Radiotherapy or not in patients with 1-3 positive axillary nodes

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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

EBCTCG (Early Breast Cancer Trialists' Collaborative Group)*

*Collaborators listed at end of report

Meta-analysis

- 8135 women treated 1964-1986 in 22 trials
- Radiotherapy to chest wall and regional LN following mastectomy and axillary surgery vs the same surgery
- Radiotherapy covers chest wall, supraclavicular and /or axillary fossa and internal mammary chain
- Median length of follow up 9.4 years

Findings

- In women who had mastectomy and axillary dissection in at least level I & II, radiotherapy that included the chest wall, the supraclavicular and /or axillary fossa and the internal mammary chain reduced loco-regional recurrence, overall recurrence, breast cancer mortality and overall mortality for all node positive women;

- Proportional reduction in rates of recurrence and breast cancer mortality did not differ significantly
  - With systemic treatment given
  - Other tumour related factors
  - One positive node vs 2-3 positive node

Table 1. Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional nodes following mastectomy and axillary surgery *versus* no radiotherapy but the same surgery.*

Nodal status§	Women	Deaths	Woman-years since diagnosis†					% women given systemic therapy‡		
			Median/ woman	Total ('000s)	Distribution by years ('000s) <10	10-	20+	Chemotherapy	Tamoxifen and ER+¶	Any
(a) Axillary dissection										
pN0	700	480	20.1	13.5	6.1	4.4	3.0	22	27	47
pN+	3131	2074	7.2	30.1	20.3	7.9	1.9	75	22	91
pN1-3	1314	759	12.3	17.3	10.3	5.3	1.6	65	24	86
pN4+	1772	1286	4.8	12.4	9.7	2.5	0.3	81	21	95
pN?+	45	29	6.7	0.4	0.3	0.1	<0.1	100	0	100
pN unknown	56	39	10.6	0.7	0.4	0.2	0.1	29	71	98
Total for (a)	3887	2593	9.0	44.3	26.8	12.5	4.9	64	24	83
(b) Axillary sampling										
pN0	870	595	17.6	15.4	7.5	5.1	2.8	10	11	21
pN+	2541	1689	7.8	24.2	17.0	6.4	0.2	56	28	84
pN unknown	654	460	9.3	7.1	4.6	2.1	0.4	44	30	74
Total for (b)	4065	2744	9.8	46.8	29.1	13.7	4.0	44	25	69
(c) Axillary surgery, but extent unknown										
pN0	24	12	8.5	0.2	0.2	<0.1	-	100	0	100
pN+	149	69	11.5	1.3	1.1	0.2	-	100	0	100
pN unknown	10	6	11.0	0.1	0.1	<0.1	-	100	0	100
Total for (c)	183	87	10.1	1.6	1.4	0.2	-	100	0	100
Total (a)+(b)+(c)	8135	5424	9.4	92.7	57.3	26.4	9.0	55	24	77

*Data were available for 22 trials, start dates 1964 to 1986, and were unavailable for 4 trials including approximately 400 women. In all 22 trials for which data were available, radiotherapy was given to the chest wall and the supraclavicular and/or the axillary fossa. In 20 of the 22 trials it was also given to the internal mammary chain. Details of the treatments given in these 22 trials are in webtable 1. Details of other trials of radiotherapy after mastectomy are in webtables 2-7.

†Numbers of woman-years of follow-up for mortality. Many trials followed women for only 10 years for recurrence.

‡Chemotherapy was usually cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). Only 3% of women were classified as oestrogen-receptor positive (ER+) and were in trials where both tamoxifen and chemotherapy were given.

§pN: pathological nodal status, pN+: pathologically node positive, pN1-3: 1-3 pathologically positive nodes, pN4+: at least 4 pathologically positive nodes, pN?+: known to be pN+ but not whether pN1-3 or pN4+, pN unknown: pathological nodal status unknown.

¶Oestrogen-receptor positive.

Figure 1. Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional recurrence and overall recurrence and on 20-year risk of breast cancer mortality in 700 women with pathologically node-negative (pN0) disease and in 3131 women with pathologically node-positive (pN+) disease. See also webfigures 2-6, 29 & 30.

