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# Supplementary appendix

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

EBCTCG (Early Breast Cancer Trialists' Collaborative Group)

## Webappendix

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

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#### Clinically node positive (cN+)

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# 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)

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 Webfigure 52
 Webfigure 52
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 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 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
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Webfigure 55 **EBCTCG collaborators, listed alphabetically by institution and then alphabetically by name.** 

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.<sup>1</sup> 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 Some women are, however, lost to follow-up and are withdrawn from the analysis.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 'at 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 stratification, ie by subdividing the data into separate groups according to the stratifying factors, carrying out the analysis separately within 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 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

#### continued overleaf

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) o	None	Ovarian RT
71B Stockholm A	MRM	Axillary sampling (644)	45 Ġy (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 Gý (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) Axillary sampling (17)	45-50 Gy (1.8-2.0 Gy/f) c	45-50 Gy (1.8-2 Gy/f) c	45-50 Gy (1.8-2 Gy/f) c or e	12 Gy (uGy/f) u	bCG+FAC or FAC
78A S Swedish BCG	MRM	Axillary dissection (771)	38 Gy (1.9 Gy/f) e,o,m or c	48-60 Gy (2.4 Gy/f) c or m	48 Gy (2.4 Gy/f) e, c or m	None	Premen: C; Postmen: tam
78G BCCA Vancouver	MRM	Axillary dissection (318)	37.5-40 Gy (2.3 Gy/f) c or m	37.5 Gy de (2.2 Gy/f) c or m	37.5 Gy de (2.3 Gy/f) c or m	None	CMFP+ovarian RT or 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) Axillary sampling (1,119)	36-50 Gy (1.8-2.2 Gy/f)	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	tam
82Q ECOG EST3181	MRM or RM	Axillary dissection (332)	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 Germanv	Patev	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, Mel=melphalan, MRM=modified radical mastectomy, NS=surgery not specified in detail (Patey mastectomy, or 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; <b>12</b> : 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; <b>48</b> : 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; <b>3</b> : 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; <b>16</b> : 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; <b>19</b> : 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; <b>28A</b> : 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; <b>10</b> : 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; <b>18</b> : 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; <b>43</b> : 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; <b>337</b> :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; <b>98</b> : 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. <i>Br J Cancer</i> 1997; <b>75</b> : 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; <b>21</b> (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; <b>35</b> : 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. <i>Radiother Oncol</i> 2009; <b>90</b> : 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; <b>353</b> : 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; <b>90</b> : 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; <b>79</b> : 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. <i>Eur J Cancer</i> 2002; <b>38</b> : 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; <b>20</b> : 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 recurrence, 5 recurrences of any type and 5 breast cancer deaths were reported among the 9 pN0 women with tumours  $\geq$  5 cm who were allocated to receive radiotherapy. 0 locoregional recurrences, 3 recurrences of any type and 4 breast cancer deaths were reported among the 11 pN0 women with tumours  $\geq$  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.)

# 700 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 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





-21.7/222.2

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. ( $r_1$  = 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

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#### 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.

Locoregional recurrence first (years 0-9)									Any	first r	recu	irren	ice (yeai	rs 0-9)	Breast cancer mortality							
Category	Allocated RT	Allocated No RT	Logrank O-E	Varlance of O–E	<u>Ratio of annu</u> RT	ial event rates ∶No RT	Rate Ratio (Standard Error)	Category	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of annua	al event rates No RT	Rate Ratio (Standard Error)	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)
(a) Age at entry ( $\gamma$	$a^2 = 0.7; 2p = 0$	.4)					- <b>8</b> -95% -≪>>95% CI	(a) Age at entry (γ	$^{2}_{1} = 0.6; 2p =$	0.5)					- <b></b> 95% CI	(a) Age at entry ( $\chi_1^2$	= 1.8; 2p =	0.2)				🖶 95% 🗢 95% CI
Age < 40 yrs	19/192	37/185	-12.1	11.4	_ <b></b>		0.35 (SE 0.18)	Age < 40 yrs	113/196	126/194	-11.4	41.4	<b>_</b>		0.76 (SE 0.14)	Age < 40 yrs	113/196	125/194	-12.1	45.9	— <u>—</u>	0.77 (SE 0.13)
Age 40 - 49 yrs	27/452	77/485	-23.6	24.1			0.38 (SE 0.13)	Age 40 - 49 yrs	209/461	262/496	-23.9	98.2	-8		0.78 (SE 0.09)	Age 40 - 49 yrs	213/461	274/496	-26.8	107.3	- <b>B</b> <u>-</u>	0.78 (SE 0.09)
Age 50 - 59 yrs	31/490	100/465	-36.5	29.9	<b>-</b>		0.30 (SE 0.11)	Age 50 - 59 yrs	273/500	296/481	-28.3	110.6	-#		0.77 (SE 0.08)	Age 50 - 59 yrs	284/500	287/481	-14.7	117.0	-##+	0.88 (SE 0.09)
Age 60+ yrs	22/385	76/403	-28.3	23.1	<b>-</b>		0.29 (SE 0.12)	Age 60+ yrs	207/393	256/410	-34.8	91.9			0.68 (SE 0.09)	Age 60+ yrs	222/393	255/410	-8.4	96.8		0.92 (SE 0.10)
(b) Tumour Grade	( χ <sub>1</sub> <sup>2</sup> = 0.1; 2p =	= 0.8)						(b) Tumour Grade	( χ <sub>1</sub> <sup>2</sup> = 0.0; 2p	= 0.9)						(b) Tumour Grade (	$\chi_1^2 = 0.1; 2p$	= 0.7)	-2.0	16.9		0.89 (SE 0.23)
Low grade	7/100	15/86	-4.6	4.2 -			0.33 (SE 0.30)	Low grade	42/102	40/86	-2.2	14.2			0.86 (SE 0.25)	Intermediate grade	102/188	140/199	-14.8	49.6	- <b>B</b> [	0.74 (SE 0.12)
High grade	8/136	35/139	-11.6	9.6 -			0.30 (SE 0.19)	High grade	86/136	101/139	-24.2	32.7		-	0.76 (SE 0.15)	High grade	88/136	99/139	-2.9	34.8		0.92 (SE 0.16)
Unknown grade	76/1095	184/1114	-55.7	58.3	Γ.		0.38 (SE 0.08)	Unknown grade	578/1124	660/1157	-55.4	238.5	(T)		0.79 (SE 0.06)	Unknown grade	595/1124	658/1157	-36.5	250.1	나비	0.86 (SE 0.06)
(c) Tumour size ( a	$c^2 = 0.0$ : 2p = 0	.9)						(c) Tumour size (γ	<sup>2</sup> = 3.0: 2p =	0.08)						(c) Tumour size ( $\chi_1^2$	= 1.1; 2p =	0.3)				
(c) tanteat eize ( )	10/224	49/240	-19.6	12.5 -			0.25 (SE 0.15)	1–19 mm	87/239	139/259	-23.7	43.0			0.58 (SE 0.12)	1-19 mm	106/239	146/259	-14.7	49.4		0.74 (SE 0.12)
20-49 mm	25/381	94/391	-36.7	26.4			0.25 (SE 0.11)	20-49 mm	239/399	261/415	-19.4	95.0			0.82 (SE 0.09)	20-49 mm	101/159	123/169	-3.9	37.5		0.90 (SE 0.16)
50+ mm	9/151	37/160	-11.4	8.6 -			0.27 (SE 0.19)	50+ mm	99/159	119/169	-5.8	33.4			0.84 (SE 0.16)	unknown	374/753	410/738	-30.5	152.9	-15-1	0.82 (SE 0.07)
unknown	55/753	111/738	-29.7	36.1	HD-		0.44 (SE 0.11)	unknown	377/753	421/738	-40.2	151.8	-[]		0.77 (SE 0.07)							
(d) Mastectomy ( )	$r_{1}^{2} = 0.1; 2p = 0$	.8)						(d) Mastectomy (χ	<sup>2</sup> = 0.9; 2p =	0.3)						(d) Mastectomy (χ <sub>1</sub>	= 0.1; 2p =	D.8)				
		•						Cimela		000/4075					0.70 (05.0.05)	Simple	716/1340	826/1375	-64.1	322.0		0.85 (SE 0.05)
Simple	90/1309	259/1332	-89.1	79.7			0.33 (SE 0.07)	Simple	700/1340	620/13/5	-02.2	302.1			0.70 (SE 0.00)	More extensive	116/210	115/206	-8.6	40.9		0.81 (SE 0.14)
More extensive	9/210	31/206	-10.3	8.4 —	•		0.29 (SE 0.20)	More extensive	102/210	112/206	-15.6	35.6			0.65 (SE 0.14)	(e) Axillary surgery	nformation	( $\chi^2_2$ = 0.5; p	o = 0.8)			
(e) Axillary surgery	information	( χ <sub>2</sub> <sup>2</sup> = 5.6; μ	o = 0.06)					(e) Axillary surgery	information	( χ <sub>2</sub> <sup>2</sup> = 0.5;	p = 0.8)					Trial protocol	258/502	268/495	-18.7	104.3		0.84 (SE 0.09)
Trial protocol	30/502	77/495	-24.5	23.5			0.35 (SE 0.13)	Trial protocol	245/502	264/495	-23.1	100.0			0.79 (SE 0.09)	Trial median	344/667	395/667	-31.5	157.6		0.82 (SE 0.07)
Trial median	54/667	125/667	-39.4	41.3	- <b>I</b> -		0.39 (SE 0.10)	Trial median	338/667	398/667	-46.0	146.9	-=		0.73 (SE 0.07)	Individual	230/381	278/419	-11.8	105.1	-##+-	0.89 (SE 0.09)
Individual	15/350	88/376	-36.6	23.6	∎		0.21 (SE 0.10)	Individual	219/381	278/419	-29.3	95.2	- <b>-</b>		0.74 (SE 0.09)	(f) Nodal status $(\gamma_{i}^{2})$	= 0.7: 2p =	0.4)				
(f) Nodal status (γ	$r^2 = 4.7$ ; 2p = 0	.03)						(f) Nodal status (γ	<sup>2</sup> = 1.5; 2p =	0.2)						pN1-3	248/632	325/682	-28.4	125.9	- <b>#</b> -	0.80 (SE 0.08)
nN1-3	19/625	112/669	-44.5	30.9			0.24 (SE 0.10)	pN1-3	211/632	304/682	-42.3	111.7	_ <b></b>		0.68 (SE 0.08)	pN4+	567/893	605/879	-31.7	237.2		0.87 (SE 0.06)
abld :	70/000	170/040	50.0				0.20 (05.0.00)	nN4+	575/893	624/879	-54.1	226.4			0.79 (SE 0.06)	pN?+	17/25	11/20	-1.9	3.9		0.61 (SE 0.40)
pN?+	2/25	172/849	-53.8	1.1			0.39 (SE 0.09) 0.14 (SE 0.41)	pN?+	16/25	12/20	-2.1	4.1			0.60 (SE 0.39)	(g) Any systemic the	rapy $(\gamma_4^2 =$	0.0; 2p = 0.9	9)			
							,	(a) Any system is th		0 2. 2 0	e)					No systemic	96/149	89/127	-6.5	33.1	— <u> </u>	0.82 (SE 0.16)
(g) Any systemic th	herapy $(\chi_1^2 = 4)$	.8; 2p = 0.	03)				0.40 (05.0.40)	(g) Any systemic tr	ierapy (χ <sub>1</sub> =	u.z; zp = u.	-10.5	27.0	_		0.60 (SE 0.16)	Chemo and/or ER+tam+	736/1401	852/1454	-53.8	330.6		0.85 (SE 0.05)
No systemic	1/149	23/12/	-10.9	5.3 -			0.13 (SE 0.18)	Champ and/as EB stams	704/4404	10/12/	-10.5	21.3			0.05 (SE 0.16)							
Chemo and/or ER+tam+	98/1370	267/1411	-89.1	82.7	<b>—</b>		0.34 (SE 0.07)	Cherio and/or ER+tain+	721/1401	002/1404	-07.0	312.5			0.70 (GE 0.03)	(h) Radiotherapy do	se ( $\chi_1^2 = 0.5$	; 2p = 0.5)			<u>L</u>	
(h) Radiotherapy d	ose $(\chi_4^2 = 0.5;$	2p = 0.5)						(h) Radiotherapy d	ose ( $\chi_1^2 = 0.4$	; 2p = 0.5)						50+ Gy	317/579	384/636	-18.0	143.7		0.88 (SE 0.08)
50+ Gy	35/548	123/593	-44.1	35.9	<b>.</b>		0.29 (SE 0.10)	50+ Gy	314/579	406/636	-45.3	137.1			0.72 (SE 0.07)	<50 Gy	515/971	557/945	-44.0	223.3	• <b>•</b> •	0.82 (SE 0.06)
<50 Gy	64/971	167/945	-56.5	52.5	<b>.</b>		0.34 (SE 0.08)	<50 Gy	488/971	534/945	-53.1	205.0			0.77 (SE 0.06)	(i) Date trial started	$(\chi_1^2 = 2.3; 2$	p = 0.1)				
					<b>—</b>								T			Started <1980	500/992	576/996	-51.0	218.4		0.79 (SE 0.06)
(i) Date trial started	i (χ <sub>1</sub> <sup>2</sup> = 3.0; 2μ	o = 0.08)						(i) Date trial started	$(\chi_1^2 = 0.6; 2)$	2p = 0.4)						Started 1980+	332/558	365/585	-10.9	148.6		0.93 (SE 0.08)
Started <1980	68/961	160/953	-51.1	52.1	<b>H</b>		0.38 (SE 0.09)	Started <1980	486/992	575/996	-66.6	207.2			0.73 (SE 0.06)							
Started 1980+	31/558	130/585	-49.4	36.4			0.26 (SE 0.09)	Started 1980+	316/558	365/585	-31.8	135.0			0.79 (SE 0.08)	(j) Period of follow-	up $(\chi_1^2 = 2.4)$	;2p = 0.1)				
		0 <b>1</b> 0						(i) Period of follow	$un (x^2 = 0.1$	· 2n = 0.7)						Years 0-4	520/6205	562/6382	-21.7	222.2		0.91 (SE 0.06)
(j) Period of follow-	$-up (\chi_1^- = 0.0;$	2p = 1.0)						() Feriod of follow-	$up(\chi_1 - 0.1)$	; 2p = 0.7)						Years 5-9 Years 10-14	196/3905 85/2608	233/3796	-23.5	89.3 38.5		0.77 (SE 0.09) 0.76 (SE 0.14)
Years 0-4	86/5335	256/5075	-88.6	77.9			0.32 (SE 0.07)	Years 0-4	677/5441	796/5241	-80.1	286.4			0.76 (SE 0.05)	Years 15-19	19/1544	33/1339	-4.6	11.4		0.67 (SE 0.24)
Years 5-9	13/3154	34/2714	-12.0	10.6 -	<b>—</b>		0.32 (SE 0.18)	Years 5-9	125/3221	144/2822	-18.3	55.8	_		0.72 (SE 0.11)	rears 20+	12/1022	14/864	-1.4	5.6		0.78 (SE 0.37)
																	0201	044				
_	99/	290/							802/	940/						Total	832/ 1550	941/ 1581	-62.0	367.0	0.84 (SE 0.05)	
Total	1519	1538	-100.5	88.5		0.32 (SE 0.06)		Total	1550	1581	-98.4	342.1	<b></b>	0.75 (SE 0.05)			(53.7%)	(59.5%)			2p= 0.001	
	(6.5%)	(18.9%)							(51.7%)	(59.5%)							2.		_			
Global between	iter u <sup>2</sup> - 22 4		e	L	<u> </u>			Global beterogenei	tv: v <sup>2</sup> = 14 a	. n > 0 1. N	IS	L		I		Global heterogeneit	γ: χ <sub>18</sub> = 12.7	; p > 0.1:N	s	0.0	0.5 1.0 15	2.0
Giobal neterogene	$\chi_{15} = 22.1;$	p = 0.1: N	3	0.0	0.5 1	1.0 1.5	2.0	Sisbai neteroyene	· · · · · · · · · · · · · · · · · · ·	, p - v.i. h		0.0	0.5 1.	0 1.5	2.0					•••	RT better	
					RT better 🛥	- RT worse							RT better 🛥 🚽	- RT worse								

