Serous Borderline Tumor - Micropapillary/Cribriform Subtype

Aka: "non-invasive low-grade serous carcinoma"

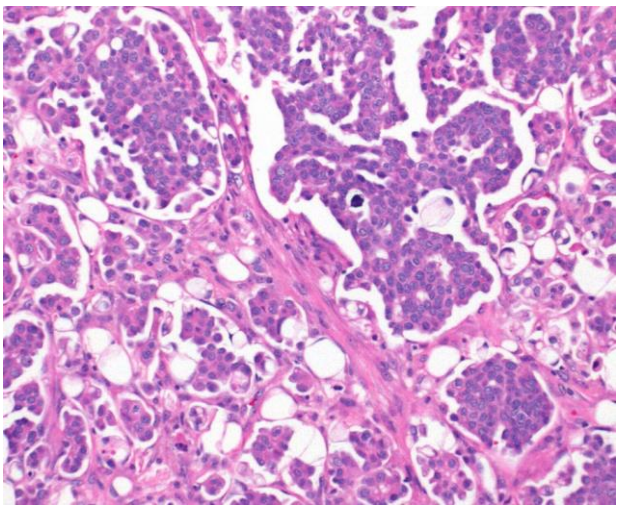


Non-hierarchical branching architecture
Fine micropapillae, 5x taller than they are wide, coming off larger fibrotic papillae (looks like a "Medusa head")
Sometimes micropapillae fuse→ cribriform growth
Cells are **cuboidal with high N:C ratios** with often prominent nucleoli

This component must be ≥ 5 mm to make Dx

When low stage→ same outcome as SBT;
Higher stage → comparatively worse outcome

Low-Grade Serous Carcinoma



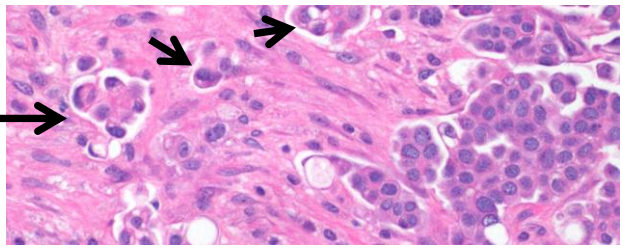
Patients about one decade younger than High-grade
Often bilateral and advanced stage

Most often arise in Serous Borderline Tumors
Several patterns of invasion:

- **Single, infiltrating pink cells**
- Irregularly-shaped **infiltrative nests**
- Micropapillae and macropapillae **surrounded by cleft-like spaces**

Frequent **psammoma bodies**→ sometimes can even obscure tumor → "psammocarcinoma"

Cells often have **moderate cytologic atypia**
(<3-fold variation in nuclear size; rare nucleoli)



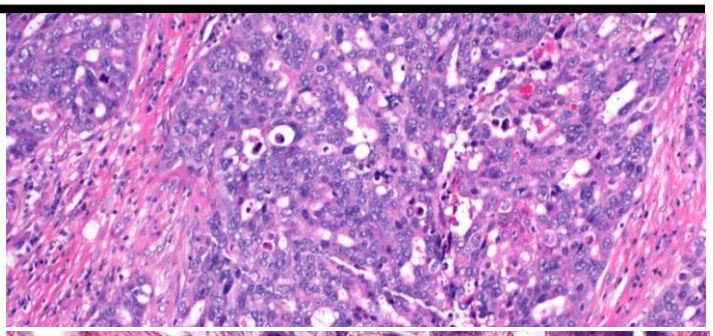
Fairly uniform population of cells and **low mitotic activity** (1-2/mm^2) compared to High-grade serous carcinoma

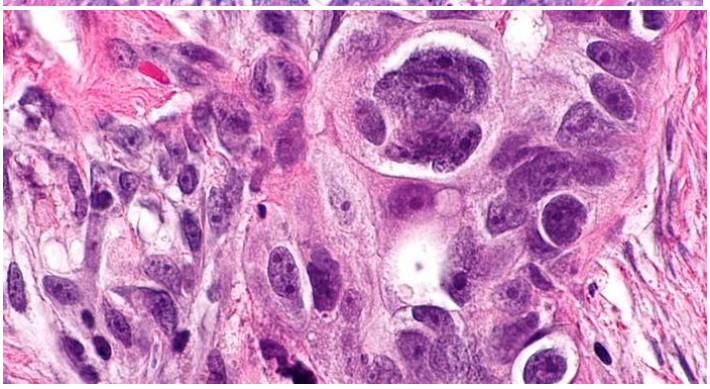
Mutations and IHC like Serous Borderline Tumor

Prognosis depends on stage. Can go to lymph nodes.
Does not respond as well to Platinum-based therapy (as less proliferative compared to High-grade)

Microinvasion: < 5mm (in any single focus)

High-Grade Serous Carcinoma





Most common ovarian carcinoma.
Usually **older women** (60s), presenting with nonspecific symptoms at **advanced stage**→ responsible for most ovarian cancer deaths

Often bilateral, solid and exophytic

Most commonly **solid areas with slit-like spaces**.
Sometimes papillary or cribriform.
Lots of necrosis and **mitoses**.
Large, **hyperchromatic, pleomorphic nuclei**.
Often prominent nucleoli.

Molecular: **TP53 mt nearly always**; about half have inactivating (germline or somatic) BRCA mutations.
Lots of chromosomal and copy number changes.

IHC: **WT-1** and PAX8 positive; Variable ER, PR, p53 overexpressed or null; P16 "Block" positive

BRCA1&2→ Very high risk → often get prophylactic salpingo-oophorectomy (entirely submitted for histologic eval, esp. fimbriae, using SEE-FIM protocol)

BRCA-related cancers often have Solid, Endometrial-like, and Transitional morphology ("SET") and lots of tumor-infiltrating lymphocytes

Most originate in fallopian tube: Normal tube → P53 mutation → Serous tubal intraepithelial carcinoma (STIC) → Invasive High-grade serous carcinoma of tube → spreads to ovary
(Essentially, tubal origin until proven otherwise. Only consider primary ovarian if both tubes are completely histologically examined and free of disease. If both tubes and ovaries negative→ primary peritoneal)

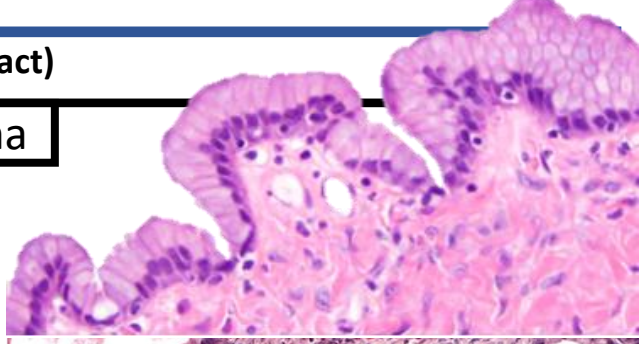
Treat with **cytotoxic chemotherapy** and often debulking staging surgery

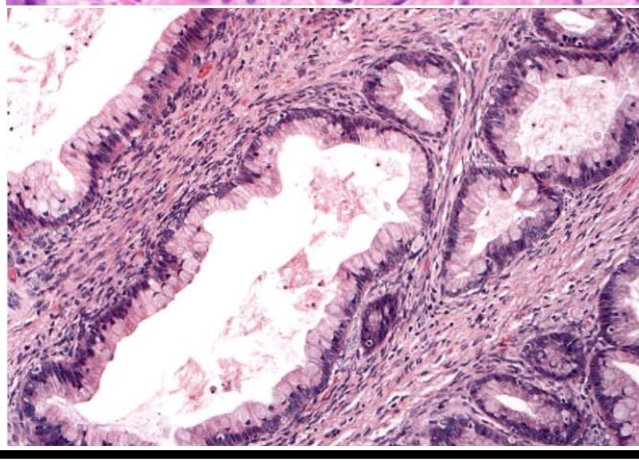
	Low-Grade Serous Carcinoma	High-Grade Serous Carcinoma
Cytology	Uniform round to oval nuclei	Pleomorphic nuclei (>3:1)
Chromatin	Even	Irregular
Mitoses	≤12 /10 HPF	>12 /10 HPF
P53	Wild-type	Mutant
P16	Patchy	Block-positive
Mutations	BRAF, KRAS	P53, BRCA
Precursor lesion	Serous Borderline Tumor	Serous Tubal Intraepithelial Carcinoma (STIC), usually
Architecture	Papillary, with hierarchical branching	Solid to papillary with slit-like spaces
Response to Chemo	Minimal (not proliferative)	Good

Mucinous

Mucinous epithelium (like GI tract)

Mucinous Cystadenoma/Adenofibroma





Benign. Usually unilateral.
Wide age range (average age 50)

Grossly cystic/multicystic with a smooth surface

Arranged in **glands and cysts.**
Single layer of mucinous epithelium either resembling **gastric** (foveolar-type) or **intestinal** (with goblet cells)

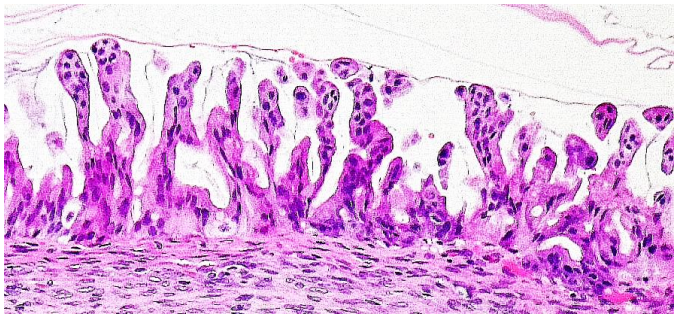
Minimal atypia; Only very rare mitoses.
No epithelial tufting or broad papillae (no complexity)

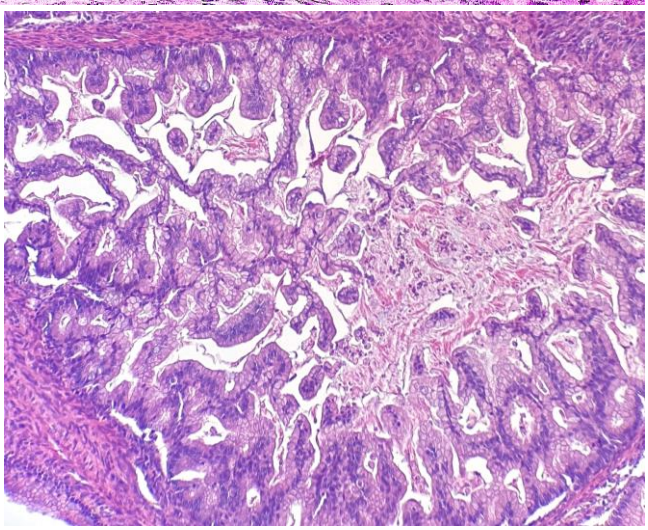
Molecular: Frequent KRAS mutations

Adenofibromas are uncommon

Can have a clonally related Brenner or dermoid cyst component

Mucinous Borderline Tumor





Wide age range. Arise from mucinous cystadenomas.

