Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial

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Summary

Background Since the introduction of breast-conserving treatment, various radiation doses after lumpectomy have been used. In a phase 3 randomised controlled trial, we investigated the effect of a radiation boost of 16 Gy on overall survival, local control, and fibrosis for patients with stage I and II breast cancer who underwent breast-conserving treatment compared with patients who received no boost. Here, we present the 20-year follow-up results.

Methods Patients with microscopically complete excision for invasive disease followed by whole-breast irradiation of 50 Gy in 5 weeks were centrally randomised (1:1) with a minimisation algorithm to receive 16 Gy boost or no boost, with minimisation for age, menopausal status, presence of extensive ductal carcinoma in situ, clinical tumour size, nodal status, and institution. Neither patients nor investigators were masked to treatment allocation. The primary endpoint was overall survival in the intention-to-treat population. The trial is registered with ClinicalTrials.gov, number NCT02295033.

Findings Between May 24, 1989, and June 25, 1996, 2657 patients were randomly assigned to receive no radiation boost and 2661 patients randomly assigned to receive a radiation boost. Median follow-up was 17·2 years (IQR 13·0–19·0). 20-year overall survival was 59·7% (99% CI 56·3–63·0) in the boost group versus 61·1% (57·6–64·3) in the no boost group, hazard ratio (HR) 1·05 (99% CI 0·92–1·19, p=0·323). Ipsilateral breast tumour recurrence was the first treatment failure for 354 patients (13%) in the no boost group versus 237 patients (9%) in the boost group, HR 0·65 (99% CI 0·52–0·81, p<0·0001). The 20-year cumulative incidence of ipsilatelal breast tumour recurrence was 16·4% (99% CI 14·1–18·8) in the no boost group versus 12·0% (9·8–14·4) in the boost group. Mastectomies as first salvage treatment for ipsilateral breast tumour recurrence occurred in 279 (79%) of 354 patients in the no boost group versus 178 (75%) of 237 in the boost group. The cumulative incidence of severe fibrosis at 20 years was 1·8% (99% CI 1·1–2·5) in the no boost group versus 5·2% (99% CI 3·9–6·4) in the boost group (p<0·0001).

Interpretation A radiation boost after whole-breast irradiation has no effect on long-term overall survival, but can improve local control, with the largest absolute benefit in young patients, although it increases the risk of moderate to severe fibrosis. The extra radiation dose can be avoided in most patients older than age 60 years.

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Introduction

Radiotherapy after breast-conserving treatment halves the chance of disease recurrence and reduces breast cancer mortality by about a sixth.[1] However, uncertainty remains as to the radiation dose needed for patients treated with lumpectomy for early breast cancer. For this reason, the European Organisation for Research and Treatment of Cancer (EORTC) did a phase 3 randomised trial[2] investigating the potential advantage of delivering a higher radiation dose to the tumour bed after whole-breast irradiation of 50 Gy in 5 weeks. 5318 patients with microscopically complete excision followed by whole-breast irradiation of 50 Gy were randomly assigned to receive either a boost dose of 16 Gy or no boost dose. The preliminary analysis after 5 years' follow-up suggested that the risk of ipsilateral breast tumour recurrence was reduced in patients who received the boost dose.[2] The largest absolute improvement occurred in patients aged 40 years or less. 10-year follow-up showed a favourable result in the boost group in terms of ipsilateral breast recurrence, with no significant interaction by age group.[3] As a result, the number of salvage mastectomies was substantially reduced. However, severe fibrosis in the tumour bed area was more common in the boost group than in the no boost group. 10-year overall survival did not differ significantly between groups.

Romestaing and colleagues[4] also investigated the effect of a boost dose in a trial including 1024 patients who received a boost of 10 Gy to the tumour bed after 50 Gy delivered with 2·5 Gy per fraction to the whole breast following limited surgery. They found that this approach

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See Online for appendix

For the **protocol** see http://research.nki.nl/ibr/protocols/EORTC-22881-10882-Boost-no-Boost.pdf

significantly reduced the risk of early ipsilateral breast tumour recurrence, with no serious deterioration of the cosmetic result.

We assessed whether the initial benefit of a boost dose, resulting in improved local control, is sustained in the very long term in patients with stage I and II breast cancer who underwent breast-conserving treatment and whether this benefit translates into an improvement in survival.

Methods

Study design and patients

We analysed the long-term results from the EORTC phase 3 randomised controlled trial.[3] The trial was done at 31 hospitals and medical centres in Australia, Belgium, France, Germany, Israel, Netherlands, Spain, Switzerland, and the UK. The protocol is available online.

Patients with T1–2, N0–1, and M0 breast cancer (stage I and II breast cancer) who had undergone macroscopically complete local excision of the breast tumour and axillary dissection were eligible for the trial. Patients were ineligible if they were older than 70 years, if they had pure carcinoma in situ, multiple tumour foci in more than one quadrant, a history of other malignant disease, an Eastern Cooperative Oncology Group performance score higher than 2, residual microcalcifications on mammography, concurrent pregnancy or lactation, or if a tumourectomy was done more than 9 weeks before the start of radiotherapy, and more than 6 months before the start of radiotherapy if chemotherapy was given. Ineligible patients were included in the analyses. The resection margins were assessed for the presence of invasive carcinoma, but not for ductal carcinoma in situ. Oral informed consent was obtained according to EORTC guidelines and the local and national rules of the participating institutes. Ethics committees of the participating institutes approved the protocol.

