Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)*

*Collaborators listed at end of report

Correspondence: EBCTCG Secretariat, CTSU, Richard Doll Building, Oxford OX3 7LF, UK. email: bc.overview@ctsu.ox.ac.uk

Summary

Background: After breast-conserving surgery, radiotherapy reduces recurrence and breast cancer death, but it may do so more for some groups of women than for others. We describe the absolute magnitude of these reductions according to various prognostic and other patient characteristics, and relate the absolute reduction in 15-year risk of breast cancer death to the absolute reduction in 10-year recurrence risk.

Methods: We undertook a meta-analysis of individual patient data for 10 801 women in 17 randomised trials of radiotherapy versus no radiotherapy after breast-conserving surgery, 8337 of whom had pathologically confirmed node-negative (pN0) or node-positive (pN+) disease.

Findings: Overall, radiotherapy reduced the 10-year risk of any (ie, locoregional or distant) first recurrence from 35·0% to 19·3% (absolute reduction 15·7%, 95% CI 13·7–17·7, 2p<0·00001) and reduced the 15-year risk of breast cancer death from 25·2% to 21·4% (absolute reduction 3·8%, 1·6–6·0, 2p=0·00005). In women with pN0 disease (n=7287), radiotherapy reduced these risks from 31·0% to 15·6% (absolute recurrence reduction 15·4%, 13·2–17·6, 2p<0·00001) and from 20·5% to 17·2% (absolute mortality reduction 3·3%, 0·8–5·8, 2p=0·005), respectively. In these women with pN0 disease, the absolute recurrence reduction varied according to age, grade, oestrogen-receptor status, tamoxifen use, and extent of surgery, and these characteristics were used to predict large (≥20%), intermediate (10–19%), or lower (<10%) absolute reductions in the 10-year recurrence risk. Absolute reductions in 15-year risk of breast cancer death in these three prediction categories were 7·8% (95% CI 3·1–12·5), 1·1% (–2·0 to 4·2), and 0·1% (–7·5 to 7·7) respectively (trend in absolute mortality reduction 2p=0·03). In the few women with pN+ disease (n=1050), radiotherapy reduced the 10-year recurrence risk from 63·7% to 42·5% (absolute reduction 21·2%, 95% CI 14·5–27·9, 2p<0·00001) and the 15-year risk of breast cancer death from 51·3% to 42·8% (absolute reduction 8·5%, 1·8–15·2, 2p=0·01). Overall, about one breast cancer death was avoided by year 15 for every four recurrences avoided by year 10, and the mortality reduction did not differ significantly from this overall relationship in any of the three prediction categories for pN0 disease or for pN+ disease.

Interpretation: After breast-conserving surgery, radiotherapy to the conserved breast halves the rate at which the disease recurs and reduces the breast cancer death rate by about a sixth. These proportional benefits vary little between different groups of women. By contrast, the absolute benefits from radiotherapy vary substantially according to the characteristics of the patient and they can be predicted at the time when treatment decisions need to be made.

Funding: Cancer Research UK, British Heart Foundation, and UK Medical Research Council.

Introduction

For many women with early stage breast cancer, breast-conserving surgery can remove any macroscopic disease that has been detected, but some microscopic tumour foci may remain in the conserved breast that could, if untreated, lead to locoregional recurrence and/or life-threatening distant metastases. This report updates previous Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analyses of individual patient data from the randomised trials of radiotherapy after breast-conserving surgery.[1-5] It includes further follow-up on 9 of the 10 trials analysed previously,[5] adds data from seven new trials, six of which were in low-risk women, and increases the total number of women by nearly 50%. The report focuses mainly on women for whom pathological axillary lymph node status is known (negative: pN0, positive: pN+), as such information is usually available. It assesses the extent to which the radiotherapy-related absolute reduction in 10-year risk of first recurrence at any site (locoregional or distant) varies for women with differing prognostic and other factors. It then relates the absolute reduction in recurrence to that in 15-year breast cancer mortality.

Methods

Trials beginning before 2000 of adjuvant radiotherapy versus no radiotherapy following breast-conserving surgery for invasive cancer were eligible. Trial identification and data handling were as before.[5] For every woman, information was sought on initial characteristics, allocated treatment, time to first recurrence, whether it was locoregional or distant (excluding contralateral breast cancer), and date last known alive or date and underlying cause of death. Where no recurrence was reported prior to breast cancer death, distant recurrence was assumed to have just preceded it. If contralateral breast cancer occurred prior to any other recurrence, follow-up was censored on that date in recurrence analyses.

Statistical methods

The methodology used here differs somewhat from that used previously.[5] Firstly, to avoid assumptions about how locoregional and distant recurrence relate to each other, the main emphasis is on analyses of any first recurrence rather than, as before, of time to locoregional recurrence as a first event. Secondly, most analyses of recurrence present data for only 10 years, as many of these trials did not follow women beyond this for recurrence. This lack of follow-up should not bias the estimated proportional effect on recurrence after year 10, but could affect absolute risk estimates substantially. Thirdly, deaths of unknown cause before recurrence are no longer attributed to breast cancer, as most

occurred many years after trial entry, by which time non-breast-cancer mortality predominated. Other aspects of methodology are as before.[5] Logrank analyses are stratified by trial, individual follow-up year, and nodal status. They are also stratified by age, either in 5 groups (<40, 40-49, 50-59, 60-69, 70+) or, where the data are also subdivided by other factors, in 2 groups (<50, 50+).

Analyses of the dependence of absolute risk, and absolute risk reduction, on several factors simultaneously use Poisson regression fitted by maximum likelihood (details in webappendix p20-25). In these analyses absolute risk of any first recurrence is adjusted not only for trial, individual follow-up year, nodal status and age (5 groups), but also for tumour grade, tumour size, oestrogen-receptor (ER) status, and whether or not tamoxifen had been used in both trial arms.

Role of the funding sources

The Secretariat had full access to all data and analyses. Funding agencies had no role in data collection, analysis, interpretation or reporting. Preliminary results were presented to collaborators in September 2010. A manuscript was circulated to collaborators for comment in January 2011 and then revised centrally. Submission for publication was decided only by the writing committee.

