Breast Cancer Outline and Update

Demographics:

- 230,000 new diagnoses, 40,000 deaths/year

Risk factors:

- Age: 1/2000 at age 30, 1/10 at age 80, average lifetime risk 1/8 (12%)
- Nulliparity, late pregnancy (>age 30), early menarche (<12), late menopause (>55) (increased duration of unopposed estrogen stimulation), no breast feeding
- Chest radiation exposure at young age (lymphoma high dose, acne low dose)
    - Risk starting 10y post radiation, 6X increased risk
- Dense (glandular) breast tissue
- Family history of first degree (mother, sister, daughter) relative (including paternal: father, aunts, second degree)
- Previous breast cancer
- Proliferative breast or endometrial disease
- History of two prior breast biopsies
- Postmenopausal hormone replacement therapy (HRT) 26% increased risk
- History of atypical ductal hyperplasia (ADH) on biopsy, ductal carcinoma in situ (DCIS), lobular carcinoma in situ/lobular neoplasia (LCIS)
    - DCIS, LCIS 1% increase in risk /year
    - 20% of LCIS go on to develop breast cancer, usually ductal, LCIS is not thought to progress to cancer as DCIS does
    - obesity (especially abdominal): estrogen production by fat stimulates breast tissue in addition to ovarian production, and acts with adrenal estrogen production in post-menopausal women
- Genetics:
    - Only 5-10% of breast and ovarian cancer is hereditary
    - Patients are tested for a deleterious mutation if they meet NCCN guidelines.

- False negative is due to
  - Technology
  - Methelation
  - Mutations in the promoter region of the gene
  - Mutations buried in the introns, and RNA
  - Being turned off by modifier genes

Features of Hereditary Cancer

- Ovarian cancer in one or more women
- Both breast and ovarian cancer diagnosed in the dame woman
- A male with breast cancer
- Ashkenazi Jewish (Eastern European) heritage
- Multiple generation of people affected with the same or related cancers
- Several relatives with breast cancer, with some women diagnosed before age of 50

Cancer Risks Associated with BRCA1 and BRCA2 Mutations

Genetic testing for a BRCA gene mutation can help guide medical care and a person with a gene mutation may benefit from different cancer risk management strategies.

The cancers and corresponding risks associated with mutations in BRCA1 and BRCA2 are presented as ranges. The presence of a BRCA gene mutation does not predict where in the range any single individual will fall or if any cancer will ever develop.

BRCA1 Cancer Risks Lifetime BRCA1 Cancer Risks for Women

Type of Cancer	**Women with BRCA1 mutation**	**Average woman in US without mutation**
Breast	50-85%	12%
Ovarian/Fallopian Tube	20-40%	1-2%

Pancreatic	2-3%	1%

Lifetime BRCA1 Cancer Risks for Men

Type of Cancer	**Men with BRCA1 mutation**	**Average man in US without mutation**
Breast	1-5%	0.1%
Prostate	*	17%
Pancreatic	2-3%	1%

*Recent studies do not suggest an increase in risk for prostate cancer; however, men with a BRCA1 mutation may develop prostate cancer at an earlier age.

BRCA2 Cancer Risks

Lifetime BRCA2 Cancer Risks for Women

Type of Cancer	**Women with BRCA2 mutations**	**Average woman in US without mutation**
Breast	50-85%	12%
Ovarian/Fallopian Tube	10-20%	1-2%
Melanoma	3-5%	1-2%
Pancreatic	3-5%	1%

Lifetime BRCA2 Cancer Risks for Men

Type of Cancer	**Men with BRCA2 mutation**	**Average man in US without mutation**
Breast	5-10%	0.1%
Prostate	15-25%	17%
Melanoma	3-5%	1-2%
Pancreatic	3-5%	1%

- Other genetic associations with breast cancer
  - P53 mutation (<1%), Li-Fraumeni (sarcoma, breast, brain, adrenocortical, adrenal)
  - PTEN (<1%), Cowden's (hamartomatous colon polyps, breast)
  - Undiscovered genes account for the other 50% of genetic-associated breast cancers
  - CDH1 associated with lobular breast cancer and gastric cancer.
  - Follicular thyroid cancer
  - Trichilemmomas
  - Endometrial cancer

