Memorial Sloan Kettering Cancer Center

Evolution of the Local Therapy of Breast Cancer

FDA General and Plastic Surgery Devices Panel
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Evolution of the Local Therapy of Breast Cancer

- Changes in locoregional therapy
  - Surgery of the breast
  - Surgery of the axilla
  - Tailoring RT to reduce morbidity
- Surgery in the context of multidisciplinary care

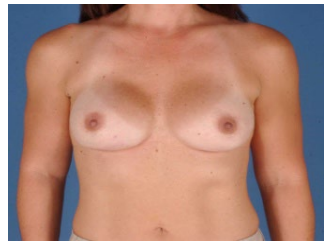
Evolution of the Surgical Therapy of Breast Cancer

1960 | 1970 | 1980 | 1990 | 2000

Radical Mastectomy | **MRM** | **BCT** | **Improved Reconstruction** | **Nipple Sparing**

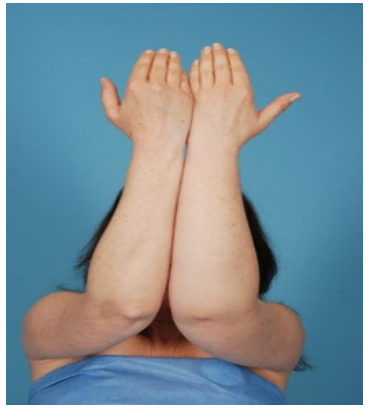
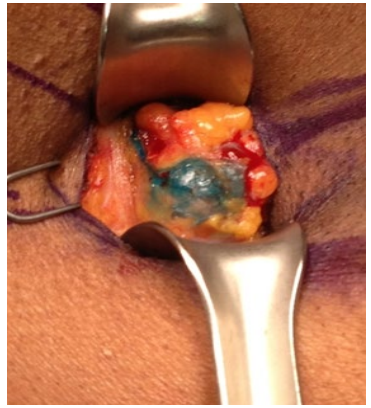






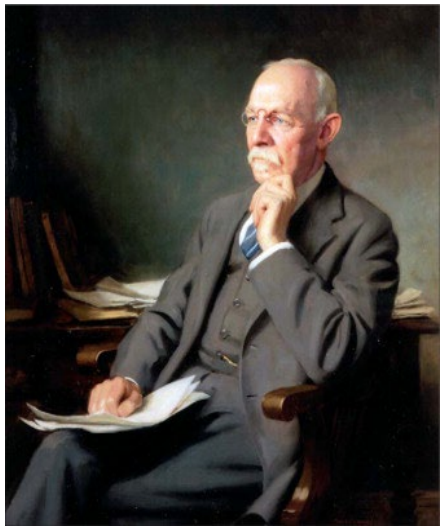
1960 | 1970 | 1980 | 1990 | 2000 | 2010 | 2023

ALND | **ALND** | **ALND** | **SN for N0** | **SN ± RT for N+** | **NAC for downstaging** | **No axillary surgery**

What Determines Local Control?

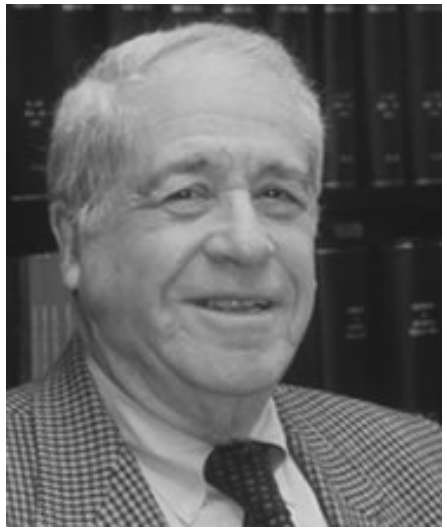
Alternate Surgical Views of Breast Cancer Biology



WS Halsted

"Though the area of disease extends from cranium to knee, breast cancer, in the broad sense, is a local affection."

Alternate Surgical Views of Breast Cancer Biology

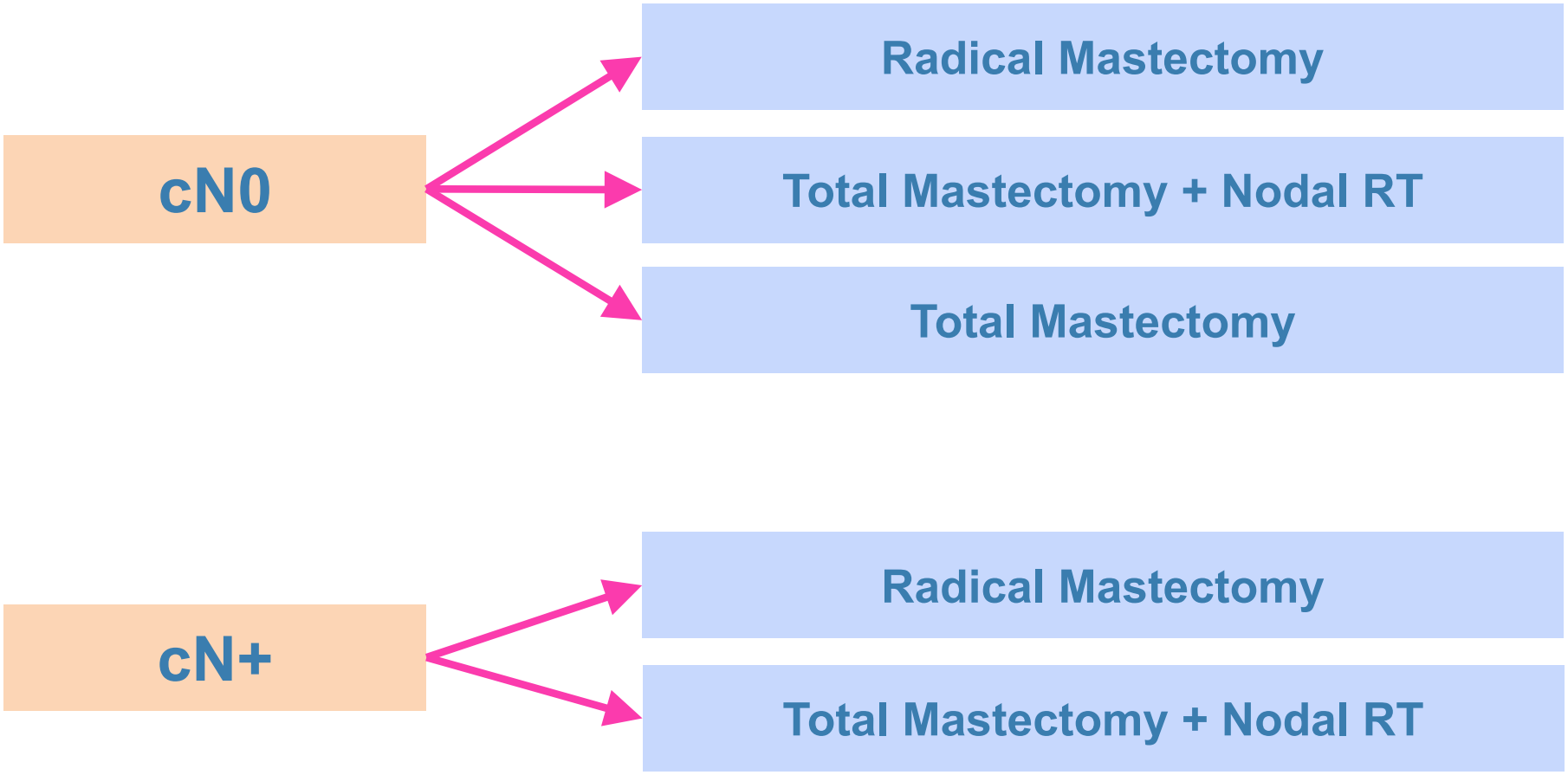


Bernard Fisher, MD

"Breast cancer is a systemic disease at diagnosis.
The metastatic phenotype is either present or absent, but is not acquired over time.
Variations in locoregional therapy are unlikely to affect survival substantially."

