Epithelial Ovarian Cancer
Germ Cell tumors
Sex Cord Stromal Tumors

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MSU SCS Board Review Coarse

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Epidemiology

- 5th most cancer in women in the U.S.
- 4% of all cancers, 31% of female genital tract cancers
- Lifetime risk 1.5%
- Risk of dying of ovarian cancer 1%

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Epidemiology

- 90% arise from coelomic epithelium
  - Neoplastic transformation occurs as cells are genetically predisposed to oncogenesis or exposed to oncogenic agent
  - Epithelial ovarian cancer from single layer of cells that covers ovary or cells that line cysts beneath ovarian surface
Pathogenesis

- **Type I tumors**
  - Arise from ovarian surface epithelium and mullerian inclusions
    - Come from endosalpingiosis or invagination of the ovarian surface during repair of ovulation or implantation of cells from endometrium
    - Slow, multistep pathway (from adenoma – borderline – carcinoma)
    - Clear cell, mucinous, low-grade serous, endometrioid tumors

- **Type II tumors** (high grade serous tumors)
  - Phenotype that resembles the fallopian tube mucosa
  - Have p53 mutations
  - Appear to develop rapidly and most commonly found at advanced stage

Pathology

- Serous (cells resemble distal fallopian tube epithelium)
  - 75-80% of tumors
- Mucinous (cells resemble endocervical glands)
  - 10%
- Endometrioid (cells resemble endometrium)
  - 10%
- Clear cell, Brenner, Undifferentiated
  - 1% each
Borderline Tumors

- Also known as low malignant potential tumors
- Confined to ovary for long periods of time, premenopausal patient (30-50 y/o)
- Metastatic implants can be found with these tumors

Peritoneal Cancer

- Ovaries are of normal size or enlarged by a benign process
- Ovarian involvement is absent or limited to the surface and/or superficial cortex with no tumor nodule within the ovarian cortex exceeding 5 x 5 mm
- Serous histology
- Volume of extraovarian disease significantly exceeds that of ovarian disease

Risk Factors

- Age
  - 50% of cases in women >65 years old
- Low parity
- Infertility
- Early menarche
- Late menopause
- Estrogen therapy without progesterone for >10 years
Prevention
- Having at least 1 child
- OCP use
  - > 5 years use decrease risk 50%
- Risk reduction BSO
  - In women with BRCA1 or BRCA2 mutations

Screening
- Ultrasound
  - >95% sensitivity for detection of early ovarian cancer
- CA-125
  - Can contribute to the early diagnosis of ovarian cancer
  - Can detect 50% of stage I and 60% of stage II disease
- The false-positive rate of CA-125 and US especially in premenopausal patients confirm that these tests are not cost-effective and should not be used for screening

Genetics
- Most ovarian cancer is sporadic
- 10-14% of epithelial ovarian cancer is associated with BRAC 1 / 2 mutations
**BRCA 1/2**

- Autosomal dominant
- Tumor Suppressor Genes
  - Loss of both alleles causes cancer formation
  - Functions in DNA repair
- BRCA 1
  - On Chromosome 17
  - Risk 28-44% of developing ovarian cancer
- BRCA 2
  - On chromosome 13
  - Risk up to 27% of developing ovarian cancer
  - Risk is 10 years younger than in those patients with non-hereditary tumors

**HNPCC / Lynch II**

- Hereditary non-polyposis colorectal cancer syndrome
- Germ line mutations in genes involved in DNA mismatch repair pathways
- High rate of ovarian, endometrial, breast cancer
- Mutation associated with MSH2, MLH1, PMS1, PMS2
- Ovarian cancer risk is ~10%

