ORIGINAL ARTICLE

Omitting Regional Nodal Irradiation after Response to Neoadjuvant Chemotherapy

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ABSTRACT

BACKGROUND

The benefit of regional nodal irradiation in the treatment of breast cancer is well established for patients with pathologically positive axillary nodes, but whether it is also beneficial for patients whose nodes become pathologically tumor free (ypN0) after neoadjuvant chemotherapy remains unclear.

METHODS

We evaluated whether regional nodal irradiation improves outcomes in patients with biopsy-proven, node-positive breast cancer who reach ypN0 status after neoadjuvant chemotherapy. Patients with breast cancer with a clinical stage of T1 to T3 (tumor size, ≤2 cm to >5 cm), N1, and M0 (indicating spread to one to three axillary lymph nodes but no distant metastasis) who had ypN0 status after neoadjuvant chemotherapy were randomly assigned to receive regional nodal irradiation or no regional nodal irradiation. The primary end point was the interval of freedom from invasive breast cancer recurrence or death from breast cancer (invasive breast cancer recurrence–free interval). Secondary end points included the locoregional recurrence–free interval, the distant recurrence–free interval, disease-free survival, and overall survival. Safety was also assessed.

RESULTS

A total of 1641 patients were enrolled in the trial; 1556 were included in the primary-event analysis: 772 in the irradiation group and 784 in the no-irradiation group. After a median follow-up of 59.5 months, 109 primary end-point events (50 in the irradiation group and 59 in the no-irradiation group) had occurred. Regional nodal irradiation did not significantly increase the invasive breast cancer recurrence–free interval (hazard ratio, 0.88; 95% confidence interval, 0.60 to 1.28; P=0.51). Point estimates of survival free from the primary end-point events were 92.7% in the irradiation group and 91.8% in the no-irradiation group. Regional nodal irradiation did not increase the locoregional recurrence–free interval, the distant recurrence–free interval, disease-free survival, or overall survival. No deaths related to the protocol-specified therapy were reported, and no unexpected adverse events were observed. Grade 4 adverse events occurred in 0.5% of patients in the irradiation group and 0.1% of those in the no-irradiation group.

CONCLUSIONS

The addition of adjuvant regional nodal irradiation did not decrease the risk of invasive breast cancer recurrence or death from breast cancer in patients who had negative axillary nodes after neoadjuvant chemotherapy. (Funded by the National Institutes of Health; NSABP B-51–Radiation Therapy Oncology Group 1304 ClinicalTrials.gov number, NCT01872975.)

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Adjuvant regional nodal irradiation has been shown to reduce the risk of locoregional recurrence, distant recurrence, and death from breast cancer among patients with early-stage breast cancer who undergo surgery first and have pathologically involved axillary lymph nodes.[1-7] These benefits are evident irrespective of the number of lymph nodes involved.[7]

Preoperative or neoadjuvant chemotherapy reduces the burden of disease in the breast and axillary lymph nodes and can allow for patients to become candidates for lumpectomy rather than mastectomy. Several randomized clinical trials have shown the efficacy of neoadjuvant chemotherapy to be equivalent to that of adjuvant chemotherapy.[8-10] Potential clinical advantages of neoadjuvant chemotherapy include reduction in the extent of surgery needed and improvement in prognostic stratification.[8,9,11-13] A pathological complete response in the breast and axilla has been consistently shown to predict better outcomes and can be used for tailoring subsequent adjuvant systemic therapy.[14]

With the increasing use and efficacy of neoadjuvant chemotherapy, clinicians often encounter patients who present with axillary-lymph-node involvement (i.e., clinically node-positive status) but whose axillary lymph nodes are pathologically tumor free (ypN0) after neoadjuvant chemotherapy. For such patients, no prospective outcome data show benefit from regional nodal irradiation. This lack of data has led to clinical uncertainty and variability in practice with respect to the use of regional nodal irradiation due to positive axillary nodes at diagnosis or its omission due to negative axillary nodes after neoadjuvant chemotherapy.[15,16]

Retrospective studies have shown that patients with clinically positive axillary nodes that reach stage ypN0 after neoadjuvant chemotherapy have better outcomes than those whose nodes remain pathologically positive, findings that create uncertainty about the need for regional nodal irradiation.[17-19] The largest retrospective analysis of two National Surgical Adjuvant Breast and Bowel Project (NSABP) trials of neoadjuvant chemotherapy (B-18 and B-27) attempted to identify independent predictors of locoregional recurrence in 3088 patients who received neoadjuvant chemotherapy, followed by breast irradiation in patients who underwent a lumpectomy, but no regional nodal irradiation and no radiation therapy to the chest wall in patients who underwent a mastectomy.[17] In multivariate analyses, a pathological complete response in the breast, with ypN0 status, was a significant predictor of lower risk of locoregional recurrence irrespective of the type of breast surgery (lumpectomy vs. mastectomy). Moreover, patients with clinically positive axillary lymph nodes before neoadjuvant chemotherapy whose nodes became ypN0 after surgery had lower rates of chest-wall and regional nodal recurrence than those whose nodes remained pathologically positive (ypN+). We conducted the NSABP B-51–Radiation Therapy Oncology Group 1304 trial to evaluate whether regional nodal irradiation would significantly increase the interval of freedom from recurrence of invasive breast cancer in patients with clinically node-positive breast cancer whose nodes reached ypN0 status after neoadjuvant chemotherapy.

