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Supplementary appendix

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Supplement to: EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014; published online March 19. http://dx.doi.org/10.1016/S0140-6736(14)60488-8.

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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

Webfigure 1 **Methodological note**

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

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

Node negative (pN0)

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

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

Node positive (pN+)

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

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

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.

1-3 positive nodes (pN1-3)

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

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

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

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

Node negative (pN0)

Node positive (pN+)

Trials of radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS). Event rate ratios, one line per trial.

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

Node negative (pN0)

Node positive (pN+)

Event rate ratios, one line per trial

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

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

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)

Webfigure 1. Methodological Note

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

Overall Mortality

In analyses of overall mortality (eg, the lower right-hand panels of webfigures 2, 4, etc), the number of women who are known to have died in each randomised group is related to the number of women at risk of dying and the length of time during which they are at risk of dying in each time-period during follow-up. Some women are, however, lost to follow-up and are withdrawn from the analysis. Thus, whilst it is reported in the lower right-hand panel of webfigure 4 that the cumulative risk of death from any cause among the 1550 women randomised to radiotherapy is 65.4% at 20 years after randomisation, this does not mean that 1014 (ie 0.654x1550) of the women are known to have died. Rather, as shown in webfigure 30, only 1001 (ie 64.6%) of the women are known to have died. The difference between these two percentages is due to the fact that for 390 of these 1550 women the most recent information held in the EBCTCG database indicates only that they were known to be alive at some period less than 20 years after randomisation. These women were withdrawn from the analysis or 'censored' on the date they were last 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 and then combining the results from the separate strata in the form of a weighted average, calculated with weights proportional to the amount of information in each stratum.

Mortality from Causes other than Breast Cancer

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

Breast Cancer Mortality

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

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

Analyses of Overall Recurrence

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

Analyses of Locoregional and Distant Recurrence

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

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

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

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

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

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

Reference

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

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

Year code and study name	Breast surgery	Axillary Surgery* (number of patients)	Chest wall RT	Supraclavicular (SC) and axillary fossa (AF) RT	Internal mammary chain RT	Boost RT to scar	Common systemic chemoendocrine therapy
64B Oslo X-ray	RM	Axillary dissection (552)	25-41 Gy (1.3-2.1 Gy/f) o	36 Gy (1.8 Gy/f) o, SC; 18 Gy (u Gy/f) o, AF	25-41 Gy (1.3-2.1 Gy/f) o	None	Ovarian RT
71B Stockholm A	MRM	Axillary sampling (644)	45 Gy (1.8 Gy/f) e	45 Gy de (1.8 Gy/f) c	45 Gy (1.8 Gy/f) e	None	None
73A Southampton UK	SM	Axillary sampling (151)	46 Gy (2.3 Gy/f) c	55 Gy (2.5 Gy/f) c & b	46 Gy (2.3 Gy/f) c	None	None
74B Edinburgh I	SM	Axillary sampling (348)	42.5-45.0 Gy (4.25-4.5 Gy/f) m	42.5-45.0 Gy (4.25-4.5 Gy/f) m	None	None	F
74D DFCI Boston	MRM or RM	Axillary dissection (218)	45 Gy (2.3 Gy/f) c or m	45 Gy (2.3 Gy/f) c or m	0-45 Gy (0-2.3 Gy/f) c or m	None	Either (AC) 5 cycles or (AC) 10 cycles; or CMF or MF
74Q Piedmont OA (pN4+)	MRM or RM	Axillary dissection (120)	50 Gy (1.5-1.8 Gy/f) c or m	45-50 Gy (1.5-2.8 Gy/f) c or m	45-50 Gy (1.8-2.8 Gy/f) c or m	None	Mel or CMF
76A SECSG 1	MRM or RM	Axillary dissection (257)	50 Gy (2 Gy/f) u	50 Gy (2 Gy/f) u	50 Gy (2 Gy/f) u	None	CMF
76C Glasgow	SM	Axillary dissection (219)	37.8 Gy (2.5 Gy/f) o	37.8 Gy (2.5 Gy/f) o	37.8 Gy (2.5 Gy/f) o	None	CMF
77J MD Ander. 7730B	MRM or SM	Axillary dissection (80) 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) 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	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 Germany	Patey	Axillary sampling (199)	50 Gy (2 Gy/f) c or m	50 Gy (2 Gy/f) c or m	44 Gy(1.8 Gy/f) c or m	None	CMF
85F Nottingham	SM	Axillary sampling (77)	45 Gy (3 Gy/f) m	45 Gy (3 Gy/f) m	None	None	Premen; CMF Postmen;tam
86C CRC, UK	NS	Unknown (71)	Various	Various	Various	Various	None

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

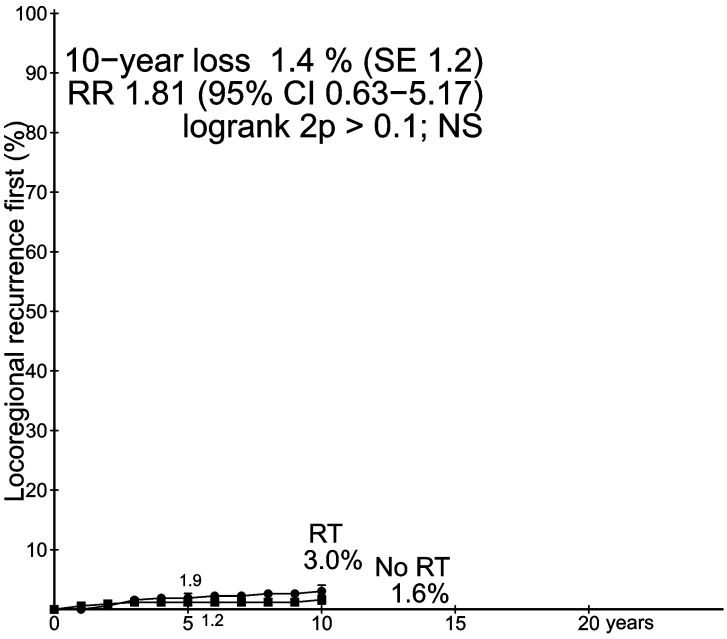
Year code and study name	Reference
64B Oslo X-ray	Host H, Brennhovd IO, Loeb M. Postoperative radiotherapy in breast cancer-long-term results from the Oslo study. *Int J Radiat Oncol Biol Phys* 1986; **12**: 727–32.
71B Stockholm A	Gyenes G, Rutqvist LE, Liedberg A, Fornander T. Long-term cardiac morbidity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

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

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

700 pN0 women with Mast+AD

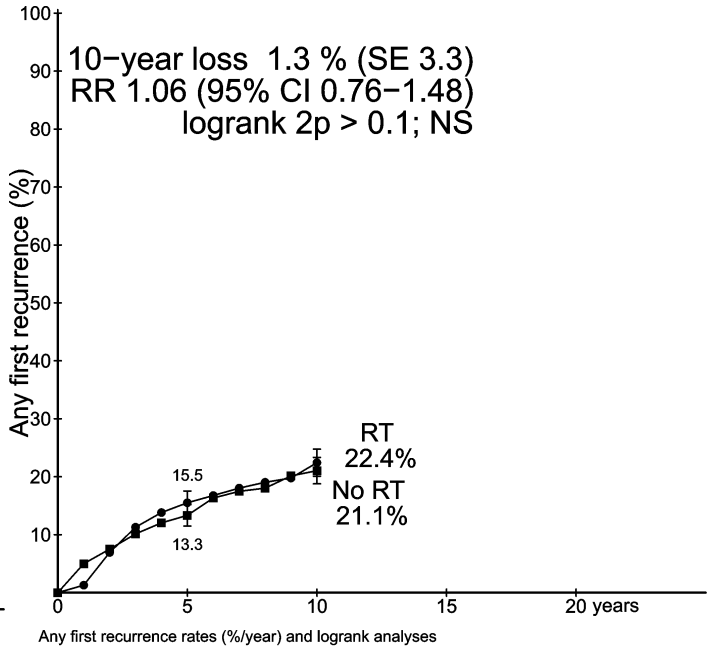
Locoregional recurrence first



Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	0.39 (6/1554)	0.23 (3/1287)
No RT	0.25 (4/1580)	0.08 (1/1317)
Rate ratio, from	1.50 SE 0.78	2.89 SE 1.78
(O−E)/V	1.0/2.5	1.1/1.0

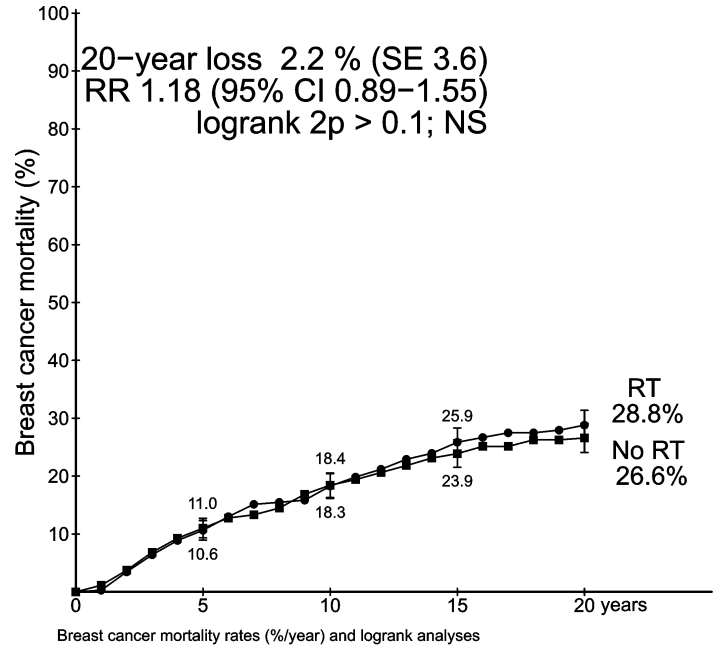
Any first recurrence



Any first recurrence rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	3.46 (54/1559)	1.62 (21/1296)
No RT	2.90 (46/1585)	2.02 (27/1339)
Rate ratio, from	1.16 SE 0.22	0.89 SE 0.28
(O−E)/V	3.3/23.0	−1.3/11.5

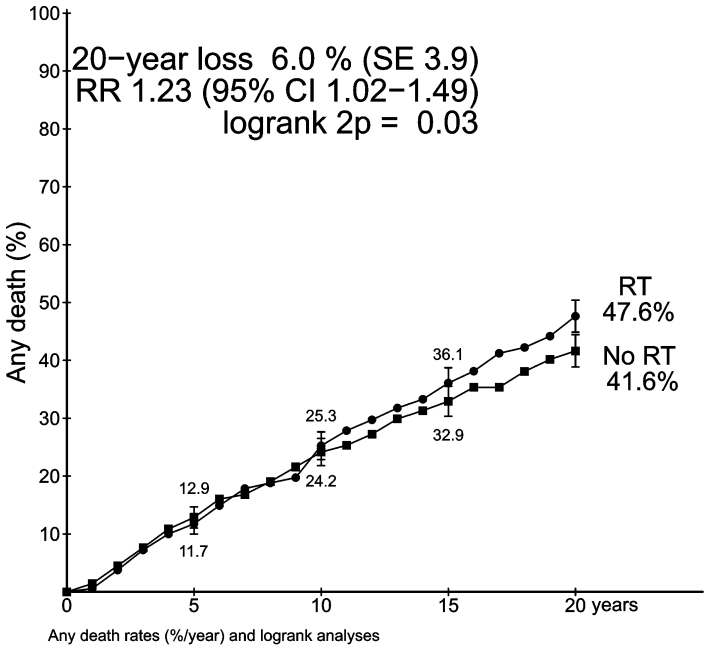
Breast cancer mortality



Breast cancer mortality rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	2.26 (37/1638)	1.77 (25/1411)	1.88 (22/1169)	0.73 (7/952)	1.45 (20/1375)
No RT	2.30 (38/1653)	1.75 (25/1430)	1.46 (18/1237)	0.87 (9/1034)	1.01 (16/1583)
Rate ratio, from	0.96 SE 0.24	1.06 SE 0.31	1.39 SE 0.39	1.16 SE 0.55	1.76 SE 0.49
(O−E)/V	−0.7/17.1	0.7/11.4	3.1/9.4	0.6/3.8	4.4/7.7

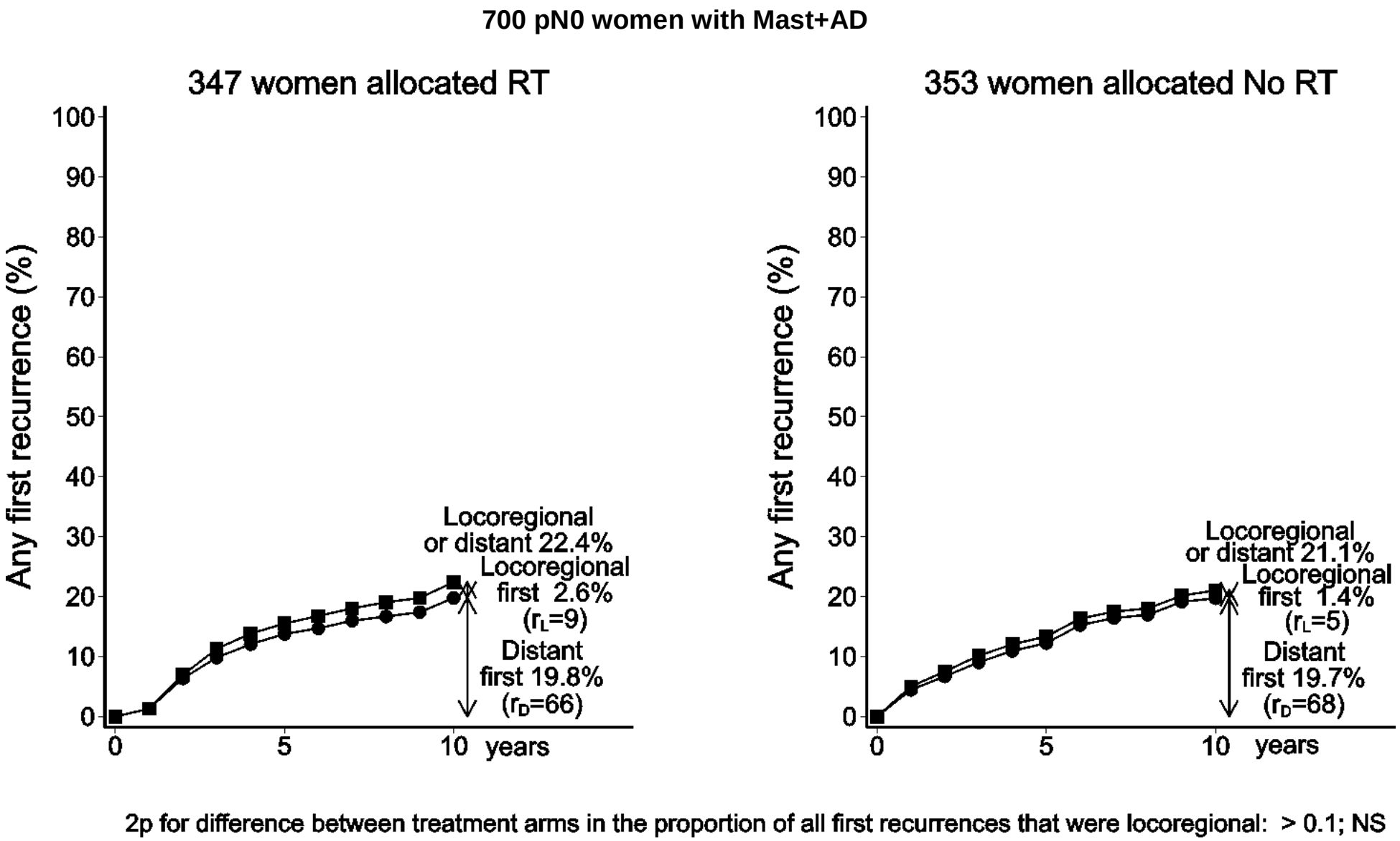
Any death



Any death rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	2.50 (41/1638)	3.26 (46/1411)	3.08 (36/1169)	3.88 (37/952)	5.96 (82/1375)
No RT	2.78 (46/1653)	2.87 (41/1430)	2.59 (32/1237)	3.09 (32/1034)	5.50 (87/1583)
Rate ratio, from	0.90 SE 0.21	1.20 SE 0.24	1.28 SE 0.28	1.45 SE 0.31	1.38 SE 0.20
(O−E)/V	−2.1/20.0	3.6/20.3	3.9/15.9	5.7/15.4	10.8/33.5

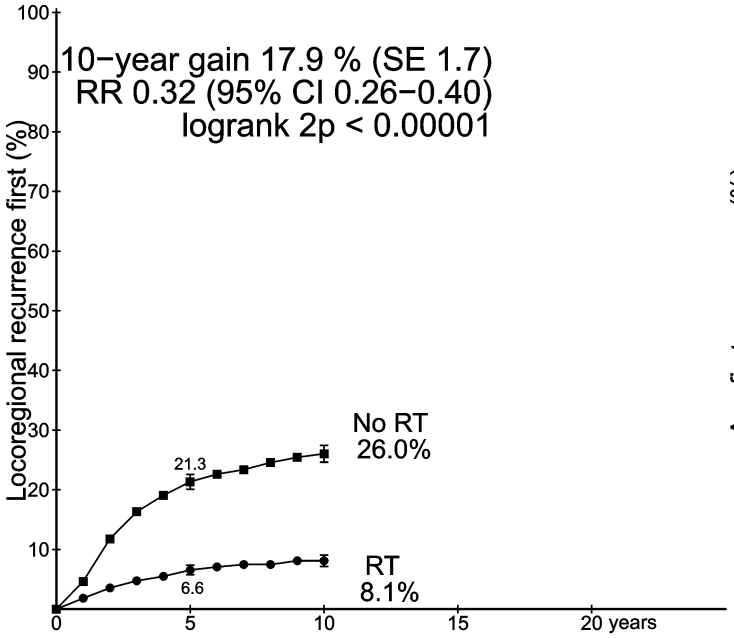
Webfigure 3. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 700 women with pathologically node-negative (pN0) disease. (r_L = number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



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

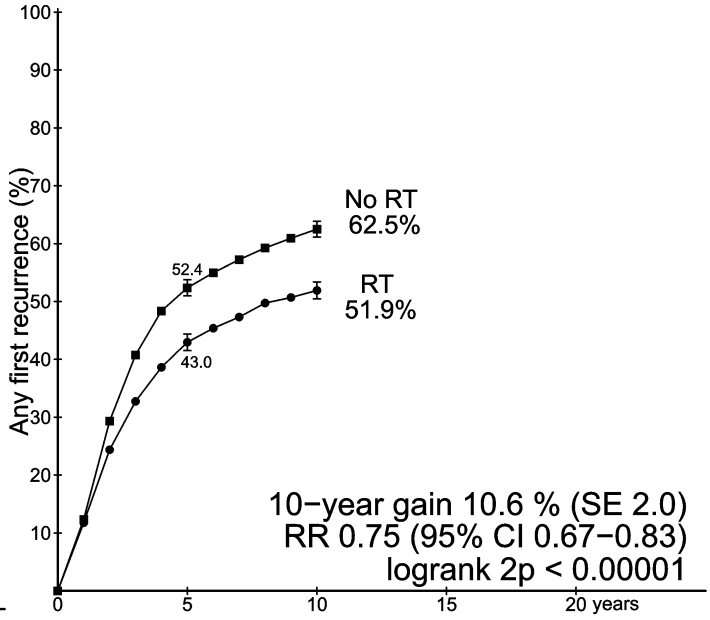
Locoregional recurrence first



Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	1.61 (86/5335)	0.41 (13/3154)
No RT	5.04 (256/5075)	1.25 (34/2714)
Rate ratio, from	0.32 SE 0.07	0.32 SE 0.18
(O−E)/V	−88.6/77.9	−12.0/10.6

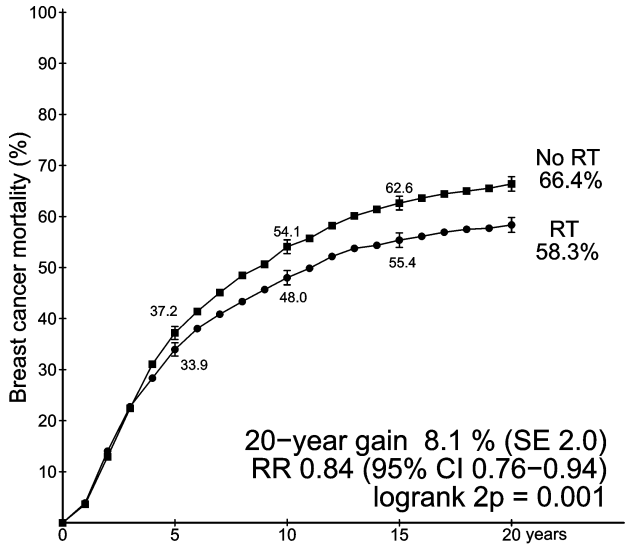
Any first recurrence



Any first recurrence rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	12.44 (677/5441)	3.88 (125/3221)
No RT	15.19 (796/5241)	5.10 (144/2822)
Rate ratio, from	0.76 SE 0.05	0.72 SE 0.11
(O−E)/V	−80.1/286.4	−18.3/55.8

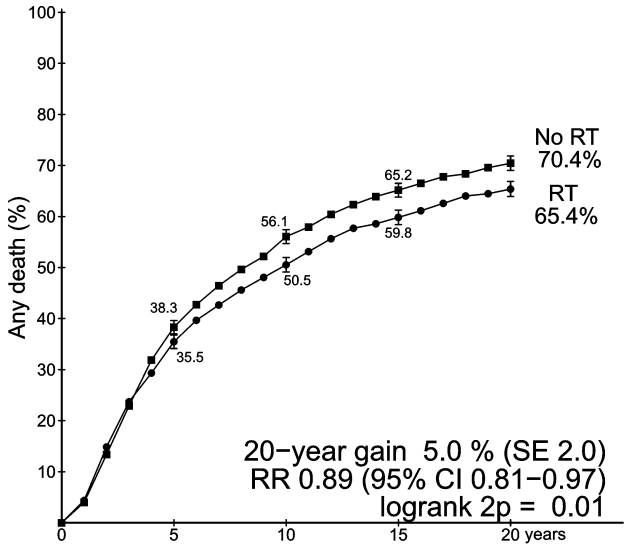
Breast cancer mortality



Breast cancer mortality rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	8.38 (520/6205)	5.02 (196/3905)	3.26 (85/2608)	1.23 (19/1544)	1.17 (12/1022)
No RT	8.81 (562/6382)	6.14 (233/3796)	4.09 (99/2420)	2.47 (33/1339)	1.62 (14/864)
Rate ratio, from	0.91 SE 0.06	0.77 SE 0.09	0.76 SE 0.14	0.67 SE 0.24	0.77 SE 0.37
(O−E)/V	−21.7/222.2	−23.5/89.3	−10.7/38.5	−4.6/11.4	−1.4/5.6

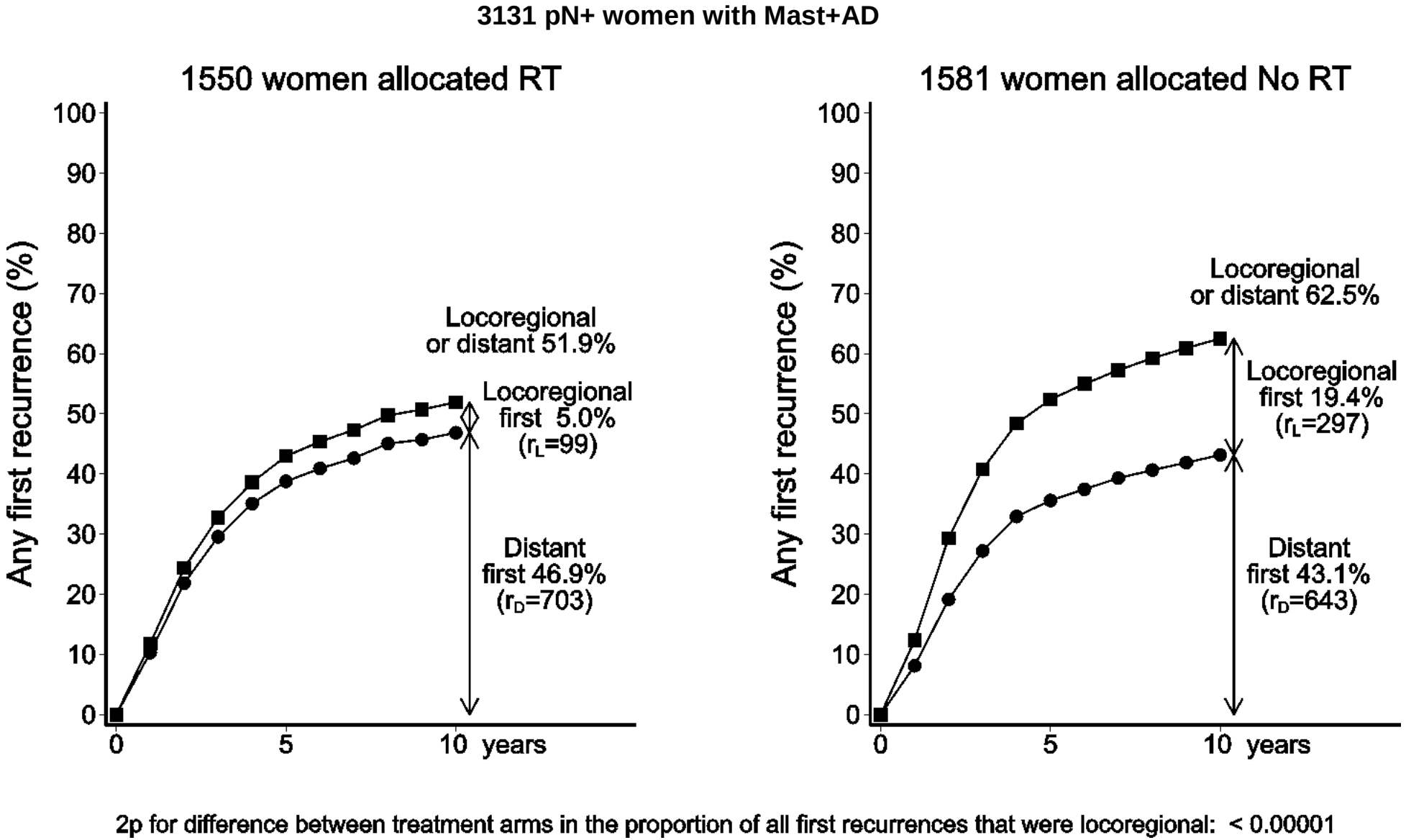
Any death



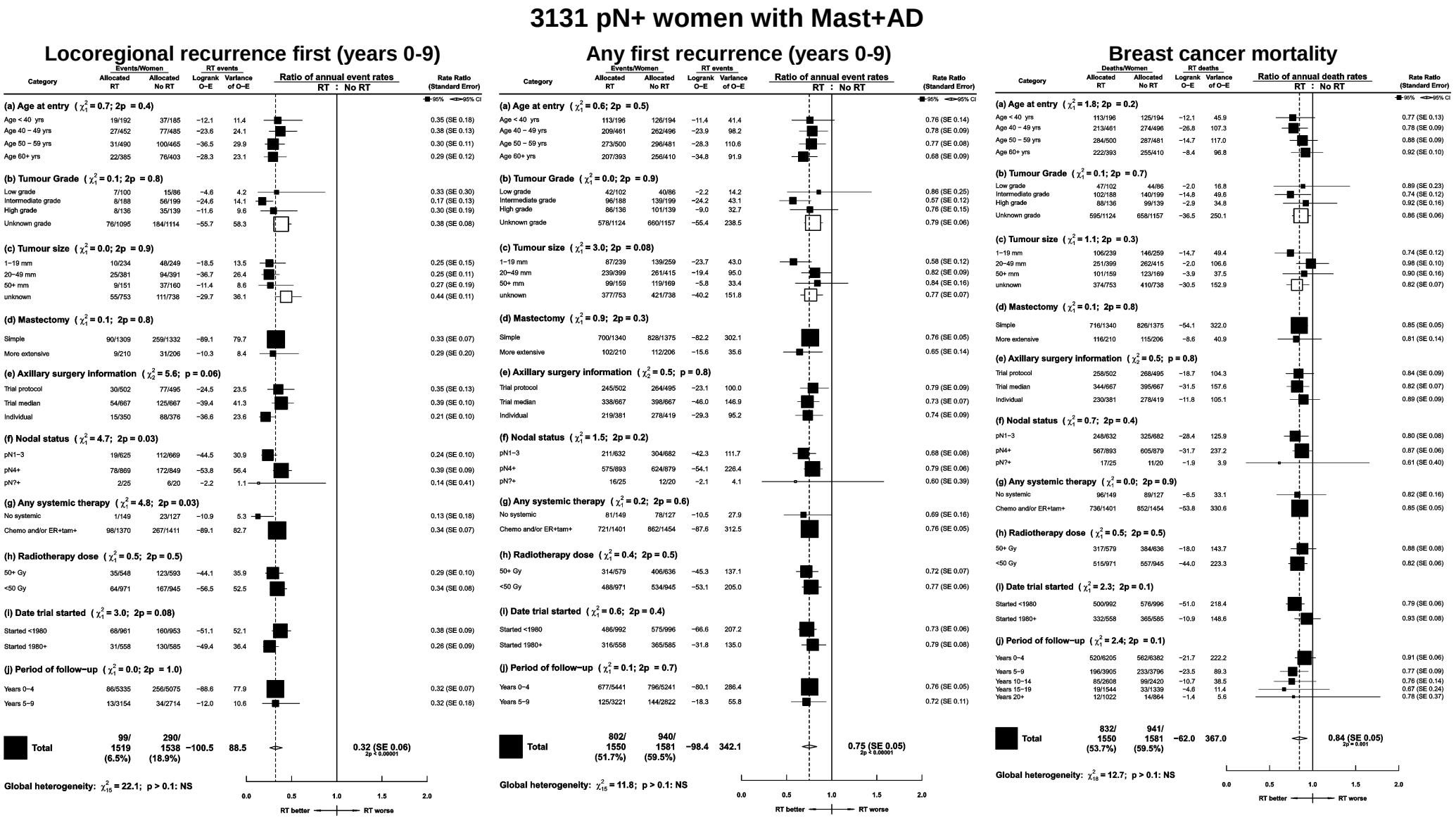
Any death rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	9.01 (559/6205)	5.89 (230/3905)	4.72 (123/2608)	3.17 (49/1544)	3.91 (40/1022)
No RT	9.35 (597/6382)	6.96 (264/3796)	5.00 (121/2420)	3.96 (53/1339)	4.40 (38/864)
Rate ratio, from	0.92 SE 0.06	0.79 SE 0.09	0.91 SE 0.13	0.94 SE 0.21	0.85 SE 0.23
(O−E)/V	−19.1/239.0	−24.4/103.7	−4.8/51.4	−1.3/20.8	−2.5/15.6

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

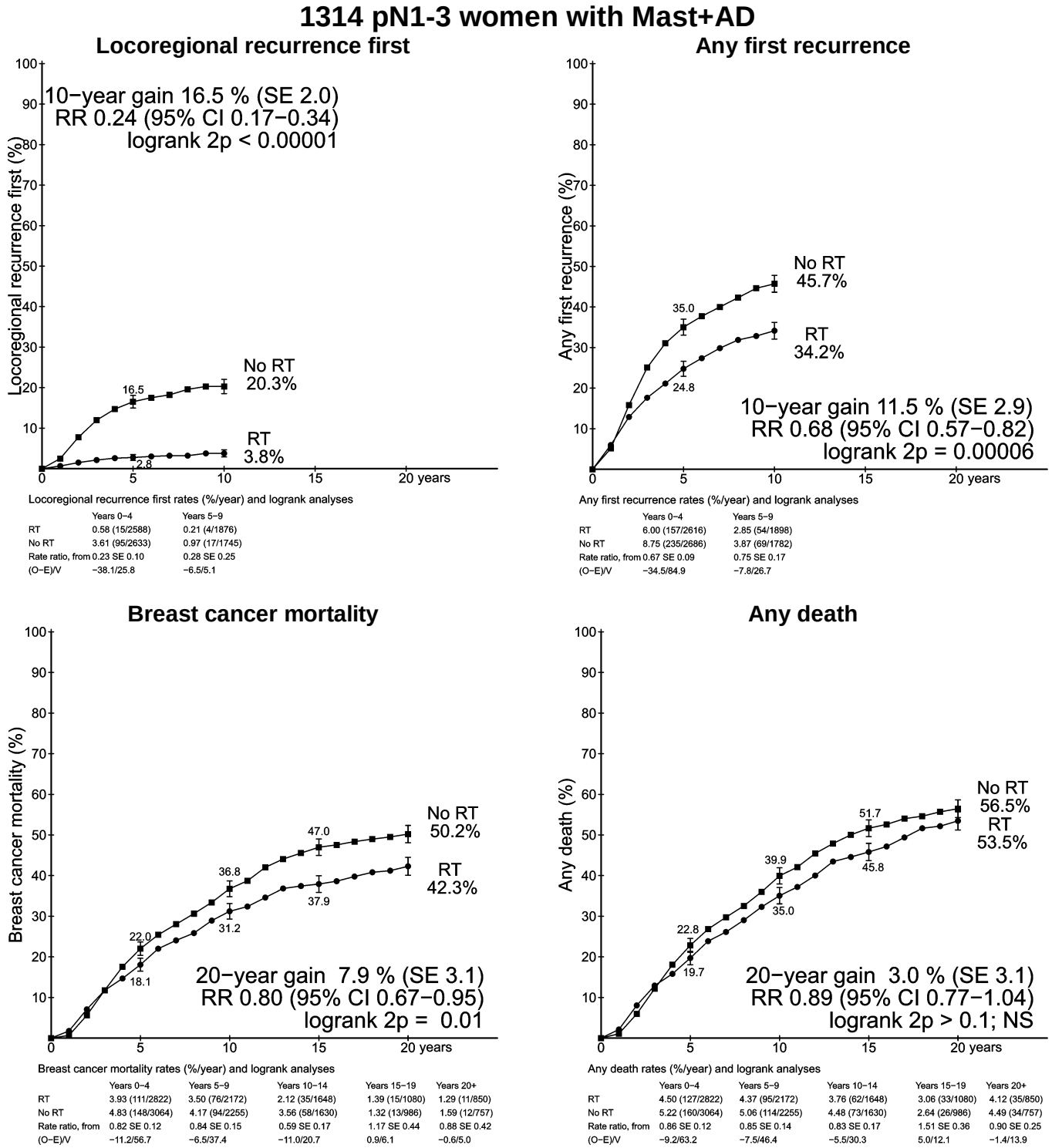


Webfigure 6. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): Event rate ratios and 95% confidence intervals for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer mortality in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

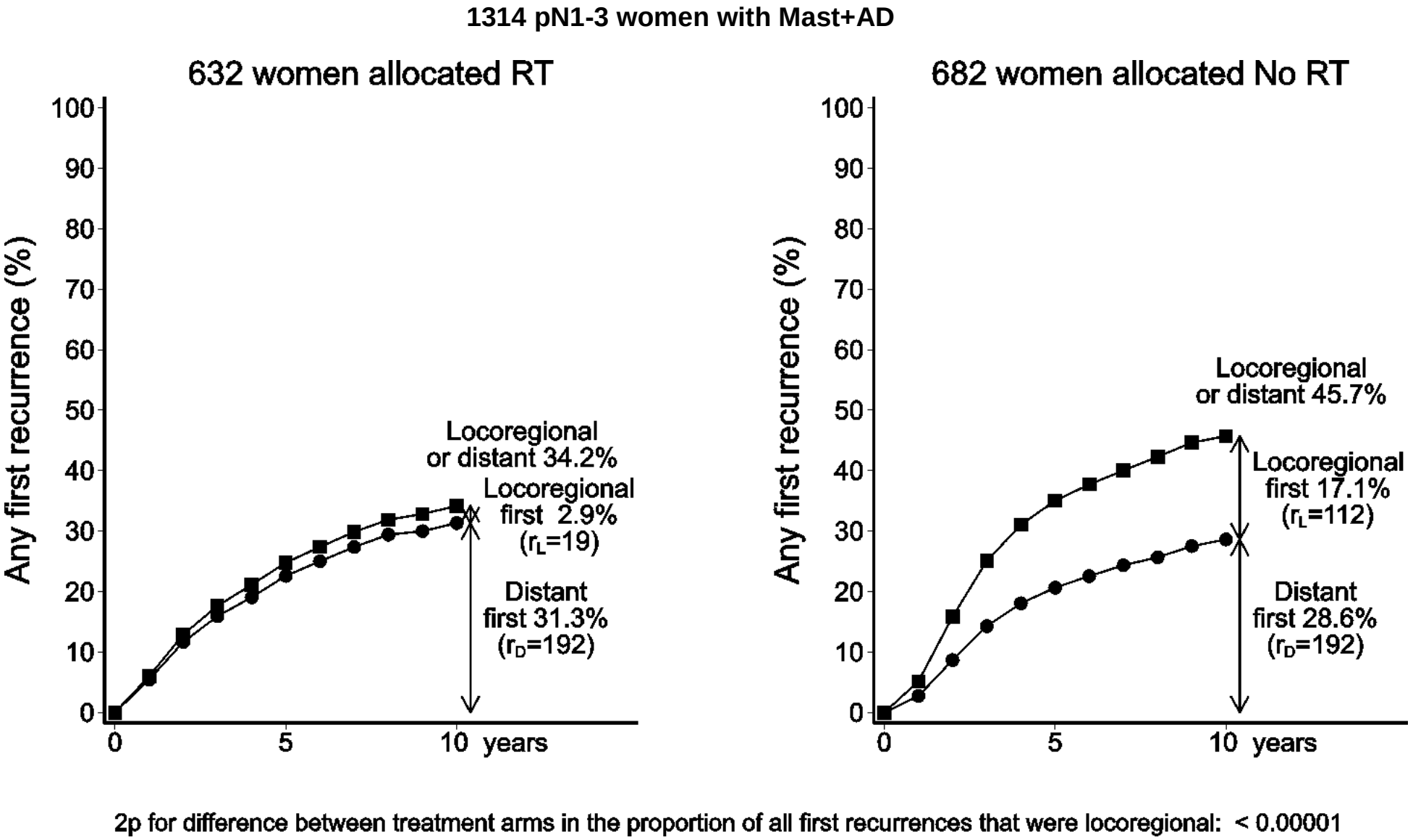


Note:In (g), 181 women who were ER positive with tamoxifen also had chemotherapy. In (h), trials that used orthovoltage irradiation are included in the <50 Gy category.

