

## 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

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

<b>Pancreatic</b>	2-3%	1%
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### Lifetime BRCA1 Cancer Risks for Men

<u>Type of Cancer</u>	<u>Men with BRCA1 mutation</u>	<u>Average man in US without mutation</u>
<b>Breast</b>	1-5%	0.1%
<b>Prostate</b>	*	17%
<b>Pancreatic</b>	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

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

## Lifetime BRCA2 Cancer Risks for Men

<u>Type of Cancer</u>	<u>Men with BRCA2 mutation</u>	<u>Average man in US without mutation</u>
<b>Breast</b>	5-10%	0.1%
<b>Prostate</b>	15-25%	17%
<b>Melanoma</b>	3-5%	1-2%
<b>Pancreatic</b>	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, 1<sup>st</sup> 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 heparin or coumadin
      - 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 upgrades 10-20% 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, comedonecrosis, 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, oncoPrint), 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 BRCA2 are 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%,
  - ◆ apocrine, 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 hybridization) 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

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

- triple negative/basal-like breast cancer (TNBC)

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

- Pregnancy

- Breast cancer is the most common cancer in pregnant women (1/3,000)
  - 10% of women under 40 with breast cancer will be pregnant
- increase w increasing age of pregnancy; commonly ER negative due to high estrogen binding
- thin bloody unilateral nipple discharge not uncommon
- local biopsy is safe at any time
- delay in diagnosis results in later stage at Dx
- 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 abortifacant, 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 + taxane 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 N1 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: mammatome 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
- virtually 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
  - fluoropyrimidines: capecitabine, 5FU
  - antimetabolites: methotrexate
  - vinca alkaloids: vinorelbine, vinblastine, vincristine
  - platinum: carboplatin, cisplatin
  - other: gemcitabine, mitomycin 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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