# 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.

1314 nN1-3 women with Mast+ $\Delta D$ 

Loco	regio	nal re	ecu	rren	ce first (year	s 0-9)		Any fi	irst re	ecu	rren	ice (yea	rs 0-9)			Br	east	cance	r morta	ality	
Category	Events/ Allocated RT	Momen Allocated No RT	<u>RT ev</u> Logrank O-E	Variance of O-E	Ratio of annual event rates RT : No RT	Rate Ratio (Standard Error)	Category	Events/ Allocated RT	Women Allocated No RT	<u>RT er</u> Logrank O-E	vents Variance of O-E	Ratio of annu	al event rates No RT	Rate Ratio (Standard Error)	Category	Deaths Allocated RT	Women Allocated No RT	RT deaths Logrank Varlance O-E of O-E	Ratio of ann RT	ual death rates : No RT	Rate Ratio (Standard Err
a) Age at entry (;	$\chi_1^2 = 0.9; 2p = 0$	0.3)				- <b>8</b> -95% ≪>>95% CI	(a) Age at entry (	$c_{1}^{2} = 0.0; 2p = 0$	0.9)					-∰-95% -≪>>95% CI	(a) Age at entry (χ	= 1.1; 2p =	0.3)				<b>₩</b> 95% <b>&gt;&gt;</b> 951
ge < 40 yrs	5/75	20/74	-8.0	5.6 —	• I	0.24 (SE 0.22)	Age < 40 yrs	27/75	43/76	-9.1	13.8	_ <b>_</b>		0.52 (SE 0.20)	Age < 40 yrs	31/75	43/76	-8.6 15.1		-	0.57 (SE 0.20
ge 40 - 49 yrs	6/203	19/211	-6.3	6.1 -		0.36 (SE 0.25)	Age 40 - 49 yrs	59/204	72/217	-3.5	29.1	+		0.89 (SE 0.17)	Age 40 - 49 yrs	65/204	81/217	-5.0 33.2			0.86 (SE 0.16
ge 50 - 59 yrs	7/200	40/199	-15.8	11.1 -	—	0.24 (SE 0.16)	Age 50 - 59 yrs	74/205	99/203	-16.1	38.0			0.65 (SE 0.13)	Age 50 - 59 yrs	84/205	106/203	-11.0 43.6			0.78 (SE 0.13
ge 60+ yrs	1/147	33/185	-14.5	8.1 -	-	0.17 (SE 0.16)	Age 60+ yrs	51/148	90/186	-13.6	30.7			0.64 (SE 0.15)	Age out yis	68/148	95/186	-3.8 34.0			0.09 (3E 0.16)
b) Tumour Grade	$(\chi_1^2 = 0.0; 2p$	= 0.9)					(b) Tumour Grade	$(\chi_1^2 = 0.2; 2p)$	= 0.6)						(b) Tumour Grade	χ <sub>1</sub> <sup>2</sup> = 0.7; 2p	= 0.4)				
ow grade	4/64	7/48	-2.5	2.2 —		0.32 (SE 0.40)	Low grade	17/64	14/48	-0.9	6.2			- 0.86 (SE 0.37)	Low grade Intermediate grade	22/64 27/81	15/48 48/95	1.3 7.4 -8.1 16.5		-	
ligh grade	4/81	21/95 9/57	-7.5	2.3 -		0.26 (SE 0.23) 0.27 (SE 0.37)	Intermediate grade	26/81	45/95	-8.5	15.0			0.57 (SE 0.20)	High grade	20/50	29/57	-3.2 10.5			0.74 (SE 0.27
Inknown grade	10/430	75/469	-30.5	19.7	<u>1</u>	0.21 (SE 0.11)	Unknown grade	150/437	29/5/ 216/482	-28.5	9.5			0.69 (SE 0.10)	Unknown grade	179/437	233/482	-18.1 86.9	-11-1-	-	0.81 (SE 0.10)
	2			-				1001101				ų.		,	(c) Tumour size (γ	= 0.0; 2p =	0.9)				
c) iumour size (;	$\chi_1 = 0.0; 2p = 0$	5.9)		_			(c) Tumour size (	( <sup>2</sup> <sub>1</sub> = 3.1; 2p = 0	0.08)						1-19 mm	46/139	63/153	-6.4 23.2		<u> </u>	0.76 (SE 0.18
-19 mm	4/138	26/148	-10.4	7.0 —		0.23 (SE 0.20)	1-19 mm	27/139	60/153	-15.9	18.4			0.42 (SE 0.16)	20-49 mm	65/151	90/192	-3.1 33.1			0.91 (SE 0.17
10-49 mm 10+ mm	5/148	37/187	-13.6	9.6 -		0.24 (SE 0.17) 0.15 (SE 0.43)	20-49 mm	63/151	88/192	-4.1	31.0	∔∎		0.88 (SE 0.17)	50+ mm	12/35	17/31	-2.3 5.2			0.64 (SE 0.35
nknown	8/307	44/306	-17.1	12.0 -	<u>†                                    </u>	0.24 (SE 0.15)	50+ mm	12/35	17/31	-2.5	4.9			0.60 (SE 0.35)	unknown	125/307	155/306	-13.8 59.3		†	0.79 (SE 0.12)
	2						unknown	109/307	139/306	-17.8	52.8	-41		0.71 (SE 0.12)	(d) Mastectomy ( $\chi$	= 0.2; 2p =	0.7)				
d) Mastectomy (;	$\chi_1^* = 0.3; 2p = 0$	0.6)		_			(d) Mastectomy (	$c_1^2 = 0.0; 2p = 0$	0.9)						Simple	195/514	258/557	-24.1 99.6		_	0.79 (SE 0.09
limple	18/507	95/544	-37.4	26.6	·	0.25 (SE 0.10)	Simple	172/514	245/557	-33.5	90.2			0.69 (SE 0.09)	More extensive	53/118	67/125	-3.8 25.9			0.86 (SE 0.18)
fore extensive	1/118	17/125	-7.2	4.3 —		0.19 (SE 0.23)	More extensive	20/118	50/125	-8.2	21.1			0.68 (SE 0.18)					F		
e) Axillary surger	y information	$(\chi_2^2 = 1.1;)$	o = 0.6)				MOLE EXISTING	00/110		0.2	21.1	-		0.00 (02 0110)	(e) Axillary surgery	information	$(\chi_2^2 = 0.1;$	p = 1.0)	1		
rial protocol	8/277	42/281	-16.6	11.8 -	_	0.24 (SE 0.16)	(e) Axillary surger	/ information	$(\chi_2^2 = 0.2; \mu$	o = 0.9)					Trial protocol	113/277	140/281	-11.5 55.5		+	0.81 (SE 0.12)
rial median	9/212	38/234	-14.4	11.4 -		0.28 (SE 0.17)	Trial protocol	97/277	127/281	-16.7	49.8			0.72 (SE 0.12)	Trial median	83/212	112/234	-11.6 43.9		+	0.77 (SE 0.13)
ndividual	2/136	32/154	-13.6	7.8 -		0.17 (SE 0.17)	Trial median	69/212	104/234	-15.8	37.3	_		0.65 (SE 0.13)	Individual	52/143	/3/16/	-5.3 26.5			0.82 (SE 0.18)
		,		_			Individual	45/143	73/167	-9.8	24.5	<b>ā</b>		0.67 (SE 0.17)	(f) Number of posit	ve nodes (;	<sup>2</sup> = 0.2; 2p	= 0.7)			
<ol> <li>Number of posi</li> </ol>	tive nodes (χ	<sup>2</sup> = 0.2; 2p	= 0.7)	_	i l		(f) Number of posi	tivo nodoc ( u	2-11.20	- 0 2)					1 positive node	67/191	88/214	-7.7 32.4			0.79 (SE 0.16)
positive node	3/189	34/209	-14.2	8.8 -		0.20 (SE 0.17)	(i) Number of posi		4 - 1.1, AP	- 0.3)		_		0.04 (05.0.45)	2-3 positive nodes	100/223	124/230	-6.5 47.8		H	0.87 (SE 0.14)
-3 positive nodes	8/218	35/222	-13.1	9.2 -	+-	0.24 (SE 0.18)	1 positive node	48/191	80/214	-13.8	27.8			0.61 (SE 0.15)	Unknown but pN1-3	81/218	113/238	-11.4 41.5	-0-	+	0.76 (SE 0.14)
Inknown but pN1-3	8/218	43/238	-17.2	11.7 -	₽	0.23 (SE 0.15)	2-3 positive nodes	89/223	116/230	-9.8	41.3		_	0.79 (SE 0.14)	(a) Any systemic th	erany (v²=	$14 \cdot 2n = 0$	5)			
a) Any systemic t	herapy $(\gamma_{i}^{2} = \gamma_{i}^{2})$	I.1: 2p = 0.	3)				Unknown bac pivi-3	74/210	100/230	-16.5	30.4	- <u>-</u>		0.02 (GE 0.13)	No systemic	16/03	52/88	-21 218			0.91 (SE 0.20)
lo systemic	0/93	12/88	-5.7	2.	i	0.00 (SE 0.26)	(g) Any systemic t	herapy $(\chi_1^2 = 0)$	0.4; 2p = 0.4	5)					Chemo and/or ER+tam+	202/520	273/504	-25.9 103.7			0.78 (SE 0.09)
hemo and/or ER+tam+	19/532	100/581	-38.9	28.0		0.25 (SE 0.10)	No systemic	34/93	42/88	-4.1	16.8			0.78 (SE 0.22)	Cherro andror El Cramo	202353	210/304	20.0 100.7			0.10 (012 0.00)
				-			Chemo and/or ER+tam+	177/539	262/594	-38.2	94.5			0.67 (SE 0.08)	(h) Radiotherapy de	se ( $\chi_1^2 = 0.0$	; 2p = 1.0)				
h) Radiotherapy d	lose ( $\chi_1^2 = 0.9$	2p = 0.4)													50+ Gy	64/180	95/216	-7.5 33.1		+	0.80 (SE 0.16)
0+ Gy	3/173	43/203	-17.7	10.6 -	┣────│	0.19 (SE 0.15)	(h) Radiotherapy d	lose ( $\chi_1^2 = 0.2$	; 2p = 0.6)			i i			<50 Gy	184/452	230/466	-20.9 92.8	-#	_	0.80 (SE 0.09)
50 Gy	16/452	69/466	-26.8	20.3	-	0.27 (SE 0.12)	50+ Gy	55/180	97/216	-14.1	31.2	_ <b>_</b>		0.64 (SE 0.14)							
							<50 Gy	156/452	207/466	-28.2	80.4	-		0.70 (SE 0.09)	(i) Date trial started	$(\chi_1^2 = 2.0; 2$	p = 0.2)		_		
i) Date trial starte	d ( $\chi_1^- = 0.4; 2$	p = 0.5)		_								T			Started <1980	173/433	232/454	-27.2 88.6			0.74 (SE 0.09)
itarted <1980	15/426	68/441	-26.8	19.8	-	0.26 (SE 0.12)	(i) Date trial starte	d (χ <sub>1</sub> <sup>2</sup> = 1.1; 2	p = 0.3)						Started 1980+	75/199	93/228	-1.2 37.4		<b>_</b>	0.97 (SE 0.16)
tarted 1980+	4/199	44/228	-17.8	11.1 -	<b>-</b>	0.20 (SE 0.15)	Started <1980	145/433	208/454	-34.1	76.6			0.64 (SE 0.09)	(i) Period of follow-	$un (x^2 = 0.0$	2n = 0.9				
i) Period of follow	$-up (\gamma^2 = 0.2)$	2n = 0.7					Started 1980+	66/199	96/228	-8.1	35.1		_	0.79 (SE 0.15)	Years 0=4	444/2922	149/20164	-11 2 58 7			0.82 (SE 0.12
j) i chica ci ichica	$up(\chi_1 = 0.2)$	<b></b>		_											Years 5=9	76/2172	04/2255	-11.2 50.7		T_	0.84 (SE 0.15)
ears 0-4	15/2588	95/2633	-38.1	25.8		0.23 (SE 0.10)	(j) Period of follow	-up (χ <sub>1</sub> <sup>2</sup> = 0.3;	;2p = 0.6)						Years 10-14	35/1648	58/1630	-11.0 20.7			0.59 (SE 0.17
'ears 5-9	4/1876	17/1745	-6.5	5.1 —		0.28 (SE 0.25)	Years 0-4	157/2616	235/2686	-34.5	84.9	-		0.67 (SE 0.09)	Years 15-19 Years 20+	15/1080	13/986	0.9 6.1		-	
							Years 5-9	54/1898	69/1782	-7.8	26.7		_	0.75 (SE 0.17)	10110 201	11,000	12/0/	0.0 0.0	-		, oloo (on ol in)
	19/	112/										E E			_	248/	325/				
Total	625 (3.0%)	669 (16 7%)	-44.6	30.9 -	0.24 (SE 0. 2p < 0.0000	10)		244/	204/						Total	632	682	-28.4 125.9	4	- 0.80 (SE 0.08	š)
	(0.0 /0)	(					Total	632	682	-42.3	111.6	4	0.68 (SE 0.08)			(39.2%)	(47.7%)			ap=0.01	
lobal heterogene	eity: $\chi^2_{16} = 6.4$ :	p > 0.1: NS		L				(33.4%)	(44.6%)				2p = 0.00006		<b>O</b> lahal hata	2 _ 4 - 4				1	
Joine	~15 511			0.0	0.5 1.0 1.5	2.0									Global heterogenei	y: χ <sub>18</sub> = 11.4	; p > 0.1: N	5	0.5	10 15	2.0
																			0.0		

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.