METHODS

TRIAL DESIGN AND ELIGIBILITY

This prospective, phase 3, multicenter, randomized trial was designed, conducted, and overseen by NRG Oncology, a member of the National Clinical Trials Network, sponsored by the National Cancer Institute (NCI). Medical institutions primarily in Australia, Canada, Ireland, Israel, Japan, South Korea, and the United States enrolled patients in the trial. The protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board at a participating institution or by the NCI Central Institutional Review Board. Written informed consent was required for enrollment. The NRG Oncology Statistics and Data Management Center collected the data. The first three authors had full access to the data, analyzed the data, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first three authors wrote the first draft of the manuscript and made the final decision to submit the manuscript for publication. The trial received no financial support from industry.

Eligible patients had breast cancer that was clinical stage T1 to T3 (tumor size, T1, ≤2 cm; T2, >2 cm but ≤5 cm; T3, >5 cm), N1, and M0 (indicating spread to one to three axillary lymph nodes but no distant metastasis) and operable at diagnosis, with pathological confirmation of the

involvement of axillary nodes by either fine-needle aspiration or core-needle biopsy. Patients must have completed at least 8 weeks of standard neoadjuvant chemotherapy with a regimen that was anthracycline based, taxane based, or both. Patients with human epidermal growth factor receptor 2 (HER2)–positive tumors had to also have received neoadjuvant anti-HER2 therapy (either with all or part of neoadjuvant chemotherapy), unless such therapy was medically contraindicated. After neoadjuvant chemotherapy, patients underwent either a lumpectomy or mastectomy plus pathological assessment of axillary lymph nodes by either sentinel-lymph-node biopsy alone (with at least two sentinel lymph nodes removed) or axillary-lymph-node dissection with or without previous sentinel-lymph-node biopsy. At surgery, all removed axillary nodes had to be pathologically negative (ypN0). Patients could receive additional adjuvant systemic therapy at the investigator's discretion.

Eligible patients were stratified according to the type of surgery (lumpectomy or mastectomy), estrogen–progesterone hormone receptor status (negative or positive), HER2 status (negative or positive), the use of adjuvant chemotherapy (yes or no), and the presence or absence of a pathological complete response in the breast. Patients were then randomly assigned to undergo regional nodal irradiation (chest-wall irradiation plus regional nodal irradiation after mastectomy or the addition of regional nodal irradiation to whole-breast irradiation after lumpectomy) or to undergo no regional nodal irradiation (with no irradiation after mastectomy or with whole-breast irradiation only after lumpectomy) (Fig. S1 in the Supplementary Appendix, available at NEJM.org).

TRIAL AIMS AND END POINTS

The primary aim of the trial was to evaluate whether patients who received regional nodal irradiation (the irradiation group) would have a longer invasive breast cancer recurrence–free interval than patients who did not receive regional nodal irradiation (the no-irradiation group). The invasive breast cancer recurrence–free interval (according to Standardized Definitions for Efficacy End Points [STEEP] criteria) was defined as the time from randomization to invasive locoregional recurrence, distant recurrence, or death from breast cancer.[20]

Secondary end points (reported herein) were overall survival (defined as the time from randomization to death from any cause); the locoregional recurrence–free interval (defined as the time from randomization to the recurrence of breast cancer within the breast [invasive or ductal carcinoma in situ] or in lymph nodes of the ipsilateral axilla, infraclavicular fossa, or ipsilateral internal mammary chain without evidence of distant disease, or death from breast cancer); the distant recurrence–free interval (defined as the time from randomization to the development of distant recurrence or death from breast cancer), and disease-free survival.[20] Safety was also evaluated. Additional secondary end points, including quality-of-life measures, are not reported here.

RADIATION THERAPY REGIMENS

Patients assigned to receive regional nodal irradiation received 50 Gy in 25 fractions delivered to the retained portion of level I to III axillary nodes after sentinel-lymph-node biopsy or axillary-lymph-node dissection, supraclavicular nodes, and internal mammary nodes within the first three to four intercostal spaces, along with the chest wall after mastectomy or the whole breast after lumpectomy. Patients assigned to omit regional nodal irradiation received no radiation therapy after mastectomy or received whole-breast irradiation after lumpectomy (a total of 50 Gy in 25 fractions followed by boosts totaling 12 to 14 Gy in 6 to 7 fractions delivered to the surgery site). A radiation boost was required after whole-breast irradiation but was allowed only with permission after chest-wall irradiation. A bolus to increase the dose to the skin was not permitted.

