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Ten-Year Survival after Postmastectomy Chest-Wall Irradiation in Breast Cancer

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ABSTRACT

BACKGROUND

The role of postmastectomy chest-wall irradiation in patients with breast cancer classified as pN1 (with involvement of one to three axillary nodes) or pN0 (pathologically node negative) with additional risk factors is uncertain.

METHODS

In this international, phase 3, randomized trial, we evaluated the omission of chest-wall irradiation in women with "intermediate-risk" breast cancer — defined as cancer that was stage pT1N1, pT2N1, or pT3N0 or stage pT2N0 with a histologic grade of 3, lymphovascular invasion, or both (tumor size: T1, ≤2 cm; T2, >2 cm to 5 cm; or T3, >5 cm) — that was treated with mastectomy, an axillary procedure, and systemic therapy. Patients were assigned to undergo chest-wall irradiation (40 to 50 Gy; the irradiation group) or not to undergo chest-wall irradiation (the no-irradiation group). The primary end point was overall survival, with 10 years of follow-up. Chest-wall recurrence, regional recurrence, disease-free survival, distant metastasis–free survival, causes of death, and radiation-related adverse events were also assessed.

RESULTS

The intention-to-treat population included 808 patients in the irradiation group and 799 in the no-irradiation group. The median follow up was 9.6 years. Overall survival was 81.4% with chest-wall irradiation and 81.9% with no chest-wall irradiation according to 10-year Kaplan–Meier estimates (hazard ratio for death, 1.04; 95% confidence interval [CI], 0.82 to 1.30; P=0.80). A total of 29 patients had a chest-wall recurrence — 9 (1.1%) in the irradiation group and 20 (2.5%) in the no-irradiation group (between-group difference, <2 percentage points; hazard ratio, 0.45; 95% CI, 0.20 to 0.99). Disease-free survival was 76.2% in the irradiation group and 75.5% in the no-irradiation group (hazard ratio for recurrence or death, 0.97; 95% CI, 0.79 to 1.18), and distant metastasis–free survival was 78.2% and 79.2%, respectively (hazard ratio for distant metastasis or death, 1.06; 95% CI, 0.86 to 1.31).

CONCLUSIONS

In this trial, chest-wall irradiation did not result in higher overall survival than no chest-wall irradiation among patients with intermediate-risk, early breast cancer treated with mastectomy and contemporary adjuvant systemic therapy. (Funded by the Medical Research Council and others; SUPREMO ISRCTN Clinical Study Registry number, 61145589.)

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CME

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Mastectomy is standard care for more than one third of patients with stage I and stage II breast cancer.[1] Stage II disease involves tumors no more than 5 cm in diameter with metastases in one to three axillary lymph nodes (N1) or tumors of at least 2 cm without nodal metastases (stages T1N1M0, T2N1M0, T2N0M0, and T3N0M0 in the TNM [tumor size, node involvement, and metastasis] system; tumor size: T1, ≤2 cm; T2, >2 cm to 5 cm; or T3, >5 cm). Patients with stage II breast cancer who have N1 disease or who have N0 (node-negative) disease but with poor histologic features (including larger tumor size, a histologic grade of 3, or lymphovascular invasion) are considered to be at intermediate risk for recurrence.[2]

Landmark Danish and Canadian randomized, controlled trials reported in 1997 and 1999 showed that postmastectomy radiotherapy for stages II and III reduced the risk of locoregional recurrence and improved 10-year survival among women with nodal metastases.[3-5] A 2014 meta-analysis of trials of postmastectomy radiotherapy by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG),[6] which included data from the Danish and Canadian trials, showed that among patients with disease classified pathologically as N1 (pN1), the cumulative incidence of locoregional recurrence as a first event at 10 years was 16.5 percentage points lower with postmastectomy radiotherapy than with no postmastectomy radiotherapy and 20-year survival was 7.9 percentage points higher. The adjuvant systemic therapy used in these trials is now considered to be suboptimal.[7,8]

Major improvements in systemic therapy and reductions in breast cancer mortality[9] have challenged the applicability of the evidence base for postmastectomy radiotherapy in current practice. Hence, the role of postmastectomy radiotherapy in patients with involvement of one to three axillary nodes is uncertain, and this uncertainty is reflected in differing guidelines[10-12] and practices.[13,14] Evaluation of postmastectomy radiotherapy in patients with one to three involved nodes became a research priority of the National Institutes of Health in 2000.[15] Patients with pN0 disease who have other factors associated with intermediate risk might also benefit from postmastectomy radiotherapy.[16]

Most locoregional recurrences occur on the chest wall,[17,18] so this area is considered to be a critical target for postmastectomy radiotherapy. Here, we report the 10-year results of the Medical Research Council–European Organisation for Research and Treatment of Cancer (EORTC) Breast International Group (BIG) 2-04 SUPREMO (Selective Use of Postoperative Radiotherapy after Mastectomy) trial, which present a more contemporary picture of the effect on overall survival of postmastectomy radiotherapy selectively delivered to the chest wall.