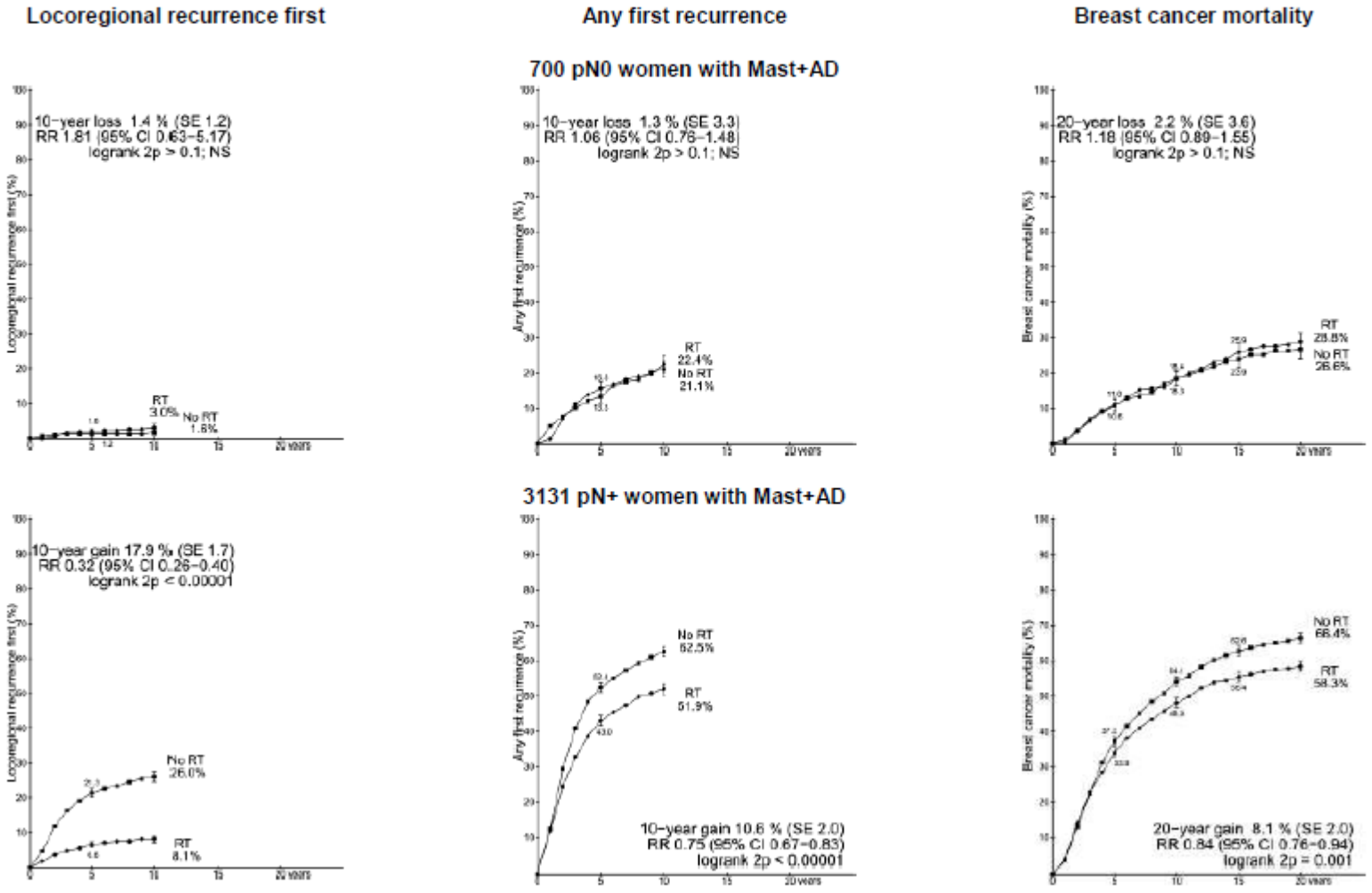


Figure 2. Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional recurrence and overall recurrence and on 20-year risk of breast cancer mortality in 1314 women with 1-3 pathologically positive nodes (pN1-3) and in 1772 women with 4+ pathologically positive nodes (pN4+). See also webfigures 7-8, 16-18, 31 & 32.

