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ORIGINAL REPORT

# Impact of a Higher Radiation Dose on Local Control and Survival in Breast-Conserving Therapy of Early Breast Cancer: 10-Year Results of the Randomized Boost Versus No Boost EORTC 22881-10882 Trial

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## ABSTRACT

### Purpose
To investigate the long-term impact of a boost radiation dose of 16 Gy on local control, fibrosis, and overall survival for patients with stage I and II breast cancer who underwent breast-conserving therapy.

### Patients and Methods
A total of 5,318 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 (2,661 patients) or no boost dose (2,657 patients), with a median follow-up of 10.8 years.

### Results
The median age was 55 years. Local recurrence was reported as the first treatment failure in 278 patients with no boost versus 165 patients with boost; at 10 years, the cumulative incidence of local recurrence was 10.2% versus 6.2% for the no boost and the boost group, respectively ($P < .0001$). The hazard ratio of local recurrence was 0.59 (0.46 to 0.76) in favor of the boost, with no statistically significant interaction per age group. The absolute risk reduction at 10 years per age group was the largest in patients ≤ 40 years of age: 23.9% to 13.5% ($P = .0014$). As a result, the number of salvage mastectomies has been reduced by 41%. Severe fibrosis was statistically significantly increased ($P < .0001$) in the boost group, with a 10-year rate of 4.4% versus 1.6% in the no boost group ($P < .0001$). Survival at 10 years was 82% in both arms.

### Conclusion
After a median follow-up period of 10.8 years, a boost dose of 16 Gy led to improved local control in all age groups, but no difference in survival.

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## INTRODUCTION

Breast-conserving therapy (BCT) is considered the standard of care for stage I and II breast cancer patients and results in survival equivalent to that observed after mastectomy.[1-7] The meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) revealed the need for radiotherapy after tumorectomy by showing that breast irradiation reduced the 5-year local recurrence rate from 26% to 7%.[8] The meta-analysis also suggested that one death from breast cancer would be avoided for every four local recurrences that could be prevented. In a previous European Organisation for Research and Treatment of Cancer (EORTC) trial in patients with stage I and II breast cancer, despite similar survival rates and a small difference in local control in both treatment arms after mastectomy or BCT,[3] two major limitations were identified. First, because of the high radiation dose given, a significant proportion of the patients experienced severe fibrosis that resulted in a poor cosmetic outcome[9]; second, major differences in local control were observed between the treating institutes, which could not be explained by patient selection.[10] These observations and the uncertainty about the optimal radiation dose led to the design of a randomized trial investigating the potential advantage of delivering a higher radiation dose to the tumor bed. For this new trial a lower boost dose was selected than in the previous EORTC trial (16 instead of 25 Gy) because of the large proportion of patients who developed

fibrosis in the earlier trial. A similar trial was carried out in France with 1,024 patients.[11]

The results on local control were published based on an average of only 5 years follow-up, as recommended by the Independent Data Monitoring Committee.[12] This preliminary analysis suggested that the hazard of local recurrence was reduced by 41% in patients who received a boost dose of 16 Gy to the tumor bed. The largest improvement was seen in patients ≤ 40 years old. No results on survival were presented at that time, given that overall survival after 10 years follow-up was the primary end point of the trial. The purpose of this article is to report on the impact of a 16-Gy boost radiation dose after BCT on local control, fibrosis, and survival for patients with stage I and II breast cancer at 10 years follow-up.

## PATIENTS AND METHODS

### Trial Design

From 1989 to 1996, 5,318 patients who received microscopically complete excision of a breast tumor and axillary dissection, followed by whole-breast irradiation to 50 Gy in 5 weeks, were randomly assigned to receive either no extra irradiation or a boost dose of 16 Gy to the original tumor bed. In a separate stratum of the trial, 251 patients with a microscopically incomplete excision were randomly assigned to receive a boost dose of either 10 or 26 Gy.[13] The resection margins were evaluated for the presence of invasive carcinoma, but not for ductal carcinoma in situ (DCIS). Random assignment occurred centrally after surgery at the EORTC Data Centre using the minimization technique.[14] Treatment allocation was balanced with respect to age, menopausal status, presence of extensive DCIS (when 10 or more ducts were involved the DCIS), clinical tumor size, nodal status, and institute where the patient received treatment. Of the 5,318 patients with complete resection, 2,657 were allocated to receive no boost and 2,661 were allocated to receive a boost. An independent data monitoring committee recommended publication of the local control results in the complete resection group, given that the results after a median of 5 years follow-up revealed a significant clinical impact of this extra radiation dose on the rate of ipsilateral breast cancer recurrence.[12] We present the final results of the trial, according to the primary statistical trial design to demonstrate a 5% improvement in the 10-year overall survival (from 80% to 85%; hazard ratio [HR] = 0.73), with 90% power at the two-sided 1% significance level. This objective requires 960 deaths, which justifies the planned sample size of 5,000 patients.

