THE AMERICAN SOCIETY OF Breast Surgeons

ACCC
ASSOCIATION OF CANCER CARE CENTERS™

Expanding indications for breast conserving therapy:

The why and the how

Kari M. Rosenkranz, MD, FACS
Professor of Surgery
Dartmouth Health/Geisel School of Medicine

Disclosures

I have no financial disclosures

Disclosures

Disclosures

Disclosures

Breast-conserving therapy (BCT) is currently the *preferred* treatment option for breast cancer

The Why

BCT compared to mastectomy

- Decreased length of stay
- Fewer surgical complications
- Lower risk of long term morbidity

The Why

Mastectomy

(with or without reconstruction)

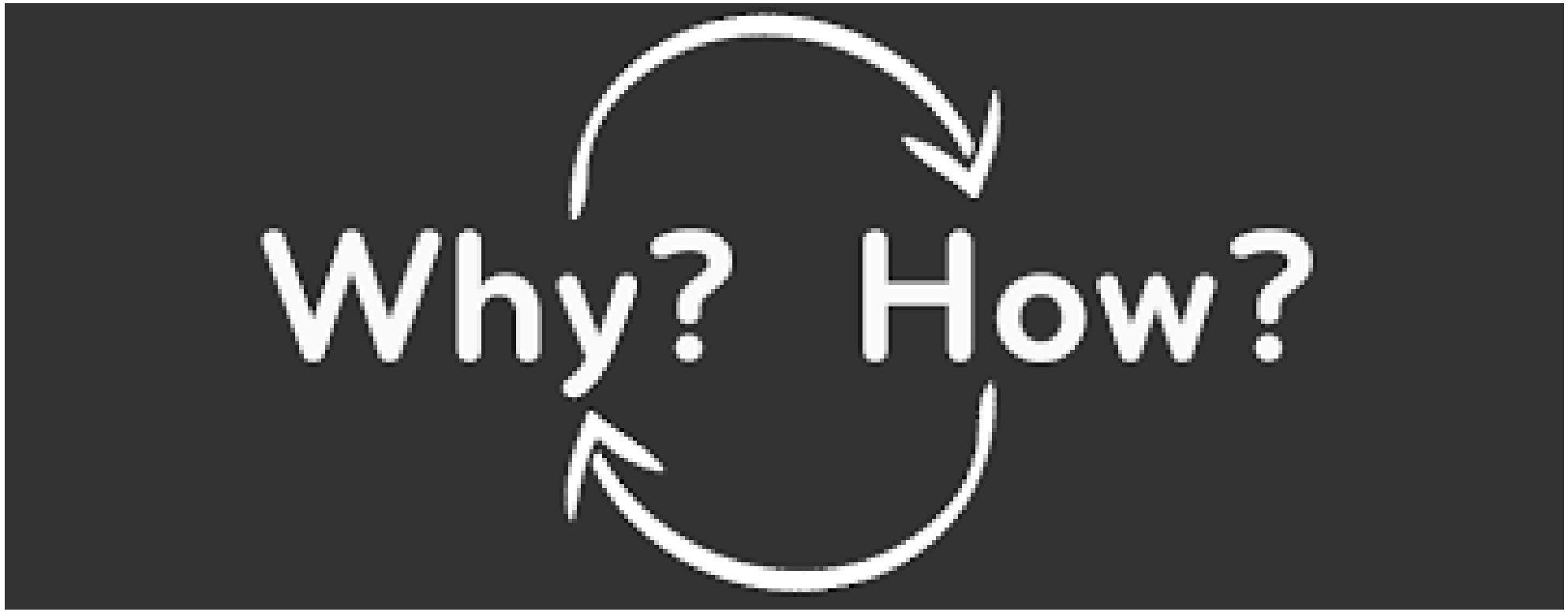
- Diminished quality of life
- Negative body image
- Lower self- esteem
- Difficulty coping
- Decreased sexuality

Hill-Kayser C, Vachani C, Hampshire M et al. Int J Radiat Oncol Biol Phys. 2011: 79(4):1048-54
Han J, Grothuesman D, Neises M, et al.. Arch Gynecol Obstet. 2010; 282, 75-82
Flanagan M, Zabor E, Romanoff A, et al. Ann Surg Oncol, 2019; 26:3133-314017

The Why

Increasing evidence that BCT offers a survival benefit for high risk subtypes

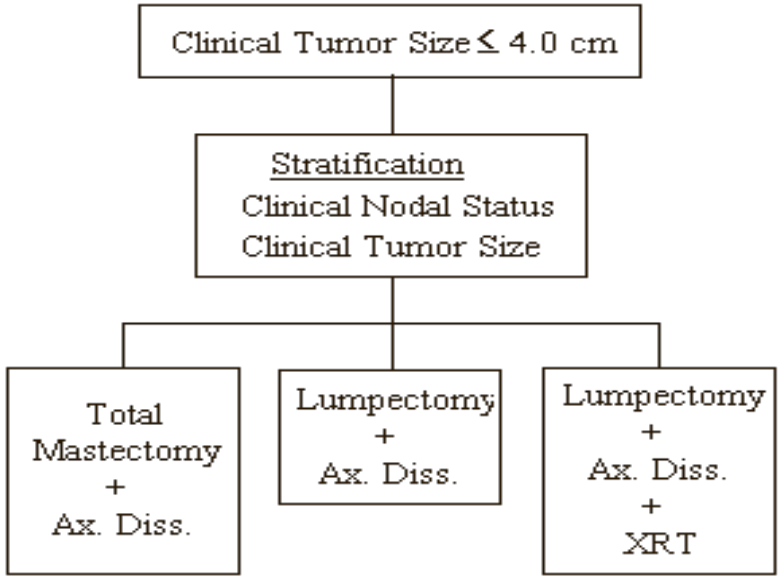
Expanding oncologically appropriate indications for BCT can improve physical and psychologic recovery for many women with breast cancer…and possibly survival


Why? How?

3500 B.C.E until 1970

NSABP B-06

Mastectomy vs lumpectomy vs lumpectomy with radiation
1976-84

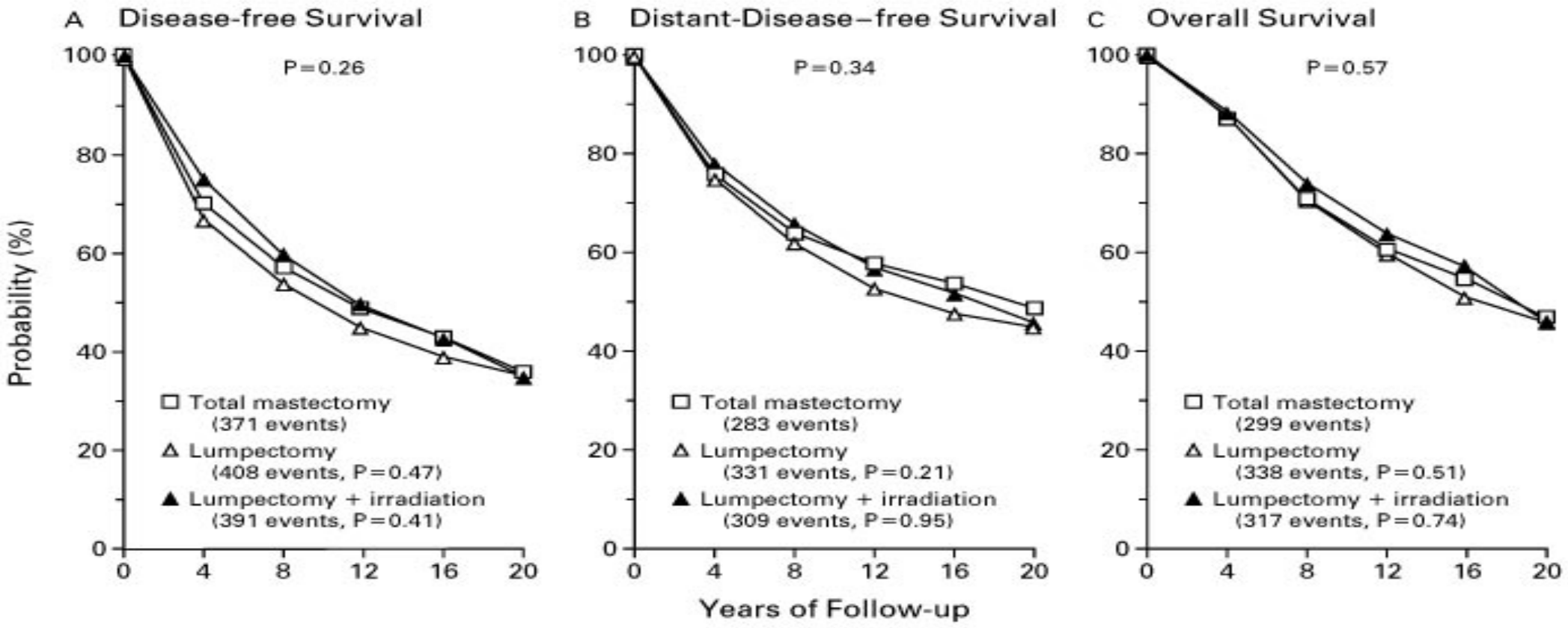


All patients with histologically positive axillary nodes receive L-PAM + 5 FU.

Total mastectomy performed in event of ipsilateral breast tumor recurrence.

Fisher et al, NEJM, 2002

B-06: 20 year follow up



Fisher et al, NEJM, 2002

Greening, W. P.. “Role of the Surgeon in Management of Breast Cancer.” *Journal of the Royal Society of Medicine* 73 **(1980):** 837 - 838.

Table II. Indications for a mastectomy

Absolute indications

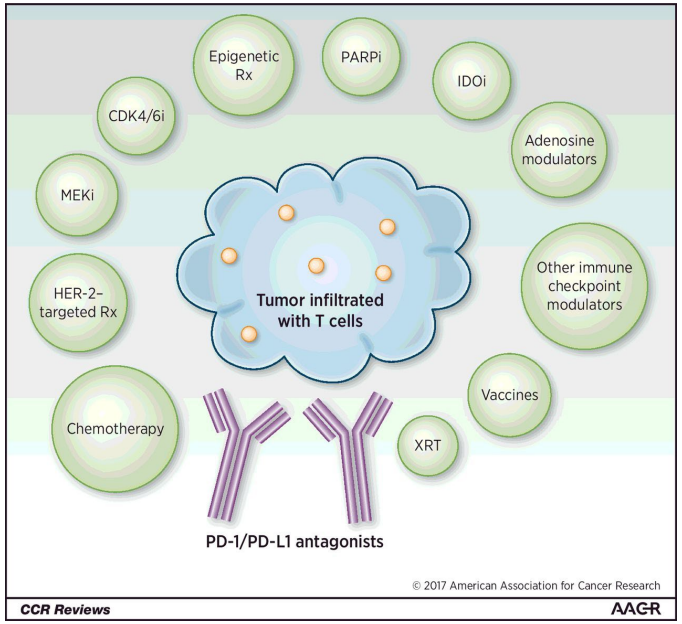
- Women with >2 tumours in separate quadrants
- Previous irradiation to the chest wall
- Pregnancy: contraindication to radiotherapy but can have breast-conserving therapy after neoadjuvant chemotherapy
- Persistent positive margins

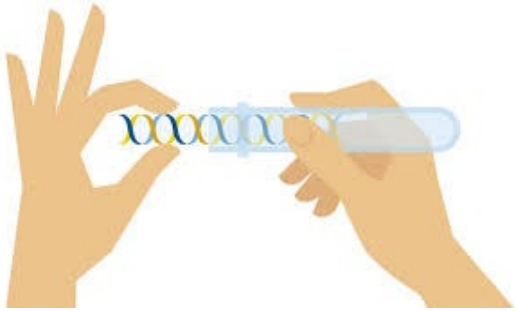
Relative indications

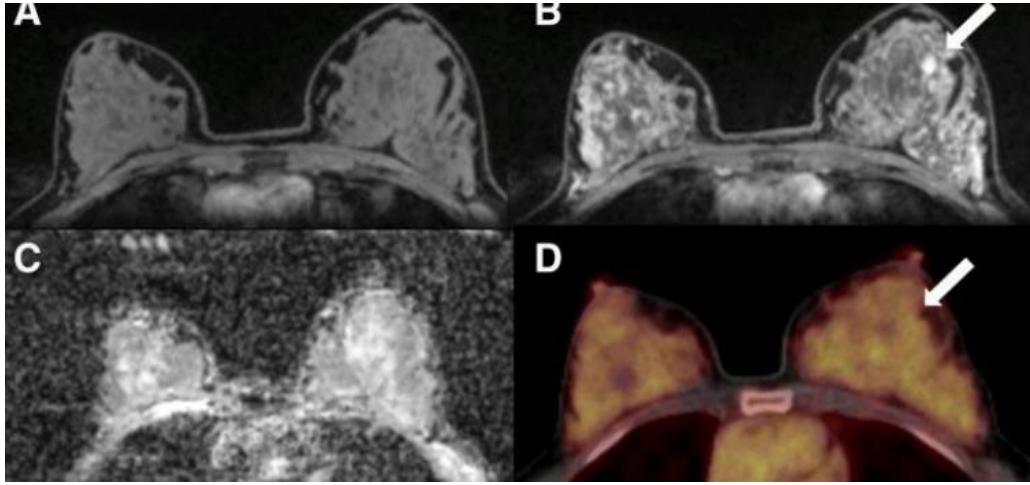
- Collagen vascular disease
- Multiple tumours in same quadrant with indeterminate microcalcifications
- Tumour size:breast size ratio

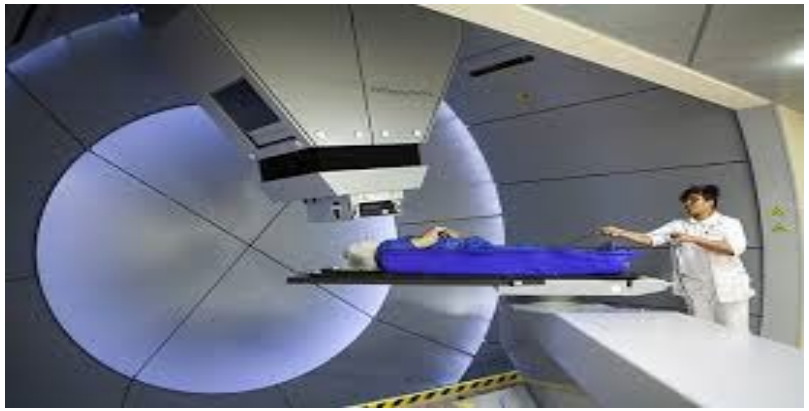
Non-mitigating factors

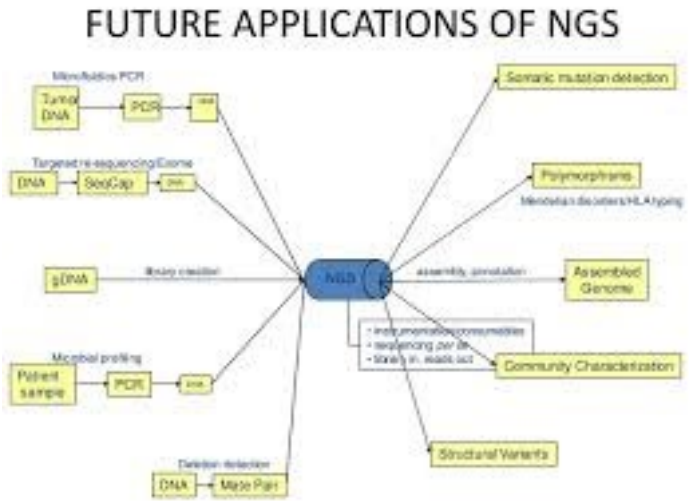
Table II. Indications for a mastectomy

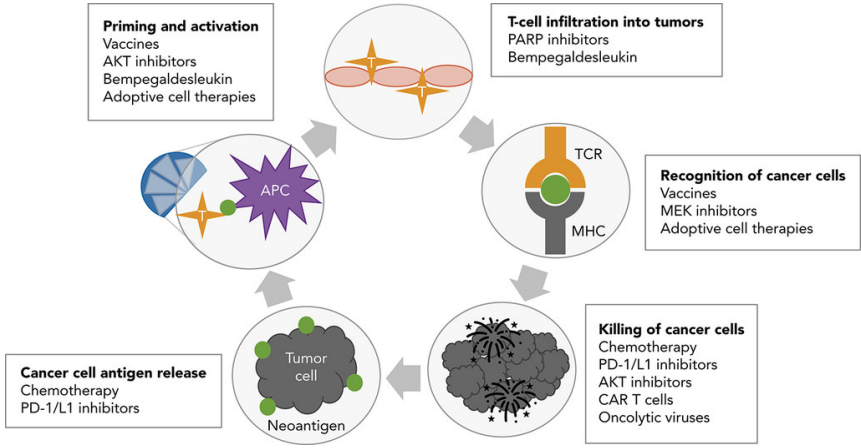

Epigenetic Rx
PARPi
IDOi
CDK4/6i
Adenosine modulators
MEKi
Tumor infiltrated with T cells
Other immune checkpoint modulators
HER-2–targeted Rx
Vaccines
Chemotherapy
XRT
PD-1/PD-L1 antagonists
© 2017 American Association for Cancer Research
CCR Reviews
AACR




A
B
C
D




FUTURE APPLICATIONS OF NGS
Somatic mutation detection
Polymorphisms
Assembled Genome
Community Characterization
Structural Variants
NGS


Priming and activation
Vaccines
AKT inhibitors
Bempegaldesleukin
Adoptive cell therapies
T-cell infiltration into tumors
PARP inhibitors
Bempegaldesleukin
TCR
MHC
APC
Recognition of cancer cells
Vaccines
MEK inhibitors
Adoptive cell therapies
Killing of cancer cells
Chemotherapy
PD-1/L1 inhibitors
AKT inhibitors
CAR T cells
Oncolytic viruses
Tumor cell
Neoantigen
Cancer cell antigen release
Chemotherapy
PD-1/L1 inhibitors

AI:
January 1, 2025

AI Overview

Contraindications to breast conservation surgery include: **pregnancy, multiple primary tumors in different breast quadrants, diffuse malignant microcalcifications, inflammatory breast cancer, persistently positive surgical margins, previous breast radiation, and a very large tumor size relative to the breast size**, which can make achieving negative margins difficult; in some cases, large tumor size may be considered a relative contraindication depending on the situation and potential for neoadjuvant chemotherapy.

1980 vs 2025

Table II. Indications for a mastectomy

Absolute indications

- Women with >2 tumours in separate quadrants
- Previous irradiation to the chest wall
- Pregnancy: contraindication to radiotherapy but can have breast-conserving therapy after neoadjuvant chemotherapy
- Persistent positive margins

Relative indications

- Collagen vascular disease
- Multiple tumours in same quadrant with indeterminate microcalcifications
- Tumour size:breast size ratio

Non-mitigating factors

Table II. Indications for a mastectomy

Key points about contraindications to breast conservation surgery:

Absolute contraindications:

- Pregnancy
- Multicentric tumors (tumors in multiple breast quadrants)
- Diffuse malignant microcalcifications
- Inflammatory breast cancer
- Positive surgical margins after surgery
- Prior breast radiation

Relative contraindications:

- Very large tumor size compared to breast size
- Collagen vascular diseases like scleroderma
- Morbid obesity
- Technical difficulties with radiation therapy due to large breast size

Where can we do better?

Key points about contraindications to breast conservation surgery:

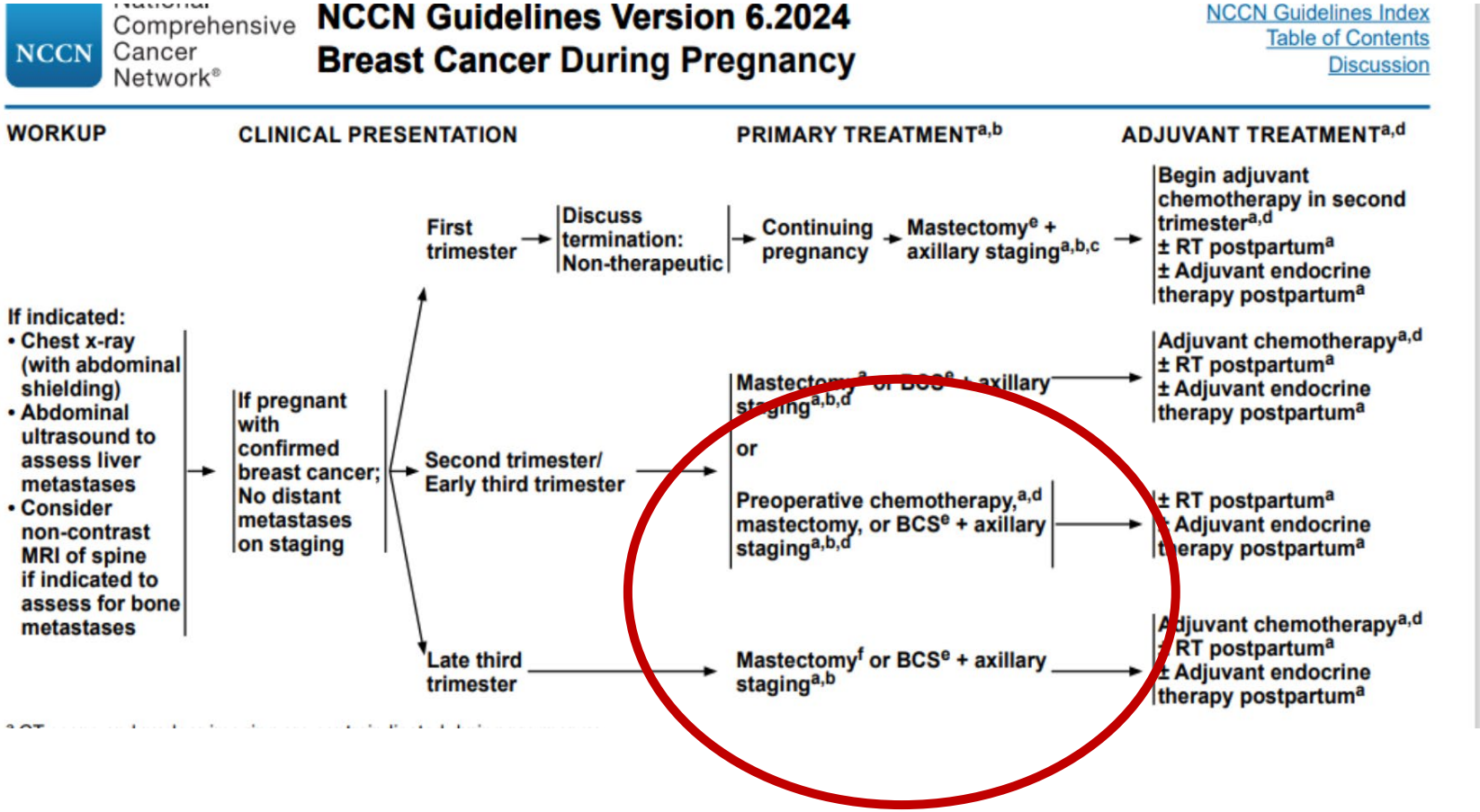
Absolute contraindications:

- Pregnancy
- Multicentric tumors (tumors in multiple breast quadrants)
- Diffuse malignant microcalcifications
- Inflammatory breast cancer
- Positive surgical margins after surgery
- Prior breast radiation

Relative contraindications:

- Very large tumor size compared to breast size
- Collagen vascular diseases like scleroderma
- Morbid obesity
- Technical difficulties with radiation therapy due to large breast size

Pregnancy



NCCN version 6.2024 accessed January 4, 2025

Second ipsilateral breast cancer

Second primary/ In breast recurrence

- Recurrence rates vary with tumor biology and stage at presentation
- Schumacher et al. Ann Surg 2023
  - Patients treated between 1997-2010
  - 5 year in breast recurrence rate of 4.2 %
- Rates will continue to decrease with improvements in systemic therapy and radiation techniques

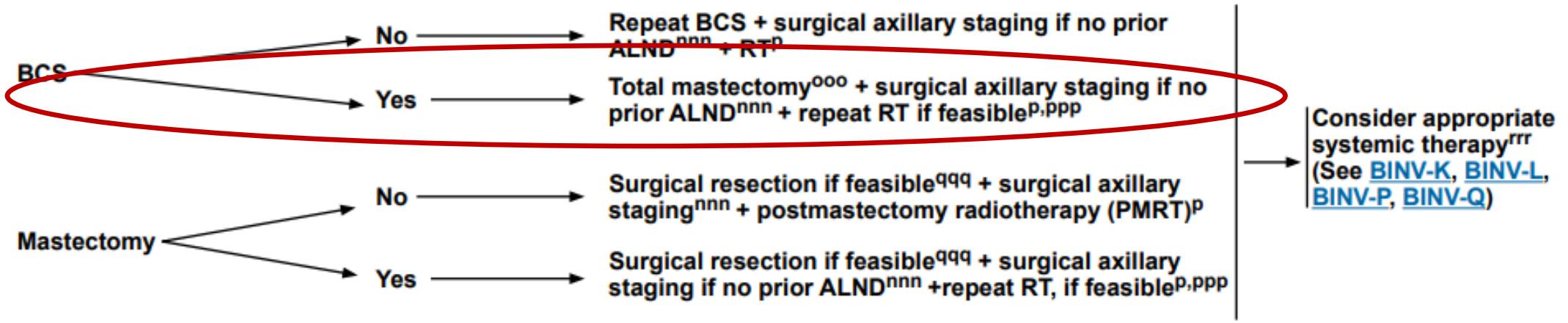
National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

TREATMENT OF LOCAL RECURRENCE: In-breast or Chest wall recurrence[mmm] (Without clinically overt axillary recurrence)

(For REGIONAL ± LOCAL RECURRENCE see BINV-20)




7,000
Women

follow the data


Ann Surg Oncol (2012) 19:3771–3776
DOI 10.1245/s10434-012-2404-5
ORIGINAL ARTICLE – BREAST ONCOLOGY
Repeating Conservative Surgery after Ipsilateral Breast Tumor Reappearance: Criteria for Selecting the Best Candidates
Oreste Gentilini, MD[1], Edoardo Botte
Andres Del Castillo, MD[1], Bettina B
Marco Colleoni, MD[6], Alberto Luir
The Oncologist
Breast Cancer
Increased Mortality with Repeat Lumpectomy Alone After Ipsilateral Breast Tumor Recurrence
Yonghui Su[a,b,†] Rong Guo[a,b,†] Jingyan Xue[a] Yayun Chi[a] Weiru Chi[a,b] Jia Wang[a,b] Benglong Yang[a] Jiong Wu[a,b]
[a]Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai
People's Republic of China; [b]Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, People's Re
China
Breast Cancer Research and Treatment (2021) 185:155–164
https://doi.org/10.1007/s10549-020-05932-8
CLINICAL TRIAL
Long-term survival outcomes of repeat lumpectomy for ips
breast tumor recurrence: a propensity score-matched analy
Soo Yeon Baek[1] · Jisun Kim[1] · Il Yong Chung[1] · Beom Seok Ko[1] · Hee Jeong Kim[1] · Jong Won L
Sei-Hyun Ahn[1] · Sae Byul Lee[1]
Journal of Surgical Oncology 2014;110:62–67
Conservative Surgery for Ipsilateral Breast Tumor Recurrence
JOSE VILA, MD,[1] CARLOS A. GARCIA-ETIENNE, MD,[2] ANDREA VAVASSORI, MD,[3]
AND ORESTE GENTILINI, MD[1]*
[1]Division of Breast Surgery, European Institute of Oncology, Milan, Italy
[2]Breast Surgery, Humanitas Cancer Center, Milan, Italy
[3]Division of Radiotherapy, European Institute of Oncology, Milan, Italy
Surg Oncol (2022) 29:6440–6453
://doi.org/10.1245/s10434-022-12197-6
ORIGINAL ARTICLE – BREAST ONCOLOGY
A Systematic Review and Meta-Analysis on the Role of Repea
Breast-Conserving Surgery for the Management of Ipsilateral
Breast Cancer Recurrence
Clare Josephine Tollan, MD[1], Eirini Pantiora, MD[2], Antonios Valachis, MD[3], Andreas Karakatsanis, MD, PhD,
FEBS[2], and Marios Konstantinos Tasoulis, MD, PhD, FEBS, FRCS[1,4]
al breast irradia
Accelerated partial breast irradiation with interstitial brachytherapy as second conservative treatment for ipsilateral breast tumour recurrence: Multicentric study of the GEC-ESTRO Breast Cancer Working Group
CrossMark
Jean-Michel Hannoun-Levi[a,*], Alexandra Resch[b], Jocelyn Gal[c], Daniela Kauer-Dorner[b], Vratislav Strnad[d],
Peter Niehoff[e], Kristina Loessl[f], Gyoergy Kovács[g], Erick Van Limbergen[h], Csaba Polgár[i],
On behalf of the GEC-ESTRO Breast Cancer Working Group

Clinical and Translational Radiation Oncology 38 (2023) 71–76

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Original Research Article

10-Year oncological outcome report after second conservative treatment for ipsilateral breast tumor event

Jean-Michel Hannoun-Levi [a,*], Jocelyn Gal [b], Renaud Schiappa [b], Marie-Eve Chand [a]

[a] Department of Radiation Oncology, Antoine Lacassagne Cancer Centre, University of Côte d'Azur, Nice, France
[b] Department of Epidemiology and Biostatistics, Antoine Lacassagne Cancer Centre, University of Cote d'Azur, Nice, France

JAMA Oncology | Original Investigation

Effectiveness of Breast-Conserving Surgery and 3-Dimensional Conformal Partial Breast Reirradiation for Recurrence of Breast Cancer in the Ipsilateral Breast

The NRG Oncology/RTOG 1014 Phase 2 Clinical Trial

Douglas W. Arthur, MD; Kathryn A. Winter, MS; Henry M. Kuerer, MD, PhD; Bruce Haffty, MD; Laurie Cuttino, MD; Dorin A. Todor, PhD; Pramila Rani Anne, MD; Penny Anderson, MD; Wendy A. Woodward, MD; Beryl McCormick, MD; Sally Cheston, MD; Walter M. Sahijdak, MD; Daniel Canaday, MD; Doris R. Brown, MD, PhD; Adam Currey, MD; Christine M. Fisher, MD, MPH; Reshma Jagsi, MD, DPhil; Jennifer Moughan, MS; Julia R. White, MD

NRG Oncology/ RTOG 1014: Prospective phase 2 Trial

- Key inclusion Criteria
  - In breast recurrence of DCIS or invasive disease > 1 year from prior treatment
  - Unifocal disease
  - ≤ 3 positive nodes
  - Recurrence ≤ 3cm
  - Margin negative excision
  - **Target lumpectomy cavity clearly defined**

Arthur DW et al. *JAMA Oncol*. 2020

Conclusions and Relevance *

For patients experiencing recurrence of breast cancer in the ipsilateral breast after lumpectomy and whole breast irradiation, a second breast conservation was achievable in 90%, with a low risk of re-recurrence of cancer in the ipsilateral breast using adjuvant partial breast reirradiation. This finding suggests that this treatment approach is an effective alternative to mastectomy.

18TH ST. GALLEN INTERNATIONAL BREAST CANCER CONFERENCE 2023

- 63 year old with stage 2 ER+ breast cancer treated with BCT with in breast recurrence **3** years later
  - **74%** strongly recommend <u>mastectomy</u>

Curigliano et al. Annals of Oncology. Nov, 2023

18TH ST. GALLEN INTERNATIONAL BREAST CANCER CONFERENCE 2023

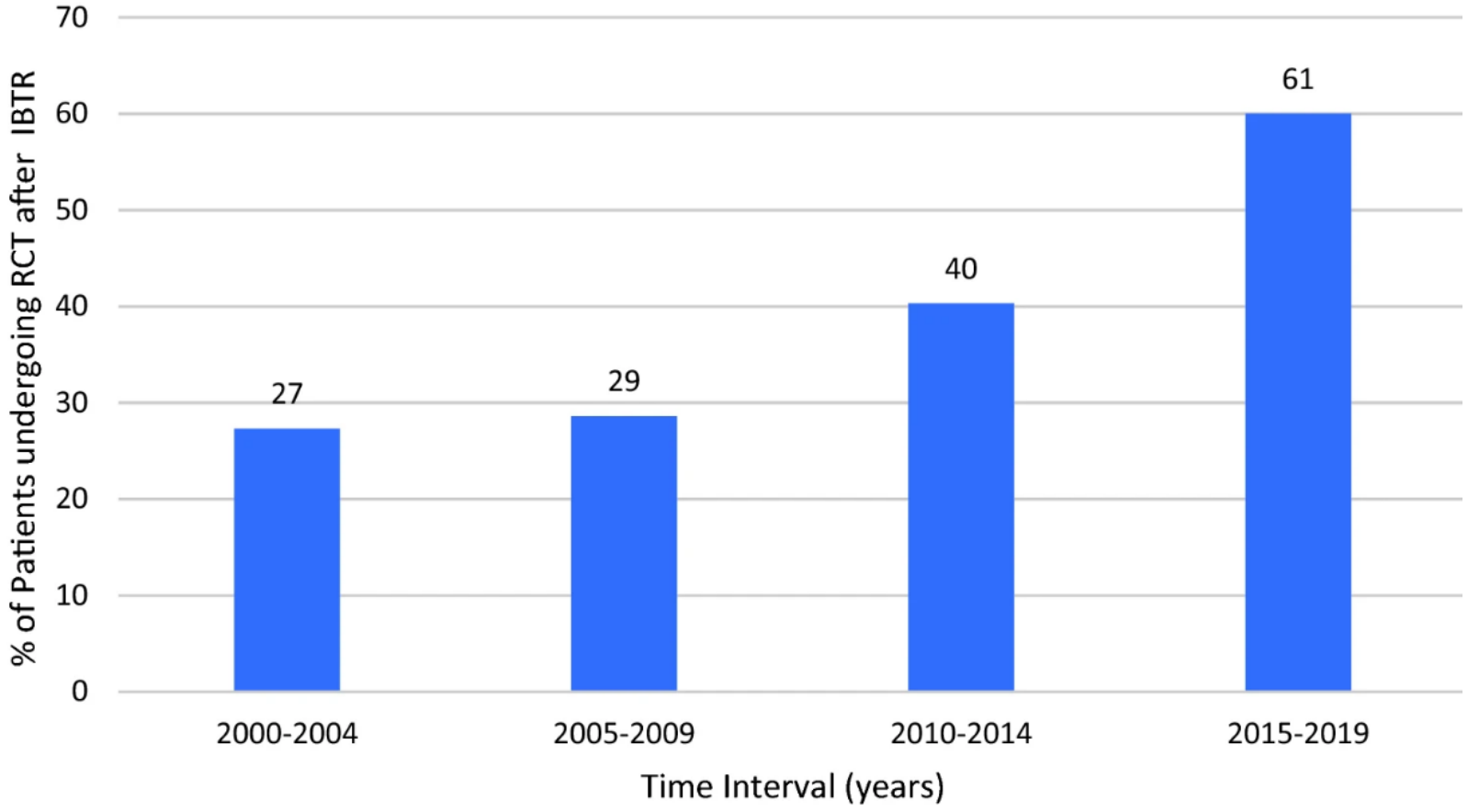
- 63 year old with stage 2 ER+ breast cancer treated with BCT with in breast recurrence **9** years later
  - **25 %** recommend mastectomy
  - **15 % recommend partial mastectomy alone**
  - **58 % recommend partial mastectomy with radiation**

- > 70% recommend BCT

Curigliano et al. Annals of Oncology. Nov, 2023

Memorial Sloan Kettering

From: Management of ipsilateral breast tumor recurrence following breast conservation surgery: a comparative study of re-conservation vs mastectomy



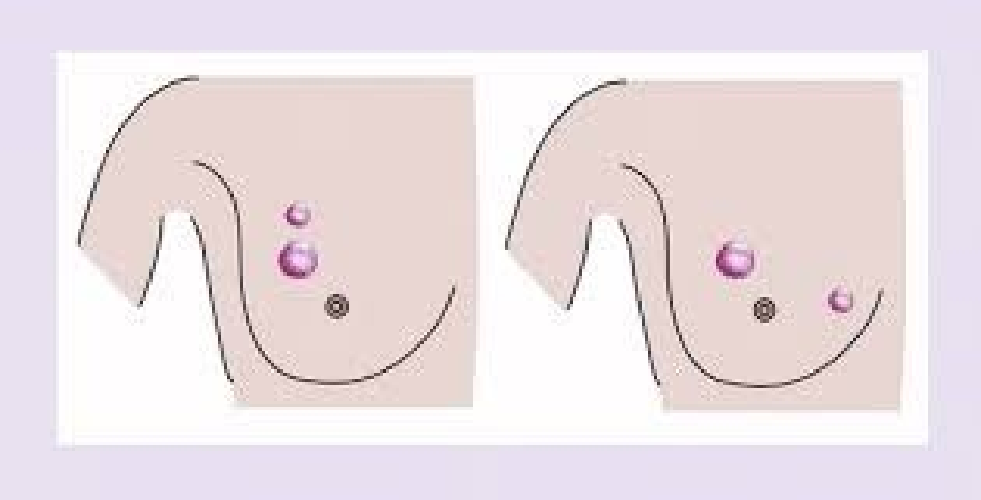
Increasing frequency of RCT over time

Van den Bruele et al Breast Cancer Treatment and Research, 2021

Second primary/ In breast recurrence: Repeat lumpectomy is an option

- Patient selection
  - Low risk tumors
  - Consider interval from initial treatment
  - Patient motivated toward BCT
- Multidisciplinary discussion
- Marking of the biopsy site (**clip the cavity**)

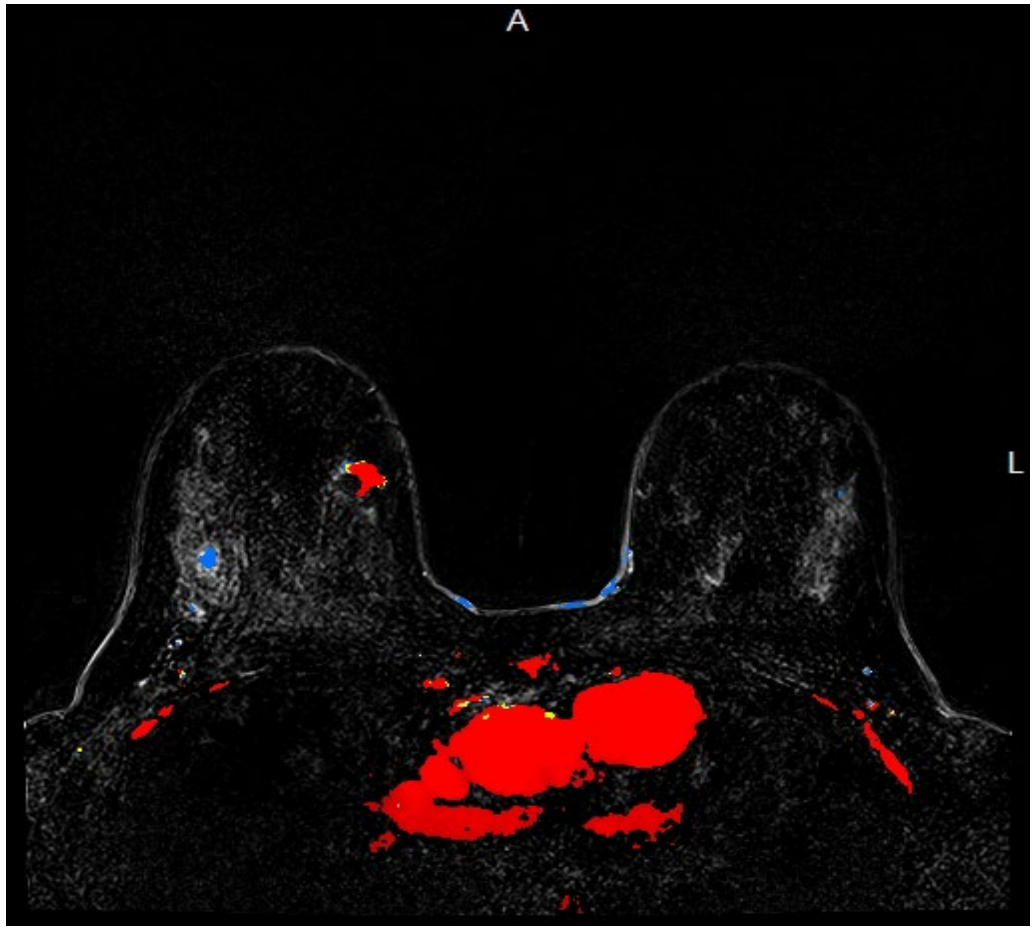
Multiple ipsilateral breast cancer
(multifocal or multicentric)