10-year gain 14.6 % (SE 5.1) RR 0.62 (95% CI 0.45-0.85)

10

Years 5-9 2.82 (17/603) 3.95 (22/558) 0.66 SE 0.28 -3.5/8.3

logrank 2p = 0.003

20 yea

Years 0-4 0.69 (6/874) 4.17 (37/888 0.21 SE 0.16

-15.1/9.8

RT

10

Years 5-9 0.34 (2/594) 1.08 (6/556) 0.36 SE 0.46

4.9%

ates (%/year) and logrank analy

15

20 year

(O-E)/

10

Loco

(O-E)/\

-year gain 15.0 % (SE 5.2)

logrank 2p = 0.08

Years 15+ 1.24 (7/565) 0.62 (3/480) 2.57 SE 1.0 2.2/2.4

20 years

RR 0.76 (95% CI 0.56-1.03)

15

Years 10- . 1.95 (9/460) 4.71 (21/446) ^ 40 SE 0.26

15

10

Years 5-9 3.63 (26/716) 4.21 (31/736) 0.87 SE 0.26 -1.8/12.4

Yes. 4.00 (38/s. 5.37 (56/1 ^74 SE 0

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

	Events	Women	RT (	events	Botio of one	augl avant rates			Events	Women	RT e	vents	Botio of onnu	al avant rates	D.4. D.4.							
Category	RT	No RT	Cogrank O-E	of O-E	RT	No RT	(Standard Error)	Category	RT	No RT	O-E	of O-E	RT :	No RT	(Standard Error)		Death:	s/Women Allocated	RT d	leaths Variance	Ratio of annual death rate	S Rate Rati
(a) Age at entry ( )		0.7)						(a) Age at entry (	$\chi_1^2 = 0.3; 2p = 1$	0.6)						Category	RT	No RT	0-E	of O-E	RT : No RT	(Standard E
Age < 40 yrs	13/111	17/109	-4.1	5.8		+	0.49 (SE 0.30)	Age < 40 yrs	81/115	82/116	-2.8	26.9			0.90 (SE 0.18) 0.73 (SE 0.10)	(a) Age at entry (	$\chi^2_1 = 1.5; 2p =$	0.2)				<b>₽</b> -95% <b>~~~</b> 9
Age 40 - 49 yrs	21/241	55/266	-16.2	17.5			0.40 (SE 0.16)	Age 50 - 59 yrs	195/288	192/271	-10.1	71.5		_	0.87 (SE 0.11)	Age < 40 yrs	77/115	, 82/116	-4.4	30.3	<b>_</b>	0.86 (SE 0.1
Age 60+ vrs	21/234	43/215	-13.8	15.0			0.40 (SE 0.17)	Age 60+ yrs	154/241	163/221	-20.0	60.3	_∎⊏		0.72 (SE 0.11)	Age 40 - 49 yrs	142/249	189/271	-22.8	72.3	_ <b>∎</b> ÷	0.73 (SE 0.1
		10/11/0	1010		-		,		•							Age 50 - 59 yrs	196/288	177/271	-1.3	72.6		0.98 (SE 0.1
(b) Tumour Grade	( χ <sub>1</sub> <sup>2</sup> = 0.5; 2p	= 0.5)						(b) Tumour Grade	$(\chi_1^2 = 0.2; 2p)$	= 0.6)						Age 60+ yrs	152/241	157/221	-3.2	62.1		0.95 (SE 0.1
Low grade	3/36	8/37	-2.1	2.0			0.35 (SE 0.44)	Low grade Intermediate grade	25/38 68/104	26/37 93/103	-1.3 -15.0	8.0 28.0			0.85 (SE 0.33) 0.59 (SE 0.15)	(b) Tumour Grade	$(\gamma_{1}^{2} = 1.3; 2p)$	= 0.3)				
High grade	7/83	24/80	-7.8	7.1			0.33 (SE 0.23)	High grade	67/83	70/80	-4.0	23.0	_ <u>_</u> _		0.84 (SE 0.19)	Low grade	25/38	28/37	-3.3	9.3		0.70 (SE 0.2
Unknown grade	64/646	106/629	-24.9	38.1			0.52 (SE 0.12)	Unknown grade	415/668	435/659	-25.5	158.8	1		0.85 (SE 0.07)	Intermediate grade High grade	73/104	91/103 68/80	-6.0	32.9		0.83 (SE 0.1 1 05 (SE 0.2
								(a) Tumour aire (	2-06.2n -	0 <i>4</i> )						Unknown grade	403/668	418/859	-17.0	161.1		0.90 (SE 0.0
(c) Tumour size (	ℓ <sub>1</sub> <sup>2</sup> = 0.0; 2p =	1.0)						(c) fumour size (	χ <sub>1</sub> = 0.0; 2p = -	70/108	-7.9	24 5	_	_	0.73 (SE 0.17)		400,000	110/000			<u>Li  </u>	(
1–19 mm	6/93	22/101	-8.1	6.5			0.29 (SE 0.22)	20-49 mm	171/242	170/218	-15.1	62.6			0.79 (SE 0.11)	(c) Tumour size (	$\chi_1^2 = 0.9; 2p =$	0.3)				
20-49 mm	19/227	55/199	-22.1	16.3			0.26 (SE 0.14)	50+ mm	86/123	101/137	-3.2	28.5			0.89 (SE 0.18)	1–19 mm	. 59/97	83/106	-8.3	26.2	<b>_</b>	0.73 (SE 0.1
50+ mm	//118	31/131	-9.2	23.6			0.29 (SE 0.21) 0.59 (SE 0.16)	unknown	259/431	274/418	-21.6	96.5			0.80 (SE 0.09)	20-49 mm	180/242	168/218	0.6	71.8		1.01 (SE 0.1
unknown	40/451	04/410	-12.3	23.0			0.00 (02 0.10)		2-0.8. 0	• •						50+ mm	88/123	105/137	-1.6	32.3		0.95 (SE 0.1
(d) Mastectomy ()	( <sup>2</sup> = 0.1; 2p =	0.7)						(d) Mastectomy (	χ <sub>1</sub> = 0.6; 2p = 1	0.4)			<u></u>			unknown	240/431	249/418	-16.1	91.8	-47	0.84 (SE 0.1
Cimela		450,5770	40.5	54.0			0.20 (PE 0.00)	Simple	514/803	574/803	-47.5	208.3			0.80 (SE 0.06)	(d) Mastectomy (	$\gamma_{4}^{2} = 0.2; 2p =$	0.6)				
Simple	70/7/9	109/773	-49.5	51.9			0.39 (SE 0.09)	More extensive	61/90	50/76	-6.6	14.1		-	0.63 (SE 0.21)							
More extensive	8/90	13/76	-3.1	4.1			0.47 (SE 0.35)	(e) Axillary surge	v information	$(\gamma_{1}^{2} = 0.9)$	p = 0.7)					Simple	506/803	559/803	-29.0	219.0		0.88 (SE 0.0
(e) Axillary surgery	y information	( χ <sub>2</sub> <sup>2</sup> = 5.6;	p = 0.06	)				Trial protocol	139/212	129/201	-5.7	47 7			0.89 (SE 0.14)	More extensive	61/90	46/76	-3.9	14.6		0.77 (SE 0.2
Trial protocol	21/212	32/201	-7.6	11.3			0.51 (SE 0.22)	Trial median	262/443	290/426	-28.8	107.9			0.77 (SE 0.08)	(e) Axillary surger	y informatior	$\chi_2^2 = 0.3;$	p = 0.8)			
Trial median	44/443	84/426	-23.2	29.3	-		0.45 (SE 0.13)	Individual	174/238	205/252	-19.5	70.7			0.76 (SE 0.10)	Trial protocol	136/212	122/201	-6.5	46.9	<b>_</b>	0.87 (SE 0.14
Individual	13/214	56/222	-23.0	15.8	∎⊣		0.23 (SE 0.13)						7			Trial median	253/443	278/426	-18.7	111.6		0.85 (SE 0.0
		2			-			(f) Number of pos	itive nodes ()	χ <sup>2</sup> <sub>1</sub> = 0.0; 2p	= 0.9)					Individual	178/238	205/252	-6.5	78.6		0.92 (SE 0.1
(f) Number of posi	tive nodes (;	( <sup>2</sup> = 0.0; 2p	= 0.8)		_			4-9 positive nodes	183/279	189/263	-16.9	69.0	-#		0.78 (SE 0.11)			2				
4-9 positive nodes	20/267	60/246	-22.8	17.9	- <b>B</b> +		0.28 (SE 0.13)	10+ positive nodes	159/213	180/218	-15.3	57.9			0.77 (SE 0.12)	(f) Number of posi	tive nodes (	$\chi_1^2 = 0.5; 2p$	= 0.5)			
10+ positive nodes	15/201	52/205	-18.4	15.3	- <b>-</b>		0.30 (SE 0.15)	Unknown but pN4+	233/401	255/398	-17.1	92.3			0.83 (SE 0.10)	4-9 positive nodes	190/279	198/263	-11.2	76.2		0.86 (SE 0.1
Unknown but pN4+	43/401	60/398	-11.1	22.6		-	0.61 (SE 0.17)	(a) Amy avatamia	theremy $(u^2 -$	1 2. 2 0	2)					10+ positive nodes	166/213	177/218	-1.5	65.1		0.98 (SE 0.1)
	horopy $(w^2 -$	26.20-0	06)					(g) Any systemic	47/58	1.3, 2p = 0	• <b>2)</b> -64	11.1			0.56 (SE 0.23)	Unknown but pN4+	211/401	230/398	-11.1	87.2	-444	0.88 (SE 0.1)
No systemic	1/56	11/20	-53	25			0.12 (SE 0.26)	Chemo and/or ER#tam#	528/837	598/840	-47.4	213.0			0.80 (SE 0.06)	(a) Any systemic t	herapy $(\gamma^2 =$	0.8: 2n = 0	.4)			
Chomo and/or ER+tam+	77/912	161/010	-49.0	52.6			0.41 (SE 0.09)	Change and Change	010001	0001040	40.4	210.0	<b>—</b>		0100 (011 0100)	No systemic	50/56	37/39	-4.4	11.3		0.68 (SE 0.2
Chemo anajor Enviante	111013	101/010	40.0	55.0	-		0.41 (02 0.00)	(h) Radiotherapy	dose ( $\gamma_4^2 = 0.5$	; 2p = 0.5)						Chemo and/or ER+tam+	517/837	568/840	-26.0	223.1		0.89 (SE 0.0
(h) Radiotherapy d	lose $(\gamma^2 = 0.4$	: 2p = 0.6)						50+ Gv	257/307	306/415	-30.4	105.4			0.75 (SE 0.08)							
(ii) reaction of up y a		, <b>_p</b> = 0.0,					0.05 (05.0.40)	307 Gy	2011381	300/413	-30.4	100.4			0.00 (00 0.00)	(h) Radiotherapy of	dose $(\chi_1^2 = 0.4$	4; 2p = 0.5)				
50+ Gy	32/373	79/385	-26.4	25.3			0.35 (SE 0.12)	<50 Gy	318/496	318/464	-23.7	120.9	-		0.62 (SE 0.08)	50+ Gv	251/397	287/415	-9.7	110.2		0.92 (SE 0.0
<50 Gy	46/496	93/464	-27.5	31.1	-		0.41 (SE 0.12)	(i) Date trial starte	ed $(\gamma_1^2 = 0.0; 2$	(p = 0.9)						<50 Gv	216/406	219/464	-22.0	127.0		0.84 (SE 0.0
(i) Doto trial starts	$d (u^2 - 40, 2)$	n = 0.05)						01-1-1 -1000		050/507		408.0			0.79 (PE.0.09)	-50 Gy	310/480	310/404	-22.0	127.0	_	0.04 (32 0.0
(i) Date trial started	u (χ <sub>1</sub> -4.0, 2	p = 0.05)			_			Staned < 1960	327/536	356/52/	-31.2	120.9			0.76 (SE 0.08)	(i) Date trial starte	d ( $\chi_1^2 = 0.6$ ;	2p = 0.4)				
Started <1980	51/512	87/497	-22.2	31.1			0.49 (SE 0.13)	Started 1980+	248/357	266/352	-22.9	99.4			0.79 (SE 0.09)	Started < 1980	312/538	335/527	-22.7	126.4		0.84 (SE 0.0
Started 1980+	27/357	85/352	-31.6	25.3	- <b>₩</b> ÷		0.29 (SE 0.11)	(i) Period of follow	$v - up (\gamma_{1}^{2} = 0.8)$	: 2p = 0.4)						Started < 1960	312/030	330/02/	-22.1	120.4		0.04 (OE 0.0
() <b>D</b>	1 2							<b>u</b> ,					<u>i</u>		( )	Started 1980+	255/357	2/0/352	-9.0	110.8		0.92 (SE 0.0
(j) Period of follow	$-up (\chi_1^{-} = 0.0)$	; 2p = 0.9)			<u> </u>			Years 0-4	508/2741	549/2487	-42.8	197.8			0.81 (SE 0.06)	(i) Period of follow	-up $(\gamma_{1}^{2} = 4.3)$	2:20 = 0.04	)			
Years 0-4	69/2663	155/2375	-48.3	50.9	-		0.39 (SE 0.09)	Years 5-9	67/1286	75/1010	-11.3	28.6			0.67 (SE 0.15)	0,			, 			
Years 5-9	9/1241	17/937	-5.5	5.5	- <b>T</b>		0.37 (SE 0.27)									Years 0-4	400/3278	406/3237	-7.9	163.1		0.95 (SE 0.0
								_	575/	624/						Years 5-9 Years 10-14	115/1678 47/931	137/1499 40/770	-17.3	51.1 17.1	-∎	0.71 (SE 0.1 0.99 (SE 0.2
								Total	893	879	-54.1	226.4	*	0.79 (SE 0.06)		Years 15-19	4/450	20/343	-5.5	5.3 -		0.35 (SE 0.2
Total	78/ 869	172/	-53.8	56.5	4	0.39 (SE 0.09)			(64.4%)	(71.0%)						idars 20+	1/166	2/98	-0.8	0.6		≫ 0.20 (SE 0.7
Total	(9.0%)	(20.3%)	00.0	00.0	T	2p < 0.00001					_	L										
						1 .		Global heterogen	eity: χ <sub>15</sub> = 8.9;	p > 0.1: N	5	0.0	0.5 1	0 1.5	2.0		567/	605/				
Global heterogene	ity: $\chi^2_{10} = 18.0$	; p > 0.1: N	IS	L	i I							0.0	BT better	- RT worse		Total	893 (63.5%)	879 (68.8%)	-31.7	237.3	0.87 (SE 20=0.	0.06)
	- ~10			0.0	0.5	1.0 1.5	2.0						it south -	111 10100			(03.3%)	(00.0%)			i l	
					RT better	- RT worse											. 2			L		
						•										Global heterogene	əπy: χ <sub>18</sub> = 18.	9; p > 0.1: N	15			

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.



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



Rate rat

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, 11 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 not to receive radiotherapy.





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.)



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	RT e	vents		
Year code,	Treatment	Allocated	Allocated	Logrank	Variance	Ratio of annu	al event rates
and study name	Information	RT	No RT	0-E	of O-E	RT :	No RT
a) Avillany dissoction						1	₽99% ₽95% 0
a) Annaly dissection	•						
AB Oslo X-ray	CW+AF+IMC	2/175	2/174	0.0	1.0 —		>
4D DFCI Boston	TCW+AF+(IMC)	) 0/8	0/2				
		0/1	0/1	47		1	
OA S Sweden II. I		0/134	3/144 0/E	1.7	2.2		-
28 DBCG 82b inremenon	TCW+AF+IMC	1/8	0/5	0.4	0.2	i	
32C DBCG 82c ipostmenop.	TCW+AF+IMC	0/6	0/12	0.4	0.2	: I	-
2Q ECOG EST3181	†CW+AF+IMC	0/9	0/4				
		Q/	5/			-	
(a) Subtotal		346	352	21	3.5		
		(2.6%)	(1.4%)		0.0	1.81 (SE 0.73)	
		(2.070)	(1.470)			2p > 0.1: NS	
b) Axillary sampling						:	
'1B Stockholm A	CW+AF+IMC	4/203	30/196	-13.2	8.2 –		
3A Southampton UK	CW+AF+IMC	3/23	4/29	0.5	1.4 -		
'4B Edinburah I	CW+AF	5/114	24/114	-9.6	6.9 —		
2B DBCG 82b inremenon	+CW+AE+IMC	0/36	4/53	-1 9	0		
32C DBCG 82c ipostmenop.	+CW+AF+IMC	2/49	10/53	-3.5	2.5	<b>•</b>	
	1	2,10		0.0	2.0	-:	
		14/	72/			-	
(b) Subtotal		425	445	-27.8	19.9 -		0.25 (SE 0.12)
		(3.3%)	(16.2%)				2p < 0.00001
c) Extent of axillary s	surgery unkn	iown				:	
6C CRC, UK	†Various	0/14	1/10	-0.7	0.2		
		0/	1/				
<ul> <li>(c) Subtotal</li> </ul>		14	10	-0.7	0.2		
- (0) 00010101		(0.0%)	(10.0%)	0.7	0.2		0.00 (SE 0.67)
		(0.070)	(10.070)			-	2p > 0.1: NS
						; I	
		23/	78/			:	
Total		785	807	-26.4	23.6	$\Leftrightarrow$	0.33 (SE 0.12)
		(2.9%)	(9.7%)			<u>!</u>	2p < 0.00001
						;	
		. 2			L		1
leterogeneity betwee	en 3 subtota	als: χ <sub>2</sub> = 12	.5; p=0.0	02			
leterogeneity within	subtotals: χ	<sup>2</sup> <sub>6</sub> = 5.8; p	> 0.1: NS		0.0	0.5 1.	0 1.5 2
leterogeneity betwee	on 9 trials:	$v^2 = 18.3$	p = 0.02			RT better	- RT worse
Second Second Second		A.g = 10.0,					