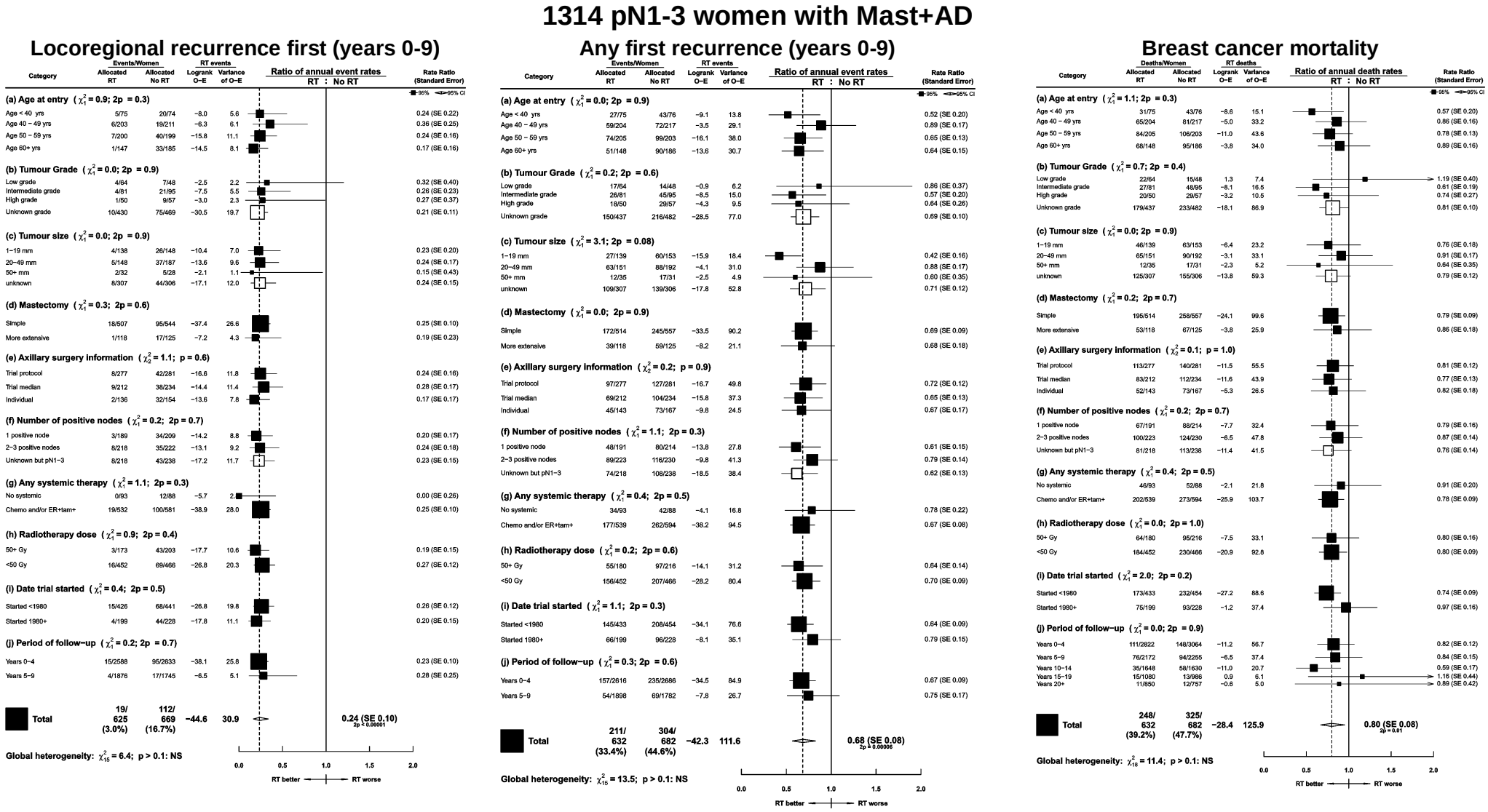
Webfigure 7. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1314 women with 1-3 pathologically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

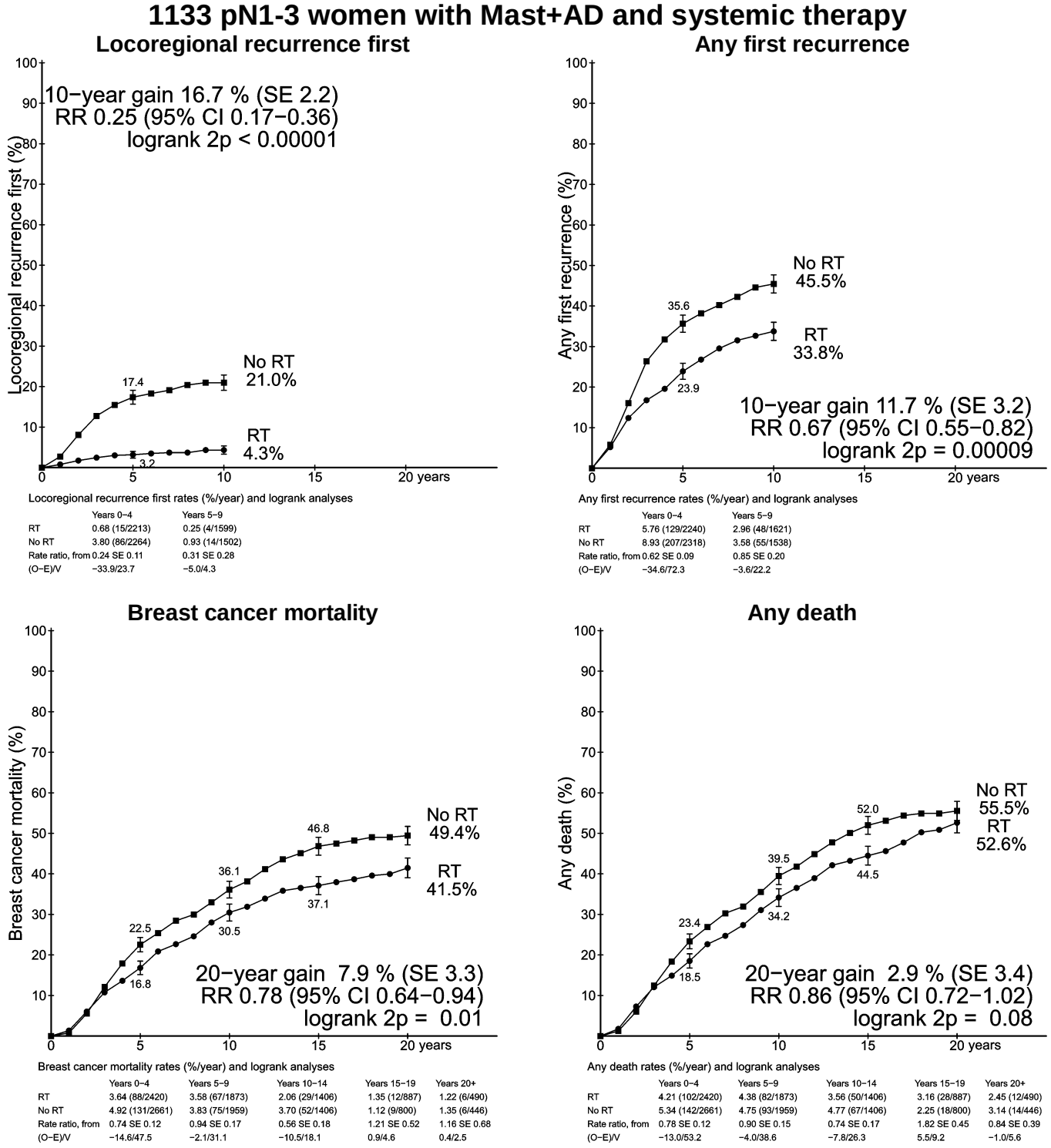


Webfigure 9. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): Event rate ratios and 95% confidence intervals for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer mortality in 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.

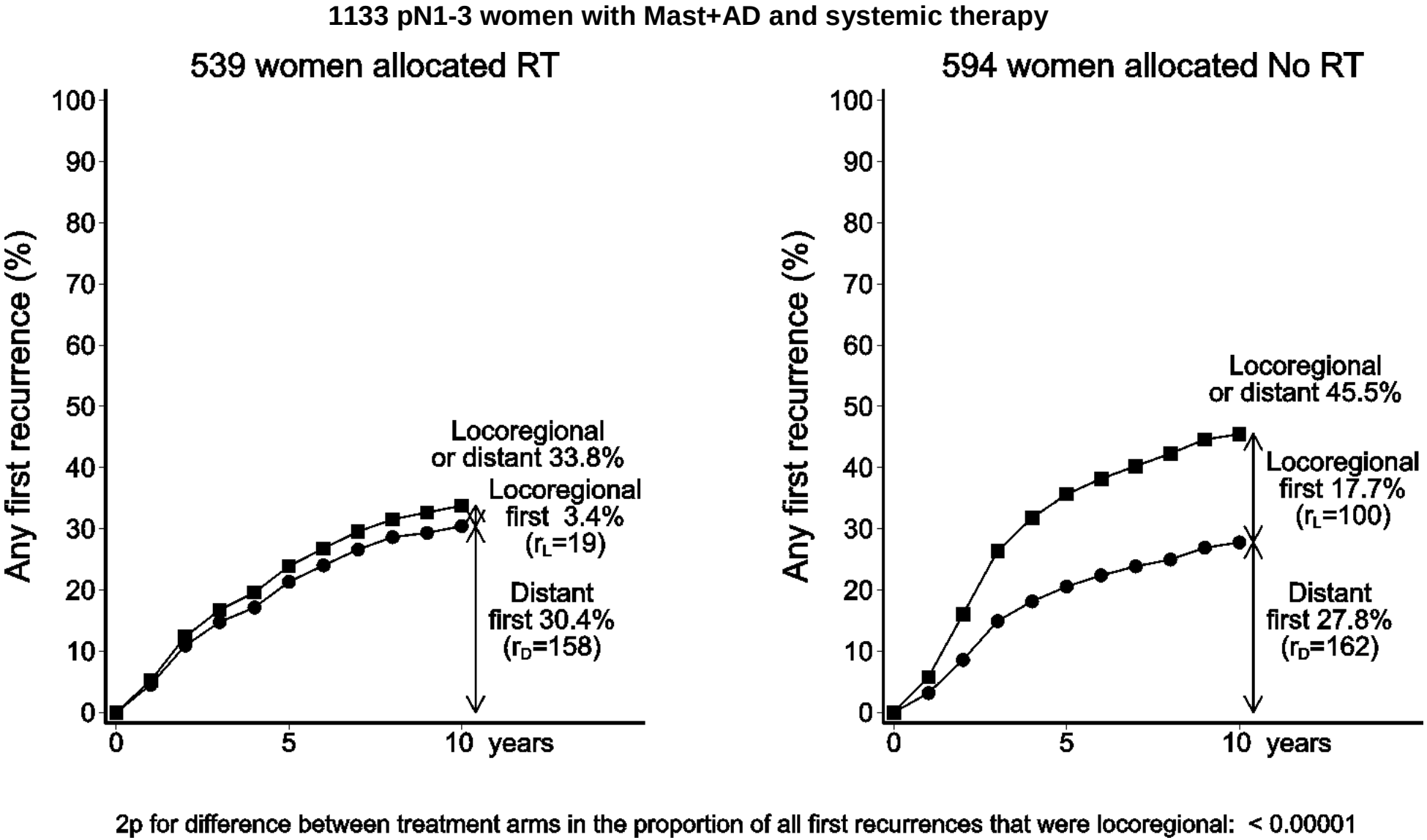


In (h), trials that used orthovoltage irradiation are included in the <50 Gy category.

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.



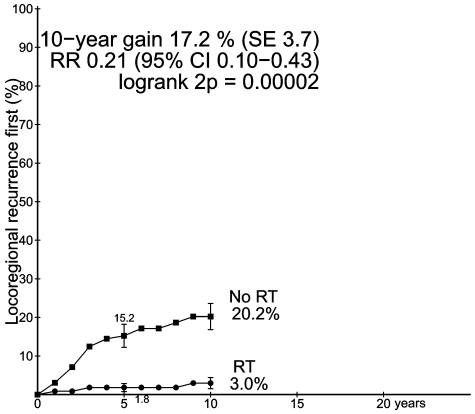
Webfigure 11. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1133 women with 1-3 pathologically positive nodes (pN1-3) in trials where 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.)



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.

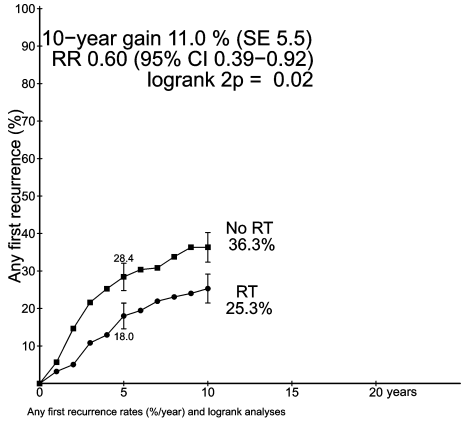
Locoregional recurrence first **Any first recurrence** **Breast cancer mortality**

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



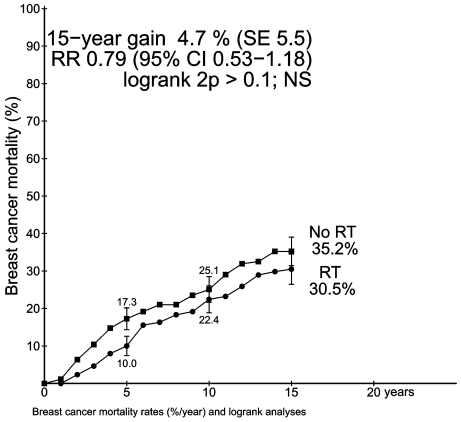
Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	0.31 (2/635)	0.20 (1/491)
No RT	3.36 (23/685)	1.18 (6/510)
Rate ratio, from	0.21 SE 0.21	0.23 SE 0.40
(O−E)/V	−9.2/5.8	−2.5/1.7



Any first recurrence rates (%/year) and logrank analyses

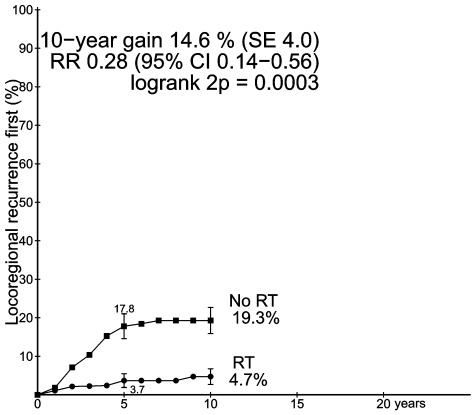
	Years 0−4	Years 5−9
RT	4.04 (26/643)	1.82 (9/496)
No RT	6.91 (49/709)	2.64 (14/530)
Rate ratio, from	0.56 SE 0.19	0.75 SE 0.39
(O−E)/V	−9.2/16.1	−1.4/5.0



Breast cancer mortality rates (%/year) and logrank analyses

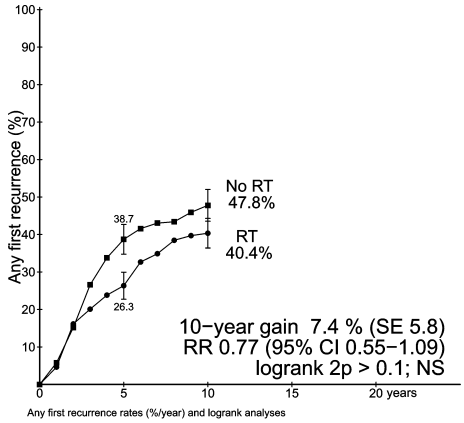
	Years 0−4	Years 5−9	Years 10−14	Years 15+
RT	2.06 (14/678)	2.91 (16/550)	2.16 (10/463)	1.46 (6/410)
No RT	3.67 (29/790)	2.14 (14/655)	3.03 (16/528)	1.64 (7/427)
Rate ratio, from	0.56 SE 0.25	1.55 SE 0.51	0.72 SE 0.35	0.67 SE 0.53
(O−E)/V	−5.5/9.4	2.7/6.1	−1.9/5.9	−1.0/2.4

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



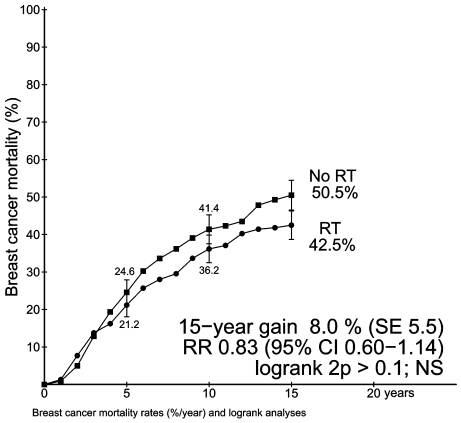
Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	1.00 (7/703)	0.19 (1/514)
No RT	3.76 (26/692)	0.46 (2/436)
Rate ratio, from	0.25 SE 0.21	0.64 SE 0.96
(O−E)/V	−9.6/7.1	−0.3/0.7



Any first recurrence rates (%/year) and logrank analyses

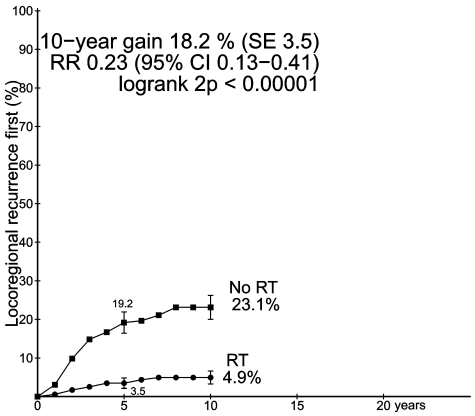
	Years 0−4	Years 5−9
RT	6.51 (47/722)	4.21 (22/522)
No RT	10.12 (73/721)	4.21 (19/451)
Rate ratio, from	0.64 SE 0.16	1.37 SE 0.41
(O−E)/V	−11.1/24.5	2.6/8.2



Breast cancer mortality rates (%/year) and logrank analyses

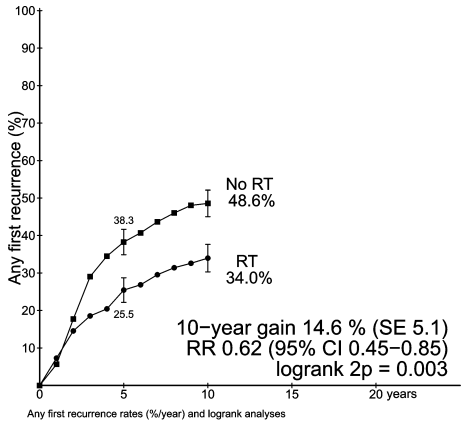
	Years 0−4	Years 5−9	Years 10−14	Years 15+
RT	4.55 (36/791)	4.12 (25/607)	2.07 (10/483)	1.24 (5/402)
No RT	5.56 (46/828)	5.29 (30/567)	3.47 (15/432)	1.48 (5/339)
Rate ratio, from	0.87 SE 0.22	0.81 SE 0.26	0.64 SE 0.35	1.18 SE 0.70
(O−E)/V	−2.5/17.4	−2.5/11.8	−2.4/5.5	0.4/2.4

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



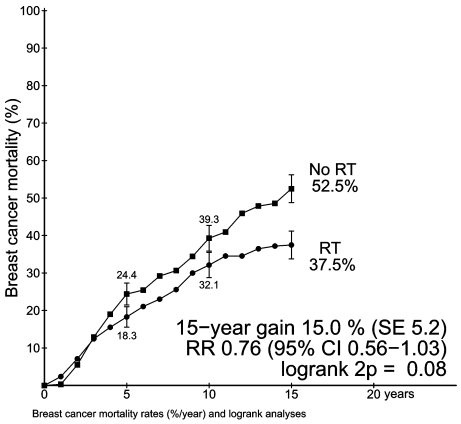
Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	0.69 (6/874)	0.34 (2/594)
No RT	4.17 (37/888)	1.08 (6/556)
Rate ratio, from	0.21 SE 0.16	0.36 SE 0.46
(O−E)/V	−15.1/9.8	−1.9/1.9



Any first recurrence rates (%/year) and logrank analyses

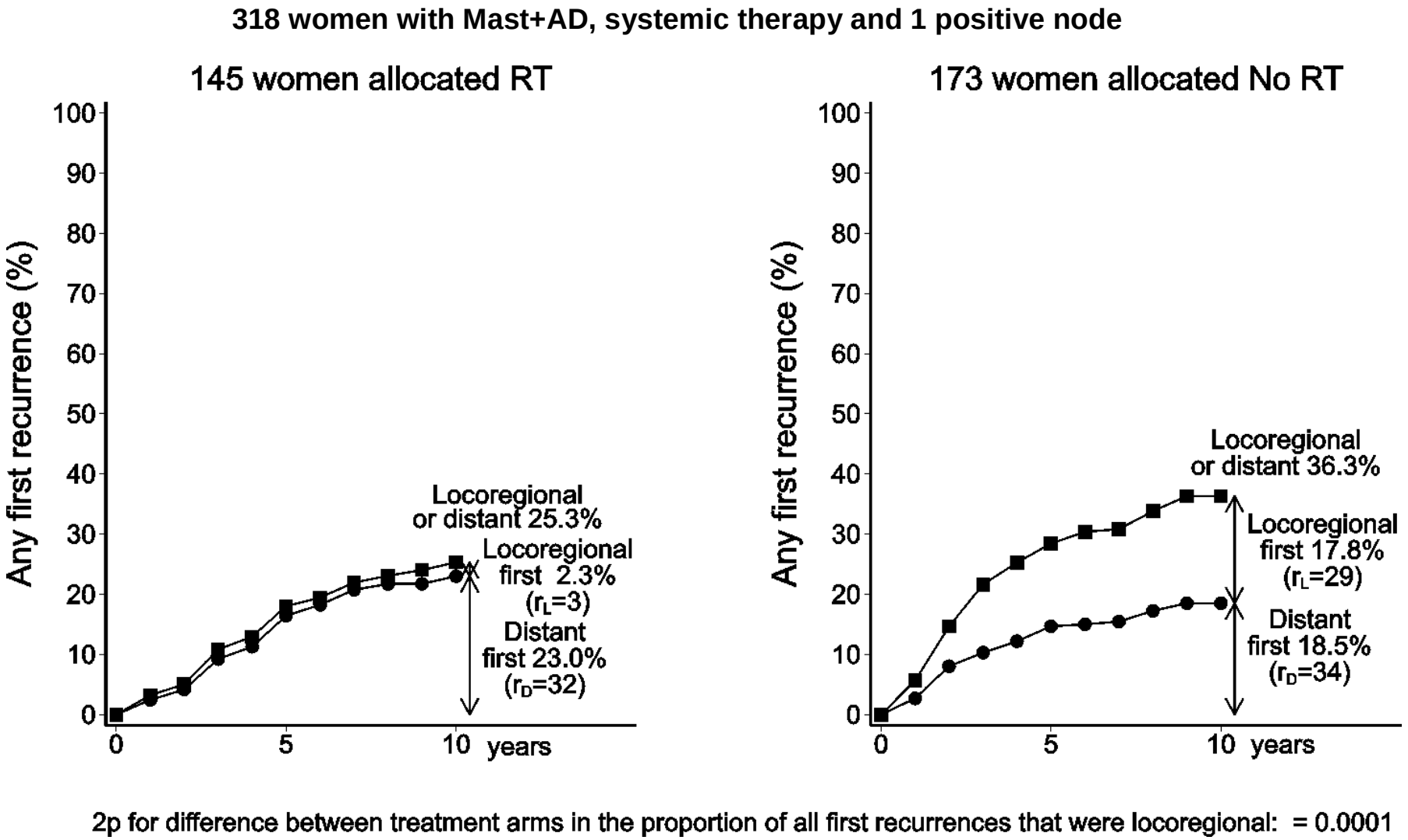
	Years 0−4	Years 5−9
RT	6.41 (56/874)	2.82 (17/603)
No RT	9.57 (85/888)	3.95 (22/558)
Rate ratio, from	0.61 SE 0.14	0.66 SE 0.28
(O−E)/V	−14.8/30.0	−3.5/8.3



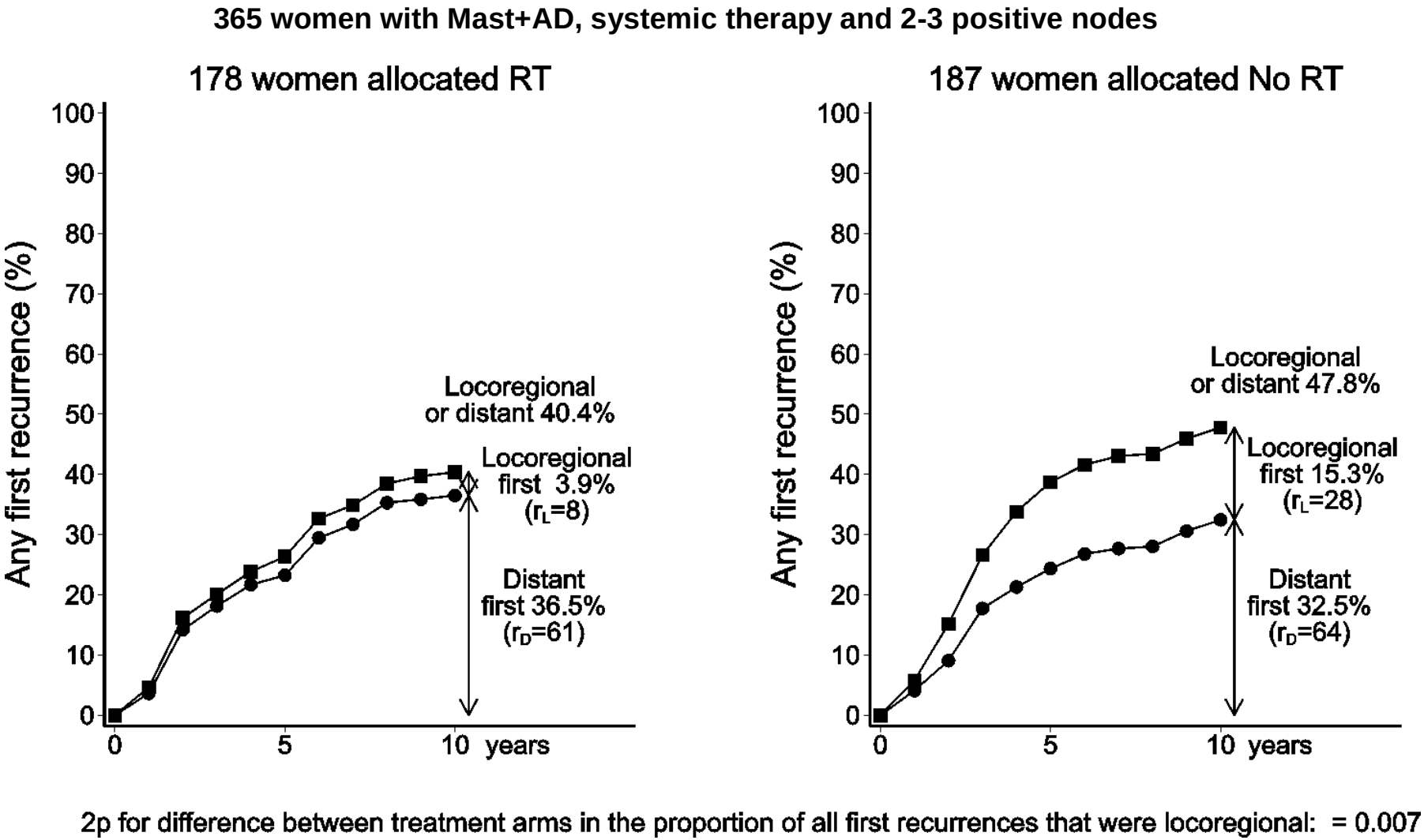
Breast cancer mortality rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15+
RT	4.00 (38/950)	3.63 (26/716)	1.95 (9/460)	1.24 (7/565)
No RT	5.37 (56/1043)	4.21 (31/736)	4.71 (21/446)	0.62 (3/480)
Rate ratio, from	0.74 SE 0.19	0.87 SE 0.26	0.40 SE 0.26	2.57 SE 1.08
(O−E)/V	−5.9/20.0	−1.8/12.4	−6.0/6.6	2.2/2.4

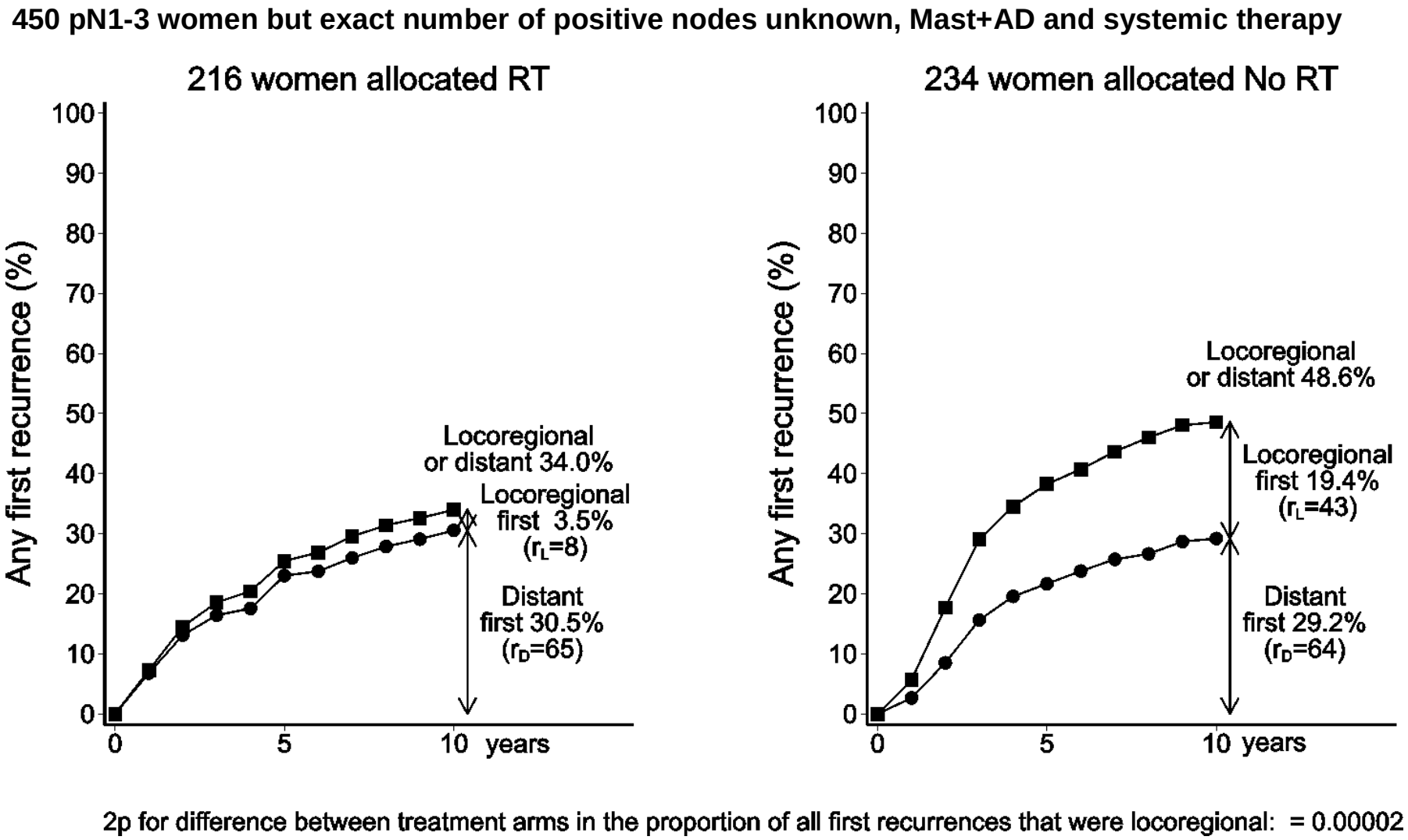
Webfigure 13. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 318 women with 1 pathologically positive node (pN1) and where systemic 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.)



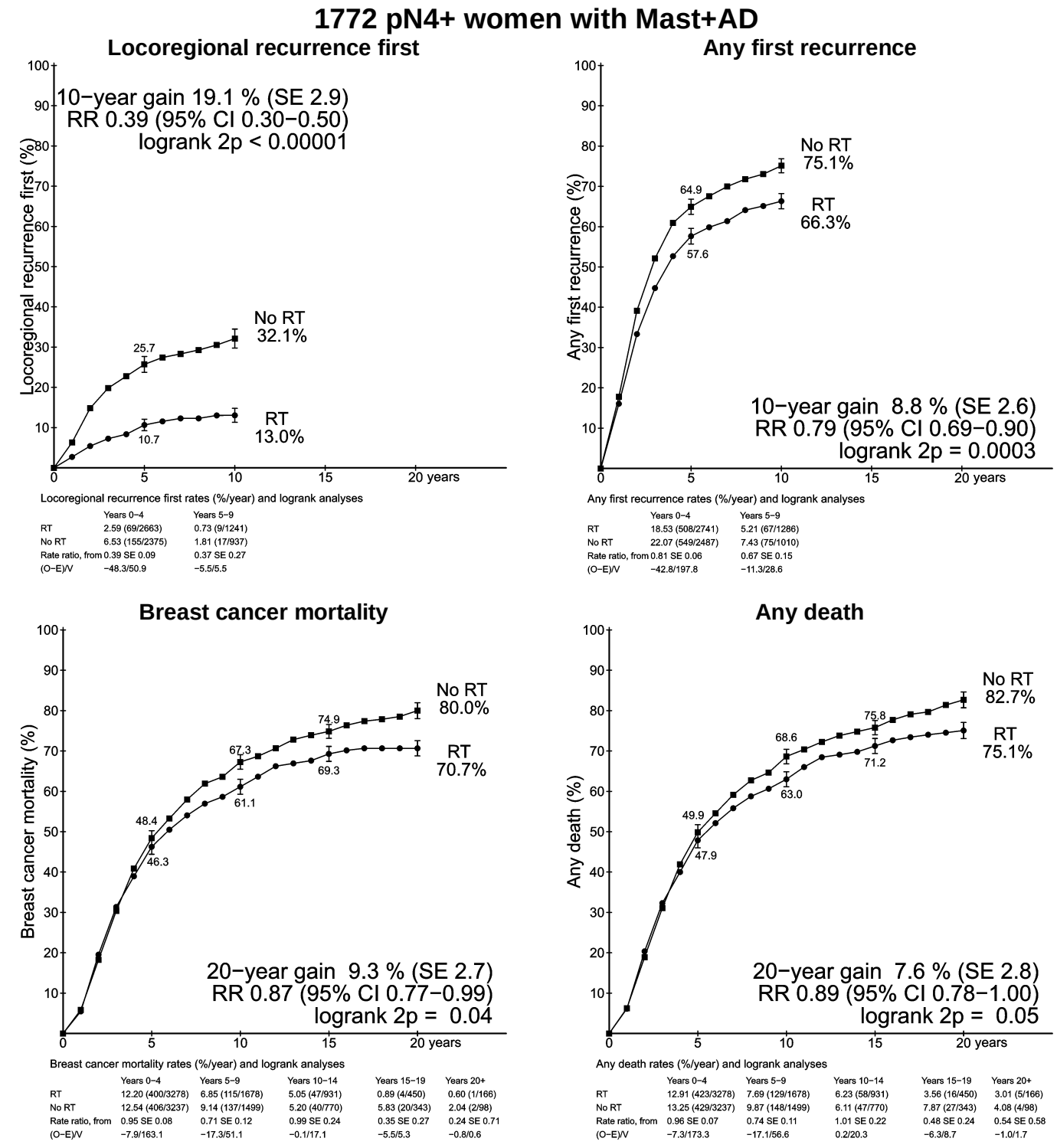
Webfigure 14. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 365 women with 2-3 pathologically positive nodes (pN2-3) and where systemic 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.)



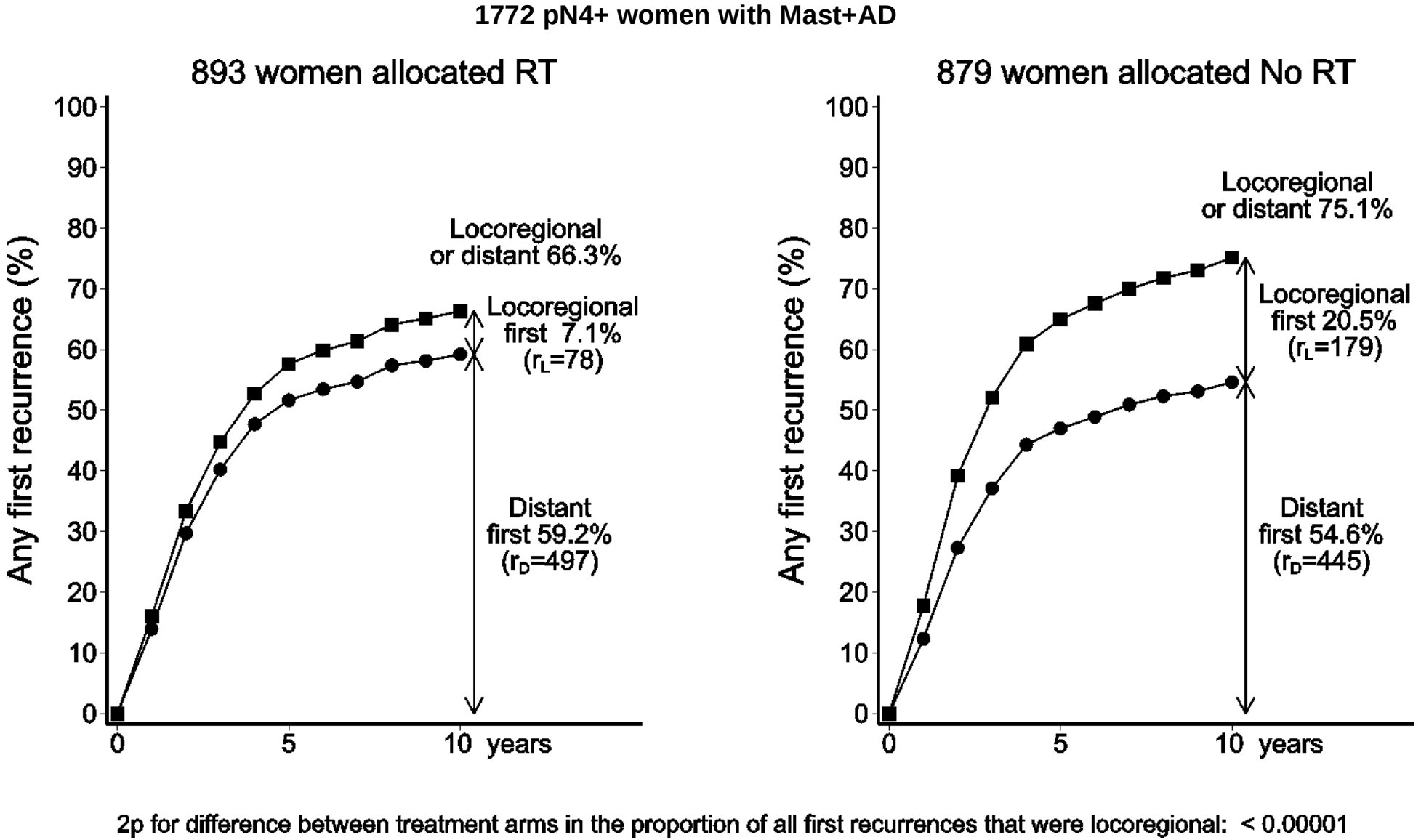
Webfigure 15. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 450 women with 1-3 pathologically positive nodes (pN1-3) but the exact 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.)



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.