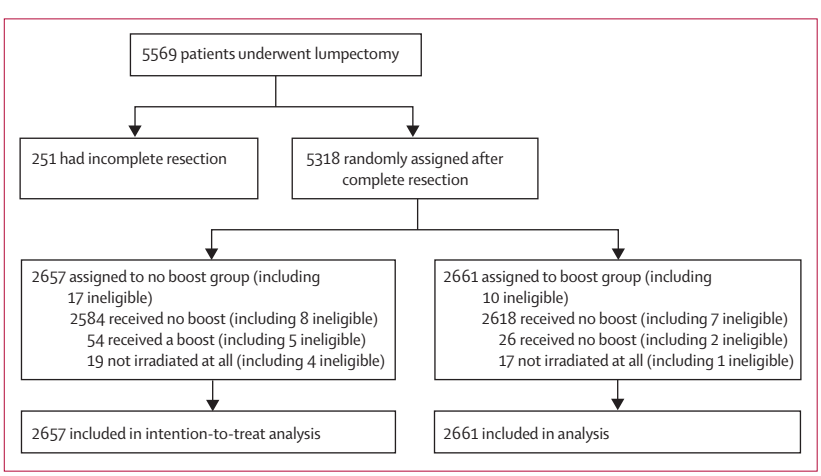

Figure 1: **Trial profile**

Randomisation and masking

Patients who had received microscopically complete excision of a breast tumour (no invasive disease at the inked margin of the surgical specimen according to the local pathologist) and axillary dissection, followed by whole-breast irradiation of 50 Gy in 5 weeks, were centrally randomised at the EORTC headquarters according to a minimisation algorithm[5] (variance method) in a 1:1 ratio to receive either no extra irradiation or a boost dose of 16 Gy aimed at the original tumour bed (appendix). Patients with a microscopically incomplete excision were randomly assigned to boost doses of 10 Gy or 26 Gy; these patients are not included further in this report, but have been reported elsewhere.[6]

Factors used in the minimisation were age, menopausal status, presence of extensive ductal carcinoma in situ (ten or more ducts involved), clinical tumour size, nodal status, and institute where the patient received treatment. Neither patients nor investigators were masked to treatment allocation.

Procedures

Patients had to undergo surgical excision of the primary tumour, with a 1–2 cm margin of macroscopically normal tissue and an axillary dissection.[2] Any removal of additional breast tissue after excision of the primary tumour was termed a re-excision, whether it was done during the same session or later. Patients with axillary lymph node involvement received adjuvant systemic treatment: premenopausal patients received chemotherapy and postmenopausal patients received tamoxifen (20 mg per day for 2 years). Patients not given adjuvant chemotherapy began radiotherapy within 9 weeks after lumpectomy.

Irradiation of the whole breast was done with two tangential opposing megavoltage photon beams (high-energy x-ray or tele-cobalt). A total dose of 50 Gy during a 5-week period, with a dose of 2 Gy in 25 fractions, was delivered at the intersection of the central axes of the beams, in agreement with International Commission of Radiation Units and Measurements report 50.[7] The boost dose was 16 Gy in eight fractions delivered with electrons or oblique wedged photon beams, or 15 Gy delivered with with an ^{192}Ir implant at a dose rate of 0·5 Gy per h (a 15 Gy internal dose is equivalent to a 16 Gy external dose). The choice between internal and external dose was at the discretion of the treating physician. The dose for the boost was specified at the centre of the tumour excision area (point B; appendix). No dose reductions were allowed.

Patients were followed up two or three times per year for 5 years, then once per year by mammography and clinical examination including scoring of fibrosis. At each visit except baseline, the physician scored the grade of fibrosis (none, minor, moderate, or severe) for the whole breast and for the boost area.

	No boost group (n=2657)	Boost group (n=2661)
Age (years)	54·9 (47·3–62·0)	54·8 (47·1–62·6)
≤35	72 (3%)	82 (3%)
35–40	156 (6%)	139 (5%)
41–50	665 (25%)	669 (25%)
51–60	943 (356%)	860 (32%)
>60	821 (31%)	911 (34%)
Menopausal status		
Unknown	10 (<1%)	8 (<1%)
Premenopausal	999 (38%)	1004 (38%)
Menopausal	1648 (62%)	1649 (62%)
Performance status		
Unknown	10 (<1%)	9 (<1%)
0	2335 (88%)	2335 (88%)
1–2	312 (12%)	317 (12%)
Tumour characteristics		
T palpation		
Unknown	336 (13%)	348 (13%)
Not palpable	569 (21%)	581 (22%)
<1 cm	315 (12%)	313 (12%)
1–2 cm	856 (32%)	829 (31%)
2–3 cm	433 (16%)	449 (17%)
>3 cm	148 (6%)	141 (5%)
Mammography		
<1 cm	576 (22%)	525 (20%)
1–2 cm	1027 (39%)	1067 (40%)
2–3 cm	397 (15%)	436 (16%)
>3 cm	110 (4%)	104 (4%)
Unknown	547 (21%)	529 (20%)
Clinical staging		
T stage		
T1	1379 (52%)	1373 (52%)
T2	1274 (48%)	1281 (48%)
T3	4 (<1%)	7 (<1%)
N stage		
N0	2409 (91%)	2383 (90%)
N1–2	182 (7%)	209 (8%)
Nx	66 (3%)	69 (3%)
Pathological staging		
Re-exision		
Unknown	8 (<1%)	8 (<1%)
No	2003 (75%)	1991 (75%)
Yes	646 (24%)	662 (25%)
Largest diameter dominant legion		
Unknown	49 (2%)	62 (2%)
<10 mm	683 (26%)	635 (24%)
10–20 mm	1402 (53%)	1451 (55%)
>20 mm	523 (20%)	513 (19%)
Histological type		
Unknown	8 (0%)	8 (<1%)
Invasive ductal carcinoma	2155 (81%)	2198 (83%)
Invasive lobular carcinoma	228 (9%)	219 (8%)
Mixed invasive pattern	65 (2%)	81 (3%)
Tubular carcinoma	99 (4%)	71 (3%)
Medullary carcinoma	58 (2%)	49 (2%)
Colloid carcinoma	37 (1%)	33 (1%)
Other	7 (<1%)	2 (<1%)
Number of nodes examined		
Unknown	69 (3%)	75 (3%)
0	21 (1%)	16 (1%)
1–5	170 (6%)	176 (7%)
6–10	813 (31%)	826 (31%)
11–15	876 (33%)	914 (34%)
>15	708 (27%)	654 (25%)
Number of positive nodes		
Unknown	25 (1%)	20 (1%)
0	2078 (78%)	2090 (79%)
1–3	452 (17%)	449 (17%)
≥4	102 (4%)	102 (4%)
Hormone receptor status*		
Oestrogen receptor positive, progesterone receptor positive	1031 (39%)	1042 (39%)
Oestrogen receptor positive, progesterone receptor negative	255 (10%)	267 (10%)
Oestrogen receptor negative, progesterone receptor positive	133 (5%)	141 (5%)
Oestrogen negative, progesterone receptor negative	345 (13%)	358 (14%)
Unknown	893 (34%)	853 (32%)

