

Early Stage Breast Cancer: Epidemiology and Pathology

Case

57 year old female with history of IBS and GERD

- 5/12/15: Bilateral screening mammo – 2.6 cm irregular density Right breast.
- 5/26/15: Diagnostic mammo + U/S with a 1.6 cm asymmetric density with spiculated margins. U/S guided bx demonstrated Invasive ductal and lobular carcinoma, mBR grade 1, ER+, PR+, Her2-
- 6/26/15: Right breast lumpectomy and SLNB. Pathology revealed a 2.5 cm mixed ductal and lobular, grade 2, DCIS +, no LVI, closest margin of invasive disease and DCIS >5.0 mm. 2 negative sentinel nodes. Stage IIA, pT2N0M0

She agreed to anastrozole endocrine therapy. She had an Oncotype DX score of 11 – no chemo indicated.

She was referred to radiation oncology for consideration of adjuvant radiotherapy.

Breast Cancer - Epidemiology

SEER Data

Common Types of Cancer	Estimated New Cases 2014	Estimated Deaths 2014
1. Prostate Cancer	233,000	29,480
2. Breast Cancer (Female)	232,670	40,000
3. Lung and Bronchus Cancer	224,210	159,260
4. Colon and Rectum Cancer	136,830	50,310
5. Melanoma of the Skin	76,100	9,710
6. Bladder Cancer	74,690	15,580
7. Non-Hodgkin Lymphoma	70,800	18,990
8. Kidney and Renal Pelvis Cancer	63,920	13,860
9. Thyroid Cancer	62,980	1,890
10. Endometrial Cancer	52,630	8,590

Breast cancer represents 14.0% of all new cancer cases in the U.S.

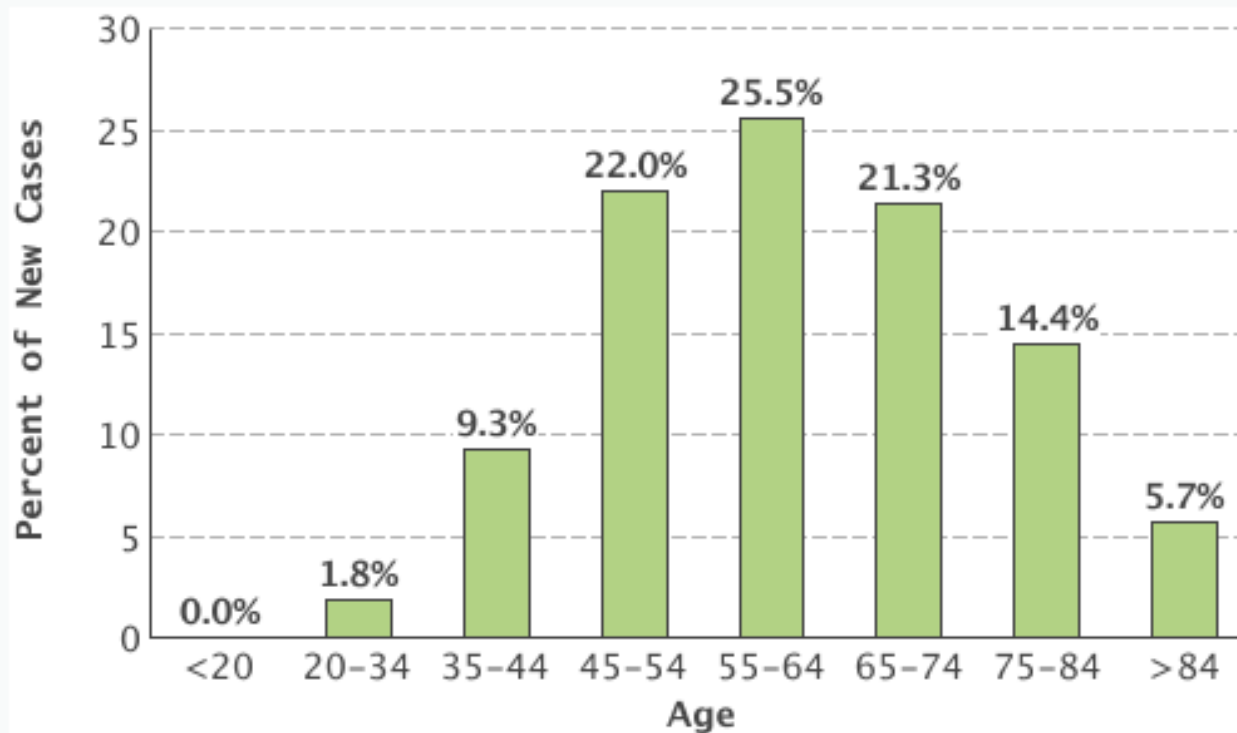


14.0%

Breast Cancer - Epidemiology

SEER Data

Percent of New Cases by Age Group: Breast Cancer



Breast cancer is most frequently diagnosed among women aged 55-64.

Median Age At Diagnosis

61



Breast Cancer: Risk factors

Risk and protective factors for developing breast cancer

	Risk group		
	Low risk	High risk	Relative risk
Risk factors			
Deleterious BRCA1/BRCA2 genes	Negative	Positive	3.0 to 7.0
Mother or sister with breast cancer	No	Yes	2.6
Age	30 to 34	70 to 74	18.0
Age at menarche	>14	<12	1.5
Age at first birth	<20	>30	1.9 to 3.5
Age at menopause	<45	>55	2.0
Use of contraceptive pills	Never	Past/current use	1.07 to 1.2
HRT (estrogen + progestin)	Never	Current	1.2
Alcohol	None	2 to 5 drinks/day	1.4
Breast density on mammography (percents)	0	≥75	1.8 to 6.0
Bone density	Lowest quartile	Highest quartile	2.7 to 3.5
History of a benign breast biopsy	No	Yes	1.7
History of atypical hyperplasia on biopsy	No	Yes	3.7
Protective factors			
Breast feeding (months)	≥16	0	0.73
Parity	≥5	0	0.71
Recreational exercise	Yes	No	0.70
Postmenopause body mass index (kg/m ²)	<22.9	>30.7	0.63
Oophorectomy before age 35 years	Yes	No	0.3
Aspirin	≥Once/week for ≥6 months	Nonusers	0.79

Breast Cancer Screening

ACS, ACR, AMA, NCI, ACOG, and NCCN

- Routine screening at age 40

USPSTF, ACP, and AAFP

- Routine screening at age 50
- Individual risk assessment and shared decision-making with patients for women 40-49 years

Breast Cancer: MRI Screening

ACS recommendations for breast MRI screening as an adjunct to mammography

Recommend annual MRI screening (based on high risk of breast cancer and high sensitivity of MRI*)
<i>BRCA</i> mutation
First-degree relative of <i>BRCA</i> carrier, but untested
Lifetime risk >20-25 percent or greater, as defined by BRCAPRO or other models that are largely dependent on family history
Recommend annual MRI screening (based on high risk of breast cancer)
Radiation to chest between age 10 and 30 years
Li-Fraumeni syndrome and first-degree relatives
Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives
Insufficient evidence to recommend for or against MRI screeningΔ
Lifetime risk 15-20 percent, as defined by BRCAPRO or other models that are largely dependent on family history
Lobular carcinoma in situ (LCIS) or atypical lobular hyperplasia (ALH)
Atypical ductal hyperplasia (ADH)
Heterogeneously or extremely dense breast on mammography
Women with a personal history of breast cancer, including ductal carcinoma in situ (DCIS)
Recommend against MRI screening (based on expert consensus opinion)
Women at <15 percent lifetime risk

Breast Cancer – Pathology

Non-invasive

- DCIS
- LCIS

Invasive

- Infiltrating ductal carcinoma - 76%
- Infiltrating lobular carcinoma - 8%
- Ductal/lobular - 7%
- Mucinous (colloid) – 2.4%
- Tubular – 1.5%
- Medullary – 1.2%
- Papillary – 1%
- Metaplastic breast cancer and invasive micropapillary breast cancer - < 5%

Infiltrating Lobular Carcinoma

Second most common type of invasive breast cancer

Incidence rates of lobular cancer are rising faster than the rates of ductal carcinoma in the US.

Postmenopausal hormone therapy may be more strongly related to lobular cancer risk than to ductal cancer risk.

Higher frequency of bilaterality and multicentricity

Tend to arise in older women

Tend to be larger and better differentiated tumors (ER+)

Tend to metastasize later and spread to unusual locations such as peritoneum, meninges and GI tract

Breast carcinoma –Subtypes

Luminal A - ~ 40% [ER+/PR+/Her2-]

- Most common subtype
- High expression of ER-related genes
- Low expression of HER2 cluster genes
- Low expression of proliferation-related gene

Luminal B - ~ 20% [ER+/PR+/Her2+]

- Lower expression of ER-related genes
- Variable expression of HER2 cluster genes
- Low expression of proliferation-related gene

Her2-enriched - ~ 10-15% [ER-/PR-/Her2+]

- High expression of HER2 cluster genes
- High expression of proliferation-related gene
- Low expression of luminal and basal clusters.