- Gail model of breast cancer risk
  - Based on SEER database
  - Factors: age, menarche, 1st degree relatives, prior biopsies, atypical ductal hyperplasia (ADH)
  - Calculates 5 year and lifetime risk compared to the general population
  - >1.7% 5y risk considered high

- Claus model: maternal and paternal family history of breast cancer: if greater than 20% lifetime risk consider annual breast MRI

- Risk modification
    - Early pregnancy (<30), breast feeding, multiple pregnancies
    - Exercise > 4h/week (maintain ideal body mass)
    - Two or less drinks of alcohol per day
    - SERMs (selective estrogen receptor modifiers)
        - weak estrogen analogs competitively bind to and block estrogen receptors, decreasing stimulation of breast cells)
        - tamoxifen 20mg/day, Evista 60mg/day
        - 5y course confers 50% risk reduction in post-menopausal, and high-risk premenopausal with several year persisting effect on cessation (NSABP P-1 prevention trial)
        - Risks: endometrial carcinoma (1-3%), pulmonary embolus, stroke, deep vein thrombosis, cataracts, hot flashes in premenopausal women
            - Enhances effect of anticoagulant, may lead to hemorrhage; contraindicated in patients on herparin of coumidin
            - Contraindicated in smokers because of increased risk of thromboembolism
    - Aromatase inhibitors/AI (block the enzyme converting androgen to estrogen, decreasing circulating estrogen levels)
        - 5y course for high-risk post-menopausal women
        - Exemestane 25mg/day
        - Slight increase in hot flashes, fatigue, increased risk of osteoporosis (no difference in fracture incidence or cardiovascular events)
        - Cannot be used for pre-menopausal women because functioning ovaries will negate the value
    - Prophylactic bilateral mastectomy: >90% risk reduction in high risk women
    - Oophorectomy: 50% reduction in breast cancer in positive gene mutation

Tumor biology

- 50% of breast cancers have a 3-month doubling time up to 1mm in size, then the growth rate slows to 15-month doubling
- negative cancer control window is before tumor reaches 1mm in size; at 1mm/10K cells angiogenesis begins and metastasis becomes possible if cancer cells have breached the basement membrane of the ducts
- 30 doubling times to reach 1cm over ~7½ years when it may be clinically palpable
- Fisher hypothesis: breast cancer should be considered a systemic disease almost from the beginning; lymph node metastasis is not primarily a nidus for spread but an indicator of tumor/host relationship and a marker for risk of systemic metastasis
- untreated breast cancer has a 17% 5-year survival
- 80% of breast cancers are ductal in origin, 20% lobular (less visible mammographically)
    - lobular has an increased incidence of multicentricity
- contraction of Cooper's/suspensory ligaments caused by desmoplastic inflammatory reaction of typical scirrhous ductal carcinoma
- rare bulky breast cancers: colloid, medullary
    - less aggressive, better prognosis
- tubular carcinoma is well differentiated, <10% nodal involvement, good prognosis
- common metastasis sites in order of frequency: bone, lung, liver, and brain
    - follow up studies are guided by symptoms, not routine screening
    - increased surveillance (Q 6mo) by clinical breast exam (CBE) and yearly mammogram of remaining breast tissue is the primary follow up strategy for non-genetic breast cancer

Detection

- 80-90% of new breast cancers are now detected by mammogram
- 5% present with pain, 5% skin or nipple retraction, 3% nipple discharge, 1% enlargement; thus most (~85%) of new diagnoses are asymptomatic

