

Breast Cancer: Current Approaches to Diagnosis and Treatment

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No Disclosures

Incidence of Breast Cancer USA 2019

- 1 in 8 American women affected
 - 1 in 1000 American men
- 268,600 new invasive breast cancers
 - 63,930 new carcinoma in situ cases
- 41,760 breast cancer deaths
- USA: >3.1 million breast cancer survivors

Identifying high risk patients

- By risk profile
- At the time of cancer diagnosis

Risk Factors for Breast Cancer

- positive family history / risk gene mutations
- Increasing age
- prior breast cancer
- LCIS, atypical hyperplasia
- hormonal factors
- lifestyle - diet, weight gain, alcohol
- radiation exposure

Goals for High Risk Patients

- Accurate assessment of degree of risk
 - Communication of risk to patient
 - Discussion of options for managing risk
- Early detection
 - More frequent screening
 - Additional screening modalities
- Prevention
 - Chemoprevention
 - Prophylactic mastectomy, oophorectomy

Risk genes: Lifetime breast cancer risk

Gene	Lifetime risk	Other risks
BRCA1	72%	75% triple (-), 44% ovary risk, prostate
BRCA2	69% female 8% male	80% ER+ 17% ovary risk, pancreas, prostate
P53	85%	Risk for many cancers, ?avoid radiation
PALB2	35-58%	
PTEN	67-85%	Thyroid, uterus, renal cancer
CHEK2	23-48%	Colon cancer
STK11	45-50%	GI, pancreas
CDH1	39-52%	Gastric
ATM	17-52%	Pancreas, prostate

Criteria for Risk Gene Testing

- Breast cancer at age 45 or younger
 - Triple negative breast cancer age 59 or younger
- 3 or more relatives with breast cancer
- Families with both breast and ovarian cancer or male breast cancer
- Ashkenazi Jewish women
 - Lower threshold for testing – founder mutation panel

Screening Mammography:

Timing and frequency still controversial

- **U.S. Preventive Services Task Force 2009:**
 - No routine mammograms ages 40-49; woman to discuss with MD
 - Ages 50 to 74, screening mammograms every two years
- **American Cancer Society 2015:**
 - Ages 40-44: annual mammogram optional
 - Annual mammogram ages 45-54
 - ≥ 55 : mammogram every 2 years or annual

American Cancer Society breast exam guidelines

- Clinical breast exam every 3 years ages 20-40, annually after 40
- Women should report breast changes promptly to their health care provider
- Breast self exam optional

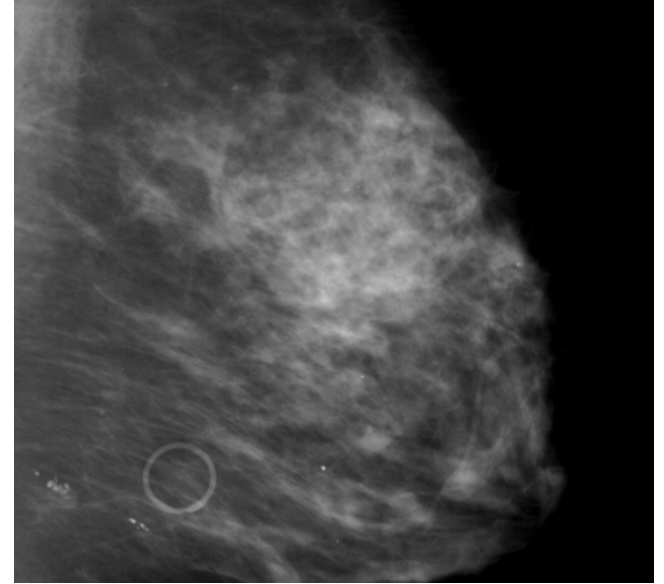
Improved imaging for early detection of breast cancer

- Improvements in mammography
 - 3D Tomosynthesis
 - Contrast mammography
- Whole breast ultrasound
- Breast MRI
- Identification of high risk patients
 - More intensive screening
 - Prevention interventions

Breast tomosynthesis

- Looks at breast tissue as individual “slices” instead of all at once
- Can see lesions missed by conventional mammography – fewer callbacks
- 3D imaging that is cheaper than MRI
- Becoming standard of care imaging

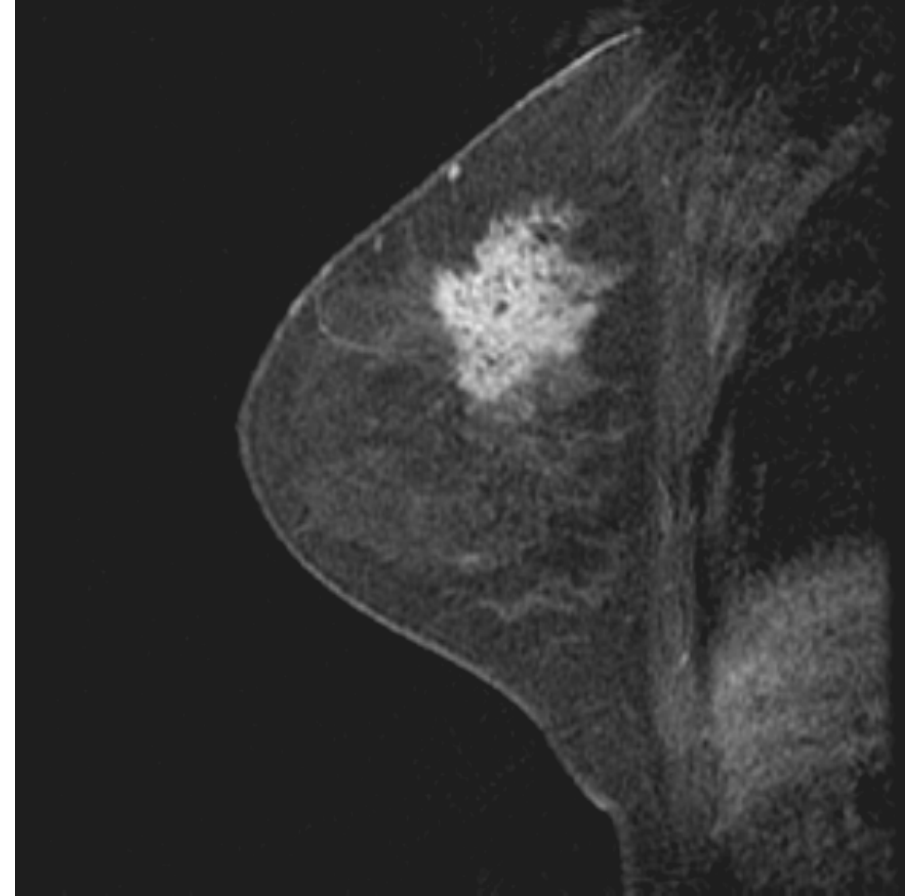
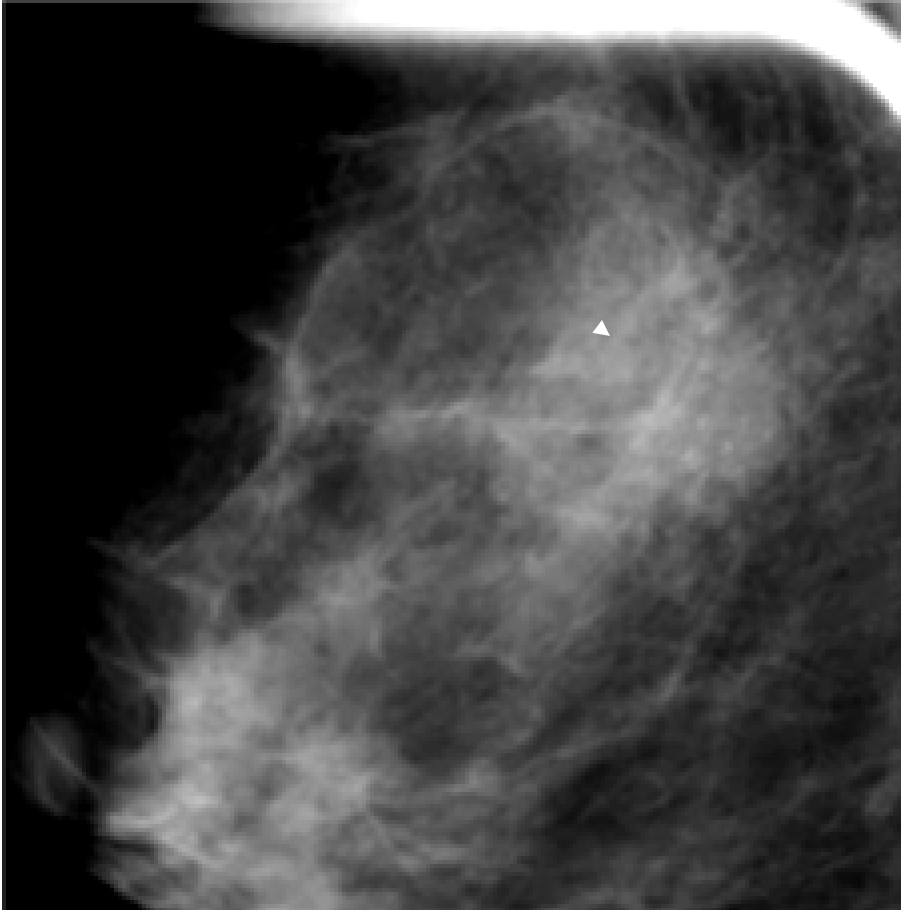
Conventional mammo



