EFFECTS OF RADIOTHERAPY AND SURGERY IN EARLY BREAST CANCER

An Overview of the Randomized Trials

EARLY BREAST CANCER TRIALISTS' COLLABORATIVE GROUP*

Abstract *Background.* Randomized trials of radiotherapy and surgery for early breast cancer may have been too small to detect differences in long-term survival and recurrence reliably. We therefore performed a systematic overview (meta-analysis) of the results of such trials.

Methods. Information was sought on each subject from investigators who conducted trials that began before 1985 and that compared local therapies for early breast cancer. Data on mortality were available from 36 trials comparing radiotherapy plus surgery with the same type of surgery alone, 10 comparing more-extensive surgery with less-extensive surgery, and 18 comparing more-extensive surgery with less-extensive surgery plus radiotherapy. Information on mortality was available for 28,405 women (97.4 percent of the 29,175 women in the trials).

Results. The addition of radiotherapy to surgery resulted in a rate of local recurrence that was three times lower than the rate with surgery alone, but there was no significant difference in 10-year survival; among a total of 17,273 women enrolled in such trials, mortality was 40.3 percent with radiotherapy and 41.4 percent without radiotherapy (P = 0.3). Radiotherapy was associated with a reduced risk of death due to breast cancer (odds ratio, 0.94; 95 percent confidence interval, 0.88 to 1.00; P = 0.03), which indicates that, after 10 years, there would

be about 0 to 5 fewer deaths due to breast cancer per 100 women. However, there was an increased risk of death from other causes (odds ratio, 1.24; 95 percent confidence interval, 1.09 to 1.42; P = 0.002). This, together with the age-specific death rates, implies, after 10 years, a few extra deaths not due to breast cancer per 100 older women or per 1000 younger women. During the first decade or two after diagnosis, the excess in the rate of such deaths that was associated with radiotherapy was much greater among women who were over 60 years of age at randomization (15.3 percent vs. 11.1 percent [339 vs. 249 deaths]) than among those under 50 (2.5 percent vs. 2.0 percent [62 vs. 49 deaths]). Breast-conserving surgery involved some risk of recurrence in the remaining tissue, but no significant differences in overall survival at 10 years were found in the studies of mastectomy versus breast-conserving surgery plus radiotherapy (4891 women), more-extensive surgery versus less-extensive surgery (4818 women), or axillary clearance versus radiotherapy as adjuncts to mastectomy (4370 women).

Conclusions. Some of the local therapies for breast cancer had substantially different effects on the rates of local recurrence — such as the reduced recurrence with the addition of radiotherapy to surgery — but there were no definite differences in overall survival at 10 years. (N Engl J Med 1995;333:1444-55.)

I N 1990, we requested information on each woman randomly assigned to treatment in any trial that began before 1985 and compared treatments for early breast cancer (i.e., breast cancer in which all clinically apparent disease can be removed surgically). Hormonal and cytotoxic therapies definitely improved 10-year survival,[1-3] but radiotherapy did not, perhaps because moderate protection was counterbalanced by a moderate increase in risk.[4,5] From 1992 through 1994, further information was sought from the organizers of the trials of radiotherapy and the trials of surgery about the details of the treatments that were compared and the causes of any deaths among women in whom breast cancer had not recurred. This overview of the trials compares the effects of these local therapies for early breast cancer on mortality and on rates of recurrence. For the most part, the studies compared radiotherapy plus surgery with the same type of surgery alone, more-extensive with less-extensive surgery, or more-extensive surgery with less-extensive surgery plus radiotherapy.

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METHODS

The procedures for identifying trials and checking data have been described previously.[1-3] Data on age, menopausal status, nodal status, and treatment assignment were sought for each woman (including patients entered later into trials begun before 1985). Dates of randomization, second primary cancer in the contralateral breast, first recurrence, first distant recurrence, and last known vital status were also sought. Causes of death were sought only for those who died without a recorded recurrence of breast cancer. After extensive checks for consistency, various tabulations and data listings (together with any queries) were sent back to the original trialists for them to review and correct. As a final check, a draft of this report was circulated for comment to all whose trial results were incorporated and the manuscript was revised in response to their suggestions and criticisms.

Statistical Analysis

Some comparisons are illustrated by pairs of survival curves, but others involve odds reductions (or, equivalently, odds ratios; an odds ratio of 0.9 implies an odds reduction of 10 percent). A persistent 10 percent reduction in the annual odds of death would eventually, when about half the subjects had died, produce a survival difference of about 4 percent (for example, 46 percent instead of 50 percent mortality).[1] Likewise, a persistent annual odds reduction of 5 percent would eventually produce a difference of about 2 percent in the absolute risk of death.[1] Two-sided P values are reported.

The main statistical methods we used for combining information from different trials are described elsewhere.[1-3] Analyses were conducted on an intention-to-treat basis.[6,7] Crude unstratified totals are provided for descriptive purposes, but in the main analyses we have adapted log-rank methods for analyses of cause-specific mortality (deaths from all causes, from breast cancer, and from causes other than breast cancer) and of the site of the first recurrence (any, isolated local, or other). Within each trial, the number of events observed in the group assigned to one treatment (O) is compared with the number of events that would be expected (E) if the probability of death were unrelated to treatment, a number that reflects the average expe-

rience of both treatment groups in that trial. The difference between the observed number and the expected number (O − E) and its variance yield the log-rank statistic for that one trial. Finally, the values for O − E from several different trials are simply added together to get an appropriately stratified overview of the results. To obtain the variance of this overall result, the separate variances are likewise summed. From these two totals, the odds ratio and its standard deviation can be calculated.[1-3] Because the number of possible statistical comparisons is large, conventional 95 percent confidence intervals are generally not reported. Instead, we have reported either 99 percent confidence intervals (to limit the number of false positive comparisons) or, more compactly, standard deviations.

Deaths attributed to causes other than breast cancer with no reported recurrence of breast cancer are described as "non–breast-cancer deaths," and all other deaths are described as "breast-cancer deaths"; the latter includes not only the deaths attributed to breast cancer but also deaths from unknown causes without reported recurrence and deaths from any cause after recurrence. These conventions necessitate the use of special statistical methods to avoid bias. These special methods compensate for the fact that if someone who would otherwise have had a recurrence of breast cancer before dying of an unrelated cause were to be given a treatment that had no effect on the time or cause of death but merely prevented the recurrence from preceding it, then instead of being categorized as due to breast cancer, that death would be recategorized as a "non–breast-cancer death."

For the log-rank analysis of mortality from all causes, O − E and its variance are calculated in the usual unbiased way, which ignores recurrences. However, to prevent delayed recurrences from biasing the analyses of cause-specific mortality, the log-rank analysis of non–breast-cancer mortality covers only the period before recurrence (i.e., data are censored at the first recurrence) and is therefore unbiased. Finally, an unbiased — although potentially diluted — log-rank analysis of breast-cancer mortality is obtained indirectly by subtracting the log-rank statistic for non–breast-cancer mortality from the log-rank statistic for mortality from all causes (i.e., the two observed values are subtracted from each other, the two expected values are subtracted from each other, and the two variances are subtracted from each other).

Table 1 lists three main types of unconfounded comparison (comparisons in which no aspects of management other than the treatments directly compared were affected by randomization): studies of radiotherapy plus surgery versus the same surgery alone, involving 17,273 women for whom data on mortality were available in 36 trials; studies of more-extensive surgery versus less-extensive surgery, involving 4818 women in 10 trials; and studies of more-extensive surgery versus less-extensive surgery plus additional radiotherapy, involving 9891 women in 18 trials. Appendix 2 describes these and other trials of local therapy.

Trials may appear more than once in Table 1. After the elimination of double counting, there were 29,175 women; 28,405 women (97 percent) from whom data on mortality were available and 770 (3 percent) without such data. Data on individual patients have been checked by the Secretariat for 26,258 of the 29,175 women (90 percent); less satisfactorily,[8] data on overall mortality were obtained from published reports for 2147 (7 percent).

RESULTS

Trials of Radiotherapy

The 36 trials of radiotherapy can be subdivided according to the type of surgery that was common to both groups, and the type of surgery influenced the type of radiotherapy that was tested (Fig. 1 and Appendix 2A). When both groups underwent full mastectomy, the trial radiotherapy included the axillary and supraclavicular fossa and usually also the chest wall and internal mammary chain. When surgery involved breast conservation, radiotherapy included the breast and chest wall (plus, in one study, the axilla), but no other sites.

Overall Mortality

Overall mortality was 40.3 percent with radiotherapy and 41.4 percent without it (Fig. 1), corresponding

Table 1. Randomized Trials of Local Therapy for Early Breast Cancer.