Results

Information was available on 10,801 women in 17 trials (table 1). Six trials (Category A, 4398 women) were of radiotherapy after lumpectomy, 4 trials (Category B, 2399 women) were of radiotherapy after sector resection or quadrantectomy and 7 relatively recent trials (Category C, 4004 women) were of radiotherapy after lumpectomy in low-risk women. There was an average of 10 years of follow-up per woman; 3143 (29%) had died.

Overall effect of radiotherapy

The 10-year risk of any (locoregional or distant) first recurrence was 19.3% in women allocated to radiotherapy and 35.0% in women allocated to breast-conserving surgery (BCS) only, corresponding to an absolute risk reduction of 15.7% (2p<0.00001) (figure 1). Nearly three-quarters of the first recurrences in the control group were locoregional, while fewer than half of those in the radiotherapy group were locoregional (control group: 25% locoregional first, 10% distant first; radiotherapy group: 8% locoregional first, 12% distant first; webappendix p9). In addition to reducing recurrence substantially, radiotherapy also reduced breast cancer mortality by a moderate amount: the 15-year absolute risk

reduction was 3.8% (95% confidence interval [CI] 1.6, 6.0, 2p=0.00005), suggesting on average about one breast cancer death avoided for every 4 recurrences avoided by radiotherapy.

Allocation to radiotherapy halved the average annual rate of any first recurrence (rate ratio [RR]=0.52 [95% CI 0.48, 0.56], webappendix p13). The proportional reduction was greatest in the first year (RR=0.31 [0.26, 0.37]), but was still substantial during years 5-9 (RR=0.59 [0.50, 0.70]). Beyond year 10 there was no evidence of any further effect on the first recurrence rate, but information on recurrence in this period was incomplete (see Methods) so the number of events was small and the CI wide. Radiotherapy reduced the annual breast cancer mortality rate by one-sixth (RR=0.82 [0.75, 0.90]). The timing of breast cancer mortality differed from that of first recurrence, with few events during the first year, and substantial numbers of breast cancer deaths after year 10.

Mortality without recurrence from non-breast-cancer causes was slightly higher in women allocated to radiotherapy but the excess was not significant (RR=1.09, 95%CI [0.97, 1.22], 2p=0.15). If the mortality rate from non-breast cancer causes in the women allocated to radiotherapy had been identical to that in the women allocated to BCS only, then the 15-year absolute risk reduction in all-cause mortality would have been 3.2%. In fact, the 15-year absolute risk reduction in all-cause mortality was 3.0% (95% CI 0.6, 5.4, 2p=0.03) (figure 1).

Effect of radiotherapy in pN0 and pN+ disease

The majority of women (7287) had pN0 disease, and among them allocation to radiotherapy also halved the average annual recurrence rate during the first decade (RR=0.46, standard error [SE] 0.04), reducing the 10-year absolute risk of any first recurrence by 15.4% (15.6% versus 31.0%, 2p<0.00001) (figure 2). For these women, radiotherapy again reduced breast cancer mortality by about one-sixth (RR=0.82, SE 0.06), with a 15-year absolute reduction of 3.3% (17.2% versus 20.5%, 95% CI for absolute reduction 0.8, 5.8; 2p=0.005).

For the 1050 women with pN+ disease, allocation to radiotherapy produced a six-fold reduction in the 1-year recurrence risk (4% versus 26%), with a moderate further effect over the next few years but little further effect after year five (figure 2). Combining these very different proportional effects at different treatment times, the average annual recurrence rate during the first 10 years was halved in

pN+ disease (RR=0.50, SE 0.07). Although the proportional reductions in the average annual recurrence rate were similar in pN0 and pN+ disease, the absolute 10-year recurrence reduction appeared somewhat larger in pN+ disease at 21.2% (42.5% versus 63.7%, 2p<0.00001). Radiotherapy also reduced breast cancer mortality in pN+ disease (RR=0.79, 95%CI 0.66, 0.95, p=0.01) with a 15-year absolute reduction of 8.5% (42.8% versus 51.3%: 95% CI for absolute reduction 1.8, 15.2).

In both pN0 and pN+ disease, the first recurrence was locoregional for a far higher proportion of those allocated to BCS only than of those allocated to BCS+RT (webappendix p10).

Some women benefit more than others

Analyses of the effects of treatment in various subgroups of women with pN0 disease are much more likely to identify differences reliably if they are based on recurrence than if they are based on mortality. This is because the significance level of the effect of radiotherapy is much more extreme for recurrence than for mortality (2p<0.00001 for recurrence [χ_1^2 = 209], 2p=0.002 for breast cancer mortality [χ_1^2= 10]).

The following analyses, which focus first on proportional and then on absolute reductions in recurrence, subdivide the women in various ways to ascertain whether some groups will benefit more from radiotherapy than others. In the first analysis, the proportional effect of radiotherapy on the rate of any first recurrence in pN0 disease during the first 10 years was estimated for each of several factors considered separately (figure 3). In most subgroups, radiotherapy approximately halved the average annual recurrence rate (except that among women who had been given lumpectomy the proportional recurrence reduction appeared somewhat less extreme in ER-poor disease [2p=0.01] and somewhat more extreme in the low-risk [category C] trials [2p=0.009]).

Halving a big risk produces a greater absolute benefit than halving a small risk, and in pN0 disease the annual recurrence rate without radiotherapy was strongly correlated with age (inversely), tumour grade, tumour size, ER status (especially if tamoxifen was used in ER+ disease), and extent of surgery (inversely), and the absolute recurrence reduction produced by radiotherapy also depended strongly on these factors (table 2). In the second analysis, the way in which the absolute reduction in 10-year recurrence risk produced by radiotherapy depended on all the potential explanatory factors listed in table 2 considered together was modelled by considering information both on those allocated to

radiotherapy and on those allocated to no radiotherapy. Methodological details are in webappendix p20-25 and results are given below.

The absolute recurrence risk with radiotherapy, and also the absolute reduction in risk produced by radiotherapy, varied substantially with age, tumour grade, and ER-status/tamoxifen use even after adjustment for all other factors (2p=0.0002, <0.00001, and 0.003 respectively, table 2). Tumour size was also independently predictive of absolute recurrence risk among women given radiotherapy.

