Montefiore Einstein
Center for Cancer Care

BREAST CANCER 2018

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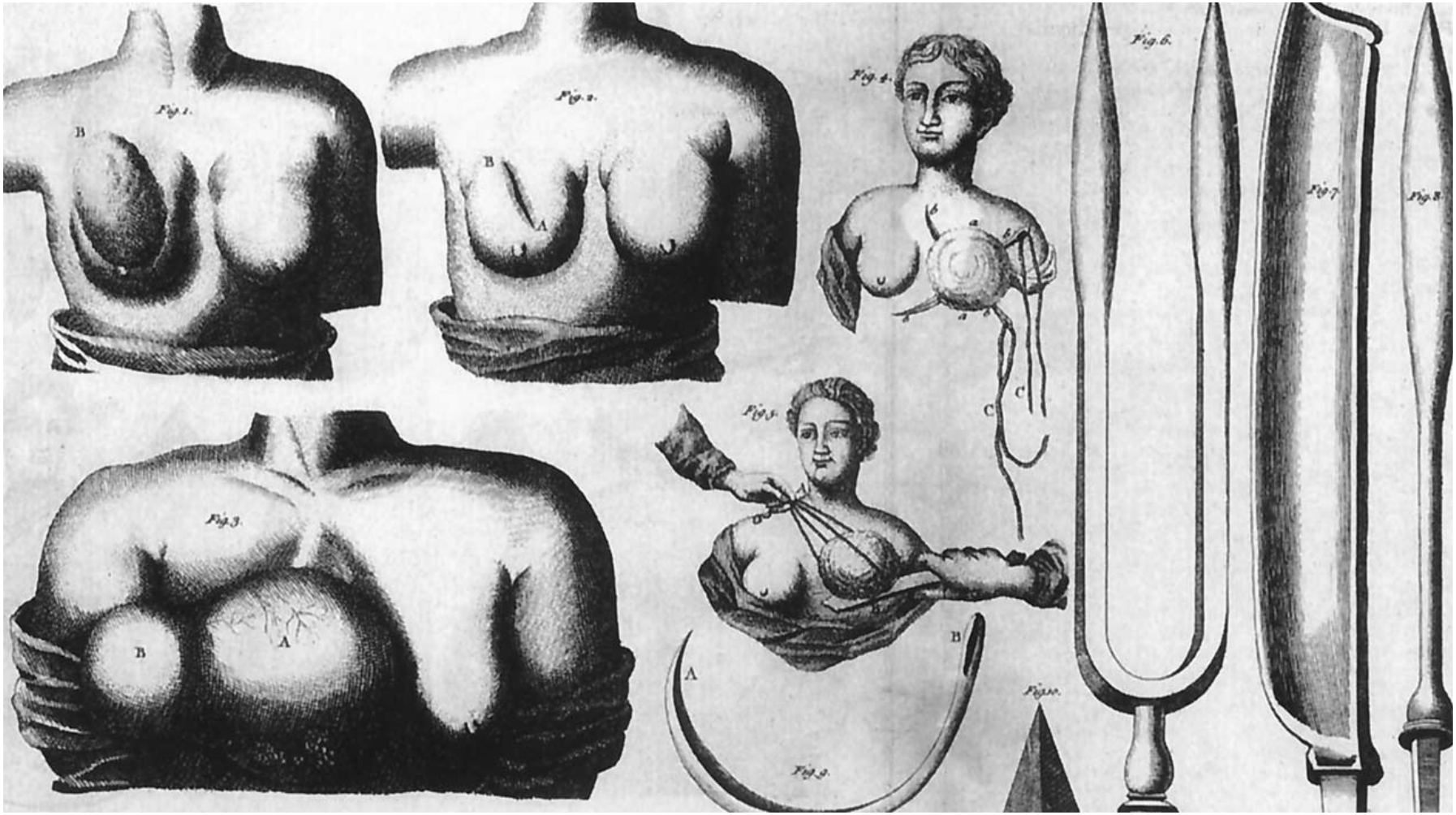
Chief Breast Surgical Oncology
Director Breast Cancer Services
Professor of Surgery
Montefiore Medical Center
Albert Einstein College of Medicine

Early History of Breast Cancer Treatment

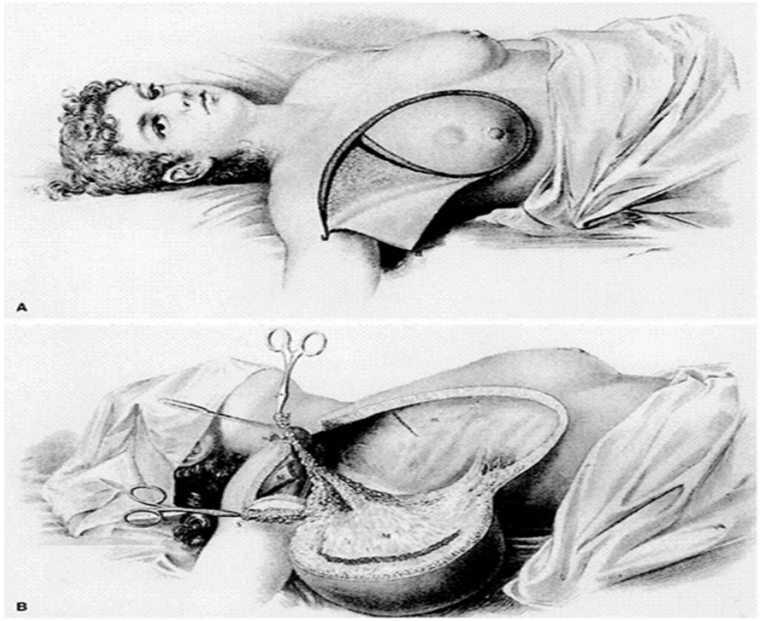
- Hippocrates(460-370,BC): “Hot Iron”
- Galen(130-200,AD):wide excision to include all roots; cancer-crab view
- Albucasis(Arabic 10th century; hot cautery with mastectomy
- Ambrose Pare(1510-1590); local excision and ligatures

Professor Lorenzo Heister 1748 breast surgery atlas

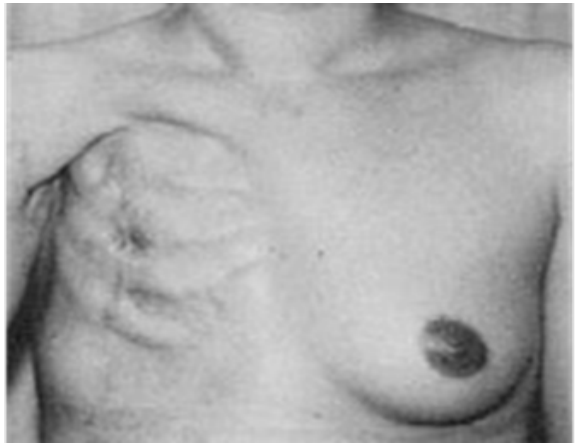


History Breast Cancer Treatment

- 1882 - Age of Halsted
  - Cancer spreads centrifugally by direct extension
  - Patients with advanced disease
  - Radical surgery
  - Skin graft reconstruction



William Halsted



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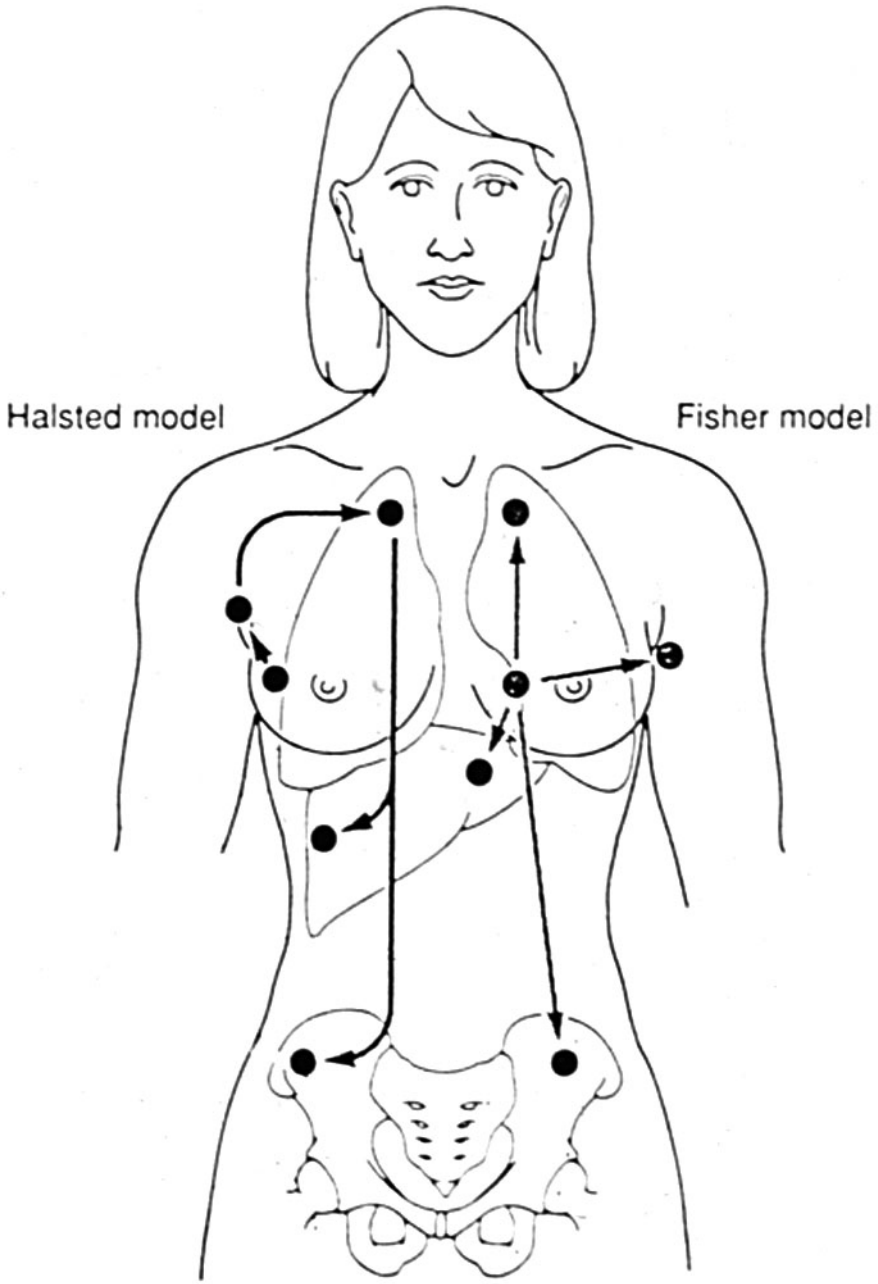
Halsted 1895

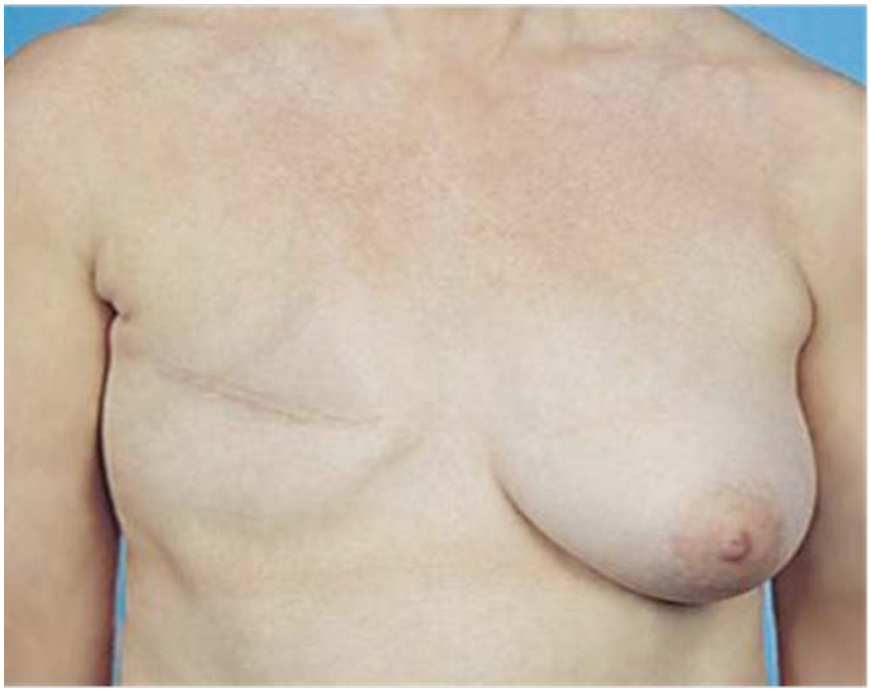
- " There is a definite, more or less uninterrupted, or quite uninterrupted connection between the original focus and the outlying deposits of cancer…the centrifugal spread annexing by continuity a very large area in some cases. Thus the liver may be involved by way of the deep fascia, the linea alba and the round ligament, the brain by the lymphatics accompanying the middle meningeal artery..."
- **" Although it undoubtedly occurs, I am not sure that I have observed from breast cancer, metastasis which seemed definitely or have been conveyed by way of the blood vessels... "**


Halsted model
Fisher model

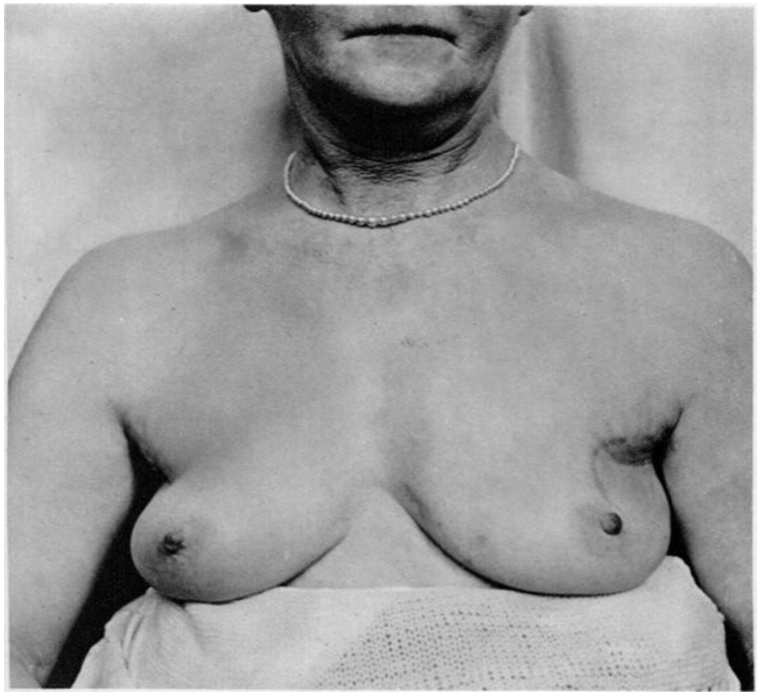
Continued Progress

- 1948 - David Patey

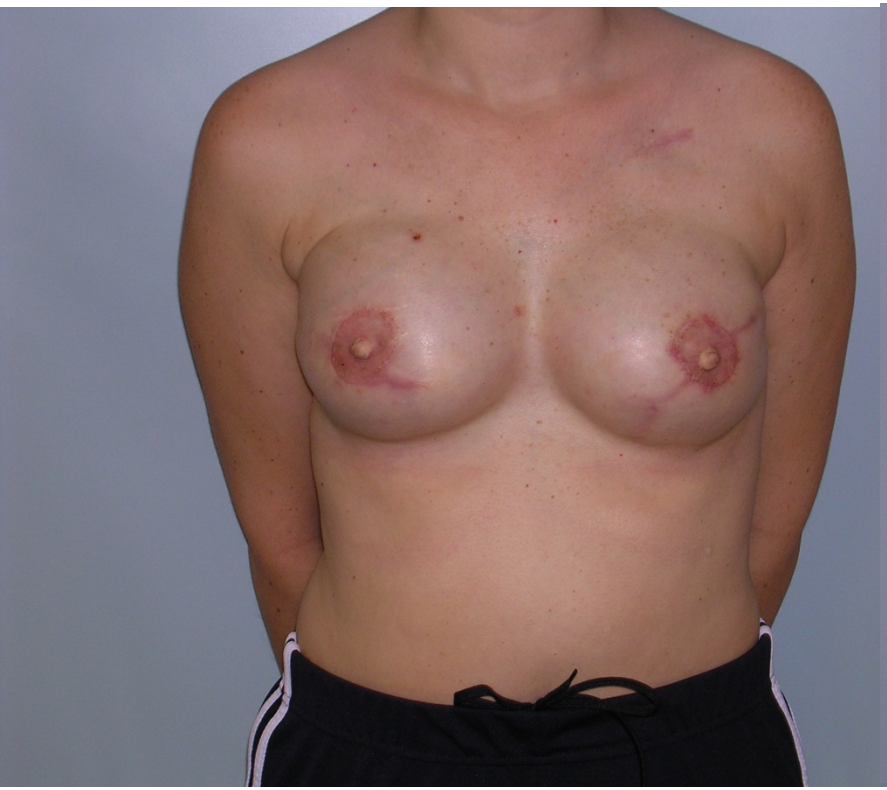
  Modified Radical Mastectomy



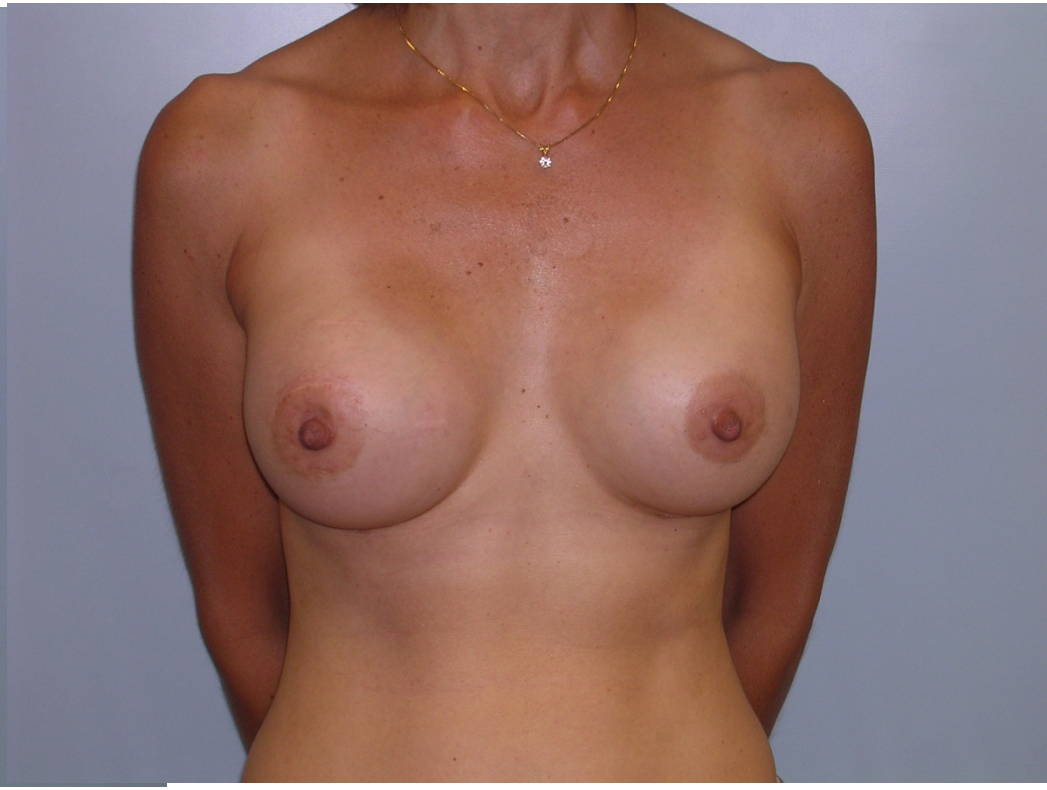
- 1932 – Geoffrey Keynes:Breast conservation therapy with interstial RT



BILATERAL SKIN SPARING MASTECTOMY WITH IMPLANTS 2001



BILTERAL NIPPLE SPARING MASTECTOMY(Hidden Scar) WITH IMPLANTS 2015



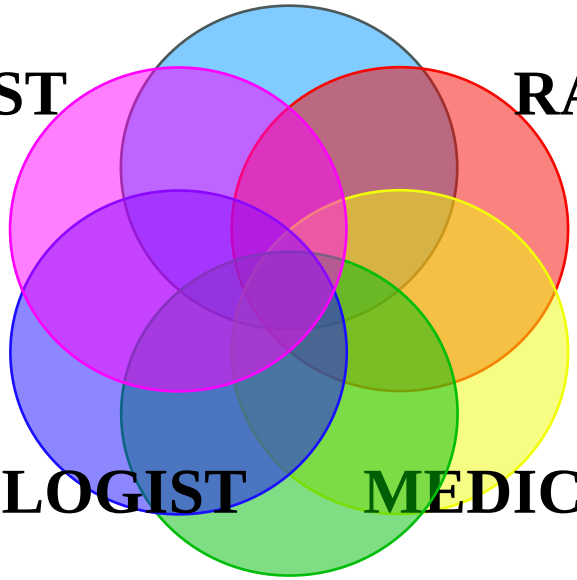
Montefiore Breast Program: Philosophy of Care

- Single standard of care clinic/private
- Compassionate patient centered individualized care by coordinated multidisciplinary team
- Prompt minimally invasive diagnostic workup and treatment
- Achieve lowest mortality with least morbidity, pain or functional change
- DE-ESCALATION of therapy; Minimal effective NOT Maximal tolerated
- Maintenance of normal appearance
- Integration of resident/student education and clinical trials

MULTIDISCIPLINARY BREAST CANCER TEAM

SURGEON

PATHOLOGIST **RADIOLOGIST**



RADIATION ONCOLOGIST **MEDICAL ONCOLOGIST**

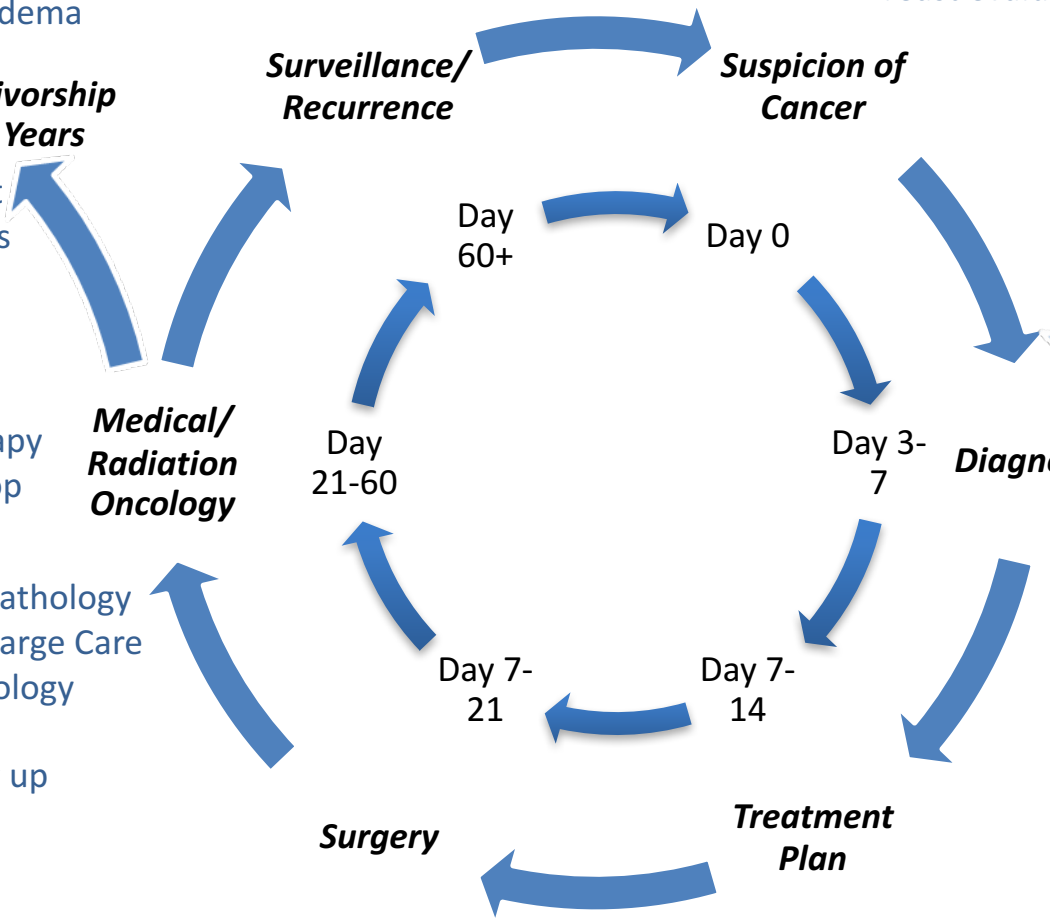
PLASTIC SURGEON

GYNECOLOGIST-GENETIC COUNSELLOR-NUTRITIONIST-PSYCHOLOGIST

Breast Cancer – Timelines of Care

Overview

Long term f/u
Rehab/PT/Lymphedema
Family screening
Nutrition
Psychosocial
- Family support
- Support groups
- Survivors day



Breast evaluation

Imaging
- Access
- Outside facility Review

Biopsy
- MRI guided

Pathology
- HER2-NEU

If Adjuvant Therapy
4-6 weeks post-op

Post-op, Surgical pathology
Coordinated Discharge Care
- Med/Rad Oncology follow-up
- Surgical follow up
- Social Services
- Nutrition
- Psychosocial
- Smoking cessation

OR Access for Surgery
OR Access for combined cases w/ Plastics
If Neo-adjuvant therapy, Chemo before surgery

Radiation Oncology
Medical Oncology
Plastic/Recon Surgery
Tumor Board – multi-disciplinary decision
Genetics consult
Genetics Testing/Results
OB/GYN Fertility consult
Psychosocial – ACS, family support, etc.
For BRCA+ patients: GYN Oncology consult

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Montefiore Multidisciplinary "DREAM" Team

- Dr. Tova Koenigsberg; Chief Breast Imaging
- Dr. Susan Klugman; Reproductive and Medical Genetics, Professor of Obstetrics & Gynecology and Women's Health
- Dr. Susan Fineberg-pathology
- Dr. Della Makower; Director therapeutic services; medical oncology
- Dr. Jana Fox; radiation oncology
- Dr. Teresa Benaquista; Program director plastic surgery
- Dr. Sheldon Feldman; Chief, Breast Surgical Oncology

Case #1: HIGH RISK/PREVENTION

HPI: 56yo healthy Askenazie jewish woman without breast symptoms: annual screening mammogram showing new 7cm area of indeterminate calcifications right breast.

Past Med Hx: G2P2, menopause 50yo, no HRT

Family Hx: breast cancer: maternal aunt(42yo) and first cousing(40yo)

P.E. No skin changes, dominant breast mass or regional adenopathy. Bra size 44D

Audience Response Question

What are the current recommendations for screening mammography?

a.annual starting at age 40

b.bienniel starting at age 50

c.I don’t know

Breast Cancer Screening - Recommendations

- ACS, ACR, and USPSTF agree that annual screening mammography beginning at age 40 will save the most lives.

- Different professional societies and organizations continue to disagree over the optimal time to initiate and discontinue screening mammography, and the optimal screening interval.

Breast Cancer Screening - Recommendations

	Comparison of Breast Cancer Screening Guidelines (January 2016)					
Recommended	**ACOG**	**ACR/SBI**	**ACS**	**AMA**	**NCCN**	**USPSTF**
Age to Start Mammograms	40	40	45 Individual choice 40-44	40	40	50
Age to Stop Mammograms	Annual as long as woman is in good health	When life expectancy is <5-7 years	When life expectancy <10 years	When life expectancy <10 years	Upper age limit not established	74
Interval	Annual	Annual	Annual 45-54; 1-2 years 55+	Annual	Annual	2 years
Tomo-synthesis (3-D Mammography)	Further study to confirm whether cost-effective replacement for digital mammography alone as first-line screening	No longer investigational; represents an advance in breast imaging	Improvement in detection, lower chance of recall	Silent	Promising; definitive studies pending	Insufficient evidence to support routine use; grade "I"
Notes		Tomosynthesis shown to improve key screening parameters compared to digital mammography	**40-44** Opportunity to begin screening; **45-54** Annual exam; **55+** 1-2 years Transition to biennial or opportunity for annual exam	Eligible at age 40, if they choose and their doctors agree; annual at 50		**40-49** Grade "C" Individual decision; **50-74** Grade "B" biennial screening; **75+** Grade "I" Insufficient Evidence

Breast Cancer Screening - Recommendations

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Breast Cancer Screening - Recommendations

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Breast Cancer Screening - Recommendations

American Cancer Society

- High Risk Women (>20% lifetime): Annual screening MRI
  - Gene mutations/syndrome
  - First degree relative with known BRCA1 or BRCA2 but have not been tested themselves
  - Chest radiation between the ages of 10-30

- Intermediate Risk Women (15-20% lifetime): Patients should consult with their physicians about possibly adding MRI screening to their yearly mammograms
  - Personal history of breast cancer
  - DCIS
  - LCIS, ADH, or ALH
  - Have extremely dense breast tissue on mammography

- How should this adjunctive screening be done?
  - NCCN Guidelines:
    - BRCA mutations carriers:
      - Begin screening annually with MRI from ages 25-29
      - Mammography and MRI ages 30-74
      - Individualized screening strategies after age 74
    - Lifetime risk >20% as determined by risk assessment tool:
      - Annual mammography and MRI at age 30

Breast Cancer Screening – Adjunctive Imaging

Detection of Breast Cancer With Addition of Annual Screening Ultrasound or a Single Screening MRI to Mammography in Women With Elevated Breast Cancer Risk

Berg WA, Zhang Z, Lehrer D, et al

- Supplemental screening ultrasound: 3.7 cancers/1000 screens
- Supplemental screening MRI: 14.7/1000 screens

JAMA. April 2012: 307(13); 1394-1404

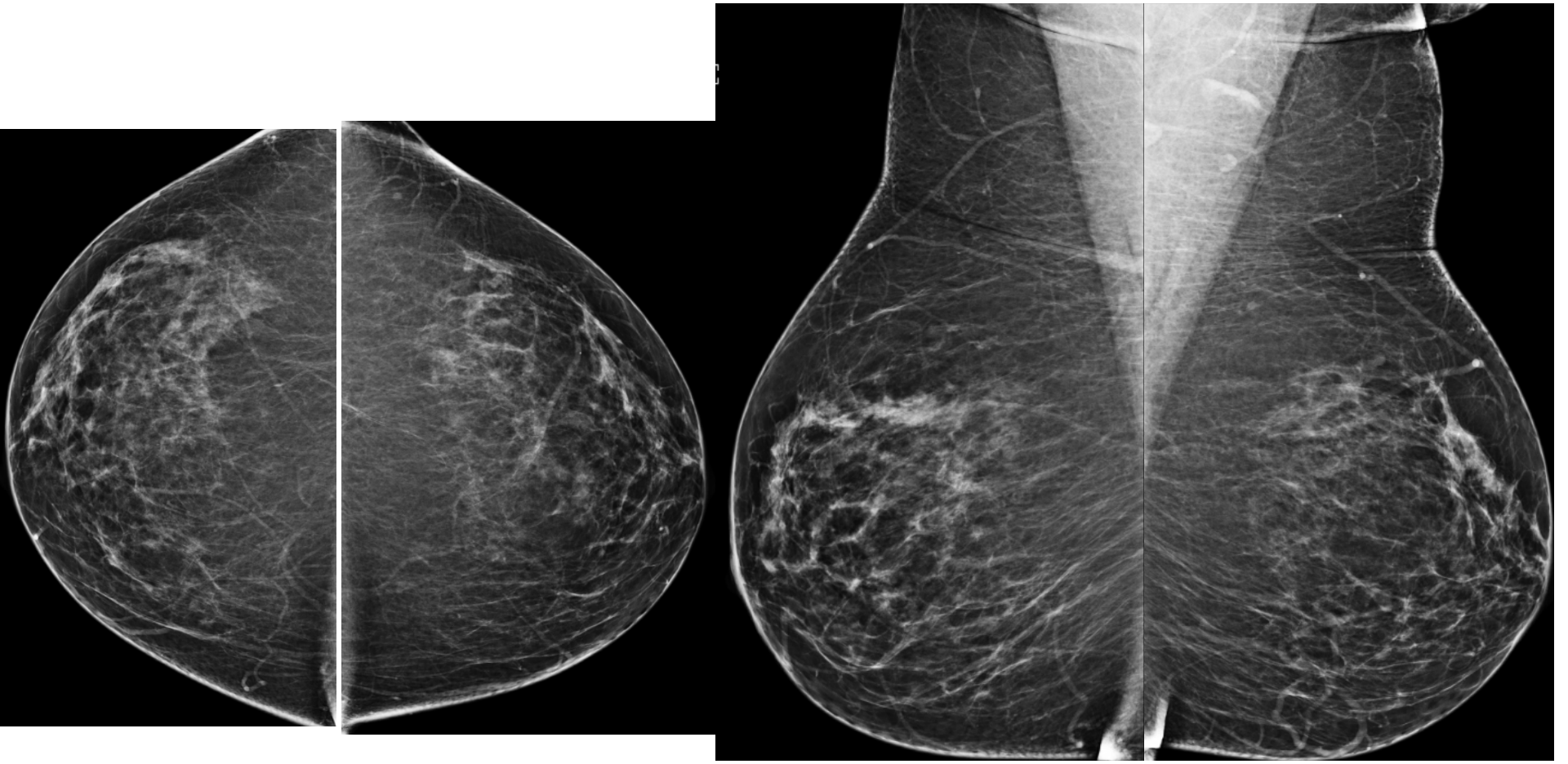
Breast Cancer Screening - Recommendations

American Society of Breast Surgeons

- Recommends formal risk assessment for women aged 40-44 (to determine who needs screening mammography)
  - > 20% lifetime risk for breast cancer: begin screening with mammography and MRI at age 40 (or younger, if clinically indicated)
  - > 15% lifetime risk: annual screening mammography at age 40 (or younger, if needed)

- When these guidelines were followed:
  - 50% of women aged 40-44 met requirements for screening mammography
  - 32% met requirement for breast MRI screening
  - 25% were eligible for genetic counseling/testing

Plichta JK, Coopey SB, Griffin ME, et al. Presented at ASBS Annual Meeting, MGH, 2016



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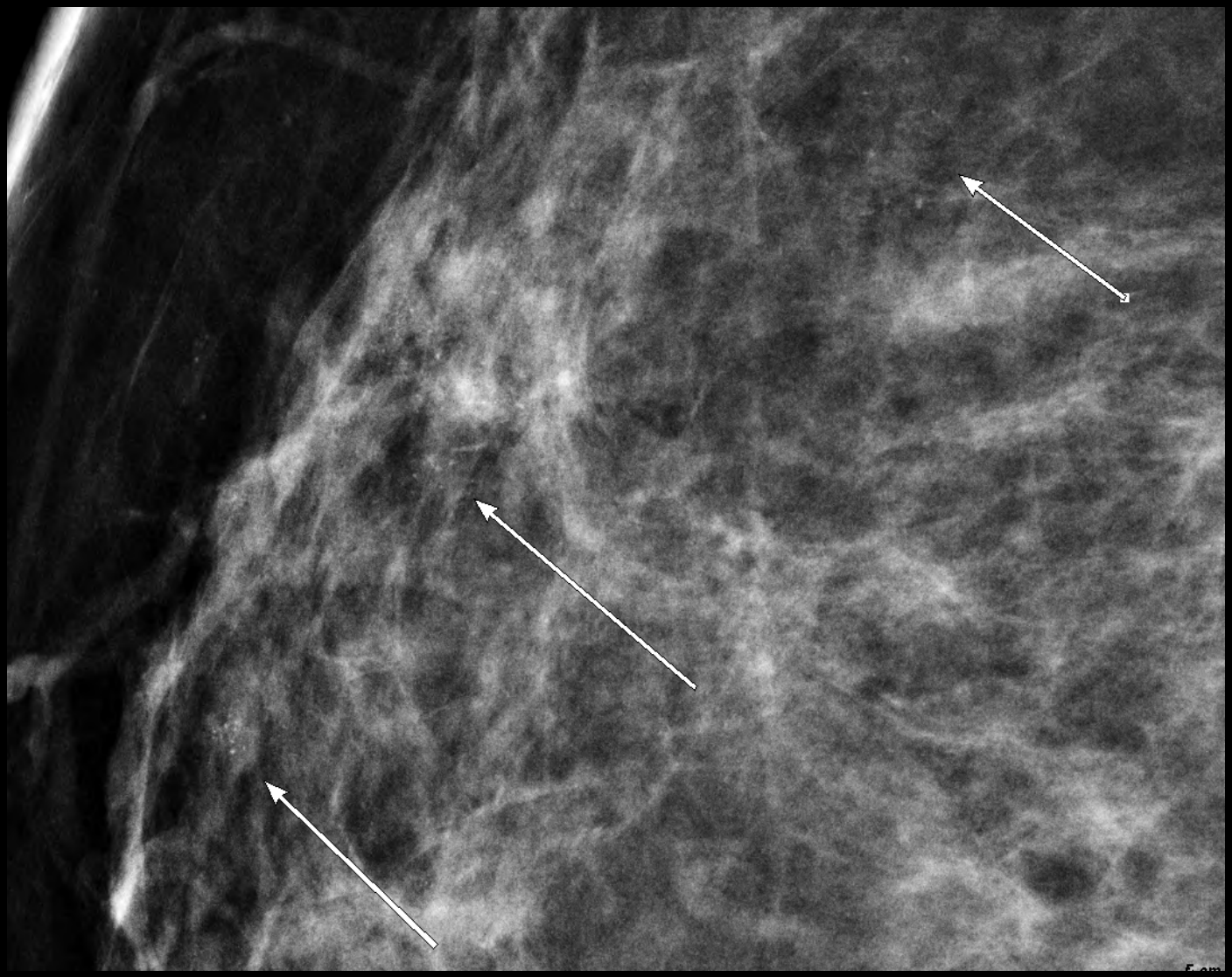

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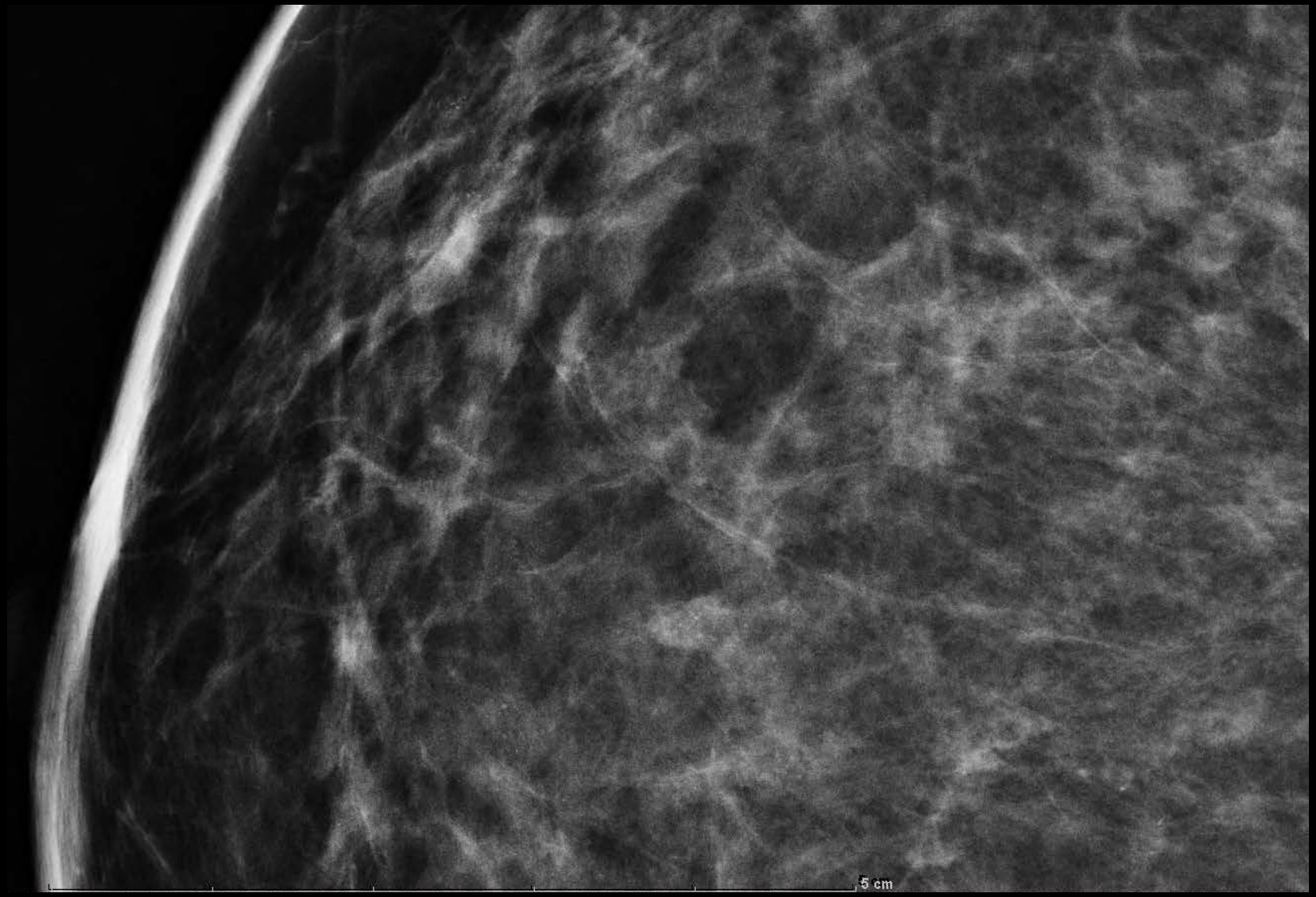

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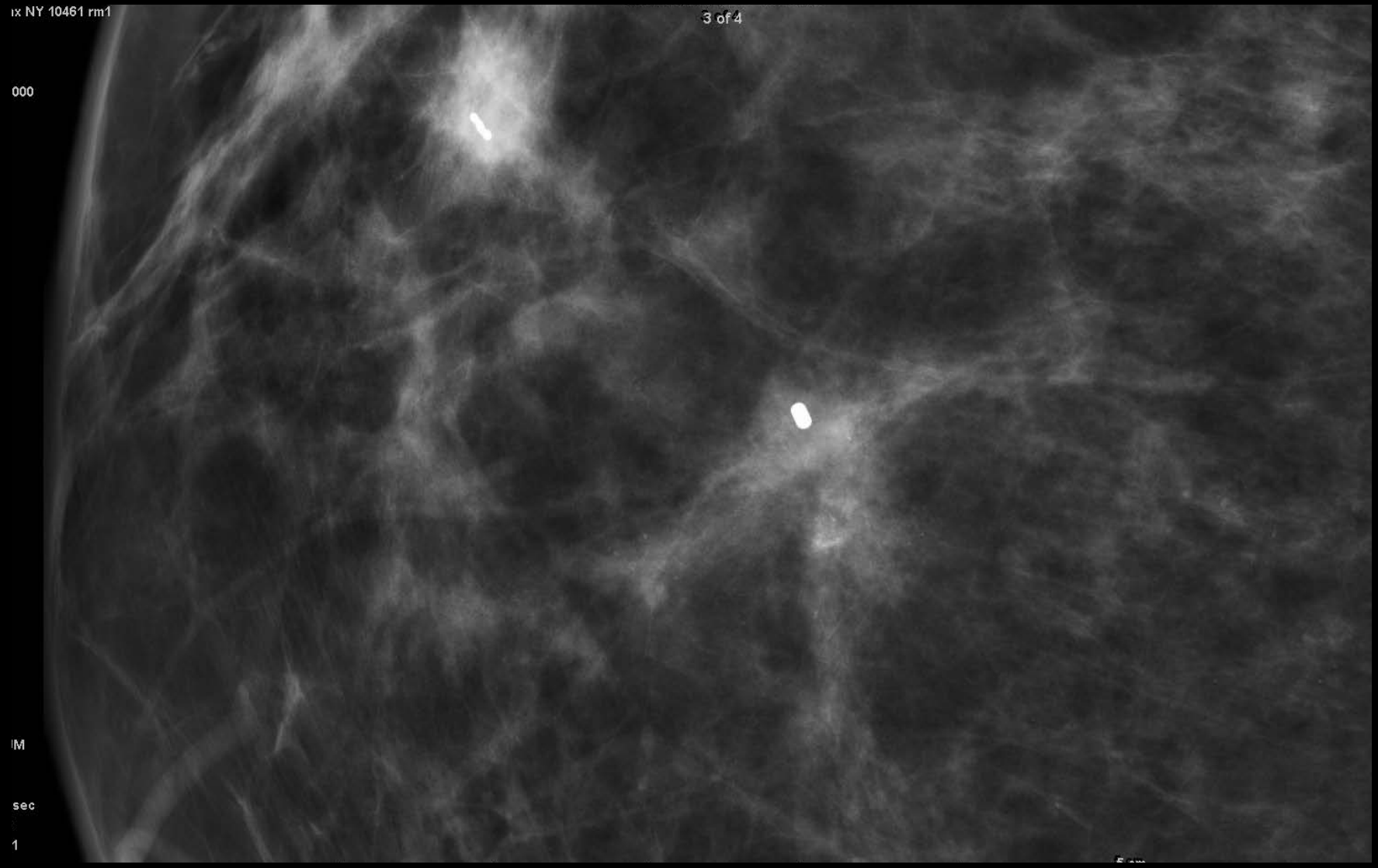

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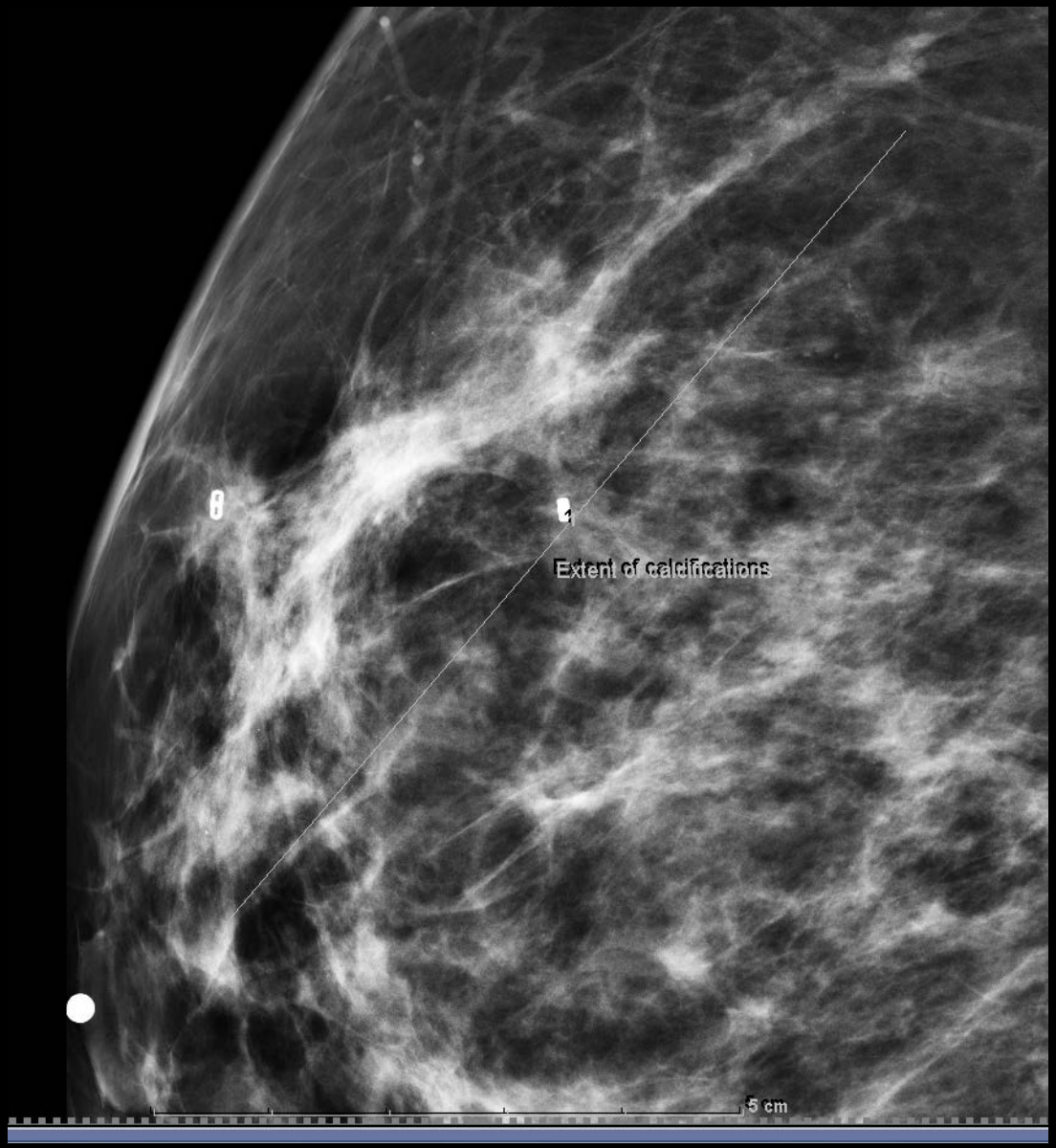
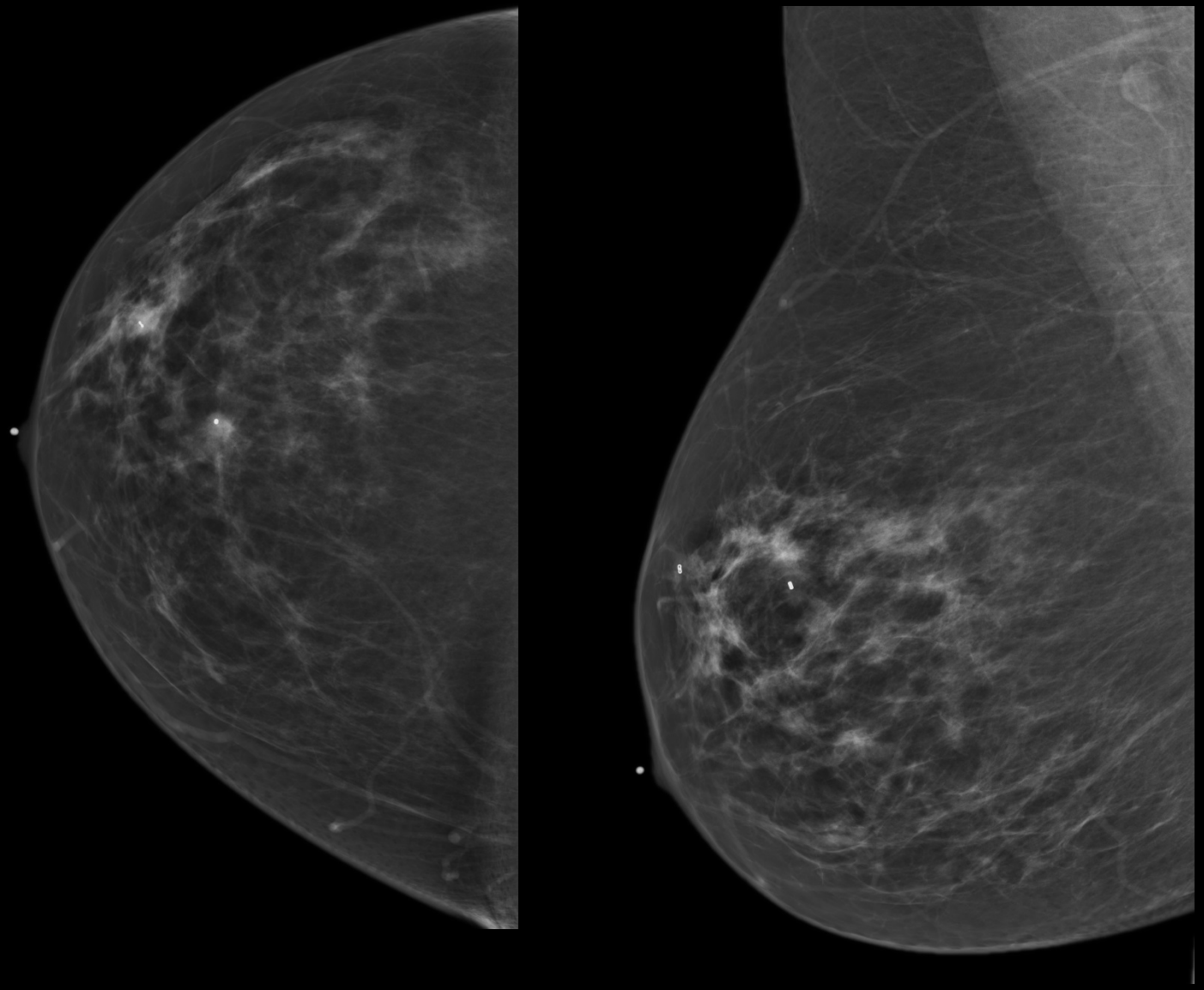
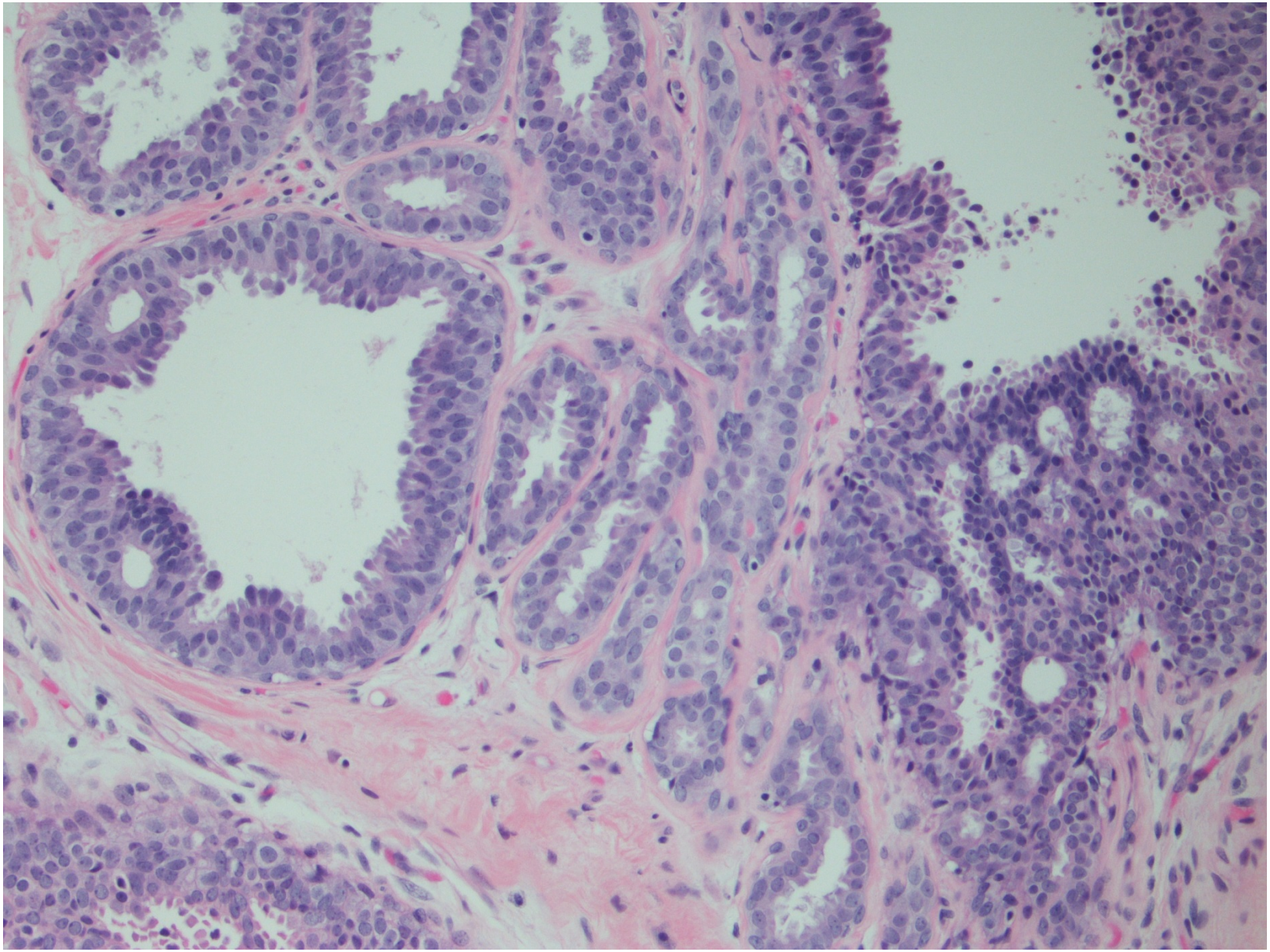