Basal-like - ~ 15-20% [ER-/PR-/Her2-]

- Low expression of HER2 cluster genes
- Low expression of luminal clusters.
- High expression of proliferation-related gene

Breast Cancer – Diagnosis and Workup

Majority of breast cancers are diagnosed as a result of abnormal mammogram.

- Further diagnostic evaluation with magnification views, spot compression views and/or targeted ultrasound and/or breast MRI
- Tissue biopsy

Concerning findings on mammography include:

- clustered, pleomorphic, and branching calcifications
- Nodule, mass, architectural distortion, and density

BREAST IMAGING REPORTING AND DATA SYSTEM (BI-RADS)

BI-RADS category	Assessment	Clinical management recommendation(s)			
0	Assessment incomplete	Need to review prior studies and/or complete additional imaging	4	Suspicious abnormality	Perform biopsy, preferably needle biopsy
1	Negative	Continue routine screening	5	Highly suspicious of malignancy; appropriate action should be taken	Biopsy and treatment, as necessary
2	Benign finding	Continue routine screening	6	Known biopsy-proven malignancy, treatment pending	Assure that treatment is completed
3	Probably benign finding	Short-term follow-up mammogram at 6 months, then every 6–12 months for 1–2 years			

Breast Cancer – Diagnosis and Workup

**CLINICAL
STAGE**

WORKUP

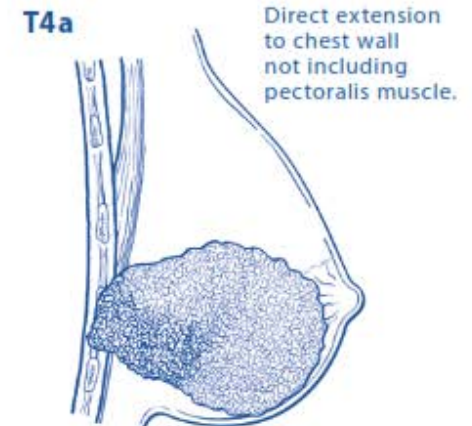
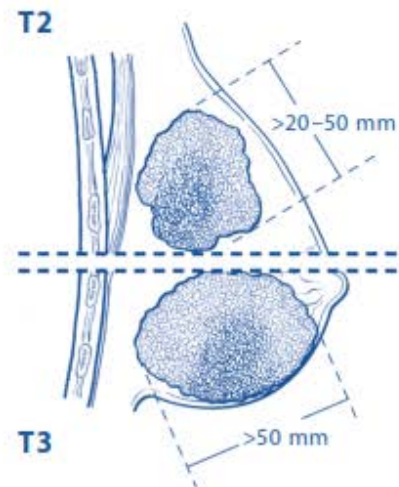
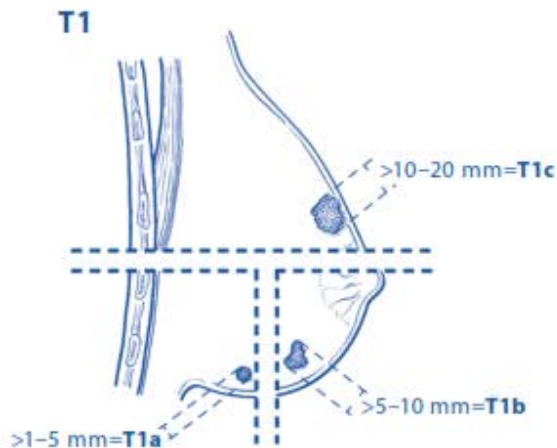
Stage I
T1, N0, M0
or
Stage IIA
T0, N1, M0
T1, N1, M0
T2, N0, M0
or
Stage IIB
T2, N1, M0
T3, N0, M0
or
Stage IIIA
T3, N1, M0

- History and physical exam
 - CBC, platelets
 - Liver function tests and alkaline phosphatase
 - Diagnostic bilateral mammogram, ultrasound as necessary
 - Pathology review^a
 - Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status^b
 - Genetic counseling if patient is high risk for hereditary breast cancer^c
 - Breast MRI^d (optional), with special consideration for mammographically occult tumors
 - Consider fertility counseling if indicated^e
- For clinical stage I-IIB, consider additional studies only if directed by signs or symptoms:^f
- Bone scan indicated if localized bone pain or elevated alkaline phosphatase
 - Abdominal ± pelvic diagnostic CT or MRI indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis
 - Chest diagnostic CT (if pulmonary symptoms present)
- If clinical stage IIIA (T3, N1, M0) consider:
- Chest diagnostic CT
 - Abdominal ± pelvic diagnostic CT or MRI
 - Bone scan or sodium fluoride PET/CT^g (category 2B)
 - FDG PET/CT^{h,i} (optional, category 2B)

[See
Locoregional
Treatment
\(BINV-2\)](#)

Breast Cancer Staging

7th EDITION



Primary Tumor (T)

- TX** Primary tumor cannot be assessed
- T0** No evidence of primary tumor
- Tis** Carcinoma in situ
- Tis (DCIS)** Ductal carcinoma in situ
- Tis (LCIS)** Lobular carcinoma in situ
- Tis (Paget's)** Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted
- T1** Tumor ≤ 20 mm in greatest dimension
- T1mi** Tumor ≤ 1 mm in greatest dimension
- T1a** Tumor > 1 mm but ≤ 5 mm in greatest dimension
- T1b** Tumor > 5 mm but ≤ 10 mm in greatest dimension
- T1c** Tumor > 10 mm but ≤ 20 mm in greatest dimension
- T2** Tumor > 20 mm but ≤ 50 mm in greatest dimension
- T3** Tumor > 50 mm in greatest dimension
- T4** Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
Note: Invasion of the dermis alone does not qualify as T4
- T4a** Extension to the chest wall, not including only pectoralis muscle adherence/invasion
- T4b** Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
- T4c** Both T4a and T4b
- T4d** Inflammatory carcinoma (see "Rules for Classification")

Staging

Regional Lymph Nodes (N)

CLINICAL

- NX** Regional lymph nodes cannot be assessed (for example, previously removed)
- N0** No regional lymph node metastases
- N1** Metastases to movable ipsilateral level I, II axillary lymph node(s)
- N2** Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
 - N2a** Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
 - N2b** Metastases only in clinically detected* ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
- N3** Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
 - N3a** Metastases in ipsilateral infraclavicular lymph node(s)
 - N3b** Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
 - N3c** Metastases in ipsilateral supraclavicular lymph node(s)

Distant Metastases (M)

- M0** No clinical or radiographic evidence of distant metastases
- cM0(i+)** No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
- M1** Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Pathologic Nodal Staging

PATHOLOGIC (PN)⁺

pNX Regional lymph nodes cannot be assessed (for example, previously removed, or not removed for pathologic study)

pN0 No regional lymph node metastasis identified histologically

Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.

pN0(i-) No regional lymph node metastases histologically, negative IHC

pN0(i+) Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)

pN0(mol-) No regional lymph node metastases histologically, negative molecular findings (RT-PCR)

pN0(mol+) Positive molecular findings (RT-PCR)⁺⁺, but no regional lymph node metastases detected by histology or IHC

pN1 Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected^{****}

pN1mi Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)

pN1a Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm

pN1b Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected^{****}

pN1c Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected

pN2 Metastases in 4–9 axillary lymph nodes; or in clinically detected^{****} internal mammary lymph nodes in the absence of axillary lymph node metastases

pN2a Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)

pN2b Metastases in clinically detected^{****} internal mammary lymph nodes in the absence of axillary lymph node metastases

