Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials

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Summary

Background

In early breast cancer, variations in local treatment that substantially affect the risk of locoregional recurrence could also affect long-term breast cancer mortality. To examine this relationship, collaborative meta-analyses were undertaken, based on individual patient data, of the relevant randomised trials that began by 1995.

Methods

Information was available on 42 000 women in 78 randomised treatment comparisons (radiotherapy vs no radiotherapy, 23 500; more vs less surgery, 9300; more surgery vs radiotherapy, 9300). 24 types of local treatment comparison were identified. To help relate the effect on local (ie, locoregional) recurrence to that on breast cancer mortality, these were grouped according to whether or not the 5-year local recurrence risk exceeded 10% (<10%, 17 000 women; >10%, 25 000 women).

Findings

About three-quarters of the eventual local recurrence risk occurred during the first 5 years. In the comparisons that involved little (<10%) difference in 5-year local recurrence risk there was little difference in 15-year breast cancer mortality. Among the 25 000 women in the comparisons that involved substantial (>10%) differences, however, 5-year local recurrence risks were 7% active versus 26% control (absolute reduction 19%), and 15-year breast cancer mortality risks were 44·6% versus 49·5% (absolute reduction 5·0%, SE 0·8, 2p<0·00001).

These 25 000 women included 7300 with breast-conserving surgery (BCS) in trials of radiotherapy (generally just to the conserved breast), with 5-year local recurrence risks (mainly in the conserved breast, as most had axillary clearance and node-negative disease) 7% versus 26% (reduction 19%), and 15-year breast cancer mortality risks 30·5% versus 35·9% (reduction 5·4%, SE 1·7, 2p=0·0002; overall mortality reduction 5·3%, SE 1·8, 2p=0·005). They also included 8500 with mastectomy, axillary clearance, and node-positive disease in trials of radiotherapy (generally to the chest wall and regional lymph nodes), with similar absolute gains from radiotherapy; 5-year local recurrence risks (mainly at these sites) 6% versus 23% (reduction 17%), and 15-year breast cancer mortality risks 54·7% versus 60·1% (reduction 5·4%, SE 1·3, 2p=0·0002; overall mortality reduction 4·4%, SE 1·2, 2p=0·0009). Radiotherapy produced similar *proportional* reductions in local recurrence in all women (irrespective of age or tumour characteristics) and in all major trials of radiotherapy versus not (recent or older; with or without systemic therapy), so large *absolute* reductions in local recurrence were seen only if the control risk was large.

To help assess the life-threatening side-effects of radiotherapy, the trials of radiotherapy versus not were combined with those of radiotherapy versus more surgery. There was, at least with some of the older radiotherapy regimens, a significant excess incidence of contralateral breast cancer (rate ratio 1·18, SE 0·06, 2p=0·002) and a significant excess of non-breast-cancer mortality in irradiated women (rate ratio 1·12, SE 0·04, 2p=0·001). Both were slight during the first 5years, but continued after year 15. The excess mortality was mainly from heart disease (rate ratio 1·27, SE 0·07, 2p=0·0001) and lung cancer (rate ratio 1·78, SE 0·22, 2p=0·0004).

Interpretation

In these trials, avoidance of a local recurrence in the conserved breast after BCS and avoidance of a local recurrence elsewhere (eg, the chest wall or regional nodes) after mastectomy were of comparable relevance to 15-year breast cancer mortality. Differences in local treatment that substantially affect local recurrence rates would, in the hypothetical absence of any other causes of death, avoid about one breast cancer death over the next 15years for every four local recurrences avoided, and should reduce 15-year overall mortality.

Introduction

In early breast cancer, surgery can remove any disease that has been detected in or around the breast or regional lymph nodes, but undetected deposits of disease may remain either locally (ie, in the residual breast tissue, scar area, chest wall, or regional lymph nodes) or at distant sites that could, if untreated, develop into life-threatening recurrence. Many randomised trials over the past half century have studied the effects of radiotherapy and of the extent of surgery on local disease control and on cause-specific mortality in early breast cancer. This report updates previous meta-analyses[1–4] of the individual patient data from those trials.

Post-BCS radiotherapy

After breast-conserving surgery (BCS), a particularly common site of local recurrence is the conserved breast itself (or the axilla, if this has not been treated effectively). The risk of recurrence in a conserved breast can be substantial even in node-negative disease that has been confirmed by axillary clearance, and it can be greatly reduced by radiotherapy.[4,5] Hence, the recent National Institutes of Health (NIH) consensus conference on early breast cancer[6] recommended that after BCS there should be radiotherapy to the conserved breast. Recent surveys in North America and Europe indicate that this treatment is generally given.[7] It is, however, not always given,[8] since later recurrence in a conserved breast can usually be removed by further surgery. Breast radiotherapy immediately after BCS could improve long-term survival (by comparison with a policy of watchful waiting for any local recurrence) only if life-threatening spread from tumour cells in the conserved breast would otherwise occur after BCS but before any clinically evident local recurrence was detected and treated, or if the local disease could then not be controlled adequately. Hence, radiotherapy is likely to have little effect on early mortality, whatever effect it might have on long-term breast cancer mortality.

Post-mastectomy radiotherapy

Even after mastectomy, an appreciable risk of local recurrence (eg, in the chest wall or lymph nodes) can remain unless some reliable method of investigation, such as axillary clearance, has found no evidence of nodal involvement. If axillary investigation reveals nodal involvement (or if the axilla has not been adequately investigated), post-mastectomy radiotherapy can produce a substantial absolute reduction in this risk of local recurrence, and previous trials[9–12] and meta-analyses[2–4] have shown that although it has little effect on breast cancer mortality during the first few years, it can produce a moderate, but definite, reduction in longer-term breast cancer mortality. Hence, the NIH consensus conference[6] recommended radiotherapy after mastectomy for women at high risk of locoregional recurrence (eg, those with four or more involved lymph nodes).

Long-term follow-up of mortality

Moderate differences in mortality that take many years to emerge can best be assessed by systematic meta-analyses of the data on every individual patient in all relevant randomised trials. Even this method of assessment, however, will yield reliable answers only if large numbers of relevant individuals have been randomised and followed up for many years. Our previous reviews of individual patient data included follow-up of the surgery trials only to 1990[3]

and follow-up of the radiotherapy trials[4] only to 1995. In the latter review,[4] the effect on long-term breast cancer mortality was only marginally significant in the trials of post-BCS radiotherapy, although more clearly significant in those of post-mastectomy radiotherapy. Moreover, in the data then available, all-cause mortality was not significantly reduced by radiotherapy after either BCS or mastectomy. More recently, a review of just the published results from the post-BCS radiotherapy trials found only a marginally significant difference in all-cause mortality, but noted that an updated meta-analysis of individual patient data would be more reliable.[13]

The present review of individual patient data from randomised trials of local treatments involves substantially longer follow-up than our previous reviews.[3,4] For the post-BCS radiotherapy trials in particular, many of which started relatively recently, and for at least the most recent post-mastectomy radiotherapy trials, this longer follow-up should offer a much more reliable assessment of the long-term effects on mortality. The main results for these two particular comparisons are presented separately, before the more general analyses that bring together data from all the local treatment comparisons.

The main aim of this report is to assess quantitatively the relationship between local control and long-term breast cancer mortality. It deals only semi-quantitatively with the effects of some radiotherapy regimens on mortality several years later from other conditions (eg, heart disease and lung cancer[14–16]), and does not investigate the extent to which the long-term fatal (or non-fatal) adverse effects of local treatment can be avoided by the substantial changes that have taken place over the past few decades in radiotherapy and surgery techniques.[17–19]

Methods

Every 5 years since 1985 evidence from the randomised trials in early breast cancer has been reviewed centrally, in a worldwide collaboration between the individuals now responsible for them (as the Early Breast Cancer Trialists' Collaborative Group, EBCTCG). An EBCTCG report published earlier this year[20] gave the results up to the year 2000 from the trials that began by 1995 of systemic treatments (chemotherapy or hormonal therapy) for early breast cancer. The present report gives the corresponding results from the trials of local treatments (various types of surgery or radiotherapy, or both), using similar methods.

Treatment comparisons and main outcomes

Information was available (table 1) from several trials of post-BCS radiotherapy (mostly to the conserved breast); of post-mastectomy radiotherapy (mostly to the chest wall and locoregional lymph nodes, after axillary clearance); of more surgery versus less surgery in the absence of radiotherapy; of more surgery versus less surgery in the presence of radiotherapy; and of surgery versus radiotherapy (ie, more surgery versus less surgery plus additional radiotherapy). Only unconfounded trials were considered (ie, trials in which there was to be no difference between the treatment groups in the use of systemic therapy). No specific studies of the relevance of newer diagnostic techniques, such as sentinel lymph node biopsy,[21] were available. Webtables 1–3 give brief design details of each of the available treatment comparisons in the three main parts of table 1.

Treatments compared (Where one trial predominates, it is named)	Available for analysis*			Not yet available**	
	Trials	Deaths	Women	Trials	Women
Radiotherapy (RT) vs no radiotherapy, but the same surgery					
Breast-conserving surgery (BCS), generally with axillary clearance, ± RT†	10	1940	7311	3	1150
Mastectomy + axillary clearance (Mast+AC) ± RT	25	6265	9933	2	165
Mastectomy + axillary sampling (Mast+AS) ± RT	4	360	647	0	0
Mastectomy alone ± RT	7	3890	5597	0	0
More surgery vs less surgery, but the same (or no) radiotherapy					
Internal mammary chain (IMC) removal vs not, both with mastectomy and no RT	2	793	1082	0	0
Pectoral muscle (PecM) removal vs not, both with mastectomy (mainly CAMS China trial)	4	1347	4925	2	~200
AC vs not in node-positive disease, both with mastectomy and some RT	2	240	266	5	~552
AC vs not in node-negative disease, both with mastectomy and no axillary RT	4	757	1154	0	0
Mastectomy+AC vs BCS+AC, neither with RT (part of NSABP B-06 trial)	1	660	1432	0	0
Mastectomy+AC vs BCS+AC, both with RT	2	185	428	0	0
BCS with more vs less breast surgery, neither with AC	0	0	0	3	~216
More surgery (active) vs less surgery plus radiotherapy (control)					
Mastectomy+AC vs mastectomy alone + RT	9	2910	4550	1	~100
Mastectomy+AC vs BCS+RT (Guy's Hospital trial)	1	509	630	0	0
Mastectomy vs BCS+RT, both with AC	7	1675	4125	3	~540
Total of tabulated numbers*	78	21 531	42 080	19	~2923 (6%)

Abbreviations: AC=axillary clearance, AF=axilla or supraclavicular fossa, or both, AS=axillary sampling, BCS=breast-conserving surgery, BW=breast and chest wall, IMC=internal mammary chain of lymph nodes, Mast=mastectomy, N+ve/N-ve=node-positive or unknown/node-negative, PecM=pectoral muscle, RT=radiotherapy, S=scar (as site of RT boost). * Some trials (e.g. NSABP B-06: ~700 Mast+AC+RT vs ~700 Mast+AC vs ~700 BCS+AC) contribute to more than one type of treatment comparison, so their control group may be counted more than once in the total. Without such double counting the total would be 70 trials available, with 19 291 deaths among 38 047 women (93% of total). ** Numbers of trials known to be unavailable: in such studies, the numbers randomised are by the year 2000, and may be uncertain (or wholly unavailable, in which case they are taken as 100, since such studies may well be small). † In 8 trials of BCS±RT all women were to have AC, but in 2 (Scottish and West Midlands) only some were to do so. In the majority of the BCS±RT trials, irradiation was generally just to the breast (BW or BW+S), but in some the irradiated sites included axilla, supraclavicular fossa and internal mammary chain (AF+IMC).

