Always think Broadly!
Consider the 4 main families of ovarian tumors

Germ Cell ~10%
- Dysgerminoma
- Choriocarcinoma

Epithelial/Surface ~70%
- Teratoma
- Embryonal
- Yolk Sac

Sex Cord-Stromal ~15%
- Brenner

Metastasis Always a possibility, often from GI tract ~5%

Always think Broadly!

2 pathways:
1) Low-grade (KRAS/BRAF mt)
2) High-grade (p53 mt and genetically unstable)

Dysgerminoma

Choriocarcinoma

Teratoma

Embryonal

Yolk Sac

Brenner

Serous

Mucinous

Endometrioid

Clear Cell

Resembles endometrial glands
Associated with Endometriosis

Mucinous epithelium
(must consider GI source if carcinoma)

Large, clear cells with pleomorphic nuclei
Associated with Endometriosis

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

~10%
~70%
~15%
~5%

Cells resembling fallopian tube

Sometimes “Mixed”

Nests of cells resembling bladder in fibrous stroma

Last updated: 4/8/2020
Prepared by Kurt Schaberg
Epithelial/Surface Subclassification:
Three levels of biologic potential

<table>
<thead>
<tr>
<th>Cystadenoma &amp; Adenofibroma</th>
<th>Borderline/Low Malignant Potential</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>Malignant</td>
<td></td>
</tr>
</tbody>
</table>

Borderline Tumors:
aka: “Atypical proliferative serous 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:

<table>
<thead>
<tr>
<th></th>
<th>Serous</th>
<th>Mucinous</th>
<th>Endometrioid</th>
<th>Clear Cell</th>
<th>Brenner/Transitional</th>
<th>Seromucinous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>50%</td>
<td>80%</td>
<td>5%</td>
<td>&lt;1%</td>
<td>99%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Borderline</td>
<td>15%</td>
<td>15%</td>
<td>20%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>99%</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>35%</td>
<td>5%</td>
<td>75%</td>
<td>99%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

**Common mixtures of Epithelial tumors:**
- Brenner + Mucinous Cystadenoma or Borderline
- Serous + Seromucinous Borderline
- Endometrioid + Clear Cell Carcinoma

Histologically exists, but likely not a true histomolecular entity that will eventually disappear as likely composed of serous and endometrioid tumors.
**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 $\rightarrow$ **Serous cystadenoma**
  - $>1$ cm in size (if $<1$cm considered a **cortical inclusion cyst**)

- Can have a prominent exophytic fibrous component $\rightarrow$ **Serous adenofibroma**

- Can have BOTH $\rightarrow$ **Serous cystadenofibroma**

- Molecular: Typically **polyclonal** (*not* neoplasms $\rightarrow$ hyperplastic expansion of epithelial inclusions)

---

**Serous Borderline Tumor**

- Typically **middle-aged** women (mean 40s)

- 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
  - **Epithelial tufting** of columnar to cuboidal cells
  - Minimal to moderate cytologic atypia

- Proliferative area must be $>10\%$ of epithelial volume $\rightarrow$ 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 $\rightarrow$ very good prognosis
  - If peritoneal implants $\rightarrow$ risk of recurrence and potentially progression to low-grade serous carcinoma

---

Can progress to low-grade serous carcinoma $\rightarrow$ so must be sampled well!
**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 often **moderate cytologic atypia**

Fairly uniform population of cells and **low mitotic activity** (<2-3/HPF) compared to High-grade serous carcinoma

**Mutations and IHC like Serous Borderline Tumor**

Prognosis depends on stage.

Does **not** respond as well to Platinum-based therapy (as less proliferative compared to High-grade)

---

**Serous Borderline Tumor-Micropapillary Variant**

Aka: “non-invasive serous carcinoma”

Non-hierarchical branching architecture

**Fine micropapillae, 5x taller than they are wide**, coming off larger fibrotic papillae

Sometimes micropapillae fuse → cribriform growth

Cells are **cuboidal with high N:C ratios** with often prominent nucleoli

This component must be larger than 5mm to make Dx

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

---

**Implants:**

*Peritoneal spread of a Serous Borderline Tumor*

**Non-invasive implant:**

No infiltration of fat or muscle, high-grade cytology, or micropapillary architecture

Can have desmoplasia → “desmoplastic implant”

**Invasive implant:**

Fat or muscle invasion.