Fisher B, Lancet 1981

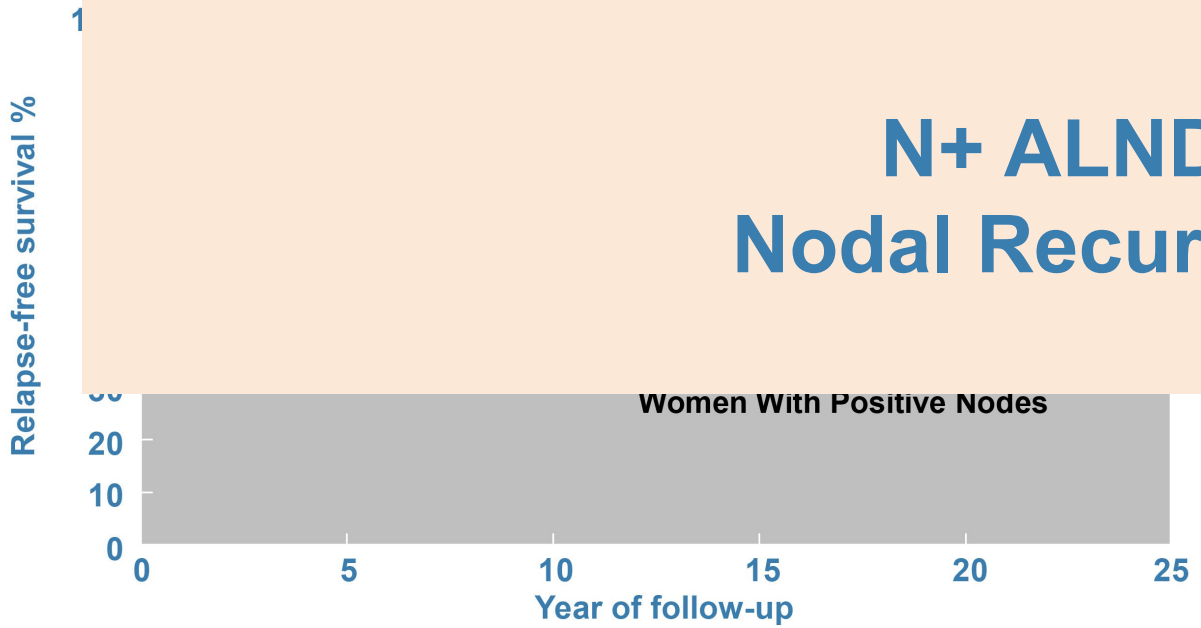
NSABP B-04



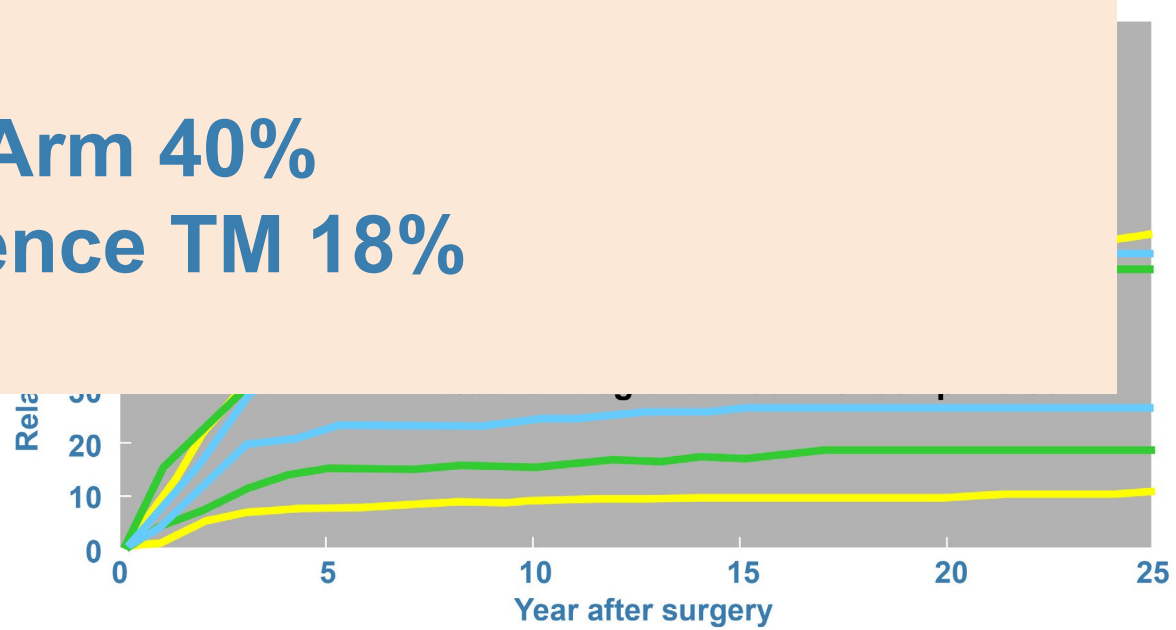
Fisher B, N Engl J Med 2002;347:567

NSABP B04: 25 Year Results

Relapse Free Survival



Locoregional and Distant Recurrence



N+ ALND Arm 40%
Nodal Recurrence TM 18%

Fisher B, N Engl J Med 2002;347:567

Why Was NSABP B04 So Important?

Repudiation of Halstedian Hypothesis Allowing:

- Breast conserving surgery

- Adjuvant systemic therapy

- Switch from RM to MRM
  - Availability of immediate reconstruction

NSABP B-06

August 1976-January 1984

Eligible

cT1 or T2, ≤ 4 cm, cN0

- **Lumpectomy Alone**
- **Lumpectomy + WBRT**
- **Total Mastectomy**

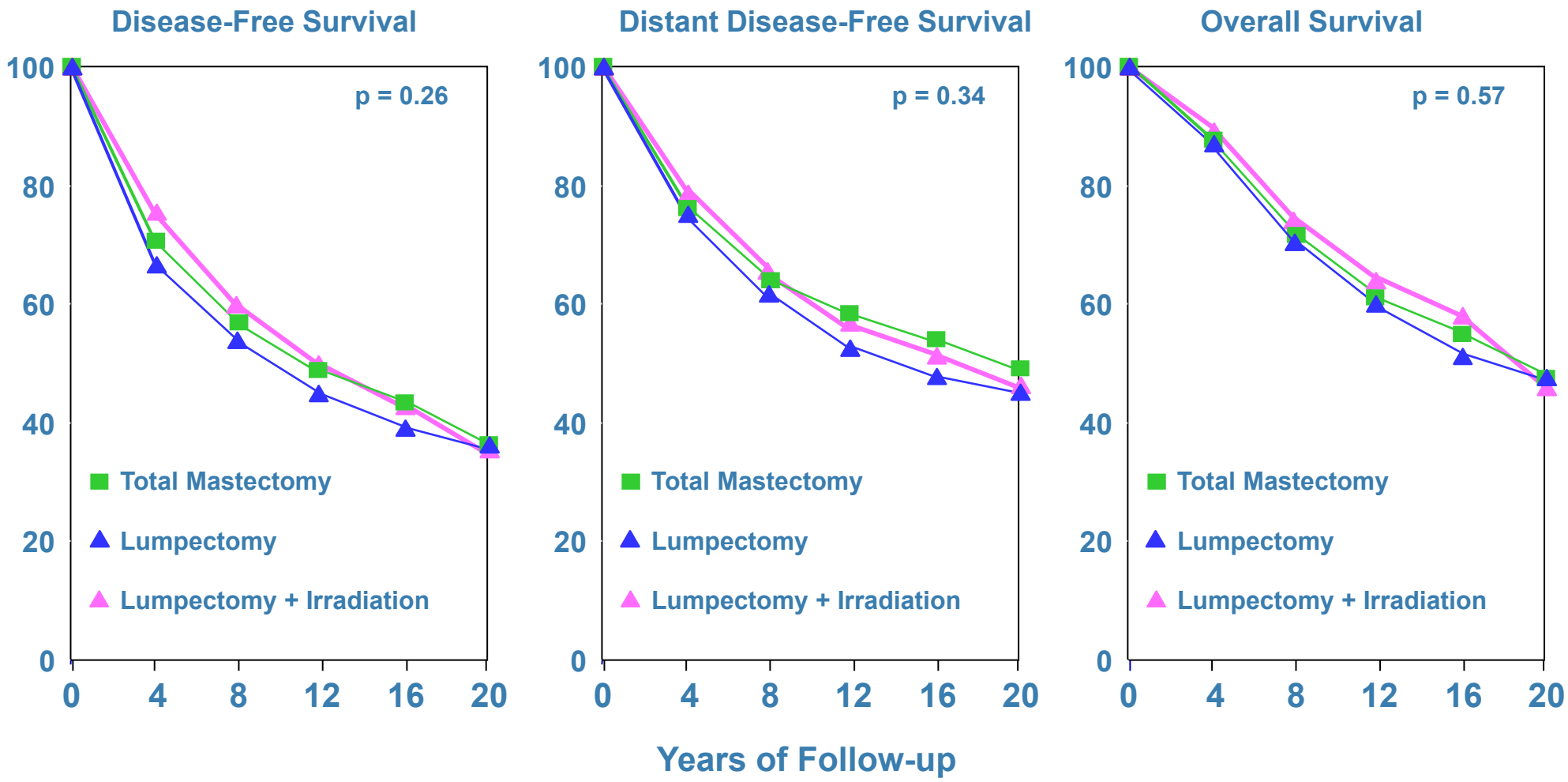
n = 2163

- All had ALND
- N+ received Melphalan + 5FU
- 50 Gy dose to breast
- No boost dose of RT, no nodal RT
- Negative margins defined as no tumor on ink