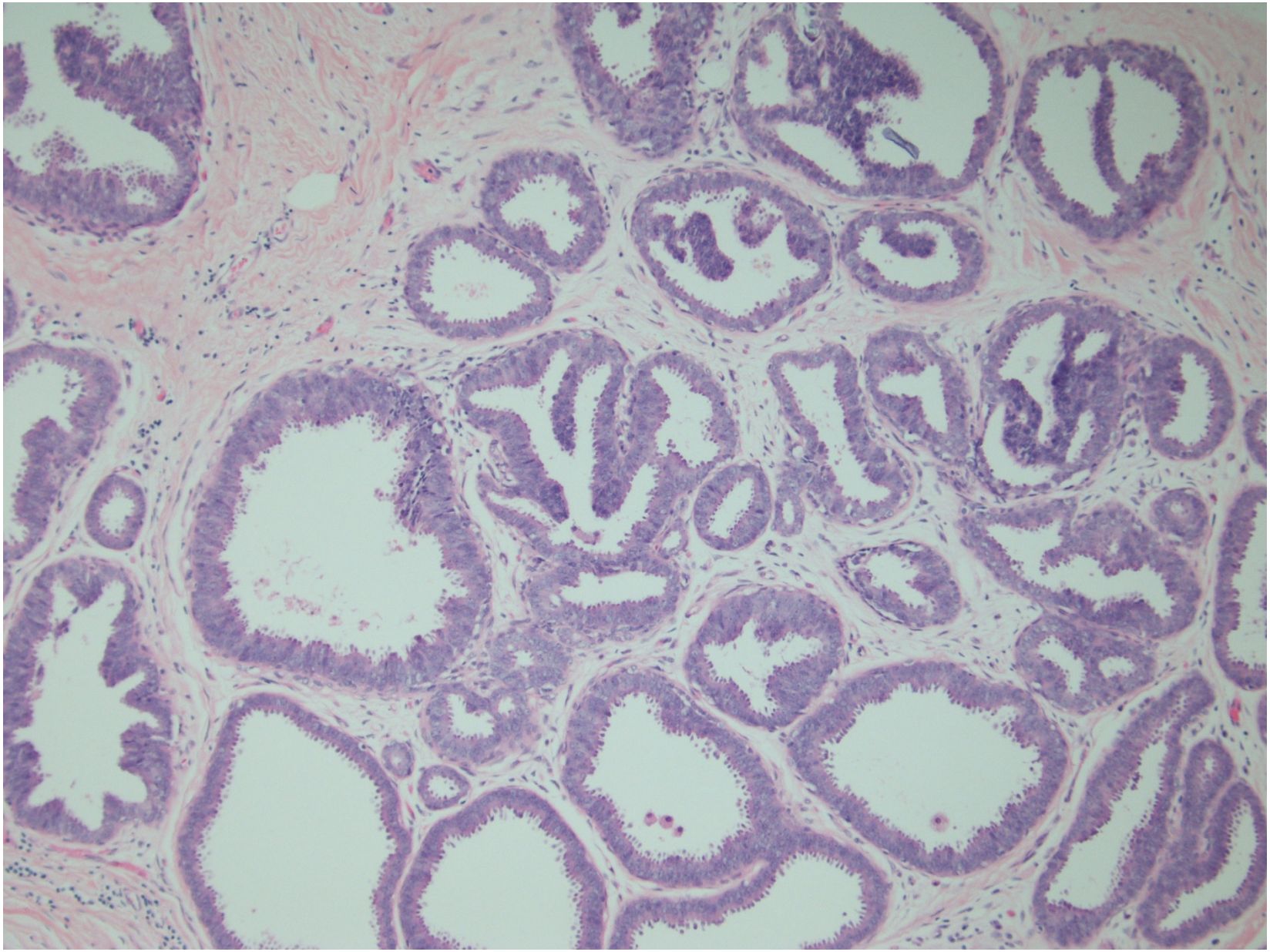
Post biopsy CC and MLO

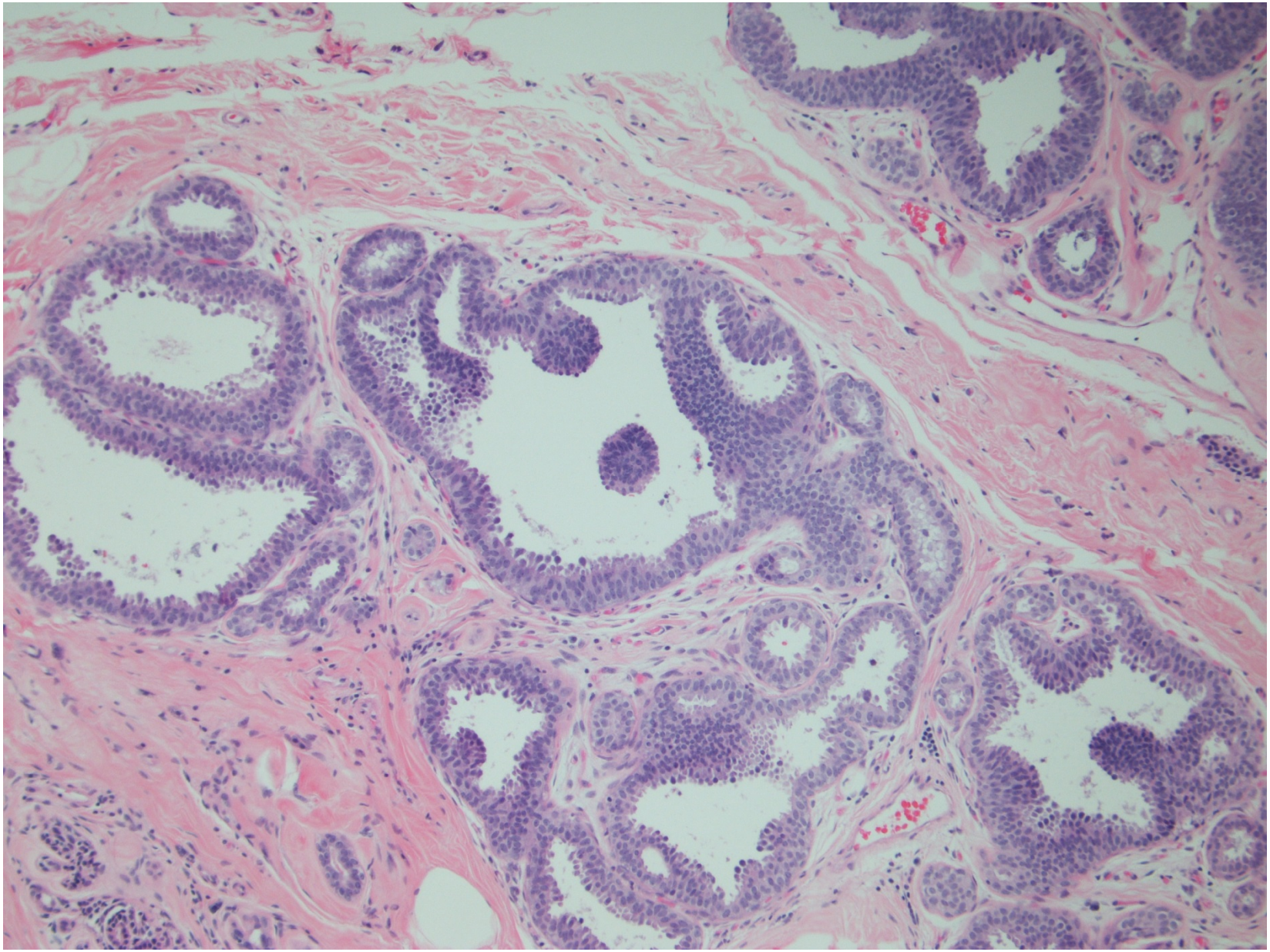


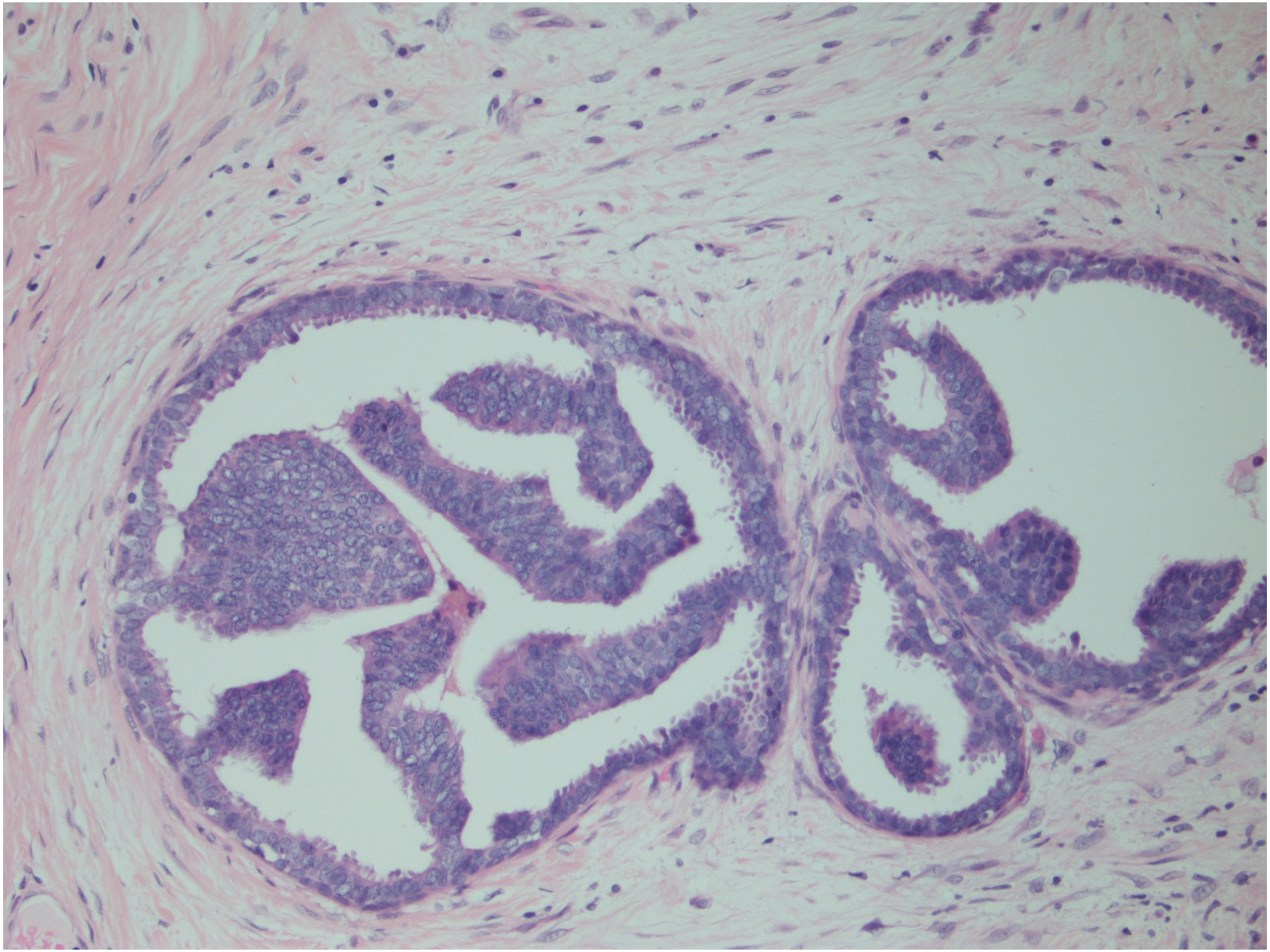
PATHOLOGY- Dr. Fineberg

- Sterotactic Core Biopsies at 2 sites:
- 9-10 o'clock 3 cm from nipple
- 12 o'clock 7cm from nipple









Consultation

Right breast,9-10 oclock , 3cm from nipple, sterotactic core biopsy

- Markedly atypical ductal hyperplasia bordering on low grade ductal carcinoma in situ (DCIS) and associated calcifications

COMMENT: Foci of markedly atypical ductal hyperplasia are present on 2 cores with a few admixed glands showing qualitative features of low grade DCIS, micropapillary type, however **quantitatively the combined foci measure about 2mm which is just at the level of /bordering on low grade DCIS**

Right breast , 12 oclock, 7cm from nipple , stereotactic core biopsy

- Markedly atypical ductal hyperplasia approaching the level of low grade DCIS and associated with calcifications

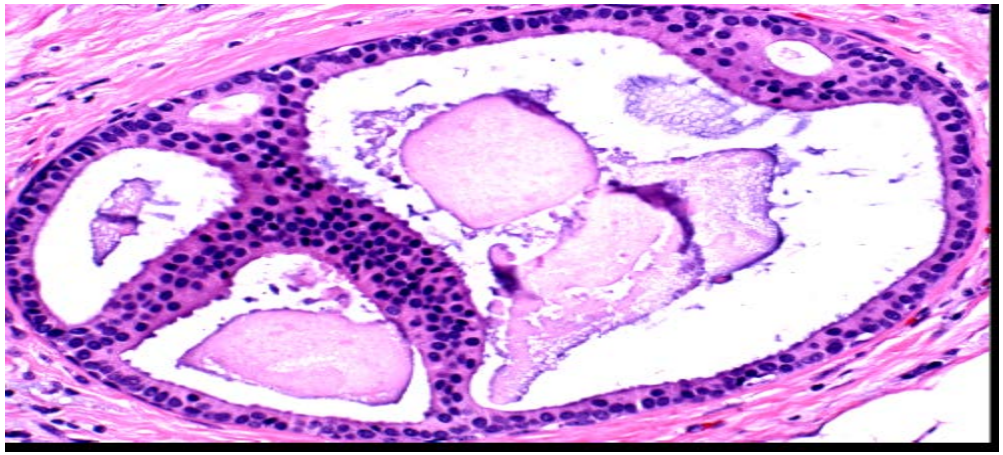
COMMENT: Multiple cores show markedly atypical ductal hyperplasia with **rare gland (<1mm) showing qualitative features of cribriform low grade DCIS . Combined with part A the size criteria for a diagnosis of low grade DCIS (over 2mm) is met , however the relationship of these two foci (one large area of DCIS vs separate distinct proliferations) can not be determined with certainty , hence their relationship can best be determined upon examination of the larger resected specimen.** All slides parts A and B reviewed with a second pathologist who concurs and case discussed iwth Dr Feldman

Outside Pathology report:

Ductal Carcinoma in Situ, low nuclear grade- Both sites

Definition of ADH

- ADH is a proliferation which fulfills some but not all criteria for a diagnosis of DCIS (Rosen's Breast Pathology page 244) (ie duct only partially involved with a proliferation with features of DCIS



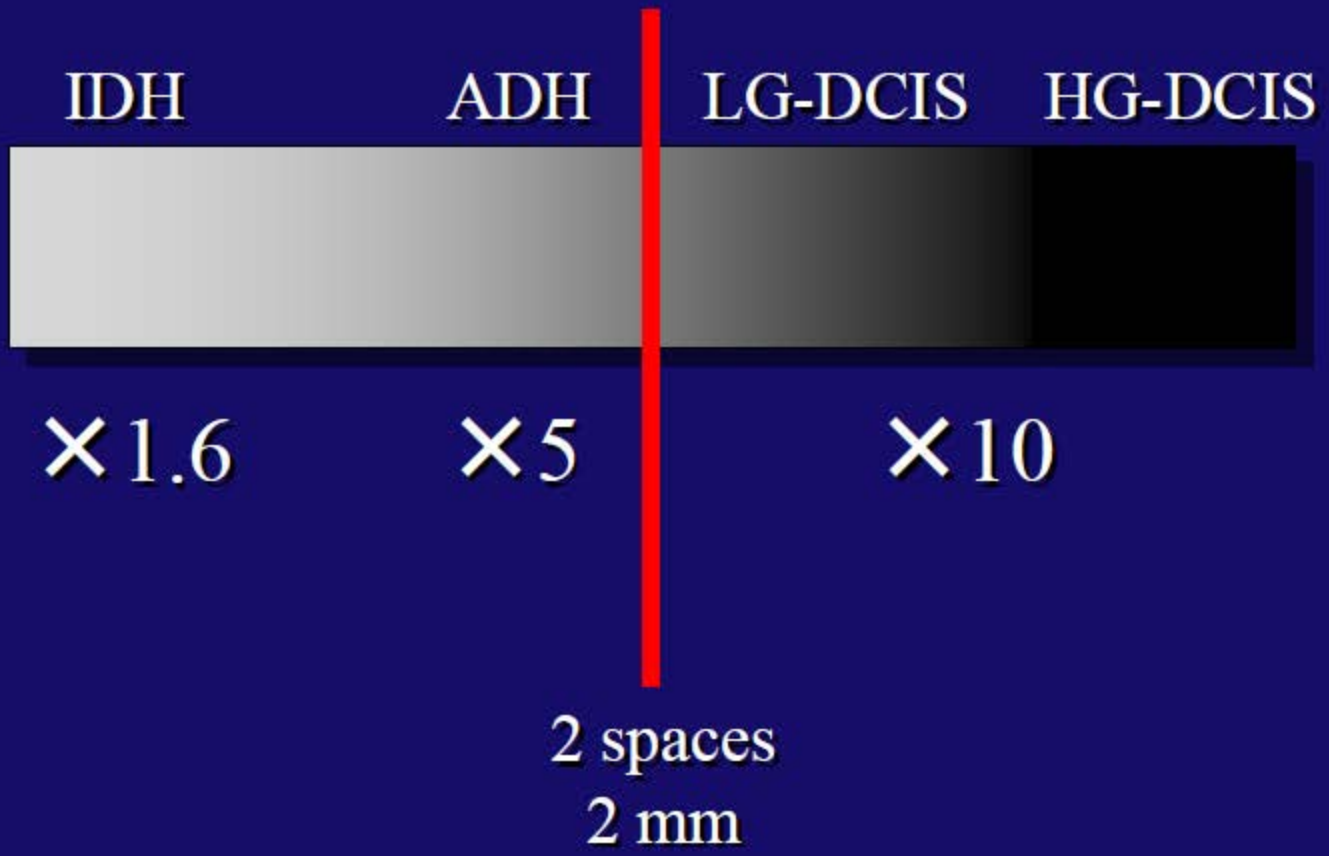
LGDCIS Criteria Vary – Quantity vs Quality

- Quantitity

1. Require atleast 2 duct cross sections fully involved by DCIS abnormality (ie cribiform pattern) – otherwise ADH
2. Dimension of involved areas showing DICS (<2mm=ADH) regardless of # of ducts involved (note Page recently increased to 3mm)

- Qualitative – Any ductal proliferation with features of DCIS regardless of size

An Arbitrary Dividing Line



Tavassoli -2mm criteria as pathologists feel hesitant to make a dx of DCIS if smaller than 2mm

Interobserver Variability (Intraductal Proliferations)

DCIS vs UDH vsADH

Standardized Criteria (24 cases)(6 pathologists)		No Standardized Criteria (17 cases)(5 pathologists)	
# of pathologist in complete Agreement	Cases (%)	# of pathologist in complete Agreement	Cases (%)
6 of 6	58	5 of 5	0
5 of 6	71	4 of 5	20
4 of 6	92	3 of 5	50

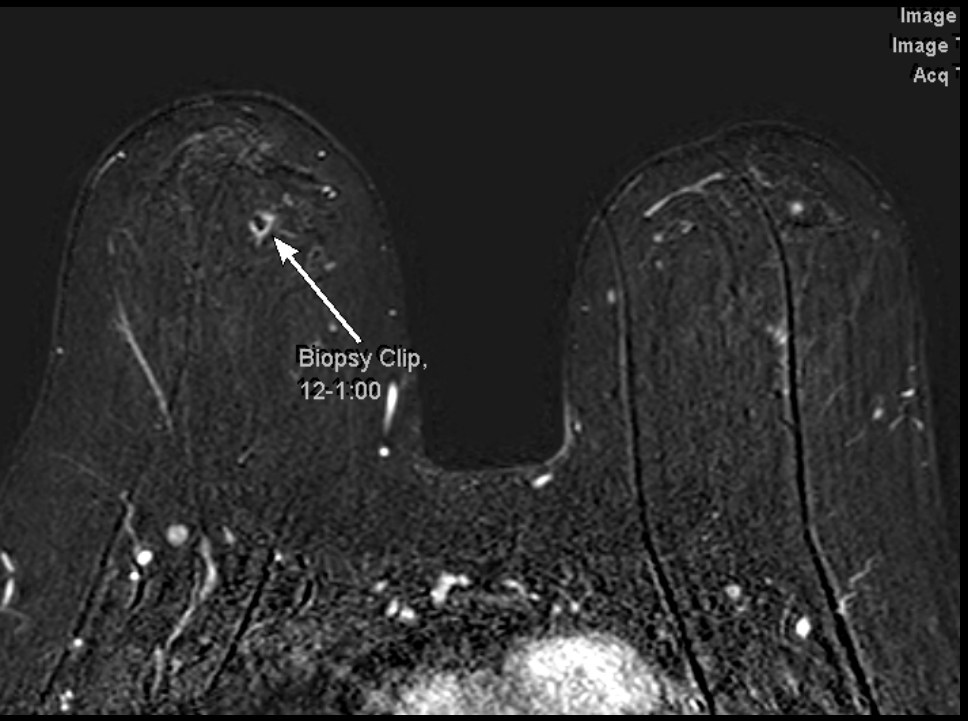
(AJCP 1993; 100:654)

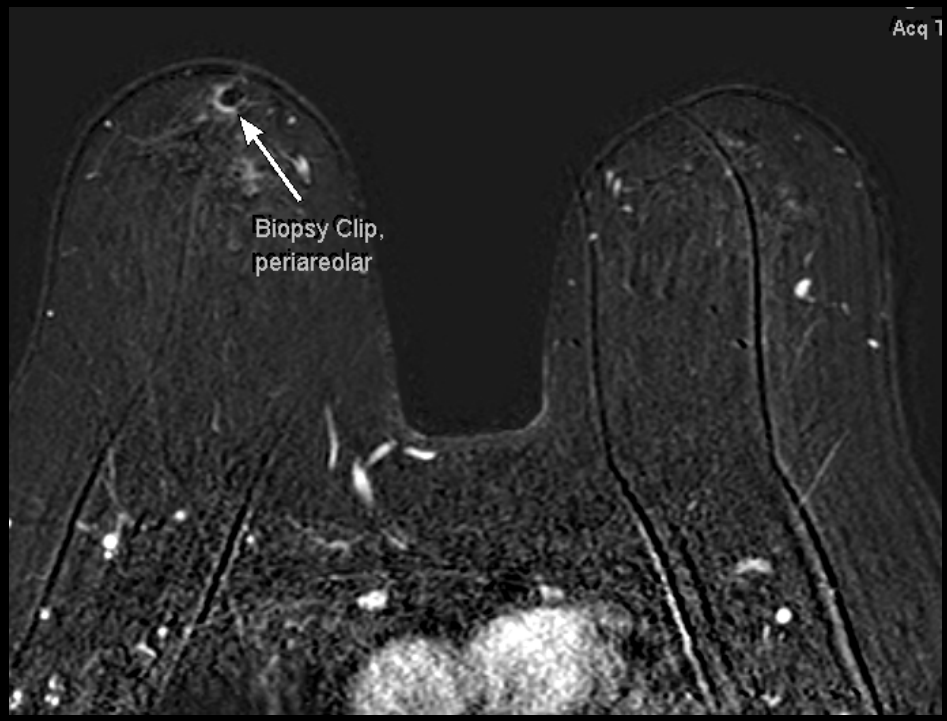
(Am J Surg Path 1991;15:209)

Tavassoli, Schnitt, Rosai, Page

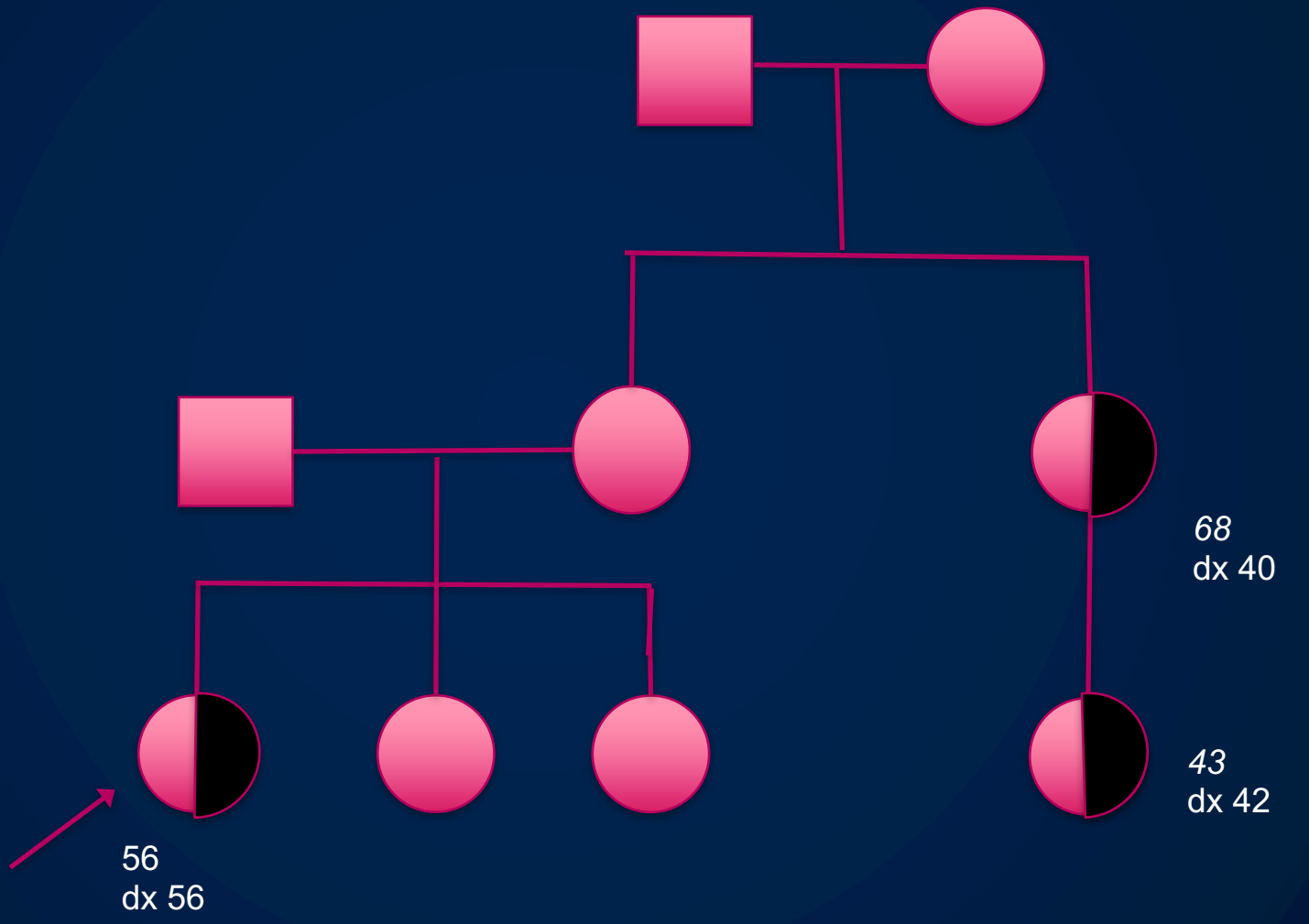
Additional workup

- Breast MRI- to be reviewed
- Genetic counseling/testing; shows Variant of undetermined significance


Biopsy Clip,
12-1:00


Biopsy Clip,
periareolar

CASE 1



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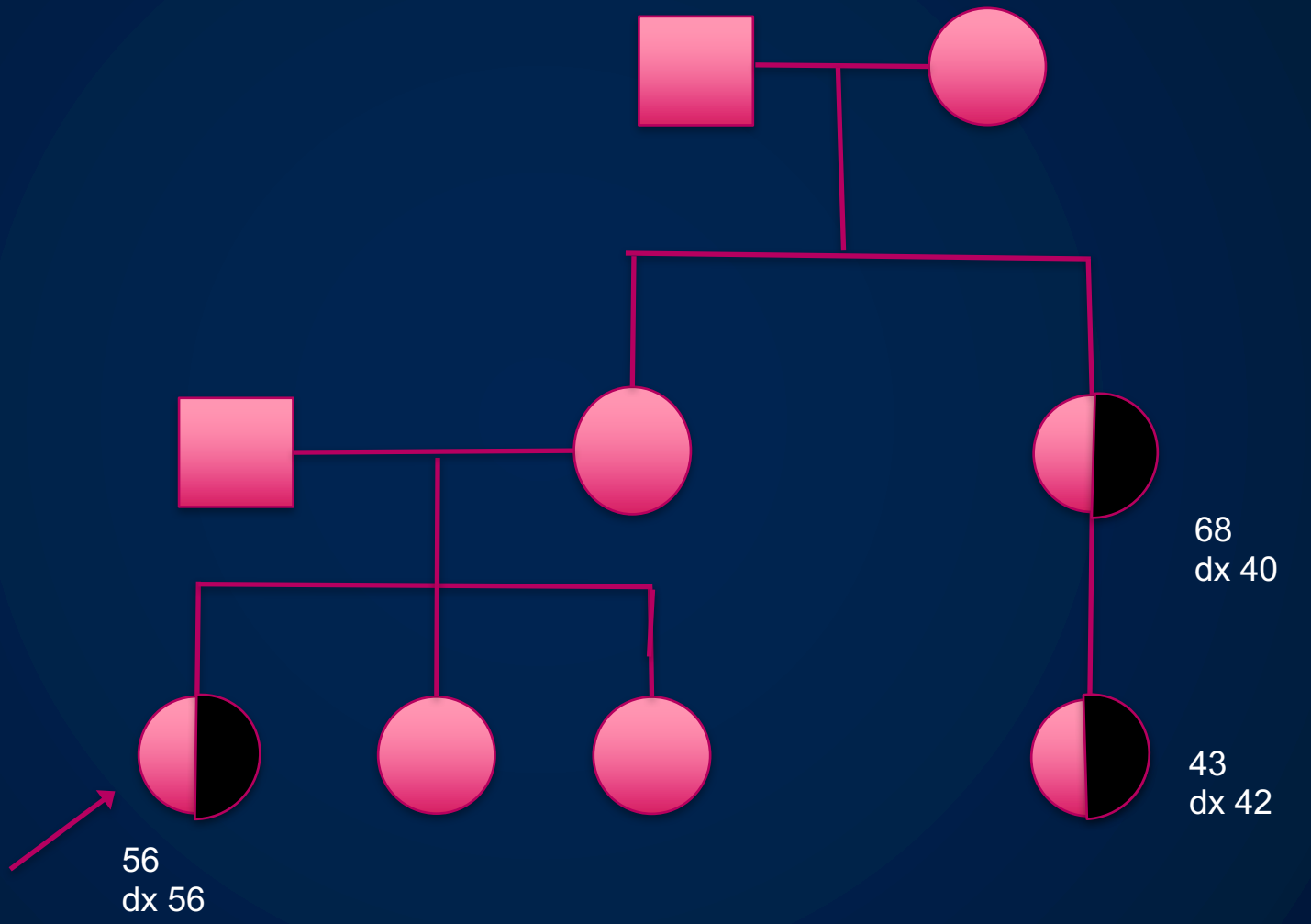
CASE 1



NO mutation - VUS

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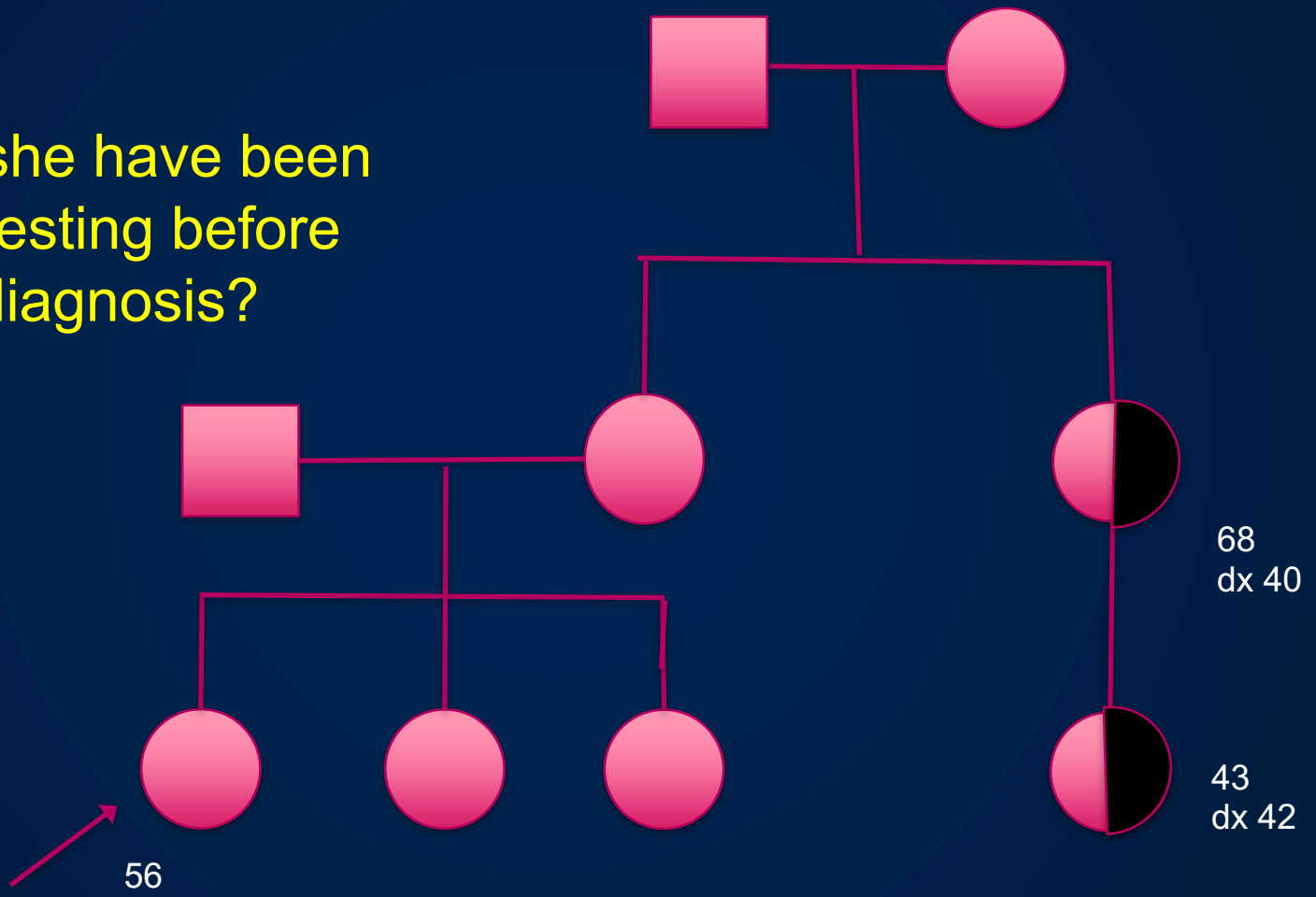
CASE 1

Should she have been offered testing before cancer diagnosis?



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CASE 1

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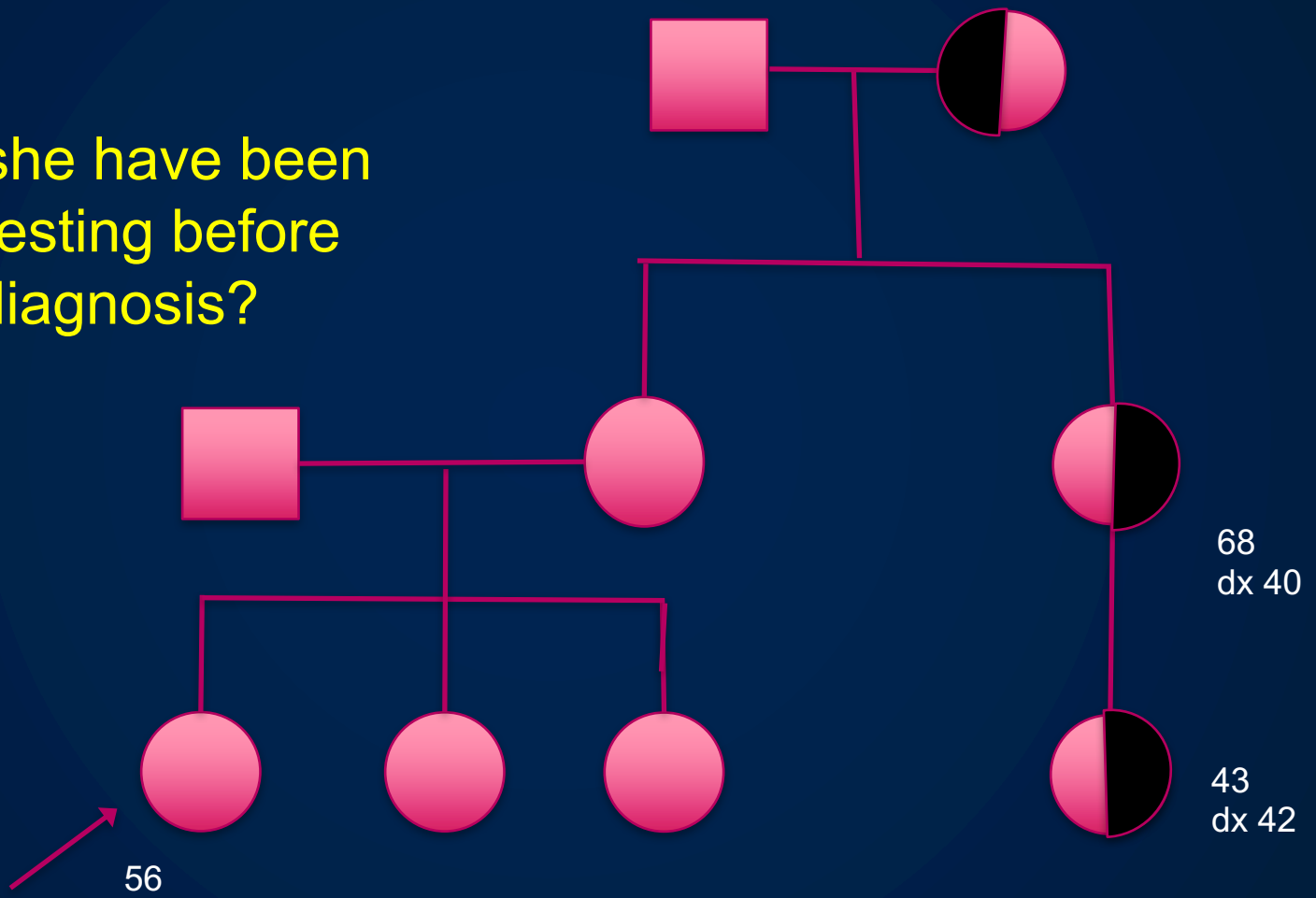

What if there was an ovarian cancer diagnosis

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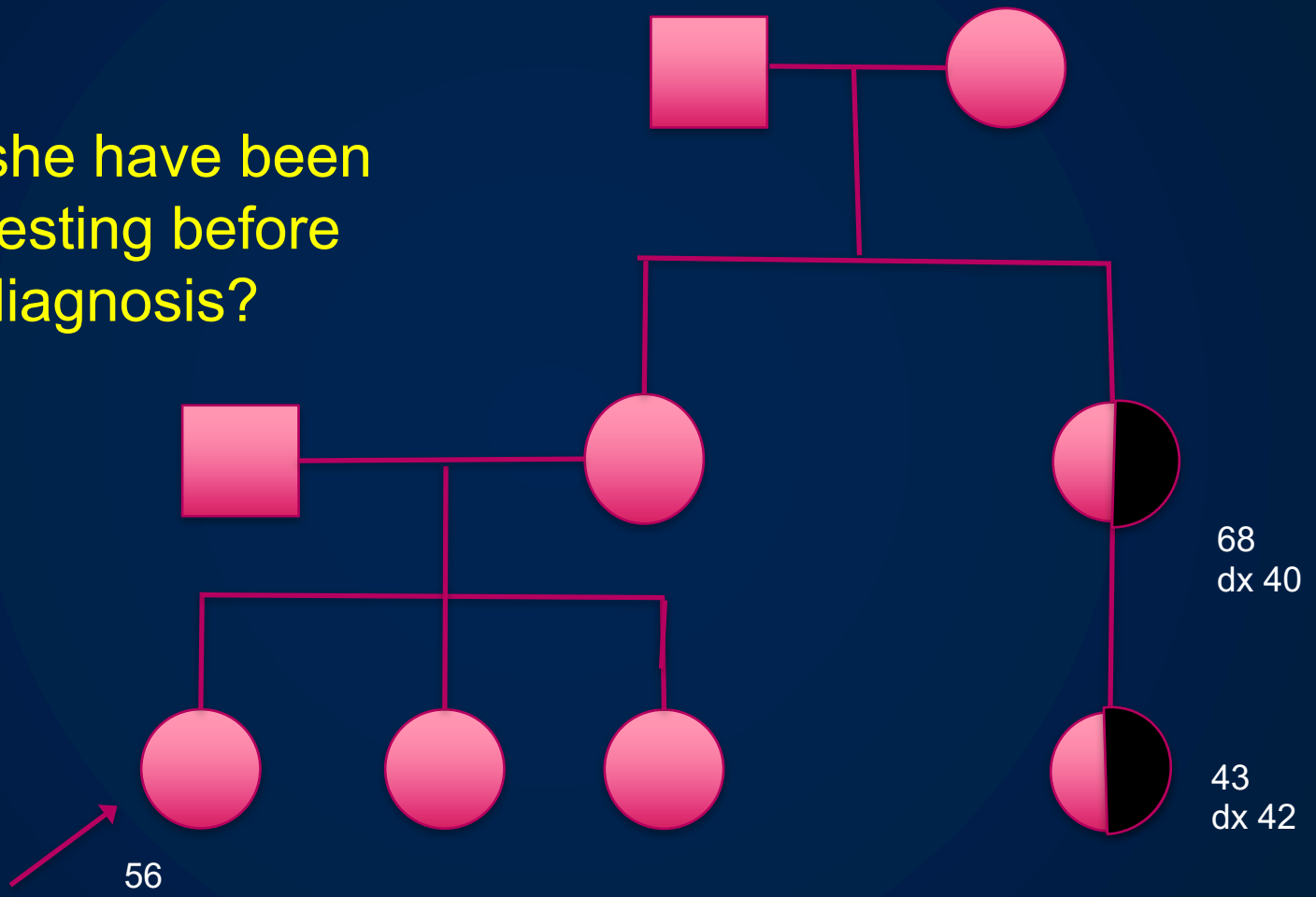
CASE 1

Should she have been offered testing before cancer diagnosis?



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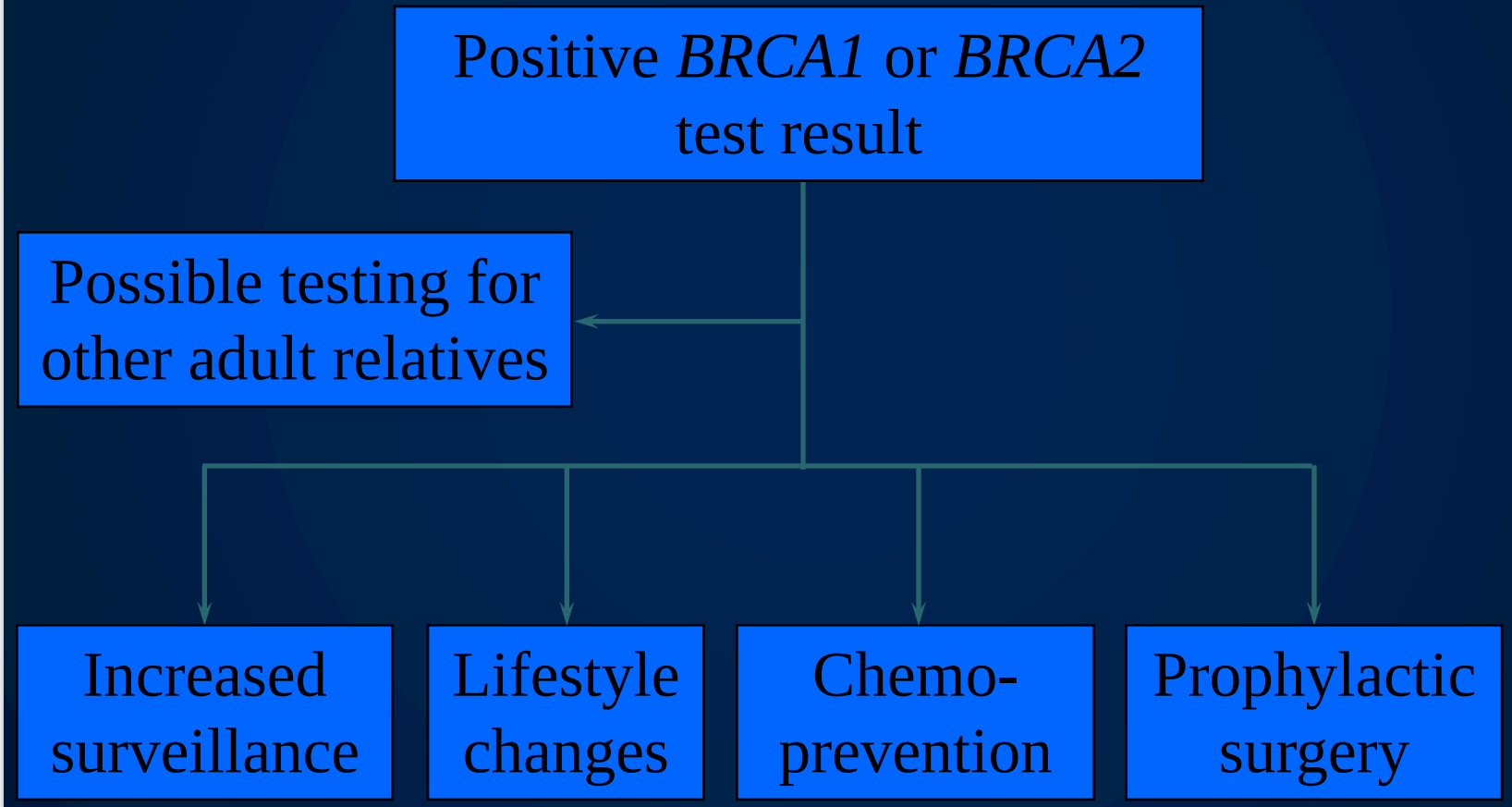
Clinical Management of BRCA Mutation-Positive Patient



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ASCO

Panel testing

- *History: BRCA1/2 (1996), Lynch (2000)*
- *Larger panels – research, clinical (2013)*
- *Offered to most patients*
- *Impossible to discuss every gene on large panels*
- *Focus on highly penetrant genes*
- *Higher percentage of VUS*

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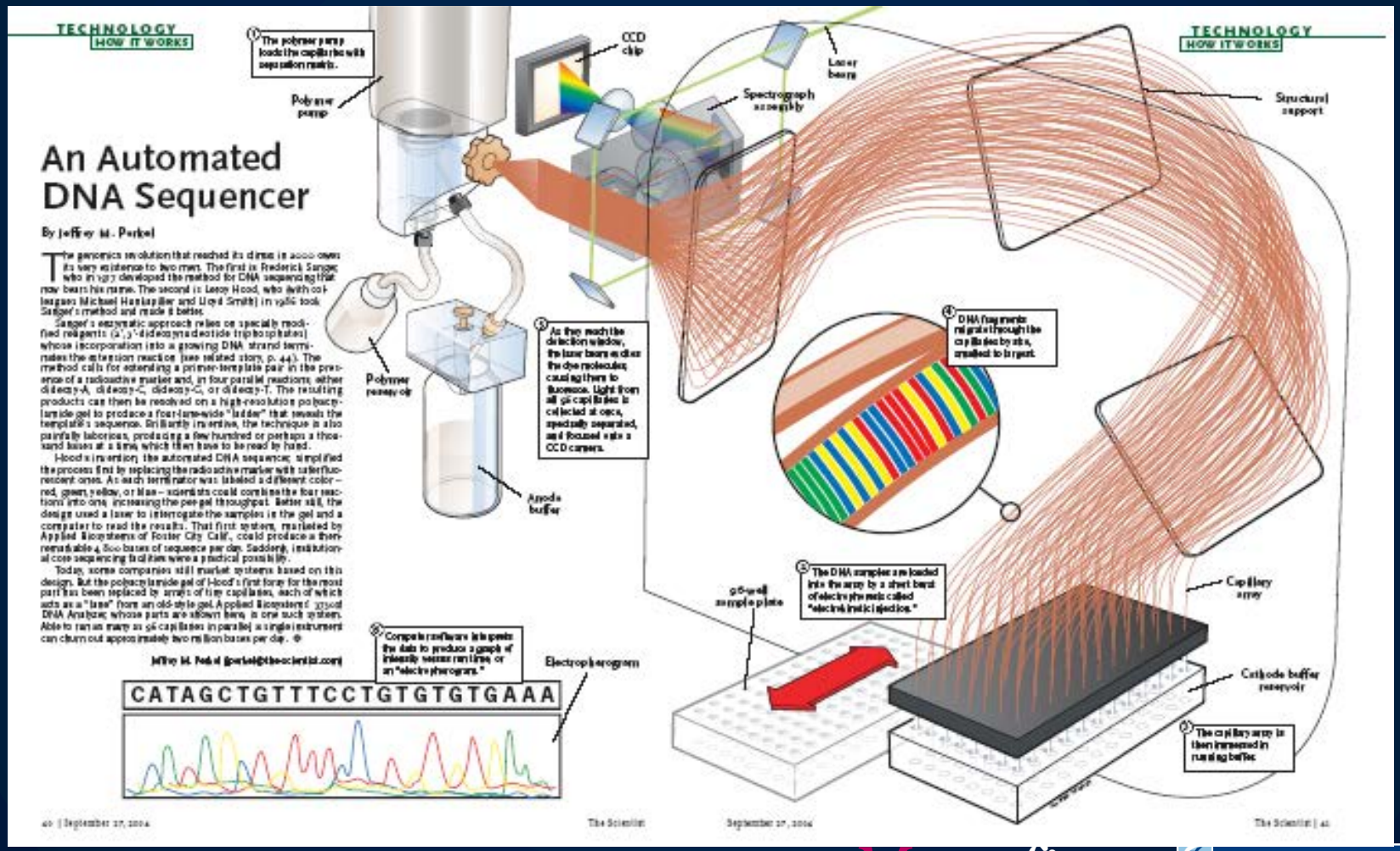
What Has Facilitated Cancer Panel Testing?



Courtesy Mayo clinic – Dr Myra Wick

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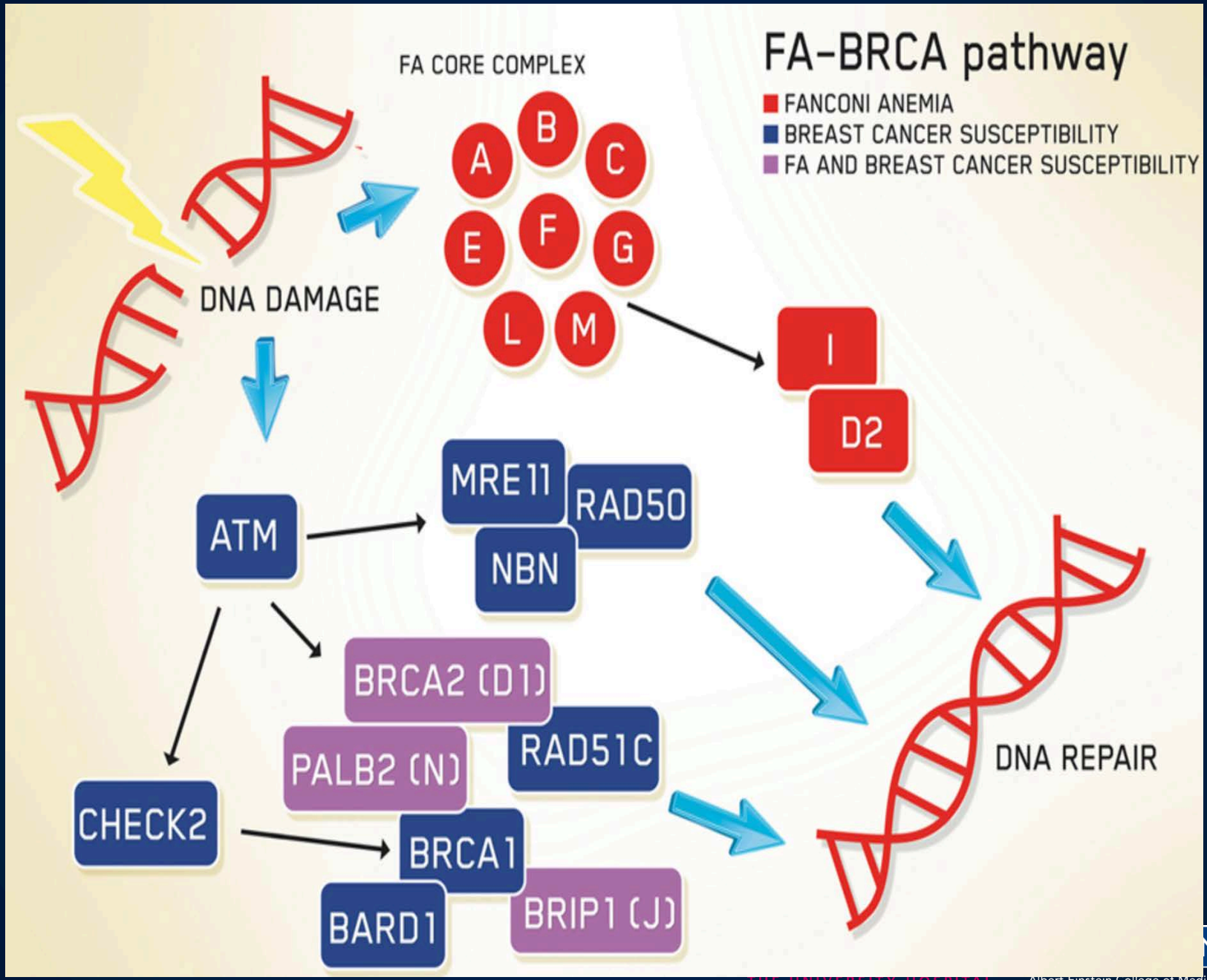
FA-BRCA pathway
FANCONI ANEMIA
BREAST CANCER SUSCEPTIBILITY
FA AND BREAST CANCER SUSCEPTIBILITY
FA CORE COMPLEX
A
B
C
E
F
G
L
M
DNA DAMAGE
I
D2
ATM
MRE11
RAD50
NBN
BRCA2 (D1)
PALB2 (N)
RAD51C
CHECK2
BRCA1
BARD1
BRIP1 (J)
DNA REPAIR

Expansion of Genetic Testing in the US

$

Patient and physician awareness (Family Hx)

Successes of Surveillance and Prophylactic Surgeries

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Current Panel Testing

Lab	Test	# of Genes	Genes
Ambry	BRCA 1 and 2	2	BRCA 1, BRCA2
Ambry	BRCAplus	6	CDH1, PTEN, TP53, BRCA1, BRCA2, PALB2
Ambry	Lynch Syndrome	5	EPCAM, MLH1, MSH2, MSH6, PMS2
Ambry	GYNplus	9	BRCA1, BRCA2, EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN, TP53
Ambry	BreastNext	17	ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, TP53
Ambry	ColoNext	17	APC, BMPR1A, CDH1, CHEK2, EPCAM, GREM1, MLH1, MSH2, MSH6, MUTYH, PMS2, POLD1, POLE, PTEN, SMAD4, STK11, TP53
Ambry	OvaNext	24	ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PMS2, PTEN, RAD50, RAD51C, RAD51D, STK11, TP53, PALB2, SMARCA4
Ambry	CancerNext	32	APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, BMPR1A, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GREM1, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, POLD1, POLE, PMS2, PTEN, RAD50, RAD51C, RAD51D, SMAD4, SMARCA4, STK11, TP53
Ambry	CancerNext-Expanded	49	APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, BMPR1A, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FLCN, MAX, MET, MITF, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PMS2, PTEN, RAD50, RAD51C, RAD51D, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, STK11, TMEM127, TP53, TSC1, TSC2, VHL, PALB2, FH, MEN1, SMARCA4, BAP1, POLD1, POLE, GREM1
Ambry	PancNext	13	APC, ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PMS2, STK11, TP53, PALB2
Ambry	RenalNext	19	MLH1, MSH2, MSH6, PMS2, PTEN, TP53, VHL, EPCAM, FLCN, TSC2, TSC1, SDHB, MET, MITF, SDHC, SDHD, SDHA, FH, BAP1
Ambry	PGLNext	12	FH, MAX, MEN1, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL
Myriad	BRACAnalysis	2	BRCA1, BRCA2
Myriad	COLARIS	6	MLH1, MSH2, MSH6, EPCAM, PMS2, MYH
Myriad	COLARIS AP	2	APC, MYH
Myriad	PANEXIA	2	BRCA2, PALB2
Myriad	myRisk	25	APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM (large rearrangement only), MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53

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Gene	Syndrome	Associated Cancers								
		BR	OV	CO	EN	ME	PA	GA	PR	OC
BRCA1	Hereditary Breast and Ovarian Cancer Syndrome (HBOC)	◉	◉				◉		◉	
BRCA2		◉	◉			◉	◉		◉	
MLH1	Lynch Syndrome / Hereditary Non-Polyposis Colorectal Cancer (HNPCC)		◉	◉	◉		◉	◉		◉
MSH2			◉	◉	◉		◉	◉		◉
MSH6			◉	◉	◉		◉	◉		◉
PMS2			◉	◉	◉		◉	◉		◉
EPCAM			◉	◉	◉		◉	◉		◉
APC	Familial Adenomatous Polyposis (FAP)/ Attenuated FAP (AFAP)			◉			◉	◉		◉
MUTYH	MUTYH-Associated Polyposis (MAP) Cancer Risk			◉						◉
CDKN2A (p16INK4A)	Melanoma-Pancreatic Cancer Syndrome (M-PCS)					◉	◉			
CDKN2A (p14ARF)	Melanoma Cancer Syndrome (MCS)					◉	◉			
CDK4						◉	◉			
TP53	Li-Fraumeni Syndrome (LFS)	◉	◉	◉	◉	◉	◉	◉	◉	◉
PTEN	PTEN Hamartoma Tumor Syndrome (PHTS)	◉		◉	◉					◉
STK11	Peutz-Jeghers Syndrome (PJS)	◉	◉	◉	◉		◉	◉		◉
CDH1	Hereditary Diffuse Gastric Cancer (HDGC)	◉		◉				◉		
BMPR1A	Juvenile Polyposis Syndrome (JPS)			◉			◉	◉		◉
SMAD4	Juvenile Polyposis Syndrome (JPS) & Hereditary Hemorrhagic Telangiectasia (HHT)			◉			◉	◉		◉
PALB2	PALB2-Associated Cancer Risk	◉					◉			
CHEK2	CHEK2-Associated Cancer Risk	◉		◉					◉	
ATM	ATM-Associated Cancer Risk	◉					◉			
NBN	NBN-Associated Cancer Risk	◉							◉	
BARD1	BARD1-Associated Cancer Risk	◉								
BRIP1	BRIP1-Associated Cancer Risk	◉	◉							
RAD51C	RAD51C-Associated Cancer Risk	◉	◉							
RAD51D	RAD51D-Associated Cancer Risk		◉							

◉ High Risk ◉ Elevated Risk

Test Outcomes

- *Positive, Negative, VUS*

- *Variant classification:*
- *Normal,*
- *Likely Benign,*
- *Unknown clinical Significance,*
- *Likely Deleterious,*
- *Deleterious*

- *Variant follow-up*

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Precision Medicine Initiative

- *Jan. 30, 2015: President Obama announces a new initiative (State of the Union address)*
- *Doctors have always recognized that every patient is unique, and … have always tried to tailor… treatments…to individuals.*

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NCCN guidelines for Panel testing (National Comprehensive Cancer Network) v1.2017

- Simultaneous analysis of sets of genes.
- Single gene testing appropriate when personal/family history suggestive of single gene disorder.
  - Panel testing may be more efficient/cost effective if phenotype associated with more than one gene/syndrome.
- Panel testing appropriate in the setting of negative (equivocal) single syndrome results, but personal/family history concerning for hereditary disorder.
- Laboratory selection is important.
- Moderate risk genes
  - Limited data, lack of screening/surveillance guidelines.
  - Assigning risks for relatives may be difficult.
  - Risk associated with moderate risk genes often similar to family history associated risk.
- Increased likelihood of identifying VUS.
- “Professional genetic expertise for pre- and post-test counseling”.