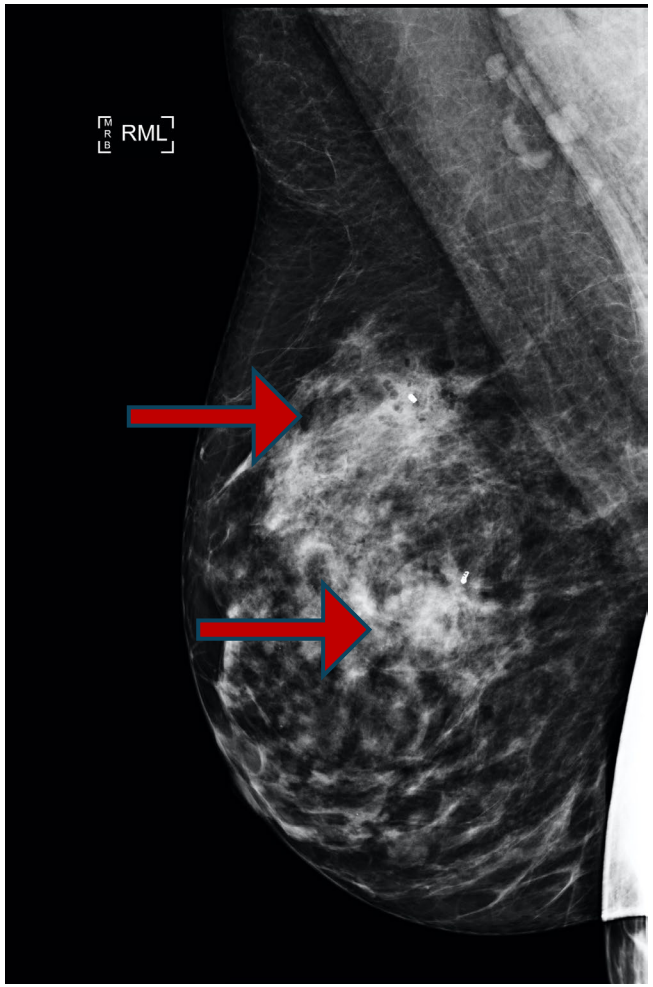


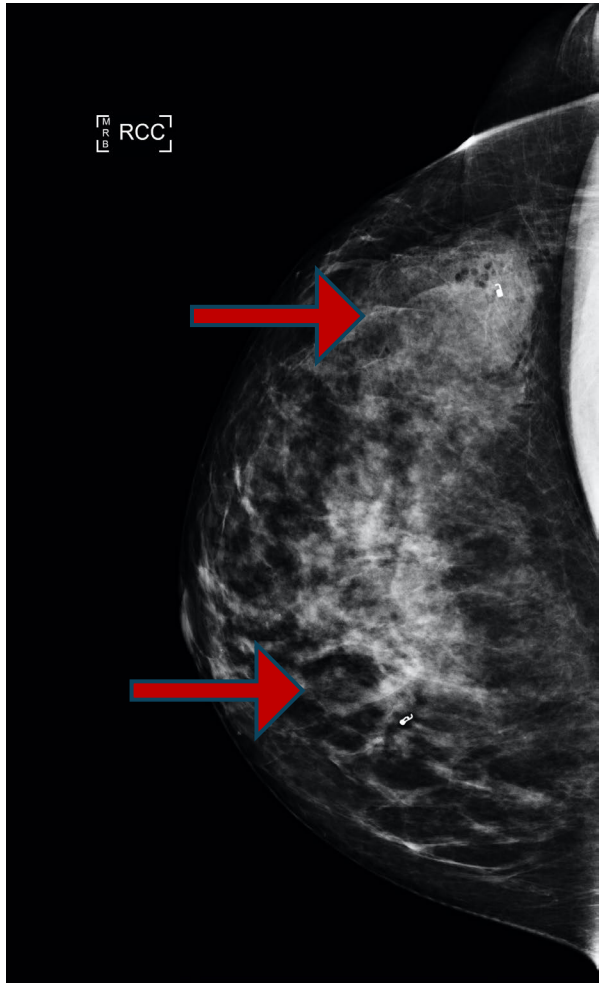
Pre-operative diagnosis is increasing

- Improved sensitivity of breast imaging
- Growing use of screening and staging breast MRI

Incidence:
6-75% of patients diagnosed pre-operatively







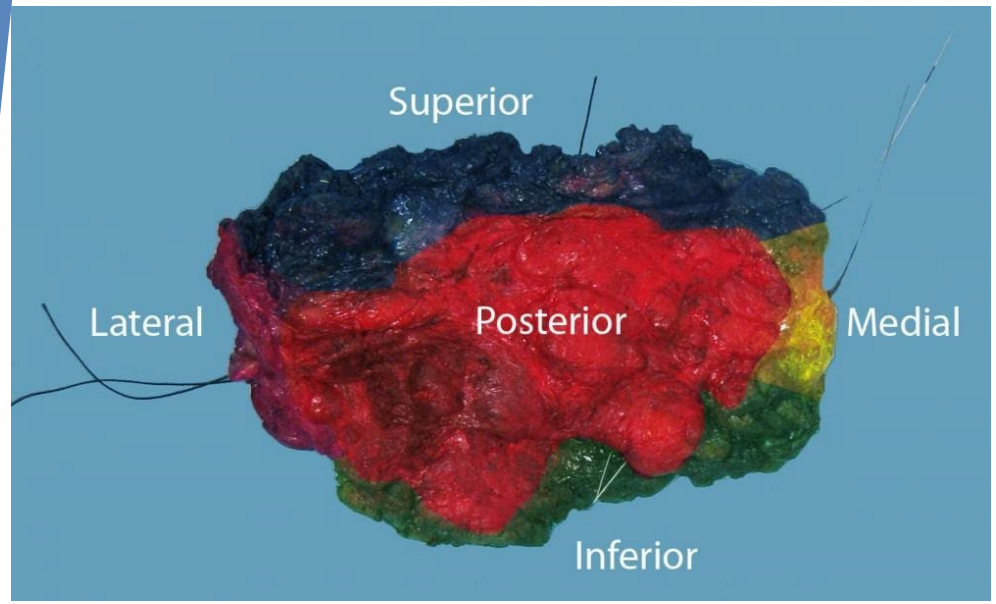
Historical, retrospective studies which reported high rates of local regional recurrence in patients with MIBC undergoing BCT

Author	Years studied	Published	MIBC patients (n)	Median f/u (mo)	MIBC LRR (n)	MIBC LRR (%)
Leopold et al	1968-1981	1989	10	64	4	40
Kurtz et al	1975-1983	1990	61	71	15	24
Wilson et al	Prior to 1989	1993	13	71	3	25

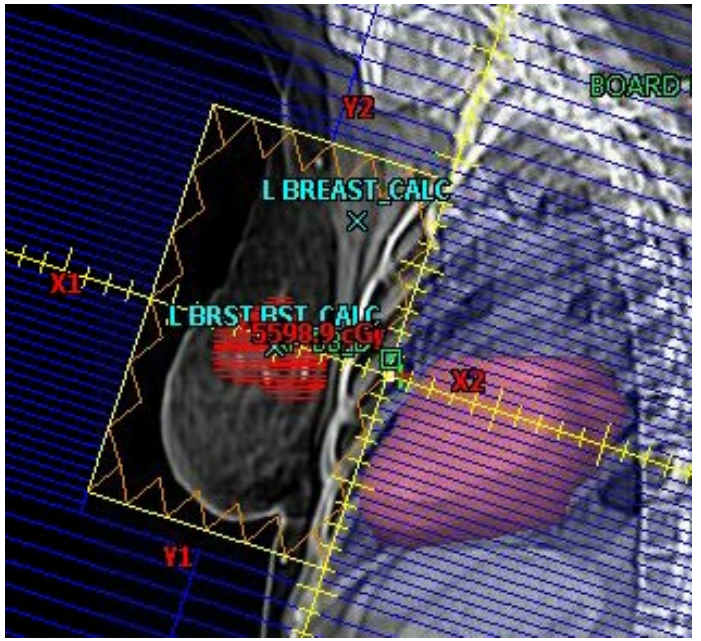
Leopold KA et al. J Radiat Oncol Biol Phys. 1989;16(1):11–6
Kurtz JM et al. Ann Surg. 1990;212:38–44.
Wilson LD et al. Cancer. 1993;72(1):137–43

Author	Years studied	Published	MIBC patients (n)	Median f/u (mo)	MIBC LRR (n)	MIBC LRR (%)
Cho et al	1989-1997	2002	15	76	0	0
Giron et al	1989-2002	2003	36	45	1	2.7
Gentilini et al	1977-2002	2009	476	73	24	5.1
Lim et al	1990- 2003	2010	147	59	3	4.7
Bauman et al	1998- 2008	2010	22	42	1	4.4
Yerushalami et al	1989-2005	2011	300	94	17	5.5

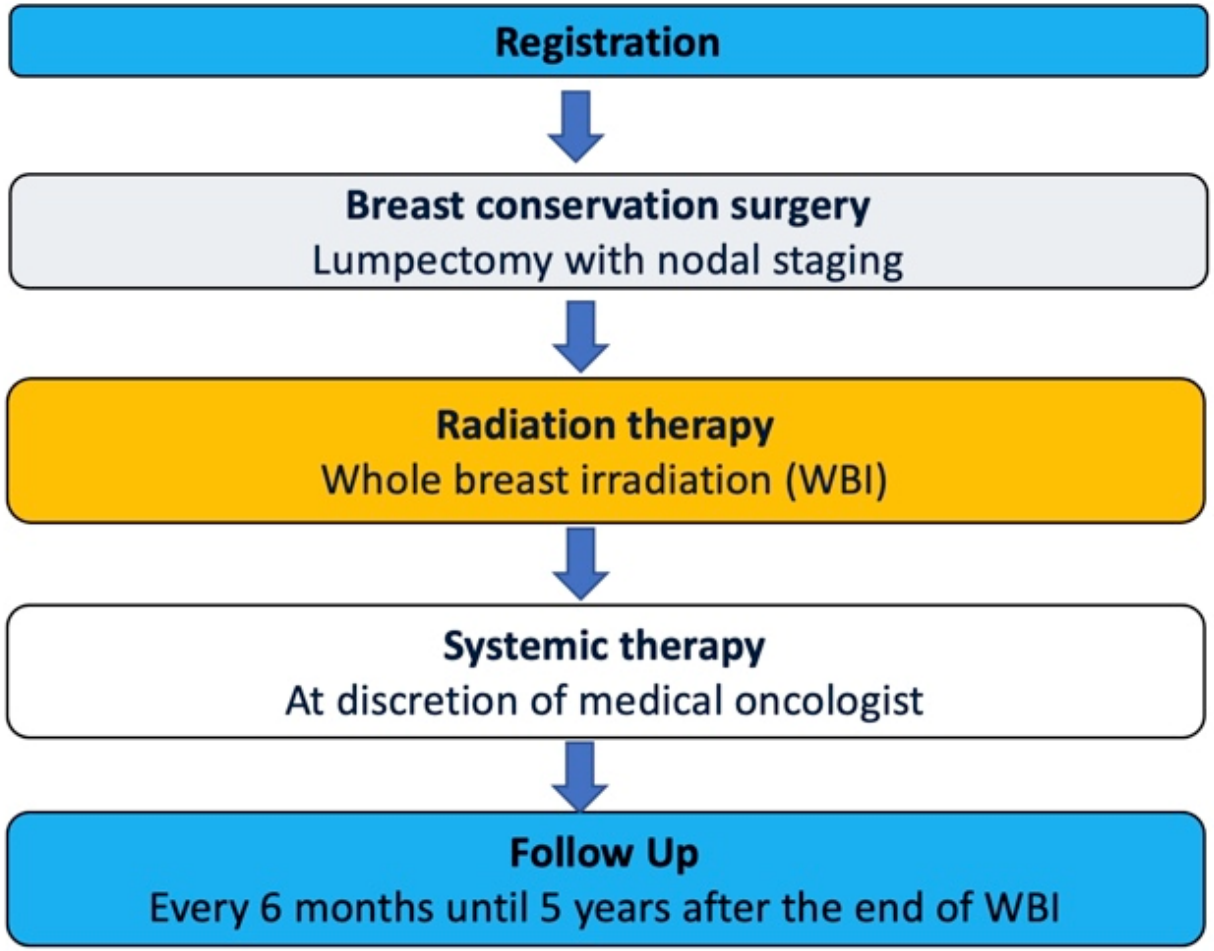
Cho LC et al. Am J Surg. 2002;183:650–4
Giron G et al. J Am Coll Surg. 2003;187:726–9
Gentilini O et al. Breast Cancer Res Treat. 2009:113(3): 577–83
Lim W et al Ann Surg. 2009;249:87–90
Bauman L et al. Ann Surg Oncol. 2010;17 430 Suppl 3:325–9
Yerushalmi R et al. Ann Oncol. 2012 Apr;23(4):876-81 Epub 2011 Aug 2


Superior
Lateral
Posterior
Medial
Inferior

Cosmesis


BOARD
Y2
L BREAST_CALC
X1
X2
Y1

ALLIANCE Z11102 Trial

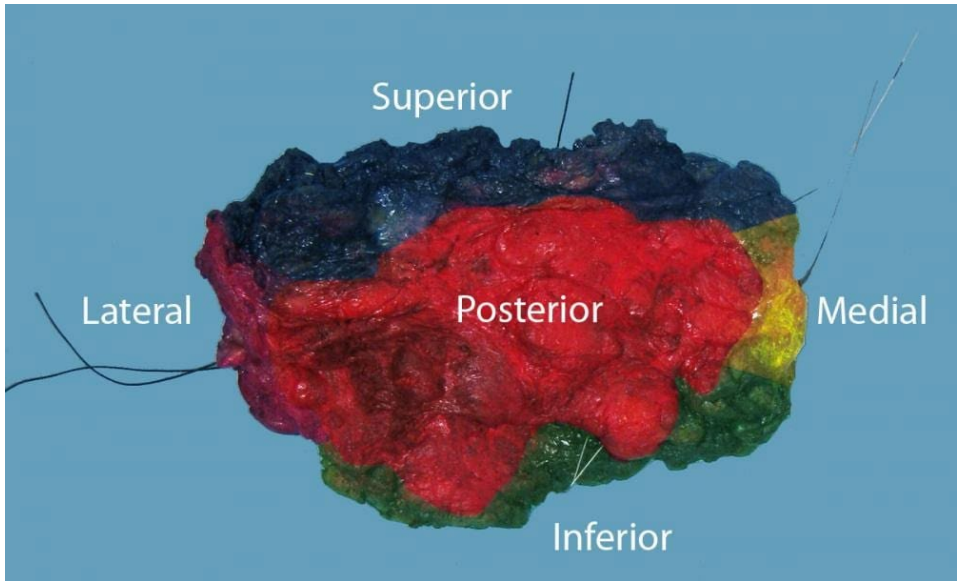


Z11102 PRIMARY ENDPOINT

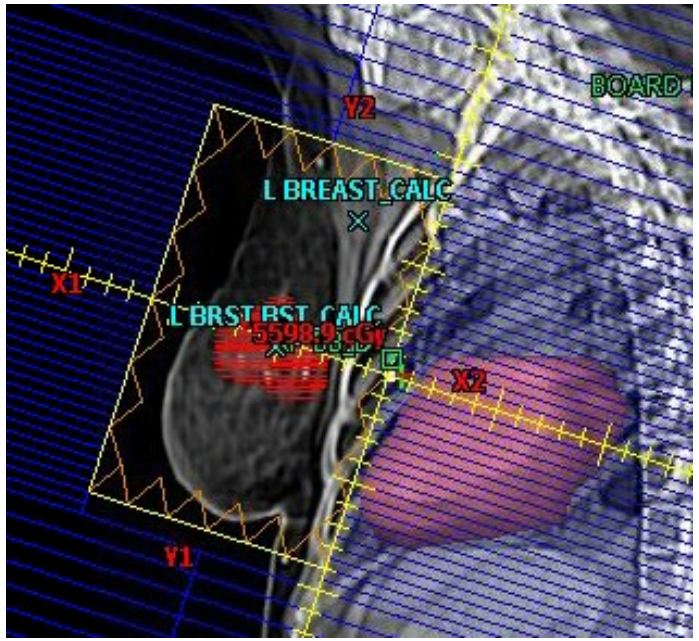
- To assess the local recurrence (LR) rate with breast conservation in patients with multiple ipsilateral breast cancer (MIBC)
  - Acceptable 5-year LR rate for BCT was defined as less than 8% based on historic recurrence rates in unifocal disease

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

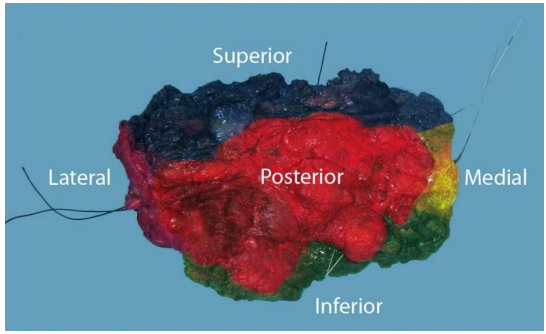
Z11102 Secondary Endpoints

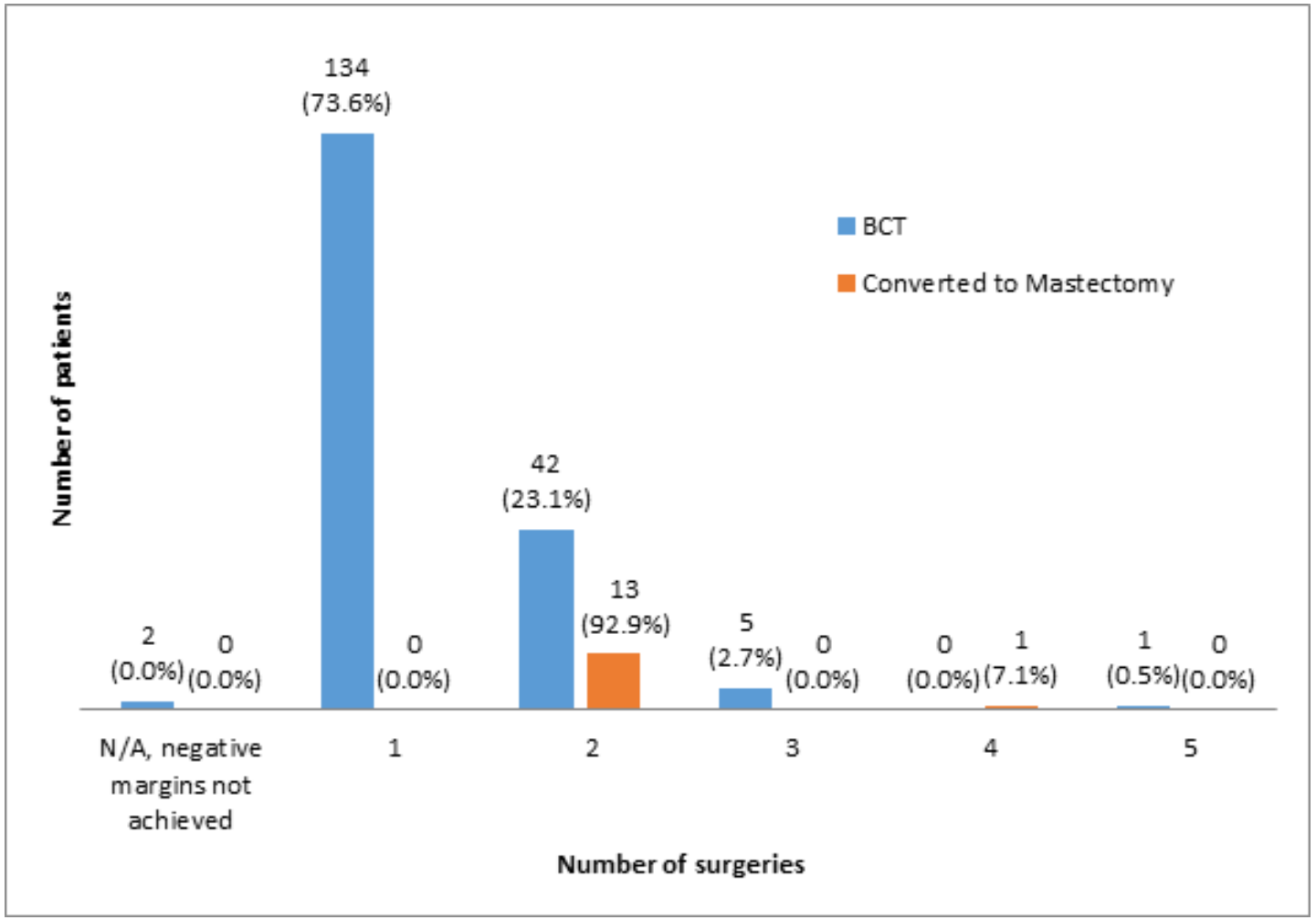


Cosmesis



ALLIANCE Z11102: Feasibility

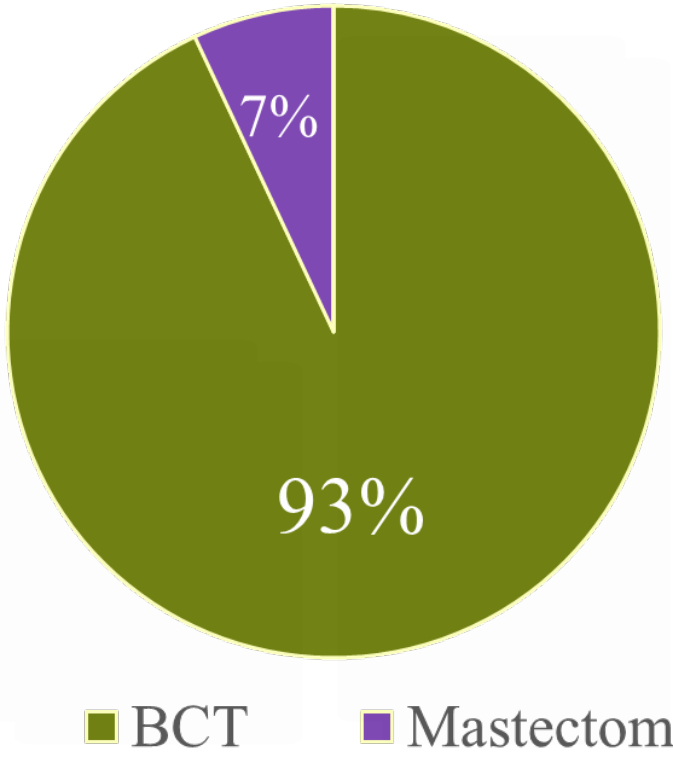




96.7% had 2 or fewer surgeries

Rosenkranz KM, Ann Surg Oncol. 2020 Nov:27(12)

Z11102 Proportion of patients with MIBC converted to mastectomy



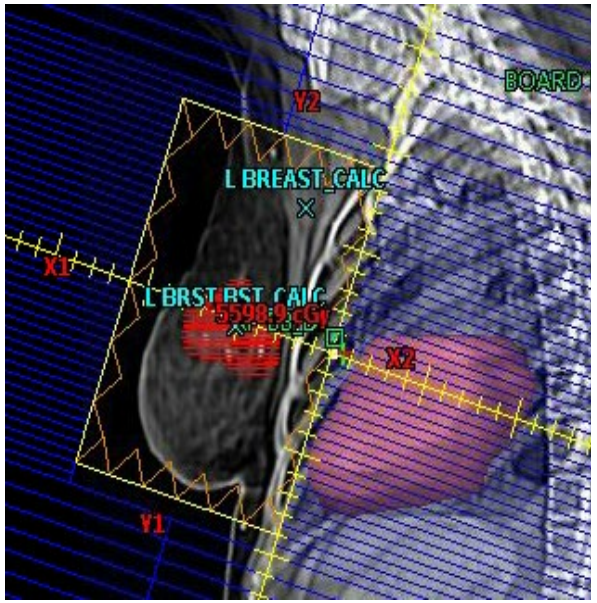
7% conversion to mastectomy

Rosenkranz KM, Ann Surg Oncol. 2020 Nov:27(12)

Z11102: Radiation

The Feasibility of Radiation Therapy after Breast-Conserving Surgery for Multiple Ipsilateral Breast Cancer: An Initial Report from ACOSOG Z11102 (Alliance) Trial

Laurie W. Cuttino, MD,* Linda McCall, MS,† Charlotte Kubicky, MD,‡ Karla V. Ballman, PhD,§ Huong Le-Petross, MD,‖ Kelly K. Hunt, MD,‖ Bruce Haffty, MD,¶ Kari M. Rosenkranz, MD,# and Judy C. Boughey, MD**



Cuttino L. Inter J Radiat Oncol Biol Phys. 2022 Mar 1: 112(3)

Z11102 and Radiation

- Cuttino et al
  - Breast conservation followed by whole breast RT plus boost to each tumor bed was **feasible** in the majority of patients with MIBC.
  - Increasing radiation boost volume was associated with increased incidence of acute dermatitis, but was **not** associated with worse overall cosmesis.

Z11102 and Cosmesis

	5-30 days (N=216)	6 months (N=205)	12 months (N=199)	18 months (N=196)	24 months (N=194)	36 months (N=165)	48 months (N=93)	60 months (N=44)
Patient Breast Cosmesis Score								
Excellent	89 (51.7%)	49 (32.5%)	43 (30.1%)	46 (33.1%)	44 (32.4%)	37 (36.6%)	20 (38.5%)	4 (21.1%)
Good	60 (34.9%)	71 (47.0%)	64 (44.8%)	64 (46.0%)	52 (38.2%)	34 (33.7%)	17 (32.7%)	10 (52.6%)
Fair	21 (12.2%)	28 (18.5%)	30 (21.0%)	24 (17.3%)	35 (25.7%)	23 (22.8%)	13 (25.0%)	5 (26.3%)
Poor	2 (1.2%)	3 (2.0%)	6 (4.2%)	5 (3.6%)	5 (3.7%)	7 (6.9%)	2 (3.8%)	0 (0.0%)
Missing or Not Done	42	54	56	57	58	64	41	25

PROs good or excellent cosmesis at 3 and 5 years: 70.3, 73.7%

PROs poor cosmesis at 3 and 5 years: 6.9, 0%

Rosenkranz KM. Ann Surg Onc 2020 Nov; 27 (12)

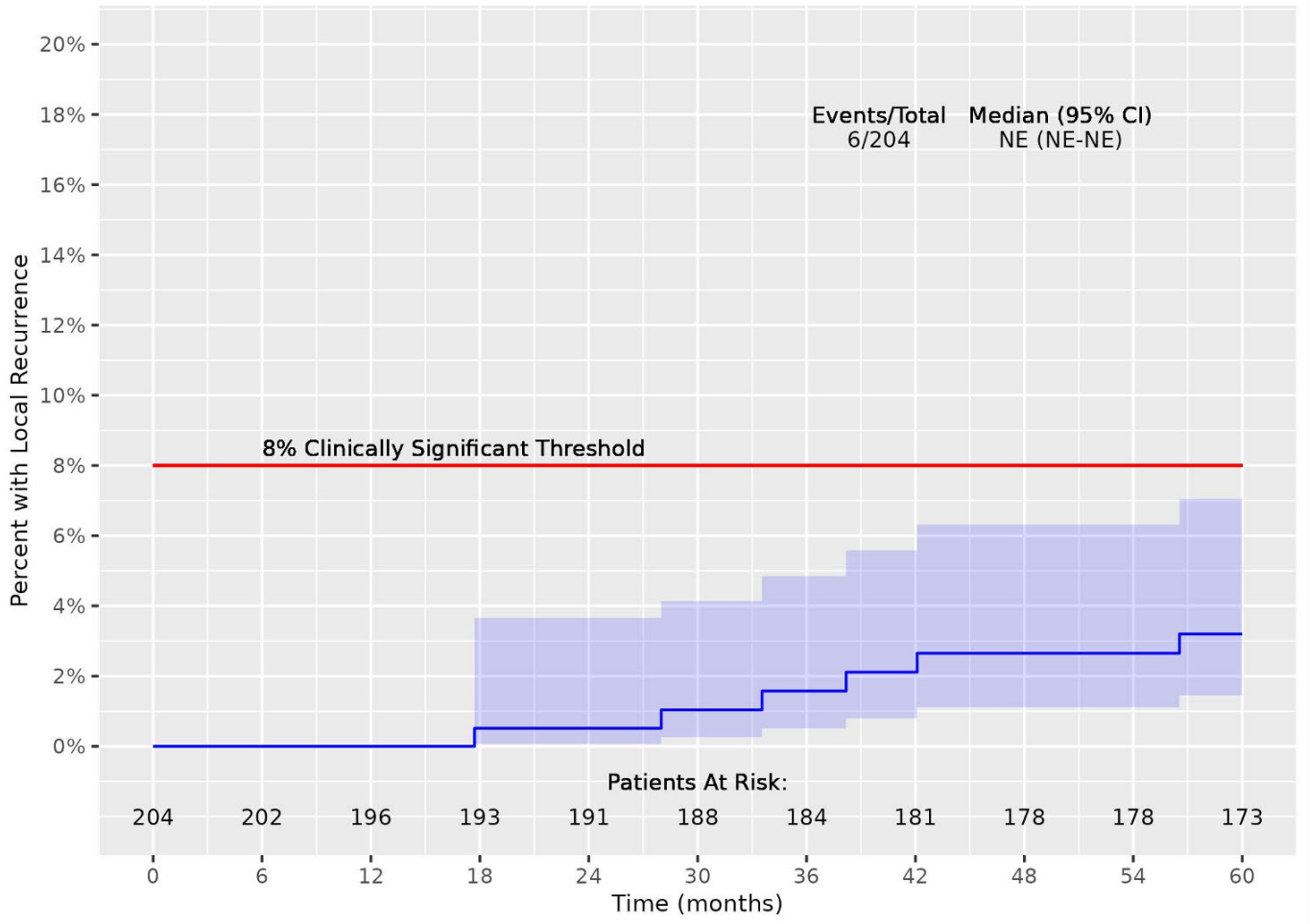
Estimated cumulative incidence of local recurrence at 5 years

3.1%

(95% CI: 1.3 - 6.4)

Boughey J. J* , Rosenkranz, KR* Clin Oncol. 2023 Jun 10(41)17

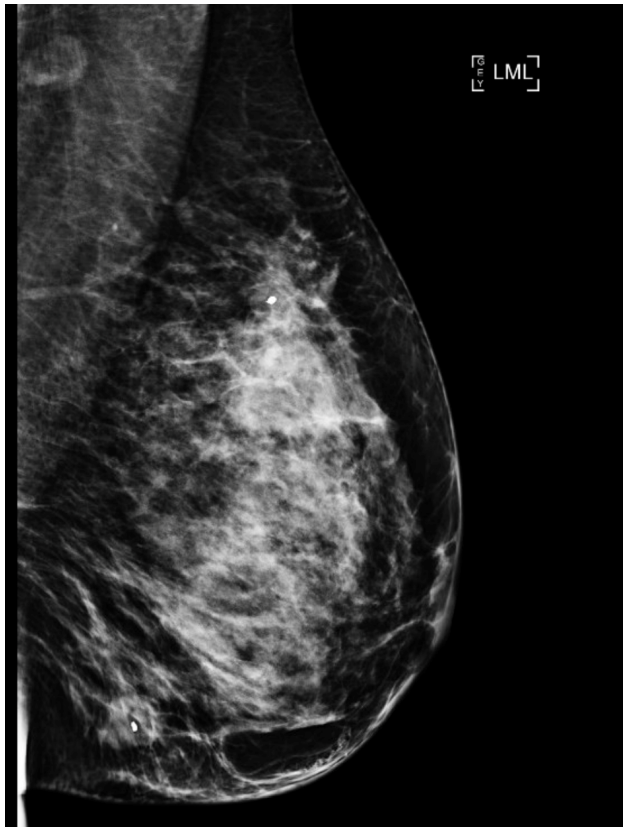
Local Recurrence Z11102

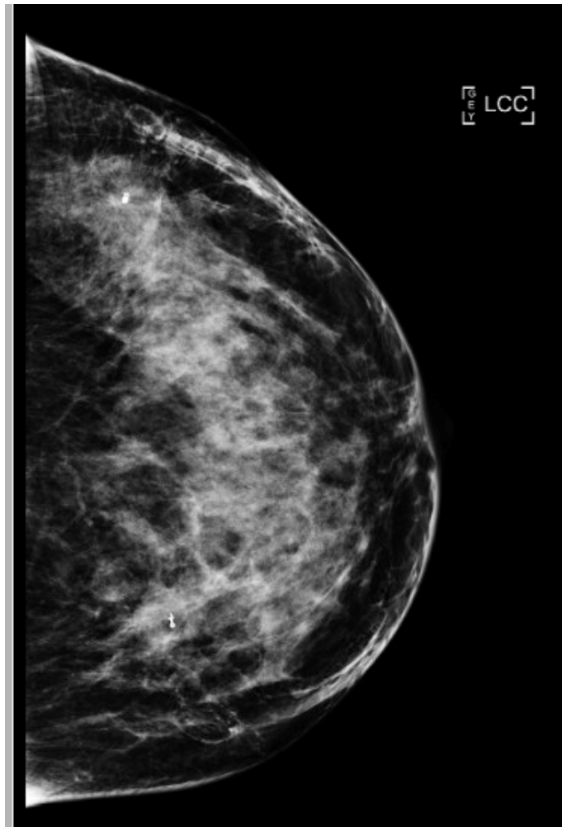


3.1%
(95% CI: 1.3 - 6.4)

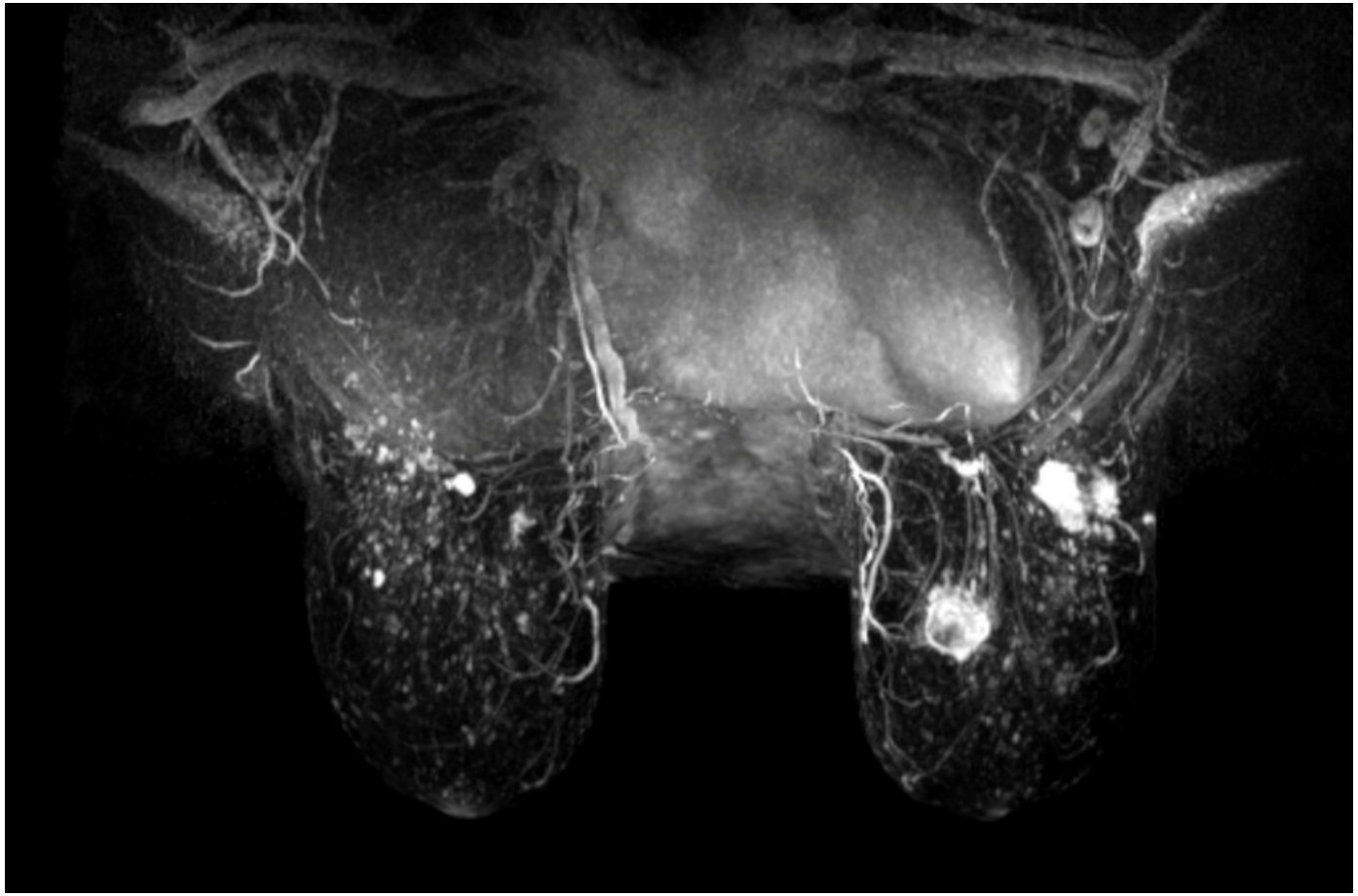
BCT for MIBC is an oncologically reasonable surgical option with low local recurrence rates

Case study: 42 yo female with MIBC diagnosed after abnormal screening mammogram





Both tumors IDC, intermediate grade, ER+/HER2-, negative for genetic mutation



CONSIDERATIONS FOR BCT in MIBC

- Patient preferences
- Breast size
- Expected cosmesis
- Mark biopsy cavities for radiation oncology boost