# Any first recurrence (years 0-9)

		Events/Women			vents		
Year code,	Treatment	Allocated	Allocated	Logrank	Variance	Ratio of annu	al event rates
and study name	Information	RT	No RT	0-E	of O-E	RT	No RT
(a) Axillary dissection	n						- <b>₩</b> -99% <b>&lt;&gt;&gt;</b> 95% Cl
64B Oslo X-ray	CWAAEAIMC	29/175	20/17/	-5.1	16.1		
		20/1/5	30/1/4	-0.1	0.1		
74D DFCI Boston 76C Glasgow		1/8	1/2	-0.3	0.2-	•	
77 I MD Ander 7730B	+CW+AF+IMC	0/1	0/1	0.5	0.2 -	i	
784 S Sweden II:1	+CW+AF+IMC	34/134	27/144	47	14 7	1	
70G Motoxee Athene	+CW+AE+IMC	2/5	2//144		0.4		
82B DBCG 82b intemenon	+CW+AF+IMC	2/3	2/10	0.7	1.0		
82C DBCG 82c ipostmenop.	+CW+AF+IMC	4/6	3/12	17	1.0		
82Q ECOG EST3181	†CW+AF+IMC	2/9	1/4	-0.4	0.5-		>
		75/	73/			1	
(a) Subtotal		347	353	20	34 5		T
(a) custom		(21 6%)	(20 7%)	2.0	04.0	1.06 (SE 0.18)	
		(21.070)	(20.770)			2p > 0.1: NS	
(b) Axillary sampling						1	
71B Stockholm A	CW+AF+IMC	39/203	61/196	-13.1	23.4		
73A Southampton UK	CW+AE+IMC	8/23	11/20	0.1	3.6		
74B Edinburgh I	CWUAE	0/25	40/44.4	_7 5	15.0	<b>•</b>	-
PAR DRCC 82h intermenen		27/114	40/114	-7.5	15.0		
826 DBCG 826 incomenop.		3/36	14/53	-3.9	3.2		
oze DBCG oze iposimenop.		17/49	24/03	-2.3	0.7		
		94/	150/			1	
(b) Subtotal		425	445	-26.8	54.6	~	0.61 (SE 0.11)
		(22.1%)	(33.7%)				2p = 0.0003
(c) Extent of axillary	surgery unkn	own				1	
86C CRC, UK	†Various	2/14	4/10	-1.4	1.4 -		>
		21	A.			1	
- (a) Subtatal		21	4/				
(c) Subtotal		14	10	-1.4	1.4		0.29 (SE 0.52)
		(14.3%)	(40.0%)			1	2p > 0.1: NS
		171/	227/				
Total		786	808	-26.1	90.6	$\sim$	0.75 (SE 0.09)
		(21.8%)	(28.1%)				2p = 0.006
Heterogeneity betwee	en 3 subtota	l <b>s:</b> χ <sub>2</sub> <sup>2</sup> = 7.0	0; p=0.03	1		• •	
Heterogeneity within	subtotals: $\chi^2$	$\frac{1}{11} = 11.3;$	p > 0.1: NS	3	0.0	0.5 1	.0 1.5 2.0
Heterogeneity betwee	en 14 trials:	$\chi^2_{13} = 18.3$	; 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.

#### 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

### Any first recurrence (years 0-9)



		Events	Women	RT e	vents		
Year code,	Treatment	Allocated	Allocated	Logrank	Variance	Ratio of annu	al event rates
and study name	Information	RT	No RT	0-е	of O-E	RT	No RT
(a) Axillary dissection	n						- <b>■</b> -99% <b>&lt;&gt;&gt;</b> 95% CI
64B Oslo X-rav	CW+AF+IMC	53/110	53/93	-10.2	19.7	<b>_</b> '	L
74D DFCI Boston	†CW+AF+(IMC)	55/103	62/105	-1.6	23.7		
74Q Piedmont OA (pN4+)	†CW+AF+IMC	41/65	40/55	-2.6	14.9		
76A SECSG 1	†CW+AF+IMC	62/126	83/129	-10.8	28.6		<del> -</del>
76C Glasgow	†CW+AF+IMC	61/110	63/100	-6.5	25.0		<u> </u>
77J MD Ander. 7730B	TCW+AF+IMC	22/31	24/43	6.4	6.5		>
78A S Sweden II:1	TCW+AF+IMC	90/225	119/228	-25.1	43.0		
78G BCCA vancouver		/1/163	88/153	-16.2	32.8		
70Q Dusseldon U.		17/34	21/04	-2.5	7.4		•
80S Heleinki	+CW+AF+IMC	14/20	22/30	-3.5	5.0		
82B DBCG 82b inremenon	+CW+AF+IMC	100/103	135/207	-21.0	45.7		-
82C DBCG 82c ipostmenon	+CW+AF+IMC	97/157	119/169	-13.8	43.0		L
82Q ECOG EST3181	†CW+AF+IMC	100/161	88/157	5.6	38.5		
		802/	940/			1	
(a) Subtotal		1550	4 5 0 4	-00 4	242.4		0.75 (SE 0.05)
(a) Subtotal		(51 7%)	(59 5%)	-90.4	342.1		2p < 0.00001
(b) Avillary sampling		(01.176)	(00.078)				
THE OLIVINE A	0.00	00//10	0.4/404	40.0	<b>00 4</b>	_ !	
71B Stockholm A	CW+AF+IMC	60/118	84/121	-18.9	28.4		
74B Edipburgh I		15/33	34/30	-12.5	0.3	_ <b>_</b> ;	
77 I MD Ander 7730B		4/7	5/10	0.5	02-	1	
79F Coimbra	+CW+AF+IMC	27/62	38/61	-4.7	11.5		
82B DBCG 82b ipremenop.	†CW+AF+IMC	245/517	326/493	-71.4	117.1	_ <b>_</b>	
82C DBCG 82c ipostmenop	tCW+AF+IMC	213/401	256/406	-33.3	97.6		
84A GBSG 03 Germany	+CW+AF+IMC	35/96	53/100	-7.0	18.2		
85F Nottingham	†CW+AF	22/36	34/41	-6.5	10.6		<u> </u>
		621/	830/				
(b) Subtotal		1270	1271	-153.5	292.0	$\Rightarrow$	0.59 (SE 0.05)
		(48.9%)	(65.3%)	10010	20210		2p < 0.00001
(c) Extent of axillary	surgery unkr	lown					
80W NSABC Israel	†CW+AF+IMC	22/54	22/58	-0.9	9.5		<b>├</b> ───>
86C CRC, UK	†Various	11/17	10/20	-0.5	2.5		>
		33/	32/			1	
(c) Subtotal		71	78	-1.4	12.0		
(-,		(46.5%)	(41.0%)				0.89 (SE 0.27) 2p > 0.1: NS
		1456/	1802/				
Total		2891	2030	-253.3	646 1	<b>•</b>	0.68 (SE 0.03)
Total		(50.4%)	(61.5%)	200.0	040.1	Ť	2p < 0.00001
						1	
Heterogeneity betwee	en 3 subtote	$ds \cdot x^2 = 0$	9· n = 0.00	7	L	1 1	
Heterogeneity within	subtotals: ~	<sup>2</sup> . = <b>47.1</b>	p = 0.0009		0.0	0.5 1	.0 1.5 2.
Heterogeneity betwe	en 24 trials:	$\gamma_{20}^2 = 56.9$	): p = 0.000	01		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.

#### Webfigure 30 cntd.

# 5821 pN+ women

#### **Breast cancer mortality**

#### Any death



		Deaths	women	RId	eaths		
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of annu RT	al death rates : No RT
(a) Axillary dissection	า						
64B Oslo X-rav	CWAAEAIMC	101/110	85/03	-5.2	35.0		
74D DECI Boston	+CW+AF+(IMC)	) 57/103	55/105	3.0	22.8		
74Q Piedmont OA (pN4+)	+CW+AF+IMC	41/65	41/55	-1.6	15.2	! <b>_</b>	-
76A SECSG 1	+CW+AF+IMC	60/126	69/129	-3.2	26.9		
76C Glasgow	+CW+AF+IMC	77/110	81/100	-7.4	31.4	<b>_</b> ;	
77J MD Ander, 7730B	TCW+AF+IMC	24/31	24/43	6.5	7.2		
78A S Sweden II:1	+CW+AF+IMC	149/225	161/228	-16.1	67.5	<b></b>	<b>L</b>
78G BCCA Vancouver	+CW+AF+IMC	89/163	100/153	-15.5	42.1		Ļ
78Q Düsseldorf U.	+CW+AF+IMC	17/34	24/54	3.3	7.8		• · · · ·
79G Metaxas Athens	TCW+AF+IMC	11/25	21/36	-3.4	5.9		
80S Helsinki	+CW+AF+IMC	24/47	25/52	1.5	9.0		•
82B DBCG 82b ipremenop.	+CW+AF+IMC	111/193	144/207	-17.0	54.7		+
82C DBCG 82c ipostmenop	+CW+AF+IMC	122/157	131/169	-1.1	54.1		
82Q ECOG EST3181	†CW+AF+IMC	118/161	112/157	4.2	50.0		▋
(a) Subtotal		1001/ 1550 (64.6%)	1073/ 1581 (67.9%)	-52.1	430.4	₽ -	0.89 (SE 0.05) 2p = 0.01
(b) Axillary sampling		(•,	(011070)				
71B Stockholm A	CW+AF+IMC	93/118	104/121	-11.2	42.6	<b>_</b> _	
73A Southampton UK	CW+AF+IMC	28/33	32/38	-3.5	11.1		
74B Edinburgh I	CW+AF	0/0	1/1				
77J MD Ander, 7730B	†CW+AF+IMC	5/7	6/10	0.0	0.5 —		l
79F Coimbra	†CW+AF+IMC	41/62	42/61	1.7	14.9		
82B DBCG 82b ipremenop.	†CW+AF+IMC	284/517	328/493	-47.2	134.4	_ <b></b>	
82C DBCG 82c ipostmenop	+CW+AF+IMC	272/401	307/406	-24 7	127.2		
844 GBSG 03 Germany	+CW+AE+IMC	45/06	48/100	13	10.0		
85F Nottingham	†CW+AF	23/36	30/41	-3.6	11.0		-
(b) Subtotal		791/ 1270 (62.3%)	/898 1271 (70.7%)	-87.1	361.6	\$	0.79 (SE 0.05) 2p < 0.00001
(c) Extent of axillary	surgery unkr	nown					
80W NSABC Israel	†CW+AF+IMC	23/54	20/58	1.6	8.9	<u> </u>	<b>⊢</b> ∎;
86C CRC, UK	†Various	13/17	13/20	0.0	3.4		
		36/	33/				
(c) Subtotal		71	79	16	12 2		
		(50.7%)	(42.3%)	1.0	12.5	1.14 (SE 0.30)	
Total		1828/ 2891 (63.2%)	2004/ 2930 (68.4%)	-137.6	804.3	- <b>♦</b>	0.84 (SE 0.03) 2p < 0.00001
					L		
Heterogeneity betwee	en 3 subtota	als: $\chi_2^2 = 3.9$	9; p>0.1:	NS	_		
Heterogeneity within	subtotals: χ	<sup>2</sup> <sub>21</sub> = 27.9;	p > 0.1: NS	3	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.

RT better

- RT worse

# 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,	Treatment	Allocated	Allocated	Logrank	Variance	Ratio of ann	nual event rates
and study name	Information	RI	NORI	0-E	OF U-E	RT	NORI
(a) Axillary dissection	ı						- <b></b> 99% <->95% CI
64B Oslo X-rav	CW+AE+IMC	0/80	6/73	-3.1	1.9	1	
74D DFCI Boston	†CW+AF+(IMC)	1/37	3/41	-0.9	1.0	•	>
76A SECSG 1	†CW+AF+ÌMC	0/1	0/0			1	
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 —		
82B DBCG 82b ipremenop.	†CW+AF+IMC	1/83	13/79	-6.3	3.1 —	1	
82C DBCG 82c ipostmenop.	†CW+AF+IMC	1/53	19/75	-7.3	4.7 —		
82Q ECOG EST3181	†CW+AF+IMC	1/34	2/36	-0.6	0.7 ——	•	>
		19/	112/			i	
(a) Subtotal		625	669	-44 5	30.9 <		0.24 (SE 0.10)
(1)		(3.0%)	(16.7%)	- 110			2p < 0.00001
(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	<b>-</b>	
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/			1	
(b) Subtotal		700	600	74.0	45.0	1	0.21 (SE 0.07)
(b) Subtotal		122	690	-/1.3	45.8 <		2p < 0.00001
		(4.2%)	(23.5%)				
(c) Extent of axillary	surgery unkn	lown					
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		20	27	-27	22-	·	0.18 (SE 0.32)
		30	3/	-3.7	2.2	1	2p = 0.01
		(3.3%)	(24.3%)			1	
		501	0001			1 1 1	
		50/	283/			1	
Total		1377	1396	-119.6	78.8 <	₽	0.22 (SE 0.06)
		(3.6%)	(20.3%)			i	20 < 0.00001
Heterogeneity betwee	en 3 subtota	$1s: \chi_2^2 = 0.3$	3; p > 0.1:	NS		•	· · ·
Heterogeneity within	subtotals: y	<sup>2</sup> / <sub>4</sub> = 7.1: n	> 0.1: NS		0.0	0.5	1.0 1.5 2.0
Heterogeneity betwee	an 17 triple:	$x^2 = 75$	n > 0 1 · N	19		RT better	- RT worse
uereindeneith netmei	en in undis:	λ <sub>16</sub> - 1.3;	h - 0.1: V	0			

### Any first recurrence (years 0-9)

		Events	Women	RT e	vents		
Year code,	Treatment	Allocated	Allocated	Logrank	Variance	Ratio of annu	ual event rates
and study name	Information	RT	No RT	0-Е	of O-E	RT	: No RT
(a) Auditan dia satis							- <b></b> 99%
(a) Axillary dissection	n					1	
64B Oslo X-ray	CW+AF+IMC	29/80	35/73	-4.2	14.6		
74D DFCI Boston	†CW+AF+(IMC)	12/37	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	; <b>=</b>	
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		<b> </b>
79G Metaxas Athens	†CW+AF+IMC	3/7	6/11	-1.2	1.2 —		>
80S Helsinki	†CW+AF+IMC	7/29	18/38	-3.1	5.5		
82B DBCG 82b ipremenop.	†CW+AF+IMC	22/83	30/79	-6.9	11.0	<b>_</b> _;	<b>+</b>
82C DBCG 82c ipostmenop.	. †CW+AF+IMC	18/53	36/75	-4.5	12.2		<u> </u>
82Q ECOG EST3181	†CW+AF+IMC	19/34	12/36	6.4	6.3	!	<b>&gt;</b>
		211/	304/			i	
(a) Subtotal		632	692	-42.3	111 7		0.68 (SE 0.08)
(d) Oubtotal		(22 40/)	(44 00/)	42.5			2p = 0.00006
		(33.4%)	(44.0%)			!	
(b) Axillary sampling							
71B Stockholm A	CW+AF+IMC	21/43	25/42	-3.3	9.7	i_	
77.1 MD Ander, 7730B	+CW+AF+IMC	3/4	3/4	0.5	0.2 —	i T	>
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 inostmenon		112/245	122/240	-17.7	55.5		
8/A GBSG 03 Germany		16/60	133/240	-17.7	00.0		T
OHA OBOO 05 Opiniany		10/02	24/07	-4.0	0.0		
<b>—</b>		303/	390/			i	
(b) Subtotal		726	694	-67.7	152.8	₽	0.64 (SE 0.07)
		(41.7%)	(56.2%)			1	2p < 0.00001
(c) Extent of avillary	surgery unkn	own	(,				
(c) Extent of axinary a	surgery unki					1	
80W NSABC Israel	TCW+AF+IMC	12/20	15/19	-2.4	5.6		
BOC CRC, UR	various	5/10	0/10	0.2	2.2		1
		17/	23/			i	
(c) Subtotal		30	37	-22	79		
- (0) Cabiotai		(56 70/)	(62.20/)		1.5		0.76 (SE 0.31)
		(30.7%)	(02.2%)				2p > 0.1: NS
						!	-
		504/	747/			i	
		531/					
Total		1388	1413	-112.2	272.3	$\diamond$	0.66 (SE 0.05)
		(38.3%)	(50.7%)			1	2p < 0.00001
Heterogeneity betwee	an 3 cubtots	$de: \alpha^2 = 0$	1	NG		I '	
include of the second s		$\lambda_2 = 0.4$	τ, με υ.ι.		0.0	0.5	10 15 2
Heterogeneity within	subtotals: χ	<sub>16</sub> = 25.3;	p = 0.07		0.0	0.5	
Heterogeneity betwee	en 19 trials:	$\chi_{18}^2 = 25.7$	;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.

