Evidence Based Radiation Oncology Fact Sheets
Breast Cancer 2023

Andrew Zhang, MD
andrewzhangmd.com

Overview:

Epidemiology:

- Globally, most common cancer in women: 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers).[1]
- 5th cause of death from cancer overall (522,000 deaths).
  - Most frequent cause of cancer death in women in less developed regions (324,000 deaths, 14.3% of total).
  - 2nd most common cause of cancer death in more developed regions (198,000 deaths, 15.4%) after lung cancer.
    - Main cause of death in women ages 20 to 59 years.
    - US per year ≈ 230,000 cases, > 40,000 deaths.
  - Incidence rates vary nearly four-fold across the world regions (27/100k in Mid. Africa and E. Asia to 96 in W. Europe).
    - This is due to risk factor modifications (diet fat intake, age of menarche, age of first birth, # pregnancies, etc.)
    - Note: incidence rates ↓ 1999 to 2007 by 1.8 % / year.[2]
      - Why? 1. Discontinuation of hormone replacement therapy (HRT). 2. Non-increasing mammography rates.

Risk Factors:

- Non-modifiable:
  - **Age** (overall most important): Birth to 39 (1 in 203 women), 40 to 59 (1 in 27), 60 to 69 (1 in 28), ≥ 70 (1 in 15).
    - A woman has 12% absolute risk of developing BCa over 80 year lifetime (1 in 8).
  - Female gender (F : M = > 100 : 1)
  - Race: White (Dx 122 in 100,000) and African Americans (Dx 117 in 100,000)
    - But the latter presents with more regional or advanced disease (45% black vs 35% white) and 41% higher breast cancer specific mortality rate (32 in 100,000 black women vs 22 in 100,000 white women).
  - BRCA WECARE Study (SEER Registry):
    - Cumulative 10-year breast CA risk: BRCA1 carrier: 20% BRCA2 carrier: 16% BRCA1 or BRCA2 carrier: 18% Non-carrier: 5%
  - Other History:[3]
    - Personal history: Having DCIS in 1 breast = higher risk of developing it in the other.
      - 2010 study (using SEER) 340,000 women with 1^{O} BCa → incidence invasive contralateral BCa = 4% at follow-up 7.5 years.
    - Family History: ↑ 2x affected 1^{O} relative, **↑ 3x** if 2 affected 1^{O} relatives (if Dxed < 30 yo vs **↑ 1.5x** if > 60).
    - Medical History: a ←M→ on the association between meningioma and breast cancer found nearly 10-fold higher odds of breast cancer in female patients with meningioma compared with the general female population.[4]
- Modifiable:
  - **Weight**. Obesity does increase mortality and morbidity, but association with BCa and BMI is also dependent on menopausal status.
    - Post-menopausal. Direct correlation between BMI and weight.[5]
      - 2000 analysis 7 cohort studies: Women BMI >33 vs BMI <21 (relative BCa risk [RR] 1.27, 95% CI 1.03-1.55).
    - Pre-menopausal. Inverse correlation between BMI and weight.
      - Same study premenopausal BMI ≥31 were 46% less likely to develop breast cancer vs. BMI <21.
    - Retrospective study suggests obesity is a risk factor for developing advanced breast cancer following a negative mammogram (McCarthy, Cancer 2021).
  - Alcohol (directly correlate with amount of drinking).
  - Smoking.
  - Hormonal Exposure:
    - Reproductive Factors that **↑ risk**: Nulliparity, early menarche, late menopause, late age 1st birth,[6] use of OCP and androgens.
    - In utero exposure to diethylstilbestrol (DES)

Anatomy:

- Superior margin (2-3rd rib). Inferior (6-7th rib). Medial (Lateral edge sternum). Lateral (anterior axillar fold).
  - Lymphatics: Primary drainage is to axillary, Internal mammary, and SVC nodes.
    - Level I – lateral to pectoralis minor. Level II – deep to pec minor. Level III – medial.
    - Internal mammary nodes are 2-3 cm lateral to midline and 2-3 cm deep. First three intercostal spaces are most likely to be involved.
      - Rotter's LN are level II interpectoral LNs.
    - Lateral primary and negative axilla, 5% risk IM involvement. Medial lesion, neg axilla 10-15%. Lat, + axilla 25% Med, + axilla 50%.

Tumor Size	T1 mic	< 1 cm	1-2 cm	2-3 cm	> 3 cm
Risk of axillary LN +	5-10%	< 15%	25%	35%	45%

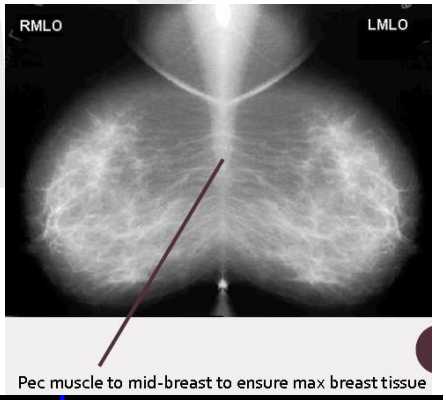
[1] http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
[2] Kohler BA, Ward E, McCarthy BJ, et al. Annual report to the nation on the status of cancer, 1975-2007, featuring tumors of the brain and other nervous system. J Natl Cancer Inst 2011; 103:714.
[3] http://www.uptodate.com/contents/brca1-and-brca2-prevalence-and-risks-for-breast-and-ovarian-cancer?source=see_link
[4] https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2806182
[5] van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol 2000; 152:514.
[6] Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. Am J Epidemiol 2000; 152:950.

Screening/Imaging:

- **NCCN RECOMMENDATIONS 2023**
  - Normal Category – Start 40 yo with yearly mammogram + tomo.
  - High risk **(Risk > 20%)**
    - Previous thoracic RT at younger age – Start 8 years after RT.
      - Yearly Mammogram (no earlier than 25 yo)
      - Yearly MRI (no earlier than 25 yo)
      - If cannot do MRI, then yearly US is added.
    - Family History of Breast CA – Starts 10 years earlier than earliest breast cancer.
      - Yearly Mammogram (no earlier than **30** yo)
      - Yearly MRI (no earlier than 25 yo)

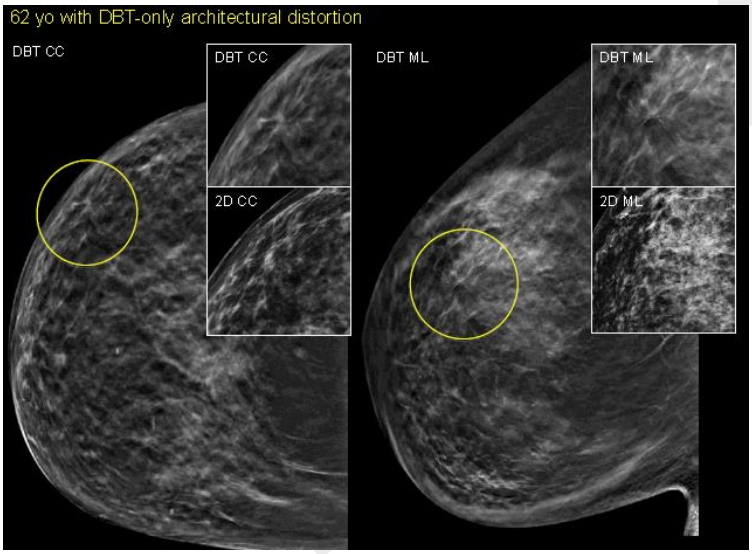
BI-RADS category	0	1	2	3	4	5	6
Risk of axillary LN +	**Incomplete assessment**	**Negative**	**Benign.**	**Probably Benign**: Short term f/u mamm at 6mo then q6/12 mos for 1-2 yrs.	**Suspicious** Biopsy	**↑ Suspicious** Biopsy	**Known Malignancy**

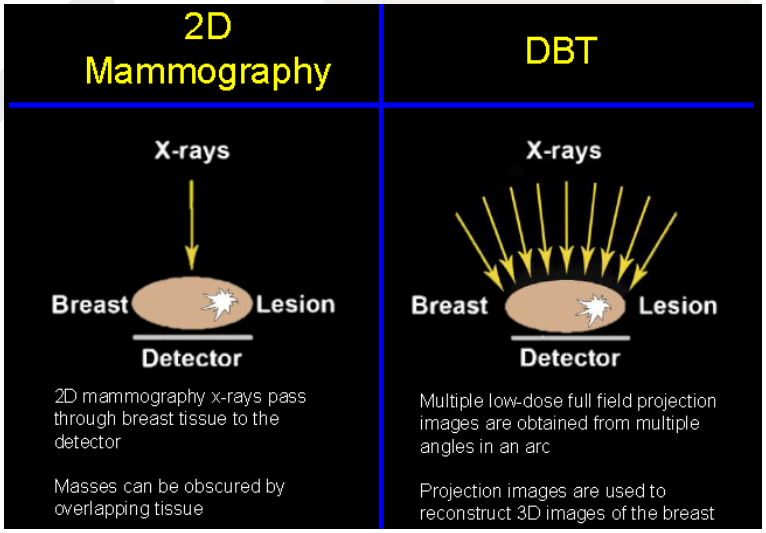
  - Annual screening using MRI is recommended by American Cancer Society for women who:
    - BRCA 1 / 2, P53, PTEN mutations, 1^{O} relative with BCRA 1 / 2 mutations and who are untested, lifetime risk 20-25% BCa, previous radiation Tx to chest at 10-30 yo.
  - Mammogram Views: medial lateral oblique (MLO) and cranial caudal (CC).
    - **Compression** for density
    - **Magnification** for calcifications
    - MLO requires pec muscle to mid-breast to ensure all breast tissue is captured.



Pec muscle to mid-breast to ensure max breast tissue

  - Digital Breast Tomosynthesis (DBT)
    - Increases detection rates of small invasive cancers
    - Decreases false positive callback rates
    - Improves margin analysis & lesion conspicuity by decreasing effect of overlying breast tissue.
    - Improves localization of "one view only" lesions
    - Helps distinguish skin lesions from breast lesions
    - Images look similar to a CT scan –you can scroll through images of the breast





- Note: Among women with extremely dense breasts and at high risk of breast cancer, screening with DBT compared with digital mammography was associated with a lower risk of advanced breast cancer (Kerlikowske, JAMA 2022).[7]

[7] https://jamanetwork.com/journals/jama/fullarticle/2793253

- MRI Breast
  - Used for selected patients & **no clear consensus** on how to select patients.
    - Difficult to detect lesions on mammo or tomo due to dense breasts, ILC, or incongruent biopsy vs. area of abnormality seen on imaging, young age and high concern for another primary.
  - Concerns: claustrophobic patients, false positive rates, timing required for premenopausal women, increased cost of imaging / insurance coverage.
- PET/CT
  - PET can identify metastatic lesions more easily than conventional imaging. This can impact treatment decisions.
    - A Canadian Trial (Dayes, JCO 2023) shows that between December 2016 and April 2022, patients ←R→ whole-body PET-CT vs. conventional staging = Forty-three (23%) PET-CT were upstaged to stage IV compared with 21 (11%) conventional staged patients (absolute difference, 12.3% [95% CI, 3.9 to 19.9]; P = .002). Consequently, treatment was changed in 35 (81.3%) of 43 upstaged PET-CT patients and 20 (95.2%) of the 21 upstaged conventional patients. Subsequently, 149 (81%) patients in the PET-CT group received combined modality treatment versus 165 (89.2%) patients in the conventional staging group (absolute difference, 8.2% [95% CI, 0.1 to 15.4]; P = .03).
  - A large prospective series so far demonstrates the clinical validity of [18F]FES-PET to determine tumor ER status in metastatic BCa (MBC). "In view of the high diagnostic accuracy of qualitatively assessed whole-body [18F]FES-PET, this noninvasive imaging modality can be considered a valid alternative to a biopsy of a metastasis to determine ER status in newly MBC." Van Geel, JCO 2022.

Important Trials

DENSE Trial **Dense Breast MRI Study**
←R→ 40,373 women between the ages of 50 and 75 years with extremely dense breast tissue on mammography → | 1. MRI | 2. No MRI |.
The groups were assigned in a 1:4 ratio, with 8061 in the MRI-invitation group and 32,312 in the mammography-only group.
1^{O} between-group Δ in incidence of interval cancers during a 2-year screening period.

Bakker, NEJM 2019.
2-year interval-cancer rate was 2.5 per 1000 screenings vs. 5.0 per 1000 screenings (P<0.001).
Of the women who were invited to undergo MRI, 59% accepted the invitation.
Of the 20 interval cancers that were diagnosed in the MRI-invitation group, 4 were diagnosed in the women who actually underwent MRI (0.8 per 1000 screenings) and 16 in those who did not accept the invitation (4.9 per 1000 screenings).
MRI cancer-detection rate among the women who actually underwent MRI screening was 16.5 per 1000 screenings (95% CI, 13.3 to 20.5).
MRI PPP = 17.4% (95% CI, 14.2 to 21.2) for recall for additional testing and = 26.3% (95% CI, 21.7 to 31.6) for biopsy.
False positive rate = 79.8 per 1000 screenings.
Among the women who underwent MRI, 0.1% had either an adverse event or a serious adverse event during or immediately after.
CONCLUSIONS The use of supplemental MRI screening in women with extremely dense breast tissue and normal results on mammography resulted in the diagnosis of significantly fewer interval cancers than mammography alone during a 2-year screening period.

AI-powered Detection Abstract (McKinney Nature, 2020) Screening mammography from US and UK institutions.
UK test included two radiologists reading screening mammos from nearly 26,000 women. US test single radiologist from 3000 women.
AI vs. human readers abs ↓ false positives of 5.7% and 1.2% (USA and UK) ↓ false negatives 9.4% and 2.7%.
In an independent study of six radiologists, the AI system outperformed all of the human readers: the area under the receiver operating characteristic curve (AUC-ROC) for the AI system was greater than the AUC-ROC for the average radiologist by an absolute margin of 11.5%. On simulation in which the AI system participated in the double-reading process used in the UK → found AI system maintained non-inferior performance and ↓ the workload of the second reader by 88%.

Canadian Screening Mammogram Prospective Cohort
69,025 women age 50-64 w/ 212,589 screening mammograms. SBC = screening detected BCa. IBC = interval BCa.
Breast Cancer Diagnosis 1,687 (705 SBC, 206 IBC, 275 noncompliant, and 501 detected outside the screening program).
Deaths 225 (170 breast cancer–specific deaths).
IBC v. SBC High Grade OR 6.33 (p<0.001)
ER negative OR 2.88 (p<0.001)
7-year BCaSM HR 3.55 (p<0.001).
Non–breast cancer mortality was similar HR 1.33 (NS).
Conclusions Interval cancers were highly prevalent in women participating in population screening, represented a worse biology, and had a hazard for breast cancer death more than 3-fold that for SBC.

UK Age Trial
←R→ 160,921 women age 39-41 1. Yearly mammogram screening up to age 48 2. Control: first screening at age 50.
Women in the control group were unaware of the study.
1^{O} endpoint mortality from breast cancers.

Duffy, Lancet 2020.
Total 22.8 year follow-up.
10-year BCa Death 83 vs. 219 (RR 0.75, p=0.029)
No significant reduction was observed thereafter, with 126 deaths versus 255 deaths occurring after more than 10 years of follow-up (RR 0·98 [0·79–1·22]; p=0·86).
Interpretation Yearly mammography before age 50 years, commencing at age 40 or 41 years, was associated with a relative reduction in breast cancer mortality, which was attenuated after 10 years, although the absolute reduction remained constant. Reducing the lower age limit for screening from 50 to 40 years could potentially reduce breast cancer mortality.

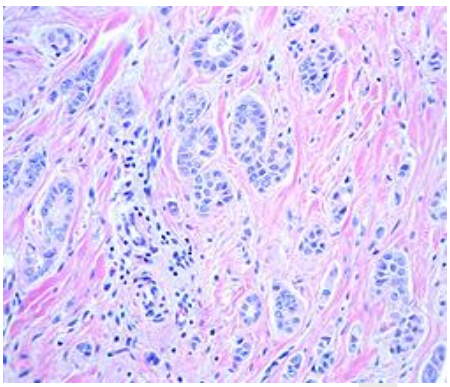
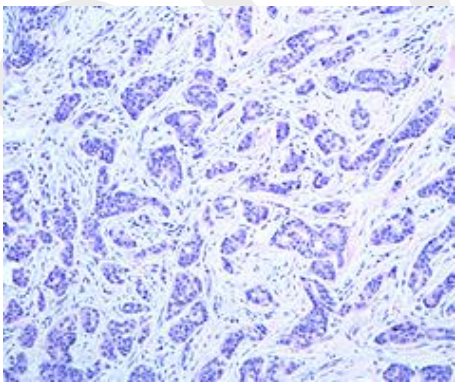
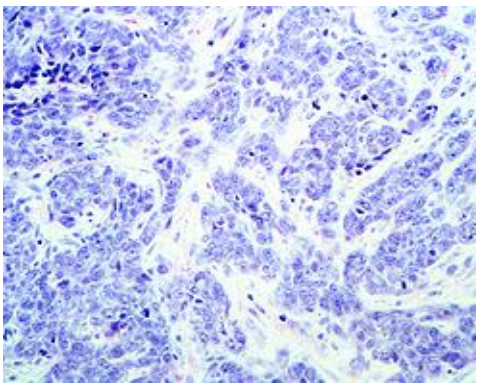
Pathology:

Invasive ductal carcinoma (IDCA) 76% of cases. Invasive lobular carcinoma (ILCA) 8%.[8] DCIS / LCIS 7%
Mucinous (colloid) 2.4%, Tubular 1.5%, Medullary 1.2%, Papillary 1%. All other (metaplastic, micropapillary) < 5%.
Mucinous must be > 90% and cannot be high grade, otherwise we will call IDC with mucinous features.

- **Size, Grade, LVI, Association of DCIS (EIC)**
- **Lymph nodes (ECE); SLNB or ALND**
- **Receptors (ER, PR, Her-2 IHC and FISH amp)**
- **Consider OncotypeDx**
- **Margins:**
  - In past, we favored margins of approximately >2mm
  - Large met-analysis for early invasive cancer and BCT performed
  - Negative margin optimizes local control (+ margin 2.4 X increase in LR)
  - HOWEVER, NO BENEFIT to wider margin
  - *Regarding close margins for re-excision, we now just look for no tumor on ink for IDC.*[9]
    - **DOES NOT APPLY to 1. APBI, 2. DCIS, 3. patients treated with neoadjuvant chemotherapy.**

- **Bloom Richardson grading depends on mitotic index, nuclear grade, and tubular grade. Each is scored from 1-3.**
  - Grade 1 tumors have a total score of **3-5**, Grade 2: **6-7**, Grade 3: **8-9**.

- DCIS has 5 major forms:
    - Comedo (central necrosis / calcification). Risk of invasion and local recurrence.
    - Cribiform (back to back glands without intervening stroma).
    - Papillary
    - Micropapillary
    - Solid (not well defined)
  - High-grade lesions: aneuploidy, ER/PR –, high proliferative rate, overexpression HER2, Δ p53, angiogenesis in surrounding stroma.
  - Low-grade lesions: diploid, ER/PR + low proliferative rate, rare HER2 and oncogene mutations.
- IDCA
  - Well differentiated Moderately Poorly

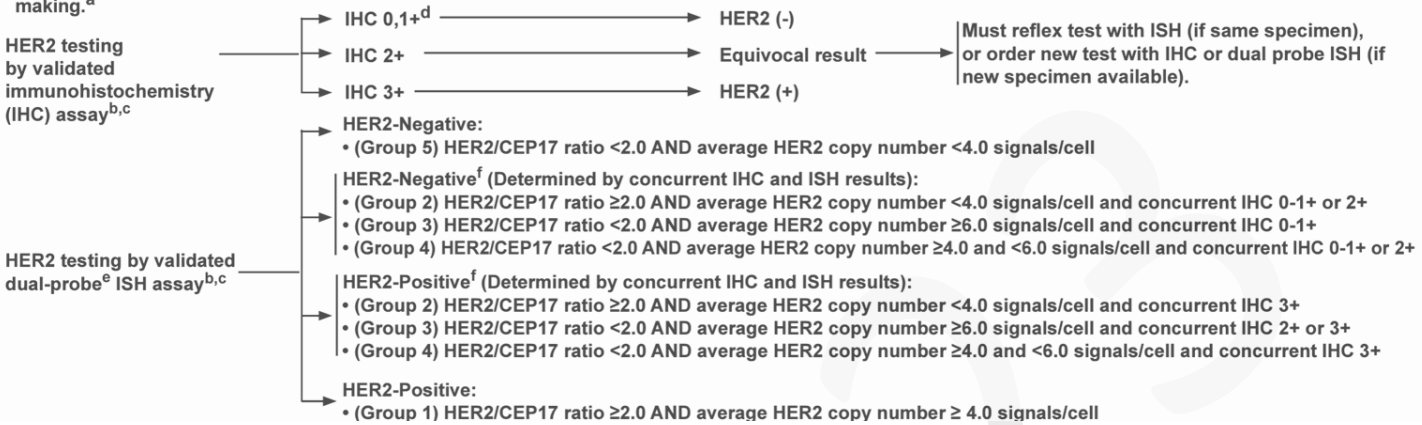




- ILCA
  - Distinguish between DICS (E-cadherin +) and LCIS (E-cadherin -).
  - ILCA has ↑ frequency of bilaterality and multicentricity than IDCA.
  - Seen in older women and are larger and better differentiated tumors.
  - As a rule, invasive lobular carcinomas are ER-positive, with variant lesions showing occasional variable expression.
  - Older series report ≈ prognosis ILCA and IDCA. Recent study suggest outcomes (at least short-term), LCIS > DCIS.[10]
    - However, variants of infiltrating lobular carcinoma exist, some of which have a poorer prognosis.[11]
  - ICLS metastasize later and spread to unusual locations such as peritoneum, meninges, and the gastrointestinal tract.

[8] Li CI, Uribe DJ, Daling JR. Clinical characteristics of different histologic types of breast cancer. Br J Cancer 2005; 93:1046.
[9] Houssami, N Ann SurgOncol2014; 21; 71 Morrow M, NEJM 2012, 367: 79 JCO 2014 volume 32; 14
[10] Cristofanilli M, Gonzalez-Angulo A, Sneige N, et al. Invasive lobular carcinoma classic type: response to primary chemotherapy and survival outcomes. J Clin Oncol 2005; 23:41.
[11] Ferlicot S, Vincent-Salomon A, Médioni J, et al. Wide metastatic spreading in infiltrating lobular carcinoma of the breast. Eur J Cancer 2004; 40:336.

PRINCIPLES OF BIOMARKER TESTING
HER2 TESTING[a,b]

- HER2 testing should be performed on all new primary or newly metastatic breast cancers using methodology outlined in the ASCO/CAP HER2 testing guideline.[a]
- A re-review of the pathology with consideration for repeat or consultative HER2 testing should be made if a Grade 1 (any histologic type), pure mucinous, pure tubular, or pure cribriform carcinoma tests HER2-positive.[a]
- After a negative HER2 test result on initial biopsy sample, consider retesting on subsequent surgical or other additional sample if the initial sample was suboptimal (eg, minimal invasive cancer was present, cold ischemic time or fixation was suboptimal), testing error is expected, additional samples contain higher grade morphologically distinct cancer from the biopsy, to rule out heterogeneity in a high grade cancer, or if it will otherwise aid in clinical decision-making.[a]



Metastatic Workup

- CBC
- CMP (include LFT's and alkaline phosphatase)
- CT chest/abdomen/pelvis & bone scan **Or PET/CT**
- Consider discussing for any N+ patient especially since many N+ patients are now not getting ALND (hard to know true # LN).
- If chest CT, MRI, or PET/CT obtained → MUST review nodes (especially IMN) prior to RT to ensure any suspicious nodes are covered.
- CEA, CA 15-3, CA 27.29 … NOT CA 19-9 (pancreatic cancer)

Recent Trends

- Surgery: 5-year survival slightly increases if surgeries are done at high volume centers vs. low volume centers.[12]

Genetics and Testing:

- Inherited genetic mutations: Approximately 10% of all breast cancer cases.
  - BRCA-1 (Chromosome 17), BRCA 2 (chromosome 13), Li-Fraumenti (p53), Cowden (PTEN).
    - By 70 yo, cumulative risk: **BCa** BRCA1 59% and BRCA2 49%, vs **OvCa** BRCA 1 40% and BRCA2 18%.
      THINK: 60 → 50 → 40 → 20. BSO surg = ↓ 75% RR Ov/Fall/Peritoneal Ca.
    - Both BRCA increase contralateral breast cancers BRCA 1 > 2.
  - In males, lifetime risk: General population 0.1%, BRCA 1 1%, **BRCA 2 6%**.
    - ALSO BRCA 2 > BRCA 1 = PROSTATE, PANCREAS, Uveal Melanoma.

NOTE: For patients with CHEK2 mutations, the NCCN guidelines on genetic/familiar high-risk assessment recommend annual screening mammogram and consideration for screening breast MRI. There is insufficient evidence for intervention to recommend risk reducing mastectomy, manage based on family history. There is no increased risk of ovarian cancer.

- MUST TEST FOR BRCA 1 and 2 IF (and maybe ATM and p53):
  - Ovarian cancer
  - Breast cancer < 50 years
  - Triple negative breast cancer < 60 years
  - Two breast cancer primaries in single individual
  - Breast cancer and:
    - >1 blood relative w/ breast cancer <50
    - >1 blood relative w/ovarian cancer
    - >2 relative with breast, prostate, or pancreatic cancer
  - Pancreatic cancer
  - increased risk population
  - Blood relative: 1^{O}, 2^{O}, or 3^{O} relative
  - Ashkenazi Jewish descent

- Pregnancy:
  - Discuss future plans for fertility for women of childbearing age & refer if appropriate to reproductive endocrinology
    - Egg preservation, embryo, other
  - Always assure that patient is not pregnant at time of treatment

- **Prophylactic mastectomy**? → women ≥2 1^{O} relatives with BCa, any 1^{O} < 45 yo, any 1^{O} with BCa and OvCa, or multiple 2^{O} with BCa.
  - Prophylactic mastectomy nearly eliminates risk breast cancer.
  - Prophylactic bilateral salpingo-oophorectomy ↓ Ov/Fall Ca 80% and ↓ BCa 50% (Rebbeck et al. 2009).

Older Model: Gail
"The Gail model was one of the initial tools that attempted to estimate a woman's risk of developing breast cancer over the next 5 years. It considers age, race, age of first menstrual period, number of first degree relatives with a history of breast cancer, and number of prior biopsies. It is thought to underestimate the need for testing as it does not take into consideration a family history of ovarian cancer, age of onset of breast cancer, occurrence of bilateral breast cancers, history of second degree relatives with breast cancers, or the biology of the breast cancer; all important in assessing risk."

NSABP Study Pairing (A Way to Remember)

B-04, B-06	Surgery ± RT	
B-17	DCIS Lumpectomy ± RT	
B-24, B-35	CHEMO DCIS	
B-14, B-21	Adjuvant Hormonal	ATLAS
B-18, B-27	NAC, no PMRT	Mamounas

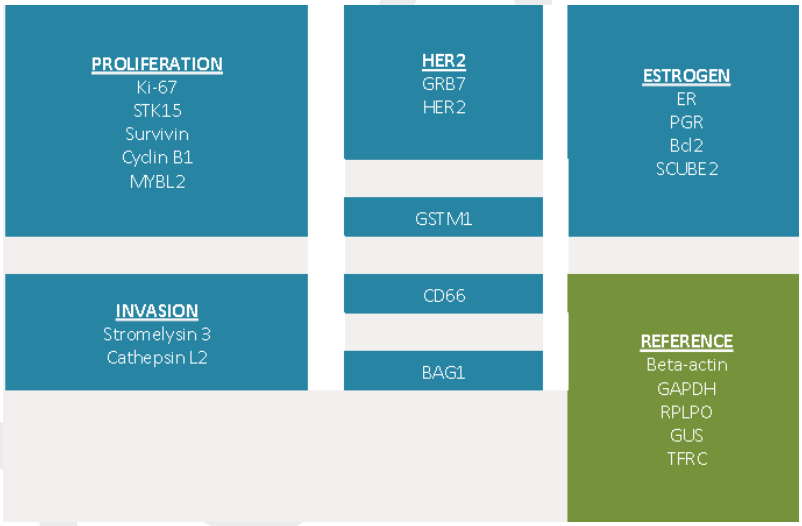
[12] https://ascopubs.org/doi/abs/10.1200/JCO.22.02012

Gene expression.

- Molecular subtypes are approximated by receptor status: CUT-OFF LOW/HIGH Ki67 10%
  - Luminal A: ER/PR +, Her2Neu -. Ki67 < 14
  - Luminal B: "Triple +" or Ki67 > 14
  - Basal like: "Triple –"
  - Her2Neu +: ER/PR - , Her2Neu +.
    - Her2Neu is a member of epidermal growth factor receptor (EGFR) family.
    - Amplification usually = aggressive and negative prognostic indicator in mastectomy and BCT patients.
- Testing:
  - MammaPrint® predicts prognostic category (low vs high risk) in terms of DMFS and OS in treated, untreated, ER +/-, and LN +/- patients. Requires fresh-frozen tissue and on-site processing.
  - Oncotype Dx® predicts prognostic category (low vs int vs high risk) in terms of DMFS and OS and magnitude of chemotherapy benefit in tamoxifen treated, ER+, LN - patients. Uses fixed specimen ∴ no need on-site testing.

- **Oncotype DX**

Score	Formula
HER2 Group Score	(0.9 × GRB7) + (0.1 × HER2) If HER2 Group Score is less than 8 then the HER2 Group Score is considered equal to 8
ER Group Score	([0.8 × ER] + [1.2 × PgR] + Bcl2 + SCUBE2])/4
Proliferation Group Score	(SURV + KI-67 + MYBL2 + Cyclin B_1 + STK15)/5 If the Proliferation Group Score is under 6.5 then the Proliferation Group Score is considered equal to 6.5
Invasion Group Score	(Cathepsin L2 + Stromelysin 3)/2



Oncotype Dx trials®.

Paik et al. 2004.[13] Among ER+, pLN- patients, the 21 gene assay of the Tamoxifen alone arm of NASBP B-14 is highly predictive of OS and DM, independent of tumor size or age. **10-year risk of occurrence was < 18 (low-risk pts) 6.8%, 18-30 (int) 14.3%, ≥31 (high) 30.5%.** The range of possible recurrence scores was 0 to 100, derived by reference-normalized expression measurements for cancer genes.

Paik et al. 2006.[14] Among ER+, pLN- patients, the 21 gene assay Recurrence Score (RS) of the tamoxifen ± chemo arm of NASBP B-20, predicts the magnitude of chemo benefit in terms of a 10-year distant recurrence rate. Highest benefit is in high-RS pt, uncertain benefit in intermediate risk pt, and small to no benefit in low-RS pt.

[13] http://www.ncbi.nlm.nih.gov/pubmed/15591335
[14] http://www.ncbi.nlm.nih.gov/pubmed/16720680

Oncotype in Node Negative, ER+ (NSABP B-14 and NSABP B-20 data)

RS was available for 895 tamoxifen-treated patients (from both trials), 355 placebo-treated patients (from B-14), and 424 chemotherapy plus tamoxifen-treated patients (from B-20). 1^{O} = LRR. Distant metastases, second primary cancers, and deaths before LRR were censored.

Mamounas, JCO 2010.

In tamoxifen-treated patients, LRR was significantly associated with RS risk groups (P < .001).
The 10-year Kaplan-Meier estimate of LRR was 4% low RS (< 18), 7.2% intermediate RS (18-30), and 15.8% high RS (> 30).
In multivariate analysis, **RS** was an independent significant predictor of LRR along with **age** and **type of initial treatment**.
CONCLUSION: Similar to the association between RS and risk for distant recurrence, a significant association exists between RS and risk for LRR. This information has biologic consequences and potential clinical implications relative to locoregional therapy decisions for patients with node-negative and ER-positive breast cancer.

Table 1. Sites of the First Locoregional Recurrence Among Tamoxifen-Treated Patients From NSABP Trials B-14 and B-20 According to Type of Initial Treatment (N = 895)

Type of Initial Treatment	Group Total (No.)	Local Site			Regional Site		
		IBTR	Chest Wall	Scar	Axilla	Supraclavicular	Local and Regional
Lumpectomy + XRT	390	34	3	0	1	3	1
Mastectomy	505	0	17	1	9	3	1

Abbreviations: NSABP, National Surgical Adjuvant Breast and Bowel Project; IBTR, ipsilateral breast tumor recurrence; XRT, radiation therapy.

Table 2. Kaplan-Meier Estimates and 95% CIs of the Proportion of Patients With Locoregional Recurrence at 10 Years for 355 Placebo-Treated Patients (NSABP B-14), 895 Tamoxifen-Treated Patients (NSABP B-14 andB-20) and 424 Tamoxifen Plus Chemotherapy–Treated Patients (NSABP B-20)

Treatment Group and Recurrence Score Group	10-Year Kaplan-Meier Estimate (%)	95% CI	Log-Rank *P*	No. of Events/No. at Risk
Placebo				
Low (< 18)	10.8	5.8% to 15.8%	.022	19/171
Intermediate (18-30)	20.0	9.9% to 30.0%		15/85
High (≥ 31)	18.4	9.5% to 27.4%		19/99
Tamoxifen				
Low (< 18)	4.3	2.3% to 6.3%	< .001	24/473
Intermediate (18-30)	7.2	3.4% to 11.0%		16/194
High (≥ 31)	15.8	10.4% to 21.2%		33/228
Chemotherapy + tamoxifen				
Low (< 18)	1.6	0.0% to 3.5%	.028	4/218
Intermediate (18-30)	2.7	0.0% to 6.4%		2/89
High (≥ 31)	7.8	2.6% to 13.0%		8/117

NOTE. Results are given for all patients and for the pre-specified recurrence score risk categories.
Abbreviation: NSABP, National Surgical Adjuvant Breast and Bowel Project.

Table 3. Multivariate Cox Regression Analysis of Predictors of Locoregional Recurrence in the Cohort of 895 Tamoxifen-Treated Patients From NSABP Trials B-14 and B-20

Variable	Hazard Ratio	95% CI	Wald Test *P*
Age (≥ 50 *v* < 50)	0.40	0.25 to 0.65	.0002
Mastectomy *v* L + XRT	0.62	0.39 to 0.99	.047
Clinical tumor size (> 2 *v* ≤ 2 cm)	0.98	0.61 to 1.59	.933
Tumor grade (moderate *v* well)	1.10	0.54 to 1.92	.113
Tumor grade (poor *v* well)	1.76	0.89 to 3.48	
Recurrence score*	2.16	1.26 to 3.68	.005

Abbreviations: L, lumpectomy; XRT, radiation therapy; LRR, locoregional recurrence; NSABP, National Surgical Adjuvant Breast and Bowel Project.
*Recurrence score was a continuous variable, with the hazard ratio for LRR calculated relative to an increment of 50 units (chosen to dichotomize the recurrence score and thus improve comparability of the hazard ratio with the hazard ratios based on the clinical covariates). The *P* value for the likelihood ratio test on RS is .007.

Staging: AJCC 8th Edition

SIMILAR = BREAST ANAL HCC

- T0 - no primary tumor found, LCIS
- **Tis - in situ (DCIS or Paget's)** **NOTE: 50% Paget's has underlying breast palpable mass.**
  - **LCIS IS BENIGN ENTITY AND NOT EVEN CANCER.**
- **T1 ≤ 2 cm** T1mi ≤ 0.1 cm (microinvasive), T1a > 0.1 to 0.5 cm, T1b > 0.5 to 1 cm, T1c > 1 to 2 cm
- T2 > 2 to 5 cm
- T3 > 5 cm
- T4 Chest wall /skin T4a Chest wall (**not including pectoralis muscle**) ≈ Serratus Anterior T4b Skin edema (peau d'orange), ulcer, or satellite skin nodules
  T4c Both 4a and 4b T4d Inflammatory carcinoma

Clinical staging		Pathologic staging	
cN0	No lymph node metastases	**pN0**	No lymph node metastases
		pN0(i+)	ITCs only (<0.2 mm)
		pN0 (mol+)	Only RT_PCR
cN1	Mets to lv I or Lv II **(MOVABLE)**		
cN1mi	Micromets (~200 cells, > 0.2mm but ≤ 2.0 mm)	**pN1mi**	← Same
		pN1a	1-3 axillary lymph nodes (at least 1 > 2.0mm) **ONLY LV 1-2**
		pN1b	Mets in IM nodes (micromets, or macromets via SLN biopsy, not clinically)
		pN1c	pN1a+pN1b
cN2a	Ipsilateral axillary lymph nodes **(fixed or matted)**	**pN2a**	4-9 axillary lymph nodes (at least 1 > 2.0 mm)
cN2b	Mets in IM nodes (**clinically**) **without** axillary LN	**pN2b**	Mets in IM nodes (**clinically detected**) **without** axillary LN
cN3a	Infraclavicular lymph nodes (level III)	**pN3a**	10 or more axillary LN (at least 1 > 2.0 mm); or infraclavicular (level III) LN.
cN3b	Mets in IM nodes (**clinically detected**) **WITH +** axillary nodes	**pN3b**	Mets in IM nodes (**clinically detected**) **WITH +** axillary nodes; or Microscopic IM nodes and ≥ 4 axillary lymph nodes.
cN3c	Supra**C**lavicular lymph nodes	**pN3c**	Supra**C**lavicular lymph nodes

ALL As are AXILLARY, B are Breast (IMs), C is supraclav.

- M0 - none
- cM0(i+) - no clinical or radiographic evidence of distant metastases, but tumor cells detected in circulating blood, bone marrow, or other tissues (e.g. prophylactically removed ovaries), ≤ 0.2 mm, in a patient without symptoms or signs of metastases.
- M1 - distant detectable metastases; or histologically proven > 0.2 mm ***Common met sites: Lung, liver, bone brain. "LLBB."

Stage 0 Disease: DCIS (Ductal Carcinoma in Situ)

"A heterogeneous group of neoplastic lesions **confined** to the breast ducts and lobules."

- **NCCN guidelines**:
  - Workup: H&P, diagnostic b/l mammogram, pathology, receptor status, genetic counseling if high risk hereditary BCa, MRI as indicated.
  - Recommended treatments:
    - Lumpectomy w/o LN surgery + whole breast radiation (WBRT) ± boost (Cat. 1).
      + partial breast irradiation (PBI) accelerated or otherwise.
      + NO RT **in carefully selected cases** (Cat. 2B).
    - Total mastectomy ± sentinel node biopsy (SNB) … ± reconstruction.
- **Major Topics**:
  - BCS + RT vs. Mastectomy
  - BCS ± RT
  - Hypofractionated Whole Breast Irradiation (DCIS)
  - Boost Studies
  - Adjuvant Hormone Therapy

Surgery:

- Total Mastectomy was initially the treatment option for DCIS, but the introduction of breast-conserving surgery (BCS) and better screening led to ↓ in rates of both mastectomy and contralateral mastectomy for DCIS. Mastectomy rates in DICS: 1992, 43%. 1999, 28%.
- Unfortunately, BCS + RT vs Mastectomy: **No randomized comparisons available.**
  - **Note**: All mastectomy vs BCS trials are invasive disease. There are no trials for DCIS.
- **Outcomes**:
  - 1%-2% local recurrence after mastectomy compares favorably to BCT
  - 1%-2% breast cancer mortality regardless of treatment approach.
- Since treatment is solely to prevent a local event, BCT is preferable to mastectomy unless extent of disease prevents complete excision with acceptable cosmesis.

- Current candidates for mastectomy include:
  - **Extensive and/or multifocal DCIS** involving 4–5 cm of disease or more than one quadrant.
  - Women with potential contraindications to breast irradiation.
  - Extremely small or large breasts.
  - Younger patients.
  - Preference.
  - Currently, 97% of patients with DCIS undergo surgical excision, of which 33% will involve mastectomy.[13]
  - Mastectomy is curative > 98% patients with DCIS and LCIS.
  - Local recurrence (LR) 1-2% usually due to unrecognized invasive carcinoma, inadequate margins, incomplete removal breast tissue.
    - Nipple sparing mastectomy also has low LR ≤ 3%.
  - **Post-mastectomy RT (PMRT)** for diffuse extent of disease, high grade, **positive margins**, and young age.

- Breast Conserving surgery (aka partial mastectomy / lumpectomy) is comparable to total mastectomy in term of long term survival, but LR is ↑.

  Dutch 2008 Study (Meijnen et al).[15] Retrospective review of 504 DCIS patients between 1986 and 2005.
  TX: wide local excision WLE (n = 91), WLE+RT 50gy/2 (n = 119) + 16gy/2 boost (36 of those pts), or mastectomy (n = 294).
  8 year LR rate is around 15% with WLE. **Although not clinically significant**, the LR rate with RT is only 8%.
  - *Note:* the 8 year LR of DCIS (not "overall LR" but only "DCIS LR"), is clinically significant.

	WLE	WLE/RT	BCT total (WLE + WLE/RT)	Mastectomy
N =	91	119	210	294
8 yr overall LR free	84.4	91.2	**88**	**99.1**
8 yr distant met free	95.7	95.8	**96**	**99.1**
8 yr contralateral free	95.5	100	97.4	93.5
8 yr OS	95.7	96.9	96.1	99.4
8 yr BCa specific survival	96.8	98	97.3	99.4

WLE and WLE+RT are **all** $p > 0.05$. In RED: $P < 0.05$.

Conclusions:
- Most women are candidates for BCT **IF**:
  - Lesion limited to one quadrant or section of the breast (maybe multiple separate foci).
    - This depends on breast size and cosmetically acceptable preference.
    - Multifocal disease is not necessarily a contraindication to BCT. However, extensive disease that cannot be encompassed within a cosmetically acceptable resection or multi-centric disease is a contraindication to BCT.
  - Histologically negative margins (tumor-filled ducts away from inked surface).
    - For women who will be treated with post-operative RT, a negative margin is no cancer on ink.
- Following BCT, post-excision mammography can be performed since residual suspicious calcifications → further resection.
- Pathologic examination and receptor testing needed.

[15] http://www.ncbi.nlm.nih.gov/pubmed?term=17987342

- **Pathologic examination**: For patients with DCIS, complete tissue processing is essential to exclude small foci of invasive carcinoma, and ascertain the presence of contiguous or multifocal distribution.
    - Also must include **1.** nuclear grade (ie, low, intermediate, or high), **2.** the size or extent of the lesion (from direct measurements and/or reconstruction), and **3.** the distance to the closest margin, and **4.** receptor status.

      Sentinel node biopsy should be considered for those patients with **1. increased likelihood of invasive cancer**, including those with multiquadrant disease, extensive comedonecrosis, or radiographic findings suspicious for invasive cancer. Also should be considered if they are **2. undergoing mastectomy**, as SLNB will be technically impossible (disruption of lymph channels) if later invasive disease is found.[16]

      Moore 2007.[17] Previously, + SLN has been reported in 6% to 13% of patients. This study = 9% (43/470 DCIS pts) at 3 institutions. Extensive disease requiring mastectomy (p = 0.02) and the presence of necrosis (p = 0.04) were associated with an ↑ risk nodal positivity. 3 (7%) of 43 pts had macrometastases (pN1), 4 (9%) micrometastases (pN1mi), and 36 (84%) single tumor cell / small clusters (pN0(i+)). 9 (21%) of 43 LN+ pts, or 9 (2%) of 470 DCIS all comers upstaged to AJCC stage I or II as a result of the SLN biopsy.

      Axillary lymph node dissection (ALND) is not necessary:

      Mabry 2006.[18] Retrospective study of 564 DCIS pts underwent ALND (393) or SLNB (171) between 1972 to 2005. In ALND group, only 2 were + LN by H&E stain only. Both received mastectomies, were upstaged, received chemotherapy, and survived > 10 yr w/o LR or distant recurrence. In SLNB group, 10 pts were IHC positive (0 were H&E positive). They were not upstaged or treated with chemotherapy. 6 pts in the ALND group developed local invasive recurrence and died of metastatic breast cancer (none had + LN).

Please see "SLN and Axillary Analysis" Below!!!

[16] http://www.ncbi.nlm.nih.gov/pubmed/?term=23544935
[17] http://www.ncbi.nlm.nih.gov/pubmed/17597346
[18] http://www.ncbi.nlm.nih.gov/pubmed/16978948

Surgical Margins

MARGIN STATUS RECOMMENDATIONS AFTER BREAST-CONSERVING SURGERY (BCS) FOR INVASIVE CANCERS AND DCIS

- Margins should be evaluated on all surgical specimens from BCS. Requirements for optimal margin evaluation include:
  - Orientation of the surgical specimens
  - Description of the gross and microscopic margin status
  - Reporting of the distance, orientation, and type of tumor (invasive or DCIS) in relation to the closest margin.
- For mammographically detected DCIS with microcalcifications, complete resection should be documented by analysis of margins and specimen radiography. Post-excision mammography can be considered if there is uncertainty.
- The NCCN Panel accepts the definitions of negative margins after breast-conservation therapy from the 2014 SSO/ASTRO Margins Guideline[1] for Stage I/II Invasive Cancers and the 2016 SSO/ASTRO/ASCO Guideline for DCIS.[2] For patients with stage I or II invasive cancers after BCS, a positive margin is defined as "ink on tumor" (any invasive cancer or DCIS cells on ink). These patients generally require further surgery—either a re-excision to achieve a negative margin or a mastectomy. If re-excision is technically feasible to allow for BCS to achieve "no ink on tumor," this can be done with resection of the involved margin guided by the orientation of the initial resection specimen or re-excision of the entire original excision cavity. There may be select patients with stage III invasive cancers who may be eligible for BCS. For these patients, the margins status would be accessed with similar definitions.

DCIS

- For patients with pure DCIS treated by BCS and WBRT, a quantitative description of any tumor close to margin resection width of at least 2 mm is associated with a reduced risk of ipsilateral breast tumor recurrence (IBTR) relative to narrower negative margin widths, while the routine practice of obtaining margins greater than 2 mm to further improve outcomes is not supported by the evidence. When there is only minimal or focal DCIS involvement near the margin, clinical judgment should be utilized to weigh the risks of re-excision with risk of recurrence for an individual patient.
- For patients with DCIS treated with excision alone (no WBRT), regardless of margin width, there is a substantially higher rate of IBTR than treatment with excision and WBRT, even in predefined, low-risk patients. Although the optimal margin width for treatment with excision alone is unknown, it should be at least 2 mm, with some evidence suggesting improved IBTR rates with margin widths wider than 2 mm.
- DCIS with microinvasion (DCIS-M), defined as an invasive focus ≤1 mm in size, should refer to the DCIS margin definition when considering the optimal margin width (>2 mm), given that the majority of DCIS-M is comprised of DCIS and systemic therapy utilization for this lesion more closely reflects the treatment pattern for DCIS than for invasive carcinoma.

Meta-analysis of margin width and ipsilateral breast tumor recurrence (IBTR) → 33 studies including 28,162 patients as the primary evidence base for consensus.
Consensus is that negative margin for DCIS is 2 mm.

TABLE 4 Summary of selected results of margins meta-analysis[1,3]

Relationship between IBTR and margin status

	No. of studies	No. of participants	Adjusted OR of IBTR[a]	95% CI	*P* (association)
Margin category (model one)		28,162			<0.001
Close/positive	33	6,178	1.96	1.72–2.24	
Negative	33	21,984	1.0	—	
Margin category (model two)		13,081			<0.001
Positive	19	1,641	2.44	1.97–3.03	
Close	19	2,407	1.74	1.42–2.15	
Negative	19	9,033	1.0	—	—
Threshold distance (model two)[b]					0.90
1 mm	6	2,376	1.0	—	—
2 mm	10	8,350	0.91	0.46–1.80	—
5 mm	3	2,355	0.77	0.32–1.87	—

Impact of margin width on IBTR adjusted for individual covariates and follow-up

Covariate	No. of studies	Threshold distance negative margin: adjusted OR (mm)			*P* (association)
		1	2	5	
Age	18	1.0	0.53	0.77	0.53
Endocrine therapy	16	1.0	0.95	0.90	0.95
Radiation boost	18	1.0	0.86	0.92	0.86

Radiation Therapy:

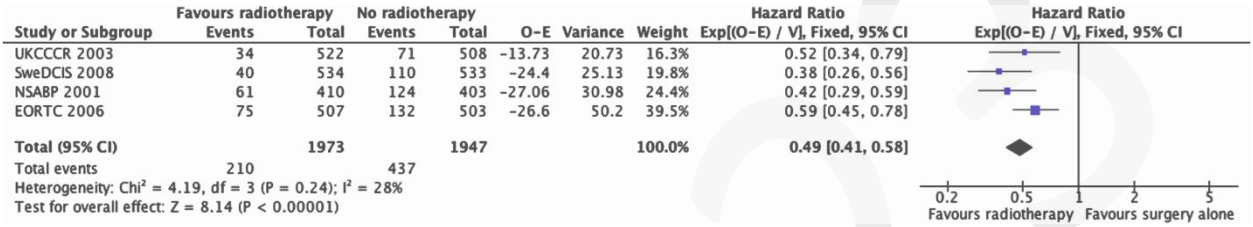
- "RT after wide excision reduces the risk of local invasive and noninvasive recurrences. However, treating all women who undergo wide excision for DCIS with adjuvant RT may be overtreatment for some. The majority of cases of DCIS do not recur when treated with excision alone and there may be subgroups of patients with DCIS in whom the risk of local recurrence is so low that RT may be of no benefit. The difficulty, however, is in reliably predicting those patients who would not recur in the absence of RT." – Uptodate.

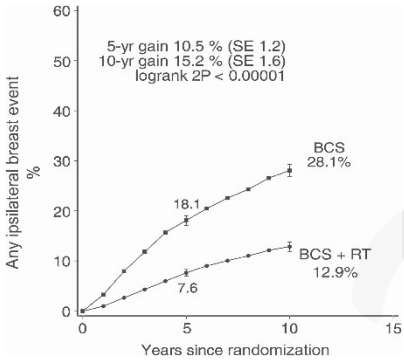
Metaanalysis (Goodwin et al 2009).[19] 4 RCT with 3925 women. This analysis confirmed significant RT benefit on **all** ipsilateral breast events (HR = 0.49; 95% CI 0.41–0.58, p < 0.00001), regardless of complete vs incomplete excision, < 50 yr vs > 50 yr (older the more responsive to RT), or comedo necrosis present vs absent.

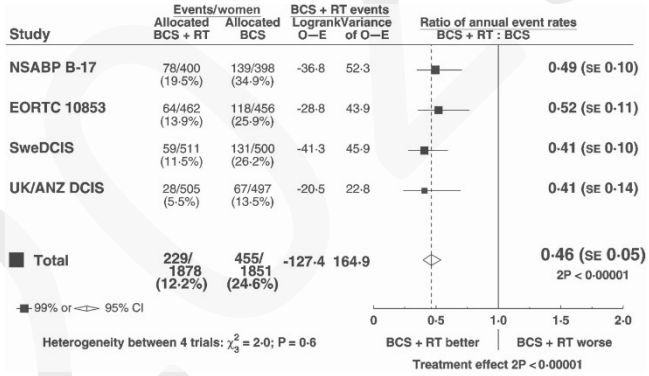
Ipsilateral recurrence 11.6% WRT + RT vs 23.9% WRT alone.

Nine women require treatment with radiotherapy to prevent one ipsilateral breast recurrence.

No Δ in contralateral breast events nor distant events.







[19] http://www.ncbi.nlm.nih.gov/pubmed?term=19447038. Includes: SweDCIS trial (SweDCIS, 2008), EORTC trial (EORTC, 2006), UKCCCR trial (UKCCCR, 2003), NSABP trial (NSABP, 2001).

First Generation RTC:

- High Local Recurrence Rates in Both Arms (25-35% Unirradiated vs. 10-20% irradiated
- Pathology/Margins not standardized or rigorously evaluated
- NSABP Review 18% Inevaluable or Involved Margins
- SWEDCIS-20% Involved/Unknown Margins
- Broad Selection Criteria (Symptomatic Presentation vs. Mammographic Detection), Size, Histology
- Less Use of Mammographic Magnification Views

Note: Let us say there are no invasive recurrence ± RT, but let's say that with DCIS recurrence is like 20-30% - RT and 8-10% with RT. If that is the case, we will NOT do radiation. Radiation is to prevent the invasive recurrence. Radiation decreases invasive component. If NSABP showed that all RT did was to decrease non-invasive recurrence, but does have invasive recurrence ± RT regardless, we would NOT do RT.

DCIS Randomized RT Trials:

		Breast Recurrences		
		No RT	RT	
NSABP B-17 (12-year)	Overall	31.4%	15.7%	p<0.000005
	Invasive	16.8%	7.7%	p<0.0001
	DCIS	14.6%	8.0%	p=0.001
EORTC 10853 (10-year)	Overall	26%	15%	p<0.0001
	Invasive	13%	8%	p=0.0065
	DCIS	14%	7%	p=0.0011
SweDCIS (5-year)	Overall	22%	8%	p<0.0001
	Invasive	9%	4%	p=sig
	DCIS	13%	4%	p=sig
UK/ANZ (5-year)	Overall	14%	6%	p<0.0001
	Invasive	6%	3%	p=0.01
	DCIS	7%	3%	p=0.0004

NSABP B-17 (Fisher et al. 1998c, 2001b). 818 DCIS (negative margins) RTC lumpectomy ± 50 Gy RT. No boost.
12 year follow up showed RT ↓ non-invasive LF 15% → 8%, invasive LF 17% → 8% with a TOTAL LF 32% → 16%. No Δ DM or OS.
↑ LR if: + margins, moderate-marked comedonecrosis, and microcalc ≥ 1cm.

EORTC 10853 (Julien 2000, Bijker 2006[20]). 100 DICS (negative margins) RTC lumpectomy ± 50 Gy RT.
10 year follow up showed RT ↓ noninvasive LF 14% → 7%, and invasive LF 13 → 8% with a TOTAL LF 26 → 15%. No Δ DM or OS.
↑ LR if: age ≤ 40, clinical symptoms/presentation, G 2-3, cribriform or solid growth pattern, + margin, omission of RT.
Criticism: 18% Inevaluable or Involved Margins.

SweDCIS (Holmberg et al. 2008).[21] 1046 pts with DCIS RTC lumpectomy ± 50 Gy RT.
5 year follow up showed RT ↓ noninvasive LF 13% → 4% and invasive LF 9% → 3% with a TOTAL LF 22% → 7%. No Δ DM or OS.
Younger women have a low protective effect of conventional RT after sector resection.
Older women benefit substantially.
Criticism: 20% positive/unknown margins on SweDCIS.

UKCCCR UK/ANK (2x2). Excision alone, excision + tam, excision + RT, all 3.
Crude incidence rate of LR 14% → 6% from no RT to with RT.
Addition of tam to RT offered minimal benefit towards ipsilateral LCR.
But tam without RT did ↓ recurrence of DCIS!

Criticism: These are not the same patient population with small mag-view DCIS seen on mammogram. These were large or clinically palpable, etc. 1980's DCIS is 5% of cases. 2018, it is 15-20%.

Long term follow-ups:p
NSABP 35 vs 20%
EORTC 31% vs 18%
SweDCIS 32 vs 20%
UK/ANZ 23 vs 9%

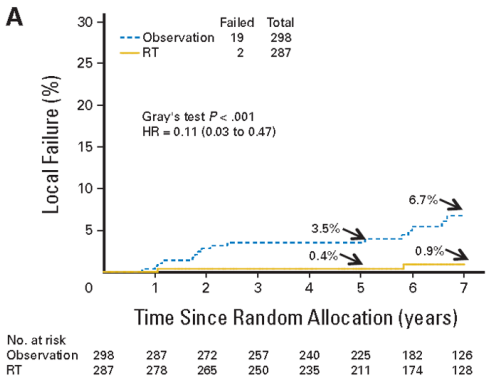
EBCTCG Metaaanlysis, Correa JNCI Mono 2010
Lumpectomy without RT 28.1% risk of LR versus 12.9% for lumpectomy + RT

[20] http://www.ncbi.nlm.nih.gov/pubmed/16801628
[21] http://www.ncbi.nlm.nih.gov/pubmed/18250350

Contemporary Trials (± RT)

- Historical Metaanalysis: Vinh-Hung, JCNI 2004.
  - BCS with and without RT metaanalysis. All these trials. Favors administration of RT when pooled.
- Also look below and see EBCTCG Darby 2011 RT after BCS in invasive cancer. All advantages.
  - EXECPT if any recurrence is < 20%. Then no difference in BCa mortality.

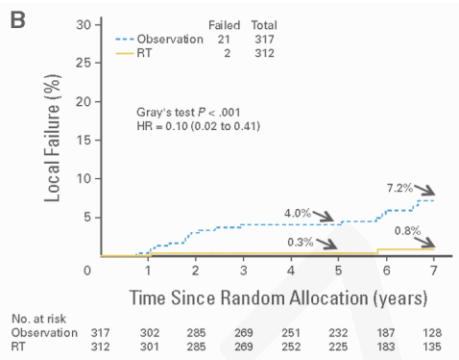
- **4 Major trials MUST KNOW: RTOG 98-04, Harvard Single Arm, Van Nuys, ECOG 5194**.

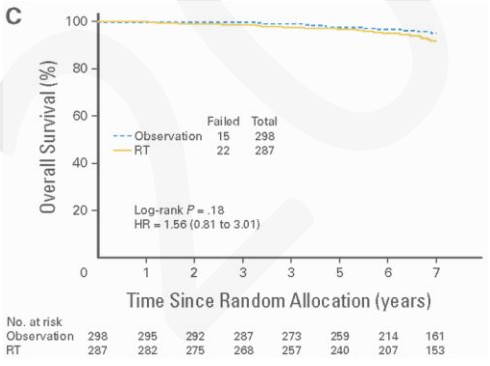


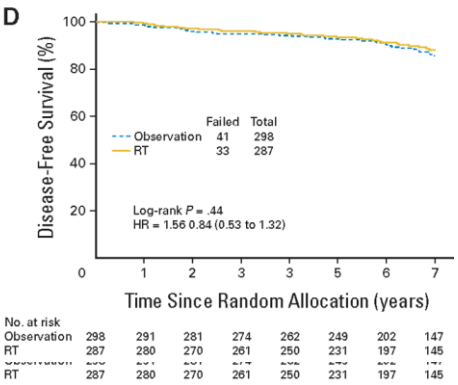
RTOG 98-04 -- RT vs. No RT. **Favorable GRADE.**
←R→ 636 out of 1,790. *Closed due to poor accrual.* "Good risk" DCIS, < 2.5 cm, margins > 3mm, grade I-II only, necrosis in < 1/3 of the ducts.
BCS → 1. RT vs. 2. no RT. **WBRT choice of 50.4 Gy in 1.8 Gy fxs, 50 Gy in 2 Gy, or 42.5 Gy in 16 fx.**
Tamoxifen at 20 mg qd x 5 yrs (choice of physician) 62% used.
Intention to use tamoxifen was balanced between arms (69%).
However, actual receipt of tamoxifen varied, 58% RT versus 66% OBS (P = .05).
Ipsilateral LF 1^{O} EP.
Mean Pathologic DCIS size 0.6 cm.

McCormick, JCO 2015. 7 years.
Two LFs occurred in the RT arm, and 19 occurred in the observation arm. At 7 years, the LF rate was 0.9% (95% CI, 0.0% to 2.2%) in the RT arm versus 6.7% (95% CI, 3.2% to 9.6%) in the observation arm (hazard ratio, 0.11; 95% CI, 0.03 to 0.47; P < .001).
Grade 1 to 2 acute toxicities: 30% obs and 76% RT; grade 3 or 4 toxicities 4.0% and 4.2% of patients, respectively.
Late RT toxicity was grade 1 in 30%, grade 2 in 4.6%, and grade 3 in 0.7% of patients.

ASTRO 2018 12-year update: Cumulate incidence IBTR: 2.8 WBRT vs 11.4 OBS (SS).
Invasive IBTR 1.5% WBRT vs. 5.8% OBS (SS)







McCormick, JCO 2021 **13.9 years FU**
15-yr IBR was RT 7.1% vs. no RT 15.1% (SS). 15-yr invasive LR 5.4% vs. 9.5% (SS).
MVA, only RT (HR = 0.34; 95% CI, 0.19 to 0.64; P = .0007) and tamoxifen use (HR = 0.45; 95% CI, 0.25 to 0.78; P = .0047) were associated with reduced IBR.
Conclusion: RT significantly reduced all and invasive IBR for good-risk DCIS with durable results at 15 years. These results are not an absolute indication for RT but rather should inform shared patient-physician treatment decisions about ipsilateral breast risk reduction in the long term following lumpectomy.

ECOG 5194 (Hughes JCO 2009, Solin JCO 2015). 665 patients. **ALL MAMMOGRAM DETECTED.**
COHORT 1 < 2.5 cm + G1-2. COHORT 2 < 1.0 cm + G3.
ALL NO RADIATION.
At least 3 mm were required, and negative post-excision mammogram was obtained for all participants. Tamoxifen following excision was allowed but not mandated. MEDIAN SIZE OF LESION 0.6 cm.
5-year LRR at for patients with low or intermediate-grade DCIS (n = 565) was 6.1% and for patients with high-grade DCIS (n = 105) was 15.3%. Too high of 15.3% You have to RT. Rigorously evaluated and selected patients with low- to intermediate-grade DCIS with margins 3 mm or wider had an acceptably low rate of ipsilateral breast events at 5 years after excision without irradiation.
12-year LRR, 14% (G1-2) vs 24% (G3s). Patients with higher grade and younger are more at risk for ipsilateral breast recurrence.

Gene expression analysis. No reliable clinical/pathologic feature that can predict the rate of local recurrence with WLE alone vs WLE/RT.

Note: When the trial was done, there was no mandate for hormonal therapy. During trial, they gave a mandate for hormonal therapy. And only eventually 30% of patients received hormones.

WLE alone may be sufficient for select patients with low- to intermediate-grade DCIS, but it is inadequate for patients with high-grade lesions.
∴ RT remains an important treatment for reducing risk of ipsilateral breast disease.
Harvard Single Arm Group Prospective group.

Purpose. It has been hypothesized that wide excision alone with margins ≥ 1 cm may be adequate treatment for small, grade 1 or 2 ductal carcinoma in situ (DCIS). To test this hypothesis, we conducted a prospective, single-arm trial WITHOUT adjuvant Tx (RT or Hormones)
Methods Entry criteria included DCIS of predominant grade 1 or 2 with a mammographic extent of ≤ 2.5 cm treated with wide excision with final margins of ≥ 1 cm or a re-excision without residual DCIS. Tamoxifen was not permitted. The accrual goal was 200 patients.

Wong, JCO 2006
Results: In July 2002, the study closed to accrual at 158 patients because the number of local recurrences met the predetermined stopping rules. The median age was 51 and the median follow-up time was 40 months.
FAILURE: 13 LR as first site of treatment failure 7 to 63 months after study entry. Rate of ipsilateral LR 2.4% per patient-year (5-yr rate 12%).
9 (69%) experienced recurrence of DCIS and 4 (31%) experienced recurrence with invasive disease.
Twelve recurrences were detected mammographically and one was palpable. Ten were in the same quadrant as the initial DCIS and three were elsewhere within the ipsilateral breast. No patient had positive axillary nodes at recurrence or subsequent metastatic disease.
Conclusion. Despite margins of ≥ 1 cm, the local recurrence rate is substantial when patients with small, grade 1 or 2 DCIS are treated with wide excision alone. This risk should be considered in assessing the possible use of radiation therapy with or without tamoxifen in these patients.
Criticism: **Low grade "predominant" but with some had high grade component were allowed in trial**. Those who recurred were those with probably high-grade component.

Characteristic	No.	No. With Local Recurrence First	Estimated Annual Percentage Rate
Predominant nuclear grade			
Unknown	2	0	0.0
1	88	7	2.3
2	68	6	2.5
Highest nuclear grade			
Unknown	2	0	0.0
1	75	5	2.0
2	71	4	1.6
3	10	4	11.8

Silverstein, Commentary in the Breast Journal.
Re: Modified DCIS-VanNuys Scoring System
Intra op pathology reporting. Not generalizable to all hospitals.

SCORE	1	2	3
SIZE	<15 mm	16-40	>41
MARGIN	≥ 10 mm	1-9 mm	< 1 mm
PATH	NOT HI GRADE NO NECROSIS	NOT HI GRADE W/ NECROSIS	HI GRADE W/WO NECROSIS
AGE	>61	40-60	<40

VNPI (Silverstein 2003). Retrospective review of 706 patients s/p BCT w/wo RT based on 4 parameters and a score of 4-12.
- Tumor size (≤ 1.5, 1.6-4.0, ≥ 4.1 cm).
- Pathology (non high-grade without necrosis, non high-grade with necrosis, high grade).
- Margins (≥1, 0.1-0.9, < 0.1 cm).
- Age (> 60, 40-60, < 40 yrs)

For low risk (score 4-6), no significant difference in 12-year local RFS (>90-95%) with or without RT.
For med risk (score 7-9) **addition of RT** provided 12-15% 12-year local RFS benefit.
For high risk (score 10-12) mastectomy recommended due to high 5-year LR (~50%) with or without RT.

Criticism: Is this exportable to the community? Silverstein was a breast surgeon. Lagios was pathologist. They did things in a very sophisticated way.

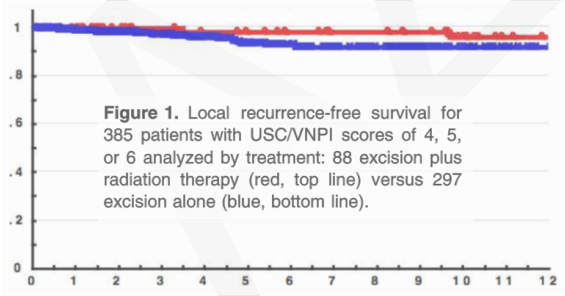


Figure 1. Local recurrence-free survival for 385 patients with USC/VNPI scores of 4, 5, or 6 analyzed by treatment: 88 excision plus radiation therapy (red, top line) versus 297 excision alone (blue, bottom line).

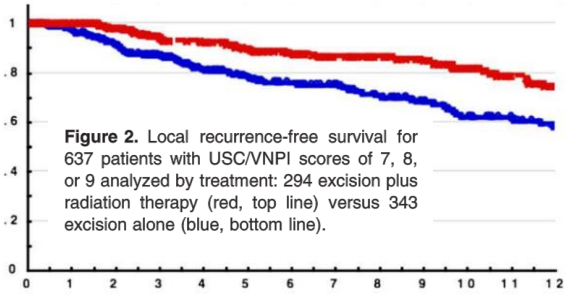


Figure 2. Local recurrence-free survival for 637 patients with USC/VNPI scores of 7, 8, or 9 analyzed by treatment: 294 excision plus radiation therapy (red, top line) versus 343 excision alone (blue, bottom line).

Table 2. Minimum Treatment Recommendations to Achieve a Local Recurrence Rate <20% at 12 years Using the USC/VNPI Scoring System

USC/VNPI	Treatment	12-year recur (%)
4, 5, or 6	Excision alone	<8
7, margins ≥3 mm	Excision alone	13
7, margins <3 mm	Radiation	19
8, margins ≥3 mm	Radiation	13
8, margins <3 mm	Mastectomy	0
9, margins ≥5 mm	Radiation	17
9, margins <5 mm	Mastectomy	0
10, 11, or 12	Mastectomy	8

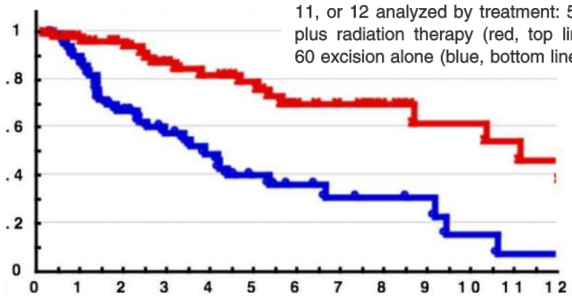
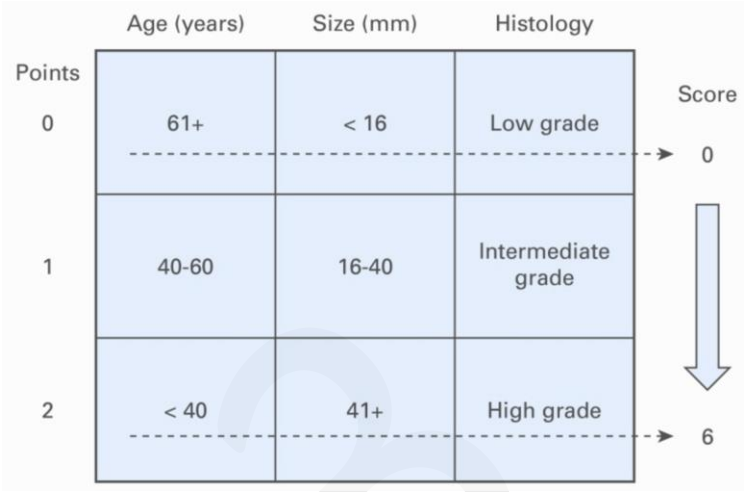
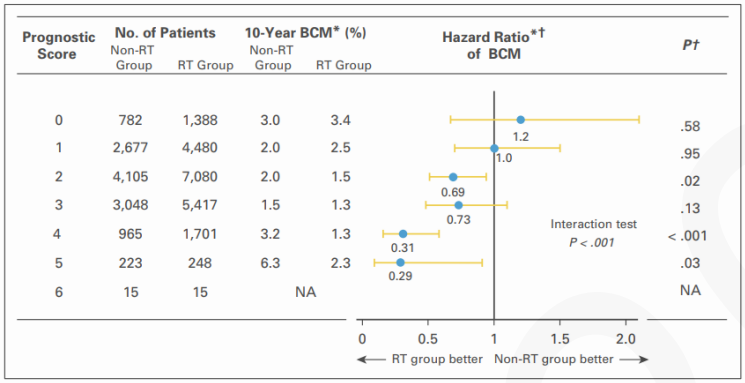


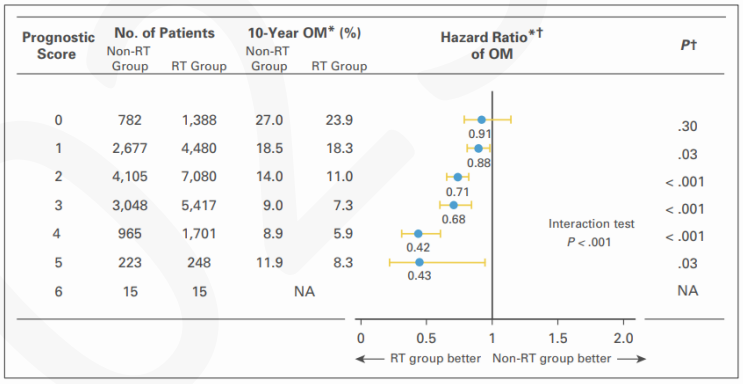
Figure 4. Local recurrence-free survival for 116 patients with USC/VNPI scores of 10, 11, or 12 analyzed by treatment: 56 excision plus radiation therapy (red, top line) versus 60 excision alone (blue, bottom line).

Yasuaki Sagara, JCO 2016. SEER DCIS patients with without RT.
Note: SEER database does NOT have margins.
Methods: Retrospective. DCIS. 2 Groups BCS+RT (RT group) and BCS alone (non-RT group). 32,144 eligible patients with DCIS, 20,329 (63%) in the RT group and 11,815 (37%) in the non-RT group.
Results: Cumulative incidence of breast cancer mortality at 10 years in the weighted cohorts of 1.8% (RT group) and 2.1% (non-RT group; hazard ratio, 0.73; 95% CI, 0.62 to 0.88). Significant improvements in survival in the RT group compared with the non-RT group were only observed in patients with higher nuclear grade, younger age, and larger tumor size. The magnitude of the survival difference with RT was significantly correlated with prognostic score (P , .001).
Conclusion
In this population-based study, the patient prognostic score for DCIS is associated with the magnitude of improvement in survival offered by RT after BCS, suggesting that decisions for RT could be tailored on the basis of patient factors, tumor biology, and the prognostic score.

This was basically a revisit of Haffty's original paper that had the criteria on the right.







Hypofractionation

- Hypofractionation (Whole breast RT over 3-4 weeks as opposed to 6-7 weeks) has become an acceptable and perhaps preferred standard of care for early stage invasive breast cancer.
- New data suggests that hypofractionation should be standard in DCIS patients.
- Historically, some radiation oncologists are reluctant to use whole breast hypo-fractionation when treating DCIS due to a previous lack of data.

BIG 3-07/TROG 07.01
←R→ 1608, four arm trial. About 50/50 split conventional or Hypofx (42.5 Gy in 16 fx). | 1. No boost | 2. Boost (16 Gy in 8 fx) |.
Eligibility, ≥18 yo "non-low risk DCIS" = age <50 or age ≥50 + 1 RF (palpable tumor, multifocal disease, tumor size ≥ 1.5cm, G2-3, central necrosis, comedo histology, Margin < 1 cm).
Adjuvant endocrine therapy = only 13% (all arms).
1^{O} time to LR.

Chua, Lancet 2022.
Median follow-up was 6.6 years.
5-yr FFLR: 93% no boost vs. 97% boost (SS; P<0.001). 45% of all LRs are invasive.
The effect of boost did not vary significantly by age, tumor size, nuclear grade, surgical margin or endocrine therapy.
5-yr FFLR: NS Conventional vs. Hypofx (94%).
Side effects: ≥G2 breast pain (10% vs 14%, p=0·003) and induration (6% vs 14%, p<0·001).
Conclusions: In patients with resected non-low-risk DCIS, a tumour bed boost after WBI reduced local recurrence with an increase in grade 2 or greater toxicity. The results provide the first randomised trial data to support the use of boost radiation after postoperative WBI in these patients to improve local control. The international scale of the study supports the generalisability of the results.

Also → Must See "Offersen, JCO 2020" → Under "Major HFx-U-Hfx Trials"
10-15% of patients with DCIS randomized between standard and hypofractionation.

Wai et al. Cancer 2011
440 Patients Treated with Canadian Hypofractionation (4250 Gy in 16 Fractions)
FU 4.4 Yrs
28% Received Boost (4 Fractions)
5-Year local Control Rate 97% = VERY HIGH CONTROL RATES.

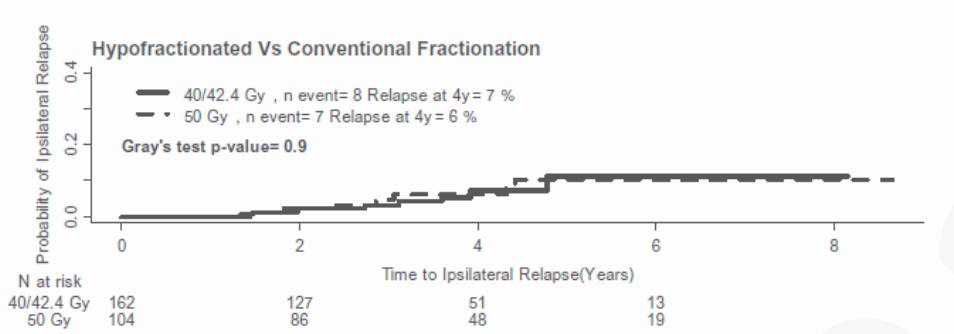


Fig. 1. Cumulative incidence of ipsilateral breast relapse for hypofractionated vs. conventional fractionation.

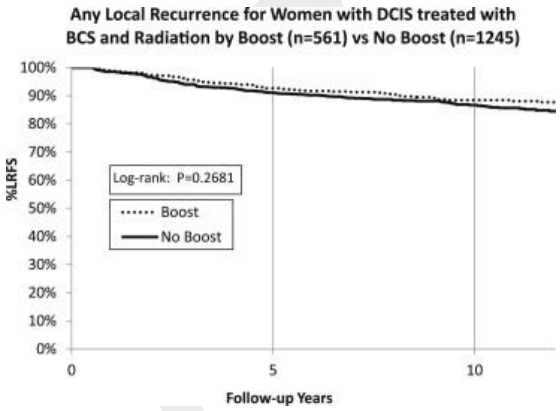
Princess Margaret.
(Williamson et al. Radiotherapy and Oncology 2010)
RR 266 patients.
Conventional 50 Gy (39%) vs.
Hypofractionation in either 42.4 in 16 fx or 40 Gy in 16 fx + 12.5 Gy boost (61%).

RESULTS:
No DIFFERENCE in LR 6%.
High grade ↑ LR 4% → 11%.

Boost

ASTRO FRACTIONATION CONSENSUS 2018.
Tumor bed boost may be used with young ≤ 50, high grade, or close margins.
But may be omitted.

Moran, JAMA 2017. POSITIVE STUDY.
4131 patients. Boost vs. No boost.
Retrospective analysis shows that higher risk comedo, margins, unknown ER were more likely to receive boost.
10-year IBTR 91.6% vs 88% to favor boost.
This is important since SS EVEN THOUGH higher risk patients.



Toronto. **Rakovitch, IJROBP 2013.** Negative Study.
RR 1895 patients with DCIS → BCS + RT. 70% hypofractionated 40-44 Gy in 16 fx. 30 with boost.
10-year LR 12-13% (NS). Invasive recurrence is 50% of all recurences.
NOTE: these are biased because of observational. Those who used boost probably have worse features. Those who didn't use boost probably had more favorable features. So… washed out.

Switzerland (Omlin, Lancet 2006) POSITIVE STUDY
RR 373 all ≤ 45, pure DCIS, breast conserving surgery. 40% RT + 10 Gy boost. 45% RT no boost.
Median whole breast RT dose: 50Gy; Median boost dose: 10Gy
Results: F-U: 6 y
LRFS at 10 y: 46% (no RT); 72% (RT, no boost); 86% (RT + boost) (p<0.0001)
Compared with patient who had no RT, those who had RT had a decreased risk of LRR (HR: 0.33 w/o boost; HR: 0.15 w/ boost)

Genomic Classifiers / Oncotype DCIS

DCISonRT Trials: https://preludedx.com/our-publications/

ASCO 2022. DCISionRT with integrated Residual Risk subtype (RRt).
926 patients → DCISionRT/RRt classified 338 (37%) women as Low Risk, 399 (43%) as Elevated Risk, and 189 (20%) as Residual Risk.
Low Risk (DS≤2.8), Elevated Risk (DS > 2.8 without RRt) and c) Residual Risk (DS > 2.8 with RRt).
All treated with BCS ± RT/ET.
1^{O} 10-yr total (invasive and in situ) IBR.

Whitworth, ASCO 2022.

10-year IBR	BCS (no RT) ± ET	Low risk = 5.6% (NS).	± ET did not make a difference.
		Elevated Risk 22.6%	+ ET ↓ to 11.6% (SS).
		Residual Risk 50.3%	+ ET ↓ to 15.4% (SS).
		Overall (HR = 0.55, p = 0.033).	+ ET improved SS IBR.
10-year IBR	BCS ± RT	Low risk	± RT did not ↓ IBR
		Elevated Risk	+ RT ↓ to 6.3% (SS)
		Residual Risk	+ RT ↓ to 12.5% (SS).
10-year IBR	BCS + RT ± ET	Elevated Risk	± ET did not make a difference.
		Residual Risk	± ET did not make a difference.

Conclusions: The DCISionRT/RRt biosignature demonstrated prognostic and predictive RT response in Elevated and Residual Risk patients. Consistent with prior RCT data, ET was associated with lower 10-yr IBR risk overall, and within the DCISionRT Elevated and Residual Risk groups without RT. However, neither ET nor RT were asssociated with significant risk reduction in the Low Risk group. There was no added benefit of ET in the Elevated and Residual Risk groups after BCS+RT; the Residual Risk group patients still had a high IBR risk after RT.

Takeaway: If LOW RISK and you OMIT adj RT, then any additional ET makes no difference.
If HIGH RISK and you ADD adj RT, then any additional ET makes no difference.

DCISonRT Validation in SweDCIS
Tumor blocks were collected, and slides were sent to PreludeDxTM for testing.
In 504 women with complete data and negative margins, DCISionRT divided 52% women into Elevated (DS > 3) and 48% in Low (DS ≤ 3) Risk groups.
Elevated Risk group, RT SS ↓←→ 10-year ipsilateral total recurrence (TotBE) and 10-year ipsilateral invasive recurrence (InvBE) rates, HR 0.32 and HR 0.24, with absolute decreases of 15.5% and 9.3%.
Low-Risk group, NS Δ with radiotherapy.
Using a cutoff of DS > 3.0, the test was **not predictive for RT benefit** (p = 0.093); however, above DS > 2.8 RT benefit was greater for InvBE (interaction p = 0.038). Recurrences at 10 years without radiotherapy increased significantly per 5 DS units (TotBE HR:1.5 and InvBE HR:1.5). Continuous DS was prognostic for TotBE risk although categorical DS did not reach significance. Absolute 10-year TotBE and InvBE risks appear sufficiently different to indicate that DCISionRT can aid physicians in selecting individualized adjuvant DCIS treatment strategies. Further analyses are planned in combined cohorts to increase statistical power.

PREDICT DCISonRT Trial

←R→ 539 women. 25 years or older who were treated with BCS for unilateral DCIS. RTOG 98-04 50% good DCIS. 32% G3.65% ≤ 1 cm.

Shah, Ann Surg Oncol 2021.

Pre DCISionRT testing, RT recommended to 69% of patients. Post-testing, a Δ in RT recommendation 42% of patients.

↓ recommended RT decreased by 20%.

For women initially recommended not to receive an RT pre-test, 35% had their recommendation changed to add RT following testing.

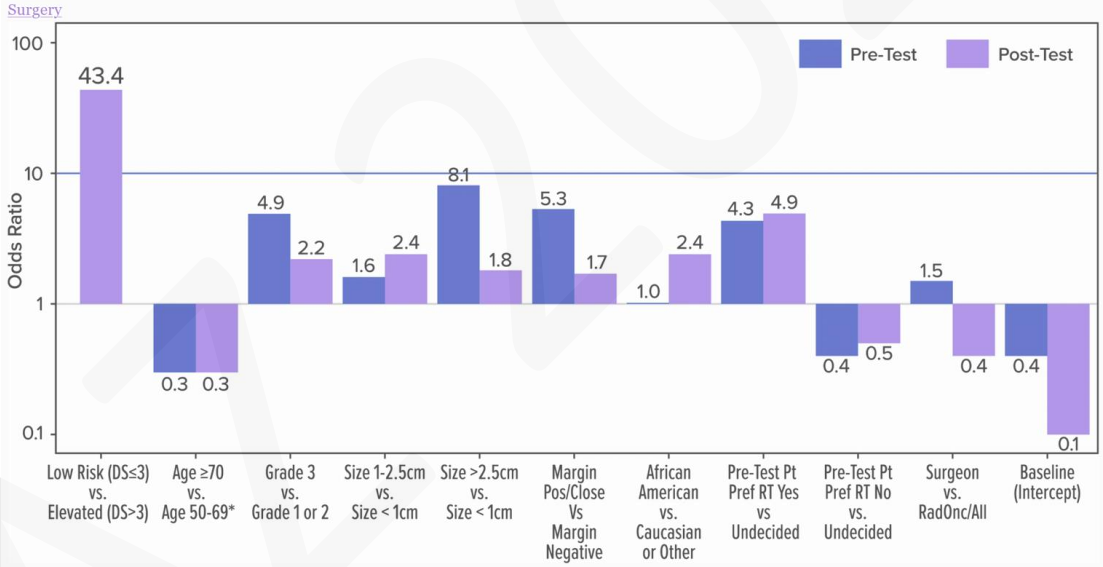
While post-test, 46% of patients had their recommendation changed to omit RT after an initial recommendation for RT.

When considered in conjunction with other clinicopathologic factors, the elevated DCISionRT score risk group (DS > 3) had the strongest association with an RT recommendation (odds ratio 43.4) compared with age, grade, size, margin status, and other factors.

Conclusions DCISionRT provided information that significantly changed the recommendations to add or omit RT. Compared with traditional clinicopathologic features used to determine recommendations for or against RT, the factor most strongly associated with RT recommendations was the DCISionRT result, with other factors of importance being patient preference, tumor size, and grade.

Recommending physician	*n*	RT recommended			Pre- to post-test change in RT recommended		Total change in RT recommended		
		Pre-test (%)	Post-test (%)	Net change (%)	Yes to no (%)	No to yes (%)	Overall change (%)	95% CI	*p*-Value
All	539	69	49	− 20	46	35	42	38–47%	< 0.001
Radiation oncologists (independently)	191	73	53	− 20	44	44	44	37–47%	< 0.001
All radiation oncologists (independently or with Tumor Board)	306	67	56	− 11	37	40	38	32–47%	0.001
Surgeons (independently)	232	72	39	− 33	57	28	49	42–47%	< 0.001

From: The Clinical Utility of DCISionRT® on Radiation Therapy Decision Making in Patients with Ductal Carcinoma In Situ Following Breast-Conserving Surgery



Factors associated with the recommendation of RT before and after DCISionRT. *RT* radiation therapy. See Table 6 for complete list of factors associated with decision making, including non-significant factors

Retrospective 21-Gene Assay
1362 DCIS ≤ 75 yo population-based analysis s/p BCS for DCIS.
16 year median FU.

Rakovitch, J Natl Cancer Inst 2020
With 16 years median follow-up, 36 (2.6%) died of BC, and 200 (14.7%) died of other causes.
Median RS = 15 (range = 0-84). 29.6% of individuals had a ↑ RS.
↑ RS (age < 50, s/p BCS alone) 11-fold increased risk of BC mortality (HR = 11.27, P < .001)
20-year risk of BC death = 9.4%.
↑ RS women (s/p BCS + RT) 20-year risk of BC death ↓ relative 71% (P=0.03), **↓ 5% abs**.
Conclusion: The 21-gene RS predicts BC mortality in DCIS and combined with age (50 years or younger) at diagnosis can identify individuals for whom radiotherapy reduces the risk of death from BC.