### Eligibility

Patients with T1-2, N0-1, and M0[15] breast cancer were eligible for the trial. Patients older than 70 years, or those with pure carcinoma in situ, multiple tumor foci in more than one quadrant, a history of other malignant disease, Eastern Cooperative Oncology Group performance score higher than 2, residual microcalcifications on mammography, or gross residual disease in the breast after lumpectomy (unless re-excision had been performed) were ineligible. Oral informed consent was obtained according to EORTC guidelines and the local and national rules of the participating institutes.

Patients were referred from 31 centers in nine countries (Appendix Fig A1, online only, and Acknowledgment, online only). There were major deviations from eligibility criteria for 26 patients: residual microcalcifications on postoperative mammography (six patients), previous history of a malignant tumor (five patients), pure intraductal carcinoma in situ (three patients), stage T3 tumor (two patients), clinically fixed axillary nodes (two patients), and various other deviations (eight patients). In addition, 107 patients were older than 70 years, and for 343 patients the delay between surgery and the start of radiotherapy was longer than allowed by the protocol. The latter two groups were considered to have minor deviations from the protocol. All patients, whether eligible or ineligible, were included in the analysis.

### Treatment

The protocol called for patients to undergo surgical excision of the primary tumor, with a 1-cm margin of macroscopically normal tissue and an axillary dissection.[12] Any removal of additional breast tissue after the excision of the primary tumor was termed a re-excision, whether it was performed during the same session or later.

Patients with axillary lymph node involvement received adjuvant systemic therapy: premenopausal patients received chemotherapy and postmenopausal patients received tamoxifen. Patients not administered adjuvant chemotherapy began radiotherapy within 9 weeks after lumpectomy.

Irradiation of the whole breast was performed using two tangential 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 per fraction, was delivered at the intersection of the central axes of the beams, in agreement with International Commission of Radiation Units and Measurements report 50.[16] The boost dose of 16 Gy had to be delivered with electrons or tangential fields administered in eight fractions, or with an iridium-192 implant at a dose rate of 0.5 Gy per hour.

### Quality Assurance Program

An intensive quality assurance program[17-21] was set up to ensure that the treatment was delivered in a standard fashion in all centers. This consisted of a dummy run procedure and on-site visits. Beam calibration in the participating centers was also verified by a team of physicists. Central pathology review was performed by J.L. Peterse at the Netherlands Cancer Institute (Amsterdam, the Netherlands).

### Statistical Methods

All analyses were carried out according to the intent-to-treat policy (ie, all randomly assigned patients are included in the analyses in the arm they were assigned by the randomization procedure. Time to local recurrence was calculated from the date of random assignment to the date of recurrence. Local recurrences in the breast as the first treatment failure were analyzed. Data for patients who remained free of local disease were censored at the date of last visit, but any other treatment failure as the first event was considered a competing risk in this analysis. Survival and local control were compared by log-rank[22] and Gray test,[23] respectively. The two-sided significance level was set at .01. Treatment effects are summarized by the HR for the boost versus no boost groups and the 99% CI.

## RESULTS

### Patient and Tumor Characteristics

A total of 5,569 early-stage breast cancer patients underwent a lumpectomy followed by whole-breast irradiation of 50 Gy within the present boost versus no boost trial. All patients in whom the tumor excision was microscopically complete according to the local pathologist were randomly assigned to receive either a boost dose of 16 Gy (2,661 patients) or no boost dose (2,657 patients). The median follow-up in this group with complete resection was 10.8 years and the median age of the patients at treatment was 55 years. Characteristics of the patients were similar in the two groups (Table 1): 90% of patients were cN0 and 78% were pN0. Treatment data were documented for 2,637 of 2,657 patients in the no boost group and 2,643 of 2,661 patients in the boost group. There were no marked differences between the groups with respect to the surgery or whole-breast irradiation (Appendix Tables A1 to A3, online only).