Endpoints: DFS, DDFS, OS
***In-breast recurrence was not a DFS event**

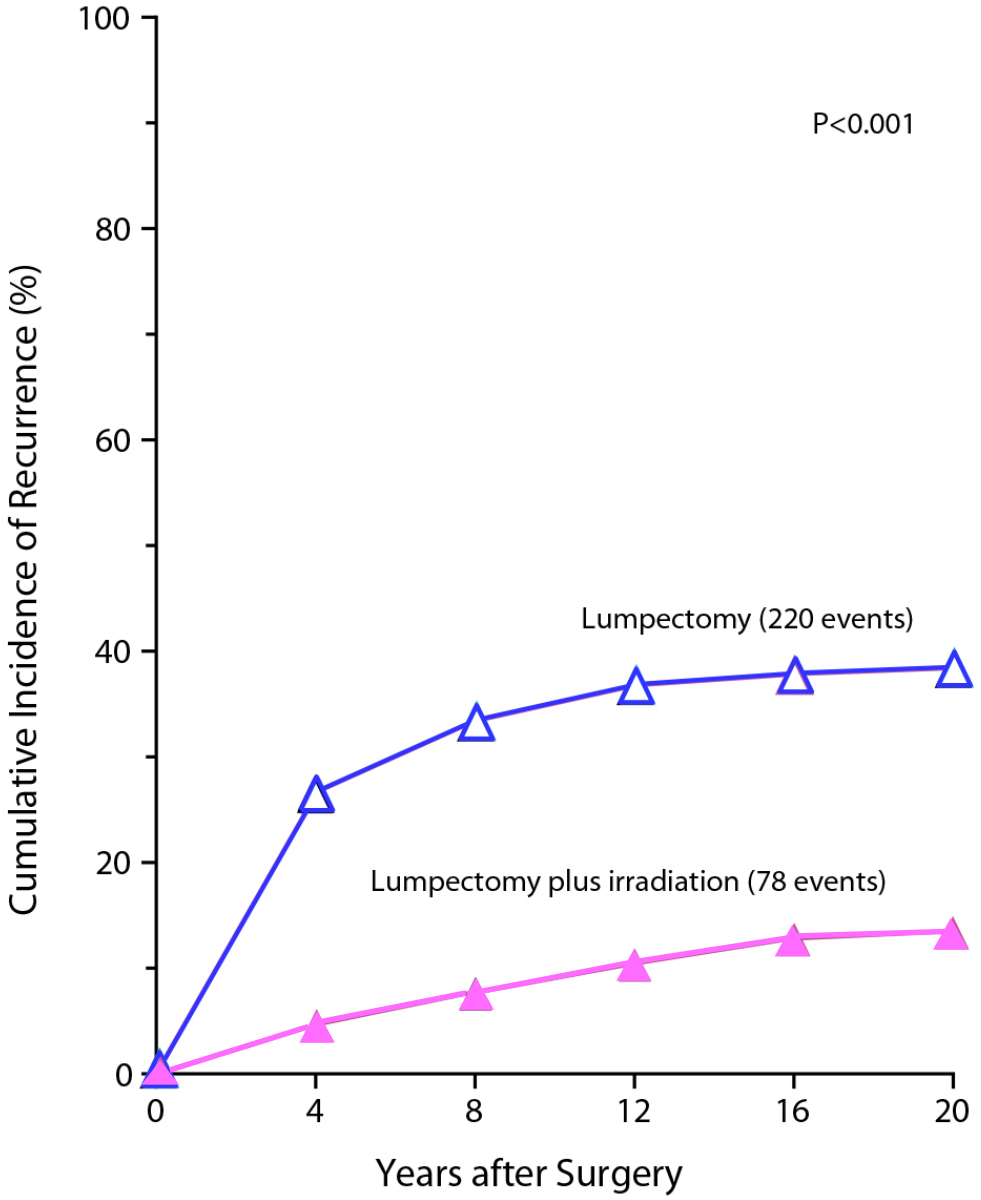
Fisher B, N Engl J Med 2002;347:1233

NSABP B06



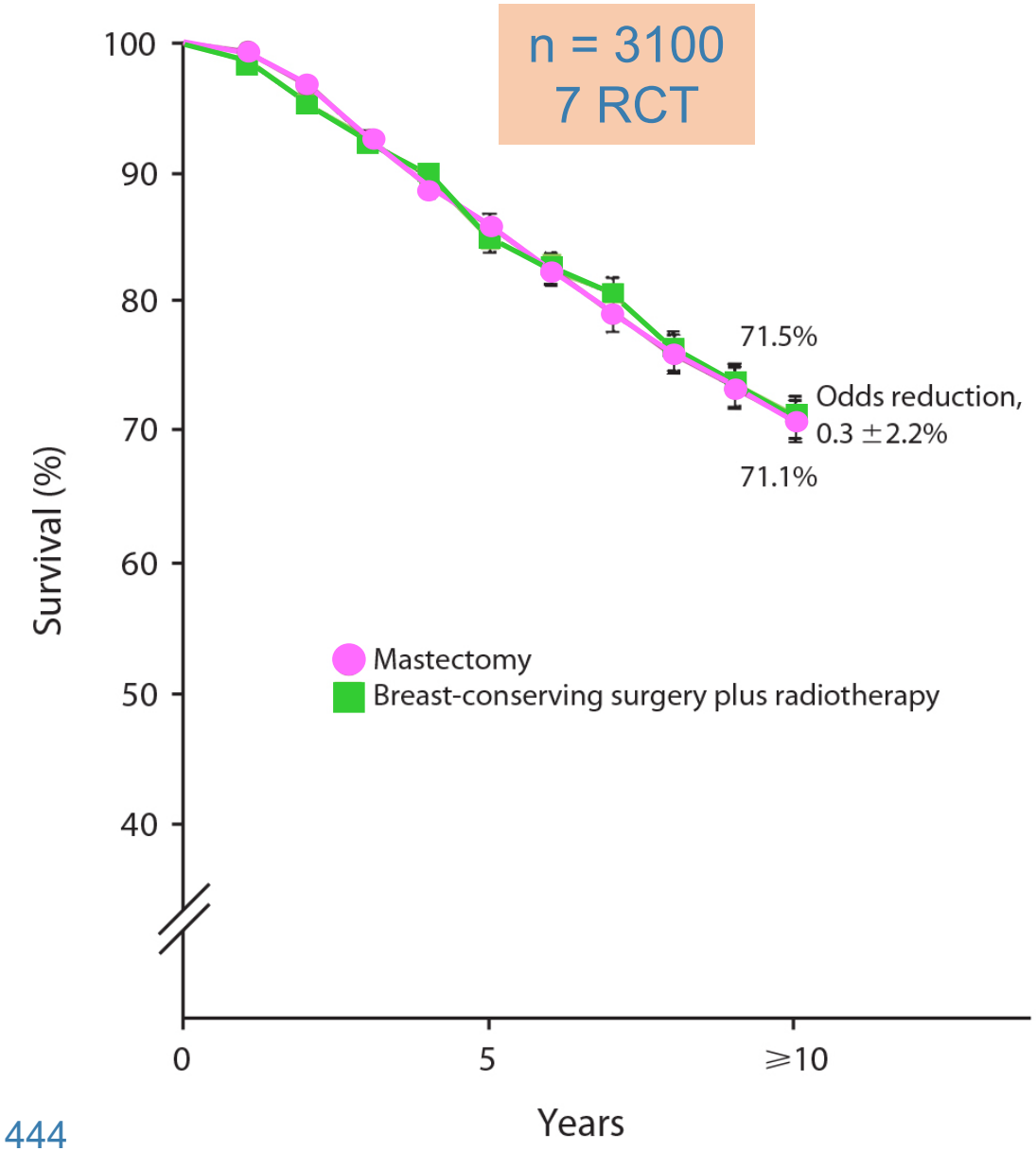
Fisher B, N Engl J Med 2002;347:1233

NSABP B-06: IBTR With and Without RT



Fisher B, N Engl J Med 2002;347:1233

EBCTCG Meta-analysis: Mastectomy vs BCT

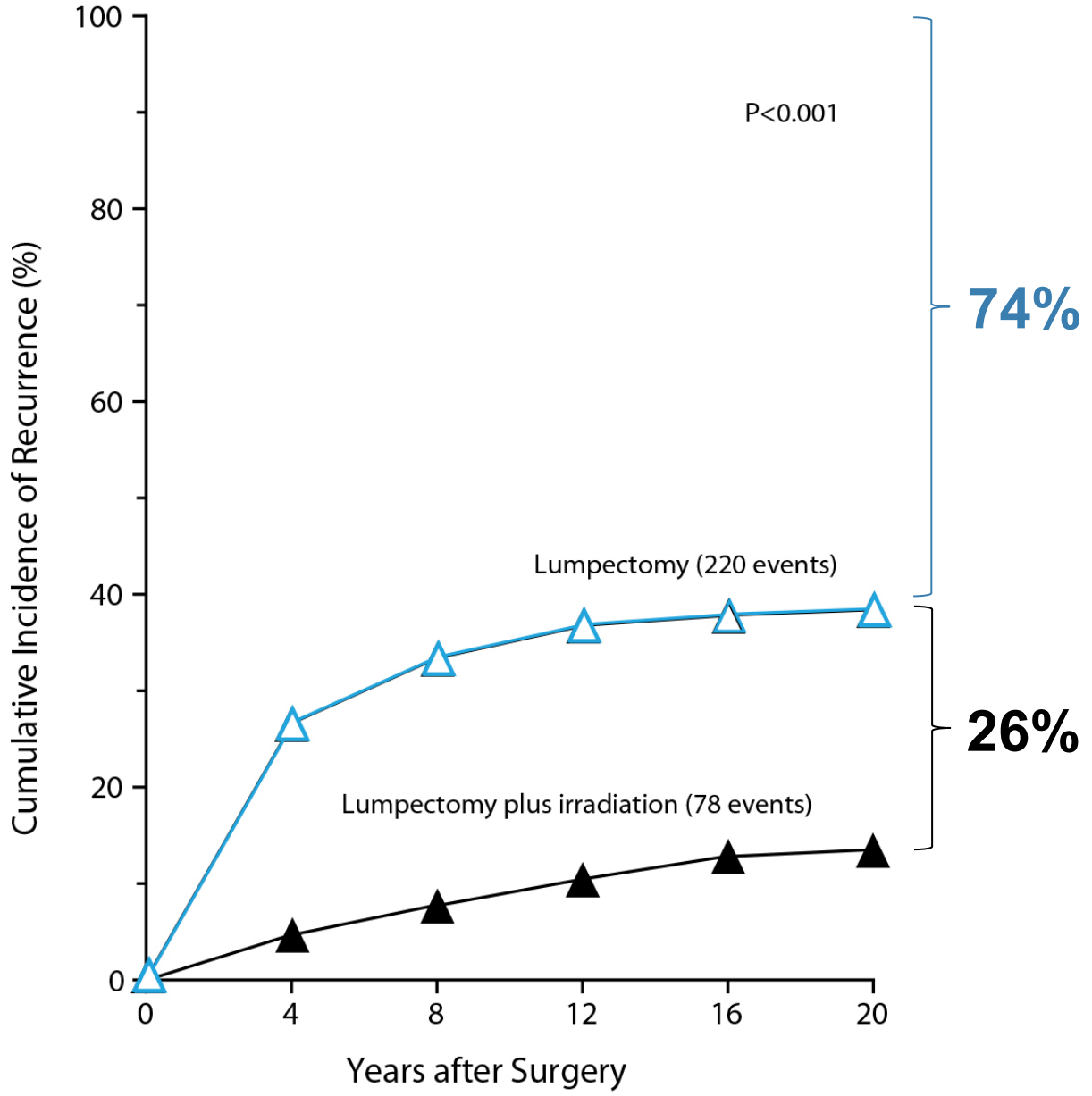


EBCTCG, N Engl J Med 1995;333:1444

Tailoring RT

- Efforts to eliminate RT
- Modifying RT

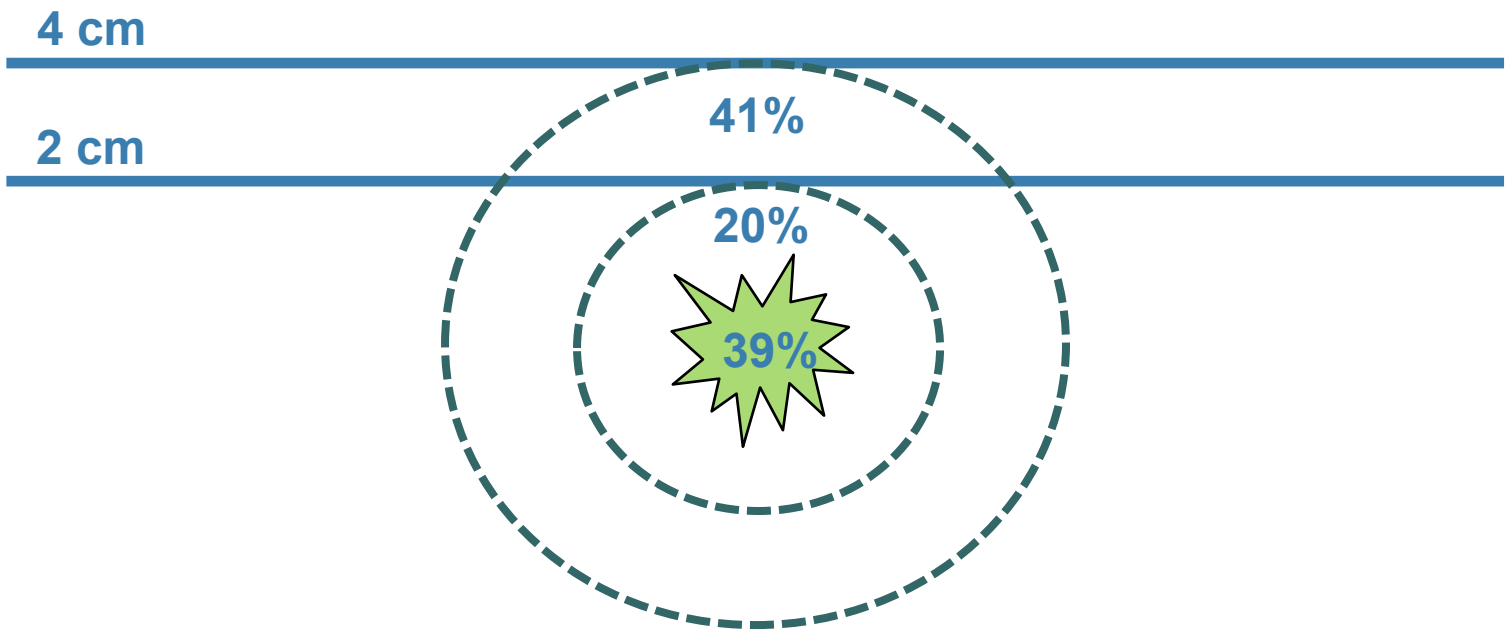
NSABP B-06: IBTR With and Without RT



Fisher B, N Engl J Med 2002;347:1233

Multifocality of "Localized" Breast Cancer

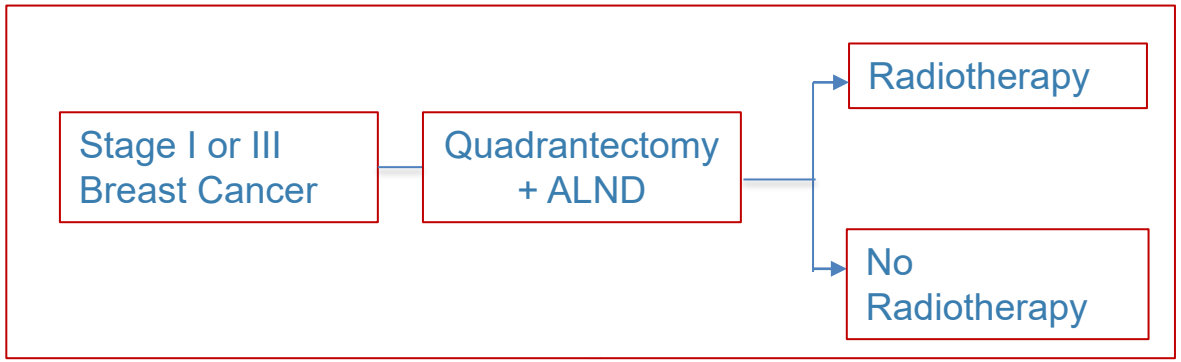
A negative margin does not imply that there is no residual tumor in the breast