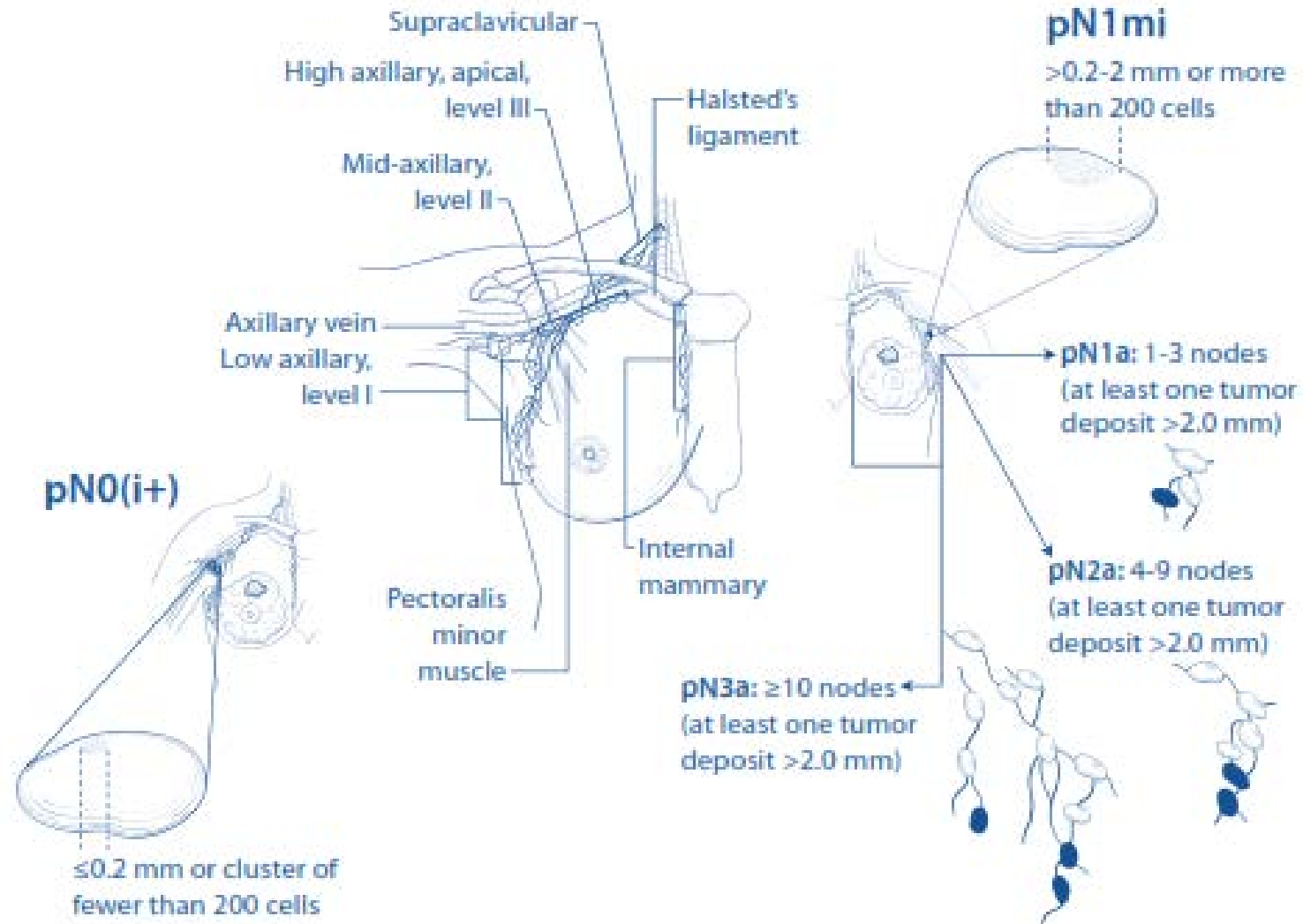
pN3 Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected^{****} ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected^{****}; or in ipsilateral supraclavicular lymph nodes

pN3a Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes

pN3b Metastases in clinically detected^{****} ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected^{****}

pN3c Metastases in ipsilateral supraclavicular lymph nodes

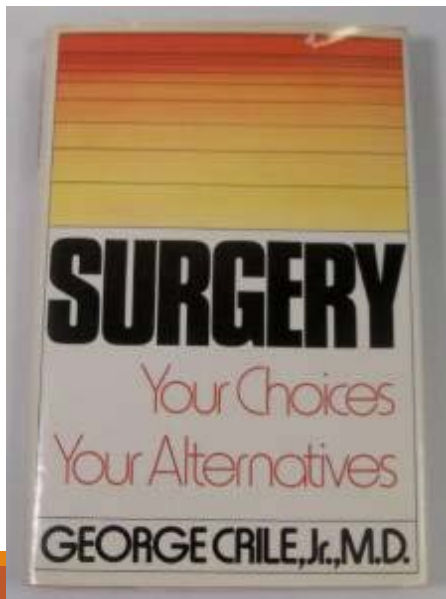
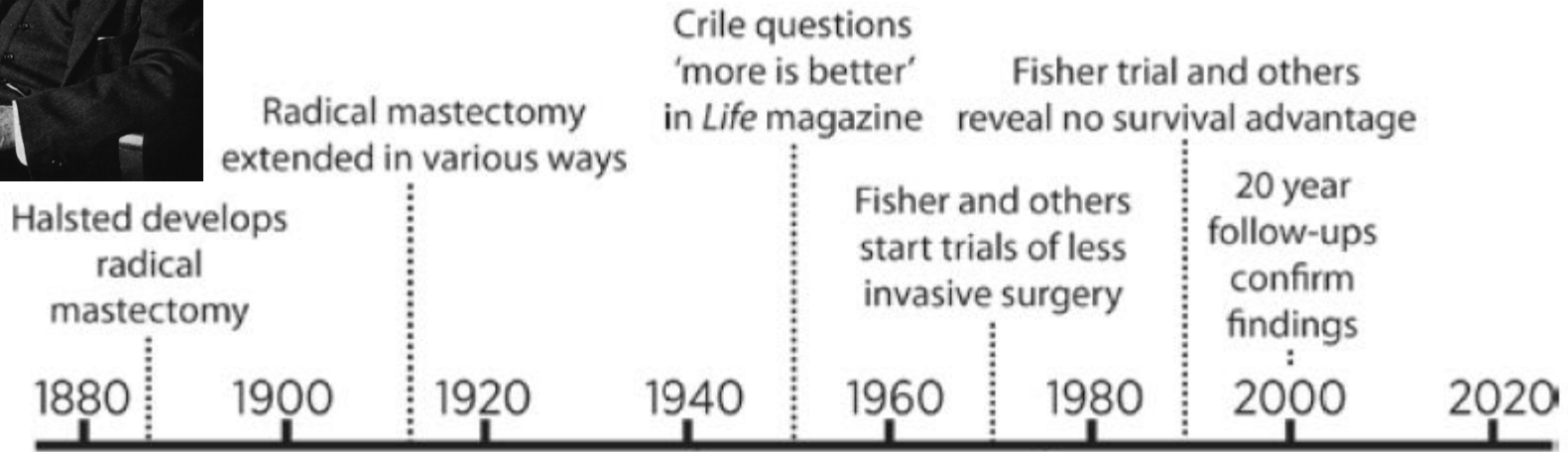
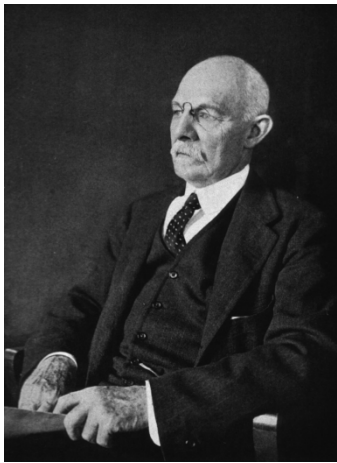
Lymph Nodes



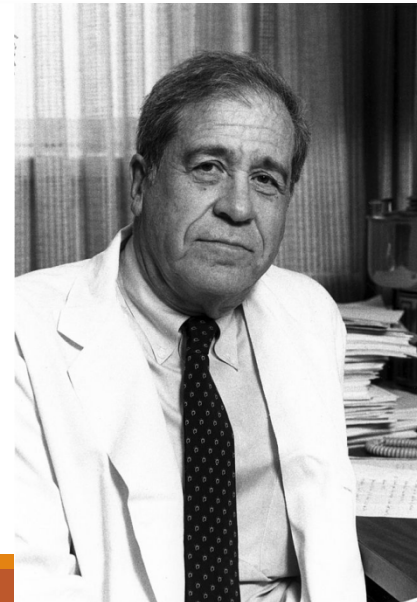
ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Breast Cancer: Management

Timeline



Some clinicians, in professional circles, question need for radical surgery



Breast Conservation Therapy (BCT)

BCT = Breast Conservation Surgery (BCS) + RT

Contraindications to BCS

- Multicentric disease (tumors in more than one quadrant)
- Persistent positive margins after re-excisions
- Diffuse or suspicious microcalcifications
- Prior RT to breast or chest wall
- Current pregnancy

Relative contraindications to BCS

- High ratio of tumor to breast volume
- Subareolar location
- BRCA 1/2
- Collagen vascular disease
- T3 – neoadjuvant chemo may be given to convert patient to a candidate for BCT