Are there small, solid nests of cells surrounded by a cleft-like space, micropapillae, and/or cribriform growth? If so → best to just call **low-grade serous carcinoma** as it behaves the same

Diffuse high-grade cytology → **High-grade serous carcinoma**

**Peritoneal spread of a Serous Borderline Tumor**

Non-invasive implant:

No infiltration of fat or muscle, high-grade cytology, or micropapillary architecture

Can have desmoplasia → “desmoplastic implant”

Invasive implant:

Fat or muscle invasion.
High-Grade Serous Carcinoma

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

Often bilateral 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 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)

BRCA-related cancers often have Solid, pseudo-Endometrioid, 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

<table>
<thead>
<tr>
<th></th>
<th>Low-Grade Serous Carcinoma</th>
<th>High-Grade Serous Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>Uniform round to oval nuclei</td>
<td>Pleomorphic nuclei (&gt;3:1)</td>
</tr>
<tr>
<td>Chromatin</td>
<td>Even</td>
<td>Irregular</td>
</tr>
<tr>
<td>Mitoses</td>
<td>≤12 /HPF</td>
<td>&gt;12 /HPF</td>
</tr>
<tr>
<td>P53</td>
<td>Wild-type</td>
<td>Mutated</td>
</tr>
<tr>
<td>P16</td>
<td>Patchy</td>
<td>Block-positive</td>
</tr>
<tr>
<td>Mutations</td>
<td>BRAF, KRAS</td>
<td>P53, BRCA</td>
</tr>
<tr>
<td>Precursor lesion</td>
<td>Serous Borderline Tumor</td>
<td>Serous Tubal Intraepithelial Carcinoma (STIC), usually</td>
</tr>
<tr>
<td>Architecture</td>
<td>Papillary, with hierarchical branching</td>
<td>Solid to papillary with slit-like spaces</td>
</tr>
<tr>
<td>Response to Chemo</td>
<td>Minimal (not proliferative)</td>
<td>Good</td>
</tr>
</tbody>
</table>
**Mucinous Cystadenoma/Adenofibroma**

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

Grossly **cystic/multicystic** with a smooth surface

**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

Molecular: Frequent **KRAS mutations**

Adenofibromas are uncommon

Can have a clonally related Brenner or dermoid cyst component

---

**Mucinous Borderline Tumor**

Wide age range.

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

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

Varying degrees of epithelial tufting, stratification, villi, and papillae.

Proliferative area **must be >10% of epithelial volume**

If there is high-grade cytologic atypia → “Intraepithelial 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 ~45

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

Two main patterns of growth:
1. Confluent/expansile glandular growth with little stroma
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 frequent

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

<table>
<thead>
<tr>
<th>Primary Ovarian</th>
<th>Metastatic Mucinous Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laterality</td>
<td>Unilateral</td>
</tr>
<tr>
<td></td>
<td>Bilateral more often</td>
</tr>
<tr>
<td>Size</td>
<td>Large (usually &gt; 20 cm)</td>
</tr>
<tr>
<td></td>
<td>Smaller (usually &lt;10 cm)</td>
</tr>
<tr>
<td>Gross</td>
<td>Multicystic ± solid component with smooth capsule</td>
</tr>
<tr>
<td></td>
<td>Nodular with cystic component</td>
</tr>
<tr>
<td>Location within ovary</td>
<td>Within stroma</td>
</tr>
<tr>
<td></td>
<td>Within surface and stroma</td>
</tr>
<tr>
<td>Microscopic</td>
<td>Well-differentiated mucinous epithelium forming organized cysts (borderline) or confluent glands (carcinoma)</td>
</tr>
<tr>
<td></td>
<td>Infiltrative mucinous glands</td>
</tr>
<tr>
<td>Extraovarian disease</td>
<td>Usually absent (Stage 1)</td>
</tr>
<tr>
<td></td>
<td>Often present</td>
</tr>
</tbody>
</table>

Adapted from a presentation by Dr. Anne Folkins, Stanford University
Primary Ovarian Mucinous Borderline Tumor

Secondary involvement by a Low-grade Appendiceal Mucinous Neoplasm (LAMN)

<table>
<thead>
<tr>
<th></th>
<th>CK7</th>
<th>CK20</th>
<th>ER/PR</th>
<th>CDX2</th>
<th>SATB2</th>
<th>PAX8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian mucinous borderline and carcinoma</td>
<td>+</td>
<td>-/+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Ovarian seromucinous borderline and carcinoma</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Metastatic Colon Cancer</td>
<td>-/+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Metastatic Gastric Cancer</td>
<td>+</td>
<td>-/+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Metastatic low-grade appendiceal mucinous neoplasm (LAMN)</td>
<td>-/+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Likely best panel: 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).