All the patients underwent computed tomography (CT) simulation, which was followed by the delineation of targets for the breast or chest wall, regional nodes, and organs at risk (namely, the heart, lungs, and thyroid) (Table S1), and were treated with the use of three-dimensional conformal or intensity-modulated radiation therapy. We required physician approval of a composite radiation treatment plan with dose–volume analyses to ensure that protocol-specified dose constraints for target areas and organs at risk were not exceeded. A two-step radiation quality-assurance process involved centralized benchmarking at each trial site and individual review of each case (Table S2).

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

Characteristic	Regional Nodal Irradiation (N=820)	No Regional Nodal Irradiation (N=821)
Age		
Median — yr	52	52
Distribution — no. (%)		
≤39 yr	120 (14.6)	119 (14.5)
40–49 yr	215 (26.2)	207 (25.2)
50–59 yr	274 (33.4)	266 (32.4)
≥60 yr	211 (25.7)	229 (27.9)
Race — no. (%)†		
Asian	53 (6.5)	64 (7.8)
Black	147 (17.9)	139 (16.9)
White	568 (69.3)	569 (69.3)
Other or unknown	52 (6.3)	49 (6.0)
Ethnic group — no. (%)†		
Hispanic or Latino	118 (14.4)	114 (13.9)
Not Hispanic or Latino	675 (82.3)	682 (83.1)
Unknown	27 (3.3)	25 (3.0)
Type of surgery — no. (%)		
Lumpectomy	473 (57.7)	474 (57.7)
Mastectomy	347 (42.3)	347 (42.3)
Clinical tumor stage — no. (%)‡		
T1	170 (20.7)	171 (20.8)
T2	499 (60.9)	484 (59.0)
T3	151 (18.4)	166 (20.2)
HR status — no. (%)		
Negative	386 (47.1)	382 (46.5)
Positive	434 (52.9)	439 (53.5)
HER2 status — no. (%)		
Negative	355 (43.3)	356 (43.4)
Positive	465 (56.7)	465 (56.6)
Tumor subtype — no. (%)		
Triple negative	191 (23.3)	175 (21.3)
HR positive and HER2 negative	164 (20.0)	181 (22.0)
HR negative and HER2 positive	195 (23.8)	207 (25.2)
HR positive and HER2 positive	270 (32.9)	258 (31.4)
Adjuvant chemotherapy — no. (%)		
No	813 (99.1)	817 (99.5)
Yes	7 (0.9)	4 (0.5)
Pathological complete response in breast — no. (%)		
Absent	176 (21.5)	182 (22.2)
Present	644 (78.5)	639 (77.8)

Table 1. (Continued.)

Characteristic	Regional Nodal Irradiation (N=820)	No Regional Nodal Irradiation (N=821)
Axillary staging — no. (%)		
Sentinel-lymph-node biopsy§	461 (56.2)	448 (54.6)
Axillary-lymph-node dissection¶	359 (43.8)	373 (45.4)

* Data are shown for all patients enrolled in the trial. Percentages may not total 100 because of rounding. HER2 denotes human epidermal growth factor receptor 2, and HR hormone receptor.
† Race and ethnic group were reported by the patients and were recorded in the National Cancer Institute Cancer Trials Support Unit Oncology Patient Enrollment Network system by the coordinator of the enrolling site at the time of enrollment.
‡ Tumors were staged according to size as T1 (≤2 cm), T2 (>2 cm but ≤5 cm), or T3 (>5 cm).
§ Numbers include only those patients who had sentinel-lymph-node biopsy alone, without axillary-lymph-node dissection.
¶ Numbers include patients who had axillary-lymph-node dissection with or without previous sentinel-lymph-node biopsy.

STATISTICAL ANALYSIS

The primary analysis was based on the intention-to-treat principle. Differences between trial groups were assessed with the use of a stratified log-rank test, which controlled for stratification factors. A pooling strategy for stratification factors was implemented so that at least five events per trial group were included in any individual stratum. The stratified Cox proportional-hazards model was used to estimate the hazard ratios and confidence intervals. The assumption of proportionality of hazards between trial groups was tested for all time-to-event end points.[21] A two-sided P value of less than 0.05 was considered to indicate statistical significance. No adjustment for multiplicity was planned for the analyses of the secondary end points and subgroup analyses.

The trial was designed to have 80% power to test the hypothesis that treatment with regional nodal irradiation would reduce the annual hazard rate of primary end-point events by 35%. We anticipated the enrollment of 1636 patients during a 5-year period (approximately 28 patients per month), with 2 additional years of follow-up. Three formal interim analyses of the primary end point for efficacy and futility — after 43, 86, and 129 events were observed — were scheduled to take place before a definitive analysis. We planned to conduct the final analysis after 172 events had been observed. The protocol also specified that if the total number of events was less than the number expected for the final analysis by 10 years after the activation of the trial (August 2023), consideration would be given to reporting the results without waiting for additional events.