Mastectomy vs BCT

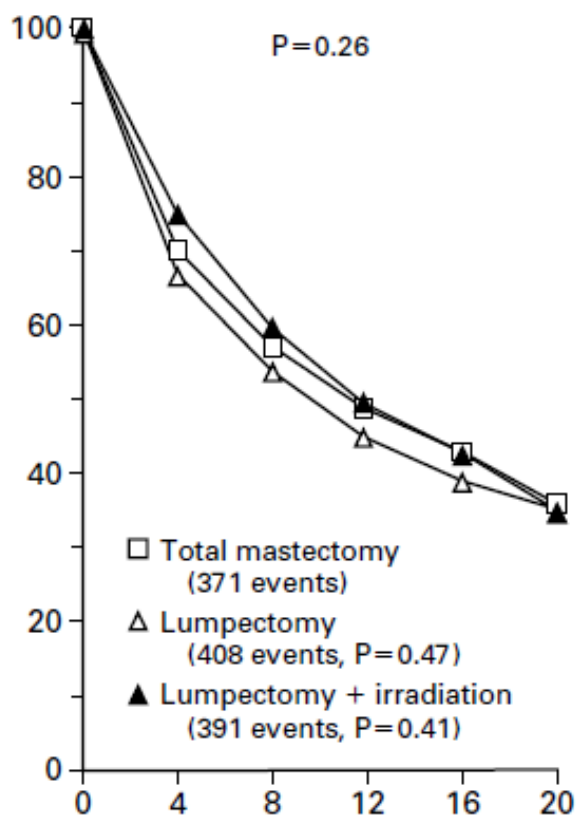
No difference in OS between mastectomy vs BCT

NSABP B-06 (1976-1984)

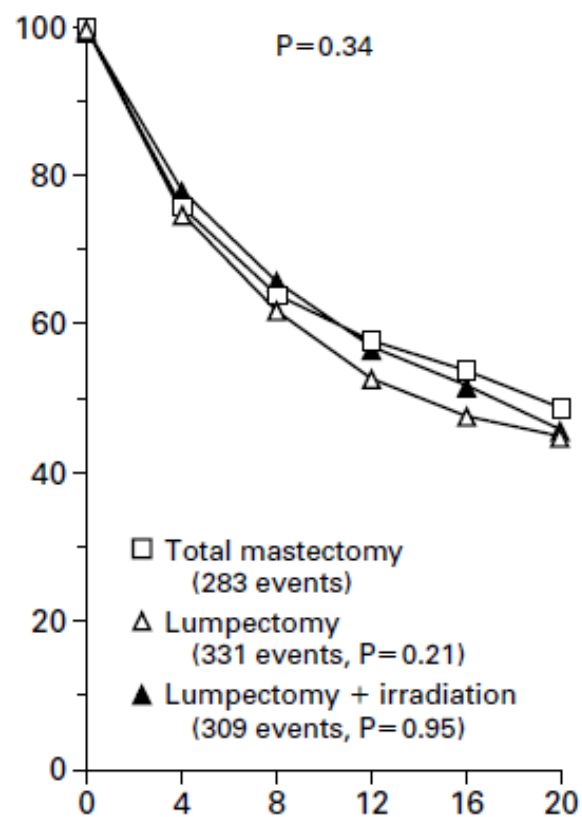
- 1851 patients
- Stage I and II with tumors ≤ 4 cm and LN+/-
- All had axillary lymph node dissections
 - level I & II for lumpectomy patients
 - axillary nodes removed en bloc with tumor for mastectomy patients
 - Patients with positive nodes received melphalan + 5-FU
- Arm 1: total mastectomy
- Arm 2: lumpectomy
- Arm 3: lumpectomy + breast irradiation (50 Gy) [no boost]

NSABP B-06 (1976-84)

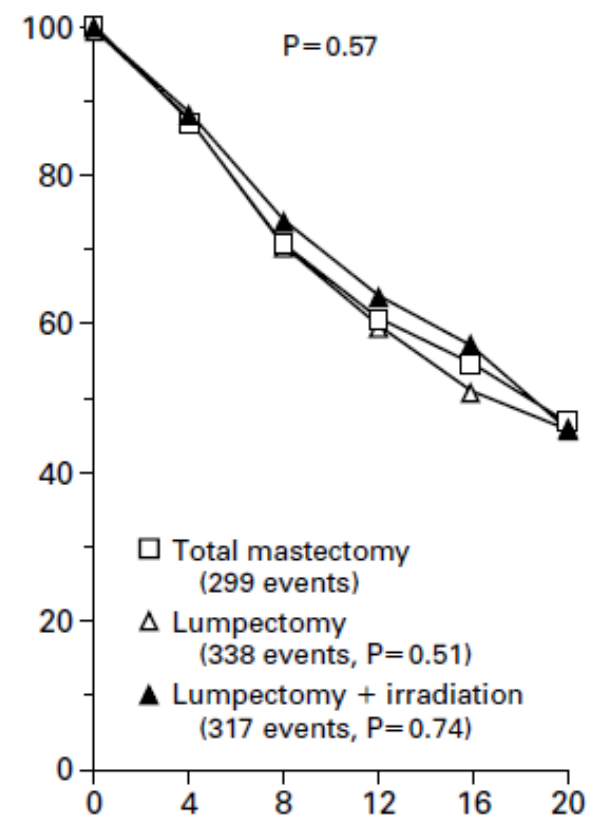
A Disease-free Survival



B Distant-Disease-free Survival



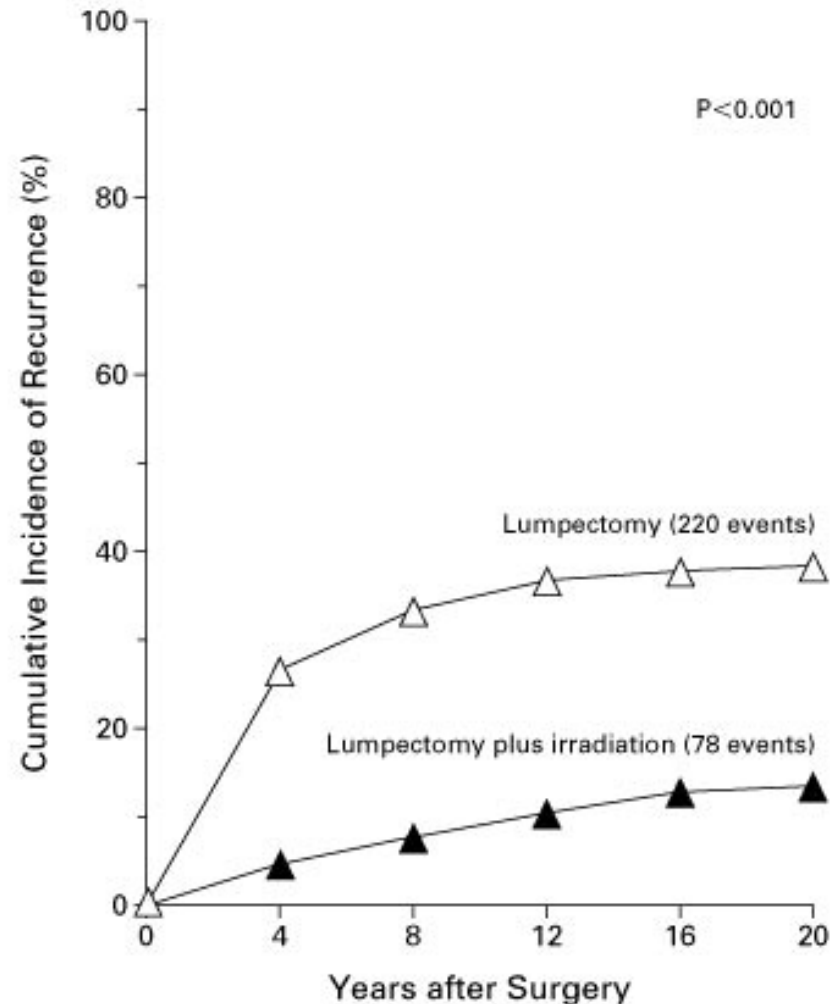
C Overall Survival



Years of Follow-up

NSABP B-06 (1976-84)

20 year ipsilateral breast recurrence: 14.3% for lumpectomy + RT vs 39.2% for lumpectomy alone (P<0.001)



Mastectomy vs BCS + RT

Trial	Patients	Local Recurrence	Survival
EORTC 10801	868	10-years: mastectomy 12% vs. BCT + RT 20% (SS)	No difference OS (66% vs. 65%, NS) and DM (66% vs. 61%, NS)
NSABP B-06	1851	20 years: IBTR lumpectomy + RT 14% vs lumpectomy alone 39% (SS)	DFS 36% vs 35% vs 35% (NS) OS 47% vs 46% vs 46% (NS)
NCI	237	18-years: 22% in-breast in BCT + RT arm vs. mastectomy 0 *Higher in-breast failure likely due to large tumors (10% >4cm) and not requiring negative surgical margins	OS (mastectomy 58% vs. BCT 54%) DFS (67% vs. 63%)
Milan	701	20 years: mastectomy 2% vs. BCS + RT 9% (SS) *This rate identical to rate of contralateral BCA	20-year OS: both groups 41% DFS: 76% vs. 74% (NS)



Mastectomy vs BCS + RT

EBCTCG Oxford meta-analysis, Lancet 2005:

7,300 women enrolled in 10 trials for lumpectomy+/- RT

5-yr LR risk reduction was 19%

- 7% in RT vs. 26% in BCS alone

The 15-yr overall mortality risk was reduced by 5.3%

- 35.2% vs. 40.5%, $p = 0.005$

“...in the hypothetical absence of any other causes of death, avoid about one breast cancer death over the next 15 years for every four local recurrences avoided...”