When the original trials with lumpectomy (category A) and the later trials with lumpectomy in low-risk women (category C) were compared, there was a substantial difference in the absolute recurrence risk without radiotherapy and in the absolute reduction in this risk produced by radiotherapy, but these differences were largely accounted for by the other recorded risk factors (table 2).

Surgery that is more extensive than lumpectomy (as in the category B trials) reduced the absolute recurrence risk without radiotherapy and also reduced the absolute reduction in this risk produced by radiotherapy. As, however, the category B trials did not recommend tamoxifen, this effect of the extent of surgery on the absolute effect of radiotherapy was apparent after adjustment for tamoxifen use (and the other recorded factors), but not before (table 2).

The characteristics that were independently predictive of the absolute risk of recurrence, or of the absolute reduction in risk with radiotherapy were included in a model to indicate how 10-year recurrence risks with and without radiotherapy depended in these trials on age, grade, ER status, tamoxifen (given much more often in the recent trials in low-risk patients) and extent of surgery. Figure 4 shows, these model-based estimates for women with T1 tumours (diameter 1-20 mm). In each row of the figure, younger women and those with higher grade tumours had substantially larger absolute recurrence risks without radiotherapy and substantially larger absolute risk reductions with radiotherapy. For a given age and grade, among women whose surgery involved only lumpectomy the highest risks and largest absolute reductions with radiotherapy were for ER+ women not given tamoxifen, although even with tamoxifen the additional effects of radiotherapy were substantial for women with high grade tumours and younger women with intermediate grade tumours. Results for women with T2 tumours (diameter 21-50 mm) are in webappendix p27.

Each woman with pN0 disease was assigned a predicted absolute reduction in 10-year recurrence risk from being allocated radiotherapy on the basis of her individual characteristics, the characteristics of the trial she was in, and the model-based estimates in figure 4 and webappendix p27-8. It was large (≥20%) for 1924 women (56%, 16% & 9% of those in trial categories A, B & C), intermediate for 3763 women, and lower (<10%) for 1600 women (12%, 10% & 38% of those in trial categories A, B & C). For these three groups, the *observed* absolute reductions in 10-year recurrence risk, calculated directly from data on individual women, were 24.3% (26.0% vs 50.3%), 12.4% (12.4% vs 24.8%) and 6.9% (12.0% vs 18.9%). The corresponding absolute reductions in 15-year breast cancer mortality in the three groups were 7.8% (95% CI 3.1, 12.5), 1.1% (-2.0, 4.2) and 0.1% (-7.5, 7.7) respectively (trend in absolute mortality reduction: 2p=0.03, figure 5, webappendix p35-37). For all three groups, the first recurrence was locoregional for a much larger proportion of those allocated to BCS only than of those allocated to BCS+RT (webappendix p38-39). As there were only 1050 women with pN+ disease in these trials, the relevance of prognostic factors could not be explored reliably among them (see webappendix p40-44).

On average among all the women in these trials, about one breast cancer death was avoided by year 15 for every 4 recurrences avoided by year 10 (figure 1). For pN+ disease and for pN0 disease with large predicted absolute recurrence benefit the observed ratio was slightly larger, while for pN0 disease with intermediate or lower predicted absolute benefit it was somewhat smaller (figure 5). However, the departure from linearity was not statistically significant (2p=0.11).

Discussion

The overall findings from these trials show that radiotherapy after breast-conserving surgery not only substantially reduces the risk of recurrence but also moderately reduces the risk of death from breast cancer. This suggests that killing microscopic tumour foci in the conserved breast with radiotherapy reduces the potential for both local recurrence and distant metastasis. Both proportional and absolute reductions in the annual recurrence rate are largest in the first year but the recurrence rate continues to be somewhat lower throughout the first decade, while the breast cancer mortality reduction becomes definite only after the first few years and may last longer. Non-breast-cancer mortality and the incidence of contralateral and other second cancers in these and other early breast cancer radiotherapy trials will be reported elsewhere, but there was no substantial adverse effect on 15-year mortality from the aggregate of all causes other than breast cancer, so 15-year all-cause mortality was reduced by almost as much as would be expected from the reduction in breast cancer mortality.

Greater absolute benefit for some women

Previous analyses had shown that in pN0 disease young age, large tumour size and high grade were each strongly predictive of the risk of locoregional recurrence and of the absolute reduction in that risk with radiotherapy.[5] This report combines the predictive value of these and other factors, such as wider tamoxifen use in the more recent trials. Taken together, they account for the absolute recurrence reduction with radiotherapy being lower in more recent post-lumpectomy trials (ie, category C trials) than in the original post-lumpectomy trials (ie, category A trials, table 2). However, even for women with pN0 disease in the recent low-risk trials the predicted absolute recurrence reduction with radiotherapy exceeded 10% in most women and exceeded 20% in some women.

Almost a quarter of the women with pN0 disease were in trials where sector resection or quadrantectomy was carried out, rather than lumpectomy. Tamoxifen was not trial policy for pN0 disease in any of these trials and their recurrence rates were appreciably lower than the recurrence rates for similar women in the trials where lumpectomy was performed and tamoxifen was not recommended (figure 4). This difference is in accord with the findings of the single directly randomised trial of quadrantectomy versus lumpectomy, both with radiotherapy, in 700 women, two-thirds of whom were node-negative.[25] The majority of the trials of radiotherapy after lumpectomy required negative surgical margins on invasive cancer (although not on ductal carcinoma in situ). However, pathological techniques have become more sensitive since these women were randomised, and it is likely that a proportion of them would have been positive with modern techniques. Therefore, it is unclear whether the lower recurrence rates seen in the trials of radiotherapy in women given sector resection or quadrantectomy is simply the consequence of reducing the number of women with positive margins or whether there is further benefit to be derived from more extensive surgery.