Tomosynthesis mammo



MRI detects some tumors missed by mammography



Current Indications for Breast MRI

- To distinguish recurrent tumor from scar tissue following lumpectomy and radiation
- Additional evaluation of mammogram or ultrasound abnormalities
- Extent of tumor after diagnosis
- Assessment of silicone implant rupture
- Screening high risk women: >20-25% lifetime risk

ACS MRI Screening Guidelines

Saslow CA: Cancer J Clin 2007;57:75-89

- **Recommended (based on evidence)**
 - BRCA gene mutation
 - untested 1st degree relatives
 - >20-25% lifetime risk by risk models
- **Recommended (based on expert consensus)**
 - chest irradiation ages 10-30
 - Li-Fraumeni Syndrome and 1st degree relatives
 - Cowden, Bannayan-Riley-Ruvalcaba syndromes
- **Insufficient evidence for or against**
 - Lifetime risk 15-20%, LCIS, ALH, ADH, prior breast cancer, dense breasts

Current issues in breast cancer management

- Early detection and improved treatment have resulted in many healthy, long term survivors
- Sequellae of cancer treatment, QOL issues, cost, more important than in past
- Local and distant recurrence risk continues 10+ years
- Ongoing risk of new primary cancers

Breast Cancer Treatment 2020

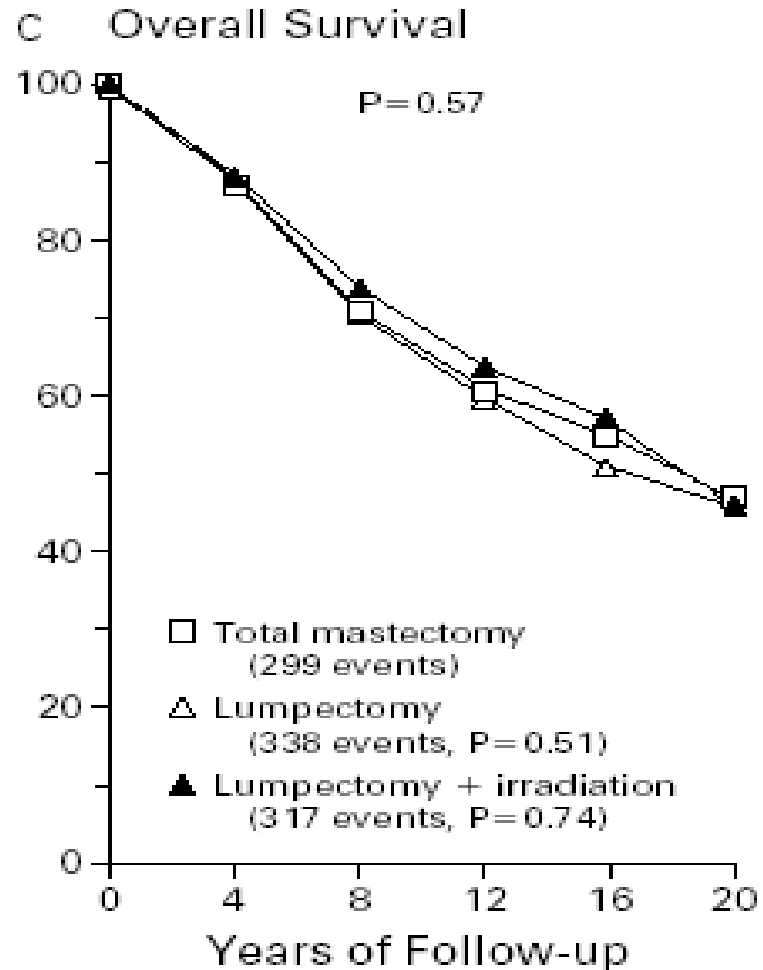
- **Surgery – remove bulk of tumor, define stage**
 - Mastectomy or lumpectomy
 - Axillary staging
 - Reconstruction, oncoplastic surgery
- **Radiation**
 - Treat microscopic residual disease
 - Reduce the extent of surgery/replace surgery for metastases
- **Systemic therapy – treat metastatic deposits**
 - Chemotherapy, endocrine therapy, targeted agents

Local Therapies: Surgery and Radiation

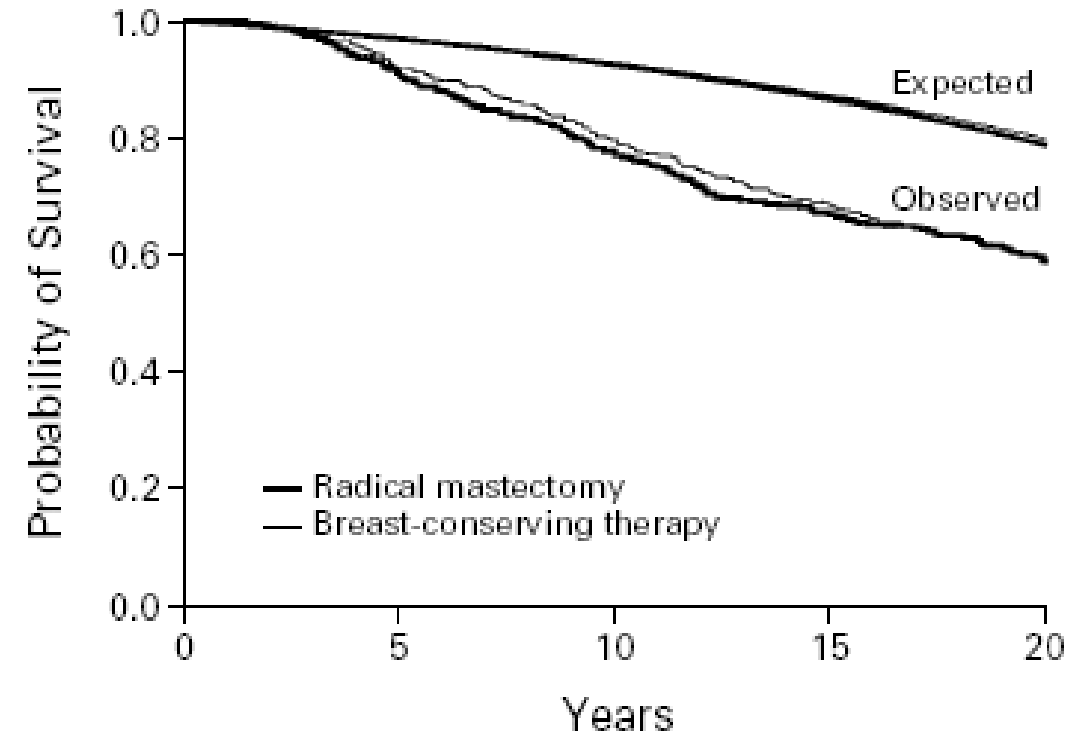
Mastectomy vs. Lumpectomy: 20-year Data

No Difference in Survival

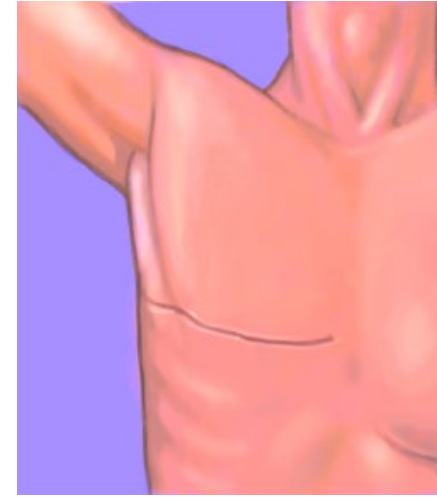
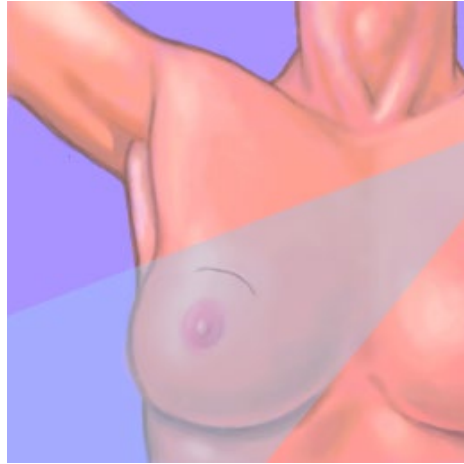
NSABP B-06



Milan I Trial



Lumpectomy vs. Mastectomy



- 20 year follow-up: lumpectomy and mastectomy provide equivalent survival
- Technical improvements in lumpectomy and radiation
 - 10-year local recurrence rates now 2-5%
 - further reduces relative benefit of mastectomy

Local recurrence reduces survival

Oxford Overview Lancet 2005;366:2087

- 42,000 patients in 78 trials
- 75% of local recurrences within 1st 5 years
- Increased local recurrence at 5 years = decreased survival at 15 years
- **4:1 ratio - 1 excess death for each 4 local failures**