Expanding Indications: Tumor Size

EXPERIMENTING

with

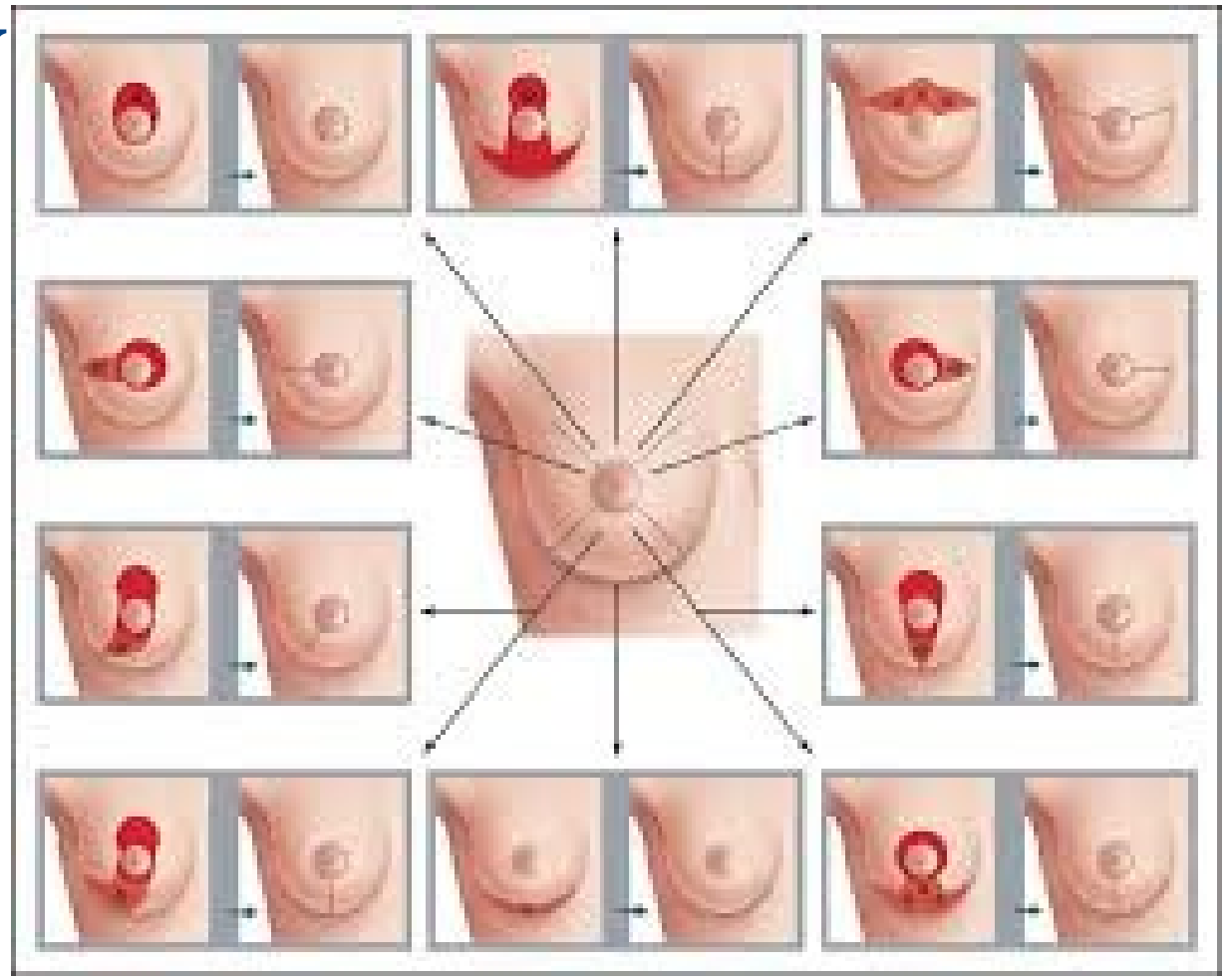
NEW

TECHNIQUES

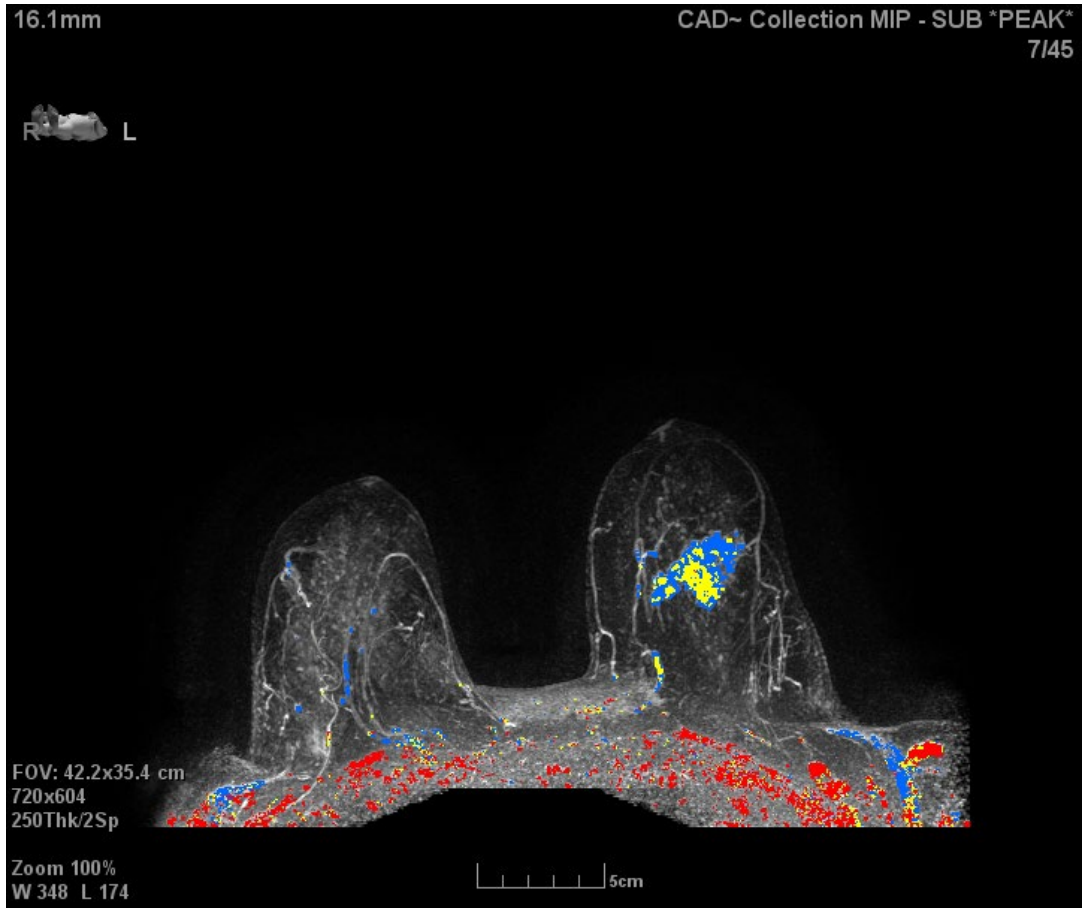
Oncoplastic surgery

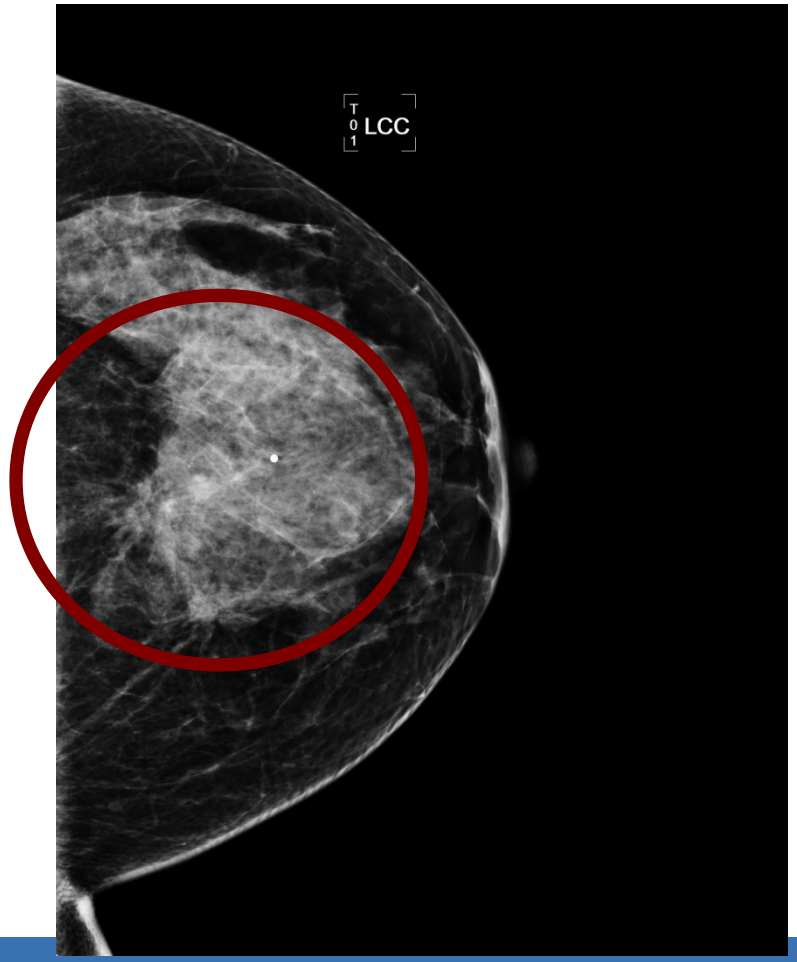
- The technical convergence of oncologic (ablative) and aesthetic breast surgery, which attempts to adequately remove end-stage breast cancer while retaining or producing a breast shape and appearance that closely approximates a normal breast

- Described initially in 2003

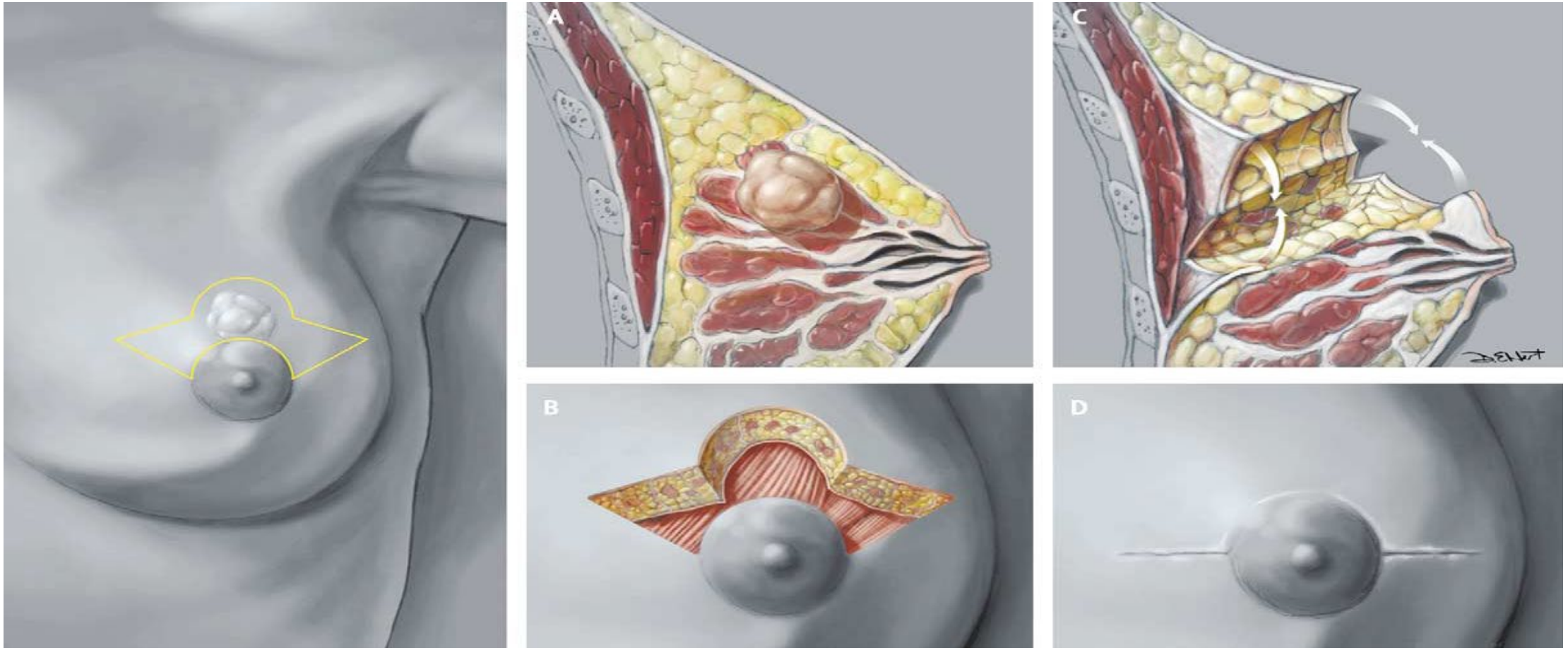


61 yo female with 7cm ER+ lobular tumor in patient with relatively small breast



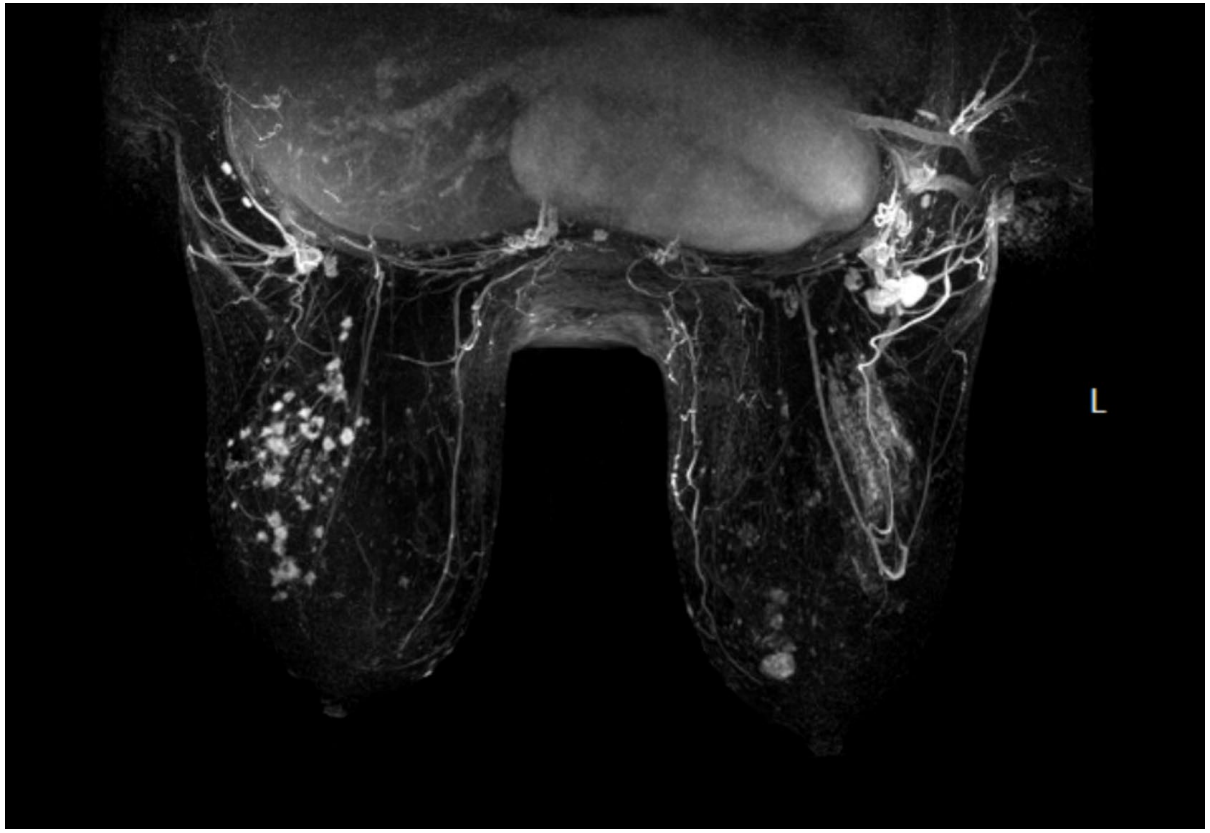


Batwing mastopexy



Batwing mastopexy

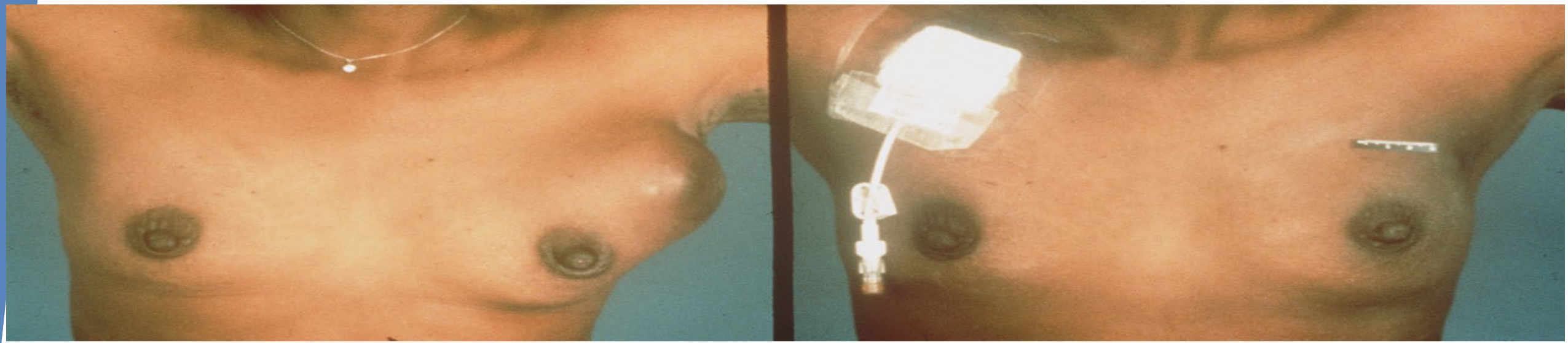
1. MRI findings suggest extensive disease in a pattern of the numerous enhancing masses in a segmental pattern, throughout the right breast involving a 12 x 6 cm area of outer breast, extending between 8 and 10 o'clock axes and from 1 to 12 cm from the nipple. The previously biopsied to masses are positioned along the 10 o'clock axis and 5 and 10 cm from the nipple. While these are representative



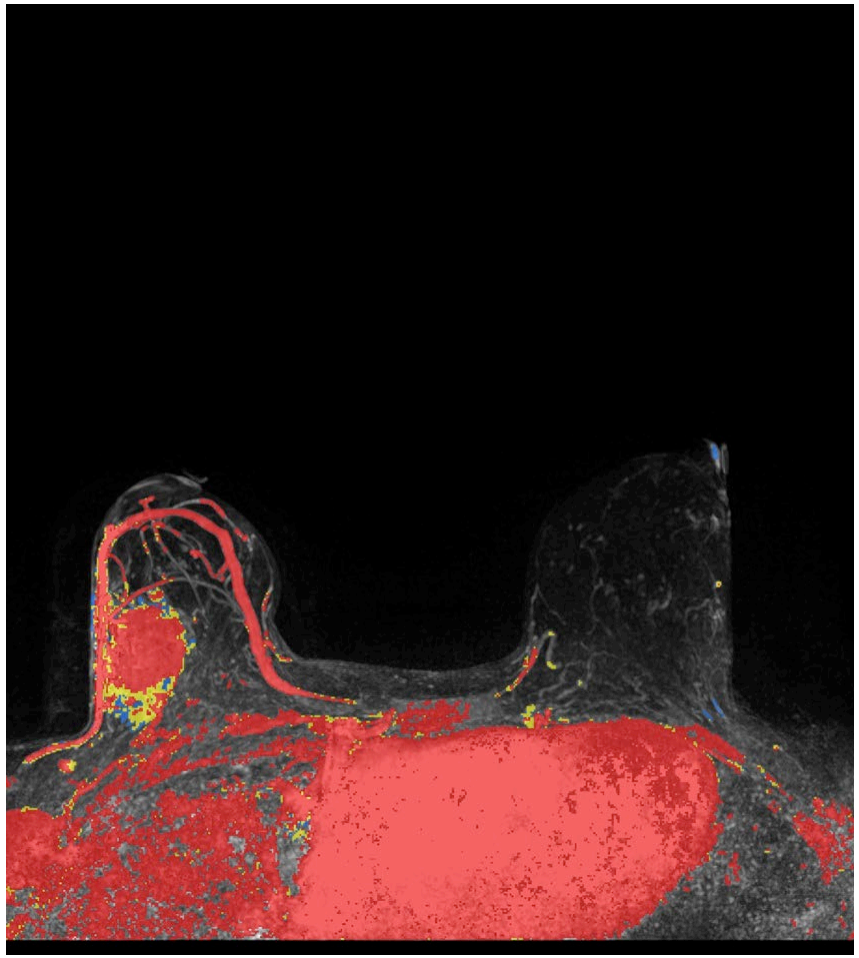
Oncoplastic reduction with contralateral symmetry procedure for 12cm x 6cm area

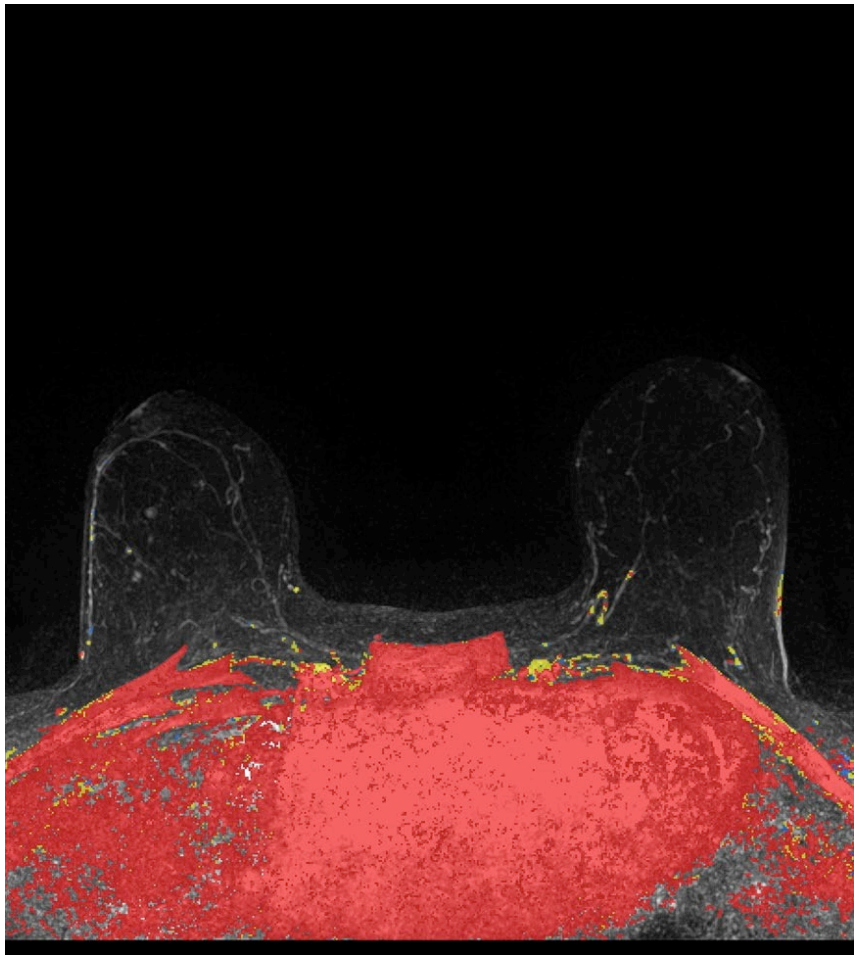

"CAN I PHONE A FRIEND?"

Neoadjuvant therapy

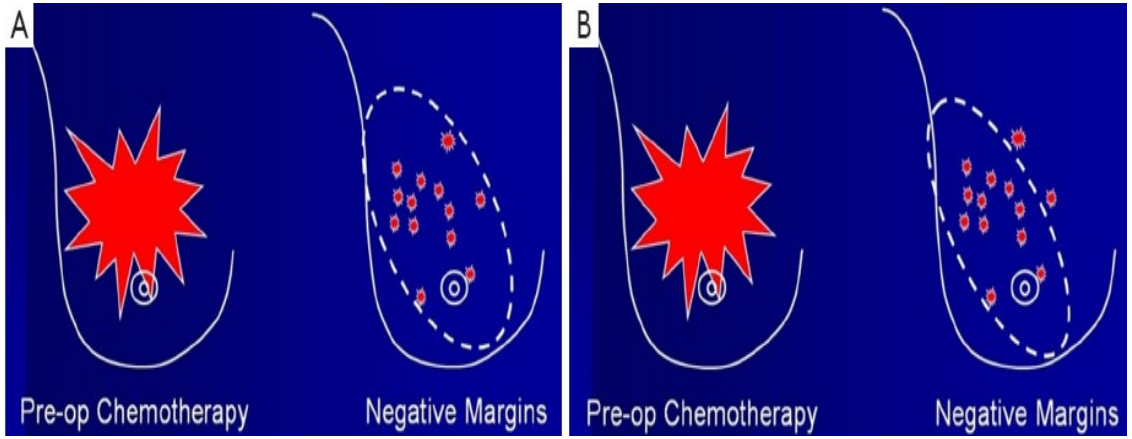


Neoadjuvant chemotherapy





Biology Matters: Patterns of response



ER+

HER2+ and triple negative

Chirappapha P et al Gland Surgery 2014

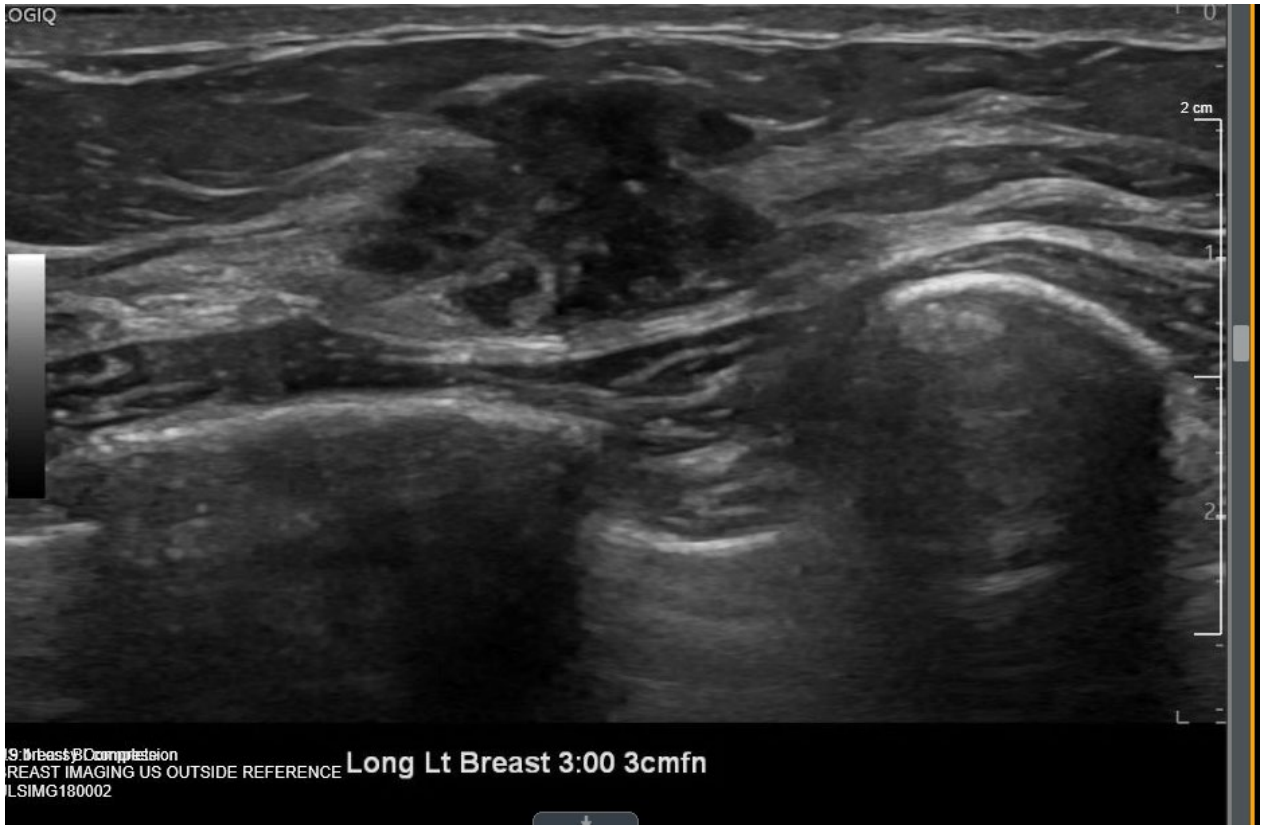
Summary

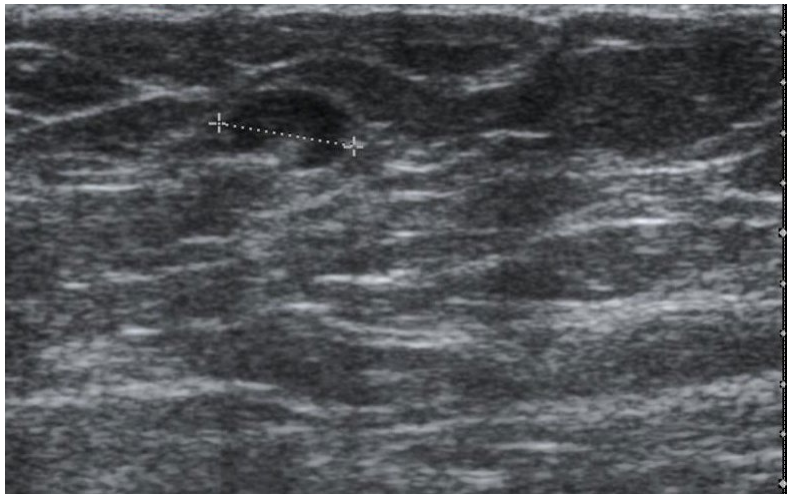
- BCT is preferred to mastectomy in eligible patients due physical and psychologic benefits and potential improved survival.

Summary

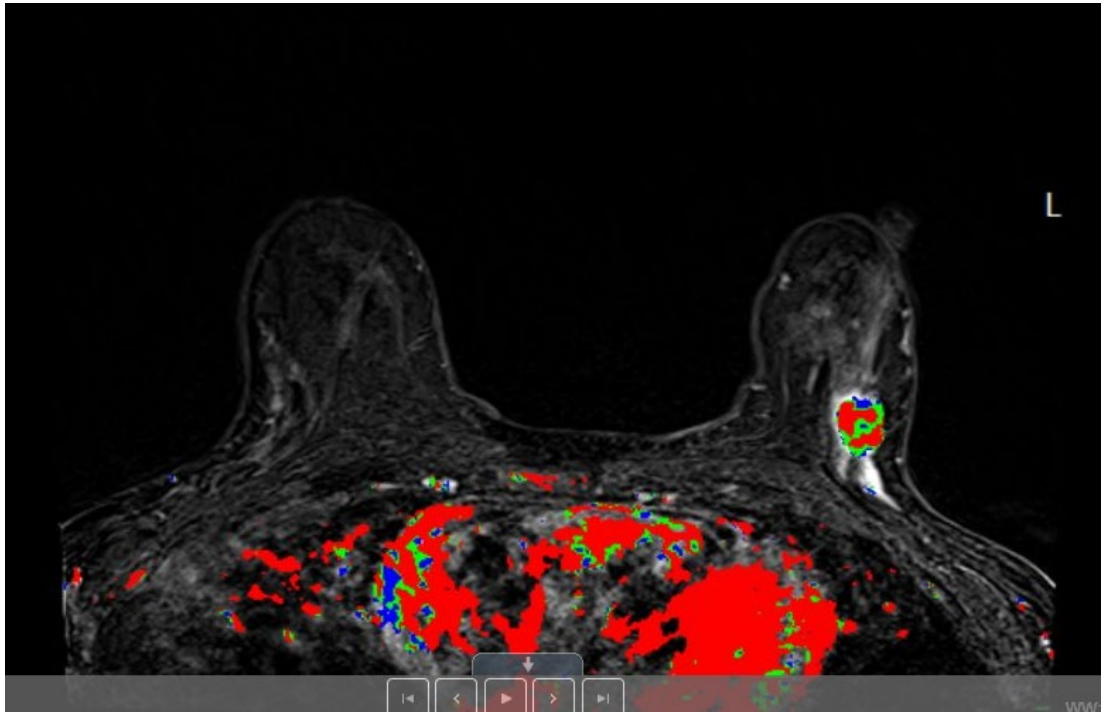
- We can expand indications for BCT
  - Consider re-irradiation in patients with low risk second primary/recurrent disease
  - Offer BCT to patients with multiple ipsilateral breast cancer
  - Incorporate oncoplastic surgical techniques
  - Utilize neoadjuvant therapies

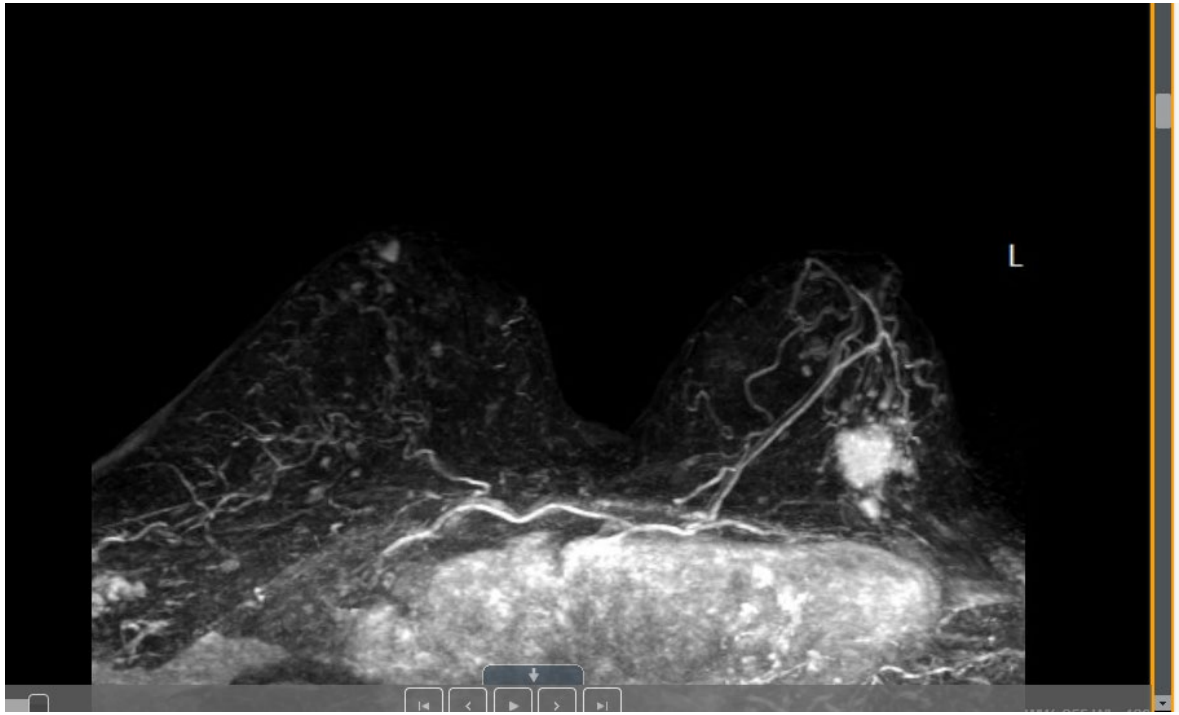
Case Study


2 cm
REAST IMAGING US OUTSIDE REFERENCE
Long Lt Breast 3:00 3cmfn



Case Study





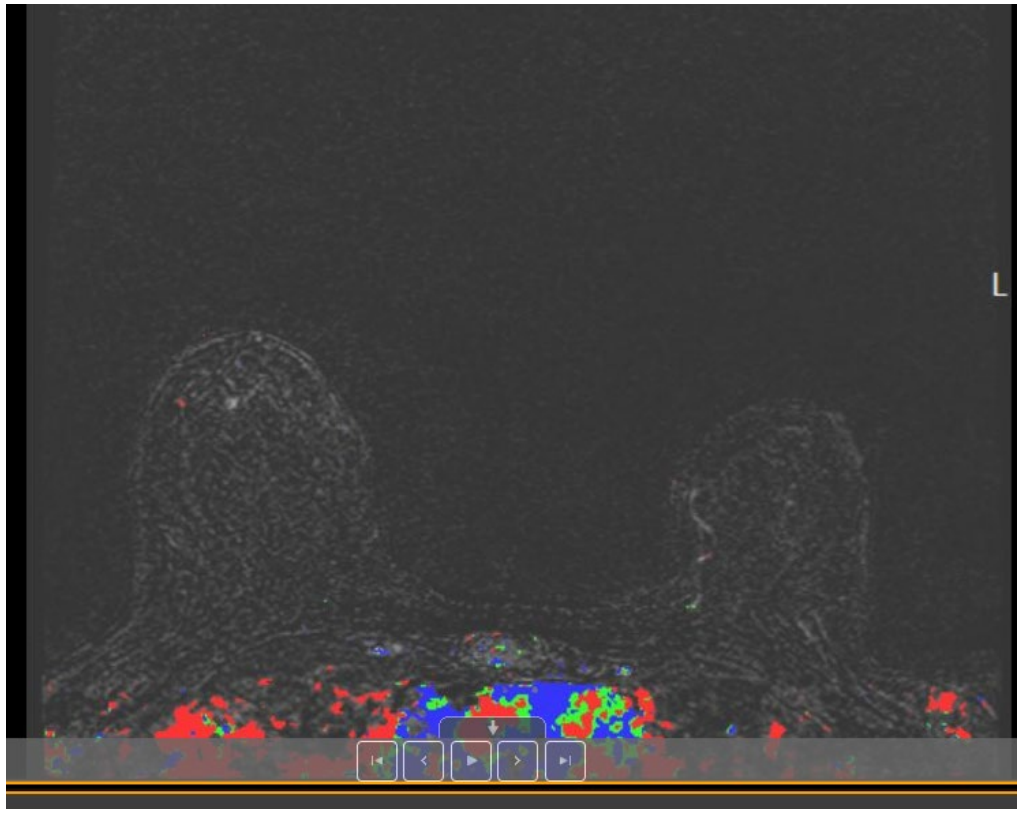
Case Study

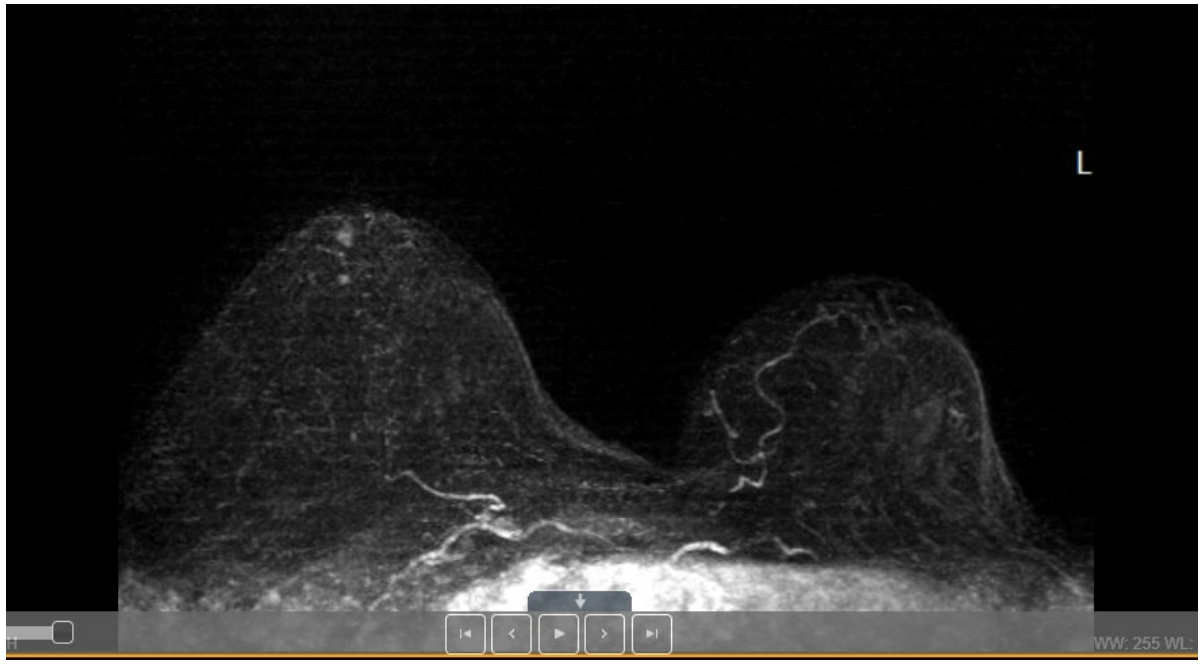
- Core biopsy demonstrated:
  - Invasive ductal cancer, Grade 2
    - ER 8/8, PR 7/8, Her2 0
    - Ki-67 15%

Case Study

- Patient initiated neoadjuvant anastrozole
- Ki-67 2 weeks post-initiation dropped to 6%

Case Study





Case Study

- Patient underwent a left partial mastectomy and SLN biopsy
  - Final pathology revealed a 4 cm tumor bed with marked treatment response
    - Residual disease measured 8 mm with 10% tumor cellularity
    - SLNs x 2 negative

THE AMERICAN SOCIETY OF Breast Surgeons

ACCC
ASSOCIATION OF CANCER CARE CENTERS™

Neoadjuvant Endocrine Therapy to Increase Rates of Breast Conservation

Julie A. Margenthaler, MD

January 22, 2025

No financial disclosures

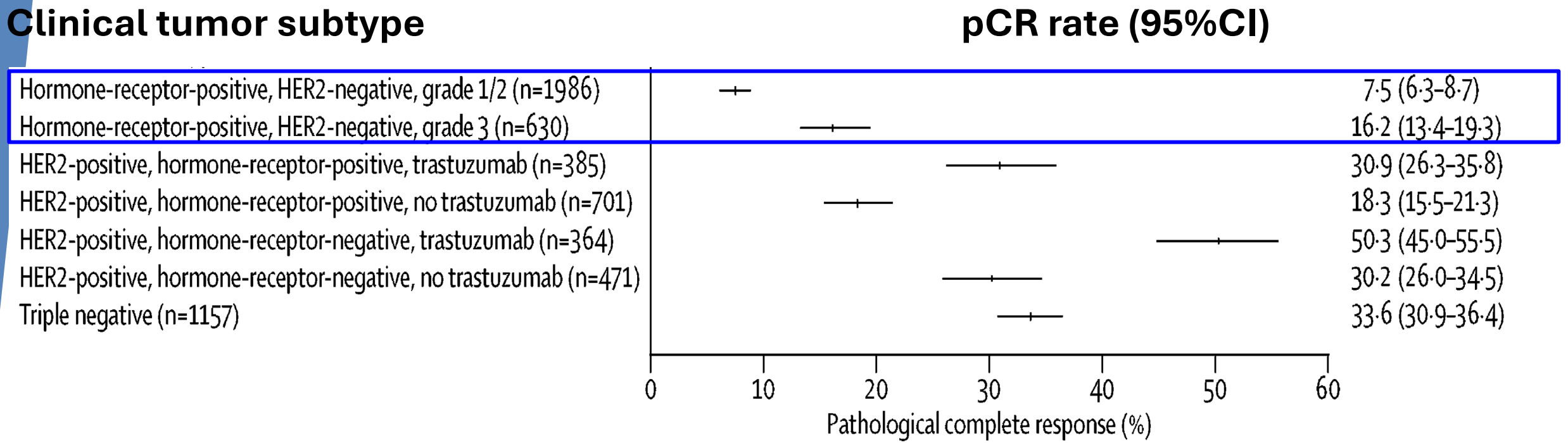
Neoadjuvant Endocrine Therapy in Breast Cancer

- Attractive features of neoadjuvant endocrine therapy for HR+ breast cancer
  - Well-tolerated toxicity profile; can be used in the peri-operative period
  - Improve the likelihood of breast conservation surgery or to make an inoperable tumor resectable
  - As a research tool:
    - Development of molecular biomarkers to predict long-term outcomes, allow for risk stratification and individualization of therapy
    - Determine the biologic basis of estrogen pathway-targeting agents
    - Drug development -> can surrogate endpoints in neoadjuvant trials predict long-term outcome in adjuvant trials?