The classification of pN0 disease into three groups with large, intermediate, and lower predicted absolute recurrence benefit from radiotherapy was derived from the recurrence data in these trials. The classification cannot be validated externally and so should not be over-interpreted. Nevertheless, the size of the difference in the absolute recurrence reduction between the three groups is striking. Also, the 15-year reduction in breast cancer mortality was about as big in pN0 disease with large predicted absolute recurrence benefit as it was in pN+ disease, while in pN0 disease with intermediate or lower predicted recurrence benefit the mortality reduction was smaller and was not separately significantly different from zero. It may be that the number of breast cancer deaths avoided per

recurrence avoided is more than one in four in pN+ disease and in pN0 disease with large predicted absolute recurrence benefit, and less than one in four for women with intermediate or lower predicted absolute benefit (figure 5). However, the present data do not depart significantly from one in four.

Locoregional recurrence and distant recurrence

The main analyses presented are of first recurrence of any type rather than, as before, locoregional recurrence as a first event. This is partly because it is now clear that radiotherapy after breast-conserving surgery reduces breast cancer mortality, so it must also reduce distant recurrence. It is also because women with higher risk of locoregional recurrence also have higher risk of distant recurrence (ie, the probabilities of locoregional and of distant recurrence are not statistically independent), so valid estimates of the separate effects of radiotherapy on local and distant recurrence cannot be obtained.[26,27] These issues are more important at 10 years than at 5 years (as presented previously), because more distant recurrences occur by 10 years than by 5 years. The fact that the proportion of first recurrences that were locoregional was much lower among irradiated women than among controls does, however, indicate that the main effect of radiotherapy was to reduce locoregional recurrence, while the reduction of the breast cancer mortality rate by one-sixth indicates that that the distant recurrence rate was reduced by at least as much. No analyses have been performed of recurrences after the first, as they are influenced by treatment policies for the first recurrence, and many trials did not record further recurrences.

Generalising to future practice

Screening, surgery, pathology, radiotherapy, and systemic therapy[28,29] have all changed substantially since most of these women were randomised, so the absolute recurrence reduction with radiotherapy in future patients may be very different from that seen in these trials. Moreover, information on additional risk factors will often be available (eg, HER2, gene expression profile, margin status) and a radiotherapy boost may be given.[30,31] Nevertheless, the observation that radiotherapy approximately halved the recurrence rate after breast-conserving surgery in a wide range of patients with very different absolute risks (figure 3) suggests that it may also approximately halve the recurrence rate in future patients given breast-conserving surgery. If so, then in future BCS patients, a reasonable way to predict the absolute recurrence benefit of radiotherapy would be to construct contemporary estimates of the absolute risk of first recurrence of any type for such patients and to assume that radiotherapy will approximately halve it.

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Writing committee

The writing committee for this paper was: S Darby, P McGale, C Correa, C Taylor, R Arriagada, M Clarke, D Cutter, C Davies, M Ewertz, J Godwin, R Gray, L Pierce, T Whelan, Y Wang, R Peto.

Contributors SD, PMcG, and CC designed and carried out the analyses with DC, RP and CT as internal advisors and TW, ME, LP and RA as external advisors. All writing committee members contributed to the report. The EBCTCG secretariat, including SD, PMcG, CC, CT, MC, DC, CD, JG, RG, YW and RP, identified trials, and received, collated and checked datasets.

Conflict of interest

The writing committee and secretariat declare that they have no conflict of interest.

Acknowledgements

The main acknowledgments are to the thousands of women who took part in the trials, to the staff who treated and cared for them and who conducted the trials and shared their data with the Secretariat, and to the Clinical Trial Service Unit (CTSU) which hosts this collaboration. Funding for the EBCTCG secretariat is from the general long-term financial support from the Cancer Research UK, the British Heart Foundation and the UK Medical Research Council to the CTSU, University of Oxford. DC was supported by the British Heart Foundation Centre for Research Excellence (RE/08/04).

Attendees at Steering Committee Meetings

K Albain, S Anderson, R Arriagada, W Barlow, J Bergh, J Bliss, *M Buyse, D Cameron, E Carrasco, *†M Clarke, C Correa, A Coates, *†R Collins, J Costantino, †D Cutter, J Cuzick, *†S Darby, N Davidson, *†C Davies, †K Davies, †A Delmestri, A Di Leo, M Dowsett, †P Elphinstone, †V Evans, *M Ewertz, R Gelber, †L Gettins, C Geyer, A Goldhirsch, †J Godwin, †R Gray, †C Gregory, D Hayes, C Hill, J Ingle, R Jakesz, †S James, M Kaufmann, †A Kerr, †E MacKinnon, †P McGale, †T McHugh, L Norton, Y Ohashi, S Paik, †HC Pan, E Perez, *†R Peto, *M Piccart (co-chair), L Pierce, G Pruneri, *K Pritchard (co-chair), V Raina, P Ravdin, J Robertson, E Rutgers, YF Shao, S Swain, †C Taylor, P Valagussa, G Viale, T Whelan, *E Winer, †Y Wang, *W Wood.

