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Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer

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ABSTRACT

BACKGROUND

Limited level 1 evidence is available on the omission of radiotherapy after breast-conserving surgery in older women with hormone receptor–positive early breast cancer receiving adjuvant endocrine therapy.

METHODS

We performed a phase 3 randomized trial of the omission of irradiation; the trial population included women 65 years of age or older who had hormone receptor–positive, node-negative, T1 or T2 primary breast cancer (with tumors ≤3 cm in the largest dimension) treated with breast-conserving surgery with clear excision margins and adjuvant endocrine therapy. Patients were randomly assigned to receive whole-breast irradiation (40 to 50 Gy) or no irradiation. The primary end point was local breast cancer recurrence. Regional recurrence, breast cancer–specific survival, distant recurrence as the first event, and overall survival were also assessed.

RESULTS

A total of 1326 women were enrolled; 658 were randomly assigned to receive whole-breast irradiation and 668 to receive no irradiation. The median follow-up was 9.1 years. The cumulative incidence of local breast cancer recurrence within 10 years was 9.5% (95% confidence interval [CI], 6.8 to 12.3) in the no-radiotherapy group and 0.9% (95% CI, 0.1 to 1.7) in the radiotherapy group (hazard ratio, 10.4; 95% CI, 4.1 to 26.1; P<0.001). Although local recurrence was more common in the group that did not receive radiotherapy, the 10-year incidence of distant recurrence as the first event was not higher in the no-radiotherapy group than in the radiotherapy group, at 1.6% (95% CI, 0.4 to 2.8) and 3.0% (95% CI, 1.4 to 4.5), respectively. Overall survival at 10 years was almost identical in the two groups, at 80.8% (95% CI, 77.2 to 84.3) with no radiotherapy and 80.7% (95% CI, 76.9 to 84.3) with radiotherapy. The incidence of regional recurrence and breast cancer–specific survival also did not differ substantially between the two groups.

CONCLUSIONS

Omission of radiotherapy was associated with an increased incidence of local recurrence but had no detrimental effect on distant recurrence as the first event or overall survival among women 65 years of age or older with low-risk, hormone receptor–positive early breast cancer. (Funded by the Chief Scientist Office of the Scottish Government and the Breast Cancer Institute, Western General Hospital, Edinburgh; ISRCTN number, ISRCTN95889329.)

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A list of the collaborators in the PRIME II trial is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

In the United States, 26% of breast cancer diagnoses are in women 65 to 74 years of age.[1] The prevalence of breast cancer among older adults is rising.[2] Underrepresentation of older patients with breast cancer in clinical trials has led to undertreatment and overtreatment.[3] A meta-analysis by the Early Breast Cancer Trialists' Cooperative Group[4] showed that radiotherapy after breast-conserving therapy, although it reduces the overall cumulative incidence of recurrence among node-negative patients, confers only a modest survival benefit. Omission of radiotherapy after breast-conserving therapy in low-risk, older patients with smaller hormone receptor (HR)–positive tumors remains controversial,[5-7] with only limited long-term level 1 evidence available to guide treatment decisions.[2,8-12] The 5-year results of the PRIME II trial showed that among women 65 years of age or older who had HR-positive T1 or T2 primary tumors (≤3 cm in the largest dimension) and no lymph-node involvement and who were treated with breast-conserving therapy and adjuvant endocrine therapy, radiotherapy was associated with a lower percentage of patients having local breast cancer recurrence (4.1% without radiotherapy vs. 1.3% with radiotherapy).[9] Despite guidelines supporting the omission of radiotherapy in women 70 years of age or older with T1[10,11] or small selected T2[12] estrogen-receptor (ER)–positive tumors treated with breast-conserving therapy and adjuvant endocrine therapy, the use of radiotherapy in the United States in this clinical context remains common.[13] Here we report the 10-year outcomes of the PRIME II trial.

Methods

Oversight

We conducted PRIME II, a phase 3 randomized clinical trial that was designed by the Scottish Cancer Trials Breast Group (SCTBG). The methods have been described previously.[9] The trial was conducted in 76 centers in the United Kingdom, Greece, Australia, and Serbia. The protocol (available with the full text of this article at NEJM.org) received U.K. ethics approval. All the patients provided written informed consent. Two of the authors designed the trial with the SCTBG. The authors wrote the article and vouch for the accuracy and completeness of the data for the adherence to the protocol. The funders of the trial had no role in its design or conduct, no access to the data, and no role in the analysis or publication of the data.