Lumpectomy: Prevent recurrence

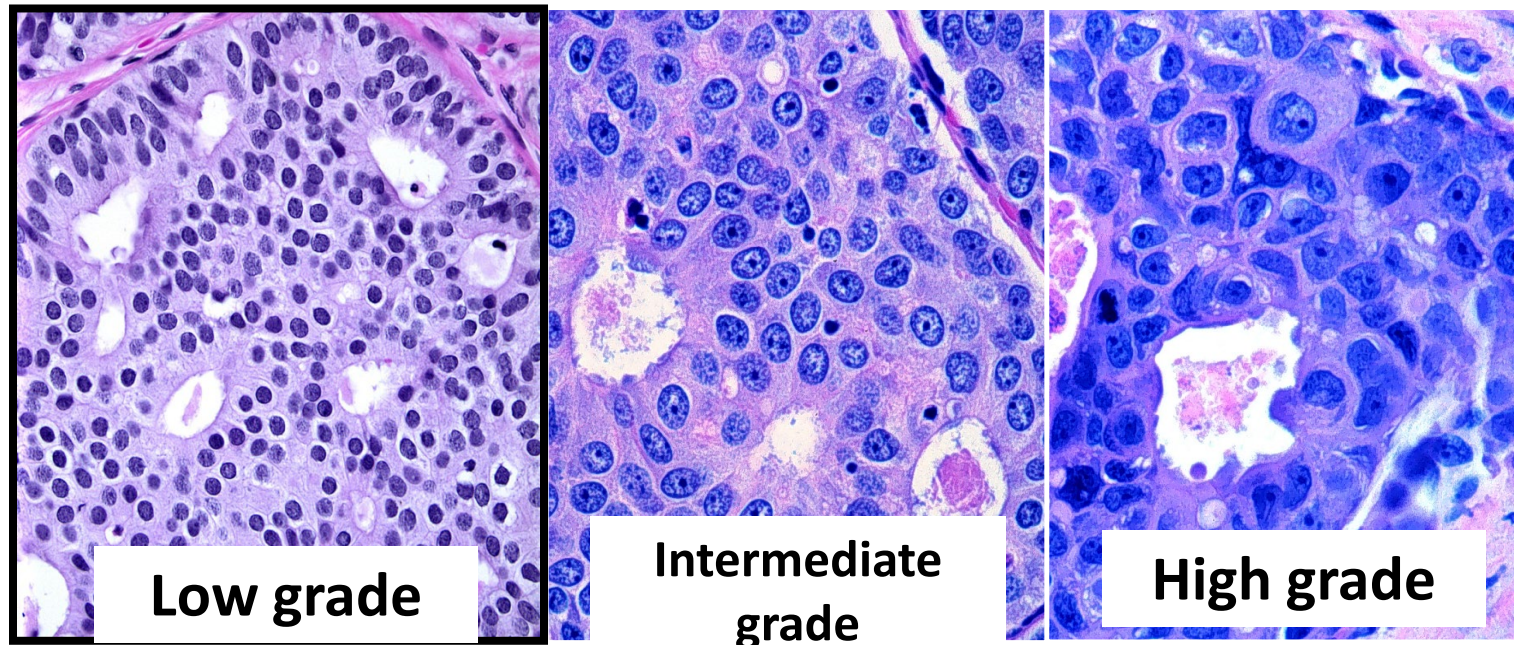
Oxford Overview: 1 excess death per 4 local recurrences

- Margins: Negative for invasive, $\geq 2\text{mm}$ for DCIS
- Radiation with boost
- Systemic therapy decreases local recurrence
- Many series $<5\%$ local failure at 10 years
(40% local failure without radiation)
- Current results approaching risk of chest wall recurrence after mastectomy

Ductal carcinoma in situ – DCIS

20-25% of all breast cancer diagnoses

- 98-99% survival if treated
- Without treatment, some, but not all, will progress to more dangerous, invasive breast cancer
- Time to progression may be long



DCIS: Local recurrence and survival

Mastectomy vs. Lumpectomy

Mastectomy: Fowble 1989 Oncology 3:51

- Local recurrence <1%
- Breast cancer mortality 1.7% at 15 years

Lumpectomy: NSABP B-17 8-year data

- **Lumpectomy:** 26.8% ipsilateral recurrence
- **Lumpectomy + RT:** 12.1% ipsilateral recurrence
- Equivalent survival, 1-2% breast cancer mortality
- **50% of recurrences after lumpectomy are invasive**
- **Use of radiation is debated**

Surgical options for high risk patients

- No increase in local failure in BRCA1/2 mutation carriers with lumpectomy
 - Higher rate of new primaries – contralateral and ipsilateral
- Bilateral mastectomy: option for treatment and risk reduction in mutation carriers and other high risk patients
- Prophylactic salpingo-oophorectomy reduces both breast and ovarian cancer risk in BRCA mutation carriers

Current indications for mastectomy

- Tumor large relative to breast size
 - Consider pre-op systemic therapy to shrink tumor
- Contraindications to radiation
 - New cancer in previously irradiated breast
- Breast cancer in high risk patient
- Patient preference

Improving cosmetic outcomes after lumpectomy and mastectomy

Oncoplastic surgery: Lumpectomies

Better Cosmesis for Large lesions

- Extensive tissue mobilization after lumpectomy to recreate breast contour
- Addition of mastopexy or reduction mammoplasty to lumpectomy – single or 2-stage procedure
- Cosmetic skin closure

Improvements in mastectomy and reconstruction surgery

- Skin-sparing mastectomy
- Nipple sparing mastectomy
- Immediate reconstruction – more options
 - Single stage implant reconstructions
 - Muscle sparing autologous tissue flaps

Nipple sparing mastectomy: Advantages



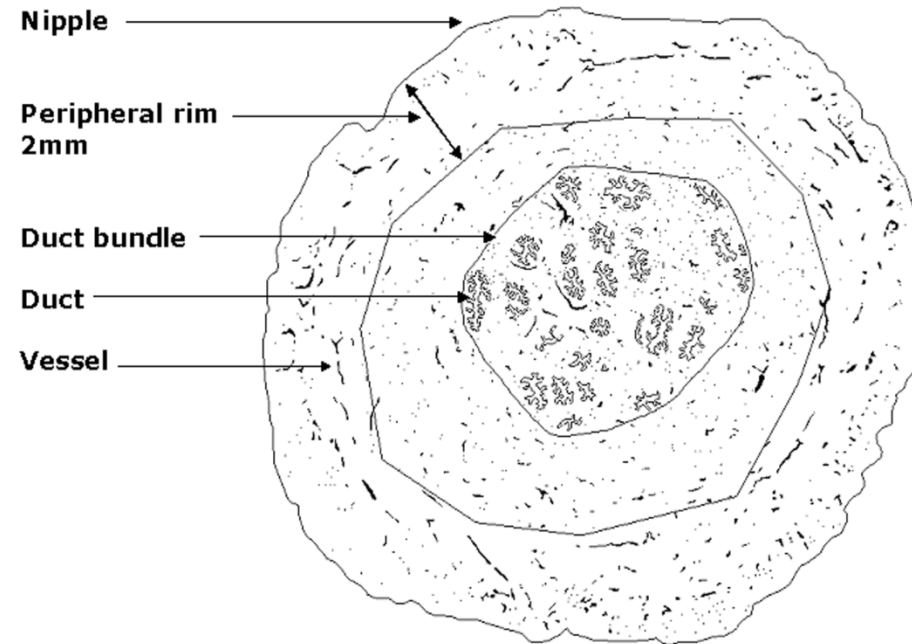
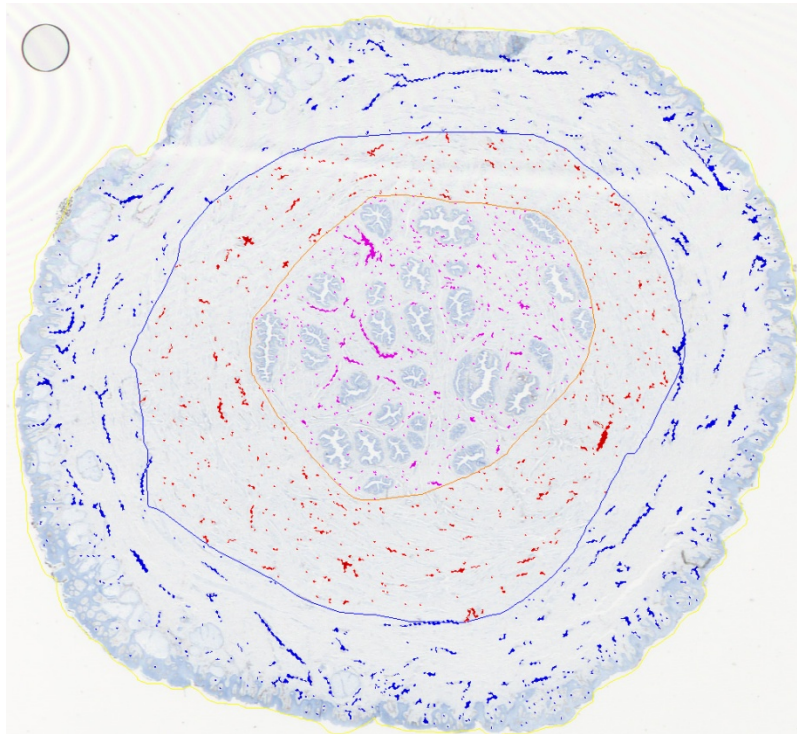
**6 wks post-op, bilateral
mastectomies, single stage
implant reconstructions**

- Superior cosmetic outcome
- Increases chance of single stage implant reconstruction
- 0-1% nipple/areola recurrence in therapeutic NSM series