Neoadjuvant Endocrine Therapy in Breast Cancer

pCR rate to neoadjuvant chemotherapy (NCT)

Pooled analysis of data from 12 international trials and 11,955 patients



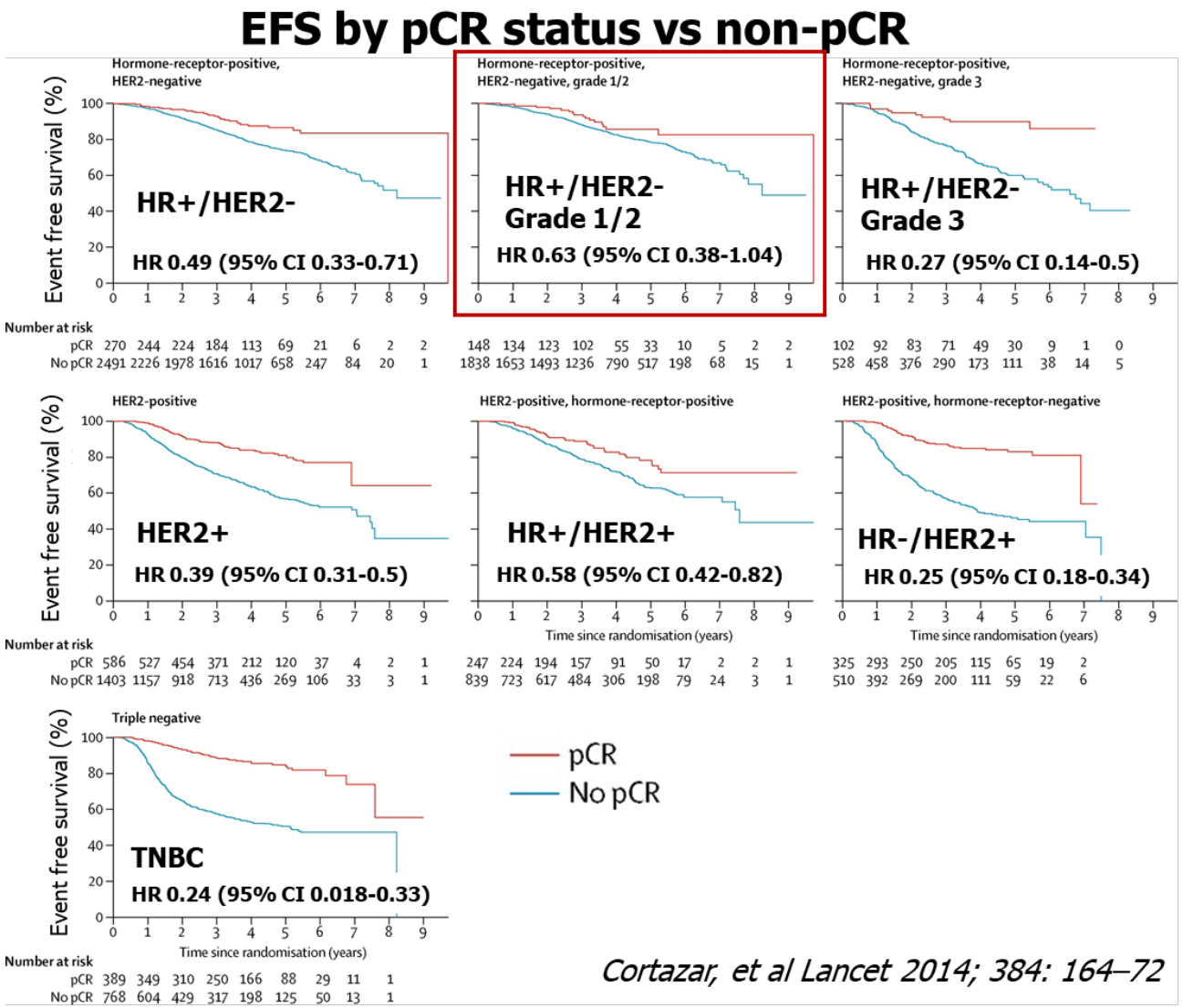
Cortazar P, et al, Lancet 2014;384:164-72.

pCR vs not in response to neoadjuvant chemotherapy is not prognostic in low grade HR+/HER2- breast cancer

HR+/HER2-

HER2+

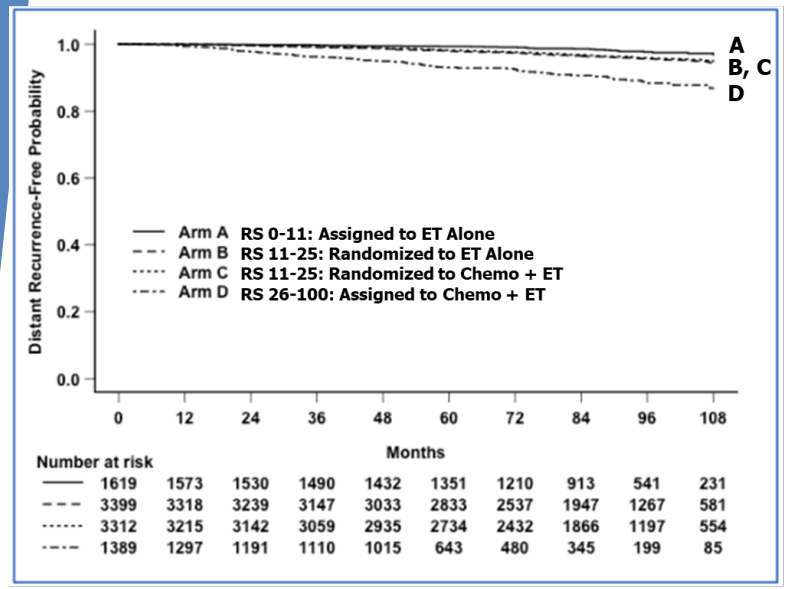
TNBC



Cortazar, et al Lancet 2014; 384: 164–72

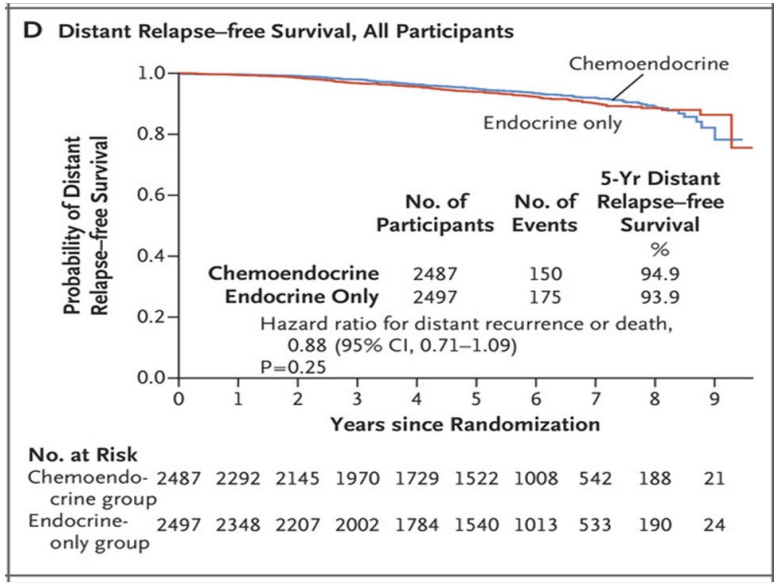
Many early stage ER+/HER2- patients do not benefit from adjuvant chemotherapy

TAILORx (N0)



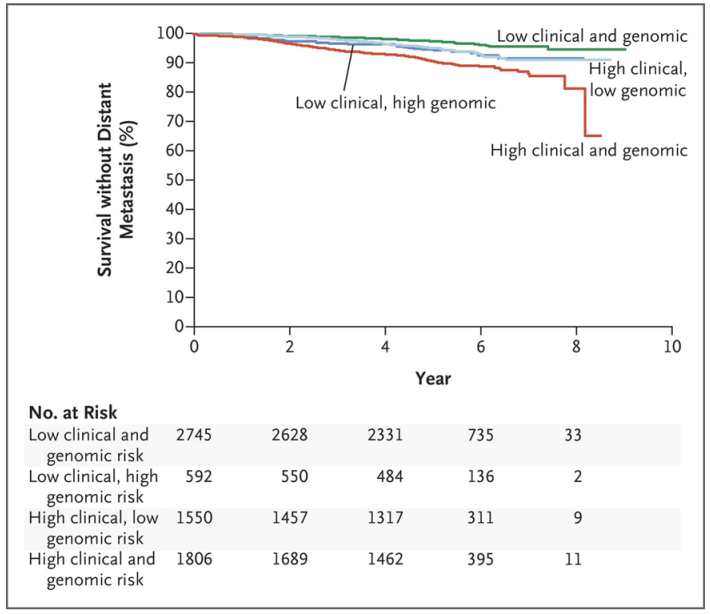
JA Sparano et al. N Engl J Med 2018;379:111-121.

RxPonder (N1)
Oncotype RS ≤ 25



K Kalinsky et al. N Engl J Med 2021;385:2336-2347.

MINDACT (N0-1)



Cardoso F et al. N Engl J Med 2016;375:717-729.

oncotype DX®
Breast Recurrence Score

Prosigna®
BREAST CANCER ASSAY

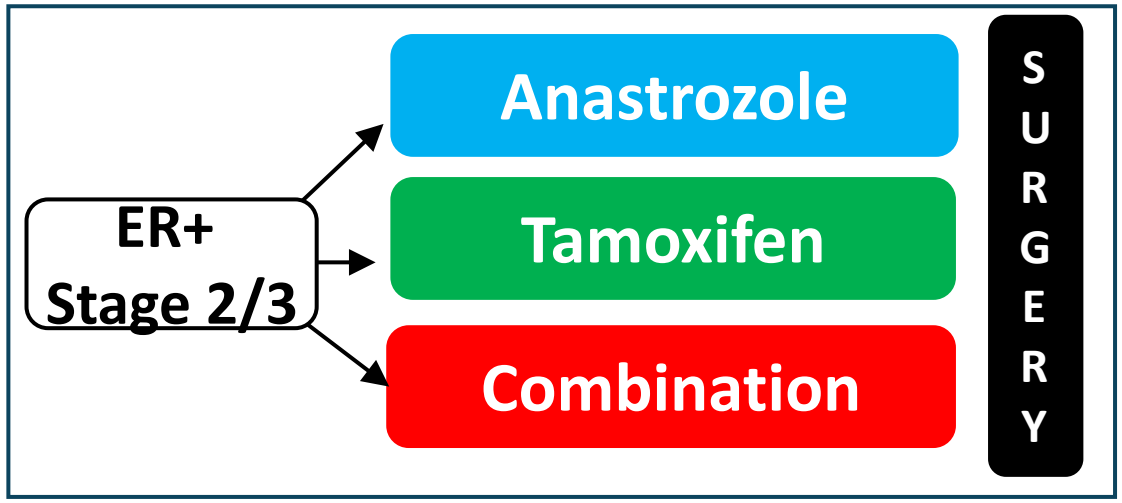
EndoPredict®
Breast Cancer Prognostic Test

Breast Cancer INDEX℠

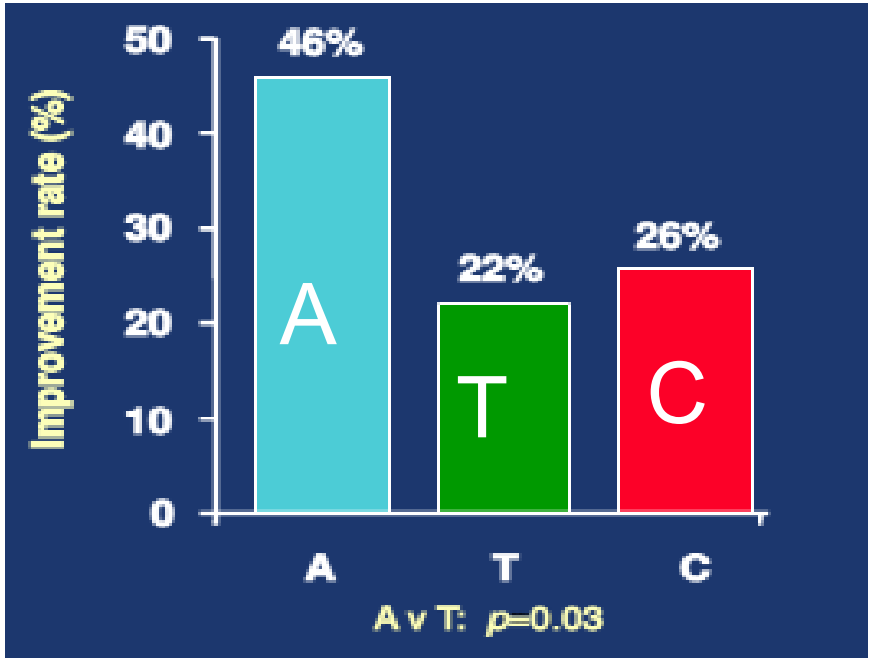
mammaprint®
decoding breast cancer.

Neoadjuvant Endocrine Therapy Improves Breast Conserving Surgery (BCS) Rate in Postmenopausal Women

IMPACT



Conversion to BCS

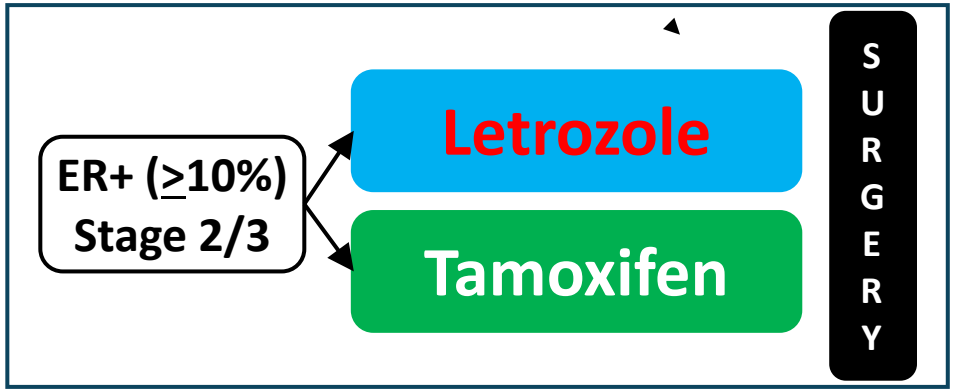


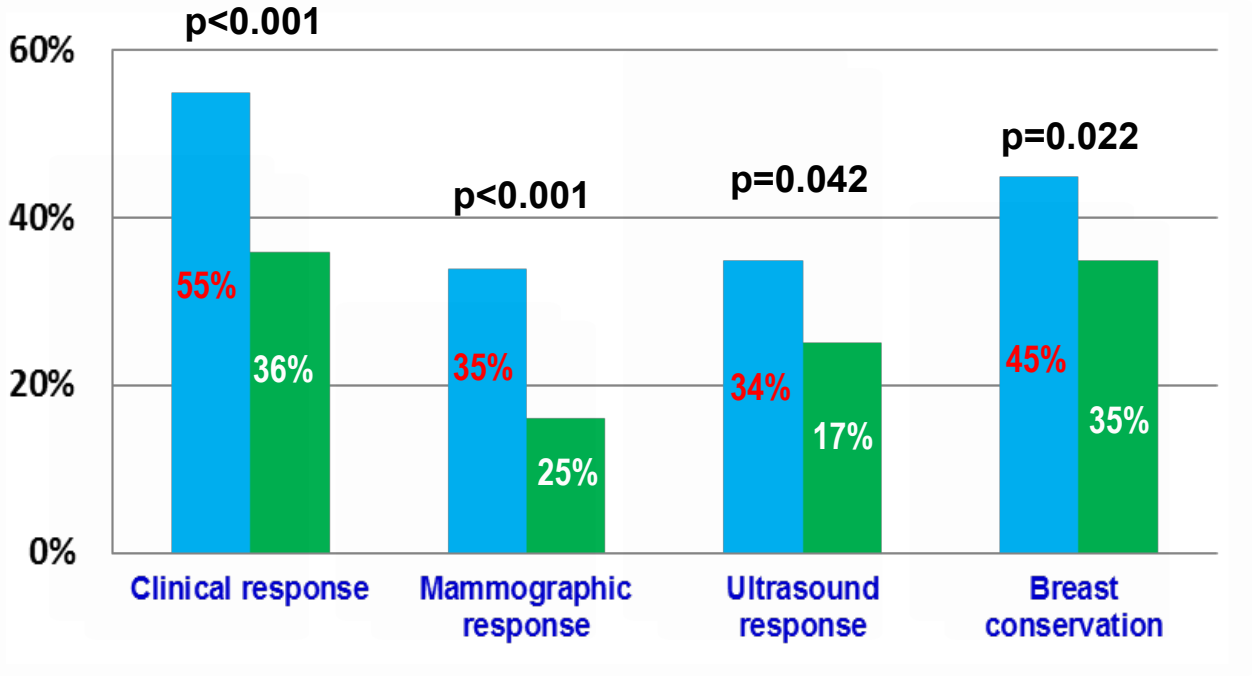
At baseline, 124 of 330 patients were ineligible for breast conservation surgery

Smith IE, et al, J Clin Oncol 23:5108-16, 2005

Neoadjuvant Endocrine Therapy Improves Breast Conserving Surgery Rate

P024



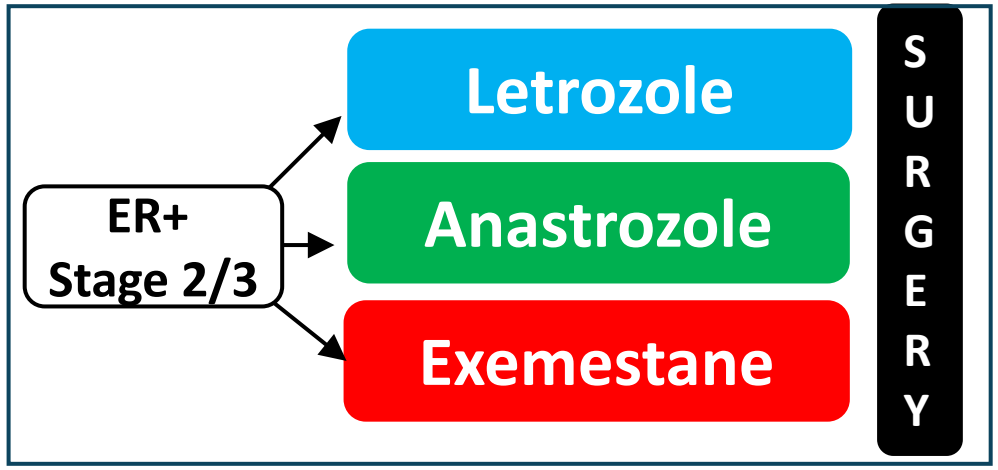


At baseline, none of the patients were eligible for breast conservation surgery

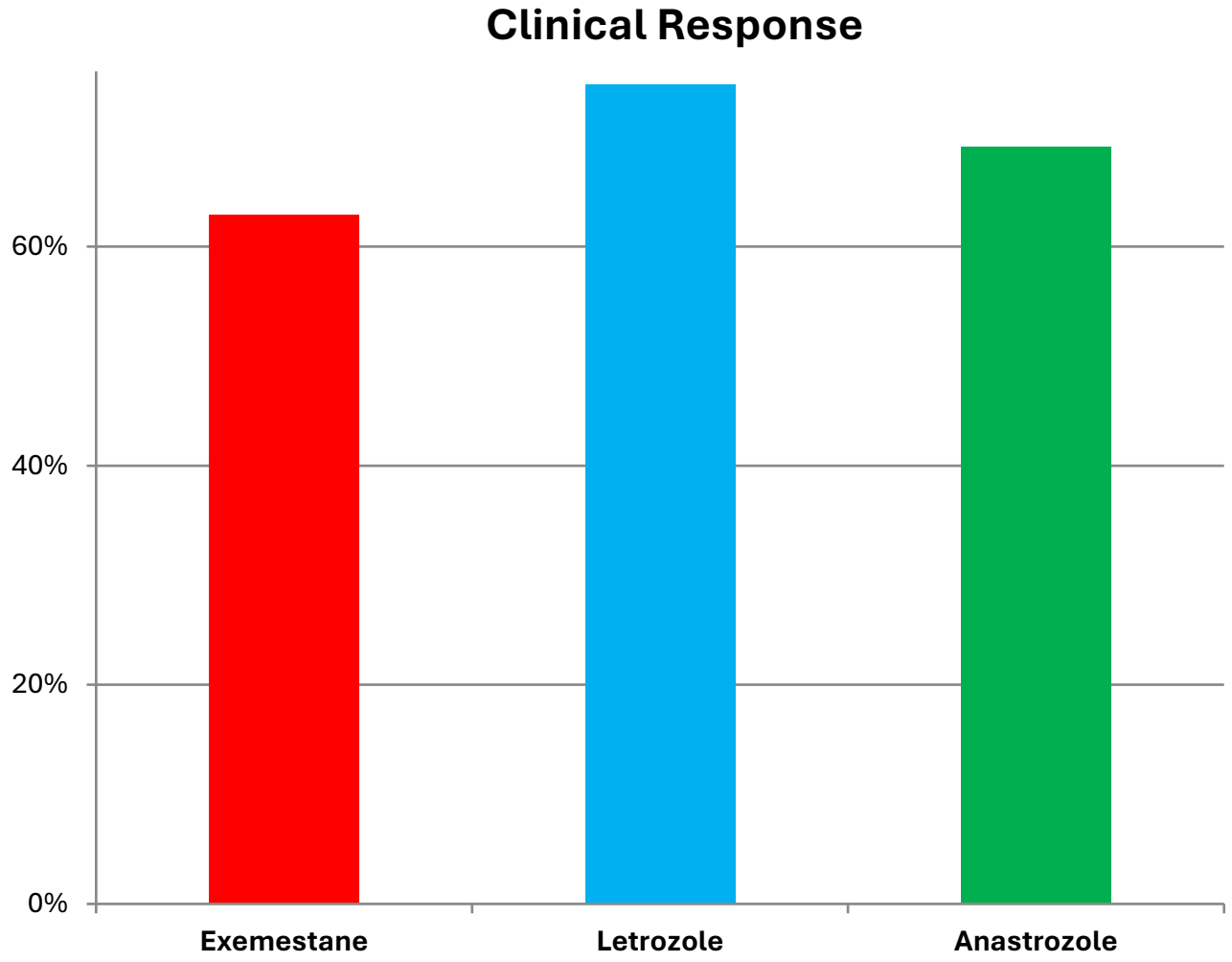
Eiermann W, et al, Ann Oncol 12:1527-32, 2001

Three Aromatase Inhibitors Are Equivalent

Z1031



Ellis, MJ, et al, J Clin Oncol 29:2342-2349, 2011



Neoadjuvant Endocrine Therapy (ET) vs Chemotherapy (CT)

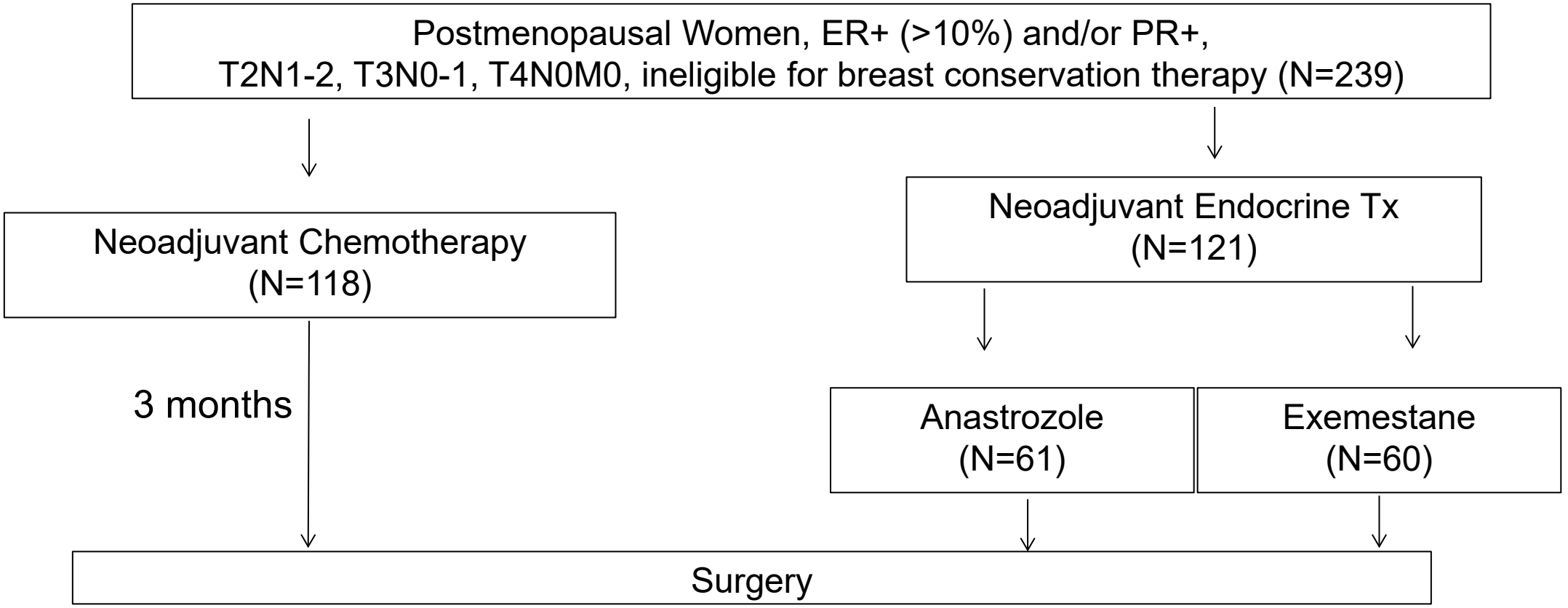
Author Year	Endocrine therapy (ET)		Chemotherapy (CT)		Sample Size (n)	Clinical Response (ET vs CT)	P Value
	Agents	Duration	Agents	Duration			
Semiglazov 2007	Anastrozole or exemestane	12 wks	Doxorubicin and Paclitaxel Q3wk x 4	12 wks	239	65% vs 64%	>0.5
Alba 2012	Exemestane plus goserelin if premenopausal	24 wks	EC-T (Epirubicin plus Cytoxan Q3w x 4 then Docetaxel Q3w x 4	24 wks	95	48% vs 66%	0.075
Palmieri 2014	Letrozole	18-23 wks	FEC x 6 or FEC x3 then T x3 if SD or PD	18 wks	44	91% vs 77%	0.32

Semiglazov VF, et al. *Cancer. 2007;110(2):244-254.*

Alba E, et al; GEICAM. *Ann Oncol. 2012;23(12):3069-3074.*

Palmieri C, et al. *Breast Cancer Res Treat. 2014;148(3):581-590.*

Neoadjuvant Endocrine Therapy (ET) vs Chemotherapy (CT)



Semiglazov VF, et al, Cancer 110:244-54, 2007

Neoadjuvant Endocrine Therapy (ET) vs Chemotherapy (CT)

	Endocrine Therapy (N=121)	Chemotherapy (N=118)
Clinical Response	65%	64%
pCR	3%	6%
Breast conservation	33%	24%

ER Allred ≥ 6	Endocrine Therapy (N=70)	Chemotherapy (N=63)	p
Clinical Response	70%	60%	0.07
Breast conservation	43%	24%	0.05

Semiglazov VF, et al, Cancer 110:244-54, 2007

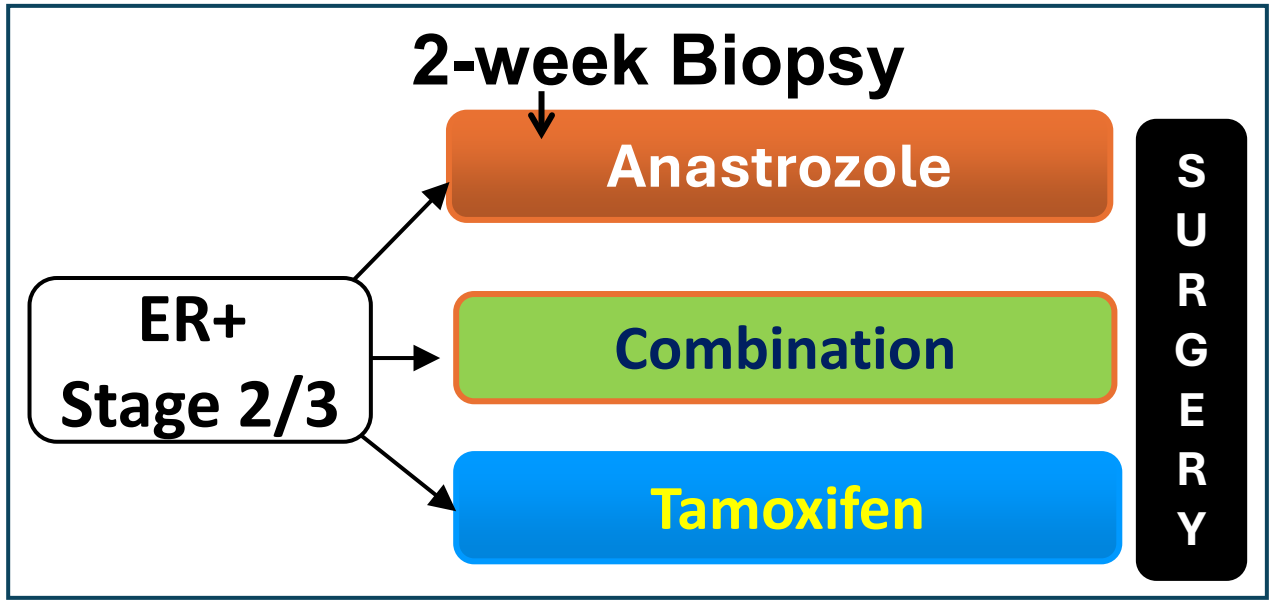
Treatment Duration for Neoadjuvant Endocrine Therapy

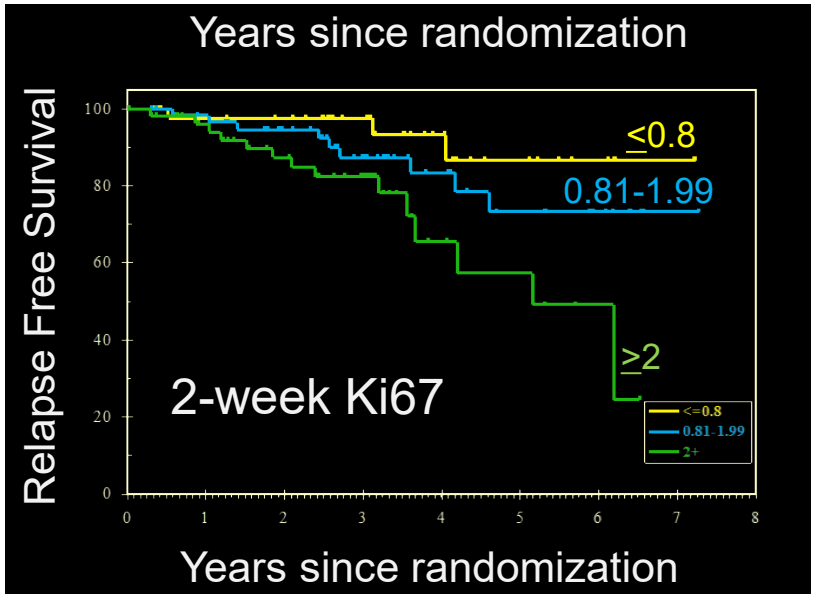
- A phase 2 trial of neoadjuvant letrozole for 4 months to 1 year in postmenopausal women
  - The median time to objective response was 3.9 (95% CI, 3.3–4.5) months;
  - The median time to maximum response was 4.2 (95% CI, 4.0–4.5) months;
  - A third reached the maximum response within 6-12 months;
    - Llombart-Cussac A, et al, Clin Transl Oncol (2012) 14:125-131
- Continuing letrozole in responding patients beyond 3-4 months achieves further tumor size reduction
  - Dixon J et al BCRT (2009) 113:145-151
  - Krainick-Strobel et al, BMC Cancer (2008) 8:62
- Increased pCR rate with prolonged letrozole therapy
  - Allevi, et al BJC (2013) 108: 1587–1592

In conclusion, 4–6 months of NET is adequate to evaluate efficacy. In patients with evidence of initial response, longer duration allows for the improvement of response and optimization of surgical treatment.

2-wk Ki67 on NET Predicts Relapse Risk

IMPACT

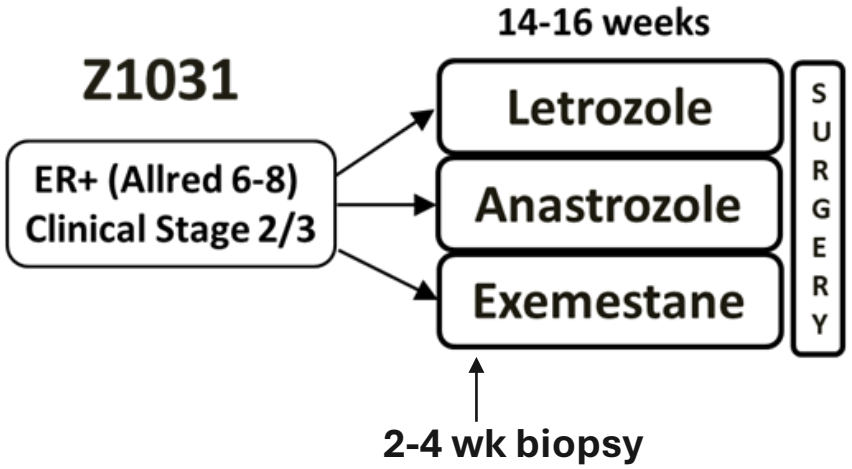


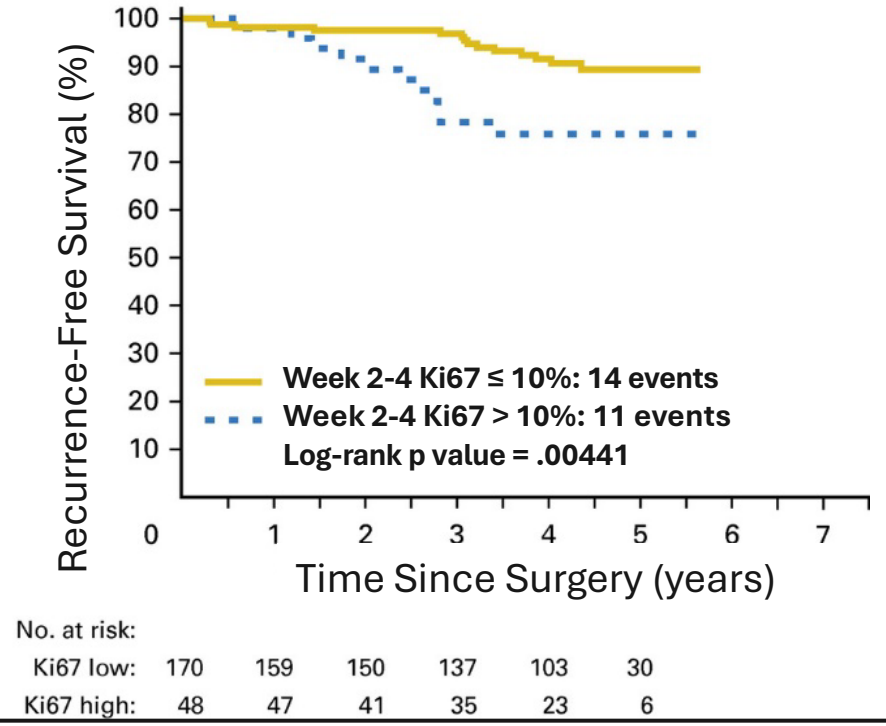


Dowsett et al, JNCI 99 (2007) 167

Ki67 >10% at Week 2-4 on NET

Recurrence-Free Survival by Week 2-4 Ki67 Using 10% Cut Point





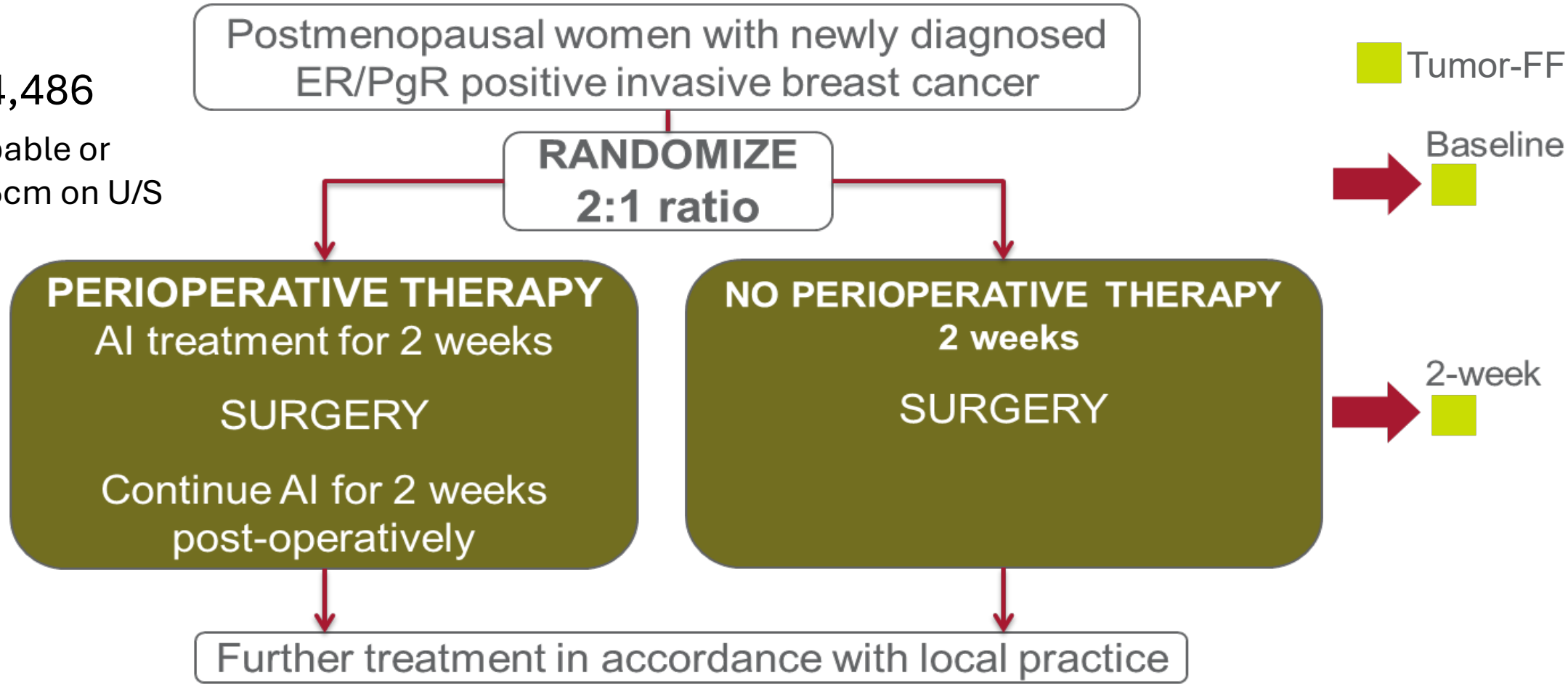
Ellis MJ et al J Clin Oncol 35:1061-9, 2017

POETIC TRIAL

PeriOperative Endocrine Therapy for Individualized Care

N=4,486

Palpable or
≥1.5cm on U/S



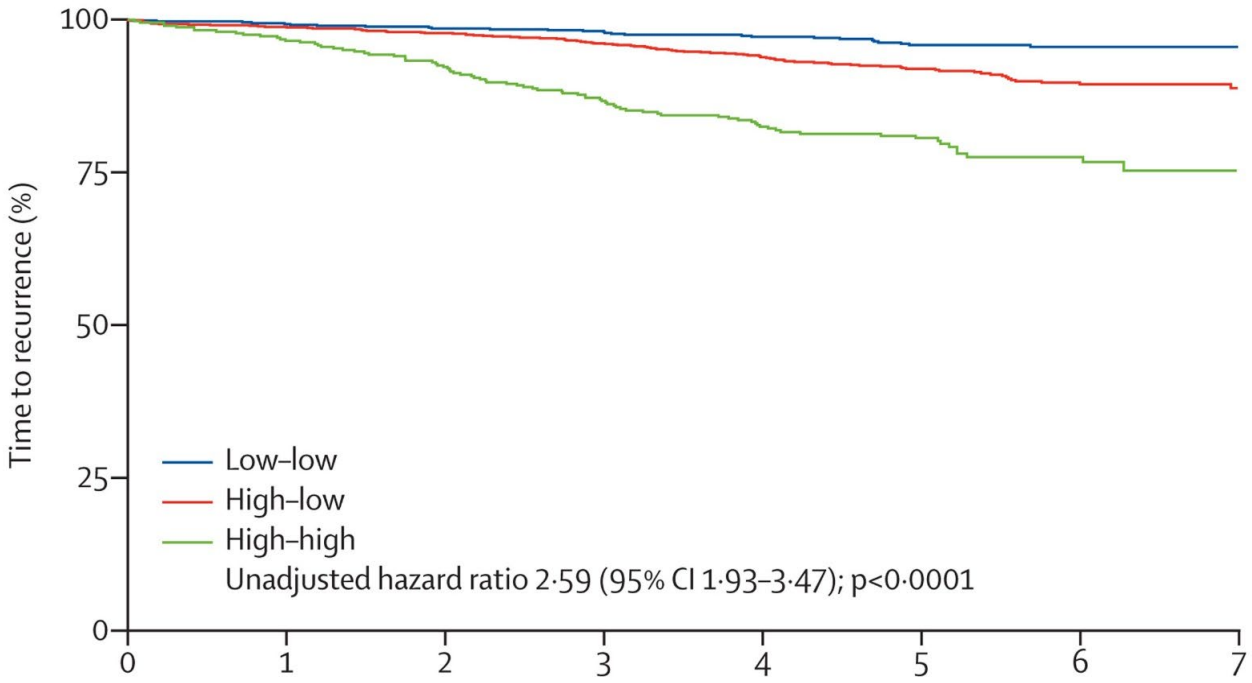
Primary endpoint: Time to recurrence

Second objective: association between Ki67 (dichotomized at 10%) and disease outcomes.