Data are median (IQR) or n (%). *Oestrogen receptor status determined according to local procedures by either charcoal or immunohistochemistry.

Table: **Patient and tumour characteristics**

Outcomes

The primary endpoint was overall survival. Survival was counted from the date of randomisation to date of death from any cause, or to last visit. For breast cancer mortality, other causes of death were analysed as competing risks. Secondary outcomes were local control (ipsilateral breast tumour recurrence), cosmesis, and fibrosis. Exploratory endpoints were breast cancer mortality, time to distant metastasis, analysis of ipsilateral breast tumour recurrence by age, analysis of fibrosis by age, disease-free survival, and overall survival after local failure. Time to ipsilateral breast tumour recurrence as first treatment failure was defined as the time from day of randomisation (instead of date of surgery as mentioned in the original protocol to reduce the risk of bias) to the day of first recurrence, or to the day of last visit for patients alive and free of recurrence.

Ipsilateral breast tumour recurrence as the first treatment failure was the event of interest and any other treatment failure as first event (including death) was considered a competing risk. Time to distant metastases was defined as the time from randomisation to the first report of distant metastases (event), death without metastases (competing risk), or last visit (censored observation). Similarly, time to second primary cancer was defined as the time from randomisation to the first report of second primary, death without the event of interest (competing risk), or last visit (censored observation).

For the analyses of overall survival and disease-free survival after local failure, time to event was counted from the first ipsilateral breast tumour recurrence for all patients with local ipsilateral breast tumour recurrence as first failure. Disease-free survival was the time from day of first report of local ipsilateral breast tumour recurrence, to the day of first report of either a subsequent local failure or a failure at another site or to death of any cause.

Cumulative incidence of severe fibrosis was counted from entry to the date of first report of severe fibrosis or until the last visit before a mastectomy. Mastectomy and death without severe fibrosis were competing risks for this analysis.

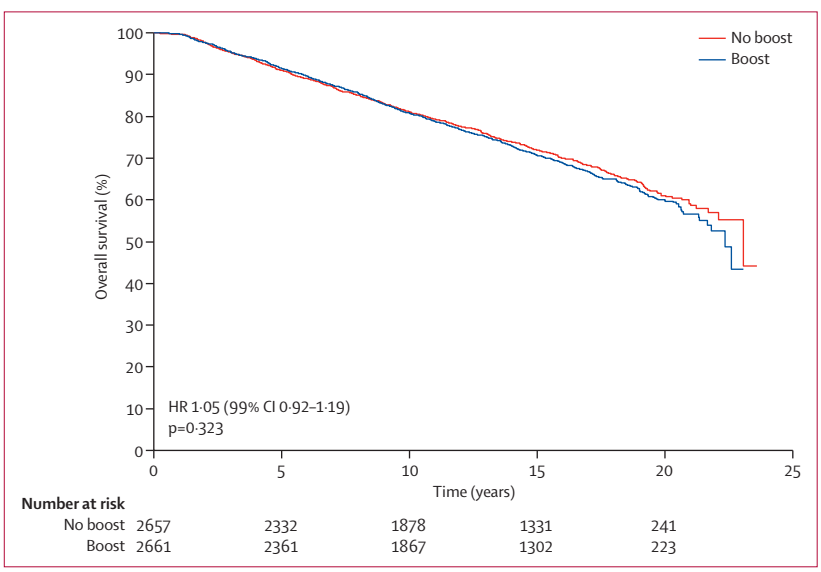

Figure 2: **Overall survival**
HR=hazard ratio.