# 2801 pN1-3 women

### **Breast cancer mortality**

### Any death

		Deaths	/Women	RTd	eaths					Deaths	/Women	RT d	leaths		
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O–E	Variance of O-E	Ratio of annu RT	al death rates	Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of annual RT :	l death rates No RT
(a) Axillary dissectio	n						₩99% ₩95%	(a) Axillary dissection	on						-∎-99% <->95% Cl
64B Oslo X-ray 74D DFCI Boston 76A SECSG 1 76C Glasgow 77J MD Ander. 7730B 78A S Sweden II:1 78G BCCA Vancouver 79G Metaxas Athens 80S Helsinki 82B DBCC 82c ipostmenop. 82C DBCC 82c ipostmenop. 82C BCC 82c ipostmenop.	CW+AF+IMC †CW+AF+(IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC	41/80 9/37 0/1 33/70 5/7 48/140 34/91 3/7 9/29 25/83 22/53 19/34	45/73 12/41 0/0 42/69 7/13 75/155 45/92 6/11 16/38 31/79 35/75 11/36	-2.0 0.2 -4.1 0.6 -14.0 -6.8 -1.1 -1.1 -5.3 -0.6 5.8	19.5 4.6 15.8 1.3 27.3 19.0 1.2 5.4 12.5 12.7 6.7			64B Osio X-ray 74D DFCI Boston 76A SECSG 1 76C Glasgow 77J MD Ander. 7730B 78A S Sweden II:1 78G BCCA Vancouver 79G Metaxas Athens 80S Heisinki 82B DBCG 82b ipremenop 82C DBCG 82c ipostmeno 82Q ECOG 82c ipostmeno	CW+AF+IMC CW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC TCW+AF+IMC D, TCW+AF+IMC D, TCW+AF+IMC TCW+AF+IMC	71/80 ) 14/37 0/1 45/70 5/7 80/140 41/91 3/7 10/29 26/83 33/53 24/34	65/73 12/41 0/0 52/69 7/13 99/155 49/92 6/11 20/38 36/79 45/75 16/36	1.4 2.0 -3.2 0.6 -11.2 -6.4 -1.1 -0.6 -7.8 0.5 7.1	29.6 5.4 20.6 1.3 40.1 21.4 5.9 13.9 17.8 8.8		
(a) Subtotal		248/ 632 (39.2%)	325/ 682 (47.7%)	-28.4	125.9		0.80 (SE 0.08) 2p = 0.01	(a) Subtotal		352/ 632 (55.7%)	407/ 682 (59.7%)	-18.7	166.0		0.89 (SE 0.07) 2p ≥ 0.1: NS
(b) Axillary sampling	I					i i		(b) Axillary sampling	g						
71B Stockholm A 77J MD Ander. 7730B 79F Coimbra 82B DBCG 82b ipremenop.	CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC	23/43 4/4 8/28 152/344	32/42 3/4 13/29 188/322	-1.6 0.0 -1.7 -28.6	12.8 0.5 4.5 78.4			71B Stockholm A 77J MD Ander. 7730B 79F Coimbra 82B DBCG 82b ipremenop	CW+AF+IMC †CW+AF+IMC †CW+AF+IMC 0. †CW+AF+IMC	32/43 4/4 15/28 175/344	35/42 3/4 18/29 194/322	-0.9 0.0 -1.0 -23.2	15.1 0.5 — 7.1 85.2		>
82C DBCG 82c ipostmenop 84A GBSG 03 Germany	+CW+AF+IMC	126/245	138/240	-12.1	59.6 7.8			82C DBCG 82c ipostmeno 84A GBSG 03 Germany	P. †CW+AF+IMC	165/245	176/240	-14.5	77.9 9.4		-
(b) Subtotal		329/ 726 (45.3%)	394/ 694 (56.8%)	-45.6	163.5		0.76 (SE 0.07) 2p = 0.0004	(b) Subtotal		413/ 726 (56.9%)	447/ 694 (64.4%)	-39.2	195.3		0.82 (SE 0.06) 2p = 0.005
(c) Extent of axillary	surgery unk	nown				:		(c) Extent of axillary	surgery unk	nown					
80W NSABC Israel 86C CRC, UK	†CW+AF+IMC †Various	12/20 6/10	13/19 7/18	-1.1 0.5	4.9 2.2		•	<ul> <li>80W NSABC Israel</li> <li>86C CRC, UK</li> </ul>	†CW+AF+IMC †Various	12/20 7/10	13/19 11/18	-1.1 0.1	4.9 2.9	B'	> >
■ (c) Subtotal		18/ 30 (60.0%)	20/ 37 (54.1%)	-0.6	7.1		0.92 (SE 0.36) 2p > 0.1: NS	■ (c) Subtotal		19/ 30 (63.3%)	24/ 37 (64.9%)	-0.9	7.8		0.89 (SE 0.34) 2p > 0.1: NS
Total		595/ 1388 (42.9%)	739/ 1413 (52.3%)	-74.6	296.5		0.78 (SE 0.05) 2p = 0.00001	Total		784/ 1388 (56.5%)	878/ 1413 (62.1%)	-58.8	369.0	÷	0.85 (SE 0.05)
Heterogeneity betwe	en 3 subtot	als: $\chi_2^2 = 0$ .	4; p > 0.1:	NS	0.0	0.5	.0 1.5	Heterogeneity betwee	een 3 subtot	als: $\chi_2^2 = 0.$	7; p > 0.1:	NS	0.0	0.5 1.0	1.5 2.0
Heterogeneity betwe	en 19 trials:	ι χ <sub>16</sub> = 15.0; χ <sub>18</sub> = 15.4	p>0.1:N: l;p>0.1:	NS		RT better	RT worse	Heterogeneity within	een 19 trials:	$\chi^2_{18} = 17.1;$ $\chi^2_{18} = 17.8$	р>0.1: N: 3; р>0.1:	S NS	-10	RT better -	

† 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



+ 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.

# 2557 pN4+ women

**Breast cancer mortality** 

#### Any death

	Women	RT d	leaths	<ul> <li>Ratio of annual death rates</li> </ul>				Deaths/	Women	RT d	eaths	Defie of one			
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of annua RT :	No RT	Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of annua	No RT
(a) Axillary dissection	n						- <b></b> 99% →95% CI	(a) Axillary dissectior	n						- <b></b> -99% <b></b> 95% CI
<ul> <li>(4) Abstarback</li> <li>(4) ObCl Boston</li> <li>(4) Piedmont OA (pN4+)</li> <li>(6) SECSG 1</li> <li>(7) MD Ander. 7730B</li> <li>(7) MD Ander. 7730B<!--</td--><td>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</td><td>27/30 30/55 36/65 54/125 30/40 18/24 58/85 37/60 14/34 8/18 11/16 79/110 81/104</td><td>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</td><td>-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</td><td>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</td><td></td><td> &gt;  &gt;  &gt;</td><td>64B Oslo X-ray 74D DFCI Boston 74Q Piedmont OA (pN4+) 76A SECSG 1 76C Glasgow 77J MD Ander. 7730B 78A S Sweden II:1 78G BCCA Vancouver 78Q Düsseldorf U. 79G Metaxas Athens 80S Helsinki 82B DBCG 82b ipremenop. 82C DBCG 82c ipostmenop. 82Q ECOG EST3181</td><td>CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC</td><td>30/30 35/55 41/65 60/125 32/40 19/24 69/85 40/60 17/34 8/18 12/16 85/110 89/104 94/127</td><td>20/20 39/56 41/55 69/129 22/31 17/30 62/73 46/54 24/54 15/25 3/9 108/128 86/94 96/121</td><td>-6.6 0.9 -1.6 -3.2 -4.2 5.9 -7.9 3.3 -2.4 3.0 -9.2 -1.6 -2.9</td><td>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</td><td></td><td></td></li></ul>	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	27/30 30/55 36/65 54/125 30/40 18/24 58/85 37/60 14/34 8/18 11/16 79/110 81/104	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		> > >	64B Oslo X-ray 74D DFCI Boston 74Q Piedmont OA (pN4+) 76A SECSG 1 76C Glasgow 77J MD Ander. 7730B 78A S Sweden II:1 78G BCCA Vancouver 78Q Düsseldorf U. 79G Metaxas Athens 80S Helsinki 82B DBCG 82b ipremenop. 82C DBCG 82c ipostmenop. 82Q ECOG EST3181	CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC †CW+AF+IMC	30/30 35/55 41/65 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 22/31 17/30 62/73 46/54 24/54 15/25 3/9 108/128 86/94 96/121	-6.6 0.9 -1.6 -3.2 -4.2 5.9 -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		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 Coimbra 82B DBCG 82b ipremenop. 82C DBCG 82c ipostmenop 84A GBSG 03 Germany	†CW+AF+IMC †CW+AF+IMC †CW+AF+IMC •†CW+AF+IMC †CW+AF+IMC	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			77J MD Ander. 7730B 79F Coimbra 82B DBCG 82b ipremenop. 82C DBCG 82c ipostmenop. 84A GBSG 03 Germany	†CW+AF+IMC †CW+AF+IMC †CW+AF+IMC • †CW+AF+IMC †CW+AF+IMC	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) 2p = 0.009	(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 unkn	iown						(c) Extent of axillary s	surgery unkr	nown					
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—		• • > >	80W NSABC Israel 86C CRC, UK	†CW+AF+IMC †Various	11/34 6/7	7/39 2/2	2.7 -0.2	4.0 0.5—		<b>*</b>
■ (c) Subtotal		14/ 41 (34.1%)	9/ 41 (22.0%)	1.5	4.0	1.47 (SE 0.61) 2p > 0.1: NS		=     ● (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	<del>-</del>	0.85 (SE 0.05) 2p = 0.002	Total		912/ 1276 (71.5%)	978/ 1281 (76.3%)	-58.2	380.9		0.86 (SE 0.05) 2p = 0.003
Heterogeneity betwee	en 3 subtota	als: χ <sub>2</sub> <sup>2</sup> = 2.3	3; p>0.1:	NS	L	! <u> </u>	I	Heterogeneity betwee	en 3 subtota	als: χ <sub>2</sub> <sup>2</sup> = 3.7	7; p > 0.1:	NS	L	1 !	1
Heterogeneity within Heterogeneity betwee	subtotals: χ en 20 trials:	$\chi^{2}_{17} = 36.1;$ $\chi^{2}_{19} = 38.4$	p=0.004 ; p=0.005	5	0.0	0.5 1.0 RT better <del></del>	- 1.5 2.0	Heterogeneity within Heterogeneity betwee	subtotals: χ en 20 trials:	$\chi^{2}_{17}$ = 31.6; $\chi^{2}_{19}$ = 35.2	p = 0.02 ; p = 0.01		0.0	0.5 1.0 RT better <del>  </del>	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 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)								Any first recurrence (years 0-9)							
Year code, and study name	Treatment Information	Events/ Allocated RT	/Women Allocated No RT	<u>RT ev</u> Logrank O-E	vents Variance of O-E	Ratio of annua	al event rates No RT	Year code, and study name	Treatment Information	Events/ Allocated RT	Women Allocated No RT	<u>RT ev</u> Logrank O-E	ents Variance of O-E	Ratio of annu RT	al event rates : No RT
(a) Axillary dissectio	n					1 1	🖶 99% 🗢 95% CI	(a) Axillary dissection	n					1	- <b>■</b> -99%
74D DFCI Boston 78G BCCA Vancouver 80S 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-∎	-	>	74D DFCI Boston 78G BCCA Vancouver 80S Helsinki	†CW+AF+(IMC) †CW+AF+IMC †CW+AF+IMC	) 7/11 7/12 2/2	5/8 4/7 3/5	0.1 -1.4 -0.8	2.0 1.6 — 0.5—		<b>∎</b> → → → → →
■ (a) Subtotal		2/ 25 (8.0%)	6/ 20 (30.0%)	-2.2	1.1 <⊐		0.15 (SE 0.42) 2p = 0.04	(a) Subtotal		16/ 25 (64.0%)	12/ 20 (60.0%)	-2.1	4.1		0.61 (SE 0.39) 2p > 0.1: NS
(b) Axillary sampling								(b) Axillary sampling						i I	
71B Stockholm A	CW+AF+IMC	6/75	32/79	-15.0	8.6 -	<b>i</b>		71B Stockholm A	CW+AF+IMC	39/75	59/79	-15.6	18.7		
73A Southampton UK 74B Edinburgh I 79F Coimbra 82B DBCG 82b ipremenop.	CW+AF+IMC CW+AF †CW+AF+IMC †CW+AF+IMC	5/33 0/0 1/2 2/27	21/38 0/1 1/3 8/28	-8.7 0.5 -3.3	5.3 — 0.2 — 2.3 —		>	73A Southampton UK 74B Edinburgh I 79F Coimbra 82B DBCG 82b ipremenop. 82C DBCG 82c ipostmenop	CW+AF+IMC CW+AF †CW+AF+IMC †CW+AF+IMC 0. †CW+AF+IMC	15/33 0/0 2/2 3/27 6/29	34/38 0/1 3/3 10/28 4/26	-12.3 -4.0 1.1	8.3 - 3.0 - 2.2		<b>_</b> >
85F Nottingham	+CW+AF+IMC	2/29 6/36	4/26 20/41	-0.7 -6.9	1.2 — 5.7 —		~~~>	85F Nottingham	†CW+AF	22/36	34/41	-6.5	10.6		
(b) Subtotal		22/ 202 (10.9%)	86/ 216 (39.8%)	-34.0	23.4 -	Γ ϕ	0.23 (SE 0.11) 2p < 0.00001	(b) Subtotal		87/ 202 (43.1%)	144/ 216 (66.7%)	-37.2	42.8		0.42 (SE 0.10) ₂p < 0.00001
Total		24/ 227 (10.6%)	92/ 236 (39.0%)	-36.2	24.5 -	<del>(</del> )	0.23 (SE 0.11) 2p < 0.00001	Total		103/ 227 (45.4%)	156/ 236 (66.1%)	-39.2	46.9		0.43 (SE 0.10) ₂ <sub>p</sub> < 0.00001
Difference between treatment effects Heterogeneity within Heterogeneity betwe	in 2 subtota subtotals: χ en 8 trials:	als: χ <sup>2</sup> <sub>1</sub> = 0.2 <sup>2</sup> <sub>6</sub> = 6.7; p χ <sup>2</sup> <sub>7</sub> = 6.9; p	2; 2p > 0.1 > 0.1: NS > 0.1: NS	: NS	0.0	0.5 1. RT better	0 1.5 2.0	Difference between treatment effects Heterogeneity within Heterogeneity betwe	in 2 subtota subtotals: χ en 8 trials: ;	lls: χ <sup>2</sup> <sub>1</sub> = 0.8 <sup>2</sup> <sub>6</sub> = 10.4;	5; 2p > 0.1 > > 0.1: NS 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.