Anatomy of a safe nipple sparing mastectomy

Location of blood vessels relative to nipple ducts: Factor VIII staining

Only 1/3 of vessels travel with ducts
2/3 of vessels are in nipple skin



Rusby, Brachtel, Taghian, Michaelson, Koerner, Smith. Am J Surg 194:433 2007

Nipple margin anatomy

**Subareolar/
nipple duct
margin**

Ductal tissue
within nipple

Superficial
retroareolar
tissue

**Tumor in subareolar/ nipple
duct margin requires nipple
excision**



Nipple recurrence rates are low after nipple sparing mastectomy for breast cancer

	Year	N	% Local rec	# NAC rec	F/U mo
Petit	2012	1001	3.6	7	50
Smith	2017	311	3.7	0	51
Benediktsson	2008	216	20.8	0	156
Vaughan	2007	206	5.3	0	58.6
Kim	2010	152	2.0	2	60
Paepke	2009	109	2.0	0	34
Jensen	2011	99	3.0	0	60
Gerber	2009	60	11.7	1	101

The nipple is just another margin

- **Increasing evidence for oncologic safety of nipple sparing with clear margins**
- **Patient selection**
 - No direct nipple involvement on exam or imaging
 - Awareness of RT, smoking, age >55, breast >800cc and incision impact on complication rate
- **Careful nipple margin assessment**
 - Excision of nipples with positive margins

Managing the axilla

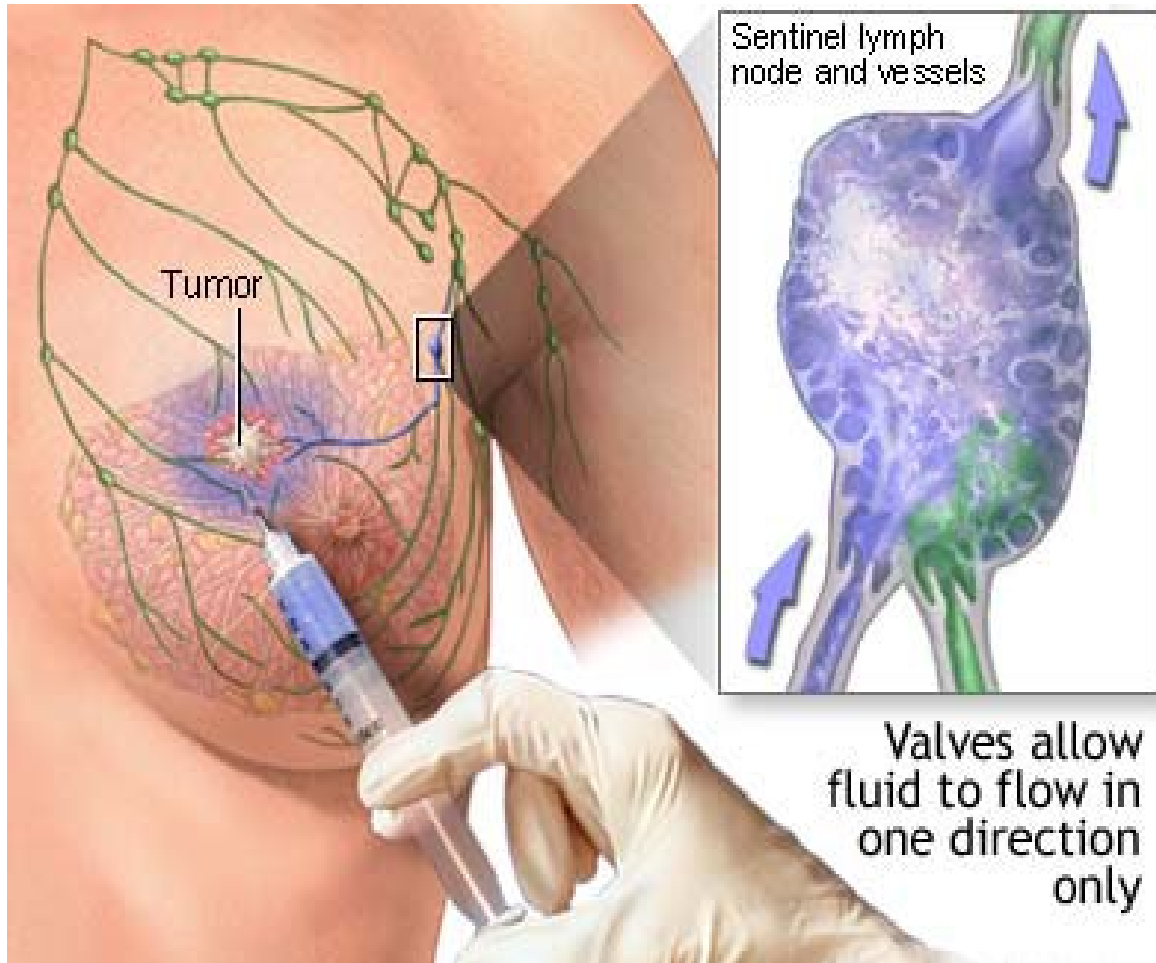
- Treat axillary disease
- Define stage to guide radiation and medical therapy

Staging the axilla: Sentinel Node Biopsy

Node status remains a strong prognostic factor

- Lymphatic drainage is to a specific “sentinel” node
- A negative sentinel node predicts that remaining nodes are negative
- Less morbidity than axillary dissection
 - Lymphedema 1-2%
 - Only rare chronic pain or reduced mobility
 - Axillary dissection: 25% edema/chronic pain
- Now standard of care for clinically node negative

Sentinel node mapping



- Radioactive and/or blue particles injected near tumor or areola
- Particles accumulate in 1st node encountered
- Sentinel node excised and examined for metastasis

Is axillary dissection necessary for a positive sentinel node?

ACOS-OG Z0011

- **891 eligible patients**
 - Lumpectomy and positive sentinel node
 - Whole breast radiation
 - Randomized to axillary dissection or no further axillary surgery
- **Other eligibility criteria:**
 - Only 1 or 2 positive nodes
 - No extracapsular extension
 - Systemic therapy

20011 Local-regional Recurrence

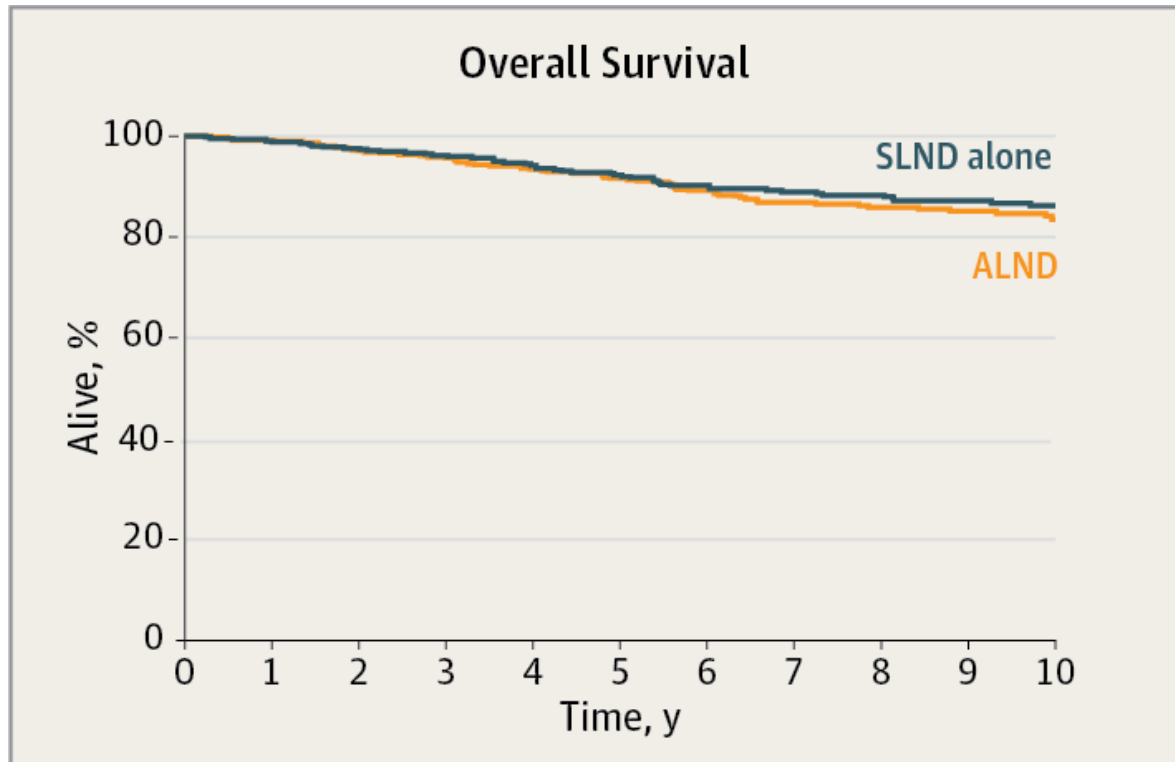
Giuliano et al Ann Surg 252:426-33 2010

Recurrence	ALND (420 pts)	SLND (436 pts)
Local (Breast)	15 (3.6%)	8 (1.8%)
Regional (Axilla, Supraclavicular)	2 (0.5%)	4 (0.9%)
Total Locoregional	17 (4.1%)	12 (2.8%)
<i>P = 0.11</i>		

