Introduction

Evidence Based Radiation Oncology Fact Sheets
Breast Cancer 2021

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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)
  - White race (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).
- 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.[3]
      - 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.
  - Alcohol (directly correlate with amount of drinking).
  - Smoking.
- Hormonal Exposure:
  - Reproductive Factors that **↑ risk**: Nulliparity, early menarche, late menopause, late age 1st birth,[4] use of OCP and androgens.
  - In utero exposure to diethylstilbestrol (DES).
- History:[5]
  - Personal history: Having DCIS in 1 breast = higher risk of developing it in the other.
    - 2010 study (using SEER) 340,000 women with 1O BCa → incidence invasive contralateral BCa = 4% at follow-up 7.5 years.
  - Family History: ↑ 2x affected first-degree relative, **↑ 3x** if 2 affected first-degree relatives (if Dxed < 30 yo vs **↑ 1.5x** if > 60).
- Contralateral Breast Ca risk if Ispilatearl Ca.
- WECARE STUDY (SEER Registry):
  - Cumulative 10 year breast cancer risk is: BRCA1 carrier: 20% BRCA2 carrier: 16% BRCA1 or BRCA2 carrier: 18% Non-carrier: 5%

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%

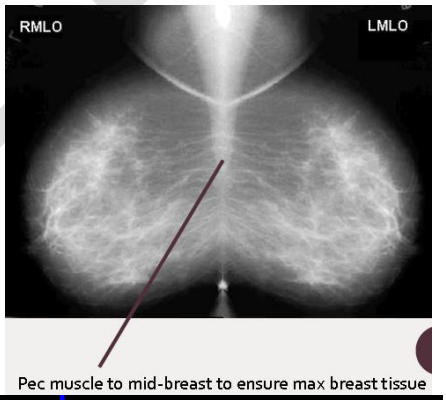
[1] http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
[2] Kohler BA, Ward E, McCarthy BJ, et al. Annual report to the nation on the status of cancer, 1975-2007, featuring tumors of the brain and other nervous system. J Natl Cancer Inst 2011; 103:714.
[3] van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol 2000; 152:514.
[4] 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.
[5] http://www.uptodate.com/contents/brca1-and-brca2-prevalence-and-risks-for-breast-and-ovarian-cancer?source=see_link

Screening/Imaging:

- **NCCN RECOMMENDATIONS 2021**
  - **Normal Category (Risk < 15%) – Start 40 yo with yearly mammogram.**
  - Previous RT at younger age – Start 8 years after RT.
    - Yearly Mammogram (no earlier than 30 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)

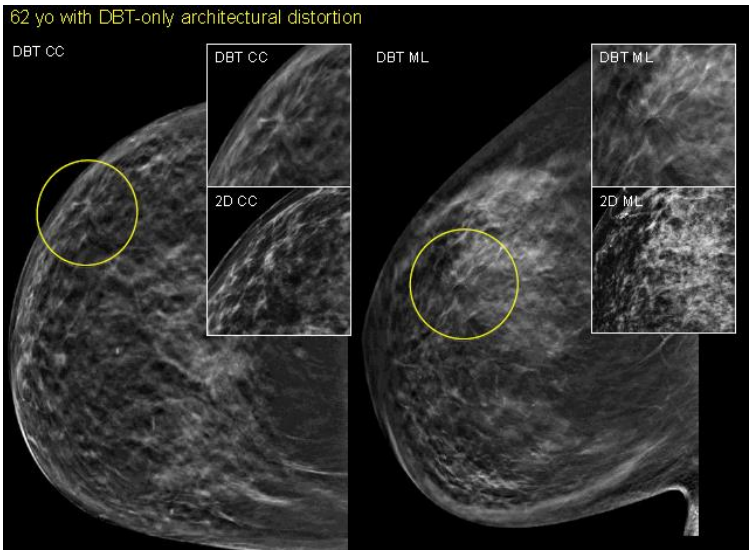
BI-RADS category	0	1	2	3	4	5	6
Risk of axillary LN +	**Incomplete assessment**	**Negative**	**Benign.**	**Probably Benign**: Short term f/u mamm at 6mo then q6/12 mos for 1-2 yrs.	**Suspicious** Biopsy	**↑ Suspicious** Biopsy	**Known Malignancy**

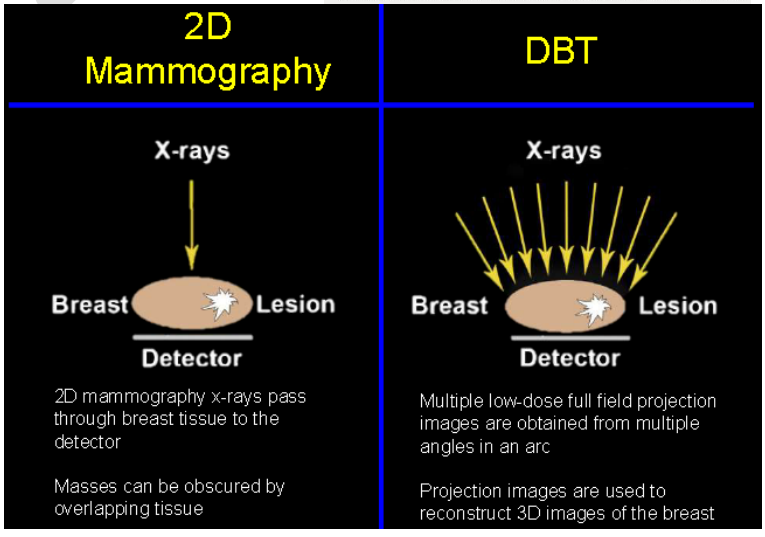
  - Annual screening using MRI is recommended by American Cancer Society for women who:
    - BRCA 1 / 2, P53, PTEN mutations, 1^{O} relative with BCRA 1 / 2 mutations and who are untested, lifetime risk 20-25% BCa, previous radiation Tx to chest at 10-30 yo.
  - Mammogram Views: medial lateral oblique (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





  - 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.

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 mammograms from nearly 26,000 women.
US test were read only with a 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%. We ran a simulation in which the AI system participated in the double-reading process that is used in the UK, and found that the AI system maintained non-inferior performance and reduced the workload of the second reader by 88%. This robust assessment of the AI system paves the way for clinical trials to improve the accuracy and efficiency of breast cancer screening.

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.

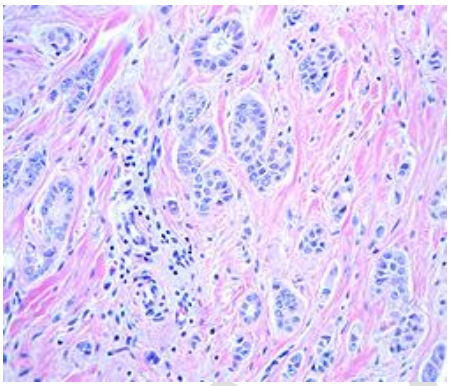
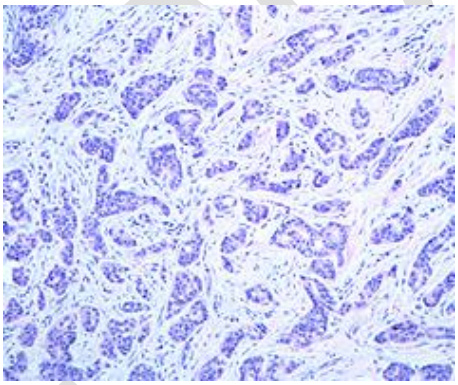
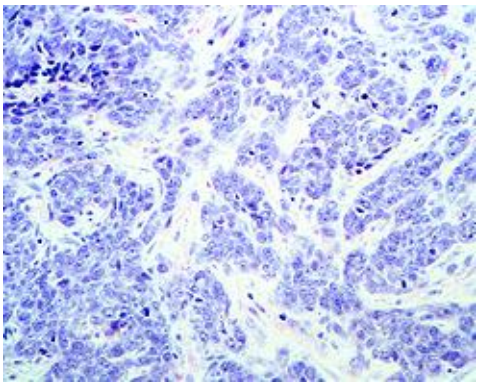
Pathology:

Invasive ductal carcinoma (IDCA) 76% of cases. Invasive lobular carcinoma (ILCA) 8%.[6] 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
  - *After years of arguing with our surgeons for re-excision, we now just look for no tumor on ink for IDC.*[7]
    - **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.[8]
    - However, variants of infiltrating lobular carcinoma exist, some of which have a poorer prognosis.[9]
  - ICLS metastasize later and spread to unusual locations such as peritoneum, meninges, and the gastrointestinal tract.

- 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)

[6] Li CI, Uribe DJ, Daling JR. Clinical characteristics of different histologic types of breast cancer. Br J Cancer 2005; 93:1046.
[7] Houssami, N Ann SurgOncol2014; 21; 71 Morrow M, NEJM 2012, 367: 79 JCO 2014 volume 32; 14
[8] 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.
[9] 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.

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)

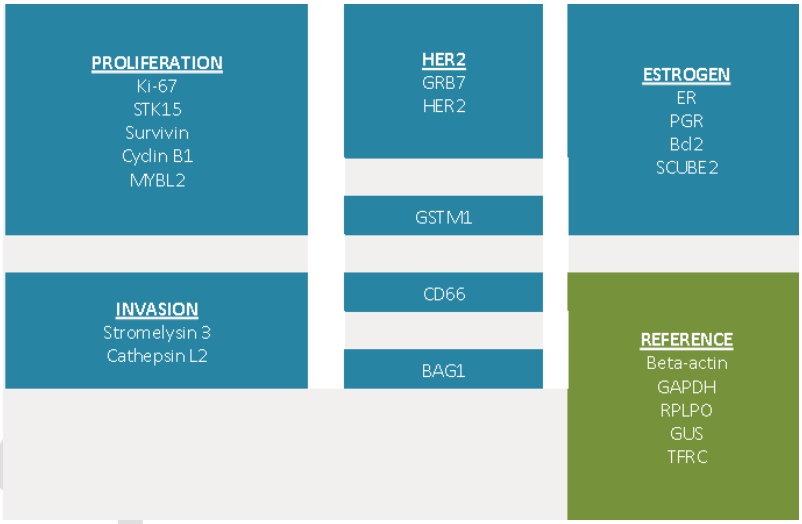
B-04, B-06	Surgery ± RT	
B-17	DCIS Lumpectomy ± RT	
B-24, B-35	CHEMO DCIS	
B-14, B-21	Adjuvant Hormonal	ATLAS
B-18, B-27	NAC, no PMRT	Mamounas

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.[10] 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.[11] 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.

[10] http://www.ncbi.nlm.nih.gov/pubmed/15591335
[11] 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 optional.
  - Recommended treatments:
    - Lumpectomy w/o LN surgery + whole breast radiation (WBR). …
    - Total mastectomy ± sentinel node biopsy (SNB) … ± reconstruction.
    - Lumpectomy w/o LN surgery w/o RT (**in carefully selected cases**) …

- **Major Topics**:
  - BCS + RT vs. Mastectomy
  - BCS ± RT
  - Need for "Boost" after WBRT
  - Hypofractionated Whole Breast Irradiation (3-4 Weeks vs. 5-6 Weeks)
  - Partial Breast Irradiation

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).[12] 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.

[12] 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.[13]

      Moore 2007.[14] 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.[15] 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!!!

Margins

:

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[13]

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

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."**

[13] http://www.ncbi.nlm.nih.gov/pubmed/?term=23544935
[14] http://www.ncbi.nlm.nih.gov/pubmed/17597346
[15] http://www.ncbi.nlm.nih.gov/pubmed/16978948

Radiation Therapy:

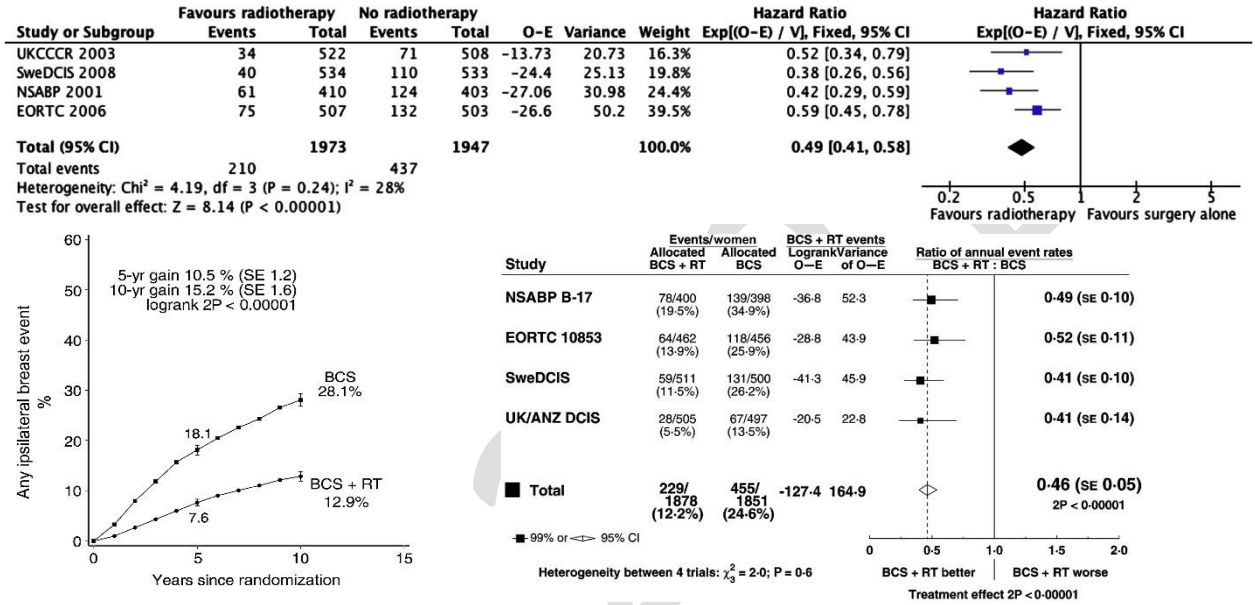
- "RT after wide excision reduces the risk of local invasive and noninvasive recurrences. However, treating all women who undergo wide excision for DCIS with adjuvant RT may be overtreatment for some. The majority of cases of DCIS do not recur when treated with excision alone and there may be subgroups 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).[16] 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.



[16] 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[17]). 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).[18] 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:
NSABP 35 vs 20%
EORTC 31% vs 18%
SweDCIS 32 vs 20%
UK/ANZ 23 vs 9%

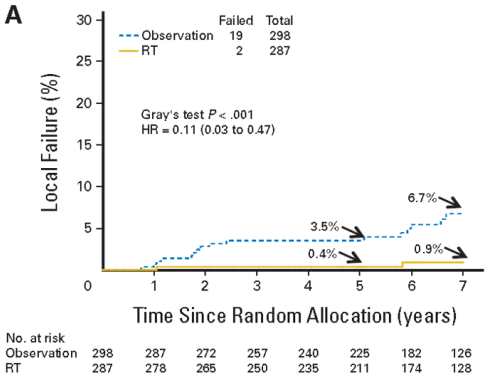
EBCTCG Metaaanlysis, Correa JNCI Mono 2010
Lumpectomy without RT 28.1% risk of LR versus 12.9% for lumpectomy + RT

[17] http://www.ncbi.nlm.nih.gov/pubmed/16801628
[18] http://www.ncbi.nlm.nih.gov/pubmed/18250350

Contemporary Trials (Can omit 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.

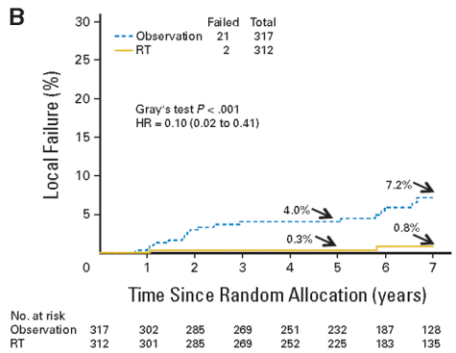
- **4 Major trials MUST KNOW: RTOG 98-04, Harvard Single Arm, Van Nuys, ECOG 5194.**

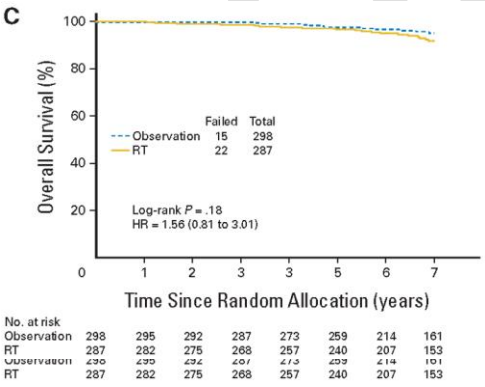


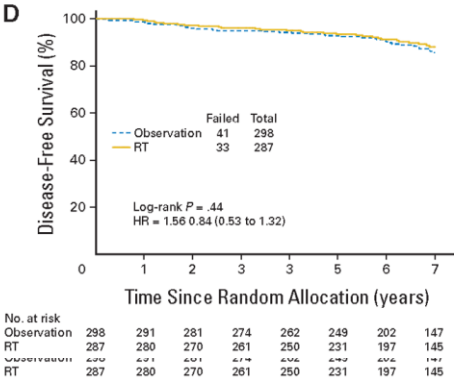
RTOG 98-04 -- RT vs. No RT. **Favorable GRADE.**
←R→ 636 out of 1,790. *Closed due to poor accrual.* "Good risk" DCIS, < 2.5 cm, margins > 3mm, grade I-II only, necrosis in < 1/3 of the ducts.
BCS → 1. RT vs. 2. no RT. **WBRT choice of 50.4 Gy in 1.8 Gy fxs, 50 Gy in 2 Gy, or 42.5 Gy in 16 fx.**
Tamoxifen 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.

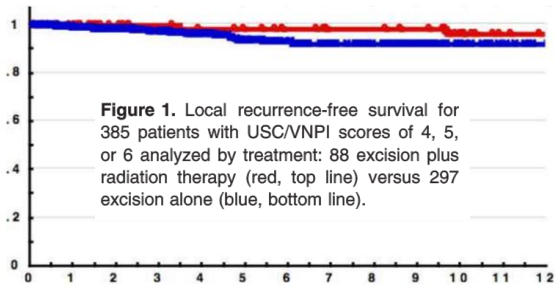


Figure 1. Local recurrence-free survival for 385 patients with USC/VNPI scores of 4, 5, or 6 analyzed by treatment: 88 excision plus radiation therapy (red, top line) versus 297 excision alone (blue, bottom line).