# 463 pN?+ women

#### **Breast cancer mortality**

### Any death

		Deaths/	Women	RT de	eaths					Deaths/	Women	RT de	aths		
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of annu RT	al death 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 death rates No RT
(a) Axillary dissection	n					1   	- <b>₽</b> 99% 95% CI	(a) Axillary dissection	n						- <b>₽</b> -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						i		(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 74B Edinburgh I 79F Coimbra 82B DBCG 82b ipremenop. 82C DBCG 82c ipostmenop	CW+AF+IMC CW+AF †CW+AF+IMC †CW+AF+IMC , †CW+AF+IMC	23/33 0/0 2/2 0/27 0/29	32/38 0/1 3/3 2/28 0/26	-5.0 -0.5 -0.9	10.4 0.2 0.5			73A Southampton UK 74B Edinburgh I 79F Coimbra 82B DBCG 82b ipremenop. 82C DBCG 82c ipostmenop	CW+AF+IMC CW+AF †CW+AF+IMC †CW+AF+IMC •, †CW+AF+IMC	28/33 0/0 2/2 0/27 0/29	32/38 1/1 3/3 2/28 0/26	-3.5 -0.5 -0.9	11.1 0.2 0. <del>5</del>		>
85F Nottingham (b) Subtotal	†CW+AF	22/36 91/ 202 (45.0%)	<sup>28/41</sup> 129/ 216 (59.7%)	-2.9 <b>-20.5</b>	10.3 <b>45.5</b>		0.64 (SE 0.12) 2p = 0.002	85F Nottingham (b) Subtotal	†CW+AF	23/36 114/ 202 (56.4%)	<sup>30/41</sup> 137/ 216 (63.4%)	-3.6 <b>-18.8</b>	11.0 <b>50.5</b>		0.69 (SE 0.12) <sub>2p = 0.008</sub>
Total		108/ 227 (47.6%)	140/ 236 (59.3%)	-22.4	49.4		0.64 (SE 0.11) ₂ <sub>P</sub> = 0.001	Total		132/ 227 (58.1%)	148/ 236 (62.7%)	-20.6	54.3		0.68 (SE 0.11) 2p = 0.005
Difference between treatment effects Heterogeneity within Heterogeneity betwe	in 2 subtota subtotals: χ en 8 trials: ;	lls: χ <sub>1</sub> <sup>2</sup> = 0.0 <sup>2</sup> <sub>6</sub> = 3.1; p χ <sub>7</sub> <sup>2</sup> = 3.1; p	); 2p > 0.1 > 0.1: NS > 0.1: NS	: NS	0.0	0.5 1 RT better —	.0 1.5 2.0	Difference between treatment effects Heterogeneity within Heterogeneity betwee	in 2 subtota subtotals: $\chi^2$ en 8 trials: $\gamma$	ls: χ <sub>1</sub> <sup>2</sup> = 0.0 <sup>2</sup> <sub>5</sub> = 3.0; p ζ <sub>7</sub> <sup>2</sup> = 3.0; p	); 2p > 0.1 > 0.1: NS > 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)

<u></u>		Events/	Events/Women		events					Events/	Women	RT e	vents		
Year code, and study name	Treatment Information	Allocated PT	Allocated	Logrank	Variance	Ratio of ann	ual event rates	Year code, and study name	Treatment Information	Allocated RT	Allocated	Logrank	Variance	Ratio of annu	al event rates
and study hame	mormation	NI NI	NORI	0-2	010-2				Information		NORI	01		KI	
(a) Axillary dissection	n					1	- <b></b> 99% <->95% Cl	(a) Axillary dissection	n					I I	
76A SECSG 1	†CW+AF+IMC	0/1	0/1			1		76A SECSG 1	†CW+AF+IMC	0/1	0/1			:	
76C Glasgow 78A S Sweden II:1	TCW+AF+IMC	1/1 0/22	0/6 2/18	0.7	0.2 -	1	>	76C Glasgow 77.I MD Ander 7730B	TCW+AF+IMC	1/1 3/4	4/6 0/0	0.1	0.4 —	1	• • • • • • • • • • • • • • • • • • •
78G BCCA Vancouver	†CW+AF+IMC	0/1	0/1	0.7	0.0-	1	2	78A S Sweden II:1	†CW+AF+IMC	7/22	5/18	1.0	2.8		<b></b> >
82Q ECOG EST3181	†CW+AF+IMC	0/1	0/0			1		78G BCCA Vancouver	†CW+AF+IMC	0/1	0/1			1	
		1/	2/			i i		620 E000 E010101	1011-AI -INO	441	0/0			:	
(a) Subtotal		26	26	-0.1	0.7 -		0.02 (SE 1.17)	(a) Subtotal		11/	9/	11	3 2		
		(3.8%)	(7.7%)				2p > 0.1: NS			(36.7%)	(34.6%)		5.2	1.41 (SE 0.67)	
(b) Axillary sampling						1		(b) Axillary sampling		. ,				2p > 0.1: NS	
71B Stockholm A 73A Southampton LIK	CW+AF+IMC	1/2 3/18	2/4 3/10	-0.5	0.2		~	71B Stockholm A	CW+AE+IMC	1/2	3/4	-0.5	0.2		
74B Edinburgh I	CW+AF	6/59	25/60	-9.3	70 -			73A Southampton UK	CW+AF+IMC	8/18	4/10	-0.9	1.6 -	• • ·	>
79F Coimbra	tCW+AF+IMC	0/0	0/1	0.0		-		74B Edinburgh I	CW+AF	24/59	33/60	-5.8	11.3	<b>B</b> ;	
82B DBCG 82b ipremenop.	+CW+AF+IMC	12/137	46/150	-17.1	13.1	_		79F Coimbra	†CW+AF+IMC	0/0	1/1			1	
000 DD00 00- in-street								82B DBCG 82b ipremenop.	†CW+AF+IMC	69/137	87/150	-9.0	32.8		
844 CBSC 02 Cormony		5/113	29/97	-13.9	8.0 -			82C DBCG 82c ipostmenop	. †CW+AF+IMC	61/113	62/97	-10.9	25.7		_
64A GBSG 05 Germany		0/2	0/1					84A GBSG 03 Germany	†CW+AF+IMC	1/2	0/1				
(b) Subtotal		27/	105/	-41.0	20.4	-	0.24 (SE 0.10)			164/	190/				
(b) Subtotal		(8.2%)	(32,5%)	-41.5	29.4	¥-	2p < 0.00001	(b) Subtotal		331	323	-27.1	71.6	 	0.68 (SE 0.10)
( .) <b>F</b>		(012 /0)	(021070)			1				(49.5%)	(58.8%)				2p = 0.001
(c) Extent of axillary	surgery unkr	iown						(c) Extent of axillary	surgery unk	nown				1	
86C CRC, UK	Tvarious	0/6	0/4					86C CRC, UK	†Various	2/6	1/4	0.1	0.7 —		• • >
(a) Subtatal		0/	0/			1				2/	1/				
(c) Subiolai		o (\%0.0)	4			1		<ul> <li>(c) Subtotal</li> </ul>		6	4	0.1	0.7		
		(0.0 %)	(0.0 %)							(33.3%)	(25.0%)			1.19 (SE 1.33) 2p > 0.1: NS	
		28/	107/												
Total		363	353	-42.0	30.1	4	0.25 (SE 0.10)			177/	200/				
		(7.7%)	(30.3%)		••••		2p < 0.00001	Total		367	353	-25.9	75.5	~	0.71 (SE 0.10)
		· ·	. ,							(48.2%)	(56.7%)				
Difference between					L										
treatment effects	in 2 subtota	als: $\chi_1^2 = 1.2$	2; 2p > 0.1	: NS	0.0	0.5	1.0 1.5 2.0	Heterogeneity betwe	en 3 subtot	als: $\chi_2^2 = 1.8$	3; p>0.1:	NS			
Heterogeneity within	subtotals: χ	<sup>2</sup> <sub>5</sub> = 4.5; p	> 0.1: NS			PT bottor	PT worro	Heterogeneity within	subtotals: 🤉	2 <sub>5</sub> <sup>2</sup> = 1.3; p	> 0.1: NS		0.0	0.5 1	.0 1.5 2.0
Heterogeneity betwe	en 7 trials:	$\chi_6^2 = 5.7; p$	> 0.1: NS			Ki better		Heterogeneity betwe	en 8 trials:	$\chi^2_7 = 3.1; p$	> 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.

# 720 pN? women

#### **Breast cancer mortality**

# Any death

Versional Transforment	Deaths	Women	RTd	leaths						Deaths	Women	RTd	eaths			
Year code,	Treatment	Allocated	Allocated	Logrank	Variance	Ratio of annu	al death rates		Year code,	Treatment	Allocated	Allocated	Logrank	Variance	Ratio of annu	al death rates
and study name	Information	RI	NORI	0-E	OT U-E	RT	NORI		and study name	Information	RI	NORI	0-е	or U-E	RT	NORI
(a) Axillary dissection	on					1	- <b>₩</b> -99% <>>95%	5 Cl	(a) Axillary dissection	n					1	- <b>₩</b> 99% 🗢 95% Cl
76A SECSG 1	†CW+AF+IMC	0/1	0/1			1			76A SECSG 1	†CW+AF+IMC	0/1	0/1			1	
76C Glasgow 77.1 MD Ander 7730B	†CW+AF+IMC †CW+AF+IMC	0/1 3/4	4/6 0/0	-0.6	0.4	1		>	76C Glasgow 77.I MD Ander 7730B	†CW+AF+IMC †CW+AF+IMC	0/1 3/4	5/6 0/0	-0.6	0.4		~~~>
78A S Sweden II:1	†CW+AF+IMC	11/22	6/18	3.3	3.6			>	78A S Sweden II:1	†CW+AF+IMC	19/22	11/18	4.9	6.7	<u> </u>	>
78G BCCA Vancouver	TCW+AF+IMC	0/1	1/1	-0.5	0.2-			>	78G BCCA Vancouver	†CW+AF+IMC	0/1	1/1	-0.5	0.2-		>
		1.4/	44/			1			62Q 2000 2313161		001	471			1	
(a) Subtotal		30	26	22	43				(a) Subtotal		22/	26	30	73	1 69 (SE 0 49)	
		(46.7%)	(42.3%)		4.0	1.69 (SE 0.64) 2p > 0.1: NS					(73.3%)	(65.4%)	5.5	7.5	2p > 0.1: NS	<u>.</u>
(b) Axillary sampling	g								(b) Axillary sampling	I					1	
71B Stockholm A	CW+AF+IMC	1/2	4/4	-0.5	0.2	• · · ·		>	71B Stockholm A	CW+AF+IMC	2/2	4/4	-0.5	0.2—	• · · ·	>
73A Southampton UK	CW+AF+IMC	10/18	4/10	-0.7	1./			>	73A Southampton UK	CW+AF+IMC	15/18	7/10	-0.8	2.6		→ ■
79E Coimbra	tCW+AF+IMC	0/0	30/00	0.0	10.0				74B Euliibuigii i	CW+AF +CW+AF+IMC	52/59	49/60	-0.6	20.9		
82B DBCG 82b ipremenor	. +CW+AF+IMC	67/137	83/150	-4 4	32.5				82B DBCG 82b intemenon	+CW+AF+IMC	76/137	95/150	-5.8	37.5		
		00//10/	00/100		02.0						10/13/	35/150	5.0	57.5		
82C DBCG 82c ipostmeno		63/113	64/97	-4.1	27.7				82C DBCG 82c ipostmenop	. †CW+AF+IMC	80/113	78/97	-6.4	34.1		
64A GBSG 03 Germany	TCW+AF+IMC	1/2	0/1						84A GBSG 03 Germany	TCW+AF+IMC	1/2	0/1				
(b) Subtotal		175/	194/	_0.9	77 0	i	0 99 (SE 0 11)		(b) Subtotal		226/	234/		05.4		0.96 (95 0.40)
		(52.9%)	(60.1%)	-9.0	11.0		2p > 0.1: NS		(b) Subtotal		(68.3%)	323 (72.4%)	-14.1	90.4		2p > 0.1: NS
(c) Extent of axillary	/ surgery unki	nown	(,						(c) Extent of axillary	surgery unk	nown	(1=1170)				
86C CRC. UK	tVarious	2/6	3/4	-0.2	0.9 -	<b>_</b> '		->	86C CRC UK	tVarious	3/6	3/4	0.2	11	I	_
	•	2/	3/			1				Transas	3/	-10 -1	0.2		1	
<ul> <li>(c) Subtotal</li> </ul>		6	4	-0.2	0.9				<ul> <li>(c) Subtotal</li> </ul>		5/	3/ A	02	11		
		(33.3%)	(75.0%)				0.79 (SE 0.94) 2p ≥ 0.1: NS		(-,		(50.0%)	(75.0%)	•		1.18 (SE 1.02) 2p > 0.1: NS	
															1	
Total		191/	208/	_7 0	02.0	1	0.01 (SE 0.10)		Tatal		251/	254/	40.0	402.0		0.04 (95.0.00)
Total		(52.0%)	(58,9%)	-7.0	02.9		2p > 0.1: NS		Iotai		307 (68.4%)	353 (72 0%)	-10.0	103.8		2p > 0.11 NS
		(0_1070)	(00.070)								(00.470)	(12.070)				
Heterogeneity betw	een 3 subtot	als: $v_1^2 = 1$	7∙n>01•	NS	L	i			Heterogeneity betwe	on 3 cubtot	ale: $\alpha^2 = 3$	2. 0 > 0 1.	NS	L		
Heterogeneity within	n subtotale: ^	$k_2^2 = 50$ n	> 0 1 NS		0.0	0.5 1	.0 1.5	2.0	Heterogeneity within	en o sublot	$\chi_2^2 = 1.7$	≤, µ ∽ 0.1: > 0 1· Ne	113	0.0	0.5 1	.0 1.5 2.0
Hotorogeneity with	oon Q trialou	<sub>26</sub> -3.0, μ	> 0.1. NO			RT better	- RT worse			on O friel-	<sub>6</sub> = 4.7; p	> 0.1: NO			PT better	PT worse
Hereingeneity betwe	een a triais.	<sub>λ8</sub> – υ.ο, μ	- 0.1. NO			iti batter			neterogeneity betwe	en s (rials:	<sub>χ8</sub> – 7.9; p	> 0.1: NS			iti bellei —	- 11 40150

† 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/	Total	Distribut	ion by ye	ars ('000s)	Chemotherany+	ER+ &
			woman	('000s)	<10	10-	20+	Chemotherapy <sub>+</sub>	Tamoxifen
Axillary dissection	465	355	17 3	8.0	3.0	26	15	3	0
pNo pN+	1029	678	6.5	10.1	5.5 6.6	2.0	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) ú	45 Gy (1.5-2.8 Gy/f) ú	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, or modified radical 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; <b>172</b> : 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. <i>J Exp Clin Cancer Res</i> 1984; <b>3</b> : 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. <i>Am J Clin Oncol</i> 1982; <b>5</b> : 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; <b>347</b> : 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; <b>19</b> : 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.





