

## Vesalius SCALpel™ : Breast cancer (see also: breast folios)

### Risk

80% of breast cancer patients have no risk factors

age: 1/2,000 at age 30, 1/10 age 80; average lifetime risk 1/8

hormone replacement therapy (HRT): > 60 26% increase cancer, risks outweigh benefits

1-5X: white, urban, higher socioeconomic class

2-4X

nulliparous until 30

obesity (postmenopausal, estrogen from fat and adrenals)

proliferative breast or endometrial disease

FH 1<sup>st</sup> degree relative

radiation exposure to chest

4-6X

family history, premenopausal, or bilat breast cancer

previous cancer

6-8X atypical ductal hyperplasia (ADH)

10X history of DCIS, LCIS, 1%/y

LCIS 30% go on to develop invasive cancer (usually ductal) without chemoprevention

no need for reexcision, clear margins

genetics

only 5-10% of breast and ovarian hereditary

BRCA1: 30% of hereditary breast cancers, BRCA2 20%

other:

p53 < 1%, Li-Fraumeni (sarcoma, breast, brain, adrenocortical, leukemia)

PTEN, < 1%, Cowden's (hamartomatous colon polyps, 50% breast)

(no breast cancer association with APC, HNPCC mutations)

undiscovered genes 50%

BRCA1, 2: normal tumor suppressor genes

loss of function 82% lifetime risk breast cancer, 44% risk ovarian (BRCA1)

bilateral mastectomy, oophorectomy after childbearing, before age 40 for risk reduction

30% false negative genetic testing; test if > 10% chance of mutation

start screening at 27, alternate mammo/MRI Q6mo

germline mutation in egg or sperm

autosomal dominant, 50% change each generation, no skip

BRCA2 associated with 10% of male breast cancers, colon cancer

most non-familial breast cancers have BRCA1 in cytoplasm, not nucleus where suppression occurs

cumulative risk @40: 15%, 50: 60%, 60: 75%, 70: 82%

early onset, bilateral, ovarian, breast and ovarian same pt, FH breast (M&F) or ovarian, Ashkenazi Jewish, male

stage for stage equivalent to non-BRCA breast cancer

higher local and contralateral recurrence and 2<sup>nd</sup> primary

BRCA1 tend to be ER negative

## GAIL model

based on SEER database

factors: age, menarche, 1<sup>st</sup> degree relatives, prior bx, atypical ductal hyperplasia  
5y and lifetime risk calculation

>1.6% 5y considered hi risk, TAM reduces risk 50%

## Tumor biology

~3mo doubling time in 50% of breast cancers early, as tumor grows

logarithmic to 1mm, then slows to 15mo doubling time (Gompertzian growth)

negative cancer control window to 1mm/10K cells at which time angiogenesis takes place  
and metastasis is possible (Fisher hypothesis: breast cancer should be considered a  
systemic disease almost from the beginning)

30 doubling times to 1cm over ~7 1/2 years when may be palpable clinically

untreated breast cancer 17% 5y survival

80% of breast cancers ER+, more differentiated

ER+ respond better to hormone/chemotherapy, better prognosis

100% of precancers ER+

ER positivity decreases with more mutations, less differentiation

ER negative worse prognosis

70% of cancers presenting as palpable lumps are invasive

80% ductal origin, 20% lobular

contraction of Cooper's/suspensory ligaments caused by desmoplastic reaction of typical  
scirrhous ductal carcinoma

rare bulky breast cancers: colloid, medullary, less aggressive

tubular carcinoma well differentiated, < 10% nodes

metastasis to liver, lung, bone and brain: f/u studies guided by symptoms

## Stage

T: is (in situ), 1: < 2cm, 2: 2-5cm, 3: > 5cm, 4: skin or muscle involvement

N: 0 negative, 1 mobile positive nodes, 2 matted nodes

M: 0 no mets, 1 distant mets

stage:

