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

EBCTCG (Early Breast Cancer Trialists' Collaborative Group)*

*Collaborators listed at end of report

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			۱.	Woman-ye	ears since	diagnosis	+	% women giv	en systemic the	erapy‡
Nodal status§	Women	Deaths	Median/	Total	Distribution by years (• •	Chamatharan	Tamoxifen	A
			woman	('000s)	<10	10-	20+	Chemotherapy	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 unknow	n								
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

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.*

*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 appendix 10-12. Details of other trials of radiotherapy after mastectomy are in appendix pp 52-53, 64-65. 70-71, 78-79.

†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. Trials included in analysis.



Figure 2. Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional and overall recurrence and on 20-year risk of breast cancer mortality in 700 women with pathologically node-negative (pN0) disease and in 3131 women with pathologically node-positive (pN+) disease. Analyses of locoregional recurrence first ignore distant recurrences, see appendix pp 8-9 for details. See appendix pp 14, 16, for analyses of both locoregional and distant recurrences and appendix pp 13, 15, for analyses of overall mortality. RR=rate ratio. NS=not significant. Vertical lines indicate 1 SE above or below the 5, 10, 15, and 20 year percentages.



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Figure 3. Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional and overall recurrence and on 20-year risk of breast cancer mortality in 1314 women with 1-3 pathologically positive nodes (pN1-3) and in 1772 women with 4+ pathologically positive nodes (pN4+). Analyses of locoregional recurrence first ignore distant recurrences, see appendix pp 8-9 for details. See appendix pp 19, 28, for analyses of both locoregional and distant recurrences and appendix pp 18, 27, for analyses of overall mortality. RR=rate ratio. NS=not significant. Vertical lines indicate 1 SE above or below the 5, 10, 15, and 20 year percentages.



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Figure 4. Effect of radiotherapy (RT) after mastectomy and axillary dissection on overall recurrence during years 0-9 and on breast cancer mortality for the entire follow-up in 1314 women with one to three pathologically positive nodes (pN1-3), according to whether or not they were in trials in which systemic therapy was given to both randomised treatment groups. Chemotherapy was usually cyclophosphamide, methotrexate, fluorouracil. ER-negative women in trials in which tamoxifen was given to both groups are included in the "no systemic" category. ER=oestrogen receptor. Tam=tamoxifen. NS=not significant. SE=standard error. Confidence intervals are 95%.

Category	Events/ Allocated RT	Women Allocated No RT	<u>RT events</u> Logrank Variance O-E of O-E		Ratio of annual event rates RT : No RT	Rate Ratio (Standard Error)
No systemic	34/93 (36.6%)	42/88 (47.7%)	-4.1	16.8		0.79 (SE 0.22)
Chemo and/or ER+tam+	177/539 (32.8%)	262/594 (44.1%)	-38.2	94.5		0.67 (SE 0.08)
Total	211/ 632 (33.4%)	304/ 682 (44.6%)	-42.3	111.4	0.68 (SE 0 2p = 0.000	.08) ⁰⁶
Difference between treatment effects in 3	2 categories:	χ ² ₁ = 0.4; 2p =	• 0.1: NS	0.0	0.5 1.0 1.5 RT better - RT worse	2.0

A) Any first recurrence (years 0-9)



	Deaths/	Women	RT d	eaths				
Category	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of annual death rates RT : No RT	Rate Ratio (Standard Error)		
No systemic	46/93 (49.5%)	52/88 (59.1%)	-2.1	21.8		0.91 (SE 0.20)		
Chemo and/or ER+tam+	202/539 (37.5%)	273/594 (46.0%)	-25.9	103.7	-	0.78 (SE 0.09)		
Total	248/ 632 (39.2%)	325/ 682 (47.7%)	-28.0	125.5	0.80 (SE 0.08)			
Difference between treatment effects in	2 categories:	χ ² ₁ = 0.4; 2p >	• 0.1: NS	0.0	0.5 1.0 1.5 RT better RT worse	2.0		

Figure 5. 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. Analyses of locoregional recurrence first ignore distant recurrences, see appendix pp 8-9 for details. See appendix pp 22 for analyses of both locoregional and distant recurrences and appendix pp 21 for analyses of overall mortality. RR=rate ratio. NS=not significant. Vertical lines indicate 1 SE above or below the 5, 10, 15, and 20 year percentages.



Figure 6. Effect of radiotherapy (RT) after mastectomy and axillary dissection on overall recurrence during years 0-9 and for breast cancer mortality for the entire period of follow-up in 1133 women with one to three pathologically positive nodes (pN1-3) in trials in which systemic therapy was given to both randomised treatment groups, by number of positive nodes. NS=not significant. SE=standard error. Confidence intervals are 95%.

RT events Events/Women Allocated RT Allocated No RT Logrank Variance O-E of O-E Ratio of annual event rates Rate Ratio (Standard Error) Category RT : No RT 35/145 (24.1%) 63/173 (36.4%) 1 positive node -10.6 21.1 0.60 (SE 0.17) 69/178 (38.8%) 92/187 (49.2%) 2-3 positive nodes -8.5 32.7 ÷ 0.77 (SE 0.15) 73/216 (33.8%) 107/234 (45.7%) Unknown but pN1-3 -18.3 38.3 -0-0.62 (SE 0.13) 177/ 262/ 594 0.67 (SE 0.08) 539 -37.5 92.1 Total \rightarrow (32.8%) (44.1%) Difference between treatment effects in 2 categories: $\chi_1^2 = 0.8$; 2p > 0.1: NS 0.0 0.5 1.0 1.5 2.0 RT better - RT worse

A) Any first recurrence (years 0-9)

B) Breast cancer mortality

	Deaths/	Women	RTd	leaths		
Category	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of annual death rates RT : No RT	Rate Ratio (Standard Error
1 positive node	46/145 (31.7%)	66/173 (38.2%)	-5.7	23.8	_	0.79 (SE 0.18)
2-3 positive nodes	76/178 (42.7%)	96/187 (51.3%)	-7.0	37.1		0.83 (SE 0.15)
Unknown but pN1-3	80/216 (37.0%)	111/234 (47.4%)	-11.4	41.4	-0-1	0.76 (SE 0.14)
Total	202/ 539	273/ 594	-24.1	102.3	0.78 (SE 0.0)	3)
	(37.5%)	(46.0%)			2p = 0.01	- /
Difference between				L		
treatment effects in	2 categories:	$\chi_1^2 = 0.0; 2p;$	> 0.1: NS	0.0	0.5 1.0 1.5	2.0
					RT better - RT worse	

Webappendix material

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)

Webappendix

Webfigure 1 Methodological note

Trials of radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD)

Webtable 1 Randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS) – treatment details.

Node negative (pN0)

- Webfigure 2 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 700 women with pathologically node-negative (pN0) disease.
- Webfigure 3 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD):10-year risk of recurrence and type of first recurrence, by allocated treatment, in 700 women with pathologically node-negative (pN0) disease.

Node positive (pN+)

- Webfigure 4 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 3131 women with pathologically node-positive (pN+) disease.
- Webfigure 5 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 3131 women with pathologically node-positive (pN+) disease.
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1-3 positive nodes (pN1-3)

Webfigure 7 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1314 women with 1-3 pathologically positive nodes (pN1-3).

Webfigure 8 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1314 women with 1-3 pathologically positive nodes (pN1-3).

Webfigure 9 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): Event rate ratios and 95% confidence intervals for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer mortality in 1314 women with 1-3 pathologically positive nodes (pN1-3) by prognostic and other factors.

1-3 positive nodes (pN1-3) who received systemic therapy

- Webfigure 10 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1133 women with 1-3 pathologically positive nodes (pN1-3) in trials where systemic therapy was given to both randomised treatment groups.
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1-3 positive nodes (pN1-3) who received systemic therapy subdivided according to number of positive nodes

- Webfigure 12 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 15-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 subdivided according to number of positive nodes.
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4+ positive nodes (pN4+)

- Webfigure 16 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1772 women with 4+ pathologically positive nodes (pN4+).
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- Webfigure 18 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): Event rate ratios and 95% confidence intervals for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer mortality in 1772 women with 4+ pathologically positive nodes (pN4+) by prognostic and other factors.

4+ positive nodes (pN4+) who received systemic therapy

- Webfigure 19 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1677 women with 4+ pathologically positive nodes (pN4+) in trials where systemic therapy was given to both randomised treatment groups.
- Webfigure 20 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1677 women with 4+ pathologically positive nodes (pN4+) in trials where systemic therapy was given to both randomised treatment groups.

4+ positive nodes (pN4+) who received systemic therapy subdivided according to number of positive nodes

Webfigure 21 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 15-year risk of breast cancer mortality in 1677 women with 4+ pathologically positive nodes (pN4+) in trials where systemic therapy was given to both randomised treatment groups subdivided according to number of positive nodes.

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Trials of radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS)

Node negative (pN0)

- Webfigure 25 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 870 women with pathologically node-negative (pN0) disease.
- Webfigure 26 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 870 women with pathologically node negative (pN0) disease.

Node positive (pN+)

- Webfigure 27 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 2541 women with pathologically node-positive (pN+) disease.
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Trials of radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS). Event rate ratios, one line per trial.

- Webfigure 29 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 1594 women with pathologically node-negative (pN0) disease.
- Webfigure 30 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 5821 women with pathologically node-positive (pN+) disease.
- Webfigure 31 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 2801 women with 1-3 pathologically positive nodes (pN1-3).
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- Webfigure 33 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 463 women with pathologically positive nodes (pN?+) but unknown if they were 1-3 or 4+ positive.

Webfigure 34 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 720 women with unknown pathological nodal status (pN?).

Trials of radiotherapy to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD)

Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after Webtable 2 mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS). Randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy and axillary Webtable 3 dissection (Mast+AD) or axillary sampling (Mast+AS) - treatment details. Node negative (pN0) Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional Webfigure 35 recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 465 women with pathologically node-negative (pN0) disease. Webfigure 36 Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 465 women with pathologically node-negative (pN0) disease. Node positive (pN+) Webfigure 37 Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1029 women with pathologically node-positive (pN+) disease. Webfigure 38 Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1029 women with pathologically node positive (pN+) disease. Event rate ratios, one line per trial Webfigure 39 Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 465 women with pathologically node-negative (pN0) disease. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling Webfigure 40 (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 1029 women with pathologically node-positive (pN+) disease. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling Webfigure 41 (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 810 women unknown with pathological nodal status (pN?).

Trials of radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy alone (Mast alone)

- Webtable 4 Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy but no axillary surgery (Mast).
- Webtable 5 Randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast) treatment details.

Clinically node positive (cN+)

- Webfigure 42 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risks of breast cancer and all-cause mortality in 2896 women with clinically node-negative (cN-) disease.
- Webfigure 43 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of recurrence and type of first recurrence in 2896 women with clinically node-negative (cN-) disease.

Clinically node negative (cN-)

- Webfigure 44 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risks of breast cancer and all-cause mortality in 1481 women with clinically node-positive (cN+) disease.
- Webfigure 45 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of recurrence and type of first recurrence in 1481 women with clinically node-positive (cN+) disease.

Trials of radiotherapy to the regional lymph nodes alone versus not after mastectomy alone (Mast alone)

- Webtable 6 Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy but no axillary surgery (Mast).
- Webtable 7 Randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy but no axillary surgery (Mast) treatment details.
- Webfigure 46 Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy but no axillary surgery (Mast): 10-year risks of recurrence, breast cancer and all-cause mortality in 192 clinically node-positive (cN+) women. Note, due to the very small number (8) of clinically node-negative women in this set of trials they are shown only in webfigure 34.
- Webfigure 47 Effect of radiotherapy (RT) to the regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of recurrence and type of first recurrence in 192 women with clinically node-positive (cN+) disease.
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- Webfigure 49 Effect of radiotherapy (RT) versus not after mastectomy but no axillary surgery (Mast): 10 year risks of recurrence during years 0-9, breast cancer mortality, and all-cause mortality in 1673 women with clinically node-positive (cN+) disease. Event rate ratios, one line per trial, trial subdivided according to whether or not radiotherapy was given to the chest wall.

Trials of radiotherapy to the chest wall and regional lymph nodes versus not BEFORE mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS)

- Webtable 8 Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS).
- Webtable 9 Randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS) treatment details.
- Webfigure 50 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 15-year risk of breast cancer and all-cause mortality in 255 women with unknown pathological nodal status (pN?) disease.
- Webfigure 51 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD): 10-year risk of

recurrence and type of first recurrence, by allocated treatment, in 255 women with unknown pathological nodal status (pN?).

- Webfigure 52 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary sampling (Mast+AS): 10-year risk of locoregional recurrence and recurrence of any type and 15-year risk of breast cancer and all-cause mortality in 637 women with unknown pathological nodal status (pN?) disease
- Webfigure 53 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary sampling (Mast+AS): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 637 women with unknown pathological nodal status (pN?).
- Webfigure 54 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 892 women with unknown pathological nodal status (pN?).

Webfigure 55 EBCTCG collaborators, listed alphabetically by institution and then alphabetically by name.

Webfigure 1. Methodological Note

The analyses presented in the main body of the accompanying paper and also in many of the figures in this webappendix are based on the methodology that has been used throughout by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) and which is described elsewhere.¹ Some of the figures in this webappendix also include additional methodological features. The purpose of this note is to point out some of the features of both types of analysis.

Overall Mortality

In analyses of overall mortality (eg, the lower right-hand panels of webfigures 2, 4, etc), the number of women who are known to have died in each randomised group is related to the number of women at risk of dying and the length of time during which they are at risk of dying in each time-period during follow-up. Some women are, however, lost to follow-up and are withdrawn from the analysis. Thus, whilst it is reported in the lower right-hand panel of webfigure 4 that the cumulative risk of death from any cause among the 1550 women randomised to radiotherapy is 65.4% at 20 years after randomisation, this does not mean that 1014 (ie 0.654x1550) of the women are known to have died. Rather, as shown in webfigure 30, only 1001 (ie 64.6%) of the women are known to have died. The difference between these two percentages is due to the fact that for 390 of these 1550 women the most recent information held in the EBCTCG database indicates only that they were known to be alive. Each censored woman is no longer considered to be at risk of dying after her date of censoring and she is excluded from all calculations relating to subsequent time-periods and, in particular, from contributing to the number of years at risk in calculations of the death rate. The technique of censoring has been used routinely by statisticians and actuaries for many decades and theoretical calculations have shown that it is valid, provided that the women who are censored are not different in any respect that affects their mortality rate from the women who remain in the study so that, from the mathematical point of view, the censoring can be considered to be 'a random'. This assumption is unlikely ever to be precisely true but many of the major factors affecting risk of overall mortality, such as trial, follow-up year, age at trial entry, and nodal status, can be taken into account through the results from the separate strata in the form of a weighted average, calculated with weights proportional to the amount of information in each stratum.

Mortality from Causes other than Breast Cancer

Analyses of causes of death other than breast cancer (eg EBCTCG, Lancet 2000; 355:1757-70, and 2005; 366: 2087-2106) are carried out in a fashion similar to that for analyses of overall mortality. Here, however, it is not only women who are lost to follow-up who are censored but all women who have a recurrence of their breast cancer are also censored on the date of that recurrence. This approach enables comparison of mortality rates from non-breast-cancer causes in the two trial arms. However, the resulting estimates of the cumulative risk of death from all non-breast-cancer causes (eg figure 6 lower panel of EBCTCG, Lancet 2000; 355:1757-70) reflect the cumulative risks that would be seen under the hypothetical scenario that no women in the trial die from breast cancer. This scenario is, of course, highly artificial. It is, however, a useful one in that it permits comparison of non-breast-cancer mortality rates in the two trial arms unencumbered by any differences in the rates of breast cancer recurrence/mortality. It therefore enables identification and characterization of specific treatment hazards such as the increased mortality from heart disease or second cancers that has undoubtedly occurred following some of the radiotherapy regimens used in the past (EBCTCG, Lancet 2005; 366: 2087-2106).

Breast Cancer Mortality

The method used in the EBCTCG meta-analyses for studying mortality from breast cancer (eg right-hand panels of figures 1, 2, 4 and lower left-hand panels of webfigures 2, 4, etc) is indirect and makes use of analyses of the two endpoints described above. The data are first subdivided into separate strata (eg, according to trial, follow-up year, age at trial entry, and nodal status). Then, for each trial arm, the mortality rate from non-breast-cancer causes during the period prior to any recurrence of breast cancer is subtracted from the overall mortality rate in the relevant stratum. This method has the advantage that it avoids the difficulties which arise for women who die after a recurrence of their breast cancer and where it is not entirely clear whether their death was, in fact, due to the cancer or due to other causes. As in analyses of non-breast-cancer mortality, the resulting estimates of the cumulative risk of death from breast cancer reflect the cumulative risks that would be seen under the hypothetical scenario that no women in the trial die from causes other than breast cancer. Once again, this is useful in the identification and characterization of the benefits of a randomised treatment separately from its hazards. It also allows comparison of the benefits of the randomised treatment separately from the effects of other factors, such as the increasing overall mortality rate that occurs in all populations with increasing attained age.

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Separate calculation of the effect of a particular treatment on breast cancer mortality and on non-breast-cancer causes can also have substantial advantages even when the main question of interest is the effect of a treatment on overall mortality. For example, information from randomised trials on the effect of radiotherapy in reducing breast cancer mortality can be combined with epidemiological information from other sources on the likely risk of death from the long-term adverse effects of radiotherapy, such as second primary cancers or heart disease.

Analyses of Overall Recurrence

Analyses of overall recurrence are presented in both the main paper (eg middle panels of figures 1,2 and 4) and in the webappendix (upper right panel of webfigures 2, 4, etc). Rather than using the indirect approach that is taken for analyses of breast cancer mortality, these analyses are carried out in a fashion similar to the analyses of mortality from non-breast-cancer causes in that the first reported recurrence of any type is related to the number of women who have not yet had a recurrence but who, if they did have one, would contribute an event. Women are censored and cease to contribute either events or years at risk after they have had a recurrence, die from a cause other than breast cancer, or are lost to follow-up. Any women who are reported as dying from breast cancer and for whom no recurrence has previously been reported are assumed to have had a distant recurrence immediately preceding their death. As with analyses of mortality from breast cancer and from causes other than breast cancer, these analyses lead to estimates of the cumulative risk of recurrence that would occur under the hypothetical scenario in which no other events occur. For analyses of overall recurrence this involves the assumption that no women in the trial die from causes other than breast cancer. This is similar to the assumption that is made for analyses of breast cancer mortality and, once again, although this assumption is unrealistic it is useful in that it enables identification and characterization of the benefits of the randomised treatment separately from its hazards.

Analyses of Locoregional and Distant Recurrence

Analyses of locoregional recurrence are also presented both in the main paper (eg left panel of figures 1,2 and 4) and in the webappendix (upper left panel of webfigures 2, 4, etc). These analyses are carried out in similar fashion to the analyses of overall recurrence described above. Only locoregional recurrences that occur before any distant recurrence are counted as events, and women are censored and cease to contribute events or to the years at risk after they have had one recurrence (either a local or a distant one), or they die from a cause other than breast cancer or are lost to follow-up. The interpretation of analyses of locoregional recurrence is in some respects, similar to that for overall recurrence and breast cancer mortality. Two aspects do, however, differ and, in some contexts it is important to be aware of them. These two aspects are discussed in the following two paragraphs.

Firstly, because estimates of the cumulative risk of locoregional recurrence make the hypothetical assumption that no distant recurrences occur, they over-estimate the cumulative risk of locoregional recurrence. In many circumstances, including most of the analyses presented in this paper and in these webappendices, this is by no means realistic as the number of women whose first recurrence is a distant one is substantial. Insight into the extent of this effect can be gained by considering the distribution of the two different types of recurrence in analyses of overall recurrence, and such analyses have been carried out to accompany all the analyses of locoregional recurrence presented in this paper. For example, webfigure 5 accompanies the analysis of locoregional recurrence shown in the bottom left panel of figure 1 (and also in the top left panel of webfigure 4). The estimated 10-year risk of a recurrence of any type is 62.5% among the women randomised to no radiotherapy (webfigure 5, right-hand panel), of which distant recurrence accounts for 43.1% and locoregional recurrence accounts for the remaining 19.4%. If distant recurrences are censored, as in the analyses of locoregional recurrences, the estimated 10-year risk of locoregional recurrence in this particular example, is 26.0% (bottom left panel of figure 1 and top left panel of webfigure 4). This is 6.6% higher (ie, 26.0% in figure 1 minus 19.4% in webfigure 5) than the estimate derived from an analysis that takes distant recurrences into account.

Secondly, as can be seen in webfigure 5, the 10-year risk of distant recurrence differs between the two treatment groups and in this example, the 10-year risk of distant recurrence is 46.9% among the women allocated to receive radiotherapy and 43.1% among the women allocated not to receive it, ie, the 10-year risk of a distant recurrence is *higher* in the women randomised to receive radiotherapy than in the women randomised to no radiotherapy. This does not, however, mean that radiotherapy increases the risk of distant recurrence. Rather, it arises from the fact that a proportion of the women who would have had a locoregional recurrence if they had not had radiotherapy have their locoregional recurrence prevented by radiotherapy. These women remain at risk of a distant recurrence for longer and their additional time at risk is taken into account by the fact that, while they remain at risk of a distant recurrence, they continue to contribute to the years at risk and to the denominator in calculation of event rates. However, women who are at a higher risk of locoregional recurrence (eg, because they have more aggressive cancers) are also at a higher risk of distant recurrence. Therefore, the additional contribution to the years at risk from these women allocated to radiotherapy. Hence the censoring that arises from the distant recurrences cannot be considered to be 'at random'. The relationship between the risks of locoregional and distant recurrence is unknown, either in the presence of radiotherapy or in its absence – and indeed the relationship is likely to differ between the two. Furthermore, the data from the trial provide no information about this relationship. Therefore it is not possible to carry out analyses of locoregional recurrence that take appropriate account of the occurrence of distant recurrences as a first event

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event, or vice versa. One consequence of this is that, in analyses of locoregional recurrence as a first event (left-hand panels of figures 1, 2, & 5 and top left panels of webfigures 2, 4, 7, 10, 12, 16, 19, 21, 25, 27, 35, 37, 42, 44 and 46), the difference between the cumulative risks in the two treatment arms is a consequence not only of the causal effect of radiotherapy on the local recurrence rate in the two treatment arms, but also of the different extent to which distant recurrence as a first event occurs in each of the two treatment arms. This has consequences both for the interpretation of cumulative risks arising from the analysis of locoregional recurrence and for the interpretation of analyses presenting the ratio of the local recurrence rate in the irradiated group compared with the unirradiated group (figures 3, and 5 and webfigures 30, 6, 9, 18, 29, 30, 31, 32, 33, 34, 39, 40, 41, 48, 49). Analyses of recurrence presenting explicitly the percentages of women whose first recurrence was locoregional or distant respectively are therefore given in this webappendix (webfigures 3,5,8,11,13, 14, 15, 17, 20, 22, 23, 24, 26, 28, 36, 38, 43, 45, 47)

These ideas are not new, but they have not previously been considered in the context of the EBCTCG analyses. A selection of papers either discussing the methodological aspects involved or applying them to other data sets is given below.

- Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and result after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med 1995; 30: 1456-1461.
- Gelman R, Gelber R, Henderson IC, Coleman CN, Harris JR. Improved methodology for analyzing local and distant recurrence. J Clin Oncol 1990; 8: 548-555.
- Moeschberger ML, Klein JP. Statistical methods for dependent competing risks. Lifetime Data Anal 1995; 1: 195-204.
- Panzarella T, Meakin JW. Analysis of cause-specific failure endpoints using simple proportions: an example from a randomized controlled clinical trial in early breast cancer. Int J Radiat Oncol Biol Phys 1998; 41: 1093-97.
- Peterson AV. Bounds for a joint distribution function with fixed sub-distribution functions: Application to competing risks. Proc Natl Acad Sci U S A 1976; 73: 11-13.
- Prentice RL, Kalbfleisch JD, Peterson AV, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. *Biometrics* 1978; 34: 541-554.
- Schulgen G, Schomoor C, Sauerbrei W, Schumacher M. A note on estimating local recurrence rates in clinical trials on the treatment of breast cancer. Breast Cancer Res Treat 1998; 49: 87-91.
- Tsiatis A. A nonidentifiability aspect of the problem of competing risks. Proc Natl Acad Sci U S A 1975; 72: 20-22.
- Dignam JJ, Kocherginsky MN. Choice and interpretation of statistical tests used when competing risks are present. J Clin Oncol 2008; 26: 4027-34.
- Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics. Stat Med 2007; 26: 2389-430.

Reference

1. http://www.ctsu.ox.ac.uk/research/meta-trials/ebctcg/original-methods-for-ebctcg-meta-analyses

Webtable 1: Randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS) – treatment details.

Year code and study name	Breast surgery	Axillary Surgery* (number of patients)	Chest wall RT	Supraclavicular (SC) and axillary fossa (AF) RT	Internal mammary chain RT	Boost RT to scar	Common systemic chemoendocrine therapy
64B Oslo X-ray	RM	Axillary dissection (552)	25-41 Gy (1.3-2.1 Gy/f) o	36 Gy (1.8 Gy/f) o, SC; 18 Gy (u Gy/f) o, AF	25-41 Gy (1.3-2.1 Gy/f)	None	Ovarian RT
71B Stockholm A	MRM	Axillary sampling (644)	45 Gy (1.8 Gy/f) e	45 Gy de (1.8 Gy/f) c	45 Gy (1.8 Gy/f) e	None	None
73A Southampton UK	SM	Axillary sampling (151)	46 Gy (2.3 Gy/f) c	55 Gy (2.5 Gy/f) c & b	46 Gy (2.3 Gy/f) c	None	None
74B Edinburgh I	SM	Axillary sampling (348)	42.5-45.0 Gy (4.25- 4.5 Gy/f) m	42.5-45.0 Gy (4.25-4.5 Gy/f) m	None	None	F
74D DFCI Boston	MRM or RM	Axillary dissection (218)	45 Gy (2.3 Gy/f) c or m	45 Gy (2.3 Gy/f) c or m	0-45 Gy (0-2.3 Gy/f) c or m	None	Either (AC) 5 cycles or (AC) 10 cycles; or CMF or MF
74Q Piedmont OA (pN4+)	MRM or RM	Axillary dissection (120)	50 Gy (1.5-1.8 Gy/f) c or m	45-50 Gy (1.5-2.8 Gy/f) c or m	45-50 Gy (1.8-2.8 Gy/f) c or m	None	Mel or CMF
76A SECSG 1	MRM or RM	Axillary dissection (257)	50 Gy (2 Gy/f) u	50 Gy (2 Gy/f) u	50 Gy (2 Gy/f) u	None	CMF
76C Glasgow	SM	Axillary dissection (219)	37.8 Gy (2.5 Gy/f) o	37.8 Gy (2.5 Gy/f) o	37.8 Gy (2.5 Gy/f) o	None	CMF
77J MD Ander, 7730B	MRM or SM	Axillary dissection (80)	45-50 Gy (1.8-2.0	45-50 Gy (1.8-2 Gy/f) c	45-50 Gy (1.8-2 Gy/f)	12 Gy	bCG+FAC or FAC
		Axillary sampling (17)	Gy/f) c		core	(uGy/f) u	
78A S Swedish BCG	MRM	Axillary dissection (771)	38 Gy (1.9 Gy/f)	48-60 Gy (2.4 Gy/f) c or m	48 Gy (2.4 Gy/f)	None	Premen: C;
			e.o.m or c		e, c or m		Postmen: tam
78G BCCA Vancouver	MRM	Axillary dissection (318)	37.5-40 Gy (2.3 Gy/f)	37.5 Gy de (2.2 Gy/f)	37.5 Gy de (2.3 Gy/f)	None	CMFP+ovarian RT or
		, , ,	corm	c or m	c or m		CMF
78Q Düsseldorf U	Patey	Axillary dissection (88)	40 Gy (2 Gy/f) c	40 Gy (2 Gy/f) c	40 Gy (2 Gy/f) c	None	LMF
79F Coimbra	NS	Axillary sampling (124)	36 Gy (3 Gy/f) o or m	39-45 Gy (3.3-3.8 Gy/f) m	39 Gy (3.3 Gy/f) m	None	AC
79G Metaxas Athens	MRM, Patey MRM, or RM	Axillary dissection (71)	45-60 Gy (2 Gy/f) m	45-60 Gy (2 Gy/f) m	45-60 Gy (2 Gy/f) m	None	CAMF & tam Premen: ovarian RT
80S Helsinki	RM	Axillary dissection (99)	45 Gy (3 Gy/f) c	45 Gy (3 Gy/f) c, SC; 45 Gy (3 Gy/f) c, AF	45 Gy (3 Gy/f) c	None	CAFt
80W NSABC Israel	NS	Unknown (112)	46-50 Gy (2 Gy/f) c or m	46-50 Gy (2 Gy/f) c or m	40 Gy (2 Gy/f) c or m	None	CMF
82B Danish BCG 82b pre	SM	Axillary dissection (418) Axillary sampling (1,386)	36-50 Gy (1.8-2.2 Gy/f) o or e	36-50 Gy (1.8-2.2 Gy/f) o or m	36-50 Gy (1.8-2.2 Gy/f) o or e	None	CMF
82C Danish BCG 82c post	SM	Axillary dissection (344)	36-50 Gy (1.8-2.2	36-50 Gy (1.8-2.2 Gy/f)	36-50 Gy (1.8-2.2 Gy/f)	None	tam
620 Danish BCG 620 post	3101	Axillary sampling (1,119)	Gy/f)	o or m	o or e	None	lan
82Q ECOG EST3181	MRM or RM	Axillary dissection (332)	o or e 46 Gy (2 Gy/f) c or m	46-50 Gy (2 Gy/f) c or m	46 Gy (2 Gy/f) c, m or e	None	CAF&H&tam
84A GBSG 03 Germany	Patey	Axillary sampling (199)	50 Gy (2 Gy/f) c or m	50 Gy (2 Gy/f) c or m	44 Gy(1.8 Gy/f) c or m	None	CMF
85F Nottingham	SM	Axillary sampling (77)	45 Gy (3 Gy/f) m	45 Gy (3 Gy/f) m	None	None	Premen; CMF
-			,				Postmen;tam
86C CRC, UK	NS	Unknown (71)	Various	Various	Various	Various	None

* Based on the description of axillary surgery in the trial protocol or publications or on information on individual women. Women were classified as having axillary dissection if they were in a trial where the protocol required removal of axillary lymph nodes in at least levels I & II or, if individual information was available (MD Ander. 7730B, Danish BCG 82b pre, Danish BCG 82c post), resection of ≥10 nodes. In other trials, women were classified as having axillary dissection if the trial publication indicated that the median number of nodes removed was ≥ 10. Women with less extensive axillary surgery were classified as having axillary sampling. A=doxorubicin (adriamycin), AC=doxorubicin and cyclophosphamide, AF=axillary fossa, b= additional posterior boost to axilla, bCG=bacillus Calmette-Guérin, C=cyclophosphamide, c=cobalt-60, de=dose at depth (of nodes), F=fluorouracil, Ft=Ftorafur, f=fraction, Gy=Gray (intended dose), H=halotestin, L=chlorambucil, m=megavoltage, M=methotrexate, MeI=melphalan, MRM=modified radical mastectomy), o=orthovoltage, P=prednisone, Patey= Patey mastectomy, RM=radical mastectomy (Halsted), RT=radiotherapy, SC=supraclavicular, SM=simple (total) mastectomy; tam=tamoxifen, u=unknown.

References for Webtable 1

Year code and study name	Reference
64B Oslo X-ray	Host H, Brennhovd IO, Loeb M. Postoperative radiotherapy in breast cancer-long-term results from the Oslo study. Int J Radiat Oncol Biol Phys 1986; 12: 727–32.
71B Stockholm A	Gyenes G, Rutqvist LE, Liedberg A, Fornander T. Long-term cardiac morbidity and mortality in a randomized trial of pre- and postoperative radiation therapy versus surgery alone in primary breast cancer. <i>Radiother Oncol</i> 1998; 48 : 185–90.
73A Southampton UK	Turnbull AR, Turner DT, Chant AD, Shepherd JM, Buchanan RB, Fraser JD. Treatment of early breast cancer. Lancet 1978; 2: 7–9.
74B Edinburgh I	Stewart HJ, Jack WJL, Everington D, Forrest APM, Rodger A, McDonald CC, et al. South-east Scottish trial of local therapy in node negative breast cancer. <i>The Breast</i> 1994; 3 : 31–9.
74D DFCI Boston	Shapiro CL, Hardenbergh PH, Gelman R, Blanks D, Hauptman P, Recht A, et al. Cardiac effects of adjuvant doxorubicin and radiation therapy in breast cancer patients. <i>J Clin Oncol</i> 1998; 16 : 3493–501.
74Q Piedmont OA	Muss HB, Cooper MR, Brockschmidt JK, Ferree C, Richards F, 2nd, White DR, et al. A randomized trial of chemotherapy (L-PAM vs CMF) and irradiation for node positive breast cancer. Eleven year follow-up of a Piedmont Oncology Association trial. <i>Breast Cancer Res Treat</i> 1991; 19 : 77–84.
76A SECSG 1	Velez-Garcia E, Carpenter JT, Jr., Moore M, Vogel CL, Marcial V, Ketcham A, et al. Postsurgical adjuvant chemotherapy with or without radiotherapy in women with breast cancer and positive axillary nodes: a South-Eastern Cancer Study Group (SEG) Trial. <i>Eur J Cancer</i> 1992; 28A : 1833–7.
76C Glasgow	McArdle CS, McMillan DC, Greenlaw N, Morrison DS. Adjuvant radiotherapy and chemotherapy in breast cancer: 30 year follow-up of survival. BMC Cancer 2010; 10: 398.
77J MD Ander. 7730B	Katz A, Strom EA, Buchholz TA, Thames HD, Smith CD, Jhingran A, et al. Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: implications for postoperative irradiation. <i>J Clin Oncol</i> 2000; 18 : 2817–27.
78A S Swedish BCG	Killander F, Anderson H, Ryden S, Moller T, Aspegren K, Ceberg J, et al. Radiotherapy and tamoxifen after mastectomy in postmenopausal women - 20 year follow-up of the South Sweden Breast Cancer Group randomised trial SSBCG II:I. <i>Eur J Cancer</i> 2007; 43 : 2100–8.
78G BCCA Vancouver	Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, et al. Adjuvant Radiotherapy and Chemotherapy in Node-Positive Premenopausal Women with Breast Cancer N Engl J Med 1997; 337 :956-962
78Q Düsseldorf U	Faber P, Jesdinsky H. Adjuvant chemotherapy in breast cancer-a multicenter trial. Cancer Treat Rev 1979; 6 Suppl: 75–8.
79F Coimbra	De Oliveira CF R, F, Gervasio H, Alves, R, Silva A, Pedro L. Adjuvant chemotherapy versus radiotherapy and chemotherapy in operable breast cancer. A randomized trial. Preliminary results. Instituto Portugues De Oncologia Coimbra, <i>Portugal</i> 1984.
79G Metaxas Athens	Papaioannou AN. Preoperative chemotherapy: advantages and clinical application in stage III breast cancer. Recent Results Cancer Res 1985; 98: 65–90.
80S Helsinki	Saarto T, Blomqvist C, Rissanen P, Auvinen A, Elomaa I. Haematological toxicity: a marker of adjuvant chemotherapy efficacy in stage II and III breast cancer. Br J Cancer 1997; 75 : 301–5.

80W NSABC Israel	H Hayat GB, R Borovik, S Chaichick, P Rathm E Robinson, S Biran, HJ Brenner. Adjuvant chemotherapy and radiation therapy vs chemotherapy alone for stage II breast cancer patients. <i>Ann Oncol</i> 1990; 21 (suppl, abstr).
82B Danish BCG 82b pre	Andersson M, Kamby C, Jensen MB, Mouridsen H, Ejlertsen B, Dombernowsky P, et al. Tamoxifen in high-risk premenopausal women with primary breast cancer receiving adjuvant chemotherapy. Report from the Danish Breast Cancer co-operative Group DBCG 82B Trial. <i>Eur J Cancer</i> 1999; 35 : 1659–66.
	Kyndi M, Overgaard M, Nielsen HM, Sorensen FB, Knudsen H, Overgaard J. High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. Radiother Oncol 2009; 90: 74–9.
82C Danish BCG 82c post	Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. <i>Lancet</i> 1999; 353 : 1641–8.
	Kyndi M, Overgaard M, Nielsen HM, Sorensen FB, Knudsen H, Overgaard J. High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. Radiother Oncol 2009; 90: 74–9.
82Q ECOG EST3181	Olson JE, Neuberg D, Pandya KJ, Richter MP, Solin LJ, Gilchrist KW, et al. The role of radiotherapy in the management of operable locally advanced breast carcinoma: results of a randomized trial by the Eastern Cooperative Oncology Group. <i>Cancer</i> 1997; 79 1138–49.
84A GBSG 03 Germany	Schmoor C, Olschewski M, Sauerbrei W, Schumacher M. Long-term follow-up of patients in four prospective studies of the German Breast Cancer Study Group (GBSG): A summary of key results. Onkologie 2002; 25: 143–50.
85F Nottingham	Morgan DA, Berridge J, Blamey RW. Postoperative radiotherapy following mastectomy for high-risk breast cancer. A randomised trial. Eur J Cancer 2002; 38: 1107–10.
86C CRC, UK	Houghton J PI, Tobias J, Baum M, Odling-Smee W. Prophylactic radiotherapy following surgery for early breast cancer: is the benefit mainly in patients with involved margins? Results from a Cancer Research Campaign trial. <i>Proc Am Soc Clin Oncol</i> 2001 20 : 31a.

Webfigure 2. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 700 women with pathologically node-negative (pN0) disease. See webfigure 1 for methodological note and also webfigure 3. Note: 1 locoregional recurrences of any type and 5 breast cancer deaths were reported among the 9 pN0 women with tumours ≥ 5 cm who were allocated to receive radiotherapy. 0 locoregional recurrences of any type and 4 breast cancer deaths were reported among the 11 pN0 women with tumours ≥ 5 cm who were allocated to not to receive radiotherapy.

700 pN0 women with Mast+AD



Webfigure 3. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 700 women with pathologically node-negative (pN0) disease. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: > 0.1; NS

Webfigure 4. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 3131 women with pathologically node-positive (pN+) disease. See webfigure 1 for methodological note and also webfigure 5.



3131 pN+ women with Mast+AD

Webfigure 5. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 3131 women with pathologically node-positive (pN+) disease. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



3131 pN+ women with Mast+AD

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Webfigure 6. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): Event rate ratios and 95% confidence intervals for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer mortality in 3131 women with pathologically node-positive (pN+) disease by prognostic and other factors. Categories with unknowns are excluded from the heterogeneity and trend tests.



3131 pN+ women with Mast+AD

Note: In (g), 181 women who were ER positive with tamoxifen also had chemotherapy. In (h), trials that used orthovoltage irradiation are included in the <50 Gy category.

Webfigure 7. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1314 women with 1-3 pathologically positive nodes (pN1-3). See webfigure 1 for methodological note and also webfigure 8.



Webfigure 8. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1314 women with 1-3 pathologically positive nodes (pN1-3). (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Webfigure 9. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection

(Mast+AD): Event rate ratios and 95% confidence intervals for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer mortality in 1314 women with 1-3 pathologically positive nodes (pN1-3) by prognostic and other factors. Categories with unknowns are excluded from the heterogeneity and trend tests.

0,5 1.0 1.5 2.0

RT better - RT worse

	Allocated	Allocated	Logrank			al event rates	Rate Ratio	Category	Allocated	Allocated	Logrank	Variance	Ratio of annu	
Category	RT	No RT	0-E	of O-E	RT :	No RT	(Standard Error)	Category	RT	No RT	Ő-E	of O-E	RT	No RT
(a) Age at entry (χ^2_1	= 0.9; 2p = 0	.3)			1		- 90%	(a) Age at entry (χ	=0.0; 2p =	0.9)				1
Age < 40 ym	5776	20/74	-8.0	5.6	- e		0.24 (SE 0.22)	Age < 40 yrs	27/76	43/78	-9.1	13.8	_ 	1
Age 40 – 49 yrs	6/203	18/211	-6.3	6.1	± 1		0.38 (BE 0.26)	Age 40 - 49 yra	59/204	72/217	-3.6	29.1	÷	<u> </u>
Age 60 – 58 ym	7/200	40/199	-15.8	11.1			0.24 (SE 0.16)	Age 50 - 59 yrs	74/205	99/203	-16.1	36.0		1
Ago 60+ ym	1/147	33/165	-14.5	a.1 -	■-		0.17 (SE 0.16)	Age 60+ yrs	51/148	92/185	-13.6	30.7	- -	1
(b) Tumour Grade (χ ² = 0.0; 2p =	= 0.9)						(b) Tumour Grade ($\gamma_{1}^{2} = 0.2; 2p$	= 0.6)				1
Low grade Intermediate grade	4/64	7/48	-2.5	2.2			0.32 (SE 0.40) 0.25 (SE 0.23)	Low grade	17/64	14/48	-0.9	5.2		L
High grade	4/81 1/60	21/95 9/57	-7.5 -3.0	5.5 2.3 -			0.25 (SE 0.23) 0.27 (SE 0.37)	Intermediate grade High grade	26/81	45/95	-8.5	15.0	_ _	1
Unknown grade	10/430	75/409	-30.5	19.7	rī- I		0.21 (SE 0.11)	High grade Univoxyn grade	18/50	29/57	-4.3 -28.6	R.S 77.0		
					Ϋ Ι			Chinesen Grane	100/44/	210402	-20.0	17.0	ųr į	1
(c) Turnour size (χ ² ₁ 1-19 mm	= 0.0; 2p = 0 4/138	1.9) 26/148	-10,4	7.0	⊥ I		0.23 (SE 0.20)	(c) Turnour size (χ^2	= 3.1; 2p =	(80.0				1
20-46 mm	5/148	205110	-13.6	9.6	1		0.24 (SE 0.17)	1-19 mm	27/138	01/153	-15.9	15.4		1
50+ mm	2/32	5/28	-2.1	1.1-			0.15 (SE 0.43)	20-49 mm	63/151	88/192	-4.1	31.0	+	
unknown	5/307	44/306	-17.1	12.0	ਗੇ⊢ ∣		0.24 (SE 0.15)	50+ mm	12/35	17/31	-2.5	4.9		
					1			unknown	109/307	139/306	-17.8	52.8	-ų-	í -
(d) Mastectomy (χ^2_1					<u> </u>			(d) Mastectomy (χ	=0.0; 2p =	0.9)				í -
Simple	16/907	95/544	-37.A	26.6			0.25 (SE 0.10)	Simple	172/514	245/557	-33.6	90.2	-	1
More extensive	1/118	17/125	-7.2	4.3 -			0.19 (SE 0.23)	More extensive	39/118	59/125	-8.2	21.1	_ T	ł
(e) Axillary surgery I					1			(e) Axillary surgery	information	$(\chi_2^2 = 0.2;$	n = 0.9)			1
Trial protocol	8/277	42/291	-16.8	11.8	-∎- I		0.24 (SE 0.16)						<u> </u>	1
Trial median	9/212	38/234	-14,4	11.4	- -		0.28 (SE 0.17)	Trial protocol	97/277	127/281	-16.7	49.8		1
Incividual	2/136	32/164	-13.8	7.8	■-		0.17 (BE 0.17)	Trial median Individual	69/212 45/143	104/234 73/167	-15.8 -9.8	37.3 24.5		1
(f) Number of positiv	ve nodes (_χ	= 0.2; 2p	= 0.7)		1							24.0	-	1
1 positive node	3/189	34/209	-14.2	a.o	∎— I		0.20 (SE 0.17)	(f) Number of positi	venodes ()	(² = 1.1; 2p	= 0.3)			1
2-3 positive notes	8/218	35/222	-13.1	9.2	-ī— ∣		0.24 (SE 0.18)	1 positive node	48/191	80/214	-13.8	27.8	_ _ !	1
Unknown but pN1-3	8(218	43/238	-17.2	11.7	-ā- I		0.23 (SE 0.15)	2-3 positive nodes	89/223	116/230	-9.8	41.3		F
(g) Any systemic the		4. 2	n		T I			Unknown but pN1-5	74/218	108/238	-18.6	38.4		1
(g) Any systemic the	arapy (X ₁ = 1 093	12/68	-5.7	2			0.00 (SE 0.26)	(g) Any systemic th	orony / -2 -	0.4. 20 - 0	6)			1
Chemp and/or ER+tam+	10/532	100/581	-38.9										_	1
Chello and/or ER+lain+	10/5/2	10045851	-36.9	28.0	F		0.25 (SE 0.10)	No systemic Cherno and/or BR+tam+	34/93 177/539	42/88 262/594	-4.1	16.8 94.5		
(h) Radiotherapy do	se ($\chi_1^2 = 0.9$;	2p = 0.4)						Chemo and/or BR+tam+	177/539	262/594	-38.2	94.5	- -	í -
50+ Gy	\$/173	43(203	-17.7	10.8	∎-		0.19 (SE 0.15)	(h) Radiotherapy do	ise $(\chi_1^2 = 0.2$; 2p = 0.6)				1
<90 Gy	16/482	694466	-26.8	20.3	₩ -		0.27 (SE 0.12)	50+ Gy	55/180	97/218	-14.1	31.2	_ 	1
(i) Date trial started	/ ~ ² = 0 4- 2	= 0.5			T I			⊲50 Gy	156/452	207/466	-28.2	80.4		í -
Blarted <1959	15/428	68441	-26.8	18.8	<u> </u>		0.28 (SE 0.12)	(i) Date trial started	(o = 0 3)				í -
Started 1982+	4/199	44/228	-17.8	11.1	.		0.20 (8# 0.15)	Startad <1980	145/433	208454	-34.1	76.6		1
					7			Started 1980+	66/199	205464	-84.1	76.6		Ĺ
() Period of follow-u					⊥ I						u.1	200.1	-	
Years 0-4	15/2588	95/2633	-38.1	25.9	■		0.23 (SE 0.10)	(j) Period of follow-	up ($\chi_1^2 = 0.3$; 2p = 0.6)				1
Yeara 5-9	4/1876	1771745	-6.5	5.1			0.28 (SE 0.25)	Years 0-4	157/2516	235/2505	-34.6	84.9	-	1
								Years 5-9	54/1898	69/1782	-7.8	25.7		+
T -1-1	19/ 625	112/ 669	-44.6	30.9		0.24 /85 0.40								1
Total	(3.0%)	(16.7%)	-44.0	30.9	T I	0.24 (SE 0.10)		_	211/	304/				1
								Total	832	682	-42.3	111.6		0.68 (SE 0.0
Global heterogeneity	y: $\chi^2_{18} = 6.4;$	p > 0.1: NS	5						(33.4%)	(44.6%)				1
				0.0	0.5 1.	0 1.5	2.0							

1314 pN1-3 women with Mast+AD

Rate Ratio (Standard Error)