POETIC TRIAL PeriOperative AI Group

ER+ HER2- (n=2,235)

median F/U 62·9 months



Number at risk (number censored)								
Low–low	704 (11)	688 (18)	676 (34)	657 (100)	585 (235)	443 (434)	243 (580)	97 (··)
High–low	1097 (7)	1077 (21)	1052 (44)	1011 (130)	902 (378)	638 (678)	327 (882)	121 (··)
High–high	406 (5)	387 (9)	366 (17)	336 (35)	302 (111)	220 (227)	98 (290)	33 (··)

Group	5-year recurrence risk (95% CI)
Low-low	**4·3% (2·9–6·3%)**
High-low	**8·4% (6·8–10·5%)**
High-high	**21·5% (17·1–27·0%)**

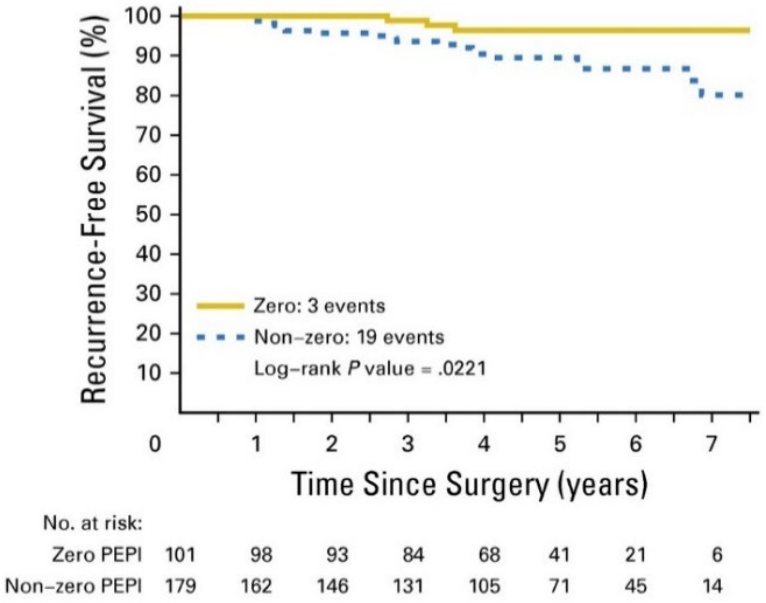
Group	Ki67	
	Baseline	2 week
Low-low	**<10%**	**<10%**
High-low	**≥10%**	**<10%**
High-high	**≥10%**	**≥10%**

- 9% time to recurrence events were reported in pts with ER+ HER2- breast cancer on PeriOperative AI.
- Pts with $Ki67_B$ <10% (732 [33%] of 2235) had a better prognosis than those with a $Ki67_B$ of ≥10% (1503 [67%] of 2235 patients).
- Pts with $Ki67_{2W}$ remained high (high–high) were significantly more likely to recur than $Ki67_{2W}$ had dropped below 10% (high–low).

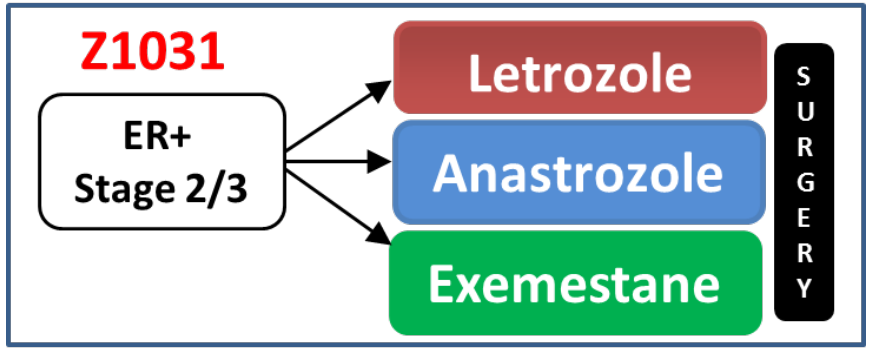
Preoperative Endocrine Prognostic Index (PEPI)

Pathology, Biomarkers Factors		RFS		BCS	
		HR	Points	HR	Points
Tumor size	T1/2	-	0	-	0
	T3/4	2.8	3	4.4	3
Node status	No	-	0	-	0
	Yes	3.2	3	3.9	3
Ln Ki67 level	0 -1	-	0	-	0
	1+ -2	1.3	1	1.4	1
	2+ -3	1.7	1	2.0	2
	3+ -4	2.2	2	2.7	3
	4+	2.9	3	3.8	3
ER Allred	0-2	2.8	3	7.0	3
	3-8	-	0	-	0

PEPI 0
pT1/2 pN0
Ki67 ≤ 2.7%
ER Allred 3-8



Ellis MJ, et al., J Natl Cancer Inst 100:1380-8, 2008



Ellis, JCO 2017

Association between pretreatment recurrence score and response to NET

Author (Year)	RS subgroups	Patients in each subgroup	Response rates (cCR + cPR)	p-value (RS as categories)
Akashi-Tanaka et al. (2009) [72]	<18	11	64%	$p = 0.11$
	18–30	16	31%	
	>30	16	31%	
Ueno et al. (2014) [73]	<18	32	59%	Ref.
	18–30	17	59%	$p = 0.970$
	>30	15	20%	$p = 0.017$
Iwata et al. (2018) [20]	<18	157	55%	$p < 0.001$
	18–30	84	42%	
	>30	54	22%	

*at multivariate analysis.

Akashi-Tanaka, et al, Breast 2009;18(3):171–4.
Ueno et al, Int J Clin Oncol 2014;19:607–13
Iwata et al, Breast Cancer Res Treat 2019;173(1):123–33.

Griguolo et al, Cancer Treatment Review 102 (2022), 102323

Society Recommendations

- St. Gallen: Panelists favor NET in women with low-grade and/or low-genomic risk tumors, and endorsed genomic assays on core biopsies as a strategy for choosing which type of neoadjuvant therapy (chemotherapy or endocrine therapy) to pursue. Several studies suggest that a short-term decline in Ki67 during initial NET is a favorable prognostic finding, identifying a cohort of patients with endocrine-sensitive tumors, unlikely to benefit from neo/adjuvant chemotherapy
- NCCN guideline: NET may be considered for patients with ER positive disease based on comorbidities or low-risk luminal biopsy based on clinical characteristics or genomic signatures.
- ASCO guideline Expert Panel recommended against the use of genomic profiles to guide clinical decision making regarding neoadjuvant treatment given the lack of prospective randomized trials directly addressing this issue.
- ASBrS Endocrine Resource Guide recommends consideration of NET for post-menopausal women with Grade 1-2 ER positive tumors to increase breast conservation rates

Conclusion

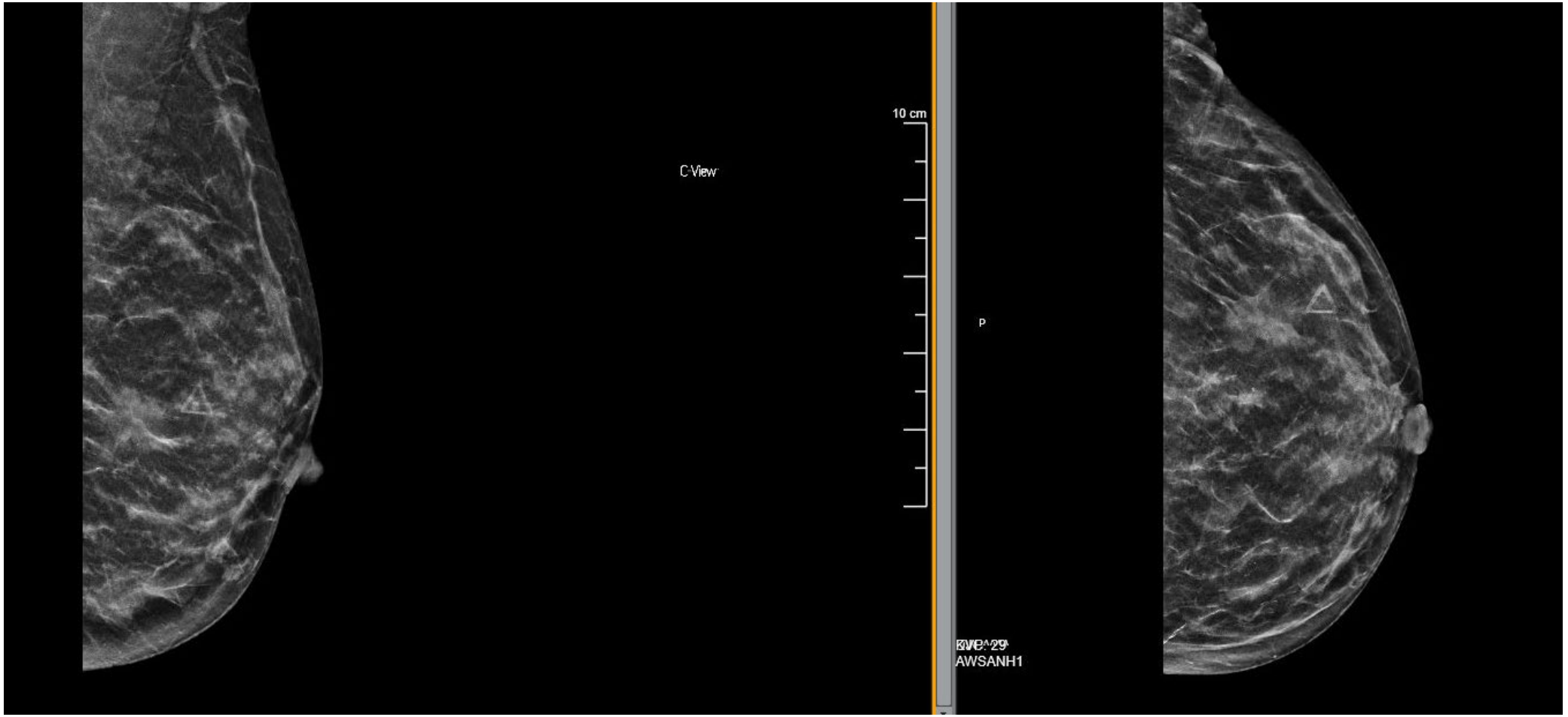
- NET is appropriate for majority of postmenopausal women with ER+/HER2- breast cancer for tumor down staging to facilitate surgery.
- Short term Ki67 response is a validated prognostic marker.
- NET trials should consider incorporating intrinsic subtype in eligibility criteria or stratification factor, and Ki67 based biological endpoints.
- Prospective studies are needed to address:
  - Which patients are better treated with NET vs NCT?
  - Could more effective ET or the addition of CDK4/6i spare patients from chemotherapy?

Thank You!

Case Study

- 57 year old post-menopausal woman palpated a mass in the left breast
  - PMH significant for asthma
  - No family history of cancers
- Physical examination revealed a firm palpable mass at the three o'clock position of the left breast that measured 4-5 cm clinically
  - Clinically negative left axilla

Case Study



THE AMERICAN SOCIETY OF Breast Surgeons

ACCC
ASSOCIATION OF CANCER CARE CENTERS™

Omission of Sentinel Lymph Node Surgery in Patients Under Age 70

Laura S. Dominici MD, FACS

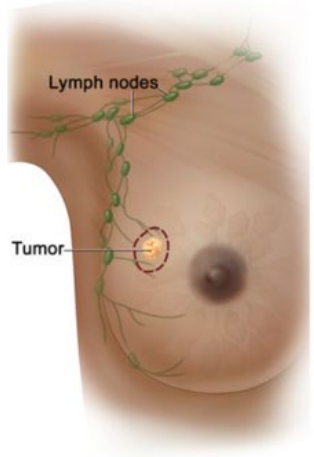
Associate Professor of Surgery, Harvard Medical School

Surgeon, Dana-Farber/Brigham Cancer Center, Boston, MA

Take Away Points

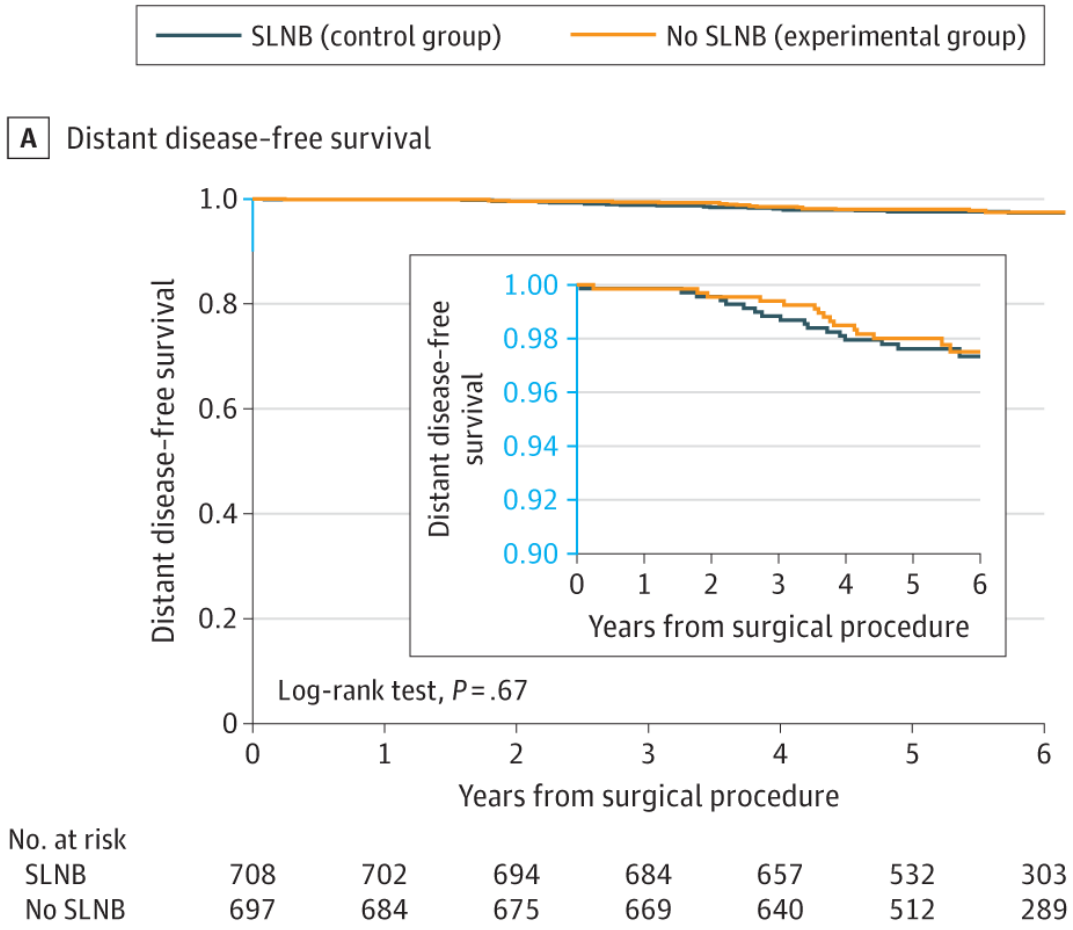
- Multidisciplinary discussion is key
- Make sure in de-escalating axillary surgery, you aren't escalating something else
- Not all patients omitting axillary surgery need an ultrasound (see prior talk)

Purpose of Lymph Node Evaluation



- Informative
  - Staging
  - Inform treatment recommendations
    - Systemic therapy
    - Radiation therapy
  - Prognostic information
- Local control
  - Clinically negative axillary nodes not evaluated pathologically and untreated by either radiation or dissection have a 20% risk of local recurrence (NSABP B-04)

Recent trials—SOUND and INSEMA



- 1400 and 5502 patients, RCTs
- >5.5yrs follow up
- Early-stage breast cancer (T1-T2, vast majority were T1)
- Negative axillary ultrasound or abnormal axillary ultrasound (single node) with negative FNA
- Breast conserving surgery, planned for whole breast radiation
- No significant differences in local and distant outcomes with/without nodal surgery

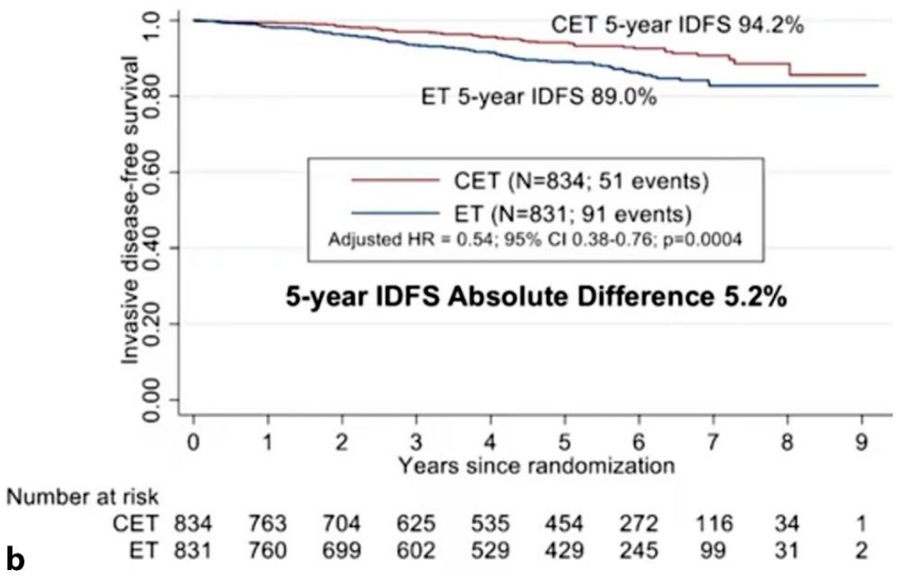
Gentilini JAMA 2023; Reimer NEJM 2024

Implementation Considerations

- Multidisciplinary decision making
- When is nodal information needed?
  - Systemic therapy decisions
  - Radiation therapy decisions
- Which patients should be having axillary US?

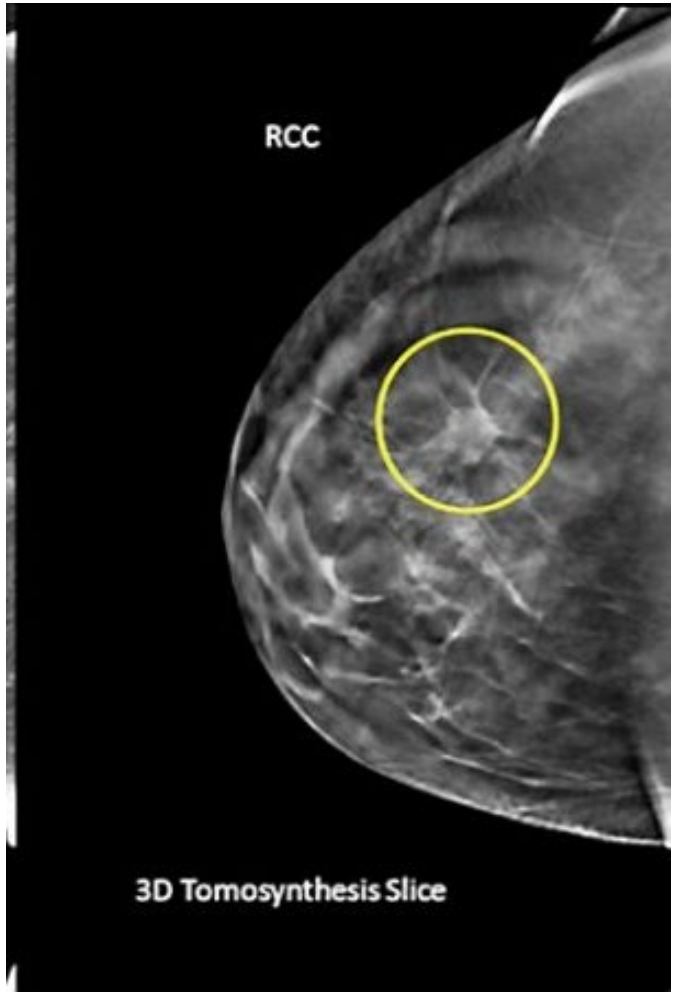
Systemic Therapy Decisions--Established

- Triple negative breast cancers
- HER2+ breast cancers
- Premenopausal patients with hormone positive breast cancer
  - RxPONDER trial
  - Chemotherapy benefit in pre-menopausal with 1-3 positive nodes even with low genomic risk score



Kalinsky, NEJM, 2021

Systemic Therapy Impact--Case



- 62yo healthy female
- 1.5cm mass on screening mammogram, confirmed on US
- US core→
  - Invasive ductal cancer grade 3
  - ER+ PR+ HER2-
- Axillary management?
  - US and consider omission if negative?
  - Recommend sentinel node biopsy?

Systemic Therapy Impact—Case

- Lumpectomy and sentinel node biopsy performed
  - 1.7cm invasive ductal cancer, grade 2 ER+ PR+ HER2- and 1 out of 3 sentinel nodes with 5mm metastasis
  - Genomic testing revealed intermediate risk score
- Adjuvant therapy recommendations:
  - Whole breast radiation with high tangents
  - No chemotherapy recommended as intermediate risk score and post-menopausal
  - Aromatase Inhibitor
  - CDK4/6 inhibitor

Systemic Therapy Decision Making—ER+ Early Breast Cancer

N0 not allowed in monarchE

AJCC Anatomical Staging[1]	TN (M0)	NATALEE[2,3]	monarchE[4]
Stage IIA	T0N1	✓	Only if grade 3 or Ki-67 ≥20%
	T1N1	✓	Only if grade 3 or Ki-67 ≥20%
	T2N0	Only if G3 or G2 with Ki-67 ≥20% or high genomic risk[a]	✗
Stage IIB	T2N1	✓	Only if grade 3 or Ki-67 ≥20%
	T3N0	✓	✗
Stage IIIA	T0N2	✓	✓
	T1N2	✓	✓
	T2N2	✓	✓
	T3N1	✓	✓
	T3N2	✓	✓
Stage IIIB	T4N0	✓	✗
	T4N1	✓	Only if tumor size ≥5 cm or grade 3 or Ki-67 ≥20%
	T4N2	✓	✓
Stage IIIC	Any TN3	✓	✓

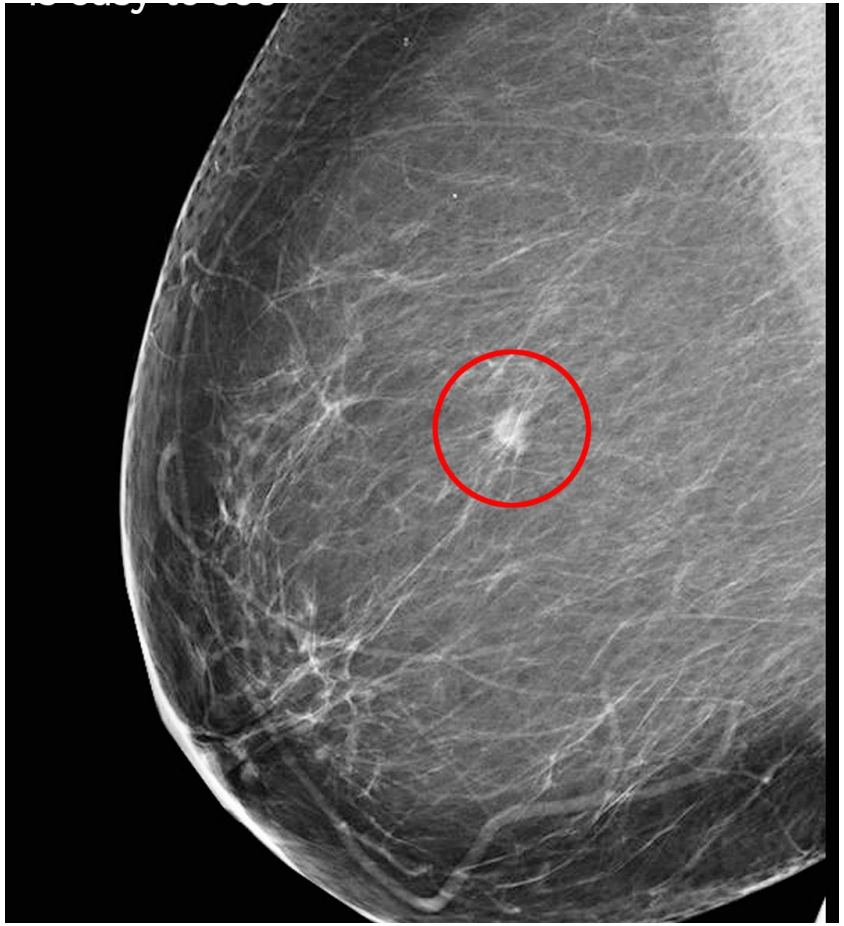
In monarchE, relatively few patients with stage II were allowed:
- N1 allowed only if grade 3 or Ki-67 ≥20%

In monarchE, within stage III,
- N0 not allowed (in IIIB)
- N1 (whether in IIIA or IIIB) allowed only if tumor size ≥5 cm, grade 3, or Ki-67 ≥20%

ribociclib **abemaciclib**

Slamon, Therapeutic Advances Medical Oncology, 2023

Radiation Therapy Impact-Case

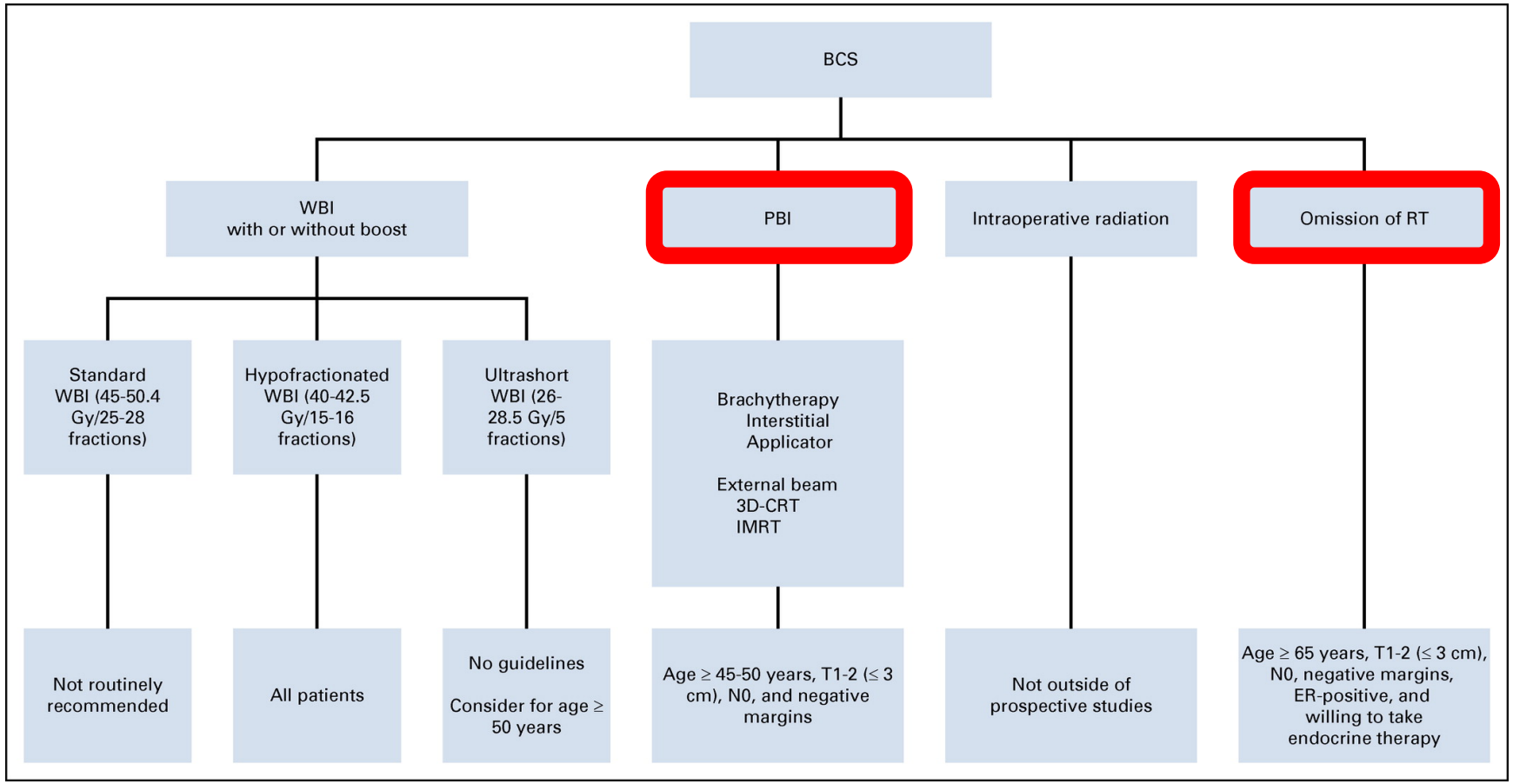


- 57yo female with chronic bronchitis/COPD
- 7mm mass seen on screen→diagnostic mammogram and US
- US core→
  - Invasive ductal cancer, grade 1
  - ER+ PR+ HER2-

Radiation Therapy Impact-Case

- Lumpectomy and sentinel node biopsy performed
  - 0.7cm invasive ductal cancer, grade 1 ER+ PR+ HER2- and 3 negative sentinel nodes
- Adjuvant therapy recommendations:
  - Partial breast radiation to minimize lung volume treated
  - Aromatase Inhibitor

Radiation Guidelines

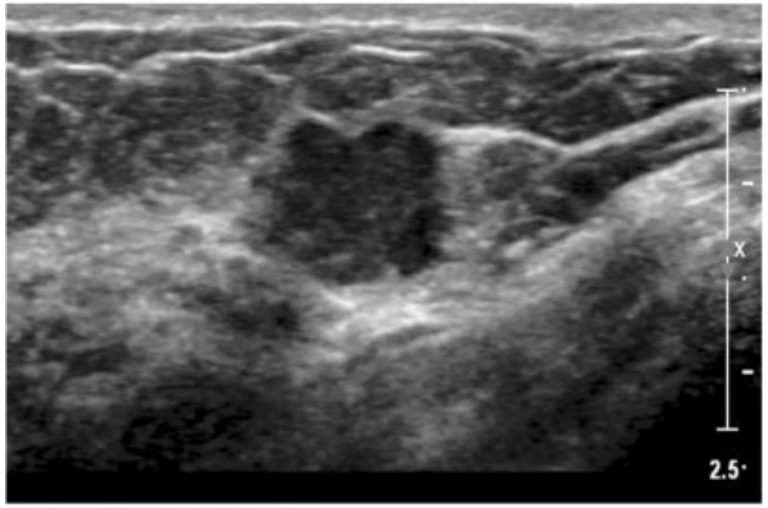


Shah, JCO Oncology Practice, 2021

Which patients do not need axillary US?

- Clinically negative axilla, planned for upfront surgery, not a candidate for omission of nodal surgery due to impact on systemic therapy or radiation decision-making
- Clinically negative axilla, planned for upfront surgery, 70 and over with small ER+ HER2- breast cancer with plans to omit axillary surgery (CALGB 9343)

Axillary Surgery Omission--Case



Hooley R J et al. Radiology 2013;268:642-659

- 63yo female
- Palpable finding noted in right breast
- 1.2cm mass identified on diagnostic imaging
- US core→
  - Invasive ductal cancer, grade 2
  - ER+ PR+ HER2-
- Axillary US demonstrates no adenopathy

Axillary Surgery Omission—Case

- Lumpectomy performed
  - 1.2cm invasive ductal cancer, grade 2 ER+ PR+ HER2-
  - Genomic testing revealed low risk score
- Adjuvant therapy recommendations:
  - Whole breast radiation
  - No chemotherapy recommended as low risk score
  - Aromatase Inhibitor

Take Away Points

- Multidisciplinary discussion is key
  - Discussion to ensure nodes will not impact adjuvant therapy decisions
- Make sure in de-escalating axillary surgery, you aren't escalating something else
  - All patients in trials received whole breast radiation, not all eligible patients will need/want this
- Not all patients omitting axillary surgery need an ultrasound
  - No need to start doing US in patients 70 and over with early-stage ER+ HER2- disease

THE AMERICAN SOCIETY OF Breast Surgeons

ACCC
ASSOCIATION OF CANCER CARE CENTERS™

Optimizing the Management of HR+/HER2- Breast Cancer:

Neoadjuvant Chemotherapy vs. Neoadjuvant Endocrine Therapy vs. Upfront Surgery

Anita Mamtani, MD, FACS

Memorial Sloan Kettering Cancer Center

Disclosures

None

Introduction

- General approach to HR+/HER2- breast cancer varies by clinical stage

Early-stage, node-negative (cT1-2, cN0)

→ **Upfront surgery**

Locoregionally advanced (cT3-4, cN2-3)

→ **Neoadjuvant therapy**

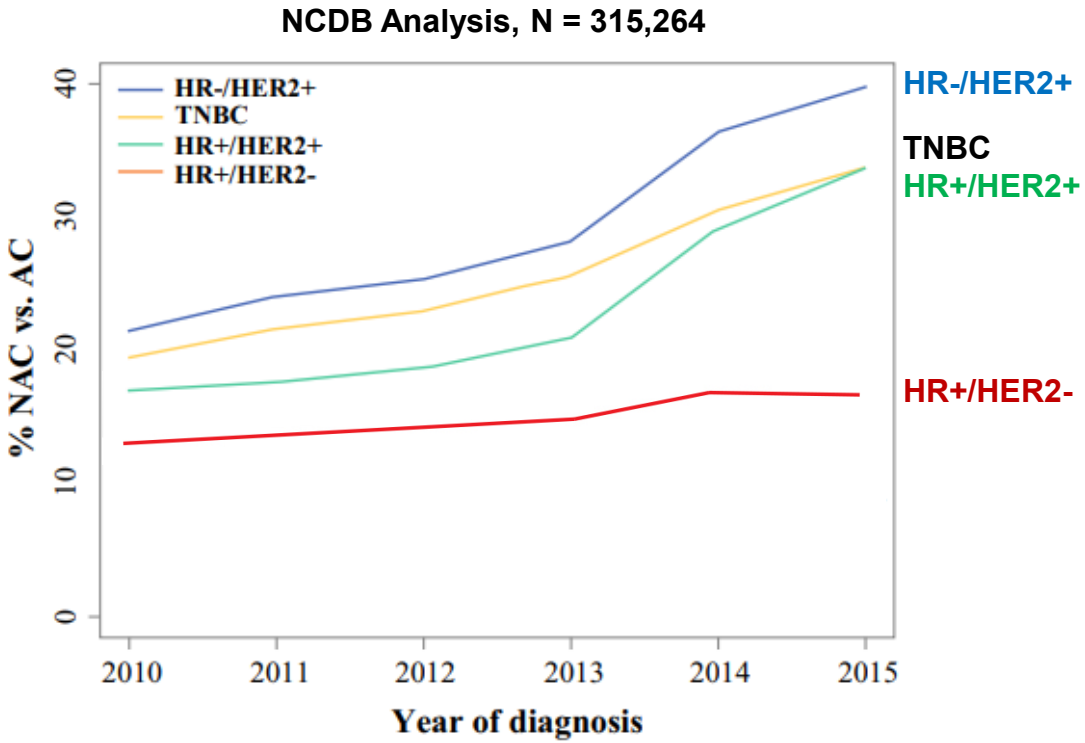
- This paradigm has evolved with greater understanding of tumor biology
- Management of **node-positive HR+/HER2-** disease is uniquely complex

Introduction

- Surgical goals: safe de-escalation to minimize morbidity of treatment, particularly in the **axilla**
- Increasing use of sentinel lymph node biopsy (SLNB) over past few decades:
  - Standard among cN0 patients who have limited nodal disease (1-2 +SLNs) at upfront surgery with adjuvant RT and systemic therapy
  - Axillary downstaging of cN1 disease with neoadjuvant chemotherapy (NAC)
- Management of **cN1 HR+/HER2-** disease is complex: unique tumor biology, poor response to neoadjuvant therapies and implications for surgical management

Use of NAC in cN+ HR+/HER2- Disease

- NAC is **not optimal** for HR+/HER2- disease:
  - Low rates of breast and nodal pathologic complete response (pCR) of **< 20%**
  - Low rates of breast and axillary downstaging
- Used less frequently for HR+/HER2- subtype compared to HER2+ and TN



Montagna G, Ann Surg Oncol 2020 Freidman-Eldar O, Ann Surg Oncol 2022 Samiei S, JAMA Surg 2021 Murphy B, Ann Surg Oncol 2018

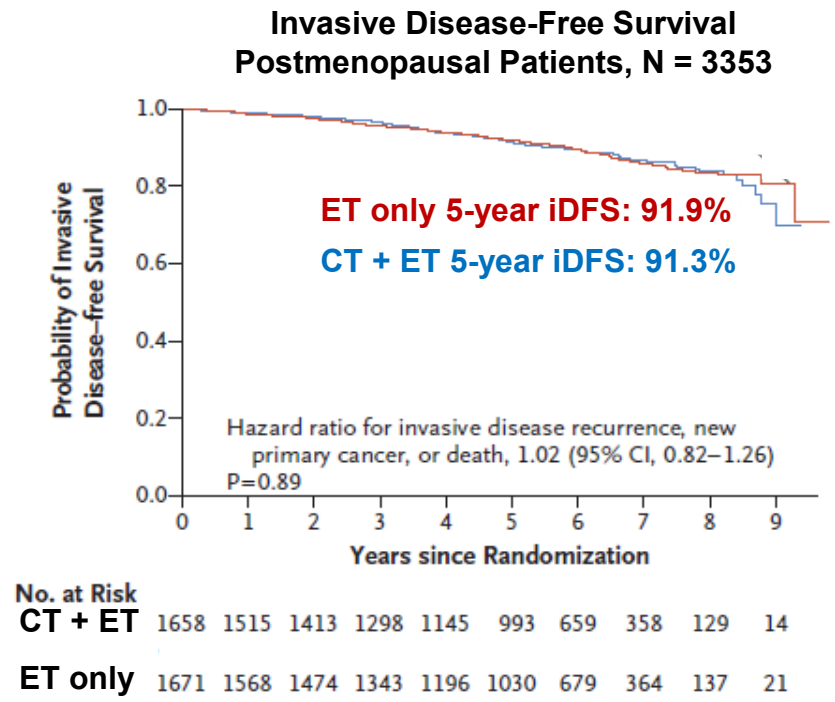
Genomic Profiling in cN1 HR+/HER2- Patients: Not All Such Patients Need Chemotherapy

- **RxPONDER trial**

  HR+/HER2-
  N1 disease (1-3 positive nodes)
  ODx ≤ 25
  Randomized: CT + ET vs. ET only

- **No benefit** from adjuvant chemotherapy among postmenopausal patients

- Use of NAC for axillary downstaging alone is **not warranted**



Kalinsky K, NEJM 2021

Upfront Surgery in cN1 HR+/HER2- Disease

- Standard of care: **ALND**
- Rationale:
  - cN1 patients were excluded from early trials of omission of ALND
  - Traditional belief that palpable disease indicates a heavier nodal burden and limits the applicability of SLNB

Omission of ALND is Standard Among cN0 Patients with 1-2 Positive SLNs at Upfront Surgery

ACOSOG Z0011

T1-2, cN0 having BCS with 1 or 2 +SLNs
N = 856; 85% HR+

Randomized

- SLNB only N = 436
- ALND N = 420

AMAROS

T1-2, cN0 having BCS or mastectomy with +SLN
N = 1425

Randomized

- Axillary RT N = 681
- ALND N = 744

SENOMAC

T1-3, cN0 having BCS or mastectomy with 1 or 2 +SLNs
N = 2540; 87% HR+/HER2-

Randomized

- SLNB only N = 1335
- ALND N = 1205

10-year axillary recurrence rate of **< 2%** in all arms and no difference in DFS/OS despite ~30% of ALND patients having additional nodal metastases

No difference in 5-year RFS, non-inferiority confirmed

Giuliano AE, Ann Surg, 2016; Bartels SA, J Clin Oncol, 2022; deBoniface J, SABCS 2023

Omission of ALND is Standard Among cN0 Patients with 1-2 Positive SLNs at Upfront Surgery

ACOSOG Z0011

T1-2, cN0 having BCS with 1 or 2 +SLNs
N = 856; 85% HR+

Randomized

- SLNB only N = 436
- ALND N = 420

AMAROS

T1-2, cN0 having BCS or mastectomy with +SLN
N = 1425

Randomized

- Axillary RT N = 681
- ALND N = 744

SENOMAC

T1-3, cN0 having BCS or mastectomy with 1 or 2 +SLNs
N = 2540; 87% HR+/HER2-

Randomized

- SLNB only N = 1335
- ALND N = 1205

10-year axillary recurrence rate of **< 2%** in all arms and no difference in DFS/OS despite ~30% of ALND patients having additional nodal metastases

No difference in 5-year RFS, non-inferiority confirmed

cN1 patients were excluded!