- 15% of single duct spontaneous nipple discharges are caused by cancer
- 85% of solitary palpable lesions in a post-menopausal woman are cancer
    - dense, nodular glandular tissue is replaced by fat as patient ages, so breasts are more uniformly soft
    - dominant mass in an elderly patient is cancer until proven otherwise
- palpable cancer is usually hard, with vague irregular borders
    - ultrasound is the primary diagnostic modality to differentiate a solid from a cystic mass
    - ultrasound characteristics of cancer are a hypoechoic irregular mass with a deep axis longer than the horizontal axis (benign growths respect tissue planes and are more horizontal)
- clinical breast exam 54% sensitivity
    - 5 cancers detected / 1000 exams
    - false negative for palpable mass 10-15%
    - always bx a dominant mass
- best time for exam 5d after menses (before progesterone kicks in)
- 20% of breast cancers detected only by breast self-exam (BSE) The 20% not detected by mammogram)
    - should be performed monthly from age 20
- 12 studies showed smaller tumors correlate with fewer positive axillary nodes
- FNA: 87% sensitivity (13% false negative), 97% specificity (3% false positive)
- when core Bx is atypical ductal hyperplasia (ADH), excisional Bx upgrades10-20% to DCIS (sampling error)

Screening/diagnostic modalities

- Mammography
    - mammography 13% false positive, 20% false negative
        - bx of mammographic findings: 13 benign to 1 malignancy
        - 10% callbacks, 10% of those get Bx, 10% of those have cancer

- cancer mimics: radial scar, fibromatosis, granular cell tumor, fat necrosis
- indeterminate calcifications have a 10-30% chance of being cancer
- invasive lobular is indistinct, hard to detect by mammography
    - US, MRI better diagnostic tools
- mucinous, medullary, cystosarcoma phyllodes difficult to detect mammographically
- dense breasts (young women) increased risk and difficult detection
- fatty hilum in an enlarged lymph node: cancer unlikely
- low radiation risk (0.2%) for yearly mammograms
- DCIS accounts for 24% of new mammographic Dx
- mammogram decreases mortality 20-30% in women over 50; 15-20% decrease in women 40-49
    - younger women lesser beneficial effect of mammography: lower incidence, more rapid growth, denser breasts
- digital mammography allows contrast adjustment, better visualization of dense areas
    - lower radiation dose, easier storage and transmission, earlier detection
- invasive cancer Dx decreasing, DCIS increased from 5% to 25% of newDx since 1970
- BI-RADS (breast imaging reporting and database system) mammographic classification
    - 0 need additional imaging
    - 1 negative
    - 2 benign
    - 3 probably benign, 6 mo FU
    - 4 suspicious, may need Bx
    - 5 highly suspicious , needs biopsy
    - 6 known/biopsy-proven malignancy

- MRI

    - hi (12%) false positive rate: only 25% of "positive" MRI findings are malignancies; increased number of negative biopsies
    - indicated to detect other subtle lesions when a cancer is found

by CBE or mammography
- modifies plan 11% of the time
- detects 3% contralateral
- more sensitive for dense breast/patients on HRT
- positive axillary LN with unknown primary

- US

  - not useful as screening tool
  - used to characterize palpable or mammographic solid lesion
  - used to guide percutaneous biopsy

Pathology

- DCIS (ductal carcinoma in situ)

  - precursor of nearly all infiltrating ductal carcinoma (IDC)
  - incomplete excision results in recurrence at local site (unlike LCIS which does not directly progress to cancer and does not need to be totally excised)
  - 25% of all new Dx, most are mammographic
    - 90% diagnosed by mammography alone
  - average age 47 for DCIS v 55 for invasive cancer
  - progression to invasive variable
    - micropapillary, papillary, solid, cribriform, comedo (more aggressive)
  - breast conservation: wide local excision + RT (50% decrease recurrence with radiation: B-17, recurrence after DCIS reduced from 32 to 16%)
  - consider SLN if high-grade, commedonecrosis, palpable or mammographic mass(increased risk of missed IDC)
  - adjuvant TAM decreases incidence of subsequent IDC 50% (B-24 trial, lumpectomy + RT+/-TAM)
  - multicentric: mastectomy without radiation
    - most DCIS not multicentric (70%)
    - consider SLN in case of missed infiltrating focus and no possibility of post-mastectomy SLN bx

- LCIS (lobular carcinoma in situ/lobular neoplasia)

- 2X increase incidence past 25y
- younger, premenopausal more commonly
- no palpable mass
- often not seen on mammo: US, MRI better for Dx
- risk marker, not a precursor for subsequent invasive carcinoma (60% are ductal) in either breast
- 1% risk/y up to 25%; TAM X5y decreases the risk by 50%
- nearly 100% of LCIS is multicentric
- options: chemoprevention (hormonal), bilateral mastectomy, monitor closely