Patient Selection

Women 65 years of age or older were eligible to participate if they had T1 or T2 primary breast cancer (tumor size, ≤3 cm in the largest dimension) that had been treated with breast-conserving therapy plus axillary staging (four-node lower axillary sample, sentinel-node biopsy, or axillary-node clearance) and was node-negative, estrogen receptor (ER)–positive or progesterone receptor–positive (or both), and had clear excision margins (≥1 mm); they also needed to have received adjuvant or neoadjuvant endocrine therapy. Patients were eligible if they had either cancer with grade 3 histologic features or lymphovascular invasion but not both. Patients were excluded if they were younger than 65 years of age, had a history of in situ or invasive carcinoma of either breast, or had had malignant disease within the previous 5 years (except nonmelanomatous skin cancer or carcinoma in situ of the cervix). Neither HER2 status (since it was not routinely measured at the initiation of the trial) nor coexisting conditions were recorded. All patients had to have a health status that would make treatment and follow-up possible.

Treatment

At trial entry, a computerized randomization service was used to randomly assign patients in a 1:1 ratio to receive either whole-breast irradiation or no irradiation. Guidelines were given for irradiation (40 to 50 Gy in total; 2.66 to 2.00 Gy per fraction in 20 to 25 fractions), which was administered over a period of 3 to 5 weeks. Boost irradiation of the breast was allowed with electrons (10 to 15 Gy) or with an iridium implant (e.g., 20 Gy to the 85% reference isodose volume). We recommended tamoxifen at a dose of 20 mg per day for 5 years as standard adjuvant endocrine therapy. Follow-up was performed through annual clinical visits for at least 5 years and subsequently through clinic visits or telephone calls to the patient or a community doctor to determine each patient's health status. Annual mammography of both breasts was rec-

ommended, but mammography performed at the first, third, and fifth years after surgery was acceptable.

TRIAL END POINTS

The primary end point was local breast cancer recurrence. The secondary end points were regional recurrence, contralateral breast cancer, distant metastases, disease-free survival, and overall survival. Local recurrence was defined as any cancer in the scar or in the same breast. Regional recurrence was defined as disease in the ipsilateral axillary or supraclavicular lymph nodes. The end points were assessed by the local investigator and were not centrally assessed.

STATISTICAL ANALYSIS

Our null hypothesis was that there would be no difference between the radiotherapy and no-radiotherapy groups in terms of local recurrence at 5 years. The trial was originally powered to detect a difference at 5 years of at least 5 percentage points (i.e., recurrence in 5% of patients in the radiotherapy group and in 10% of those in the no-radiotherapy group) with 80% power at a significance level of 5% with a target of enrolling 1000 patients. Ethics approval was granted on November 14, 2008, to increase the sample size to 1294, because both randomized and nonrandomized studies[14] suggested that our initial estimate of the local recurrence rate was excessive. Our revised estimates enabled the detection of a difference of at least 3 percentage points (2% in the radiotherapy group and 5% in the no-radiotherapy group) at 5 years with 80% power at a significance level of 5% and with a 10% allowance for loss to follow-up. Our planned statistical analysis of primary and secondary end points of the trial was documented on March 3, 2020, before the analysis was performed. Adherence to adjuvant endocrine therapy was included as an additional secondary end point.

Data were analyzed with Kaplan–Meier plots and by log-rank testing (Mantel–Cox statistic for the equality of survival distributions between the two groups). Hazard ratios and 95% confidence intervals were estimated with the Cox proportional-hazards model, with the proportional-hazards assumption tested for each model with the use of the graphical and numeric methods described by Lin et al.[15] All the analyses were performed on an intention-to-treat basis with two-tailed tests. Because no procedure for type I error control was implemented for secondary end points, the results for these end points are reported as point estimates and confidence intervals only, without hypothesis testing. The widths of the confidence intervals have not been adjusted for multiple testing and therefore may not be used in place of hypothesis testing. The effect of the duration of endocrine therapy and the level of tumor ER on outcomes were prespecified exploratory end points.

