

Landmark Studies in Breast Cancer

Post-Mastectomy Radiotherapy

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Table 1 Landmark randomized controlled trials supporting use of PMRT

Trial	N	Years	Follow-up	Menopausal status	Chemotherapy	OS			LRR		
						MRM (%)	MRM + RT (%)	P value	MRM (%)	MRM + RT (%)	P value
British Columbia	318	1979–1986	20	Pre	CMF	37	47	0.03	28	10	0.002
DBCG 82b	1,708	1982–1989	15	Pre	CMF	45	54	<0.001	32	9	<0.001
DBCG 82c	1,460	1982–1990	10	Post	Tamoxifen*	36	45	0.03	35	8	<0.001

*, tamoxifen required for only 1 year in DBCG 82c. PMRT, postmastectomy radiation therapy; OS, overall survival; LRR, locoregional recurrence; MRM, modified radical mastectomy; RT, radiation therapy; CMF, cyclophosphamide, methotrexate, and fluorouracil; Pre, premenopausal

Table 2 Important trials supporting use of PMRT in lymph node positive (pN+) breast cancer patients

Trial	N	Years	Follow-up (years)	BCM			Any recurrence			LRR		
				No RT (%)	RT (%)	P value	No RT (%)	RT (%)	P value	No RT (%)	RT (%)	P value
EBCTG meta-analysis (pN+)	3,131	1964–1986	10	66.4	58.3	0.001	62.5	51.9	<0.00001	26.0	8.1	<0.00001
EORTC 22922*	4,004	1996–2004	10.9	14.4	12.5	0.02	22.9	19.4	0.015	9.5	8.3	–

Any recurrence defined as any first breast recurrence which includes local/regional recurrence, distant progression, second ipsilateral breast cancer or death due to breast cancer. *, in EORTC 22922, only 955 patients underwent mastectomy and a separate subanalysis of outcomes not performed. PMRT, postmastectomy radiation therapy; DNR, did not report.

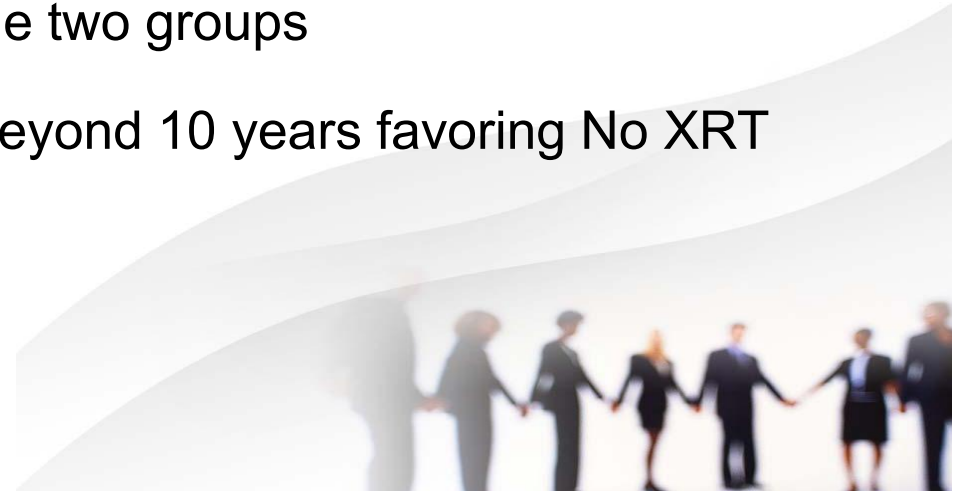
Table 3 Important randomized controlled trials supporting use of RT in lymph node negative (pN0) patients

Trial	N	Years	Follow-up (years)	DFS			OS		
				No RT (%)	RT (%)	P value	No RT (%)	RT	P value
EORTC 22922	4,004	1996–2004	10.9	72.1	69.1	0.04	80.7	82.3	0.06
MA-20*	1,832	2000–2007	9.5	77.0	82.0	0.01	81.8	82.8	0.11
Fourth Military Medical University (China)**	681	2001–2006	7.2	74.6	88.3	0.02	78.7	90.4	0.03

*, MA-20 was not a PMRT trial, but still informs radiation in lymph node negative patients. **, Fourth Military Medical University investigated triple negative stage I–II breast cancer patients with 86.1% being node negative. RT, radiation therapy; DFS, disease-free survival; OS, overall survival.

❖ Cuzick's Meta-analysis: 1987

- 3400 patients
- Included all 8 randomized trials (good and bad) of **radical** mastectomy
- Few trials started as early as 1950s
- Randomization by envelope method
- 1683 No XRT v/s 1679 XRT
- 10 year all cause mortality (N=3400): **No difference** in the two groups
- >10 years (N=1400): difference increased continuously beyond 10 years favoring No XRT
- Cause of death was not available



❖ Cuzick's Meta-analysis: 1994

- 7941 (10 RCTs), with 3363 (radical, 6 trials) & 4579 (simple, 4 trials)
- No chemotherapy given in adjuvant setting
- **Standardized mortality ratios** were compared between two treatment arms

Table 1. Details of Trials

Trial	Period of Entry	Date of Last Follow-Up	Type of Therapy	Dose (Gy)	No. of Fractions	Duration (days)	Biological Dose (ret ^{1/2})
Radical mastectomy ± XRT							
Manchester Q ³	1949-52	12/82	250 kV	35.0-40.0	15	21	1,438-1,693
Manchester P ³	1952-55	12/82	250 kV	32.5-42.5	15	21	1,335-1,746
Oslo I ²	1964-68	12/87	200 kV	18.0-36.0	20	28	681-1,362
Oslo II ²	1968-72	12/87	⁶⁰ Co	50.0	20	28	1,689
Heidelberg ¹⁴	1969-72	10/89	⁶⁰ Co	54.0	30	42	1,905
Stockholm ⁵	1971-76	12/89	Nodal, ⁶⁰ Co	45.0	25	35	1,406*
Simple mastectomy ± XRT							
Manchester Regional I ¹⁵	1970-75	4/91	300 kV	37.0	15	21	1,493
			or nodal (4 meV)	40.0	15	21	1,464 (1,211†)
				30.0	15	21	
CRC ⁴	1970-75	12/91	Ortho or meV	32.5-46.0	—	21-42	1,335-1,483
				35.7-50.6	—	21-42	1,306-1,453
NSABP-B04 ¹⁶	1971-74	12/86	meV	40.0-50.0	25	35	1,224-1,530
Edinburgh ⁶	1974-79	8/92	4 meV	42.5	10	28	1,661

Abbreviations: ret, rad equivalent therapy; XRT, radiotherapy; Ortho, orthovoltage regimen; meV, megavoltage regimen.

*Chest wall, 10-15 meV.

†Chest wall, 300 kV.



Survival favors No XRT

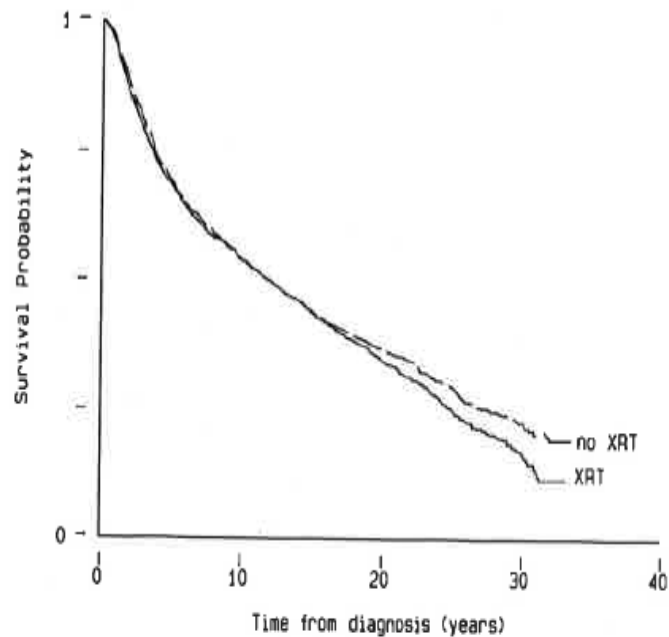


Fig 1. Combined survival curves according to allocated treatment for trials using radical mastectomy.

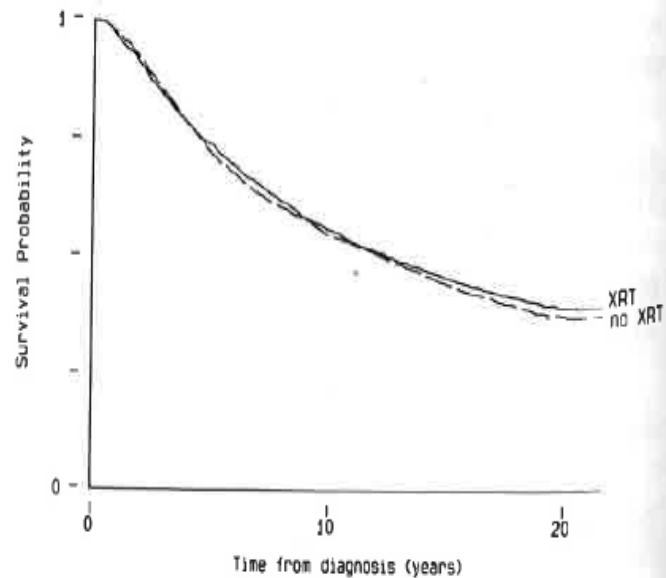


Fig 2. Combined survival curves according to allocated treatment for trials using simple mastectomy.

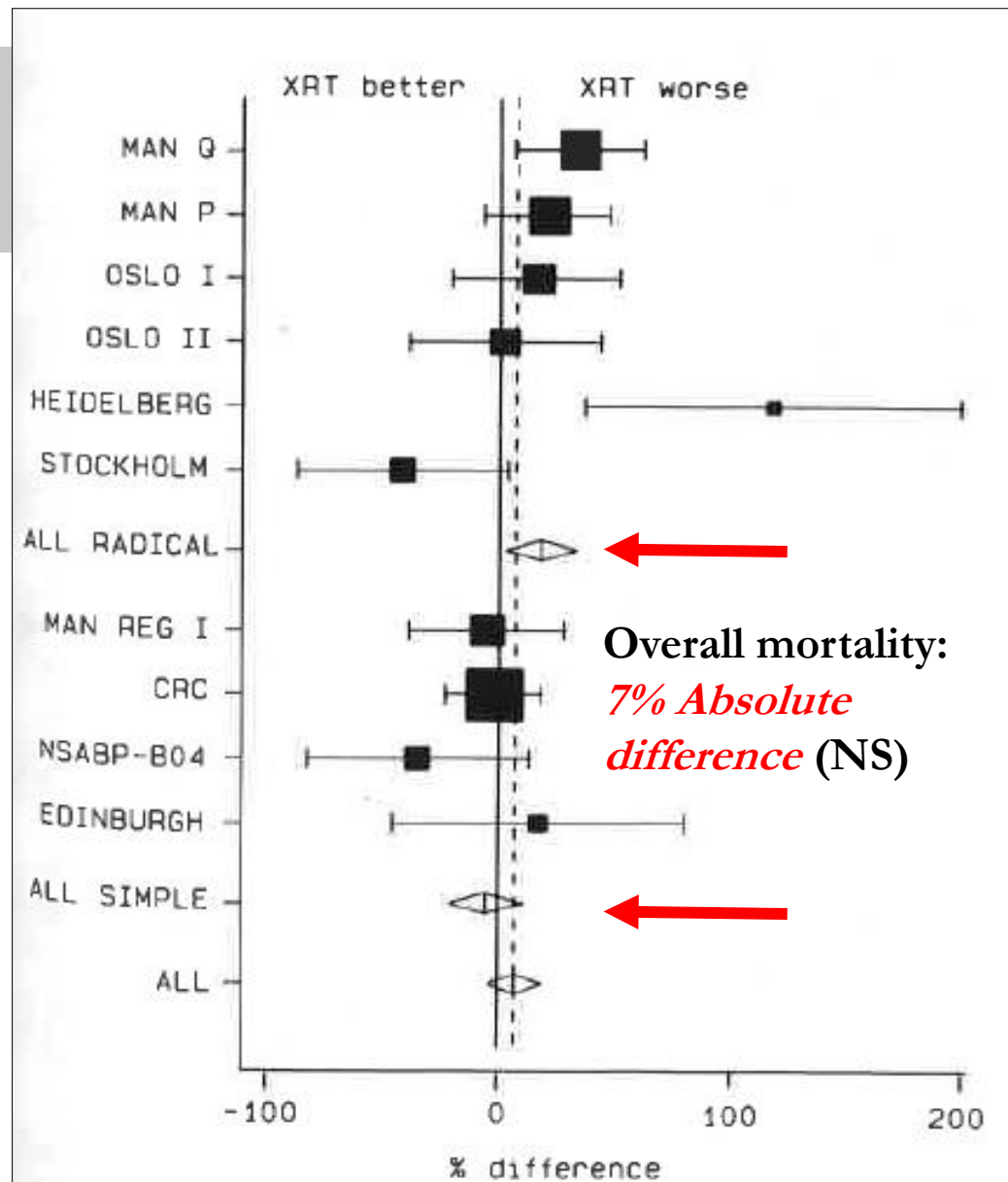


Fig 3. Percentage difference in the death rates and 95% CI for all causes after 10 years.

Overall SMR for cardiac death: 1.62-1.82

Conclusion-

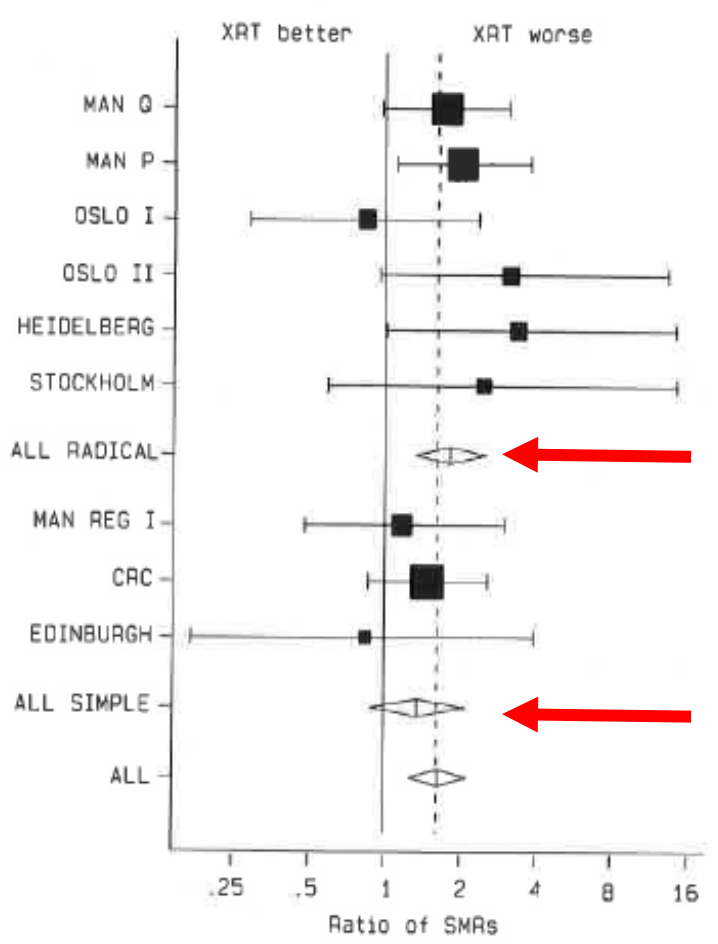


Fig 4. SMRs (radiotherapy/no radiotherapy) and 95% CIs by trial for cardiac mortality (after 10 years).

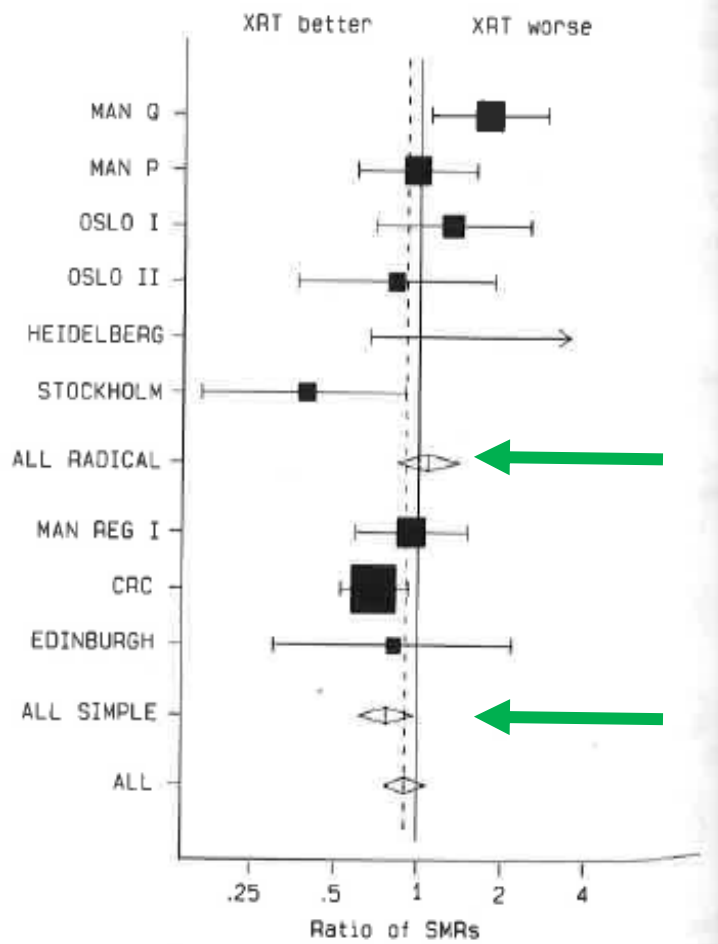


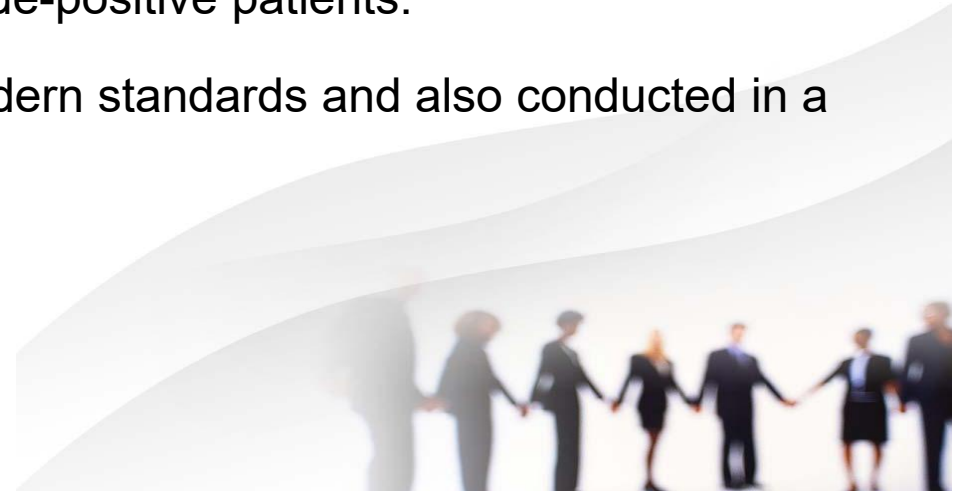
Fig 5. SMRs (radiotherapy/no radiotherapy) and 95% CIs by trial for breast cancer mortality (after 10 years).

- Difference in OS had reduced compared to last analysis (1987)
- Largely due to contribution of more recent trials which even increased OS
- Major contributor for excess cardiac deaths due to older techniques (large fraction size, cobalt, kilovoltage, IMN irradiation) and receipt of high doses to the coronaries
- Emphasized individual treatment planning and avoiding large fraction sizes



❖ Danish 82b & 82c Trials (NEJM, 1997)

- RCTs conducted in Denmark with a larger sample size and rigorous design
- Enrolled high-risk, node-positive breast cancer patients
- Compared PMRT + systemic therapy vs systemic therapy alone
- A significant reduction in locoregional recurrence, leading to improved overall survival at 10 years with an absolute mortality reduction ~9%
- Provided the earliest high-quality evidence that PMRT reduces mortality in node-positive disease → foundational evidence for recommending PMRT in high-risk/node-positive patients.
- However, systemic therapy regimens used are outdated by modern standards and also conducted in a homogeneous population (generalizability limits)



82b

- 1708 Premenopausal
- Stage II & III
- After MRM
- N0 and N+
- 9 # CMF vs. 8 # CMF +RT

82c

- 1375 Postmenopausal
- Stage II & III
- After MRM
- 10-15% were LABC/LOBC
- Tam x 1 yr vs. Tam x 1 yr + RT

- Median number of axillary nodes removed: **7**
- Radiotherapy protocol:
 - RT to the chest wall + IMC using electrons
 - SCF/AX using anterior photons
 - Megavoltage (50Gy/25#) or 250kv orthovoltage (36Gy/20# in 7.5%)

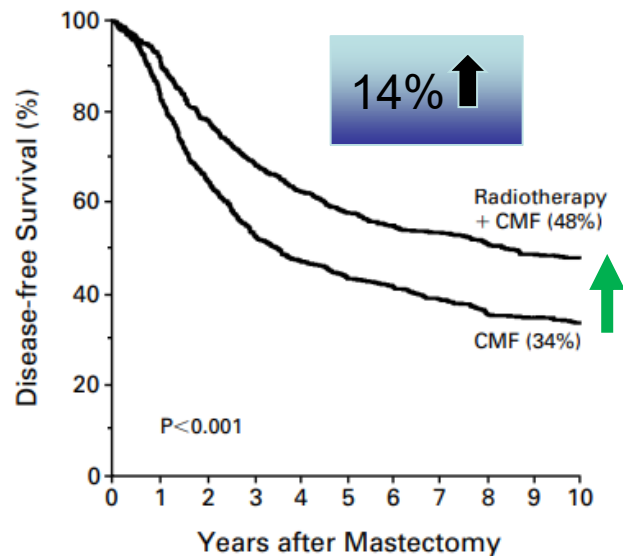


TABLE 2. TYPES OF FIRST RECURRENCES OR EVENTS.