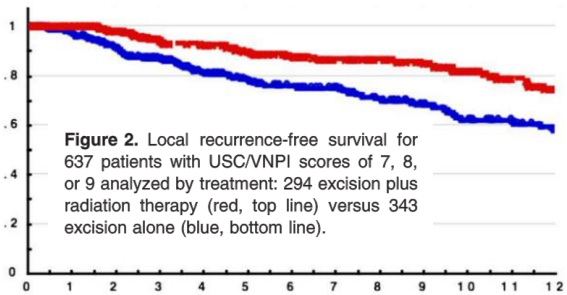


Figure 2. Local recurrence-free survival for 637 patients with USC/VNPI scores of 7, 8, or 9 analyzed by treatment: 294 excision plus radiation therapy (red, top line) versus 343 excision alone (blue, bottom line).

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

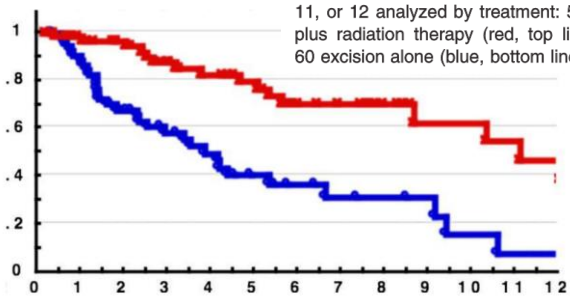
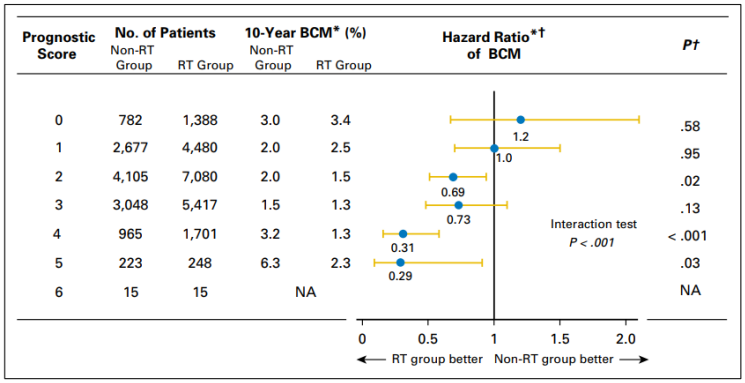


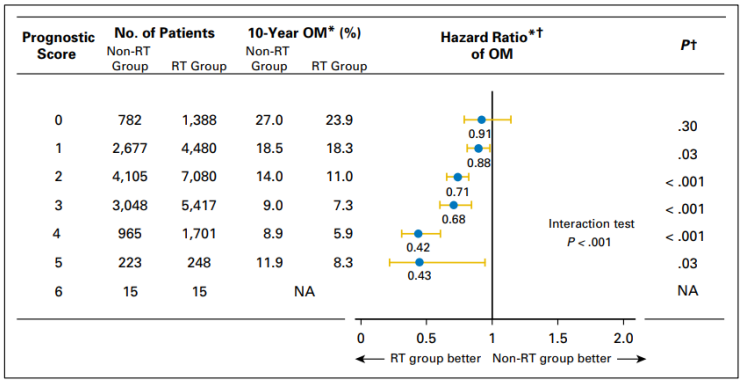
Figure 4. Local recurrence-free survival for 116 patients with USC/VNPI scores of 10, 11, or 12 analyzed by treatment: 56 excision plus radiation therapy (red, top line) versus 60 excision alone (blue, bottom line).

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.

Points	Age (years)	Size (mm)	Histology	Score
0	61+	< 16	Low grade	0
1	40-60	16-40	Intermediate grade	
2	< 40	41+	High grade	6





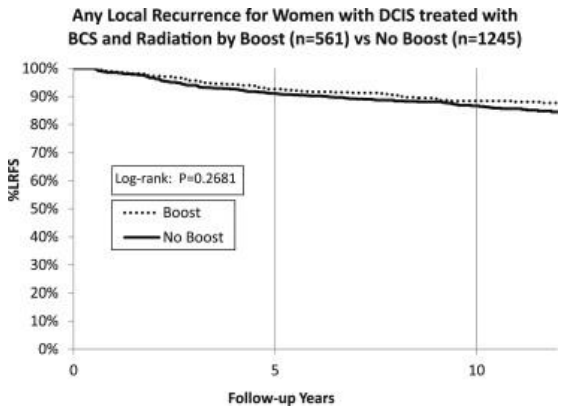
Boost

BIG 3-07/TROG 07.01
←R→ 1608, four arm trial. Conventional vs. Hypofx (42.5 Gy in 16 fx). Boost (16 Gy in 8 fx) vs. No Boost.
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 13% (all arms).
1^{O} time to LR.

Chua, Abstract GS2-04.
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%).
The rates of grade ≥2 breast pain (12% vs. 16%, P=0.84) and skin and subcutaneous tissue fibrosis (6% vs.15%, P=0.14).
Conclusions: In women with non-low risk DCIS treated with breast conserving surgery, the addition of tumor bed boost following conventional or hypofractionated WBI reduced local recurrence rates. There was no difference in local recurrence rates between conventional WBI and hypofractionated WBI. (Registered with ClinicalTrials.gov, NCT00470236.)

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

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)

Hypofractionation

- No pure randomized trial in DCIS → The randomized trials supporting hypofractionation were done with invasive breast cancer.
- 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.
- Therefore, some radiation oncologists are reluctant to use whole breast hypo-fractionation when treating DCIS.
    - However, the new trend is that it is very safe to use hypofractionation (see below!)

→ Must See "Offersen, JCO 2020" → Under "Major HFx-U-Hfx Trials"
This is the only trial I know of to date that included 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.

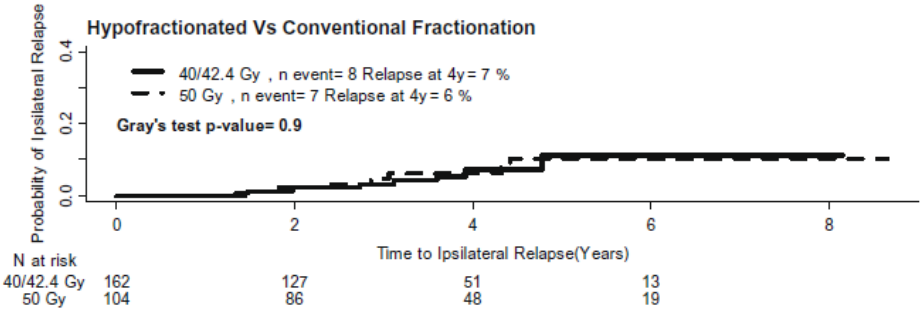


Fig. 1. Cumulative incidence of ipsilateral breast relapse for hypofractionated vs. conventional fractionation.

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%.

Genomic Classifiers / Oncotype DCIS

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

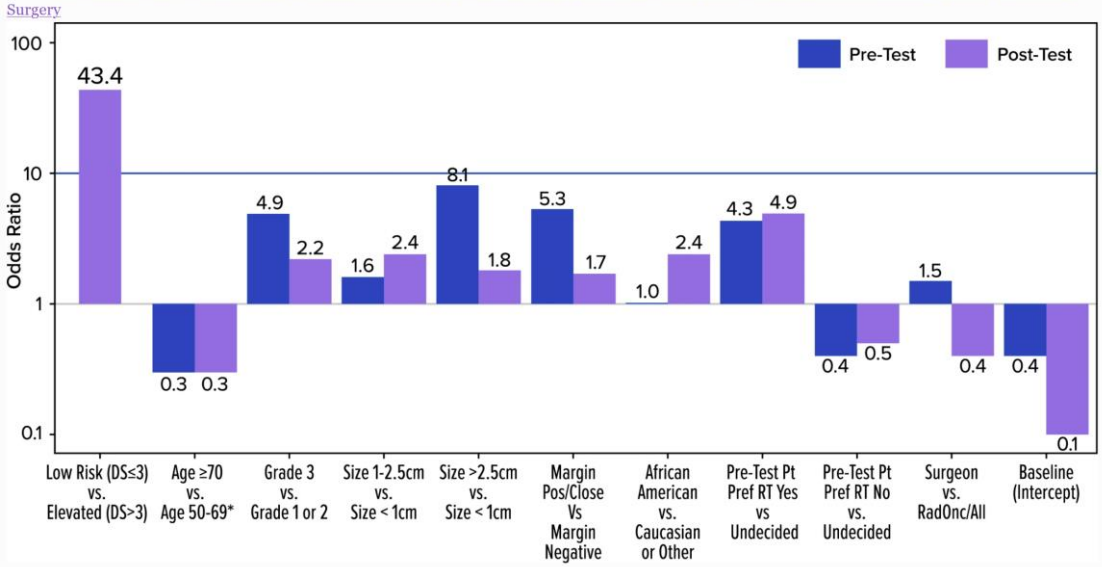
DCISonRT Validation in SweDCIS
Tumor blocks were collected, and slides were sent to PreludeDxTM for testing.
In 504 women with complete data and negative margins, DCISionRT divided 52% women into Elevated (DS > 3) and 48% in Low (DS ≤ 3) Risk groups. Elevated Risk group, RT SS ↓←→ 10-year ipsilateral 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/Her2 Therapy for DCIS

- **Chemotherapy**: 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**.

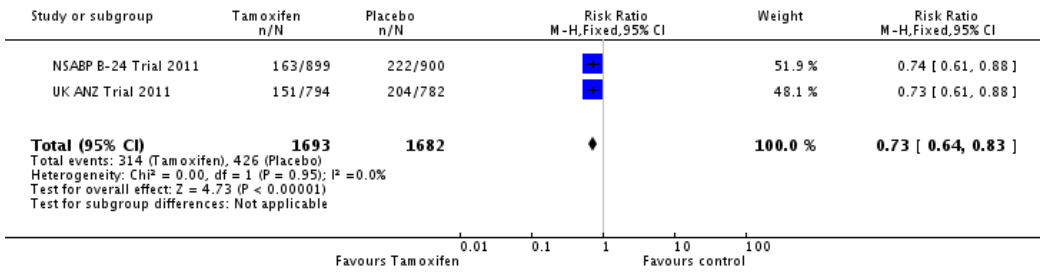
TAM01 Study
←R→ 500 women ≤ 75 yo with ER+ DCIS s/p BCS | 1. 5 mg Tam daily for 3 years | 2. Placebo |.
1^{O} incidence of invasive breast cancer or ductal carcinoma in situ.

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).[19] 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).

Analysis 1.8. Comparison 1 Tamoxifen versus no tamoxifen, Outcome 8 All breast events.



[19] http://www.ncbi.nlm.nih.gov/pubmed?term=23076938

NSABP B-24 (Fischer et al 1999, 2001, 2002, 2007**; Allred 2012[20])**. 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).

[20] 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.[21]
  - 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).[22] 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).[23] 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** [24] **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.

[21] http://www.ncbi.nlm.nih.gov/pubmed?term=11346867
[22] http://www.ncbi.nlm.nih.gov/pubmed/16110014?dopt=Abstract
[23] http://www.ncbi.nlm.nih.gov/pubmed/16754727
[24] 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)

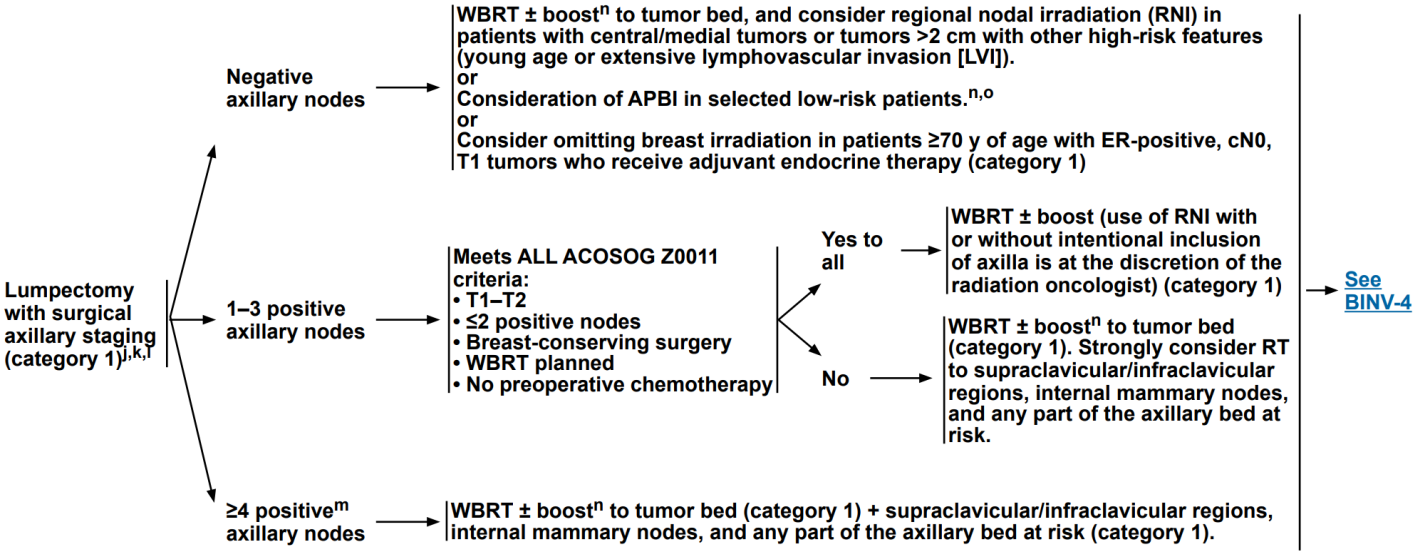
- **NCCN guidelines**:

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

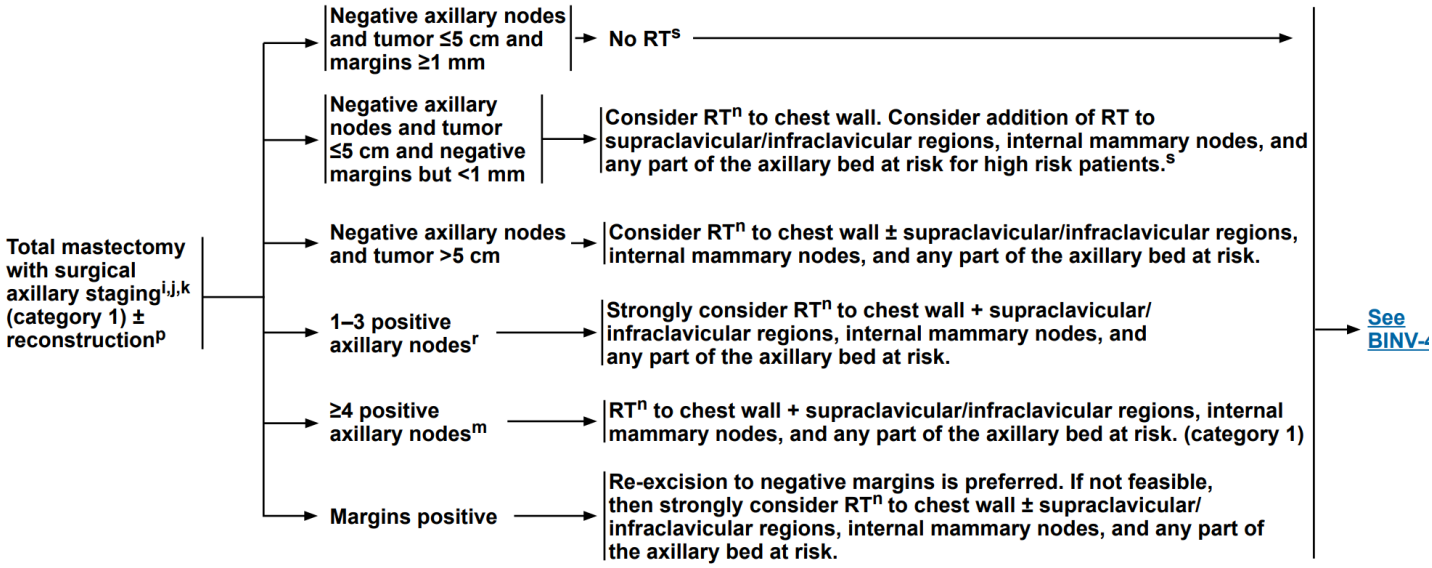
  - Workup: H&P, diagnostic b/l mammogram, pathology, receptor status, genetic counseling if high risk hereditary BCa, MRI optional.
    - Bone Scan **if** bone pain or elevated Alk Phos.
    - Abdominal CT / MRI **if** ↑ LFT, alk phos, GI symptoms, abnormal physical exam.
    - Chest CT **if** pulmonary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

  - Recommended Local Treatments:

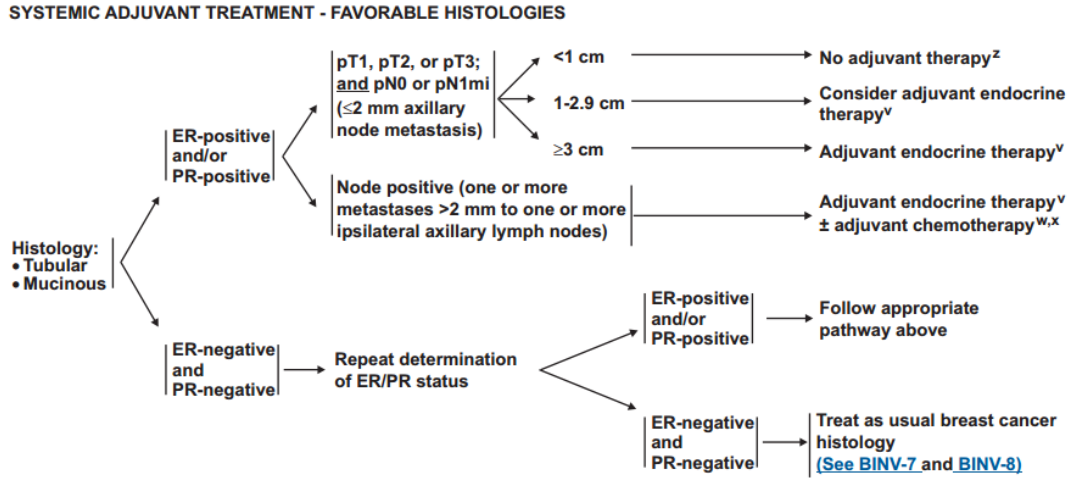
LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE:[a]
BREAST-CONSERVING THERAPY



LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE:[a,q]
MASTECTOMY FOLLOWED BY RT



- Recommended Systemic treatments:

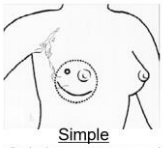


Adjuvant Chemo decision (aggressive histologies: Ductal, Lobular, mixed, micropapillary)

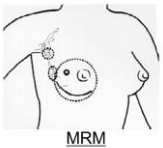
- ER/PR +, Her2 + → pT1a N0/mic → ± Endocrine ± Chemo w/ **Trastuzumab (Herceptin)**
  pT1b N0/mic → **Endocrine** or **Chemo w/ Trastuzumab** + endocrine.
  ≥ pT1c or N+ → **Chemo w/ Trastuzumab** + **Endocrine**.
- ER/PR +, Her2 - → pT1a N0 → ± Endocrine
  → ≥ pT1b N0 → **21 gene RT-PCR.**
  < 26 low = Endo. 26-30 int = Endo or C→E. ≥31 high = **C→E both**.
  → pNmic or 1-3 N+ → **Chemo + endocrine (Cat 1)** or endocrine. Can consider RT-PCR
  → ≥ 4 N+ → **Chemo + endocrine (Cat 1)**
- ER/PR -, Her2 + → Same as triple positive, just without endocrine therapy
- ER/PR -, Her2 - → Same as triple positive, just without endocrine therapy or Her2 directed therapy

Surgery:

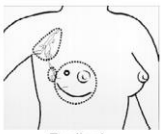
- Breast conservation therapy (lumpectomy + RT), is now commonly used and **considered the standard of care** in early stage BCa patients to provide locoregional control, similar DFS and OS compared to total mastectomy, and cosmetically acceptable surgical option.
  - **Contraindications** for BCT include:
    - Multicentric 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.[25] LN involvement is NOT a contraindication to BCT.
  - **Relative Contraindications:**
    - Scleroderma[26], 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)[27] 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)[28], 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.