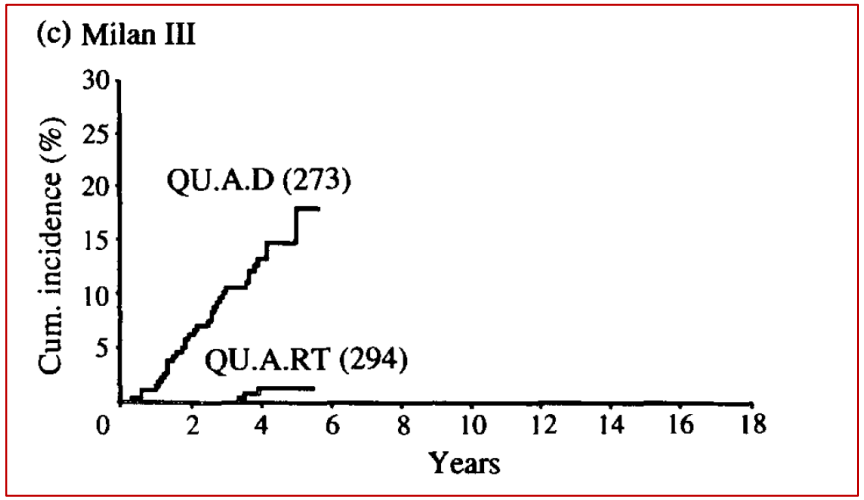


Holland R, Cancer 1985;56:979

Does Wider Resection Eliminate the Need for RT?

Milan III
(1987-1989)
567 patients
< 2.5 cm
N0, N+





Cumulative incidence
(median follow-up 6.8 years)

11.7% vs 3.3%
(p < 0.001)

No difference in OS

Veronesi U, Eur J Cancer 1995;31A:1574

Elimination of RT: NSABP B21

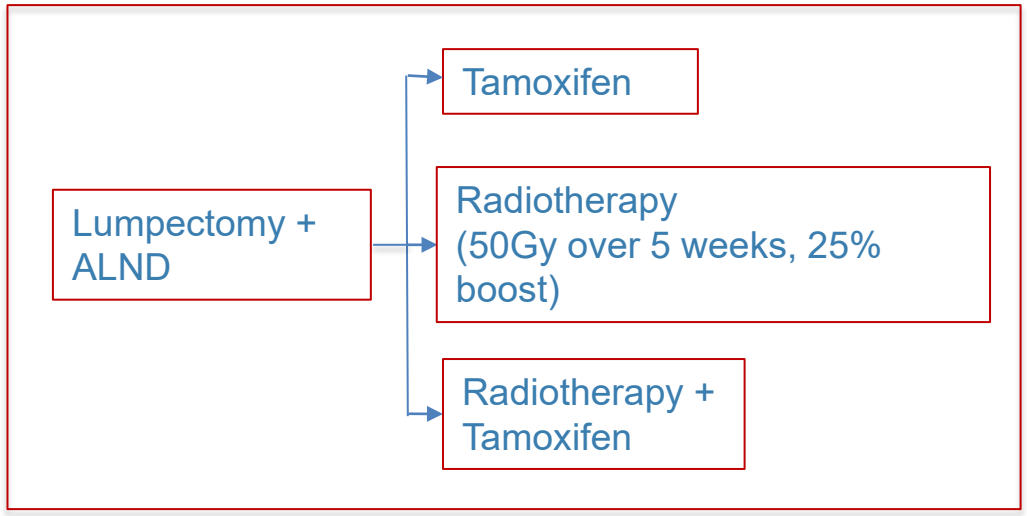
Impetus

- Smaller cancers due to uptake of screening mammography
- Use of tamoxifen as adjuvant therapy in node-negative cancer

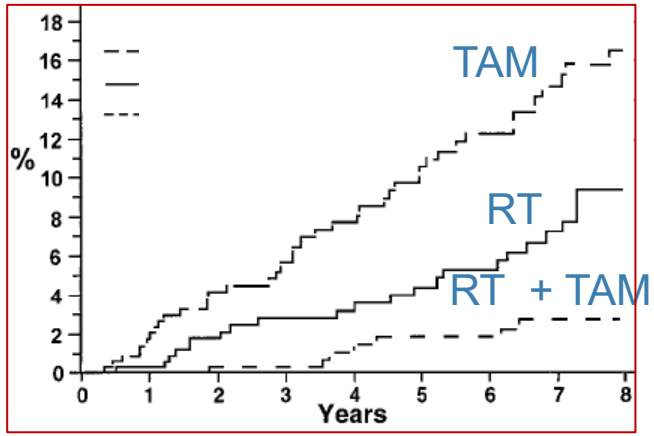
Is RT necessary in clinically low-risk breast cancer patients treated with tamoxifen?

NSABP-B21

1989-1998
n = 1009
T size < 1 cm
pN0



ER positive: 57%
ER unknown: 30%
ER negative: 13%



IBTR at a median follow-up 7.2 years:

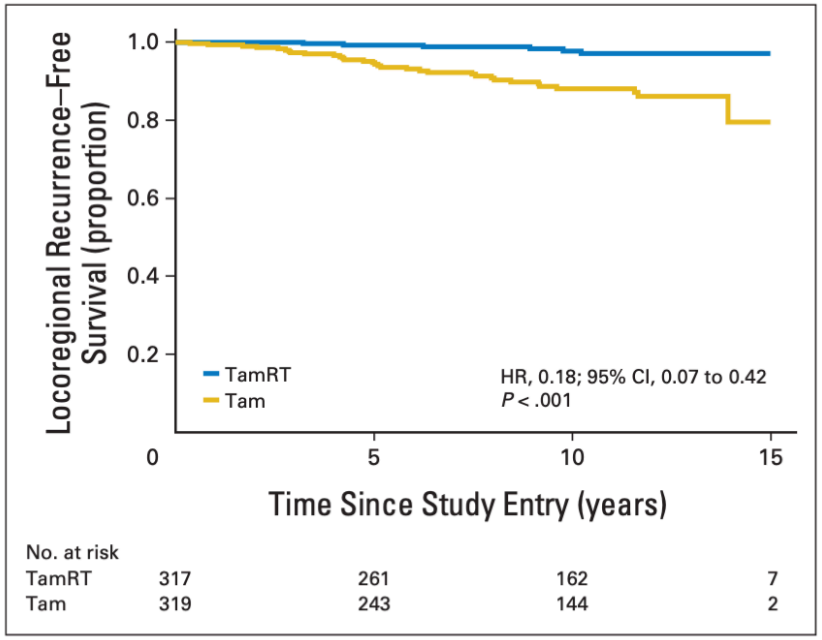
TAM only: 16.5%
RT only: 9.3%
RT + TAM: 2.8%
($p < 0.001$)

No difference in OS

Fisher B, J Clin Oncol 2002;20:4141

CALGB 9343

- 636 women (age ≥ 70 years) with T1N0 ER+ treated with lumpectomy (no tumor on ink), 36% ALND
- 10 patients had ER- tumors and 13 had tumors ≥ 2 cm
- Randomization: Tam (5 years) +/- RT
- **Median age: 75 years**



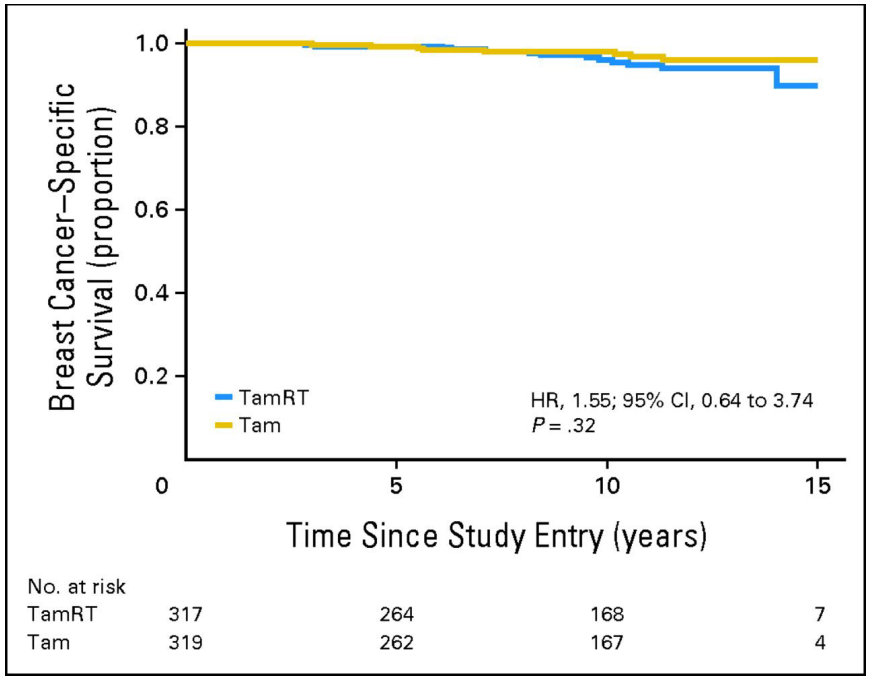
Median follow-up: 12.6 years

Locoregional recurrence
10% vs 2%
(p < 0.01)