TYPE OF COMPARISON	NO. OF TRIALS	NO. OF WOMEN	NO. OF DEATHS
Radiotherapy plus surgery versus the same surgery alone			
Common surgery was mastectomy alone	5	4,541	2,642
Common surgery was mastectomy plus axillary sampling	4	3,286	817
Common surgery was mastectomy plus axillary clearance	23	6,378	2,936
Common surgery was breast conservation plus axillary clearance	4	3,068	629
Subtotal	36	17,273	7,024
More-extensive surgery versus less-extensive surgery			
Less extensive was radical or total mastectomy	5	2,090	1,062
Less extensive was simple mastectomy	4	1,296	805
Less extensive was breast-conserving surgery	1	1,432	497
Subtotal	10	4,818	2,364
More-extensive surgery versus less-extensive surgery plus radiotherapy			
Mastectomy versus breast conservation plus radiotherapy	9	4,891	1,120
Axillary clearance versus radiotherapy	8	4,370	2,396
Mastectomy plus axillary clearance versus conservation plus radiotherapy	1	630	428
Subtotal	18	9,891	3,944
Total available for analyses of mortality*	58	28,405	11,834
Total not yet available†	5	770	—

*This total (58 trials, not 64) avoids double counting and excludes the other comparisons of local therapy listed in Appendix 2D, which involved an additional 3358 women, of whom 1131 died, in 15 trials.

†The numbers known not to be available were as follows: mastectomy plus axillary clearance, with or without radiotherapy, two trials with a total of about 600 women; radical mastectomy versus simple mastectomy, one trial with 15 women; mastectomy versus breast-conserving surgery, one trial with 16 women; and mastectomy versus breast-conserving surgery plus radiotherapy, one trial with about 10 women.

to a nonsignificant reduction (±SD) of 2.6±2.5 percent in the odds of death. The reduction that is produced by radiotherapy in the odds of death appeared slightly larger after mastectomy with axillary sampling (Fig. 1b) (odds reduction, 14±7 percent) or after breast-conserving surgery (Fig. 1d) (odds reduction, 12±9 percent) than after mastectomy alone (Fig. 1a) (odds reduction, 3±4 percent) or after mastectomy with axillary clearance (Fig. 1c) (odds reduction, −3±4 percent [a negative number indicates an increase in the odds of death]). There is no significant heterogeneity, however, among these four subgroups — or among the 36 trials — and hence no good statistical evidence that radiotherapy helped in some surgical subgroups and not others. (Tests for heterogeneity, however, generally have low sensitivity.[3])

Figure 2 shows survival among the approximately 16,000 women in the 35 trials of radiotherapy for whom individual data on survival were collected, categorized according to nodal status. There was no statistically significant effect of radiotherapy in women with node-positive or node-negative cancer.

Non–Breast-Cancer Mortality

Data were available from 28 trials, involving 13,627 women, on causes of death among women who died without a recurrence of breast cancer. Of the 986 such deaths, 93 percent (918) were from known causes other
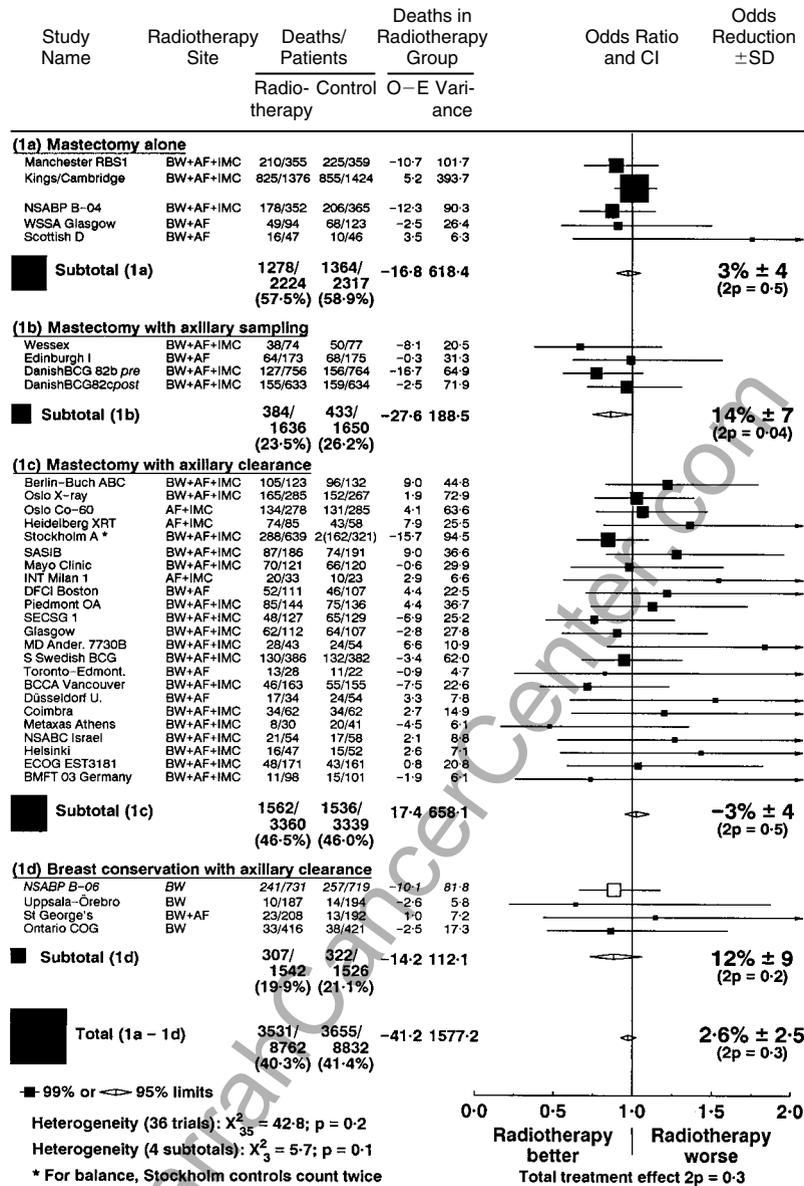
Study Name	Radiotherapy Site	Deaths/Patients Radio-therapy	Deaths/Patients Control	Deaths in Radiotherapy Group O−E	Deaths in Radiotherapy Group Variance	Odds Ratio and CI	Odds Reduction ±SD
(1a) Mastectomy alone							
Manchester RBS1	BW+AF+IMC	210/355	225/359	−10·7	101·7		
Kings/Cambridge	BW+AF+IMC	825/1376	855/1424	5·2	393·7		
NSABP B-04	BW+AF+IMC	178/352	206/365	−12·3	90·3		
WSSA Glasgow	BW+AF	49/94	68/123	−2·5	26·4		
Scottish D	BW+AF	16/47	10/46	3·5	6·3		
Subtotal (1a)		1278/2224 (57·5%)	1364/2317 (58·9%)	−16·8	618·4		**3% ± 4** (2p = 0·5)
(1b) Mastectomy with axillary sampling							
Wessex	BW+AF+IMC	38/74	50/77	−8·1	20·5		
Edinburgh I	BW+AF	64/173	68/175	−0·3	31·3		
DanishBCG 82b pre	BW+AF+IMC	127/756	156/764	−16·7	64·9		
DanishBCG82cpost	BW+AF+IMC	155/633	159/634	−2·5	71·9		
Subtotal (1b)		384/1636 (23·5%)	433/1650 (26·2%)	−27·6	188·5		**14% ± 7** (2p = 0·04)
(1c) Mastectomy with axillary clearance							
Berlin–Buch ABC	BW+AF+IMC	105/123	96/132	9·0	44·8		
Oslo X-ray	BW+AF+IMC	165/285	152/267	1·9	72·9		
Oslo Co-60	AF+IMC	134/278	131/285	4·1	63·6		
Heidelberg XRT	AF+IMC	74/85	43/58	7·9	25·5		
Stockholm A *	BW+AF+IMC	288/639	2(162/321)	−15·7	94·5		
SASIB	BW+AF+IMC	87/186	74/191	9·0	36·6		
Mayo Clinic	BW+AF+IMC	70/121	66/120	−0·6	29·9		
INT Milan 1	AF+IMC	20/33	10/23	2·9	6·6		
DFCI Boston	BW+AF	52/111	46/107	4·4	22·5		
Piedmont OA	BW+AF+IMC	85/144	75/136	4·4	36·7		
SECSG 1	BW+AF+IMC	48/127	65/129	−6·9	25·2		
Glasgow	BW+AF+IMC	62/112	64/107	−2·8	27·8		
MD Ander. 7730B	BW+AF+IMC	28/43	24/54	6·6	10·9		
S Swedish BCG	BW+AF+IMC	130/386	132/382	−3·4	62·0		
Toronto–Edmont.	BW+AF	13/28	11/22	−0·9	4·7		
BCCA Vancouver	BW+AF+IMC	46/163	55/155	−7·5	22·6		
Düsseldorf U.	BW+AF	17/34	24/54	3·3	7·8		
Coimbra	BW+AF+IMC	34/62	34/62	2·7	14·9		
Metaxas Athens	BW+AF+IMC	8/30	20/41	−4·5	6·1		
NSABC Israel	BW+AF+IMC	21/54	17/58	2·1	8·6		
Helsinki	BW+AF+IMC	16/47	15/52	2·6	7·1		
ECOG EST3181	BW+AF+IMC	48/171	43/161	0·8	20·8		
BMFT 03 Germany	BW+AF+IMC	11/98	15/101	−1·9	6·1		
Subtotal (1c)		1562/3360 (46·5%)	1536/3339 (46·0%)	17·4	658·1		**−3% ± 4** (2p = 0·5)
(1d) Breast conservation with axillary clearance							
NSABP B-06	BW	241/731	257/719	−10·1	81·8		
Uppsala–Örebro	BW	10/187	14/194	−2·6	5·8		
St George's	BW+AF	23/208	13/192	1·0	7·2		
Ontario COG	BW	33/416	38/421	−2·5	17·3		
Subtotal (1d)		307/1542 (19·9%)	322/1526 (21·1%)	−14·2	112·1		**12% ± 9** (2p = 0·2)
Total (1a – 1d)		3531/8762 (40·3%)	3655/8832 (41·4%)	−41·2	1577·2		**2·6% ± 2·5** (2p = 0·3)