**Risk reduction surgery**

- BRCA 1/2
  - Prophylactic BSO reduces risk by 96% of developing BRCA associated gynecologic cancer (After age 35 y/o or when childbearing complete)
  - Most BRCA 1 ovarian cancer after age 40
  - Most BRCA 2 ovarian cancer postmenopausal
  - Reduces breast cancer in premenopausal patients by 50-80%
  - Consider prophylactic hysterectomy if patient will be taking tamoxifen since they are at higher risk of endometrial lesions and cancer
  - Patients still have risk of primary peritoneal cancer 3-4%
Symptoms
- Pelvic or abdominal pain
- Urinary frequency or urgency
- Increased abdominal size or bloating
- Difficulty eating or feeling full
- Symptoms suspicious when last < 1 year and longer than 12 days out of a month

Signs
- Pelvic mass
  - Solid, irregular, fixed mass
- Upper abdominal mass / Ascites
- Pleural effusion

Diagnosis
- Ultrasound
  - Complex pelvic mass
    - Irregular borders, multiple echogenic patterns
    - Dense, multiple, irregular septae
    - Bilateral more likely to be malignant
- CT scan
  - Look for widespread disease
  - Lung / liver disease
Diagnosis

- CA-125
  - Best study to determine epithelial ovarian cancer
  - Postmenopausal patient with a pelvic mass and CA-125 of 65 had a sensitivity of 97% and a specificity of 78% for ovarian cancer

What elevates CA-125

- Ovarian cancer
- Uterine cancer
- Colon cancer
- Pancreatic cancer
- Stomach cancer
- Endometriosis
- Pregnancy
- Leiomyomata
- Salpingitis
- Cirrhosis
- Pancreatitis
- Renal Failure

Surgical Intervention

- Premenopausal
  - Large, predominantly solid, relatively fixed, irregular shaped
- Postmenopausal
  - Complex mass of any size
Patterns of Spread

- **Transcoelomic**
  - Exfoliation of cells that follow the circulatory path of the peritoneal fluid
  - Follow the pelvis up to the right paracolic gutter to the right diaphragm

- **Lymphatic**
  - Pelvic and Para-aortic lymph nodes
  - Spread through the lymphatic channel of the diaphragm can lead to disease above the diaphragm (supraclavicular node)

- **Hematogenous**
  - Spread to parenchyma of organs
  - Lung / Liver

FIGO Staging

- **IA** – Tumor limited to 1 ovary, negative washings, no rupture, capsule intact, no tumor on surface
- **IB** – Stage IA with involvement of both ovaries
- **IC** – Tumor in 1 or Both ovaries
  - **IC1** – Surgical Spill
  - **IC2** – Capsule Rupture before surgery or tumor on ovarian surface
  - **IC3** – Malignant cells in ascites or peritoneal washing

- **IIA** – Extension or implant on uterus or fallopian tube
- **IIB** – Extension to other pelvic intraperitoneal tissues
FIGO Staging

- IIIA (i) – Met to lymph nodes ≤ 10 mm
- IIIA1 (ii) – Met to lymph nodes > 10 mm
- IIIA2 – Microscopic, extra-pelvic (above pelvic brim) intra-peritoneal involvement +/- lymph node involvement
- IIIB – Macroscopic, extra-pelvic, peritoneal mets ≤ 2 cm +/- positive lymph nodes. Includes extension to capsule of liver / spleen
- IIIC – Macroscopic, extra-pelvic, peritoneal mets > 2 cm +/- positive lymph nodes. Includes extension to capsule of liver / spleen

FIGO Staging

- IVA – Pleural effusion with positive cytology
- IVB – Hepatic or Splenic parenchymal mets, mets to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Staging Procedure

- Free fluid in abdomen / pelvis sent or peritoneal washing done with 50-100 mL of saline
- Infracolic omentectomy
- TAH BSO
- Pelvic and para-aortic lymph nodes
- Biopsies of peritoneal surfaces / diaphragms
Physiologic benefit of tumor excision
- Ascites better controlled after removal of primary tumor and large omental cake
- Omental cake remove – removes the nausea / emesis / satiety
- Removal of intestinal mets can restore adequate intestinal function and improve nutrition status
- Improved tumor perfusion and increased growth fraction
- Large, bulky tumors have poor vascularity which exposes to suboptimal chemo
- Large tumors have more cells in resting phase which are resistant to chemotherapy
- Debulking produces less residual mass with a higher growth fraction
### Goals of Cytoreductive Surgery