Twenty-six patients in the boost group did not receive the boost, whereas 53 patients in the no boost group received a boost. In most instances, the reason for protocol deviation was either patient choice or administrative error. In the boost group, 225 patients received an interstitial boost (10% of boost treatments) at a median dose of 15 Gy,

**Table 1.** Patient and Tumor Characteristics of the Overall Population: Baseline Information (N = 5,318)

| Characteristic | Randomized: No Boost (n = 2,657) No. of Patients | % | Randomized: Boost (n = 2,661) No. of Patients | % |
|---|---|---|---|---|
| Patient | | | | |
| Age, years | | | | |
| Median | 54.9 | | 54.8 | |
| Range | 22.7-83.5 | | 25.6-78.8 | |
| ≤ 35 | 72 | 2.7 | 82 | 3.1 |
| 36-40 | 156 | 5.9 | 139 | 5.2 |
| 41-50 | 665 | 25.0 | 669 | 25.1 |
| 51-60 | 943 | 35.5 | 860 | 32.3 |
| > 60 | 821 | 30.9 | 911 | 34.2 |
| Menopausal status | | | | |
| Unknown | 10 | 0.4 | 8 | 0.3 |
| Premenopausal | 999 | 37.6 | 1,004 | 37.7 |
| Menopausal | 1,648 | 62.0 | 1,649 | 62.0 |
| PS (WHO) | | | | |
| Unknown | 10 | 0.4 | 9 | 0.3 |
| 0 | 2,335 | 87.9 | 2,335 | 87.7 |
| 1-2 | 312 | 11.7 | 317 | 11.9 |
| Tumor | | | | |
| T palpation, cm | | | | |
| Unknown | 336 | 12.6 | 348 | 13.1 |
| Not palpable | 569 | 21.4 | 581 | 21.8 |
| < 1 | 315 | 11.9 | 313 | 11.8 |
| 1-2 | 856 | 32.2 | 829 | 31.2 |
| 2-3 | 433 | 16.3 | 449 | 16.9 |
| > 3 | 148 | 5.6 | 141 | 5.3 |
| T mammography, cm | | | | |
| < 1 | 576 | 21.7 | 525 | 19.7 |
| 1-2 | 1,027 | 38.7 | 1,067 | 40.1 |
| 2-3 | 397 | 14.9 | 436 | 16.4 |
| > 3 | 110 | 4.1 | 104 | 3.9 |
| Unknown | 547 | 20.6 | 529 | 19.9 |
| Clinical staging | | | | |
| Clinical T | | | | |
| T1 | 1,379 | 51.9 | 1,373 | 51.6 |
| T2 | 1,274 | 47.9 | 1,281 | 48.1 |
| T3 | 4 | 0.2 | 7 | 0.3 |
| Clinical N | | | | |
| N0 | 2,409 | 90.7 | 2,383 | 89.6 |
| N1-2 | 182 | 6.8 | 209 | 7.9 |
| Nx | 66 | 2.5 | 69 | 2.6 |
| Pathologic staging | | | | |
| Re-excision | | | | |
| Unknown | 8 | 0.3 | 8 | 0.3 |
| No | 2,003 | 75.4 | 1,991 | 74.8 |
| Yes | 646 | 24.3 | 662 | 24.9 |
| Largest diameter dominant lesion, mm | | | | |
| Unknown | 49 | 1.8 | 62 | 2.3 |
| < 10 | 683 | 25.7 | 635 | 23.9 |
| 10-20 | 1,402 | 52.8 | 1,451 | 54.5 |
| > 20 | 523 | 19.7 | 513 | 19.3 |
| Histologic type | | | | |
| Unknown | 8 | 0.3 | 8 | 0.3 |
| Invasive ductal carcinoma | 2,155 | 81.1 | 2,198 | 82.6 |
| Invasive lobular carcinoma | 228 | 8.6 | 219 | 8.2 |
| Mixed invasive pattern | 65 | 2.4 | 81 | 3.0 |
| Tubular carcinoma | 99 | 3.7 | 71 | 2.7 |
| Medullary carcinoma | 58 | 2.2 | 49 | 1.8 |
| Colloid carcinoma | 37 | 1.4 | 33 | 1.2 |
| Other, to specify | 7 | 0.3 | 2 | 0.1 |
| No. of nodes examined | | | | |
| Unknown | 69 | 2.6 | 75 | 2.8 |
| None | 21 | 0.8 | 16 | 0.6 |
| 1-5 | 170 | 6.4 | 176 | 6.6 |
| 6-10 | 813 | 30.6 | 826 | 31.0 |
| 10-15 | 876 | 33.0 | 914 | 34.3 |
| > 15 | 708 | 26.6 | 654 | 24.6 |
| No. of positive nodes | | | | |
| Unknown | 25 | 0.9 | 20 | 0.8 |
| None | 2,078 | 78.2 | 2,090 | 78.5 |
| 1-3 | 452 | 17.0 | 449 | 16.9 |
| 4+ | 102 | 3.8 | 102 | 3.8 |
| Hormone receptor status* | | | | |
| Estrogen | | | | |
| Negative | 525 | 19.8 | 528 | 19.8 |
| Positive | 1,391 | 52.4 | 1,409 | 53.0 |
| Unknown | 741 | 27.8 | 724 | 27.1 |
| Progesterone | | | | |
| Negative | 601 | 22.6 | 625 | 23.5 |
| Positive | 1,168 | 44.0 | 1,187 | 44.6 |
| Unknown | 888 | 33.4 | 849 | 31.9 |
| Unknown | 893 | 33.6 | 853 | 32.1 |
| ER positive, PR positive | 1,031 | 38.8 | 1,042 | 39.2 |
| ER positive, PR negative | 255 | 9.6 | 267 | 10.0 |
| ER negative, PR positive | 133 | 5.0 | 141 | 5.3 |
| ER negative, PR negative | 345 | 13.0 | 358 | 13.5 |