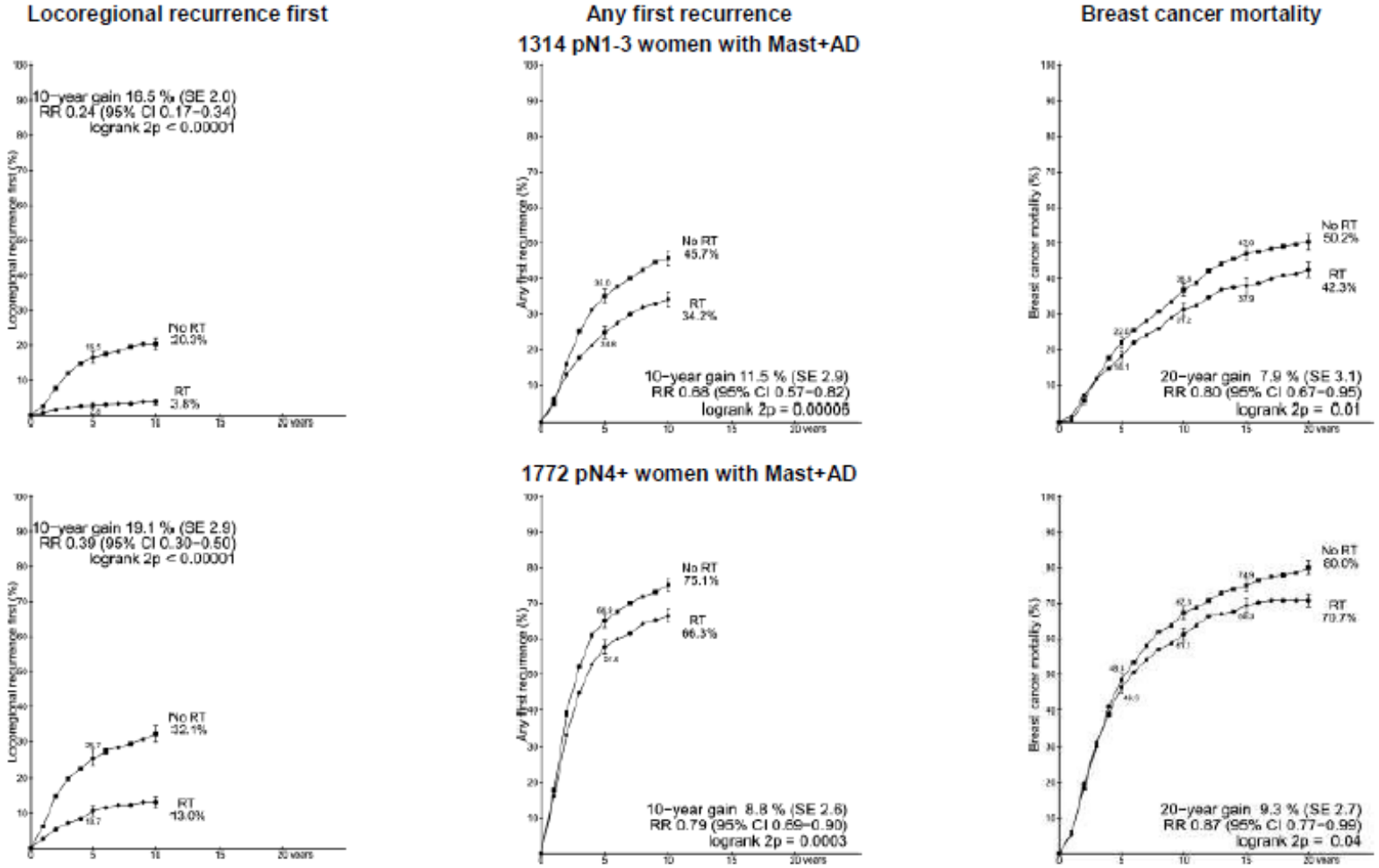
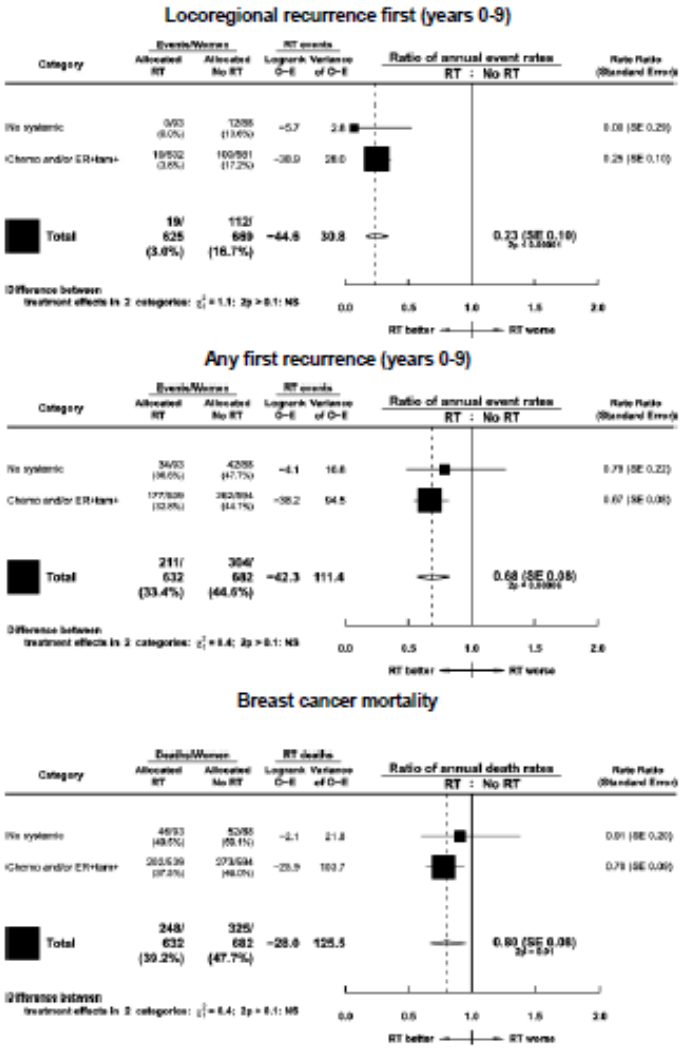