- Primary goal to removal all of the primary cancer and all of the met disease
- If resection of all the mets is not feasible then the goal is to reduce the burden by resection of all individual tumor to an optimal status (< 1 cm)
  - Survival increases with less disease left
  - <1.5 cm (25 months), >1.5 cm -10 cm (15 months), >10 cm (9 months)
  - Optimal cytoreduction <1cm (39 months), >1 cm (17 months)

### Prognostic Factors

- Tumor Stage
- Volume of Residual disease
  - 22 month improved survival with optimal debulking
- Histologic subtype and grade

### Early stage

- Stage IA or IB, grade 1 or 2
  - Observation after surgery is acceptable
- All other stages receive chemotherapy after surgery
- Stage IC or II
  - 3 vs 6 cycles of chemotherapy
    - Standard is carboplatin / paclitaxel
Stage III / IV

- Standard chemotherapy today is Carboplatin / paclitaxel for 6 cycles after surgery

Intraperitoneal Chemotherapy

- Chemotherapy inside the abdominal cavity
- Studies show that IP chemotherapy had a significantly better OS of 16 months
- Recommended to give IP chemotherapy to optimally debulked stage III ovarian cancer patients
- Drawbacks are catheter related complications as well as increase toxicity (esp. Nausea / emesis)

Neoadjuvant Chemotherapy

- Chemotherapy before surgical debulking procedure
- Despite multiple studies, initial surgical debulking is still the standard of care in the US
- Neoadjuvant chemo appropriate in those patients
  - At high risk of operative morbidity and mortality
  - Significant cardiac disease
  - Large pleural effusions
  - Unresectable disease
**Current first line therapy guidelines**

- Carboplatin + paclitaxel for 6-8 cycles
- Consider IP chemo in optimally debulked stage III patients
- Consider clinical trials
- If frail can consider single agent carboplatin

**Follow-up when in remission**

- Office visits every 2-4 months for first 2 years, every 3-6 months for next 3 years, then yearly after 5 years
- Physical exam including pelvic exam, CA-125 or other markers
- CT or other imaging
  - Only if clinically indicated (symptoms or elevating markers)

**Recurrent disease?**

- Treat a patient on rising CA-125 or wait for disease to appear on radiologic imaging
  - Similar survival if you treat based on rising CA-125 or wait for CT scans to show recurrent disease.
Secondary Cytoreduction

- Debulking surgery after initial surgery and chemotherapy is complete
- Best candidates
  - Disease free interval of at least 12 months (preferably 24 months)
  - All macroscopic disease can be resected
    - Isolated disease
    - One or a few spots of disease, not widespread disease

Second Line Chemotherapy

- Many different combinations can be used
- Need to determine platinum sensitivity or not
- Platinum sensitive
  - Patients who recur > 6 months after primary chemo.
- Platinum Resistant
  - Patients who recur < 6 months after primary chemo
- Platinum Refractory
  - Patients who progress while on initial chemotherapy

Second line Chemo

- Response rate 10-40%
- Platinum sensitive patients should be given a platinum based combination in second line chemo
- Platinum resistant patients often use single agent treatment
  - Paclitaxel, docetaxel, topotecan, liposomal doxorubicin, gemcitabine, oral etoposide, tamoxifen, bevacizumab
**Survival by Stage**

- Stage I – 90%
- Stage II – 70%
- Stage III – 40%
- Stage IV - 20%

**Ovarian cancer Pearls**

- Papillary serous and Serous are the most common pathologies
- More common in low parity and infertility type patient
- Protective is OCP use, pregnancy, breast feeding
- BRCA 1 and 2 patients have increased risk thus prophylactic BSO when child bearing complete (consider after >35 yo)
- Spread patterns
  - Transcoelomic, lymphatic, hematogenous