TREATMENT	NO. OF PATIENTS	DISTANT METASTASES ALONE	LOCOREGIONAL RECURRENCE		OTHER EVENTS*	CENSORED OBSERVATIONS†
			ALONE OR WITH DISTANT METASTASES	ALONE		
			number of patients (percent)			
Radiotherapy + CMF	852	287 (34)	75 (9)	44 (5)	50 (6)	440 (52)
CMF alone	856	219 (26)	277 (32)	221 (26)	37 (4)	323 (38)
All patients	1708	506 (30)	352 (21)	265 (16)	87 (5)	763 (45)

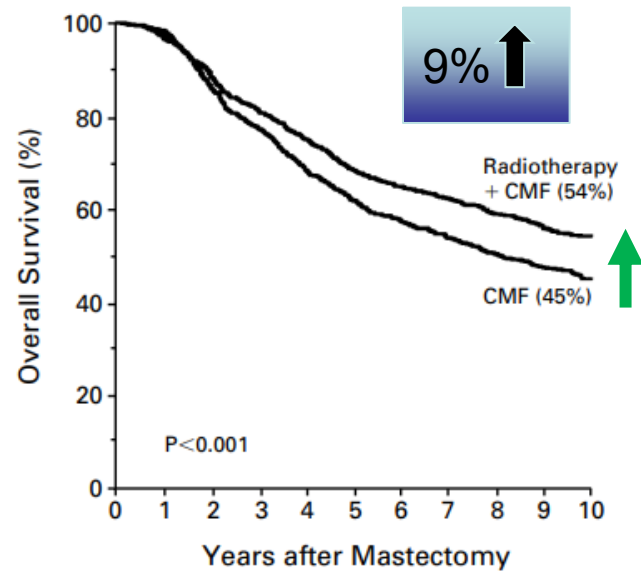
*Other events were other malignant disease and death without recurrence.

†Censored observations indicate patients without recurrences or other events.



Radiotherapy + CMF	852	643	505	429	308	102
CMF	856	537	382	327	216	74

Figure 1. Kaplan-Meier Estimates of Disease-free Survival among Women Treated with Radiotherapy plus CMF and CMF Alone. Values in parentheses are disease-free survival at 10 years.



Radiotherapy + CMF	852	755	641	555	392	188
CMF	856	738	587	494	329	163

Figure 2. Kaplan-Meier Estimates of Overall Survival among Women Treated with Radiotherapy plus CMF and CMF Alone. Values in parentheses are overall survival at 10 years.

82B

TABLE 3. ESTIMATED DISEASE-FREE SURVIVAL AND OVERALL SURVIVAL.*

VARIABLE	10-YR ACTUARIAL DISEASE-FREE SURVIVAL		10-YR ACTUARIAL OVERALL SURVIVAL	
	RADIOTHERAPY + CMF	CMF ALONE	RADIOTHERAPY + CMF	CMF ALONE
	percent			
All patients	48	34	54	45
Age (yr)				
<40	44	26	55	38
40-49	54	36	59	48
50-59	40	34	45	45
Tumor size (mm)				
<21	57	45	67	58
21-50	43	28	47	38
>50	37	22	40	33
No. of nodes removed				
0-3	42	38	58	48
4-9	50	32	55	45
>9	46	34	49	45
No. of positive nodes				
None	74	62	82	70
1-3	54	39	62	54
>3	27	14	32	20
Frequency of positive nodes (%)				
<34	65	49	70	63
34-67	44	31	51	46
>67	27	15	37	20
Histopathological classification of tumor†				
Ductal	48	32	54	43
Lobular	36	41	45	53
Medullary	65	54	66	65
Grade of anaplasia (ductal carcinoma only)				
Grade I	63	47	71	62
Grade II	46	29	52	40
Grade III	35	20	39	27

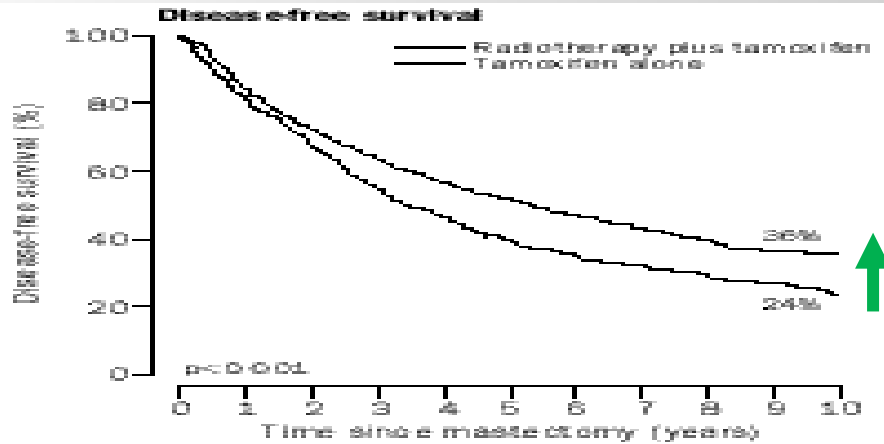
82C

1469 Randomised



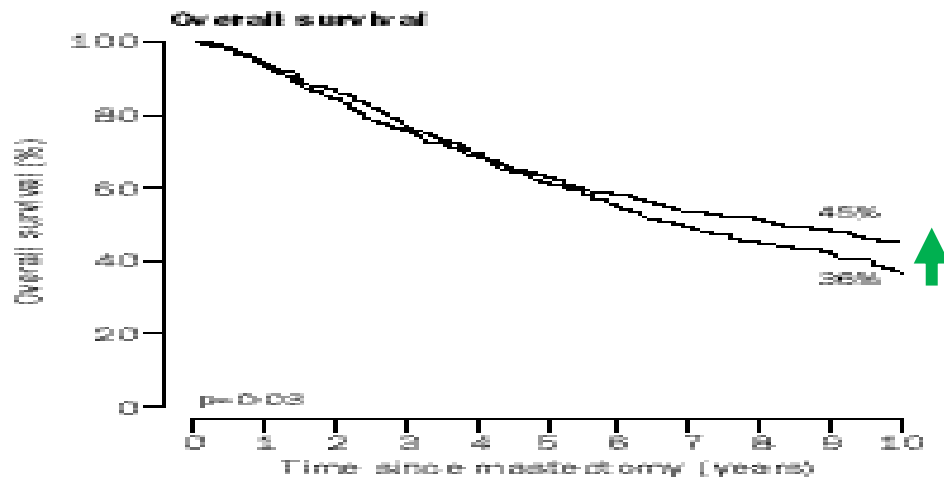
686 RT + Tam

689 Tam Only



Patients at risk

Radiotherapy plus tamoxifen	686	485	373	295	194	62
Tamoxifen only	689	465	307	226	150	39

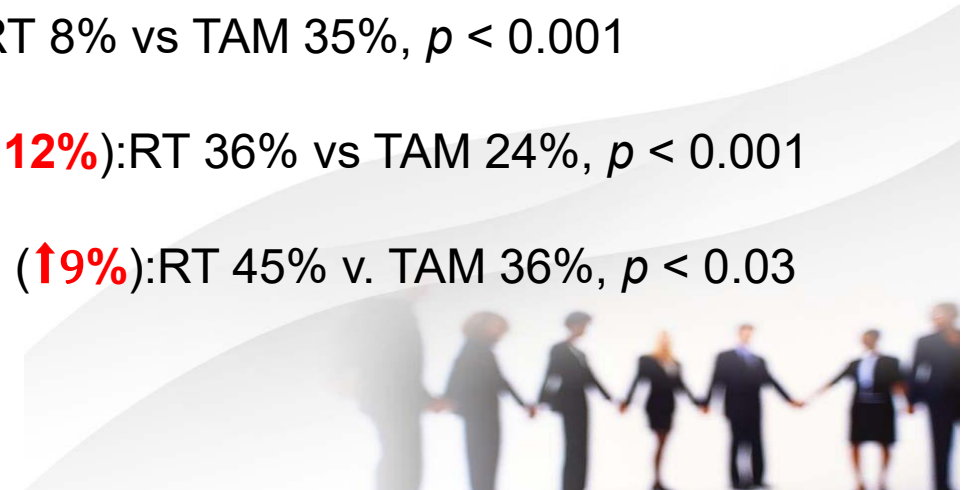


Patients at risk

Radiotherapy plus tamoxifen	686	580	469	358	265	175
Tamoxifen only	689	568	479	378	281	136

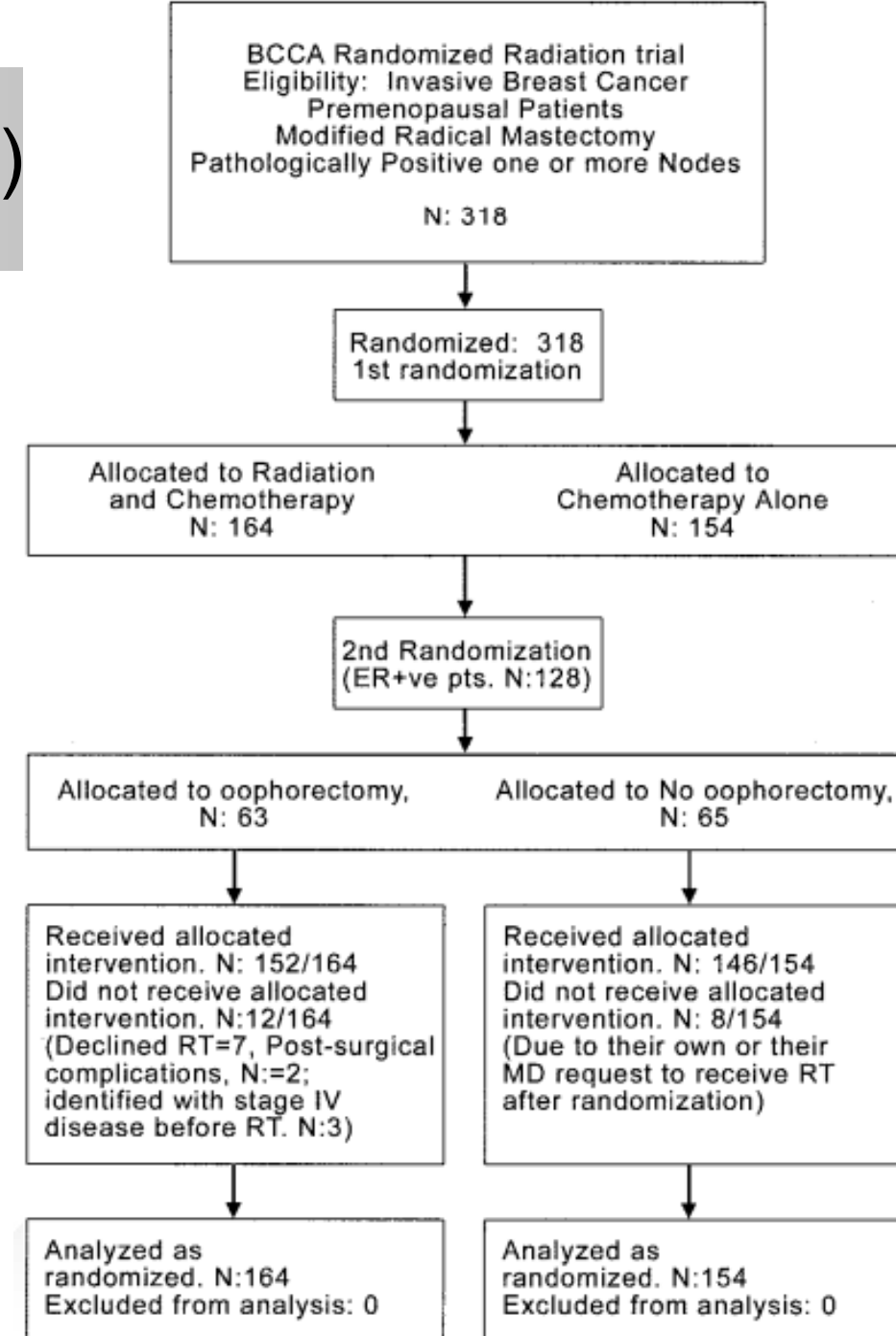
Site of first recurrence	Radiotherapy plus tamoxifen (n=686)	Tamoxifen only (n=689)	All patients (n=1375)
Distant metastases only	269 (39%)	169 (25%)	438 (32%)
Locoregional only	30 (4%)	203 (29%)	233 (17%)
Distant metastases and locoregional	22 (3%)	39 (6%)	61 (4%)
All recurrences	321 (47%)	411 (60%)	732 (53%)

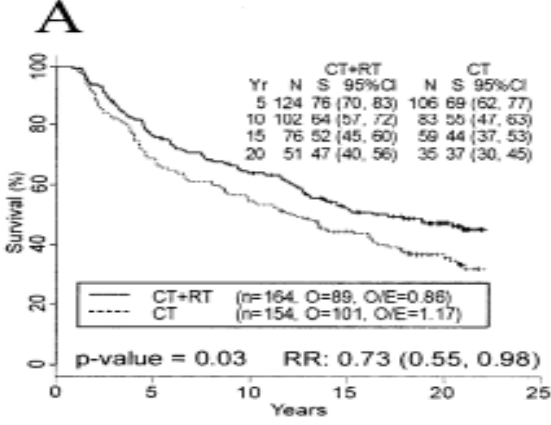
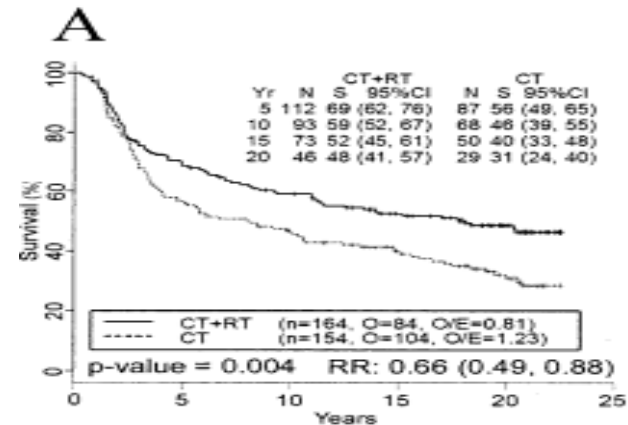
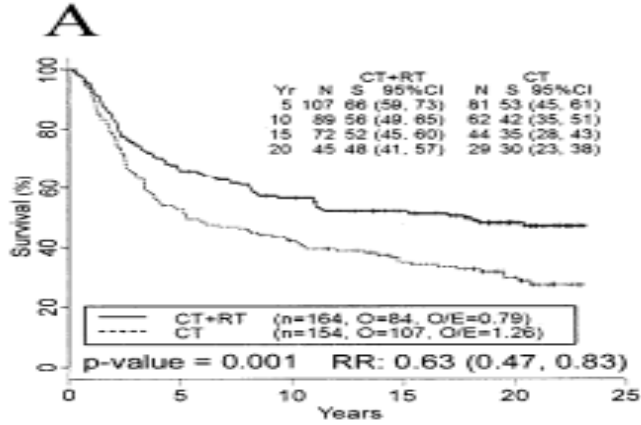
- LRF (**↓27%**): RT 8% vs TAM 35%, $p < 0.001$
- 10-year DFS (**↑12%**): RT 36% vs TAM 24%, $p < 0.001$
- Overall survival (**↑9%**): RT 45% v. TAM 36%, $p < 0.03$



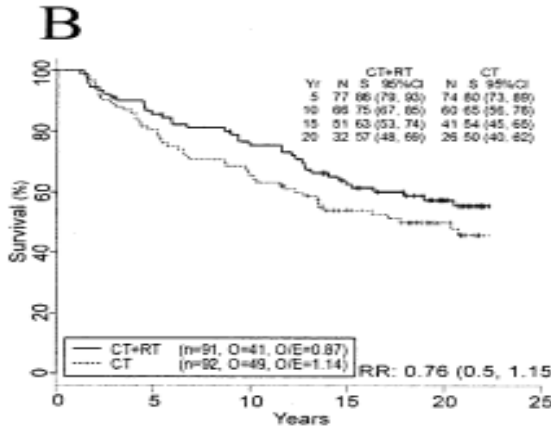
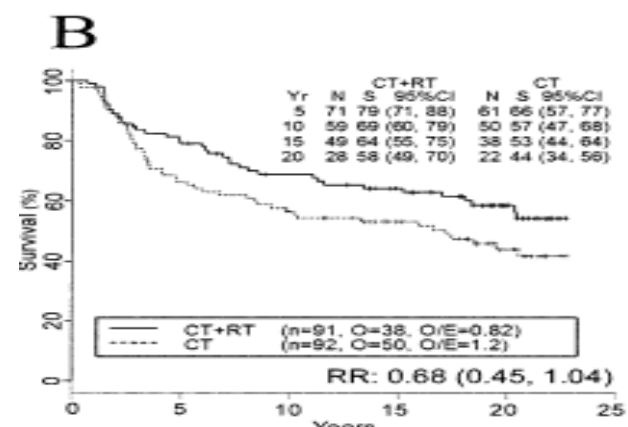
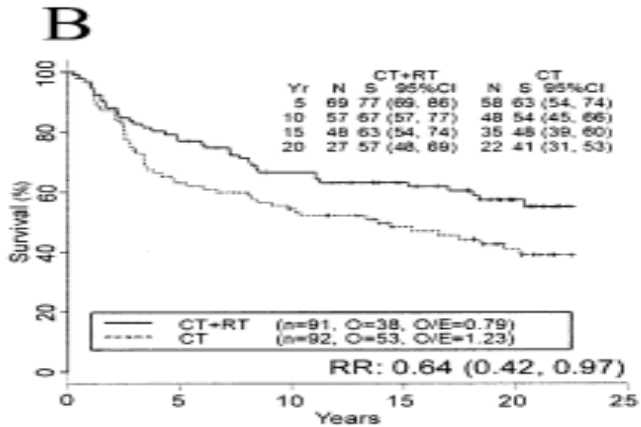
❖ British Columbia Trial (JNCI,2005)

- Study by Joseph Ragaz et al,
- 318 Node positive post mastectomy patients
- Randomised to PMRT + CMF v/s CMF alone
- Sample size was smaller than Danish but was having long term follow-up
- LRR decreased with PMRT + CMF; long-term OS benefit (~10% at 20 yr)
- Independent confirmation of survival benefit → increased confidence in PMRT for node-positive disease

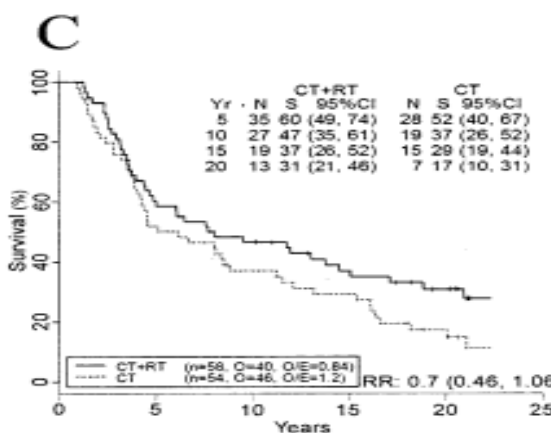
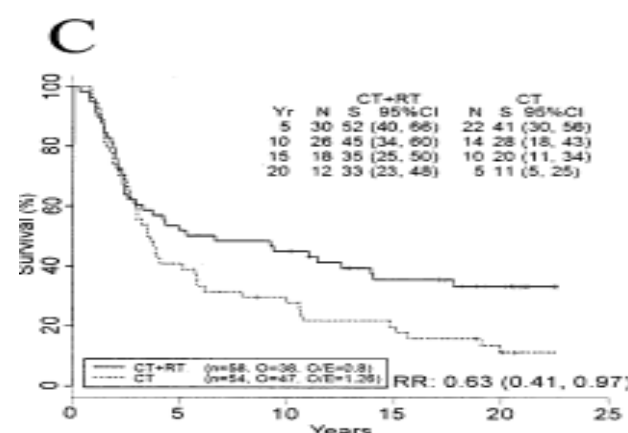
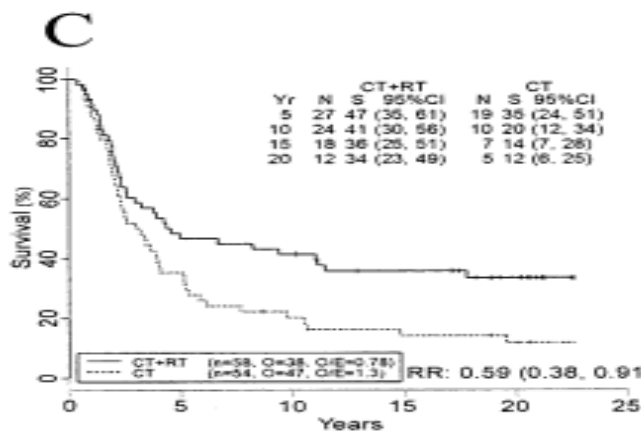




← All 318 Patient



← 1-3 Axillary Ln +ve 183 Patients



← >4 Axillary LN +ve 112 Patients

Breast Cancer Free Survival

Systemic Breast Cancer Free Survival

Overall Survival



❖ Whelan's meta-analysis (JCO 2000)

- 18 randomized trials: 1967-1999, 6367 mastectomy patients
- First MA, examined the effect of RT in patients treated with definitive surgery and systemic therapy
- Variation in the extent of Axillary Sx as well as Systemic Therapy (both CT and HT)
- Variation in dose (35 to 60 Gy), fractionation (12-30#), target volume (majority treated comprehensive RNI) and timing (sandwich v/s concurrent v/s adjuvant t/t)
- Endpoints: Any, LRR and mortality
- Two methods for analysis:
 - Fixed effect model: weighting of two largest Danish studies was 50.4% of the total
 - Random effects model: weighting for the two Danish studies was 37.8%
- Results were similar, and those of the random effects model are shown because they are the most conservative
- The pooled treatment effect was expressed as an odds ratio (\pm 95% confidence interval [CI]) such that estimates more than 1.0 favor control and those less than 1.0 favor radiation therapy
- All P values and 95% CIs were two-sided
- Assessments of homogeneity and overall association were undertaken by use of χ^2 tests