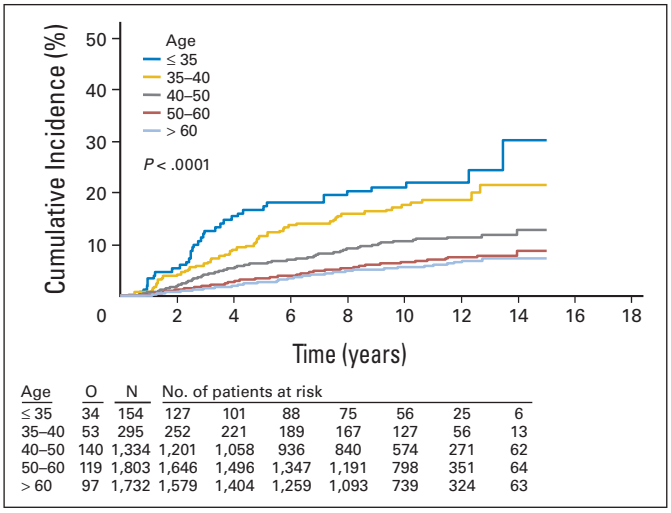
Abbreviations: PS, performance score; ER, estrogen receptor; PR, progesterone receptor.
*Determined according to local procedures either by charcoal or immunohistochemistry.

whereas the other 90% received an external boost at a median dose of 16 Gy.

There was no significant difference between the two randomly assigned groups with regard to the use of chemotherapy or tamoxifen as adjuvant treatment (Appendix Table A1). However, chemotherapy seems to have been prescribed slightly more frequently in the boost arm, in the premenopausal N+ patients (87.6% *v* 78.7%; Appendix Table A1).

### *Local Recurrence As First Treatment Failure*

Local recurrence was correlated with the patient's age (Fig 1). Disease recurrence in the ipsilateral breast occurred as first failure in 278 versus 165 patients (no boost *v* boost), respectively. Regional recurrence in the axilla and/or supraclavicular area was the first event in 59 versus 56 patients (no boost *v* boost), respectively. At 10 years, the cumulative incidence of local recurrence was 10.2% (95% CI, 8.7% to 11.8%) without boost and 6.2% (95% CI, 4.9% to 7.5%) with boost ($P < .0001$). The HR for local recurrence as first event was 0.59 (99% CI, 0.46 to 0.76) after a boost (Fig 2). Overall, 47% of the local recurrences occurred in the primary tumor bed, 10% occurred in the scar, 29% occurred outside the original tumor area, and 13% were diffuse.



