HHS Public Access

Author manuscript

N Engl J Med. Author manuscript; available in PMC 2025 July 17.

Published in final edited form as:

N Engl J Med. 2025 June 05; 392(21): 2113–2124. doi:10.1056/NEJMoa2414859.

Omitting Regional Nodal Irradiation in Responders to Neoadjuvant Chemotherapy

Eleftherios P. Mamounas, M.D.[1], **Hanna Bandos, Ph.D**[2], **Julia R. White, M.D.**[3], **Thomas B. Julian, M.D.**[4], **Atif J. Khan, M.D.**[5], **Simona F. Shaitelman, M.D.**[6], **Mylin A. Torres, M.D.**[7], **Frank A. Vicini, M.D.**[8], **Patricia A. Ganz, M.D.**[9], **Susan A. Mc Closkey, M.D.**[10], **Peter C. Lucas, M.D., Ph.D.**[11], **Nilendu Gupta, Ph.D.**[12], **X. Allen Li, Ph.D.**[13], **Beryl McCormick, M.D.**[5], **Benjamin Smith, M.D.**[6], **Rahul D. Tendulkar, M.D.**[14], **Vivek S. Kavadi, M.D.**[15], **Koji Matsumoto, M.D.**[16], **Samantha Andrews Seaward, M.D.**[17], **William J. Irvin Jr., M.D.**[18], **Jolinta Y. Lin, M.D.**[7], **Robert W. Mutter, M.D.**[19], **Thierry M. Muanza, B.A., M.Sc.**[20], **Jannifer Stromberg, M.D.**[21], **Reshma Jagsi, M.D. Ph.D.**[7], **Anna C. Weiss, M.D.**[22], **Walter J. Curran Jr, M.D.**[23], **Norman Wolmark, M.D.**[24]

[1]AdventHealth Cancer Institute, Orlando, FL

[2]NRG Oncology Statistical and Data Management Center, and the University of Pittsburgh School of Public Health, Department of Biostatistics and Health Data Science, Pittsburgh, PA

[3]University of Kansas Medical Center Comprehensive Cancer Center, Kansas City, KS

[4]Allegheny Health Network Cancer Institute, Pittsburgh, PA

[5]Memorial Sloan-Kettering Cancer Center, New York, NY

[6]University of Texas MD Anderson Cancer Center, Houston, TX

[7]Emory University School of Medicine, Winship Cancer Institute, Atlanta, GA

[8]Michigan Healthcare Professionals, Pontiac, MI

[9]UCLA Jonsson Comprehensive Cancer Center at UCLA, and UCLA Fielding School of Public Health, Los Angeles, CA

[10]University of California, Los Angeles, CA

[11]NSABP Pathology Lab; and UPMC Hillman Cancer Center, and University of Pittsburgh School of Medicine, Pittsburgh, PA (Conducted); and the Department of Laboratory Medicine and Pathology at Mayo Clinic (Current), Rochester, MN

[12]The Ohio State University, James Cancer Hospital, Columbus, OH

[13]Medical College of Wisconsin, Milwaukee, WI

Correspondence address: Eleftherios P. Mamounas, M.D., AdventHealth Cancer Institute, 2501 N. Orange Ave, Orlando, FL 32804. Dr. Mamounas and Dr. White are co-first authors.

Trial Registration: NCT01872975

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

[14]CWRU Case Comprehensive Cancer Center, and Taussig Cancer Center, Cleveland Clinic, Cleveland, OH

[15]Texas Oncology, US Oncology Network, The Woodlands, TX

[16]Hyogo Cancer Center, Akashi, Hyogo, Japan

[17]Kaiser Permanente NCI Community Oncology Research Program, Vallejo, CA

[18]Bon Secours Cancer Institute, and Southeast Clinical Oncology Research Consortium NCORP, Midlothian, VA

[19]Mayo Clinic, Radiation Oncology, Rochester, MN

[20]McGill University, Lady Davis Institute for Medical Research, Sir Mortimer B. Davis Jewish General Hospital, Montreal, QC, Canada

[21]Corewell Health, Oakland University Beaumont School of Medicine, Sterling Heights, MI

[22]University of Rochester School of Medicine and Dentistry, Rochester, New York, USA

[23]Piedmont Oncology Institute, Atlanta, GA

[24]NSABP Foundation, Inc.; UPMC Hillman Cancer Center; University of Pittsburgh School of Medicine, Pittsburgh, PA

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 movable, ipsilateral level I and II 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 1,641 patients were enrolled in the trial; 1,556 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.