METHODS

TRIAL OVERSIGHT

We conducted this phase 3, randomized, clinical trial at 125 sites in the United Kingdom, 25 sites in seven countries in continental Europe and 1 site each in Israel and Turkey (overseen by the EORTC and hereafter referred to collectively as EORTC sites), and an additional 21 international sites (see Section S1.1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial design has been described previously.[19] The protocol received ethical approval in the United Kingdom (Medical Research and Ethics Committee reference number, 05/S0501/106) and equivalent approval in the applicable jurisdictions outside the United Kingdom. All the patients provided written informed consent. Patients in the United Kingdom could consent to participation in studies of quality of life, cardiac health, and health economics within the trial. Patients in the United Kingdom and those enrolled by the EORTC could participate in the translational TRANS-SUPREMO study within the trial. The trial management group (which included patient representatives) designed the trial (Section S1.2). The Scottish Clinical Trials Research Unit in Edinburgh provided data management and remote monitoring to ensure adherence with the International Council for Harmonisation guidelines for Good Clinical Practice. The trial steering committee and the data monitoring and ethics committee provided trial oversight (Sections S1.3 and S1.4). The third author performed the analysis. The first author wrote the first draft of the manuscript. All the authors approved the manuscript and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org. The funders had no role in the design of the trial, the analysis of the data,

or the decision to submit the manuscript for publication.

PATIENT ELIGIBILITY CRITERIA

Women were eligible for the trial if they had undergone a mastectomy for stage II, intermediate-risk cancer in one breast without distant metastases (specified as stage pT1N1 or pT2N1 or as pT2N0 with a histologic grade of 3, lymphovascular invasion, or both) and had a minimum clear margin of 1 mm. Patients undergoing immediate breast reconstruction were eligible if they met the other criteria for inclusion. According to the protocol as amended in 2010 (version 29), patients were also eligible with stage II breast cancer classified as pT3N0, and patients who had received neoadjuvant chemotherapy were eligible to participate.

A level II axillary-node clearance of a minimum of 10 nodes (according to version 27 of the protocol) or 8 nodes (according to version 29) was mandatory for patients with N1 disease. For patients with pN0 disease, axillary staging was performed with the use of a sample of 4 axillary nodes, a sentinel-node biopsy, or axillary-node clearance. Full inclusion and exclusion criteria according to both versions 27 and 29 of the protocol are provided in Section S2.1.

TREATMENT AND TRIAL PROCEDURES

Patients were randomly assigned in a 1:1 ratio to undergo chest-wall irradiation (the irradiation group) or not to undergo chest-wall irradiation (the no-irradiation group) with the use of permuted blocks with varied block sizes to minimize the effects of entry bias. Randomization was stratified according to the treating center.

The protocol specified guidelines for pathological analysis, surgery, radiotherapy, and adjuvant systemic therapy. We reviewed the pathology reports for all patients in the trial to check eligibility (Section S2.2). Two authors who are pathologists conducted a central pathological review of histologic slides from patients in the United Kingdom and those enrolled at EORTC sites.[20]

Patients assigned to the irradiation group received doses ranging from 40 Gy in 15 fractions to 50 Gy in 25 fractions. The clinical target volume encompassed the chest-wall skin flaps and soft tissues from 5 mm under the skin surface down to the deep fascia. Axillary irradiation was not permitted, but the staff at participating centers could elect to irradiate the supraclavicular fossa or internal mammary chain in patients with N1 disease in the United Kingdom or in patients with N0 or N1 disease outside the United Kingdom, irrespective of the assigned trial group. Quality assurance for radiotherapy was performed at the institute level and at the patient level. The full protocols for radiotherapy and quality assurance are provided in Section S2.3.

Adjuvant or neoadjuvant chemotherapy with anthracyline-containing regimens, with or without taxanes, was recommended. Trastuzumab was administered according to local policy. A minimum of 5 years of adjuvant endocrine therapy was recommended for patients with estrogen receptor (ER)–positive tumors. Tamoxifen, an aromatase inhibitor, or a sequential combination was advised for postmenopausal patients, and for premenopausal women, tamoxifen, ovarian ablation, or both were recommended.

Patients attended a follow-up clinic appointment in the first year for assessment of acute side effects; this follow-up took place at the end of the course of radiotherapy for patients who had received radiotherapy, 3 months after chemotherapy for patients who had received chemotherapy but not radiotherapy, or 3 months after the date of mastectomy (or the date of the final definitive surgery, if applicable) for patients who had not received radiotherapy or chemotherapy. All the patients were then seen annually from the date of mastectomy for 10 years. Contralateral mammography, if appropriate, was recommended every 2 years for 10 years. Follow-up forms that recorded disease status, any active treatments, and side effects were completed at each visit. Side effects of treatment were assessed with the EORTC–Radiation Therapy Oncology Group (RTOG) radiation morbidity scale.[21]

TRIAL END POINTS

The primary end point was overall survival. Secondary end points were chest-wall recurrence (with or without recurrence elsewhere), regional recurrence, disease-free survival, distant metastasis–free survival, cause of death, short-term and long-term radiation-related adverse events, quality of life, and cost-effectiveness. Assessments of quality of life and cost-effectiveness are being analyzed.

STATISTICAL ANALYSIS

The null hypothesis was that chest-wall irradiation has no effect on overall survival among women with intermediate-risk breast cancer treated with mastectomy, axillary surgery, and adjuvant systemic therapy. The protocol (version 27) specified a target sample of 3500 patients in a superiority design to provide the trial with 80% power to detect a between-group difference in overall survival at a significance level of 5%. We estimated that 5-year survival would be 79% with irradiation and 75% with no irradiation, and we planned for accrual to take place over a period of 4 years. Because initial accrual was slower than projected, we reduced the sample size, extended the follow-up to a 10-year period, and widened the eligibility criteria to include patients who had received neoadjuvant systemic therapy. The extension of follow-up to 10 years was supported by the findings from a subgroup analysis in patients with node-positive disease in two Danish trials, which showed that survival at 15 years was higher by 9 percentage points with irradiation than with no irradiation (57% vs. 48%; P=0.03). This survival advantage emerged only after 5 years.[22] The protocol was modified accordingly, and the amended version (version 29) was approved by the funders and by each of the medical ethics committees that approved the original version.