- Invasive Ductal Carcinoma (IDC): molecular subtypes/profiling

    - molecular subtypes/profiling factors are ER, HER2 status, gene profiling microarray or RT/PCR (reverse transcription/polymerase chain reaction: mammaprint, oncotype), menopause/>50
    - molecular profiling is in a research setting, not part of standard practice at present
        - Major types (most common characteristics)
            - luminal A: ER/PR+, HER2neg, low Ki67, low or moderate grade, low % p53 mutations, inner/luminal ductal type cells, best prognosis, low recurrence; ~50%
            - luminal B: ER/PR+, HER2+, high Ki67 (high number of actively dividing cells), inner/luminal ductal type cells, younger age than A, higher grade, larger tumor, more p53, high survival, but lower than A; ~14%
            - basal-like/triple negative: most are ER/PR/Her (triple) neg, cytokeratin 5/6+ and/or HER1+, outer/basal duct cell type, HER1 and/or cytokeratin 5/6 proteins, many p53, younger, African-American (especially premenopausal, may explain poorer prognosis in younger black women), most BRCA1 and many BRCA2are basal, aggressive, poorer prognosis; (possible future targets EGF recep, aB-crystallin,

cyclin); ~17%
        - ♦ HER2+: ER/PR neg, HER2+, high LN+, higher grade, many p53 mutations, poor prognosis, early and frequent recurrence and metastases, younger at Dx ; ~10%
    - minor:
        - ♦ normal breast-like: small, good prognosis; ~8%,
        - ♦ aprcrine, claudin-low
    - p53 mutations associated with poorer prognosis

- Her2-neu overexpression

    - human epithelial growth factor receptor 2 codes for transmembrane growth factor receptor tyrosine kinase protein that stimulates cell growth
    - 20% of breast cancers are HER+
    - in situ stage carcinoma: amplification of the gene causes overexpression of HER2 protein
    - surface excess growth receptor protein makes the breast cell more sensitive to stimulation
    - associated with poorly differentiated tumor, high proliferative rate, positive nodes, decreased ER/PR expression
    - hi risk of recurrence and death
    - low or intermediate HER positivity (1+, 2+) sent for FISH (fluorescent in situ hypridization) definitive characterization
    - trastuzumab/Herceptin
        - ♦ humanized mouse monoclonal antibody against HER2 membrane receptor
        - ♦ 33% relative reduction in risk of death, 12% absolute reduction
        - ♦ combined with chemotherapy, potentiates the effect: paclitaxel, doxorubicin, cyclophosphamide
        - ♦ binds to HER2 protein, down-regulates surface HER2 expression causing apoptosis (natural cell death)

- ♦ alters downstream signaling and regulatory pathways in the cell cycle
- ♦ suppresses production of vascular endothelial growth factor (VEGF)
- ♦ also extracellular effect mediating antibody-dependent immune recognition

- Paget's disease of the nipple
    - o differentiate from eczema, limited trial of steroid ointment before punch Bx
    - o keratin staining for Paget's cells
    - o 90% have underlying cancer which spreads to the nipple/areolar complex (v primary epidermal carcinoma)
    - o 50% of patients with Paget's have palpable mass
    - o role for MRI to diagnose deeper lesions

- triple negative/basal-like breast cancer (TNBC)
    - o ER/PR, HER2 negative
    - o Chemotherapy is the standard treatment
        - ▪ Higher response rate than non-TNBC
    - o Emerging poly-polymerase inhibitors (ADP-ribose, PARP)
        - ▪ enzymes involved in multiple cell processes including DNA repair (similar to BRCA mutation effects)

