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*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet 2023; 402: 1991–2003

Published Online November 3, 2023 https://doi.org/10.1016/S0140-6736(23)01082-6

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*Members are listed at the end of the Article (see EBCTCG writing committee, EBCTCG secretariat, and EBCTCG steering committee); affiliations are listed in the appendix (pp 46–50)

Correspondence to: EBCTCG secretariat, Clinical Trial Service Unit, Nuffield Department of Population Health, Oxford OX3 7LF, UK
bc.overview@ndph.ox.ac.uk

See Online for appendix

Summary

Background Radiotherapy has become much better targeted since the 1980s, improving both safety and efficacy. In breast cancer, radiotherapy to regional lymph nodes aims to reduce risks of recurrence and death. Its effects have been studied in randomised trials, some before the 1980s and some after. We aimed to assess the effects of regional node radiotherapy in these two eras.

Methods In this meta-analysis of individual patient data, we sought data from all randomised trials of regional lymph node radiotherapy versus no regional lymph node radiotherapy in women with early breast cancer (including one study that irradiated lymph nodes only if the cancer was right-sided). Trials were identified through the EBCTCG's regular systematic searches of databases including MEDLINE, Embase, the Cochrane Library, and meeting abstracts. Trials were eligible if they began before Jan 1, 2009. The only systematic difference between treatment groups was in regional node radiotherapy (to the internal mammary chain, supraclavicular fossa, or axilla, or any combinations of these). Primary outcomes were recurrence at any site, breast cancer mortality, non-breast-cancer mortality, and all-cause mortality. Data were supplied by trialists and standardised into a format suitable for analysis. A summary of the formatted data was returned to trialists for verification. Log-rank analyses yielded first-event rate ratios (RRs) and confidence intervals.

Findings We found 17 eligible trials, 16 of which had available data (for 14 324 participants), and one of which (henceforth excluded), had unavailable data (for 165 participants). In the eight newer trials (12 167 patients), which started during 1989–2008, regional node radiotherapy significantly reduced recurrence (rate ratio 0·88, 95% CI 0·81–0·95; p=0·0008). The main effect was on distant recurrence as few regional node recurrences were reported. Radiotherapy significantly reduced breast cancer mortality (RR 0·87, 95% CI 0·80–0·94; p=0·0010), with no significant effect on non-breast-cancer mortality (0·97, 0·84–1·11; p=0·63), leading to significantly reduced all-cause mortality (0·90, 0·84–0·96; p=0·0022). In an illustrative calculation, estimated absolute reductions in 15-year breast cancer mortality were 1·6% for women with no positive axillary nodes, 2·7% for those with one to three positive axillary nodes, and 4·5% for those with four or more positive axillary nodes. In the eight older trials (2157 patients), which started during 1961–78, regional node radiotherapy had little effect on breast cancer mortality (RR 1·04, 95% CI 0·91–1·20; p=0·55), but significantly increased non-breast-cancer mortality (1·42, 1·18–1·71; p=0·00023), with risk mainly after year 20, and all-cause mortality (1·17, 1·04–1·31; p=0·0067).

Interpretation Regional node radiotherapy significantly reduced breast cancer mortality and all-cause mortality in trials done after the 1980s, but not in older trials. These contrasting findings could reflect radiotherapy improvements since the 1980s.

Funding Cancer Research UK, Medical Research Council.

Introduction

During the past five decades, there have been major changes in radiotherapy. Doses to target regions have become more uniform and unwanted incidental irradiation of nearby organs has been reduced, limiting side-effects.[1] These changes have improved outcomes in many cancer types.

Radiotherapy is often given after surgery for early breast cancer.[2] Although surgery can remove macroscopic disease, microscopic tumour foci can remain in breast tissue, the chest wall, or the regional lymph nodes that could, if untreated, lead to recurrence and death. Trials have shown that, following breast-conserving surgery or following mastectomy for node-positive disease, postoperative radiotherapy can reduce breast cancer mortality.[3,4] Some of those trials irradiated just the breast or chest wall, but others also irradiated some of the regional lymph nodes. It is not known how much of the effect of radiotherapy was due to this nodal irradiation. Several trials, however, have been conducted

Research in context

Evidence before this study

Previous Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analyses have shown that radiotherapy after breast-conserving surgery, or after mastectomy in node-positive disease, reduces breast cancer recurrence and mortality. Some of those trials irradiated just the breast or chest wall, but others also irradiated some of the regional lymph nodes, and it is not known how much of the protective effect was due to irradiation of the nodes. The separate effects of irradiating regional lymph nodes after surgery have been assessed in individual trials. The EBCTCG's ongoing searches of bibliographic databases including MEDLINE, Embase, the Cochrane Library and relevant meeting abstracts identified 17 trials which started before 2009 and compared radiotherapy to regional lymph nodes versus no radiotherapy to regional lymph nodes, with randomisation, or allocation by tumour laterality, but did not identify any individual patient data meta-analyses.

Added value of this study

This collaborative meta-analysis collated, checked, and analysed individual patient data on 14 324 women in 16 trials that started during 1961–2008 and assessed the effects of irradiating the internal mammary chain, supraclavicular fossa, and axillary lymph nodes. The trials were done during the past six decades. During this time, there were major changes in breast cancer radiotherapy, and these are reflected by our findings. Eight trials, which started during 1961–78 assessed older radiotherapy techniques and did not usually involve radiotherapy to the chest wall in node-positive disease. Radiotherapy in these trials did not reduce breast cancer mortality. Eight trials, which started during 1989–2008 assessed more tailored radiotherapy. Most of these newer trials assessed the addition of regional node irradiation to chest wall or breast radiotherapy in node-positive disease. In analyses of data on 12 167 women, regional node radiotherapy significantly reduced breast cancer recurrence, breast cancer mortality, and all-cause mortality. With 15 years of follow-up, no increase was seen in non-breast-cancer mortality. This meta-analysis provides more precise estimates of the effects of regional node radiotherapy than the individual trials. Absolute improvements in breast cancer recurrence and mortality from regional node radiotherapy in the 1990s–2000s were greatest for women with the highest breast cancer recurrence and mortality risks. The absolute reductions in 15-year breast cancer mortality were 1–2% for women with no positive axillary lymph nodes, 2–3% for those with one to three positive nodes, and 4–5% for those with four or more positive nodes.

Implications of all the available evidence

Our results show the benefits of irradiating the regional lymph nodes in women who also receive effective local and systemic therapies. For women being considered for radiotherapy today, the proportional benefits of regional node radiotherapy could be greater than those in the newer trials due to further improvements in radiotherapy. The absolute breast cancer mortality benefits could be somewhat lower than in the trials due to reductions in population breast cancer death rates. Our findings have implications for policy and for patients. Implementation of regional node radiotherapy could improve breast cancer survival at little or no additional cost. Clinicians and patients can use this information to estimate survival gains from regional node radiotherapy in shared decision making.

in which the only difference between the two treatment groups involved irradiation of regional lymph nodes in one or more of three sites: the internal mammary chain, supraclavicular fossa, and axilla.

These trials recruited patients over many decades (1961–2013) and, during this time, regional node radiotherapy changed substantially. In the 1960s and 1970s, radiotherapy typically involved photon beams that often irradiated the heart and lungs.[5,6] In the 1980s and 1990s, these techniques were replaced by more tailored methods that involved much lower exposure of the heart and lungs, and more uniform coverage of target regions.[1] We therefore categorised regional node radiotherapy trials as older (1961–78) or newer (1989–2008).

The main mortality risks from the side-effects of regional node radiotherapy, heart disease and lung cancer, vary according to organ dose.[5] The risks from particular regimens can be estimated by combining regimen-specific heart and lung doses with dose–response relationships, perhaps using the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of radiotherapy risks.[5]

The main aim of this meta-analysis was to assess the effects of regional node radiotherapy on breast cancer recurrence and mortality, reporting separate meta-analyses of the newer and older trials. Statistically stable results among all patients have been accompanied by exploratory results subdivided by the nodal regions irradiated and by the nature and location of the tumour.

Methods

Search strategy and selection criteria

We performed a meta-analysis of individual patient data from randomised trials that started before 2009 and assessed the effects of radiotherapy versus no radiotherapy to particular lymph node regions that included some or all of the internal mammary chain, supraclavicular fossa (node level medial 3 and 4)[7] and axilla (node levels 1–3; appendix p 3).