Mastectomy vs BCT + RT.

NSABP B-06 (Fisher 2002).[29] 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+.**

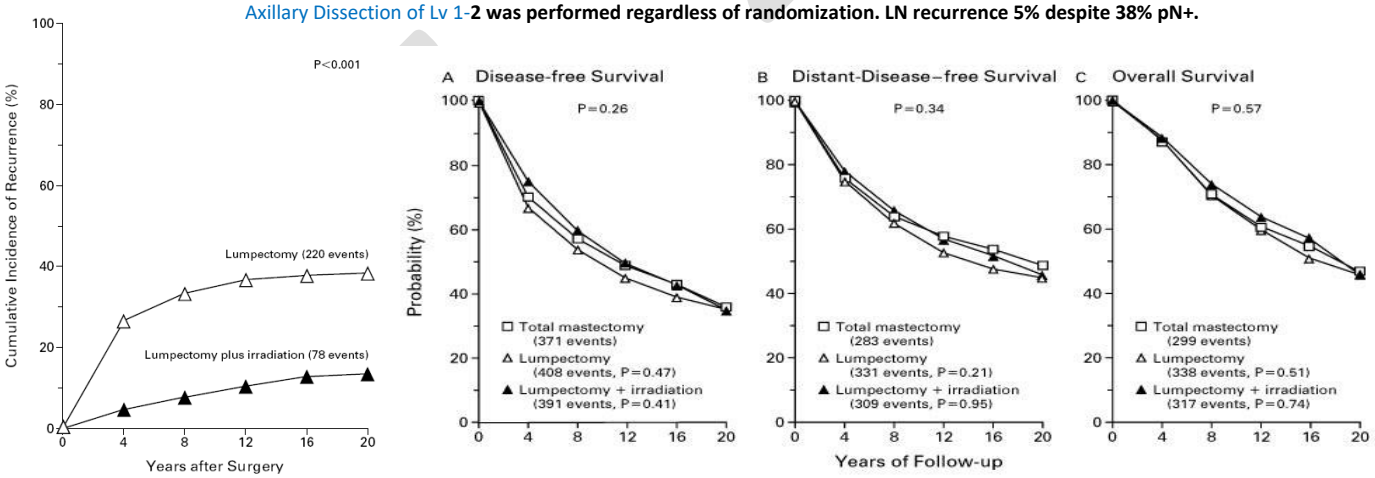


Figure 1. Cumulative Incidence of a First Recurrence of Cancer in the Ipsilateral Breast during 20 Years of Follow-up among 570 Women Treated with Lumpectomy Alone and 567 Treated with Lumpectomy plus Breast Irradiation.

	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	

[25] http://www.ncbi.nlm.nih.gov/pubmed/17275207?dop`=Abstract
[26] http://www.ncbi.nlm.nih.gov/pubmed?term=11769860
[27] http://www.ncbi.nlm.nih.gov/pubmed/12192016?dopt=Abstract
[28] http://www.ncbi.nlm.nih.gov/pubmed/18465331?dopt=Abstract
[29] http://www.ncbi.nlm.nih.gov/pubmed/12393820?dopt=Abstract

ETORC 10801 (Van Dongen 2000).[30] 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).[31] 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.

Surgical Margins:

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

Park 2000.[32] 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. +).

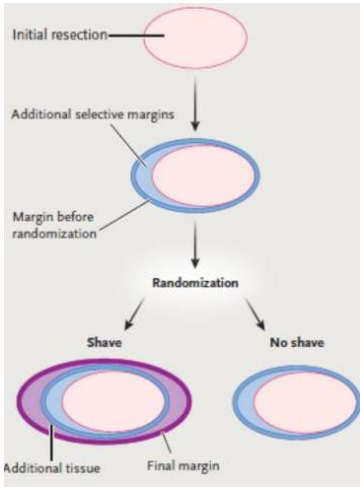
EORTC 22881/10882 (Jones 2009).[33] (See above for actual study results). Subset analysis of boost versus no boost trial in 1989, 5,569 patients. All pts lumpectomy + ALND → WBI; total dose of 50/25 Gy. Pt with microscopically neg margin → RTC WBI with either no boost or 16 Gy tumor bed. Pt with positive 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.[34] 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).



[30] http://www.ncbi.nlm.nih.gov/pubmed/10904087?dopt=Abstract
[31] http://www.ncbi.nlm.nih.gov/pubmed/12393819?dopt=Abstract
[32] http://www.ncbi.nlm.nih.gov/pubmed/10764427?dopt=Abstract
[33] http://www.ncbi.nlm.nih.gov/pubmed/19720914?dopt=Abstract
[34] http://www.ncbi.nlm.nih.gov/pubmed/19720895?dopt=Abstract

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)**.[35]
        - **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.

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

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)

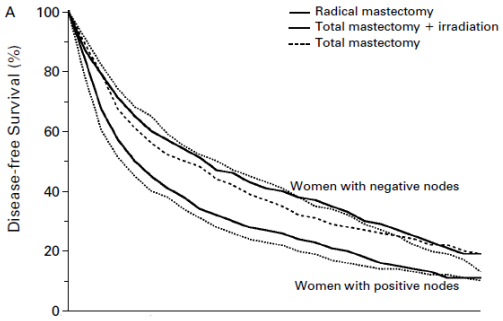
For clinically N- pts, ←R→ **1.** radical mastectomy (+ ax dissection) (362)
2. total/simple mastectomy (+ ax dissection only if evidence of nodal recurrence) (365)
3. total mastectomy + PMRT (axilla, SCV, IM nodes included). (352)

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.

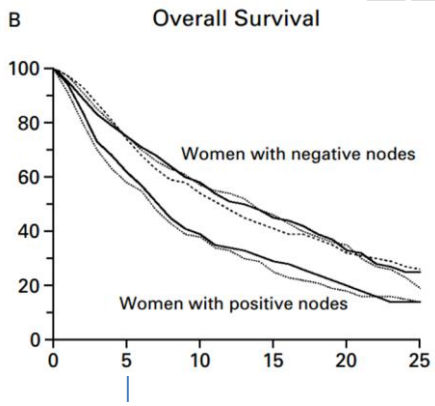
Only about 50% of patients with untreated nodal disease will recur in axilla.

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



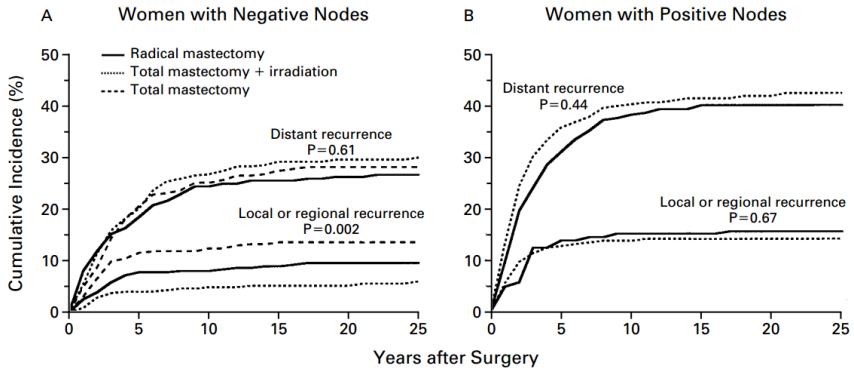
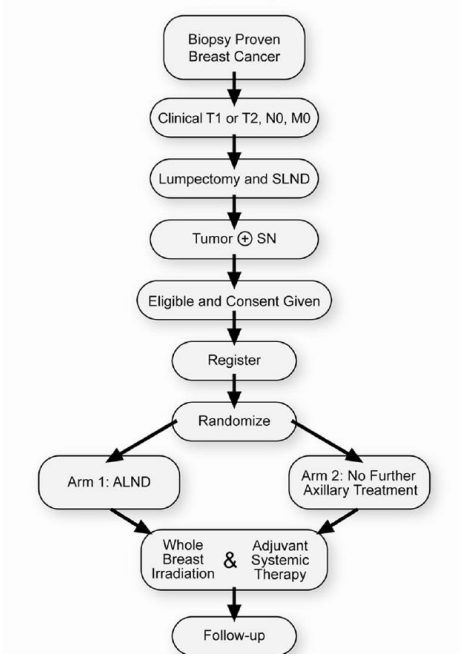


Figure 2. Cumulative Incidence of Local or Regional Recurrence and Distant Recurrence during 25 Years of Follow-up after Surgery among Women with Clinically Negative Axillary Nodes (Panel A) and Women with Clinically Positive Axillary Nodes (Panel B), According to Treatment Group.

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



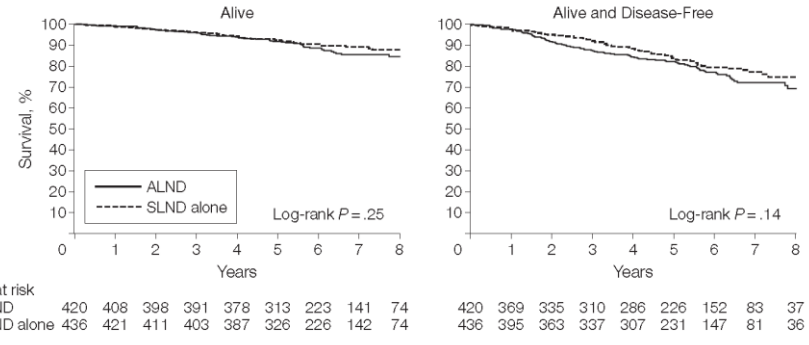
Giuliano, Ann Surg 2010.
Outcome: Further involved nodes with cALND 27%.
5-year breast recur ALND 3.1% vs SNB 1.6% (NS); axilla recur 0.5% vs 0.9% (NS); year OS 92% vs 92% (NS).
No difference in LRR based on systemic therapy.
Conclusion: NS; SLND without completion ALND may be a reasonable management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

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

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



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

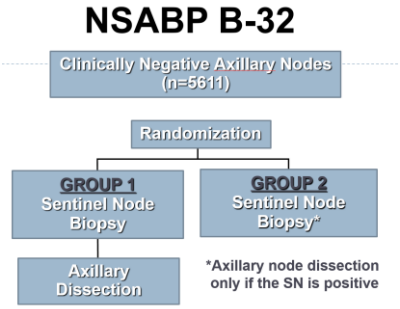
Jagsi, San Antonio Breast Conference 2013, Poster Session: P5-14-19.
Among 605 pts completed adjuvant RT, 89% receive WBRT. Of these, 89 patients (15%) also RT to the supraclavicular region.
Detailed RT records available on 228 patients: 104/389 (26.7%) and 124/404 (30.7%) on the ALND and SLND arms, 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).
Between year 5 and year 10, 1 regional recurrence was seen in the SLND alone group vs none in the ALND group.
Ten-year regional recurrence did not differ significantly between the 2 groups.
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 Barrio Annal Surgical Onc
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.

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.

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.

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.

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.

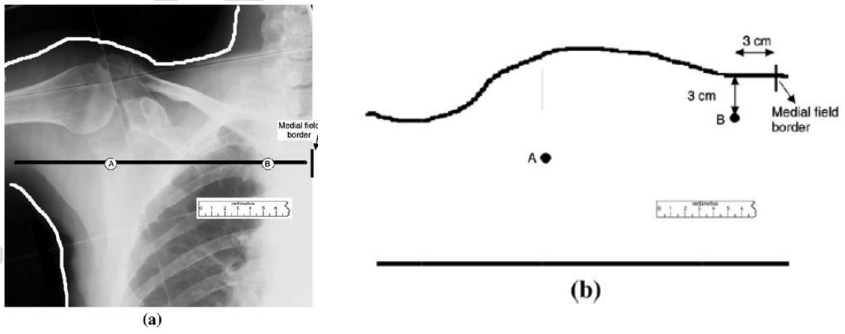


Fig. 1. Frontal view (radiograph) of axillary region. Dose specification points A and B are indicated. The axial patient contour given in (b) is indicated by a black line. (b) Axial contour at the cranio-caudal level of the black line indicated in (a).

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.

Important Small Institutional Studies

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.**

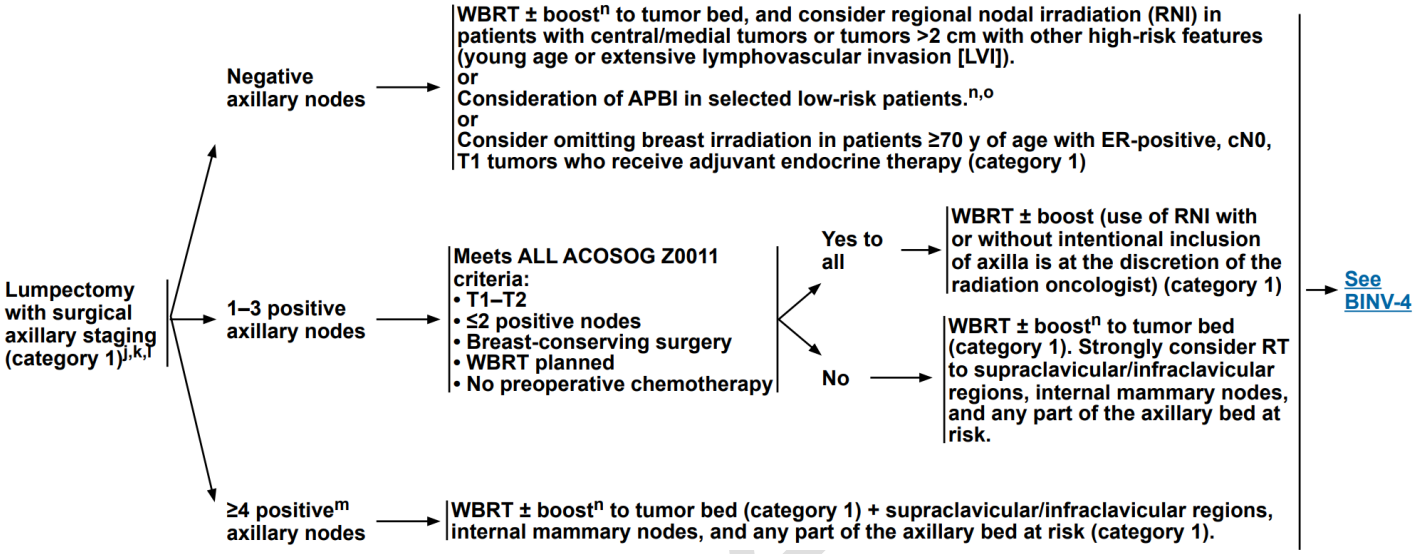
Harvard ELDERLY no SLNB, HIGH TANGENT STUDY (Wong, IJROBP 2008)
Prospective single arm **74 patients** > 55 yo, stage I/II, cN0, ER+ breast cancer with lumpectomy (negative margins) without ALND or SLNB and WBI with high tangents (blocked humeral head) + tumor bed boost + 5 years hormonal therapy. **Median 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:

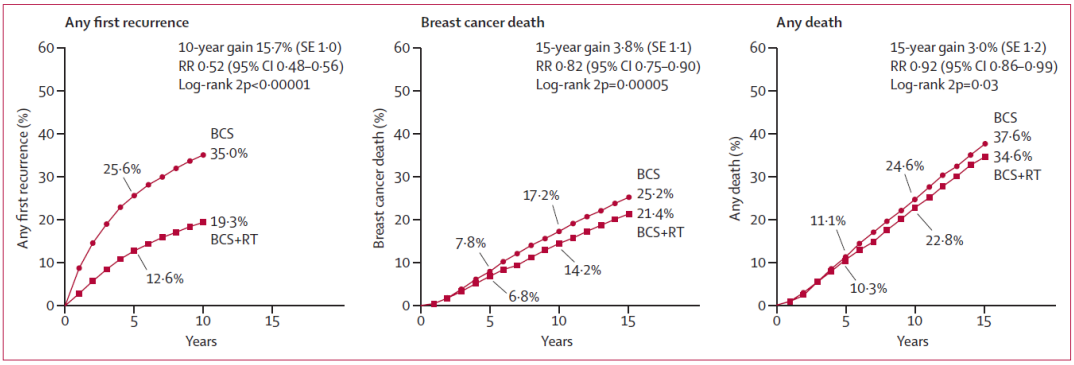
- Of date, 18 RTC have been performed regarding BCS ± RT. Note that eligibility criteria and adjuvant tamoxifen and chemotherapy varied significantly within these studies. **Conclusion** is that RT ↓ ipsilateral BCA recurrence by approximately 66%, which better effects in LN + patients and younger women, 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

LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE:[a]
BREAST-CONSERVING THERAPY



BCS ± RT

Early Breast Cancer Trialists' Collaborative Group (EBCTCG, Lancet 2011).[36] 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%).