Mastectomy vs BCS + RT

EBCTCG meta-analysis update, Lancet 2011:

- 10,801 women enrolled in 17 trials for BCS +/- RT

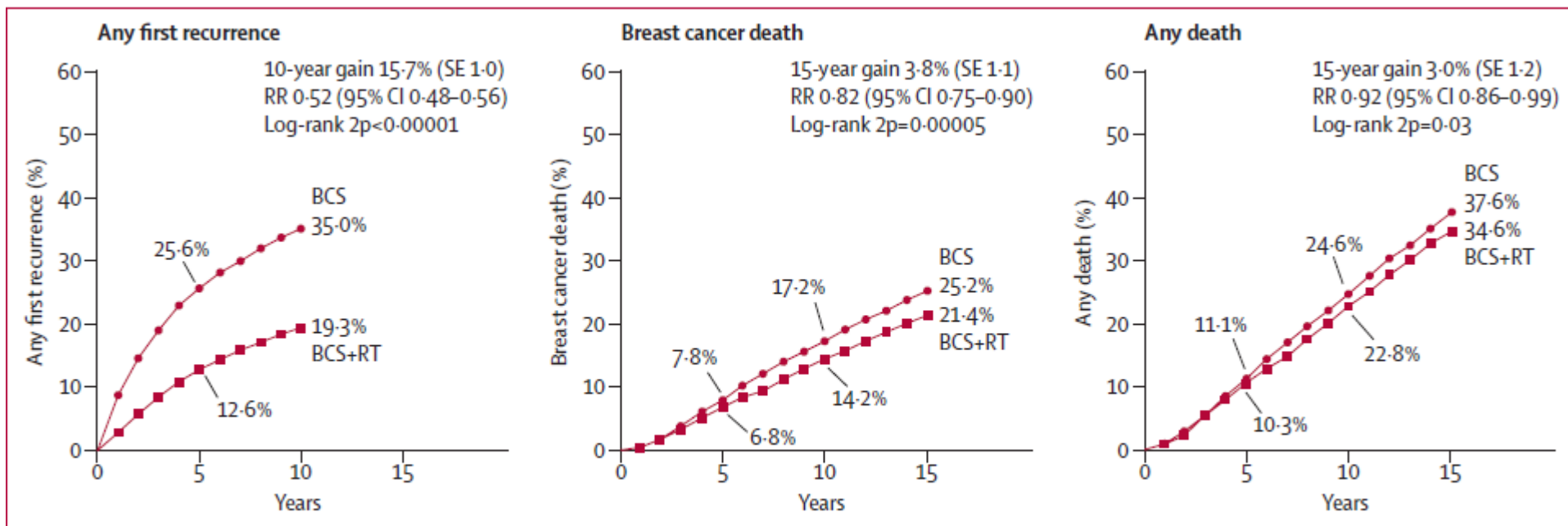


Figure 1: Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence and on 15-year risks of breast cancer death and death from any cause in 10 801 women (67% with pathologically node-negative disease) in 17 trials

BCS + Tamoxifen +/- RT

NSABP B-21 (1989-1998)

- 1009 patients
- Invasive tumors < 1 cm (1989-1994) and 1 cm tumor allowed (1996-1998)
- All had lumpectomy and axillary lymph node dissections
- Negative margins and negative lymph nodes
- Arm 1: Tamoxifen
- Arm 2: XRT + placebo
- Arm 3: Tamoxifen + XRT

BCS + Tamoxifen +/- RT

NSABP 21: 8 year data

Women with tumors ≤ 1 cm, IBTR occurs with enough frequency after lumpectomy to justify XRT regardless of ER status, and Tam+XRT when ER+

BREAST TUMOR RECURRENCE AFTER LUMPECTOMY

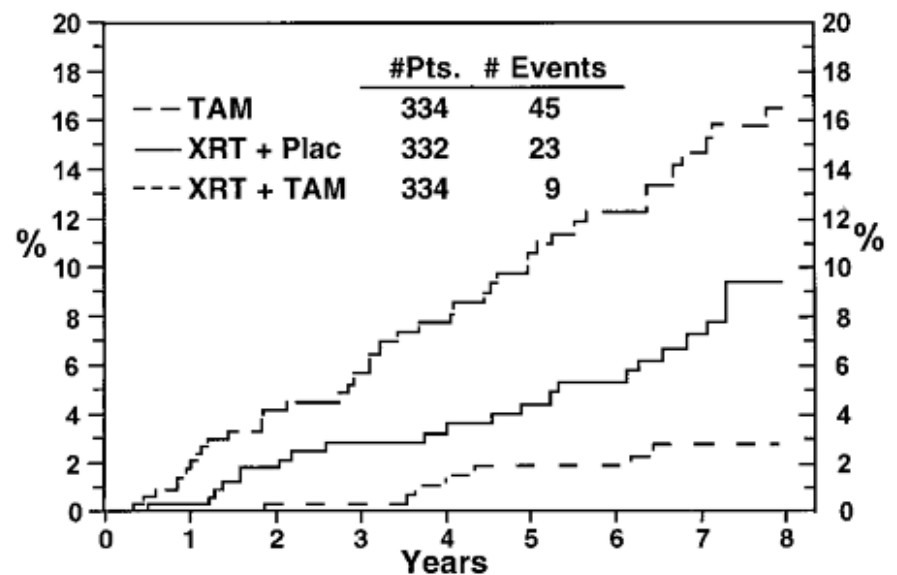


Fig 1. Cumulative incidence of IBTR after treatment with TAM, XRT and placebo, or XRT and TAM. Pairwise comparisons: TAM v XRT + placebo: $P = .008$; TAM v XRT + TAM: $P < .0001$; XRT + placebo v XRT + TAM: $P = .01$.

BCS + Tamoxifen +/- RT

CALGB 9343 [1994-1999]

- 636 patients
- 70 years or older, cT1N0, ER+
- Axillary lymph node dissection allowed but discouraged
- Negative margins
- Arm 1: Tamoxifen 20 mg daily for 5 years.
- Arm 2: Tamoxifen + XRT (45/25 + 14/7 boost)

BCS + Tamoxifen +/- RT

Radiation produces proportional reductions in local recurrence

Absolute reductions are dependent on the baseline risk

Results of CALGB 9343 are self-evident

- Tamoxifen + XRT has lower recurrence rate
- No difference in DM or survival
- ASCO Abstract 2010 – 10 years:
 - RT results in absolute reduction of 7% in local recurrence.
 - No impact on OS, cancer-specific survival.

BCS + Tamoxifen +/- RT

CALGB 9343 [1994-1999]

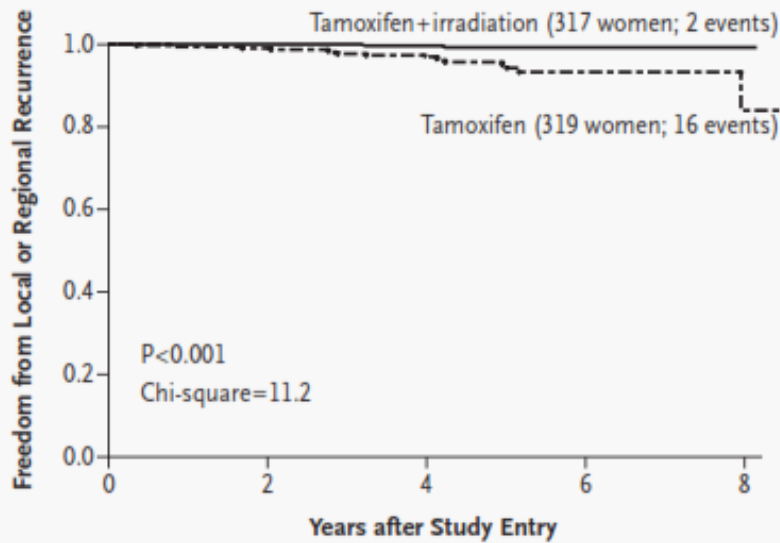


Figure 1. Time to First Local or Regional Recurrence.