Eligible studies included randomisation or, in the Danish Breast Cancer Group (DBCG) study, allocation by laterality (left-sided *vs* right-sided tumours), in which the only difference between treatment groups was the use, or extent, of nodal irradiation. We term all these studies as

trials. Surgery, any radiotherapy to the breast or chest wall, and systemic therapies had to be the same in both trial groups to obtain unconfounded evidence of the effects of regional node radiotherapy. Identification of published and unpublished trials and obtaining the most up-to-date outcome data from these trials involved the EBCTCG's regular systematic searches of databases including MEDLINE, Embase, the Cochrane Library and meeting abstracts, and conference proceedings, plus extensive input from the EBCTCG steering committee and collaborative group (appendix pp 4–6). Data handling was as reported previously.[8–10] The EBCTCG methods conform to PRISMA (Individual Patient Data).[11]

Unbiasedness of EBCTCG meta-analyses depends not on whether there would have been publication bias if the dataset had been restricted to published data (for it was not), but whether, despite all efforts, any material ascertainment bias remains. Formal statistical tests for publication bias or ascertainment bias are weak, so some bias might have escaped them, so although the results of formal tests of ascertainment bias have been reported (finding no significant evidence for ascertainment bias in the EBCTCG dataset), judgements about the potential for such bias should chiefly be based on understanding EBCTCG procedures for identifying randomised trials and obtaining and updating their results (appendix p 4).

For every woman, information was sought about patient and tumour characteristics, allocated treatment, time to and site of recurrence, time to any contralateral or second cancer before recurrence, and date last known to be alive or date and cause of death.

Before any analyses, trials were categorised according to radiotherapy technique: older trials with direct anterior photon beams alone, all of which started during 1961–78, and newer trials with more tailored techniques, all of which started during 1989–2008 (appendix pp 15, 16–18, 20). The follow-up period spanned between 1961 and 2020. A full list of the search terms used is provided in the appendix (p 5).

Data analysis

Although recurrence in the regional nodes could be a relevant endpoint, few nodal recurrences were reported, which could have been partly because routine clinical follow-up can miss nodal recurrences, particularly in the internal mammary chain nodes (appendix p 24). The main recurrence endpoint was therefore time to first breast cancer recurrence at any site (ie, locoregional recurrence, newly incident ipsilateral disease, or distant metastasis) as a first event. Subsidiary analyses were provided of recurrence at any locoregional site as a first event (occurring at least 7 days before any other event) and distant recurrence as an event at any time.

Deaths from an unknown cause before recurrence were assumed to be from causes other than breast cancer as most occurred many years after trial entry, by which time non-breast-cancer mortality predominated. Log-rank analyses (appendix p 10) were stratified by trial, single year of follow-up, age at entry (<40 years, 40–49 years, 50–59 years, 60–69 years, or ≥70 years), and nodal status, classified as pN0 (pathologically node-negative), pN1–3 (one to three involved axillary nodes), or pN4+ (four or more involved axillary nodes). If pathological nodal status was unavailable, clinical nodal status was used, classified as cN– (clinically node-negative), or other (clinically node-positive, or unknown).

For each outcome, log-rank analyses were of the first occurrence of that event, and yield estimates, with 95% CIs, of the overall event rate ratio (RR). The overall RR reflects a weighted average of the RRs in specific circumstances. Calculation of the overall RR does not, however, imply that the true event RR is identical in all these circumstances, and exploratory analyses cite separate RRs for particular follow-up periods, strata, and trials.

In the DBCG study (with 3089 women), internal mammary chain radiotherapy was allocated on the basis of laterality rather than from randomisation,[12] which could be considered equivalent to mendelian randomisation. The Danish national protocol during the study period was to irradiate the internal mammary chain of women with right breast cancer, but not of women with left breast cancer. All eligible Danish women were analysed, including those who did not get protocol treatment. Women with right breast cancer were analysed as allocated to internal mammary chain irradiation. Women with left breast cancer were analysed as allocated to no internal mammary chain irradiation. For heart disease mortality, analyses compared higher versus lower heart dose trial groups. For the DBCG study, analyses were of left breast cancer with no nodal radiotherapy (higher dose) versus right breast cancer with nodal radiotherapy (lower dose), whereas for all other trials, analyses were of nodal versus no nodal radiotherapy. Analyses of contralateral breast cancer incidence, and sensitivity analyses excluded the DBCG study (appendix p 10).

To give more reliable estimates of the absolute effects of regional node radiotherapy on 15-year cumulative risk according to nodal status in the newer trials, the overall RRs for any recurrence and breast cancer death were applied to the annual rates of recurrence and breast cancer death in the trials, averaged over treatment groups. Heterogeneity between studies was assessed using a chi-square test. The chi-square test was also used to assess heterogeneity between subtotals (when studies were grouped as in table 1) and to assess the residual heterogeneity between studies after accounting for differences between groups. Bespoke scripts for log-rank analyses were written in Stata (version 17).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit.

	Number of trials	Number of women	Number of deaths	Woman-years since diagnosis					Women given systemic therapy, %		
				Median follow-up (IQR)	Total ('000s)	Distribution by years ('000s)			Chemo-therapy*	ER+ and endocrine therapy	Any
						<10	10 to <20	≥20			
Older trials (1961–78)†											
IMC, SCF, and axilla‡	7	1940	1424	29·3 (16·3–41·8)	23·9	13·5	6·5	3·9	22·6%	0·0%	22·6%
IMC	..	..	..	..	..	..	..	..	..	..	..
SCF and axilla§	1	217	117	9·9 (9·5–10·0)	1·5	1·5	0·0	0·0	0·0%	0·0%	0·0%
Subtotal	8	2157	1541	25·6 (12·4–41·7)	25·4	15·0	6·5	3·9	20·3%	0·0%	20·3%
Newer trials (1989 onwards)†											
IMC, SCF, axilla‡	2	5836	1446	13·5 (10·1–16·2)	66·7	50·6	16·1	0·0	66·0%	60·4%	89·2%
IMC¶	4	5420	2041	14·3 (11·2–15·8)	58·6	43·6	13·8	1·3	58·8%	60·9%	91·9%
SCF and axilla§	2	911	107	5·4 (3·2–11·4)	6·8	5·2	1·5	0·1	55·9%	65·1%	92·5%
Subtotal	8	12 167	3594	13·7 (9·9–16·0)	132·1	99·3	31·4	1·4	62·0%	61·0%	90·7%
All trials											
IMC, SCF, and axilla‡	9	7776	2870	14·1 (10·4–17·4)	90·6	64·1	22·6	4·0	55·2%	45·3%	72·6%
IMC	4	5420	2041	14·3 (11·2–15·8)	58·6	43·6	13·8	1·3	58·8%	60·9%	91·9%
SCF and axilla§	3	1128	224	6·3 (3·6–11·2)	8·2	6·6	1·5	0·1	45·1%	52·6%	74·7%
All	16	14 324	5135	14·0 (10·0–16·4)	157·5	114·3	37·9	5·4	55·7%	51·8%	80·1%

Treatment to the breast and chest wall was the same in both groups and might have included radiotherapy. IMC=internal mammary chain. SCF=supraclavicular fossa (level medial 3/4). Axilla=nodes in levels 1–3. ER=oestrogen receptor. *In women who received chemotherapy, the type given was anthracycline (no taxane) in 2079 (26·0%) of 7986 women, taxane-containing in 1254 (15·7%) women, and unknown or other in 4653 (58·3%) women. In the newer trials, chemotherapy was received by 7548 (62·0%) of 12 167 women and endocrine therapy by 7421 (61·0%) women. †Data were available for 16 trials, start dates from 1961 to 2008, and unavailable for one trial including 165 women, starting in 1985 (appendix pp 17–20). ‡IMC, SCF, and axilla: two trials were IMC and SCF radiotherapy versus no radiotherapy to these nodal regions (4060 women), and seven were IMC, SCF, and axilla radiotherapy versus no radiotherapy to these nodal regions (3716 women). §SCF and axilla: one trial was axilla radiotherapy versus no radiotherapy to this nodal region (435 women), one trial was SCF radiotherapy versus no radiotherapy to this nodal region (476 women), and one trial was SCF and axilla radiotherapy versus no radiotherapy to these nodal regions (217 women). ¶IMC: all four trials were IMC radiotherapy versus no radiotherapy to this nodal region (5420 women) including a study in which nodal radiotherapy was allocated by laterality. Patients with right breast cancers received IMC radiotherapy, and patients with left breast cancers did not.

Table 1: **Availability of data from trials beginning before 2009 and comparing radiotherapy versus no radiotherapy to the regional nodes**

Results

Information was available on 98·9% (14 324 of 14 489) of the women in all relevant trials (16 trials; appendix p 18) with 14 324 participants available and one trial, henceforth ignored, with 165 participants unavailable (table 1; appendix pp 17–23). There were differences between available trials in the outcomes recorded, and for one of them,[13] the only outcome recorded was death from any cause. Median follow-up was 14·0 woman-years (IQR 10·0–16·4), with 3838 (29·5%) of 12 990 women with a (first) breast cancer recurrence, 3230 (24·9%) of 12 990 women who died with recurrence, and 5135 (35·8%) of 14 324 women who died overall (appendix pp 21, 22).