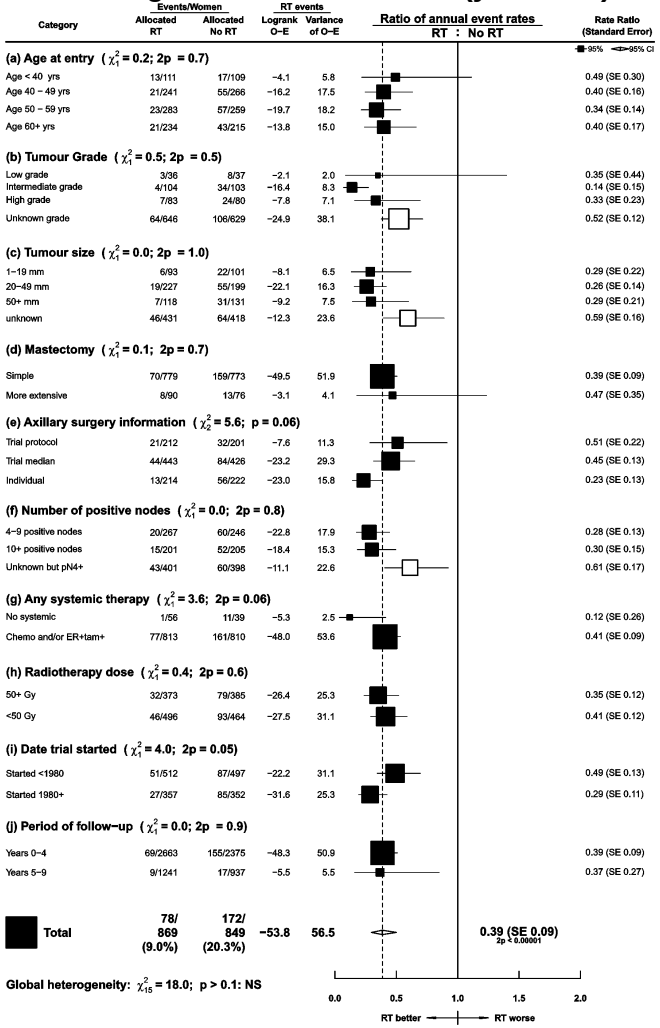
Webfigure 17. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1772 women with 4+ pathologically positive nodes (pN4+). (r_L = number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



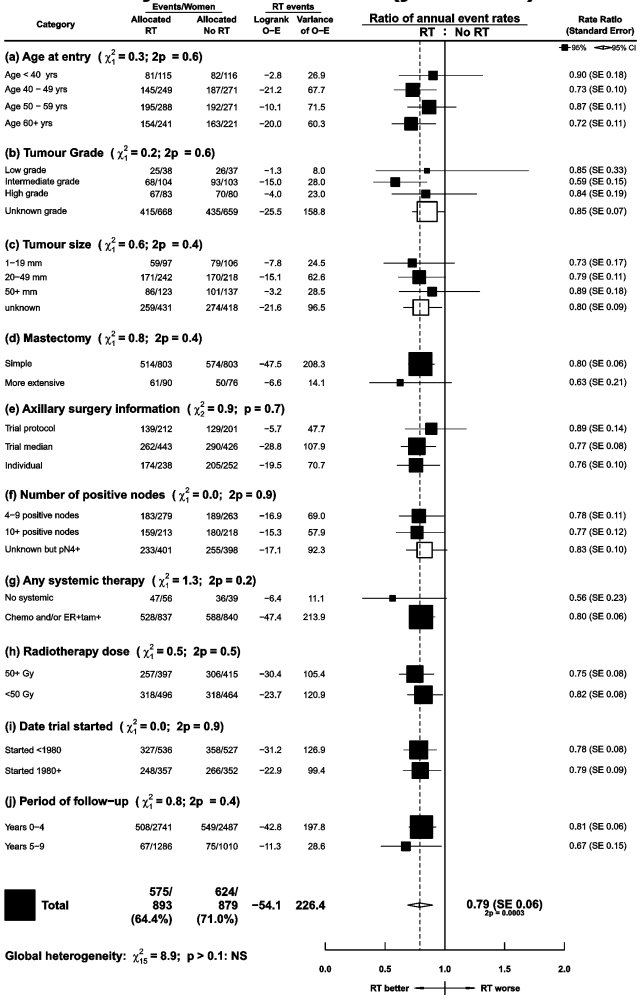
Webfigure 18. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): Event rate ratios and 95% confidence intervals for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer mortality in 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

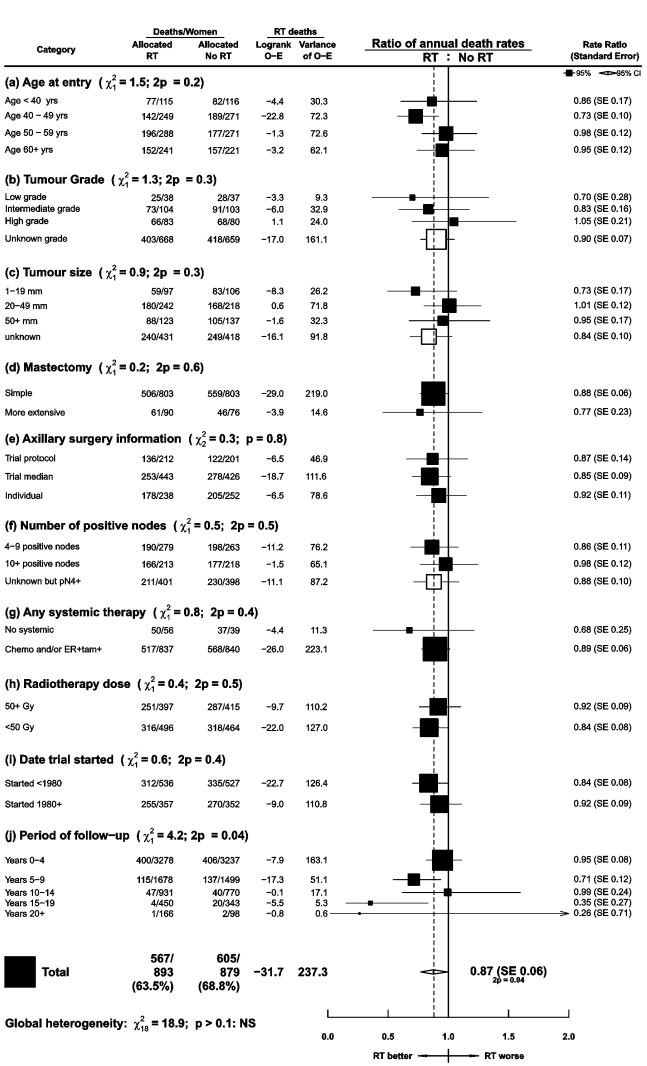
Locoregional recurrence first (years 0-9)



Any first recurrence (years 0-9)

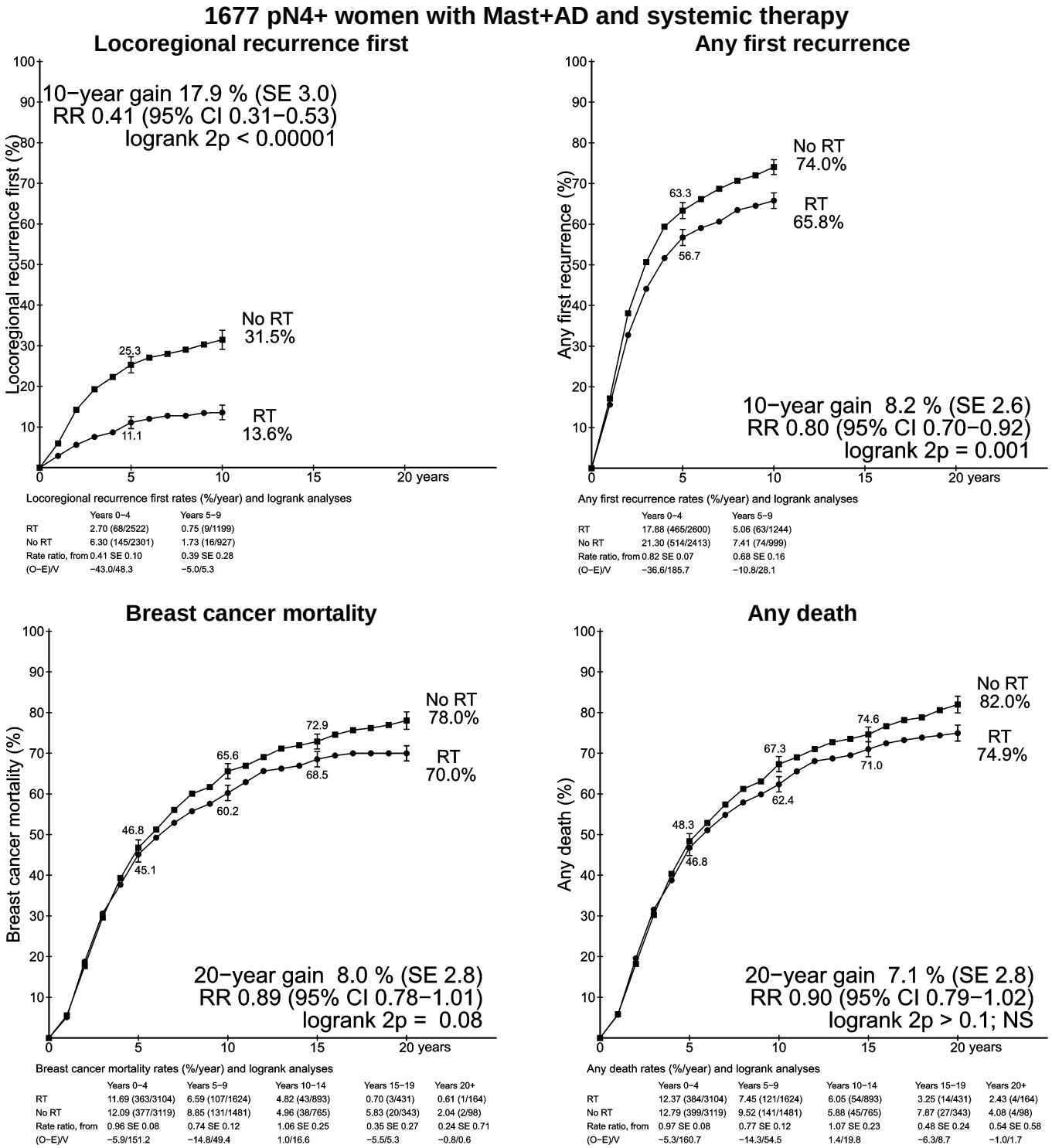


Breast cancer mortality

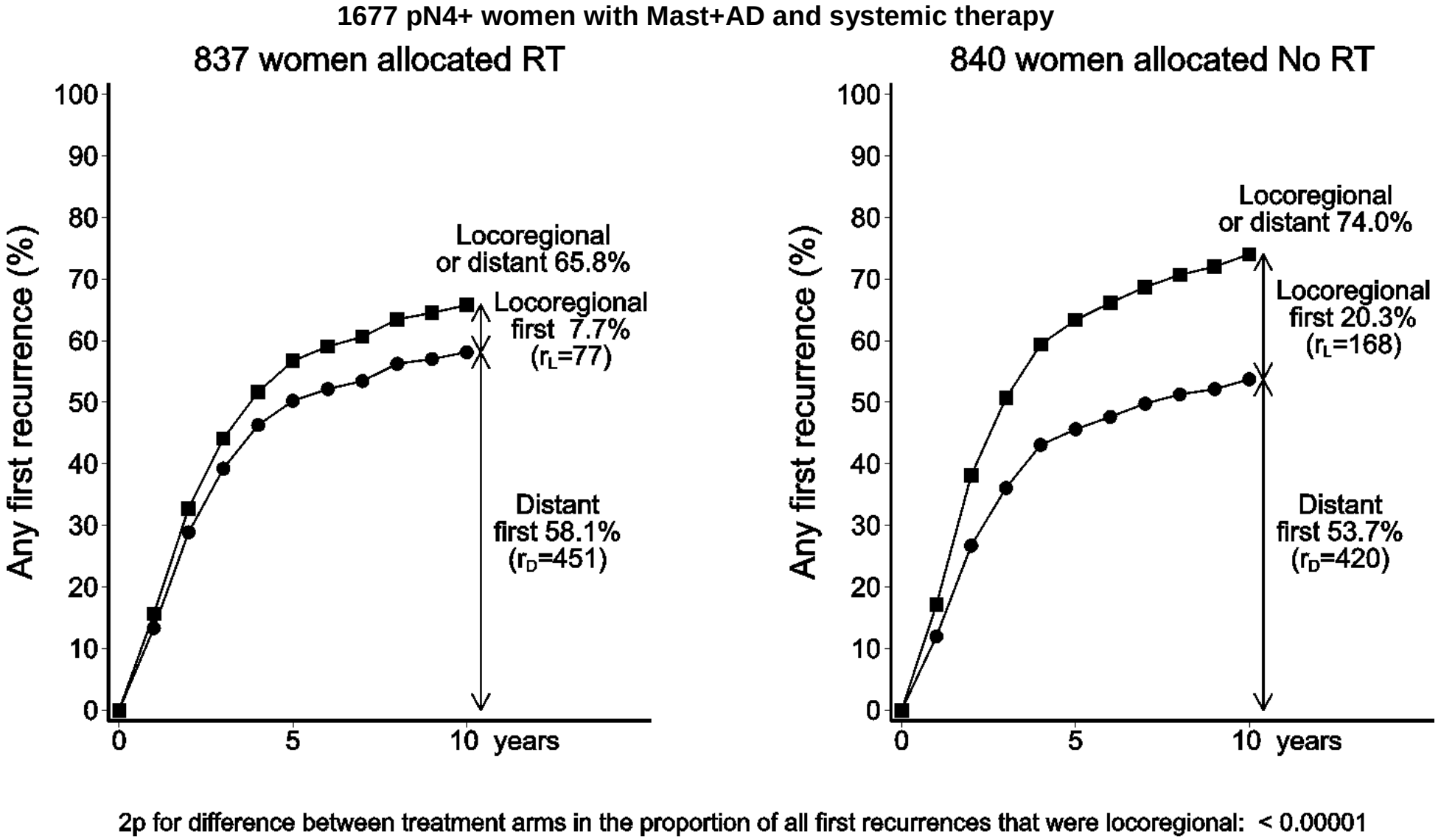


Note:In (g), 135 women who were ER positive with tamoxifen also had chemotherapy. In (h), trials that used orthovoltage irradiation are included in the <50 Gy category.

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.



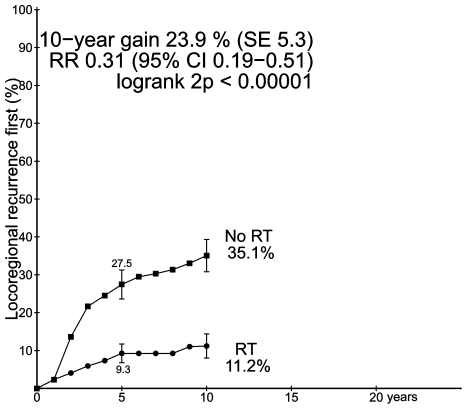
Webfigure 20. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1677 women with 4+ pathologically positive nodes (pN4+) in trials where 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.)



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.

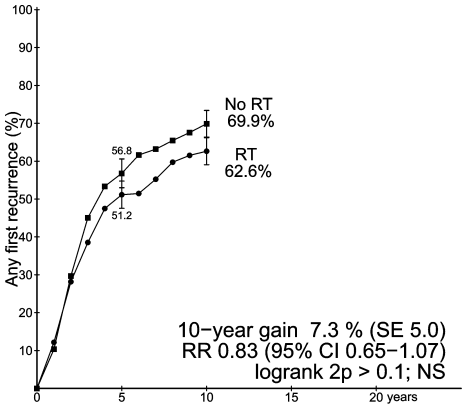
Locoregional recurrence first **Any first recurrence** **Breast cancer mortality**

479 women with Mast+AD, systemic therapy and 4-9 positive nodes



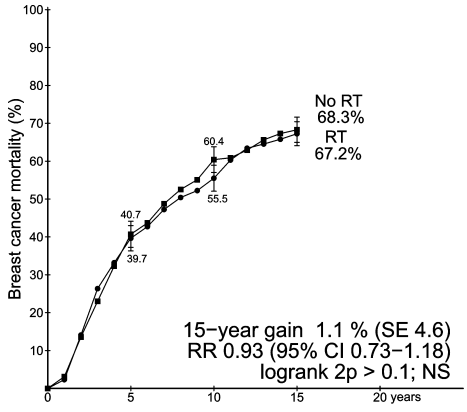
Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	2.16 (17/787)	0.68 (3/438)
No RT	6.67 (46/689)	1.88 (6/319)
Rate ratio, from	0.33 SE 0.16	0.18 SE 0.35
(O−E)/V	−15.5/14.2	−3.2/1.8



Any first recurrence rates (%/year) and logrank analyses

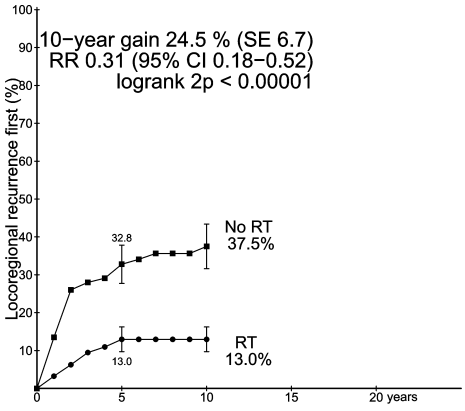
	Years 0−4	Years 5−9
RT	15.14 (126/832)	6.06 (26/462)
No RT	17.67 (134/758)	7.95 (29/365)
Rate ratio, from	0.86 SE 0.13	0.71 SE 0.26
(O−E)/V	−7.5/50.0	−3.8/10.9



Breast cancer mortality rates (%/year) and logrank analyses

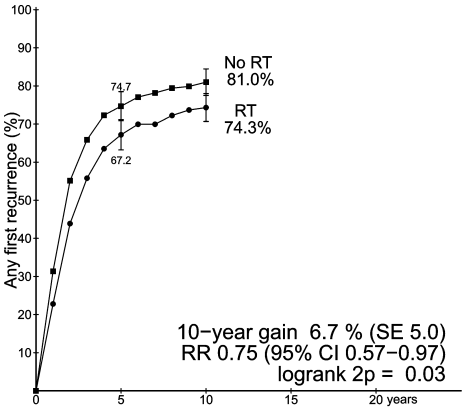
	Years 0−4	Years 5−9	Years 10−14	Years 15+
RT	9.78 (96/982)	6.31 (38/602)	5.54 (22/397)	0.75 (2/268)
No RT	10.01 (95/949)	7.72 (43/557)	5.15 (19/369)	6.02 (14/233)
Rate ratio, from	0.99 SE 0.16	0.78 SE 0.22	1.52 SE 0.43	0.23 SE 0.32
(O−E)/V	−0.5/39.9	−4.2/16.5	3.6/8.5	−4.0/2.7

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



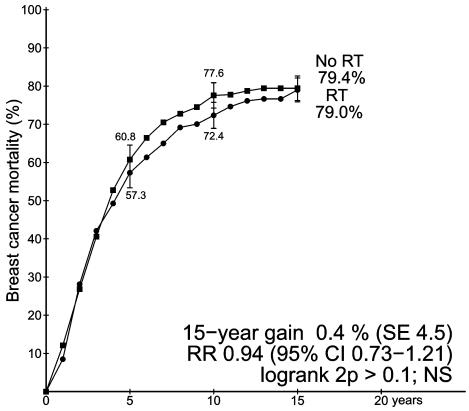
Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	2.83 (14/494)	0.00 (0/240)
No RT	10.55 (46/436)	1.93 (3/155)
Rate ratio, from	0.32 SE 0.16	0.16 SE 0.54
(O−E)/V	−15.4/13.6	−1.3/0.7



Any first recurrence rates (%/year) and logrank analyses

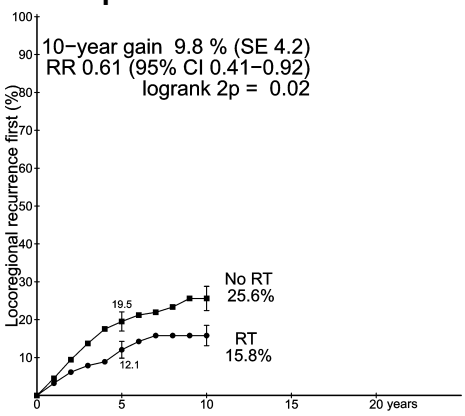
	Years 0−4	Years 5−9
RT	24.49 (129/527)	5.19 (13/250)
No RT	33.00 (158/479)	7.32 (13/178)
Rate ratio, from	0.74 SE 0.12	0.80 SE 0.40
(O−E)/V	−14.8/49.5	−1.1/4.9



Breast cancer mortality rates (%/year) and logrank analyses

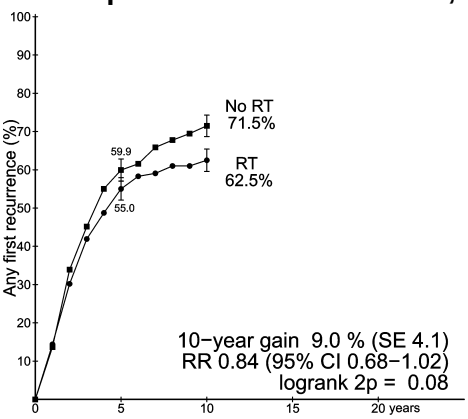
	Years 0−4	Years 5−9	Years 10−14	Years 15+
RT	16.59 (109/657)	8.28 (27/326)	5.22 (11/211)	1.68 (2/119)
No RT	18.01 (127/705)	12.41 (34/274)	1.86 (3/162)	5.19 (4/77)
Rate ratio, from	0.91 SE 0.14	0.77 SE 0.25	2.66 SE 0.99	1.85 SE 1.41
(O−E)/V	−4.0/44.9	−3.1/11.9	2.9/2.9	0.6/1.0

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



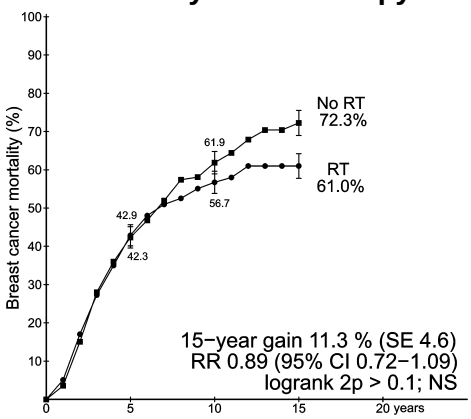
Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	2.98 (37/1242)	1.15 (6/521)
No RT	4.51 (53/1176)	1.55 (7/452)
Rate ratio, from	0.59 SE 0.17	0.83 SE 0.57
(O−E)/V	−10.6/20.1	−0.5/2.6



Any first recurrence rates (%/year) and logrank analyses

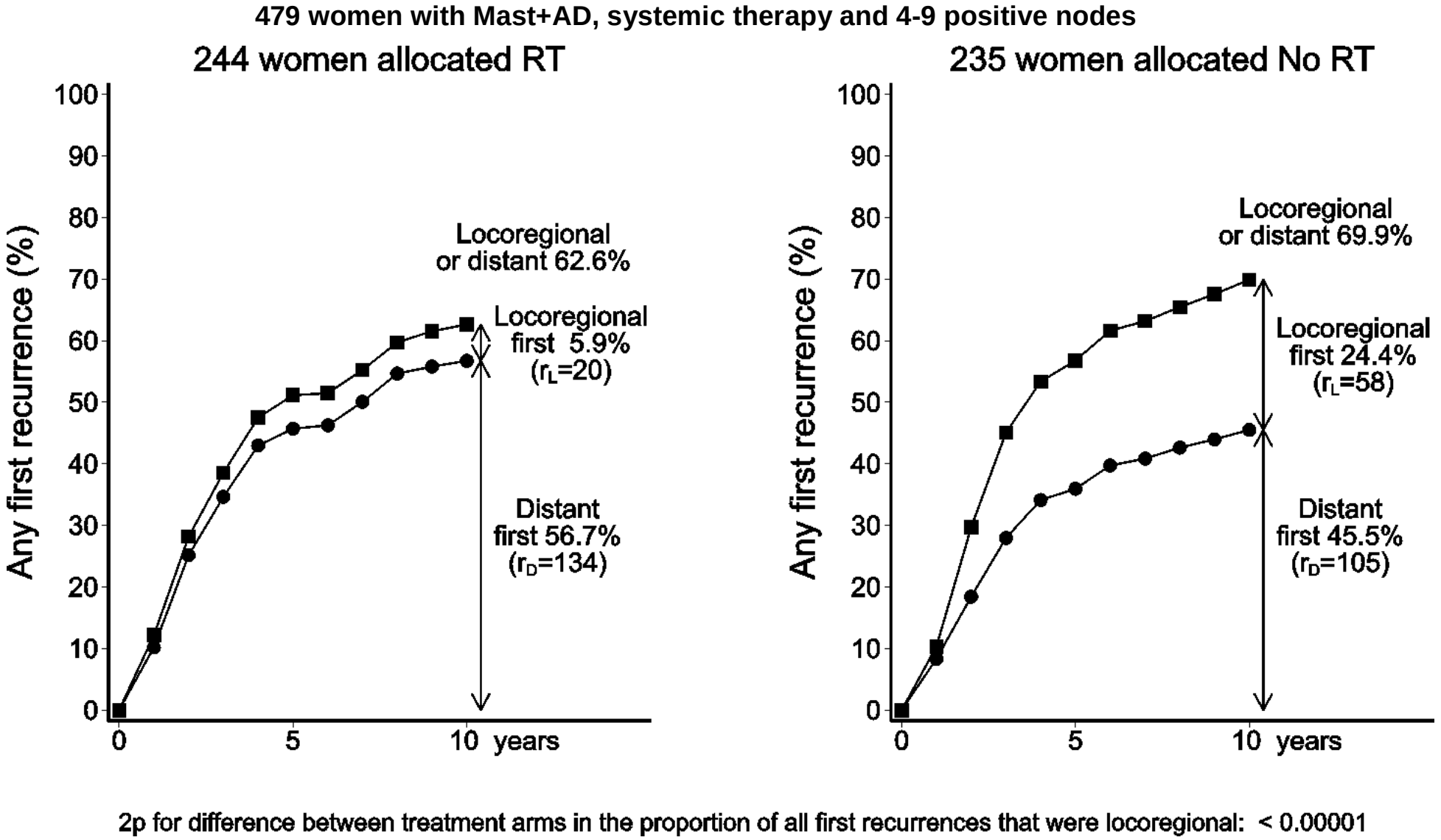
	Years 0−4	Years 5−9
RT	16.91 (210/1242)	4.14 (22/532)
No RT	18.88 (222/1176)	7.00 (32/457)
Rate ratio, from	0.88 SE 0.10	0.58 SE 0.23
(O−E)/V	−10.7/81.2	−5.9/10.9



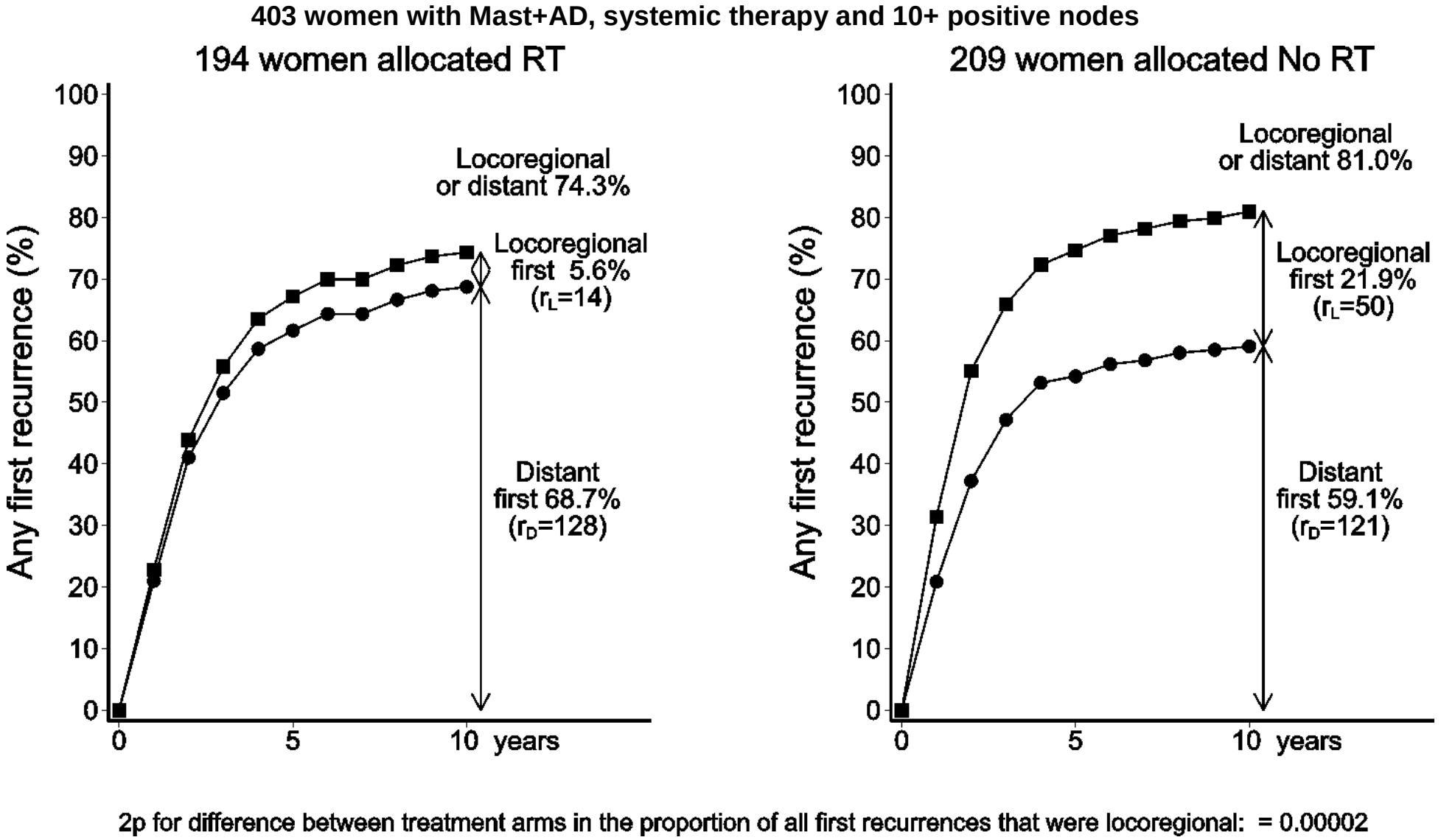
Breast cancer mortality rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15+
RT	10.78 (158/1466)	6.04 (42/695)	3.51 (10/285)	0.00 (0/209)
No RT	10.58 (155/1464)	8.31 (54/650)	6.81 (16/235)	3.05 (4/131)
Rate ratio, from	1.02 SE 0.13	0.68 SE 0.19	0.45 SE 0.33	0.47 SE 0.64
(O−E)/V	1.3/62.2	−7.5/19.1	−3.5/4.5	−0.9/1.2

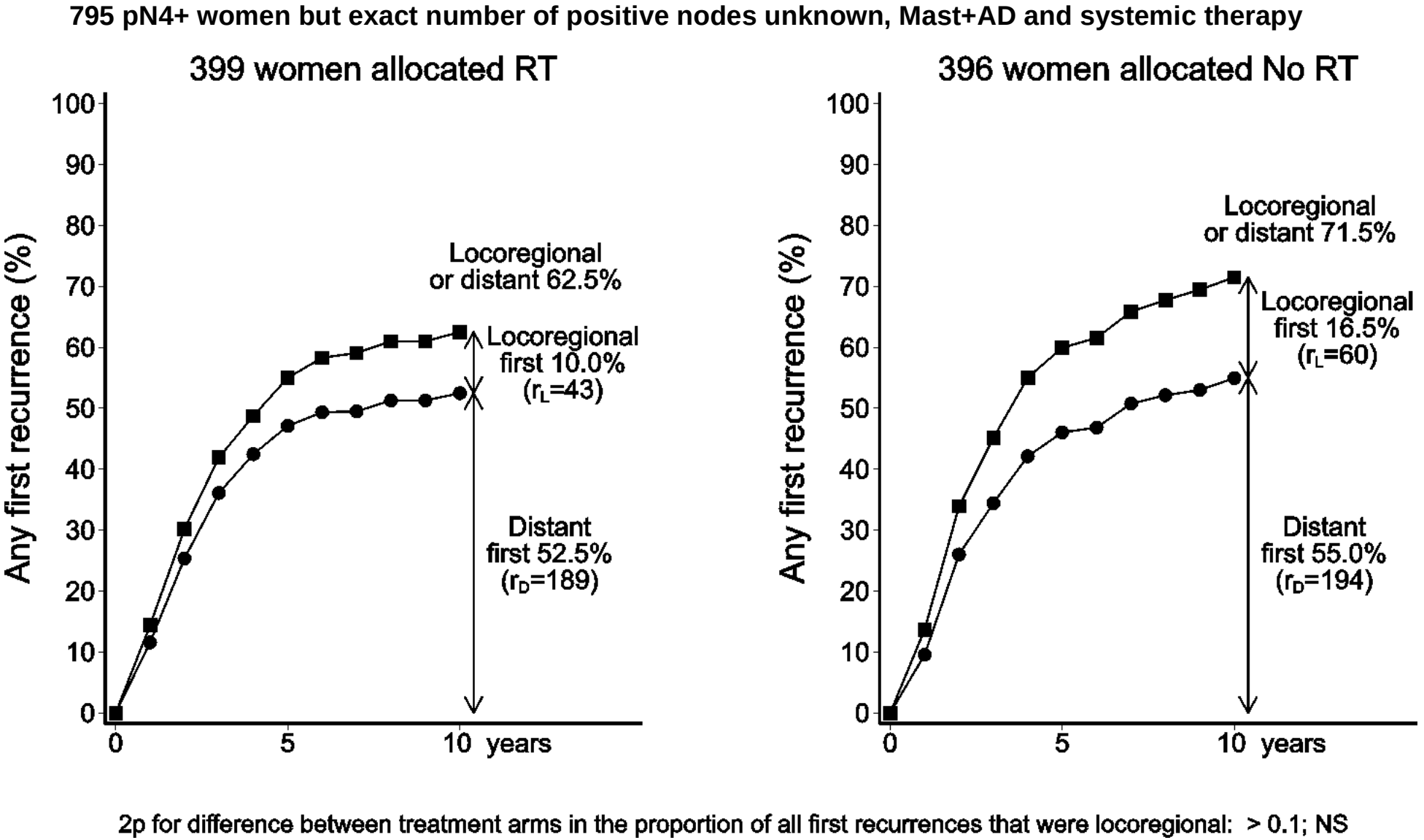
Webfigure 22. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 479 women with 4-9 pathologically positive nodes (pN4-9) in trials where 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.)



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.)



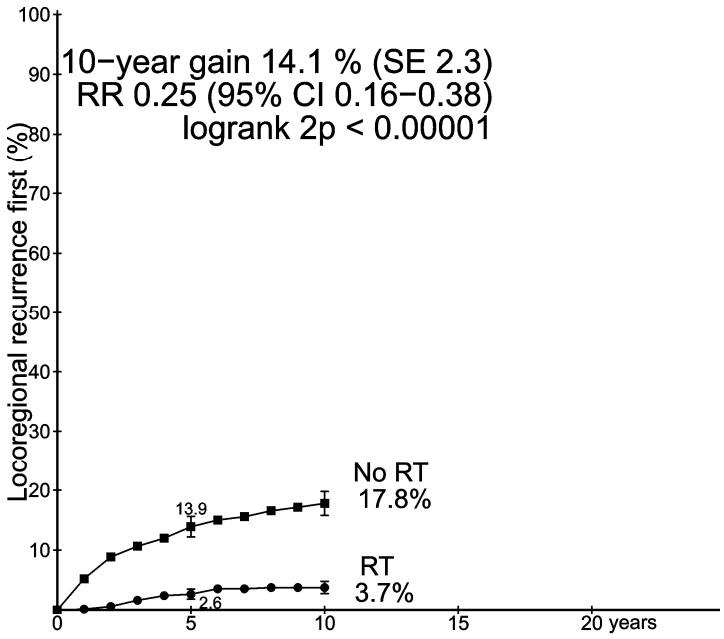
Webfigure 24. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 795 women with 4+ pathologically positive nodes but the exact number 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.)



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 ⩾ 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 ⩾ 5 cm who were allocated to not to receive radiotherapy.

870 pN0 women with Mast+AS

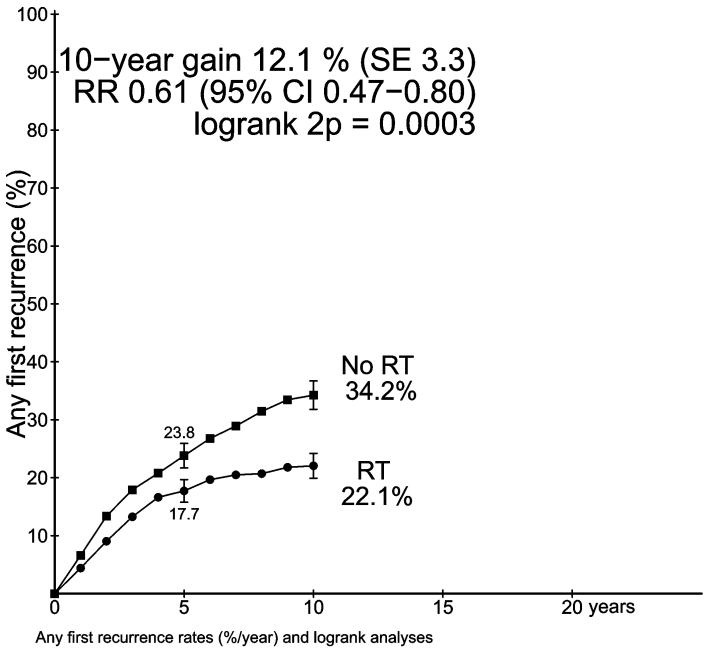
Locoregional recurrence first



Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	0.54 (10/1849)	0.27 (4/1504)
No RT	3.11 (58/1862)	1.02 (14/1373)
Rate ratio, from	0.23 SE 0.13	0.32 SE 0.29
(O−E)/V	−23.0/15.8	−4.8/4.2

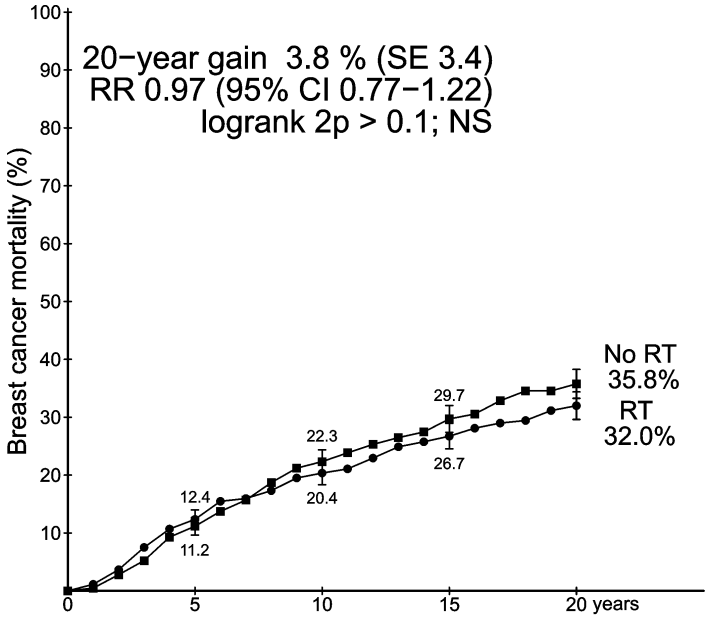
Any first recurrence



Any first recurrence rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	4.11 (76/1849)	1.20 (18/1504)
No RT	5.58 (104/1862)	3.35 (46/1373)
Rate ratio, from	0.71 SE 0.13	0.40 SE 0.17
(O−E)/V	−13.8/40.7	−12.9/14.0

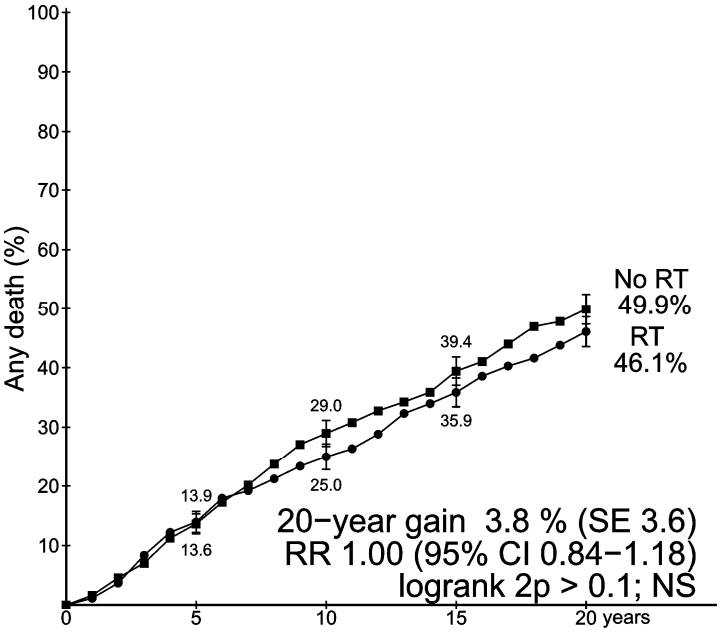
Breast cancer mortality



Breast cancer mortality rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	2.67 (53/1986)	1.91 (32/1679)	1.51 (22/1455)	1.47 (17/1155)	2.07 (30/1451)
No RT	2.30 (48/2089)	2.72 (47/1729)	2.14 (31/1450)	1.86 (20/1075)	1.85 (25/1349)
Rate ratio, from	1.13 SE 0.22	0.73 SE 0.20	0.84 SE 0.26	0.83 SE 0.31	1.46 SE 0.36
(O−E)/V	2.8/23.4	−5.6/17.7	−2.2/12.6	−1.6/8.5	4.3/11.3

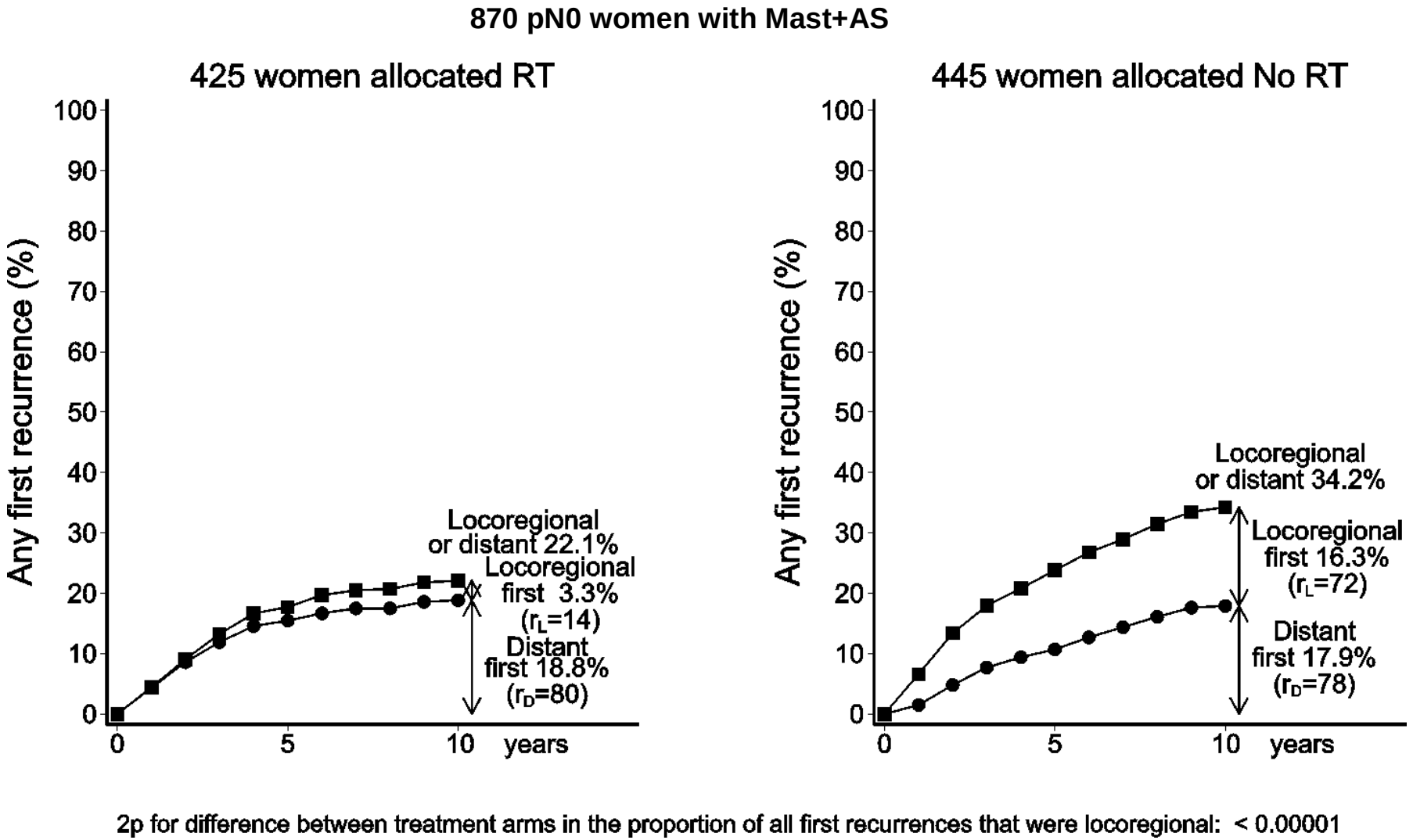
Any death



Any death rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	3.12 (62/1986)	2.86 (48/1679)	3.16 (46/1455)	3.55 (41/1155)	6.96 (101/1451
No RT	2.97 (62/2089)	3.93 (68/1729)	3.17 (46/1450)	3.91 (42/1075)	5.86 (79/1349)
Rate ratio, from	1.03 SE 0.19	0.71 SE 0.16	0.99 SE 0.21	0.92 SE 0.22	1.29 SE 0.18
(O−E)/V	0.8/28.5	−9.2/26.5	−0.2/21.6	−1.6/18.8	9.8/38.2