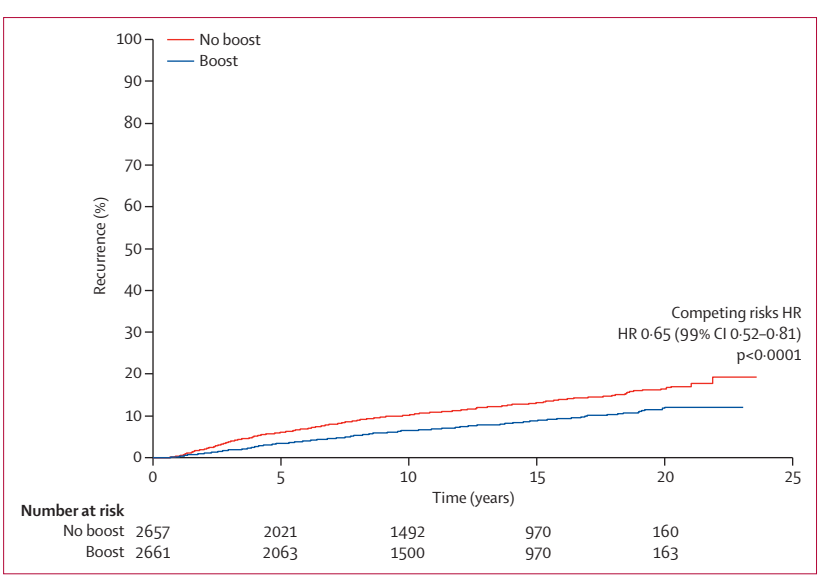

Figure 3: **Ipsilateral breast tumour recurrence**
HR=hazard ratio.

Statistical analysis

Initially, the endpoint of interest was the cosmetic effect, with 90% confidence that the difference in ipsilateral breast tumour recurrence did not differ between groups by more than 5%. However, after 3 years, the study was enlarged and survival was added as the primary endpoint to show a difference of 5% in 10-year overall survival (from 80% to 85%, hazard ratio [HR] 0·728) with a power of 90% and a significance level of 1% using a two-sided log-rank test. Local control, cosmesis, and fibrosis were also added as secondary endpoints. 960 deaths were needed to provide adequate power for the test, with 5000 patients to be recruited (appendix).[2]

All tests were done at the two-sided 0·01 significance level. The analyses were by intention to treat. Survival was estimated by Kaplan-Meier analysis and compared with a log-rank test;[8] cumulative incidences of ipsilateral breast tumour recurrence, distant metastases, second primary cancers, breast-cancer mortality, and fibrosis were compared with Fine and Gray tests.[9] We estimated HRs and 99% CIs with Cox models for endpoints not subject to competing risks, and we estimated competing risk-adjusted HRs and 99% CIs from Fine and Gray models.[9] The analyses were done with SAS computer software (version 9.4).

The trial is registered with ClinicalTrials.gov, number NCT02295033.

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 24, 1989, and June 25, 1996, 5569 participants with early stage breast cancer underwent a lumpectomy followed by whole-breast irradiation of 50 Gy. 5318 patients had microscopically complete tumour excision and were randomly assigned—2661 to the boost group and 2657 to the no boost group (figure 1). 251 patients with microscopically incomplete excision were randomly assigned to a boost dose of 10 Gy or 26 Gy—however, these results have been described elsewhere[6] and will not