**Ovarian Cancer Pearls - Surgery**

- Stage I-IV
  - TAH BSO, P and A LN, omentectomy, pelvic washing for those who can be debulked
  - Stage I patients need peritoneal biopsies to rule out met disease
  - Stage IVA – IVB patients
    - Can use neoadjuvant (chemo before surgery) for those with large pleural effusions or those who cannot be optimally debulked
    - Optimal debulking surgery
      - < 1 cm residual disease
Ovarian Cancer Treatment Pearls

- Stage IA, low grade – monitor, no chemo
- Stage IB, IC – 3 or 6 cycles of carboplatin / paclitaxel
- Stage II – IVB – 6 cycles of carboplatin / paclitaxel
- Intraperitoneal chemotherapy (direct chemo into the abdominal cavity) for those with stage III disease who were optimally debulked
- Neoadjuvant chemotherapy
  - 3-4 cycles of chemotherapy before surgery in order to make those patients who were not candidates for surgery able to have surgery.

Germ Cell Tumors

Background

- Derived from primordial germ cells of the ovary
- Arise from gonad of undifferentiated germ cells
- Type of curable cancer
- 20-25% of ovarian tumors, only 3% of these are malignant
- Account for 70% of ovarian tumors in first 2 decades of life, 1/3 are malignant
### Signs and Symptoms
- Pelvic pain due to rapid growth, capsular distention, hemorrhage or necrosis
- Bladder and rectal complaints due to mass effect
- Menstrual irregularities
- Can develop torsion symptoms
- Abdominal distention secondary to ascites

### Diagnosis
- >2 cm complex mass in premenarch or >8cm complex mass in premenopausal patient requires surgical exploration
- βhCG, AFP, CBC, liver function test in young patient; +/- CA-125
- CXR
  - Due to propensity to have lung mets
- Consider karyotype in premenarch
  - Due to these tumors being seen in dysgenetic gonads
- MRI or CT - to determine retroperitoneal lymphadenopathy or liver mets

### Types of GCT’s
- Dysgerminoma
- Yolk Sac tumor
- Embryonal carcinoma
- Polyembryoma
- Nongestational choriocarcinoma
- Mixed germ cell tumor
- Immature teratoma
- Mature teratoma
- Thyroid tumor
  - Struma Ovari
- Carcinoid
- Neuroectodermal tumor
- Sarcoma
- Pituitary-type tumor
- Melanocytic
**Dysgerminoma**

- Most common malignant GCT
- 30-40% of all GCT’s
  - 75% between ages 10-30
  - 5% associated with abnormal gonads
    - Pure gonadal dysgenesis, mixed gonadal dysgenesis, androgen insensitivity syndrome
- 65% found in stage I
  - 85-90% found in 1 ovary
  - 10-15% bilateral
- Only GCT that has a significant bilaterality rate
- - BhCG, - AFP

**Dysgerminoma Spread**

- Spread to para-aortic LN via lymphatic's
- Hematogenous spread
- Direct extension through the capsule of the ovary with exfoliation and dissemination of cells throughout the peritoneal surfaces

**Gross tissue**

- Large
- White to gray
- Fleshy, lobulated masses
- Focal area of hemorrhage or necrosis
- They contain cytoplasmic glycogen that can be seen with periodic acid-Schiff (PAS) stain
**Treatment**

- Surgery including USO, and unilateral P and A LN, inspect opposite ovary
- Can inspect other ovary but can leave in place due to sensitivity of tumor to chemotherapy
- If childbearing complete then can perform TAH, BSO and LN’s
- If karyotype contains a Y chromosome then both ovaries should be removed

**Chemotherapy**

- Stage IA can be monitored without chemo, all other stages treated
- BEP chemotherapy for 3-4 cycles
  - Bleomycin, Etoposide, Cisplatin
- If contraindication to Bleomycin then can treat with etoposide and cisplatin for 4 cycles