RESULTS

TRIAL DATES AND TIMING OF ANALYSES

The trial was activated in August 2013 and closed to enrollment in December 2020. The first two interim analyses were conducted on the basis of data-cutoff dates of October 31, 2019, and October 31, 2021. As of August 2023, the number of events expected for the third interim analysis had not occurred. We therefore conducted the final analysis on the basis of the time elapsed, as prespecified in the protocol. Analyses reported here include all data accumulated as of September 14, 2023. We enrolled a total of 1641 patients (100.3% of the prespecified target of 1636 patients) (Fig. S2); 2 patients were not at risk for the primary end point and were excluded from the final analysis. As of the final data-cutoff date, follow-up information was available for 1602 patients (800 in the irradiation group and 802 in the no-irradiation group). The median follow-up was 59.5 months (interquartile range, 40.7 to 74.1). Among 1602 patients for whom follow-up data were available, 46 (28 in the irradiation group and 18 in the no-irradiation group) did not have a clinical assessment. Therefore, the primary-event analysis included 1556 patients with clinical follow-up (772 in the irradiation group and 784 in the no-irradiation group).

PATIENT AND TREATMENT CHARACTERISTICS

The characteristics of the patients at baseline were well balanced between trial groups (Table 1). The median age was 52 years (interquartile range, 44 to 60), with 40.3% of patients under 50 years of

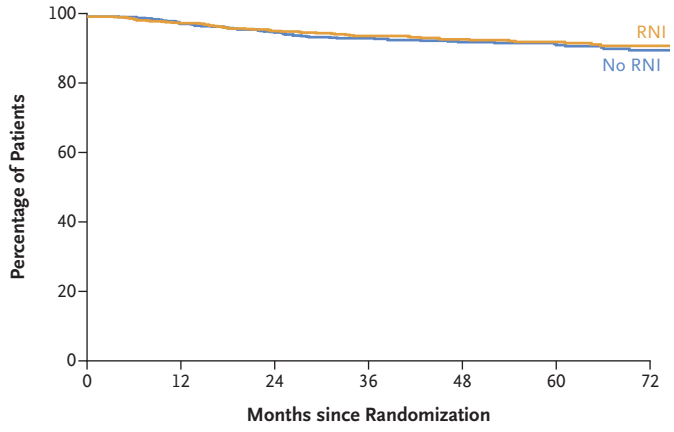
Table 2. Primary and Secondary End-Point Events.*

Event	Regional Nodal Irradiation (N=772)	No Regional Nodal Irradiation (N=784)
	number (percent)	
Primary end point		
Invasive breast cancer recurrence or death from breast cancer	50 (6.5)	59 (7.5)
Distant recurrence†	41 (5.3)	36 (4.6)
Synchronous locoregional recurrence and distant recurrence‡	2 (0.3)	9 (1.1)
Isolated locoregional recurrence	4 (0.5)	11 (1.4)
Death from breast cancer	3 (0.4)	3 (0.4)
Secondary end points		
Locoregional recurrence	6 (0.8)	11 (1.4)
Local recurrence§	6 (0.8)	2 (0.3)
Regional recurrence¶	0	8 (1.0)
Locoregional recurrence‖	0	1 (0.1)
Distant recurrence or death from breast cancer	46 (6.0)	48 (6.1)
Distant recurrence	43 (5.6)	45 (5.7)
Death from breast cancer	3 (0.4)	3 (0.4)
Disease recurrence or death	85 (11.0)	83 (10.6)
Distant recurrence	43 (5.6)	45 (5.7)
Locoregional recurrence	6 (0.8)	11 (1.4)
Second primary cancer	19 (2.5)	16 (2.0)
Death from any cause	17 (2.2)	11 (1.4)

* Data are shown for all patients included in the efficacy analysis (all those who underwent randomization and had clinical follow-up data available).
† Numbers include those with distant recurrence with no evidence of locoregional recurrence.
‡ Numbers include those with locoregional recurrence and evidence of distant recurrence within 60 days.
§ Local recurrence included 2 cases of ductal carcinoma in situ (both in patients who received regional nodal irradiation), 4 cases of invasive recurrence in the breast (3 in patients who received regional nodal irradiation and 1 in a patient who did not), and 2 cases of invasive recurrence in the chest wall (1 in each group).
¶ Regional recurrence was defined as recurrence in axillary, infraclavicular, supraclavicular, or internal mammary nodal sites.
‖ Locoregional recurrence in one case was reported in the chest wall, axilla, and internal mammary lymph nodes.

age; 17.4% were Black, and 14.1% were Hispanic or Latino. Information regarding the representativeness of the trial population is shown in Table S3.