Characteristics of the included studies

Table 1. RCTs of Locoregional Radiation Therapy: Patient Characteristics

Trial (first author, year initiated)	No. of Patients	Stage	Surgery	Extent of AX Dissection	Chemotherapy
DeBoer, ²² 1979	50	NS	M	NS	CMFP ± BCG
Foroglou, ²³ 1979	71	NS	M	NS	Chemo-endocrine
Grohn, ²⁴ Klefstrom, ²⁵ 1976	79	III	MRM	AX fat removed	VAC ± levamisole
Tramprisch, ²⁶ 1977	88	NS	M	NS	LMF
Blomqvist, ²⁷ 1981	99	II	MRM	AX evacuation	CAFT + tamoxifen
Hayat, ²⁸ 1981	112	II	MRM	NS	CMF
Amparo, ²⁹ Gervasio, ³⁰ 1980	112	II	MRM	NS	AC
Cooper, ³¹ Muss, ³² 1976	159	II	RM/MRM	≥ 10 nodes removed	CMF, L-PAM
Schmoor, ³³ 1984	199	II	MRM	> six nodes dissected	CMF
Griem, ³⁴ 1974	218	II & III	MRM	NS	CMF, MF, AC
McArdle, ^{35,36} 1976	219	II	MRM	Clearance of AX contents	CMF
Vélez-García, ³⁷⁻⁴⁰ 1976	239	II & III	RM/MRM	Complete dissection ≥ 10 nodes	CMF
Ahmann, ⁴¹ Martínez, ⁴² 1973	241	II & III	MRM	Complete removal of AX contents	CFP
Olson, ⁴³ 1982	312	III	MRM	> eight nodes (median, 17)	CAFTH
Ragaz, ⁴ 1976	318	II	MRM	Level II	CMF
Arwidi, ⁴⁴ Ryden, ⁴⁵ Tennvall-Nittby, ⁴⁶ 1978	768	I & II	MRM	Dissection to AX vein	Cyclophosphamide, tamoxifen
Overgaard, ^{5,47} 1981	1,375	II & III	TM + AD	Level I and part of II	Tamoxifen
Overgaard, ³ Mouridsen, ⁴⁸ 1981	1,708	II & III	TM + AD	Level I and part of II	CMF

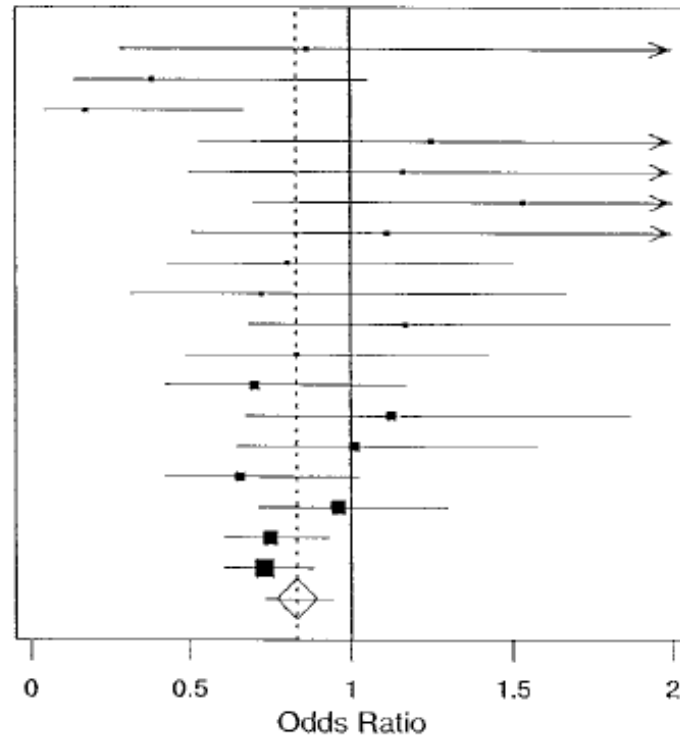
Abbreviations: AC, doxorubicin, cyclophosphamide; AD, axillary dissection; AX, axillary; BCG, bacille Calmette-Guérin; CAFT, cyclophosphamide, doxorubicin, fluorouracil; CAFTH, cyclophosphamide, doxorubicin, fluorouracil, tamoxifen, fluoxymesterone; CFP, cyclophosphamide, fluorouracil, prednisone; CMF, cyclophosphamide, methotrexate, fluorouracil; CMFP, cyclophosphamide, methotrexate, fluorouracil, prednisone; LMF, Leukeran, methotrexate, fluorouracil; L-PAM, melphalan; M, mastectomy, not otherwise specified; MF, methotrexate, fluorouracil; MRM, modified radical mastectomy; NS, not specified; RCT, randomized controlled trial; RM, radical mastectomy; TM, total mastectomy; VAC, vincristine, doxorubicin, cyclophosphamide.

9 Trails CMF, 5 Trails Antracyclins, 2 Trials Tamoxifen



❖ Survival benefit demonstrated with LRRT for the first time

Study	N	OR	95% CI
DeBoer	50	0.87	0.28, 2.65
Foroglou	71	0.38	0.14, 1.05
Klefstrom	79	0.17	0.04, 0.67
Tramprisch	88	1.25	0.53, 2.95
Blomqvist	99	1.16	0.50, 2.70
Hayat	112	1.53	0.70, 3.37
Gervasio	112	1.11	0.51, 2.43
Muss	159	0.81	0.43, 1.50
Schmoor	199	0.72	0.32, 1.67
Griem	218	1.17	0.68, 1.99
McArdle	219	0.83	0.49, 1.43
Velez-Garcia	239	0.70	0.42, 1.17
Martinez	241	1.12	0.67, 1.87
Olson	312	1.01	0.65, 1.58
Ragaz	318	0.66	0.42, 1.02
Tennvall-Nittby	768	0.96	0.71, 1.30
Overgaard(TAM)	1375	0.75	0.61, 0.93
Overgaard(CMF)	1708	0.73	0.61, 0.89
Random Effects		OR = 0.83	95% CI = 0.74, 0.94



OR for any recurrence and LRR was 0.69 and 0.25 respectively

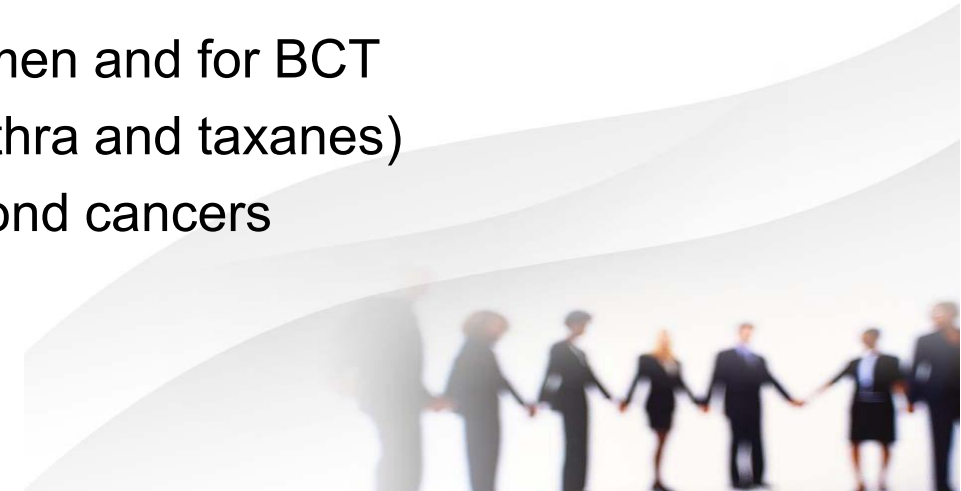
On univariate analysis, only timing of radiation therapy [≥ 6 months (OR 1.14) v , < 6 months (OR 0.78)] was statistically significant

On multivariate analysis, timing of radiation and radiation technique (mega vs. ortho) were predictive of treatment response



❖ Conclusion

- Results were consistent with individual trial findings
- Many trials had longer follow up
- Use of relatively modern RT techniques
- Proved the hypothesis: that patients required adjuvant systemic therapy to allow locoregional radiation to manifest its effect
 - In patients who have distant failures reduced with chemotherapy, the effect of radiation therapy on preventing locoregional recurrence and resulting secondary systemic recurrence may be more evident
- Unanswered issues:
 - Can results be generalized for node negative women and for BCT
 - In the setting of more effective chemotherapy (anthra and taxanes)
 - Increased toxicity: cardiac, lymphedema and second cancers



❖ EBCTCG: Lancet 2000

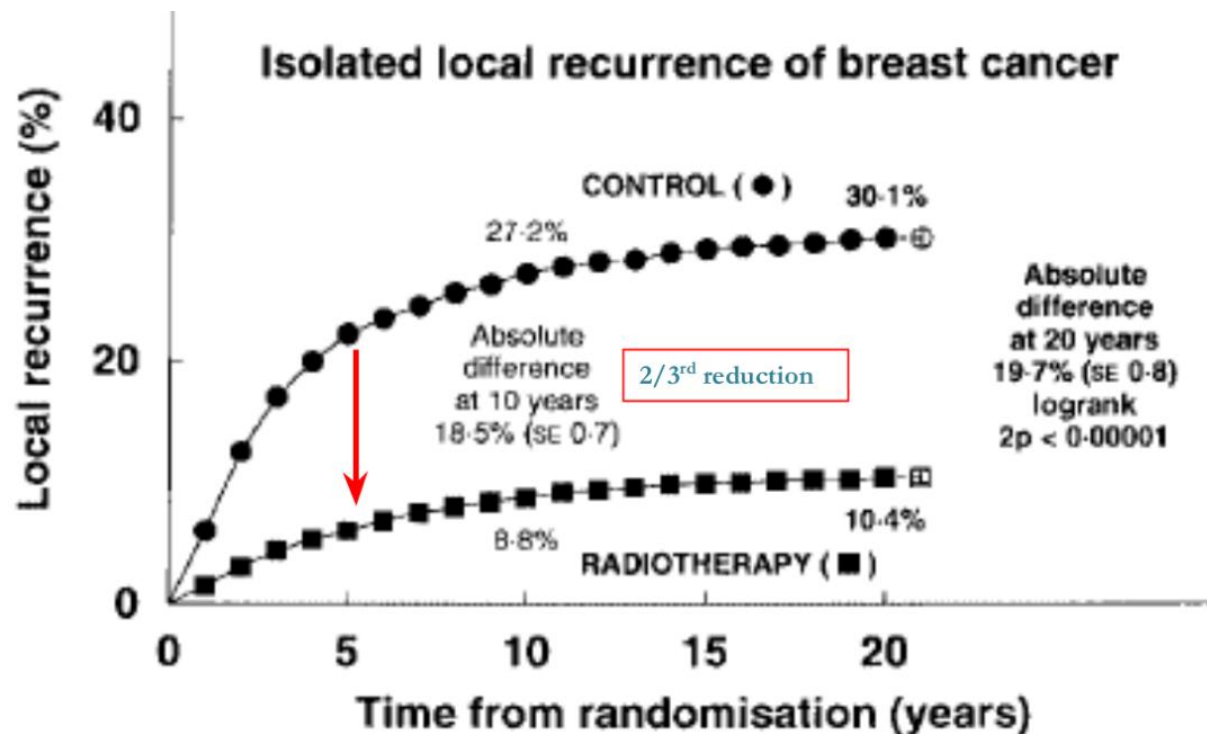
	Isolated local recurrence (%)			Any recurrence (%)			Logrank 2p value
	Radiotherapy	Control	Absolute difference (SE)	Radiotherapy	Control	Absolute difference (SE)	
Mastectomy alone (18% node positive)	N=5125 (5 trials)						
Node negative	11.3	28.6	17.3 (1.5)	43.0	49.8	6.8 (1.7)	<0.00001
Node positive	15.5	44.9	29.4 (4.0)	59.8	68.4	8.7 (3.2)	0.004
Mastectomy with axillary sampling (80% node positive)	N=3901 (6 trials)						
Node negative	7.2	23.1	15.9 (2.8)	36.7	43.7	7.0 (3.8)	0.05
Node positive	6.3	37.7	31.4 (1.9)	55.0	69.2	14.2 (2.0)	<0.00001
Mastectomy with axillary clearance (72% node positive)	N=6379 (23 trials)						
Node negative	2.7	9.2	6.5 (1.3)	28.2	30.2	2.0 (2.3)	>0.1
Node positive	9.0	24.4	15.4 (1.4)	53.8	60.0	6.2 (1.6)	0.0001
Breast conservation with axillary clearance (25% node positive)	N=4177 (6 trials)						
Node negative	7.8	25.0	17.3 (1.7)	28.6	44.7	16.1 (2.3)	<0.00001
Node positive	16.1	35.4	19.4 (3.4)	49.8	58.0	8.2 (3.7)	0.002
Subtotals	N=19,582 (40 trials)						
All node negative	7.9	23.2	15.3 (0.9)	35.1	43.6	8.4 (1.1)	<0.00001
All node positive	9.3	32.0	22.7 (1.0)	54.3	63.8	9.5 (1.1)	<0.00001
Total (50% node positive)	8.8	27.2	18.5 (0.7)	45.2	53.8	8.7 (0.8)	<0.00001

*37 trials with data on local recurrence. All logrank tests for local recurrence yield 2p<0.00001.

Table 3: Effects of radiotherapy allocation on 10-year probability of recurrence, by type of surgery and nodal status*

❖ Effect on LR/Any recurrence

Effective across all age groups, nodal status, dose fractionation, target volume

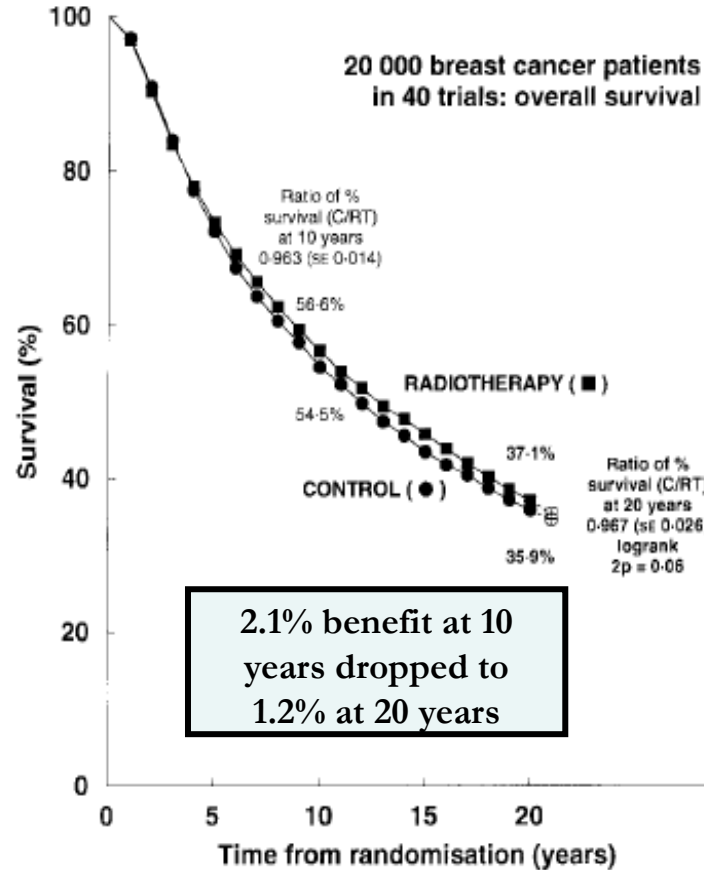


Events / 1000 woman-years and absolute difference in annual local recurrence / 1000

	Years 0-4	Years 5-9	Years 10-14	Years 15-19	Years ≥20
Radiotherapy	511/36.8	141/21.2	29/10.3	5/4.6	0/1.7
Control	1766/33.1	245/17.6	50/8.4	9/3.7	0/1.5
Difference	39.5 (SE 1.4)	7.3 (SE 1.1)	3.1 (SE 1.0)	1.4 (SE 0.9)	0

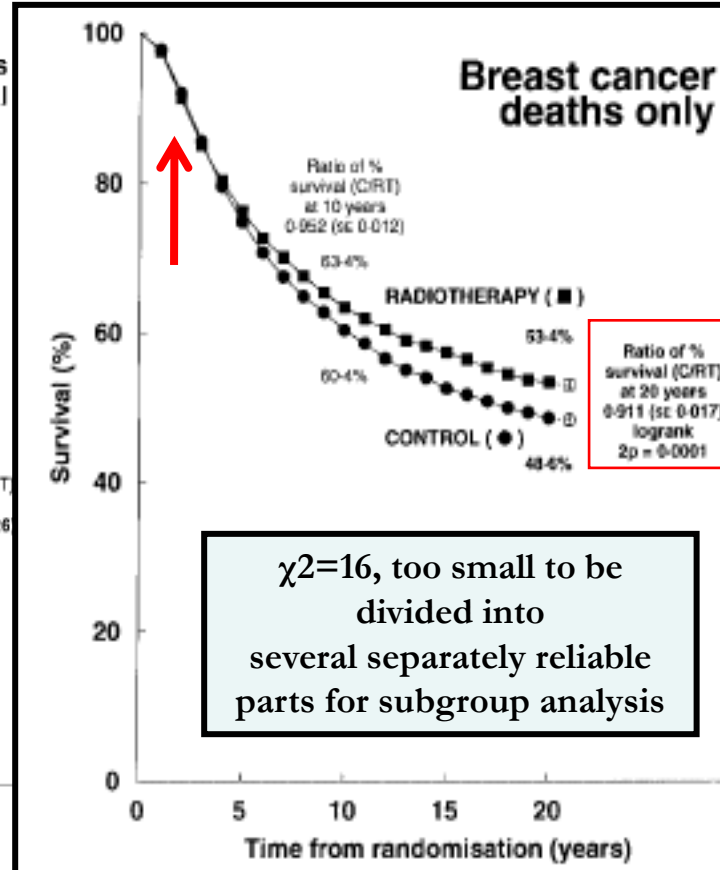


❖ Effect on OvM/BCM/NBCM



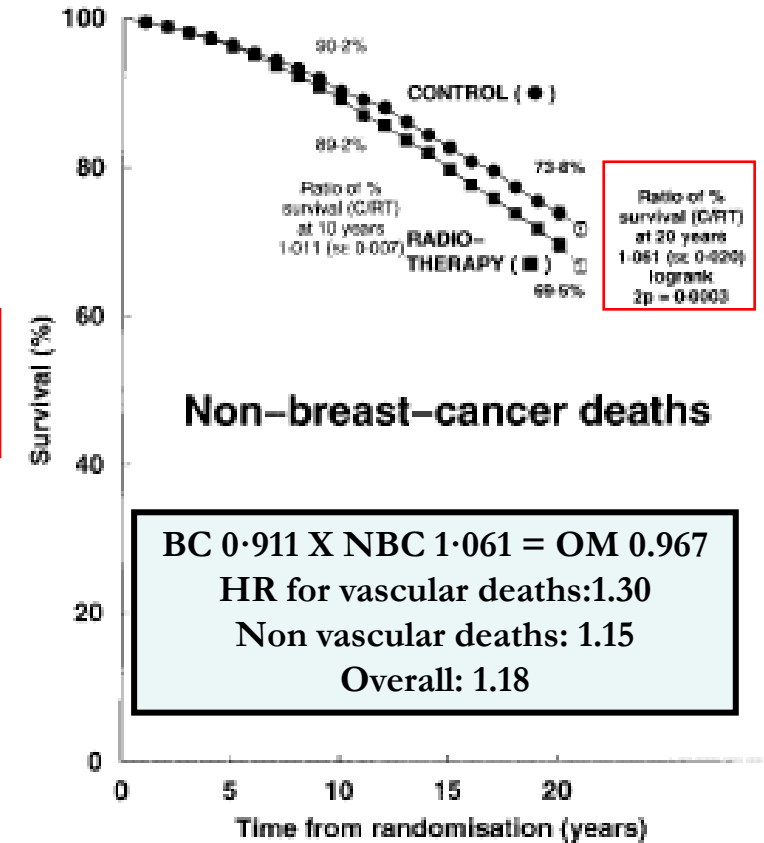
Deaths / 1000 woman-years and absolute difference in annual mortality / 1000

	Years 0-4	Years 5-9	Years 10-14	Years 15-19	Years ≥20
Radiotherapy	2612/42.7	1363/26.1	584/13.5	314/7.4	130/2.6
Control	2599/40.8	1371/23.9	547/12.1	238/6.4	80/2.4
Difference	2.4 (SE 1.7)	5.2 (SE 2.1)	2.1 (SE 2.6)	-5.3 (SE 3.4)	-16.4 (SE 5.7)



Death rate and absolute difference in annual mortality / 1000

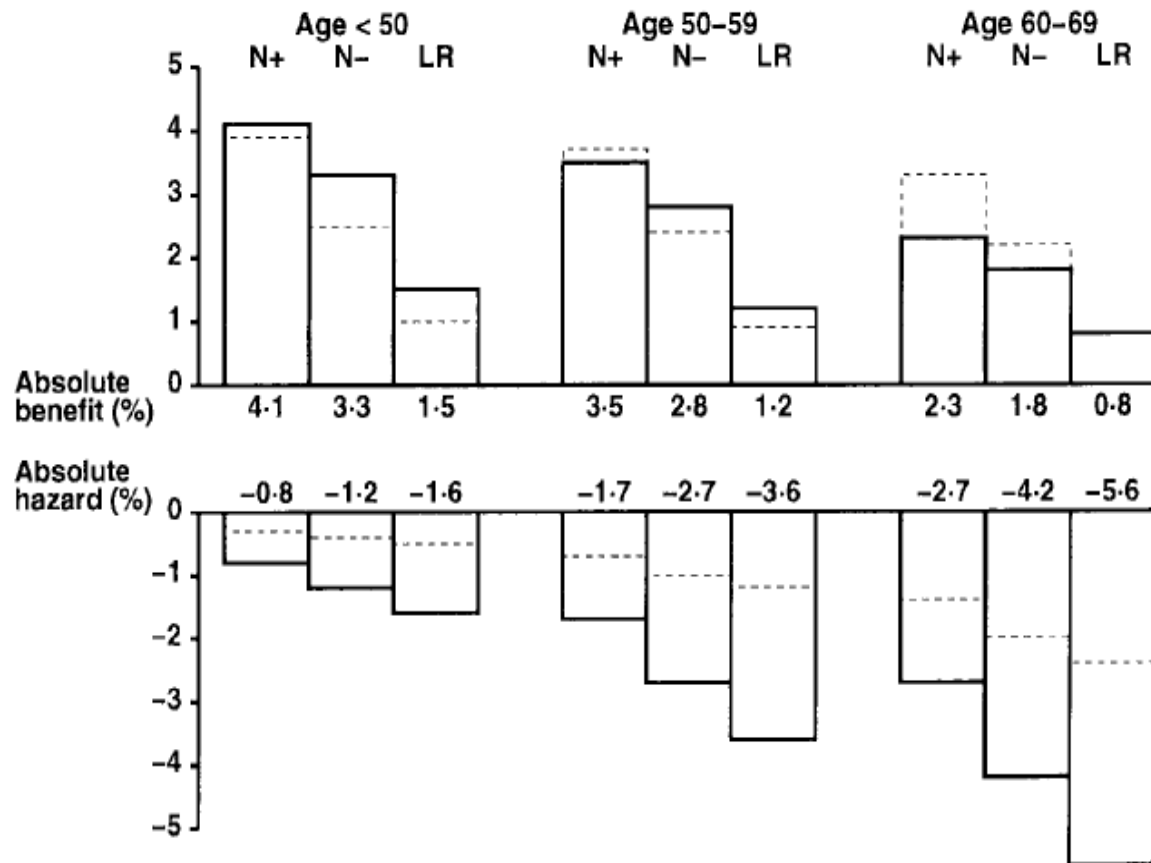
	Years 0-4	Years 5-9	Years 10-14	Years 15-19	Years ≥20
Radiotherapy	63.7	37.6	20.9	16.2	7.2
Control	66.6	44.3	28.6	15.4	5.8
Difference	2.9 (SE 1.6)	6.7 (SE 1.8)	7.8 (SE 1.9)	0.1 (SE 1.9)	-1.4 (SE 1.9)