■ 99% or ◁▷ 95% limits

Heterogeneity (36 trials): $X^2_{35} = 42·8$; p = 0·2

Heterogeneity (4 subtotals): $X^2_3 = 5·7$; p = 0·1

* For balance, Stockholm controls count twice

Odds Ratio scale: 0·0 0·5 1·0 1·5 2·0
Radiotherapy better | Radiotherapy worse
Total treatment effect 2p = 0·3

Figure 1. Mortality among Women in 36 Trials Comparing Surgery plus Radiotherapy with Surgery Alone, According to the Type of Surgery.

Each trial is described by a single line of information, showing the name of the trial, radiotherapy fields, numbers of deaths and patients, and statistical results. The analysis is based chiefly on the comparison between the number of deaths actually observed (O) in the radiotherapy group and the number that would be expected (E) if radiotherapy had no effect, with the use of a log-rank analysis. (Therefore, a negative value for O−E suggests a benefit of radiotherapy.) The values for O−E and its variance are presented both numerically and graphically. For each trial, the ratio of the annual death rate in the radiotherapy group to that in the control group (the odds ratio) is plotted as a solid square, along with its 99 percent confidence interval (CI), shown by the horizontal line. (Formally, the log of the odds ratio is calculated by dividing O−E by its variance.[1-3]) For trials for which it was not possible to obtain data on individual patients, published results have been included; these are represented by an open square. The vertical line indicates an odds ratio of 1.0 (i.e., no difference between the groups); the squares to the left of this line therefore indicate benefit in the radiotherapy group. To combine results in an unbiased fashion from several trials, the log-rank O−E values from each trial were summed, as were the separate variances. These summed statistics can be used to estimate the "typical odds ratio" in the trials that contributed to the total[1-3]; this overall odds ratio, together with its 95 percent confidence interval, is denoted by a diamond-shaped symbol. The percentage odds reduction and its standard deviation are also given, along with the two-sided P value (2p). The results of crude tests for heterogeneity among all the trial results and among the results for each type of trial are given at the bottom of the figure. The difference between these gives a test of heterogeneity among the results of the various specific types of trial. For a list of the trials, see Appendix 3. BW denotes breast or chest wall, AF axilla or supraclavicular fossa, and IMC internal mammary chain.
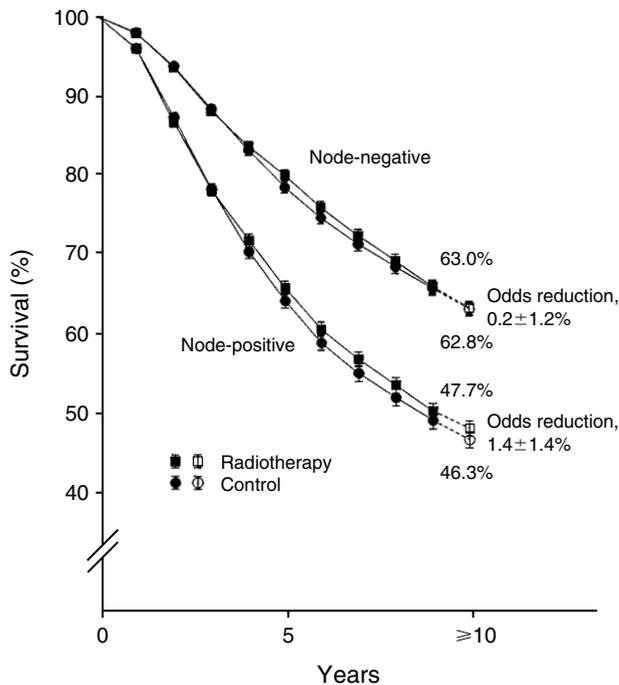
Figure 2. Ten-Year Survival among Approximately 16,000 Women in 35 Randomized Trials Comparing Surgery plus Radiotherapy with Surgery Alone.

Squares represent the women assigned to radiotherapy, and circles those in the control groups. The bars indicate standard deviations. The percentages at the ends of the curves show overall survival rates. Overall survival curves, based on a combination of the results of individual trials, were produced by an adaptation of the standard life-table method that permits the unbiased combination of information from heterogeneous trials.[1-3] The slopes of the broken lines from year 9 to year ≥10 are based on the overall death rates in the 10th and subsequent years. The results are shown for women with node-negative cancer (as determined by dissection or by sampling) and for those with node-positive cancer (all other women, including the few with unrecorded nodal status) and are restricted to trials that supplied data on individual patients that included nodal status.

than breast cancer; the remaining 7 percent of deaths, from unknown causes, are included with the deaths due to breast cancer. Table 2 shows the numbers of non–breast-cancer deaths plus the numbers of breast-cancer deaths according to the type of surgery, nodal status, age at diagnosis, and length of time to death.

Overall, about one third more women in the radiotherapy groups than in the non-radiotherapy groups died of "non–breast-cancer" causes (7.7 percent vs. 5.7 percent [527 vs. 391]), but this difference occurred partly because those assigned to radiotherapy had slightly longer recurrence-free survival and were therefore at risk for death without recurrence for slightly longer. After we allowed for this, there was an increase of only about one quarter in such deaths (odds ratio, 1.24±0.08; 95 percent confidence interval, 1.09 to 1.42; P=0.002). This increase of about one quarter was found among women in all age groups: under 50, 50 through 59, and 60 or older, at randomization. But, at least during the first decade or two after diagnosis, the absolute excess was much greater among those who were 60 or older at randomization (15.3 percent vs. 11.1 percent [339 vs. 249

deaths]) than among those under 50 (2.5 percent vs. 2.0 percent [62 vs. 49]). The odds ratios were 1.07±0.13 in the first 4 years; 1.37±0.15 in years 5 through 9; and 1.29±0.13 10 or more years after surgery. This trend was not significant.

There was no significant heterogeneity among the proportional increases in non–breast-cancer mortality among the different trials, among different types of surgery, or among different nodal-status categories. Radiotherapy generally included the internal mammary chain (Fig. 1 and Appendix 2A), but when this was not included the proportional increase in non–breast-cancer mortality still appeared to be at least as great as when the internal mammary chain was included (odds ratios, 1.54±0.32 vs. 1.22±0.08).

The proportional increase in non–breast-cancer mortality appeared to be about as great in the trials in which at least some orthovoltage radiotherapy was used (odds ratio, 1.28±0.10) as in the trials in which all women received megavoltage therapy (odds ratio, 1.23±0.12); in this analysis, the study by Høst et al.,[9] which included both orthovoltage and megavoltage radiotherapy, was included as two separate trials (Oslo X-ray and Oslo Co-60). In only one trial[10] was the increase in non–breast-cancer mortality significant, and it had used some orthovoltage and some megavoltage therapy.

Mortality Excluding Non–Breast-Cancer Deaths

In the 28 trials that supplied data on causes of death, 34.1 percent of the women assigned to radiotherapy (2325 of 6811 women) died of breast cancer, as compared with 36.9 percent of the controls (2512 of 6816), but a small part of this difference is artifactual. When, as described in the Methods section, non–breast-cancer deaths are subtracted from deaths from all causes, an unbiased analysis remains of deaths from breast cancer, indicating an odds ratio of 0.94±0.03 (95 percent confidence interval, 0.88 to 1.00; P=0.03) (Table 2). The lower confidence limit for this result corresponds to about twice as much benefit as the point estimate of 0.94 suggests, but the upper limit corresponds to about zero benefit. Hence, although such radiotherapy may well produce a moderate reduction in deaths due to breast cancer, the findings are also statistically consistent with a negligibly small effect from radiotherapy. These uncertainties cannot be resolved by subgroup analyses. Whether or not there is any real effect of radiotherapy on mortality due to breast cancer, chance may make it seem that there is benefit in some subgroups and none in others. Such patterns (Table 2) are untrustworthy, especially since rates of local recurrence were reduced substantially in all subgroups.