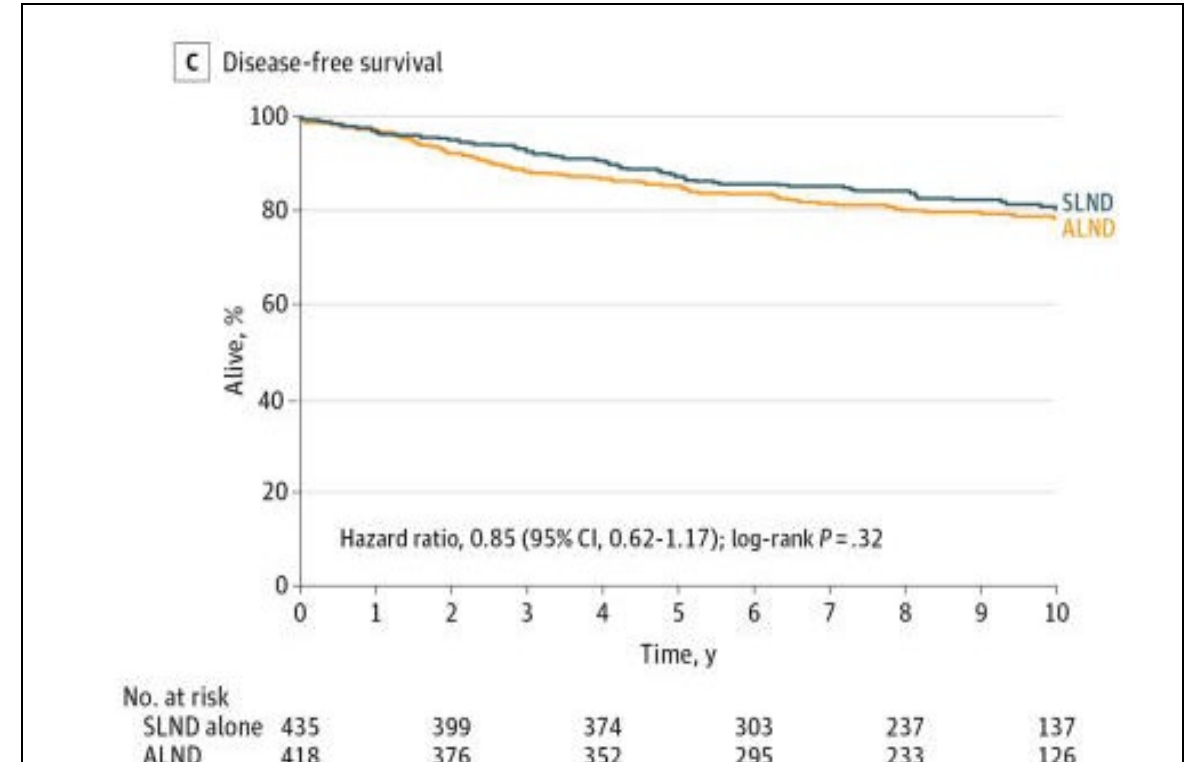
Median follow-up = 6.3 years

Z0011 10-yr outcomes: axillary dissection vs. SNB+RT in sentinel node(+) breast cancer

No survival difference with axillary dissection



No difference in disease free survival



AMAROS Trial: Radiation vs. dissection

1425 sentinel node (+) patients

10-year follow-up			
	Radiation	Dissection	p-value
Local recurrence	1.82%	0.93%	NS
Distant disease free survival	78.2%	81.7%	NS
Overall survival	81.4%	84.6%	NS

- Included lumpectomies and mastectomies
- 3rd radiation field to axilla

SABCS 2018

Z0011 and AMAROS Conclusions

For clinically node negative patients, 3 or fewer positive sentinel nodes:

“Routine use of axillary node dissection in this patient population is not justified”

Post Z0011: Which patients still need axillary dissection?

- Clinically node positive
- >3 positive sentinel nodes
- Gross extranodal tumor extension
- Residual palpable nodes after SLNB
- Patients who will not receive radiation and systemic therapy
- Patients for whom dissection data will change other therapy

Why add radiation after lumpectomy?

- NSABP-B06 trial
 - Lumpectomy alone vs. lumpectomy + radiation
- In-breast recurrence rates
 - **40% without radiation**
 - **3-5% with current radiation**

Radiation after lumpectomy: More options, lower costs

- Whole breast irradiation
 - Standard: 25 fractions plus 8 fraction boost
 - Canadian: 16 daily fractions
 - FAST: 5 weekly fractions
- Partial breast irradiation – equivalent control
 - External beam 2x daily for 5 days, 1x daily for 10 days
 - Brachytherapy catheters 5 days
- Elderly, ER+ may safely omit radiation

Do Women Over 70 Need Radiation?

CALGB 9343: 636 women ≥ 70

- Tumor $\leq 2\text{cm}$, ER+, clinical N0
- All had lumpectomy and tamoxifen
- Randomized to radiation or no radiation

Hughes ASCO 2010

Do women over 70 need radiation?

CALGB 9343: 12 yr follow-up Hughes ASCO 2010

	Tam-RT	Tam	P-value
# patients	317	319	ns
Any local recurrence	2%	9%	<0.0001
Breast recurrence	2%	8%	ns
Axillary recurrence	0%	1%	ns
Mastectomy rate	2%	4%	ns
Distant metastases	7%	5%	ns
All-cause mortality	39%	37%	ns
Breast-ca specific death	4%	2%	ns

Do women over 70 need radiation?

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Conclusions: For favorable ER+ tumors in women age ≥ 70

- Radiation decreases locoregional recurrence
 - 2% vs. 9% at 12 years median f/u
- However, radiation
 - Has no impact on overall, distant disease-free or breast cancer specific survival
 - Has no significant impact on mastectomy rate
 - Does add to morbidity
- Axillary surgery had no impact on local recurrence or survival

Role of radiation after mastectomy

- Reduces risk of local recurrence by 50-75%
- Good local control improves survival
- **Benefits patients at high risk for local failure**
 - Node positive
 - Tumors >5cm – T3
 - LVI, young age, close margins

Post mastectomy radiation benefit

Oxford Overview Lancet 2014;383;2127-35

**3786 women in 22 randomized trials, 10 yr f/u:
MRM +/- RT to chest wall and regional nodes**

		Radiation vs. No Radiation			
Number +nodes	N	RR overall recurrence	p-value	RR breast ca mortality	p-value
0	700	1.06 (0.76-1.48)	>0.1	1.18 (0.89-1.55)	>0.1
1-3	1314	0.68 (0.57-0.82)	0.00006	0.80 (0.67-0.95)	0.01
≥4	1772	0.79 (0.69-0.90)	0.0003	0.87 (0.77-0.99)	0.04

Medical Therapies for Breast Cancer

Adjuvant Systemic Therapy

- IV and oral medications given to clinically disease-free patients based on ***predicted*** risk of metastatic disease
 - Cytotoxic chemotherapy
 - Endocrine therapy – anti-estrogen
 - Targeted therapy – drugs and antibodies

Who should receive systemic therapy?