We estimated that a revised sample size of 1600 patients — with 609 primary end-point events for analysis, after allowance for 5% loss to follow-up — would provide the trial with 80% power at a significance level of 5% under the assumption that overall survival at 10 years would be 63% with irradiation and 56% with no irradiation (a between-group difference of 7 percentage points, which would correspond to a hazard ratio of 1.255). All analyses were performed according to the intention-to-treat principle, and two-tailed significance tests and confidence intervals were used throughout. No multiplicity adjustments were made (see Section S4.3). For overall survival and other end points assessed in a time-to-event analysis, 95% confidence intervals were calculated for the hazard ratios from a Cox proportional-hazards model, with adjustment for three geographic clusters (the United Kingdom, EORTC sites, and other international locations). Proportional-hazards checks were made for every covariate with the use of Schoenfeld residuals. Kaplan–Meier calculations and plots were used for graphic display and estimation of end-point values at 10 years. We report the results of three of the most relevant prespecified subgroup analyses — those for age group, nodal status, and molecular subtype — which were performed with the use of stratum-specific estimates and confidence intervals.

RESULTS

PATIENTS

Between August 4, 2006, and April 29, 2013, a total of 1679 patients underwent randomization. The intention-to-treat population included 808 patients in the irradiation group and 799 in the no-irradiation group. Screening, randomization, and follow-up are summarized in Figure 1, and characteristics of the patients in the intention-to-treat population are listed in Table 1. Additional details with respect to tumor characteristics and treatment are provided in Table S3.1. The representativeness of the trial population is shown in Table S3.9. Irradiation of the supraclavicular fossa was performed in 97 patients (12.0%) in the irradiation group and 12 patients (1.5%) in the no-irradiation group. Irradiation of the internal mammary chain was performed in 12 patients (1.5%) and 7 patients (0.9%), respectively. Overall, 84.8% of patients received chemotherapy (which was delivered according to local protocol in 87.4% of cases), 78.7% received endocrine therapy, and 19.8% received trastuzumab. The median follow-up was 9.6 years. The trial database was locked on June 19, 2024.

A total of 78.6% of the patients in the United Kingdom consented to participate in both the main trial and the quality-of-life substudy.[19] For the TRANS-SUPREMO study, tumor tissue and blood samples were collected from 1397 of the 1491 patients (93.7%) who participated at sites in the United Kingdom or at EORTC sites.

PRIMARY END POINT

A total of 295 deaths occurred (150 in the irradiation group and 145 in the no-irradiation group). There was no evidence of a significant between-group difference in overall survival at 10 years, which was estimated to be 81.4% with irradiation and 81.9% with no irradiation (hazard ratio for death, 1.04; 95% confidence interval [CI], 0.82 to 1.30; P=0.80) (Fig. 2). Most deaths (194 of 295; 65.8%) were due to breast cancer (Table S3.2).

SECONDARY END POINTS

Only 29 patients had a chest-wall recurrence: 9 (1.1%) in the irradiation group and 20 (2.5%) in the no-irradiation group. The absolute between-group difference was less than 2 percentage points. However, a reduction in the risk of chest-wall recurrence with irradiation was observed (hazard ratio, 0.45; 95% CI, 0.20 to 0.99) (Fig. 3A); the confidence interval is wide owing to the low number of events. Locoregional recurrence occurred in 22 patients (2.7%) in the irradiation group and 36 (4.5%) in the no-irradiation group (hazard ratio, 0.61; 95% CI, 0.36 to 1.03) (Fig. 3B).

A distant metastasis or death occurred in 176 patients (21.8%) in the irradiation group and 166 (20.8%) in the no-irradiation group. Distant metastasis–free survival at 10 years was estimated to be 78.2% and 79.2%, respectively (hazard ratio for distant metastasis or death, 1.06; 95% CI, 0.86 to 1.31) (Fig. 3C). Breast cancer recurrence or death occurred in 192 patients (23.8%) in the irradiation group and 196 (24.5%) in the no-irradiation group. Disease-free survival at 10 years was estimated to be 76.2% and 75.5%, respectively (hazard ratio for recurrence or death, 0.97; 95% CI, 0.79 to 1.18) (Fig. 3D).

PREPLANNED SUBGROUP ANALYSES

We observed no differential effect of irradiation on overall survival according to nodal status (Fig. 4). Among patients with pN0 disease, death occurred in 45 of 191 patients (23.6%) in the irradiation group and in 42 of 211 patients (19.9%) in the no-irradiation group; among patients with pN1 disease, death occurred in 104 of 614 patients (16.9%) in the irradiation group and in 103 of 587 patients (17.5%) in the no-irradiation group (hazard ratio for death with pN1 disease vs. with pN0 disease, 0.82; 95% CI, 0.63 to 1.05). Kaplan–Meier plots for overall survival according to nodal status are shown in Figure S3.4A.