Rates of Recurrence

Dates of first recurrence were available from 35 studies, of which 32 specified whether the recurrence was local, distant, or both (but not the exact site). Overall, 38.1 percent of the women assigned to radiotherapy and 45.9 percent of those not assigned to radiotherapy

Table 2. Selected Outcomes in Trials of Radiotherapy.

| VARIABLE | "NON–BREAST-CANCER DEATHS" + "BREAST-CANCER DEATHS"/ NO. OF WOMEN*† | | ODDS RATIO (±SD) | | |
	RADIOTHERAPY	NO RADIOTHERAPY	DEATH DUE TO BREAST CANCER†	DEATH FROM ANY CAUSE‡	ISOLATED LOCAL RECURRENCE§
Type of axillary surgery					
None	215+836/1778	149+941/1829	0.94±0.05	0.97±0.04	0.37±0.05
Sampling	40+344/1636	37+396/1650	0.85±0.07	0.86±0.07	0.26±0.06
Clearance	264+1120/3002	197+1156/2951	0.97±0.05	1.03±0.07	0.36±0.05
Clearance plus breast conservation¶	8+25/395	8+19/386	0.84±0.30	0.87±0.09	0.25±0.09
Nodal status and method of axillary investigation					
Node-negative, clearance	110+147/876	90+138/877	1.12±0.13	1.13±0.09	0.28±0.09
Node-positive, clearance	98+748/1834	57+748/1765	0.96±0.05	1.00±0.05	0.38±0.05
Node-negative, sampling	42+109/408	31+122/456	0.98±0.13	1.09±0.12	0.38±0.13
Node-positive, sampling	38+384/1499	29+428/1464	0.82±0.07	0.83±0.06	0.23±0.06
Node-negative, clinical	204+704/1698	147+803/1730	0.92±0.05	0.95±0.04	0.36±0.05
Node-positive, clinical	34+218/465	37+256/482	0.90±0.10	0.89±0.09	0.29±0.09
Unknown	1+15/31	0+17/42	—	1.01±0.09	—
Age at diagnosis					
<50 yr	62+798/2524	49+851/2486	0.91±0.05	0.91±0.05	0.36±0.05
50–59 yr	126+747/2062	93+796/2089	0.97±0.05	1.00±0.05	0.33±0.05
≥60 yr	339+778/2221	249+865/2241	0.93±0.05	1.01±0.04	0.30±0.05
Unknown	0+2/4	0+0/0	—	0.87±0.10	—
Time to death					
0–4 yr	145+1479/6811	130+1565/6816	0.94±0.03	0.95±0.03	—
5–9 yr	168+579/3735	107+615/3664	0.96±0.05	1.02±0.05	—
≥10 yr	214+267/2140	154+332/2139	0.90±0.08	1.02±0.07	—
Unknown	—	—	—	0.87±0.10	—
All women	527+2325/6811	391+2512/6816	0.938±0.030	0.974±0.025	0.33±0.03
Proportion dead	7.7%+34.1%	5.7%+36.9%			

*"Non–breast-cancer deaths" include only deaths without reported recurrence that were stated not to involve breast cancer. In the overall log-rank analysis of these deaths, the observed number of deaths minus the expected number of deaths (O − E) = 45.7 and the variance = 210.5 (odds ratio, 1.243±0.077; 95 percent confidence interval, 1.09 to 1.42; P = 0.002).

†Data are from 28 trials that reported causes of death.   ‡Data are from all 36 trials.

§Data are from 32 trials that reported sites of recurrence.   ¶Women in all other categories underwent mastectomy that did not conserve the breast.

had reported recurrences (odds ratio, 0.76±0.02). The reduction in the rates of recurrence was significant in each subgroup used in Table 2 (data not shown; P<0.001 for each comparison). As expected, radiotherapy produced an even greater reduction in the rate of isolated local recurrences (6.7 percent [501 of 7473 women] vs. 19.6 percent [1480 of 7570]; odds ratio, 0.33) (Table 2). The size of this protective effect was not significantly affected by the type of axillary surgery, nodal status, or age at diagnosis.

Because radiotherapy reduced the rate of local recurrence by about two thirds, many patients whose first recurrence would have been local had distant recurrences instead as a first event. Hence, because the risks of local recurrence and of other recurrences are correlated,[11,12] radiotherapy was artifactually associated with an apparent increase in non-local recurrences as first events (odds ratio, 1.13±0.04). This made it impossible to assess, on the basis of the data currently available, whether radiotherapy had any protective effect against distant recurrence.

Trials Comparing More Extensive with Less Extensive Surgery

The 10 trials comparing more extensive with less extensive surgery can be subdivided according to the extent of surgery among controls — radical or total mastectomy, simple mastectomy, or breast conservation — yielding three types of surgical comparison (Fig. 3 and Appendix 2B).

Overall Mortality

Overall, 48.0 percent of the women assigned to more extensive surgery and 50.1 percent of those assigned to less extensive surgery died (Fig. 3); this corresponds to a nonsignificant reduction of 3 percent in the odds of death. There was no significant heterogeneity among the 10 trials or among the three types of surgical comparison. Data on causes of death were available for only 53 percent of the women who died without a recurrence of breast cancer; these data also showed no significant differences.

Figure 4 shows survival according to nodal status for the approximately 3400 women in trials comparing more extensive with less extensive surgery. The less extensive surgery was total or radical mastectomy in some of these trials (Fig. 3a) and simple mastectomy in all the others (Fig. 3b), since data on individual patients were not yet available from the trial of breast-conserving surgery (Fig. 3c). No difference in survival was apparent among either women with node-positive cancer or those with node-negative disease.

Rates of Recurrence

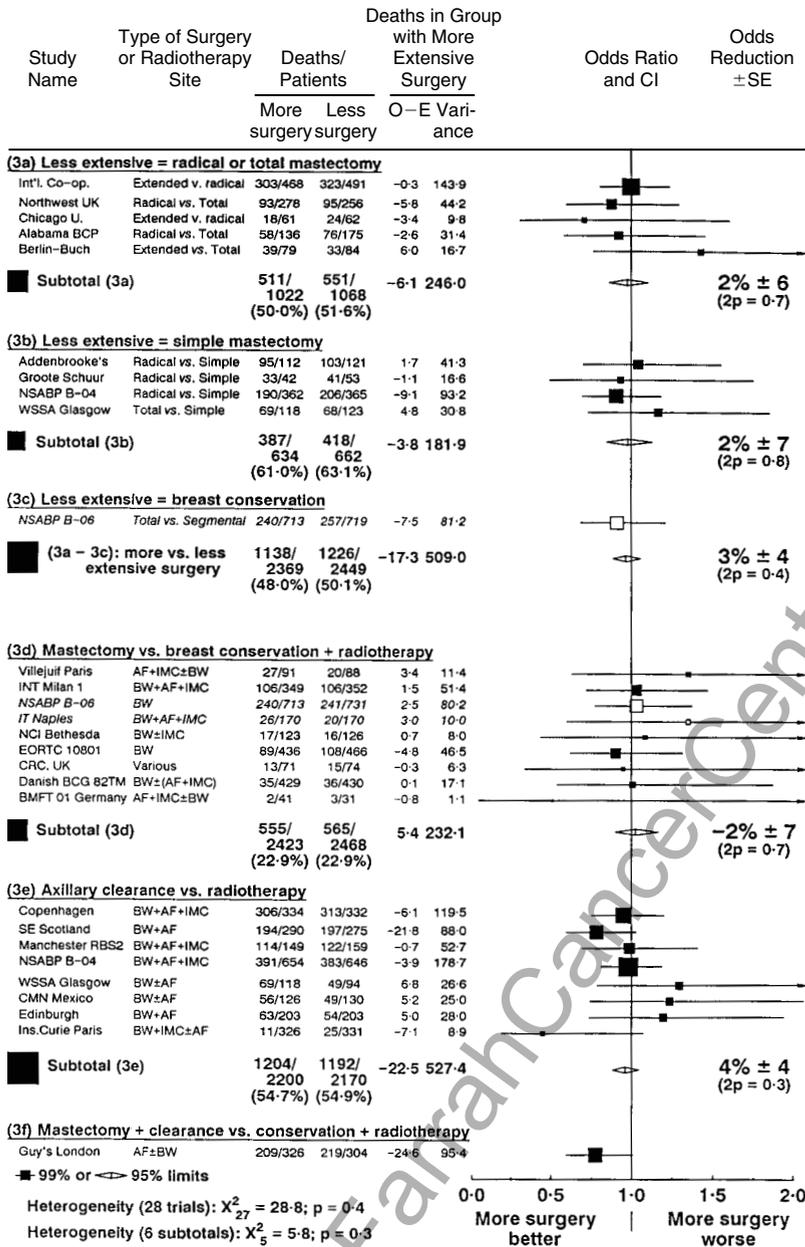Among the women whose outcomes are summarized in Figure 4, more-extensive surgery involved a nonsig-