Clinicians were asked to note on the annual clinical research form whether a patient was still taking adjuvant endocrine therapy, and if not, when the patient had stopped. This allowed an analysis of the data with adjuvant endocrine therapy as a time-varying covariate, in which the risk of local recurrence at time t for patients taking adjuvant endocrine therapy was compared with the risk for patients not taking adjuvant endocrine therapy at time t.

Post hoc subgroup analysis of local recurrence according to ER score was performed. Patients were classified as having either ER-high or ER-low tumors. Tumors were defined as ER-high if they had an Allred score of 7 or 8 (on a scale from 0 to 8, with higher scores indicating greater staining for ER), an ER level of at least 20 fmol per milligram of protein, or more than 50% of cells staining positive for ER, or when the only information available on the case-report form was classification as "+++" (indicating strong staining for ER), "strongly positive," or "ER-positive." Tumors without these characteristics were defined as ER-low. Data were analyzed with SPSS software, version 22 (IBM), and SAS software, version 9.4, for Windows (SAS Institute).

RESULTS

PATIENTS

From April 16, 2003, to December 22, 2009, a total of 1326 patients underwent randomization; 658 were randomly assigned to receive postoperative irradiation, and 668 were assigned to receive no postoperative irradiation (Fig. 1). Patients were recruited from the United Kingdom (1263 patients), Greece (22 patients), Australia (16 patients), and Serbia (25 patients). Table 1