We saw no differential effect of irradiation on any of the secondary end points according to nodal status (N0 vs. N1) (Fig. S3.5). Kaplan–Meier plots for chest-wall recurrence, distant metastasis–free survival, and disease-free survival according

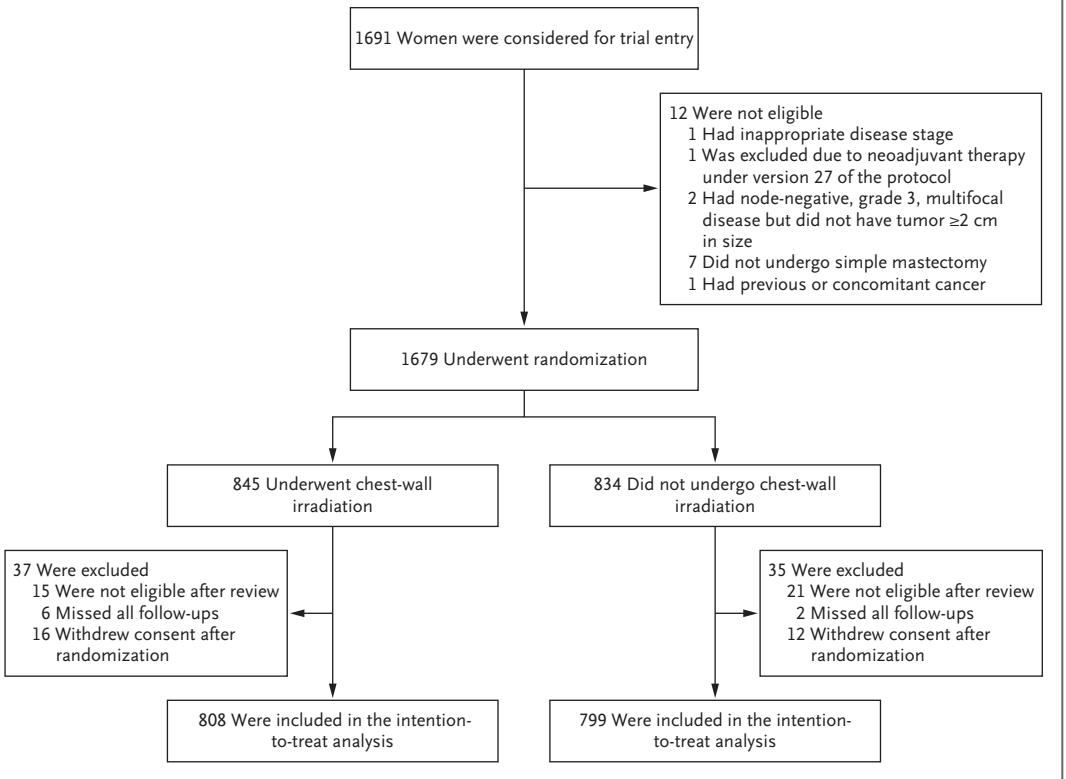

Figure 1. Screening, Randomization, and Follow-up.

Table 1. Demographic and Clinical Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Chest-Wall Irradiation (N=808)	No Chest-Wall Irradiation (N=799)
Geographic region — no. (%)		
United Kingdom	582 (72.0)	586 (73.3)
Continental Europe, Israel, or Turkey	165 (20.4)	158 (19.8)
Other location	61 (7.5)	55 (6.9)
Age		
Median (IQR) — yr	54.0 (47.0–64.0)	55.0 (48.0–64.0)
Distribution — no. (%)		
<45 yr	130 (16.1)	121 (15.1)
45–54 yr	285 (35.3)	267 (33.4)
55–69 yr	283 (35.0)	309 (38.7)
≥70 yr	110 (13.6)	102 (12.8)
Invasive tumor type — no. (%)		
Ductal, no special type	672 (83.2)	669 (83.7)
Lobular carcinoma	75 (9.3)	78 (9.8)
Other	57 (7.1)	51 (6.4)
Not available	4 (0.5)	1 (0.1)
Histologic grade — no. (%)		
1	57 (7.1)	42 (5.3)
2	323 (40.0)	333 (41.7)
3	416 (51.5)	421 (52.7)
Not available	12 (1.5)	3 (0.4)
Molecular subtype — no. (%)		
ER positive and HER2 negative or ER positive with HER2 status unknown	517 (64.0)	520 (65.1)
ER positive and HER2 positive	110 (13.6)	95 (11.9)
ER negative and HER2 positive	61 (7.5)	64 (8.0)
Triple negative	91 (11.3)	84 (10.5)
Other subtype or data missing	29 (3.6)	36 (4.5)
Breast cancer stage — no. (%)†		
T1N1	246 (30.4)	226 (28.3)
T2N0	183 (22.6)	205 (25.7)
T2N1	368 (45.5)	361 (45.2)
T3N0	4 (0.5)	3 (0.4)
T0N0 or T1N0‡	4 (0.5)	3 (0.4)
Other or data missing	3 (0.4)	1 (0.1)
Median no. of nodes examined (IQR)	14.0 (10.0–18.0)	14.0 (9.0–18.0)
Total no. of nodes involved — no. (%)		
0	191 (23.6)	211 (26.4)
1	330 (40.8)	312 (39.0)
2	195 (24.1)	171 (21.4)
3	89 (11.0)	104 (13.0)
Not available	3 (0.4)	1 (0.1)

Table 1. (Continued.)