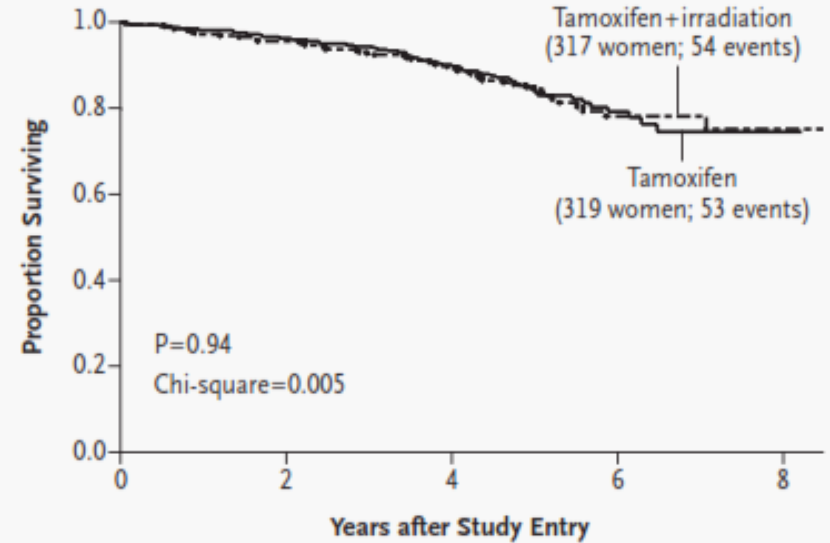


Figure 2. Overall Survival.

Role of Chemo/Hormone Rx

Stage I

- T1aN0; triple negative -> chemo
- T1b or T1c N0; ER negative -> chemo
- T1b or T1c N0; ER positive -> oncoprotein testing

Stage II

- ER negative, Her2 negative -> chemo
- ER negative, Her2 positive -> chemo with trastuzumab

Stage III/IV -> chemo

Post menopausal -> anastrozole (Aromatase Inhibitor)

Pre or post menopausal -> tamoxifen (SERM)

SLNB vs ALND

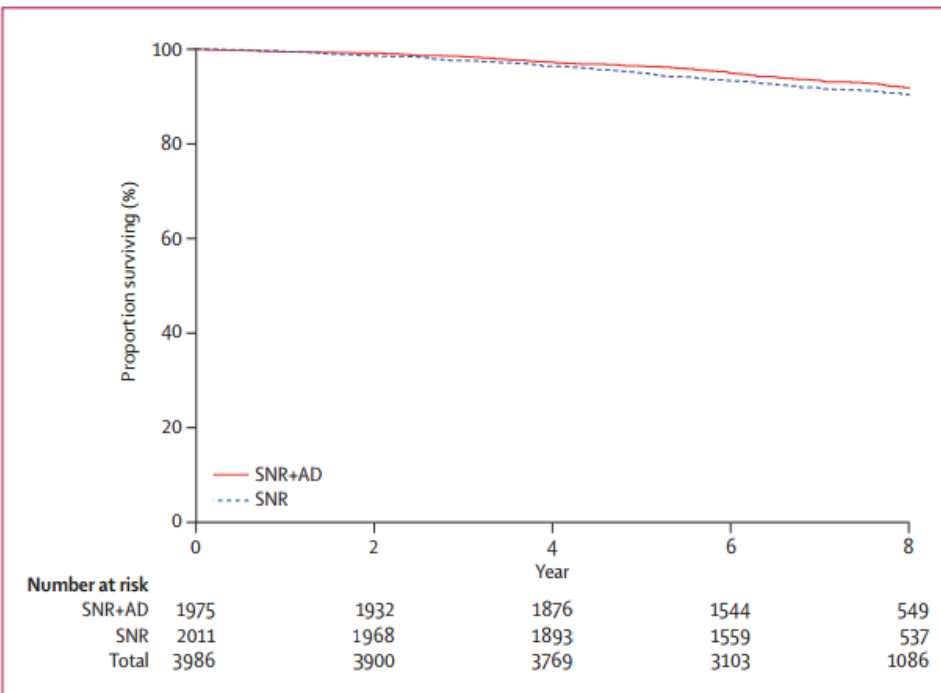
NSABP B-32 [1999-2004]

- 5611 patients with operable invasive breast cancer and clinically negative axillary LNs
- Arm 1: SLNB followed by immediate completion ALND
- Arm 2: SLNB
 - If SLN negative → no further intervention.
 - If SLN not found → Full ALND
 - If SLN positive → Full ALND

SLNB vs ALND

NSABP B-32 [1999-2004]

Overall Survival



Disease-Free Survival

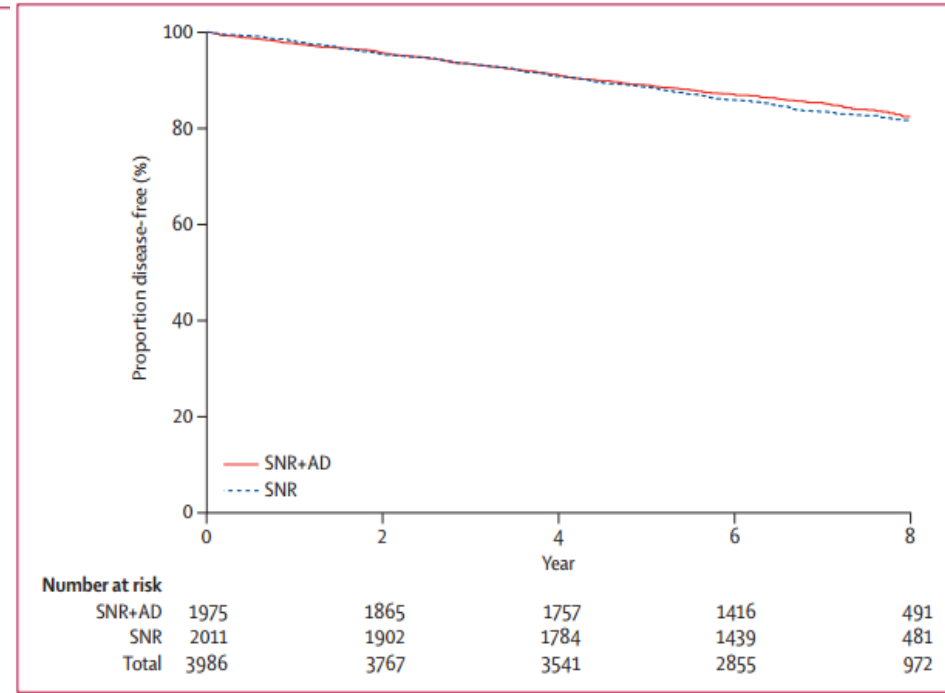


Figure 2: Overall survival for sentinel-node (SLN)-negative patients

Data as of Dec 31, 2009. For sentinel node resection (SNR) plus axillary dissection (AD), N=1975, 140 deaths. For SNR, N=2011, 169 deaths. Hazard ratio 1.20, 95% CI 0.96-1.50; p=0.12.

Figure 3: Disease-free survival for sentinel-node (SLN)-negative patients

Data as of Dec 31, 2009. For sentinel node resection (SNR) plus axillary dissection (AD), N=1975, 315 events. For SNR, N=2011, 336 events. Hazard ratio 1.05, 95% CI 0.90-1.22; p=0.54.

SLNB vs ALND

NSABP B-32 [1999-2004]