Usually **Unilateral**, **multicystic**, with a smooth surface

Lined by **mucinous epithelium** with mild to moderate nuclear atypia (not high-grade)

Architectural complexity, including epithelial tufting, stratification, villi, and papillae.

Proliferative area must be >10% of epithelial volume

If there is high-grade cytologic atypia→ "Intraepithelial carcinoma"

Microinvasion if < 5mm of invasive carcinoma

Can rupture→ leak mucin into stroma → "pseudomyxoma ovarii"

Can have nodules in wall with atypical spindled cells and lots of mitoses, but CK-negative→ "Sarcoma-like mural nodules" → Benign clinical course

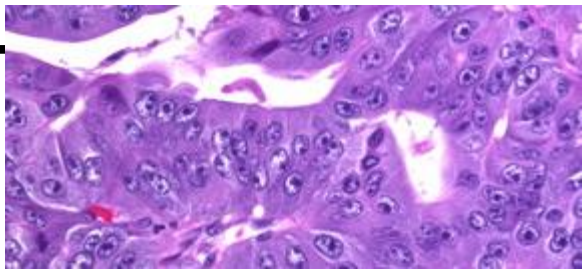
Molecular: Frequent **KRAS Mutations**

Prognosis is generally very good, even with intraepithelial carcinoma. And still not bad with microinvasive carcinoma.

Can progress to mucinous carcinoma→ must be sampled well to exclude an invasive component!

If it is truly just borderline, subsequent transformation to carcinoma is rare.

Mucinous Carcinoma

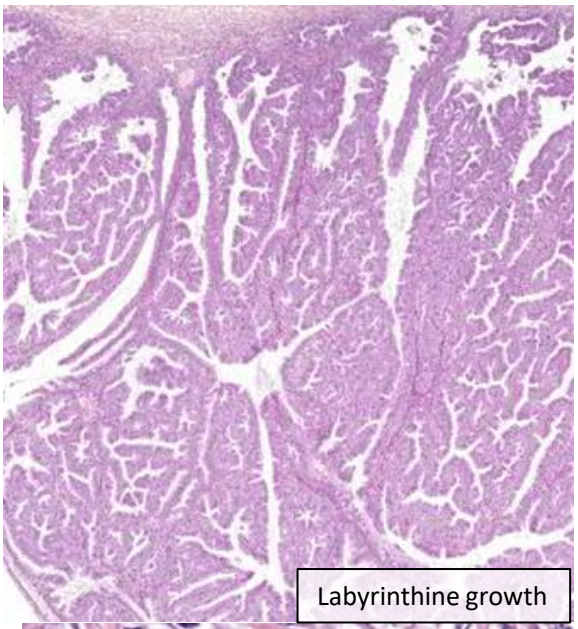


Malignant. Average age ~55

Most tumors confined to ovary at presentation. **Unilateral**. **Large**, complex solid and cystic mases without surface involvement.

Two main patterns of invasive growth:

1. **Confluent/expansile glandular growth** with little stroma
   Marked gland crowding. Labyrinthine appearance.
2. **Destructive stromal invasion** with infiltrating irregular glands, nests, and single cells in desmoplastic stroma
   (This pattern is less common and should prompt consideration for a metastasis)



Increased cytologic atypia and mitoses

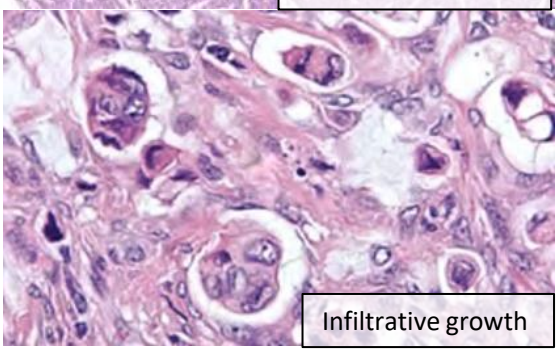
Often exist on a spectrum with concurrent cystadenoma and borderline components

Can have mural nodules with large atypical spindled to rhabdoid cells that react with cytokeratin→ "Anaplastic carcinoma" (in contrast to sarcoma-like nodules in borderline tumors)

If destructive invasive component is <5mm in greatest dimension→ microinvasion

Molecular: KRAS mutations and CDKN2A frequently

Prognosis: Since disease is usually confined to the ovary, often good prognosis. However, if advanced stage, then poor prognosis.



	Primary Ovarian	Metastatic Mucinous Tumors
Laterality	Unilateral	Bilateral
Size	Large (usually > 20 cm)	Smaller (usually <10 cm)
Gross	Multicystic ± solid component with smooth capsule	Nodular with cystic component
Location within ovary	Within stroma	Within surface and stroma
Microscopic	Well-differentiated mucinous epithelium forming organized cysts (borderline) or confluent expansile glands (carcinoma)	Infiltrative mucinous glands. Signet ring cells
Extraovarian disease	Usually absent (Stage 1)	Often present

Adapted from a presentation by Dr. Anne Folkins, Stanford University

Mucinous Tumor Immunohistochemistry:

	CK7	CK20	ER/PR	CDX2	SATB2	PAX8
Ovarian mucinous borderline and carcinoma	+	-/+	-	+/-	-	+/-
Ovarian seromucinous borderline	+	-	+	-	-	+
Metastatic Colon Cancer	-/+	+	-	+	+	-
Metastatic Gastric Cancer	+	-/+	-	+	-	-
Metastatic low-grade appendiceal mucinous neoplasm (LAMN)	-/+	+	-	+	+	-

Good panel: CK7, SATB2, PAX8
CK7 (strong positive in ovarian) and SATB2 (strong positive in lower GI).
PAX8 is helpful if positive but isn't always positive in primary ovarian (specific, but not sensitive).
SATB2 is usually specific for lower GI, but can be seen in ovarian tumors derived from teratomas.
CDX2 is positive in most mucinous epithelium, and is non-specific as to GI vs GYN.

Similar mutation profile--both often have KRAS/BRAF, TP53, CDKN2, mutations

Mucinous Borderline Tumors vs. Low-grade Appendiceal Mucinous Neoplasm

I remember that the appendix often has mucinous neoplasms, could this cytologically low-grade tumor be a metastasis from the appendix?

	Primary Ovarian Mucinous Borderline Tumor	Secondary involvement by a Low-grade Appendiceal Mucinous Neoplasm (LAMN)
Size	Large (>20 cm)	Variable (usually <20 cm)
Laterality	Unilateral	Bilateral
Location of Tumor	Within stroma, rarely on surface	Surface and stromal involvement
Pseudomyxoma Ovarii	Usually absent	Prominent
Amount and Pattern of Epithelium	Abundant; organized cysts	Scant; haphazard
Appendiceal Tumor	Absent	Present

Adapted from a presentation by Dr. Anne Folkins, Stanford University

Endometrioid

Endometrial glands, like in the uterus

Endometriotic Cyst

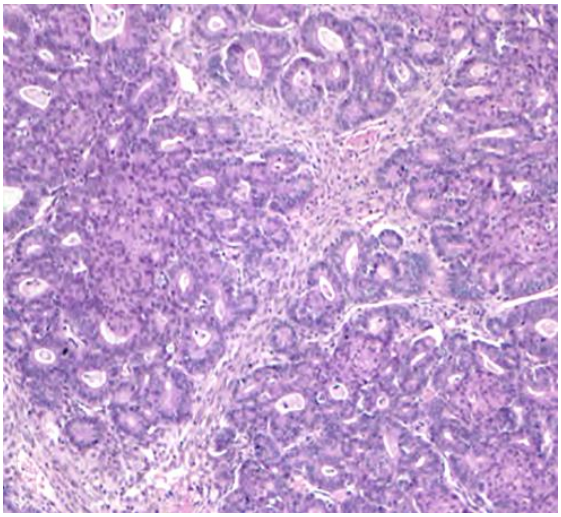
Aka: Endometrioma

Benign. Common, usually middle aged. **Cystic form of endometriosis**. Non-neoplastic.
Frequently associated with endometriosis elsewhere in pelvis.
Grossly hemorrhagic/dark brown → "chocolate cyst"
Endometrial glands + Endometrial stroma (often with hemorrhage + hemosiderin-laden macrophages)
Can undergo malignant transformation → Endometrioid, Clear cell, and Seromucinous carcinoma

Endometrioid Cystadenoma/Adenofibroma

Benign. Uncommon. Cystic lesion lined by endometrial glands **without** any endometrial stroma.
Associated with endometriosis.
When dense fibrous component → adenofibroma.
Likely just endometriomas in which stroma is indistinct.

Endometrioid Borderline Tumor



Uncommon. Middle-aged. **Associated with endometriosis**.
Unilateral, solid or cystic. Hemorrhagic.