0: in situ

I: T < 2cm

II: T > 2cm, mobile positive nodes

III: locally advanced

IV distant mets

10y survival: I 90%, II 70, III 40, IV 10

early detection: N0 90% 5y survival, N1 59%

## Fischer hypothesis

lymph node metastasis not primarily a nidus for spread but an indicator of poor  
tumor/host relationship and marker for risk of systemic metastasis

## Detection

70% of new breast cancers detected by mammogram  
5% present with pain, 5% skin or nipple retraction, 3% nipple discharge, 1% enlargement  
15% of single duct bloody nipple discharge are cancer  
solitary palpable lesion post-menopausal 85% cancer  
palpable cancer usually hard, distinct borders  
clinical breast exam 54% sensitivity, 5 cancers/ 1000 exams  
best time 5d before menses (before progesterone kicks in)  
20% detected by breast self-exam (BSE)  
Q 1mo from age 20  
12 studies: smaller tumors, fewer axillary nodes  
false negative for palpable mass 10-15%  
always bx dominant mass  
dominant mass in elderly is cancer until proven otherwise  
FNA: 87% sensitivity, 97% specificity  
when core Bx is atypical ductal hyperplasia (ADH), excisional Bx upgrades 1/3 to DCIS

## Screening/diagnostic

### mammo

13% false positive, 20% false negative  
cancer mimics: radial scar, fibromatosis, granular cell tumor, fat necrosis  
indeterminate calcifications 10-30% chance of cancer  
invasive lobular indistinct, hard to detect by mammo, US, MRI better Dx  
also mucinous, medullary, cystosarcoma phyllodes difficult  
fat within mass: cancer unlikely  
DCIS 24% of new mammo Dx  
10% callbacks, 10% of those get Bx, 10% of those cancer  
mammogram decreases mortality 20-30% in women > 50; 40-49 15-20% decrease  
younger women lesser effect: 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 20% of new  
Dx since 1970  
bx of mammographic findings 13 benign to 1 malignancy

### MRI indications

to detect other subtle lesions when a cancer is found, modify plan 11%  
detects 3% contralateral  
more sensitive for dense breast/patients on HRT  
discharge  
ax LN with no primary  
hi (12%) false positive

### US

not useful as screening tool

used to characterize palpable or mammographic solid lesion  
used to guide percutaneous biopsy

## **Pathology**

### **DCIS**

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)  
50% of all new Dx, most are mammographic findings (3 ductal: 1 lobular)  
average age 47 for DCIS v 55 for invasive  
breast conservation: wide local excision + RT (50% decrease recurrence: 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%  
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  
VanNuys prognostic index for DCIS recurrence or invasive after excision  
    nuclear grade, size, comedo, margin  
    does not describe prognosis for IDC

### **LCIS**

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

### **Paget's disease of the nipple**

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

## Locally advanced (stage III)

10-30% of all breast cancers

T4 invasion of skin or chest wall and/or N2 (matted nodes)

inflammatory: invasion of dermal lymphatics by cells from underlying cancer  
causes skin edema, redness (peau d'orange)

w/u: bone scan, CT chest, abdomen, pelvis

neoadjuvant (now called primary systemic therapy) indicated

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

if LN+ by FNA pre-adjuvant, no need for SLN at time of surgery

## Treatment

locoregional: surgery, radiotherapy

future: mammotome excision, radiofrequency, cryo?

systemic: chemotherapy, hormonal chemoprevention/therapy, monoclonal antibody

future: proteomics, genetic?

hormonal chemoprevention

SERMs (selective estrogen receptor modulators) :tamoxifen (TAM), raloxifene

weak analogs of estrogen, bind to estrogen receptors, competitive inhibition of natural  
estrogen binding, reducing estrogen stimulation of breast cells

can be used pre and post-menopausal

may increase bone density (original use for raloxifene)