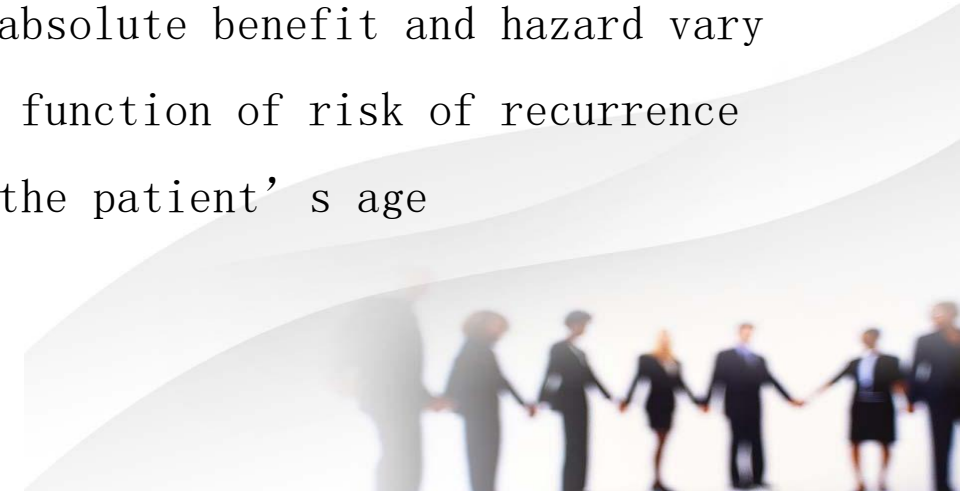
Deaths / 1000 woman-years and absolute difference in annual mortality / 1000

	Years 0-4	Years 5-9	Years 10-14	Years 15-19	Years ≥20
Radiotherapy	291/38.9	327/22.5	261/11.8	176/6.5	103/2.4
Control	244/34.4	239/18.4	153/9.6	114/5.2	60/2.1
Difference	-9.4 (SE 0.6)	-1.6 (SE 1.3)	-5.7 (SE 1.9)	-5.9 (SE 2.9)	-14.4 (SE 3.5)

❖ Discussion & conclusion



- RT regimens resulting in 2/3 reduction in LR, but without long-term hazard, would be expected to produce an absolute increase in 20-year survival of about 2-4% (except for women at particularly low risk of local recurrence)
- The absolute benefit and hazard vary as a function of risk of recurrence and the patient's age



❖ EBCTCG Lancet 2005

- ❖ Mastectomy with Axillary Clearance : Node negative **1400** patients +/- RT (CW + Regional LN area)
 - ✓ 5 year Local recurrence risk **reduction**: 4% (2% v/s 6%)
 - ✓ 15 year breast cancer mortality risk **increase**: 3.6% (p=0.01)
 - ✓ 15 year overall mortality risk **increase**: 4.2% (p=0.0002)

- ❖ Mastectomy with Axillary Clearance : Node positive **8500** patients +/- RT (CW + Regional LN area)
 - ✓ 5 year Local recurrence risk reduction: 17% (6% v/s 23%)
 - ✓ 15 year breast cancer mortality risk **reduction**: 5.4% (p=0.0002)
 - ✓ 15 year overall mortality risk **reduction**: 4.4% (p=0.0009)

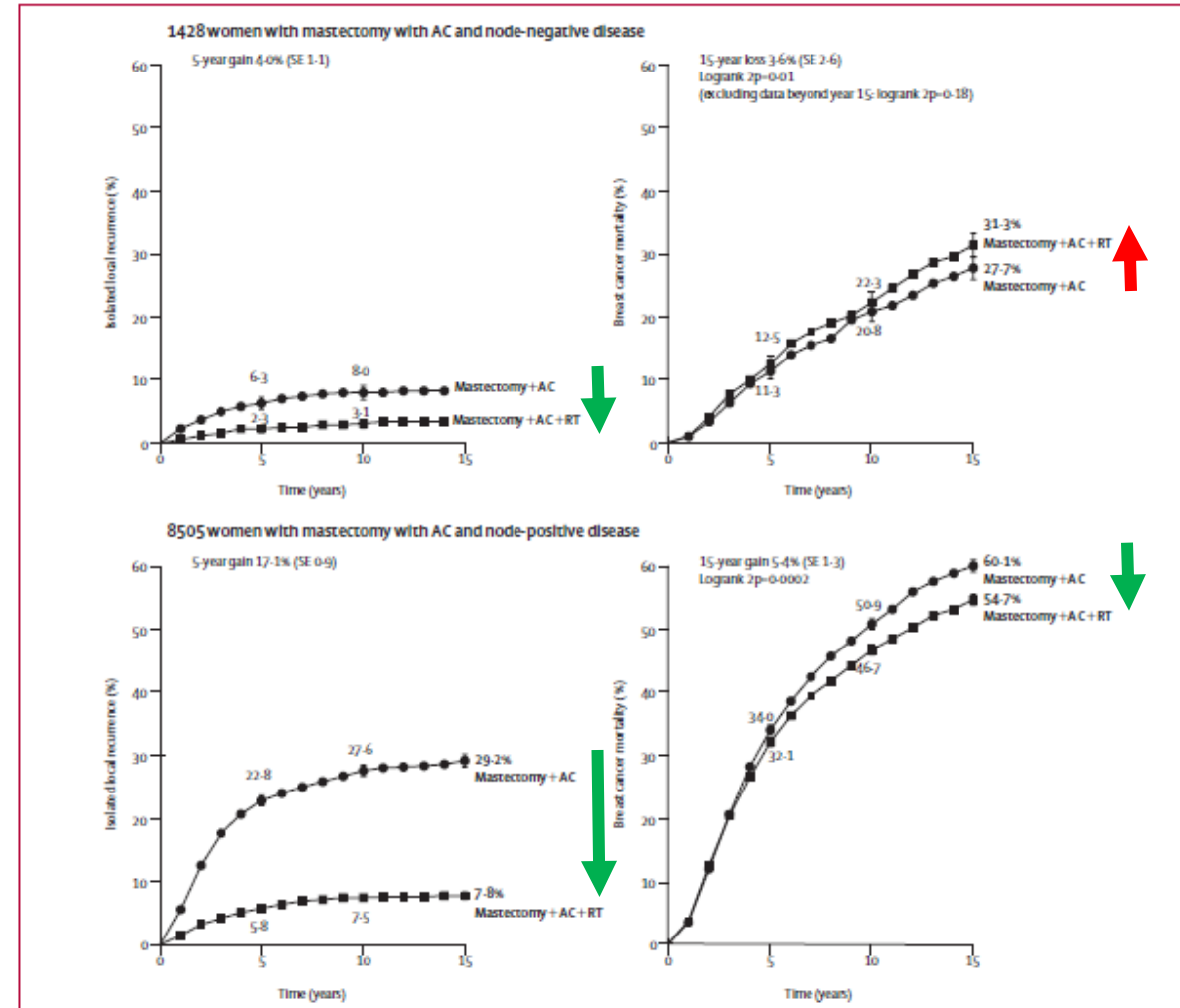


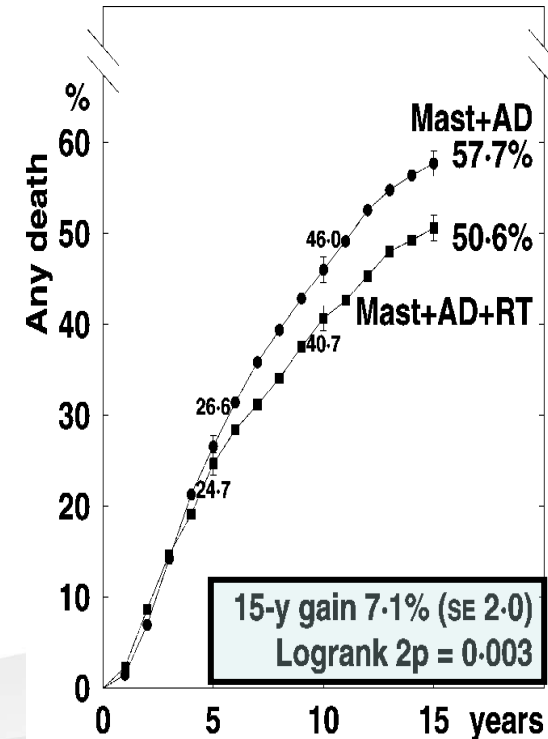
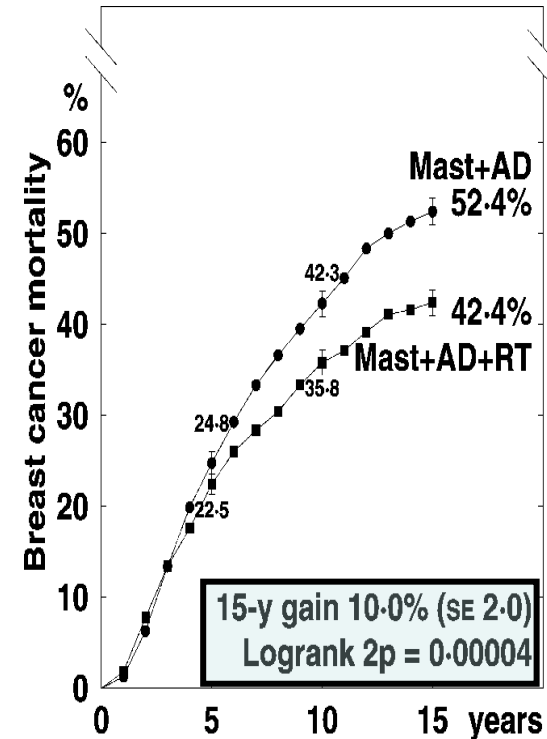
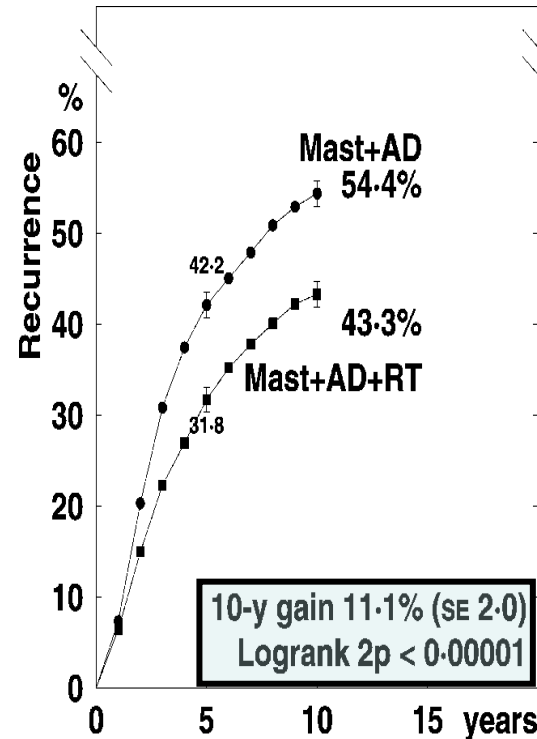
Figure 3: Effect of radiotherapy (RT) after mastectomy and axillary clearance (AC) on local recurrence and on breast cancer mortality—15-year probabilities. Data from 25 trials. Vertical lines indicate 1 SE above or below the 5, 10, and 15 year percentages.

Benefit reported for 3222 pN1-3

❖ Reservations:

- Incompleteness of the surgical resections (median no of axillary nodes removed 7)
- Use of older methotexate-based regimens
- Use of 1 year only of adjuvant tamoxifen
- Lack of ER data in patient recruitment and data analysis
- Higher axillary failure rates (13%)

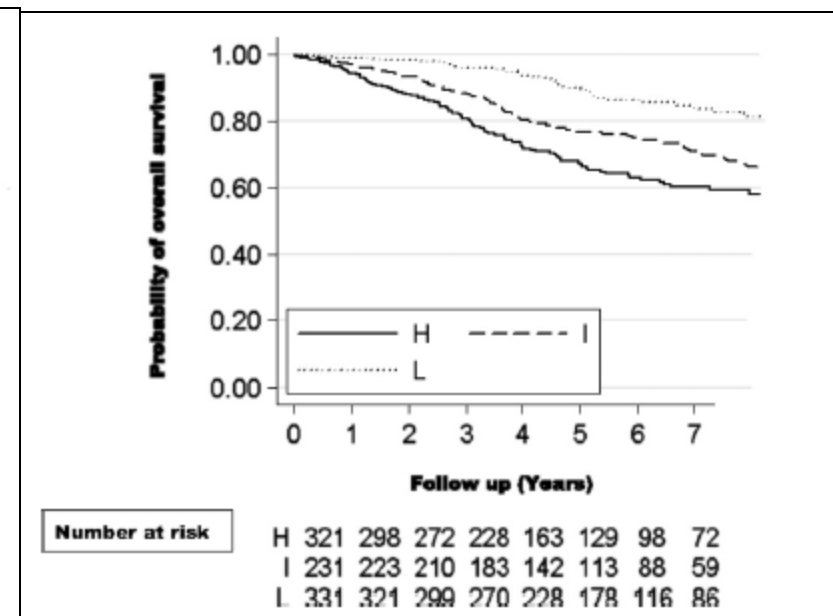
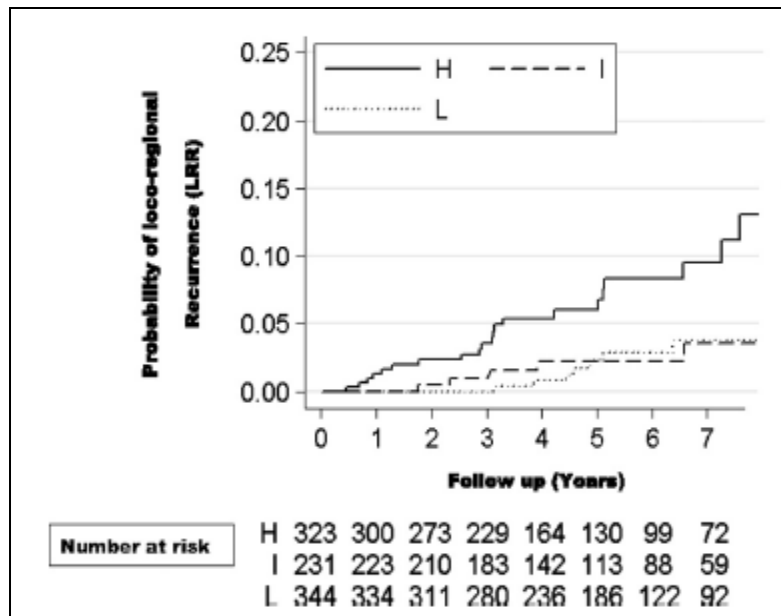
❖ PMRT for 1-3 LN + **NEVER** adopted as standard of care



The Cambridge post-mastectomy radiotherapy (C-PMRT) index: A practical tool for patient selection Radioth Oncol 2014

- ✓ N = 898, FU 5.2 yrs
- ✓ RT for score ≥ 3
- ✓ No RT for score < 3
- ✓ CW RT alone in patients with 1-3 LN +ve

Score	3	2	1
No + ve LN/LVI	≥ 4	1-3	LVI
Tumor size	T3-T4	30-50 mm	20-29 mm
Excision margin	< 1 mm	-	-
Grade	-	-	Grade 3



Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

Lancet 2014; 383: 2127–35

EBCTCG (Early Breast Cancer Trialists' Collaborative Group)*

700 pN0 women

RT: No significant benefit

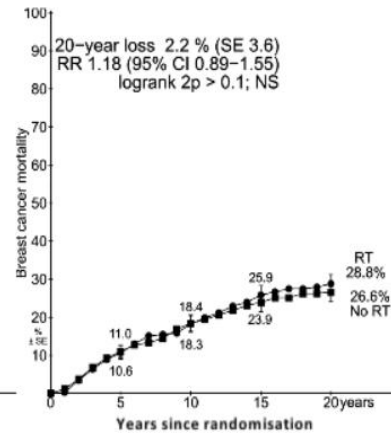
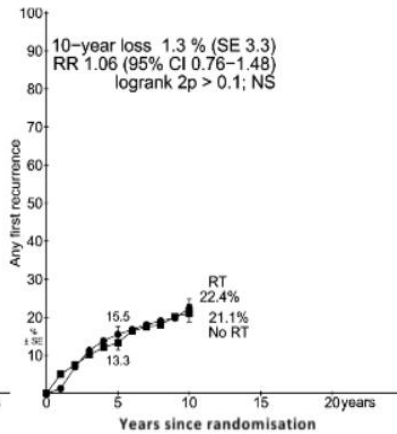
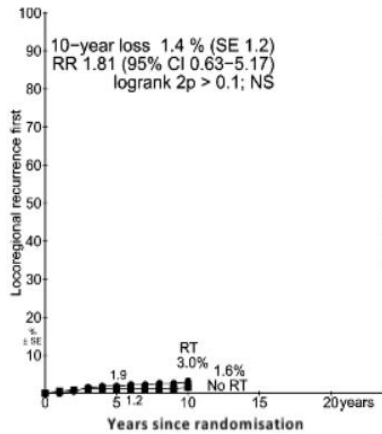
1314 pN1-3 women

RT: Significant benefit

Locoregional recurrence first

Any first recurrence

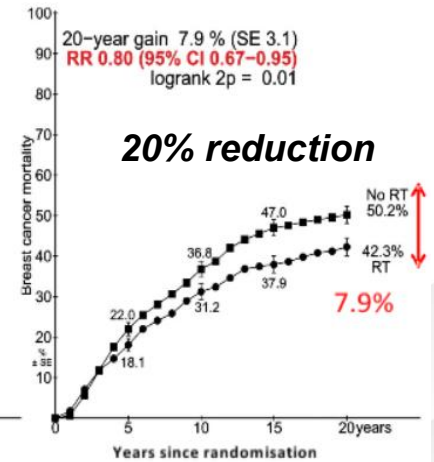
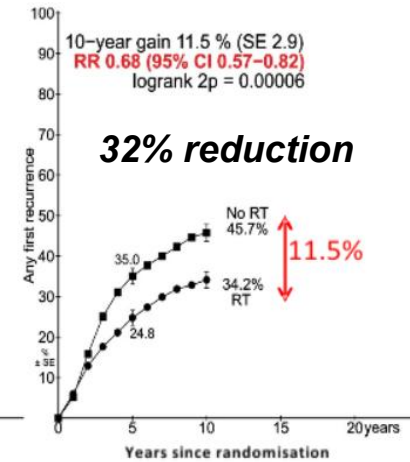
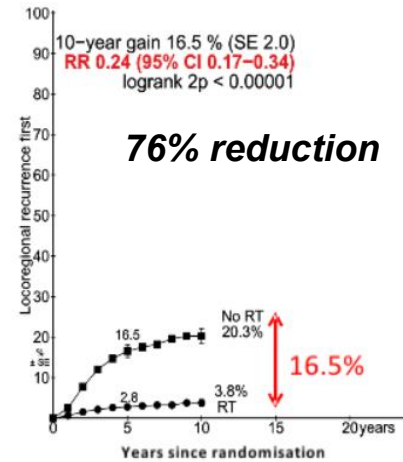
Breast cancer mortality