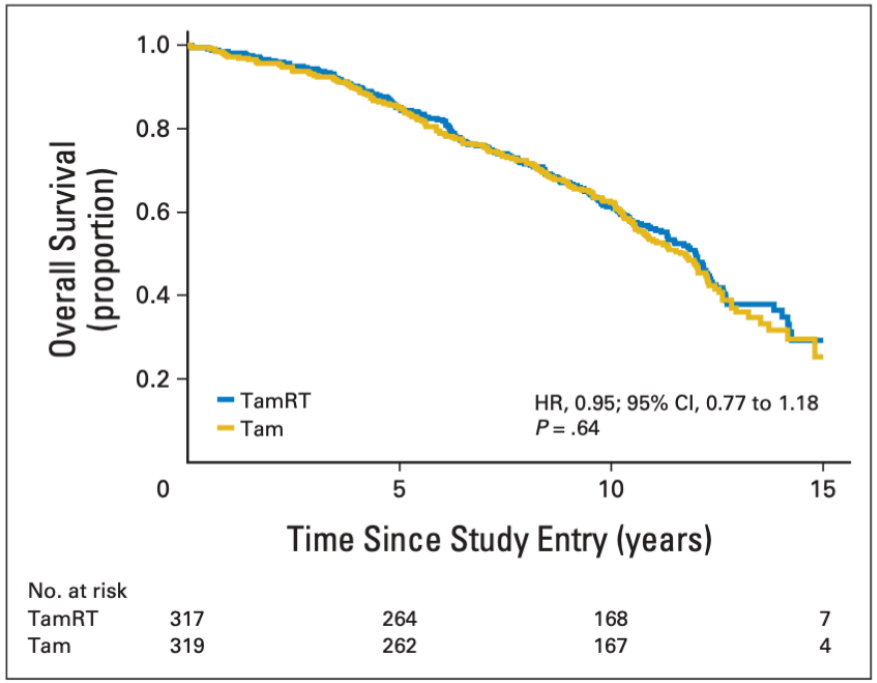
Hughes K, J Clin Oncol 2013;;31:2382

CALGB 9343: Survival Outcomes

Breast Cancer Specific Survival



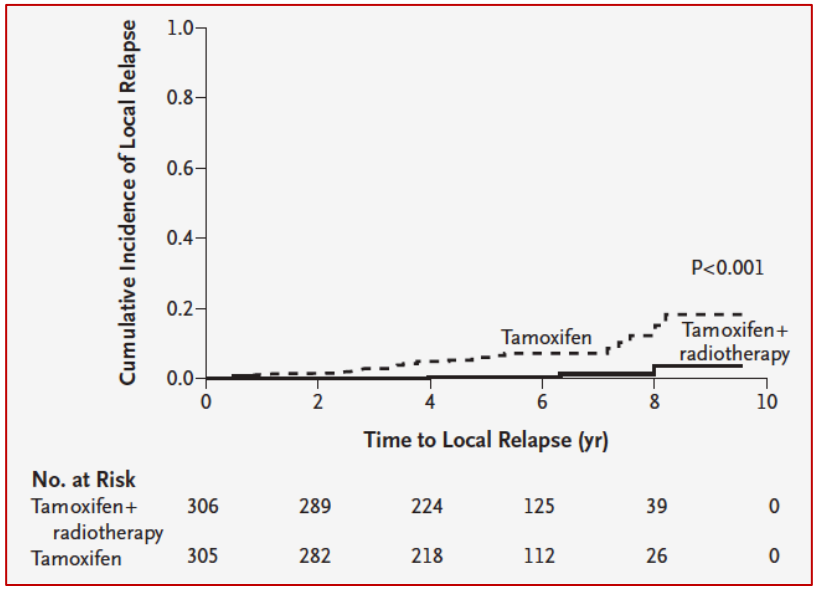
Overall Survival



Hughes K, J Clin Oncol 2013;;31:2382

TBC
(Toronto-British Columbia)

- 769 women **(age ≥ 50 years)** with T1-T2N0 (81% ER+) treated with lumpectomy (no tumor on ink)
- Randomization: Tam + RT (40Gy + boost) vs Tam alone
- **Median age: 68 years**



Median follow-up: 5.6 years

Local recurrence:
7.7% vs 0.6%
(p < 0.001)

DFS 84% vs 91%
(p = 0.004)

Fyles A, N Engl J Med 2004;351:963

Trials of Omission of RT With Adjuvant Systemic Therapy

Study	Sample size (n)	Inclusion criteria	Median follow-up (years)	Rate of local recurrence without RT (%)	Rate of local recurrence with RT (%)	Overall mortality
Toronto-British Columbia (TBC)	769	≥ 50 years T1-2N0	5.6	7.7	0.6	NS
BASO II	1135	< 70 years T1N0 ER+	10	7.5	0	NS
CALGB 9343	636	≥ 70 years T1N0 ER+	12.6	10	2	NS
ABCSG study 8A	869	≥ 50 years T1-2 (< 3 cm) N0 ER+	9.9	7.6	2.5	NS
PRIME II	1326	≥ 65 years T1-2 (< 3 cm) N0 ER+/PR+	10	9.8	0.9	NS

Montagna G, Clin Breast Cancer 2021;21:112

EBCTCG Meta-analysis

17 trials, 1081 women

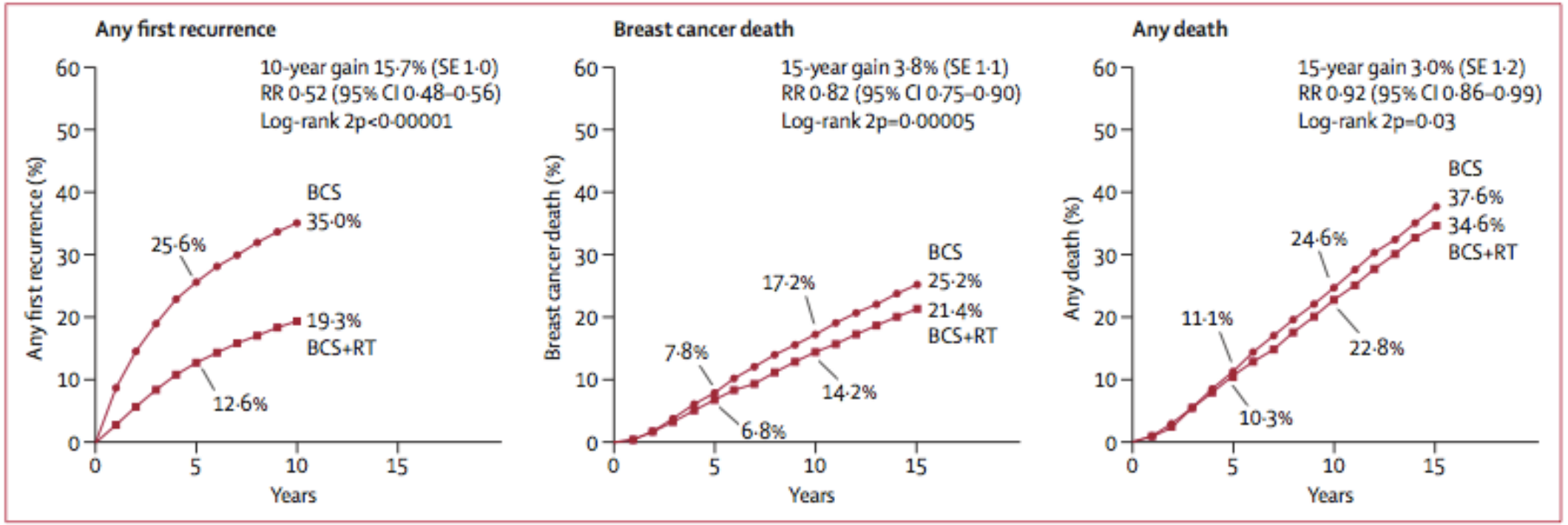


Figure 1: Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence and on 15-year risks of breast cancer death and death from any cause in 10 801 women (67% with pathologically node-negative disease) in 17 trials

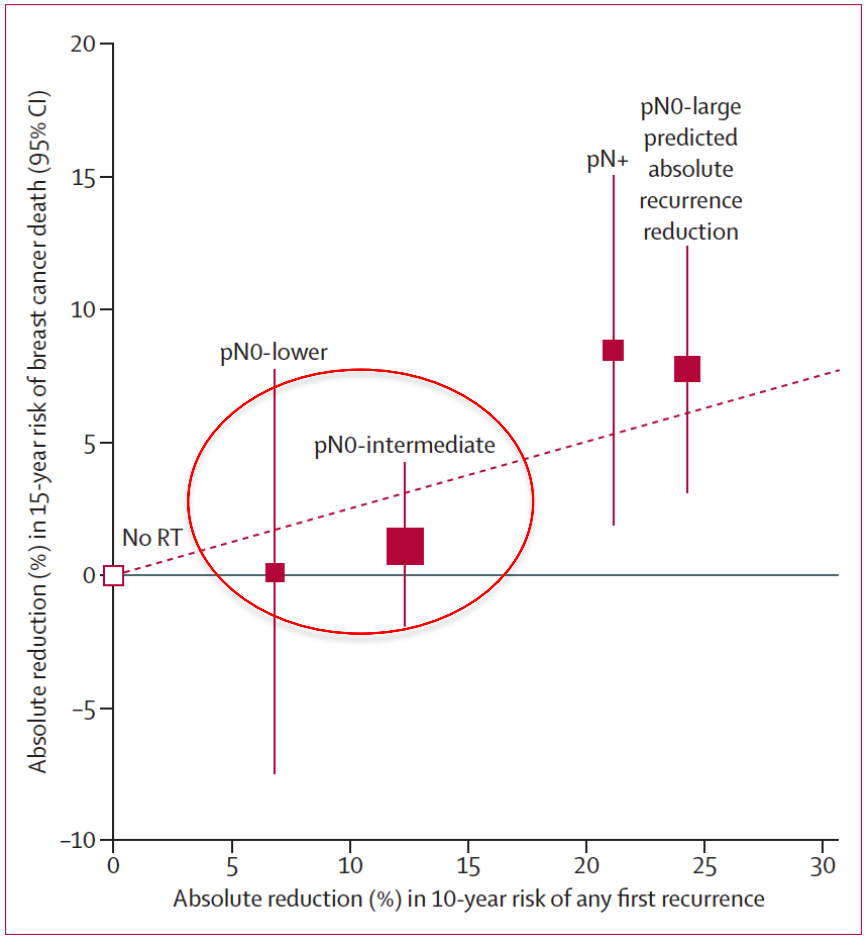
Addition of RT improved time to first recurrence, breast cancer-specific death, and overall survival