**Recurrence**

- Most recurrences will occur in 1st year
- If no chemo given prior then use BEP
- If prior BEP then can give TIP
  - Paclitaxel, Ifosfamide, Cisplatin
- Usual site of recurrence is peritoneal cavity or lymph nodes
  - Follow with pelvic exams and CT scans
**Endodermal Sinus tumors / Yolk Sac tumors**
- Derived from the primitive yolk sac
- 3rd most frequent malignant GCT
- 1/3 of patients are premenarchal
- Present with pelvic or abdominal pain
- +AFP
- Grow very rapidly and often evident in less than 1 month

**Gross tissue**
- Tan to gray
- Abundant hemorrhage and necrosis
- Partially solid, but contain many cysts
- Cysts are mucoid, slimy or gelatinous
- Contain Schiller-Duvall bodies

**EST / YST treatment**
- USO with LN's
- Bilaterality is rare
- Tumor usually solid and large (7-28 cm)
- Most early stage (71% stage I)
- All patients receive therapy
- BEP for 3-4 cycles or EP for 4 cycles where bleomycin is contraindicated
Embryonal Carcinoma

- Rare
- Patients 4-28 y/o
- Can secrete estrogen thus patients may present with precocious pseudo puberty or irregular bleeding
- Large masses, 2/3 seen only in one ovary
- +AFP, +hCG
- Surgery – USO with LN's
- Chemo – BEP for 3-4 cycles

Choriocarcinoma of the ovary

- Patients <20 y/o
- +hCG
- Isosexual precocity has been seen
- Treatment – surgical removal
- Chemo – MAC (methotrexate, actinomycin D, cyclophosphamide) like in GTD or BEP
- Prognosis is poor d/t most found in advanced disease state.

Mixed GCT

- Mixture of 2+ GCT's
- Most frequent combination is dysgerminoma and EST
- Can secrete AFP or hCG depending on the mixture
- Treat with BEP
Teratomas
- Derived from 2 or 3 embryonic layers
- Divided in mature (benign) or immature (malignant)

Mature Teratomas
- Contain differentiated tissue components such as skin, cartilage, glia, glandular elements and bone
- Benign tumors

Immature Teratoma
- Resemble tissue derived from the embryo
- Second most common malignant GCT
  - 10-20% of ovarian malignancy in patient <20 y/o
- Present with a mass, often unilateral
- Mostly solid, but can have cystic components
- Soft and fleshy, often contain hemorrhage and necrosis
- Continue immature neural tissue in form of small round blue cells
Treatment

- Surgery – USO and LN’s in premenopausal
- TAH BSO, LN in postmenopausal
- Chemotherapy
  - Stage IA, Grade 1 – no treatment
  - Stage IA, Grade 2 / 3 or other stages
    - BEP chemo 3-4 cycles

Summary

- Almost all patients with early stage, completely resected ovarian GCT survive after surgical staging and 3 courses of BEP
- 50-80% of patients with incompletely resected or advanced tumors are long term survivors
- Most times fertility can be preserved in these patients

Germ Cell Tumors Pearls

- Dysgerminomas (-BhCG, -AFP), yolk sac tumors (+AFP, -BhCG), embryonal carcinoma (+AFP, +BhCG), polyembryonal, mixed germ cell tumor, immature and mature teratoma (-BhCG, -AFP)
- Often see BhCG or AFP elevated
- Rapid growing masses, causing pain
- Early aged patients
  - >2 cm mass in premenarch and >8cm complex mass in premenopausal requires surgical intervention
- Often Stage IA monitored and the rest are treated with chemotherapy
Sex Cord Stromal Tumors

SCST

- 5-8% of ovarian malignancies
- Derived from sex cords and ovarian stoma or mesenchyme
- Female cells (granulosa and theca cells)
- Male cells (sertoli and leydig cells)

SCST’s

- Granulosa cell tumor
  - Adult type granulosa cell tumor
  - Juvenile type granulosa cell tumor
- Theca-fibroma group
  - Thecoma
  - Fibroma
  - Fibrosarcoma
  - Sclerosing stromal tumor
  - Signet-ring stromal tumor
Sertoli – stromal cell tumor