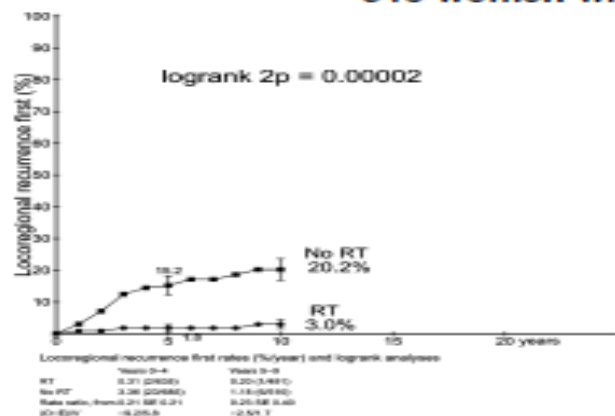
Locoregional recurrence first

Any first recurrence

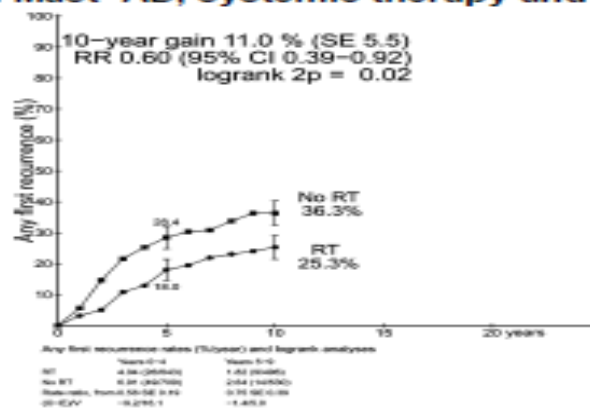
Breast cancer mortality



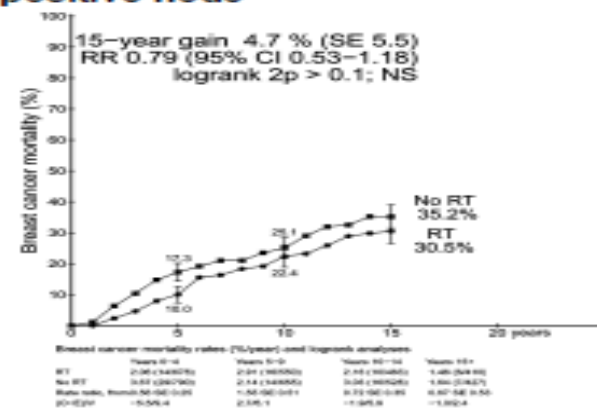
Locoregional recurrence first



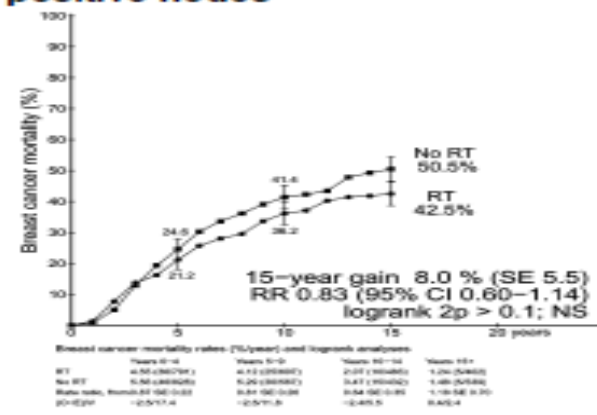
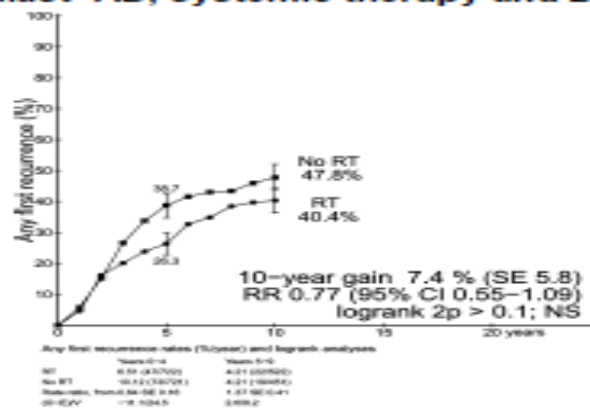
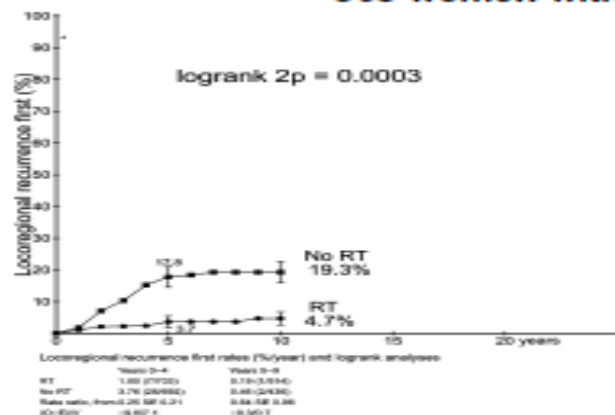
Any first recurrence



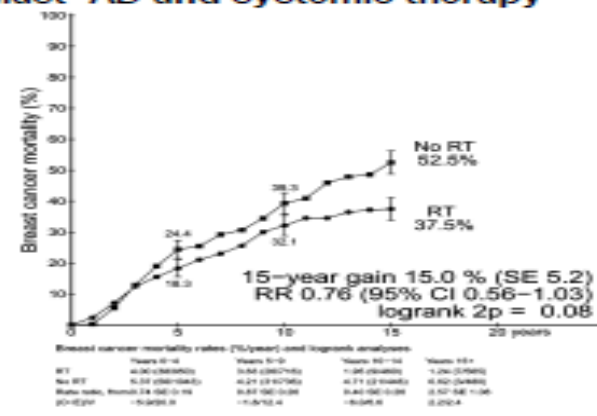
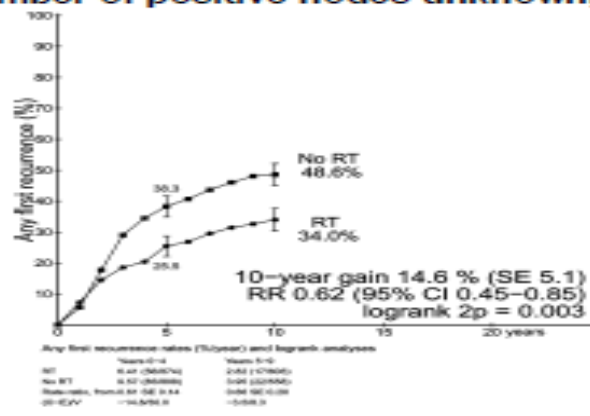
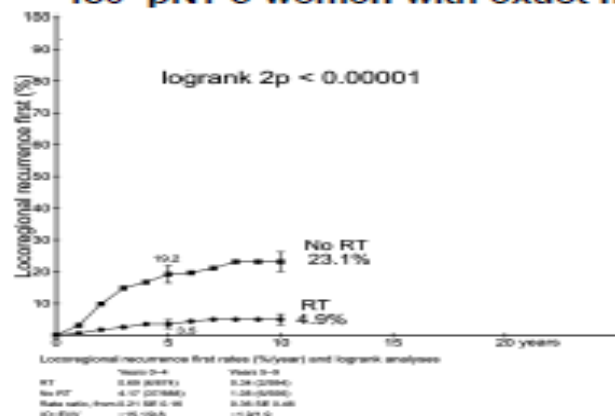
Breast cancer mortality



365 women with Mast+AD, systemic therapy and 2-3 positive nodes



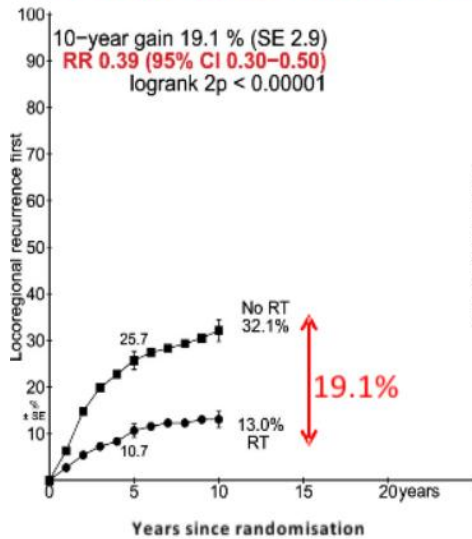
450 pN1-3 women with exact number of positive nodes unknown, Mast+AD and systemic therapy



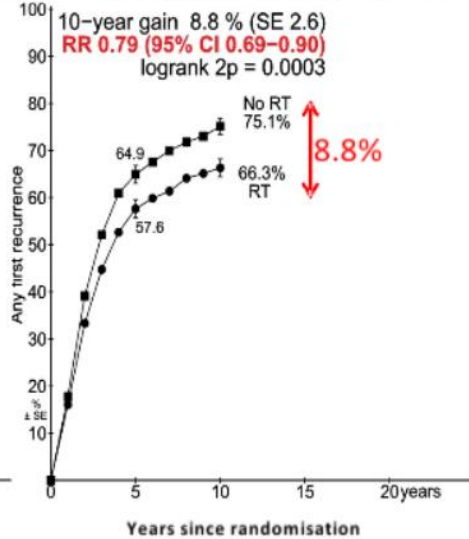
1772 pN4+ women

RT: Significant benefit

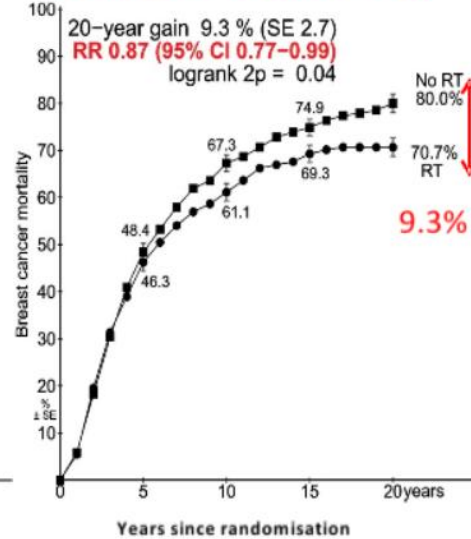
Locoregional recurrence first



Any first recurrence



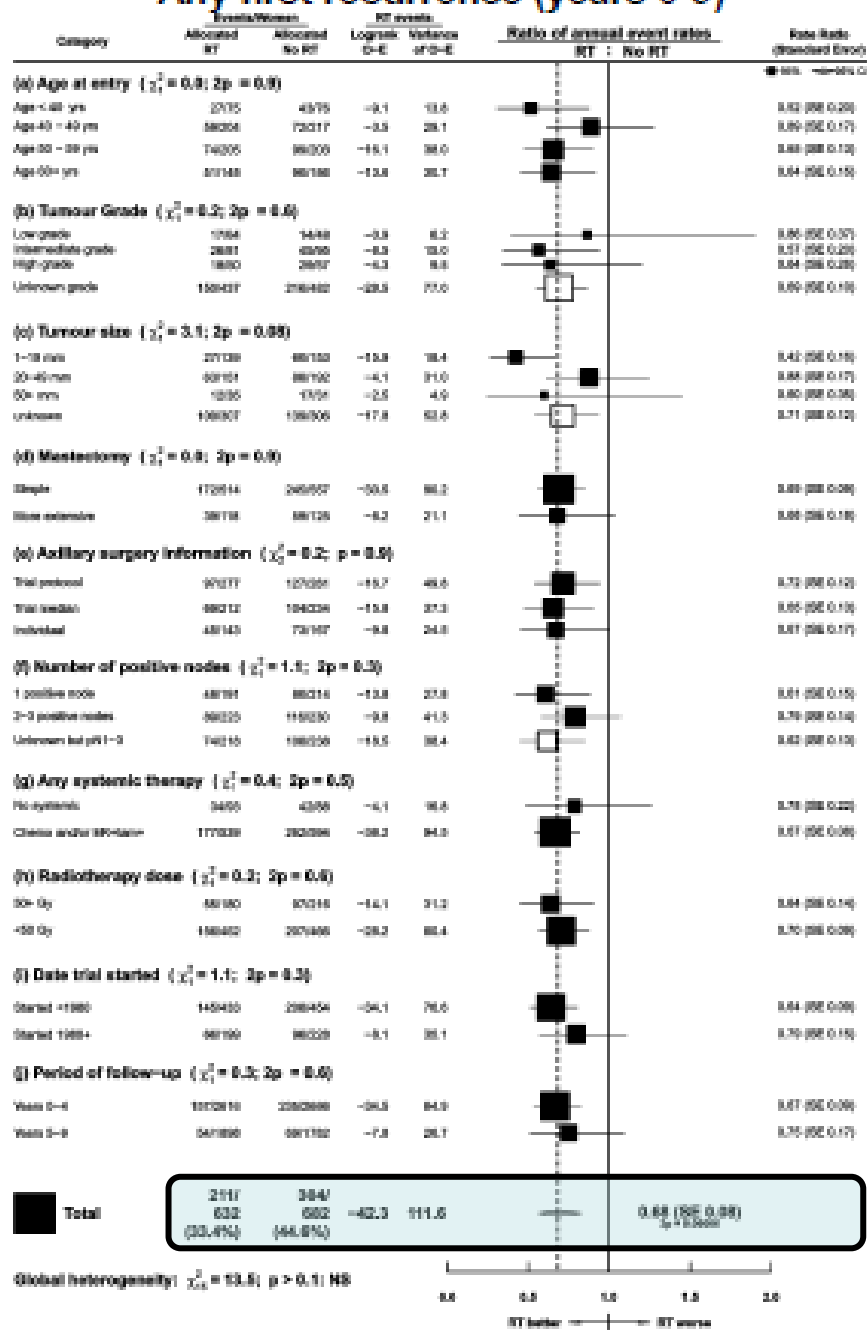
Breast cancer mortality



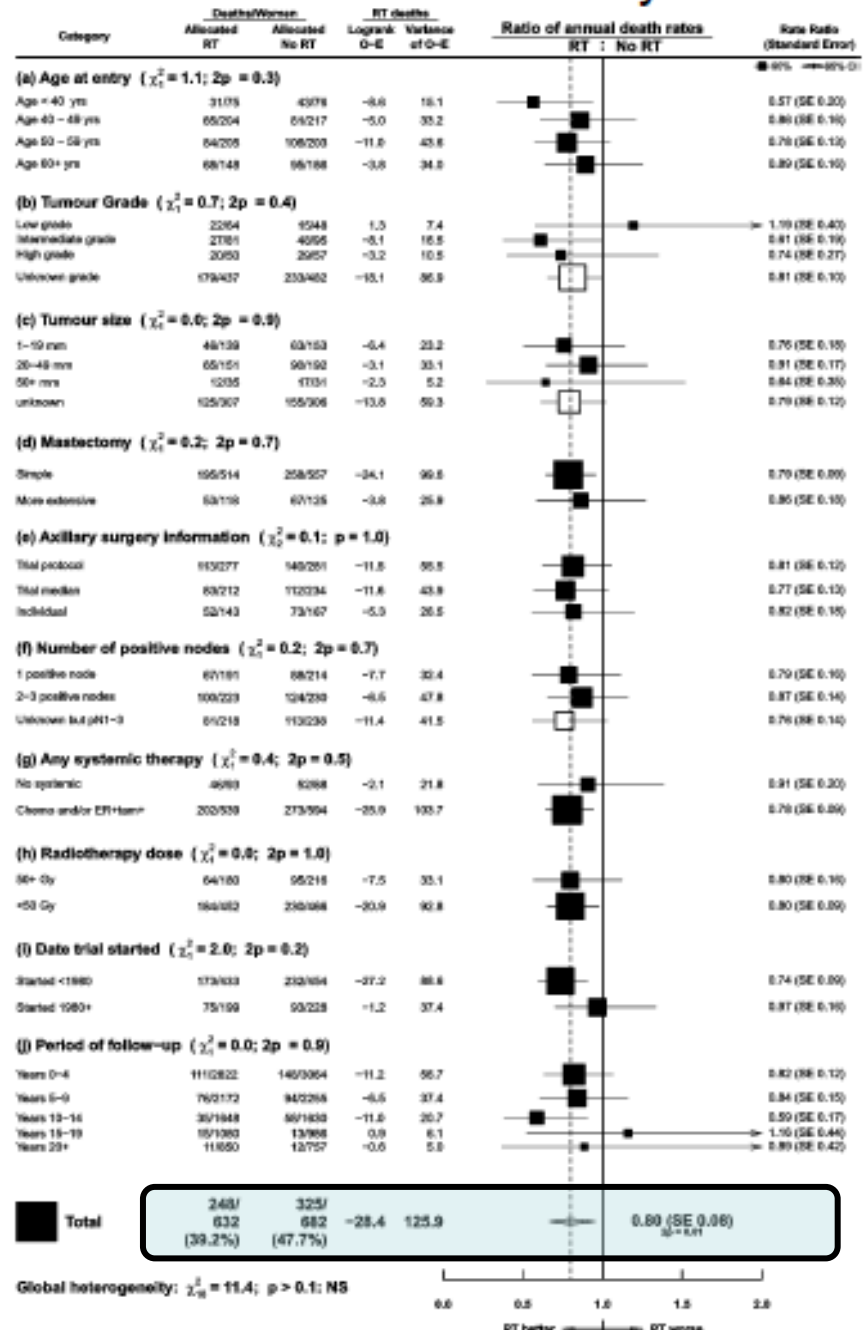
- > 8000 patients from different 22 RCTs : Radiotherapy post Mastectomy with Axillary Dissection
- Studies were PMRT v/s No PMRT
- ≥ 4 nodes: large mortality reduction;
- 1–3 nodes: similar benefit
- Node-negative: no survival benefit
- Provided quantitative estimates of absolute benefit by nodal burden.
- Directly informed guideline nuance: strong recommendation for PMRT with ≥ 4 nodes; consideration for 1–3 nodes with additional risk factors



Any first recurrence (years 0-9)



Breast cancer mortality



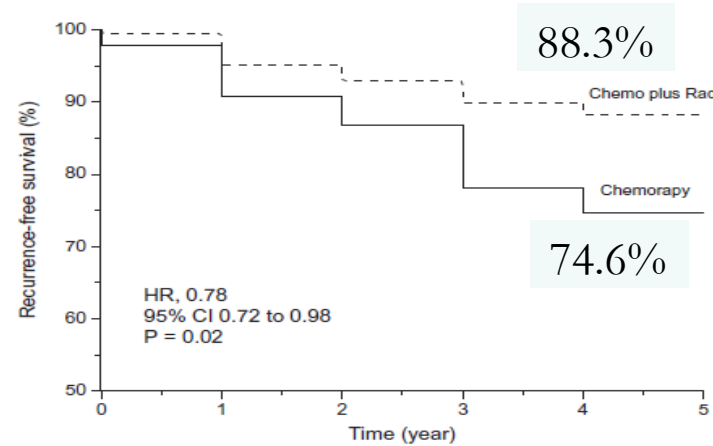
Adjuvant chemotherapy and radiotherapy in triple-negative breast carcinoma: A prospective randomized controlled multi-center trial

Jianhua Wang^{a,1}, Mei Shi^{a,*,1}, Rui Ling^{b,*,1}, Yuesheng Xia^{a,1}, Shanquan Luo^a, Xuehai Fu^a, Feng Xiao^a, Jianping Li^a, Xiaoli Long^a, Jianguo Wang^c, Zengxia Hou^d, Yunxia Chen^e, Bin Zhou^a, Man Xu^a

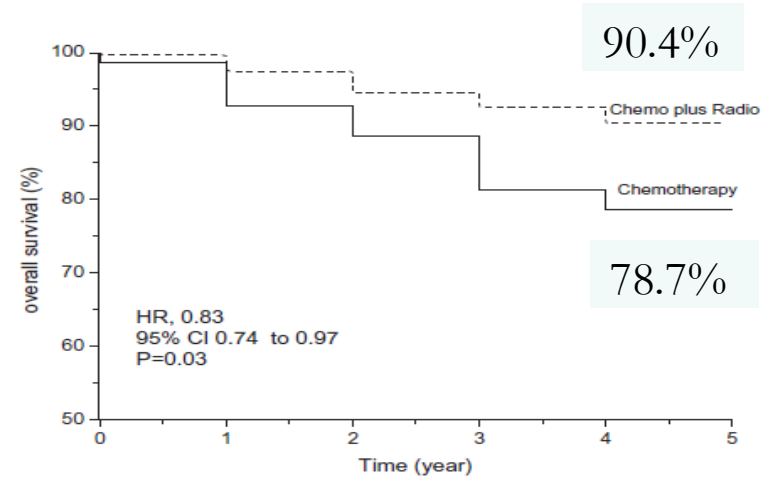
^a Department of Radiation Oncology; ^b Department of Breast Surgery, Fourth Military Medical University, Xi'an; ^c Department of Radiation Oncology, Shanxi Province Tumor Hospital, Taiyuan; ^d Medical Technical Group, Second Military Medical University, Shanghai; and ^e Department of Radiation Oncology, Fifth Hospital, Shanxi Province, China

Wang et al, RO (100) 2011: 200-204

	Adjuvant chemo		Adjuvant chemo + radio		P
	No.	%	No.	%	
Age, years					
≤50	195	61.9	227	62.0	>0.05
>50	120	38.1	139	38.0	
Tumor size					
≤2 cm	119	37.8	132	36.1	>0.05
2.1–5.0 cm	196	62.2	234	63.9	←
Nodal status					
N0	263	83.5	295	80.6	>0.05 ←
N1–3	47	14.9	62	16.9	
N4–9	5	1.6	9	2.5	
Clinical stage					
Stage I	233	74.0	259	70.8	>0.05
Stage II	82	26.0	107	29.2	



No. at Risk
 Chemotherapy 315 308 286 273 246 235
 Chemo plus Radio 366 364 348 340 329 323



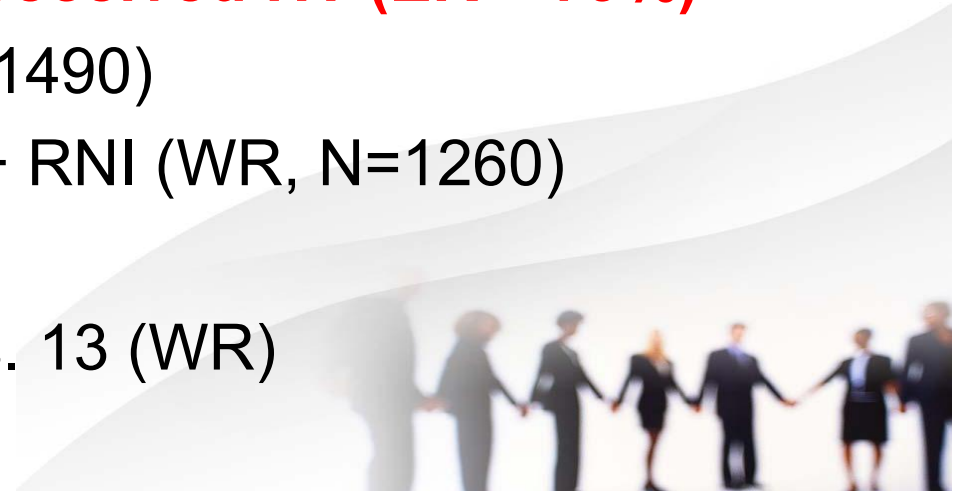
No. at Risk
 Chemotherapy 315 311 292 279 256 248
 Chemo plus Radio 366 365 357 346 339 331