*Executive Group, †Secretariat

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

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

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

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

St Luke's Hospital, Dublin, Ireland—N Corcoran.
Sardinia Oncology Hospital A Businico, Cagliari, Sardinia—N Deshpande, L di Martino.
SASIB International Trialists, Cape Town, South Africa—P Douglas, A Hacking, H Høst, A Lindtner, G Notter.
Saskatchewan Cancer Foundation, Regina, Canada—A J S Bryant, G H Ewing, L A Firth, J L Krushen-Kosloski.
Scandinavian Adjuvant Chemotherapy Study Group, Oslo, Norway—R Nissen-Meyer.
South Sweden Breast Cancer Group, Lund, Sweden—H Anderson, F Killander, P Malmström, L Rydén.
South-East Sweden Breast Cancer Group, Linköping, Sweden—L-G Arnesson, J Carstensen, M Dufmats, H Fohlin, B Nordenskjöld, M Söderberg.
South-Eastern Cancer Study Group and Alabama Breast Cancer Project, Birmingham, AL, USA—J T Carpenter.
Southampton Oncology Centre, UK—N Murray, G T Royle, P D Simmonds.
Southwest Oncology Group, San Antonio, TX, USA—K Albain, W Barlow, J Crowley, D Hayes, J Gralow, S Green, G Hortobagyi, R Livingston, S Martino, C K Osborne, P M Ravdin.
Stockholm Breast Cancer Study Group, Sweden—J Adolfsson, J Bergh, T Bondesson, F Celebioglu, K Dahlberg, T Fornander, I Fredriksson, J Frisell, E Göransson, M Iiristo, U Johansson, E Lenner, L Löfgren, P Nikolaidis, L Perbeck, S Rotstein, K Sandelin, L Skoog, G Svane, E af Trampe, C Wadström.
Swiss Group for Clinical Cancer Research (SAKK), Bern, and OSAKO, St Gallen, Switzerland—M Castiglione, A Goldhirsch, R Maibach, H J Senn, B Thürlimann.
Tampere University Hospital, Finland—K Holli, K Rouhento.
Tel Aviv University, Israel—H Brenner, A Hercbergs.
The High-Dose Chemotherapy for Breast Cancer Study Group (PEGASE), France—A L Martin, H Roché.
Tokyo Cancer Institute Hospital, Japan—M Yoshimoto.
Toronto-Edmonton Breast Cancer Study Group, Canada—A H G Paterson, K I Pritchard.
Toronto Princess Margaret Hospital, Canada—A Fyles, J W Meakin, T Panzarella, K I Pritchard.
Tunis Institut Salah Azaiz, Tunisia—J Bahi.
UK Multicentre Cancer Chemotherapy Study Group, London, UK—M Reid, M Spittle.
UK/ANZ DCIS Trial—H Bishop, N J Bundred, J Cuzick, I O Ellis, I S Fentiman, J F Forbes, S Forsyth, W D George, S E Pinder, I Sestak.
UK/Asia Collaborative Breast Cancer Group, London, UK—G P Deutsch, R Gray, D L W Kwong, V R Pai, R Peto, F Senanayake.
University and Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy on behalf of GROCTA trialists—F Boccardo, A Rubagotti.
University Federico II, Naples, Italy—A R Bianco, C Carlomagno, M De Laurentiis, S De Placido.
University of Edinburgh, UK—L Williams.
University of Texas MD Anderson Cancer Center, Houston, TX, USA—K Broglio, A U Buzdar.
University of Wisconsin, USA—R R Love.
Uppsala-Örebro Breast Cancer Study Group, Sweden—J Ahlgren, H Garmo, L Holmberg, G Liljegren, H Lindman, F Wärnberg.
U.S. Oncology, Houston, USA—S E Jones, D M Loesch.
Vienna University Hospital 1st Department of Gynaecology and Department of Medicine I, Austria—M Janauer, M Seifert, P Sevelda, C C Zielinski.
West German Study Group (WSG), Germany—O Gluz, N Harbeck, C Liedtke, U Nitz.
West of Scotland Breast Trial Group, Glasgow, UK—A Litton.
West Sweden Breast Cancer Study Group, Gothenburg, Sweden—A Wallgren, P Karlsson.
Western Cancer Study Group, Torrance, CA, USA—R T Chlebowski.
Würzburg University, Germany—H Caffier.

Table 1. **Availability of data from randomised trials of radiotherapy following breast-conserving surgery for invasive cancer that began before the year 2000.**

	Number of trials available*	Years trials began	Women	Deaths	Woman-years at risk						
					Median/ woman	Total ('000s)	Distribution by years since diagnosis ('000s)				
							<5	5-	10-	15-	20+
Trial category[†]											
A. Lumpectomy, original 6 trials[6-11]	6	1976-86	4398	1982	11.8	52.9	20.3	16.0	10.1	4.8	1.7
B. Sector resection or quadrantectomy[12-15]	4	1981-91	2399	708	12.4	29.4	11.6	10.3	6.0	1.4	0.1
C. Lumpectomy in low-risk women[16-22]	7	1989-99	4004	453	6.6	26.9	17.9	7.9	1.1	0.0	0.0
Pathological nodal status											
Negative (pN0)			7287	1801	9.7	73.7	34.0	23.3	11.3	3.9	1.2
Positive (pN+)			1050	585	10.3	11.8	4.6	3.2	2.2	1.3	0.5
Unknown			2464	757	8.8	23.6	11.3	7.6	3.7	1.0	0.0
All women	17	1976-99	10,801	3143	9.5	109.1	49.8	34.1	17.2	6.3	1.7

* Only unconfounded trials are considered, that is, trials in which there was to be no difference between the treatment groups in the type or extent of surgery or in the use of systemic therapy. Two further eligible trials,[23,24] both category A with a total of 133 women, were identified but unavailable. Details of the 17 available trials are given in webappendix p4.

† Elsewhere, these trial categories are abbreviated to: A. Lump: original, B. >Lump, C. Lump: low-risk. In category A, 55% were pN0, 5% age 70+, 10% low-grade tumours, 54% T1 tumours (1-20 mm), 81% ER+ or unknown, 44% tamoxifen use. In category B, 81% pN0, 10% age 70+, 9% low-grade tumours, 89% T1 tumours, 86% ER+ or unknown, 6% tamoxifen use. In category C, 73% pN0, 40% age 70+, 33% low-grade tumours, 90% T1 tumours, 98% ER+ or unknown, 88% tamoxifen use.

Table 2. Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk (%) of any (locoregional or distant) first recurrence in 7287 pN0 women, subdivided by patient and trial characteristics. Information on numbers of events and woman-years is in webappendix p26. Results for 5-year risks are in webappendix p31.

