Cancer in Women
Breast Cancer, Endometrial Cancer, Ovarian Cancer

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Breast Cancer

- For women, the most common occurring malignancy in the U.S.
- Nearly 200,000 cases will occur this year
- Second in cause of cancer death in women (lung cancer is first)
- Median age at diagnosis=55 years
- Male:Female Ratio—1:100
- One woman in 8 will develop breast cancer in her lifetime
Risk Factors

- Older age (>55 years of age)
- Family history of breast cancer
- May also increase risk for cancer at younger age
- Early menarche and late menopause
- ? high fat diet
- Oral contraceptives/estrogen replacement
Risk Factors

- **Cancer Family syndromes:**
  - Li Fraumeni Syndrome — sarcomas, brain tumors, leukemia, adrenal carcinoma
  - Cowden's Disease — facial trichilemmomas, papillomatosis of lips and oral mucosa, acral keratoses, gastrointestinal polyps, uterine leiomyosarcoma
  - Muir's Syndrome — basal cell carcinoma, benign/malignant gastrointestinal tumors
Risk Factors

- Breast Cancer Susceptibility Genes
  - *BRCA1*—antioncogene that may be altered in 5-10% of women with breast cancer under age 40
  - *BRCA2*—similar role to *BRCA1* and, when mutated, may pose 85% lifetime risk of developing breast cancer and 10% lifetime risk of developing ovarian cancer
  - May be responsible for most male cases
HER2 oncogene

- Member of Type 1 growth factor receptor family
- Expression may confer adverse prognosis
- Present in ~25% of all breast cancers
- Target for monoclonal antibody trastuzumab (Herceptin®)
Prognostic Factors and Breast Cancer

- **Nuclear grade**
  - A variety of grading systems that evaluate cellular anaplasia, nuclear/cytoplasmic ratio, tendency of cells to form glands, etc.
  - Describes the level of aggressivity of tumor specimen
  - Tumors with poorly differentiated features fare worse than tumors with well or moderately well differentiated features
Prognostic Factors and Breast Cancer

- Lymph node status
  - The most important prognostic factor
  - Patients with 4 or more nodes involved fare worse than women with only one node involved or 2-3 nodes involved
Lumpectomy—the removal of the breast mass with a surrounding margin of grossly normal tissue

Not sufficient by itself, requires radiotherapy
Rationale

- Breast cancers usually metastasize in contiguity to lymph nodes
- Sampling the first draining node (the sentinel node) allows for screening for nodal involvement
- Women with negative sentinel nodes may be spared ALND and its potential complications
- Women with positive sentinel nodes should undergo ALND
Management of Breast Cancer

- Radiotherapy
  - Valuable in management of patients with breast conservative therapy
  - Local radiation to the remaining breast and axillary region is REQUIRED in all patients who receive lumpectomy
Management of Breast Cancer

- Radiotherapy

  - Of value for palliative intent in women with metastatic breast cancer and...

  - Painful isolated bony metastases
  - Spinal cord compression
  - Brain metastases
  - Isolated pulmonary metastases
## Management of Breast Cancer

### Chemotherapy

- **Major active drugs include…**
  - Methotrexate
  - 5-fluorouracil
  - Doxorubicin
  - Epirubicin
  - Cyclophosphamide
  - Mitoxantrone
  - Docetaxel
  - Paclitaxel
  - Vinblastine
  - Vinorelbine
  - Ifosfamide
  - Trastuzumab
  - Cisplatin
  - Carboplatin
  - Capecitabine
  - Others
Management of Breast Cancer

- Standard chemotherapy regimens include...
  - Anthracycline-based—doxorubicin or epirubicin as backbone
  - Taxane-based—docetaxel or paclitaxel as backbone
  - Combinations—include both anthracycline and taxane
Management of Breast Cancer

- Hormonal therapy

- 67% of postmenopausal women will have estrogen and/or progesterone receptors on the surface of malignant breast tissue