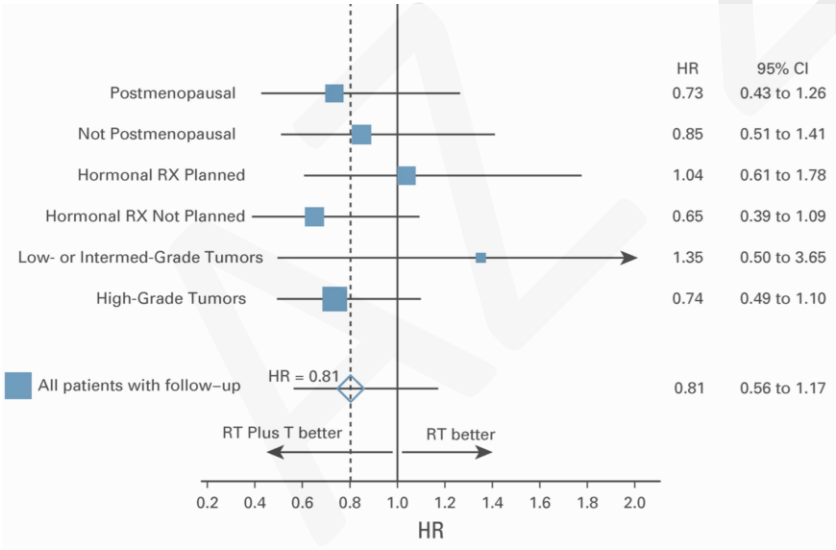
ECOG 5194 Subset (Solin JNCI 2013).
Subset of 327 patients, which identified 3 groups (70% low risk, 16% intermediate, 14% high).
IBTR risks of 10.6%, 26.7%, and 25.9% respectively.
Invasive risk 3.7%, 12.3%, and 19.2% respectively.

DCIS Oncotype (Rakovitch, Breast Cancer Res Treat 2015).
Retrospective population based cohort of 718 cases with surgery and negative margins. FU 9.6 years.
10-year LR 12.7%, 33%, 27.8%.
High enough that regardless of grade, you have to treat with RT.

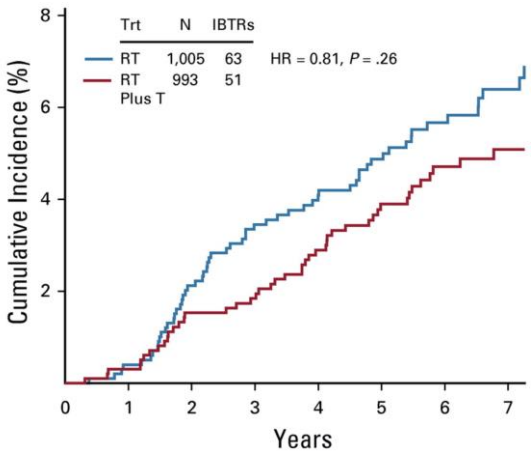
Adj Hormonal TX for DCIS

- **Hormonal Therapy**: Based on long term NSABP B-17 and B-24 data, Tamoxifen for ER/PR+ DCIS reduces local recurrence after lumpectomy and RT.
  - 15 year cumulative incidence of invasive ipsilateral recurrence for BCT + tam (8.5%) vs BCT + placebo (10.0%).
  - 15-year cumulative incidence of all contralateral breast cancers for BCT + tam (7.3%) vs BCT + placebo (10.8%)
  - 15-year cumulative risk of breast cancer death was similar (2.3 versus 2.7 percent). **No Difference in DM or OS**.

B-43. Reason Trastuzumab is not given in DCIS.
←R→ 2014 all DCIS → lumpectomy → | 1. WBRT alone | 2. WBRT concurrently with Trastuzumab (T) |.
1% G1, 15% G2, 84% G3. 40% ER neg, 60% ER pos.



Cobleigh, JCO 2021. FU 79.2 months.
IBRT Events (n=114) RT 63 vs. RT+T 51 (HR 0.81; NS)
IBRT Invasive (n=34) RT 18 vs. RT+T 20 (NS).
IBRT DCIS (n=76) RT 45 vs. RT+T 31 (NS).
Annual IBTR% rates RT 0.99%/y vs. RT+T arm, 0.79%/y.
The study did not reach the 163 protocol-specified events, so the definitive analysis was triggered by all patients having been on study for ≥ 5 years.



CONCLUSION
Addition of T to RT did not achieve the objective of 36% reduction in IBTR rate but did achieve a modest but statistically nonsignificant reduction of 19%. Nonetheless, this trial had negative results. Further exploration of RT plus T is needed in HER2-positive DCIS before its routine delivery in patients with DCIS resected by lumpectomy.

Cost-Effective DCIS Adj Tx Study
Comparing 6 TXs: 1. Obs, 2. tamoxifen (TAM) alone, 3. aromatase inhibitor (AI) alone, 4. radiation treatment (RT) alone, 5. RT + TAM, and 6. RT + AI.
Recurrence rates adopted from NSABP B17 (Std- Risk) and RTOG 9804 (Good-risk) DCIS.
RT cost evaluated as hypofractionation.

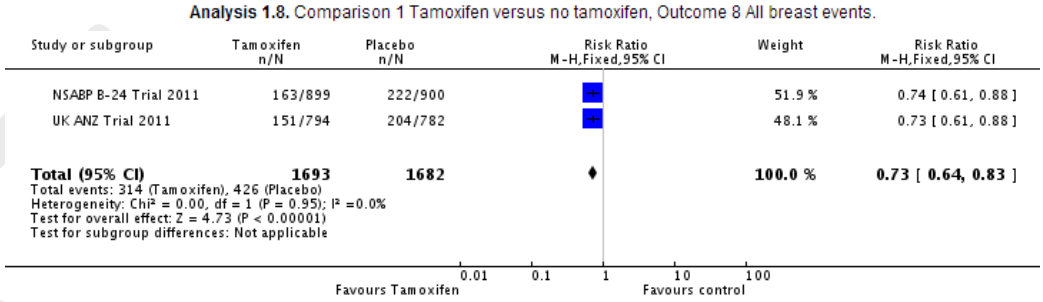
Gupta, JCO 2021.
Key Points:
1. "We found that for patients of any age with standard-risk disease, RT alone was cost-effective, whereas for patients with good-risk disease, observation was cost-effective."
2. "The poor QOL that patients experience while on hormonal therapy is evidenced by their poor tolerability, leading to only 30% compliance with a full 5-year course."[22,23]
3. "In summary, the trade-off between efficacy and side effects is not favorable for hormonal treatment, either alone or in combination with RT."
4."Hormonal therapy is likely suboptimal for most patients with DCIS."

TAM01 Study
←R→ 500 women ≤ 75 yo with ER+ DCIS s/p BCS | 1. 5 mg Tam daily for 3 years | 2. Placebo |.
1^{O} incidence of invasive breast cancer or ductal carcinoma in situ.

DeCensi, JCO 2019.
5-year IBR n = 14 vs. 28 (11.6 v 23.9 per 1,000 person-years) = HR 0.48; P = .02.,
5-year number needed to treat = 22 (95% CI, 20 to 27).
Tamoxifen ↓ contralateral breast events by 75% (3 vs. 12 events; HR 0.25; P = .02).
Patient-reported outcomes ↑ slight increase in frequency of daily hot flashes with tamoxifen (P = .02).
There were 12 serious adverse events with tamoxifen and 16 with placebo, including one deep vein thrombosis and one stage I endometrial cancer with tamoxifen and one pulmonary embolism with placebo.
CONCLUSION
Tamoxifen at 5 mg/d for 3 years can halve the recurrence of breast intraepithelial neoplasia with a limited toxicity, which provides a new treatment option in these disorders.

Older RTC DCIS Trials with BCS/RT ± Tamoxifen.

Metaanalysis (Staley 2012).[24] 2 RTC with 3375 women. With the addition of tamoxifen to BCT for DCIS…
↓ recurrence ipsilateral DCIS (hazard ratio [HR] 0.75, 95% CI **0.61-0.92**). ↓Contralateral DCIS (relative risk [RR] 0.50, 95% CI **0.28-0.87**).
↓ recurrence ipsilateral invasive carcinoma (HR 0.79, 95% CI **0.61-1.01**). ↓ Contralateral invasive carcinoma (RR 0.57, 95% CI **0.39-0.83**).
There was no benefit of tamoxifen in all-cause mortality (RR 1.11, 95% CI 0.89-1.39).



[22] Zhao H, Hei N, Wu Y, et al: Initiation of and adherence to tamoxifen and aromatase inhibitor therapy among elderly women with ductal carcinoma in situ. Cancer 123:940-947, 2017
[23] Flanagan MR, Rendi MH, Gadi VK, et al: Adjuvant endocrine therapy in patients with ductal carcinoma in situ: A population-based retrospective analysis from 2005 to 2012 in the National Cancer Data Base. Ann Surg Oncol
[24] http://www.ncbi.nlm.nih.gov/pubmed?term=23076938

NSABP B-24 (Fischer et al 1999, 2001, 2002, 2007**; Allred 2012[25])**. RTC 1804 DCIS (16% + margins, all unknown ER/PR status) s/p lumpectomy + 50Gy → randomized to 902 tamoxifen vs 902 placebo → after follow-up and finding pts with sufficient tissue for receptor status → only 41% of total: 368 tamoxifen vs 364 placebo. ER + in 76% pts. ER+ DCIS treated w/ tamoxifen (vs placebo): significant ↓ in LR BCa 10 years (hazard ratio [HR], 0.49; P < .001) and overall follow-up (HR, 0.60; P = .003), → remained significant multivariable analysis.

The only independently significant predictors of LR BCa were treatment status (tamoxifen vs placebo; HR, 0.64; P = .003) and age at entry (≤ 49 v ≥ 50 years; HR, 0.61; P < .001).

Subgroup analysis JCO Allred 2012: Chart:

Model Variable‡	Time to Any Breast Cancer As First Event		
	HR	95% CI	*P*
Patients with known ER status (n = 732)			
Treatment (tamoxifen vs. placebo)	0.643	0.481 to 0.861	.003
Age at entry, years (≤ 49 v ≥ 50)	0.609	0.457 to 0.812	< .001
All patients with follow-up (n = 1,799)			
Treatment (tamoxifen vs. placebo)	0.687	0.563 to 0.837	< .001
Age at entry, years (≤ 49 v ≥ 50)	0.621	0.510 to 0.756	< .001

BUT IF ER-, NO BENEFIT.

Similar but less significant results when subsequent ipsilateral and contralateral, invasive and noninvasive, BCa considered separately. No significant benefit was observed in ER-negative DCIS. PgR and either receptor were positive in 66% and 79% of patients, respectively, and neither was more predictive than ER alone.

B-35 Anastrozole Study.

←R→ Phase III 3104 post-menopausal ER or PR + DCIS | 1. anastrozole 1 mg/d | 2. Tamoxifen 20 mg/d | for 5 years. 1^{O} BCFI (free interval). 8.6 FU.

Margolese, ASCO 2015.

	ALL DFS	ALL BCFI	< 60 DFS	< 60 BCFI	> 60 DFS	> 60 BCFI
Tam	77.9%	89.1%	86%	91%	80%	93%
Anastrozole	82.7%	93.1%	90%	95%		
	--	SS	SS	SS	--	--

10-year OS 92% NS

REMINDER: Side effect: Anaztrozole: (fractures, MSK, HLD, CVA). Tamoxifen (PE, DVT, muscle spasm, vasomotor or gyn symtpoms).

[25] http://www.ncbi.nlm.nih.gov/pubmed/22393101

Stage 0 Disease: LCIS (Lobular Carcinoma In Situ):

"NOT A CANCER ANYMORE IN AJCC 8TH. It is ONLY A RISK of developing ipsilateral and contralateral invasive ductal or lobular carcinoma."

- **NCCN guidelines (AJCC 8th)**: REMOVED….(7th edition was present, but now it is removed).

- **NOTES**:
  - **PLEOMORPHIC LCIS is even in a more molecular perspective is like DCIS and many treat like DCIS.**
    - **Pleomorphic lobular carcinoma is a histologic variant of invasive lobular carcinoma that is associated with a poor prognosis. Pleomorphic LCIS has similar features to standard LCIS except for the finding of central necrosis with calcifications. It is associated with development of pleomorphic lobular carcinoma. There is no distinct mammographic appearance for pleomorphic LCIS. Management recommendation for pleomorphic LCIS is complete surgical excision with negative surgical margins.**
  - LCIS is detected in association with an invasive carcinoma in approximately 5% of malignant breast specimens.[26]
  - LCIS can present up to 90% mastectomy specimens with multicentric breast involvement and bilateral involvement in 35-59% cases.
  - **E-Cadherin (CDH1) gene lost in 95% cases. THIS TEST CONFIRMS LOBULAR vs Ductal.**
  - LCSI ↑ RISK OF developing IDC compared to normal population ↑ 10x.
  - Because LCIS is without clinical or mammograpahic indicators, LCIS is often just incidental during biopsy. (NOT VISIBLE ON MAMMO).
  - Manage breast → according to dominant histologic findings (DCIS or invasive disease) and **disregard** the LCIS presence.
    - Additional surgery not pursued to obtain LCIS clean margins.
  - If LCIS is sole histologic characteristic, there is no role for radiation.
    - You either observe, or if high risk (young, diffuse involvement, strong fam hx) → tamoxifen or bilateral mastectomy.

  ➢ **Studies on LCIS observation vs SERM**.
  SEER (Chuba 2005).[27] Retrospective 4,853 pts having LCIS (1973 to 1998). Incidence IBCa ↑ from DX, 7.1% (10 yr) and 18% (25 yr). IBCas detected **after WLE** → 46% ipsilateral and 54% contralateral; however, **after mastectomy** → IBCs were contralateral (94.7%). IBCs occurring after LCIS more often represented invasive lobular histology (23.1%) compared with primary IBCs (6.5%).

  NSABP (Fisher 2003). 12 year results: 180 patients LCIS treated with WLE and observation only.
  Overall → 26 IBTRs (14.4%) and 14 CBTRs (7.8%). 9 IBTRs (5.0% of the total cohort) and 10 CBTRs (5.6%) were invasive carcinomas.
  Conclusion: LCIS is an indolent disease. "There is no compelling reason to surgically treat LCIS other than conservatively."

  See above ***NSABP BCPT (P-1) Trial (Fischer et al 1998)*** : Tamoxifen (vs. placebo) ↓ invasive BCa 49%, ↓non-invasive BCa 50%.

Chemoprevention

Papers to consider: Chlebowski, JCO Pract Oncol 2021, Cuzik, Lancet 2019

Indications for chemoprevention.
Atypical hyperplasia, LCIS, ≥ 1.7 % 5-year risk breast cancer (Gail model), ±? Flat epithelial atypia.

NSABP BCPT (P-1) Trial (Fischer et al 1998): Non-blinded, randomized 13,388 ↑ risk women (≥60 yo, 5yr Gail predicted risk ≥ 1.66%, Hx LCIS) to placebo vs tamoxifen 20mg/day for 5 years. 54 mo follow up, tamoxifen ↓ invasive BCa 49%, ↓non-invasive BCa 50%, ↑ Endo.Ca RR 4.01. All EndoCa were stage 1 and NONE died from EndoCa. Tamoxifen also ↑ stroke, DVT, cataracts, MI, death.
No effect on ER – Bca. Recommended as chemoprevention, unless elderly with co-morbidities.

Multiple Outcomes Raloxifene Evaluation (MORE 1999). Multicenter, double blind, RCT → Raloxifene 60 or 120 mg/day vs placebo. Raloxifene at 36 weeks ↓ 30% vertebral fracture and ↑ 3.1 RR venous thromboembolus, ↓ ER + BCa 72% during 4 years of TX.

NSABP BCPT (P-2) STAR (Vogel et al 2006).[28] Multicenter, RCT 19,747 post-menopausal ↑ risk women (5yr Gail predicted risk ≥ 1.66%, + others). Tamox 20mg/day vs Ralox 50mg/day 5 years. Incidence same invasive BCa. Noninvasive (T 0.15%, R 0.21%).
Raloxifene ↓ uterine cancer (0.7% → 0.5%), cataracts, thromboembolic events, osteoporotic fractures, other cancers, heart disease.
After 8 years, **CORE** [29] **study** shows raloxifene continues to offer significant *durable* ↓ in invasive disease.

NSABP P-4 STELLAR (Rejected by NCI 2007). Raloxifene vs. letrozole (aromatase inhibitor) in high risk postmenopausal women.

[26] http://www.ncbi.nlm.nih.gov/pubmed?term=11346867
[27] http://www.ncbi.nlm.nih.gov/pubmed/16110014?dopt=Abstract
[28] http://www.ncbi.nlm.nih.gov/pubmed/16754727
[29] Martino, S, et al. 2004. Continuing outcomes relevant to evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J. Natl. Cancer Inst. 96: 1751–1761.

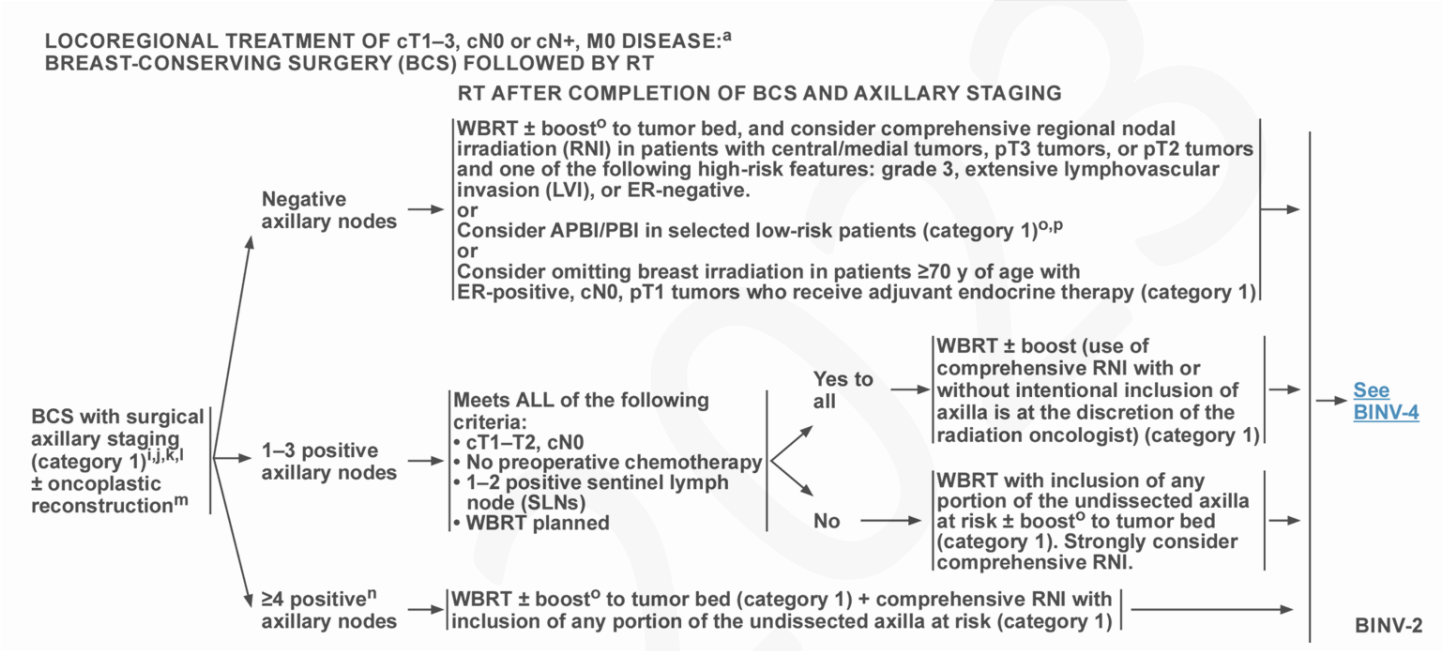
Early N0 Invasive BCa (T1-2)

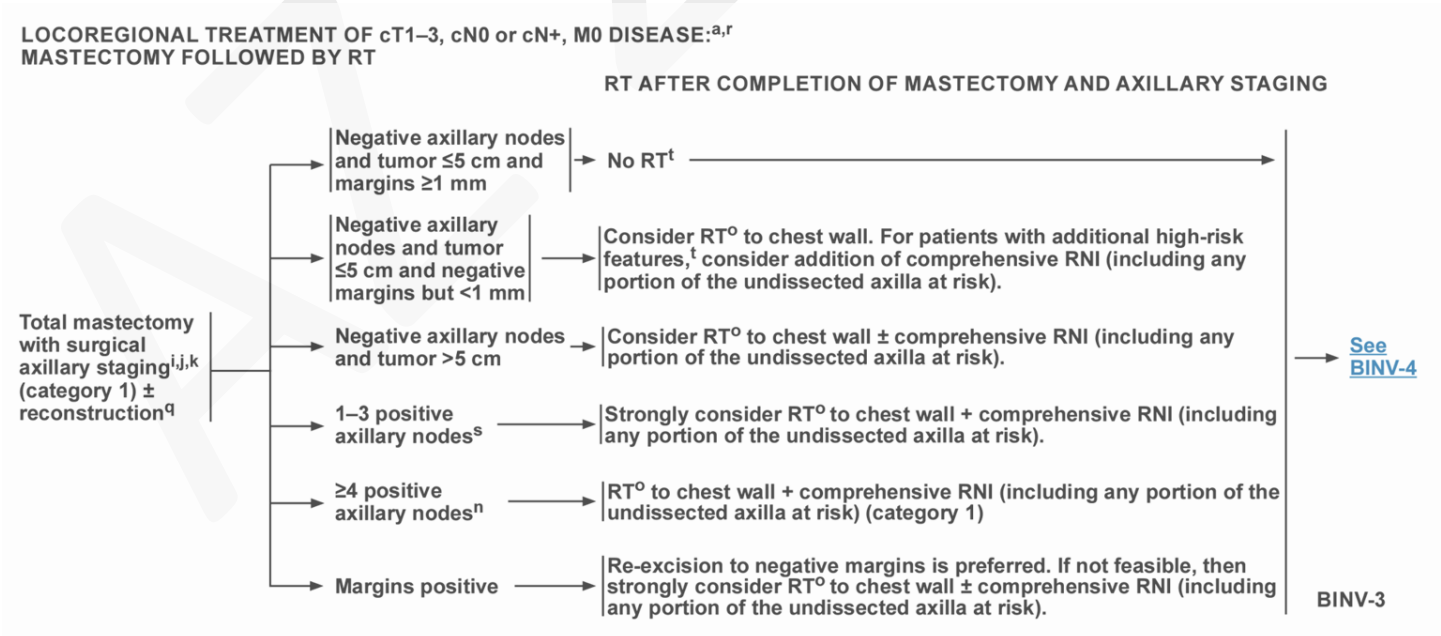
- **NCCN guidelines**:

  Generally…SCREENING mammo → DIAGNOSTIC mammo w/ spot compression + magnification → then stereotactic (aka image guided) biopsy.

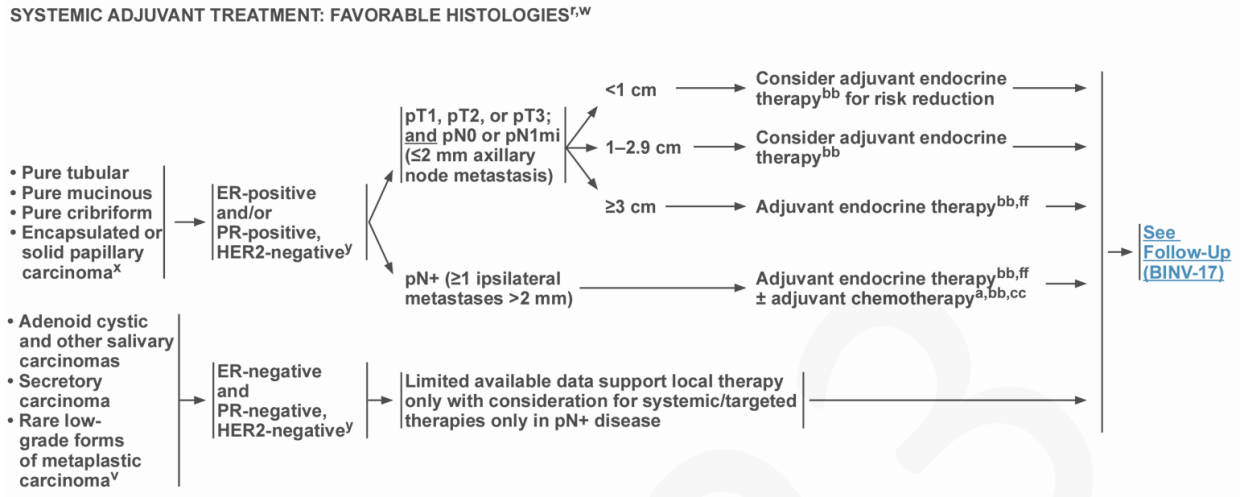
  - Workup: H&P, diagnostic b/l mammogram, pathology, receptor status, genetic counseling if high risk hereditary BCa, MRI optional.
    - Bone Scan **if** bone pain or elevated Alk Phos.
    - Abdominal CT / MRI **if** ↑ LFT, alk phos, GI symptoms, abnormal physical exam.
    - Chest CT **if** pulmonary symptoms.

  - Recommended Local Treatments:





- Recommended Systemic treatments:



Adjuvant Chemo decision (**aggressive histologies**: Ductal, Lobular, mixed, micropapillary)

- ER/PR +, Her2 + → pT1a N0 → ± Endocrine ± Chemo w/ **Trastuzumab (Herceptin)**
  pT1b N0 or pN1mi → **Endocrine** or **Chemo w/ Trastuzumab** + **endocrine**.
  ≥ pT1c or N+ → **Chemo w/ Trastuzumab** + **Endocrine**.

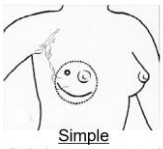
- Post-Menopausal
  ER/PR +, Her2 - → pT1a N0 → ± Endocrine
  → ≥ pT1b or pNmi/pN1 → **21 gene RT-PCR.**
  < 26 low = Endo
  ≥ 26 high (or not done) = **C→E both**
  → pN2/pN3 → **Chemo + endocrine (Cat 1)**

- Pre-Menopausal
  ER/PR +, Her2 - → pT1a N0 → ± Endocrine
  → ≥ pT1b N0 → **21 gene RT-PCR.**
  < 15 low = Endo → ovarian suppression/ablation
  16-25 int = either ↑ or ↓
  ≥ 26 high (or not done) = **C→E both**
  → pNmi/pN1 → **Chemo + endocrine** **if chemo candidate**
  → **endocrine** → ovarian suppression/ablation **otherwise**
  → pN2/pN3 → **Chemo + endocrine (Cat 1)**

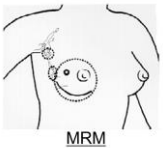
- ER/PR -, Her2 + → ≈ staging breakdown as triple positive, just without endocrine therapy
- ER/PR -, Her2 - → ≈ staging breakdown as triple positive, just only chemo

Surgery:

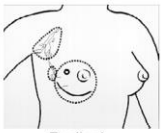
- Breast conservation therapy (lumpectomy + RT), is now commonly used and **considered the standard of care** in early stage BCa patients to provide locoregional control, similar DFS and OS compared to total mastectomy, and cosmetically acceptable surgical option.
  - **Contraindications** for BCT include:
    - Multi**centric** disease.
    - ↑ ratio of tumor size to breast size.
    - Diffuse malignant-appearing calcifications on imaging (mammogram or MRI).
    - Prior history of chest wall RT.
    - Pregnancy.
    - Persistently positive margins despite attempts at re-excision.
  - **Note**: young age is NOT considered a contraindication to BCT.[30] LN involvement is NOT a contraindication to BCT.
  - **Note:** Multi**focal** is NOT considered a contraindication to BCT according to recent data 2023.[31]
  - **Relative Contraindications:**
    - Scleroderma[32], CREST syndrome, mixed connective tissue diseases.
    - >5cm tumors
    - Fixation to the chest wall involvement of the nipple or overlying skin
    - Women ≤35yo with known BRCA1/2 mutation
      - Increased risk of ipsilateral or contralateral breast recurrence w/ BCT
      - Prophylactic b/l mastectomy for risk reduction may be considered



Simple
Only breast removed



MRM
Breast tissue + axillary LN (I-II)



Radical
Breast tissue + axillary LN (I-III) + pectoralis major & minor

- Total Mastectomy is also considered when patients are not candidates for BCT or per choice. Post-mastectomy RT is indicated for local control for those with cancer involving the deep margins and pathologically involved axillary lymph nodes. This will be discussed separately along with reconstruction timing. **Note**: Historically, radical mastectomy was performed, but this was an extremely morbid procedure. The advent of NSABP B-04 challenged the survival benefits between radical mastectomy vs. total mastectomy + RT vs. total mastectomy alone. There were 2 randomizations based on LN status: 1079 women with clinically LN – and 586 women with clinically LN +. 25 year follow up (Fisher 2002)[33] shows no advantage to radical mastectomy compared to total mastectomy + RT. Also, there was no survival advantage to removing occult positive nodes at the time of initial surgery or from radiation therapy. In a separate study in Copenhagen (Johansen 2008)[34], it is shown TM + RT to have less complications due to lymphedema (4% to 12%) over 50 years.

- TECHNICALLY ANY MODIFICATION OF A RADICAL IS A MODIFIED RADICAL MASTECTOMY.
  - THERE ARE DIFFEREN MRM. YOU TAKE PEC MINOR ANCHOLOSS VS PATEY's ETC.

- **Important Surgical Notes:**
  - Longer wait times (delays) from biopsy diagnosis to definitive surgery can be detrimental to survival (Weiner, JAMA Surg 2023).
    - "Findings of this case series study suggest the use of 8 weeks or less as a quality metric for time to surgery. Time to surgery of greater than 8 weeks may partly be associated with disadvantageous social determinants of health."[35]

[30] http://www.ncbi.nlm.nih.gov/pubmed/17275207?dop`=Abstract
[31] ACOSOG Z11102 https://ascopubs.org/doi/full/10.1200/JCO.22.02553
[32] http://www.ncbi.nlm.nih.gov/pubmed?term=11769860
[33] http://www.ncbi.nlm.nih.gov/pubmed/12192016?dopt=Abstract
[34] http://www.ncbi.nlm.nih.gov/pubmed/18465331?dopt=Abstract
[35] https://jamanetwork.com/journals/jamasurgery/article-abstract/2802104

BCS > Mastectomy

National Breast Cancer Registries 6-year Data
48986 women T1-2 N0-2 with surgery from 2008-2017 separated into 3 groups | 1. BCS + RT | 2. Mx alone | 3. Mx + RT |.
Median FU 6.28 years.

Boniface, JAMA 2021
All-cause death occurred in 6573 cases, with death caused by breast cancer in 2313 cases.
5-year OS 91.1% (95% CI, 90.8-91.3) 5-year BCSS 96.3%.
Mx-RT cohort were older, ↓ education, and ↓ income, ↑ comorbidity burden.
After stepwise adjustment for all covariates, OS and BCSS were significantly worse after Mx alone and Mx+RT vs. BCS + RT.

Mx alone (vs. BCS + RT)	HR OS 1.79 (95% CI, 1.66-1.92)	HR BCSS 1.66 (95% CI, 1.45-1.90)
Mx + RT (vs. BCS + RT)	HR OS 1.24 (95% CI, 1.13-1.37)	HR BCSS 1.26 (95% CI, 1.08-1.46)

Conclusions and Relevance: "Despite adjustment for previously unmeasured confounders, BCS+RT yielded better survival than Mx irrespective of RT. If both interventions are valid options, mastectomy should not be regarded as equal to breast conservation."

Mastectomy vs BCT + RT

NSABP B-06 (Fisher 2002).[36] RTC initiated in 1976, 1851 women Stage I, II BCa (< 4cm, - margins, ± LN) randomized to TM vs. WLE vs. WLE + RT 50 Gy. Axillary dissection of the lower two levels of lymph nodes were performed regardless of the treatment assignment. 20 year follow up showed no Δ among 3 groups regards to DFS, DDFS, or OS. Only +LN pts received 5-FU and Melphalan.
RT ↓ LF (regardless of LN status) 39.2% → 14.3% (p < 0.001). **The benefit of radiation therapy was independent of the nodal status.**
Axillary Dissection of Lv 1-**2 was performed regardless of randomization. LN recurrence 5% despite 38% pN+.**

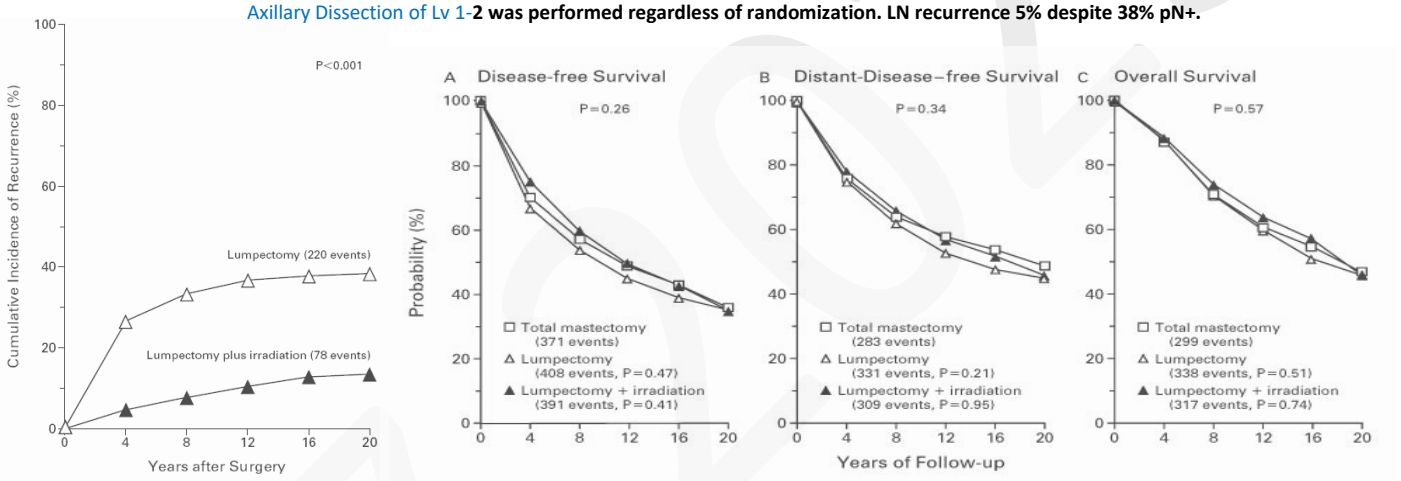


Figure 1. Cumulative Incidence of a First Recurrence of Cancer in the Ipsilateral Breast during 20 Years of Follow-up among 570 Women Treated with Lumpectomy Alone and 567 Treated with Lumpectomy plus Breast Irradiation.

	Node (-)		Node (+)	
	LF	OS / DFS	LF	OS / DFS
Lumpectomy	36.2	52.3 / 68	44.2	36.7 / 45.8
Lumpectomy + RT	17.0		8.8	
P	< 0.001		< 0.001	

ETORC 10801 (Van Dongen 2000).[37] RTC in 1980 with 868 patients, tumors ≤ 5cm (80% 2-5cm) randomized MRM vs. WLE with 1cm margin, complete axillary clearance, and RT 50Gy with 25 Gy IR-192 boost. IM RT given if central/medial tumor or if lateral tumor and axilla positive (45%). Margins not inked, re-excision only for macroscopic residual disease (48% in WLE group had + margins). Chemo CMF given if >55 years, or ≤44 + axillary LN+. At 10-years: LF **MRM 12**% vs. **BCT 20**% (p = 0.01). No Δ OS (66% vs. 65%) or DM (66% vs. 61%).

- **48% in lumpectomy arm had +margins**

Milan I (Veronesi 2002).[38] RTC in 1973 with 701 patients TXed with radical (Halsted) mastectomy (349 pts) vs. quadrantectomy followed by RT (352 pts) 50 Gy + boost 10 Gy. After 1976, patients with LN + received adjuvant CMF. BCa ≤ 2cm. LN+ in 25% (but possibly 35% due to inadequate pathology at that time). At 20-years f/u Ipsilateral LF: mastectomy 2% vs. BCS + RT 9% (p < 0.001). But interestingly, this rate is *identical* to rate of contralateral BCa, **suggesting "new primary carcinomas"** rather than recurrence. Actual in-quadrant recurrence was comparable to mastectomy (8 cases vs. 10 cases). No Δ DM, 20-year OS (41% death from all causes). **Conclusion**: BCS is the treatment of choice for women with relatively small breast cancers. Also, RT does not appreciably increase risk of contralateral BCA.

[36] http://www.ncbi.nlm.nih.gov/pubmed/12393820?dopt=Abstract
[37] http://www.ncbi.nlm.nih.gov/pubmed/10904087?dopt=Abstract
[38] http://www.ncbi.nlm.nih.gov/pubmed/12393819?dopt=Abstract

Surgical Margins

MARGIN STATUS RECOMMENDATIONS AFTER BCS FOR INVASIVE CANCERS AND DCIS

Invasive Breast Cancer

- For invasive breast cancers that have a component of DCIS, regardless of the extent of DCIS, the negative margin definition of "no ink on tumor" should be based on the invasive margin guideline. In this setting, "no ink on tumor" is recommended for either DCIS or invasive cancer cells, primarily because the natural history, treatment, and outcomes of these lesions are more similar to invasive cancer than DCIS. For specifically challenging cases, clinical judgment and discussion with the patient should precede routine re-excision.
- These margin recommendations cannot be applied directly to patients undergoing APBI/PBI,[1] where data regarding local recurrence are more limited. Furthermore, individualized clinical judgment should be utilized on a case-by-case basis, using postoperative mammography to identify residual calcifications and clinical-pathologic factors such as quantitative extent of disease near margin, presence of extensive intraductal component (EIC),[3] young age, or multiple close margins to assist in identifying patients who may have an increased risk of IBTR and therefore may be selected to benefit from re-excision.
- For patients with invasive breast cancer after BCS, with microscopically focally positive margins (in the absence of an EIC),[3] the use of a higher radiation boost dose to the tumor bed may be considered, since generally a boost to the tumor bed is recommended for patients at higher risk of recurrence. See BINV-I.

	No ink on tumor	2-mm margin	No margin necessary
Invasive breast cancer	X		
Invasive breast cancer + DCIS	X		
Invasive breast cancer + extensive DCIS	X		
Pure DCIS		X	
DCIS with microinvasion		X	
Pure LCIS* at surgical margin			X
Atypia at surgical margin			X

*For pleomorphic Lobular Carcinoma In Situ (LCIS), the optimal width of margins is not known.

- Poor surgical margins can lead to ↑ rates of LF.

Park 2000.[39] 533 patients clinical stage I or II BCa who had assessable margins, received at least 60 Gy primary tumor bed, and > 8 years f/u. Margin scored (by presence of invasive or in situ disease touching inked surgical margin) = neg, close, focally +, or extensively +. RT doses were not adjusted according to margin status. 8 yr LR: 7% (negative), 7% (close), 14% (focally +), and 27% (extens. +).

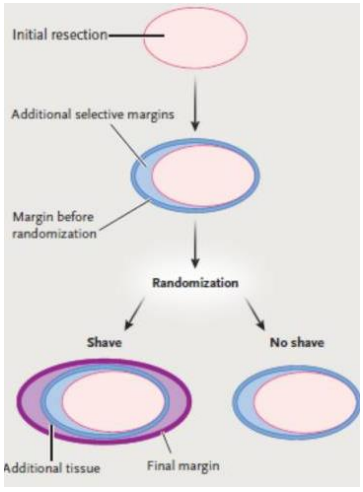
EORTC 22881/10882 (Jones 2009).[40] (See above for actual study results). Subset analysis of boost versus no boost trial in 1989, 5,569 patients. All pts lumpectomy + ALND → WBI; total dose of 50/25 Gy. Pt with microscopically neg margin → RTC WBI with either no boost or 16 Gy tumor bed. Pt with positive margins received WBI of 50 Gy to the breast → RTC extra boost dose of 10 or 26 Gy to the tumor bed. F/U 10 years.
Multivariate predictors LR: ↑ grade (SS), age <50 (SS), 16 Gy boost (SS). If ↑ grade, no boost 19% vs. boost 9% (SS). If age <50, 19% vs. 11% (SS).
Multivariate NON predictor: Margin of tumor (p = 0.33), systemic treatment. Yet, a criticism is that only 3.4% of invasive cases had + margins.

Comment on this study by MacDonald 2009.[41] Surgical re-excision should continue to be performed based on strength of multiple other studies. Age and grade worthy of further investigation.

- Automatic Shaving ↓ +SM

Yale Shave Margin Trial
←R→ 235 breast cancer stage 0 to III lumpectomy
| 1. Resection of selective margins | 2. No further cavitary shave margins |.
Randomization occurred intraoperatively after surgeons had completed standard partial mastectomy.
Positive margins = IDC inked surface or DCIS < 1mm. 1^{O} = rate of positive margins.
Median age 61.

Chagpar, NEJM 2015.
Before randomization, rate of positive margins 36% vs. 34% (NS).
After randomization, rate of positive margins 19% vs. 34% (SS).
After randomization, rate of 2nd surgery margin clearance 10% vs. 21% (SS).



[39] http://www.ncbi.nlm.nih.gov/pubmed/10764427?dopt=Abstract
[40] http://www.ncbi.nlm.nih.gov/pubmed/19720914?dopt=Abstract
[41] http://www.ncbi.nlm.nih.gov/pubmed/19720895?dopt=Abstract

Kaiser Shave Margin Trial

9054 BCS over 5 years (2016-2020) and 55 surgeons had a re-excision rate of 18.8%.

Individual surgeon's 5-year re-excision rates ranged from 7.8% to 36.8%, with a 3.3-fold difference between the 10th and 90th percentile.

In the survey, 53% of surgeons reported being in practice for more than 10 years, 31% having fellowship training (breast or surgical oncology), and 45% having breast-focused (>50% of cases) specialty practices.

Chakedis, JAMA Net Open 2022

Surgeons who always used cavity shave margins had lower mean re-excision rates (14.1% vs 21.7%; P = .004).

Since the onset of cavity shave margin use in a subset of patients in 2018 (n = 4803), shave margins have been used in 18% of patients.

Re-excision rate ↓ in BCS in which shave margins were used vs. with BCS without shave margins (13.9% vs 19.4%; P < .001).

Table. Factors Associated With Lower Re-excision Rates in Univariable and Multivariable Linear Regression Models

	Univariable model		Multivariable model	
Surgeon-specific variable	β (95% CI)	*P* value	β (95% CI)	*P* value
Mastectomy rate	0.22 (−0.06 to 0.51)	.12	0.14 (−0.13 to 0.41)	.29
Percentage of operations for DCIS	0.18 (−0.25 to 0.61)	.42	0.13 (−0.25 to 0.51)	.49
SSO-ASTRO margin guidelines	−1.95 (−8.44 to 4.55)	.55	−2.05 (−7.58 to 3.48)	.46
BCS per year	−0.11 (−0.21 to −0.006)	.04	−0.04 (−0.15 to 0.06)	.42
Neoadjuvant chemotherapy use	−0.62 (−1.09 to −0.16)	.01	−0.48 (−0.94 to −0.02)	.04
Ultrasonography-guided localization use	−5.64 (−10.2 to −1.11)	.02	−2.89 (−7.06 to 1.28)	.17
Medical center location	0.47 (0.02 to 0.92)	.04	0.34 (−0.9 to 0.76)	.12
Breast-focused practice (>50% of total cases)	−4.46 (−8.65 to −0.27)	.04	−0.06 (−4.86 to 4.74)	.98
Routine or always use of oncoplastic techniques	−6.25 (−10.5 to −2.01)	.005	−2.05 (−6.19 to 2.09)	.32
Intraoperative gross margin analysis	−6.19 (−11.6 to −0.81)	.03	−4.86 (−9.86 to 0.13)	.06
Always use of cavity shave margins	−7.65 (−12.9 to −2.42)	.005	−6.11 (−11.0 to −1.64)	.009

Microinvasive Disease

HypoFx and Microinvasive Disease Study
←R→ 1234 patients T1-2 N0 all BCS → | 1. WBI 42.5 Gy in 16 fx | 2. 50 Gy in 25 fx |. Analysis T1mi tumors vs. T1a-2 disease was performed.
1^{O} Kaplan-Meier estimates of local recurrence (LR), distant recurrence, and overall survival (OS) were compared using the log-rank test.
T1mi was found in 3% (n = 38) of patients

Goldberg, Breast 2023. **12 year FU**

10-year LR	T1mi 22.6%	vs. T1a-2 6.9%	(HR=3.73, p < 0.001].
10-year DRR	T1mi 5.1%	vs. T1a-2 12.1%	(HR=0.56; p = 0.36).
10-year OS	T1mi 91.5%	vs. T1a-2 84.4%	(HR=0.48; p = 0.14).

Rates of LR did not differ whether treated by hypofractionation or conventional fractionation (HR = 1.21; 95% CI: 0.35, 4.18; p = 0.77).
T1mi Recurrences (n=8) → 5 (62.5%) invasive and 3 (37.5%) DCIS.
T1a-2 Recurrences (n=73) → 64 (87.7%) invasive and 9 (12.3%) DCIS.
Conclusions The risk of LR was considerably higher in patients with T1mi compared to T1a-2 tumors, but OS remained very good. Future research should evaluate the utility of wider local excision and boost radiation to optimize local control for microinvasive breast cancer.

Lidocaine Injection

Indian Lidocaine Injection Trial
←R→ 1583 women early breast cancer w/o NAC | 1. Peritumoral injection of 0.5% lidocaine, 7-10 minutes before surgery | 2. No lidocaine |.
Primary and secondary end points were DFS and overall survival (OS), respectively.

Badwe, JCO 2023. **68 months.**
5-year DFS 86.6% vs. 82.6% (HR 0.74; P = .017) 5-year OS 90.1% vs. 86.4% (HR, 0.71; P = .019).
The impact of LA was similar in subgroups defined by menopausal status, tumor size, nodal metastases, and hormone receptor and human epidermal growth factor receptor 2 status.
5-year CI rates of LR 3.4% vs. 4.5% (NS) 5-year CI rates of DR 8.5% vs. 11.6% (SS).
There were no adverse events because of lidocaine injection.
CONCLUSION Peritumoral injection of lidocaine before breast cancer surgery significantly increases DFS and OS. Altering events at the time of surgery can prevent metastases in early breast cancer (CTRI/2014/11/005228).

SLN and Axillary Analysis

Criteria	Primary Evaluation	Follow-up Evaluation	
If cN0 (± 1-2 suspicious nodes on imaging).	SLNB	if pN0 if pN+ (with Ni, Nmic, or meets Z0011)	→ obs
		if pN+ (other than above) If SLNB not identified	→ **ALND**
If cN+ (≥ 3 LN on imaging / exam concerning LN). or If ≥ N1 and neoadjuvant chemotherapy planned.	FNA / core biopsy	if biopsy neg if biopsy pos (and meets Z0011)	→ SLNB
		if biopsy pos (± high volume disease ± pre-op Chemo given).	→ **ALND**

- **Pathologic examination**: SLND is now accepted as the initial approach for women with early stage breast cancer. In patients with clinically node negative breast cancer, SLND identifies patients without axillary node involvement, thereby obviating the need for more extensive surgery.

    - Certain risk factors ↑ likelihood of LN involvement.
        - **Larger tumors** are associated with a higher likelihood of axillary involvement and the likelihood of ALN involvement increases as the size of the primary tumor increases. Tis 0.8 %, T1a 5%, T1b 16%, T1c 28%, T2 47%, T3 68%, T4 86%.
        - Low-grade (grade 1) (3.4%) tumors have a significantly lower rate of ALN metastases compared to **grade 2 or grade** 3 (21%) tumors.
        - **Lateral breast tumors** > ALN mets than central.

    - **ASCO recommendations (Lyman 2014)**.[42]
        - **Consider SLNB** in women with operable breast cancer and:
            - Multicentric tumors.
            - DCIS who will undergo mastectomy.
            - Previously underwent breast and/or axillary surgery,
            - Previously received preoperative/neoadjuvant systemic therapy.
        - **No SLNB** in women with early stage breast cancer and:
            - Large or locally advanced invasive breast cancer (tumor size T3/T4)
            - Inflammatory breast cancer,
            - DCIS (when breast-conserving surgery is planned)
            - Pregnant.
        - Yes ALND if: women **with SLN metastases** who will undergo mastectomy.
        - No ALND if: women **without SLN metastases**, or **with one to two metastatic SLNs** planning to undergo BCS + WBRT.

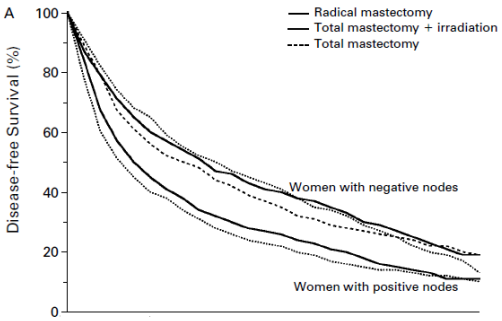
[42] http://www.ncbi.nlm.nih.gov/pubmed/24663048

Randomized Studies to Know

NSABP B-04 1985 (1971-4)

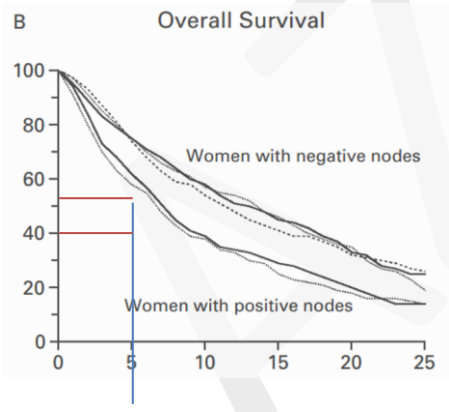
1665 pts, operable, potentially curable cancer confined to the breast and axilla; nodes not fixed.
Eligibility: Operative breast cancer, No systemic therapy.
For clinically N+ pts, ←R→ **1.** radical mastectomy (N=292) **2.** total mastectomy + PMRT. (294)
For clinically N- pts, ←R→ **1.** radical mastectomy (+ ax dissection) (362)
2. total/simple mastectomy (+ ax dissection only if evidence of nodal recurrence) (365)
3. total mastectomy + PMRT (axilla, SCV, IM nodes included). (352)
Pts treated without axillary dissection or regional RT who later developed biopsy-proven axillary disease then went on to axillary dissection. These pts were not considered to have a LR (unless the nodes were unresectable, only in 1 pt).
Dose was 50 Gy / 25 fx to chest wall, with 10-20 Gy boost for LN+ pts. 45 Gy to SCLV and IM nodes.
No systemic therapy was given.

In clinically N+ disease, the DFS between the 2 arms are the same, but this is because in the total mastectomy arm with RT, axillary recurrence is MORE, but supraclav recurrence is LESS.



Fisher, NEJM 2002. 25-years.
82% of pts had "an event:" LR (57% LN+, 37% LN-), death without evidence of cancer (25%), 2nd 1O cancer (6%), contralat BCa (6%). Most recurrences (74%) were distant. (30% LN-, 42% LN+). 5% had local recurrence, and 4% had regional recurrence. Note the continued relapses even after 10 years.
19% axillary first recurrence noted. Vs 0.9% in the SLND-alone arm in Z0011.
Note: 68 of the 365 women randomized with cLN- to total mastectomy without RT (18.6%) had pLN+.
A total of 40% of women with cLN- treated with radical mastectomy had pLN+.
18.5% in axillary observation arm required delayed dissection.
Only about 50% of patients with untreated nodal disease will recur in axilla.
Summary: No difference in DFS or RFS among the three LN- groups or among the two LN+ groups.
Conclusion: Failed to show a benefit of axillary dissection for clinically LN - pts (compared with a wait-and-watch approach).
NOTE:. cN+ disease: ALND = 1% ax recur. Ax RT = 7% ax recur. Very old 1985 fisher paper of B-04 TABLE 1.

If cN0	→ ALND (362)	→ 40% pN+	→ 4% nodal recurrence as first recurrence
	→ RT (352)		→ Same
	→ No Axillary TX (365)		→ 6% (roughly the same)
If cN+	→ Axillary Dissection	→ 75% pN+	→ 1% axillary recurrence
	→ Axillary RT		→ 7 % axillary recurrence



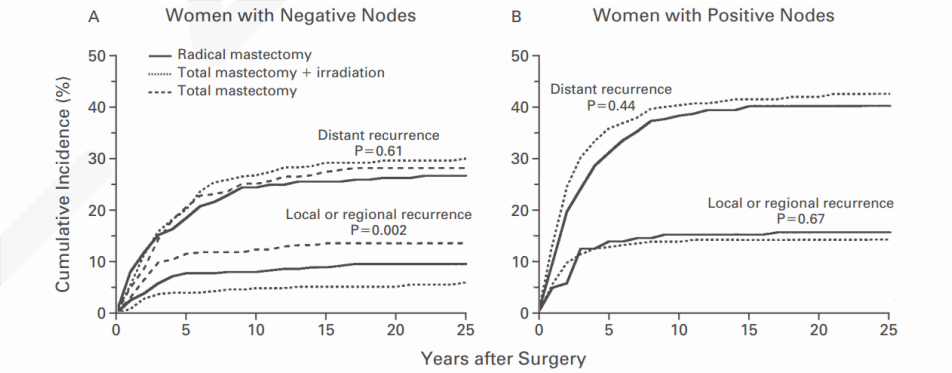


Figure 2. Cumulative Incidence of Local or Regional Recurrence and Distant Recurrence during 25 Years of Follow-up after Surgery among Women with Clinically Negative Axillary Nodes (Panel A) and Women with Clinically Positive Axillary Nodes (Panel B), According to Treatment Group.
In Panel A, the P values are for the three-way comparisons among treatment groups.

ACOSOG Z0011 (1999-2004) Non-inferiority trial comparing SLNBx | SLNBx + ALND.

←R→ *Closed prematurely due to low accrual and low rate of events.* Non-inferiority trial. 856 of expected 1900 patients, T1-T2 (≤ 5cm), **clinically N0**, **SNB+** (1 or 2 SNB+ on H&E, frozen section or touch prep; patients SNB+ by IHC were not eligible but ultimately 41% were micromets or ITCs).
16% were ER-/PR-.
EXCLUDED: Neoadjuvant chemo or HT, bilateral BCa, Multicentric, matted nodes, M1 at time of SLND, ≥ 3 LN+.
TX: All underwent lumpectomy with SM- and tangents RT, but no dedicated axillary RT.
Adj. systemic therapy 97% (hormones 46%, chemotherapy 58%).
1. completion ALND (median 17 LN removed)
2. no further dissection (median 2 LN removed).
Nearly 20% received a 1/3 supraclavicular axillary radiation field. ~50% received a high tangential field RT.
A lot of surgeons had patients from the community. They sent them to radiation oncologist, who often didn't even know they were on trial. And they only were told "treat the breast." 2nd, they knew, and the radiation oncologist were like…She has 2 SLN+ and the protocol says only breast? No Way!

Z0011 Study Design Schema

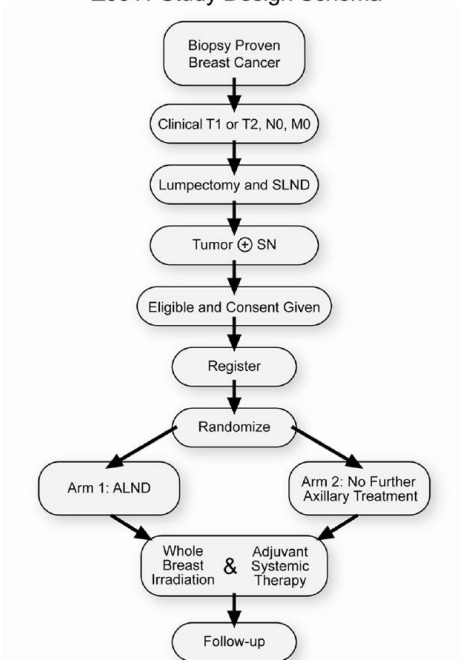


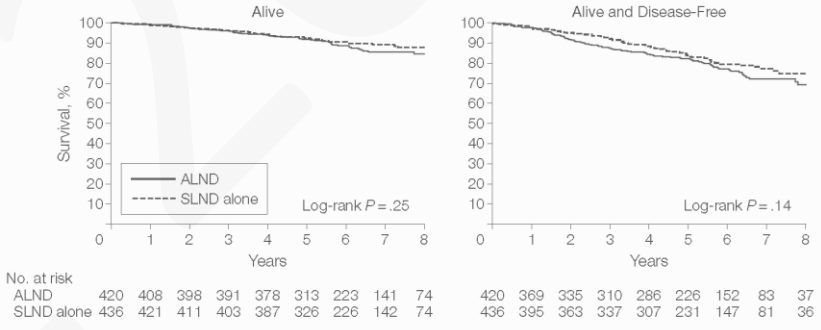
Table 1. Baseline Patient and Tumor Characteristics by Study Group

Characteristic	No. (%) ALND (n = 420)	SLND Alone (n = 436)
Age, median (range), y	56 (24-92)	54 (25-90)
Missing	7	10
Clinical T stage		
T1	284 (67.9)	303 (70.6)
T2	134 (32.1)	126 (29.4)
Missing	2	7
Tumor size, median (range), cm	1.7 (0.4-7.0)	1.6 (0.0-5.0)
Missing	6	14
Receptor status		
ER+/PR+	256 (66.8)	270 (68.9)
ER+/PR−	61 (15.9)	54 (13.8)
ER−/PR+	3 (0.8)	4 (1.0)
ER−/PR−	63 (16.5)	64 (16.3)
Missing	37	44

Giuliano, Ann Surg 2010.
Outcome: Further involved nodes with cALND 27%.
5-year breast recur ALND 3.1% vs SNB 1.6% (NS); axilla recur 0.5% vs 0.9% (NS); year OS 92% vs 92% (NS).
No difference in LRR based on systemic therapy.
Conclusion: NS; SLND without completion ALND may be a reasonable management options with tangent RT and systemic therapy.

Giuliano, JAMA 2011. Median F/U 6.3 years.
Results: 5-yr OS 91.8% (ALND) vs 92.5% (SLND). 5-yr DFS 82.2% vs 83.9%.
Median # of nodes removed: 17 for ALND and 2 for SLND. Number of positive nodes (not including micromets) - median: 1 (ALND) vs 1 (SLND). However, 21% of ALND had ≥ 3 positive LN.
Sentinel lymph node biopsy contained micromets: 37.5% (ALND group) and 44.8% (SLND).
In ALND group, axillary dissection revealed additional metastases in 27.3%; 10% of ALND pts with micromets in SLN had additional positive (non-micromet) non-SLN lymph nodes.
≥ 4 LN+ in 13.7%.
Conclusion: among pts with limited positive SLN disease, treated with breast conservation +/- systemic therapy, the use of SLND alone compared with ALND did not result in inferior survival.

Figure 2. Survival of the ALND Group Compared With SLND-Alone Group



ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

Jagsi, San Antonio Breast Conference 2013, Poster Session: P5-14-19.
Among 605 pts completed adjuvant RT, 89% receive WBRT. Of these, 89 patients (15%) also RT to the supraclavicular region.
Detailed RT records available on 228 patients: 104/389 (26.7%) and 124/404 (30.7%) on the ALND and SLND arms, respectively.
185 patients (81.1%) received tangent-only treatment:
High tangents (cranial tangent border within 2 cm of the humeral head) were used in 52.6% (40/76) patients randomized to the ALND arm and 50% (33/66) patients randomized to the SLND arm.
Of the 228 patients reviewed, 43 (18.9%) received directed regional nodal RT using ≥3 fields: 22 in the ALND and 21 in the SLND arm.
Those receiving directed nodal RT tended to have greater nodal involvement (p<0.001).
Conclusion: Most patients treated on the Z0011 trial received tangential field RT alone, and some received no radiotherapy at all.
Some patients received directed nodal irradiation via a 3rd field.
In a subgroup for whom detailed RT records were available, highest rates of directed nodal irradiation were those with multiple nodes involved.
No conclusions can be drawn from this analysis on whether this additional radiation treatment was necessary or beneficial.

Guiliano, JAMA 2017. 10-year update.
RESULTS: 10-year OS 83.6% vs. 86.3% (NS). 10-year DFS 78.2% vs. 80.2% (NS). 10-year Regional recurrence NS.
Between year 5 and year 10, 1 regional recurrence was seen in the SLND alone group vs none in the ALND group.
CONCLUSIONS AND RELEVANCE: Among women with T1 or T2 invasive primary breast cancer, no palpable axillary adenopathy, and 1 or 2 sentinel lymph nodes containing metastases, 10-year overall survival for patients treated with sentinel lymph node dissection alone was noninferior to overall survival for those treated with axillary lymph node dissection. These findings do not support routine use of axillary lymph node dissection in this patient population based on 10-year outcomes
Z0011-Eligible ECE Management Study
811 prospective study with Z0011 criteria with ALND if ≥ 2 LNs or gross ECE. Patients cT1-2N0 and + SLNB.

Median tumor size 1.7 cm.
Outcomes are compared in patients with 1-2 LNs+ ± microscopic ECE treated with SLNB alone.

Barrio, Annal Surgical Onc 2020
Results: mECE was identified in 210 (31%) patients.
Patients with mECE were older, had larger tumors, and were more likely to be hormone receptor positive and HER2 negative, have two positive SLNs, and receive nodal radiation.
At a median follow-up of 41 months, no isolated axillary failures were observed.
There were 11 nodal recurrences; two supraclavicular ± axillary, four synchronous with breast, and five with distant failure.
The five-year rate of any nodal recurrence was 1.6% and did not differ by mECE (2.3% vs. 1.3%; p = 0.84).
No differences were observed in local (p = 0.08) or distant (p = 0.31) recurrence rates by mECE status.
Conclusions: In Z0011-eligible patients, nodal recurrence rates in patients with mECE are low after treatment with SLN biopsy alone, even in the absence of routine nodal radiation. The presence of mECE should not be considered a routine indication for ALND.

SINODAR-ONE **Non-Inferiority Trial**
←R→ 889 women either BCS (75%) or Mastectomy T1-2 **+ SLNB** = #1-2 Macrometastatic SLNs → | 1. ALND → adj Tx (Standard) | 2. No ALND (exp) |.
ALND = removal of ≥ 10 axillary level I/II non-SLNs.
All BCS patients received WBRI w/o RNI. PMRT < 20% of mastectomy patients. 50% received adjuvant chemotherapy.
ALND revealed an additional 44% patients with ≥1 +LN! → 1 (22.1%), 2 (8.9%), 3 (3.2%), and ≥ 4 (9.8%).
Similar to Z0011 findings.

Tinterri, Ann Surg Oncol 2022. 34 month follow-up.
5-year mortality of 5.8% vs. 2.1% (NS).
5-year Recurrences 6.9% vs. 3.3% (NS).
Only one axillary lymph node recurrence was observed in each arm.
5-year OS rates 99% NS.
Conclusions The 3-year survival and relapse rates of T1–2 BC patients with one or two macrometastatic SLNs treated with SLNB only, and adjuvant therapy, were not inferior to those of patients treated with ALND. These results do not support the use of routine ALND.

OPTIMAL Trial (OPTimizing **I**rradiation through **M**olecular **A**ssessment of **L**ymph node) **Non-inferiority Trial**
←R→ 487 (of planned ~1400 patients) T1-2 cN0 IDC s/p BCS + SLN patients received OSNA (One-Step Nucleic Acid Amplification) of 250–15,000 copies mRNA CK19/μL in sentinel LN.
Therefore cancer burden in LN was assess not by #, but by [CK19].
RT = 50 Gy in 25 fractions. RNI = Ax 1-3 + SCV. NO IMs were irradiated.
| 1. Incidental Radiation of Axillary LNs (INC) | 2. Intentional nodal irradiation (INT) |.
1^{O} 5-year disease-free survival (DFS).
Closed Early for poor accual.

Algara, Radiother Oncol 2022.
5-year DFS 93.7% vs. 93.8% (non-inferiority p = 0.075). Cumulative Incidences of LRR all 3.5%. were 3.5% (INC) and 3.4% (INT) (difference of 0.1% [<4.8%]; p = 0.021), and 5% (INC) and 3.5% (INT) (difference 1.4% [<6.0%]; non-inferiority p = 0.101) for DR. CT was more Incident with INT (26.9%) than with INC (19.2%), though the difference was not statistically significant (HR 1.39 [95% CI: 0.92, 2.10]; p = 0.11).
Conclusion Intentional does not outperform incidental irradiation by more than 5.7% in terms of 5-year DFS, 4.8% for LRR, and 6% for DR.

Table 3
Mean dose received by volume. *Referred to patients that received "boost", 141 and 135 patients in the intentional and incidental irradiation groups, respectively.

	Intentional irradiation (N = 220)	Incidental irradiation (N = 222)
Breast (Gy), mean (SD)	49.8 (4.8)	50.2 (4.7)
Tumor bed (Gy), mean (SD)*	59.4 (6.64)	59.6 (6.62)
Axillary level 1 (Gy), mean (SD)	48.0 (4.6)	31.3 (13.4)
Axillary level 2 (Gy), mean (SD)	47.5 (6.0)	20.3 (15.3)
Axillary level 3 (Gy), mean (SD)	47.6 (7.6)	9.1 (11.2)
Supraclavicular (Gy), mean (SD)	50.0 (8.4)	1.0 (8.4)
Internal mammary chain (Gy), mean (SD)	24.3 (14.6)	19.8 (13.2)

Table 4
Acute radiation toxicity events reported and their frequency (number and percentage of patients).

Event	Intentional irradiation (N = 220)	Incidental irradiation (N = 222)
Dermatitis	207 (94.1%)	212 (95.5%)
Skin Hyperpigmentation	28 (12.7%)	36 (16.2%)
Pruritus	19 (8.6%)	14 (6.3%)
Pain of skin	9 (4.1%)	8 (3.6%)
Breast pain	4 (1.8%)	6 (2.7%)
Skin ulceration	1 (0.4%)	none
Unspecified event	3 (1.4%)	1 (0.4%)

EORTC 10981 / AMAROS ("aka ALLIANCE TRIAL without Neoadjuvant chemotherapy")
EORTC Trial 10981-22023 (AMAROS) ("After Mapping of the Axilla, Radiotherapy Or Surgery") -- **SLN+ → ALND vs RT**
Randomized. Surgery, T1-T2 (<3cm), if SLN+ then **1.** completion ALND **2.** axillary RT 50/25.
Mastectomy 18%, BCS 82%. Grade 1 (24%), Grade 2 (46-48%), Grade 3 (26-29%). All arms balanced.
If ALND with 4+ lymph nodes, axillary RT allowed per institutional protocol
RT: target all three levels of axilla and medial part of supraclavicular fossa to 50 Gy in 25 fractions

Population less favorable than Z11, since 5% had > 2 +SLN.
BUT ALSO, you only have T < 3 cm. Z11 OK up to 5 cm.

	Axillary lymph node dissection (n=744)	Axillary radiotherapy (n=681)
(Continued from previous page)		
Adjuvant radiotherapy		
Breast	597 (80%)	546 (80%)
Chest wall	34 (5%)	51 (7%)
Internal mammary chain	72 (10%)	65 (10%)
Systemic treatment administered		
Any systemic treatment	666 (90%)	612 (90%)
Chemotherapy	453 (61%)	418 (61%)
Hormonal therapy	585 (79%)	525 (77%)
Immunotherapy	45 (6%)	44 (6%)
Sentinel node characteristics		
Number of sentinel nodes removed		
1	332 (45%)	293 (43%)
2	201 (27%)	217 (32%)
3	127 (17%)	105 (15%)
≥4	84 (11%)	66 (10%)
Number of positive sentinel nodes		
1	581 (78%)	512 (75%)
2	127 (17%)	134 (20%)
3	29 (4%)	27 (4%)
≥4	7 (1%)	8 (1%)
Size of the largest sentinel node metastasis		
Macrometastasis	442 (59%)	419 (62%)
Micrometastasis	215 (29%)	195 (29%)
Isolated tumour cells	87 (12%)	67 (10%)
Number of positive additional nodes (besides sentinel node)		
0	451/672 (67%)*	26/69 (38%)†
1-3	168/672 (25%)*	24/69 (35%)†
≥4	52/672 (8%)*	17/69 (25%)†
Missing	1/672 (<1%)*	2/69 (3%)†

Straver, JCO 2010. **Subset analysis**.
First 2000 patients, 566 with SLN+. Patterns of adjuvant chemo use.
Outcome: Chemotherapy ALND 58% vs ART 61% (NS); hormones 78% vs 76% (NS)
Conclusion: Absence of knowledge about extent of LN involvement doesn't impact administration of adjuvant chemo

Straver, Ann Surg Oncol. 2010. **Subset analysis**.
First 2000 patients. SLN identification rate 97%
Outcome: SLN- in 65%; **SLN+ in 34% (macromets 63%, micromets 25%, ITCs 12%)**.
Further nodal involvement if macromet 41%, if micromet 18%, if ITC 18%
Conclusion: SLN procedure highly effective; further nodal involvement in patients with micromets and ITCs was 18%

Donker, Lancet Oncology 2014.
Outcome: 5-year axillary recurrence ALND 0.43% vs RT 1.19%.
5-year DFS ALND 87% vs 83% RT (NS). 5-year OS ALND 93% vs RT 93% (NS).
Morbidity: ↑ lymphedema with ALND **23% vs 11%** (SS). ↑ arm circumference at 13% vs 6% (SS).
But no difference in arm range of motion nor overall QoL.
Conclusion: ALND and RT after SLN+ provide excellent and comparable control for T1-2, cN0. RT results in significantly less morbidity.
Criticism: Underpowered to show non-inferiority (assumed "incorrectly" Axillary recurrence 2% vs 4% with non-inferiority HR margin of 2).

Hurkman, Radiother Oncol 2003. **AMAROS, RT QA.**

Table 1
Protocol guidelines for irradiation of the axilla

	Protocol guidelines
Target volume	All three levels of the axilla and medial part of the supraclavicular fossa
Patient position	Supine, arm 90° abducted.
Preferred treatment technique	One large AP beam covering levels I, II and III. One small AP beam covering level III. This beam may be omitted if a transmission plate is used in the large AP beam. One PA beam covering levels I and II.
Dose specification	At half patient thickness for levels I and II and at 3 cm depth for level III.

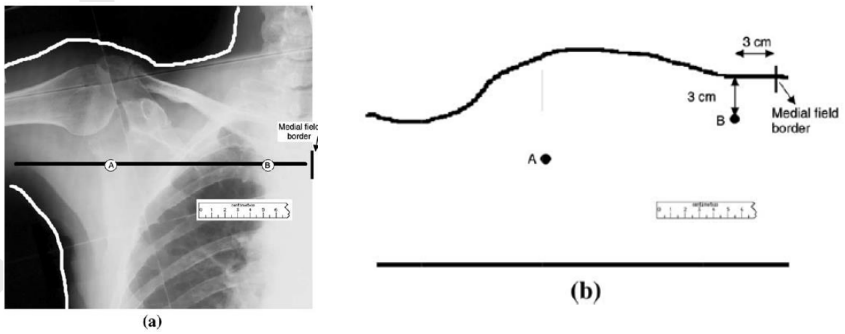
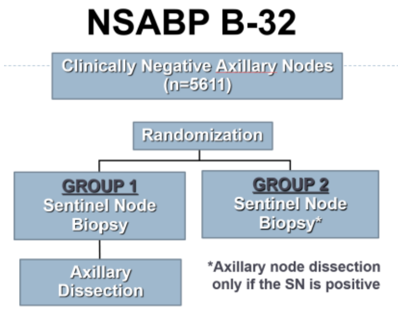


Fig. 1. Frontal view (radiograph) of axillary region. Dose specification points A and B are indicated. The axial patient contour given in (b) is indicated by a black line. (b) Axial contour at the cranio-caudal level of the black line indicated in (a).

Bartels, JCO 2022 **10-year Long Term Data.**
RESULTS Per intention-to-treat analysis, 10-year AxRR CI 0.93% (n=7) vs. 1.82% (n=11) NS.
No differences in OS or DFS.
ALND was associated with a higher lymphedema rate in updated 5-year analyses (24.5% v 11.9%; P < .001). Quality-of-life scales did not differ by treatment through 5 years. Exploratory analysis showed a 10-year cumulative incidence of second primary cancers of 12.1% (95% CI, 9.6 to 14.9) after ART and 8.3% (95% CI, 6.3 to 10.7) after ALND.
CONCLUSION
This 10-year analysis confirms a low ARR after both ART and ALND with no difference in OS, DFS, and locoregional control. Considering less arm morbidity, ART is preferred over ALND for patients with SN-positive cT1-2 breast cancer.

NSABP B-32 (1999-2004) -- SLN + ALND vs. SLN alone
←R→. 5611 with operable invasive breast cancer and cLN- axillary (T1 80%, T2 18%; lumpectomy 86%).
1. SLN followed by immediate completion ALND **2.** SLN alone, if SLN-; full ALND if no SLN identified or if SLN+.
Identification included technetium scan, blue dye, and clinically suspicious lymph nodes



Krag, Lancet Oncology 2007. Technical outcome: Technical success in 97%. Location in Level I/II in 99% (Level I 83%, Level II 16%, Level III 0.5%, IM 0.5%, SCV 0.1%. Mean number removed 2.1.
Clinical outcome: SLN+ in both groups 26% (NS). If SLN- (74%), ALND- 96% and ALND+ 4% (**false negative rate 9.7%**). Overall accuracy 97%. If only one SLN removed, false negative rate 18%. FNR decreased with 2 SLN and 3 SLN removed.
FALSE NEGATIVE by # LN removed: 1 (18%), 2 (10%), 3 (7%), 4 (5.5%), ≥ 5 (1%) SS!!!
FALSE NEGATIVE by tumor location: lateral (12%), central (5.5%), medial (9.1%). SS!!!
False negative rate NS: by lump vs. mast, age, clinical size, by quadrant.

In the 26% of SLN+ patients, 61% had no further LN disease on completion ALND.
Conclusion: Success of SLN resection is high.

Krag, Lancet Oncology 2010.
Findings A total of 309 deaths were reported in the 3986 SLNB negative patients with FU information.
8-year OS 90-91%. 8-year DFS 81-82%.
There were 8 regional node recurrences as first events in Group 1 and 14 in Group 2 (P=0.22).
Interpretation Overall survival, disease-free survival, and regional control were statistically equivalent between groups. When the sentinel node is negative, sentinel node surgery alone with no further axillary dissection is an appropriate, safe, and effective therapy for breast cancer patients with clinically negative lymph nodes.

Axillary Evaluation Omission

- More than 80% of women > 70 yo with low risk cT1N0 ER+ BCa still routinely receive SLNB.
    - Choosing Wisely recommended against the use of SLNB in this population.
    - There is a concern that without a SLNB, adjuvant therapy decision-making will be impacted.
- Questions:
    - Does the benefits of knowing a patient's Axillary Status (ie SLNB result) outweigh the cost of side effects?
    - What clinical tests (like an axillary US), can help us make this decision?

SOUND Study Non-Inferior Study
SOUND (Sentinel Node vs Observation After Axillary Ultra-Sound)
←R→ 1463 women prospective noninferiority phase 3 with BC up to 2 cm + Neg preoperative axillary US → all BCS.
| 1. SLNB | 2. No Axillary Surgery |.
Suspicious nodes received FNA.
Nearly all received Adj RT and Adj Endocrine therapy.
Median (IQR) tumor size was 1.1 (0.8-1.5) cm, and 1234 patients (87.8%) had ER+ ERBB2 (formerly HER2 or HER2/neu), nonoverexpressing BC.
1^{O} 5-year DFS.

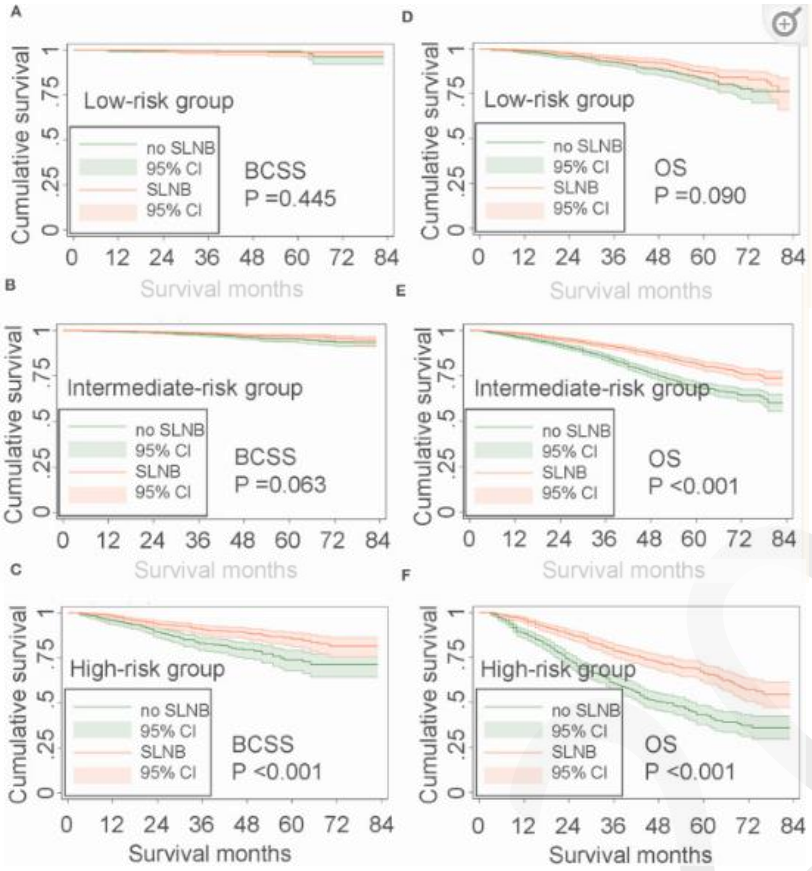
Gentilini, JAMA Oncol 2023
In the SLNB group, 97 patients (13.7%) had positive axillary nodes.
5-year distant DDFS was 97.7% vs. 98.0% (NS).
A total of 12 (1.7%) locoregional relapses, 13 (1.8%) distant metastases, and 21 (3.0%) deaths were observed in the SLNB group
A total of 11 (1.6%) locoregional relapses, 14 (2.0%) distant metastases, and 18 (2.6%) deaths were observed in the no axillary surgery group.
Conclusions and Relevance In this randomized clinical trial, omission of axillary surgery was noninferior to SLNB in patients with small BC and a negative result on ultrasonography of the axillary lymph nodes. These results suggest that patients with these features can be safely spared any axillary surgery whenever the lack of pathological information does not affect the postoperative treatment plan.

UPMC Elderly Patient Study
Cohort 2109 women age > 70 yo with ER+, ERBB2-, cN0 from 2010 – 2014 → 65% received SLNB and 54% received Adj. RT.
1^{O} 5-year DFS.

Carleton, JAMA Net Open 2021. Avg follow-up 4.1 years.
Rates of SLNB steadily ↑ (1.0% per year), a trend that persisted after the 2016 adoption of the Choosing Wisely guideline.
Rates of RT ↓ slightly (3.4% per year).
No association was found between SLNB and either LRFS (HR, 1.26; 95% CI, 0.37-4.30; P = .71) or DFS (HR, 1.92; 95% CI, 0.86-4.32; P = .11).
In addition, RT was not associated with LRFS (HR, 0.33; 95% CI, 0.09-1.24; P = .10) or DFS (HR, 0.99; 95% CI, 0.46-2.10; P = .97).
Subgroup analysis showed that stratification by tumor grade or comorbidity was not associated with LRFS or DFS. Low absolute rates of recurrence were observed when comparing the groups that received SLNB (3.5%) and those that did not (4.5%) as well as the groups that received RT (2.7%) and those that did not (5.5%).
Conclusions and Relevance This study found that receipt of SLNB or RT was not associated with improved LRFS or DFS in older patients with ER-positive, clinically node-negative breast cancer. Despite limited follow-up time and wide 95% CIs, this study supports the continued deimplementation of both SLNB and RT in accordance with the Choosing Wisely and National Comprehensive Cancer Network guidelines.

SEER Elderly Patient SLNB Study

39962 patients ≥70-year-old patients diagnosed with T1–T2 breast cancer in 2010–2015. Training set (n = 29,971) and the validation set (n = 9,991).
Axillary surgery was not specified in the SEER database.
SLNB defined as 1-5 LNs removed.



Xu, Front Oncol 2020.

In the training set, patients with SLNB had better OS (aHR 0.57, P < 0.001) and BCSS (aHR 0.55, P < 0.001) than patients without SLNB. Multivariate COX analysis identified age, marital status, grade, subtype, T stage, and radiation as independent risk factors for OS and BCSS in both SLNB and non-SLNB groups (all P < 0.05). They were subsequently incorporated to establish nomograms to predict 3- and 5-year OS and BCSS for patients with or without SLNB. The concordance index ranged from 0.687 to 0.820, and calibration curves in the internal set and external set all demonstrated sufficient accuracies and good predictive capabilities. Further, we generated a risk stratification model which indicated that SLNB improved OS and BCSS in high-risk group (OS: HR 0.49, P < 0.001; BCSS: HR 0.54, P < 0.001), but not in the low-risk group (all P > 0.05).

Conclusion: Well-validated nomograms and a risk stratification model were constructed to evaluate survival benefit from SLNB in elderly patients with early-stage breast cancer. SLNB was important for patients in the high-risk group but could be omitted in the low-risk group without sacrificing survival. This study could assist clinicians and elderly patients to weigh the risk–benefit of SLNB and make individualized decisions. We look forward to more powerful evidence from prospective trials.

LN Micromets

Micromets SLNB IBCSG 23-01
←R→ 931 patients with micrometastatic (<2 mm) deposit in the SLNB. | 1. ALND | 2. no additional surgery |
97% received adjuvant RT without regional nodal irradiation (RNI). In the ALND arm, additional axillary nodal involvement = 13%.
Median 21 LN removed at ALND.

Galimberti, Lancet 2013.
5-year DFS ~85% (NS) 5-year OS ~97% (NS).
Conclusion: Although the study closed before meeting target accrual, the authors concluded that breast cancer patients with limited SLN involvement could be spared the morbidity of an ALND.

Retrospective Micromet ITC Study
10,271 patients referred between 2006 and 2011 with newly diagnosed pT1-T2, pN0, pN0(i+), pN1mi, or pN1a, M0 breast cancer.

Dosani, IJROBP 2022. Median follow-up was 9.3 years.

10-year	pN0 (n = 7492)	pN0(i+) (n = 305)	pN1mi (n = 619)	pN1a (n = 1855)
LR Radiation Tx Use	1.1%	24.3$	45.7%	71.1%
LRRFS	96%	92%	97%	96%
Distant RFS	94%	91%	90%	84%
BCaSS	95%	90%	93%	87%

10-year LRRFS pN0(i+) for BCS alone 81% vs. BCS + breast RT 93% vs. BCS + WBRT+RNI 91% (NS).
pN1mi for BCS alone 94%, vs. BCS + breast RT 96% vs. BCS + WBRT+RNI 100% (SS).
10-year LRRFS pN0(i+) for mastectomy alone 93% vs. mastectomy + PMRT 100% (NS).
pN1mi for mastectomy alone 95% vs. mastectomy + PMRT 99% (NS).
On multivariable analysis of patients with pN0(i+) and pN1mi, **systemic therapy** was associated with improved LRRFS in patients with pN0(i+) (hazard ratio [HR], 0.2; [0.06-0.6]; P = .005) and patients with pN1mi (HR, 0.1; [0.03-0.5]; P = .006). In patients with pN1mi, **LRRT** was associated with a trend toward increased LRRFS (HR, 0.2; [0.03-1.1]; P = .07). **LRRT** was not significantly associated with improved RFS in pN0(i+) or pN1mi disease.
Conclusions In the era of sentinel node staging and modern systemic therapy, patients with pN0(i+) and PN1mi treated with LRRT experienced 10-year LRR risks ≤10% after breast-conserving surgery or mastectomy and RT. LRRT was associated with a trend toward increased LRRFS in pN1mi but not pN0(i+) disease

Lymphedema

Korean Model for Lymphedema based on **Axillary–lateral thoracic vessel juncture (ALTJ)** and **number of LNs removed on ALND.**
Retrospective 1345 patients "The number of lymph nodes dissected and ALTJ V35 were found to be the most important factors influencing lymphedema after radiation therapy."

Patients were classified as 3 risk categories in the entire cohort at institution A for simplified patient stratification

High-risk	LNDno >10 and ALTJ V35 >39.9%	
Moderate risk	LNDno >10 and ALTJ V35 ≤39.9%	LNDno ≤10 and ALTJ V35 >39.9%
Low risk	LNDno ≤10 and ALTJ V35 ≤39.9%.	

Park, IJROBP 2023

3-year CI lymphedema for the high-, moderate-, and low-risk groups was	18.7%, 5.9%, and 0.5%.
5-year CI	25.0%, 5.9%, and 0.9%.

The lymphedema risk was significantly greater in high-risk patients with both LNDno and V35 exceeding cutoff values (P < .001).

MGH Lymphedema Study
1800 prospective IBC comparing lymphedema rate (10% ↑ in arm volume at least 3 months after surgery).
Number of patients with SLNB alone (74%), ALND alone (5%), SLNB + RNI (7%), ALND + RNI (14%).