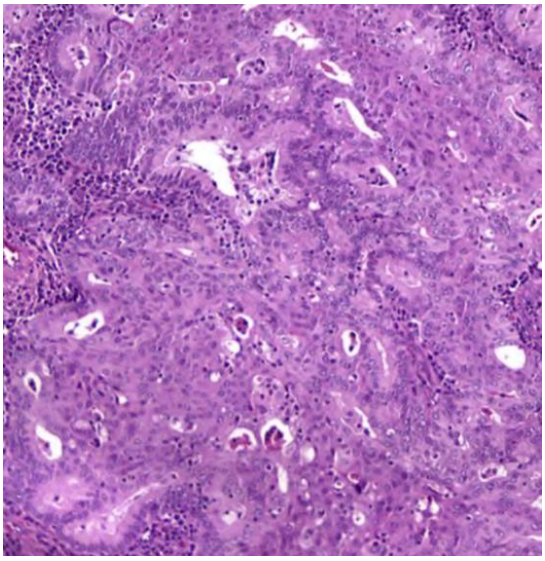
Crowded or back to back endometrial glands with lobular architecture lined by cells with mild to moderate cytologic atypia → **resembles atypical hyperplasia / Endometrial Intraepithelial Neoplasia (EIN)**

Can be papillary, protruding into cystic lumen.
Can have mucinous or squamous metaplasia

No destructive stromal invasion and/or confluent/expansile glandular growth > 5mm

Prognosis: Excellent

Endometrioid Carcinoma



Malignant. Late middle-age. Often unilateral, low-stage.
Often associated with endometriosis.

Resembles endometrial cavity endometrioid adenocarcinoma → **Back-to-back glands with confluent, cribriform growth or destructive growth.**

Squamous morules/differentiation common.
Occasional mucinous metaplasia → most previously diagnosed "Seromucinous carcinomas" fall into this category

Molecular: β-Catenin/Wnt pathway dysregulation, PTEN inactivation, PIK3CA, ARID1A, and TP53 (in high-grade)

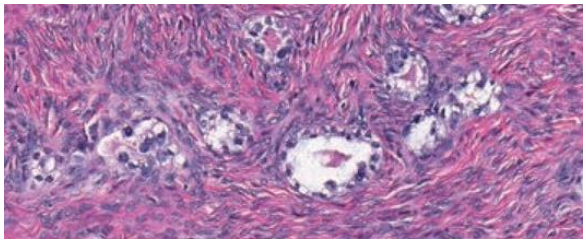
IHC: Usually ER/PR positive; WT-1 negative; P53 can be positive in high-grade endometrioid.
If ER/PR negative → consider mesonephric-like carcinoma

Prognosis: Good if low-stage. Bad if high-stage.

Clear Cell

Clear cells (the name says it all!), with no normal counterpart

Clear Cell Cystadenoma/Adenofibroma

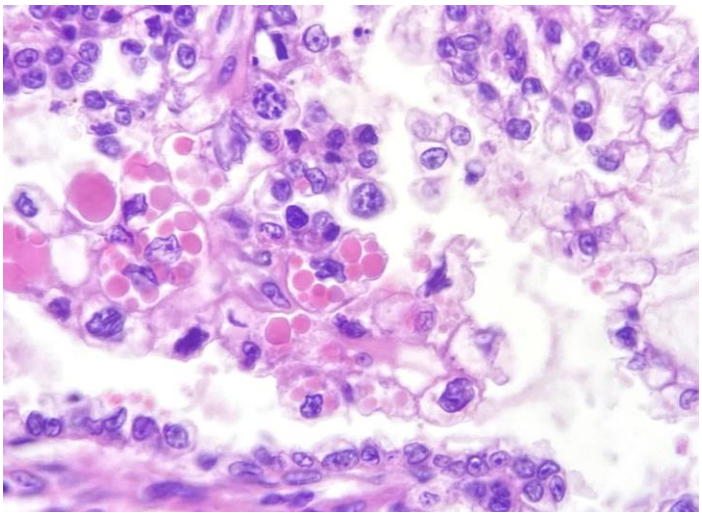


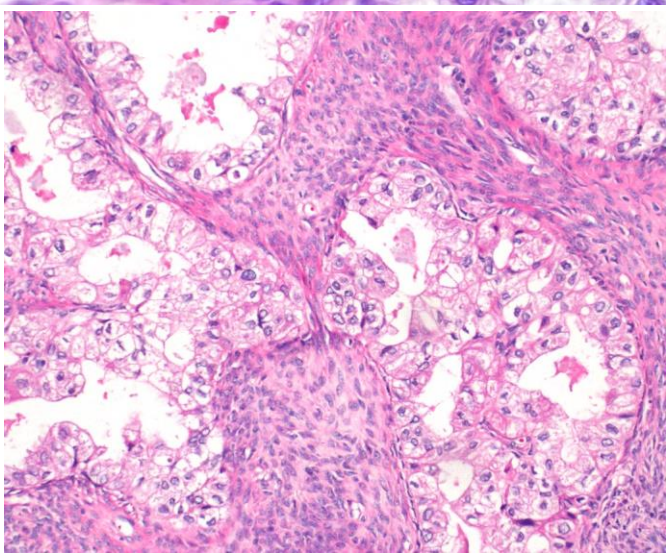
Benign. Extremely RARE! **Associated with endometriosis.** Widely spaced simple glands in fibrous stroma. Cells clear to eosinophilic with bland nuclei. No mitoses.

Clear Cell Borderline Tumor

Extremely **RARE**! Associated with endometriosis.
Round to oval glands in fibrous stroma. Clear to eosinophilic cells with **Moderate nuclear pleomorphism**. Mild epithelial layering. **NO invasion** with stromal reaction or papillary architecture. Infrequent mitoses. Good prognosis.

Clear Cell Carcinoma





Malignant. Older middle age.

Usually unilateral, solid to cystic

Associated with endometriosis

High-grade (but no need to grade)

Clear cell morphology:

- **Clear or eosinophilic granular cytoplasm**
- Angulated, **pleomorphic, hyperchromatic nuclei**, with prominent nucleoli
- Hobnail cells
- Varied architecture: Papillary, tubulocystic, glandular, or solid sheets
- Hyaline globules, Stromal hyalinization.

Low mitotic index

Molecular: ARID1A mts most common. Also PIK3CA.

IHC: (+) HNF-1β, Napsin A, CK7, PAX8, (none of these are specific though, so rely on morphology most)
WT-1 and ER/PR negative; Usually wild-type p53
Glycogen-rich cytoplasm is PAS positive, diastase sensitive

Prognosis: Depends on stage (low stage behaves well).

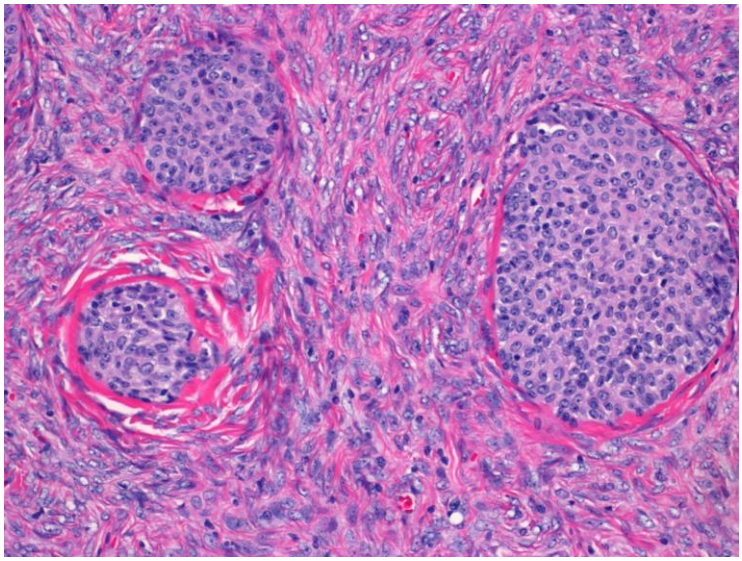
Can be associated with vascular thrombosis and paraneoplastic hypercalcemia

DDX: Yolk sac tumor→ Positive Glypican-3, AFP, SALL4; Negative CK7
Dysgerminoma→ Positive Oct3/4, SALL4 ; Negative CK7
Serous carcinoma→ Positive WT-1, often ER; Diffuse or Null p53
Endometrioid carcinoma→ Positive ER (usually)

Transitional/Brenner

Transitional epithelium, resembling urothelium of GU tract

Brenner Tumor



Benign. Often older adults, but can get at any age.

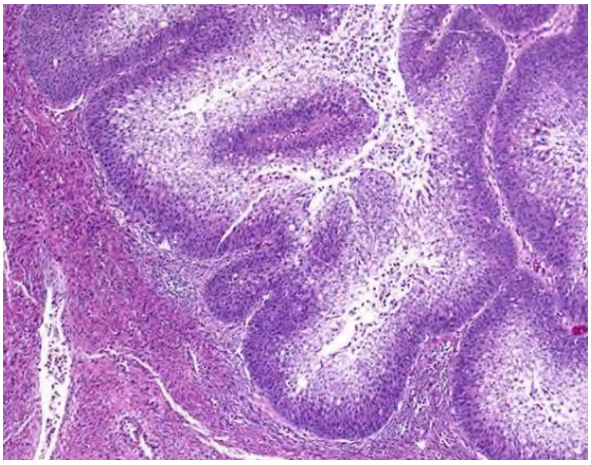
Usually small, unilateral, solid, firm mass with small cysts

Nests of **Transitional epithelium/urothelium** (resembling Walthard's rests) set in **dense fibrous stroma**

Mucinous differentiation can be common. Can be seen with mucinous neoplasms, most commonly mucinous cystadenoma. Calcifications common

IHC: Urothelial immunophenotype (+p63, p40, CK7, GATA-3, uroplakin III, thrombomodulin)

Borderline Brenner Tumor



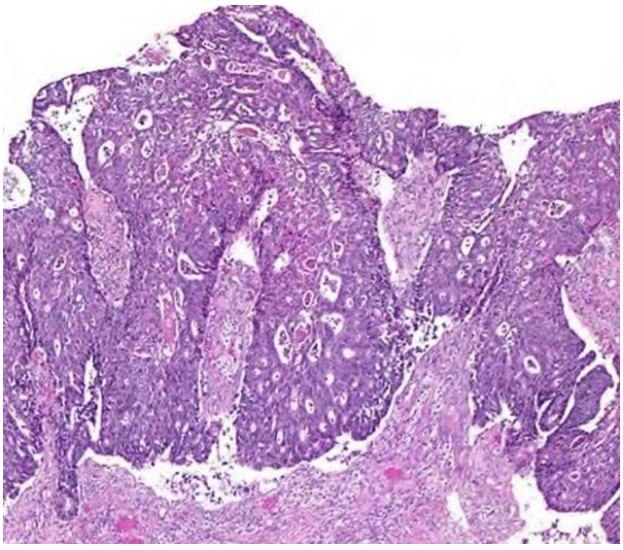
Brenner tumor **with papillary areas resembling non-invasive, low-grade papillary urothelial carcinoma**

No destructive stromal invasion

Often large, cystic tumors

Prognosis: Generally benign with some local recurrences

Malignant Brenner Tumor



Brenner tumor with **papillary areas resembling invasive, high-grade papillary urothelial carcinoma**

Stromal invasion: Irregular nests, confluent growth, Marked cytologic atypia

Need to see underlying Brenner tumor! Otherwise, likely serous carcinoma (sometimes can have a Transitional look) or metastatic urothelial carcinoma

Seromucinous — Epithelium with both serous and mucinous appearance

Although this exists histologically, it is likely not a true histomolecular entity and will eventually disappear as likely composed of serous and endometrioid tumors. Nevertheless, it is in the WHO (for now).