Conclusion: 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 [RTOG] 1304 ClinicalTrials.gov number, NCT01872975.)

INTRODUCTION

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 demonstrated equivalent efficacy between neoadjuvant chemotherapy and adjuvant chemotherapy.[8–10] Potential clinical advantages of neoadjuvant chemotherapy include reduction in the extent of surgery and improvement in prognosis stratification.[8, 9, 11–13] Achieving pathologic complete response (pCR) in the breast and axilla has been consistently shown to predict for improved outcomes and can be utilized 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 whose nodes convert to ypN0 after neoadjuvant chemotherapy have better outcomes compared to those whose nodes remain pathologically node-positive, creating uncertainty regarding the need for regional nodal irradiation.[17,18,19] 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 3,088 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, pCR in the breast with ypN0 was a significant predictor of lower risk for locoregional recurrence irrespective of breast surgery type. Moreover, patients with

clinically positive axillary lymph nodes before neoadjuvant chemotherapy who became ypN0 at surgery had low rates of chest wall and regional nodal recurrence compared to those who remained ypN+.

We conducted the NSABP B-51/RTOG 1304 trial to evaluate whether regional nodal irradiation would significantly improve 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. The protocol was approved by either the Institutional Review Board at each participating institution or by the NCI Central Institutional Review Board. Written informed consent was required for enrollment. The first three authors had full access to the data, analyzed the data, and they vouch for the accuracy of the data and analyses and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org). The first three authors wrote the first draft of the manuscript and made the final decision to submit the manuscript for publication. The funders had no role in the design of the trial; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the 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 movable, ipsilateral level I and II 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 ≥8 weeks of standard neoadjuvant chemotherapy with an anthracycline and/or taxane-based regimen. Patients with HER2-positive tumors must also have received neoadjuvant anti-HER2 therapy (either with all or part of neoadjuvant chemotherapy), unless medically contraindicated. After neoadjuvant chemotherapy, patients had either lumpectomy or mastectomy plus pathologic axillary lymph node assessment with either sentinel lymph node biopsy (SLNB) with ≥2 SLNs removed, or axillary lymph node dissection (ALND) +/− prior SLNB. 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, 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 and 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 omit regional nodal irradiation (with no irradiation after mastectomy

or whole-breast irradiation only after lumpectomy) (Figure S1 in the Supplementary Appendix).

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 (referred to as the 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 aims (reported here) were to compare the two study arms for overall survival (defined as time from randomization to death from any cause); loco-regional recurrence-free interval (LRRFI) (defined as time from randomization to breast cancer recurrence within the breast [invasive or DCIS] 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); distant recurrence-free interval (DRFI) (defined as time from randomization to development of distant recurrence or death from breast cancer), and disease-free survival (DFS-DCIS)[20]. Also, toxicity within each study arm was evaluated. Additional secondary endpoints, including Quality-of-life substudy, will be reported separately.

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 twostep radiation quality-assurance process involved centralized benchmarking at each trial site and individual review of each case (Table S2).

Statistical Analysis: The primary analysis was based on the intent-to-treat principle. Differences between treatment arms were assessed by stratified log rank test, controlling

for stratification factors. Pooling strategy for stratification factors was implemented so the number of events per treatment group within any individual stratum was ≥5. The stratified Cox proportional hazards model was used to estimate the hazard ratios and confidence intervals. Assumption of proportionality of hazards between treatment groups was tested for all time-to-event endpoints [21]. Statistical tests were two-sided and were carried out at the 0.05 level. No adjustment for multiplicity was planned for the analyses of the secondary endpoints 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 invasive breast cancer recurrence-free interval events by 35%. Accrual of 1,636 patients during a five-year period (~28 patients/month) with two additional years of follow-up was planned. Three formal interim analyses of the primary endpoint for efficacy and futility were scheduled before definitive analysis - - after 43, 86, and 129 events were observed, respectively. Final analysis was planned for when 172 events were observed. The protocol also specified that if at 10-years post-trial activation the total number of events was less than the number required for final analysis, consideration would be given to report the results.