Naoum, JCO 2020.

5-year Lymphedema risk	SLNB 8%	ALND 11%	SLNB + RT 25%	ALND + RT 30%.
5-year LRC	SLNB 2.3	ALND 3.8%	SLNB + RT 0%	ALND + RT 2.8%

MVA adjusted for age, BMI, surgery, and reconstruction type showed = **ALND-alone group** (vs. SLNB + RNI) **↑ Lymphedema risk** (HR, 2.66; P = .02).
CONCLUSION
Although RLNR adds to the risk of lymphedema, the main risk factor is the type of axillary surgery used.

Other Important Studies

SCV Dissection with Benefit?
293 patients with SCV disease. All received NAC → surgery for primary tumor → ALND → adj RT.
Most patients (71%) received radiation alone to the SCV while 29% had a SCV lymph node dissection.
The latter were more likely treated earlier in the study period (2008-2014), more likely to have multiple positive SCV nodes, and more likely to have incomplete response to systemic therapy. Radiation fields typically covered the primary site, upper axilla, and supraclavicular fossa with only 15.7% having IMN coverage and 4.8% low axilla coverage. Patients who didn't have SCV dissection had a higher cumulative dose to the SCV (>60 Gy v 50 Gy).

Song, Radiother Oncol 2023.
5-year SCV RFS of those who had RT alone 91.7% vs RT + surgery 85.5%
5-year LR RFS 79.1% vs 73.1% 5-year DFS 57.6% vs. 49.7% 5-year OS 71.9% vs 62.2%.
Based on four risk factors of DFS, patients were classified into three risk groups: the intermediate- and high-risk groups had significantly lower survival outcomes than the low-risk group.
Four risk factors: LVI+, ER-, Ki67 > 30%, and axillary LN+.
Conclusions: Patients with synchronous ipsilateral supraclavicular lymph node metastasis **may not benefit from supraclavicular lymph node dissection**. Distant metastasis remained the major failure pattern, especially for intermediate- and high-risk groups.

Haffty/Mehta Single institution ≥ 4+ LN
PURPOSE: The purpose of this study was to review management strategies with respect to systemic therapy, radiation therapy treatment techniques, and patient outcome (local regional control, distant metastases, and overall survival) in patients undergoing conservative surgery and radiation therapy (CS + RT) who had four or more lymph nodes involved at the time of original diagnosis.
RR 1040 CS + RT (579 patients underwent ALND → 167 pLN+ → **51 p LN ≥ 4+**. All had RT to with subsequent e- boost tumor bed median dose of 64 Gy.
Of the 51 patients, 40 RT SCV (without axilla) median dose of 46 Gy, 10 RT SCV (with axilla) median dose of 46 Gy.
30/51 pts separate internal mammary port with a mixed beam of photons and electrons. 1 RT tangents alone without RNI.
Adjuvant systemic therapy was used in 49 of the 51 patients (96%) with 27 patients receiving chemotherapy alone, 14 patients receiving cytotoxic chemotherapy and tamoxifen, and 8 patients receiving tamoxifen alone.

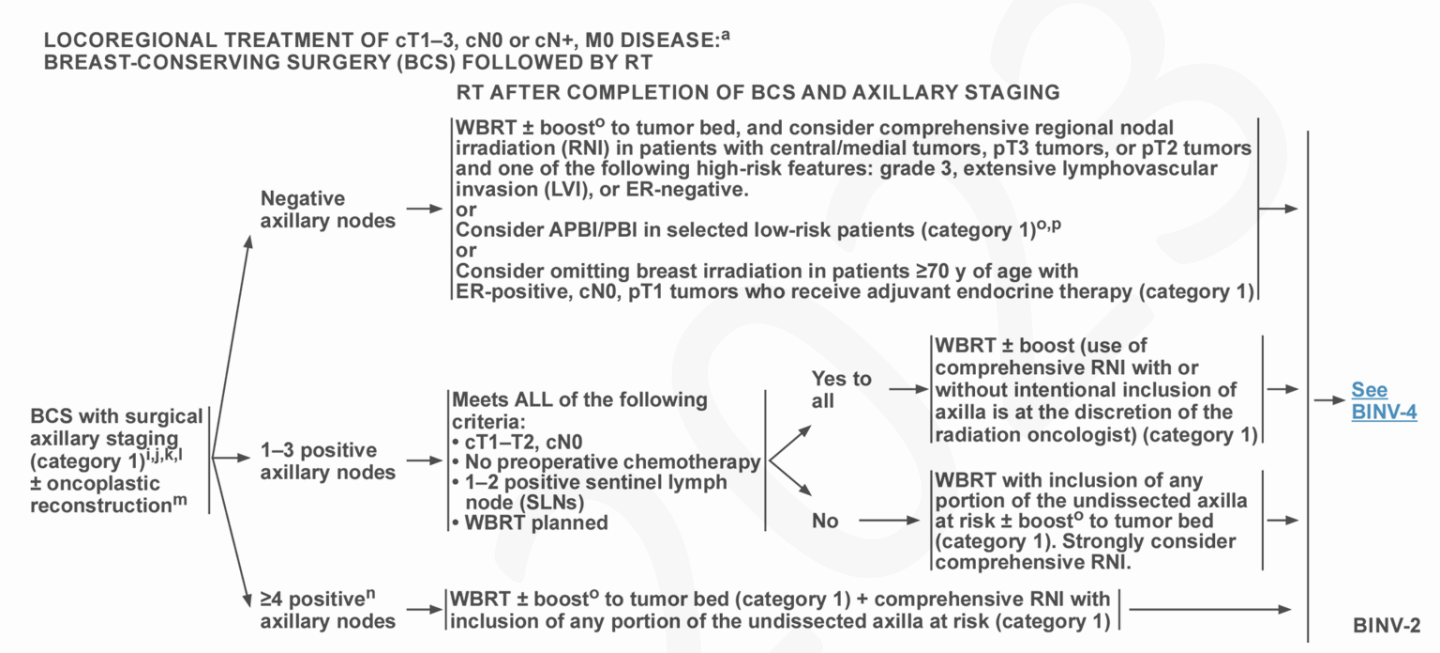
RESULTS: Median follow-up of 9.29 years
18 distant relapses, 2 nodal relapses, 5 breast relapses.
10-year OS 58%.
10-year DM RFS 65% 10-year RLN RFS 96% 10-year IB RFS 82%. All 5 with breast relapse = successfully salvaged with mastectomy. 2 patients with nodal relapses (one supraclavicular and one axillary/supraclavicular) failed within the irradiated volume. Of the 40 patients treated to the supraclavicular fossa (omitting complete axillary radiation), none failed in the dissected axilla. With a median follow-up of nearly 10 years, 29 of the 51 patients (57%) remain alive without evidence of disease, 15 (29%) have died with disease, 2 (4%) remain alive with disease, and 5 (10%) have died without evidence of disease.
CONCLUSIONS: We conclude that in patients found to have four or more positive lymph nodes at the time of axillary lymph node dissection, conservative surgery followed by radiation therapy to the intact breast with appropriate adjuvant systemic therapy results in a reasonable long-term survival with a high rate of local regional control. **Omission of axillary radiation in this subset of patients appears appropriate because there were no axillary failures among the 41 dissected but unirradiated axillae.**

Harvard ELDERLY no SLNB, HIGH TANGENT STUDY (Wong, IJROBP 2008)
Prospective single arm **74 patients** > 55 yo, stage I/II, cN0, ER+ breast cancer with lumpectomy (negative margins) without ALND or SLNB and WBI with high tangents (blocked humeral head) + tumor bed boost + 5 years hormonal therapy. **Median age 74, median tumor size 1.2 cm.** MFU 52 months.
Results: NO PATIENTS HAD LOCAL OR AXILLARY RECURRENCE.
CONCLUSION: Our results have indicated that sentinel node biopsy is not necessary in a selected population such as the one described in our report. ALSO, no need for RNI if high tangent in these older patients.

ECE Study Michigan, Pierce IJROBP 1995 RR 82 breast cancer excisional biopsy tumor bed → Ax Dissection Lv I, II ± III , RT, adjuvant systemic therapy.
RT = WBRT 45-50 Gy → Boost cavity to 60-66 Gy. If + LN, then RT to SCV. 37.5% had ECE (50/50 minimal vs. extensive ECE).
Results -ECE/+ECE: OS 83% vs. 53% (p=0.068), DFS 72% vs. 57% (p=0.12), Axilla as site for 1st recurrence (0% vs. 4%), Isolated axillary failure (0% both).

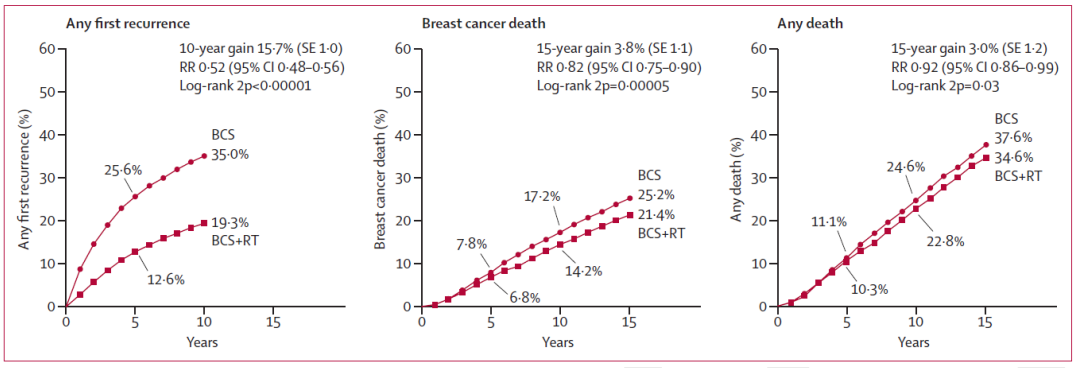
Radiation Therapy:

- While multiple RTC have been performed regarding BCS ± RT, eligibility criteria and adjuvant tamoxifen and chemotherapy varied significantly within these studies. **Conclusion**: RT ↓ ipsilateral BCA recurrence by approximately 50-66%, with better effects in LN + patients and younger women, but persists even in low risk small, WLE tumors.
    - Timing: If pt is to receive chemo, then RT after chemo (3-4 weeks)
      If XRT begins w/in 8 weeks of surgery, LF will be unaffected
    - Fields:
        - Neg Axillary LNs — Whole Breast + Boost lumpectomy site
        - 1-3 + LNs — Whole Breast + boost +/- supraclav, and/or IM
        - ≥ 4 + LNs — Whole Breast + boost + supraclav and/or IM



BCS ± RT

Early Breast Cancer Trialists' Collaborative Group (EBCTCG, Lancet 2011).[43] 10,801 women in 17 randomized trials of BCS ± RT; 8337 (77%) were pathologically confirmed pN0 or pN+. 6 RTC = WLE ± RT and included both low-risk and high-risk women (category A, 4398 women). 4 RTC were sector resection or quadrantectomy ± RT (category B, 2399 women). 7 more recent RTC were lumpectomy ± RT in low-risk women (category C, 4004 women).10 yr risk of any first recurrence (LR or distant) ↓ 35.0% to 19.3% (absolute: 15.7%).15-yr risk of breast cancer death ↓ 25.2% to 21.4% (absolute: 3.8%).

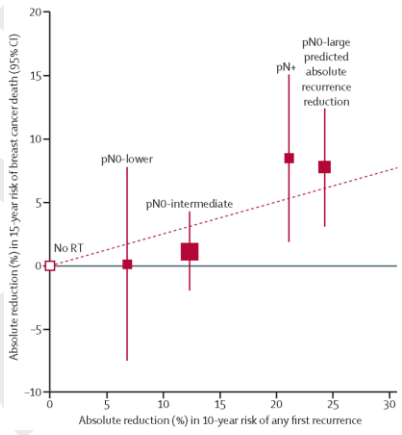


For pN0 subset: ↓ any recurrence 31.0% to 15.6% (abs: 15.4%) and ↓ death 20.5% to 17.2% (abs: 3.3%).
Absolute 10-yr recurrence risk reduction depended on factors (age, grade, ER, tamoxifen, and margins).
Worst = ER -, no Tam, young, ↑ grade, + margins). Best = ER +, yes Tam, old age, ↓ grade, - margins).
These factors predict large (≥ 20%), intermediate (10-19%), and lower (< 10%) benefits. Abs ↓ in 15-yr risk of breast cancer death in these categories was: 7.8% (ss), 1.1% (ns), and 0.1% (ns).

For pN+ subset: ↓ any recurrence 63.7% to 42.5% (abs: 21.2%) and ↓ death 51.3% to 42.8% (abs: 8.5%).

Overall, 1 breast cancer death was avoided for every 4 recurrences avoided. The reduction in mortality did not differ significantly between the pN0 and pN+ subsets.

But the survival advantage is LIMITED to only a subgroup. Not ALL patient's need radiation!!!!!
See below…RT benefit if any recurrence > 20%.



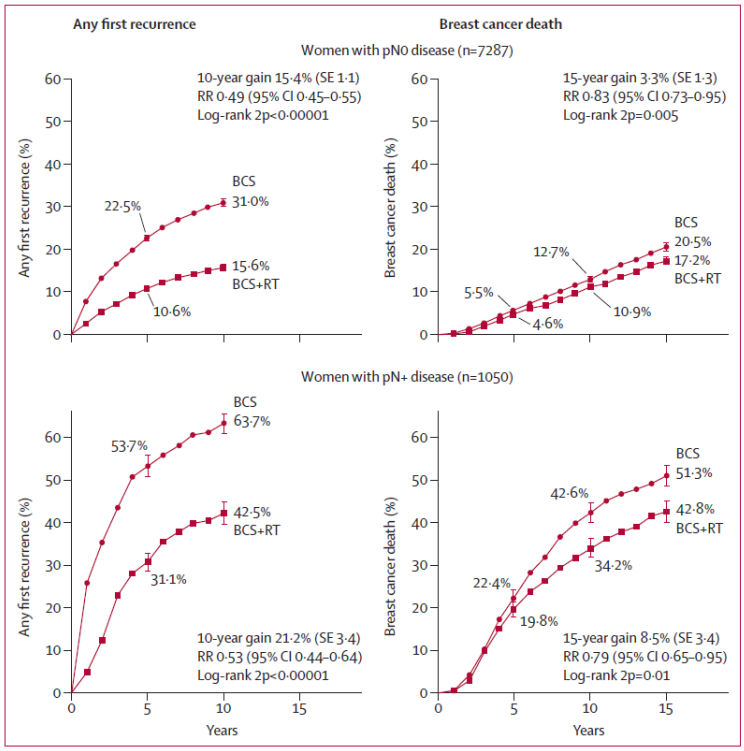


***Figure 5*: Absolute reduction in 15-year risk of breast cancer death with radiotherapy (RT) after breast-conserving surgery versus absolute reduction in 10-year risk of any (locoregional or distant) recurrence**
Women with pN0 disease are subdivided by the predicted absolute reduction in 10-year risk of any recurrence suggested by regression modelling (pN0-large ≥20%, pN0-intermediate 10–19%, pN0-lower <10%; further details are in webappendix pp 35–39). Vertical lines are 95% CIs. Sizes of dark boxes are proportional to amount of information. Dashed line: one death from breast cancer avoided for every four recurrences avoided. pN0=pathologically node-negative. pN+=pathologically node-positive.

[43] http://www.ncbi.nlm.nih.gov/pubmed/22019144?dopt=Abstract

RT Omission Trials

- There has been a push in the medical community to limit unnecessary treatment and procedures for elderly patients.
  - Surgically, this represented a decrease in SLNB for example (see "Axillary Evaluation Omission").
  - In radiation, this represented a significant drop in adjuvant RT usage.
- Interestingly, omission of hormone therapy has NOT been seen or pushed in the medical community.
  - This is unfortunate because of several reasons:
    - Hormone therapy has significant side effects in elderly patients.
    - *Nearly half* of women prescribed hormone therapy *do NOT* finish the recommended course.
    - These women also do not receive adjuvant radiation.
- Historically, adjuvant radiation and hormone therapy have a similar rate of decreasing recurrences especially in early stage breast cancer and DCIS.
  - Radiation may be associated with improved survival vs. hormone therapy (Jhawar, Cancer Med 2020).
- With the advent of facile radiation therapy techniques (APBI) and fractionations (FAST/FAST Forward), improved RT (5 fractions) may be better than 5 years of hormone therapy:
  - See article for further in-depth discussion:
  - Endocrine Treatment for 5 Years or Radiation for 5 Days for Patients With Early Breast Cancer Older Than 65 Years: Can We Do It Right? Naoum, JCO 2023. https://ascopubs.org/doi/full/10.1200/JCO.22.02171
- Soon, there may be better ways (genetic markers) to identify which patients may benefit from RT other than age.

PENDING TRIALS:

EUROPA	←R→ ≥ 70 yo BCS pT1N0 Luminal A (ER+PR+, Her2-, Ki67 ≤ 20%) SM- → | 1. RT | 2. ET |.
CAMERAN	←R→ > 65 yo tumor size <2cm, grade 1-2, node-negative BCS → | 1. APBI alone | 2. Endocrine Tx alone |.
DEBRA (NRG-BR007)	←R→ (BCS) Stg 1, HR+, HER2-, RS ≤18 breast cancer | 1. Breast RT + 5 years Hormones | 2. 5 years Hormones |.

Recent Studies

Canadian Real-World Evaluation of Radiation of Elderly Patients.
1100 women > 70 yo age who received BCS → either RT + ET (42.5%), ET alone (14%), or RT alone (32.5%), or no further Tx (11%).
Of those taking ET, < 60% completed 5 years.

Joseph, Radiother Oncol 2021
Of those taking ET, < 60% completed 5 years.
RFS (all compared to no further Tx) ↑ RT (HR = 0.174; $p < 0.001$), ↑ ET (HR = 0.414; $p = 0.007$), ↑ RT + ET (HR = 0.236; $p < 0.001$).
Determinants of OS were age, tumor grade, comorbidities, and adjuvant therapy. Increased comorbidity scores (0 vs. 1; 0 vs. ≥2) were associated with reduced OS (HR = 1.40; $p = 0.013$ and HR = 1.98; $p < 0.001$), without impact on RFS or BCSS.
Conclusions
Adjuvant RT-alone is a reasonable alternative to ET or RT + ET for older women with biologically favorable EBC. No difference in RFS or BCSS was noted between RT, ET, and RT + ET. Comorbidity was independently associated with reduced overall survival.

UAB Hormone Therapy Real World Usage Study
800 women s/p lumpectomy → (64% RT). Median age 74 yo. All patients ≥ 65 with stage 0-1 BCa from 2012-2014.

Wallace, Cancer 2017
Omission of RT was more likely in older patients, stage 0 patients, and patients with more comorbidities (P < .01).
Hormonal blockade was used in 41% of the patients who did not receive RT.
The utilization of hormonal blockade with the omission of RT was more likely in patients with fewer comorbidities (P < .01).
CONCLUSIONS In an older cohort of patients who otherwise would have qualified for the omission of radiation, two-thirds were treated with radiation. Future guideline recommendations should address omission in the context of hormonal blockade compliance because only 41% of the patients used hormonal blockade when radiation was not delivered.

Metaanalysis on How to ↑ Adjuvant Endocrine Therapy (AET) Compliance
←M→ 33 studes with 375,951 women.

Bright, JCO 2023.
"Interventions that educated patients about how to manage side effects generally failed to improve AET adherence."
"Policy changes that lowered AET costs consistently improved adherence."
Medication reminders, communication, and psychological/coping strategies showed varied efficacy.
Takeaway: Communicating one of the most important aspects of any new treatment (discussion on side effects) ↓ the likelihood of compliance.

NCDB Radiation Usage Study

~550,000 women who underwent lumpectomy with early stage BCa separated into 2 cohorts regardless of age.

Cohort 1 n = 160,990 ("Higher Risk") = ER-, endocrine therapy not planned, final margins positive, or size >3 cm. "Was appropriate for radiation."

Cohort 2 n = 394,946 = HR + with tumors >5 mm "Was appropriate for endocrine therapy."

Talcott, IJROBP 2023.

In cohort 1, radiation recommendation ↓ sharply at age 70. Age 50-69 = 90% to 92% recommended.
Age > 70 = 81%.
MVA age 70 vs. 69 (OR, 0.47; P < .001).

In cohort 2, endocrine therapy recommendation showed a small ↓ at age 70.
MVA 70 versus 69 (OR, 0.86; CI, 0.74-0.99; P = .001).

"When controlling for 21 other disease-specific, demographic and patient-health related factors among patients with higher-risk features, age 70 at diagnosis was associated with 53% lower odds of being recommended adjuvant radiation therapy and 39% lower odds of receiving radiation versus patients aged 69."

Conclusions We observed a unique decline in appropriate adjuvant therapy recommendation between ages 69 and 70. This suggests use of an age cutoff heuristic to process patient age in this population as a categorical, binary variable. This is a previously undescribed phenomenon in early-stage breast cancer.

POLAR 16-gene Sequencing Trial (**P**rofile for the **O**mission of **L**ocal **A**djuvant **R**adiation)

Analysis of 2 ←R→ BCS → | 1. radiotherapy or | 2. no radiotherapy |.

SweBCG91-RT trial (stage I–II, no adjuvant systemic therapy) Divided into training (n = 243) and validation (n = 354) cohorts.

Princess Margaret trial (age ≥ 50 years, T1-T2, adjuvant tamoxifen) Only used as a validation cohort (n = 132).

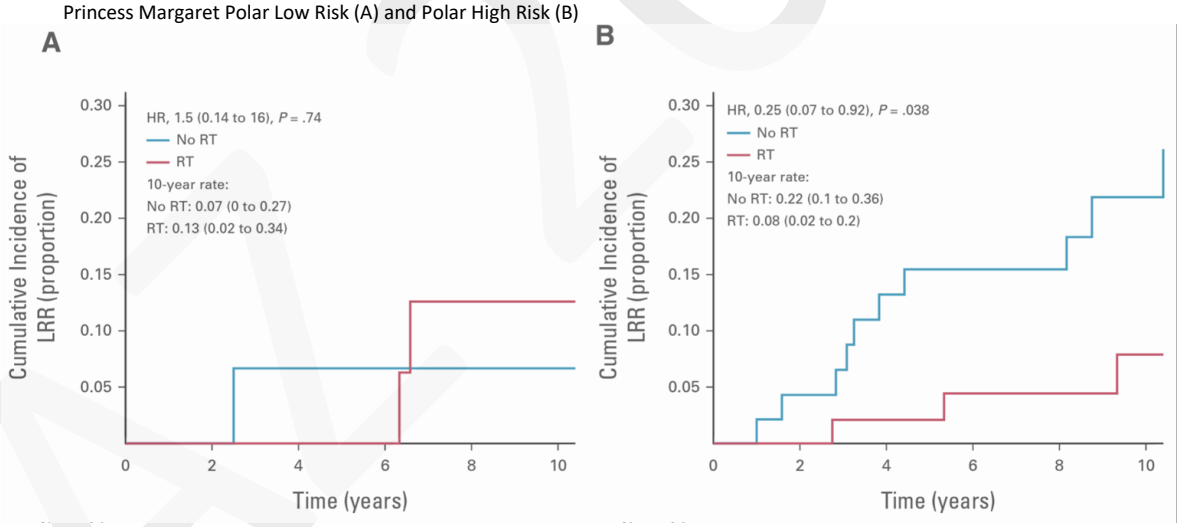
Transcriptome-wide profiling was performed, and the 16-gene POLAR signature was trained to predict locoregional recurrence.

Sjostrom, JCO 2022

10-year LRR of POLAR low-risk	SweBCG91-RT	5-6% with or without RT.
	Princess Margaret	7% no RT vs. 13% RT (HR = 1.5, NS)
10-year LRR **of POLAR High Risk**	SweBCG91-RT	19% No RT vs. 8% RT (HR = 0.43, P = .0055).
	Princess Margaret	22% No RT vs. 8% RT (HR = 0.25, P = .038).

Conclusions: "The novel POLAR genomic signature on the basis of locoregional recurrence biology may identify patients with a low risk of locoregional recurrence despite not receiving radiotherapy, and thus may be candidates for radiotherapy omission."

Princess Margaret Polar Low Risk (A) and Polar High Risk (B)



RS Gene Sequencing NCDB Trial

Retrospective 11891 NCDB age ≥ 70 with pT1N0 ER+/PR + HER2- breast cancer treated with BCS and ET.

RS (low risk [LR] = 1–10, intermediate risk [IR] = 11–25, high risk [HR] = 26–99).

N=3364 in the LR cohort, 7305 in the IR cohort, and 1222 in the HR cohort.

Total 79 % received RT: 77 % in the LR cohort, 79 % in the IR cohort, and 85 % in the HR cohort.

Because PSM could not be efficiently performed in the HR cohort alone, the IR and HR cohort were merged (IRHR) for matching.

Chevli, Radiother Oncol 2022.

5-year OS	LR cohort	RT 91% vs. no RT 89% (NS).
	IRHR cohort	RT 91% vs. no RT 87% (SS).

On MVA in the LR cohort, RT (p = 0.727) was not predictive of improved OS.

On MVA in the IRHR cohort, RT (p = 0.010) was a positive prognostic factor for OS.

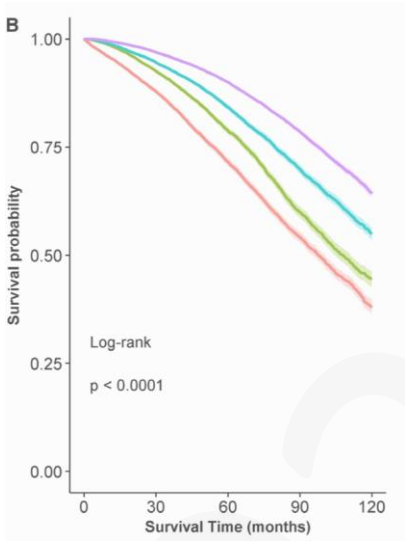
Conclusion In this older cohort of patients, there is an OS benefit with the use of RT in patients with IRHR RS but not in patients with LR RS. Pending prospective evaluation, assessment of RS in this older subset of patients is recommended with consideration of RT when RS is ≥11.

NCDB Survival Outcomes ET vs. RT

RR 130,194 women ≥65 years with invasive ER+, N0 diagnosed between 2004 and 2015. All patients underwent BCS.

TABLE 4 Overall survival by adjuvant treatment time in a propensity-matched cohort (n=21,326)*

	5 Year Survival		
	Survival Percent (95% CI)	***P***	**HR (95% CI)**
Hormone Therapy Alone	80.2 (79.3-81.2)		1.00 (ref)
Radiotherapy Alone	83.0 (82.2-83.9)	<.0001	0.84 (0.78-0.92)
	10 Year Survival		
	Survival Percent (95% CI)	***P***	**HR (95% CI)**
Hormone Therapy Alone	46.7 (44.5-48.8)		1.00 (ref)
Radiotherapy Alone	49.3 (47.2-51.4)	0.0002	0.87 (0.81-0.94)



Jhawar, Cancer Med 2020.

Unadjusted 5/10-year OS rates were in **4 groups**.

90.0% / 64.3% for HT and RT
84.2% / 54.9% for RT alone
78.7% / 44.5% for HT alone
71.6% / 38.0% for no treatment;

p<0.001 for all.

Compared to HT alone, the 10-year multivariable hazard ratio (HR) for death for RT alone was 0.86 (95% CI 0.82-0.91).

In propensity-matched patients who received RT alone or HT alone (n=21,326), RT alone had significantly better survival at 5 (HRadj : 0.84) and 10 (HRadj : 0.87) years.

Conclusions: Older women with early stage ER+ breast cancer who undergo BCS and receive both HT and RT have the best survival, while RT as single-modality therapy had higher rates of OS at 5 and 10 years compared to HT alone.

SEER RT without ET Study

RR 13,321 women age ≥ 66 years stage I ER+ breast cancer from 2007 to 2012 all BCS.

4 groups: (1) ET + RT (reference); (2) ET alone; (3) RT alone; and (4) neither RT nor ET (NT).

Most women underwent both treatments, with 44% undergoing ET + RT, 41% RT alone, 6.6% ET alone, and 8.6% NT.

From 2007 to 2012, RT ↓ from 49% to 30%, whereas ET alone ↑ and ET + RT ↑ (ET alone, 5.4%-9.6%; ET + RT, 38%-51%).

Compared with patients age 66 to 69 years, patients age 80 to 85 years were more likely to receive NT (odds ratio [OR], 8.9), RT (OR, 1.9), or ET (OR, 8.8) versus ET + RT (P < .01).

Gerber, IJROBP 2022.

Secondary Breast Cancer Events (SBCE) total = 3%

2.2% ET + RT
3.0% RT alone
3.2% ET alone
7.0% NT

Relative to ET + RT, NT and ET alone were associated with higher SBCE (NT: SHR, 3.7, P < .001; ET alone: SHR, 2.2, P = .008).
RT alone was **not associated** with a higher SBCE (SHR 1.21; P = .137).

Clinical factors associated with higher SBCE were HER2 positivity and pT1c (SHR, 1.7; P = .006).

Conclusions Treatment with RT alone in older women with stage I ER+ disease is decreasing. RT alone is not associated with an increased risk for SBCE. By contrast, NT and ET are both associated with higher SBCE in multivariable analysis with propensity weighting. Further study of the omission of endocrine therapy in this patient population is warranted.

LUMINA Single Arm Prospective Trial

500 women ≥ 55 yo T1N0, G1-2, Luminal A (ER+PR+,Her2-, Ki67 ≤ 13.25%), and had received ET.

Patients with KI67 ≤ 13.25% did NOT receive RT.

1^{O} local recurrence in the ipsilateral breast.

Whelan, NEJM 2023.

5-year recurrence was reported in 2.3% of the patients.

Breast cancer occurred in the contralateral breast in 1.9% of the patients and recurrence of any type was observed in 2.7% (90% CI, 1.6 to 4.1).

CONCLUSIONS Among women who were at least 55 years of age and had T1N0, grade 1 or 2, luminal A breast cancer that were treated with breast-conserving surgery and endocrine therapy alone, the incidence of local recurrence at 5 years was low with the omission of radiotherapy.

Comment 1: The Background Section of this NEJM 2023 paper begins with a somewhat outdated assumption which does not consider the recent fractionation changes which are also associated with good cosmesis. Considering the low % of patients adhering to ET (along with known side effects), the phrase "However, radiotherapy is inconvenient, costly, and associated with both short-term and long-term side effects" may not be only applicable to RT.

Comment 2: Study did not address the more significant question of recurrence in the setting of BCS alone vs. BCS + RT vs. BCS + ET.

CALGB C9343 / RTOG 97-02, ECOG (Hughes, 2010).[44]
←R→ 636 women > 70 yo (56% >75 y/o), cT1N0, ER+.
Lumpectomy → tamoxifen +/- RT. **ALND 37%.** RT = 45 Gy in 25 fx + boost 14 Gy in 7 fx . F/U at 10.5 years.

Results: + RT to Tam ↑ time to first recurrence (p = 0.015) due to improved local control by Tam-RT.
Site of first recurrence was local for 9% Tam vs. 2% Tam+RT → @ ipsilateral breast in 8% vs. 2% or @ solely in the axilla in 1% vs. 0%.
The remaining endpoints NS. 10-year freedom from mastectomy 96% (Tam) vs 98% (Tam+RT), freedom from DM 95% vs 93%. Nor, BCa spec survival 98% vs 96%, OS 63% vs 61%. Only 7% deaths were due to breast cancer.
Conclusion: RT results in absolute reduction of 7% in LR (6% IBTR + 1% Axilla). No impact on overall survival, cancer specific survival, breast conservation, or distant DFS.

- 5-year f/u study: Lumpectomy + tamoxifen alone is acceptable for women **70 years or older with T1N0 ER+ tumors**.

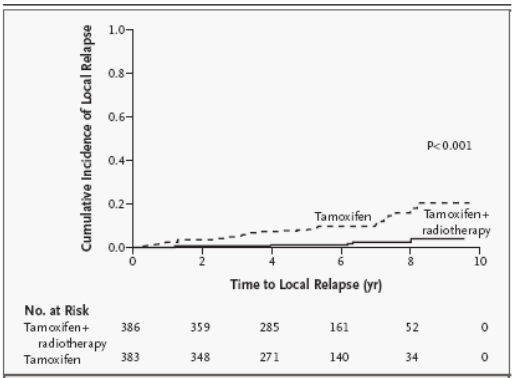


Figure 3. Cumulative Incidence of Local Relapse.

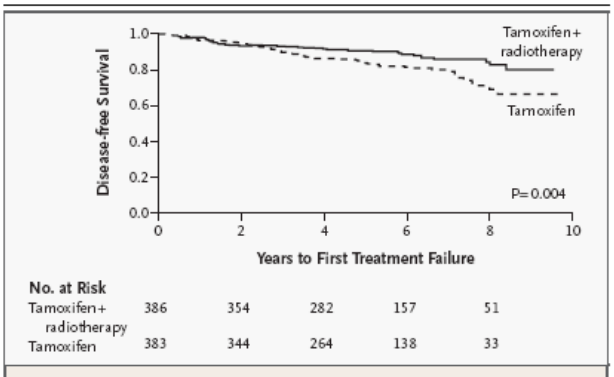


Figure 2. Disease-free Survival.

Fyles (NEJM, 2004). FYLES age FIFTY + hypofractionated
←R→ 769 women with early breast cancer (cT1-2N0, 80% ER+)
Lumpectomy → tamoxifen ± RT. RT = 40 Gy in 16 fx + 12.5 Gy / 5 fx boost.

RESULTS
All comers 5-year LR Tam 7.7% vs. Tam+RT 0.6% (P<0.001). 5-year DFS 84% vs. 91% (P=0.004).
T1N0 ER+ planned subgroup of 611 women 5-year LR Tam 5.9% vs. Tam+RT 0.4% (P<0.001).
All comers 5-year AXILLARY RELAPSE 2.5% vs. 0.5% (p=0.049)
No significant difference in the rates of distant relapse or overall survival.
CONCLUSIONS
As compared with tamoxifen alone, radiotherapy plus tamoxifen significantly reduces the risk of breast and axillary recurrence after lumpectomy in women with small, node-negative, hormone-receptor–positive breast cancers.

Milan III (Veronesi, Annals of Oncology, 2001).
←R→ 579 pts, Stage I/II. Operable breast cancer, cT < 2.5 cm. Quadrantectomy + LND **± RT**.
Mean F/U: 9 yrs. XRT: 50 Gy + 10 Gy boost. + LNs: ER(-) CMF, ER (+) Tam
LR 23.5% → 5.8%. OS NS.
Conclusions: BCT is indicated for: **<55 yo** and/or **+LNs**. N0-N1 >66 yo with neg. margins → 4% LF without XRT.

[44] http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/507

	No radiotherapy (n=668)	Radiotherapy (n=658)	p value
Local recurrence	26 (4%)	5 (<1%)	
Tumour size (mm)			
0–10	10/258 (4%)	3/265 (1%)	0·04
10·1–20	10/326 (3%)	1/319 (<1%)	0·008
20·1–30	6/84 (7%)	1/74 (1%)	0·08
Margins			
<1 mm	1/10 (10%)	0/9 (0%)	0·32
1–5 mm	10/315 (3%)	4/296 (1%)	0·15
>5 mm	9/227 (4%)	1/239 (<1%)	0·01
Re-excision	6/112 (5%)	0/110 (0%)	0·01
Grade			
1	8/271 (3%)	2/292 (<1%)	0·04
2	15/368 (4%)	3/352 (<1%)	0·006
3	3/23 (13%)	0/13 (0%)	0·21
Age (years)			
65–69	8/308 (3%)	2/331 (<1%)	0·05
≥70	18/360 (5%)	3/327 (1%)	0·002
Lymphovascular involvement			
No	24/631 (4%)	5/628 (<1%)	0·0004
Yes	2/32 (6%)	0/27 (0%)	0·29
Oestrogen receptor status			
Rich	20/593 (3%)	5/601 (<1%)	0·002
Poor	6/65 (9%)	0/55 (0%)	0·03

PRIME II

←R→ 1326 ≥ 65 years "low-risk" INVASIVE, not DCIS, ER+, cN0, T1-T2 up to 3 cm size, margin neg (…and grade 3 or LVI+, but not both), and must receive either neoadj or adj hormones.

Lumpectomy → ALND or SLNB →

| 1. WBI (40-50 Gy in 15-25 fractions → boost 10-20 Gy) |

| 2. No RT |. 1^{O} ipsilateral breast tumor recurrence.

ALL GOT AXILLARY STAGING. Vs hughes only 1/3 got axillary staging.

Grade 1 40%, Grade 2 50%, **Grade 3 5%.** **LVSI pos 5%.**

SLNB only 30%, "Sample" only 25-30%, Sample + SLNB 15%, ALND 20%. ER Rich 90%, ER Poor 10%.

Kunkler, Lancet Oncology 2015.

Results: 5 years, ipsilateral breast recurrence was 1·3% (n=5) vs. 4·1% (n=26) no RT (p=0·0002).

5-year overall survival was 93·9% both groups.

Unplanned subgroup analysis (see LEFT) **LVSI, ER Poor, All Grade, GOOD margins, all size.**

Conclusion: Omission of RT in ≥ 65, pT1-2 up to 3 cm pN0, ER+ or PR+ with BCS with endocrine therapy, is probably OK.

Kunkler, NEJM 2023

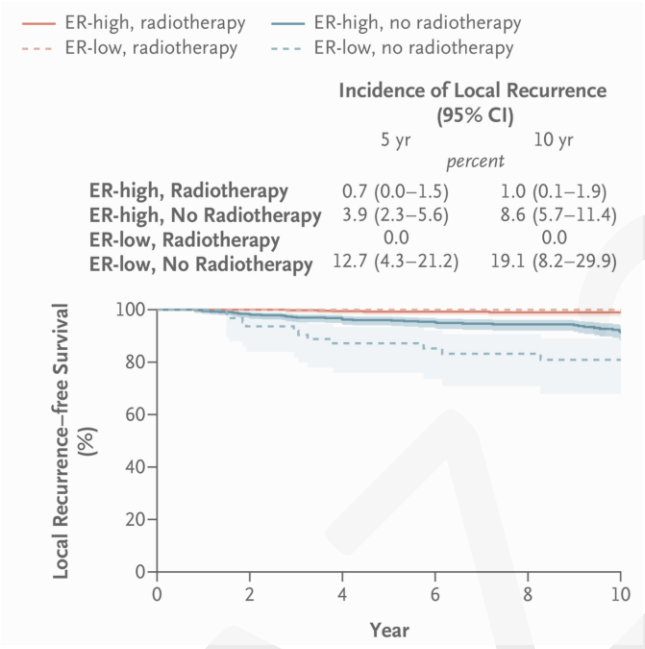
Results: 10 years, CI local breast cancer recurrence 0.9% vs. 9.5% (HR; P<0.001).

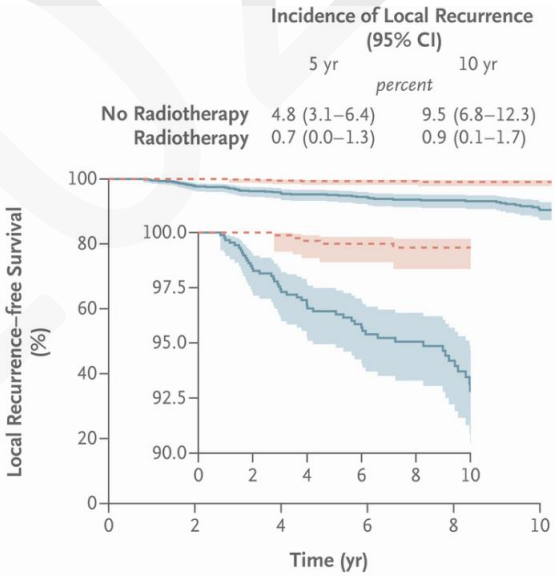
10-year Distant Recurrence 3.0% vs. 1.6% (NS)

10-year OS was the same at 80-81%.

The incidence of regional recurrence and breast cancer–specific survival also did not differ substantially between the two groups.

CONCLUSIONS Omission of radiotherapy was associated with an increased incidence of local recurrence but had no detrimental effect on distant recurrence as the first event or overall survival among women 65 years of age or older with low-risk, hormone receptor–positive early breast cancer.





Low-Risk Luminal A (Benefit of TAM ± RT)

RR classified luminal A (n = 265), luminal B (n = 165), or high-risk subtype (luminal HER2, n = 22; HER2 enriched, n = 13; basal like, n = 30; or triple-negative nonbasal, n = 6). IHC → ER, PR, HER2, cytokeratin 5/6, EGFR, and Ki-67 (501 of 769 available blocks).

Median follow-up was 10 years.

Liu, JCO 2015.

10-year IBR: luminal A, 5.2%; luminal B, 10.5%; high-risk subtypes, 21.3%; (P < .001).

Luminal subtypes seemed to derive less benefit from RT (luminal A HR 0.40; luminal B HR 0.51) than high-risk subtypes (HR, 0.13).

Unplanned subset low-risk (> 60 yo cT1, G1-2, luminal A tumors, n = 151) vs. high risk = 10-year IBR was 3.1% versus 11.8% (SS).

Clinical low-risk luminal A patients had a 10-year IBR of 1.3% with tamoxifen versus 5.0% with tamoxifen plus RT (P = .42).

Multivariable analysis showed that RT (HR, 0.31; P < .001), clinical risk group (HR, 2.2; P = .025), and luminal A subtype (HR, 0.25; P < .001) were significantly associated with IBR.

CONCLUSION: IHC subtyping was prognostic for IBR but was not predictive of benefit from RT. Further studies may validate the exploratory finding of a low-risk luminal A group who may be spared breast RT.

Other Trials:
Jagsi (Michigan) Luminal A and Low Oncotype OMIT RT.
Fyles (Canada) Luminal A and Low Ki-67.
Sjostrom JCO 2017… 20% no RT vs. 6% adjuvant RT. Shows necessity of RT.

RCTs	F/U	Surgery	Systemic	Nodes	RT Dose	LR RT(-)	LR RT(+)
NSABP B-06 (1976)	20 years	lumpectomy	N+: melphalan + 5-FU		50	39%	14%
Uppsala-Orebro (1981)	10 years	sector resection	none		54	24%	8%
St. George's (1981)	5 years	WLE	ER+: tamoxifen ER-: CMF		?	35%	13%
Ontario (1984)	8 years	lumpectomy	none		40/16 + 12.5/5	35%	11%
Scotland (1985)	6 years	WLE	ER+: tamoxifen ER-: CMF		50 + 10-30	24%	6%
Tokyo (1985)	8 years	sector resection	yes		?	9%	7%
St. Petersburg (1985)	5 years	quadrantectomy	yes		?	17%	4%
Milan 3 (1987)	10 years	quadrantectomy	N+ high risk: chemo N+ low risk: tamoxifen		50 + 10	23%	6%
NSABP B-21 (1989)	8 years	lumpectomy	tamoxifen or none	pN0	50 +/- boost	16%	3%
Finland (1990)	12 years	lumpectomy	none		50	27%	12%
SweBCG (1991)	5 years	sector resection	at discretion (in 9%)		48-54	14%	4%
German GBSG (1991)	10 years	BCS	2x2: +/- TAM	pN0	50 + 10-12	8%	5%
Canada (1992)	5 years	BCS	tamoxifen		40/16 + 12.5/5	8%	1%
CALGB 9343 (1994)	5 years	lumpectomy	tamoxifen		45 + 14	4%	1%

Hypofractionation Guidelines

Hypofractionation 2018 NEW GUIDELINES:

1. For women with invasive breast cancer receiving whole-breast radiation with or without inclusion of the low axilla, the preferred dose-fractionation scheme is hypofractionated whole-breast radiation to a dose of 4000 Centigray (cGy) in 15 fractions or 4250 cGy in 16 fractions.
2. Hypofractionation should be INDEPENDENT of: tumor grade; whether the tumor is in the left or right breast; prior chemotherapy; prior or concurrent trastuzumab or endocrine therapy; and breast size, provided that homogenous dosing can be achieved.
3. It MAY BE independent of the following factors: hormone receptor status; HER2 receptor status; margin status following surgical resection; and age.
4. For patients with ductal carcinoma in situ (DCIS), hypofractionated whole-breast radiation may be used as an alternative to conventional fractionation.
5. For invasive cancer cases, a tumor bed boost is recommended for patients with a positive margin following surgical resection, patients aged 50 and younger, and patients aged 51 to 70 with a high-grade tumor. Omitting a tumor bed boost is suggested for patients with invasive cancer who are older than 70 years and have low-to- intermediate-grade, hormone-positive tumors resected with widely negative margins.
6. For DCIS, a boost is recommended for patients aged 50 and younger, patients with high- grade tumors, or those with positive or close margins following resection. A boost may be omitted for patients with DCIS who are older than 50 years; have been screen detected; have smaller, low-to- intermediate grade tumors; and have widely negative margins following surgery.
7. Recommend = homogenous radiation dosing and full coverage of the tumor bed.
8. Approaches that incorporate deep inspiration breath hold, target and organ-at- risk contouring, and optimal patient positioning are recommended to minimize the radiation dose affecting nearby organs and normal tissue, including the heart, lungs and opposite breast.

HISTORICAL ASTRO Fractionation Guidelines (Smith 2010).[45]

1. Pt population that CF-WBI and HF-WBI have ≈ results: **1. ≥ 50 yo at Dx**, **2. p T1–2 N0** and s/p BCS, **3. NOT tx chemo**, and…
   …within the breast along the central axis, the minimum dose is no less than 93% and **4. maximum dose is no greater than 107%** of the prescription dose (±7%;) (as calculated with 2-dimensional treatment planning without heterogeneity corrections).

			ARM					IBTR		LRF		DFS		OS	
Trial	**Median Follow- up (years)**	**Time point for outcome reporting (years)**	**Dose (Gy)**	**# Fx∝**	**# Days**	***N***	**%**	***p***	**%**	***p***	**%**	***p***	**%**	***p***
Canada	12	10	50	25	35	612	7.5	<.001					84.4	0.79
			42.5	16	22	622	7.4						84.6	
RMH/GOC	9.7	10	50	25	35	470	12	†						
			42.9	13	35	466	9.6							
			39	13	35	474	15							
START A	5.1	5	50	25	35	749	3.2	††	3.6	††	86	††	89	††
			41.6	13	35	750	3.2	0.74	3.5	0.86	88	0.33	89	0.81
			39	13	35	737	4.6	0.40	5.2	0.35	85	0.33	89	0.99
START B	6.0	5	50	25	35	1105	3.3	0.21	3.3	0.35	86	0.02	89	0.03
			40	15	21	1110	2.0		2.2		89		92	

† 42.9 Gy vs 39 Gy was p = 0.027 (SS). 50 vs others p > 0.05. †† 50 Gy arm vs 41.6 and 50 Gy arm vs 39.

2. Although the majority thought sufficient data showing safety of HF-WBI → tumor bed boost, a minority believed that CF-WBI should be used instead when a tumor bed boost is indicated

	Canada	RMH/GOC	START A	START B
# Patients	1234	1410	2236	2215
Treated with BCS	100%	100%	85%	92%
Age > 50	75%	70%	77%	79%
pT 1-2	100%	94%	Majority	Majority
Chemo used	11%	14%	35%	22%
Percent receiving boost	0%	75%	61%	43%
Boost dose	–	14 Gy, 7 fx	10 Gy, 5 fx	10 Gy, 5 fx
Boost modality	–	Electrons	Electrons	Electrons
Percent receiving regional nodal irradiation	0%	21%	14%	7%

3. HF-WBI without boost should be done to 42.5 / 16 fx over 22 days. HF-WBI with boost dose is not determined.

[45] http://www.ncbi.nlm.nih.gov/pubmed/20638191?dopt=Abstract

Major HFx U-Hfx Trials

Recent Studies

FAST FORWARD

←R→ 4096 patients invasive carcinoma of the breast (pT1–3, pN0–1, M0) after breast conservation surgery or mastectomy were eligible.
| 1. 40 Gy in 15 fx |
| 2. 27 Gy in 5 fx (1 week) |
| 3. 26 Gy in 5 fx (over 1 week) |
to the whole breast or chest wall.

1^{O} endpoint was ipsilateral breast tumour relapse. Assuming a 2% 5-year incidence for 40 Gy, non-inferiority defined as ≤1·6% (HR = 1.81).

Brunt, Lancet 2020.
5-year LF 2·1%, –0·3%, –0·7% (NS).
Non-inferior and within ≤ 1.6% as previously defined.

Technique:
The breast CTV was all parenchymal soft tissue 5 mm below the skin, excluding muscle and bone. The PTV margin was 1 cm. The planning goals were that 1) at least 95% of the PTV receives 95% of the dose, 2) max dose <110%, 3) <2% receives >107%, and 4) <5% receives >105%. Organ-at-risk goals were 1) ipsilateral lung V8Gy < 15%, 2) heart V1.5Gy < 30%, and 3) heart V7Gy < 5%. These goals were for the whole breast portion only—any additional boost dose didn't count toward the constraints. Again, there was no clever boost scheme, so patients had to double treatment time with a whole extra week of 10 Gy in 5 fractions boost. TBL: If you're comfortable with 15-16 fraction breast planning, there's nothing dramatically different with this 5-fraction approach.

	Number of moderate or marked events/total number of assessments over follow-up	Odds ratio for schedule (95% CI)	p value for comparison with 40 Gy	p value for comparison between 27 Gy and 26 Gy	Odds ratio for years of follow-up (95% CI); p value
Any adverse event in the breast or chest wall*	..	..	..	..	0·98 (0·96–1·00); 0·055
40 Gy	651/6121 (10·6%)	1 (ref)	..	..	..
27 Gy	1004/6303 (15·9%)	1·55 (1·32–1·83)	<0·0001	..	..
26 Gy	774/6327 (12·2%)	1·12 (0·94–1·34)	0·20	0·0001	..
Breast distortion†	..	..	..	..	0·99 (0·95–1·02); 0·38
40 Gy	232/5724 (4·0%)	1 (ref)	..	..	..
27 Gy	363/5953 (6·1%)	1·51 (1·15–1·97)	0·0028	..	..
26 Gy	299/5945 (5·0%)	1·20 (0·91–1·60)	0·19	0·083	..
Breast shrinkage†	..	..	..	..	1·03 (1·00–1·06); 0·023
40 Gy	330/5728 (5·8%)	1 (ref)	..	..	..
27 Gy	503/5944 (8·5%)	1·50 (1·20–1·88)	0·0004	..	..
26 Gy	369/5943 (6·2%)	1·05 (0·82–1·33)	0·71	0·0018	..
Breast induration (tumour bed)†	..	..	..	..	1·00 (0·96–1·04); 0·95
40 Gy	185/5713 (3·2%)	1 (ref)	..	..	..
27 Gy	304/5948 (5·1%)	1·56 (1·19–2·05)	0·0013	..	..
26 Gy	236/5937 (4·0%)	1·19 (0·90–1·59)	0·23	0·047	..
Breast induration (outside tumour bed)†	..	..	..	..	0·96 (0·90–1·02); 0·17
40 Gy	45/5712 (0·8%)	1 (ref)	..	..	..
27 Gy	137/5943 (2·3%)	2·79 (1·74–4·50)	<0·0001	..	..
26 Gy	97/5930 (1·6%)	1·90 (1·15–3·14)	0·013	0·059	..
Telangiectasia	..	..	..	..	1·21 (1·14–1·29); <0·0001
40 Gy	63/6087 (1·0%)	1 (ref)	..	..	..
27 Gy	100/6272 (1·6%)	1·68 (1·07–2·65)	0·025	..	..
26 Gy	102/6300 (1·6%)	1·53 (0·96–2·43)	0·070	0·65	
Breast or chest wall oedema	..	..	..	..	0·73 (0·69–0·78); <0·0001
40 Gy	89/6097 (1·5%)	1 (ref)	..	..	..
27 Gy	217/6287 (3·4%)	2·18 (1·57–3·03)	<0·0001	..	..
26 Gy	155/6318 (2·4%)	1·47 (1·03–2·09)	0·032	0·0097	..
Breast or chest wall discomfort	..	..	..	..	0·93 (0·89–0·97); 0·0003
40 Gy	234/6086 (3·8%)	1 (ref)	..	..	..
27 Gy	269/6285 (4·3%)	1·10 (0·86–1·40)	0·44	..	..
26 Gy	250/6309 (4·0%)	0·98 (0·76–1·26)	0·86	0·35	..

Results for years of follow-up show trend in normal tissue effects over follow-up across all fractionation schedules. p values are calculated by Wald test; odds ratios are estimated from the generalised estimating equations model including all follow-up data and show relative odds of moderate or marked adverse event (vs none or mild) for each pairwise comparison of fractionation schedules across all follow-up assessments. *Includes shrinkage, induration, telangiectasia, or oedema. †Patients who had breast conservation surgery or mastectomy with reconstruction.

Table 4: **Longitudinal analysis of moderate or marked clinician-assessed late normal tissue effects for patients with at least one annual clinical assessment (n=3975)**

FAST (NOT fast-forward)

←R→ 915 patients ≥ 50 yo. All pT1-2 pN0 | 1. 50 Gy/25 fr (5 weeks) | 2. 30 or 28.5 Gy in 5 once-weekly fr of 6.0 or 5.7 Gy |. 1^{O} photographic cosmesis at 2, 5 yrs.

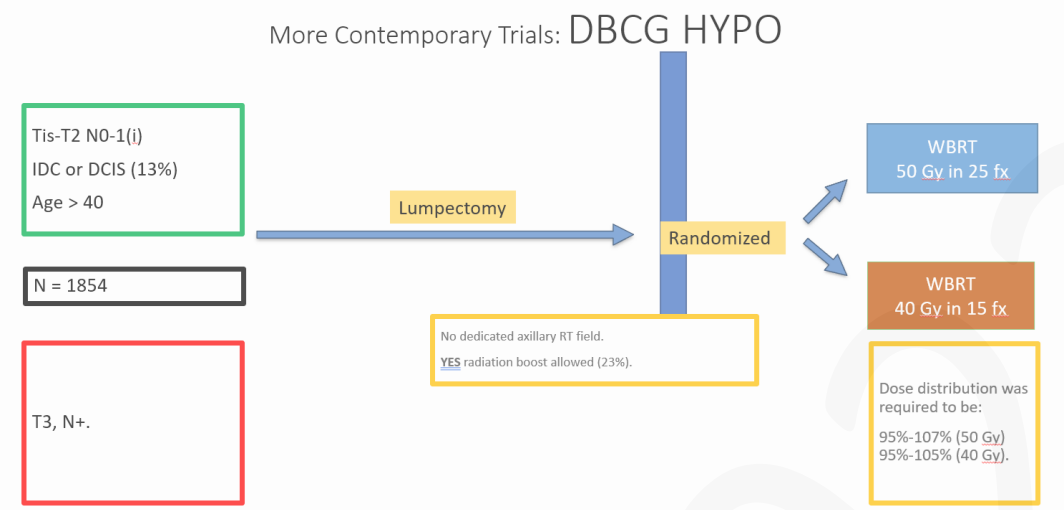
Brunt, JCO 2020.
Five-year photographs were available for 615/862 (71%) eligible patients.
Photographic cosmesis ORs 1.64 (30 Gy, p = 0.019) and ORs 1.1 (28.5 Gy, NS).
α/β estimate for photographic end point was 2.7 Gy, giving a 5-fr schedule of 28 Gy estimated to be isoeffective with 50 Gy/25 fr.
Moderate/marked physician-assessed breast NTE ORs (shrinkage, induration, telangiectasia, edema) were 2.12 (30 Gy; P < .001) and 1.22 (28.5 Gy, NS)
With 9.9 years median follow-up, 11 ipsilateral breast cancer events (50 Gy: 3; 30 Gy: 4; 28.5 Gy: 4) and 96 deaths (50 Gy: 30; 30 Gy: 33; 28.5 Gy: 33) have occurred.
Conclusion: At 10 years, there was no significant difference in NTE rates after 28.5 Gy/5 fr compared with 50 Gy/25 fr, but NTE were higher after 30 Gy/5 fr. Results confirm the published 3-year findings that a once-weekly 5-fr schedule of whole-breast radiotherapy can be identified that appears to be radiobiologically comparable for NTE to a conventionally fractionated regimen.

Chinese Population Hypo Fx 2020
←R→ 734 women from 4 Chinese institutions all BCS w/ T1-2N0-3 invasive breast cancers → WBRT ± RNI → tumor bed boost.
Note: **>80% of patients were T1, N0, and ER+, and <5% actually received RNI. . Median age was low at 46 years, and 65% received chemotherapy.**
| 1. 50 Gy in 25 fractions over 5 weeks with a boost of 10 Gy in five fractions | 2. 43.5 Gy in 15 fx over 3 weeks → boost 8.7 Gy in 3 fractions|.
1^{O} 5-year local recurrence (LR), and a 5% margin of 5-year LR was used to establish noninferiority.

Wang, JCO 2020 Median FU 73/5 months
5-year LR 1.2% vs. 2.0% (P = .017 for noninferiority). NS all survival endpoints.
HFRT group had less grade 2-3 acute skin toxicity than the CFRT group (P = .019).
CONCLUSION
CFRT and HFRT with a tumor-bed boost may have similar low LR and toxicity.

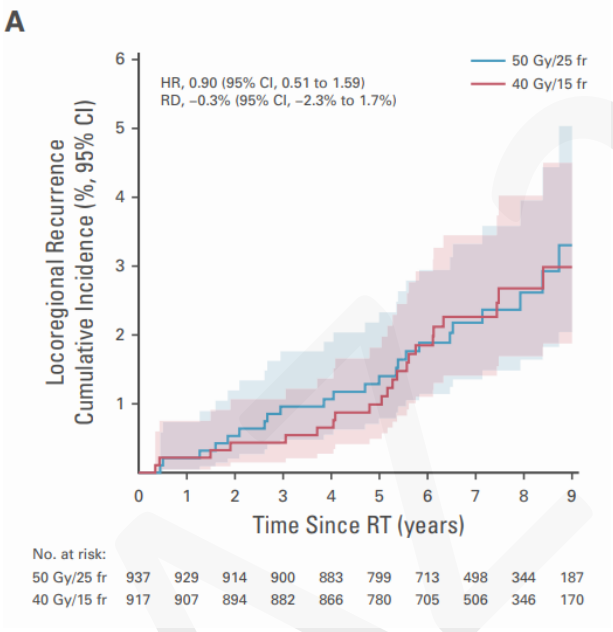
DBCG Hypo: IDC **and DCIS** Randomized Trial

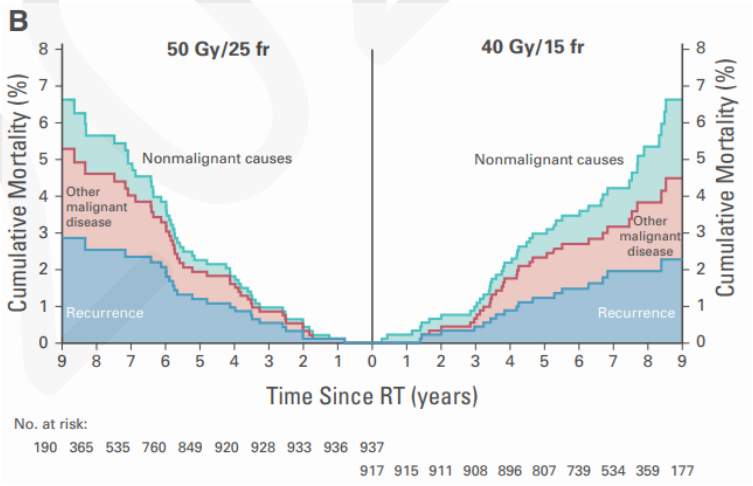
Endocrine monotherapy was prescribed for 34.6% (n = 557) of patients—5.2% (n = 84) received tamoxifen and 29.6% (n = 476) received letrozole.
A radiotherapy boost was delivered to 23.1% (n = 430) patients, the majority (85.6%) a dose of 10 Gy.
682 patients (42.4%) with carcinoma received adjuvant chemotherapy, and for the Danish cohort 35.9% of patients (n = 578) received adjuvant chemotherapy and 7.6% (n = 122) also received trastuzumab.



Offersen, JCO 2020.
9-year LRR 3.3% vs. 3.0%.
9-year OS both 93%.

The occurrence of radiation-associated cardiac and lung disease was rare and not influenced by the fractionation regimen.





Michigan HFx in Triple Negative Breast Cancer Patients

Prospective 538 women in 18 centers in Michigan (307 CFX and 231 HFX) with node negative, triple neg status s/p lumpectomy.
5-year Median Follow-up.

Jagsi, IJROBP 2021.
5-year FFLR 93.6% vs. 94.4% (HR 1.05, NS). 5-year RFS were 87.8% vs. 88.4% (NS). 5-year OS 96.6% vs. 93.4% (NS).
Conclusion Analysis of outcomes in this large observational cohort of patients with triple-negative, node-negative breast cancer treated with whole breast irradiation reveals no differences by dose fractionation. This adds evidence to support the use of moderate hypofractionation in patients with triple-negative disease.

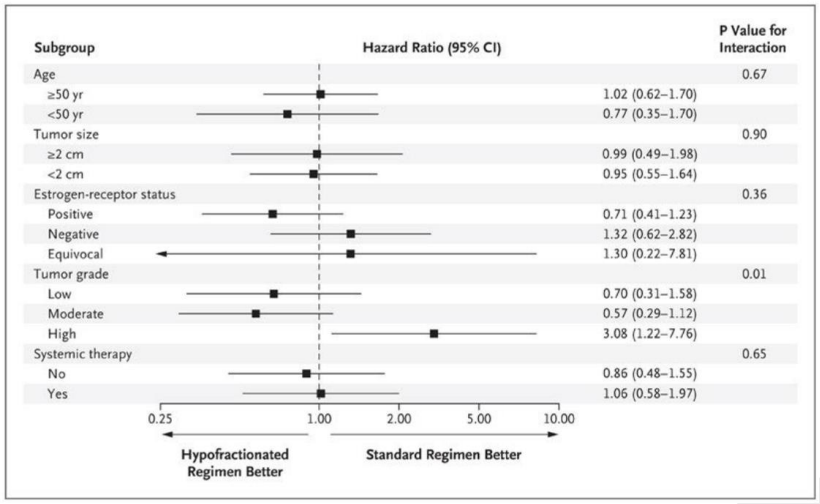
Michigan HFx High Risk Study

Prospective 300 women early-stage (T1-2, N0, M0) BCa high-risk tumors (RS high > 25, Triple Neg, or HER2+) + received systemic chemotherapy.
| 1. WBRT Conventional 45-50.4 Gy + Boost 10-20 Gy | 2. WBRT HF 40-42.56 Gy + 7.5-16 Gy Boost |.

Willen, PRO 2022.
5-year LR similar < 3%.

Historical Studies

Canadian (Whelan 2010).[46] RTC in 1993, 1234 patients with invasive T1-2 N0 (by ALND) s/p BCS, margins negative. Age <50 in 25%, tumors >2 cm in 31%, adjuvant TAM 42%, adjuvant chemo 11%. **EXCLUDED large breasted patients (> 25 cm separation)**. Treated with Arm 1) 42.5/16 (2.66 Gy/fx) vs Arm 2) 50/25; No boost.



Outcome: 10-year LF: HF 7.4% (invasive 6.2%) vs CF 7.5% (invasive 6.7%) (NS). No difference in 10-year DFS or OS.

Subgroup analysis - ONLY high-grade tumors LR hypo-fx 16% vs. control 5% (SS) local control.
Age, tumor size, ER status, chemo ± NS. 10-year DSS both groups 87% (NS); OS both groups 84% (NS).

Toxicity: All Grades NS. No Grade 4 toxicity. Excellent/good cosmetic HF 70% vs. CF 71% (NS).

Conclusion: Accelerated hypofractionated WBRT was not inferior to standard conventional fractionation WBRT.

NOTE: There is a pooled analysis that reviewed Whelan and START A and B, that showed that in G3 patients, there were no change in LF. The Whelan analysis might have been a fluke.

MRC START A (START 2008).[47] RTC in 1998 2236 patients with operable invasive BCA, pT1-3a N0-1, 23% < 50 yo, 54% TAM/no chemo, 11% chemo/no TAM, 24.5% both, + requiring RT after surgery. CMFSurgery either BCS or mastectomy (15%).

Arm 1, 50/25 | Arm 2, 41.6/13 | Arm 3, 39/13; all arms given over 5 weeks to eliminate treatment time variable.
Boost given at discretion (61%) 10/5. Regional RT 14%.

Outcome: 5-year LRR 50 Gy 3.6%, 41.6 Gy 3.5%, 39 Gy 5.2% (NS). Cosmesis: Lower rate of late adverse effects in 39 Gy, same in 41.6 Gy compared with 50 Gy. α/β estimate: 4.6 Gy for tumor control, 3.4 Gy for late breast changes.
Conclusion: Breast cancer and normal breast tissues respons similarly to fraction size. No difference in local control.
Note: 60% had discretionary boost 10/5, 35% had chemotherapy and its interaction with fraction size unclear.
Note: Toxicity results in 2010 shows significant ↓ moderate/marked change in skin appearance in 39 Gy group (HR 0.63, SS), but not 41.6 Gy group (HR 0.83, NS). 5yr breast symptoms, shoulder pain, arm/shoulder symptoms (~20%), or body image problems (~40%). No difference between 40 Gy and 50 Gy.

MRC START B (START 2008).[48] RTC in 1999 2215 patients with perable invasive BCA, pT1-3a N0-1, 20% < 50 yo, 71% TAM/no chemo, 7% chemo/no TAM, 15% both, + requiring RT after surgery. Surgery either BCS or mastectomy (8%).

Arm 1, 50/25 | Arm 2, 40/15 over 3 weeks. Boost given at discretion (43%) 10/5. Regional RT 14%.

Outcome: LRR 50 Gy 3% → 40 Gy 2% (NS); But, **DFS** (86 → 89), and **OS** (89 → 92%) all better (SS) in 40 Gy group.
Toxicity: Lower rate of late toxicity in 40 Gy group (SS).
Conclusion: 40 Gy over 3 weeks has at least as favorable control and toxicity as 50 Gy over 5 weeks.

Royal Marsden Hospital / GO3 (Owen Lancet Oncology 2006).[49] RTC in1986 1410 patients with T1-3N0-1 (max 1 positive node).
30% < 50yo, 14% had chemotherapy. 75% boost. F/u 10 yr.
RT: WBRT; 25% randomly assigned to no boost, 26% randomly assigned to boost, 50% boost at MD discretion (comparable in all 3 groups).

Arm 1, 50/25 | Arm 2, 39/13 (3.0 Gy/fx) | Arm 3, 42.9/13 (3.3 Gy/fx) all over 5 weeks.
Primary outcome late side effects; trial extended to allow power for LR evaluation but then stopped early due to start of START trial.

Outcome: 10-year IBTR: 12% (50Gy) vs. 14.8% (39 Gy) vs. 9.6% (42.9 Gy) | NS vs 50/25, but SS between 39/13 and 42.9/13.
Estimate of LR-based α/β = 4.0 Gy (and possibly as low as 3.0 Gy).
Conclusion: Breast cancer tissue is probably just as sensitive to fraction size as dose-limiting healthy tissues. If confirmed, RT schedules → simplified by the delivery of fewer, larger fractions without compromising effectiveness or safety. Possibly ↑ both.

[46] http://www.ncbi.nlm.nih.gov/pubmed/20147717?dopt=Abstract
[47] http://www.ncbi.nlm.nih.gov/pubmed/18356109?dopt=Abstract
[48] http://www.ncbi.nlm.nih.gov/pubmed/18355913?dopt=Abstract
[49] http://www.ncbi.nlm.nih.gov/pubmed/16750496?dopt=Abstract

Boost (Role and Technique):

- Most will advocate a boost in patients with invasive breast cancer undergoing BCS. This is more controversial in DCIS.
- Patients who may not need adjuvant RT at all also will not need a boost.

SIB (Simultaneous Integrated Boost)

Swiss Simultaneous Integrated Boost Study
Prospective 424 patients began to be treated in July 20172-2021. Stage I-III invasive breast cancer (n = 391) and/or ductal carcinoma in situ (n = 33).
SIB-mhWBRT 40 Gy in 15 fx (START B) + SIB tumor bed to 48 Gy (RTOG 10-05/UK-IMPORT-HIGH).
Boost = 3DCRT (RT; n = 402), IMRT (n = 4), or VMAT (n = 18). The mean patient age was 60 years (range, 27-88).
Since May 2018, patients with indications for lymphatic pathway RT were included (n = 62).

Unterkirhere, Adv Rad Onc 2023 **30-month FU**
EOT Acute toxicity grade 0, 1, 2, and 3 was observed in 25.0%, 61.4%, 13.3%, and 0%, respectively.

	6mo	1 year	2 year	3 year	4 year
Grade 2 late effects	8.5%	6.0%	4.9%,	2.2%	10.2%
Grade 3 late effects	2.8%	1.1%	1.2%	0%	0%

Medical treatment of breast edema was the only grade 3 late effect observed.
Patient Reported 97% excellent or good overall 6 month – 4 years.
3-year overall, cancer-specific, and disease-free survival rates were 98.2%, 99.1%, and 95.9%, respectively.
3-year LRR 0.6%.
No mortality or relapse was observed in patients with ductal carcinoma in situ.
Conclusions
SIB-mhWBRT demonstrated very favorable side effect profiles and cosmesis/PROMs. Three-year results demonstrate excellent locoregional control. This short-term regimen offers substantial patient comfort and improves institutional efficacy.

UK IMPORT HIGH (**CRUK/06/003)** Abstract SIB Boost Trial
←R→ 2617 women pT1-3 pN0-pN3a invasive ≥ 18 yo randomized 1:1:1.
| 1. 40Gy/15fx WBRT + 16Gy/8fx sequential |
| 2. 36 Gy WBRT + 40 Gy partial breast + 48 Gy boost all 15fx SIB |
| 3. 36 Gy WBRT + 40 Gy partial breast + 53 Gy boost all 15fx SIB |.
9%, 38% & 53% were tumour grade 1, 2 & 3 respectively; 30% were node positive. 66% received chemotherapy and 73% endocrine therapy.
1^{O} breast induration at 3 years. Scored from none, mild, moderate, marked.
Median boost clinical target volume was 13 cc.
Clinician Reviewed: Breast induration, shrinkage, distortion. Patient reported: Δ cosmesis Photograph: Breast appearance.
Median age 49 yo.

Coles, Oral 2018. Median FU 49.1 months.
Rates of moderate/marked AEs at 3 years were broadly similar between the randomised groups; with a suggestion of a slightly increased risk for breast induration in 53Gy compared with control (borderline significance)

Coles, Lancet 2023 Median FU 74 months.
5-year IBTR 1·9%, 2·0%, 3·2%.
"Acute toxicity was not recorded in the trial as we have shown previously that acute normal tissue effects are mild even with boost using hypofractionated radiotherapy and that acute toxicity is not associated with development of late normal tissue events."
Clinician Moderate or marked breast 12%, 11%, **↑↑ 16%**.
Interpretation In all groups 5-year IBTR incidence was lower than the 5% originally expected regardless of boost sequencing. Dose-escalation is not advantageous. 5-year moderate or marked adverse event rates were low using small boost volumes. Simultaneous integrated boost in IMPORT HIGH was safe and reduced patient visits.

Beth Israel (Chadha 2013). Prospective 160 pt in 2004-2010. TisN0, T1N0, and T2N0. Chemo = ineligible. WBI 40.5 Gy | 2.7 Gy fx + concurrent lumpectomy boost of 4.5 Gy | 0.3 Gy fx. Boost used at physician discretion. Total @ lumpectomy = 45 Gy | 15 fx, 19 days. F/U med 3.5 yrs. Outcome: 5-year OS 95% (SS) and DFS 97% (SS). 5 yr local relapse free survival 99% (SS). Toxicity grade 1 (70%) + 2 (5%) skin. The median dose heart D05 was 215 cGy, and median lung V20 was 7.6%. Conclusions: Accelerated WBRT + boost can be given with minimal side effects and excellent LC.

HERA TRIAL SUBSET ANALYSIS

1082 patients with HER-2 positive breast cancer who were originally enrolled in the HERA trial.

1^{O} was to determine the effect of a radiation boost on local recurrence.

S/p WBRT, 441 (40.8%) received RT boost and 641 (59.2%) who did not.

Jaoude, IJROBP 2020.

11-year LC RT-boost 93% vs. no boost 91% (P=0.33).

When analyzing patients by age, patients <40 years of age had a higher risk for local recurrence; however, this was not significantly lowered by the addition of boost. Furthermore, no local control benefit for boost was noted in both hormone receptor (HR) subtypes (HR+: *P* = .11; HR–: *P* = .98).

Conclusions Patients with HER-2 positive breast cancer treated with breast-conserving surgery, whole breast radiation, and trastuzumab have excellent local control. Delivery of an additional radiation boost in this patient population was not shown to improve local control. Future studies are needed to identify subgroups of HER-2 positive patients who derive a clinically relevant benefit from radiation boost.

Netherlands (Hurkmans, 2006).[50] Ongoing phase III trial comparing a boost of 16 Gy as part of whole-breast irradiation to a high boost of 26 Gy in young women.

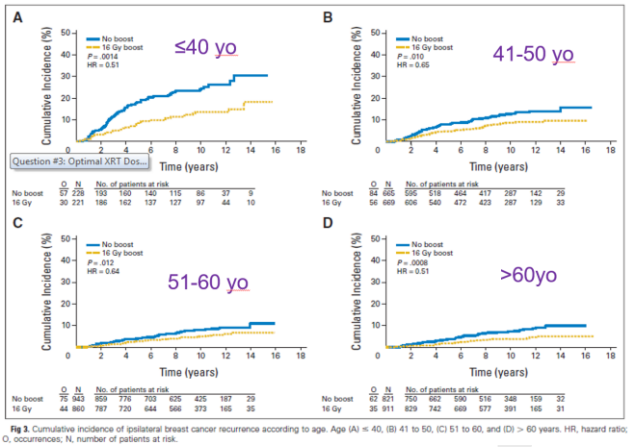


Fig 3. Cumulative incidence of ipsilateral breast cancer recurrence according to age. Age (A) ≤ 40, (B) 41 to 50, (C) 51 to 60, and (D) > 60 years. HR, hazard ratio; O, occurrences; N, number of patients at risk.

EORTC 22881/10882 (Bartelink, 2001).[51] RTC in 1989-1996, 5318 women stage I-II BCa s/p lumpectomy and axillary dissection given 50 Gy to the entire breast ± 16 Gy boost. Median follow-up 5.1 years. 5 year follow-up actuarial LF with boost ↓ 7.3% to 4.3% (p < 0.001).

For patients ≤ 40 yo, they benefited the most, with 5 yr LF boost drastically ↓ 19.5% to 10.2% (p = 0.002).

For patients 41 to 50 years old, no differences were found in rates of metastasis or OS (which were 87 and 91 percent, respectively). **Conclusion**: patients especially < 50 yrs old need boost.

Bartelink, 2007.[52] 10 year: LF: boost 6% vs. no boost 10% (SS).

Age **<40**, 24% → 13% | **41-50** 12% → 8% | **51-60** 7% → 4% | **>60** 7% → 4% | **ALL SS**

RADIATION BOOST ↓ LF by about 50%

As a result of boost, salvage mastectomy reduced by 41%.

Survival 82% in both arms (NS).

Toxicity: severe fibrosis boost 4.4% vs. no boost 1.6% (SS).

Conclusion: Improved local control in all age groups, but no difference in survival.

Lyon, France (Romestaing, JCO 1997).

1024 pts, Stage I/II.

5 yr LR: 3.6% (boost) vs 4.5% (no boost) p = .044

RR boost= 0.3 (0.12-0.95)

Boost group had a higher rate of grade 1 and 2 telangiectasia (12.4% v 5.9%)

- So why are younger patients more at risk for LF?

EORTC 22881/10882 (Vrieling 2003).[53] 5 year LF rates based on age. ≤ 35, 18%. 36-40, 15%. 41-50, 8%. 51-60 4%. > 60, 3%. Younger patients are found to have significantly larger tumors, ER/PR – tumors, high grade invasive and non-invasive tumors, incompletely resected intraductal component, more re-excisions (probably related to more incomplete initial excisions), and smaller volume of breast tissue removed. Despite this, the only significant variable in a multi-variate analysis related to tumor recurrence were age and the use of a boost (p < 0.0001).

[50] http://www.ncbi.nlm.nih.gov/pubmed/16904837?dopt=Abstract
[51] http://www.ncbi.nlm.nih.gov/pubmed/11794170
[52] http://www.ncbi.nlm.nih.gov/pubmed/17577015?dopt=Abstract
[53] http://www.ncbi.nlm.nih.gov/pubmed/12706362

Systemic Therapy:

- Adjuvant Therapy: Typically given to LN+, ER-, HER2+, and women with adverse features (young age, or high Oncotype DX).
  - In the absence of high-risk features, no recommendations for chemotherapy.
  - Following chemotherapy, patients with ER-positive disease should also receive adjuvant endocrine therapy

- Neoadjuvant Therapy: Equivalent survival as adjuvant (NSABP B-18).
  - Big role for downstaging.
  - Role in women ≥ 70 unclear since these are excluded from previous trials.
  - There should be a balance between side effects and benefit.

- HER2-positive with a tumor size >1 cm (pT1b) should receive a combination of chemotherapy plus HER2-directed therapy.
  - The management of small (≤1 cm) HER2-positive breast cancers is controversial.
  - Trastuzumab has 1 year OS advantage compared to C.
  - Cannot give Trastuzumab with Adriamycin due to cardiac toxicity.
  - Trastuzumab + Pertuzumab = dual anti-HER2 and pCR rates of 50-60%.

- For triple-negative, adjuvant chemotherapy if the tumor size ≥ 0.5 cm (pT1b). Not candidates for endocrine therapy or HER2-directed agents.
  - ∴ chemotherapy is their only option for adjuvant treatment, following or before radiotherapy.
  - Patients with a triple-negative breast cancer < 0.5 cm in size may forgo adjuvant chemotherapy since minimal survival advantage.

HER2-Negative
Preferred Regimens

- **Dose-dense AC followed by paclitaxel**[2]
  - Doxorubicin 60 mg/m² IV day 1
  - Cyclophosphamide 600 mg/m² IV day 1
    - ◊ Cycled every 14 days for 4 cycles.[l]
    - ◊ Followed by:
  - Paclitaxel 175 mg/m² by 3 h IV infusion day 1
    - ◊ Cycled every 14 days for 4 cycles.[l]
- **Dose-dense AC followed by weekly paclitaxel**[2]
  - Doxorubicin 60 mg/m² IV day 1
  - Cyclophosphamide 600 mg/m² IV day 1
    - ◊ Cycled every 14 days for 4 cycles.[l]
    - ◊ Followed by:
  - Paclitaxel 80 mg/m² by 1 h IV infusion weekly for 12 weeks.
- **TC**[3]
  - Docetaxel 75 mg/m² IV day 1
  - Cyclophosphamide 600 mg/m² IV day 1
    - ◊ Cycled every 21 days for 4-6 cycles.[l]
- **Preoperative pembrolizumab + chemotherapy followed by adjuvant pembrolizumab**[4]
  - Preoperative:
    - ◊ Pembrolizumab 200 mg IV Day 1
    - ◊ Paclitaxel 80 mg/m² IV Days 1, 8, 15
    - ◊ Carboplatin AUC 5 IV Day 1
      Or
    - ◊ Carboplatin AUC 1.5 IV Days 1, 8, 15
      – Cycled every 21 days x 4 cycles (cycles 1–4)
    Followed by:
    - ◊ Pembrolizumab 200 mg IV Day 1
    - ◊ Doxorubicin 60 mg/m² IV Day 1 or Epirubicin 90 mg/m² IV Day 1
    - ◊ Cyclophosphamide 600 mg/m² IV Day 1
      – Cycled every 21 days x 4 cycles (cycles 5–8)
    Followed by:
  - Adjuvant pembrolizumab 200 mg IV Day 1
    - ◊ Cycled every 21 days x 9 cycles
- **Capecitabine**[5]
  - 1,000–1,250 mg/m² PO twice daily on days 1–14
    - ◊ Cycled every 21 days for 6–8 cycles
- **Olaparib**[6]
  - 300 mg PO twice daily
  - Cycled every 28 days for 1 y

HER2-Positive[m,n,o]
Preferred Regimens

Paclitaxel + trastuzumab[20]
- Paclitaxel 80 mg/m² IV weekly for 12 weeks
  - ◊ With:
- Trastuzumab 4 mg/kg IV with first dose of paclitaxel
  - ◊ Followed by:
- Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment. As an alternative, trastuzumab 6 mg/kg IV every 21 days may be used following the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment.

TCH[21]
- Docetaxel 75 mg/m² IV day 1
- Carboplatin AUC 6 IV day 1
  - ◊ Cycled every 21 days for 6 cycles
  - ◊ With:
- Trastuzumab 4 mg/kg IV wk 1
  - ◊ Followed by:
- Trastuzumab 2 mg/kg IV for 17 wks
  - ◊ Followed by:
- Trastuzumab 6 mg/kg IV
  - ◊ Cycled every 21 days to complete 1 y of therapy.[p]

OR
- Trastuzumab 8 mg/kg IV wk 1
  - ◊ Followed by:
- Trastuzumab 6 mg/kg IV
  - ◊ Cycled every 21 days to complete 1 y of therapy.[p]

TCH + pertuzumab[22]
- Docetaxel 75 mg/m² IV day 1
- Carboplatin AUC 6 IV day 1
  - ◊ Cycled every 21 days for 6 cycles

With:
- Trastuzumab 8 mg/kg IV day 1
- Pertuzumab 840 mg IV day 1
  - ◊ Followed by:
- Trastuzumab 6 mg/kg IV on day 1
- Pertuzumab 420 mg IV day 1
  - ◊ Cycled every 21 days to complete 1 y of therapy.[p]

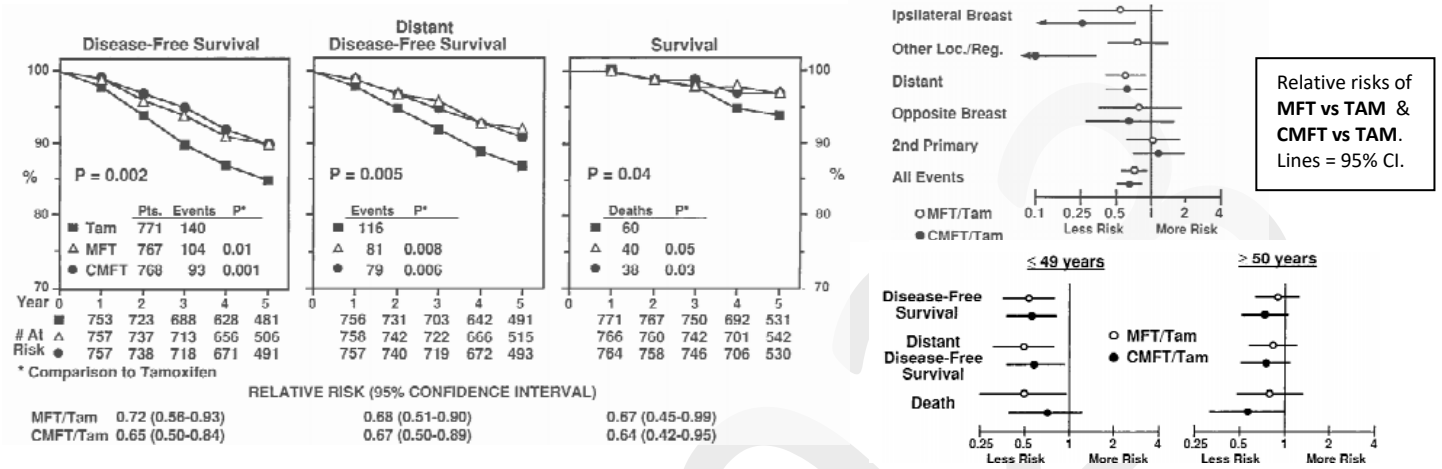
HER2-Negative[b]	
Preferred Regimens: • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by paclitaxel every 2 weeks[c] • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by weekly paclitaxel[c] • TC (docetaxel and cyclophosphamide) • Olaparib, if germline *BRCA1/2* mutations[d,e] • High-risk[f] TNBC: Preoperative pembrolizumab + carboplatin + paclitaxel, followed by preoperative pembrolizumab + cyclophosphamide + doxorubicin or epirubicin, followed by adjuvant pembrolizumab • TNBC and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy:[e] Capecitabine	
Useful in Certain Circumstances: • Dose-dense AC (doxorubicin/cyclophosphamide) • AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B) • CMF (cyclophosphamide/methotrexate/fluorouracil) • AC followed by weekly paclitaxel[c] • Capecitabine (maintenance therapy for TNBC after adjuvant chemotherapy)	Other Recommended Regimens: • AC followed by docetaxel every 3 weeks[c] • EC (epirubicin/cyclophosphamide) • TAC (docetaxel/doxorubicin/cyclophosphamide) • Select patients with TNBC:[g,1] ▸ Paclitaxel + carboplatin (various schedules) ▸ Docetaxel + carboplatin[g,1] (preoperative setting only)

HER2-Positive	
Preferred Regimens: • Paclitaxel + trastuzumab[h] • TCH (docetaxel/carboplatin/trastuzumab) • TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab) • If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab[j] (category 1) ± pertuzumab. • If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete one year of therapy.[i,j] If node positive at initial staging, trastuzumab + pertuzumab (category 1)[k]	
Useful in Certain Circumstances: • Docetaxel + cyclophosphamide + trastuzumab • AC followed by T[c] + trastuzumab[j] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules) • AC followed by T[c] + trastuzumab + pertuzumab[j] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab, various schedules) • Neratinib[i] (adjuvant setting only) • Paclitaxel + trastuzumab + pertuzumab[j] • Ado-trastuzumab emtansine (TDM-1) (adjuvant setting only)	Other Recommended Regimens: • AC followed by docetaxel[c] + trastuzumab[j] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab) • AC followed by docetaxel[c] + trastuzumab + pertuzumab[j] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + pertuzumab)

Regimens + Effectiveness

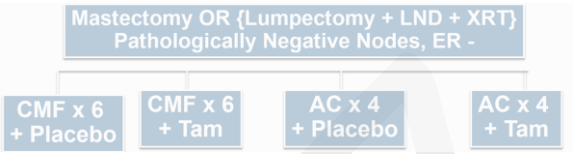
NSABP B-20 (Fisher 1997).[54] RTC 2306 women s/p surg, node negative, ER + BCa randomized Tam, and Tam + 5-FU + methotrexate (MFT), or MFT + cyclophosphamide (CMFT). 5 year follow up. **Conclusion**: **ALL** subgroup of patients evaluated in this study benefited from chemotherapy, regardless of age, lymph node status, tumor size, or estrogen receptor status.