Seromucinous Cystadenoma/Adenofibroma

Benign. **RARE**.
Cystic with two or more Müllerian cell types, including mucinous and serous.
Less often also endometrioid, transitional, and/or squamous

Seromucinous Borderline Tumor

Usually younger (~30s), and Unilateral.
Cystic tumor with smooth surface and inside papillary excrescences

Non-invasive, proliferative epithelial tumor containing at least 2 types of epithelium. Most often: 1) Serous and 2) Endocervical-type mucinous

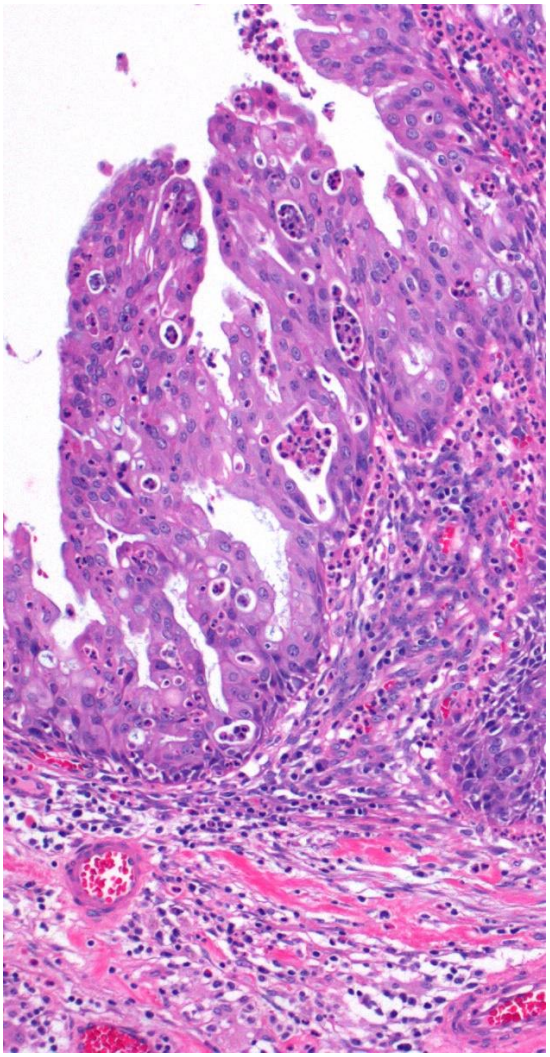
Can also include endometrioid, clear cell, transitional. If these are present, use term "Müllerian Borderline Tumor"

Complex papillary growth. Stroma often edematous.
Often lots of **neutrophilic inflammation.**

Similarities with serous borderline tumor:
- **Hierarchical and papillary growth**
- Dissemination of **peritoneal implants**
- Can (rarely) progress to carcinoma

Differences from serous borderline tumor:
- Strong association with endometriosis
- Lower malignant potential
- Morphologically resembles endometrioid tumors with mucinous metaplasia
- Little/no WT-1 staining
- ARID1A mutations in many (like some endometrial)

Prognosis: Generally good, even with implants

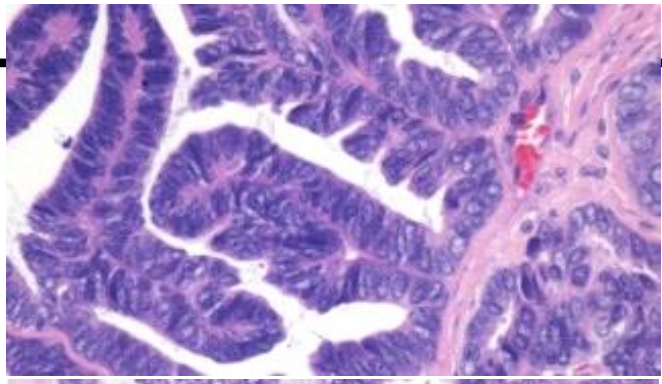


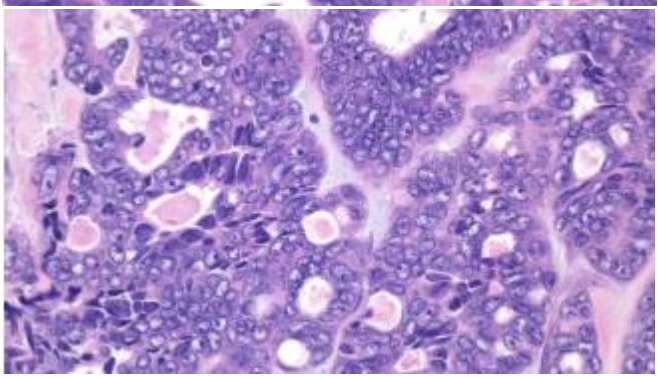
(Seromucinous Carcinoma)

Defunct diagnosis that is no longer used.
Most cases were endometrial carcinomas with mucinous metaplasia.

Other

Mesonephric-like adenocarcinoma





Adenocarcinoma with mesonephric-like differentiation.

Tubular, glandular, slit-like, papillary, and solid growth.
Can have eosinophilic **colloid-like material**.
Dense to vesicular nuclei

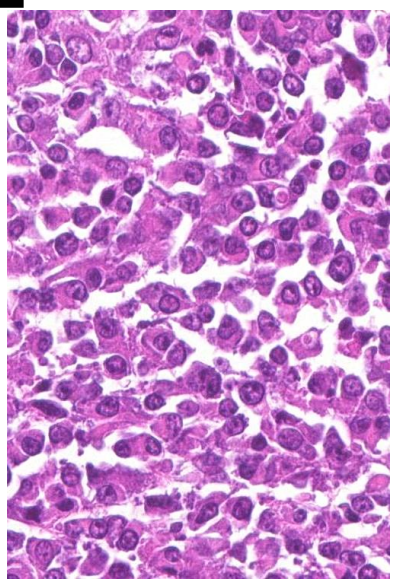
Frequently associated with endometriosis.

IHC: (+) TTF1, GATA3, CD10 (luminal), PAX8
(-) ER, PR, WT1; Wild-type p53

Molecular: frequent KRAS mutations

Consider this Dx if you ever have something that looks endometrioid but is ER negative!

Undifferentiated and Dedifferentiated carcinoma



Undifferentiated carcinoma: Malignant epithelial tumor lacking overt evidence of any specific line of differentiation.

Dedifferentiated carcinoma: Undifferentiated carcinoma with an abrupt transition to a differentiated component (usually endometroid).

Sheet-like growth. Geographic necrosis. High mitotic activity.
Monotonous, discohesive, round cells with minimal cytoplasm.

IHC/Molecular: **Frequent loss of MMR proteins and/or SWI/SNF proteins** (ARID1A/B and SMARCA4/A2/B1)

Aggressive!

DDX: *Small cell carcinoma, hypercalcemic type*—younger women, WT-1 positive, almost always lacks SMARCA4 (BIRG1)

Other

Carcinosarcoma: Biphasic neoplasm composed of high-grade carcinomatous (usually High-grade serous carcinoma) and sarcomatous elements. Both components usually p53 mutant.

Mixed Carcinoma: Ovarian carcinoma composed of 2 or more histologic types. Most common is endometrioid and clear cell carcinomas (both associated with endometriosis).