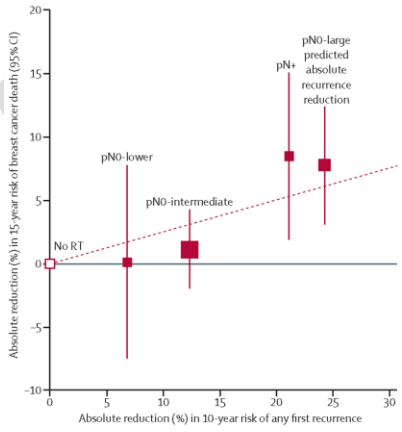


For pN0 subset: ↓ any recurrence 31.0% to 15.6% (abs: 15.4%) and ↓ death 20.5% to 17.2% (abs: 3.3%).
Absolute 10-yr recurrence risk reduction depended on factors (age, grade, ER, tamoxifen, and margins).
Worst = ER -, no Tam, young, ↑ grade, + margins). Best = ER +, yes Tam, old age, ↓ grade, - margins).
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%.



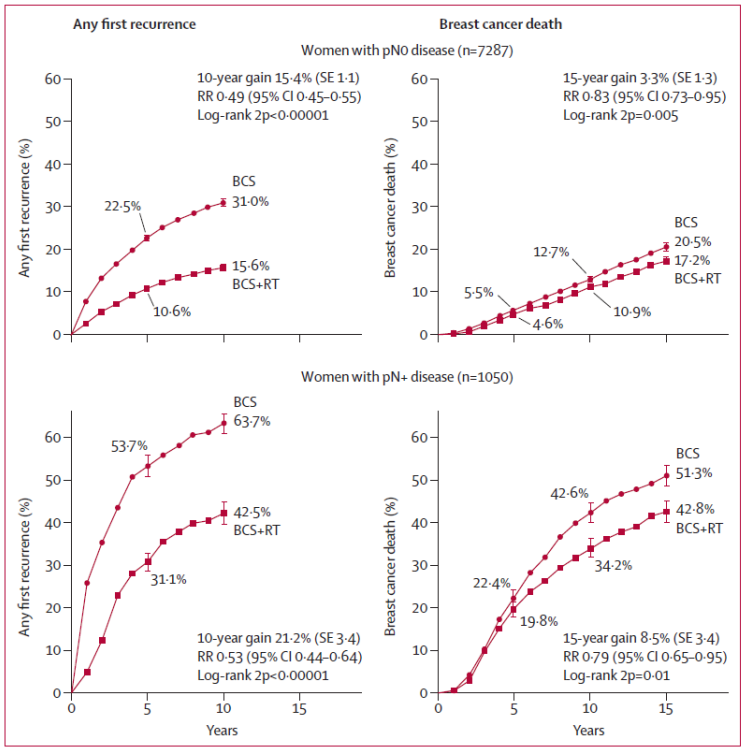


Figure 5: **Absolute reduction in 15-year risk of breast cancer death with radiotherapy (RT) after breast-conserving surgery versus absolute reduction in 10-year risk of any (locoregional or distant) recurrence**
Women with pN0 disease are subdivided by the predicted absolute reduction in 10-year risk 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.

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

De-Escalation: Elderly Patients.

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.

CALGB C9343 / RTOG 97-02, ECOG (Hughes, 2010).[37]
←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**.

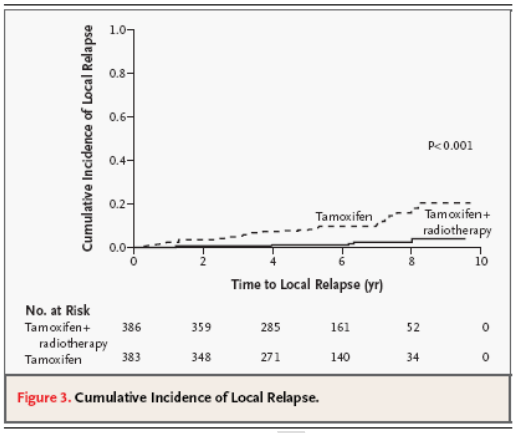


Figure 3. Cumulative Incidence of Local Relapse.

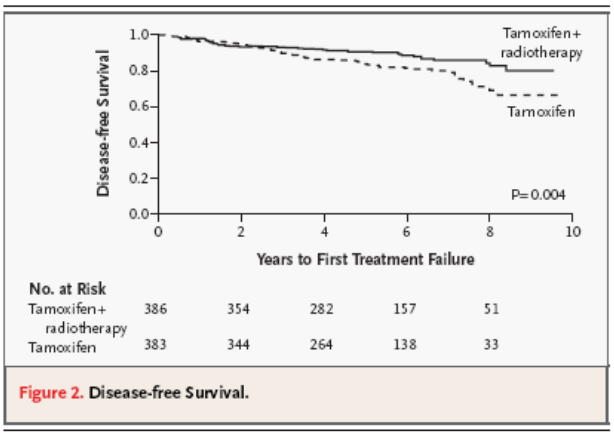


Figure 2. Disease-free Survival.

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.

[37] 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 received 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° 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.

Low-Risk Luminal A

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… no RT 6% adjuvant RT. No RT IBTR at 10 years = 20% . Shows necessity of tamoxifen.

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).[38]

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.

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

Major HFx U-Hfx Trials

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.

Real-World Expectations of Side effects (Standard Fx vs. Hypo Fx)

Jagsi, JCO 2020
8,711 patients treated between 2012 and 2019 at 27 practices.

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).

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

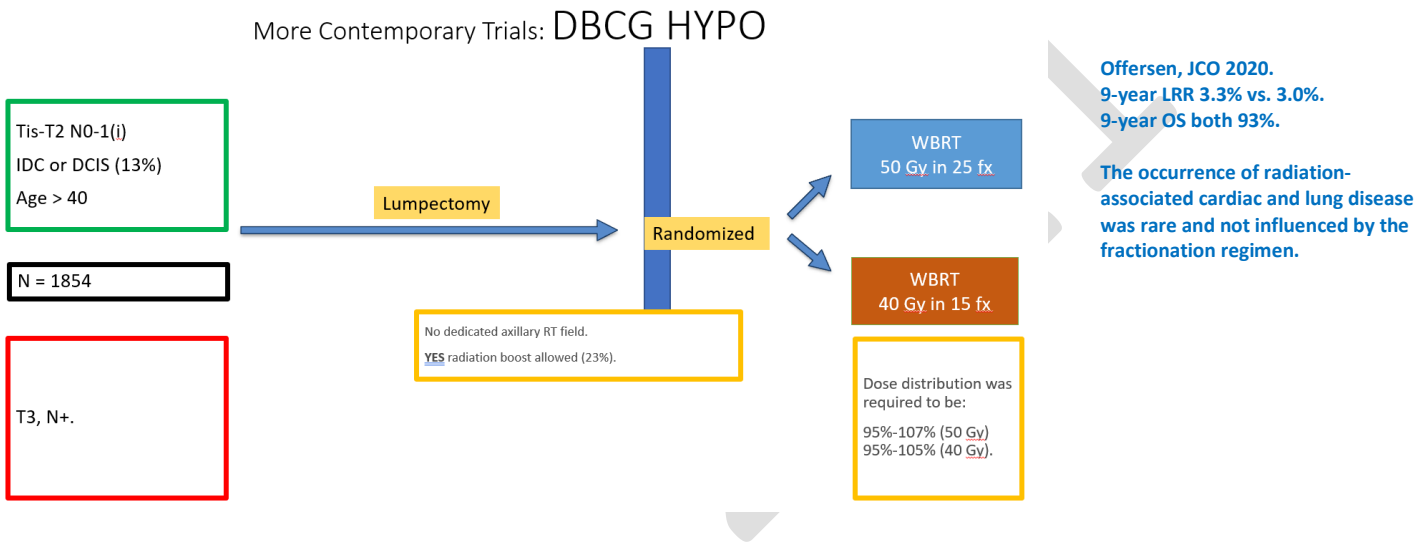
CFRT and HFRT with a tumor-bed boost may have similar low LR and toxicity.

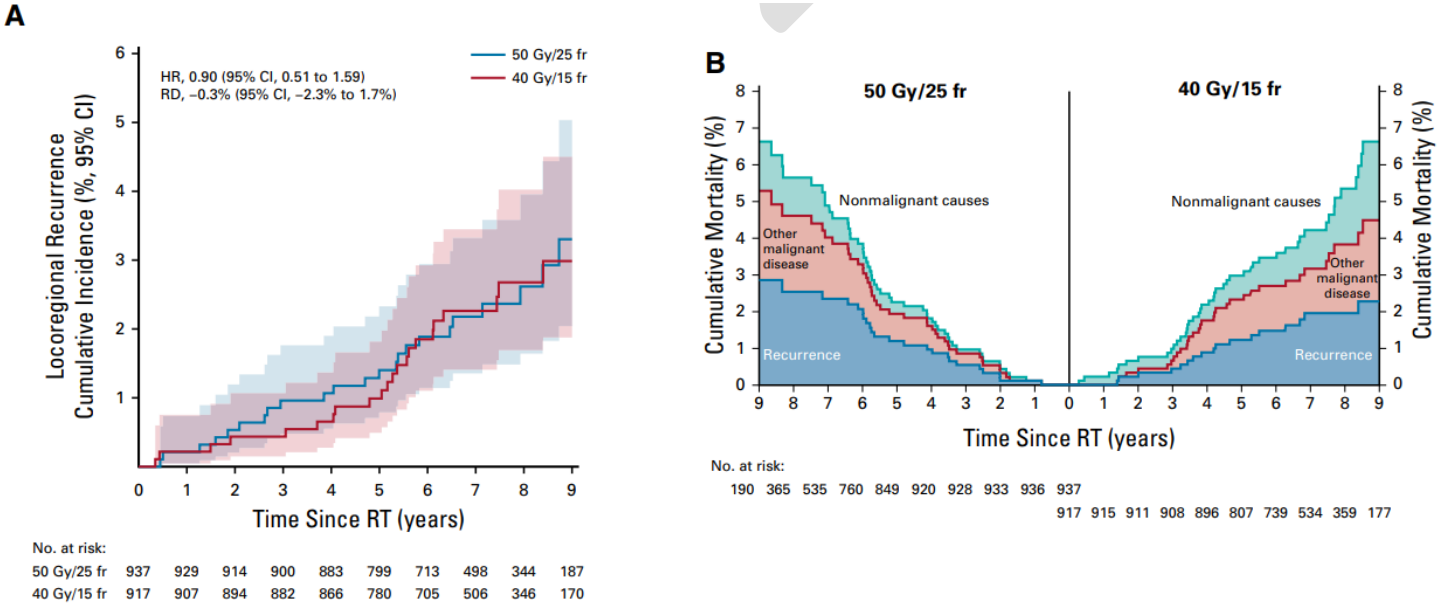
DBCG Hypo: IDC **and DCIS** Randomized Trial

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.





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).

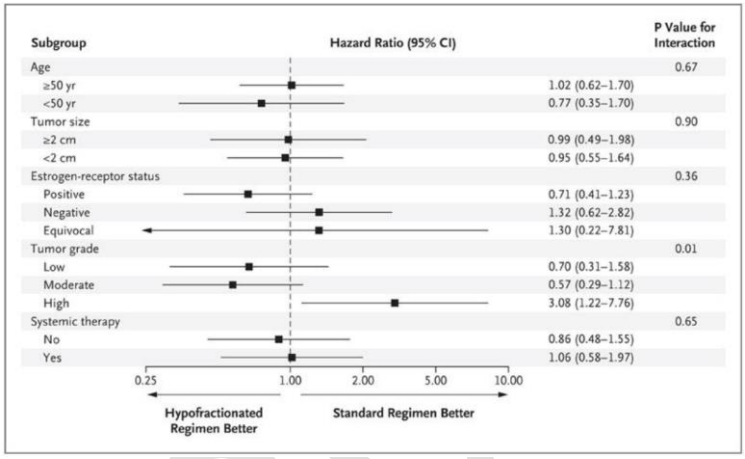
Conclusion Analysis of outcomes in this large observational cohort of patients with triple-negative, node-negative breast cancer treated with whole breast irradiation reveals no differences by dose fractionation. This adds evidence to support the use of moderate hypofractionation in patients with triple-negative disease.

Older Trials

Canadian (Whelan 2010).[39] 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 outcome 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).[40] 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).[41] 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).[42] 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.

[39] http://www.ncbi.nlm.nih.gov/pubmed/20147717?dopt=Abstract
[40] http://www.ncbi.nlm.nih.gov/pubmed/18356109?dopt=Abstract
[41] http://www.ncbi.nlm.nih.gov/pubmed/18355913?dopt=Abstract
[42] 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.

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).[43] 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.

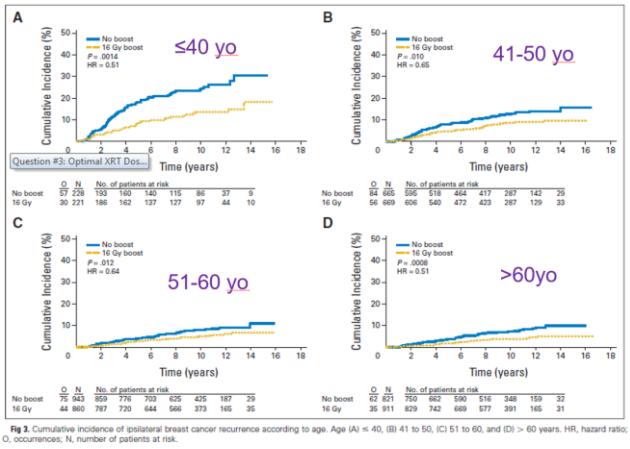


Fig 3. Cumulative incidence of ipsilateral breast cancer recurrence according to age. Age (A) ≤ 40, (B) 41 to 50, (C) 51 to 60, and (D) > 60 years. HR, hazard ratio; O, occurrences; N, number of patients at risk.

EORTC 22881/10882 (Bartelink, 2001).[44] 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.[45] 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).[46] 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).

Concurrent/SIB boost?

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.

RTOG 1005 (protocol).
(Arm I) Standard Whole Breast Irradiation with Sequential Boost.
50 Gy in 25 fractions of 2 Gy. Optional: 42.7 Gy in 16 fractions of 2.67 Gy.
Lumpectomy Cavity: Total dose of 12 Gy in 6 fractions or 14 Gy in 7 fractions per institutional preference.
(Arm II) Hypofractionated Whole Breast Irradiation with Concurrent Boost.
40.0 Gy in 15 fractions of 2.67 Gy fractions per day.
Lumpectomy Cavity: Total dose of 48.0 Gy in 15 fractions (3.2 Gy/day)

[43] http://www.ncbi.nlm.nih.gov/pubmed/16904837?dopt=Abstract
[44] http://www.ncbi.nlm.nih.gov/pubmed/11794170
[45] http://www.ncbi.nlm.nih.gov/pubmed/17577015?dopt=Abstract
[46] http://www.ncbi.nlm.nih.gov/pubmed/12706362

Other trials: IMRT-MC2 (MINT) Lumpectomy Boost with SIB

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. 40 Gy partial breast + 48 Gy boost all 15fx SIB | 3. 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.
Clinician Reviewed: Breast induration, shrinkage, distortion. Patient reported: Δ cosmesis Photograph: Breast appearance.
Median FU 49.1 months. Median age 49 yo.

Coles, Oral 2018.
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)

Systemic Therapy:

HER2-Negative Preferred Regimens
• **Dose-dense AC followed by paclitaxel[1]** ▸ Doxorubicin 60 mg/m² IV day 1 ▸ Cyclophosphamide 600 mg/m² IV day 1 ◊ Cycled every 14 days for 4 cycles.[r] ◊ Followed by: ▸ Paclitaxel 175 mg/m² by 3 h IV infusion day 1 ◊ Cycled every 14 days for 4 cycles.[r]
• **Dose-dense AC followed by weekly paclitaxel[1]** ▸ Doxorubicin 60 mg/m² IV day 1 ▸ Cyclophosphamide 600 mg/m² IV day 1 ◊ Cycled every 14 days for 4 cycles.[r] ◊ Followed by: ▸ Paclitaxel 80 mg/m² by 1 h IV infusion weekly for 12 weeks.
• **TC[2]** ▸ Docetaxel 75 mg/m² IV day 1 ▸ Cyclophosphamide 600 mg/m² IV day 1 ◊ Cycled every 21 days for 4 cycles.[r]

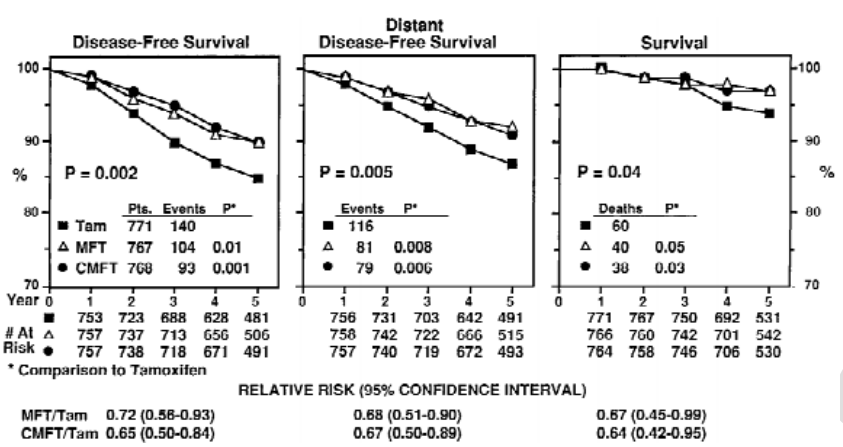
- Adjuvant Therapy: Typically given to LN+, ER-, HER2+, and women with adverse features (young age, or high Oncotype DX).
  - In the absence of high-risk features, no recommendations for chemotherapy.
  - Following chemotherapy, patients with ER-positive disease should also receive adjuvant endocrine 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.
- 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.
- Common Dosages
  - AC Adriamycin 60 mg/m² + cyclophosphamide 600 mg/m² q3weeks x 4c.
  - AC→T: AC above and paclitaxel 175 mg/m² q3weeks x 4c or 80 mg/m² q1week x 12 cycle.
    Dose dense regimen is q2 weeks w/ filgrastim or pegfilgrastim for support.
  - AC→TH: AC→T above and trastuzumab 4 mg/kg loading dose followed by 2 mg/kg per week concurrently with paclitaxel
    → trastuzumab monotherapy (6mg/kg q3 weeks) for 1 year.
  - TC: Docetaxel 75 mg/m² and cyclophosphamide 600 mg/m².
  - TCH: Docetaxel 75 mg/m² and carboplatin AUC 6mg/mL/min q 3weeks x6c + trastuzumab (4 mg/kg loading dose followed by 2mg/kg weekly concurrently with TC) → trastuzumab monotherapy (6mg/kg q3weeks) for 1 year.