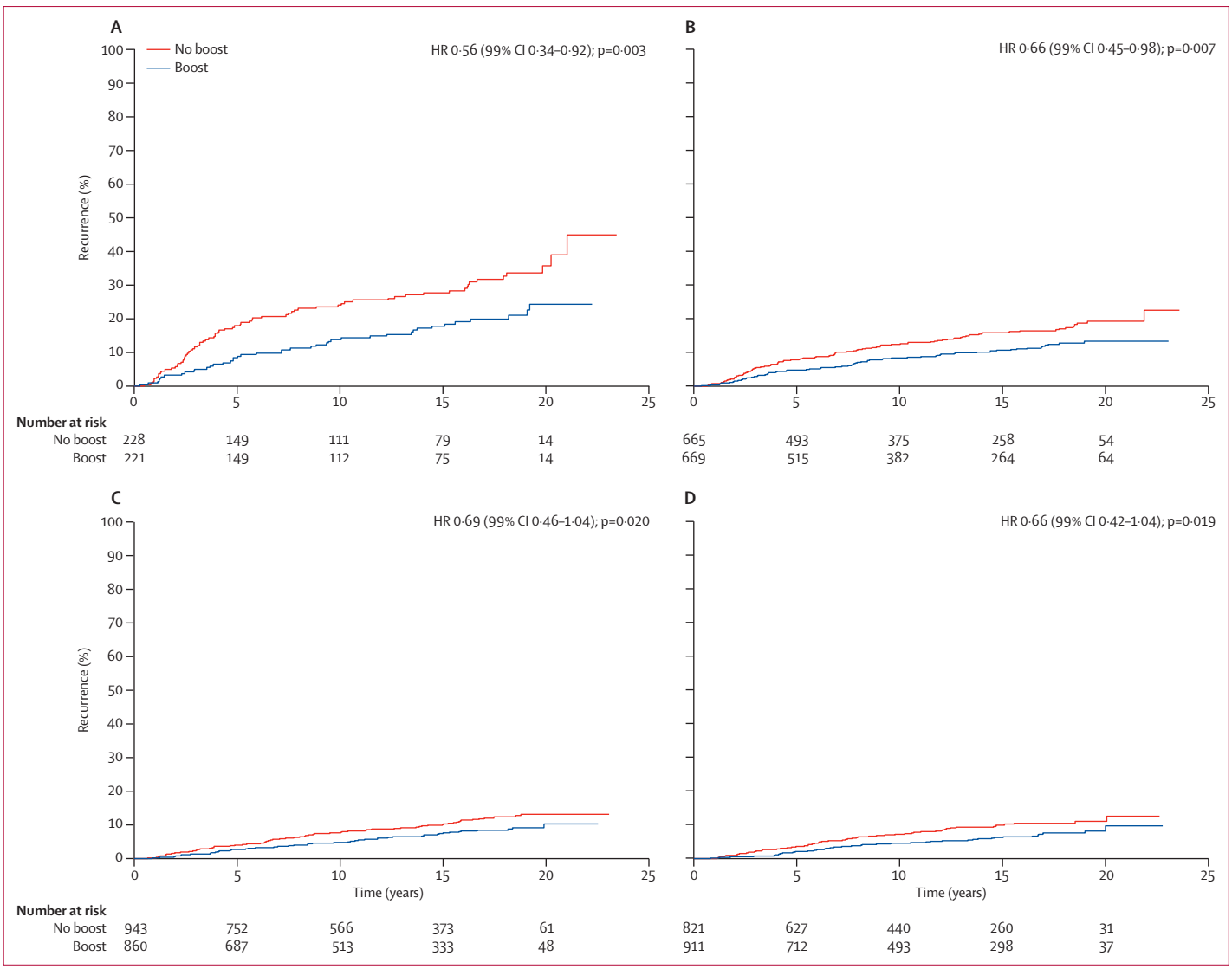

Figure 4: **Cumulative incidence of ipsilateral breast tumour recurrence by age**
For patients aged ≤40 years, 71 patients in the no boost group versus 42 in the boost group had recurrence (A); for patients aged 41–50 years, 108 versus 74 had recurrence (B); for patients aged 51–60 years, 100 versus 64 had recurrence (C); and for patients aged >60 years, 75 versus 57 had recurrence (D). HR=hazard ratio.

be considered further in this report. 26 patients assigned to the boost group did not receive the boost (16 refused, four because of administration errors, two because of microcalcification, two because of metastases, one had psychiatric problems, and one because of dermolysis during whole-breast irradiation), whereas 54 patients assigned to the no boost group received a boost (19 in error, 13 for medical decision [eg, disease extension, more advanced stage, incomplete resection], 22 because of patient request).

Reasons for ineligibility were different histology (four patients in the no boost group *vs* two in the boost group), microcalcifications on postoperative mammogram (four *vs* three), previous malignancy (four *vs* three), incomplete surgery (one *vs* none), and higher TNM stage or tumour in more than one quadrant (three *vs* three; appendix); but all patients were included in the analyses.

The main reasons for deviation from treatment allocation were patient choice and administrative error. Median follow-up of patients with complete resection was 17·2 years (IQR 13·0–19·0) and median age of the patients at treatment was 55 years (47–62). Patient characteristics were similar in the two groups (table): 90% of patients were clinically N0 and 78% were pathologically N0. Surgery or whole-breast irradiation differed little between groups (appendix). 225 (8%) of 2661 patients in the boost group received an interstitial boost at a median dose of 15 Gy (IQR 15–15), whereas 2393 (90%) of 2661 received an external boost at a median dose of 16 Gy (IQR 16–16). 17 received no irradiation at all (five had no information on

treatment, six refued, three because of medical decision based on microcalcification, metastases, or age, and three in error).

Use of chemotherapy or tamoxifen as adjuvant treatment did not differ significantly between groups (appendix). However, in premenopausal patients with positive lymph nodes, chemotherapy was prescribed more often in the boost group than in the no boost group (197 [87·6%] of 225 *vs* 174 [78·7%] of 221).

799 (30%) of 2657 patients died in the no boost group versus 832 (31%) of 2661 patients in the boost group. 20-year overall survival was 61·1% in the no boost group (99% CI 57·6–64·3) versus 59·7% in the boost group (56·3–63·0; HR 1·05, 99% CI 0·92–1·19, p=0·323; figure 2). Cumulative incidence of breast cancer mortality did not differ significantly between groups (447 events *vs* 456 events, HR 1·01, 99% CI 0·86–1·20, p=0·82). The cumulative risk of distant metastases did not differ significantly (568 events *vs* 602 events); risk of distant relapse at 20 years was 24·8% (99% CI 22·3–27·4) in the no boost group versus 26·0% (23·4–28·7) in the boost group (HR 1·06, 99% CI 0·92–1·24; p=0·29). We recorded no significant difference in the cumulative incidence of second primary tumour in the contralateral breast (208 in the no boost group *vs* 232 in the boost group), or at sites other than the breast (216 *vs* 240; appendix). There was also no difference in overall incidence of breast

