Germ Cell and Stromal Tumors of the Ovary

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Gynecologic Oncology
Clinical Profile and Classification

Germ Cell Tumors
Ovarian Neoplasms

- Coelomic epithelium: 50-70%
- Germ cell: 15-20%
- Specialized gonadal stroma: 5-10%
- Nonspecific mesenchyme: 5-10%
- Metastatic tumors: 5-10%
Germ Cell Tumors

- 20% of all ovarian tumors
- 2-3% of ovarian malignancies
- Presentation at young age
- Tumor markers
  - hCG
  - αFP
  - LDH
Germ Cell Tumors
WHO Classification

- Dysgerminoma
- Endodermal sinus tumor
- Teratoma
  - Immature
  - Mature
  - Struma ovarii
  - Carcinoid
- Choriocarcinoma
- Embryonal carcinoma
- Polyembryoma
- Mixed GCT
- Combo GCT/Stromal
  - Gonadoblastoma
  - Other
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Frequency of OGCT</th>
<th>Benign/Malignant</th>
<th>Uni- or Bi-lateral</th>
<th>Tumour Markers Expressed</th>
<th>Metastasis Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgerminoma</td>
<td>35-50%</td>
<td>Malignant</td>
<td>10-15% are bilateral</td>
<td>Serum lactic dehydrogenase and serum hCG</td>
<td>Lymphatic system</td>
</tr>
<tr>
<td>Endodermal sinus tumor EST</td>
<td>20%</td>
<td>Malignant</td>
<td>Usually unilateral</td>
<td>AFP (commonly), alpha1-antitrypsin (rarely)</td>
<td>Intraperitoneally and hematogenously</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>Rare</td>
<td>Malignant</td>
<td>Usually unilateral</td>
<td>AFP and hCG</td>
<td>Intraperitoneally</td>
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<tr>
<td>Polyembryoma</td>
<td>Rare</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>Very rare</td>
<td>Malignant</td>
<td>Usually unilateral</td>
<td>HCG</td>
<td></td>
</tr>
<tr>
<td>Teratoma</td>
<td>Immature account for 20% of malignant GCT</td>
<td>Benign or malignant</td>
<td>12-15% are bilateral</td>
<td>Immature teratomas sometimes secrete AFP serum LDH and CA-125</td>
<td></td>
</tr>
<tr>
<td>Mixed GCT</td>
<td>10-15%</td>
<td>Dependent upon the cell types present</td>
<td></td>
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</table>
Dysgerminoma

Embryonal Carcinoma

Polyembryoma

Teratoma

Endodermal sinus tumor

Choriocarcinoma

Germ cell

Morula

Blastula

Embryo

Yolk sac
Ovarian Germ Cell Tumors

Primordial germ cell (totipotent)

Primordial germ cell
(Seminoma/Dysgerminoma)

Embryonal

Extra-embryonal

Mature teratoma

Immature teratoma

Trophoblast (Chorio-carcinoma)

Yolk sac carcinoma
(Endodermal sinus tumor)
Specific Tumor Types

Germ Cell Tumors
Dysgerminoma

- **It’s Not About the Bike**
- **Incidence**
  - 1-2% of ovarian tumors
  - 3-5% of ovarian malignancies
  - 40% of all GCT
  - Peak incidence age 19
  - 67% stage IA
- **10-15% bilaterality**
  - 20% in “normal appearing opposite”
Dysgerminoma
Ovarian Dysgerminoma
Dysgerminoma

- **Presentation**
  - Solid, lobulated, and can be large
  - 15% associated with MCT
  - Associated with gonadal dysgenesis and gonadoblastoma
  - High growth fraction, lymphatic spread

- **Tumor markers**
  - LDH, placental alkaline phosphatase

- **Survival**
  - Overall = 86%
  - Stage I = 90%
Dysgerminoma

- Fertility-sparing surgery
  - 85% of patients are younger than 35 yo
  - Consider uterine preservation (IVF)

- Radiosensitive

- Chemotherapy
  - Combination, dose-intense regimen
Dysgerminoma

- Large, round, ovoid or polygonal cells
- Pure or mixed cell type
- Lymphocyte stromal infiltration
- Lymphatic space invasion is common
# Dysgerminoma

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<tr>
<th>Stage</th>
<th>Incidence</th>
<th>Survival</th>
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<tr>
<td>Stage IA</td>
<td>70%</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-year</td>
</tr>
<tr>
<td>Stage IB</td>
<td>10%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-year</td>
</tr>
<tr>
<td>Stage II, III</td>
<td>15%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>5%</td>
<td>80%</td>
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</table>
Endodermal Sinus Tumor

- **Presentation**
  - 20% of all GCT
  - Median age 19 yo
  - Abdominal pain, large mass
  - 10-30 cm common
  - Very rapid growth, intra-abdominal and hematological spread