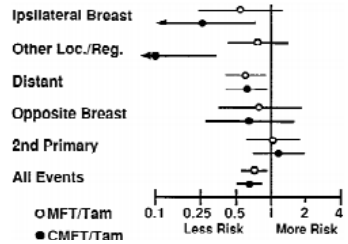
HER2-Positive[k,l,m] Preferred regimens		
Paclitaxel + trastuzumab[11] ▸ Paclitaxel 80 mg/m² IV weekly for 12 weeks ◊ With: ▸ Trastuzumab 4 mg/kg IV with first dose of paclitaxel ◊ Followed by: ▸ Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment. As an alternative, trastuzumab 6 mg/kg IV every 21 days may be used following the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment.	**TCH[12]** ▸ 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.[s] 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.[s]	**TCH + pertuzumab[13]** ▸ 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.[s]

Which chemo is most effective?

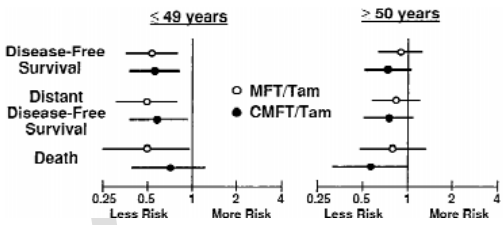
NSABP B-20 (Fisher 1997).[47] RTC 2306 women s/p surg, node negative, ER + BCa randomized Tam, and Tam + 5-FU + methotrexate (MFT), or MFT + cyclophosphamide (CMFT). 5 year follow up. **Conclusion**: **ALL** subgroup of patients evaluated in this study benefited from chemotherapy, regardless of age, 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.

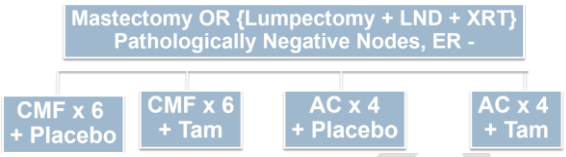




Relative risks of **MFT vs TAM** & **CMFT vs TAM**. Lines = 95% CI.

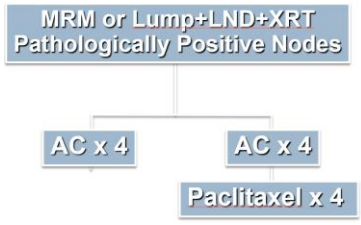


5 year	DFS	DDFS	OS
TAM	85%	87%	94%
MFT	**90%**	**92%**	**97%**
CMFT	**89%**	**91%**	**96%**
p	0.001	0.005	0.05



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: There was no significant difference in 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.

[47] 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.

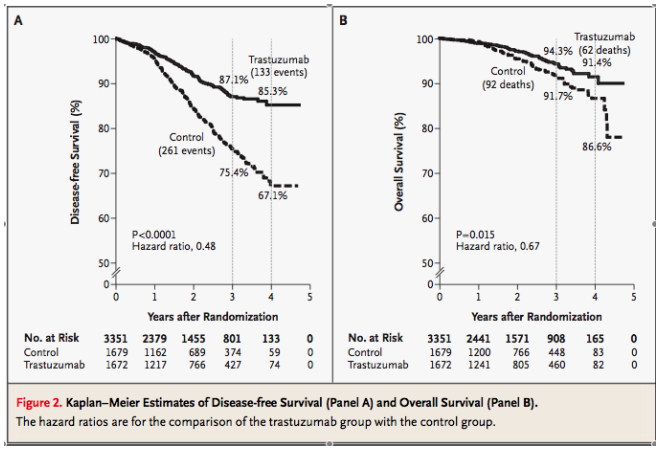


Figure 2. Kaplan–Meier Estimates of Disease-free Survival (Panel A) and Overall Survival (Panel B).
The hazard ratios are for the comparison of the trastuzumab group with the control group.

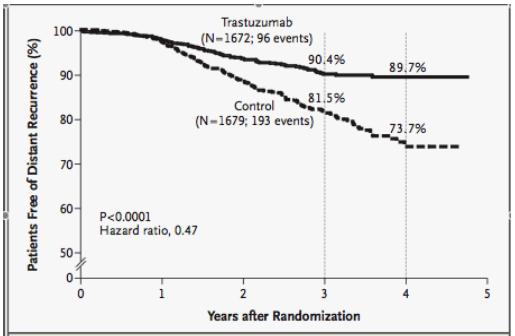
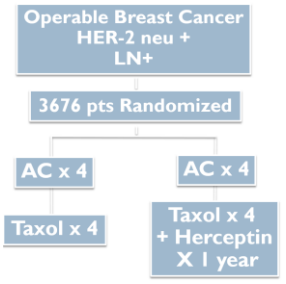


Figure 3. Kaplan–Meier Estimates of Freedom from Distant Recurrence.
The hazard ratios are for the comparison of the trastuzumab group with the control group.



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 of chemo?

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?

Chemotherapy 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 of chemotherapy (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.

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.

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;

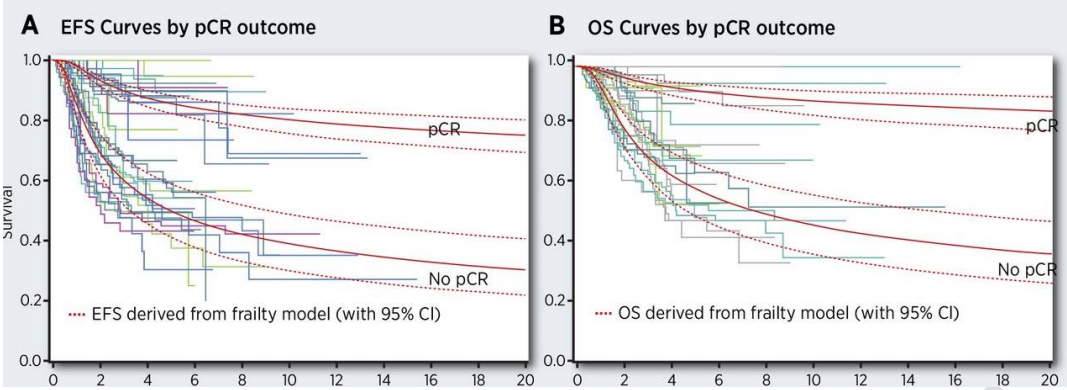
NOTE: Most do RT first then Xeloda.

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.

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**

EBCTCG, Lancet 2015.
←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.

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

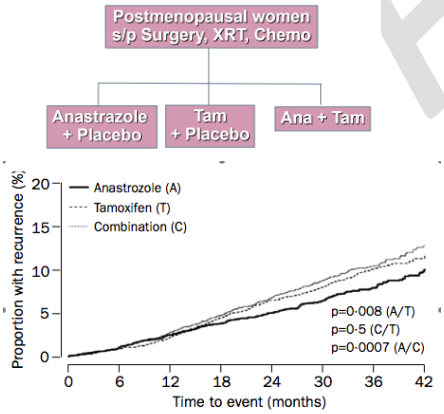


Figure 3: **Probability of recurrence in the intention-to-treat population**

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 anastrazole 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 anastrazole.

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).

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%)

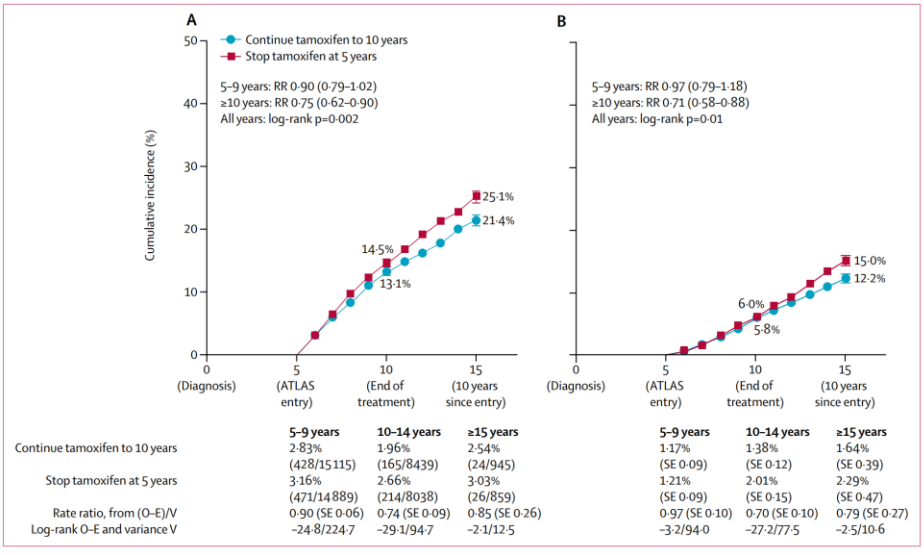


***Figure 3*: Recurrence (A) and breast cancer mortality (B) by treatment allocation for 6846 women with ER-positive disease**
Bars show SE. Recurrence rates are percentage per year (events/patient-years of follow-up). Death rates (overall rate–rate in women without recurrence) are percentage per year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

Canadian Aromatase

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.

Oncotype (TailorX, RxPonder)

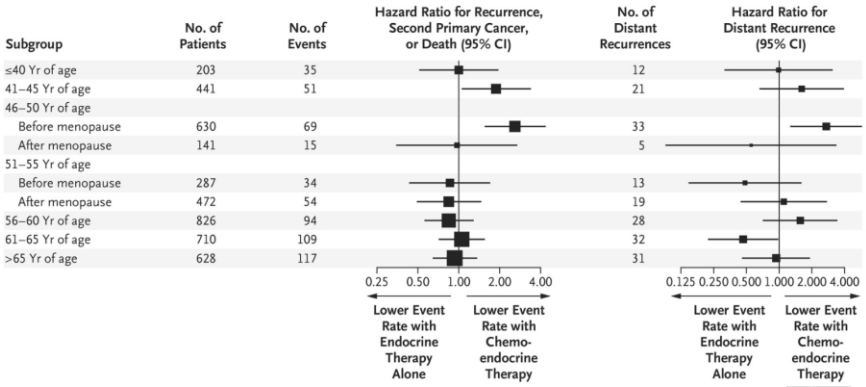
TailorX Non-inferiority Intermediate Score Trial.
←R→ 10273, but only 6711 had mid-range recurrence score. ER+, Her2-, N0, ←R→ midrange recurrence 11-25 score | 1. C+Endo | 2. Endo |.
All ≤ 10 was endo only. All > 25 is C+Endo.

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).

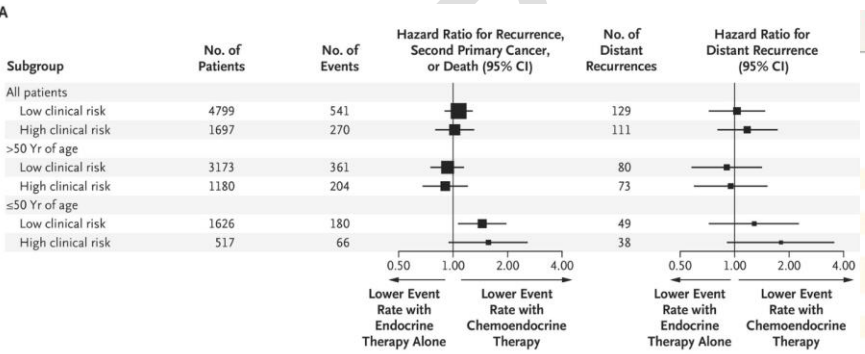
Sparano, NEJM 2018.
Mid Range COHORT: 9-year Invasive DFS 83.3% vs. 84.3% 9-year FF-disease recurrence ~95% 9-year OS ~94%.
The chemotherapy benefit for invasive DFS varied with the combination of recurrence score and age (P=0.004), with some benefit of chemotherapy found in women 50 years of age or 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,



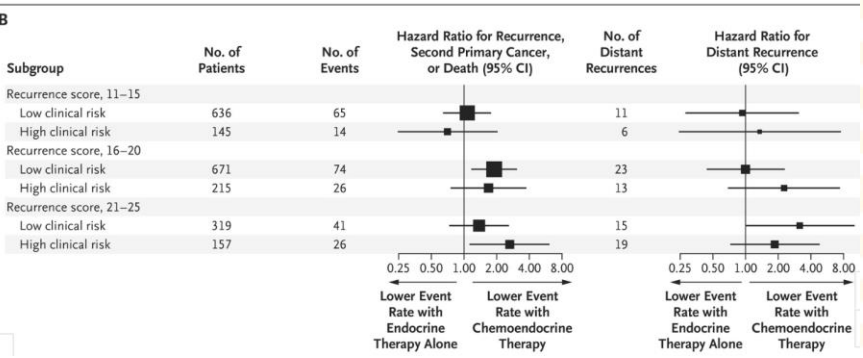


Table 1. Distant or Locoregional Disease Recurrence, Second Primary Cancer, or Death, and Distant Recurrence at 9 Years, According to Use or Nonuse of Adjuvant Chemotherapy, Stratified According to Age, Recurrence Score, and Clinical Risk (Intention-to-Treat Population).*

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	

RXPONDER SWOG S1007 **Aka LN+ ORS ≤ 25.**

←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.

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.

Forest Plot – everyone benefited from chemo!

Prospective LN+ ORS?

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

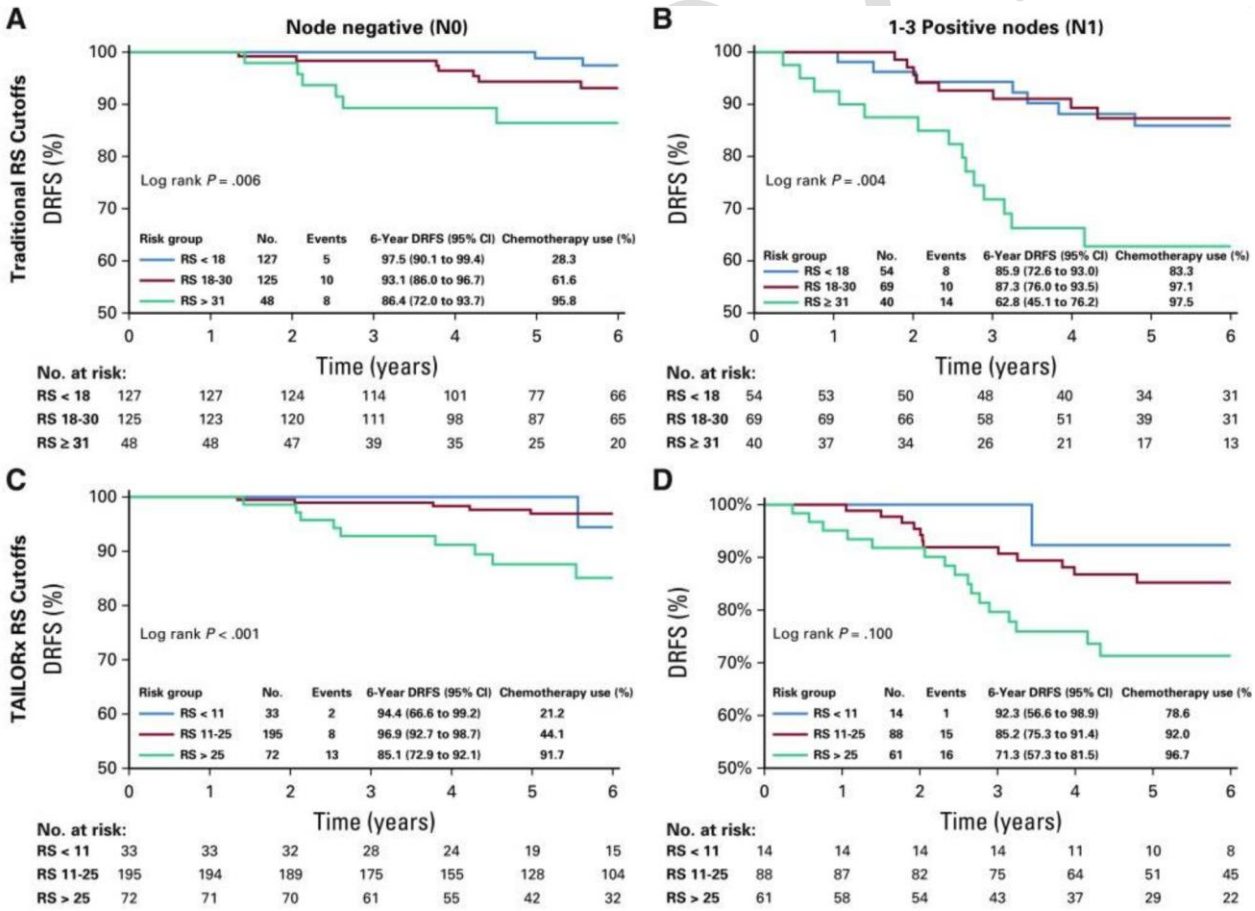
300 of 509 patients (59%) had N0 breast cancer, of whom 195 (65%) had an RS of 11-25 and fewer than half (86 of 195; 44%) received chemotherapy.

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.



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) Thank goodness too, the above was way too complicated.

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

- **Upfront Surgery (T2-3 and N0-1)**
  - Adjuvant Chemo decision (aggressive histologies: Ductal, Lobular, mixed, micropapillary)
    - ER/PR +, Her2 + → pT1a N0/mic → ± Endocrine ± Chemo w/ **Trastuzumab (Herceptin)**
      pT1b N0/mic → **Endocrine** or **Chemo w/ Trastuzumab** + endocrine.
      ≥ pT1c or N+ → **Chemo w/ Trastuzumab** + **Endocrine**.
    - ER/PR +, Her2 - → pT1a N0 → ± Endocrine
      → ≥ pT1b N0 → **21 gene RT-PCR.**
      < 26 low = Endo. 26-30 int = Endo or C→E. ≥31 high = **C→E both**.
      → pNmic or 1-3 N+ → **Chemo + endocrine (Cat 1)** or endocrine. Can consider RT-PCR
      → ≥ 4 N+ → **Chemo + endocrine (Cat 1)**
    - ER/PR -, Her2 + → Same as triple positive, just without endocrine therapy
    - ER/PR -, Her2 - → Same as triple positive, just without endocrine therapy or Her2 directed therapy

  - **Lumpectomy** or **Mastectomy** with Surgical Axillary Staging *
    → ≥ 4 pLN+ → RT + RNI
    → 1-3 pLN+ → RT + **Strongly 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.