The most frequent comparison was of internal mammary chain radiotherapy versus no internal mammary chain radiotherapy, with 5420 women randomised in four trials (including 3089 women allocated by laterality). Other comparisons were of internal mammary chain and supraclavicular fossa radiotherapy versus no radiotherapy to these nodal regions (n=4060) and of internal mammary chain, supraclavicular fossa, and axilla radiotherapy versus no radiotherapy to these nodal regions (n=3716). The three trials without internal mammary chain irradiation involved supraclavicular fossa or axilla radiotherapy or both versus no radiotherapy to these nodal regions (n=1128; appendix p 18).

For details of each trial, see the appendix (pp 16–22). In the eight older trials, which started during 1961–78, radiotherapy used only direct anterior photon beams, with field-based radiotherapy planning. Most older trials did not include chest wall radiotherapy for node-positive disease, so the comparison was usually radiotherapy to regional nodes versus no radiotherapy.

In the eight newer trials, which started during 1989–2008, radiotherapy was more tailored. In seven of these trials, radiotherapy quality assurance was conducted. In the eighth trial[13], mixed energy fields were used to optimise doses. In contrast to the older trials, all newer trials included breast or chest wall radiotherapy for most or all of the women in both treatment groups, so they compared more versus less radiotherapy. There was a 10-year gap (1978–89) between the start dates of the last of the older and the first of the newer trials.

Axillary dissection was recommended for all patients in 12 trials. Two trials included patients after sentinel node biopsy or axillary dissection and there was no axillary

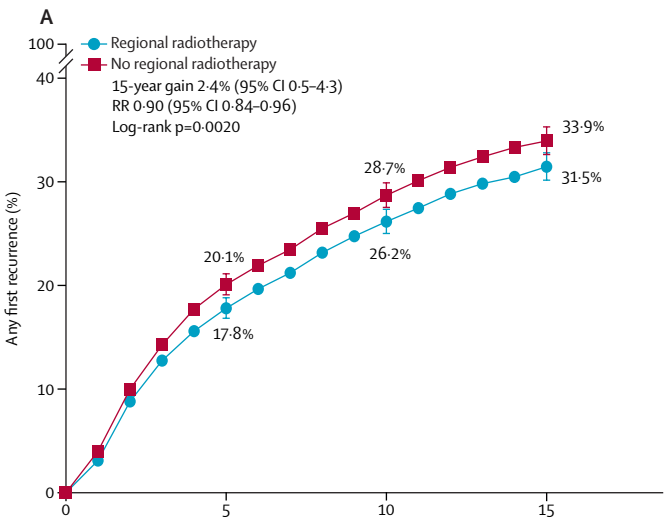
surgery in two trials. Pathological node status was available for only 51·1% (1103 of 2157) of the women in the older trials, but for 96·1% (11 693 of 12 167) women in the newer trials. Breast surgery was breast-conserving for 1·6% (34 of 2157) of women in the older trials and for 57·7% (7017 of 12 167) of women in the newer trials. In the older trials, few women (438 [20·3%] of 2157) had chemotherapy and none were recorded as having endocrine therapy, but in the newer trials, 62·0% (7548 of 12 167) had chemotherapy and 61·0% (7421 of 12 167) had endocrine therapy for oestrogen receptor-positive cancer.

Figure 1 combines results from the 15 older and newer trials with information on breast cancer outcomes, regardless of any differences in radiotherapy technique. Averaging the results from these trials, regional node radiotherapy somewhat reduced the overall risk of breast cancer recurrence (RR 0·90, 95% CI 0·84–0·96; p=0·0020) and of breast cancer mortality (0·91, 0·85–0·98; p=0·012).

Analyses of any recurrence, locoregional recurrence, distant recurrence, breast cancer mortality, non-breast-cancer mortality, heart disease mortality, second cancer incidence, contralateral breast cancer, and all deaths by individual trial are shown in the appendix (pp 25–33). Comparisons of older and newer trials are shown in the appendix (p 34). An analysis of lymphoedema in the newer trials is shown in the appendix (p 36). For other toxicity endpoints, data from trial publications are summarised in the appendix (p 23). Subsequent analyses consider the effects of regional node radiotherapy in the newer and in the older trials separately. Tests of publication bias took account of trial era, and all p values were greater than 0·1.

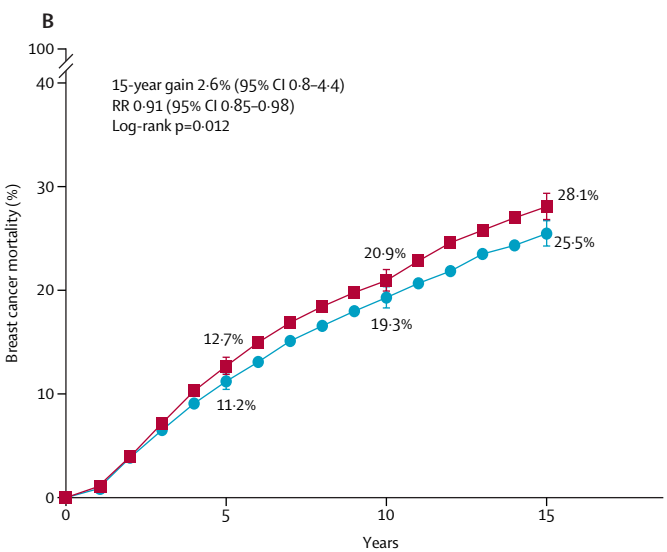
In the eight newer trials (total 12 167 women), median follow-up was 13·7 (IQR 9·9–16·0) woman-years with 3594 deaths from any cause (table 1). In the seven trials (total 10 833 women) with breast cancer outcome data, there were 2824 recurrences and 2260 deaths with recurrence (appendix p 21). The eight newer trials assessed radiotherapy to various sites, generally including the internal mammary chain (sites randomised: internal mammary chain only in four trials, 5420 women [including 3089 allocated by laterality]; internal mammary chain and supraclavicular fossa in one trial, 4004 women; internal mammary chain, supraclavicular fossa, and axilla in one trial, 1832 women; supraclavicular fossa in one trial, 476 women; axilla in one trial, 435 women; appendix p 33).

In the seven newer trials with information on breast cancer outcomes, regional node radiotherapy reduced overall breast cancer recurrence (RR 0·88, 95% CI 0·81–0·95; p=0·00083; figure 2). Few regional node recurrences were reported (appendix p 24), so the main effect was on distant recurrence (0·86, 0·80–0·93; p=0·00026; appendix p 35). Radiotherapy significantly reduced breast cancer mortality (0·87, 0·80–0·94; p=0·0010; figure 2) with no significant effect on non-breast-cancer mortality (0·97, 0·84–1·11; p=0·63; figure 2) or on heart disease mortality, contralateral breast cancer incidence, or other second cancer incidence (appendix pp 30–32). Considering all eight newer trials, regional node radiotherapy



Any first recurrence rates (% per year [events per woman-years]) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Regional radiotherapy	4·14% (1170/28 232)	2·18% (450/20 662)	1·57% (192/12 231)	1·20% (68/5664)
No regional radiotherapy	4·48% (1237/27 628)	2·32% (464/20 007)	1·67% (195/11 711)	1·00% (62/6182)
RR (95% CI), from	0·87 (0·80–0·95)	0·95 (0·83–1·08)	0·96 (0·78–1·18)	0·96 (0·66–1·40)
log-rank (O–E)/V	−74·2/532·5	−11·8/214·9	−4·0/90·2	−1·0/26·9