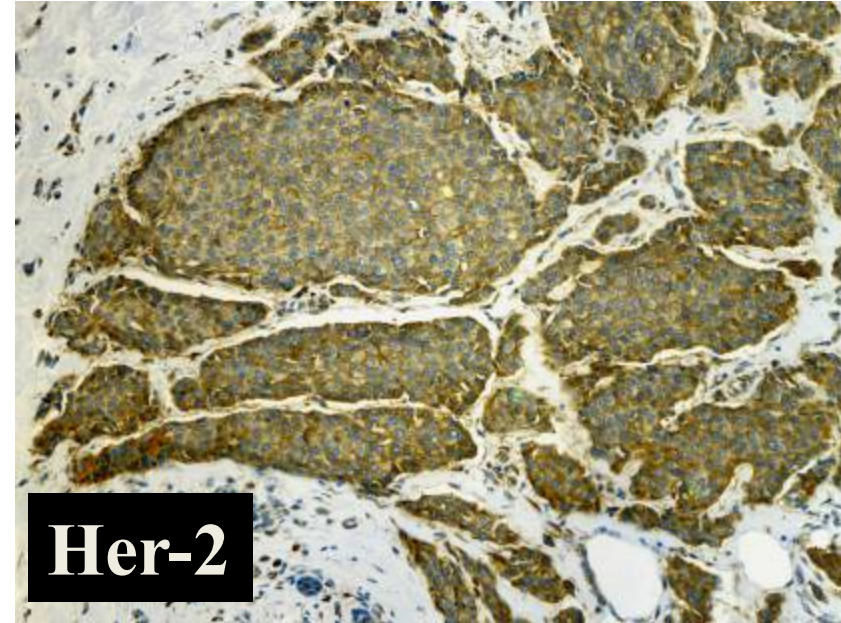
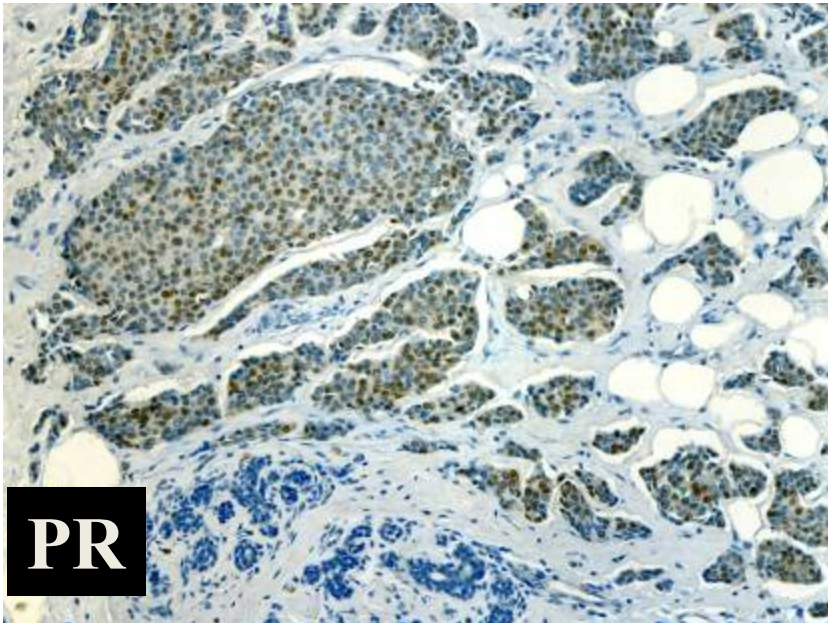
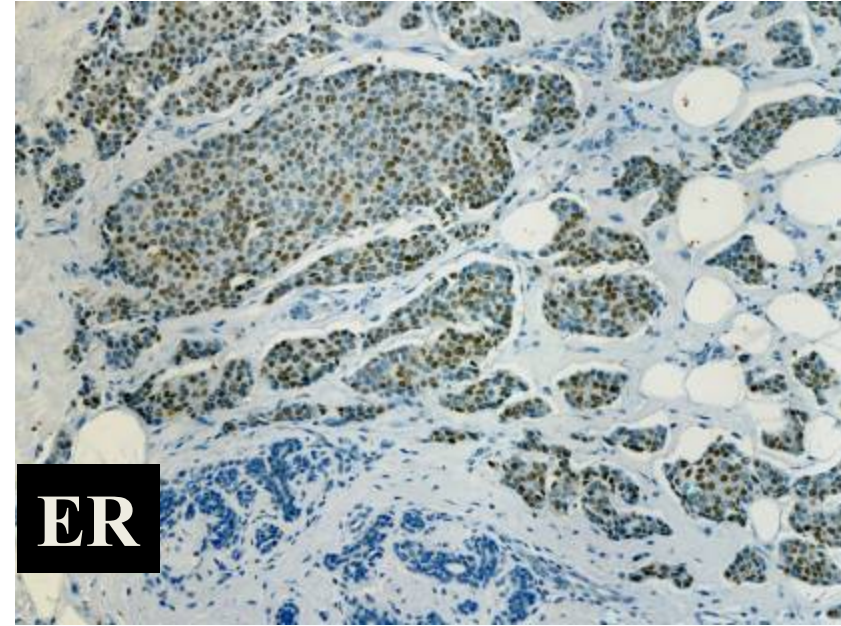
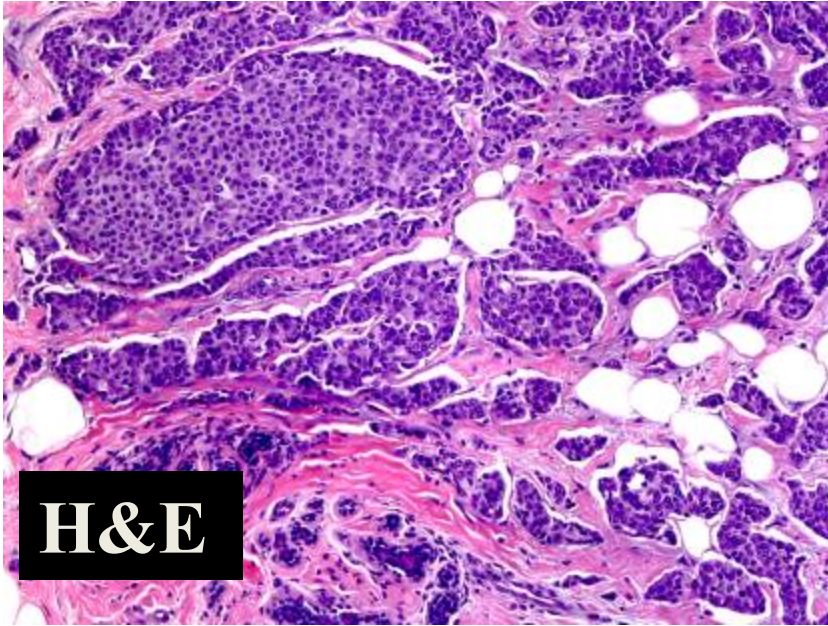
- What is this patient's risk of fatal metastasis?
- What treatments are available to reduce the risk of metastasis?
- How much do these treatments reduce risk of relapse?
- What are the side effects of applicable treatments for this patient?

Systemic Therapy: Impact vs. Toxicity

- Cytotoxic chemotherapy
 - 20-30% reduction in recurrence
 - Greater benefits in selected tumors and patients?
- Endocrine “anti-estrogen” therapy
 - 50% reduction in recurrence in hormone receptor positive tumors
- Anti-HER2 monoclonal antibody therapy
 - 50% reduction in recurrence for sensitive tumors

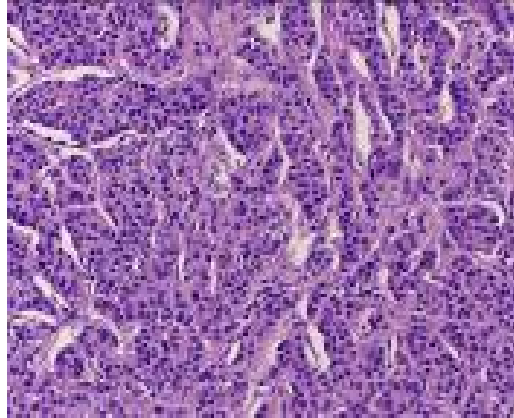
**** All systemic therapies decrease local recurrence**

Tumor factors guide treatment



Patient 1

**1.4 cm
node (-)**



**ER+
PR+**



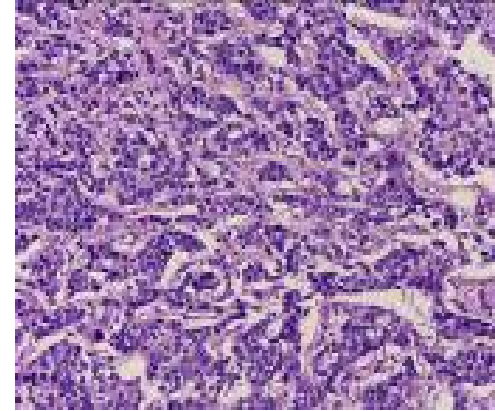
Adjuvant tamoxifen



**Metastatic disease 3yrs after
initiation of tamoxifen**

Patient 2

**1.2 cm
node (-)**



**ER+
PR+**



Adjuvant tamoxifen



Disease free at 12 yrs

Prognostic Factors Guide Treatment

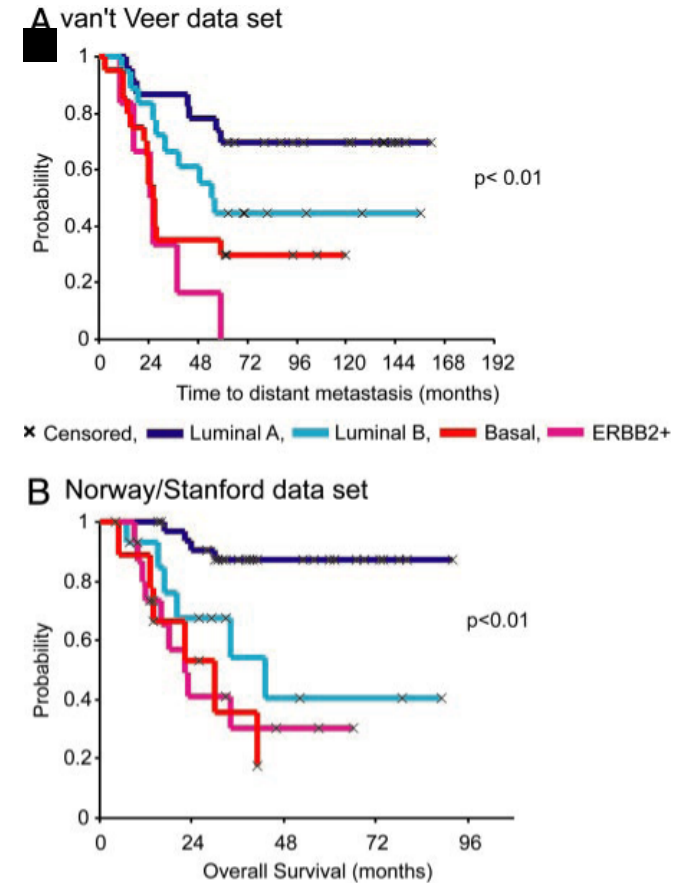
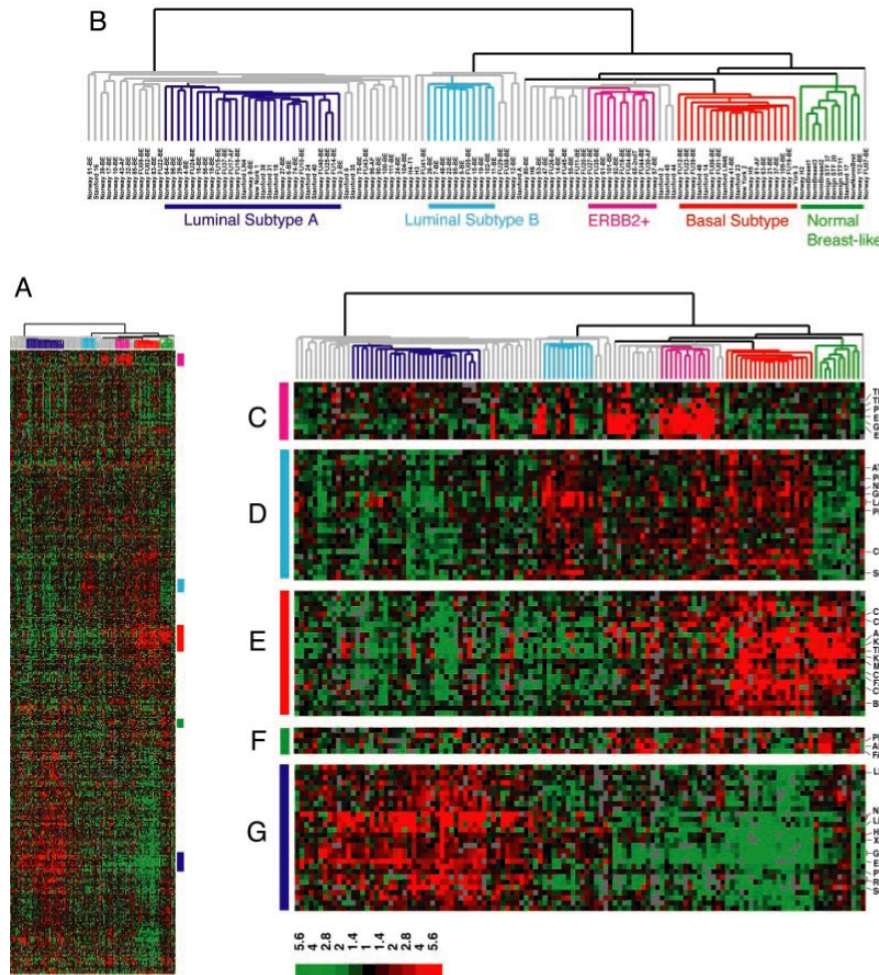
Classic and standard prognostic factors