Characteristic	Chest-Wall Irradiation (N=808)	No Chest-Wall Irradiation (N=799)
Axillary surgery — no. (%)		
Sentinel-node biopsy only	115 (14.2)	118 (14.8)
Clearance only	393 (48.6)	349 (43.7)
Sentinel-node biopsy or sampling plus clearance	239 (29.6)	245 (30.7)
Sampling only	31 (3.8)	40 (5.0)
Not available	30 (3.7)	47 (5.9)
Immediate breast reconstruction — no. (%)	95 (11.8)	80 (10.0)
Chemotherapy — no. (%)		
Yes	696 (86.1)	666 (83.4)
No	108 (13.4)	131 (16.4)
Not available	4 (0.5)	2 (0.3)
Endocrine therapy — no. (%)		
Yes	640 (79.2)	624 (78.1)
No	147 (18.2)	152 (19.0)
Not available	21 (2.6)	23 (2.9)
Treatment with trastuzumab — no. (%)		
Yes	168 (20.8)	150 (18.8)
No	605 (74.9)	582 (72.8)
Not available	35 (4.3)	67 (8.4)
Prescribed radiotherapy dose to chest wall — no. (%)		
40 Gy in 15 fractions or 43 Gy in 16 fractions	444 (55.0)	1 (0.1)
50 Gy in 25 fractions	230 (28.5)	6 (0.8)
Other	101 (12.5)	3 (0.4)
Not applicable	33 (4.1)§	789 (98.7)

* Percentages may not total 100 because of rounding. ER denotes estrogen receptor, HER2 human epidermal growth factor receptor 2, and IQR interquartile range.
† Staging according to tumor size (T0, no evidence of a primary tumor; T1, ≤2 cm; T2, >2 to 5 cm; or T3, >5 cm) and the extent of nodal involvement (N0, node negative, or N1, one to three axillary nodes involved) is shown.
‡ Data are included for patients who had T0N0 or T1N0 status after neoadjuvant chemotherapy.
§ Data are included for 28 patients who did not receive chemotherapy owing to treatment crossover and 5 patients who withdrew from the trial early or for whom data were incomplete.

to nodal status are shown in Figure S3.4B, S3.4C, and S3.4D.

There was no differential effect of irradiation on primary and secondary end points according to age group (Fig. 4). The Kaplan–Meier plots for end points according to age group are shown in Figure S3.6.

In the subgroup analysis according to molecular subtype, we observed no differential effect of irradiation on overall survival among patients with ER-positive and human epidermal growth factor receptor 2 (HER2)–negative cancer, those with ER- and HER2-positive cancer, and those with ER-negative and HER2-positive cancer (Fig. 4). The exception was patients with triple-negative breast cancer (ER negative, progesterone receptor negative, and HER2 negative), who appeared to have lower overall survival with chest-wall irradiation than with no irradiation (hazard ratio for death, 1.91; 95% CI, 1.06 to 3.46) (Fig. 4 and Fig. S3.7). Only a small number of chest-wall recurrences occurred, but the risk of chest-wall recurrence appeared to be lower with irradiation than with no irradiation after adjustment for treating center and molecular subtype (hazard ratio, 0.44; 95% CI, 0.19 to 1.02); however, no

substantial difference in risk was observed among the patients with triple-negative breast cancer (Fig. S3.8).

SAFETY

Safety information for the 1607 patients included in the intention-to-treat analysis is summarized in Table S3.3. Toxic effects of radiotherapy were mild. The incidence of lung-related adverse events of grade 2 or higher was less than 2% overall, but this category of adverse events had the greatest between-group difference: 13 lung-related adverse events of grade 2 or higher occurred in the irradiation group, as compared with 5 in the no-irradiation group (odds ratio, 2.59; 95% CI, 0.97 to 8.12). The incidence of heart-related adverse events and the incidence of bone-related adverse events did not differ as much between the two groups. Causes of death are listed in Table S3.2. Death from cardiac causes occurred in 6 of 808 patients (0.7%) in the irradiation group and in 8 of 799 (1.0%) in the no-irradiation group. Death from lung cancer occurred in 7 of 808 patients (0.9%) and in 7 of 799 patients (0.9%), respectively.

DISCUSSION

We found no evidence of an effect of irradiation on overall survival, disease-free survival, or distant metastasis–free survival among patients with intermediate-risk breast cancer, and irradiation had minimal effect on the incidence of chest-wall recurrence over a 10-year period (a between-group difference of <2 percentage points). We had estimated that adjuvant irradiation would prevent a sufficient number of chest-wall recurrences to show a clear benefit for overall survival at 10 years (we had projected a between-group difference of 7 percentage points, for a hazard ratio of 1.255), under the assumption that survival with no chest-wall irradiation would be 56%. However, we found 10-year survival to be approximately 81% in both groups, and the cumulative incidence of local recurrence was low — the trial results must therefore be interpreted in that context. The 95% confidence interval for the hazard ratio for the primary end point (0.82 to 1.30) is compatible with an absolute difference in overall survival (increase or decrease) of up to 3.8 percentage points. Although the prespecified hazard ratio of 1.255 is contained