- **Pre-operative Systemic Therapy (T4 and ≥ N2)**
  - **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.**

* 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).

Neoadjuvant Chemotherapy (NAC).

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.

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.

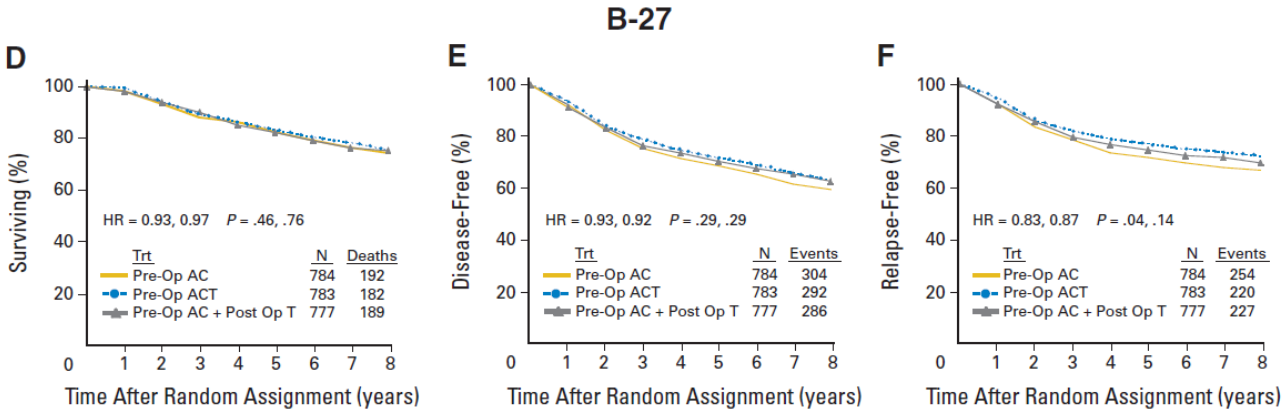
Previous French European trials (Mauriac, Ann Oncol 1991; Scholl Eur J Cancer 1994) that compared neoadjuvant vs adjuvant chemo showed OS advantage with neoadjuvant. However, these trials had imbalances in systemic and local therapy. First, all preoperative chemo patient received chemo. Only LN+ patients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

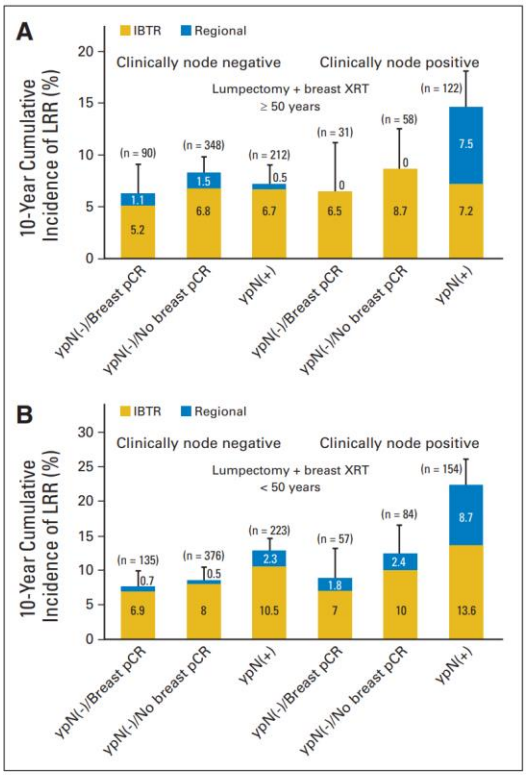


Fig 2. Ten-year cumulative incidence of locoregional recurrence (LRR) in patients (A) age ≥ 50 years treated with lumpectomy plus breast external radiotherapy (XRT) and (B) younger than age 50 years treated with lumpectomy plus breast XRT. IBTR, ipsilateral breast tumor recurrence; pCR, pathologic complete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

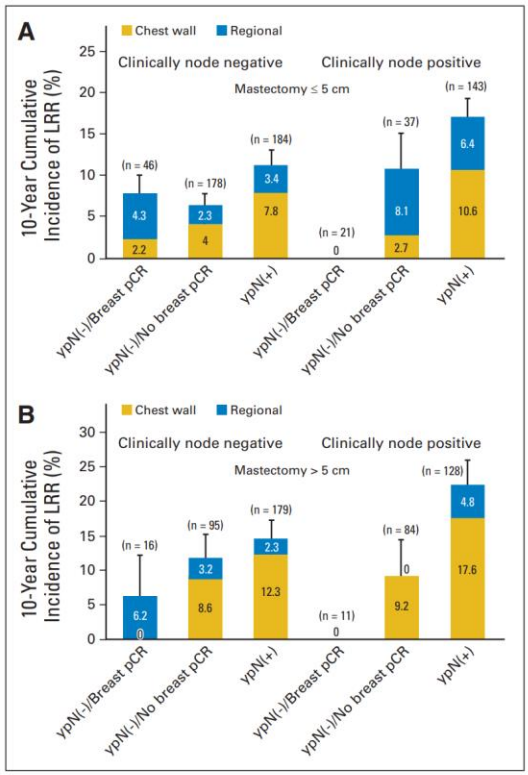


Fig 3. Ten-year cumulative incidence of locoregional recurrence (LRR) in patients with (A) ≤ 5-cm tumors treated with mastectomy and (B) > 5-cm tumors treated with mastectomy. pCR, pathologic complete response [after neoadjuvant chemotherapy]; ypN, pathologic nodal status [after neoadjuvant chemotherapy].

Nodal evaluation in NAC

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

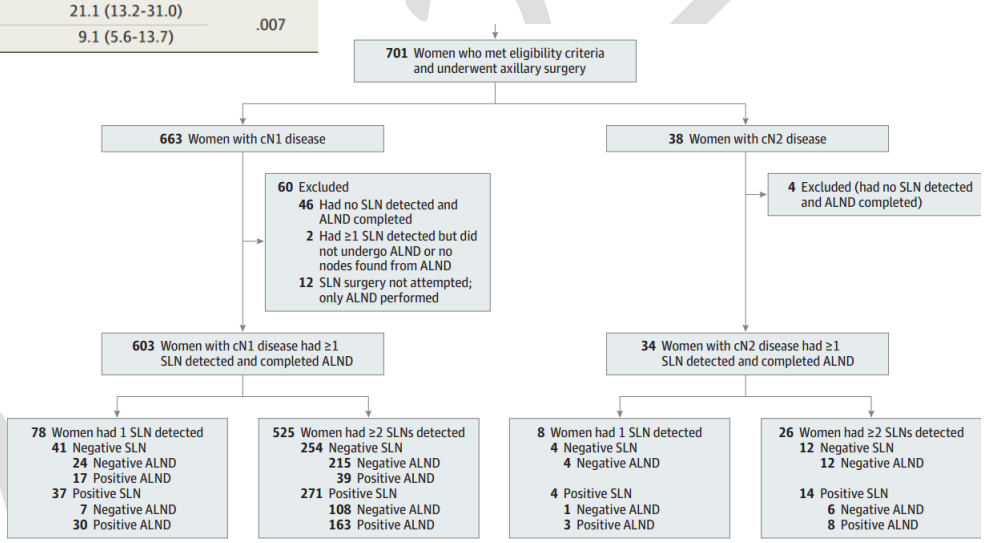
	False-Negative SLN Findings, No. (Total)	FNR (95% CI), %	Fisher Exact Test, *P* Value
Clinical T category prior to chemotherapy			
Tis, T0, T1, or T2	32 (225)	14.2 (9.9-19.5)	.18
T3 or T4	7 (85)	8.2 (3.4-16.2)	
Chemotherapy duration, mo			
≤4.0	20 (201)	10.0 (6.2-15.0)	.07
≥4.1	19 (109)	17.4 (10.8-25.9)	
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.



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 |.

1^{o} 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.

Other Studies: pCR + RCB

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%

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.

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.

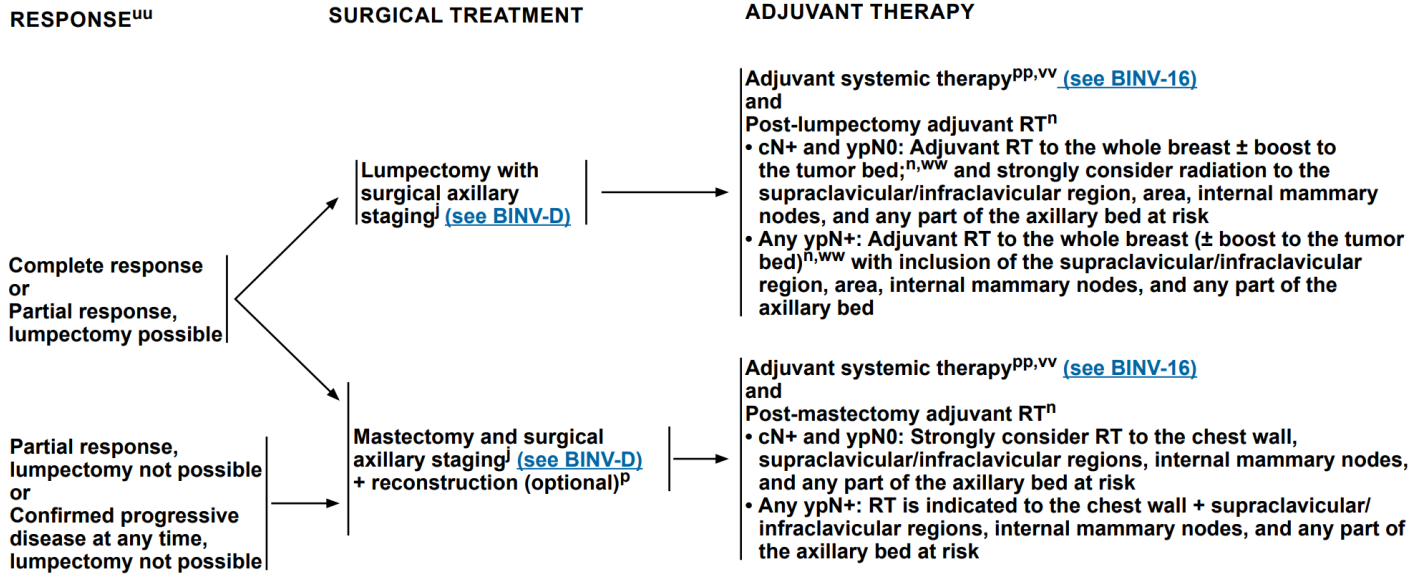
Postmastectomy Radiation Therapy (PMRT)

Indications for PMRT

- 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	Highly Consider - RT to chest wall + supraclav +/- IM nodes	
≥4 Axillary + LNs	RT to chest wall + supraclav +/- IM nodes	

OPERABLE DISEASE:
SURGICAL TREATMENT AND ADJUVANT THERAPY AFTER PREOPERATIVE SYSTEMIC TREATMENT



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		0.004	ER		0.02	Pec Fascia Involvement		0.007
≤ 2 cm	9%		+	8%		+	29%	
2-5 cm	9%							
> 5 cm	19%		-	14%		-	10%	
N		0.006	Necrosis		0.002			
1-3	7%		+	17%				
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).[48] 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.

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)[49] 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.

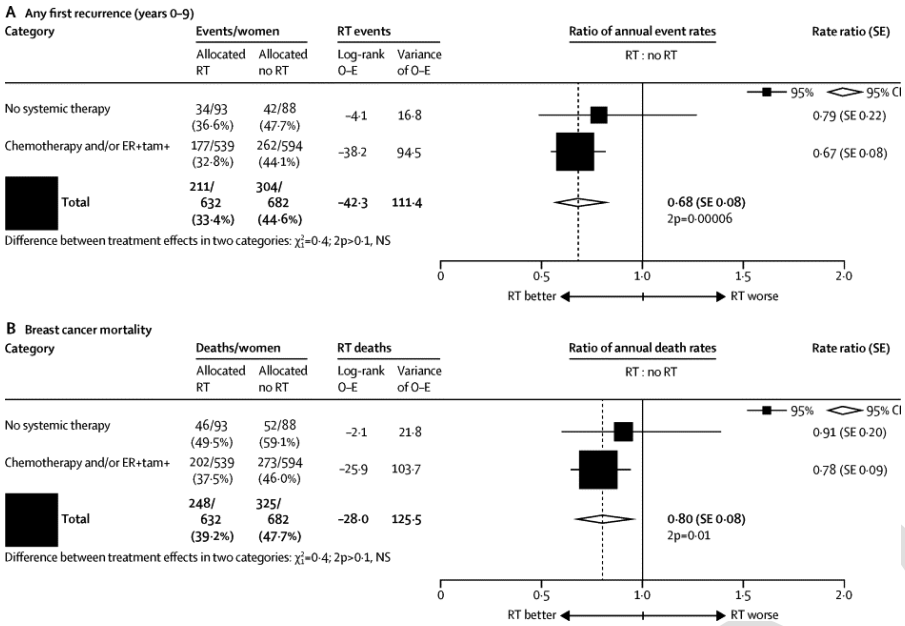
Conclusion: PMRT provides significant clinical benefit for Stage III patients with pCR after neoadjuvant chemo and mastectomy

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.

[48] http://www.ncbi.nlm.nih.gov/pubmed/18996609?dopt=Abstract
[49] http://www.ncbi.nlm.nih.gov/pubmed/17418973?dopt=Abstract



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.

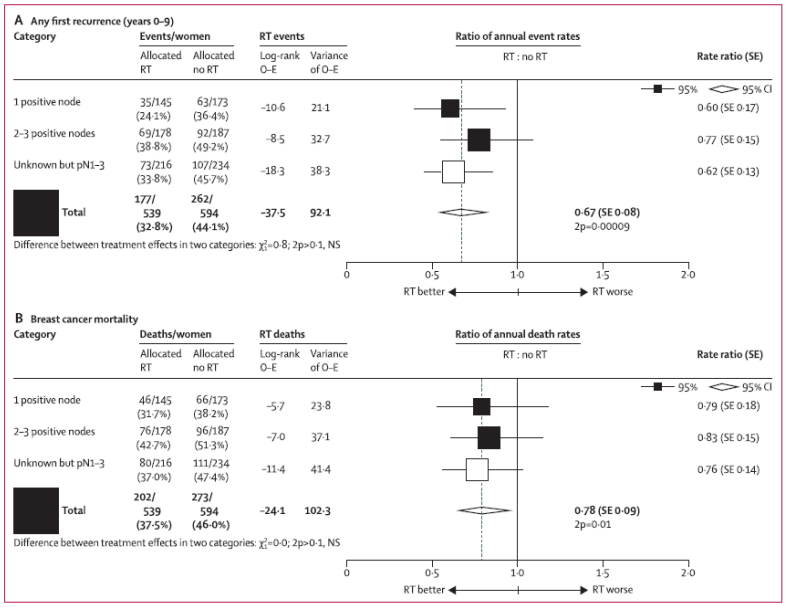


Figure 6: **Effect of radiotherapy (RT) after mastectomy and axillary dissection on overall recurrence during years 0–9 and on breast cancer mortality for the entire follow-up in 1133 women with one to three pathologically positive nodes (pN1–3) in trials in which systemic therapy was given to both randomised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

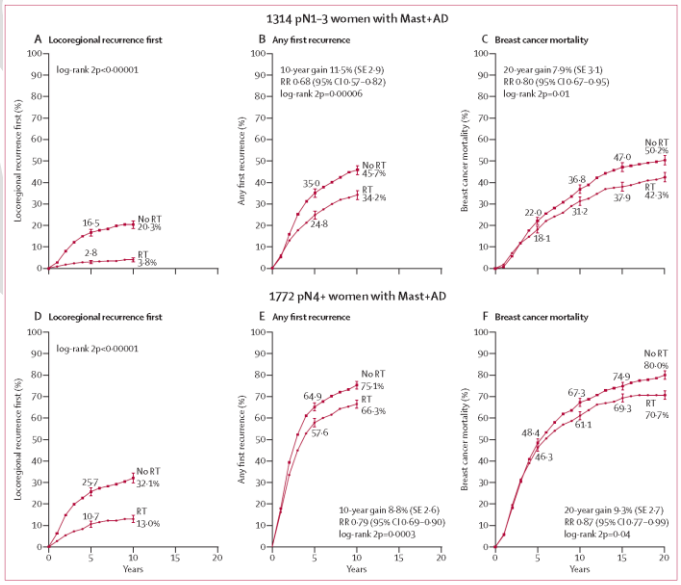


Figure 3: **Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional and overall recurrence and on 20-year risk of breast cancer mortality in 1314 women with one to three pathologically positive nodes (pN1–3) and in 1772 women with four or more pathologically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

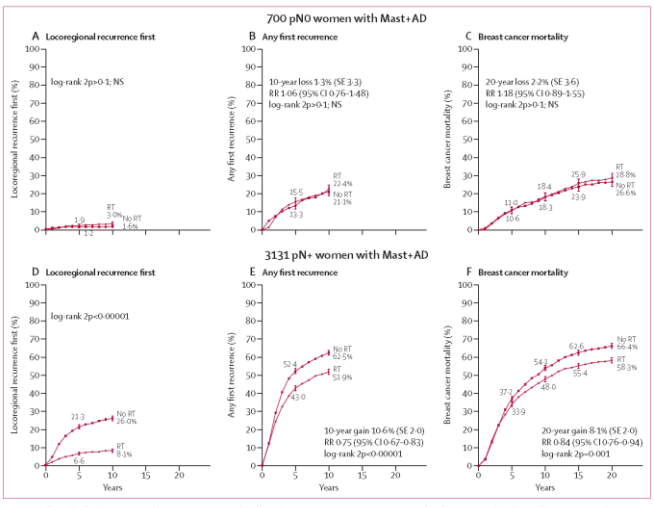


Figure 2: **Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional and overall recurrence and on 20-year risk of breast cancer mortality in 700 women with pathologically node-negative (pN0) disease and in 3131 women with pathologically node-positive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

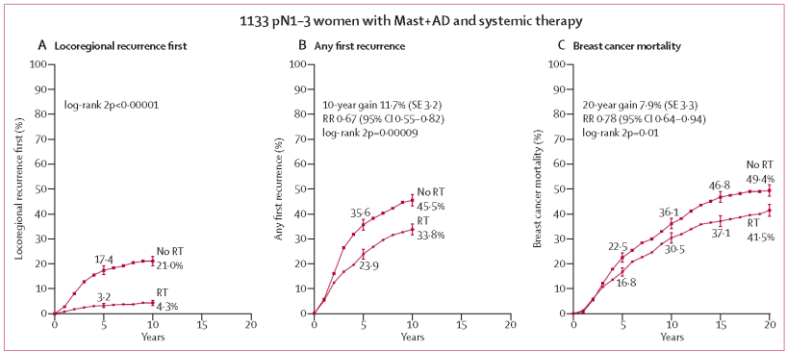


Figure 5: **Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional and overall recurrence and on 20-year risk of breast cancer mortality in 1133 women with one to three pathologically positive nodes (pN1–3) in trials in which systemic therapy was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

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%.