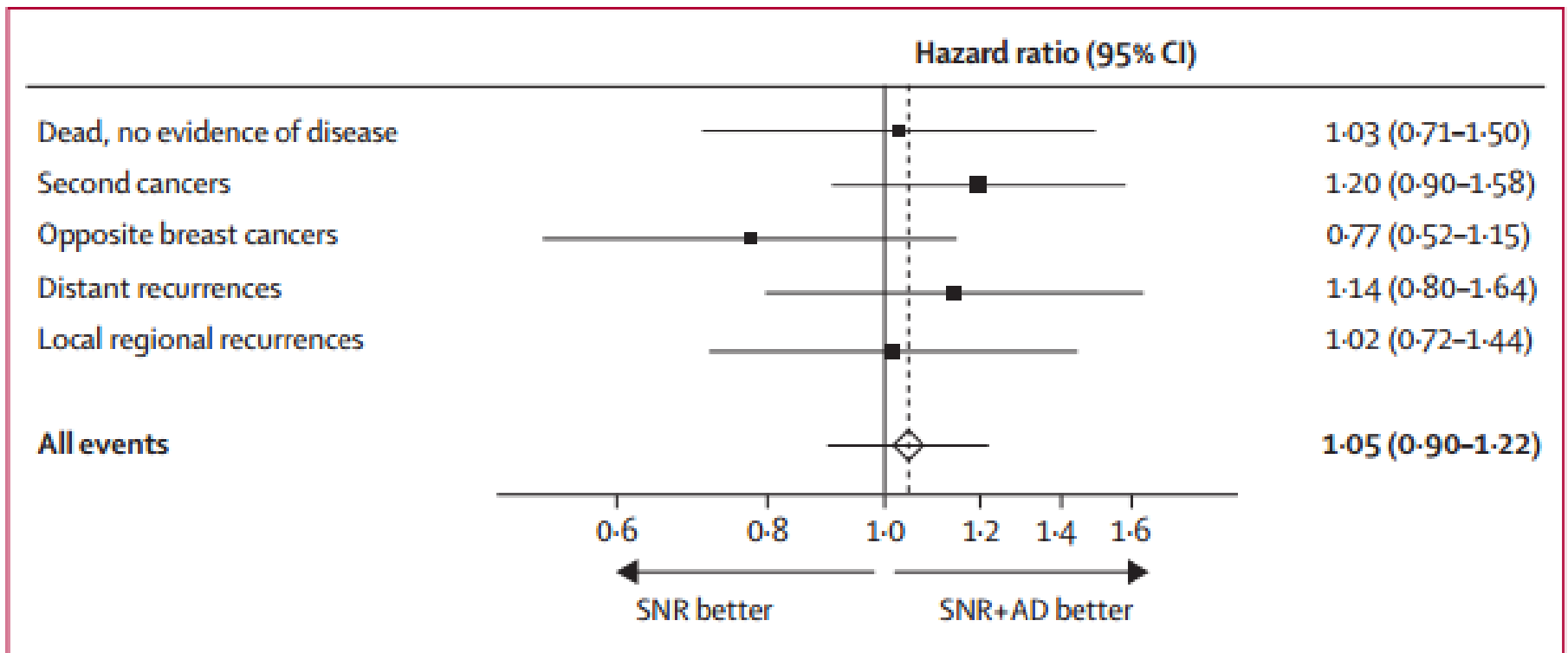


Figure 4: Forest plot for sentinel-node (SLN)-negative patients

SNR=sentinel node resection. SNR+AD=sentinel node resection plus axillary dissection.

Surgeons Oncology Group Trial Z0011

Equivalent survival in pts with 1-2 nodes positive regardless of SLNB or SLNB + ALND

Equally importantly, regional recurrence rate only 1% in SLNB alone arm despite estimate of 27% of patients having additional metastases in undissected nodes.

After BCS patients got whole breast with tangent fields and systemic therapy as appropriate

Regional nodal irradiation not allowed

Historically radiation oncologists have relied on ALND findings to decide on level III/sclav irradiation

- More than 4 nodes positive
- Select patients with 1-3 nodes positive

If + SLNB without ALND, what to do?

Positive Sentinel Nodes Without Axillary Dissection: Implications for the Radiation Oncologist

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Regional recurrence rate only 1% in SLNB alone arm despite estimate of 27% of patients having additional metastases in undissected nodes.

Why?

- Chemo?
- Hormones?
- SLN +, but with such a low burden of disease that immune system is eliminating disease?
- TFs delivered enough dose to lower axilla to eradicate disease

Table 1. Suggested Approach for Radiation Field Design in Patients With Sentinel Node–Positive Disease Not Undergoing Axillary Lymph Node Dissection

Clinical Scenario	No. of Positive Sentinel Nodes	Total No. of Sentinel Nodes Sampled	Probability of Additional Nodes* (%)	Probability of Additional Nodes† (%)	Probability of Four or More Nodes Involved‡ (%)	Field Design
IDC, 1.0 cm, ER positive, LVI negative	1 (IHC only)	3	3	8	< 1	Tangents only
IDC, 1.8 cm, G3, ER positive, LVI negative, unifocal	1 (macro)	2	27	24	2	High tangents
IDC, 2.0 cm, ER negative, LVI positive	2 (macro)	2	63	55	30	High tangents/consider full nodal treatment
ILC, 4.0 cm, ER positive, multifocal, LVI negative	2 (macro)	2	77	64	40	High tangents/consider full nodal treatment
IDC, 3 cm, ER negative, LVI positive, multifocal	3 (macro with ENE)	3	78	95	80	Full nodal treatment

Abbreviations: ENE, extranodal extension; ER, estrogen receptor; G, grade; IDC, infiltrating ductal carcinoma; IHC, immunohistochemistry; ILC, infiltrating lobular carcinoma; LVI, lymphovascular invasion; macro, macroscopic.

*On the basis of the Memorial Sloan-Kettering Cancer Center nomogram.¹⁹

†On the basis of the MD Anderson Cancer Center nomogram.¹⁹

‡Katz et al.²³

Axillary lymph node nomograms

MSKCC nomogram

- Size, tumor type and grade, # of + SLN, # of -SLN, LVI, multifocality, ER status
- Calculates probability of spread to additional lymph nodes

Katz nomogram

- Tumor size, # of + SLN, LVI, lobular histology, ENE, macromet in SLN, any -SLN
- Calculates probability of spread to 4 or more lymph nodes
- Consider treating Level III and Sclav if >10% risk of 4 or more nodes

Nomograms can be used in patients without ALND for determining fields in patients requiring RT after BCS



Tumor Bed Boost

EORTC boost trial (1989-96)

- 5318 women with BCT:
 - Arm 1: 50 Gy, no boost
 - Arm 2: 50 Gy plus 16 Gy boost
- At 10 years, local failure rates
 - Boost: 6.2%
 - No boost: 10.2%
- Absolute benefit highest women < 50
 - Boost: 13.5%
 - No Boost: 24%

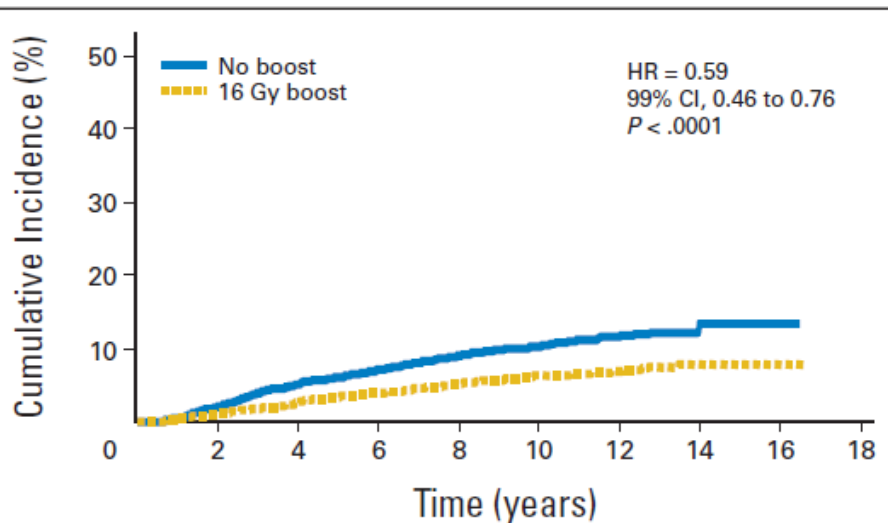
Lyon Boost Trial (1986-92)

- 1024 pts
 - 50 Gy vs 50 Gy + 10 Gy boost
 - At 5 years: Local recurrence: 3.6% (boost) vs 4.5% (no boost) (SS)
 - Cosmesis: telangiectasia 12.4% vs. 5.9%, but no difference in self-assessment of cosmesis

EORTC boost trial (1989-96)

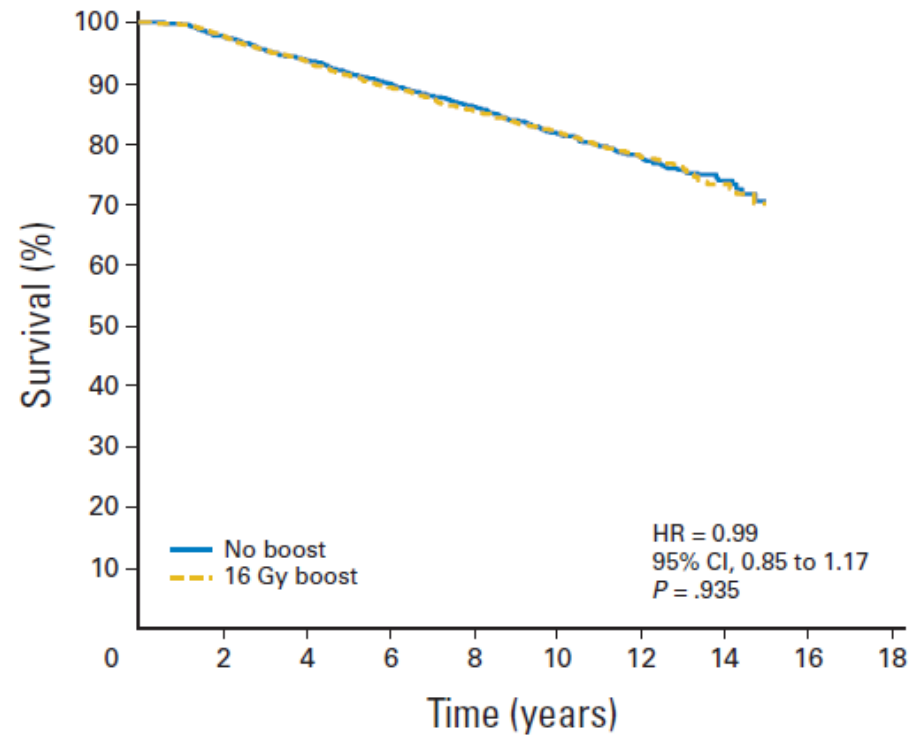
10 year median follow up

Local Recurrence



	O	N	No. of patients at risk							
No boost	278	2,657	2,397	2,116	1,897	1,673	1,146	525	99	2
16 Gy	165	2,661	2,408	2,164	1,922	1,693	1,148	503	109	3

Survival



	O	N	No. of patients at risk						
No boost	522	2,657	2,555	2,402	2,206	2,043	1,432	661	127
16 Gy	521	2,661	2,560	2,420	2,227	2,046	1,416	637	140

Higher Boost?