EBCTCG, Lancet 2011;378:1707

Relationship Between Local Control and Survival

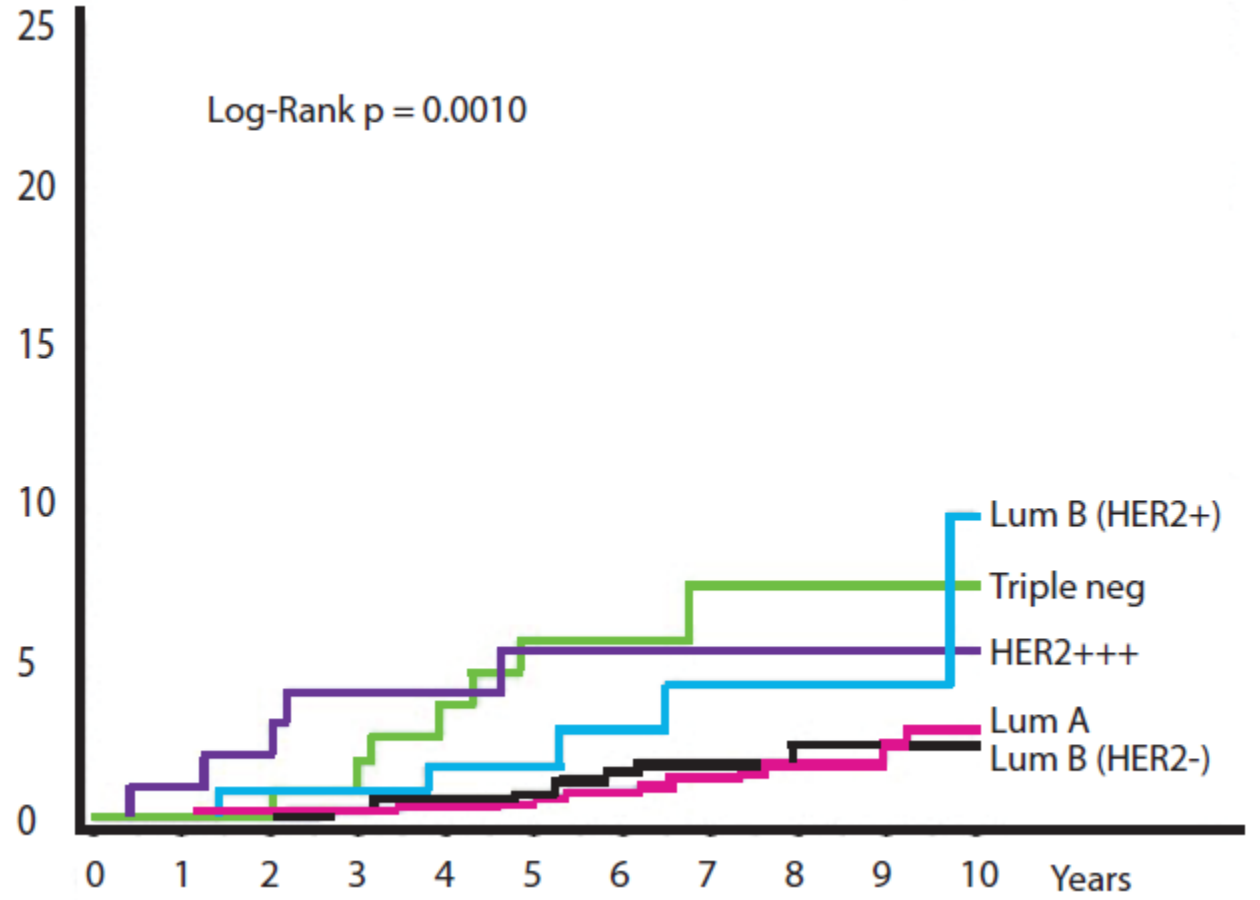
1 life saved for every 2-4 local recurrences prevented

- **OS benefit much clearer for node positive and high-risk node negative**
- **Less clear for low-risk node negative**



EBCTCG, Lancet 2005;366:2106

Locoregional Recurrence in T1mic, T1a, T1b Cancer by Subtype



Cancello G, Breast Cancer Res Treat 2011;127:713

Omission of RT Based on Biology: LUMINA

Eligible
T1N0, age ≥ 55 years
Grade 1 or 2
ER ≥ 1%, PR > 20%
HER2 negative
Ki 67 ≤ 13.25%

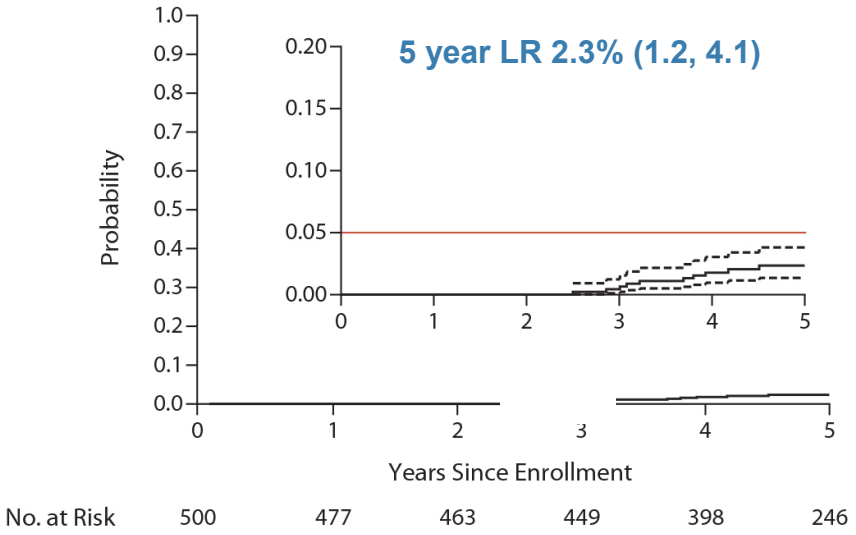
Design
Single arm, prospective
1º outcome: IBTR

Patient Characteristics (n = 500)
Median age: 67.1 years (12% < 60 years)
Median T size: 1 cm (49% 1.1-2 cm)
Grade: 66% Grade 1
Histology: 67% Ductal

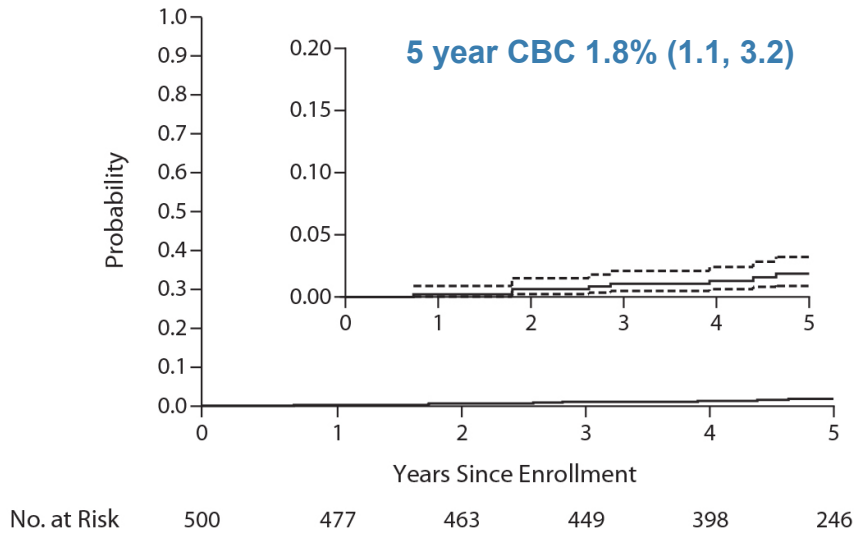
Whelan T, N Engl J Med 2023;389:612

LUMINA: Results

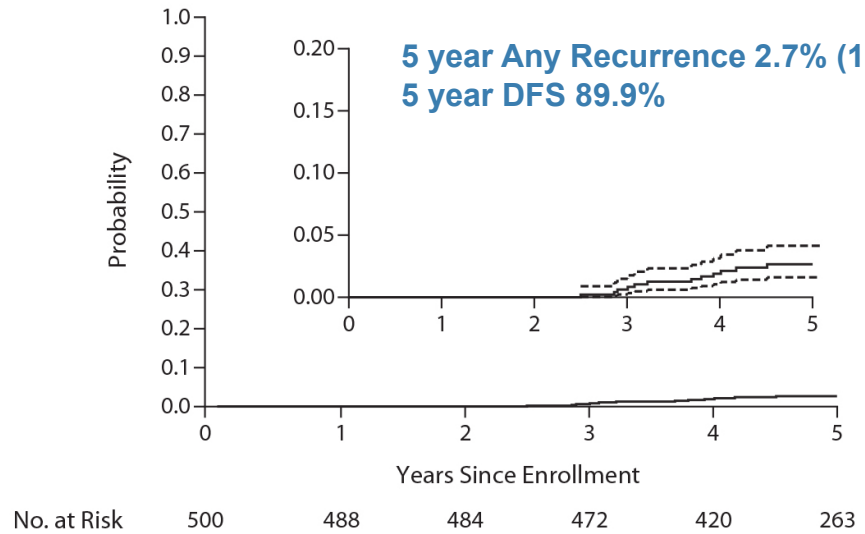
Local Recurrence



Contralateral Breast Cancer



Any Recurrence (local, regional, or distant)



Whelan T, N Engl J Med 2023;389:612

Omission of RT Based on Biology: IDEA

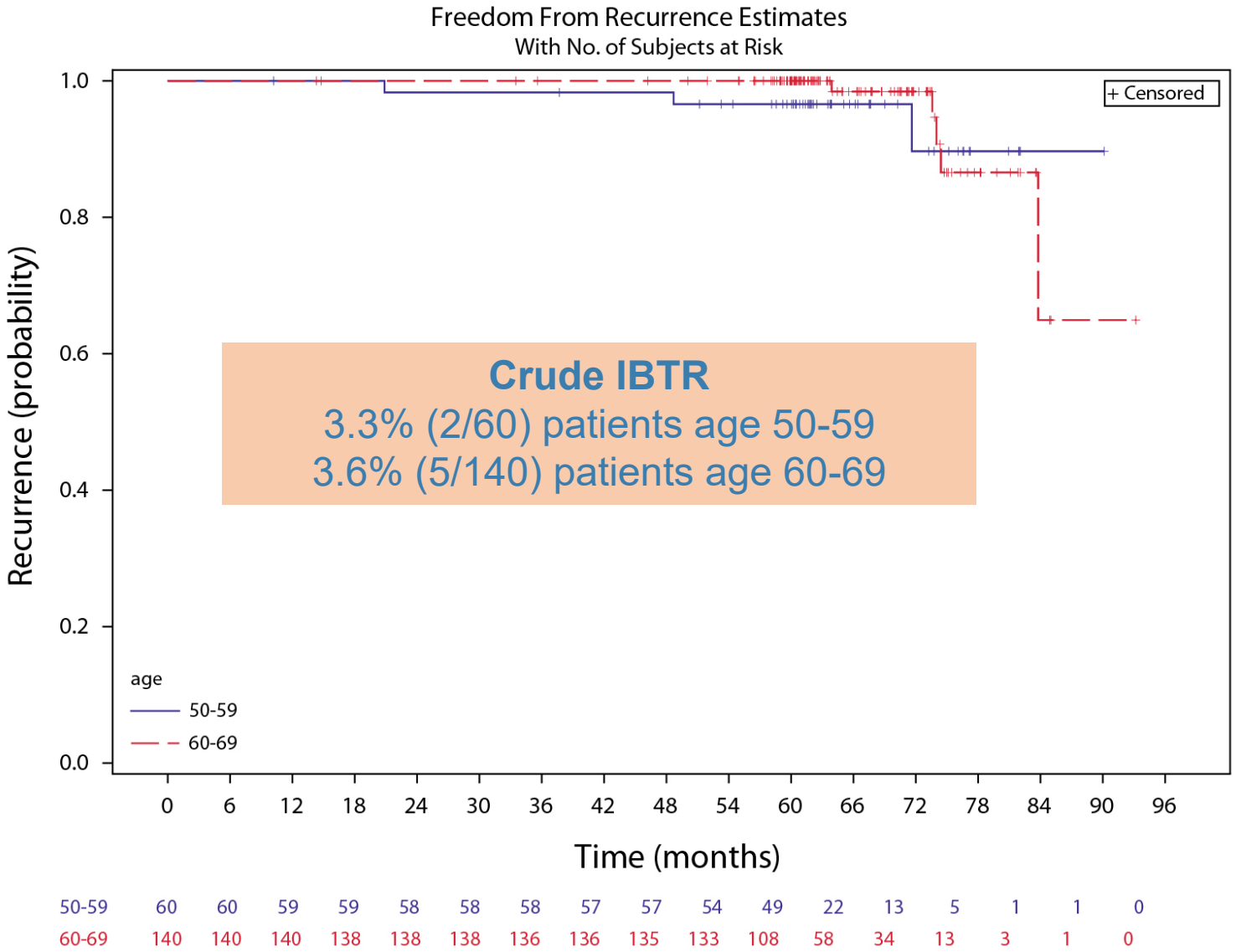
Eligible
pT1N0, age 50-69 years
Postmenopausal
ER+, PR+, HER2-
Margin ≥ 2 mm
Oncotype RS ≤ 18