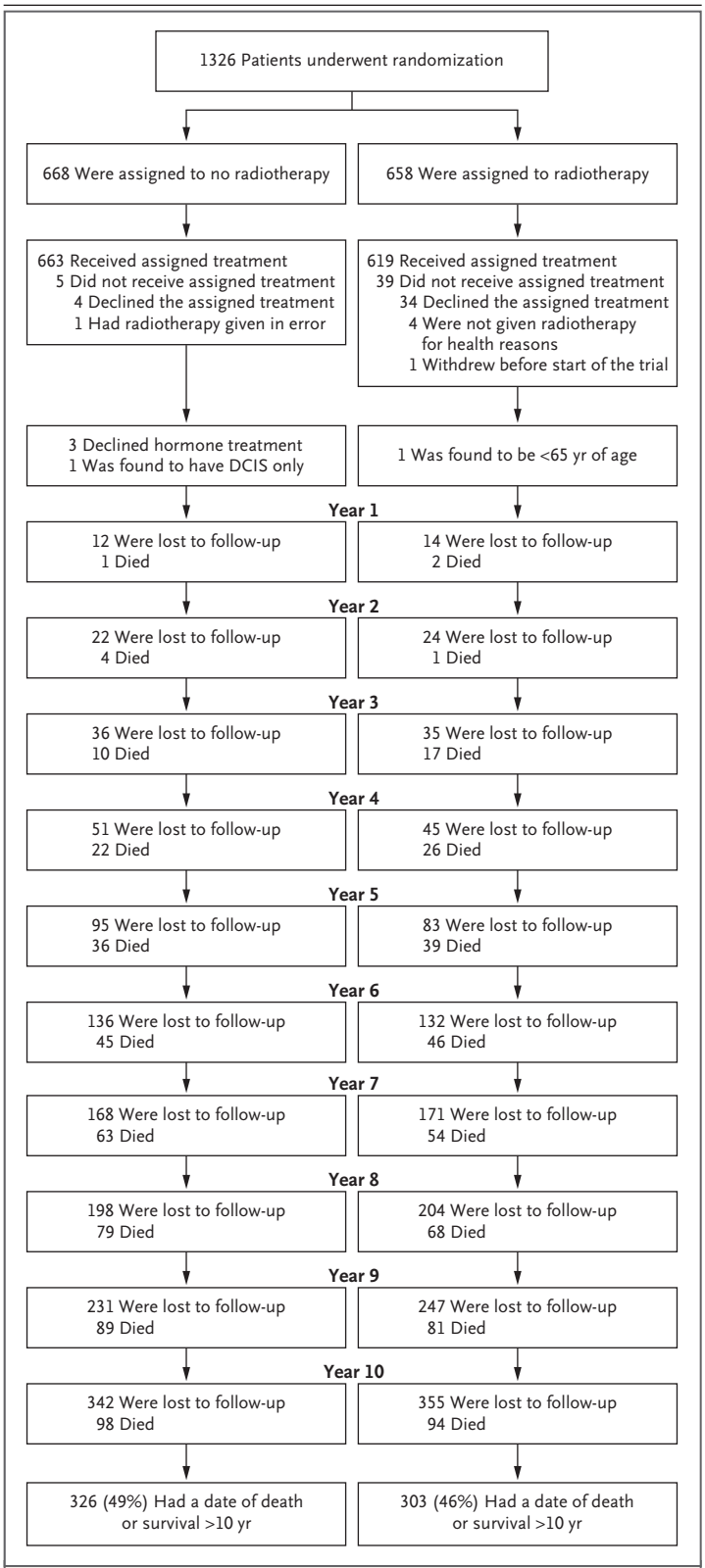

Figure 1. Randomization and Follow-up.

shows the baseline characteristics of the trial population, which were similar in the two treatment groups. The median age of the patients at trial entry was 70 years (interquartile range, 67 to 74), and less than 10% of patients had ER-low tumors. Of the 584 patients for whom radiotherapy data were available, 91 (15.6%) received a tumor-bed boost after whole-breast irradiation.

END POINTS

After 10 years of follow-up, the cumulative incidence of local recurrence was 9.5% (95% confidence interval [CI], 6.8 to 12.3) in the no-radiotherapy group and 0.9% (95% CI, 0.1 to 1.7) in the radiotherapy group (Fig. 2A). The hazard ratio for local recurrence (no radiotherapy vs. radiotherapy) was 10.4 (95% CI, 4.1 to 26.1; P<0.001) (full data, not censored at 10 years). Local recurrence of breast cancer developed in 51 patients assigned to no radiotherapy and in 5 patients assigned to radiotherapy. In the no-radiotherapy group, 48 of 51 local recurrences occurred as the first event, including 37 in patients who had only local recurrence.

The 10-year cumulative incidence of distant recurrence as the first event was 1.6% (95% CI, 0.4 to 2.8) without radiotherapy and 3.0% (95% CI, 1.4 to 4.5) with radiotherapy (Fig. 2B). No substantial differences at 10 years were noted in the cumulative incidence of regional recurrence, contralateral breast cancer (data not shown), or new cancers or in survival free from new cancer (Table S1 and Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Disease-free survival at 10 years was 68.9% (95% CI, 64.7 to 73.0) in the no-radiotherapy group and 76.3% (95% CI, 72.5 to 80.2) in the radiotherapy group (Fig. S2). Breast cancer–specific survival at 10 years was 97.4% (95% CI, 96.0 to 98.8) among patients assigned to no radiotherapy and 97.9% (95% CI, 96.5 to 99.2) among patients assigned to radiotherapy (Fig. 2C). Sixteen deaths in the no-radiotherapy group and 15 deaths in the radiotherapy group were due to breast cancer (Table S2). Most causes of death were not breast cancer; 25% of all deaths (59 of 231) were due to cancers other than breast cancer. Overall survival at 10 years was 80.8% (95% CI, 77.2 to 84.3) in the no-radiotherapy group and 80.7% (95% CI, 76.9 to 84.3) in the radiotherapy group (Fig. 2D).

SUBGROUP ANALYSIS

In a subgroup analysis of local recurrence according to ER status, the cumulative incidence of local recurrence was lower among patients with ER-high cancers than in the overall trial population (Fig. 3). The 10-year cumulative incidence of local recurrence among patients with ER-high tumors was 8.6% (95% CI, 5.7 to 11.4) in the no-radiotherapy group and 1.0% (95% CI, 0.1 to 1.9) in the radiotherapy group (hazard ratio, 8.23; 95% CI, 3.24 to 20.85). The 10-year cumulative incidence of local recurrence among patients with ER-low tumors in the no-radiotherapy group was 19.1% (95% CI, 8.2 to 29.9) (hazard ratio [vs. patients with ER-high tumors in the radiotherapy group], 23.93; 95% CI, 8.43 to 67.93). No local recurrence was observed among patients with ER-low tumors in the radiotherapy group, but the sample was very small (53 patients). Data were collected on the duration of adjuvant endocrine therapy, and the time-dependent analysis showed an increased risk of local recurrence among patients in the no-radiotherapy group who were no longer taking endocrine therapy (hazard ratio [vs. patients who continued to take endocrine therapy], 4.66; 95% CI, 1.77 to 12.25). Other studies[16] have shown that less than 80% adherence is associated with significantly decreased benefit from adjuvant endocrine therapy.