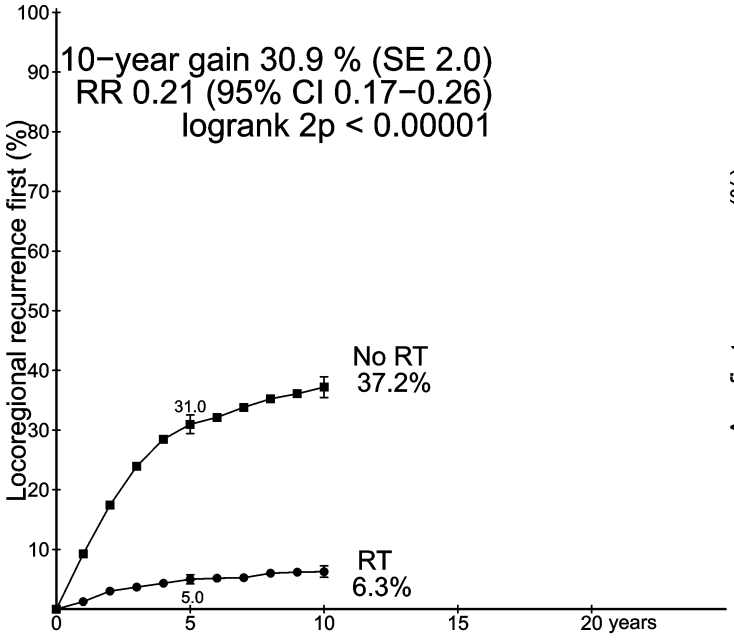
Webfigure 26. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 870 women with pathologically node negative (pN0) disease. (r_L = number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



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

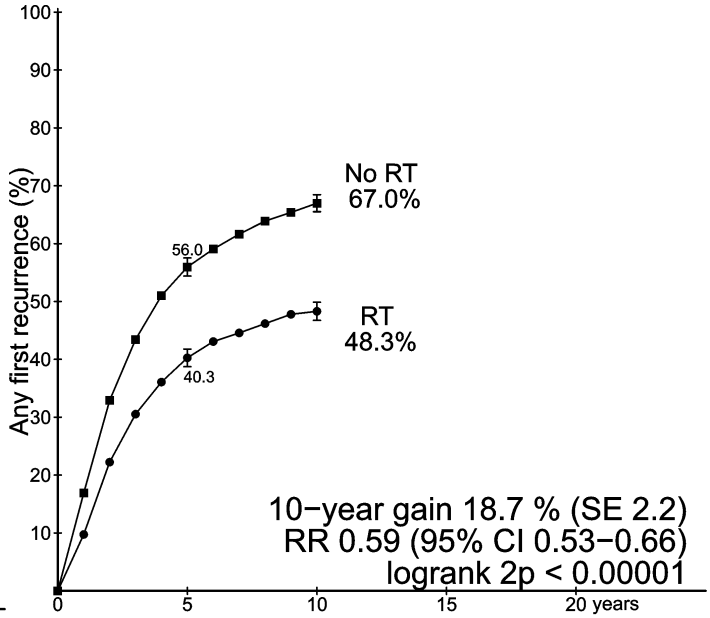
Locoregional recurrence first



Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	1.31 (61/4667)	0.44 (13/2977)
No RT	8.10 (325/4011)	2.06 (43/2087)
Rate ratio, from	0.21 SE 0.05	0.22 SE 0.15
(O−E)/V	−139.0/88.6	−18.9/12.6

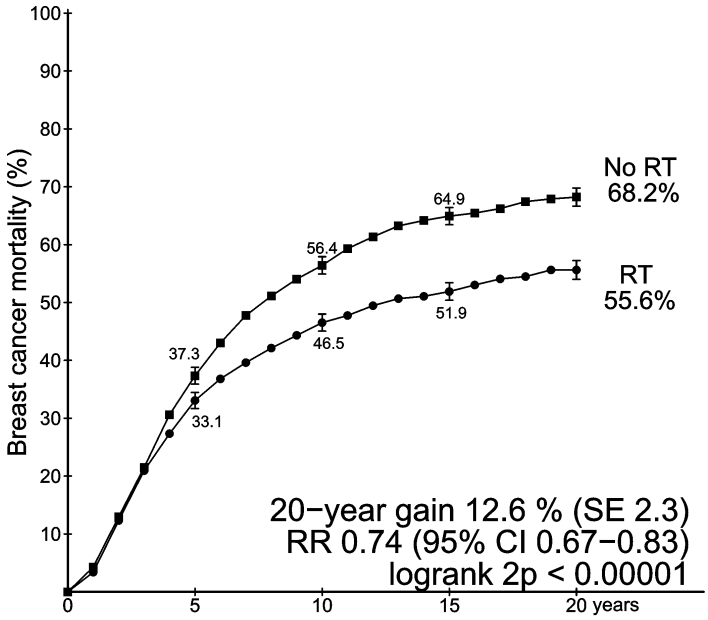
Any first recurrence



Any first recurrence rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	11.05 (519/4698)	3.41 (102/2996)
No RT	17.29 (700/4050)	6.15 (130/2114)
Rate ratio, from	0.61 SE 0.05	0.51 SE 0.10
(O−E)/V	−120.1/242.0	−33.4/50.0

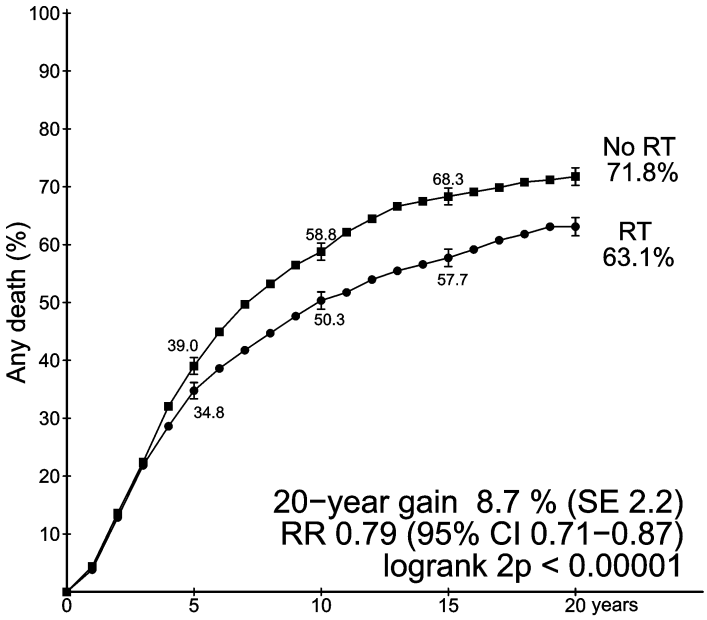
Breast cancer mortality



Breast cancer mortality rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	7.77 (410/5278)	4.63 (164/3539)	2.30 (57/2473)	1.78 (22/1239)	1.25 (6/480)
No RT	9.16 (473/5163)	7.55 (229/3032)	4.80 (87/1813)	2.14 (19/888)	2.35 (8/340)
Rate ratio, from	0.86 SE 0.07	0.61 SE 0.09	0.48 SE 0.13	0.93 SE 0.33	1.14 SE 0.63
(O−E)/V	−27.7/187.2	−42.2/85.3	−23.0/31.5	−0.6/8.3	0.4/2.9

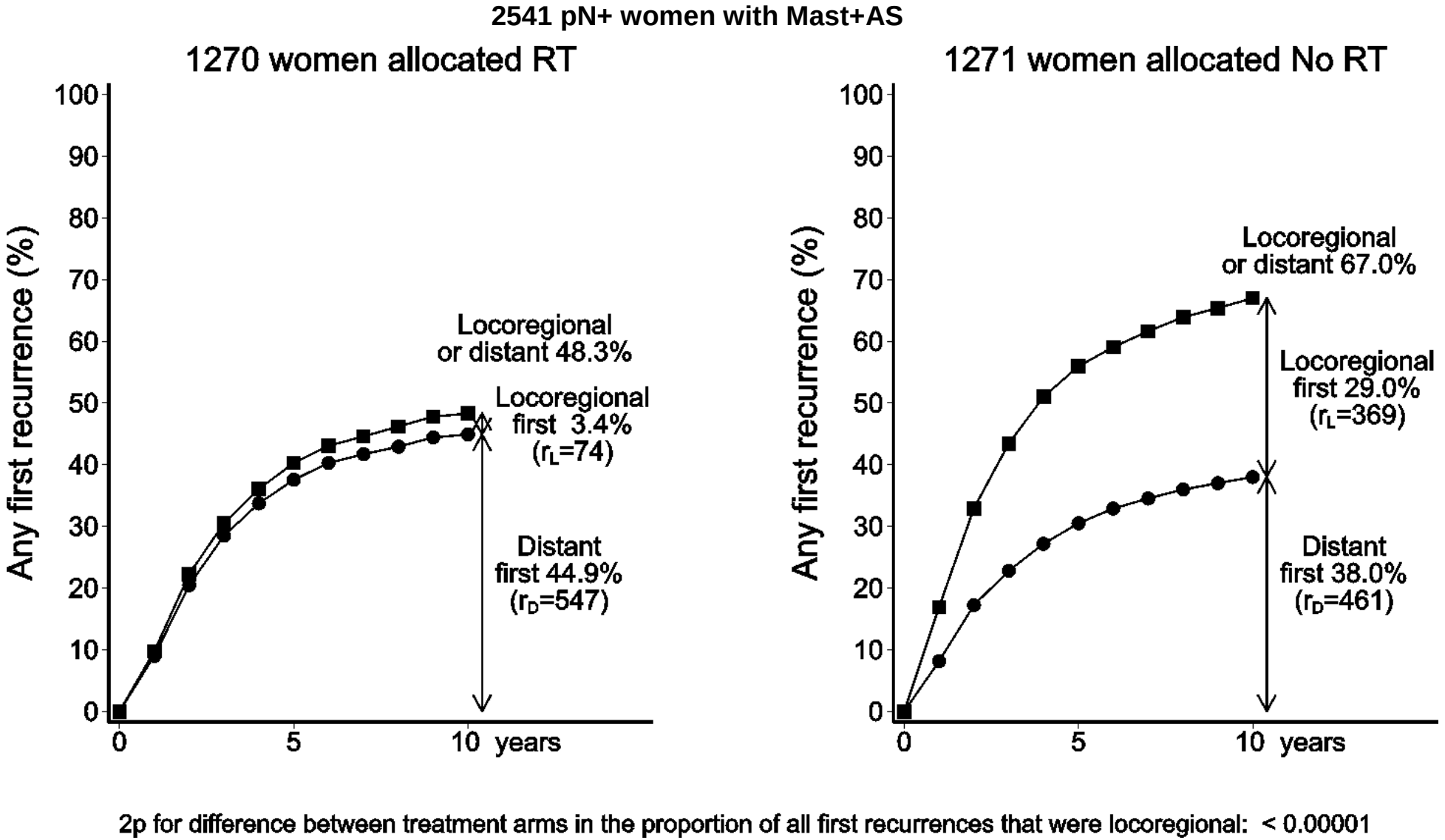
Any death



Any death rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	8.36 (441/5278)	5.77 (204/3539)	3.56 (88/2473)	3.23 (40/1239)	3.75 (18/480)
No RT	9.72 (502/5163)	8.24 (250/3032)	5.90 (107/1813)	2.70 (24/888)	4.41 (15/340)
Rate ratio, from	0.87 SE 0.07	0.68 SE 0.08	0.59 SE 0.12	1.28 SE 0.31	0.87 SE 0.39
(O−E)/V	−28.9/201.6	−38.0/98.7	−22.7/42.5	3.3/13.1	−0.8/5.7

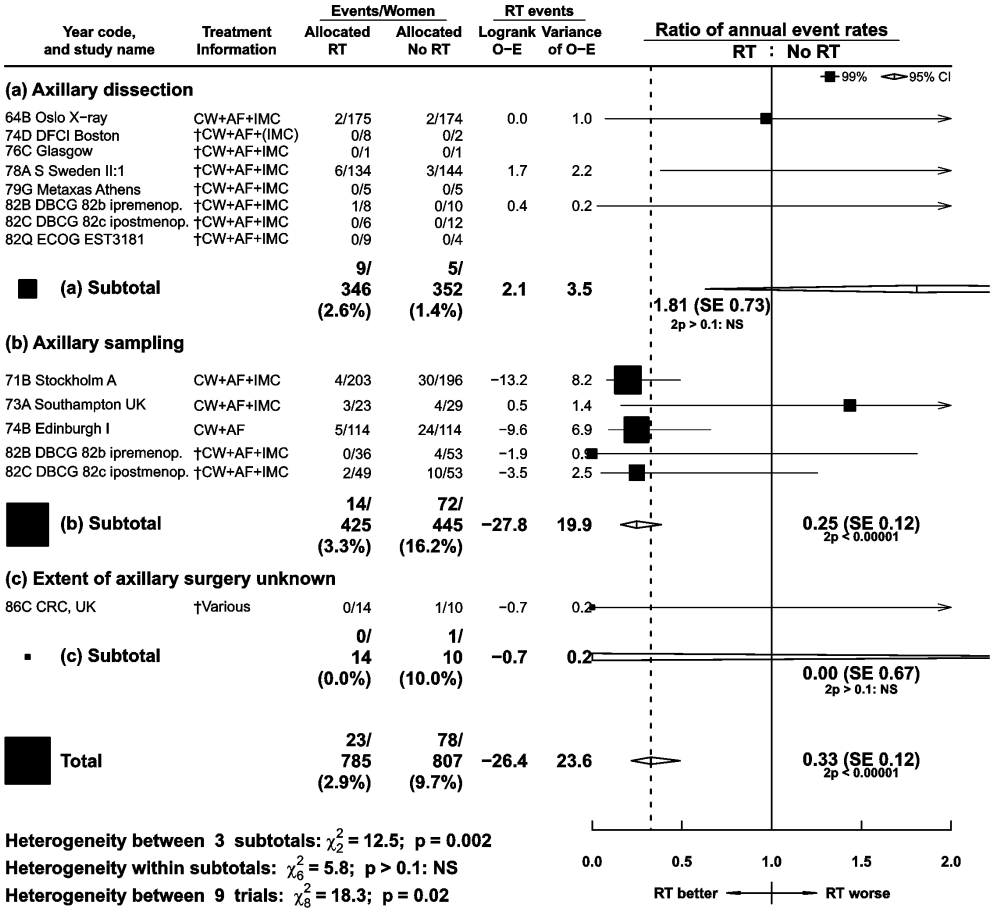
Webfigure 28. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 2541 women with pathologically node-positive (pN+) disease. (r_L = number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



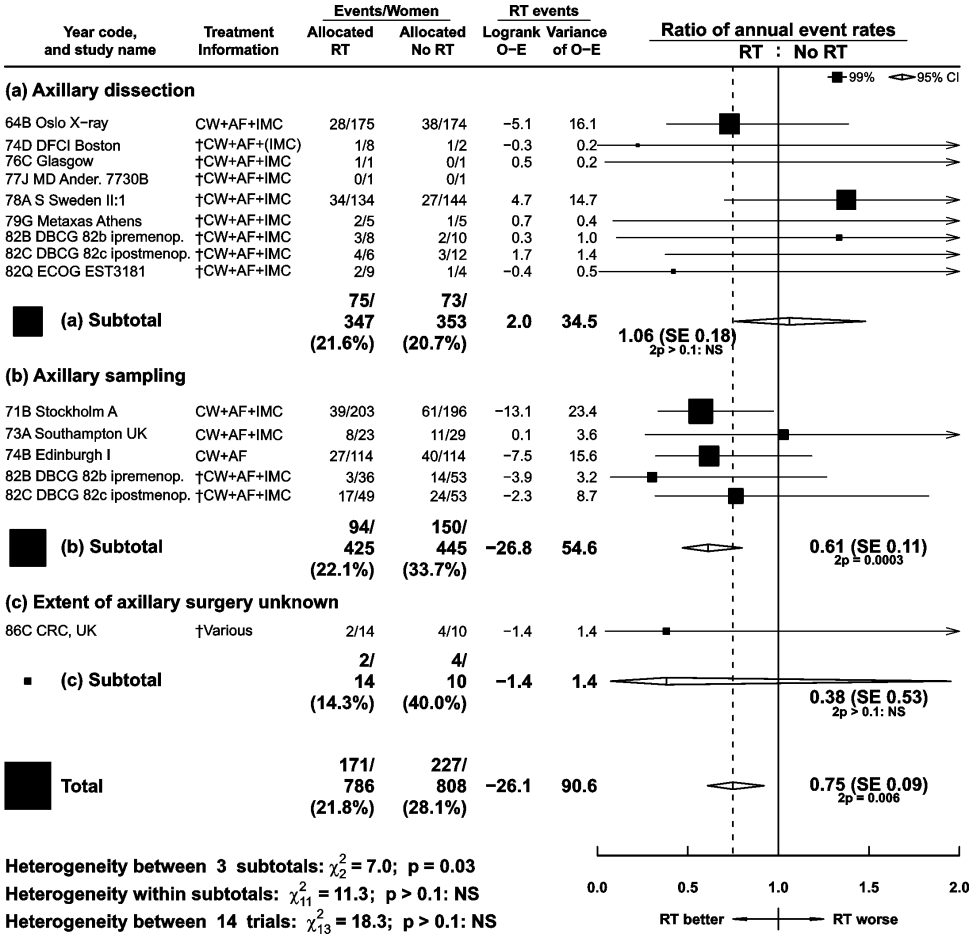
Webfigure 29. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast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

1594 pN0 women

Locoregional recurrence first (years 0-9)



Any first recurrence (years 0-9)



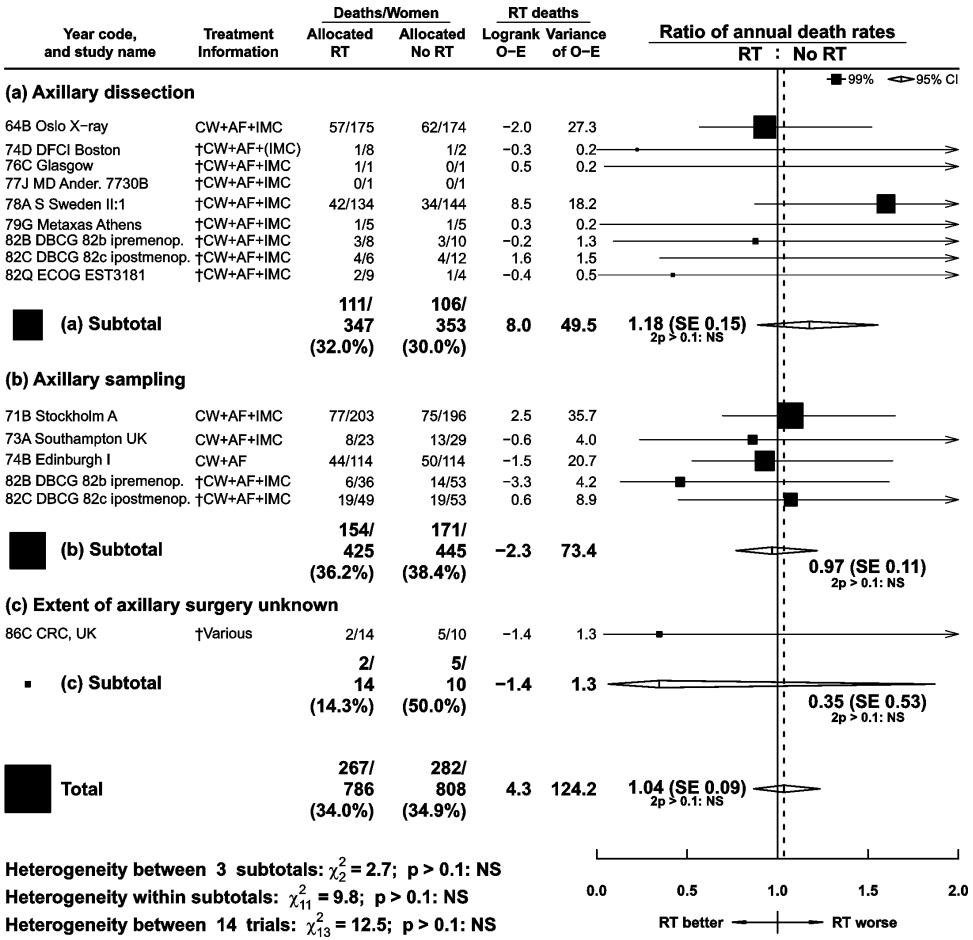
† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

Webfigure 29 cntd.

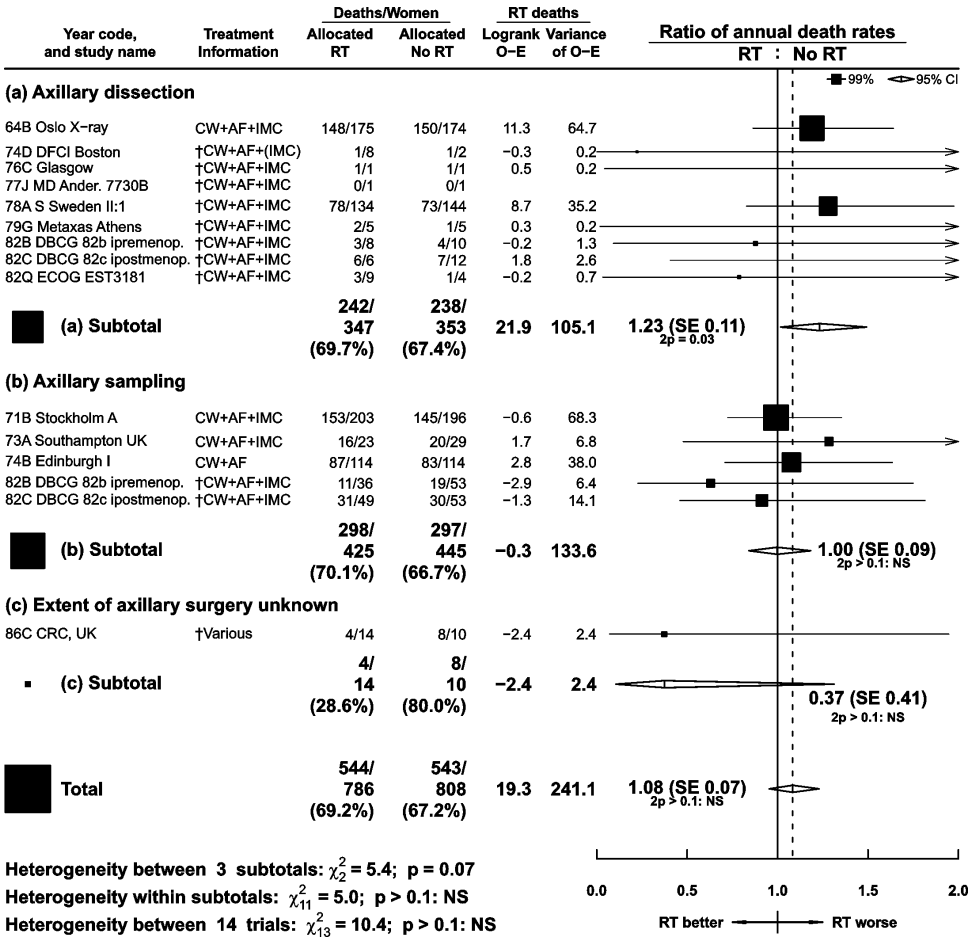
1594 pN0 women

Breast cancer mortality



Heterogeneity between 3 subtotals: $\chi^2_2 = 2.7$; **p > 0.1: NS**
Heterogeneity within subtotals: $\chi^2_{11} = 9.8$; **p > 0.1: NS**
Heterogeneity between 14 trials: $\chi^2_{13} = 12.5$; **p > 0.1: NS**

Any death



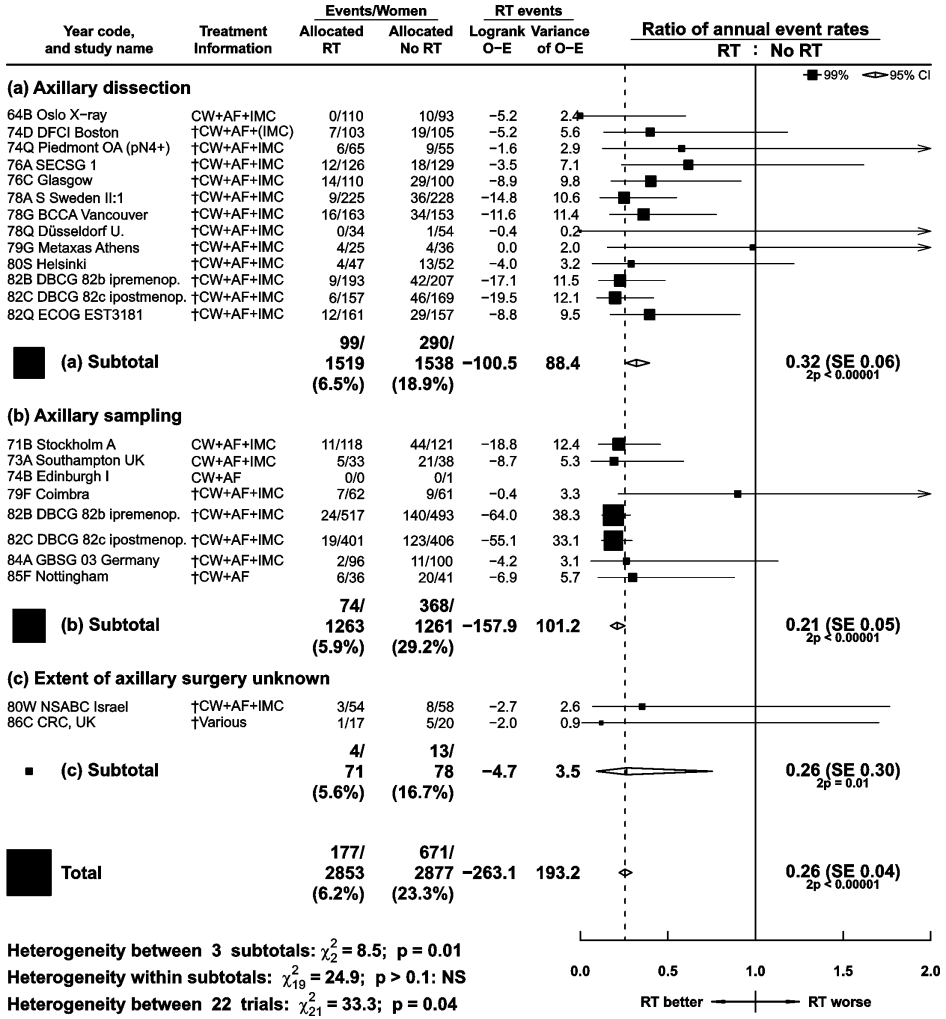
Heterogeneity between 3 subtotals: $\chi^2_2 = 5.4$; **p = 0.07**
Heterogeneity within subtotals: $\chi^2_{11} = 5.0$; **p > 0.1: NS**
Heterogeneity between 14 trials: $\chi^2_{13} = 10.4$; **p > 0.1: NS**

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

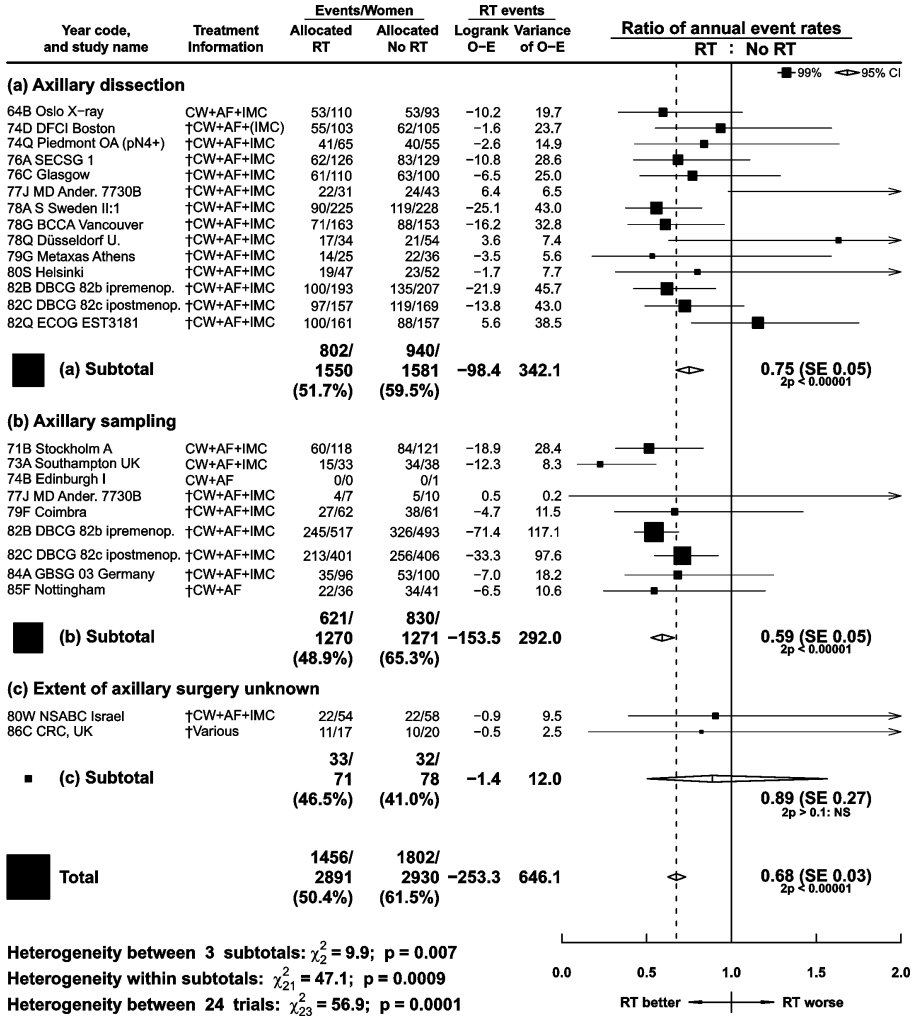
Webfigure 30. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast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

5821 pN+ women

Locoregional recurrence first (years 0-9)



Any first recurrence (years 0-9)



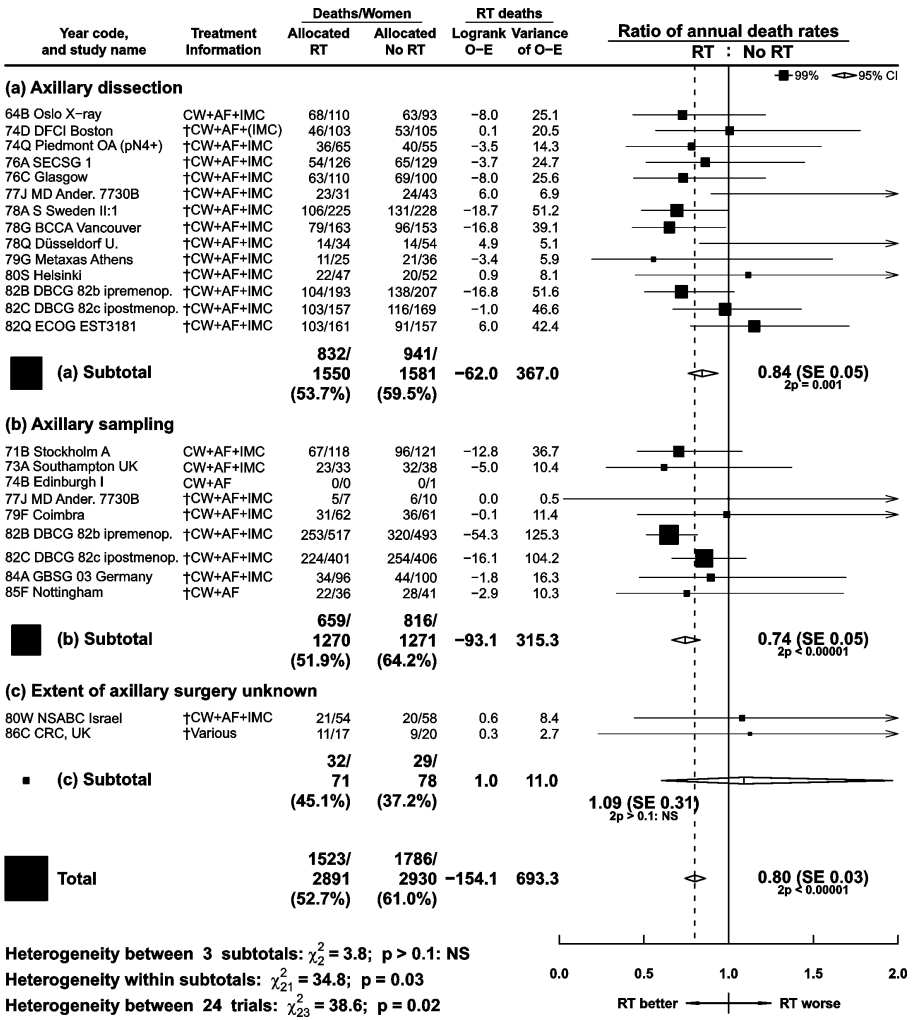
† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

Webfigure 30 cntd.

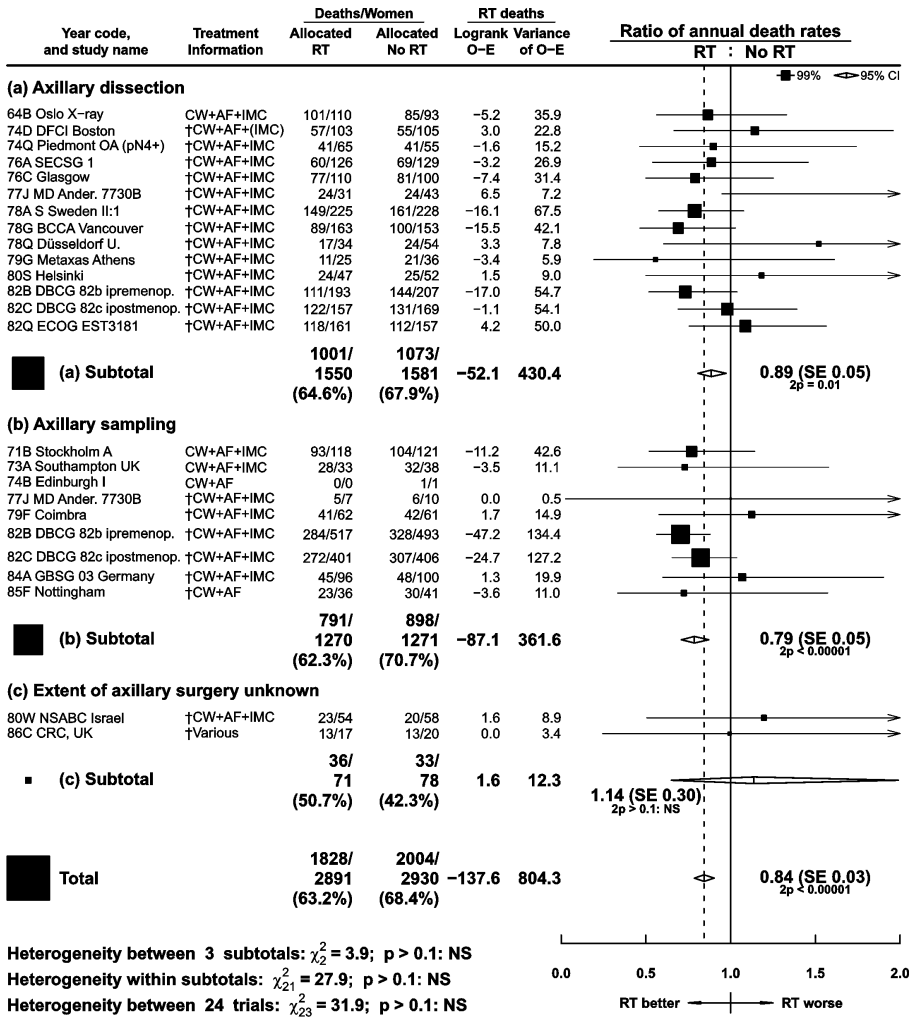
5821 pN+ women

Breast cancer mortality



Heterogeneity between 3 subtotals: $\chi^2_2 = 3.8$; p > 0.1: NS
Heterogeneity within subtotals: $\chi^2_{21} = 34.8$; p = 0.03
Heterogeneity between 24 trials: $\chi^2_{23} = 38.6$; p = 0.02

Any death



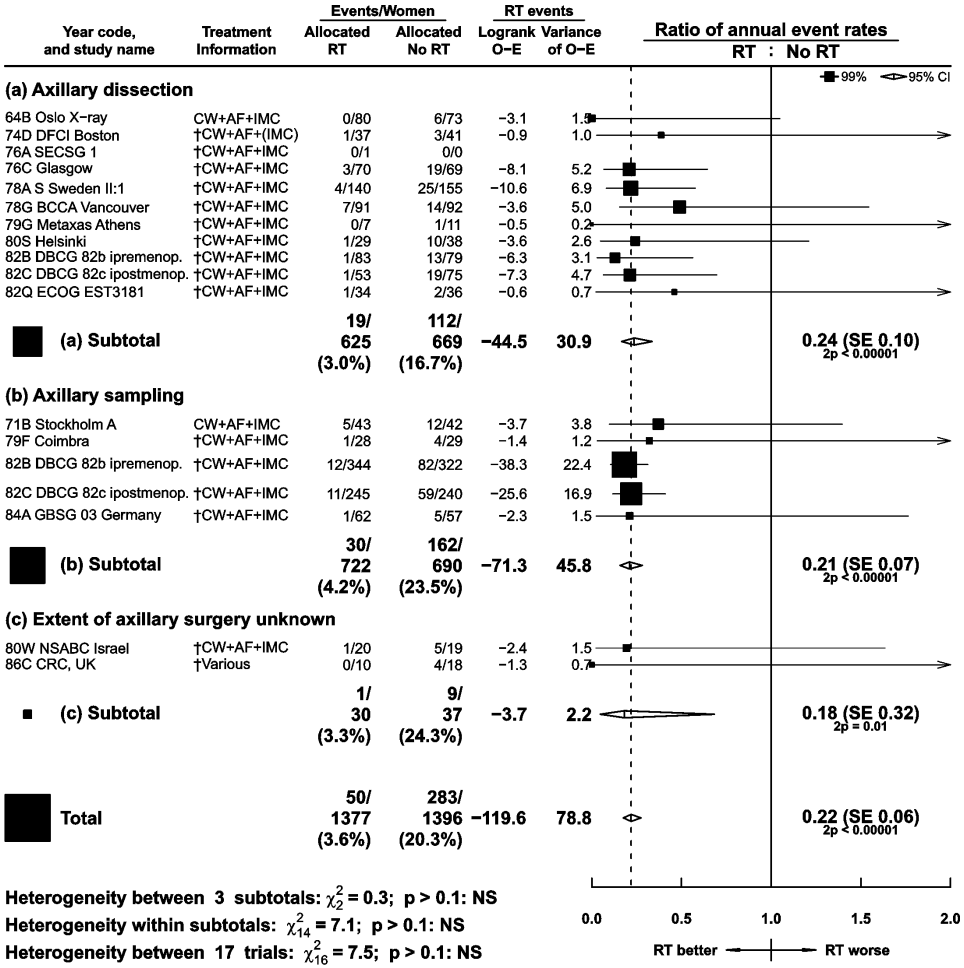
Heterogeneity between 3 subtotals: $\chi^2_2 = 3.9$; p > 0.1: NS
Heterogeneity within subtotals: $\chi^2_{21} = 27.9$; p > 0.1: NS
Heterogeneity between 24 trials: $\chi^2_{23} = 31.9$; p > 0.1: NS

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

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

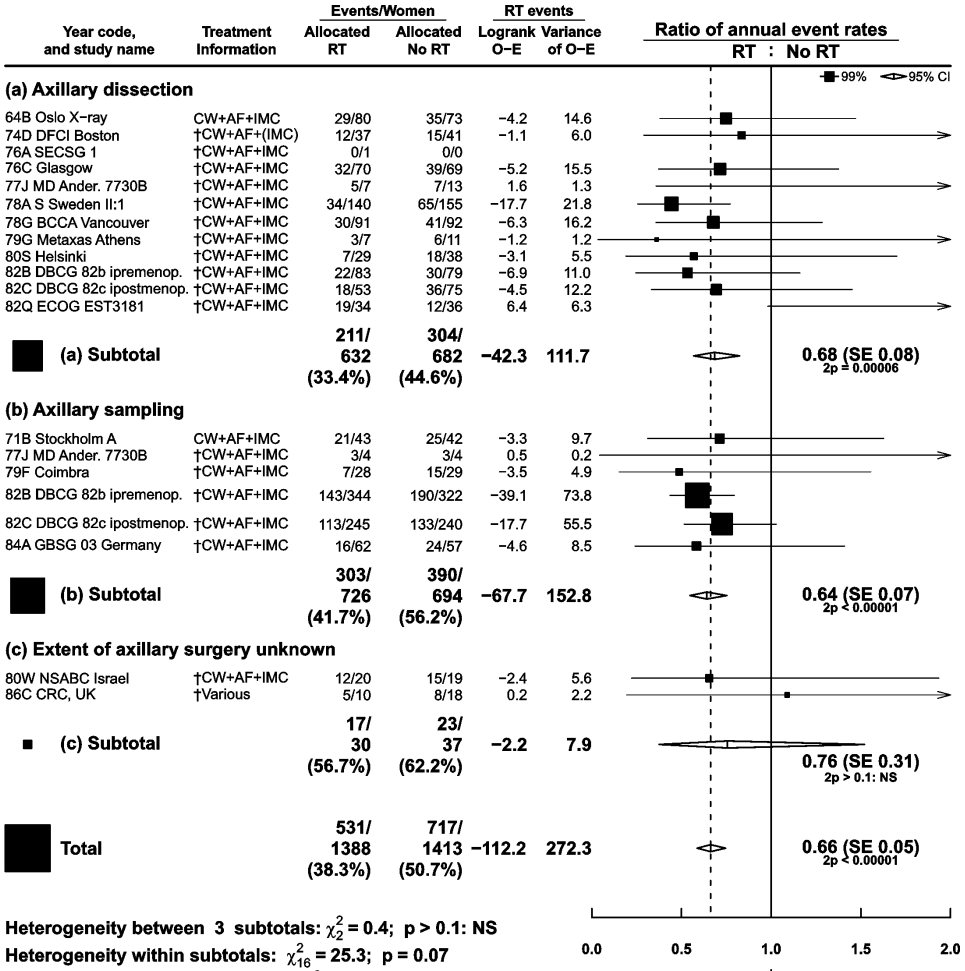
2801 pN1-3 women

Locoregional recurrence first (years 0-9)



Heterogeneity between 3 subtotals: $\chi^2_2 = 0.3$; **p > 0.1: NS**
Heterogeneity within subtotals: $\chi^2_{14} = 7.1$; **p > 0.1: NS**
Heterogeneity between 17 trials: $\chi^2_{16} = 7.5$; **p > 0.1: NS**

Any first recurrence (years 0-9)



Heterogeneity between 3 subtotals: $\chi^2_2 = 0.4$; **p > 0.1: NS**
Heterogeneity within subtotals: $\chi^2_{16} = 25.3$; **p = 0.07**
Heterogeneity between 19 trials: $\chi^2_{18} = 25.7$; **p > 0.1: NS**

† 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.