Giuliano AE, Ann Surg, 2016; Bartels SA, J Clin Oncol, 2022; deBoniface J, SABCS 2023

Nodal Disease Burden in cN1 Patients

- cT1-3, cN1 (palpable) HR+/HER2- patients who had upfront ALND:

Study	N	% with only pN1 disease	Pertinent findings
Crown et al	180	**57%**	# of nodes on **axillary US** and lower **T stage** were predictive of < 3 positive nodes
Angarita et al	68	**43%**	Higher **T stage** and **lobular** histology were predictive of ≥ 3 positive nodes
Ye et al	57	**40%**	Higher **T stage** predictive of heavier nodal disease burden

Crown A, Ann Surg Oncol 2021
Treat 2022
Angarita S, Ann Surg Oncol 2021
Ye L, Breast Cancer Res

A Unique Opportunity

Upfront SLNB is standard among **cN0** with **1-2 positive SLNs**

Nearly **50%** of cN1 HR+/HER2- patients have **only 1-2 positive nodes**

Can we use upfront SLNB and potentially omit ALND among select cN1 HR+/HER2- patients with limited nodal disease burden?

Can We Omit ALND in Select cN1 Patients?

- No prospective data

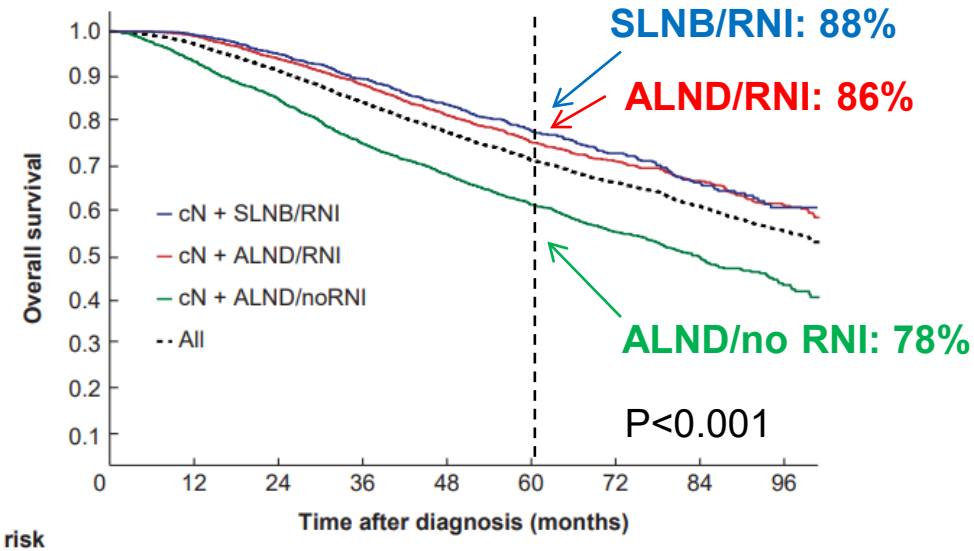
NCDB Analysis:

- T1-T2 cN+ patients, 65% **HR+/HER2-**, treated 2010-2016 with upfront surgery:
  - SLNB/RNI (N = 3030): **24%**
  - ALND/RNI (N = 5446): **43%**
  - ALND/no RNI (N = 4084): **33%**

- SLNB group: median 1 of 3 SLN positive

- Similar 5-year OS for SLNB/RNI and ALND/RNI

Overall Survival



No. at risk									
All	12 560	12 143	11 040	8976	7087	5417	3851	2403	942
cN + ALND/noRNI	4084	3815	3429	2831	2321	1765	1194	723	287
cN + ALND/RNI	5446	5362	4937	4077	3211	2530	1875	1248	512
cN + SLNB/RNI	3030	2966	2674	2068	1555	1122	782	432	143

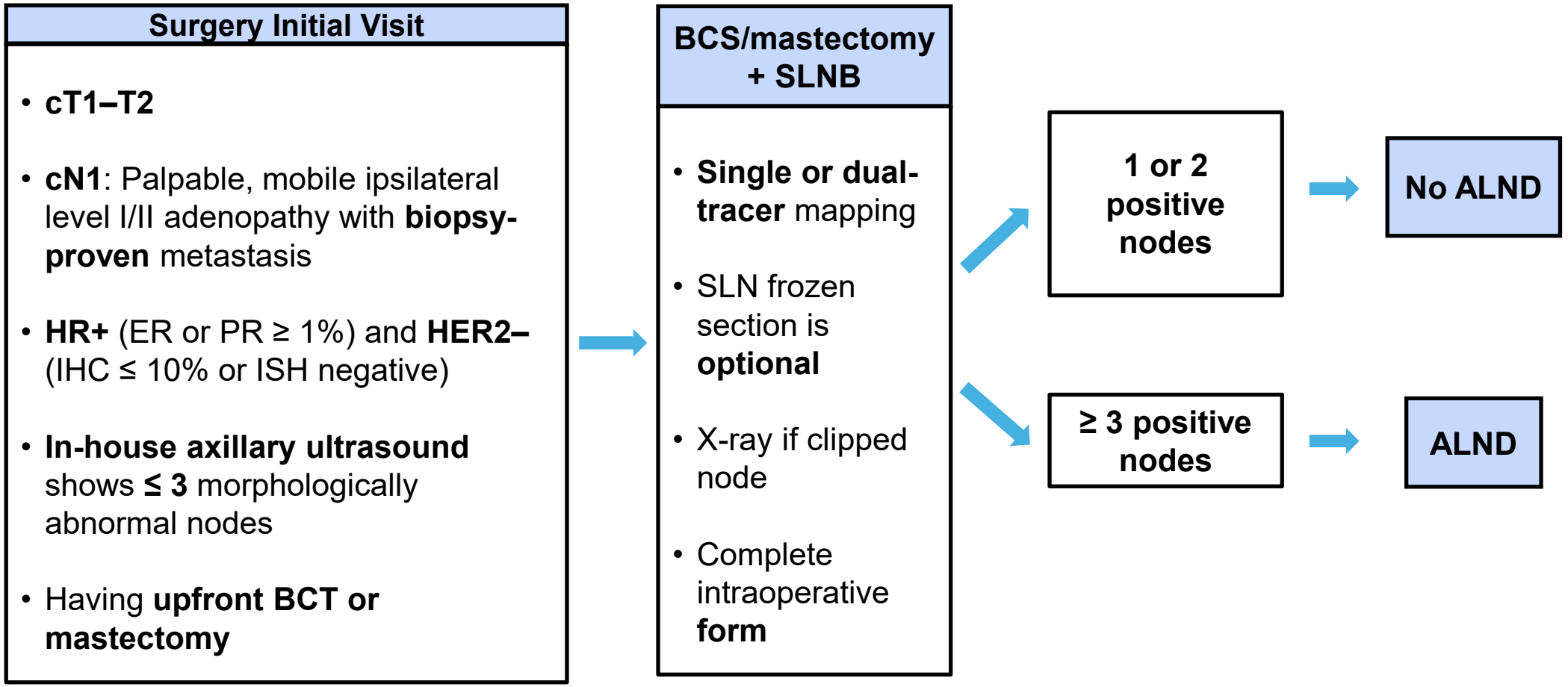
Cocco D, British J Surg, 2022

Can We Omit ALND in Select cN1 Patients?

- Need to confirm feasibility, accuracy and safety of upfront SLNB among cN1 patients
- Await results of prospective studies:
  - TAXIS trial (European RCT of cN+, evaluating excision of palpable diseased node and SLNs, enrolling both a neoadjuvant and an upfront surgery arm)
  - MSKCC trial: results being presented at Society of Surgical Oncology meeting in March 2025

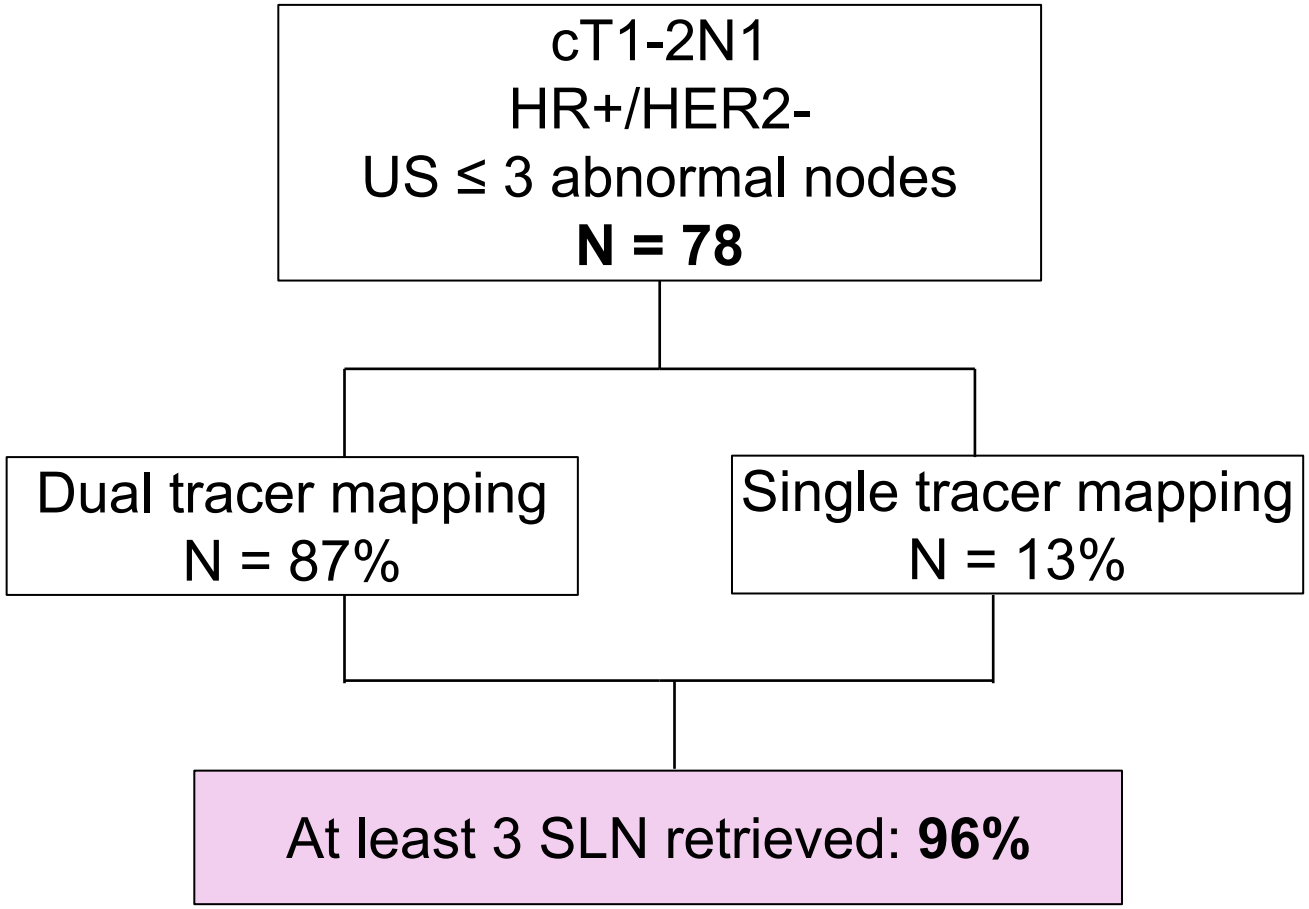
TAXIS ClinicalTrials.gov Identifier NCT03513614 MSK study ClinicalTrials.gov Identifier NCT04854005

SLNB in cT1-2N1 HR+/HER2- Breast Cancer: Prospective Trial



PI: Anita Mamtani; Co-PI: Monica Morrow, ClinicalTrials.gov Identifier NCT04854005

SLNB in cT1-2N1 HR+/HER2- Breast Cancer: Prospective Trial



Trial closed Aug 2024

Accrued **N = 78**

Endpoints of interest:

Feasibility of SLNB
Rate of ALND
5-year LRR

Results will be presented at Society of Surgical Oncology Annual Meeting in March

PI: Anita Mamtani; Co-PI: Monica Morrow, ClinicalTrials.gov Identifier NCT04854005; figure courtesy of A. Barrio

What About Neoadjuvant Endocrine Therapy (NET)?

- NET is less frequently utilized
- Typical indications for use:
  - Primary therapy for **poor surgical candidates**
  - **Tumor shrinkage to facilitate lumpectomy**
  - **Delay strategy** (e.g., COVID-19 pandemic)
- Data are limited on axillary downstaging and approach to the cN+ axilla after NET

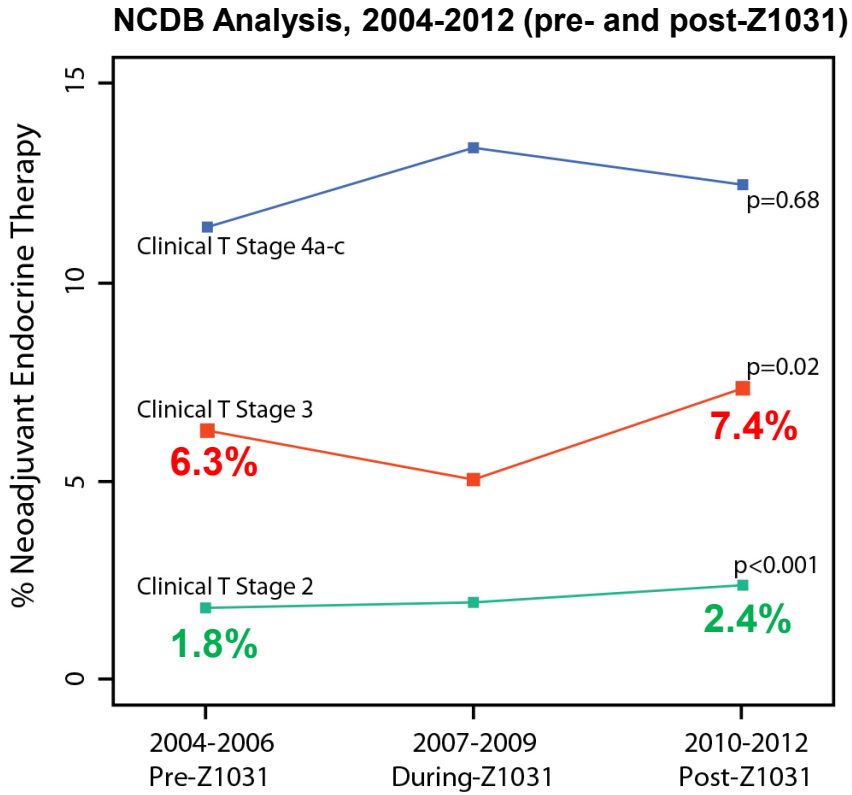


FIG. 1 Neoadjuvant endocrine therapy use by clinical T stage over time

Chiba A, Ann Surg Oncol 2017

Impact of NET on Breast

ACOSOG Z1031 Trial

- Evaluated 3 neoadjuvant AIs
- Analysis of N=509 stage 2-3 ER+ breast cancers
  - Breast/nodal pCR was rare (**1%**)
  - Among N=221 who required mastectomy at presentation, **50%** were able to downstage to BCS
  - 5-year cumulative incidence rate of LRR: **1.5%**
- Although pCR is rare after NET, significant downstaging is possible to permit BCS

Hunt KK, Ann Surg Oncol 2023

Impact of NET on Breast

Validated: NCDB Cohort, MSKCC Cohort

- NCDB
  - N=19,829 NAC vs. N=5,8045 NET patients age>50 with cT2-4 HR+ breast cancer, 2010-2016
  - Breast downstaging achieved by **41%** of patients with NET, breast pCR in **9%**
- MSKCC
  - N=338 NAC vs. N=127 NET patients with stage 1-3 breast cancer, 2009-2019
  - Breast downstaging achieved by **77%** of patients with NET, breast pCR in **2%**
- Although pCR is rare after NET, significant downstaging is possible to permit BCS

Cao L, Ann Surg Oncol 2021

Montagna G, Ann Surg Oncol 2020

Impact of NET on Axilla

Study	N	% nodal pCR	NET Duration (median/mean)	
U of Miami	178	7.3%	8.4 mo	Biopsy-proven node-positive
Mayo Clinic (AZ)	39	3%	4.5 mo	
MSKCC	127	11%	4.6 mo	
Mayo Clinic (MN)	84	4.8%	6.25 mo	
Netherlands Registry	561	7.3%	8.8 mo	
NCDB (2012-2015)	571	13.3%	5 mo	cN+ but not biopsy-proven
NCDB (2010-2016)	1915	13.5%	NR	

Nodal pCR rates are low: 3-14%

Freidman-Eldar O, Ann Surg Oncol 2022
Stafford A, Ann Surg Oncol 2021
Hammond J, J Clin Oncol 2020
Cao L, Ann Surg Oncol 2021
Montagna G, Ann Surg Oncol 2020
Schipper RJ, Eur J Surg Oncol 2021
Weiss A, Ann Surg Oncol 2019
Murphy B, Ann Surg Oncol 2021

Use of SLNB After NET

- Optimal surgical management of the axilla after NET **remains unclear**
- No trials evaluating feasibility (IR) or accuracy (FNR) of SLNB after NET
  – Extrapolated from data in post-NAC setting
- Despite low rates of pCR, there is **increasing use of SLNB only** among **cN1** patients after NET

Study	N	% nodal pCR	% SLNB only
Mayo Clinic (AZ)	39	3%	10%
Mayo Clinic (MN)	84	4.8%	16.7%
NCDB (2012-2016)	675	10%	18%

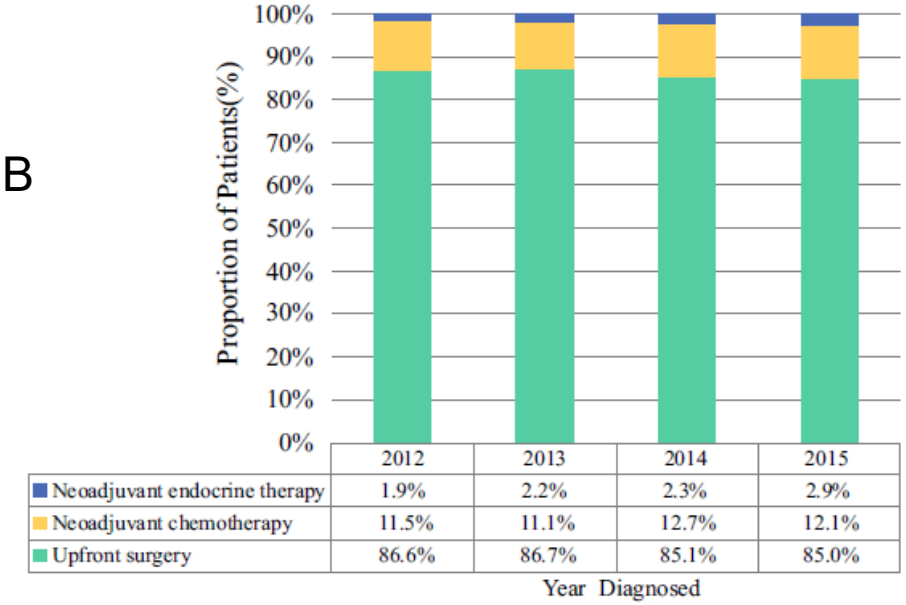
Hammond J, J Clin Oncol 2020 Kantor O, Ann Surg Oncol 2021 Murphy B, Ann Surg Oncol 2021 Weiss A, Ann Surg Oncol 2019

Use of SLNB After NET

- NCDB Analysis: Stage 2-3 HR+/HER2- patients (2012-2015)
  - 2,138 NET vs. 11,014 NAC vs. 79,052 upfront surgery
  - Among N = 8688 cN1 patients with **pN1** disease, use of SLNB only:

    50% after NET

    46% at upfront surgery



	2012	2013	2014	2015
Neoadjuvant endocrine therapy	1.9%	2.2%	2.3%	2.9%
Neoadjuvant chemotherapy	11.5%	11.1%	12.7%	12.1%
Upfront surgery	86.6%	86.7%	85.1%	85.0%

- **Data are needed** to support omission of ALND among patients with positive nodes after NET

- Complexities: no standardized duration/regimen of NET, NET is only a fraction of overall treatment, and prognostic significance of minimal residual disease is uncertain

Weiss A, Ann Surg Oncol 2019

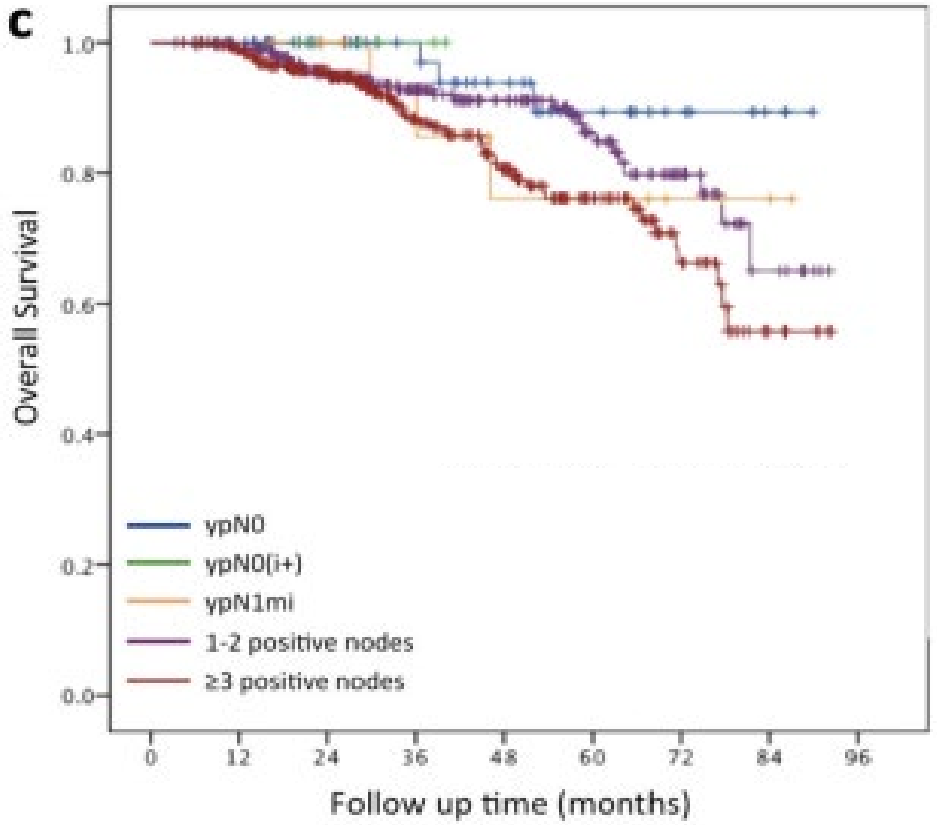
Prognostic Significance of ypN+ After NET: Outcomes Data Are Limited

NCDB Analysis

- NET patients 2010-2016, among cN1 subset (N=773):

Residual Disease	%	5-year OS
ypN0	**10%**	89%
ypN0(i+) or ypN1mi	**4%**	76%
1-2 positive nodes	**38%**	86%
≥3 positive nodes	**49%**	76%

- **No difference in 5-year OS** for NET vs. matched cohort upfront surgery patients for each nodal category
- Suggests: outcomes mirror upfront surgery



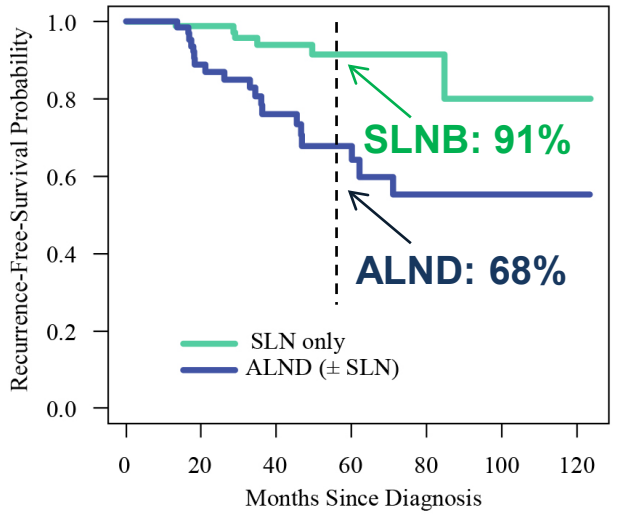
Kantor O, NPJ Breast Cancer 2020

Prognostic Significance of ypN+ After NET: Outcomes Data Are Limited

Mayo Analysis

- NET patients 2008-2019, cN1 subset (N = 84) of which 4.8% had nodal pCR, but:
  - SLNB only: 17%
  - SLNB+ALND: 32%
  - ALND: 51%
- Median of 3.5 positive lymph nodes
- At 35 months follow-up: **no nodal recurrences**
  - Suggests minimal disease after NET may be managed similar to upfront surgery

5-Year Recurrence-Free Survival

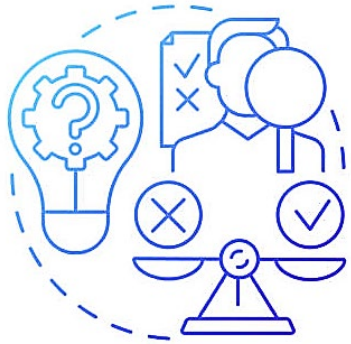


Need long-term data on safety of SLNB alone among cN1 patients after NET

Murphy B, Ann Surg Oncol 2021

Surgical Approach After NET

- Both **breast and nodal pCR are rare** after NET
- NET may permit tumor shrinkage and **facilitate BCS**
- Prognostic significance of residual nodal disease after NET is likely similar to the upfront surgery setting
- **Hypothesize** that axillary management strategies after NET can mirror upfront surgery practices in appropriately selected patients
- **More data are required** to support omission of ALND in patients with residual nodal disease after NET
- Next frontiers: regimens with targeted agents (e.g., CDK4/6i, PI3Ki), biomarkers to predict sensitivity, biologic risk stratification



Conclusions

- **Neoadjuvant chemotherapy (NAC) is not an optimal choice** for cN1 HR+/HER2- disease
  - Low rates of breast and nodal pCR = infrequent downstaging
  - Chemotherapy not always indicated (genomic profiling)
- **Breast and nodal pCR is infrequent** (< 10%) **after NET**
- **Tumor downstaging** may be facilitated by **NET** for some HR+/HER2- patients
- **Upfront SLNB may be preferrable** among those with **limited** nodal burden
- **Suggestions for general approach in non-metastatic HR+/HER2- disease:**
  - **Early-stage node-negative** → upfront surgery
  - **Very locally advanced** → multidisciplinary discussion, most often neoadjuvant therapy (NAC +/- NET)
  - **Node-positive but limited nodal burden (cN1)** → consider upfront surgery
  - **Delay strategy** if needed (pre-operative clearance etc.) → NET

Patient Case

60F with screen-detected RIGHT breast cT1N1 ILC

- **PMH/PSH**: None; bilateral breast implants (augmentation) 2014
- **GYN**: G2P2, menarche at 14, OCP <1 year, post-menopausal (LMP age 51)
- **FH**: Maternal aunt with post-menopausal breast cancer
- **SH**: Former smoker, occasional EtOH, works as secretary

- **Physical exam**:
  - No palpable breast masses bilaterally. Right axilla with a **palpable mobile axillary node**.

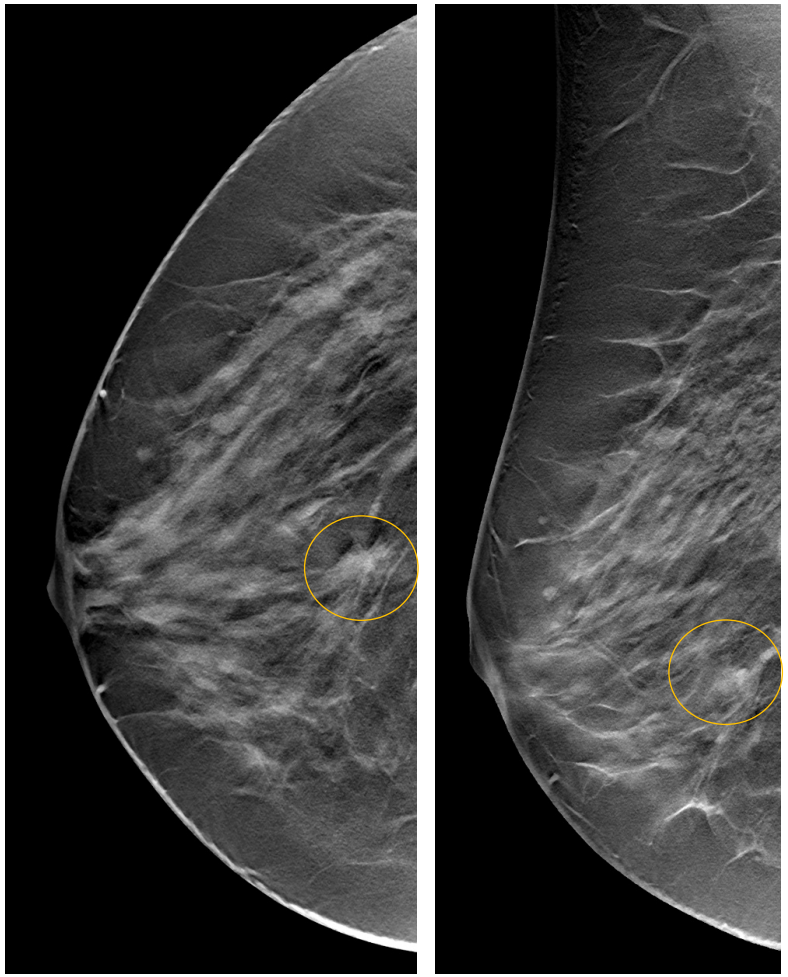
Patient Case

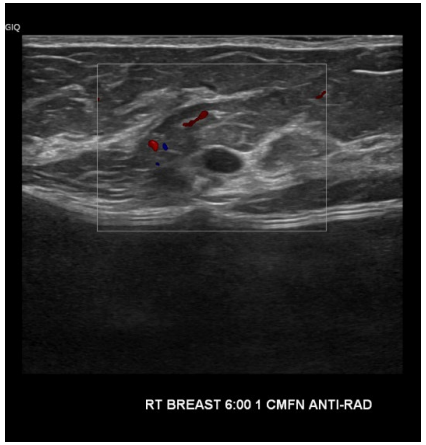
- **Bilateral mammogram/US**:
  - – Left breast with no suspicious findings
  - – Right breast with small mass in central breast posterior depth at 6:00 1cmFN. Axilla contains a single abnormal lymph node with thickened cortex.
- **Right axillary biopsy:**
  - – Invasive lobular carcinoma metastatic to axillary node, ER 98% PR 15% HER2-.
- **Right mammogram/US:**
  - – Persistent central posterior asymmetry, correlating to 0.5cm sonographic mass at 6:00 1cmFN. Single abnormal axillary node.

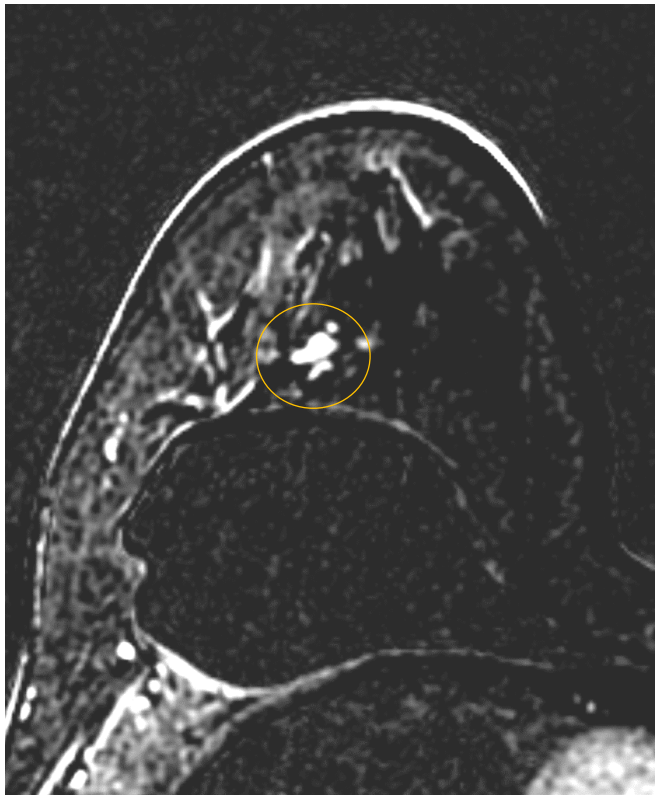
Patient Case

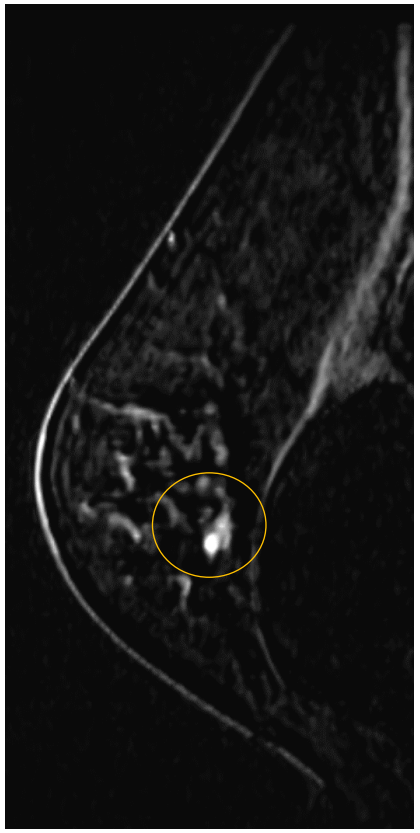
- **Bilateral breast MRI:**
  - Left breast with no suspicious findings.
  - Right breast with 2cm non-mass enhancement in central breast corresponding to mammographic finding; additional two sites of NME in lower breast (1.2cm) and UIQ (0.9cm). Single abnormal axillary node.
- **Right breast 6:00 core biopsy:**
  - Invasive lobular carcinoma metastatic to axillary node, ER 100% PR 30% HER2-.
- **PET/CT:** Known right breast/nodal malignancy, no metastatic disease.
- **Right breast MR-guided biopsies x2:**
  - Lower breast and UIQ: Benign, concordant.

Film Review









Treatment

- Multidisciplinary discussion, proceeded with upfront surgery on trial of SLNB among cN1 HR+/HER2- patients

- **Right lumpectomy/SLNB**:

  – 1.2cm of moderately differentiated ILC, margins negative, ER+/PR+/HER2-, with 2 of 5 SLN positive.