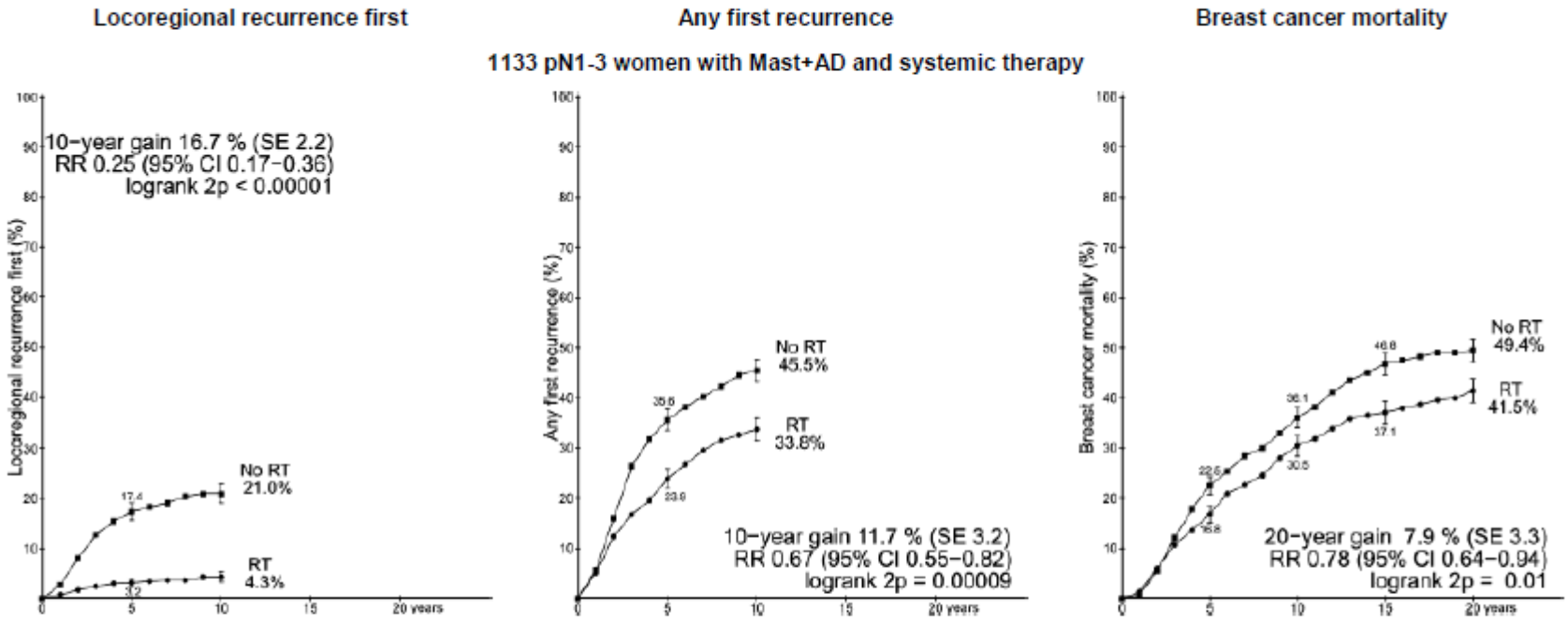