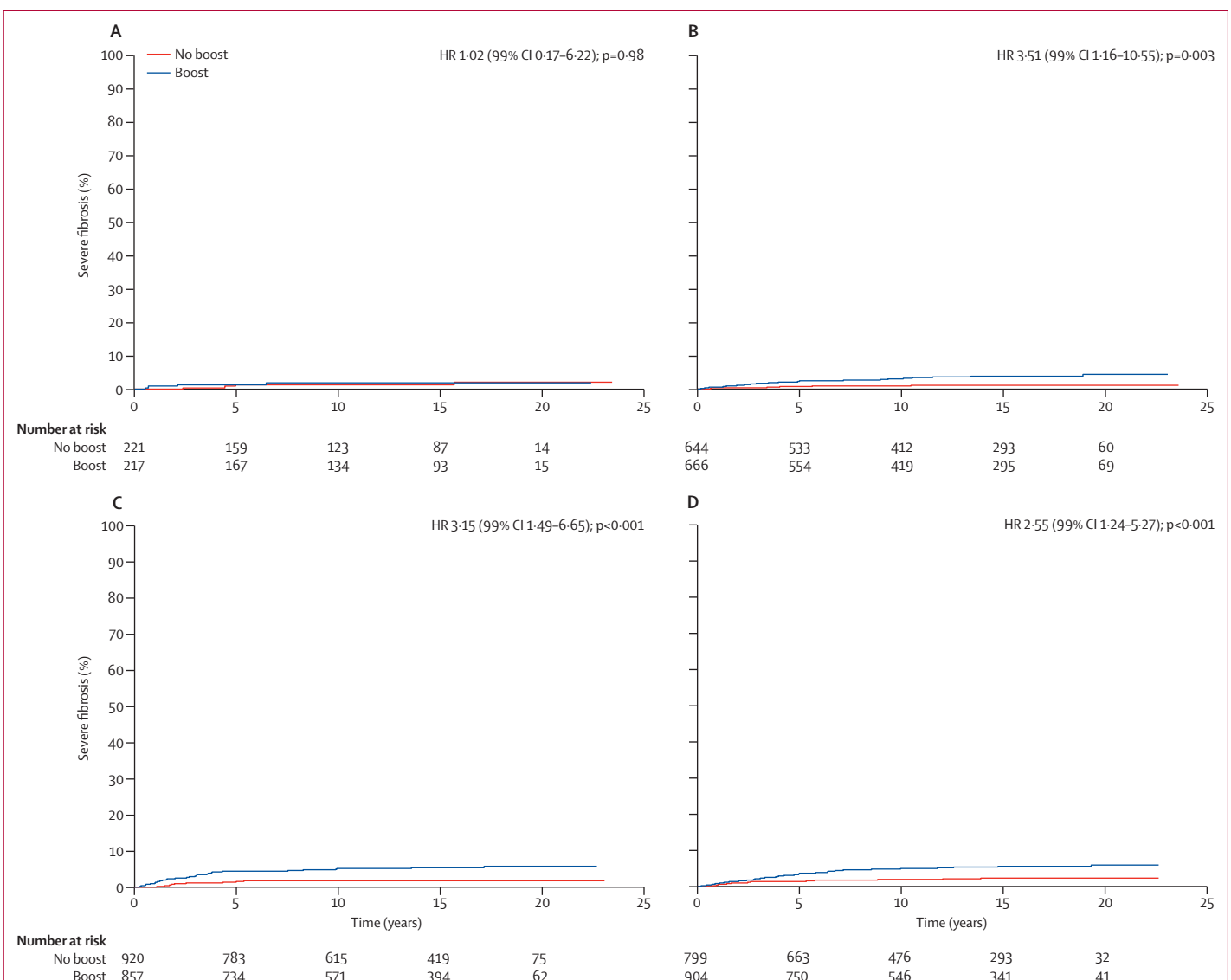

Figure 5: **Cumulative incidence of severe fibrosis by age**

For patients aged ≤40 years, four patients in the no boost group versus four in the boost group had severe fibrosis (A); for patients aged 41–50 years, seven versus 25 had severe fibrosis (B); for patients aged 51–60 years, 16 versus 46 had severe fibrosis (C); and for patients aged >60 years, 17 versus 49 had severe fibrosis (D). HR=hazard ratio.

cancer-related events, disease-free survival, or time to any recurrence (appendix).

Local breast recurrence was first failure for 354 (13%) patients in the no boost group versus 237 (9%) patients in the boost group (figure 3); any locoregional failure occurred in 480 versus 352 patients. Ipsilateral breast tumour recurrence increased in both treatment groups: from 10·2% (99% CI 8·7–11·8) at 10 years to 16·4% (14·1–18·8) at 20 years for the no boost group, and from 6·4% (5·2–7·7) to 12·0% (9·8–14·4) for the boost group. The HR for an ipsilateral breast tumour recurrence as a first event was 0·65 (99% CI 0·52–0·81, p<0·0001). Patients' age was strongly correlated with the absolute risk of ipsilateral breast tumour recurrence. 20-year cumulative incidence ranged from 34·5% (99% CI 21·9–47·2) for patients 35 years or younger, to 11·1% (7·6–14·6) for patients older than 60 years (appendix). The relative reduction of risk by giving a boost dose was significant for younger age groups (for age ≤40 years, p=0·003; and for age 41–50 years, p=0·007) but not for the two older age groups (for age 51–60 years, p=0·02; for age >60 years, p=0·019); the effect was not significantly different by age group ($p_{interaction}$=0·67; figure 4, appendix). The absolute risk reduction was largest in the youngest patient group: 20-year risk was 36·0% (99% CI 25·8–46·2) in the no boost group versus 24·4% (14·9–33·8) in the boost group for patients younger than 40 years; 19·4% (14·7–24·1%) versus 13·5% (9·5–17·5) for patients aged 41–50 years; 13·2% (9·8–16·7) versus 10·3% (6·3–14·3) for patients aged 51–60 years; and 12·7% (CI 7·4–18·0) versus 9·7% (5·0–14·4) for patients older than 60 years (figure 4). Results for ipsilateral breast tumour recurrence were essentially unchanged when adjusted for baseline factors and other treatments (data not shown). Overall, 261 (44%) of 591 ipsilateral breast tumour recurrences occurred in the primary tumour bed, 47 (8%) of 591 occurred in the scar, 66 (11%) of 591 were diffuse in the breast, 165 (28%) of 591 occurred outside the original tumour area, and for 52 (9%) of 591 location was not specified (appendix). The type of boost did not have a significant effect on the cumulative incidence of ipsilateral breast tumour recurrence, whether it was given by electrons, ^{60}Co, megavoltage x-rays, or ^{192}Ir boost (appendix). Regional recurrence in the axilla or supraclavicular area was the first event in 66 (2%) patients in the no boost group versus 59 (2%) patients in the boost group.