Study Name	Type of Surgery or Radiotherapy Site	Deaths/Patients More surgery	Deaths/Patients Less surgery	Deaths in Group with More Extensive Surgery O−E	Deaths in Group with More Extensive Surgery Variance	Odds Ratio and CI	Odds Reduction ±SE
(3a) Less extensive = radical or total mastectomy							
Int'l. Co-op.	Extended v. radical	303/468	323/491	−0·3	143·9		
Northwest UK	Radical vs. Total	93/278	95/256	−5·8	44·2		
Chicago U.	Extended v. radical	18/61	24/62	−3·4	9·8		
Alabama BCP	Radical vs. Total	58/136	76/175	−2·6	31·4		
Berlin–Buch	Extended vs. Total	39/79	33/84	6·0	16·7		
Subtotal (3a)		511/1022 (50·0%)	551/1068 (51·6%)	−6·1	246·0		2% ± 6 (2p = 0·7)
(3b) Less extensive = simple mastectomy							
Addenbrooke's	Radical vs. Simple	95/112	103/121	1·7	41·3		
Groote Schuur	Radical vs. Simple	33/42	41/53	−1·1	16·6		
NSABP B-04	Radical vs. Simple	190/362	206/365	−9·1	93·2		
WSSA Glasgow	Total vs. Simple	69/118	68/123	4·8	30·8		
Subtotal (3b)		387/634 (61·0%)	418/662 (63·1%)	−3·8	181·9		2% ± 7 (2p = 0·8)
(3c) Less extensive = breast conservation							
NSABP B-06	Total vs. Segmental	240/713	257/719	−7·5	81·2		
(3a – 3c): more vs. less extensive surgery		1138/2369 (48·0%)	1226/2449 (50·1%)	−17·3	509·0		3% ± 4 (2p = 0·4)
(3d) Mastectomy vs. breast conservation + radiotherapy							
Villejuif Paris	AF+IMC±BW	27/91	20/88	3·4	11·4		
INT Milan 1	BW+AF+IMC	106/349	106/352	1·5	51·4		
NSABP B-06	BW	240/713	241/731	2·5	80·2		
IT Naples	BW+AF+IMC	26/170	20/170	3·0	10·0		
NCI Bethesda	BW±IMC	17/123	16/126	0·7	8·0		
EORTC 10801	BW	89/436	108/466	−4·8	46·5		
CRC. UK	Various	13/71	15/74	−0·3	6·3		
Danish BCG 82TM	BW±(AF+IMC)	35/429	36/430	0·1	17·1		
BMFT 01 Germany	AF+IMC±BW	2/41	3/43	−0·8	1·1		
Subtotal (3d)		555/2423 (22·9%)	565/2468 (22·9%)	5·4	232·1		−2% ± 7 (2p = 0·7)
(3e) Axillary clearance vs. radiotherapy							
Copenhagen	BW+AF+IMC	306/334	313/332	−6·1	119·5		
SE Scotland	BW+AF	194/290	197/275	−21·8	88·0		
Manchester RBS2	BW+AF+IMC	114/149	122/159	−0·7	52·7		
NSABP B-04	BW+AF+IMC	391/654	383/646	−3·9	178·7		
WSSA Glasgow	BW±AF	69/118	49/94	6·8	26·6		
CMN Mexico	BW±AF	56/126	49/130	5·2	25·0		
Edinburgh	BW+AF	63/203	54/203	5·0	28·0		
Ins.Curie Paris	BW+IMC±AF	11/326	25/331	−7·1	8·9		
Subtotal (3e)		1204/2200 (54·7%)	1192/2170 (54·9%)	−22·5	527·4		4% ± 4 (2p = 0·3)
(3f) Mastectomy + clearance vs. conservation + radiotherapy							
Guy's London	AF±BW	209/326	219/304	−24·6	95·4		

■ 99% or ⬦ 95% limits

Heterogeneity (28 trials): $\chi^2_{27} = 28·8$; p = 0·4
Heterogeneity (6 subtotals): $\chi^2_5 = 5·8$; p = 0·3

0·0   0·5   1·0   1·5   2·0
More surgery better | More surgery worse

Figure 3. Mortality among Women in 10 Trials Comparing More-Extensive Surgery with Less-Extensive Surgery and 18 Trials Comparing More-Extensive Surgery with Less-Extensive Surgery plus Radiotherapy.

For an explanation of information included in the figure, the format, and the symbols, see the legend to Figure 1. The subtotals for the subsections of the figure are included in the test for heterogeneity shown at the bottom of the figure. For the 10 trials in subsections 3a through 3c, $\chi^2_9 = 6.3$. In this case the odds ratio shows the rate of death in the groups assigned to more-extensive surgery, as compared with the rate in the groups assigned to less-extensive surgery; the odds reduction represents the decrease in the risk of death among women treated with more-extensive surgery. For a list of the trials, see Appendix 3. AF denotes axilla or supraclavicular fossa, IMC internal mammary chain, and BW breast or chest wall.

nificant reduction in the rate of recurrence; 48.8 percent of those treated with more-extensive surgery and 50.3 percent of those with less-extensive surgery had a reported recurrence (odds ratio, 0.98±0.05, with no significant heterogeneity among different trials or among different types of surgery). For isolated local recurrence, the odds ratio of 0.89±0.12 was also not significant.

Trials of Breast-Conserving Surgery

In the nine trials of mastectomy versus breast-conserving surgery plus radiotherapy (Fig. 3d and Appendix 2C), there was no apparent difference in total mortality (22.9 percent vs. 22.9 percent) and little information on the causes of death. For six studies (involving 3107 women) in which data on recurrence were available, there were fewer recurrences with mastectomy,

but the difference was not significant (odds ratio, 0.96±0.08). Few local recurrences were recorded, and the definition of local recurrence varied, particularly for recurrences in the remaining breast tissue (which, even with radiotherapy, may affect a substantial minority of women, and which some trials ignore in counting "local recurrences"). Once again there was no significant difference (6.2 percent had local recurrences with mastectomy, as compared with 5.9 percent with breast conservation). As Figure 5 shows, no difference in survival was apparent between mastectomy and breast-conserving therapy plus radiotherapy in seven trials.

Trials of Axillary Clearance versus Radiotherapy

In the eight trials of axillary clearance versus radiotherapy (Fig. 3e and Appendix 2C), there was no apparent difference in total mortality (54.7 percent vs.

54.9 percent) or in recurrence as a first event (odds ratio, 1.01), but radiotherapy was associated with fewer isolated local recurrences (odds reduction, 15±8 percent; P = 0.06).

Trials Involving Other Comparisons

Of the remaining comparisons of mortality, only one was statistically significant (Fig. 3f and Appendix 2C); in this trial mastectomy plus axillary clearance plus some radiotherapy appeared to be better than breast-conserving surgery without axillary clearance but with additional radiotherapy. The difference in mortality (64 percent vs. 72 percent; P = 0.01) was greater than would be expected from the other results presented here. This may reflect the particular treatments used in this study[13] or the effects of chance, as is possible in any trial. Analyses of mortality in various other trials of local therapy are listed in Appendix 2D.

DISCUSSION

Some of the local therapies for breast cancer had substantially different effects on the rates of local recurrence, but there were no definite differences in overall 10-year survival. It has long been accepted that radiotherapy can delay or prevent local or regional recurrence in women with early breast cancer, as may more extensive surgery. More recently, it has appeared that
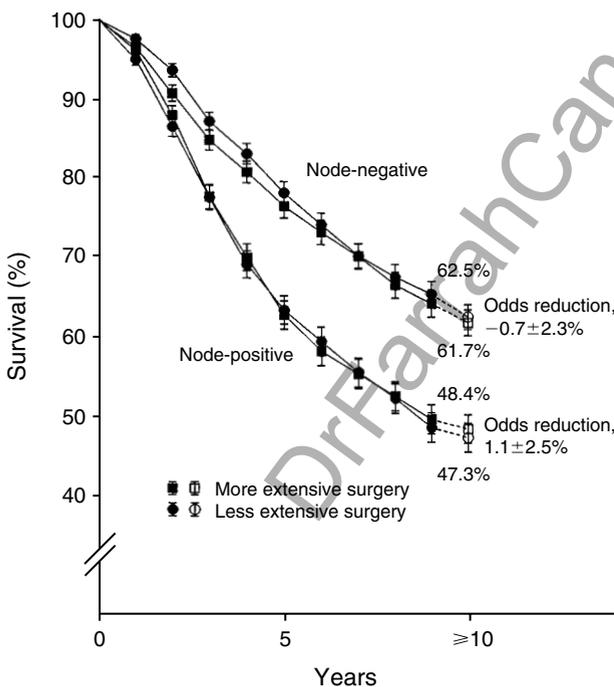
Figure 4. Ten-Year Survival among Approximately 3400 Women in Nine Randomized Trials Comparing More-Extensive Surgery with Less-Extensive Surgery, with Neither Conserving the Breast.