TAM: side effects thrombosis, endometrial cancer (1-3%), hot flashes in  
premenopausal

prophylactic TAM in hi risk (NSABP P-1 prevention trial)

over age 60, <60 with GAIL score >1.7, Hx of LCIS

49% decreased incidence with TAM, 65% with raloxifene

TAM contraindicated in smokers because of increased risk of thromboembolism

enhances effect of anticoagulants, may lead to hemorrhage, contraindicated in pts on  
heparin or coumidin

surgery

needle localization Bx/lumpectomy

excision of ADH, DCIS or IDC proven by core Bx

when core Bx not technically possible: small breast, close to chest wall

breast conservation (stage0 [in situ], I and II)

DCIS: lumpectomy plus radiation

IDC: lumpectomy, SLN, radiation (+/- chemo, hormonal Rx)

contraindications: pregnancy (unless radiation postponed to post partum), prior radiation, more than one tumor/multicentric, cosmesis, collagen vascular disease (not RA)

## mastectomy

### absolute indications

prior RT to breast or chest wall precluding post-op radiotherapy

recurrence in breast after lumpectomy/breast conservation therapy

multicentricity

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 multicentricity)

clinically positive nodes

large breasts (preclude tumoricidal RT)

logistics (remote area), no motive to preserve

### prevention

bilateral mastectomy decreases risk 90-95%

hi risk pts, dense breasts making CBE and mammo difficult

5% local recurrence after mastectomy

local recurrence usually associated with distant mets, poor prognosis

### skin-sparing mastectomy

for early lesions, 0-7% local recurrence

related to pathology and stage, not degree of excision

local recurrence rate low at core bx site, no need to excise skin

immediate reconstruction no difference recurrence or delay Dx of recurrence

## excision of isolated lung mets

20% 5y survival after curative resection

## sentinel lymph node (SLN)

LN status most important prognostic factor

25-30% of all breast cancers have axillary disease

contraindications: palpable/clinically suspicious node, tumor > 4cm, inflammatory, prior axillary surgery or disease (hidradenitis), prior extensive breast surgery

negative sentinel node, <2% chance of other nodes being positive

cytokeratin staining upgrades H&E eval by 10%

borderline positive SLN

< 0.2mm considered N0

0.2-2mm = micrometastasis, staged pN1mic

indication for completion axillary lymph node dissection

3% lymphedema v 20% with level I & II axillary lymph node dissection (ALND)

## Pregnancy

10% of women < 40 with breast cancer will be pregnant

stage by stage same outcomes as non-pregnant

abortion does not alter course of cancer positively, may decrease survival  
BCT + RT contraindicated unless can be given post-partum  
diagnostic delay: usually present with more advanced disease  
nipple discharge including thin bloody common  
    investigate persistent thin unilateral discharge  
local bx safe at any time  
mammography can be performed safely (fetal dose 0.4 mRad)  
MRI no additional benefit  
chemo cannot be given in 1<sup>st</sup> trimester: methotrexate is abortifacient, leading cause of  
    birth defects  
sentinel lymph node bx probably OK (isosulfan blue not recommended, 1.5% allergic  
    reaction)  
methotrexate, 5FU, alkylating agents excreted in breast milk  
metastatic w/u in pregnancy lo yield, does not increase survival  
lactating adenoma: may resolve, otherwise excise

### **Breast malignancy in children**

most are primary non-breast tumor or metastasis  
    lymphoma, rhabdomyosarcoma, neuroblastoma

### **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 in the male breast  
Rx MRM, rare muscle involvement

### **Local adjuvant therapy**

radiotherapy

90% of local recurrences at lumpectomy bed  
breast conservation early stage (I & II) IDC + RT local recurrence decreased from 42% to  
    12% @ 9y (NSABP B-06), no difference overall survival  
chest, axilla, supraclav: 50Gy (1 Gy = 100rads, 1 rad = 1 cGy), 25 fractions  
side effect fatigue, possible lung, heart radiation  
standard therapy after breast conservation  
neo-adjuvant: inflammatory, large tumor  
    T > 5cm usually not candidate for BCT, RT may downstage  
    some do SLN before neo for accurate staging  
post-mastectomy indications: T3 (> 5cm), > 4 nodes, extracapsular nodal disease, positive  
    margins, skin, fascia, muscle involvement  
contraindications: prior radiation, can't abduct arm, marginal pulmonary function, SLE,  
    scleroderma  
chemo before radiation

no increased incidence lymphoma after breast radiation, negligible lung, cardiac injury with modern technique