AND ADDRESS OF

0.52 (SE 0.20)

0.89 (SE 0.17)

0.85 (SE 0.13)

0.64 (SE 0.15)

0.86 (SE 0.37)

0.57 (SE 0.20

0.64 (SE 0.26)

0.69 (SE 0.10)

0.42 (SE 0.16)

0.88 (SE 0.17)

0.80 (SE 0.35)

0.71 (SE 0.12)

0.09 (SE 0.09)

0.63 (SE 0.18)

0.72 (SE 0.12)

0.65 (SE 0.13) 0.87 (SE 0.17)

0.01 (SE 0.15)

0.79 (SE 0.14)

D.62 (SE 0.13)

0.78 (SE 0.22)

0.67 (SE 0.08)

0.64 (SE 0.14)

0.70 (SE 0.09)

0.84 (SE 0.09)

0.79 (SE 0.15)

0.67 (SE 0.09)

0.75 (SE 0.17)

Breast cancer mortality Allocated RT Allocated No RT Logrank Varlance D-E of O-E Ratic of annual death rates RT : No RT Rate Rati Category (Standard Erro (a) Age at entry ($\chi_1^2 = 1.1$; 2p = 0.3) Age < 40 yrs Age 40 - 49 yrs 31/76 15 0.57 (SE 0.20) 43/76 -8.6 65/204 81017 -5.0 33.2 0.88 (SE.0.16) Ago 60 - 59 yrs 84/205 105(203 -11.0 43.8 0.78 (SE.0.13) Age 6D+ yrs 68/148 95/158 -3.8 34.0 0.60 (SE 0.16) (b) Turnour Grade (x = 0.7; 2p = 0.4) 7.4 10.5 10.5 1.19 (SE 0.40) 0.61 (SE 0.19) Low grade Intermediate grade 22/64 27/81 20/50 15/48 48/95 29/67 1.3 -8.1 -3.2 High grade 0.74 (BE 0.27) Đ Unknown grade 179437 233482 -18.1 86.9 0.81 (SE.0.10) (c) Tumour size $(\gamma^2 = 0.0; 2p = 0.9)$ 1-19 mm 48/139 -6.4 23.2 0.75 (SE 0.18) 63/153 20-40 mm 65/151 90/192 17/51 -3.1 -2.3 33.1 5.2 0.91 (SE 0.17) 50+ mm 12/35 0.64 (SE 0.35) 0.79 (SE.0.12) unknown 125/307 155/306 -13.859.3 (d) Mastectomy ($\chi_1^2 = 0.2; 2p = 0.7$) 0.79 (SE 0.09) Simple -24.1 99.0 196/514 258/567 More extensive 55/118 67/125 -3.8 26.9 0.65 (SE 0.18) (e) Axillary surgery information $\chi_2^2 = 0.1; p = 1.0$ -11.5 56.5 0.81 (SE.0.12) Thisi protocol 183/277 140/281 Trial median AN212 112/234 -11.0 43.8 0.77 (SE 0.13) Individual 52/143 73/167 -6.3 26.5 0.82 (SE.0.18) (f) Number of positive nodes { $\chi_1^2 = 0.2$; 2p = 0.7} -7.7 0.79 (SE 0.16) 1 positive node 67/191 88/214 32.4 2-3 positive nodes 100/223 124/250 -6.5 47.8 0.87 (SE 0.14) Unknown but oN1-3 81/218 113/238 -11.4 41.5 0.78 (SE.0.14) (g) Any systemic therapy (χ²₁ = 0.4; 2p = 0.5) 46/63 52/88 -2.1 21.8 0.01 (SE 0.20) No systemic Chemo and/or ER+tam+ 202/039 273/594 -25.9 103.7 0.78 (SE 0.09) (h) Radiotherapy dose (\u03c2² = 0.0; 2p = 1.0) 504 Gy 84/190 95/216 -7.5 33.1 0.80 (SE 0.16) <50 Gy -20.9 52.8 0.80 (SE.0.09) 184/452 2304488 Date trial started (χ² = 2.0; 2p = 0.2) na 0.74 (SE 0.05) Started <1990 173/433 2329454 -27.2 fearteri 1960 -75/100 93/228 -12 37.4 0.97 (SE 0.16) ()) Period of follow-up (\(\chi_1^2 = 0.0; 2p = 0.9\)) 0.82 (SE 0.12) Voters 0-4 111/2622 143/3064 -11.2 56.7 Veers 5-9 76/21/2 94/2258 -6.5 37.A 0.84 (SE.0.15) Years 10-14 35/1648 15/1090 11/350 58/1650 13/966 12/757 -11.0 0.9 -0.8 20.7 6.1 6.0 0.58 (SE 0.17) . Wears 15-19 Wears 20+ ⇒ 1.16 (8E 0.44) > 0.89 (8E 0.42) 248/ 632 325/ 682 -28.4 125.9 0.80 (SE 0.08) Total -(39.2%) (47.7%) Global heterogeneity: $\chi^2_{cs} = 11.4$; $p \ge 0.1$: NS 0.0 0.5 1.0 1.5 2.9 - RT worse RT better

In (h), trials that used orthovoltage irradiation are included in the <50 Gy category.

Webfigure 10. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause 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 webfigure 1 for methodological note and also webfigure 11.



Webfigure 11. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1133 women with 1-3 pathologically positive nodes (pN1-3) in trials where systemic therapy was given to both randomised treatment groups. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Webfigure 12. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 15-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 subdivided according to number of positive nodes. See webfigure 1 for methodological note and also webfigures 13-15.



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







Webfigure 13. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 318 women with 1 pathologically positive node (pN1) and where systemic therapy was given to both randomised treatment groups. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



318 women with Mast+AD, systemic therapy and 1 positive node

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: = 0.0001

Webfigure 14. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 365 women with 2-3 pathologically positive nodes (pN2-3) and where systemic therapy was given to both randomised treatment groups. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



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

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: = 0.007

Webfigure 15. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 450 women with 1-3 pathologically positive nodes (pN1-3) but the exact number of positive nodes unknown and where systemic therapy was given to both randomised treatment groups. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



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

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: = 0.00002

Webfigure 16. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1772 women with 4+ pathologically positive nodes (pN4+). See webfigure 1 for methodological note and also webfigure 17.


Webfigure 17. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1772 women with 4+ pathologically positive nodes (pN4+). (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Webfigure 18. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection

(Mast+AD): Event rate ratios and 95% confidence intervals for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer mortality in 1772 women with 4+ pathologically positive nodes (pN4+) by prognostic and other factors. Categories with unknowns are excluded from the heterogeneity and trend tests.

1772 pN4+ women with Mast+AD

Any first recurrence (years 0-9)

Breast cancer mortality



Note:In (g), 135 women who were ER positive with tamoxifen also had chemotherapy. In (h), trials that used orthovoltage irradiation are included in the <50 Gy category.

Locoregional recurrence first (years 0-9)

Webfigure 19. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1677 women with 4+ pathologically positive nodes (pN4+) in trials where systemic therapy was given to both randomised treatment groups. See webfigure 1 for methodological note and also webfigure 20.



Webfigure 20. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1677 women with 4+ pathologically positive nodes (pN4+) in trials where systemic therapy was given to both randomised treatment groups. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Webfigure 21. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 15-year risk of breast cancer mortality in 1677 women with 4+ pathologically positive nodes (pN4+) in trials where systemic therapy was given to both randomised treatment groups subdivided according to number of positive nodes. See webfigure 1 for methodological note and also webfigures 22-24.



403 women with Mast+AD, systemic therapy and 10+ positive nodes







Webfigure 22. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 479 women with 4-9 pathologically positive nodes (pN4-9) in trials where systemic therapy was given to both randomised treatment groups. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Webfigure 23. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 403 women with 10+ pathologically positive nodes (pN10+) in trials where systemic therapy was given to both randomised treatment groups. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: = 0.00002

Webfigure 24. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 795 women with 4+ pathologically positive nodes but the exact number of positive nodes unknown in trials where systemic therapy was given to both randomised treatment groups. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



795 pN4+ women but exact number of positive nodes unknown, Mast+AD and systemic therapy

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: > 0.1; NS

Webfigure 25. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 870 women with pathologically node-negative (pN0) disease. See webfigure 1 for methodological note and also webfigure 26. Note: 0 locoregional recurrences, 8 recurrences of any type and 10 breast cancer deaths were reported among the 36 pN0 women with tumours \geq 5 cm who were allocated to receive radiotherapy. 4 locoregional recurrences of any type and 9 breast cancer deaths were reported among the 36 pN0 women with tumours \geq 5 cm who were allocated to receive radiotherapy.



870 pN0 women with Mast+AS

Webfigure 26. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 870 women with pathologically node negative (pN0) disease. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



870 pN0 women with Mast+AS

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Webfigure 27. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 2541 women with pathologically node-positive (pN+) disease. See webfigure 1 for methodological note and also webfigure 28.



2541 pN+ women with Mast+AS

Webfigure 28. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 2541 women with pathologically node-positive (pN+) disease. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Webfigure 29. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 1594 women with pathologically node-negative (pN0) disease.

1594 pN0 women

Locoregional recurrence first (years 0-9)

		Events/	Women	RTe	vents	
Year code, and study name	Treatment	Allocated	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of annual event rates
and study name	Information	RI	NORI	0-E	or O-E	RT : No RT
(a) Axillary dissection	n					-∎-99%95% Ci
64B Oslo X-ray		0/475	0474	0.0	4.0	
74D DFCI Boston	CW+AF+IMC †CW+AF+(IMC)	2/175 0/8	2/174 0/2	0.0	1.0 -	
76C Glasgow	TCW+AF+IMC	0/1	0/1			
78A S Sweden II:1	TCW+AF+IMC	6/134	3/144	1.7	2.2	
79G Metaxas Athens	TCW+AF+IMC	0/5	0/5	1.7	2.2	-
82B DBCG 82b ipremenop.		1/8	0/10	0.4	0.2 -	
82C DBCG 82c ipostmenop		0/6	0/12	0.4	0.2	
82Q ECOG EST3181	+CW+AF+IMC	0/9	0/4			
						:
		9/	5/			
 (a) Subtotal 		346	352	2.1	3.5	4 94 (SE 0 73)
		(2.6%)	(1.4%)			1.81 (SE 0.73)
(b) Axillary sampling						20-0.1.100
71B Stockholm A	CW+AF+IMC	4/203	30/196	-13.2	8.2 -	
73A Southampton UK	CW+AF+IMC	3/23	4/29	0.5	1.4	
74B Edinburgh I	CW+AF	5/114	24/114	-9.6	6.9	
82B DBCG 82b ipremenop.	TCW+AE+IMC	0/36	4/53	-1.9	0.9	
82C DBCG 82c lpostmenop		2/49	10/53	-3.5	2.5 -	• '
ozo bboo ozo iposimenop				-0.0	2.0 -	
_		14/	72/			· · · · · · · · · · · · · · · · · · ·
(b) Subtotal		425	445	-27.8	19.9	0.25 (SE 0.12) 2p < 0.00001
		(3.3%)	(16.2%)			2p < 0.00001
(c) Extent of axillary	surgery unkn	own	,			
86C CRC, UK	†Various	0/14	1/10	-0.7	0.2-	
		0/	1/			:
 (c) Subtotal 		14	10	-0.7	0.2	
- (0) Subtotui		(0.0%)	(10.0%)	0.7	0.2	0.00 (SE 0.67)
		(0.0%)	(10.0%)			2p > 0.1: NS
_		23/	78/			:
Tatal		785	807	-26.4	23.6	0.33 (SE 0.12)
Total				-20.4	23.0	
		(2.9%)	(9.7%)			
Heterogeneity betwe	en 3 subtota	ls: $\gamma_{0}^{2} = 12$.5: p = 0.0	02		
Heterogeneity within					0.0	0.5 1.0 1.5 2.0
						PT holiar
Heterogeneity betwe	en 9 trials:)	(₈ = 18.3;	p = 0.02			RT better RT worse

					vents		
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E		al event rates_ No RT
a) Axillary dissection						1	- ∎99% <>>95% (
a) Axillary dissection	•						
4B Oslo X-ray	CW+AF+IMC	28/175	38/174	-5.1	16.1		
4D DFCI Boston	†CW+AF+(IMC)	1/8	1/2	-0.3	0.2-		;
6C Glasgow	†CW+AF+IMC	1/1	0/1	0.5	0.2 -		
7J MD Ander, 7730B	†CW+AF+IMC	0/1	0/1				_
'8A S Sweden II:1	†CW+AF+IMC	34/134	27/144	4.7	14.7	+	,
9G Metaxas Athens	†CW+AF+IMC	2/5	1/5	0.7	0.4		· · · · · · · · · · · · · · · · · · ·
2B DBCG 82b ipremenop.		3/8	2/10	0.3	1.0	i	
2C DBCG 82c ipostmenop		4/6	3/12	1.7	1.4		
2Q ECOG EST3181	†CW+AF+IMC	2/9	1/4	-0.4	0.5-		
_		75/	73/				
(a) Subtotal		347	353	2.0	34.5		T
		(21.6%)	(20.7%)			1.06 (SE 0.18)	
		(,	()			2p > 0.1: NS	
b) Axillary sampling						1	
1B Stockholm A	CW+AF+IMC	39/203	61/196	-13.1	23.4		
3A Southampton UK	CW+AF+IMC	8/23	11/29	0.1	3.6		 ;
4B Edinburah I	CW+AF	27/114	40/114	-7.5	15.6		
32B DBCG 82b ipremenop.	+CW+AE+IMC	3/36	14/53	-3.9	3.2		
32C DBCG 82c ipostmenop		17/49	24/53	-2.3	8.7		
		94/	150/				
(b) Subtotal		425	445	-26.8	54.6		0.61 (SE 0.11)
(b) Subtotal		(22.1%)	(33.7%)	-20.0	34.0		0.61 (SE 0.11) 2p = 0.0003
		,	(33.1%)				
c) Extent of axillary	surgery unkn	lown					
86C CRC, UK	†Various	2/14	4/10	-1.4	1.4 -	• +	;
		2/	4/				
 (c) Subtotal 		14	10	-1.4	14		
- (0) Oubtotui		(14.3%)	(40.0%)	1.4	1.4		0.38 (SE 0.53)
		(14.3%)	(40.0%)				2p > 0.1: NS
—		171/	227/				A (A A AA)
Total		786	808	-26.1	90.6	~	0.75 (SE 0.09) 2p = 0.006
		(21.8%)	(28.1%)				2p = 0.000
leterogeneity betwee	en 3 subtota	lis: $\chi_2^2 = 7.0$	0; p = 0.03			I	
		2			0.0	0.5 1	.0 1.5
leterogeneity within	subtotals: v	1. = 11.3:	D > 0.1: NS	ś	0.0	0.0 1	

Any first recurrence (years 0-9)

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

Webfigure 29 cntd.

1594 pN0 women

Breast cancer mortality

Any death



† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

Webfigure 30. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 5821 women with pathologically node-positive (pN+) disease.

5821 pN+ women

Locoregional recurrence first (years 0-9)

Any first recurrence (years 0-9)



† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

Webfigure 30 cntd.

5821 pN+ women

Breast cancer mortality

Any death

-**₽**-99% -----95% Cl

2.0

	Deaths/			eaths	Defie of energy	death antes				Women		eaths	Dette of one	al da ath anta a
Year code, Treatment and study name Information	Allocated RT	Allocated No RT		Variance of O-E	Ratio of annua RT :	No RT		Treatment Information	Allocated RT	Allocated No RT		Variance of O-E	Ratio of annua RT :	al death rates
a) Axillary dissection						₽ 99% ↔95%	(a) Axillary dissection							- 99% ↔95
648 Oslo X-ray CW+AF+IMC	68/110	63/93	-8.0	25.1				CW+AF+IMC	101/110	85/93	-5.2	35.9		
74D DFCI Boston †CW+AF+(IMC) 46/103	53/105	0.1	20.5				CW+AF+(IMC)	57/103	55/105	3.0	22.8		
4Q Piedmont OA (pN4+) +CW+AF+IMC	36/65	40/55	-3.5	14.3				CW+AF+IMC	41/65	41/55	-1.6	15.2		
6A SECSG 1 +CW+AF+IMC	54/126	65/129	-3.7	24.7				CW+AF+IMC	60/126	69/129	-3.2	26.9		
6C Glasgow †CW+AF+IMC	63/110	69/100	-8.0	25.6				†CW+AF+IMC	77/110	81/100	-7.4	31.4	_	
7J MD Ander. 7730B †CW+AF+IMC	23/31	24/43	6.0	6.9	! -+			CW+AF+IMC	24/31	24/43	6.5	7.2	! +	
78A S Sweden II:1 †CW+AF+IMC	106/225	131/228	-18.7	51.2				†CW+AF+IMC	149/225	161/228	-16.1	67.5		-
78G BCCA Vancouver †CW+AF+IMC	79/163	96/153	-16.8	39.1				CW+AF+IMC	89/163	100/153	-15.5	42.1		-
8Q Düsseldorf U. †CW+AF+IMC	14/34	14/54	4.9	5.1	!+			CW+AF+IMC	17/34	24/54	3.3	7.8		
9G Metaxas Athens †CW+AF+IMC	11/25	21/36	-3.4	5.9				CW+AF+IMC	11/25	21/36	-3.4	5.9		
0S Helsinki †CW+AF+IMC	22/47	20/52	0.9	8.1	i	•		†CW+AF+IMC	24/47	25/52	1.5	9.0		•
328 DBCG 82b ipremenop. +CW+AF+IMC	104/193	138/207	-16.8	51.6				CW+AF+IMC	111/193	144/207	-17.0	54.7		-
2C DBCG 82c ipostmenop. +CW+AF+IMC	103/157	116/169	-1.0	46.6			82C DBCG 82c ipostmenop.		122/157	131/169	-1.1	54.1		
2Q ECOG EST3181 †CW+AF+IMC	103/161	91/157	6.0	42.4	. +	-	82Q ECOG EST3181	†CW+AF+IMC	118/161	112/157	4.2	50.0	<u>+</u>	-
-	832/	941/					_		1001/	1073/				
(a) Subtotal	1550	1581	-62.0	367.0	<>>	0.84 (SE 0.05) 2p=0.001	(a) Subtotal		1550	1581	-52.1	430.4	_	0.89 (SE 0.05) 2p = 0.01
	(53.7%)	(59.5%)				2p = 0.001			(64.6%)	(67.9%)			:	2p = 0.01
) Axillary sampling							(b) Axillary sampling						:	
1B Stockholm A CW+AF+IMC	67/118	96/121	-12.8	36.7		_	71B Stockholm A 0	CW+AF+IMC	93/118	104/121	-11.2	42.6		
3A Southampton UK CW+AF+IMC	23/33	32/38	-5.0	10.4				CW+AF+IMC	28/33	32/38	-3.5	11.1		
4B Edinburgh I CW+AF	0/0	0/1						CW+AF	0/0	1/1				
J MD Ander. 7730B †CW+AF+IMC	5/7	6/10	0.0	0.5 —				CW+AF+IMC	5/7	6/10	0.0	0.5 -	· · ·	
F Coimbra †CW+AF+IMC	31/62	36/61	-0.1	11.4				CW+AF+IMC	41/62	42/61	1.7	14.9		•
2B DBCG 82b ipremenop. +CW+AF+IMC	253/517	320/493	-54.3	125.3			82B DBCG 82b ipremenop.	†CW+AF+IMC	284/517	328/493	-47.2	134.4		
2C DBCG 82c ipostmenop. †CW+AF+IMC	224/401	254/406	-16.1	104.2		_	82C DBCG 82c ipostmenop.	CW+AF+IMC	272/401	307/406	-24.7	127.2		-
34A GBSG 03 Germany +CW+AF+IMC	34/96	44/100	-1.8	16.3				CW+AF+IMC	45/96	48/100	1.3	19.9		-
5F Nottingham †CW+AF	22/36	28/41	-2.9	10.3				CW+AF	23/36	30/41	-3.6	11.0		-
(b) Subtotal	659/	816/				0.74 (85.0.05)	(b) Subtotal		791/	898/	07.4	204.0	-	0.70 (85.0.05)
(b) Subtotal	1270 (51.9%)	1271 (64.2%)	-93.1	315.3	₩	0.74 (SE 0.05) 2p < 0.00001	(b) Subtotal		1270 (62.3%)	1271 (70.7%)	-87.1	361.6		0.79 (SE 0.05) 2p < 0.00001
c) Extent of axillary surgery unk		(041270)					(c) Extent of axillary su			(1 011 /0)				
		20/50	0.6			-		trgery unkn †CW+AF+IMC	23/54	20/58	16	8.9		-
30W NSABC Israel †CW+AF+IMC 36C CRC, UK †Various	21/54 11/17	20/58 9/20	0.6 0.3	8.4 2.7		•		Various	23/54	13/20	1.6 0.0	3.4		-
	32/	29/			1				36/	33/				
 (c) Subtotal 	71	78	1.0	11.0		T ==	–		71	78	1.6	12.3		
	(45.1%)	(37.2%)			1.09 (SE 0.31) 2p > 0.1: NS				(50.7%)	(42.3%)			1.14 (SE 0.30) 2p > 0.1: NS	
					2p ≥ 0.1: NS								ap - viii No	
	1523/	1786/					_		1828/	2004/				
Total	2891		-154.1	693.3	4	0.80 (SE 0.02)	Total		2891		-137.6	804.3	4	0.84 (SE 0.02)
Total			-154.1	093.3	₽	0.80 (SE 0.03) 2p < 0.00001	Iotai				-13/.6	004.5	₽	0.84 (SE 0.03) 2p < 0.00001
	(52.7%)	(61.0%)				-			(63.2%)	(68.4%)				
							1							
Heterogeneity between 3 subtot			NS				Heterogeneity between							
Heterogeneity between 3 subtot Heterogeneity within subtotals:)			NS	0.0	0.5 1.0	0 1.5	2.0 Heterogeneity between Heterogeneity within s					0.0	0.5 1.	.0 1.5

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups. Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

Webfigure 31. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 2801 women with 1-3 pathologically positive nodes (pN1-3).