Squares represent the women assigned to more-extensive surgery, and circles those assigned to less-extensive surgery. The bars indicate standard deviations. The percentages at the ends of the curves show overall survival rates. Curves were derived as described in the legend to Figure 2.
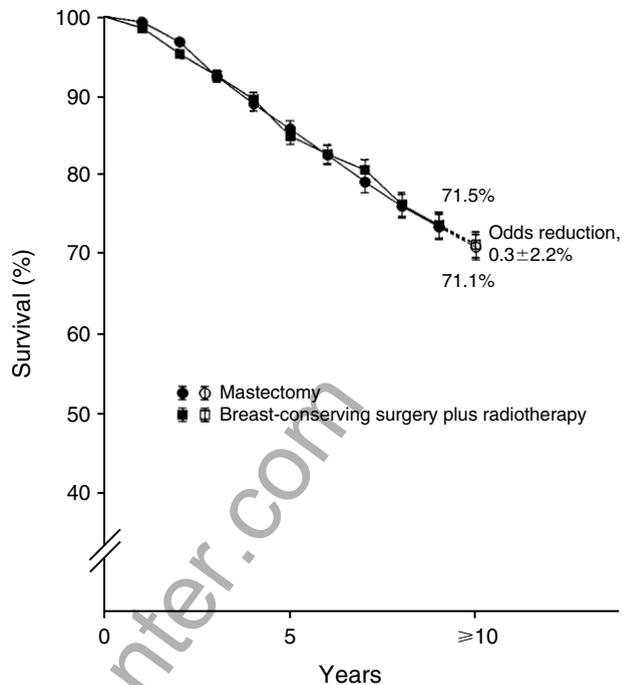
Figure 5. Ten-Year Survival among Approximately 3100 Women in Seven Randomized Trials Comparing Mastectomy with Breast-Conserving Surgery plus Radiotherapy.

Squares represent the women assigned to mastectomy, and circles those assigned to breast-conserving surgery plus radiotherapy. The bars indicate standard deviations. The percentages at the ends of the curves show overall survival rates. Curves were derived as described in the legend to Figure 2.

radiotherapy can also produce a small increase in the rate of death from causes other than breast cancer.[4] In this extensive overview, we confirmed these findings, but we could not assess separately the effects of treatment on deaths from cardiovascular or other specific causes or the relevance of particular details of radiologic or surgical technique. Our findings indicate, however, that the absolute excess rate of non–breast-cancer mortality during the first decade or so after radiotherapy is strongly related to age. Among women who were under 50 when they underwent irradiation, the apparent excess is just a few deaths not due to breast cancer per 1000 women, whereas among women who were 60 or older at the time of radiotherapy, it is a few per 100. As Table 2 suggests, the excess may persist for more than 10 years. If such a proportional excess persists indefinitely, the absolute excess might become appreciable even among women who were under 50 when they received radiotherapy. Although the radiotherapy techniques differed substantially among the studies, the overall result still provides a valid measure of the value of such treatment.

A central question about local therapy for early breast cancer is whether more-extensive treatment significantly reduces long-term mortality from breast cancer. The current analyses show that any reduction cannot be large, at least during the first decade. But even a small difference could be important, especially if

any hazards of the treatment could be limited. With radiotherapy, there is a small, marginally significant (P = 0.03) reduction in mortality due to breast cancer but not in overall mortality. However, because the "breast-cancer" deaths do include some deaths from other causes, the effect could be somewhat larger than the 6 percent reduction seen in this overview. In the comparisons of different types of surgery, no significant differences in survival were found.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-06 is the largest trial of surgical strategies included in this overview.[14] After 12 years of follow-up in Protocol B-06, no significant differences in survival have been found in it between women treated with total mastectomy and those treated with lumpectomy, with or without irradiation, as reported in this issue of the *Journal*.[14] Information from this trial on the length of time to death was not included in this overview, so, although Figures 1 and 3 include the overall results from Protocol B-06 (with the analyses of all available data on mortality among all randomized patients), the survival curves in Figures 2 and 5 do not include data from this study. The analyses in Figure 5 are therefore independent of (and strongly supportive of) the conclusion from the NSABP trial that, in suitable patients, survival is about as good with appropriate breast-conserving surgery plus radiotherapy as with mastectomy. When one combines the results from Protocol B-06 and Figure 5, the evidence that 10-year survival is approximately equivalent with these two strategies is therefore now based on a total of almost 5000 women (Fig. 3d).

Survival differences are not the only factors influencing choices about surgery and radiotherapy for the treatment of early breast cancer, but if any such differences could be reliably demonstrated they would be important. Any differences between these local therapies do not involve large effects on 10-year survival, but they could still involve worthwhile effects on longer-term survival. As follow-up continues, an increasing proportion of the natural history of the disease becomes accessible to study. The next five-yearly analysis of the Early Breast Cancer Trialists' Collaborative Group will include trials that began during 1985 through 1989, plus five additional years of follow-up on the present trials and (for some studies) more details of sites of recurrence and causes of death.

APPENDIX 1. MEMBERS OF THE EARLY BREAST CANCER TRIALISTS' COLLABORATIVE GROUP

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APPENDIX 2. RANDOMIZED TRIALS OF RADIOTHERAPY AND SURGERY IN THE TREATMENT OF EARLY BREAST CANCER

For a complete list of the trials, listed alphabetically by their short names, see Appendix 3. This appendix contains some trials from which data on mortality were not available for analysis.

The following abbreviations are used in this appendix: o denotes orthovoltage; f fractions; d days; m megavoltage; OvAbl ovarian ablation; IMC internal mammary chain; N nodal stage; R radiotherapy; Tam tamoxifen; CMF cyclophosphamide, methotrexate, and fluorouracil; OvIrr ovarian irradiation; CFP cyclophosphamide, fluorouracil, and prednisone; AC axillary clearance; MF methotrexate and fluorouracil; Mel melphalan; T tumor size; FAC fluorouracil, adriamycin, and cyclophosphamide; BCG bacille Calmette–Guérin; Pre premenopausal; Cyclo cyclophosphamide; Post postmenopausal; CMFP cyclophosphamide, methotrexate, fluorouracil, and prednisone; ER estrogen receptor; Pr prednisone; LMF chlorambucil, methotrexate, and fluorouracil; CAFt cyclophosphamide, doxorubicin, and futrofur; FMel fluorouracil and melphalan; M mastectomy; IMND internal mammary-node dissection; PME pectoral-muscle excision; AB axillary biopsy (sampling); BW breast or chest wall; Ooph oophorectomy; C breast conserving surgery; AF axilla and supraclavicular fossa; MThio methotrexate and thiotepa; MPA medroxyprogesterone acetate; ± not all patients; periop perioperative.