Toxicity reported in 2326 (98.4%) patients. CMFT > MFT > Tam alone.
↑ grade 2-4 overall toxicities: especially nausea (not vomiting), alopecia, leukopenia. Some ↑ infection rates and phlebitis/thromboembolism rates.



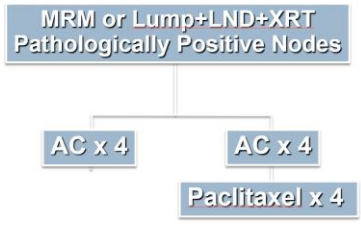
Relative risks of **MFT vs TAM** & **CMFT vs TAM**. Lines = 95% CI.

5 year	DFS	DDFS	OS
TAM	85%	87%	94%
MFT	**90%**	**92%**	**97%**
CMFT	**89%**	**91%**	**96%**
p	0.001	0.005	0.05



NSABP B-23 (Fisher, JCO 2001). 2008 pts, Stage I/II. Median f/up: 5 yrs.
AC = Doxorubicin + Cyclophosphamide
RESULTS: 5 YR RFS: same in all groups for all ages (~87%)
5 YR OS: same in all groups for all ages
Tamoxifen did not provide any significant advantage to RFS or OS, as compared to placebo group
For LN-, ER-: CMF = AC for RFS and OS Tam = Placebo for RFS and OS
Conclusion: No significant Δ the outcome of patients who received AC or CMF. TAM with either regimen resulted in no significant advantage over that achieved from chemotherapy alone.

NSABP B-28 (Mamounas, JCO 2005). 3060, Stage T1-3, N0-1, ER+/-. XRT: 50 Gy
RESULTS: Addition of Taxane improved 5yr DFS 72%→76% (SS). 5-year OS ~85% NS.
Conclusion: The addition of PTX to AC resulted in significant improvement in DFS but no significant improvement in OS with acceptable toxicity. No significant interaction between treatment effect and receptor status or tamoxifen administration was observed.



Combined NSABP B-31 and N9831. T given for 52 weeks.
4046 patients with HER2-positive operable breast cancer → ACT ± T
B-31 (2 arm) ACT ± Trastuzumab concurrent with T. N9831 (3 arm) ACT ± Trastuzumab (one arm concurrent with T, one arm sequential after T).

Perez, JCO 2014 **Median 8.4 years**
Adding trastuzumab relative ↑ 37% OS (HR, P < .001). 10-year OS 75.2% → 84% (SS).
Adding trastuzumab relative ↑ 40% DFS (HR, P < .001). 10-year OS 62.2% → 73.7% (SS).
All patient subgroups benefited from addition of this targeted anti-HER2 agent.
Conclusion: The addition of trastuzumab to paclitaxel after doxorubicin and cyclophosphamide in early-stage HER2-positive breast cancer results in a substantial and durable improvement in survival as a result of a sustained marked reduction in cancer recurrence.

Romond, NEJM 2005
RESULTS: 5-year total events (recur, second 1^{O} cancer, death before recurrence) = 133 in group with T vs. 261 in control group (HR 0.48, SS).
3-year Trastuzumab ↓ 12% Abs Δ DFS. Trastuzumab ↓ 33% Risk of Death (P=0.015).
3-year CI of class III/IV CHF or Cardiac Death w/ T was 4.1% (B-31) and 2.9% (N9831).
CONCLUSIONS: Trastuzumab combined with paclitaxel after doxorubicin and cyclophosphamide improves outcomes among women with surgically removed HER2-positive breast cancer.

[54] http://www.ncbi.nlm.nih.gov/pubmed/9390536

NSABP B-31. Role of Herceptin Gebheart 2005 NEJM. Trastuzumab
52% reduction of recurrence of BCa with addition of Herceptin in Her2/Neu cancers.

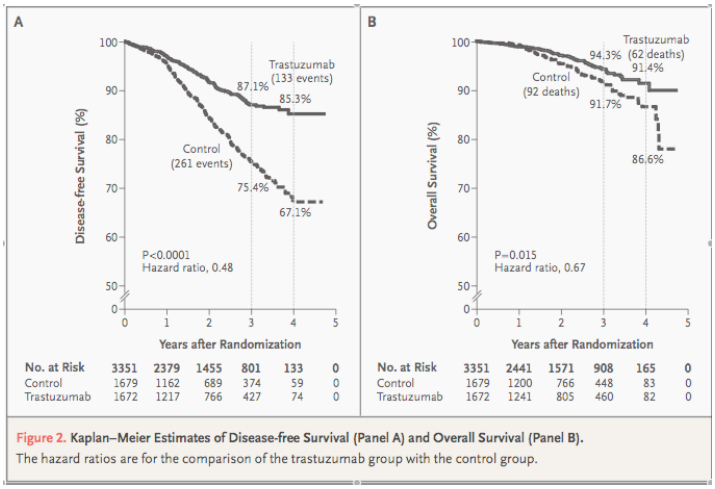


Figure 2. Kaplan–Meier Estimates of Disease-free Survival (Panel A) and Overall Survival (Panel B).
The hazard ratios are for the comparison of the trastuzumab group with the control group.

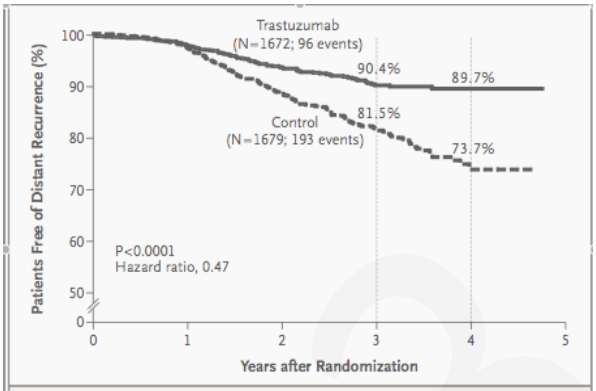
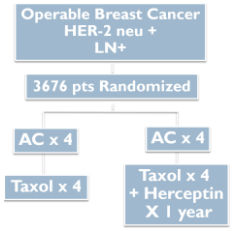


Figure 3. Kaplan–Meier Estimates of Freedom from Distant Recurrence.
The hazard ratios are for the comparison of the trastuzumab group with the control group.



HERA Big 1-01 Trial (Adjuvant Herceptin)
←R→ 3387 women breast cancer HER2+ and either 1. LN- or 2. LN+ s/p locoregional therapy and ≥ 4 cycles of NAC or Adj chemo.
| 1. Trastuzumab 2 years | 2. Trastuzumab 1 year | 3. Obs |.

Cameron, Lancet 2017 Final 11 year follow-up.
Trastuzumab x 1 year ↓ DFS HR 0.76 (SS), and ↓ Death HR 0.74 (SS).
2 years of adjuvant trastuzumab did not improve DFS or death compared with 1 year.
10-year DFS 69%, 69%, 63% (SS).
Incidence of cardiac secondary endpots 7.3%, 4.4%, 0.9%.
Interpretation: 1 year of adjuvant trastuzumab after chemotherapy for patients with HER2-positive early breast cancer significantly improves long-term disease-free survival, compared with observation. 2 years of trastuzumab had no additional benefit.

Piccart-Gebhart, NEJM 2005
Events observed (recurrence, contralateral BCa, 2^{O} cancers, death) showed HR (vs. Obs group) 0.54 Trastuzumab (SS).
2-year ↑ DFS of 8.4% of Trastuzumab.
Severe Cardiotoxicity in 0.5% patients with trastuzumab.

NAC pCR Dutch TRAIN-2 **AKA it is OK to remove Epirubicin.**
←R→ ≥ 18 yo Stage II-III HER2+ breast Ca. ALL TO RECEIVE NAC.
| 1. 5-FU, Epi, Cyclo q3 weeks x 3c → paclitaxel + carboplatin q3 weeks x 6c| 2. Paclitaxel + carboplatin x 9c | + BOTH GROUPS Trast + Pertuz concurrently.
Chemo: 5-fluorouracil (500 mg/m2), epirubicin (90 mg/m2), and cyclophosphamide (500 mg/m2) every 3 weeks for three cycles followed by paclitaxel (80 mg/m2 on days 1 and 8) and carboplatin (AUC 6 mg/mL per min on day 1 or optionally, as per hospital preference, AUC 3 mg/mL per min on days 1 and 8) every 3 weeks for six cycles, or to receive nine cycles of paclitaxel and carboplatin at the same dose and schedule as in the anthracycline group.
Trastuzumab (6 mg/kg, loading dose 8 mg/kg) and pertuzumab (420 mg, loading dose 840 mg) concurrently with all chemotherapy cycles.
1^{O} pCR in breast and axilla (ypT0/is ypN0) in the intention-to-treat population.

Van Ramshorst, Lancet 2018.
pCR 67% in the anthracycline group vs. 68% in the non-anthracycline group (p=0·95).
Serious adverse events 28% vs. 22%.
Most common ≥ G3 neutropenia 60% vs. 54%, ≥ G3 diarrhea 12% vs. 18%, ≥ G2 peripheral neuropathy 30% vs 31%). All NS.
≥ Grade 3 febrile neutropenia 10% vs 1%, (p<0·0001).
Interpretation In view of the high proportion of pathological complete responses recorded in both groups and the fact that febrile neutropenia was more frequent in the anthracycline group, omitting anthracyclines from neoadjuvant treatment regimens might be a preferred approach in the presence of dual HER2 blockade in patients with early HER2-positive breast cancer. Long-term follow-up is required to confirm these epresults.

ABC (Three) Trials

Purpose Docetaxel and cyclophosphamide (TC) was superior to doxorubicin and cyclophosphamide (AC) in a trial in early breast cancer. However, activity of TC relative to AC regimens with a taxane (TaxAC) is unknown.

Methods. 2125 patients in a series of three adjuvant trials, women ←R→ | 1. TC for six cycles (TC6) | 2. standard TaxAC regimen |.

US Oncology Research (USOR) 06-090 compared TC6 with docetaxel, doxorubicin, and cyclophosphamide (TAC6).

NSABP B-46-I/USOR 07132 compared TC6, TAC6, or TC6 plus bevacizumab.

NSABP B-49 compared TC6 with several standard AC and taxane combination regimens.

Before any analysis of individual trials, a joint efficacy analysis of TC vs. TaxAC regimens was planned, with invasive disease-free survival (IDFS) as 1^{O}

Did NOT include TC6 + bevacizumab on NSABP B-46-I/USOR 07132.

Blum, JCO 2016 3.3 Years Median FU

There were 334 IDFS events, and the HR for TC6 vs. TaxAC was 1.202 (95% CI, NS), which triggered early reporting for futility.

4-year IDFS 88.2% vs. 90.7% (P = .04).

Tests for treatment interaction by protocol, hormone receptor status, and nodal status were negative.

Conclusion: The TaxAC regimens improved IDFS in patients with high-risk human epidermal growth factor receptor 2–negative breast cancer compared with the TC6 regimen.

Timing and Dose

SECRAB UK Trial Concurrent OLD Chemo+RT?

←R→ 2297 patients with early stage invasive breast cancer. ONLY CMF and antracycline CMF were allowed. | 1. Synchronous RT | 2. Sequential RT |.

Synchronous radiotherapy was administered between cycles two and three for CMF or five and six for anthracycline-CMF (45%).

Sequential radiotherapy was delivered on chemotherapy completion.

Radiotherapy schedules included 40 Gy/15F over three weeks, and 50 Gy/25F over five weeks.

NOTE: This trial was running in parallel with START trials from 1998 to 2004.

Fernando, Radiother Oncol 2019

10-year LRR 4.6% and 7.1% (SS, p = 0.012). There was no significant difference in OS or DFS.

In a planned sub-group analysis of anthracycline-CMF, the 10-year LRR 3.5% vs. 6.7% (HR 0.48 95% CI: 0.26–0.88; p = 0.018).

Moderate/severe skin reactions 24% vs. 15% (p<0.0001).

There were no significant differences in late adverse effects apart from telangiectasia (p = 0.03).

Interpretation Synchronous chemo-radiotherapy significantly improved local recurrence rates. This was delivered with an acceptable increase in acute toxicity. The greatest benefit of synchronous chemo-radiation was in patients treated with anthracycline-CMF.

Important Q: How does this translate to modern dose-dense and taxane-containing regimens?

Sequence

CT → RT vs RT → CT

Harvard (Bellon 2005). RTC 244 pts s/p BCS with substantial risk for distant mets to receive 12 weeks CT before or after RT. F/U is 11 years.

No SS differences between either arm including time to first event, distant mets, or death.

Recht 1996 initially showed that at 5 years, neoadjuvant CT is better than adjuvant CT in recurrence free survival (33 vs 31%, p=0.17) survival without distant recurrence (36% vs 25%, p=0.05), and OS (81% vs 73%, p=0.11).

Conclusion: initially for distant mets, CT first is better than RT first. This did not hold up in the updated Bellon paper.

Sequential CT → RT vs Concurrent CRT

ARCOSEIN French Trial (Toledano 2007). RTC 1996, 716 women stage I-II s/p BCS. About 50% patients (those who were post/peri menopausal women with ER and or PR + tumors had 20mg daily tamoxifen) received hormonal therapy. Adjuvant CT began within 6 weeks of surgery. CT was mitoxantrone, 5-FU, cyclophosphamide on day 1 and repeated every 3 weeks for 6 total courses. In the concurrent arm, Rt was started on the first day of CT. Results: No difference in DFS (80%), LRFS (95%), DMFS (85%), or OS (90%). In node + subgroup, 5 year LRFS concurrent 97% > sequential 91% (p = 0.02).

(Toledano 2007) Cosmesis and satisfaction follow-up paper. Overall satisfaction with cosmesis was not statistically different between the two arms with approximately 92% with at least satisfactory results (p = 0.72), although Δ between Tx and unTx breasts were greater after the concurrent arm (29% vs 14%, p = 0.0015). However, physician assessment of overall cosmesis suggested that concurrent led to less satisfactory results (60% vs 85%, p = 0.001).

Conclusion: Only in Node + patients is concurrent better. However, concurrent possibly causes a worse cosmesis.

Sequential vs alternating CT.

NCI Milan (Bonadonna 1995). RTC of 403 patients with ≥3 N+, Arm 1 sequential (Adriamycin x 4 → CMF x 8), Arm 2 (alternating CMF x2 → Adriamycin x1 for a total of 12 cycles). F/U 10 years. Results: Benefit of sequential regimen was evident in all patient subgroups. RFS 42% vs 28% (p=0.002), OS 58% vs 44% (p=0.002). Conclusion: Possible reason for this is that CT must be given in a "dose-dense" course.

Dose Dense!

Petrelli, Breast Cancer Res Treat. 2015. Dose-dense chemotherapy.
Metaanalysis. A total of 8 phase III trials encompassing 17,188 randomized patients met the inclusion criteria.
DD-CT ↑ OS: HR 0.86, 95 % CI, 0.79-0.93, P = 0.0001, and ↑ DFS: HR 0.84, 95 % CI 0.77-0.91, P < 0.0001 vs. than those on the conventional schedule.
SS ↑ OS observed ER- tumors (HR 0.8, P = 0.002), but not in those with ER-positive BC (HR 0.93, 95 % CI 0.82-1.05; P = 0.25).
DD-CT leads to better OS and DFS, particularly in women with ER- early BC. These results suggest that the DD strategy should be the standard care offered to high-risk ER- BC patients.

TNBC

- Patients with triple-negative breast cancer (TNBC) and residual invasive disease (RD) after completion of neoadjuvant chemotherapy (NAC) have a high-risk for recurrence, which is reduced by adjuvant capecitabine.
- Platinum agents (↑ side effects with no additional benefit) cannot replace CAPE.

Create-X
←R→ 910 patients with TNBC **RESIDUAL CANCER** after NAC (anthracycline, taxane, or both) → standard postsurgical treatment either with | 1. Cape | 2. Obs |.
1^{O} DFS. Postsurgical radiotherapy could be given (73%) before or after randomization and could be concomitant with postsurgical endocrine therapy.
TERMINATED EARLY DUE TO END POINT MEETING

Masuda, NEJM 2017.
Overall 5-year DFS 74.1% vs. 67.6%, (P=0.01). OS 89.2% vs. 83.6%, (P=0.01).
TNBC 5-year DFS 69.8% vs. 56.1%, (SS) OS 78.8% vs. 70.3%, (SS)
The hand–foot syndrome, the most common adverse reaction to capecitabine, occurred in 73.4% of the patients in the capecitabine group.
CONCLUSIONS
After standard neoadjuvant chemotherapy containing anthracycline, taxane, or both, the addition of adjuvant capecitabine therapy was safe and effective in prolonging disease-free survival and overall survival among patients with HER2-negative breast cancer who had residual invasive disease on pathological testing. (Funded by the Advanced Clinical Research Organization and the Japan Breast Cancer Research Group;

NOTE: Most do RT first then Xeloda.

SYSUCC-001 Chinese Adj Chemo → ± Maintenance Xeloda for 1 year?
←R→ 443 TNBC early stage having completed standard adjuvant chemotherapy. | 1. Cape 650 mg/m^2 BID 1 year | 2. Obs. |
Avg Age 46, T1/T2 stage, 93.1%; node-negative, 61.8%

Wang, JAMA 2020. Follow-up of 61 months.
5-year DFS 82.8% vs.73.0% (*P* = .03). 5-year Distant DFS 85.8% vs 75.8% (*P* = .02)
5-year OS 85.5% vs 81.3% (NS), and the estimated 5-year locoregional recurrence-free survival was 85.0% vs 80.8% (HR for risk of locoregional recurrence or death, 0.72 [95% CI, 0.46-1.13]; *P* = .15). The most common capecitabine-related adverse event was hand-foot syndrome (45.2%), with 7.7% of patients experiencing a grade 3 event.
Conclusions and Relevance Among women with early-stage triple-negative breast cancer who received standard adjuvant treatment, low-dose capecitabine maintenance therapy for 1 year, compared with observation, resulted in significantly improved 5-year disease-free survival.

GEICAM/2003-11_CIBOMA/2004-01
←R→ 867 TNBC N+ or N- with ≥ 1cm w/ prior anthracycline and/or taxane chemotherapy. | 1. Cape | 2. Obs |.
Median age was 49 years, 55.9% were lymph node negative, 73.9% had a basal phenotype, and 67.5% received previous anthracyclines plus taxanes.
1^{O} DFS.

Lluch, JCO 2020. 7 year FU
DFS was not changed HR 0.82 NS. Preplanned subgroup analysis, nonbasal patients seemed to derive benefit from the addition of capecitabine with a DFS HR of 0.53 versus 0.94 in those with basal phenotype (interaction test P = .0694) and an HR for overall survival of 0.42 versus 1.23 in basal phenotype (interaction test P = .0052). Tolerance of capecitabine was as expected, with 75.2% of patients completing the planned 8 cycles.
Conclusion: This study failed to show a statistically significant increase in DFS by adding extended capecitabine to standard chemotherapy in patients with early TNBC. In a preplanned subset analysis, patients with nonbasal phenotype seemed to obtain benefit with capecitabine, although this will require additional validation.

CBCSG010 Chinese Upfront Surgery
←R→ 636 TNBC having upfront surgery | 1. **Cape** + Docetaxel x 3c → Cape, Epi, Cyclo | 2. Docetaxel alone x 3c → Cape, Epi, Cyclo |.
The primary end point was disease-free survival (DFS).

Li, JCO 2020 67 month FU
5-year DFS 86.3% *v* 80.4% (*P* = .044). 5-year OS 93.3% v 90.7% (NS).
Overall, 39.1% of patients had capecitabine dose reductions, and 8.4% reported grade ≥ 3 hand-foot syndrome.
G ≥ 3 Neutropenia (45.8% vs. 41.0%) and febrile neutropenia (16.8% vs. 16.0%).
CONCLUSION Capecitabine when added to 3 cycles of docetaxel followed by 3 cycles of a 3-drug anthracycline combination containing capecitabine instead of fluorouracil significantly improved DFS in TNBC without new safety concerns.

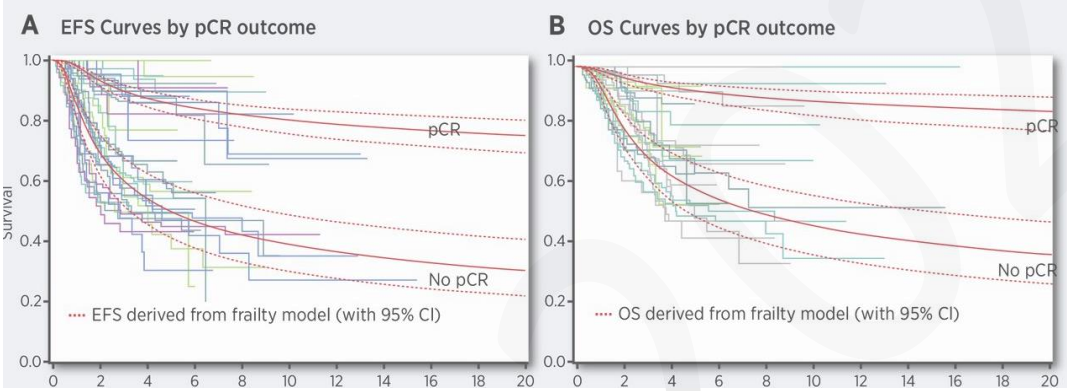
ECOG EA1131 **Non-inferiority**

←R→ 410 clinical stage II or III TNBC with ≥ 1 cm RD in the breast post-NAC | 1. platinum (carboplatin or cisplatin) q 3 weeks x 4c | 2. Cape |.
Cape = capecitabine 14 out of 21 days every 3 weeks for six cycles.
Carbo 88% Cisplatin 12%.
TNBC subtype (basal v nonbasal) was determined by PAM50 in the residual disease.
A noninferiority design with superiority alternative was chosen, assuming a 4-year iDFS of 67% with capecitabine.

Mayer, JCO 2021. 20 months.
3-year invasive DFS (iDFS) 42% vs. 49%.
Grade 3 and 4 toxicities were more common with platinum agents.
The Data and Safety Monitoring Committee recommended stopping the trial as it was unlikely that further follow-up would show noninferiority or superiority of platinum.
CONCLUSION Platinum agents do not improve outcomes in patients with basal subtype TNBC RD post-NAC and are associated with more severe toxicity when compared with capecitabine. Participants had a lower than expected 3-year iDFS regardless of study treatment, highlighting the need for better therapies in this high-risk population.

Other Studies:

https://cancerres.aacrjournals.org/content/80/24/5427
METAANALYSIS of pCR



TNBC https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2773097
T1N0 Does RT or Chemo help? YES, both do!

Table 3. Adjusted Hazard Ratio for OS and BCSS Associated With Adjuvant Therapies After Different Surgical Procedures in Patients With Different Cancer Stages and Ages

	BCS				Other[a]			
	Chemotherapy		Radiotherapy		Chemotherapy		Radiotherapy	
Characteristic	AHR (95% CI)	*P* Value	AHR (95% CI)	*P* Value	AHR (95% CI)	*P* Value	AHR (95% CI)	*P* Value
Age								
<70								
OS	0.574 (0.400-0.824)	.003	0.977 (0.673-1.417)	.9	0.610 (0.395-0.941)	.03	2.514 (1.408-4.490)	.002
BCSS	0.812 (0.512-1.287)	.38	1.023 (0.651-1.608)	.92	0.835 (0.493-1.413)	.50	3.149 (1.708-5.805)	<.001
≥70								
OS	0.464 (0.305-0.704)	<.001	0.507 (0.349-0.736)	<.001	0.506 (0.268-0.954)	.04	1.324 (0.406-4.320)	.64
BCSS	1.252 (0.665-2.358)	.49	0.478 (0.251-0.913)	.03	0.940 (0.435-2.030)	.87	1.336 (0.309-5.774)	.70
Stage								
T1ab								
OS	0.533 (0.290-0.980)	.04	0.446 (0.254-0.782)	.005	1.159 (0.609-2.208)	.65	2.267 (0.980-5.243)	.06
BCSS	1.367 (0.565-3.307)	.49	0.469 (0.191-1.148)	.10	1.454 (0.661-3.200)	.35	2.786 (1.098-7.070)	.03
T1c								
OS	0.564 (0.419-0.760)	<.001	0.812 (0.606-1.088)	.16	0.416 (0.273-0.634)	<.001	2.240 (1.153-4.350)	.02
BCSS	0.821 (0.541-1.245)	.35	0.915 (0.613-1.366)	.66	0.579 (0.338-0.990)	.04	2.916 (1.432-5.938)	.003

Abbreviations: AHR, adjusted hazard ratio; BCS, breast-conserving surgery; BCSS, breast cancer-specific survival; OS, overall survival.

[a] Other included patients receiving simple mastectomy, radical mastectomy, or other surgical procedures.

NOMOGRAM TNBC for survival
https://pubmed.ncbi.nlm.nih.gov/30210925/

Adjuvant Hormonal Therapy

Hormonal Therapy:

- It is known that 5 years of tamoxifen ↓ 47% in disease recurrence rates and ↓ 26% overall mortality (EBCTCG Lancet 351, 1998).
- Tamoxifen (blocks Estrogen receptor) reduces disease recurrence and incidence of contralateral breast cancer by about 50% and mortality by 28% in ER+ tumors
- 63% have adverse effects and 23-40% patients discontinue it
- Long term tamoxifen is associated with ↑ risk for hot flashes, vaginal bleeding and discharge, endometrial cancer, ischemic cerebrovascular events and DVT
- Tamoxifen beyond 5 years is under consideration (new abstract?).

Aromatase inhibitors:

- 3rd generation aromatase inhibitors (AIs): anastrazole, letrozole and exemestane
  - Prevent estrogen synthesis by inhibiting the aromatase enzyme which convert androgens into estrogen.
  - Detrimental effects on bone density
- **Nonsteroidal AIs include: Arimidex/anastrazole and Femara/Letrozole**
- **Steroidal AI: Exemestane**

Pregnancy and Pausing Endocrine Tx

516 women Single Arm Prospective ≤ 42 yo w/ previous stage I, II, or III disease BCa s/p adjuvant endocrine therapy for 18 to 30 months.
1^{O} breast cancer events (defined as local, regional, or distant recurrence of invasive breast cancer or new contralateral invasive breast cancer).
Median age 37. Median time from breast cancer diagnosis to enrollment was 29 months.
93.4% had stage I or II disease.

Partridge, NEJM 2023.

Among 497 women followed for pregnancy status, 368 (74.0%) had at least one pregnancy and 317 (63.8%) had at least one live birth.
In total, 365 babies were born.
At 1638 patient-years of follow-up (Median FU 41 months), 44 patients had a breast cancer event (did NOT exceed the safety threshold).
3-year breast cancer events 8.9% treatment-interruption group vs. 9.2%) in the control cohort.

CONCLUSIONS

Among select women with previous hormone receptor–positive early breast cancer, temporary interruption of endocrine therapy to attempt pregnancy did not confer a greater short-term risk of breast cancer events, including distant recurrence, than that in the external control cohort. Further follow-up is critical to inform longer-term safety.

Timing of RT → HT NCDB

RR 144,103 patients = 142 916 (99.2%) women, 11 574 (8.0%) Black patients, and 126 013 (87.4%) White patients.
TTH = time interval from the definitive curative operation to the start of AHT. Delayed AHT (ie, a TTH past 150 days).
Of these, 134 873 patients (93.6%) had a TTH of 150 days or less and 9230 patients (6.4%) had a TTH longer than 150 days.

Fu, JAMA Net Open 2022.

Delayed AHT ↓ survival vs. timely treatment (TTH ≤150 days).

Conclusions and Relevance The delay of the initiation of AHT past 150 days was associated with diminished survival in hormone receptor–positive, ERBB2-negative patients with breast cancer who did not receive chemotherapy. Efforts should be made to address factors associated with delayed treatment to improve survival.

EBCTCG, Lancet 2015. **AI vs TAM Post-menopausal**

←M→ 31,920 postmenopausal ER+ | 5 years AI | 5 years Tam |.

10-year BCaM 12·1% vs 14·2% (SS).

INTERPRETATION:

Aromatase inhibitors reduce recurrence rates by about 30% (proportionately) compared with tamoxifen while treatments differ, but not thereafter. 5 years of an aromatase inhibitor reduces 10-year breast cancer mortality rates by about 15% compared with 5 years of tamoxifen, hence by about 40% (proportionately) compared with no endocrine treatment.

EBCTCG, Lancet 2022. **AI vs TAM Pre-menopausal** WITH ovarian suppression

←M→ 7030 women Premenopausal ER+ from 1999 to 2015 | 1. AI | 2. Tam |.

AI = anastrozole, exemestane, or letrozole) TAM = 3 or 5 years. Ovarian Suppression = goserelin or triptorelin or ablation.

Four identified trials (ABCSG XII, SOFT, TEXT, and HOBOE trials)

FU 8 years.

Rate of breast cancer recurrence ↓ with AI (vs. Tam) RR 0·79, p=0·0005).

Main benefit seen in years 0–4 (RR 0·68, p<0·0001). No further benefit years ≥ 5.

5-year rate recurrence 6·9% vs 10·1%.

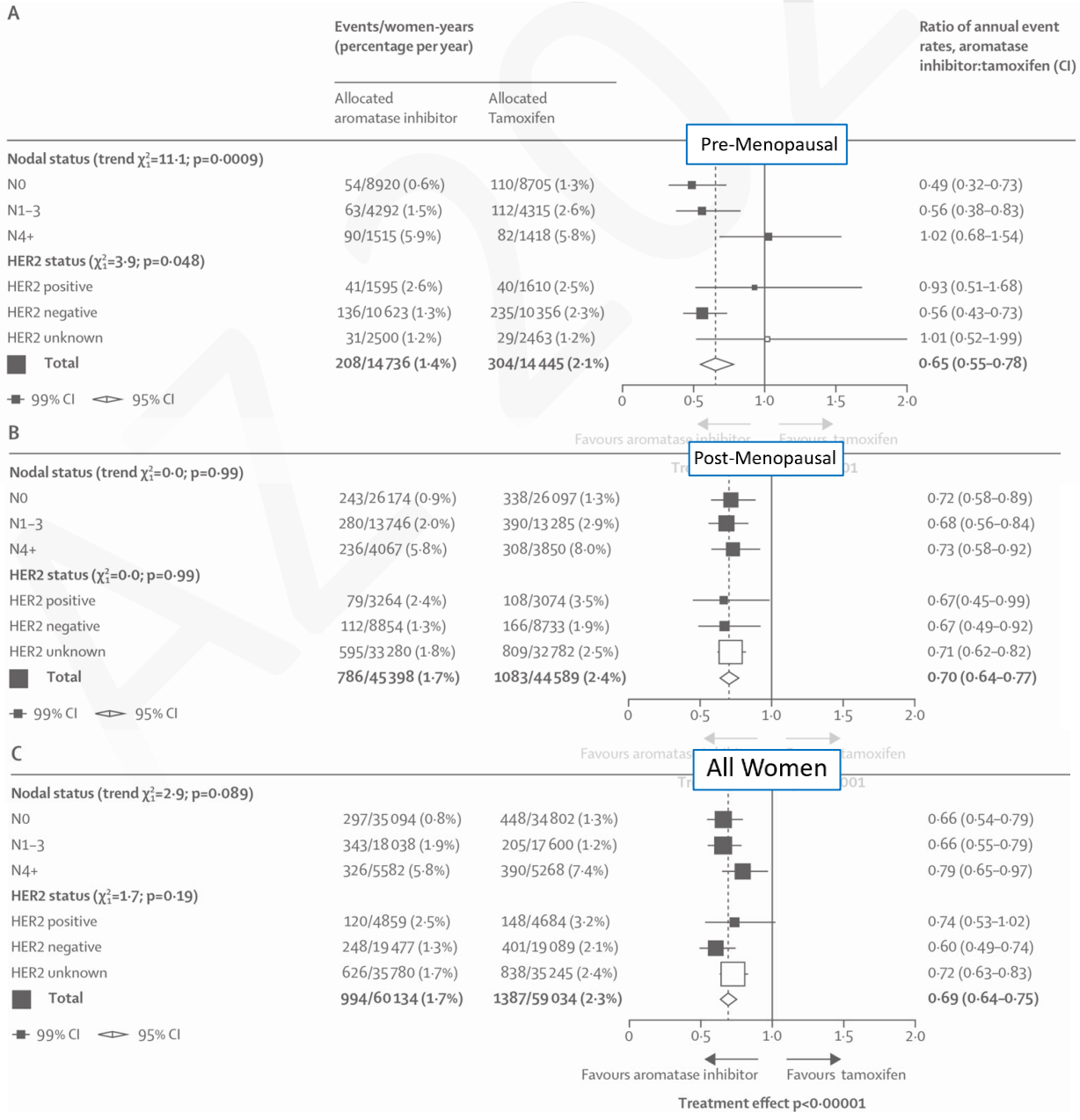
Distant recurrence ↓ with AI (RR 0·83, p=0·018).

BCM, OS NS.

Side effects: AI ↑ bone fractures 6·4% vs. 5·1% (RR 1·27; p=0·017). Non-breast cancer deaths (30 [0·9%] vs 24 [0·7%]; 1·30 [0·75–2·25]; p=0·36) and endometrial cancer (seven [0·2%] vs 15 [0·3%]; 0·52 [0·22–1·23]; p=0·14) were rare.

INTERPRETATION:

Using an aromatase inhibitor rather than tamoxifen in premenopausal women receiving ovarian suppression reduces the risk of breast cancer recurrence. Longer follow-up is needed to assess any impact on breast cancer mortality.



STO-3
←R→ 1780 post-menopausal women with invasive, early stage < 3 cm, N0 disease | 1. Tam 2 or 5 years | 2. No Tam |.
Tam = 40 mg daily.
Among high-risk patients the treatment was given against a background of either adj radiation or CMF-type chemotherapy.

Rutqvist, Acta Oncol 2007. Follow up 18 years.
PgR-status had little additional predictive value.
Among ER+ tamoxifen ↓ LRR by 48%, ↓ contralateral Bca by 54%, ↓DM by 28%, and ↓ all events by 24% (p <0.001).
On the other hand, there was a substantial ↑ of endometrial cancer associated with tamoxifen.
There was no effect of tamoxifen on intercurrent mortality.
Breast cancer deaths were ↓ by 31% (p <0.001) and overall mortality ↓ by 15% (p =0.01).
Conclusion: Tamoxifen produced long-term benefits among estrogen receptor positive patients in terms of breast cancer-related events, but also an increased incidence of endometrial cancer. Despite long-term follow-up we observed no benefit with tamoxifen in terms of cardiovascular mortality.

Huma Dar, JAMA Netw 2021 Secondary Analysis 25 year follow-up
A Subset of 565 women with ER+ ERBB2-.
Mean age 62 yo.
Long-term DRF interval (DRFI) by tumor size 88% T1a/b vs 76% T1c vs 63% T2 (P < .001)
by tumor grade 81% grade 1 vs 77% grade 2 vs 65% grade 3 (P = .02)
NOT by PR status
NOT by Ki-67 status.
25-year risk DM. T1a/b (vs. T2) ↓ HR 0.31, SS.
T1c (vs T2) ↓ HR 0.58, SS.
G1 (vs. G3) ↓ HR 0.48, SS
Tamoxifen Benefit seen with Larger Tumors Tam ↓ T1c HR 0.53, SS
Tam ↓ T2 HR 0.34, SS
Lower Grades Tam ↓ G1 HR 0.24, SS
Tam ↓ G2 HR 0.50, SS
PR-positive status Tam ↓ PR+ HR, 0.38; 0.24-0.62.
Conclusions and Relevance This secondary analysis of data from the STO-3 clinical trial indicated that, among the selected subgroup of patients, **tumor size** followed by **tumor grade** were the markers most significantly associated with long-term survival. Furthermore, a significant long-term tamoxifen treatment benefit was observed among patients with larger tumors, lower tumor grades, and PR-positive tumors.

SOFT (Suppression of Ovarian Function)
←R→ 3066 | 1. 5 years of tamoxifen |
| 2. tamoxifen + ovarian suppression |
| 3. exemestane plus ovarian suppression|.
1^{O} arm 2 ↑ DFS.
Ovarian suppression: bilat oophorectomy, ovarian RT, or triptorelin

TEXT ←R→ | 1. PO exemestane |
| 2. PO tamoxifen + Trelstar Depot |
Triptorelin (Trelstar) = GnRH Agonist

Eligibility: premenopausal status, operable breast cancer, and tumor that expressed estrogen or progesterone receptors in at least 10% of the cells. Total mastectomy with subsequent optional radiotherapy or breast-conserving surgery with subsequent radiotherapy. Either axillary dissection or a sentinel-node biopsy was required.

Pagani, NEJM 2014
Combined SOFT and TEXT. Exemestane (AI) + Ovarian Suppress vs. Tamoxifen + Ovarian Suppress.
5-year DFS 91.1% vs. 87.3% (HR 0.72; SS) 5-year FFBCa 92.8% vs. 88.8% (HR 0.66; SS). OS NS.
Selected adverse events of grade 3 or 4 were reported for 30.6% vs. 29.4% (NS).
CONCLUSIONS:
In premenopausal women with hormone-receptor-positive early breast cancer, adjuvant treatment with exemestane plus ovarian suppression, as compared with tamoxifen plus ovarian suppression, significantly reduced recurrence.

Francis, NEJM 2018.
LONG TERM UPDATE. 8-year.
When the SOFT and TEXT trials were presented in 2014, the conclusions were that ovarian function suppression was good, especially with exemestane, and oncologists should go and do it, at least in higher-risk patients.
Tam vs. Tam+Ovarian Suppression vs. exemestane + ovarian Suppression.
8-year OS | 98.8% | 97.9% | 97.7% | **8-year DFS | 87.4% | 90.6% | 92.5% |.**
The benefit of adding ovarian function suppression to tamoxifen in this population is a 2.1% reduction in 8-year distant events (to 17.9% from 20.0%, HR = 0.84) and a 4.3% reduction in deaths (to 10.6% from 14.9%, HR = 0.59). Using exemestane plus ovarian function suppression did reduce distant events compared with tamoxifen (to 15.5%, HR = 0.74), but the reduction in deaths of 2.1% was smaller (HR = 0.79).
NOTE HER2: HR DFS for adding ovarian function suppression is 0.41 for women with HER2-positive cancers, but only 0.83 for those with HER2-negative cancers (the 95% confidence limit for the latter overlaps 1.0).

NSABP B-14 (Fisher 1996). RTC in 1982 in node negative, ER + women with breast cancer s/p surgery (mastectomy or lumpectomy) double blinded randomized to Tam (5 years 10mg BID) vs. placebo. Patients who were disease free (and previously were on tamoxifen for 5 years) were re-randomized after 5 years for another 5 years of Tam vs placebo. Subset ≤ 49 yr and ≥ 50 yr both showed benefits. Tamoxifen ↓ ipsilateral, contralateral, and distant failure.

Conclusion: Tam ↑ DFS and OS and the benefit after 5 years *persists*, but there is no *additional* benefit for > 5 year tamoxifen.

1-5 years (1st randomize)	DFS	DDFS	OS
Placebo	57%	67%	76%
Tam	69%	76%	80%
P	< 0.0001	< 0.0001	0.02

5-10 years (2nd randomize)	DFS	DDFS	OS
Placebo (previously Tam).	92%	96%	96%
Tam (continued Tam).	86%	90%	94%
P	0.003	0.01	0.08 (NS)

NSABP B-21 (Fisher, 2002, Fisher 2007). RTC 1009 pN0 s/p lumpectomy women **with tumors ≤ 1cm (T1a-T1b)** , both ER/PR ±, randomized to TAM (n = 336), XRT and placebo (n = 336), or XRT and TAM (n = 337). 8-year f/u, tamoxifen and RT independently ↓ LF TAM 16.5% | RT 9% | RT+TAM 3%. But effect of TAM on IBTR had disappeared at 14-year f/u (though Tam still ↓ contralateral breast 1^{O}).

Did not find that tumor size correlates directly with recurrence rates. In fact, IBTRs were somewhat more frequent in women who had smaller primary tumors, ie, those of ≤ 5 mm, than in women who had larger tumors (6 to 10 mm).

Conclusion: In women with tumors ≤ 1 cm, IBTR occurs with enough frequency after lumpectomy to justify **considering** XRT, regardless of tumor ER status, and TAM plus XRT when tumors are ER positive.

14- year follow-up	LR free survival	DFS (ns)	OS (ns)
Tam	80.5	61.5	82.2
RT	89.2	60.6	82.1
Tam + RT	89.9	56	77.8

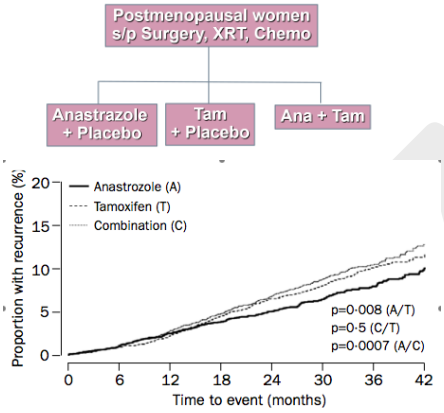


Figure 3: **Probability of recurrence in the intention-to-treat population**

ATAC: Arimidex, Tamoxifen Alone or in Combination (2002). RTC of 9366 post-menopausal women s/p surgery for a total adjuvant treatment of 5 years. TX began average 6-8 months after diagnosis and could be combined with RT. Early results showed that anastrozole (compared to Tam) ↓ contralateral breast cancer, ↓ DFS in patients only with R+ tumors, ↓ endometrial cancer, ↓ vaginal bleeding and discharge, ↓ CV events, ↓ hot flashes, ↓ venous thromboembolic events, BUT ↑ musculoskeletal disorders and ↑ fractures. DFS at 3 years, was better for anastrozole compared to either tamoxifen or combination (SS, p = 0.013, p = 0.006). No difference in annual recurrence rates in the first year, but the second and third year, anastrozole alone was better than either one. In subgroup analysis for time to recurrence anastrozole trended better for ALL subgroups EXCEPT hormone/Estrogen negative cancer and patients with previous chemotherapy. Anastrozole was SS better for patients with hormone/estrogen positive cancer, age ≥ 65, no hysterectomy, + hormone replacement therapy, conservative surgery (not mastectomy), + RT, no previous chemo, lower BMI, and negative nodal status. The Combination Arm was soon stopped.

ATAC 2005. 5 year F/U. End points that favor anastrozole: DFS, TTR, TTDR, Contralateral BCa. Note that OS, TTBCa death no SS Δ.

ATAC 2008. 9 year F/U. For HR+ patients DFS HR favored anastrozole 0.85 (p = 0.003), as did TTR 0.76 (p = 0.0001), TTDR 0.84 (0.022), and contralateral BCa 0.6 (p = 0.004). Absolute Δ in population with recurrence ↑ over time 5 yr Δ 2.8% (A 9.7%, T 12.5%) and 9 yr Δ 4.8% (A 17%, T 21.8%). No Δ in CV morbidity or mortality between anastrozole and tamoxifen arms. Interestingly, fractures were ↑ while on Tx, but rates were no different off treatment.

NOTE: This study did not test sequential treatment and they cannot recommend changing tamoxifen to anastrozole.

ATLAS (Adjuvant Tamoxifen: Longer Against Shorter)
←R→ 12,894 early breast cancer all who completed 5-yr tamoxifen, then randomized to | 1. continue tamoxifen 10 years | 2. Stop now at 5 years |. We report effects on breast cancer outcomes among the 6846 women with ER-positive disease, and side-effects among all women (with positive, negative, or unknown ER status). Long-term follow-up still continues. This study is registered, number ISRCTN19652633.

Davies, Lancet 2013.
10-year LR 18% vs. 20.7% (p=0·002), BCM 9.7% vs. 11.6% (p=0·01), and OS 81.4% vs. 79% (p=0·01).
Reductions in adverse breast cancer outcomes = less extreme **before** than after year 10.
If ER-, no effect. If ER indeterminate, some effect.
RRs were as follows: pulmonary embolus 1·87 (SS), stroke 1·06 (NS), ischaemic heart disease 0·75 (SS), and endometrial cancer 1·74 (SS).
The cumulative risk of endometrial cancer during years 5–14 was 3·1% (mortality 0·4%) for women allocated to continue versus 1·6% (mortality 0·2%) for controls (absolute mortality increase 0·2%).
Interpretation For women with ER-positive disease, continuing tamoxifen to 10 years rather than stopping at 5 years produces a further reduction in recurrence and mortality, particularly after year 10. These results, taken together with results from previous trials of 5 years of tamoxifen treatment versus none, suggest that 10 years of tamoxifen treatment can approximately halve breast cancer mortality during the second decade after diagnosis.

	Any ER status		ER-positive	
	Continue tamoxifen to 10 years (n=6454)	Stop tamoxifen at 5 years (n=6440)	Continue tamoxifen to 10 years (n=3428)	Stop tamoxifen at 5 years (n=3418)
Status at diagnosis				
ER status				
ER-positive	3428 (53%)	3418 (53%)	..	..
ER-negative	625 (10%)	623 (10%)	..	..
ER-unknown	2401 (37%)	2399 (37%)	..	..
Age, years				
<45 (median 40)	1246 (19%)	1236 (19%)	640 (19%)	630 (18%)
45–54 (median 49)	2070 (32%)	2076 (32%)	1090 (32%)	1099 (32%)
55–69 (median 61)	2557 (40%)	2567 (40%)	1373 (40%)	1357 (40%)
≥70 (median 73)	581 (9%)	561 (9%)	325 (9%)	332 (10%)
Nodal status				
Node-negative	3360 (52%)	3354 (52%)	1832 (53%)	1845 (54%)
N1–3	1667 (26%)	1621 (25%)	938 (27%)	893 (26%)
N4 or more	968 (15%)	965 (15%)	536 (16%)	534 (16%)
Unknown	459 (7%)	500 (8%)	122 (4%)	146 (4%)
Tumour diameter				
1–20 mm	2462 (38%)	2463 (38%)	1660 (48%)	1620 (47%)
21–50 mm	2749 (43%)	2727 (42%)	1309 (38%)	1328 (39%)
>50 mm	620 (10%)	628 (10%)	251 (7%)	252 (7%)
Unknown	623 (10%)	622 (10%)	208 (6%)	218 (6%)

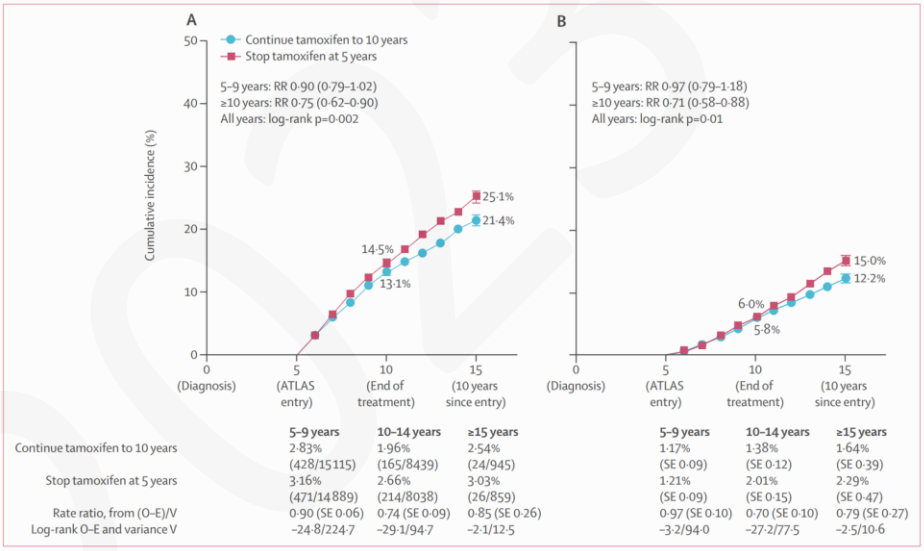


Figure 3: **Recurrence (A) and breast cancer mortality (B) by treatment allocation for 6846 women with ER-positive disease**
Bars show SE. Recurrence rates are percentage per year (events/patient-years of follow-up). Death rates (overall rate–rate in women without recurrence) are percentage per year (SE). ATLAS=Adjuvant Tamoxifen: Longer Against Shorter.

Canadian Aromatase **"Extend HT 5 more years = 10 Total Years?"**
BACKGROUND: Treatment with an aromatase inhibitor for 5 years as up-front monotherapy or after tamoxifen therapy is the treatment of choice for hormone-receptor-positive early breast cancer in postmenopausal women. Extending treatment with an aromatase inhibitor to 10 years may further reduce the risk of breast-cancer recurrence.
←R→ 1918 women all received hormones for 5 years | 1. Letrozole 5 more years | 2. Placebo |.

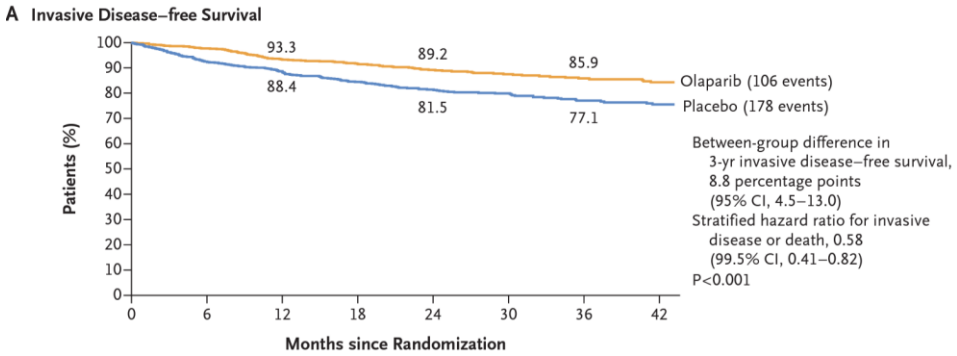
Goss, NEJM 2016.
5-year DFS 95% vs. 91% (HR 0.66, SS). 5-year OS 93%-94% (NS).
The annual incidence rate of contralateral breast cancer 0.21% vs 0.49% (HR 0.42, SS).
Bone-related toxic effects occurred more frequently among patients receiving letrozole than among those receiving placebo, including a higher incidence of bone pain, bone fractures, and new-onset osteoporosis. No significant differences between letrozole and placebo were observed in scores on most subscales measuring quality of life.
CONCLUSIONS: The extension of treatment with an adjuvant aromatase inhibitor to 10 years resulted in significantly higher rates of disease-free survival and a lower incidence of contralateral breast cancer than those with placebo, but the rate of overall survival was not higher with the aromatase inhibitor than with placebo.

NOTE: HOWEVER, CURRENT TRIALS: DATA, NASBP B-42 seems to have different results.

C+E vs. E alone

BTxCHOICE On-line Predictor Tool

BRCA and PARP



OlympiA Trial

Background: Poly(adenosine diphosphate–ribose) polymerase inhibitors target cancers with defects in homologous recombination repair by synthetic lethality. New therapies are needed to reduce recurrence in patients with BRCA1 or BRCA2 germline mutation–associated early breast cancer.
←R→ 1836 women with HER2- early breast cancer with BRCA 1 or BRCA 2 germine variants + local treatment and neoadjuvant or adjuvant chemotherapy.
| 1. 1 year PO olaparib | 2. Placebo | .
1^{O} invasive DFS.

Table 2. Adverse Events According to Grade.*

Adverse Event	Olaparib (N=911)				Placebo (N=904)			
	Any Grade	Grade 1	Grade 2	Grade ≥3†	Any Grade	Grade 1	Grade 2	Grade ≥3†
	number of patients (percent)							
Nausea	518 (56.9)	390 (42.8)	121 (13.3)	7 (0.8)	211 (23.3)	185 (20.5)	26 (2.9)	0
Fatigue	365 (40.1)	240 (26.3)	109 (12.0)	16 (1.8)	245 (27.1)	188 (20.8)	53 (5.9)	4 (0.4)
Anemia	214 (23.5)	68 (7.5)	67 (7.4)	79 (8.7)	35 (3.9)	19 (2.1)	13 (1.4)	3 (0.3)
Vomiting	206 (22.6)	160 (17.6)	40 (4.4)	6 (0.7)	74 (8.2)	64 (7.1)	10 (1.1)	0
Headache	180 (19.8)	145 (15.9)	33 (3.6)	2 (0.2)	152 (16.8)	120 (13.3)	31 (3.4)	1 (0.1)
Diarrhea	160 (17.6)	125 (13.7)	32 (3.5)	3 (0.3)	124 (13.7)	96 (10.6)	25 (2.8)	3 (0.3)
Decreased neutrophil count	146 (16.0)	36 (4.0)	66 (7.2)	44 (4.8)	59 (6.5)	17 (1.9)	35 (3.9)	7 (0.8)
Decreased white-cell count	143 (15.7)	41 (4.5)	75 (8.2)	27 (3.0)	52 (5.8)	27 (3.0)	22 (2.4)	3 (0.3)
Decreased appetite	119 (13.1)	101 (11.1)	16 (1.8)	2 (0.2)	53 (5.9)	45 (5.0)	8 (0.9)	0
Dysgeusia	107 (11.7)	101 (11.1)	6 (0.7)	0	38 (4.2)	36 (4.0)	2 (0.2)	0
Dizziness	104 (11.4)	91 (10.0)	12 (1.3)	1 (0.1)	67 (7.4)	61 (6.7)	5 (0.6)	1 (0.1)
Arthralgia	84 (9.2)	60 (6.6)	22 (2.4)	2 (0.2)	107 (11.8)	85 (9.4)	20 (2.2)	2 (0.2)

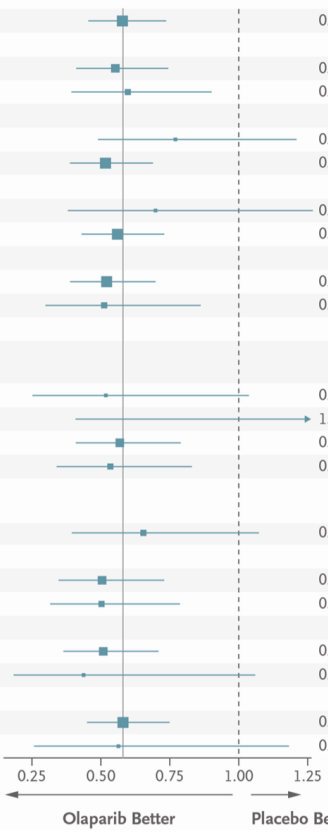
Tutt, NEJM 2021

3-year invasive DFS 85.9% vs. 77.1% (HR 0.58; P<0.001).
3-year DDFS 87.5% vs. 80.4% (HR 0.57; P<0.001).
Olaparib was associated with fewer deaths than placebo (59 and 86, respectively) (HR 0.68; P=0.02).

However, the between-group difference was not significant at an interim-analysis boundary of a P value of less than 0.01. Safety data were consistent with known side effects of olaparib, with no excess serious adverse events or adverse events of special interest.

CONCLUSIONS Among patients with high-risk, HER2-negative early breast cancer and germline BRCA1 or BRCA2 pathogenic or likely pathogenic variants, adjuvant olaparib after completion of local treatment and neoadjuvant or adjuvant chemotherapy was associated with significantly longer survival free of invasive or distant disease than was placebo. Olaparib had limited effects on global patient-reported quality of life.

Subgroup	Olaparib	Placebo	3-Yr Invasive Disease–free Survival		Stratified Hazard Ratio for Invasive Disease or Death (95% CI)
			Olaparib	Placebo	
	no. of patients with an event/total no.		%		
All patients	106/921	178/915	85.9	77.1	0.58 (0.46–0.74)
Timing of previous chemotherapy					
Neoadjuvant	70/460	117/460	82.5	68.0	0.56 (0.41–0.75)
Adjuvant	36/461	61/455	89.3	85.4	0.60 (0.39–0.90)
Previous platinum-based chemotherapy					
Yes	34/247	43/239	82.0	77.0	0.77 (0.49–1.21)
No	72/674	135/676	87.3	77.1	0.52 (0.39–0.69)
Hormone-receptor status					
HR+ and HER2–	19/168	25/157	83.5	77.2	0.70 (0.38–1.27)
TNBC	87/751	153/758	86.1	76.9	0.56 (0.43–0.73)
Germline *BRCA* mutation					
BRCA1	70/558	126/558	85.0	73.4	0.52 (0.39–0.70)
BRCA2	22/230	38/209	88.6	78.0	0.52 (0.30–0.86)
BRCA1 and *BRCA2*	0/1	0/3	NC	NC	NC
Hormone-receptor status and timing of previous chemotherapy					
HR+ and HER2–, NACT	13/104	20/92	86.0	67.0	0.52 (0.25–1.04)
HR+ and HER2–, ACT	6/64	5/65	76.4	89.3	1.36 (0.41–4.71)
TNBC, NACT	57/354	97/368	81.4	67.7	0.57 (0.41–0.79)
TNBC, ACT	30/397	56/390	90.3	84.8	0.54 (0.34–0.83)
Previous platinum-based chemotherapy and timing of previous chemotherapy					
Yes, NACT	26/169	39/169	81.8	70.1	0.66 (0.40–1.07)
Yes, ACT	8/78	4/70	NC	NC	NC
No, NACT	44/291	78/291	83.1	66.8	0.51 (0.35–0.73)
No, ACT	28/383	57/385	90.4	84.2	0.51 (0.32–0.79)
CPS+EG score in patients with previous NACT					
Score of 2, 3, or 4	55/398	96/387	84.3	68.9	0.51 (0.37–0.71)
Score of 5 or 6	11/22	10/15	50.0	17.9	0.44 (0.19–1.06)
Primary database					
Breast International Group	95/810	160/806	86.0	76.7	0.58 (0.45–0.75)
NRG Oncology (United States)	11/111	18/109	85.0	80.6	0.57 (0.26–1.18)



Oncotype / Genomic Scores

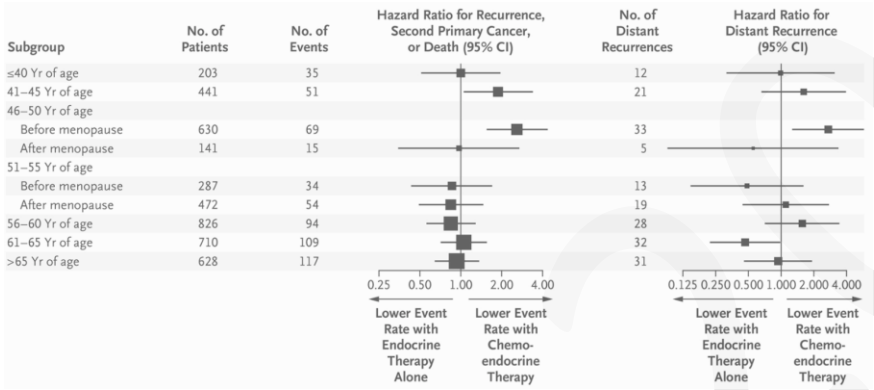
TailorX Non-inferiority Intermediate Score Trial.
←R→ 10273, but only 6711 had mid-range recurrence score. ER+, Her2-, N0, ←R→ midrange recurrence 11-25 score | 1. C+Endo | 2. Endo |.
All ≤ 10 was endo only. All > 25 is C+Endo.

The trial was designed to show noninferiority of endocrine therapy alone for invasive disease-free survival (defined as freedom from invasive disease recurrence, second primary cancer, or death).

Sparano, NEJM 2018.
Mid Range COHORT: 9-year Invasive DFS 83.3% vs. 84.3% 9-year FF-disease recurrence ~95% 9-year OS ~94%.
The chemotherapy benefit for invasive DFS varied with the combination of recurrence score and age (P=0.004), with some benefit of chemotherapy found in women 50 years of age or younger with a recurrence score of 16 to 25.
RS 16-20: 9-year Invasive DFS 90% vs. 80%
RS 21-25: 9-year Invasive DFS 86% vs. 79%
Conclusion: 70% of patients will not need chemotherapy. **30% will**.

Avoid Chemotherapy:	Age > 50,	Score 11-25	45%
	Age ≤ 50,	Score 11-15.	<10%
	Any age,	Score 0-10	15%
Give Chemotherapy:	Age ≤ 50,	Score 16-25	14%.
	Any age,	Score 26-100	17%

However, it is unclear if this benefit is due to the effect of chemotherapy or to endocrine suppression caused by chemotherapy-induced menopause.



Sparano, NEJM 2019.
Stratification: binary classification from MINDACT trial (Microarray in Node-Negative Disease May Avoid Chemotherapy), which divided patients into high or low risk based on tumor size and histologic grade.
Clinical risk low *≤ 3 cm G1, ≤2 cm G2, < 1 cm G3.*
Age ≤ 50 with Endocrine Tx alone, 9-year distant recurrence.
Score 0-10 w/ low any clinical risk **< 5%**
Score 11-25 with low clinical risk **4.7±1.0%**.
Score 11-25 with high clinical risk **12.3 ±2.4%**
Score > 25 with any clinical risk (had C+Endo) **15.2 ± 3.3%**.
"It is clear that young women with ORS 16-20 do NOT need chemo"
Note: This study is very exploratory. If you were to follow this as practice changing, you will have to basically plug and chug,

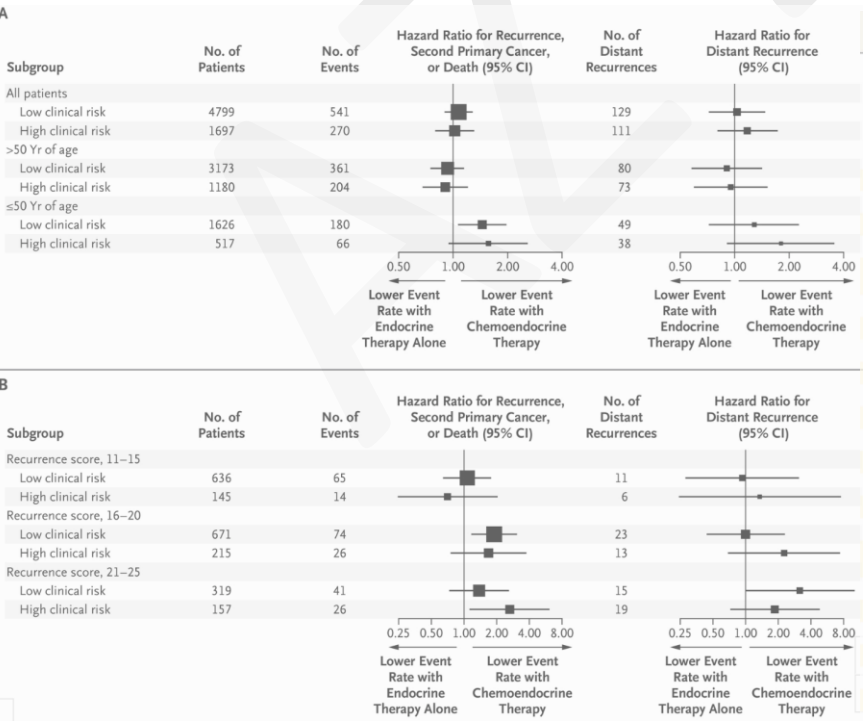


Table 1. Distant or Locoregional Disease Recurrence, Second Primary Cancer, or Death, and Distant Recurrence at 9 Years, According to Use or Nonuse of Adjuvant Chemotherapy, Stratified According to Age, Recurrence Score, and Clinical Risk (Intention-to-Treat Population).*

Variable	Clinical Risk	No. of Patients	Estimated Probability of Recurrence, Second Primary Cancer, or Death	Hazard Ratio for Recurrence, Second Primary Cancer, or Death (95% CI)†	Estimated Probability of Distant Recurrence	Hazard Ratio for Distant Recurrence (95% CI)†
			percent		*percent*	
Patients >50 yr		6469				
Low recurrence score (0–10)						
No chemotherapy	High	281	27.2±4.5	2.09 (1.47–2.96)	7.4±3.4	2.20 (0.95–5.08)
No chemotherapy	Low	879	13.3±1.5		2.6±0.8	
Intermediate recurrence score (11–25)						
No chemotherapy	High	577	23.2±2.6	1.56 (1.21–2.00)	9.3±1.9	2.61 (1.65–4.11)
No chemotherapy	Low	1605	13.6±1.1		3.5±0.6	
Chemotherapy	High	603	22.6±2.3	1.61 (1.27–2.04)	8.3±1.5	2.49 (1.60–3.87)
Chemotherapy	Low	1568	15.7±1.3		4.0±0.7	
High recurrence score (26–100)						
Chemotherapy	High	542	32.1±4.4	1.85 (1.28–2.66)	19.8±3.9	3.35 (1.82–6.14)
Chemotherapy	Low	414	19.3±3.8		7.0±2.4	
Patients ≤50 yr		2958				
Low recurrence score (0–10)						
No chemotherapy	High	64	9.3±4.5	0.68 (0.24–1.92)	0	0
No chemotherapy	Low	348	13.3±2.3		1.8±0.9	
Intermediate recurrence score (11–25)						
No chemotherapy	High	265	19.8±3.0	1.27 (0.89–1.83)	12.3±2.4	3.06 (1.78–5.25)
No chemotherapy	Low	835	17.4±1.8		4.7±1.0	
Chemotherapy	High	252	13.5±3.0	1.19 (0.76–1.88)	6.1±1.8	2.20 (1.10–4.40)
Chemotherapy	Low	791	11.3±1.4		3.9±1.0	
High recurrence score (26–100)						
Chemotherapy	High	228	24.0±4.2	2.27 (1.22–4.19)	15.2±3.3	2.87 (1.23–6.65)
Chemotherapy	Low	175	14.8±4.2		6.2±2.5	

WSG-German ADAPT Trial **3 week Pre-op ET → RS → ?**

←R→ ITT 2290 patients induction pre-op ET 3 (± 1) weeks – (TAM Pre-meno, AI Post-meno), RS at that time calculated low RS (RS0-11), intermediate RS (RS12-25), or high RS (RS > 25). ET response was defined as central Ki67post ≤ 10%.

26.3% versus 34.6% premenopausal and 27.4% versus 24.0% pN1

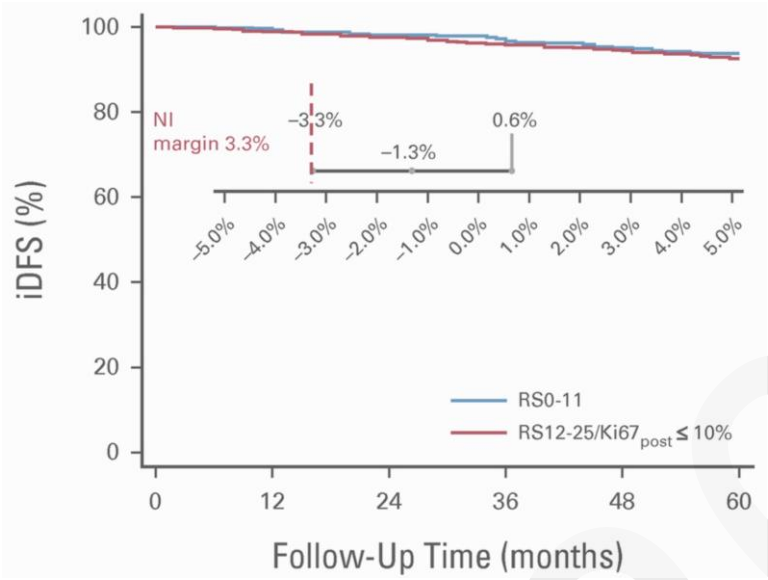
ENDOCRINE TRIAL Eligibility: pN0-1 (ie, 0-3 involved lymph nodes) - ALL RECEIVED EXCLUSIVELY ET.

| 1. Control arm if RS ≤ 11 |.

| 2. Experimental arm if RS12-25 with ET response (Ki67post ≤ 10%) |.

CHEMOTHERAPY TRIAL Eligibility: All other patients (including N0-1 RS12-25 without ET response) **received ddCT → ET.**

1^{O} endocrine trial was noninferiority of 5-year invasive disease-free survival (5y-iDFS) in experimental (v control) arm.



Nitz, JCO 2022. Only ENDOCRINE TRIAL.

5y-iDFS was 93-94%. 5-year dDFS ~96%. 5-year OS 97-98%.

Subgroup:

Age ≤ 50 years 5y-iDFS 94.8% vs. 92.5% vs. 89.4% (ET nonresponders)

Age > 50 years 5y-iDFS 93.5% vs. 92.6% vs. 92.2% (ET nonresponders)

In N0-1 RS12-25, outcome of ET responders (ET alone) was comparable with that of ET nonresponders (CT) for age > 50 years and superior for age ≤ 50 years.

ET response more likely with AI (mostly postmenopausal) than with tamoxifen (mostly premenopausal): 78.1% versus 41.1% (P < .001).

ET response was 78.8% in RS0-11, 62.2% in RS12-25, and 32.7% in RS > 25 (n = 4,203, P < .001).

CONCLUSION

WSG-ADAPT-HR+/HER2– demonstrates that guiding systemic treatment by both RS and ET response is feasible in clinical routine and spares CT in pre- and postmenopausal patients with ≤ 3 involved lymph nodes.

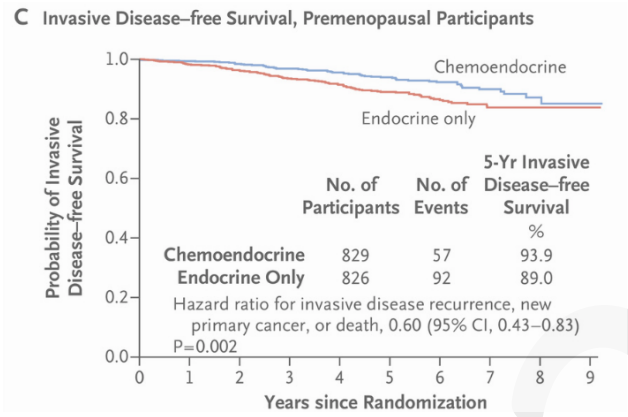
"Since ET response is primarily dependent on the type of ET, ovarian suppression and also AI have a potential role in increasing ET response (and thus ET efficacy) in premenopausal patients, even in those at high clinical risk, irrespective of CT use… In view of our results, future application of short preoperative ET in premenopausal patients should involve ovarian suppression to maximize their probability for ET response."

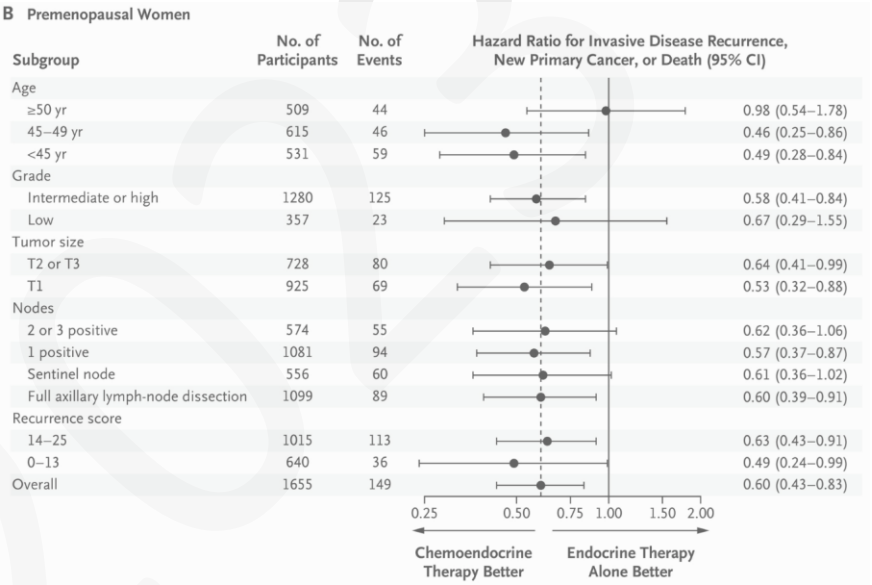
RXPONDER SWOG S1007 **Aka LN+#1-3 ORS ≤ 25.** **Premenopausal vs. Post!**
←R→ 5083 HR+, HER-, with 1-3 LNs involved. ≤ ORS 25. | 1. Hormone alone | 2. Hormone + Standard Chemo (anthracycline and/or taxane) |.
2/3 patients post-menopausal. 60% had 1 LN+. Only 10% had 3 LN+ and 10% had G3. About 50% receiving chemo only had TC and not any A.
Within 12 months after ←R→, 12.7% of the premenopausal women (19% E only, 6.3% E+C) had suppression of ovarian function.
In the endocrine-only group, of the 101 participants who were 40 years of age or younger, 36.6% had received ovarian suppression.

Kalinsky, 2020 Follow-up 5.1 Years
No association between chemotherapy benefit and RS values between 0–25 for the entire population (*P* = .30).
SS between chemotherapy benefit and menopausal status (*P* = .004), triggering further analyses of menopausal subsets.
Post-menopausal = no benefit with chemo. **Premenopausal women had 46% ↓ risk for invasive disease.**
5-year DFS = 92% (NS) 5-year DFS = 89% vs, 94.2% (p=0.0004) Abs Benefit of 5.2% at 5 years.
5-year OS = 96% (NS) 5-year OS 97.3% vs. 98.6% (p=0.032) Abs Benefit of 1.3% at 5 years.
Question: a direct benefit of chemotherapy, or an indirect effect of ovarian suppression. NOT addressed by this trial.

Forest Plot – Premenopausal = almost all SS benefited from chemo! Postmenopausal = none SS benefited from chemo.

Kalinsky, NEJM 2021 Follow-up 5.3 years





Jagsi, JAMA Network 2023. Secondary Analysis. 6.1 years.
Prospectively collected radiotherapy information was collected from 4871 patients treated in diverse settings.
Of 3852 patients received radiotherapy and had complete information on targets, 2274 (59.0%) received RNI.

5-year LRR 0.85% BCS → WBRT+RNI 0.11% mastectomy → PMRT
0.55% BCS → WBRT only 1.7% mastectomy alone.

Similarly low LRR was observed within the group assigned to endocrine therapy without chemotherapy.
The rate of IDFS did not differ by RNI receipt (premenopausal: hazard ratio [HR], 1.03; 95% CI, 0.74-1.43; P = .87; postmenopausal: HR, 0.85; 95% CI, 0.68-1.07; P = .16).
Conclusions and Relevance In this secondary analysis of a clinical trial, RNI use was divided in the setting of biologically favorable N1 disease, and rates of LRR were low even in patients who did not receive RNI. Disease-free survival was not associated with RNI receipt; omission of chemotherapy among patients similar to those enrolled in the S1007 trial is not an independent indication for use of RNI.

Prospective LN+ ORS

577 Prospective, age ≤ 40, Stage I-III, HER2 neg cancers. Median age 37.2.

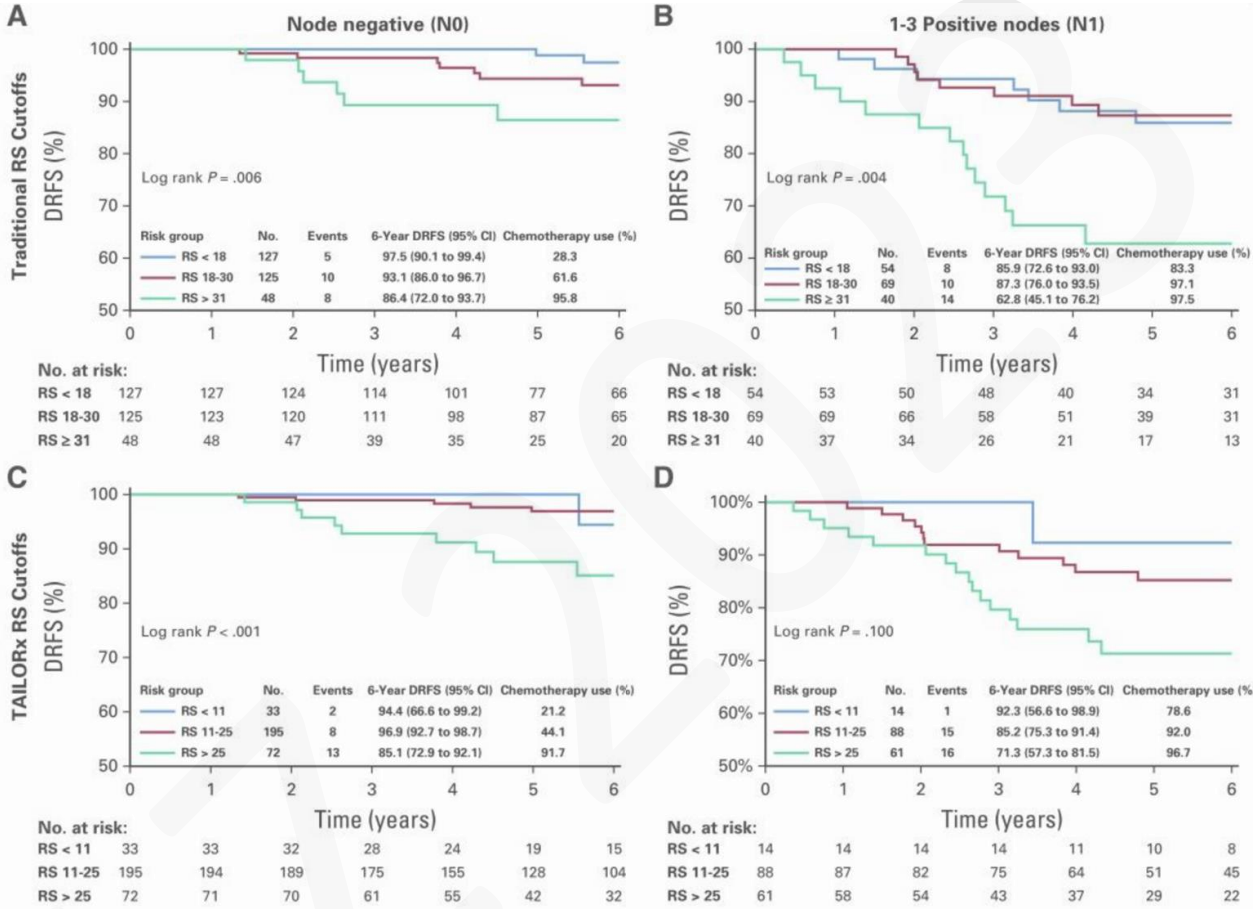
300 of 509 patients (59%) had N0 breast cancer, of whom 195 (65%) had an RS of 11-25 and fewer than half (86 of 195; 44%) received chemotherapy.

Poorvu, JCO 2019

6-year DRFS **N0** 94.4% and **N1** 92.3% (RS < 11), 96.9% and 85.2% (RS 11-25), and 85.1% and 71.3% (RS ≥ 26), respectively.

CONCLUSION The RS assay is prognostic among young women with node-negative and limited node-positive breast cancer, representing a valuable tool for risk stratification. Disease outcomes with a median follow-up of 6 years among young women with N0 disease and an RS of 0-25, a minority of whom received chemotherapy, and node-positive disease with an RS < 11 were very good, whereas those with N0 disease and an RS ≥ 26 or N1 disease with an RS ≥ 11 experienced substantial risk of early distant recurrence.

NOTE: Perhaps omitting chemo in selected young women with N1 breast cancer may not be terrible! Especially if very low Oncotype scores <11.



MINDACT MammaPrint
←R→ 6693 women with early-stage breast cancer (pT1-2 or T3 operable, N0-1).
Low clinical risk = 10-year BCaSS > 88% ER+ or > 92% ER- patients. "to account for the 4-percentage-point average absolute benefit of adjuvant endocrine therapy for ER-positive tumors."
If BOTH LR Clinically and LR Genomically = NO Chemotherapy. If BOTH HR = chemotherapy.
Patients with DISCORDANT results (any one HR and the other LR) | 1. Chemo | 2. No Chemo |.
Optional Randomization anthracycline regimen or a docetaxel+capecitabine regimen.
70-gene signature test (MammaPrint) in selecting patients for adjuvant chemotherapy.
1^{O} 5-year DMFS.

Cardoso, NEJM 2016
HR clinical LR Genomic 5-year DMFS 96.3% vs. 94.7% (Abs Δ + chemo = 1.5%).
Similar rates of survival without distant metastasis were reported in the subgroup of patients who had estrogen-receptor–positive, human epidermal growth factor receptor 2–negative, and either node-negative or node-positive disease.
Subgroup (Prespecified Exploratory Analysis):

CONCLUSIONS
Among women with early-stage breast cancer who were at high clinical risk and low genomic risk for recurrence, the receipt of no chemotherapy on the basis of the 70-gene signature led to a 5-year rate of survival without distant metastasis that was 1.5 percentage points lower than the rate with chemotherapy. Given these findings, approximately 46% of women with breast cancer who are at high clinical risk might not require chemo.

Piccart, Lancet 2021		**Long term 8.7 year**
HR clinical LR Genomic		8-year DMFS 92·0% vs. 89·4% (HR 0·66; SS)
Exploratory analysis (HR+, Her2-)	Age ≤ 50	8-year DMFS 93·6% vs. 88·6% (NS)
	Age ≥ 50	8-year DMFS 90·2% vs. 90·0% (NS).
	LN-	8-year DMFS 91·7% vs. 89·2% (NS).
	LN+ #1-3	8-year DMFS 91·2% vs. 89·9% (NS).

Interpretation
With a more mature follow-up approaching 9 years, the 70-gene signature shows an intact ability of identifying among women with high clinical risk, a subgroup, namely patients with a low genomic risk, with an excellent distant metastasis-free survival when treated with endocrine therapy alone. For these women the magnitude of the benefit from adding chemotherapy to endocrine therapy remains small (2·6 percentage points) and is not enhanced by nodal positivity. However, in an underpowered exploratory analysis this benefit appears to be age-dependent, as it is only seen in women younger than 50 years where it reaches a clinically relevant threshold of 5 percentage points. Although, possibly due to chemotherapy-induced ovarian function suppression, it should be part of informed, shared decision making. Further study is needed in younger women, who might need reinforced endocrine therapy to forego chemotherapy.

ONGOING and Other Studies:

Tailor RT

Inclusion:
IDC, M0 s/p BCS or mastectomy ER > 1% , Her2 neg, Oncotype < 18 with axillary evaluation with pN+ with plan for ≥ 5 years endocrine therapy (concurrent with RT or adjuvant).
If ALND, 1-3 axillary LN, macrometastases > 2 mm.
If BCS + SLNB, 1-2 LN+.
If Mastectomy + SLNB, only 1 LN+ allowed.

THIS HAS BEEN CHANGED IN THE RECENT UPDATES (2021).

NEW Changes: ORS now ≤ 25.
Patients with micromets eligible.
T3N0 eligible
Both BCS or Mastectomy → SLNB 1-2 LN+ allowed.
Patients > 35 yo allowed.

Randomization…
If BCS | 1. WBI | 2. WBI + RNI |
If Mast | 1. No RT | 2. Chest wall irradiation + RNI |

RT CHARM

Other studies:
Mamounas 2017: Evaluated ORS to predict LRR in LN+ cancer
1065 patients treated on a NSABP-B28 comparing AC vs. AC-T. In this study, BCS → WBI only and mastectomy → no PMRT.
MVA adjusting for systemic therapy and type of surgery, demonstrated the RS was an independent predictor of LRR (HR=2.86, SS) for a 50 point difference, p=0.008). For BCS patients with 1-3 LNs, the risk of LRR was 3.9%, 6.2%, 10.5% for low, moderate, or high RS patients.
For Mastectomy with 1-3 LNs, the risk of LRR was 2.4%, 4.1%, 6.0%, respectively.

TailorX JAMA Oncology 2019. 9/30/2019. High RS subset.

SWOG S8814 Woodward, JAMA Oncol 2020
ARTIC Genomic. Women with Hormone +, LN+, ORS correlates with risk of LR, , even among women with N1 disease treated with mastectomy.