2801 pN1-3 women

Locoregional recurrence first (years 0-9)

		Events	Women	RT e	vents		
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E		ual event rates : No RT
				• -			• NO KI
(a) Axillary dissection	n						
64B Oslo X-ray	CW+AF+IMC	0/80	6/73	-3.1	1.5		+
74D DFCI Boston	†CW+AF+(IMC)		3/41	-0.9	1.0	•	>
76A SECSG 1	†CW+AF+IMC	0/1	0/0		_	-	
76C Glasgow	†CW+AF+IMC	3/70	19/69	-8.1	5.2 —		
78A S Sweden II:1	†CW+AF+IMC	4/140	25/155	-10.6	6.9 —		
78G BCCA Vancouver	†CW+AF+IMC	7/91	14/92	-3.6	5.0 -		
79G Metaxas Athens	†CW+AF+IMC	0/7	1/11	-0.5	0.2		>
80S Helsinki	†CW+AF+IMC	1/29	10/38	-3.6	2.6		<u> </u>
82B DBCG 82b ipremenop.		1/83	13/79	-6.3	3.1 -	1	
82C DBCG 82c ipostmenop		1/53	19/75	-7.3	4.7 —		
82Q ECOG EST3181	†CW+AF+IMC	1/34	2/36	-0.6	0.7	•	>
		19/	112/			•	
(a) Subtotal		625	669	-44.5	30.9 <		0.24 (SE 0.10)
(1)		(3.0%)	(16.7%)		00.0	1	0.24 (SE 0.10) 2p < 0.00001
		(0.070)	(10.17.0)				
(b) Axillary sampling							
71B Stockholm A	CW+AF+IMC	5/43	12/42	-3.7	3.8		
79F Coimbra	†CW+AF+IMC	1/28	4/29	-1.4	1.2	•	>
82B DBCG 82b ipremenop.	†CW+AF+IMC	12/344	82/322	-38.3	22.4	-	
82C DBCG 82c ipostmenop	. †CW+AF+IMC	11/245	59/240	-25.6	16.9 -		
84A GBSG 03 Germany	†CW+AF+IMC	1/62	5/57	-2.3	1.5		
_		30/	162/				
(b) Subtotal		722	690	-71.3	45.8 <	i b	0.21 (SE 0.07)
(b) Subtotal		(4.2%)	(23.5%)	/1.5	40.0	1	0.21 (SE 0.07) 2p < 0.00001
		(4.270)	(23.5%)				
(c) Extent of axillary	surgery unkn	own					
80W NSABC Israel	†CW+AF+IMC	1/20	5/19	-2.4	1.5		
86C CRC, UK	†Various	0/10	4/18	-1.3	0.7	1	>
		1/	9/			1	
 (c) Subtotal 		30	37	-3.7	2.2 -		0.18 (SE 0.32)
- (0) 04510141				0.7		1	2p = 0.01
		(3.3%)	(24.3%)			:	
		50/	283/				0.00 (05.0.00)
Total		1377	1396	-119.6	78.8 <	•	0.22 (SE 0.06) 2p < 0.00001
		(3.6%)	(20.3%)				2p < 0.00001
Heterogeneity betwee	an 3 cubtoto	$ \mathbf{e}_{1} ^{2} = 0^{2}$	8· n > 0 4·	NG	L	· · ·	
					0.0	0.5	1.0 1.5 2.0
Heterogeneity within					0.0		
Heterogeneity betwee	en 17 trials:	$\chi^2_{16} = 7.5;$	p > 0.1: N	S		RT better	- RT worse

Any first recurrence (years 0-9)

		Events	Women	RT e	vents			
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E		ual event rates : No RT	
						K	- Ho Ki	6 CI
(a) Axillary dissection	า					:		
64B Oslo X-ray	CW+AF+IMC	29/80	35/73	-4.2	14.6			
74D DFCI Boston	+CW+AF+(IMC)		15/41	-1.1	6.0			~
76A SECSG 1	†CW+AF+IMC	0/1	0/0			:		
76C Glasgow	†CW+AF+IMC	32/70	39/69	-5.2	15.5	; 	<u> </u>	
77J MD Ander. 7730B	†CW+AF+IMC	5/7	7/13	1.6	1.3			~
78A S Sweden II:1	†CW+AF+IMC	34/140	65/155	-17.7	21.8			
78G BCCA Vancouver	†CW+AF+IMC	30/91	41/92	-6.3	16.2		<u> </u>	
79G Metaxas Athens	+CW+AF+IMC	3/7	6/11	-1.2	1.2			\rightarrow
80S Helsinki	+CW+AF+IMC	7/29	18/38	-3.1	5.5		<u> </u>	
82B DBCG 82b ipremenop. 82C DBCG 82c ipostmenop.	+CW+AF+IMC	22/83 18/53	30/79	-6.9	11.0			
82Q ECOG EST3181	TCW+AF+IMC	19/34	36/75 12/36	-4.5 6.4	12.2 6.3			-
824 EGOG ES13181	1011+AL +IMC	19/34	12/30	0.4	0.5	i		-
_		211/	304/					
(a) Subtotal		632	682	-42.3	111.7	<e></e>	0.68 (SE 0.08) 2p = 0.00006	
		(33.4%)	(44.6%)			:	2p = 0.00006	
		(,	(******					
(b) Axillary sampling								
71B Stockholm A	CW+AF+IMC	21/43	25/42	-3.3	9.7			
77J MD Ander. 7730B	†CW+AF+IMC	3/4	3/4	0.5	0.2			~
79F Coimbra	†CW+AF+IMC	7/28	15/29	-3.5	4.9 -			
82B DBCG 82b ipremenop.	†CW+AF+IMC	143/344	190/322	-39.1	73.8			
82C DBCG 82c ipostmenop.	†CW+AF+IMC	113/245	133/240	-17.7	55.5		+	
84A GBSG 03 Germany	†CW+AF+IMC	16/62	24/57	-4.6	8.5			
_		303/	390/			:		
(b) Subtotal		726	694	-67.7	152.8	-	0.64 (SE 0.07) 2p < 0.00001	
(,		(41.7%)	(56.2%)	••••		1	2p < 0.00001	
(c) Extent of axillary	surgery unkr	own	,			1		
•••••						1		
80W NSABC Israel 86C CRC, UK	†CW+AF+IMC †Various	12/20 5/10	15/19 8/18	-2.4	5.6 2.2		-	_
800 OK0, OK	various	5/10	0/10	0.2	2.2		•	-
		17/	23/			i		
 (c) Subtotal 		30	37	-2.2	7.9			
.,		(56.7%)	(62.2%)				0.76 (SE 0.31)	
		(,,	(,.,			:	2p > 0.1: NS	
						1		
		531/	717/					
Total		1388	1413	-112.2	272.3	4	0.66 (SE 0.05) 2p < 0.00001	
		(38.3%)	(50.7%)			1	2p < 0.00001	
Heterogeneity betwee	an 3 subtots	$s_{1}^{2} = 0$	4: n > 0 1.	NS				
				110	0.0	0.5	1.0 1.5	2.0
Heterogeneity within	subtotals: χ	16 - 20.3; 2	p = 0.07		'			
Heterogeneity betwee	en 19 trials:	$\chi_{18} = 25.7$;p>0.1:	NS		RT better	- RT worse	

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

2801 pN1-3 women

Breast cancer mortality

Year code, and study name	Treatment	Allocated	Allocated	I a super-		Detio of annu	
•	Information	RT	No RT	C-E	Variance of O-E		al death rates No RT
							- 99% <->95% C
a) Axillary dissection	1						
4B Oslo X-ray	CW+AF+IMC	41/80	45/73	-2.0	19.5	 _	
4D DFCI Boston	†CW+AF+(IMC)	9/37	12/41	0.2	4.6		•
6A SECSG 1	†CW+AF+IMC	0/1	0/0				
	†CW+AF+IMC	33/70	42/69	-4.1	15.8	ė	
7J MD Ander, 7730B	†CW+AF+IMC	5/7	7/13	0.6	1.3 -		· · · >
8A S Sweden II:1	†CW+AF+IMC	48/140	75/155	-14.0	27.3		
8G BCCA Vancouver	†CW+AF+IMC	34/91	45/92	-6.8	19.0		
9G Metaxas Athens	†CW+AF+IMC	3/7	6/11	-1.1	1.2		
0S Helsinki	†CW+AF+IMC	9/29	16/38	-1.1	5.4		~ ~ ~
2B DBCG 82b ipremenop.	†CW+AF+IMC	25/83	31/79	-5.3	12.5		
2C DBCG 82c ipostmenop.	†CW+AF+IMC	22/53	35/75	-0.6	12.7		
2Q ECOG EST3181	†CW+AF+IMC	19/34	11/36	5.8	6.7	:	>
		248/	325/				
						1	
(a) Subtotal		632	682	-28.4	125.9	-	0.80 (SE 0.08) 2p = 0.01
—		(39.2%)	(47.7%)				20-0.01
b) Axillary sampling						:	
						! _	
	CW+AF+IMC	23/43	32/42	-1.6	12.8		
	†CW+AF+IMC	4/4	3/4	0.0	0.5	1	
	†CW+AF+IMC	8/28	13/29	-1.7	4.5		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2B DBCG 82b ipremenop.	†CW+AF+IMC	152/344	188/322	-28.6	78.4	— — —	
2C DBCG 82c ipostmenop.	†CW+AF+IMC	126/245	138/240	-12.1	59.6		
4A GBSG 03 Germany	TCW+AF+IMC	16/62	20/57	-1.6	7.8		
art obbo to outiliarly				1.0	110		
-		329/	394/			i i	
(b) Subtotal		726	694	-45.6	163.5	~	0.76 (SE 0.07) 2p = 0.0004
.,		(45.3%)	(56.8%)				2p ≌ 0.0004
c) Extent of axillary s	urgery unkn	own					
0W NSABC Israel	+CW+AF+IMC	12/20	13/19	-1.1	4.9		
	†Various	6/10	7/18	0.5	2.2		
00 010, 010	Trancas			0.0	AA.		
		18/	20/			1	
 (c) Subtotal 		30	37	-0.6	7.1		
.,		(60.0%)	(54.1%)				0.92 (SE 0.36)
		(00.076)	(34.176)			;	2p > 0.1: NS
						:	
—		595/	739/			:	A 70 (OF A AS)
Total		1388	1413	-74.6	296.5	\Rightarrow	0.78 (SE 0.05) 2p = 0.00001
		(42.9%)	(52.3%)			1	2p = 0.00001
						1	
I		2 - 0			L	1 1	
leterogeneity betwee	n 3 subtota	$x_2 = 0.4$	∔; p > 0.1:	NS			
leterogeneity within	subtotals: y	a = 15.0:	p > 0.1: NS	3	0.0	0.5 1.	.0 1.5 2
	n 19 trials:	2				RT better -	- RT worse

Any death

		Deaths	Women	_ KI d	eaths						
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O–E	Variance of O-E	Ratio of annua RT :	l death rates No RT				
a) Axillary dissection							₽99% ↔95%(
							_				
34B Oslo X-ray	CW+AF+IMC	71/80	65/73	1.4	29.6						
4D DFCI Boston	+CW+AF+(IMC)		12/41	2.0	5.4						
76A SECSG 1	+CW+AF+IMC	0/1	0/0			<u> </u>					
6C Glasgow	+CW+AF+IMC	45/70	52/69	-3.2	20.6						
7J MD Ander. 7730B	+CW+AF+IMC	5/7	7/13	0.6	1.3 -		· · · · ·				
78A S Sweden II:1	†CW+AF+IMC	80/140	99/155	-11.2	40.1						
78G BCCA Vancouver	+CW+AF+IMC	41/91	49/92	-6.4	21.4						
9G Metaxas Athens	†CW+AF+IMC	3/7	6/11	-1.1	1.2		2				
30S Helsinki	†CW+AF+IMC	10/29	20/38	-0.6	5.9		*				
32B DBCG 82b ipremenop.	†CW+AF+IMC	26/83	36/79	-7.8	13.9						
32C DBCG 82c ipostmenop.		33/53	45/75	0.5	17.8						
32Q ECOG EST3181	†CW+AF+IMC	24/34	16/36	7.1	8.8						
		352/	407/								
(a) Subtotal		632	682	-18.7	466.0	-	0 90 (SE 0 07)				
(a) Subtotal				-18.7	166.0	~13	 0.89 (SE 0.07) 2p > 0.1: NS 				
		(55.7%)	(59.7%)			:					
b) Axillary sampling											
1B Stockholm A	CW+AF+IMC	32/43	35/42	-0.9	15.1						
7J MD Ander, 7730B	TCW+AF+IMC	4/4	3/4	0.0	0.5						
9F Coimbra	+CW+AF+IMC	15/28	18/29	-1.0	7.1						
	1	175/344	194/322	-23.2	85.2						
32C DBCG 82c lpostmenop.		165/245	176/240	-14.5	77.9						
34A GBSG 03 Germany	+CW+AF+IMC	22/62	21/57	- 14.5	9.4		-				
An object to contaily	1011-1410			0.4	5/4						
—		413/	447/								
(b) Subtotal		726	694	-39.2	195.3	~	0.82 (SE 0.06)				
		(56.9%)	(64.4%)				2p= 0.005				
c) Extent of axillary s	suraery unkr	Iown									
IOW NSABC Israel	+CW+AF+IMC	12/20	13/19	-1.1	4.9						
BC CRC, UK	†Various	7/10	11/18	0.1	2.9						
					210		-				
		19/	24/								
 (c) Subtotal 		30	37	-0.9	7.8						
		(63.3%)	(64.9%)				0.89 (SE 0.34)				
		()	(,				2p > 0.1: NS				
		784/	878/								
Total		1388	1413	-58.8	369.0	4	0.85 (SE 0.05)				
Iotai				-30.0	209.0	~	2p = 0.002				
		(56.5%)	(62.1%)				-				
leterogeneity betwee	an 3 subtota	als: $\chi_2^2 = 0.3$	7; p > 0.1:	NS	L	· · · ·	1				
					0.0	0.5 1.) 1.5				
leterogeneity betwee leterogeneity within leterogeneity betwee	subtotals: χ	² ₁₆ = 17.1;	p > 0.1: NS	8	0.0	0.5 1.) 1.5				

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

Webfigure 32. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 2557 women with 4+ pathologically positive nodes (pN4+).

2557 pN4+ women

		Events/	Women	RTe	rents					Events/	Women	RTe	/ents		
Year code,	Treatment	Allocated	Allocated	Logrank			al event rates	Year code,	Treatment	Allocated	Allocated	Logrank			al event rates
and study name	Information	RT	No RT	0-E	of O-E	RT	No RT	and study name	Information	RT	No RT	0-E	of O-E	RT	No RT
Axillary dissection	ı						- 99% -<>95% CI	(a) Axillary dissectior	n						- ₽ -99% -∞ -95%
	CW+AF+IMC	0/30	4/20	-2.2	0.9			64B Oslo X-ray	CW+AF+IMC	24/30	18/20	-6.0	5.2	e	
	†CW+AF+(IMC)		14/56	-4.0	4.2 —		<u> </u>	74D DFCI Boston	†CW+AF+(IMC		42/56	-0.6	15.7		
	†CW+AF+IMC	6/65	9/65	-1.6	2.9 —		>	74Q Piedmont OA (pN4+)	†CW+AF+IMC	41/65	40/55	-2.6	14.9		<u> </u>
	†CW+AF+IMC	12/125	18/129	-3.5	7.1			76A SECSG 1	†CW+AF+IMC	62/125	83/129	-10.8	28.6		<u>+</u>
	†CW+AF+IMC †CW+AF+IMC	11/40 5/85	10/31 11/73	-0.8 -4.2	4.6 3.7 —		>	76C Glasgow	+CW+AF+IMC +CW+AF+IMC	29/40 17/24	24/31	-1.4 4.8	9.5	•	
	TCW+AF+IMC	5/85 8/60	11//3	-4.2	3.7 — 5.7 —			77J MD Ander, 7730B	TCW+AF+IMC	17/24 56/85	17/30	4.8	5.2 21.2		
	TCW+AF+IMC	0/34	1/54	-0.4	0.2-	-	1 ~	78A S Sweden II:1 78G BCCA Vancouver	TCW+AF+IMC	34/60	54/73 43/54	-7.4	21.2		
	TCW+AF+IMC	4/18	3/25	0.5	1.7 .	i		78Q Düsseldorf U.	+CW+AF+IMC	17/34	43/54	-8.5	7.4		_
	TCW+AF+IMC	3/16	2/9	-0.3	0.7			79G Metaxas Athens	+CW+AF+IMC	11/18	16/25	-2.3	4.4		-
B DBCG 82b ipremenop.		8/110	29/128	-10.8	8.4 -		-	80S Helsinki	†CW+AF+IMC	10/16	2/9	2.2	1.7		
C DBCG 82c ipostmenop.		5/104	27/94	-12.3	7.4 -				+CW+AF+IMC	78/110	105/128	-15.0	34.8		
	†CW+AF+IMC	11/127	27/121	-8.3	8.8 -			82C DBCG 82c ipostmenop.		79/104	83/94	-9.4	30.7		
2 2003 2013101	10411411100	11/12/	20121	-0.0	0.0				TCW+AF+IMC			-0.8	32.2		
		78/	172/			1		82Q ECOG EST3181	TCW+AF+IMC	81/127	76/121	-0.8	32.2		
(a) Subtotal		869	849	-53.8	56.4		0.39 (SE 0.09) 2p < 0.00001	_		575/	624/				
.,		(9.0%)	(20.3%)			1	2p < 0.00001	(a) Subtotal		893	879	-54.1	226.4		0.79 (SE 0.06) 2p = 0.0003
		(0.070)	(20.0 /0)			1		(1)		(64.4%)	(71.0%)	•			2p = 0.0003
Axillary sampling						1		(b) Assillant committee		(0-11/0)	(71.076)				
0.01110101	†CW+AF+IMC	5/32	4/29	0.5	1.8		• >	(b) Axillary sampling							
B DBCG 82b ipremenop.		10/146	50/143	-22.4	13.6 -	-		77J MD Ander, 7730B	+CW+AF+IMC +CW+AF+IMC	1/3 18/32	2/6		6.6		
C DBCG 82c ipostmenop.	†CW+AF+IMC	6/127	60/140	-28.8	15.0 -	-:		79F Coimbra			20/29	-1.1			
A GBSG 03 Germany	†CW+AF+IMC	1/34	6/43	-1.9	1.7	•	>		†CW+AF+IMC	99/146	126/143	-28.3	40.3	;	
						1		82C DBCG 82c ipostmenop.		94/127	119/140	-16.8	39.8		
—		22/	120/			i		84A GBSG 03 Germany	†CW+AF+IMC	19/34	29/43	-2.4	9.7	i•	
(b) Subtotal		339	355	-52.6	32.1 ⊲	>!	0.19 (SE 0.09) 2p < 0.00001			231/	296/			!	
-		(6.5%)	(33.8%)				2p < 0.00001	(b) Subtotal				40.0		-	0.00 (05 0.00)
Extent of axillary s	urgery unkn	own				1		(b) Subtotal		342 (67.5%)	361 (82.0%)	-48.6	96.4	~13~	0.60 (SE 0.08) 2p < 0.00001
	tCW+AF+IMC	2/34	3/39	-0.3	1.1 —		>	(c) Extent of axillary	auroory unkr		(02.070)			1	
CRC, UK	†Various	1/7	1/2	-0.7	0.2	-	>	80W NSABC Israel	+CW+AF+IMC	10/34	7/39	1.5	3.9		
(.) 0		3/	4/					86C CRC, UK	†Various	6/7	2/2	-0.7	0.2-		-
 (c) Subtotal 		41	41	-0.9	1.3		0.49 (SE 0.62)	•		16/	9/				
		(7.3%)	(9.8%)			1	2p > 0.1: NS	 (c) Subtotal 		41	41	0.8	4.1		
								- (0) oubtotal		(39.0%)	(22.0%)	0.0	4.1	1.21 (SE 0.54)	
						!				(39.0%)	(22.0%)			2p > 0.1: NS	
		103/	296/												
Total		1249	1245	-107.4	89.8	Φ	0.30 (SE 0.06) 2p < 0.00001							i i	
		(8.2%)	(23.8%)			1	2p < 0.00001			822/	929/			1	
		(0.270)	(2010/0)			i i		Total		1276	1281	-101.9	326.9	*	0.73 (SE 0.05) 2p < 0.00001
						1 .				(64.4%)	(72.5%)				2p < 0.00001
erogeneity betwee	n 3 subtota	is : $\chi_2^2 = 9.9$	9; p=0.00	7											
erogeneity within a					0.0	0.5 1	.0 1.5 2.0	Heterogeneity betwee	an 3 subtat	$de \cdot x^2 = 5.1$	8· n = 0.05		L		
rogeneity betwee						RT better 🗕	RT worse						0.0	0.5 1	.0 1.5
and a served	in to undis.	A18 - 04.0	, p-0.01					Heterogeneity within	suptotals: v	7 = 31.6:	p = 0.02		0.0	0.0	

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

Webfigure 32 cntd.

2557 pN4+ women

Breast cancer mortality

Any death

Year code.	Treatment	 Allocated	Women Allocated		eaths Variance	Ratio of annua	al death rates	Year code.	Treatment	 Allocated	Women Allocated		eaths Varlance	Ratio of annu	al death rates
and study name	Information	RT	No RT		of O-E		No RT		Information	RT	No RT		of O-E		No RT
(a) Axillary dissectio	n						🖶 99% 🗢 95% Cl	(a) Axillary dissection	1						-∎-99% ↔95% CI
648 Oslo X-ray 740 DFCI Boston 740 Piedmott OA (pN4+) 764 SECSG 1 765 Clasgow 77J MD Ander, 7730B 784 SECA Vancouver 789 DECA Vancouver 780 Düsseldorf U. 79G Metaxas Athens 805 Helsinki 828 DBCG 82b ipremenop. 82C DBCG 82c iportmenop 82C DBCG 82c iportmenop 82C BECG 82c iportmenop	CW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC	27/30) 30/55 36/55 54/125 30/40 18/24 58/85 37/60 14/34 8/18 11/16 8/79/110 81/104 84/127	18/20 37/56 40/55 65/129 27/31 17/30 56/73 46/54 14/54 15/25 2/9 107/128 81/94 80/121	-5.9 -0.2 -3.5 -3.7 -3.9 5.4 -4.6 -8.8 4.9 -2.4 2.8 -11.5 -0.4 0.1	5.6 14.6 14.3 24.7 9.8 5.7 23.9 18.0 5.1 4.7 2.1 39.1 33.9 35.7			74D DFCI Boston 740 DFCI Boston 76A SECSG 1 76C Glasgow 77J MD Ander, 7730B 78A S weden II:1 78G Düsseldorf U. 79G Metaxes Athens 80S Helsinki 82B DBCG 82b ipremenop. 82C DBCG 82c lostmenop.	CW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC	30/30 35/55 60/125 32/40 19/24 69/85 40/60 17/34 8/18 12/16 85/110 89/104 94/127	20/20 39/56 41/55 69/129 29/31 17/30 62/73 48/54 24/54 15/25 3/9 108/128 86/94 96/121	-6.6 0.9 -1.6 -3.2 -4.2 5.9 -5.0 -7.9 3.3 -2.4 3.0 -9.2 -1.6 -2.9	6.3 16.0 15.2 26.9 10.8 5.9 27.4 18.6 7.8 4.7 2.6 40.8 36.3 41.3		
(a) Subtotal		567/ 893 (63.5%)	605/ 879 (68.8%)	-31.7	237.2	Ą	0.87 (SE 0.06) 2p = 0.04	(a) Subtotal		631/ 893 (70.7%)	655/ 879 (74.5%)	-31.5	260.5		0.89 (SE 0.06) 2p = 0.05
(b) Axillary sampling								(b) Axillary sampling							
77J MD Ander. 7730B 79F Colmbra 82B DBCG 82b ipremenop. 82C DBCG 82c ipostmenop 84A GBSG 03 Germany		1/3 21/32 101/146 98/127 18/34	3/6 20/29 130/143 116/140 24/43	2.1 -24.8 -4.1 -0.3	6.7 46.4 44.7 8.5		_•	 79F Coimbra 82B DBCG 82b ipremenop. 82C DBCG 82c ipostmenop. 		1/3 24/32 109/146 107/127 23/34	3/6 21/29 132/143 131/140 27/43	3.2 -23.2 -10.2 0.9	7.5 48.7 49.3 10.5		• • • • • • • • • • • • • • • • • • •
(b) Subtotal		239/ 342 (69.9%)	/293 361 (81.2%)	-27.0	106.3		0.78 (SE 0.09)	(b) Subtotal		264/ 342 (77.2%)	314/ 361 (87.0%)	-29.2	115.9		0.78 (SE 0.08) 2p = 0.007
(c) Extent of axillary	surgery unkr	nown						(c) Extent of axillary s	urgery unkn	lown					
80W NSABC Israel 86C CRC, UK	†CW+AF+IMC †Various	9/34 5/7	7/39 2/2	1.7 -0.2	3.5 0.5 —				†CW+AF+IMC †Various	11/34 6/7	7/39 2/2	2.7 -0.2	4.0 0.5-	<u>-</u>	
 (c) Subtotal 		14/ 41 (34.1%)	9/ 41 (22.0%)	1.5	4.0	1.47 (SE 0.61) 2p > 0.1: NS		e (c) Subtotal		17/ 41 (41.5%)	9/ 41 (22.0%)	2.5	4.5	1.75 (SE 0.63) 2p > 0.1: NS	
Total		820/ 1276 (64.3%)	907/ 1281 (70.8%)	-57.2	347.5		0.85 (SE 0.05)	Total		912/ 1276 (71.5%)	978/ 1281 (76.3%)	-58.2	380.9		0.86 (SE 0.05) 2p = 0.003
Heterogeneity betwe Heterogeneity within Heterogeneity betwe	subtotals: χ	² ₁₇ = 36.1;	p = 0.004		0.0	0.5 1. RT better —	0 1.5 2.	Heterogeneity between Heterogeneity within a Heterogeneity between	subtotals: χ^2	² ₁₇ = 31.6;	p = 0.02	NS	0.0	0.5 1. RT better	0 1.5 2.0

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups. Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

Webfigure 33. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 463 women with pathologically positive nodes (pN?+) but unknown if they were 1-3 or 4+ positive.