		Number allocated BCS+RT/BCS	10-year risk of any locoregional or distant recurrence (%)				Test for trend/heterogeneity in absolute reduction	
			BCS+RT	BCS	Absolute reduction with RT	95% CI	2p unadjusted*	2p adjusted*
Age at entry (years)	< 40	189/174	36.1	60.7	24.6	(13.2, 36.0)	<0.00001	0.0002
	40 – 49	576/582	20.8	41.4	20.6	(15.1, 26.1)		
	50 – 59	1093/1028	15.0	29.7	14.7	(10.8, 18.6)		
	60 – 69	1138/1167	14.2	28.3	14.1	(10.4, 17.8)		
	70+	679/661	8.8	17.7	8.9	(4.0, 13.8)		
Tumour grade	Low	750/757	11.0	22.4	11.4	(6.3, 16.5)	<0.00001	<0.00001
	Intermediate	816/843	16.4	31.6	15.3	(10.4, 20.2)		
	High	448/431	28.6	53.3	24.7	(17.6, 31.8)		
	Unknown	1661/1581	14.7	28.2	13.5	(10.4, 16.6)		
Tumour size	T1 (1-20 mm)	2942/2920	12.4	27.5	15.1	(12.7, 17.5)	0.02	0.06
	T2 (21-50 mm)	513/487	30.7	50.0	19.3	(12.6, 26.0)		
	Other/unknown	220/205	24.9	32.6	7.6	(-1.8, 17.0)		
ER status & trial policy of tamoxifen use†	ER-poor	448/427	28.9	43.8	14.9	(8.0, 21.8)	<0.00001	0.003
	ER+Tam-	1686/1626	18.6	36.0	17.4	(14.3, 20.5)		
	ER+Tam+	1541/1559	8.7	22.0	13.3	(10.0, 16.6)		
Trial policy of using additional therapy†	No	1498/1471	15.8	31.6	15.8	(12.7, 18.9)	0.06	0.45
	Yes	2127/2085	16.1	31.8	15.6	(12.3, 18.9)		
	Some/Unknown	50/56	-	-	-	-		
Trial category‡	A. Lump: original	1223/1197	27.8	47.9	20.1	(16.0, 24.2)	A vs C: 2p<0.00001	A vs C: 2p= 0.16
	B. >Lump	986/970	6.3	19.9	13.6	(9.7, 17.5)		
	C. Lump: low risk	1466/1445	14.3	25.9	11.6	(7.9, 15.3)	A+C vs B: 2p= 0.90	A+C vs B: 2p=0.00003
Total		3675/3612	15.6	31.0	15.4	(13.2,17.6)		

* unadjusted: each factor alone. adjusted: each factor adjusted for all others using regression modelling. Categories including unknowns excluded from test for trend/heterogeneity.

† A trial policy of tamoxifen use gives it to both treatment groups if the disease is ER+ (or ER unknown, here counted with ER+); additional therapy could be chemotherapy (usually cyclophosphamide, methotrexate, 5-fluorouracil [CMF]) for both treatment groups, or additional radiotherapy (nodal RT or a boost or both) for those allocated BCS+RT.

‡ Definitions of trial categories A, B and C are in Table 1

Figure 1. Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence and on 15-year risks of breast cancer mortality and all-cause mortality among 10,801 women (67% pathologically node-negative) in 17 trials.
Vertical lines indicate 1 SE above or below the 5, 10 and 15 year percentages. Further details are in webappendix p5.

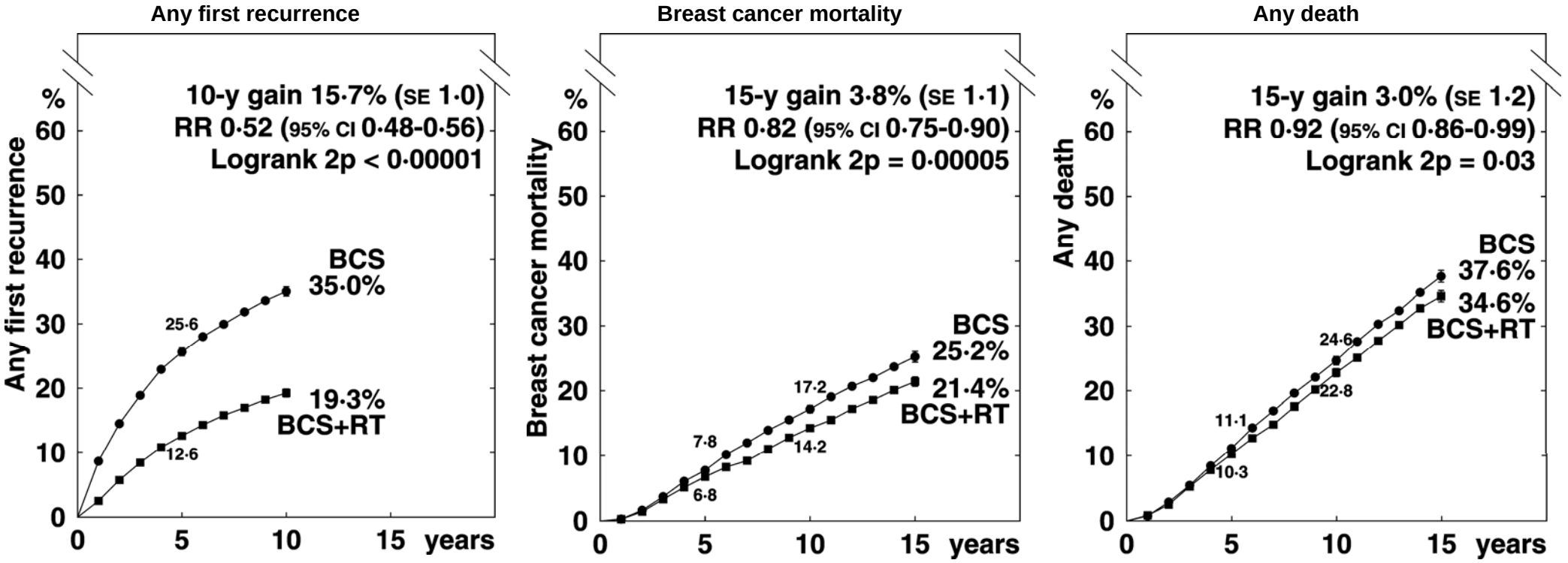


Figure 2. Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence and on 15-year risk of breast cancer mortality in women with pathologically verified nodal status. Vertical lines indicate 1 SE above or below the 5, 10 and 15 year percentages. Further details are in webappendix p6-7.