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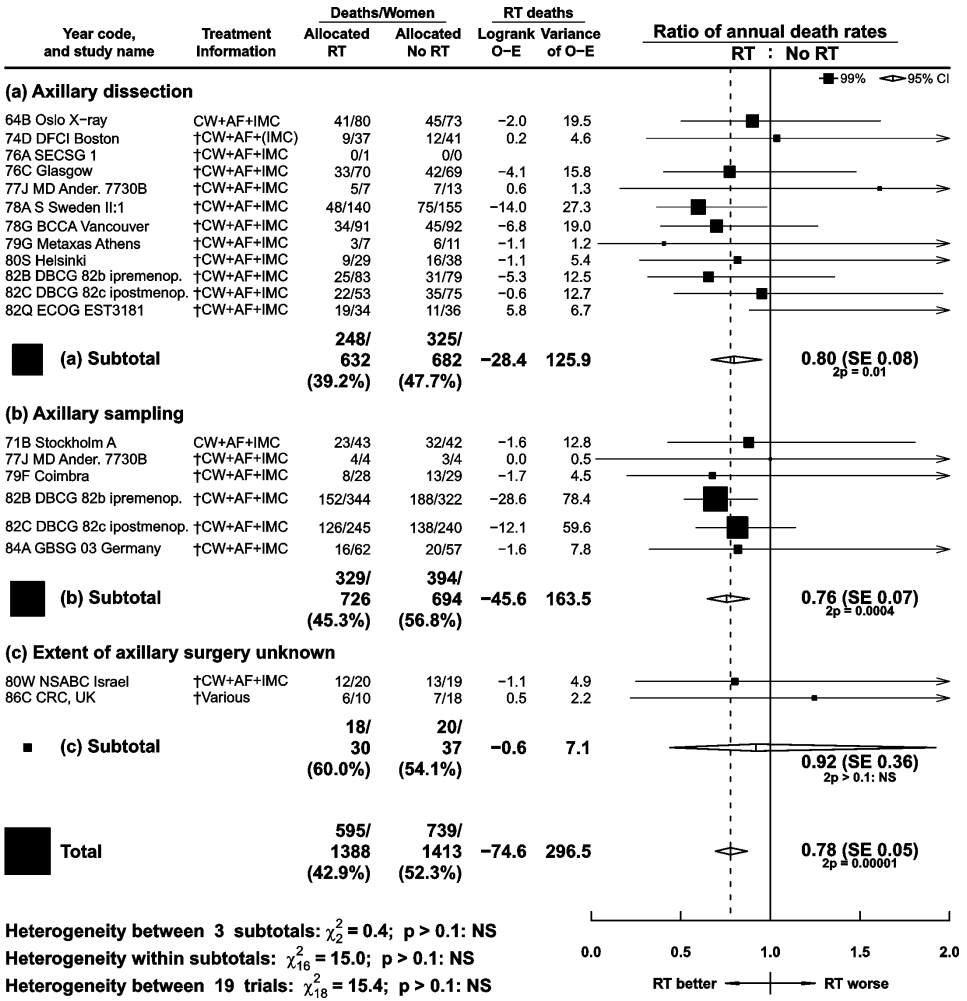
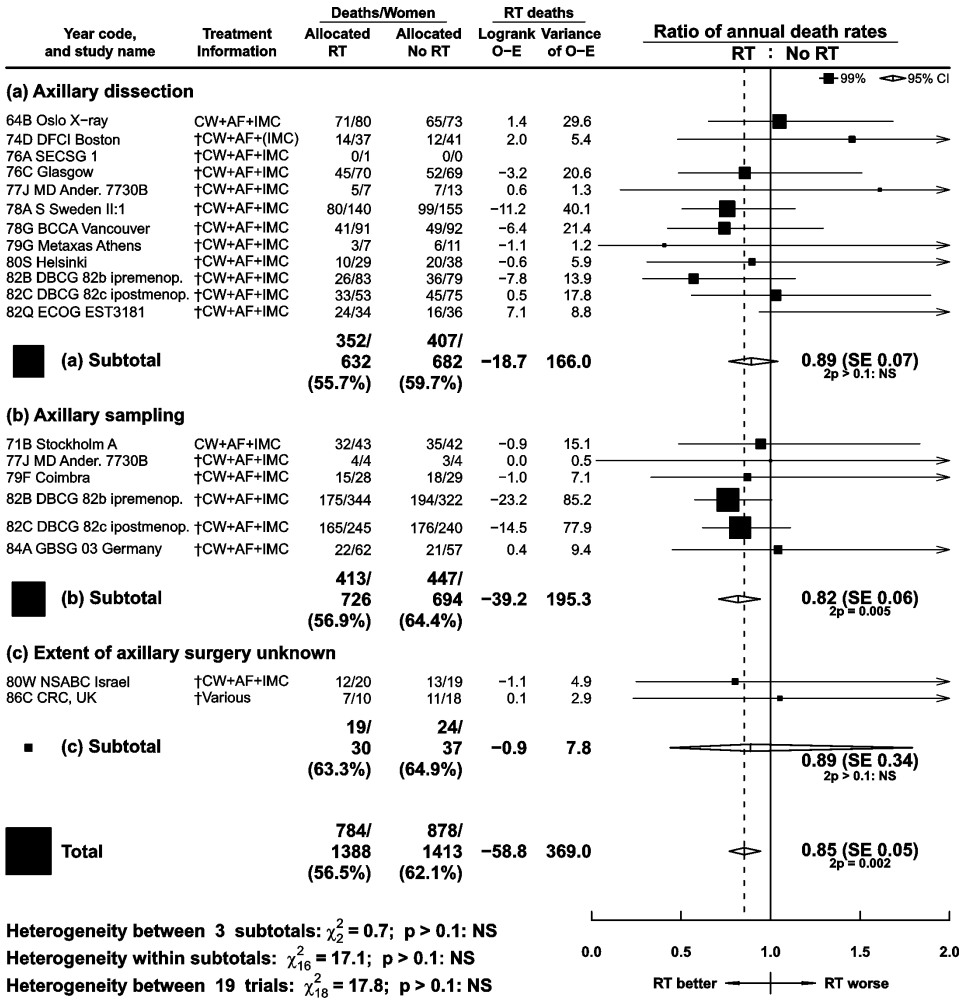
Webfigure 31 cntd.

2801 pN1-3 women

Breast cancer mortality

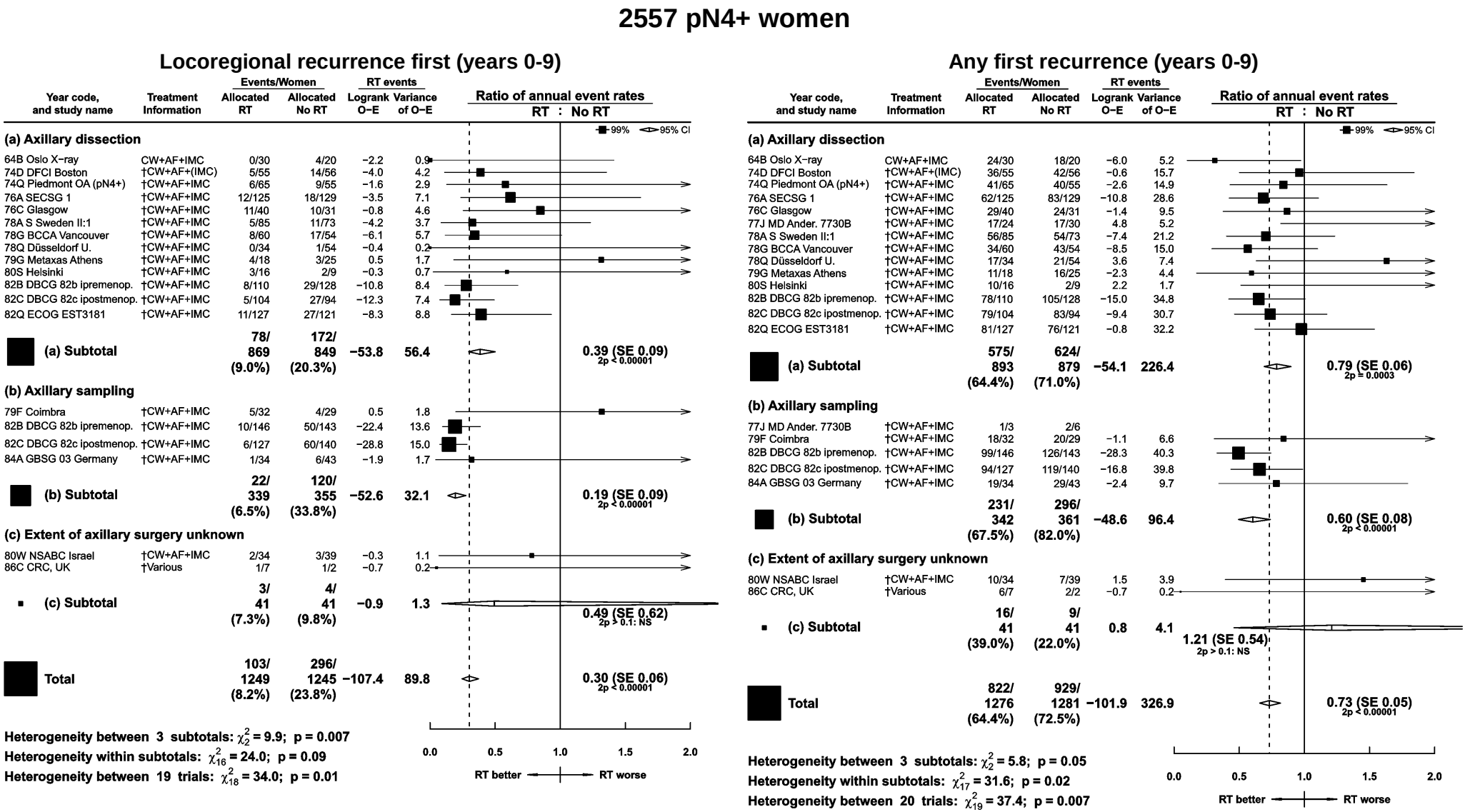


Any death



† 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 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+).

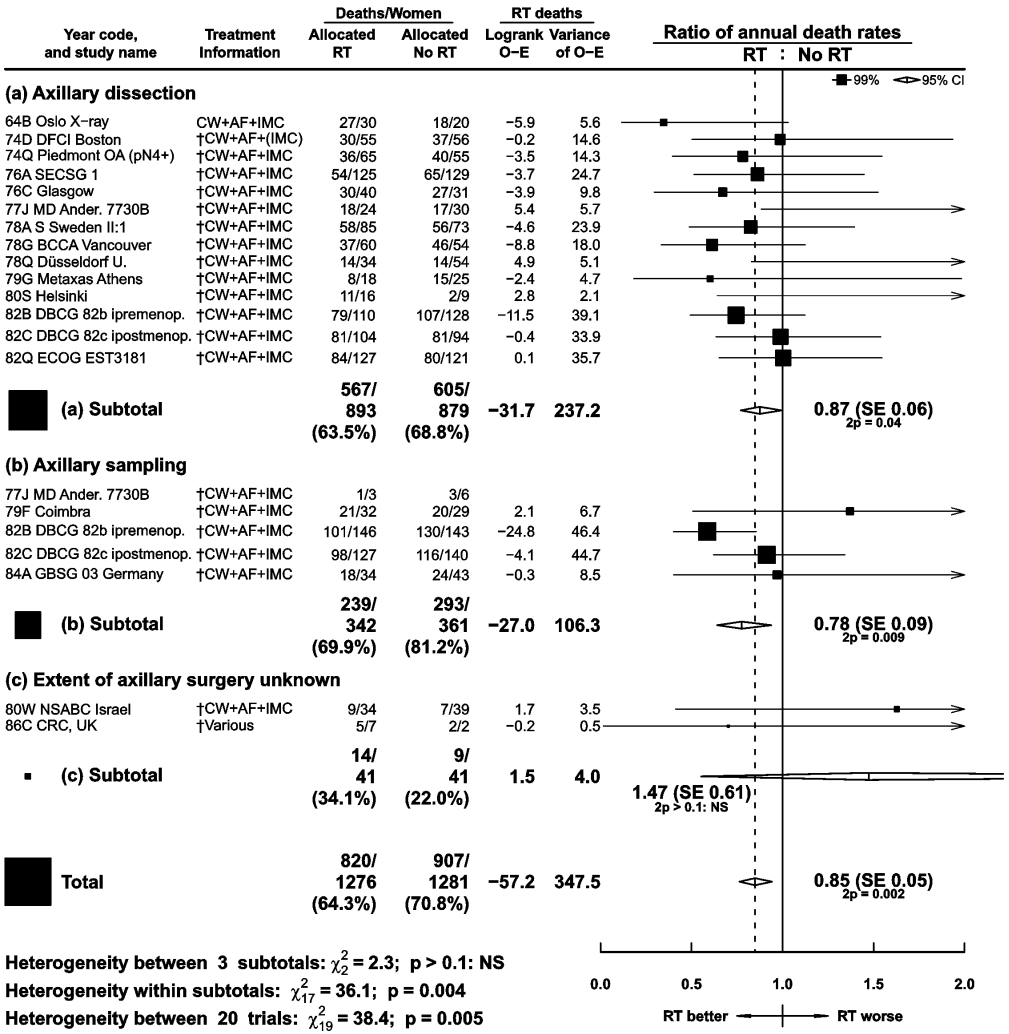


† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

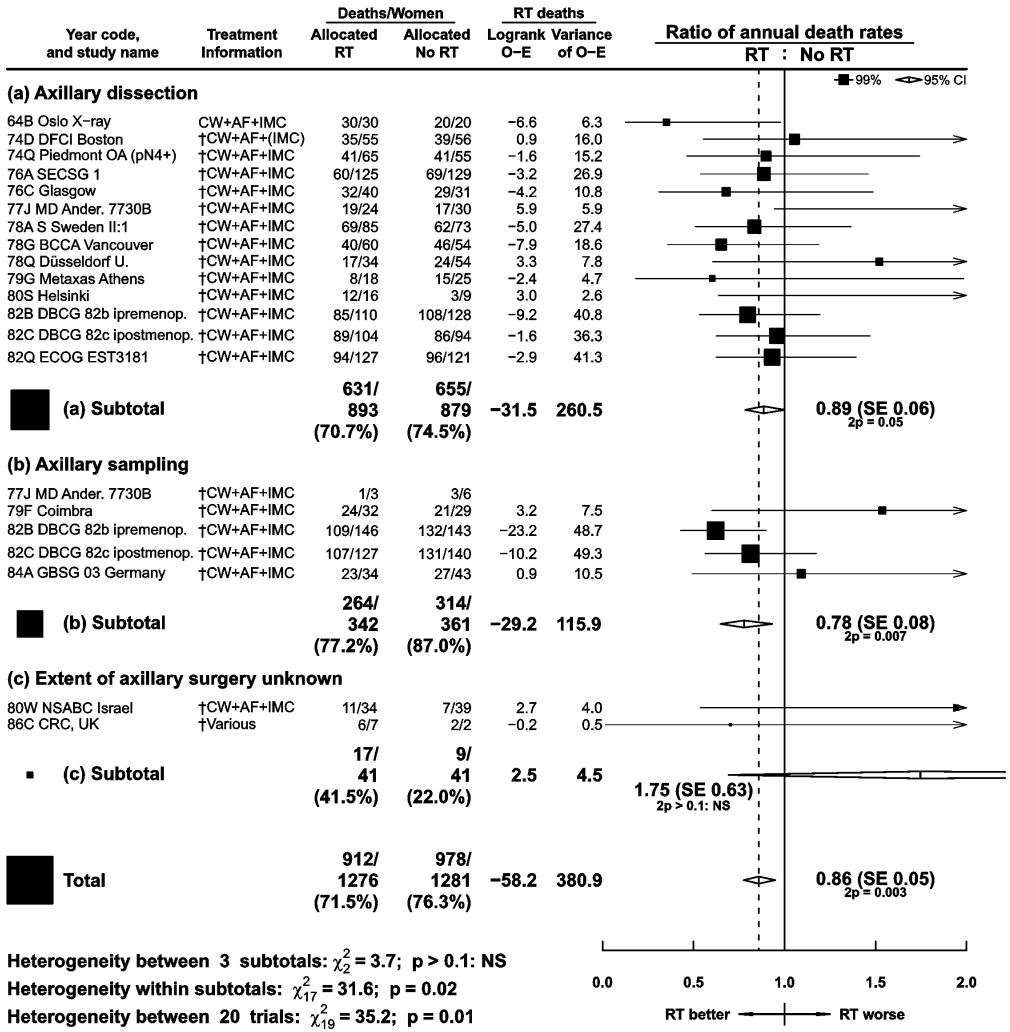
2557 pN4+ women

Breast cancer mortality



Heterogeneity between 3 subtotals: $\chi^2_2 = 2.3$; **p > 0.1: NS**
Heterogeneity within subtotals: $\chi^2_{17} = 36.1$; **p = 0.004**
Heterogeneity between 20 trials: $\chi^2_{19} = 38.4$; **p = 0.005**

Any death

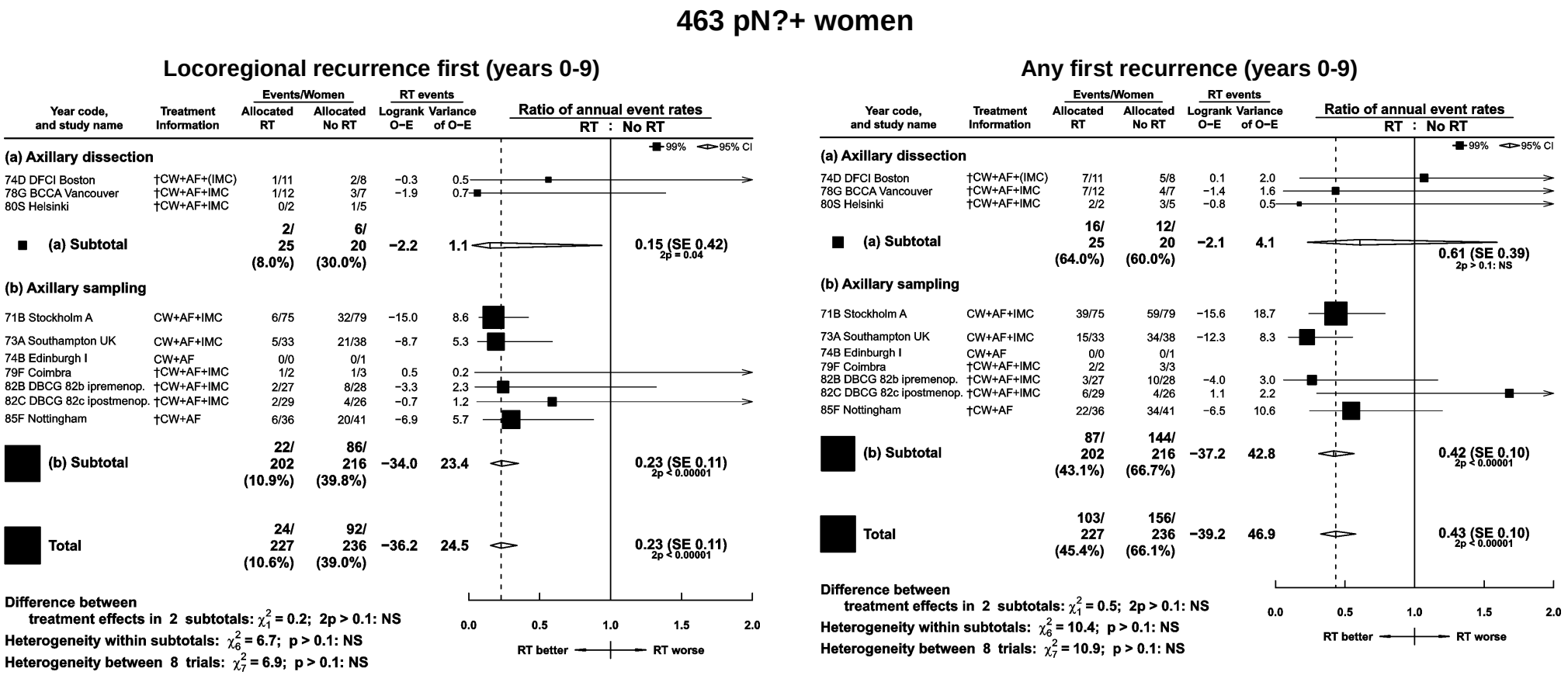


Heterogeneity between 3 subtotals: $\chi^2_2 = 3.7$; **p > 0.1: NS**
Heterogeneity within subtotals: $\chi^2_{17} = 31.6$; **p = 0.02**
Heterogeneity between 20 trials: $\chi^2_{19} = 35.2$; **p = 0.01**

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

continued overleaf

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



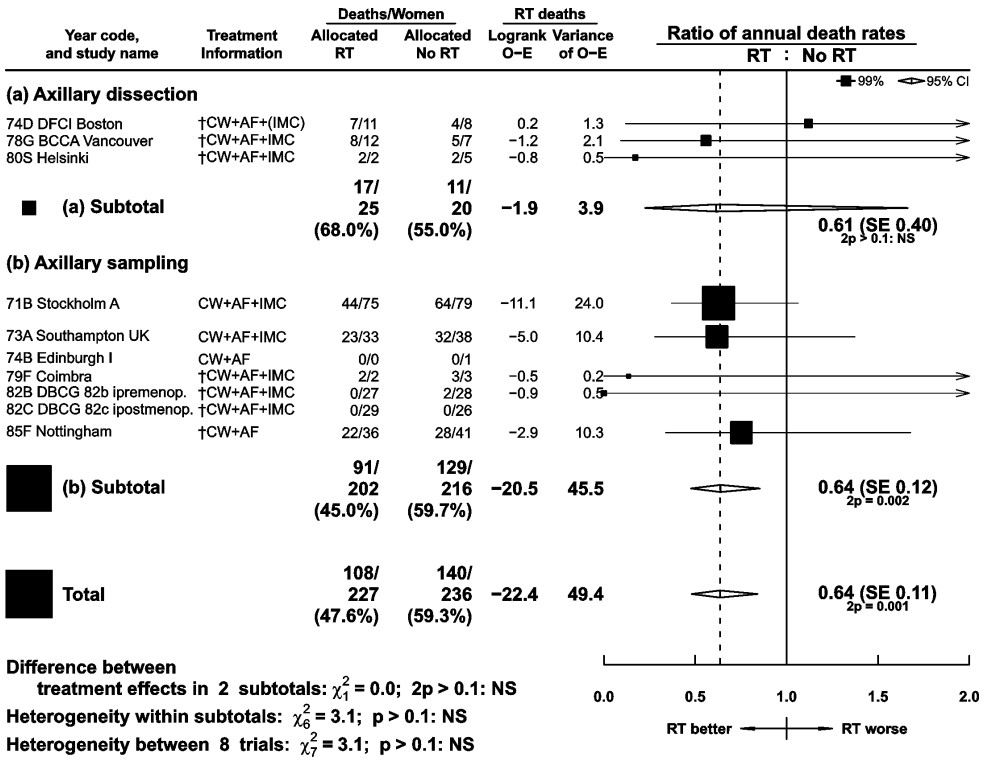
† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

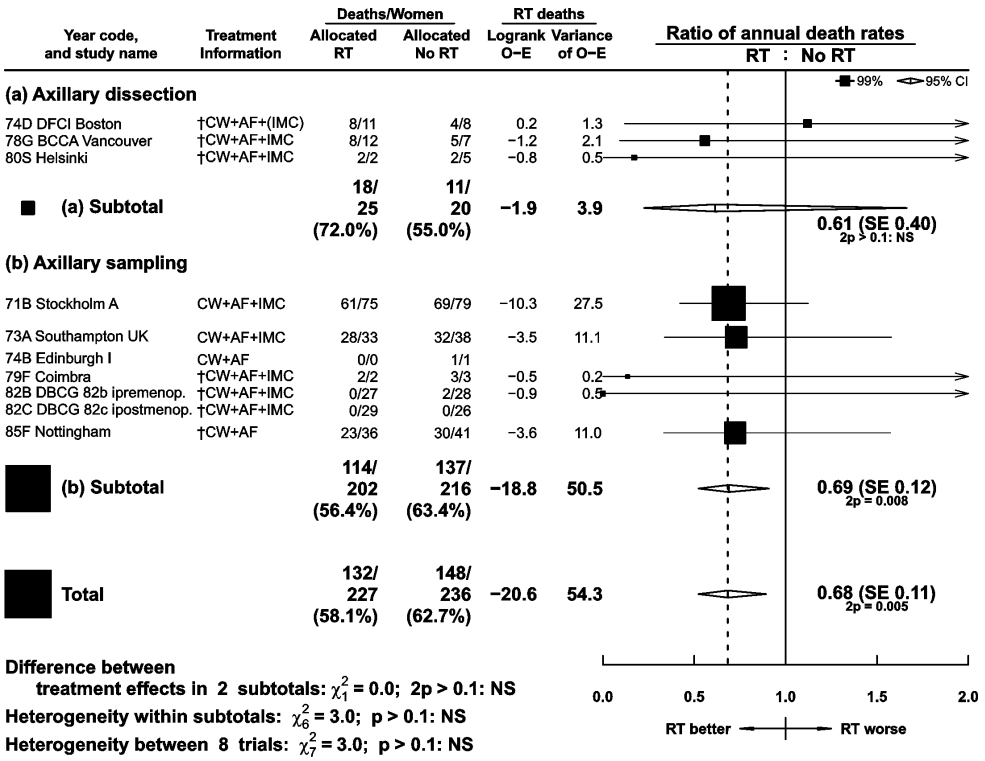
Webfigure 33 cntd.

463 pN?+ women

Breast cancer mortality



Any death

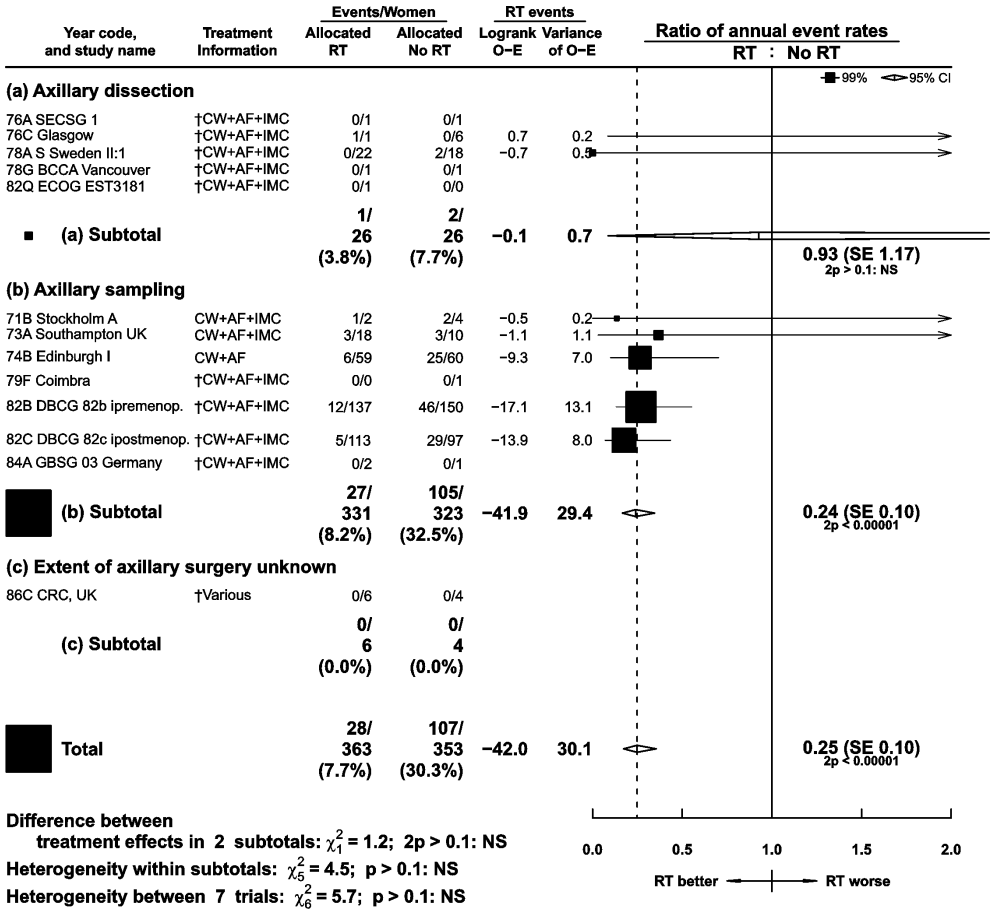


† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

Webfigure 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?).

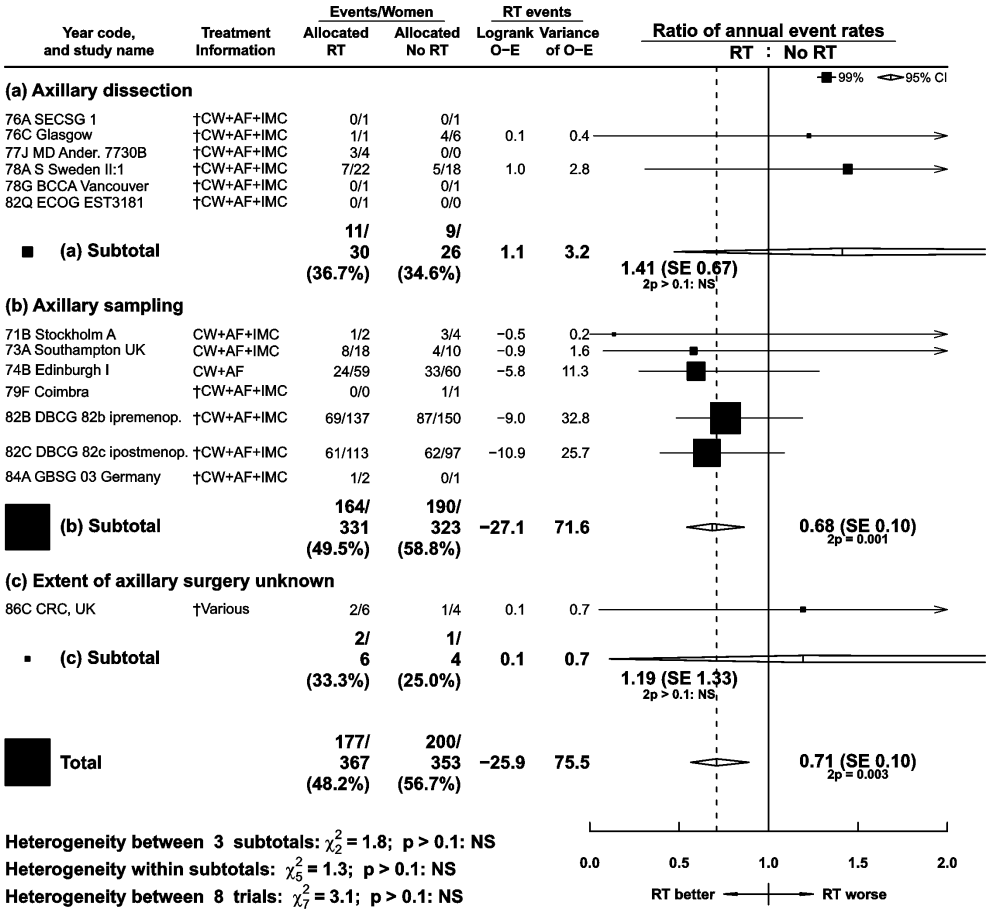
720 pN? women

Locoregional recurrence first (years 0-9)



Difference between treatment effects in 2 subtotals: $\chi^2_1 = 1.2$; 2p > 0.1: NS
Heterogeneity within subtotals: $\chi^2_5 = 4.5$; p > 0.1: NS
Heterogeneity between 7 trials: $\chi^2_6 = 5.7$; p > 0.1: NS

Any first recurrence (years 0-9)



Heterogeneity between 3 subtotals: $\chi^2_2 = 1.8$; p > 0.1: NS
Heterogeneity within subtotals: $\chi^2_5 = 1.3$; p > 0.1: NS
Heterogeneity between 8 trials: $\chi^2_7 = 3.1$; p > 0.1: NS

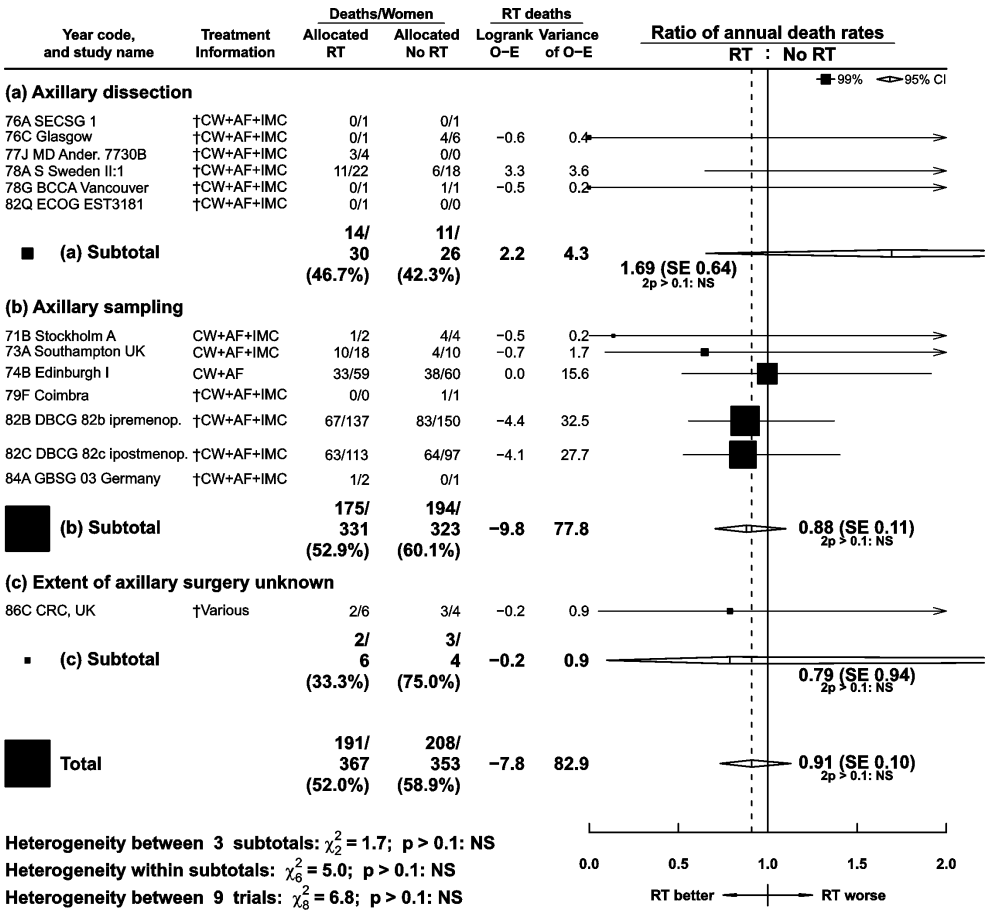
† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

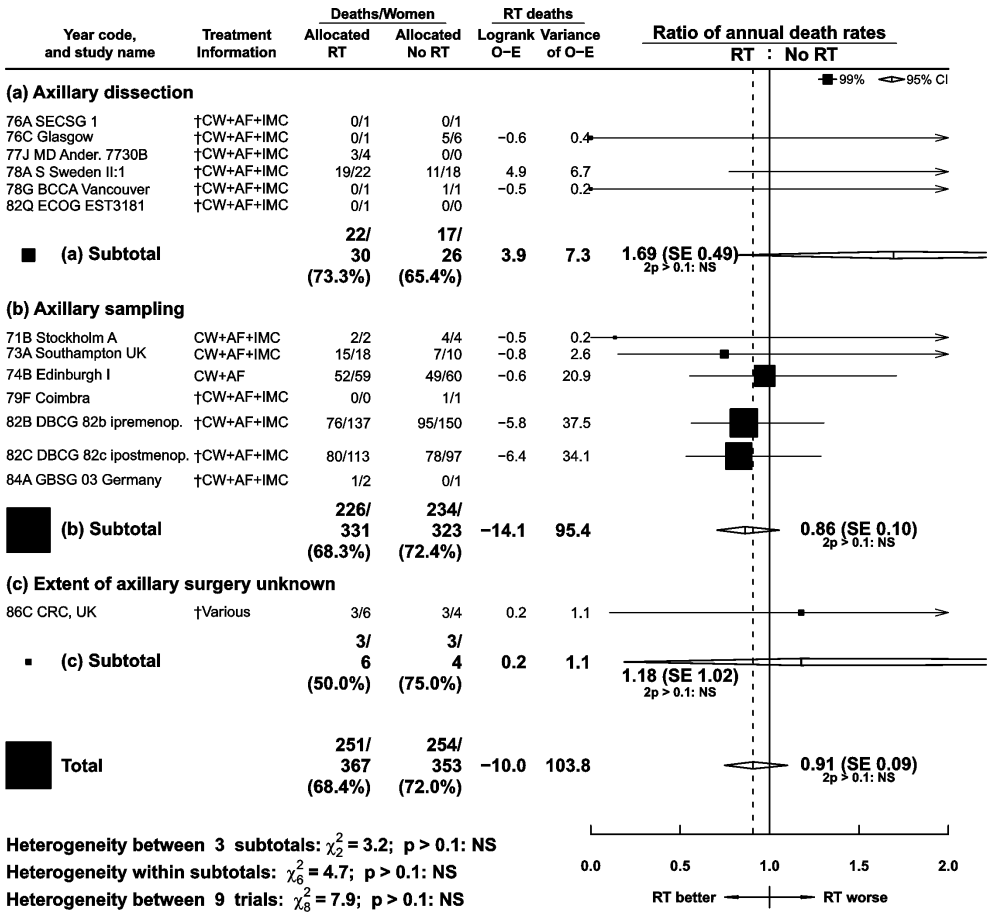
Webfigure 34 cntd.