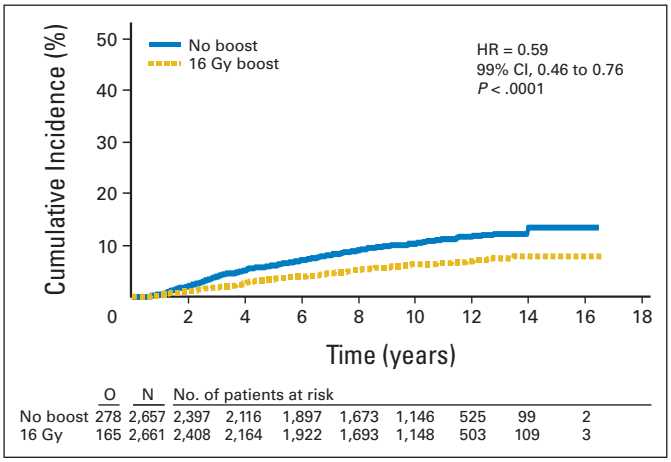

| Age | O | N | No. of patients at risk | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ≤ 35 | 34 | 154 | 127 | 101 | 88 | 75 | 56 | 25 | 6 |
| 35–40 | 53 | 295 | 252 | 221 | 189 | 167 | 127 | 56 | 13 |
| 40–50 | 140 | 1,334 | 1,201 | 1,058 | 936 | 840 | 574 | 271 | 62 |
| 50–60 | 119 | 1,803 | 1,646 | 1,496 | 1,347 | 1,191 | 798 | 351 | 64 |
| > 60 | 97 | 1,732 | 1,579 | 1,404 | 1,259 | 1,093 | 739 | 324 | 63 |

**Fig 1.** Cumulative incidence of recurrence of tumor in the ipsilateral breast after 50 Gy irradiation or 50 Gy irradiation and a boost by age. O, occurrences; N, number of patients at risk.

There was no statistically significant interaction between the magnitude of the relative risk reduction and patients' age ($P > .1$). The relative risk reduction was significant in all age groups. However, in relation to the higher absolute risk in younger age groups, the observed absolute risk reduction at 10 years seemed to be larger in the younger patients: reduced from 23.9% to 13.5% in those age ≤ 40 years, from 12.5% to 8.7% in the 41- to 50-year age group, from 7.8% to 4.9% in the 51- to 60-year age group, and from 7.3% to 3.8% in those older than 60 years (Fig 3 and A2, online only).

### *Fibrosis*

Fibrosis was scored on a 4-point scale by the treating physician as follows: 1 = none, 2 = minor, 3 = moderate, and 4 = severe. The boost dose significantly increased the worst reported grade of fibrosis in both the whole breast and the boost area: the cumulative incidence of severe fibrosis at 10 years was 4.4% (99% CI, 3.5% to 5.7%) with boost versus 1.6% (99% CI, 1% to 2.3%) without boost ($P < .0001$; Fig 4). Moderate fibrosis was also more commonly observed in the boost group, with a 10-year cumulative incidence of moderate to severe fibrosis of 28.1% (99% CI, 27.6% to 28.6%) versus 13.2% (99% CI, 11.5% to 15.0%; $P < .0001$).




| | O | N | No. of patients at risk | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| No boost | 278 | 2,657 | 2,397 | 2,116 | 1,897 | 1,673 | 1,146 | 525 | 99 | 2 |
| 16 Gy | 165 | 2,661 | 2,408 | 2,164 | 1,922 | 1,693 | 1,148 | 503 | 109 | 3 |

**Fig 2.** Cumulative incidence of recurrence of tumor as first event in the ipsilateral breast after 50 Gy whole-breast irradiation or 50 Gy whole-breast irradiation and a boost of 16 Gy. HR, hazard ratio; O, occurrences; N, number of patients at risk.

### *Distant Metastases, Breast Cancer Mortality, and Survival*

With the current follow-up, there was no statistically significant difference in the cumulative risk of distant metastases between the two groups, with 16.1% distant relapse at 10 years in both groups. The cumulative incidence of second primary tumor in the contralateral breast, or at other sites, also did not differ ($P > .1$ for both groups).