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?

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

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

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** or stromal reaction. Infrequent mitoses. Good prognosis.

Clear Cell Carcinoma

**Malignant.** Older middle age.
Usually unilateral, solid to cystic
Associated with endometriosis
Considered 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

Low mitotic index
Molecular: ARID1A mts most common. Also PIK3CA.

**IHC:** CK7, **HNF-1β**, and Napsin A positive (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)
Endometriotic Cyst

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


When dense fibrous component → adenofibroma.

**Likely just endometriomas in which stroma is indistinct.**

Associated with endometriosis

Endometrioid Borderline Tumor

Uncommon. Middle-aged. **Associated with endometriosis.**

Unilateral, solid or cystic. Hemorrhagic.

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

Can be papillary, protruding into cystic lumen

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

If severe enough atypia → Intraepithelial carcinoma

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 or cribiform growth** → Complex villoglandular, papillary, or Labyrinthine glands

Less commonly destructive growth

Squamous morules/differentiation common.

Occasional mucinous metaplasia

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

Prognosis: Good if low-stage. Bad if high-stage.
**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 and extensive

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. Very 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
- Malignant potential lower
- 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

Rare.
Carcinoma containing predominantly serous and endocervical-type mucinous epithelium
Fibroma/Thecoma

**Fibroma:**
*Benign* stromal tumor composed of **spindled cells with abundant collagen.**
Grossly solid, firm, chalky **white**.
Bland nuclear features. Varying patterns including storiform to bundled.
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 cores** within nests

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. Set in normal ovarian stroma.

Granulosa Cell Tumors

Two types, occurring in different settings with different prognoses:

**Adult Granulosa Cell Tumors**
Wide age range, but often **middle-aged**. Usually unilateral, low-stage. Solid with some cystic, hemorrhagic areas

**Secrete estrogen** → **menorrhagia**, post-menopausal bleeding, or amenorrhea.
Cells: Scant pale architecture with **grooved nuclei**

**Varied architecture**: Sheet-like, trabecular, ribbon-like, microfollicular (with “**Call-Exner bodies**” filled with pink secretions). Occasional macrofollicular architecture.
Frequent mitoses

IHC: Usual sex-cord stromal stains, plus WT-1, some keratins, and others
Molecular: Majority have **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**

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

Cells with abundant pink, granular cytoplasm

Regular round nuclei with vesicular chromatin

May contain rod-like eosinophilic crystals (Reinke crystals)

Fibrinoid necrosis of vessels

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...

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

Usually Benign, but can be malignant.

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)
Signet-Ring Stromal Tumor
Microcystic Stromal Tumor
Leutinized thecoma-associated with sclerosing peritonitis

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 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

Dysgerminoma

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

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

Elevated serum LDH, rarely hCG

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

Prognosis: Good if treated.

Embryonal Carcinoma

Think: Purple color

Rare.
Rudimentary epithelial differentiation

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
(Can get choriocarcinoma after a molar, ectopic, or normal pregnancy)

Malignant cytotrophoblasts (mononuclear) and syncytiotrophoblasts (multinucleated)
Abundant Hemorrhage

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

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

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

**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 → 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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
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<tr>
<td>1</td>
<td>Rare foci of immature neuroepithelium (&lt;1 in a 4x field on any slide)</td>
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<tr>
<td>2</td>
<td>1-3 foci per 4x field on any slide</td>
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<tr>
<td>3</td>
<td>&gt; 3 foci per 4x field on any slice</td>
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Germ Cell Tumor IHC:

<table>
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<tr>
<th>IHC Stain</th>
<th>Seminoma</th>
<th>Embryonal Carcinoma</th>
<th>Yolk Sac Tumor</th>
<th>ChorioCA</th>
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<tr>
<td>Glypican 3</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
</tr>
</tbody>
</table>
**Small Cell Carcinoma, 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

IHC: Diffuse WT-1; Focal CK, EMA;

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

**Wolffian Tumor**

Aka: “*Female Adnexal Tumor of Probable Wolffian Origin*” or “*FATWO*”

Often unilateral, older women, and solid.
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
Usually *benign*. 