DISCUSSION

In this trial involving older women with HR-positive breast cancer treated with adjuvant endocrine therapy, the 10-year incidence of local cancer recurrence after breast-conserving surgery was significantly lower among patients who received whole-breast irradiation than among those who did not receive irradiation. The incidence of local recurrence up to 10 years among patients who received radiotherapy remained low, whereas that among patients who did not receive radiotherapy continued to increase with no apparent plateau. However, the absolute difference in the incidence of local recurrence at 10 years was modest (8.6 percentage points). Despite this difference, irradiation had no substantial effect on the incidence of regional or distant metastases or on breast cancer–specific or overall survival. The low cumulative incidence of local recurrence at 10 years after breast-conserving surgery and irradiation is consistent with the results of the earlier Cancer and Leukemia Group B (CALGB) 9343 trial, which involved patients 70 years of age or older who had T1, node-negative, HR-positive tumors treated with breast-conserving surgery and tamoxifen[8]; in that trial, the incidence of local recurrence within 10 years was 7 percentage points lower among patients who received irradiation than among those who did not. Our observations in a higher-risk population show a similar between-group difference in the incidence of local recurrence. Earlier trials of irradiation after breast-conserving surgery,[17-23] apart from the Italian trial,[23] were not exclusive to older patients, which limited their generalizability to an older population.

The 9.5% cumulative incidence of local recurrence at 10 years among the patients who did not receive radiotherapy in our trial lies within range from the European Society of Mastology (EUSOMA) guidelines, which cited a maximum rate of locoregional recurrence of 10% at 10 years.[24] Our results are also consistent with the small benefit from irradiation that was found in the low-risk group of older patients in a meta-analysis of trials of adjuvant radiotherapy after breast-conserving surgery.[4] EUSOMA guidelines recommend that patients older than 70 years of age receiving adjuvant endocrine therapy for low-risk tumors may be treated without irradiation,[25] similar to the recommendations of the U.K. National Institute for Health and Care Excellence[26] and the National Comprehensive Cancer Network guidelines, which allow omission of irradiation in women 65 years of age or older[26] or 70 years of age or older[11] with stage 1, ER-positive breast cancer after breast-conserving surgery. Our findings provide additional data indicating that although the omission of irradiation increases the cumulative incidence of local recurrence, it does not have a similar effect on distant disease–free or overall survival.

The applicability of these results to clinical practice will be influenced by the balance of the risks and benefits of radiation as compared with those of adjuvant endocrine therapy. Irradiation has associated complications, including cardiac events and second cancers.[27,28] We did not collect data on toxic effects of radiation in our trial. However, an analysis of treatment-related complications in the PRIME I trial, in which patients were also randomly assigned to receive or not