Table 1: Availability of data from unconfounded randomised trials of local therapy that began by 1995

For all unconfounded randomised trials that began recruitment by 1995, information was sought for every patient on her initial characteristics, allocated treatment, and time to various outcomes. These outcomes were: breast cancer recurrence; whether the first such recurrence was a distant or an isolated local recurrence (ie, an ipsilateral locoregional recurrence occurring before any contralateral or other distant recurrence); cause-specific and overall mortality; and the incidence of second primary cancers before breast cancer recurrence.

Data management procedures

Trial identification and data handling procedures were as in the EBCTCG report on systemic therapies,[20] except that: (i) more detail was sought of the surgical procedures, radiotherapy regimens, and definitions of local recurrence (from protocols, publications, or correspondence; see webtables 1–3); (ii) breast cancer in the contralateral breast was not counted as local recurrence; (iii) more detail was sought (by correspondence) about the underlying causes of many of the deaths, particularly from circulatory disease, lung cancer, or uncertain causes, before any recurrence of breast cancer; and (iv) more definite information was sought (by correspondence) if it was unclear whether the first recurrence was just an isolated local recurrence.

In treatment comparisons where the extent of axillary surgery was identical in both groups, classification of axillary nodal status as positive or negative was based on pathological information where available, and on clinical information where not. The few women with unknown nodal status were combined with those with clinically node-positive disease. In treatment

comparisons where the extent of axillary surgery differed between the groups (eg, axillary surgery vs axillary radiotherapy), classification of nodal status was based only on clinical information, to avoid bias.

For every randomised treatment comparison, local recurrence was defined in the same way for both groups. In the trials of radiotherapy versus not, this generally included recurrence (or a new breast cancer) in the residual breast tissue, scar area, chest wall, or ipsilateral regional lymph nodes, and in the trials involving surgery, trial-specific local recurrence definitions are given in webtables 2 and 3. Where recurrences just in a conserved breast or axilla had not originally been reported to the collaboration, information on them was sought, and they are now included as local recurrences.

Statistical analysis

All analyses were stratified by trial, by time since randomisation in single years, and by nodal status (negative or positive). The main analyses of local recurrence, breast cancer mortality, and overall mortality were also stratified by age in 5 groups (40, 40–49, 50–59, 60–69, 70 years at randomisation). Only two groups (50 and 50 years) were used, however, for analyses that were further subdivided by tumour characteristics (grade, size, oestrogen-receptor [ER] status, or actual number of involved nodes). Other aspects of the statistical methods and the formats of the figures are as before,[20] unless otherwise indicated, and are described on the EBCTCG website (see panel).

Panel: Webtables 1–4 and webfigures 1–10 on the Lancet website

> Webtables 1–3 provide brief details of every available trial (including the anatomic sites treated surgically and the radiotherapy doses and sites irradiated), and webtable 4 shows how the statistics for breast cancer mortality are derived by logrank subtraction (ie, subtraction of the logrank statistics for mortality from causes other than breast cancer from the logrank statistics for any death). The 15-year time-to-event graphs in webfigures 1–3 provide more detail for some of the main meta-analyses (including the logrank statistics for local recurrence, breast cancer mortality, and any death during years 0–4, 5–9, 10–14, and 15), webfigures 4 and 5 relate the effect on local recurrence to the proportional effect on breast cancer mortality, and webfigure 6 gives various subgroup analyses. Webfigure 7 (radiotherapy side-effects) gives 15-year time-to-event graphs for the incidence of contralateral breast cancer and for mortality from causes other than breast cancer. Finally, the forest plots in webfigures 8–10 give summary results for every separate trial (separating women with node-negative and node-positive disease) for local recurrence, breast cancer mortality, and any death. This report and the webtables and webfigures are also available on the EBCTCG website (www.ctsu.ox.ac.uk/projects/ebctcg), along with Powerpoint images of some of them.

In early breast cancer, most local recurrences become apparent within the first few years, but much of the distant recurrence and breast cancer mortality occurs later.[4] The main analyses involve 5-year local recurrence risks and 15-year breast cancer mortality risks. Both are generally illustrated by 15-year graphs (for comparability with the EBCTCG report[20] on systemic therapies), but the logrank observed minus expected (O–E) values that yield the significance tests associated with such graphs are based on events throughout the entire period of follow-up, both during and after the first 15 years, unless otherwise indicated. For the major treatment comparisons, results for overall mortality (“any death”) are also given, mainly on the website.

Collaborative review

Preliminary meta-analyses of the trials of local treatments had been presented and discussed at a meeting of collaborators in September, 2000, after which much additional detail was sought about methods and outcomes in these trials, and restructured, corrected meta-analyses emerged in 2004. A draft of the present report was circulated for comment by the collaborating trialists in June, 2005, was presented and discussed at a further meeting of collaborators in September, 2005, and was available for further comment in October, 2005. It was revised substantially in the light of these comments and recirculated when submitted for publication in November, 2005 (and, during the editorial process page proofs were posted on the password-protected EBCTCG website).

Role of the funding sources

This collaboration is funded from the general long-term financial support of the CTSU by organisations that had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The EBCTCG secretariat had full access to all the data and analyses and, after consultation with the collaborators, had final responsibility for the decision to submit for publication.

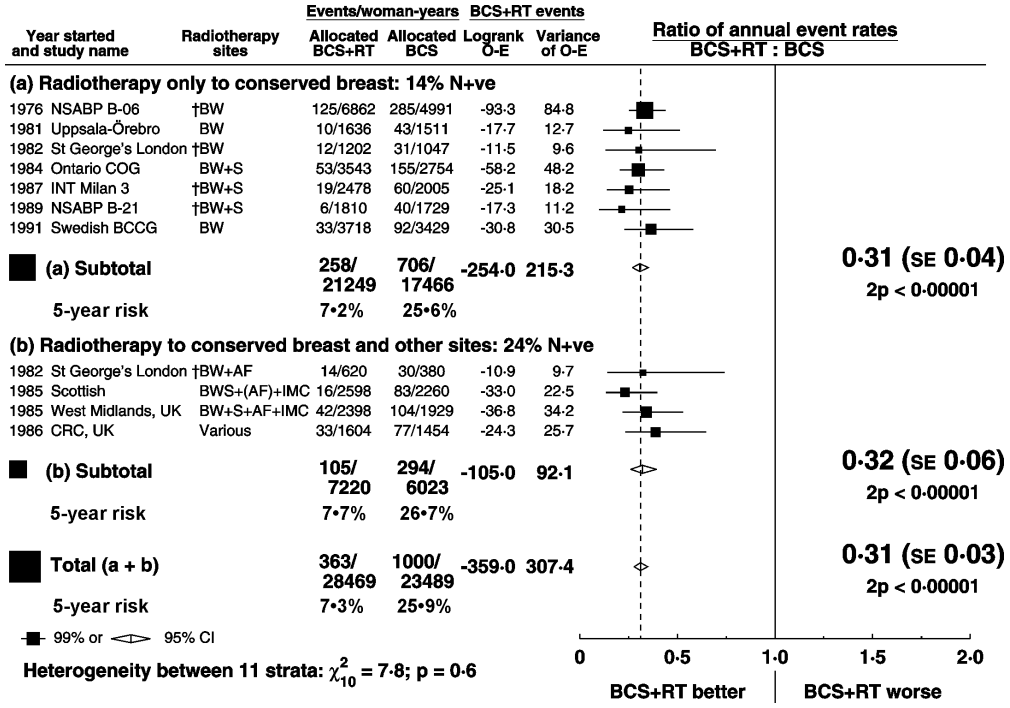
Results

Table 1 shows the numbers of trials and the numbers of randomised women who contributed to various local treatment comparisons. The two most extensively studied aspects of local treatment are radiotherapy after BCS (7311 women in 10 trials) and radiotherapy after mastectomy and axillary clearance (9933 women in 25 trials). The results (subdivided by nodal status, thereby making four separate treatment comparisons) for these two particular sets of trials are presented first. Then information from all the treatment comparisons in table 1 (again subdivided by nodal status, making a total of 24 comparisons) is used to relate the magnitude of the effect on local recurrence to that on breast cancer mortality. Finally, the effects of the radiotherapy regimens in these trials on the incidence of second cancers and on mortality from diseases other than breast cancer are presented.