Locally Adv. IBCa Stage III, IV (≥T3, N+)

Guidelines

- **Pre-operative Systemic Therapy** (Currently Unresectable, HER+ or TNBC, or **T4 and ≥ N2**)
  ASCO Guidelines 2021: https://ascopubs.org/doi/full/10.1200/JCO.20.03399

  - **If CR (± PR) → Lumpectomy or Mastectomy + Surgical Axillary Staging ***
    - **Always consider** Adjuvant systemic therapy (endocrine / Her2 directed therapy).
    - **Always consider** Adjuvant Comprehensive Radiation (WBRT/CWRT + RNI)
    - If Triple negative and < pCR → consider capecitabine.
  - **If no response or disease progression → individualized treatment.**

- **Upfront Surgery (Resectable T2-3 and N0-1)**
  - Adjuvant Chemo decision (aggressive histologies: Ductal, Lobular, mixed, micropapillary)
    - ER/PR +, Her2 + → pT1a N0 → ± Endocrine ± Chemo w/ **Trastuzumab (Herceptin)**
      pT1b N0 or pN1mi → **Endocrine** or **Chemo w/ Trastuzumab** + **endocrine**.
      ≥ pT1c or N+ → **Chemo w/ Trastuzumab** + **Endocrine**.
    - **Post**-Menopausal
      ER/PR +, Her2 - → pT1a N0 → ± Endocrine
      → ≥ pT1b or pNmi/pN1 → **21 gene RT-PCR.**
      < 26 low = Endo
      ≥ 26 high (or not done) = **C→E both**
      → pN2/pN3 → **Chemo + endocrine (Cat 1)**
    - **Pre**-Menopausal
      ER/PR +, Her2 - → pT1a N0 → ± Endocrine
      → ≥ pT1b N0 → **21 gene RT-PCR.**
      < 15 low = Endo → ovarian suppression/ablation
      16-25 int = either ↑ or ↓
      ≥ 26 high (or not done) = **C→E both**
      → pNmi/pN1 → **Chemo + endocrine** **if chemo candidate**
      → **endocrine** → ovarian suppression/ablation **otherwise**
      → pN2/pN3 → **Chemo + endocrine (Cat 1)**
    - ER/PR -, Her2 + → ≈ staging breakdown as triple positive, just without endocrine therapy
    - ER/PR -, Her2 - → ≈ staging breakdown as triple positive, just only chemo
  - **Lumpectomy or Mastectomy** with **Surgical Axillary Staging ***
    → ≥ 4 pLN+ → RT + RNI
    → 1-3 pLN+ → RT + **Consider** RNI
    → neg pLN-, ≥ T3 → RT ± RNI (if done, avoid dissected axilla)
    → neg pLN-, < T3 → obs
    → Margins < 1mm → ± RT
    → R1 or R2 → re-excision first, then reassess.

* **Surgical Axillary Staging**

Criteria	Primary Evaluation	Follow-up Evaluation
If cN0 (± 1-2 suspicious nodes on imaging).	SLNB	Obs… if pN0, if pN+ (with Ni, Nmic, or meets Z0011)
		ALND… if pN+ (other than above), If SLNB not identified.
If cN+ (≥ 3 LN on imaging / exam concerning LN). or If ≥ N1 and neoadjuvant chemotherapy planned.	FNA / core biopsy	SLNB… if biopsy neg If biopsy pos (and meets Z0011)
		ALND… if biopsy pos (± high volume disease ± pre-op Chemo given).

Note: Recent Data Questioning Need for Surgery in pCR patients.
Note 2: This is NOT standard of care but currently experimental.

Neoadjuvant Chemotherapy (NAC).

PRINCIPLES OF PREOPERATIVE SYSTEMIC THERAPY

Known Benefits of Preoperative Systemic Therapy
- Facilitates breast conservation
- Can render inoperable tumors operable
- Treatment response provides important prognostic information at an individual patient level, particularly in patients with TNBC or HER2-positive breast cancer
- Identifies patients with residual disease at higher risk for relapse to allow for the addition of supplemental adjuvant regimens, particularly in patients with TNBC or HER2-positive breast cancer.
- Allows time for genetic testing
- Allows time to plan breast reconstruction in patients electing mastectomy
- Allows time for delayed decision-making for definitive surgery

Opportunities
- May allow SLNB alone if initial cN+ becomes cN0 after preoperative therapy
- May provide an opportunity to modify systemic treatment if no preoperative therapy response or progression of disease
- May allow for more limited radiation fields in patients with cN+ who become cN0/pN0 after preoperative therapy
- Provides excellent research platform to test novel therapies and predictive biomarkers

Cautions
- Possible overtreatment with systemic therapy if clinical stage is overestimated
- Possible undertreatment locoregionally with radiotherapy if clinical stage is underestimated
- Possibility of disease progression during preoperative systemic therapy

Candidates for Preoperative Systemic Therapy
- Patients with inoperable breast cancer:
  - IBC
  - Bulky or matted cN2 axillary nodes
  - cN3 nodal disease
  - cT4 tumors
- In select patients with operable breast cancer
  - Preoperative systemic therapy is preferred for:
    - ◊ HER2-positive disease and TNBC, if ≥cT2 or ≥cN1
    - ◊ Large primary tumor relative to breast size in a patient who desires breast conservation
    - ◊ cN+ disease likely to become cN0 with preoperative systemic therapy
  - Preoperative systemic therapy can be considered for cT1c, cN0 HER2-positive disease and TNBC
- Patients in whom definitive surgery may be delayed.

Non-candidates for Preoperative Systemic Therapy
- Patients with extensive in situ disease when extent of invasive carcinoma is not well-defined
- Patients with a poorly delineated extent of tumor
- Patients whose tumors are not palpable or clinically assessable

pCR + RCB

Single Prospective "No Surgery" Study
50 patients Single Arm Phase II ≥ 40 yo unicentric cT1–2N0–1M0 TNBC or HER2+ a NAC → residual breast lesion < 2 cm on imaging.
Eligible patients had 1 biopsy (minimum of 12 cores) of the tumour bed. If no disease identified → NO SURGERY → WBRT (40 Gy in 15 or 50 Gy in 25) + boost (14 Gy in seven fractions). Median age 62 years, 42% TNBC, 58% HER2+. pCR in in 31 patients (62%).

> **Kuerer, Lancet 2022** Median follow-up of 26·4 months.
> **No ipsilateral breast tumour recurrences occurred in these 31 patients.**
> No serious biopsy-related adverse events or treatment-related deaths occurred.

pCR (only DCIS, no Invasive)
RR of 337 patients of the I-SPY2 trial who had NAC → RCB0 (no residual invasive disease. 70 (21% had residual DCIS).

> Osdoit, JAMA Surg 2022
> Residual DCIS was present in 8.5% of TNBC, 15.6% of HR+ tumors, and 36.6% of ERBB+.
> Among those participants with pCR, there was no significant difference in EFS, DRFS, or LRR based on presence or absence of residual DCIS.
> **Conclusions and Relevance** The analysis supports the definition of pCR as the absence of invasive disease after NAC regardless of the presence or absence of DCIS.

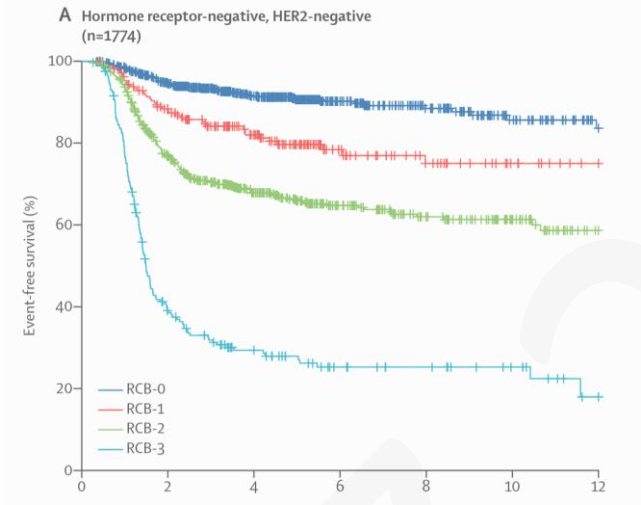
Taiwanese NET / NACT Cohort.
640 patients in HR+HER2- IDC evaluating the benefit of NET or NACT.
1^{O} All Cause Mortality

> Zhang, JAMA Netw Open 2021.
> MVA aHR for all-cause mortality NET (vs. NACT) = 2.67 (*P* < .001). **AKA Risk of death is nearly ↑ 3x if no NACT (only NET)**.
> Compared to age < 50 yo, all-cause mortality aHRs for age were 50-59 = 1.13 (SS), 60-69 = 1.25 (SS), and 70-79 = 1.37 (SS).
> Compared with post-meno, all-cause mortality aHR among premenopausal 1.35 (SS). compared with postmenopausal women (*P* < .001).
> Conclusions: The findings of this study suggest that for patients with strongly HR-positive and *ERBB2*–negative IDC, NACT may be considered the first choice for neoadjuvant treatment.

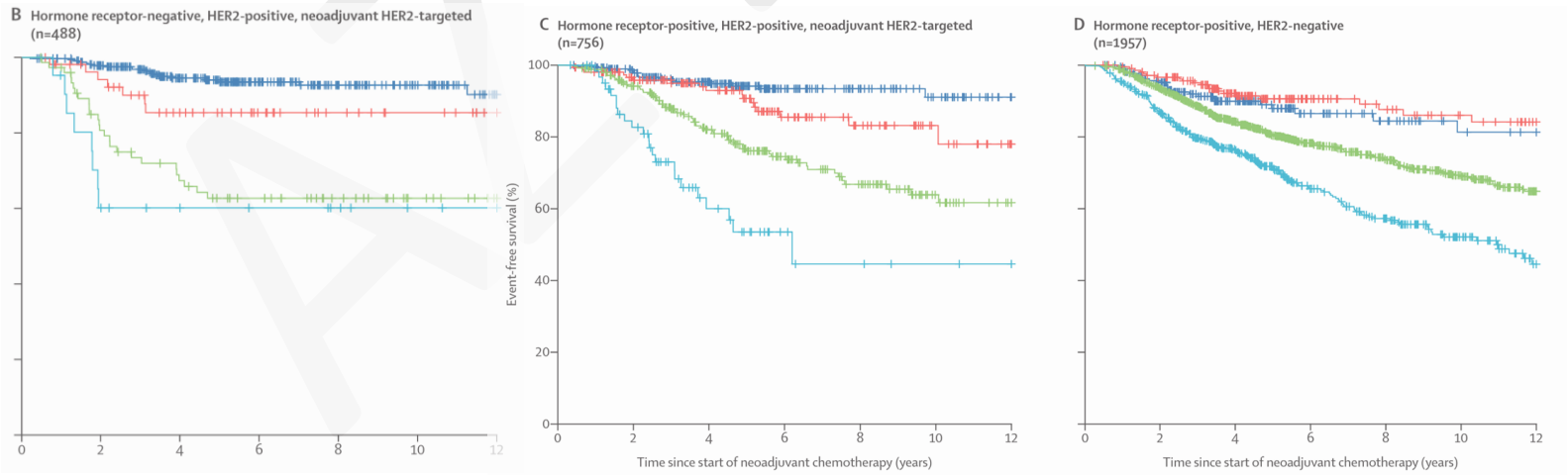
Platinum TNBC Metaaanalysis
←M→ 9 RTCs with 2109 patients.

Poggio, Annals of Oncology 2018.
Overall, platinum-based NAC SS↑ pCR 37.0% to 52.1% (OR 1.96, P < 0.001).
Platinum-based neoadjuvant chemotherapy remained significantly associated with increased pCR rate also after restricting the analysis to the three RCTs (N = 611) that used the same standard regimen in both groups of weekly paclitaxel (with or without carboplatin) followed by anthracycline and cyclophosphamide (OR 2.53, 95% CI 1.37–4.66, P = 0.003).
Among the 96 BRCA-mutated patients included in two RCTs, the addition of carboplatin was not associated with significantly increased pCR rate (OR 1.17, 95% CI 0.51–2.67, P = 0.711).
Two RCTs (N = 748) reported survival outcomes: no significant difference in EFS (HR 0.72, 95% CI 0.49–1.06, P = 0.094) and OS (HR 0.86, 95% CI 0.46–1.63, P = 0.651) was observed.
A significant higher risk of grade 3 and 4 hematological AEs, with no increased risk of grade 3 and 4 neuropathy was observed with platinum-based neoadjuvant chemotherapy.
Conclusion: In TNBC patients, platinum-based neoadjuvant chemotherapy is associated with significantly increased pCR rates at the cost of worse hematological toxicities. Platinum-based neoadjuvant chemotherapy may be considered an option in TNBC patients.

Prognostic RCB
5161 patients pooled analysis all NAC between 1994 – 2019.
Median age was 49 years.



Yau, Lancet 2022.
RCB score was prognostic within each breast cancer subtype, with higher RCB score significantly associated with worse event-free survival.
Univariable hazard ratio (HR) associated with one unit ↑ in RCB ranged from HR+HER2- 1·55 to HR-HER2+ 2·16 (with or without HER2-targeted therapy; p<0·0001 for all subtypes).
RCB score remained prognostic for event-free survival in multivariable models adjusted for age, grade, T category, and nodal status at baseline: the adjusted HR ranged from 1·52 (1·36–1·69) in the hormone receptor-positive, HER2-negative group to 2·09 (1·73–2·53) in the hormone receptor-negative, HER2-positive group (p<0·0001 for all subtypes).
Interpretation RCB score and class were independently prognostic in all subtypes of breast cancer, and generalisable to multiple practice settings. Although variability in hormone receptor subtype definitions and treatment across patients are likely to affect prognostic performance, the association we observed between RCB and a patient's residual risk suggests that prospective evaluation of RCB could be considered to become part of standard pathology reporting after neoadjuvant therapy.



Symmans, JAMA Oncol 2021
I-SPY2 showing that pathologic response to neoadjuvant therapy can prognosticate based on RCB.
↓ EFS with ↑ residual cancer burden (RCB) class at time of surgery.
Conclusion: Residual cancer burden as a continuous response measure exhibits favorable attributes for neoadjuvant trials in breast cancer, providing additional information beyond pathologic complete response rate and pretreatment disease characteristics.

Rates: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4845895/

> HR and/or HER2 status was unknown for 254 patients. Among the remaining patients, rates of axillary pCR were 16.4% for HR-positive/HER2-negative tumors, 40.8% for HR-positive/HER2-positive tumors, 40.8% for HR-negative/HER2-negative tumors, and 55.2% for HR-negative/HER2-positive tumors. Rates of pCR in both breast and axilla were 7.3% for HR-positive/HER2-negative tumors, 28.8% for HR-positive/HER2-positive tumors, 28.7% for HR-negative/HER2-negative tumors, and 40.9% for HR-negative/HER2-positive tumors.

Total pCR based on Subtypes
ER+/Her2- 7%
ER+/Her2+ 28%
ER-/Her2- 28%
ER-/Her2+ 40%

Samiei, JAMA Surg 2021
This systematic review and meta-analysis, including 33 unique studies with 57 531 unique patients, showed that the hormone receptor (HR)–negative/ERBB2-positive subtype was associated with the highest axillary pCR rate (60%).
The remaining subtypes were associated with the following axillary pCR rates in decreasing order:
59% for ERBB2-positive
48% for triple-negative
45% for HR-positive/ERBB2-positive
35% for luminal B
18% for HR-positive/ERBB2-negative
and 13% for luminal A breast cancer.

https://clincancerres.aacrjournals.org/content/clincanres/early/2020/02/11/1078-0432.CCR-19-3492.full.pdf

RCB Yau C, van der Noordaa M, Wei J, et al. Residual cancer burden after neoadjuvant therapy and long-term survival outcomes in breast cancer: A multi-center pooled analysis. 2019 San Antonio Breast Cancer Symposium. Abstract GS5-01. Presented December 13, 2019

Phenotype	Outcome	pCR	RCB-I	RCB-II	RCB-III
HR+/HER2-	Frequency (%)	11%	10%	52%	27%
(N=1467)	5 yr EFS (95% CI)	91% (86-96)	93% (89-98)	82% (79-85)	70% (65-75)
	10 yr EFS (95% CI)	84% (75-93)	88% (82-95)	71% (67-75)	52% (46-58)
HR+/HER2+	Frequency (%)	38%	18%	35%	9%
(N=762)	5 yr EFS (95% CI)	94% (91-97)	93% (88-98)	78% (73-84)	49% (37-65)
	10 yr EFS (95% CI)	91% (86-96)	79% (70-90)	65% (59-73)	42% (29-60)
HR-/HER2+	Frequency (%)	66%	11%	18%	5%
(N=550)	5 yr EFS (95% CI)	93% (90-96)	88% (79-97)	60% (50-71)	45% (30-69)
	10 yr EFS (95% CI)	90% (86-94)	84% (74-95)	56% (46-68)	45% (30-69)
HR-/HER2-	Frequency (%)	41%	13%	33%	13%
(N=1293)	5 yr EFS (95% CI)	92% (90-94)	85% (79-91)	68% (63-72)	28% (21-36)
	10 yr EFS (95% CI)	87% (82-91)	80% (72-88)	63% (58-68)	24% (18-33)

A pathologic complete response (RCB-0) was most likely to be achieved by hormone receptor–negative/HER2-positive patients (69%) and least likely by the hormone receptor–positive/HER2-negative group (11%); the triple-negative group (43%) and hormone receptor–positive/HER2-positive group (38%) fell in between.

NAC alone vs. NAC + PMRT

MDACC. Huang, JCO 2004.
RR 542 patients treated on 6 consecutive prospective trials with NAC → mastectomy + PMRT vs. 134 patients on same trials WITHOUT PMRT. 10-year LRR PMRT 11% vs no RT 22% (SS). CSS (SS) ↑ if subset ≥ Stage IIIB, cT4, or ≥ 4 LN+.
On multivariate analyses of LRR and CSS, the hazard ratios for lack of radiation were 4.7 (95% CI, 2.7 to 8.1; P < .0001) and 2.0 (95% CI, 1.4 to 2.9; P < .0001), respectively.
CONCLUSION:
After neoadjuvant chemotherapy and mastectomy, comprehensive radiation was found to benefit both local control and survival for patients presenting with clinical T3 tumors or stage III-IV (ipsilateral supraclavicular nodal) disease and for patients with four or more positive nodes. Radiation should be considered for these patients regardless of their response to initial chemotherapy.

Krug, JCO 2015. Meta-analysis of Gepar Trials **BASICALLY RT IMPROVES ALL LRC.**
←M→ 3,481 operable and non-operable breast cancer. 94% received any RT. Median follow-up of 4.5 years.
Results: Overall LR 8.3%.
5-year LRFS RT 90% vs. no RT 81.5%, (p < 0.001). 5-year DFS 75.4% vs. 67.4%, (p < 0.001).
Absolute advantage of RT regarding both LRFS and DFS was highest among patients with **clinically positive lymph nodes at first diagnosis** (HR 2.32, 95% CI 1.54-3.50; p < 0.001; HR 1.97, 95% CI 1.48-2.62; p < 0.001 respectively).
In patients with pCR, 5-yr LRFS 95.7% vs. 86.6% (p = 0.051) 5-yr DFS 86.9% vs. 56.1% (p < 0.001).
In patients without pCR, 5-yr LRFS 88.6% vs. 80.7% (p < 0.001) 5-yr DFS 72.6% vs. 65.7% (p = 0.014).
MVA = RT as an independent prognostic factor for LRFS (HR 0.54, p = 0.004) and DFS (HR 0.69, p = 0.016).
Conclusions: This retrospective analysis suggests that patients managed without RT after neoadjuvant chemotherapy for breast cancer have a significantly worse outcome even if they achieved a pCR.

Indications for NAC

Overall Indications: **Definite**: Inflammatory
Locally advanced (unresectable). ≥ T3 ≥ N2.
+/-: Locally advanced (resectable).
BCS (desired, but would be suboptimal cosmetic result w/o down-staging prior to surgery).
Early Stage invasive breast cancer-depending on physician and institutional preference even early stage patients who can be conservatively treated may consider neo-adjuvant chemotherapy prior to surgery.
Not Indicated: T1, N0, Ni, Nmic

NSABP B-18. RTC 1523 patients T1-3 N0-1 (Stage I-IIIA but no cN2 disease) randomized to PREOP (760) or POSTOP (763). **No PMRT.**
Adjuvant RT: If mastectomy + ALND, no RT. If lumpectomy, then you get breast radiation 50 Gy whole breast no boost.

| BCS and ALND or radical mastectomy → 4 cycles AC every 21 days | AC → surgery |.
Tamoxifen x5 years for ≥ 50 yr, regardless of ER/PR status. No PMRT. cT1 30%. cN0 75%.

Fisher JCO, 1997. Tumor size ↓ by 80% in neoadjuvant CT (NeoCT) (aka 80% had either partial or complete).

16-year data	pN+	BCS rate	IBTR	DFS	OS
Pre-op C	42%	68%	13%	42%	55%
Post-op C	58%	60%	10%	36%	
P value	0.001	0.001	-	-	-

Breast: Overall response 80%. 44% cPR. **36% cCR**. In women who had cCR, 26% had pCR. 9% total pCR.
pCR by cStage: cT1 14%, cT2 9%, cT3 4%.
LN: 73% cCR. In women who had cCR, 44% had pCR. 32% total pCR.
CONCLUSION: Preoperative therapy should be considered for the initial management of breast tumors judged too large for lumpectomy.
Note: Surgeons had to score the patient upfront before anything else, if they were mastectomy or BCS.
If ≥ 5.1 cm size and especially node + and ≥ 5.1 in size, a LOT more patients who were proposed for mastectomy could get BCS.
12% more lumpectomies performed in the preoperative group; with tumors ≥ 5.1 cm, there was 175% ↑.
Aka, NAC can ↑ rate lumpectomy, especially in patients w/ large tumors who otherwise would have gotten radical mastectomy.
Note: LR for BCS (large tumor shrinks after NeoC response) was 2x that in patients with smaller tumors with upfront surgery first, 15.7 vs 7.6%.
Wolmark, J Natl Cancer Inst Monogr 2001. 9-year F/U. OS 69% neoadjuvant vs 70 adjuvant (p = 0.8). DFS: 55 vs 53 (p = 0.5).
But OS according to RESPONSE… if you have a pCR, these patients at 9 year did BETTER 85% vs 70% in OS than other responses.

There was hope that neo-adjuvant chemotherapy may eliminate micromet disease. Unfortunately, from this study, the OS and DFS were nearly identical in this study. There, however seems to be an advantage of neoadjuvant in younger and adjuvant chemo in older patients.

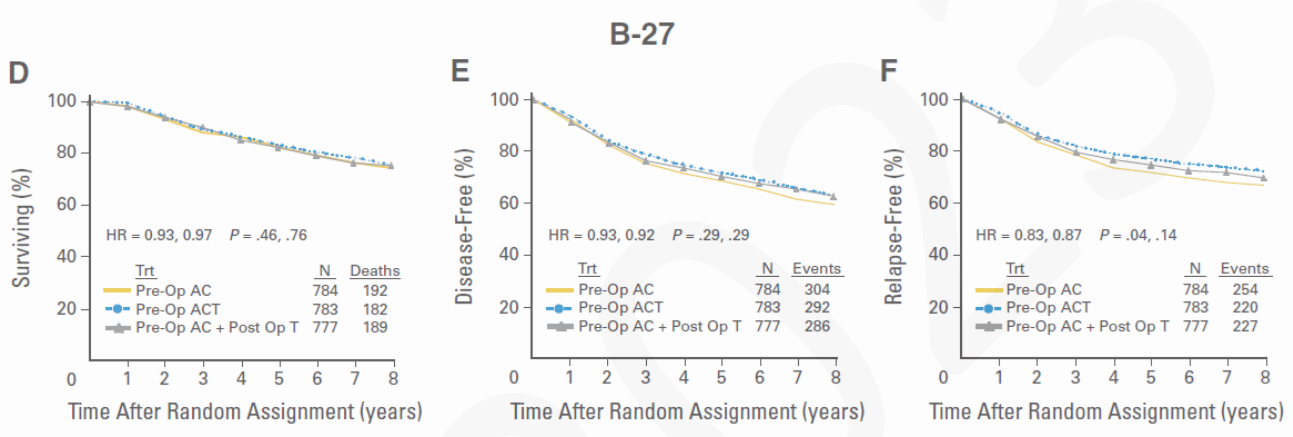
Previous French European trials (Mauriac, Ann Oncol 1991; Scholl Eur J Cancer 1994) that compared neoadjuvant vs adjuvant chemo showed OS advantage with neoadjuvant. However, these trials had imbalances in systemic and local therapy. First, all preoperative chemo patient received chemo. Only LN+ patients in postoperative received chemo. Also, preoperative patients received LESS surgery than postoperative. Therefore, preoperative patients had more LR.

NSABP B-27. RTC 2411 women with operable BCa randomized to 3 arms
| 1. AC x 4 cycles / Tam 5 yrs → lumpectomy/ALND or mastectomy **| 2. ACx4/Tam → docetaxelx4 → surg | 3**. ACx4/Tam → surg → Tax x4 |.
All patients received tamoxifen 5 years regardless of ER/PR status. No radiation allowed. Primary tumor in breast must be > 1cm (cT1c-T3, N0-1, M0). For clinically suspicious axillary adenopathy, the primary breast tumor could be any size (cT1-3, N1, M0).

Rastogi 2008. Addition of T to AC did not significantly impact DFS or OS. See chart for Recurrence Free Interval (SS).
pCR: Arm 1 9%, **Arm 2 16.9%,** Arm 3, 10%. **No impact of DFS**. UNLESS you look at DFS and OS ACCORDING TO PATH RESPONSE.
Docetaxel (neoadjuvant or adjuvant) also reduce LR.

Note: Despite pCR being increased, there is no evidence for ↑ breast conservation therapy.

Overall Conclusion: Preoperative T + AC significantly ↑ pCRs compared with preoperative AC alone (26% vs 13%, p < 0.0001). In both studies, patients who achieved a pCR continue to have a significantly superior DFS and OS outcomes than those who did not.
In subset of patients who had pPR response to AC, there was a benefit to addition of taxol in terms of DFS in the ADJUVANT setting (not, neoadjuvant…I think)..



EORTC 10902 Van Der Hgae, 2009. 4c FEC → surg or the reverse. EORTC FEC (5-FU, epirubicin, and cyclophosphamide).
No difference DFS or OS

Analysis of B-18 and B-27. 10-year FU.

Initial	Post-chemo	CW recurrence	Regional recurrence
T>5 cm, N0 (n=16)	pCR	0%	6.2%
T>5 cm, N0 (n=95)	ypN-/not breast pCR	8.6%	3.2%
T>5 cm, N0 (n=179)	ypN+	12.3%	2.3%
T>5 cm, N+ (n=11)	**pCR**	**0%**	**0%**
T>5 cm, N+ (n=84)	**ypN-/not breast pCR**	**9.2%**	**0%**
T>5 cm, N+ (n=128)	ypN+	17.6%	4.8%
T≤5 cm, N0 (n=46)	pCR	2.2%	4.3%
T≤5 cm, N0 (n=178)	ypN-/not breast pCR	4%	2.3%
T≤5 cm, N0 (n=184)	ypN+	7.8%	3.4%
T≤5 cm, N+ (n=21)	**pCR**	**0%**	**0%**
T≤5 cm, N+ (n=37)	**ypN-/not breast pCR**	**2.7%**	**8.1%**
T≤5 cm, N+ (n=143)	ypN+	10.6%	6.4%

Mamounas, JCO 2012. No PMRT.

Note: until 1990, the NSABP did not allow for chest wall, regional nodal XRT after mastectomy, or regional nodal XRT after BCS.

NAC: AC or AC → T **TX: Lumpectomy → or MRM alone.**

Results: 10-year LRR was and 12.2%. (local 8.9%, 3.4% regional)

Docetaxel significant decreased LRR. LR was 12.6% for mastectomy and 10.3% for lumpectomy.

Multivariate predictors.

Lumpectomy: **age**, cN status (before NC), and ypN/breast tumor response pCR

Mastectomy: **cT size** (before NC), cN status (before NC), and ypN/breast tumor response pCR

Summary: < 50 yo, clinical size > 5cm, ypN status, pCR

BCS NOTE: Among clinically node +, if you have BCS and have neoadjuvant chemo, if you END UP STILL N+, you have a much higher chance of regional nodal failure, than N0.

MASTECTOMY NOTE: STILL, cN+ is worse than pN+. Size > 5 cm matter. Basically if you have cancer left over, you have a bad time.

For residual node positive disease after neoadjuvant chemo, in these groups of patients with operable breast cancer the 8-year risk of LRR was 15% suggesting the need for PMRT in patients with residual node positive disease.

For those with residual node negative disease, the risk of LRR was < 10% suggesting no need for radiation.

Table 3. Multivariate Analysis of Independent Predictors of 10-Year LRR According to Type of Surgery

Variable	No. of Patients	LRR Events	HR	95% CI	*P*
Patients treated with mastectomy*	1,071	131			
Clinical tumor size > 5 *v* ≤ 5 cm†			1.58	1.12 to 2.23	.0095
Clinical nodal status cN(+) *v* cN(−)†			1.53	1.08 to 2.18	.017
Nodal/breast pathologic status					< .001
ypN(−)/no breast pCR *v* ypN(−)/breast pCR†			2.21	0.77 to 6.30	
ypN(+) *v* ypN(−)/breast pCR†			4.48	1.64 to 12.21	
Patients treated with lumpectomy plus breast XRT*	1,890	189			
Age ≥ 50 *v* < 50 years†			0.71	0.53 to 0.96	.025
Clinical nodal status cN(+) *v* cN(−)†			1.70	1.26 to 2.31	< .001
Nodal/breast pathologic status					< .001
ypN(−)/no breast pCR *v* ypN(−)/breast pCR†			1.44	0.90 to 2.33	
ypN(+) *v* ypN(−)/breast pCR†			2.25	1.41 to 3.59	

Abbreviations: HR, hazard ratio; LRR, locoregional recurrence; pCR, pathologic complete response; XRT, external radiation therapy.
*Includes only patients for whom all covariates are known.
†Category used as baseline for comparison of risk.

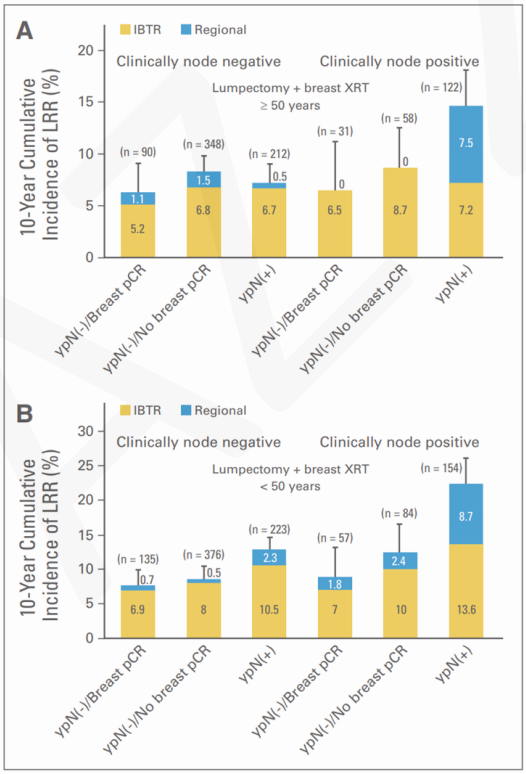


Fig 2. Ten-year cumulative incidence of locoregional recurrence (LRR) in patients (A) age ≥ 50 years treated with lumpectomy plus breast external radiotherapy (XRT) and (B) younger than age 50 years treated with lumpectomy plus breast XRT. IBTR, ipsilateral breast tumor recurrence; pCR, pathologic complete response [after neoadjuvant chemotherapy]; ypN, pathologic nodal status [after neoadjuvant chemotherapy].

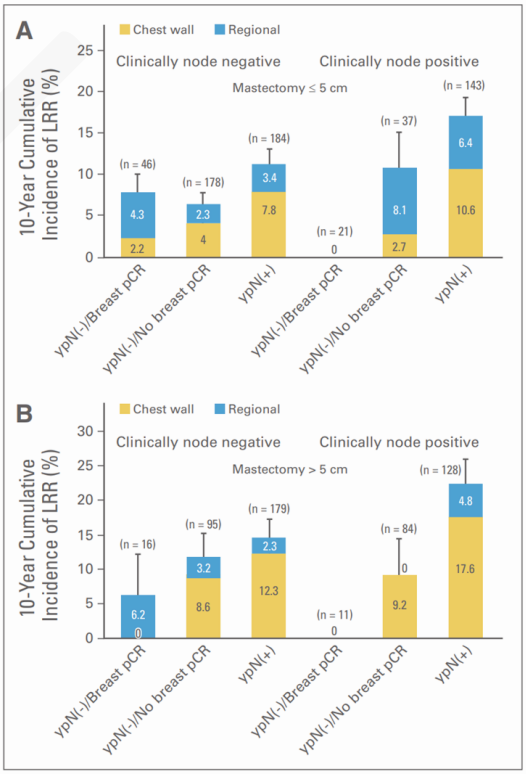


Fig 3. Ten-year cumulative incidence of locoregional recurrence (LRR) in patients with (A) ≤ 5-cm tumors treated with mastectomy and (B) > 5-cm tumors treated with mastectomy. pCR, pathologic complete response [after neoadjuvant chemotherapy]; ypN, pathologic nodal status [after neoadjuvant chemotherapy].

Nodal evaluation in NAC

German SenTA Trial
Prospectie 199 women median age 52 with cN+ → clipping of most suspicious LN before NAC. Then after NAC → marked LNed and SLN were excised = Targetd Axillary Dissection (TAD) → physician's choice of additional ALND.
A total of 182 patients (91.5%) had 1 to 3 suspicious LNs.
119 received TAD alone 80 received TAD → ALND.

Kuemmel, JAMA Surg 2023.
Unadjusted invasive DFS 82.4% TAD → ALND vs. 91.2% TAD alone (P = .04)
Axillary recurrence rates 1.4% TAD → ALND vs. 1.8% TAD alone (NS).
TAD alone was NS RR (HR 0.83; P = .69) or death (HR, 1.07; P = .91).
Similar results were obtained for 152 patients with clinically node-negative breast cancer after NAC
Invasive DFS: (HR, P = .77) OS (HR, 0.81; P = .74).
Conclusions and Relevance These results suggest that TAD alone in patients with mostly good clinical response to NST and at least 3 TAD LNs may confer survival outcomes and recurrence rates similar to TAD with ALND.

MSK RR NAC → SLNB alone
RR 610 patients cT1 to cT3 biopsy-proven N1 breast cancer.
All NAC → cN0 (cCR)→ SLNB with dual tracer mapping → **omission of ALND if 3 or more SLNs were identified and all were pN0**.
Metastatic nodes were not routinely clipped, and localization of clipped nodes was not performed.
91% = doxorubicin-based NAC 88% = adjuvant radiotherapy (RT) 70% = also received nodal RT.

Barrio, JAMA Oncol 2021.
cN0 = 555 (91%) → SLNB ≥3 SLNB neg = 234 (42%) without ALND.
The median (IQR) age of these 234 patients was 49 (40-58) years; median tumor size was 3 cm; 144 (62%) were ERBB2 (formerly HER2)-positive, and 43 (18%) were triple negative.
At a median follow-up of 40 months, there was 1 axillary nodal recurrence synchronous with local recurrence in a patient who refused RT.
Among patients who received RT (n = 205), there were no nodal recurrences.
Conclusions and Relevance This cohort study found that in patients with cN1 disease rendered cN0 with NAC, with 3 or more negative SLNs with SLNB alone, nodal recurrence rates were low, without routine nodal clipping. These findings potentially support omitting ALND in such patients.

SENTINA (SENTinel NeoAdjuvant) Trial
1737 patients in a 4-arm prospective study.
|1. cN0, SLNB → NAC |. If this SLNB is +, then |2. SECOND SLNB done after NAC |.
|3. cN+, NAC → if yp cCR → SLNB + ALND | Patients who < yp cCR, then |4. If yp cN1 → ALND only |.
1º is accuracy (FNR) of SLNB after NAC for patients who converted from cN1 → yp cN0 (ARM 3).

Kuehn Lancet, 2013.
ARMS 1 and 2 showed and **INITIAL SLNB** had a detection rate of 99.1%.
ARM 3, **the detection rate was 80·1%, with a FNR of 14·2%.** **FNR 24·3% (17 of 70) for 1 LN SLNB vs. 18·5% with 2 LN SLNB.**
ARM 2, the detection rate was 60·8%, with a FNR of 51·6%. This was for the SECOND SLNB.
Interpretation: Sentinel-lymph-node biopsy is a reliable diagnostic method before neoadjuvant chemotherapy. After systemic treatment for early sentinel-lymph-node biopsy, the procedure has a lower detection rate and a higher false-negative rate compared with sentinel-lymph-node biopsy done before neoadjuvant chemotherapy. These limitations should be considered if biopsy is planned after neoadjuvant chemotherapy.

TATA Memorial NAC → SLNB vs. LAS (Lower Axillary Sampling) → completion ALND all.
Prospective 751 NAC → cN0 patients. 730 used dual tracer technique. LAS = LN and fat below first intercostobrachial nerve.
Median tumor size 5 cm, and 71% were N1 or N2 on presentation.

Parmar, JCO 2020.
Post-NAC, 290 (38.6%) of 751 women had residual positive lymph nodes on pathology.
FNR of SNB (blue, hot, and adjacent palpable nodes) was 19.7% vs. 9.9% of LAS (*P* < .001).
If SNB was confined to blue/hot node, excluding adjacent palpable nodes, the FNR was 31.6%.
FNR could be brought down to < 8.8% ≥3 LNs were identified by LAS.
Conclusions: LAS is superior to SNB in identification rate, FNR, and negative predictive value in predicting node-negative axilla post-NACT. LAS can be safely used to predict negative axilla with < 10% chance of leaving residual disease.

ACOSOG z1071

Phase II, 756 women with cT0-4, cN1-2, M0, ECOG 0-1 breast cancer who (then received FNA to make it pN1-2) then received neoadjuvant chemotherapy (discretion of medical team) followed by both definitive surgery with SLN followed by ALND. cN1 = mobile, cN2 = fixed/matted. cN0 FNR of SLN = 10%.

Table 3. Factors Affecting the Likelihood of a False-Negative Sentinel Lymph Node Finding in the 310 Women With cN1 Disease at Presentation, 2 or More SLNs Examined, and Residual Nodal Disease After Neoadjuvant Chemotherapy

	False-Negative SLN Findings, No. (Total)	FNR (95% CI), %	Fisher Exact Test, *P* Value
Clinical T category prior to chemotherapy			
Tis, T0, T1, or T2	32 (225)	14.2 (9.9-19.5)	.18
T3 or T4	7 (85)	8.2 (3.4-16.2)	
Chemotherapy duration, mo			
≤4.0	20 (201)	10.0 (6.2-15.0)	.07
≥4.1	19 (109)	17.4 (10.8-25.9)	
Palpable, fixed, or matted nodes after chemotherapy[a]			
Yes	10 (52)	19.2 (9.6-32.5)	.17
No	28 (247)	11.3 (7.7-16.0)	
Mapping agents used			
Single	12 (59)	20.3 (11.0-32.8)	.05
Dual	27 (251)	10.8 (7.2-15.3)	
No. of SLNs examined			
2	19 (90)	21.1 (13.2-31.0)	.007
≥3	20 (220)	9.1 (5.6-13.7)	

Conclusions: Among women with cN1 breast cancer receiving neoadjuvant chemotherapy who had 3 or more SLNs examined, the FNR was not found to be 10% or less. Given this FNR threshold, changes in approach and patient selection that result in greater sensitivity would be necessary to support the use of SLN surgery as an alternative to ALND.

Boughey JAMA 2013

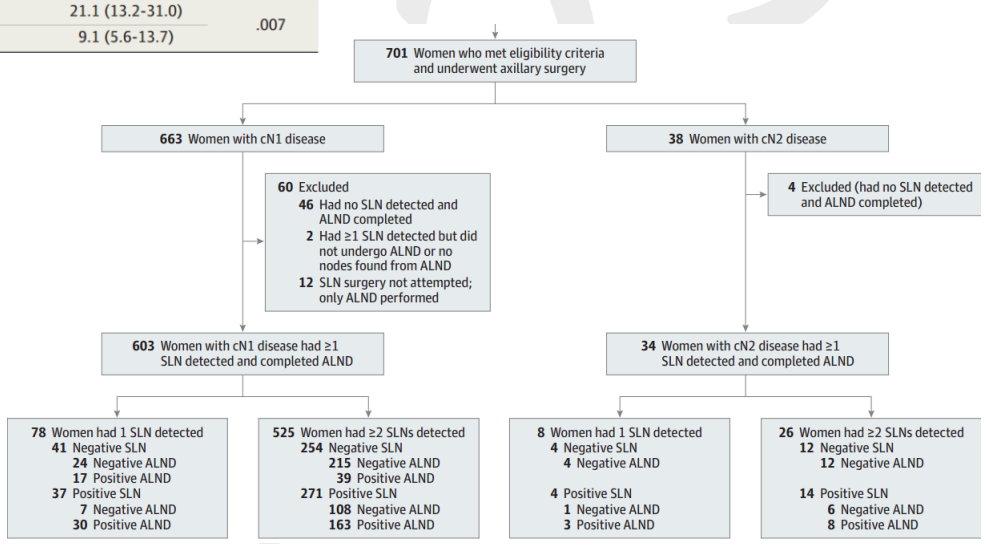
663 women cN1, 38 cN2. 98% underwent both SLN and ALND.

525 cN1 (≥ 2 SLNs excised → ALND), yielding a nodal pCR rate of 41.0%. Of 310 patients, residual nodal disease was confined to the SLNs in 108 patients (20.6%), confined to the nodes removed on ALND in 39 patients (7.4%), and present in nodes from both procedures in 163 patients (31.1%). Thus, 39/310 pts = FNR 12.6%.

26 cN2 (≥ 2 SLNs excised → ALND), pCR 46% (12 patients). 14 patients had residual nodal disease either confined to the SLNs (6 patients) or present in both SLNs and nodes removed on ALND (8 patients), yielding an FNR of 0%.

Of Note: The FNR was significantly lower when a dual-agent mapping technique (10.8%) vs a single-agent mapping (20.3%; P = .05).

FNR was ↓ when ≥ 3 SLNs are evaluated vs only 2 SLNs being evaluated. In NSABP B-27 trial, this issue was not addressed. The NSABP B-32 trial, in which SLN surgery was performed before any chemotherapy, reported that there was a significant decrease in the FNR as more SLNs were resected: 18% with 1 SLN resected, 10% with 2 SLNs resected, and 7% with 3 SLNs resected.



Pending Publications

NSABP B-51.
The NSABP-B51/RTOG1304 trial takes patients with involved axillary nodes before induction chemotherapy who DO convert to node negativity after neoadjuvant chemotherapy (ie path CR in the nodes) and randomizes them to regional RT vs not. For lumpectomy patients the randomization is whole-breast alone vs whole-breast and nodal RT. For mastectomy patients the randomization is no PMRT vs PMRT. The trial fundamentally asks the question of whether regional RT is warranted in cases where chemotherapy seems to have "cleared" axillary disease.

ALLIANCE
Alliance 011202 study takes patients with involved axillary nodes before induction chemotherapy who fail to convert to node-negativity post-induction, and randomizes them to axillary dissection vs not. Everyone on the trial gets comprehensive regional RT. There are options for intra-op vs post-op sentinel LN evaluation followed by registration and randomization. Note that in patients randomized to ax dissection, the contouring guidelines exclude the the dissected volume from RT (ie this area has been "addressed" by the dissection). The trial fundamentally asks the question of whether an ax dissection contributes to breast cancer control, or whether comprehensive RT alone is sufficient.

BOTH HAVE DOSE CONTRAINTS:
Mean Dose is less than 4 Gy, volume receiving more than 25 Gy (V25) is no more than 5% volume, and volume receiving more than 15 Gy (V15) is no more than 30% volume.

TAXIS Trial Deescalation ALND in cN+
296 patients Prospective → NAC 125 (42.2%) → pCR 24.0%.
Axillary metastases were detectable only by imaging in 145 (49.0%) patients.
Palpable in 151 (51.0%) patients → 63 underwent NACT → 21 had residual palpable disease after NACT.
Tailed Axillary Surgery (TAS) removed the biopsied and clipped node in 279 (94.3%) patients. In
225 patients with nodal disease at the time of surgery, TAS removed a median of five (IQR 3-7) nodes, two (IQR 1-4) of which were positive. Of these 225 patients, 100 underwent ALND after TAS, which removed a median of 14 (IQR 10-17) additional nodes and revealed additional positive nodes in 70/100 (70%) of patients. False-negative rate of TAS in patients who underwent subsequent ALND was 2.6%.

Neoadjuvant Immunotherapy (NAI)

Triple Negative Keynote 522

602 patients with untreated **Stage II or III TNBCa (T1cN1-2 or T2-4N0)**
2:1 Ratio | 1. NAC 4c x pembro + paclitaxel/carboplatin | 2. Placebo + paclitaxel/carboplatin | .
Pembro = q3 weeks (200 mg) or q6 weeks (400 mg)

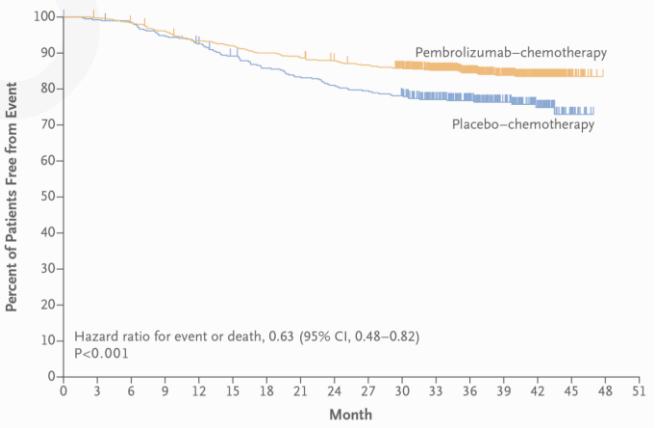
Then both group → an additional four cycles of pembrolizumab or placebo
Then both groups→ doxorubicin–cyclophosphamide or epirubicin–cyclophosphamide.
After definitive surgery, the patients received adjuvant pembrolizumab or placebo every 3 weeks for up to nine cycles.
1^{o} pCR at the time of definitive surgery and EFS in the intention-to-treat population.

Schmid, NEJM 2020. 1st interim analysis pCR
pCR 64.8% vs. 51.2% (SS). Absolute 13.6% (SS).
15.5 months adverse events 7.4% vs. 11.8% (SS) = either disease progression that precluded definitive surgery, had local or distant recurrence or a second primary tumor, or died from any cause.
Toxicity grade ≥ 3 78.0% vs. 73%.
Toxicity grade 5 death 0.4% (3 patients) and 0.3% (1 patient), respectively.
CONCLUSIONS
Among patients with early triple-negative breast cancer, the percentage with a pathological complete response was significantly higher among those who received pembrolizumab plus neoadjuvant chemotherapy than among those who received placebo plus neoadjuvant chemotherapy.

Schmid, NEJM 2022. 4th interim Analysis 3 years. EFS (See FOREST PLOT NEXT PAGE)
3-year EFS 84.5% vs. 76.8% (HR 0.63; P<0.001).
Adverse events occurred predominantly during the neoadjuvant phase and were consistent with the established safety profiles of pembrolizumab and chemotherapy.
CONCLUSIONS In patients with early triple-negative breast cancer, neoadjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab after surgery, resulted in significantly longer event-free survival than neoadjuvant chemotherapy alone.

Table 2. Adverse Events in the Combined Neoadjuvant and Adjuvant Phases (As-Treated Population).*

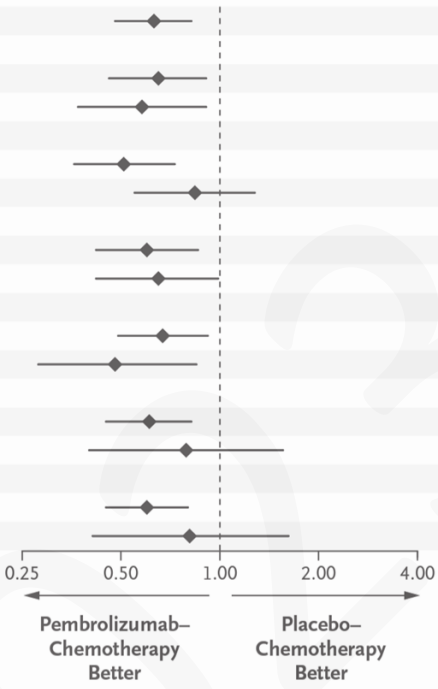
Event	Pembrolizumab–Chemotherapy (N=783)		Placebo–Chemotherapy (N=389)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	777 (99.2)	645 (82.4)	389 (100)	306 (78.7)
Treatment-related adverse event†	774 (98.9)	604 (77.1)	388 (99.7)	285 (73.3)
Nausea	495 (63.2)	27 (3.4)	245 (63.0)	6 (1.5)
Alopecia	471 (60.2)	0	220 (56.6)	0
Anemia	429 (54.8)	141 (18.0)	215 (55.3)	58 (14.9)
Neutropenia	367 (46.9)	270 (34.5)	185 (47.6)	130 (33.4)
Fatigue	330 (42.1)	28 (3.6)	151 (38.8)	6 (1.5)
Diarrhea	238 (30.4)	20 (2.6)	98 (25.2)	5 (1.3)
Alanine aminotransferase increased	204 (26.1)	43 (5.5)	98 (25.2)	9 (2.3)
Vomiting	200 (25.5)	19 (2.4)	86 (22.1)	6 (1.5)
Asthenia	198 (25.3)	28 (3.6)	102 (26.2)	9 (2.3)
Rash	196 (25.0)	12 (1.5)	66 (17.0)	1 (0.3)
Constipation	188 (24.0)	0	85 (21.9)	0
Neutrophil count decreased	185 (23.6)	146 (18.6)	112 (28.8)	90 (23.1)
Aspartate aminotransferase increased	157 (20.1)	20 (2.6)	63 (16.2)	1 (0.3)
Peripheral neuropathy	154 (19.7)	15 (1.9)	84 (21.6)	4 (1.0)
Immune-mediated adverse event‡	262 (33.5)	101 (12.9)	44 (11.3)	4 (1.0)
Hypothyroidism	118 (15.1)	4 (0.5)	22 (5.7)	0
Severe skin reaction	45 (5.7)	37 (4.7)	4 (1.0)	1 (0.3)
Hyperthyroidism	41 (5.2)	2 (0.3)	7 (1.8)	0
Adrenal insufficiency	20 (2.6)	8 (1.0)	0	0
Pneumonitis	17 (2.2)	7 (0.9)	6 (1.5)	2 (0.5)
Thyroiditis	16 (2.0)	2 (0.3)	5 (1.3)	0
Hypophysitis	15 (1.9)	10 (1.3)	1 (0.3)	0



ASCO RECOMMENDATION 2022

Korde, JCO 2022
For patients with T1cN1-2 or T2-4N0 (stage II or III), early-stage TNBC, the Panel recommends use of pembrolizumab (200 mg once every 3 weeks or 400 mg once every 6 weeks) in combination with neoadjuvant chemotherapy, followed by adjuvant pembrolizumab after surgery. Adjuvant pembrolizumab may be given either concurrent with or after completion of radiation therapy. Given that irAEs associated with pembrolizumab therapy can be severe and permanent, careful screening for and management of common toxicities are required. The ASCO guideline for management of irAEs in patients treated with immune checkpoint inhibitor therapy offers detailed practice recommendations and should be consulted by clinicians who prescribe pembrolizumab for patients with early-stage TNBC.

Subgroup	Pembrolizumab–Chemotherapy	Placebo–Chemotherapy	Hazard Ratio for Event or Death (95% CI)
	no. of patients with event/total no. (%)		
Overall	123/784 (15.7)	93/390 (23.8)	0.63 (0.48–0.82)
Nodal status			
Positive	80/408 (19.6)	57/196 (29.1)	0.65 (0.46–0.91)
Negative	43/376 (11.4)	36/194 (18.6)	0.58 (0.37–0.91)
Tumor size			
T1 to T2	64/581 (11.0)	59/290 (20.3)	0.51 (0.36–0.73)
T3 to T4	59/203 (29.1)	34/100 (34.0)	0.84 (0.55–1.28)
Carboplatin schedule			
Weekly	71/444 (16.0)	56/220 (25.5)	0.60 (0.42–0.86)
Every 3 wk	50/334 (15.0)	37/167 (22.2)	0.65 (0.42–0.99)
PD-L1 status			
Positive	98/656 (14.9)	68/317 (21.5)	0.67 (0.49–0.92)
Negative	25/128 (19.5)	25/69 (36)	0.48 (0.28–0.85)
Age			
<65 yr	103/700 (14.7)	79/342 (23.1)	0.61 (0.45–0.82)
≥65 yr	20/84 (24)	14/48 (29)	0.79 (0.40–1.56)
ECOG performance-status score			
0	101/678 (14.9)	80/341 (23.5)	0.60 (0.45–0.80)
1	22/106 (20.8)	13/49 (27)	0.81 (0.41–1.62)



IMpassion050 HER+ Trial
←R→ 454 > 2 cm T2-4, N1-3, M0 assigned 1:1 | 1. Atezolizumab | 2. placebo | + with ddAC→T + PH (pertuzumab-trastuzumab).
Post-surgery → al continue atezolizumab/placebo and PH (total: 1 year of HER2-targeted therapy).
If RCB > 0, residual disease can switch to ado-trastuzumab emtansine + atezolizumab/placebo.
1^{O} pCR and ypT0/is ypN0 rates in ITT and PD-L1+ populations.

Huober, JCO 2022.
pCR IIT population ~62% both. pCR PDL1+ population 64.2% vs. 72.5% (P = .1846).
Grade 3-4 and serious adverse events were more frequent in the atezolizumab versus placebo group.
Five grade 5 adverse events occurred (four neoadjuvant, one adjuvant; two assigned to study treatment), all with atezolizumab.
Overall, the safety profile was consistent with that of atezolizumab in other combination studies.
CONCLUSION Atezolizumab with neoadjuvant dose-dense doxorubicin/cyclophosphamide–paclitaxel and PH for high-risk, HER2-positive early breast cancer did not increase pCR rates versus placebo in the ITT or PD-L1–positive populations. PH and chemotherapy remains standard of care; longer follow-up may help to inform the long-term impact of atezolizumab.

Postmastectomy Radiation Therapy (PMRT)

Overview

2023 ARS Appropriateness Criteria

- **TOPIC 1: Limited LN+ 1-3**
  - EBCTCG Trial ←M→ of patients with 1-3 LNs showed SS ↓ LR (1/3) and ↓ BCM (1/5) with PMRT.
  - Li et. al[55] ←M→ T1-2 BCa with 1-3 LNs showed an absolute LRR ↓ of 6.9% without a benefit in OS.
  - Analysis of BIG 02-98[56] < 4 LN+ and T1-2 disease SS↓ LRR with PMRT (6.5% → 2.5%; P = .005) with no OS difference.
  - If Mastectomy with no ALND…
    - OTOASOR trial mastectomy and cT <3 cm, N0 BCa ←R→ | 1. Completion ALND | 2. RNI |. Additional positive LNs were found in 38.5% of the patients with ALND, but NS in terms of survival or axillary recurrence.
    - AMAROS trial cN0 T1-2 breast cancer and 1-3 LN+, 18% of whom underwent mastectomy. ←R→ | 1. completion ALND | | 2. axillary RT 50/25 | showed comparable axillary control, but significantly ↓ morbidity with PMRT.
    - Therefore, omission of ALND in the setting of positive sentinel LNs during mastectomy likely warrants the use of postmastectomy radiation to deliver regional LN irradiation.
  - Other topics…
    - SLN w/ micromets. Limited data. Probably no PMRT.
    - HER2+ breast cancer. RR of patients on HERA[57] trial treated with mastectomy and trastuzumab ± PMRT after a median follow-up of 11 years. PMRT patients were much more likely to have more involved nodes and larger tumor size. In LN+ 1-patients, PMRT was associated with ↑ LRR-free survival (97% with PMRT vs 90% without PMRT) and a trend to improved OS (87% vs 82%). Thus, PMRT provides at least local-regional control benefit in HER2-positive patients with limited nodal disease after mastectomy even in the setting of adjuvant trastuzumab.

- **TOPIC 2: "High Risk Node Negative"**
  - Overall, EBCTCG showed that patients with ALND and pN0 BCa had LRR of 1.4% and a higher mortality with PMRT. In contrast, patients with axillary sampling (<10 LNs excised) had a baseline LRR rate of 16.3% and PMRT ↓ recurrence (HR, 0.61; 95% CI, 0.47-0.80), but NS in survival. However, this analysis did include data from patients treated with older techniques and several studies omitted treatment of the chest wall.
  - TNBC….
    - ←R→ Wang et. Al.[58] showed that with TNBC early stage I-II BCa s/p mastectomy + systemic chemo., at 5-year follow-up, PMRT ↑ RFS 74.6% to 88.3% (P = .02) and ↑ OS 78.7% to 90.4% (P = .03.
    - RR Tseng et. Al[59] of a large national database, showed the benefit of PMRT on preventing LRR. This was highest for patients with luminal A subtype and lowest for patients with TNBC. None of the patients who received trastuzumab for HER2-positive disease had LRR.
  - RS…
    - Goodman et. Al.[60] showed with NCBD and SEER of T1-2N1 ER+ with known 21-gene RS, undergoing mastectomy with or without radiation, showed a significantly better OS in women with a low RS who underwent PMRT, but not in these with intermediate or high RS, suggesting radiation most benefits women at the lower risk of distant metastases.
  - pT3N0…
    - There are multiple RR that showed an OS benefit with PMRT.[61, 62, 63, 64]
    - **Comment**: T3N0 patients without risk factors have classically < 10% risk of recurrence without PMRT + RNI (Metaanalysis Clarke et al., PMID 16360786 and Retrospective Taghian et al., PMID 16921044). PMRT is not indicated for these patients due to low risk of LR, and potential/higher risk of DM as the first site of recurrence.
    - **Comment 2**: On the other hand, common BCa risk factors impact LR (e.g., ECOG Pooled Analysis, Fowble et al., PMID 3292711: Large Size, LN+, ER-, Necrosis, Pre-Fascia Involvement. Retrospective Jagsi et al., PMID 15990006: ≥ 2 cm size, margin < 2 mm, premenopausal, LVI).
  - +SM…
    - There are multiple RR that showed a potential LRR that needs to be addressed with PMRT in SM+ or close margin (<2 mm) after total mastectomy.[65, 66, 67, 68]

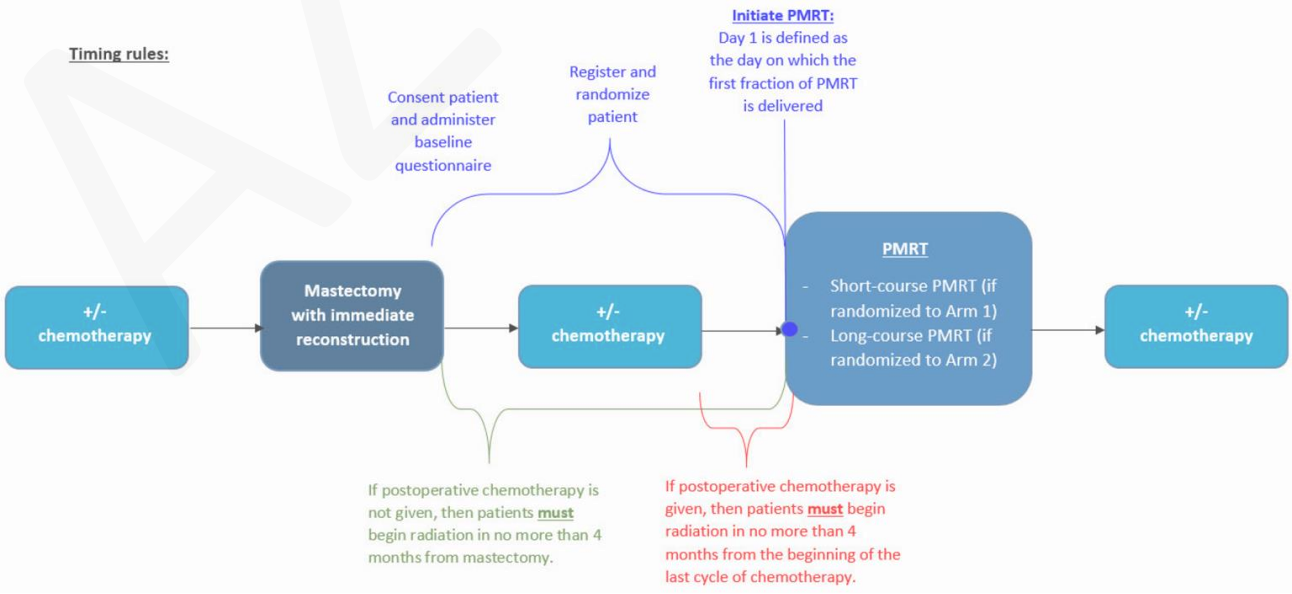
[55] Li Y, Moran MS, Huo Q, Yang Q, Haffty BG, Post-mastectomy radiotherapy for breast cancer patients with T1-T2 and 1-3 positive lymph nodes: A meta-analysis. PLoS One. 2013; 8: e81765
[56] Zeidan YH, Habib JG, Ameye L, et al. Postmastectomy radiation therapy in women with T1-T2 tumors and 1 to 3 positive lymph nodes: Analysis of the Breast International Group 02-98 trial. Int J Radiat Oncol Biol Phys. 2018; 101: 316-324
[57] Abi Jaoude J, de Azambuja E, Makki M, et al., Post-mastectomy radiation therapy in human epidermal growth factor receptor 2 positive breast cancer patients: Analysis of the HERA trial. Int J Radiat Oncol Biol Phys. 2020; 106: 503-510
[58] Wang S-L, Li Y-X, Song Y-W, et al., Triple-negative or HER2-positive status predicts higher rates of locoregional recurrence in node-positive breast cancer patients after mastectomy. Int J Radiat Oncol Biol Phys. 2011; 80: 1095-1101
[59] Tseng YD, Uno H, Hughes ME, et al., Biological subtype predicts risk of locoregional recurrence after mastectomy and impact of postmastectomy radiation in a large national database. Int J Radiat Oncol Biol Phys. 2015; 93: 622-630
[60] Goodman CR, Seagle B-LL, Kocherginsky M, Donnelly ED, Shahabi S, Strauss JB, 21-gene recurrence score assay predicts benefit of post-mastectomy radiotherapy in T1-2 N1 breast cancer. Clin Cancer Res. 2018; 24: 3878-3887
[61] Cassidy RJ, Liu Y, Kahn ST, et al., The role of postmastectomy radiotherapy in women with pathologic T3N0M0 breast cancer.
Cancer. 2017; 123: 2829-2839
[62] Almahariq MF, Quinn TJ, Siddiqui ZA, et al., Post-mastectomy radiotherapy is associated with improved overall survival in T3N0 patients who do not receive chemotherapy. Radiother Oncol. 2020; 145: 229-237
[63] Francis SR, Frandsen J, Kokeny KE, Gaffney DK, Poppe MM. Outcomes and utilization of postmastectomy radiotherapy for T3N0 breast cancers. Breast. 2017; 32: 156-161
[64] Chen J, Wu X, Christos P, Yan W, Ravi A. Adjuvant radiation therapy for T3N0 breast cancer patients older than 75 years after mastectomy: A SEER analysis. Clin Breast Cancer. 2018; 18: e967-e973
[65] Sheikh F, Rebecca A, Pickaj B, et al, Inadequate margins of excision when undergoing mastectomy for breast cancer: Which patients are at risk?.Ann Surg Oncol. 2011; 18: 952-956
[66] Al-Himdani S, Timbrell S, Tan KT, Morris J, Bundred NJ, Prediction of margin involvement and local recurrence after skin-sparing and simple mastectomy. Eur J Surg Oncol. 2016; 42: 935-941
[67] Glorioso JM, Gonzalez Juarrero AB, Rodysill BR, et al., Margin proximity correlates with local recurrence after mastectomy for patients not receiving adjuvant radiotherapy. Ann Surg Oncol. 2017; 24: 3148-3156
[68] Childs SK, Chen Y-H, Duggan MM, et al., Surgical margins and the risk of local-regional recurrence after mastectomy without radiation therapy. Int J Radiat Oncol Biol Phys. 2012; 84: 1133-1138

- **TOPIC 3: NAC → PMRT Recommendations**
  - The NSABP B18 and B27 trials ←R→ operable breast cancer to various NAC regimens.
    - Mastectomy patients did NOT get PMRT = 10-year LRR <10% in cN0 patients **with a pCR.**
    - Risk chest wall recurrence ↑ if tumors >5 cm and < pCR.
    - Regional recurrence ↑ if cN+ or residual LN+ after NAC.
    - Using an LRR rate of >10% as a threshold, these data suggest that patients with residual disease after NAC, especially residual positive nodes, will benefit from PMRT.
  - German Breast Group pooled data from 3 prospective ←R→ randomized trials of NAC in 817 noninflammatory patients with breast cancer who underwent mastectomy, 83% of whom had PMRT. In a retrospective analysis from these trials of 5-year LRR, PMRT lowered the HR by 50%.38 The effect was most pronounced in patients with cT3/4 disease and clinical node positive before NAC, whereas those with a pCR had no difference in LRR with or without PMRT.

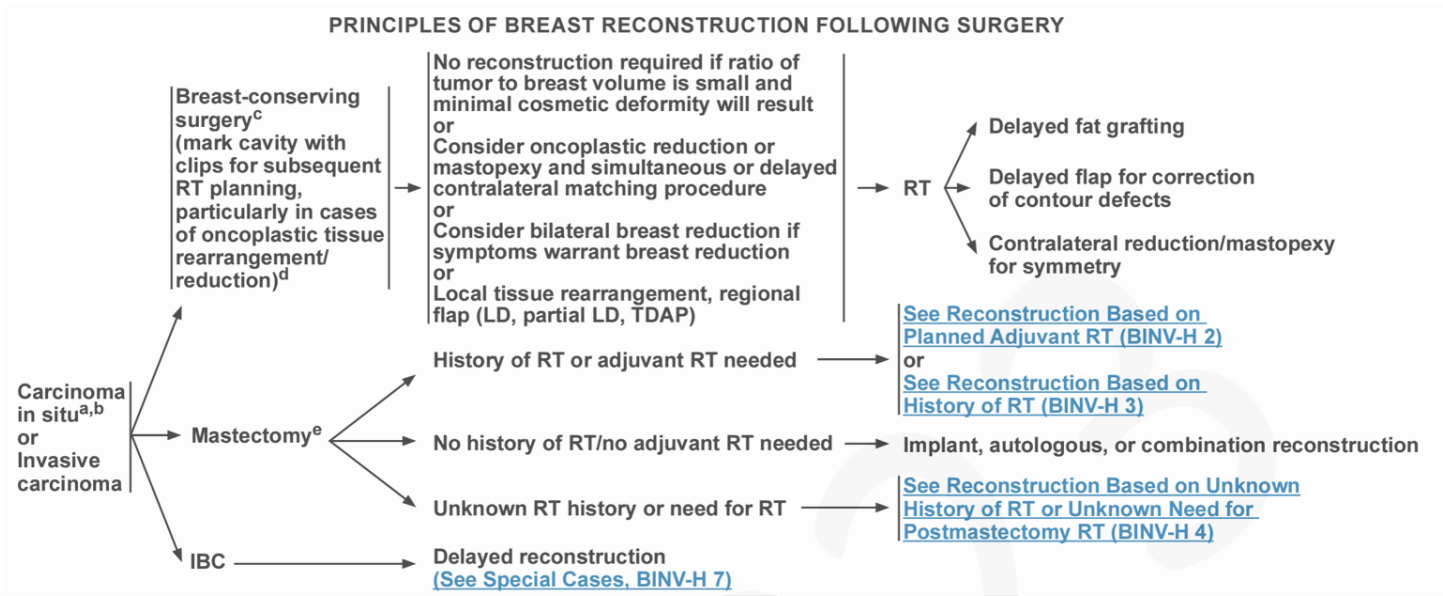
- **Technical Topic 1: Hypofractionated PMRT**
  - The Alliance for Clinical Trials in Oncology is currently conducting a phase 3 study of 880 participants the effect of a hypofractionated regimen of PMRT on patients who have breast reconstruction.
  - **Comment**: FABREC trial ←R→ post-mastectomy patients with immediate reconstruction to either | 1. conventional PMRT | 2. Hypofx PMRT |. Side effects were similar between the two arms.
  - **Comment 2**: MA.39 ←R→ lumpectomy and mastectomy patients with limited nodal burden. When enrolled, lumpectomy patients are randomized between WBRT vs. WBRT + RNI, and mastectomy patients are randomized between PMRT to the chest wall + RNI vs. no RT. The trial in short compares BCa recurrence-free intervals between patients receiving regional RT or not.
    - Patients who are randomized to receive RNI are permitted to receive either conventional (2 Gy/fx to 50) or hypofractionated (2.66 Gy/fx to 42.56) regimens with an option for boost and dose reduction by to the SCV and axillary nodes.
  - **Comment 3**: When applying good constraints, hypofractionated PMRT is very safe.
    - Personal constraints for RNI are as follows when treated with 3D (not IMRT):
      - Ipsilateral Lung V20 Gy < 35% (std), V17.5 Gy < 35% (hypofx), V5 Gy < 60% (all).
      - Variation acceptable: V20 = 35% → 40% and V5 = 60% → 65%.
      - Heart (L Side BCa) Mean < 3 Gy, V25 Gy < 10%. Variation Mean < 5 Gy
      - Heart (R Side Bca) Mean < 2 Gy, V25 Gy < 2%. Variation Mean < 5 Gy
      - Treatment structures (LNs, PTV breast) requires 95%/95% coverage (variation 90/90) with the IM LNs being the sole exception requiring only V95% > 95% (variation V90% > 80%).
      - Maximum dose for treatment structures constraints are 0.03 cc < ~115 ish%.
      - All maximum doses < 110% for all individual fields (107% is recommended if hypofx).

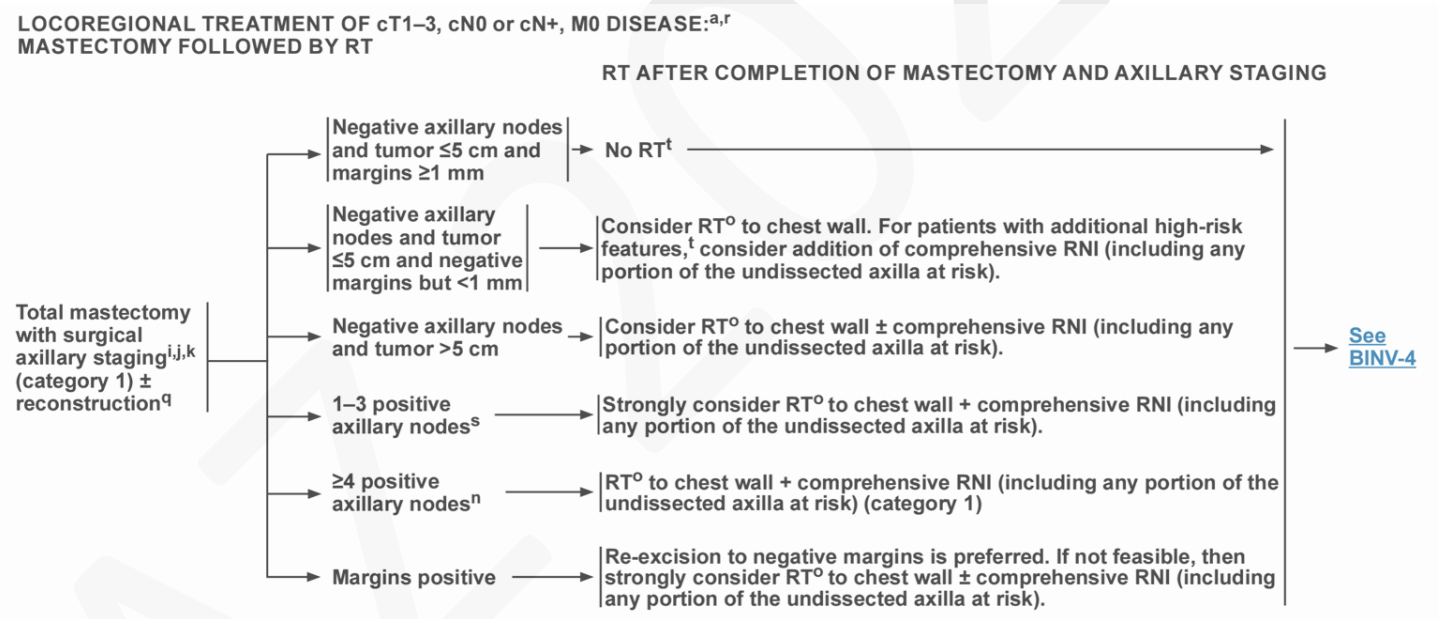
- **Technical Topic 2: Use of Bolus**
  - A survey[69] of radiation oncologists in 2004 revealed that 82% of North American responders reported always using bolus compared with 31% of European responders.
    - Frequency of bolus use was every day in 33% and alternate days in 46% of all responders. Bolus thickness was ≥1 cm in 48% and <1 cm in 35%. Only 7% of responders used bolus until brisk erythema or moist desquamation.
  - **Comment**: Although this topic has no consensus due to extensive institutional variability, most centers do offer some regimen.
  - **Comment 2**: On a standard PMRT plan, one way would be to 5mm bolus the first few fractions. If hypofractioned 4256 cGy in 16 fractions, bolus first 6 → no bolus last 10. If std fx 5000 cGy in 25 fractions, bolus first 10 → no bolus last 15. Other centers do QOD.

- **Technical Topic 3: Timing of PMRT with Reconstruction**
  - **Comment**: While this varies with institution, a good way to think about this is to follow a protocol like FABREC (see diagram below).



[69] Vu TT, Pignol J-P, Rakovitch E, Spayne J, Paszat L. Variability in radiation oncologists' opinion on the indication of a bolus in post-mastectomy radiotherapy: An international survey. Clin Oncol. 2007; 19: 115-119


PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY
Breast-conserving surgery[c] (mark cavity with clips for subsequent RT planning, particularly in cases of oncoplastic tissue rearrangement/ reduction)[d]
No reconstruction required if ratio of tumor to breast volume is small and minimal cosmetic deformity will result
or
Consider oncoplastic reduction or mastopexy and simultaneous or delayed contralateral matching procedure
or
Consider bilateral breast reduction if symptoms warrant breast reduction
or
Local tissue rearrangement, regional flap (LD, partial LD, TDAP)
RT
Delayed fat grafting
Delayed flap for correction of contour defects
Contralateral reduction/mastopexy for symmetry
Carcinoma in situ[a,b] or Invasive carcinoma
Mastectomy[e]
History of RT or adjuvant RT needed
See Reconstruction Based on Planned Adjuvant RT (BINV-H 2)
or
See Reconstruction Based on History of RT (BINV-H 3)
No history of RT/no adjuvant RT needed
Implant, autologous, or combination reconstruction
Unknown RT history or need for RT
See Reconstruction Based on Unknown History of RT or Unknown Need for Postmastectomy RT (BINV-H 4)
IBC
Delayed reconstruction
(See Special Cases, BINV-H 7)


LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE:[a,r]
MASTECTOMY FOLLOWED BY RT
RT AFTER COMPLETION OF MASTECTOMY AND AXILLARY STAGING
Total mastectomy with surgical axillary staging[i,j,k] (category 1) ± reconstruction[q]
Negative axillary nodes and tumor ≤5 cm and margins ≥1 mm
No RT[t]
Negative axillary nodes and tumor ≤5 cm and negative margins but <1 mm
Consider RT[o] to chest wall. For patients with additional high-risk features,[t] consider addition of comprehensive RNI (including any portion of the undissected axilla at risk).
Negative axillary nodes and tumor >5 cm
Consider RT[o] to chest wall ± comprehensive RNI (including any portion of the undissected axilla at risk).
1–3 positive axillary nodes[s]
Strongly consider RT[o] to chest wall + comprehensive RNI (including any portion of the undissected axilla at risk).
≥4 positive axillary nodes[n]
RT[o] to chest wall + comprehensive RNI (including any portion of the undissected axilla at risk) (category 1)
Margins positive
Re-excision to negative margins is preferred. If not feasible, then strongly consider RT[o] to chest wall ± comprehensive RNI (including any portion of the undissected axilla at risk).
See BINV-4

Add. PMRT For/Against

- Overall indications:
  - **Classically Absolute:** Stage III – IV (think: pN2 ≥ 4 pLN+, T3-4).
  - **Highly Consider:** + margins, gross ECE > 2mm, neoadjuvant chemotherapy with residual disease, T3N0.
  - **Relative**: age < 40, cLN+, pN+ 1-3, < 10 ALN dissected, ER -, LVSI +, G3, multicentric disease, muscle involvement, Her2+, ORS > 18.
- Not indicated:
  - T1, T2, N0, Ni, Nmic

LN status		Recommendations
Negative Axillary LN	Tumor >5cm or + margins	**RT to chest wall** **Consider** RT to supraclavicular area + IM nodes
	Tumor ≤5cm and ≥1mm margin	**No RT**
1-3 Axillary + LNs	**Consider** - RT to chest wall + supraclav +/- IM nodes	
≥4 Axillary + LNs	**RT to chest wall + supraclav +/- IM nodes**	

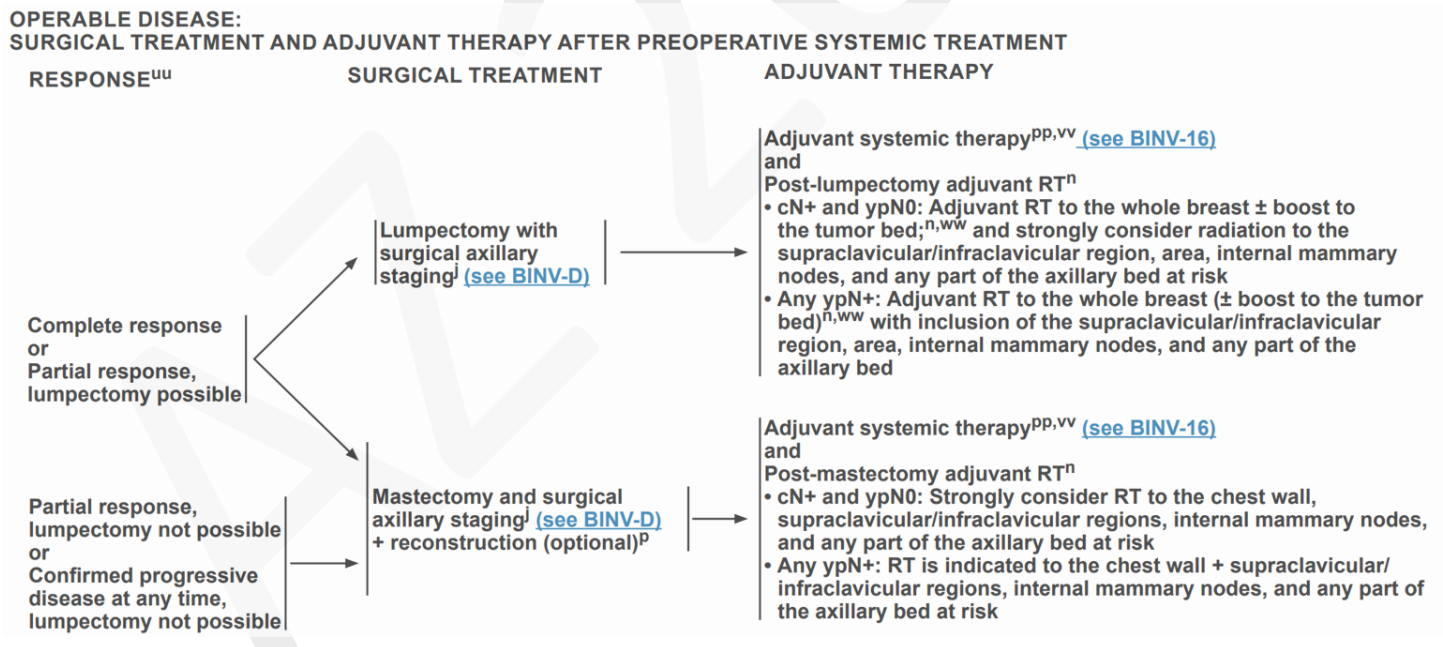
Some Basic Thoughts:

Data supporting PMRT in "Grey Areas"

- NSABP-04 – for cN0 patients, 40% were actually pN+. PMRT could account for the benefit seen in cN0 patients randomized to PMRT.
  For pN0 patients, radical mastectomy axillary failure rates (100% cN+ → 75% pN+ → 1% axillary recurrence. Thes patients failed in the SCV where surgery couldn't access. But for mastectomy → PMRT patients = 7% axillary recurrence.
- Combined 82 B/C Trials – LLR of 1-3 LN+ patients were SS in favor of PMRT. Small number needed to treat to avoid LRR (5) or death (10).
- EBCTCG 2014 ←M→ - LRR and BCaM of 1-3 LN+ patients were in favor of PMRT. Even patients with 1 LN (in forest plot favored SS PMRT for LRR).
  - Criticism: EBCTCG heavily depended on 82 B/C patients, which many patients had < 4 LN removed (median 7 LNs), Tamoxifen was given for only 1 year, and chemo was CMF.
- Taiwan RR shows with Mastectomy w/o PMRT has ↑ LRR if 3 of 4 RFs (age <40 years, tumor ≥ 3 cm, ER neg, and LVIS pos) → 66% vs. 7.8%.
- BIG 02-98 trial and HERA subset showed that 10-year LRR ↑ with PMRT, which benefited TNBC patients the most.

Data against PMRT in "Grey Areas"

- RXPONDER Secondary Analysis – ER+Her-, LN+ #1-3, ORS ≤ 25. Mastectomy ± PMRT low benefit in 5 years.



ECOG Pooled Analysis, Fowble JCO 1988
RR 627 treated with mastectomy → C (without RT). Eligibility < 66 yo, primary disease confined to breast and ipsilateral axilla w/o fixation, arm edema, T4d, ulceration, skin nodules, T4b, or skin infiltration.
Conclusion: Patients with four to seven positive nodes or tumor size greater than or equal to 5 cm had a chance of developing an isolated LR recurrence almost equal to the risk of distant metastases. *These findings suggest a potential for improved survival in this subset of patients with the addition of postmastectomy radiation to chemotherapy* and continue to emphasize the presence of a group of patients at high risk for isolated LR recurrence despite adjuvant chemotherapy.

Factors Associated with LRR

	LRR	p		LRR	p		LRR	p
Tumor			**ER**			**Pec Fascia Involvement**		
≤ 2 cm	9%	0.004	+	8%	0.02	+	29%	0.007
2-5 cm	9%							
> 5 cm	19%		-	14%		-	10%	
N			**Necrosis**					
1-3	7%	0.006	+	17%	0.002			
4-7	15%							
≥ 8	15%		-	8%				

Retrospective Review Purpose: PMRT ↓ LRR and ↑ survival. Does node negative patients benefit from PMRT?
RR 877 cases of node-negative breast cancer treated with mastectomy, without adjuvant radiation, from 1980 to 2000.

Jagsi, IJROBP 2004
10-year cumulative incidence of LRR as first event was 6.0%. Factors: ≥ 2 cm size, margin < 2 mm, premenopausal, LVI.
10-year LRR **0 RF = 1.2%** **1 RF = 10%** **2 RF = 17.9%** **3 RF = 40.6%**
The chest wall was the site of failure in 80% of patients.
Conclusion: Postmastectomy radiation therapy has not been recommended for node-negative patients because the LRR rate is low in that population overall. This study suggests, however, *that node-negative patients with multiple risk factors, including close margins, T2 or larger tumors, premenopausal status, and LVI, are at higher risk for LRR and might benefit from PMRT*. Because the chest wall is the most common site of failure, treating the chest wall alone in these patients to minimize toxicity is reasonable.

SEER analysis PMRT in T-12 N+. 18038 women with T1-2 N+ breast cancer s/p mastectomy (only 2648 women 15% received PMRT.
Q: In smaller tumors, at what nodal status threshold would there be a nodal benefit in PMRT?
Conclusion: that PMRT only seen in ≥7 LN +. Propensity scored matched!

TNBC Prospective Chinese
←R→ 681 **TNBC** stage I-II breast cancer received mastectomy | 1. C alone | 2. C → RT |.
All total mastectomy and partial axillary dissections. 86.1% of the patients were without positive lymph nodes. Must be M0 and < 70 yo.
Chemo choice 1 CMF x 6c; day 1 and q21 days (cyclophosphamide 600 mg/m2 , methotrexate 40 mg/m2, 5-fluorouracil 600 mg/ m2)
Chemo choice 2 CAF (cyclophosphamide 500 mg/m2, doxorubicin 50 mg/m2, 5-fluorouracil 500 mg/ m2).
In the radiotherapy group, radiotherapy was started 2–3 weeks after the sixth cycle of chemotherapy.
RT 6 MeV X-ray, the prescribe dose was 50 Gy/25fractions, five fractions per week, Regional nodal irradiation, was added as clinically indicated
Recurrence-free survival (RFS) and overall survival (OS) were estimated. Simultaneously local and systemic toxicity were observed.

Table 2
Distant metastasis in TNBC patients.

	Adjuvant chemo		Adjuvant chemo + radio		*P*
	No. (n = 33)	%	No. (n = 26)	%	
Time to metastasis					
<2 years	19	57.6	9	34.6	<0.05
⩾2 years	14	42.4	17	65.4	
No. of metastasis					
1–2	8	24.2	10	38.5	<0.05
>2	25	75.8	16	61.5	
Place of metastasis					
Bone	2	6.1	2	7.7	>0.05
Lung	20	60.6	14	53.9	>0.05
Liver	8	24.2	8	30.8	>0.05
Brain	3	9.1	1	3.9	>0.05

Abbreviation: Chemo plus Radio denote Chemotherapy plus Radiotherapy.

Wang, Radiother Oncol 2011. After a median follow-up of 86.5 months
5-year RFS = C alone 74.6% vs. C→RT 88.3 (p = 0.02).
5-year OS 78.7% vs. 90.4% (p = 0.03).
No severe toxicity was reported.
CONCLUSIONS: Patients received standard adjuvant chemotherapy plus radiation therapy was more effective than chemotherapy alone in women with triple-negative early-stage breast cancer after mastectomy.