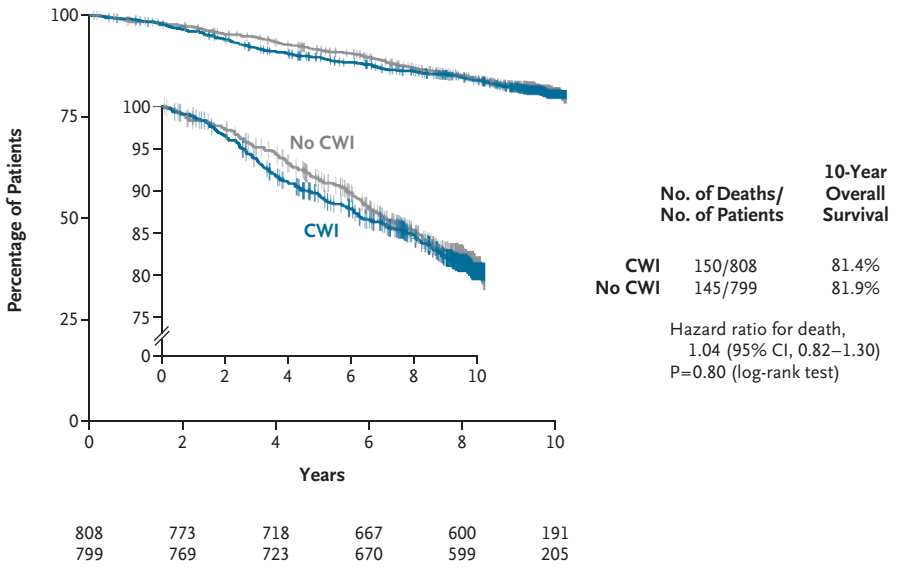

Figure 2. Kaplan–Meier Estimates of Unadjusted Overall Survival (Intention-to-Treat Population).

For clarity, the horizontal scale has been truncated at 10 years (which excludes a small proportion of follow-up that extended beyond this period). The inset shows the same data on an expanded y axis. CWI denotes chest-wall irradiation.

within this confidence interval, the interval represents a far smaller absolute change relative to the observed survival than was originally estimated. We consider that the original calculation of the power of the trial is no longer informative, because breast cancer mortality has fallen considerably since the trial started.[9] Consequently, we consider that the trial provides robust data on the effect of radiotherapy, despite the lower-than-expected number of events owing to improved survival. Although we cannot rule out small positive or negative effects on overall survival, it is biologically implausible that an absolute difference in chest-wall recurrences of less than 2 percentage points would translate into a meaningful survival benefit.

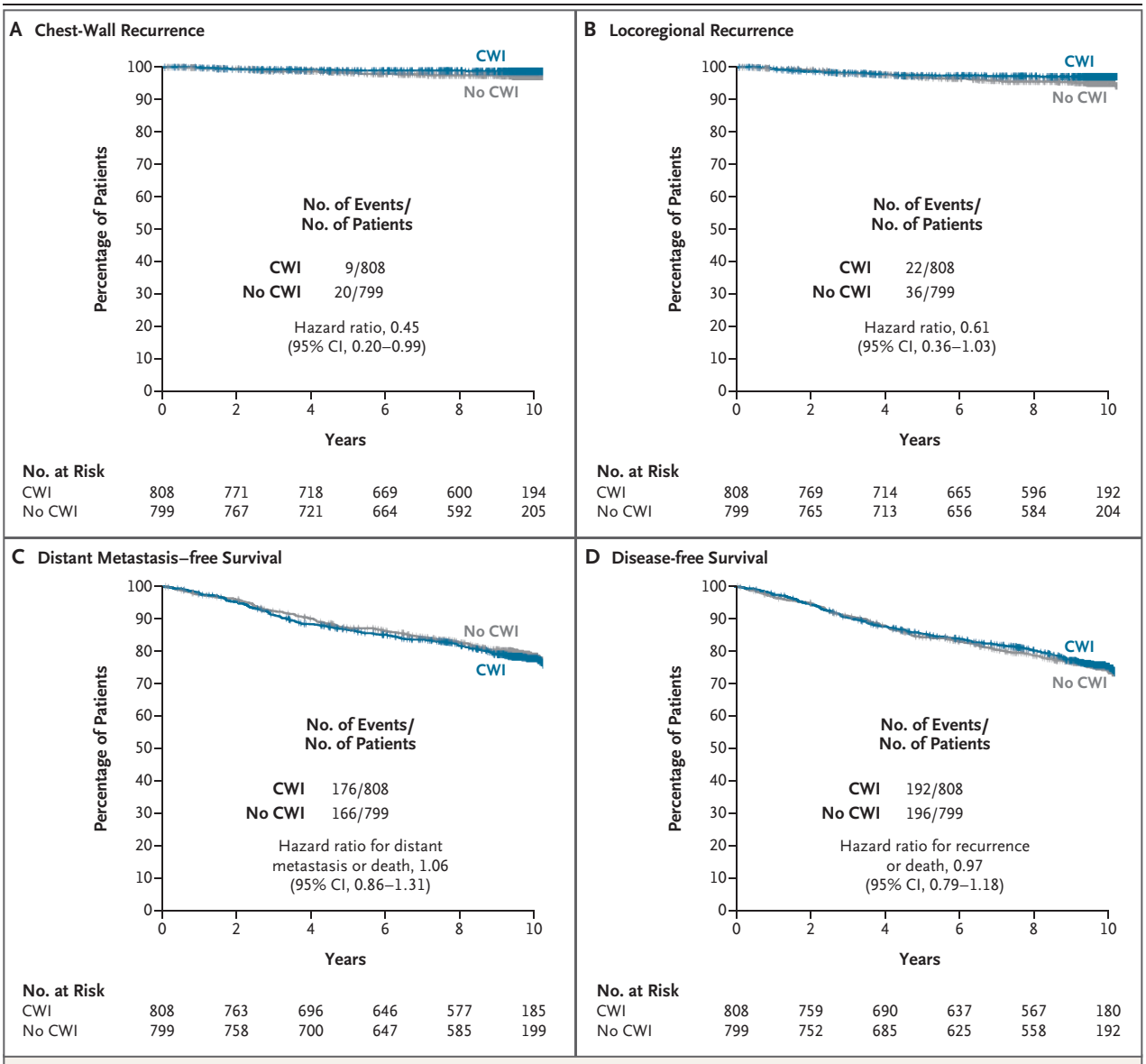

Figure 3. Analyses of Secondary End Points (Intention-to-Treat Population).