- ▪ Pregnancy
    - o Breast cancer is the most common cancer in pregnant women (1/3,000)
        - ▪ 10% of women under 40 with breast cancer will be pregnant
    - o increase w increasing age of pregnancy; commonly ER negative due to high estrogen binding
    - o thin bloody unilateral nipple discharge not uncommon
    - o local biopsy is safe at any time
    - o delay in diagnosis results in later stage at Dx
    - o mammography with shielding incurs little fetal risk (0.4 mRad fetal dose), but low yield (25% false negative) because of breast

density
- termination of pregnancy, suppression of lactation (except if surgery or chemo planned) are no benefit and may decrease survival
- nuclear scans cause fetal radiation exposure
- CXR OK
- bone scan delivers less radiation than skeletal series
- liver evaluation with US
- MRI for brain symptoms (gadolinium crosses placenta, assoc w fetal abnormalities)
- subsequent pregnancy does not change survival
  - wait 2y to rule out early recurrence
- MRM treatment of choice
  - sentinel lymph node biopsy probably OK
  - BCT with postpartum RT is an alternative
- early stage (I & II): chemotherapy after 1st trimester (may be assoc w premature labor and fetal wastage; methotrexate is abortifactant, leading cause of birth defects)
- late stage (III & IV): 10% 5y survival; therapeutic abortion does not improve survival, but fetal risk is increased with 1st trimester chemotherapy
- methotrexate, 5FU, alkylating agents are excreted in breast milk

- Male breast cancer
  - Male breast cancer presents as more advanced, but no difference stage for stage
  - associated w BRCA2 (also prostate, pancreas, larynx, colon)
  - male breast cancer is always ductal: no lobules are present in the male breast
  - treatment is MRM, pectoral muscle rarely involved

- Locally advanced (stage III)
  - 10-20% of all breast cancers have T4, invasion of skin or chest wall and/or N2 (matted nodes)
  - inflammatory carcinoma
    - invasion of dermal lymphatics by cells from underlying cancer
      - underlying tumor often not felt
    - causes skin edema, redness (peau d'orange)

        - defined by involvement of > 1/3 of breast
    - 1-5% of breast cancers
    - most are stage III or IV
        - stage III 40% 5y survival, IV 10%
    - younger age at diagnosis (55 v 60)
    - increased incidence in blacks
    - often ER/PR negative, HER2 positive
    - workup: bone scan, CT of chest, abdomen and pelvis
    - neoadjuvant (now called primary systemic therapy) indicated: 6 cycles over 4-6 months
        - 80% size reduction, 23% downstaging
        - 36% complete clinical response (not a predictor of prognosis)
        - 26% complete pathologic response
        - 12% more breast conservation Rx
        - no benefit for survival, progression-free survival or locoregional recurrence
        - anthracycline + taxanee preferred Rx, continue post-op
    - standard surgery in responsive patient is modified radical mastectomy followed by radiation
        - if LN+ by FNA pre-adjuvant, no need for SLN at time of surgery, proceed to axillary node dissection (ALND)
        - radiation is done after implant reconstruction, but before flap reconstruction

Staging AJCC (American Joint Committee on Cancer) TNM

Primary tumor

TX cannot be assessed
T0 no evidence of primary tumor
Tis in situ
Tis (DCIS)
Tis (LCIS)
Tis (Paget) not assoc w DCIS, LCIS or invasive
T1 <2cm
T1mi <1mm
T1a 1-5mm

T1b 5-10mm
T1c 1-2cm
T2 2-5cm
T3 >5cm
T4 any size chest wall (a) or skin (b) both (c) inflammatory (d)

Nodes

NX can't be assessed
N0 none
N1 mobile ipsilateral I, II
N2 (a) matted/fixed (b) internal mammary
N3 (a) infraclav, (b) IM+I/II, (c) supraclav
pN1mic <2mm

Stage

0	Tis, N0; M0
1A	up to T1c with N0; M0
1B	T0 or up to T1c with N1mic; M0
IIA	T0 or up to T1c with N1 or T2 with N0; M0
IIB	T2 with NI or T3 with N0; M0
IIIA	T0, 1, or 2 with N2; T3 with N1 or 2; M0
IIIB	T4, N0, 1, or 2; M0
IIIC	any T with N3; M0
IV	any T, any N, M1

5-year survival by stage

0	100%
I	98%
II	88%
IIIA	56%
IIIB	49%
IV	16%

- Most women with early (stage I or II) breast cancer will die of something else

Treatment

- Locoregional: surgery, radiation
  - Future: mammotome excision, radiofrequency ablation, cryotherapy?