463 pN?+ women

Locoregional recurrence first (years 0-9)

		Events/	Women	RT e	rents		
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E		al event rates No RT
a) Axillary dissection	1						🖶 99% 🗢 95% CI
4D DFCI Boston 8G BCCA Vancouver 0S Helsinki	†CW+AF+(IMC) †CW+AF+IMC †CW+AF+IMC	1/11 1/12 0/2	2/8 3/7 1/5	-0.3 -1.9	0.5 0.7-∎	•	>
(a) Subtotal		2/ 25 (8.0%)	6/ 20 (30.0%)	-2.2	1.1		0.15 (SE 0.42)
b) Axillary sampling							
1B Stockholm A	CW+AF+IMC	6/75	32/79	-15.0	8.6 -	<u> </u>	
3A Southampton UK 4B Edinburgh I	CW+AF+IMC CW+AF	5/33 0/0	21/38 0/1	-8.7	5.3 —		
9F Coimbra 2B DBCG 82b ipremenop. 2C DBCG 82c ipostmenop.	†CW+AF+IMC †CW+AF+IMC †CW+AF+IMC	1/2 2/27 2/29	1/3 8/28 4/26	0.5 -3.3 -0.7	0.2		`>
5F Nottingham	†CW+AF	6/36	20/41	-6.9	5.7 —		
(b) Subtotal		22/ 202 (10.9%)	86/ 216 (39.8%)	-34.0	23.4 🚽	>	0.23 (SE 0.11) 2p < 0.00001
Total		24/ 227 (10.6%)	92/ 236 (39.0%)	-36.2	24.5 🚽	•	0.23 (SE 0.11) 2p < 0.00001
Difference between treatment effects Heterogeneity within Heterogeneity betwee	subtotals: χ	² = 6.7; p	> 0.1: NS	: NS	0.0	0.5 1 RT better	.0 1.5 2.0

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

(a) Axillary dissection 74D DFCI Boston 160/10000000000000000000000000000000000	
(a) Axillary dissection + 0.0 + 0.1 + 0.0 + 0.1 + 0.0 + 0.1 + 0.0 +	ates
(a) Axillary dissection 74D DFCI Boston TO DFCI Boston 1760 DFC1 Boston 1772 DFC1 Boston 1772 DFC1 Boston 1772 DFC1 Boston 1772 DFC1 Boston 1780 DFC1 Boston 1790 DFC1 Boston 1791 DFC1 Boston 1792 DFC1 Boston 1795 Colmbar 1795 Colmbar 1797 CW+AF+IMC 1797 DFC1 Boston 1797 CW+AF+IMC 1798 Edinburgh I 1797 CW+AF+IMC 1797 DFC1 Boston 1797 CW+AF+IMC 1797 DFC1 Boston <	
TRG BCCA Vancouver iCW+AF+IMC 7/12 4/7 -1.4 1.5 SoS Helsinki iCW+AF+IMC 2/2 3/3 -0.8 0.5 Image: CW+AF+IMC 2/2 3/3 -0.8 0.5 0.5 Image: CW+AF+IMC 2/2 3/3 -0.8 0.5 0.5 Image: CW+AF+IMC 2/2 3/3 -0.8 0.5 0.6 Image: CW+AF+IMC 2/2 2/2 -2.1 4.1 0.61 (jp) (b) Axillary sampling r r 16/1 12/2 3/3 71B Stockholm A CW+AF+IMC 15/33 3/4/38 -12.3 8.3 - 73A Southampton UK CW+AF+IMC 15/33 3/4/38 -12.3 8.3 - 74B Edinburgh I CW+AF+IMC 2/2 3/3 -1.1 2.2 - 76 Coimbar CCW+AF+IMC 3/27 10/28 -4.0 3.0 - 82D BCG B2b (premenop. tCW+AF+IMC 3/27 10/28 -4.0 3.0 - 825 Nottingham tCW+AF 2/2/36 3/4/41 <td< td=""><td>% ↔95% 0</td></td<>	% ↔95% 0
TRG BCCA Vancouver iCW+AF+IMC 7/12 4/7 -1.4 1.5 SoS Helsinki iCW+AF+IMC 2/2 3/3 -0.8 0.5 Image: CW+AF+IMC 2/2 3/3 -0.8 0.5 0.5 Image: CW+AF+IMC 2/2 3/3 -0.8 0.5 0.5 Image: CW+AF+IMC 2/2 3/3 -0.8 0.5 0.6 Image: CW+AF+IMC 2/2 2/2 -2.1 4.1 0.61 (jp) (b) Axillary sampling r r 16/1 12/2 3/3 71B Stockholm A CW+AF+IMC 15/33 3/4/38 -12.3 8.3 - 73A Southampton UK CW+AF+IMC 15/33 3/4/38 -12.3 8.3 - 74B Edinburgh I CW+AF+IMC 2/2 3/3 -1.1 2.2 - 76 Coimbar CCW+AF+IMC 3/27 10/28 -4.0 3.0 - 82D BCG B2b (premenop. tCW+AF+IMC 3/27 10/28 -4.0 3.0 - 825 Nottingham tCW+AF 2/2/36 3/4/41 <td< td=""><td></td></td<>	
16/ 12/ 25 20 (64.0%) (60.0%) (64.0%) (60.0%) (b) Axillary sampling 71B Stockholm A CW+AF+IMC 39/75 59/79 -15.6 71B Stockholm A CW+AF+IMC 16/ 15/33 34/38 74B Edinburgh I CW+AF-IMC 174B Edinburgh I CW+AF+IMC 1727 10/28 120 DEC 6 82b ipremenop. TCW+AF+IMC 202 DEC 6 32b ipremenop. CW+AF 202 E 216 426 DEC 6 82b ipremenop. CW+AF 202 2 216 -37.2 42.8 0.42 ((43.1%) (66.7%) 103/ 156/ 103/ 156/ 227 236 -39.2 46.9 0.43 (
(a) Subtotal 25 20 -2.1 4.1 (64.0%) (60.0%) (60.0%) (60.0%) (60.0%) (60.0%) (60.0%) (60.0%) (60.0%) (60.0%) (60.0%) (718 Stockholm A CW+AF+IMC 39/75 59/79 -15.6 18.7 748 Scinthampton UK CW+AF+IMC 15/33 34/38 -12.3 8.3 748 Scinthampton UK CW+AF+IMC 15/33 34/38 -12.3 8.3 Tef Coimbra TCW+AF+IMC 2/2 34/38 -12.3 8.3 Tef Coimbra TCW+AF+IMC 2/2 3/2 426 Diptemenop. TCW+AF+IMC 2/2 3/2 426 Diptemenop. TCW+AF+IMC 2/2 3/4/4 -6.5 10.5 (43.1%) (66.7%) Total 103/ 156/ 227 236 -39.2 46.9 0.43 (5)	~ ~ ~
(a) Subtotal 25 20 -2.1 4.1 (64.0%) (60.0%) (71 (74 AF+IMC 15/33 3/38 -12.3 8.3 (74 (74 AF+IMC 15/3 3/38 -12.3 8.3 (74 (74 AF+IMC 10/2 1/1 22 3/2 200 4/26 (1.1 2.2 (43.1%) (66.7%) (66.7%) (66.7%) (66.7%) (744)	
(64.0%) (60.0%) 0.61 (2 (b) Axillary sampling 718 Stockholm A CW+AF+IMC 39/75 59/79 -15.6 18.7 73A Southampton UK CW+AF+IMC 15/33 34/38 -12.3 8.3 - 74B Edinburgh I CW+AF+IMC 2/2 3/3 - - - 74B Edinburgh I CW+AF+IMC 2/2 3/3 - - - 74B Edinburgh I CW+AF+IMC 2/2 3/3 - - - 74B Edinburgh I CW+AF+IMC 2/2 3/3 - - - - 820 B02G 82b ipremenop. fCW+AF+IMC 6/29 4/26 1.1 2.2 - - - 827 DBCG 82c ipostmenop. fCW+AF 20/29 216 -37.2 42.8 - 0.42 (2) - 85F Notingham fCW+AF 20/2 216 -37.2 42.8 - 0.42 (2) - - - - - - - - - 20/2 20/2 20/2 - - -<	
71B Stockholm A CW+AF+IMC 39/75 59/79 -15.6 18.7 71B Stockholm A CW+AF+IMC 15/33 34/38 -12.3 8.3 74B Edinburgh I CW+AF-IMC 2/2 3/3 -12.3 8.3 74D Edinburgh I CW+AF-IMC 2/2 3/3 -12.3 8.3 74D Edinburgh I CW+AF-IMC 3/2 -4.0 3.0 -14.1 82C DBC6 82c ipostmenop. TCW+AF-IMC 6/2.9 4/2.2 1.1 2.2 -4.0 85F Nottingham TCW+AF 22/3 3/4/4 -6.5 10.6 -14.1 (b) Subtotal 202 216 -37.2 42.8 -24.2 -24.5 (c) A3 (156/ 10/3 156/ -27.2 28.6 -44.9 <td>SE 0.39) 0.1: NS</td>	SE 0.39) 0.1: NS
73A Southampton UK CW+AF+IMC 15/33 34/38 -12.3 8.3 - 74B Edinburgh I CW+AF+IMC 100 0/1 -	
74B Edinburgh I CW+AF 00 0/1 79F Celimbra TCW+AF-IIIIC 2/2 3/3 82B DBCG 62b Ipremenop, TCW+AF-IIIIC 3/27 10/28 -4.0 3.0 82C DBCG 82c Ipostmenop, TCW+AF-IIIIC 6/29 4/26 1.1 2.2 85F Notingham TCW+AF-IIIIC 2/2/3 3/4/41 -6.5 10.6 (b) Subtotal 87/ 144/ -6.5 0.42 ((43.1%) (66.7%) 103/ 156/ Total 227 236 -39.2 46.9	
748 Edinburgh I CW+AF 0/0 0/1 756 Cainburgh I CW+AF+IMC 0/2 3/3 828 DBCG 82b Ipremenop, rCW+AF+IMC 3/27 10/28 -4.0 3.0 826 DBCG 82c Ipostmenop, rCW+AF+IMC 3/27 10/28 -4.0 3.0 85F Notingham rCW+AF+IMC 6/29 4/28 1.1 2.2 85F Notingham rCW+AF 20/2 3/4/4 -6.5 10.6 (b) Subtotal 87/ 144/ -6.5 0.42 ((43.1%) (66.7%) 0.42 (20/2 Total 227 236 -39.2 46.9	
Tot W+AF+IMC 2/2 3/3 28D BCG 682: Ipromono +CW+AF+IMC 3/27 10/28 -4.0 3.0 82D BCG 682: Ipromono +CW+AF+IMC 6/29 4/26 1.1 2.2 85F Notlingham †CW+AF 22/36 34/41 -6.5 10.6 (b) Subtotal 202 216 -37.2 42.8 0.42 ((43.1%) (66.7%) 103/ 156/ 0.43 (Total 227 236 -39.2 46.9 0.43 (
82C DBCG 82c ipostmenop. †CW+AF+IMC 6/29 4/26 1.1 2.2 85F Notlingham †CW+AF 22/36 34/41 -6.5 10.6 (b) Subtotal 202 216 -37.2 42.8	
85F Notlingham TCW+AF 22/36 34/41 -6.5 10.6 87/ 144/ 202 216 -37.2 42.8	
87/ 144/ 202 216 -37.2 42.8 (43.1%) (66.7%) 0.42 (2020) Total 103/ 156/ 0.43 (300)	-
(b) Subtotal 202 216 -37.2 42.8 - 0.42 ((43.1%) (66.7%) - 103/ 156/ Total 227 236 -39.2 46.9 - 0.43 (
(43.1%) (00.7%) 103/ 156/ Total 227 236 -39.2 46.9 - 0.43 (
(43.1%) (00.7%) 103/ 156/ Total 227 236 -39.2 46.9 - 0.43 (3E 0.10)
Total 227 236 -39.2 46.9 - 0.43 (3.00001
Total 227 236 -39.2 46.9 - 0.43 (
	SE 0 10)
(45.4%) (50.1%)	0.00001
Difference between treatment effects in 2 subtotals: $\chi_1^2 = 0.5$; 2p > 0.1: NS 0.0 0.5 1.0	1.5 2
Heterogeneity within subtotals: $\chi_{a}^{2} = 10.4$; p > 0.1: NS	
Heterogeneity between 8 trials: $\chi_{0} = 10.4$; p > 0.1: NS RT better - RT better	vorse

Any first recurrence (years 0-9)

Heterogeneity between 8 trials: $\chi_7^2 = 10.9$; p > 0.1: NS

continued overleaf

Lancet 2014; 383: 2127-35

463 pN?+ women

Breast cancer mortality

Any death

		Deaths	Women	RT de	aths					Deaths	Women	RT de	eaths		
Year code,	Treatment	Allocated	Allocated		Variance		al death rates	Year code,	Treatment	Allocated	Allocated		Variance	Ratio of annu	
and study name	Information	RT	No RT	О-Е	of O-E	RT	No RT	and study name	Information	RT	No RT	0-E	of O-E	RT	No RT
(a) Axillary dissection	n						🖶 99% - 🖘 95% CI	(a) Axillary dissection	n						🖶 99% 🗢 95% CI
74D DFCI Boston 78G BCCA Vancouver 80S Helsinki	†CW+AF+(IMC) †CW+AF+IMC †CW+AF+IMC) 7/11 8/12 2/2	4/8 5/7 2/5	0.2 -1.2 -0.8	1.3 - 2.1 - 0.5		• >	74D DFCI Boston 78G BCCA Vancouver 80S Helsinki	†CW+AF+(IMC) †CW+AF+IMC †CW+AF+IMC	8/11 8/12 2/2	4/8 5/7 2/5	0.2 -1.2 -0.8	1.3 2.1 - 0.5		• ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~
■ (a) Subtotal		17/ 25 (68.0%)	11/ 20 (55.0%)	-1.9	3.9		0.61 (SE 0.40) 2p > 0.1: NS	(a) Subtotal		18/ 25 (72.0%)	/11 20 (55.0%)	-1.9	3.9		0.61 (SE 0.40) 2p > 0.1: NS
(b) Axillary sampling	3							(b) Axillary sampling							
71B Stockholm A	CW+AF+IMC	44/75	64/79	-11.1	24.0		-	71B Stockholm A	CW+AF+IMC	61/75	69/79	-10.3	27.5		_
73A Southampton UK	CW+AF+IMC	23/33	32/38	-5.0	10.4			73A Southampton UK	CW+AF+IMC	28/33	32/38	-3.5	11.1		
74B Edinburgh I	CW+AF	0/0	0/1					74B Edinburgh I	CW+AF	0/0	1/1				
79F Coimbra 82B DBCG 82b ipremenop	†CW+AF+IMC †CW+AF+IMC	2/2 0/27	3/3 2/28	-0.5 -0.9	0.2		2	79F Colmbra 82B DBCG 82b ipremenop.	†CW+AF+IMC †CW+AF+IMC	2/2 0/27	3/3 2/28	-0.5 -0.9	0.2		~ ~
82C DBCG 82c lpostmeno		0/27	0/26	-0.9	0.3			82C DBCG 82c ipostmenop		0/27	0/26	-0.9	0.5		
85F Nottingham	†CW+AF	22/36	28/41	-2.9	10.3			85F Nottingham	†CW+AF	23/36	30/41	-3.6	11.0	i	
(b) Subtotal		91/ 202 (45.0%)	129/ 216 (59.7%)	-20.5	45.5		0.64 (SE 0.12) 2p= 0.002	(b) Subtotal		114/ 202 (56.4%)	137/ 216 (63.4%)	-18.8	50.5		0.69 (SE 0.12) 2p=0.008
Total		108/ 227 (47.6%)	140/ 236 (59.3%)	-22.4	49.4		0.64 (SE 0.11) 2p = 0.001	Total		132/ 227 (58.1%)	/148 236 (62.7%)	-20.6	54.3	A	0.68 (SE 0.11) 2p = 0.005
Difference between treatment effects Heterogeneity within Heterogeneity betwee	n subtotals: χ	² ₆ = 3.1; p	> 0.1: NS	: NS		0.5 1 RT better —	.0 1.5 2.0	Difference between treatment effects Heterogeneity within Heterogeneity betwee	subtotals: χ	² ₆ = 3.0; p	> 0.1: NS	: NS	0.0	0.5 1. RT better —	0 1.5 2.0

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups. Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

Webfigure 34. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 720 women with unknown pathological nodal status (pN?).

720 pN? women

Locoregional recurrence first (years 0-9)

Any first recurrence (years 0-9)

			Women		vents	Datia of onny	al event rates		-		Women		vents	Potio of annu	al event rates
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	of O-E		No RT	Year code, and study name	Treatment Information	Allocated RT	Allocated No RT		Variance of O-E		No RT
a) Axillary dissection	n						- ₽ -99%95% Ci	(a) Axillary dissection	n						🖶 99% 🖘 95% Cl
6A SECSG 1 6C Glasgow 6A S Sweden II:1 8G BCCA Vancouver 2Q ECOG EST3181	†CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC	0/1 1/1 0/22 0/1 0/1	0/1 0/6 2/18 0/1 0/0	0.7 -0.7	0.2 — 0. 9 —		>	76A SECSG 1 76C Glasgow 77J MD Ander. 7730B 78A S Sweden II:1 78G BCCA Vencouver 82Q ECOG EST3181	†CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC	0/1 1/1 3/4 7/22 0/1 0/1	0/1 4/6 0/0 5/18 0/1 0/0	0.1 1.0	0.4 — 2.8		>
 (a) Subtotal 		1/ 26 (3.8%)	2/ 26 (7.7%)	-0.1	0.7 —		0.93 (SE 1.17) 2p > 0.1: NS	■ (a) Subtotal	101111	11/ 30 (36.7%)	9/ 26 (34.6%)	1.1	3.2	1.41 (SE 0.67)	
b) Axillary sampling								(b) Axillary sampling		(00.170)	(04.070)			2p > 0.1: NS	
1B Stockholm A 3A Southampton UK 4B Edinburgh I 9F Coimbra 2B DBCG 82b ipremenop.	CW+AF+IMC CW+AF+IMC CW+AF †CW+AF+IMC †CW+AF+IMC	1/2 3/18 6/59 0/0 12/137	2/4 3/10 25/60 0/1 46/150	-0.5 -1.1 -9.3	0.2 1.1 7.0 13.1	<u>;</u> ₽ ■	>	71B Stockholm A 73A Southampton UK 74B Edinburgh I 79F Coimbra 82B DBCG 82b ipremenop.	CW+AF+IMC CW+AF+IMC CW+AF †CW+AF+IMC †CW+AF+IMC	1/2 8/18 24/59 0/0 69/137	3/4 4/10 33/60 1/1 87/150	-0.5 -0.9 -5.8	0.2 1.6 - 11.3 32.8		>
2C DBCG 82c ipostmenop 4A GBSG 03 Germany	. †CW+AF+IMC †CW+AF+IMC	5/113 0/2	29/97 0/1	-13.9	8.0 -			82C DBCG 82c ipostmenop 84A GBSG 03 Germany	· †CW+AF+IMC †CW+AF+IMC	61/113 1/2	62/97 0/1	-10.9	25.7		_
(b) Subtotal		27/ 331 (8.2%)	105/ 323 (32.5%)	-41.9	29.4		0.24 (SE 0.10) 2p < 0.00001	(b) Subtotal		164/ 331 (49.5%)	/190 323 (58.8%)	-27.1	71.6	-	0.68 (SE 0.10)
c) Extent of axillary	surgery unkr	nown						(c) Extent of axillary	surgery unkr	,,	(,				
6C CRC, UK (c) Subtotal	†Various	0/6 0/ 6 (0.0%)	0/4 0/ 4 (0.0%)					sec CRC, UK	†Various	2/6 2/ 6 (33.3%)	1/4 1/ 4 (25.0%)	0.1 0.1	0.7 – 0.7	1.19 (SE 1.33) 20 > 0.1; NS	•
Total		28/ 363 (7.7%)	/107/ 353 (30.3%)	-42.0	30.1 ·		0.25 (SE 0.10) 2p < 0.00001	Total		177/ 367 (48.2%)	200/ 353 (56.7%)	-25.9	75.5		0.71 (SE 0.10) 2p=0.003
Difference between treatment effects Heterogeneity within Heterogeneity betwe	subtotals: x	² ₅ = 4.5; p	> 0.1: NS		0.0	0.5 1 RT better —	.0 1.5 2.0	Heterogeneity betwee Heterogeneity within Heterogeneity betwee	subtotals: y	² ₅ = 1.3; p	> 0.1: NS	NS	ــــ 0.0	0.5 1 RT better	.0 1.5 2.0

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

720 pN? women

Breast cancer mortality

Any death

		Deaths	Women	RT d	eaths					Deaths	Women	RT d	eaths		
Year code,	Treatment	Allocated	Allocated		Variance	Ratio of annu		Year code,	Treatment	Allocated	Allocated		Variance	Ratio of annu	
and study name	Information	RT	No RT	0-E	of O-E	RT	No RT	and study name	Information	RT	No RT	0-E	of O-E	RT	No RT
(a) Axillary dissectio	'n						- 99% <>95% CI	(a) Axillary dissection	n						- 99% <>95% CI
76A SECSG 1 76C Glasgow 77J MD Ander, 7730B 78A S Sweden II:1 78G BCCA Vancouver 82Q ECOG EST3181	TCW+AF+IMC TCW+AF+IMC CW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC	0/1 0/1 3/4 11/22 0/1 0/1	0/1 4/6 0/0 6/18 1/1 0/0	-0.6 3.3 -0.5	0.4		> >	76A SECSG 1 76C Glasgow 77J MD Ander. 7730B 78A S Sweden II:1 78G BCCA Vancouver 82Q ECOG EST3181	†CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC	0/1 0/1 3/4 19/22 0/1 0/1	0/1 5/6 0/0 11/18 1/1 0/0	-0.6 4.9 -0.5	0.4		> >>>
(a) Subtotal		14/ 30 (46.7%)	11/ 26 (42.3%)	2.2	4.3	1.69 (SE 0.64) 2p > 0.1: NS		≕ 🔳 (a) Subtotal		22/ 30 (73.3%)	17/ 26 (65.4%)	3.9	7.3	1.69 (SE 0.49)	
b) Axillary sampling	1							(b) Axillary sampling							
71B Stockholm A 73A Southampton UK 74B Edinburgh I 79F Coimbra	CW+AF+IMC CW+AF+IMC CW+AF †CW+AF+IMC	1/2 10/18 33/59 0/0	4/4 4/10 38/60 1/1	-0.5 -0.7 0.0	0.2 1.7 15.6			71B Stockholm A 73A Southampton UK 74B Edinburgh I 79F Coimbra	CW+AF+IMC CW+AF+IMC CW+AF †CW+AF+IMC	2/2 15/18 52/59 0/0	4/4 7/10 49/60 1/1	-0.5 -0.8 -0.6	0.2— 2.6 20.9	·•	
32B DBCG 82b ipremenop.	†CW+AF+IMC	67/137	83/150	-4.4	32.5			82B DBCG 82b ipremenop.	†CW+AF+IMC	76/137	95/150	-5.8	37.5		<u> </u>
82C DBCG 82c ipostmenop 84A GBSG 03 Germany	p. †CW+AF+IMC †CW+AF+IMC	63/113 1/2	64/97 0/1	-4.1	27.7			82C DBCG 82c ipostmenop 84A GBSG 03 Germany	+CW+AF+IMC +CW+AF+IMC	80/113 1/2	78/97 0/1	-6.4	34.1		
(b) Subtotal		175/ 331 (52.9%)	194/ 323 (60.1%)	-9.8	77.8		- 0.88 (SE 0.11) 2p ≥ 0.1: NS	(b) Subtotal		226/ 331 (68.3%)	234/ 323 (72.4%)	-14.1	95.4	~	- 0.86 (SE 0.10) 2p > 0.1: NS
c) Extent of axillary	surgery unkr	nown						(c) Extent of axillary	surgery unk	nown					
BEC CRC, UK	†Various	2/6	3/4	-0.2	0.9 -		~~~>	86C CRC, UK	†Various	3/6	3/4	0.2	1.1		- - ->
 (c) Subtotal 		2/ 6 (33.3%)	3/ 4 (75.0%)	-0.2	0.9		0.79 (SE 0.94) 2p > 0.1: NS	e (c) Subtotal		3/ 6 (50.0%)	3/ 4 (75.0%)	0.2	1.1	1.18 (SE 1.02) 2p > 0.1: NS	
Total		191/ 367 (52.0%)	208/ 353 (58.9%)	-7.8	82.9		0.91 (SE 0.10) 2p ≥ 0.1: NS	Total		251/ 367 (68.4%)	254/ 353 (72.0%)	-10.0	103.8		- 0.91 (SE 0.09) 2p ≥ 0.1: NS
Heterogeneity betwe Heterogeneity within Heterogeneity betwe	n subtotals: χ	² ₆ = 5.0; p	> 0.1: NS	NS	0.0	0.5 1. RT better -	0 1.5 2.0	Heterogeneity betwee Heterogeneity within Heterogeneity betwee	subtotals:)	² ₆ = 4.7; p	> 0.1: NS	NS	ـــ 0.0	0.5 1. RT better —	.0 1.5 2.0

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups. Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

Webtable 2. Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS)*.