- **Tumor marker** = αFP, α₁ antitrypsin

- **Synonyms**
  - Yolk sac tumor, Mesonephroma

- **Survival**
  - Overall survival = 70%
  - Stage I = 90%
Endodermal Sinus Tumor

- Solid tumor with hemorrhage and gelatinous necrosis
- Microscopy
  - Hyaline globules
  - Schiller-Duval bodies
    - Single blood vessel surrounded by neoplastic cells
Endodermal Sinus Tumor

Hyaline globules → $\alpha_1$ anti-trypsin
Endodermal Sinus Tumor

Schiller-Duval bodies
Teratoma Classification

- Immature
- Mature
- Specialized
  - Struma ovarii
  - Carcinoid
Immature Teratoma

- **Presentation**
  - 20% of all GCT
  - 75% in first 2 decades of life
  - 12-15% bilateral
  - 60-70% are Stage I

- **Rarely** produce tumor markers- αFP and CA-125

- Grade is determined by % neural tissue

- **Stage IA grade 1 → no adjuvant therapy**

- **Survival**
  - Overall =63%
  - Stage I =75%
Immature Teratoma
Immature Teratoma

Primitive neural elements
# Immature Teratoma Grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>Scully</th>
<th>Norris</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Well differentiated</td>
<td>All mature; rare mitoses</td>
</tr>
<tr>
<td>1</td>
<td>Well differentiated; rare embryonal tissue</td>
<td>Some immature and neuroepithelium</td>
</tr>
<tr>
<td>2</td>
<td>Moderate embryonal; atypia and mitoses</td>
<td>Immature and neuroepithelium $\leq 3$ lpf</td>
</tr>
<tr>
<td>3</td>
<td>Large embryonal; atypia and mitoses</td>
<td>Immature and neuroepithelium $\geq 4$ lpf</td>
</tr>
</tbody>
</table>
# Importance of Grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number</th>
<th>Tumor Deaths</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>9 (37%)</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>7 (70%)</td>
</tr>
</tbody>
</table>
Mature Cystic Teratoma

- 5-25% of all ovarian tumors
  - 10-20% bilateral
- Most common ovarian tumor of young women
- Sonography
  - Complex, cystic and solid
  - Fat/fluid or hair/fluid level, calcifications
  - High MI score
- 1-2% with malignant degeneration
  - Rokitansky’s protuberance
  - Squamous cell cancers possible
Bilateral ovarian dermoids with typical features:

- Cystic with linear strands
- Solid echogenic mass
- Predominantly cystic
Mature Cystic Teratoma
Mature Cystic Teratoma
Mature Cystic Teratoma

Sebaceous glands
Mature Cystic Teratoma

Intestinal gland formation
Specialized Teratomas

- **Struma ovarii**
  - 2-3% of all teratomas
  - 25-35% have symptoms of hyperthyroidism
  - Usually benign, but may undergo malignant transformation
    - Follicular type

- **Carcinoid tumors**
  - Associated with GI or respiratory epithelium
  - Primary ovarian tumors are rare (N=50)
  - Often PMP
  - 1/3 have carcinoid syndrome from serotonin
  - Symptoms resolve with excision
  - 5-hydroxyindoleacetic acid in urine
Struma Ovarii

- Follicles contain vividly eosinophilic, acellular colloid
- Variation in follicular size is typical
- Can have rich vascularity
Ovarian Carcinoid

- Insular pattern
- Round uniform cells
- Fibroconnective tissue background
- 80% with neurosecretory granules
Choriocarcinoma

- **Presentation**
  - Uncommon, aggressive tumor
  - Often part of mixed GCT
  - Consider met from gestational chorioCA
  - Mean age 20 yo, children common
  - Half of premenarchal → precocious puberty

- **Tumor marker**
  - hCG
Choriocarcinoma

- **Cytotrophoblast**
  - Smaller cells
  - Smaller nuclei
- **Syncitiotrophoblast**
  - Larger cells
  - Eosinophilic cytoplasm
  - Bizarre nuclei
- **Hemorrhage**
Embryonal Carcinoma

- **Presentation**
  - Mean age < 30 yo
  - Only 4% of GCT and often part of mixed tumor
  - 60% Stage IA
  - Poorly differentiated germ cell tumor
  - Aggressive, intra-abdominal spread and mets common

- **Tumor markers:** hCG, αFP

- **Survival**
  - Overall = 40%
  - Stage I = 75%
Embryonal Cell Cancer

- Large, primitive cells
- Papillary or gland-like formation, occasional
- Sheets and ribbons
Polyembryoma