Figure 3. Effect of radiotherapy (RT) after mastectomy and axillary dissection. Event rate ratios and 95% confidence intervals for locoregional recurrence and overall recurrence during years 0-9 and for breast cancer mortality for the entire period of follow-up in 1314 women with 1-3 pathologically positive nodes (pN1-3), according to whether or not they were in trials where systemic therapy was given to both randomised treatment groups. See also webfigure 9.



Note: One trial did not supply locoregional events for 20 women. Chemotherapy was usually cyclophosphamide, methotrexate, 5-fluorouracil (CMF). ER negative women in trials where tamoxifen was given to both arms are included in the "No systemic" category.

Figure 4. Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional recurrence and overall recurrence and on 20-year risk of breast cancer mortality in 1133 women with 1-3 pathologically positive nodes (pN1-3) in trials where systemic therapy was given to both randomised treatment groups. See also webfigures 10 & 11.



CAVEATS

- Neoadjuvant Chemotherapy uncommonly employed
- Sentinel node biopsy was not used
- Era before the use of taxane, herceptin and aromatase inhibitors
- Outdated radiation planning, treatment delivery and quality assurance

MA 20 Canadian Trial

- High risk node negative and node positive women treated with BCT (1832)
- WBI plus regional radiotherapy (internal mammary + medial supraclavicular) vs WBI
- Median follow up 62 months
- LR DFS 96.8% vs 94.8%

  Distant DFS 92.4% vs 87% p=0.002

  Overall DFS 89.7% vs 84% p=0.003

  Overall survival 91.9% vs 89.5% p=0.07

EORTC-22922 Trial

- 4004 node positive women with BCT (76%) or mastectomy (24%)
- WBI plus IM-MSRT vs WBI alone
- HR for reduction in DFS 0.89 (p=0.04)

  HR for reduction in survival 0.87 (p=0.056)