Radiotherapy after BCS

Figure 1 gives, for the ten trials of post-BCS radiotherapy, logrank analyses of the effects on local recurrence (upper part of figure) and on breast cancer mortality (lower part). Separate subtotals are given (a) for trials in which the conserved breast was the only site irradiated (sometimes with an additional boost to the scar) and (b) for those where other sites were also irradiated, such as the axilla and supraclavicular fossa. One of the ten trials contributed to both subtotals, so there are 11 strata in figure 1. The reduction in local recurrence (mainly in the conserved breast) produced by allocation to radiotherapy is substantial and highly significant ($p<0{\cdot}00001$) in every separate trial. There is no significant heterogeneity between the proportional reductions in local recurrence in the 11 different strata in figure 1, or in the two subtotals. The recurrence rate ratio, comparing those allocated radiotherapy with those not, is about 0·3 in every trial, corresponding to a proportional reduction of 70%. Considering all ten trials together, the 5-year risk of local

Isolated local recurrence (denominator: woman-years)



Breast cancer mortality (denominator: women)

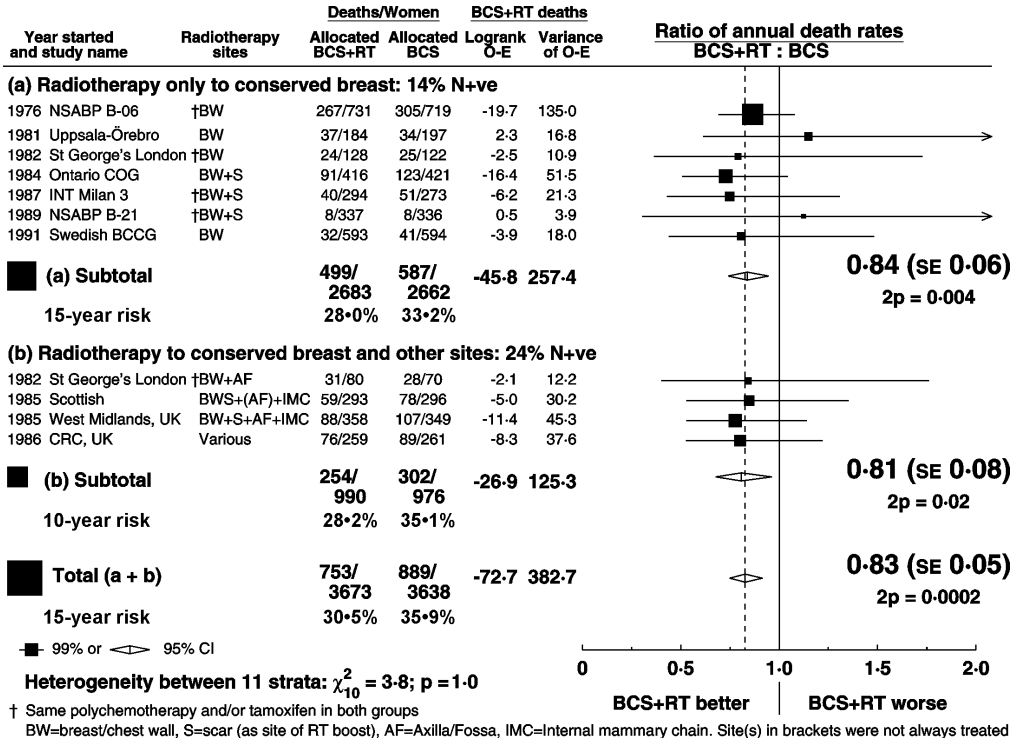


Figure 1: Effect of radiotherapy (RT) after BCS (ten trials) on local recurrence and on breast cancer mortality— event rate ratios.

O–E=observed–expected. 99% CIs are given for trial-specific results (black squares) and 95% CIs are given for subtotals and totals (white diamonds).

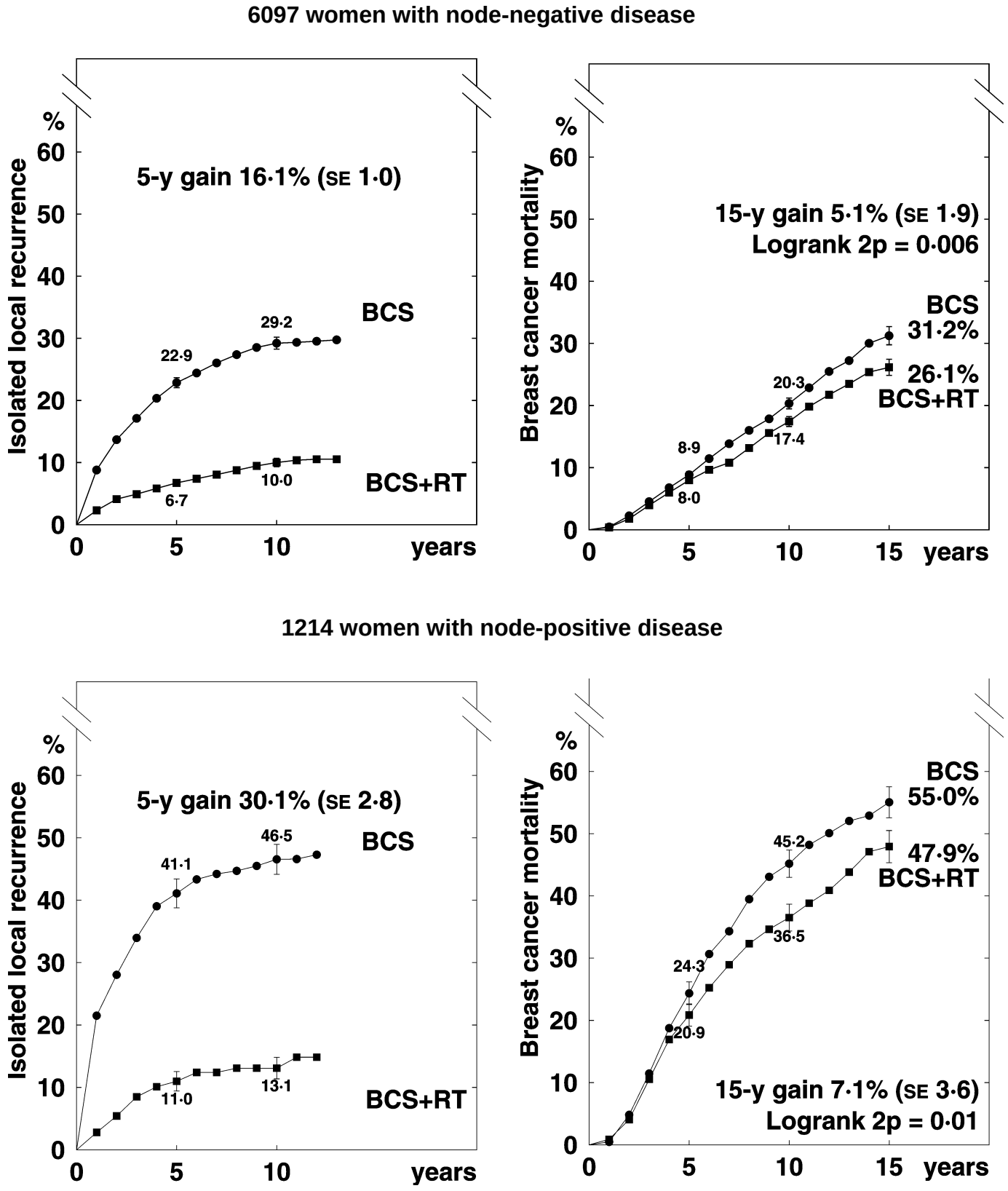


Figure 2: Effect of radiotherapy (RT) after BCS on local recurrence and on breast cancer mortality—15-year probabilities

Data from 10 trials. Vertical lines indicate 1 SE above or below the 5, 10, and 15 year percentages.

recurrence is 7% among those allocated radiotherapy and 26% among those not, corresponding to an absolute reduction of 19% in this 5-year risk.

The proportional risk reduction for breast cancer mortality is much less extreme than that for local recurrence, and none of the trial-specific breast cancer mortality results is clearly significant on its own (as each of the 99% CIs overlaps unity). The total result at the bottom of figure 1 is, however, highly significant (breast cancer death rate ratio 0·83, SE 0·05, 95% CI 0·75–0·91, 2p=0·0002), indicating a reduction of about one-sixth in the annual breast cancer mortality rate. The 15-year risk of death from breast cancer (in the hypothetical absence of other causes) is 30·5% among those allocated post-BCS radiotherapy and 35·9% among those not (corresponding to an absolute reduction of 5·4%, SE 1·7). The similarity of the subtotals (a) and (b) in the upper part of figure 1 is because all of the effect in (a), and much of that in (b), is from irradiating the conserved breast, and the clear reduction in breast cancer mortality given in the total (a+b) at the foot of figure 1 shows the effectiveness of breast irradiation in these patients.

The total results in figure 1 for local recurrence and for breast cancer mortality are plotted in figure 2 by year since randomisation, separating node-negative and node-positive disease. The 5-year risk of local recurrence is substantially bigger in node-positive disease, as is the absolute reduction in this recurrence risk (ie, the 5-year gain: figure 2). The absolute reduction in breast cancer mortality also appears somewhat larger for women with node-positive disease, but the numbers are too small for this finding to be statistically reliable.

Radiotherapy after mastectomy and axillary clearance

Figure 3 gives the corresponding results for women with axillary clearance in the trials of post-mastectomy radiotherapy. In the majority of these trials radiotherapy was given to the chest wall and to the lymph nodes in the axilla, supraclavicular fossa, and internal mammary chain (webtable 1, webfigure 8).

For women with node-negative disease, the 5-year local recurrence risk after mastectomy and axillary clearance was only 6% even in the absence of radiotherapy. Although radiotherapy reduces it to 2% (2p=0·0002), the absolute 5-year gain is only 4% and there is no significant reduction in 15-year breast cancer mortality (indeed, there appears if anything to be a slight increase, but the numbers of events are small).

By contrast, for women with node-positive disease the 5-year local recurrence risk after mastectomy and axillary clearance is 23% in the absence of radiotherapy, which is substantial, and radiotherapy reduces it to 6%. Therefore, although the proportional reduction in the local recurrence rate produced by radiotherapy is similar in node-positive disease and in node-negative disease, the absolute 5-year gain is much larger (17%). In node-positive disease the 15-year breast cancer mortality with and without post-mastectomy radiotherapy is 54·7% versus 60·1%, an absolute reduction of 5·4% (SE 1·3, 2p=0·0002).