- Tumor size, histologic features, nodal status
- Estrogen and progesterone receptor
- HER2 overexpression

Newer factors

- Gene expression profiling of individual tumors
 - For prognosis
 - For response to specific treatments
 - Targeted therapy

Gene Expression Subtypes and Clinical Outcome



Sorlie et al. PNAS 2003,100:8418-8423

Re-classification of breast cancers:

Gene expression profiling

- **70%:** Luminal A, ER+, PR+, HER2-, favorable
 - less aggressive treatment possible
- **15%:** HER2+ (ER+ or ER-)
 - benefit from anti-HER2 therapy - trastuzumab
- **15%:** Basal-like, “triple negative”: ER-, PR-, HER2-
 - poor prognosis, poor response to current chemotherapy

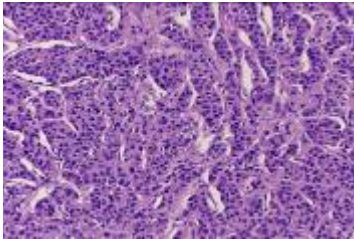
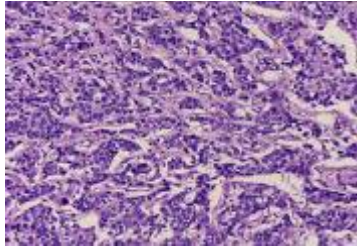
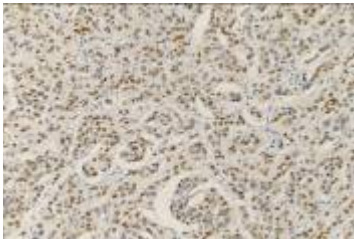
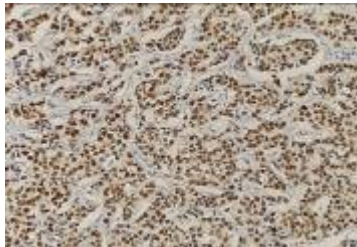
Local and Distant Recurrence Rates by Subtype

799 Breast Conservation Cases Nguyen JCO 26: 2373, 2008

Group	Receptors	5-year local failure	Adjusted HR (95%CI) p-value	5-yr distant failure	Adjusted HR (95%CI) p-value
LumA n=599	ER/PR+, HER2-	0.7%	Baseline	3.0%	Baseline
LumB n=78	ER/PR+, HER2+	1.3%	NS	11.5%	2.7 (1.2-6.0), p=0.014
HER2+ n=33	ER/PR- /HER2+	12.4%	6.7 (1.7-26.7) p=0.007	15.2%	NS
Basal n=89	ER/PR-, HER2-	6.8%	3.9 (1.1-13.7) p=0.036	14.8%	2.1 (0.9-4.6), p=0.07

Which ER+ patients will do well with tamoxifen alone?

30-40% of ER+ cases fail to respond or develop resistance to tamoxifen

Patient 1		Patient 2	
1.4 cm LN-			1.2 cm LN-
ER+ PR+			ER+ PR+
Adjuvant tamoxifen ↓		Adjuvant tamoxifen ↓	
Metastatic disease 3yrs after initiation of tamoxifen		Disease free at 12 yrs	

OncotypeDx: 21 Gene Assay Recurrence Score (RS) Algorithm

- Measure expression of genes related to HER2, ER, proliferation, invasion and genes CD68, GSTM1, BAG1
- Score (0-100) derived from weighted sum of expression levels

RESULTS

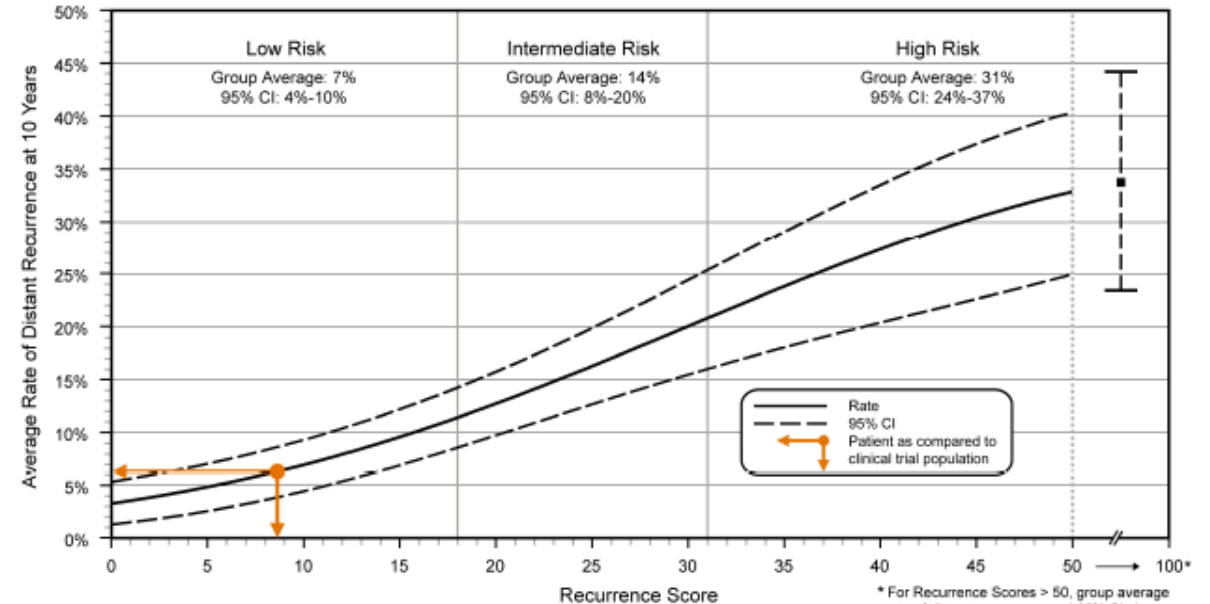
Recurrence Score = **9**

Test results should be interpreted using the information in the Clinical Experience section below, which applies only to patients consistent with this clinical experience.

CLINICAL EXPERIENCE

Patients with a Recurrence Score of 9 in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of **6% (95% CI: 4%-9%)**

The following results are from a clinical validation study with prospectively-defined endpoints involving 668 patients. The patients enrolled in the study were female, stage I or II, node negative, ER-positive, and treated with tamoxifen. *N Engl J Med* 2004; 351: 2817-26.



* For Recurrence Scores > 50, group average rate of distant recurrence and 95% CI shown

Who needs chemotherapy?

Tailor Rx Trial – Rx by Oncotype result

- 10,253 ER+, HER2- breast cancers
- Oncotype performed
- Low risk (0-10) - 1626 patients (16%)
 - 99% DFS at 5 years without chemo
- Intermediate risk (11-25) – 6907 patients (67%)
 - Randomized: **chemo + endocrine** vs. **endocrine alone**
 - No difference in overall or disease free survival at 9yrs

Sparano NEJM 2015;373:2005-14
Sparano NEJM 2018; 379:111-21

Who needs chemotherapy?