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Cancer Panels

- Next generation sequencing
- Sequence many genes at once
- Cost effective/ faster than reflex testing

- Variants – rate of 1% per gene
- Genes w/ unknown risks penetrance
- Establishing guidelines for most genes

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When to consider a panel

- *Strong FHx of HBOC – neg BRCA1/2*
- *Early onset cancer*
- *Two primaries*
- *Male breast cancer*
- *Other cancer clusters*

- *ALWAYS?*

- *Counseling, counseling, counseling*

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ASCO - guidelines

- *Multi-gene panels – germline and somatic*
- *Traditional counseling still applies (mutations, insurance, tests not informative, residual risk, psychological implications, research, disclosure of results, family)*
- *Consent: difficult - batched genes, must discuss VUS, reproductive and family implications*
- *mutations – consider surrogate to receive information if patient unable*

Robson et al, J Clinical Oncol Nov2015

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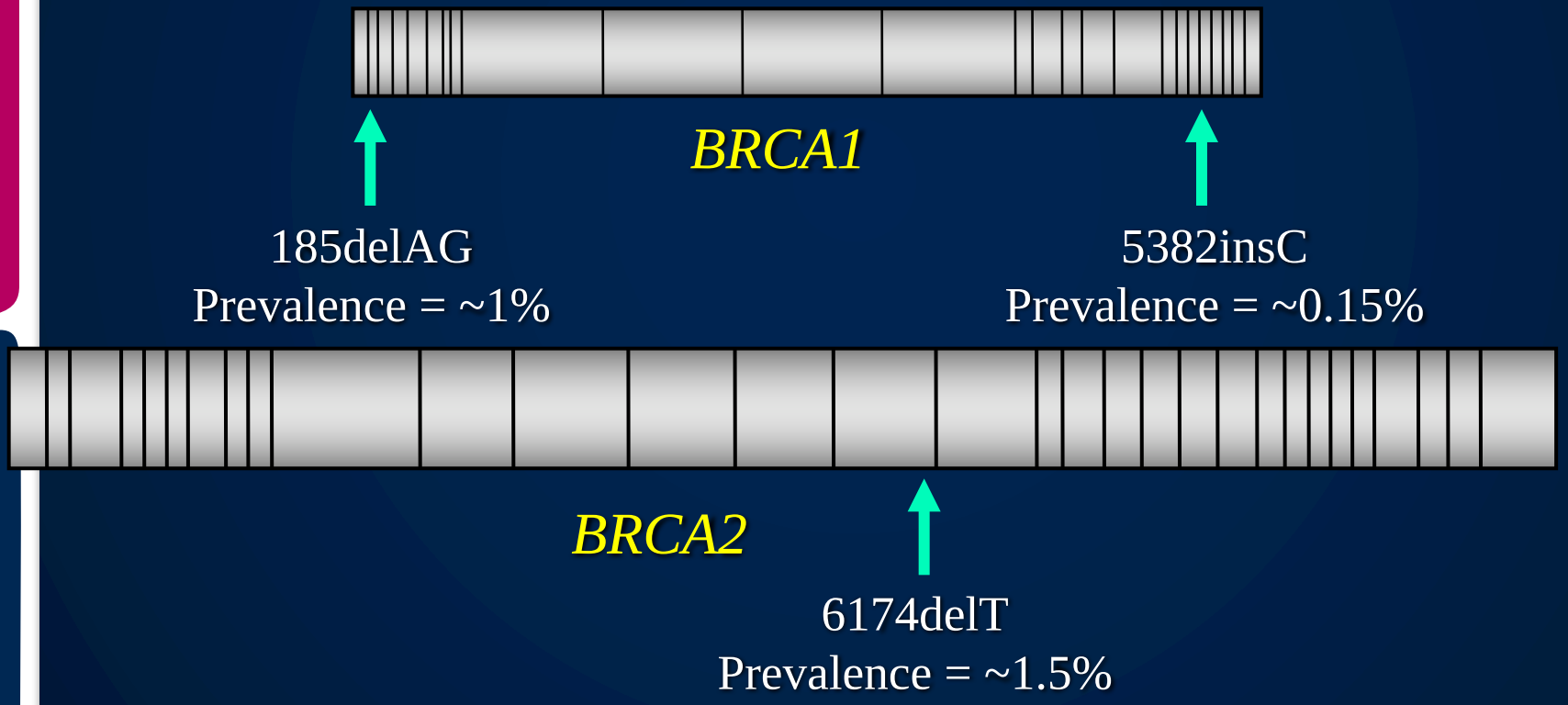
Ethical Issues: Genetic Testing

- Confidentiality/Privacy
  - Preserve other family members' confidentiality when documenting family history
- Sharing information with at-risk relatives
  - What if patient refuses?
  - Positive results on one family member suggest risk in others without their consent
- Potential insurance, employment, social discrimination

  (GINA 2008 Federal Law)

BRCA1 and BRCA2 Mutations in the Ashkenazi Jewish Population



Roa BB et al. *Nat Genet* 14:185, 1996
Oddoux C et al. *Nat Genet* 14:188, 1996
Struewing JP. *N Engl J Med* 336:1401, 1997

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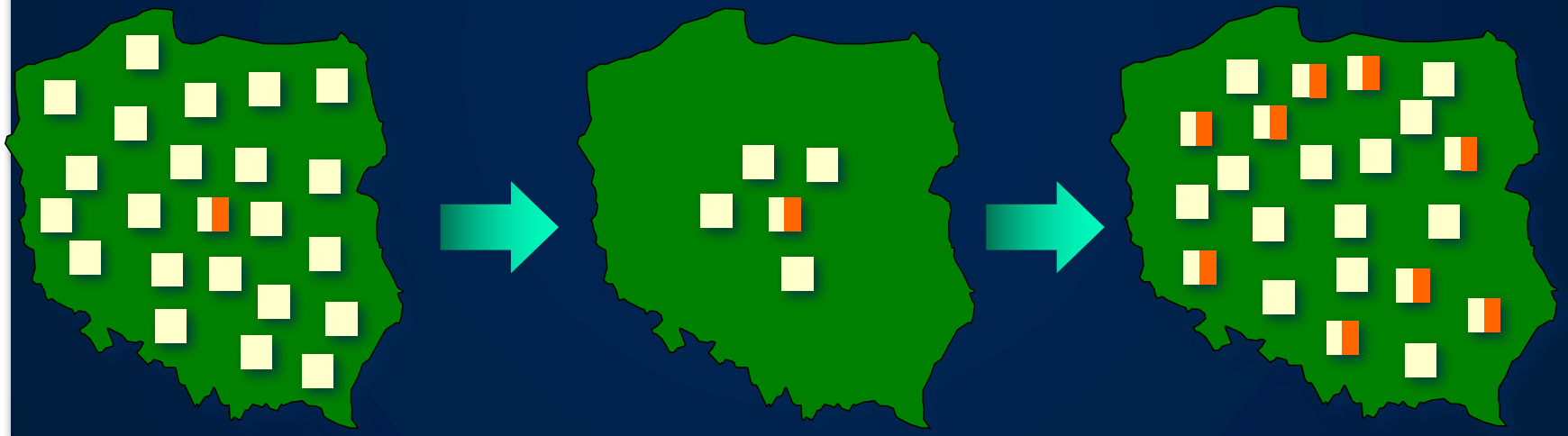
Founder Effect

A high frequency of a specific gene mutation in a population founded by a small ancestral group



Original population

Marked population decrease, migration, or isolation

Generations later

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BRCAcommunity initiative

- *Started by Program for Jewish Genetic Health*
- *Community asking for low cost testing for Ashkenazi Jews who have a 1/40 carrier rate (general population 1/350)*
- *Patients separated into high risk and low risk to carry a mutation. High risk, standard of care session. Low risk group session*
- *Carriers identified in both groups, 35% of high risk patients identify themselves as low risk (mother with breast cancer, 38% of patients who qualified for testing by NCCN guideline never had a provider discuss genetic counseling or testing*
- *$100 fee attractive*
- *Also able to use the $100 for high risk Medicare patient who does not have cancer and would not otherwise be covered*

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THEMES

- *Patients and providers do not realize that Ashkenazi Jews have a much lower threshold for BRCA testing.*
- *36% of patients had a mother with breast cancer and did not feel they were high risk*
- *38% of patients who were classified as high risk had never been recommended for testing by any health care provider*

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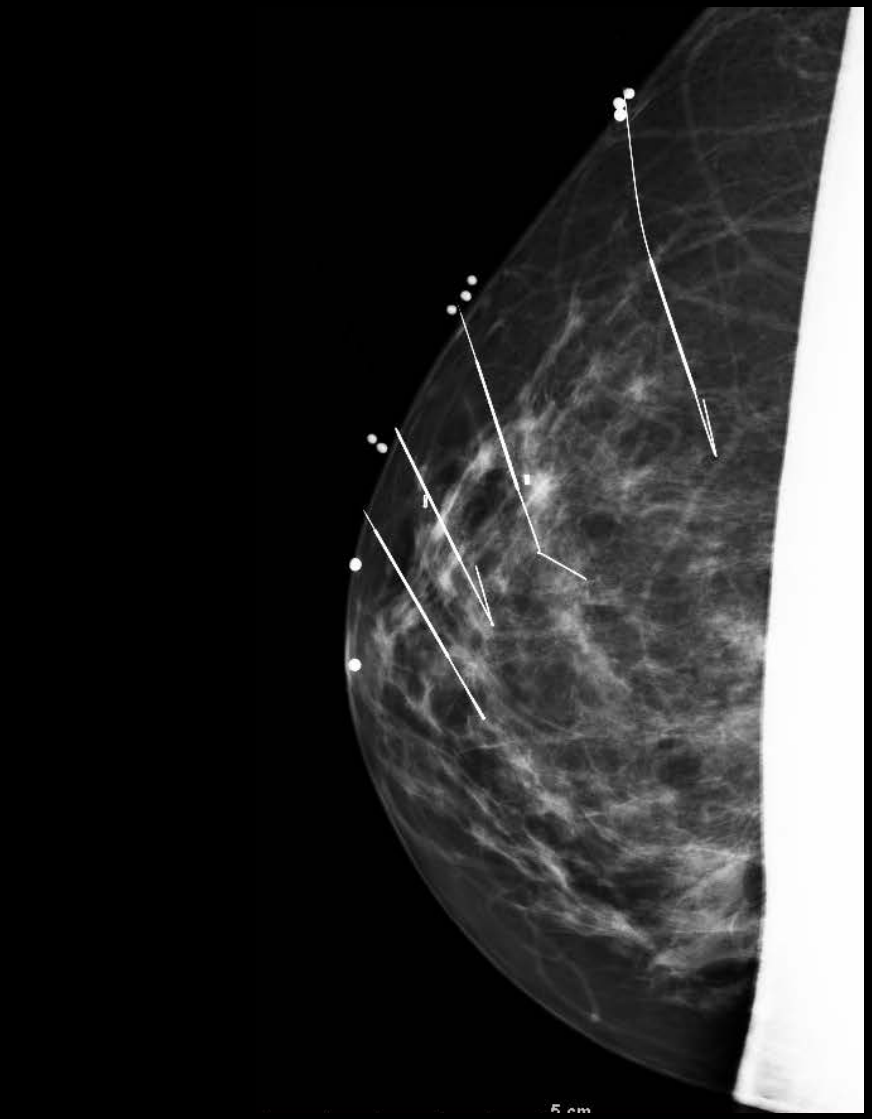
Audience Response Question

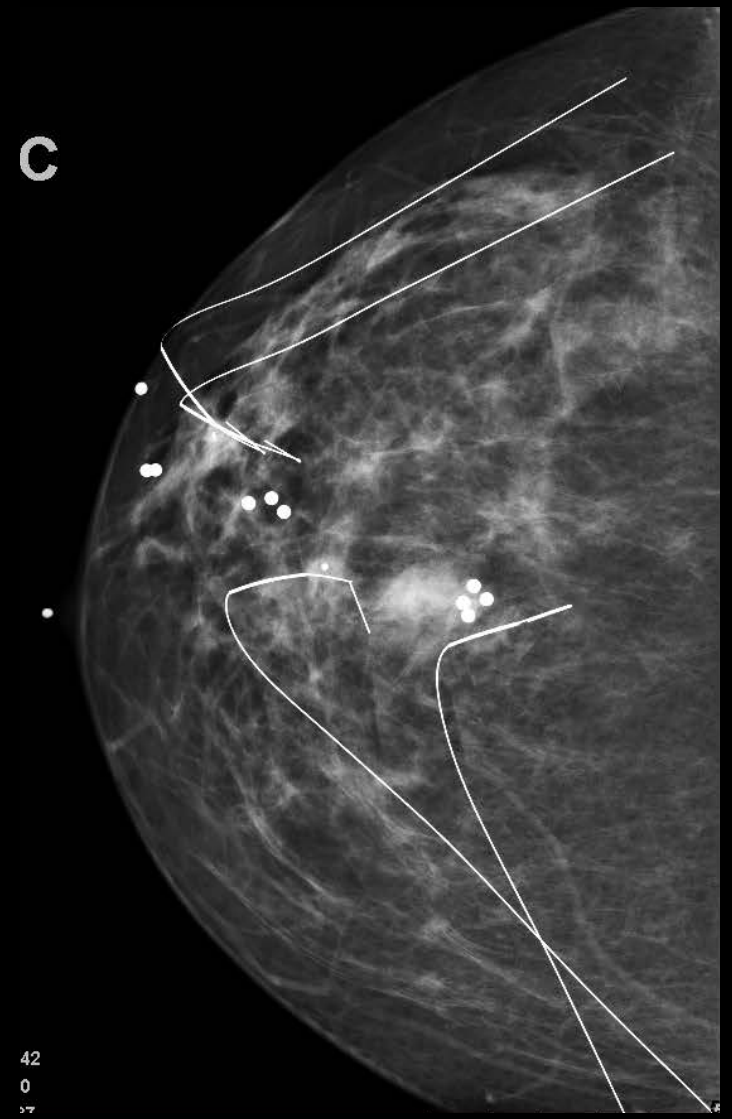
Which of the following is the best approach for this patient?

a. Bilateral nipple sparing mastectomy with DIEP flap reconstruction
b. Bracketed partial mastectomy(lumpectomy) with oncoplastic mastopexy
c. No surgery and active surveillance with anti-estrogen meds

Clinical Course

Patient underwent bracketed partial mastectomy(lumpectomy) with oncoplastic mastopexy

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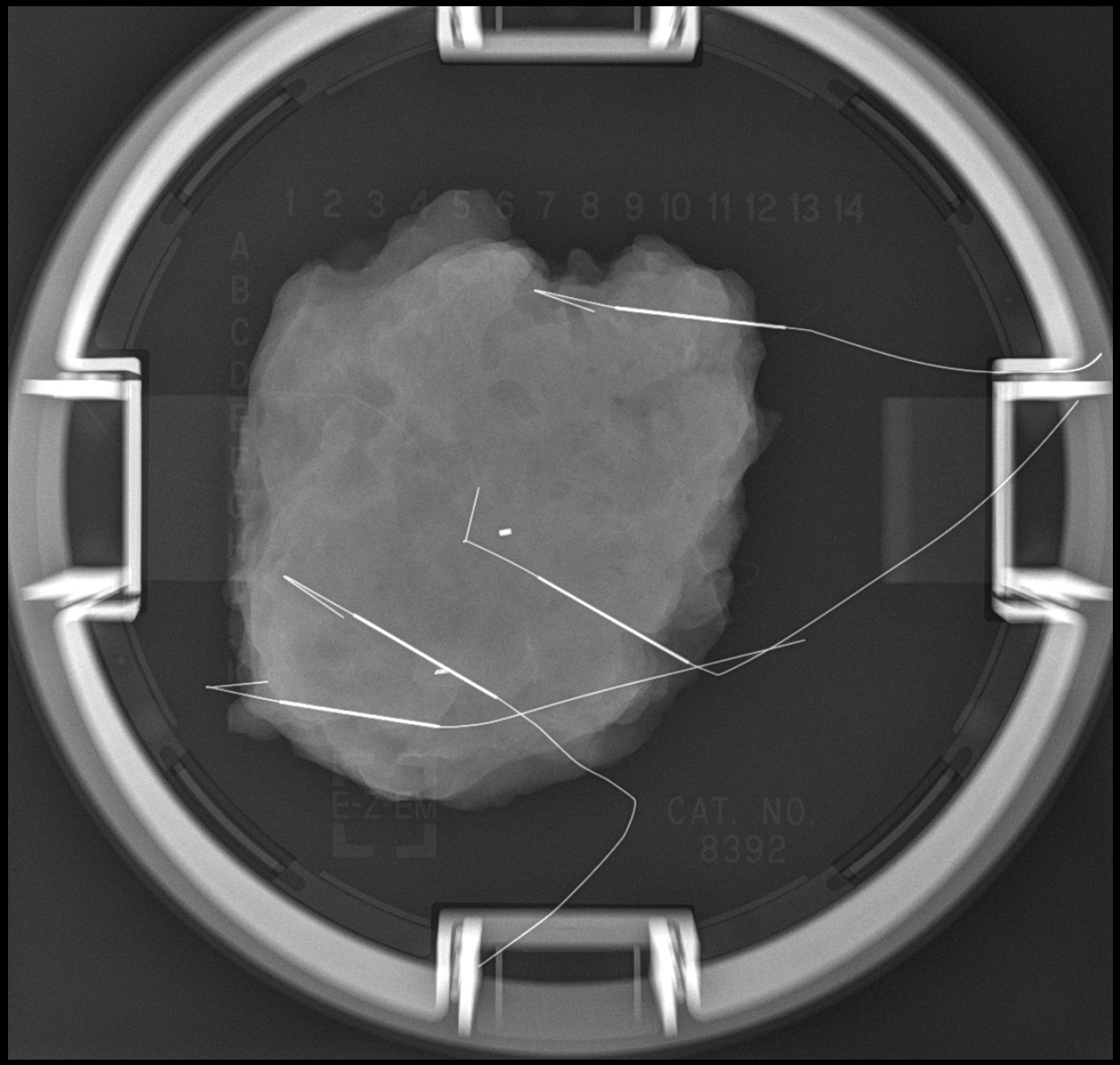
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Seed Localization vs. Needle Localization

Advantages

- I-125 seed can be placed up to 5 days before surgery and allows uncoupling of the radiology and surgery schedules
  - The seed has a 60 day half life
  - 27-keV gamma radiation emission peak
- Does not interfere with Tc – 99m that is used for SLN mapping
  - 140 keV gamma radiation emission peak
- Offers more flexibility than wire for placement of the seed and surgical incision site
- Improved patient satisfaction
- No risk of wire dislodgement or migration

Seed Localization vs. Needle Localization

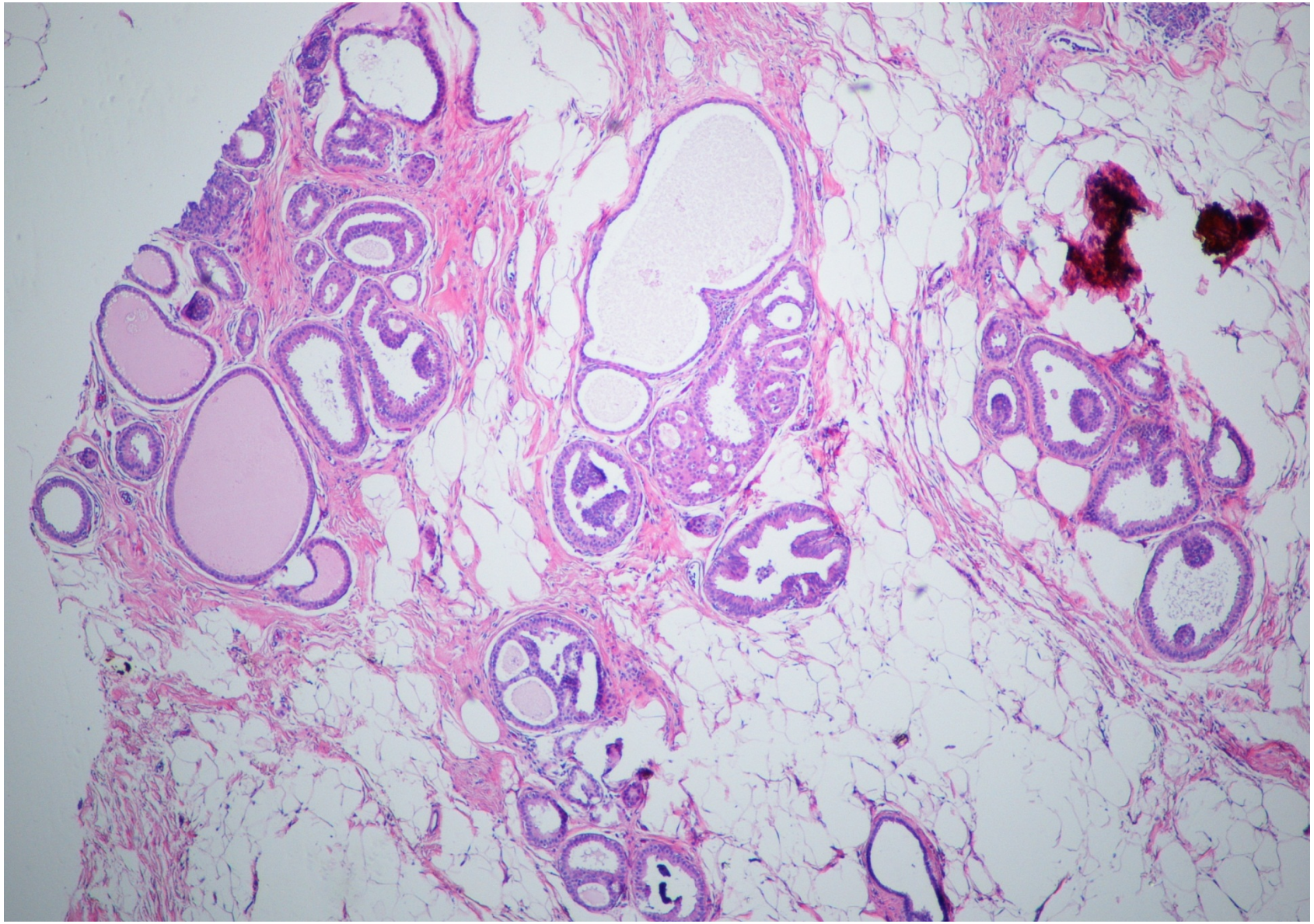
Potential Disadvantages

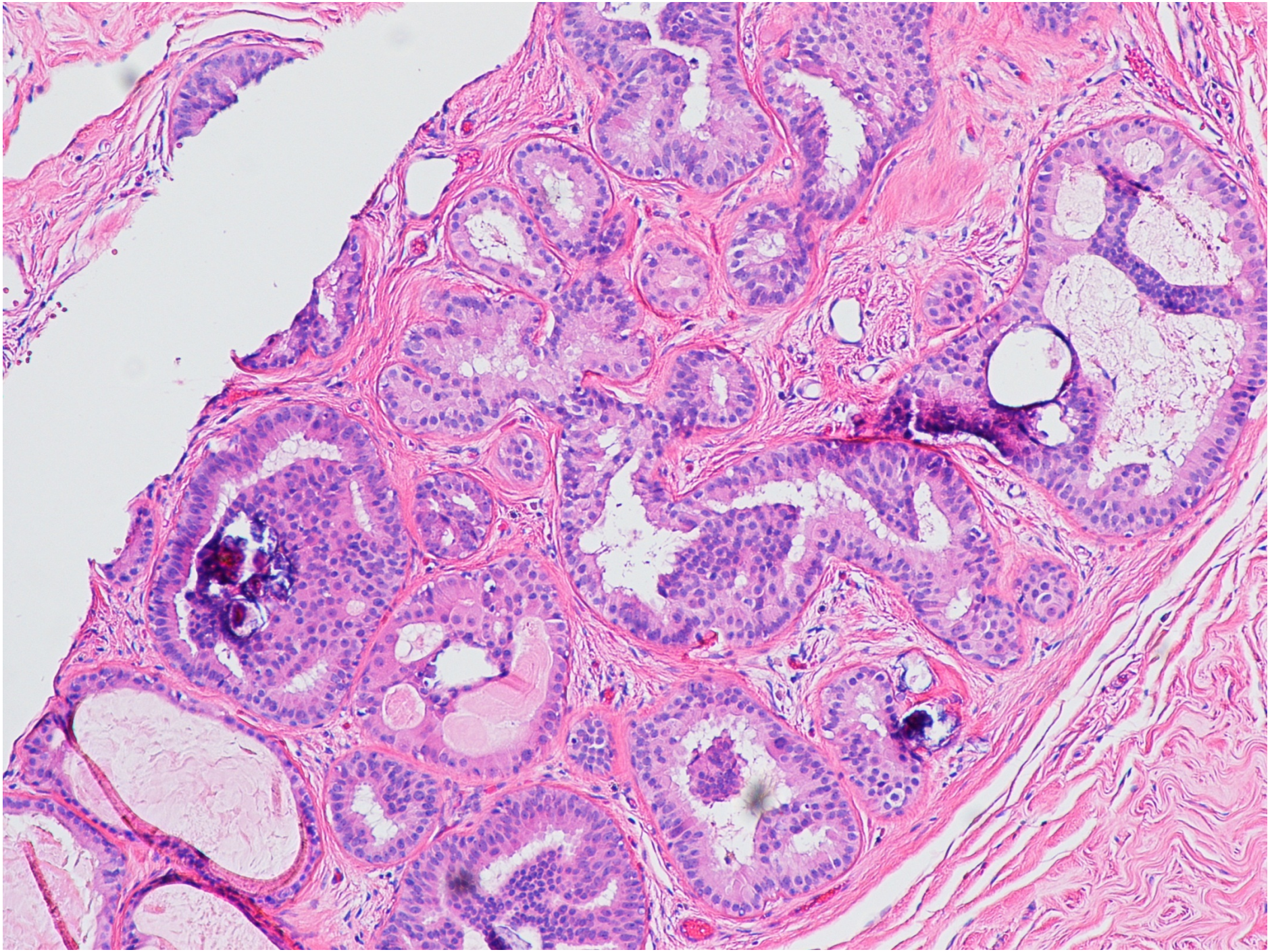
- Patient and environmental radiation exposure
  - Radioactivity levels of 0.1-0.3mCi
    - Considered safe for human exposure by NRC
  - Proper handling, use, and disposal of the radioactive seed requires the oversight of a Radiation Safety Officer and proper facility licensing.
  - Trained personnel must oversee the ordering, storage, transport, and disposal of the seed.
- If seed is improperly placed within the breast, it cannot be removed pre-operatively.
  - 0.3-7.2% documented deployment failures
  - <1% report significant seed migration

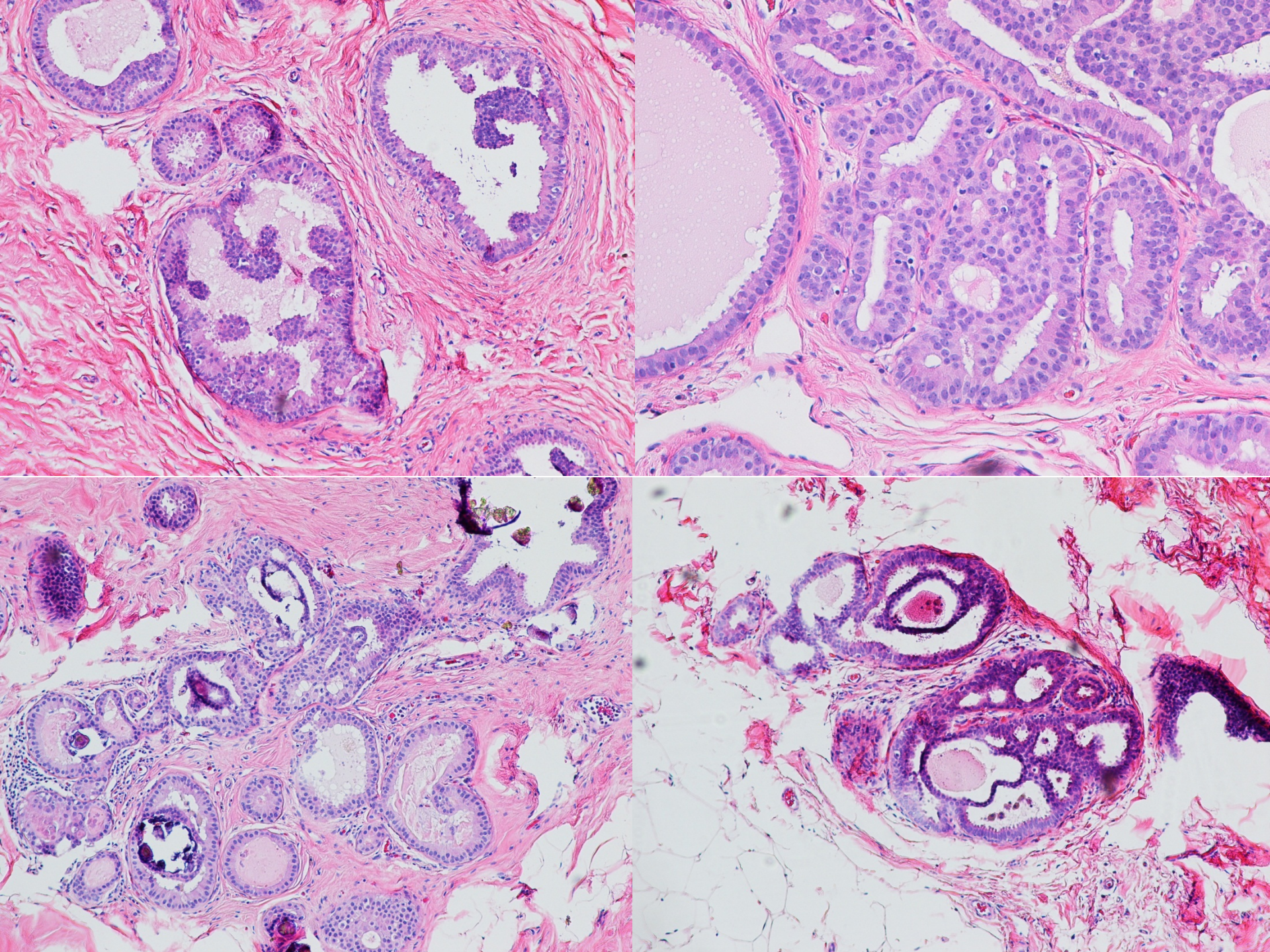
Right partial mastectomy

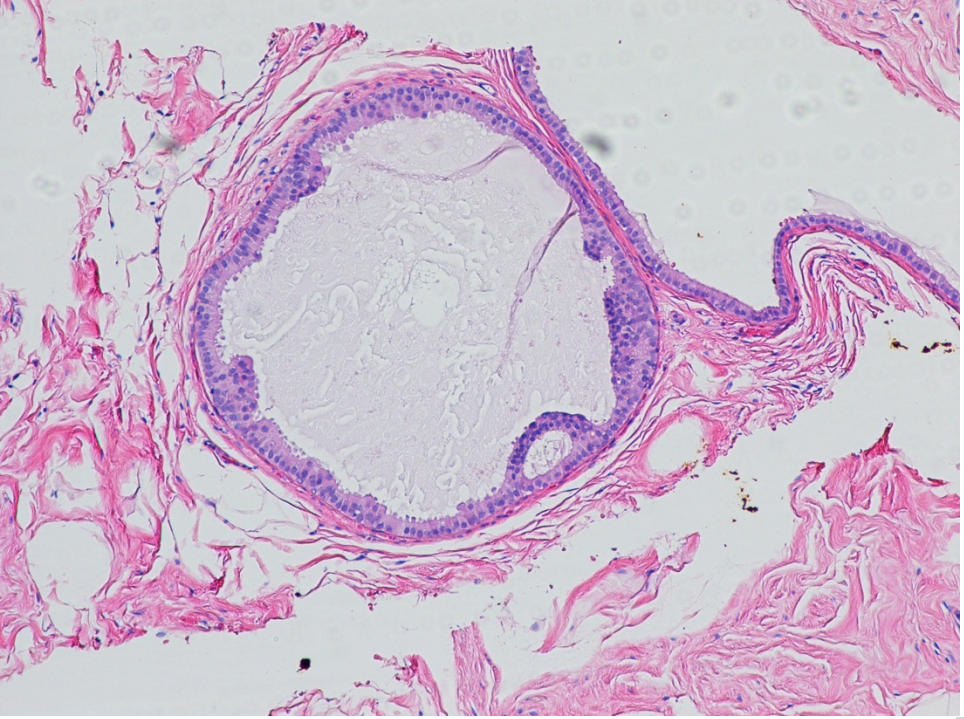
Size9.8X8.1cm

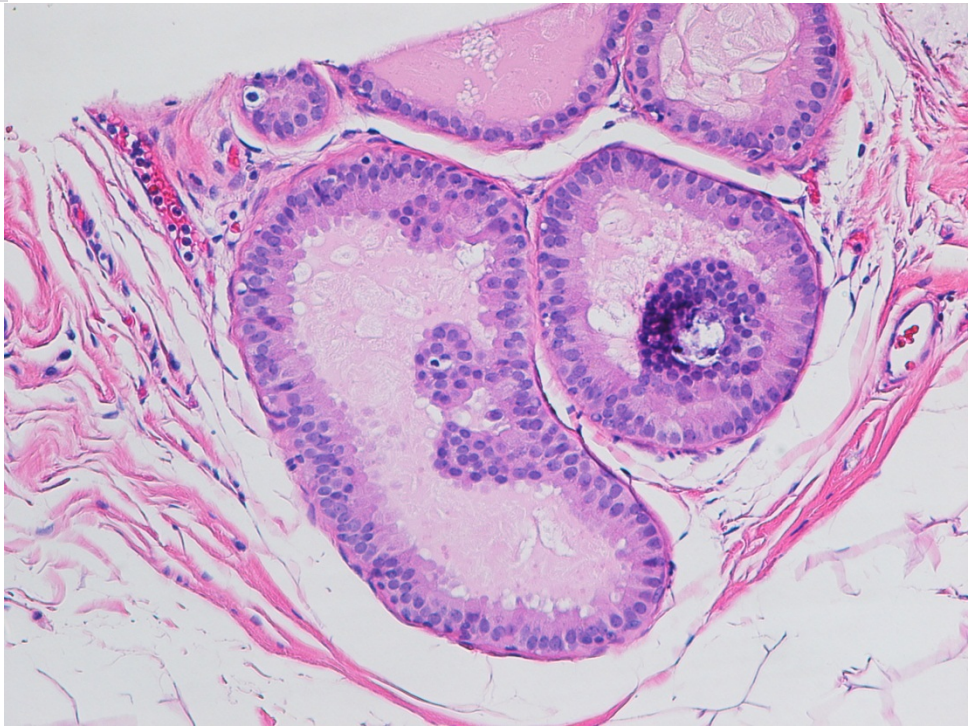
Right breast lumpectomy
Multiple foci of ADH











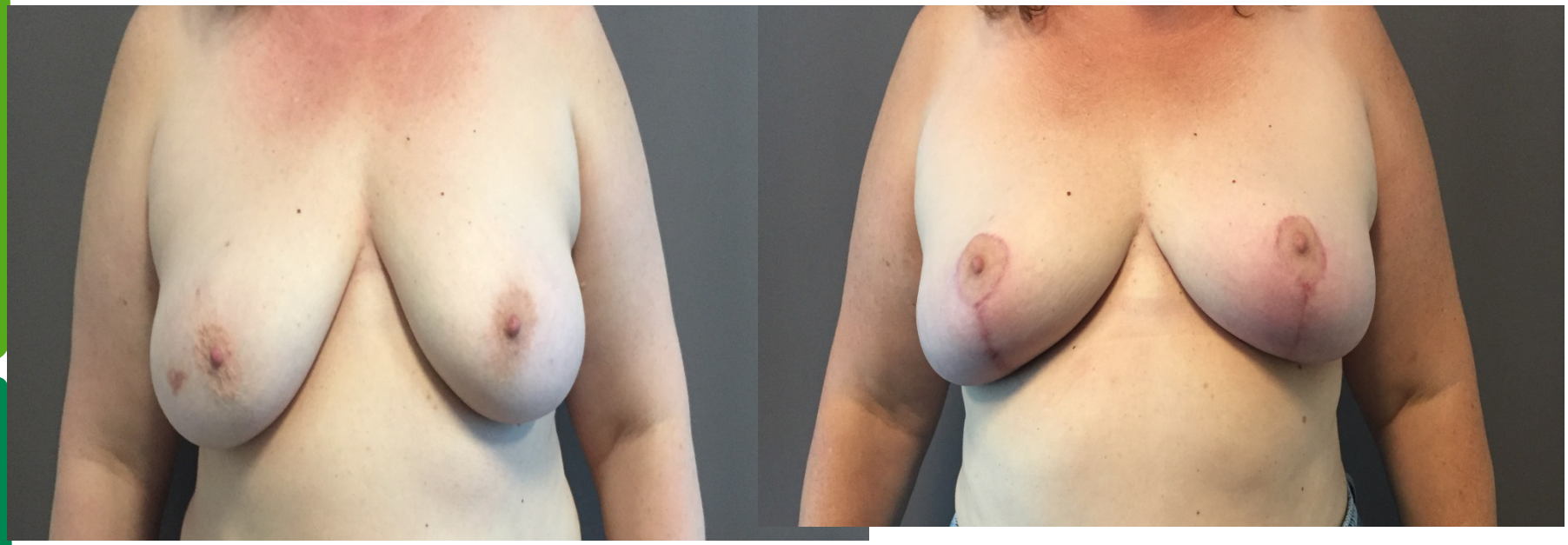
Breast, RIGHT, lumpectomy with needle localization:

- **Multiple scattered foci of atypical ductal hyperplasia (ADH) with associated epithelial microcalcifications**.
- Breast tissue with fibrocystic and columnar change, papillary/micropapillary apocrine metaplasia, usual/florid and papillary duct epithelial hyperplasia, sclerosing adenosis with associated epithelial microcalcifications, radial scar, fibroadenomatoid nodules, and **sclerosing papilloma with usual duct epithelial hyperplasia**.
- Two separate prior biopsy site changes identified.

ONCOPLASTIC MASTOPEXY

PREOP

POSTOP



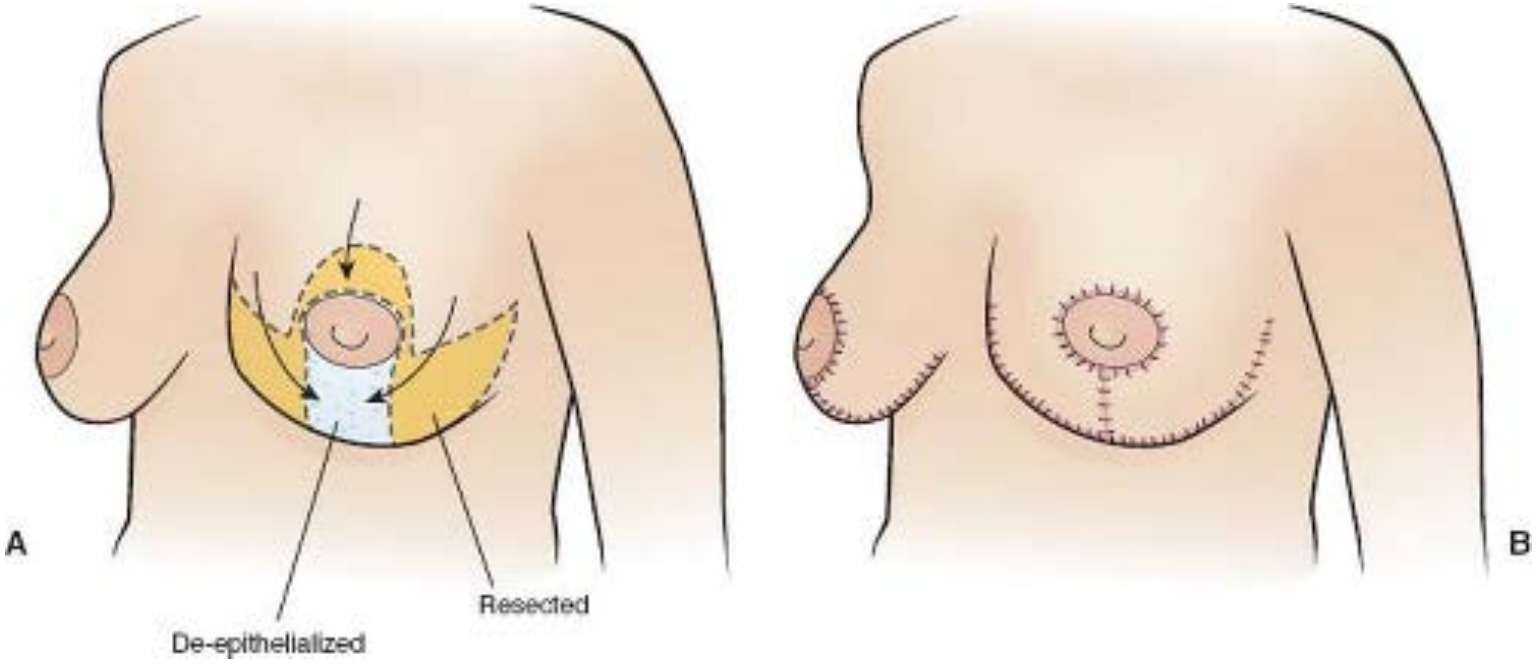
ONCOPLASTIC REDUCTION MAMMOPLASTY

Teresa Benacquista, M.D
Division of Plastic and Reconstructive Surgery
Montefiore Medical Center

Oncoplastic Breast Surgery

- Used extensively in Europe-performed by breast surgeons
- Gaining popularity in the US-performed by plastic surgeons with breast surgeons
- Uses techniques of mastopexy and reduction mammoplasty to recontour the breast after lumpectomy
- Usually is accompanied by contralateral symmetrization procedure

Common Technique



Patient Selection

- Patients with macromastia
- Ptotic breasts
- Patients with small breasts with small tumors
- Tumor away from NAC

Pros

- Allows for extensive resections without cosmetic deformity
- Allows for greater margins around tumors with decrease incidence of positive margins
- A smaller residual breast results in significantly less fibrosis, fat necrosis and cosmetic deformity after radiation
- Allows for tissue sampling of the contralateral breast

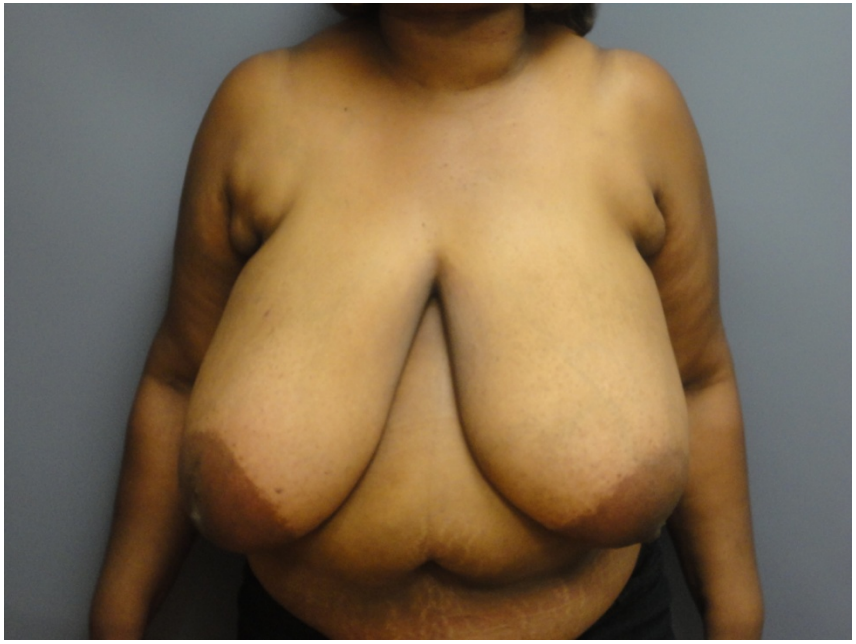
Cons

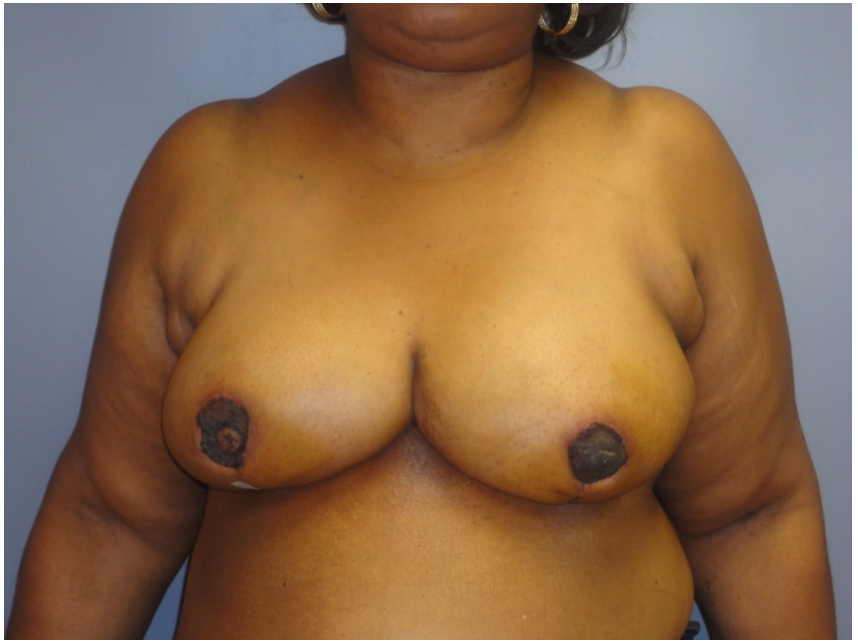
- Leaves longer scars
- Requires surgery on the contralateral breast
- Requires expertise in the techniques
- In the US – 2 surgeons to coordinate schedules
- Positive margins requiring mastectomy

Oncoplastic lumpectomy vs mastectomy

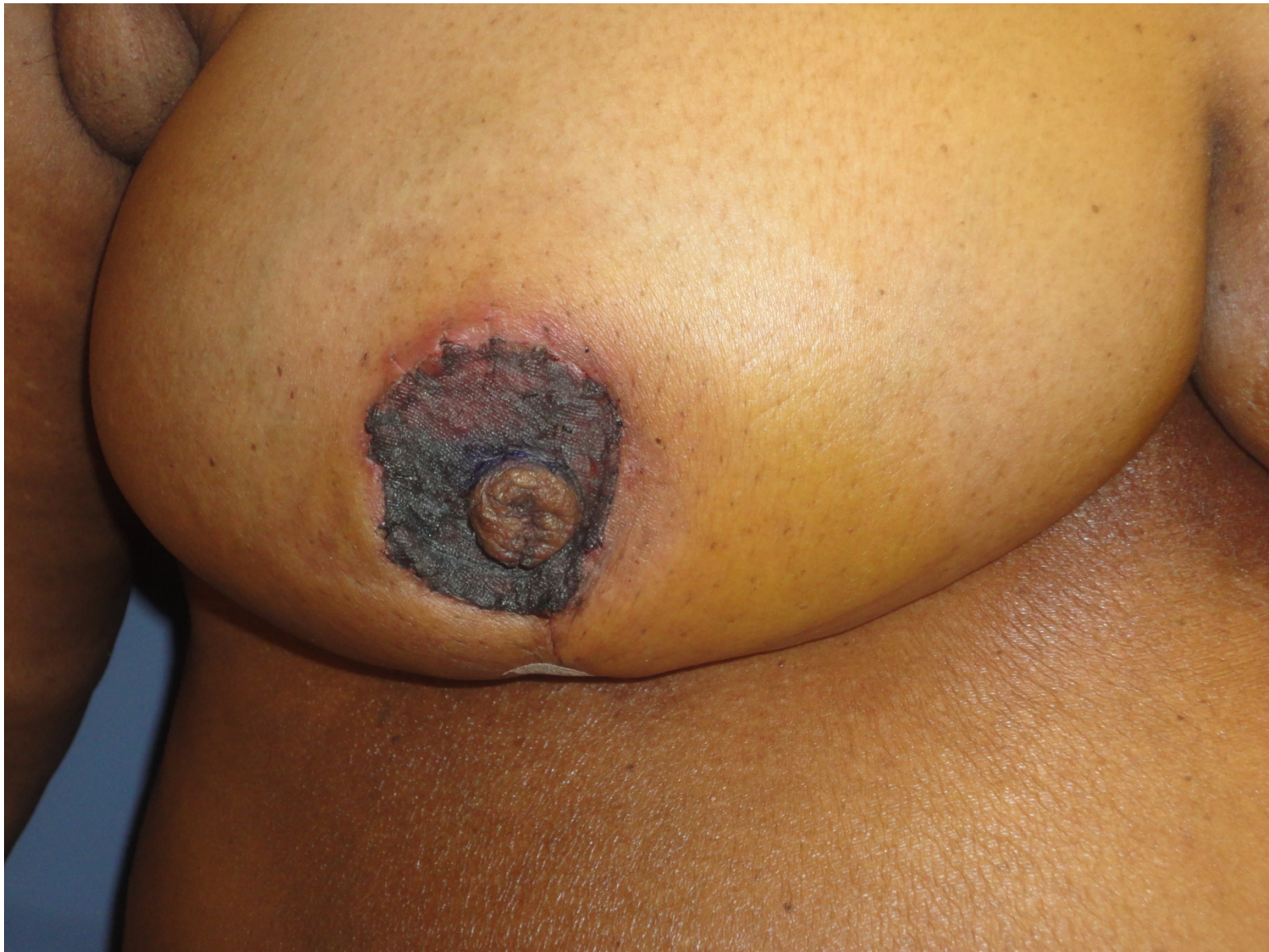
- Oncoplastic lumpectomy may give better cosmetic results in large breasted women
- Maintains sensation of the breast and NAC
- Less surgery than flap reconstructions without donor site morbidity
- Avoids complications of implants and need for replacement over the patient's lifetime
- Pt's with macromastia will often require contralateral reduction mammoplasty to match a mastectomy reconstruction

Oncoplastic lumpectomy with reduction mammoplasty





Nipple areola reconstruction



Risk factors for breast cancer

- Family history
- Demographics
  - Female gender
  - Increasing age
  - Race/Ethnicity
- Reproductive/Hormonal
  - Early menarche
  - Late menopause
  - Nulliparity or late maternal age at first birth
  - Lack of breastfeeding
  - Postmenopausal hormone replacement therapy

Risk factors for breast cancer

- Lifestyle
  - Obesity (especially postmenopausal weight gain)
  - Sedentary lifestyle
- Exposures (radiation)
- Breast related
  - Atypical ductal/lobular hyperplasia
  - LCIS
  - Breast density

Calculation of Risk

- Breast Cancer Risk Assessment Tool (Modified Gail Model)
  - https://www.cancer.gov/bcrisktool/
  - Assesses 5 year and lifetime risk of developing breast cancer, compared to the average woman
  - Variables: age, race, age at menarche, age at first live birth, first degree relatives with BCA, number and histology of prior breast biopsies
  - Limitations
    - Not used for women with LCIS, BRCA or p53 mutations, or prior thoracic RT
    - Underestimates risk for AH

Calculation of Risk

- Tyrer-Cuzick Model (IBIS Model)
  - http://www.ems-trials.org/riskevaluator/
  - http://ibis.ikonopedia.com/
  - Assesses 10 year and lifetime risk of developing breast cancer, compared to the average woman, and risk of carrying BRCA mutation
  - Variables: age, height, weight, age at menarche and menopause, age at first live birth, extensive FH, breast density, histology of prior breast biopsy
  - Limitations
    - Incorporates Ashkenazi Jewish heritage, but not race
    - Overestimates risk for women with AH

Risk Reduction Options

- Lifestyle modifications
- Risk-Reducing Endocrine Therapy
- Risk-Reducing Surgery

Lifestyle Modifications

- Weight loss
- Exercise
- Diet
- Decrease alcohol consumption
- Breastfeeding
- Discontinue hormone replacement therapy

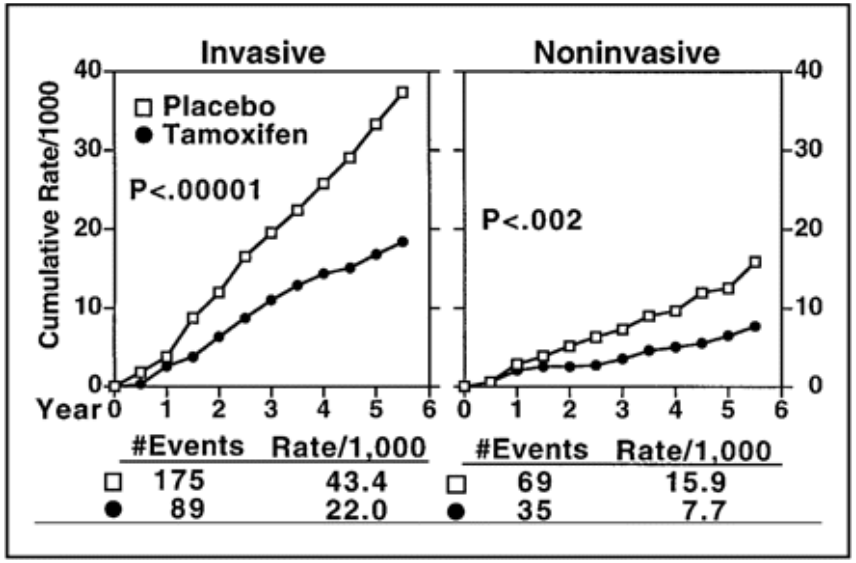
Endocrine Therapies

- Tamoxifen
- Raloxifene
- Exemestane
- Anastrozole

Tamoxifen for Breast Cancer Prevention – NSABP P-1 trial

- 13388 women at high risk for BCA randomized to tamoxifen vs placebo x 5 years
- Criteria for high risk:
  - ≥ 60 years
  - History of LCIS
  - 5 yr risk of BCA ≥ 1.66% by Gail model

NSABP P-1 results



- Study stopped early due to significant reduction in risk of invasive and noninvasive BCA in tamoxifen arm
- Decrease in BCA entirely due to decrease in ER+ tumors
- Updated results – BCA reduced 43% after 7 yrs follow-up

Fisher, JNCI 2005

Other Tamoxifen Trials

- Royal Marsden Trial (Powles, JNCI 2007)
  - 2471 women age 30-70 at high risk due to FH randomized to tamoxifen vs placebo x 8 yrs
  - With 20 year follow-up, decreased ER+ BCA in tamoxifen arm
  - Results became significant with longer follow-up
- IBIS-1 (Cuzick, Lancet Oncol, 2015)
  - 7152 high risk women randomized to 5 yrs tamoxifen vs placebo
  - Significant decrease in ER+ BCA and DCIS in tamoxifen arm
  - No change in ER negative cancer

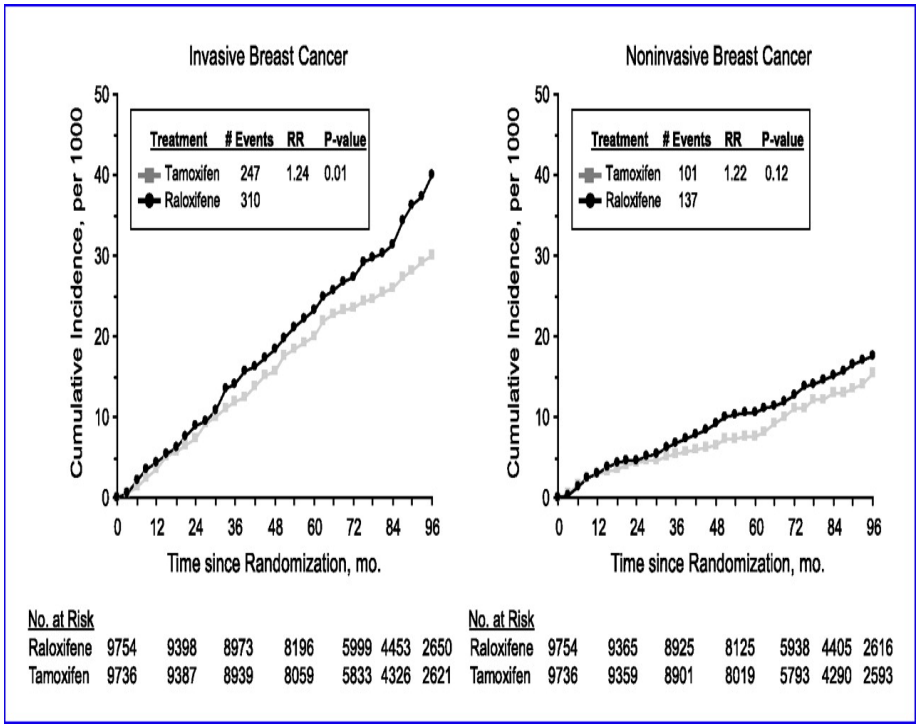
Raloxifene

- Second generation SERM
- Less endometrial stimulation than tamoxifen
- Efficacy in treating postmenopausal osteoporosis (vs placebo) shown in MORE trial
- BCA incidence was a secondary endpoint in MORE trial (although risk of BCA not prospectively assessed)
- Decreased risk of ER+ BCA seen in MORE trial

NSABP P2 (STAR) Trial

- 19747 postmenopausal women with 5-year BCA risk $\geq$ 1.66% by modified Gail model
- Randomized to 20 mg tamoxifen + placebo vs 6 mg raloxifene + placebo x 5 years