This analysis of the effects of post-mastectomy radiotherapy in node-positive disease is limited to the 8500 women who had had axillary clearance. Its findings for local recurrence and for breast cancer mortality would not have been materially altered, however, by inclusion of the additional 2500 women who had had only axillary sampling, or no axillary surgery (webfigure 8b). In every large trial of post-mastectomy radiotherapy in women with node-positive

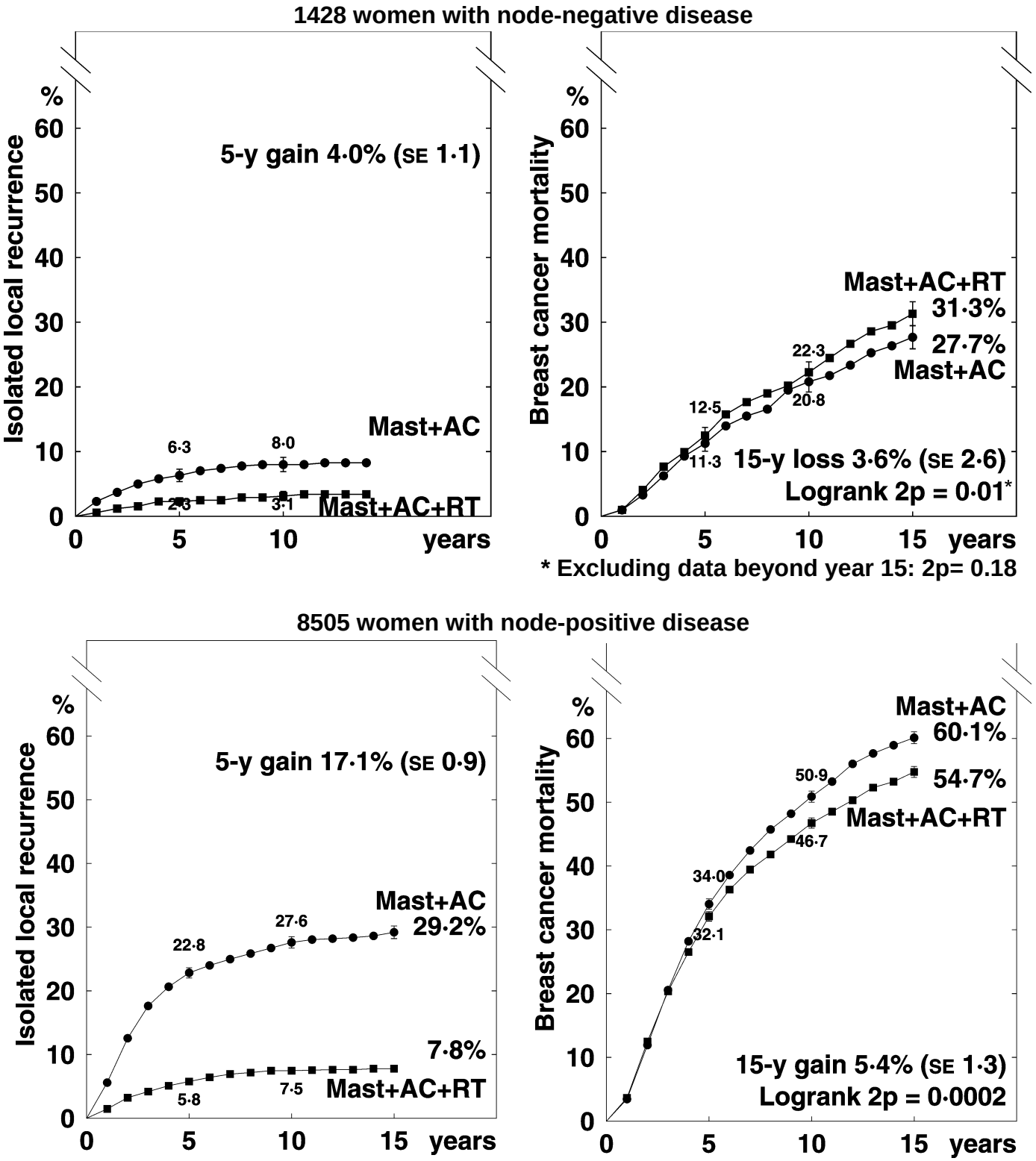


Figure 3: Effect of radiotherapy (RT) after mastectomy and axillary clearance (AC) on local recurrence and on breast cancer mortality—15-year probabilities
Data from 25 trials. Vertical lines indicate 1 SE above or below the 5, 10, and 15 year percentages.

disease there was a similar proportional reduction in local recurrence, showing that the radiotherapy regimens used in all the main trials, recent or

older, were of comparable efficacy in achieving local control (webfigure 8b). Hence, when assessing the relevance of local control to long-term breast cancer mortality, it is appropriate to consider the evidence from both recent and older trials.

Comparison of post-BCS and post-mastectomy radiotherapy trials

In the post-BCS radiotherapy trials, the site of local recurrence was generally available. When it was, over 90% (578 of 636) of the local recurrences among controls involved the conserved breast, as did over 90% of the effect of radiotherapy on local recurrence. In the post-mastectomy radiotherapy trials, the site of local recurrence was not generally available. However, little breast tissue remains after mastectomy, so the main effect of radiotherapy on local recurrence in these post-mastectomy trials must involve other sites, such as the chest wall or regional lymph nodes.

Coincidentally, the 5-year risks of local recurrence without radiotherapy, and the reduction in those risks produced by radiotherapy, were similar among women with node-negative disease in the post-BCS trials and among women with node-positive disease in the post-mastectomy trials (figure 2, upper panels, and figure 3, lower panels). The control 15-year breast cancer mortality was, of course, lower among women in the post-BCS trials (about 80% of whom had small tumours [greatest dimension 20 mm] and node-negative disease) than among women in the post-mastectomy trials with node-positive disease. For both, however, it was substantial, and for both the absolute reduction in breast cancer mortality with radiotherapy was about 5%. The apparent similarity of the absolute reductions in 15-year breast cancer mortality in these two types of radiotherapy trial after similar absolute reductions in 5-year local recurrence risk suggests that the effect on long-term survival of avoiding a recurrence in a conserved breast is approximately comparable with that of avoiding a recurrence at other locoregional sites.

Three categories of local treatment comparison

To examine the general relationship between the effects of local treatment differences on local recurrence and their effects on breast cancer mortality, all the treatment comparisons listed in table 1 were subdivided by nodal status, making a total of 24 such comparisons. These were then grouped arbitrarily into three categories according to the absolute reduction (<10%, 10–20%, or >20%) in the 5-year local recurrence risk. The 24 white squares and their 99% CIs in figure 4 display these absolute reductions in risk. (The length of the side of each white square is inversely proportional to the standard error of the absolute reduction.) The vertical broken lines correspond to absolute reductions of 10% and 20% in risk, and have been used as arbitrary cut-points to group these 24 types of comparison into three categories, according to the absolute reduction in this risk. These categories involve, respectively, 17 000, 20 000, and 5000 women, with mean absolute reductions of 1%, 17%, and 26% in the 5-year local recurrence risk.

Most of the substantial absolute reductions in local recurrence risk involved the addition of radiotherapy. (The others involved conservation of the breast or axilla [or both] without effective radiotherapy to the conserved tissue.)

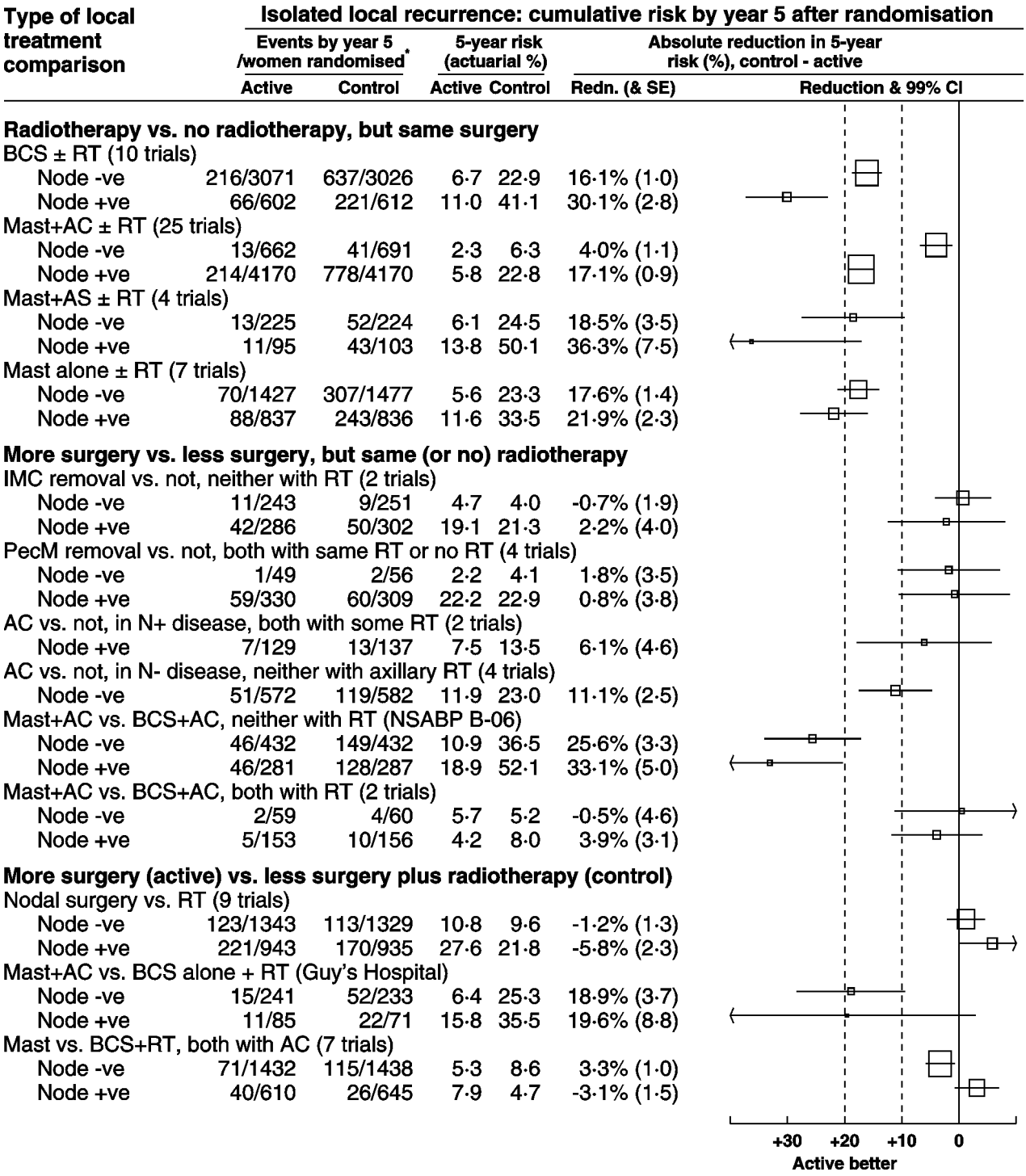


Figure 4: Absolute reduction in 5-year local recurrence risk—78 randomised comparisons grouped into 24 types of local treatment comparison, based on treatments compared and nodal status

RT=radiotherapy. AC=axillary clearance. AS=axillary sampling. IMC=internal mammary chain of lymph nodes.
*A few trials did not provide data on local recurrence, so in some comparisons numbers differ from table 1.