- Best classified as a mixed tumor
  - Never found in pure form
  - fewer than 50 cases
  - All under age 40
- Resembles embryonal carcinoma
  - Embryo days 13-15
- Treated like other mixed GCT
- Tumor markers: hCG, αFP
Mixed GCT
Embryonal and Choriocarcinoma
Gonadoblastoma

- Combined Germ Cell / Sex Cord Stromal Tumor

- Presentation
  - Age 1-38
  - Small tumors
  - Phenotypic ♀ with virilization
    - 90% have Y chromosome
    - 22% from streak gonads
  - Bilaterality 30-50%

- Check chromosomes for dysgenic gonads
  - BSO if Y
  - If TFS, await puberty before BSO
Gonadoblastoma

- Large germ cells, clear cytoplasm
- Nests of primordial germ cells surrounded by specialized stromal cells
- Associated sex chord stromal cells

Gonadoblastoma  Dysgerminoma
## GCT Tumor Markers

<table>
<thead>
<tr>
<th>Histology</th>
<th>AFP</th>
<th>hCG</th>
<th>LDH</th>
<th>PLAP</th>
<th>CA-125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgerminoma</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Endodermal sinus tumor</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Immature teratoma</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Embryonal CA</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>ChorioCA</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Treatment

Germ Cell Tumors
Surgery

- Importance of staging in early disease
- Fertility-sparing surgery often required
  - Can preserve uterus for future IVF, even if BSO
- Debulking improves outcome
Chemotherapy for GCT

- **BEP**
  - Bleomycin 20 U/m² weekly x 9
  - Etoposide 100 mg/m² days 1-5 q 3 weeks x 3
  - Cisplatin 20 mg/m² days 1-5 q 3 weeks x 3

- **VAC**
  - Vincristine 105 mg/m² weekly x 12
  - Act D 0.5 mg days 1-5 q 4 weeks
  - Cytoxan 5-7 mg/kg days 1-5 q 4 weeks

- **VBP**
  - Vinblastine 12 mg/m² q 3 weeks x 4
  - Bleomycin 20 U/m² weeks x 7, 8 on week 10
  - Cisplatin 20 mg/m² days 1-5 q 3 weeks x 3
Classification

Stromal Tumors
Ovarian Stromal Tumors

- **Fibroma**
- **Granulosa cell tumors**
  - Inhibin, CA-125
- **Sertoli-Leydig tumors**
  - CA-125, αFP, sTest
- **Steroid cell tumors**
  - sTest as 50-75% virilized
- **Gynandroblastoma**
  - ♀ and ♂ components
Ovarian Fibroma
Granulosa Cell Tumor

- **Presentation**
  - Adult (95%) and juvenile types
  - Solid and/or cystic- variable
  - Estrogen, occasional androgen
  - 80% palpable on examination
  - Hemoperitoneum in 15%
  - 80-90% Stage I
  - Low grade, late relapse

- **Estrogen excess and the endometrium**
  - 25% proliferative
  - 55% hyperplastic
  - 13% adenocarcinoma
Granulosa Cell Tumor
Treatment

- **Juvenile**
  - High cure rate

- **Adult**
  - Resection
  - Chemotherapy
    - BEP
    - Carboplatin and Taxol
    - GnRH analogs
Granulosa Cell Tumor
Granulosa Cell Tumor
Granulosa Cell Tumor
Granulosa Cell Tumor
Granulosa Cell Tumor

Call-Exner bodies
Sertoli-Leydig Cell Tumors

- **Benign**
  - Sertoli cell tumors → no hormones
  - Leydig tumors → testosterone

- **Potentially Malignant**
  - Sertoli-Leydig tumors
  - Arrhenoblastoma, androblastoma
  - Grade 3
    - 44% five-year survival

<table>
<thead>
<tr>
<th>Grade</th>
<th>% Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
</tr>
</tbody>
</table>
Sertoli-Leydig Tumor

Well-differentiated tubules
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Treatment Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgerminoma</td>
<td>USO staging if possible</td>
</tr>
<tr>
<td>Endodermal sinus tumor</td>
<td>Debulk but preserve fertility</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>As above</td>
</tr>
<tr>
<td>Malignant teratoma</td>
<td>As above</td>
</tr>
<tr>
<td>Granulosa cell tumor</td>
<td>USO if young o/w TAH/BSO</td>
</tr>
<tr>
<td>Sertoli-leydig cell</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td>BEP or VAC x 3-4 cycles</td>
</tr>
<tr>
<td></td>
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</tr>
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</tr>
<tr>
<td></td>
<td>BEP x 3 cycles if stage II-IV</td>
</tr>
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Conclusions

1. Common in young women
2. Tumor markers
3. Treatment
   - Fertility-sparing surgery
   - Chemosensitive $\rightarrow$ BEP for 3-6 cycles
   - Radiosensitive
4. No adjuvant chemo for:
   - Stage I pure dysgerminoma
   - Stage IA grade 1 IT