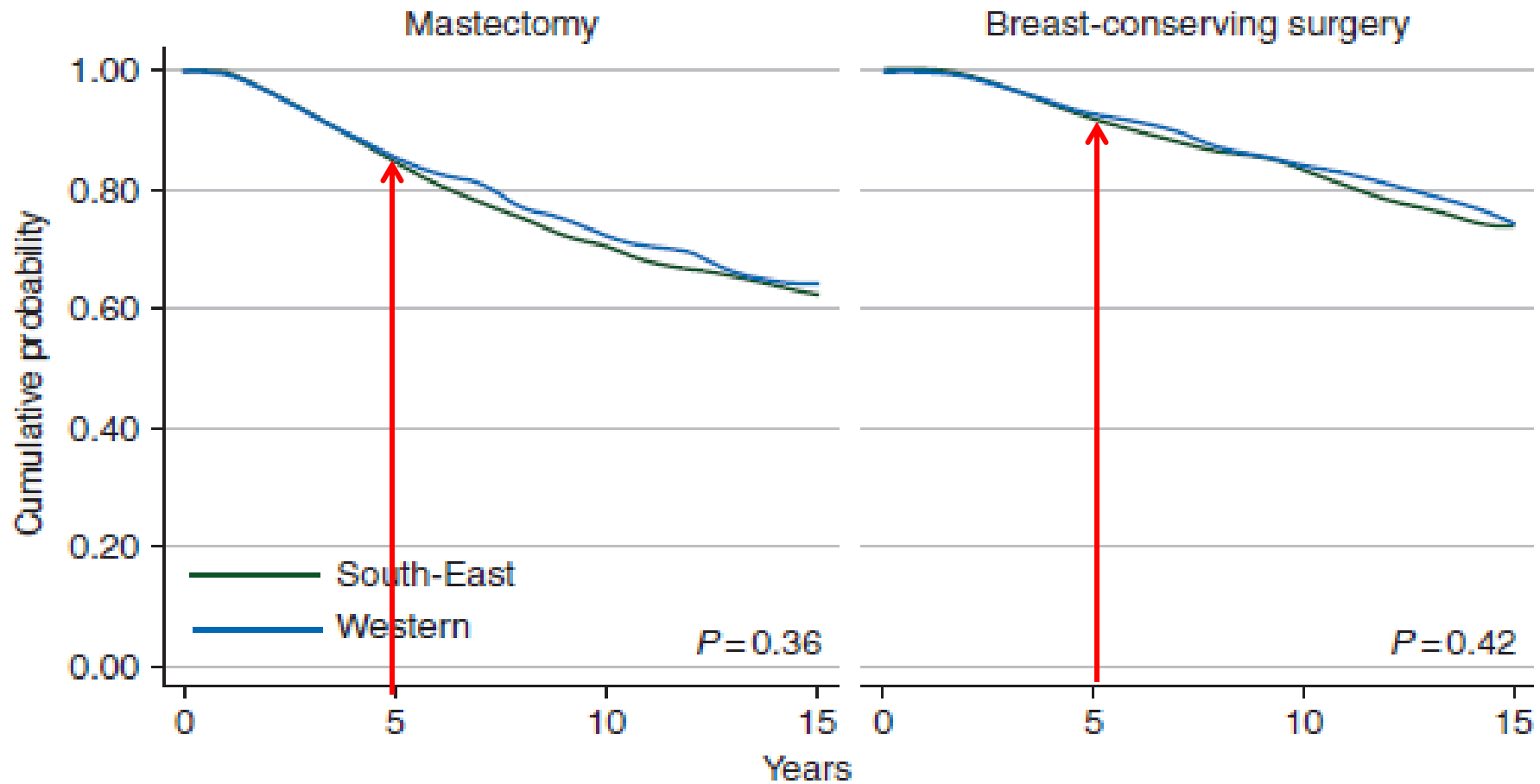
- Duration: 2000-2006, N=681, median FU: 86.5 months
- 50Gy/25 fractions to CW, RNI: >2LN+ or >25% LN +
- Primary endpoint: treatment compliance and toxicity
- Secondary endpoint: RFS/OS



❖ Contradictory evidence: Swedish population based study for 1-3 LN

- Study duration: 1989-2006
- Clinical outcome compared between south east region (SER) and west region (WR)
- Majority of the patients in both regions had participated in **population-based mammography-screening programs**
- N=1698 (SER) vs. 2750 (WR)
- **Only 36% received chemo while only 56% received HT (ER + 79%)**
- PMRT (SER, N=1012) vs. no PMRT (WR, N=1490)
- BCS: Breast alone (SER, N=686) vs. Breast + RNI (WR, N=1260)
- CT-based planning
- Median number of LNs removed: 10 (SER) vs. 13 (WR)





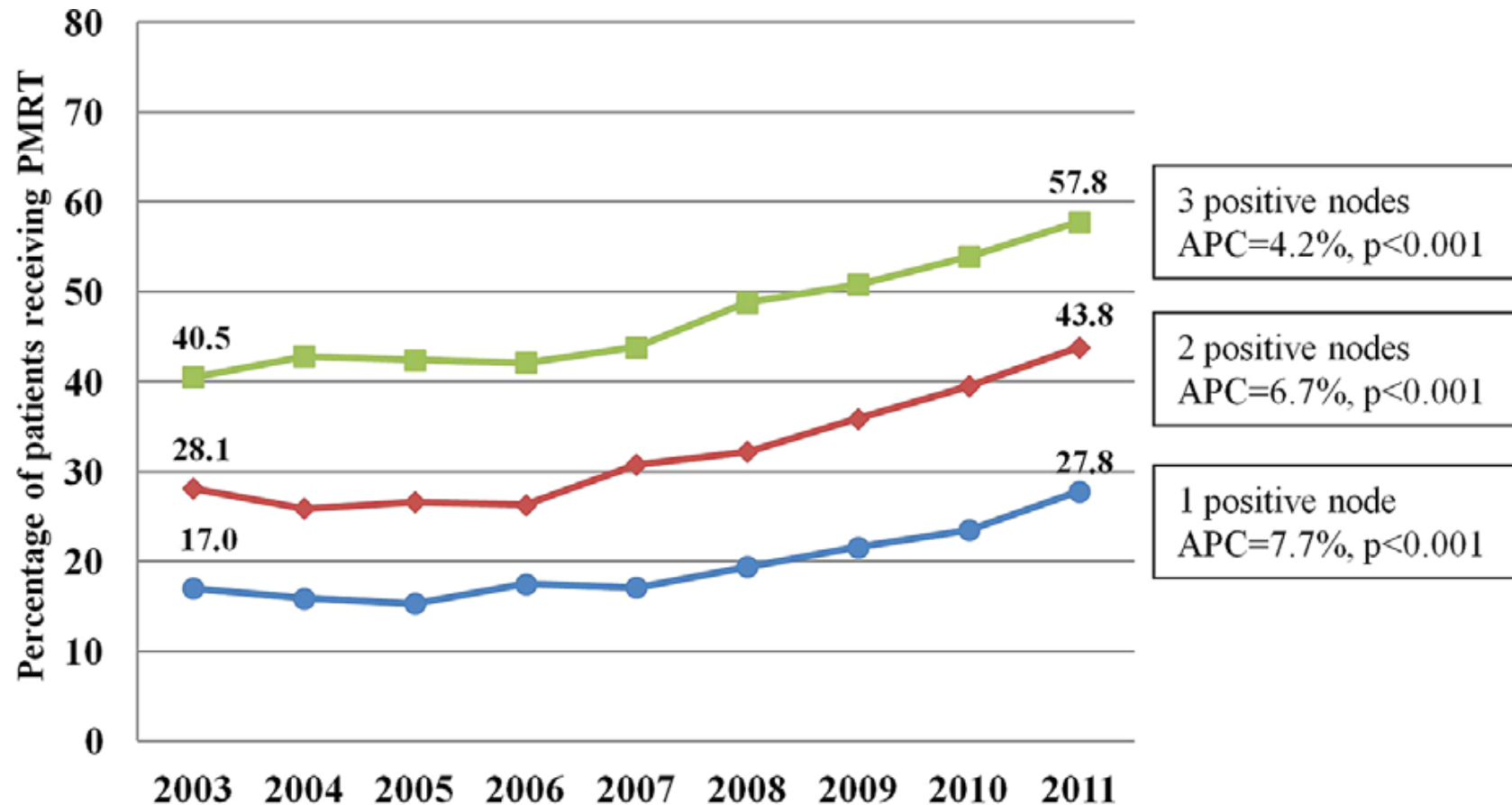
Authors conclude that their patient cohort had excellent survival

THERE WAS DIFFERENCE IN SURVIVAL BETWEEN BCS AND MRM THOUGH NO EFFECT OF PMRT SEEN

Nordenskjöld AE, Ann Onco 2015

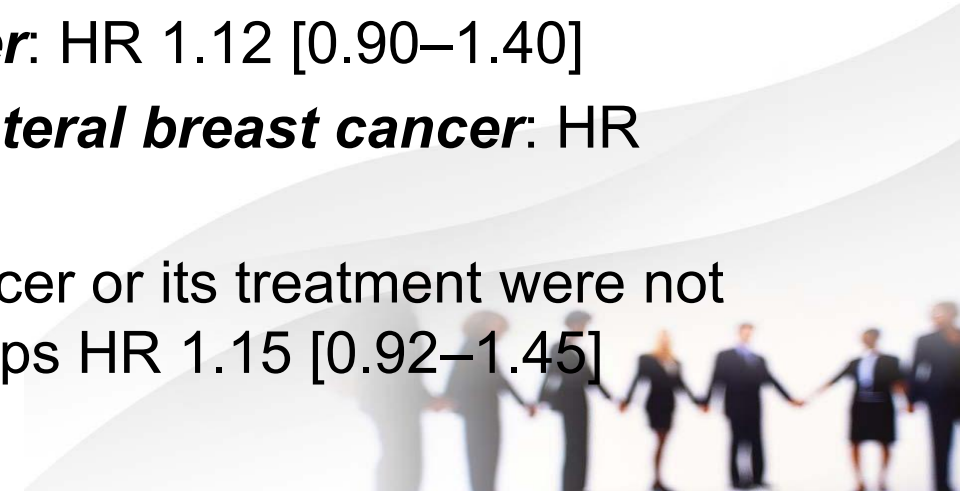


❖ Utilization of PMRT for 1-3+ nodes



❖ 30-year long-term report from DBCG 82b&c trial (RO, 2022)

- DBCG 82b&c RCT recruited between 1982-1990
- 3083 patients address the importance PMRT to high-risk BC who also received adjuvant systemic treatment
- **Fourfold reduction** of the 30-year LRF rate from 37% to 9%, $p < 0.0001$
- **5% reduction** in Overall mortality after 30-years 81% vs 86% $p < 0.0001$
- Significantly reduced risk for **distant metastasis**: **HR 0.77** [0.70–0.84]; the failure due to **any recurrence**: **HR 0.65** [0.59–0.71]; and **death** from breast cancer: **HR 0.75** [0.69–0.82]
- **No** significant difference in death from **other cancer**: HR 1.12 [0.90–1.40]
- **No** increase in the risk for development of **contralateral breast cancer**: HR 0.78 [0.61–0.98]
- Other causes of death not related to the breast cancer or its treatment were not significantly different among the two treatment groups HR 1.15 [0.92–1.45]



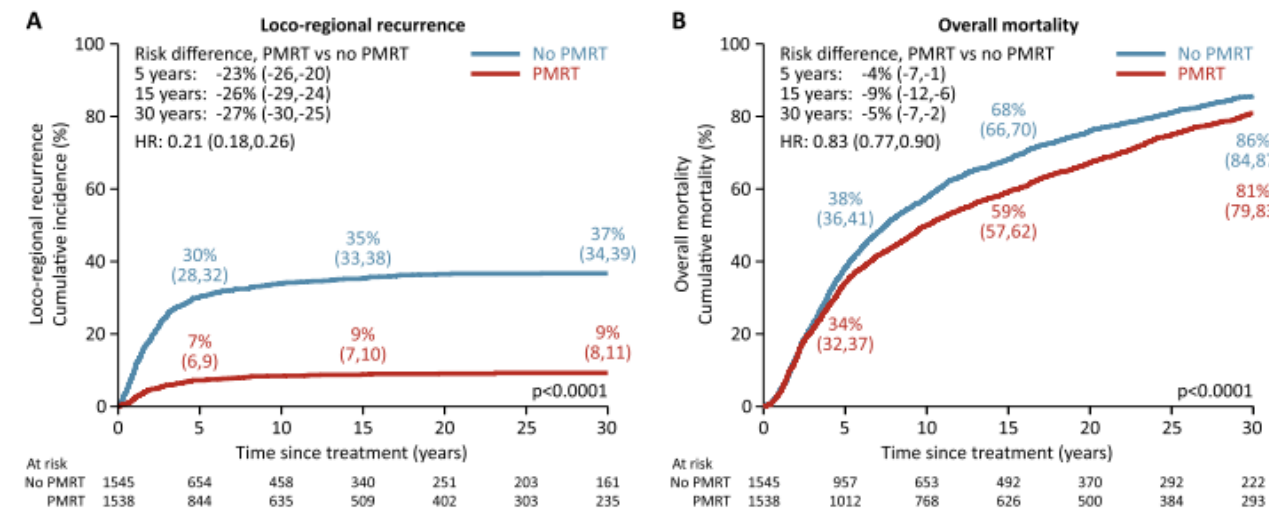


Fig. 1. Effect of radiotherapy on loco-regional recurrence (A) and overall mortality (B).

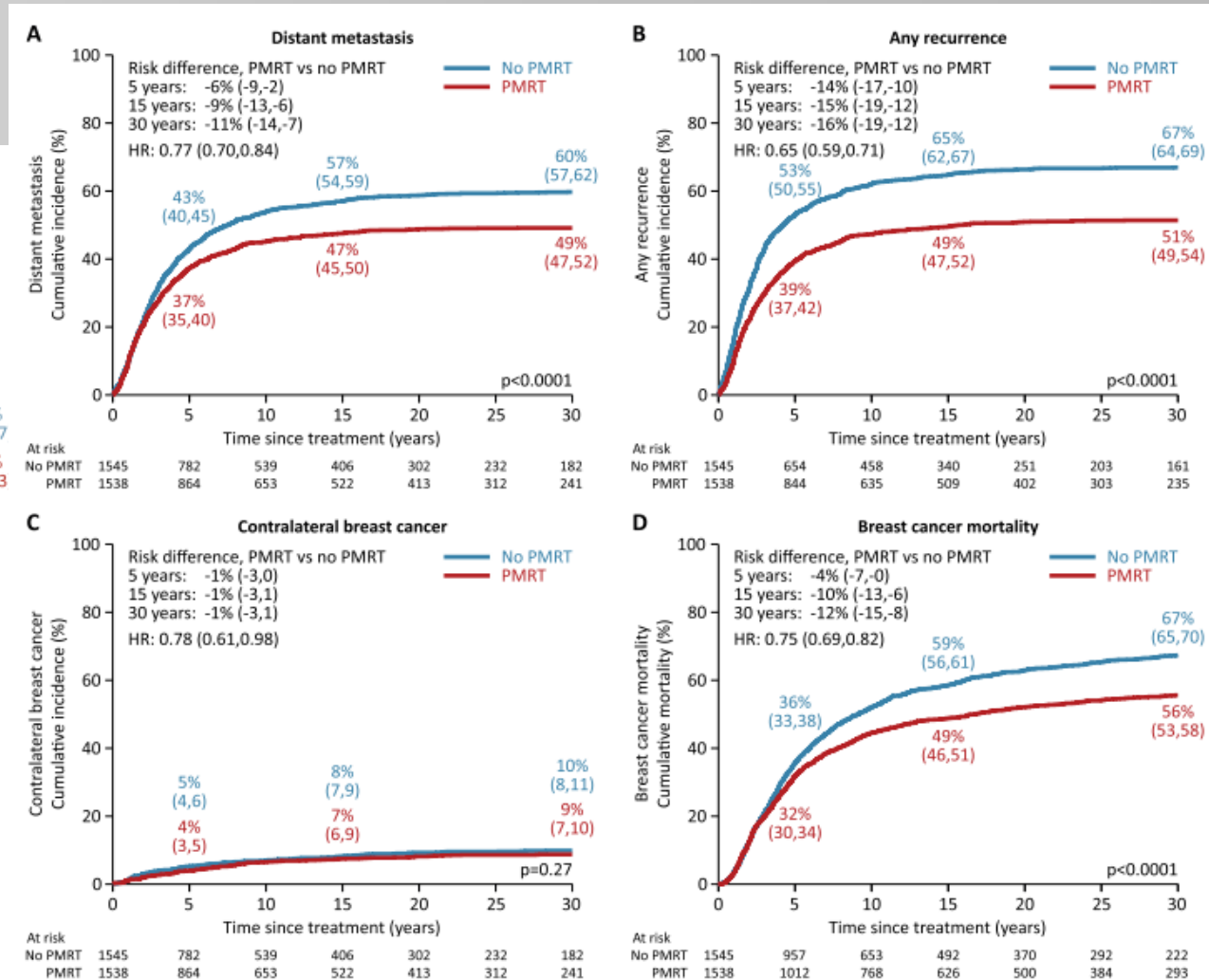
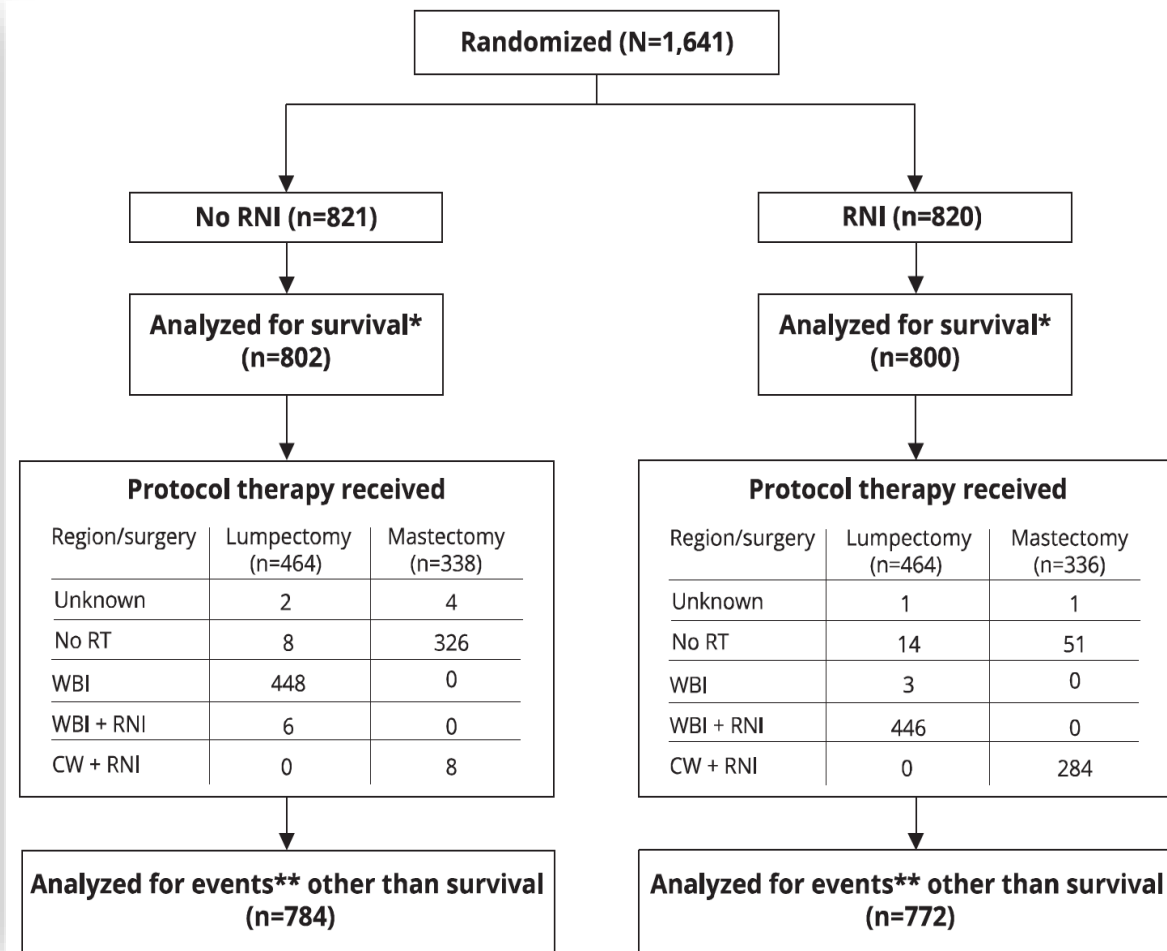
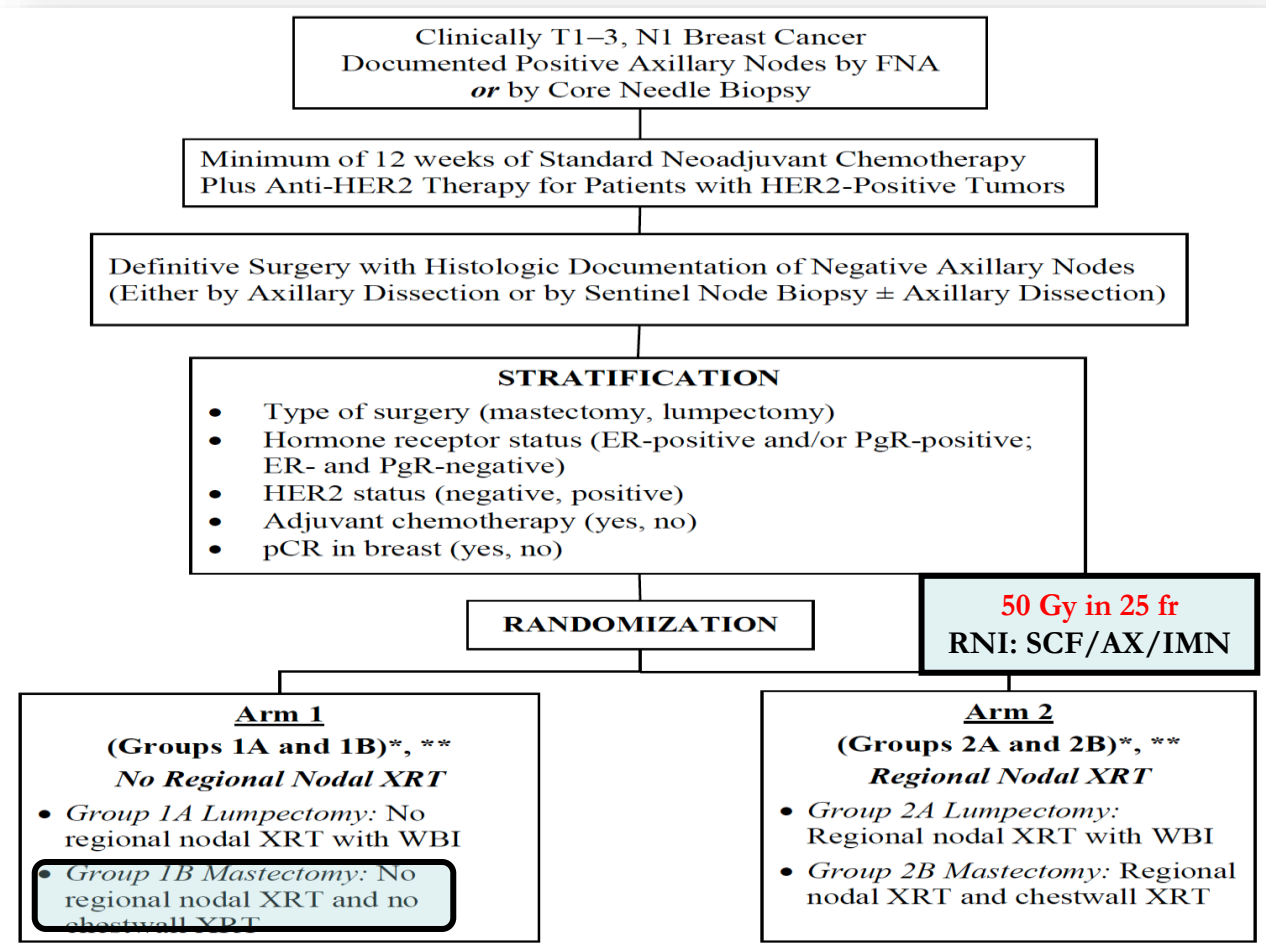


Fig. 2. Effect of radiotherapy on distant recurrence (A), any recurrence (B), contralateral breast cancer (C), and breast cancer mortality (D).