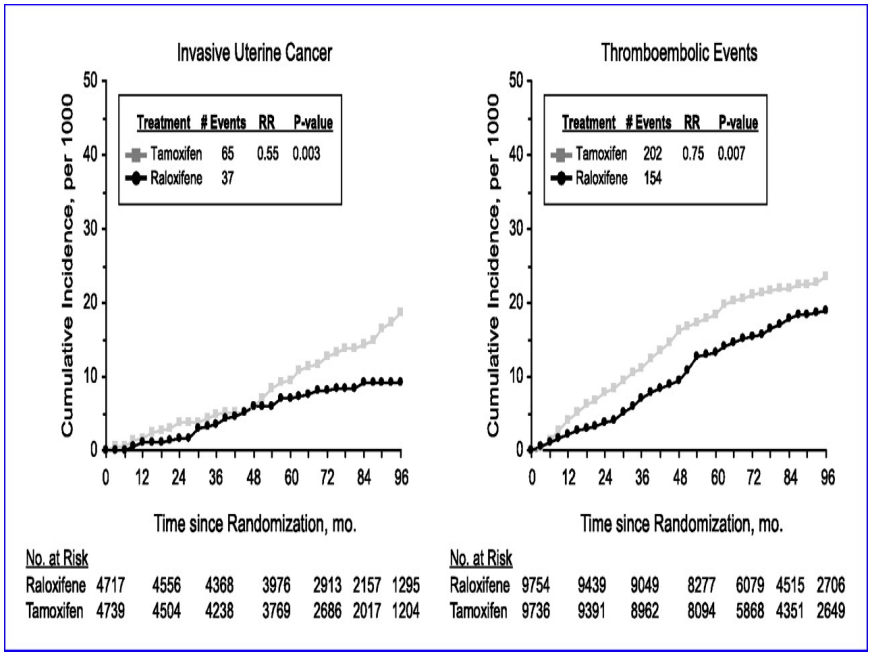
STAR Trial Results



- Raloxifene is about 76% as effective as tamoxifen in preventing invasive breast cancer
- Raloxifene is about 78% as effective as tamoxifen in preventing *in situ* disease

Vogel, Cancer Prevention Research, 2010

STAR Trial Results



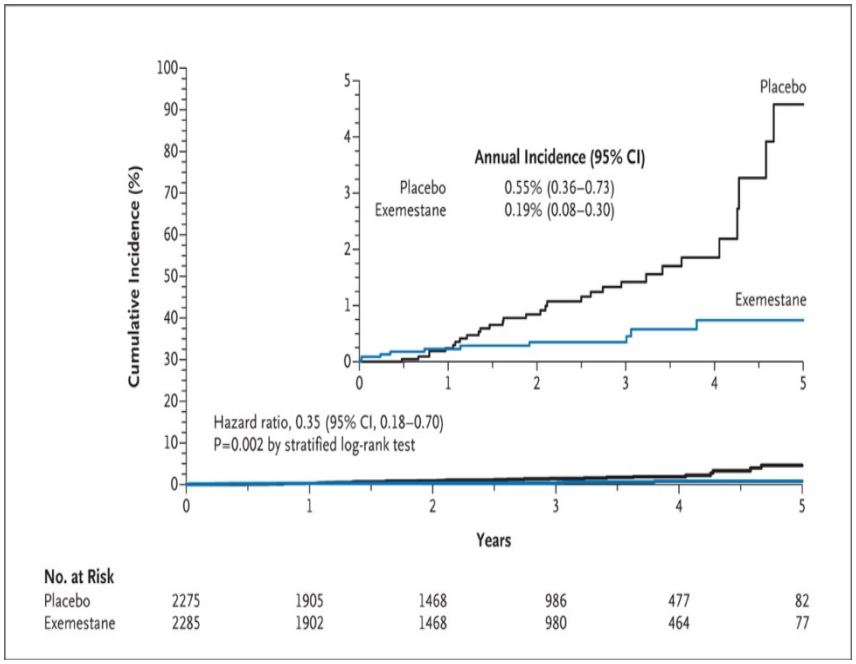
- Decreased incidence of endometrial cancer, thromboembolism and cataracts in raloxifene arm

Vogel, Cancer Prevention Research, 2010

Exemestane for risk reduction MAP.3 trial

- 4560 postmenopausal women at increased risk of BCA randomized to exemestane 25 mg daily x 5 yrs vs placebo
- Risk factors
  - Age ≥60 (50% of study participants)
  - 5 yr BCA risk ≥1.66% by Gail model
  - Prior ADH, ALH, or LCIS
  - Prior DCIS treated with mastectomy
- Primary endpoint – incidence of invasive BCA

MAP.3 Trial



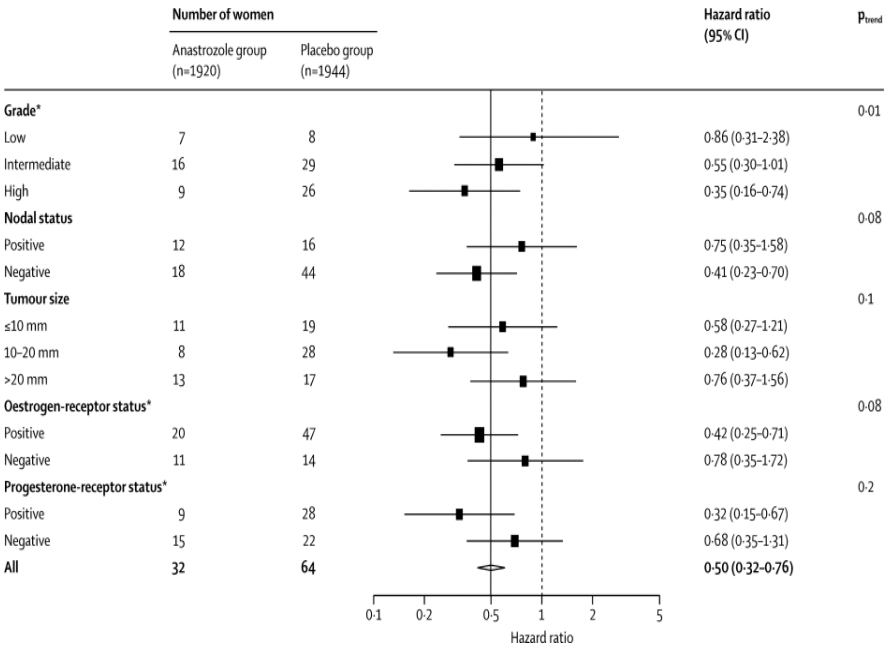
Goss, NEJM 2011

- Median follow-up 3 years
- 65% reduction in invasive breast cancer in exemestane group
- Toxicities
  - Increased pain in exemestane group
  - No increase in fractures, osteoporosis, or cardiac disease
  - Short follow-up

Anastrozole for risk reduction IBIS II Trial

- 3684 postmenopausal women age 40-70 at increased risk for BCA randomized to anastrozole 1 mg daily x 5 yrs vs placebo
- Risk Factors
  - Based on age and FH
    - Age 60-70 – risk 1.5x general population
    - Age 45-60 – risk 2x general population
    - Age 40-44 – risk 4x general population
  - LCIS, AH, DCIS

IBIS-II Results



Cuzick, Lancet 2014

- Primary endpoint – breast cancer (invasive or DCIS)
- 7 yrs follow-up
- Anastrozole decreased incidence of invasive and in situ breast cancer
- Greater prevention of high grade tumors

Toxicities and Adherence

- Women taking anastrozole had significantly higher incidence of:
  - Musculoskeletal AEs
  - Moderate arthralgia (not mild or severe)
  - Vasomotor symptoms
  - Vaginal dryness
  - Dry eyes
- BUT many women on placebo had similar symptoms
- 20% of women taking anastrozole discontinued treatment due to AEs
- 15% of women on placebo discontinued treatment due to AEs

Cuzick, Lancet 2014

Summary

- Risk reducing endocrine therapy should be offered to women with life expectancy >10 yrs who have AH, LCIS or 5 year risk of breast cancer $\geq$1.7%
- Options in postmenopausal women (all NCCN Category 1)
  - Tamoxifen
  - Raloxifene
  - Exemestane
  - Anastrozole
- AI's not FDA approved for risk reduction

Summary

- Options for premenopausal women – tamoxifen
- Women receiving risk reducing endocrine therapy should be monitored for expected toxicities of therapy
- All women should be counseled about lifestyle modifications that may decrease breast cancer risk

Radiation for DCIS

NSABP B-17
Results – 12/17 year data

B-17 Results/Conclusions

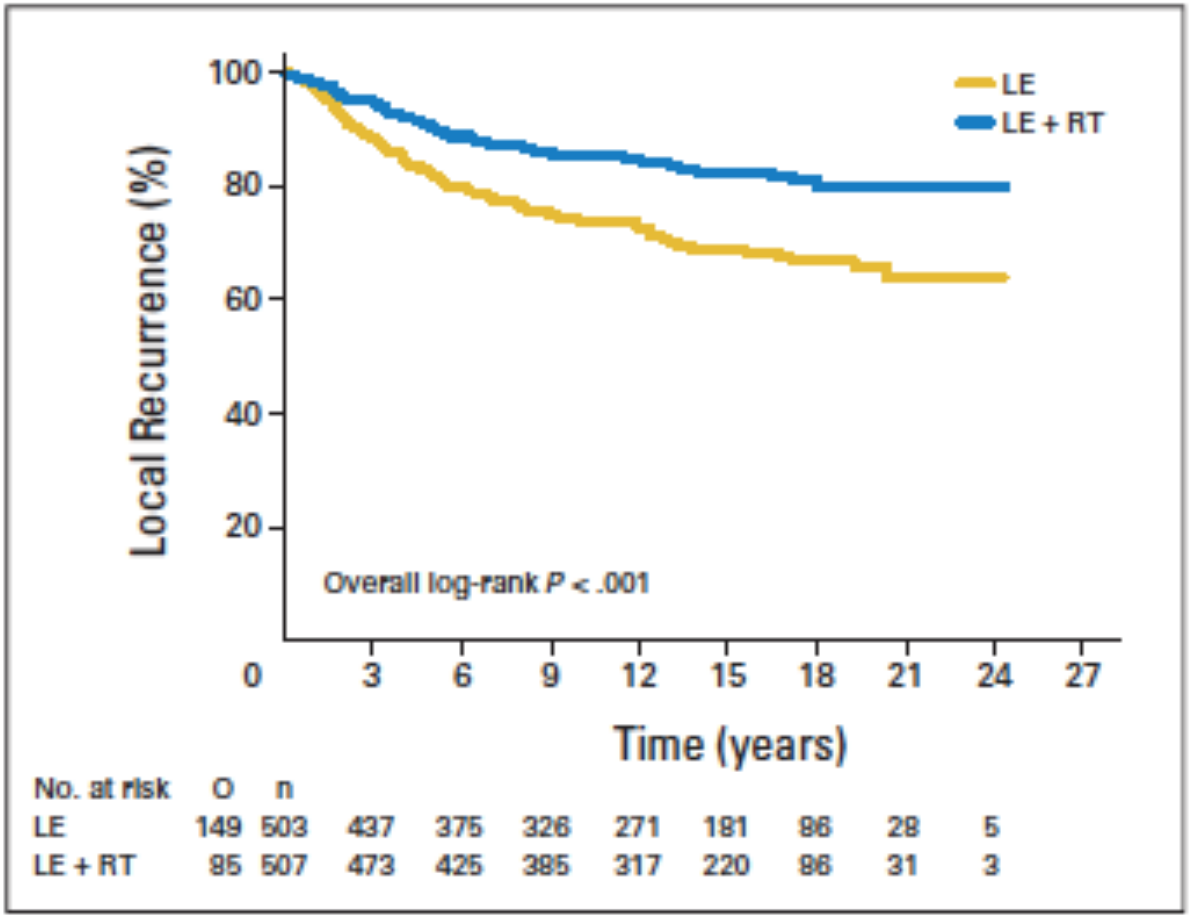
- OS equivalent at 12 yrs (86-87%)
- Risk of invasive recurrence about 50%
- Both invasive and non-invasive recurrences significantly reduced with RT
- Lumpectomy + RT an alternative to mastectomy for DCIS

EORTC 10853 Results @4.25/10yrs

	lumpectomy	Lumpectomy+RT
IBF (overall)	16/26%	9/15% p<0.0001
IBF (DCIS)	8/14%	5/7% p=0.011
IBF (invasive)	8/13%	4/8% p=0.064
DM rate	2/4%	1/4% NS
Contralateral	1/4%	3/8% NS

EORTC 10853 15yr results

- 30vs 17% LR



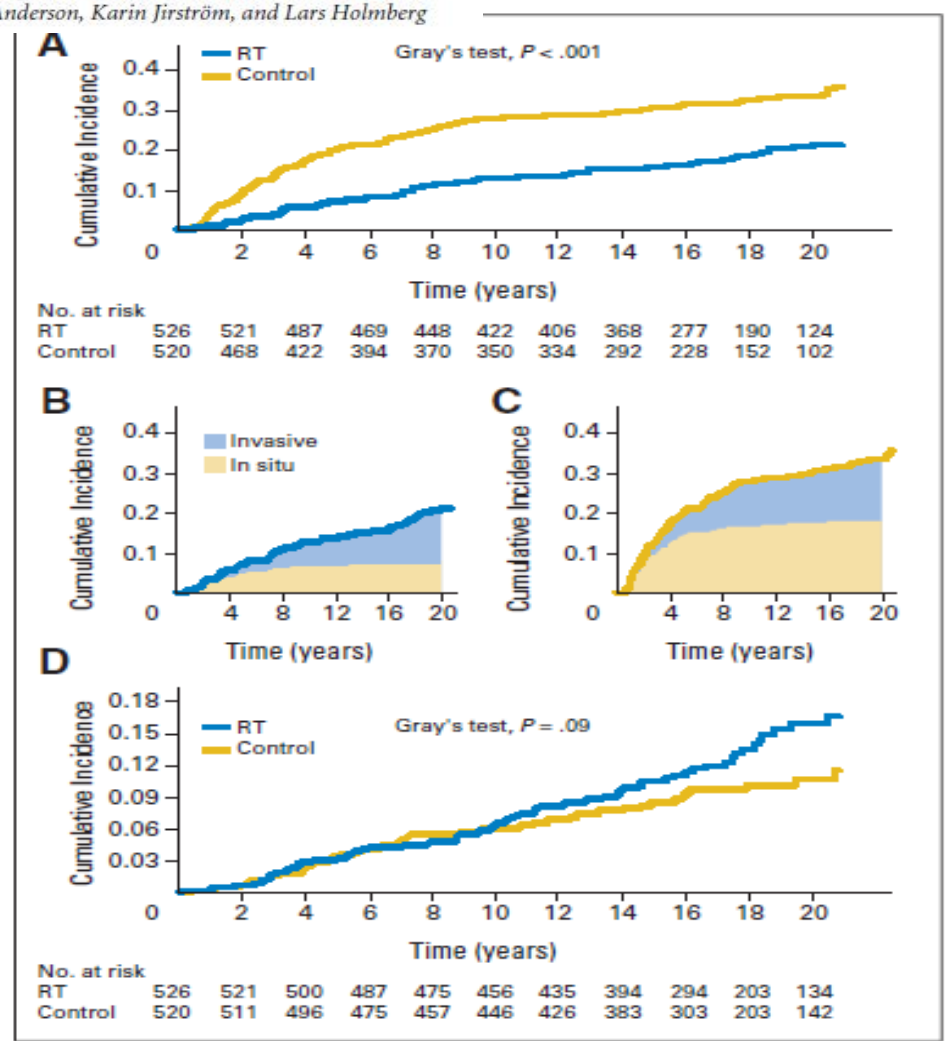
RTOG 98-04

- Closed early due to low accrual (636/1790)
  - Eligibility criteria: age > 25 yr, DCIS < 2.5 cm, (-)margins > 3 mm, grade 1-2
  - Randomization: Lumpectomy +/- RT
  - Tamoxifen allowed (used in 62%)
  - 7yr LR 6.7% vs 0.9%

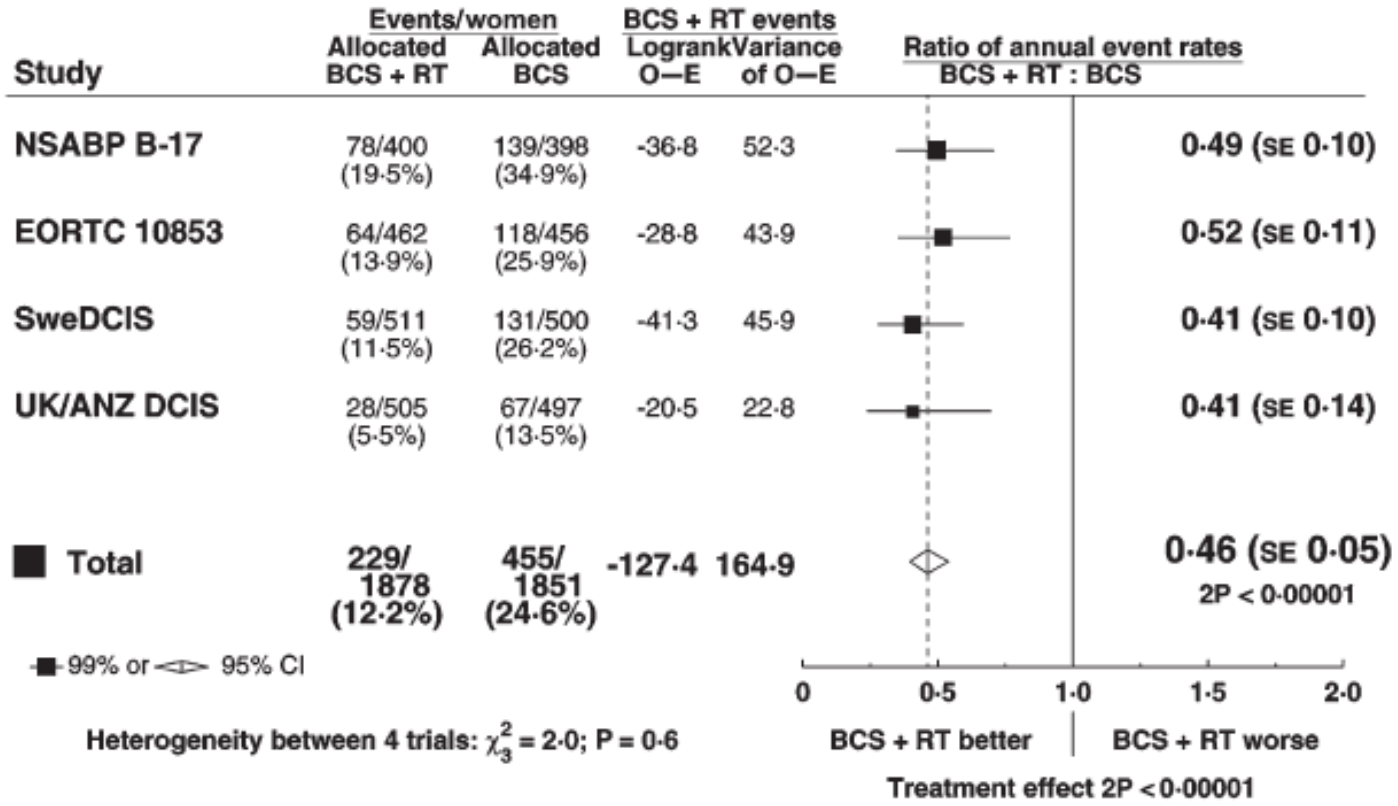
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Effect of Radiotherapy After Breast-Conserving Surgery for Ductal Carcinoma in Situ: 20 Years Follow-Up in the Randomized SweDCIS Trial

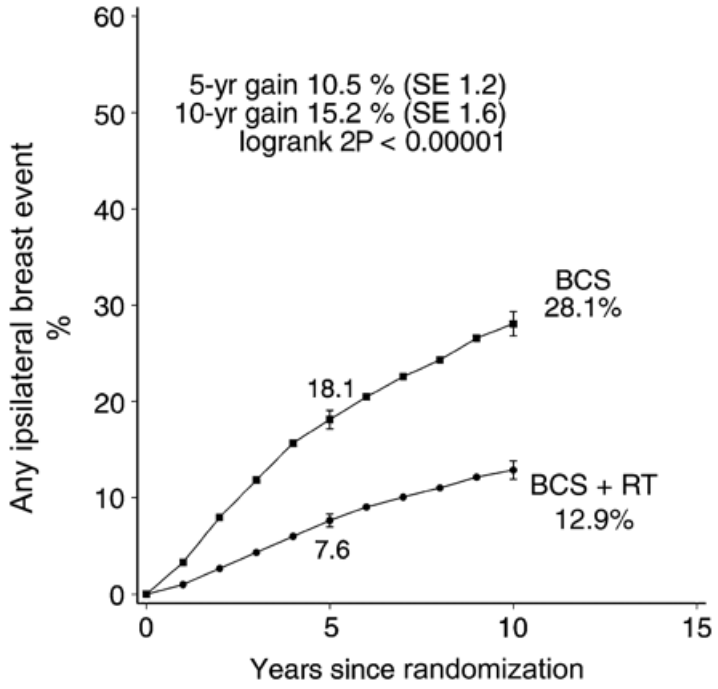
Fredrik Wärnberg, Hans Garmo, Stefan Emdin, Veronica Hedberg, Linda Adwall, Kerstin Sandelin, Anita Ringberg, Per Karlsson, Lars-Gunnar Arnesson, Harald Anderson, Karin Jirström, and Lars Holmberg



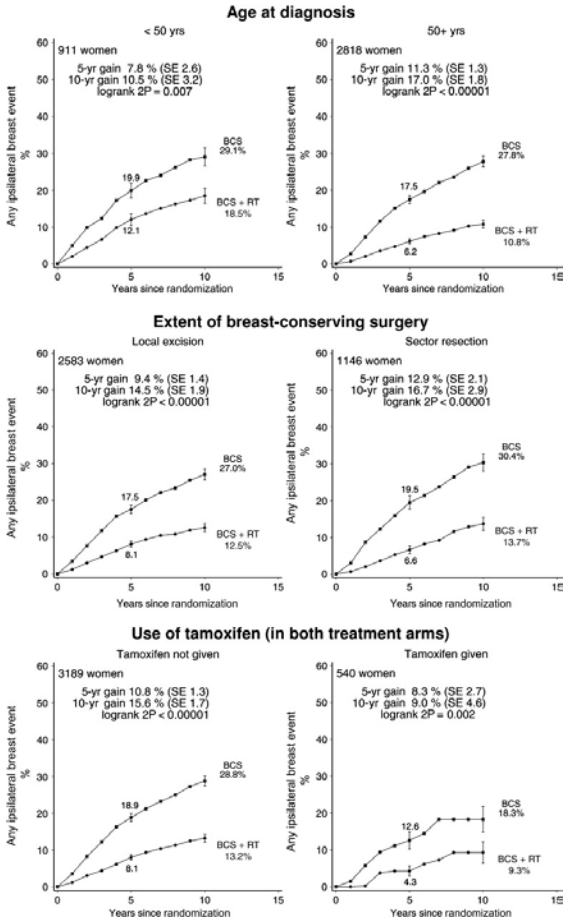
EBCTCG Overview



EBCTG Meta-Analysis



EBCTG Meta-analysis



DCIS – Omission of RT

ECOG 5194, Low Risk

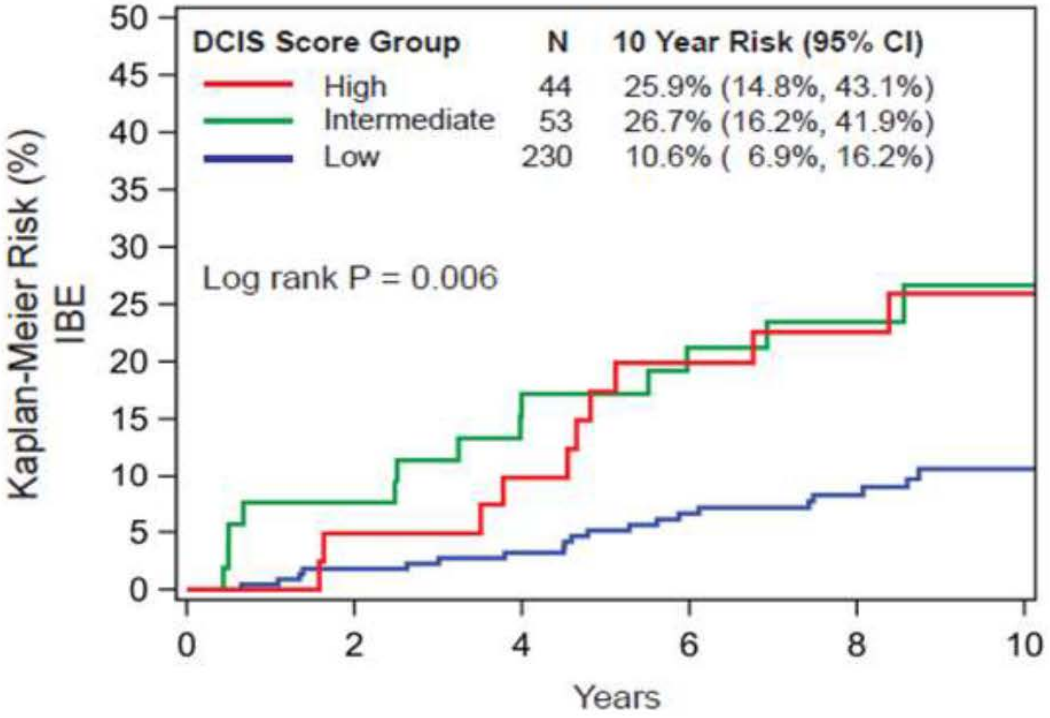
	Any Ipsi Breast Event (%)	Invasive Ipsi Breast Event (%)
5 years	6 (4.0-8.1)	2.7 (1.3-4.1)
7 years	9.5 (7.0-12.0)	4.8 (2.9-6.6)
10 years	12.5 (9.5-15.4)	6.4 (4.2-8.6)
12 years	14.4 (CI 11.2-17.6)	7.5 (5.1-10.0)

N=561
Median follow-up 12.3 years

Solin LJ, JCO epub ahead of print, 2015

Genomic Assay to Guide RT

Oncotype DCIS Score: ECOG 5194



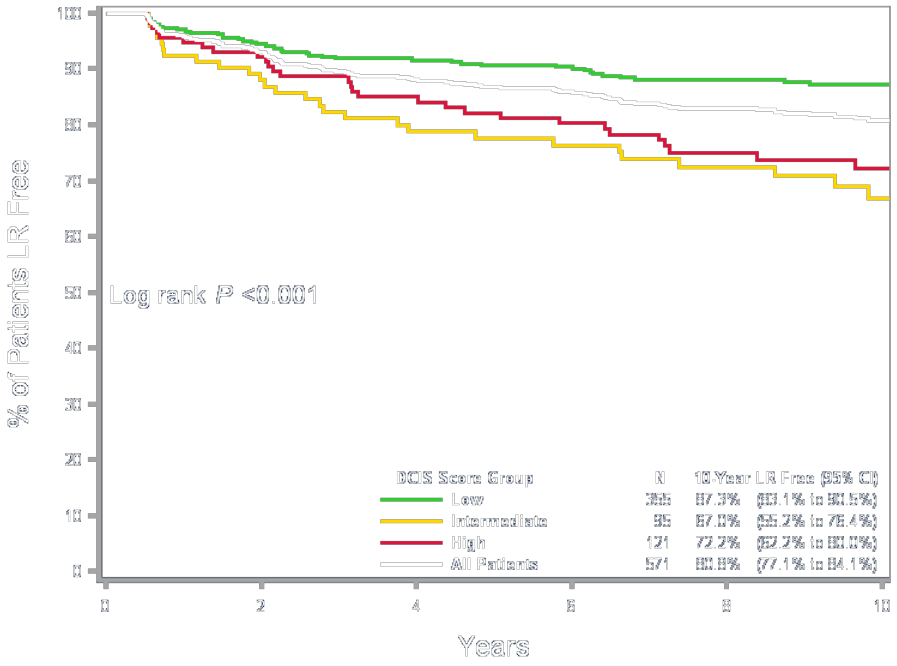
<2.5 cm, grade I or II

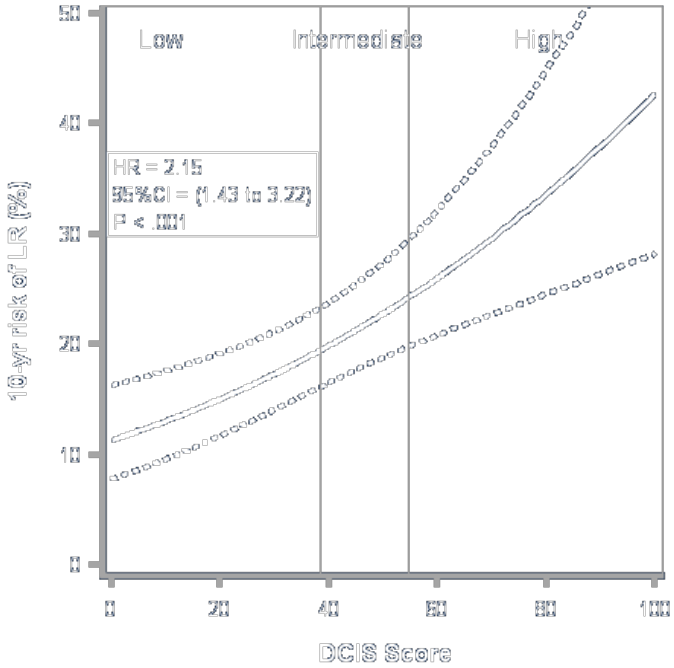
≤1.0 cm, grade III

Margins > 3mm

Solin LJ, et al JNCI 2013, 105

DCIS Score™ Result: 10-Year Risk of Any Local Recurrence by Risk Group in the Ontario Provincial DCIS Cohort





- **The results confirmed the association of the DCIS Score result with LR and stratification of recurrence risk based on underlying biology that is not apparent in the population as a whole**
- **The proportion of patients within each risk group is also similar to what was observed in the E5194 study with the majority of patients (62%) having a low score**

RESULTS

DCIS Score = 42

The findings summarized in the Clinical Experience sections of this report are applicable to the defined patient population. It is unknown whether the findings apply to patients outside these criteria.

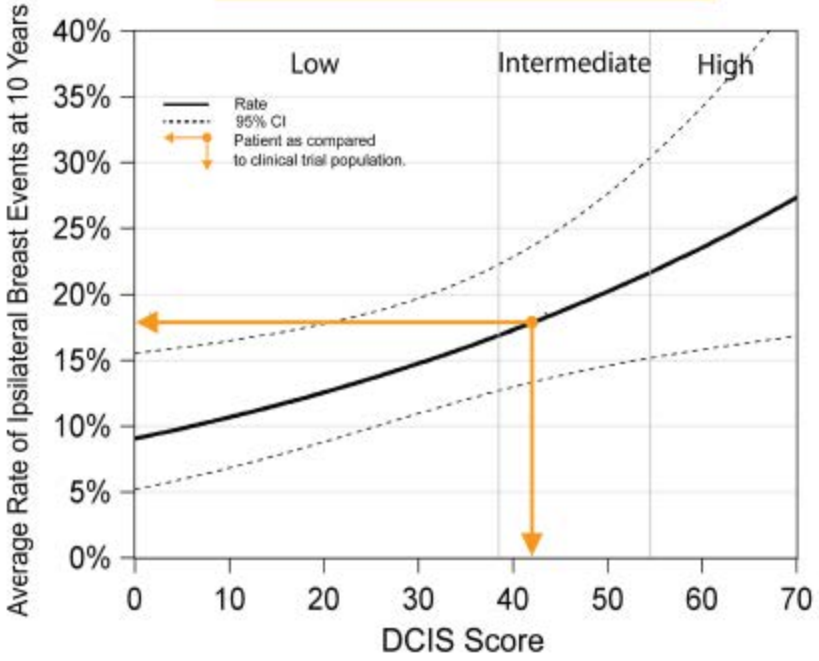
CLINICAL EXPERIENCE: PROGNOSIS FOR DCIS PATIENTS

The Clinical Validation study included female patients with DCIS treated with local excision without irradiation, and required clear surgical margins ≥ 3 mm and a lesion size of ≤ 2.5 cm. Approximately a third of patients were treated with tamoxifen.

The average 10 year rate for ipsilateral breast events for patients who had a DCIS Score of 42 was:

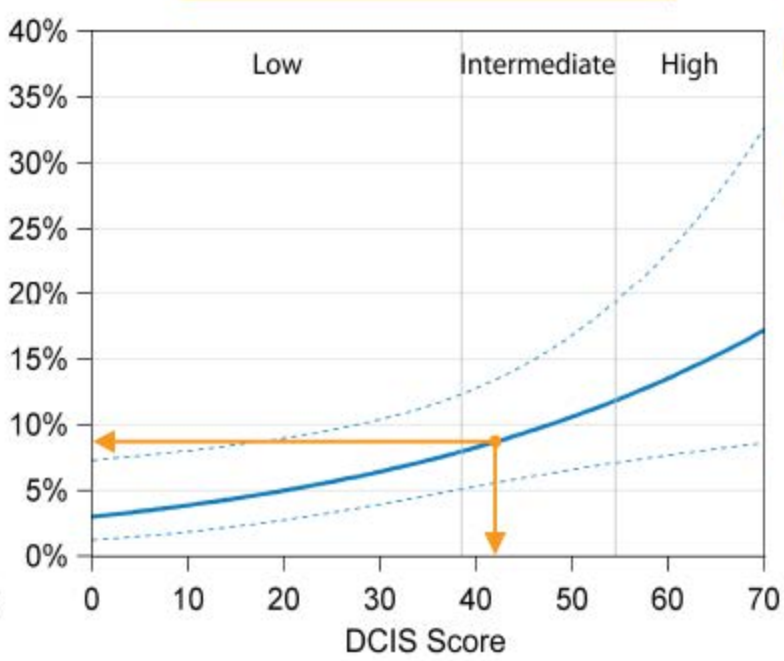
Any Local Event (DCIS or Invasive)

18% (95% CI: 13%-24%)



Invasive Local Event

9% (95% CI: 6%-13%)



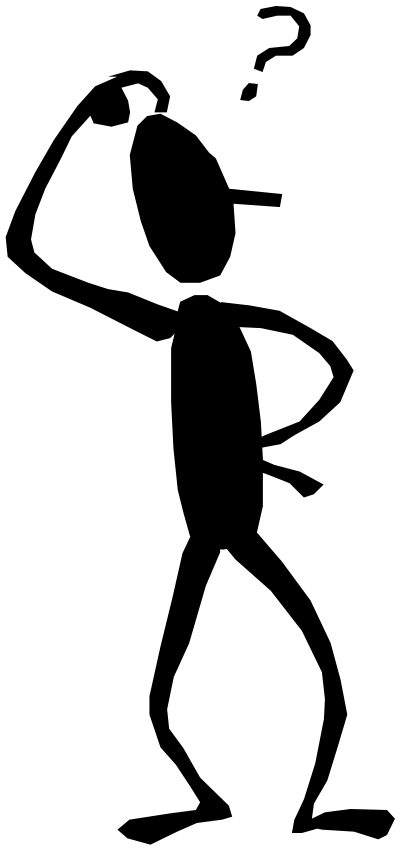
DCIS

These results are from a clinical validation study of 327 patients from the ECOG 5194 study (Solin et al., SABCS 2011. Abstract S4-6).

Conclusion

- Patient with 7cm area of microcalcifications; initial core bxs suggested ductal carcinoma in situ(DCIS)
- DCIS not confirmed on pathology review or surgical resection
- Atypical ductal hyperplasia and elevated risk(family hx)
- Tamoxifen and healthy lifestyle for risk reduction and annual screening mammogram

ANY QUESTIONS



Case #2: Early Breast Cancer

HPI: 32yo healthy woman noted new right breast mass. Excellent health, newly married. BMI 20

Past Med Hx: G0P0

Family Hx: adopted

P.E. No skin changes, 1cm firm, not fixed right breast mass 12 oclock location 5cm from areola edge. No regional adenopathy. Bra size 32B

Audience Response Question

Recommended initial evaluation of palpable mass in a young woman:

a.Office needle biopsy by palpation

b.Mammogram

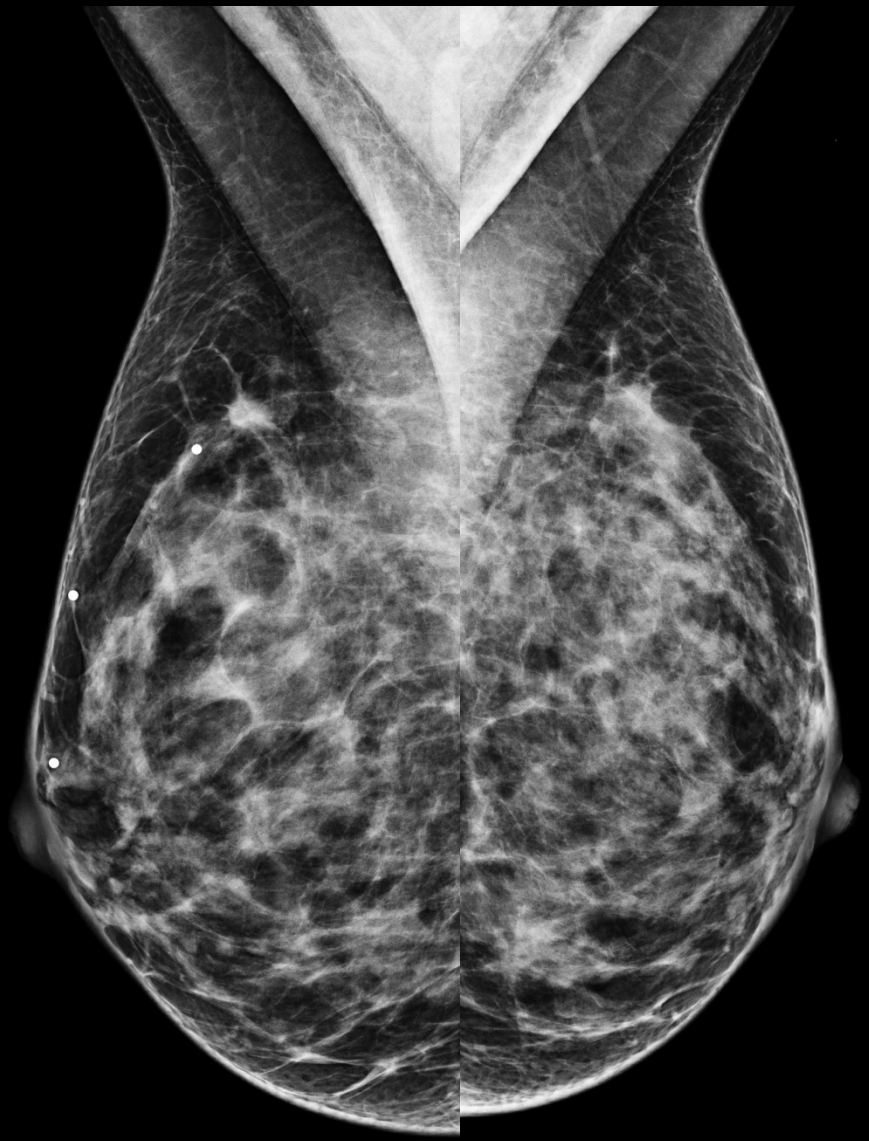
c.Targeted ultrasound

ACR Appropriateness Criteria

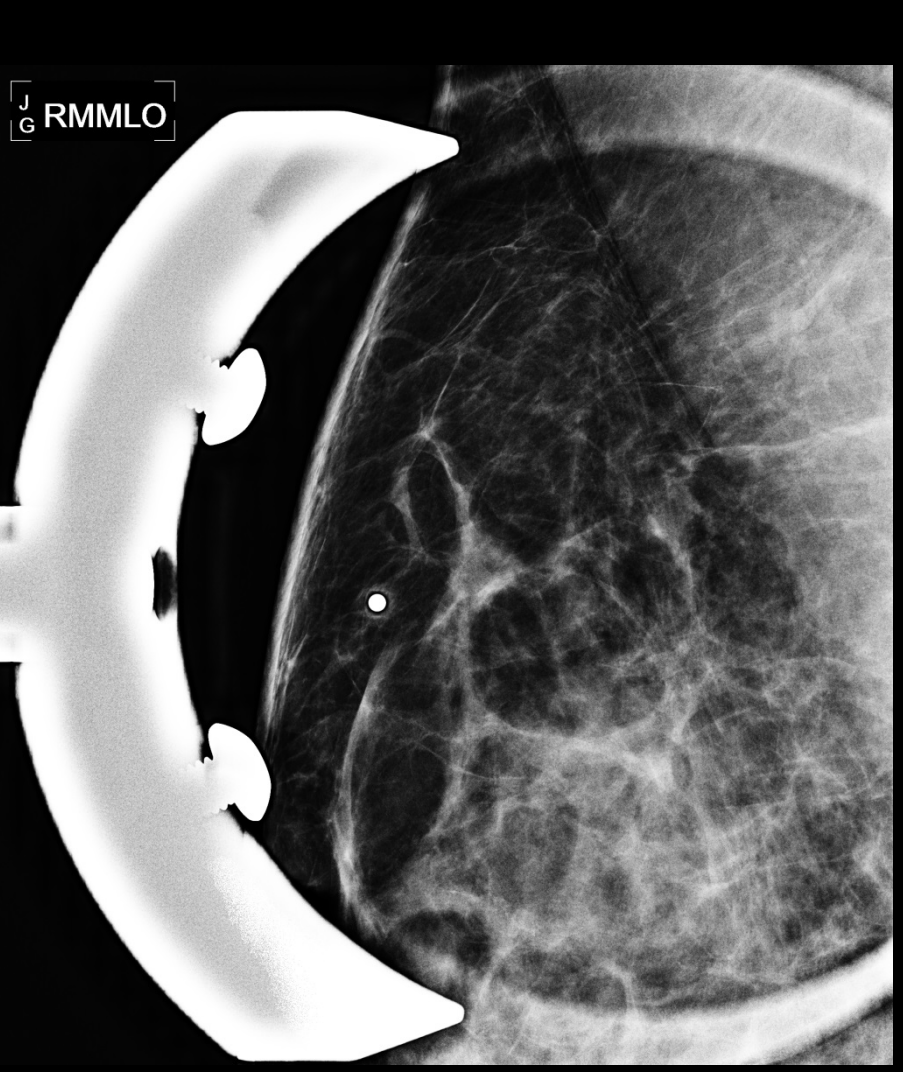
Evaluation of a palpable mass

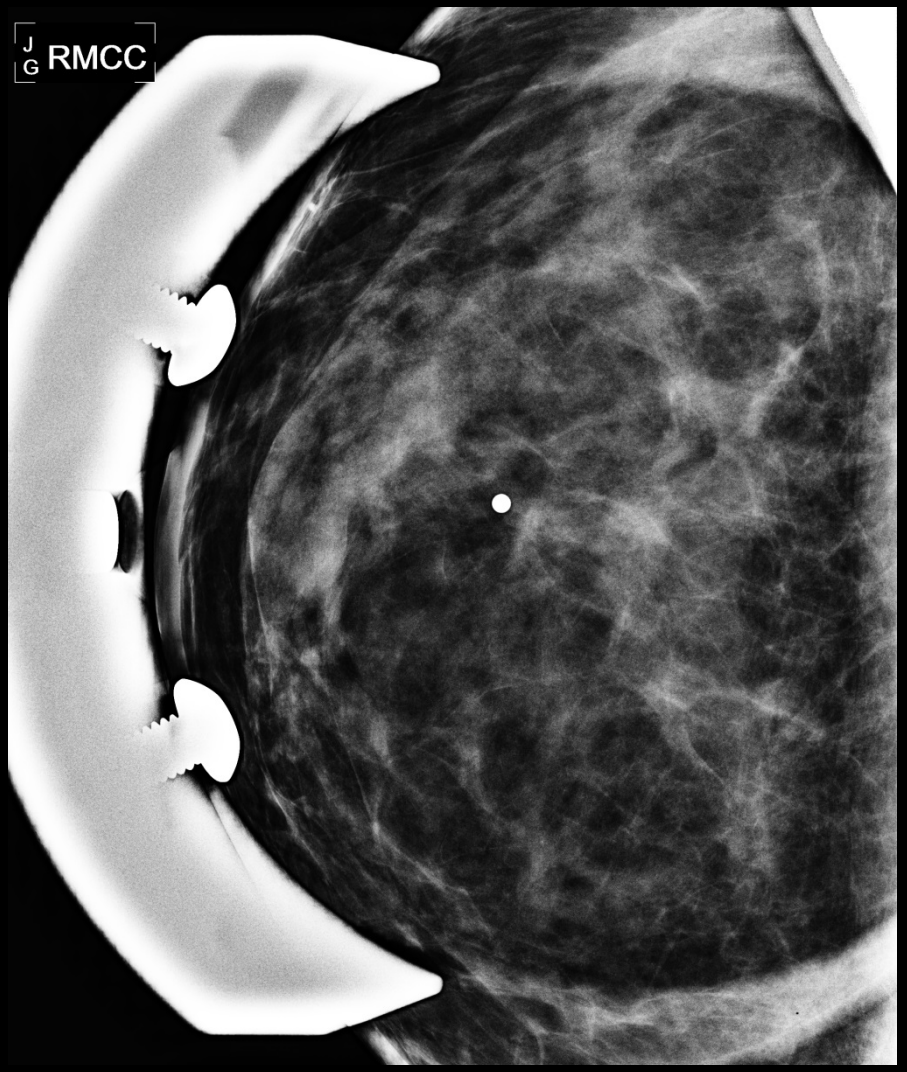
- Age dependent
  - ≥ 40 years: Diagnostic Mammography is initial imaging test
  - < 30 years or pregnant/lactating: Ultrasound is initial test
  - 30-39 years: Either ultrasound or diagnostic mammography may be initial imaging test
- MRI is rarely indicated to evaluate a clinically detected finding
- Correlation between imaging and the clinical finding is essential

Diagnostic mammogram

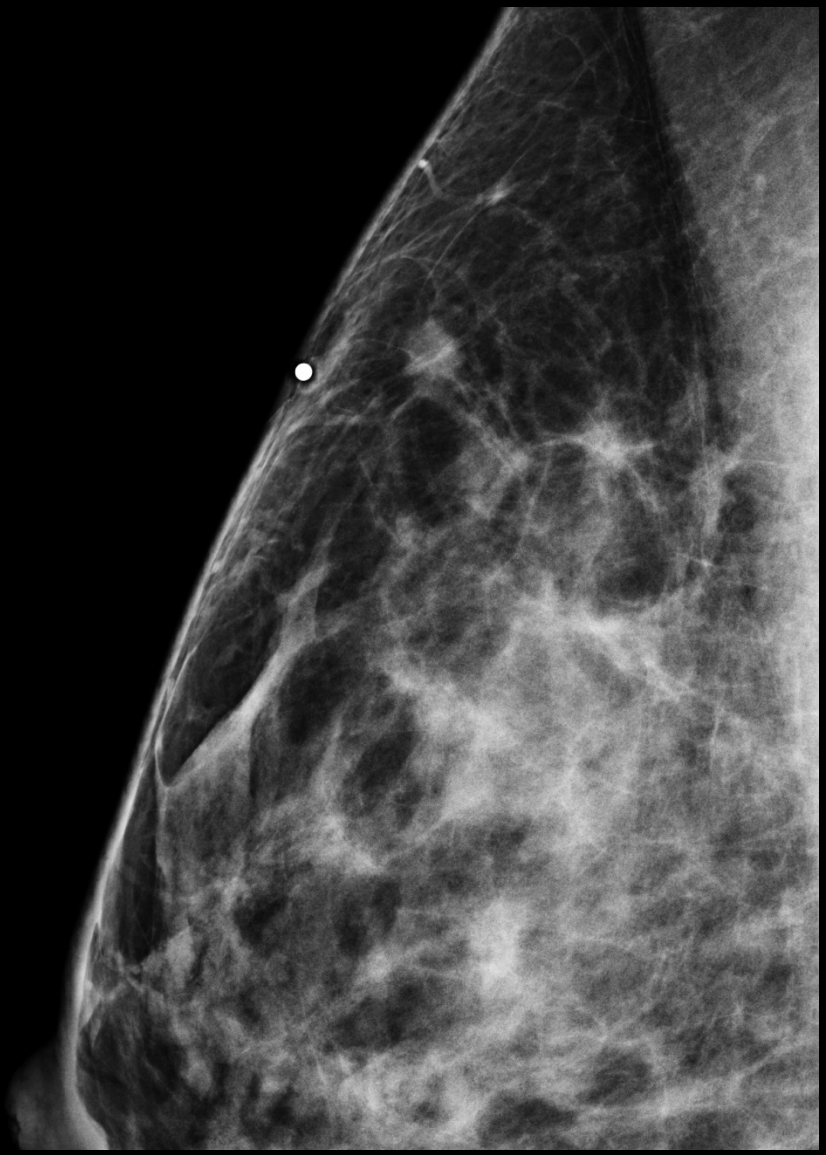


Diagnostic mammogram





Diagnostic mammogram



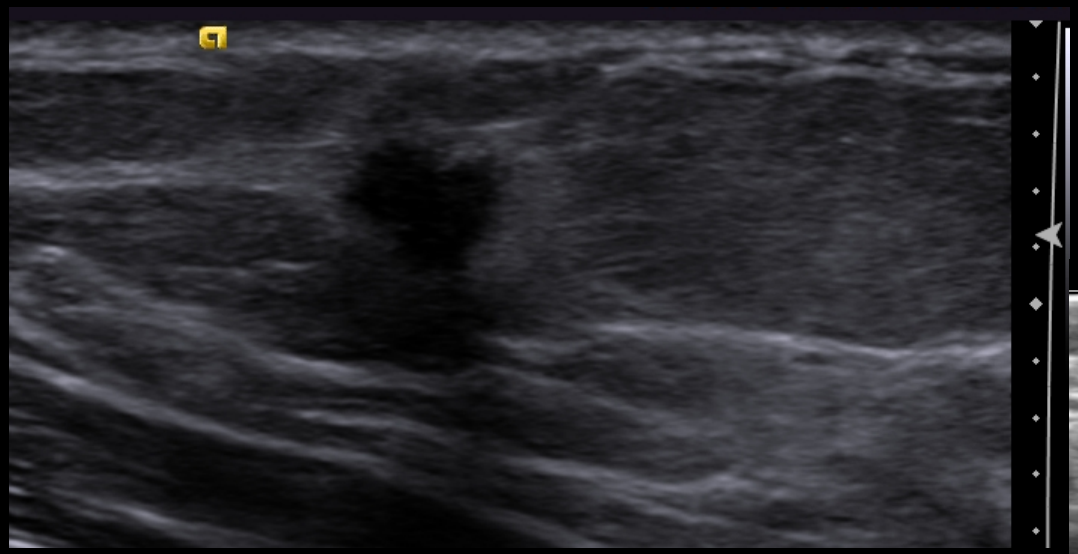
Evaluation of Patients with Dense Breasts

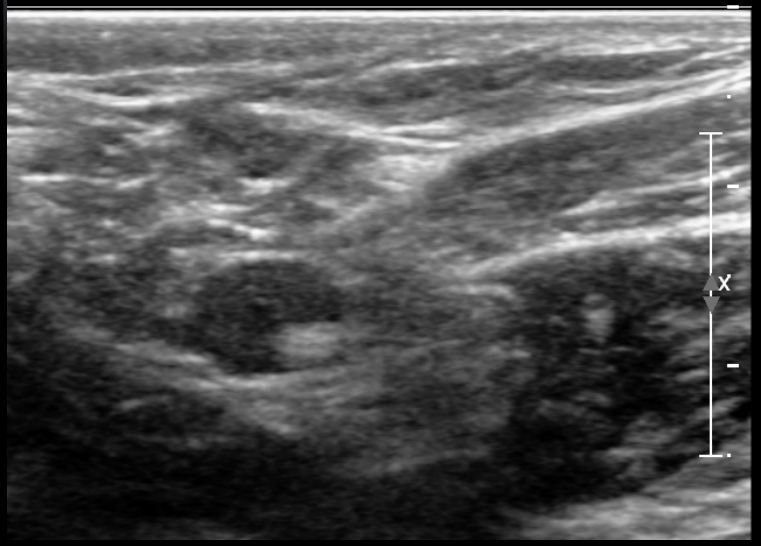
Evaluation of a palpable mass

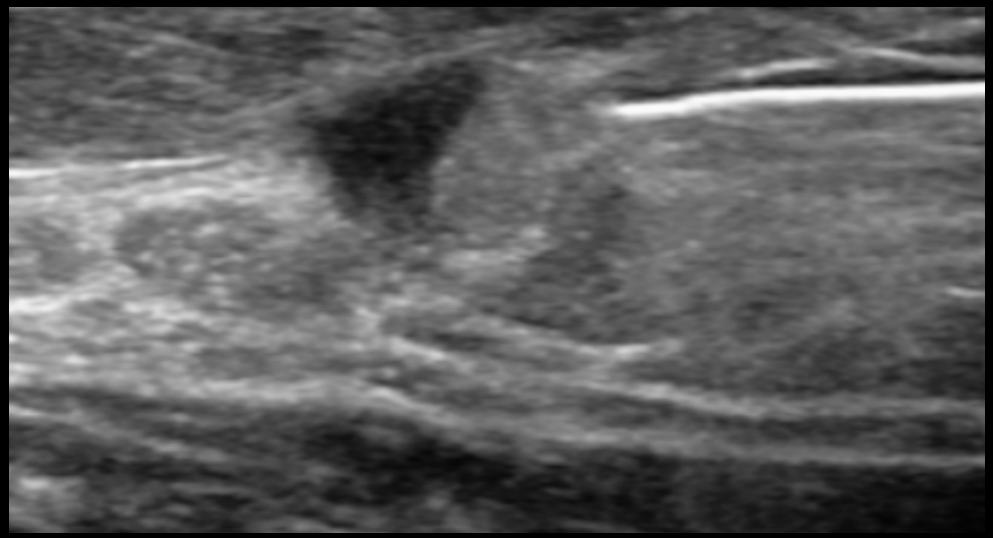
- 40% of patients are heterogeneously dense and 10% are extremely dense.
- Mammographic density is an independent risk factor for breast cancer
  - Increased risk of 4-6X for women with extremely dense breasts
- Decreased mammographic sensitivity in patients with dense breast occurs due to masking effect of overlapping dense fibroglandular tissue.
- Digital mammography significantly improves diagnostic accuracy in women with dense breast tissue.