				Woman-y	ears since	% women given systemic therapy			
Nodal status†	Women	Deaths	Median/ woman	Total ('000s)	Distribut <10	ion by ye 10-	ars ('000s) 20+	Chemotherapy‡	ER+ & Tamoxifen
Axillary dissection									
pN0	465	355	17.3	8.0	3.9	2.6	1.5	3	0
pN+	1029	678	6.5	10.1	6.6	2.4	1.1	39	0
pN unknown	810	499	5.6	6.4	4.7	1.5	0.2	2	0
Total	2304	1532	7.2	24.5	15.2	6.5	2.8	19	0

*Data available for 8 trials, start dates 1961 to 1978. In all trials radiotherapy was given to the axilla/supraclavicular fossa and the internal mammary chain. In 3 of the 8 trials radiotherapy to the chest wall was occasionally given. Full details of the trials are given in webtable 3.

† pN0: pathologically node negative, pN+: pathologically node positive, pN unknown: status not reported or staging method was clinical or unknown.

‡ Chemotherapy was cyclophosphamide, methotrexate, 5-fluorouracil [CMF], cyclophosphamide, 5-fluorouracil, prednisone [CFP], or melphalan.

Webtable 3. Randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS) – treatment details.

Year code and study name	Breast surgery	Axillary Surgery* (number of patients)	Chest wall RT	Supraclavicular and axillary fossa RT	Internal mammary chain RT	Boost RT to scar	Common systemic chemoendocrine therapy
61H NSABP B-03	RM	Axillary dissection (748)	None	35-45 Gy (1.8-2.3 Gy/f) o or c	35-45 Gy (1.8-2.3 Gy/f) o or c	None	None
64E Oslo Co-60	RM	Axillary dissection (563)	None	50 Gy de (2.5 Gy/f) c	50 Gy de (2.5 Gy/f) c	None	Ovarian irradiation
69A Heidelberg XRT	MRM	Axillary dissection (143)	None	65 Gy (2.2-2.7 Gy/f) c	65 Gy (2.2-2.7 Gy/f) c	None	None
71D SASIB	MRM, RM	Axillary dissection (377)	None for over half, others 45 Gy (4.5 Gy/f) o or c	45-60 Gy (2-4.5 Gy/f) c	40-60 Gy (2-4 Gy/f) c or e	None	None
73C Mayo 70-56-32	MRM, RM	Axillary dissection (241)	None or if skin involvement 50 Gy (2.1 Gy/f) m	50 Gy de (2.1 Gy/f) m	50 Gy de (2.1 Gy/f) m	None	CFP or not
73E INT Milan 1	RM	Axillary dissection (22)	None	40-45 Gy (1.8-2 Gy/f) c or m	40-45 Gy (1.8-2 Gy/f) c or m	None	None^
74Q Piedmont OA (excl pN4+)	MRM or RM	Axillary dissection (160)	None	45 Gy (1.5-2.8 Gy/f) u	45 Gy (1.5-2.8 Gy/f) u	None	Mel or CMF
78B Toronto-Edmont	MRM	Axillary dissection (50)	None	40 Gy de (2.5 Gy/f) c	40 Gy de (2.5 Gy/f) c	None	CMF+ovarian irradiation+P±bCG

* Based on the description of axillary surgery in the trial protocol or publications or on information on individual women. Women were classified as having axillary dissection if they were in a trial where the protocol required removal of axillary lymph nodes in at least Levels I & II or, if individual information was available, resection of ≥10 nodes. In other trials, women were classified as having axillary dissection if the trial publication indicated that the median number of nodes removed was ≥ 10. bCG=bacillus Calmette-Guérin, C=cyclophosphamide, c=cobalt-60, de=dose at depth (of nodes), F=fluorouracil, f=fraction, Gy=Gray (intended dose), m=megavoltage, M=methotrexate, Mel=melphalan, RM=modified radical mastectomy, NS=surgery not specified in detail (Patey mastectomy, o=orthovoltage, P=prednisone, Patey=Patey mastectomy, RM=radical mastectomy (Halsted), RT=radiotherapy. u=unknown, ^After 1976 all patients in this trial with positive nodes received CMF chemotherapy.

References for Webtable 3

Year code and study name	Reference
61H NSABP B-03	Fisher B, Slack NH, Cavanaugh PJ, Gardner B, Ravdin RG. Postoperative radiotherapy in the treatment of breast cancer: results of the NSABP clinical trial. Ann Surg 1970; 172 : 711–32.
64E Oslo Co-60	Host H, Brennhovd IO, Loeb M. Postoperative radiotherapy in breast cancer-long-term results from the Oslo study. Int J Radiat Oncol Biol Phys 1986; 12: 727–32.
69A Heidelberg XRT	Friedl W, Scheurlen, H.R., Amberger, H., Henningsen, B. Radiotherapy in operable breast cancer- 10 year results of a prospective randomized trial. J Exp Clin Cancer Res 1984; 3: 71–7.
71D SASIB	Personal Correspondence from Dr A Hacking
73C Mayo 70-56-32	Ahmann DL, O'Fallon JR, Scanlon PW, Payne WS, Bisel HF, Edmonson JH, et al. A preliminary assessment of factors associated with recurrent disease in a surgical adjuvant clinical trial for patients with breast cancer with special emphasis on the aggressiveness of therapy. Am J Clin Oncol 1982; 5: 371–81.
73E INT Milan 1	Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002; 347: 1227–32.
74Q Piedmont OA	Muss HB, Cooper MR, Brockschmidt JK, Ferree C, Richards F, 2nd, White DR, et al. A randomized trial of chemotherapy (L-PAM vs CMF) and irradiation for node positive breast cancer. Eleven year follow-up of a Piedmont Oncology Association trial. Breast Cancer Res Treat 1991; 19: 77–84.
78B Toronto-Edmont	Personal Correspondence from Dr K Pritchard

Webfigure 35. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 465 women with pathologically node-negative (pN0) disease. See webfigure 1 for methodological note and also webfigure 36.



465 pN0 women with Mast+AD

Webfigure 36. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 465 women with pathologically node-negative (pN0) disease. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)

465 pN0 women with Mast+AD



2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: > 0.1; NS

Webfigure 37. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1029 women with pathologically node-positive (pN+) disease. See webfigure 1 for methodological note and also webfigure 38.



1029 pN+ women with Mast+AD

Webfigure 38. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1029 women with pathologically node positive (pN+) disease. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



1029 pN+ women with Mast+AD

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Webfigure 39. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 465 women with pathologically node-negative (pN0) disease.

465 pN0 women



Locoregional recurrence first (years 0-9)

† Same polychemotherapy and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

Any first recurrence (years 0-9)

465 pN0 women

Breast cancer mortality



Year code.	Treatment	Deathsi Allocated	Allocated		eaths	Patio of annu	al death rates
and study name	Information	RT	No RT	Cogrank	Variance of O-E		No RT
a) Nodal radiotherap	oy only, disse	ction					- 99%
4E Oslo Co-60	AF+IMC	154/179	134/187	28.7	61.9		│ _
9A Heidelberg XRT	AF+IMC	36/44	19/31	5.8	12.1		≣ →
4Q Piedmont OA (IpN4+)	†AF+IMC	1/4	6/9	-0.3	0.2	•	
(a) Subtotal		191/ 227 (84.1%)	159/ 227 (70.0%)	34.2	74.3	1.59 (SE 0.15) 2p = 0.00007	
b) Some with chest	wall radiothe	rapy, disse	ection				
1D SASIB	(CW)+AF+IMC	3/6	2/5	0.0	0.5 -		
(h) 0 -14-4-1		3/	2/				
 (b) Subtotal 		6 (50.0%)	5 (40.0%)	0.0	0.5 -	1.00 (SE 1.41) 2p > 0.1: NS	
		194/	161/				
Total		233 (83.3%)	232 (69.4%)	34.2	74.8	1.58 (SE 0.15) 2p = 0.00008	
ifference between					L		
treatment effects	in 2 subtota	ils: $\chi_1^2 = 0.1$	1; 2p > 0.1	: NS	0.0	0.5 1	.0 1.5 2.
leterogeneity within leterogeneity betwe					0.0	RT better	RT worse

Any death

† Same polychemotherapy and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

Webfigure 40. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 1029 women with pathologically node-positive (pN+) disease.

1029 pN+ women

Any first recurrence (years 0-9)

		Events/	Women	RT e	vents					Events/	Women	RT e	vents		
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E		ual event rates : No RT	Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O–E	Variance of O-E	Ratio of annu RT	al event rates No RT
(a) Nodal radiothera	oy only, disse	ction					- #-99% ← 95% CI	(a) Nodal radiotherap	oy only, disse	ction					₽99%9
64E Oslo Co-60 73E INT Milan 1 74Q Piedmont OA (IpN4+) 78B Toronto-Edmont.	AF+IMC AF+IMC †AF+IMC †AF+IMC	1/99 0/15 0/67 6/28 7/	6/98 1/7 8/61 4/21 19/	-2.4 -4.2 -0.5	1.6 - 1. 9 1.6	•		64E Oslo Co-60 69A Heidelberg XRT 73E INT Milan 1 74Q Piedmont OA (IpN4+) 78B Toronto-Edmont.	AF+IMC AF+IMC AF+IMC †AF+IMC †AF+IMC	33/99 25/39 8/15 32/67 15/28	47/98 16/27 2/7 19/61 10/21	-7.6 1.0 1.8 4.5 1.7	17.2 8.2 1.4 11.0 3.9		
 (a) Subtotal (b) Some with chest 	wall radiother	209 (3.3%) apy. disse	187 (10.2%) ection	-7.0	5.1		0.25 (SE 0.24) 2p = 0.002	(a) Subtotal		113/ 248 (45.6%)	94/ 214 (43.9%)	1.3	41.7	1.03 (SE 0.16)	
71D SASIB	(CW)+AF+IMC	13/162	38/164	-13.3	11.6	-		(b) Some with chest	wall radiothe	· ·	, ,			2p > 0.1: NS	
73C Mayo 70-56-32	†(CW)+AF+IMC	14/121	38/120	-12.2	10.2	- E		71D SASIB	(CW)+AF+IMC	85/162	93/164	-6.7	36.9	 _	
(b) Subtotal		27/ 283 (9.5%)	76/ 284 (26.8%)	-25.5	21.8		0.31 (SE 0.13) 2p < 0.00001	73C Mayo 70-56-32	†(CW)+AF+IM(67/121 152/ 283 (53.7%)	75/120 168/ 284 (59.2%)	-8.3 -15.0	26.9 63.8		0.79 (SE 0.11 2p = 0.06
Total		34/ 492 (6.9%)	95/ 471 (20.2%)	-32.5	26.9		0.30 (SE 0.11) 2p < 0.00001	Total		(33.7%) 265/ 531 (49.9%)	(59.2%) 262/ 498 (52.6%)	-13.7	105.5	Ŷ	- 0.88 (SE 0.09 2p > 0.1: NS
Difference between treatment effects Heterogeneity within Heterogeneity betwe	subtotals: χ ₃	² ₃ = 3.3; p	> 0.1: NS	: NS	0.0	0.5 RT better	1.0 1.5 2.0	Difference between treatment effects Heterogeneity within Heterogeneity betwe	subtotals: y	² ₅ = 8.6; p	> 0.1: NS		ــا 0.0	0.5 1. RT better	0 1.5

Locoregional recurrence first (years 0-9)

† Same polychemotherapy and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

0.79 (SE 0.11)

0.88 (SE 0.09) 2p > 0.1: NS

2.0

1029 pN+ women

Breast cancer mortality

Any death

Year code, and study name	Treatment Information	Deaths/ Allocated RT	Women Allocated No RT		eaths Variance of O-E		al death rates : No RT	Year code, and study name	Treatment Information	Deaths/ Allocated RT	Women Allocated No RT	<u>RT đ</u> Logrank O-E	eaths Variance of O-E	Ratio of annua RT :	al death rate No RT	5
(a) Nodal radiothera	py only, disse	ection					- ₩ 99%	(a) Nodal radiothera	py only, disse	ction					-∎- 99%	←95% Ci
64E Oslo Co-60 69A Heidelberg XRT 73E INT Milan 1 74Q Piedmont OA (IpN4+) 78B Toronto-Edmont.	AF+IMC AF+IMC AF+IMC †AF+IMC †AF+IMC	47/99 27/39 9/15 32/67 14/28	58/98 18/27 4/7 18/61 13/21	-8.7 0.9 1.5 6.5 0.0	22.1 8.6 2.1 11.0 4.2			64E Oslo Co-60 69A Heidelberg XRT 73E INT Milan 1 74Q Piedmont OA (IpN4+) 78B Toronto-Edmont.	AF+IMC AF+IMC AF+IMC †AF+IMC †AF+IMC	88/99 37/39 11/15 38/67 15/28	79/98 24/27 5/7 23/61 13/21	-0.6 1.3 1.5 6.8 0.5	32.4 11.9 2.1 12.8 4.4			→ ●→ >
(a) Subtotal		129/ 248 (52.0%)	111/ 214 (51.9%)	0.2	48.0	1.00 (SE 0.14)		(a) Subtotal		189/ 248 (76.2%)	/144 214 (67.3%)	9.4	63.7	1.16 (SE 0.14) -		
(b) Some with chest	wall radiothe	rapy, disse	ection					(b) Some with chest	wall radiothe	rapy, disse	ection					
71D SASIB	(CW)+AF+IMC	68/162	62/164	2.8	27.4			71D SASIB	(CW)+AF+IMC	76/162	65/164	4.7	29.8			
73C Mayo 70-56-32	†(CW)+AF+IMC	84/121	85/120	-3.5	32.3			73C Mayo 70-56-32	†(CW)+AF+IMC	104/121	100/120	-3.2	37.3			
(b) Subtotal		152/ 283 (53.7%)	147/ 284 (51.8%)	-0.7	59.6	-	0.99 (SE 0.13) 2p > 0.1: NS	(b) Subtotal		180/ 283 (63.6%)	/165 284 (58.1%)	1.5	67.1	1.02 (SE 0.12) 2p > 0.1: NS		
Total		281/ 531 (52.9%)	258/ 498 (51.8%)	-0.5	107.6	~		Total		369/ 531 (69.5%)	309/ 498 (62.0%)	10.9	130.8	1.09 (SE 0.09) -	-	
Difference between treatment effects Heterogeneity within Heterogeneity betwee	subtotals: χ	² ₅ = 9.0; p	> 0.1: NS	: NS	ــــ 0.0	0.5 1 RT better] 1.0 1.5 2.0 → RT worse	Difference between treatment effects Heterogeneity within Heterogeneity betwe	subtotals: χ	² ₅ =4.4; p	> 0.1: NS		0.0	0.5 1. RT better 	0 1.5	2.0 Se

† Same polychemotherapy and/or tamoxifen in both groups. Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

Webfigure 41. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 810 women with unknown pathological nodal status (pN?).

810 pN? women



			Women		vents	Define of annual annual anti-
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of annual event rates RT : No RT
(a) Nodal radiothera	oy only, disse	ction				- ■ -99% <>>95% C
61H NSABP B-03*	AF+IMC	196/476	216/544	-0.3	57.2	
69A Heidelberg XRT 74Q Piedmont OA (!pN4+) 78B Toronto-Edmont.	AF+IMC †AF+IMC †AF+IMC	0/2 4/8 0/0	0/0 5/11 1/1	-0.1	1.6	
(a) Subtotal		200/ 486 (41.2%)	222/ 556 (39.9%)	-0.4	58.8	0.99 (SE 0.13)
(b) Some with chest	wall radiothe	rapy, disse	ection			
71D SASIB	(CW)+AF+IMC	15/18	11/22	4.3	4.8	
■ (b) Subtotal		15/ 18 (83.3%)	/11 22 (50.0%)	4.3	4.8	2.44 (SE 0.74)
Total		215/ 504 (42.7%)	233/ 578 (40.3%)	3.8	63.5	1.06 (SE 0.13)
Difference between treatment effects				6	0.0	0.5 1.0 1.5 2
Heterogeneity within						RT better - RT worse
Heterogeneity betwe	en 3 trials:	χ ₂ ² = 3.6; p	> 0.1: NS			

Any first recurrence (years 0-9)

Locoregional recurrence first (years 0-9)

* For balance, control patients in NSABP B-03 count twice in subtotal and final total of events/deaths/women.

† Same polychemotherapy and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

810 pN? women

Breast cancer mortality

		Deaths	Women	RT d	eaths						
Year code, and study name	Treatment Information	Allocated	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of annual death rates RT : No RT					
and study name	momation	RI	NURI	0-E	010-6	RI					
a) Nodal radiothera	oy only, disse	ction						◆95% Cl			
1H NSABP B−03∗	AF+IMC	185/476	198/544	2.7	54.6						
9A Heldelberg XRT 4Q Piedmont OA (!pN4+) 8B Toronto-Edmont.	AF+IMC †AF+IMC †AF+IMC	0/2 5/8 0/0	0/0 5/11 1/1	0.6	1.8		-				
(a) Subtotal		190/ 486 (39.1%)	204/ 556 (36.7%)	3.3	56.4	1.06 (SE 0.14)					
b) Some with chest	wall radiothe	rapy, disse	ection								
1D SASIB	(CW)+AF+IMC	9/18	7/22	2.6	3.3		1	>			
■ (b) Subtotal		9/ 18 (50.0%)	7/ 22 (31.8%)	2.6	3.3	2.22 (SE 0.84) 2p ≥ 0.1: NS					
Total		199/ 504 (39.5%)	211/ 578 (36.5%)	5.9	59.8	1.10 (SE 0.14) 2p > 0.1: NS					
Difference between					L	1					
treatment effects	in 2 subtota	ds: $\chi_1^2 = 1.5$	7; 2p > 0.1	: NS	0.0	0.5	1.0 1.5	2.			
leterogeneity within	subtotals: χ	² = 0.1; p	> 0.1: NS		0.0	RT better -					
Heterogeneity betwe	en 3 trials:	$\chi_2^2 = 1.8; p$	> 0.1: NS			Ri better	- RI WO	30			

		Deaths/	Women	RTd	eaths						
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of annua RT :	I death rate No RT	8			
a) Nodal radiothera	oy only, disse	ction					- -99%	◆95% CI			
1H NSABP B-03*	AF+IMC	303/476	334/544	1.2	89.8		<u> </u>				
i9A Heidelberg XRT '4Q Pledmont OA (!pN4+) '8B Toronto-Edmont.	AF+IMC †AF+IMC †AF+IMC	1/2 5/8 0/0	0/0 5/11 1/1	0.6	1.8		-	>			
(a) Subtotal		309/ 486 (63.6%)	340/ 556 (61.2%)	1.8	91.7	1.02 (SE 0.11)					
b) Some with chest	wall radiothe	rapy, disse	ection								
1D SASIB	(CW)+AF+IMC	10/18	7/22	3.3	3.5			>			
■ (b) Subtotal		10/ 18 (55.6%)	7/ 22 (31.8%)	3.3	3.5	2.55 (SE 0.88)					
Total		319/ 504 (63.3%)	347/ 578 (60.0%)	5.1	95.2	1.05 (SE 0.11)					
Difference between					L	1					
treatment effects				9	0.0	0.5 1.0) 1.5	2.			
Heterogeneity within Heterogeneity betwe						RT better	- RT wors	50			

Any death

* For balance, control patients in NSABP B-03 count twice in subtotal and final total of events/deaths/women.

F Same polychemotherapy and/or tamoxifen in both groups.
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.
Webtable 4. Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy but no axillary surgery (Mast)*.

				Woman-y	ears since	diagnosi	% women given systemic therapy			
Nodal status†	Women	Deaths	Median/ woman	Total ('000s)	Distribut <10	ion by ye 10-	ars ('000s) 20+	Chemotherapy	ER+ & Tamoxifen	Any
Axillary dissection cN- cN+	2896 1481	2098 1188	12.4 9.6	45.3 21.5	21.7 10.5	12.8 5.9	10.8 5.1	0 0	2 1	2 1
Total	4377	3286	11.5	66.8	32.2	18.7	15.9	0	2	2

*Data available for 4 trials, start dates 1970 to 1978. In all trials radiotherapy was given to the axilla/supraclavicular fossa and the internal mammary chain. Full details of the trials are given in webtable 5.

† cN-: negative clinical nodal status, cN+: positive clinical nodal status.

Webtable 5: Randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast) – treatment details.