720 pN? 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.

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)*.

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

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

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

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

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

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

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

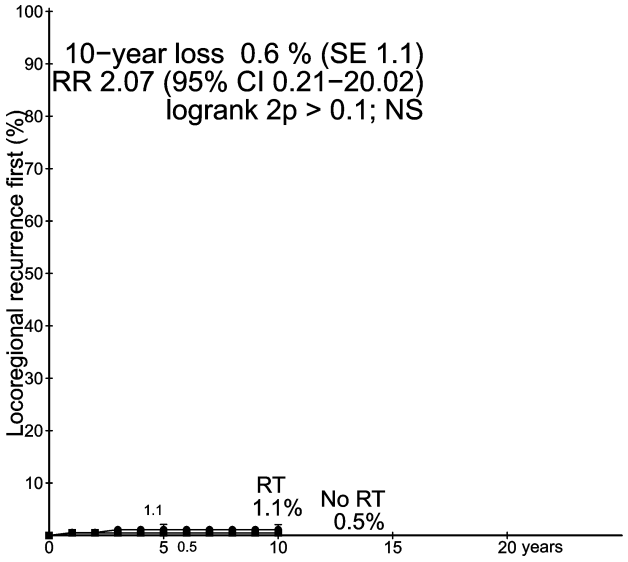
References for Webtable 3

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

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

465 pN0 women with Mast+AD

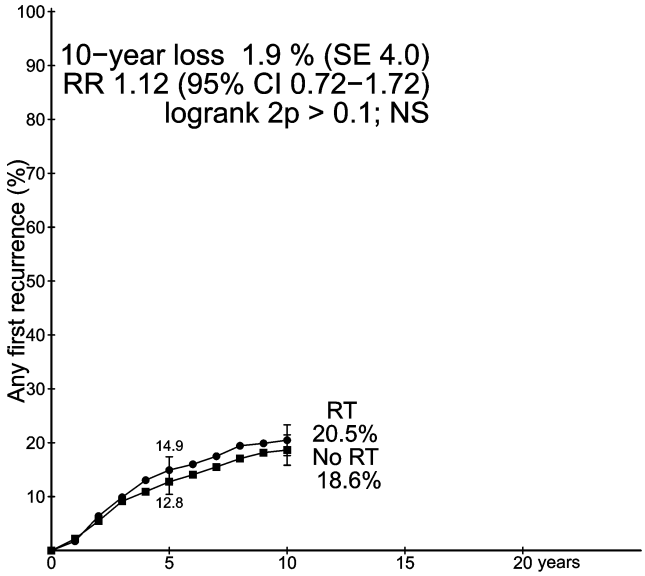
Locoregional recurrence first



Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	0.35 (3/855)	0.00 (0/686)
No RT	0.11 (1/926)	0.00 (0/774)
Rate ratio, from	2.07 SE 1.70	. SE .
(O−E)/V	0.5/0.7	0.0/0.0

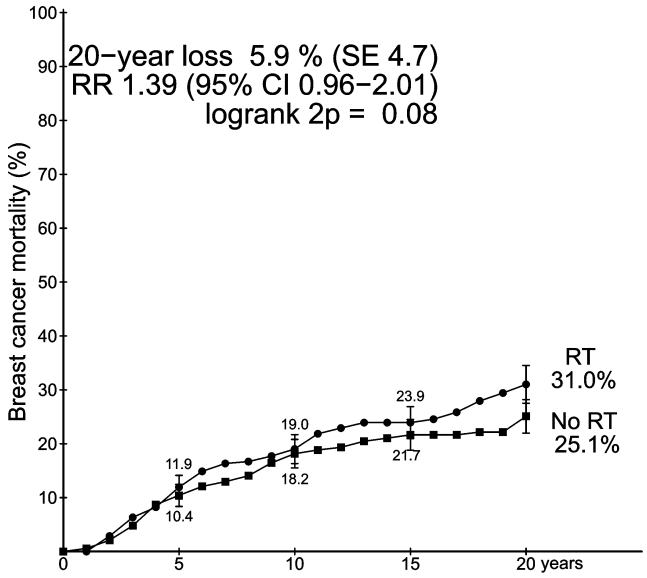
Any first recurrence



Any first recurrence rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	3.33 (34/1022)	1.39 (11/793)
No RT	2.94 (31/1054)	1.63 (14/858)
Rate ratio, from	1.18 SE 0.28	0.97 SE 0.42
(O−E)/V	2.4/14.8	−0.2/5.6

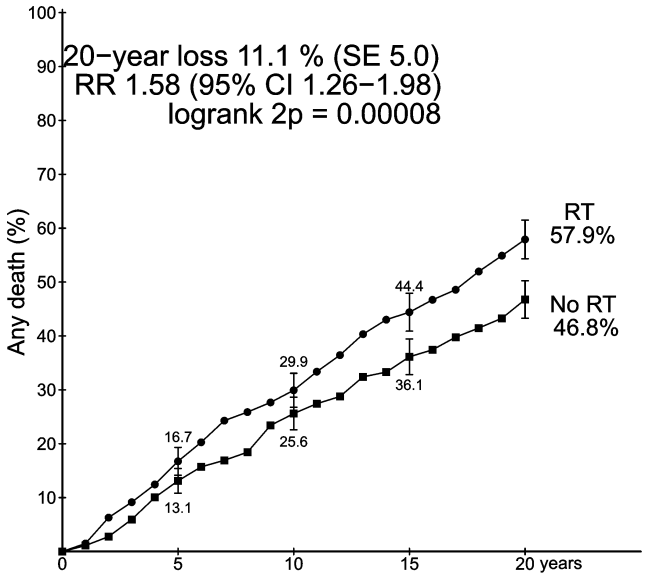
Breast cancer mortality



Breast cancer mortality rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	2.44 (26/1066)	1.65 (14/850)	1.33 (9/679)	1.98 (10/505)	2.40 (13/541)
No RT	2.19 (24/1098)	1.84 (17/924)	0.90 (7/775)	0.79 (5/631)	0.87 (8/924)
Rate ratio, from	1.17 SE 0.33	0.97 SE 0.37	1.30 SE 0.63	2.61 SE 0.92	2.79 SE 0.90
(O−E)/V	1.7/10.8	−0.3/7.1	0.9/3.2	3.2/3.4	3.9/3.8

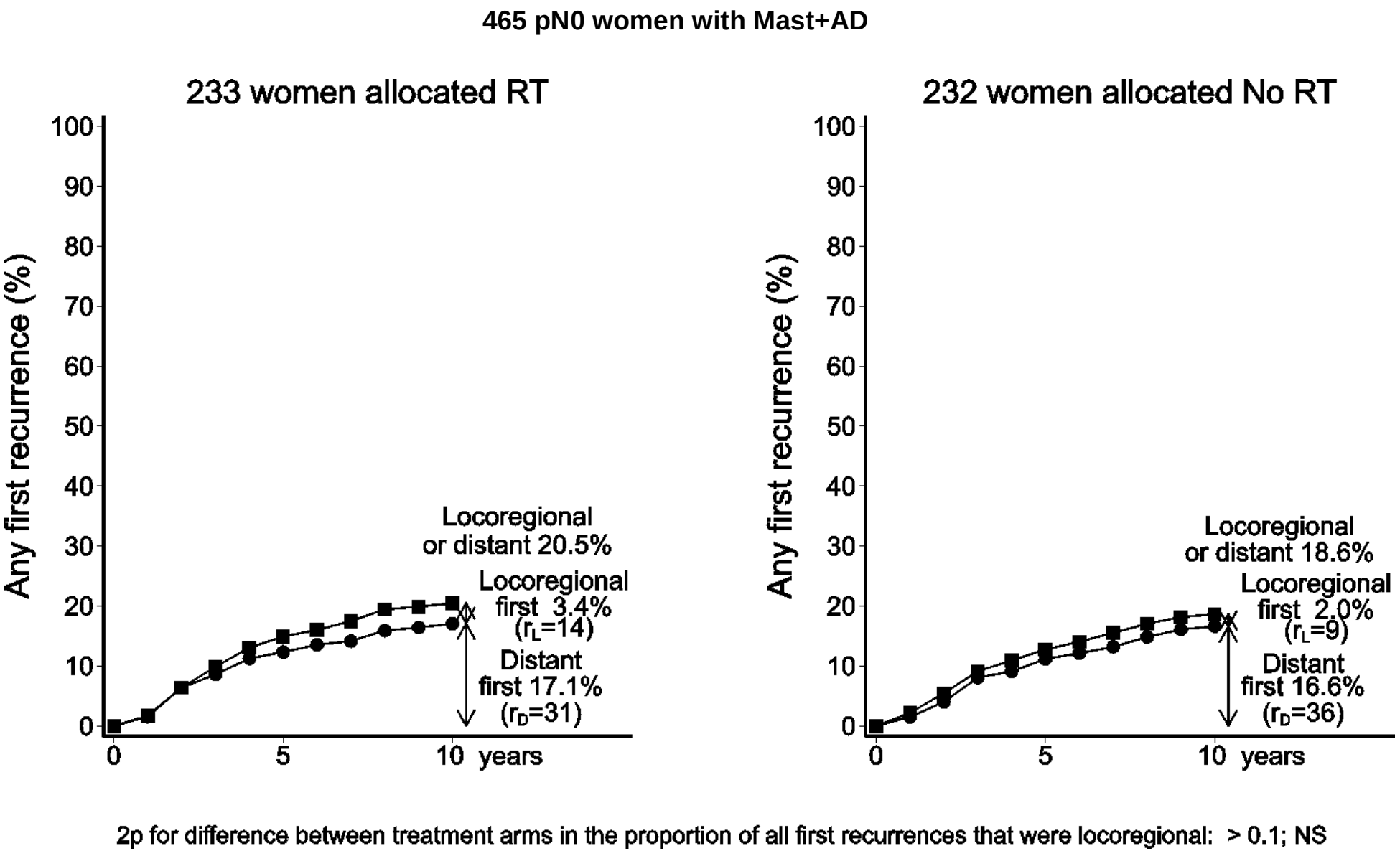
Any death



Any death rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	3.85 (41/1066)	3.53 (30/850)	5.15 (35/679)	5.75 (29/505)	10.91 (59/541)
No RT	2.82 (31/1098)	3.35 (31/924)	3.10 (24/775)	3.65 (23/631)	5.63 (52/924)
Rate ratio, from	1.31 SE 0.29	1.13 SE 0.29	1.56 SE 0.35	1.55 SE 0.36	2.37 SE 0.36
(O−E)/V	4.3/16.0	1.7/13.8	5.9/13.2	5.2/11.9	17.1/19.9

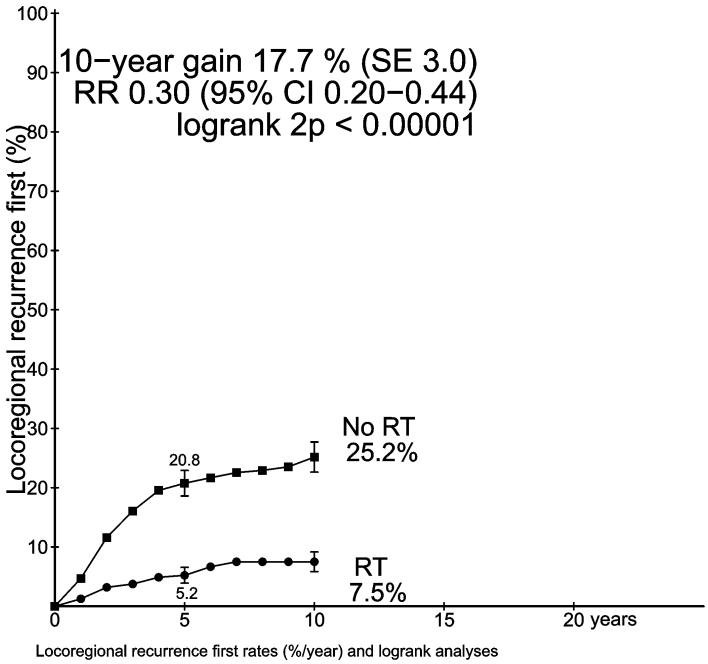
Webfigure 36. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 465 women with pathologically node-negative (pN0) disease. (r_L = number of women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



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

1029 pN+ women with Mast+AD

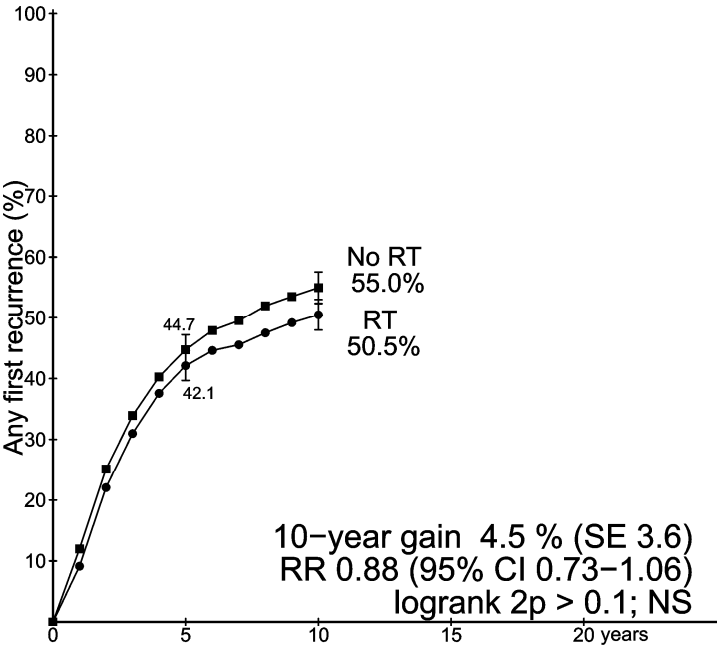
Locoregional recurrence first



Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	1.53 (28/1827)	0.62 (6/962)
No RT	5.01 (84/1678)	1.31 (11/843)
Rate ratio, from	0.28 SE 0.12	0.47 SE 0.39
(O−E)/V	−30.0/23.6	−2.5/3.3

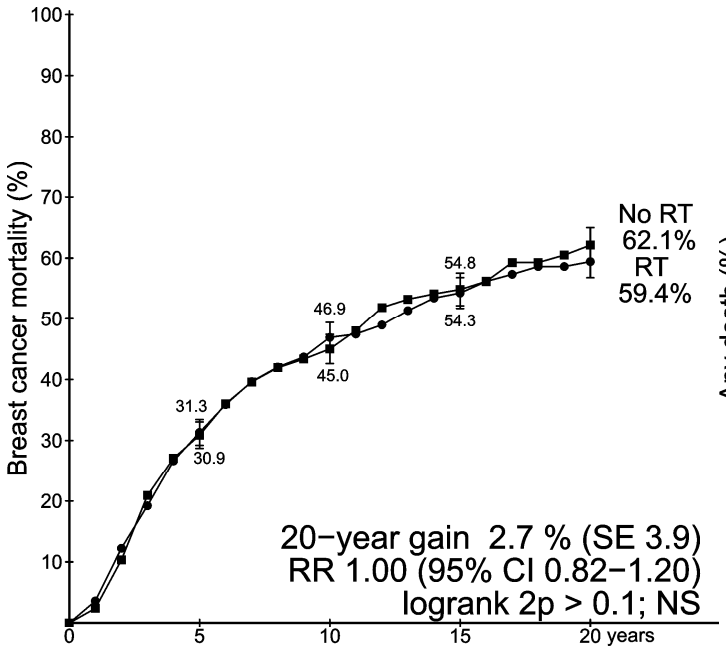
Any first recurrence



Any first recurrence rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	11.84 (230/1943)	3.43 (35/1020)
No RT	12.56 (222/1767)	4.55 (40/879)
Rate ratio, from	0.90 SE 0.10	0.75 SE 0.22
(O−E)/V	−9.3/90.0	−4.4/15.5

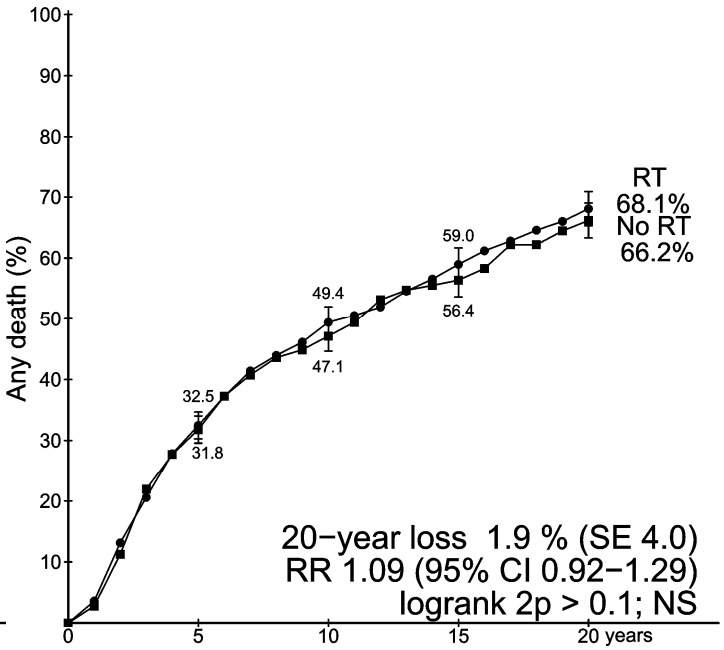
Breast cancer mortality



Breast cancer mortality rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	7.48 (165/2206)	5.69 (69/1212)	2.48 (19/767)	2.64 (13/493)	2.69 (15/558)
No RT	7.17 (149/2078)	4.42 (50/1132)	4.74 (33/696)	3.56 (16/449)	1.87 (10/536)
Rate ratio, from	1.02 SE 0.13	1.09 SE 0.21	0.69 SE 0.26	0.72 SE 0.35	1.85 SE 0.86
(O−E)/V	1.6/65.0	2.1/24.0	−3.8/10.2	−2.0/5.9	1.6/2.6

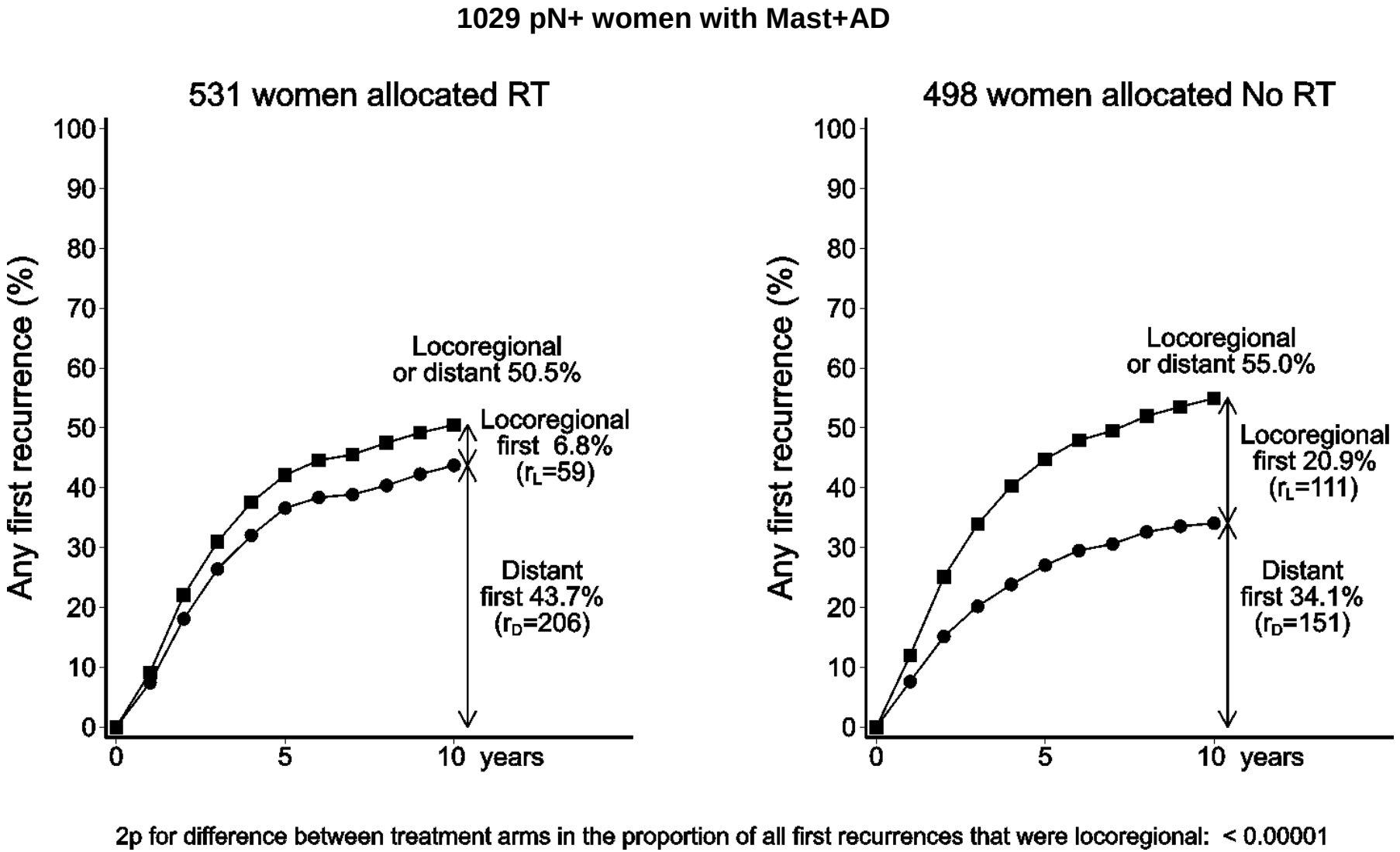
Any death



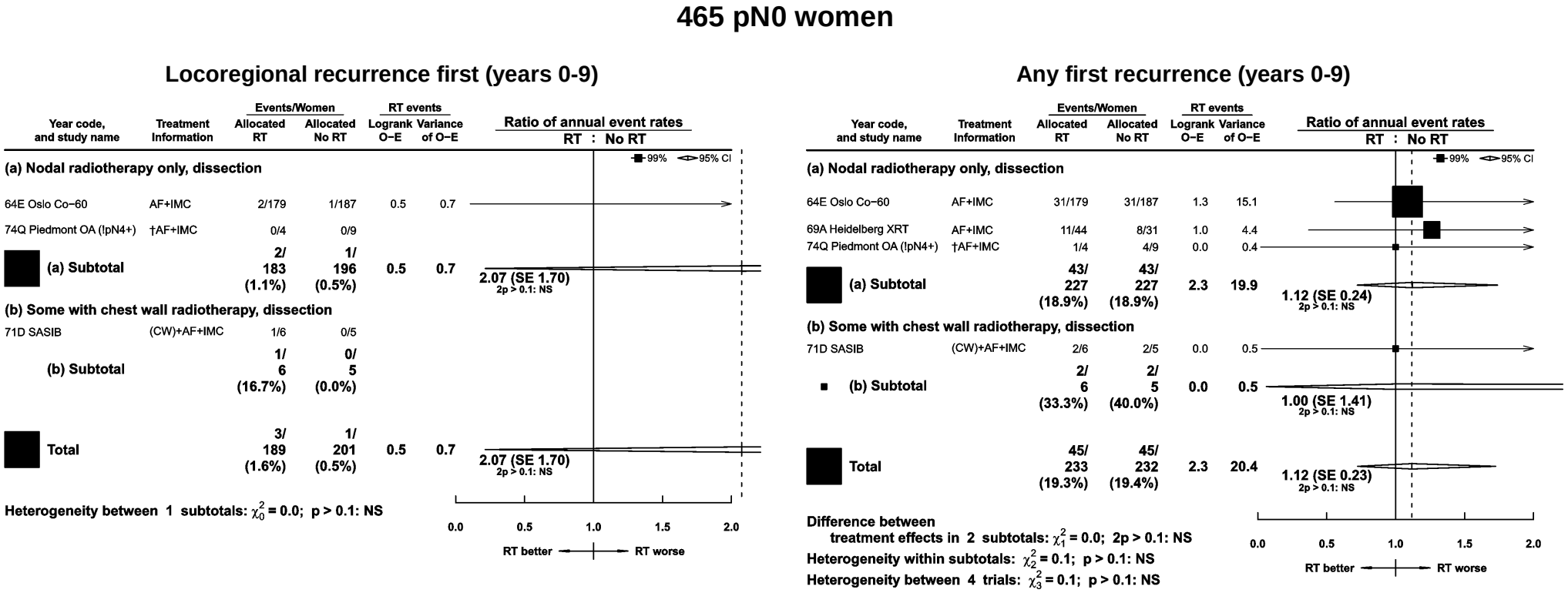
Any death rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	8.07 (178/2206)	7.01 (85/1212)	4.43 (34/767)	6.29 (31/493)	7.34 (41/558)
No RT	7.75 (161/2078)	5.13 (58/1132)	5.17 (36/696)	5.34 (24/449)	5.60 (30/536)
Rate ratio, from	1.03 SE 0.12	1.10 SE 0.20	0.99 SE 0.28	0.94 SE 0.30	2.23 SE 0.52
(O−E)/V	2.0/70.4	2.7/28.5	−0.2/12.8	−0.7/10.4	7.0/8.8

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.)



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.



† 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.

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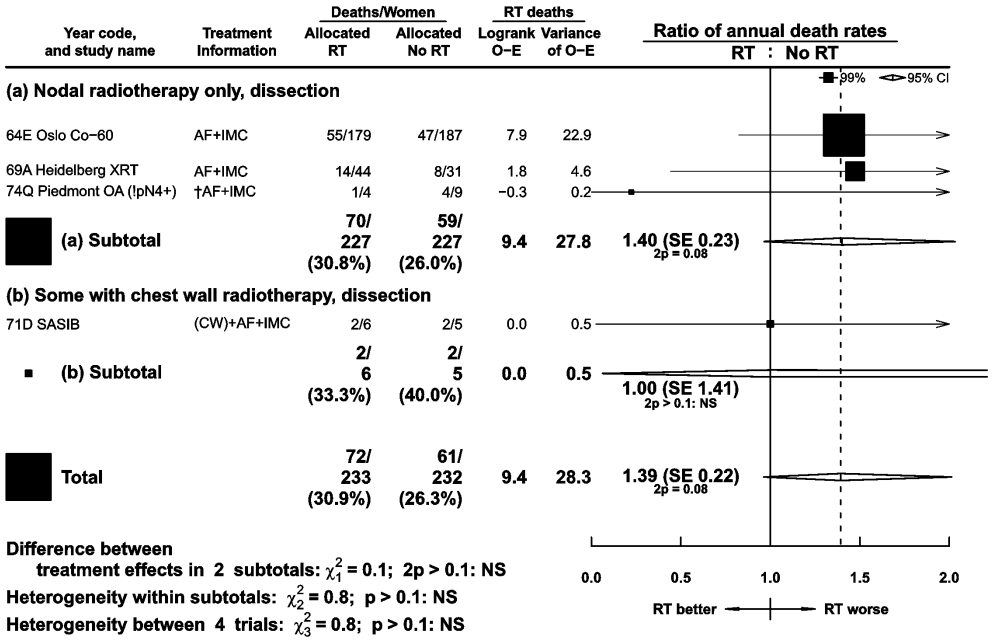
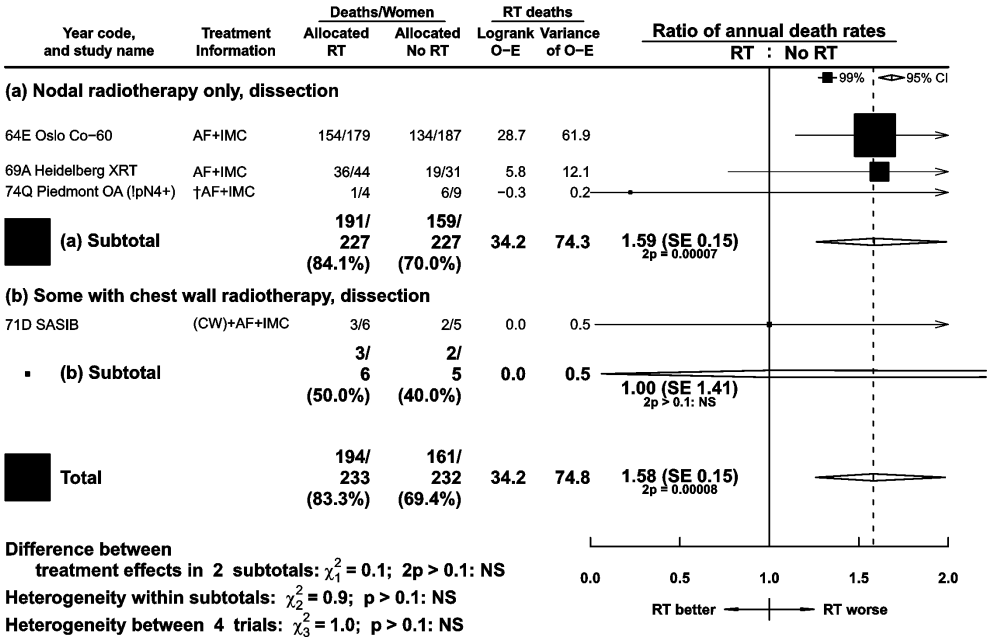
Webfigure 39 cntd.

465 pN0 women

Breast cancer mortality

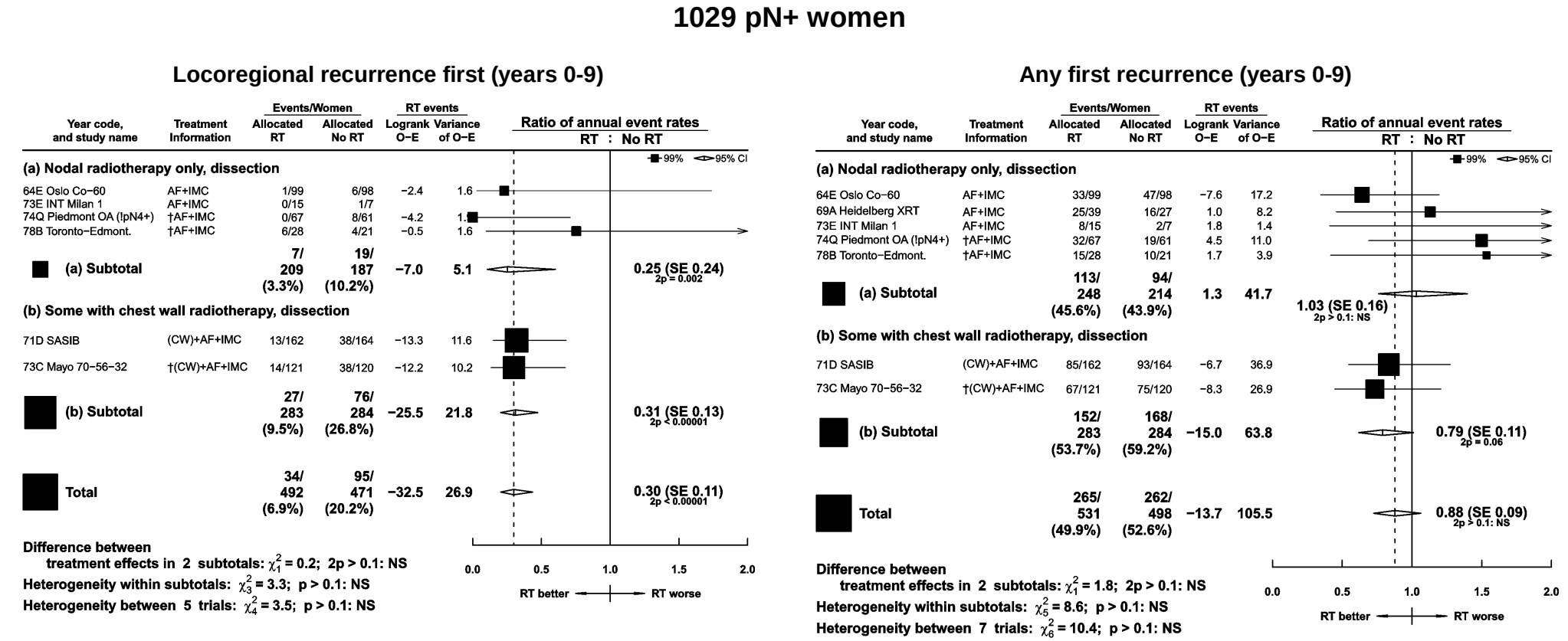


Any death



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

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



† 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.

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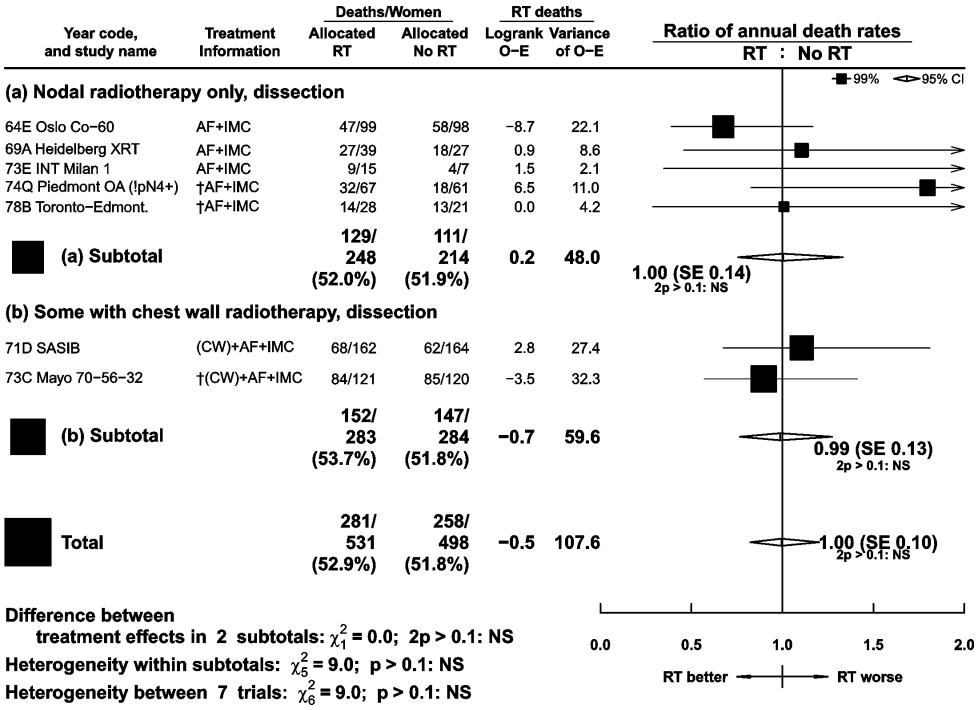
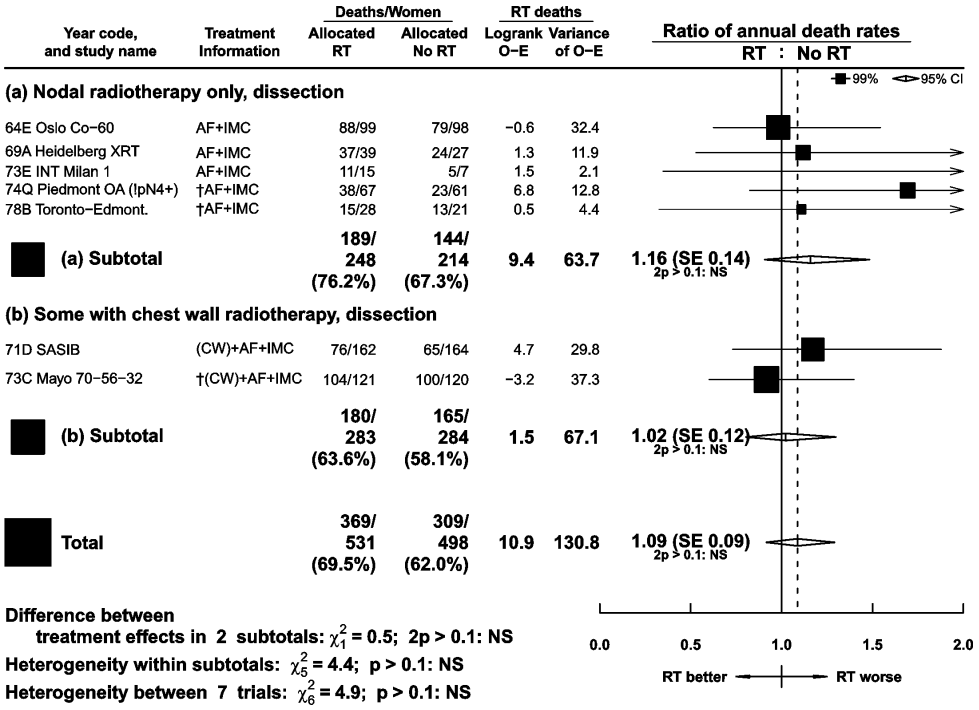
Webfigure 40 cntd.

1029 pN+ women

Breast cancer mortality



Any death

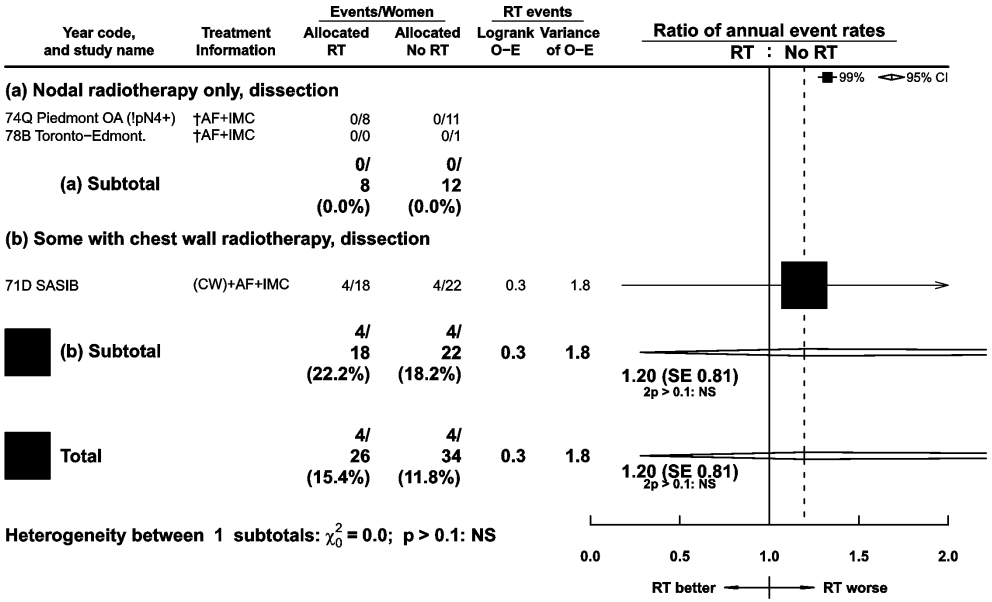


† Same polychemotherapy and/or tamoxifen in both groups.
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

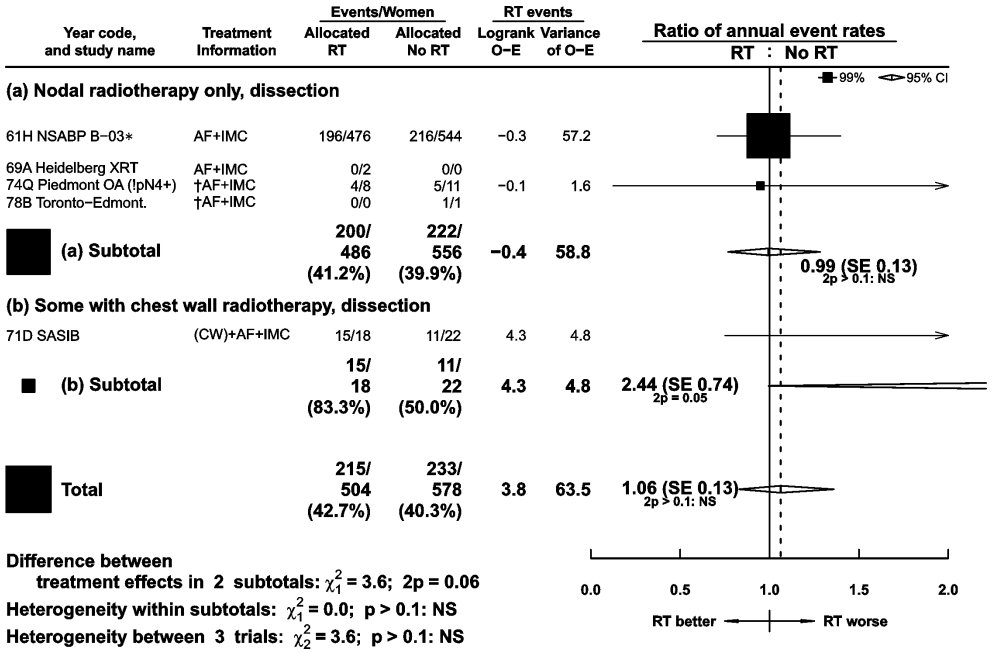
Webfigure 41. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer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

810 pN? women

Locoregional recurrence first (years 0-9)



Any first recurrence (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.