The majority of patients (59.9%) had a clinical T2 tumor (>2 cm but ≤5 cm); 53.2% had hormone receptor–positive cancer, and 56.7% had HER2-positive cancer. A total of 79.0% of patients had either triple-negative or HER2-positive cancer. A pathological complete response to treatment (in the breast and nodes) occurred in 78.2% of patients; 57.7% underwent a lumpectomy, 42.3% underwent a mastectomy, and 55.4% underwent sentinel-lymph-node biopsy. Few patients (0.7%) received adjuvant chemotherapy. The proportion of patients who received anti-HER2 therapy was similar in the two trial groups (Table S4). A quality-assurance review of radiation treatment was completed for 80.7% of patients. When the quality-assurance review was performed, the per-protocol or acceptable-variation standards for delineating target volume and organs at risk were met in 94.4% of cases (92.0% with regional nodal irradiation vs. 98.4% without regional nodal irradiation), and the per-protocol or acceptable-variation standards for radiation-dose deliv-



	No. of Events	5-Year Estimate
		percent
RNI	50	92.7
No RNI	59	91.8

Hazard ratio for invasive breast cancer recurrence or death from breast cancer 0.88 (95% CI, 0.60–1.28)
P=0.51

No. at Risk							
RNI	772	717	644	544	427	294	172
No RNI	784	744	663	557	437	309	192

Figure 1. Effect of Regional Nodal Irradiation on the Invasive Breast Cancer Recurrence–free Interval.
Shown is the 5-year estimate of survival free from invasive breast cancer recurrence or death from breast cancer. RNI denotes regional nodal irradiation.

ery according to dose–volume analysis were met in 95.8% of cases (94.5% with regional nodal irradiation vs. 98.0% without regional nodal irradiation).

EFFICACY ANALYSES

A total of 109 primary end-point events (50 in the irradiation group and 59 in the no-irradiation group) occurred (Table 2). Regional nodal irradiation did not significantly increase the interval to invasive breast cancer recurrence or death from breast cancer (hazard ratio, 0.88; 95% confidence interval [CI], 0.60 to 1.28; P=0.51) (Fig. 1). Point estimates of survival free from primary end-point events at 5 years were 92.7% in the irradiation group and 91.8% in the no-irradiation group.

Similarly, no reduction in the locoregional recurrence–free interval with regional nodal irradiation was observed (hazard ratio, 0.57; 95% CI, 0.21 to 1.54) (Fig. 2A), with 17 events having occurred by the data-cutoff date (Table 2). Eight (47.1%) of the recurrences were in the axilla or infraclavicular area. Point estimates of locoregional recurrence–free survival at 5 years were 98.9% in the irradiation group and 98.4% in the no-irradiation group.

No difference in the distant recurrence–free interval was noted between trial groups (hazard ratio, 1.00; 95% CI, 0.67 to 1.51); the point estimate of distant recurrence–free survival at 5 years was 93.4% with or without regional nodal irradiation (Fig. 2B). No apparent difference in disease-free survival was observed (hazard ratio, 1.06; 95% CI, 0.79 to 1.44); point estimates of disease-free survival at 5 years were 88.3% in the irradiation group and 88.5% in the no-irradiation group (Fig. 2C).

Among 1802 patients included in the analysis of overall survival, 94 patients died: 49 in the irradiation group and 45 in the no-irradiation group (hazard ratio, 1.12; 95% CI, 0.75 to 1.68) (Fig. 2D). Point estimates of 5-year overall survival were 93.6% in the irradiation group and 94.0% in the no-irradiation group.

The effect of regional nodal irradiation in subgroups defined according to stratification variables (the type of breast surgery [lumpectomy vs. mastectomy], hormone receptor status, HER2 status, the presence or absence of a pathological complete response in the breast, and the receipt or lack of adjuvant chemotherapy) was consistent with the effect among the trial population overall (Fig. 3A). In an exploratory analysis, the effect of regional nodal irradiation was examined according to age, race, breast cancer subtype, and the type of axillary surgery (Fig. 3B); the results indicated potential differences in the effect of regional nodal irradiation among patients with cancer that was triple negative (hazard ratio for invasive breast cancer recurrence or death from