In total, 522 and 521 patients died in the no boost and the boost group, respectively. Survival at 10 years was 81.7% (99% CI, 79.5% to 83.7%) for both arms (Fig 5). There was also no difference between the two groups with respect to breast cancer mortality (344 *v* 346 events), overall incidence of breast cancer–related events, or disease-free survival ($P > .1$).

### *Salvage Treatment for Recurrences in the Ipsilateral Breast*

Mastectomy was used as salvage treatment for local recurrence in the ipsilateral breast in 352 patients (223 of 278 in the no boost group and 129 of 165 in the boost group). Lumpectomy was the salvage treatment in 42 patients (27 without boost and 15 with boost). The salvage treatment in the remaining 43 patients (24 without boost and 19 with boost) was mainly systemic chemotherapy. No salvage treatment was documented in two patients in the boost arm and four patients in the no boost arm.

## DISCUSSION

The 10-year results of this large trial of 5,318 early breast cancer patients demonstrated that a boost dose of 16 Gy to the original tumor bed significantly reduced the rate of local recurrence after BCT, with a microscopically complete lumpectomy and 50 Gy whole-breast irradiation. The boost dose resulted in a relative reduction of the hazard of local recurrence of 0.59. The results with 10 years of follow-up confirmed that younger patients are at an increased risk of local recurrence after BCT (Fig 1).[12] An earlier multivariate analysis, based on 5-year follow-up, indicated young age as the most important prognostic factor for local recurrence.[24] Other studies similarly concluded that young patients with early-stage breast cancer have a worse prognosis than older patients, not only for local relapse but also for survival.[25-30] Because of this, the largest absolute benefit of the boost in reducing the 10-year local recurrence rate was seen in young patients: the risk was decreased from 23.9% to 13.5% (Fig 2). The first report of the trial (with a 5-year follow-up) already established the benefit of the boost in patients younger than age 50 years.[12] With the present analysis after 10.8 years of follow-up, we also confirm a statistically significant reduction of the local recurrence rate in the older age groups. Although the absolute difference in local recurrence rate is smaller in the older patients than in the younger patients, it was similar in all age groups older than age 40 years. Our conclusion that local control improves with higher radiation doses is in line with the data of a smaller trial by Romestaing et al,[11] with a median follow-up of only 3.3 years, which compared a boost dose of 10 Gy with no boost in patients with early breast cancer. One might expect that with increased use