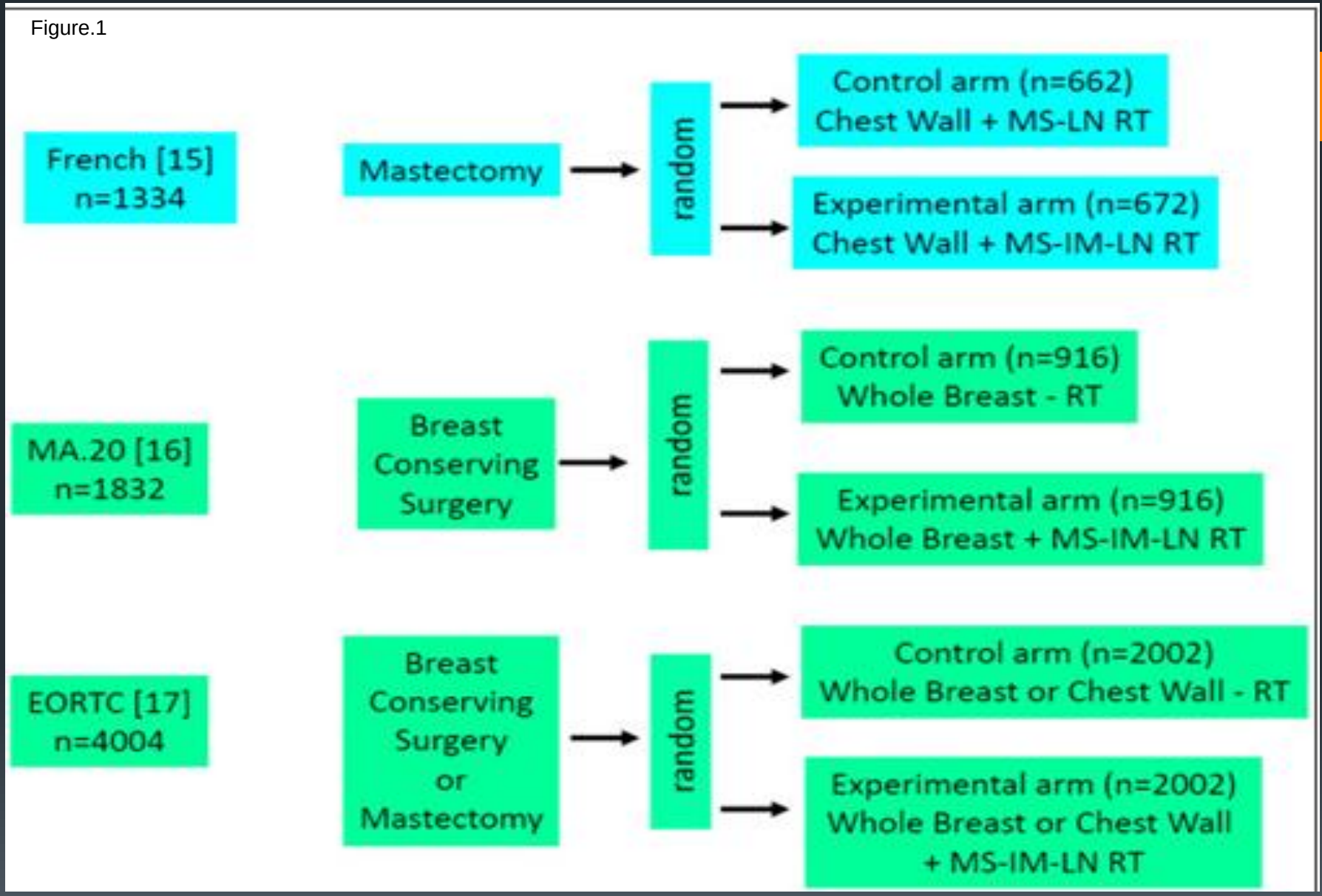
Table 1

Patient characteristic

	MA.20[16]	EORTC[17]	French[15]
Recruitment years	2000-2007	1996-2004	1991-1997
Number of patients	1832	4004	1334
Median age	54	54	57
Node positive	85%	56%	75%
Breast surgery	100% breast conserving	75% breast conserving	100% mastectomy
CHX	91%	85%	61%
ER/PR negative	25%	16%	7%
Unknown ER/PR status	n.a.	6%	40%
Main inclusion criteria	N + or high risk* N0 any location	N + or medial/central tumor	N + or medial/central tumor
Breast/chest wall	Both arms: 50 Gy / 25 fx	Both arms 50 Gy / 25 fx	Both arms according to practice of the center
Medial supraclavicular nodes	Experimental arm: 45 Gy / 25 fx	50 Gy / 25 fx	All patients: dose and fractionation according to practice of the center
Internal mammary nodes	Experimental arm: 45 Gy / 25 fx	Experimental arm: 50 Gy / 25 fx	Experimental arm: 45 Gy / 20 fx

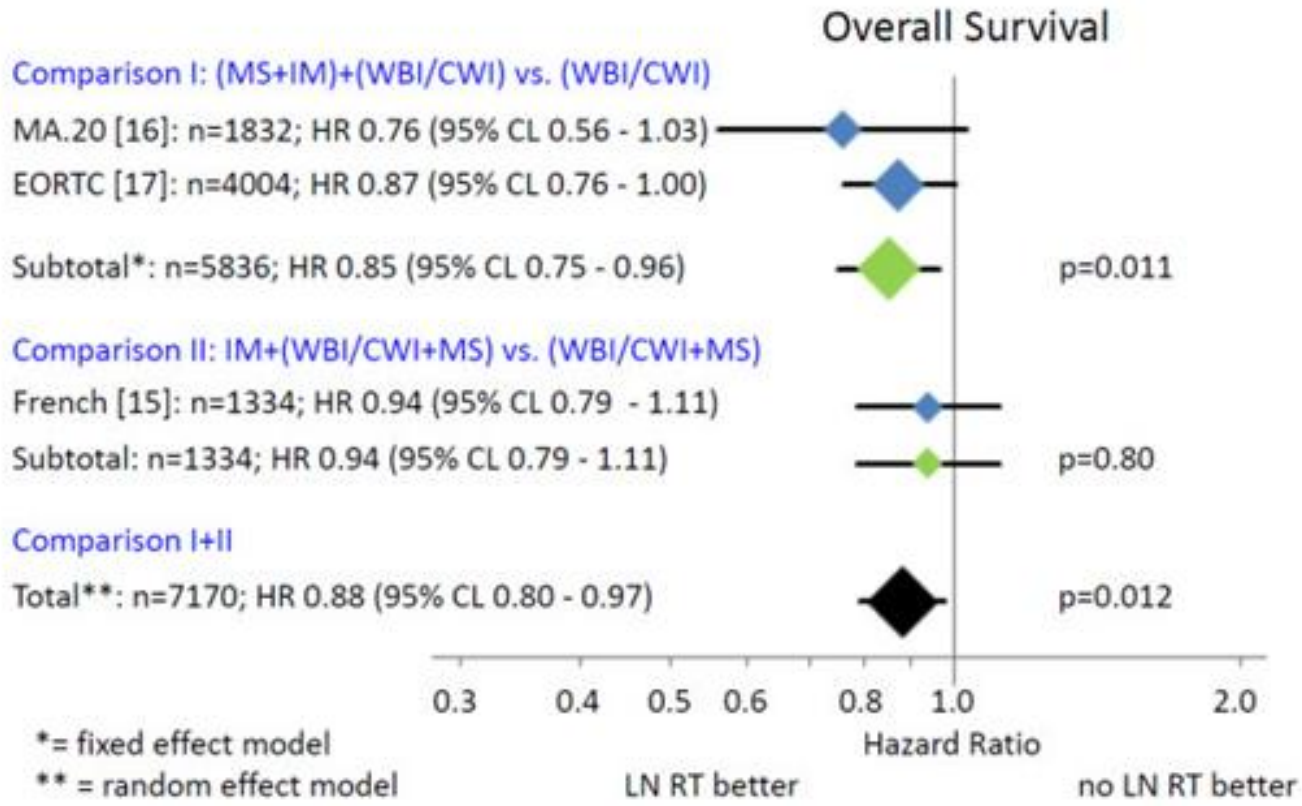
*=>= 5 cm tumor, >= 2 cm tumor, and <10 axillary nodes removed with ER-, G3, or lymph vacular invation; n.a. = not available; fx = fractions; ER = estrogene receptor; PR = progesterone receptor.