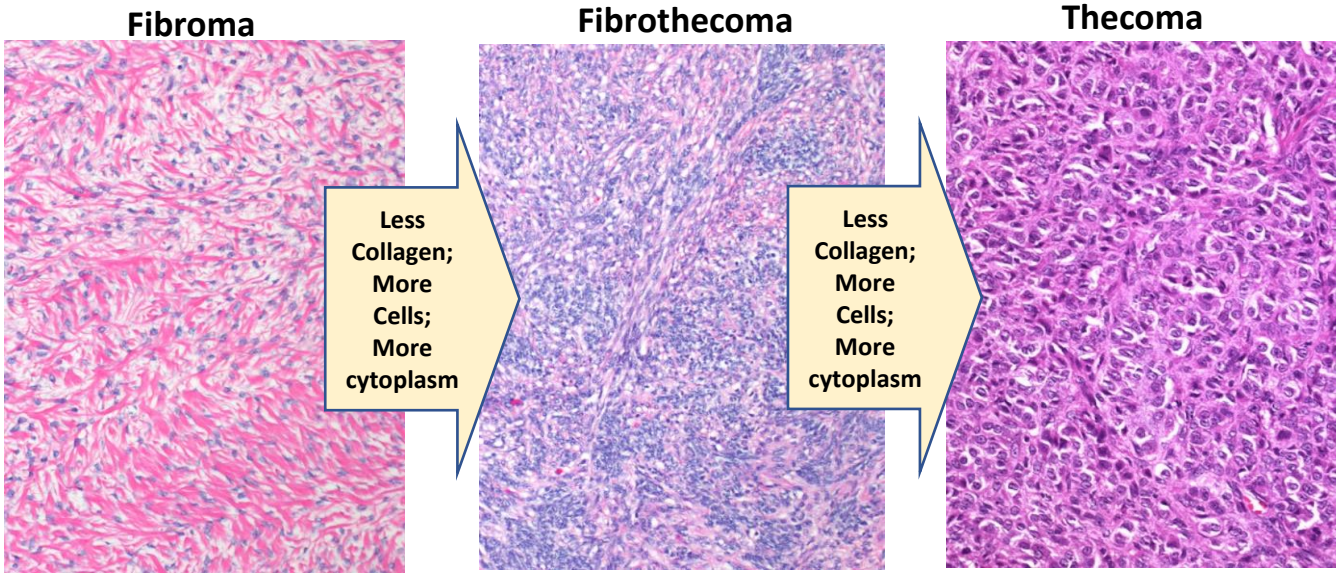
Sex Cord-Stromal

A little variable, but often stain with some combination of:
Inhibin, calretinin, SF-1, FOXL2, Melan A

Fibroma/Thecoma

Fibroma: Most common ovarian stromal tumor.
Benign stromal tumor composed of bland **spindled cells in fascicles with abundant collagen**.
Grossly solid, firm, chalky **white**.
Varying patterns including storiform to bundled. Hyalinized plaques.
Usually middle-aged and unilateral. If young/bilateral, and esp. if lots of calcifications → consider Gorlin syndrome (Nevoid Basal Cell Carcinoma Syndrome)
Meig's syndrome = fibroma + ascites + pleural effusion; relatively rare
"Cellular Fibroma:" Cellular with scant collagen, only mild atypia, increased mitoses

Thecoma:
Benign stromal tumors composed of **sheets of uniform cells with pale greyish-pink cytoplasm**.
Cytologically bland. Reticulin surrounds individual cells.
Usually unilateral, post-menopausal women. Often **Estrogen producing**!
Grossly solid and **yellow** (as full of lipid/fat)



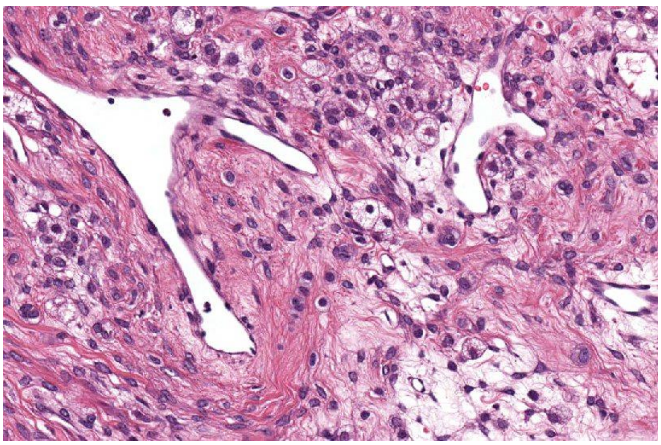
Sclerosing Stromal Tumor

Benign. **Rare**! Young women. Unilateral.

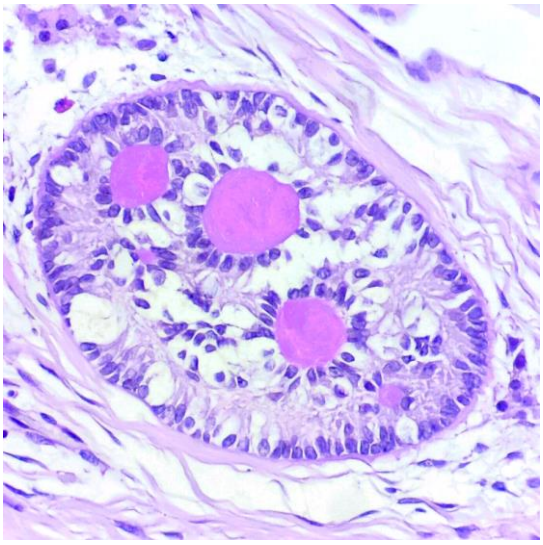
Bland rounded and spindled cells with eosinophilic to vacuolated cytoplasm

Pseudolobular architecture: arranged in cellular nodules in a hypocellular, edematous to collagenous background

Dilated, thin-walled, branching, **Stag-horn vessels**



Sex Cord Tumor with Annular Tubules (SCTAT)



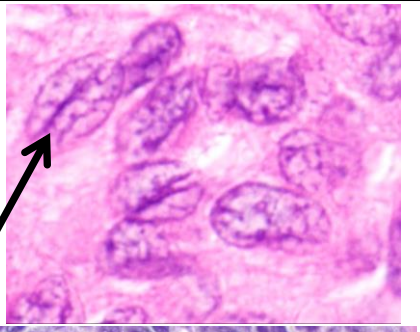
Composed of aggregates of **simple or complex annular tubules**
Cells are **columnar with clear cytoplasm** with an "antipodal" arrangement of the nuclei (at opposite ends)
Hyaline basement membrane-like material within nests

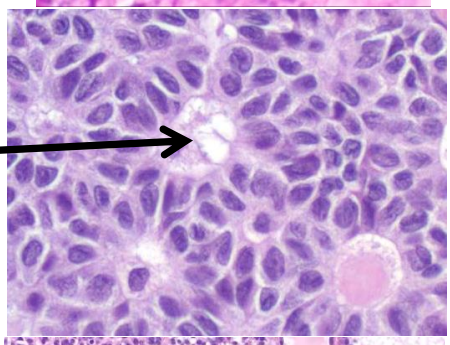
Occur in Two Settings. Generally, broad age range.
Often younger.

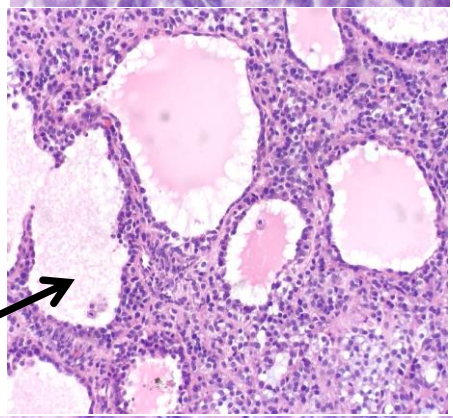
1) **Sporadic**: Can have a low-grade malignant course. Often unilateral, larger. Set in fibrous stroma. More complex growth.

2) **Peutz-Jeghers Syndrome**: Benign, often incidental finding. Often multiple, small, bilateral tumors with calcifications. Set in normal ovarian stroma. Germline STK11 mutations.

Granulosa Cell Tumors







Two types, occurring in different settings with different prognoses:

Adult Granulosa Cell Tumors

Most common sex cord-stromal tumor.
Wide age range, but **often middle-aged**. Usually unilateral, low-stage.
Solid with some cystic, hemorrhagic areas
Secrete estrogen→ menorrhagia, post-menopausal bleeding (and hyperplasia/EIN), or amenorrhea.
Cells: Scant pale architecture with **grooved nuclei**
Varied architecture: Sheet-like, trabecular, ribbon-like, microfolicular (with "**Call-Exner bodies**" filled with pink secretions).
Occasional macrofollicular architecture.
IHC: Usual sex-cord stromal stains, plus WT-1, FOXL2 some keratins, and others. Reticulin surrounds groups of cells.
Molecular: **FOXL2 point mutations**

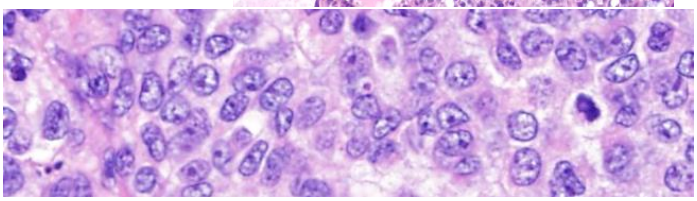
Low-grade malignant: can recur and even metastasize, even after long intervals, but not very common

Juvenile Granulosa Cell Tumors

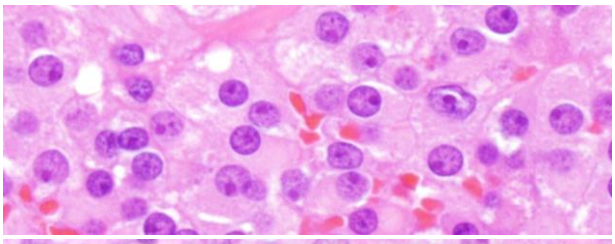
Occurs mainly in **children and young adults**. Less common.
Secrete estrogen→ precocious puberty, menorrhagia, or amenorrhea
Cells: Round, with abundant eosinophilic cytoplasm and
***NO* GROOVES.** Vesicular chromatin.
Architecture: **Macrofollicular** with usually basophilic secretions
Frequent mitoses.

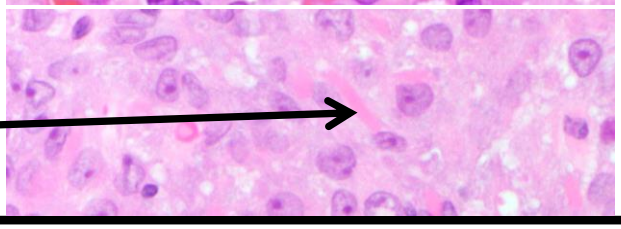
Molecular: *NO* FOXL2 mutations

Prognosis: Good, with infrequent recurrences



Leydig Cell Tumor

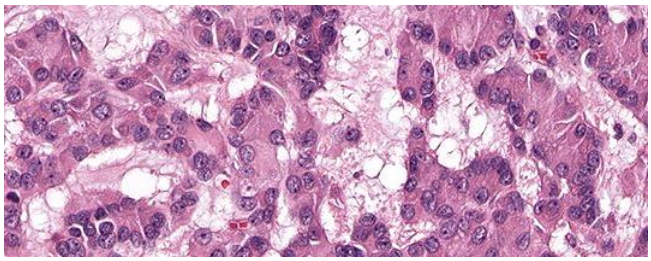


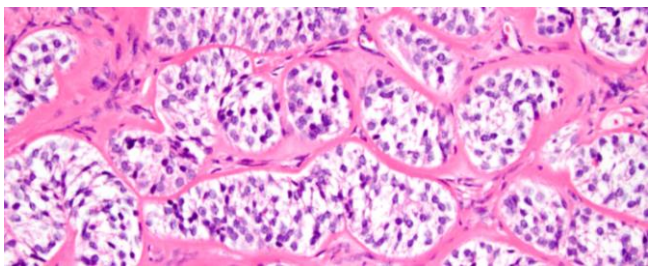


Benign. Usually older middle-aged women. Unilateral
Secrete androgens → **Masculinization**
Changes include: hirsutism, amenorrhea, breast atrophy, clitoral hypertrophy, and hoarseness

Steroid cells with **abundant pink, granular cytoplasm**
Regular round nuclei with vesicular chromatin
May contain rod-like eosinophilic crystals (**Reinke crystals**)
Fibrinoid necrosis of vessels. Located in Hilus.