Design
Single arm, prospective
1° outcome: 5 year IBTR

Patient Characteristics (n = 200)
Median age: 62 years (30% < 60 years)
Median T size: 0.9 cm
Grade: 43% Grade 1
Histology: 85% Ductal
Mean Oncotype RS: 11

Jagsi R, J Clin Oncol 2023;42:390

IDEA: Results



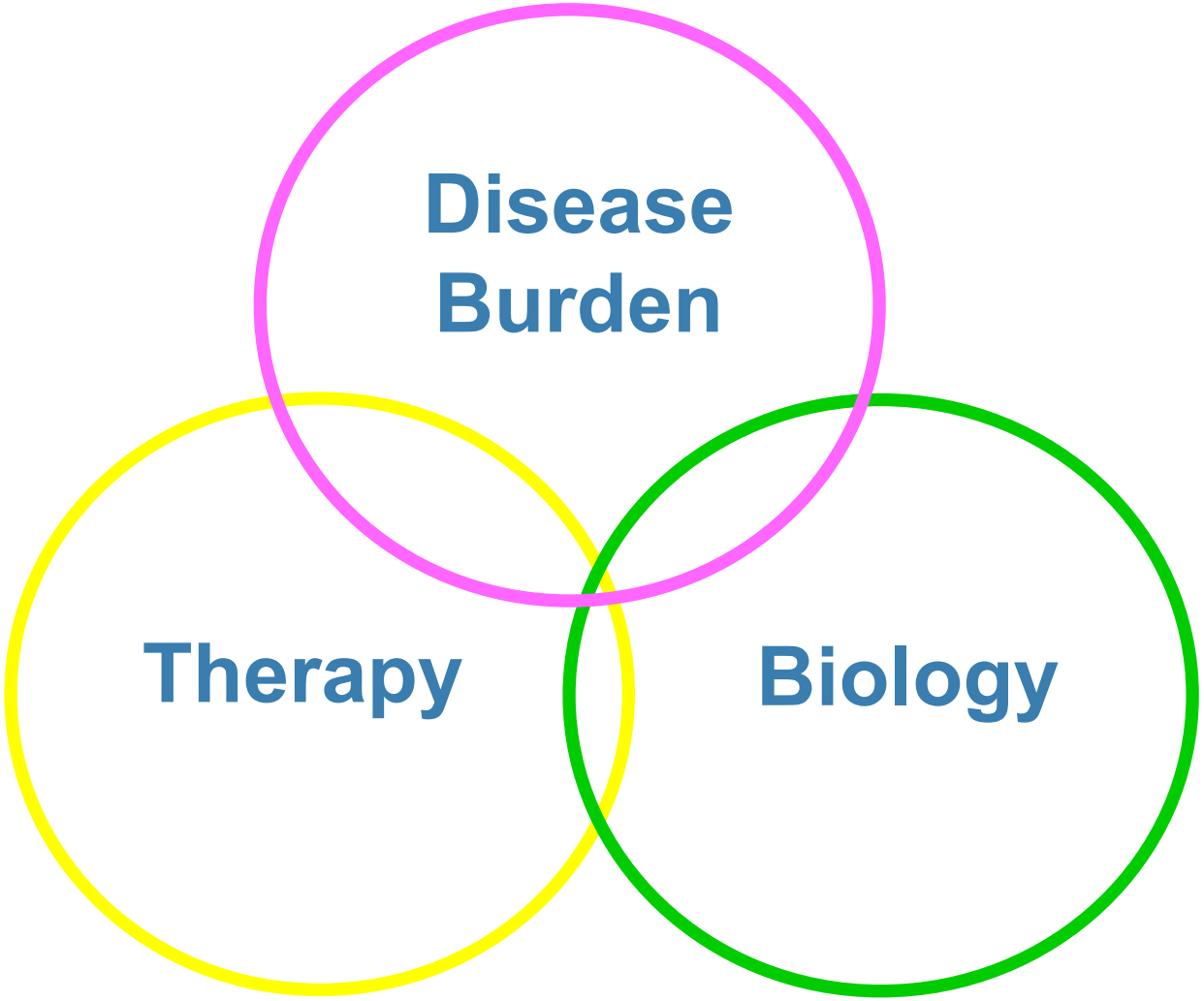
Jagsi R, J Clin Oncol 2023;42:390

Trials of Omission of RT Based on Biology

	Design	Begin	Country	n	Age	Inclusion criteria	
						Clinicopathological criteria	Subtype/Genomic Assay
LUMINA	Multicenter single-arm study (BCS + ET)	2013	Canada	500	≥ 55	pT1N0 Grade I-II Unifocal tumor	**Luminal A by IHC (ER ≥ 1%, PR > 20%, HER2-, Ki-67 ≤ 13.25%)**
IDEA	Multicenter single-arm study (BCS + ET)	2015	United States	200	50–69	pT1N0 Unifocal tumor	**ER/PR+, HER2- Oncotype-DX RS ≤ 18**
PRECISION	Multicenter single-arm study (BCS + ET)	2016	United States	690	50–75	pT1N0 Grade I-II	**ER+ (≥10%) or PR+, HER2- Prosigna (PAM50) ROR score low risk**
PRIMETIME	Multicenter single-arm study (BCS + ET)	2017	United Kingdom	1,550	≥ 60	pT1N0 Grade I-II	**ER/PR+, HER2- IHC4+C score very low**
EXPERT	Multicenter non-inferiority RCT (BCS + ET +/- RT)	2017	Australia/ New Zeeland	1,167	≥ 50	pT1N0 Unifocal tumor Grade I-II	**ER ≥ 10%, PR ≥ 10%, HER2- Prosigna (PAM50) ROR score ≤ 60**

Montagna G, Clin Breast Cancer 2021;21:112

What Determines Local Control?



Surgery in the Context of Multidisciplinary Care

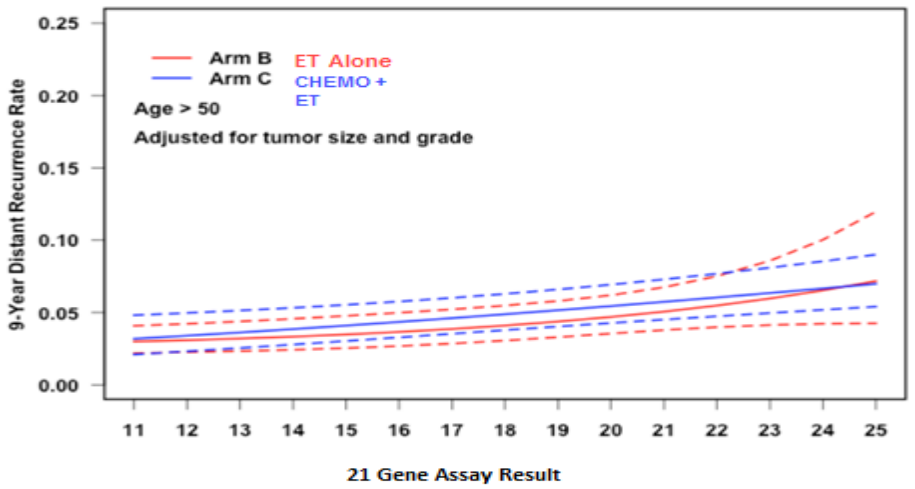
Is the primary tumor important for decision making?

Surgery of the axilla
Partial breast irradiation

Surgery of the Axilla 2024

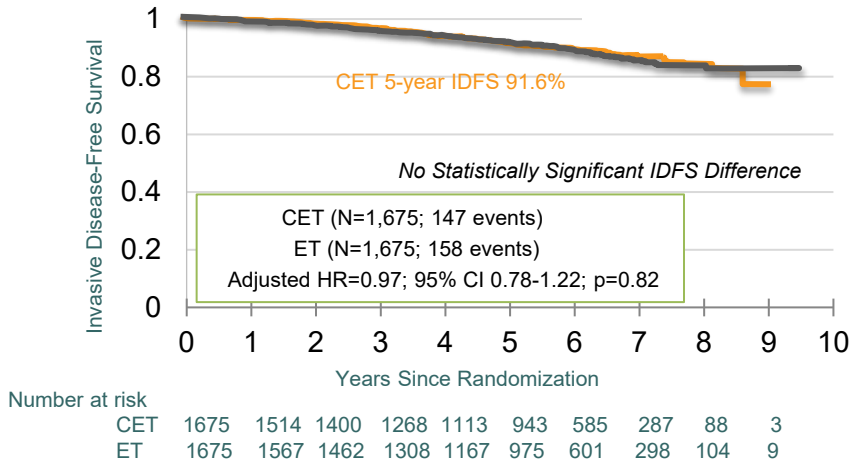
- Does not improve survival
- Is not necessary for local control in cN0
- Nodal status is not the determinant of systemic therapy in postmenopausal HER+/HER2- patients

TAILORx: RS 11-25



Sparano J, N Engl J Med 2018;379:111

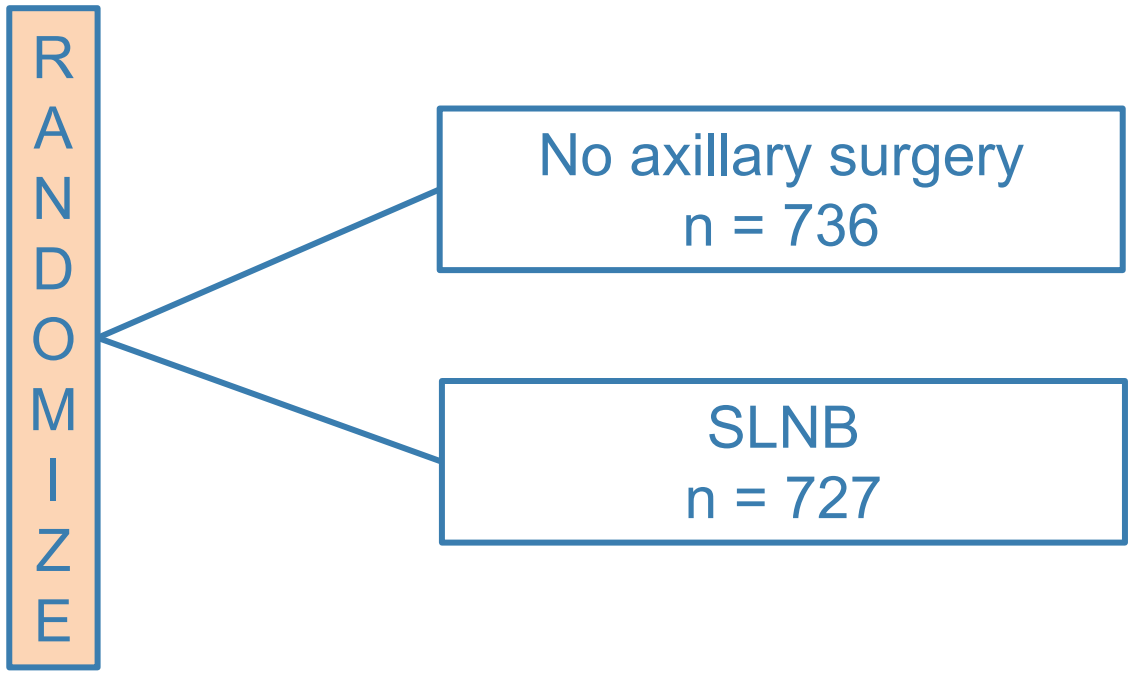
RxPonder: RS 0-25



Kalinsky K, N Engl J Med 2021;385:2336

SOUND Trial

cT1N0 cancer
Negative axillary US



81% ≥ 50 years of age
Median 60 years
78% ductal cancer
50% T1c
93% ER+, 93% HER2-