EORTC boost trial (1989-96)

251 patients with SM+

Arm 1) low boost 10 Gy

Arm 2) high boost 26 Gy

Median F/U 11.3 years

10-year local recurrence low boost 17% vs high boost 11% (HR 0.8, NS)

No difference in OS

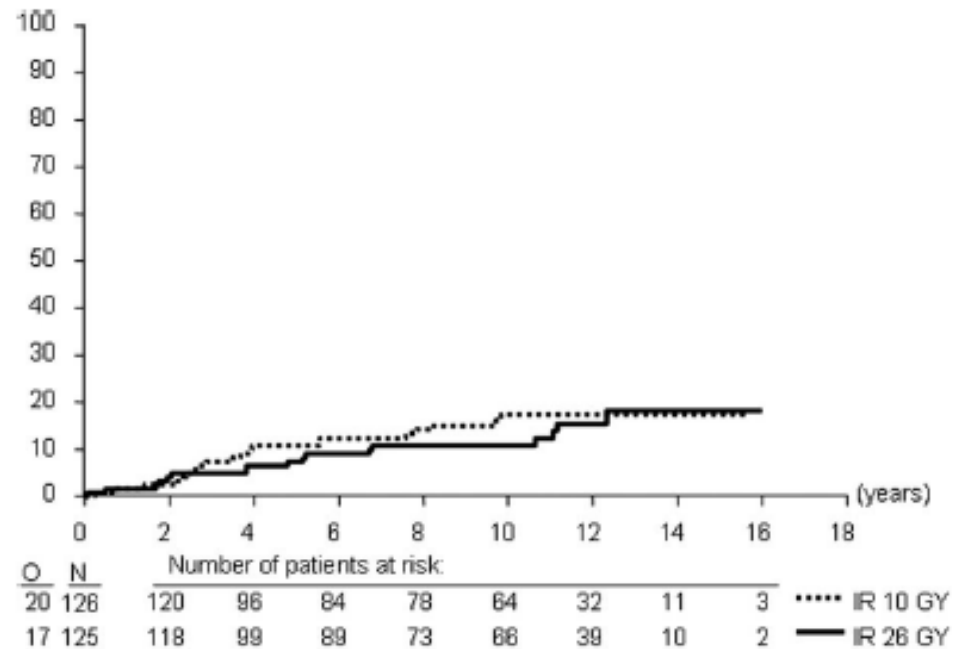
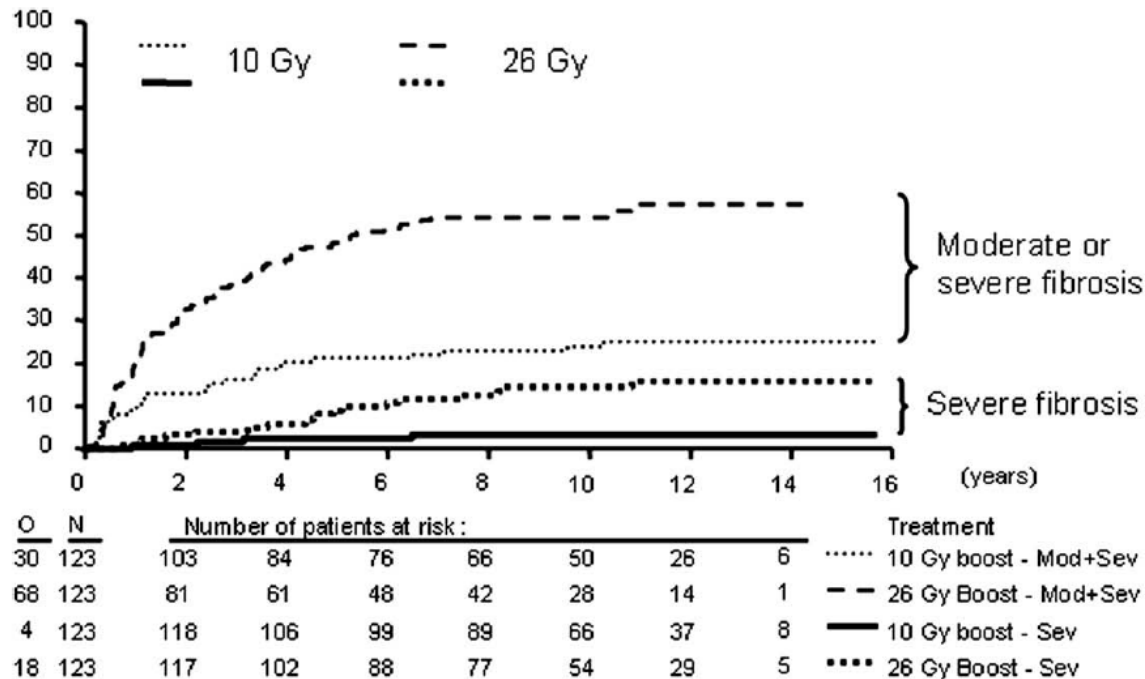


Fig 1. Cumulative incidence of local failure (as first event).

Higher Boost?



Fibrosis was scored by treating physician at follow up visits on a 4-point scale (1=none, 2=minor, 3=moderate, 4=severe)

Hypofractionation in BCT

Improve patient experience



Decrease costs

Improve access to BCT

Concerns

- Long-term control
- Cosmetic outcome

Hypofractionation in BCT

Trial	Patients	Randomization	Local control	Cosmesis
	1234*	50/25 vs 42.5/16 (3 weeks)	10 years: 6.2 vs 6.7 %	10 years, excellent/ good: 70 vs 71%
 START B	2215	50/25 vs 40/15 (3 weeks)	6 years: 2.2% vs 3.3%	Photographic change in appearance more likely with 50 Gy (SS)

Other notable trials

MRC START A (1998-2002) - 50/25 vs. 41.6/13 vs. 39/13 over 5 weeks

- 5-year LRR 50 Gy 3.6%, 41.6 Gy 3.5%, 39 Gy 5.2% (NS)

Royal Marsden (UK) (1986-1998) - 50/25 vs 39/13 vs 42.9/13 all over 5 weeks.

- 10-year IBTR: 12% vs. 14.8% vs. 9.6% (NS vs 50/25, but SS between 39/13 and 42.9/13)

*women with breast width >25cm excluded from trial

ASTRO Consensus 2011

Table 1. Evidence supports the equivalence of hypofractionated whole breast irradiation with conventionally fractionated whole breast irradiation for patients who satisfy all of these criteria*

1. Patient is 50 years or older at diagnosis.
 2. Pathologic stage is T1–2 N0 and patient has been treated with breast-conserving surgery.
 3. Patient has not been treated with systemic chemotherapy.
 4. Within the breast along the central axis, the minimum dose is no less than 93% and maximum dose is no greater than 107% of the prescription dose ($\pm 7\%$) (as calculated with 2-dimensional treatment planning without heterogeneity corrections).
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* For patients who do not satisfy all of these criteria, the task force could not reach consensus and therefore chose not to render a recommendation either for or against hypofractionated whole breast irradiation in this setting. Please see the text for a thorough discussion of tumor grade. Patients receiving any type of whole breast irradiation should generally be suitable for breast-conserving therapy with regards to standard selection rules (*e.g.*, not pregnant, no evidence of multicentric disease, no prior radiotherapy to the breast, no history of certain collagen-vascular diseases).

Clinical Case:

Case: 57 year old woman who with Stage IIA, pT2N0M0 right breast mixed ductal/lobular, grade 2, DCIS+, ER+, PR+, HER2 negative, and >5 mm margins for DCIS and invasive disease.

Plan for hypofractionated regimen

- 40.05 Gy (2.67 Gy/fx)
- Boost to tumor bed 10 Gy (2 Gy/fx)