Evaluation of Patients with Dense Breasts

- Breast Density Legislation
  - More than ½ of the United States have enacted such laws since 2009
- Supplemental screening with ultrasound and MRI are complimentary to mammography
  - Incremental cancer yield with US: 2-4/1000
  - Incremental cancer yield with MRI (high risk women): 14/1000



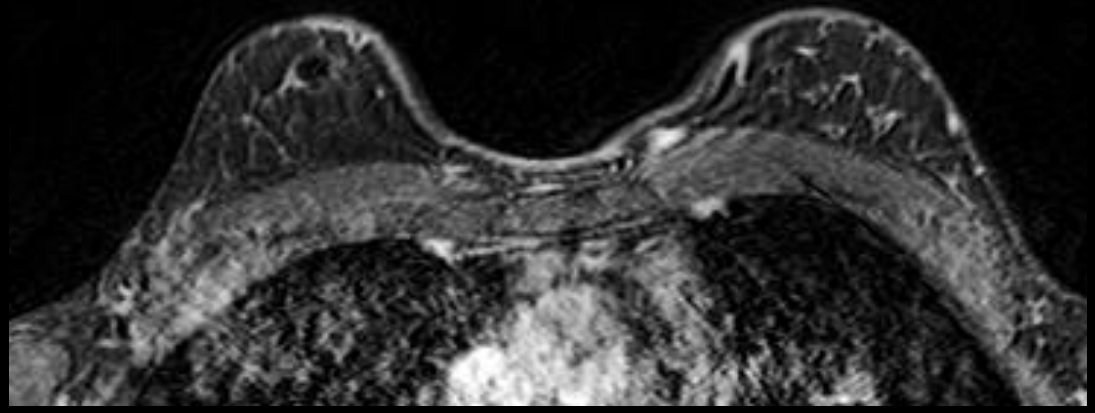


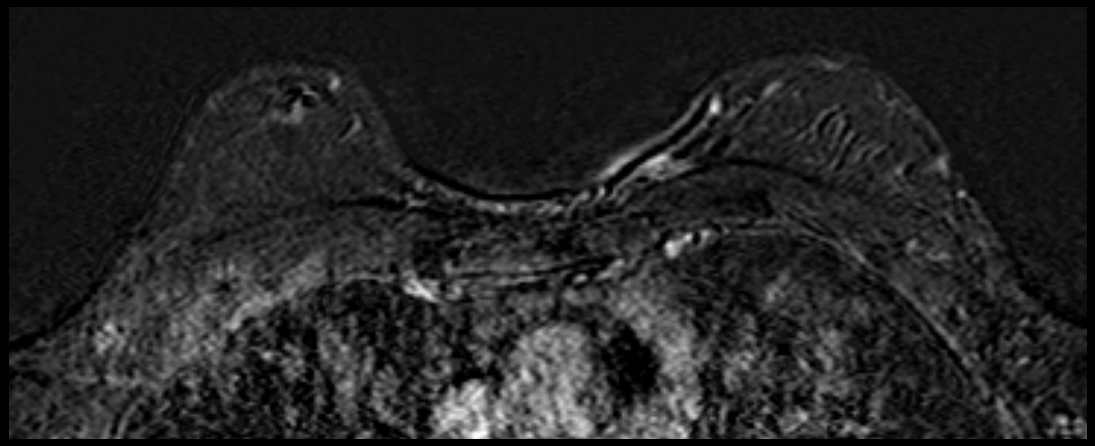


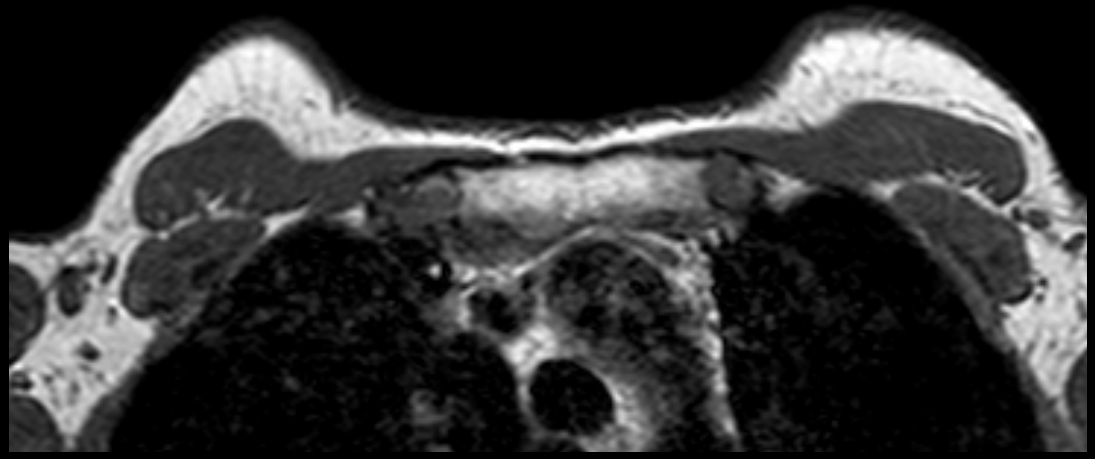
Ultrasound Guided Core Biopsy

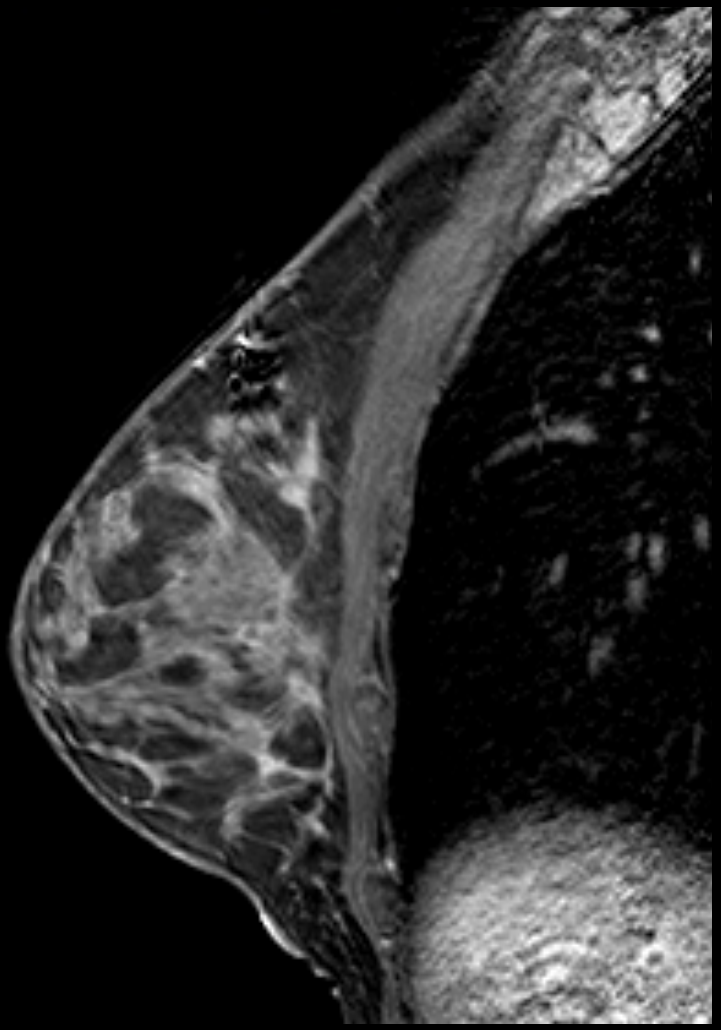
Evaluation of a palpable mass

- Technique has high sensitivity (97.5%)
- Offers many advantages:
  - No radiation
  - Low cost
  - Full control of the needle in real time
  - Accessibility in difficult locations
  - Excellent patient comfort
  - Minimal scarring
  - Minimal complications (less than 1/1000)
- Adequate radiology/pathology correlation is necessary









Future Directions

- Abbreviated MRI
  - Shorter acquisition times (9 minutes vs. 24 minutes) with comparable diagnostic accuracy
  - ACRIN Trial EA1141A
    - Compared 3D mammography with Abbreviated MRI
- Contrast Enhanced Mammography
  - Uses dual energy image pairs and iodinated contrast
  - Studies show equivalent cancer detection rates as well as comparable sensitivity and specificity with MRI
  - Currently unable to performed CEDM guided biopsy

PATHOLOGY: Core biopsy

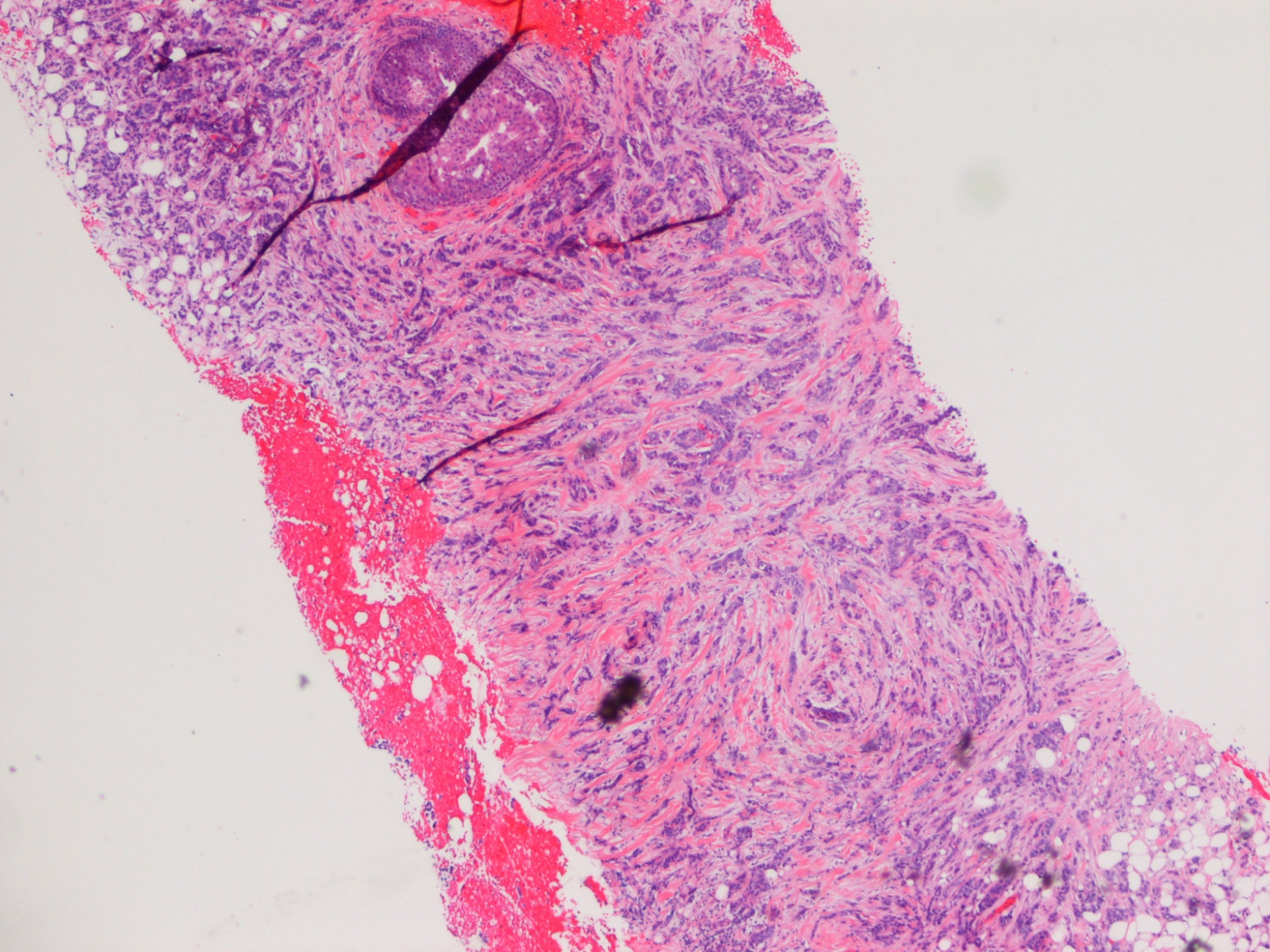
A. Mass at 12 o'clock, RIGHT breast, ultrasound-guided core biopsy:

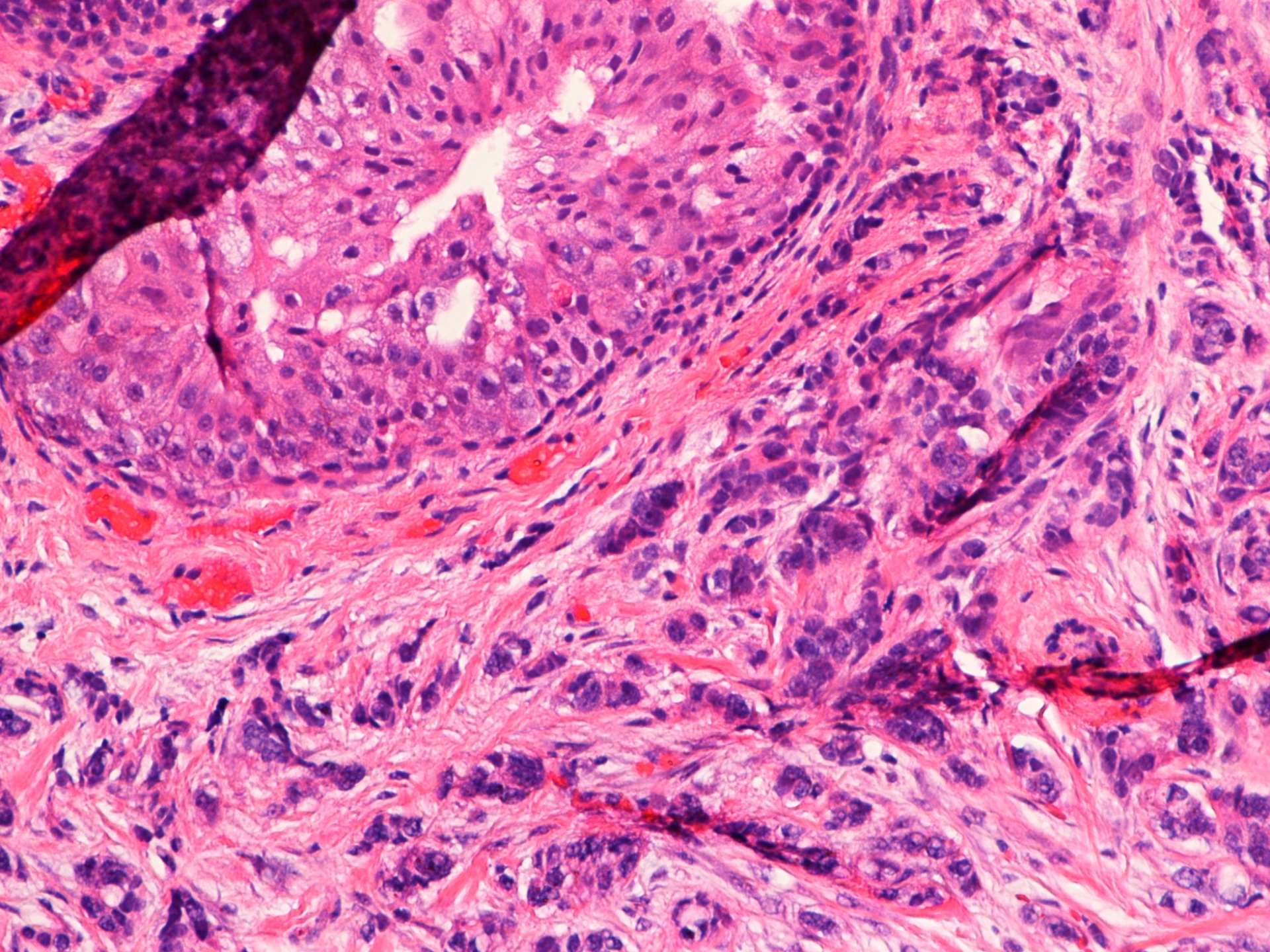
- Invasive ductal carcinoma, poorly differentiated (tubular differentiation score 3/3, nuclear pleomorphism score 3/3, mitotic rate score 2/3; total Nottingham score 8/9), present on 3 out of 3 tissue cores, spanning 0.6 cm in greatest length.
- Ductal carcinoma in situ, solid pattern, with intermediate-grade nuclei, also present.

HER2: 2+ IHC, FISH: Negative.

ER: Positive, >95%, Strong

PR: Positive, >95%, Strong





Additional workup

- Expedited genetic testing- no mutation
- Fertility consultation
- Plastic surgery consult

Audience Response Question

What is the recommended treatment?

a. Bilateral nipple sparing mastectomy and sentinel node biopsies with reconstruction

b. Neoadjuvant chemotherapy

c. Lumpectomy and sentinel node biopsy

Genetic Testing in Young Patients

- *What is young?*
- *More likely to have a mutation*
- *Counseling important*
- *Risk for a mutation around the time of pregnancy - 30% + chance*

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Expedited testing

- *Single Site v Single disease v Panel*
- *Talk with lab*
- *Generally 2-4 weeks, can be shorter*
- *Best to test prior to surgery if making surgical management decisions*
- *Cost*
- *Pre-authorization/Insurance*

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Other Issues

- *Parental guilt*
- *“Marriageability” of family*
- *Reproduction*
- *Egg Freezing*
- *Preimplantation genetic diagnosis*

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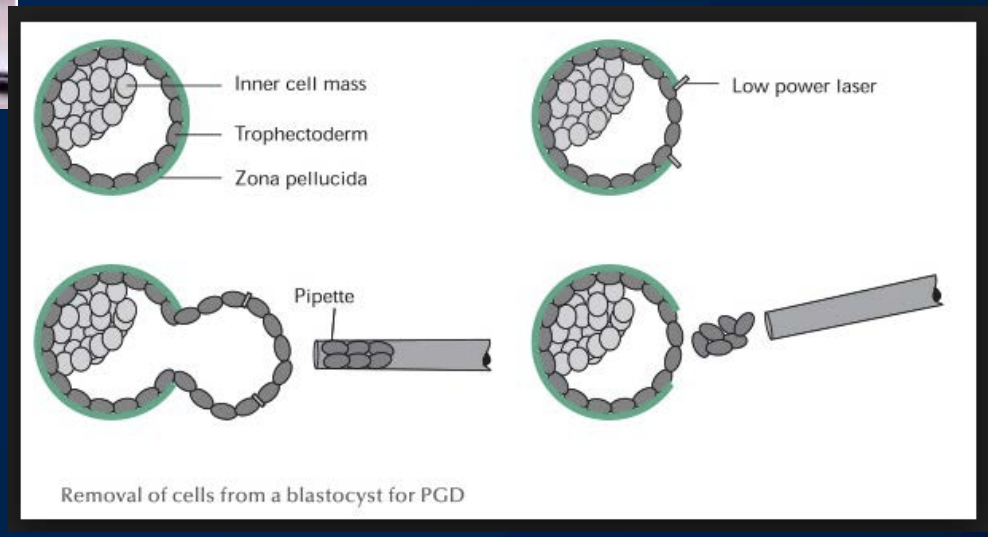
Pre-implantation Genetic Diagnosis



Removal of cells from a blastocyst for PGD

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Embryo vs. Egg Freezing- Issues

- Timing
- Embryo more successful?
- Egg: - No need for a partner
- Embryo storage
  - Legal issues
  - Ethical issues
- Simplifies oocyte donation
- Fertility preservation: medical & social indications

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Cryopreservation

- Can be problematic
- Improving protocols
- Survival rate: 83% vs. 91% ($p<0.05$)
- Live Birth rate/cycle: 36% vs. 24% ($p>0.05$)
- Limited Data on children

Papatheodorou et al, 2013 RBM Online

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BREAST RECONSTRUCTIVE OPTIONS IN THIN PATIENTS

- Autologous vs implant based reconstruction
- In thin patients, implant based reconstruction is usually indicated due to lack of adipose tissue

Implant based reconstruction

- One stage vs two stage reconstruction
- One stage-straight to implant (with acellular dermal matrix) at the time of mastectomy
- Two stage-tissue expander placed first

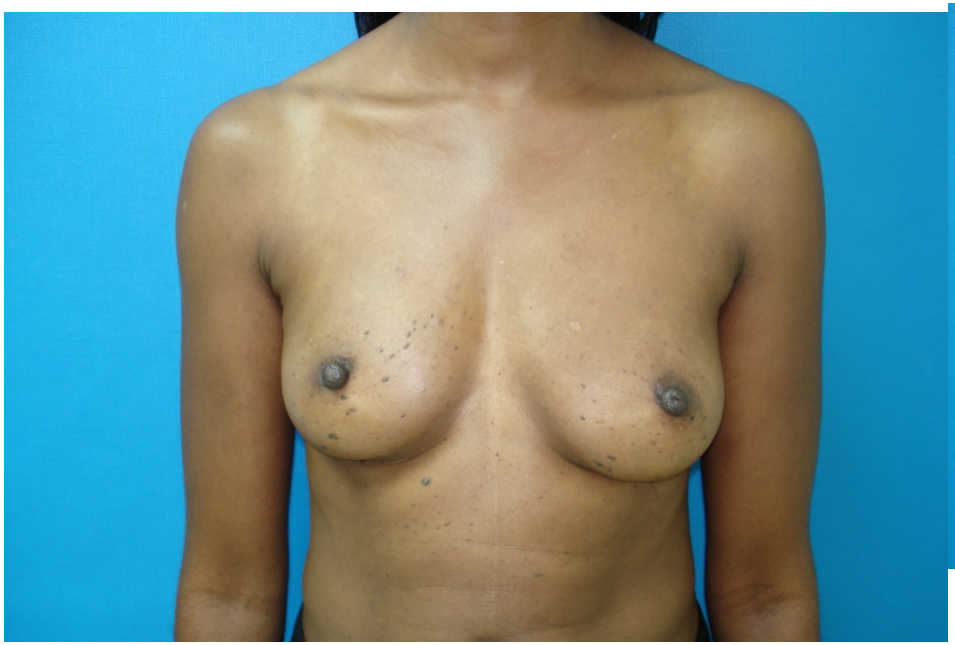
Tissue Expansion

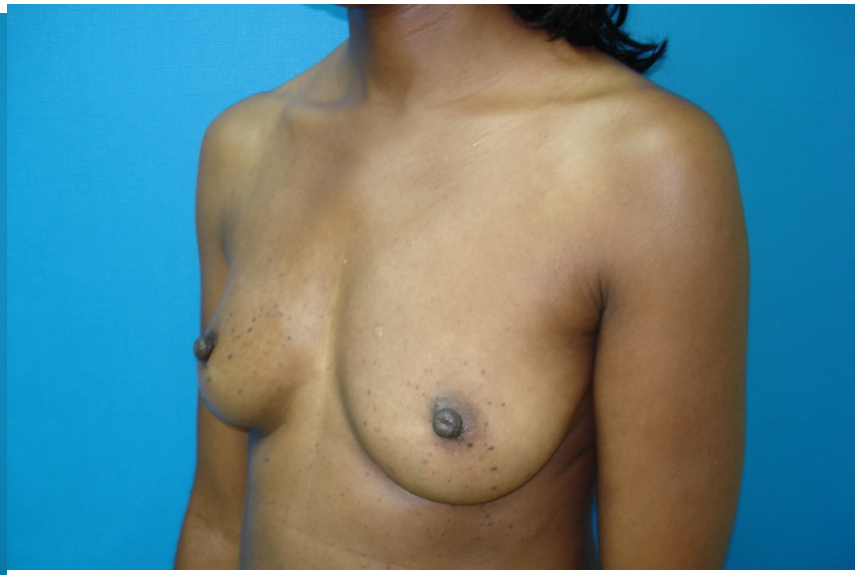
- Usually two procedures
- Place a TE at the time of the mastectomy under the pectoralis major muscle, prepectoral implants over the muscle are gaining popularity in selected cases
- Expand the skin until a proper size
- Second procedure-exchange TE for a permanent implant (silicone or saline)

Unilateral vs bilateral mastectomy

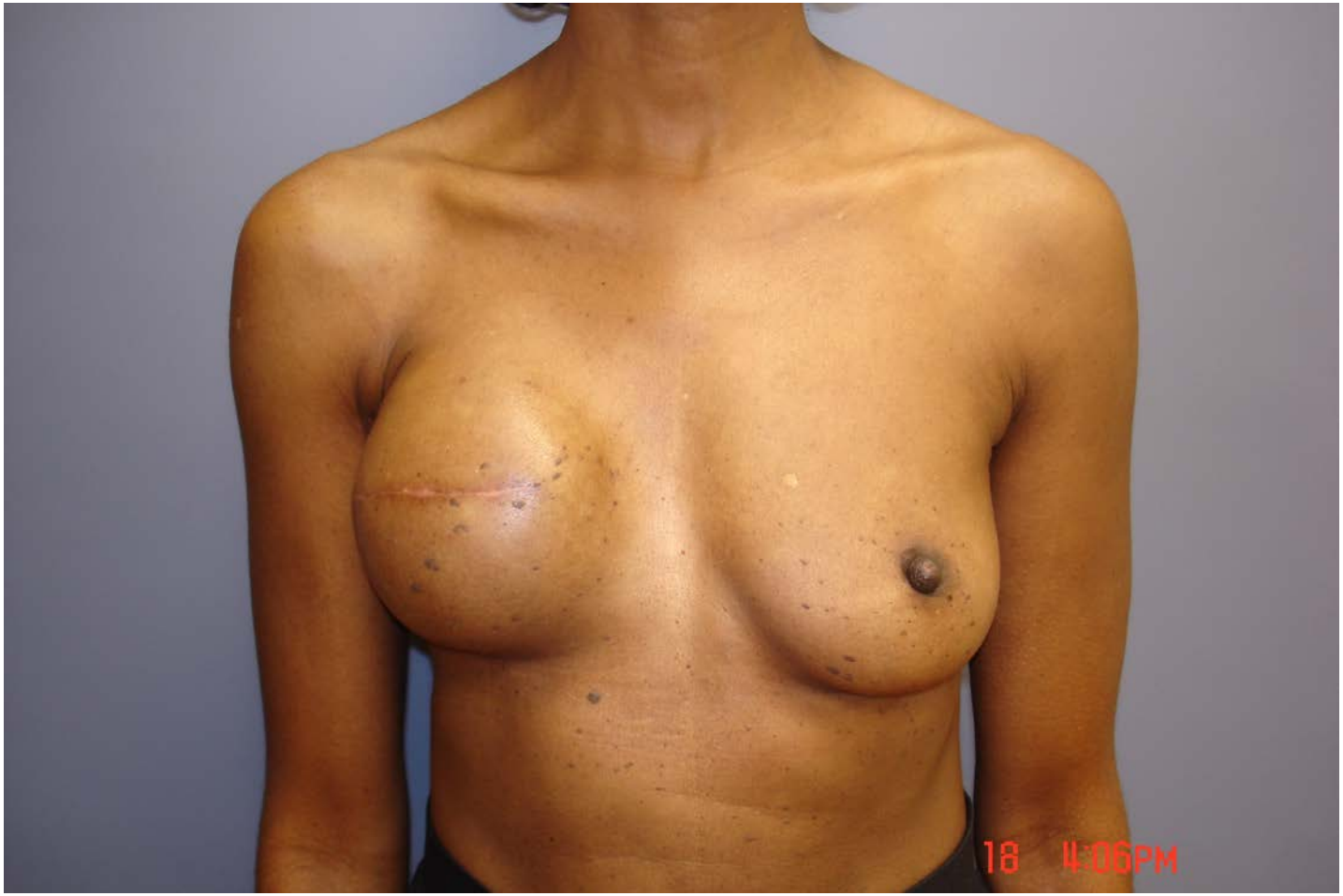
- More difficult to achieve symmetry with unilateral mastectomy than bilateral mastectomies
- Unilateral mastectomy reconstruction may require contralateral augmentation and/or mastopexy
- Easier to achieve symmetry with nipple sparing mastectomies

Unilateral right skin sparing mastectomy

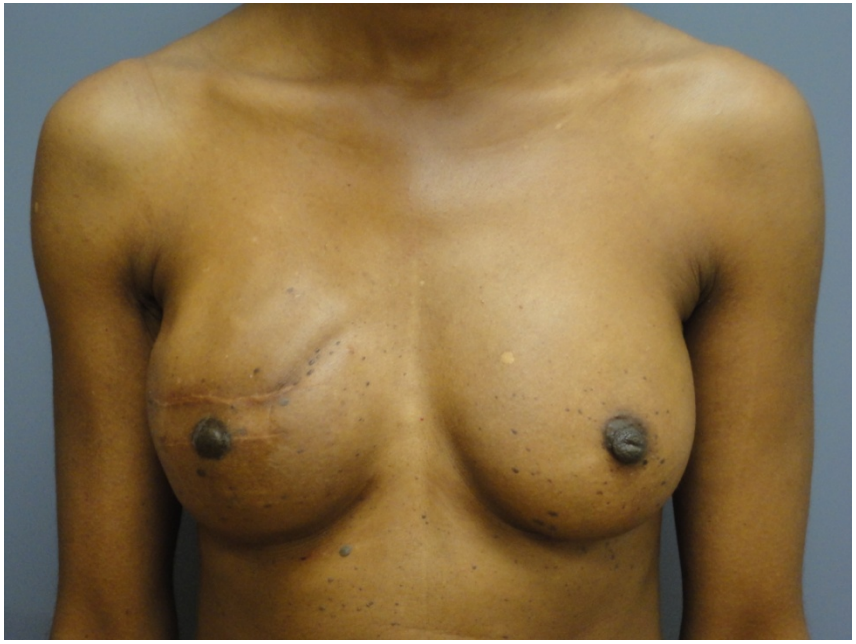


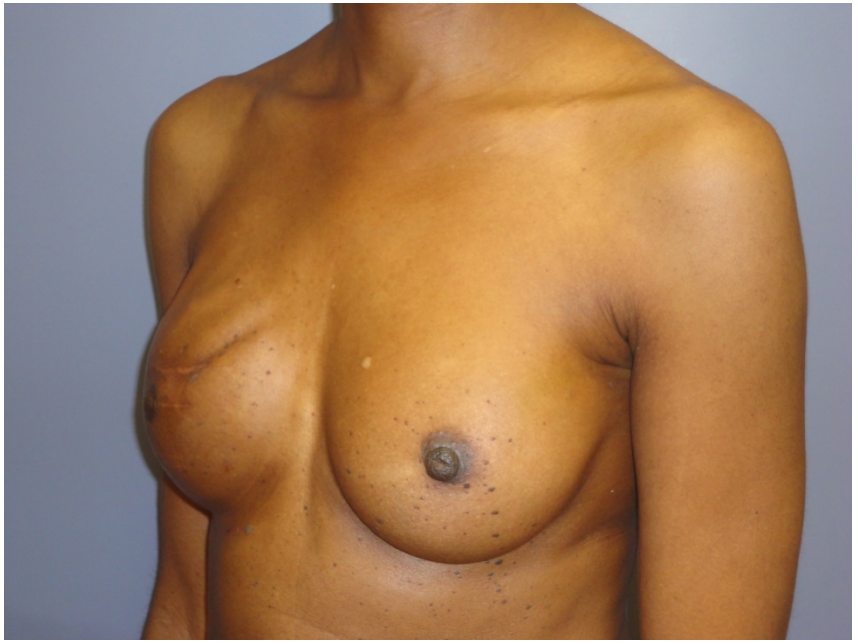


Tissue expander in place

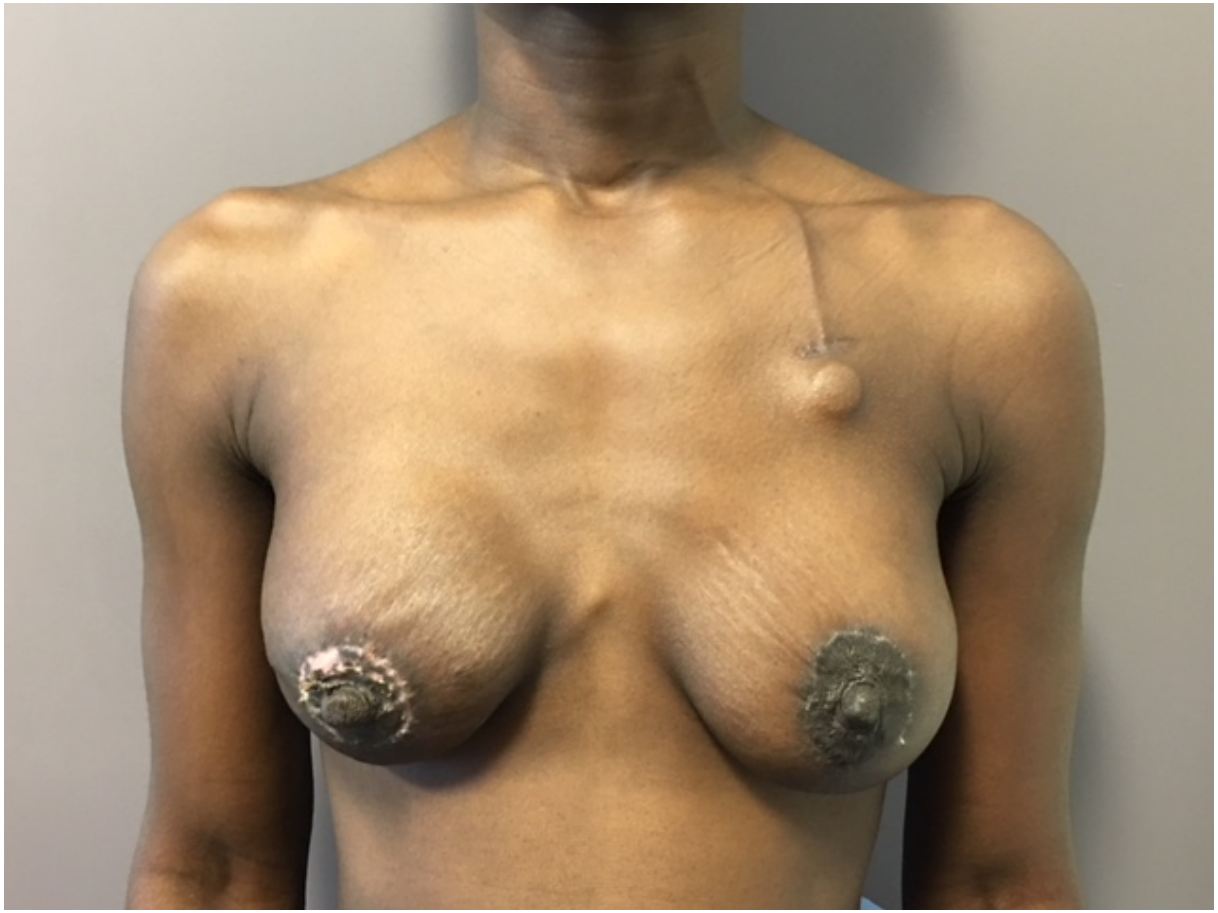


Implant Reconstruction/Contralateral augmentation

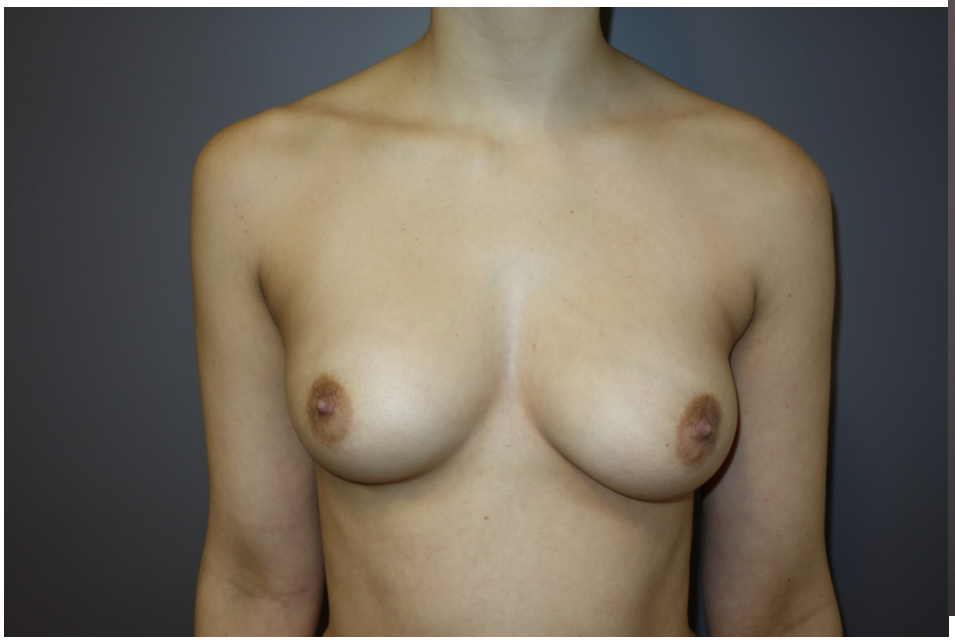


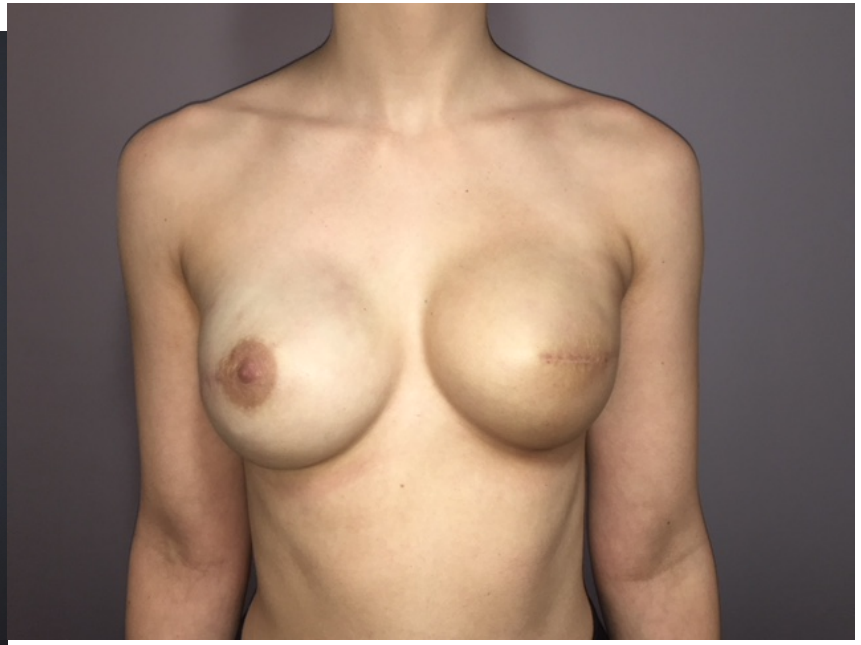


Unilateral right nipple sparing mastectomy, left augmentation/mastopexy

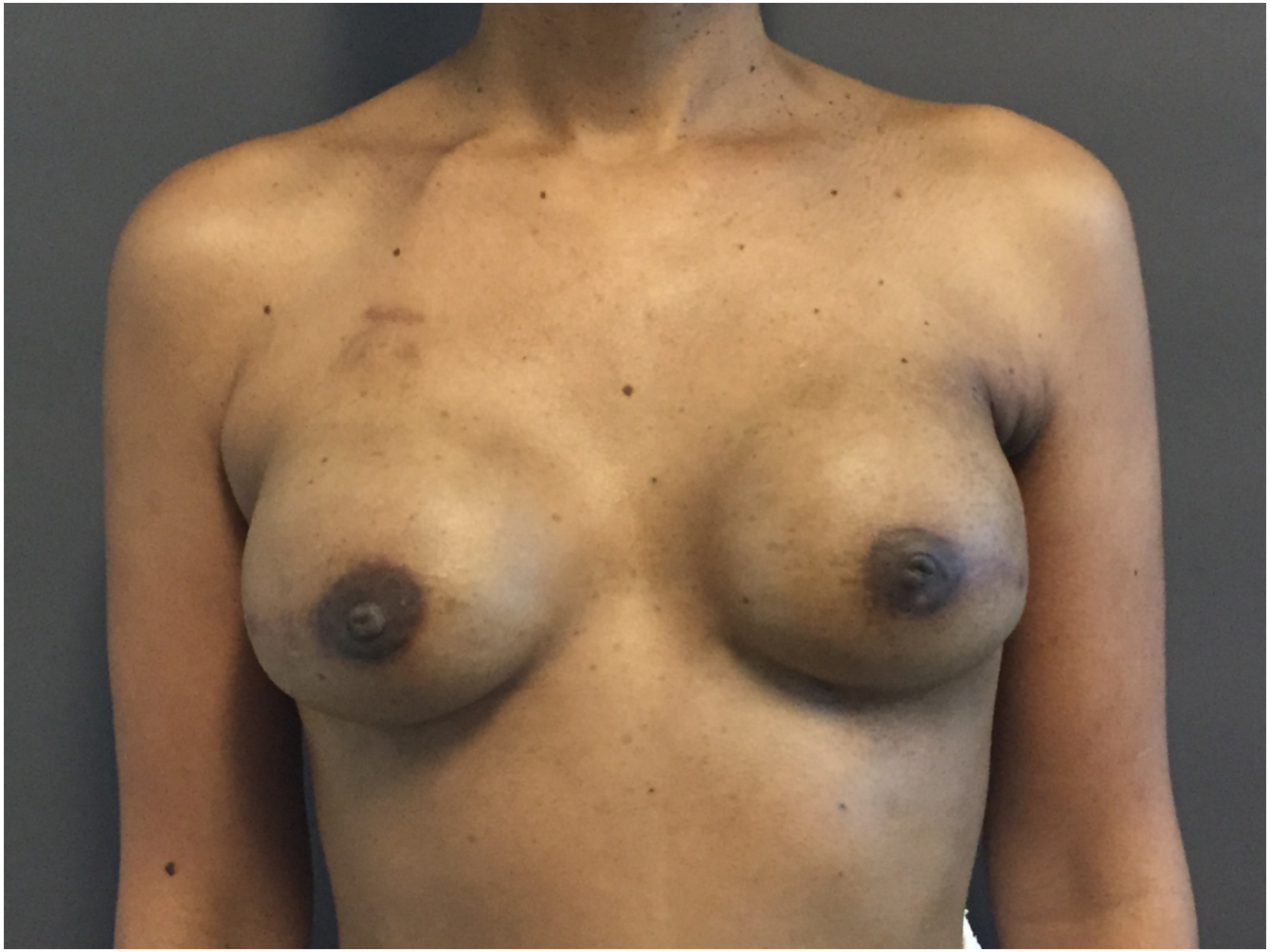


Bilateral mastectomy –right nipple sparing, left skin sparing with RT

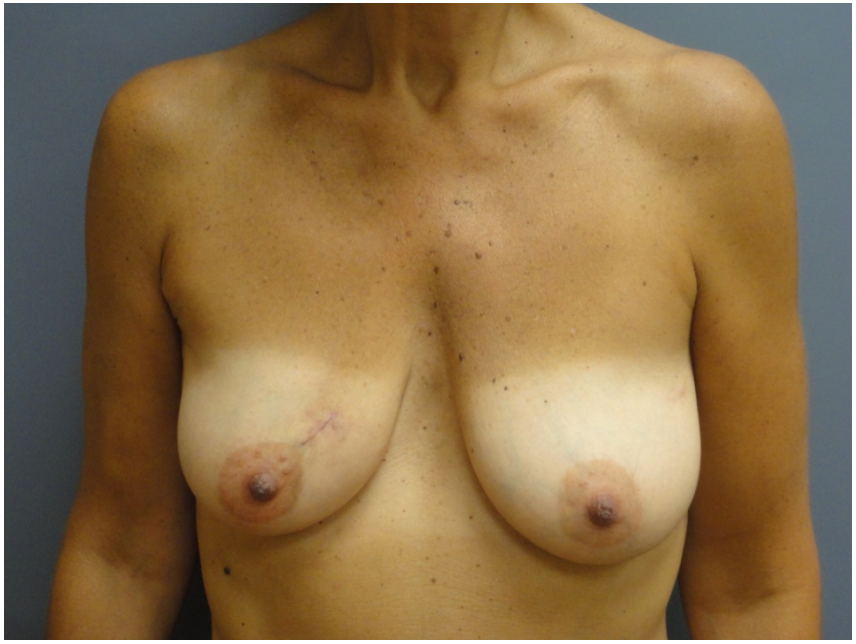


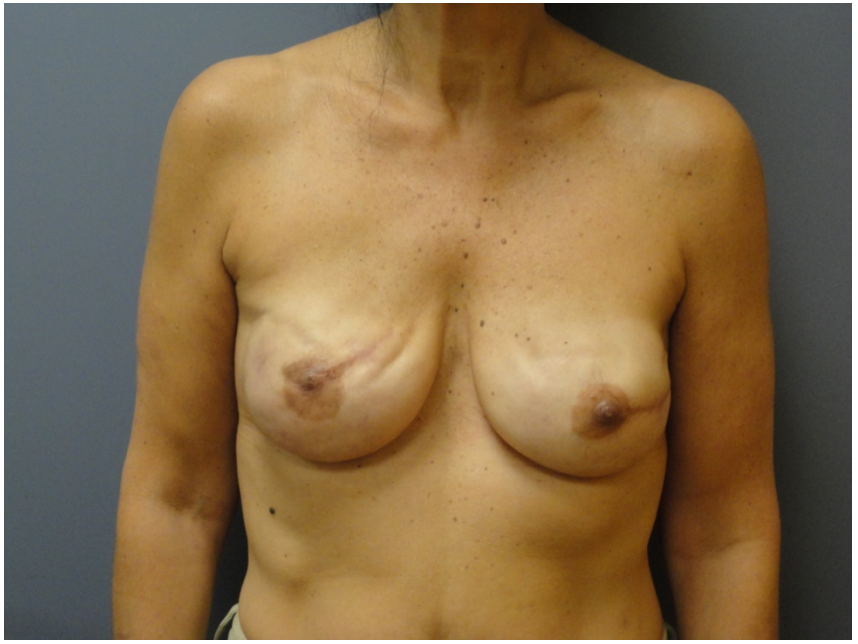


Bilateral nipple sparing mastectomy with RT



Bilateral nipple sparing-one stage straight to implant





TWENTY-YEAR FOLLOW-UP OF A RANDOMIZED TRIAL COMPARING TOTAL MASTECTOMY, LUMPECTOMY, AND LUMPECTOMY PLUS IRRADIATION FOR THE TREATMENT OF INVASIVE BREAST CANCER

BERNARD FISHER, M.D., STEWART ANDERSON, PH.D., JOHN BRYANT, PH.D., RICHARD G. MARGOLESE, M.D., MELVIN DEUTSCH, M.D., EDWIN R. FISHER, M.D., JONG-HYEON JEONG, PH.D., AND NORMAN WOLMARK, M.D.

TOTAL MASTECTOMY VERSUS LUMPECTOMY

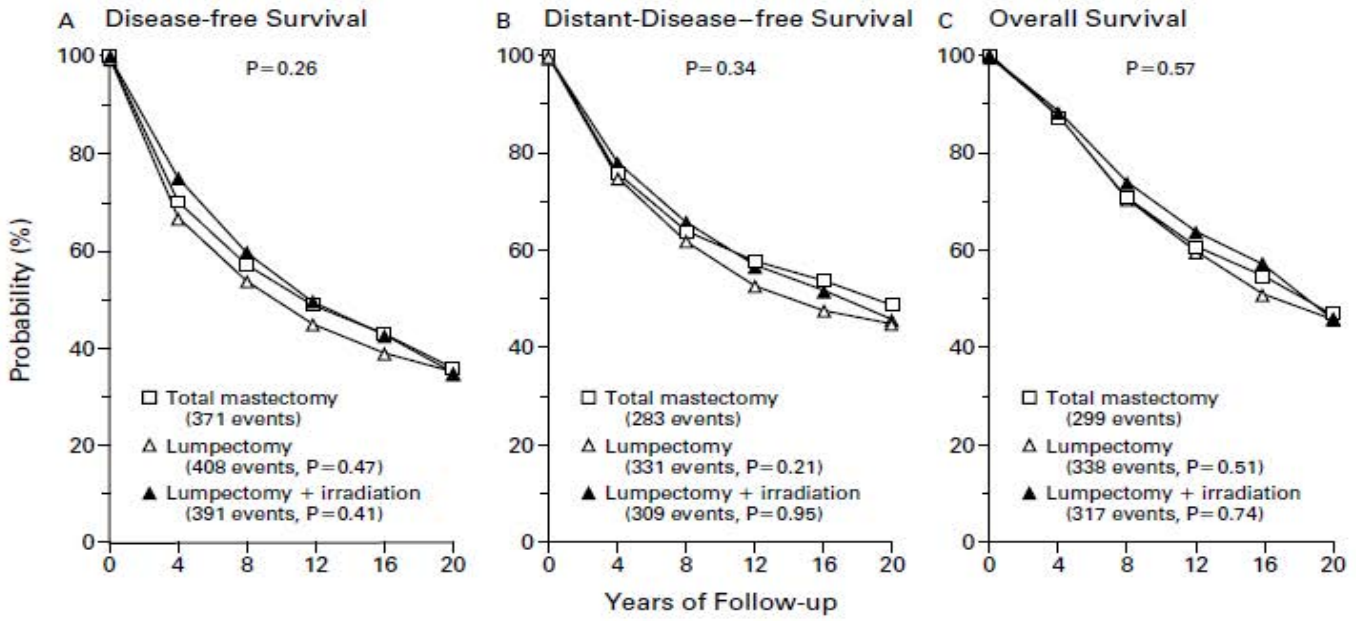


Figure 2. Disease-free Survival (Panel A), Distant-Disease–free Survival (Panel B), and Overall Survival (Panel C) among 589 Women Treated with Total Mastectomy, 634 Treated with Lumpectomy Alone, and 628 Treated with Lumpectomy plus Irradiation.

In each panel, the P value above the curves is for the three-way comparison among the treatment groups; the P values below the curves are for the two-way comparisons between lumpectomy alone or with irradiation and total mastectomy.

Fisher B. et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med.2002(347)16:1233-1241

Contraindications to Breast Conservation

- Multicentric (not multifocal) cancer
- Radiation concern-prior RT, active collagen vascular disease, pregnancy
- Inflammatory breast cancer
- Unfavorable tumor/breast size-feasible after preoperative chemo/hormonal Rx
- Nipple involvement-central lumpectomy
- Strongly + family hx; deleterious mutation, BRCA, PALB 2, etc.

Nationwide Trends in Mastectomy for Early-Stage Breast Cancer

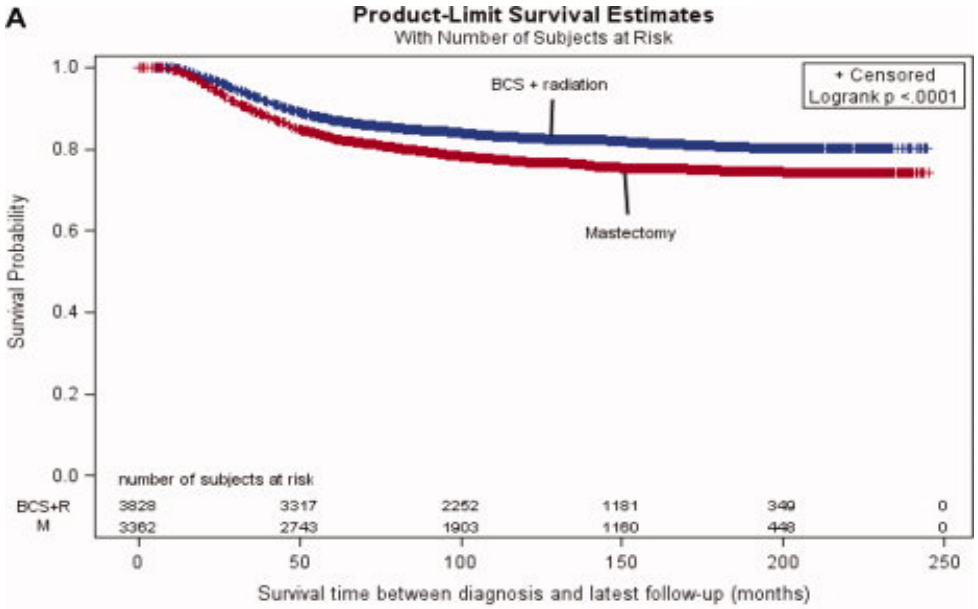
- NCDB review >1.2 million women 1998-2011
- 35.5% mastectomy
- 34% increase mastectomy in BCS eligible pts last 8 years
- Greatest increase in mastectomy with clinically node negative and DCIS
- Bilateral mastectomy for unilateral disease increased from 1.9%(1998) to 11.2%(2011)

Kummerow; JAMA Surgery 2015

Reasons for choosing mastectomy

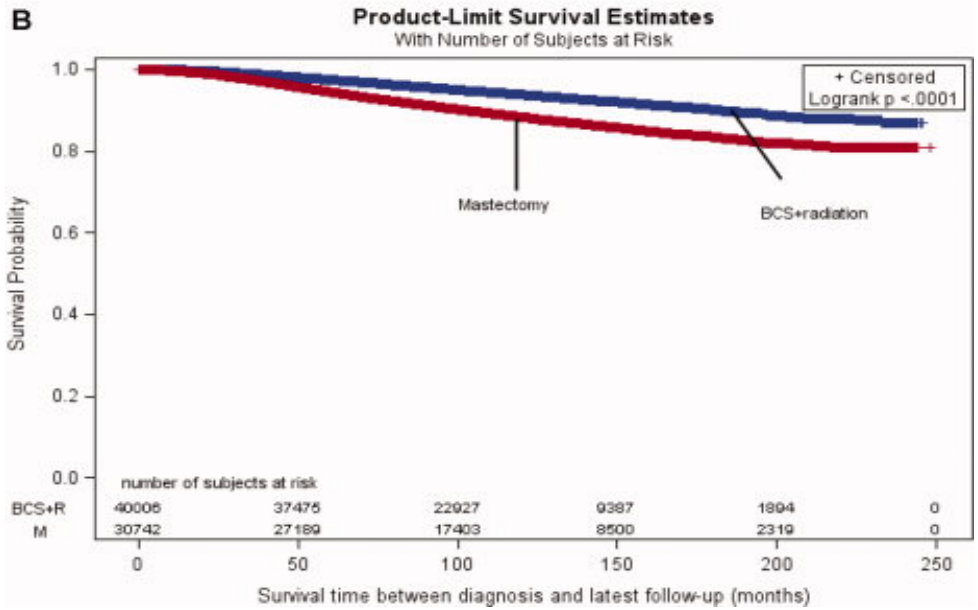
- Increased use of skin sparing and nipple sparing mastectomy with immediate reconstruction
- Peace of mind-if bilateral, better symmetry, NO MORE MAMMOGRAMS/MRI
- Patients are more proactive, and are given information through support groups, media, and the internet
- Breast MRI
- HOWEVER: BREAST CANCER SPECIFIC SURVIVAL MAY ACTUALLY BE WORSE!!

Survival after lumpectomy and mastectomy for early stage invasive breast cancer



112,154 pts
From 1990-2004

Age < 50 ER-



Age>50 ER+

Hwang,
Cancer 2013

How can breast conservation have a better survival than mastectomy?