SUPREMO Trial **Q: What about intermediate risk (early stage N+ or high-risk node negative).**
←R→ 1688 > 18 yo intermediate-risk breast cancer (pT1–2N1; pT3N0; or pT2N0 if also grade III or with lymphovascular invasion).
All mastectomy → if pN+ axillary surgery → RANDOMIZED | 1. PMRT (50 Gy in 25 fx, 45 Gy in 20 fx, or 40 Gy in 15 fx) | 2. No RT |.
1^{O} 10-year OS.

Velikova, Lancet 2018. 2-year QOL only.
989 (79%) of 1258 patients from 111 UK centres consented to participate in the QOL substudy.
2-year "chest wall symptoms" worse with RT mean score 14·1 vs. 11·6, p = 0.016.
However, there was an improvement in both groups between years 1 and 2 (visit effect −1·34, 95% CI −2·36 to −0·31; p=0·010).
No differences were seen between treatment groups in arm and shoulder symptoms, body image, fatigue, overall QOL, physical function, or anxiety or depression scores.
Conclusion: The main finding of this QOL substudy of the SUPREMO trial is that postmastectomy radiotherapy was associated with **worse self-reported chest wall symptoms** (pain, swelling, oversensitivity, and skin problems in the area of the affected breast) than no radiotherapy, although these symptoms improved over time

10 YEAR RESULTS PENDING UNTIL PROBABLY 2026

N0 Disease:

EBCTCG (Clarke 2005). Metaanalysis to assess local control and long term mortality. Information available on 42 000 women in 78 RTC. 24 different types of local treatments identified, but the two most studied are RT after BCS (7311 pts in 10 trials) and RT after mastectomy and axillary clearance (9933) pts in 25 trials.
Results: RT after BCS: In short, the ↓ in 5-yr LR (mainly in the conserved breast) by RT is SS (p < 0.00001) in every trial. Although BCaM in 15 years is not SS in any one trial, the metaanalysis of them all is SS (BCa death rate ratio 0.83, SE 0.05, 95% CI 0·75–0·91, 2p=0·0002), indicating ↓ of ~ 1/6 in the annual breast cancer mortality rate.
RT (usually chest wall, axillary LN, supraclavicular fossa, and IMN) after mastectomy and axillary clearance, for node - women is 5-yr LR 6 → 2% (2p=0·0002), and no SS ↓ in 15-year BCaM. For node +, 5-yr LR 23 → 6% (SS). Note: proportional ↓in LRR is ≈ in node + or -, but absolute 5-yr gain is much larger in node + (4 vs 17%). 15-yr BCaM with RT 60 → 55% (2p = 0.0002).
Conclusion: ↓ 5yr LRR + RT similar among LN - post-BCS trials and among LN + post-mastectomy trials. 15yr BCaM lower for BCS node – than for mastectomy node + patients, but the absolute ↓ in RT is the same 5%. Thus, ≈ ↓ 5yr LRR and the absolute ↓ 15yr BCaM suggests that avoiding recurrence in conserved breast ≈ avoiding in other locoregional sites in terms of effect on long-term survival.

NHS Trust, UK (Rowell 2009).[70] Metaanalysis.
Results: Risk factors LRR: LVI, Grade 3, T2+, close SM, age < 50, premenopausal. Rate of LRR by risk factors: 0 RF 5% | 1 RF 10% | ≥ 2 RF ≥ 15%.
Metaanalysis of 3 RTC of mastectomy and axillary clearance (667 patients), RT ↓ risk of LRR by 83% (p < 0.00001) and ↑ 14% survival (p = 0.16).
Conclusion: Use of PMRT in N0 women requires re-evaluation; RT should be considered for those with ≥ 2 risk factors.

T1-2N0:

Ankara Oncology Hospital; Turkey (Yildirim 2007). Retrospective 502 patients, T1-2 tumors. F/U 6.5 years, 14 (2.8%) pts had LR and 55 (11%) had distant recurrence (DR). All patients complete ALND, s/p mastectomy, no RT.
Results: SS risk factors for DR: cErbB2 status (HR 10.0) = LVI (HR 10.0) > ER status (HR 6.3) > grade (HR 2.4) > tumor size (HR 1.2).
SS for LR in ≤ 40 yr pts is LVI (HR 9.0) > tumor size 2+cm (HR 5.4). SS for LR ≥ 40 yr pts is LVI (HR 18) > tumor size 3+cm (HR 8.6) > grade (HR 7.0).
Conclusions: Patients that have a high risk for LR based on age, LVI, tumor size, and ± grade, may benefit from postmastectomy RT.

T3N0:

Fox Chase; SEER (Johnson 2014). Retrospective 2525 women. T3N0 from 2000 to 2010 s/p modified radical mastectomy. 1063 received PMRO. F/U 4.5 years. 1^{O} endpoints were OS and CSS. Results: Univariate PMRT ↑ OS 62% → 77% and CSS 82.4% → 85% (both p < 0.01) at 8 years. At multivariable, PMRT ↑ OS (HR 0.63, p < 0.001) and↑ CSS (HR 0.77, p = 0.045). Low grade (p < 0.01) and being married (p = 0.01) also ↑ CSS.
Conclusions: PMRT should be strongly considered in T3N0M0 patients.

Although Fox Chase's most recent retrospective study suggests a benefit for PMRT in T3N0 patients, previous studies argue otherwise. A SEER Yale study in 2008 suggests that PMRT in this patient subset is not associated with an ↑ in OS, while a SEER Colorado study in 2008 concludes that there is no ↑ CSS despite an increase in 10-year OS 58 → 71% (SS). Because these three studies all incorporate from the SEER database, patient selection bias is most likely the reason for such disparate data. Other notable studies have shown that PMRT should be considered in grade 3 cancers or patients not undergoing hormonal therapy (Goulart 2011). Most studies agree that LVI is highly correlated with poor outcome (Floyd 2006) and such patients must be considered for PMRT.

Fox Chase (Abramowitz 2009) argues that LVI (and also inflammatory breast cancer) are independent predictors or recurrence after PMRT. A Harvard study (Childs 2012) adds that patients with positive margins have a 5 yr LRR of 6.2%, which is much higher than close margins 1.5% and negative margins 1.9%. Although these studies were not solely with T3N0 patients, these criteria must also be considered in this subclass.

[70] http://www.ncbi.nlm.nih.gov/pubmed/18996609?dopt=Abstract

PMRT and Chemotherapy:

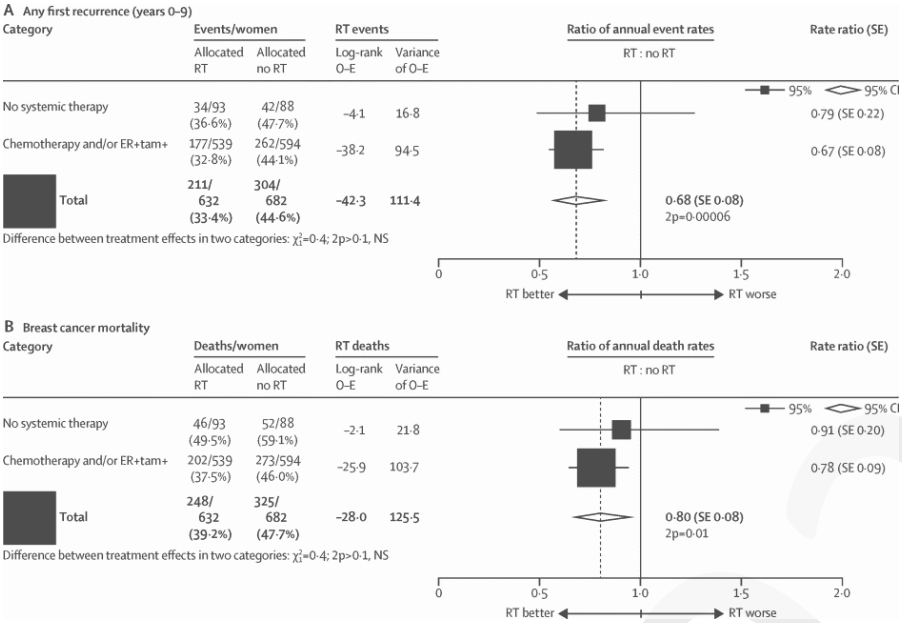
Scottish Cancer Registry (McArdle 2010). RTC 3 arms, 322 women (between 1976 – 1982), ≤ 70 yrs with pN+. 1) PMRT, 2) PMRT → CMF, 3) CMF alone. Median F/U 27 years. Results: 260 (81%) patients died, 204 (78% died from breast cancer). No Δ in all-cause mortality or cancer specific survival in each of the 3 treatment arms. LN+ ≥3 ↑ BCaSM (HR 1.88, SS) after adjust for age, socioeconomic status, and adjuvant TX.

AC→T if you can't handle it, you get CMF. Triple negative you get CMF.

MD Anderson (McGuire 2007)[71] Retrospective. 106 Locally advanced BCa (LABCa) TX neoadjuvant chemo → pCR on mastectomy.
Clinical stages at Dx I: 2%, II: 31%, IIIA: 30%, IIIB: 25%, and IIIC: 11%. **No inflammatory**. Chemo 92% anthracycline-based, 38% also taxane.
Post-mastectomy RT in 72 pts (68%). Median F/U 5.2 years. Results: 10-year LR failure: Stage I-II 0% for both w/wo RT.
Stage III: significantly improved w/ RT (7.3% +/- 3.5%) vs without RT (33.3% +/- 15.7%), p = 0.040. Within this cohort, RT also ↑ DSS and OS.
Conclusion: PMRT provides significant clinical benefit for Stage III patients with pCR after neoadjuvant chemo and mastectomy

NCI (Low 2004) Retrospective. 107 patients with Stage III BCa (**46 inflammatory**, IBCa) prospectively treated on protocol. Patients were treated to best response with cyclophosphamide, doxorubicin, methotrexate, fluorouracil, leucovorin, and hormonal synchronization with conjugated estrogens and tamoxifen. Median F/U 16.8 years.
∴ Initial chemo (CAFM), if pCR → PMRT concurrent with CAF chemo and conjugated hormones;
if pPR → mastectomy/ALND and PMRT concurrent with CAF chemo and conjugated hormones.
Results: Median OS: IBCa 3.8 yrs | IIIA 12.2 yrs | IIIB 9.0 years. 15-year OS: 20% vs. 50% vs. 23%. + dermal lymph invasion did not change the probability of survival in clinical IBCa patients. Conclusions: pCR not associated with improved survival. IBCa have poor outcome.

[71] http://www.ncbi.nlm.nih.gov/pubmed/17418973?dopt=Abstract



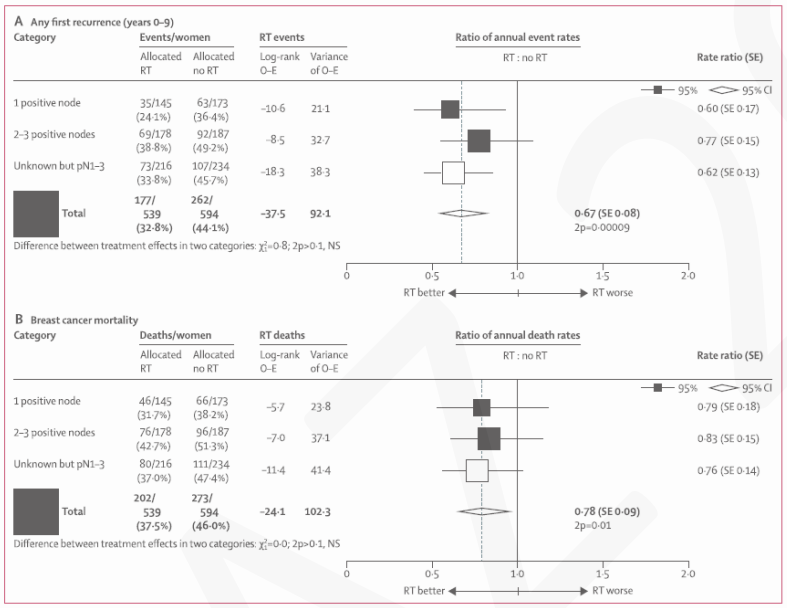


Figure 6: Effect of radiotherapy (RT) after mastectomy and axillary dissection on overall recurrence during years 0–9 and on breast cancer mortality for the entire follow-up in 1133 women with one to three pathologically positive nodes (pN1–3) in trials in which systemic therapy was given to both randomised treatment groups, by number of positive nodes
See also appendix pp 23–26. NS=not significant. SE=standard error.

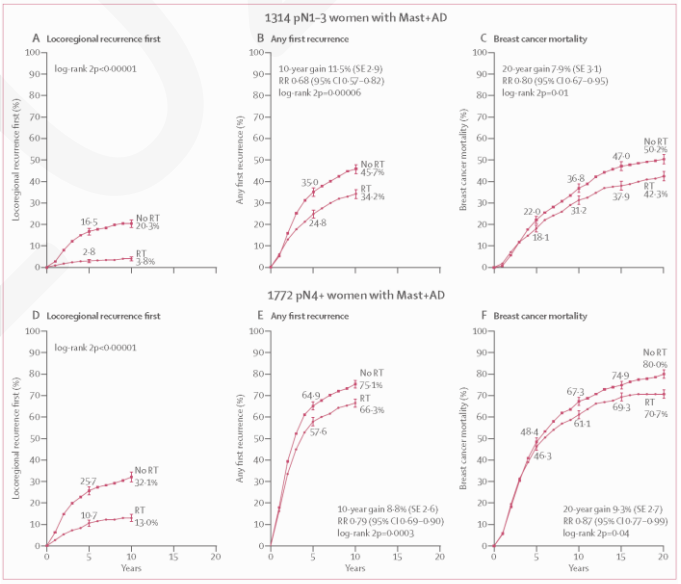


Figure 3: Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional and overall recurrence and on 20-year risk of breast cancer mortality in 1314 women with one to three pathologically positive nodes (pN1–3) and in 1772 women with four or more pathologically positive nodes (pN4+)

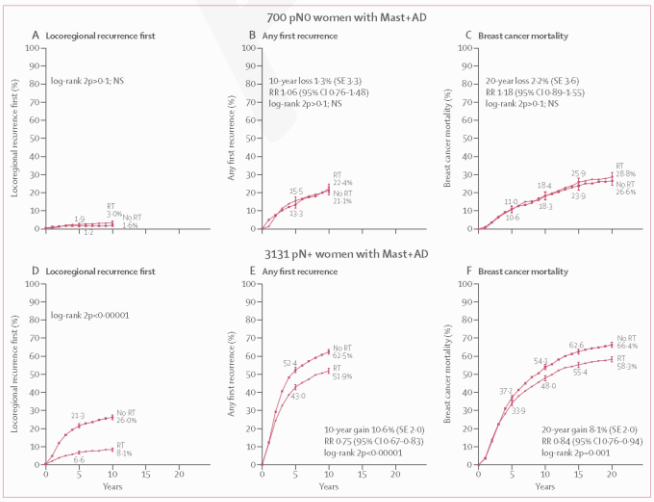


Figure 2: Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional and overall recurrence and on 20-year risk of breast cancer mortality in 700 women with pathologically node-negative (pN0) disease and in 3131 women with pathologically node-positive (pN+) disease

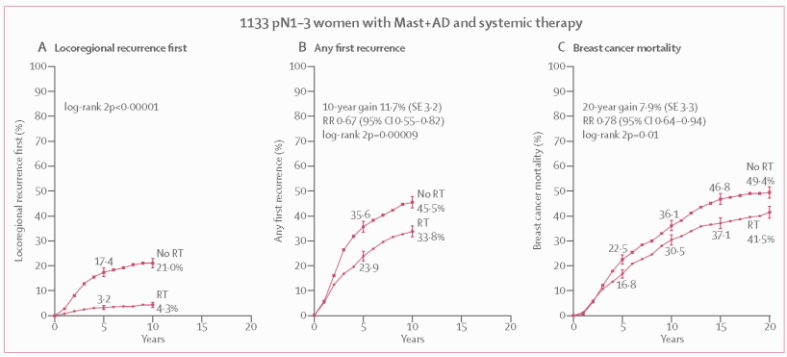


Figure 5: Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional and overall recurrence and on 20-year risk of breast cancer mortality in 1133 women with one to three pathologically positive nodes (pN1–3) in trials in which systemic therapy was given to both randomised treatment groups

Metaanalysis:

Early Breast Cancer Trialists' Collaborative Group (Lancet 2014). 8135 women from 22 RTC during 1964-1986 of ± RT to chest wall and regional lymph nodes s/p mastectomy. 5821 women with node-positive disease, 3131 (54%) had ALND. Follow-up 10 years. Chemo usually cyclophos, MTX, 5-FU.

Of the 3131:
For pN0 n = 700, RT had no effect on LRR, overall recurrence, or BCaSM.
For pN+ (1-3 nodes) n = 1314 **(SEE GRAPH)**, RT ↓ LRR (3.8% vs 20.3%), ↓ overall recurrence (RR 0.68), and ↓ BCSM (RR 0.80). In these n = 1314 women, ± RT was SS (LRR 1st 9 yrs and BCaSM) ONLY in subset of + chemo ± tamoxifen pts. Combined data, however, shows SS regardless of systemic TX. Patients who didn't receive systemic tx, CI 95% includes 1.
For pN+ (4+ nodes) n = 1772, RT ↓ LRR (13.0% vs 32.1%), overall recurrence (RR 0.79), and BCSM (RR 0.87).

Conclusion: s/p mastectomy and ALND, RT ↓ LRR and BCa mortality in the women with one to three positive lymph nodes **regardless if** systemic therapy was given.

Danish trial 82b (1982-89) Importance: Previous trials of post-operative RT had not used chemotherapy.
←R→, 1708 pts. **Premenopausal** high-risk pts, ≥ 1 risk factors (positive axillary LN, tumor > 5 cm, invasion of skin or pectoral fascia).
Surgery → **1.** RT + CMF chemotherapy **2.** CMF alone **3.** CMF + tamoxifen* *3rd group was stopped after 1986 due to higher mortality.
Surgery = total mastectomy + ALND (level I and part of level II). Median # of LN removed was 7 (probably understaged).
RT was to chest wall, SCLV fossa, infraclavicular LN, axillary, and IMN in first 4 intercostal spaces. 50 Gy in 25 fx (or 48 Gy in 22 fx, 4days/wk).
Recommended use of anterior electron field to treat CW and IMN.
Chemotherapy: 8 cycles of CMF with RT, or 9 cycles if given alone. RT was sandwiched between first 2 cycles of chemo.

Overgaard, NEJM 1997. Median f/u 114 months.

	10-year LRF	10-year DFS	10-year OS
CMF + RT	9%	48%	54%
CMF	32%	34%	45%
P	< 0.001	< 0.001	< 0.001

Variable	10-yr Actuarial Disease-free Survival		10-yr Actuarial Overall Survival	
	Radiotherapy + CMF	CMF alone	Radiotherapy + CMF	CMF alone
	percent			
No. of positive nodes				
None	74	62	82	70
1–3	54	39	62	54
>3	27	14	32	20

Therefore, a subgroup analysis was done in the cohort of 1,152 patients that had ≥8 lymph nodes removed (Overgaard et al. Rad Onc 2007). In the group of patients with 1-3 positive lymph nodes, there was still a benefit in outcomes.

- 15-year locoregional failure was 4% (with RT) vs. 27% (no RT), p<0.001.
- 15-year overall survival (OS) was 57% (with RT) vs. 48% (no RT), p=0.03.

In patients with ≥4 lymph nodes involved, there was also a benefit to RT.

- 15-year locoregional failure was 10% (with RT) vs. 51% (no RT) vs. p<0.001.
- 15-year overall survival (OS) was 21% (with RT) vs. 12% (no RT), p=0.03.

Danish trial 82c (1982-90)
←R→ 1375 pts. **Postmenopausal** high-risk pts (SAME RISK FACTORS)
Surgery → **1.** RT + Tam. **2.** tamoxifen (30mg for 1 yr concomitantly with RT).
Surgery and RT same as Danish 82b.

Overgaard, Lancet 1999.

	Disease-free survival (%)		Overall survival (%)	
	10-years value*		10-years value*	
	RT+T	T alone	RT+T	T alone
Positive nodes				
None	43	40	56	55
1–3	44	31	55	44
>3	18	6	24	17

	LRR as 1st recurrence	DM as 1st recurrence	10-year DFS	5-year OS	10-year OS
Tam + RT	**8%**	**39%**	**36%**	**63%**	**45%**
Tam	**35%**	**25%**	**24%**	**62%**	**36%**
P	**< 0.001**	-	**< 0.001**	-	**0.03**

Conclusion: improved survival with post-op RT.
PROBLEM: ALSO ONLY MEDIAN 7 LN: From Haffty "They figured out LN+ by just cutting it in half and If there is + lN or not. Nowadays, there is more extensive LN evaluation than just cutting it in half."

Combined Danish 82b and 82c
Overgaard, Radiotherapy and Oncology 2007 (https://pubmed.ncbi.nlm.nih.gov/17306393/)
Subgroup analysis. 1152 pts with **positive nodes and ≥ 8 nodes removed** (i.e. above the median of 7). 552 pts with 1-3 positive nodes, 600 pts with 4+ positive nodes.

	15-year OS ALL	15-year OS 1-3 LN+	15-year OS 4+ LN+	15-year LRF 1-3 LN+	15-year LRF 4+ LN+
Systemic + PMRT	39%	57%	21%	4%	10%
Systemic alone	29%	48%	12%	27%	51%
	0.015	0.03	0.03	< 0.001	< 0.001

Greater survival benefit for smaller tumors (≤ 2cm) but greater LRR benefit for larger tumors. ↓ # needed to treat to avoid LRR (5) / death (10).
Of note, The 57% and the 27% are higher than US trials!
Conclusion: Similar and significant improvement in survival in irradiation pts in both groups (absolute survival of 9% at 15 yrs). Receptor status;

Kyndi, JCO 2008. Subset analysis.
1000 patients analyzed with tissue microarray → 4 groups: ERPR+/HER2- (63%), Triple Pos (10%), Triple Neg, 15%, and Her2+ (12%).
17-years Follow-up.
Outcome: Improved OS after PMRT only in patients Rec+/her2-. No OS benefit for patients that were Rec- or her2+.
LR control: Triple Negative had worst LRC.
All subgroups significant benefit to RT over observation.

British Columbia trial, 1997 (1979-86)

←R→ 318 pts. **Premenopausal**, pN+, s/p MRM + ALND → 1. CMF alone 2. CMF → RT → CMF.

Surgery	MRM + ALND (median 11 nodes removed)		
Systemic Treatment	CMF q3weeks for 6-12 months		
Radiation	CW	37.5 Gy	in 16 fractions with tangent fields
	Axilla/SCV	35.0 Gy	in 16 fractions with AP field and PAB field
	Bilat IM	37.5 Gy	in 16 fractions with direct field

Chemotherapy: **NOTE:** 128 pts with ER+ tumors = 2nd ←R→ to oophorectomy (using RT to the ovaries).
RT technique: Chest wall, 37.5 Gy (16 fx; 2.34 Gy/fx) using tangents; supraclav/axillary field (with PAB), 35 Gy/16 fx; bilateral IM, 37.5 Gy/16fx. RT given between 4th and 5th chemo cycles. RT was cobalt-60.

Ragaz, J Natl Cancer Inst. 2005.

	15-year LRC	20-year LRC	15-year DFS	20-year DFS	15-year OS	20-year OS
CMF + PMRT	87%	90%	50%	48%	54%	47%
CMF alone	67%	74%	33%	30%	46%	37%
	0.003	0.002	0.007	0.001	-	0.03

Outcome	Chemotherapy-alone arm Survival, %‡	Chemotherapy-alone arm No. of events/ No. of patients	Chemotherapy and radiation therapy arm Survival, %‡	Chemotherapy and radiation therapy arm No. of events/ No. of patients	RR (95% CI)	P†
All 318 patients						
Event-free survival	25	116/154	35	105/164	0.70 (0.54 to 0.92)	.009
Breast cancer–free survival	30	107/154	48	84/164	0.63 (0.47 to 0.83)	.001
Survival free of isolated locoregional disease	74	27/154	90	12/164	0.36 (0.18 to 0.71)	.002
Systemic breast cancer–free survival	31	104/154	48	84/164	0.66 (0.49 to 0.88)	.004
Breast cancer–specific survival	38	95/154	53	75/164	0.67 (0.49 to 0.90)	.008
Overall survival	37	101/154	47	89/164	0.73 (0.55 to 0.98)	.03
Comparison by lymph node status						
Event-free survival						
N1–3 (n = 183)	32	62/92	44	51/91	0.71 (0.49 to 1.03)	
N≥4 (n = 112)	12	47/54	26	44/58	0.68 (0.45 to 1.03)	
P for interaction§						.8
Breast cancer–free survival						
N1–3 (n = 183)	41	53/92	57	38/91	0.64 (0.42 to 0.97)	
N≥4 (n = 112)	12	47/54	34	38/58	0.59 (0.38 to 0.91)	
P for interaction§						.7
Survival free of isolated locoregional disease						
N1–3 (n = 183)	79	14/92	91	7/91	0.46 (0.18 to 1.13)	
N≥4 (n = 112)	59	12/54	84	5/58	0.30 (0.10 to 0.85)	
P for interaction§						.6
Systemic breast cancer–free survival						
N1–3 (n = 183)	44	50/92	58	38/91	0.68 (0.45 to 1.04)	
N≥4 (n = 112)	11	47/54	33	38/58	0.63 (0.41 to 0.97)	
P for interaction§						.7
Breast cancer–specific survival						
N1–3 (n = 183)	53	43/92	64	31/91	0.67 (0.42 to 1.06)	
N≥4 (n = 112)	17	46/54	35	37/58	0.66 (0.43 to 1.01)	
P for interaction§						.9
Overall survival						
N1–3 (n = 183)	50	49/92	57	41/91	0.76 (0.50 to 1.15)	
N≥4 (n = 112)	17	46/54	31	40/58	0.70 (0.46 to 1.06)	
P for interaction§						.7

Chest wall irradiation can eradicate the source of metastasis in more than 30% of patients who would otherwise be at risk for distant spread

Chinese Retrospective NAC → ± PMRT
1813 patients NAC → ypLN either ypN0 (27%), ypN1 (31.3%), and ypN2-3 (41.7%). The role of PMRT was separately evaluated in each group.
Median follow-up of 72.9 months,

Huang, IJROBP 2020.
5-year entire cohort LRR 86.3%, OS 68.4%, DFS 83.1%.
PMRT significantly ↑ 5-year OS in the ypN2-3 group (74.2% vs 55.9%; P < .001).
PMRT had NO EFFECT on 5-year OS in ypN0 group (93.1% vs 95.5%; P = .517) or ypN1 group (88.4% vs 87.8%; P = .549).
Conclusions With modern systemic therapy, PMRT significantly improved OS in the ypN2-3 group but not in the ypN0 and ypN1 groups. Whether PMRT can be safely omitted in the ypN0 and ypN1 groups should be addressed prospectively.

Patterns of Failure

- With chemotherapy, LR for ≥ 4 + LN = 15-36%. LR for T3 tumor = 20-30%.
- Postmastectomy RT ↓ LR in high-risk group to about 5-10%.

Korean Cohort
RR 16,462 women 2019 - 2023.

Cheun, JAMA Surgery 20213.
10-year IBTR-, RR-, and CBC-free survival rates were 95.9%, 96.1%, and 96.5%, respectively.
UVA HR−/ERBB2+ tumors had the worst IBTR-free survival (vs HR+/ERBB2− subtype: adjusted hazard ratio, 2.95; 95% CI, 2.15-4.06)
HR−/ERBB2− subtype had the worst RR- and CBC-free survival among all subtypes (vs HR+/ERBB2− subtype, RR: adjusted hazard ratio, 2.95; 95% CI, 2.37-3.67; CBC: adjusted hazard ratio, 2.12; 95% CI, 1.64-2.75).
Younger patients (age ≤40 years) had greater differences in IBTR, RR, and CBC patterns between subtypes than did older patients.
Conclusions and Relevance In this study, locoregional recurrence occurred with different patterns according to BC subtypes, with younger patients having greater differences in patterns among subtypes than older patients. The findings suggest that tailoring surveillance should be recommended regarding differences in locoregional recurrence patterns according to tumor subtypes, particularly for younger patients.

University of Florence (Livi 2007).[72] Retrospective. 2064 patients Jan 1971 to Dec 2003 TX: mastectomy (majority Halsted), 99% underwent total ALND, none had adjuvant RT. Chemo in only 27%. Tamoxifen in 35%. Median age 55.2 years (30–80 yrs). Median FU 16.6 years (1–31 yrs). Results: LRF at follow up was 18% (378/2064). Of these, single chest wall > multiple chest wall > supraclavicular >> axillary 16 (0.8%) relapse. Only trending prognostic factor tumor size was T stage (NS, p = 0.06). LN status, chemo, tamoxifen, age, skin/nipple infiltration does not matter. Conclusion: If adequate axillary clearance is surgically established, no need for axillary RT since low rate of relapse. ↑ LN+ doesn't necessitate radiation as LN itself is not a prognostic factor.

NSABP Pooled B-15, B-16, B-18, B-22, B-25 (Taghian 2004).[73] Retrospective. 5,758 from trials. Median follow-up time was 11.1 years, s/p mastectomy, + ALND, and 90% doxorubicin-based and 10% CMF-based chemo. Results: 10 year, 12.2% had isolated LRF, 19.8% LRF ± DF, and 43.3% had DF alone as a first event. LRF ± DF as first event for patients: 13% for 1-3 LN, 24.4% for 4-9 LN, and 31.9% for ≥ 10 LN (p < 0.0001). Similarly, tumor size < 2 cm: 14.9%, 2-5 cm: 21.3%, **and >5 cm: 24.6% (p < 0.0001).** Multivariate analysis showed age, tumor size, premenopausal status, number of LN+, and number of dissected LN as significant predictors for LRF as first event.
Conclusion: recommend post-mastectomy + XRT for large tumors > 5 cm and 4 or more LN.

MDACC (Katz 2001).[74] Retrospective. 1031 stage II-IIIA patients s/p mastectomy and doxorubicin-based CT w/o Tamoxifen or RT on 5 prospective clinical trials. FU 116 months (6-262 mo). Results: At 10 years, LRR multicentric 37% vs multifocal 17%. LVSI LRR 25%. Positive or close (< 5 mm) margins LRR 45%. Conclusion: In addition to the extent of primary and nodal disease, other factors that predict for high rates of LRR include + LVSI, involvement of the skin, nipple or pectoral fascia, close or positive margins, or gross multicentric disease *regardless* of the number of involved axillary nodes.

MDACC (Katz, JCO 2000).[75] Same study above. Results: 10-yr rate isolated LRR 4% (0 LN), 10% (1-3), 21% (4-9), and 22% (≥ 10) with p < 0.001. Chest wall (68%) and supraclavicular nodes (41%) were the most common sites of LRR. T-stage, tumor size, and ≥ 2 mm extranodal extension (ENE) predicted for LRR (all 3 were p < 0.01). For subgroup pts with T1-T2 and 1-3 LN (n = 404), those with < 10 nodes examined had↑ risk LRR, 24% vs 11%, compared to those with ≥ 10 nodes examined (p < 0.02). Either tumor size > 4 cm or ENE, led to LRR > 20%.
Conclusion: For pts with **tumors ≥ 4 cm or ≥ 4 involved nodes**, LRR is > 20% and pts should be offered RT. Additionally, pts with 1-3 LN and large tumors, extranodal extension, or inadequate axillary dissection may benefit from postmastectomy RT.

[72] http://www.ncbi.nlm.nih.gov/pubmed/17368813?dopt=Abstract
[73] http://www.ncbi.nlm.nih.gov/pubmed/15452182?dopt=Abstract
[74] http://www.ncbi.nlm.nih.gov/pubmed/11395242?dopt=Abstract
[75] http://www.ncbi.nlm.nih.gov/pubmed/10920129?dopt=Abstract

Hypofractionation

Excellent Summary 2021: Sayan, Adv Rad Onc 2021.
https://www.advancesradonc.org/article/S2452-1094(20)30348-1/fulltext

Phase II Short B
67 patients stage II-IIIa breast cancer. 69 enrolled, but 67 women were eligible for analysis.
PMRT 3.33 Gy daily to the chest wall (or reconstructed breast) and RNI in 11 fractions with an optional 4 fraction mastectomy scar boost.

Poppe, IJROBP 2020. 5-year FU.
54 months, there were no acute or late grade 3 and 4 non-reconstruction reported toxicities.
Grade ≥ 2 late toxicity rate was 12% which comprised grade 2 pain, fatigue and lymphedema that persisted > 6 months after RT.
Only 3 (4.6%) women experienced a chest wall or nodal recurrence, as a first site of relapse.
5-year FFF (including local failure after distant relapse) 92%.
5-year OS 90%.
Conclusion: This is the first prospective trial conducted in the United States to demonstrate the safe and effective use of hypofractionated PMRT. ↓ complication rate and ↑ LC. Toxicity was better than anticipated based on previously published series of PMRT toxicities. Although our fractionation was novel, the RBE similar to other hypofractionation schedules. This trial was the basis for the creation of Alliance Trial which is currently accruing patients in a phase 3 randomized design.

Poppe, IJROBP 2020. EQD2 evaluation.
The EQD2 for the above regimen was estimated to be 45 Gy with a total of 60 Gy when the boost is included.
In contrast to the randomized Chinese trial, they used primarily photons and 3D-planning.
Goal chest wall coverage was at least 90% of prescription with a maximum dose of 115%.
The RTOG chest wall and nodal volumes were not utilized in planning, but a random evaluation of target coverage showed that D95% for the chest wall and axilla was 97% and 92% of prescription, respectively, on average.
The main volumetric constraint was brachial plexus max dose of 39.2 Gy (107%).
The heart was blocked as much as possible and tangent depth into the lung was ideally < 3 cm, but volume-based planning and optimization was limited.
In retrospect, this led to a mean heart dose of just 1.3 Gy (range 0.3 to 3.8 Gy), a heart V20 of 0.3%, and an ipsilateral lung V15 (felt to be equivalent to conventional V20) of 24.8%.
Conclusion: While this trial used conventional planning techniques and a unique dose schedule, look for more volume-based planning and a more "conventional" 42.56 Gy in 16 fractions from RT CHARM.

French Ultrahypofractionated PMRT
RR 454 women stage I to III breast → HFRT-PM between 2000 and 2009.
RT = 4 fractions of 4 Gy (days 1, 3, 15, 17) and then 2 fractions of 5 Gy (days 29 and 31) over 5 weeks.
3-dimensional conformal radiation therapy of the chest wall with regional nodal volume if required.
Regional nodal irradiation was done in 84.1% of patients.

Mignot, IJROBP 2023 10.6 years FU Results
10-year LRR 15.1%.
MVA → ≥4 nodes = ↓ LRC (HR = 1.68; P = .03) and OS (HR, 2.16; P < .001).
The toxicities were acceptable.
The incidence of cardiac disorders (3.3%), and symptomatic lung fibrosis (1.5%) was low during follow-up.
10 years CI arm lymphedema was 9.5% and considered severe in 20 patients (4.4%).
Conclusions The long-term results of this study show that HFRT-PM of 26 Gy in 6 fractions over 5 weeks seems safe, but locoregional recurrence seems slightly higher than that observed in the literature, highlighting the need for long-term follow-up and for randomized trials for hypofractionated radiation therapy postmastectom

Chinese Hypofractionation
←R→ 820, 18–75 yo, s/p mastectomy **+ ALND**. **Eligibility either ≥ 4 LN+ or T3-4.**
All PMRT to chest wall and nodes 1. 50 Gy in 25 fractions over 5 weeks 2. 43·5 Gy in 15 fractions over 3 weeks.
1^{O} 5-year locoregional recurrence, and a 5% margin was used to establish non-inferiority (equivalent to a hazard ratio <1·883).
All patients had adjuvant 75% or neoadjuvant 25% chemo (anthracycline + taxane-based 88%, taxane-based 9%, anthracycline-based 3%).
Median 6 cycles.

Wang, Lancet 2019.
Results: Median follow-up of 58·5 months ~ 5 years.
5-year locoregional recurrence 8.1% vs. 8·3% p<0·0001 for non-inferiority.
5-year OS 85% NS. 5-year DFS 70-74% NS.
Fewer patients in the hypofractionated radiotherapy group had grade 3 acute skin toxicity 3% vs. 8%; p<0·0001.
+ ALND : G1-2- 20% G3 1%. | ≈ | AMAROS ↑ lymphedema with ALND **23% vs 11%** (SS). ↑ arm circumference at 13% vs 6% (SS).

Limitations: 1st, trial only allowed mastectomy w/o reconstruction. 2nd no SCV or IM mets allowed.
Interpretation: Postmastectomy hypofractionated radiotherapy was non-inferior to and had similar toxicities to conventional fractionated radiotherapy in patients with high-risk breast cancer. Hypofractionated radiotherapy could provide more convenient treatment and allow providers to treat more patients.

Other 1-3 pLN+ RRs

HERA Trial Subpatient population
RR analysis of HERA prospective data of 1633 trial patients → TX mastectomy + adjuvant trastuzumab.
Overall, the HERA trial had > 5000 women enrolled, 1600 of whom had mastectomy and adjuvant trastuzumab with 940 patients (57.6%) who received PMRT and 693 patients (42.4%) who did not. Of note, PMRT was at physician discretion.

Jaoude, IJROBP 2020.
Of note: Patients in the PMRT group had worse prognostic disease characteristics.
11-year OS, PMRT in node negative (N0) patients (NS).
Patients 1-3 pLN+ had 10-year LRR-free survival of 97% (PMRT) vs. 90% (no PMRT) with HR 0.28 (SS), but unfortunately OS was NS (but "trending").
Also, triple negative patients benefited from PMRT most.
Conclusions: PMRT delivery in HER-2 positive breast cancer patients with 1 to 3 positive lymph nodes decreases the risk of LRR. Although the magnitude of PMRT benefit is lower than historic studies, the present findings are in favor of PMRT for HER-2 positive breast cancer patients with 1 to 3 involved nodes. Future studies are needed to determine which HER-2 positive breast cancer patients benefit the most from PMRT.

Takeaway1: Since PMRT was at physician discretion, that means the people who received PMRT had **more aggressive clinical features**: young age, extensive nodal disease, large tumor size, and negative hormone-receptor status. Specifically, 63% of the PMRT patients had ≥ 4 pLN+, while 56% of no PMRT patients had pN0 status…and LRR-FS was **STILL** SS beneficial for PMRT.
Takeaway2: Despite the amazing HER2 directed therapy given, these patients can still benefit from PMRT.

Table 3 Clinical outcomes of patients with 1 to 3 positive lymph nodes

	(event-free proportion at 10 years with 95% CI)			
	PMRT	No PMRT	HR	*P* value
LRRFS	0.97 (0.95-0.99)	0.90 (0.86-0.94)	***0.28 (0.12-0.67)***	***.004***
DMFS	0.83 (0.79-0.88)	0.80 (0.75-0.85)	0.75 (0.49-1.16)	.19
DFS	0.77 (0.72-0.83)	0.70 (0.64-0.75)	***0.64 (0.45-0.92)***	***.01***
OS	0.87 (0.83-0.91)	0.82 (0.78-0.87)	0.63 (0.39-1.02)	.06

Abbreviations: CI = confidence interval; DFS = disease free survival; DMFS = distant metastasis free survival; HR = hazard ratio; LRRFS = loco-regional recurrence-free survival; OS = overall survival.
HRs were adjusted for patient's age, tumor size, tumor grade, and anthracycline or taxane administration. Bold and italic *P* values indicate statistical significance.

BIG 02-98
←R→ 684 patients with mastectomy → ALND with pT1-2 pN1a (1-3 LN+) | 1. Anthracycline with taxane | 2. Antracycline alone) |.
337 patients (49%) received PMRT.

Zeidan, IJROBP 2018.
RR of the PMRT vs. No PMRT patients.
10-year LRR PMRT is better! 2.5% PMRT vs. 6.5% no PMRT (HR 0.29, SS).
No Δ BCaSS (83-84%). No Δ OS ~80%.
Conclusion: Our analysis of the BIG 02-98 trial shows excellent outcomes in women with T1-T2 tumors and 1 to 3 positive lymph nodes found in axillary dissection. Although PMRT improved LRR in this cohort, the number of events remained low at 10 years. In all groups, 10-year rates of LRR were relatively low compared with historical studies. As such, the use of PMRT in women with 1 to 3 positive nodes should be tailored to individual patient risks.

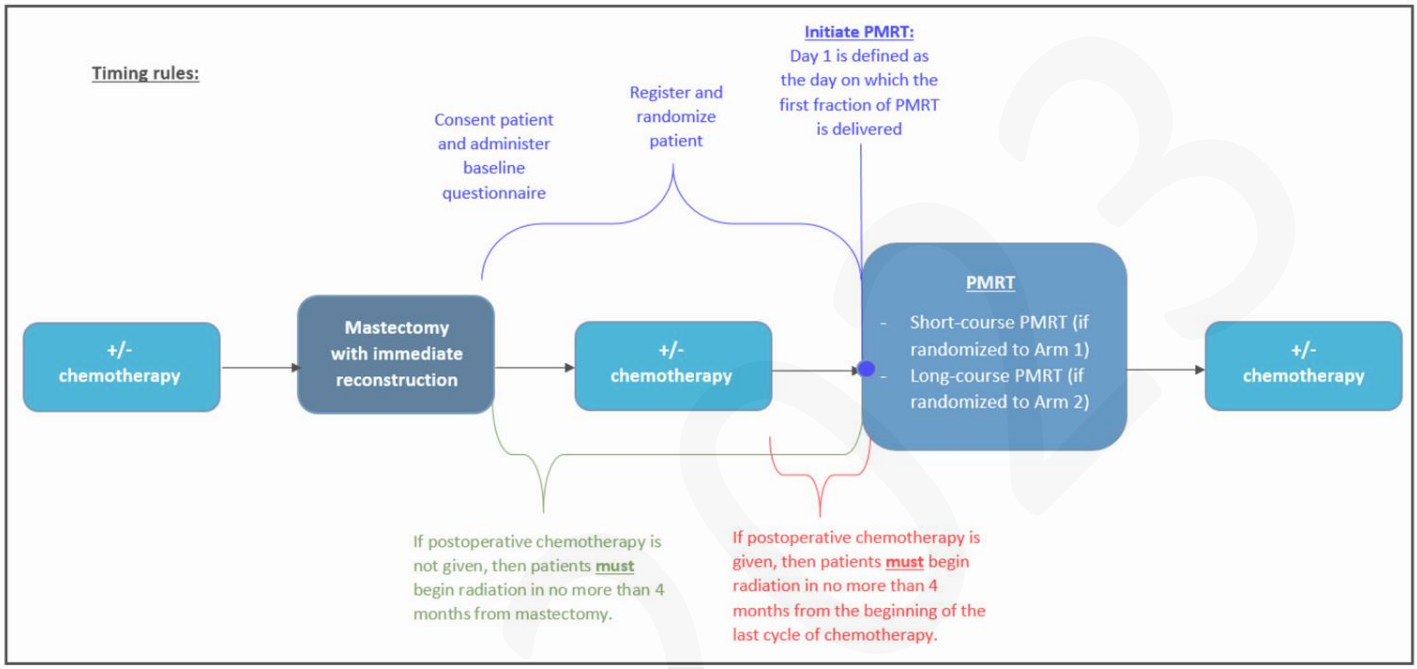
Taiwan Study
RR 125 patients initially with T1-2 → MRM and 1-3 pLN+. Of these 110 were treated WITHOUT PMRT and included in this study to evaluate LR. Median number nodes examined was 17. Adjuvant chemotherapy was given to 69 patients. Adjuvant hormonal therapy (tamoxifen) was given to 84.

Cheng, IJROBP 2002.
4-year LRR rate was 16.1% All but one LRR were isolated LRR without preceding or simultaneous distant metastasis.
According to UVA, age <40 years, T2 classification, tumor size ≥ 3 cm, ER neg, and LVSI pos = SS ↑ LRR.
According to MVA, only tumor size SS ↑ LRR.
According to patient stratification on basis of the 4 patient-related factors (age <40 years, tumor ≥ 3 cm, ER neg, and LVIS pos)
4-year LRR of high-risk group (with 3 or 4 factors) = 66.7%.
4-year LRR of low-risk group (with 0-2 factors) = 7.8%.
4-year distant metastasis rate of 49.0% (9 of 17, 95% CI 24.6-73.4%). For patients without LRR, it was 13.3% (SS).
4-year OS with and without LRR was 75.1% (95% CI 53.8-96.4%) and 88.7% (95% CI 82.1-95.4%; p = 0.049), respectively.
LRR was independently associated with a higher risk of distant metastasis and worse survival in multivariate analysis.

Conclusion: LRR after mastectomy is not only a substantial clinical problem, but has a significant impact on the outcome of patients with T1 or T2 primary tumor and 1-3 positive axillary nodes. Patients with risk factors for LRR may need adjuvant RT. Randomized trials are warranted to determine the potential benefit of postmastectomy RT on the survival of patients with a T1 or T2 primary tumor and 1-3 positive nodes.

Reconstruction / Bolus

FABREC
←R→ 400 patients pTis-T3 with mastectomy and immediate reconstruction (Tissue Expander TE or Implant I).
RT either | 1. 4256 cGy CW + 3990 cGy LN (15-16 fx) | 2. 5000 cGy CW + 4600-5000 cGy LN (23-25 fx) |.
Boost to scar at physician discretion.
DMax per plan ≤ 110% (ideally 107%).
Preop Chemo 67.8% and preop Endo 21.5%
1O Physical Well-Being (PWB) domain of FACT-B at 6months.



Wong, ASTRO 2023
MVA CW toxicity Post-op infection before RT (HR 3.31, SS)
RT of TE (vs I) (HR 7.74, SS)
Preop ET (HR 3.45, SS)
+ LN removed (HR 1.06/node, SS)
Fractionation HF (HR=1.19, p=0.63).
Conclusions: Support Hypofractionation for patients with mastectomy and immediate reconstruction.

Prospective Bolus Study
←R→ 58 patients either standard-risk (SR n=34, without skin involvement) and high-risk (HR n=24, with skin involvement).
SR was randomized | 1. no bolus | 2. 5mm-bolus on alternate days |.
HR was randomized | 3. 5mm-bolus on alternate days | 4. 5mm-bolus daily |.
Skin changes were graded weekly with the Radiation Therapy Oncology Group (RTOG) toxicity scale (single-blinded). Subsequently, patients were followed to assess local control (LC) in the chest wall (CW).
Median Age 48, 35.3% had BMI > 30 kg/m2.
All the baseline characteristics were similar between each arm within the same risk subgroup.
(3D) in 30 cases (58.8%) and conventional (2D) in 21 cases (41.2%).

Sapienza, IJROBP 2022 6.2 years
Overall, the maximal radiodermatitis rates were 29.4% (G2) and 15.7% (G3).
SR → NS Δ G2 radiodermatitis (p=0.70) and no G3 event occurred.
HR → G2 44.5% vs. 100% (SS) and G3 radiodermatitis 11.1% vs. 70%, (SS).
G2 events occurred earlier with daily bolus, but four of the six G3 events occurred 1-3 weeks after the last RT fraction.
5-year LC was SR 95.8% and HR 91.7%.
Per randomization arm, there was no LC difference between the SR arms (p=0.90) or between the HR arms (p=0.70).
All CW failures occurred in the tangent field's margins and when using 2D technique.
Conclusion Within the same risk subgroup, no difference in LC was detected with a more intense bolus regimen. Due to increased G3 radiodermatitis and location of the CW failures (field borders), further studies testing the benefit of increasing superficial dose within the field (by adding bolus or increasing its intensity) are warranted.

Great Review (Naoum, 2023): https://link.springer.com/article/10.1007/s12609-023-00505-2
Excellent PMRT Online Tool: https://www.mgh-rt-sg.org/

Dutch BREAST Trial
←R→ 193 women 2015- 2021 s/p mastectomy → breast reconstruction| 1. Autologous fat transfer (AFT) + expansion | 2. Implant w/ 2 phases |.
Excluded PMRT patients.
1^{O} 12-months post-surgery QoL BREAST-Q questionnaire 0-100 (best).

Piatkowski, JAMA Network 2023.
BREAST-Q scores were higher in the AFT group in all 5 domains and significantly higher in 3: satisfaction with breasts (difference, 9.9; P = .002), physical well-being: chest (difference; 7.6; P = .007), and satisfaction with outcome (difference, 7.6; P = .04).
Linear mixed-effects regression analysis showed that QoL change over time was dependent on the treatment group in favor of AFT.
The mean (SD) breast volume achieved differed between the groups (AFT: 300.3 [111.4] mL; IBR: 384.1 [86.6] mL).
No differences in oncological serious adverse events were found.
Conclusions and Relevance This randomized clinical trial found higher QoL and an increase in QoL scores over time in the AFT group compared with the IBR group. No evidence was found that AFT was unsafe. This is encouraging news since it provides a third, less invasive reconstruction option for patients with breast cancer.

PMRT Bolus Use
Nichol, IJROBP 2012.
Notes: Evaluated 1900 PMRT patients regarding LR and LRR for patients with bolus and no bolus. Bolus use was in 51% with reconstruction but nearly all 96% without reconstruction. 10-year LR was 1-2% NS. MVA did not show bolus use to improve LR. Systemic therapy was used in 98% of patients.

SCV and IM RT

- In patients with N1 disease (1-3 nodes positive).
  - Overall SCV failure without SCR RT may be 6-9%, but isolated SCV failure without concurrent DM is only 2-3%.
  - Several factors appear to predict for >10-15% risk of overall SCV failure: LVI+, ECE+, 2-3 involved LNs (vs 1 involved), involved Level II/III LNs (vs Level I only), >20% LN+, age <50, Grade III, and ER- disease.
  - Given that SCV recurrence salvage is challenging, it may be reasonable to offer SCV RT to these patients.

Handley Internal mammillary study (risk of IM positive by node + and location in breast)
Node negative: All quadrants and central are 5% EXCEPT Upper inner, which is 15%.
Node positive: all lateral is 20-25% … central is 45. Upper Medial is 45, and LOWER medial is 75%.

Major Trials to Know

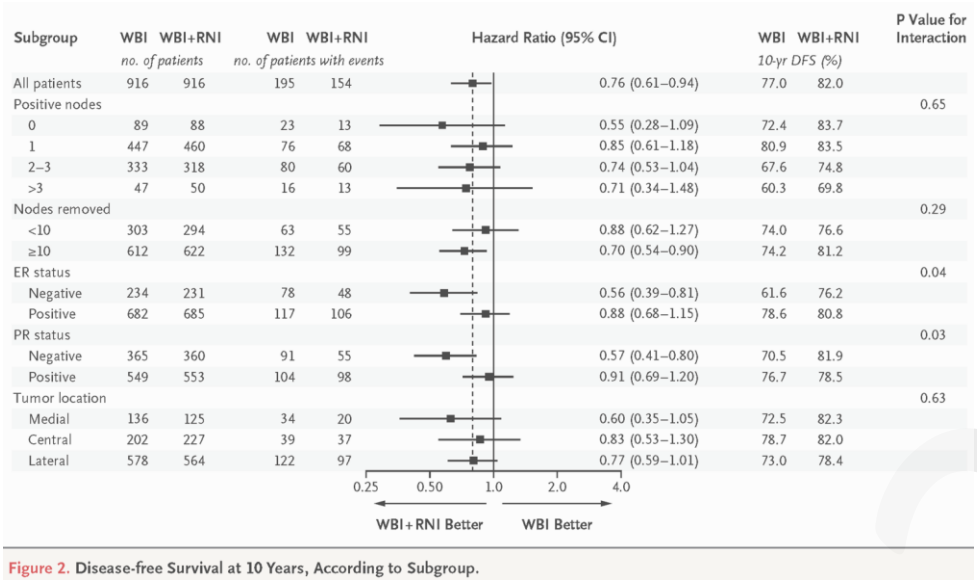
KROG 08-06 Korean Partially Wide Tangent IMNI Study
←R→ 735 pLN+ breast cancer s/p BCS or mastectomy. All patients had RNI + breast or CW. | 1. IMNI | 2. No IMNI |.
Exclusion: M+ or if NAC. Radiation RNI 45-50.4 Gy.
1^{O} 7-year DFS.

Kim, JAMA Oncol 2021.
7-year DFS 81.9% vs 85.3% (NS).
Ad hoc subgroup analysis showed significantly higher DFS rates with IMNI among patients with **mediocentrally located tumors**.
7-year DFS (MC tumors) 91.8% vs. 81.6% (HR, 0.42; *P* = .008) 7-year BCaM 4.9% vs. 10.2% (HR, 0.41; *P* = .04).
NS 2 groups in the incidence of adverse effects, including cardiac toxic effects and radiation pneumonitis.
Conclusions: This randomized clinical trial found that including IMNI in regional nodal irradiation did not significantly improve the DFS in patients with node-positive breast cancer. However, patients with medially or centrally located tumors may benefit from the use of IMNI.

2-D French Trial
←R→ 1334 pN+ or central/medial tumors, age <75, KPS ≥70. MRM + ALND I/II → PMRT + SCV ± IMN.
RT dose was 50 Gy or equivalent. The first 5 intercostal spaces were included in the IMN target volume, and two-thirds of the dose (31.5 Gy) was given by electrons. The primary outcome was overall survival at 10 years. Disease-free survival and toxicity were secondary outcomes.

Hennequin, IJROBP 2013.
10-year OS IMN yes RT 62.6 vs. IMN no RT 59.3% (NS).
According to stratification factors, we defined 6 subgroups (medial/central or lateral tumor, pN0 [only for medial/central] or pN+, and chemotherapy or not). In all these subgroups, IMN irradiation did not significantly improve overall survival.
CONCLUSIONS: In patients treated with 2-dimensional techniques, we failed to demonstrate a survival benefit for IMN irradiation. This study cannot rule out a moderate benefit, especially with more modern, conformal techniques applied to a higher risk population.

Intergroup / NCIC-CTG MA.20 - Whole breast RT +/- regional nodal irradiation



Subgroup	WBI	WBI+RNI	WBI	WBI+RNI	Hazard Ratio (95% CI)	WBI	WBI+RNI	P Value for Interaction
	no. of patients		no. of patients with events			10-yr DFS (%)		
All patients	916	916	195	154	0.76 (0.61–0.94)	77.0	82.0	
Positive nodes								0.65
0	89	88	23	13	0.55 (0.28–1.09)	72.4	83.7	
1	447	460	76	68	0.85 (0.61–1.18)	80.9	83.5	
2–3	333	318	80	60	0.74 (0.53–1.04)	67.6	74.8	
>3	47	50	16	13	0.71 (0.34–1.48)	60.3	69.8	
Nodes removed								0.29
<10	303	294	63	55	0.88 (0.62–1.27)	74.0	76.6	
≥10	612	622	132	99	0.70 (0.54–0.90)	74.2	81.2	
ER status								0.04
Negative	234	231	78	48	0.56 (0.39–0.81)	61.6	76.2	
Positive	682	685	117	106	0.88 (0.68–1.15)	78.6	80.8	
PR status								0.03
Negative	365	360	91	55	0.57 (0.41–0.80)	70.5	81.9	
Positive	549	553	104	98	0.91 (0.69–1.20)	76.7	78.5	
Tumor location								0.63
Medial	136	125	34	20	0.60 (0.35–1.05)	72.5	82.3	
Central	202	227	39	37	0.83 (0.53–1.30)	78.7	82.0	
Lateral	578	564	122	97	0.77 (0.59–1.01)	73.0	78.4	

Figure 2. Disease-free Survival at 10 Years, According to Subgroup.

←R→. Multicenter (Canada-86%; US, Australia). 1832. IDC. high risk node-negative **(15%)** (pT3N0, or pT2 and < 10 LN removed and grade 3 or ER- or LVI +) or node-positive (pN1), **treated with BCS** and adjuvant chemo ± endocrine therapy. **All had level 1-2 axillary dissection**. All patients were BCS and SLN or ALND (a level 1-2 ax dissection required for + results on SLN biopsy).
1. Whole breast RT (50 Gy / 25 fx) **± boost** 10-16 Gy (33%).
2. Whole breast RT + regional nodal irradiation (45 Gy / 25 fx) to internal mammary, SCLV, and comprehensive nodal irradiation.
TREAT UNDISSECTED AXILLA SO SCV FIELD IS CUT OFF AT MEDIAL BORDER OF HUMERAL HEAD aka Coracoid process.
They did allow full SCV/axilla if you had a lot of LN+.
Herceptin included after 2005.

Table 3. Adverse Events of Grade 2 or Higher.*

Adverse Event	WBI (N=927)				WBI+RNI (N=893)				P Value†
	Grade 2	Grade 3	Grade 4	Total	Grade 2	Grade 3	Grade 4	Total	
	no. of patients with event (%)								
Acute									
Fatigue	156	13	0	169 (18.2)	154	16	0	170 (19.0)	0.67
Pain‡	35	5	0	40 (4.3)	46	7	0	53 (5.9)	0.14
Pneumonitis§	2	0	0	2 (0.2)	11	0	0	11 (1.2)	0.01
Radiation dermatitis	349	23	0	372 (40.1)	397	45	0	442 (49.5)	<0.001
Delayed									
Cardiac¶	2	2	0	4 (0.4)	0	6	2	8 (0.9)	0.26
Lymphedema‖	38	4	0	42 (4.5)	65	10	0	75 (8.4)	0.001
Neuropathy**	16	1	0	17 (1.8)	16	5	1††	22 (2.5)	0.42
Pneumonitis or fibrosis§‡‡	2	1	0	3 (0.3)	4	0	0	4 (0.4)	0.72
Joint	12	2	0	14 (1.5)	21	0	0	21 (2.4)	0.23
Skin§§	38	2	0	40 (4.3)	51	11	0	62 (6.9)	0.02
Subcutaneous tissue	19	0	0	19 (2.0)	34	3	0	37 (4.1)	0.01
Second cancer¶¶	NA	NA	NA	93 (10.0)	NA	NA	NA	98 (11.0)	0.54

Whelan, NEJM 2015. Median 9.5 years.
Outcome: 10-year OS RNI 82.8% vs WB 81.8% (NS); breast cancer survival 89.7% vs. 87.7% (NS);
DFS 82% vs 77% (SS, p = 0.01)
Incidence of distant mets 13.4% vs 17.3% (0.02)
Isolated locoregional recurrence 4.5% vs 7.2% (0.02)
Toxicity:
acute pneumonitis G2+ 1.2% vs 0.2% (SS)
lymphedema 8.4% vs 4.5% (SS)
Conclusion: Addition of regional nodal irradiation does not improve OS but ↓ rate of breast cancer recurrence
Note Benefits (See ←): ER/PR -.
Note Toxicity (See ←): Acute Pneumonitis, acute dermatitis, lymphedema.
NO Δ cardiac, neuropathy, long term pneumonitis.

Goodwin, JAMA 2022 METFORMIN analysis
←R→ | 1. 850 mg of oral metformin twice a day (n = 1824) | 2. oral placebo twice a day (n = 1825) for 5 years |.
iDFS 2.78 per 100 patient-years vs 2.74 per 100 patient-years (HR = 1.01; NS).
Grade 3 nonhematological toxic events occurred more frequently in patients taking metformin than in patients taking placebo (21.5% vs 17.5%, respectively, P = .003). The most common grade 3 or higher adverse events in the metformin vs placebo groups were hypertension (2.4% vs 1.9%), irregular menses (1.5% vs 1.4%), and diarrhea (1.9% vs 7.0%).
Conclusions and Relevance Among patients with high-risk operable breast cancer without diabetes, the addition of metformin vs placebo to standard breast cancer treatment did not significantly improve invasive disease–free survival.

EXCEPT: Exploratory Analysis of HER2+
ERBB2+ BCA iDFS 1.93 vs 3.05 events per 100 patient-years (HR, 0.64; 95% CI, 0.43-0.95; P = .03)
OS 0.78 vs. 1.43 deaths per 100 patient-years (HR, 0.54; 95% CI, 0.30-0.98; P = .04).
NOTE: Chemotherapy can induce metabolic syndrome, which metformin perhaps can prove to have a further ↑ effect.

EORTC 22922/10925 (1996-2004) **45% node negative!!!!!! If node negative, it has to be centrally or medially node negative.**
←R→ 4004 women, 46 institutions. **BCT 76%, mastectomy 24%**, Stage I-III with central/medial tumor location or lateral tumor with axillary involvement.
Full ALND or SNB followed by ALND if positive. pN0 44%; pN1 43%; pN2 10%.
Standard RT (breast / chest wall, boost) as per institutional preference. Nearly 100% of BCT → WBRT.
RT randomized: | 1. Internal mammary and medial supraclavicular 50/25 | 2. No IM-RNI|. Boost in 85% of whole breast.
NO ER STATUS IN A LOT OF THESE PATIENTS SO THEY COULDN'T DO THAT ANALYSIS.

Matzinger, O Acta Oncol Toxicity; 2010
Toxicity: Any lung toxicity standard RT 1.3% vs IM-MS RT 4.3% (SS); cardiac toxicity 0.3% vs 0.4% (NS).
No difference in performance status
Outcome: Well tolerated at 3 years

Poortman, NEJM 2015.
Outcome: 10-year OS RNI 82% vs control 80.7% (NS) 10-year DFS 72.1% vs 69.1% (0.04)
Distant mets-free survival 78% vs 75% (0.02) Breast cancer mortality 12.5% vs 14.4% (0.02).
7-8% Local Control NS.
Toxicity: **pulmonary fibrosis 4.4% vs 1.7% (SS)**; cardiac disease 6.5% vs 5.6% (NS); lymphedema 10-12% (NS).
Conclusion: Irradiation of regional nodes marginal effect on overall survival; DFS and distant mets-free survival improved, and breast cancer mortality reduced.

Poortman, Lancet 2020. **Median 15.7 years.** **15-Year Benefits**
15-year OS 73·1% vs. 70·9% (HR 0·95, p=0·36).
15-year any breast cancer recurrence 24·5% vs 27·1%, (p=0·024) 15-year BCaM 16·0% vs. 19·8%, (p=0·0055).
15-year DFS 60·8% vs. 59·9%, (NS), or distant metastasis-free survival 70·0% vs. 68·2% (NS).
Causes of death between groups were similar.
Interpretation The 15-year results show a significant reduction of breast cancer mortality and any breast cancer recurrence by IM-MS irradiation in stage I–III breast cancer. However, this is not converted to improved overall survival.

Poortmans, J Natl Cancer Inst 2021 **15-year Risks**
Lung fibrosis 2.9% → 5.7% (SS), cardiac fibrosis 1.1% → 1.9% (NS), any cardiac disease 9.4% → 11.1% (SS).
There was no evidence for differences between left- and right-sided breast cancer for cardiac fibrosis and for any cardiac disease.
No difference was observed in the incidence of second malignancies, contralateral breast cancer, or cardiovascular deaths.
Conclusions The incidence of late pulmonary side effects was statistically significantly higher after IM-MS lymph node irradiation, as were some of the cardiac events, without a difference between left- and right-sided treatments. Absolute rates and differences were very low, without increased non-breast cancer– related mortality, even before introducing heart-sparing techniques.

Patterns of Recurrence
In total, 282 (7%) patients experienced LR and 165 (4.1%) RR, respectively.
15-year LR mastectomy (3.1%) vs. BCS + RT (7.3%) (F&G: HR (Hazard Ratio) = 0.421, p-value < 0.0001).
LR were similar up to 3 years for both mastectomy and BCS but continued to occur at a steady rate for BCS + RT, only.
The spatial location of the recurrence was related to the locoregional therapy applied and the absolute gain of RT correlated to stage of disease and extent of surgery.

If BCS vs. Mastectomy,		LR "in-field" 72% vs. 57%.	BCS only had 1/3 recurrences near tumor bed.
		RR BCS	(4.8% without RNI, 2.8% with RNI).
		RR mastectomy	(5.8% without RNI, 4.8% with RNI)
		Rate of RR was lower after RNI (3.2% v 5%).	
Location of failures	after RNI	Axilla 1.7%, SCV 1.6%, IMN 0.2%.	
	If no RNI	Axilla 2.4%, SCV 2.5%, IMN 0.8..	

The absolute benefit of RT in reducing locoregional recurrence increased with stage and with less extensive surgery (i.e. breast conservation and limited axillary surgery.
Conclusions The extent of locoregional therapies impacts significantly on LR and RR rates and spatial location.

Danish DBCG-IMN.

Prospective 2 arm trial. 3089 unilateral LN+ mastectomy (65%) or BCS (35%) with ALND I/II.

All patients had RNI to SCV and Lv II-III (include LV1 if ≥ 6 positive macromets).

Subgroup	IMNI Patients	IMNI Events	No IMNI Patients	No IMNI Events	HR (95% CI)	8-year survival rate (%) IMNI	8-year survival rate (%) No IMNI
Lateral 1–3 nodes	511	91	564	91	1.13 (0.84 to 1.51)	82.9	85.7
Medial/central 1–3 nodes	353	67	382	88	0.80 (0.58 to 1.10)	83.2	78.8
Lateral ≥ 4 nodes	392	137	384	170	0.71 (0.57 to 0.89)	68.0	58.3
Medial/central ≥ 4 nodes	224	86	259	131	0.81 (0.61 to 1.06)	61.9	53.8
All patients	1,480	381	1,589	480	0.82 (0.72 to 0.94)	75.9	72.2
Test for heterogeneity, $P = .10$							

If R breast → IMNI. If L breast → no IMNI.

Breast/CW/Scar/All LN → 48 Gy in 24 fx.

1^{O} OS Analyses were by intention to treat.

Thorsen, JCO 2015.

8-year OS 75.9% with IMNI versus 72.2% without IMNI (p = 0.005).

BCM 20.9% vs. 23.4% (p = 0.03).

Distant recurrence 27.4% vs. 29.7% (NS).

The effect of IMNI was more pronounced in patients at high risk of internal mammary node metastasis. Equal numbers in each group died of ischemic heart disease.

CONCLUSION: In this naturally allocated, population-based cohort study, IMNI increased overall survival in patients with early-stage node-positive breast cancer.

Subgroup	IMNI Patients	IMNI Events	No IMNI Patients	No IMNI Events	HR (95% CI)	8-year survival rate (%) IMNI	8-year survival rate (%) No IMNI
Age at surgery, years							
< 35	37	10	40	13	0.70 (0.31 to 1.61)	75.7	72.3
35–49	418	90	433	115	0.77 (0.59 to 1.02)	78.9	76.2
50–59	530	140	574	170	0.82 (0.66 to 1.03)	75.8	72.9
≥ 60	495	141	542	182	0.87 (0.69 to 1.08)	73.6	68.4
Test for heterogeneity, $P = .91$							
Tumor size, mm							
≤ 20	620	109	649	138	0.81 (0.63 to 1.04)	82.9	80.3
21–50	770	235	834	278	0.87 (0.73 to 1.04)	72.4	69.9
≥ 51	90	37	106	64	0.63 (0.42 to 0.95)	57.1	40.6
Test for heterogeneity, $P = .37$							
No. of positive nodes							
1–3	864	158	946	179	0.97 (0.78 to 1.20)	83.0	82.8
4–9	399	111	414	159	0.71 (0.56 to 0.91)	73.5	65.7
≥ 10	217	112	229	142	0.77 (0.60 to 0.99)	52.4	39.8
Test for heterogeneity, $P = .16$							
Grade of malignancy							
1	351	573	82	63	0.93 (0.65 to 1.33)	87.1	85.5
2	714	178	747	228	0.79 (0.65 to 0.96)	76.6	72.2
3	415	146	460	189	0.83 (0.67 to 1.03)	65.7	61.2
Test for heterogeneity, $P = .73$							
Tumor location							
Medial or central	577	153	641	219	0.81 (0.66 to 1.00)	74.9	68.7
Lateral	903	228	948	261	0.83 (0.70 to 0.99)	76.4	74.6
Test for heterogeneity, $P = .87$							
Menopausal status							
Premenopausal	607	131	648	180	0.71 (0.57 to 0.90)	79.3	74.8
Postmenopausal	873	250	941	300	0.89 (0.75 to 1.05)	73.5	70.4
Test for heterogeneity, $P = .16$							
All patients	1,480	381	1,589	480	0.82 (0.72 to 0.94)	75.9	72.2

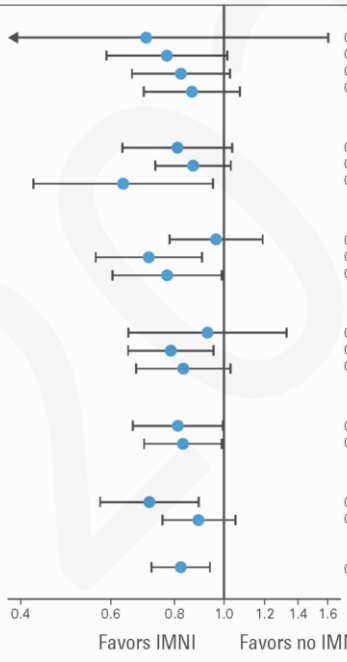


Fig 3. Overall survival rates and corresponding hazard ratios (HR) with versus without internal mammary node irradiation (IMNI) within subgroups in the multivariate Cox proportional hazards model. Information on covariates was complete in 3,069 patients.

Thorsen, JCO 2022 15 year update

15-year OS 60.1% and 55.4% (HR 0.86, P = .007) in favor of IMNI.

15-year DM 35.6% and 38.6% (aHR, 0.88 P = .04]).

15-year BCaM 31.7% and 33.9% (aHR, 0.88 P = .05]). The distribution of other deaths was similar across groups.

Conclusion: In patients with node-positive early breast cancer treated with IMNI or without IMNI depending on breast cancer laterality, IMNI reduced the risk of distant recurrence and death from breast cancer, thereby improving long-term survival.

IM Metaanalysis

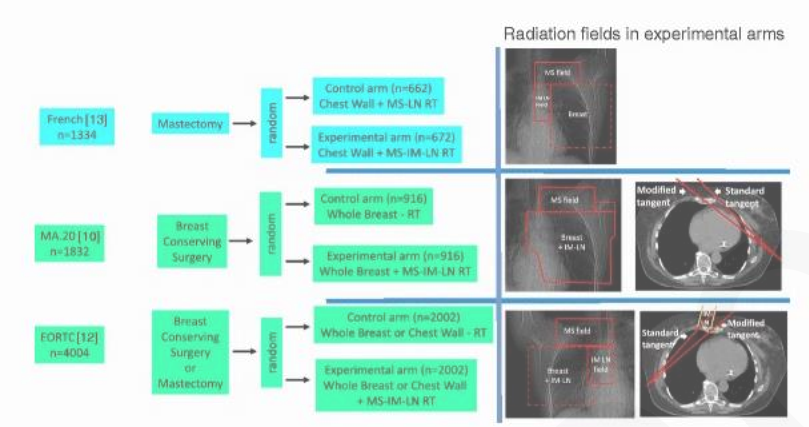
←M→ MA.20 (n = 1832), the EORTC22922-10925 (EORTC) (n = 4004) trial and the French trial (n = 1334).

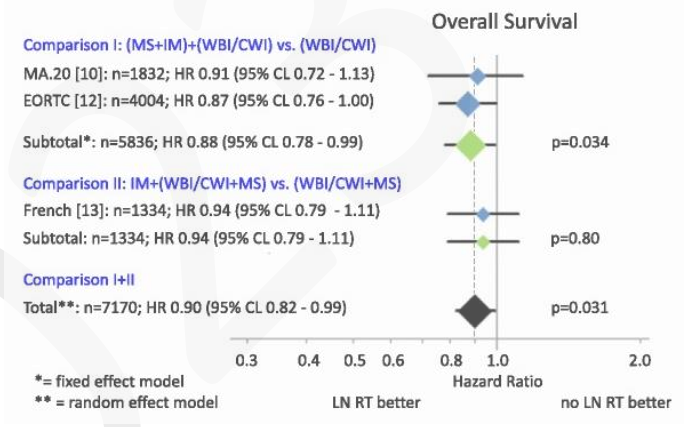
Major eligibility criteria were positive i) axillary LN (all trials), ii) LN negative disease with high risk for recurrence (MA.20), and iii) medial/central tumor location (French, EORTC). The MA.20 and the EORTC trial analyzed the effect of additional regional RT to the internal mammary (IM) LN and medial supraclavicular (MS) LN, whereas in the French trial all patients received RT to the MS-LN and solely RT to the IM-LN was randomized. Primary endpoint was OS.

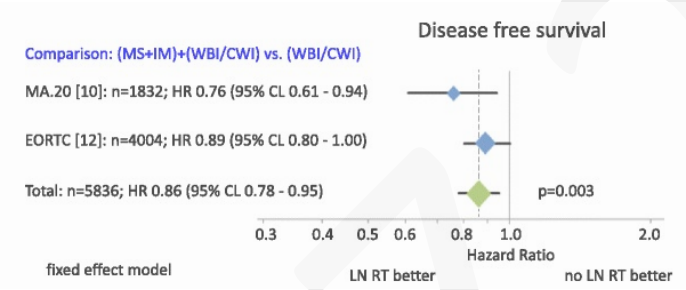
Budach, IJROBP 2015.

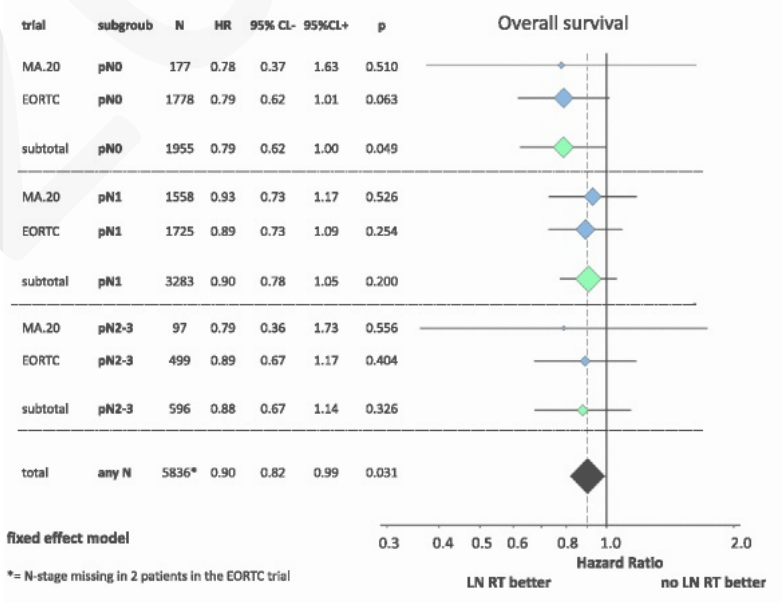
Regional RT of MS-LN and IM-LN (MA.20 and EORTC) resulted in a significant improvement of OS [Hazard Ratio (HR) 0.88 (95 % CL 0.78 - 0.99)]. Adding results of the French trial and using a random effects model to respect the different design of the French trial, the effect on OS of regional RT remained significant [HR 0.90 (95 % CL 0.82 - 0.99)]. The absolute benefits in OS were 1 % in the MA.20 trial at 10 years, 1.6 % in the EORTC trial at 10 years, and 3.3 % in the French trial at 10 years (not significant in single trials). Regional RT of MS-LN and IM-LN (MA.20 and EORTC) yielded to a significant improvement of DFS [HR 0.86 (95 % CL 0.78 - 0.95)] and DMFS [HR 0.84 (95 % CL 0.75 - 0.94)].

CONCLUSION: Additional regional RT to the internal mammary and medial supraclavicular LN statistically significantly improved DFS, DMFS, and OS in stage I-III breast cancer.









Other Studies

Dutch RAPCHEM Trial

←R→ 838 women cT1-2 N1 BCa (1-3 Suspicious LN on imaging → at least 1 biopsied confirmed) → NAC → surgery of the breast and axilla.
Low risk → ypN0. Int risk → 1-3 residual LN+ High risk → ≥ 4 or more residual LN+.
RT recommendations: LOW RISK group = no RT, INT RISK group = WBRT alone, HIGH RISK group = RNI.
RT = BED of 25 fractions of 2 Gy, ± boost.
IM irradiation was 6%.
2/3 of patients received RT per guidelines.
Major variations in recommendation. Low risk = ↑ 37% received more extensive RT than recommended. INT = ↓ 17% received less. HIGH = ↓ 14%.

De Wild, Lancet 2022

5-year LRR ALL 2·2% (95% CI 1·4–3·4). 5-year LRR each group was 2.1-2.3%.
If the study guideline was followed, the locoregional recurrence rate was 2·3% (0·8–5·3) for the low-risk group, 1·0% (0·2–3·4) for the intermediate-risk group, and 1·4% (0·3–4·5) for the high-risk group.

Interpretation

In this study, the 5-year locoregional recurrence rate was less than 4%, which supports our hypothesis that it is oncologically safe to de-escalate locoregional radiotherapy based on locoregional recurrence risk, in selected patients with cT1–2N1 breast cancer treated with primary chemotherapy, according to this predefined, consensus-based study guideline.

UK Phase II **IMN Technique Study**

←R→ 21 patients all requiring IM Chain (IMC) RNI | 1. Wide Tangent (WT) (vDIBH) | 2. **VMAT** |.
1^{O} TTT total treatment time.

Ranger, Clinical Oncology 2022.

Mean TTT per fraction 28.1 min vs. **13.2 min.**
There were no statistically significant differences in patient set-up errors in between groups.
Mean Heart Dose 2.6 Gy vs. 3.4 Gy (P = 0.13). Mean Lung V17Gy 32.8% vs. 34.4% (P = 0.2).
Mean humeral head 16.8 Gy vs. 2.8 Gy. MAX oesophagus 37.3 Gy vs. 20.1 Gy), Mean Thyroid 22.0 Gy vs. 11.2 Gy.
There were no statistically significant differences in skin, lung or oesophageal toxicity within 3 months of treatment.
Patient-reported outcomes of shoulder toxicity, pain, fatigue, breathlessness and breast symptoms were similar between groups at 1 year.

Conclusion

VMAT(vDIBH) and WT(vDIBH) are feasible options for locoregional breast radiotherapy including the IMC. VMAT improves nodal coverage and delivers treatment more quickly, resulting in less breath holds for the patient. This is at the cost of increased dose to some non-target tissues. The latter does not appear to translate into increased toxicity in this small study.

Immunotherapy + Other Trials

Summary of New Immunotherapies:

ASCENT Trial Trodelvy "Sacituzumab govitecan is an antibody–drug conjugate composed of an antibody targeting the human trophoblast cell-surface antigen 2 (Trop-2), which is expressed in the majority of breast cancers, coupled to SN-38 (topoisomerase I inhibitor) through a proprietary hydrolyzable linker."

←R→ 468 patients with advanced TNBC failing 2 previous tx | 1. Sacituzumab | 2. Another chemotherapy |.

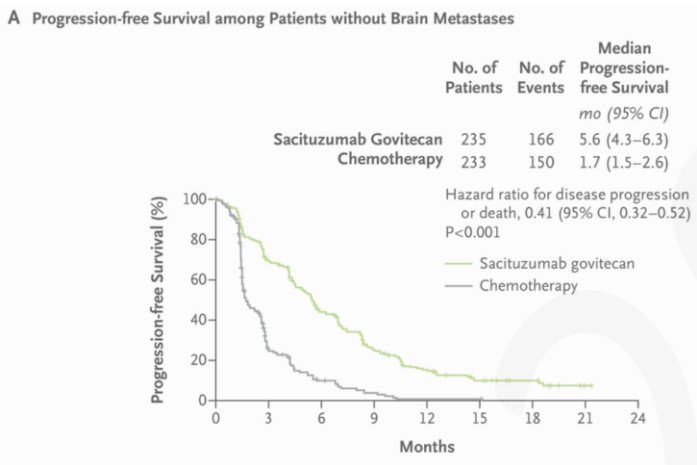
Bardia, NEJM 2021

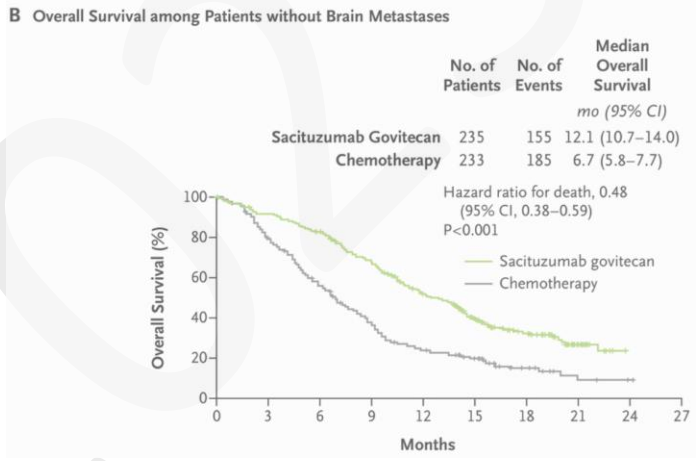
Median PFS 5.6 months vs. 1.7 months. Median OS 12.1 months vs. 6.7 months (SS).

Objective response 35% vs. 5%.

Adverse events of G ≥ 3 neutropenia (51% with sacituzumab govitecan and 33% with chemotherapy), leukopenia (10% and 5%), diarrhea (10% and <1%), anemia (8% and 5%), and febrile neutropenia (6% and 2%). There were three deaths owing to adverse events in each group; no deaths were considered to be related to sacituzumab govitecan treatment.

CONCLUSIONS Progression-free and overall survival were significantly longer with sacituzumab govitecan than with single-agent chemotherapy among patients with metastatic triple-negative breast cancer. Myelosuppression and diarrhea were more frequent with sacituzumab govitecan.





KEYNOTE 355

←R→ 847 patients previously untreated locally recurrence inoperable or metastatic TNBC 2:1 | 1. Pembro | 2. Other Chemo |

Investigator's choice of chemotherapy (nanoparticle albumin-bound paclitaxel, paclitaxel, or gemcitabine–carboplatin) or placebo plus chemotherapy.

1^{O} PFS (reported previously) and OS among patients whose tumors expressed PD-L1 with a CPS of 10 or more (the CPS-10 subgroup), among patients whose tumors expressed PD-L1 with a CPS of 1 or more (the CPS-1 subgroup), and in the intention-to-treat population. Safety was also assessed.

Cortes, NEJM 2022. The median follow-up was 44.1 months.

CPS-10 subgroup Median OS 23.0 months vs. 16.1 months (HR 0.73; SS)

CPS-1 subgroup Median OS 17.6 months vs. 16.0 months (HR 0.86; SS)

ITT population, Median OS 17.2 months vs. 15.5 months (HR 0.89; 95% CI, 0.76 to 1.05 [significance not tested]).

Adverse events of grade 3, 4, or 5 that were related to the trial regimen occurred in 68.1% of the patients in the pembrolizumab–chemotherapy group and in 66.9% in the placebo–chemotherapy group, including death in 0.4% of the patients in the pembrolizumab–chemotherapy group and in no patients in the placebo–chemotherapy group.

CONCLUSIONS Among patients with advanced triple-negative breast cancer whose tumors expressed PD-L1 with a CPS of 10 or more, the addition of pembrolizumab to chemotherapy resulted in significantly longer overall survival than chemotherapy alone.

SONIA Trial CDK 4/6 inhibitors as 1st vs. 2nd line Tx.

←R→ 1050 pre and post menopausal patients with no prior therapy for advanced BCa. | 1. 1st line Tx NSAI + CDK4/6i → progression = fulvestrant (F) | | 2. 1st line Tx NSAI → progression = F + CDK4/6i).

Any CDK4/6i (abemaciclib, palbociclib, ribociclib).

1^{O} time from ←R→ to second objective disease progression.

Sonke, 2023 ASCO Abstract. 37.3 months

Median PFS was 31.0 months vs. 26.8 months (HR 0.87; P=0.10).

The treatment effect was consistent across the levels of pre-defined subgroups. The safety profile was characteristic for ET + CDK4/6i.

Median time on CDK4/6i was 24.64 months vs. 8.08 months (Δ 16.56 months).

The number of grade ≥3 adverse events 2782 vs. 1620.

Conclusions: First-line use of CDK4/6i + ET does not provide statistically significant, nor clinically meaningful PFS benefit compared to second-line use in women with HR+, HER2- ABC. Use in first-line prolongs the time on CDK4/6i by 16.56 months and increases toxicity and costs. Second-line use may thus be a preferred option for the majority of patients.

NATALEE
←R→ 5101 men and pre/post menopausal women stage II or III HR+ Her2- early BC (as opposed to post-menopausal HR+ Her2- metastatic BC).
| 1. RIB (400 mg/day; 3 wk on/1 wk off for 3 y) + ET (letrozole 2.5 mg/day or anastrozole 1 mg/day, for ≥ 5 y) | 2. ET alone |.
Men and premenopausal women also received goserelin.
Eligible pts had an ECOG PS of 0-1 and BC anatomic stage IIA (either N0 with additional risk factors or 1-3 axillary lymph nodes [N1]), stage IIB, or stage III per AJCC (8th ed); prior (neo)adjuvant ET was allowed if initiated ≤ 12 mo before randomization.