- Sertoli-Leydig cell tumor group (androblastoma)
  - Well differentiated, intermediate and poor differentiated
- Sertoli cell tumor
- Stromal-Leydig cell tumor

Granulosa cell tumors

- Adult or Juvenile type
- May secrete estrogen
- Only 2% bilateral
- Symptoms
  - 75% associated with sexual pseudo precocity (d/t estrogen secretion)
  - Menstrual irregularities in reproductive age women
  - Endometrial cancer in 5% and hyperplasia in 25-50%
  - Virilization
    - Rarely seen if androgens are produced
- Ascites
  - Rare and only seen in 10% of cases
- Hemoperitoneum
  - Due to the ovarian mass being hemorrhagic and this is produced when they rupture

Granulosa cell tumor

- Most stage 1 at diagnosis
- Recur later in life (5-30 years after initial diagnosis)
- Heme spread
  - Can see mets in lungs, liver, brain years later
**GCT Diagnosis**

- Inhibin
  - Secreted by granulosa cell tumors
  - Polypeptide hormone and is an inhibitor of pituitary FSH
  - Inhibin is not detectable in postmenopausal women
  - Inhibin elevated in premenopausal women with amenorrhea and infertility suggests a GCT
  - Inhibin A and B can be measured
    - Inhibin B has been found to be more sensitive to show disease status and recurrence

**GCT Treatment**

- Surgery
  - Can do fertility sparing surgery
  - Premenopausal or young women
    - Unilateral salpingoophorectomy, unilateral nodes, peritoneal biopsies, washings, omental biopsy, biopsy contralateral ovary if lesion seen
  - Postmenopausal women or perimenopausal who ovarian preservation not warranted
    - TAH BSO, nodes, biopsies, omentectomy, washings
  - D and C
    - If uterus left d/t risk of malignancy or hyperplasia

**GCT Treatment**

- RT
  - No evidence to support RT
- Chemotherapy
  - No chemo for stage 1 patients
  - Others
    - BEP (bleomycin, etoposide, cisplatin) (ORR 58-83%)
    - Carboplatin / paclitaxel (ORR 60%, less toxicity)
Recurrence and prognosis

- Recurrence
  - Median rec. time is 4-6 years
  - Surgery or chemotherapy
- Prognosis
  - Most are found in stage I and curable
    - Stage I cure rate is 75-92%
    - 5 year survival is 94%
  - Stage II – IV
    - 5 year survival is 55%

Juvenile Granulosa cell tumors

- Rare, making up only 5% of ovarian tumors
- 90% are stage I
- Less aggressive then adult type
- Advanced stages treated successfully with BEP

Sertoli-Leydig tumors

- Commonly in 3rd and 4th decade
- 75% in women <40 y/o
- Less than 0.2% of ovarian cancers
- Mostly are low-grade malignancies
- Symptoms
  - Virilization due to androgen production (70-85%)
    - Oligomenorrhea, amenorrhea, breast atrophy, acne, hirsutism, clitoromegaly, deepening of voice, receding hairline
- Diagnosis
  - Elevated testosterone, androstenedione, slightly elevated DHEA-s
Treatment / prognosis

- **Treatment**
  - Surgery
    - USO, evaluated other ovary (bilateral in <1%), lymph nodes, washing, biopsies
    - Menopause / fertility complete
    - TAH BSO
  - Chemo
    - Advanced stages
    - Cisplatin / doxorubicin / ifosfamide
    - BEP, EP, PAC, carboplatin / paclitaxel
- **Survival**
  - 70-90%

Krukenberg tumors

- 30-40% of metastatic tumors to the ovary
- Mucin-filled, signet-ring cells in the ovarian stroma
- Most common primary is Stomach
  - But also see colon, breast, biliary tract
  - Usually see these bilaterally
  - Usually found when the primary tumor is advanced
  - Most die within 1 year