- Mastectomy does not remove all breast tissue
- Radiation can treat larger region of breast tissue completely
- MA 20 trial suggests comprehensive radiation may improve survival
- Complex since tumor subtype and targeted systemic therapy major impact on local control
- Consider current trials with no surgery after neoadjuvant chemotherapy and clinical CPR

Clinical Course;

- Patient opted for lumpectomy with oncoplastic repair and sentinel node biopsy
- No contraindication to breast conservation for very young patients with small favorable tumors who do NOT have a deleterious gene mutation

Optimizing Breast Conservation

- Complete preop imaging workup including non-surgical needle biopsy, MRI if young, dense, lobular cancer
- Precise radiology localization of non-palpable tumors. Radioisotope seed vs. wire.
- Hidden scar approach
- Preoperative chemo/hormonal rx for unfavorable tumor/breast size ratio

Optimizing Breast Conservation(continued)

- Intraoperative ultrasound
- Intraop- margin assessment- cytology,f.s.; specimen radiography, sono, specimen orientation, shaved margins
- Marking tumor bed; clips vs BioZorb
- Oncoplastic principles including contralateral balancing procedure

Optimizing Breast Conservation(continued)

- Targeted tumor ablation-cryotherapy, laser, RFA, microwave, HIFU
- No surgery after neoadjuvant chemotherapy with evidence of a complete pathological response-NRG-BR005 TRIAL
- Active surveillance trials for Ductal Carcinoma in Situ(DCIS) COMET and LORIS

Hidden Scar Lumpectomy: Key Considerations in Choosing an Incision Location

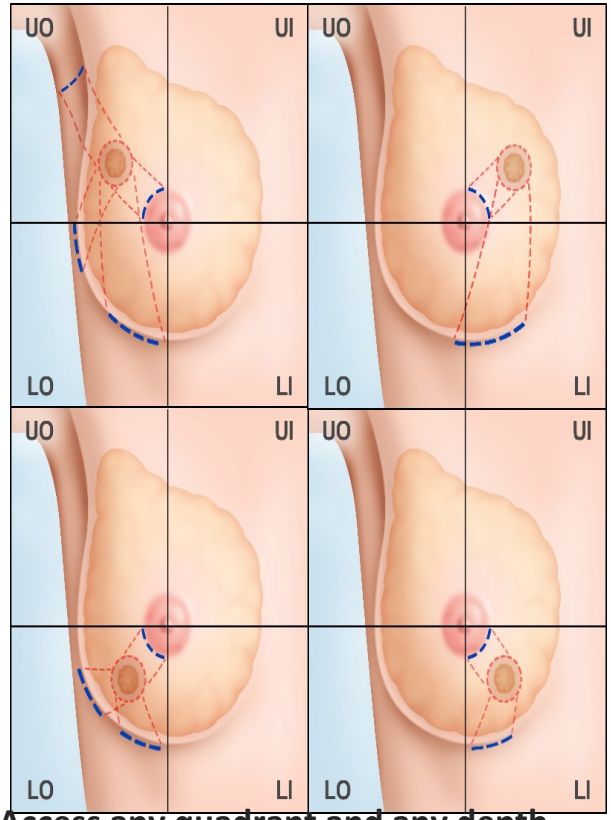
Three Hidden Incisions:

1. Areolar
2. Axillary
3. Inframammary

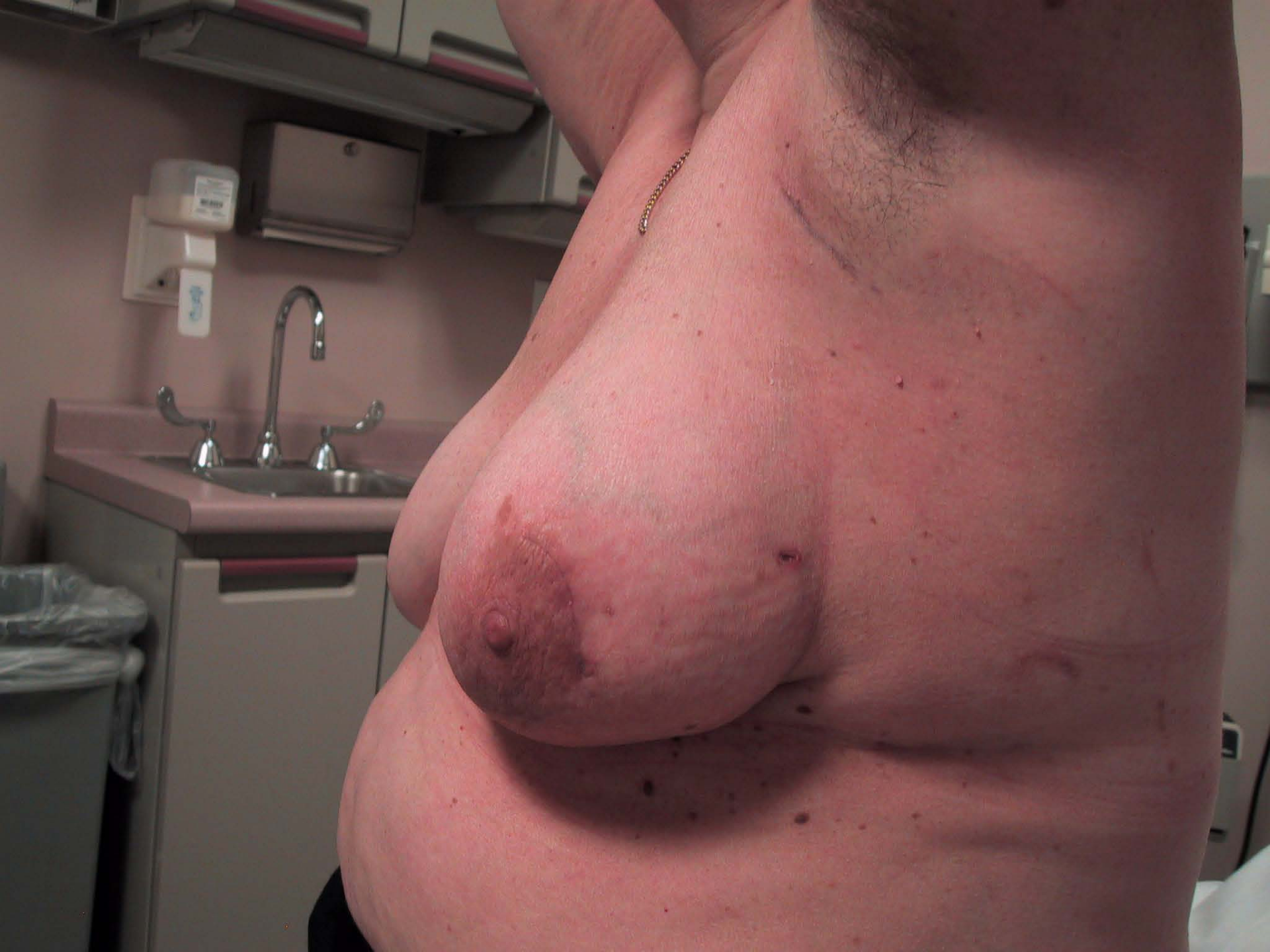
Select an incision based on ease and feasibility

Considerations for Incision Location

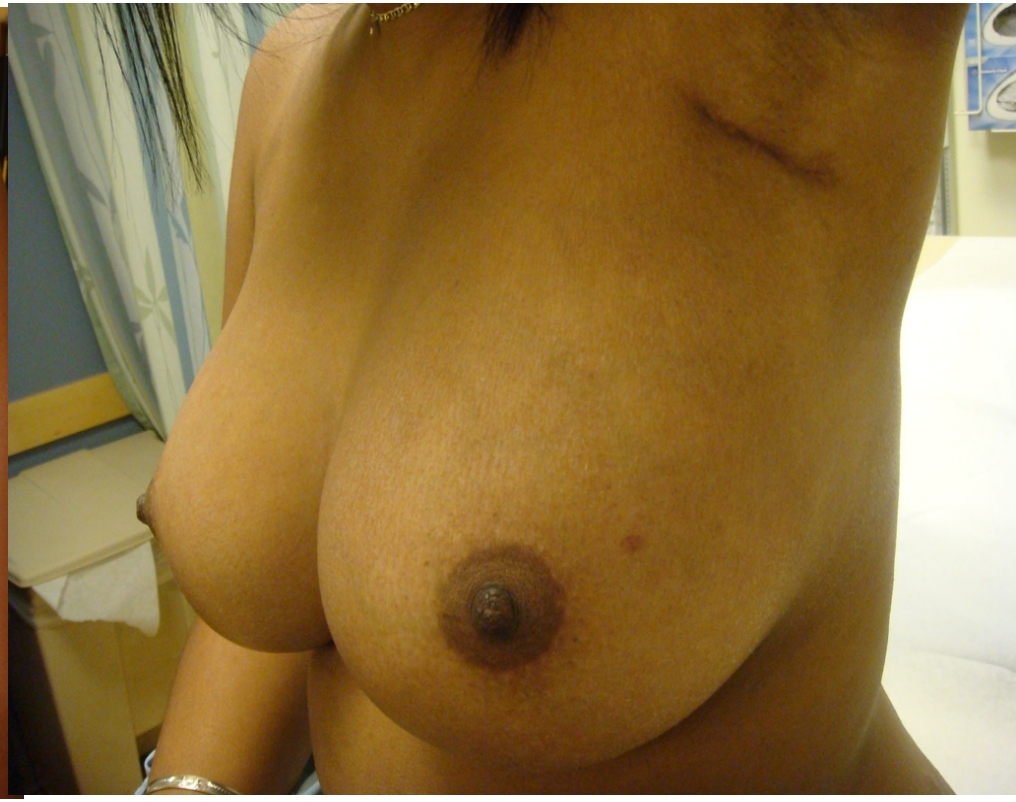
- **Areolar:**
  - Lesions in two separate quadrants
  - Potential for one incision vs. multiple
  - Small areolas can be challenging
  - Avoid if nipple sensation is a priority
- **Axillary:**
  - SNL biopsy
- **Inframammary:**
  - Place in fold

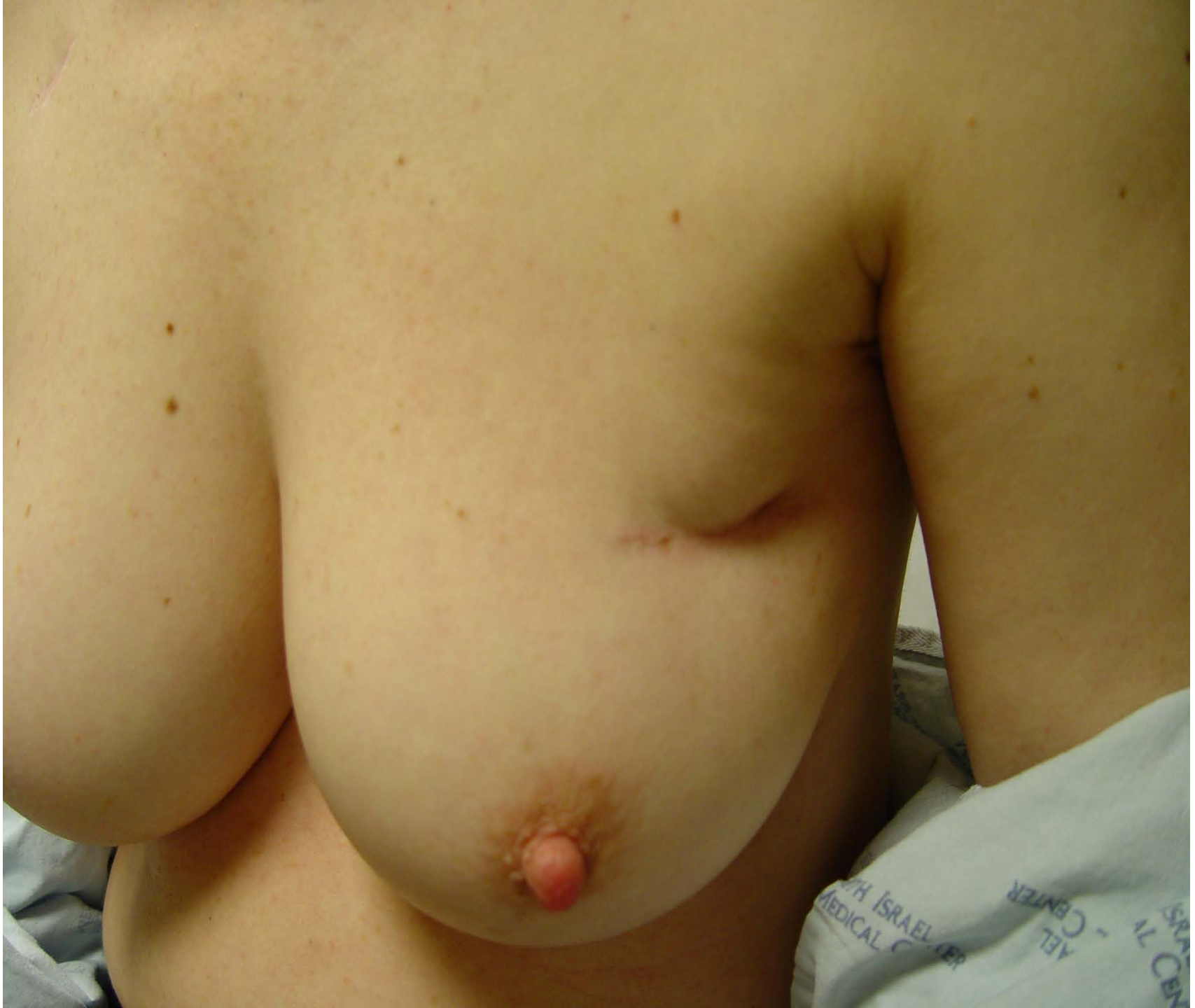


Access any quadrant and any depth of the breast from a hidden incision



S/P Neoadjuvant Chemo (transaxillary segmentectomy)





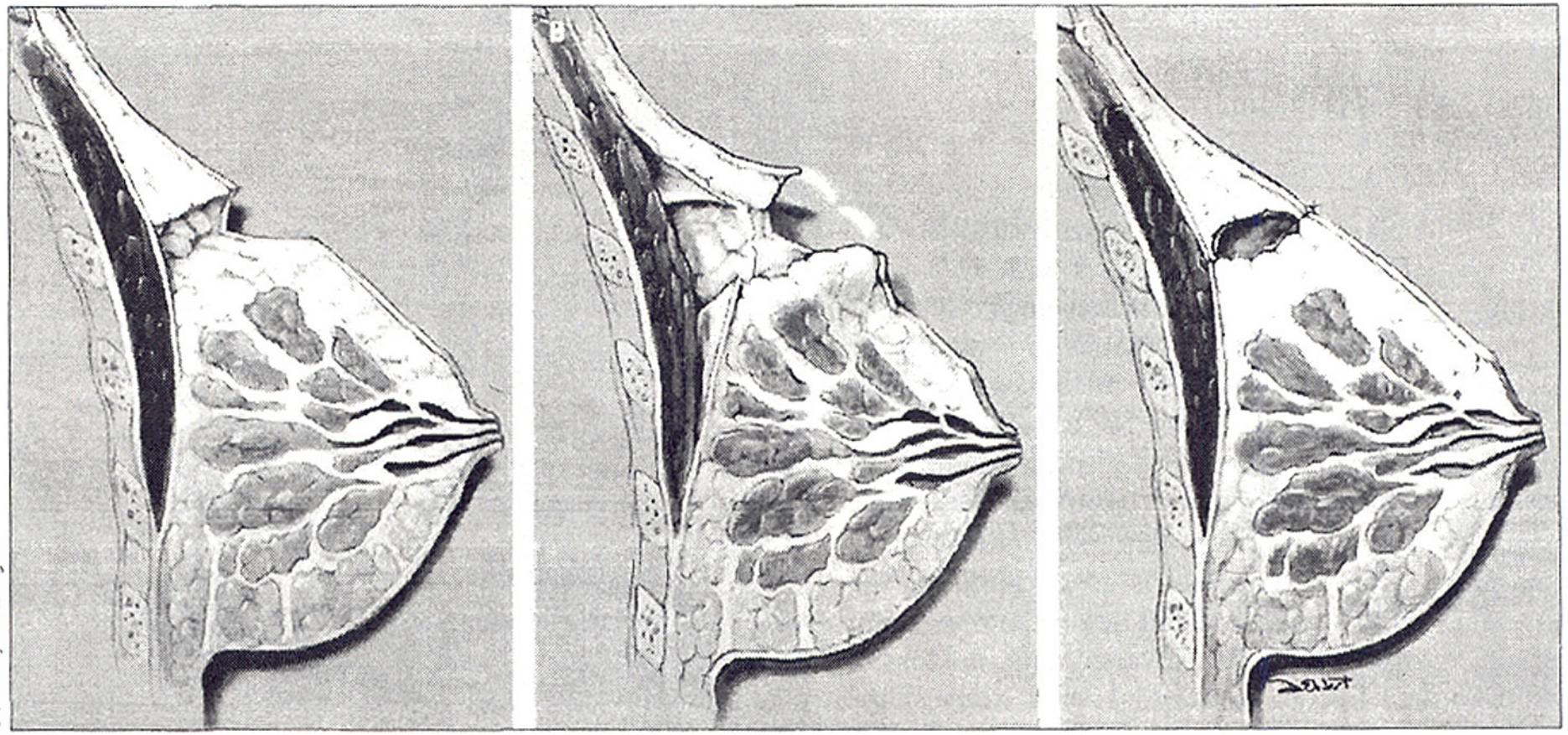
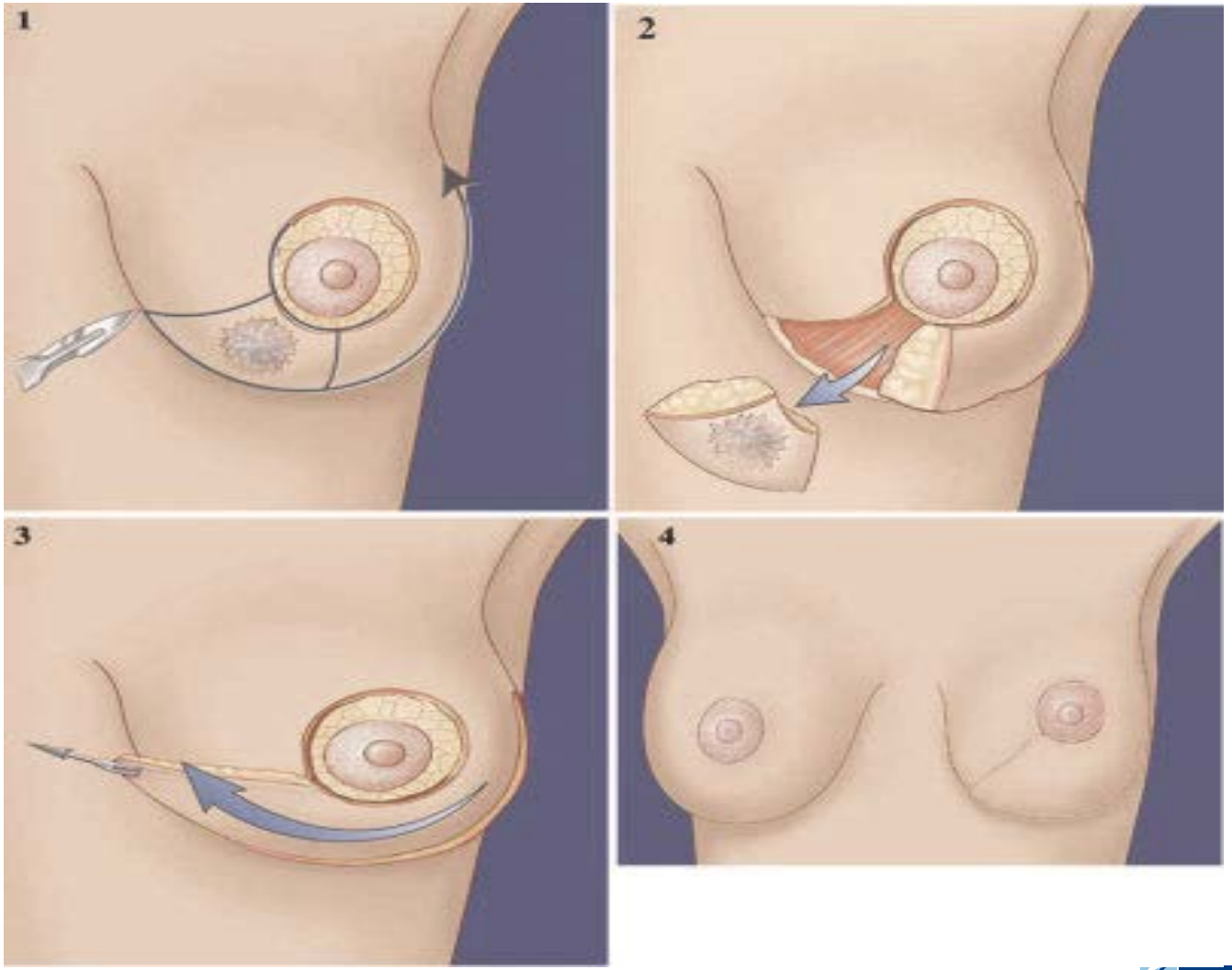


Figure 2: **Closure of breast-flap mastopexy advancement in oncoplastic partial mastectomy resection**
(A) Resection at full thickness from pectoralis fascia to skin, with an overlying skin island to allow proportional reduction in skin and fibroglandular tissue. (B) Fibroglandular tissue lifted off the pectoralis muscle to allow its advancement over the chest wall. (C) Closure of defect.

Oncoplastic Approach

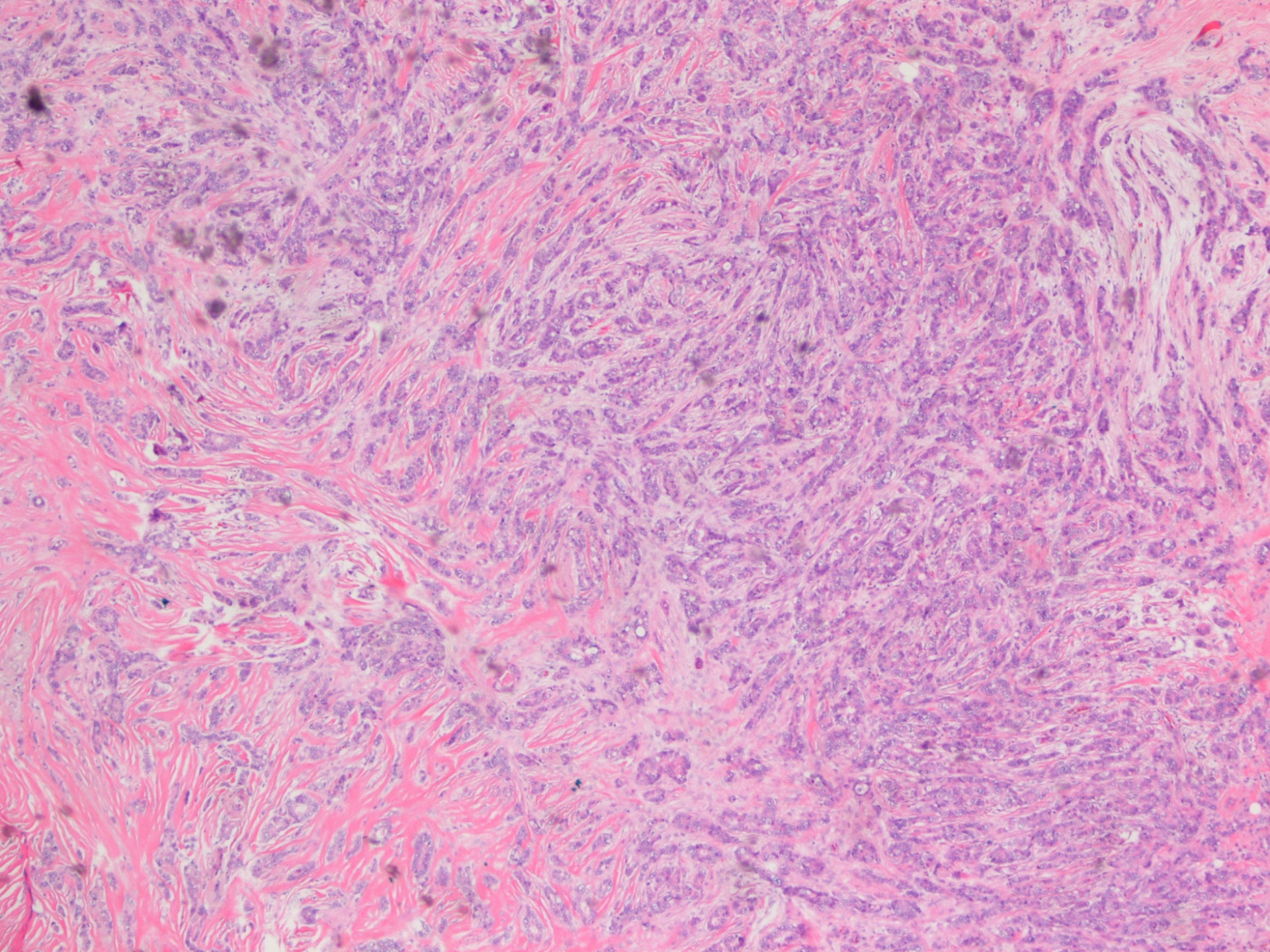


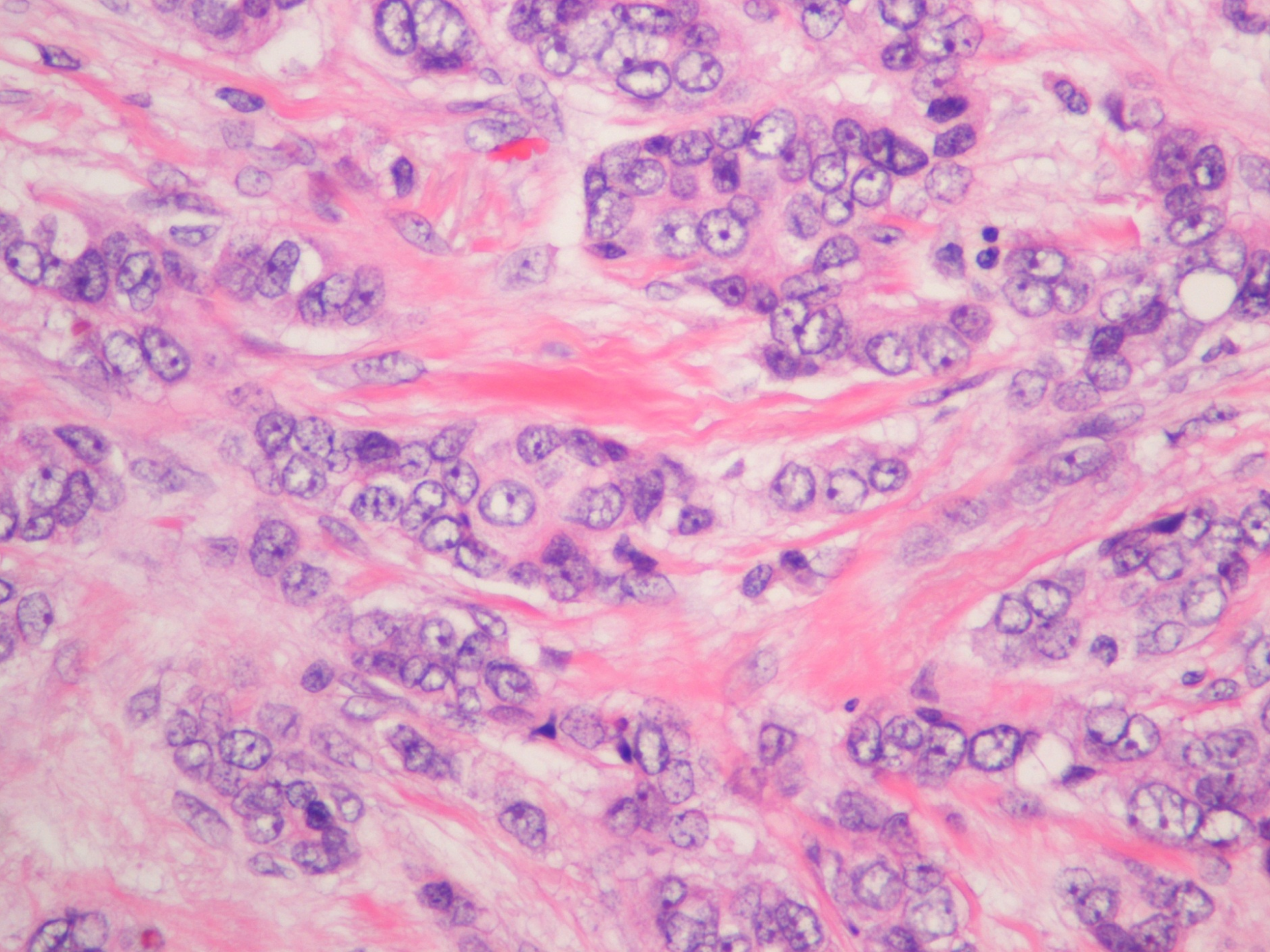
Montefiore Einstein
Center for Cancer Care

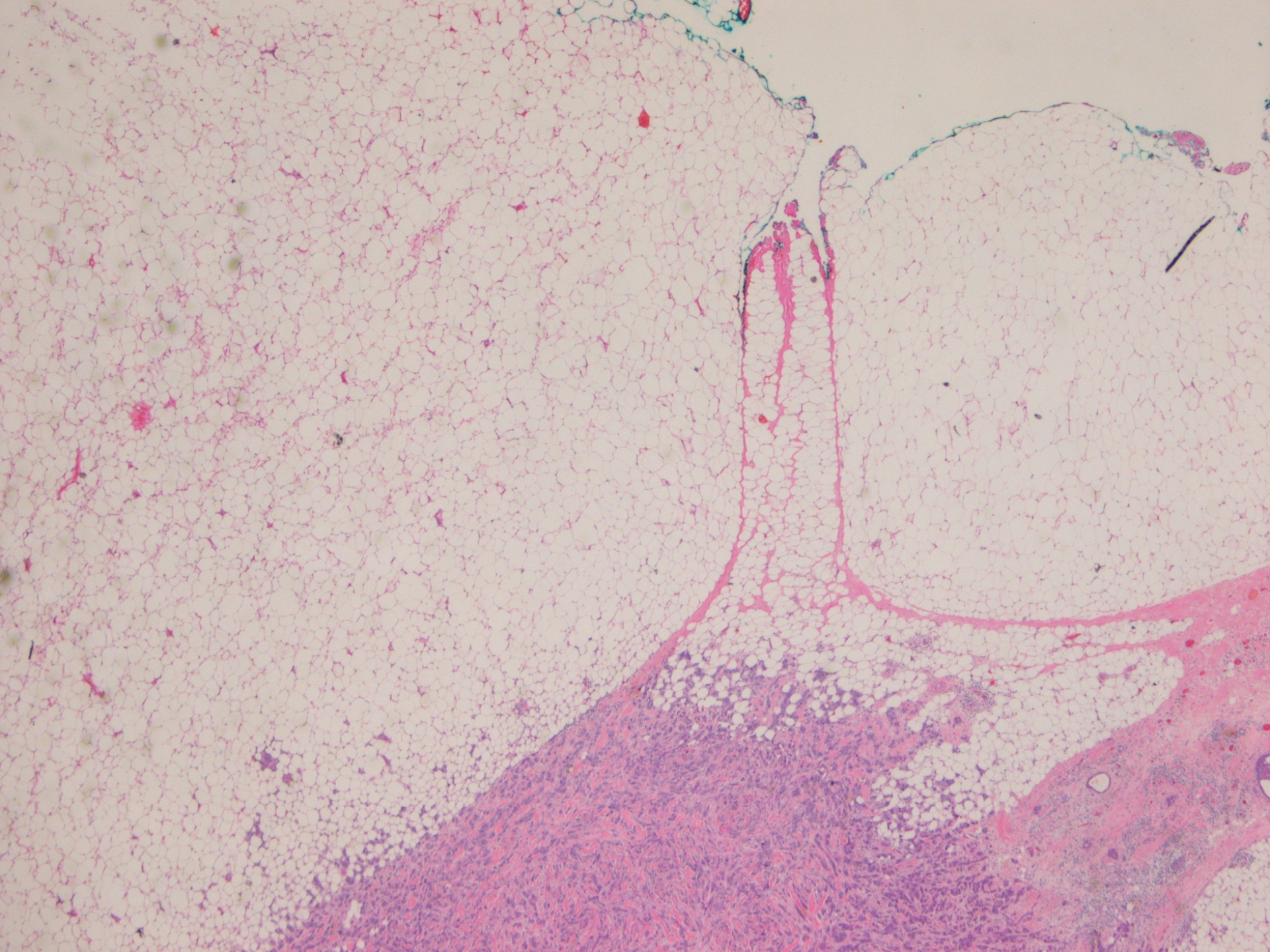
EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

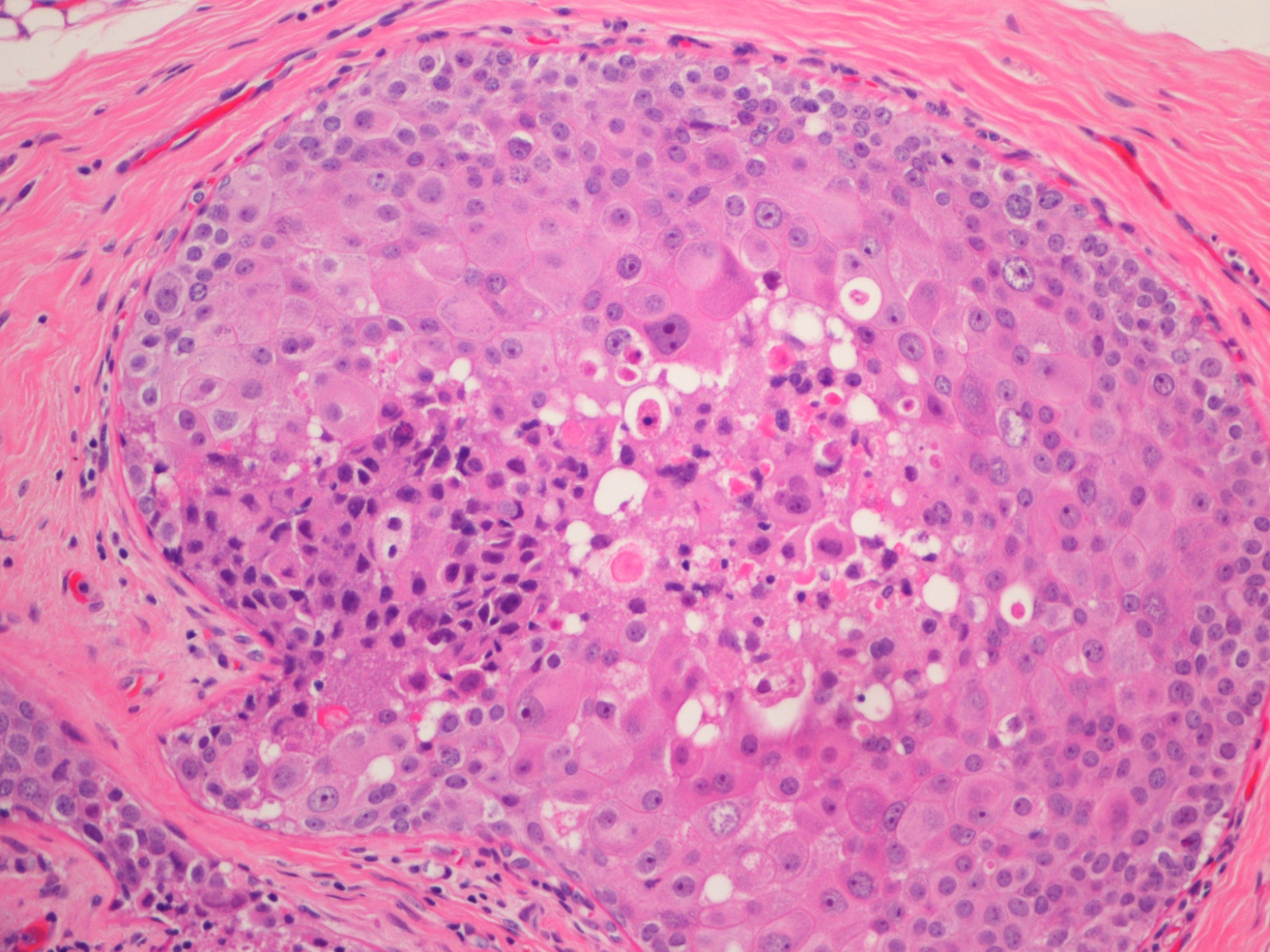
PATHOLOGY

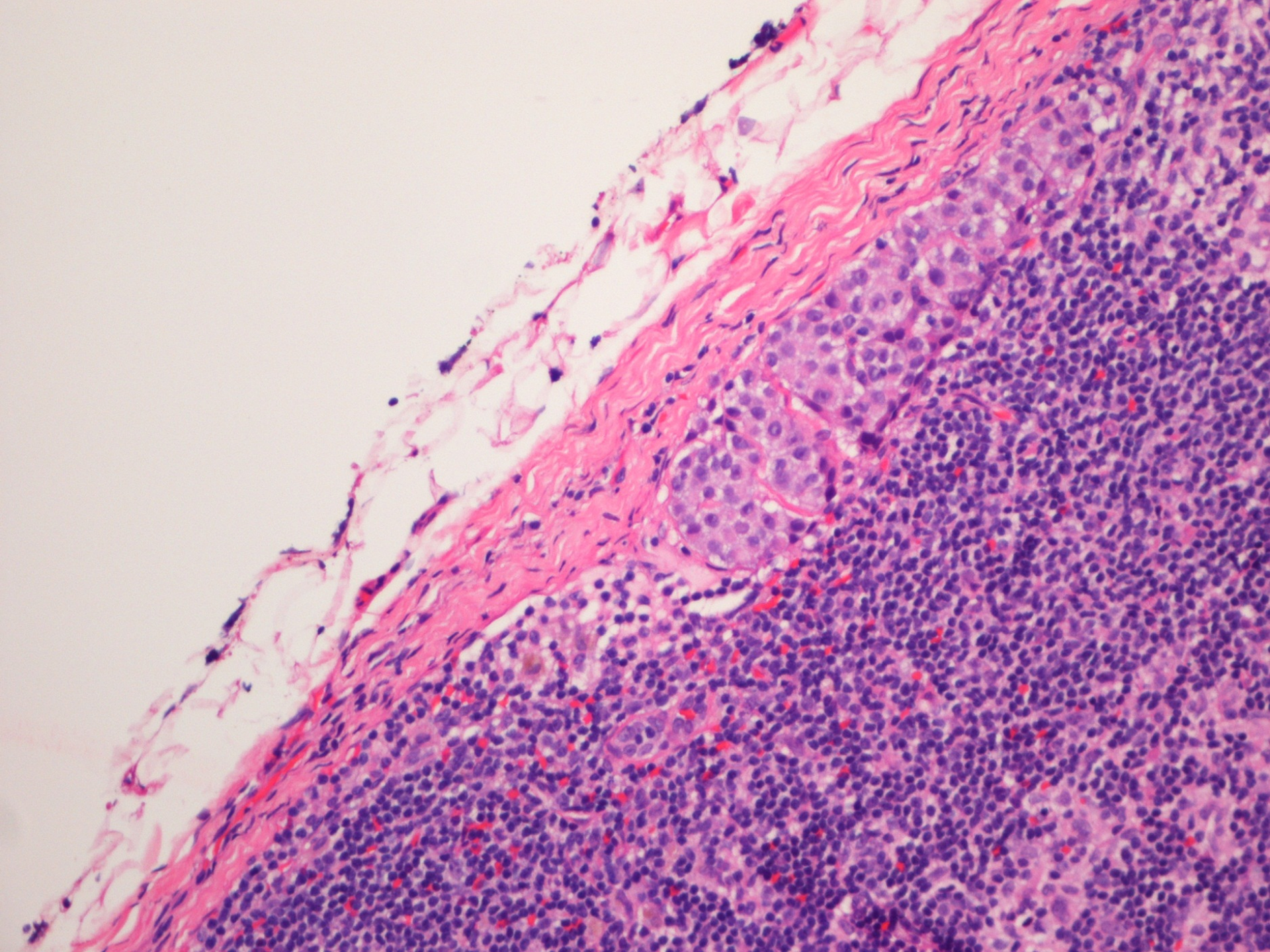
- Lumpectomy+ Separate margins + One sentinel Lymph Node

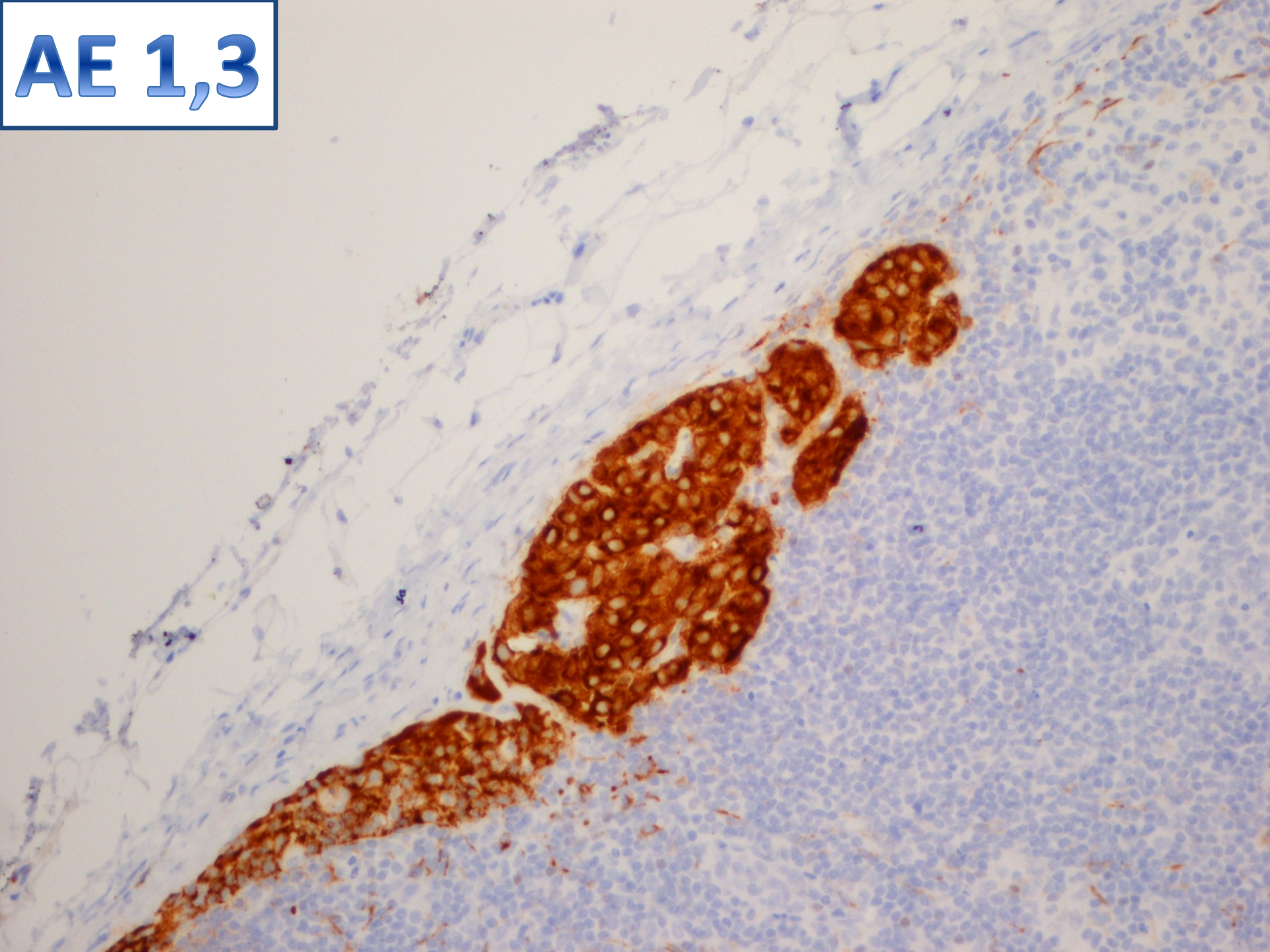











AE 1,3

-Invasive ductal Carcinoma , Poorly differentiated – Tubule Score 3, Nuclear Pleomorphism Score 3 and Mitotic Rate Score 2 =

-Combined Nottingham Score 8/9

- Size 12mm

-1 Sentinel Lymph node positive for micrometastasis (0.3mm)

- Widely Negative Resection Margins(>5mm)

-ER and PR 95% strong and Her2neu negative by FISH

-T1cN1(mi)

- Genomic Testing- Oncotype Recurrence Score =9 (low)

Pathologists role in Oncotype Dx testing

- Oncotype Dx is a genomic assay (genomic health) which is used to determine both risk of recurrence and benefit from chemotherapy in pts with ER+ BC
- AJCC 8th edition staging incorporates Oncotype Dx Recurrence score (RS) into Prognostic Staging- for pts with node negative disease and RS <11= Stage 1A (10 yr recurrence risk 6% with tamoxifen)

Appropriate Tissue Selection by the Pathologist is CRITICAL for Genomic assays :

- Oncotype Dx RS - 5 out of 16 genes assayed are related to proliferation- Breast cancers are heterogeneous – must select most mitotically active areas of tumor –Highest grade
- Select areas with largest volume of invasive tumor and lesser amounts of DCIS or benign breast tissue
- Core vs Excision- Both give comparable results

Is axillary dissection necessary for a positive sentinel node?

ACOS-OG Z0011 Trial

Positive SN patients randomized to axillary dissection or no further axillary treatment

Giuliano et al Ann Surg 252:426-33 2010
Giuliano et al. JAMA 2011;305:569-575

Z0011 Inclusion/Exclusion Criteria

Eligible

- Clinical N0,T1-2
- H&E-detected SN metastases
- Lumpectomy with whole breast irradiation
- Adjuvant systemic therapy

Ineligible

- IHC-only nodal metastases
- 3 or more involved SN
- Matted nodes, gross extranodal extension
- Third field (nodal irradiation) or APBI

From: **Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node MetastasisThe ACOSOG Z0011 (Alliance) Randomized Clinical Trial**

JAMA. 2017;318(10):918-926. doi:10.1001/jama.2017.11470

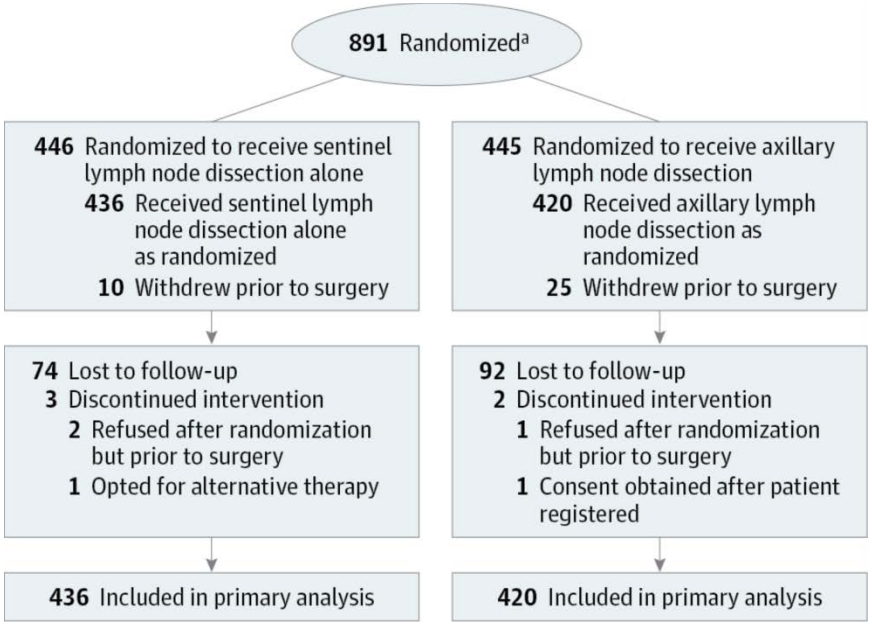


Figure Legend:

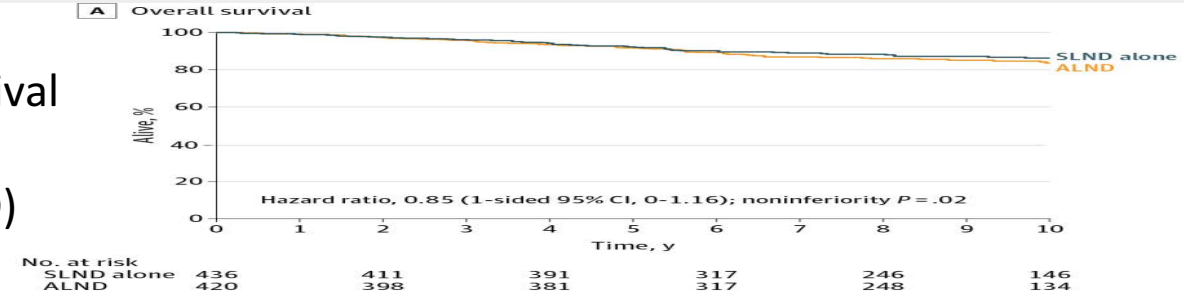
Flow of Patients Through Treatment and Follow-up in the ACOSOG Z0011 (Alliance) TrialACOSOG indicates American College of Surgeons Oncology Group; Alliance, Alliance for Clinical Trials in Oncology.

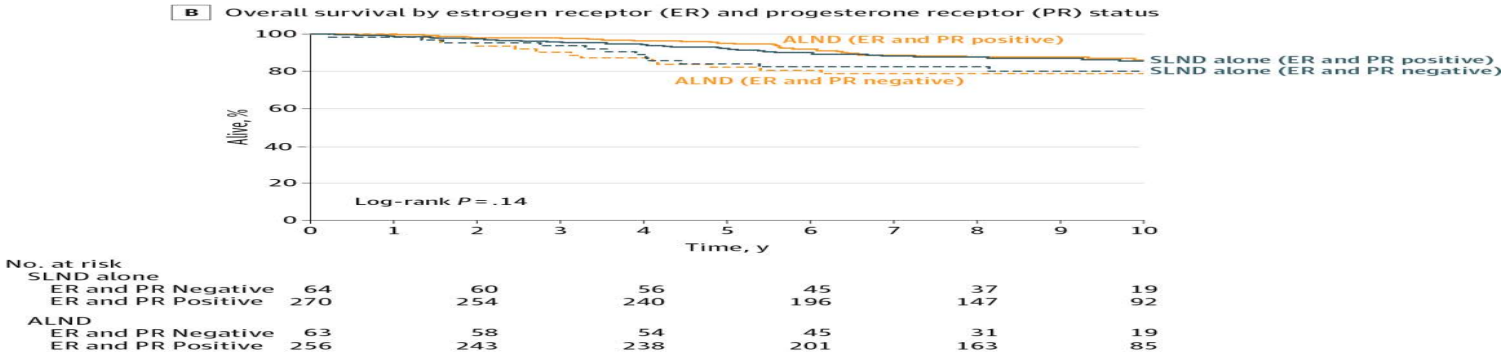
[a]Data are not available for the number of patients screened for eligibility.

From: **Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node MetastasisThe ACOSOG Z0011 (Alliance) Randomized Clinical Trial**

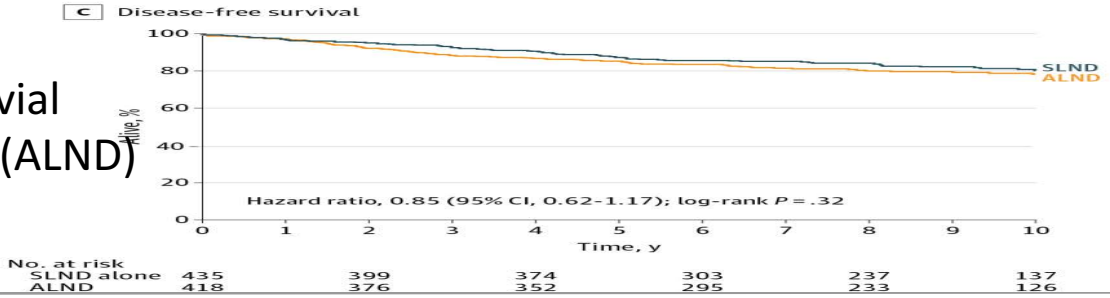
JAMA. 2017;318(10):918-926. doi:10.1001/jama.2017.11470

Overall survival
86.3(SN) vs
83.6%(ALND)





Disease free survivial
80.2(SN) vs 78.2%(ALND)



Z0011: Additional positive nodes

- 27.4% of completion axillary dissections showed additional positive nodes
- BUT - in SNB alone arm only 0.9% axillary relapse

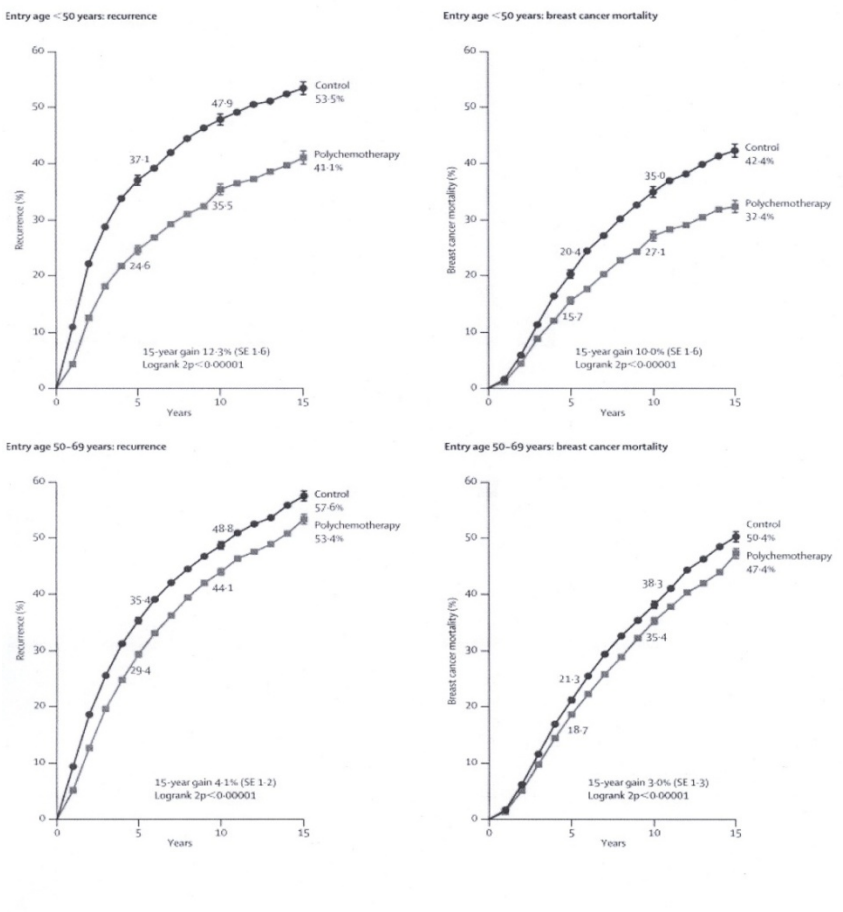
→ Significant contribution of radiation and systemic therapy to local control

  - All received whole breast RT
  - 96% ALND, 97% SNB received systemic Rx

Adjuvant chemotherapy for breast cancer

- Decisions regarding adjuvant chemotherapy are based on patient-specific and tumor-specific factors

Benefit of adjuvant chemotherapy



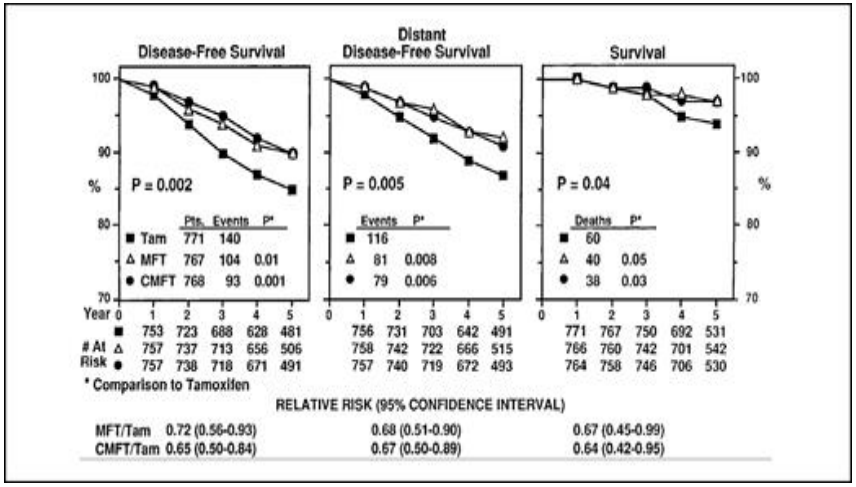
- EBCTCG meta-analysis of 194 randomized trials involving >100,000 patients
- Combination chemotherapy led to decrease in recurrence and improvement in mortality for women >70yo with operable BCA

EBCTCG Lancet 2005

Standard prognostic factors: early breast cancer

- Stage
  - Tumor size
  - Lymph node involvement
- Tumor behavior
  - Grade
  - Estrogen and progesterone receptors
  - HER2
  - (Ki67)

NSABP B20



Fisher, JNCI 1997

- 2300 women with ER+ node neg BCA randomized to tamoxifen vs tamoxifen plus chemotherapy
- Adding chemotherapy improved DFS, DDFS and OS

Multigene Panels

- Evaluate expression of certain genes in tumor tissue
- Determine risk of recurrence of early breast cancer and assist with treatment decision-making
- Primarily used to determine whether a patient with ER+/HER2 negative breast cancer should receive adjuvant chemotherapy

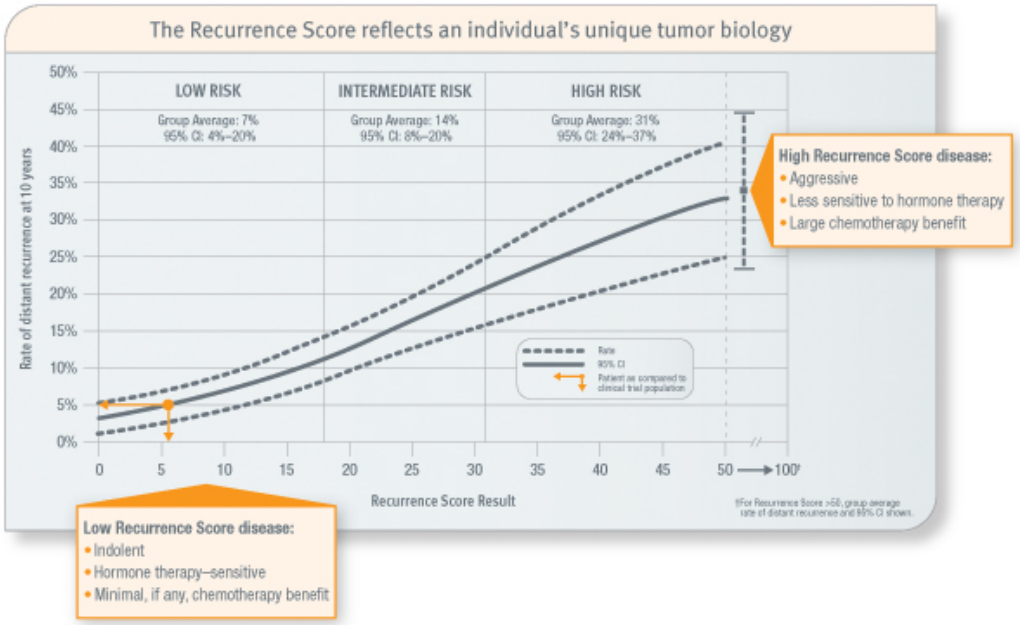
Multigene Panels

- Oncotype Dx
- MammaPrint
- Prosigna (PAM50)
- Breast Cancer Index
- EndoPredict

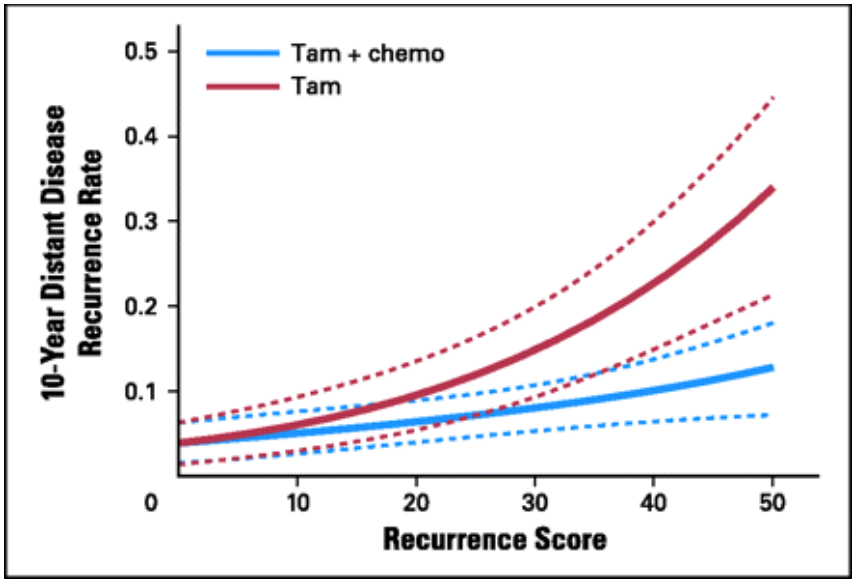
Oncotype Dx

- 21 gene assay
  - 16 tumor-related genes
    - Proliferation, invasion, ER signaling, Her2 signaling
  - 5 reference genes
- Gene expression measured by RT-PCR
- Performed on fixed, paraffin-embedded tissue
- Recurrence score from 0-100 generated
- Predicts both risk of recurrence and likelihood of chemotherapy benefit

Oncotype and risk of recurrence



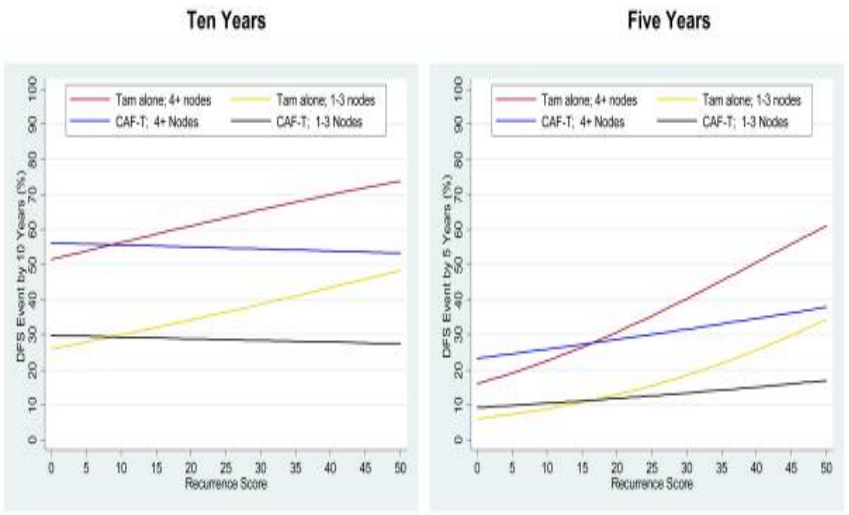
Oncotype and chemotherapy benefit



Paik, JCO 2006

- Data based on retrospective evaluation of tissue samples from NSABP B20
- Chemotherapy primarily benefited patients with high recurrence score

Oncotype and chemotherapy benefit Node positive



- Evaluation of tissue samples from SWOG 8814, which evaluated addition of CAF to tamoxifen in node+ BCA, showed similar findings

Albain, Lancet Oncol 2010

TAILORx Trial

- Prospective trial evaluating whether Oncotype can be used to assign patients to the most effective treatment
- Enrolled over 10,000 women with node negative, ER+ breast cancer in the US and Canada between 2006-2010
- All patients had Oncotype test performed on their tumor
- Women with low recurrence scores (>11) did not receive chemotherapy
- Women with high scores (<25) received chemotherapy
- Women with intermediate scores (11-25) were randomized to chemotherapy vs. no chemotherapy
- All patients received endocrine therapy

TAILORx Trial

- Results from the low risk group were published in 2015.
- 98.7% of the women were free of recurrence after 5 years
- Confirmed that women with low recurrence scores do not need chemotherapy
- Results from intermediate risk group are not yet available (maybe in about 2 years)

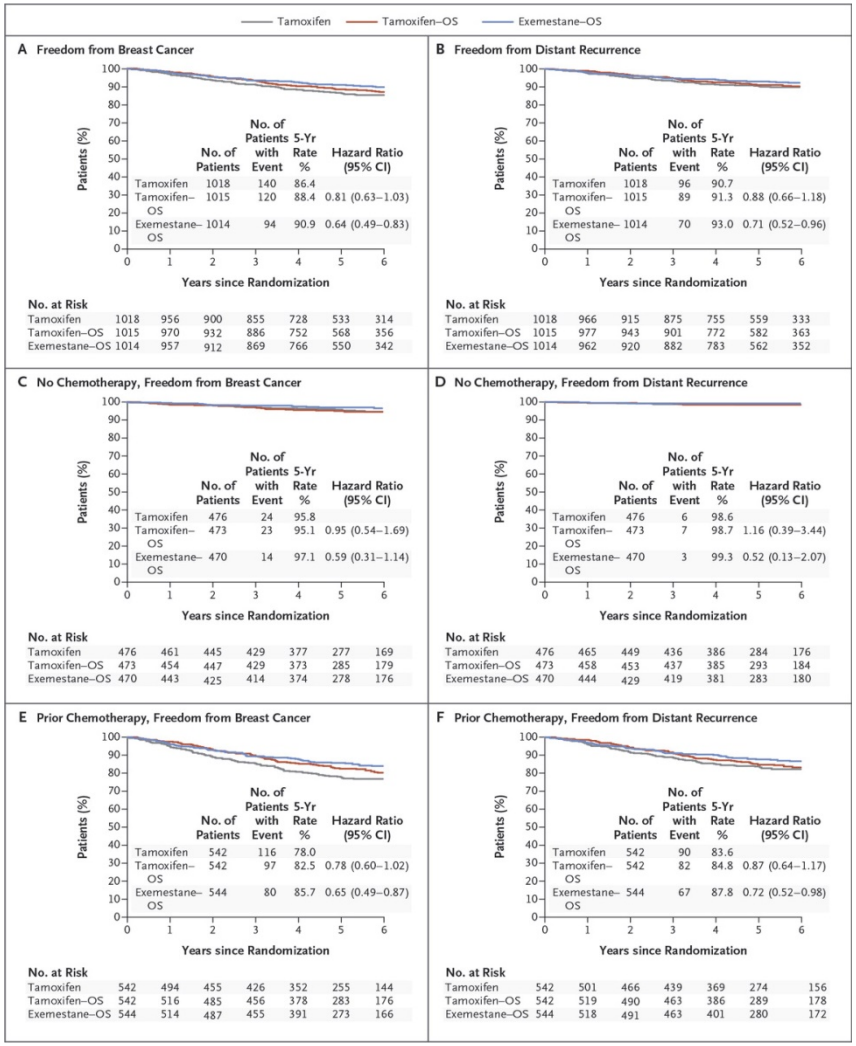
RxPONDER Trial

- Adjuvant chemotherapy is currently standard of care for node positive breast cancer
- Randomized trial evaluating chemotherapy benefit in women with ER+ breast cancer and 1-3 + nodes
- Women with RS≤25 are randomized to chemo vs. no chemo
- All women receive hormonal therapy
- Completed accrual in 2015
- Awaiting results

Endocrine Therapy for Premenopausal Women

- Tamoxifen
  - ATLAS and aTTom trials showed that 10 yrs tamoxifen decreased recurrence and mortality compared with 5 yrs
  - 19% of ER+ ATLAS patients were <45 at diagnosis
- Ovarian suppression
  - SOFT and TEXT trials evaluated addition of ovarian suppression to endocrine therapy
  - Initial results - improved DFS in subgroups of patients with addition of ovarian suppression
  - With longer follow-up (8 yrs), improved DFS seen in overall population

Ovarian Suppression -SOFT



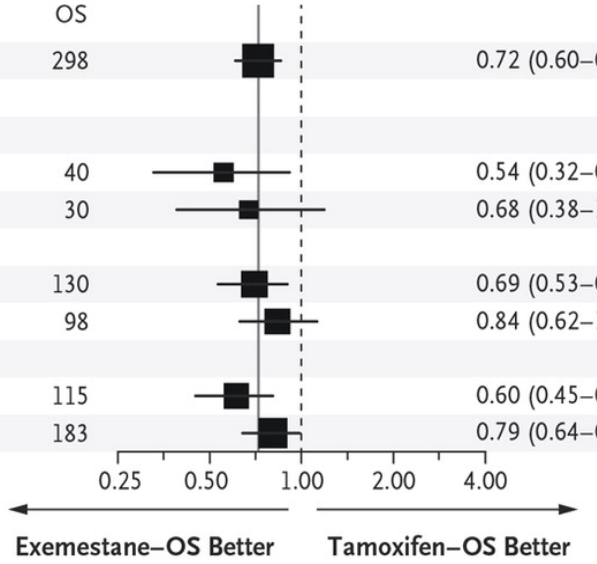
- Women who received chemotherapy and remained premenopausal had improved outcomes with addition of ovarian suppression
- Small OS benefit seen at 8 yrs follow-up

Francis, NEJM 2015

Benefits of AI vs Tamoxifen

Data from SOFT and TEXT trials were combined to evaluate benefit of exemestane vs tamoxifen when combined with ovarian suppression

Subgroup	No. of Patients		No. of Patients with Event		Hazard Ratio (95% CI)	5-Yr Disease-free Survival (%)	
	Exemestane–OS	Tamoxifen–OS	Exemestane–OS	Tamoxifen–OS		Exemestane–OS	Tamoxifen–OS
All patients	2346	2344	216	298	0.72 (0.60–0.85)	91.1	87.3
Cohort							
No chemotherapy							
TEXT	526	527	22	40	0.54 (0.32–0.92)	96.1	93.0
SOFT	470	473	20	30	0.68 (0.38–1.19)	95.8	93.1
Chemotherapy							
TEXT	806	801	93	130	0.69 (0.53–0.90)	89.8	84.6
SOFT	544	543	81	98	0.84 (0.62–1.13)	84.3	80.6
Lymph-node status							
Negative	1362	1350	70	115	0.60 (0.45–0.81)	95.1	91.6
Positive	984	994	146	183	0.79 (0.64–0.98)	85.6	81.4



Pagani, NEJM 2014

Fertility Issues

- Reproductive endocrinology consultation for women wishing to preserve fertility
- Nonhormonal contraception when pregnancy not desired
- Avoidance of pregnancy while receiving treatment

Fertility Preservation (POEMS study)

- 257 premenopausal women with ER-/PR- BCA receiving (neo)adjuvant chemotherapy
- Patients randomized to chemo +/- monthly goserelin
- Addition of goserelin improved pregnancy outcomes
- No worsening of BCA outcomes

Table 3. Pregnancy Outcomes.