Table 1. Demographic and Clinical Characteristics of the Patients.*

Characteristic	No Radiotherapy (N=668)	Radiotherapy (N=658)
Age — yr		
Mean	71.1±5.0	70.8±4.7
Median (IQR)	70 (67–74)	69 (67–73)
Tumor size — no. (%)		
0–1.0 cm	258 (38.6)	265 (40.3)
1.1–2.0 cm	326 (48.8)	319 (48.5)
2.1–3.0 cm	84 (12.6)	74 (11.2)
Excision margins — no. (%)		
<1 mm	10 (1.5)	9 (1.4)
1–5 mm	315 (47.2)	296 (45.0)
>5 mm	227 (34.0)	239 (36.3)
Reexcision†	112 (16.8)	110 (16.7)
Unknown	4 (0.6)	4 (0.6)
Tumor grade — no. (%)		
1	271 (40.6)	292 (44.4)
2	368 (55.1)	352 (53.5)
3	23 (3.4)	13 (2.0)
Unknown	6 (0.9)	1 (0.2)
Tumor location — no. (%)		
Left breast	359 (53.7)	345 (52.4)
Right breast	302 (45.2)	305 (46.4)
Side unknown	7 (1.0)	8 (1.2)
Lymphovascular invasion — no. (%)		
No	631 (94.5)	628 (95.4)
Yes	32 (4.8)	27 (4.1)
Unknown	5 (0.7)	3 (0.5)
Axillary surgery — no. (%)		
Sentinel-node biopsy only	223 (33.4)	198 (30.1)
Sample only	174 (26.0)	211 (32.1)
Sample with sentinel-node biopsy	105 (15.7)	107 (16.3)
Clearance of <10 nodes	43 (6.4)	35 (5.3)
Clearance of ≥10 nodes	109 (16.3)	99 (15.0)
Unknown	14 (2.1)	8 (1.2)
Preoperative endocrine therapy — no. (%)		
No	608 (91.0)	598 (90.9)
Yes	60 (9.0)	54 (8.2)
Unknown	0	6 (0.9)
ER status — no. (%)‡		
High	593 (88.8)	601 (91.3)
Low	65 (9.7)	55 (8.4)
Unknown	10 (1.5)	2 (0.3)

Table 1. (Continued.)

Characteristic	No Radiotherapy (N=668)	Radiotherapy (N=658)
Radiotherapy — no./total no. (%)§		
Within 40 to 50 Gy	—	573/584 (98.1)
Boost	—	91/584 (15.6)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† Excision margins of at least 1 mm were required by the protocol, which in some cases required reexcision; reexcision margins also had to be at least 1 mm.
‡ Tumors were defined as estrogen receptor (ER)–high if they had an Allred score of 7 or 8 (on a scale from 0 to 8, with higher scores indicating greater staining for ER), an ER level of at least 20 fmol per milligram of protein, or at least 50% of cells staining positive for ER, or when the only information available on the case-report form was classification as "+++" (indicating strong staining for ER), "strongly positive," or "ER-positive." In 12 patients, data on ER were not reported.
§ Only 584 copies of the postradiotherapy form were returned. One patient did not complete radiotherapy after it had been started, and one patient had the boost dose altered after it had begun. The majority of patients whose radiotherapy dose was outside the guidance-recommended range of 40 to 50 Gy were from countries other than the United Kingdom.

receive irradiation after breast-conserving surgery, showed no difference in global quality of life between the two groups.[29,30] An increased risk of cardiovascular events has been reported in association with tamoxifen and aromatase inhibitors.[31] In contemporary practice, higher-risk patients (i.e., those with T2 or grade 3 HR-positive tumors) are likely to be treated with an aromatase inhibitor as endocrine therapy rather than with tamoxifen. The results of the current trial are similar to those of the British Association of Surgical Oncology II trial,[20] in which local disease was controlled with tamoxifen or irradiation given alone. Viable options for patients who meet the entry criteria for our current trial are a short course of irradiation or adjuvant endocrine therapy. The advantage of endocrine therapy is that it also reduces the risk of cancer recurrence in the contralateral breast.

The risk–benefit ratio of irradiation and endocrine therapy in older patients with low-risk, ER-positive disease has become more nuanced,[32] with hypofractionated dose schedules,[33] accelerated partial breast irradiation,[34] and improved delivery techniques.[35] Given the limitations of partial-breast irradiation (which demands localization of the treatment site and associated quality assurance) as compared with whole-breast irradiation, we concur with the view[36] that adjuvant endocrine therapy without irradiation is the principal competitor to whole-breast irradiation. For patients who do not receive irradiation and do have subsequent development of local recurrence, the option of further breast-conserving therapy and irradiation is available, so recurrence does not necessarily mean loss of the breast.

Women in either group in the current trial were more likely to die from other causes than from breast cancer. Of the 231 deaths that occurred, only 31 (13%) were due to breast cancer. Patients and clinicians can balance the harms and benefits of irradiation knowing that avoiding it does not increase the risk of death from breast cancer.