- Only about 10% of premenopausal women will have hormone receptor positive tumors
Management of Breast Cancer

- Hormonal therapy
  - Major agents include...
    - Tamoxifen (Nolvadex®)—estrogen receptor antagonist, may also act as partial agonist (tumor flare). May increase risk of endometrial cancer—yearly gynecologic exam required!
    - Anastrozole (Arimidex®)—aromatase inhibitor that decreases conversion of androgens to estrogen
      - Appears slightly more effective than TAM in adjuvant setting
      - Approved for adjuvant use as well as in metastatic setting
      - Increased risk of osteoporosis—watch bone density!
Management of Breast Cancer

- Hormonal therapy

- Major agents...
  - Letrozole (Femara®)—aromatase inhibitor similar in activity to anastrozole
  - Approved for adjuvant use, as well as “switching” scenarios after TAM
  - Exemestane (Aromasin®)—another AI that is steroidal in nature
  - Improves survival after 2-3 years’ TAM use compared to continuation of TAM for full 5 years
Management of Breast Cancer

Tamoxifen: How long is long enough?

Two major trials demonstrated that adjuvant TAM for a period of 10 years lowered the recurrence rate in the second decade after diagnosis by nearly 50%

Currently…TAM utilized for 10 years in women who are likely to benefit most (<70 years of age, life expectancy >15 years)

NO data yet on aromatase inhibitors longer than 5 years!
General Principles…

Breast cancer is a heterogeneous disease and more than one acceptable treatment may be available for a given patient.

Major focus of nonmetastatic breast cancer treatment is curative.

Major focus of metastatic breast cancer treatment is palliative.
Early Stage Breast Cancer

- Small primary, lymph node negative
- Breast conservative surgery followed by radiation therapy
- Adjuvant systemic therapy considered if...
- Tumor 1cm or larger in size
- Adverse prognostic features
Management considerations…

- Size of primary lesion
  - Lesions >4cm in size can be managed by mastectomy or preoperative chemotherapy in hope of breast conservation
  - Adjuvant systemic therapy indicated in all cases
Metastatic Breast Cancer

- Management considerations…
  - Surgical treatment of the breast is not required, but patients may gain some psychological benefit from mastectomy
  - Patients are treated primarily for palliative intent
  - The disease course can be extremely variable
Ductal Carcinoma *in Situ*

- Diagnosis increased with the extensive use of mammograms
- Microcalcification or soft-tissue abnormality
- Histologic types
  - Comedocarcinoma
  - Noncomedo carcinoma: micropapillary, papillary, solid, cribriform
Ductal Carcinoma *in Situ*

- **Treatment**
  - Lumpectomy plus radiation
  - Post-lumpectomy/RT, tamoxifen reduced the risk of breast cancer recurrence (ipsilateral and contralateral)
  - Simple mastectomy is an alternative to lumpectomy with radiation—required in cases of extensive DCIS
Lobular Carcinoma *In Situ*

- Not considered cancer, but a marker of increased risk for developing invasive breast cancer
- Also known as lobular neoplasia or atypical lobular hyperplasia
- Usually multicentric and bilateral
- There is a 21% chance of developing breast cancer in 15 years
Lobular Carcinoma *In Situ*

- **Management**
  - Close follow-up…
  - Clinical breast examination every 4 to 12 months
  - Annual mammogram
  - Tamoxifen may be used for prevention of breast cancer
  - Bilateral prophylactic mastectomy in selected patients
Breast Reconstruction

- Offers many women improvement in self-esteem and body image
- Reconstruction can be done at the time of mastectomy or can be delayed until later
- Some women prefer to wear a breast prosthesis
Breast Reconstruction
Breast Cancer Prevention

- Goals of cancer prevention
  - Identify women at risk
  - Encourage modifications known to decrease likelihood of developing breast cancer
  - Utilize drug therapy to further decrease risk of cancer development
    - Tamoxifen (Nolvadex®) and raloxifene (Evista®) equally effective in lowering risk of 2nd primary by 50%
    - Raloxifene does not decrease risk of *in situ* carcinoma!