Year code and study name	Breast surgery	Axillary Surgery* (number of patients)	Chest wall RT	Supraclavicular and axillary fossa RT	Internal mammary chain RT	Boost RT to scar	Common systemic chemoendocrine therapy
70A Manchester RBS1	SM	Axillary sampling (714)	30-37 Gy (2-2.5 Gy/f) o	37-40 Gy (2.5-2.7 Gy/f) o or m	37-40 Gy (2.5-2.7 Gy/f) o or m	None	Ovarian ablation
70B Kings/Cambridge	SM	Axillary sampling (2,800)	28.5-46 Gy (1.5-3.2 Gy/f) o or s	28.5-46 Gy (1.5-3.2 Gy/f) o or s	28.5-46 Gy (1.5-3.2 Gy/f) o or s	None	None
71C NSABP B-04	SM	Axillary sampling (770)	50 Gy (2 Gy/f) s	45-50 Gy de (1.8-2.0 Gy/f) s	45 Gy de (1.8 Gy/f) s	None	None
78D Scottish D	SM	Axillary sampling (93)	37-45 Gy (2.3-3.7 Gy/f) o or m	38.4-45.9 Gy (2.3-3.8 Gy/f) o or m	40-45 Gy (2.3-2.7 Gy/f) o or m	None	Tamoxifen or not

* Based on the description of axillary surgery in the trial protocol or publications or on lymph node information on individual women. Women were classified as having axillary sampling if they were in a trial where the protocol specified axillary sampling or, if individual information was available, resection of <10 nodes. In other trials, women were classified as having axillary sampling if the trial publication indicated that the median number of nodes removed was < 10, f=fraction, Gy=Gray (intended dose), m=megavoltage, RM=modified radical mastectomy, o=orthovoltage, RM=radical mastectomy (Halsted), RT=radiotherapy, SM=simple (total) mastectomy.

References for Webtable 5

Year code and study name	Reference
70A Manchester RBS1	Lythgoe JP, Palmer MK. Manchester regional breast study-5 and 10 year results. Br J Surg 1982; 693–6.
70B Kings/Cambridge	Houghton J, Baum M, Haybittle JL. Role of radiotherapy following total mastectomy in patients with early breast cancer. The Closed Trials Working Party of the CRC Breast Cancer Trials Group. <i>World J Surg</i> 1994; 18 : 117–22.
71C NSABP B-04	Fisher B, Montague E, Redmond C, Deutsch M, Brown GR, Zauber A, et al. Findings from NSABP protocol no. B-04- comparison of radical mastectomy with alternative treatments for primary breast cancer. I. Radiation compliance and its relation to treatment outcome. <i>Cancer</i> 1980; 46 : 1–13.
	Deutsch M, Land S, Begovic M, Sharif S. The incidence of arm edema in women with breast cancer randomized on the National Surgical Adjuvant Breast and Bowel Project study B-04 to radical mastectomy versus total mastectomy and radiotherapy versus total mastectomy alone. <i>Int J Radiat Oncol Biol Phys</i> 2008; 70 : 1020–4.
78D Scottish D	Stewart HJ, Prescott RJ, Forrest AP. Scottish adjuvant tamoxifen trial: a randomized study updated to 15 years. <i>J Natl Cancer Inst</i> 2001; 93 : 456–62.

Webfigure 42. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of locoregional recurrence and recurrence

of any type and 20-year risks of breast cancer and all-cause mortality in 2896 women with clinically nodenegative (cN-) disease. See webfigure 1 for methodological note and also webfigure 43



2896 cN- women with Mast

Webfigure 43. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of recurrence and type of first recurrence in 2896 women with clinically node-negative (cN-) disease. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Webfigure 44. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risks of breast cancer and all-cause mortality in 1481 women with clinically node-positive (cN+) disease. See webfigure 1 for methodological note and also webfigure 45



1481 cN+ women with Mast

Webfigure 45. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of recurrence and type of first recurrence in 1481 women with clinically node-positive (cN+) disease. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Webtable 6. Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy but no axillary surgery (Mast)*.

		Deaths		Woman-y	ears since	diagnosi	% women given systemic therapy‡			
Nodal status†	Women		Median/ woman	Total ('000s)	Distribut <10	ion by ye 10-	ars ('000s) 20+	Chemotherapy	ER+ & Tamoxifen	Any
Axillary dissection										
cN-	8	6	3.5	<0.1	<0.1			100	0	100
cN+	192	97	6.8	1.2	1.2	<0.1		100	0	100
Total	200	103	6.5	1.3	1.2	<0.1		100	0	100

*Data available for 2 trials, start dates 1985 to 1988. In all trials radiotherapy was given to the axilla/supraclavicular fossa and the internal mammary chain. Full details of the trials are given in webtable 7.

† cN-: negative clinical nodal status, cN+: positive clinical nodal status.

‡ Chemotherapy was cyclophosphamide, methotrexate, 5-fluorouracil [CMF].

Webtable 7. Randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy but no axillary surgery (Mast) – treatment details.

Year code and study name	Breast surgery	Axillary dissection* (number of patients)	Chest wall RT	Supraclavicular and axillary fossa RT	Internal mammary chain RT	Boost RT to scar	Common systemic chemoendocrine therapy
85Z Tokyo CIH PS	EM	Axillary sampling (100)	None	42-48 Gy (2-3 Gy/f)	42-48 Gy (2-3 Gy/f)	None	CMF
88U Tokyo CIH CZ	EM	Axillary sampling (100)	None	42-48 Gy (2-3 Gy/f)	42-48 Gy (2-3 Gy/f)	None	CMF

*Based on the description of axillary surgery in the trial protocol or publications or on information on individual women. Women were classified as having axillary sampling if they were in a trial where the protocol specified no axillary dissection or, if individual information was available, resection of <10 nodes. In other trials, women were classified as having axillary sampling if the trial publication indicated that the median number of nodes removed was < 10, C=cyclophosphamide, EM=Extended mastectomy (ipsilateral parasternal and supraclavicular lymph node dissection), F=fluorouracil, f=fraction, Gy=Gray (intended dose), M=methotrexate, RT=radiotherapy.

References for Webtable 7

Year code and study name	Reference
85Z Tokyo CIH PS	Yamashita TH, Masahiko; Sekiguchi, Kenji; Kobayashi, Masao; Tanaka, Emiko; Uki, Akiyoshi; Kasumi, Fujio; Yoshimoto, Masataka. Efficacy of loco-regional lymphnodes irradiation after mastectomy for breast cancer with biopsy proven parasternal lymphnodes metastases — A randomized study. <i>Int J Radiat Oncol Biol Phys</i> 1996; 36 : 277.
88U Tokyo CIH CZ	Personal Correspondence from Dr M Yoshimoto

Webfigure 46. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy but no axillary surgery (Mast): 10-year risks of recurrence, breast cancer and all-cause mortality in 192 clinically node-positive (cN+) women. See webfigure 1 for methodological note and also webfigure 47. Note, due to the very small number (8) of clinically node-negative women in this set of trials they are shown only in webfigure 48.



192 cN+ women with Mast

Webfigure 47. Effect of radiotherapy (RT) to the regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of recurrence and type of first recurrence in 192 women with clinically node-positive (cN+) disease. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)





2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: > 0.1; NS

Webfigure 48. Effect of radiotherapy (RT) versus not after mastectomy but no axillary surgery (Mast): 10 year risks of recurrence during years 0-9, breast cancer mortality, and all-cause mortality in 2904 women with clinically node-negative (cN-) disease. Event rate ratios, one line per trial, trial subdivided according to whether or not radiotherapy was given to the chest wall.

2904 cN- women

Locoregional recurrence first (years 0-9) Any first recurrence (years 0-9) RT events Events/Women RT events Events/Women Ratio of annual event rates Ratio of annual event rates Treatment Allocated Allocated Logrank Variance Allocated Allocated Logrank Variance Year code. Year code. Treatment and study name Information RT No RT Ó-E of O-E RT : No RT and study name Information RT No RT О-E of O-E RT : No RT - 99% <> 95% Cl (a) Mastectomy without axillary surgery but with CW radiotherapy (a) Mastectomy without axillary surgery but with CW radiotherapy 70B Kings/Cambridge CW+AF+IMC 348/1049 -100.0 119.7 70B Kings/Cambridge CW+AF+IMC 435/996 532/1049 -55.7 222.2 153/996 71C NSABP B-04 CW+AF+IMC 16/386 92/384 -40.124.4 71C NSABP B-04 CW+AF+IMC 139/386 178/384 -30.4 69.6 78D Scottish D †CW+AF+IMC 6/42 11/39 -2.9 3.8 78D Scottish D CW+AF+IMC 19/42 15/39 0.3 7.1 175/ 451/ 593/ 725/ (a) Subtotal 1472 -143.0 148.0 0.38 (SE 0.05) 1424 (a) Subtotal 1424 0.75 (SE 0.05) 1472 -85.9 298.9 4 (12.3%) (30.6%) (41.6%) (49.3%) (b) Mastectomy without axillary surgery and no CW radiotherapy (b) Mastectomy without axillary surgery and no CW radiotherapy 85Z Tokyo CIH PS +AF+IMC 0/3 1/5 -0.2 85Z Tokyo CIH PS †AF+IMC 0.2 3/3 3/5 1.2 0.9 0/ 1/ 3/ 3/ (b) Subtotal . 3 5 -0.2 0.2 . (b) Subtotal 3 1.2 0.9 5 0.26 (SE 1.28) 4.13 (SE 2.35) (0.0%) (20.0%) (100.0%) (60.0%) 175/ 452/ 596/ 728/ 0.38 (SE 0.05) 1477 -143.2 148.2 Total 1427 1427 1477 -84.6 299.8 0.75 (SE 0.05) Total 4 (12.3%) (30.6%) (41.8%) (49.3%) Difference between Difference between treatment effects in 2 subtotals: $\chi_1^2 = 0.0$; 2p > 0.1: NS treatment effects in 2 subtotals: $\chi_1^2 = 2.6$; 2p > 0.1: NS 0.0 0.5 1.0 1.5 2.0 0.0 0.5 1.5 2.0 1.0 Heterogeneity within subtotals: $\chi^2_2 = 13.4$; p = 0.001 Heterogeneity within subtotals: $\chi_2^2 = 2.6$; p > 0.1: NS RT better - RT worse RT better RT worse Heterogeneity between 4 trials: $\chi_3^2 = 13.5$; p = 0.004 Heterogeneity between 4 trials: $\chi_3^2 = 5.2$; p > 0.1: NS

† Same polychemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

2904 cN- women

Breast cancer mortality

Any death

Year code, and study name	Treatment Information	Deaths Allocated RT	Women Allocated No RT		Variance of O-E	Ratio of annual death rates RT : No RT	Year code, and study name	Treatment Information	Deaths Allocated RT	Women Allocated No RT	Logrank	eaths Variance of O-E	<u>Ratio of ann</u> RT	ualdo : No		
(a) Mastectomy with	out axillary s	urgery but	with CW r	adiothe	rapy	- ■ 99% ح⊃ 95% Cl	(a) Mastectomy with	out axillary su	urgery but	with CW r	adiothe	rapy			- 99% <>95% Cl	
70B Kings/Cambridge	CW+AF+IMC	523/996	590/1049	-3.7	270.0	-	70B Kings/Cambridge	CW+AF+IMC	740/996	762/1049	15.3	355.4				
71C NSABP B-04 78D Scottish D	CW+AF+IMC †CW+AF+IMC	169/386 18/42	181/384 17/39	-6.5 -0.2	81.3 7.6		71C NSABP B-04 78D Scottish D	CW+AF+IMC †CW+AF+IMC	279/386 24/42	266/384 27/39	11.9 1.0	124.1 10.2		Ţ.	>	
(a) Subtotal		710/ 1424 (49.9%)	/88/ 1472 (53.5%)	-10.5	358.8		(a) Subtotal		1043/ 1424 (73.2%)	1055/ 1472 (71.7%)	28.2	489.6	1.06 (SE 0.05) 2p > 0.1: NS			
(b) Mastectomy with	out axillary s	urgery and	i no CW ra	diother	ару		(b) Mastectomy with	out axillary s	urgery and	ino CW ra	diothera	ару		- E		
85Z Tokyo CIH PS	†AF+IMC	3/3	3/5	0.9	0.9	>	85Z Tokyo CIH PS	†AF+IMC	3/3	3/5	0.9	0.9		+	>	
• (b) Subtotal		3/ 3 (100.0%)	3/ 5 (60.0%)	0.9	0.9	2.83 (SE 1.87) 2p > 0.1: NS	• (b) Subtotal		3/ 3 (100.0%)	3/ 5 (60.0%)	0.9	0.9	2.83 (SE 1.87) 2p ≥ 0.1: NS			-
Total		713/ 1427 (50.0%)	791/ 1477 (53.6%)	-9.6	359.7	→ 0.97 (SE 0.05) 2p > 0.1: NS	Total		1046/ 1427 (73.3%)	1058/ 1477 (71.6%)	29.1	490.5	1.06 (SE 0.05) 2p ≥ 0.1: NS			
Difference between treatment effects Heterogeneity within Heterogeneity betwee	n subtotals: χ	² ₂ =0.3; p	> 0.1: NS		0.0	0.5 1.0 1.5 2.0 RT better - RT worse	Difference between treatment effects Heterogeneity within Heterogeneity betwe	n subtotals: χ	² ₂ = 0.3; p	> 0.1: NS		L. 0.0	0.5 RT better	1.0	1.5 2.0 RT worse	

† Same polychemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups. Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

Webfigure 49. Effect of radiotherapy (RT) versus not after mastectomy but no axillary surgery (Mast): 10 year risks of recurrence during years 0-9, breast cancer mortality, and all-cause mortality in 1673 women with clinically node-positive (cN+) disease. Event rate ratios, one line per trial, trial subdivided according to whether or not radiotherapy was given to the chest wall.

1673 cN+ women

Locoregional recurrence first (years 0-9) Any first recurrence (years 0-9) Events/Women RT events Events/Women RT events Ratio of annual event rates Ratio of annual event rates Year code, Treatment Allocated Allocated Logrank Variance Treatment Allocated Allocated Logrank Variance Year code. and study name Information RT No RT Ó-E of O-E RT : No RT and study name Information RT No RT Ó-E of O-E RT : No RT (a) Mastectomy without axillary surgery but with CW radiotherapy (a) Mastectomy without axillary surgery but with CW radiotherapy 70A Manchester RBS1 CW+AF+IMC 49/355 120/359 -39.7 39.5 70A Manchester RBS1 CW+AF+IMC 140/355 192/359 -36.174.3 70B Kings/Cambridge 70B Kings/Cambridge CW+AF+IMC 66/380 168/375 -58.7 53.4 CW+AF+IMC 209/380 249/375 -36.7 98.5 78D Scottish D 4/7 78D Scottish D †CW+AF+IMC 3/7 CW+AF+IMC 3/5 0.5 0.2 1/5 445/ 291/ 352/ 116/ (a) Subtotal 740 0.66 (SE 0.06) (a) Subtotal 0.35 (SE 0.06) 741 -72.3 173.0 740 741 -98.3 92.9 -(60.1%) (47.6%) (15.7%) (39.3%)(b) Mastectomy without axillary surgery and no CW radiotherapy (b) Mastectomy without axillary surgery and no CW radiotherapy 85Z Tokyo CIH PS 85Z Tokyo CIH PS tAF+IMC †AF+IMC 27/47 26/45 7/47 11/45 1.3 9.8 -2.337 TAF+IMC 88U Tokyo CIH N2 88U Tokyo CIH N2 TAF+IMC 34/50 35/50 -2.4 12.4 6/50 7/50 -0.6 3.1 13/ 18/ 61/ 61/ 22.2 (b) Subtotal 97 (b) Subtotal 95 -3.0 6.8 97 95 -1.1 0.64 (SE 0.31) 0.95 (SE 0.21) (13.4%) (18.9%) (62.9%) (64.2%) 129/ 309/ 413/ 506/ 0.36 (SE 0.06) 0.69 (SE 0.06) Total 837 836 -101.3 99.7 Total 837 836 -73.4 195.3 \Rightarrow (15.4%) (37.0%) (49.3%) (60.5%) Difference between Difference between treatment effects in 2 subtotals: $\chi_1^2 = 2.4$; 2p > 0.1: NS treatment effects in 2 subtotals: $\chi_1^2 = 2.7$; 2p > 0.1: NS 0.0 0.5 1.0 1.5 2.0 0.0 0.5 1.0 1.5 2.0 Heterogeneity within subtotals: $\chi_3^2 = 2.6$; p > 0.1: NS Heterogeneity within subtotals: $\chi^2_2 = 0.5$; p > 0.1: NS **RT** better RT better RT worse RT worse Heterogeneity between 4 trials: $\chi_3^2 = 2.9$; p > 0.1: NS Heterogeneity between 5 trials: $\chi_4^2 = 5.3$; p > 0.1: NS

† Same polychemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

1673 cN+ women

Breast cancer mortality

Year code.	Treatment	Deaths	Women Allocated		eaths Variance	Ratio of annual death rates
and study name	Information	RT	No RT	0-E	of O-E	RT : No RT
(a) Mastectomy with	out axillary s	urgery but	with CW r	adiothe	rapy	- ■ -99% <>>95% CI
70A Manchester RBS1	CW+AF+IMC	178/355	215/359	-14.5	93.7	
70B Kings/Cambridge	CW+AF+IMC	235/380	255/375	-17.3	114.6	
78D Scottish D	†CW+AF+IMC	3/5	4/7	0.5	0.2	
(a) Subtotal		416/ 740 (56.2%)	474/ 741 (64.0%)	-31.2	208.6	0.86 (SE 0.06)
b) Mastectomy with	out axillary s	urgery and	i no CW ra	diother	ару	
85Z Tokyo CIH PS 88U Tokyo CIH N2	†AF+IMC †AF+IMC	18/47 25/50	21/45 27/50	-0.1 -1.2	7.8 11.1	
■ (b) Subtotal		43/ 97 (44.3%)	48/ 95 (50.5%)	-1.4	18.9	0.93 (SE 0.22) 2p > 0.1: NS
Total		459/ 837 (54.8%)	522/ 836 (62.4%)	-32.6	227.5	0.87 (SE 0.06)
Difference between treatment effects	sin 2 subtota	als: χ ² = 0.4	l; 2p > 0.1	: NS	0.0	0.5 1.0 1.5 2
Heterogeneity within					0.0	
Heterogeneity betw						RT better RT worse

Year code, and study name	Treatment Information	Deaths Allocated RT	Women Allocated No RT		Variance of O-E	Ratio of annual death rates RT : No RT
(a) Mastectomy with	nout axillary s	urgery but	with CW r	adiothe	rapy	- ₽ -99%>95% CI
70A Manchester RBS1	CW+AF+IMC	274/355	286/359	-11.9	130.0	
70B Kings/Cambridge	CW+AF+IMC	303/380	316/375	-14.4	140.5	
78D Scottish D	†CW+AF+IMC	5/5	4/7	0.5	0.2 —	
(a) Subtotal		582/ 740 (78.6%)	/606 741 (81.8%)	-25.8	270.8	0.91 (SE 0.06) 2p > 0.1: NS
(b) Mastectomy with	hout axillary s	urgery and	i no CW ra	diother	ару	
85Z Tokyo CIH PS 88U Tokyo CIH N2	†AF+IMC †AF+IMC	20/47 26/50	23/45 28/50	0.4 -1.3	8.5 11.6	>
■ (b) Subtotal		46/ 97 (47.4%)	51/ 95 (53.7%)	-0.9	20.0	0.96 (SE 0.22) 2p > 0.1: NS
Total		628/ 837 (75.0%)	657/ 836 (78.6%)	-26.7	290.8	0.91 (SE 0.06) 2p \$ 0.1: NS
Difference between treatment effect Heterogeneity withi	s in 2 subtota n subtotals: ;	² ₃ =1.2; p	> 0.1: NS	: NS	0.0	0.5 1.0 1.5 2.0
Heterogeneity betw						RT better 🛥 🚽 🖛 RT worse

† Same polychemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups. Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

Any death

Webtable 8. Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS) *.

				Woman-y	ears sinc	% women given systemic therapy			
Nodal status†	Women	Deaths	Median/ woman	Total ('000s)	Distribu <10	tion by ye 10-	ars ('000s) 20+	Chemotherapy‡	ER+ & Tamoxifen
			woman	(0003)	10	10-	20.		Tunioxiten
Axillary dissection pN unknown	255	201	6.6	2.0	1.6	0.4	<0.1	0	0
Axillary sampling pN unknown	637	497	16.6	10.7	5.1	3.4	2.2	0	0
Total	892	698	12.1	12.7	6.7	3.8	2.2	0	0

*Data available for 2 trials, start dates 1962 to 1971. In all trials radiotherapy was given to the axilla/supraclavicular fossa and the internal mammary chain.. Full details of the trials are given in webtable 9.

† pN unknown: as radiotherapy was given before surgery, to avoid bias pathological nodal status is regarded as unknown.

Webtable 9. Randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS) – treatment details.

Year code and study name	Breast surgery	Axillary Surgery* (number of patients)	Chest wall RT	Supraclavicular and axillary fossa RT	Internal mammary chain RT	Boost RT to scar	Common systemic chemoendocrine therapy
62B Berlin-Bruch	RM	Axillary clearance (255)	55 Gy (u Gy/f) c	55 Gy (u Gy/f) c	55 Gy (u Gy/f) c	None	None
71B Stockholm A	MRM	Axillary sampling (637)	45 Gy (1.8 Gy/f) e	45 Gy de (1.8 Gy/f) c	45 Gy (1.8 Gy/f) e	None	None

* Based on the description of axillary surgery in the trial protocol or publications or on information on individual women. Women were classified as having axillary dissection if they were in a trial where the protocol required removal of axillary lymph nodes in at least Levels I & II or, if individual information was available, resection of ≥10 nodes. In other trials, women were classified as having axillary dissection if the trial publication indicated that the median number of nodes removed was ≥ 10. c=cobalt-60, e=electron, f=fraction, Gy=Gray (intended dose), MRM=modified radical mastectomy, RM=radical mastectomy (Halsted), RT=radiotherapy, u=unknown,

References for Webtable 9

Year code and study name	Reference
62B Berlin-Bruch	Berndt H, Eichhorn HJ, Widow W et al. Ein kontrollierter klinischer Versuch zur Zusatztherapie des operablen Brustdrusenkrebses mit Vorbestrahlung oder Cyclophosphamid. Arch. Gesch 1980; 50: 168-479
71B Stockholm A	Gyenes G, Rutqvist LE, Liedberg A, Fornander T. Long-term cardiac morbidity and mortality in a randomized trial of pre- and postoperative radiation therapy versus surgery alone in primary breast cancer. Radiother Oncol 1998; 48: 185–90.

Webfigure 50. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 15-year risk of breast cancer and all-cause mortality in 255 women with unknown pathological nodal status (pN?) disease. See webfigure 1 for methodological note and also webfigure 51.



255 pN? women with Mast+AD

Webfigure 51. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 255 women with unknown pathological nodal status (pN?). (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: = 0.04

Webfigure 52. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary sampling (Mast+AS): 10-year risk of locoregional recurrence and recurrence of any type and 15-year risk of breast cancer and all-cause mortality in 637 women with unknown pathological nodal status (pN?) disease. See webfigure 1 for methodological note and also webfigure 53.



637 pN? women with Mast+AS

Webfigure 53. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary sampling (Mast+AS): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 637 women with unknown pathological nodal status (pN?). (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Webfigure 54. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 892 women with unknown pathological nodal status (pN?).