University of Florence (Livi 2007).[50] 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).[51] 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).[52] 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).[53] 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.

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 regional lymphatics 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. We have demonstrated a low complication rate while achieving excellent local control. Toxicity was better than anticipated based on previously published series of PMRT toxicities. Although our fractionation was novel, the radiobiological equivalent dose is similar to other hypofractionation schedules. This trial was the basis for the creation of Alliance Axxxxx (xxxxx), 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.

[50] http://www.ncbi.nlm.nih.gov/pubmed/17368813?dopt=Abstract
[51] http://www.ncbi.nlm.nih.gov/pubmed/15452182?dopt=Abstract
[52] http://www.ncbi.nlm.nih.gov/pubmed/11395242?dopt=Abstract
[53] http://www.ncbi.nlm.nih.gov/pubmed/10920129?dopt=Abstract

RT-CHARM
PENDING.

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.

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.

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.

Triple negative Keynote 522
602 patients with untreated Stage II or III TNBCa | 1. NAC 4c x pembro + paclitaxel/carboplatin | 2. Placebo + paclitaxel/carboplatin | .
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.
The primary end points were a pathological complete response at the time of definitive surgery and event-free survival in the intention-to-treat population.

Schmid, NEJM 2020.
1^{st} interim analysis 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.

Inflammatory Breast Cancer

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

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%.

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.

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	

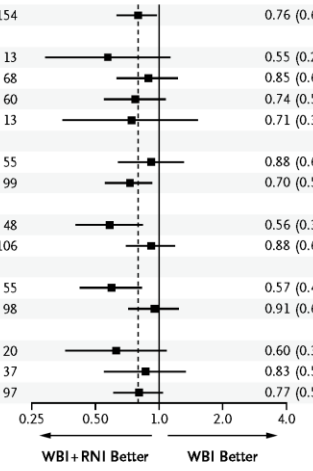


Figure 2. Disease-free Survival at 10 Years, According to Subgroup.

Intergroup / NCIC-CTG MA.20 - Whole breast RT +/- regional nodal irradiation
←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.

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.
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.

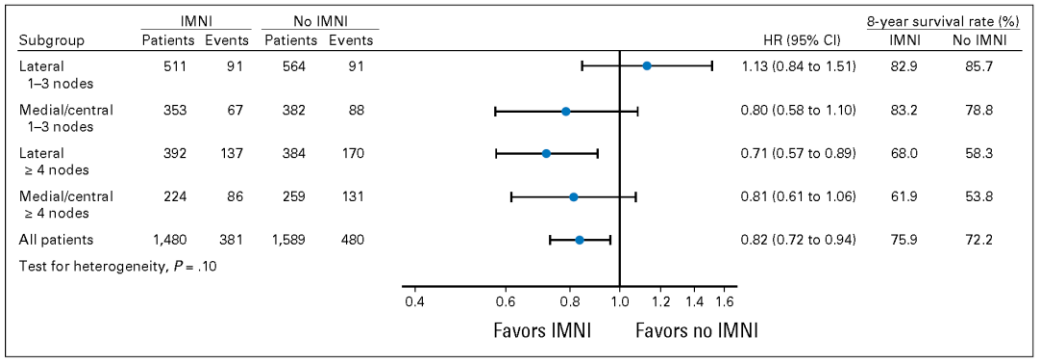
Matzinger, O Acta Oncol Toxicity; 2010
Toxicity: Any lung toxicity standard RT 1.3% vs IM-MS RT 4.3% (SS); cardiac toxicity 0.3% vs 0.4% (NS).
No difference in performance status
Outcome: Well tolerated at 3 years

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.

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).

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.

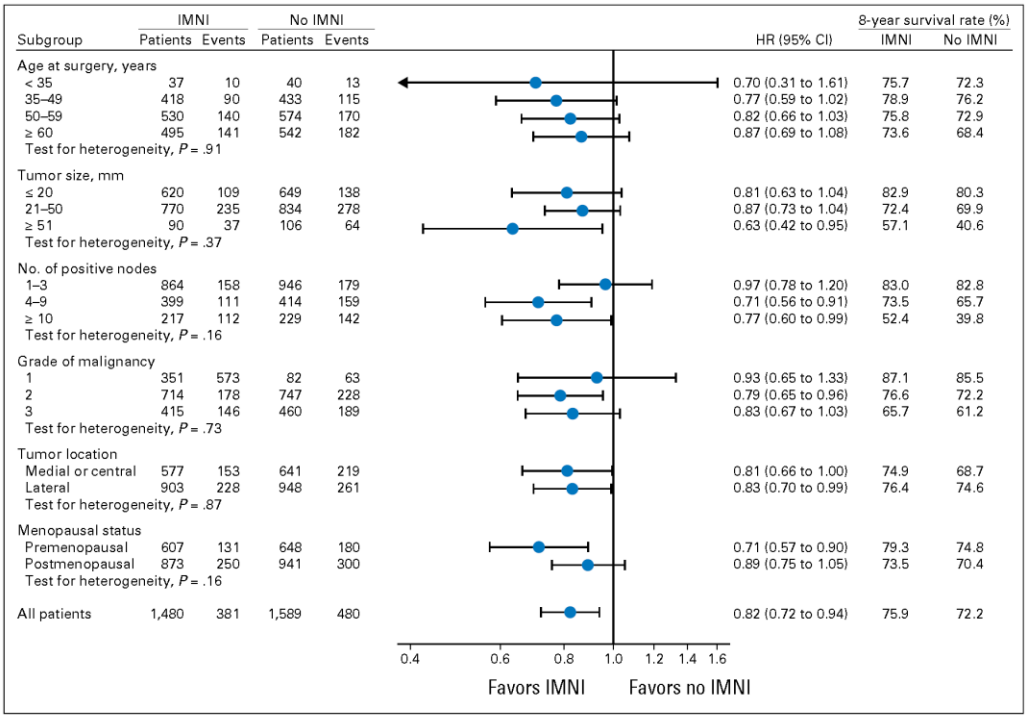


Fig 3. Overall survival rates and corresponding hazard ratios (HR) with versus without internal mammary node irradiation (IMNI) within subgroups in the multivariate Cox proportional hazards model. Information on covariates was complete in 3,069 patients.

IM Metaanalysis

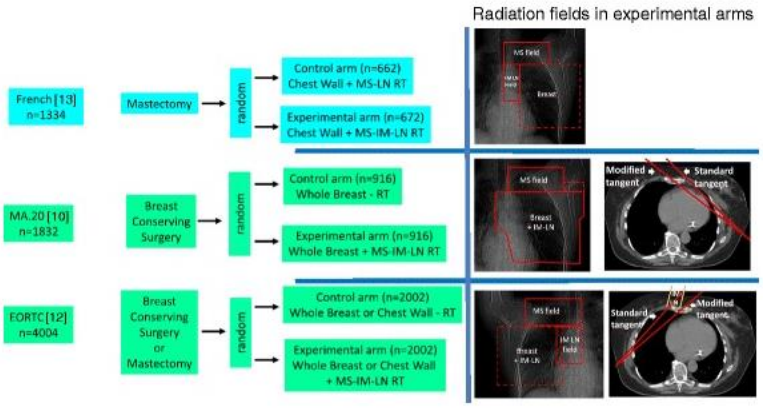
←M→ MA.20 (n = 1832), the EORTC22922-10925 (EORTC) (n = 4004) trial and the French trial (n = 1334).

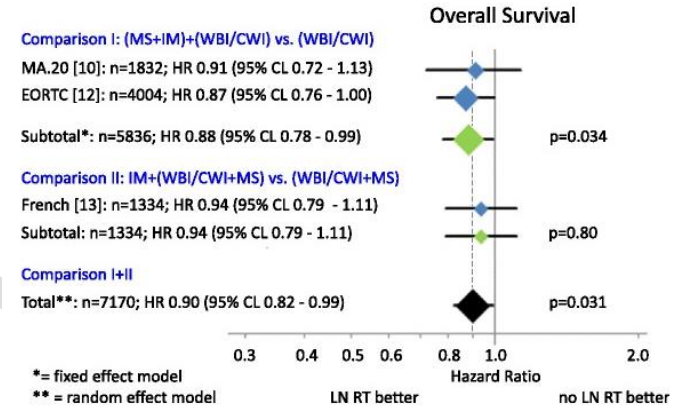
Major eligibility criteria were positive i) axillary LN (all trials), ii) LN negative disease with high risk for recurrence (MA.20), and iii) medial/central tumor location (French, EORTC). The MA.20 and the EORTC trial analyzed the effect of additional regional RT to the internal mammary (IM) LN and 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.

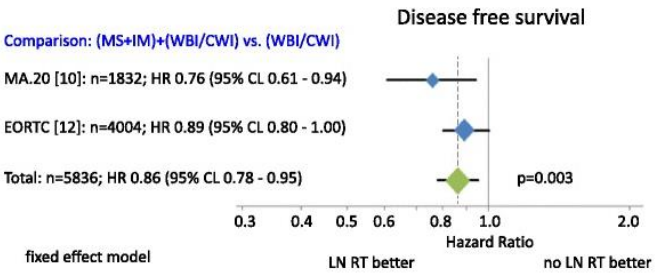
Budach, IJROBP 2015.

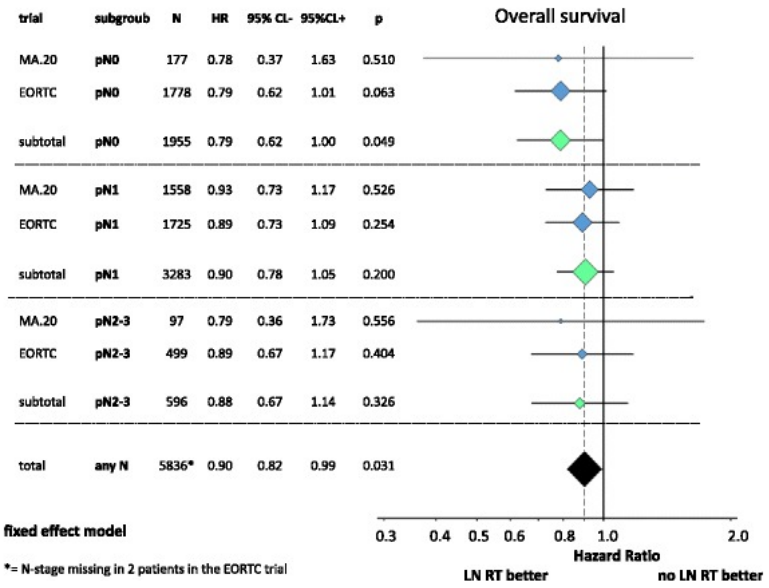
Regional RT of MS-LN and IM-LN (MA.20 and EORTC) resulted in a significant improvement of OS [Hazard Ratio (HR) 0.88 (95 % CL 0.78 - 0.99)]. Adding results of the French trial and using a random effects model to respect the different design of the French trial, the effect on OS of regional RT remained 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.









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.

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.4

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."

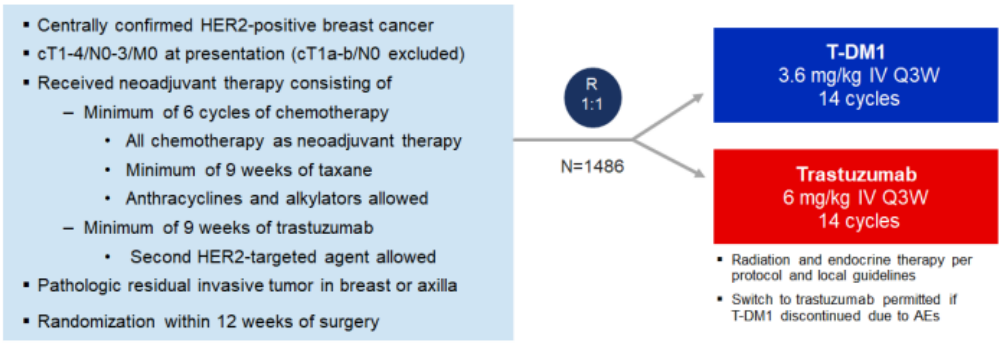
KATHERINE T-DM1 Trials. **NAC → Surgery →** Kadcyla for residual disease **otherwise if pCR Herceptin for 1 year.**

←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.



Stratification factors:
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

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.

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

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

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.

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.

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.
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.

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 |. 1^{O} 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.

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

Local Therapy

Consolidative Use of RT to Block Oligoprogression (CURB) Trial Tsai, ASTRO 2021
←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.

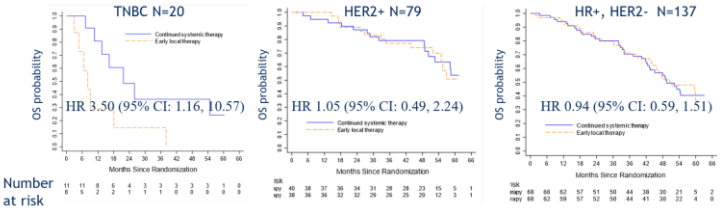
Tata Memorial
Intro: The role of locoregional treatment in women with metastatic breast cancer at first presentation is unclear.
←R→ 350 treatment naïve patients (≤65 yo + life expectancy ≥ 1 yr) + de-novo metastatic breast cancer from Tata Memorial Centre, Mumbai, India.
| 1. locoregional tx to primary 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.

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 |.
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.

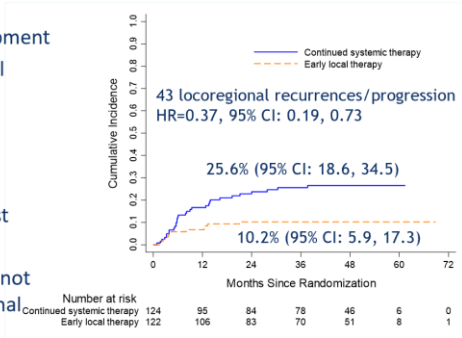
Definitions

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



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

CLEOPATRA TPH Study.

SERD - Fulvestrant

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]	

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.

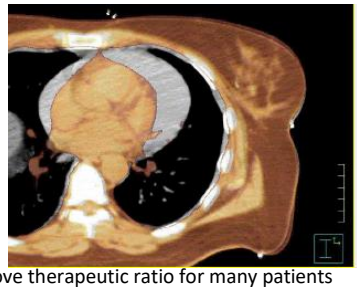
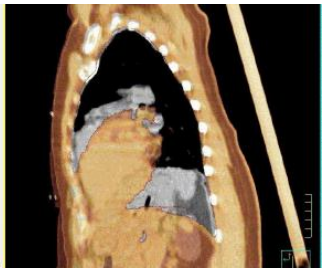
MONALEESA-2 Ribociclib + Letrozole vs. letrozole alone
Also PFS benefit
HR-positive, HER2-negative recurrent or metastatic breast cancer who **had not received previous systemic therapy** for advanced disease.

MONALEESA-3 Ribociclib vs. placebo in **ER+ Her2-**.
←R→ 484 patients phase 3 Locally advanced | 1. Ribo + Fulvestrant | 2. Placebo + Fulvestrant | as 1st line or 2nd 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.

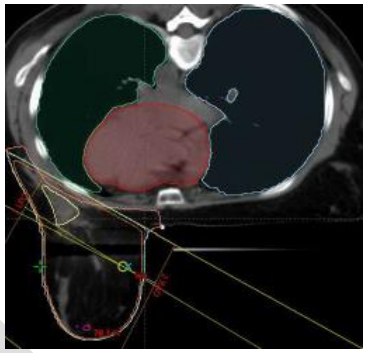
To followup: MONALEESA-7 Interim

RT Fields + Nodal Guidelines:

Common Terms Used:

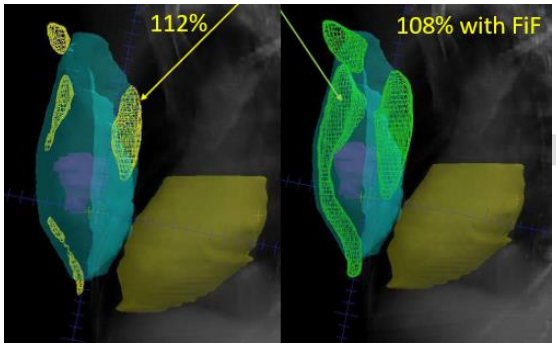
- Supine Breast Treatment
    - Breath hold
        - Displaces heart inferior and posterior to improve therapeutic ratio for many patients
        - Requires verification of position

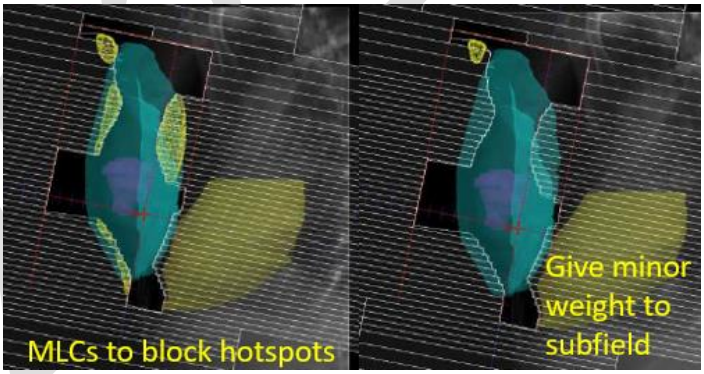


- Prone Breast Treatment
    - Displaces breast tissue anteriorly and can remove tumor bed or breast tissue away from chest wall
    - Great for pendulous breasts and tumor beds more anterior and in center of breast tissue
    - Improves homogeneity for the whole breast (decreases separation)
    - Very 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 SURGEON ALREADDY DID A GREAT SURGERY, THEN YOU DON'T HAVE TO EXTEND SCV FIELD PAST THE MEDIAL BORDER OF HUMEROUS.