The first two interim analyses were conducted based on 10/31/2019 and 10/31/2021 data cutoff. As of the 10-year anniversary of the trial activation, the number of events required for the third interim analysis had not been achieved. This triggered the final, time-driven analysis, as prespecified in the protocol. Analyses reported here include all data as of 09/14/2023.

RESULTS

Trial Dates and Timing of Analyses

The trial was activated in 08/2013, and closed to accrual in 12/2020, with 1,641 patients (100.3%) (Figure S2). Two patients were not at risk for the primary endpoint and were excluded from analysis. As of data cutoff, follow-up information was available for 1,602 patients (No regional nodal irradiation: 802, regional nodal irradiation: 800). Median follow-up was 59.5 months (IQR 40.7–74.1). Of 1,602 patients with follow-up data, 46 (No NRI: 18, regional nodal irradiation: 28) did not have clinical assessment. Primary event analysis is based on 1,556 patients with clinical follow-up.

Patient and Treatment Characteristics

Patient entry characteristics were well balanced between treatment arms (Table 1). Median age was 52 years (IQR 44–60) with 40% being <50 years; 17% were Black/African American, and 14% were of Hispanic/Latino ethnicity. Information regarding the representativeness of the trial population is shown in Table S3. In the trial, T2 clinical tumor size was most common (60%); estrogen receptor (ER) was positive in 53%; and HER-2 receptor was positive in 57%; triple-negative plus HER-2 positive subtypes comprised 79% of the study population; and 78% of patients achieved breast pCR. Surgery was lumpectomy in 58%, mastectomy in 42% and 55% underwent SLNB; adjuvant chemotherapy use was rare (<1%). Anti-HER2 therapy was well-balanced between the treatment groups (Table S4).

Radiation QA review was completed for 80.7% of the patients. When the quality-assurance review was performed, the per-protocol or variation acceptable standards were met in 94.4% of cases for delineating target volume and organs at risk (92.0% with regional nodal irradiation vs. 98.4% without regional nodal irradiation); and the per protocol or acceptable-variation standards for radiation dose delivery by 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 improve the interval until 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) (Figure 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 locoregional recurrence-free interval with regional nodal irradiation was observed (hazard ratio, 0.57; 95% CI, 0.21 to 1.54) (Figure 2A), with 17 events having occurred by the data-cutoff date (Table 2). Eight (47%) of 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 between treatment arms was noted in DRFI (HR=1.00, 95%CI 0.67–1.51; five-year point estimates of No regional nodal irradiation: 93.4% and regional nodal irradiation: 93.4%; Figure 2B) or DFS (HR=1.06, 95%CI 0.79–1.44; five-year DFS point estimates of No regional nodal irradiation: 88.5% and regional nodal irradiation: 88.3%; Figure 2C).

A total of 94 patients died of 1,802 evaluated for the overall survival endpoint (Figure S2): 49 in the irradiation group and 45 in the no irradiation group (hazard ratio, 1.12; 95% CI, 0.75 to 1.68) (Figure 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 (Figure 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 (Figure 3B); the results indicated potential differences in the effect of regional nodal irradiation among patients with cancer that was triple negative (hazard ratio for primary end point event, 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

Toxicity information had been received for 1,559 patients (No regional nodal irradiation:800; regional nodal irradiation:759). There were no study-related deaths and no unexpected toxicities. Grade 4 toxicity was rare (No regional nodal irradiation: 0.1%, vs. regional nodal irradiation: 0.5%); Grade 3 toxicity was uncommon (No regional nodal irradiation: 6.5%, regional nodal irradiation:10%). Most common Grade 3 toxicity was radiation dermatitis (No regional nodal irradiation: 3.3%, regional nodal irradiation: 5.7%) (Table S5).

DISCUSSION

Safety information was available for 1,559 patients (759 in the irradiation group and 800 in the no-irradiation group). There were no trial-related deaths 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).