Slamon, ASCO Abstract 2023 median follow-up was 34 mo
3- and 2-y RIB tx was completed by 515 pts (20.2%) and 1449 pts (56.8%), respectively
3810 (74.7%) remained on study tx (RIB+ET, n = 1984; ET alone, n = 1826)
3-y iDFS rates 90.4% vs 87.1%. iDFS benefit was generally consistent across stratification factors and other subgroups.
Conclusions: Ribociclib added to standard-of-care ET demonstrated a statistically significant, clinically meaningful improvement in iDFS with a well-tolerated safety profile. The NATALEE results support ribociclib + ET as the tx of choice in a broad population of pts with stage II or III

EMERALD
←R→ 477 patient ER+ Her2- advanced BCa with one-two lines of endocrine therapy → pretreatment CDK 4/6 inhibitor, and ≤ 1 chemotherapy.
| 1. elacestrant 400 mg orally once daily | 2. SOC endocrine monotherapy |.
1^{O} PFS by blinded independent central review in all patients and patients with detectable ESR1 mutations.
ESR1 mutation was detected in 47.8% of patients, and 43.4% received two prior endocrine therapies.

Bidard, JCO 2022.
PFS was prolonged in all patients (HR 0.70; P = .002) and patients with ESR1 mutation (HR 0.55; P = .0005).
Treatment-related grade 3/4 adverse events 7.2% vs. 3.1%.
Treatment-related adverse events leading to treatment discontinuations were 3.4% in the elacestrant arm versus 0.9% in SOC. Nausea of any grade occurred in 35.0% receiving elacestrant and 18.8% receiving SOC (grade 3/4, 2.5% and 0.9%, respectively).
Conclusion: Elacestrant is the first oral selective ER degrader demonstrating a significant PFS improvement versus SOC both in the overall population and in patients with ESR1 mutations with manageable safety in a phase III trial for patients with ER-positive/HER2-negative advanced breast cancer.

monarchE (Abemaciclib in ++-, LN+, High Risk, Early Stage)
←R→ 5637 women with who had surgery and, as indicated, RT ± adjuvant/neoadjuvant C. | 1. ET | 2. ET+CDK4/6 Abemaciclib 150 mg BID 2 yrs |.
Eligibility: ≥4 LNs, 1-3 LNs + either tumor size ≥ 5 cm, histologic grade 3, or central Ki-67 ≥ 20%.
1^{O} invasive disease-free survival (IDFS), and secondary end points included distant relapse-free survival, overall survival, and safety.

Johnston JCO 2020. Preplan Interim
323 IDFS events were observed in the intent-to-treat population.
2-year I-DFS 88.7% vs. 92.2% (HR 0.75, SS).
Safety data were consistent with the known safety profile of abemaciclib.
Conclusion: Abemaciclib when combined with ET is the first CDK4/6 inhibitor to demonstrate a significant improvement in IDFS in patients with HR+, HER2- node-positive EBC at high risk of early recurrence.

PALLAS
←R→ 5796 women HR+ HER2- early breast cancer | 1. 2 years of palbociclib + adjuvant ET | 2. adjuvant ET alone (for at least 5 years) |.
1^{O} invasive disease-free survival (iDFS).

Gnant, JCO 2021 median follow-up of 31 months
iDFS events occurred 8.8% vs. 9.1%.
4-year iDFS 84.2% v 84.5% (NS).
No significant differences were observed for secondary time-to-event end points, and subgroup analyses did not show any differences by subgroup. There were no new safety signals for palbociclib in this trial.
CONCLUSION At this final analysis of the PALLAS trial, the addition of adjuvant palbociclib to standard endocrine therapy did not improve outcomes over endocrine therapy alone in patients with early hormone receptor–positive breast cancer.

Impassion031 TNBC pCR NAC ± Atezolizumab
←R→ 333 patients stage II-III TNBC | 1. Chemo + IV atezo | 2. Chemo + placebo | → ALL Then Surgery.
Atezo = 840 mg q2 weeks **Chemo =** nab-paclitaxel at 125 mg/m^2 every week for 12 weeks → doxorubicin at 60 mg/m^2 + cyclophosphamide at 600 mg/m^2 every 2 weeks for 8 weeks.
Co 1^{O} endpoints were pCR in all-randomised (ie, all randomly assigned patients in the intention-to-treat population) and PD-L1-positive (≥1%).
Median FU 20 months.

Mittendorf, Lancet 2020.
pCR 58% vs. 41%, (p=0·0044). In the PD-L1-positive population, pCR 69% vs. 49% (p=0·021).
In NAC, grade 3–4 adverse events were balanced 37 (23%) vs. 26 (16%) patients.
Interpretation: In patients with early-stage TNBC, neoadjuvant treatment with atezolizumab in combination with nab-paclitaxel and anthracycline-based chemotherapy significantly improved pathological complete response rates with an acceptable safety profile.

Stem Cell Transplant Trial.
←R→ 885 women < 56 yo with ≥ 4 LN+. | 1. "Conventional" chemo alone | 2. High dose chemo → **stem cell transplant** |.
"Conventional" Chemo = 5 cycles of CEF = fluorouracil, 500 mg/m2, epirubicin, 90 mg/m2, and cyclophosphamide, 500 mg/m2
High dose Chemo = 4 cycles of CEF → 1 cycle of CTP = cyclophosphamide, 6000 mg/m2, thiotepa, 480 mg/m2, and carboplatin, 1600 mg/m2.

Steenbruggen, JAMA Oncol 2020.
20-year OS 41.5% vs. 45.3% (NS). with HDCT and 41.5% with CDCT (hazard ratio, 0.89; 95% CI, 0.75-1.06).
20-year OS if ≥ 10 LN+ = ↑ 14.6% (HR 0.72, SS) aka 30% vs. 45%.
20-year OS if triple neg = ↑ 15.4% (NS) aka 37% vs. 53%.
The cumulative incidence risk of a second malignant neoplasm at 20 years or major cardiovascular events was similar in both treatment groups (20-year cumulative incidence risk for second malignant neoplasm was 12.1% in the HDCT group vs 16.2% in the CDCT group, P = .10), although patients in the HDCT group more often had hypertension (21.7% vs 14.3%, P = .02), hypercholesterolemia (15.7% vs 10.6%, P = .04), and dysrhythmias (8.6% vs 4.6%, P = .005).
Conclusions: High-dose chemotherapy provided no long-term survival benefit in unselected patients with stage III breast cancer but did provide improved overall survival in very high-risk patients (ie, with ≥10 involved axillary lymph nodes). High-dose chemotherapy did not affect long-term risk of a second malignant neoplasm or major cardiovascular events.

Takeaway 1: Maybe good for the highest risk patients! Especially the untargetable triple negative subset.

Inflammatory Breast Cancer

NCDB Unfortunate SLNB in Trends In Inflammatory BCa
RR 1096 patients with ↑ use of SLNB increased during the study period from 11% in 2012 to 22% in 2017.
Age 56 yo.

Sosa, JAMA Network 2022.
Of the 186 of 1096 women (17%) who received any SLNB, 137 (73.7%) were White individuals; and of the 910 of 1096 women (83%) who received an ALND only, 676 (74.3%) were White individuals. Among women undergoing any SLNB, 119 of 186 (64%) did not undergo a completion ALND.
SS ↑ trend in the use of SLNB from 2012 to 2017 (22 of 205 patients [11%] vs 32 of 148 patients [22%]; P = .004).
MVA, the use of SLNB was associated with diagnosis year (2017 vs 2012; odds ratio [OR], 2.26; 95% CI, 1.26-4.20), clinical nodal status (cN3 vs 0; OR, 0.39; 95% CI, 0.22-0.67), and receipt of reconstructive surgery (OR, 1.80; 95% CI, 1.09-2.96).
Conclusions and Relevance The findings of this cohort study suggest that there is frequent and increasing use of SLNB in patients with IBC that is not evidence-based or supported by current treatment guidelines.

Dose Escalation MD Anderson
RR 256 patients IBC planned course of chemotherapy, mastectomy, and postmastectomy radiation vs. those who cannot complete it.
1970s: 50 Gy → 60 Gy. 1980s: 45-51 Gy 1.5 Gy BID → 66 Gy (15 Gy boost). Total dose is 66 Gy BID.

Bristol, IJROBP 2008.
5-year LRC (84% vs. 51%), DMFS (47% vs. 20%), and OS (51% vs. 24%) (p < 0.0001 for all comparisons).
Univariate factors LRC **1.** response to NeoAdjC, **2.** SM status, **3.** # involved lymph nodes, and **4.** use of taxanes.
60 Gy → 66 Gy SS ↑ LRC in patients if **1.** NeoAdjC < PR, **2.** +, close, or ? margins, **3.** and patients <45 years of age.
However Dose Escalation ↑ G3-4 late complications 15% → 29% (NS p = 0.08)

CONCLUSIONS: Patients with IBC who are able to complete treatment with chemotherapy, mastectomy, and postmastectomy radiation have a high probability of locoregional control. Escalation of postmastectomy radiation dose to 66 Gy appears to benefit patients with disease that responds poorly to chemotherapy, those with positive, close, or unknown margin status, and those <45 years of age.

Other Studies: 2019 NOMOGRAM SEER

HER2 (NAC, Adj, M+)

Trastuzumab binds close to the transmembrane domain, inhibiting HER2 dimerization. Pertuzumab binds to the dimerization domain, inhibiting HER2 heterodimerization with other HER family receptors. Both antibodies induce antibody-dependent cell-mediated cytotoxicity.

NAC

TRAIN-2 Netherlands Reason for TCHP!
←R→ 438 Stage II-III Her2+ breast cancer for NAC | 1. 5-FU, epirubicin, cyclophosphamide → Carbotaxol | 2. Carbotaxol |. ALL ARMS HAD T+P.
Dose ARM 1: 5-fluorouracil (500 mg/m 2), epirubicin (90 mg/m 2), cyclophosphamide (500 mg/m 2) every 3 weeks for 3c → paclitaxel (80 mg/m 2 on days 1 and 8) and carboplatin (AUC 6 mg/mL per min on day) q 3 weeks x 6c.
Dose ARM 2: nine cycles of paclitaxel and carboplatin at the same dose and schedule.
BOTH ARMS: Trastuzumab (6 mg/kg, loading dose 8 mg/kg) and pertuzumab (420 mg, loading dose 840 mg) concurrently with all chemotherapy cycles.
1^{O} pCR. Patients completed one year of trastuzumab, radiotherapy and endocrine therapy as indicated.

Van Ramshorst, 2018. 19 months.
pCR 67% vs. 68% (NS).
Serious adverse events 28% vs. 22%.
Grade ≥3 neutropenia 60% vs. 54%, Grade ≥3 diarrhea 12% vs 18% Grade ≥2 peripheral neuropathy 30-31%.
Grade ≥3 febrile neutropenia 10% vs 1%, (p<0·0001).
Symptomatic left ventricular systolic dysfunction was rare in both groups (two [1%] of 220 vs 0 of 218).
One patient in the anthracycline group died because of a pulmonary embolism, which was possibly treatment related.
Interpretation: In view of the high proportion of pathological complete responses recorded in both groups and the fact that febrile neutropenia was more frequent in the anthracycline group, omitting anthracyclines from neoadjuvant treatment regimens might be a preferred approach in the presence of dual HER2 blockade in patients with early HER2-positive breast cancer. Long-term FU is required to confirm these results.

Van der Voort, JCO 2020 ABSTRACT FU 48.8 months
3-year EFS 92.7% vs. 93.6%. 3-year OS 98%. These results were irrespective of hormone receptor and nodal status.
LVEF decline ≥10% from baseline and < 50% = more common of anthracyclines than in the PTC-Ptz arm (8.6% vs. 3.2%, p = 0.021).
Two patients in the FECT-PTC-Ptz arm developed acute leukemia. No other new safety concerns were seen.
Conclusions: The 3-year follow-up of the TRAIN-2 study confirms the results of the primary outcome that anthracylines do not improve efficacy and are associated with clinically relevant toxicity. A neoadjuvant carboplatin-taxane based regimen with dual HER2-blockade can be considered in all stage II-III breast cancer patients, regardless of hormone receptor and nodal status.

HER2 Alone Non-inferiority Trial
←R→ 275 women aged 70-80 yo with HER2+ breast cancer | 1. Trastuzumab alone | 2. Trastuzumab + chemo |.
Stage: I (pT > 0.5 cm), 43.6%; IIA, 41.7%; IIB, 13.5%; and IIIA, 1.1%.
1^{O} DFS.

Sawaki, JCO 2020.
3-year DFS 89.5% vs. 93.8% (NS).
3-year restricted mean survival time (RMST) differed by −0.39 months between arms (NS).
3-year RFS 92.4% vs. 95.3% (NS).
Common AEs were anorexia (7.4% vs. 44.3%; P < .0001) and alopecia (2.2% vs. 71.7%; P < .0001), and grade 3/4 nonhematologic AEs occurred in 11.9% vs. 29.8% (P = .0003).
Clinically meaningful HRQoL deterioration rate showed significant differences at 2 months (31% vs. 48%, SS). and at 1 year (19% vs 38%; P = .009).
CONCLUSION The primary objective of noninferiority for trastuzumab monotherapy was not met. However, the observed loss of survival without chemotherapy was < 1 month at 3 years. Therefore, and in light of the lower toxicity and more favorable HRQoL profile, trastuzumab monotherapy can be considered an adjuvant therapy option for selected older patients.

Trastuzumab Biosimilar – SB3
Pivot, JAMA Netw Open 2023 https://ascopubs.org/doi/full/10.1200/JCO.2017.74.0126

Adjuvant

APHINITY **Surgery → chemo /trastuzumab ± pertuzumab**
←R→ 4805 patients with node-positive or ~~high-risk node-negative (aka size > 1.0 cm)~~ **~~(protocol amendment)~~** HER2-positive
Surgery → and standard chemo within 8 weeks + | **1. pertuzumab** | **2. placebo** |. + 1 year of treatment with trastuzumab.

von Minckwitz, NEJM. 2017
All comers 3-year invasive DFS 94.1% vs. 93.2% (P=0.045)
In node-positive disease, 3-year invasive DFS 92.0% vs. 90.2% (P=0.02).
In node-negative disease 3-year invasive-DFS 97.5% vs. 98.4% (NS).
ratio for an invasive-disease event, 1.13; 95% CI, 0.68 to 1.86; P=0.64).
Side effects: Heart failure, cardiac death, and cardiac dysfunction were infrequent < 1% in both treatment groups. Diarrhea of grade 3 or higher occurred almost exclusively during chemotherapy and was more frequent with pertuzumab than with placebo (9.8% vs. 3.7%).
CONCLUSIONS Pertuzumab significantly improved the rates of invasive-disease–free survival among patients with HER2-positive, operable breast cancer when it was added to trastuzumab and chemotherapy

Radiation NOTES: Radiotherapy was given as clinically indicated at the end of chemotherapy and concomitantly with anti-HER2 treatment.
In the adjuvant APHINITY trial, where radiation was given concurrently with trastuzumab/pertuzumab or trastuzumab, grade ≥ 3 adverse events were similar between the arms, though the unique contribution of the radiation was not examined.

Piccart, JCO 2021. 6 years
This interim OS analysis comparing pertuzumab versus placebo did not reach the *P* = .0012 level required for statistical significance (*P* = .17, hazard ratio 0.85).
6-year OS were 95%. 6-year IDFS of 91% and 88% for pertuzumab and placebo groups, respectively.
Subset: N+ (n=3006) 6-year IDFS 88% v. 83% (SS)
N- (N=1799) 6-year IDFS NS
In a subset analysis, IDFS benefit from pertuzumab showed a hazard ratio of 0.73 (95% CI, 0.59 to 0.92) for HR-positive disease and a hazard ratio of 0.83 (95% CI, 0.63 to 1.10) for HR-negative disease. Primary cardiac events remain < 1% in both the treatment groups. And this all should be remembered in the context of pertuzumab more than doubling rates of grade 3+ diarrhea (4% versus 10%, respectively) and undoubtedly compounding financial toxicity.
CONCLUSION This analysis confirms the IDFS benefit from adding pertuzumab to standard adjuvant therapy for patients with node-positive HER2-positive early BC. Longer follow-up is needed to fully assess OS benefit.

> "APHINITY probably signals the end of treatment escalation for the node-negative [HER2+] subgroup and suggests that strategies to reduce the burden of chemotherapy experienced by these patients should be evaluated."

Elderly RESPECT Trial
←R→ 275 patients stage I-IIIA, age 70-80 years HER2+ BCa → surgery → | 1. trastuzumab (T) |2. T + chemotherapy (T + C) |.

Taira, JCO 2021 **QoL analysis**
At 2, 12, and 36 months, 198, 177, and 178 patients completed surveys, and the mean FACT-G scores at each survey point were 78.9, 80.4, 82.7, and 79.1 in group T and 79.5, 74.5, 78.4, and 78.5 in group T + C.
Compared with group T + C, the proportion of patients showing QoL deterioration (≥ 5 points decrease from baseline in FACT-G) was significantly lower at 2 months (31% v 48%; P = .016) and 12 months (19% v 38%; P = .009).
In group T, the Hospital Anxiety and Depression Scale score (P = .003) and the proportion of severe sensory peripheral neuropathy (P = .001) were significantly lower at 2 months, and Philadelphia Geriatric Center Morale Scale and Tokyo Metropolitan Institute of Gerontology Index of Competence scores were significantly higher (P = .024, .042) at 12 months. At 36 months, there were no significant differences in any QoL items.
CONCLUSION
Detrimental effects of adjuvant chemotherapy on global QoL, morale, and activity capacity lasted for at least 12 months but were not observed at 36 months.

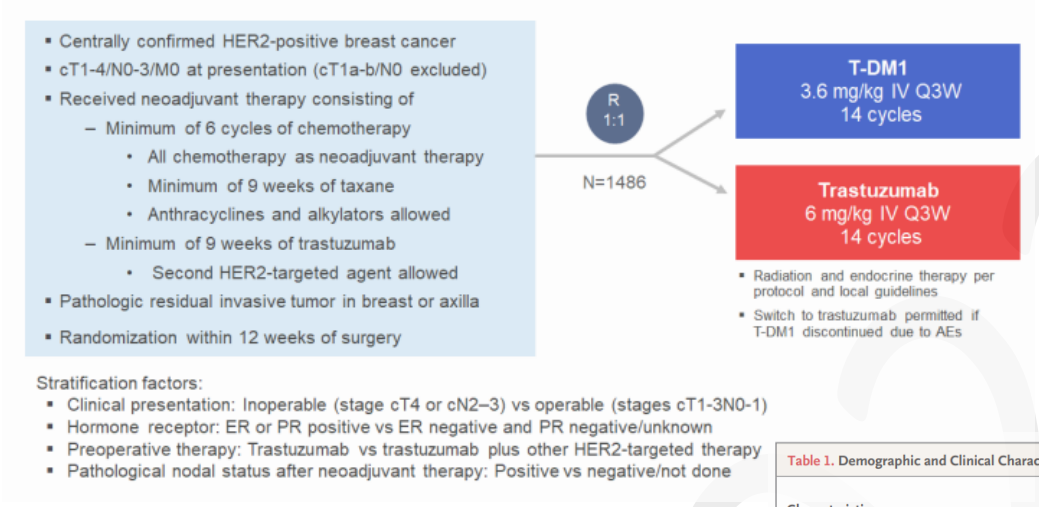
KATHERINE T-DM1 Trials. **NAC → Surgery → Kadcyla for residual disease** **otherwise if pCR Herceptin for 1 year.**

←R→ 1486 Her2+ early breast cancer s/p NAC (Trastuzumab + taxane ± A) → surgery → | 1. Adjuvant T-DM1 x 14c | 2. Trastuzumab x 14c |

T (trastuzumab) conjugate to cytotoxic drug (DM1).

1^{O} invasive DFS. T1-T4 Nany M0 (cannot be T1aN0 or T1bN0)

Exclusion: Mastectomy → gross tumor left behind or Lumpectomy → SM+; progressive disease during NAC; and cardiopulmonary dysfunction (including heart failure of New York Heart Association (NYHA) class II (mild symptoms and function limitation) or higher or a history of ↓ LV EF < 40% with previous therapy.



Von Minckwitz, NEJM 2019. INTERIM

3-years DFS 88.3% vs. 77.0% (p<0.001)
The safety data were consistent with the known safety profile of T-DM1, with more adverse events associated with T-DM1 than with trastuzumab alone.

CONCLUSIONS Among patients with HER2-positive early breast cancer who had residual invasive disease after completion of neoadjuvant therapy, the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant T-DM1 than with trastuzumab alone

Radiation NOTES: In the seminal KATHERINE trial, patients with residual cancer after neoadjuvant trastuzumab plus a taxane generally received radiation within 60 days of surgery, given concurrently with trastuzumab or T-DM1.Radiation pneumonitis was slightly more common with T-DM1 (1.5%) than with trastuzumab (0.7%), but radiation skin injury was similar (27.6% vs 25.4%). In one reported series, however, 50% of patients developed radiation brain necrosis when T-DM1 and radiosurgery were given concurrently to treat brain metastases, vs 29% when the treatments were sequential. Given these findings, Dr. Torres believes that T-DM1 plus radiotherapy is "probably safe," though there are caveats: "I generally avoid radiation to the brain with concurrent T-DM1. I also generally avoid concurrent T-DM1 with regional nodal radiation, due to the proximity of the radiation to the brachial plexus and the increased amount of the lung in the radiation field, which could increase the risk of pneumonitis."

Only 18% of adjuvant Her2 therapy was with Pertuzumab.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Trastuzumab Group (N=743)	T-DM1 Group (N=743)
Median age (range) — yr	49 (23–80)	49 (24–79)
Race or ethnic group — no. of patients (%)†		
White	531 (71.5)	551 (74.2)
Asian	64 (8.6)	65 (8.7)
Black	19 (2.6)	21 (2.8)
American Indian or Alaska Native‡	50 (6.7)	36 (4.8)
Multiple or unknown	79 (10.6)	70 (9.4)
Clinical stage at presentation — no. of patients (%)		
Inoperable breast cancer§	190 (25.6)	185 (24.9)
Operable breast cancer¶	553 (74.4)	558 (75.1)
Hormone-receptor status — no. of patients (%)		
Estrogen-receptor–negative and progesterone-receptor–negative or status unknown	203 (27.3)	209 (28.1)
Estrogen-receptor–positive, progesterone-receptor–positive, or both	540 (72.7)	534 (71.9)
Previous use of anthracycline — no. of patients (%)	564 (75.9)	579 (77.9)
Neoadjuvant HER2-targeted therapy — no. of patients (%)		
Trastuzumab alone	596 (80.2)	600 (80.8)
Trastuzumab plus pertuzumab	139 (18.7)	133 (17.9)
Trastuzumab plus other HER2-targeted therapy‖	8 (1.1)	10 (1.3)

Metastatic

Metastatic Trials	Drug Arms	Her2 + mBC	mPFS (mo)	mOS (mo)	ORR	Notes
CELOPATRA	Taxane Tras Pertuz Taxane Tras	1st line	18.5 12.4	**56.5** 40.8	80.5% 69.3%	This is still 1st line.
EMILIA	TDM1 Lapatinib Cape	2nd line	9.6 6.4	**30.9** 25.1	43.6% 30.8%	For now, 2nd line.
DESTINY-Breast01	DS-8201 (TDxd)	After median 6 prior Her2 tx	**16.4**	Not reach	**60.9%**	Great 3rd line choice if NO brain mets.
DESTINY-Breast04 HER2 "Low"						Trastuzumab Deruxtecan approved reclassifying 60% of formerly HER2- BCa.
SOPHIA	Margetuximab + C Tras + C	3nd line	5.8 4.9	21.6 19.8	22.1% 16%	
NALA	Neratinib + Cape Lapatinib + Cape	Some "Asymptomatic CNS disease"	8.8 6.6	24 22	33% 27%	
HER2CLIMB	Tras Cape Tucatinib Tras Cape	**50% + brain mets**	7.8 5.6	**21.9** 17.4	41% 23%	Survival advantage especially in **brain mets.**

HER2 CLIMB-02: New drug trastuzumab deruxtecan TDxd. This new drug is basically the same as TDM1, but instead of emestasine, this new drug is not a tubulin inhibitor but similar to irinotecan in mechanism. Also, TDM1 has like a payload of 3-4 emestasine per antibody, and this new has around 8. Also, once the drug gets into the cell, emestasine cannot diffuse OUT of the cell. But this new drug can, so it can potentially be good for a mixed HER2 expressing cancer that can get active in HER2 cells and diffuse out to HER2 negative surrounding cells.

PHOEBE **Pyrotinb (irreversible pan-HER blocker) vs. lapatinb.**
←R→ 267 women with HER2+ metastatic breast cancer. Previously treated with trastuzumab and taxanes
| 1. PO pyrotinib 400 mg + Cape | 2. Lapatinib 150mg + Cape | + PO cape 1000 mg/m2 BUD ib days 104 of each 21-day cycle.
1^{O} PFS.

Xu, Lancet 2021 **Interim Findings**
Median PFS 12·5 months vs. 6·8 months (HR 0·39, p<0·0001).
≥ G3 diarrhea 31% vs. 8% ≥ G3 hand–foot syndrome 15-16%.
No treatment-related deaths were reported in the pyrotinib group and 1 sudden death in the lapatinib group was considered tx related.
Interpretation Pyrotinib plus capecitabine significantly improved progression-free survival compared with that for lapatinib plus capecitabine, with manageable toxicity, and can be considered an alternative treatment option for patients with HER2-positive metastatic breast cancer after trastuzumab and chemotherapy.

DESTINY-Breast04
Background: Among breast cancers without human epidermal growth factor receptor 2 (HER2) amplification, overexpression, or both, a large proportion express low levels of HER2 that may be targetable. Currently available HER2-directed therapies have been ineffective in patients with these "HER2-low" cancers.
←R→ 557 women HER2-low metastatic breast cancer w/ 1-2 previous lines of chemotherapy.
494 (88.7%) had hormone receptor–positive disease and 63 (11.3%) had hormone receptor–negative disease.
Low expression of HER2 = IHC 1+ or IHC 2+ and neg. FISH.
2:1 ratio | 1. trastuzumab deruxtecan | 2. physician's choice of chemotherapy |.
1^{O} PFS in hormone receptor–positive cohort.

Modi, NEJM 2022
Hormone receptor–positive cohort Median PFS 10.1 vs. 5.4 months (HR disease progression or death, 0.51; P<0.001)
Median OS 23.9 vs. 17.5 months (HR for death, 0.64; P=0.003).
Among all patients Median PFS 9.9 vs. 5.1 (HR 0.50; P<0.001)
Median OS 23.4 vs. 16.8 (HR 0.64; P=0.001).
Adverse events of grade 3 or higher occurred in 52.6% of the patients who received trastuzumab deruxtecan and 67.4% of those who received the physician's choice of chemotherapy. Adjudicated, drug-related interstitial lung disease or pneumonitis occurred in 12.1% of the patients who received trastuzumab deruxtecan; 0.8% had grade 5 events.
CONCLUSIONS In this trial involving patients with HER2-low metastatic breast cancer, trastuzumab deruxtecan resulted in significantly longer progression-free and overall survival than the physician's choice of chemotherapy.

COMMENT: HER2-low breast cancer reclassified 60% of formerly HER2-negative breast cancers that historically had little options outside chemo or endocrine therapy.

DESTINY-Breast03 Trial

Background: Trastuzumab emtansine is the current standard treatment for patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer whose disease progresses after treatment with a combination of anti-HER2 antibodies and a taxane.

T-DM1 = conjugate anti-HER2 monoclonal antibody + cytotoxic microtubule inhibitor DM1.

T-DXd = conjugate anti-HER2 monoclonal antibody + cytotoxic topoisomerase I inhibitor.

←R→ 524 women HER2-positive metastatic breast cancer | 1. trastuzumab deruxtecan | 2. trastuzumab emtansine |.

Cortes, NEJM 2022

12-month Alive without disease progression 75.8% vs. 34.1% (HR progression or death from any cause, 0.28; P<0.001).

12-month OS 94.1% vs. 85.9% (HR 0.55; prespecified significance boundary not reached).

Overall response (CR or PR) 79.7% vs. 34.2%.

Drug-related adverse events of any grade was 98.1% vs. 86.6%. Grade 3 or 4 was 45.1% vs. 39.8%.

Adjudicated drug-related interstitial lung disease or pneumonitis occurred in 10.5% of the patients in the trastuzumab deruxtecan group and in 1.9% of those in the trastuzumab emtansine group; none of these events were of grade 4 or 5.

CONCLUSIONS

Among patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane, the risk of disease progression or death was lower among those who received trastuzumab deruxtecan than among those who received trastuzumab emtansine. Treatment with trastuzumab deruxtecan was associated with interstitial lung disease and pneumonitis.

Chinese PERMEATE

78 women prospective Phase II single-arm, two-cohort, RT-naive HER2-positive brain metastases (cohort A) or progressive disease after RT (cohort B).

→ received pyrotinib 400 mg PO qD + capecitabine 1000 mg/m2 PO BID for 14 days → 7 days off every 3 weeks until progression or unacceptable toxicity.

51 (86%) of 59 patients in cohort A and 18 (95%) of 19 patients in cohort B had previous exposure to trastuzumab.

1^{O} confirmed intracranial objective response rate.

Yan, Lancet 2022 15.7 months

Intracranial objective response rate 74·6% and 42·1%.

The most common grade 3 or worse treatment-emergent adverse event was diarrhoea (14 [24%] in cohort A and four [21%] in cohort B).

Two (3%) patients in cohort A and three (16%) in cohort B had treatment-related serious adverse events.

No treatment-related deaths occurred.

Interpretation

To our knowledge, this is the first prospective study showing the activity and safety of pyrotinib plus capecitabine in patients with HER2-positive breast cancer and brain metastases, especially in radiotherapy-naive population. This combination deserves further validation in a randomised, controlled trial.

KATE2 Phase 2

←R→ 330 HER2+ advanced breast cancer. Previously treated with tastuzumab and taxanes.

| 1. T-DM1 + Atezolizumab | 2. T-DM1 + Placebo |. All study drugs q3 wek infusion.

1^{O} progression-free survival in the intention-to-treat population.

Emens, Lancet 2020. Median FU 8.5 months = FUTILITY

Treatment assignment was unmasked on Dec 11, 2017, due to futility and the ↑ adverse events among patients assigned atezolizumab.

This date was set as the clinical cutoff for the primary analysis.

Median PFS was 8·2 months vs. 6.8 months (HR 0·82, p=0·33).

≥ G3 ↑ thrombocytopenia 13% vs. 4%, ↑ AST 8% vs. 3%, ↑ anaemia 5% vs. 0%, ←→ neutropenia 5% vs. 4%, and ↑ ALT 5% vs. 3%.

Serious adverse events ↑ 33% vs. 19% (SS).

One patient who received atezolizumab died due to a treatment-related adverse event (haemophagocytic syndrome).

Interpretation: Addition of atezolizumab to trastuzumab emtansine **DID NOT SHOW** a clinically meaningful improvement in progression-free survival and was associated with more adverse events. Further study of trastuzumab emtansine plus atezolizumab is warranted in a subpopulation of patients with PD-L1-positive, HER2-positive advanced breast cancer.

NALA TKI Trial Neratinb (Irreversible pan-HER2 TKI) vs. Lapatinb (Reversible Dual TKi).

←R→ 621 patients metastatic HER2+, (including those with stable neurological disease)

| 1. Neratinb + Cape | 2. Lapatinb + Cape |.

Neratinib 240 mg daily + Cape 750 mg/m2 BID w/ loperamide. Lapainib 1250 mg daily + Cape 1000 mg/m2 BID.

Co-primary 1^{O} PFS and OS.

Saura, JCO 2020.

↑ PFS N+C (HR, 0.76; *P* = .0059). OS was a wash.

↓ interventions for CNS disease 22.8% vs. 29.2% (*P* = .043).

Median Duration of Response (DoR) 8.5 vs. 5.6 months (HR, 0.50; *P* = .0004).

All-grade adverse events were diarrhea 83% vs. 66% and nausea 53% *v* 42%.

Discontinuation rates and HRQoL were similar between groups.

CONCLUSION

N+C significantly improved PFS and time to intervention for CNS disease versus L+C. No new N+C safety signals were observed.

MonarcHER HER2+ breast cancer w/ ≥2 previous therapies for advanced disease.
←R→ Phase 2, 237 HR+, HER2+ unresectable, locally advanced, or metastatic breast CA. MUST have received ≥ 2 HER2+ targeted prior therapies.
| 1. abemaciclib, trastuzumab, and fulvestrant (group A) | 2. abemaciclib and trastuzumab (group B) | 3. SoC chemotherapy + trastuzumab (group C) |.
PO abemaciclib 150 mg 12 hourly was administered on days 1–21 of a 21-day cycle.
IV trastuzumab 8 mg/kg on cycle 1 day 1 → 6 mg/kg on day 1 of each subsequent 21-day cycle
IM fulvestrant 500 mg on days 1, 15, and 29 and once every 4 weeks thereafter.
SoC Standard-of-care chemotherapy = as specified by the product label.
1^{O} PFS in the intention-to-treat population, first testing group A versus group C and, if this result was significant, then group B versus group C.

Tolaney, Lancet 2020. **19 months follow-up.**
Median PFS group A 8·3 months vs. group C 5·7 months (HR 0·67; p=0·051).
Median PFS group B 5·7 months vs. group C 5.7 months (HR 0·94, NS)
G3-4 Tox neutropenia 27% vs. 22% vs. 26%.
Serious adverse events: A pyrexia (three [4%]), diarrhoea (two [3%]), UTI (two [3%]), and acute kidney injury (two [3%])
B diarrhoea (two [3%]), and pneumonitis (two [3%])
C neutropenia (four [6%]) and pleural effusion (two [3%]).
Two deaths were attributed to treatment: one due to pulmonary fibrosis in group B and one due to febrile neutropenia in group C.
Interpretation The combination of abemaciclib, fulvestrant, and trastuzumab significantly improved progression-free survival versus standard-of-care chemotherapy plus trastuzumab while showing a tolerable safety profile. Our results suggest that a chemotherapy-free regimen might potentially be an alternative treatment option for patients with hormone receptor-positive, HER2-positive advanced breast cancer.

HERA Trial
←R→ 5102 women with HER2-positive early breast cancer. After all primary therapy (surgery, C, RT) →
| 1. Trastuzumab 1 year once at 8 mg/kg → then 6 mg/kg q3wks) | 2. Trastuzumab 2 years | 3. Obs |.
Primary endpoint is disease-free survival, and analyses are in the intention-to-treat population.

Cameron, Lancet 2017. **11-year FU.**
1 year of trastuzumab SS ↓ DFS (HR 0·76, 95% CI 0·68–0·86) and death (0·74, 0·64–0·86) compared with observation. 2 years of adjuvant trastuzumab did NOT ↑ DFS compared with 1 year of this drug (HR 1·02).
10-year DFS disease-free survival 69%, 69% vs. 63%.
NOTE: 884 (52%) patients assigned to the observation group selectively crossed over to receive trastuzumab.
Toxicity The incidence of secondary cardiac endpoints was 122 (7·3%) in the 2-years trastuzumab group, 74 (4·4%) in the 1-year trastuzumab group, and 15 (0·9%) in the observation group.
Interpretation: 1 year of adjuvant trastuzumab after chemotherapy for patients with HER2-positive early breast cancer significantly improves long-term disease-free survival, compared with observation. 2 years of trastuzumab had no additional benefit.

NOTE: Fehrenbacher, J Clin Oncol 2019 Patient's with a low-level HER2 expression via immunohistochemistry (IHC), should NOT receive HER2 targeted therapy. NSABP B-47 study randomized 3270 such patients to chemo +/- one year of trastuzumab. 5-year invasive DFS, distant RFS, or OS all null.

HER2CLIMB **Tucatinib Trial (PO small TKI Her2 highly selective)**
←R→ 612 HER2-positive metastatic breast cancer previously treated with trastuzumab (Herceptin), pertuzumab (Perjeta), and trastuzumab emtansine (Kadcyla).
Traztuzumab + Cape + |1. tucatinib | 2. Placebo |. 1O PFS
The patients with brain metastases (almost 50%) couldn't be in need of immediate treatment (i.e. symptomatic)—but if they did need treatment, they could get it and then enroll. In addition, patients with stable brain mets over 2 cm could enroll, but patients with leptomeningeal disease (nodular or classic?) could not enroll.

Murthy, NEJM 2019.
1-year PFS 33.1% vs. 12.3% (P<0.001). Median PFS 7.8 vs. 5.6 months.
2-year OS 44.9% vs. 26.6% (HR 0.66, P=0.005). Median OS 21.9 vs. 17.4 months.
1-year PFS **WITH BRAIN METS** 24.9% vs. 0% (HR 0.48, P<0.001). Median PFS 7.6 vs. 5.4 months.
Common adverse events in the tucatinib group included diarrhea, palmar–plantar erythrodysesthesia syndrome, nausea, fatigue, and vomiting. Diarrhea and elevated aminotransferase levels of grade 3 or higher were more common in the tucatinib-combination group than in the placebo-combination group.
NOTE: One of the many interesting side effects of tucatinib is that it increases serum creatinine without affecting GFR. Something to ponder when ordering your surveillance imaging.

CONCLUSIONS In heavily pretreated patients with HER2-positive metastatic breast cancer, including those with brain metastases, adding tucatinib to trastuzumab and capecitabine resulted in better progression-free survival and overall survival outcomes than adding placebo; the risks of diarrhea and elevated aminotransferase levels were higher with tucatinib.

Lin, JCO 2020 Brain Met Subset
Present: 291 patients with BMs: 198 (48%) in the tucatinib arm and 93 (46%) in the control arm.
Risk of intracranial progression or death was ↓ by 68% in the tucatinib arm (HR, *P* < .0001).
Median CNS-PFS was 9.9 months in the tucatinib arm versus 4.2 months in the control arm.
Risk of death was ↓ 42% in the tucatinib arm (OS HR, 0.58; *P* = .005). Median OS was 18.1 vs. 12.0 months (SS).
ORR-IC (intracranial objective response rate) was ↑ in the tucatinib arm 47.3% vs. 20.0% (SS).

CONCLUSION In patients with HER2-positive breast cancer with BMs, the addition of tucatinib to trastuzumab and capecitabine doubled ORR-IC, reduced risk of intracranial progression or death by two thirds, and reduced risk of death by nearly half. To our knowledge, this is the first regimen to demonstrate improved antitumor activity against BMs in patients with HER2-positive breast cancer in a randomized, controlled trial.

NOTE: Khatri, J Neuro Oncol 2023
RR of 22 patients (multiple brain lesions) SRS + Tucatinib. Radionecrosis 4%. 1 year LC 94% and 2 year LC 81%.
1-year distant brain relapse 39%. 1-year extracranial control 89%.

Other Trials

Modi, NEJM Destiny Phase 2. N Engl J Med 2019 (Kadcyla Refractory Study)
Trastuzumab deruxtecan (aka DS-8201) is an antibody conjugate (≈ Kadcyla) that links a HER2-targeted antibody to a cytotoxic agent (topoisomerase I inhibitor deruxtecan. Response Rate > 60% of 134 patients enrolled (Median OR > 16 months). Note: number of previous therapies was six. 1 in 6 patients developed interstitial lung disease.

ATEMPT Trial. Phase II TDM1 vs. Paclitaxel trial. ≤ 2 cm. 75% ER+. 75% Grade 3.
3-year DFS. 97.7 TDM1.
No real difference. 3-year follow-up is short for these ER+ patients.

TRYPHAENA Cardiac Safety Phase II (Antracycline w/wo)

KRISTINE Trial
Phase III results of the KRISTINE trial demonstrated that patients with HER2-positive early breast cancer had a significantly higher pathological complete response (pCR) rate when they received the neoadjuvant regimen of docetaxel, carboplatin, and trastuzumab plus pertuzumab (TCH+P) versus trastuzumab emtansine (T-DM1) plus pertuzumab (T-DM1+P).

Metastatic

Prognostic/Survival Tool

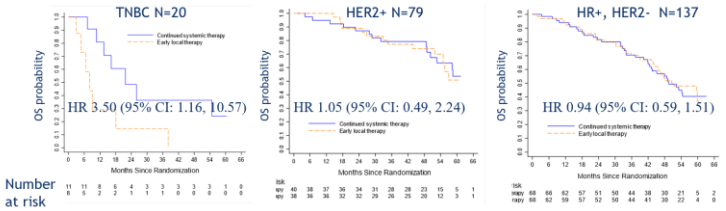
- https://ascopubs.org/doi/full/10.1200/CCI.21.00020

Oligometastatic and Local Therapy

ECOG E2108
←R→ 390 patients Stage I with intact primary tumor (IPS) → s/p optimal systemic therapy (OST) → if NO PROGRESSION…. | 1. LR Tx | 2. No LR Tx |.
Locoregional TX = surgery and radiotherapy per standards for nonmetastatic disease.
1^{O} overall survival (OS), with locoregional disease control as a secondary endpoint.

Khan, ASTRO 2020. 59 month FU.
3-year OS 68.4% vs. 67.9% (NS). 3-year PFS NS
3-year LR progression 10.2% vs. 25.6% (SS, p = 0.003).
Health-related quality of life (HRQOL) measured by FACT-B Trial Outcome Index ↓↓ SS in the OST+LRT arm at 18 months (60% completion).
BUT, there was no HRQOL Δ observed at time points 6 months (74% completion) or 30 months (56% completion).
Conclusions: Early local therapy does not improve survival in patients with de novo metastatic breast cancer and an IPT. Although there was a 2.5-fold higher risk of local disease progression without LRT, LRT of the IPT did not lead to improved HRQOL.

Results: overall survival by tumor subtype



- For 20 women with TNBC, survival was worse in the early local therapy arm.

Locoregional progression.

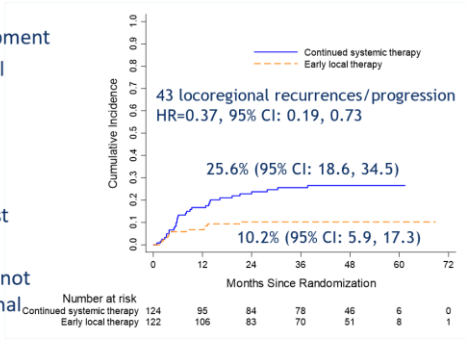
Definitions

Continued systemic therapy arm: Development of symptoms leading to a decision for local therapy.

Early local therapy arm

1) Regional nodal progression
2) Chest wall disease or invasive in-breast recurrence;

The occurrence of distant progression did not preclude the reporting of later local-regional recurrence/progression



Khan, JCO 2022.
3-year OS was 67.9% without and 68.4% with early locoregional therapy (NS).
Median OS was 53 – 55 months (NS).
Locoregional progression was less frequent in those randomly assigned to locoregional therapy (3-year rate: 16.3% v 39.8%; P < .001).
Quality-of-life measures were largely similar between arms.
Conclusion: Early locoregional therapy for the primary site did not improve survival in patients presenting with metastatic breast cancer. Although it was associated with improved locoregional control, this had no overall impact on quality of life.

Consolidative Use of RT to Block Oligoprogression (CURB) Trial
←R→ Phase 2 with 102 oligometastatic breast or NSCLC. 47% had > 5 total metastatic lesions. | 1. SBRT to all sites | 2. Palliative SOC |.
86% NSCLC w/o actionable driver mutation. 32% breast TNBC.
1^{O} PFS.

Tsai, ASTRO 2021. Interim 51 week FU.
Median PFS 22 weeks vs. 10 weeks (p=0.005).
This was **driven entirely by the PFS benefit from SBRT in the NSCLC patients** (44 weeks with SBRT vs. 9 weeks with SOC; p=0.004).
No difference in median PFS was seen in the breast cohort (18 weeks with SBRT vs. 17 weeks with SOC; p=0.5).
MVA, the PFS benefit of SBRT remained substantial in the NSCLC cohort (Hazard Ratio: 0.38; 95% CI: 0.18-77; p=0.007).
Grade ≥2 adverse events occurred in 8 patients in the SBRT arm, including 1 grade 3 pneumonitis.
Conclusion: In this pre-planned interim analysis of the first and largest randomized trial of radiotherapy for oligoprogressive metastatic NSCLC and breast cancer, we demonstrated the benefit of SBRT to sites of oligoprogression on overall PFS, meeting the primary endpoint. The mechanism of the differential benefits between NSCLC and breast cohorts merits further evaluation.

NRG-BR002

←R→ 125 patients Phase IIR/III trial, sought to determine the efficacy of SOC Systemic Tx (SOC ST) + MDT (SBRT or SR) as first line treatment of OMBC.
Methods: Oligometastatic BCa (OMBC) pts with ≤ 4 extracranial mets (standard imaging) + controlled primary disease were eligible if on first line SOC ST for ≤ 12 months without progression | 1. SOC ST (mainly chemotherapy, endocrine therapy, anti-HER2) | 2. ARM 2 – SOC ST with MDT of all mets |.
Median age 54, 79% ER+ or PR+/HER2-, 13% HER2+, 8% triple negative. 60% had 1 metastasis and 20% presented synchronously with primary disease.
Following randomization, systemic therapy was delivered to 95% in ARM 1 and 93% in ARM 2; ablation: SBRT 93%, SR 2%, and 5% none.

Chmura, 2022 ASCO Abstract 30 month

mPFS (70% CI) 23 mo vs. 19.5 mo.
24 and 36-mo PFS 45.7% and 32.8% vs. 46.8 and 38.1. NS.
Median OS was not reached in either arm
36-mo OS 71.8% vs. 68.9% (NS).
Analysis of first failure showed new mets outside index area (Arm 1) /RT field (Arm 2) developed similarly in both arms at 40%.
There were fewer new mets inside treated/index area for Arm 2 6.7% vs ARM 1 29.2%, respectively.
There were no grade 5 treatment-related adverse events (AEs), 1 grade 4 AE in ARM 1, and 9.7% and 5.3% grade 3 AEs in ARMS 1 and 2, respectively. Circulating tumor cell counts (0 vs ≥1) at baseline were similar in both arms and were not prognostic HR (95% CI): 1.04 (0.54, 2.02).
Conclusions: The addition of MDT to SOC ST did not show signal for improved PFS, nor OS difference in patients with OMBC. The trial will not proceed to the Phase III component.

Tata Memorial

Intro: The role of locoregional treatment in women with metastatic breast cancer at first presentation is unclear.
←R→ 350 treatment naïve patients (≤65 yo + life expectancy ≥ 1 yr) + de-novo metastatic breast cancer from Tata Memorial Centre, Mumbai, India.
| 1. locoregional tx to primary breast tumour + ALN | 2. No locoregional tx |.
Stratified by site of distant metastases, number of metastatic lesions, and hormone receptor status.
If resectable primary tumour in the breast that could be treated with endocrine therapy, there were randomly assigned upfront.
If unresectable primary tumour, then first chemotherapy → randomisation. These patients with C → randomization were randomized if objective tumour response after six to eight cycles of chemotherapy. 1^{o} OS by intention to treat.

Badwe, Lancet 2015.

Median OS 19·2 vs. 20·5 months (NS). 2-year OS 41·9%vs. 43·0% (NS).
IMPROVED Median PFS (NOT ATTAINED) vs. 18.2 mo (SS). **WORSENING** Distant PFS 11.3 mo vs. 19,8 mo (SS).
Only 10% of patients WITHOUT treatment required palliative surgery at time of recurrence.
The only adverse event noted was wound infection related to surgery in one patient in the locoregional treatment group.
INTERPRETATION: There is no evidence to suggest that locoregional treatment of the primary tumour affects overall survival in patients with metastatic breast cancer at initial presentation who have responded to front-line chemotherapy, and this procedure should not be part of routine practice.

SBRT Oligometastatic Metaanalysis
Objectives Stereotactic ablative radiotherapy (SABR) has been reported to be an effective treatment for oligometastatic disease from different primary cancer sites. Here we assess the effectiveness and safety of SABR for oligometastatic breast cancer patients by performing a meta-analysis.
←M→ 467 patients and 653 treated metastases.

Viani, Radiother Oncol 2021.

The 1- and 2-year local control rates were 97% (95% CI 95–99%), and 90% (95% CI 84–94%), respectively.
Overall survival (OS) was 93% (95% CI 89–96%) at 1 year, 81% (95% CI 72–88%) at 2 years.
The rate of any grade 2 or 3 toxicity was 4.1 % (95% CI 0.1–5%), and 0.7% (0–1%), respectively.
In the meta-regression analysis, only prospective design (p = 0.001) and bone-only metastases (p = 0.01) were significantly associated with better OS.
In the subgroup analysis, the OS at 2y were significantly different comparing HER2+, HR+/HER2(-) and triple negative breast cancer 100%, 86% and 32%, p = 0.001. For local control outcomes, hormone receptor status (p = 0.01) was significantly associated on meta-regression analysis.
Conclusion
SABR for oligometastatic breast cancer is safe and associated with high rates of local control. Longer follow-up of existing data and ongoing prospective trials will help further define the role of this management strategy.

Commentary: RT dose not defined well with heterogeneity - 20 Gy in 1 fraction to 75 Gy in 3 fractions to 50 Gy in 10 fractions.

Retrospective Reviews:
Canadian RR https://www.thegreenjournal.com/article/S0167-8140(21)06584-1/fulltext
MSK RR https://onlinelibrary.wiley.com/doi/10.1002/cam4.4068

Chemotherapy

HER2-Positive and Postmenopausal[g,h,i] or Premenopausal Receiving Ovarian Ablation or Suppression
• Aromatase inhibitor ± trastuzumab • Aromatase inhibitor ± lapatinib • Aromatase inhibitor ± lapatinib + trastuzumab • Fulvestrant ± trastuzumab • Tamoxifen ± trastuzumab

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression	
Preferred Regimens **First-Line Therapy** • Aromatase inhibitor + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1) • Selective ER down-regulator (fulvestrant, category 1)[b] ± non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[b] • Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1) • Non-steroidal aromatase inhibitor (anastrozole, letrozole) • Selective estrogen receptors modulator (tamoxifen or toremifene) • Steroidal aromatase inactivator (exemestane)	**Preferred Regimens** **Second- and Subsequent-Line Therapy** • Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[c] • For *PIK3CA*-mutated tumors, see additional targeted therapy options (see BINV-R)[c,d] • Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[c,f] • Non-steroidal aromatase inhibitor (anastrozole, letrozole) • Steroidal aromatase inactivator (exemestane) • Selective ER down-regulator (fulvestrant) • Selective estrogen receptors modulator (tamoxifen or toremifene)
Useful in Certain Circumstances[d] • Megestrol acetate • Estradiol • Abemaciclib[c,e]	

HR-Positive or -Negative and HER2-Positive[j,k]	
Setting	**Regimen**
First Line[l]	Pertuzumab + trastuzumab + docetaxel (Category 1, preferred)
	Pertuzumab + trastuzumab + paclitaxel (preferred)
Second Line[n]	Fam-trastuzumab deruxtecan-nxki[m] (Category 1, preferred)
Third Line	Tucatinib + trastuzumab + capecitabine[n] (Category 1, preferred)
	Ado-trastuzumab emtansine (T-DM1)[o]
Fourth Line and Beyond (optimal sequence is not known)[p]	Trastuzumab + docetaxel or vinorelbine
	Trastuzumab + paclitaxel ± carboplatin
	Capecitabine + trastuzumab or lapatinib
	Trastuzumab + lapatinib (without cytotoxic therapy)
	Trastuzumab + other chemotherapy agents[q,r]
	Neratinib + capecitabine
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)
	Additional Targeted Therapy Options see BINV-Q (6)

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	PD-L1 CPS ≥10[g] regardless of germline *BRCA* mutation status[b]	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[h] (Category 1, preferred)
	PD-L1 CPS <10[g] and no germline *BRCA1/2* mutation[b]	Systemic chemotherapy see BINV-Q (5)
	PD-L1 CPS <10[g] and germline *BRCA1/2* mutation[b]	• PARPi (olaparib, talazoparib) (Category 1, preferred) • Platinum (cisplatin or carboplatin) (Category 1, preferred)
Second Line	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib) (Category 1, preferred)
	Any	Sacituzumab govitecan[i] (Category 1, preferred)
		Systemic chemotherapy see BINV-Q (5)
	No germline *BRCA1/2* mutation[b] and HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
Third Line and beyond	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)
	Any	Systemic chemotherapy see BINV-Q (5)

ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
HR-positive/ HER2-negative[v]	*PIK3CA* activating mutation	PCR (blood or tissue block if blood negative)	Alpelisib + fulvestrant[w]	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2-negative[x]	*ESR1* mutation	NGS, PCR (blood)	Elacestrant	Category 2A	Other recommended regimen
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[y] Entrectinib[y]	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, NGS, PCR (tissue block)	Pembrolizumab[z,aa] Dostarlimab-gxly[bb]	Category 2A	
Any	TMB-H (≥10 mut/mb)	NGS	Pembrolizumab[z,aa]	Category 2A	
Any	*RET*-fusion	NGS	Selpercatinib[cc]	Category 2A	

Immunotherapy

I-SPY 2. ASCO 2017 TLDR: Pembro + standard therapy ↑↑ pCR rates in all HER2- BCs that meet I-SPY 2 eligibility, especially in TNBC. 29 TNBC ↑ pCR 20% → 60%. 40 HR+/HER– pts, ↑ pCR 13% → 34%.

I-SPY 2. JAMA Oncol 2020 TLDR: Prospective > 900 patients tumor > 2.5 cm with high risk receptor ± genome scores → 1 of 9 investigational NAdj Tx. Only about 35% had pCR, but those that di d ↑ 3-year 80% RR ↓ in breast recurrence (HR 0.19) + DM (HR 0.21)

PALOMA-3 Fulvestrant plus palbociclib versus fulvestrant

Background: CDK4 and CDK6 inhibitor palbociclib and fulvestrant was associated with ↑SS in PFS vs. fulvestrant plus placebo in metastatic breast cancer. Identification of patients most suitable for the addition of palbociclib to endocrine therapy after tumour recurrence is crucial for treatment optimisation in metastatic breast cancer. We aimed to confirm our earlier findings with this extended follow-up and show our results for subgroup and biomarker analyses.

←R→ double blind 521 patients randomized 2:1 age > 18, ER/PR+ Her2-, who **progressed on previous endocrine therapy** during treatment or within 12 months of completion of adjuvant therapy | 1. PO palbociclib + IM fulvestrant | 2. Placebo + fulvestrant |
Palbociclib (125 mg daily for 3 weeks followed by a week off over 28-day cycles)
Fulvestrant (500 mg intramuscular injection on days 1 and 15 of cycle 1; then on day 1 of subsequent 28-day cycles) 1^{O} PFS.

Cristofanilli, Lancet 2016

Median PFS 9·5 vs. 4·6 months (SS). NO OS BENEFIT.
Grade 3 or 4 events 73% vs. 22% (SS). neutropenia (65% vs. 1%) anaemia (2-3%) leucopenia (28% vs. 1%).
PIK3CA mutation was detected in the plasma DNA of 129 (33%) of 395 patients for whom these data were available. Neither PIK3CA status nor hormone-receptor expression level significantly affected treatment response.
INTERPRETATION: Fulvestrant plus palbociclib was associated with significant and consistent improvement in progression-free survival compared with fulvestrant plus placebo, irrespective of the degree of endocrine resistance, hormone-receptor expression level, and PIK3CA mutational status. The combination could be considered as a therapeutic option for patients with recurrent hormone-receptor-positive, HER2-negative metastatic breast cancer that has progressed on previous endocrine therapy.

PALOMA-2 Palbociclib + Letrozole vs. letrozole alone
Also PFS benefit 25mo vs 15mo
ER-positive, HER2-negative breast cancer, who had **"not had prior treatment"** for advanced disease
50% prior C, 56% prior endocrine tx.

MONALEESA-2 Ribociclib + Letrozole vs. letrozole alone
Also PFS benefit
HR-positive, HER2-negative recurrent or metastatic breast cancer who **had not received previous systemic therapy** for advanced disease.

Hortobagyi, NEJM 2022 6.6 years

Median OS was 63.9 months vs. 51.4 months (HR death, 0.76; P=0.008). No new safety signals were observed.
CONCLUSIONS
First-line therapy with ribociclib plus letrozole showed a significant overall survival benefit as compared with placebo plus letrozole in patients with HR-positive, HER2-negative advanced breast cancer. Median overall survival was more than 12 months longer with ribociclib than with placebo. (Funded by Novartis; MONALEESA-2 ClinicalTrials.gov number, NCT01958021. opens in new tab.)

MONALEESA-3 Ribociclib vs. placebo in **ER+ Her2-**.
←R→ 484 patients phase 3 Locally advanced | 1. Ribo + Fulvestrant | 2. Placebo + Fulvestrant | as 1^{st} line or 2^{nd} line Tx.

Slamon, NEJM 2020.
42 month – OS 57.8% vs. 45.9% (HR 0.72; P=0.00455). The benefit was consistent across most subgroups.
In a descriptive update, median PFS among patients receiving first-line treatment was 33.6 months vs. 19.2 months (SS).
CONCLUSIONS Ribociclib plus fulvestrant showed a significant overall survival benefit over placebo plus fulvestrant in patients with hormone-receptor–positive, HER2-negative advanced breast cancer.

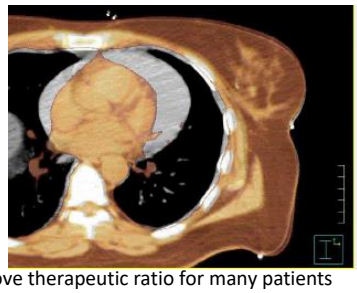
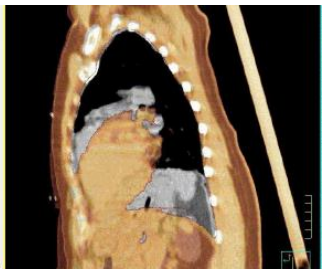
MONALEESA-7 Ribociclib + ET vs. ET alone
←R→ 672 premenopausal or perimenopausal HR+ Her2- locoregionally recurrent or metastatic disease that was not amenable to curative therapy.

Im, NEJM 2019.

42-month OS 70.2% vs. 46.0% (HR 0.71; P=0.00973 by log-rank test).
The survival benefit seen in the subgroup of 495 patients who received an aromatase inhibitor was consistent with that in the overall intention-to-treat population (hazard ratio for death, 0.70; 95% CI, 0.50 to 0.98). The percentage of patients who received subsequent antineoplastic therapy was balanced between the groups (68.9% in the ribociclib group and 73.2% in the placebo group).
Time from ←R→ to disease progression during receipt of second-line therapy or to death was also longer in the ribociclib group than in the placebo group (hazard ratio for disease progression or death, 0.69; 95% CI, 0.55 to 0.87).

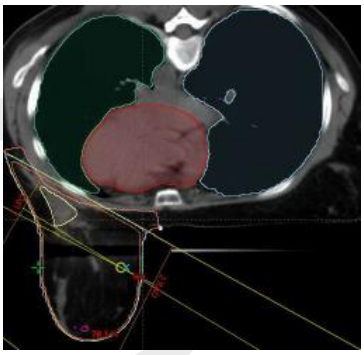
CONCLUSIONS This trial showed significantly longer overall survival with a CDK4/6 inhibitor plus endocrine therapy than with endocrine therapy alone among patients with advanced hormone-receptor–positive, HER2-negative breast cancer. No new concerns regarding toxic effects emerged with longer follow-up.

RT Fields + Nodal Guidelines

Common Terms Used:

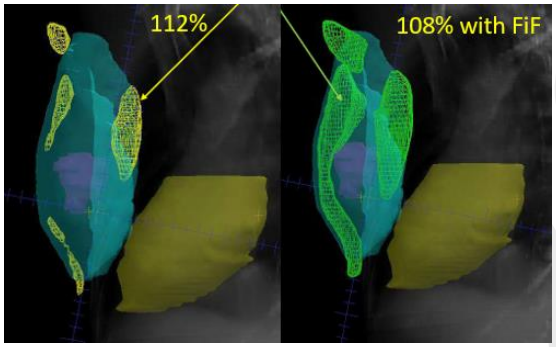
- Supine Breast Treatment
    - Breath hold
        - Displaces heart inferior and posterior to improve therapeutic ratio for many patients
        - Requires verification of position

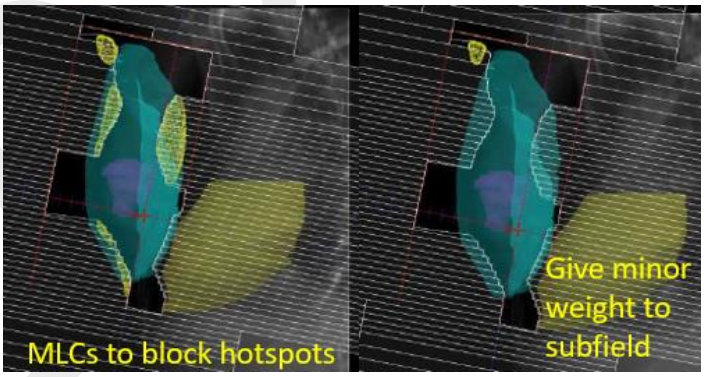


- Prone Breast Treatment
    - Displaces breast tissue anteriorly and can remove tumor bed or breast tissue away from chest wall
    - Great for pendulous breasts and tumor beds more anterior and in center of breast tissue
    - Improves homogeneity for the whole breast (decreases separation)
    - Very low lung dose; often improved cardiac sparing
    - Great for pre-invasive/early disease when target is just breast tissue
    - Can be difficult position to tolerate (uncomfortable and sometimes causes more anxiety);
        - Good to ask patients that have had MRI how they tolerated it
    - Some large breasted women contralateral breast tissue gets in the way
    - Medial tumors may require treatment through board or be harder to reach

- Field in Field Technique

  Alternative to IMRT to decrease hotspot and provide more uniformity





BCS

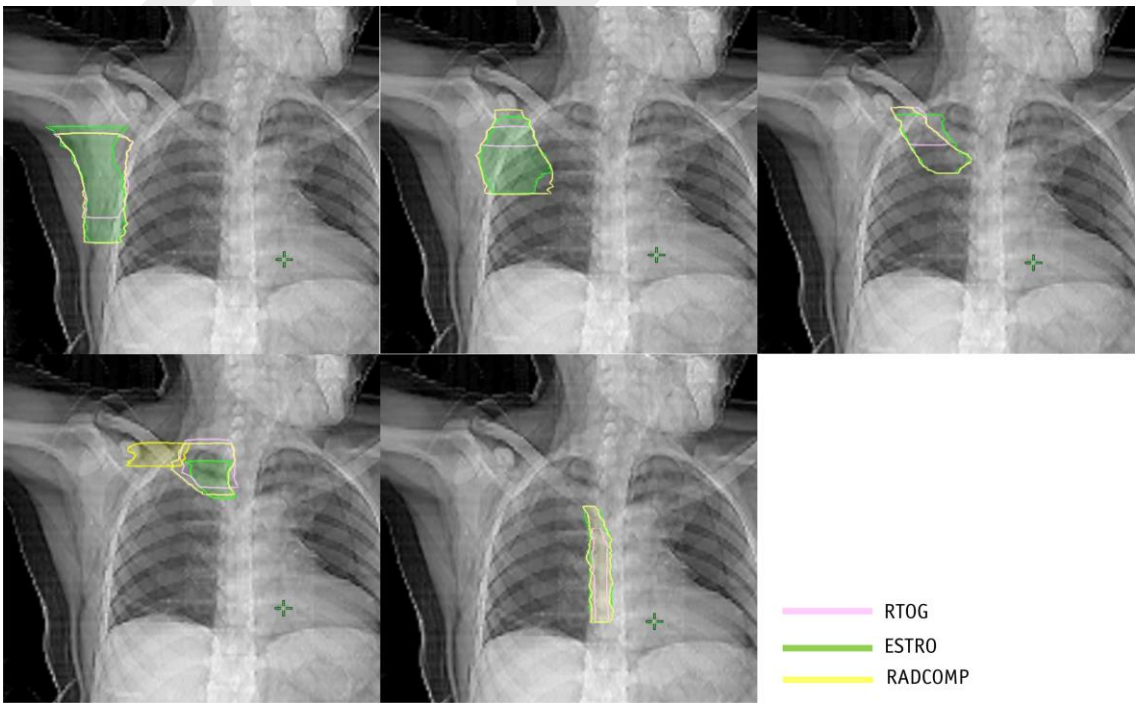
1. Supraclav Field: ≥4 Axillary + LNs or ECE
    - Borders
        - Inferior border-inferior aspect clavicular head
        - Superior border- top of T1/first rib (short of flash)
        - Medial-pedicles of vertebral bodies
        - Lateral-coracoid or lateral to humeral head
    - Depth traditionally 3cm, now use CT planning
    - Angled at 10-15º to prevent dose to spinal cord/esophagus
    - Lower portion of beam is half-beam blocked to eliminate divergence/prevent overlap with tangential field
    - If the ALND was excellent, SCV field may not necessary need to extend past the medial border of the humorus.
    - **Consider full coverage of the medial inferior SCV space**: https://www.practicalradonc.org/article/S1879-8500(22)00318-6/fulltext Marks, PRO 2022
2. Posterior Axillary Boost (PAB) Field
    - Used in an inadequately dissected axilla, >2.5cm LNs, fixed nodes, ECE, ≥4 axillary LNs or for underdosed axilla
    - PAB field supplements midline dose, treating posterior axillary LNs that may have otherwise been underdosed
    - Borders
        - Superior/Medial -bisect clavicle
        - Inferior-match superior border of tangential field
        - Lateral-bisects humeral head
3. Partially Wide
    - Trying to get IM, but it is PARTIALLY wide because you block excess heart and lung.
4. Shallow Tangent
    - This requires combination photons and elections.
    - Be careful of the cold triangle. You need to angle the electron just a tad (about 5 degrees) to minimize the triangle.
    - The matching point where the 2 fields meet are at the skin.
5. High Tangents
    - This is to increase the superior border of tangents to the bottom of the humeral head probably to decrease the amount of lung treated by the supraclav.
    - You can do high and partially wide tangents to cover nodes as needed.

TRONE (TransAtlantic Radiation Oncology Network) Evaluation of Nodal Volumes Variation **Loganadane, IJROBP 2020.**

Guidelines	RTOG	ESTRO	RADCOMP	Differences
Anatomic boundaries	Level I			
Cranial	Axillary vessels lateral edge of pectoral minor muscle	Medial: 5-mm cranial to the axillary vein; lateral: max up to 1 cm below the edge of the humeral head, 5 mm around the axillary vein	Axillary vessels cross lateral edge of pectoral minor muscle and below the humeral head	The cranial limit of level I is slightly (5 mm) higher than RTOG/RADCOMP atlases
Caudal	Pectoralis major muscle insert into rib	To the level of rib 4-5, taking into account the visible effects of the SLNB	Pectoralis major insertion on the ribs (difficult to see on CT and requires some clinical judgment, around fourth-fifth ribs)	The caudal limit in the ESTRO and the RADCOMP may be more generous because they are supposed to include surgical clips (Fig. 3 [1a])
Anterior	Plane defined anteriorly by surface of pectoralis major muscle and latissimus dorsi muscle	Pectoralis major and minor muscles	Pectoralis major or skin	The posterior limit of the CTV (anterior border of the subcapularis and latissimus dorsi) in the RTOG/RADCOMP guidelines is more generous compared with the ESTRO atlas (Fig. 3 [1b])
Posterior	Anterior surface of subscapularis muscle	Cranially up to the thoracodorsal vessels and more caudally up to an imaginary line between the anterior edge of the latissimus dorsi muscle and the intercostal muscles	Anterior border of subscapularis and latissimus dorsi	SLNB
Medial	Lateral border of pectoralis minor muscle	Level II, the interpectoral level, and the thoracic wall	Lateral border of pectoralis minor/level II	
Lateral	Medial border of latissimus dorsi muscle	Cranially up to an imaginary line between the major pectoral and deltoid muscles and further caudal up to a line between the major pectoral and latissimus dorsi muscle	Latissimus dorsi, at line connecting latissimus dorsi and dorsi and deltoid or up to skin	
Anatomic boundaries	Level II			
Cranial	Axillary vessels cross medial edge of pectoralis minor muscle	Includes the cranial extent of the axillary artery (ie, 5 mm cranial to axillary vein)	Pectoralis minor muscle insertion on coracoid	Level II in the RTOG is relatively small
Caudal	Axillary vessels cross lateral edge of pectoralis minor muscle	The caudal border of the minor pectoral muscle if appropriate: top of surgical ALND	Obliteration at fat space between pectoralis major and pectoralis minor or chest wall	In the craniocaudal direction compared with ESTRO and RADCOMP definition
Anterior	Anterior surface of pectoralis minor muscle	Minor pectoral muscle	Posterior pectoralis major	Similar to level I, the level II in the RTOG and RADCOMP is more generous in the posterior direction (anterior border of the subcapularis and latissimus dorsi)
Posterior	Ribs and intercostal muscles	Up to 5 mm dorsal to axillary vein or to costae and intercostal muscles	Chest wall	Level II in the RTOG and RADCOMP guidelines includes the interpectoral nodes, whereas it is a distinct entity in the ESTRO atlas (Fig 3 [2])
Medial	Medial border of pectoralis minor muscle	Medial edge of minor pectoral muscle	Medial border of pectoralis minor/level III	ALND
Lateral	Lateral border of pectoralis minor muscle	Lateral edge of minor pectoral muscle	Level I/lateral pectoralis minor	
Anatomic boundaries	Level III			
Cranial	Pectoralis minor muscle insertion on coracoid	Includes the cranial extent of the subclavian artery (ie, 5 mm cranial to subclavian vein)	Pectoralis minor muscle insertion on coracoid	The cranial limit of RTOG/RADCOMP is higher than the ESTRO definition
Caudal	Axillary vessels cross medial edge of pectoralis minor muscle	5 mm caudal to the subclavian vein if appropriate: top of surgical ALND	Obliteration at fat space between pectoralis major and pectoralis minor or chest wall	The retroclavicular nodes are part of the level III in the ESTRO atlas, whereas they are included in the SCV nodes in the RADCOMP atlas. Importantly, this volume was not considered in the RTOG atlas (there is a gap between supraclavicular and subclavicular nodes) (Fig 3 [3])
Anterior	Posterior surface of pectoralis major	Major pectoral muscle	Pectoralis major	-
Posterior	Ribs and intercostal muscles	Up to 5 mm dorsal to axillary vein or to costae and intercostal muscle	Chest wall	-
Medial	Thoracic inlet	Junction of subclavian and internal jugular veins—level IV	Obliteration of fat space and supraclavicular volume	-
Lateral	Medial border of pectoralis minor muscle	Medial side of the minor pectoral muscle	Level II/medial border of pectoralis minor	-
Anatomic boundaries	Level IV (supraclavicular nodes)			

Cranial	Caudal to the cricoid cartilage	Includes the cranial extent of the subclavian artery (ie, 5 mm cranial to subclavian vein)	Cricoid	The cranial limit defined by RTOG and RADCOMP by the cricoid cartilage is much higher than the cranial limited of the subclavian artery defined by ESTRO (Fig 3 [4b])
Caudal	Junction of brachiocephalic axillary veins/caudal edge clavicle head	Includes the subclavian vein with 5-mm margin, thus connecting to the cranial border of CTVn IMN	IMN (included subclavian vein)	The RADCOMP atlas proposed as an optional volume the posterolateral region of the supraclavicular fossa in patients with high-risk features
Anterior	SCM muscle	SCM muscle, dorsal edge of the clavicle	Dorsal surface of the SCM, clavicle, or strap muscles	-
Posterior	Anterior aspect of the scalene muscle	Pleura	Scalenus (anterior and medial), elevator scapulae, posterior edge of SCM and vascular region/no more posterior than pleura	-
Medial	Excludes thyroid and trachea	Includes the jugular vein without margin; excludes the thyroid gland and common carotid artery	Medial edge of carotid artery	Unlike ESTRO and RTOG, RADCOMP includes retroclavicular nodes (Fig 3 [4a])
Lateral	Cranial: lateral edge of SCM muscle, caudal: junction first rib-clavicle	Includes the anterior scalene muscles and connects to the medial border of the level III	Lateral edge of SCM, clavicle, and level III	-
Anatomic boundaries	Internal mammary nodes			
Cranial	Superior aspect of the medial first rib	Caudal limit of the level IV	Supraclavicular nodes or caudal to head of clavicle	In the ESTRO guidelines CTV is larger compared with RTOG. RTOG considers the internal mammary vessels; ESTRO proposes 5-mm margins around the vessels. (Fig 3 [5])
Caudal	Cranial aspect of the fourth rib	Cranial side of the fourth rib	Cranial border of fourth rib	IMN CTV in the RTOG extends in the first intercostal spaces; the ESTRO and RADCOMP extend superiorly up to the subclavian vein.
Anterior	Ribs and intercostal spaces	Ventral limit of the vascular area	Chest wall	-
Posterior	Pleura	Pleura	Pleura	-
Medial		5 mm from the internal mammary artery	Sternum	-
Lateral		5 mm from the internal mammary vein (artery in cranial part down to and including first intercostal space)	Includes any visible fat	-

RTOG 10-05 expansions of boost in high risk early stage. GTV + 1.0 cm = CTV. CTV + 0.7 cm = PTV.



Quality of RT

VA Quality of RT Publication: https://www.practicalradonc.org/article/S1879-8500(22)00271-5/fulltext

Proton Therapy

- **The more complex the case, it seems the better protos are suited (think: bilateral breast cancer, etc).**

Mayo IMPT Synchronous bilateral breast cancer (SBBC)
RR 11 patients with CTV = breast or CW + RNI (+IMs) plans of both IMPT and VMAT generated → goal 90% CTV receive ≥ 90% dose (D90 ≥ 90%).
All conventional RT 50 Gy in 25 fx. 5/11 patients tx with Arms DOWN IMPT.

Garda, Adv Rad Oncol 2022
Median CTV D90 was 99.9% for IMPT and 97.6% for VMAT (P = .001).
Mean heart dose was 0.7 Gy versus 7.2 Gy (P = .001), the total lung mean dose was 7.8 Gy versus 17.3 Gy (P = .001), and the total lung volume recieving 20 Gy was 13.0% versus 27.4% (P = .001).
The most common acute toxic effects were dermatitis (mostly grade 1-2 with 1 case of grade 3) and grade 1 to 2 fatigue. The most common toxic effects at the last-follow up (median, 32 months) were grade 1 skin hyperpigmentation, superficial fibrosis, and extremity lymphedema. No nondermatologic or nonfatigue adverse events of grade >1 were recorded.
Conclusions Bilateral breast and/or chest wall and comprehensive nodal IMPT is technically feasible and associated with low rates of severe acute toxic effects. Treatment with IMPT offered improved target coverage and normal-tissue sparing compared with photon therapy. Long-term follow-up is ongoing to assess efficacy and toxic effects.Proton Therapy / IMPT

Mayo Clinic HypoFx PMRT (Protons)
←R→ 82 patients protocol tx → | 1. 50 Gy in 25 fractions | 2. 40·05 Gy in 15 fractions | All proton PMRT.
All patients were treated with pencil-beam scanning. All mastectomy ± immediate reconstruction (66% vs. 73%) with indications for PMRT.
84% staged tissue expander.
1^{O} 24-month complication rate ≥G3 occurring from 90 days after last radiotherapy or unplanned surgical interventions in patients with immediate reconstruction.

Mutter, Lancet 2023 39 months
Median mean heart dose 0·54 Gy vs. 0·49 Gy.
Within 24 months of first radiotherapy, 14 protocol-defined complications 15% vs. 20% (NS).
The complications in the conventionally fractionated group were contracture (five [12%] of 41 patients]) and fat necrosis (one [2%] patient) requiring surgical intervention. All eight protocol-defined complications in the hypofractionation group were due to infections, three of which were acute infections that required surgical intervention, and five were late infections, four of which required surgical intervention. All 14 complications were in patients with immediate expander or implant-based reconstruction.
Interpretation After a median follow-up of 39·3 months, non-inferiority of the hypofractionation group could not be established. However, given similar tolerability, hypofractionated proton PMRT appears to be worthy of further study in patients with and without immediate reconstruction.

Accelerated Partial Breast Irradiation (APBI)

Consensus

- **Quick Summary**
  - **Standard radiation can be inconvenient and expensive for patients.**
  - **Not all patients will receive RT for these reasons and "Financial Toxicity" to patients is becoming an increasing concern.**
  - **APBI offers a short treatment (1 day to 2 weeks) and may allow more patients to receive RT.**
  - **Intraop APBI consistently leads to ↑ LF rates (vs. WBI) and should generally be avoided since other RT techniques are readily available.**

- **PROS**
  - Vast majority of recurrences (80-90%) occur in the tumor bed
  - More convenient
  - May allow more patients to undergo BCT
  - Decreased exposure of normal tissues

- **CONS**
  - No expectation that PBI will improve upon local control
  - EBCTG meta-analysis demonstrated OS benefit for WBI
  - Shorter WBI courses are another alternative
  - With Phase III RTC and longer follow up
  - Intra-operative APBI has consistently a SS higher risk of IBTR at 5 and 10 years.
  - Technique and machine does make a difference as well (ie Cyberknife…)

- Techniques include intraoperative electron or X-rays, interstitial brachytherapy (HDR more common than LDR), balloon brachy, or 3DCRT.

Accelerated Partial Breast Irradiation (APBI)/Partial Breast Irradiation (PBI)

- **APBI/PBI offers comparable local control to WBRT in selected low-risk patients with early-stage breast cancer. However, the optimal external beam-APBI/PBI technique/fractionation for minimizing long-term cosmesis effects has not been determined.**
  - **Patients are encouraged to participate in clinical trials.**
  - **The NCCN Panel recommends APBI/PBI for any patient who is *BRCA* negative and meets the 2016 ASTRO criteria.**
  - **The 2016 ASTRO criteria define patients aged ≥50 years to be considered "suitable" for APBI/PBI if:**
    - **Invasive ductal carcinoma measuring ≤2 cm (pT1 disease) with negative margin widths of ≥2 mm, no LVI, and ER-positive**
      or
    - **Low/intermediate nuclear grade, screening-detected DCIS measuring size ≤2.5 cm with negative margin widths of ≥3 mm.**
- **RT dosing:**

Regimen	Method	Reference
30 Gy/5 fractions QOD (preferred)	**External beam RT (EBRT)[e]**	Livi L, Meattini I, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Eur J Cancer 2015;51:451-463. Meattini I, Marrazzo L, Saieva C, et al. Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: Long-term results of the randomized phase III APBI-IMRT-Florence Trial. J Clin Oncol 2020;38:4175-4183.
40 Gy/15 fractions	**EBRT**	Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet 2017;390:1048-1060.
34 Gy/10 fractions BID	**Balloon/ Interstitial**	Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after BCS for early-stage breast cancer: a randomised, phase 3, equivalence trial. Lancet 2019;394:2155-2164.
38.5 Gy/10 fractions BID	**EBRT**	Whelan TJ, Julian JA, Berrang TS, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. Lancet 2019;394:2165-2172.

- **American Society of Breast Surgeon's (ASBS) and American Brachytherapy Society (ABS) listed selection criteria in lieu of WBRT.**

	Age	Histology	Tumor size	Path Margin	LN status
ASBS	≥ 45	IDCA or DCIS	Total (invasive + DICS) ≤ 3cm	Neg microscopic	SLN: Negative
ABS	≥ 50	Unifocal, IDCA	≤ 3 cm	Neg microscopic	ALND (Lv I-II) or SLND.

- **ASTRO Consensus Statement (Smith 2009) (2016 update).**

	Age	T	N	ER	LVI	Margin	#	Histology	Chemo	Others
Suitable	≥ 60 (>50)	T1 (T1,Tis) ≤ 2.5 cm	pN0	ER+	LVI -	- > 2mm	unicentric Unifocal	No pure DCIS **DCIS***	No Tx	No EIC, Not ILCA, no BRCA 1/2 Δ.
Cautionary	50-59 (40-49)	2.1-3cm,	---	ER-	Limited	0-2 close	---	Pure DCIS ≤ 3cm ≤ 3cm size	---	EIC ≤3cm, Yes ILCA, -----
Unsuitable	< 50 (<40)	> 3 cm	pN+ or no LN surg	---	Extensive	Positive	Multi/multi	Pure DCIS > 3	Yes Tx	EIC > 3cm, ---- , yes BRCA 1/2 Δ

DCIS* Low risk RTOG 98-04
Mammogram detected, Size < 2.5 cm, margins 3mm.

Modern Studies

Randomized Trials APBI vs WBI						
	N / FU	**Eligibility**	**Technique**	**Dose**	**IBTR**	**Toxicity**
Hungary Polgar 2013	258 10.2 yrs	pT1N0-mi, G1-2 neg margins, > 40 yo	Interstitial Electrons	36.4 Gy / 7 fx 50 Gy / 25 fx	5.9% 5.1%	PBI ↑ cosmesis 81% vs 63%.
GEC-ESTRO Strnad Lancet 2016	1184 6.6 yrs	pT1-2 (< 3cm) N0-1mi IDC/ILC/DCIS, No LVSI, **margins > 2mm**, > 40 yo	Interstitial	32 Gy / 8 fx HDR 30.2 Gy / 5 fx HDR 50 Gy PDR	1.4% 0.9%	**APBI ↓ breast pain.** **APBI ↓ Less late G2-3 skin toxicity**
Florence Livi 2015	520 5 yrs	pT1-2 (< 2.5cm), clips in cavity neg margins, > 40 yo	IMRT	30 Gy / 5 fx QOD	1.5%	APBI less toxicity
Barcelona Rodriguez 2013	102 5 yrs	pT1-2 (< 3 cm) N0, G1-2 IDC neg margins, > 60 yo	3D-CRT	37.5 / 10 fx	0%	Low rates toxicity no Δ cosmesis
RAPID Olivotto 2013	2135 3 yrs	pT1-2 (< 2cm) N0 IDC/DCIS Neg margins,**> 40 yo**	3D-CRT	38.5 Gy / 10 fx BID	NR	APBI ↑ G1-2 toxicity, ADVERSE cosmesis
NSABP B-39 (RTOG 04-13) Closed / NR	**4300 3.5 yrs**	**pT1-2 (< 3cm) N0-1 IDC/DCIS Neg margins, >18 yrs.**	**3D-CRT Brachy intersitial**	**38.5 Gy / 10 fx BID 34 Gy / 10 fx BID**	**NR**	**3D subset: G2 fibrosis 12%, G3 3%.**
IMPORT LOW Coles 2017	**2018 6 yrs**	**pT1-2 (< 3cm) N0-1 IDC Margins ≥ 2mm, ≥ 50 yo.**	**IMRT**	**40 Gy / 15 WBRT 36 Gy WBRT + 40 Gy APBI 40 Gy / 15 APBI**	**1.1% 0.2% 0.5%**	**APBI ↓ patient reported toxicity in BOTH exp. arms.**
DBCG PBI Offerson, JCO 2022	**2022 5 yrs**	**pT1-2 N0 HR+Her2- IDC Margins > 2 mm**	**3D-CRT Both Arms**	**40 Gy / 15 fx Both Arms**	**NS < 1%**	3-year rate of induration 9.7% WBI vs. 5.1% PBI (SS)

DBCG PBI Trial **Non-inferiority**

←R→ 965 women 2009-2016 low-risk breast cancer | 1. WBI | 2. PBI |. RT ALL = 40 Gy/15 fractions.
Eligibility: HR+HER2-, G 1-2 IDC <2cm with clean margins (>2mm).
PBI CTV = tumor bed + 1.5cm margin. + 5mm PTV margin (-5mm from the skin surface).
In both arms, FiF with tangents.
1^{O} was 3-year grade 2-3 breast induration.

Offerson, JCO 2022 **5-years Follow-up**

3-year rate of induration 9.7% WBI vs. 5.1% PBI (P = .014).
If Large Breast, 3-year incidence 13% (WBI) and 6% (PBI)
If Small Breast, 3-year incidence 6% (WBI) and 5% (PBI).
PBI showed no increased risk of dyspigmentation, telangiectasia, edema, or pain, and patient satisfaction was high.
Letrozole and smoking did not increase the risk of radiation-associated morbidity.
Sixteen patients had a locoregional recurrence (six WBI and 10 PBI; P = .28), 20 patients had a contralateral breast cancer, and eight patients had distant failure (five WBI and three PBI).
A non-breast second cancer was detected in 73 patients (8.4%), and there was no difference between groups.
CONCLUSION External-beam PBI for patients with low-risk breast cancer was noninferior to WBI in terms of breast induration. Large breast size was a risk factor for radiation-associated induration. Few recurrences were detected and unrelated to PBI.

Thomsen, Radiother Oncol 2022 **Induration and Technique 2^{O} Analysis**

Median and interquartile ranges (IQR) for CTVp_breast were 710 mL (467–963 mL; PBI) and 666 mL (443–1012 mL; WBI) (p = 0.98).
Median and IQR for CTVp_breast treated to ≥40 Gy was 24.9% (18.6–32.6%; PBI) and 59.8% (53.6–68.5%; WBI).
Grade 2–3 induration was observed in 5% (PBI) and 10% (WBI) of the patients.
A dose–response relationship was established between irradiated breast volume and frequency of breast induration.
From the model, 5% and 10% risks of breast induration were observed for ≥40 Gy delivered to CTVp_breast volumes of 177 mL (95%CI, 94–260 mL) and 426 mL (95%CI, 286–567 mL), respectively.
CONCLUSION The frequency of breast induration increased significantly with increasing irradiated breast volume, strongly favouring small volumes and PBI. Thus, treated breast volume – not the breast size itself - is the risk factor for induration. This is the first report directly linking the 40 Gy irradiated breast volume to breast induration.

Canadian ACCEL **27 Gy in 5 Daily Fractions**

55 patients prospective APBI IMRT 27 Gy in 5 daily fractions.