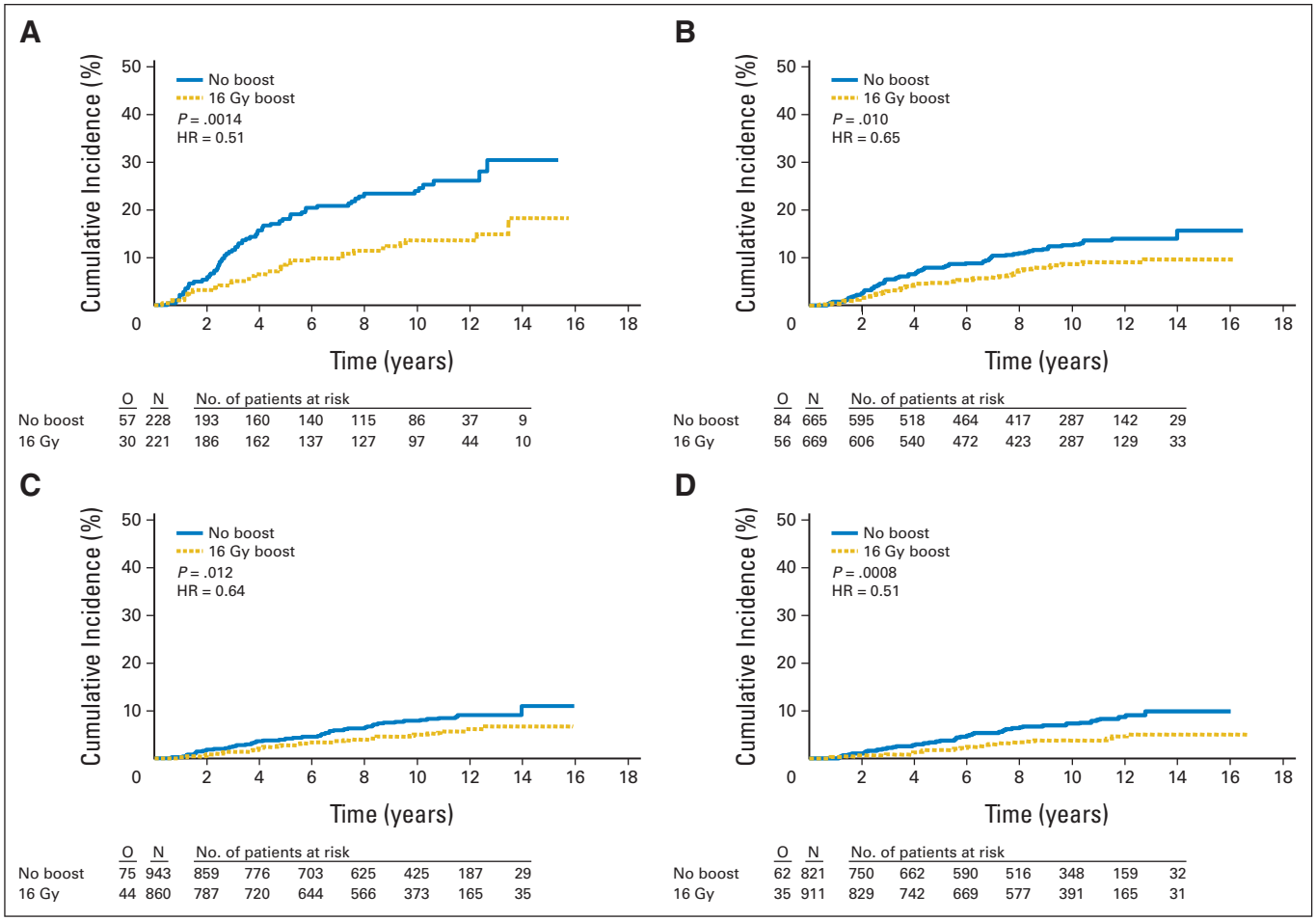



**Fig 3.** Cumulative incidence of ipsilateral breast cancer recurrence according to age. Age (A) ≤ 40, (B) 41 to 50, (C) 51 to 60, and (D) > 60 years. HR, hazard ratio; O, occurrences; N, number of patients at risk.

of adjuvant treatment, an additional reduction of the local recurrence rate will occur.[12,31]

Most of the local recurrences seen in our study occurred in the area of the primary tumor, justifying the concept of administering a higher radiation dose to the original tumor bed; 47% of the local recurrences occurred at the site of the primary tumor and 9% occurred at the site of the scar. This higher local control rate has lead to a 41% reduction of the salvage mastectomy rate in patients who received the boost dose.

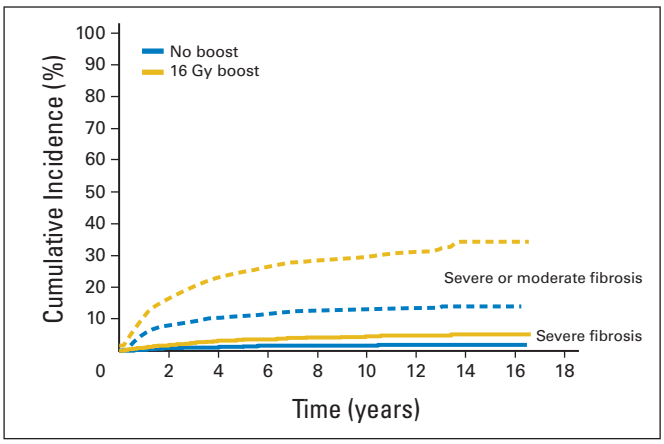



**Fig 4.** Cumulative incidence of moderate or severe fibrosis after 50 Gy irradiation or 50 Gy irradiation and a boost of 16 Gy.

However, especially in the older patients, the improvement in local control resulting from a higher radiation dose must be weighed against the increase in treatment adverse effects, in particular breast fibrosis. The gain in local control should therefore be discussed with the patients on an individual base. In our analysis, moderate or severe fibrosis increased from 13% to 28% when a boost was added. In a previous publication, we also demonstrated that the higher radiation dose was associated with a limited but statistically significant worsening of the cosmetic result.[32] However, the boost dose was not the sole factor that affected the cosmetic outcome negatively: the location of the primary tumor in the lower quadrants of the breast, the volume of the excision, breast infection and/or hematoma, and clinical T2 stage were all independent predictors of worse cosmetic results, in addition to the boost treatment. Romestaing et al[11] similarly reported a modest negative impact on the cosmetic outcome in the patients receiving a higher radiation dose. In their study, the boost group also had a higher rate of grade 1 and 2 telangiectasia (12.4% *v* 5.9%), which probably results from a biologically more aggressive approach.[11]