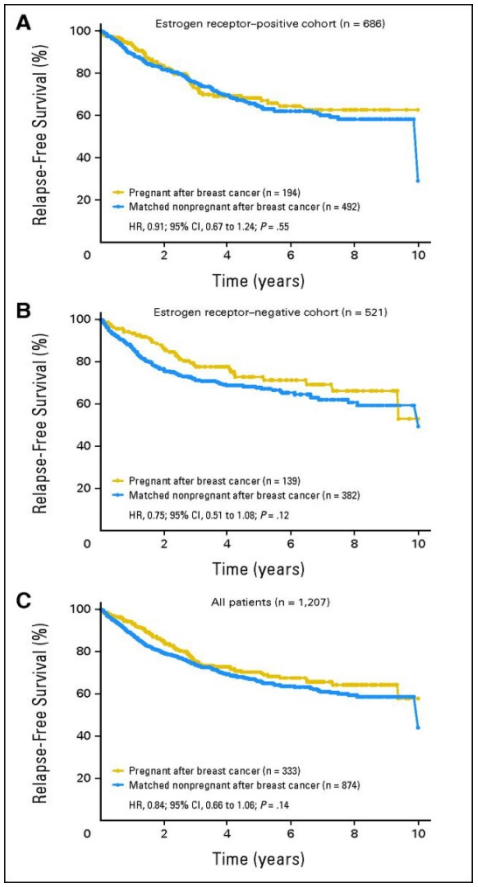
Outcome	Chemotherapy Alone (N=113)	Chemotherapy plus Goserelin (N=105)	Odds Ratio with Goserelin	P Value*
Attempted pregnancy — no. of patients (%)	18 (16)	25 (24)	1.78	0.12
Achieved pregnancy — no. of patients (%)	12 (11)	22 (21)	2.45	0.03
≥1 delivery — no. of patients (%)	8 (7)	16 (15)	2.51	0.05
Delivery or ongoing pregnancy — no. of patients (%)	10 (9)	19 (18)	2.45	0.04
Babies born — no.†	12	18		
Ongoing pregnancies at last report — no.	3	5		
Adverse pregnancy event — no. of events				
Miscarriage	5	4		
Elective termination	3	2		
Delivery complication	2	2		

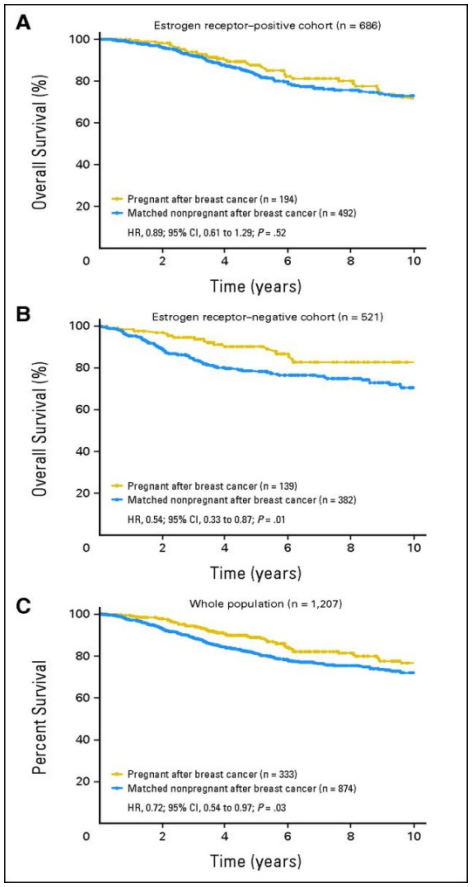
* P values were adjusted for the stratification factors of age and type of planned chemotherapy. The cutoff date for data analysis was January 22, 2014; data up to that date are included.
† This category may include more than one baby born to a woman.

Moore, NEJM 2015

Pregnancy after Breast Cancer Therapy

- Retrospective cohort study matched 333 women who became pregnant after BCA treatment with 864 women who did not
- No difference in DFS or OS





Azim, JCO 2013

POSITIVE Trial

Pregnancy Outcome and Safety of Interrupting Therapy for patients with endocrine responsIVE breast cancer

POSITIVE Trial

- Phase II trial to evaluate safety and pregnancy outcomes of interrupting endocrine therapy for women with ER+ breast cancer who desire pregnancy
- Currently enrolling
- Premenopausal women, completed 18-30 months endocrine therapy
- Participants stop therapy for up to 2 years to attempt pregnancy, and then resume treatment

Summary

- Multigene panels can be used to assist in chemotherapy decision-making process for patients with early ER+/Her2 neg breast cancer
- Endocrine therapy options for premenopausal women with ER+ breast cancer include 10 years of tamoxifen or ovarian suppression plus either tamoxifen or aromatase inhibitor
- Addition of ovarian suppression improves outcomes, and should be considered, especially in women with higher risk disease
- Fertility concerns in premenopausal women need to be addressed

Adjuvant Radiation after Breast Conservation

Case

- 32yo female with Gr3, ER+ pT1bN1mic(i+) s/p lumpectomy and SLNBx
- Options
  - Whole breast radiation + boost
    - Z-11
  - Whole breast with high tangents
    - Z-11
  - Whole breast + axillary/supraclavicular field + boost
    - MA.20, AMAROS

ACOSOG Z-11
Is SLND Enough for RT?

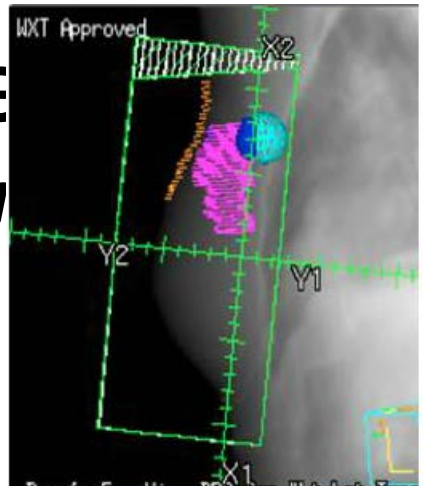
- Phase 3 non-inferiority trial to determine the effects of ALND vs. SLND

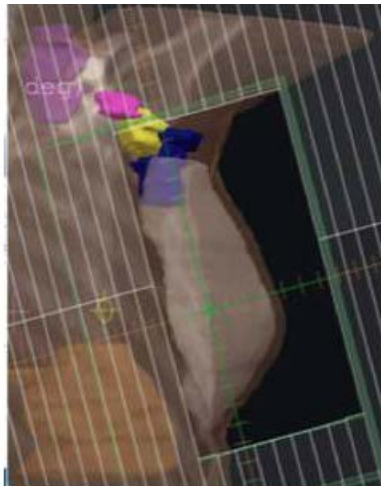
- 115 sites, 5/99-12/04
- Enrollment: cT1-T2, cN0, with 1-2 SLN+
- Randomization: ALND (n=445) vs. SLND alone (n=446)

- All patients: Breast Conserving Surgery + Systemic Therapy as appropriate

- Trial closed early (1,900 original accrual target) because mortality was lower than expected
- Median FU: 6.3 years

ACOSOG
Resu





- Equivalent OS: ALND = 91.8% vs. SNLD = 92.5%
- Equivalent DFS: ALND = 82.2% vs. SNLD = 83.9%
- Regional Recurrence after SLND alone: <1%
- This is despite the fact that 27% of patients had additional metastasis in undissected axillary nodes
- Whole Breast Irradiation by tangent fields ONLY allowed: *no nodal irradiation*
- Concept of *high tangents* irradiating nodes

MA.20 – Regional Nodal Irradiation

- Node+ or High-Risk (T>5cm or T>2cm w/ <10 LN removed + G3, ER-, LVI)
- *Excluded if: T4, N2-3*
- 1832 women randomized to whole breast +/- regional LN (IM, SCV,AX)
- 91% received chemotherapy
- 10 year FU:
  - +Nodal RT vs –Nodal RT
    - OS: 82.8% vs 81.8% (NS)
    - DFS: 82% vs 77% (p=0.01)

MA.20 Trial: *Results a 10yr F/L*

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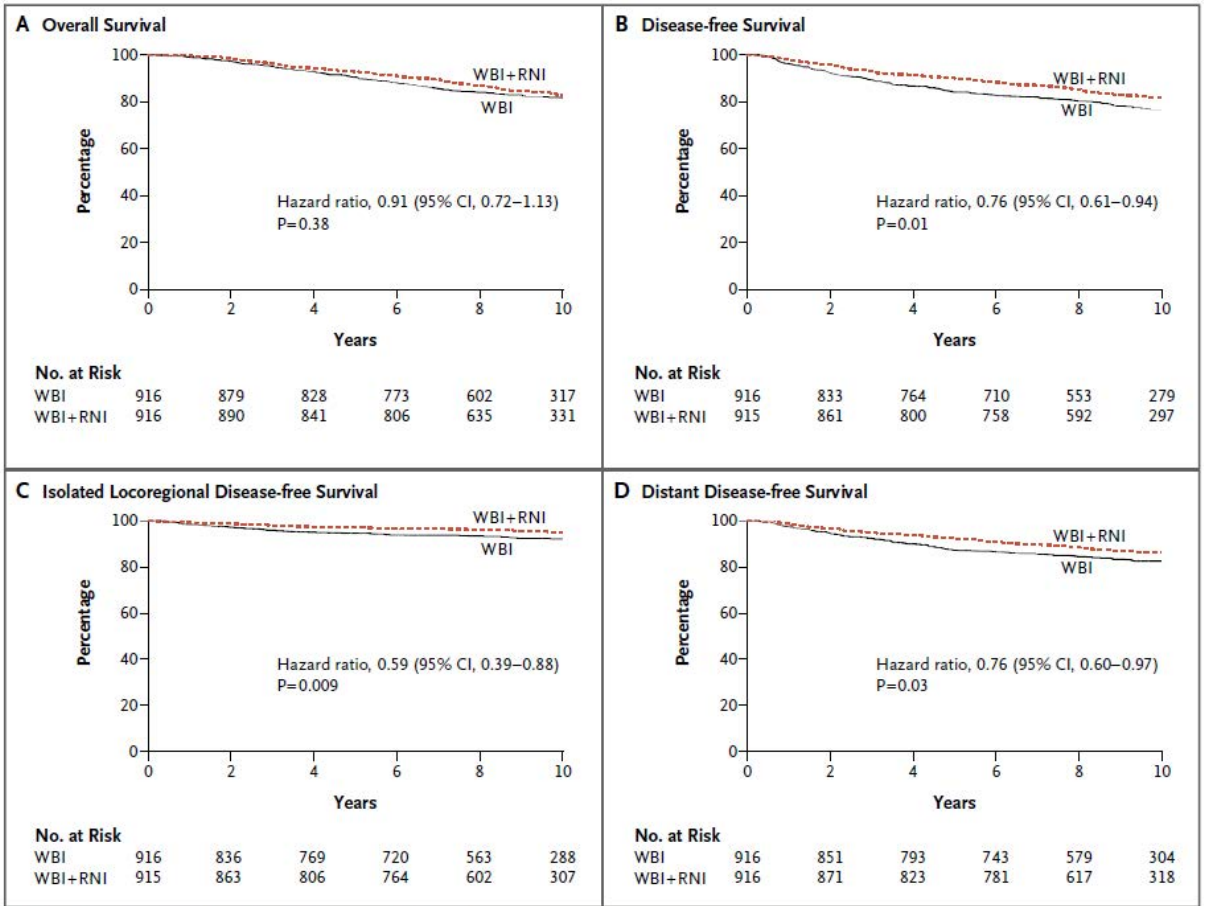
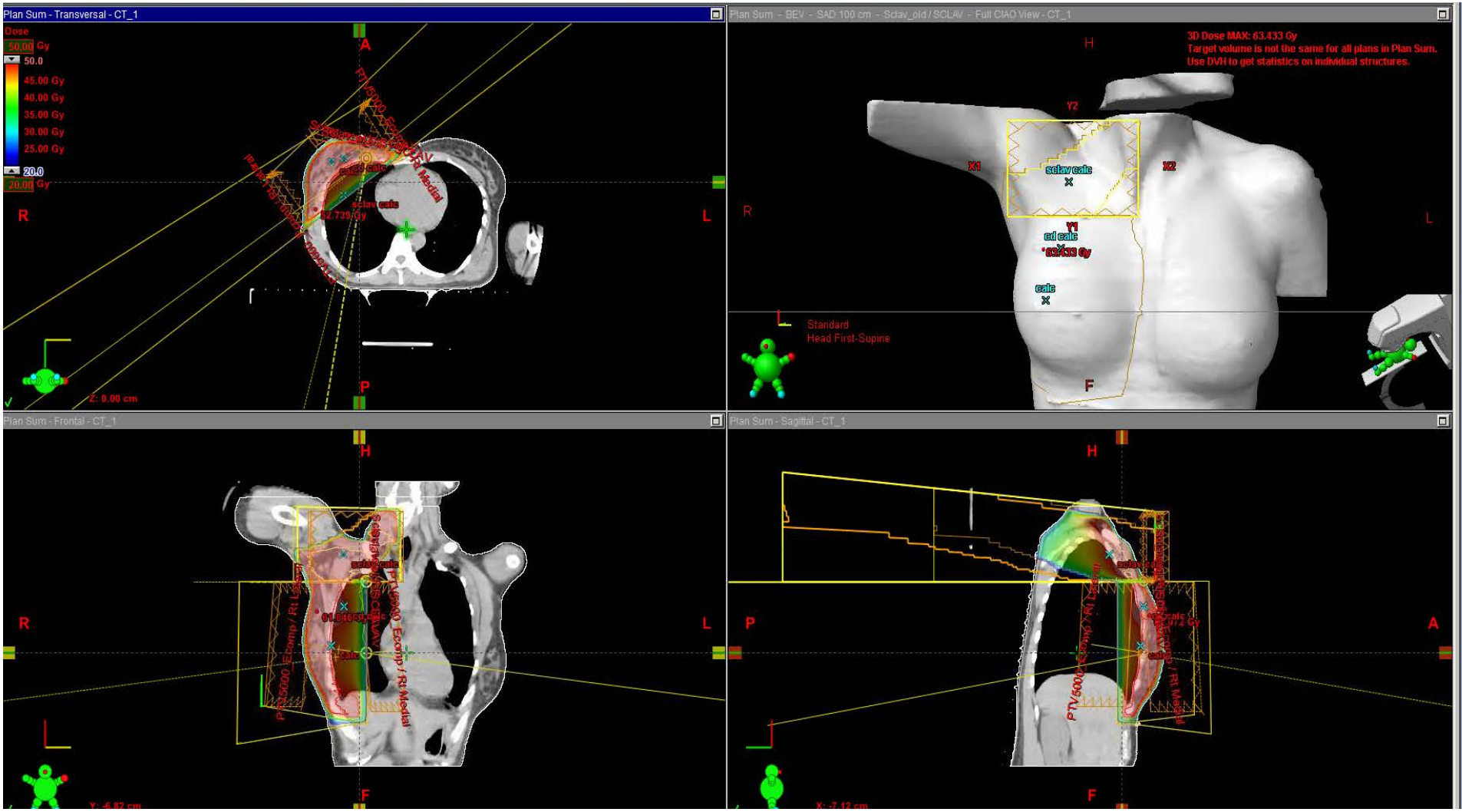
ESTABLISHED IN 1812 JULY 23, 2015 VOL. 373 NO. 4



EORTC 10981-22023 / After Mapping of the Axilla, Radiotherapy or Surgery (AMAROS)

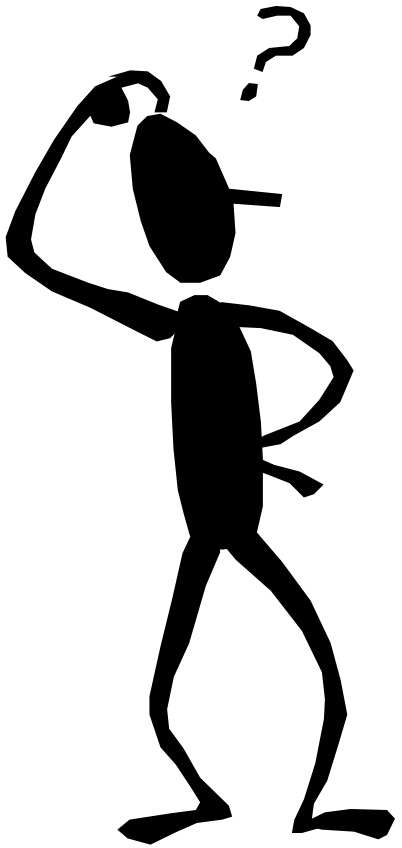
- T1-2, cN0 -> SLNB
- If SLNB+ then randomized to:
  - Axillary LN dissection (ALND) vs Axillary RT (ART)
- 4823 patients enrolled
- 5 year axillary recurrence: ALND 0.43% vs ART 1.19%
- 5 year DFS 87% vs 83% (NS)
- 5 year OS 93% vs 93% (NS)


Plan Sum - Transversal - CT_1
Dose
50.00 Gy
50.0
45.00 Gy
40.00 Gy
35.00 Gy
30.00 Gy
25.00 Gy
20.0
20.00 Gy
A
P
R
L
sclav calc
62.739 Gy
Z: 0.00 cm
Plan Sum - BEV - SAD 100 cm - Sclav_old / SCLAV - Full CIAO View - CT_1
3D Dose MAX: 63.433 Gy
Target volume is not the same for all plans in Plan Sum.
Use DVH to get statistics on individual structures.
H
F
Y2
X1
X2
Y1
sclav calc
calc
Standard
Head First-Supine
Plan Sum - Frontal - CT_1
Plan Sum - Sagittal - CT_1

Conclusion

- Patient received adjuvant radiation and is taking tamoxifen
- Genomic profile(Oncotype)suggested no significant benefit of chemotherapy for her.
- Breast imaging with annual mammogram and sonogram
- May attempt pregnancy in future after completing at least 2 years of tamoxifen(10 years recommended)

ANY QUESTIONS



Case # 3: Locally Advanced Breast Cancer

HPI: 63yo F presents with a 1 month history of a rapidly enlarging right breast mass.

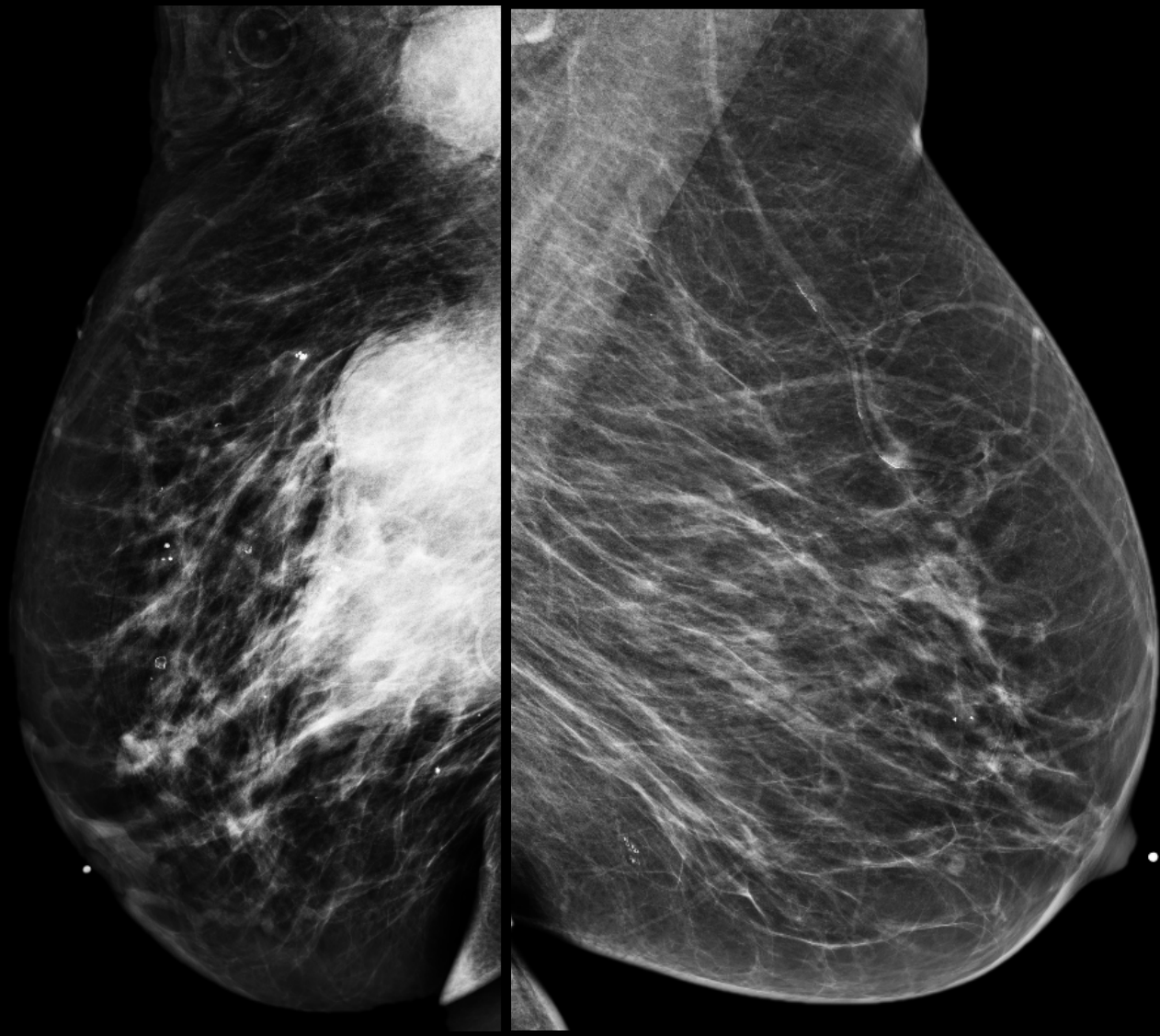
Past Med hx: depression,G0P0, maternal grandmother breast cancer(70s)

P.E.10cm fixed mass central right breast with 4cm fixed right axillary node. No other regional adenopathy, no skin changes

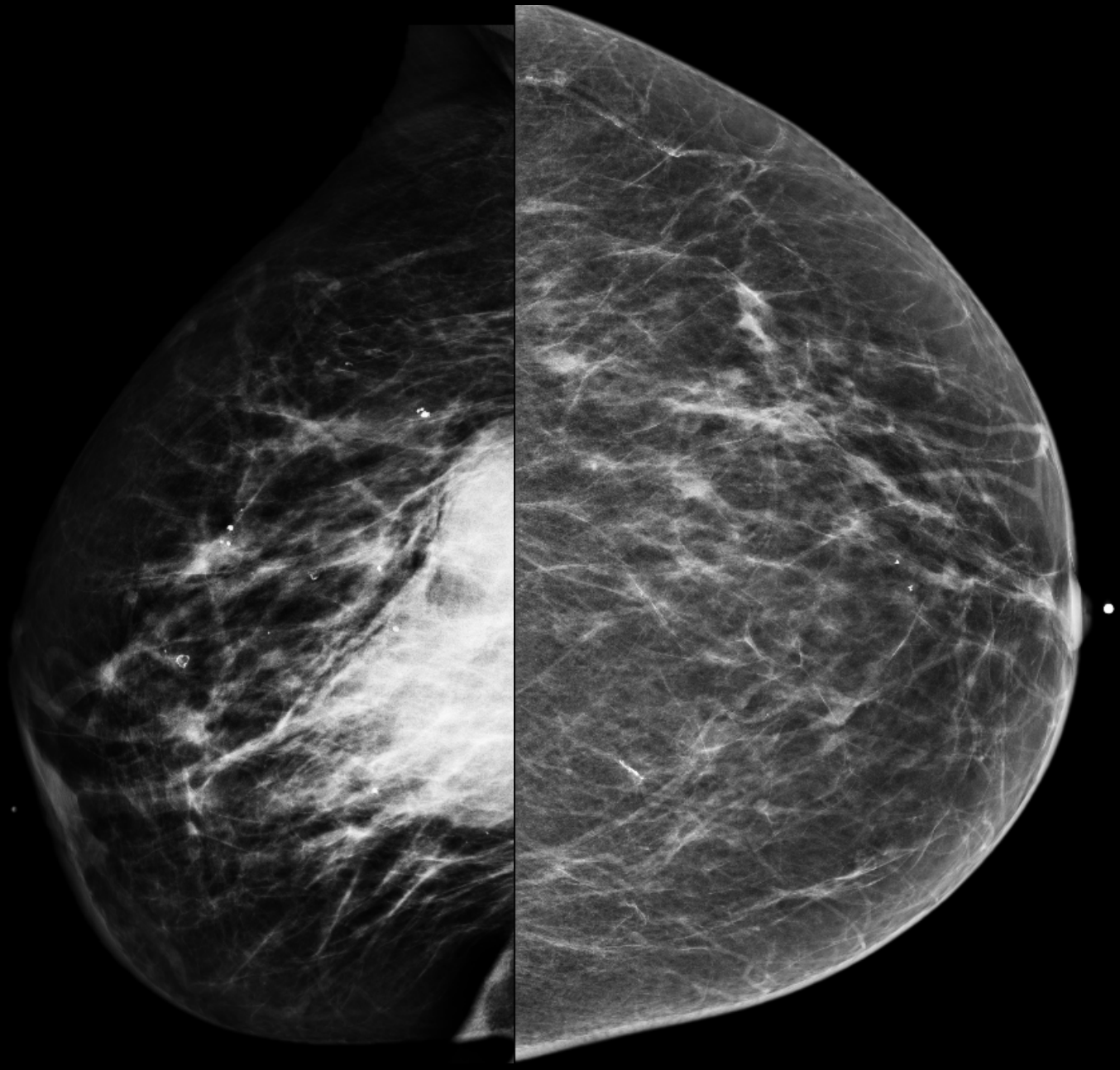
Clinical course: core biopsy of palpable mass yielded triple negative invasive ductal cancer

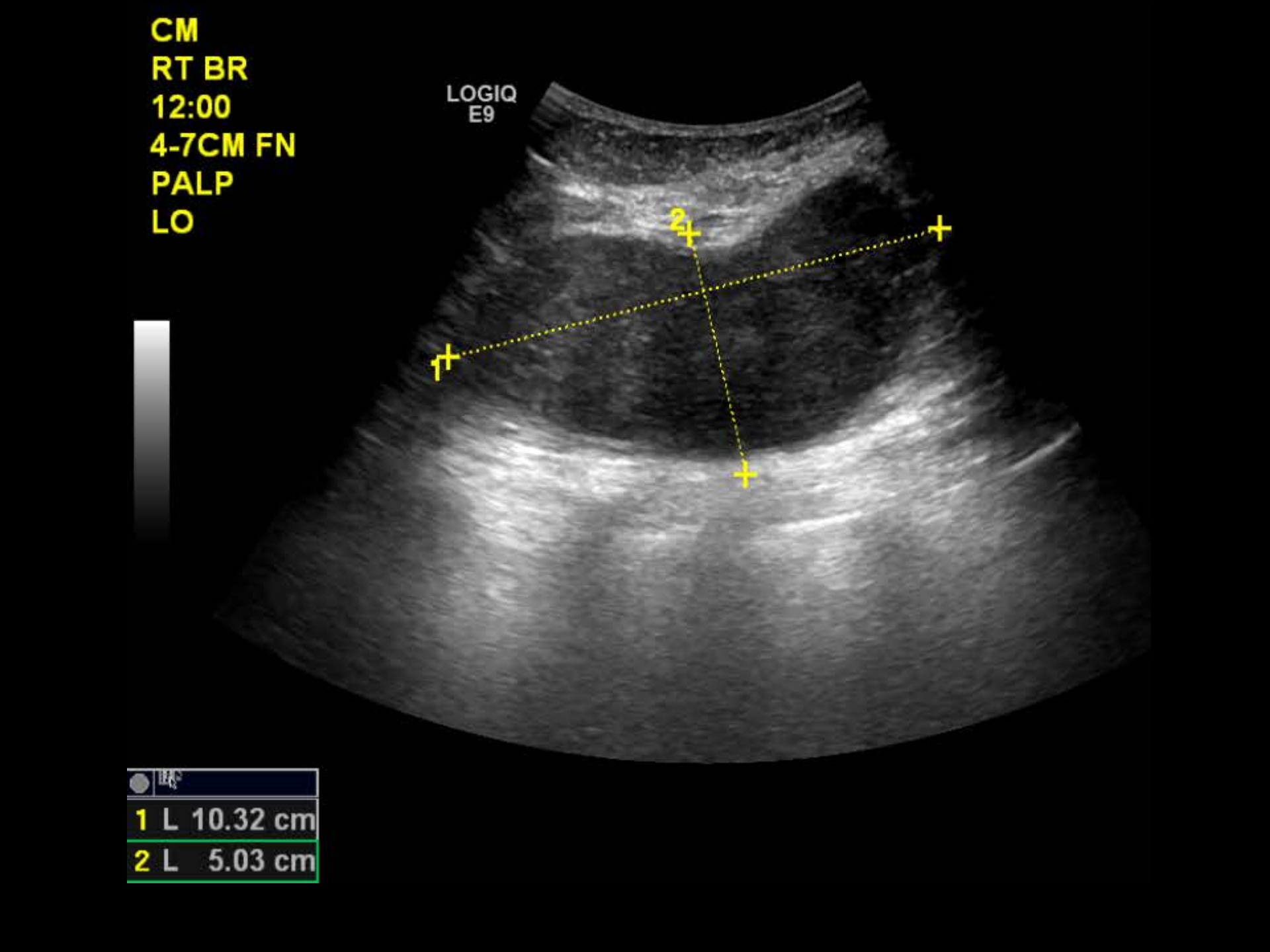
PET/CT and bone scan without distant metastases

Diagnostic Mammography: MLO views



Diagnostic Mammography: CC views




CM
RT BR
12:00
4-7CM FN
PALP
LO
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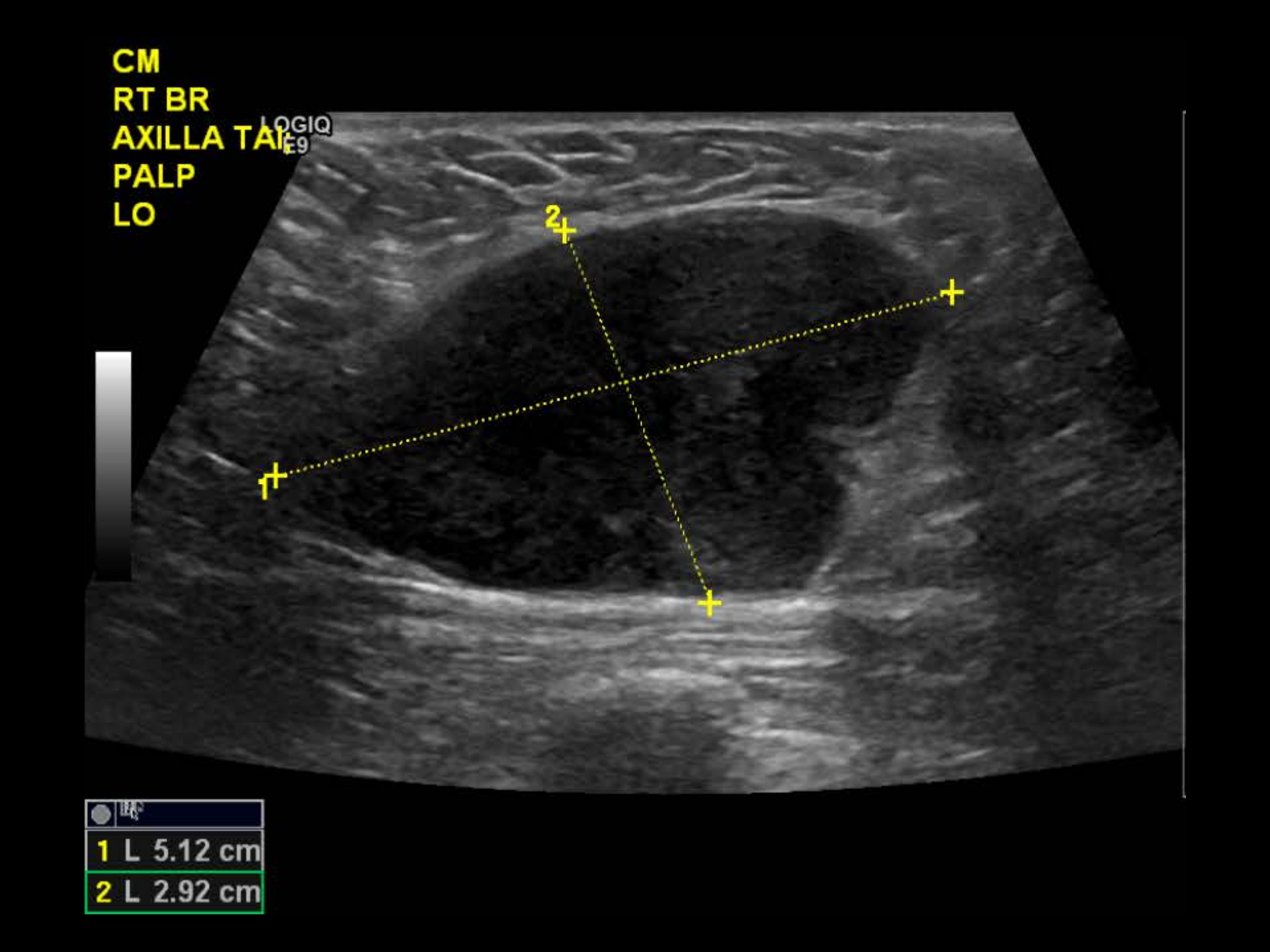
E9
1 L 10.32 cm
2 L 5.03 cm


CM
RT BR
AXILLA TAN
PALP
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LOGIQ
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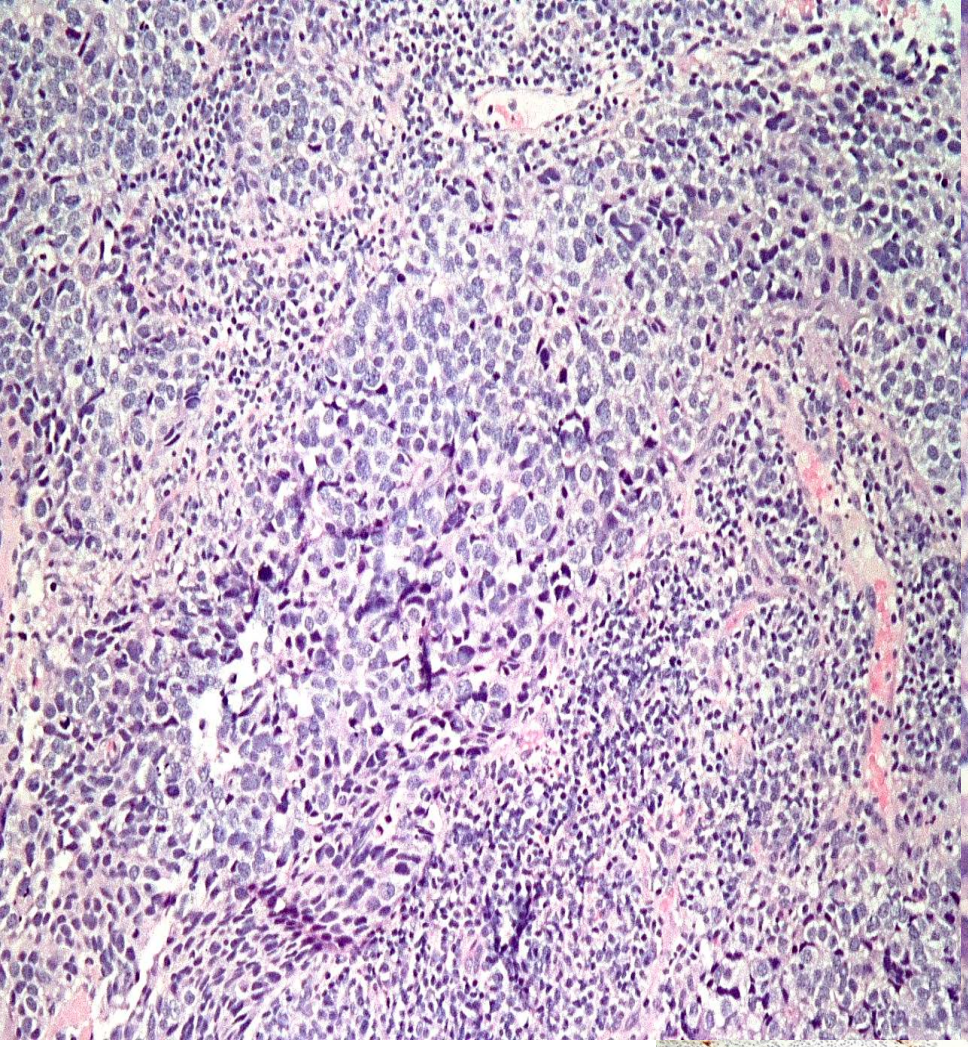
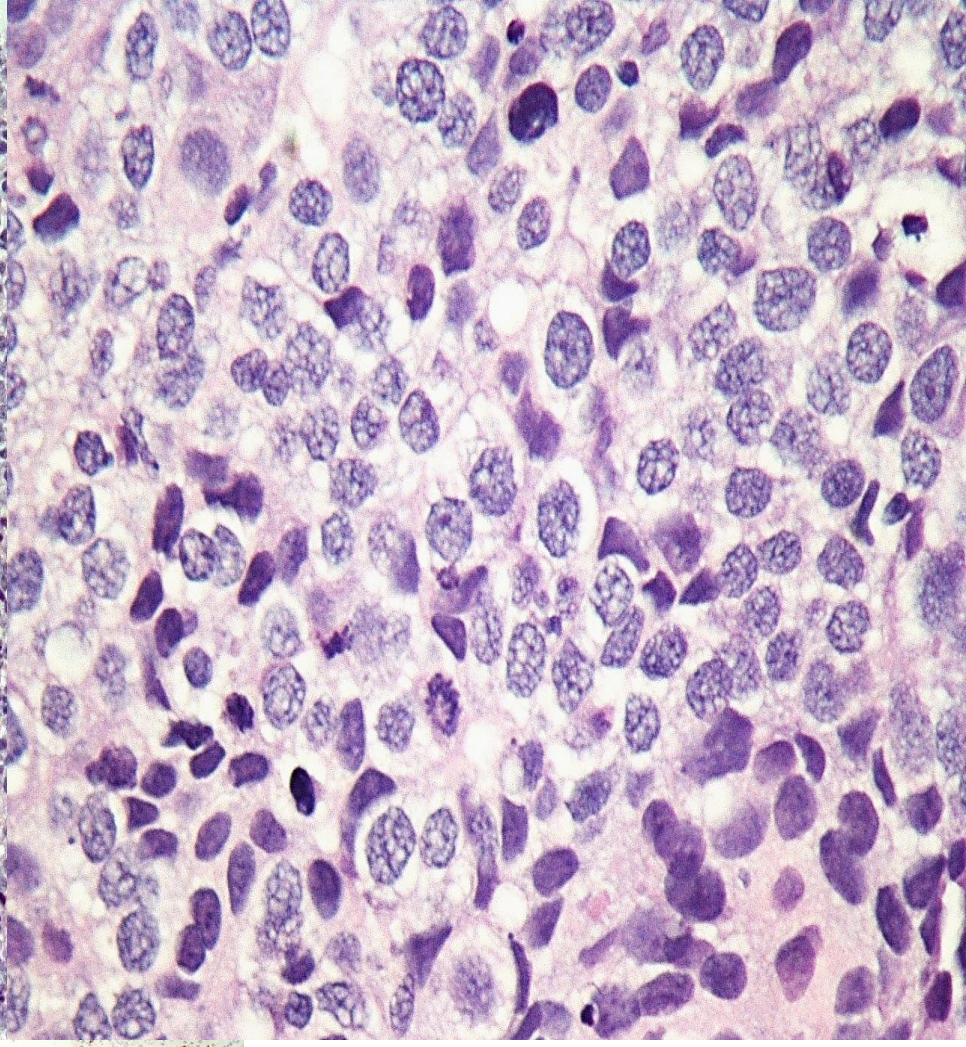
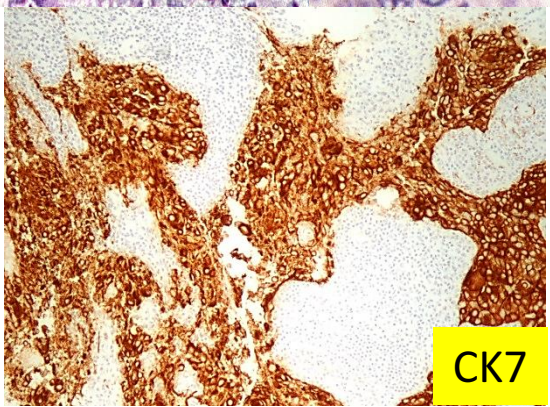
1
1 L 5.12 cm
2 L 2.92 cm

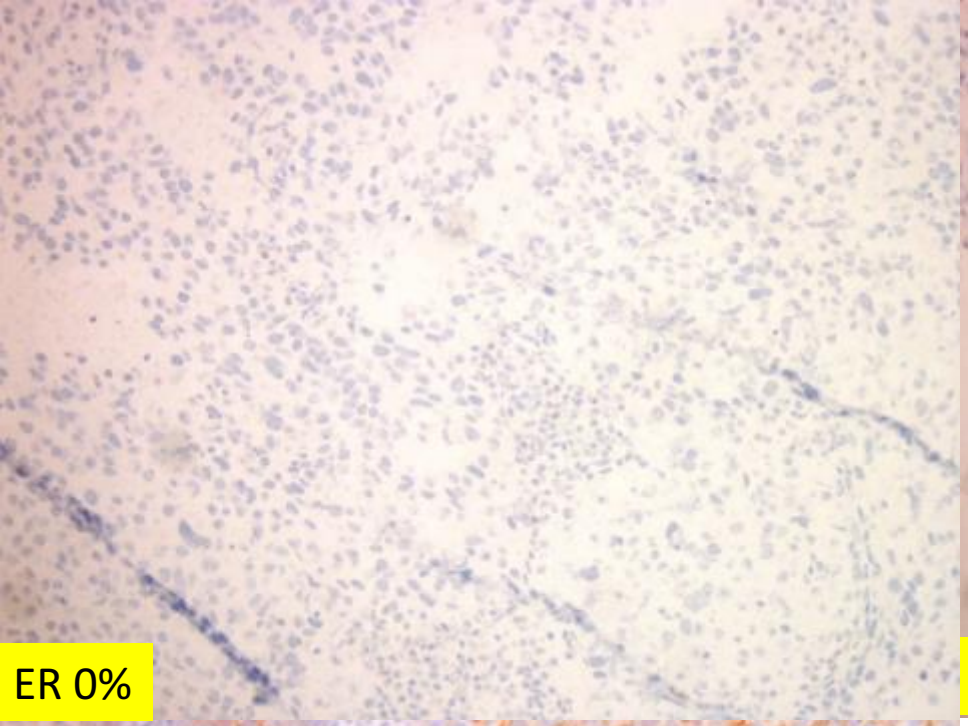
PATHOLOGY

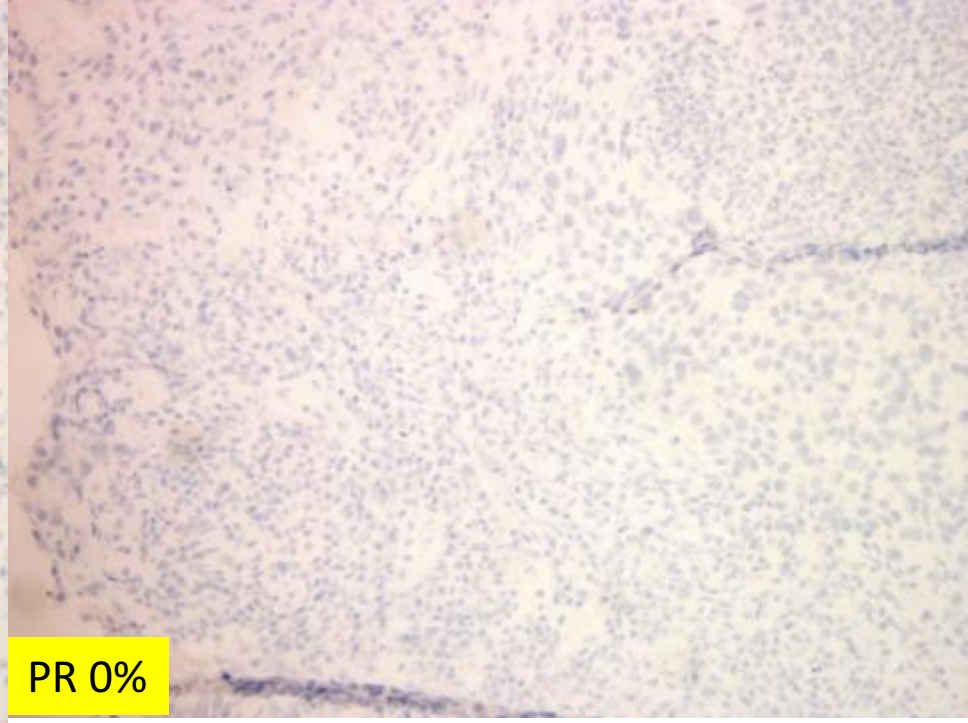
- Specimens Received
  - Breast Core Biopsy
  - Axillary LN Biopsy

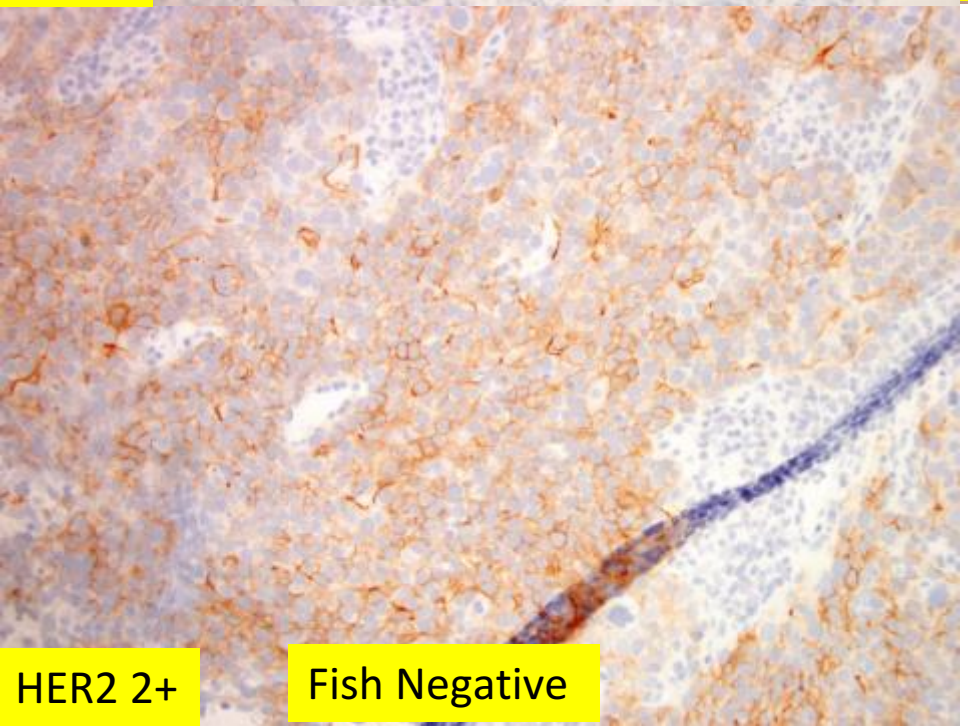





CK7


ER 0%


PR 0%


HER2 2+
Fish Negative

Invasive Ductal Carcinoma, Poorly differentiated , in both lymph node and breast

Triple negative – Hormone receptors estrogen and progesterone are negative and Her 2Neu negatve

Treatment of locally advanced breast cancer

- Neoadjuvant chemotherapy
- Surgery
- Radiation
- Targeted therapy
  - Neoadjuvant trastuzumab/pertuzumab, with maintenance anti-Her2 therapy, for Her2+ disease
  - Adjuvant endocrine therapy for ER+ disease

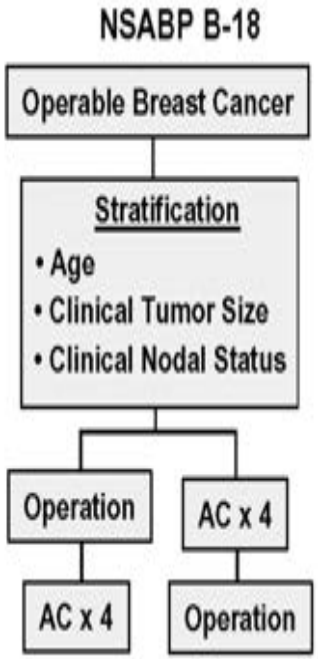
Goals/benefits of neoadjuvant therapy

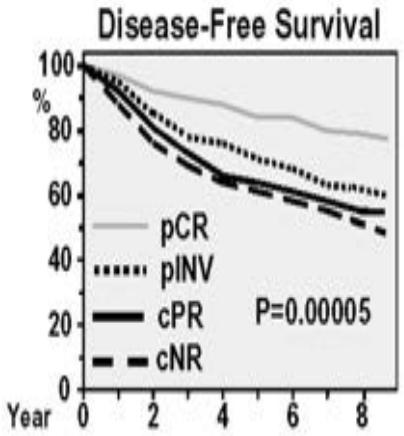
- Render inoperable patients operable
- Enable breast conservation for operable patients (and possibly less axillary surgery)
- Achieve pathologic CR
- Monitor response to therapy
- Allows time for genetic testing or planning of reconstruction
- Allows testing of novel agents

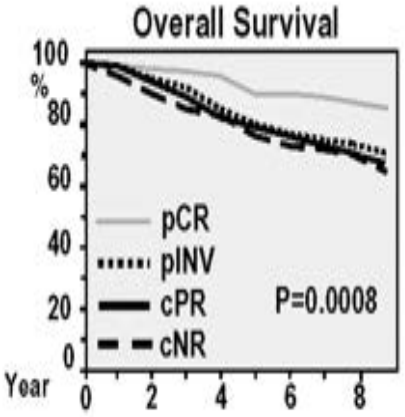
Poor candidates for neoadjuvant therapy

- Patients with a large amount of in situ disease
- Patients with poorly delineated extent of tumor
- Patients with nonpalpable or nonassessable tumors

Adjuvant vs Neoadjuvant Chemo- NSABP B-18







- 1523 women with operable breast cancer randomized to preop vs. postop chemotherapy (AC x 4)
- No difference in DFS or OS between two arms
- 12% more lumpectomies performed in preop arm
- Women who achieved pCR (13%) had improved DFS and OS

Response to Neoadjuvant Therapy and Long-Term Survival in Patients With Triple-Negative Breast Cancer

Cornelia Liedtke, Chafika Mazouni, Kenneth R. Hess, Fabrice André, Attila Tordai, Jaime A. Mejia, W. Fraser Symmans, Ana M. Gonzalez-Angulo, Bryan Hennessy, Marjorie Green, Massimo Cristofanilli, Gabriel N. Hortobagyi, and Lajos Pusztai

Treatment	No.	TNBC	Non-TNBC
Single agent taxane	166	12%	2%
FAC/FAC/AC	308	20%	5%
T-FAC/T-FEC	588	28%	17%