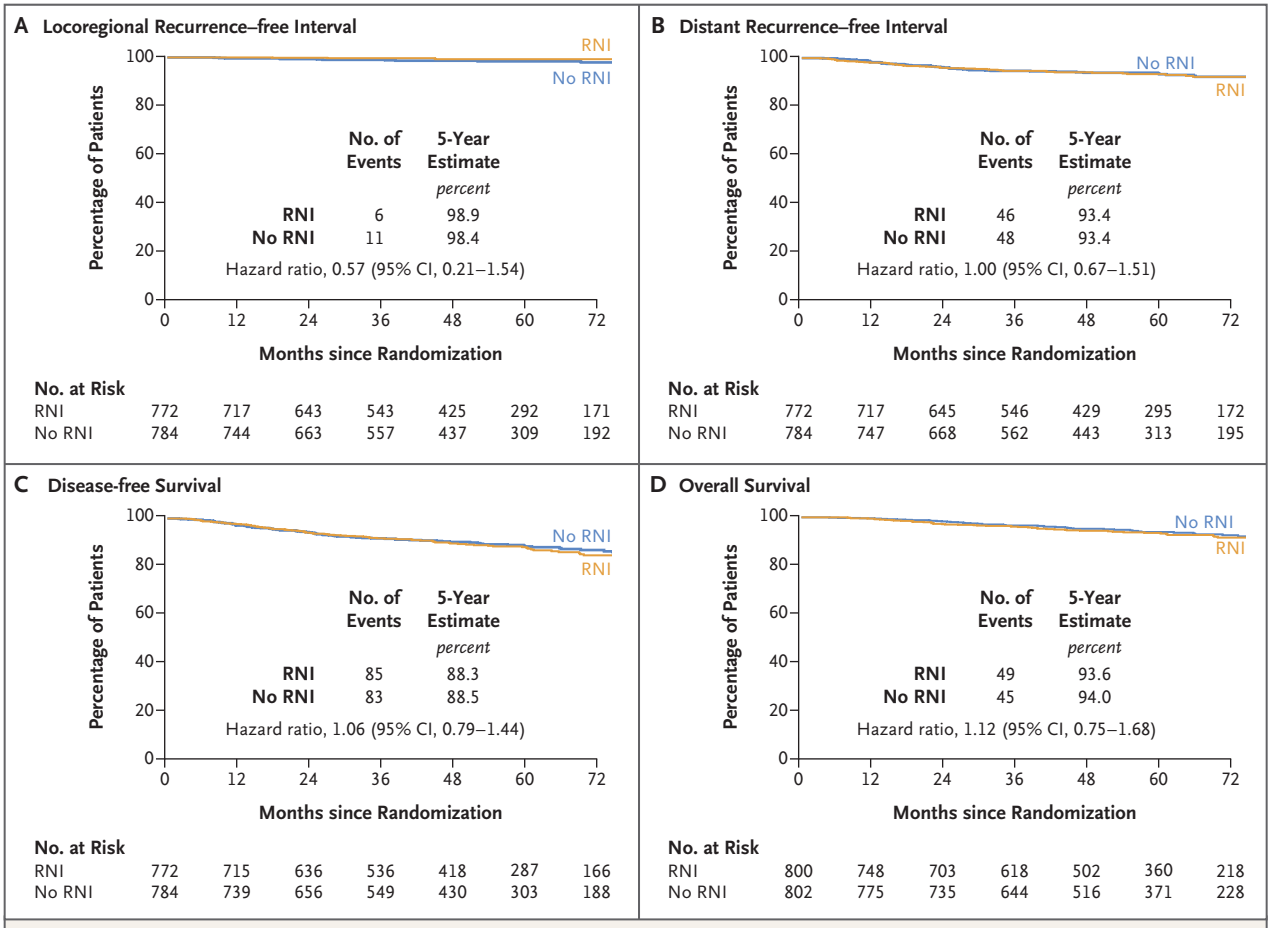


Figure 2. Effects of Regional Nodal Irradiation on Secondary End Points.

Shown are effects of regional nodal irradiation on the locoregional recurrence–free interval (Panel A), the distant recurrence–free interval (Panel B), disease-free survival (Panel C), and overall survival (Panel D).

breast cancer, 2.30; 95% CI, 1.00 to 5.25) or hormone receptor positive and HER2 negative (hazard ratio, 0.41; 95% CI, 0.17 to 0.99).

SAFETY

Safety information was available for 1559 patients (759 in the irradiation group and 800 in the no-irradiation group). There were no deaths related to protocol-specified therapy and no unexpected adverse events. Grade 4 adverse events occurred in 0.5% of patients in the irradiation group and 0.1% of those in the no-irradiation group; grade 3 adverse events occurred in 10.0% and 6.5%, respectively. The most common grade 3 adverse event was radiation dermatitis, which occurred in 5.7% of patients in the irradiation group and 3.3% of those in the no-irradiation group (Table S5).

DISCUSSION

Whether regional nodal irradiation should be used in patients with breast cancer who present with axillary-lymph-node involvement but reach ypN0 status after neoadjuvant chemotherapy has been uncertain. The results of our trial indicate that patients with positive axillary lymph nodes who reach stage ypN0 after neoadjuvant chemotherapy have low rates of disease recurrence and do not receive a statistically significant benefit from regional nodal irradiation at 5 years. These results support a shift in treatment strategy in that regional nodal irradiation can be tailored in patients treated with neoadjuvant chemotherapy on the basis of their pathological nodal response.