Second primary ipsilateral breast cancers (different histology compared with the primary tumour) occurred in 51 patients (30 [1%] in the no boost group *vs* 21 [1%] in the boost group; appendix). Second primary contralateral breast cancers occurred in 440 patients (208 [8%] in the no boost *vs* 232 [9%] in the boost group).

The cumulative incidence of severe fibrosis at 20 years was 5·2% (99% CI 3·9–6·4) in the boost group versus 1·8% (1·1–2·5) in the no boost group (p<0·0001; appendix). Severe fibrosis was more common in the boost group than in the no boost group for all age groups except patients younger than 41 years (figure 5). Moderate or severe fibrosis was also more common in the boost group versus the no boost group, with a 20-year cumulative incidence of 30·4% (99% CI 28·0–32·9) versus 15·0% (13·0–17·1; p<0·0001). The cumulative incidence of any degree of fibrosis (minor, moderate, or severe) was 71·4% (69·0–73·7) versus 57·2% (54·6–59·8; p<0·0001).

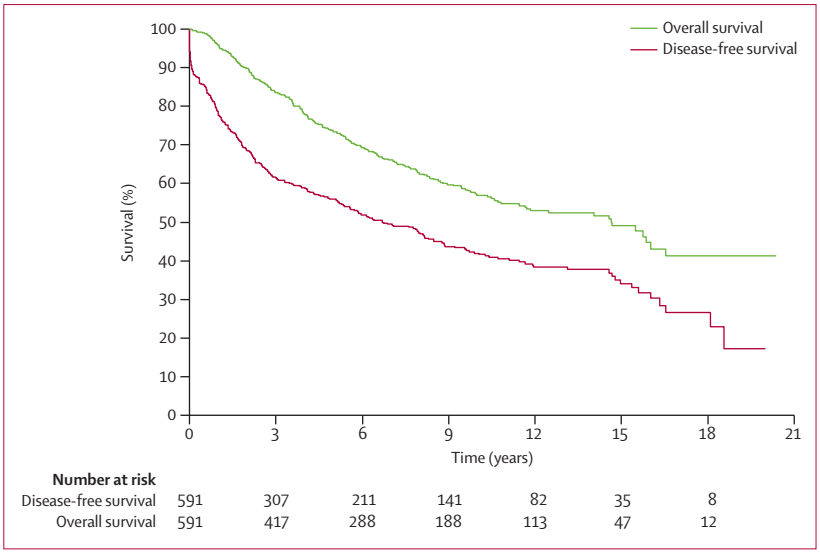

Figure 6: **Overall survival and disease-free survival after local failure**
The drop of the curve at 0 years is a result of 34 patients who had ipsilateral breast tumour recurrence with failure at another site as the first event. For both endpoints, censoring was done at the date of last visit.

Salvage treatment for a breast recurrence was done for 354 (13%) patients in the no boost group and 237 (9%) patients in the boost group. Mastectomy was the initial salvage treatment for ipsilateral breast tumour recurrence for 457 patients (279 [79%] of 354 in the no boost group and 178 [75%] of 237 in the boost group). The cumulative incidence of salvage mastectomy at 10 years was 6·4% (99% CI 5·2–7·7) for the boost group and 10·3% (8·7–11·8) for the no boost group.

Lumpectomy was the salvage treatment for 52 patients (32 [1%] in the no boost group *vs* 20 [1%] in the boost group). The salvage treatment in the remaining 69 patients (38 [1%] in the boost group *vs* 31 [1%] in the no boost group) was mainly systemic chemotherapy. No information about salvage treatment was obtained for five patients in the no boost group and eight in the boost group. For patients in both groups together, at 10 years after local relapse, disease-free survival (counted from local relapse to any next failure) was 42·0% (99% CI 35·9–48·0) and overall survival was 57·0% (99% CI 50·4–63·0; figure 6).

Discussion

20 years after breast-conserving treatment, about 60% of patients with breast cancer were still alive, but survival did not differ between patients who received or did not

receive a boost of 16 Gy after whole-breast irradiation. However, a boost dose did reduce the incidence of ipsilateral breast tumour recurrence.

The failure of improved local control to improve breast cancer mortality or overall survival seems contradictory to the findings of the EBCTCG trial.[1] However, in our study only about 20% of patients were node positive; in the EBCTCG trial the survival benefit of radiotherapy was recorded in node-positive patients. Nevertheless, we detected no substantial difference in survival in relation to nodal status (data not shown), or first time to any recurrence. The most likely explanation is successful salvage mastectomy treatment for these breast recurrences, as reported in a previous trial in which the high rate of local recurrence in the breast-conserving treatment group compared with the mastectomy group did not affect survival (panel).[13]

The relative benefit of the boost dose for local control was independent of age, but with increasing age the absolute gain in local control decreased (in proportion to the absolute risk of relapse) but remained statistically significant. Younger patients had more ipsilateral breast tumour recurrences than older patients, as reported in other studies.[15,16,17] Fortunately, the largest absolute benefit of the boost dose occurred in younger patients.

A similar effect of a boost dose has been reported in some other trials, including that by Romestaing and colleagues,[4] in which patients were treated with external irradiation and that by Polgar and colleagues,[18] in which patients received boost with an iridium implant.

The site of local recurrence was, in almost half of patients, in the primary tumour bed (appendix), which supports use of an non-uniform dose distribution, with the highest dose directed to the primary tumour site. The survival of patients after ipsilateral breast recurrence was high. The success of the salvage treatment will be investigated further.