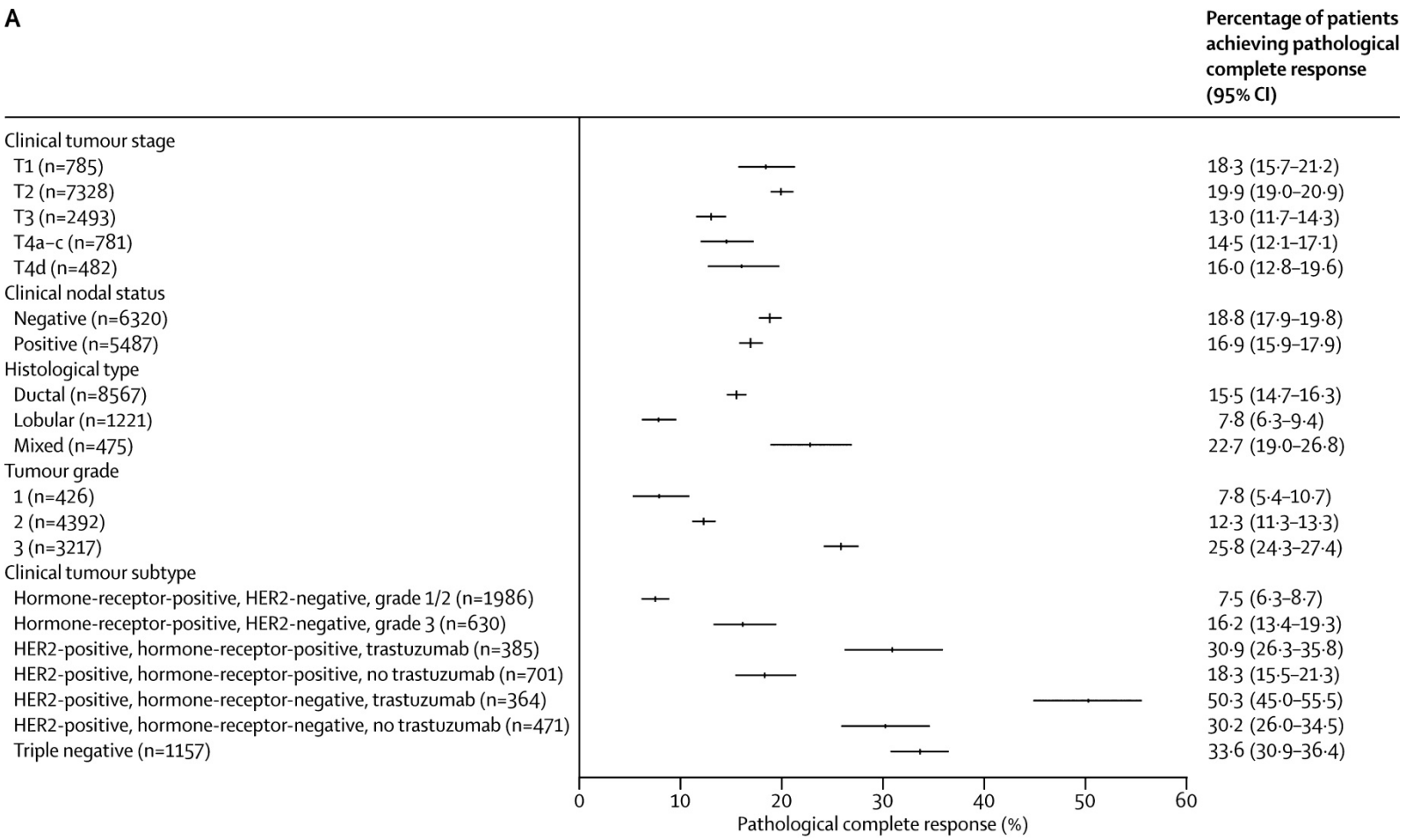
J Clin Oncol 2008; 26(8):1275-81

AJCC TNM stage after neoadjuvant chemotherapy and breast cancer outcome

Carey et al. JNCI *2005 Aug 3;97(15):1137-42*

Stage	TN	No. of patients (%)	5-year DDFS (95% CI)	5-year OS (95% CI)
0	0	22 (17%)	95% (72%-99%)	95% (72%-99%)
I	T1N0	20 (15%)	84% (58%-95%)	90% (65%-97%)
II	IIA-T0-1N1;T2N0 IIB-T2N1;T3N0	38 (29%)	72% (52%-85%)	71% (49%-85%)
III	III A-T0-3N2;T3N1 IIIB-Any T4 IIIC-Any N3	52 (39%)	47% (32%-61%)	61% (45%-74%)
			P_{trend}<.001	P_{trend} <.001

Likelihood of Achieving pCR



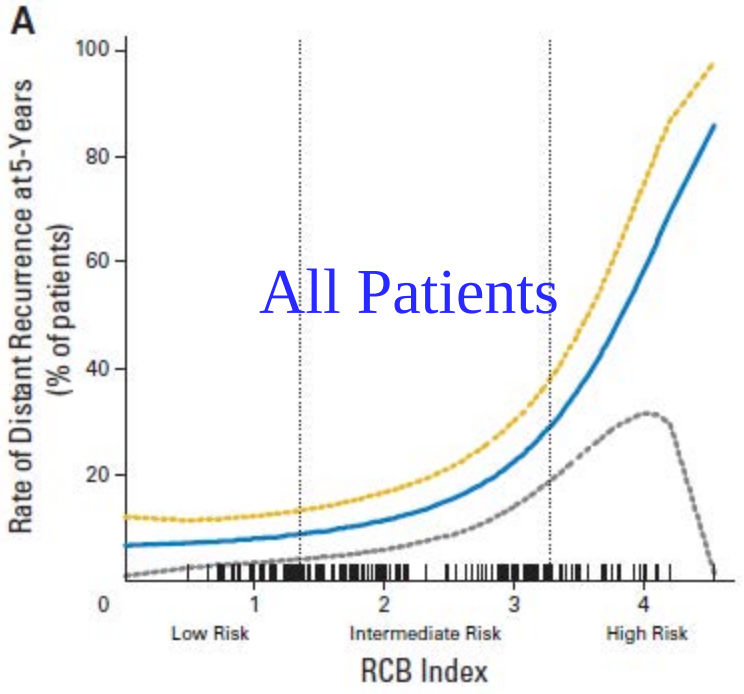
Cortazar, *Lancet* 2014

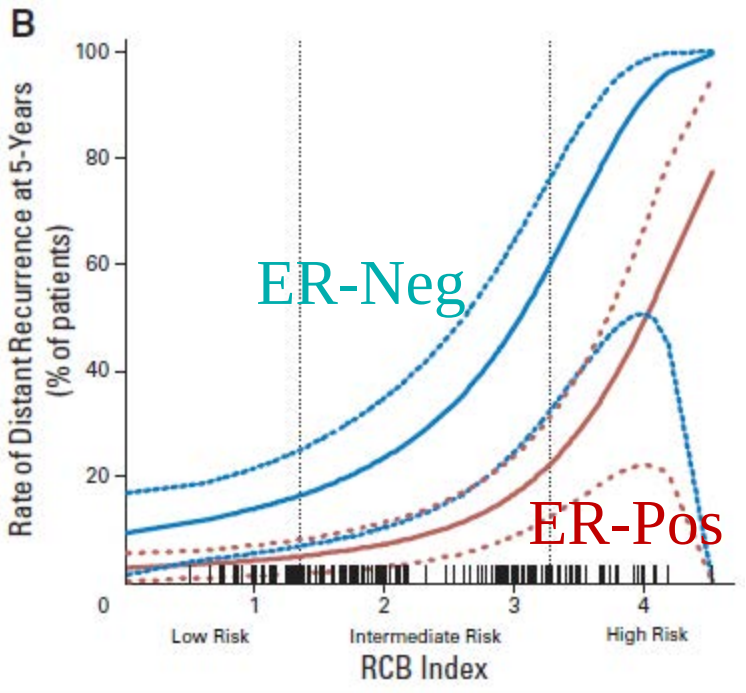
Measurement of Residual Breast Cancer Burden to Predict Survival After Neoadjuvant Chemotherapy

Symmans et al. J Clin Oncol 2007; 25:4414-4422

http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

Pathologic Review of Specimen:	HR (P Value)
Primary Tumor Bed Area (mm x mm)	1.24, p=0.02
Overall invasive cancer cellularity (as % of area)	7.37, p=0.001
Number of positive lymph nodes	1.11, p=0.002
Largest diameter of lymph node metastasis (mm)	1.17, p=0.06

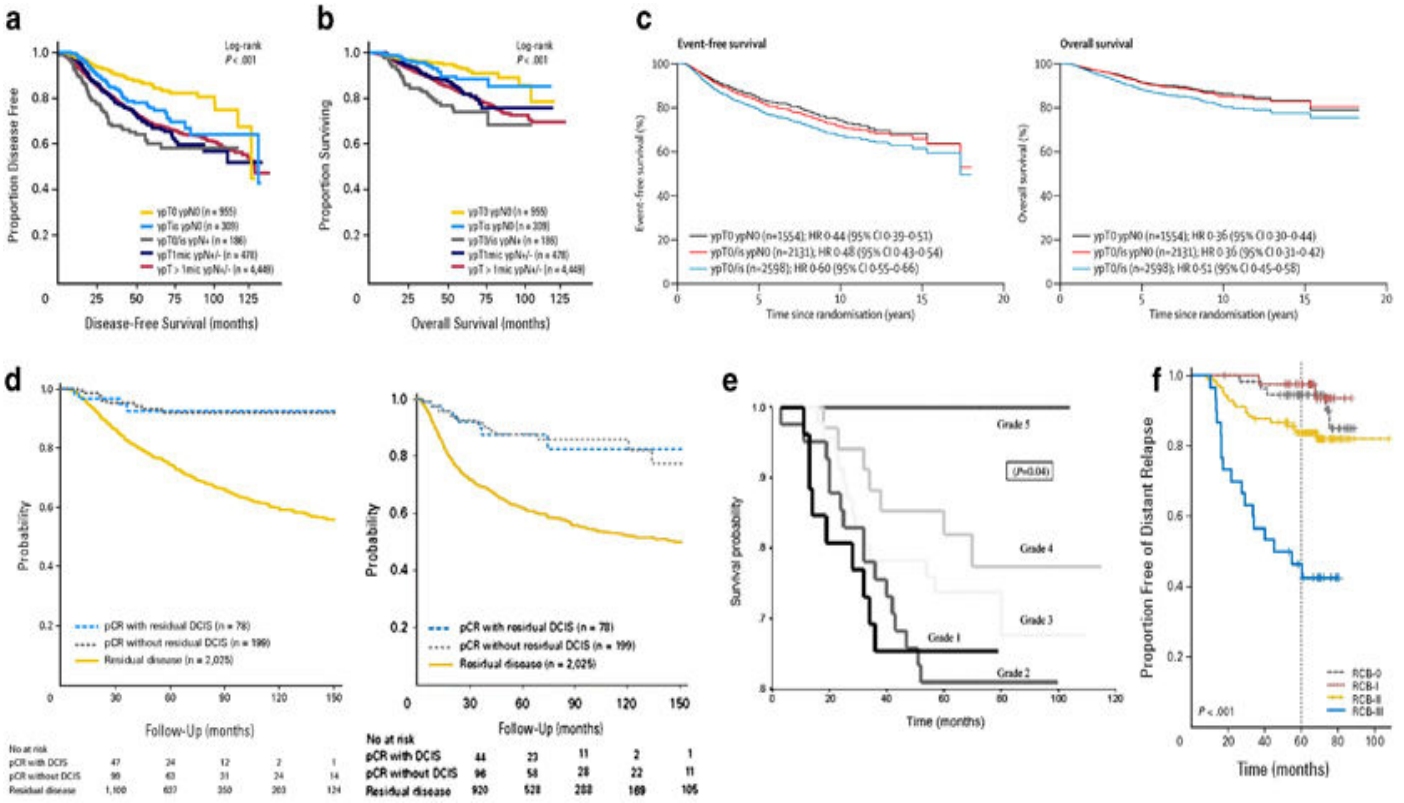




Definition of Pathologic CR

- Breast only or breast + axillary nodes?
- What about residual *in situ* disease?

pCR Definition and Outcome



(**a/b**) German Breast Group and AGO-B trials: reduced DFS for ypTisypN0 *vs* ypT0ypN0, but no difference in OS; worse DFS and OS for ypT0/isypN+ (**c**) CTNeoBC analysis: ypT0pN0 and ypT0/isypN0, similar EFS and OS, and more strongly associated with improved EFS and OS than ypT0/is alone. (**d**) MD Anderson study: 5- and 10-year OS and DFS identical for pCR *vs* pCR+DCIS. (**f**) RCB score independently predicts likelihood of relapse. Minimal residual disease (RCB-I) carries same prognosis as pCR.

Provenzano, *Modern Pathology* 2015

FDA Public Breast Cancer Workshop

Innovations in Breast Cancer Drug Development
NEOADJUVANT BREAST CANCER WORKSHOP

March 22, 2013
8:00 a.m. to 5:00 p.m.
Federal Research Center

FDA

ASCO
American Society of Clinical Oncology

AACR American Association for Cancer Research

CO-SPONSORED BY THE:

U.S. Food & Drug Administration (FDA) &
American Society of Clinical Oncology (ASCO)
with support from the American Association for Cancer Research (AACR)

CO-CHAIRS: **DR. SANDRA SWAIN AND DR. PATRICIA CORTAZAR**

The NEW ENGLAND JOURNAL of MEDICINE

Pathological Complete Response and Accelerated Drug Approval in Early Breast Cancer

Tatiana M. Prowell, M.D., and Richard Pazdur, M.D.

N Engl J Med. 2012;366: 2438-41

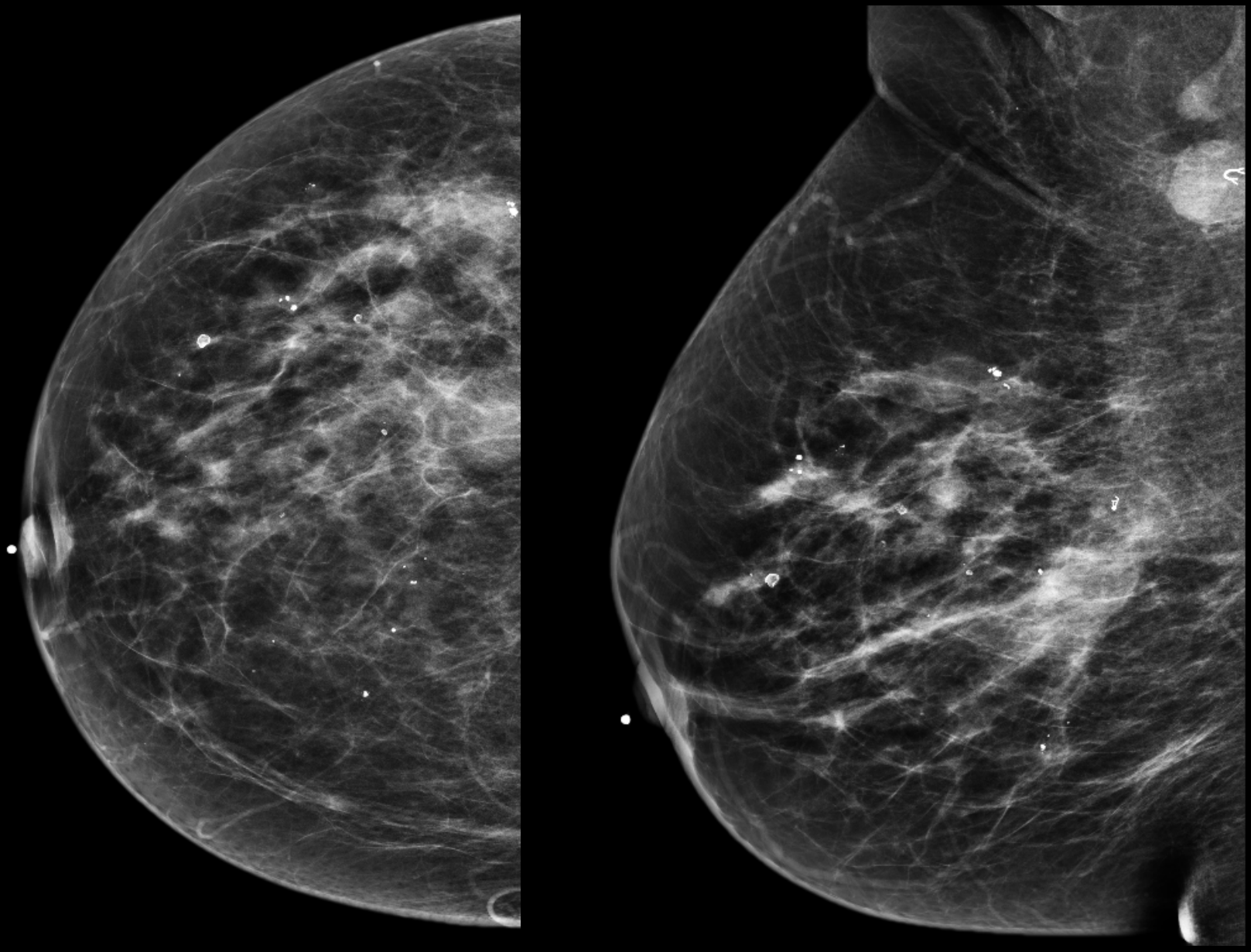
Neoadjuvant Therapy - Summary

- Neoadjuvant chemotherapy can downsize LABC, rendering inoperable breast cancer operable, and potentially enabling breast conservation for large operable breast tumors
- Optimal neoadjuvant chemotherapy regimens for Her2-neg BCA include both an anthracycline and a taxane
- Optimal neoadjuvant regimens for Her2+ include 2 anti-Her2 agents
- Response to neoadjuvant therapy is associated with improved survival
- RCB nomogram can be used to predict survival
- Improvement in pCR can be used as an endpoint for accelerated approval of new drugs

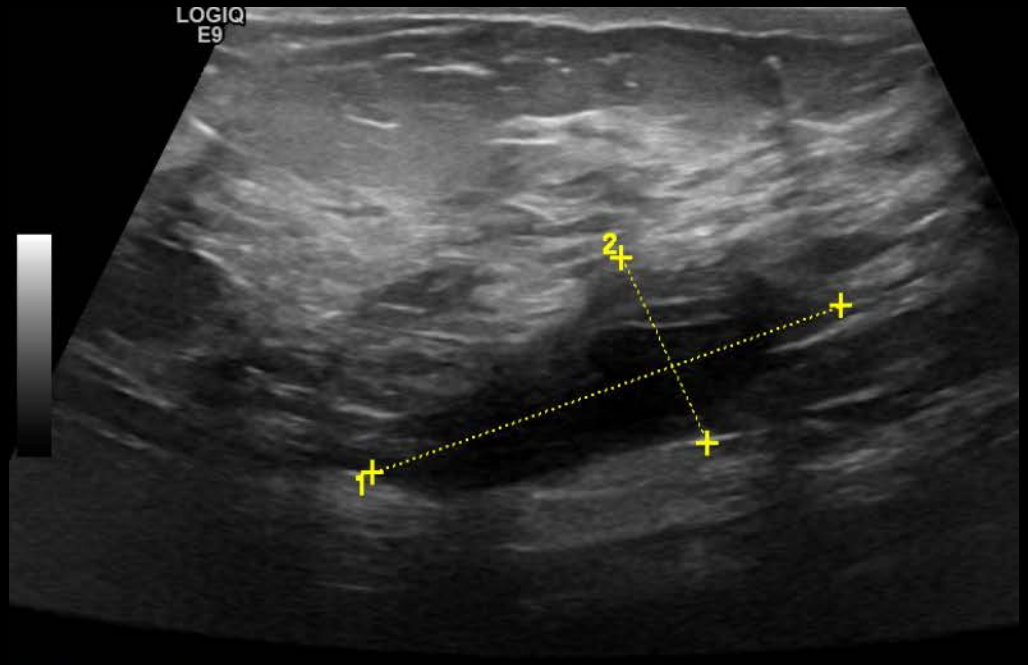
Clinical Course

- Patient completed preop chemotherapy
- Taxol weekly x 12
- Adriamycin and cytoxan q 2 weeks x4
- Rapid clinical response with resolution breast mass and axillary nodes

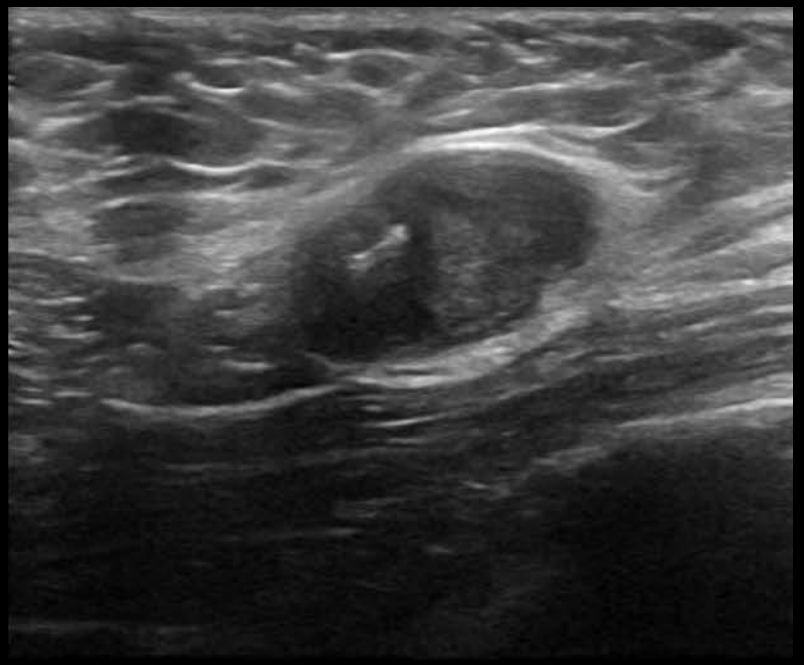
Diagnostic Mammography post neoadjuvant chemotherapy



Ultrasound post neoadjuvant chemotherapy

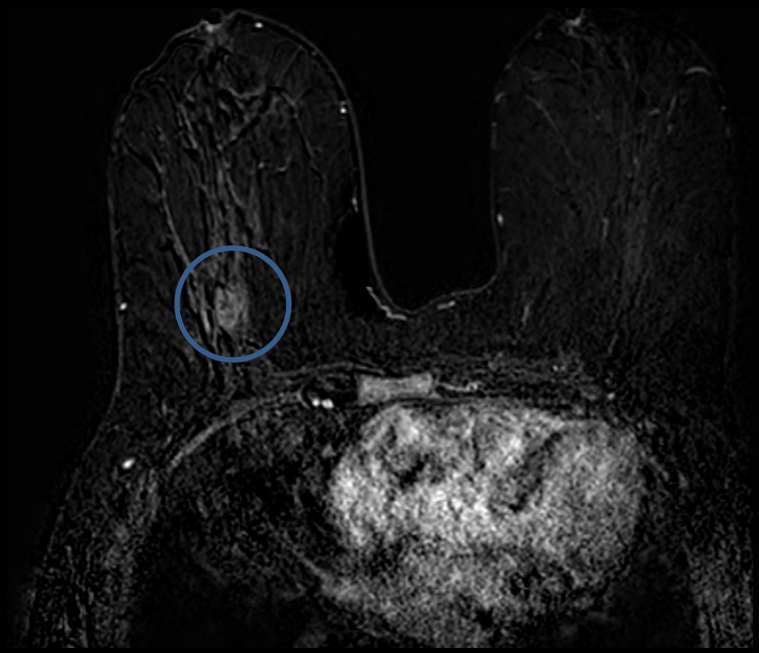


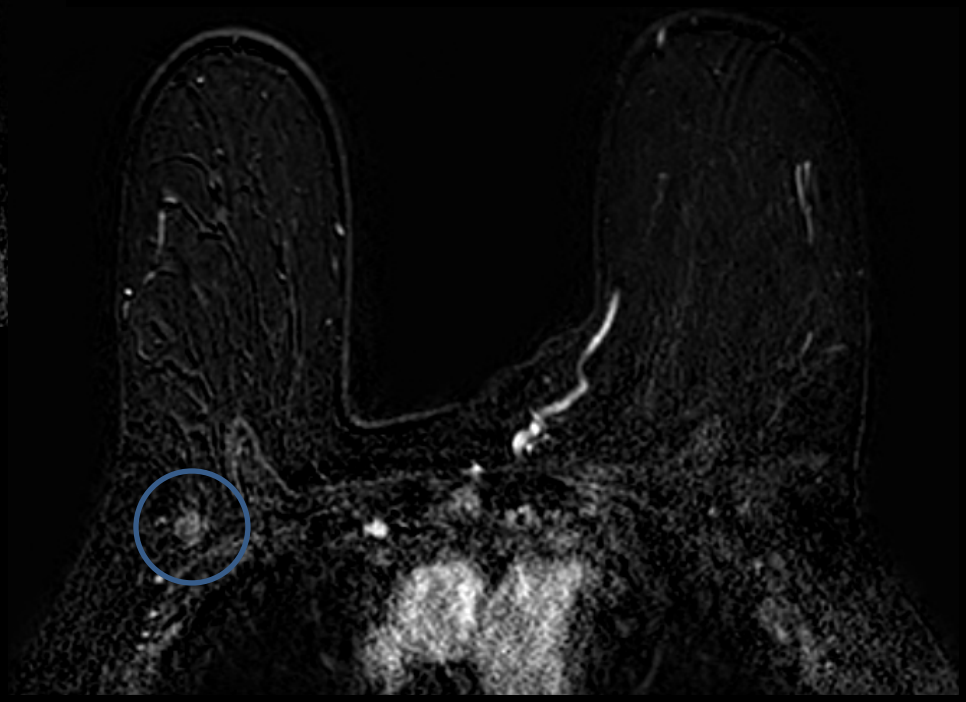
RIGHT BREAST 12 O'CLOCK 4CM FN LO



RIGHT AXILLA LO

Breast MRI post neoadjuvant chemotherapy





Breast MRI following neoadjuvant chemotherapy

- Most accurately predicts surgical pathology in:
  - triple negative
  - HER2 positive
  - hormone receptor negative tumors
  - Particularly if they appear solid on MRI imaging
- Lower concordance is seen in:
  - Hormone receptor positive cancers
  - Those with non mass enhancement
- I-SPY trial with serial MRI's over the course of neoadjuvant therapy
  - MRI underestimated extent of disease in 4.3% of cases
    - Discordant cases were either hormone receptor positive or had diffuse phenotypes on MRI

Price ER et al. World Journal o f Clinical Cases. 2015;3(7); 607-613

Audience Response Question

My recommendation for this patient is:

a. Lumpectomy and axillary node dissection

b. Lumpectomy and sentinel node biopsy

c. Modified radical mastectomy with immediate reconstruction

Clinical Course:

- Patient opted for breast conservation approach and underwent seed localized lumpectomy and sentinel node biopsy
- Genetic counseling/testing not performed

Genetic Testing in Older Patients

- *Breast cancer lifetime risk - 1/8*
- *Likely sporadic not germline*
- *This patient would not have qualified for genetic testing via NCCN guidelines or insurance because of her age and relative with breast cancer was older*
- *HOWEVER - If patient is under 60, triple negative breast cancer DOES meet criteria and no family hx needed*
- *Over 60, need a "significant" family history*

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Triple Negative

- *10-30% of patients with triple negative breast cancer will have a BRCA1 or BRCA2 mutation*
- *A small % will have another mutation*
- ***studies change NCCN guidelines*

- *Higher in African Americans*
- *Higher in Obese patients -?insulin signalling*
- *Directed chemotherapy*

J Clinical Oncol 2014
Newman JAMA Surg Oncol 2017
Dietze, AmJ Pathol 2017

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Neoadjuvant chemotherapy(NAC)

- Shown to decrease rate of nodal positivity by 30-40% in triple negative and HER2+ tumors
- In pts with HER2+ disease, trastuzumab tx can eliminate axillary metastases in 70% pts getting neoadjuvant therapy
- Axillary complete pathologic response shown to be associated with improved DFS

Accuracy of sentinel node biopsy after(NAC)

TABLE 2. Randomized Trials of Sentinel Lymph Node Biopsy After Neoadjuvant Systemic Therapy in Patients With Biopsy-Proven Axillary Lymph Node Metastases at Presentation

Study and Year	No. of Patients	SLNB Identified (%)	Average SLN Removed	Patients With ≥3 SLNs Removed (%)	Overall (%)	False-Negative Rate (%)			
						1 SLN	2 SLN	≥3 SLN	Dual Mapping
Z1071 (2013)	689	93	3.1	56	13	—	21	9	11
SENTINA Arm C (2013)	592	80	2.5	34	15	24	19	5	9
SN-FNAC (2014)	145	88	2.7	—	8	18	5*	—	5
Total [n/N (%)]	1426	1240/1426 (87)	2.8	589/1281 (46)	78/619 (13)	21/92 (23)	46/270 (17)	40/490 (8)	65/645 (10)

*SN-FNAC study reported false-negative rate only for 1 versus 2 or more SLNs removed.

SLNB indicates sentinel lymph node biopsy; SLN, sentinel lymph node.

Complete pathological response by subtype after neoadjuvant chemotherapy

TABLE 1. Axillary Pathologic Complete Response Rates in Patients With Biopsy-Proven Axillary Lymph Node Metastases After Neoadjuvant Systemic Therapy

References	No. of Patients	SLNB Success Rate (%)	Axillary pCR (%)	Molecular Subtype (%)			
				ER+ HER2−	ER+ HER2+	ER− HER2+	ER− HER2−
Mamtami et al[13]	195	98	49	21	70	97	47
Park et al[14]	178	95	41	24	52	52	59
Dominici et al[15]	109	—	—	—	67	79	—
Boughey et al[16]	689	93	40	—	—	—	—
Yagata et al[17]	95	85	33	—	—	—	—
Newman et al[18]	54	98	32	—	—	—	—
McVeigh et al[19]	78	—	37	—	—	—	—
Total [n/N (%)]	—	1067/1144 (93)	497/1236 (40)	33/148 (22)	71/111 (64)	96/125 (77)	46/89 (52)

pCR indicates pathologic complete response; ER; estrogen receptor; HER2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy.

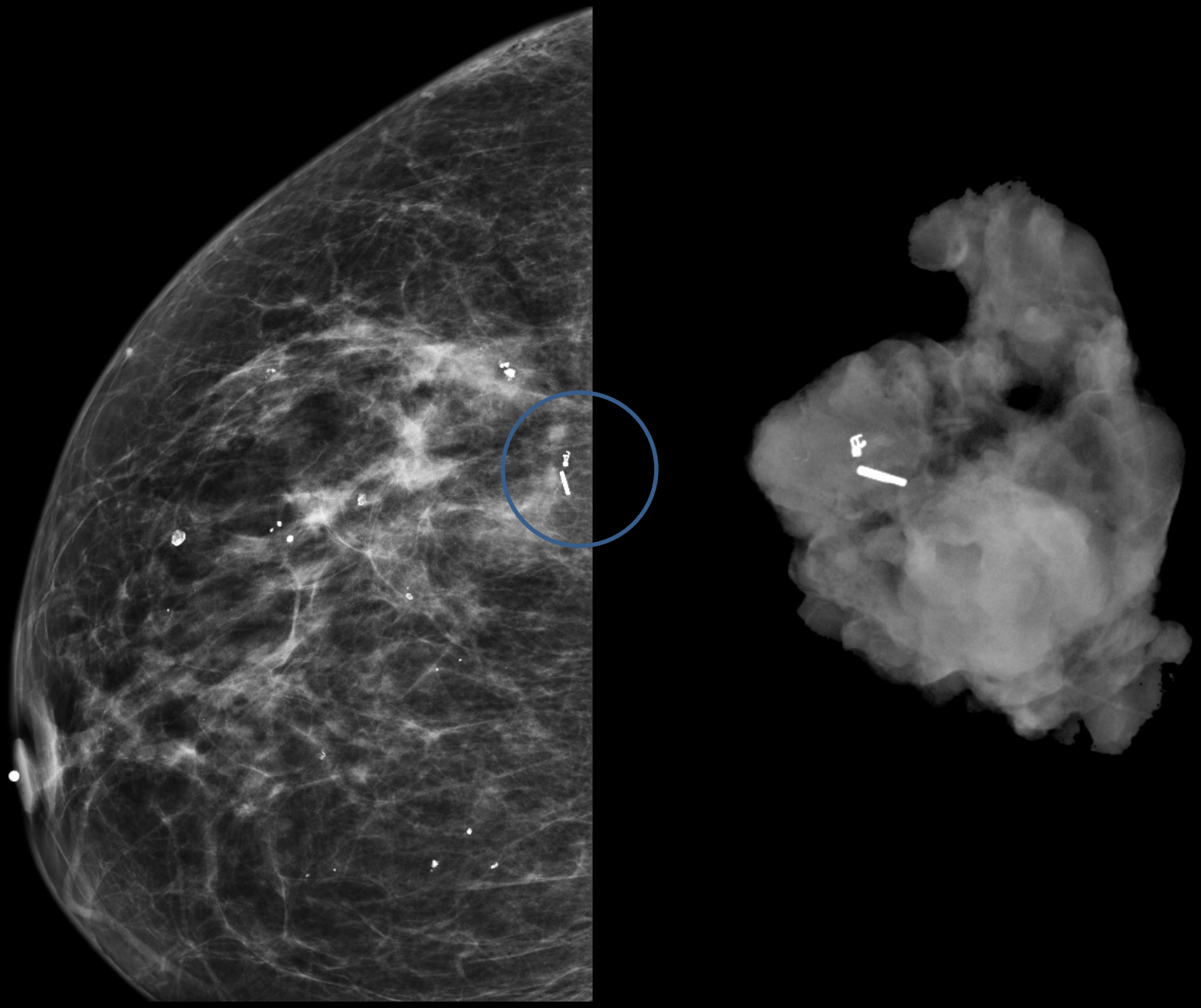
TAD: TARGETED AXILLARY DISSECTION
Caudle et al ; JCO 2016

- Clip placed in metastatic axillary node at time of core biopsy
- Radioisotope seed localization post NAC preoperatively
- Surgery; sentinel node biopsy(tracer) and removal of clipped node
- False negative rate 4.2%
- Success rate 77%

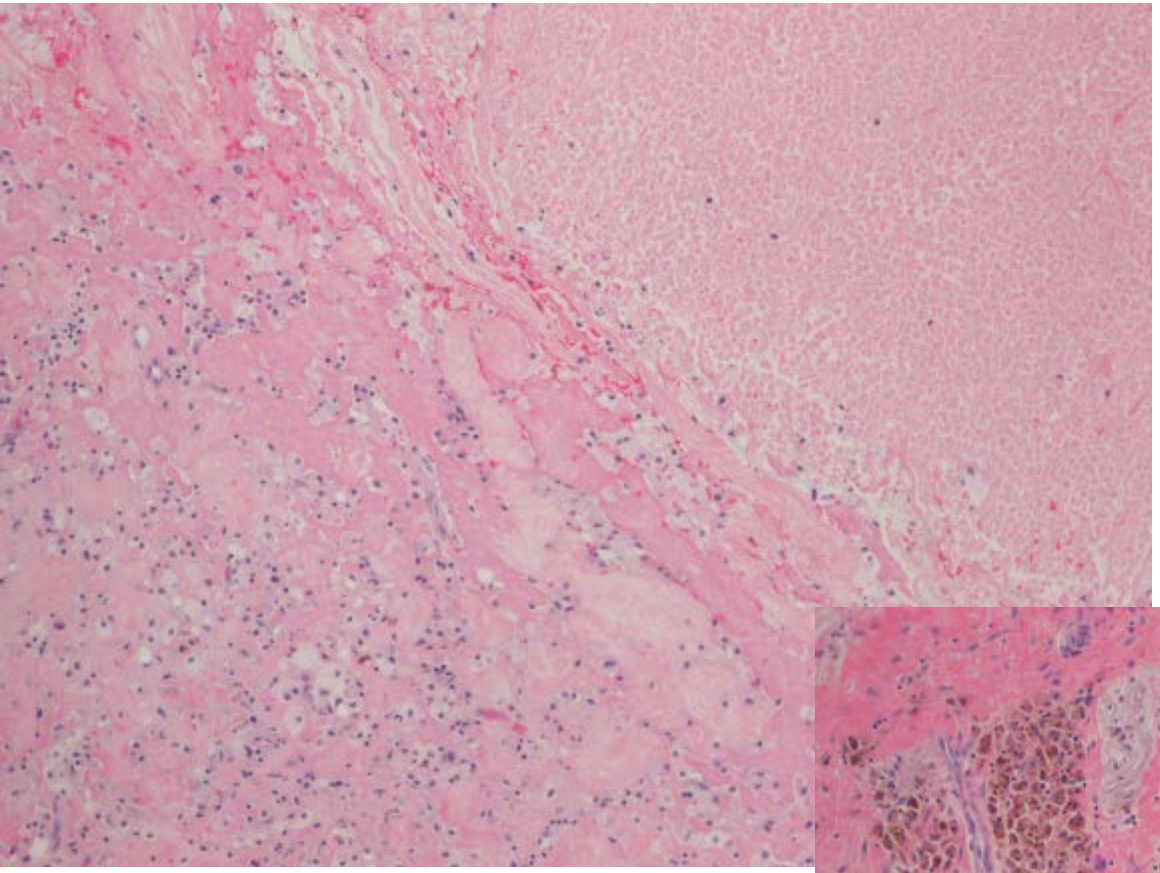
Neoadjuvant therapy conclusions

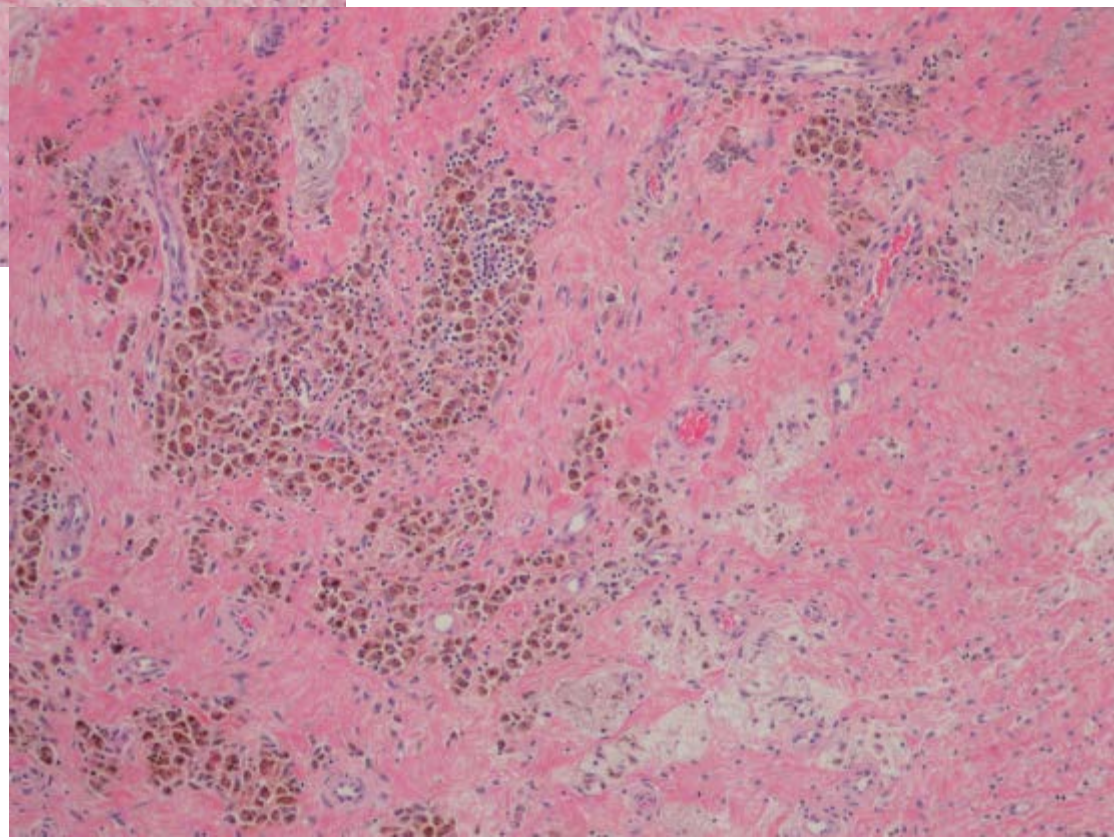
- Neoadjuvant therapy downstages axillary disease and associated with improved DFS
- SLNB has high FNR but can be improved with
- >3 SLN
- Clip placement in positive node
- TAD
- Sentinel lymph node positivity after neoadjuvant therapy patients can be randomized to Alliance trial A11202(RT vs ALND)

Radioactive Seed Localization

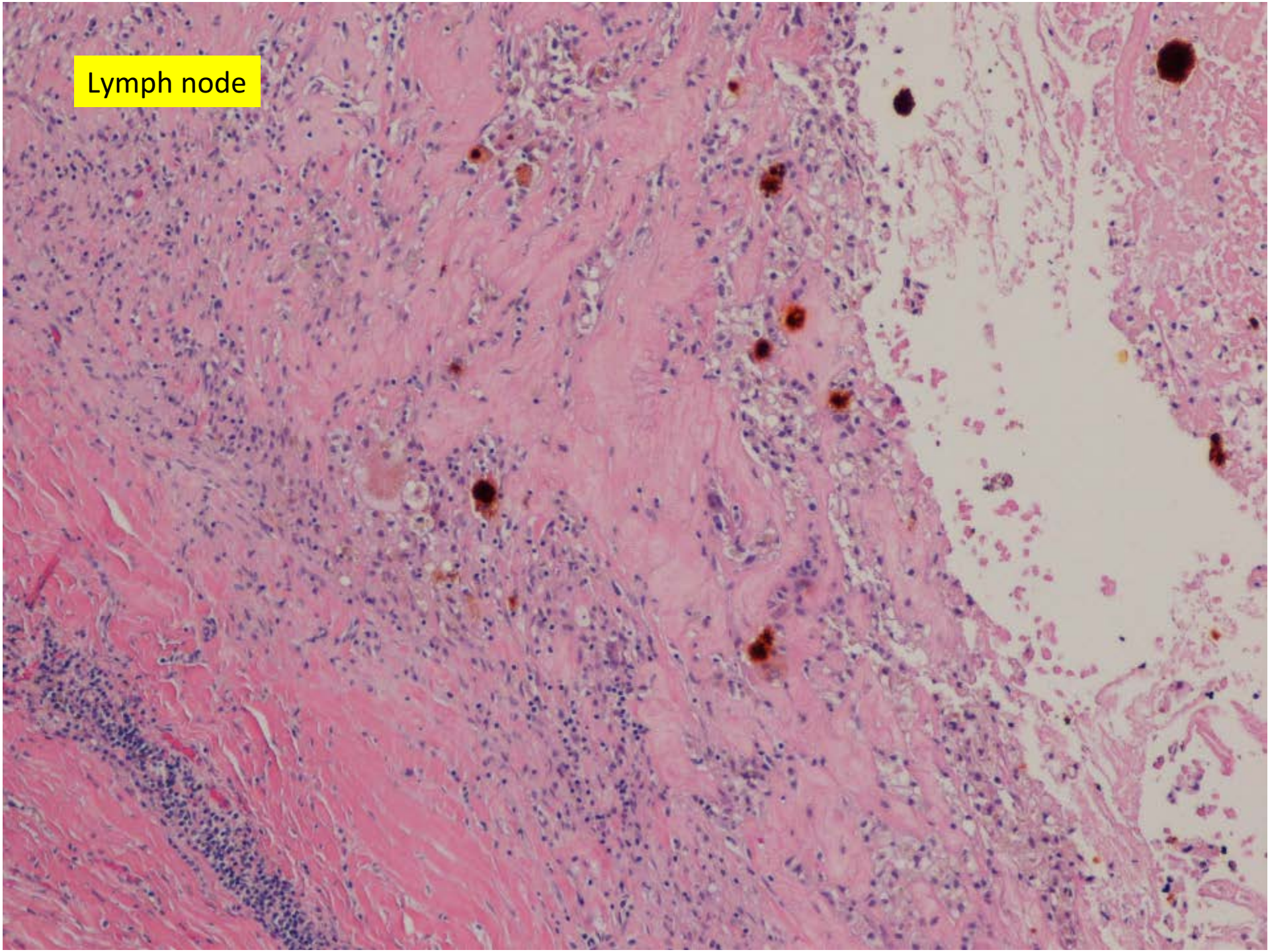


Lumpectomy with margins + sentinel and axillary nodes





19mm gross mass


Lymph node

Lumpectomy- Area of tumor regression with histiocytes, fibrosis, inflammation, hemosiderin and necrotic tumor over 19mm area- NO VIABLE TUMOR

Axillary lymph nodes- 12 nodes , two with treatment effect including fibrosis hemosiderin and necrotic tumor ; no viable tumor

Pathology after Neoadjuvant Chemotherapy

- Quantifying residual tumor :

Pre therapy = T2

Post therapy – Multiple foci of cancer spread out in tumor bed and the Largest contiguous 5mm=ypT1a(m)

Two measures of residual tumor :

- 1- TNM- Measure largest contiguous tumor focus in tumor bed -
- 2- RCB score – Based on size of tumor bed and tumor bed cellularity (3cm, 10% cellularity) and lymph node status - Scores (pCR , RCB=1 minimal residual disease, RCB2= moderate disease, RCB3= significant residual disease)

- Lymph Node assessment
  - When lymph nodes are negative after chemotherapy it is important to describe features of regression in nodes in order to:
    1- provide information on number of positive nodes pretherapy
    2- If positive node pretherapy evidence of regression helps confirm that +nodes were removed

Definition of Pathologic Complete Response

- No residual invasive carcinoma in the breast or lymph nodes
- DCIS only is allowed
- Tumor in lymphatics only in breast is not considered pathologic complete response

Radiation After NeoAdjuvant Chemotherapy

Radiation in Context of Neoadjuvant Chemotherapy+BCS

- Pre-chemo clinical staging currently drives recommendations
- Radiate breast + regional nodes if pt cN+ and/or pN+
  - MA.20
    - Improved DFS, trend for OS
  - Undissected axilla, supraclavicular fossa
    - +/-IMNs

PMRT in Context of Neoadjuvant Chemotherapy

- Traditional PMRT recommendations from adjuvant chemotherapy era
- No randomized data as of yet on which pts receiving neoadjuvant chemotherapy would benefit from PMRT
- Pre-chemo clinical staging currently drives recommendations

NSABP Experience

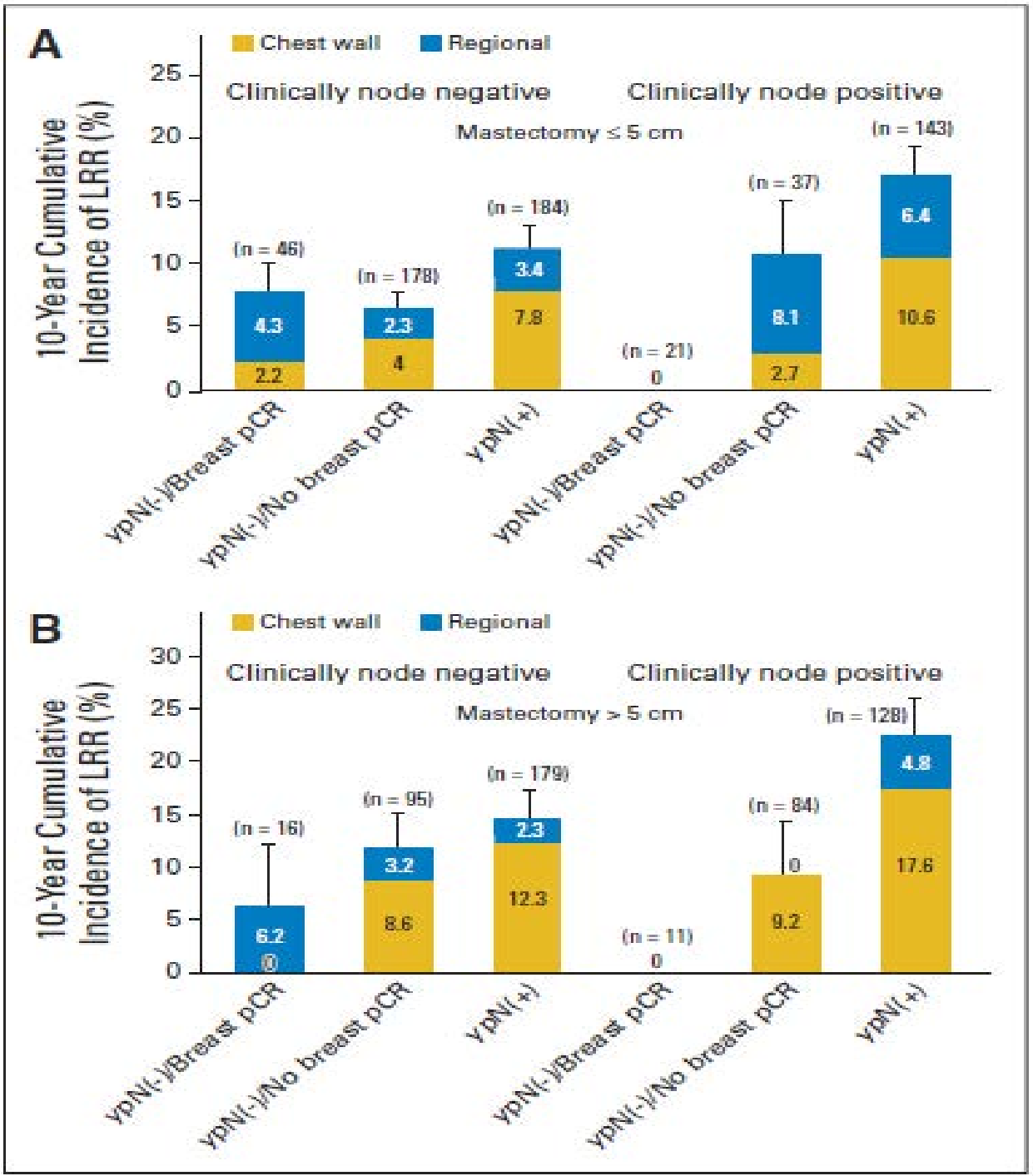
- Pre-Op AC arm from B-18
- Pre-Op AC +/-T arm from B-27
- Pts had lump+RT or mastectomy, no PMRT
- LRR 12.6% @10yr among 1947 mastectomy pts (9%LR)
- Multivariate analysis to identify predictors of LRR as first event amongst 1071 with all info

Mamounas, JCO 2012

Mamounas et al: MVA

Variable	HR	95% CI	p
cT: > 5 vs ≤ 5 cm	1.58	1.12 – 2.23	.0095
cN+ vs cN-	1.53	1.08 - 2.18	.017
pCR nodes vs Complete pCR	2.21	0.77 – 6.30	< .001
Node positive vs Complete pCR	4.48	1.64 – 12.21	< .001

Mamounas E et al JCO 2012 30: 3960


A
Chest wall
Regional
Clinically node negative
Clinically node positive
Mastectomy ≤ 5 cm
10-Year Cumulative Incidence of LRR (%)
25
20
15
10
5
0
(n = 46)
4.3
2.2
(n = 178)
2.3
4
(n = 184)
3.4
7.8
(n = 21)
0
(n = 37)
8.1
2.7
(n = 143)
6.4
10.6
ypN(-)/Breast pCR
ypN(-)/No breast pCR
ypN(+)
ypN(-)/Breast pCR
ypN(-)/No breast pCR
ypN(+)
B
Chest wall
Regional
Clinically node negative
Clinically node positive
Mastectomy > 5 cm
10-Year Cumulative Incidence of LRR (%)
30
25
20
15
10
5
0
(n = 16)
6.2
0
(n = 95)
3.2
8.6
(n = 179)
2.3
12.3
(n = 11)
0
(n = 84)
0
9.2
(n = 128)
4.8
17.6
ypN(-)/Breast pCR
ypN(-)/No breast pCR
ypN(+)
ypN(-)/Breast pCR
ypN(-)/No breast pCR
ypN(+)

T≤5cm

T>5cm

Predictors of LRR after Mastectomy: MVA

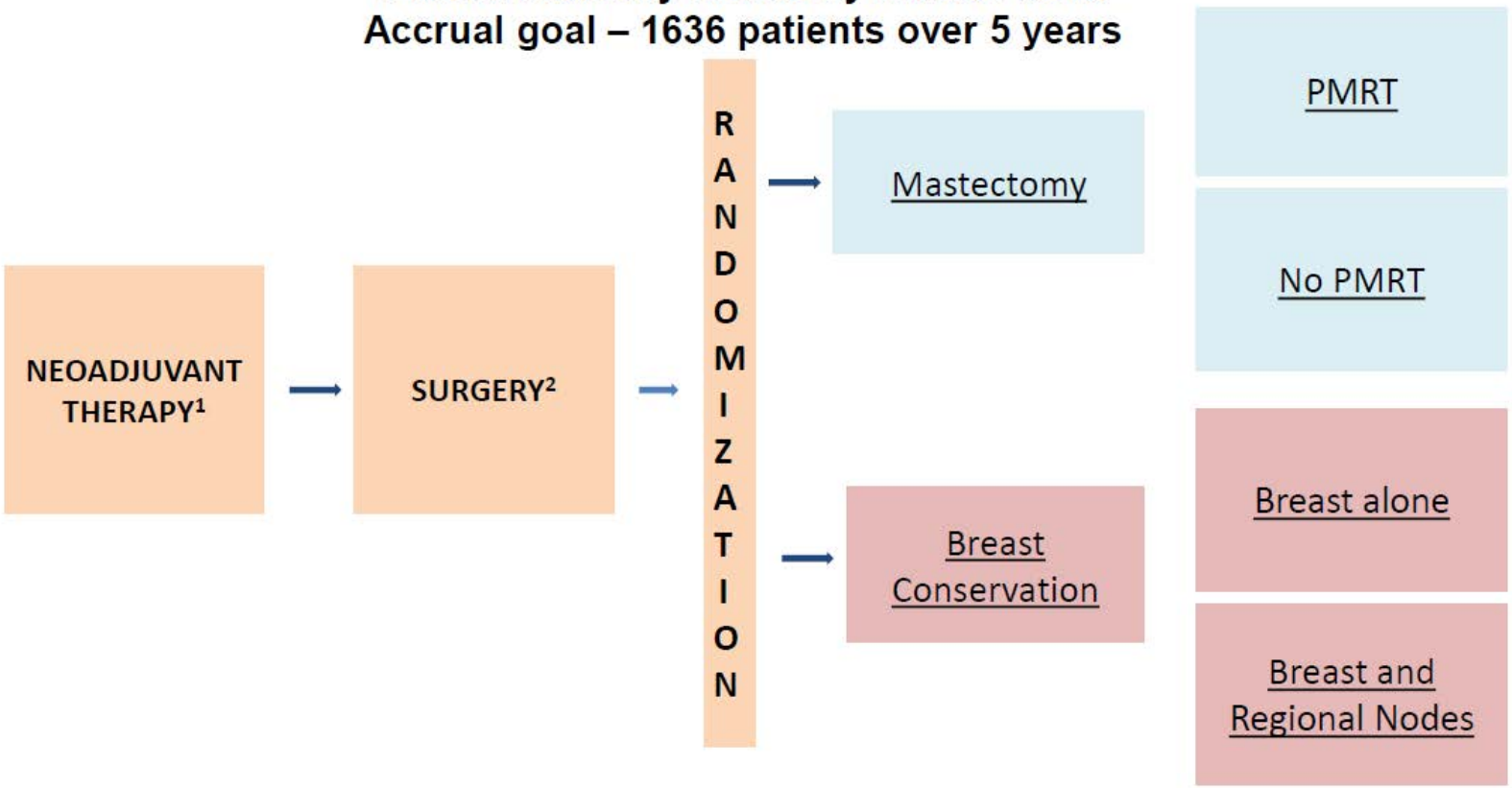
- Clinical tumor size at presentation
- Clinical node status at presentation
- Path node status after chemotherapy
- Path response in the breast

Both the initial clinical and the final path stage must be used to determine LR risk

Mamounas E et al JCO 2012 30: 3960

NSABP B-51/RTOG 1304

Clinical T1–3, N1
Positive Axillary Nodes by FNA or Core
Accrual goal – 1636 patients over 5 years



[1]Minimum 12 weeks, trastuzumab when appropriate
[2]Path Documentation of Negative Axillary Nodes (by ALND or by SLNBx ± ALND)

Post Lumpectomy Imaging

Evidence Based Guidelines for Imaging Surveillance After Treatment of Primary Breast Cancer

Organization, Imaging Modality	Routine Imaging Surveillance Recommendation
ACS and ASCO, 2015 (general survivorship guidelines post treatment):	
Mammography	Initiation not specified; annual
Breast MRI	If patient meets high risk criteria (>20% lifetime
Ultrasound	Not specified
NCCN, 2016:	
Mammography	Initiation 6-12 months after RT; annual
Breast MRI	Not specified
Ultrasound	Not specified
ACR, 2014:	
Mammography	Initiation and frequency per local institution
Breast MRI	Based on risk assessment
Ultrasound	Based on risk assessment if MRI contraindicated

AJR Am J Roentgenol. 2017 Mar; 208(3): 676–686.

Post Lumpectomy Imaging

MRI

	Year	No. of Women With Personal History of Breast Cancer	Age (y), Mean (Range)	No. of MRI Examinations	No. of MRI detected cancers	Cancer Detection Rate (No. of Cancers/1000 Examinations)
Elmore and Margenthaler	2010	141[a]	51 (24–73)	202	2	9.9
Brennan et al. [	2010	144	49 (22–73)	NR (1–11 examinations/ woman)	18[b]	10.6[c]
Schacht et al.	2014	208	52 (NR)	NR	6	28.8[c]
Gweon et al. [	2014	607	48[d] (20–72)	932	13	13.9[e]
Giess et al.	2015	691[f]	52[d] (26–86)	1194	12	10.1
Weinstock et al. [	2015	249	46[d] (25–64)	571	11	19.3
Lehman et al.	2016	915	NR (< 40 to ≥ 70)	915	18	19.7

AJR Am J Roentgenol. 2017 Mar; 208(3): 676–686.

Post Lumpectomy Imaging

Summary and Recommendations for Breast Practices

- Minimum of annual screening
  - Variability for surveillance initiation, interval, and cessation
  - Use of 3D mammography is still being studied
- Most guidelines do not support whole breast ultrasound screening in breast cancer surveillance
- Surveillance MRI may be indicated in a select group of patients
  - Currently only those with >20% lifetime risk
- Patient, tumor, imaging, and treatment factors are important in developing patient centered surveillance regimens

AJR Am J Roentgenol. 2017 Mar; 208(3): 676–686

Conclusion

- Patient underwent lumpectomy and sentinel node biopsy after completion of neoadjuvant chemotherapy
- Pathology shows complete response!
- Excellent prognosis!
- Undergoing adjuvant radiation
- Imaging surveillance with yearly mammograms

ANY QUESTIONS