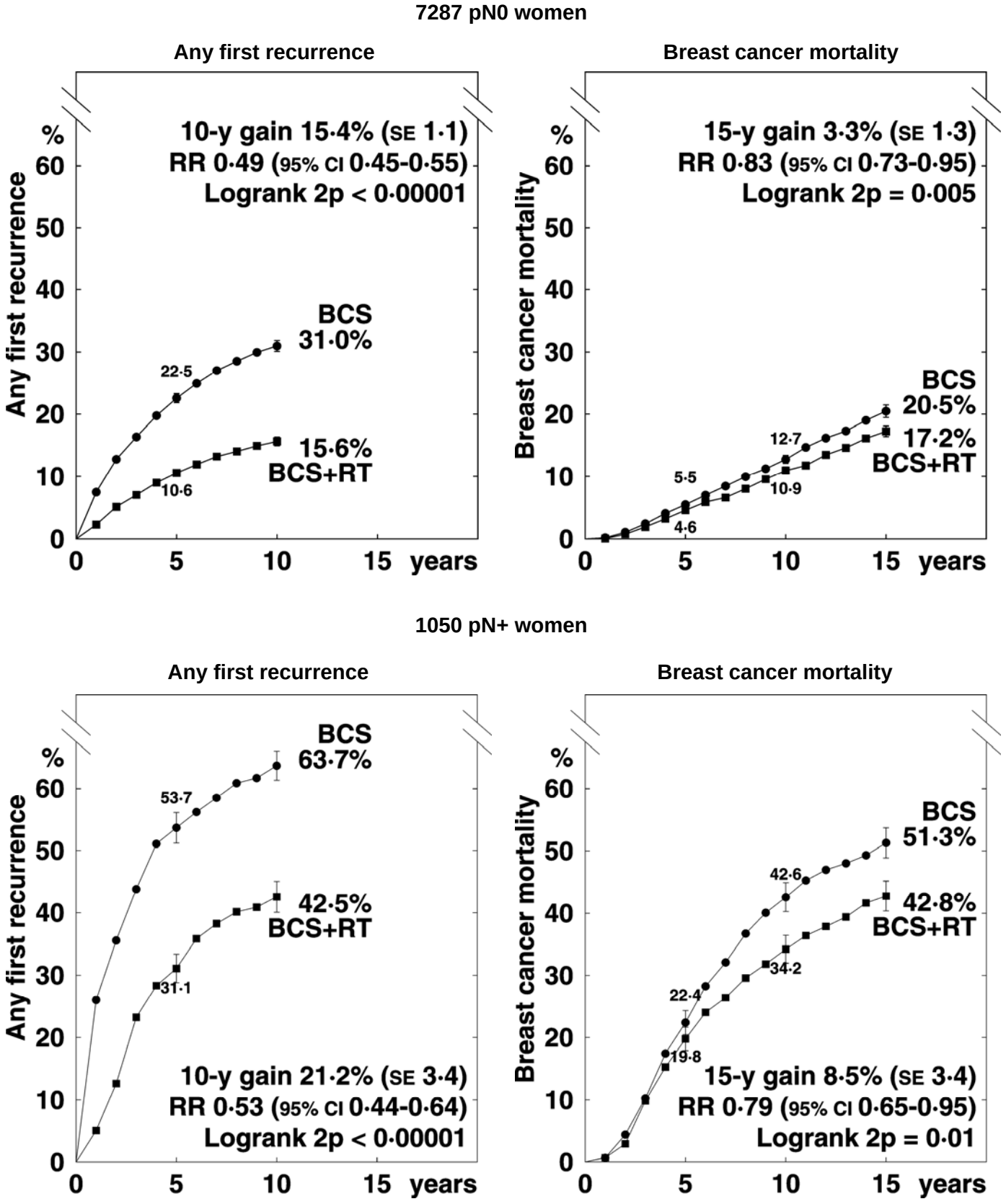
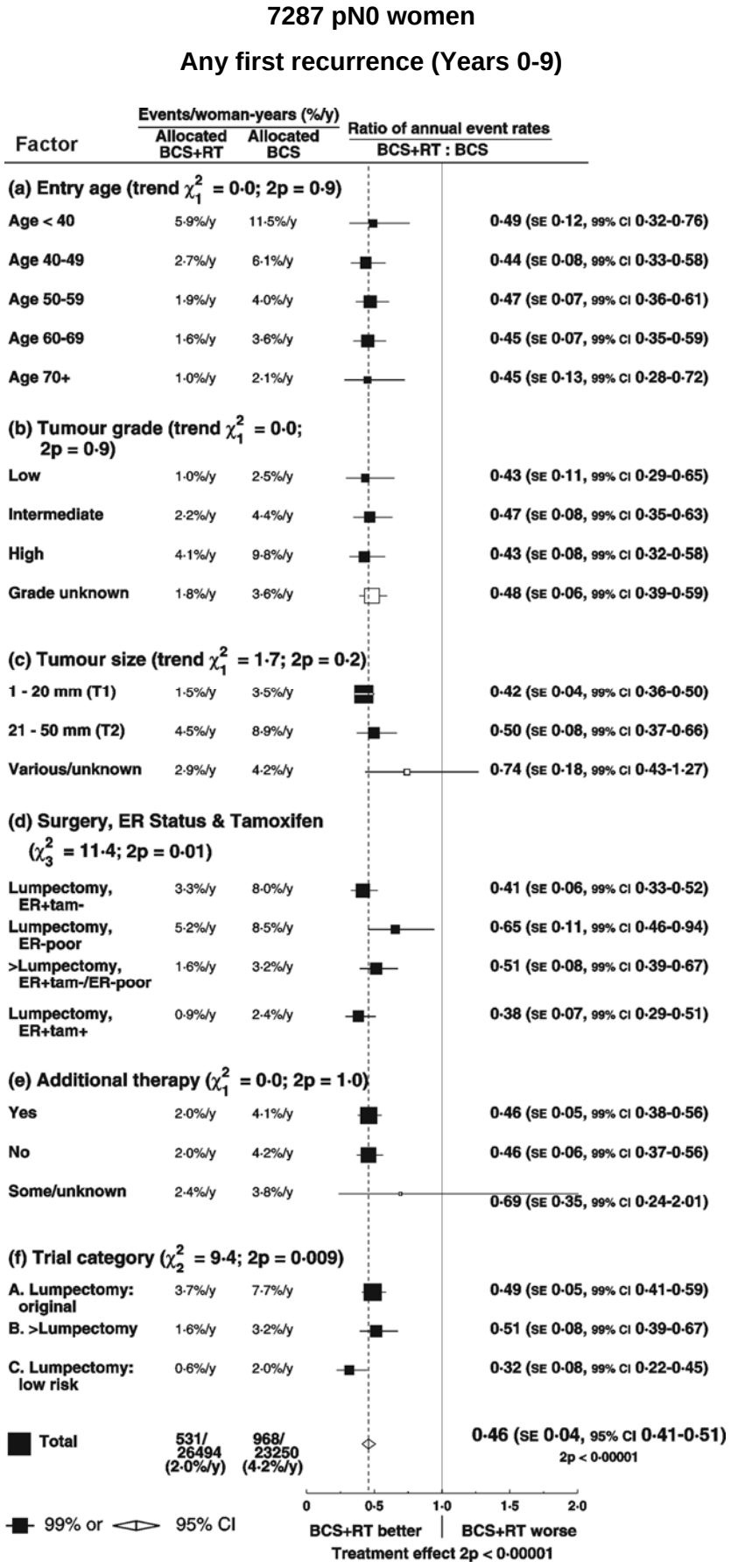