  – Oncotype RS 20

- Received adjuvant XRT, ongoing AI (did not receive chemotherapy)

- Follow-up at 1 year: doing well, NED and excellent functional result (no lymphedema, full ROM)

Thank You


MEMORIAL SLOAN-KETTERING CANCER CENTER
Evelyn H. Lauder Breast Center
300

THE AMERICAN SOCIETY OF Breast Surgeons

ACCC
ASSOCIATION OF CANCER CARE CENTERS™

Nodal Surgery After Neoadjuvant Chemotherapy

Mediget Teshome MD MPH FACS

University of California Los Angeles

Jonsson Comprehensive Cancer Center, David Geffen School of Medicine

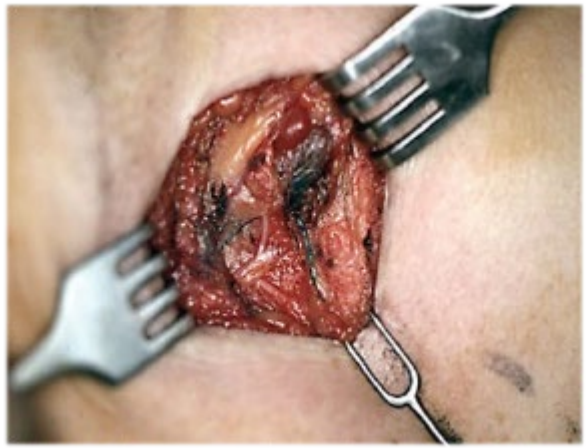
January 29, 2025

Rationale for neoadjuvant chemotherapy (NCT)

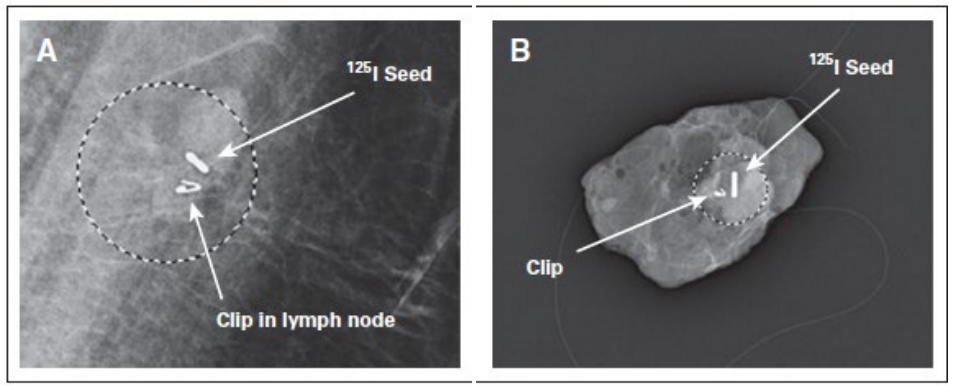
- Downstaging of disease
- *In vivo* assessment of tumor response
- Identification of residual disease
- De-escalation of surgical therapy
- Prognostic of outcome
- Informs adjuvant therapy
  - Systemic therapy
  - Radiation therapy

Axillary surgery after NCT remains highly important

Nodal surgery after neoadjuvant chemotherapy **Operative approaches**

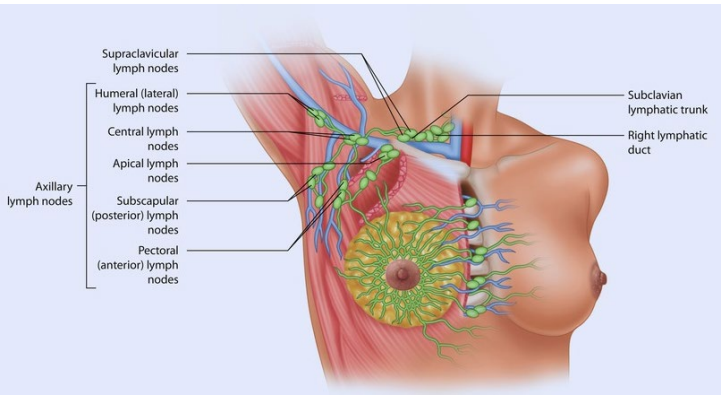


Sentinel lymph node biopsy (SLNB)



Targeted axillary dissection (TAD)

SLNB and excision of clipped (biopsy-proven) node

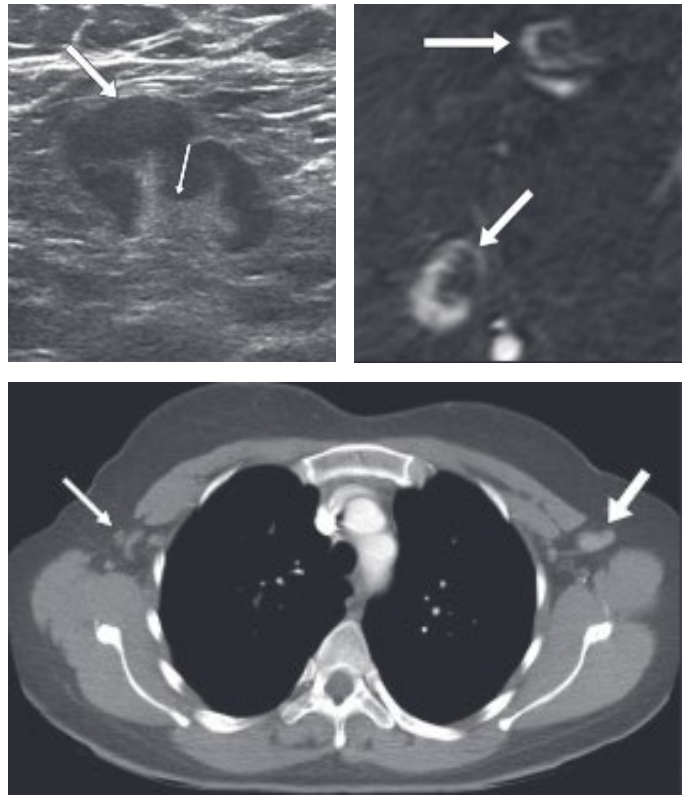


Axillary lymph node dissection (ALND)

Operative Standards for Cancer Surgery, Vol. 1 2015
Caudle et al. J Clin Oncol 2016
Palhazi P. Breast cancer management for surgeons 2018

Nodal surgery after neoadjuvant chemotherapy (NCT) **Key principles**

- Axillary evaluation at presentation & after NCT
  - Clinical exam
  - Axillary Ultrasound, MRI, staging CT
  - Biopsy of suspicious nodes
- Surgical approach
  - Dependent on the extent/burden of axillary disease
  - Independent of subtype
- De-escalation trials in the upfront surgery setting excluded NCT patients, *should not extrapolate to this population*
  - ACOSOG Z11, AMAROS, SENOMAC, SOUND



Sun et al. AJR 2020

Nodal surgery after neoadjuvant chemotherapy (NCT)
Clinical nodal staging

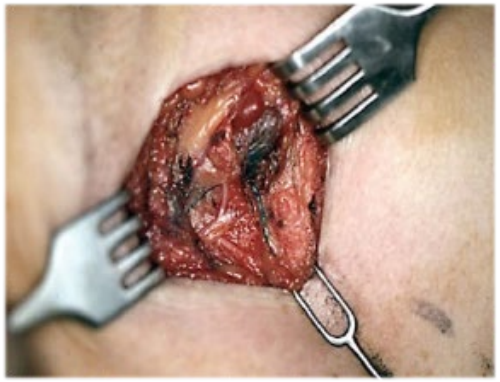
Category	Ipsilateral lymph node involvement
cNX	Not assessed
cN0	None
cN1	Level I/II axilla
cN2	Fixed or matted level I/II axilla Isolated internal mammary
cN3	Infraclavicular Supraclavicular Internal mammary and axillary

- Classified by location of nodal metastasis in contrast to pathologic staging which is classified by number of positive nodes & size of nodal metastasis

Nodal surgery after neoadjuvant chemotherapy (NCT) **cN0**

Sentinel lymph node biopsy (SLNB) is standard of care

- Performed after receipt of NCT
- Dual tracer mapping (blue dye & radioisotope) recommended
- Majority of patients remain ypN0 and require no further surgery
- Approximately 12-18% will be SLN+ (ypN+)
  - Varies by subtype
    - HR+HER2- >> TNBC, HER2+
  - Less common in patients with breast pCR, radiographic CR
  - Excluded from ACOSOG Z11, AMAROS, etc.
  - ALND remains standard of care for these patients

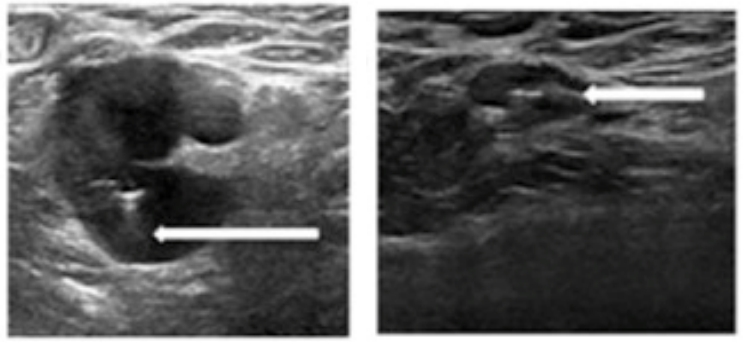


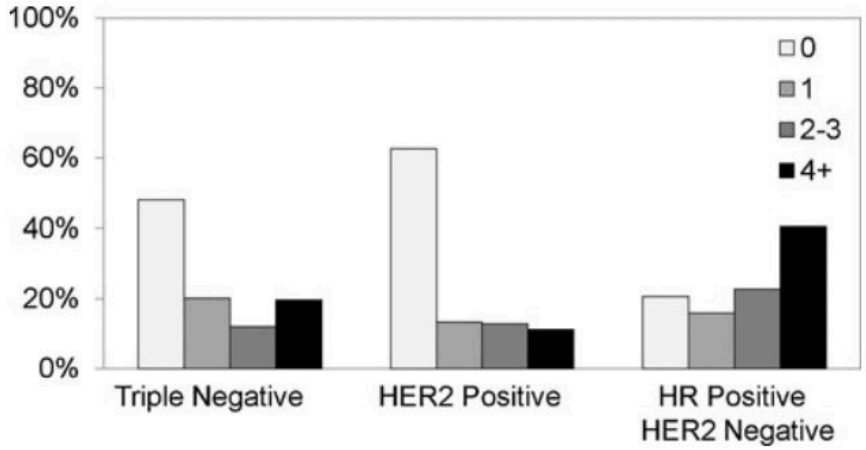
Operative Standards for Cancer Surgery, Vol. 1 2015
Zamborowski et al. Br J Surg 2024
So et al. Ann Surg Oncol 2025

Nodal surgery after neoadjuvant chemotherapy (NCT) **cN1-3**

Axillary surgery dependent on burden of nodal disease at presentation and clinical response to NCT

- Historically all received ALND however, approximately 40-70% will have axillary pCR





Kuerer et al. Ann Surg 1999
Hennessy et al. J Clin Oncol 2005
Boughey et al. Ann Surg 2014

Nodal surgery after neoadjuvant chemotherapy (NCT) **cN1**

Clinical trials evaluating SLNB in cN1 after NCT

- Demonstrated false negative rate (FNR) >10%
- <u>Decreased FNR with</u>
  - Dual mapping technique (blue dye & radioisotope)
  - ≥3 SLNs excised
  - Excision of clipped (biopsy-proven) node
  - IHC evaluation for ITCs (considered ypN+)

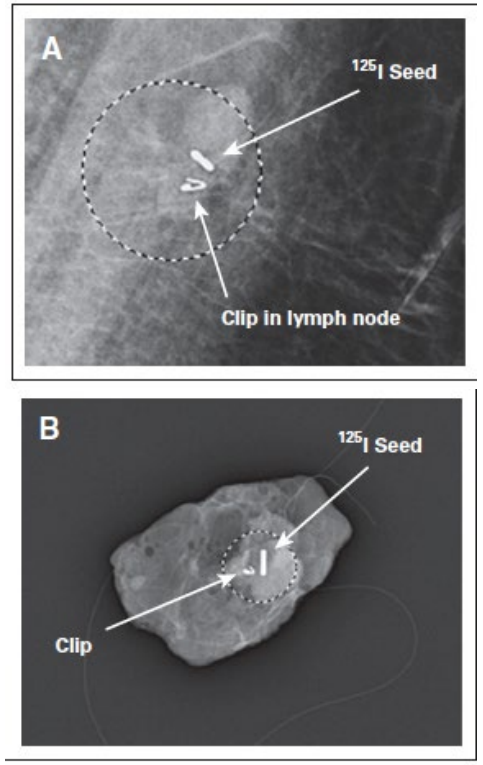
	Axillary pCR	SLN ID rate	Overall FNR	Factors improving FNR	FNR
ACOSOG Z1071 (n=525)	41%	92.9%	12.6%	≥3 SLNs Dual mapping Excision clipped LN IHC evaluation	9.1% 10.8% 6.8% 8.7%
SENTINA Arm C (n=592)	52.3%	80.1%	14.2%	≥3 SLNs Dual mapping	<10% 8.6%
SN FNAC (n=153)	34.5%	87.6%	8.4% (IHC) 13.3% (H&E)	>2 SLNs Dual mapping	4.9% 5.2%

Boughey et al. JAMA 2013, Ann Surg 2016
Kuehn et al. Lancet Oncol 2013
Boileau et al. J Clin Oncol 2015

Nodal surgery after neoadjuvant chemotherapy (NCT) **cN1**

Targeted axillary dissection (TAD)

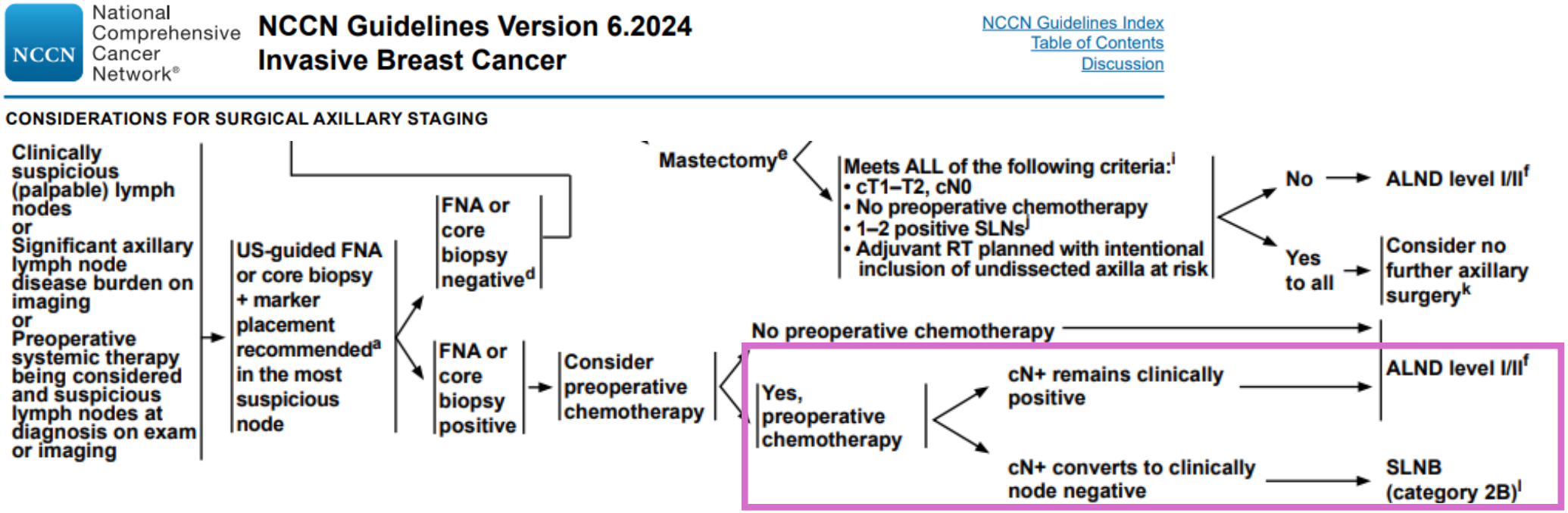
- SLNB and excision of clipped (biopsy proven) axillary node
- Improved false negative rate (FNR)
  - SLN 10.1%
  - Clipped node alone 4.2%
  - TAD 2%
- Clipped node localized because 23% were non-SLN
  - Associated with ≥4 abnormal nodes on initial US



Caudle et al. J Clin Oncol. 2016

Nodal surgery after neoadjuvant chemotherapy (NCT) **cN1 with clinical response**

SLNB/TAD is recommended for nodal staging



[l]*Among patients shown to be N+ prior to preoperative systemic therapy, SLNB has a >10% false-negative rate when performed after preoperative systemic therapy, which can be improved by marking and removing the most suspicious biopsied node, using dual tracers, and by obtaining ≥3 sentinel nodes (targeted axillary lymph node dissection).*
(Caudle AS, et al. J Clin Oncol 2016;34:1072-1078.)

Nodal surgery after neoadjuvant chemotherapy (NCT)
cN1 → ypN0 after SLNB/TAD

ALND omission for patients with axillary pCR (ypN0)

- Low rates of axillary recurrence (0-1.8%) reported in patients with omission of ALND
- Multi-institution retrospective cohort study:
  - 1144 patients treated with SLNB or TAD, median follow up 3.5 years
  - 4 axillary recurrences overall, no difference if SLNB or TAD

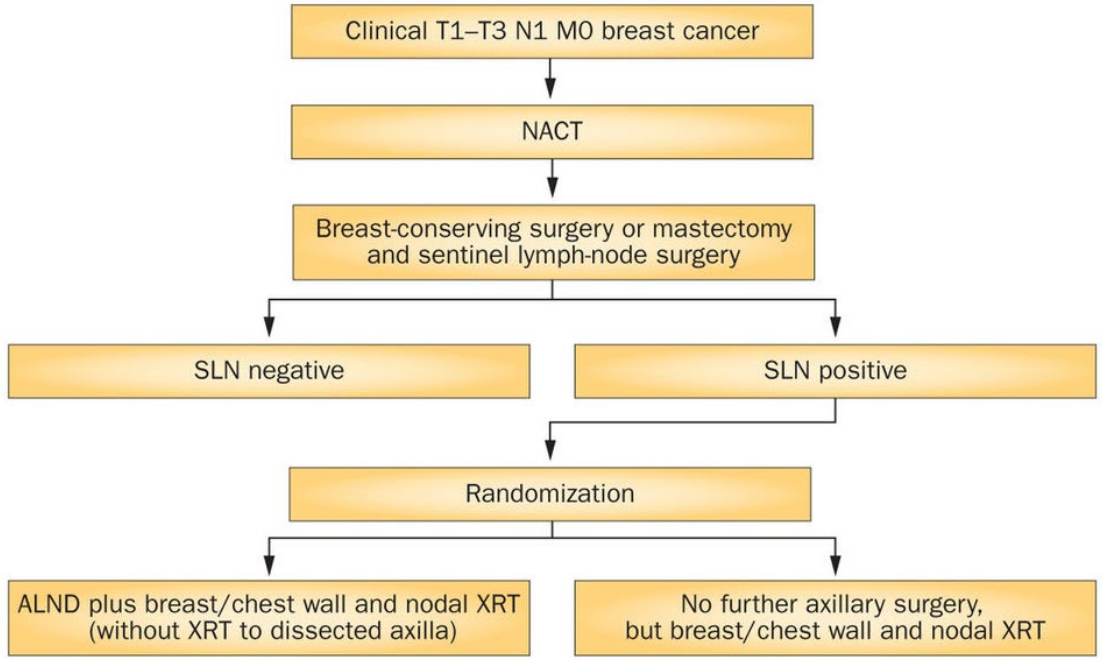
Recurrence type	3 years	5 years
Axillary	0.65%	1.0%
Local regional	1.5%	2.7%
Any invasive	7.5%	10.0%

Kahler et al. EJSO 2020
Piltin et al. Ann Surg Oncol 2020
Barrio et al. Ann Surg Oncol 2021
Martelli et al. Ann Surg 2022
Montagna et al. JAMA Oncol 2024

Nodal surgery after neoadjuvant chemotherapy (NCT)
cN1 → ypN+ after SLNB/TAD

ALND for residual axillary disease (ypN+)

- Alliance A11202
  - cN1 –> ypN+ (micro or macrometastasis)
  - SLNB/TAD
  - Randomized to ALND+RNI vs RNI alone (including axilla)
- Awaiting results to assess impact of omission of ALND on oncologic outcomes

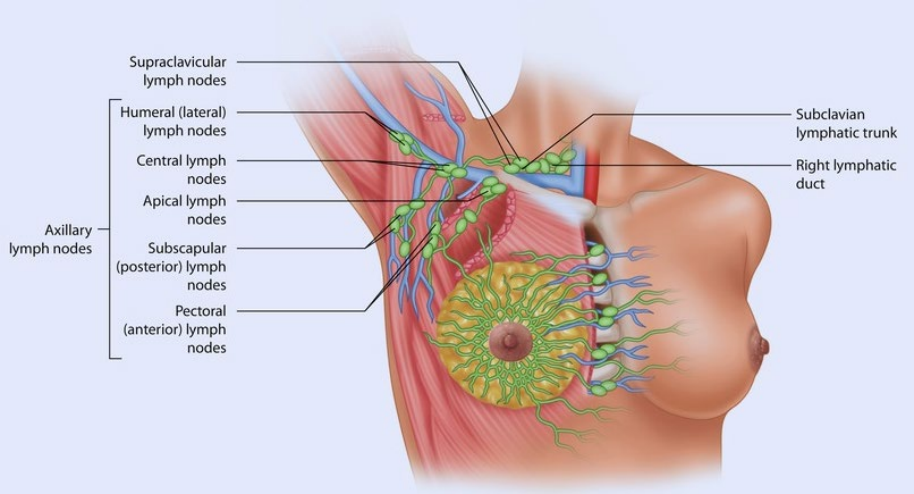


https://clinicaltrials.gov/ct2/show/NCT01901094

Nodal surgery after neoadjuvant chemotherapy (NCT) **cN2/3**

ALND remains standard of care

- Accuracy of SLNB or TAD is unknown in patients with higher burden of disease at presentation

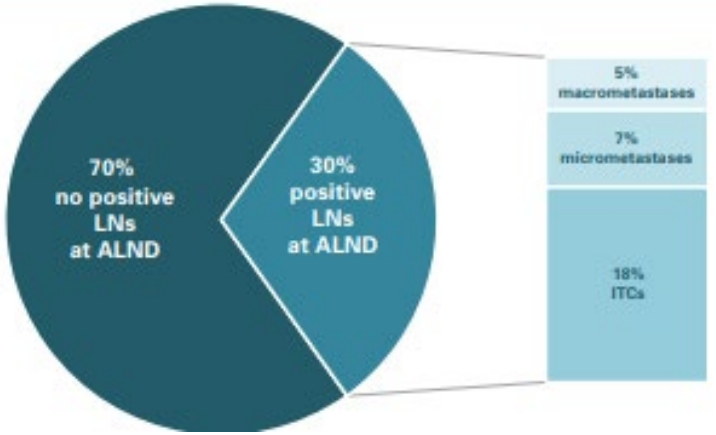


Palhazi P. Breast cancer management for surgeons 2018

Nodal surgery after neoadjuvant chemotherapy (NCT) **ypN0(i+)**

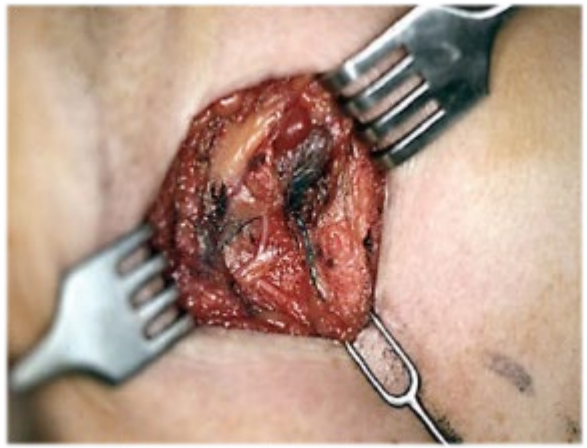
Residual isolated tumor cells (ITCs) after NCT

- Classified as pathologically node-positive in contrast to upfront surgery setting
- Prevalence 2.8%, increased risk of recurrence compared to ypN0 (i-)
- OPBC-05/ICARO study:
  - 583 patients ypN0(i+) on SLN-TAD-MARI, cT1-4, N0-3
  - 31% ALND, 70% received nodal radiation
  - 3-year rate of recurrence
    - Any axillary 2%, Isolated axillary 0.58%
    - No difference based on receipt of ALND



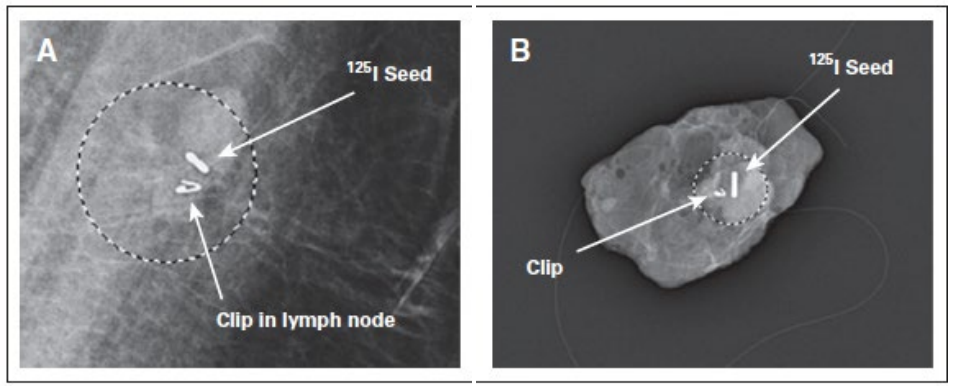
Wong et al. Ann Surg Oncol 2019
Montagna et al. J Clin Oncol 2024

Nodal surgery after neoadjuvant chemotherapy
Operative approaches & indications



Sentinel lymph node biopsy (SLNB)

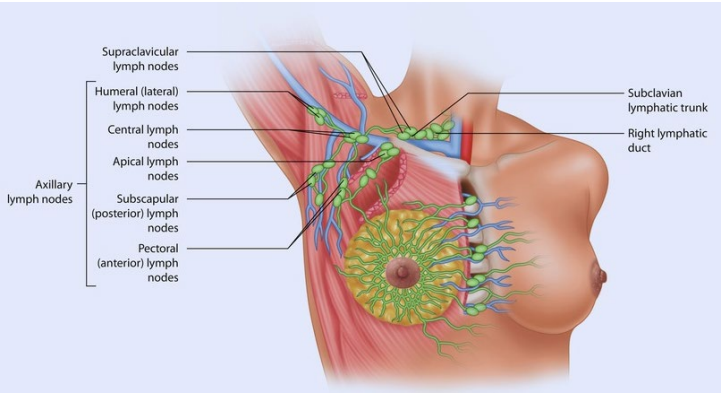
cN0
cN1 with clinical response
(*dual mapping, 3 SLNs)



Targeted axillary dissection (TAD)

SLNB and excision of clipped (biopsy-proven) node

cN1 with clinical response



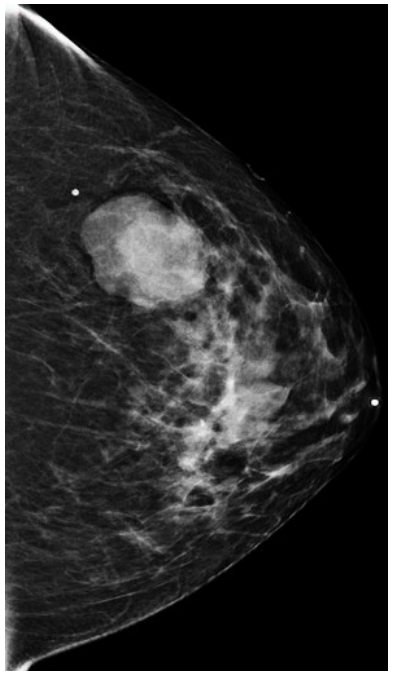
Axillary lymph node dissection (ALND)

cN2/N3
Any cN with residual disease (ypN+)

Operative Standards for Cancer Surgery, Vol. 1 2015
Caudle et al. J Clin Oncol 2016
Palhazi P. Breast cancer management for surgeons 2018

Nodal surgery after neoadjuvant chemotherapy
Case Presentation

- 41-year-old woman with left breast mass
- Exam: breast mass palpable, no adenopathy
- Imaging
  - Mammogram & breast US: 4.2 x 3.1 cm mass left breast 3 o'clock position, 5 cm from nipple
  - Axillary US: 2 suspicious nodes (level I)
- Biopsy
  - Breast: invasive ductal carcinoma, grade 2, ER- PR- HER2+
  - Axillary node: positive for malignancy, clip placed
- Genetic testing: negative

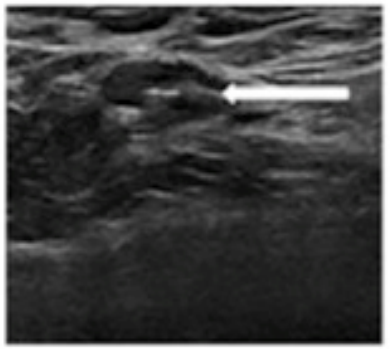


cT2N1M0

Nodal surgery after neoadjuvant chemotherapy
Case Presentation

- 41-year-old woman with left cT2N1M0 invasive ductal carcinoma, grade 2, ER- PR- HER2+

- After multidisciplinary discussion, started on neoadjuvant TCHP
- Completed 6 cycles of TCHP
- Post-treatment imaging shows clinical response
- Elects for breast conserving surgery and TAD
- Breast and axillary node localized for excision



Nodal surgery after neoadjuvant chemotherapy **Case Presentation**

- 41-year-old woman with left cT2N1M0 invasive ductal carcinoma, grade 2, ER- PR- HER2+ treated with TCHP x 6 cycles and clinical response

- Receives breast conserving surgery and TAD
- Nodal pathology (including clipped node) shows **3 negative axillary SLNs**

No further surgery
Adjuvant radiation
Adjuvant HP

Nodal surgery after neoadjuvant chemotherapy **Case Presentation**

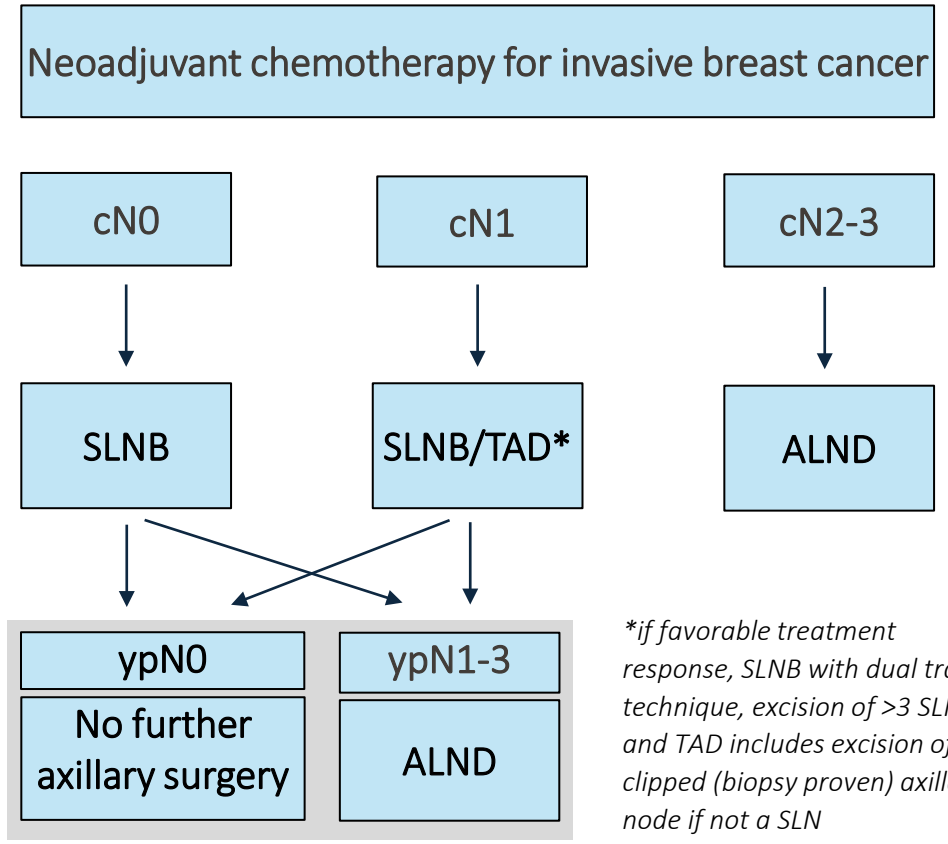
- 41-year-old woman with left cT2N1M0 invasive ductal carcinoma, grade 2, ER- PR- HER2+ treated with TCHP x 6 cycles and clinical response

- Receives breast conserving surgery and TAD
- Nodal pathology (including clipped node) shows **2 of 3 positive axillary SLNs (micrometastasis)**

ALND
Adjuvant radiation
Adjuvant TDM-1

Nodal surgery after neoadjuvant chemotherapy (NCT) **Summary**

- Pathologic assessment of axilla after NCT remains critically important
  - Informs prognosis
  - Adjuvant treatment planning
- Pre- and post-NCT imaging & clinical evaluation is essential
- For cN1, SLNB/TAD can be utilized, operative technique facilitates improved accuracy
- If ypN+, ALND is standard of care
- Multidisciplinary discussion recommended



**if favorable treatment response, SLNB with dual tracer technique, excision of >3 SLNs and TAD includes excision of the clipped (biopsy proven) axillary node if not a SLN*

Thank you!

Mediget Teshome MD MPH FACS
mteshome@mednet.ucla.edu

SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research
DECEMBER 10–13, 2024
HENRY B. GONZALEZ CONVENTION CENTER • SAN ANTONIO, TX

COMET & INSEMA:

Optimizing locoregional treatment of low-risk breast cancer

Puneet Singh, MD, MS, FACS, FSSO
UT MD Anderson Cancer Center, Houston, TX
2.20.2025

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center®

Disclosure Information

Puneet Singh

I have the following relevant financial relationships to disclose:

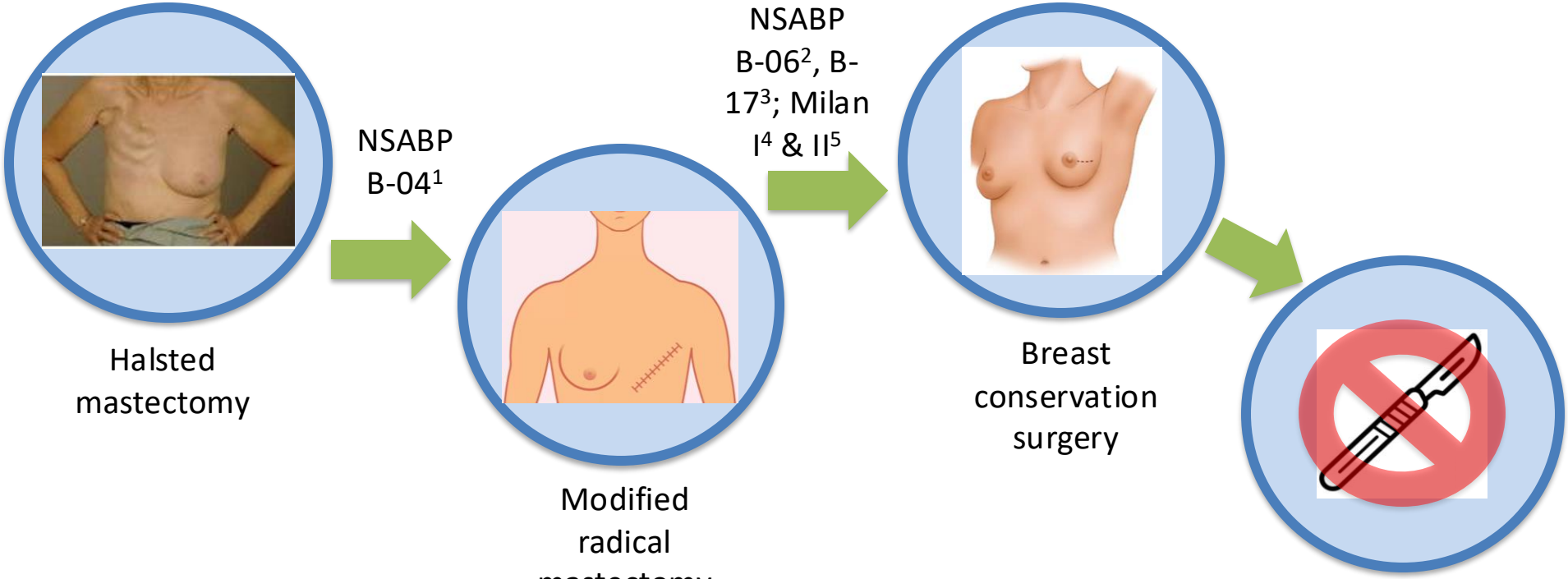
Grant/Research support from: UT MD Anderson Cancer Center, Houston, TX

Honoraria from: Physicians' Education Resource

Some slides are courtesy of the presenters

Presentation has been updated to include additional slides since SABCS 2024

De-escalation of breast surgery



[1]Fisher et al. N Engl J Med. 1985;312:674-81.
[2]Fisher et al. *N Engl J Med*. 2002;347:1233-41.
[3]Fisher et al. *Semin Oncol*. 2001;28:400-18.
[4]Veronesi et al. *Eur J Cancer*. 1990;26:668-70.
[5]Veronesi et al. *N Engl J Med*. 2002;347:1227-32.

JAMA | Preliminary Communication

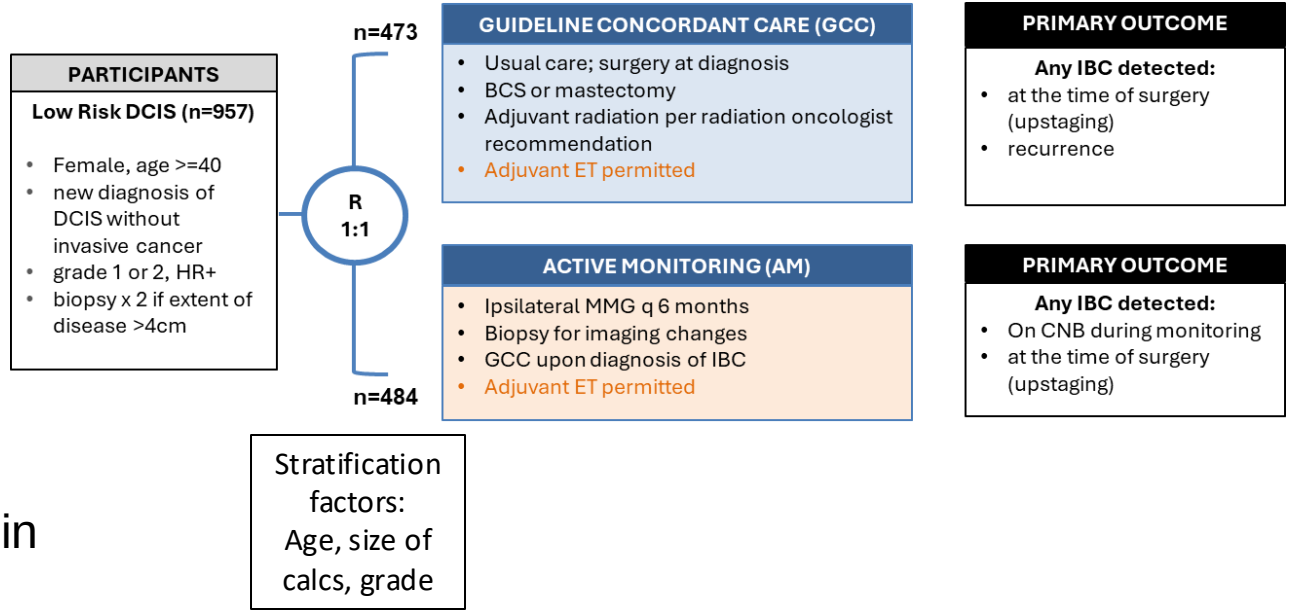
Active Monitoring With or Without Endocrine Therapy for Low-Risk Ductal Carcinoma In Situ
The COMET Randomized Clinical Trial

E. Shelley Hwang, MD, MPH; Terry Hyslop, PhD; Thomas Lynch, PhD; Marc D. Ryser, PhD; Anna Weiss, MD; Anna Wolf, BA; Kelsey Norris, MPH; Meredith Witten, MD; Lars Grimm, MD; Stuart Schnitt, MD; Sunil Badve, MD; Rachel Factor, MD; Elizabeth Frank, MA; Deborah Collyar, BSc; Desiree Basila, MSc; Donna Pinto, BA; Mark A. Watson, MD, PhD; Robert West, MD, PhD; Louise Davies, MD, MS; Jenny L. Donovan, PhD; Ayako Shimada, MS; Yutong Li, MS; Yan Li, PhD; Antonia V. Bennett, PhD; Shoshana Rosenberg, ScD; Jeffrey Marks, PhD; Eric Winer, MD; Marc Boisvert, MD; Armando Giuliano, MD; Kelsey E. Larson, MD; Kathleen Yost, MD; Priscilla F. McAuliffe, MD; Amy Krie, MD; Nina Tamirisa, MD; Lisa A. Carey, MD; Alastair M. Thompson, MBChB, MD; Ann H. Partridge, MD, MPH; for the COMET Study Investigators

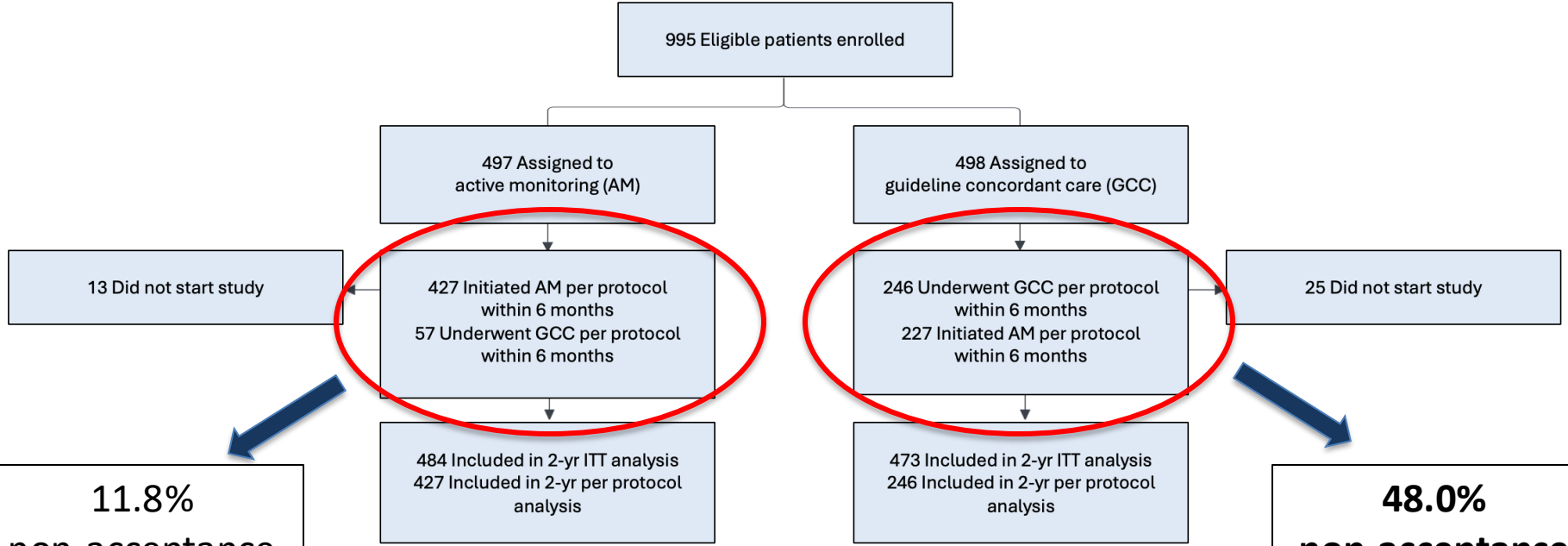
JAMA. doi:10.1001/jama.2024.26698
Published online December 12, 2024.