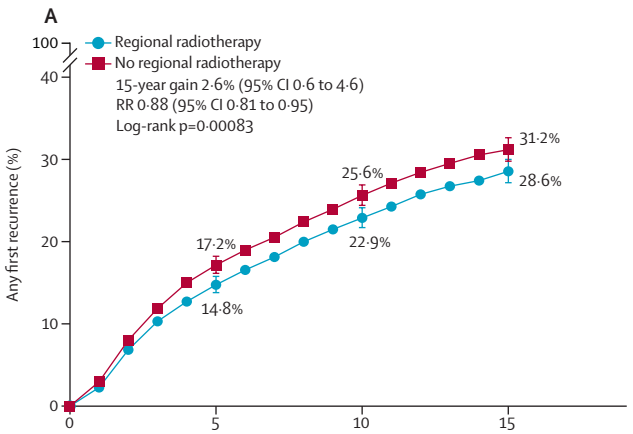


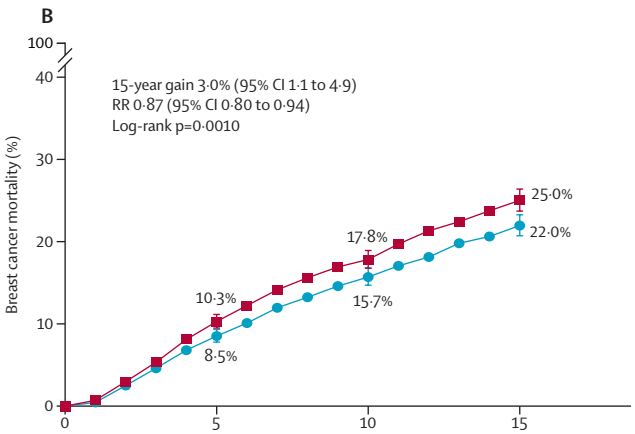
Death rates (% per year: total rate minus rate in women without recurrence [95% CI]) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Regional radiotherapy	2·44 (2·23–2·65)	1·95 (1·70–2·20)	1·61 (1·25–1·97)	1·21 (0·46–1·97)
No regional radiotherapy	2·61 (2·39–2·82)	2·01 (1·75–2·27)	1·97 (1·60–2·34)	1·00 (0·37–1·63)
RR (95% CI), from	0·88 (0·79–0·98)	0·95 (0·84–1·09)	0·83 (0·69–0·99)	1·28 (0·95–1·72)
log-rank (O–E)/V	−44·4/337·2	−10·2/216·7	−23·8/125·6	10·8/43·7

Figure 1: **Effect of regional node radiotherapy on (A) any recurrence and (B) breast cancer mortality in 12 990 women in 15 trials**

2157 women in eight older trials and 10 833 women in seven newer trials. One newer trial of 1334 women that reported only all-cause mortality was excluded. RR=rate ratio.



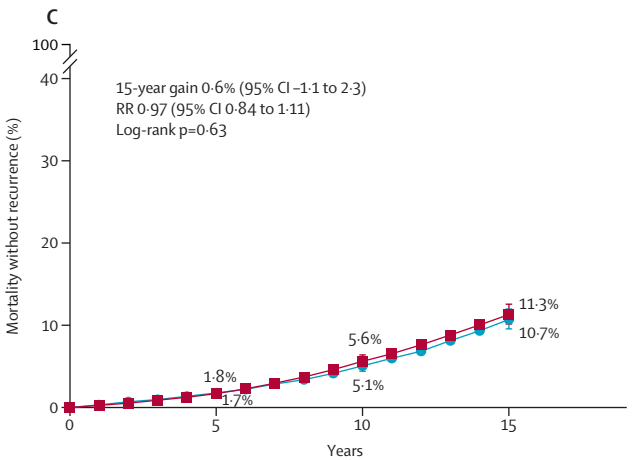


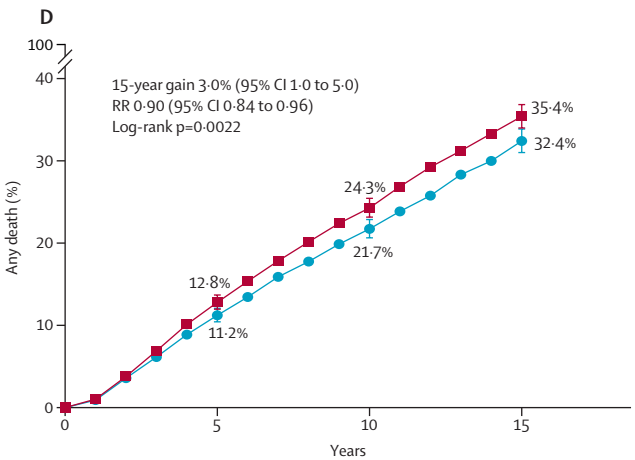
Any first recurrence rates (% per year [events per woman-years]) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Regional radiotherapy	3·23% (768/23 804)	2·02% (362/17 900)	1·57% (163/10 384)	1·11% (33/2964)
No regional radiotherapy	3·80% (909/23 942)	2·16% (380/17 618)	1·65% (168/10 167)	1·40% (41/2920)
RR (95% CI), from	0·84 (0·76–0·93)	0·93 (0·81–1·08)	0·96 (0·77–1·20)	0·74 (0·46–1·19)
log-rank (O–E)/V	−66·0/390·8	−12·0/178·9	−3·1/79·8	−5·2/17·3

Death rates (% per year: total rate minus rate in women without recurrence, 95% CI) and log-rank analyses

Years 0–4	Years 5–9	Years 10–14	Years ≥15
1·76% (1·56–1·95)	1·66% (1·42–1·91)	1·55% (1·19–1·92)	1·11% (0·30–1·92)
2·14% (1·94–2·35)	1·80% (1·54–2·06)	1·87% (1·49–2·25)	0·98% (0·21–1·75)
0·82 (0·72–0·93)	0·92 (0·79–1·07)	0·83 (0·68–1·00)	1·22 (0·81–1·83)
−46·5/233·4	−13·8/170·3	−20·1/105·7	4·6/23·1





Mortality without recurrence rates (% per year [deaths per woman-years]) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Regional radiotherapy	0·36% (85/23 804)	0·68% (121/17 900)	1·20% (125/10 384)	2·33% (69/2964)
No regional radiotherapy	0·33% (80/23 942)	0·78% (138/17 618)	1·19% (121/10 167)	2·02% (59/2920)
RR (95% CI), from	1·06 (0·78–1·44)	0·83 (0·65–1·06)	0·97 (0·76–1·26)	1·16 (0·80–1·69)
log-rank (O–E)/V	2·4/40·6	−11·6/63·4	−1·5/59·6	4·1/27·3

Any death rates (% per year [deaths per woman-years]) and log-rank analyses

Years 0–4	Years 5–9	Years 10–14	Years ≥15
2·37% (660/27 902)	2·55% (554/21 743)	2·96% (382/12 916)	3·46% (128/3700)
2·70% (760/28 173)	2·83% (607/21 467)	3·14% (395/12 566)	2·99% (108/3606)
0·87 (0·78–0·97)	0·89 (0·79–1·00)	0·90 (0·78–1·04)	1·20 (0·91–1·58)
−47·0/334·5	−32·7/277·4	−18·6/183·9	9·3/50·8

***Figure 2*: Effect of regional node radiotherapy in the eight newer trials on (A) any recurrence, (B) breast cancer mortality, (C) non-breast-cancer mortality, and (D) any death**
One newer trial of 1334 women that reported only all-cause mortality is included only in graph D. RR=rate ratio.

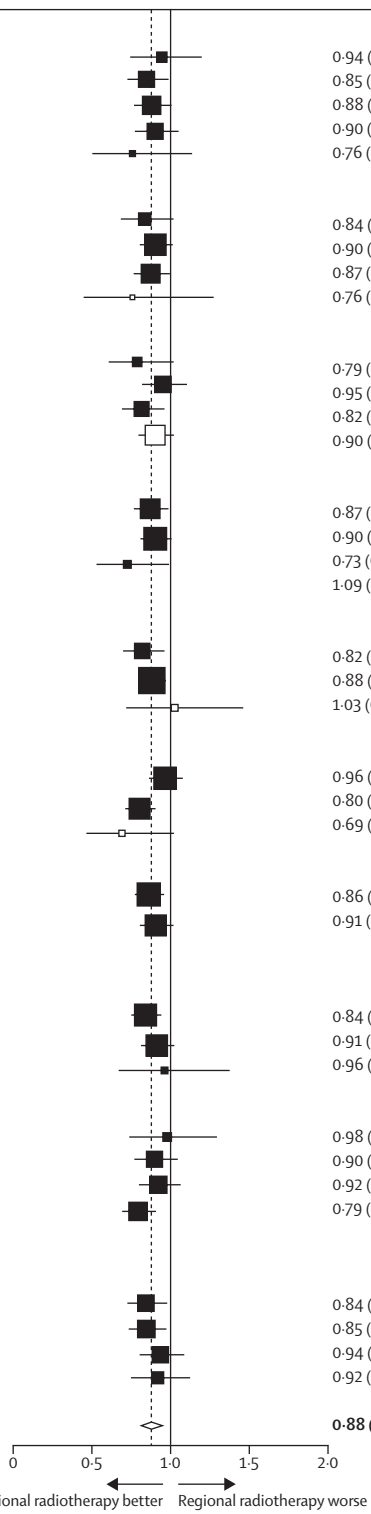
significantly reduced overall mortality (0·90, 0·84–0·96; p=0·0022; figure 2). The absolute 15-year gains were 2·6% (95% CI 0·6–4·6) for any recurrence, 3·0% (1·1–4·9) for breast cancer mortality, and 3·0% (1·0–5·0) for overall mortality.

Repeating these analyses excluding the study that allocated radiotherapy according to laterality did not materially change the results (any recurrence RR 0·86, 95% CI 0·78–0·95; p=0·0025; breast cancer mortality 0·85, 0·76–0·95; p=0·0051; and any death 0·93, 0·85–1·01; p=0·087; appendix pp 40–42).