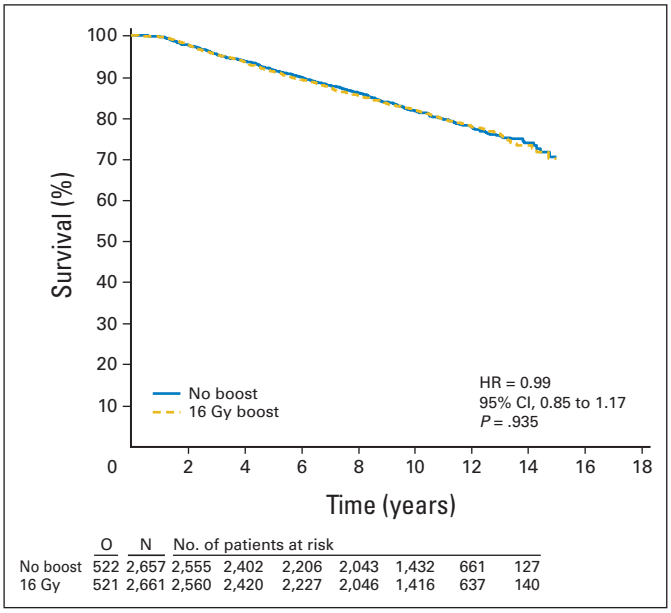



**Fig 5.** Survival after 50 Gy irradiation of the breast or 50 Gy irradiation and a boost. HR, hazard ratio; O, occurrences; N, number of patients at risk.

Several other trials in BCT focused on the role of whole-breast irradiation in addition to lumpectomy. All demonstrated that adding radiotherapy significantly reduces the local recurrence rate.[8] The recent update of the EBCTCG meta-analysis revealed that the higher local control rate translated into an improved survival in patients receiving radiotherapy as part of their BCT.[8] Despite the improvement seen in local control by adding a boost dose in our study, no impact has been seen so far in overall or breast cancer–specific survival, or in the risk of distant relapse. This contrasts somewhat with the EBCTCG findings, which suggested that for four local recurrences prevented, one death from breast cancer would be avoided at 15 years of follow-up.[8] Possible explanations for the absence of any benefit of the boost on survival in our study may be that true recurrences in the breast have a different meaning than recurrences in the chest wall, or that mastectomy was an effective salvage treatment, thus masking any impact on survival in our study. In our trial mastectomy or tumorectomy was indeed carried out in 82% of the patients. In addition, 76% of the patients were still alive and free of disease at the time of this analysis. All of these patients are therefore still at risk for recurrence.

The major difference of this long-term follow-up with the previous analysis is the ability of the present analysis to demonstrate a statistically significant reduction of the local recurrence rate by administration of a higher radiation dose in all age groups. Although a subgroup analysis of the 5-year follow-up data could only demonstrate statistical significance of the benefit in patients younger than 50 years, with longer follow-up and increased statistical power after more events, we are now able to demonstrate that the improvement in local control is statistically significant in all age categories.

In summary, our study demonstrates that addition of a boost of 16 Gy to the standard 50 Gy breast radiation therapy significantly lowers the risk of local recurrence rates in all age groups. The risk of fibrosis leading to a poorer cosmetic outcome is somewhat higher with the boost, but this complication affects only a very small subset of patients. The boost does not seem to improve overall survival after 10 years of follow-up. It is possible that a survival benefit will emerge with longer follow-up. However, reasons that survival might not be enhanced include the possibility that salvage mastectomy at the time of local recurrence is a life-saving intervention. This salvage mastectomy was required significantly less often in patients receiving the boost dose of 16 Gy.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Harry Bartelink, Jean-Claude Horiot
**Provision of study materials or patients:** Harry Bartelink, Jean-Claude Horiot, Philip M. Poortmans, Henk Struikmans, Walter Van den Bogaert, Alain Fourquet, Jos J. Jager, Willem J. Hoogenraad, S. Bing Oei, Carla C. Wárlám-Rodenhuis
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## *Appendix*

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).