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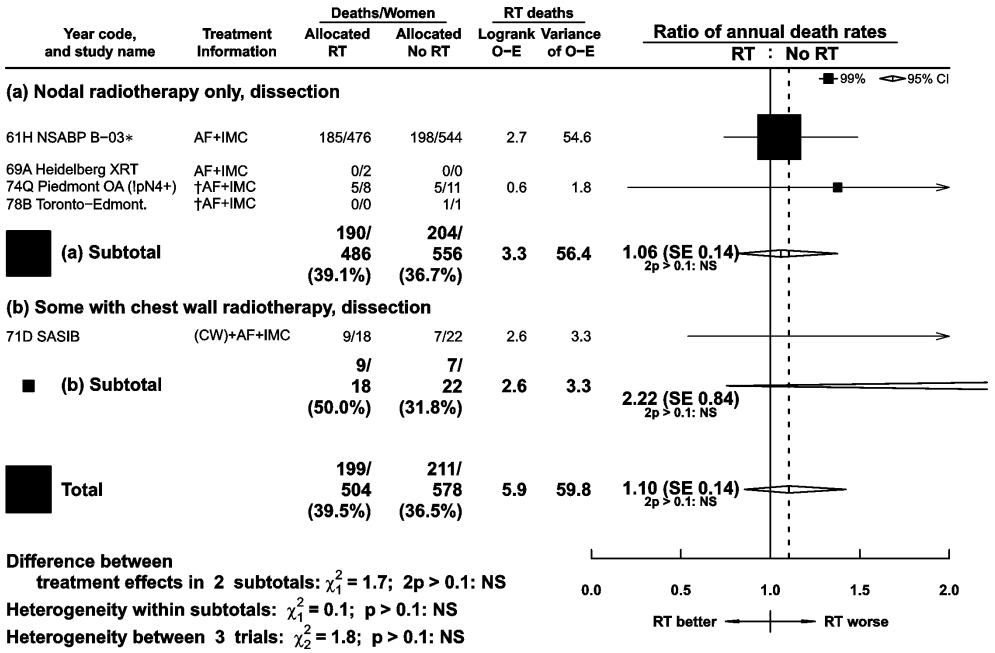
Webfigure 41 cntd.

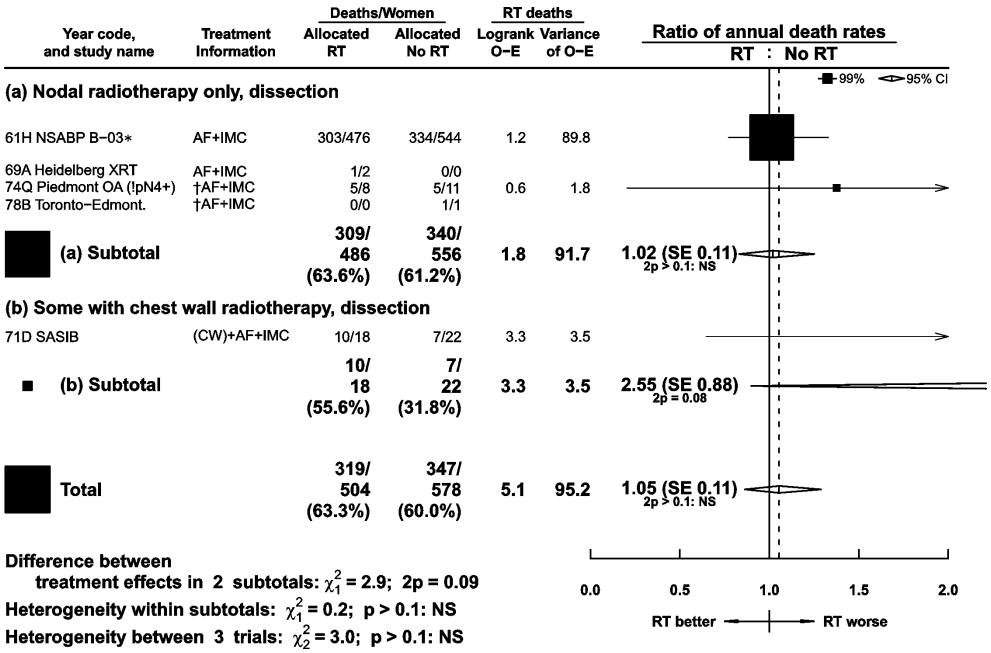
810 pN? women

Breast cancer mortality



Difference between treatment effects in 2 subtotals: $\chi^2_1 = 1.7$; **2p > 0.1: NS**
Heterogeneity within subtotals: $\chi^2_1 = 0.1$; **p > 0.1: NS**
Heterogeneity between 3 trials: $\chi^2_2 = 1.8$; **p > 0.1: NS**

Any death



Difference between treatment effects in 2 subtotals: $\chi^2_1 = 2.9$; **2p = 0.09**
Heterogeneity within subtotals: $\chi^2_1 = 0.2$; **p > 0.1: NS**
Heterogeneity between 3 trials: $\chi^2_2 = 3.0$; **p > 0.1: NS**

* 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)*.

Nodal status†	Women	Deaths	Woman-years since diagnosis					% women given systemic therapy		
			Median/ woman	Total ('000s)	Distribution by years ('000s) <10	10-	20+	Chemotherapy	ER+ & Tamoxifen	Any
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; **69**: 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. *World J Surg* 1994; **18**: 117–22.
71C NSABP B-04	Fisher B, Montague E, Redmond C, Deutsch M, Brown GR, Zauber A, et al. Findings from NSABP protocol no. B-04-comparison of radical mastectomy with alternative treatments for primary breast cancer. I. Radiation compliance and its relation to treatment outcome. *Cancer* 1980; **46**: 1–13.
	Deutsch M, Land S, Begovic M, Sharif S. The incidence of arm edema in women with breast cancer randomized on the National Surgical Adjuvant Breast and Bowel Project study B-04 to radical mastectomy versus total mastectomy and radiotherapy versus total mastectomy alone. *Int J Radiat Oncol Biol Phys* 2008; **70**: 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

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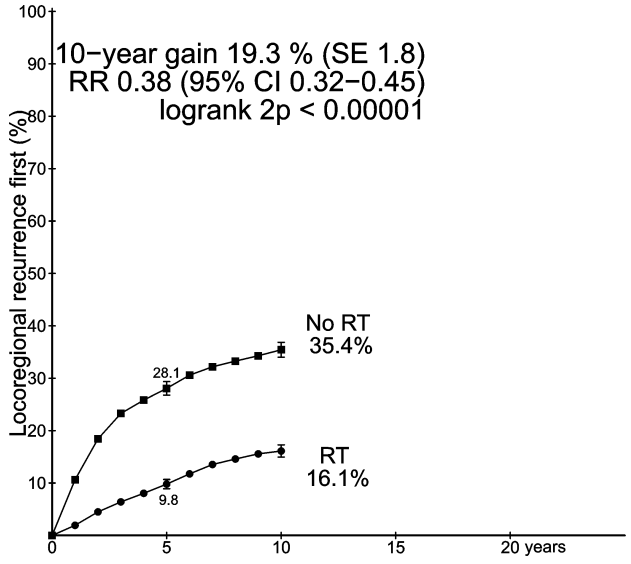
2896 cN- women with Mast

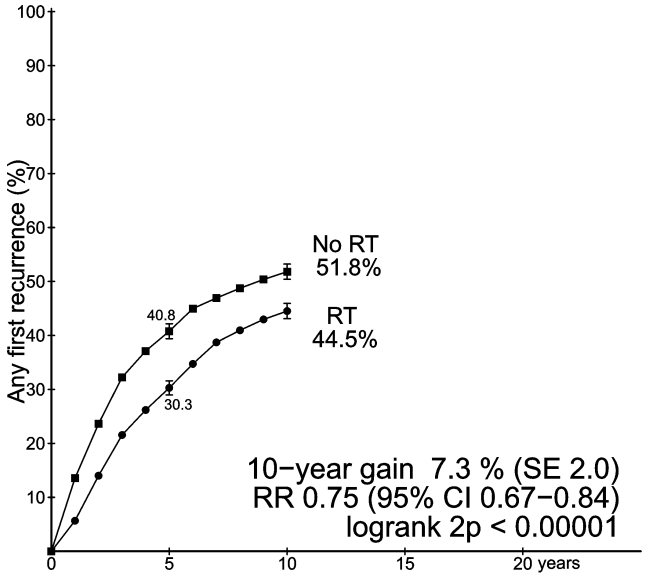
Locoregional recurrence first



Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	2.12 (119/5612)	1.51 (56/3714)
No RT	7.11 (374/5259)	2.25 (77/3422)
Rate ratio, from	0.32 SE 0.06	0.68 SE 0.15
(O−E)/V	−130.5/115.8	−12.5/32.2

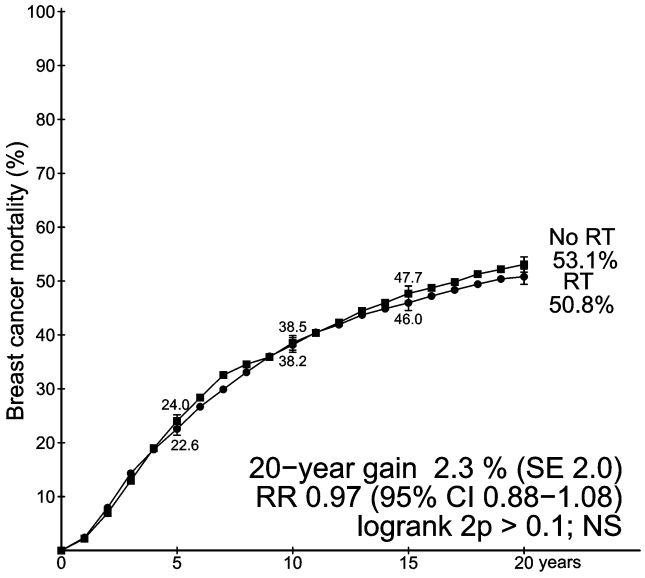
Any first recurrence



Any first recurrence rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	7.35 (415/5647)	4.67 (178/3810)
No RT	10.94 (577/5274)	4.24 (148/3492)
Rate ratio, from	0.66 SE 0.05	1.11 SE 0.12
(O−E)/V	−93.9/222.5	8.0/76.4

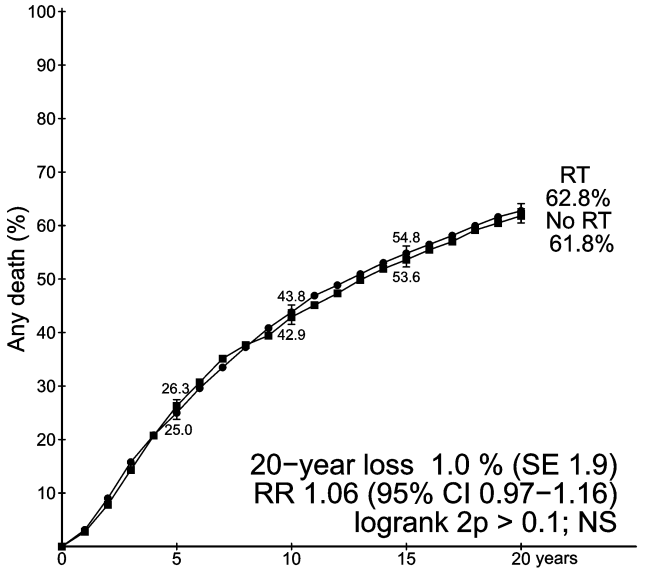
Breast cancer mortality



Breast cancer mortality rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	5.04 (308/6111)	4.51 (204/4523)	2.67 (93/3489)	1.87 (51/2733)	1.05 (54/5157)
No RT	5.37 (345/6428)	4.35 (203/4669)	3.28 (121/3688)	2.22 (63/2842)	0.98 (56/5686)
Rate ratio, from	0.94 SE 0.08	1.05 SE 0.11	0.84 SE 0.13	0.88 SE 0.18	1.16 SE 0.18
(O−E)/V	−8.6/151.6	4.9/94.3	−8.5/50.2	−3.6/27.2	5.3/35.6

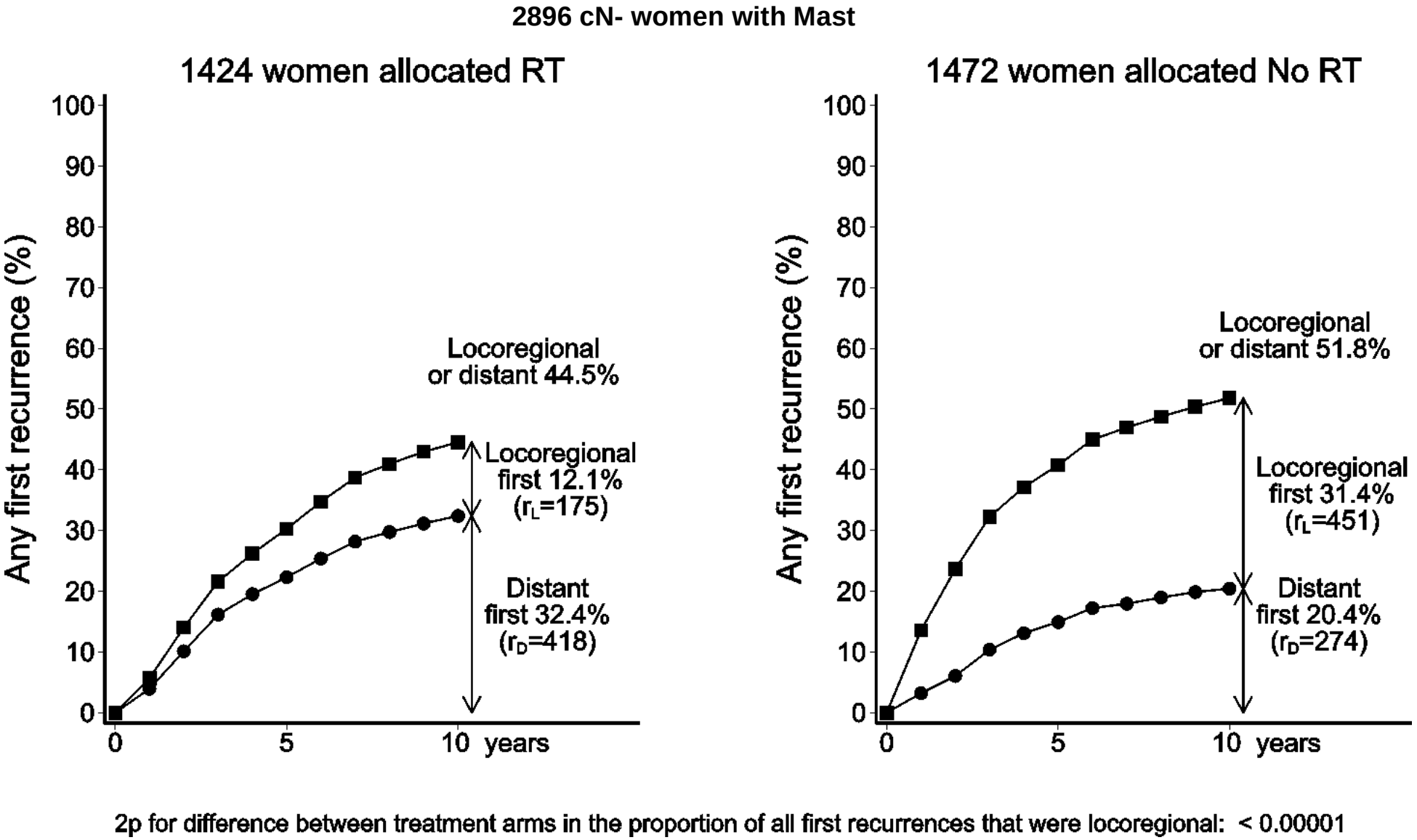
Any death



Any death rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	5.69 (348/6111)	5.77 (261/4523)	4.36 (152/3489)	3.84 (105/2733)	3.43 (177/5157)
No RT	5.94 (382/6428)	5.20 (243/4669)	4.28 (158/3688)	3.98 (113/2842)	2.80 (159/5686)
Rate ratio, from	0.96 SE 0.07	1.13 SE 0.10	1.05 SE 0.12	0.99 SE 0.14	1.26 SE 0.13
(O−E)/V	−7.5/170.3	14.5/117.3	3.8/72.3	−0.5/51.1	17.9/78.6

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.)

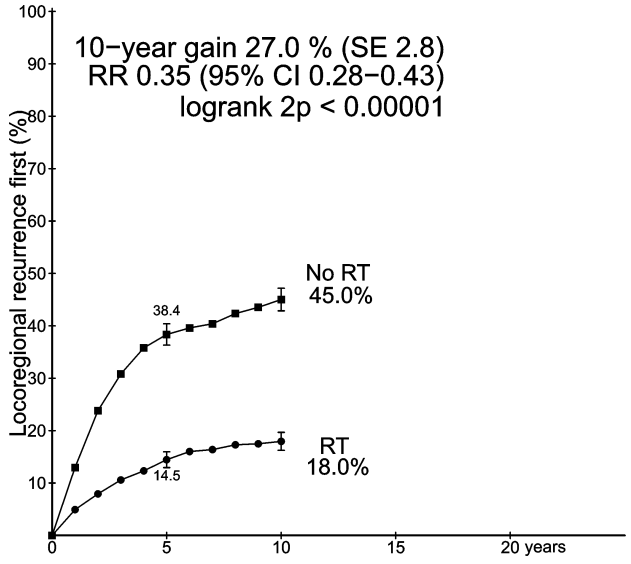


Webfigure 44. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risks of breast cancer and all-cause mortality in 1481 women with clinically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

.

1481 cN+ women with Mast

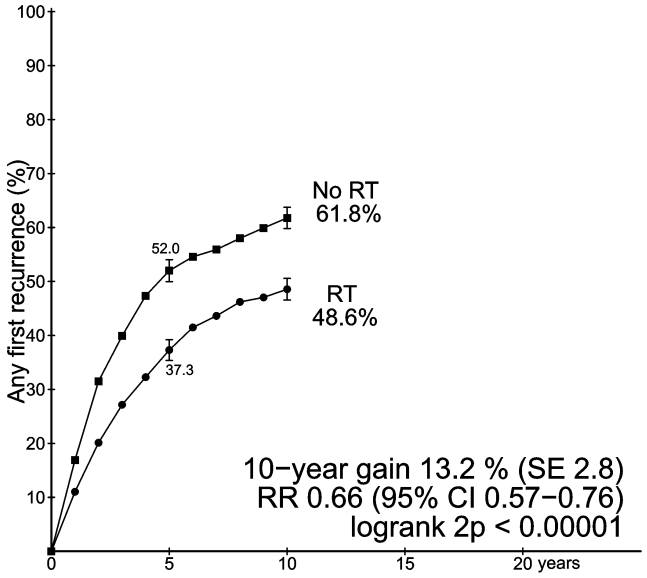
Locoregional recurrence first



Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	3.55 (99/2787)	0.96 (17/1765)
No RT	10.55 (256/2425)	2.44 (35/1433)
Rate ratio, from	0.34 SE 0.07	0.40 SE 0.19
(O−E)/V	−87.5/81.0	−10.8/11.8

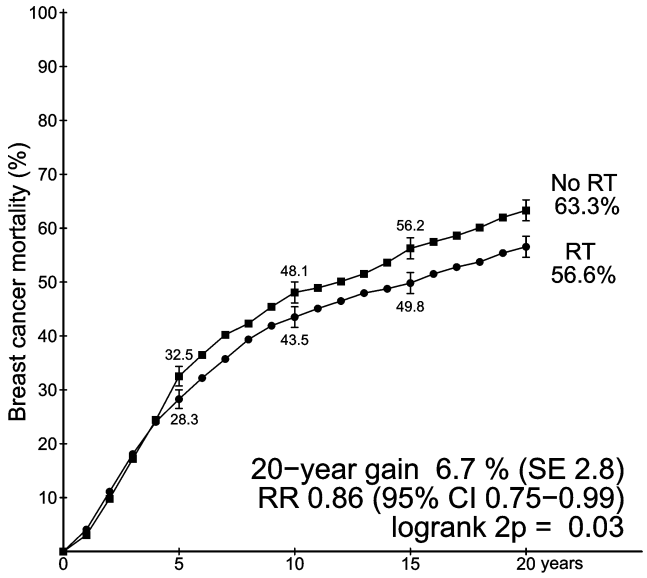
Any first recurrence



Any first recurrence rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	9.90 (277/2798)	4.16 (75/1802)
No RT	15.57 (378/2428)	4.63 (67/1448)
Rate ratio, from	0.61 SE 0.07	0.89 SE 0.17
(O−E)/V	−68.5/140.8	−3.7/32.2

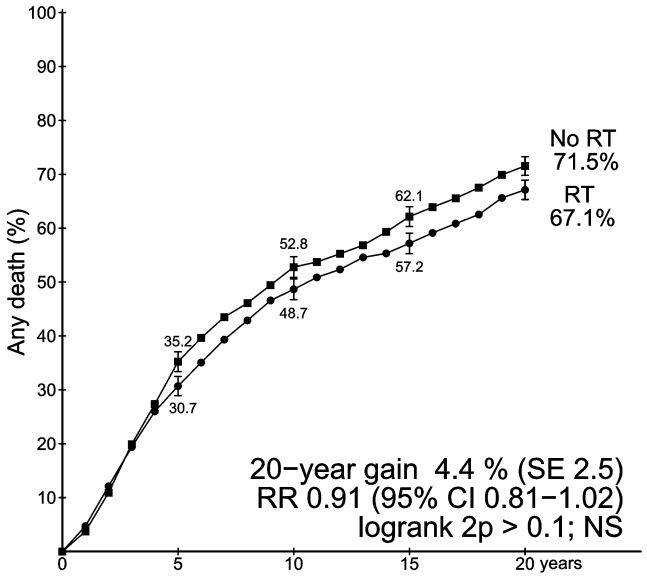
Breast cancer mortality



Breast cancer mortality rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	6.60 (206/3123)	4.79 (104/2169)	2.34 (40/1709)	2.76 (38/1379)	1.02 (28/2740)
No RT	7.54 (235/3116)	5.34 (110/2059)	3.41 (55/1611)	3.66 (45/1229)	1.23 (29/2358)
Rate ratio, from	0.87 SE 0.09	0.91 SE 0.14	0.72 SE 0.18	0.83 SE 0.21	0.89 SE 0.21
(O−E)/V	−13.8/99.7	−4.4/48.3	−7.1/21.9	−3.5/18.5	−2.4/20.1

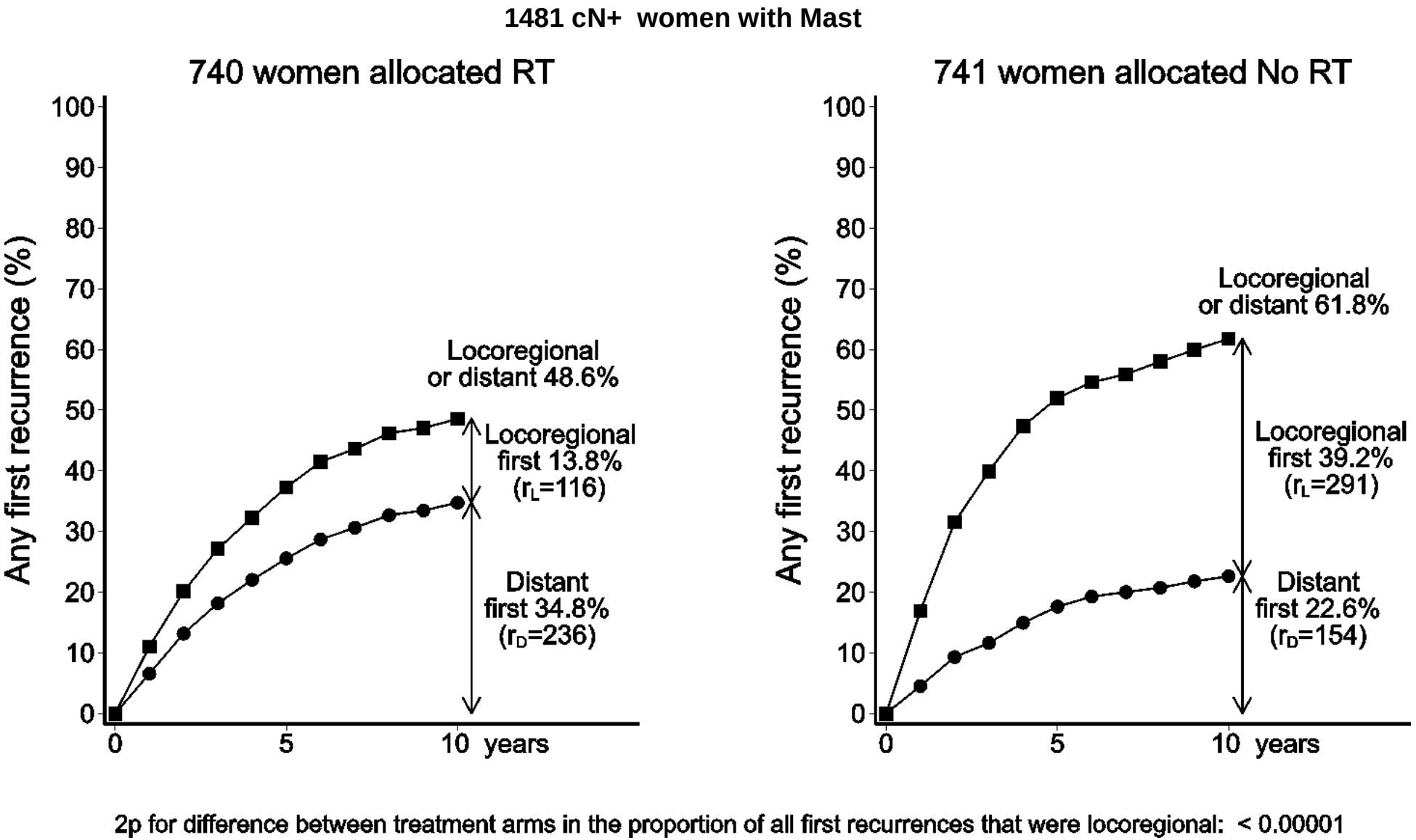
Any death



Any death rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	7.36 (230/3123)	6.22 (135/2169)	3.69 (63/1709)	5.29 (73/1379)	2.96 (81/2740)
No RT	8.34 (260/3116)	6.31 (130/2059)	4.41 (71/1611)	5.86 (72/1229)	3.10 (73/2358)
Rate ratio, from	0.86 SE 0.09	0.96 SE 0.13	0.84 SE 0.17	0.92 SE 0.17	1.04 SE 0.17
(O−E)/V	−16.4/111.7	−2.8/60.2	−5.3/30.9	−2.6/32.3	1.3/35.7

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.)



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)*.

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

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

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

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

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

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

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

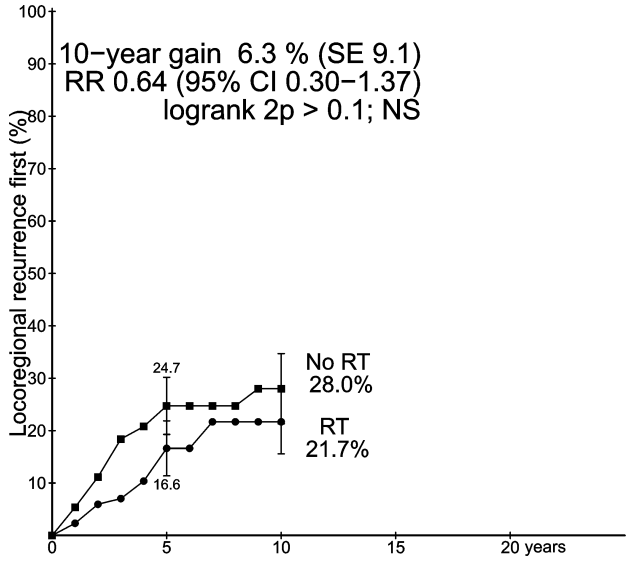
References for Webtable 7

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

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

192 cN+ women with Mast

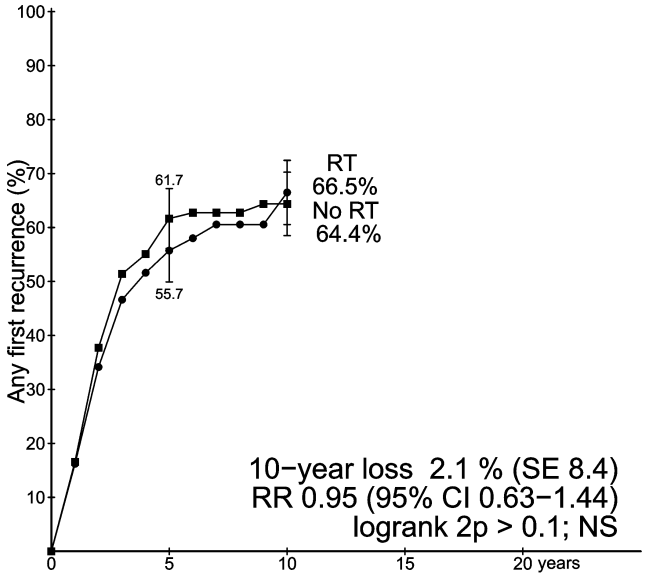
Locoregional recurrence first



Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	3.60 (11/305)	1.46 (2/137)
No RT	5.54 (16/289)	1.64 (2/122)
Rate ratio, from	0.57 SE 0.31	1.86 SE 1.61
(O−E)/V	−3.4/6.1	0.5/0.7

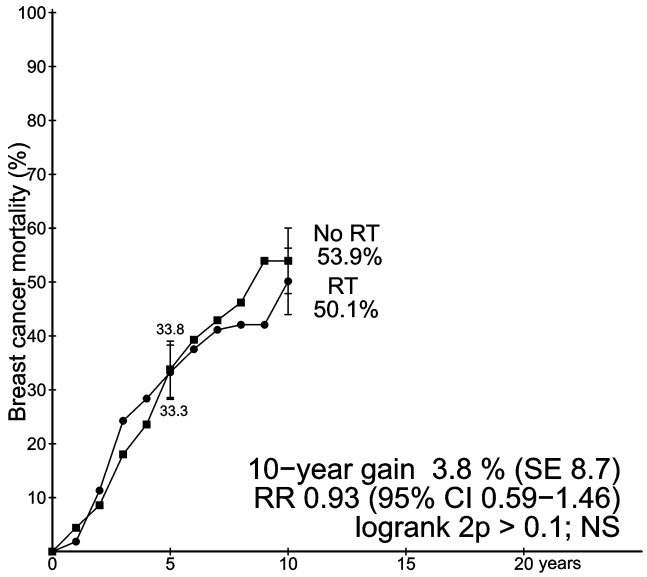
Any first recurrence



Any first recurrence rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	17.68 (54/305)	5.12 (7/137)
No RT	19.73 (57/289)	3.28 (4/122)
Rate ratio, from	0.86 SE 0.21	3.02 SE 1.35
(O−E)/V	−3.1/20.4	2.0/1.8

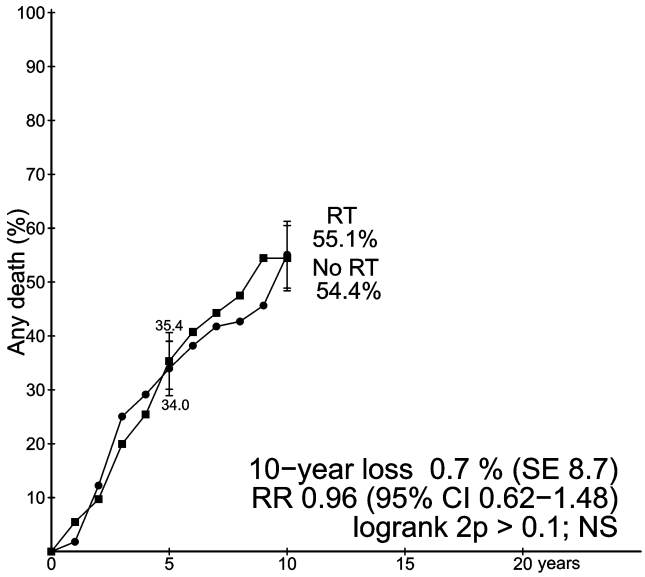
Breast cancer mortality



Breast cancer mortality rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10+
RT	7.75 (31/400)	5.33 (11/206)	3.71 (1/27)
No RT	8.01 (32/399)	7.71 (15/195)	5.18 (1/19)
Rate ratio, from	1.01 SE 0.28	0.71 SE 0.36	2.10 SE 2.26
(O−E)/V	0.1/13.0	−1.8/5.4	0.3/0.4

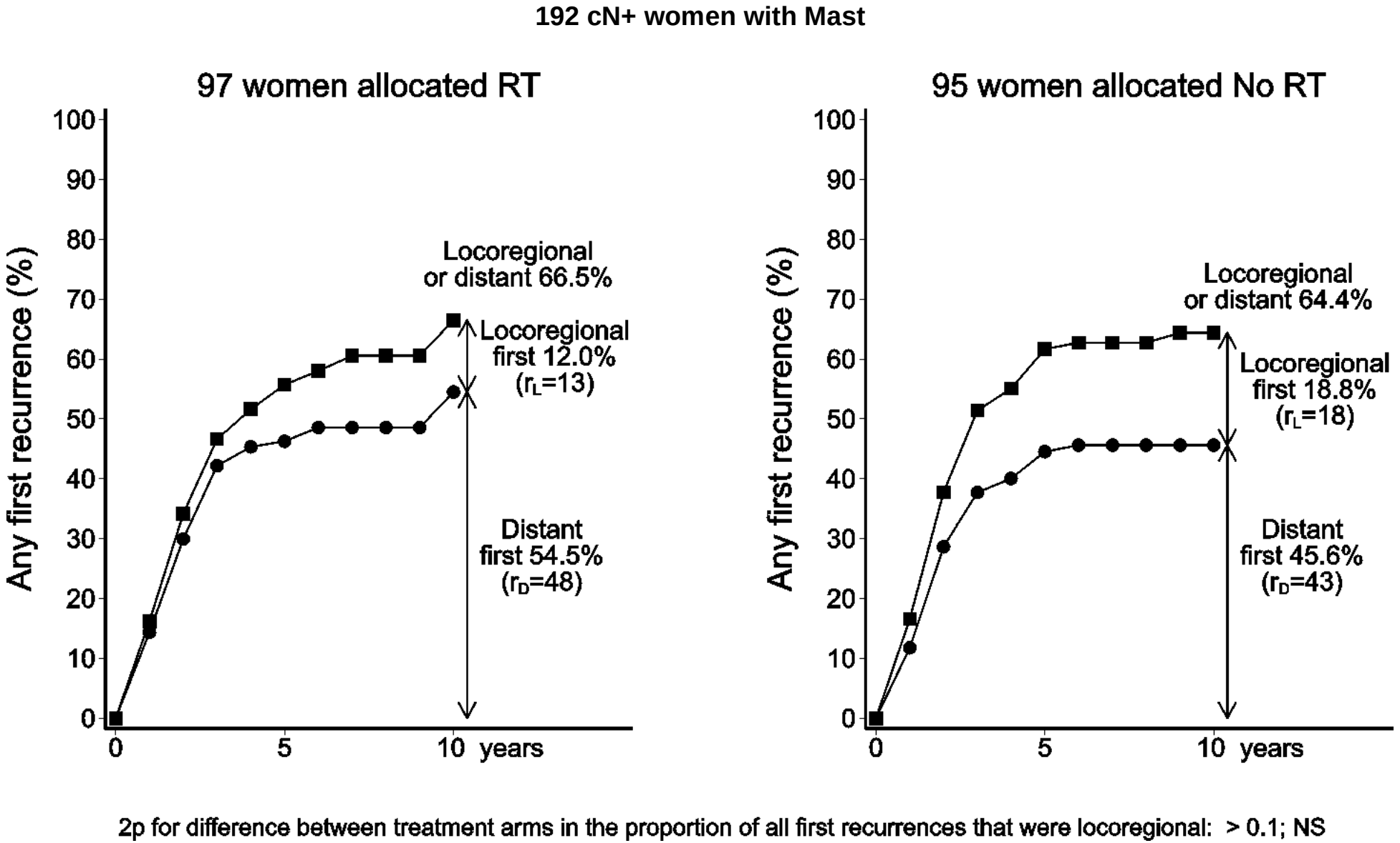
Any death



Any death rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10+
RT	8.00 (32/400)	6.30 (13/206)	3.71 (1/27)
No RT	8.51 (34/399)	7.71 (15/195)	10.36 (2/19)
Rate ratio, from	0.98 SE 0.27	0.86 SE 0.38	2.10 SE 2.26
(O−E)/V	−0.3/13.8	−0.9/5.8	0.3/0.4

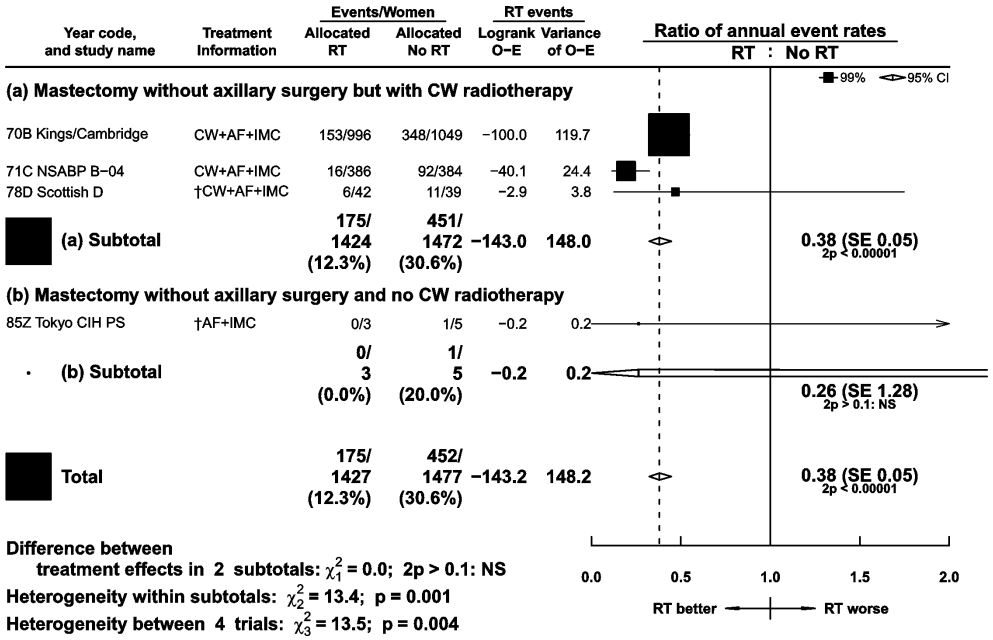
Webfigure 47. Effect of radiotherapy (RT) to the regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of recurrence and type of first recurrence in 192 women with clinically node-positive (cN+) disease. (r_L = number of women for whom first recurrence was locoregional,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



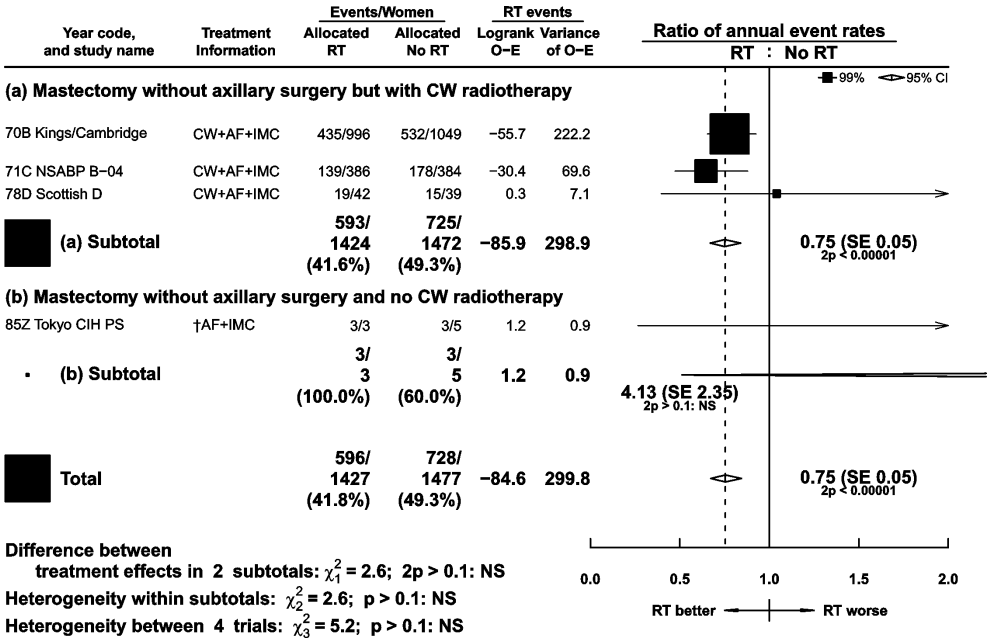
Webfigure 48. Effect of radiotherapy (RT) versus not after mastectomy but no axillary surgery (Mast): 10 year risks of recurrence during years 0-9, breast cancer mortality, and all-cause mortality in 2904 women with clinically node-negative (cN-) disease. Event rate ratios, one line per trial, trial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



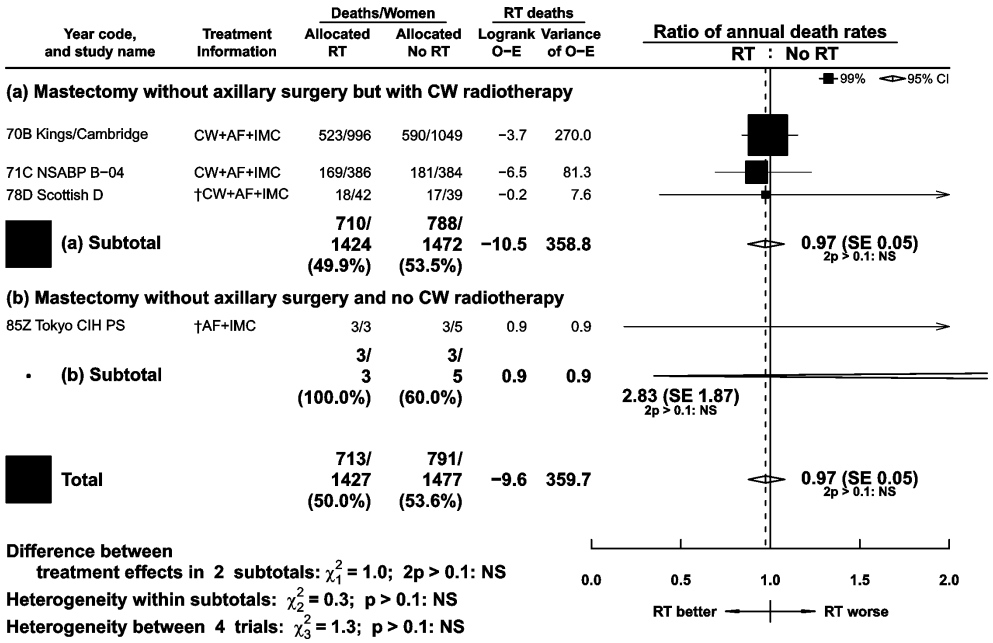
† Same polychemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

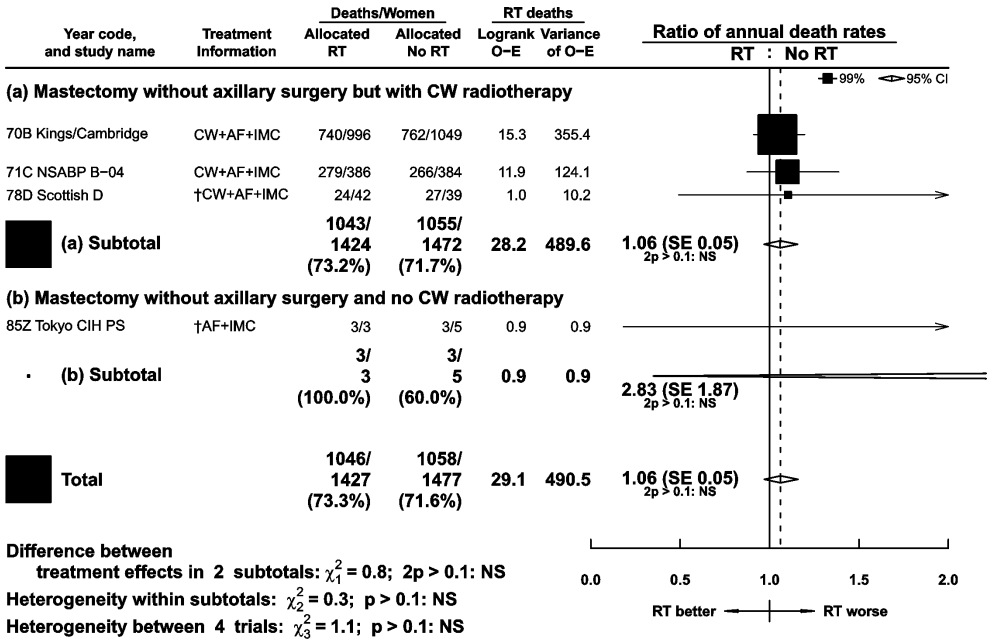
Webfigure 48 cntd.