Figure 3. Relevance of various factors, considered separately, to the effect of radiotherapy (RT) after breast conserving surgery (BCS): event rates for any (locoregional or distant) first recurrence (% per year) and recurrence rate ratios (BCS+RT:BCS) during years 0-9 in pN0 disease. Definitions of trial categories A, B and C are in Table 1. Further details are in webappendix p14.



SE: standard error, CI: confidence interval

Figure 4. 10-year recurrence risks with radiotherapy (RT, black bars) and without radiotherapy (black+white bars) after breast-conserving surgery in T1 pN0 disease: dependence on age, grade, ER status, extent of surgery (lumpectomy, or more extensive surgery) and tamoxifen use suggested by regression modelling of the data on 7287 pN0 women in BCS±RT trials. Results for T2 tumours and further details are in webappendix p27-30. 5-year recurrence risks are in webappendix p31-34.

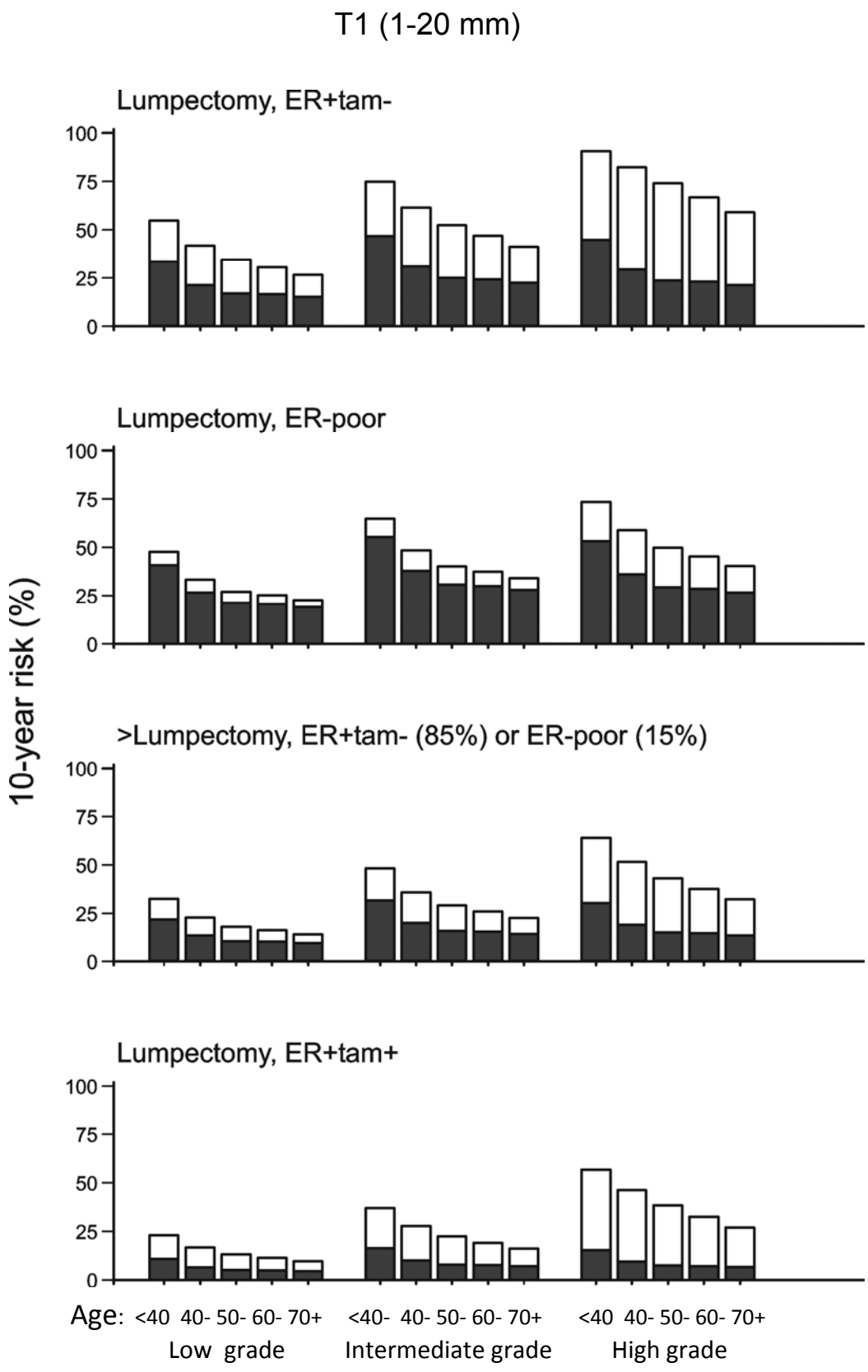


Figure 5. Absolute reduction in 15-year breast cancer mortality with radiotherapy after breast-conserving surgery versus absolute reduction in 10-year risk of any (locoregional or distant) recurrence. pN0 patients are subdivided by the predicted absolute reduction in 10-year risk of any recurrence suggested by regression modelling (pN0-large: ≥20%, pN0-int:10-19%, pN0-lower: <10%; further details are in webappendix p35-39). Vertical lines are 95% confidence intervals. Sizes of black boxes are proportional to amount of information. Dashed line: 1 breast death avoided for every 4 recurrences avoided.