APPENDIX 2A. RANDOMIZED TRIALS COMPARING RADIOTHERAPY PLUS SURGERY WITH THE SAME SURGERY ALONE

Study	Breast or chest wall	Axilla & fossa	Internal mammary chain	Common systemic
Common surgery: mastectomy alone				
Manchester RBS1	37-45Gy (15f/21d) o	37-40Gy (15f/20d) om	37-40Gy (15f/20d) om	OvAbl
Kings/Cambridge	Various om	Various om	Various om	None
NSABP B-04	50Gy (25f/35d) m	As IMC + 10-20Gy if N1b	50Gy (25f/35d) m	None
WSSA Glasgow	42Gy (20f/28d) o for all	42Gy (20f/28d) m for R arm	Not included	None
Scottish D	37-45Gy (10-20f/19-30d) om	38-46Gy (10-20f/19-29d) m	Not included	Tam vs control
Common surgery: mastectomy with axillary sampling				
Wessex	46Gy (20f/28d) m	55Gy (22f/30d) m	46Gy m	None
Edinburgh I	43Gy (10f/28d) m	45Gy (10f/28d) m	Not included	None
DBCG 82b pre	50Gy (25f/35d) om	50Gy (25f/35d) om	50Gy (25f/35d) om	CMF
DBCG 82c post	50Gy (25f/35d) om	50Gy (25f/35d) om	50Gy (25f/35d) om	Tam
Common surgery: mastectomy with axillary clearance				
NSABP B-02	Not included	35-45Gy (21-35d) om	35-45Gy (21-35d) om	None
Berlin-Buch ABC	55Gy (40d) m	55Gy (40d) m	55Gy (40d) m	None
Oslo, X-ray	25-31Gy (28d)	36-52Gy (28d) o	25-31Gy (28d) o	OvIrr
Oslo, Co-60	Not included	50Gy (20f/28d) m	50Gy (20f/28d) m	OvIrr
Heidelberg XRT	Not included	65Gy (24-30f/42d) m	65Gy (24-30f/42d) m	None
Stockholm A	45Gy (25f/35d) m	45Gy (25f/35d) m	45Gy (25f/35d) m	None
SASIB	34-60Gy (10-24f/24-42d) m	44-60Gy (10-24f/31-42d) m	44-60Gy (10-24f/31-42d) m	None
Mayo Clinic	50Gy (24f/52d) m	50Gy (24f/52d) m	50Gy (24f/52d) m	CFP vs control
INT Milan 1	Not included	45Gy (20f/28d) m	45Gy (20f/28d) m	None
DFCI Boston	45Gy (20f/35d) m	45Gy (20f/35d) m	Not included	AC vs CMF vs MF
Piedmont OA	45-50Gy (30f/42d) m; none if N1-3 or T<3cm	45-50Gy (30f/42d) m; 45Gy (16f/28d) if N1-3 or T<3cm	45-50Gy (30f/42d) m; 45Gy (16f/28d) if N1-3 or T<3cm	Mel vs CMF
SECSG 1	50Gy (35d) m	50Gy (35d) m	50Gy (35d) m	CMF
Glasgow	38Gy (15f/21d) o	38Gy (15f/21d) o	38Gy (15f/21d) o	CMF
Cologne	50Gy (35d) m	50Gy (35d) m		AC
MD Ander. 7730B	45-50Gy (25-27f/32-35d) m	45-50Gy (25-27f/32-35d) m	45-50Gy (25-27f/32-35d) m	FAC ± BCG
S Swedish BCG	35Gy (20f/48d) m	48Gy (20f/48d) m; 60Gy (25f/55d) m if perigland(+)	48Gy (20f/48d) m	Pre: Cyclo; Post: Tam
Toronto-Edmont.	40 Gy (14f/16d) m	40 Gy (14f/16d) m	Not included	OvIrr+CMFP ± BCG
BCCA Vancouver	40Gy (16f/21d)	38Gy (16f/21d)	38Gy (16f/21d)	CMF; ER+: OvIrr+Pr

APPENDIX 2A (CONTINUED). RANDOMIZED TRIALS COMPARING RADIOTHERAPY PLUS SURGERY WITH THE SAME SURGERY ALONE

Study	Breast or chest wall	Axilla & fossa	Internal mammary chain	Common systemic
Common surgery: mastectomy with axillary clearance (continued)				
Düsseldorf U	40Gy (20f/28d) m	40Gy (20f/28d) m	Not included	LMF
Coimbra	36Gy (12f/28d) om	39-45Gy (12f/28d) m	39Gy (12f/28d) m	AC
Metaxas Athens	50-60Gy (25-30f/35-42d) om	50Gy (25f/35d) om	50Gy (25f/35d) om	Chemoendocrine
NSABC Israel	46-50Gy (23-25f/28-35d) m	46-50Gy (23-25f/28-35d) m	40Gy (20f/28d) m	CMF
Helsinki	45Gy (15f) m	45Gy (15f) m	30Gy (10f) m	CAFt
ECOG EST3181	46Gy (23f/31d) m	46Gy (23f/31d) m	46Gy (23f/31d) m	CAF+Tam+Halotestin
BMFT 03 Germany	50Gy (25f/35-42d) m	50Gy (25f/35-42d) m	44Gy (25f/35-42d) m	CMF
Common surgery: breast conservation with axillary clearance				
NSABP B-06	50Gy (25f/35d) m	Not included	Not included	N+: FMel
Uppsala-Örebro	54Gy (27f/38d) m	Not included	Not included	None
St George's	54Gy (27f/39d) m	50Gy (25f/25d) m if N+	Not included	ER+ Tam; ER- CMF
Ontario COG	53Gy (21f/28d) m	Not included	Not included	None

APPENDIX 2B. RANDOMIZED TRIALS COMPARING MORE EXTENSIVE SURGERY WITH LESS EXTENSIVE SURGERY

Study	Surgery 1	Surgery 2	Common systemic and radiotherapy
Less extensive surgery: radical or total mastectomy			
Int'l. Co-Op.	M + AC + IMND	M + AC	None
Northwest UK	M + AC + PME	M + AC	None
Chicago U	M + AC + IMND	M + AC	None
Alabama BCP	M + AC + PME	M + AC	N+: Mel vs CMF
Berlin-Buch	M + AC + IMND	M + AC	None
Less extensive surgery: simple mastectomy			
Addenbrooke's	M + AC + PME ± IMND	M ± AB	BW + AF + IMC: 33Gy (15-20f/21-28d)
Charing Cross	M + AC	M + AB	R for all pts; Pre- & peri: Ooph
Groote Schuur	M + AC + PME	M	None
NSABP B-04	M + AC + PME	M	None
WSSA Glasgow	M + AC	M	BW: 42Gy (20f/28d)
Less extensive surgery: breast conservation			
NSABP B-06	M + AC	C + AC	N+: Chemotherapy
Scottish	M	C	

APPENDIX 2C. RANDOMIZED TRIALS COMPARING MORE EXTENSIVE SURGERY WITH LESS EXTENSIVE SURGERY PLUS RADIOTHERAPY

Study	Surgery 1	Surgery 2	Radiotherapy 2	Common systemic and radiotherapy
Mastectomy versus breast conservation plus radiotherapy				
Villejuif Paris	M + AC	C + AC	BW: 45Gy (18f/28d) m	AF + IMC: 45Gy (18f/28d) o; N+, pre: Ovlrr
INT Milan 1	M + AC	C + AC	BW: 50Gy (42d); AF + IMC: 40-45Gy (28-35d)	Chemotherapy for some
PMH Toronto	M + AC	C + AC	BW: 40Gy (21d) o	None
NSABP B-06	M + AC	C + AC	BW: 50Gy (25f/35d) m	N+: Chemotherapy
IT Naples	M + AC	C + AC	BW + AF + IMC	None
NCI Bethesda	M + AC	C + AC	BW: 45-50Gy (25-28f/35d) m + 15-20Gy If N+, IMC: 45Gy (25f/35d) m	N+: AC; Post: Tam
EORTC 10801	M + AC	C + AC	BW: 50Gy (25f/35d) m + 25Gy	R; chemotherapy for some
CRC UK	M + AB	C + AB	Boost	R; Tam ± periop cyclo for some
DBCG 82TM, pN0	M + AC	C + AC	BW: 50Gy (25f/35d) m + 10-20Gy	None
DBCG 82TM, pN+	M + AC	C + AC	BW: 10-20Gy boost	BW + AF + IMC: 50Gy (25f/35d); Pre: CMF; Post: Tam
BMFT 01 Germany	M + AC	C + AC	BW: 60Gy (30f/42-49d) m	AF + IMC: 50Gy (25f/35-42d) m
Axillary clearance versus radiotherapy				
Copenhagen	M + AC + IMCD	M	BW + AF + IMC: 42-45Gy (18f/21d) o	None
SE Scotland	M + AC	M	BW + AF + IMC: 45Gy (10f/28d)	OvAbl for some
Manchester RBS2	M + AC	M	BW + AF + IMC	Endocrine therapy for some
NSABP B-04	M + AC + PME	M	See entry under (2A)	None
WSSA Glasgow	M + AC	M	AF: 42Gy (20f/28d) m	BW: 42Gy (20f/28d) o
Mexico	M + AC	M	BW + AF + IMC: 50Gy (25f/70d)	None
Edinburgh	M + AC	M + AB	BW: 45Gy (10f/28d) m; AF: 43Gy (10f/28d) m	Tam vs control for some
Ins. Curie Paris	C + AC	C	BW + IMC ± AF	N+: FAC
Mastectomy with clearance versus breast conservation plus radiotherapy				
Guy's London	M + AC	C	BW: 36Gy (15f/21d)	AF: 30Gy (10f/14d)

APPENDIX 2D. OTHER RANDOMIZED TRIALS FOR WHICH DATA ON INDIVIDUAL PATIENTS WERE AVAILABLE

Study	Treatment 1	Treatment 2	Systemic	Treatment 1	Treatment 2	O−E	Var
Cardiff	M + AC (+ radical R if N+)	M (+ axillary R if N+)	None	66/97	83/103	-7.2	33.2
Berlin MQ	Radical M + peripheral R	Extended radical M	None	13/51	23/52	-6.1	8.4
Huguenin France	R	M + AC	None	39/84	35/82	1.4	17.4
Tunisia	R	Surgery	CMF	12/47	7/44	2.0	4.4
CRC, UK	Optimal surgery	No surgery	Tam	34/201	48/203	-6.3	19.1
Nottingham City	M	Tam	None	28/65	28/66	1.4	12.1
St George's E	M or local excision	Tam	None	24/100	27/100	-1.8	11.7
Bradford RI	R	MThio	Ooph for some	25/89	16/86	4.7	9.5
Stockholm	R	CMF	Tam for some	161/462	201/558	-4.4	82.0
Wurzburg U.	R	CMF	None	37/150	30/150	5.2	16.1
NSABC Israel B	R	MF	None	22/32	15/35	5.2	8.4
Scottish	R	CMF	None	6/26	8/25	-1.0	3.1
ICCRSG Bologna	R	MPA	None	50/142	60/146	-0.9	24.4
Scottish	R	Tam	None	7/43	1/41	3.1	2.0

APPENDIX 3. RANDOMIZED TRIALS OF LOCAL THERAPY FOR BREAST CANCER

The trials included in this overview are listed below with a short name (as used in Fig. 1 and 3 and Appendix 2; an asterisk indicates that data on causes of death were supplied); the full name of the trial, if different; the year in which the trial was begun (in parentheses); and the name or location of the institution or study group.