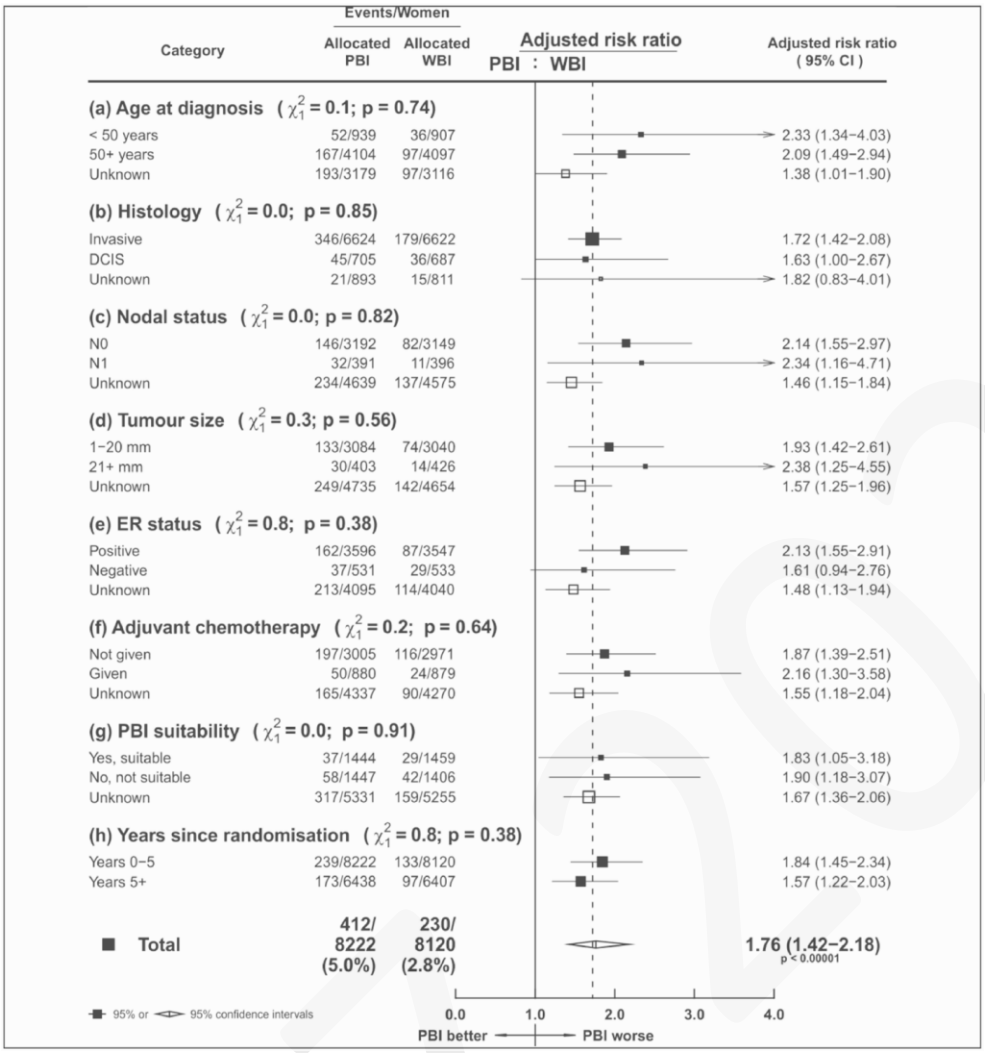
Grendarova, PRO 2019

Baseline and 1-year post-RT images available. Most patients had either an improvement (53%) or no change (40%) in cosmesis from baseline to 1-year. Among 49 patients with excellent or good panel-assessed score at baseline, only 2 (4%) patients had a fair score at 1-year post-RT, indicating cosmetic deterioration. No patients had evidence of telangiectasia or grade 2 or higher fibrosis. There were no recurrences.
Conclusions: APBI using 27 Gy in 5 daily fractions achieved acceptable 1-year cosmesis and no grade 2 fibrosis. A preplanned stopping rule of 5% grade 2+ fibrosis was not observed. The trial will continue to the planned target accrual of 274 patients.

APBI Metaanalysis

←M→ 15 trials 16,474 patients >60 years T1N0 G1-2 tx with hormone therapy.

Ipsilateral breast events PBI vs. WBI (5.0% vs 2.8%; risk ratio [RR], 1.72; SS).



Heterogeneity (P = .0002) was observed between the 4 PBI techniques:

EBRT without CT planning (RR, 2.06; SS)
Brachytherapy (RR, 1.21; SS)
Intraoperative RT (RR, 2.79; SS)
EBRT with CT planning (RR, 1.25; NS).

When external beam RT without CT planning and intraoperative RT trials were excluded, the percent of ipsilateral breast events was 3.3% versus 2.6%, respectively (RR, 1.25; 95% CI, 1.00-1.55; P = .05), and no heterogeneity was observed (P = .92).

Overall, acute toxicity was less with PBI, and the effect on late toxicity varied by technique.

qD vs. BID Breast RT Trial

Question: Could it be that the accelerated part of APBI contributes to worse cosmesis? The BED for the B-39 and RAPID dose schedule of 3.85 Gy x 10 twice daily fractions approaches, not 50 Gy, but closer to 70 Gy, which could be similar to the boost arm of EORTC 22881–10882 (to 66 Gy) to the tumor bed. In other words, the twice daily regimen may deliver too high of a dose over too short of an interval that doesn't allow for optimal inter-fraction normal tissue recovery.

←R→ 113 DCIS or IDC, cN-, size ≤ 3 cm | 1. APBI 38.5 Gy in 10 fractions once daily Tx (oAPBI) | 2. APBI 38.5 Gy in 10 fractions twice daily Tx (tAPBI) |.

Boutrus IJROBP 2021 FU 3 years.

Median pain score during treatment 3 out of 10 vs. 5 out of 10 (*P* = .001).

Early G3 skin toxicity (NS) or early pulmonary toxicity (NS).

Late G3 skin developed in 3.8% vs. 11.7% (*P* = .001). GIII subcutaneous fibrosis 1.9% vs. 8.3% (*P* = .001).

Rate of patients with adverse cosmesis (poor or fair) at 1-year/2-year was 7.5%/7.5% vs. 21.7%/26.7% (SS).

Conclusions oAPBI is a safe, well-tolerated schedule with more favorable outcomes than the tAPBI schedule with regards to late toxicity and cosmesis.

RAPID

←R→ 2135 DCIS or pN0 BCa | 1. EBRT APBI (38.5 Gy in 10 fx BID) | 2. WBRT 42.5 Gy in 16 fx or 50 Gy in 25 fx |.

Designed on the basis of an expected 5-year IBTR rate of 1·5% in the whole breast irradiation group with 85% power to exclude a 1·5% increase in the APBI group; non-inferiority was shown if the upper limit of the two-sided 90% CI for the IBTR hazard ratio (HR) was less than 2·02. This trial is registered with ClinicalTrials.gov, NCT00282035.

Whelan, Lancet 2019. FU 8·6 years (IQR 7·3–9·9).

8-year IBTR were 3·0% vs. 2·8%. The HR for APBI versus WBRT 1·27 (90% CI 0·84–1·91).

Acute radiation toxicity (grade ≥2, within 3 months of radiotherapy start) 28% vs. 45%, p<0·0001.

Late radiation toxicity (grade ≥2, later than 3 months) 32% vs. 13%, p<0·0001.

Adverse cosmesis (defined as fair or poor) was more common in patients treated with APBI. 3 years absolute Δ 11·3%, 5-yr 16·5%, 7-yr 17·7%.

Interpretation

External beam APBI was non-inferior to whole breast irradiation in preventing IBTR. Although less acute toxicity was observed, the regimen used was associated with an increase in moderate late toxicity and adverse cosmesis, which might be related to the twice per day treatment. Other approaches, such as treatment once per day, might not adversely affect cosmesis and should be studied.

Comment: Published results of B-39 and RAPID bring accelerated partial breast irradiation (APBI) back into the spotlight so let pause to reflect on the much more widely available and readily implementable external beam techniques. First up, target volumes. This was the main difference between the trials. In RAPID the CTV was a 1 cm expansion of the lumpectomy cavity excluding the chest wall, muscles, and 5 mm of subcutaneous tissue. For B39, it was 1.5 cm with the same exclusions.The PTV in both trials was a 1 cm expansion and was used for beam arrangement. The "dose evaluation volume" (DEV) in RAPID and the PTV_EVAL in B39 used for DVH analysis was the PTV with the same exclusions as the CTV. Ok, beam arrangements. In RAPID there were four non-coplanar fields: a pair of medial and lateral tangents and a pair of anterior/superior and posterior/inferior beams using couch kicks. Anything was allowed in B39 but similar arrangements to RAPID were encouraged. In both, 3.85 Gy was prescribed to isocenter of the PTV and was delivered twice daily for 10 fractions. The contralateral breast, lung, and heart were excluded from each of the beam's eye views. In RAPID, < 25-35% of the breast could get 95% of the prescription while in B39 it was 100%. In both, < 50-60% of the breast could get 50% of the prescription.

IRMA BID Trial

←R→ 3309 women stage I-IIA BCa → BCT age ≥ 49 years | 1. WBI | 2. EBRT APBI (38.5 Gy/10 fraction twice daily) |.

Meduri, JCO 2023 5.6 years

Adverse cosmesis 9.2% vs. 12.7% (P = .009) 5-years 9.8% vs. 14% (P = .012).

Late soft tissue toxicity G ≥ 3 was 1% WBI vs. 2.8% APBI (P < .0001) Late bone toxicity G ≥ 3: 0% WBI vs. 1.1% APBI (P < .0001)

There were no significant differences in late skin and lung toxicities.

Conclusion: External beam radiation therapy-APBI with a twice-daily IRMA schedule was associated with increased rates of late moderate soft tissue and bone toxicities, with a slight decrease in patient-reported cosmetic outcomes at 5 years when compared with WBI, although overall toxicity was in an acceptable range.

Korean APBI Cyberknife – Byun IJROBP 2023

Prospective Cohort of 204 patients evaluating Cyberknife APBI vs. WBI. APBI = 30 Gy in 5 nonconsecutive, once-daily fractions. WBI = VMAT 40.05 Gy in 15 fractions → SIB 48 Gy in 15 (92%). 12-months APBI ↓ patient-reported breast hardness (8 vs. 20%), dryness (7 vs. 18%), and skin reaction (10 vs. 24%) as well as physician-reported dermatitis (1 vs. 7%).

Dutch Trial Vasmel, IJROBP 2019

20 Gy in 1 single fraction to gross tumor for favroable breast cancer + pCR 45% at time of surgery 6-8 months s/p RT.

Side effects = very low ≥G3 toxicity. No recurrences at 2-year timepoint.

Polgar IJROBP 2020.

20-year followup single institution. ←R→ Fractionated PBI or WBRT after lumpectomy. PBI was either APBI using a multicatheter HDR technique (5.2 Gy BID x 7, used in 2/3) or conventionally fractionated PBI using an electron field to deliver 50 Gy in 25 fractions (used in 1/3). Trial closed earlier (because of other entrollments on GEC-ESTRO APBI trial). 18 years of median FU, IBTR 7.8% APBI vs. 6.2% WBRT. The 20-year actuarial rate of local recurrence was 9.6 vs 7.9%.

Intraop and Interstitial

Comment: Modern trials comparing and Intraop and Interstitial RT techniques to conventional fractionation instead of hypofractionation are not tremendously useful (in terms of cosmesis) as hypofx has been consistently shown to have at least similar if not better cosmesis than conventional fx.
Comment 2: The discomfort of the actual interstitial insertion itself is underreported.
Comment 3: Local recurrence of interstitial APBI has never been shown to be "better" than EBRT. For most studies showing "non-inferiority," interstitial shows a numerical disadvantage.
Comment 4: With the ease (and excellent LC and cosmesis) of non-invasive EBRT APBI 30 Gy in 5 fractions, there is no need for interstitial APBI techniques requiring more fractions as well as a surgical approach.

RCT APBI	**Organization**	**Year**	**Arm 1**	**Arm 2**	**Status**
Intraoperative	ELIOT	2000-2007	WBRT 50/25	IORT 21/1	12 yr LR WBRT 16 (2%) vs. IORT 70 (11%)
Intraoperative	TARGIT-A	2000-2012	WBRT 45-56	IORT 20/1	IORT Non-inferior
Interstitial	Hungary	1998-2004	WBRT 50/25	HDR 36.4/7	Similar control, better cosmesis with HDR
SAVI	Arizona				
Balloon	Mammosite	2002-2004	---	----	Similar control.
EBRT	Yorkshire	1986-1990	WBRT 40/15	EBRT 55/20	WBRT superior
EBRT	Christie	1982-1987	WBRT 40/15	Electrons 42.5/8	WBRT superior

Intraop Failure Rates Metaaanlysis – Shumway, JNCI 2023
←M→ 17234 of PBI and WBI from 14 randomized trials and 6 comparative observational studies. In general, PBI was not statistically significantly different from WBI for IBR at 5 years (RR = 1.34, 95% CI = 0.83 to 2.18; high strength of evidence [SOE]) and 10 years (RR = 1.29, 95% CI = 0.87 to 1.91; high SOE). Evidence for cosmetic outcomes was insufficient. Statistically significantly fewer acute AEs were reported with PBI compared with WBI, with no statistically significant difference in late AEs. Data from subgroups according to patient, tumor, and treatment characteristics were insufficient. Intraoperative radiotherapy was associated with higher IBR at 5, 10, and over than 10 years (high SOE) compared with WBI.

Italian **ELIOT**
←R→ 1305 women 48-75 years clinical unicentric breast carcinoma + US diameter ≤ 25 mm, cN0 suitable for BCT | 1. WBI | 2. ELIOT |.
WBT = conventional fractionation (50 Gy given as 25 fractions of 2 Gy → 10 Gy boost)
ELIOT = 21 Gy IORT electrons (ELIOT) single dose to the tumour bed during surgery.

Jacobs, IJROBP 2022 12.4 years
12-year LR 2% vs. 11% (SS).

ELIOT 5-year IBTR rate was 4·2% (95% CI 2·8-5·9), the 10-year rate was 8·1% (6·1-10·3), and the 15-year rate was 12·6% (9·8-15·9).
WBI 5-year IBTR rate was 0·5% (95% CI 0·1-1·3), the 10-year rate was 1·1% (0·5-2·2), and the 15-year rate was 2·4% (1·4-4·0).

ELIOT OS 96·8% at 5 years, 90·7% (88·2-92·7) at 10 years, and 83·4% (79·7-86·4) at 15 years
WBI OS 96·8% at 5 years, 92·7% (90·4-94·4) at 10 years, and 82·4% (78·5-85·6) at 15 years.
We did not collect long-term data on adverse events.
Interpretation: The long-term results of this trial confirmed the higher rate of IBTR in the ELIOT group than in the WBI group, without any differences in overall survival. "ELIOT should be offered to selected patients at low-risk of IBTR."

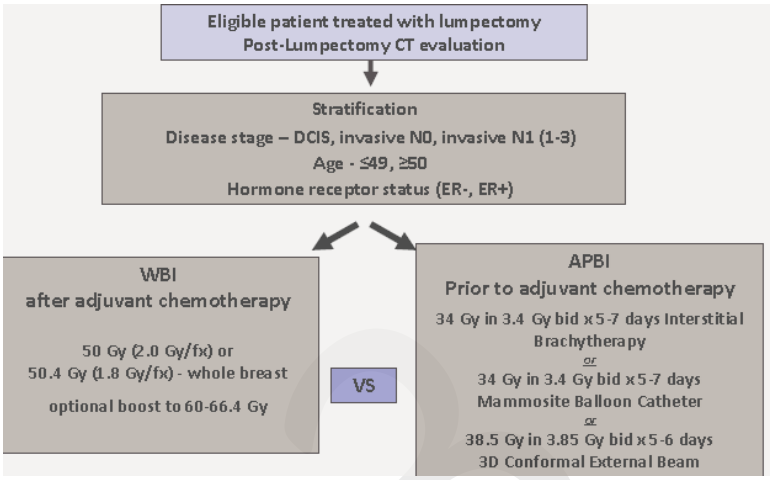
Comment: Considering the ease and effectiveness of EBRT (ultrahypofractionation, APBI, etc), there is little reason other to recommend or offer a treatment that has a higher SS rate of LF.

NSABP B-39/RTOG 0413
←R→ 4216. Whole breast vs. APBI for stage 0, I and II patients
Technique: multi-catheter brachytherapy (34 Gy), MammoSite (34 Gy) or External Beam (38.5 Gy)
| 1. WBRT 50 Gy no boost | 2. APBI 34 Gy brachy or 38·5 Gy EBRT in 10 fx over 5 treatment days within an 8-day period |.

The CTV uniform expansion of 15 mm on the excision site limited to 5 mm from the skin surface and by the posterior breast tissue extent (chest wall and pectoralis muscles). CTV + 10 = PTV
PTV eval excludes first 5 mm of skin and excludes expansions into pectoralis, heart, and lung.

Interstitial dose prescribed to 15 mm from lumpectomy cavity.
PTV limited to 5 mm from skin surface to limit toxicity.

Balloon dose is 10 mm from lumpectomy cavity.



Vicini, Lancet 2019.
10-year IBTR was 3.9% vs. 4.6%. 2% from both arms died of recurring breast cancer.
Second cancers and treatment-related toxicities were similar between the two groups. G1,2,3 31,59,7 vs. 40,44,10 %
Interpretation APBI did **not meet the criteria for equivalence** to whole-breast irradiation in controlling IBTR for breast-conserving therapy. Our trial had broad eligibility criteria, leading to a large, heterogeneous pool of patients and sufficient power to detect treatment equivalence, but was not designed to test equivalence in patient subgroups or outcomes from different APBI techniques. For patients with early-stage breast cancer, our findings support whole-breast irradiation following lumpectomy; however, with an absolute Δ of less than 1% in the 10-year cumulative incidence of IBTR, APBI might be an acceptable alternative for some women.

GEC-ESTRO Interstitial APBI Trial
←R→ 1328 patients ≥ 40 years 2004-2009 early IDC or DCIS → BCT | 1. whole-breast irradiation | 2. APBI using multicatheter brachytherapy |.
WBRT = 25 daily fractions of 50 Gy over 5 weeks → boost of 10 Gy to the tumour bed.
APBI = 30·1 Gy (seven fractions) and 32·0 Gy (eight fractions) of high-dose-rate brachytherapy in 5 days or as 50 Gy of pulsed-dose-rate brachytherapy over 5 treatment days.

Strnad, IJROBP 2023 10.36 years Follow-up
10-year LR 1·58% vs. 3·51% (Δ 1·93%; p=0·074).
Adverse events were mostly G1-2 60% vs. 67%.
G3 late side-effects 4% vs. 1% (SS).
At 10 years, the most common type of grade 3 adverse event in both treatment groups was fibrosis (six [2%] of 313 patients for whole-breast irradiation and three [1%] of 375 patients for APBI, p=0·56). No grade 4 adverse events or treatment-related deaths have been observed.
Interpretation
Postoperative APBI using multicatheter brachytherapy after breast-conserving surgery in patients with early breast cancer is a valuable alternative to whole-breast irradiation in terms of treatment efficacy and is associated with fewer late side-effects.

TARGIT-A (Vaidya 2014).[76] IORT 20/1 vs WBRT 40-56 Gy. RCT, non-inferiority. 11 countries. 3451 patients, age ≥ 45 (≥ 65 in 42%), IDC (ILC excluded), unifocal, BCS + SNB/ALND, T1 (86%), N0 (83%), and low/intermediate grade (84%). Allowed entry prior to surgical pathology results (66%) or post pathology results (34%). Arm 1) Intra-op RT with Intrabeam 50 kV device 20 Gy at surface | Arm 2) WBRT (hospital specific, typically 40-56 Gy ± boost 10-16 Gy). Postop RT for predefined factors (e.g. LCIS, EIC, N+, LVI+ or others pre-defined per each individual center) done as WBRT without boost (a prior expected rate 15%, actual rate 15.2%).

NOTE: Final pathology wasn't available for review until after the IORT was delivered.
If high risk features [margin <1 mm, extensive (>25%) in situ component, invasive lobular component, grade 3, node positivity, lymphovascular invasion] was present on surgical path, women in the IORT arm proceeded with standard adjuvant whole breast irradiation with the IORT serving as the boost.

Results: **5-year LF** TARGIT 3.3% | EBRT 1.3% (p = 0.04). BCa specific mortality same, 2.6% | 1.9% (*p* = 0.56). Non-BCa mortality better in TARGIT, 1.4% | 3.5% (*p* = 0.0086) attributable ↓ CV causes and other Ca. Regional recurrence, OS (3.9% | 5.3%) NS. If concurrent with lumpectomy, 2.1% versus 1.1% (NS); if delayed after lumpectomy 5.4% versus 1.7% (*p* = 0.07). Toxicity: Wound-related complications same, Grade 3/4 skin toxicity lower 0.2% | 0.7% (SS). Conclusion: TARGIT concurrent with lumpectomy should be considered an option for eligible patients.
Side note: 4-year LF IORT 1.2% | WBRT 0.95% (NS).

Vaidya, BMJ 2020. 20-year FU.
1 of every 5 women receiving IORT still required whole breast irradiation based on high-risk features discovered at surgery.

TARGIT-A approach was inferior to standard WBI for the postpathology stratum, with 5-year local recurrence rates of 3.96 vs. 1.05%

Summary of Criticisms (Too many to List Here): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8914270/#B9
Attempt to Discern the Real LF rate: https://www.redjournal.org/article/S0360-3016(21)03434-9/fulltext

[76] http://www.ncbi.nlm.nih.gov/pubmed/24224997

Hungary (Polgár 2007).[77] RTC stopped prematurely, since patients offered entry onto GEC-ESTRO Phase III APBI trial. 258 of expected 570 patients with T1N0-1mic, G1-2 nonlobular BCA, no EIC, SM-. WLE + ALND/SLND. Arm 1) PBI 36.4/7 @ 5.2 Gy/fx BID multicatheter HDR (69%) | Arm 2) WBI 50/25. Limited field electron PBI 50/25 if unsuitable for HDR (tumor bed + 2cm margin). Primary endpoint 5-year LR , noninferiority was 6% difference. Adjuvant chemo/hormones 72%. Results: **5-year LF** 5-year LR WBI 3.4% vs. PBI 4.7% (NS); no difference in DFS or OS. Toxicity: excellent/good cosmesis WBI 63% vs. PBI 78% (SS); HDR 81% and EB-APBI 70%. Conclusion: Similar outcomes, better cosmesis with HDR APBI.

Polgar IJROBP 2020.
20-year followup single institution. Trial closed earlier (because of other entrollments on GEC-ESTRO APBI trial). 18 years of median FU, IBTR 7.8% APBI vs. 6.2% WBRT. The 20-year actuarial rate of local recurrence was 9.6 vs 7.9%.

SAVI (Yashar 2011).[78] Retrospective. 102 Pts Txed with SAVI to completion. Arizona Oncology Services and UC San Diego. PTV = tumor bed + 1cm, minus CW/ribs/skin. 34/10 twice daily. Median F/U 1.7 years. Results: V90 = 96%; max median skin dose 2.8 Gy. Local recurrence 1% Toxicity: grade 1 hyperpigmentation 10%, Grade 2 fibrosis 2%, telangiectasia 2%, fat necrosis 2%.
Conclusion: SAVI appears safe and increase eligibility for APBI over balloon brachytherapy.

385 EBRT dose. And 340 BRACHY.

GEC/ESTRO European Trial: 8 treatment fractions. 400 x 8.

Mammosite (Beitsch 2012).[79] 1,449 early-stage BCa txed on American Society of Breast Surgeons MammoSite Registry Trial with lumpectomy plus balloon-based APBI (34 Gy, 10 BID fractions). 1,255 cases (87 %) had invasive breast cancer, and 194 patients (13 %) had ductal carcinoma in situ. Rates of true recurrence (TR) versus elsewhere failure (EF) were calculated and compared to historical WBI controls. Results: Median follow-up was 60 (range 0-109) months. 50 (3.5 %) = IBTR. The 5-year actuarial rate IBTR was 3.6 % (invasive breast cancer 3.6 %, ductal carcinoma in situ 3.4 %). 14 IBTR (1.1 %) were TR, while 36 (2.6 %) were EF. ER - status ~ with IBTR for invasive malignancies as well as for EF only ($p < 0.001$).↑ EF trends with ↑ tumor size ($p = 0.067$) and extensive intraductal component ($p = 0.087$). No pathologic factors were explicitly associated with TR. Conclusions: IBTR after balloon-based APBI is low and similar to rates reported for WBI. In this data set, APBI had fewer tumor bed recurrences (presumably initial cancer recurrences) than EF (presumably new primary lesions). This suggests that balloon-based APBI has a tumor bed control rate that is at least equal to (and potentially higher than) WBI.

[77] http://www.ncbi.nlm.nih.gov/pubmed/17531400?dopt=Abstract
[78] http://www.ncbi.nlm.nih.gov/pubmed/20646847?dopt=Abstract
[79] http://www.ncbi.nlm.nih.gov/pubmed/22836556?dopt=Abstract

Techniques

Interstitial Brachytherapy	Longest followup. Catheters placed 1-1.5 cm intervals. Dose 34 Gy / 10 fx, 32 Gy / 8 fx, 30.2 Gy, or 36.4 Gy / 7 fx usually BID with 6 hours between each fraction. Target PTV = tumor cavity + 1.5 cm and limited by 5 mm from skin and posterior breast tissue.
Intercavitary Brachytherapy	MammoSite was the first FDA approved device. Easy and good reproducivitiy. A silocone balloon is connected to double lumen catheter with inflation channel and port for HDR source passage. A cavity evaluation device can be placed in the cavity at the time of surgery, which is replaced by the treatment device post-operatively (after pathology confirmation) under US guidance. Balloon is filled with saline 30-70cc and mixed with small amount of 1-2 cc contrast to achieve diameter of 4-6 cm. Recently, multilumen catheters have been developed. Dose 34 Gy / 10 fx BID with 6-year interfraction window. Target PTV = tumor cavity + 1 cm and limited by 5 mm from skin and posterior breast tissue. Exclusion criteria = air/fluid > 10% PTV_EVAL, skin spacing or chest wall spacing < 3-5 mm (ideally want ≥ 7mm with single lumen device), poor cavity delineation.
EBRT	Non-invasive technique. Easy technically Dose 38.5 Gy / 10 fx BID, 40 Gy / 15 fx QOD, or 30 Gy / 5 fx QOD (IMRT). Target CTV = tumor cavity + 1.5 cm and limited by 5 mm from skin and posterior breast tissue. Target PTV = CTV + 1 cm, excluding volume outside breast and 5 mm from skin, and beyond posterior breast.
Prone?	See **Shah Prac Rad Oncol 2021.** Single institution of 5-fx APBI in the prone position. PTV = 1.5 cm + lumpectomy cavity (- 6 mm skin). RT = 30 Gy in 5 fractions covering 95% of the target. Two-thirds of patients were treated on consecutive days. The ipsilateral breast constraints were V50% < 60% and V100% < 35%. The average actual ipsilateral V50% was 41% and the average V100% was 20.3%. 5 years median follow-up, the IBTR rate was 2.1% with most of those occurring outside the original quadrant. The rate of acute grade 1-2 skin toxicity was 35% with no grade 3 toxicity.

Recurrence and Re-irradiation

RTOG 10-14
PURPOSE: To determine the associated toxicity, tolerance, and safety of partial-breast reirradiation.
Phase II 58 patients eligibility = in-breast recurrence occurring >1 year after whole-breast irradiation, <3 cm, unifocal, and resected w/ neg margins.
Median age was 68 years. DCIS n=22. Invasive n=33;19 ≤1 cm, 13 >1 to ≤2 cm, and 1 >2 cm. All patients were clinically node negative.
Partial-breast reirradiation was targeted to the surgical cavity plus 1.5 cm; a prescription dose of 45 Gy in 1.5 Gy twice daily for 30 treatments was used. 3D_CRT.
The primary objective was to evaluate the rate of grade ≥3 treatment-related skin, fibrosis, and/or breast pain adverse events (AEs), occurring ≤1 year from re-treatment completion.
Systemic therapy was delivered in 51%.

Arthur, IJROBP 2017
Side effects: Treatment-related skin, fibrosis, and/or breast pain AEs were recorded as grade 1 in 64% and grade 2 in 7%, with only 1 (<2%) grade ≥3 and identified as grade 3 fibrosis of deep connective tissue.
CONCLUSION: Partial-breast reirradiation with 3-dimensional conformal radiation therapy after second lumpectomy for patients experiencing in-breast failures after whole-breast irradiation is safe and feasible, with acceptable treatment quality achieved. Skin, fibrosis, and breast pain toxicity was acceptable, and grade 3 toxicity was rare.

Arthur, JAMA Oncology 2019
Of the recurrences of breast cancer in the ipsilateral breast, 23 (40%) were noninvasive and 35 (60%) were invasive. In all 58 patients, 53 (91%) had tumors 2 cm or smaller. All tumors were clinically node negative. A total of 44 patients (76%) tested positive for estrogen receptor, 33 (57%) for progesterone receptor, and 10 (17%) for ERBB2 (formerly HER2 or HER2/neu) overexpression. Four patients had breast cancer recurrence, with a 5-year cumulative incidence of 5% (95% CI, 1%-13%). Seven patients underwent ipsilateral mastectomies for a 5-year cumulative incidence of 10% (95% CI, 4%-20%). Both distant metastasis–free survival and overall survival rates were 95% (95% CI, 85%-98%). Four patients (7%) had grade 3 and none had grade 4 or higher late treatment adverse events.

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.

CALOR (Chemotherapy as Adjuvant for LOcally Recurrent breast cancer)
←R→ 85 patients s/p lumpectomy or mastectomy with clear margins, now with ILRR. 1. chemotherapy 2. no chemotherapy.
IF ER+, received endocrine. If SM + (microscopic), received RT. Anti- HER2 therapy was optional. 1^{O} DFS.

Aebi, Lancet 2014.
5-year DFS 69% vs. 57% (SS). Adjuvant chemotherapy was significantly more effective for women with ER neg ILRR (SS).
Of the 81 patients who received chemotherapy, 12 (15%) had serious adverse events. The most common adverse events were neutropenia, febrile neutropenia, and intestinal infection.
Interpretation: Adjuvant chemotherapy should be recommended for patients with completely resected ILRR of breast cancer, especially if the recurrence is oestrogen-receptor negative.

Wapnir, JCO 2018.
10-year DFS, 70% vs. 34% in ER-negative ILRR (SS). 10-year DFS, 50% vs. 59% in ER-positive ILRR (NS).
Conclusion: The final analysis of CALOR confirms that CT benefits patients with resected ER-negative ILRR and does not support the use of CT for ER-positive ILRR.

SEER Study RE-BCS?
RR 3648 patients with small IBTR between 1999 and 2015. 2831 (77.6%) underwent mastectomy and 817 (22.4%) underwent re-BCS.

Li, Cancer 2022
The multivariate Cox model showed that **re-BCS was associated with a worse OS (hazard ratio [HR], 1.342; 95% confidence interval [CI], 1.084–1.663) and BCSS (HR, 1.454; 95% CI, 1.004–2.105) compared with mastectomy**.
The omission of radiation after re-BCS was associated with worse survival overall and especially in patients with estrogen receptor (ER)-negative IBTR (HR, 1.384; 95% CI, 1.110–1.724; and HR, 1.577; 95% CI, 1.075–2.314, respectively).
No statistically significant differences were observed in the OS and BCSS between re-BCS with radiation and mastectomy. Subgroup analysis indicated that the surgical approach was not an independent factor for survival in the ER-positive patients with IBTR.
Conclusions
Re-BCS should be considered with caution in patients with small IBTR. However, a positive ER status can be an important factor for choosing re-BCS, and radiation therapy may improve oncological safety after re-BCS.

Toxicity

Skin

Why is Hypofractionated Better (vs. Conventional?): Looking at "High-Risk patients" – large breast, concurrent with HER2 therapy, etc.

- Jagsi, IJROBP 2021. See below.
- The ATEMPT Trial had a secondary analysis,[80] which asked if T-DM1 concurrent with adjuvant RT ↑ toxicity vs. RT concurrent + trastuzumab.
  - 40-42% received hypofractionated WBRT. These had SS ↓ grade ≥2 skin toxicity vs. conventional RT (17.9% vs. 44.7%).
- Purswani, PRO 2021. See below.

IMRT Toxicity (Real World Data 2021)

Prospective BCa women WBRT w/o RNI either **3DCRT** vs. **IMRT-fp** (forward-planned, using ≥5 segments per gantry angle), vs. **IMRT-ip** (inverse planned). We evaluated associations between technique and toxicity using multivariable models with inverse-probability-of-treatment weighting, adjusting for treatment facility as a random effect.

Jagsi, IJROBP 2021.

"Experienced acute toxicity"	Conventional Fx	54.9% vs. 59.2% vs. 42.2%
	Hypofractionated	33.3% vs. 32.0% vs. 26.3%.
MVA OR acute toxicity	Conventional Fx	IMRT-ip vs. 3DCRT was 0.64 (SS)
	Hypofractionated	IMRT-ip vs. 3DCRT was 0.41 (SS)

Conclusions This large, prospective, multicenter comparative effectiveness study found a significant benefit from inverse-planned IMRT compared with 3DCRT in reducing acute toxicity of breast radiation therapy. Future research should identify the dosimetric differences that mediate this association and evaluate cost-effectiveness.

WBRT Maximal Toxicity (Real World Data 2020)

8,711 patients treated between 2012 and 2019 at 27 practices.

Jagsi, JCO 2020

Side effects:	Moderate or severe breast pain	3,233 (37.1%)	Hypo Fx 1,282 (28.9%)	Std Fx 1,951 (45.7%).
	≥ 1 one breast symptom	4,424 (50.8%)	Hypo Fx 1,833 (41.3%)	Std Fx 2,591 (60.7%).
	Severe fatigue	2,008 (23.1%)	Hypo Fx 843 (19.0%)	Std Fx 1,165 (27.3%)

Breast Pain ↑ MVA (if receiving Hypo Fx): younger age (P < .001), ↑ BMI; P < .001), Black (P < .001) or other race (P = .002), smoking status (P < .001), larger breast volume (P = .002), lack of chemotherapy receipt (P = .004), receipt of boost treatment (P < .001), and treatment at a nonteaching center.

Breast Pain ↑ MVA (if receiving Std Fx):, younger age (P < .001), ↑ BMI (P = .003), Black (P < .001) or other race (P = .002), diabetes (P = .001), smoking status (P < .001), and larger breast volume (P < .001).

CONCLUSION

In this large observational data set, substantial differences existed according to radiotherapy dose fractionation. Race-related differences in pain existed despite controlling for multiple other factors; additional research is needed to understand what drives these differences to target potentially modifiable factors. Intensifying supportive care may be appropriate for subgroups identified as being vulnerable to greater toxicity.

Hypofractionation in Autoimmune Connective Tissue Disorders

92 women with autoimmune disease CF-RT (35%) and HF-RT (65%).

WBRT alone 70%, WBI + RNI (12%), APBI (18%).

Purswani, PRO 2021.

CF-RT SS ↑ autoimmune disease (AD) symptoms (78% vs 37%, P <.001).
SS ↑ managed on disease-modifying antirheumatic drugs (DMARDs; 41% vs 15%, P = .013)
SS ↑ active autoimmune disease (84% vs 43%, P <.001).

MVA, HF-RT was associated with a SS ↓ OR acute and late grade 2/3 toxicity compared with CF-RT fractionation (acute: OR 0.200, 95% CI 0.064-0.622, P = .005; late: OR 0.127, 95% CI 0.031-0.546, P = .005).

Conclusions

Hypofractionation including accelerated partial-breast irradiation is associated with less acute or late grade 2/3 toxicity in this population.

[80] https://www.redjournal.org/article/S0360-3016(21)03446-5/fulltext

Canadian Prone vs. Supine Large Breast

←R→ 357 women large breast size (bra band ≥40 in and/or ≥D cup) | 1. prone | 2. supine positions |.

RT changes April 2013 - June 2016 50 Gy in 25 fractions ± boost (range, 10-16 Gy).
Trial amendment in June 2016 42.5 Gy in 16 fractions.

1^{O} moist desquamation (desquamation).

Table 2. Analysis of Factors Associated With Any Moist Desquamation

	Univariate analysis		Multivariate analysis	
Factor	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Supine position	1.78 (1.24-2.56)	.001	1.99 (1.48-2.65)	<.001
Chemotherapy	1.53 (1.11-2.12)	.01	1.38 (0.96-2.01)	.08
Bra band size >40 in	2.01 (1.38-2.91)	<.001	2.59 (1.51-4.36)	<.001
Boost delivery	2.06 (2.01-2.10)	<.001	2.71 (1.95-3.77)	<.001
Extended fractionation	2.56 (1.49-4.34)	<.001	2.85 (1.41-5.79)	.003
Age (per year)	0.98 (0.98-0.99)	<.001	1.00 (0.98-1.00)	.27
Body mass index	1.00 (0.99-1.01)	.16	NA	NA

Table 3. Effect of Position Stratified by Fractionation Regimen

	Extended fractionation (n = 180)				Hypofractionation (n = 177)			
	No. (%)				No. (%)			
End point	Supine (n = 92)	Prone (n = 88)	OR (95% CI)	*P* value	Supine (n = 90)	Prone (n = 87)	OR (95% CI)	*P* value
MD, Any grade	47 (51.1)	31 (35.2)	1.92 (1.62-2.72)	<.001	25 (27.8)	16 (18.4)	1.71 (0.86-3.39)	.13
MD, Grade 3	22 (23.9)	9 (10.2)	2.76 (2.45-3.10)	<.001	6 (6.7)	5 (5.7)	1.17 (0.65-2.09)	.59
Pain, grade 2	12 (13.0)	5 (5.7)	2.49 (1.48-4.19)	<.001	2 (2.2)	4 (4.6)	0.47 (0.03-6.22)	.57

Abbreviation: MD, moist desquamation.

Table 4. Effect of Fractionation Regimen Stratified by Position

	Supine (n = 182)				Prone (n = 175)			
	No. (%)				No. (%)			
End point	Extended fractionation (n = 92)	Hypofractionation (n = 90)	OR (95% CI)	*P* value	Extended fractionation (n = 88)	Hypofractionation (n = 87)	OR (95% CI)	*P* value
MD, Any grade	47 (51.1)	25 (27.8)	2.72 (1.18-6.24)	.02	31 (35.2)	16 (18.4)	2.41 (1.65-3.52)	<.001
MD, Grade 3	22 (23.9)	6 (6.7)	4.40 (1.83-10.57)	<.001	9 (10.2)	5 (5.7)	1.87 (1.05-3.32)	.03
Pain, grade 2	12 (13.0)	2 (2.2)	6.60 (0.91-48.32)	.06	5 (5.7)	4 (4.6)	1.25 (0.36-4.33)	.72

Abbreviation: MD, moist desquamation.

Vesprini, JAMA Network 2022

Desquamation in patients 26.9% vs. 39.6% (OR, 1.78; P = .002). MVA (OR, 1.99; P < .001)

Other independent factors
- use of boost (OR, 2.71; P < .001)
- extended fractionation (OR, 2.85; P = .004)
- bra size (OR, 2.56; P < .001).

Conclusions and Relevance This randomized clinical trial confirms that treatment in the prone position decreases desquamation in women with large breast size receiving adjuvant RT. It also shows increased toxic effects using an RT boost and conventional fractionation.

Bacterial Skin / Mucosal Decolonization Study

Background: Bacteria play a role in other inflammatory dermatoses. As our group recently showed nasal colonization with Staphylococcus aureus (SA) prior to RT was an independent predictor of grade ≥2 RD,

←R→ Phase II 80 adult patients with breast cancer or head and neck cancer → receive fractionated (≥ 15 fractions) RT.

| 1. intranasal mupirocin ointment twice daily and chlorhexidine body wash once daily for 5 consecutive days before RT start and repeated for 5 days every other week during RT | 2. SC arm of emollient |.

78 breast and 2 head and neck cancer patients.

1^{O} grade ≥2 RD.

Grade 2 RD was further differentiated for more refined statistical analysis: “moderate to brisk erythema” defined as grade 2 and “patchy moist desquamation” defined as grade 2 with moist desquamation (2-MD).

Bacterial culture swabs of the nares and skin at RT beginning, middle, and end were obtained for both groups.

Kost, JCO 2022

RD grades 2-MD or higher 0% vs. 23.68% (P=0.002).

Median RD grade 1.19±0.7 vs 1.58±0.75 (P=0.019).

Linear regression model showed a SS association between BD and ↓ RD grade (estimate=-0.431, p=0.010), adjusting for other RD RF.

Most patients reported no difficulty with BD and only one patient discontinued due to itch.

There was no difference in QoL outcomes between arms.

Conclusions: Our results support the use of a BD regimen to prevent moist desquamation in patients receiving RT for breast or head and neck cancer. Our study included mainly breast cancer patients; thus BD efficacy needs to be tested in other solid tumors receiving RT. This is the first study demonstrating efficacy of BD to reduce RD. Given the safety and availability of this regimen, we suggest adding BD to RD prophylaxis protocols.

Mepitel Film (MF) Benefit Confirmatory Randomized Trial Silicone Polyurethane
←R→ 376 patients modified ITT 2:1 large breasts after lumpectomy (bra size ≥ 36 inches or cup size ≥ C) or after mastectomy | 1. MF | 2. SOC |.
MF placed on the RT day 1 and replaced on the last day of treatment. It stayed in place for EOT → 2 weeks.
RT = 93.4% hypofractionated
1^{O} Radiation Dermatitis (RD).

Behroozian, JCO 2022
Incidence of G2-3 RD 15.5% vs. 45.6% (OR 0.20, P < .0001).
G3 RD 2.8% vs. 13.6% (SS) G3 moist desquamation (8.0% vs. 19.2%; SS).
When evaluating the combined patient and health care provider score using Radiation-Induced Skin Reaction Assessment Scale, the MF arm had significantly lower scores (P < .0001). Individual items on the Radiation-Induced Skin Reaction Assessment Scale also favored the MF for both patient- and clinician-reported outcomes. Blistering/peeling, erythema, pigmentation, and edema were significantly reduced in the MF arm. Three patients removed the film prematurely because of rash (n = 2) and excessive pruritus (n = 1).
CONCLUSION MF significantly reduces RD in patients undergoing breast radiotherapy.

Previous Mepitel Trials

New Zealand Trial – Herst, Radiother Oncol 2014.
←R→ 78 breasts to either Mepitel or aqueous cream. Overall skin reaction severity ↓ 92% ($p < 0.0001$) in favour of Mepitel Film. All patients developed some form of reaction in cream-treated skin which progressed to moist desquamation in 26% of patients (RTOG grades I: 28%; IIA: 46%; IIB: 18%; III: 8%). Only 44% of patients had a skin reaction under the Film, which did not progress to moist desquamation in any of the patients (RTOG grades I: 36%; IIA: 8%).

Denmark Trial – Moller, SDU 2016
←R→ 101 breasts to either Mepitel or patient's choice. Mepitel patients reported a SS ↓ level of pain (p < .001), itching (p = 0.005), burning sensation (p = 0.005) as well as edema (p = 0.017) and reduced sensitivity (p < .001). Most patients (76%) would have preferred film on the entire treatment area (p < 0.001) and Mepitel Film as a standard treatment option (84%) (p < 0.001). Patients treated after mastectomy had a significantly lower severity of radiation-induced dermatitis with film at the end of RT compared to standard care (p = 0.005). However, in the blinded staff evaluation, no significant differences were found at follow-up.

Canadian Prospective – Yee PRO, 2020.
Prospective 30 breasts EBRT or chest wall were enrolled. Two patients (6.7%) discontinued use of the Mepitel film before completing radiation therapy. No patients developed grade 3 RD or higher. Five patients (17.9%) developed grade 2 RD: 3 (10.7%) had moist desquamation, and 2 (7.1%) had brisk erythema without moist desquamation.
Conclusion: Mepitel film completely prevented grade 3 RD. Rates of moist desquamation and grade 2 RD were lower with Mepitel film than in studies using aqueous cream, but unlike previous trials of Mepitel film we did not achieve complete prevention of moist desquamation.

Cardiac

Summary on HER2 and Radiation and CV

- The HERA trial showed that of the patients who received RT (38% left-sided RT, 38% right-sided RT, 24% no RT), ↓ LVEF and cardiovascular events (1% or less in all arms) were similar among groups.
    - MVA NS b/t RT use or sidedness and CV events.

The APHINITY trial → Radiotherapy was given as clinically indicated at the end of chemotherapy and concomitantly with anti-HER2 treatment.

- Radiation was given concurrently with trastuzumab/pertuzumab or trastuzumab, grade ≥ 3 adverse events were similar between the arms, though the unique contribution of the radiation was not examined.

- The ATEMPT Trial had a secondary analysis,[81] which asked if T-DM1 concurrent with adjuvant RT ↑ toxicity vs. RT concurrent + trastuzumab.
    - Grade ≥2 skin toxicity ↑ with T-DM1 33.9% vs. 23.2% (NS).
    - Pneumonitis 1% NS.
    - 40-42% received hypofractionated WBRT. These had SS ↓ grade ≥2 skin toxicity vs. conventional RT (17.9% vs. 44.7%).
    - RT NS cardiac function or events in women receiving trastuzumab.
    - Toxicity with concurrent T-DM1 appears comparable to that of trastuzumab.

Anthracycline and Cardiotoxicity

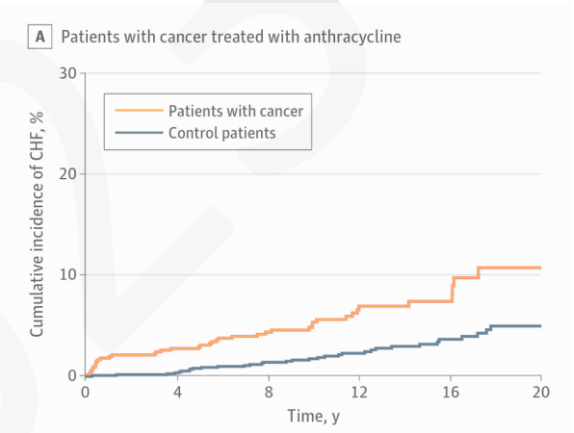
←R→ 2196 patients (812 patients with cancer and 1384 participants without cancer).
Mean (SD) age was 52.62 years. 78% were female.

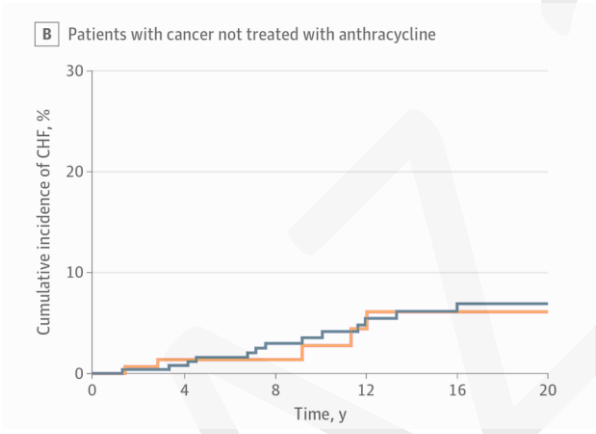
Larsen, JAMA Network 2023.

Patients with cancer had ↑ risk of CHF (compared with the control cohort) even after adjusting for age, sex, diabetes, hypertension, coronary artery disease, hyperlipidemia, obesity, and smoking status (HR, 2.86; P < .001).

After adjusting for the same variables, CHF risk was greater for patients with cancer receiving anthracycline (HR, 3.25; P < .001)

→ Attenuated and lost SS for patients with cancer **IF NOT RECEIVING anthracyclines** (HR, 1.78; P = .14).





↑ CI for CHF anthracyclines vs no anthracyclines
1 year (1.81% vs 0.09%)
5 years (2.91% vs 0.79%)
10 years (5.36% vs 1.74%)
15 years (7.42% vs 3.18%)
20 years (10.75% vs 4.98%) (P < .001).

NS Δ risk of CHF for patients receiving anthracycline at a dose of less than 180 mg/m2
vs. dose of 180 to 250 mg/m2 (HR, 0.54 [95% CI, 0.19-1.51])
vs. dose of more than 250 mg/m2 (HR, 1.23 [95% CI, 0.52-2.91]).

At diagnosis, age was an independent risk factor associated with CHF (HR per 10 years, 2.77 [95% CI, 1.99-3.86]; P < .001).

Conclusions and Relevance In this retrospective population-based case-control study, anthracyclines were associated with an increased risk of CHF early during follow-up, and the increased risk persisted over time. The cumulative incidence of CHF in patients with breast cancer or lymphoma treated with anthracyclines at 15 years was more than 2-fold that of the control group.

Table 3. Multivariable Model of Risk Factors Associated With Congestive Heart Failure

Risk factor	Hazard Ratio (95% CI)	*P* value
Anthracycline use	2.56 (1.02-6.41)	.04
Chest or mediastinal radiation	0.32 (0.13-0.76)	.01
Age (per 10 y)	2.77 (1.99-3.86)	<.001
Male sex	0.90 (0.42-1.94)	.80
At diagnosis		
Diabetes	1.90 (0.88-4.10)	.10
Hypertension	0.90 (0.42-1.94)	.80
Coronary artery disease	1.56 (0.64-3.82)	.33
Hyperlipidemia	1.04 (0.52-2.07)	.92
BMI >30	1.25 (0.67-2.34)	.48
Ever smoker	1.60 (0.84-3.02)	.15
HL vs breast cancer	1.63 (0.37-7.25)	.52
NHL vs breast cancer	0.50 (0.20-1.27)	.15

"Use of concomitant radiation therapy (chest or mediastinal) was inversely associated with risk of CHF (HR, 0.32 [95% CI, 0.13-0.74]; P = .009) even when comparing left and right radiotherapy. There was no evidence of an association of concomitant radiation therapy with CHF risk by cancer type."

"Interestingly, radiation therapy to the chest and mediastinum did not emerge as an independent risk factor for CHF. Consistent with our study, a prospective cohort study of patients with newly diagnosed lymphoma found that patients had increased risk of cardiovascular disease, especially CHF, at 10 years, but receipt of radiation therapy was not associated with this outcome and this was also found in the study by Salz et al using a Danish registry cohort. However, not all chest radiation affects the heart to the same degree. We compared the difference between right and left radiotherapy (chest or mediastinal) in a multivariable model and found that it was not an independent risk factor. Data on the cardiac-specific radiation dose were unavailable."

Kaiser Cardiac Risk Study

[81] https://www.redjournal.org/article/S0360-3016(21)03446-5/fulltext

RR 13,642 women with invasive BC diagnosed from 2005 to 2013 were matched 1:5 to controls without BC on birth year and race/ethnicity.

Greenlee, JCO 2022 7-year average follow-up

Women who received anthracyclines and/or trastuzumab had high risk of heart failure/cardiomyopathy relative to controls.

If both anthracyclines and trastuzumab (HR, 3.68).

If Radiation therapy (HR, 1.38).

If aromatase inhibitor (HR, 1.31), relative to their controls.

Elevated risks for stroke, arrhythmia, cardiac arrest, venous thromboembolic disease, CVD-related death, and death from any cause were also observed in women with BC on the basis of cancer treatment received.

Conclusion: Women with BC had increased incidence of CVD events, CVD-related mortality, and all-cause mortality compared with women without BC, and risks varied according to the history of cancer treatment received. Studies are needed to determine how women who received BC treatment should be cared for to improve cardiovascular outcomes.

Italian SAFE Trial

←R→ 174 women 4-arm, phase 3, double-blind, placebo-controlled, 2015 – 2020 Italy. All receive 1st line anthracycline chemo.
|1 Placebo | 2. ACEi ramipril 5mg PO daily | 3. βBlocker Bisoprolol 5 mg PO daily | 4. Both 2+3 |.
1^{O} LV-EF ↓ by at least 10%.

Livi, JAMA Oncol 2021

1-year 3D-LVEF ↓ by 4.4% vs. 3.0% vs. 1.9% vs. 1.3%, respectively (P = .01).
3D-LVEF ≥ 10% ↓ 19% vs. 11.5% vs. 11.4% vs. 6.8%, respectively.

15 patients (35.7%) who received placebo showed a 10% or greater worsening of GLS compared with 7 (15.9; ramipril), 6 (13.6%; bisoprolol), and 6 (13.6%; ramipril plus bisoprolol) (P = .03).

Global longitudinal strain ↓ by 6.0% vs. 1.5% vs. 0.6% vs. NS , respectively (P < .001).

Conclusions and Relevance The interim analysis of this randomized clinical trials suggested that cardioprotective pharmacological strategies in patients who were affected by breast cancer and were receiving an anthracycline-based chemotherapy are well tolerated and seem to protect against cancer therapy–related LVEF decline and heart remodeling.

Long Term "More Contemporary" Heart Toxicity Study

←R→ 1187 T1-2 N0 patients | 1. WBRT | 2. No RT |.

The prescription dose to the clinical target volume was 48-54 Gy. For a cohort of patients (n=157) with accessible CT-based 3D treatment plans in Dicom-RT format, dose-volume descriptors for OR were derived. In addition, these were compared with dose-volume data for a cohort of patients treated with contemporary RT techniques.

Killander, IJROBP 2020. 20 year follow-up on survival

Cumulative incidence of cardiac mortality 13% vs. 12.4% (NS).

↑ stroke mortality, 6.7% vs. 3.4% (p = 0.018).

Median D mean (range) heart dose for left-sided RT was 3.0 Gy (1.1-8.1). Corresponding value for patients tx in 2017 was 1.5 Gy (0.4-6.0).

Conclusion: In this trial serious late side effects of whole breast radiotherapy were limited and less than previously reported in large meta-analyses. We observed no increased cardiac mortality in irradiated patients with doses to the heart were median D mean 3.0 Gy for left-sided RT. The observed increase in stroke mortality may partly be secondary to cardiac side effects, complications to anticoagulant treatment, or to chance, rather than a direct side effect of tangential whole breast irradiation.

AI Heart Dose Evaluation

RR 5300 RT tomographic (CT) scans and plans utilized. Using an AI method, the cardiac structures (heart, cardiac chambers, large arteries, 3 main coronary arteries) were segmented. The planned radiation dose to each structure separately and to the whole heart were determined.

Patients were assigned to a **low-, medium-, or high-dose group** based on the dose to the respective heart structure.

Information on heart disease (HD) hospitalization and mortality was obtained for each patient.

The association of planned radiation dose to cardiac structures with risk of HD was investigated in patients with and without CAC using Cox proportional hazard analysis in the long follow-up population. Tests for interaction were performed.

Van Velzen, IJROBP 22022 **96 months follow-up**

135 patients were hospitalized for HD or died of HD.

If the dose to a structure ↑ 1 Gy, the relative HD risk increased by 3% to 11%.

The absolute increase in HD risk was substantially higher in patients with coronary artery calcification (CAC) vs. No CAC.

YES CAC Event-rate low-dose = 14-15 vs event-rate high-dose = 15-34 per 1000 person-years
NO CAC Event-rate low-dose = 6-8 vs event-rate high-dose = 5-17 per 1000 person-years.

No interaction between CAC and radiation dose was found.

Conclusions: Radiation exposure of cardiac structures is associated with increased risk of HD. Automatic segmentation of cardiac structures enables spatially localized dose estimation, which can aid in the prevention of radiation therapy-induced cardiac damage. This could be especially valuable in patients with breast cancer and CAC.

WECARE Young Women BCA Study
←R→ 1583 women <55 years of age BCa between 1985 and 2008.
Risk of radiation-associated CAD was evaluated by comparing women treated with left-sided RT with women treated with right-sided RT using multivariable Cox proportional hazards models. Effect modification by treatment and cardiovascular risk factors was examined.

Carlson, JACC: CardioOnc 2021 14 years
27.5-year CI of CAD for women receiving Left Side RT 10.5% vs. Right Side RT 5.8% (HR 2.5, P = 0.010).
There was no statistically significant effect modification by any factor evaluated.
Conclusions Young women treated with RT for left-sided breast cancer had over twice the risk of CAD compared with women treated with RT for right-sided breast cancer. Laterality of RT is independently associated with an increased risk of CAD and should be considered in survivorship care of younger breast cancer patients.

Comment: Older Radiation Techniques from 1985 to 2008.

LAD Dose RR
RR 375 consecutively treated female patients from 2012 to 2018 → L WBRT or CW RT (± RNI).
Medical records were queried to identify cardiac events after radiation therapy.
Mean and maximum LAD and heart doses (LAD Dmean, LAD Dmax, heart Dmean, and heart Dmax) were converted to 2-Gy equivalent doses (EQD2).

Zureick, IJROBP 2022 **4 years**
UVA/MVA ↑ LAD Dmean, LAD Dmax, and heart Dmean were all SS with ↑ risk of any cardiac event and a major cardiac event.
ROC curve analysis → Threshold **LAD Dmean EQD2 of 2.8 Gy** (area under the ROC curve, 0.69) risk any cardiac event (P = .001).
Threshold **LAD Dmax EQD2 of 6.7 Gy** (P = .005)
Threshold **heart Dmean EQD2 of 0.8 Gy** (P = .01).
Conclusions Dose to the LAD correlated with adverse cardiac events in this cohort. Contouring and minimizing dose to the LAD should be considered for patients receiving radiation therapy for left-sided breast cancer.

"Typical Anatomy" Heart Toxicity Study
2168 population-based case control. Between 1958 and 2001 in Sweden and Denmark. 963 women with major coronary events and 1205 controls.
For each woman, the mean RT whole heart and LAD "were estimated" from her radiotherapy chart.

Darby, NEJM 2013.
Estimated overall average of the mean doses to the whole heart was 4.9 Gy (range, 0.03 to 27.72).
Rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray (P<0.001), with no apparent threshold.
The increase started within the first 5 years after radiotherapy and continued into the third decade after radiotherapy.
The proportional increase in the rate of major coronary events per gray was similar in women with and women without cardiac risk factors at the time of radiotherapy.
Note: Absolute events remain low.
50-year-old female without baseline risk factors with MHD of 3 Gy would
↑ abs risk cardiac death before age 80 above baseline by 0.5% (1.9% → 2.4%)
↑ acute coronary event by 0.9% (4.5 → 5.4%).
If pre-existing heart disease, you have SAME RELATIVE EFFECTS, but all higher absolute effects.
Comment: The paper examined outdated 2D techniques that they then extrapolated and fitted by "virtual simulation" onto a phantom with a woman's "typical anatomy." NEJM article!

Lymphedema

Reconstruction Techniques and Lymphedema
664 RR immediate reconstruction from 2008 to 2014 were reviewed.
Categorized based on reconstruction method: 1. tissue expander/implant, 2. abdominal flaps, 3. latissimus dorsi (LD) muscle flaps.
402 prostheses, 180 abdominal flaps, and 82 LD flaps
The rate of axillary lymph node dissection was significantly higher in the LD flap group than in the other two groups.

Lee, EJSO 2023 **Follow-up 83 months.**
5-year CI lymphedema 10.9% vs. 10.6%, vs. 3.7%.
The use of abdominal flaps or prostheses was not associated with the outcomes.
Conclusions
Our results suggest that the method of immediate breast reconstruction might be associated with the development of postmastectomy lymphedema.

Sec. Malignancy

Population SEER Kaiser STS Risk
RR 15,940 (KP cohort) and 457,300 (SEER) BCa from Jan 1, 1992, to Dec 31, 2016. Stage I–III aged 20–84 breast cancer surgery → RT.
KP cohort median follow-up was 9·3 years. SEER median follow-up of 8·3 years

Veiga, Lancet Oncology 2022
KP COHORT:
94·7% thoracic soft tissue sarcomas occurred in women treated with radiotherapy
RT SS ↑ RR 8·1; p=0·0052). "But there was no association with prescribed dose, fractionation, or boost."
Angiosarcoma after anthracyclines RR 3·6 (p=0·058).
Alkylating agents SS ↑ other sarcomas (RR 7·7; p=0·026).
History of hypertension (RR 4·8; p=0·017) and diabetes (5·3; p=0·036) were each associated with around a 5x ↑ SS risk of angiosarcoma.
SEER COHORT:
77·9% thoracic STS cases occurred after radiotherapy
RT SS ↑ RR 3·0; p<0·0001.
For angiosarcomas, the RR for breast-conserving surgery plus radiotherapy versus mastectomy plus radiotherapy was 1·9 (1·1–3·3; p=0·012).
By 10 years after radiotherapy, the cumulative incidence of thoracic soft tissue sarcoma was 0·21% (95% CI 0·12–0·34) in the KP cohort and 0·15% (95% CI 0·13–0·17) in SEER.
Interpretation
Radiotherapy was the strongest risk factor for thoracic soft tissue sarcoma in both cohorts. This finding, along with the novel findings for diabetes and hypertension as potential risk factors for angiosarcomas, warrant further investigation as potential targets for prevention strategies and increased surveillance.

Other

Alopecia Toxicity

Bhoyrul, JAMA Dermatol 2021 – Alopecia (https://jamanetwork.com/journals/jamadermatology/fullarticle/2784689)

Conclusions and Relevance This case series outlines previously unreported features of persistent chemotherapy-induced alopecia (pCIA) in patients with breast cancer, including a trichoscopic description. Cosmetically significant regrowth was achieved for a significant proportion of patients with topical or systemic treatments, suggesting that pCIA may be at least partly reversible.

Thyroid Toxicity

Retrospective 4073 women w/ adjuvant RT for breast cancer from 2007 to 2016.
1^{O} was hypothyroidism development after RT.
3 groups: WBRT (n = 2468), RNI–Lv.4 (n = 215; ↑ border subclavian artery, ESRO guideline), and RNI-SCV (n = 1390; ↑border cricoid cartilage).
In general, RNI-Lv.4 was used in the patients with high-risk pN0 and pN1 breast cancer.
In auxiliary analysis, the mean thyroid dose was estimated in each group (total n = 600, 200 from each group). All the doses were converted to the equivalent dose in 2 Gy fractions (EQD2) with α/β ratios of 3.

Choi, IJROBP 2021. Results 84 months.

3-year hypothyroidism incidence rate 0.8% vs. 0.9% vs. 2.2% (HR 2.25, SS).
Adjusted HR 2.25 (SS) for RNI-SCL vs WB-alone, 1.69 (SS) for adjuvant systemic therapies, and 2.07 (SS) for age <60 years.
Subgroup analysis, the hypothyroidism risk became more prominent in patients aged <60 years.
Mean exposure doses to the thyroid were 0.23 vs. 1.93 vs. 7.89 Gy EQD2 (SS).
No statistically different locoregional recurrence rates were seen between groups (5-year rate: <3%).
Conclusions The risk of hypothyroidism increases after RNI-SCL for breast cancer but not after RNI-Lv 4. These data support routine contouring of the thyroid in the RNI setting, and future studies are required to develop optimal dose-volume constraints.

CDK + RT toxicity. Ratosa, Clin Breast Cancer 2020.
Retrospective Review: 46 patients RT + CDK concurrently.
Thirty patients (65.2%) received palbociclib, 15 (32.6%) received ribociclib, and one patient received abemaciclib (2.2%).
Median total prescribed RT dose was 20 Gy (range, 8-63 Gy). Sites of RT were bone (n = 50; 80.7%), visceral (n = 7; 11.3%), or brain metastases (n = 3; 4.8%), as well as primary tumor of the breast (n = 2; 3.2%).
Overall, ≥ G3 AEs were 6.5%, 4.3%, 15.2%, and 23.9% before the start of RT, during RT, 2 and 6 weeks after RT completion, respectively.
N correlation between dose distribution to organs at risk and the development of AEs.
6-month LC 98%, 12-month LC 90%.
Overall, pain relief (complete or partial) was experienced by 80% (24/30) of patients who initially reported pain at the treated metastatic site.
Conclusion: We observed a modest increase in the rates of grade 3 or higher AEs after combined RT and CDK4/6i, with maintained efficacy of concomitant RT.

Add'l Studies

HYPORT Palliative RT Chatterjee, IJROBP 2023

Tata Memorial shows two studies (35 Gy/10 fractions; HYPORT) and (26 Gy to breast/32 Gy tumor boost in 5 fractions; HYPORT B) designed with increasing hypofractionation to save overall treatment time from 10 to 5 days. 58 women (most pretreated with systemic therapy) completed the treatment.
No grade 3 toxicity was reported. Response assessment at 3 months showed improvement in ulceration (58% vs 22%, P = .013) and bleeding (22% vs 0%, P = .074) within the HYPORT study. Similarly, in the HYPORT B study, ulceration (64% and 39%, P = .2), fungating (26% and 0%, P = .041), bleeding (26% and 4.3%, P = .074), and discharge (57% and 8.7%, P = .003) was reduced. Metabolic response was noted in 90% and 83% of patients, respectively, in the 2 studies. Improvement in the QOL scores were evident in both studies. Only 10% of the patients relapsed locally within 1 year.

Conclusions

Palliative ultrahypofractionated radiation therapy to the breast is well tolerated, is effective, and results in a durable response with improved QOL. This could be considered a standard for locoregional symptom control.

Belgian PREOP 5 fx APBI Mulliez, Radiother Oncol 2022

Pre-operative 5-fraction RT → immediate breast-sparing surgery and SLNB feasible in 14 patients with 15 clinical early-stage breast cancers.
However wound problems occurred frequently and was documented in 5 of the 14 patients: 2 patients with a mastitis needing antibiotics, 2 patients developed a fistula with exudate needing antibiotics and local disinfection and 1 patient developed a fistula needing surgical reintervention. Other acute and late iatrogenic events were rather limited. Two patients had a pathological lymph node involvement, which underlines the importance to perform the sentinel node procedure before pre-operative radiotherapy.

MALE Trial Reinish, JAMA Oncol 2021

What are the changes in estradiol levels in male patients with breast cancer after 3 months of therapy?
←R→ 56 HR+ BCa men | 1. tamoxifen alone | 2. tamoxifen + GnRHa | 3. AI + GnRHa | all for 6 months.
1^{O} estradiol levels from baseline to 3 months.
After 3 months, median estradiol levels ↑ by 67% (a change of +17.0 ng/L), vs. ↓ by 85% (−23.0 ng/L) vs. ↓ by 72% (−18.5 ng/L) (P < .001).
After 6 months, median estradiol levels ↑ by 41% (a change of +12 ng/L), vs. ↓ by 61% (−19.5 ng/L), vs. ↓ by 64% (−17.0 ng/L) (P < .001).
Sexual function and quality of life decreased when GnRHa was added but were unchanged with tamoxifen alone.
Conclusions and Relevance This phase 2 randomized clinical trial found that AI or tamoxifen plus GnRHa vs tamoxifen alone led to a sustained decrease of estradiol levels. The decreased hormonal parameters were associated with impaired sexual function and quality of life.

IMRT Study Choi, Radiother Oncol 2020.

Notes: prospective ←R→ of early stage breast cancer among 700 women, 3-year LC is 99% either with 3D WBRT or IMRT (+ SIB tumor bed boost). IMRT improved ≥ G2 dermatitis from 38% to 28%. This could have been caused by 4mm skin sparking techniques / volumes.

Autoimmune CTD Purswani, IJROBP 2021.

Retrospective breast cancer patients with CTD matched with controls. Late G2-3 ↑ from 11% without CTD to 42% with ACTIVE CTD (aka symptomatic or on medication).

BMI Patients and Docetaxel Desmedt, JCO 2020.

Subset of RTOG 94-13.
Among patients with receiving a docetaxel regimen who are ↑ BMI or are overweight, these patients had a ↓ DFS and OS as well as a ↑ rate of DM. Lipophilic docetaxel can be problematic in ↑ BMI women.

Cost of Peg-Filgrastim Vaz-Luis, JCO 2020.

In 2018, CMS spent $1.4 billion on peg-filtrastim (aka Neulasta) vs. ~$2.4 billion spent on ALL radiation.
This phase 2 trial of 125 women age < 65 with excellent PFS, evaluated the safety of omitting peg-filgrastim during the paclitaxel portion of the ddACT adjuvant chemo. It is thought that while the chance of neutropenia are high during the AC portion of therapy, it is lower during paclitaxel. 90% were able to complete the four planned cycles of paclitaxel in under 7 weeks. The most common reasons for not finishing were non-hematologic. 4% developed neutropenia, and only 6% were prescribed peg-filgrastim, which resulted in a >95% reduction in peg-filgrastim use during dose-dense paclitaxel.

Single Fx Breast SBRT Kennedy, IJROBP 2020

Phase 1/2 of 50 patients age > 50, T1 or DCIS s/p lumpectomy. RT = prescribing 20 Gy to the surgical bed and 5 Gy to the breast tissue within 1 cm of the surgical bed simultaneously in 1 fraction using external beam. Surgical cavity was limited to >5 mm from skin, and a 1 cm margin from the cavity excluding 5 mm from skin and chest wall musculature. The cavity was prescribed a minimum of 15 Gy x 1 with a max dose of 22 Gy, while the 1 cm expansion received a minimum of 5 Gy x 1 (although the median D95% was ~10 Gy). Most patients were treated on a Cobalt unit with MRI guidance. 2 years follow-up showed only 100% LC. Only 1 patient had a new in situ lesion in a different quadrant. 1 patient had an isolated axillary recurrence. There was no grade 3+ toxicity events. 100% had good-to-excellent cosmesis.

PR importance (vs. ER?) Li, JAMA Netw Open 2020
Retrospective SEER analysis > 800,000 patients showed 66% were ER/PR(+), 19% ER/PR(-), 12% ER(+)/PR(-) and <2% ER(-)/PR(+). Mean BCSS ER/PR(+) was ↑ 20 months vs. ER(+)/PR(-) cases (HR 1.4) and ↑ 28 months beyond that of ER(-)/PR(+) cases (HR 1.6). When compared to one another, BCSS was significantly higher for ER(+)/PR(-) cases than for ER(-)/PR(+).

CORALEEN PAM50 Trial Prat, Lancet 2019
←R→ early-stage, Luminal B, ER+PR+Her2- breast Ca post-menopausal s/p either AC→ T) or letrozole + ribociclib for 6 months. All needed PAM50 testing.
The PAM50 test generates a risk of recurrence (ROR) score that estimates 10-year DM w/o chemo. 85% had a high ROR.
1^{O} % of patients that s/p NAC, went from high ROR to low ROR (aka molecular downstaging vs. pathologic downstaging). At surgery, 46% of patients in each group were molecularly ↓ ROR score. 22% still had a ↑ high ROR.
Consider: Neoadjuvant letrozole and ribociclib achieve ≈ rates of "molecular down-staging" vs. cytotoxic chemo for women with luminal B type breast cancer.

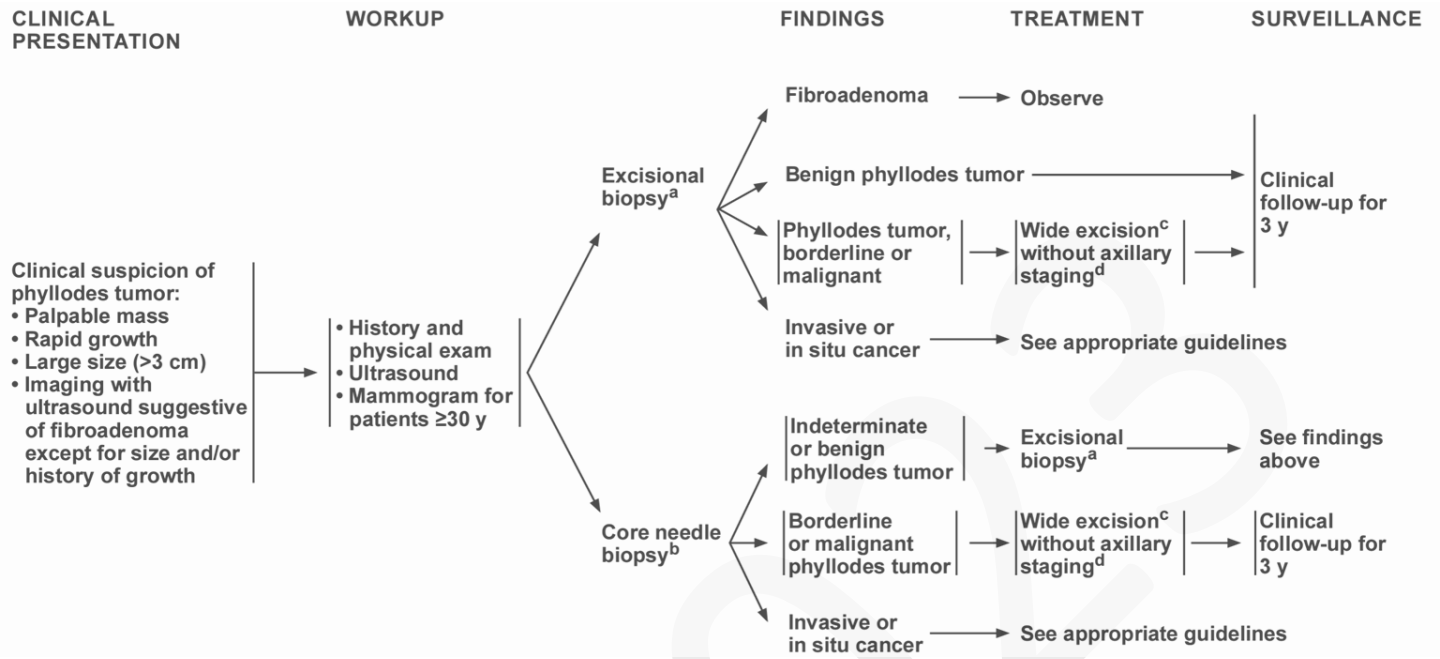
Antioxidant Use Trial Ambrosone, JCO 2020
Patients who received chemotherapy (ACT) were evaluated for use of supplements at registration and during treatment.
Use of ANY antioxidant supplements (ACE, carotenoids, coenzyme Q10) before and during Tx associated with ↑ HR recurrence (HR =1.41; *P* = .06) and ↑ death (adjHR, 1.40; *P* = .14). Relationships with individual antioxidants were weaker perhaps because of small numbers.
For nonantioxidants, vitamin B12 ↓ DFS (adjHR, 1.83; P < .01) and ↓ OS (adjHR, 2.04; P < .01).
Use of iron during chemotherapy ↑ Recurrence (adjHR, 1.79; P < .01) as was use both before and during treatment (adjHR, 1.91; 95% CI, 0.98 to 3.70; P = .06).
Results were similar for overall survival.
Multivitamin use was not associated with survival outcomes.
CONCLUSION Associations between survival outcomes and use of antioxidant and other dietary supplements both before and during chemotherapy are consistent with recommendations for caution among patients when considering the use of supplements, other than a multivitamin, during chemotherapy.

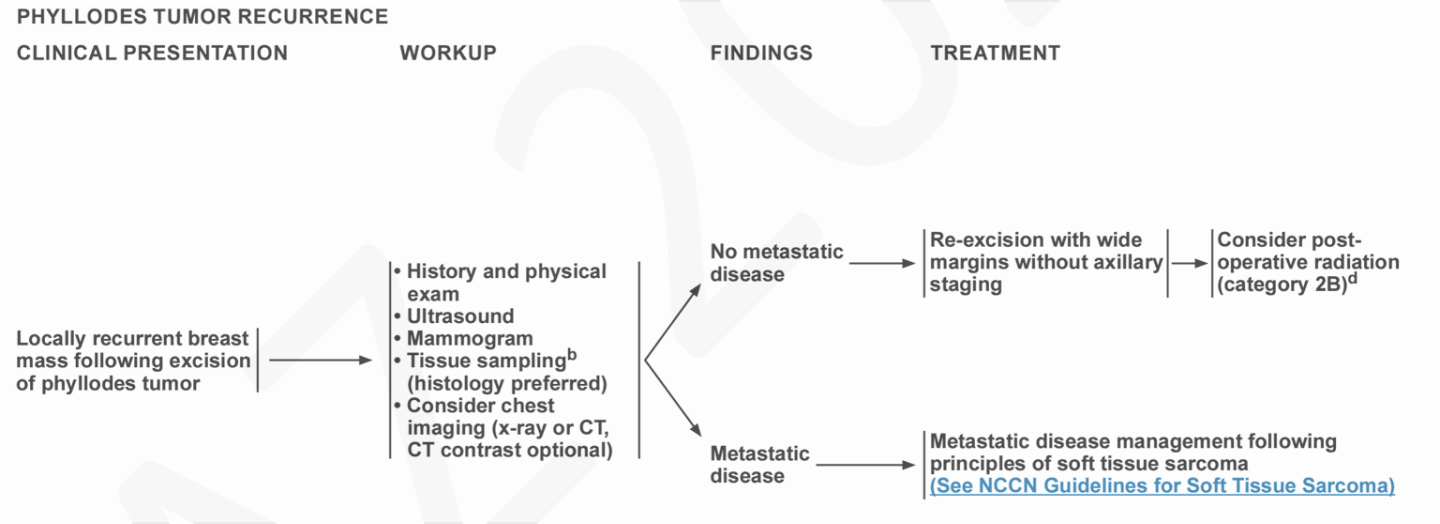
Denosumab D-CARE Trial Coleman, Lancet 2019.
TLDR: Denosumab, an --| RANKL (prevents osteoclast maturation) does NOT prevent bone mets in women with early-stage breast cancer.
NS ↑ bone mets-free survival.

Observational Study of Chemical Hair Dyes Eberle, Int J Cancer 2019
Large observational study ? Possible chemical hair dyes or straighteners ↑↑ development of novo breast cancer.

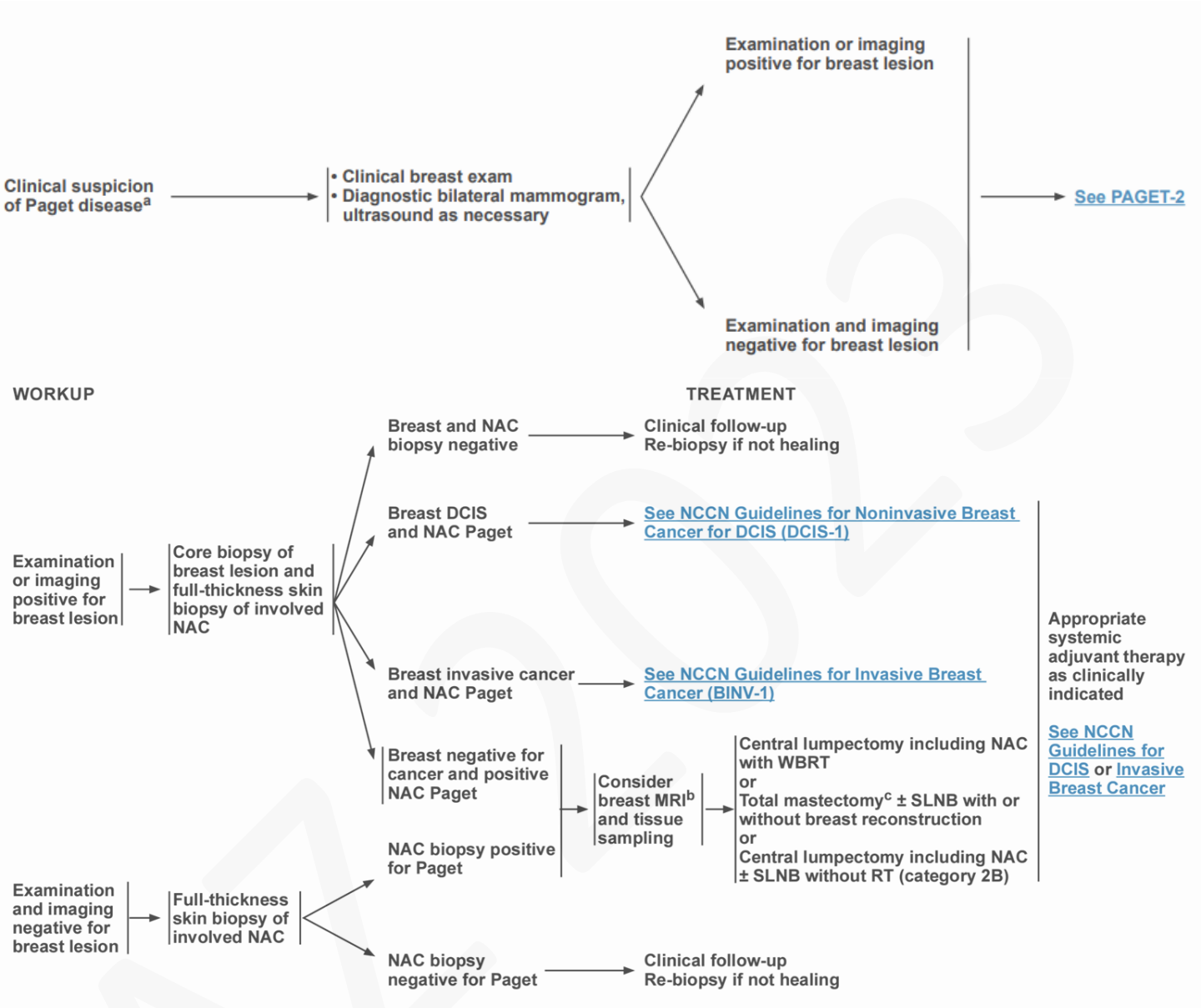
CT scan BMI Study Cespedes Feliciano, JAMA Oncol 2019
CT scans to quantify body composition, ↑ fat = ↓ <85% of the planned dose of chemo. This leads to ↓ survival outcomes.

Phyllodes

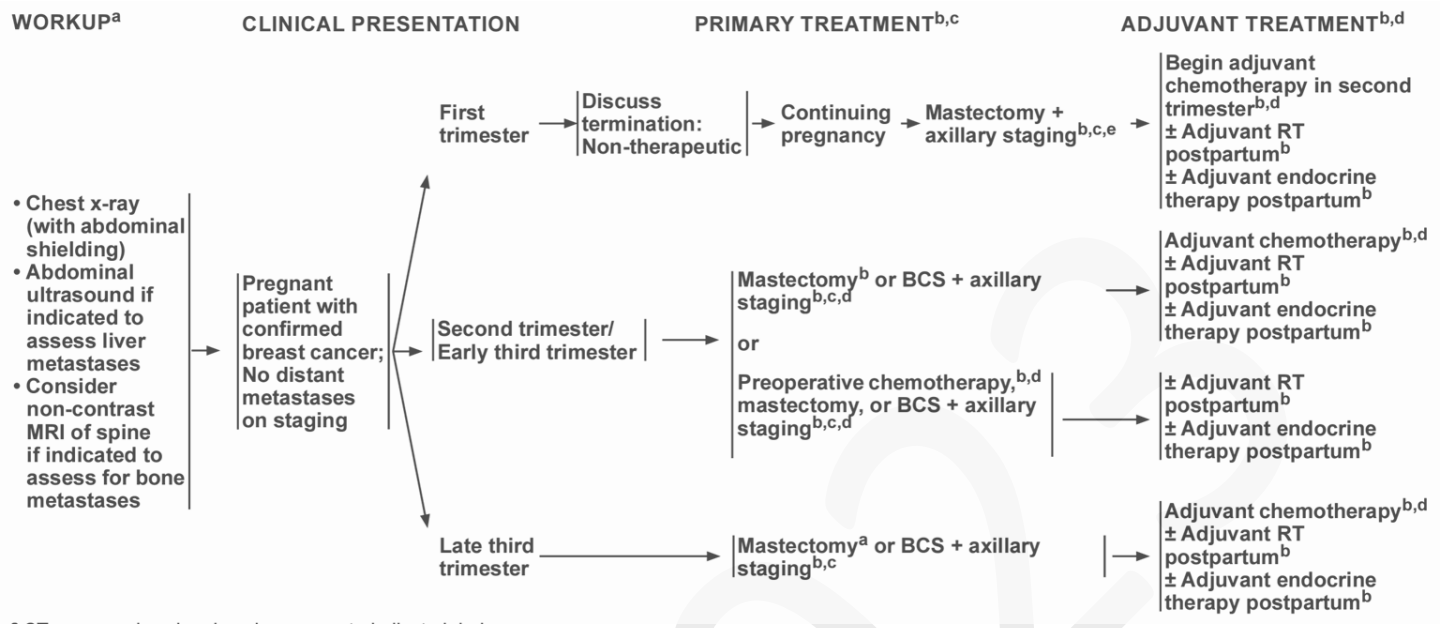




Paget's


Clinical suspicion of Paget disease[a]
• Clinical breast exam
• Diagnostic bilateral mammogram, ultrasound as necessary
Examination or imaging positive for breast lesion
Examination and imaging negative for breast lesion
See PAGET-2
WORKUP
TREATMENT
Examination or imaging positive for breast lesion
Core biopsy of breast lesion and full-thickness skin biopsy of involved NAC
Breast and NAC biopsy negative
Clinical follow-up
Re-biopsy if not healing
Breast DCIS and NAC Paget
See NCCN Guidelines for Noninvasive Breast Cancer for DCIS (DCIS-1)
Breast invasive cancer and NAC Paget
See NCCN Guidelines for Invasive Breast Cancer (BINV-1)
Breast negative for cancer and positive NAC Paget
NAC biopsy positive for Paget
Consider breast MRI[b] and tissue sampling
Central lumpectomy including NAC with WBRT
or
Total mastectomy[c] ± SLNB with or without breast reconstruction
or
Central lumpectomy including NAC ± SLNB without RT (category 2B)
Appropriate systemic adjuvant therapy as clinically indicated
See NCCN Guidelines for DCIS or Invasive Breast Cancer
Examination and imaging negative for breast lesion
Full-thickness skin biopsy of involved NAC
NAC biopsy negative for Paget
Clinical follow-up
Re-biopsy if not healing

Pregnancy



Note: van Gerwen et. al[82] shows that chemotherapy was associated with an increased risk of major congenital malformations **only in the first 12 weeks of pregnancy**. The risk of congenital malformations when chemotherapy was administered during the first trimester and the high number of incidental pregnancies during cancer treatment in the INCIP registry underscore the importance of contraceptive advice and pregnancy testing at the start of chemotherapeutic treatment in young women with cancer.

[82] https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2780797