Clinical vs. genomic risk assessment

- **70-gene assay MINDACT trial**
- Clinical risk and Mammaprint genomic risk assessed
 - Discordant randomized to chemo or no chemo
 - High clinical – low genomic
 - Low clinical – high genomic
 - Chemo based on clinical risk – 95% 5-yr DDFS
 - Chemo based on genomic risk – 94.5% 5-yr DDFS with much lower use of chemotherapy

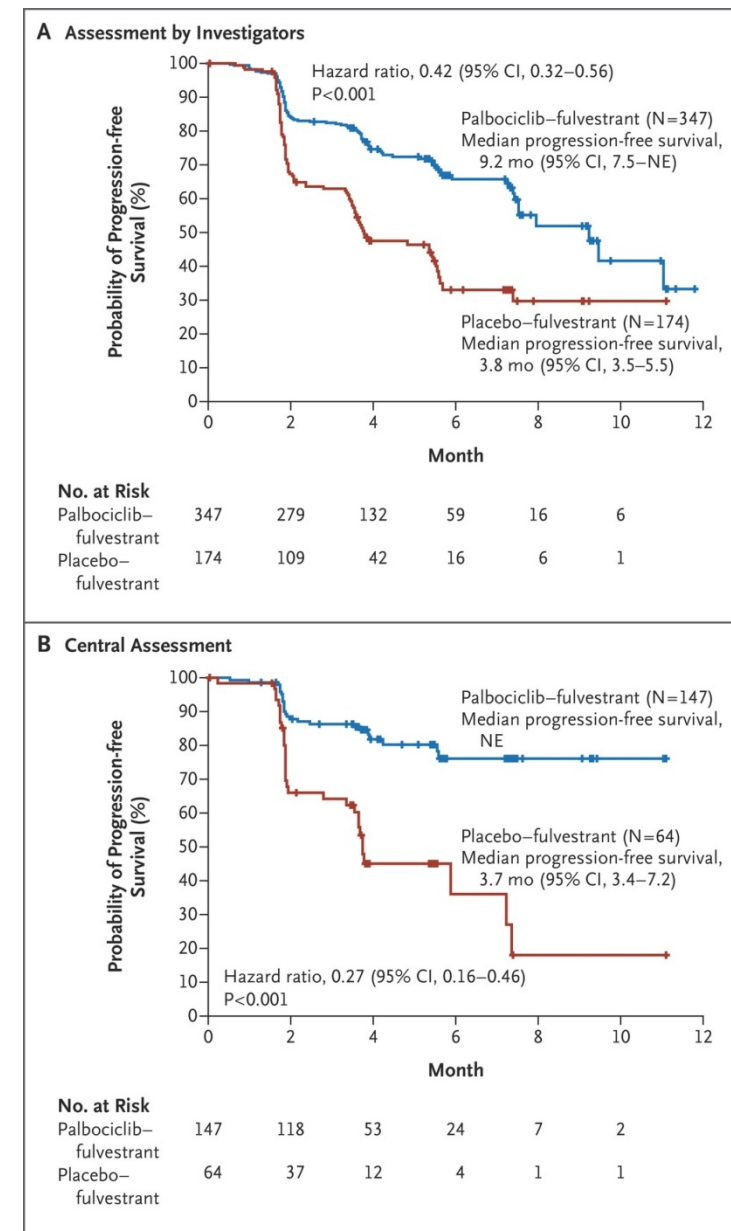
Improving response to endocrine therapy with CDK inhibition: Palbociclib

ER+ breast cancer growth depends on cyclin-dependent kinases (CDK4, CDK6), for G1 to S phase cell cycle progression.

Palbociclib - CDK4 and CDK6 inhibitor

- Used with endocrine therapy
- Improves progression free survival - advanced disease
- Some neutropenia, anemia, hair loss

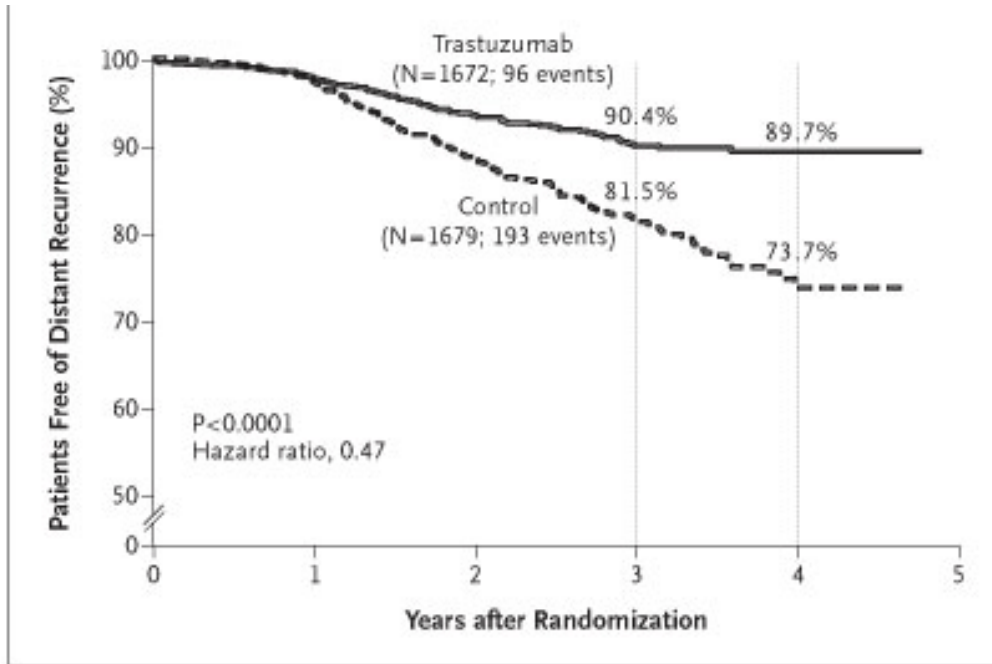
Being explored in earlier stage disease



Targeted anti-HER2 antibody therapy improves outcomes in HER2+ cancers – 15% of breast cancers

NSABP B-31

AC-T chemo +/- trastuzumab



% Free of distant recurrence

Dual antibody blockade with trastuzumab + pertuzumab

- Incremental improvement in outcomes with dual blockade
- Benefit in metastatic and early stage disease

Metastatic breast cancer

Stage IV breast cancer

- Stage IV breast cancer survival linked to
 - Pattern and extent of initial metastases
 - Estrogen receptor status
 - Tumor grade
 - Gene expression profile
- Median survival range 12-42 months
- Local disease may progress and become symptomatic while distant disease remains controlled

Stage IV breast cancer: Goals of therapy

- **Symptom control with minimal morbidity**
- **Slow progression of disease**
- Endocrine Rx rather than chemotherapy for ER+
- Targeted therapies – anti HER2 antibodies
- Radiation for symptomatic bone lesions, CNS
- Surgery reserved for local symptoms

Preventing Breast Cancer

Prevention: Tamoxifen - 50% Reduction in Breast Cancers - NSABP P-1 Trial

Equal risk reduction in:

- all age groups
- +/- LCIS
- all ranges of predicted risk
- # relatives with breast cancer

?Greater risk reduction in those with ADH

Less efficacy in BRCA1 than BRCA2 carriers

NSABP P-1 Trial: Adverse Effects by Age

Tamoxifen risks mainly in women over 50

	Age $\leq$ 50 Relative risk	Age > 50 Relative risk
Endometrial cancer	1.21	3.05
CVA	0.76	1.75
DVT	1.39	1.71

Other endocrine therapy prevention agents

- Raloxifene – estrogen agonist-antagonist
 - 50% reduction in invasive, less reduction in situ
 - Thromboembolic risk, menopausal symptoms
 - No increase endometrial cancer
- Exemestane – aromatase inhibitor
 - 65% risk reduction
 - Menopausal and joint symptoms

JAMA 2006 295:2727

NEJM 364:2381 2011

Limits of Current Prevention Strategies

- All current prevention agents reduce a fraction of estrogen receptor positive tumors
- None of the currently available agents reduce the risk of estrogen receptor negative tumors

Prophylactic Mastectomy

- Effective prevention approach
 - 90-95% reduction in risk
 - Prophylactic BSO reduces risk in premenopausal BRCA
- Significant psychological and physical impact
 - Increasing use of nipple-sparing mastectomy
- Careful assessment of magnitude of risk
 - Increasing role for genetic testing prior to prophylactic mastectomy
- Thorough review of limitations and benefits with patient

NSM is safe in BRCA mutation carriers

Endorsed by current NCCN guidelines

	# NSM	# pts	# pts cancer	months f/u	# NAC recurrence
Jakub 2016	551	348	145	34	0
Yao 2015	397	201	51	33	0
Manning 2014	177	-	26	28	0
Peled 2014	106	53	27	51	0
Hartmann 2001	52	26	0	156	0

Bilateral prophylactic nipple sparing mastectomies
BRCA mutation carrier - Pre-op



Single stage implant reconstruction 6 weeks post op

Breast Cancer 2020

- **Equivalent outcomes with smaller surgery**
 - Lumpectomy, sentinel node biopsy
 - Nipple sparing mastectomy
- **Radiation after lumpectomy, after mastectomy if advanced disease**
 - Shorter more focused options for some
- **Medical therapies targeted to tumor subtypes and genomic profile**
 - More endocrine therapy, less chemotherapy
 - Anti-HER2 antibody therapy
 - Treatment revised based on response