Internal mammary chain or supraclavicular fossa radiotherapy should not cause lymphoedema, and only one of the two newer trials (the MA.20 trial) that randomised axillary radiotherapy (appendix p 20) provided lymphoedema data. In the MA.20 trial, lymphoedema rates (after axillary dissection or sentinel node biopsy) were 8·3% (76 of 916) with nodal

A

	Events/women		Regional radiotherapy events		Rate ratio (95% CI)
	Allocated regional radiotherapy	Allocated no regional radiotherapy	Log-rank O–E	Variance of O–E	
Age at entry (years)					
<40	153/425	155/429	−4·0	70·2	0·94 (0·75–1·19)
40–49	342/1462	389/1500	−28·8	173·6	0·85 (0·73–0·98)
50–59	437/1874	509/1929	−29·0	225·8	0·88 (0·77–1·00)
60–69	346/1327	391/1365	−17·9	173·4	0·90 (0·78–1·05)
≥70	48/271	54/251	−6·6	23·8	0·76 (0·51–1·13)
χ^2_4=0·1; p=0·81					
Nodal status					
pN0	194/1093	228/1095	−18·3	101·9	0·84 (0·69–1·01)
pN1–3	603/2812	682/2910	−31·6	311·0	0·90 (0·81–1·01)
pN4+	502/1219	553/1232	−32·4	239·5	0·87 (0·77–0·99)
pN unknown	27/235	35/237	−4·0	14·4	0·76 (0·45–1·27)
χ^2_3=0·0; p=0·85					
Grade					
Low grade	111/672	140/689	−14·2	59·5	0·79 (0·61–1·02)
Intermediate grade	377/1442	405/1488	−9·1	182·4	0·95 (0·82–1·10)
High grade	302/1072	371/1130	−30·6	150·4	0·82 (0·70–0·96)
Unknown grade	536/2173	582/2167	−27·4	265·6	0·90 (0·80–1·02)
χ^2_4=0·1; p=0·78					
Tumour size					
1–20 mm	509/2774	589/2826	−36·3	261·5	0·87 (0·77–0·98)
21–50 mm	713/2286	789/2361	−35·9	349·5	0·90 (0·81–1·00)
>50 mm	100/274	115/262	−13·1	40·8	0·73 (0·53–0·99)
Unknown	4/25	5/25	0·1	1·2	1·09 (0·18–6·50)
χ^2_4=0·1; p=0·71					
ER status					
ER poor	325/1138	399/1221	−31·8	160·2	0·82 (0·70–0·96)
ER positive	923/3963	1024/4002	−58·8	464·3	0·88 (0·80–0·96)
ER unknown	78/258	75/251	0·8	31·2	1·03 (0·72–1·46)
χ^2_4=0·6; p=0·43					
Breast quadrant					
Lateral	704/2601	742/2702	−12·1	338·0	0·96 (0·87–1·07)
Medial or central	567/2409	691/2438	−64·5	293·9	0·80 (0·72–0·90)
Unknown	55/349	65/334	−9·5	25·7	0·69 (0·47–1·02)
χ^2_4=5·3; p=0·021					
Breast surgery					
BCS	707/3502	808/3515	−54·2	363·1	0·86 (0·78–0·95)
Mastectomy	619/1857	690/1958	−29·7	299·9	0·91 (0·81–1·01)
None, other, or unknown	0/0	0/1			
χ^2_4=0·4; p=0·52					
Nodes irradiated					
IMC, SCF, and axilla	631/2918	727/2918	−56·6	326·6	0·84 (0·75–0·94)
IMC	631/1982	704/2104	−28·5	309·7	0·91 (0·82–1·02)
SCF or axilla	64/459	67/452	−1·2	30·5	0·96 (0·67–1·37)
χ^2_2=1·3; p=0·52					
Use of systemic therapy					
None reported	111/488	109/457	−1·1	50·1	0·98 (0·74–1·29)
Chemotherapy only	370/1189	412/1236	−18·8	174·5	0·90 (0·77–1·04)
Endocrine only	403/1539	446/1606	−16·1	199·5	0·92 (0·80–1·06)
Both	441/2135	531/2165	−53·0	228·5	0·79 (0·70–0·90)
Other or unknown	1/8	0/10			
χ^2_3=3·5; p=0·32					
Period of follow-up					
Years 0–1	366/5359	432/5474	−31·4	184·0	0·84 (0·73–0·97)
Years 2–4	402/4852	477/4897	−34·6	206·8	0·85 (0·74–0·97)
Years 5–9	362/4189	380/4149	−12·0	178·9	0·94 (0·81–1·08)
Years ≥10	196/2796	209/2729	−8·3	97·1	0·92 (0·75–1·12)
χ^2_4=1·1; p=0·30					
Overall p=0·00083	**1326/5359 (24·7%)**	**1498/5474 (27·4%)**	**−86·3**	**666·8**	**0·88 (0·81–0·95)**



(Figure 3 continues on next page)

B

	Deaths/number of women		Regional radiotherapy deaths		Rate ratio (95% CI)
	Allocated regional radiotherapy	Allocated no regional radiotherapy	Log-rank O–E	Variance of O–E	
Age at entry (years)					
<40	112/425	112/429	−3·2	52·7	0·94 (0·72–1·23)
40–49	255/1462	305/1500	−30·3	133·5	0·80 (0·67–0·94)
50–59	338/1874	399/1929	−23·1	175·5	0·88 (0·76–1·02)
60–69	305/1327	340/1365	−13·6	150·0	0·91 (0·78–1·07)
≥70	43/271	51/251	−5·7	20·7	0·76 (0·49–1·17)
χ^2_1=0·0; p=0·84					
Nodal status					
pN0	126/1093	162/1095	−16·4	68·6	0·79 (0·62–1·00)
pN1–3	481/2812	543/2910	−23·7	247·3	0·91 (0·80–1·03)
pN4+	437/1219	483/1232	−32·3	210·5	0·86 (0·75–0·98)
pN unknown	9/235	19/237	−3·5	6·0	0·56 (0·25–1·24)
χ^2_1=0·1; p=0·82					
Grade					
Low grade	82/672	97/689	−4·3	41·5	0·90 (0·67–1·22)
Intermediate grade	293/1442	326/1488	−17·4	144·2	0·89 (0·75–1·04)
High grade	263/1072	317/1130	−21·8	131·3	0·85 (0·71–1·01)
Unknown grade	415/2173	467/2167	−29·4	208·6	0·87 (0·76–0·99)
χ^2_1=0·2; p=0·67					
Tumour size					
1–20 mm	363/2774	441/2826	−35·7	189·7	0·83 (0·72–0·96)
21–50 mm	601/2286	664/2361	−29·3	295·8	0·91 (0·81–1·02)
>50 mm	85/274	100/262	−12·7	35·6	0·70 (0·50–0·97)
Unknown	4/25	2/25	0·8	0·5	4·95 (0·31–79·19)
χ^2_1=0·0; p=1·00					
ER status					
ER poor	280/1138	347/1221	−27·5	141·1	0·82 (0·70–0·97)
ER positive	710/3963	794/4002	−46·3	356·1	0·88 (0·79–0·97)
ER unknown	63/258	66/251	−3·5	26·3	0·88 (0·60–1·28)
χ^2_1=0·4; p=0·51					
Breast quadrant					
Lateral	568/2601	607/2702	−16·1	275·1	0·94 (0·84–1·06)
Medial or central	453/2409	556/2438	−51·7	234·8	0·80 (0·71–0·91)
Unknown	32/349	44/334	−7·8	14·8	0·59 (0·35–0·98)
χ^2_1=3·3; p=0·069					
Breast surgery					
BCS	502/3502	590/3515	−43·9	261·1	0·85 (0·75–0·95)
Mastectomy	551/1857	617/1958	−29·8	269·3	0·90 (0·79–1·01)
None, other, or unknown	0/0	0/1			
χ^2_1=0·4; p=0·51					
Nodes irradiated					
IMC, SCF, and axilla	472/2918	555/2918	−46·2	246·4	0·83 (0·73–0·94)
IMC	544/1982	615/2104	−30·7	269·4	0·89 (0·79–1·01)
SCF or axilla	37/459	37/452	1·1	16·7	1·07 (0·66–1·73)
χ^2_2=1·4; p=0·49					
Use of systemic therapy					
None reported	74/488	74/457	−1·9	32·6	0·94 (0·67–1·33)
Chemotherapy only	316/1189	362/1236	−21·3	154·2	0·87 (0·74–1·02)
Endocrine only	334/1539	371/1606	−12·3	163·0	0·93 (0·80–1·08)
Both	328/2135	400/2165	−43·1	172·1	0·78 (0·67–0·90)
Other or unknown	1/8	0/10			
χ^2_3=2·9; p=0·40					
Period of follow-up					
Years 0–1	133/5359	162/5474	−12·4	69·3	0·84 (0·66–1·06)
Years 2–4	312/5107	387/5194	−34·1	164·1	0·81 (0·70–0·95)
Years 5–9	344/4566	369/4567	−13·8	170·3	0·92 (0·79–1·07)
Years ≥10	264/3198	289/3141	−15·5	128·8	0·89 (0·75–1·05)
χ^2_1=0·7; p=0·41					
Overall p=0·0010	**1053/5359 (19·6%)**	**1207/5474 (22·0%)**	**−75·9**	**532·4**	**0·87 (0·80–0·94)**