Few patients in the trial had grade 3 cancers (36 patients) or lymphovascular invasion (39 patients), and therefore whether radiotherapy can be avoided in these patients is not clear. On the basis of studies of neoadjuvant endocrine therapy (Dixon JM and Turnbull A: personal communication), ER-high grade 3 tumors do not respond less well than lower-grade tumors. However, the current trial was underpowered to detect any difference in local recurrence between grade 3 and grade 1 or 2 tumors. For grade 3 tumors and lymphovascular invasion, our estimates of effect size are not very precise as a result of low numbers. We can speculate that in selecting suitable patients for the trial, clinicians were cautious in enrolling patients with grade 3 tumors or lymphovascular invasion because the risk of local recurrence is doubled in patients who have cancer with grade 3 histologic features or lymphovascular invasion,[37,38] although the relevance of these characteristics as risk factors in older patients is unclear. Confining the option of omission of irradiation to grade 1 and 2 tumors is also in line with current European guidelines.[24,25]

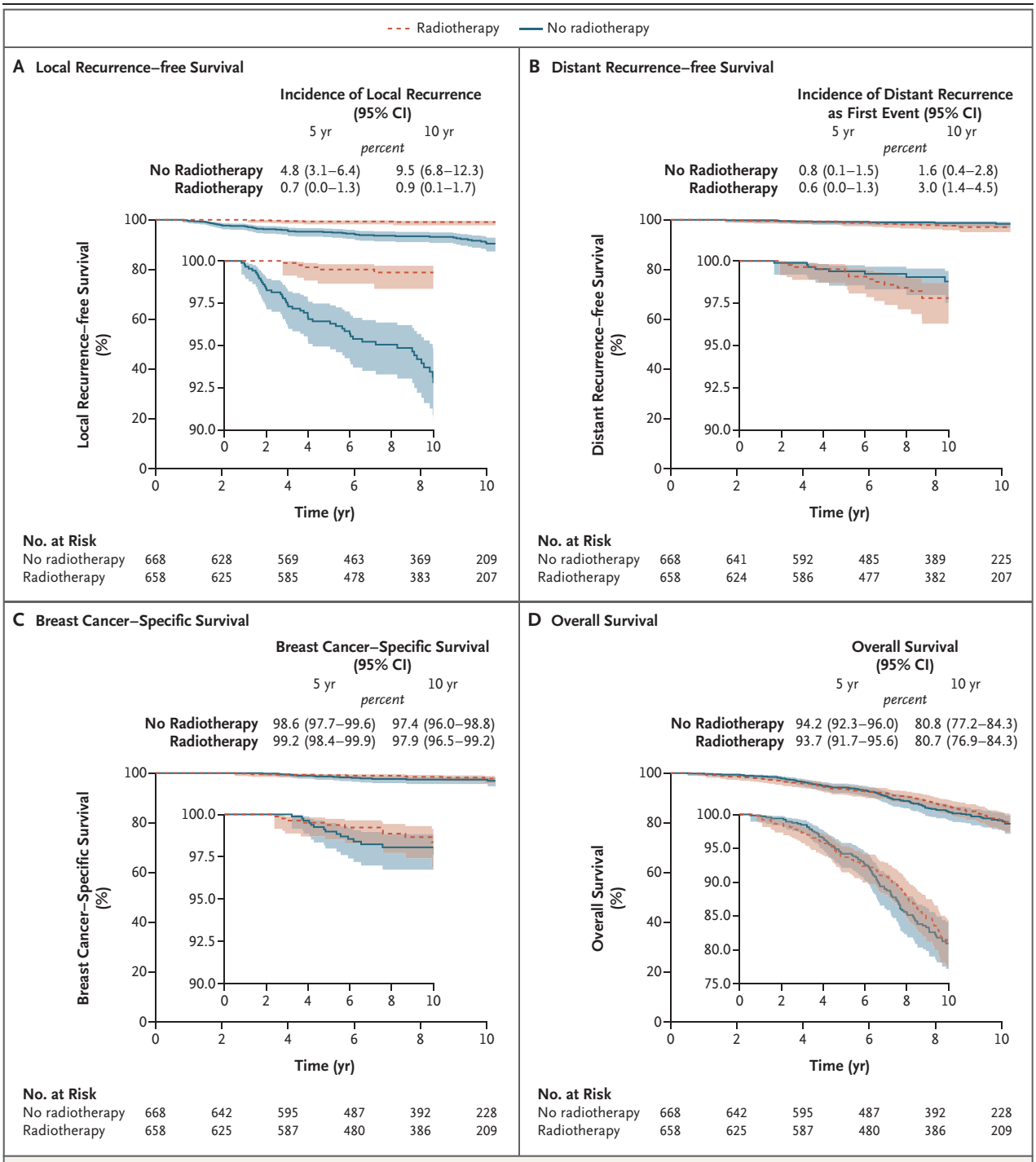

Figure 2. Local Recurrence, Distant Recurrence as the First Event, Breast Cancer–Specific Survival, and Overall Survival.

In each panel, the inset shows the same data on an expanded y axis. Shaded areas around the curves indicate the 95% confidence interval. Confidence intervals in Panels B, C, and D have not been adjusted for multiple testing and should not be used in place of hypothesis testing.

No grade 3 tumors were included in the CALGB 9343 trial.[8]