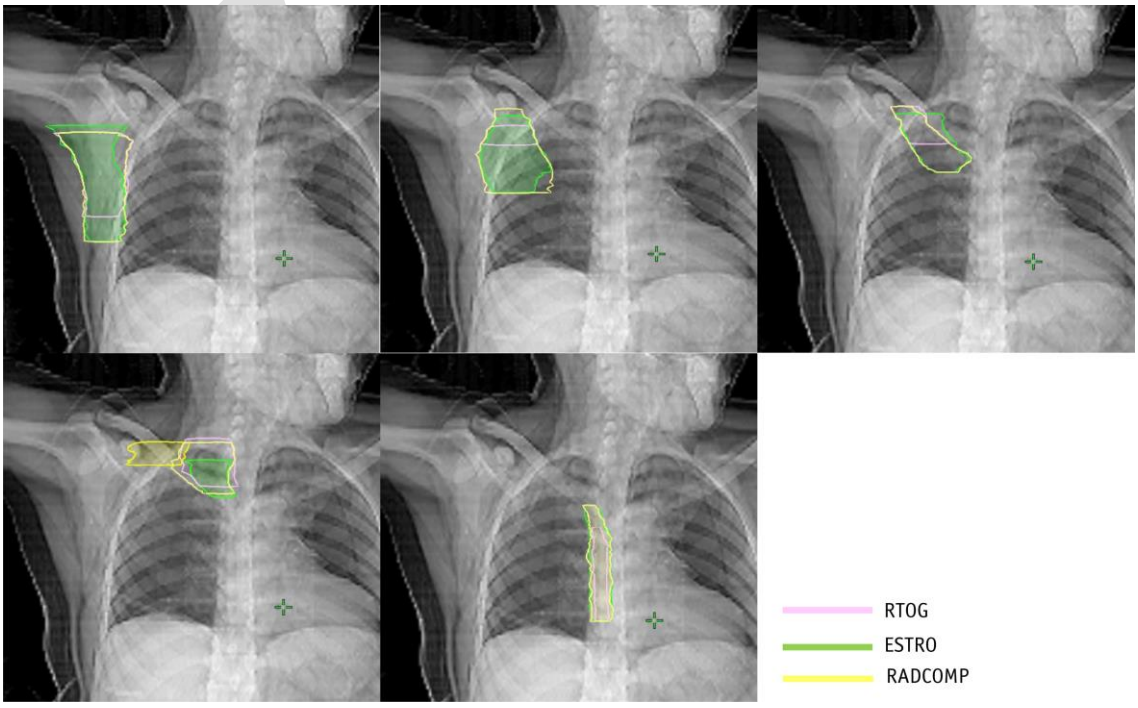
2. Posterior Axillary Boost (PAB) Field
    - Used in an inadequately dissected axilla, >2.5cm LNs, fixed nodes, ECE, ≥4 axillary LNs or for underdosed axilla
    - PAB field supplements midline dose, treating posterior axillary LNs that may have otherwise been underdosed
    - Borders
        - Superior/Medial -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.

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.



Accelerated Partial Breast Irradiation (APBI)

Consensus

- **Although RT is great,**
  - **Standard radiation is inconvenient and expensive**
  - **Not all patients will receive for these reasonsand "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 and some regimens are less expensive; patients at a distance need only a short hotel stay to receive treatment**

- **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

- Techniques include intraoperative electron or X-rays, interstitial brachytherapy (HDR more common than LDR), balloon brachy, or 3DCRT.

PRINCIPLES OF RADIATION THERAPY

Accelerated Partial Breast Irradiation (APBI)

- **Studies of APBI suggest that rates of local control in selected low-risk patients with early-stage breast cancer may be comparable to those treated with standard WBRT. However, compared to standard WBRT, several studies document an inferior cosmetic outcome with external beam delivery methods of APBI. Follow-up is limited and studies are ongoing.**
  - **Patients are encouraged to participate in clinical trials.**
  - **The NCCN Panel accepts the updated 2016 version of the ASTRO APBI guideline consensus statement, which now defines patients age ≥50 years to be considered "suitable" for APBI if:**
    - **Invasive ductal carcinoma measuring ≤2 cm (pT1 disease) with negative margin widths of ≥2 mm, no LVI, ER-positive, and BRCA negative; 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)[a]**	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 breast-conserving surgery 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

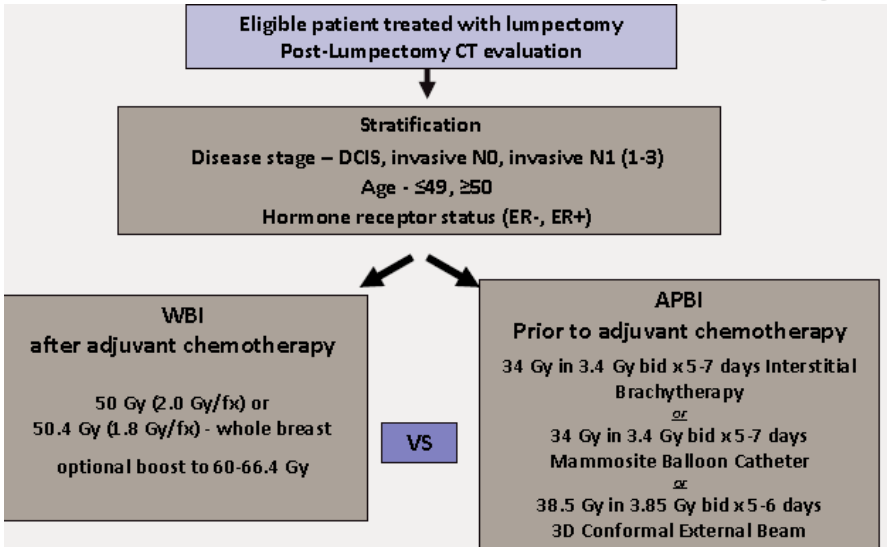
DCIS* Low risk RTOG 98-04
Mammogram detected, Size < 2.5 cm, margins 3mm.

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**	**pT-12 (< 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.**

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.



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 difference of less than 1% in the 10-year cumulative incidence of IBTR, APBI might be an acceptable alternative for some women.

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.

NOTE: 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.

Other Trials: 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%.

- **Situational APBI Studies**.

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

TARGIT-A (Vaidya 2014).[54] 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.

Hungary (Polgár 2007).[55] 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).[56] 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).[57] 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.

[54] http://www.ncbi.nlm.nih.gov/pubmed/24224997
[55] http://www.ncbi.nlm.nih.gov/pubmed/17531400?dopt=Abstract
[56] http://www.ncbi.nlm.nih.gov/pubmed/20646847?dopt=Abstract
[57] 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 55 patients eligibility = in-breast recurrence occurring >1 year after whole-breast irradiation, <3 cm, unifocal, and resected w/ neg margins. 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. 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.

Arthur, IJROBP 2017
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. Systemic therapy was delivered in 51%.
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 2019

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.

"At Duke we have traditionally treated patients with gross disease after breast surgery with concurrent radiation and capecitabine. I personally have had several patients with recurrent unresectable chest wall nodules after mastectomy that have had a complete response and retain local control 5-7 years later. I have not increased dose beyond 60 Gy (which includes the boost) but rely on capecitabine for radiosensitization. Only published data that I am aware of is a MDACC trial published last year by Wendy Woodward using concurrent pre-operative RT/capecitabine."

Toxicity

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.

Mepitel

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.

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.

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.

"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 <3 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!

Stats to be left behind | Carlson, JACC CardioOncol 2021

Top Line: We can talk forever about the relative and absolute benefits of adjuvant radiation for breast cancer across various scenarios, but it seems less often we weigh individualized risks.
The Study: The WECARE study is here to show we care about risks, too. This is really an epidemiologic study at heart, pun intended. In its first phase, conducted from 2001-2012, data was collected on women who received breast radiation at an age <55 years between 1985-2008. In its second phase, conducted 2013-2015, these women were contacted again to collect nonfatal cardiac events. The reported analysis is on 972 women without preexisting cardiac disease who completed both phases of the study. The crux is not a comparison to women who did not receive radiation, but rather a comparison of those who received radiation to the right versus left breast. Indeed, at a median follow-up of 14 years, the cumulative incidence of coronary artery disease was 5.8% after right breast treatment versus 10.5% after left breast treatment. The takeaway in 2021? Well, probably not that our women with left-sided breast radiation are at higher risk with modern techniques using deep inspiratory breath hold, especially in light of more modern data, further supported by no difference in risk per laterality in EORTC 22922.
TBL: Techniques such as DIBH and IMRT to lower cardiac dose for left-sided breast cancer closer to what has been historically achieved with right-sided breast cancer should have a clinically meaningful impact on long term cardiac disease risk.

V5 < 5% Data

OTHER

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.

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.

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.
What is the cost 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.

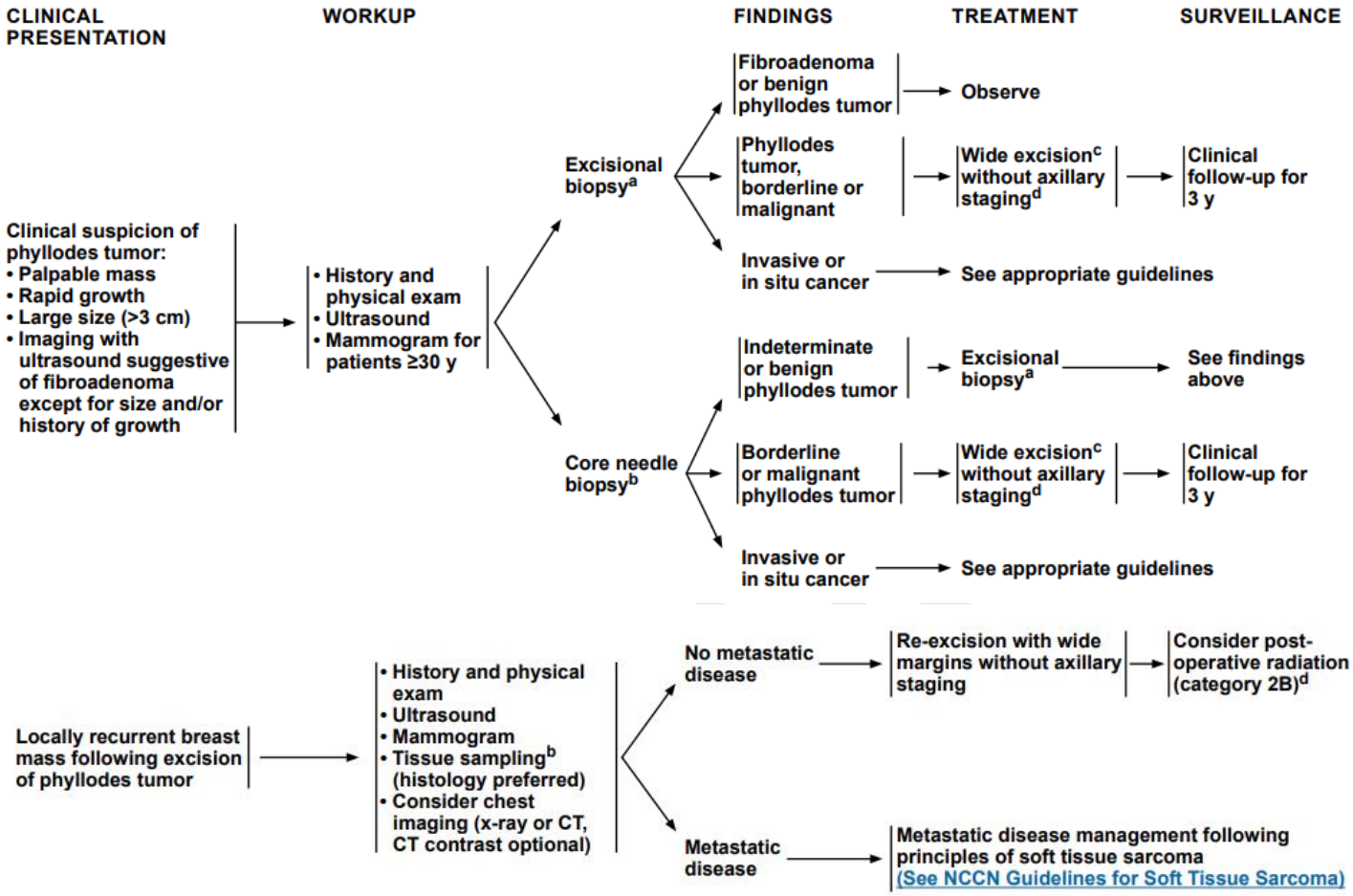
Antioxidant Use Trial Ambrosone, JCO 2020
Patients who received chemotherapy (ACT) were evaluated for use of supplements at registration and during treatment.
Use of ANY antioxidant supplements (ACE, carotenoids, coenzyme Q10) before and during Tx associated with ↑ HR recurrence (HR =1.41; *P* = .06) 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.

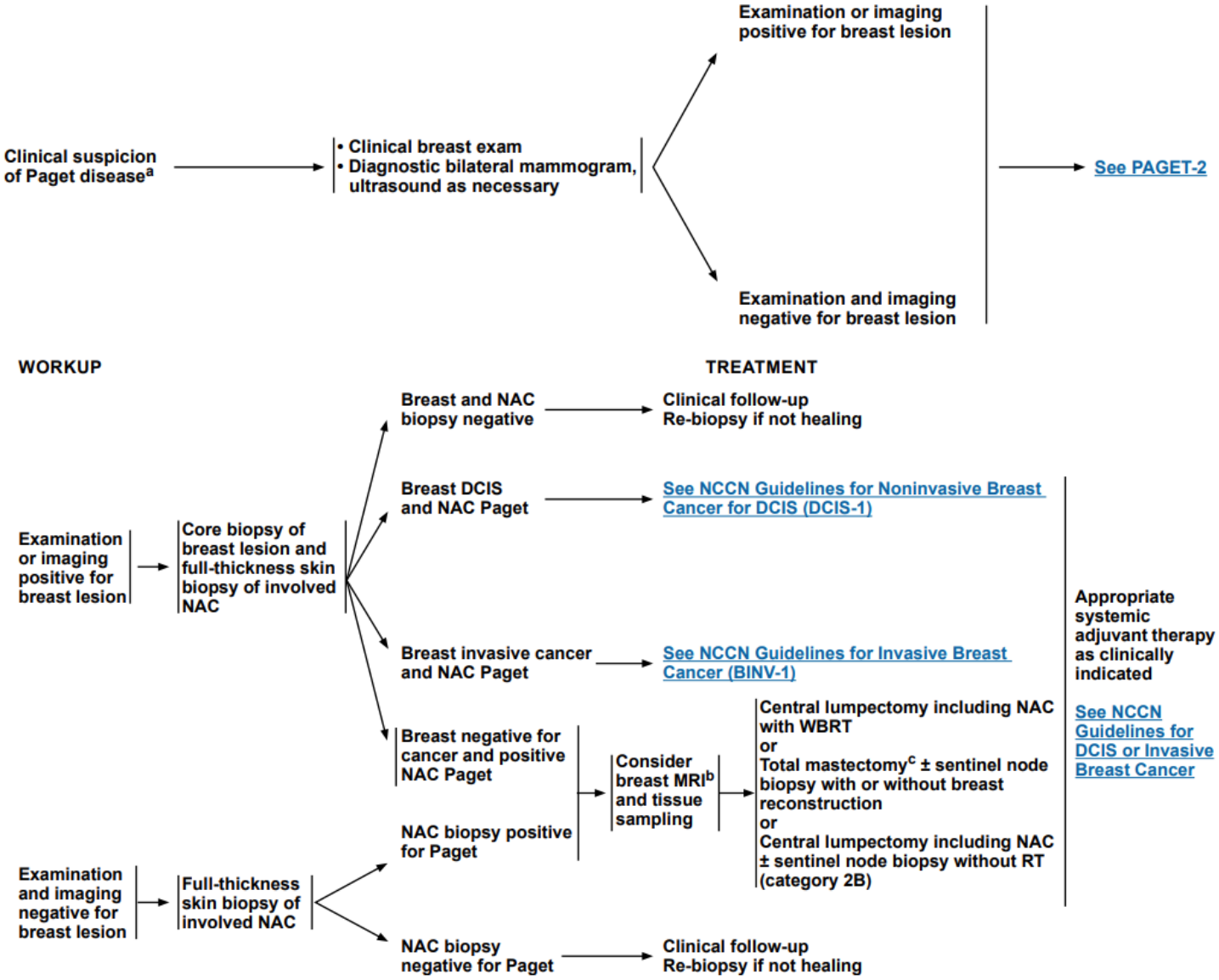
Observational Study of Chemical Hair Dyes Eberle, Int J Cancer 2019
Large observational study ? Possible chemical hair dyes or straighteners ↑↑ development of novo breast cancer.

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


CLINICAL PRESENTATION
WORKUP
FINDINGS
TREATMENT
SURVEILLANCE
Clinical suspicion of phyllodes tumor:
• Palpable mass
• Rapid growth
• Large size (>3 cm)
• Imaging with ultrasound suggestive of fibroadenoma except for size and/or history of growth
• History and physical exam
• Ultrasound
• Mammogram for patients ≥30 y
Excisional biopsy[a]
Core needle biopsy[b]
Fibroadenoma or benign phyllodes tumor
Observe
Phyllodes tumor, borderline or malignant
Wide excision[c] without axillary staging[d]
Clinical follow-up for 3 y
Invasive or in situ cancer
See appropriate guidelines
Indeterminate or benign phyllodes tumor
Excisional biopsy[a]
See findings above
Borderline or malignant phyllodes tumor
Wide excision[c] without axillary staging[d]
Clinical follow-up for 3 y
Invasive or in situ cancer
See appropriate guidelines
Locally recurrent breast mass following excision of phyllodes tumor
• History and physical exam
• Ultrasound
• Mammogram
• Tissue sampling[b] (histology preferred)
• Consider chest imaging (x-ray or CT, CT contrast optional)
No metastatic disease
Re-excision with wide margins without axillary staging
Consider post-operative radiation (category 2B)[d]
Metastatic disease
Metastatic disease management following principles of soft tissue sarcoma
(See NCCN Guidelines for Soft Tissue Sarcoma)

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] ± sentinel node biopsy with or without breast reconstruction
or
Central lumpectomy including NAC ± sentinel node biopsy 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