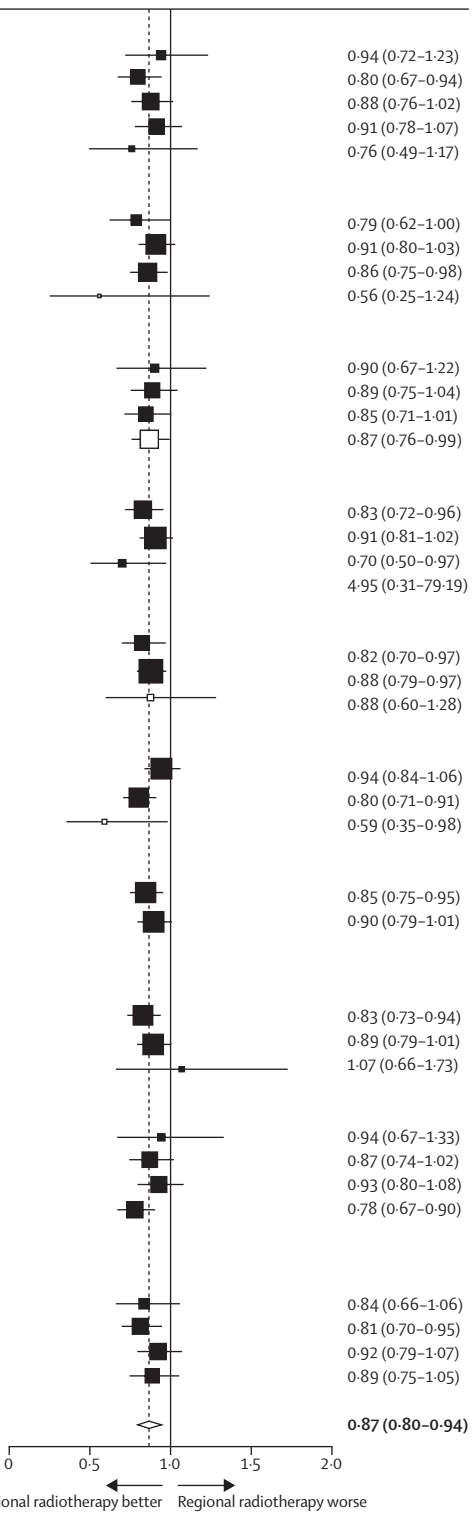


Figure 3: **Subgroup analyses for event rate ratios and 95% CIs for (A) any recurrence and (B) breast cancer mortality in 10 833 women in the seven newer trials with data on recurrence by patient, tumour, and treatment factors, and period of follow-up**

Internal mammary chain, supraclavicular fossa, and axilla included one trial of IMC and SCF versus no radiotherapy to those nodal regions and one trial of IMC, SCF radiotherapy, and axilla radiotherapy versus no radiotherapy to these nodal regions. SCF and axilla included one trial of axilla radiotherapy versus no radiotherapy to this nodal region, and one trial of SCF radiotherapy versus no radiotherapy to this nodal region. In graph B, the total numbers of deaths with recurrence are cited (regardless of the causes of death), but the analyses are of breast cancer mortality, allowing (by log-rank subtraction) for any mortality from non-breast cancer causes after recurrence. BCS=breast conserving surgery. ER=oestrogen receptor. IMC=internal mammary chain. N0=node negative. N1–3=one to three involved axillary lymph nodes. N4+=four or more involved axillary lymph nodes. pN=pathological lymph node status. SCF=supraclavicular fossa.

radiotherapy (to internal mammary chain, supraclavicular fossa, and axilla) versus 4·5% (41 of 916) without (appendix p 36).

Proportional reductions in recurrence and breast cancer mortality did not vary significantly according to most patient or tumour characteristics: age, nodal status, grade, tumour size, and oestrogen receptor status. There was some evidence to support a previous hypothesis that the proportional effects of nodal radiotherapy were greater for women with medial or central tumours than for women with lateral tumours (p value for heterogeneity of effect for medial or central *vs* lateral: any recurrence 0·021; distant recurrence 0·052; breast cancer mortality 0·069; overall mortality 0·40; figure 3; appendix pp 37–38).

There was no significant variation in the RRs for any recurrence or breast cancer mortality according to type of breast surgery, nodal regions irradiated, use of systemic therapy, or period of follow-up (figure 3). Repeating these analyses excluding the study that allocated radiotherapy according to laterality did not materially change the results (appendix pp 39–42).

This lack of heterogeneity in the RRs for any recurrence and breast cancer death means they can be applied to annual rates of recurrence and breast cancer death averaged over treatment groups for different subgroups of women. These analyses showed that absolute gains for different groups of women increased according to their absolute risks of recurrence and breast cancer mortality, with the greatest gains for the women with the greatest risks (table 2). The estimated 15-year absolute breast cancer recurrence reductions from nodal radiotherapy were 2·3% for women with node-negative disease, 2·9% for women with one to three positive axillary nodes, and 4·3% for women with four or more positive nodes. The corresponding 15-year absolute breast cancer mortality reductions were: 1·6%, 2·7%, and 4·5%.

The eight older trials began during 1961–78 and included 2157 women, with 1014 recurrences, 970 deaths with recurrence, and 1541 deaths overall (table 1; appendix pp 21–22). Median follow-up was 25·6 woman-years (IQR 12·4–41·7; table 1). Seven of the eight older trials assessed radiotherapy to the internal mammary chain, supraclavicular fossa, and axilla (1940 women). The other trial assessed radiotherapy to the supraclavicular fossa and axilla (217 women).

In these older trials, regional node radiotherapy did not reduce overall breast cancer recurrence (RR 0·98, 95% CI 0·85–1·12; p=0·74) or breast cancer mortality (1·04, 0·91–1·20; p=0·55; appendix p 43). Regional node radiotherapy significantly increased non-breast-cancer mortality (1·42, 1·18–1·71; p=0·00023), with little effect during the first 15 years, but a substantial excess thereafter, leading to a net increase in overall mortality (1·17, 1·04–1·31; p=0·0067; appendix p 43). The excess was mainly from one trial in which direct cobalt-60 internal mammary chain fields were used (appendix p 29). The non-breast-cancer mortality in these trials has been reported in a previous EBCTCG meta-analysis.[5] Analyses of any recurrence and breast cancer mortality in the older trials by patient, tumour, and treatment factors are in the appendix (pp 44–45).

	Regional radiotherapy	No regional radiotherapy	Gain from regional radiotherapy
Any recurrence			
pN0	19·0%	21·3%	2·3%
pN1–3	25·6%	28·5%	2·9%
pN4+	46·8%	51·1%	4·3%
Breast cancer mortality			
pN0	10·9%	12·5%	1·6%
pN1–3	20·3%	23·0%	2·7%
pN4+	40·5%	45·0%	4·5%

Data are 15-year cumulative risks. The overall rate ratios (RRs) for any recurrence (RR=0·88; figure 3) and breast cancer mortality (0·87; figure 3) were applied to annual rates of any recurrence and breast cancer mortality in the trials, averaged over treatment groups (there was no significant heterogeneity in the proportional reductions [RRs] for any recurrence and breast cancer mortality). pN0=pathologically node negative. pN1–3=one to three involved axillary lymph nodes. pN4+=four or more involved axillary lymph nodes.

Table 2: **Absolute effect of regional node radiotherapy on 15-year risk of any recurrence and breast cancer mortality by nodal status in 10 833 women in the seven newer trials with data on recurrence**

Discussion

The trials in this meta-analysis span half a century. During this time, there were major changes in breast cancer radiotherapy, and these are reflected in our findings. Regional node radiotherapy in the early trials, which started during the 1960s and 1970s, had little effect on overall recurrence or breast cancer mortality and increased non-breast-cancer mortality, leading to a net increase in overall mortality. In contrast, regional node radiotherapy in the newer trials, which would have been delivered in the 1990s and 2000s, significantly reduced breast cancer recurrence and mortality, with no apparent increase in non-breast-cancer mortality, resulting in significantly reduced overall mortality. These effects were seen despite the reductions in risks of breast cancer recurrence and mortality that have occurred over time, partly due to improvements in local and systemic therapies.