Furthermore, almost all the comparisons of radiotherapy versus no radiotherapy involved substantial absolute reductions in local recurrence; the one exception was that after mastectomy and axillary clearance in women with pathologically node-negative disease, the risk of local recurrence without

radiotherapy was so low that no large absolute reduction was possible (figures 3 and 4). In the lower part of figure 4 the four earliest trials (those starting during 1951–1970: webfigure 10) had high local recurrence risks despite radiotherapy. Omission of these early trials from subsequent analyses would make no material difference to the main conclusions.

Local control and long-term breast cancer mortality

The absolute reductions in breast cancer mortality that correspond to the three categories of local treatment comparison are shown in table 2. The differences in breast cancer mortality are greater at 15 years than at 5 years, and the 15-year differences in breast cancer mortality in the three categories are approximately proportional to the differences in 5-year local recurrence risk. The regression line through zero, relating the absolute effects on local recurrence to those on breast cancer mortality, suggests that a local treatment difference that reduces the 5-year local recurrence risk by 20% would reduce the 15-year breast cancer mortality by 5·2% (SE 0·8, 2p<0·00001).

Category of absolute reduction in 5-year local recurrence risk	Breast cancer mortality (%)			
	5-year risk	5-year absolute reduction	15-year risk	15-year absolute reduction
	Active vs control		Active vs control	
(a) <10% (mean 1%)	18.8 vs 19.5	0.6 (SE 0.6)	41.3 vs 42.3	1.0 (SE 0.9)
(b) 10-20% (mean 17%)	21.8 vs 23.3	1.5 (SE 0.6)	44.0 vs 48.5	4.5 (SE 0.8)
(c) >20% (mean 26%)	24.9 vs 26.7	1.8 (SE 1.3)	47.4 vs 53.4	6.0 (SE 1.6)
Subtotal (b+c) >10% (mean 19%)	22.4 vs 24.0	1.6 (SE 0.6)	44.6 vs 49.5	5.0 (SE 0.8)

Weighted regression line through zero relating mortality reduction to recurrence reduction: 5.2% (SE 0.8) absolute reduction in 15-year breast cancer mortality for 20% absolute reduction in 5-year local recurrence risk.

Table 2: Breast cancer mortality risks by time since randomisation and by category of absolute reduction in 5-year local recurrence risk (from figure 4)

A quantitatively similar conclusion can be obtained by combining the second and third categories (b and c in table 2), and analysing the resulting total of 25 000 women. Among them, treatment reduced the 5-year local recurrence risk by a mean of 19% and reduced the 15-year breast cancer mortality by 5·0% (SE 0·8, 2p<0·00001). The findings for these 25 000 women are plotted against time since randomisation in figure 5 (lower panels). The effect on local recurrence is substantial, and is seen rapidly; indeed, much of it is apparent within the first two or three years. In contrast, there is no apparent effect on

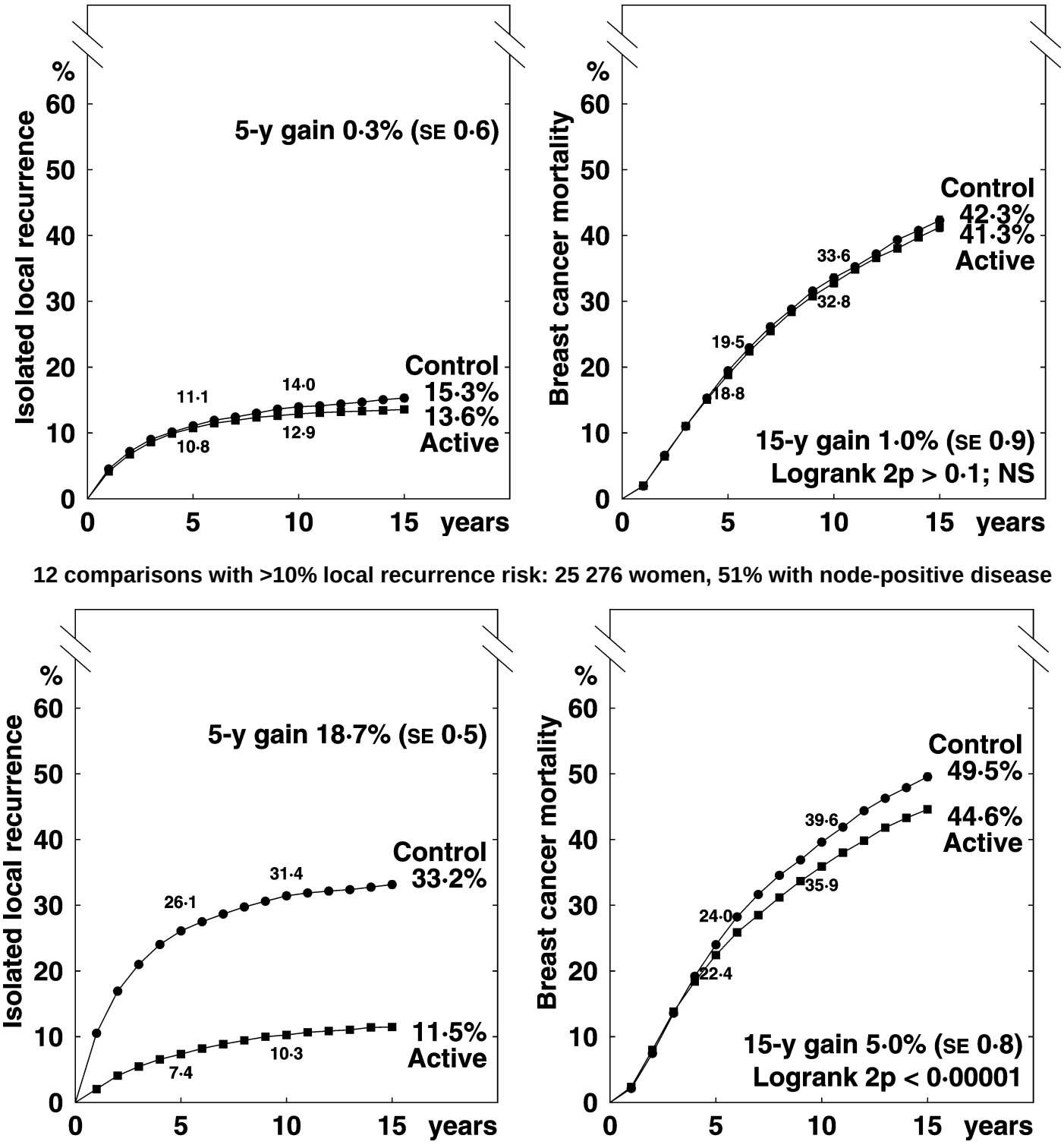


Figure 5: Local recurrence and breast cancer mortality for treatment comparisons that produce a less than 10% (upper panels) or more than 10% (lower panels) absolute reduction in 5-year local recurrence risk—15-year probabilities
Vertical lines indicate 1 SE above or below the 5, 10, and 15 year percentages.

breast cancer mortality within the first two or three years, although there is a moderate but definite effect on 15-year breast cancer mortality. Most of these

25 000 women were in trials of radiotherapy and half had node-negative disease, so the results for them are intermediate between those for post-BCS radiotherapy in node-negative disease (figure 2, upper panels) and post-mastectomy radiotherapy in node-positive disease (figure 3, lower panels).

Further details of these comparisons are given on the website (webtable 4, webfigures 3–6). For the treatment comparisons involving more than a 10% reduction in local recurrence risk, logrank analyses by period of follow-up provide formal confirmation that the main reduction in local recurrence occurs during just the first few years. By contrast, for breast cancer mortality there is no material effect during years 0–2. Subsequently, however, there are highly significant reductions in breast cancer mortality: 2p<0·00001 during each of the time periods 3–4 years and 5–9 years, and 2p=0·0003 during the time period 10–14 years after randomisation. After year 15, however, there is no evidence of any further gain (or loss of the earlier gain) in breast cancer mortality (webfigure 6c). Among those of the 25 000 women who survived to year 15, the ratio, treatment versus control, of the annual breast cancer mortality rates in subsequent years was 1·03, SE 0·08.

Tests of heterogeneity

For each of the three categories of treatment comparison in table 2, webfigure 4 shows the breast cancer mortality ratios (treatment versus control) separately during the first 5 years after randomisation and in later years, giving a total of six mortality ratios. For none of these six mortality ratios is there any significant heterogeneity between the contributions to it from different types of treatment comparison (webfigure 5). Moreover, the sum of the six heterogeneity test statistics (χ^2_{42}=41·2, p=0·5) provides no significant evidence of heterogeneity between the proportional effects on breast cancer mortality of local treatments that have similar absolute effects on local recurrence risks. Such overall tests of heterogeneity with many degrees of freedom are, however, not very sensitive to any real heterogeneity that might exist. A more relevant observation is that in 3 quite different circumstances the avoidance of local recurrence (mainly during the first 5 years) appeared to be of comparable relevance to breast cancer mortality (mainly after the first 5 years): (i) in the trials of post-BCS radiotherapy; (ii) in those of post-mastectomy radiotherapy; and (iii) in the aggregated results from the trials of breast conservation or axillary conservation without effective radiotherapy to the conserved tissue (total logrank O–E –28·9 [15·75·18·1] with variance 145·2, breast cancer mortality ratio 0·82, SE 0·08, 2p=0·02; webfigure 5).

Subgroup analyses

Analyses of selected treatment comparisons in subgroups of age and of tumour characteristics (grade, size, ER status, and amount of nodal involvement, where avail-able) are given in webfigure 6. Any apparent differences or similarities between the subgroup-specific treatment effects are likely to be much more trustworthy for local recurrence than for breast cancer mortality, because differences in local treatment can have such large effects on local recurrence rates. For women with node-negative disease in the trials of radiotherapy after BCS (web-figure 6a), and for women with node-positive disease in the trials of radiotherapy after mastectomy and axillary clearance (webfigure 6b), radiotherapy produced similar *proportional* reductions in local recurrence risk, irrespective of age, tumour grade, tumour size, ER status, or

amount of nodal involvement. Consequently, within each subgroup the *absolute* benefit produced by radiotherapy was determined principally by the magnitude of the local recurrence risk in unirradiated women.