892 pN? women

		Events/	Women	RT e	vents		
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of annual event rates RT : No RT	а
(a) Axillary dissectio	'n					- ■ 99% <> 95% Ci	(a) Ax
62B Berlin-Buch ABC	CW+AF+IMC	7/123	17/132	-3.6	5.4		62B Be
(a) Subtotal		7/ 123 (5.7%)	/17 132 (12.9%)	-3.6	5.4	0.52 (SE 0.31) 2p > 0.1: NS	
(b) Axillary sampling	I						(b) Ax
71B Stockholm A	CW+AF+IMC	20/316	76/321	-30.5	23.1		71B St
(b) Subtotal		20/ 316 (6.3%)	76/ 321 (23.7%)	-30.5	23.1	0.27 (SE 0.12)	
Total		27/ 439 (6.2%)	93/ 453 (20.5%)	-34.1	28.5	0.30 (SE 0.11)	
Difference between					L		Differ
treatment effects	in 2 subtot	als: $\chi_1^2 = 1.9$	9; 2p > 0.1	: NS	0.0	0.5 1.0 1.5 2.0	tre
Difference between treatment effects	in 2 trials:	χ ² ₁ = 1.9; 2	p > 0.1: NS	5		RT better RT worse	Differ tre

Locoregional recurrence first (years 0-9)

Events/Women RT events Logrank Variance Ratio of annual event rates Year code. Treatment Allocated Allocated of O-E and study name Information RT No RT O-E RT : No RT xillary dissection Berlin-Buch ABC CW+AF+IMC 60/123 64/132 2.0 26.8 60/ 64/ (a) Subtotal 123 132 2.0 26.8 1.08 (SE 0.20) 2p > 0.1: NS (48.8%) (48.5%) xillary sampling Stockholm A CW+AF+IMC 110/316 148/321 -26.758.5 110/ 148/ (b) Subtotal 316 321 -26.7 58.5 0.63 (SE 0.11) (34.8%) (46.1%) 170/ 212/ Total 0.75 (SE 0.09) 439 453 -24.6 85.2 (38.7%) (46.8%) rence between reatment effects in 2 subtotals: χ_1^2 = 5.2; 2p = 0.02 0.0 0.5 1.0 1.5 2.0 erence between RT better treatment effects in 2 trials: $\chi_1^2 = 5.2$; 2p = 0.02 RT worse

Any first recurrence (years 0-9)

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain.

continued overleaf

892 pN? women

Breast cancer mortality

Year code, and study name	Treatment Information	Deaths Allocated RT	Women Allocated No RT		Variance of O-E	Ratio of annual death rates RT : No RT
(a) Axillary dissection	on					- ■ -99%
62B Berlin-Buch ABC	CW+AF+IMC	67/123	70/132	3.6	29.3	
(a) Subtotal		67/ 123 (54.5%)	70/ 132 (53.0%)	3.6	29.3	1.13 (SE 0.20)
(b) Axillary samplin	g	(0-1.070)	(00.070)			2p > 0.1: NS
71B Stockholm A	CW+AF+IMC	152/316	175/321	-8.6	77.1	_
(b) Subtotal		152/ 316 (48.1%)	175/ 321 (54.5%)	-8.6	77.1	0.89 (SE 0.11)
Total		219/ 439 (49.9%)	245/ 453 (54.1%)	-4.9	106.4	
Difference between treatment effect Difference between treatment effect					0.0	0.5 1.0 1.5 2.0 RT better

			eaths			
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of annual death rates RT : No RT
(a) Axillary dissection	'n					- ■ -99% ~ ∞> -95% Ci
62B Berlin-Buch ABC	CW+AF+IMC	105/123	96/132	8.1	43.1	
(a) Subtotal		105/ 123 (85.4%)	96/ 132 (72.7%)	8.1	43.1	1.21 (SE 0.17)
(b) Axillary sampling)					
71B Stockholm A	CW+AF+IMC	244/316	253/321	-12.3	116.1	-
(b) Subtotal		244/ 316 (77.2%)	253/ 321 (78.8%)	-12.3	116.1	0.90 (SE 0.09)
Total		349/ 439 (79.5%)	349/ 453 (77.0%)	-4.1	159.2	
Difference between treatment effects Difference between treatment effects		-	0.0	0.5 1.0 1.5 2.0 RT better		

Any death

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain.

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Webfigure 55. EBCTCG collaborators, listed alphabetically by institution and then name

ACETBC, Tokyo, Japan-O Abe, R Abe, K Enomoto, K Kikuchi, H Kovama, H Masuda, Y Nomura, Y Ohashi, K Sakai, K Sugimachi, M Toi, T Tominaga, J Uchino, M Yoshida. Addenbrooke's Hospital, Cambridge, UK-J L Haybittle. Anglo-Celtic Cooperative Oncology Group, UK-C F Leonard. ARCOSEIN Group, France—G Calais, P Geraud. ATLAS Trial Collaborative Study Group, Oxford, UK-V Collett, C Davies, A Delmestri, J Sayer. Auckland Breast Cancer Study Group, New Zealand—V J Harvey, I M Holdaway, R G Kay, B H Mason. Australian New Zealand Breast Cancer Trials Group, Sydney, Australia—J F Forbes, N Wilcken. Austrian Breast Cancer Study Group, Vienna, Austria-R Bartsch, P Dubsky, C Fesl, H Fohler, M Gnant, R Greil, R Jakesz, A Lang, G Luschin-Ebengreuth, C Marth, B Mlineritsch, H Samonigg, C F Singer, G G Steaer, H Stöger, Beatson Oncology Centre, Glasgow, UK-P Canney, H M A Yosef. Belgian Adjuvant Breast Cancer Project, Liège, Belgium-C Focan. Berlin-Buch Akademie der Wissenschaften, Germany-U Peek. Birmingham General Hospital, UK-G D Oates, J Powell, Bordeaux Institut Bergonié, France-M Durand, L Mauriac. Bordet Institute, Brussels, Belgium-A Di Leo, S Dolci, D Larsimont, J M Nogaret, C Philippson, M J Piccart. Bradford Royal Infirmary, UK-M B Masood, D Parker, J J Price. Breast Cancer International Research Group (BCIRG)—M A Lindsay, J Mackey, M Martin. Breast Cancer Study Group of the Comprehensive Cancer Centre, Limburg, Netherlands-PSGJ Hupperets. British Association of Surgical Oncology BASO II Trialists, London, UK-T Bates, R W Blamey, U Chetty, I O Ellis, E Mallon, D A L Morgan, J Patnick, S Pinder. British Columbia Cancer Agency, Vancouver, Canada-I Olivotto, J Ragaz. Cancer and Leukemia Group B, Washington DC, USA-D Berry, G Broadwater, C Cirrincione, H Muss, L Norton, R B Weiss. Cancer Care Ontario, Canada—H T Abu-Zahra, Cancer Research Centre of the Russian Academy of Medical Sciences, Moscow, Russia-S M Portnoj. Cancer Research UK Clinical Trials Unit (CRCTU), NCRI, Birmingham, UK-S Bowden, C Brookes, J Dunn, I Fernando, M Lee, C Poole, D Rea, D Spooner. Cardiff Trialists Group, UK-P J Barrett-Lee, R E Mansel, I J Monypenny. Case Western Reserve University, Cleveland, OH, USA-N H Gordon. Central Oncology Group, Milwaukee, WI, USA-H L Davis, Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary, University of London, UK—J Cuzick. Centre Léon-Bérard, Lyon, France-Y Lehingue, P Romestaing. Centre Paul Lamarque, Montpellier, France-J B Dubois, Centre Regional François Baclesse, Caen, France-T Delozier, B Griffon, J Mace Lesech. Centre René Huguenin, Paris, St Cloud, France E Brain, B de La Lande, E Mouret-Fourme Centro Oncologico, Trieste, Italy-G Mustacchi. Charles University in Prague, First Faculty of Medicine, Department of Oncology of the First Faculty of Medicine and General Teaching Hospital, Czech Republic—L Petruzelka, O Pribylova. Cheltenham General Hospital, UK-J R Owen, Chemo N0 Trial Group, Germany-N Harbeck, F Jänicke, C Meisner, M Schmitt, C Thomssen. Chicago University, IL, USA-P Meier. Chinese Academy of Medical Sciences, Beijing, People's Republic of China (in collaboration with the Oxford CTSU)—Y Shan, Y F Shao, X Wang, D B Zhao (CTSU: Z M Chen, H C Pan). Christie Hospital and Holt Radium Institute, Manchester, UK-A Howell, R Swindell. Clinical Trial Service Unit, Oxford, UK (ie, EBCTCG Secretariat)—J A Burrett, M Clarke, R Collins, C Correa, D Cutter, S Darby, C Davies, K Davies, A Delmestri, P Elphinstone, V Evans, L Gettins, J Godwin, R Grav, C Gregory, D Hermans, C Hicks, S James, A Kerr, H Liu, E MacKinnon, M Lav, P McGale, T McHugh, P Morris, H C Pan, R Peto, J Sayer, C Taylor, Y Wang. Coimbra Instituto de Oncologia, Portugal-J Albano, C F de Oliveira, H Gervásio, J Gordilho. Copenhagen Breast Cancer Trials, Copenhagen, Denmark—B Ejlertsen, M-B Jensen, H Johansen, H Mouridsen, T Palshof, Dana-Farber Cancer Institute, Boston, MA, USA-R S Gelman, J R Harris, D Hayes, C Henderson, C L Shapiro, E Winer. Danish Breast Cancer Cooperative Group, Copenhagen, Denmark- P Christiansen, B Ejlertsen, M

Ewertz, M-B Jensen, S Møller, H T Mouridsen, Düsseldorf University, Germany-H J Trampisch. Dutch Working Party for Autologous Bone Marrow Transplant in Solid Tumours, Amsterdam & Groningen, Netherlands-O Dalesio, E G E de Vries, S Rodenhuis, H van Tinteren. Eastern Cooperative Oncology Group, Boston, MA, USA-R L Comis, N E Davidson, R Grav, N Robert, G Sledge, L J Solin, J A Sparano, D C Tormey, W Wood. Edinburgh Breast Unit, UK-D Cameron, U Chetty, J M Dixon, P Forrest, W Jack, I Kunkler. Elim Hospital, Hamburg, Germany—J Rossbach. Erasmus MC/Daniel den Hoed Cancer Center, Rotterdam, Netherlands- J G M Klijn, A D Treurniet-Donker, W L J van Putten. European Institute of Oncology, Milan, Italy-N Rotmensz, U Veronesi, G Viale. European Organization for Research and Treatment of Cancer, Brussels, Belgium—H Bartelink, N Bijker, J Bogaerts, F Cardoso, T Cufer, J P Julien, E Rutgers, C J H van de Velde. Evanston Hospital, IL, USA-M P Cunningham. Finnish Breast Cancer Group, Finland-R Huovinen, H Joensuu. Fondazione Maugeri Pavia, Italy-A Costa. Fondazione Michelangelo, Milan, Italy-G Bonadonna, L Gianni, P Valagussa. Fox Chase Cancer Center, Philadelphia, PA, USA-L J Goldstein, French Adjuvant Study Group (GFEA), Guyancourt, France—J Bonneterre, P Fargeot, P Fumoleau, P Kerbrat, E Luporsi, M Namer. German Adjuvant Breast Group (GABG), Frankfurt, Germany-W Eiermann, J Hilfrich, W Jonat, M Kaufmann, R Kreienberg, M Schumacher. German Breast Cancer Study Group (BMFT), Freiburg, Germany-G Bastert, H Rauschecker, R Sauer, W Sauerbrei, A Schauer, M Schumacher, German Breast Group (GBG), Neu-Isenburg, Germany-J U Blohmer, S D Costa, H Eidtmann, B Gerber, C Jackisch, S Loibl, G von Minckwitz. Ghent University Hospital, Belgium-A de Schryver, L Vakaet. GIVIO Interdisciplinary Group for Cancer Care Evaluation, Chieti, Italy—M Belfiglio, A Nicolucci, F Pellegrini, M C Pirozzoli, M Sacco, M Valentini. Glasgow Victoria Infirmary, UK-C S McArdle, D C Smith, S Stallard. Groote Schuur Hospital, Cape Town, South Africa-D M Dent, C A Gudgeon, A Hacking, E Murray, E Panieri, ID Werner. Grupo Español de Investigación en Cáncer de Mama (GEICAM), Spain-E Carrasco, M Martin, M A Segui. Gruppo Oncologico Clinico Cooperativo del Nord Est, Aviano, Italy-E Galligioni. Gruppo Oncologico Dell'Italia Meridionale (GOIM), Rome, Italy-M Lopez. Guadalajara Hospital de 20 Noviembre, Mexico-A Erazo, J Y Medina. Gunma University, Japan-J Horiguchi, H Takei. Guy's Hospital, London, UK-I S Fentiman, J L Hayward, R D Rubens, D Skilton. Heidelberg University I, Germany-H Scheurlen. Heidelberg University II, Germany-M Kaufmann, H C Sohn. Helios Klinikum Berlin-Buch, Germany-M Untch. Hellenic Breast Surgeons Society, Greece-U Dafni, C Markopoulos. Hellenic Cooperative Oncology Group, Athens, Greece-U Dafni, G Fountzilas. Hellenic Oncology Research Group, Greece-D Mavroudis. Helsinki Deaconess Medical Centre, Finland-P Klefstrom. Helsinki University, Finland-C Blomovist, T Saarto, Hospital del Mar, Barcelona, Spain-M Gallen. Humanitas Cancer Center, Milan, Italy-C Tinterri. Innsbruck University, Austria-R Margreiter. Institut Claudius Regaud, Toulouse, France—B de Lafontan, J Mihura, H Roché. Institut Curie, Paris, France-B Asselain, R J Salmon, J R Vilcoq. Institut Gustave-Roussy, Paris, France—F André, R Arriagada, S Delaloge, C Hill, S Koscielny, S Michiels, C Rubino. Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU, NCRI), UK-R A'Hem, J Bliss, P Ellis, L Kilburn, J R Yarnold. Integraal Kankercentrum, Amsterdam, Netherlands-J Benraadt, M Kooi, A O van de Velde, J A van Dongen, J B Vermorken. International Breast Cancer Study Group (IBCSG), Bern, Switzerland—M Castiglione, A Coates, M Colleoni, J Collins, J Forbes, R D Gelber, A Goldhirsch, J Lindtner, K N Price, M M Regan, C M Rudenstam, H J Senn, B Thuerlimann.

International Collaborative Cancer Group, Charing Cross Hospital, London, UK—J M Bliss, C E D Chilvers, R C Coombes, E Hall, M Marty. International Drug Development Institute, Louvain-la-Neuve, Belgium-M Buyse. International TABLE Study Group, Berlin, Germany—K Possinger, P Schmid, M Untch, D Wallwiener. ISD Cancer Clinical Trials Team (incorporating the former Scottish Cancer Therapy Network), Edinburgh, UK-L Foster, W D George, H J Stewart, P Stroner. Israel NSABC, Tel Aviv, Israel—R Borovik, H Hayat, M J Inbar, T Peretz, E Robinson. Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy-P Bruzzi, L Del Mastro, P Pronzato, M R Sertoli, M Venturini. Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy-T Camerini, G De Palo, M G Di Mauro, F Formelli, P Valagussa, Istituto Oncologico Romagnolo, Forli, Italy-D Amadori. Italian Cooperative Chemo-Radio-Surgical Group, Bologna, Italy—A Martoni, F Pannuti, Italian Oncology Group for Clinical Research (GOIRC), Parma, Italy- R Camisa, G Cocconi, A Colozza, R Passalacqua. Japan Clinical Oncology Group-Breast Cancer Study Group, Matsuyama, Japan-K Aogi, S Takashima. Japanese Foundation for Multidisciplinary Treatment of Cancer, Tokyo, Japan-O Abe, T Ikeda, K Inokuchi, K Kikuchi, K Sawa, Kawasaki Medical School, Japan-H Sonoo. Krakow Institute of Oncology, Poland-S Korzeniowski, J Skolyszewski. Kumamoto University Group, Japan-M Ogawa, J Yamashita. Leiden University Medical Center, Netherlands-E Bastiaannet, C J H van de Velde, W van de Water, J G H van Nes. Leuven Akademisch Ziekenhuis, Gasthuisberg, Belgium-R Christiaens, P Neven, R Paridaens, W Van den Bogaert. Ludwig-Maximilians University, Munich, Germany—S Braun. Marseille Laboratoire de Cancérologie Biologique APM, France-P Martin, S Romain. Medical University Vienna – General Hospital - Department of Obstetrics and Gynaecology and Department of Medicine I, Vienna, Austria-M Janauer, M Seifert, P Sevelda, C C Zielinski. Memorial Sloan-Kettering Cancer Center, New York, NY, USA-T Hakes, C A Hudis, L Norton, R Wittes. Metaxas Memorial Cancer Hospital, Athens, Greece—G Giokas, D Kondylis, B Lissaios. Mexican National Medical Center, Mexico City, Mexico-R de la Huerta, M G Sainz. National Cancer Institute, Bethesda, MD, USA-R Altemus, K Camphausen, K Cowan, D Danforth, A Lichter, M Lippman, J O'Shaughnessy, L J Pierce, S Steinberg, D Venzon, J A Zujewski. National Cancer Institute of Bari, Italy-C D'Amico, M Lioce, A Paradiso. NCIC Clinical Trials Group, Kingston, Ontario, Canada—J-A W Chapman, K Gelmon, P E Goss, M N Levine, R Meyer, W Parulekar, J L Pater, K I Pritchard, L E Shepherd, D Tu, T Whelan. National Kyushu Cancer Center, Japan-Y Nomura, S Ohno National Surgical Adjuvant Breast and Bowel Project (NSABP), Pittsburgh, PA, USA-S Anderson, G Bass, A Brown (deceased), J Brvant (deceased), J Costantino, J Dignam, B Fisher, C Gever, E P Mamounas, S Paik, C Redmond, S Swain, L Wickerham, N Wolmark, Nolvadex Adjuvant Trial Organisation, London, UK-M Baum, I M Jackson (deceased), M K Palmer. North Central Cancer Treatment Group, Mayo Clinic, Rochester, MN, USA-E Perez, J N Ingle, V J Suman. North Sweden Breast Cancer Group, Umeå, Sweden-N O Bengtsson, S Emdin, H Jonsson. North-West Oncology Group (GONO), Italy-L Del Mastro, M Venturini, North-Western British Surgeons, Manchester, UK-J P Lythgoe, R Swindell. Northwick Park Hospital, London, UK-M Kissin. Norwegian Breast Cancer Group, Oslo, Norway-B Erikstein, E Hannisdal, A B Jacobsen, J E Varhaug. Norwegian Radium Hospital, Oslo, Norway-B Erikstein, S Gundersen, M Hauer-Jensen, H Høst, A B Jacobsen, R Nissen-Meyer, K Reinertsen Nottingham City Hospital, UK-R W Blamey, A K Mitchell, D A L Morgan, J F R Robertson, Oita Prefectural Hospital, Japan-H Ueo. Oncofrance, Paris, France-M Di Palma, G Mathé (deceased), J L Misset. Ontario Clinical Oncology Group, Hamilton, Canada-M Levine, K I Pritchard, T Whelan. Osaka City University, Japan-K Morimoto. Osaka National Hospital, Japan-K Sawa, Y Takatsuka. Oxford Radcliffe Hospitals NHS Trust, Churchill Hospital, Oxford, UK-E Crossley, A Harris, D Talbot, M Taylor. Parma Hospital, Italy-G Cocconi, B di Blasio.

Petrov Research Institute of Oncology, St Petersburg, Russia—V Ivanov, R Paltuev, V Semiglazov, Piedmont Oncology Association, Winston-Salem, NC, USA-J Brockschmidt, M R Cooper. Pretoria University, South Africa-C I Falkson. Royal Marsden NHS Trust, London and Sutton, UK-R A'Hem, M Dowsett, A Makris, M Parton, K Pennert, T J Powles, I E Smith, J R Yarnold, St George's Hospital, London, UK-J C Gazet. St George Hospital, Sydney, Australia—L Browne, P Graham. St Luke's Hospital, Dublin, Ireland-N Corcoran. Sardinia Oncology Hospital A Businico, Cagliari, Sardinia-N Deshpande, L di Martino. SASIB International Trialists, Cape Town, South Africa-P Douglas, A Hacking, H Høst, A Lindtner, G Notter. Saskatchewan Cancer Foundation, Regina, Canada—A J S Bryant, G H Ewing, L A Firth, J L Krushen-Kosloski. Scandinavian Adjuvant Chemotherapy Study Group, Oslo, Norway-R Nissen-Meyer. South Sweden Breast Cancer Group, Lund, Sweden-H Anderson, F Killander, P Malmström, L Rydén. South-East Sweden Breast Cancer Group, Linköping, Sweden-L-G Amesson, J Carstensen, M Dufmats, H Fohlin, B Nordenskiöld, M Söderbera. South-Eastern Cancer Study Group and Alabama Breast Cancer Project, Birmingham, AL, USA-JT Carpenter. Southampton Oncology Centre, UK-N Murray, G T Royle, P D Simmonds. Southwest Oncology Group, San Antonio, TX, USA-K Albain, W Barlow, J Crowley, D Hayes, J Gralow, G Hortobagyi, R Livingston, S Martino, C K Osborne, P M Ravdin. Stockholm Breast Cancer Study Group, Sweden—J Adolfsson, J Bergh, T Bondesson, F Celebioglu, K Dahlberg, T Fornander, I Fredriksson, J Frisell, E Göransson, M liristo, U Johansson, E Lenner, L Löfgren, P Nikolaidis, L Perbeck, S Rotstein, K Sandelin, L Skoog, G Svane, E af Trampe, C Wadström. SUCCESS-Study Group, University of Düsseldorf, Germany—W Janni. Swiss Group for Clinical Cancer Research (SAKK), Bern, and OSAKO, St Gallen, Switzerland—M Castiglione, A Goldhirsch, R Maibach, H J Senn, B Thürlimann. Tampere University Hospital, Finland M Hakama, K Holli, J Isola, K Rouhento, R Saaristo, Tel Aviv University, Israel-H Brenner, A Hercbergs. Tokyo Cancer Institute Hospital, Japan-M Yoshimoto. Toronto-Edmonton Breast Cancer Study Group, Canada—A H G Paterson, K I Pritchard. Toronto Princess Margaret Hospital, Canada—A Fyles, J W Meakin, T Panzarella, K I Pritchard. Tunis Institut Salah Azaiz, Tunisia-J Bahi, UK Multicentre Cancer Chemotherapy Study Group, London, UK-M Reid, M Spittle, UK/ANZ DCIS Trial—H Bishop, N J Bundred, J Cuzick, I O Ellis, I S Fentiman, J F Forbes, S Forsyth, W D George, S E Pinder, I Sestak. UK/Asia Collaborative Breast Cancer Group, London, UK-G P Deutsch, R Gray, D L W Kwong, V R Pai, R Peto, F Senanayake. Unicancer Breast Group— A L Martin, H Roché. University and Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy on behalf of GROCTA trialists—F Boccardo, A Rubagotti. University College London, UK-M Baum, S Forsyth, A Hackshaw, J Houghton, J Ledermann, K Monson, JS Tobias. University Federico II, Naples, Italy-C Carlomagno, M De Laurentiis, S De Placido. University of Edinburgh, UK-L Williams, University of Michigan, USA-D Hayes, L J Pierce. University of Texas MD Anderson Cancer Center, Houston, TX, USA-K Broglio, A U Buzdar, L Hsu. University of Wisconsin, USA-R R Love. Uppsala-Örebro Breast Cancer Study Group, Sweden—J Ahlgren, H Garmo, L Holmberg, G Liljegren, H Lindman, F Wärnberg, U.S. Oncology, Houston, USA-L Asmar, S E Jones. West German Study Group (WSG), Germany-O Gluz, N Harbeck, C Liedtke, U Nitz. West of Scotland Breast Trial Group, Glasgow, UK—A Litton. West Sweden Breast Cancer Study Group, Gothenburg, Sweden—A Wallgren, P Karlsson, B K Linderholm. Western Cancer Study Group, Torrance, CA, USA-R T Chlebowski. Würzburg University, Germany—H Caffier