2904 cN- women

Breast cancer mortality



Any death

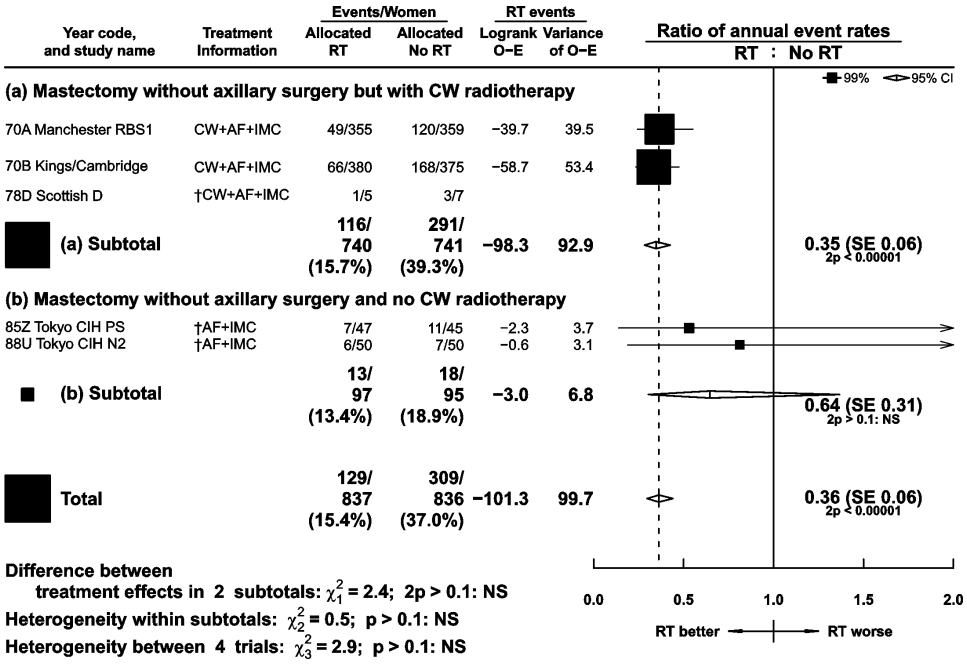


† Same polychemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

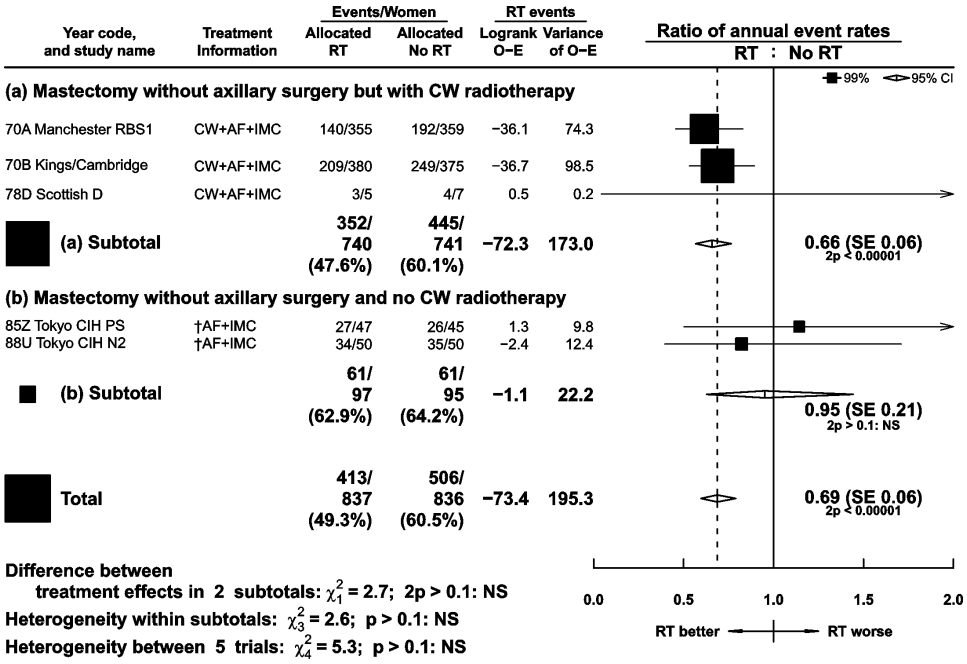
Webfigure 49. Effect of radiotherapy (RT) versus not after mastectomy but no axillary surgery (Mast): 10 year risks of recurrence during years 0-9, breast cancer mortality, and all-cause mortality in 1673 women with clinically node-positive (cN+) disease. Event rate ratios, one line per trial, trial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



† 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.

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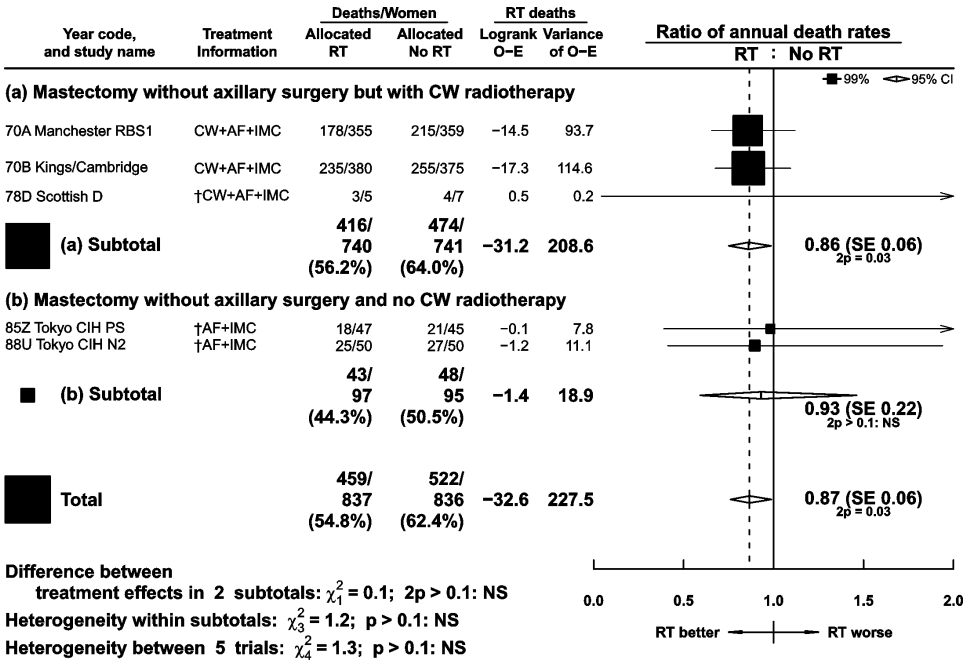
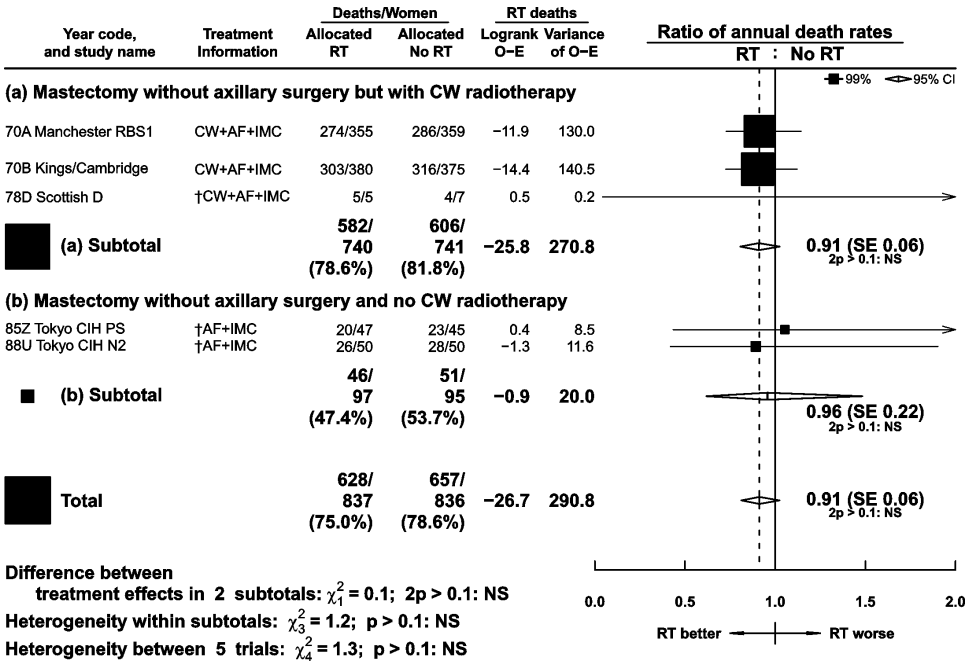
Webfigure 49 cntd.

1673 cN+ women

Breast cancer mortality



Any death



† 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.

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) *.

Nodal status†	Women	Deaths	Woman-years since diagnosis					% women given systemic therapy	
			Median/ woman	Total ('000s)	Distribution by years ('000s) <10	10-	20+	Chemotherapy‡	ER+ & 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,

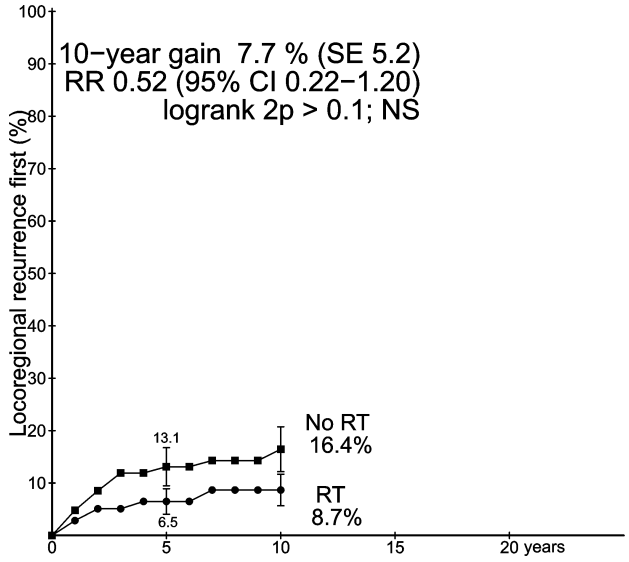
References for Webtable 9

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. *Radiother Oncol* 1998; **48**: 185–90.

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

255 pN? women with Mast+AD

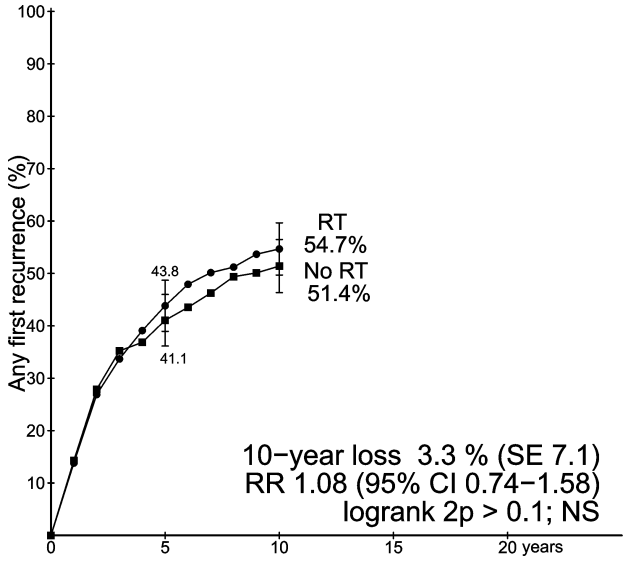
Locoregional recurrence first



Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	1.43 (6/421)	0.43 (1/235)
No RT	3.37 (15/445)	0.76 (2/264)
Rate ratio, from	0.50 SE 0.33	0.65 SE 0.97
(O−E)/V	−3.3/4.7	−0.3/0.7

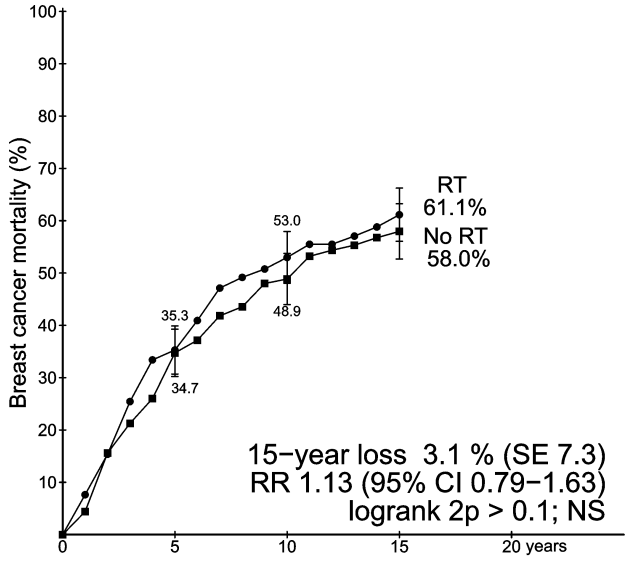
Any first recurrence



Any first recurrence rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	11.88 (50/421)	4.26 (10/235)
No RT	11.91 (53/445)	4.17 (11/264)
Rate ratio, from	1.07 SE 0.22	1.13 SE 0.48
(O−E)/V	1.4/21.8	0.6/4.9

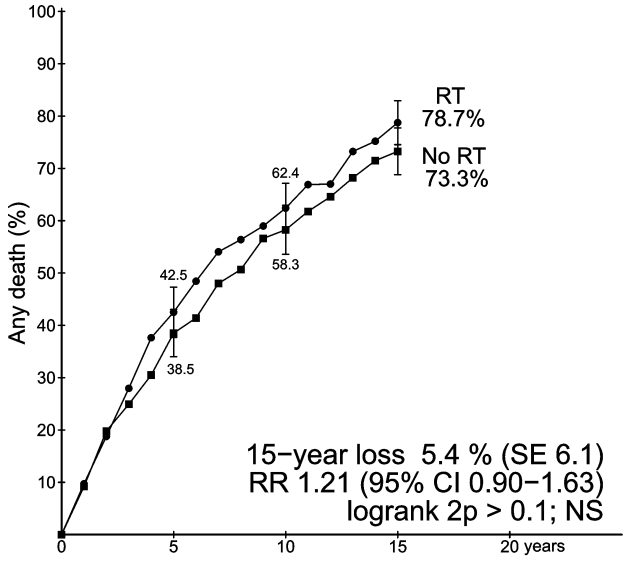
Breast cancer mortality



Breast cancer mortality rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15+
RT	8.56 (40/467)	6.58 (18/274)	3.21 (5/156)	9.47 (4/42)
No RT	8.52 (44/516)	5.14 (16/311)	4.57 (8/175)	3.17 (2/63)
Rate ratio, from	1.06 SE 0.24	1.43 SE 0.45	0.84 SE 0.56	1.52 SE 1.14
(O−E)/V	1.1/18.3	2.5/7.1	−0.5/2.7	0.5/1.2

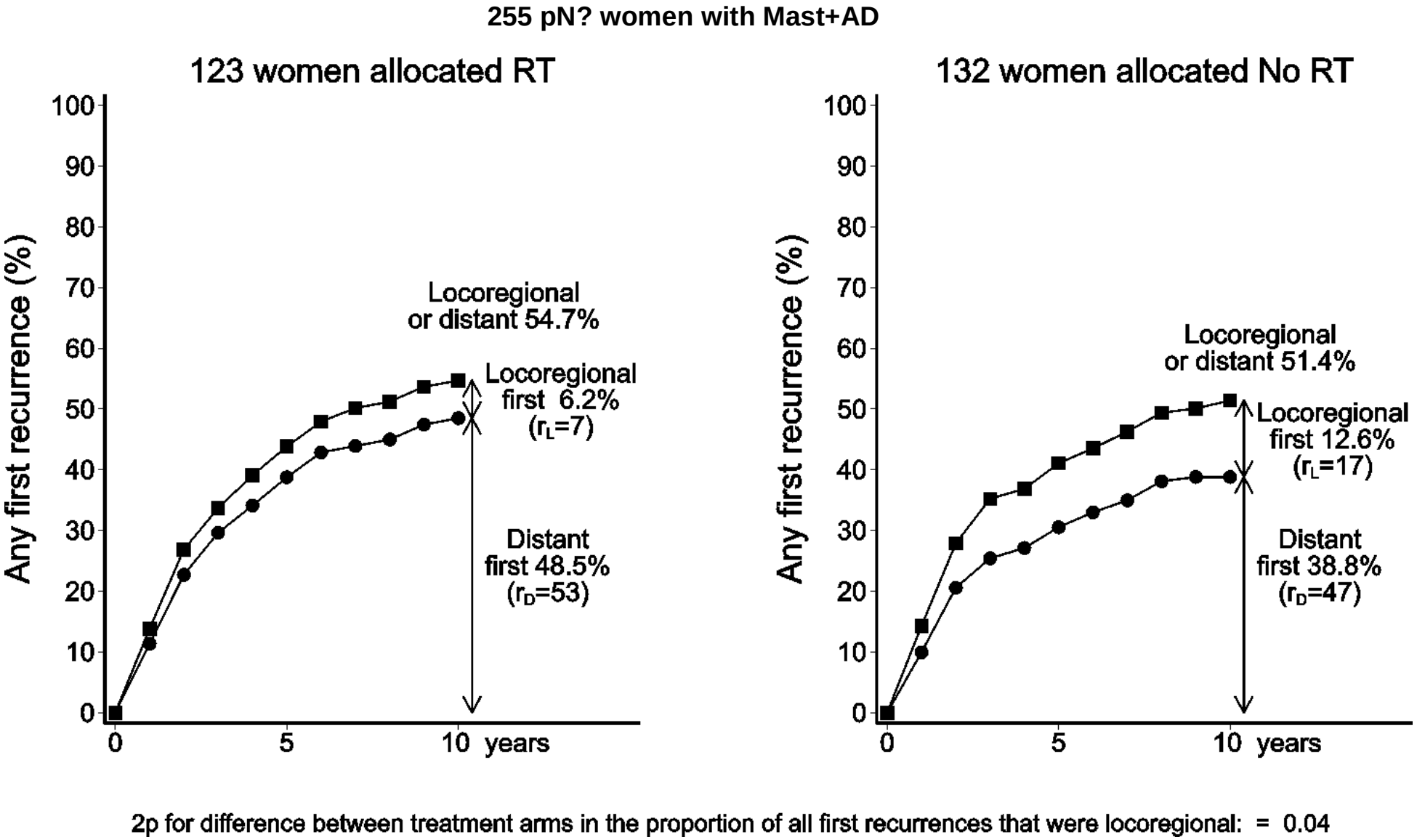
Any death



Any death rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15+
RT	11.13 (52/467)	9.14 (25/274)	11.54 (18/156)	23.66 (10/42)
No RT	9.88 (51/516)	8.03 (25/311)	9.13 (16/175)	6.34 (4/63)
Rate ratio, from	1.14 SE 0.22	1.13 SE 0.32	1.22 SE 0.41	2.70 SE 1.13
(O−E)/V	3.1/22.8	1.3/10.8	1.5/7.2	2.3/2.3

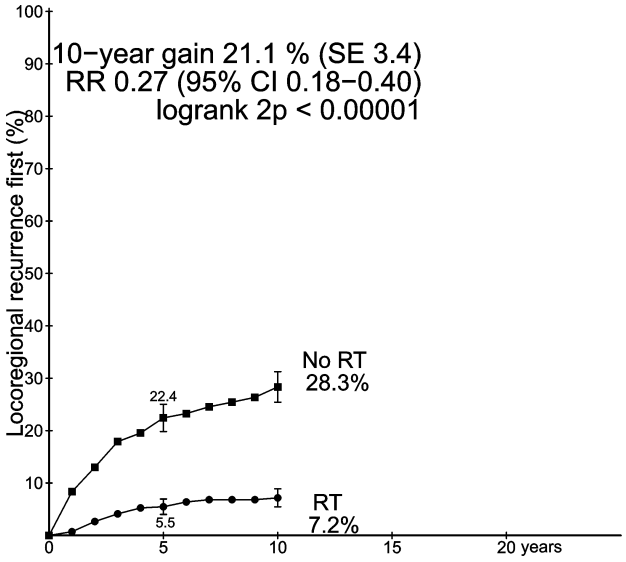
Webfigure 51. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 255 women with unknown pathological nodal status (pN?). (r_L = number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



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

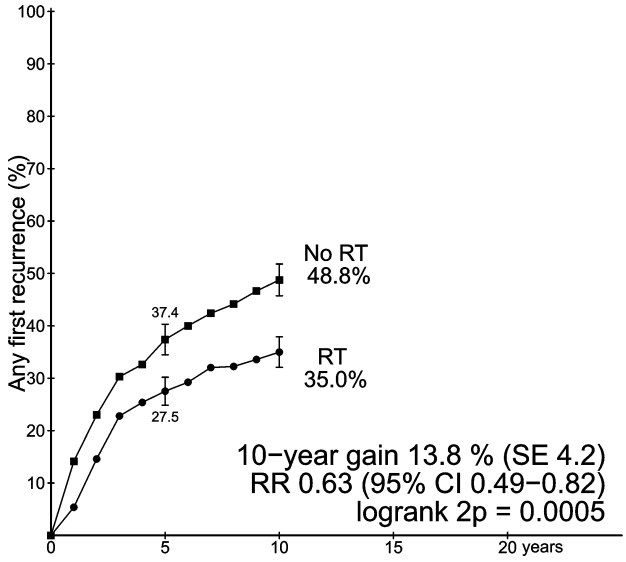
Locoregional recurrence first



Locoregional recurrence first rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	1.24 (16/1290)	0.41 (4/968)
No RT	5.41 (63/1164)	1.61 (13/808)
Rate ratio, from	0.26 SE 0.13	0.28 SE 0.28
(O−E)/V	−25.2/18.9	−5.3/4.2

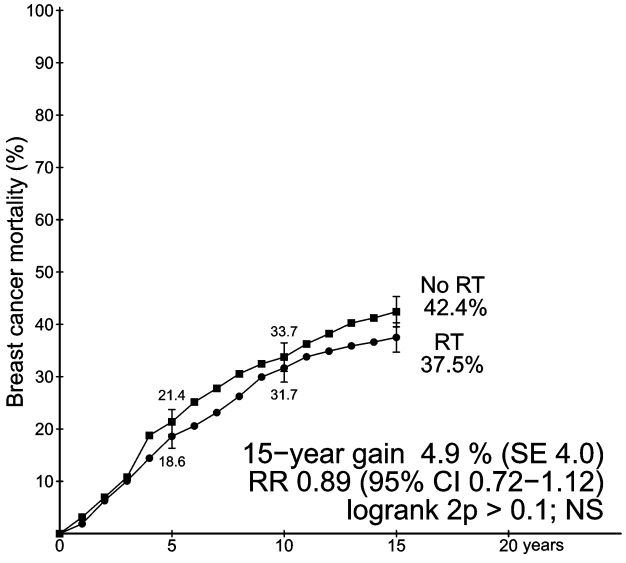
Any first recurrence



Any first recurrence rates (%/year) and logrank analyses

	Years 0−4	Years 5−9
RT	6.67 (86/1290)	2.48 (24/968)
No RT	9.88 (115/1164)	4.08 (33/808)
Rate ratio, from	0.66 SE 0.12	0.55 SE 0.21
(O−E)/V	−18.8/45.3	−7.8/13.2

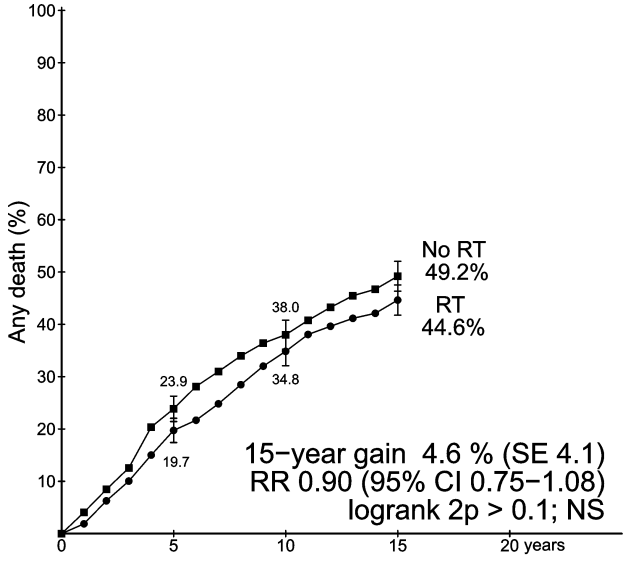
Breast cancer mortality



Breast cancer mortality rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15+
RT	4.10 (59/1440)	3.48 (40/1151)	1.70 (16/939)	1.89 (37/1962)
No RT	4.70 (67/1427)	3.48 (38/1090)	2.98 (27/907)	2.38 (43/1805)
Rate ratio, from	0.85 SE 0.17	1.00 SE 0.23	0.64 SE 0.25	1.05 SE 0.24
(O−E)/V	−4.9/29.7	−0.0/18.4	−4.6/10.3	0.9/18.8

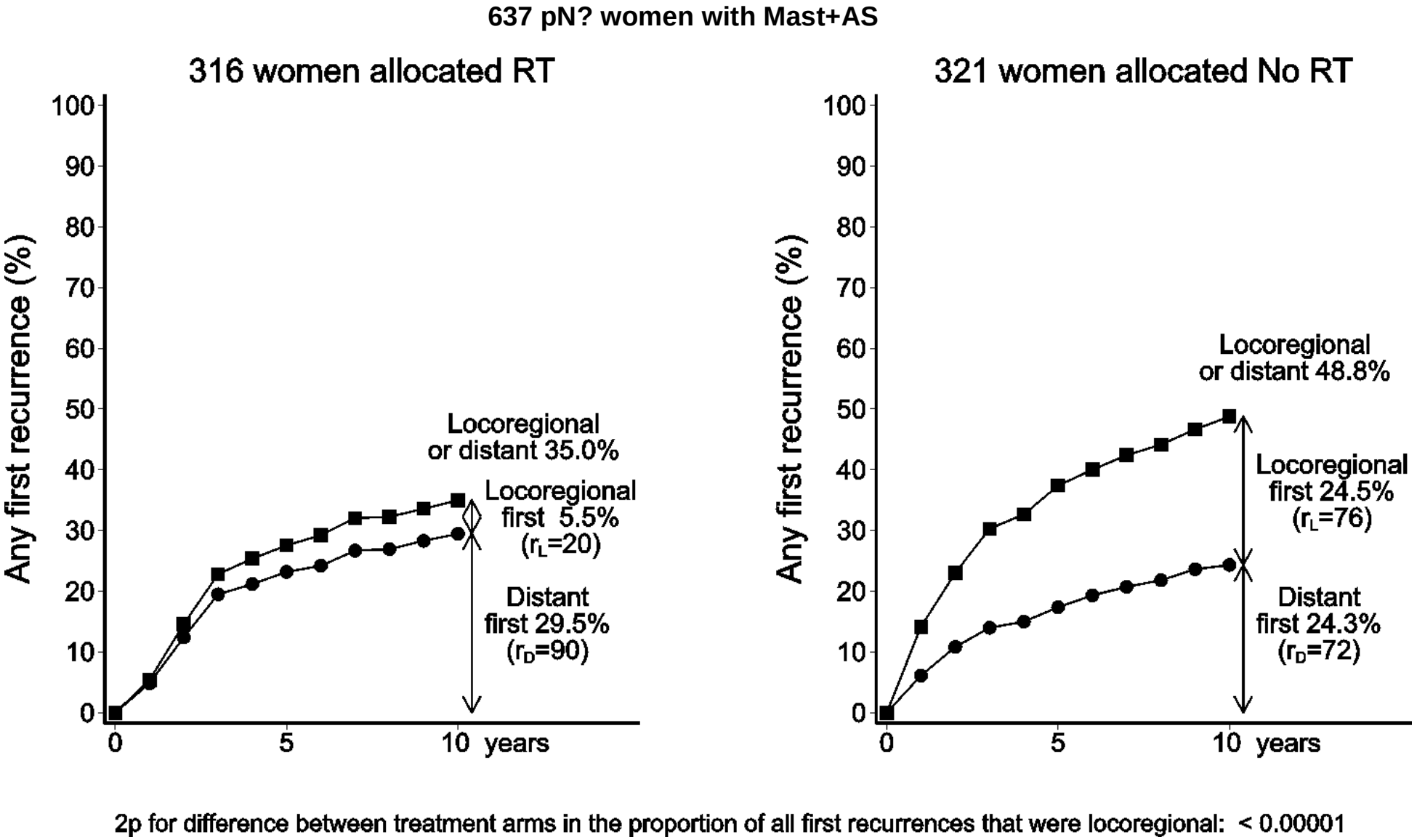
Any death



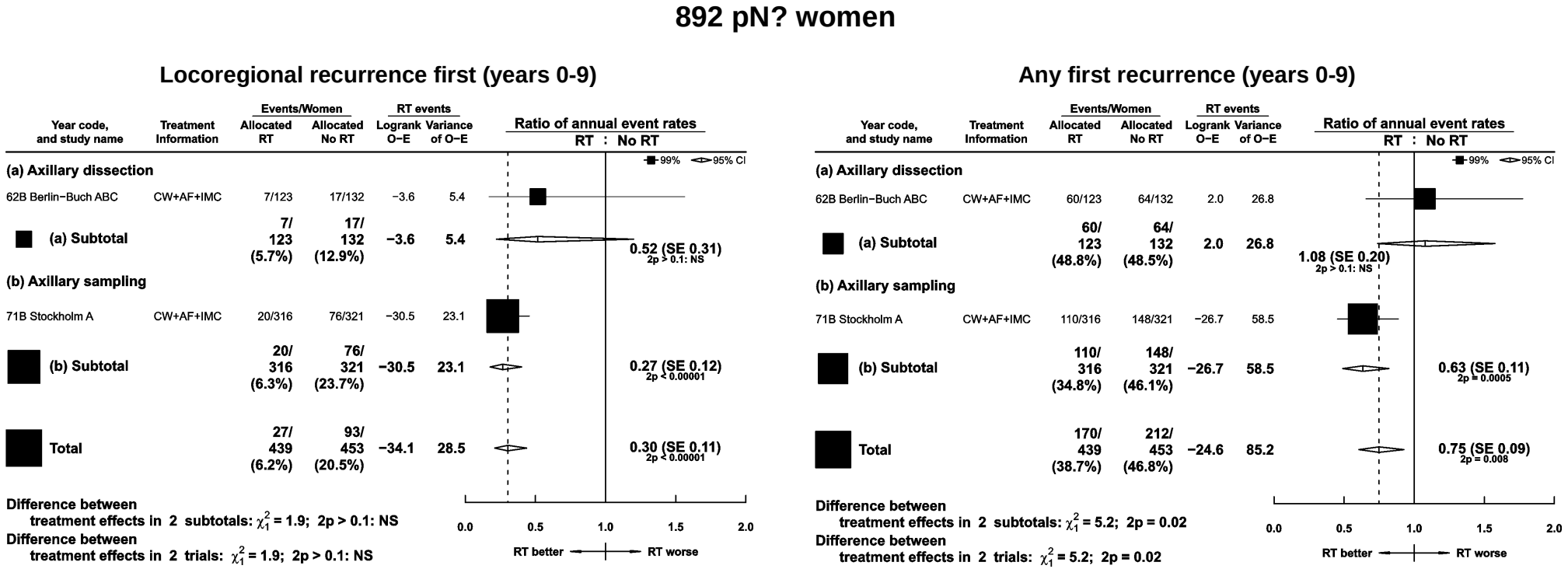
Any death rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15+
RT	4.38 (63/1440)	4.17 (48/1151)	3.41 (32/939)	5.15 (101/1962)
No RT	5.33 (76/1427)	4.13 (45/1090)	3.97 (36/907)	5.32 (96/1805)
Rate ratio, from	0.79 SE 0.16	0.99 SE 0.21	0.82 SE 0.23	0.97 SE 0.15
(O−E)/V	−7.6/32.9	−0.3/22.0	−3.2/15.9	−1.2/45.2

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.)



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?).



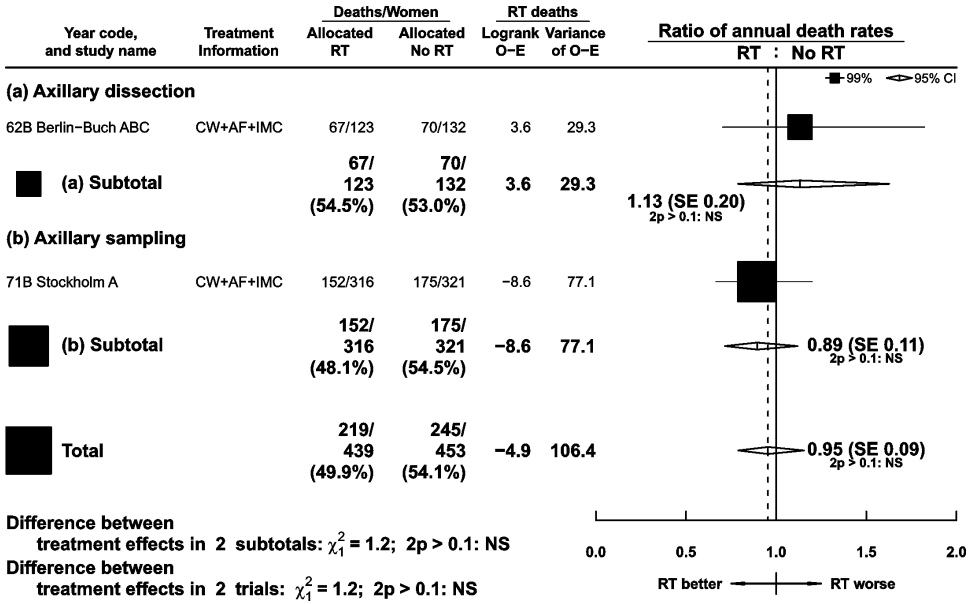
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain.

continued overleaf

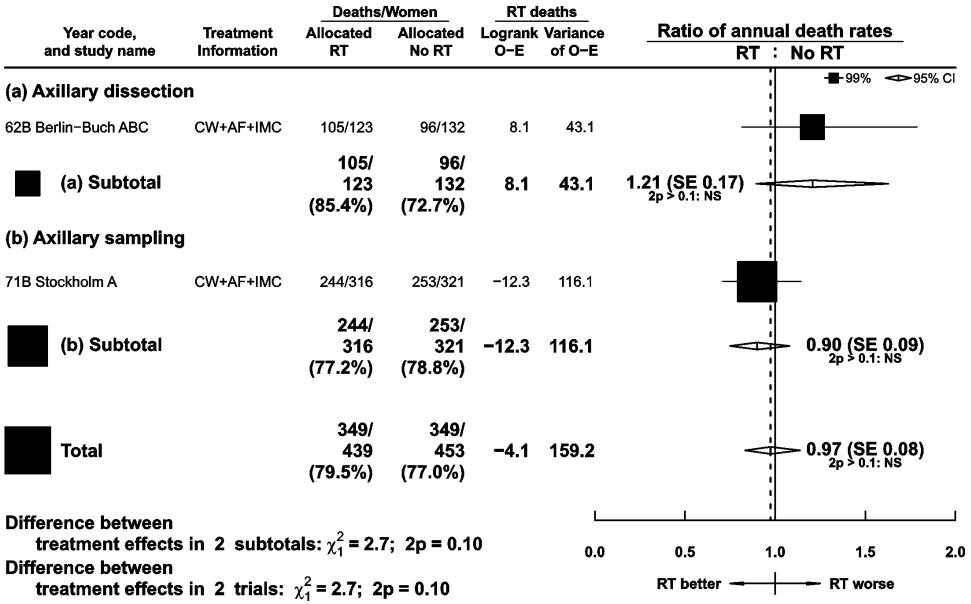
Webfigure 54 cntd.

892 pN? women

Breast cancer mortality



Any death



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

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