14% positive SLNs
9% macrometastases
0.6% > 3 positive nodes

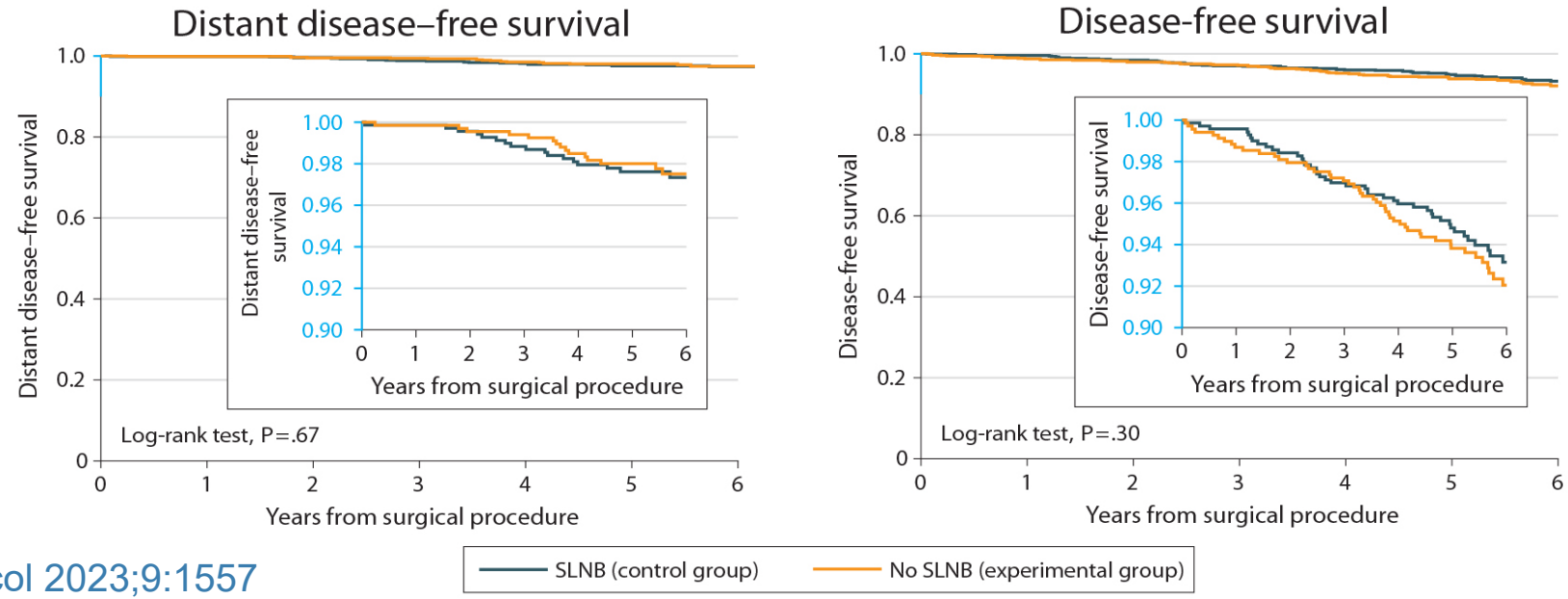
Gentilini O, JAMA Oncol 2023;9:1557

SOUND Trial

Median follow-up: 5.7 years

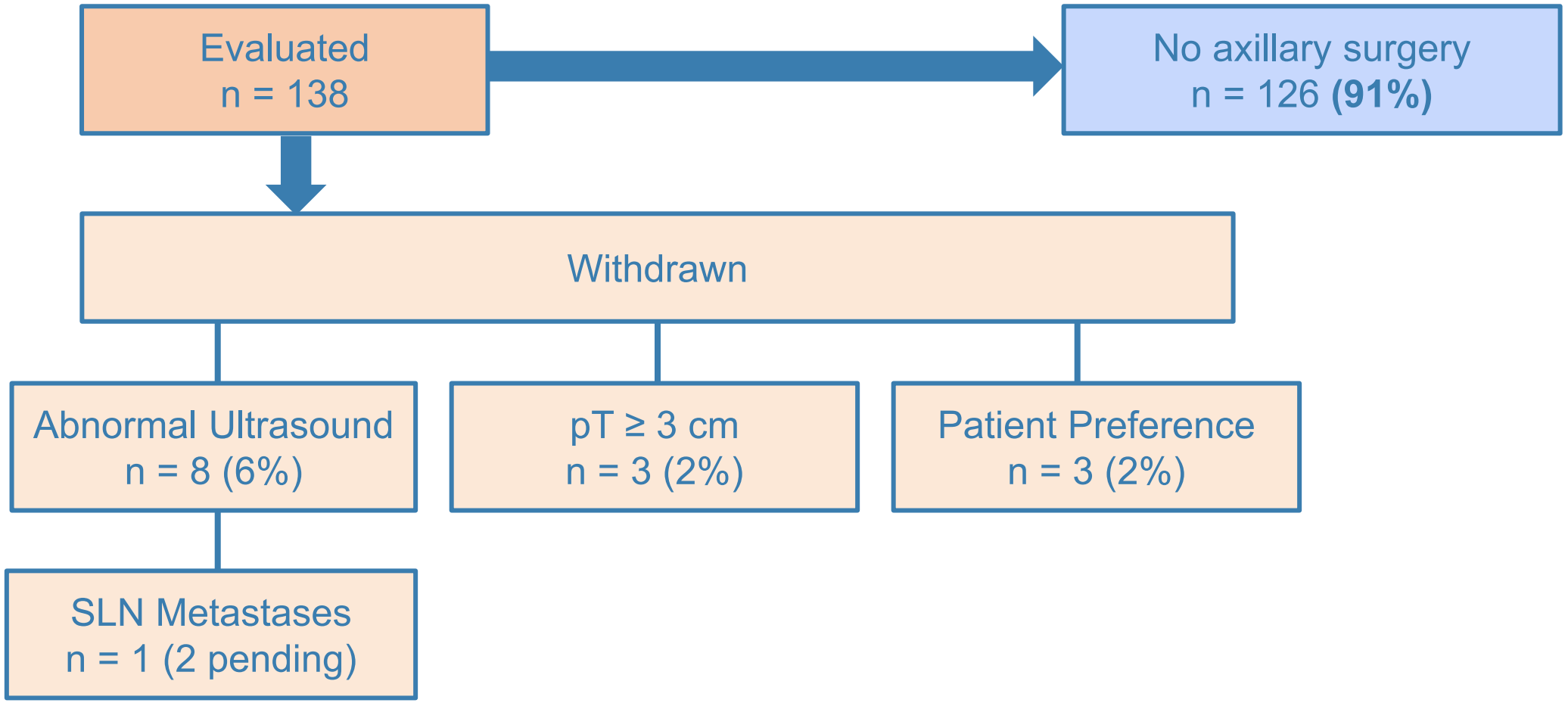
	No Axillary Surgery	SLNB	p value
Axillary recurrence	0.4%	0.4%	p = NS
Locoregional recurrence	1.6%	1.7%	p = NS
5 year DDFS	98%	97.7%	p = NS

Primary Endpoint: Non-Inferiority 5 year DDFS
HR 0.84; 90% CI 0.45-1.54 p = 0.024



Gentilini O, JAMA Oncol 2023;9:1557

Impact of SOUND Trial on Practice at MSKCC



Morrow M, unpublished

Randomized Trials: WBI vs APBI

Trial	Years	Patients (n)	EXP Arm	Age < 50 (%)	ER- (%)	Grade 3 (%)	T2 (%)	Systemic (endo/chemo%)	N+ (%)
Florence	2005-2013	520	30 Gy/5 IMRT	17	4	13	6	64/1.5	7
GEC-ESTRO	2004-2009	1184	32Gy/8 or 30.2/7 HDR or 50 Gy PDR	14	19	10	11	87/10	1
RAPID	2006-2011	2135	38.5 Gy/10 BID 3DCRT	12	8	17	NR	69/15	0
IMPORT LOW	2007-2010	2018	40 Gy/15 QD 3DCRT	0	5	9	0	91/5	2
B39	2005-2013	4216	38.5 Gy/10 BID 3DCRT (also 34 Gy/10 brachy)	39	19	N/R	9	NR	10

Randomized Trials: WBI vs APBI

Trial	Patients (n)	5 year IBTR WBI	5 year IBTR APBI	Absolute diff	Result	Toxicity	Follow-up
Florence	520	1.5	1.5	0%	NON-INF	WBI > PBI	5
GEC-ESTRO	1184	1.4	0.9	0.5%	NON-INF	WBI > PBI	7
RAPID	2135	1.7 2.8% @8yr	2.3 3% @8yr	0.6%	NON-INF	PBI > WBI	8.6
IMPORT LOW	2018	1%	1%	0%	NON-INF	WBI > PBI	6
B39	4216	3.9 (10 yr)	4.6 (10 yr)	0.7%	Not Equiv	WBI = PBI?	10

Randomized Trials: WBI vs APBI

2022 American Brachytherapy Society Selection Criteria for PBI

Age ≥ 45 years

Histology: Any

Receptors: Any

Extensive LVI: No

Nodes: Negative

T size ≤ 3 cm

Margin: No ink on tumor (invasive)

≥ 2 mm DCIS

Anderson B, Brachytherapy 2022;21:726

Conclusions

- Changes in our understanding of what determines local control, the detection of smaller tumors through increased uptake of screening mammography, and improvements in systemic therapy have allowed the de-escalation of both surgery and RT, reducing the burden of treatment for patients

Conclusions

- Even in the era of molecular medicine, primary tumor characteristics remain important in treatment selection
- Appropriate treatment selection requires multidisciplinary collaboration and an understanding of the entire therapeutic pathway, toxicity tradeoffs, and patient preference