- Systemic: hormonal, chemotherapy, monoclonal antibody
    - Future: proteomics, genetic manipulation?
- Surgery
    - Breast conserving therapy (BCT)
        - Early stage (0/in situ, I and II)
        - Diagnosis by mammographic, ultrasound-guided or MRI-guided biopsy for non-palpable lesions
        - Core biopsy of palpable lesion and suspicious adenopathy for pre-op planning
            - Wide excision of proven atypical ductal hyperplasia (ADH), in situ or invasive lesion
            - For infiltrating carcinoma do lumpectomy and sentinel lymph node (SLN) biopsy
            - Consider SLN for high grade/comedo DCIS
            - Local recurrence at core biopsy site rare, so no need to excise skin
        - Contraindicated in multicentric disease
        - Small breast and resulting significant deformity may present a cosmetic contraindication
        - There is a slightly higher local recurrence rate with BCT v mastectomy
        - Higher incidence of residual disease with large (T2) tumor, palpable lesion, lobular pathology, extensive intraductal component, positive sentinel node
        - Radiation post-op is standard to reduce risk of recurrence (+/- chemo and/or hormonal therapy)
            - Exception may be older (>70) patient with low grade disease and negative nodes
            - BCT/RT Contraindicated in pregnancy
            - local recurrence usually associated with distant mets, poor prognosis

    - Mastectomy
        - Absolute indications
            - Multicentric disease
            - prior RT to breast or chest wall precluding post-op radiotherapy
            - recurrence in breast after lumpectomy/breast

conservation therapy
        - steroid dependent collagen vascular disease (RT would cause deformity)
        - desire to maintain pregnancy (can't shield fetus)
    - relative indications
        - breast size v tumor
        - central lesion (subareolar higher incidence of multicentricity)
        - clinically positive nodes
        - large breasts (preclude tumoricidal RT)
        - logistics (patient lives in remote area)
        - no motivation by patient to preserve/patient choice, anxiety
            - when BCT proved equivalent to mastectomy for early disease in the 70's trend was for women to choose conservation; recent rebound to choosing mastectomy and reconstruction
    - 5% local recurrence after mastectomy
    - if mastectomy is done for DICS, SLN may be indicated in case invasive component is discovered and subsequent ability to do SLN may be compromised

- prophylactic mastectomy
    - bilateral mastectomy decreases risk 90-95%
    - consider in hi risk patients
        - genetic breast cancer
        - dense breasts making CBE and mammo difficult
        - fibrocystic disease with history of multiple biopsies

- sentinel lymph node (SLN)
    - LN status is the most important prognostic factor
    - 25-30% of all breast cancers have axillary disease
    - contraindications to SLN:
        - palpable/clinically suspicious node
        - positive node by core biopsy
        - tumor > 4cm
        - inflammatory breast cancer
        - prior axillary surgery or disease (hidradenitis)

            - prior extensive breast surgery
        - negative sentinel node(s), < 2% chance of other nodes being positive
        - cytokeratin staining upgrades H&E evaluation by 10%
        - borderline positive SLN
            - < 0.2mm considered N0
            - 0.2-2mm = micrometastasis, staged pN1mic
                - possible indication for completion axillary lymph node dissection
        - 3% incidence of lymphedema with SLN v 20% with level I & II axillary lymph node dissection (ALND)

- adjuvant radiation therapy (RT)
    - goal is to eradicate residual disease after BCT and reduce local recurrence
        - NSABP B-06: 9-year decrease in local recurrence from 42% to 12% with radiation
    - 5% reduction in mortality in early breast cancer
    - high risk for local recurrence after mastectomy an indication for RT
        - Four+ positive nodes
        - Extracapsular extension
        - Large tumor (T3, >5cm)
        - Close or positive deep margin
        - Skin, fascia or muscle involvement
    - chest, axilla, supraclav: 50Gy (Gy/gray: 1 Gy = 100rads, 1 rad = 1 cGy), 25 fractions
    - side effect fatigue, possible lung, heart radiation
        - negligible lung and cardiac injury with modern technique
    - contraindications
        - prior radiation
        - can't abduct arm
        - marginal pulmonary function
        - systemic lupus
        - scleroderma
    - no increased incidence of lymphoma after breast RT