Shown are unadjusted Kaplan–Meier estimates of chest-wall recurrence (Panel A), locoregional recurrence (Panel B), distant metastasis–free survival (Panel C), and disease-free survival (Panel D). For clarity, the horizontal scale excludes follow-up beyond 10 years.

Our results contrast with those of the EBCTCG overview[6] of trials that preceded modern testing of ER and HER2 status, in which irradiation was associated with a lower cumulative incidence of locoregional recurrence as a first event than no irradiation at 10 years (3.8% vs. 20.3%), as well as a lower cumulative incidence of any first recurrence at 10 years (34.2% vs. 45.7%) and lower breast cancer mortality at 20 years (42.3% vs. 50.2%), among 1314 patients with N1 disease. Our trial included a similar number of patients with N1 disease (1201). A likely explanation for the contrast in the findings from the EBCTCG meta-analysis and our trial is higher breast cancer survival,[9] owing to advances in multidisciplinary management, especially in the areas of diagnostics and systemic therapy.[23-26] A Cochrane review of postmastectomy radiotherapy indicated that the evidence base from older studies is inapplicable to current practice.[27] Our data challenge the concept that chest-wall irradiation should remain a central tenet of locoregional postmastectomy radiotherapy.

Our results fit with the hypothesis that the survival benefit from local therapy increases with more effective systemic therapy — but only to a threshold, beyond which the benefit declines.[28] We suggest that contemporary systemic therapy has breached this threshold, and therefore, we are observing a decline in benefit from chest-wall irradiation.

Adherence to systemic therapy guidelines was high. The radiotherapy quality-assurance program and the observed between-group difference in chest-wall recurrence — albeit a clinically insignificant absolute difference of 11 patients in 10 years — provide reassurance that the lack of effect of chest-wall irradiation on overall survival is unlikely to be due to inadequate radiotherapy. We believe that our pragmatic guidelines for pathological analysis and treatment among trial participants who were widely spread across international locations reflect real-world experience and underpin the generalizability of the findings. Since the recruitment period for the trial, advances in systemic therapy have further improved survival, which strengthens the rationale for omitting chest-wall irradiation for patients with intermediate risk.

Chest-wall recurrence was rare in this trial: the cumulative incidence over 10 years was less than 3% with no irradiation, much lower than the 5 to 15% estimated for intermediate-risk disease at the time the trial was designed. Other studies have also shown a similarly low incidence of local recurrences with modern therapy that incorporates

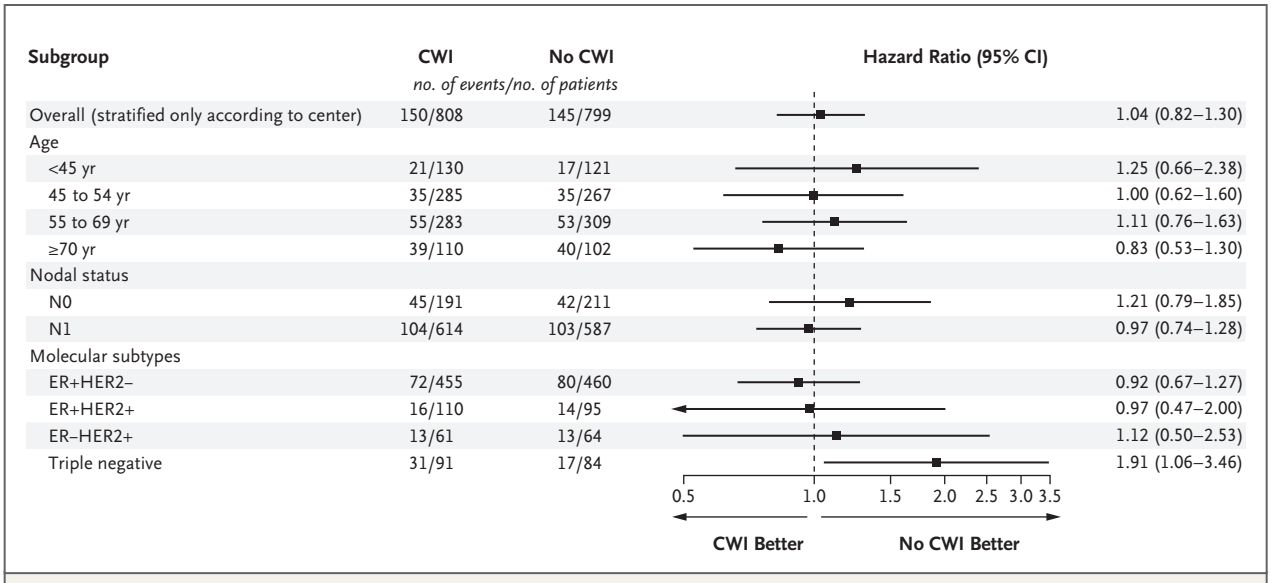

Figure 4. Subgroup Analysis of Overall Survival (Intention-to-Treat Population).