Endometrial Cancer

- Introduction
- Pathology
- Signs and Symptoms
- Diagnosis and Staging
- Treatment Options
Introduction

- Most common gynecologic cancer...about 33,000 cases/year
- 75% of cases occur after age 50, only 4% prior to age 40
- Hereditary in some families
- Rate increased in industrialized societies
Adenocarcinoma risk increased with...

- Obesity
- Unopposed estrogenic stimulation—causes adenomatous hyperplasia (USE PROGESTERONE!)
- Anovulation—Stein Leventhal syndrome, premature ovarian failure
- Family cancer syndromes—Lynch syndrome II, Li Fraumeni syndrome
Risk Factors

- Atypical adenomatous hyperplasia
  - Risk of endometrial CA is 10-30% at 10 years if untreated
- Tamoxifen
  - Risk of endometrial CA slightly increased with use of this agent
  - Yearly gynecologic exam in women taking TAM
  - Investigate vaginal bleeding in any woman taking TAM
Pathology

- Adenocarcinoma accounts for over 90% of all types
- Other types include...
  - Clear cell carcinoma
  - Small cell carcinoma
  - Sarcoma—leiomyosarcoma most frequent
  - Lymphoma
Signs and Symptoms

- Most patients asymptomatic
- Vaginal spotting/bleeding most frequent complaint
- Such complaints in ANY postmenopausal woman warrant investigation for endometrial CA!...risk of malignancy about 35%
Signs and Symptoms

- With advanced disease...
  - Pelvic fullness/pain
  - Constitutional symptoms
  - Ascites
Diagnosis

- Aspiration curettage—most often employed but can't detect precursor lesions
- Dilation and curettage (D&C)—accurate about 90% of cases
- Currently no good technique to screen women in general or those at risk
Staging

- Follows FIGO (International Federation of Gynecology and Obstetrics) criteria
- Stage is completed surgically in most cases, but additional studies help...
  - Laboratory studies—CBC, tests of liver/renal function
  - Radiologic studies—CXR, CT abdomen/pelvis, pelvic US
  - Tumor grade plays a role in treatment of stage I disease
Treatment of Stage I Disease

- TAH/BSO with pelvic lymphadenectomy if involvement of outer half myometrium
- Pelvic RT is added postoperatively if...
  - Involvement of outer half myometrium
  - Lymph nodes positive (these patients are technically Stage III)
  - Grade 3 histology
Treatment of Stage II Disease

- Treatment must include parametria, vagina, and pelvic lymph nodes
- Combination of surgery and RT
  - Extended TAH/BSO
  - Radiotherapy—vaginal brachytherapy followed by pelvic RT
Treatment of Stage III Disease

- TAH/BSO with pelvic and paraaortic lymphadenectomy, omentectomy
- Chemotherapy followed by RT
- Chemotherapy regimens (backbone is platinum agent plus additional agents)...
  - Cisplatin/doxorubicin ± paclitaxel
  - Carboplatin/paclitaxel
  - Carboplatin/docetaxel
Treatment of Stage IV Disease

- Mostly palliative
- Chemotherapy given for control of symptoms
- RT with or without hormonal therapy (megesterol acetate, LHRH agonists) are given as options to chemotherapy
- Limited role for surgery, mostly for avoidance of obstruction of hollow viscera
Ovarian Cancer

- Introduction
- Pathology
- Signs and Symptoms
- Diagnosis and Staging
- Treatment Options
Introduction

- Arise from epithelial tissue 75% of the time
- 5% germ cell tumors BUT GCT's account for 65% of all ovarian malignancy in women < 20 years of age
- Account for 20-25,000 cases and 12,000 deaths per year
- More common in Westernized cultures
- Median age at onset about 48 years
Introduction

Factors which decrease risk of developing ovarian CA...