### 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**

		Deaths	Women	RT d	eaths		
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of annu RT	ial death rates :No RT
(a) Nodal radiothera	oy only, disse	ection					- <b>■</b> -99%
64E Oslo Co-60	AF+IMC	55/179	47/187	7.9	22.9		<b></b> >
69A Heidelberg XRT	AF+IMC	14/44	8/31	1.8	4.6		
74Q Piedmont OA (!pN4+)	†AF+IMC	1/4	4/9	-0.3	0.2—		,>
(a) Subtotal		70/ 227 (30.8%)	59/ 227 (26.0%)	9.4	27.8	1.40 (SE 0.23)	
(b) Some with chest	wall radiothe	rapy, disse	ection				
71D SASIB	(CW)+AF+IMC	2/6	2/5	0.0	0.5 —		• · · · · · · · · · · · · · · · · · · ·
■ (b) Subtotal		2/ 6	2/ 5	0.0	0.5 -		
		(33.3%)	(40.0%)			1.00 (SE 1.41) 2p > 0.1: NS	
Total		72/ 233	61/ 232	94	28.3	1.39 (SE 0.22)	
lota		(30.9%)	(26.3%)	0.4	20.0	2p = 0.08	
Difference between	in 2 subtots	$det w^2 = 0$	1. 2n > 0 1	• NS	L	I	
Heterogeneity within		$\lambda^2 = 0.8 \cdot n^2$	-, 2p - 0.1 > 0 1 · NS		0.0	0.5 1	.0 1.5 2.0
Ustors you sity between	$\lambda$ $\lambda$	$p_2^2 = 0.0, p_1^2$	> 0.1. NO			RT better 🗕	- RT worse
neterogeneity betwe	en 4 mais:	χ <sub>3</sub> = υ.8; p	20.1: NS				

V	<b>T</b> er - 4	Deaths/	Women	RT d	eaths	Patio of annu	al doath rates
and study name	Information	RT	No RT	Cogrank O-E	of O-E	RT	No RT
(a) Nodal radiothera	oy only, disse	ction					- <b>₩</b> -99%95% CI
64E Oslo Co-60	AF+IMC	154/179	134/187	28.7	61.9		
69A Heidelberg XRT 74Q Piedmont OA (!pN4+)	AF+IMC †AF+IMC	36/44 1/4	19/31 6/9	5.8 -0.3	12.1 0.2—	<b>.</b>	
(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 —		<u> </u>
<ul> <li>(b) Subtotal</li> </ul>		3/ 6 (50.0%)	2/ 5 (40.0%)	0.0	0.5 -	1.00 (SE 1.41) 2p > 0.1: NS	
Total		194/ 233 (83.3%)	161/ 232 (69.4%)	34.2	74.8	1.58 (SE 0.15) 2p = 0.00008	
Difference between					L	I	
treatment effects	in 2 subtotals: v	lis: χ <sub>1</sub> <sup>2</sup> = 0.1 <sup>2</sup> = 0.9: n.:	l;2p>0.1	: NS	0.0	0.5 1	.0 1.5 2.
leterogeneity betwe	en 4 trials:	2 <sup>2</sup> = 0.0, β γ <sub>2</sub> <sup>2</sup> = 1.0; β	> 0.1: NS			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.

#### 15 September 2014

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

#### Locoregional recurrence first (years 0-9)





Heterogeneity between 7 trials:  $\chi_6^2 = 10.4$ ; p > 0.1: NS

† 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)

1.5

RT worse

2.0

Ratio of annual event rates

RT : No RT

0.5

RT better

1.0

# 1029 pN+ women

### **Breast cancer mortality**

# Any death

		Deaths	/Women	RT d	eaths					Deaths	/Women	RT d	eaths			
Year code,	Treatment	Allocated	Allocated	Logrank	Variance	Ratio of annu	al death rates	Year code,	Treatment	Allocated	Allocated	Logrank	Variance	Ratio of ann	ual death ra	ates
and study name	Information	RI	NORI	0-E	of U-E	RI	NORI	and study name	Information	RI	NORI	0-е	OT U-E	RI	NORI	
(a) Nodal radiothera	py only, disse	ection					- <b></b> -99% <b>&gt;</b> 95% Cl	(a) Nodal radiothera	py only, disse	ction					- <b>-</b> 99	% 🗢 95% Cl
64E Oslo Co-60	AF+IMC	47/99	58/98	-8.7	22.1			64E Oslo Co-60	AF+IMC	88/99	79/98	-0.6	32.4			
69A Heidelberg XRT	AF+IMC	27/39	18/27	0.9	8.6		-∎>	69A Heidelberg XRT	AF+IMC	37/39	24/27	1.3	11.9		Ţ <b>ġ</b>	>
73E INT Milan 1	AF+IMC	9/15	4/7	1.5	2.1		<b></b> >	73E INT Milan 1	AF+IMC	11/15	5/7	1.5	2.1			>
74Q Piedmont OA (!pN4+)		32/67	18/61	6.5	11.0			74Q Piedmont OA (!pN4+)	†AF+IMC	38/67	23/61	6.8	12.8	·	1:	
78B Toronto-Edmont.	TAF+IMC	14/28	13/21	0.0	4.2		>	78B Toronto-Edmont.	†AF+IMC	15/28	13/21	0.5	4.4		╞	>
		129/	111/							189/	144/					
(a) Subtotal		248	214	0.2	48.0	1.00 (85.0.14)		(a) Subtotal		248	214	9.4	63.7	1.16 (SE 0.14) -		-
		(52.0%)	(51.9%)			2p > 0.1: NS				(76.2%)	(67.3%)			2p = 0.1. No		
(b) Some with chest	wall radiothe	rapy, diss	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+IM0	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	V	→1.00 (SE 0.10) 2p >0.1: NS	Total		369/ 531 (69.5%)	309/ 498 (62.0%)	10.9	130.8	1.09 (SE 0.09) - 2p > 0.1: NS		
Difference between					L	1		Difference between					L	I	1	
treatment effects	in 2 subtota	als: $\gamma_4^2 = 0.4$	0:2p>0.1	: NS				treatment effects	in 2 subtota	als: $\gamma_{4}^{2} = 0.5$	5:2p>0.1	: NS				
Heterogeneity within	subtotals:	$v^2 = 9.0 \cdot n$	> 0 1 NS		0.0	0.0 1	.0 1.0 2.0	Heterogeneity within	subtotals: v	$^{2} = 44 \cdot n$	> 0 1 · NS		0.0	0.0		1.5 2.0
Heterogeneity within		$^{2}-0.0, p$	- 0.11 NO			RT better 🛥	- RT worse	listene new site is store		2 – 4 0. –	> 0.1. NO			RT better 🗕	+ <del>-</del> RT w	vorse
neterogeneity betwe	en / triais:	$\chi_6 = 9.0; p$	> 0.1: NS					neterogeneity betwe	en <i>i</i> triais:	χ <sub>6</sub> = 4.9; p	> 0.1: NS					

† 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

Year code.	Treatment	Allocated	Allocated	Logrank	Variance	Ratio of ann	ual event rates
and study name	Information	RT	No RT	0-Е	of O-E	RT	: No RT
a) Nodal radiothera	oy only, disse	ction					- <b></b>
4Q Piedmont OA (!pN4+) 8B Toronto-Edmont.	†AF+IMC †AF+IMC	0/8 0/0	0/11 0/1				
(a) Subtotal		0/ 8 (0.0%)	0/ 12 (0.0%)				
b) Some with chest	wall radiothe	rapy, disse	ection				
1D SASIB	(CW)+AF+IMC	4/18	4/22	0.3	1.8		+>
(b) Subtotal		4/ 18 (22.2%)	4/ 22 (18.2%)	0.3	1.8	1.20 (SE 0.81) 2p > 0.1: NS	
Total		4/ 26 (15.4%)	4/ 34 (11.8%)	0.3	1.8	1.20 (SE 0.81) 2p > 0.1: NS	
leterogeneity betwe	en 1 subtota	als: $\chi_0^2 = 0.0$	); p>0.1:	NS	ــــ 0.0	0.5	i 1.0 1.5 2.0
						RT better	+ - RT worse

### 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.

# 810 pN? women

#### **Breast cancer mortality**

# Any death

Year code,	Treatment	 Allocated	Women Allocated	<u> </u>	eaths Variance	Ratio of annu	al death rates	Year code,
and study name	Information	RT	No RT	Ŏ-Е	of O-E	RT :	No RT	and study name
(a) Nodal radiothera	py only, disse	ction					- <b>₩</b> -99% <b>&lt;&gt;&gt;</b> 95% CI	(a) Nodal radiother
61H NSABP B-03*	AF+IMC	185/476	198/544	2.7	54.6			61H NSABP B-03*
69A Heidelberg XRT 74Q Piedmont OA (!pN4+) 78B Toronto-Edmont.	AF+IMC †AF+IMC †AF+IMC	0/2 5/8 0/0	0/0 5/11 1/1	0.6	1.8			69A Heidelberg XRT 74Q Piedmont OA (!pN4+ 78B Toronto-Edmont.
(a) Subtotal		190/ 486 (39.1%)	/204 556 (36.7%)	3.3	56.4	1.06 (SE 0.14)		(a) Subtotal
(b) Some with chest	wall radiothe	rapy, disse	ection					(b) Some with ches
71D SASIB	(CW)+AF+IMC	9/18	7/22	2.6	3.3		<u> </u>	71D SASIB
■ (b) Subtotal		9/ 18 (50.0%)	7/ 22 (31.8%)	2.6	3.3	2.22 (SE 0.84) 2p > 0.1: NS		■ (b) Subtotal
Total		199/ 504 (39.5%)	211/ 578 (36.5%)	5.9	59.8	1.10 (SE 0.14) 2p > 0.1: NS		Total
Difference between treatment effects	in 2 subtot	als: γ <sup>2</sup> = 1.3	7:2p>0.1	: NS	L 00			Difference betweer treatment effec
Heterogeneity within	subtotals: 2	<sup>2</sup> = 0.1; p	> 0.1: NS		0.0	U.Ə 1.	u 1.5 2.0	Heterogeneity with
Heterogeneity betwee	en 3 trials:	χ <sup>2</sup> <sub>2</sub> = 1.8; p	> 0.1: NS			RT better	RT worse	Heterogeneity betv

		Deaths/	Women	RT d	eaths			
Year code,	Treatment Information	Allocated	Allocated	Logrank	Variance	Ratio of annu	ual death rate	<u>s</u>
	monnation	N	Norki	0 2	010 2	KI	- NO KI	€ 95% Cl
(a) Nodal radiothera	oy only, disse	ction						- 00/001
61H NSABP B-03*	AF+IMC	303/476	334/544	1.2	89.8	_		
69A Heidelberg XRT 74Q Piedmont OA (!pN4+) 78B 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) 2p > 0.1: NS		
(b) Some with chest	wall radiothe	rapy, disse	ection					
71D 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) — 2p = 0.08		
Total		319/ 504 (63.3%)	347/ 578 (60.0%)	5.1	95.2	1.05 (SE 0.11)		
Difference between treatment effects	in 2 subtota	l <b>is:</b> χ <sub>1</sub> <sup>2</sup> = 2.9	); 2p = 0.0	9	L			
Heterogeneity within	subtotals: x	$^{2}_{1} = 0.2; p$	> 0.1: NS		0.0	U.3 1	1.0 1.5	2.0
Heterogeneity betwe	en 3 trials:	$\chi_2^2 = 3.0; p$	> 0.1: NS			RI better	H RI wor	se

\* 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.

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/	Total	Distribut	ion by ye	ars ('000s)	Chamotharany	ER+ &	Δηγ
			woman	('000s)	<10	10-	20+	Chemotherapy	Tamoxifen	Ally
Axillary dissection										
cN-	2896	2098	12.4	45.3	21.7	12.8	10.8	0	2	2
cN+	1481	1188	9.6	21.5	10.5	5.9	5.1	0	1	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; <b>18</b> : 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; <b>46</b> : 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; <b>70</b> : 1020–4.
78D Scottish D	Stewart HJ, Prescott RJ, Forrest AP. Scottish adjuvant tamoxifen trial: a randomized study updated to 15 years. J Natl Cancer Inst 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 node-negative (cN-) disease. See webfigure 1 for methodological note and also webfigure 43



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 nodepositive (cN+) disease. See webfigure 1 for methodological note and also webfigure 45



# 1481 cN+ women with Mast

90 80 Breast cancer mortality (%) 70 60 50 40 30 20 20-year gain 6.7 % (SE 2.8) RR 0.86 (95% CI 0.75-0.99) 10  $\log rank 2p = 0.03$ r 10 15 20 years 5 Breas mortality (%/year) and log ank analyses Years 0-4 Years 5-9 Years 10-14 Years 15-19 Years 20+ 6.60 (206/3123) 4.79 (104/2169) 2.34 (40/1709) 1.02 (28/2740) 2.76 (38/1379) RT No RT 7.54 (235/3116) 5.34 (110/2059) 3.41 (55/1611) 3.66 (45/1229) 1.23 (29/2358) 0.87 SE 0.09 0.72 SE 0.18 0.83 SE 0.21 0.89 SE 0.21 0.91 SE 0.14



(O-E)/V

-13.8/99.7

-4.4/48.3

-7.1/21.9

-3.5/18.5

-2.4/20.1

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)\*.

	Women	Deaths	Woman-years since diagnosis					% women given systemic therapy‡		
Nodal status†			Median/	Total	Distribution by years ('000s)			Chamatharapy	ER+ &	Δηγ
			woman	('000s)	<10	10-	20+	Chemotherapy	Tamoxifen	Ally
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; <b>36</b> : 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)

		Events	/Women	RTe	events						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 a	INNUAL RT : I	event rates	Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of annu	al event rates
(a) Mastectomy with	nout axillary s	urgery but	t with CW	radiothe	erapy			- <b>₽</b> -99%	(a) Mastectomy with	nout axillary s	urgery but	with CW r	adiothe	rapy		-∎-99% <>>95% CI
70B Kings/Cambridge	CW+AF+IMC	153/996	348/1049	-100.0	119.7				70B Kings/Cambridge	CW+AF+IMC	435/996	532/1049	-55.7	222.2	- <b>-</b>	
71C NSABP B-04 78D Scottish D	CW+AF+IMC †CW+AF+IMC	16/386 6/42	92/384 11/39	-40.1 -2.9	24.4 3.8				71C NSABP B-04 78D Scottish D	CW+AF+IMC CW+AF+IMC	139/386 19/42	178/384 15/39	-30.4 0.3	69.6 7.1		>
(a) Subtotal		175/ 1424 (12.3%)	451/ 1472 (30.6%)	-143.0	148.0	<del>Q</del>		0.38 (SE 0.05) 2p < 0.00001	(a) Subtotal		593/ 1424 (41.6%)	725/ 1472 (49.3%)	-85.9	298.9	· <del>\</del>	0.75 (SE 0.05) 2p < 0.00001
(b) Mastectomy with	nout axillary s	urgery and	d no CW ra	adiother	ару		(b) Mastectomy without axillary surgery and no CW radiotherapy									
85Z Tokyo CIH PS	†AF+IMC	0/3	1/5	-0.2	0.2—			>	85Z Tokyo CIH PS	†AF+IMC	3/3	3/5	1.2	0.9	i	> >
· (b) Subtotal		0/ 3	1/ 5	-0.2	0.2-				• (b) Subtotal		3/ 3	3/ 5	1.2	0.9		
		(0.0%)	(20.0%)					0.26 (SE 1.28) 2p > 0.1: NS			(100.0%)	(60.0%)	1.2		4.13 (SE 2.35) 2p > 0.1: NS	
Total		175/ 1427 (12.3%)	452/ 1477 (30.6%)	-143.2	148.2	·		0.38 (SE 0.05) 2p < 0.00001	Total		596/ 1427 (41.8%)	728/ 1477 (49.3%)	-84.6	299.8		0.75 (SE 0.05) 2p < 0.00001
Difference between treatment effect: Heterogeneity withi Heterogeneity betw	s in 2 subtota n subtotals:	als: $\chi_1^2 = 0.4$ $\chi_2^2 = 13.4; \mu_3^2 = 13.5;$	0; 2p > 0.1 p = 0.001 p = 0.004	I: NS	∟ 0.0	0.5 RT better —	1.0 -	1.5 2.0	Difference between treatment effects Heterogeneity within Heterogeneity betwe	s in 2 subtot n subtotals: ; een 4 trials:	als: $\chi_1^2 = 2.6$ $\chi_2^2 = 2.6; p$ $\chi_3^2 = 5.2; p$	6; 2p > 0.1 > 0.1: NS > 0.1: NS	: NS	ـــ 0.0	0.5 1 RT better	.0 1.5 2.0