Sertoli Cell Tumor





Any age, usually younger. Unilateral. Solid to cystic.
Can be estrogenic.

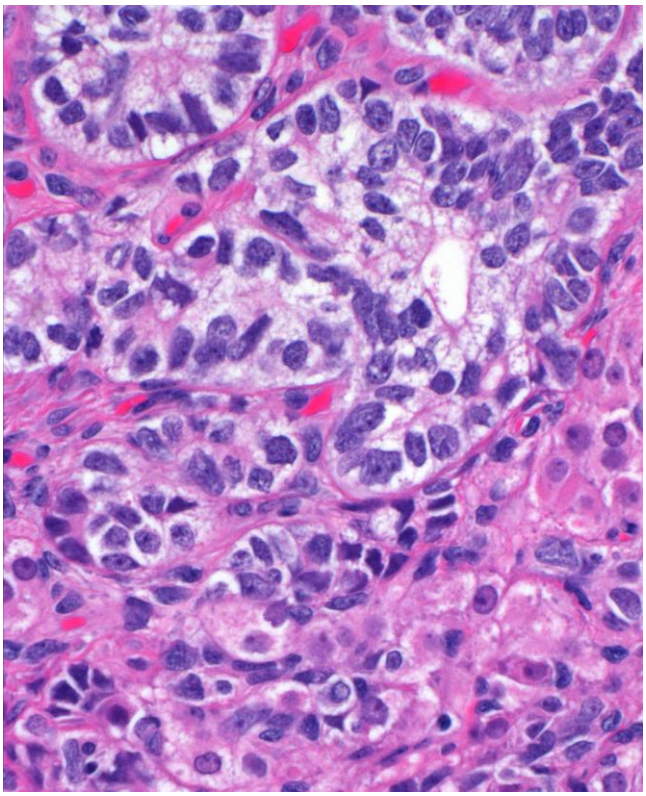
Very Varied architecture: **Tubular** (with or without lumens), trabecular, diffuse, alveolar, pseudopapillary, etc… May see a *few* Leydig cells.

Cells with eosinophilic to pale cytoplasm and round nuclei with visible nucleoli

Usually Benign, but can be malignant.
IHC: (+) CK, WT1, sex cord-stromal markers

DDX: Neuroendocrine tumor (which would be + for synaptophysin)

Sertoli-Leydig Cell Tumors



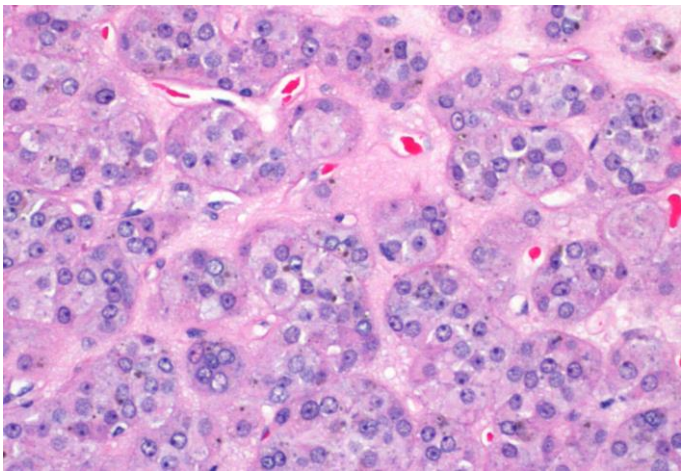
Any age, often younger. Solid. Unilateral.
Contain varying proportions of **Sertoli *and* Leydig cells**
Leydig cell component secretes androgens→ masculinization

Sertoli cell component can have very **varied architecture.**
Varying degrees of differentiation.
Can have slit-like areas resembling rete testis→ "retiform"
Can have heterologous differentiation, including mucinous epithelium

Molecular: **DICER 1 mutations common**
Germline DICER 1 mutations→ multinodular goiter, Sertoli-Leydig cell tumors, pleuropulmonary blastoma

Prognosis: Well-differentiated→ very good
Worse is higher grade/stage

Steroid Cell Tumor



Middle-aged. Unilateral.
Secrete androgens (usually), estrogens, or corticosteroids (rarely)

Polygonal cells with abundant cytoplasm that is eosinophilic (lipid poor) to vacuolated (lipid rich). Round nuclei.
NO Reinke crystals

Usually benign, but can be malignant (if large, lots of mitoses, atypia, and/or necrosis)

Rare Types (Where the Name Says It All)

Myxoma—paucicellular tumor with extensive myxoid matrix. Bland spindled cells. Abundant capillaries.

Signet-Ring Stromal Tumor—Signet ring cells within a background of fibromatous stroma. Lack expression of EMA; Absence of intracytoplasmic mucin.

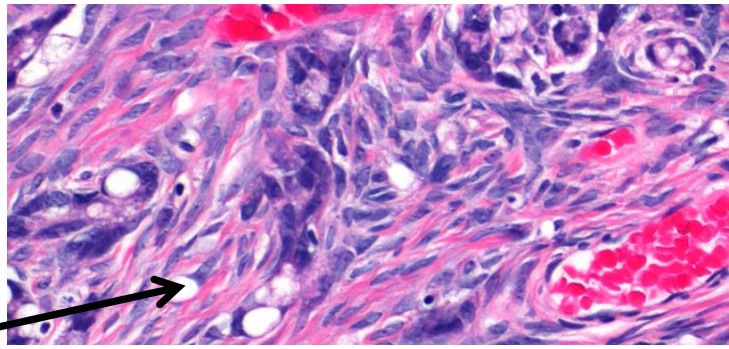
Microcystic Stromal Tumor—Distinctive microcystic appearance. Diffuse nuclear β-catenin and cyclin D1. IHC: (+) CD10, WT1, FOXL2, SF1; (-) inhibin and calretinin.

Luteinized thecoma-associated with sclerosing peritonitis—Cellular spindle cell proliferation with luteinized cells, typically associated with sclerosing peritonitis.

Ovarian Fibrosarcoma—Overtly malignant fibroblastic neoplasm. Extremely rare.

Gyandroblastoma—Sex cord-stromal tumor with elements of both male (Sertoli cell tumor) and female differentiation (granulomas cell tumor).

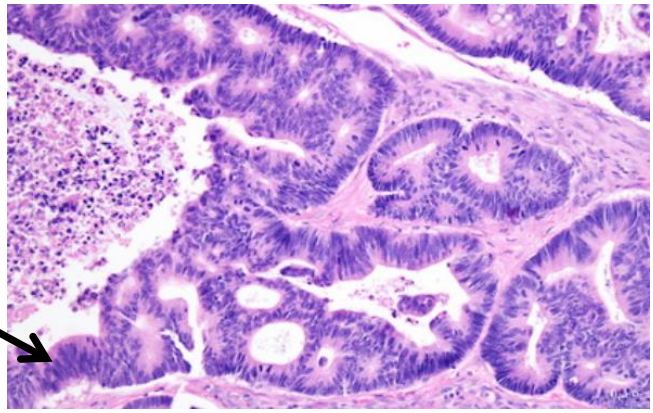
Metastasis



Spread from extraovarian sites→
most commonly GI tract

More often **bilateral**

Especially hard to discriminate from primary for mucinous tumors (see previous table/discussions)



Signet ring cells strongly favor a metastasis (Krukenberg tumor) from the stomach or breast

Colon cancer is the most common metastasis and often has a distinctive look with “dirty necrosis” and a “garland” pattern of growth

After GI, breast is the most common

Germ Cell Tumors

Derived from Germ Cells. **Rapidly growing→ Chemo-sensitive**
Almost exclusively in <u>young</u> women and girls.

If ≥2 malignant germ cell components → ***<u>Mixed</u>* germ cell tumor**

Dysgerminoma

Think: Clear/White color

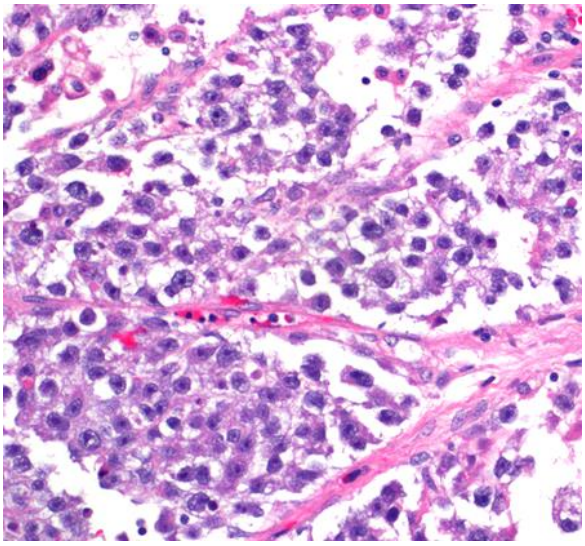
Most common germ cell tumor.
Large, solid, fleshy. Usually unilateral.