Our trial has multiple important aspects. Although numerous previous clinical trials have

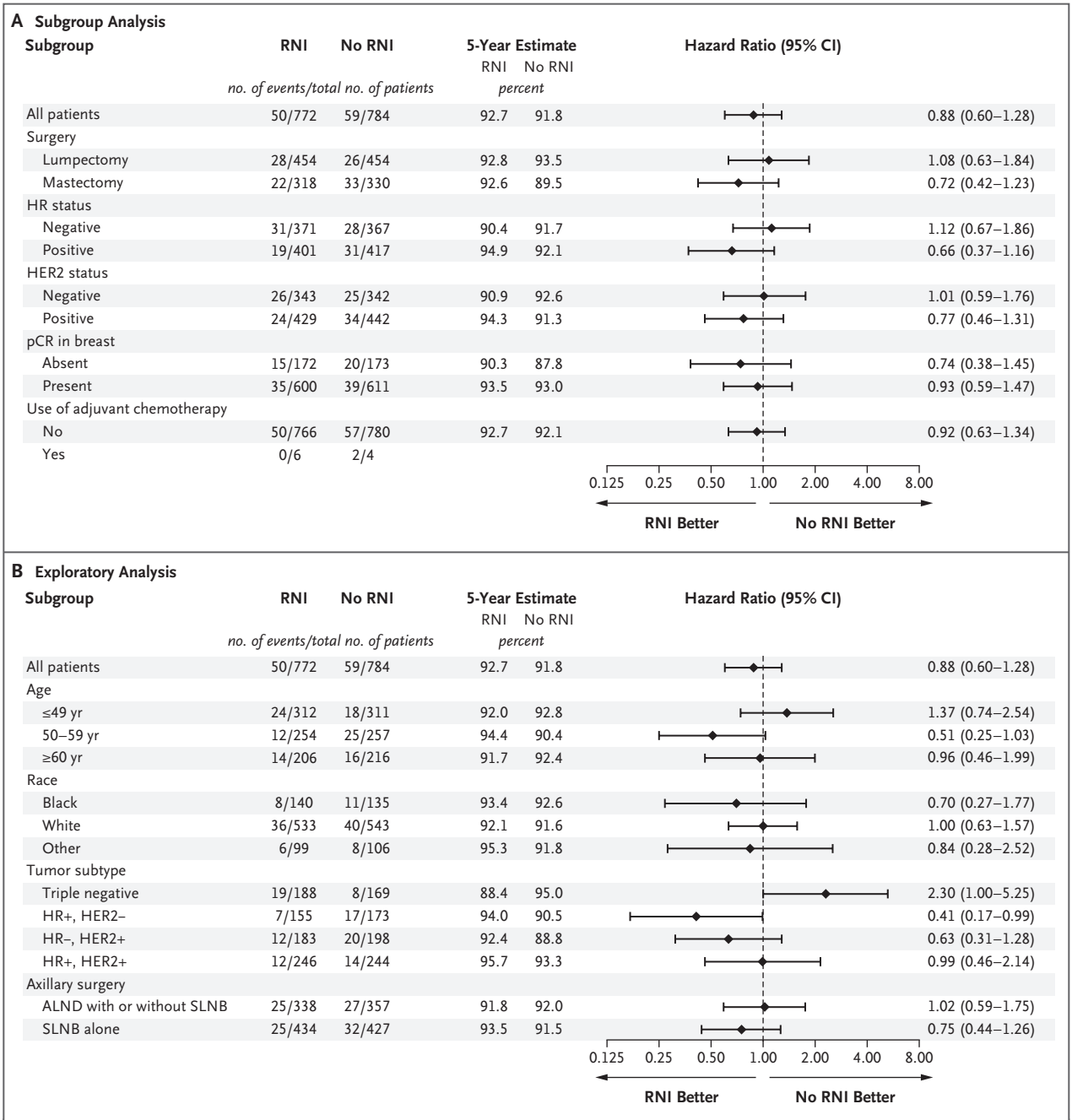


Figure 3. Subgroup Analysis of the Invasive Breast Cancer Recurrence–free Interval.

Shown are results from the analysis of the invasive breast cancer recurrence–free interval in prespecified subgroups (Panel A) and results from an exploratory analysis according to additional variables (Panel B). ALND denotes axillary-lymph-node dissection, HER2 human epidermal growth factor receptor 2, HR hormone receptor, pCR pathological complete response, and SLNB sentinel-lymph-node biopsy.

shown benefit from regional nodal irradiation in patients with positive axillary lymph nodes who undergo surgery first,[1-7] this trial evaluated regional nodal irradiation in patients who presented with node-positive breast cancer but whose axillary lymph nodes were pathologically negative after neoadjuvant chemotherapy. Our trial results show that a pathological complete response in

axillary lymph nodes was predictive of a lack of benefit from regional nodal irradiation.

In previous trials of regional nodal irradiation in patients treated with upfront surgery, the majority of patients had hormone receptor–positive, HER2-negative cancer, which reflects the typical distribution of subtypes in newly diagnosed disease. In contrast, the majority of patients (79.0%) in our trial had breast cancer that was HER2 positive (56.7%) or triple negative (22.3%) owing to the higher likelihood of a pathological response in patients with these subtypes.