The local recurrence rate in our study was higher than that reported in other studies, such as the Young Boost Trial,[14] which reported 5-year local recurrence rates as low as 1·2% in patients younger than 51 years. Similar local control rates were reported in the control groups of trials comparing whole-breast irradiation with partial breast irradiation.[19,20] Possible explanations for the lower rate in other trials are better preoperative staging imaging procedures, use of image-guided surgery with pathological assessment of the margins, optimised radiotherapy with 3D treatment planning, and more widespread use of effective adjuvant systemic treatment. 80% of patients received adjuvant systemic treatment in the Young Boost Trial[14] compared with only 30% in our trial. The high number of second surgeries might also relate to the higher local recurrence rate—it was higher than the number of second surgeries usually achieved presently, especially considering that a margin greater than 1 cm was used. The use of image-guided surgery has reduced the proportion of re-excisions to less than 10%,[21] and might also improve local control. The boost dose did not cause a significant increase in cardiac mortality, second primary tumours, or contralateral breast cancer (appendix). However, it did harm the cosmetic results and increased fibrosis,[22,23] although the boost did not significantly increase severe fibrosis in patients younger than 40 years, who benefited most from the boost. Fibrosis could also be reduced by lowering the total dose of whole-breast irradiation, or using techniques such as simultaneously integrated boost or intensity-modulated radiation treatment.[24–27] Because the size of the absolute benefit for tumour control decreases with increasing age, the gain in local control in older patients needs to be weighed against the increase in risk of fibrosis associated with a boost dose using nomograms.[22,28] (Neo)-adjuvant systemic treatment significantly reduces ipsilateral breast tumour recurrence, restricting the need for a boost dose. The development of gene or protein profiles that predict radiosensitivity might help to select patients for radiation and the dose to use.[29,30]

A treatment boost reduced the number of salvage mastectomies for initial local recurrence by more than a third compared with the no boost group. The choice of a salvage treatment is related to the type of relapse—eg, systemic treatment is used instead of mastectomy for diffuse ipsilateral breast tumour recurrence or local recurrences that occur in combination with distant spread of disease.

Panel: Research in context

Systematic review

This trial was designed shortly after a few randomised trials were published,[10–12] all showing equal survival after breast-conserving treatment or mastectomy,[13] the latter being the standard treatment for early breast cancer at the time. Uncertainty existed with regard to the required radiation dose, leading to the question: is a radiation dose equivalent to 50 Gy in 5 weeks targeted at the whole breast sufficient, or is an extra radiation dose to the tumour bed needed? A search of published work showed that no extra radiation or radiation doses between 10 Gy and 25 Gy to the tumour bed were given after whole-breast irradiation. As a result of this paradox, a randomised trial was initiated to investigate the possibility of reducing the high radiation dose used in the previous EORTC 10801 trial.[13] To obtain better cosmetic results and less fibrosis without exceeding a difference of 5% in local control, an extra radiation dose was omitted. Later, the trial was extended to investigate the effect of differences in local control on survival.

Interpretation

Our long-term follow-up findings show that an extra radiation dose to the tumour bed led to better local control after breast-conserving treatment and therefore fewer salvage mastectomies. Although the relative benefit of a boost dose was similar in all age groups, the absolute gain of a boost dose was largest in patients younger than 51 years. However, better local control coincided with more fibrosis, and cosmetic results were somewhat worse. To decide the proper radiation dose for an individual patient, one should therefore take into account the age of the patient. One should also consider the more local control reported in more recent trials, probably as a result of better screening, image-guided surgery and radiotherapy, and more use of adjuvant systemic treatment.[14] In patients older than 60 years, the gain in local control from a boost dose is small; therefore, it should only be given to patients with microscopically incomplete excision, especially because survival was not improved in our study.

Our study has several limitations. Central pathology review was done for only a third of patients, although a serious discrepancy between the original pathology report and the review occurred in only a few patients.[31] Ductal carcinoma in situ reaching the inked margin of the surgical specimen was not recorded. However, for 1616 patients, the 10-year cumulative risk of local breast cancer relapse as a first event was not significantly affected if the margin was scored negative, close, or positive for invasive tumour or ductal carcinoma in situ according to central pathology review.[32] Also, clinical practice guideline recommendations of the Society of Surgical Oncology and the American Society for Radiation Oncology were generally followed, such as repeated mammography or radiography of the specimen, advised in case of preoperative microcalcifications.[32] The whole-breast irradiation dose of 50 Gy in 5 weeks is different from the shorter fractionation schedules in the START trial.[33] However, because local control and side-effects were not substantially different in the START trial, one might expect that the effect of the boost dose is similar in patients treated with shorter fractionation schedules.[33] Fibrosis is difficult to measure objectively, although cosmetic outcome can be measured more objectively.[34] Finally, the effect of a boost dose seems to be independent of tumour characteristics such as grade and stage, but also of giving adjuvant systemic treatment, as reported previously.[2]

Contributors

HB and J-CH designed the study. HB, PM, PP, CW, AF, JJ, DS, BO, CR, J-CH, HS, EVL, YK, PE, RB, RM, DM, J-BD, VR, and ROM collected data. LC and SC analysed data. HB, LC, PM, PP, CW, AF, JJ, DS, BO, CR, J-CH, HS, EVL, YK, PE, RB, RM, DM, J-BD, VR, R-OM, and SC interpreted data and wrote the first draft. All authors approved the report.

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Declaration of interests

We declared no competing interests.

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