Figure.1



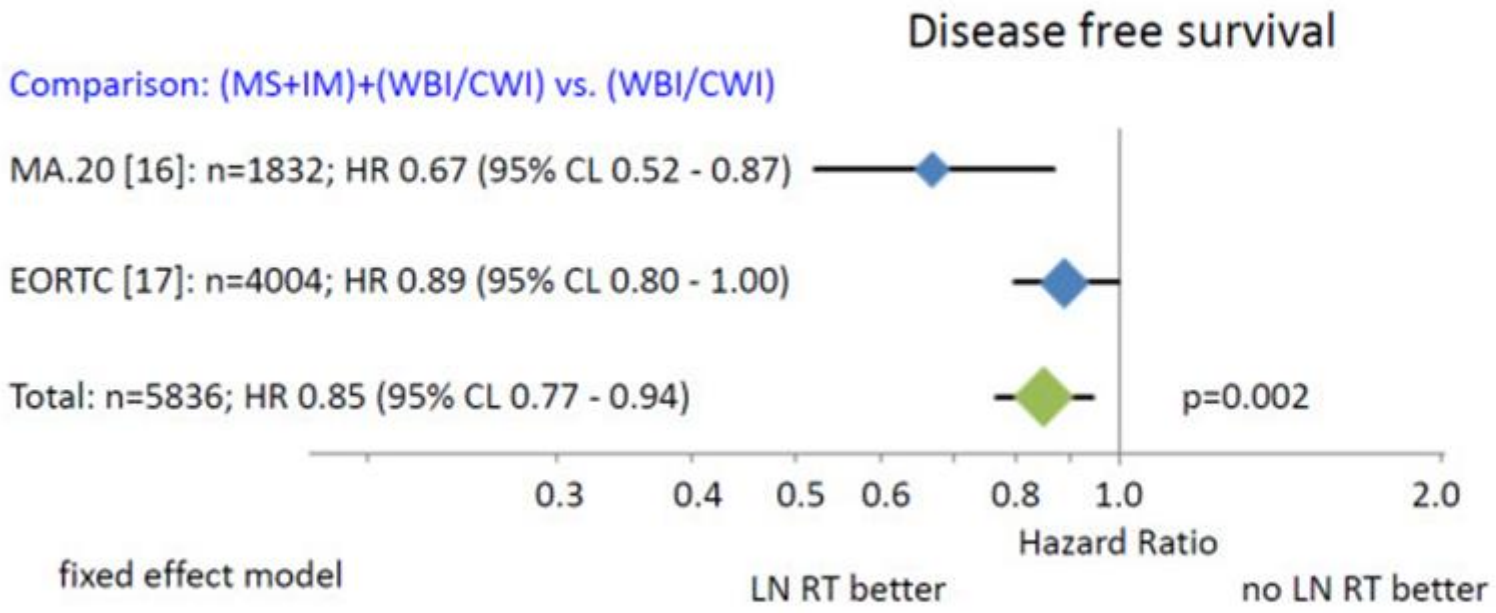
Trial designs. Random=randomization. RT=radiotherapy. MS-LN-RT=radiotherapy of medial supraclavicular lymph nodes. MS-IM-RT=radiotherapy of medial supraclavicular and internal mammary lymph nodes.

Figure 2



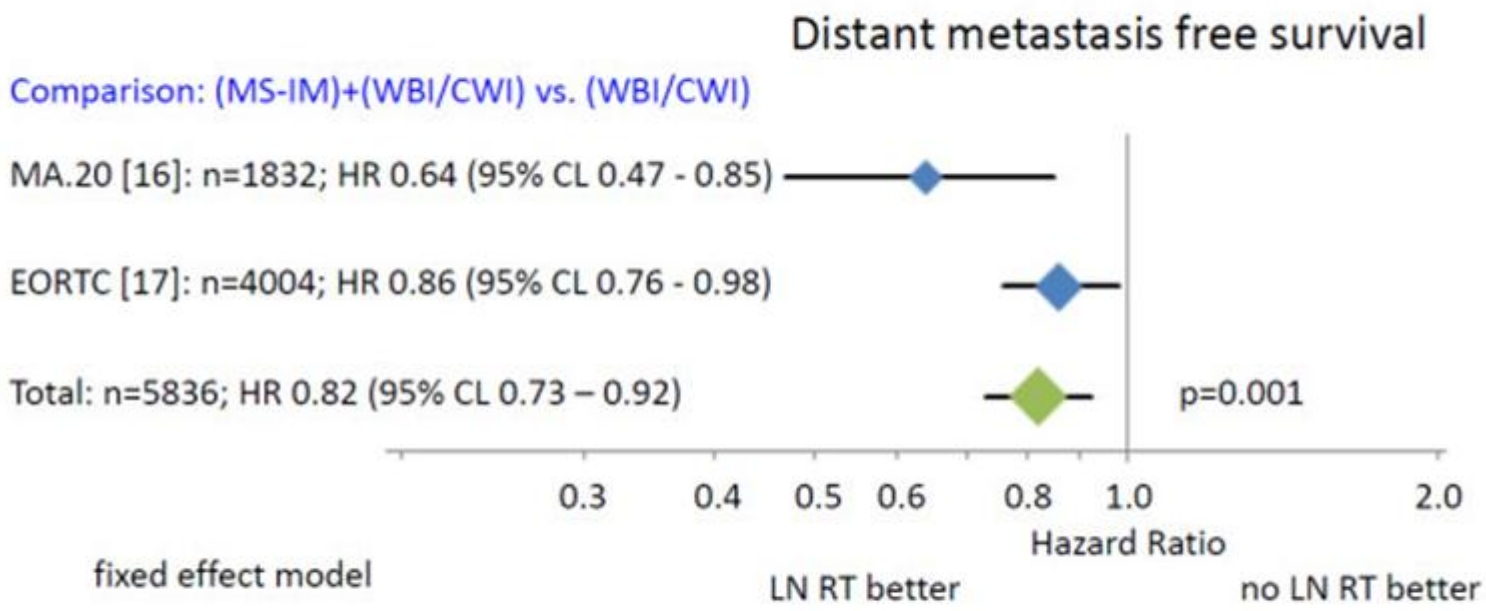
Overall survival. The area of the symbols reflect the number of patients, MS+IM=medial supraclavicular and internal mammary lymph node irradiation, WBI/CWI=whole breast irradiation or chest wall irradiation, MS=medial supraclavicular lymph node irradiation.