❖ Omitting Regional Nodal Irradiation after Response to NACT NSABP B-52/RTOG 1304

- Mamounas et al, Phase 3, randomized, multicentre trial (NRG Oncology, NEJM 2025)



❖ Primary Endpoint: Invasive breast cancer recurrence free survival

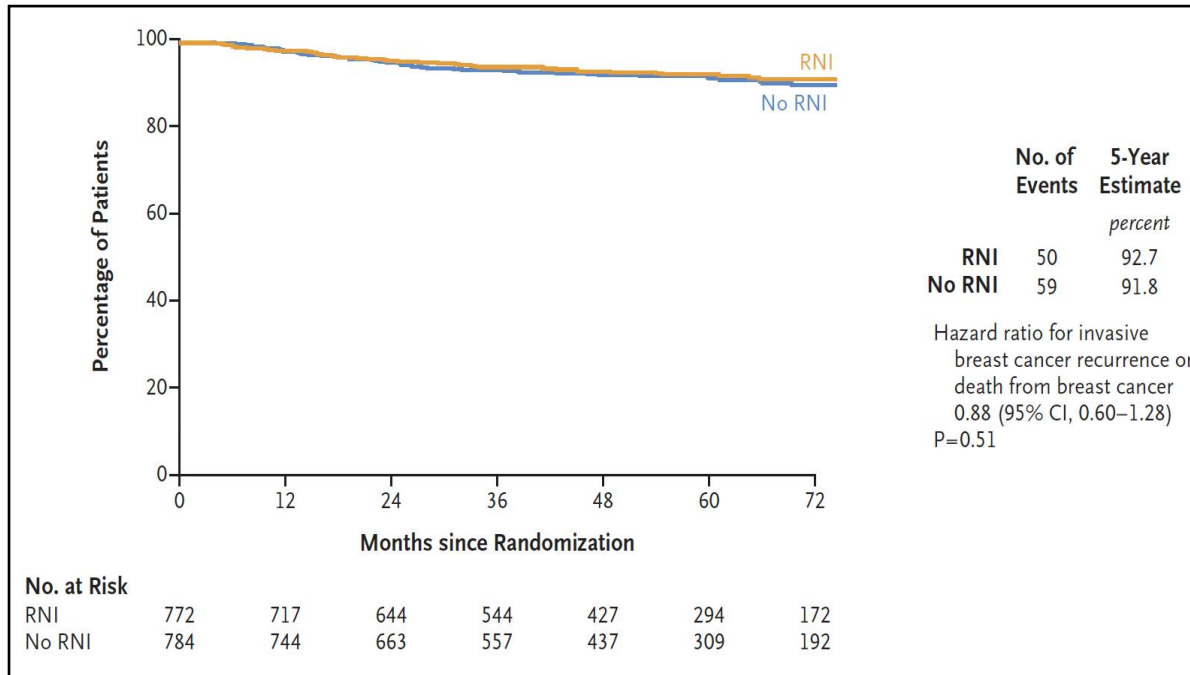


Figure 1. Effect of Regional Nodal Irradiation on the Invasive Breast Cancer Recurrence-free Interval. Shown is the 5-year estimate of survival free from invasive breast cancer recurrence or death from breast cancer. RNI denotes regional nodal irradiation.

Clinical tumor stage — no. (%)‡		
T1	170 (20.7)	171 (20.8)
T2	499 (60.9)	484 (59.0)
T3	151 (18.4)	166 (20.2)
HR status — no. (%)		
Negative	386 (47.1)	382 (46.5)
Positive	434 (52.9)	439 (53.5)
HER2 status — no. (%)		
Negative	355 (43.3)	356 (43.4)
Positive	465 (56.7)	465 (56.6)
Tumor subtype — no. (%)		
Triple negative	191 (23.3)	175 (21.3)
HR positive and HER2 negative	164 (20.0)	181 (22.0)
HR negative and HER2 positive	195 (23.8)	207 (25.2)
HR positive and HER2 positive	270 (32.9)	258 (31.4)
Adjuvant chemotherapy — no. (%)		
No	813 (99.1)	817 (99.5)
Yes	7 (0.9)	4 (0.5)
Pathological complete response in breast — no. (%)		
Absent	176 (21.5)	182 (22.2)
Present	644 (78.5)	639 (77.8)

Predominantly **high-risk** population 80%

Dual anti-her2 therapy 81.7%

Remarkable **pCR** >77%

Non compliance to PMRT in 15% of group 2B



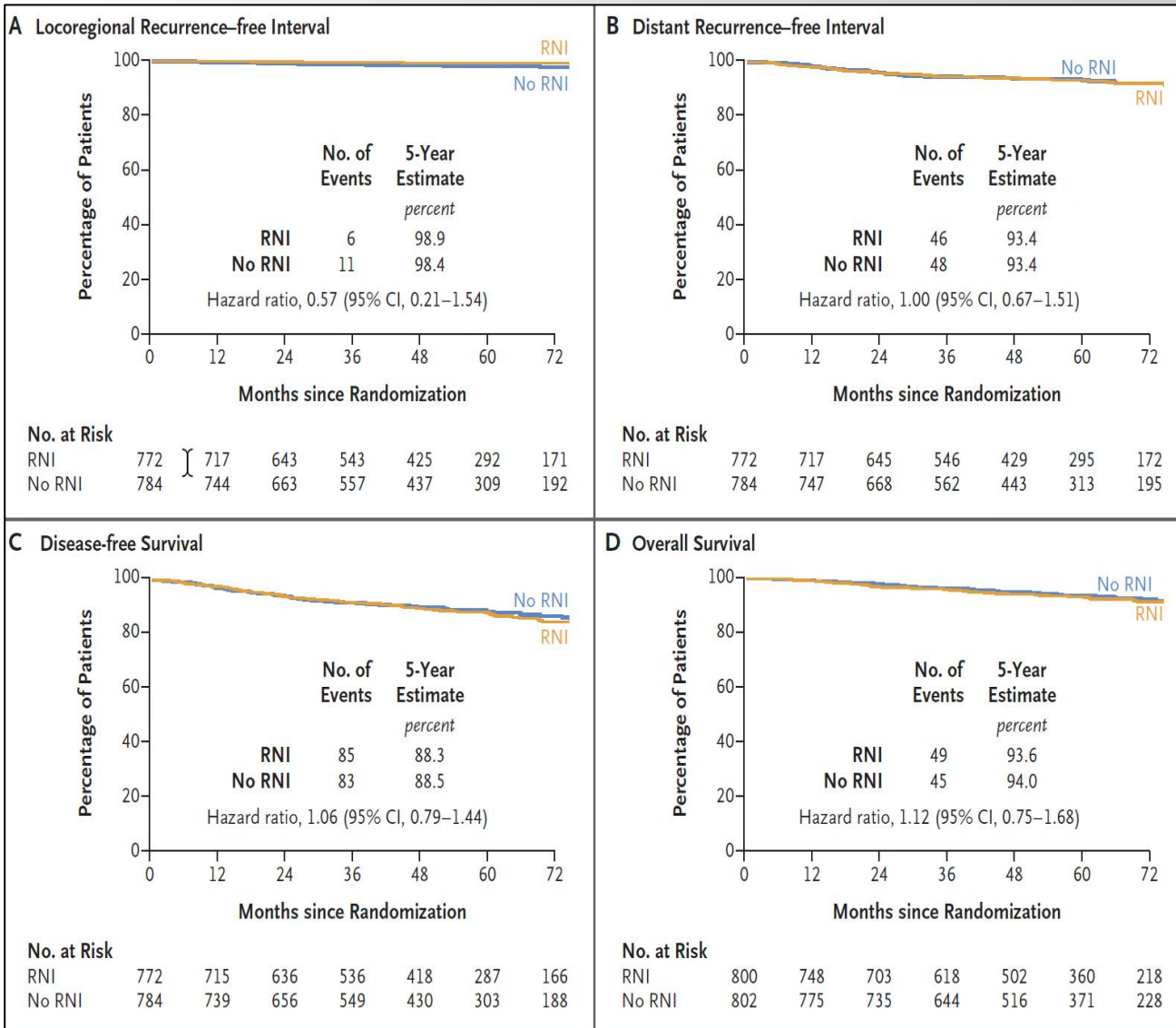


Figure 2. Effects of Regional Nodal Irradiation on Secondary End Points.

Shown are effects of regional nodal irradiation on the locoregional recurrence-free interval (Panel A), the distant recurrence-free interval (Panel B), disease-free survival (Panel C), and overall survival (Panel D).

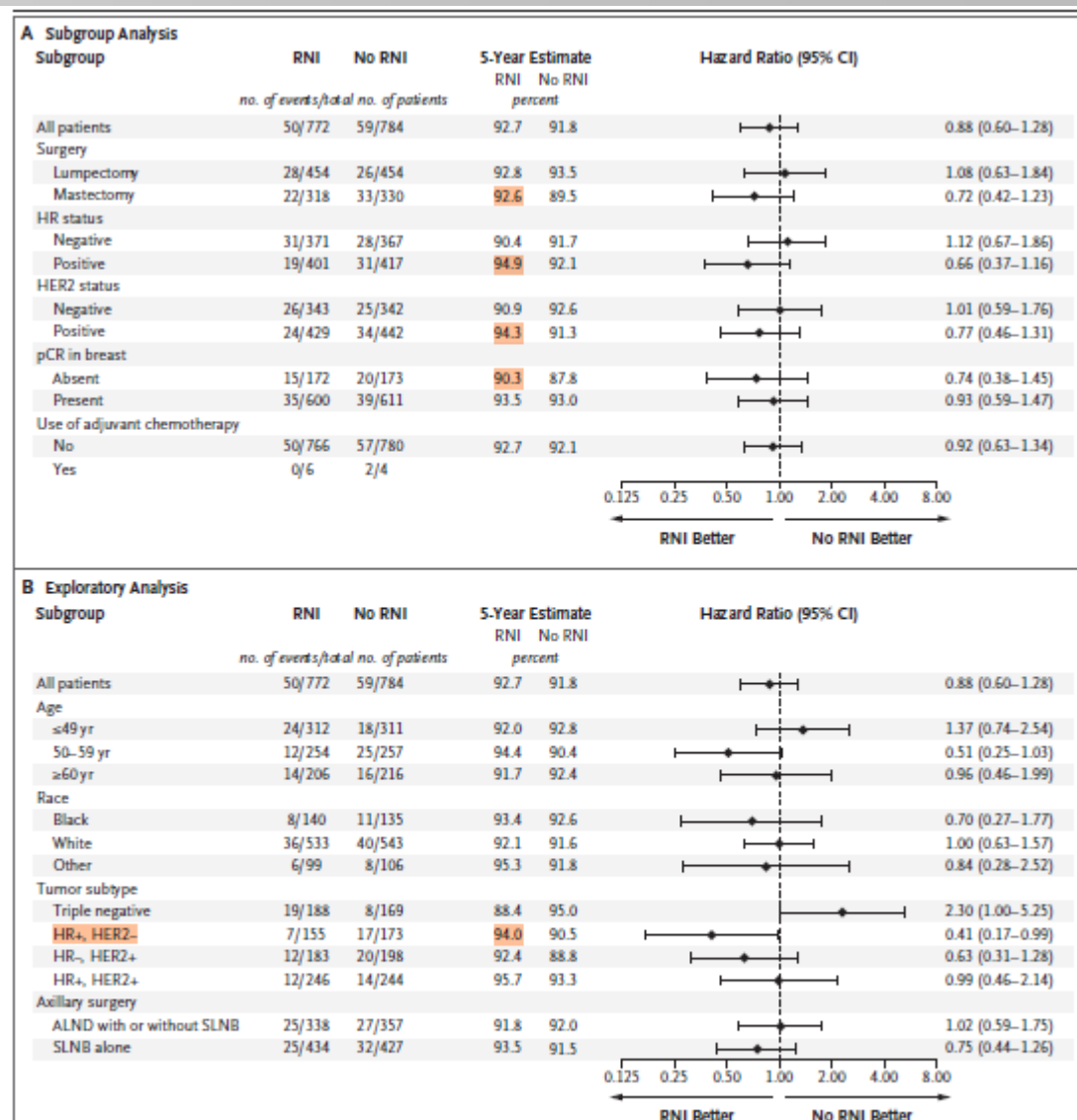


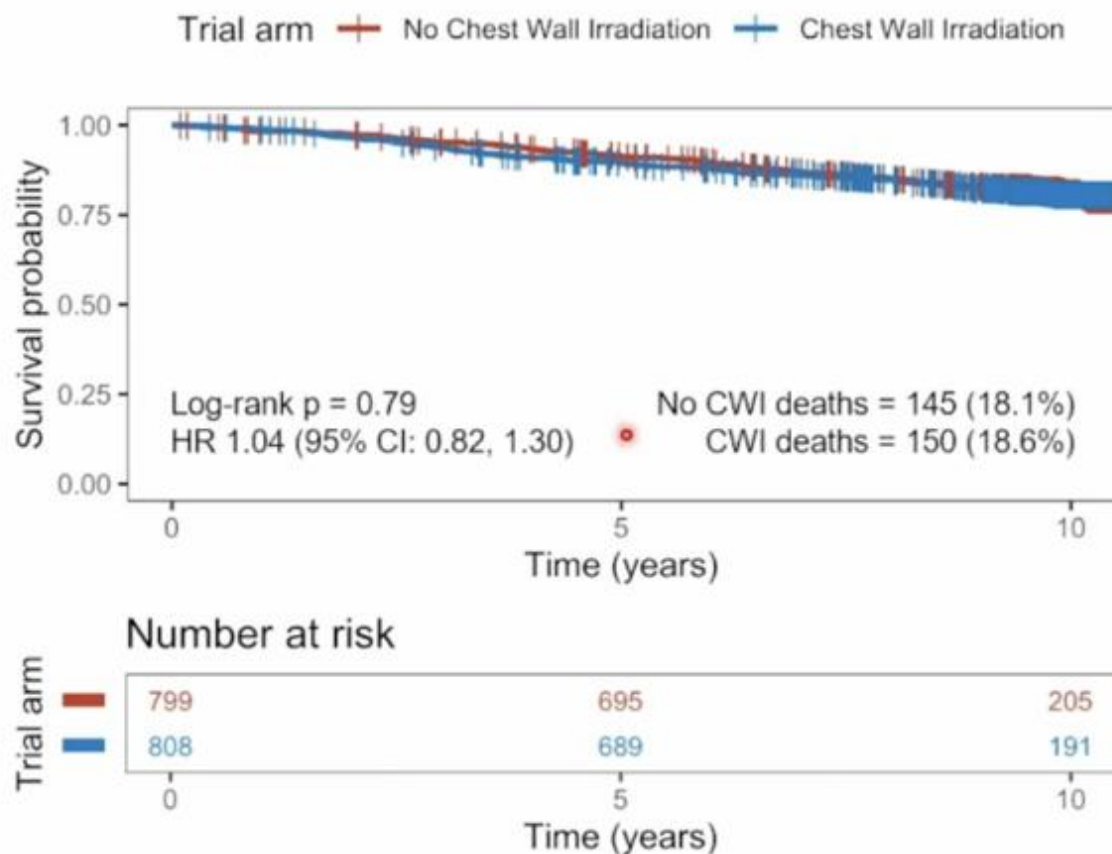
Figure 3. Subgroup Analysis of the Invasive Breast Cancer Recurrence-free Interval.

Shown are results from the analysis of the invasive breast cancer recurrence-free interval in prespecified subgroups (Panel A) and results from an exploratory analysis according to additional variables (Panel B). ALND denotes axillary-lymph-node dissection, HER2 human epidermal growth factor receptor 2, HR hormone receptor, pCR pathological complete response, and SLNB sentinel-lymph-node biopsy.

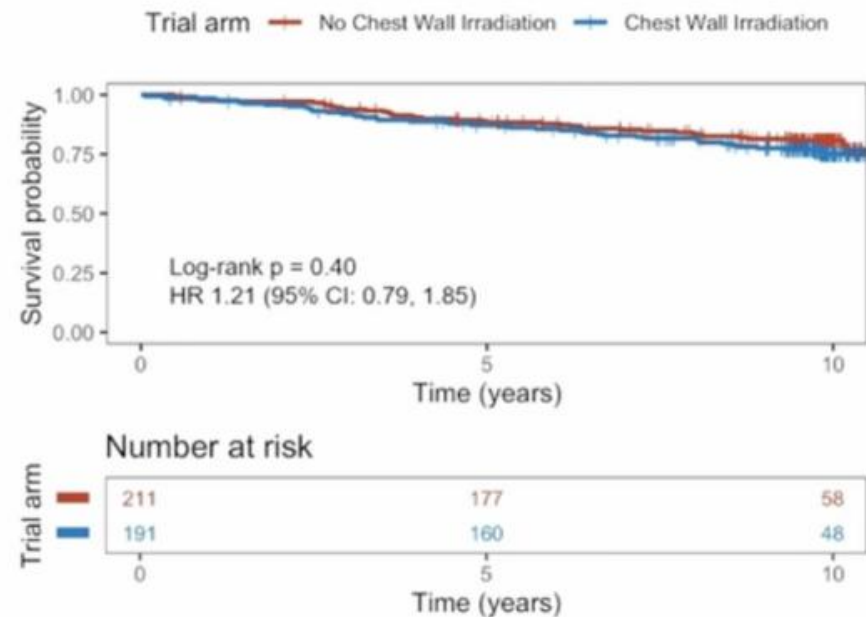
Does postmastectomy radiotherapy in 'intermediate-risk' breast cancer impact overall survival? 10 year results of the BIG 2-04 MRC randomized trial on behalf of the SUPREMO trial investigators

- Study by Kunkler et al,
- pT1-2N1, pT2N0M0 with G III+/-LVI, pT3N0 patients
- Randomized to CWI v/s NO CWI
- If Axillary sampling +ve-> Axillary LN clearance
- 1679 patients randomized
- Primary Endpoint: 10 year OS (7% improvement from 56% to 63%)
- RT dose: 40-50 Gy/ 15-25#

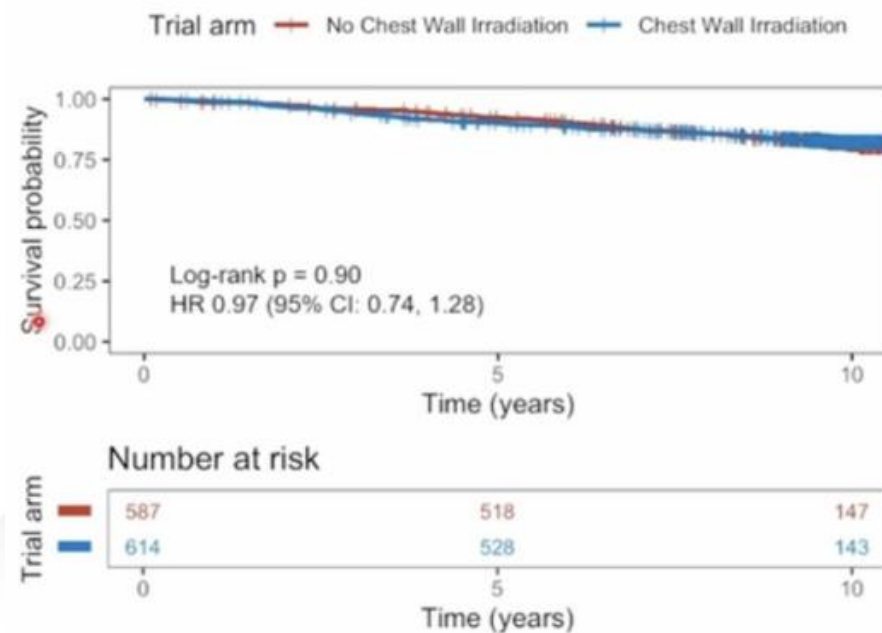
Kaplan-Meier Curves for ITT Population: Overall Survival by Randomized Treatment



N0 Patients

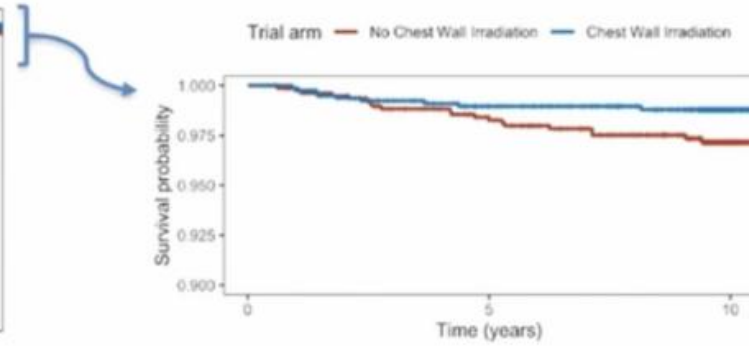
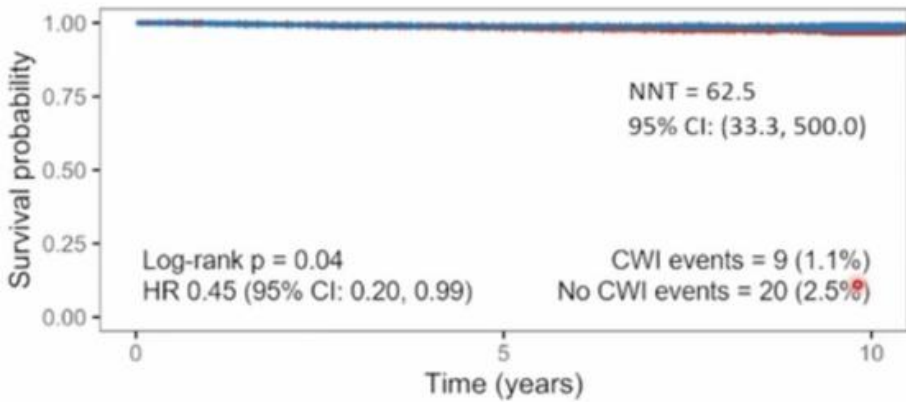