This multicenter trial required volume-based CT planning for regional nodal irradiation, with the use of three-dimensional conformal radiation therapy or intensity-modulated radiation therapy, and the protocol specified goals based on dose–volume histograms for target coverage and avoidance of organs at risk. A centralized program of quality assurance ensured accurate delivery of radiation therapy, so variation in treatment quality or delivery cannot explain the lack of benefit from regional nodal irradiation. The incidence of grade 3 dermatitis, an adverse event commonly associated with radiation therapy, was 5.7% among patients who received regional nodal irradiation, a finding that reflects the safety that is achievable with the use of these methods for the delivery of regional nodal irradiation when indicated. Radiation therapy was delivered with conventional fractionation (a total dose of 50 Gy was given in 25 fractions); however, our findings are equally applicable to moderately hypofractionated radiation therapy.[22]

The results of the exploratory analysis of subgroups stratified according to breast cancer subtypes should be viewed with caution because the number of patients in each subgroup was approximately a quarter of the overall patient population, which resulted in wide confidence intervals around the estimates. Longer follow-up may influence these results, especially for some biologic subtypes. For patients with triple-negative breast cancer, it is hard to explain results indicating greater risk of recurrence among patients who received regional nodal irradiation. Because most recurrences of triple-negative breast cancer occur within the first 5 years, it is unlikely that longer follow-up would substantially change the event rates such that the results would show a benefit from regional nodal irradiation. On the other hand, evidence of a benefit from regional nodal irradiation was observed among patients with hormone-sensitive, HER2-negative disease. Patients with this disease subtype generally have a longer time to recurrence, typically more than 5 years,[23] so additional follow-up is needed for more-definitive assessment of the benefit of regional nodal irradiation. In cases involving upfront surgery, previous data have shown a greater benefit from postmastectomy radiation therapy and regional nodal irradiation in patients with luminal cancers than in those with other subtypes.[24,25]

Our trial has some limitations. The observed 5-year cumulative incidence of invasive breast cancer recurrence or death from breast cancer (8.2%) was approximately 40% lower than projected on the basis of the combined analysis of the NSABP B-18 and B-27 trials,[19] and the estimate based on that analysis had been adjusted downward by 15% to account for the fact that estimates of recurrence rates based on data from older clinical trials tend to be higher than actual recurrence rates in the current breast cancer population. This pattern has been seen across other breast cancer trials.[26] As a result of the low incidence of events, we conducted a time-driven analysis as specified in the protocol, but the number of primary end-point events included was considerably less than the number that would have been included in an event-driven analysis (109 vs. 172). Patient follow-up continues, and we expect to report updated analyses when the number of events specified for the event-driven analysis is reached. Patients with negative axillary nodes after surgery were eligible for the trial even if they had isolated tumor cells remaining (ypN0i+ status). However, we did not collect this information upon trial enrollment, so we do not know the proportion of patients with ypN0i+ status or the specific outcomes in these patients. Previous studies have shown that the prevalence of ypN0i+ status is low (approximately 1.5 to 6.0%),[27-29] and thus the effect of including such patients in our trial would probably be negligible.

One of the challenges in deescalating locoregional therapy (radiation therapy or surgery) is the potential for escalation of adjuvant systemic therapy. This effect was not observed in our trial, since only 0.7% of patients received adjuvant chemotherapy (0.9% of those in the irradiation

group and 0.5% of those in the no-irradiation group).

Outcomes among patients with breast cancer will probably continue to improve owing to several important developments in neoadjuvant systemic therapy, including the use of dual anti-HER2 therapy for HER2-positive breast cancer, as well as carboplatin and checkpoint inhibitors for triple-negative breast cancer. These treatments will probably continue to increase the number of patients whose axillary lymph nodes convert from positive to negative, making the findings from this trial applicable to more patients in the future. In addition, new developments in postneoadjuvant systemic therapy — such as antibody–drug conjugates for HER2-positive breast cancer; capecitabine for triple-negative breast cancer; CDK4/6 inhibitors for hormone receptor–positive, HER2-negative breast cancer; and poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitors for patients with deleterious mutations in BRCA genes — will probably continue to improve outcomes in patients treated with neoadjuvant chemotherapy, which will further minimize the potential benefit from locoregional treatments. Most of these developments were not part of standard clinical practice during the enrollment period in our trial.

Our trial showed that in patients with biopsy-proven axillary-lymph-node involvement whose positive axillary lymph nodes reached ypN0 status with neoadjuvant chemotherapy, the use of regional nodal irradiation did not improve oncologic outcomes at 5 years. The use of pathological response to neoadjuvant chemotherapy to guide the use of regional nodal irradiation expands the clinical utility of the neoadjuvant approach. Patient follow-up continues for evaluation of longer-term outcomes.

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