Age

Table 3 gives 5-year local recurrence risks for various subgroups in the trials of radiotherapy after BCS (generally with axillary clearance) in node-negative disease and in the trials of radiotherapy after mastectomy and axillary clearance in node-positive disease. In the former, most local recurrences are in the conserved breast, and the 5-year risk of such recurrence in the breast is known to be about twice as great in younger as in older women.[22–25] Hence, the absolute effects of post-BCS radiotherapy on local recurrence (mainly in the conserved breast) were greater in younger than in older women (5-year risk reductions of 22%, 16%, 12%, and 11% for those aged <50, 50–59, 60–69, and ≥70 years respectively; test for trend in absolute benefits 2p=0·00002). By contrast, there was no trend with age in the 5-year risks of local recurrence (mainly in the chest wall or lymph nodes) among women with mastectomy, axillary clearance, and node-positive disease. Hence, the absolute effects of post-mastectomy radiotherapy on the risk of such local recurrence were also approximately independent of age (local recurrence reductions of 17%, 18%, and 18% for women aged <50, 50–59, and 60–69 years respectively; there were few older women in these trials).

Tumour characteristics

In both types of trial, the 5-year local recurrence risk without radiotherapy was higher, and the absolute reduction in this risk from radiotherapy was correspondingly greater, in women with tumours that were large or with direct extension to the skin or chest wall (T2/T3/T4 tumours) or poorly differentiated, but there was little relevance of ER status to these risks. For women with mastectomy, axillary clearance, and node-positive disease, the number of involved nodes (1–3 or ≥4) was unavailable for more than half the women (webfigure 6b). Where it was available, the 5-year local recurrence risks, irradiated versus control, were 4% versus 16% for women with one to three involved nodes (reduction 12%, SE 2) and 12% versus 26% for women with four or more involved nodes (reduction 14%, SE 2; table 3). The 15-year local recurrence reductions differed more substantially, however, and were 14% and 20% for women with one to three and for those with four or more involved nodes, respectively (webfigures 2d and 2e).

Systemic therapy

In trials of systemic therapy,[20] 5 years of tamoxifen reduced the local recurrence rate by about one half in women with ER-positive disease (local recurrence rate ratio 0·47, SE 0·08) and, irrespective of ER status, polychemotherapy reduced it by about one third (ratios 0·63, SE 0·08, and 0·70, SE 0·05, for women aged 50 and 50–69 years, respectively); webfigures 9R, 4aR, 4bR in the recent EBCTCG report[20] on systemic therapy.

The local treatment comparisons that produced more than a 10% absolute reduction in 5-year local recurrence risk were, however, effective in the presence or in the absence of systemic therapy (ie, of chemotherapy or

Characteristics (where known*)	5-year local recurrence risk (%) in trials of: (a) BCS ± RT node-negative		(b) Mast+AC ± RT node-positive	
	Radiotherapy vs control	Absolute reduction (SE)	Radiotherapy vs control	Absolute reduction (SE)
Age (years)				
< 50	11 vs 33	22 (2)	6 vs 23	17 (1)
50 – 59	7 vs 23	16 (2)	6 vs 24	18 (2)
60 – 69	4 vs 16	12 (1)	5 vs 23	18 (2)
70+	3 vs 13	11 (2)	-	-
Tumour grade				
Well differentiated	4 vs 14	10 (2)	4 vs 22	18 (3)
Moderately differentiated	9 vs 26	17 (2)	4 vs 30	26 (2)
Poorly differentiated	12 vs 34	22 (3)	6 vs 40	34 (4)
Tumour size (T category)				
1-20 mm (T1)	5 vs 20	15 (1)	5 vs 22	17 (2)
21-50 mm (T2)	14 vs 35	21 (3)	6 vs 30	24 (2)
>50 mm (T3) or T4[†]	-	-	8 vs 36	28 (4)
ER status				
ER-poor	12 vs 30	18 (3)	8 vs 28	20 (2)
ER-positive	6 vs 25	19 (2)	6 vs 24	18 (2)
Number of involved nodes				
1-3	-	-	4 vs 16	12 (2)
4 or more	-	-	12 vs 26	14 (2)
All women	**7 vs 23**	**16 (1)**	**6 vs 23**	**17 (1)**

*Annex-figures 6a and 6b give more details, including separate results for those where the relevant characteristic is not known. [†]T4: tumour of any size with direct extension to skin or chest wall

Table 3: Effects of age and tumour characteristics on 5-year risks of local recurrence in trials of radiotherapy (RT) (a) after BCS in women with node-negative disease and (b) after mastectomy and axillary clearance (AC) in women with node-positive disease

tamoxifen [or both] to both trial groups, or to neither). Among the women who received systemic therapy, the mean absolute reduction in 5-year local recurrence risk was 20% (8% vs 28%, webfigure 6c), and the 15-year reduction in breast cancer mortality was 5·9% (SE 1·2; 49·1% vs 55·1%: 2p<0·00001). Thus, better local treatment adds to the effects of systemic therapy on local recurrence and on breast cancer mortality.

Four-to-one ratio of absolute effects

Although in the present analyses subgroup-specific results derived for local recurrence might well be fairly reliable (as the effects of local treatment on local recurrence can be so extreme), subgroup-specific results for breast cancer mortality might well not be. Hence, unduly selective emphasis on particularly favourable or unfavourable mortality results from particular subgroups or particular trials, or even from particular types of treatment

comparison, could give rise to misleading over-estimation or under-estimation of the real relevance of local disease control to long-term breast cancer mortality. Instead, the most reliable estimate of the effect on breast cancer mortality of a particular local treatment comparison in particular subgroups of women might come not from the apparent results for breast cancer mortality in those subgroups, but from estimating the effect of that treatment comparison on local recurrence risk in those subgroups, and then applying the general finding that a 20% absolute reduction in 5-year local recurrence risk leads to about a 5% absolute reduction in 15-year breast cancer mortality (ie, a four-to-one ratio of absolute effects).

Diseases other than the original breast cancer

Table 4 shows the incidence of second cancers and of mortality from causes other than breast cancer in all the trials in table 1 that tested radiotherapy (ie, all trials of radiotherapy vs not [with the same surgery] and all trials of more surgery vs radiotherapy [with active and control reversed]). There was an excess cancer incidence among women allocated radiotherapy that mainly involved contralateral breast cancer (2p=0·002) and lung cancer (2p=0·0007), and there was an excess mortality from causes other than breast cancer that mainly involved heart disease (2p=0·0001) and lung cancer (2p=0·0004). Based on much smaller numbers, there was also a moderately significant excess mortality from pulmonary embolism and excess incidence of oesophagus cancer, leukaemia and soft tissue sarcoma.

The effects of these radiotherapy regimens on contralateral breast cancer and on mortality from causes other than breast cancer are plotted against time since randomisation in webfigure 7. The averaged effects on 15-year outcome are not large (9·3% vs 7·5% for contralateral breast cancer, 15·9% vs 14·6% for non-breast-cancer mortality), but they may well vary substantially from one regimen to another, and the absolute 15-year mortality differences could also depend strongly on tumour laterality (which can affect cardiac radiation dose), smoking habits (which affect both vascular and lung cancer risks), other vascular risk factors, and, particularly, on age.

The excess of contralateral breast cancer with radiotherapy appears mainly during the period 5–14 years after randomisation (table 4, webfigure 7) and is significant even among women aged 50 years or older when randomised (table 4). When the excess mortality from causes other than breast cancer is subdivided by time since randomisation, the proportional excess again appears to be less during the first 5 years than in subsequent years, but it is separately significant for the periods 5–14 years and 15 years or more after randomisation. The mean dates of randomisation for those who died 5–14 years and 15 years or more after randomisation were, however, 1975 and 1970, respectively, and the radiotherapy regimens of the early 1970s may well have involved greater hazards than many current regimens. The excess mortality from causes other than breast cancer is significant both for women younger than 50 years of age and for women older than 50 years of age when randomised (2p=0·02 for both), but the CIs for the age-specific risks are wide. The numbers are not sufficient for the main hazards (contralateral breast cancer, lung cancer, or heart disease) to be reliably subdivided by both follow-up duration and age.

Cause of death or site of cancer (ICD-9 categories)	Events	Logrank O-E*	Variance of (O-E)	Ratio of rates†	2p
Incidence of contralateral breast cancer:					
- by years since randomisation (and, for cases, mean year of randomisation)					
0-4 (1980)	673	1.3	161.1	1.01 (0.08)	0.9
5-14 (1980)	627	53.5	150.2	1.43 (0.10)	0.00001
15+ (1975)	151	2.1	33.4	1.06 (0.18)	0.7
- by age at randomisation					
<50	600	11.7	143.0	1.09 (0.09)	0.3
50+	851	45.1	201.3	1.25 (0.08)	0.002
- by use of systemic therapy					
with chemotherapy or tamoxifen	649	21.7	158.0	1.15 (0.09)	0.08
without chemotherapy or tamoxifen	802	35.1	186.4	1.21 (0.08)	0.01
Total contralateral breast cancer	**1451**	**56.9**	**344.4**	**1.18 (0.06)**	**0.002**
Incidence of other specified cancers: ‡					
Lung cancer (162)	215	24.3	51.1	1.61 (0.18)	0.0007
Oesophagus cancer (150)	31	5.4	7.5	2.06 (0.53)	0.05
Leukaemia (204-208)	59	7.5	13.9	1.71 (0.36)	0.04
Soft-tissue sarcoma (158, 171)	26	5.4	6.4	2.34 (0.62)	0.03
Thyroid cancer	26	-2.3	6.2	0.69 (0.34)	0.4
Bone cancer	28	1.7	6.9	1.28 (0.43)	0.5
Other specified malignancy	966	16.4	220.7	1.08 (0.07)	0.3
Total other specified cancers	**1351**	**58.4**	**312.7**	**1.20 (0.06)**	**0.001**
Mortality before recurrence from causes other than breast cancer:					
- by cause					
Circulatory disease	**1510**	**77.6**	**345.4**	**1.25 (0.06)**	**0.00003**
Heart disease, etc §	1106	60.7	252.7	1.27 (0.07)	0.0001
Stroke	345	9.1	80.9	1.12 (0.12)	0.3
Pulmonary embolism	59	7.8	11.8	1.94 (0.41)	0.02
Other specified cause	**1455**	**6.4**	**335.8**	**1.02 (0.06)**	**0.7**
Lung cancer	156	21.7	37.5	1.78 (0.22)	0.0004
Oesophagus cancer	23	4.9	5.6	2.40 (0.68)	0.04
Leukaemia	31	2.4	7.0	1.40 (0.45)	0.4
Soft-tissue sarcoma (158, 171)	7	1.3	1.7	2.13 (1.14)	0.3
Respiratory disease (460-519, 786)	241	-1.0	55.5	0.98 (0.13)	0.9
Other known cause	997	-22.9	228.5	0.90 (0.06)	0.1
Unspecified cause, not breast cancer	**701**	**7.8**	**159.4**	**1.05 (0.08)**	**0.5**
- by years since randomisation (and, for deaths, mean year of randomisation)					
0-4 (1976)	756	7.4	176.4	1.04 (0.08)	0.6
5-14 (1975)	1513	37.7	348.4	1.11 (0.06)	0.05
15+ (1970)	1397	46.9	304.8	1.17 (0.06)	0.01
- by age at randomisation					
<50	554	27.4	129.6	1.24 (0.10)	0.02
50+	3112	64.4	699.8	1.10 (0.04)	0.02
Total non-breast-cancer deaths ‖	**3666**	**91.8**	**829.4**	**1.12 (0.04)**	**0.001**