Shown are analyses of overall survival with respect to age group, nodal status, and molecular subtype. For comparison, the hazard ratio for the overall intention-to-treat population (stratified only according to treating center) is provided at the top of the graph. Values are plotted on a natural logarithmic scale. ER denotes estrogen receptor, and HER2 human epidermal growth factor receptor 2.

multiple treatment approaches.[29,30] The cumulative incidence of local recurrence at 5 years in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-51–RTOG 1304 trial,[29] which also recruited patients with one to three cancer-positive nodes, was less than 1% among patients who did not undergo irradiation. This incidence is similar to that in our trial at 5 years. If very few patients have locoregional recurrence as a first event without radiotherapy, chest-wall irradiation is unlikely to reduce mortality.[6] The apparent lack of effect of omission of chest-wall irradiation on disease-free survival and distant metastasis–free survival is reassuring.

Chest-wall irradiation did not appear to have a differential effect on overall survival among patients with pN0 or pN1 disease. The 10-year overall survival among patients who had pN0 tumors with other risk factors was similar to that among patients with pN1 tumors, which justifies the inclusion of patients with intermediate-risk pN0 disease. We confirm that a histologic grade of 3, lymphovascular invasion, and larger tumor size are associated with a level of risk that is similar to that associated with N1 disease.

Subgroup analysis according to molecular subtype suggested a worse outcome with radiotherapy than with no radiotherapy for patients with triple-negative breast cancer. This finding could be due to low numbers of patients with triple-negative breast cancer but is consistent with data from the NSABP B-51–RTOG-1304 trial, which showed a hazard ratio of 2.30 (95% CI, 1.00 to 5.25) for invasive breast cancer recurrence among patients with triple-negative breast cancer who underwent irradiation as compared with those who did not.[29] We speculate that this negative effect of radiotherapy among patients with triple-negative breast cancer might be due to a detrimental effect of radiation on immune modulation.

We recognize the recent shift from axillary-node clearance to regional nodal irradiation as primary treatment. The EBCTCG overview of trials showed that regional nodal irradiation was associated with modestly lower breast cancer mortality than no regional nodal irradiation among patients with N1 disease,[31] whereas our trial showed no evidence of a survival benefit from chest-wall irradiation as a component of postmastectomy radiotherapy. If regional nodal irradiation is warranted, modern radiotherapy techniques can deliver a homogeneous dose to the lymph-node target volumes while avoiding the chest wall or reconstructed breast.

Our trial has some limitations. First, the trial was initiated nearly two decades ago. There have been many improvements in practice since then, which have led to a lower incidence of local recurrence.

Second, many patients with intermediate risk are now treated with neoadjuvant systemic therapy, but this practice was very limited in our trial. The EBCTCG meta-analysis[32] showed no difference in survival between patients treated with adjuvant therapy and those treated with neoadjuvant chemotherapy. The NSABP B-51–RTOG-1304 trial[29] included patients with clinical N1 disease who were pathologically node negative after neoadjuvant chemotherapy. Postmastectomy radiotherapy had no effect on the invasive breast cancer recurrence–free interval among the patients who had undergone mastectomy. Invasive breast cancer–free survival at 5 years among the patients who had undergone mastectomy was approximately 90%, which was similar to the survival in our trial at the same time point.

Third, considerable reductions in axillary surgery have become standard practice. In our trial, axillary-node clearance was mandatory for N1 disease. Since the beginning of the trial, it has become apparent that no particular axillary-node staging procedure influences overall survival in early breast cancer.[33] Axillary-node clearance has been replaced by alternative approaches, such as sentinel-node biopsy, axillary irradiation, or the omission of further treatment, which may be an option for patients, including those treated with neoadjuvant chemotherapy.[34]

Finally, the importance of identifying the number of pathologically involved axillary nodes in predicting prognosis is evolving and being superseded by an approach that incorporates multiple factors, including a combination of tumor characteristics, axillary imaging, and gene-expression profiling, to predict the risk of recurrence and death from breast cancer. The TAILOR RT (Regional Radiotherapy in Biomarker Low-Risk Node Positive and T3N0 Breast Cancer) trial (ClinicalTrials.gov number, NCT03488693), for example, is using gene-expression profiling with Oncotype DX in N1, ER-positive, and HER2-negative disease to tailor indications for adjuvant locoregional radiotherapy. The TRANS-SUPREMO

tissue archive is available for investigation of prognostic and predictive biomarkers.

The low levels of toxic effects such as radiation pneumonitis in this trial, as well as the low incidence of death from cardiac causes (≤1%), probably reflects the application of modern radiotherapy techniques. We are aware that radiation-induced cardiac disease and carcinogenesis[35,36] can manifest more than 10 years after treatment. If chest-wall irradiation is no longer required in women at intermediate risk, these and other late-onset effects, including fibrosis, bone necrosis, and muscle and skin atrophy, could all be avoided. Our results have implications for breast reconstruction in contexts in which its use is controversial.[37] Some surgeons consider postmastectomy radiotherapy to be a relative contraindication to immediate and implant-based reconstruction because radiation increases the risk of complications and is associated with poorer cosmesis. Our findings are likely to reassure surgeons whose patients wish to undergo breast reconstruction, especially in situations in which implants are used.

We hope that our results stimulate a reevaluation of the evidence base for indications for chest-wall irradiation. Continuing to recommend chest-wall irradiation, in contexts in which evidence of benefit is marginal and the procedure is potentially detrimental, may divert limited resources from more effective treatments.[38]

In this trial, chest-wall irradiation did not lead to higher overall survival at 10 years than no chest-wall irradiation among patients with intermediate-risk, early breast cancer treated with mastectomy and contemporary adjuvant systemic therapy.

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