Our trial has multiple important aspects. Although numerous prior clinical trials have demonstrated 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 present with node-positive breast cancer but whose axillary lymph nodes convert to pathologically negative after neoadjuvant chemotherapy. Our study results demonstrate that pCR in axillary lymph nodes is predictive of lack of benefit from regional nodal irradiation.

In previous regional nodal irradiation trials for patients treated with upfront surgery, hormone receptor-positive, HER2-negative subtype predominated, reflecting the typical distribution of newly diagnosed disease. In contrast, given the higher likelihood of pathologic response in HER2-positive and triple-negative breast cancer patients, these subtypes comprise the majority (79%) of our trial’s patient population (HER2+ 57%; TNBC 22%).

This multicenter trial is the first to require 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, a common adverse event, was 5.7% among patients who received regional nodal irradiation, reflecting the safety 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 subset analysis according to breast cancer subgroups should be viewed with caution because the number of patients in each subgroup represents roughly a quarter of the overall patient population, resulting 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, likely supporting a spurious finding. Because most recurrences from TNBC occur in the first five years, it is unlikely that longer follow-up will substantially change the event rates to support radiation benefit. On the other hand, a trend for regional nodal irradiation benefit was noted for patients with hormone-sensitive/HER2-negative disease (HR=0.41, 95%CI 0.17–0.99). These patients generally have a longer time to recurrence, typically greater than five years,[23] so additional follow-up is needed for more definitive assessment of regional nodal irradiation benefit. 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 rate of the primary end point (8.2%) was around one third lower than the rate projected on the basis of the combined analysis of the NSABP B-18 and B-27 trials,[19] which 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 is a pattern that has been seen across other breast cancer trials.[26] As a result of the low event rate, 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{q43} 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 de-escalating loco-regional therapy (radiotherapy or surgery) is the potential for escalation of adjuvant systemic therapy. This was not observed in our study, as only 1% of the patients received adjuvant chemotherapy (no regional nodal irradiation: <1%; regional nodal irradiation:1%).

It is likely that outcomes of breast cancer patients will continue to improve based on several additional important developments in neoadjuvant systemic therapy, such as use of dual anti-HER2 therapy for HER-2 positive breast cancer, as well as carboplatin and checkpoint inhibitors for TNBC. These treatments will likely 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 post-neoadjuvant systemic therapy such as antibody-drug conjugates for HER-2 positive breast cancer, capecitabine for TNBC, CDK4/6 inhibitors for ER/PR-

positive/HER2-negative breast cancer, and PARP inhibitors for patients with deleterious mutations in BRCA genes, will likely continue to improve outcomes of patients treated with neoadjuvant chemotherapy, further minimizing the potential benefit from loco-regional treatments. Most of these developments were not part of standard clinical practice during patient accrual to our study.

In conclusion, our study has demonstrated that for patients who present with biopsy-proven axillary lymph node involvement whose positive axillary lymph nodes convert to ypN0 with neoadjuvant chemotherapy, use of regional nodal irradiation does not improve oncologic outcomes at five years. Using pathologic response to neoadjuvant chemotherapy to optimize use of regional nodal irradiation expands the clinical utility of the neoadjuvant approach. Patient follow-up continues for evaluation of longer-term outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the patients and their families as well as the staff members of NSABP/NRG Oncology/SDMC. We also thank Wendy L. Rea, BA, Editorial Associate, for assistance with manuscript editing and preparation for submission and Ana A. Stephens, BA, Publications and Graphics Specialist, for graphical and publication assistance, both of whom are employees of NSABP Foundation. They were not compensated beyond their normal salaries for this work.

Supported by

Supported by grants from the National Institutes of Health, U10CA180868, U10CA180822, UG1CA189867, and U24CA196067

The funding source played no role in the design of the study, collection, analysis, or interpretation of the date, nor in the writing of the manuscript or the decision to submit it for publication.

No authors have been paid by any pharmaceutical companies or other agencies to write this article.

The corresponding author and biostatistician had full access to all the data in the study and have final responsibility for the decision to submit for publication.