*Approximate excess number of events in radiotherapy group is 2(O-E). †Ratio of annual event rates (and its standard error), irradiated vs unirradiated, estimated from O-E and its variance V as exp([O-E]/V).[20] ‡Primary cancers of all specified sites (140-194, 200-208) except non-melanoma skin (173) and breast. Includes RT vs not; 3 vs 2 thyroid cancer (193), 1 vs 0 bone cancer (170). §All circulatory (390-459, 785, 798) except stroke (430-438) and pulmonary embolism (415, 451, 453, 673). ‖The analyses in this table (and in the corresponding webfigure 7) are stratified by only 2 groups of age; had they been stratified by 5 age-groups, as in the main analyses, and the node-negative patients from 80 Y Edinburgh appropriately removed (see footnotes "added in proof" to annex-tables 2 & 3), these mortality results would have been only very slightly more extreme (eg, for total non-breast cancer deaths the logrank O-E would have been 93.4 with variance 789.2, rate ratio 1.126 SE 0.04, 2p=0.0009).

Table 4: Effect of radiotherapy on incidence of second cancers before recurrence of breast cancer, and on mortality from causes other than breast cancer (23 500 women in 46 trials of adding radiotherapy, and 9300 in 17 trials of radiotherapy vs more surgery)

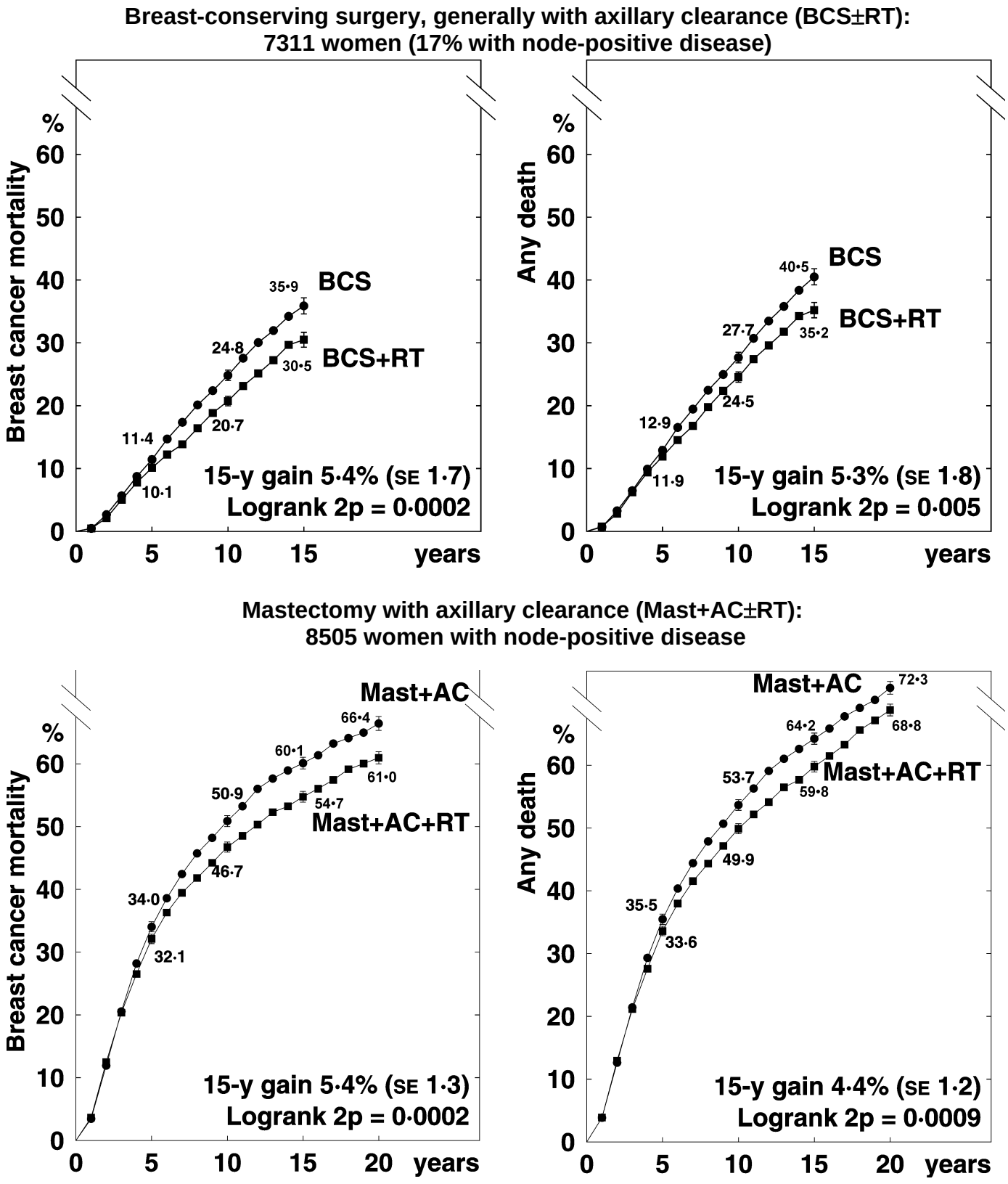


Figure 6: Effect of radiotherapy (RT) on breast cancer mortality and on all-cause mortality after BCS or after mastectomy with axillary clearance (AC)—15-year or 20-year probabilities

Vertical lines indicate 1 SE above or below the 5, 10, and 15 year percentages.

Results of similar analyses of the trials of more versus less surgery indicate no significant effect of more surgery on non-breast-cancer mortality (mortality ratio 1·11, SE 0·09).

Overall mortality in radiotherapy trials

Figure 6 compares, for the two main radiotherapy analyses, the effects on breast cancer mortality with the effects on overall mortality. In the post-BCS radiotherapy trials the absolute reduction in 15-year overall mortality is about as large as that in 15-year breast cancer mortality. For these post-BCS trials there is as yet, however, little follow-up beyond year 15—indeed, many women have not yet been followed to year 15. In the trials of radiotherapy after mastectomy and axillary clearance in node-positive disease, the reduction in 15-year all-cause mortality is 4·4% (SE 1·2, 64·2% vs 59·8%, 2p=0·0009). This is less than the 5·4% reduction in 15-year breast cancer mortality. At 20 years, the reduction in breast cancer mortality remains unchanged at 5·4% (66·4% vs 61·0%), while that for all-cause mortality, although still significant, is only 3·5% (72·3% vs 68·8%), indicating a continuing excess of non-breast-cancer mortality long after treatment with the older radiotherapy regimens.

Discussion

Main findings

About three-quarters of the local recurrence risk (and more than three-quarters of any treatment effects on local recurrence) occurred during the first 5 years after randomisation. By contrast, more than half the 15-year breast cancer mortality (and much more than half of any such treatment effects on breast cancer mortality) occurred after the first 5 years. Some local treatment comparisons (eg, axillary clearance vs effective axillary radiotherapy; mastectomy vs BCS plus effective radiotherapy; post-mastectomy radiotherapy in node-negative disease) involved little (<10%) absolute difference in the 5-year risk of local recurrence and, in aggregate, these comparisons also involved little difference in 15-year breast cancer mortality (figure 5, upper panel).

Local recurrence and breast cancer mortality

The other local treatment comparisons are those that involved absolute differences of more than 10% in the 5-year risk of local recurrence (eg, post-BCS radiotherapy, mainly to the conserved breast; post-mastectomy radiotherapy in node-positive disease; conservation of the breast or axilla without effective radiotherapy to the conserved tissue). In the aggregate of all such comparisons, involving a total of 25 000 women, the 5-year local recurrence risks were 7% active versus 26% control (reduction 19%) and the 15-year breast cancer mortality risks were 44·6% versus 49·5% (reduction 5·0% SE 0·8, 2p<0·00001). Treatment comparisons that produced similar-sized effects on local recurrence tended to produce similar-sized effects on breast cancer mortality (webfigure 5). In particular, both for the 7300 women in trials of post-BCS radiotherapy (mostly with axillary clearance and pathologically node-negative disease) and for the 8500 women in trials of post-mastectomy radiotherapy after axillary clearance in node-positive disease, the absolute reductions in 5-year local recurrence and in 15-year breast cancer mortality were similar in magnitude to those in the aggregated

results in all 25 000 women, and were highly significant. This finding indicates that the avoidance of recurrence in a conserved breast and the avoidance of other local recurrence (eg, in the chest wall or regional lymph nodes) are of comparable relevance to 15-year breast cancer mortality. In these two particular radiotherapy comparisons, as in the aggregated results, differences in local treatment that substantially affect locoregional recurrence would, in the hypothetical absence of other causes of death, avoid about one breast cancer death over the next 15 years for every four such recurrences avoided. Moreover, even when it does not affect survival, avoiding a local recurrence can be of substantial benefit.

