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.
- Over 240,000 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

Prognostic Factors and Breast Cancer

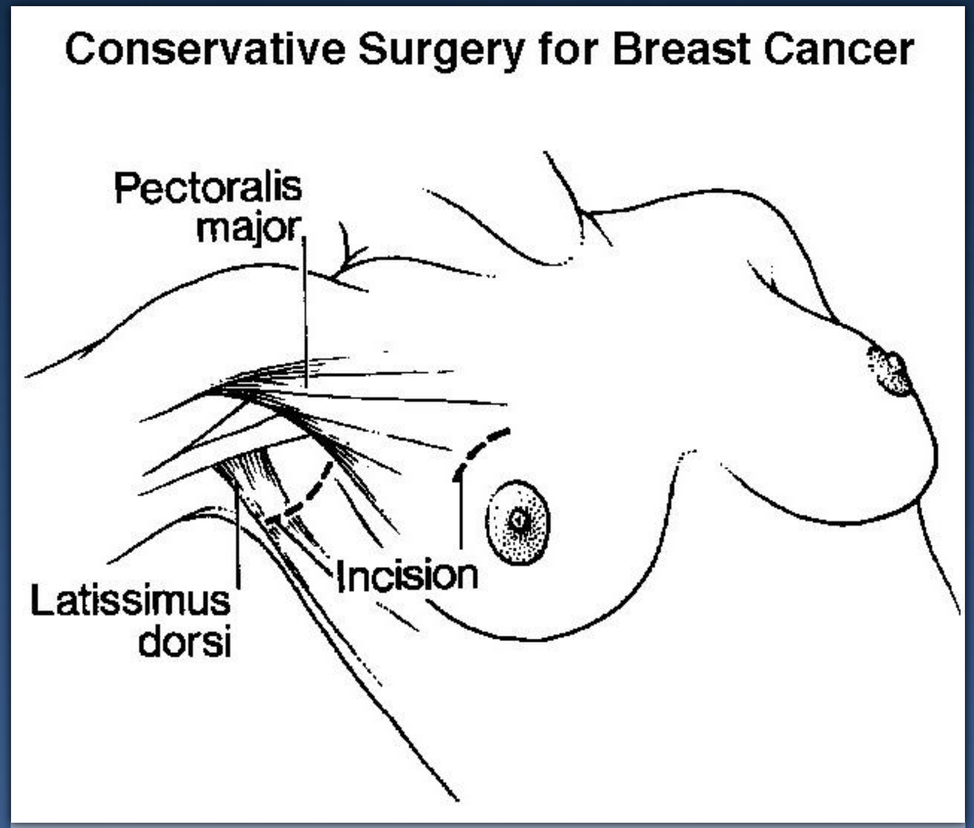
- *HER2* oncogene
  - Member of Type 1 growth factor receptor family
  - Present in ~25% of all breast cancers
  - Target for monoclonal antibody trastuzumab (Herceptin®)

Prognostic Factors and Breast Cancer

- Grade of the primary tumor
  - 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

Management of Breast Cancer

- Surgery
  - Lumpectomy—the removal of the breast mass with a surrounding margin of grossly normal tissue
    - Not sufficient by itself, requires radiotherapy



Sentinel Lymph Node Mapping

- 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
  - Women with very small tumors can be treated with brachytherapy (MammoSite) as alternative to EBRT
  - Local radiation of some sort 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!

Treatment of Breast Cancer

- 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

Lymph Node Positive Breast Cancer

- 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

Locally Advanced (Inflammatory) Breast Cancer

- Multimodality therapy is the key…
  - Chemotherapy initially
  - Surgery/RT second
  - Additional systemic therapy as indicated

https://breastwellnesscenter.files.wordpress.com/2015/04/amy_calatrava_14dec27-1.jpg