Figure 3



Disease free survival. The area of the symbols reflect the number of patients. MS + IM = medial supraclavicular and internal mammary lymph node irradiation, WBI/CWI = whole breast irradiation or chest wall irradiation.

Figure 4



Distant metastasis free survival. The area of the symbols reflect the number of patients, MS + IM = medial supraclavicular and internal mammary lymph node irradiation, WBI/CWI = whole breast irradiation or chest wall irradiation.

Table 2

Late toxicity in breast cancer trials on regional radiotherapy

Trial late toxicity	MA.20[16]			EORTC[17]			French[15]		
	MS-IM-	IM-IM+	p	MS-IM-	IM-IM+	p	MS+	IM-IM+	p
Lung									
Grade 2	0.2%	1.3	0.01	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Grade >2	0%	0%	n.a.	n.s.					
Any grade n.a	n.a.	n.a.	n.a.	1.3%	4.3%	<0.0001	n.a.	n.a.	n.a.
Lymphedema									
Grade 2	3.7%	6.8%	0.004	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Grade >2	0.4%	0.4%	n.s.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Any grade (arm)	n.a.	n.a.	n.a.	3.6%	3.8%	n.s.	n.a.	n.a.	n.a.
Cardiac									
Any grade	n.a.	n.a.	n.a.	1.4%	1.6%	n.s.	1.7%	2.2%	n.s
Total late									
Any grade	n.a.	n.a.	n.a.	21.8%	25.5%	0.006	n.a.	n.a.	n.a.
Grade >2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	2.3%	3.1%	n.s.

Late toxicitiy.
n.a.=not available; n.s.=not significant; MS-IM-: no radiotherapy of the medial supraclavicular and internal mammary lymph nodes; MS-IM+: radiotherapy of the medial supraclavicular and internal mammary lymph nodes; MS+: radiotherapy of the medial supraclavicular lymph nodes.

Use of Radiation Therapy (RT) 50 Years Ago and Now

	50 Years Ago	Now
Measuring the benefit of RT	Reduction in LRR	Reduction in "any first event (LRR or DM)"
Breast-conserving therapy (BCT)	Highly experimental	A standard of care with survival and LRR rates similar to mastectomy
Post-mastectomy RT	The deleterious effects negated the beneficial effects.	Clearly improves survival in appropriate patients
Fractionation	1.8-2 Gy/d was standard for BCT	2.66 Gy/d is just as effective and safe in BCT shortening RT from 6 to 3-4 wk
Adjuvant systemic therapy	Not yet developed	Effective and serendipitously makes RT more effective and more important
Delivery of RT	• Cobalt-60 is the only megavoltage machine • Rudimentary treatment planning and delivery	• Multiple-energy linear accelerators • CT-based simulation • 3-D beam modulation for much greater dose homogeneity • On-board imaging as needed for greater accuracy • Deep breath hold to reduce cardiac dose
Cardiac toxicity	High cardiac doses and no knowledge of the problem	Cardiac doses are minimized by the use of heart blocks, prone technique, and deep inspiration breath hold techniques

Abbreviations: LLR, local-regional recurrence; DM, distant metastasis; wk, weeks; CT, computed tomography.

Risks factors for Loco-regional Recurrance

- Large T2 tumour
- Lymphovascular permeation
- 3 positive nodes
- Age <40
- Gross extracapsular extension
- Skin or nipple invasion
- Bloom and Richardson grade 3
- Inadequate axillary node dissection
- Triple negative disease
- Size of LN metastases

Thank you!