N+ Patients



Kaplan-Meier Curves for ITT Population: Local Recurrence by Randomized Treatment

Trial arm — No Chest Wall Irradiation — Chest Wall Irradiation

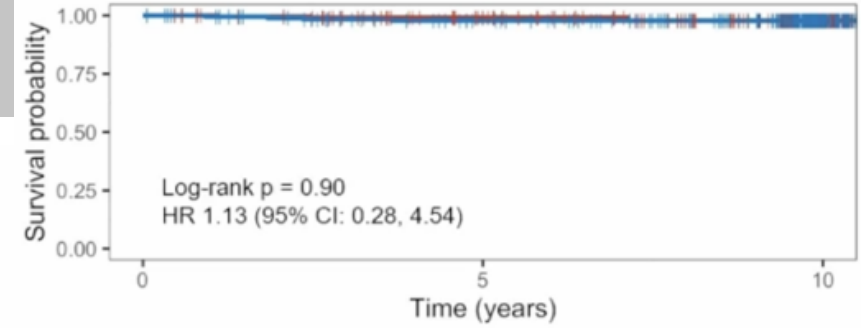


Number at risk

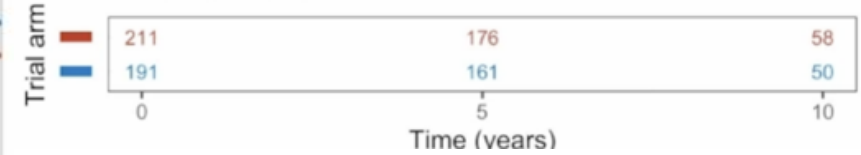


N0 Patients

Trial arm — No Chest Wall Irradiation — Chest Wall Irradiation

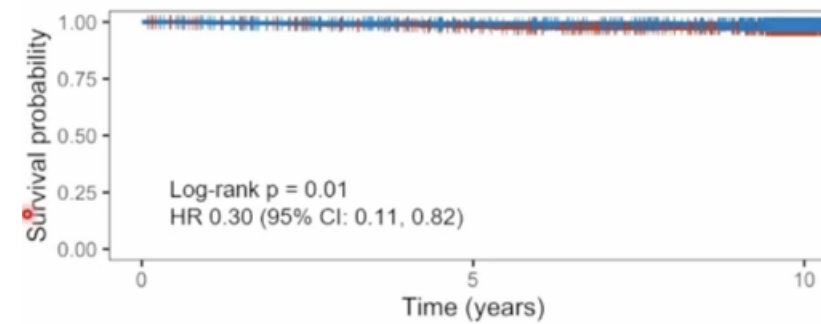


Number at risk

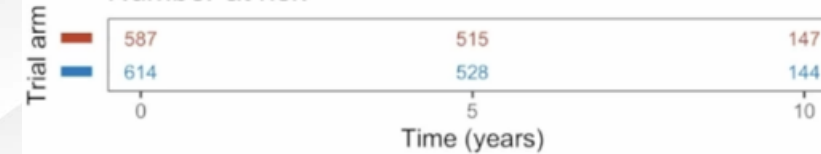


N+ Patients

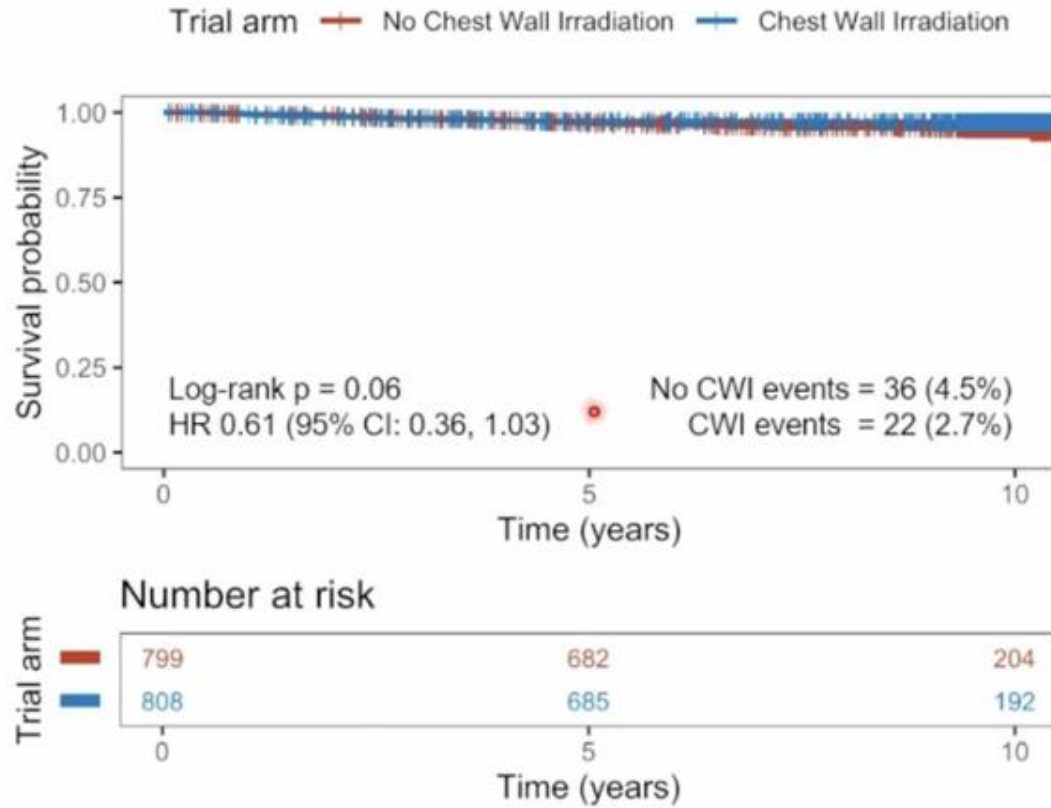
Trial arm — No Chest Wall Irradiation — Chest Wall Irradiation



Number at risk



Kaplan-Meier Curves for ITT Population: Regional Recurrence by Randomized Treatment



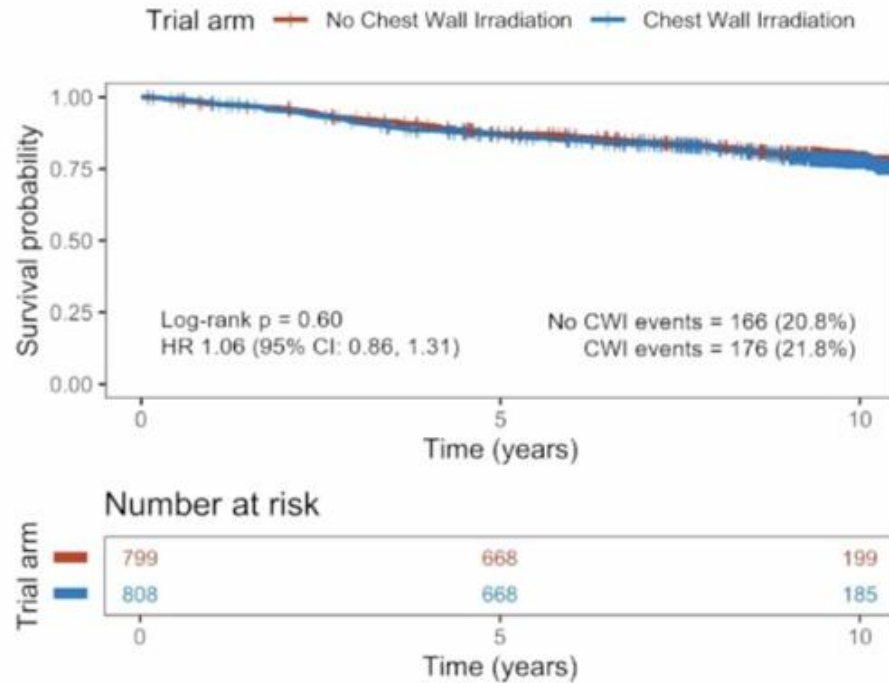
N0 Patients



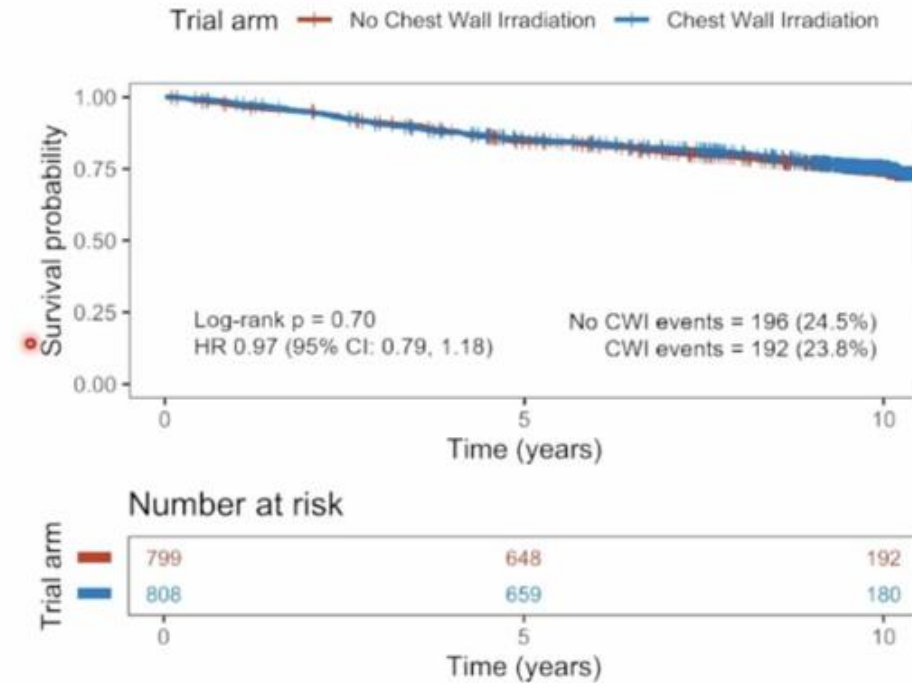
N+ Patients



Kaplan-Meier Curves for ITT Population: Metastasis-free Survival by Randomized Treatment



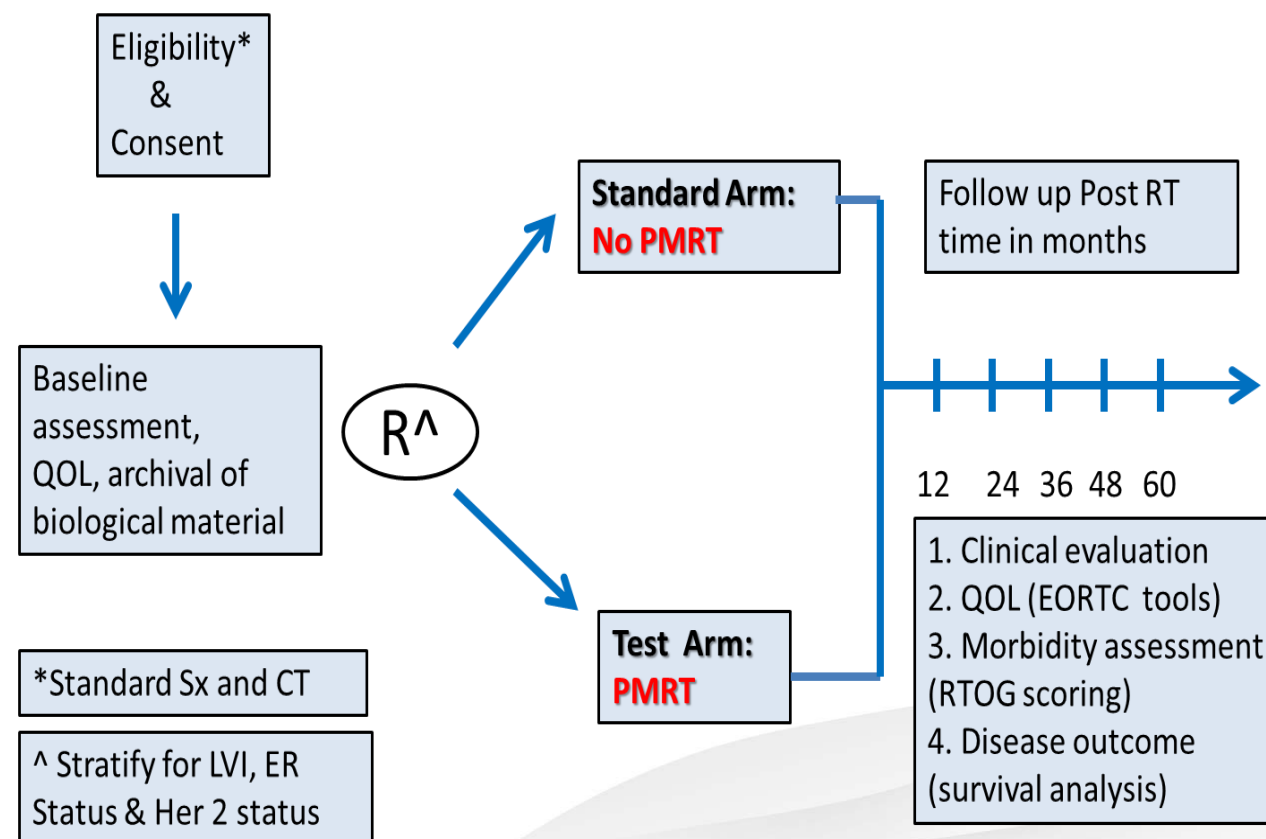
Kaplan-Meier Curves for ITT Population: Disease-free Survival by Randomized Treatment



- ❖ PMRT did not improve outcomes in low-intermediate risk patients who were predominantly accrued in the trial
- ❖ Question still REMAINS unanswered about the efficacy of PMRT in HIGH RISK BC N0-1 BC
- ❖ Final results and full paper are awaited

Post-Mastectomy Radiation Therapy in High Risk, Node Negative women with Early Breast Cancer (PMRT-NNBC)

- Multi-institutional, prospective, phase III trial
- Superiority design, RCT evaluating role of PMRT in NNBC with high-risk features
- Sample size: 1022
- Randomization arm: PMRT v/s No PMRT
- Current accrual: 510 (on 18.08.25)
- RT dose: 40Gy/15 fr
- RT Target: CW + SCF



Comparison of NNBC vs. SUPREMO

		ENTIRE* (N=777)	NNBC (N=481)	SUPREMO (N=1607)	Comparison of Entire with SUPREMO	Comparison of NNBC with SUPREMO
Age range (years)	< 45	181(23%)	118(24.5%)	251(15.6%)	<0.001	<0.001
	45-54	260(34%)	175(36%)	552(34.3%)		
	55-69	282(36%)	161(33.5%)	592(36.8%)		
	>70	54(11%)	27(6%)	212(13.2)		
Grade	I/II	51(6.5%)	27(6%)	753(46.9%)	<0.001	<0.001
	III	726(93.5%)	454(93.5%)	834(52%)		
	Missing	-	-	20(1.1%)		
T	T1	86(11%)	40(8%)	492(30.6%)	<0.001	<0.001
	T2	691(89%)	441(92%)	1104(68.7%)		
N	N0/Nm	777(100%)	481(100%)	402(25.1%)	<0.001	<0.001
TN	T1/T2N0	777(100%)	481(100%)	388(24.1%)	<0.001	<0.001
ER/PR	Positive	357 (46%)	182 (38%)	Data Not Provided		
	Negative	420 (54%)	299 (62%)	Data Not Provided		
Her2	Positive	273(35%)	177(37%)	331(20.6%)	<0.001	<0.001
	Negative	496(64%)	304(63%)	1110(85.5%)		
	Missing	8(1%)	-	166(10.3%)		
TNBC	Yes	257(33%)	177(37%)	173(10.8%)	<0.001	<0.001
	No	512(66%)	304(63%)	1374(85.5%)		
	Missing	8(1%)	-	60(3.7%)		
LVI	Present	300(39%)	179(37%)	618(38.5%)	0.8616	0.370
	Absent	467(60%)	302(63%)	947(58.9%)		
	Missing	10(1%)	-	42(2.6%)		

*accrued + screen failure

- The patient characteristics are markedly different in the two trials
- Significantly more high-risk patients accrued in the NNBC trial
- Raises the question of the generalizability of the SUPREMO trial results to the high-risk population
- Applicability in e



Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update



Practical Radiation Oncology (2016) 6, e219-e234

- Is PMRT indicated in patients With T1-2 tumors with one to three positive axillary lymph nodes who undergo ALND?

Recommendations: The panel unanimously agreed that available evidence shows that PMRT reduces the risks of locoregional failure (LRF), any recurrence, and breast cancer mortality for patients with T1-2 breast cancer with one to three positive axillary nodes. However, some subsets of these patients are likely to have such a low risk of LRF that the absolute benefit of PMRT is outweighed by its potential toxicities. In addition, the acceptable ratio of benefit to toxicity varies among patients and

Similarly, PMRT is endorsed by NCCN, ESMO St Gallen guidelines

- Some subsets with low risk may not benefit

Patient factors

- Age
- Life expectancy
- Comorbidities increasing risk of complications

Pathologic factors

- T1 tumors
- No LVE
- One node +
- LN ratio
- Small size of nodal met
- Significant response to NACT

Biologic factors

- Low grade
- Strong HR +

Treatment factors

- Planned systemic therapy



❖ Ongoing PMRT Studies

Study Name	Sample Size	Primary Endpoint	Methods	Details
POTENTIAL (NCT04320979)	1800	DFS with or w/o IMNI	Phase III, Multicenter, Open-label PMRT with IMNI vs PMRT without IMNI (both include chest wall ±SCF/axilla as indicated)	POMRT in Node-positive breast cancer with or without Internal mammary nodal irradiation RT dose: Conventional or hypofractionation RT Randomization / stratification: By center, tumor location (medial/central vs lateral), nodal burden (1–3, 4–9, ≥10), neoadjuvant chemo (yes/no).
Hypofractionated Radiation Fractionation in Breast Cancer Patients with Implant-Based Reconstruction (NCT06830083)	840	Safety/ Reconstruction complication rate and efficacy of hypofractionated regime vs conventional in patients with implant-based reconstruction	RCT Mastectomy patients with implant/tissue expander reconstruction with indications of PMRT randomized to different dose fractionation	PMRT; Randomised to Conventional 50Gy/25# vs Hypofractionation 40-42.56 Gy/15-16#
Post-Rad in N1 BC (NCT05440149)	1106	7-year DFS non-inferiority	Multicentre, Phase III, Non-inferiority PMRT vs No PMRT WBI+RNI vs WBI alone	Comparing standard PORT vs de-escalation/omission strategy in pN1
Omit PMRT after Neoadjuvant (NCT05993559)	1314	5-year DFS non-inferiority	Phase III Randomised Open-label Randomise: PMRT vs No PMRT	NACT-> Mastectomy, If complete pathological response RCB score 0-1
TAILOR RT (NCT03488693)	2140	9.5-year breast cancer recurrence-free interval	Multicentre, Phase III, Non-inferiority PMRT vs No PMRT WBI+RNI vs WBI alone	Testing omission of RNI in BCS and PMRT in MRM

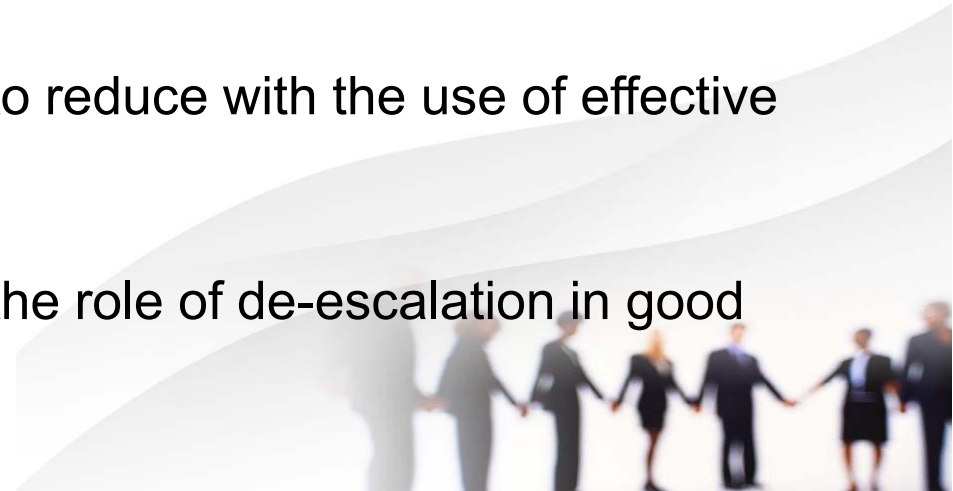
❖ PMRT SUMMARY

- The role of PMRT has evolved tremendously over the last few decades.
- The benefit of PMRT depends on the extent of axillary surgery and systemic therapy
- EBCTCG Meta-analysis (2014) gives robust evidence of the benefit of PMRT for **ALL** node-positive patients
- However, recent SUPREMO data suggests a lack of benefit in the intermediate-risk N0-N1 population when contemporary systemic therapy is used >> full results awaited
- The SUPREMO population had the **majority of low-intermediate risk** patients compared to the NNBC trial subjects >> generalizability is a questionable
- **Current practices** deviate from the standards used in SUPREMO
 - SNB+ do not undergo ALND (contrary to SUPREMO)
 - SNB+ patients receive axillary RT



❖ PMRT SUMMARY

- A more nuanced approach is required to **decipher N1 patients' subgroup** that will benefit from PMRT
 - Number of LNs + or LNR
 - Age
 - Life expectancy
 - Competing risk
 - Clinico-pathological characteristics
- As treatment protocols evolve, the role of PMRT is likely to reduce with the use of effective systemic therapy
- Ongoing trials in the neoadjuvant setting are addressing the role of de-escalation in good responders



THANK YOU!