Large polygonal cells with <u>clear to eosinophilic cytoplasm</u>, <u>distinct cell membranes</u>, vesicular chromatin, and <u>prominent nucleoli</u>
Fibrous septae and **nested architecture**
Lymphocytic infiltrate; Sometimes granulomas

Elevated serum LDH, rarely hCG

Molecular: majority have **isochrome 12p**; ckit mutations in many.

Prognosis: **Good, if treated.**



Embryonal Carcinoma

Think: Purple color

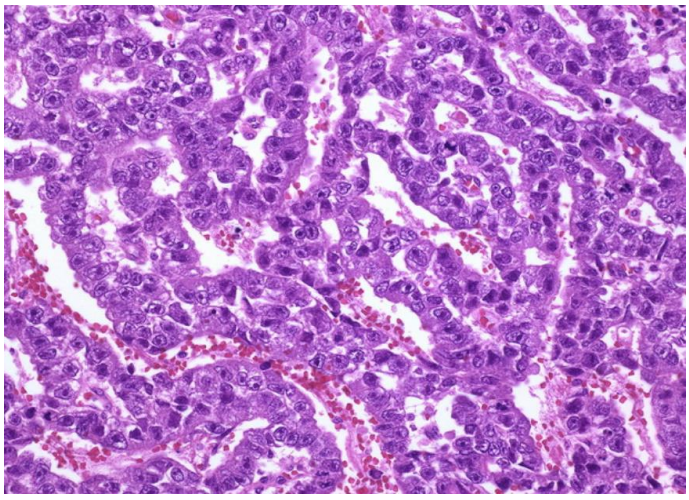
Rare.

Rudimentary epithelial differentiation

High-grade, large "Primitive" cells
Vesicular nuclei with prominent nucleoli
Coarse, basophilic chromatin
Amphophilic cytoplasm
Variable architecture (nests, sheets, glands)

Molecular: Isochrome 12p

Aggressive, but respond to chemotherapy



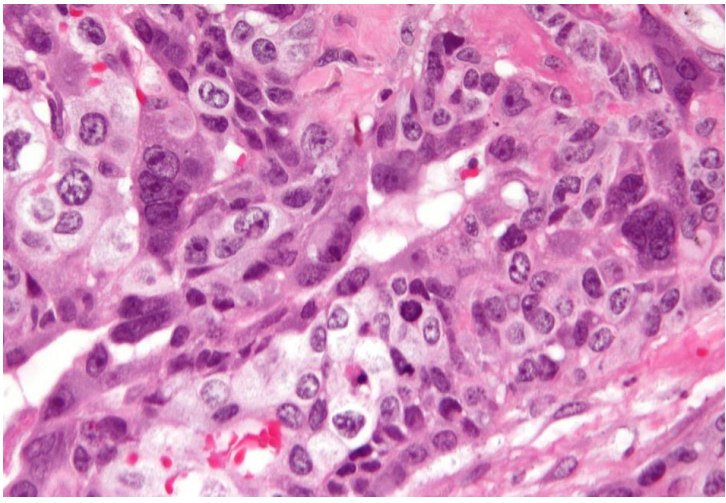
Choriocarcinoma

Think: Red color

In ovary, usually **non-gestational.**
Young patients.
(Can get choriocarcinoma after a molar, ectopic, or normal pregnancy)

Malignant cytotrophoblasts (mononuclear) *<u>and</u>* syncytiotrophoblasts (multinucleated)
Abundant **Hemorrhage** and necrosis.

Very elevated Serum hCG → precocious puberty, vaginal bleeding, or mimics pregnancy



Yolk Sac Tumor

Think: Pink color

Aka: "Endodermal Sinus Tumor"

Large, white, soft with cystic degeneration

Many patterns/architecture

Most common = reticular/microcystic

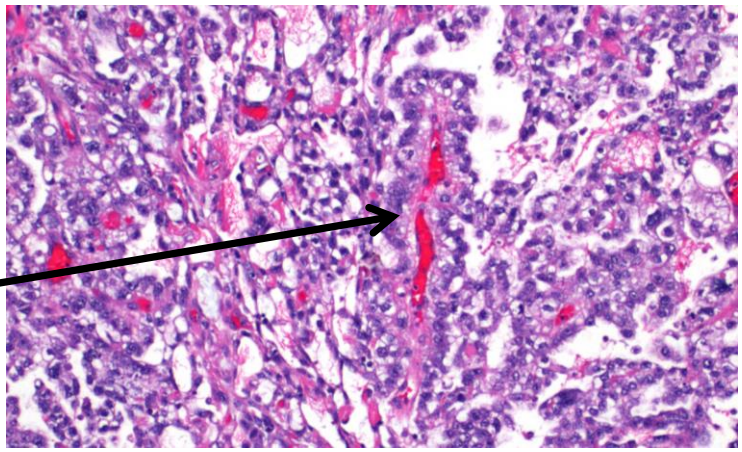
Can also be solid, papillary, etc…

Often hypocellular myxoid areas

Classic: **Schiller-Duval Bodies**

Hyaline globules

Elevated Serum AFP



Teratoma

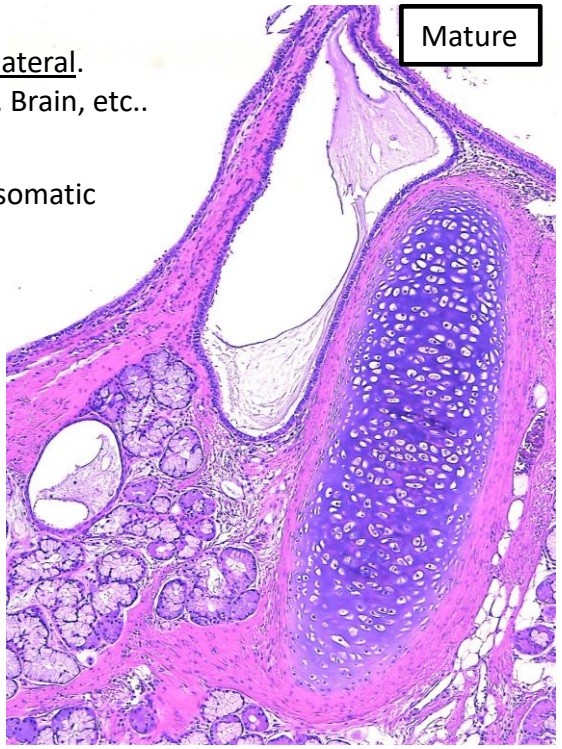
Think: Rainbow

Composed of tissues from 2-3 germ layers. Often cystic and unilateral.
Common elements: Skin (with adnexal structures), Cartilage, GI, Brain, etc..
Associated with anti-NMDA receptor encephalitis.

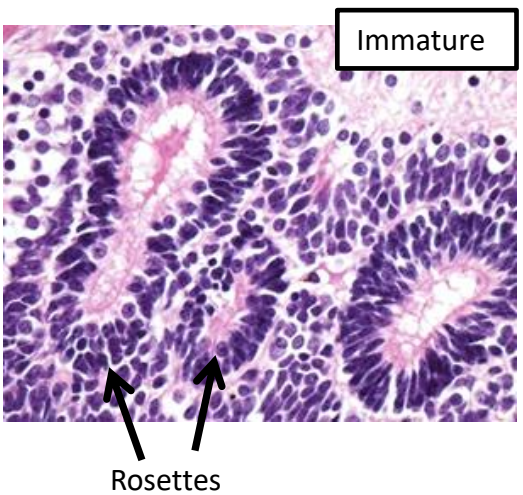
Mature – exclusively mature tissue; Benign unless a secondary somatic malignancy develops (usually carcinoma such as SCC or PTC).

Immature – contains immature tissues, typically primitive/embryonal neuroectodermal tissues (mitotically active hyperchromatic cells with high N:C ratios)→ Malignant
Often see neuroectodermal tubules and rosettes
Grade based on amount of immature neuroepithelium (below)

Immature elements can mature to look like cerebral tissue with chemotherapy even if spread to peritoneum → "Gliomatosis peritonei"
Generally good prognosis with treatment



Immature Teratoma Grading	Grade	Criteria
	1	Rare foci of immature neuroepithelium (< 1 in a 4x field on any slide)
	2	1-3 foci per 4x field on any slide
	3	> 3 foci per 4x field on any slice



Germ Cell Tumor IHC:

IHC Stain	Dysgerminoma	Embryonal Carcinoma	Yolk Sac Tumor	ChorioCA
SALL4	+	+	+	+/-
OCT 3/4	+	+	-	-
D2-40	+	-	-	-
CD117	+	-	-/+	-
CD30	-	+	-	-
Glypican 3	-	-	+	-

Teratoma *(continued)*

"Monodermal" teratomas – composed of only/primarily one tissue type

Struma ovarii – mostly or all benign thyroid tissue

Carcinoid – resemble well-differentiated neuroendocrine tumors of GI tract. Considered a type of monodermal teratoma. When combined with struma ovarii→ "strumal carcinoid." Good prognosis.

Neuroectodermal-type tumors— Primitive tumors with variable neuroectodermal differentiation, resembling brain tumors (e.g., medulloblastoma, etc…). Stain like brain counterparts.

Miscellaneous

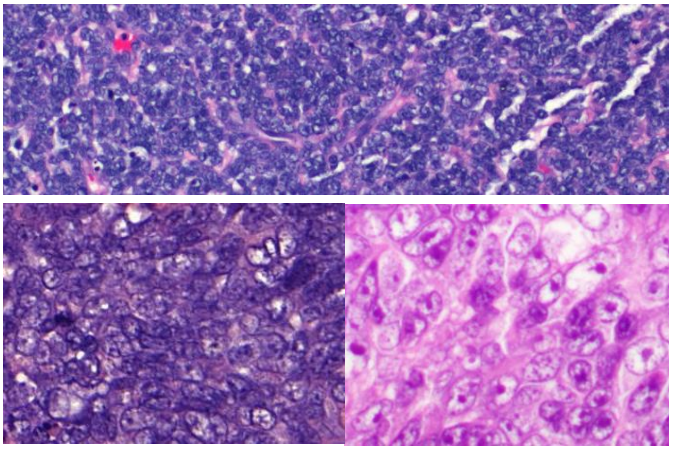
Small Cell Carcinoma of the ovary, Hypercalcemic-type

Young women. Unilateral.
Associated with **paraneoplastic hypercalcemia**

Undifferentiated tumor with diffuse growth
Small, monotonous cells with scant cytoplasm
Often focal macrofollicle-like spaces
Often a component of larger cells with more cytoplasm and rhabdoid morphology

IHC: Diffuse WT-1; Focal CK, EMA; Loss of BIRG1
Molecular: **SMARCA4 mutations**

Very **Aggressive**!!