† 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

#### Any death Deaths/Women RT deaths Deaths/Women RT deaths Allocated Logrank Variance Ratio of annual death rates Allocated Logrank Variance Ratio of annual death rates Allocated Allocated Year code Treatment Year code Treatment and study name Information RT No RT 0-е of O-E RT : No RT and study name Information RT No RT Ŏ-Е of O-E RT : No RT -∎-99% - 95% CI (a) Mastectomy without axillary surgery but with CW radiotherapy (a) Mastectomy without axillary surgery but with CW radiotherapy 70B Kings/Cambridge CW+AF+IMC 270.0 70B Kings/Cambridge CW+AF+IMC 740/996 355.4 523/996 590/1049 -3.7 762/1049 15.3 71C NSABP B-04 71C NSABP B-04 CW+AF+IMC 169/386 181/384 -6.5 81.3 CW+AF+IMC 279/386 266/384 11.9 124.1 78D Scottish D †CW+AF+IMC -0.2 7.6 78D Scottish D +CW+AF+IMC 18/42 17/39 24/42 27/39 1.0 10.2 710/ 788/ 1043/ 1055/ 0.97 (SE 0.05) (a) Subtotal (a) Subtotal 1.06 (SE 0.05) 1424 1472 -10.5 358.8 < 1424 1472 28.2 489.6 (49.9%) (53.5%) (73.2%) (71.7%) (b) Mastectomy without axillary surgery and no CW radiotherapy (b) Mastectomy without axillary surgery and no CW radiotherapy 85Z Tokyo CIH PS †AF+IMC 85Z Tokyo CIH PS 3/3 3/5 0.9 0.9 †AF+IMC 3/3 3/5 0.9 ΛQ 3/ 3/ 3/ 3/ (b) Subtotal (b) Subtotal . 3 5 0.9 0.9 3 0.9 0.9 -5 2.83 (SE 1.87) 2.83 (SE 1.87) (100.0%) (60.0%) (100.0%) (60.0%) 1058/ 713/ 791/ 1046/ 1427 1477 -9.6 359.7 0.97 (SE 0.05) 1427 1477 29.1 490.5 1.06 (SE 0.05) Total Total (50.0%) (53.6%) (71.6%) (73.3%) Difference between **Difference between** treatment effects in 2 subtotals: $\chi_1^2 = 1.0$ ; 2p > 0.1: NS treatment effects in 2 subtotals: $\chi_1^2 = 0.8$ ; 2p > 0.1: NS 0.0 0.5 1.5 2.0 0.0 0.5 2.0 1.0 10 1.5 Heterogeneity within subtotals: $\chi_2^2 = 0.3$ ; p > 0.1: NS Heterogeneity between 4 trials: $\chi_3^2 = 1.3$ ; p > 0.1: NS Heterogeneity within subtotals: $\chi_2^2 = 0.3$ ; p > 0.1: NS Heterogeneity between 4 trials: $\chi_3^2 = 1.1$ ; p > 0.1: NS RT better RT better RT worse RT worse

#### **Breast cancer mortality**

† 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 e	vents						Events	Women	RT e	vents		
Year code,	Treatment	Allocated	Allocated	Logrank	Variance	Ratio	of annu	al event rates	Year code,	Treatment	Allocated	Allocated	Logrank	Variance	Ratio of annu	al event rates
	intormation	NI	NUKI	0-2	010-2		RI			intormation	NI	NORI	0-2	010-2		
(a) Mastectomy with	nout axillary s	urgery but	t with CW ı	radiothe	rapy			- <b></b> 99% <->95% Cl	(a) Mastectomy with	nout axillary s	urgery but	with CW r	adiothe	rapy		- <b></b> 99%>95% CI
70A Manchester RBS1	CW+AF+IMC	49/355	120/359	-39.7	39.5	-			70A Manchester RBS1	CW+AF+IMC	140/355	192/359	-36.1	74.3		
70B Kings/Cambridge	CW+AF+IMC	66/380	168/375	-58.7	53.4	<b>_</b>			70B Kings/Cambridge	CW+AF+IMC	209/380	249/375	-36.7	98.5		
78D Scottish D	†CW+AF+IMC	1/5	3/7						78D Scottish D	CW+AF+IMC	3/5	4/7	0.5	0.2 —		>
(a) Subtotal		/116 740 (15.7%)	/291 741 (39.3%)	-98.3	92.9	+		0.35 (SE 0.06) 2p < 0.00001	(a) Subtotal		352/ 740 (47.6%)	445/ 741 (60.1%)	-72.3	173.0		0.66 (SE 0.06) 2p < 0.00001
(b) Mastectomy with	nout axillary s	urgery and	d no CW ra	diother	ару	i			(b) Mastectomy with	nout axillary s	urgery and	l no CW ra	diothera	ару		
85Z Tokyo CIH PS 88U Tokyo CIH N2	†AF+IMC †AF+IMC	7/47 6/50	11/45 7/50	-2.3 -0.6	3.7 3.1			<u> </u>	85Z Tokyo CIH PS 88U Tokyo CIH N2	†AF+IMC †AF+IMC	27/47 34/50	26/45 35/50	1.3 -2.4	9.8 12.4		
■ (b) Subtotal		13/ 97 (13.4%)	/18 95 (18.9%)	-3.0	6.8		<u>'</u>	0.64 (SE 0.31) 2p ≥ 0.1: NS	(b) Subtotal		61/ 97 (62.9%)	61/ 95 (64.2%)	-1.1	22.2		0.95 (SE 0.21) 2p > 0.1: NS
Total		129/ 837 (15.4%)	309/ 836 (37.0%)	-101.3	99.7	+		0.36 (SE 0.06) ₂ <sub>₽</sub> ≤ 0.00001	Total		413/ 837 (49.3%)	506/ 836 (60.5%)	-73.4	195.3		0.69 (SE 0.06) 2p < 0.00001
Difference between					L	i			Difference between					L		
treatment effect	s in 2 subtot	als: $\chi_1^2 = 2$ .	4;2p>0.1	: NS	0.0	0.5	1	.0 1.5 2.0	treatment effects	s in 2 subtot	als: $\chi_1^2 = 2$ .	7;2p>0.1	: NS	0.0	0.5 1	0 1.5 2.
Heterogeneity withi	n subtotals: 🤈	χ <sup>2</sup> <sub>2</sub> =0.5; p	> 0.1: NS			RT bette			Heterogeneity within	n subtotals: 🤉	χ <sup>2</sup> <sub>3</sub> = 2.6; p	> 0.1: NS			RT better	
Heterogeneity between 4 trials: $\chi_3^2 = 2.9$ ; p > 0.1: NS			AT belle		Heterogeneity between 5 trials: $\chi_4^2$ = 5.3; p > 0.1: NS				IT boller	11 10136						

† 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

#### Deaths/Women RT deaths Deaths/Women RT deaths Logrank Variance Ratio of annual death rates Allocated Logrank Variance Ratio of annual death rates Allocated hetecollA Allocated Year code. Treatment Year code. Treatment and study name Information RT No RT O-E of O-E RT : No RT and study name Information RT No RT O-E of O-E RT : No RT - 99% ↔ 95% CI (a) Mastectomy without axillary surgery but with CW radiotherapy (a) Mastectomy without axillary surgery but with CW radiotherapy 93.7 70A Manchester RBS1 CW+AF+IMC 178/355 215/359 -14.5 70A Manchester RBS1 CW+AF+IMC 274/355 286/359 -11 9 130.0 70B Kings/Cambridge 70B Kings/Cambridge CW+AF+IMC 235/380 255/375 -17.3 114.6 CW+AF+IMC 303/380 316/375 -14.4 140.5 78D Scottish D †CW+AF+IMC 3/5 4/7 0.5 0.2 78D Scottish D †CW+AF+IMC 5/5 4/7 0.5 0.2 416/ 474/ 582/ 606/ 0.91 (SE 0.06) 2p > 0.1: NS (a) Subtotal 0.86 (SE 0.06) 740 741 -31.2 208.6 (a) Subtotal 740 741 $\triangleleft$ -25.8 270.8 $\Leftrightarrow$ (56.2%) (64.0%) (78.6%) (81.8%) (b) Mastectomy without axillary surgery and no CW radiotherapy (b) Mastectomy without axillary surgery and no CW radiotherapy 85Z Tokyo CIH PS †AF+IMC 18/47 21/45 85Z Tokyo CIH PS +AF+IMC -0.1 7.8 20/47 23/45 0.4 8.5 88U Tokyo CIH N2 TAF+IMC -1.2 11.1 †AF+IMC 25/50 27/50 88U Tokyo CIH N2 26/50 28/50 11.6 -1.3 43/ 48/ 46/ 51/ (b) Subtotal 97 95 -1.4 18.9 (b) Subtotal 97 95 -0.9 20.0 0.93 (SE 0.22) 2p ≥ 0.1: NS 0.96 (SE 0.22) 2p > 0.1: NS (44.3%) (50.5%) (47.4%) (53.7%) 459/ 522/ 628/ 657/ 0.91 (SE 0.06) 2p > 0.1: NS Total 837 836 -32.6 227.5 0.87 (SE 0.06) -26.7 290.8 Total 837 836 $\Rightarrow$ $\triangleleft$ (54.8%) (62.4%) (75.0%) (78.6%) Difference between Difference between treatment effects in 2 subtotals: $\chi_1^2 = 0.1$ ; 2p > 0.1: NS treatment effects in 2 subtotals: $\chi_1^2 = 0.1$ ; 2p > 0.1: NS 0.0 0.5 1.0 1.5 2.0 0.0 0.5 1.0 1.5 Heterogeneity within subtotals: $\chi_3^2 = 1.2$ ; p > 0.1: NS Heterogeneity within subtotals: $\chi_3^2 = 1.2$ ; p > 0.1: NS RT better RT worse RT better RT worse Heterogeneity between 5 trials: $\chi_4^2 = 1.3$ ; p > 0.1: NS Heterogeneity between 5 trials: $\chi_4^2 = 1.3$ ; p > 0.1: NS

**Breast cancer mortality** 

† 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.

2.0

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) \*.

		Deaths		Woman-y	ears since	% women given systemic therapy				
Nodal status†	Women		Median/	Total	Distribution by years ('000s)			Chemotherany+	ER+ &	
			woman	('000s)	<10	10-	20+	onemotierapy <sub>+</sub>	Tamoxifen	
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. <i>Radiother Oncol</i> 1998; <b>48</b> : 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	RTe	vents					Events	/Women	RTe	vents
Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E	Ratio of ann RT	ual event rates : No RT	Year code, and study name	Treatment Information	Allocated RT	Allocated No RT	Logrank O-E	Variance of O-E
(a) Axillary dissecti	on						- <b></b> 99%95% Cl	(a) Axillary dissectio	n				
62B Berlin-Buch ABC	CW+AF+IMC	7/123	17/132	-3.6	5.4			62B Berlin-Buch ABC	CW+AF+IMC	60/123	64/132	2.0	26.8
(a) Subtotal		7/ 123 (5.7%)	/17 132 (12.9%)	-3.6	5.4		0.52 (SE 0.31) 2p > 0.1: NS	(a) Subtotal		60/ 123 (48.8%)	/64 132 (48.5%)	2.0	26.8
(b) Axillary samplin	g							(b) Axillary sampling	1				
71B Stockholm A	CW+AF+IMC	20/316	76/321	-30.5	23.1			71B Stockholm A	CW+AF+IMC	110/316	148/321	-26.7	58.5
(b) Subtotal		20/ 316 (6.3%)	76/ 321 (23.7%)	-30.5	23.1	∯	0.27 (SE 0.12)	(b) Subtotal		110/ 316 (34.8%)	/148 321 (46.1%)	-26.7	58.5
Total		27/ 439 (6.2%)	93/ 453 (20.5%)	-34.1	28.5		0.30 (SE 0.11) 2p < 0.00001	Total		170/ 439 (38.7%)	/212 453 (46.8%)	-24.6	85.2
Difference between treatment effect Difference between treatment effect	ts in 2 subtot ts in 2 subtot ts in 2 trials:	cals: $\chi_1^2 = 1.9$ ; $\chi_1^2 = 1.9$ ; 2	9; 2p > 0.1 p > 0.1: N\$	: NS 8	ـــ 0.0	0.5 RT better —	1.0 1.5 2.0	Difference between treatment effects Difference between treatment effects	in 2 subtot in 2 trials:	cals: $\chi_1^2 = 5.2$ ; 2	2; 2p = 0.0 p = 0.02	)2	L 0.0

## Locoregional recurrence first (years 0-9)

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

## Any first recurrence (years 0-9)

0.0

1.08 (SE 0.20)

 $\dot{-}$ 

1.0

0.5

RT better

continued overleaf

Ratio of annual event rates

RT : No RT

0.63 (SE 0.11)

0.75 (SE 0.09)

1.5

RT worse

2.0

# 892 pN? women

## **Breast cancer mortality**

		Deaths	Women	RT d	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 dissectio	n					₽ 99% ◆	►95% CI
62B Berlin-Buch ABC	CW+AF+IMC	67/123	70/132	3.6	29.3		_
		67/	70/				
(a) Subtotal		123 (54.5%)	132 (53.0%)	3.6	29.3	1.13 (SE 0.20)	
(b) Axillary sampling	I						
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 0.1 2p > 0.1: NS	1)
Total		219/ 439 (49.9%)	245/ 453 (54.1%)	-4.9	106.4	0.95 (SE 0.0 2p > 0.1: NS	9)
Difference between		. 2 .	L		1		
treatment effects	in 2 subtot	als: $\chi_1^2 = 1.2$	2; 2p > 0.1	: NS	0.0	0.5 1.0 1.5	2.0
treatment effects	in 2 trials:	$\chi_1^2 = 1.2; 2$		RT better RT worse			

		Deaths	Women	RT d	eaths				
Year code, and study name	Treatment Information	Allocated	Allocated	Logrank	Variance	Ratio of annual death rates			
	internation		No Ki	01					
(a) Axillary dissection	on					99% → 95% Cl			
62B Berlin-Buch ABC	CW+AF+IMC	105/123	96/132	8.1	43.1				
		105/	96/			:			
(a) Subtotal		123	132	8.1	43.1	1.21 (SE 0.17)			
_		(85.4%)	(72.7%)			2p > 0.1: NS			
(b) Axillary sampling	g								
71B Stockholm A	CW+AF+IMC	244/316	253/321	-12.3	116.1	-			
_		244/	253/						
(b) Subtotal		316	321	-12.3	116.1	0.90 (SE 0.09)			
		(77.2%)	(78.8%)			2p > 0.1: NS			
		3/0/	3/0/						
Total		439	453	-4 1	159 2	→ 0.97 (SE 0.08)			
Total		(79.5%)	(77.0%)			2p > 0.1: NS			
Difference between		. 2 .		•					
treatment effects in 2 subtotals: $\chi_1^2 = 2.7$ ; 2p = 0.10						0.5 1.0 1.5 2.0			
treatment effects	s in 2 trials:	$\chi_1^2 = 2.7; 2$		RT better RT worse					

Any death

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

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

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Cancer Care Ontario, Canada—H T Abu-Zahra.

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I Fernando, M Lee, C Poole, D Rea, D Spooner.

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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.

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