GS2-05: The COMET Study

- Randomized, pragmatic non-inferiority trial from 2017–2022
- **Primary objective: 2-year ipsilateral invasive cancer rate**
  - Estimated 10% rate in GCC arm
  - <5% non-inferiority margin



GS2-05: The COMET Study



* 30% non-acceptance to allocation estimated

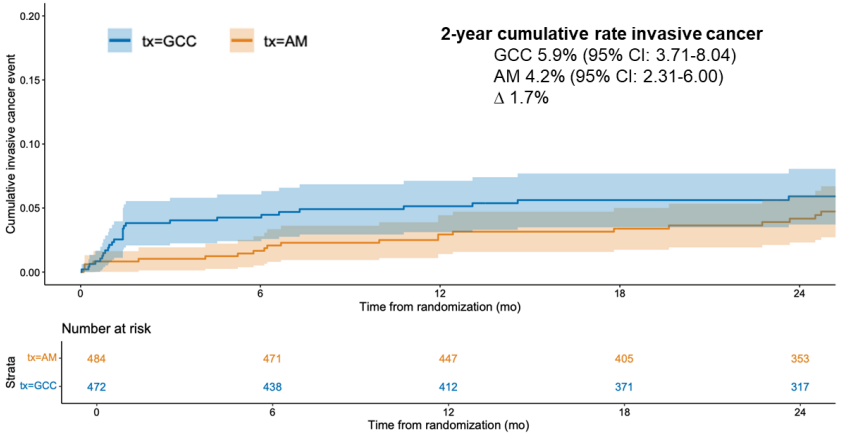
Patient Characteristics: ITT groups

	All Patients N=957 (100%)	GCC N=473 (49.4%)	AM N=484 (50.6%)
Age			
<55	226 (23.6%)	114 (24.1%)	112 (23.1%)
55-65	328 (34.3%)	164 (34.7%)	164 (33.9%)
>65	403 (42.1%)	195 (41.2%)	208 (43%)
Race			
Black	150 (15.7%)	70 (14.8%)	80 (16.5%)
White	718 (75%)	359 (75.9%)	359 (74.2%)
Unknown/Other	89 (9.3%)	44 (9.3%)	45 (9.3%)
DCIS Grade at Diagnosis			
1	252 (26.3%)	127 (26.8%)	125 (25.8%)
2	705 (73.7%)	346 (73.2%)	359 (74.2%)
Comorbidities--any			
No	323 (33.8%)	175 (37%)	148 (30.6%)
Yes	540 (56.4%)	256 (54.1%)	284 (58.7%)
Unknown	94 (9.8%)	42 (8.9%)	52 (10.7%)

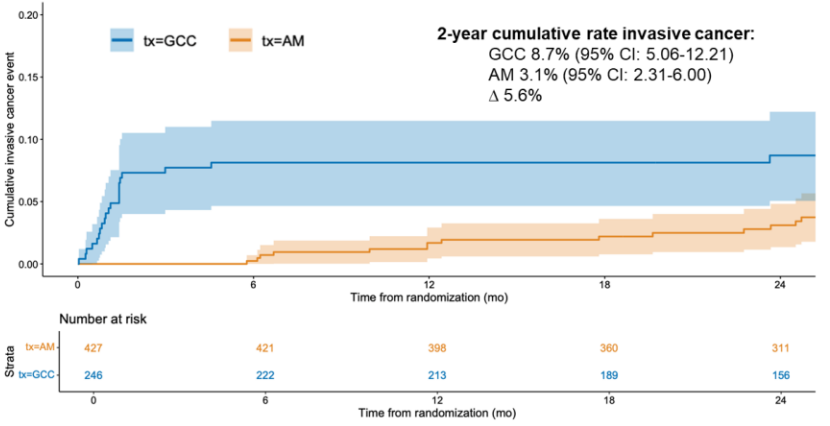
GS2-05: The COMET Study

- Non-inferiority of AM compared to GCC in both analyses
  - Majority of invasive cancers in GCC arm were due to upstage

ITT



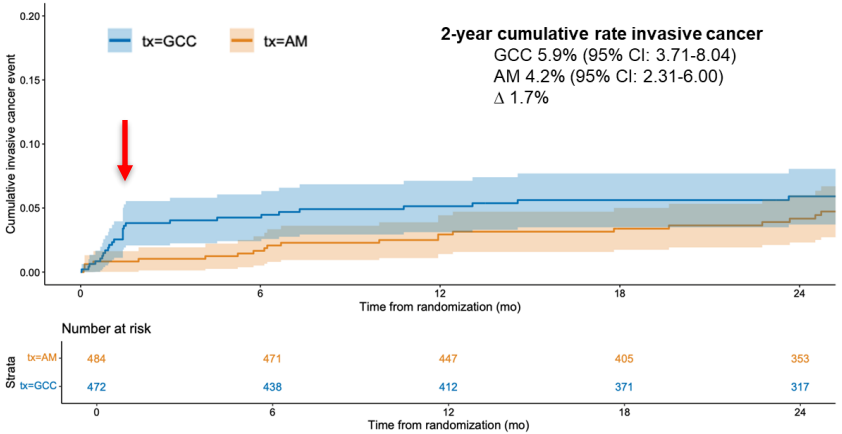
PP



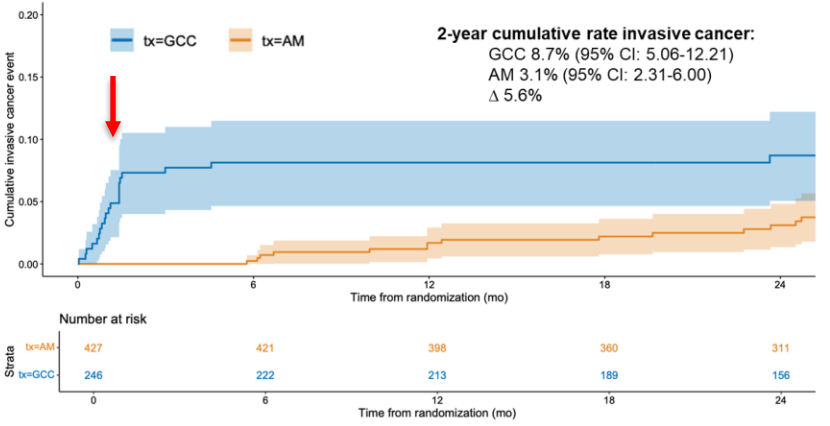
GS2-05: The COMET Study

- Non-inferiority of AM compared to GCC in both analyses
  - Majority of invasive cancers in GCC arm were due to upstage

ITT



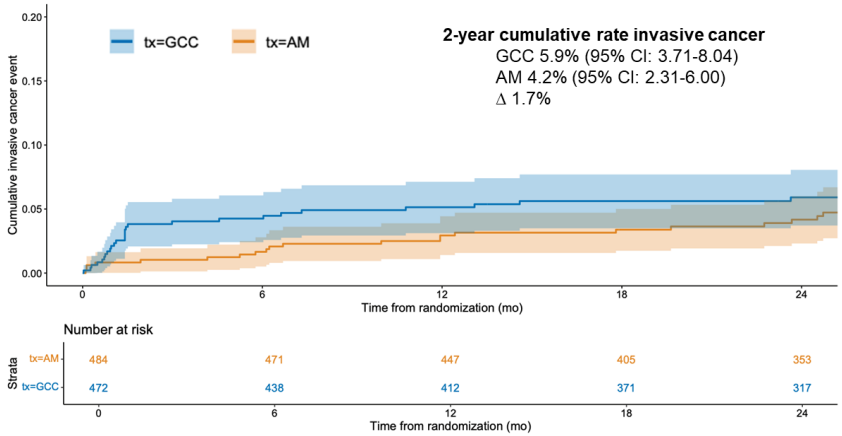
PP



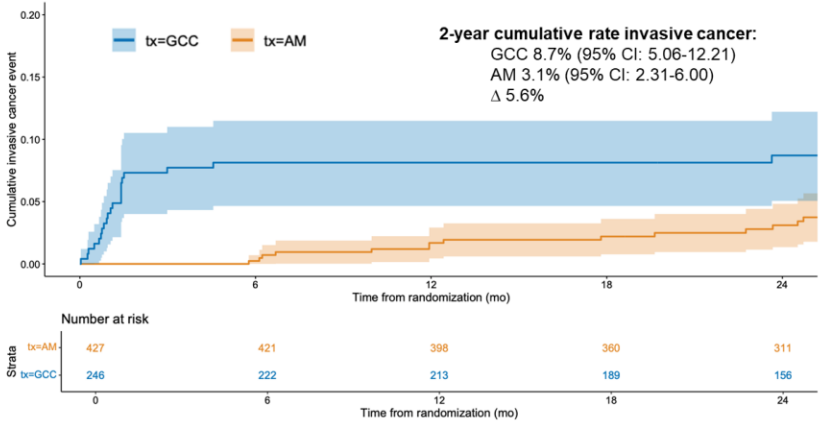
GS2-05: The COMET Study

- Non-inferiority of AM compared to GCC in both analyses
  - Majority of invasive cancers in GCC arm were due to upstage
- 26.6% GCC vs 7.4% AM received RT
- 65.5% GCC vs 71.3% AM received any ET in 2 years
- Majority of invasive cancers small (mean 0.45cm, 0.23−1.1)
- 10.5% vs 1.8% mastectomy rate in GCC vs AM

ITT



PP



SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research

JAMA Oncology | Original Investigation

Patient-Reported Outcomes for Low-Risk Ductal Carcinoma In Situ
A Secondary Analysis of the COMET Randomized Clinical Trial

Ann H. Partridge, MD, MPH; Terry Hyslop, PhD; Shoshana M. Rosenberg, ScD, MPH; Antonia V. Bennett, PhD; Sarah Drier, MPH; Mattias Jonsson; Ayako Shimada, MS; Yutong Li, MS; Yan Li, PhD; Thomas Lynch, PhD; Elizabeth Frank, MA; Deborah Collyar, BS; Desiree Basila, MSc; Donna Pinto, BA; Anna Weiss, MD; Anna Wolf, BA; Kelsey Norris, MPH; Meredith Witten, MD; Marc Boisvert, MD; Armando Giuliano, MD; Kelsey E. Larson, MD; Kathleen Yost, MD; Priscilla F. McAuliffe, MD; Amy Krie, MD; Nina Tamirisa, MD; Sonja Darai, MPH; Lisa Carey, MD; Alastair Thompson, MBChB; E. Shelley Hwang, MD, MPH; for the COMET Study Consortium

JAMA Oncol. doi:10.1001/jamaoncol.2024.6556
Published online December 12, 2024.

GS2-06: The COMET Study

- Patient-reported outcomes (PROs) prospectively collected at baseline, 6, 12, 24 months
- Validated questionnaires evaluating:
  - Health-related quality of life
  - Psychological/emotional symptoms
  - DCIS treatment-related symptoms
- 99.5% completed at least 1 survey with responses at each timepoint > 83%

Survey Measures: 3 Domains

Health-Related QOL

SF-36

- 8 domains: general health, physical functioning, role physical, role emotional, social functioning, bodily pain, vitality, mental health
- Mental and Physical Component Scores (MCS and PCS)

EQ-5D-5L

- 5 functional dimensions
- Visual analog scale

Psychological/ Emotional

State Trait Anxiety Inventory (**STAI**)

Center for Epidemiologic Studies Depression Scale-10 (**CES-D-10**)

Quality of Life in Adult Cancer Survivors (**QLACS**)

- 4 items adapted to worries about DCIS

DCIS Treatment-Related Symptoms

Breast Cancer Prevention Trial (**BCPT**) Symptom Checklist (modified)

- 8 symptom clusters: hot flashes, nausea, bladder control, vaginal problems, musculoskeletal pain, cognitive problems, weight problems, arm problems

Breast Cancer Pain Questionnaire (**BCPQ**)

Brief Pain Inventory (**BPI**)

GS2-06: The COMET Study PROs

QOL

- No differences in general health, mental and physical component scores, QOL
- **Physical functioning differed by group over time (p=0.008)**

Psychological/emotional symptoms

- Low levels of anxiety & depression though increased in both groups over time
- **No differences in worry about DCIS between baseline and 24 months**

DCIS treatment-related symptoms

- Low levels of menopausal and body image symptoms
- **Mean pain higher at baseline in AM group but higher in GCC group at 24 months (p=0.09)**

Per protocol analysis showed worse arm symptoms at 6 & 12 mos and pain in GCC group but improved over time

Active surveillance for DCIS

- Significant interest with multiple trials evaluating AS

COMET (USA)	LORIS (UK)	LORD (The Netherlands)
2017-2022	2014-2020	2017-
≥ 40 years	≥ 46 years	≥ 45 years
Mammo-detected calcifications	Mammo-detected calcifications	Mammo-detected calcifications
Low to intermediate grade	Low to intermediate grade	Low to intermediate grade
ER+	ER+ or ER-	ER+
Accrued N=995 (goal 1200)	Accrued N=227 (Goal 932)	Goal N=2500
2-yr ipsilateral invasive ca rate	5-yr ipsilateral invasive ca free survival rate	10-yr ipsilateral invasive ca free percentage

Wheelwright et al. *Trials*. 2023;24:670. Schmitz et al. *Eur J Cancer*. 2023;192:113276.

LORD experience

- In 2020, trial design was changed to a patient preference model due to slow accrual (unwillingness to accept randomization)
- n=377 → 76% active surveillance, 24% standard care

Patient Reported Motives for Preference

Active Surveillance	Standard Care
• Treatment not yet necessary (59%)	• Cancer worry (51%)
• High level of trust (39%)	• Perceived certainty (29%)
• Avoiding side effects (30%)	• Seeking closure (13%)

Schmitz et al. *Eur J Cancer.* 2023;192:113276.

Slide courtesy of Dr. Olga Kantor

GS2-05 & GS2-06: The COMET Study

- Low rate of 2-year invasive cancer: 5.9% GCC vs 4.2% AM
- Similarly small invasive cancer and nodal status between groups
- Overall PROs comparable between the groups over time in both per protocol and intention to treat analyses
  - No significant negative impact in either group over 2 years

Additional considerations for active surveillance of DCIS

- Longer follow up needed – pre-specified analyses at 5 and 7 years
- 48% of patients on GCC did not receive per protocol treatment
  - Indication of significant patient interest in active surveillance of DCIS
- Role of endocrine therapy in AM
- Frequency of additional imaging and biopsies with AM and associated healthcare costs
- Translational endpoints including ongoing development of a genomic signature to identify high-risk DCIS using the COMET & LORD cohorts

Take home points for active surveillance of DCIS

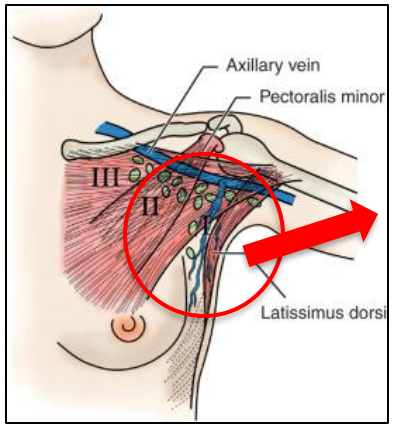
- Need more evidence to become standard of care

> "The overarching hypothesis of the study is that management of low-risk DCIS using an active monitoring (AM) approach does not yield inferior cancer or quality of life outcomes compared to surgery."

- Data support the importance of continuing evaluation of AM as a treatment strategy for low-risk DCIS
- Informing patients and actively engaging in shared decision-making necessary
- May be appropriate in select patients such as those who are high-risk for surgery

De-escalation of axillary surgery

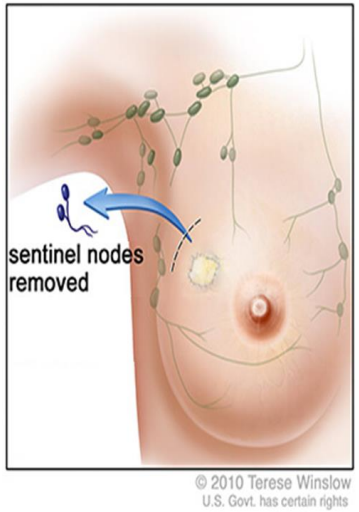
ALND



NSABP B-32[1]

ACOSOG Z0011[2]
AMAROS[3]
IBCSG 23-01[4]
SENOMAC[5]

SLNB



No axillary surgery?

- SLNB has always been a staging technique rather than a therapeutic intervention

[1]Krag DN et al. *Lancet Oncol.* 2010;11:927-33.
[2]Giuliano AE et al. *JAMA.* 2017;318:918-26
[3]Bartels et al. *J Clin Oncol.* 2023;41:2159-65.
[4]Galimberti V et al. *Lancet Oncol.* 2018;19(10):1385-93.
[5]de Boniface et al. *N Engl J Med.* 2024;25;1222-1230.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

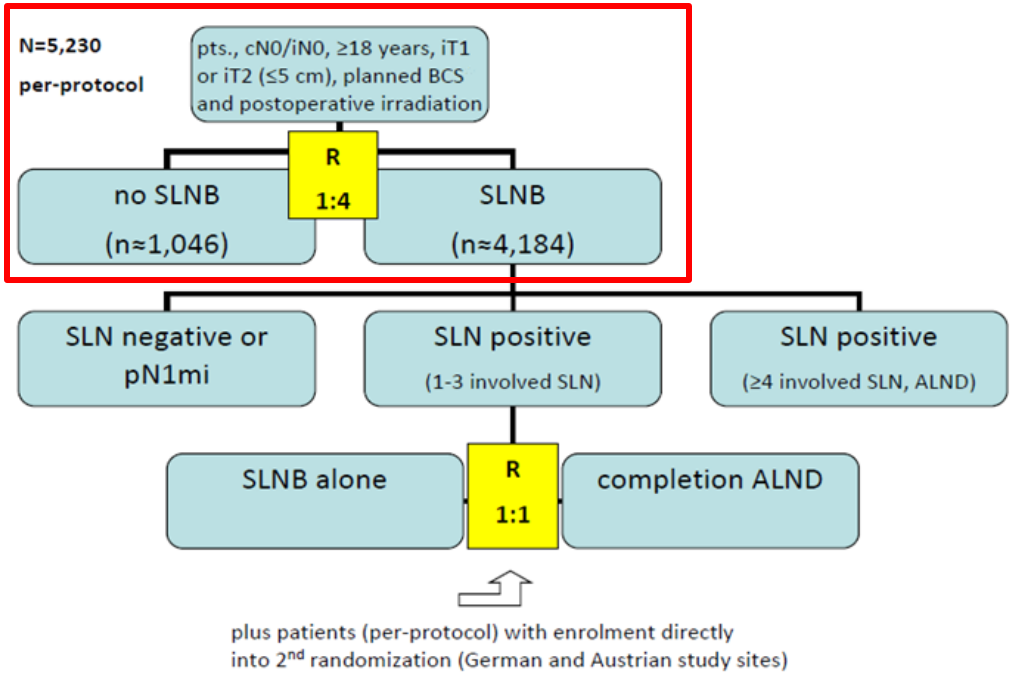
Axillary Surgery in Breast Cancer — Primary Results of the INSEMA Trial

T. Reimer, A. Stachs, K. Veselinovic, T. Kühn, J. Heil, S. Polata, F. Marmé, T. Müller, G. Hildebrandt, D. Krug, B. Ataseven, R. Reitsamer, S. Ruth, C. Denkert, I. Bekes, D.-M. Zahm, M. Thill, M. Golatta, J. Holtschmidt, M. Knauer, V. Nekljudova, S. Loibl, and B. Gerber

This article was published on December 12, 2024, at NEJM.org.

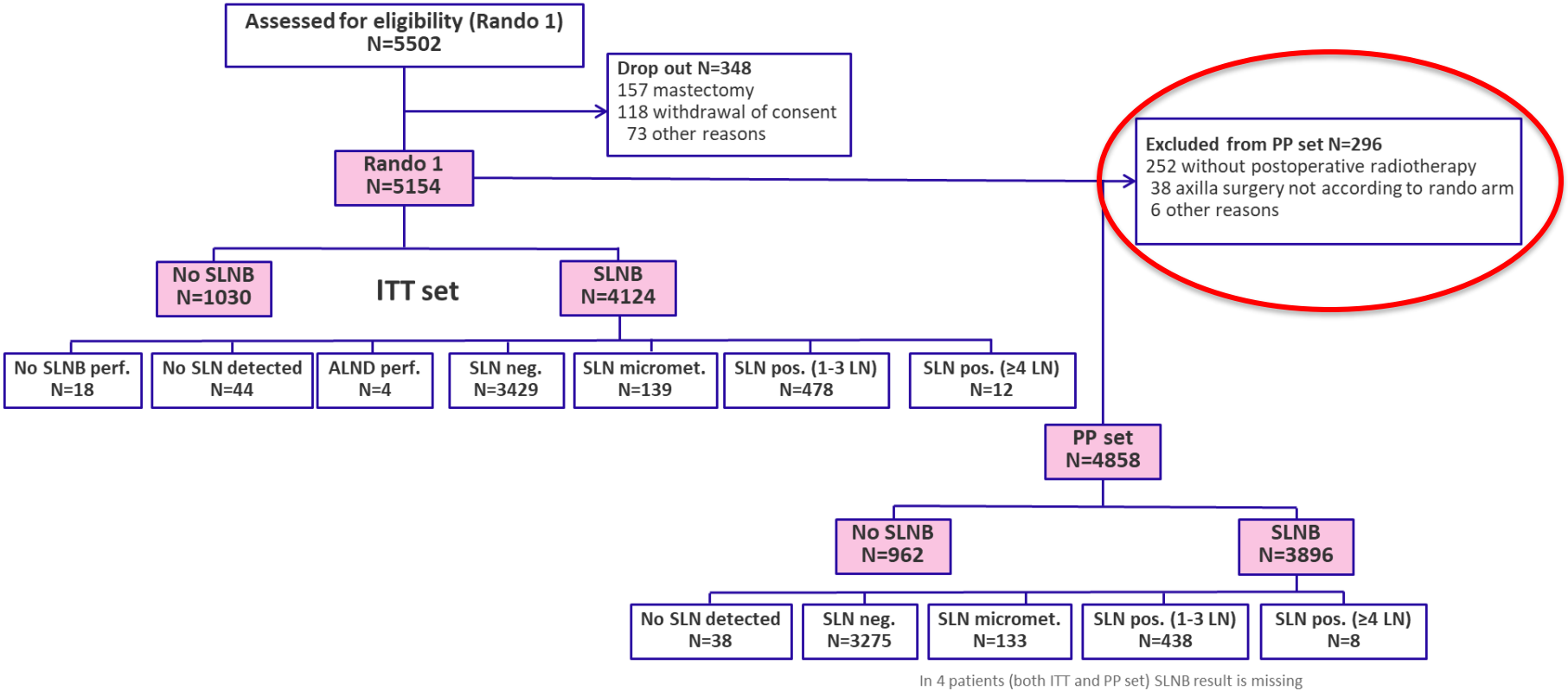
DOI: 10.1056/NEJMoa2412063

GS2-07: The INSEMA Study



- Enrolled patients from Germany and Austria from 2015−2019
- Non-inferiority randomized design
- **Primary objective:** to compare invasive disease-free survival (iDFS) between no axillary surgery and SLNB
  - Non-inferiority demonstrated if HR 1.271 excluded using Cox proportional hazard model
- Time-driven analysis at 5.5yrs follow up of last enrolled patient

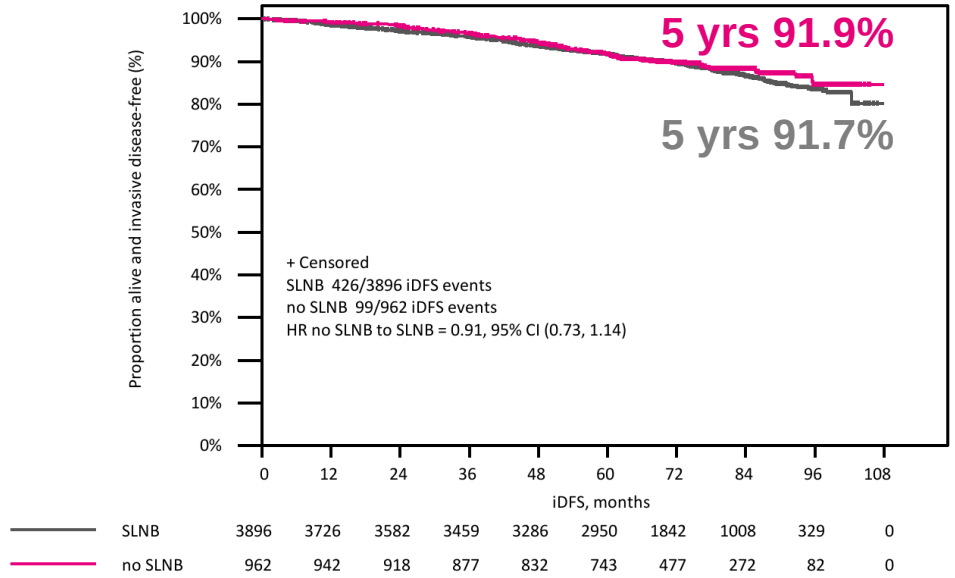
GS2-07: The INSEMA Study



Baseline Characteristics, PP set

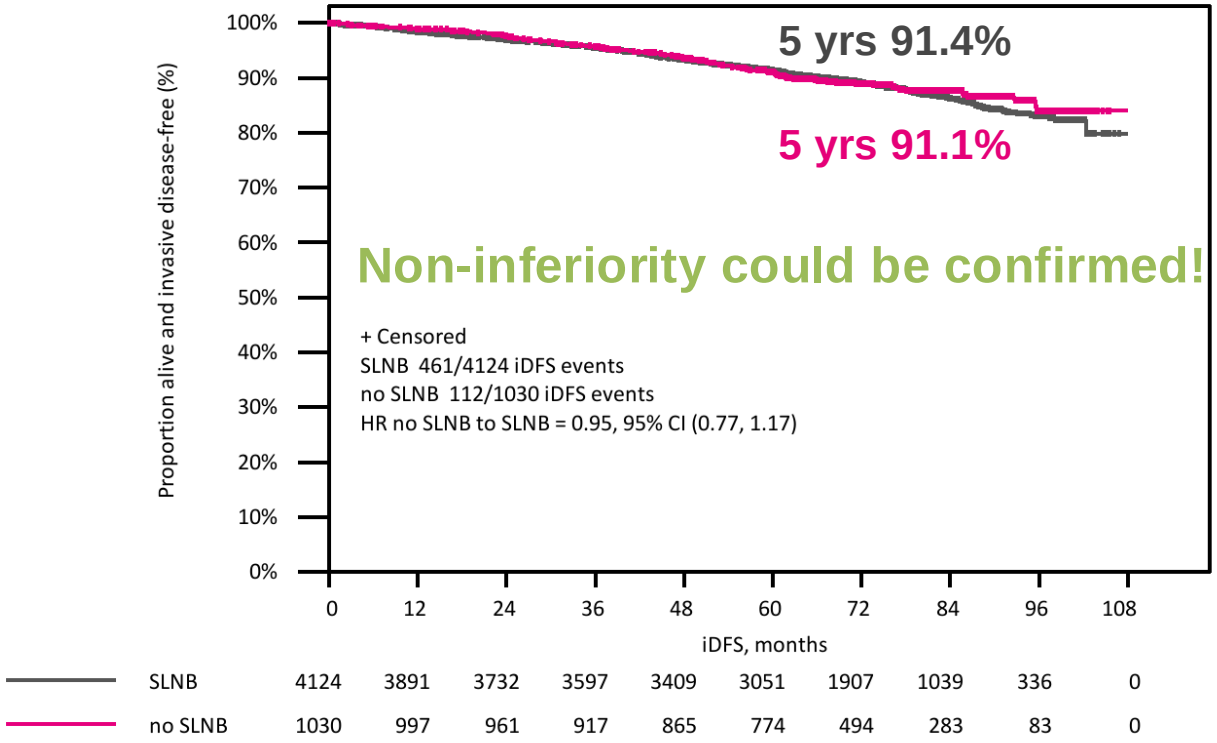
Parameter	Category	No SLNB N=962 N(%)	SLNB N=3896 N(%)
Age (strat.)	**<65 years**	**583 (60.6)**	**2387 (61.3)**
	≥65 years	**379 (39.4)**	**1509 (38.7)**
Tumor size (strat.)	**≤2 cm**	**871 (90.5)**	**3521 (90.4)**
	>2 cm	**91 (9.5)**	**375 (9.6)**
Grading (strat.)	**G1**	**372 (38.7)**	**1463 (37.6)**
	G2	**552 (57.4)**	**2294 (58.8)**
	G3	**38 (3.9)**	**139 (3.6)**
Tumor type	NST	726 (75.5)	2828 (72.6)
	Invasive/mixed lobular carcinoma	125 (13.0)	491 (12.6)
	other	111 (11.5)	576 (14.8)
ER/PgR	both negative	15 (1.6)	58 (1.5)
	ER and/or PgR positive	946 (98.4)	3835 (98.5)
HER2 status	negative	914 (95.4)	3755 (96.7)
	positive	44 (4.6)	130 (3.3)

GS2-07: The INSEMA Study

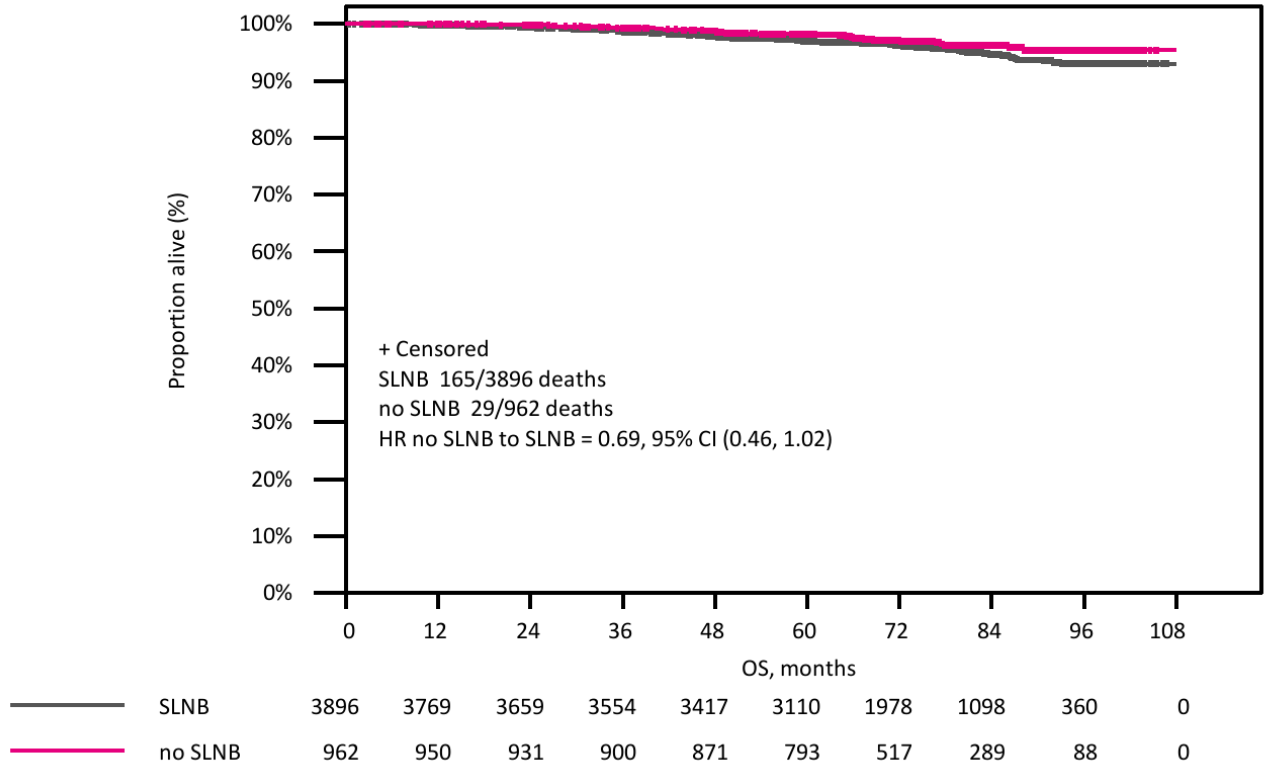


- Per protocol analysis
- Time-driven since fewer events than predicted
- Median follow up: 73.6 months
- HR 0.91 (95% CI 0.73-1.14)
- **No SLNB non-inferior to SLNB**

Results: iDFS results of the ITT set



Results: OS results of the PP set

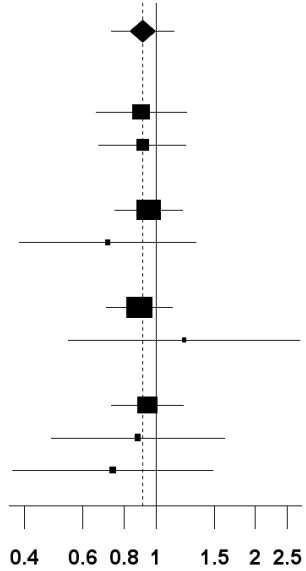


5 yrs 98.2%

5 yrs 96.9%

Results: iDFS results in subgroups

Subgroup	N patients	Hazard Ratio (95% CI)	p-Value	Test for Interaction
Overall	4858	.913 (.734, 1.14)	0.417	
Age as stratified				0.954
< 65	2970	.903 (.658, 1.24)	0.527	
>= 65	1888	.911 (.673, 1.23)	0.546	
TS as stratified				0.389
<= 2cm	4392	.951 (.752, 1.20)	0.674	
>2cm	466	.715 (.387, 1.32)	0.285	
Grading as stratified				0.446
G1/G2	4682	.891 (.710, 1.12)	0.320	
G3	176	1.22 (.545, 2.72)	0.631	
Histological tumor type				0.806
Invasive carcinoma NST	3554	.943 (.735, 1.21)	0.647	
Invasive or mixed lobular carcinoma	616	.882 (.483, 1.61)	0.683	
other	687	.741 (.368, 1.49)	0.400	



HR

longer iDFS without SLNB ← → **longer iDFS with SLNB**

Omission of SLNB

	SOUND	INSEMA
Randomization	SLNB vs no SLNB	SLNB vs no SLNB (4:1)
N	1,405 708 SLNB vs 697 no SLNB	4,858 3,896 SLNB vs 962 no SLNB
Population	cT <2cm, cN0 (including negative axillary ultrasound) invasive breast cancer, BCT	cT ≤5cm (90% ≤2cm), cN0 (including negative axillary ultrasound invasive breast cancer, BCT
Age	Median (IQR) 60 years (52-68)	Median (IQR) 62 years (53-68) Only 10.8% < 50 years of age
Survival	5-year DDFS: 97.7% SLNB vs 98.0% no SLNB HR 0.84 (90% CI 0.45-1.54) 5-year OS: 98.2% vs 98.4% (p=0.72)	5-year iDFS: 91.7% SLNB vs 91.9% no SLNB HR 0.91 (95% CI 0.73-1.14) 5-year OS: 98.2% vs 96.9%
Recurrence	Local 1.0% SLNB vs 0.9% no SLNB Axillary 0.4% vs 0.7%	Local 1.1% SLNB vs 0.8% no SLNB Axillary 0.3% vs 1.0%

Gentilini OD et al. *JAMA Onc*. 2023;e233759.

INSEMA

- Adds to the evidence that SLNB can be omitted in select patients

- Excellent survival outcomes and low rates of recurrence

Additional considerations of SLNB omission

- Appropriate for smaller tumors (i.e. ≤ 2cm)
  - Higher rate of SLN positivity with larger tumors
- Very low percentage of non HR+/HER2- tumors
- Role of preoperative axillary imaging, e.g. axillary US
- Low percentage of lobular histology

Implications of SLNB omission

- Positive SLNs impact adjuvant therapy decision-making, both medical therapies and radiotherapy
- Premenopausal patients with SLN-positive, HR+ breast cancer may be recommended chemotherapy[1] and/or CDK4/6i
- Without axillary staging, patients may be limited in terms of:
  - Radiotherapy options such as partial breast irradiation
  - Clinical trials evaluating radiotherapy omission (IDEA[2], DEBRA[3])

SLNB is a staging modality that is still necessary for many patients

[1]Kalinsky K et al. *N Engl J Med.* 2021;385:2336-47.
[2]Jagsi R et al. *J Clin Oncol.* 2024;42:390-8.
[3]NCT04852887, NRG BR-007

Implications of SLNB omission

Take home point: Shared decision-making with patients and the multidisciplinary team are critical when determining in whom omission of SLNB can be safely done without compromising oncologic care or limiting adjuvant therapy options.

- Ongoing multidisciplinary discussion at MDACC to identify patients eligible for SLNB omission

Summary

- Both the COMET and INSEMA studies provide data on omitting surgical treatment for low-risk DCIS and low-risk invasive breast cancer, respectively
- While questions remain, these studies bring us closer to individualizing and optimizing the care of patients with breast cancer
- Engaging patients in treatment decisions is critical
- COMET and other studies on active surveillance of DCIS highlight the challenges of RCTs of de-escalation and opportunities to design patient-driven clinical trials

Thank you!

- Dr. E. Shelley Hwang
- Dr. Ann H. Partridge
- Dr. Toralf Reimer

- All the investigators and patients who participated!

@puneetsinghmd

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center