- adjuvant chemotherapy

- polychemotherapy decreases relapse and death
  - patients under 50: 40 decrease relapse and 30% decrease mortality
  - patients over 50: 20 and 10%
  - 10% and 3% 15y absolute increase in survival under and over age 50
  - 20% annual decreased risk of contralateral breast cancer
- prognostic factors
  - negative nodes: 20% recurrence @10y
  - 1-3 nodes 60% “
  - more than 4 nodes 80%
  - ER/PR negative: worse outcome; high S-phase
  - HER2neu positive have worse prognosis (but highly treatable w herceptin)
- hi-dose chemotherapy has no role as adjuvant
- virturally all node positive and node negative with T > 1cm get chemo
  - (younger patients have better results with adjuvant chemo)
- neoadjuvant: more BCT, less axillary treatment, same survival
  - 13% complete pathologic response (cPR)
  - 80% of I/II patients responded with >50% reduction size
    - increase from 60% to 68% who are able to have BCT
- agents:
  - anthracyclines (cardiotoxicity): doxorubicin, epirubicin, mitoxantrone
  - taxanes: paclitaxel, docetaxel
  - alkylating agents: cyclophosphamide
  - flororpyrimidines: capecitabine, 5FU
  - antimetabolites: methotrexate
  - vinca alkaloids: vinorelbine, vinblastine, vinctistine
  - platinum: carboplatin, cisplatin
  - other: gemcitabine, mitomucin C
- common regimens:
  - AC-T: adriamycin, cytoxan followed by taxane; better survival than CMF
  - CMF: cytoxan, methotrexate, 5FU
- start 4w after surgery
- common toxicity: nausea and vomiting, myelosuppression, alopecia, mucositis
- rare toxicity: congestive heart failure (anthracycline),

thromboembolic events, premature menopause, leukemia

- adjuvant hormonal therapy
    - SERMs (see prevention above):
        - ER+ 10% greater disease free survival
        - PR status is a marker for response to hormone Rx after recurrence
        - TAM decreases recurrence 25%, mortality 16% in patients > 50 regardless of nodal status
            - TAM not indicated in patients who have bilateral mastectomy for DCIS: no breast tissue to protect, and no systemic disease to treat
            - indicated for infiltrating ductal after bilateral mastectomy for systemic effect
    - aromatase inhibitors: block adrenal conversion of androgens to estrogen, decrease bone density
        - post-menopausal use only (for adrenal and fat production of estrogen)
        - in pre-menopausal ovaries override effect
        - indicated for all post-menopausal ER+ pts
        - more effective, safer than TAM (ATAC trial '02)
- Her2-neu overexpression
    - human epithelial growth factor receptor 2
    - surface excess growth receptor protein makes cell more sensitive to stimulation
    - codes for transmembrane growth factor receptor tyrosine kinase protein that stimulates cell growth
    - associated with poorly differentiated tumor
    - high proliferative rate
    - increased incidence positive nodes
    - decreased ER/PR expression
    - hi risk of recurrence and death
    - 20% of breast cancers HER+
    - in situ stage: amplification of the gene causes overexpression of HER2 protein
    - trastuzumab/Herceptin: humanized mouse monoclonal antibody

against HER2 membrane receptor
    - standard 1-year therapy
    - 33% reduction risk of death, 12% absolute difference
      combined with CT: paclitaxel, doxorubicin, cyclophosphamide binds to HER2 protein, down-regulates surface HER2 expression causing apoptosis
- lapatinib: tyrosine kinase inhibitor of both HER2/neu and epithelial growth factor receptor
    - alters downstream signaling and regulatory pathways in cell cycle
    - suppresses production of vascular endothelial growth factor (VEGF) and potentiates effect of chemo
    - extracellular effect mediating antibody-dependent immune recognition

Follow-up

- 90% of recurrences found by clinical breast exam (CBE) or patient complaint
- yearly mammogram of residual breast tissue
- clinical breast exam Q 6mo
- no other screening tests are effective before symptoms appear

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