Our data are consistent with an earlier observation[9] that patients with ER-high cancers have a lower cumulative incidence of local recurrence at 10 years than do patients with ER-low cancers (Fig. 3). The percentage of patients who completed 5 years of endocrine therapy was between 60% and 70%. Patients who are less than 80% adherent to endocrine therapy are thought to have poorer outcomes.[16,39] We did not collect data on adherence. Instead, using the reported end of endocrine therapy as a surrogate measure, we found a risk of local recurrence that was 4 times as high among patients who were not taking endocrine therapy as among those who continued the therapy in the no-radiotherapy group.

Our trial has some limitations. We did not collect data on coexisting conditions or monitor adherence to endocrine therapy prospectively. Omission of postoperative irradiation after breast-conserving surgery and adjuvant endocrine therapy for ER-positive tumors varies and is influenced by coexisting conditions. Relatively high levels of use of irradiation for such patients have been reported from nonrandomized studies conducted in the United States.[13]

Our trial provides robust evidence indicating that irradiation can be safely omitted in women 65 years of age or older who have grade 1 or 2, ER-high cancers treated by breast-conserving therapy, provided that they receive 5 years of adjuvant endocrine therapy.

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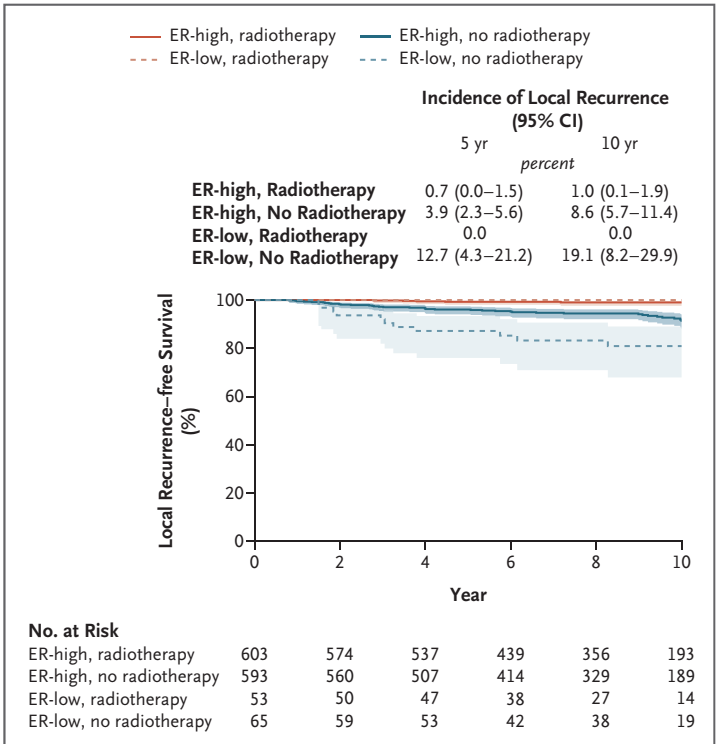

Figure 3. Local Recurrence According to Estrogen Receptor (ER) Status and Receipt of Radiotherapy.

Shaded areas around the curves indicate the 95% confidence interval. Confidence intervals have not been adjusted for multiple testing and should not be used in place of hypothesis testing.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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