Addenbrooke's* (1958): Addenbrooke's Hospital, Cambridge, United Kingdom.

Alabama BCP* (1975): Alabama Breast Cancer Project, Birmingham, Ala.

BCCA Vancouver,* BCCA G1 Trial (1978): British Columbia Cancer Agency, Vancouver, B.C., Canada.

Berlin MQ (1976): Berlin–Buch Akademie der Wissenschaften, Berlin, Germany.

Berlin–Buch, CMEA Multicentre Trial (1976): Berlin–Buch Akademie der Wissenschaften, Berlin, Germany.

Berlin–Buch ABC (1962): Berlin–Buch Akademie der Wissenschaften, Berlin, Germany.

BMFT 01 Germany,* GBSG Protocol 01 (1983): Bundesminsterium für Forschung und Technologie, Freiburg, Germany.

BMFT 03 Germany,* GBSG Protocol 03 (1984): Bundesminsterium für Forschung und Technologie, Freiburg, Germany.

Bradford RI (1974): Bradford Royal Infirmary, Bradford, United Kingdom.

Cardiff (1967): Cardiff Surgery Trialists, Cardiff, United Kingdom.

Charing Cross, Hammersmith Trial (1965): Charing Cross Hospital, London.

Chicago U* (1973): University of Chicago, Chicago.

Coimbra* (1979): Coimbra Instituto de Oncologia, Coimbra, Portugal.

Cologne (1976): Cologne, Germany.

Copenhagen* (1951): Copenhagen Radium Center, Copenhagen, Denmark.

CRC UK,* CRC Breast Conservation Trial (1982): Cancer Research Campaign, London.

CRC UK, Elderly Trial (1984): Cancer Research Campaign, London.

Danish BCG 82b pre,* DBCG 82b premenopausal (1982): Danish Breast Cancer Cooperative Group, Copenhagen, Denmark.

Danish BCG 82c post,* DBCG 82b postmenopausal (1982): Danish Breast Cancer Cooperative Group, Copenhagen, Denmark.

Danish BCG 82TM,* DBCG 82TM (1983): Danish Breast Cancer Cooperative Group, Copenhagen, Denmark.

DFCI Boston,* DFCI 74-063/75-122 (1976): Dana–Farber Cancer Institute, Boston.

Düsseldorf U (1977): Düsseldorf University, Düsseldorf, Germany.

ECOG EST3181 (1982): Eastern Cooperative Oncology Group, Boston.

Edinburgh,* Edinburgh Surgery Trial (1980): Edinburgh, United Kingdom.

Edinburgh I,* Edinburgh Radiotherapy Trial I (1974): Edinburgh, United Kingdom.

EORTC 10801 (1980): European Organisation for Research and Treatment of Cancer, Brussels, Belgium.

Glasgow,* Victoria-Gartnavel Study (1976): Victoria Infirmary, Glasgow, United Kingdom.

Groote Schuur,* (1967): Groote Schuur Hospital, Cape Town, South Africa.

Guy's London, Guy's Surgery I and II Trials (1961): Guy's Hospital, London.

Heidelberg XRT,* Heidelberg Radiotherapy Trial (1969): Heidelberg University, Heidelberg, Germany.

Helsinki* (1980): Helsinki University, Helsinki, Finland.

Huguenin France, Fédération Nationale des Centres de Lutte contre le Cancer Trial (1974): Centre René Huguenin, St. Cloud, France.

ICCRSG Bologna (1975): Italian Cooperative Chemo-Radio-Surgical Group, Bologna, Italy.

Ins. Curie Paris, S4 Trial (1982): Institut Curie, Paris.

INT Milan1* (1973): Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.

Int'l. Co-Op.,* International Cooperative Study (1963): International Cooperative Study Trialists, Villejuif, France.

IT Naples (1977): Istituto Tumori, Naples, Italy.

Kings/Cambridge,* Cancer Research Campaign 1 (1970): Cancer Research Campaign, London.

Manchester RBS1,* Regional Breast Study 1 (1970): North-Western British Surgeons, Manchester, United Kingdom.

Manchester RBS2,* Regional Breast Study 2 (1970): North-Western British Surgeons, Manchester, United Kingdom.

Mayo Clinic,* Mayo 70-56-32 (1973): Mayo Clinic, Rochester, Minn.

MD Ander. 7730B,* M.D. Anderson Study 77-30B (1978): M.D. Anderson Cancer Center, Houston.

Metaxas Athens (1979): Metaxas Memorial Cancer Hospital, Athens, Greece.

Mexico* (1974): Mexican National Cancer Center, Mexico City, Mexico.

NCI Bethesda,* 79-C-111 (1979): National Cancer Institute, Bethesda, Md.

Northwest UK,* Lister Trial (1969): North-Western British Surgeons, Manchester, United Kingdom.

Nottingham City (1982): Nottingham City Hospital, Nottingham, United Kingdom.

NSABC Israel,* BR81 (1980): Israel National Study for Adjuvant Treatment of Breast Cancer, Israel.

NSABC Israel B (1977): Israel National Study for Adjuvant Treatment of Breast Cancer, Israel.

NSABP B-02 (1961): National Surgical Adjuvant Breast and Bowel Project, Pittsburgh.

NSABP B-04 (1971): National Surgical Adjuvant Breast and Bowel Project, Pittsburgh.

NSABP B-06 (1976): National Surgical Adjuvant Breast and Bowel Project, Pittsburgh.

Ontario COG (1984): Ontario Clinical Oncology Group, Toronto.

Oslo Co-60* (1967): Oslo Radium Hospital, Oslo, Norway.

Oslo X-ray* (1964): Oslo Radium Hospital, Oslo, Norway.

Piedmont OA,* POA 74176 (1975): Piedmont Oncology Association, Winston-Salem, N.C.

PMH Toronto* (1973): Princess Margaret Hospital, Toronto.

S Swedish BCG,* SB II (1978): South Swedish Breast Cancer Group, Lund, Sweden.

SASIB* (1971): Scandi-Afro-Swiss-Immuno-Breast International Trialists' Group, Cape Town, South Africa.

Scottish, Scottish Surgery Trial (1982) or Scottish Conservation Trial (1983): Scottish Cancer Trials Office, Edinburgh, United Kingdom.

Scottish D* (1980): Scottish Cancer Trials Office, Edinburgh, United Kingdom.

SE Scotland,* South-East Scotland Radiotherapy Trial (1964): Scottish Cancer Trials Office, Edinburgh, United Kingdom.

SECSG 1* (1976): Southeastern Cancer Study Group, Birmingham, Ala.

St George's,* T1/T2 study (1982): St George's Hospital, London.

St George's E (1982): St George's Hospital, London.

Stockholm (1976): Stockholm Breast Cancer Study Group, Stockholm, Sweden.

Stockholm A* (1971): Stockholm Breast Cancer Study Group, Stockholm, Sweden.

Toronto-Edmont.,* Toronto–Edmonton Radiotherapy Trial (1978): Toronto–Edmonton Breast Cancer Study Group, Toronto.

Tunisia (1977): Institut Salah Azaiz, Tunis, Tunisia.

Uppsala–Örebro* (1981): Uppsala–Örebro Cancer Study Group, Uppsala, Sweden.

Villejuif Paris* (1972): Institut Gustave-Roussy, Villejuif, France.

Wessex* (1973): Wessex Radiotherapy Centre, Southampton, United Kingdom.

WSSA Glasgow (1972): West of Scotland Surgery Trial, Glasgow, United Kingdom.

Wurzburg U., Trial 1 (1977): Wurzburg University, Wurzburg, Germany.

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