Small Cell Carcinoma, Pulmonary Type

As the name implies, it's **like the lung** (so must exclude a metastasis)!
Older women. Often bilateral with extra-ovarian spread (Advanced, like in the lung!)
Diffuse growth of small cells with scant cytoplasm, "salt and pepper" chromatin, and moulding.
Lots of mitoses and apoptotic bodies. Poor prognosis.

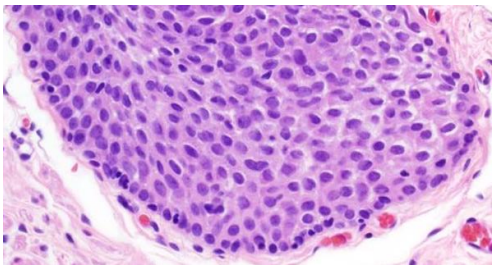
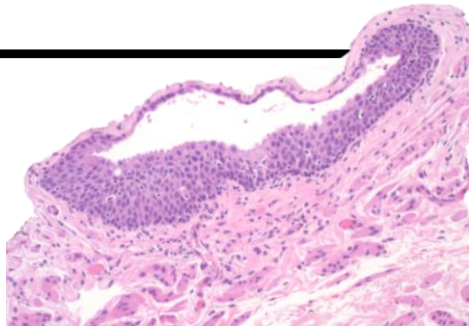
Gonadoblastoma

Contains a mixture of immature sex cord cells and germ cells
Predominantly in young women with **gonadal dysgenesis**. Not uncommonly bilateral.
Sex cord component: SCTAT-like with nests with hyalinized basement-membrane material in lumens
Germ cell component: often dysgerminoma-like germ cell neoplasia in situ (GCNIS)
Good prognosis→ essentially an in-situ lesion like GCNIS in the testis

Adnexal tumors/lesions

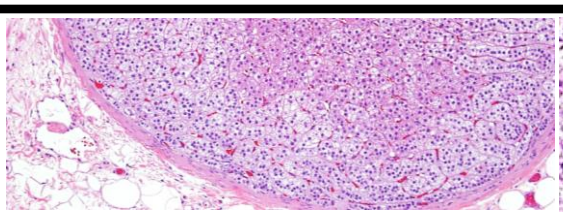
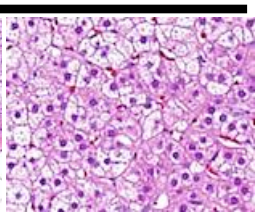
Walthard's Rests

Common. Incidental.
Nests of transitional epithelium.

Adrenocortical remnants

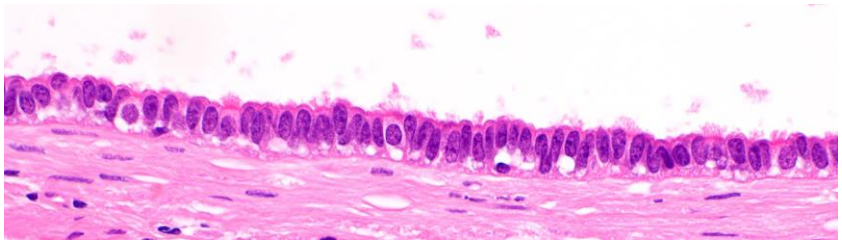
Round nests or cords of pale lipid-rich cells resembling the cortex of the adrenal gland.
Incidental finding.

Paratubal cyst

Cystic structures around fallopian tube.
Lined by **ciliated to cuboidal epithelium**.
Very common.

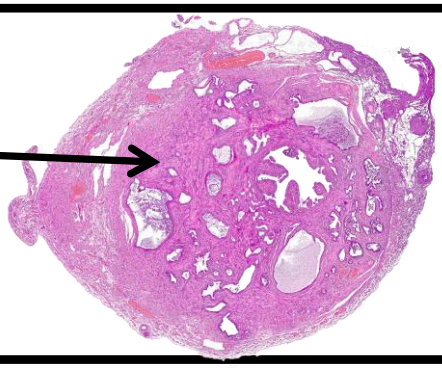
If >1cm→ Serous cystadenoma



Reactive/Inflammatory changes

Salpingitis Isthmica nodosa—Diverticulosis of the fallopian tube with associated smooth muscle hypertrophy

Tubo-ovarian abscess—fibroinflammatory mass involving fallopian tube/ovary. Often secondary to pelvic inflammatory disease (PID) after upper genital tract infection.

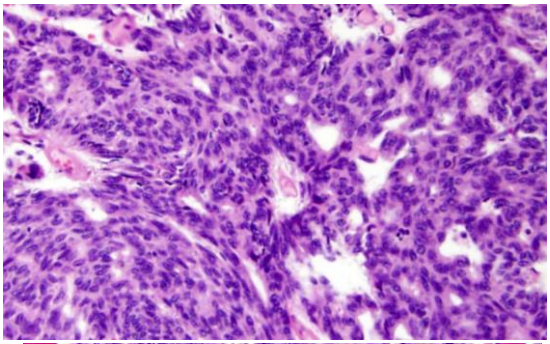
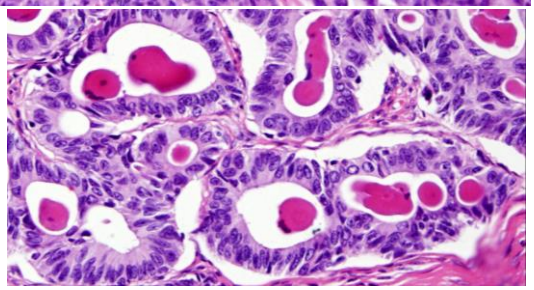


Wolffian Tumor

Aka: "**Female Adnexal Tumor of Probable Wolffian Origin**" or "**FATWO**"
Often unilateral, older women, and solid. Well-circumscribed.
Often in **adnexa, but distinct from ovary** (esp. Broad ligament)
Variable patterns: Sieve-like, retiform tubules, or solid
Cuboidal to columnar cells, but lining cells may be flattened.
Bland nuclei.
May have prominent hyalinized bands or eosinophilic secretions

IHC: (+)CK, Vimentin, AR, CD10 (luminal).
(+/-) Sex cord-stromal markers
(-)ER, EMA, GATA3, PAX8, TTF1 (as opposed to Mesonephric-like carcinoma)

Usually **benign**.

Miscellaneous tumors

Leiomyoma—benign smooth muscle tumor (as in uterus).

Adenomyoma—benign admixture of endometrial-type glands (with or without endometrial stroma) and prominent smooth muscle.

Adenomatoid tumor—variably-sized slit-like, tubular, and cystic spaces lined by mesothelial cells (stain with mesothelial markers). Benign.

Papillary cystadenoma—Benign papillary cystic tumor of probable mesonephric origin. Minimal clear to eosinophilic cytoplasm, non-ciliated. Associated with von Hippel-Lindau syndrome (VHL).

High-grade Serous Carcinoma

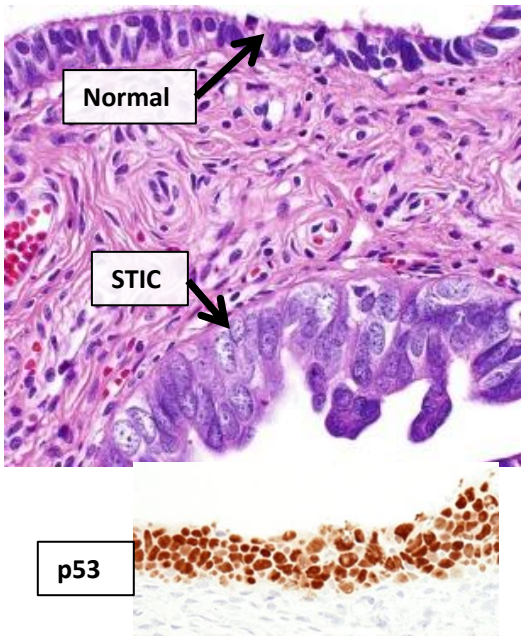
High-grade carcinoma with serous differentiation.
Identical morphology to in ovary (see prior section).

STIC

Non-invasive form is called ***S***erous ***T***ubal ***I***ntraepithelial ***C***arcinoma→ ***"STIC"***
Usually found at tuboperitoneal junction (fimbriae)
High N:C ratio, nuclear enlargement, pleomorphism, hyperchromasia, loss of cilia/polarity.
Lots of mitoses.
Even though "intraepithelial," it can still metastasize/spread to the ovary and peritoneum (i.e., it's essentially still malignant!)

IHC: p53 mutant; Ki67 >10%

Increased risk with BRCA mutation→ often get prophylactic BSO, which must be entirely submitted (SEE-FIM protocol) to rule out.



Serous Tubal Intraepithelial Lesion (STIL)—atypical, but falls short of criteria for STIC

Criteria for assigning primary site of extrauterine high-grade serous carcinoma:

Site	Criteria
Fallopian tube *(Most common site)*	STIC present, or Mucosal HGSC present, or Part or entire length of tube inseparable from tubo-ovarian mass
Ovary	Both fallopian tubes separate from ovarian mass, *and* No STIC or mucosal HGSC in either tube
Tubo-ovarian *(Default catchall, often used post-therapy or on cytology specimens)*	Fallopian tubes and ovaries not available for complete examination, and Pathologic findings consistent with extrauterine HGSC
Peritoneal	Both tubes and both ovaries fully examined, *and* No gross or microscopic evidence of STIC or HGSC

Adapted from WHO Classification of Tumors: Female Genital Tumors. 5th ed.