## **Systemic adjuvant therapy**

adjuvant chemotherapy

prognosticators:

nodes: negative 20% recurrence @10y, 1-3 nodes 60%, > 4 nodes 80%

ER/PR negative: worse outcome; high S-phase

HER2 neu positive worse prognosis (but highly treatable w herceptin)

hi dose chemo no role as adjuvant

virtually all node positive, negative with T > 1cm get chemo

<50 27% reduction recurrence, 17% reduction mortality

>50 17% “ “ 9% “ “

(younger better results with adjuvant chemo)

neoadjuvant: more BCT, less axillary treatment, same survival

13% complete pathologic response (cPR)

common regimens:

AC-T: adriamycin, cytoxan followed by taxane

better survival than CMF

CMF: cytoxan, methotrexate, 5FU

adjuvant hormonal therapy

SERMs:

ER+ 10% greater disease free survival

PR status marker for response to hormone Rx after recurrence

aromatase inhibitors: block adrenal conversion of androgens to estrogen

decrease bone density

post-menopausal only (for adrenal and fat production of estrogen)

pre-menopausal ovaries override effect

all post-menopausal ER+ pts, more effective, safer than TAM (ATAC trial '02)

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

## **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 HER+

in situ stage: amplification of the gene causes overexpression of HER2 protein, fixed

phenotype for invasive tumor

surface excess growth receptor protein makes cell more sensitive to stimulation  
poorly differentiated tumor, high proliferative rate, positive nodes, decreased ER/PR  
expression, hi risk recurrence and death  
trastuzumab/Herceptin  
humanized mouse monoclonal antibody against HER2 membrane receptor  
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,  
alters downstream signaling and regulatory pathways in cell cycle, suppresses  
production of vascular endothelial growth factor (VEGF) and potentiates effect  
of chemo; also extracellular effect mediating antibody-dependent immune recognition

### **Follow-up**

90% of recurrences found by clinical breast exam (CBE) or patient complaint  
yearly mammo, CBE Q 6mo  
no other screening tests effective before symptoms

### **References:**

- Veronesi U, Boyle P, Goldhirsch A, Orecchia R, Viale G. Breast Cancer. *Lancet* 2005; 365(9472): 1727-41.
- Punglia RS, Morrow M, Winder EP, Harris JR. Local therapy and survival in breast cancer. *N Engl J Med* 2007; 356(23): 2399-405.
- Porter P. "Westernizing" women's risks? Breast cancer in lower-income countries. *N Engl J Med* 2008; 358(3): 213-215.
- Silverstein M et al. Image-detected breast cancer: state of the art diagnosis and treatment. *JACS*, 201(4), Oct. '05: 586-596.
- Kepple J et al. Minimally invasive breast surgery. *JACS*, 199(6), Dec. '04: 961-974.
- Newman L. Lymphatic mapping and sentinel lymph node biopsy in breast cancer patients: a comprehensive review of variations in performance and technique. *JACS*, 199(5), Nov. '04: 804-816,
- Bickenbach K. Aromatase inhibitors: an overview for surgeons. *JACS*, 203(3), Sept. '06: 376-389.
- Stolier A. Areola-sparing mastectomy: defining the risks. *JACS*, 201(1), July '05: 118-124
- Axelrod D et al. Breast cancer in young women. *JACS*, 206(6), June '08: 1193-1203.
- Morrow M (ed). Practice guidelines for the management of ductal carcinoma in-situ of the breast (DCIS). *JACS*, 205(1), July '07: 145-161.