- Pregnancy < 25 years
- Early menopause (< 50 years)
- Oral contraceptives
Factors which increase risk of developing ovarian CA...

- Late menopause
- Nulliparity
- Age > 30 at first pregnancy
- Family history—ovarian, BUT risk also increased for fam. hx. of breast, endometrial, colorectal
Pathology

Several varieties…

- Epithelial Tumors—90% of total
  - Benign
  - Low malignant potential ("borderline")
  - Malignant

- Sex Cord/Stromal Tumors—< 10% of total

- Germ Cell Tumors
Epithelial Ovarian Tumors

- **Benign**—surgical removal sufficient
- **Borderline**—surgery usually enough; rarely metastasize
- **Malignant**—surgery plus other modalities (for staging)
Stromal Ovarian Tumors

- More indolent than epithelial tumors
- Surgery is primary treatment
- Chemotherapy/radiation used in advanced cases
Germ Cell Tumors

- Tend to occur in young women
- Very aggressive!
- Surgery for initial diagnosis
- Very sensitive to chemotherapy, which is primary modality of treatment
Staging

- Includes detailed surgery with washings of peritoneum, multiple biopsies, and resection of as much tumor as possible ("cytoreductive surgery")

- Radiographic studies—CXR, CT Abdomen/Pelvis, ± IVP

- Lab studies—CBC, Biochemical profile, tumor markers do NOT help in diagnosis but may assist in management (CA 125)
Treatment

- Will discuss only epithelial ovarian CA
- Surgery is primary treatment for ovarian cancer of all stages and types
- Assists with diagnosis and treatment
Treatment

- Surgery
  - Cytoreductive surgery...
    - Removal of as much of tumor as possible in cases of metastases
    - Patients who can be debulked such that total tumor mass $< 2$cm in maximum dimension have survivals 2-4 times that of patients with residual tumor mass $> 2$cm
Chemotherapy

Active agents include platinum compounds, cyclophosphamide, ifosfamide, taxanes (taxol, taxotere), melphalan, hexamethylmelamine, doxorubicin (Adriamycin), new liposomal doxorubicin, topotecan

Combinations generally more active than single agents—taxane plus platinum compound currently favored
Chemotherapy

- Mainstay of treatment for metastatic ovarian cancer
- Of value for adjuvant therapy for disease beyond Stage I
- Intraperitoneal instillation of chemo. may be of palliative benefit
Treatment

- Hormonal Therapy
  - Limited role in all but most futile of cases
- Radiotherapy
  - Limited role, but may be of value in palliation
Treatment of Stage I Disease

- Surgery...
  - TAH/BSO—can do USO alone in young women with Stage Ia disease who desire to preserve fertility; these come out upon completion of childbearing

- Surgical staging

- Chemotherapy—only if peritoneal washings positive (Stage Ic) or poor histology
Treatment of Stages II-IV Disease

- Surgery...
- TAH/BSO with cytoreductive surgery, omentectomy
- Adjuvant chemotherapy for 6 cycles is recommended
Treatment of Borderline Tumors

- Low metastatic potential
- Removal of involved ovary should be sufficient in 95% of cases
- Reoperation with subsequent chemotherapy if disease recurs
Prognosis

- 5 year survival rates...
  - Stage I: 80-100%
  - Stage II: 30-40%
  - Stage IIIa: 30-40%
  - Stage IIIb: 20%
  - Stage IV: < 5%

- Age at diagnosis, grade of tumor, performance status are important cofactors in individual survival rates
Metastatic Ovarian Tumors

- 5% of ovarian tumors are metastatic
- Most frequently from genital tract, breast, or GI tract
- In autopsy studies of women with metastatic breast CA, ovaries are involved about 25% of the time
Metastatic Ovarian Tumors

- Krukenberg Tumor
  - 30-40% of metastatic ovarian tumors
  - Signet ring adenocarcinoma arising primarily from the stomach, colon, breast, biliary tract, cervix, or bladder
  - Most patients die of metastases from primary site within one year