There are two main differences between the older and newer trials. First, breast cancer regional node radiotherapy techniques improved substantially. The greatest improvements were during the 1980s and 1990s when visualisation of radiation dose on cross-sectional images started to be used in radiotherapy planning.[1] These improvements substantially reduced the incidental radiation doses received by organs near the breast and lymph nodes, such as the heart and lungs. The most frequently used technique in the older trials (direct anterior

internal mammary chain field) delivered around 15 Gy mean heart dose in left radiotherapy and 10 Gy mean heart dose in right radiotherapy.[14] In the newer trials, heart doses were much lower than in the older trials. For example, in the largest newer trial (the DBCG trial), around 1 Gy was received by the heart in right-internal mammary chain radiotherapy[15] so the corresponding risks of heart disease would also be lower than in older trials.[5] Radiotherapy improvements were incremental, making it difficult to attribute the improved safety of radiotherapy to any one particular change. Second, six of the eight older trials in this meta-analysis did not include chest wall radiotherapy after mastectomy in women with node-positive cancer, which would be considered suboptimal today (appendix p 17). After mastectomy, the most frequent site of local recurrence is the chest wall.[16,17] Failure to irradiate the chest wall in most older trials might have diluted any beneficial effect of nodal radiotherapy by recurrences in the chest wall and lower axilla. In contrast, in the newer trials, over half of the women received breast conserving surgery with breast irradiation, and most women with mastectomy also received chest wall irradiation, both of which often include the lower axilla. Therefore, the newer trials address additional radiotherapy, beyond that included by chest wall or breast fields.

Individual patient data meta-analyses maximise statistical precision by combining all relevant trials. Therefore, they include a larger number of patients and events than in the individual trials and longer follow-up of some trials, avoiding various types of publication bias and limiting some other biases. In contrast to reviews of published trial reports, unpublished additional follow-up data can be included, yielding more reliable assessment of long-term effects. Inclusion of all potentially available randomised data is important because trial results, which do not show significant treatment effects, are less likely to be published (and re-published) than other trial results. The need to include all potentially relevant randomised evidence in a disease requiring long-term follow-up to assess risks and benefits has led the EBCTCG to develop comprehensive methods of identifying and obtaining data from both published and unpublished trials. The EBCTCG search strategy involves regular searches of databases and conference proceedings, with further input to trial identification from hundreds of breast cancer trialists worldwide who collaborate with the EBCTCG (appendix p 4). By Jan 1, 2023, the EBCTCG database included some 40 000 articles of potential relevance to EBCTCG meta-analyses. This process assures that no material ascertainment biases remain. Although formal tests of ascertainment bias yielded non-significant results, such tests might not be informative about the slight ascertainment biases that could plausibly affect this meta-analysis.

A minor limitation of our meta-analysis is that one small trial, including only 165 women, was unavailable; it reported its results only for overall mortality (which slightly favour radiotherapy; appendix p 18). Another limitation was that few endpoints were available for assessing non-fatal side-effects. For the life-threatening side-effects of radiotherapy, however, a detailed EBCTCG meta-analysis has already been conducted including not only trials of regional node radiotherapy, but also trials of other types of breast cancer radiotherapy.[5] A further limitation is that the DBCG study allocated nodal radiotherapy based on tumour laterality rather than randomisation. Although both doctor and patient knew the allocation in advance, all eligible patients in the Danish population were to be included and compliance was high, so selection bias was minimal.[12] The DBCG study was, to our knowledge, the largest study of internal mammary chain radiotherapy, hence it provides valuable evidence on its effects.

The effects of nodal radiotherapy in the 1990s and 2000s on breast cancer recurrence and mortality have been shown in three large individual studies.[12,18–21] Although these studies each contained more than 1500 women, they were not large enough individually to assess whether radiotherapy benefits varied according to factors such as tumour location, nodal involvement, or use of systemic therapy. This uncertainty is reflected by variation in guidelines and practice.[22,23] For example, some international guidelines recommend regional node radiotherapy in selected patients with node-negative disease, whereas others do not.[23] Some guidelines are more likely to recommend internal mammary chain radiotherapy for medial cancers than for lateral cancers, but others do not consider tumour location.[23]

In the newer trials, even patients who had negative axillary nodes appeared to receive modest benefit from regional node radiotherapy reflecting possible eradication of occult disease in the lymphatic drainage vessels, internal mammary nodes, or supraclavicular fossa despite having pathologically uninvolved axillary nodes. There was some evidence that the proportional benefit of nodal radiotherapy was greater for women with medial or central tumours than for women with lateral tumours. This finding supports a previous hypothesis that internal mammary chain radiotherapy could be more effective at reducing recurrences from medial or central cancers than from lateral cancers.

We found little variation in the proportional benefits of nodal radiotherapy according to most factors. Therefore, our statistically stable overall RRs could be applied to rates of recurrence and breast cancer death in groups of women with different characteristics to estimate, at least approximately, their absolute treatment benefits up to year 15. These benefits, together with estimates of absolute risks, can be used to help determine for which patient groups regional node radiotherapy should be recommended in clinical guidelines.

The trials assessed radiotherapy to different nodal regions. In the newer trials, most of the evidence was on radiotherapy to the internal mammary chain alone or to

the internal mammary chain and supraclavicular fossa combined, with no significant heterogeneity in the RRs for different nodal regions irradiated. The main effect of radiotherapy in these newer trials was on distant recurrence, rather than on locoregional recurrence. This finding could be because internal mammary chain recurrences are not readily detected. Therefore, eradication of internal mammary chain cancer deposits could be reflected mainly in reductions in the detection of distant rather than locoregional recurrence. After axillary surgery, axillary radiotherapy can cause lymphoedema, which can have long-term implications for the patient's quality of life.

Many women today receive primary systemic therapy before surgery. There is uncertainty concerning the effects of regional node radiotherapy in this setting, and the results of randomised trials are awaited.

Radiotherapy has improved further since the newer trials were conducted. Techniques now include intensity-modulated beams to improve target coverage, deep inspiratory breath-hold to minimise heart and lung doses, and imaging during treatment to enable consistent dose delivery.[1] In addition, there are international guidelines for nodal contouring, target coverage, and organ avoidance.[7,24] Therefore, for women being considered for radiotherapy today, the proportional benefits of regional node radiotherapy on breast cancer recurrence and death could be somewhat greater than in the newer trials. However, the absolute breast cancer mortality benefits for these women could be somewhat lower than in the trials due to reductions in population breast cancer death rates.

For women with negative lymph nodes, in this meta-analysis, regional node radiotherapy reduced their absolute 15-year risk of breast cancer death by about 1–2%. The absolute benefit for an individual woman would also depend on factors such as tumour size, grade, molecular subtype, and systemic therapy received. For example, the absolute benefit would be greater for a woman with a large, high-grade, node-negative cancer than for a woman with a small screen-detected node-negative cancer. For women with one to three positive nodes, regional node radiotherapy reduced their absolute 15-year risk of breast cancer death by about 2–3% and for women with four or more positive nodes, the reduction in breast cancer death was about 4–5%.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) writing committee

Carolyn Taylor (joint first author), David Dodwell (joint first author), Paul McGale, Robert K Hills, Richard Berry, Rosie Bradley, Jeremy Braybrooke, Mike Clarke, Richard Gray, Francesca Holt, Zulian Liu, Hongchao Pan, Richard Peto, Ewan Straiton (Clinical Trial Service Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK), Jonas Bergh (Karolinska Institutet and Karolinska Comprehensive Cancer Centre and University Hospital, Stockholm, Sweden), Charlotte Coles (Department of Oncology, University of Cambridge, Cambridge, UK), Fran Duane (St Luke's Radiation Oncology Network and Trinity St James's Cancer Institute, Dublin, Ireland), Christophe Hennequin (Department of Radiation Oncology, Hôpital Saint Louis, Paris, France), Glenn Jones (International Atomic Energy Agency, Vienna, Austria), Thorsten Kühn (Department of Obstetrics and Gynaecology, Klinikum Esslingen, Esslingen, Germany), Sileida Oliveros (Oxford University Hospitals NHS Foundation Trust, Oxford, UK), Jens Overgaard (Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark), Kathy Pritchard (Sunnybrook Odette Cancer Centre, Toronto, ON, Canada), Chang-Ok Suh (Department of Radiation Oncology, CHA Bundang Medical Center, CHA University, Seongnam, South Korea), Sandra Swain (Georgetown University Medical Center, Washington, DC, USA), Tim Whelan (joint last author; McMaster University and the Juravinski Cancer Centre, Hamilton, ON, Canada), Philip Poortmans (joint last author; Iridium Netwerk, Wilrijk-Antwerp, Belgium).