Non-breast-cancer mortality and overall mortality

The absence of other causes of death is, of course, not a realistic assumption, particularly for older patients. Even the general mortality that is not caused by breast cancer or its treatment makes the 15-year survival gain somewhat smaller for overall mortality than for breast cancer mortality (as it reduces, by a similar factor, the proportion of 15-year survivors in both the treatment group and the control group). Moreover, most of the substantial differences in local recurrence in these trials were produced by radiotherapy, and some of the radiotherapy regimens, at least in the older trials of post-mastectomy radiotherapy, appreciably increased mortality more than 5 years later from diseases other than breast cancer, with most of this excess mortality involving heart disease and lung cancer. In addition, this overview confirms the previous evidence[26,27] that radiotherapy can increase the incidence of contralateral breast cancer more than 5 years later, which would slightly reduce its net beneficial effect on 15-year breast cancer mortality. (We cannot ascertain from the present data whether therapeutic doses of radiation affect the incidence of new ipsilateral breast cancer in a conserved breast, as new and recurrent tumours are not separated.) Nevertheless, at least in the post-BCS radiotherapy trials, and among women with axillary clearance and node-positive disease in the post-mastectomy radiotherapy trials, the radiotherapy regimens that were tested produced moderate but definite reductions not only in 15-year breast cancer mortality but also in 15-year overall mortality (figure 6).

Further effects after year 15

The evidence as to what will happen after year 15 is still limited. Thus far, these trials have shown that the treatments that substantially reduced the 5-year local recurrence risk moderately reduced 15-year breast cancer mortality and 15-year overall mortality. They also suggest that there will be little additional gain or loss after year 15 in breast cancer mortality (ratio, treatment vs control, of annual breast cancer death rates during the period after year 15=1·03, SE 0·08: webfigure 3b). There is, however, evidence from the aggregate of all radiotherapy trials of a somewhat higher death rate during the period after year 15 from causes other than breast cancer (ratio, radiotherapy vs not, of annual non-breast-cancer death rates after year 15=1·17, SE 0·06), but the mean date of randomisation for those dying in this late period was 1970, and the late hazards could well be substantially lower for modern radiotherapy regimens than for those of the 1960s and 1970s.

Breast cancer mortality rates remain substantial throughout at least the second decade after diagnosis (and perhaps beyond) as does the incidence

of contralateral breast cancer, while lung cancer and heart disease rates increase with advancing age. If long-term follow-up of many of these trials is continued to 20 or more years, or even to 30 or more years, distinguishing between different causes of death (and, to the extent possible, between new and recurrent tumours in a conserved breast), the ensuing data will clarify substantially the long-term risks and benefits of the post-BCS radiotherapy regimens in these trials, as three-quarters of the women were still alive in the present analyses (table 1). It will also help clarify substantially the benefits and risks of both the older and the more recent post-mastectomy radiotherapy regimens in these trials.

Low and high local recurrence risks

Radiotherapy produces its greatest absolute effects on local recurrence in women who are at greatest risk of local recurrence (table 3, figures 2 and 3). For, whether the underlying risk is low or high, about 70% of it can be avoided by radiotherapy. In the trials of post-BCS radiotherapy, the risk of local recurrence among controls depended strongly on nodal status (5-year risks: 23% node-negative, 41% node-positive) and, among those with node-negative disease, young age, poor tumour differentiation, and large tumour size all indicated a high local recurrence risk (table 3). The large majority (78%) of the node-negative tumours in the post-BCS radiotherapy trials were small (1–20 mm in their longest diameter), but, even with such small tumours, without radiotherapy the 5-year risk of local recurrence was 20% (table 3).

In the trials of radiotherapy after mastectomy and axillary clearance, the 5-year risk of local recurrence among the controls depended strongly on the number of involved nodes, where this information was available (risks 6%, 16%, and 26% respectively for 0, 1–3, and ≥4 involved nodes). Among women with mastectomy, axillary clearance, and node-negative disease the absolute reduction in 5-year local recurrence risk after radiotherapy was only 4% (2% vs 6%), so if one death from the original breast cancer is avoided for every four local recurrences avoided, then the expected reduction in 15-year breast cancer mortality after radiotherapy would be only 1% (less the adverse effects of any increase in contralateral disease). Relatively few such women were randomised, however, and among them the apparent effect of radiotherapy on breast cancer mortality happened to be slightly unfavourable.

Only where the absolute effects of radiotherapy on local recurrence are substantial can they be used to help quantify any proportional relationship between effects on local control and on breast cancer mortality. Among all women with mastectomy, axillary clearance, and node-positive disease, the absolute effects of radiotherapy on the 5-year local recurrence risk were substantial (6% vs 23%), particularly if the tumour was poorly differentiated or large, and breast cancer mortality was correspondingly reduced. In these post-mastectomy trials, however, age was of little or no relevance to local recurrence (mainly in the nodes or chest wall), even though in the post-BCS trials age was of substantial relevance to local recurrence (mainly in the conserved breast): table 3.

Generalisability of findings

Changes in practice

There have been, and will continue to be, substantial changes in the use, or methods, of screening, surgery, pathology, radiotherapy, and systemic

adjuvant therapy since many of these trials began.[28–30] In particular, tumour sizes are generally smaller, systemic therapy is more effective, radiotherapy is less likely to be given to the internal mammary chain of lymph nodes or to a surgically-cleared axilla, and there has been increasing recognition of the late side-effects of radiotherapy and of the need when treating early breast cancer to limit doses to the heart and lungs. Hence, depending mainly on the doses to the heart, lungs, and contralateral breast, the late hazards of current and future radiotherapy regimens might well be much lower than those of the regimens studied in the older trials. Moreover, advances in early diagnosis, surgery, and systemic therapy mean that the 5-year risks of local recurrence might well be much less than in these trials. Nevertheless, some risk is likely to remain, since the desire to control local recurrence (after either BCS or mastectomy) has to be balanced not only against the late adverse effects but also against the cosmetic and functional effects of excessive local treatment.

Prediction of absolute risks and benefits

Prediction from these trials of the long-term risks of current radiotherapy regimens will depend on approximate comparison of current and previous radiation doses to the heart, lungs, etc, while prediction of the eventual effects on breast cancer mortality will depend on what the local recurrence risks would currently be without radiotherapy.

The absolute risks of local recurrence in these trials and the absolute benefits and hazards of radiotherapy in these trials cannot be generalised because of the continuing changes in practice since the trials began. Nevertheless, the quantitative relationship in these trials between local disease control and 15-year breast cancer mortality should still be relevant to current and future treatment decisions. Where it is possible to estimate the absolute risk of a particular type of local recurrence after a particular type of surgery, it is also possible to estimate the absolute reduction in this risk that effective radiotherapy would achieve (as radiotherapy avoids about 70% of the risk of recurrence in the irradiated sites) or that would have been avoided by more extensive surgery (as surgery eliminates the possibility of recurrence in the excised tissue). From the absolute reduction in local recurrence the absolute reduction in breast cancer mortality can be inferred.

For example, if additional local treatment led to an estimated reduction in the 5-year local recurrence risk of, say, about 12% then, from the general four-to-one relationship between effects on local recurrence and on breast cancer mortality, it could reasonably reliably be inferred that the 15-year reduction in breast cancer mortality would be about 3%, even though directly randomised proof of such a small mortality difference would be difficult to obtain.

Combination of effects of local and systemic therapy

Likewise, as the risk of recurrence in a conserved breast is about twice as great in younger as in older women, it could reasonably reliably be inferred that radiotherapy to a conserved breast (or, in the absence of radiotherapy, mastectomy rather than BCS) would have a correspondingly greater effect on breast cancer mortality in younger than in older women, even though the age-specific subgroup analyses of mortality have wide confidence intervals (webfigure 6a). Furthermore, avoidance of death from breast cancer gains more additional years of life expectancy for younger than for older women.

Systemic therapy can approximately halve the 5-year risks of both local and distant recurrence.[20] In the absence of radiotherapy, the risk of local recurrence, although reduced by surgery and systemic therapy, may still be substantial. If it is, then addition of radiotherapy (or in some cases more extensive surgery) would further reduce it by a substantial amount and thereby further reduce 15-year breast cancer mortality by a moderate amount.[10–12,31,32] Indeed, webfigure 6c suggests that the relationship between local control and breast cancer mortality is much the same with or without systemic therapy. This conclusion may be of general validity, even though it is based on the methods of local control and types of systemic therapy studied in these particular trials. If so, the moderate differences in 15-year breast cancer mortality produced by better local control can be combined with the moderate differences produced by chemotherapy and hormonal therapy (and, probably, by newer systemic therapies), yielding in total quite substantial effects on 15-year breast cancer mortality. Hence, although for the addition of radiotherapy (or for other ways of improving local control) the effects on breast cancer mortality are only moderate, several such moderate reductions in mortality (from earlier diagnosis, from improvements in local control, from the introduction of systemic therapy, and from progressive changes in its efficacy) may, in combination, approximately halve a middle-aged patient's 15-year risk of death from breast cancer. In some countries the introduction of several such improvements in diagnosis or treatment has, in aggregate, already led to substantial reductions since 1990 in the national breast cancer mortality rates in middle age.[20]

Conclusion

The main purpose of the present overview is to help predict the effects of different treatment strategies on long-term survival. It makes no treatment recommendations, nor does it assess the costs or the functional, cosmetic, or psychological effects of different treatments. In early breast cancer, local treatments that substantially improve local control have little effect on breast cancer mortality during the first few years, but have definite, although moderate, effects by 15 years, and avoidance of local recurrence in a conserved breast and elsewhere are of comparable relevance to 15-year breast cancer mortality. These trials of radiotherapy and of the extent of surgery show that, in the hypothetical absence of other causes of death, about one breast cancer death over the next 15 years would be avoided for every four local recurrences avoided. Although the management of early breast cancer continues to change, it is reasonable to assume that this approximate four-to-one relationship will continue to apply and will still be of relevance to future treatment choices.

Contributors

The main contributors are the individuals or collaborative groups who undertook, or are now continuing follow-up of, the trials that are reviewed, and who provided trial data or other relevant information (including comments on previous versions of the manuscript). Acting on their behalf, the EBCTCG secretariat (M Clarke, R Collins, S Darby, C Davies, P Elphinstone, V Evans, J Godwin, R Gray, C Hicks, S James, E MacKinnon, P McGale, T McHugh, R Peto, C Taylor, Y Wang) accept full responsibility for the overall content of this report on the data provided and on the other relevant information received. S Darby, P McGale, R Peto, and C Taylor also accept responsibility for the data and information provided on the trials of local treatments being accurately reported on the study website.

Conflict of interest statement
The secretariat declare that they all have no conflict of interest.

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