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

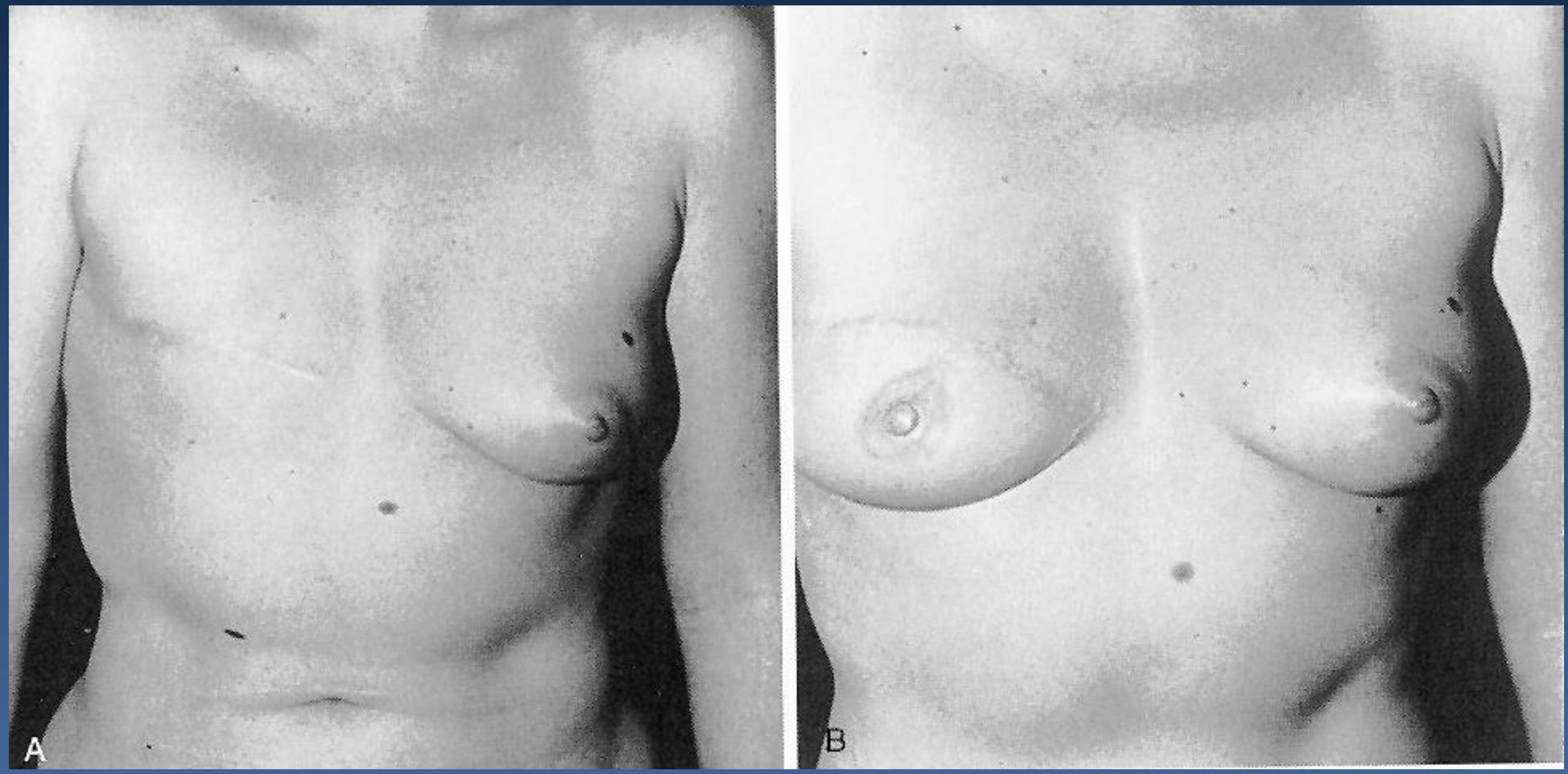
Lobular Carcinoma *In Situ*

- 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 60,000 cases/year
- 75% of cases occur after age 50, only 4% prior to age 40
- Hereditary in some families
- Rate increased in industrialized societies

Risk Factors

- Adenocarcinoma risk increased with…
  - Obesity
  - Hyperinsulinemia
  - Unopposed estrogenic stimulation—causes adenomatous hyperplasia (USE PROGESTERONE!)
  - Anovulation—Stein-Leventhal syndrome (polycystic ovary 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 22,000 cases and 14,000 deaths per year
- More common in Westernized cultures
- Median age at onset about 48 years; 50% of all cases occur in women over age 65

Introduction

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

Introduction

- 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
  - BRCA1/BRCA2—some studies suggest mutation carriers may have a better response to chemotherapy than non-carriers

Pathology

- Several varieties…
  - Epithelial Tumors—90% of total
    - Benign
    - Low malignant potential ("borderline")
    - Malignant
  - Sex Cord/Stromal Tumors— < 10% of total
  - Germ Cell Tumors

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

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, PET
- 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 < 2cm in maximum dimension have survivals 2-4 times that of patients with residual tumor mass > 2cm

Treatment

- 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

Treatment

- 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

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