EBCTCG secretariat

Graham Beake, Richard Berry, Clare Boddington, Rosie Bradley, Jeremy Braybrooke, Mike Clarke, Christina Davies, Lucy Davies, David Dodwell, Fran Duane, Vaughan Evans, Jo Gay, Lucy Gettins, Jon Godwin, Richard Gray, Robert K Hills, Francesca Holt, Sam James, Amanda Kerr, Hui Liu, Zulian Liu, Elizabeth MacKinnon, Gurdeep Mannu, Paul McGale, Theresa McHugh, Philip Morris, Mariko Nakahara, Hongchao Pan, Richard Peto, Simon Read, Ewan Straiton, Carolyn Taylor, and Hannah Taylor. For the full list of members, see https://www.ctsu.ox.ac.uk/research/ebctcg.

Groups (lead investigators) contributing data to the meta-analysis

Canadian Cancer Trials Group, ON, Canada: Tim Whelan; Centre Hospitalier Lyon Sud, France: Christophe Hennequin; Danish Breast Cancer Cooperative Group, Denmark: Jens Overgaard; EORTC Breast Cancer Cooperative Group, Belgium: Philip Poortmans; Glasgow West of Scotland Surgical Association, UK: John Ferguson; Heidelberg, Germany: Hans Scheurlen; Korean Radiation Oncology Group, South Korea: Chang-Ok Suh; Italian Oncological Senology Group (GrISO), Italy: Stefano Zurrida and Viviana Galimberti; Mayo Clinic, USA: James Ingle; Milan Istituto Nazionale per lo Studio e la Cura dei Tumori, Italy: Pinuccia Valagussa and Umberto Veronesi; National Surgical Adjuvant Breast & Bowel Project (NSABP), USA: Stewart Anderson, Gong Tang, and Bernard Fisher; Norwegian Radium Hospital, Oslo, Norway: Sophie Fossa, Kristin Valborg Reinertsen, and Herman Høst; Piedmont Oncology Association, USA: Hyman Muss; Tampere University Hospital, Finland: Kaija Holli; Toronto-Edmonton Clinical Trials Group, Canada: Kathy Pritchard.

EBCTCG steering committee

Jonas Bergh, Sandra Swain (co-chairs), David Cameron (vice-chair), Kathy Albain, Stewart Anderson, Rodrigo Arriagada, John Bartlett, Elizabeth Bergsten-Nordström, Judith Bliss, Rosie Bradley, Etienne Brain, Jeremy Braybrooke, Lisa Carey, Mike Clarke, Robert Coleman, Jack Cuzick, Nancy Davidson, Lucia Del Mastro, Angelo Di Leo, James Dignam, David Dodwell, Mitch Dowsett, Fran Duane, Bent Ejlertsen, Prue Francis, José Angel García-Sáenz, Rich Gelber, Michael Gnant, Matthew Goetz, Pam Goodwin, Richard Gray, Pat Halpin-Murphy, Dan Hayes, Catherine Hill, Robert K Hills, Reshma Jagsi, Wolfgang Janni, Zulian Liu, Sibylle Loibl, Elizabeth MacKinnon, Stuart McIntosh, Eleftherios Mamounas, Gurdeep Mannu, Miguel Martín, Paul McGale, Hirofumi Mukai, Valentina Nekljudova, Larry Norton, Yasuo Ohashi, Hongchao Pan, Richard Peto, Martine Piccart, Lori Pierce, Philip Poortmans, Kathy I Pritchard, Vinod Raina, Daniel Rea, Meredith Regan, John Robertson, Emiel Rutgers, Roberto Salgado, Dennis Slamon, Tanja Spanic, Joseph Sparano, Guenther Steger, Carolyn Taylor, Gong Tang, Masakazu Toi, Andrew Tutt, Giuseppe Viale, Xiang Wang, Tim Whelan, Nicholas Wilcken, Norman Wolmark, and Ke-Da Yu.

Contributors

The EBCTCG secretariat was responsible for maintaining collaboration, identifying trials, and obtaining and checking datasets. PMG, DD, RKH, and CT designed and did the analyses. PMG and RKH accessed and verified the data. FD, FH, TW, DD, and CT reviewed the trial radiotherapy regimens. RG, RP, and JB acted as internal advisors and SS, JBe, KP, CC, CH, C-OS, GJ, TK, SO, JO, PP, and TW as external advisors. All writing committee members contributed to drafting and revising the manuscript. Interim analyses were discussed by the steering

committee and trialists who supplied data for the analysis. The EBCTCG secretariat had full access to all the data in the study and the writing committee had final responsibility for the decision to submit for publication.

Declaration of interests

RG and RKH report that EBCTCG is supported by a Cancer Research UK grant (reference 27691) paid to the University of Oxford. JBe reports institutional grants or contracts from Amgen, AstraZeneca, Bayer, Merck, Pfizer, Roche, and Sanofi-Aventis; honoraria from UpToDate to Asklepios Medicine for breast cancer prediction or prognostication for early beast cancer; has been offered stock options and stocks in Stratipath artificial intelligence for early breast cancer and was asked to arrange an international advisory board for Stratipath; has had a leadership or fiduciary role in other board, society, committee, or advocacy groups; and has a leadership or fiduciary role with the WNTRESEARCH Group (https://www.wntresearch.com) since June, 2022. CC reports institutional grants or contracts from: Radiation Research Network Project Seed Funding Award—Multi-modal Imaging-Guided Radiotherapy for small Animals with a Technological and Extensible System; Cancer Research UK (ref: RRNPSF-Jul21\100012); Addenbrooke's Charitable Trust fund 9701 (Tomlinson Radiotherapy legacy); The *Lancet* Breast Cancer Commission; Efficacy and Mechanism Evaluation Project (grant number: NIHR131120; Radiation Research Network Project Seed Funding Award for the Hamlet.RT multi-centre expansion (reference: RRNPSF-Jan21\100004), The National Institute for Health and Care Research (reference NIHR300024), and Cancer Research UK Radiation Research Unit at the University of Cambridge (reference C17918/A28870). CC reports the following board participation: Chair of Independent Data Monitoring Committee for UK PivotalBoost trial, Member of the independent data monitoring committee for TORPEdO Proton Beam Therapy trial; European HYPO-G01 breast fractionation trial; and the UK NIMRAD trial, and Member of International Scientific Advisory Board, Institute Curie. CC is a chair of The *Lancet* Breast Cancer Commission. KP reports royalty or license payments from UpToDate, and payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from Pfizer, Roche, Amgen, Novartis, Eisai, Genomic Health, and Myriad Genetic Laboratories; and payment for data safety monitoring board or advisory board participation from Pfizer and Gilead Sciences. SS reports grants or contracts from Genentec/Roche, Kailos Genetics, and Breast Cancer Research Fellowship; consulting fees from Genentech, Roche, and Molecular Therapeutics; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Genentech, Roche, and Daiichi Sankyo; support for attending meetings and travel from Genentech and Roche, and travel to Boston in November, 2019; participation on a data safety monitoring board for AstraZeneca; participation on an advisory board for AstraZeneca, Daiichi Sankyo, Exact Sciences, Biotheranostics, Natera, Merck, Silverback Therapeutics, and Athenex, Lilly; scientific advisory board participation for Inivata; leadership or fiduciary role in other board, society, committee, or advocacy group for NSABP as a vice chairman, Conquer Cancer Foundation, and American Society of Clinical Oncology Director; and writing services for third party writing for Genentech, Roche, and AstraZeneca. TW reports grants or contracts from Exact Sciences for In-Kind research funding, including non-direct financial support for biomarker testing from Exact Sciences for related and unrelated ongoing studies. All other authors declare no competing interests.

Data sharing

Our data sharing policy is available online at https://www.ndph.ox.ac.uk/data-access.

Acknowledgments

The chief acknowledgment is to the women in these trials and the trial personnel. The 650 EBCTCG collaborating trialists are listed in the supplementary material (appendix pp 46–50) and at https://www.ctsu.ox.ac.uk/research/ebctcg. We acknowledge EBCTCG Patient Representatives Elizabeth Bergsten Nordstrom, Tanja Spanic, and Pat Halpin Murphy who reviewed and provided comments in face-to-face meetings and teleconferences, and had agreed to help with dissemination of these findings. The EBCTCG secretariat is funded by Cancer Research UK (grant 27691), with additional support from core funding to the Clinical Trial Service Unit and to the Population Health Research Unit, Nuffield Department of Population Health, University of Oxford, from Cancer Research UK and the UK Medical Research Council. CT, DD, and PMG received funding from Cancer Research UK (grants C8225/A21133 and PRCRPG-Nov21\100001). CEC is funded by the National Institute of Health Research (NIHR) and supported by the NIHR Cambridge Biomedical Research Centre. The views expressed are those of the writing committee and not necessarily those of the NIHR.

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