Funded by National Institutes of Health and others

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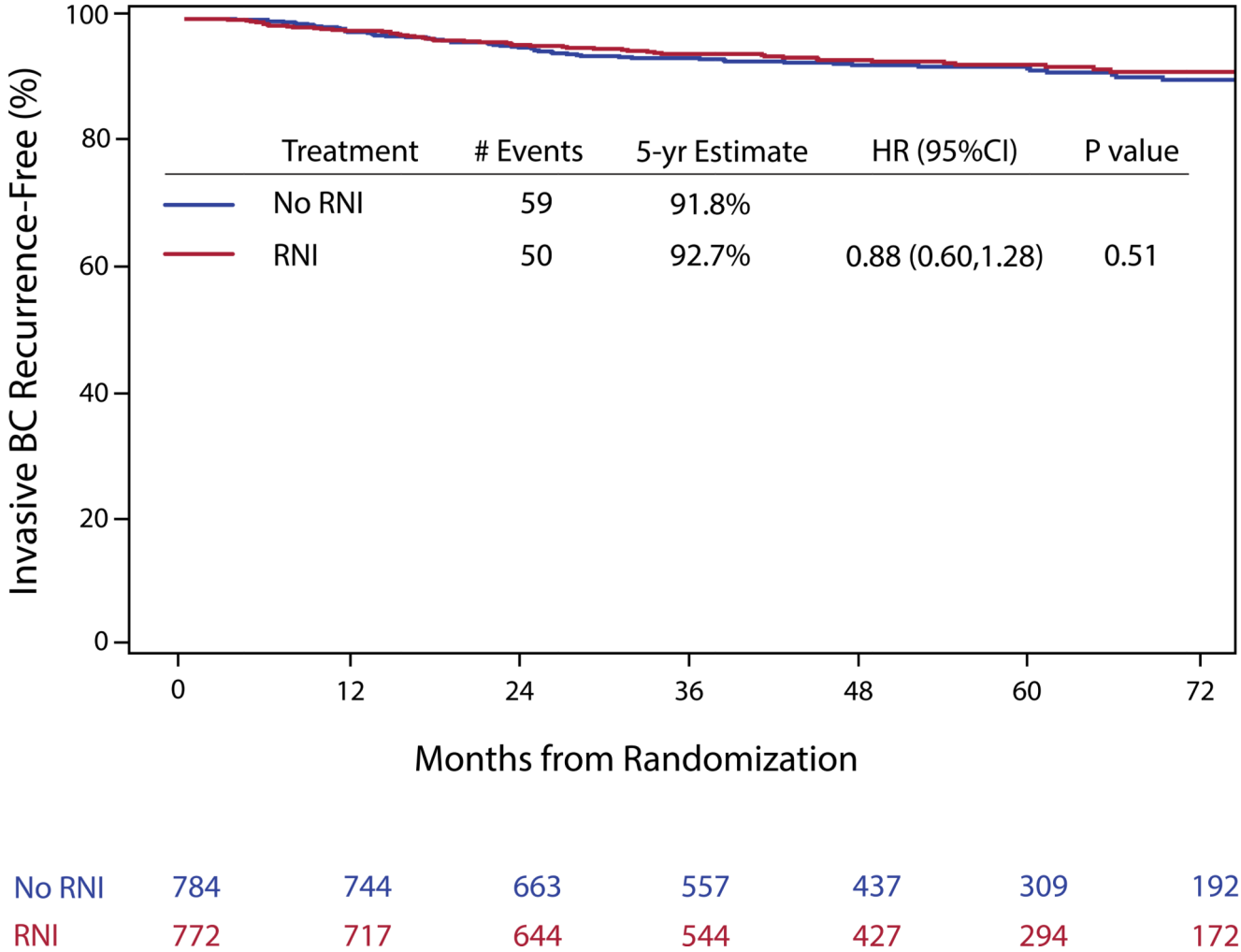

Figure 1: Effect of Regional Nodal Irradiation on Invasive Breast Cancer Recurrence-Free Interval.

Shown is the 5-year estimate of survival free from invasive breast cancer recurrence or death from breast cancer. RNI denotes regional nodal irradiation.

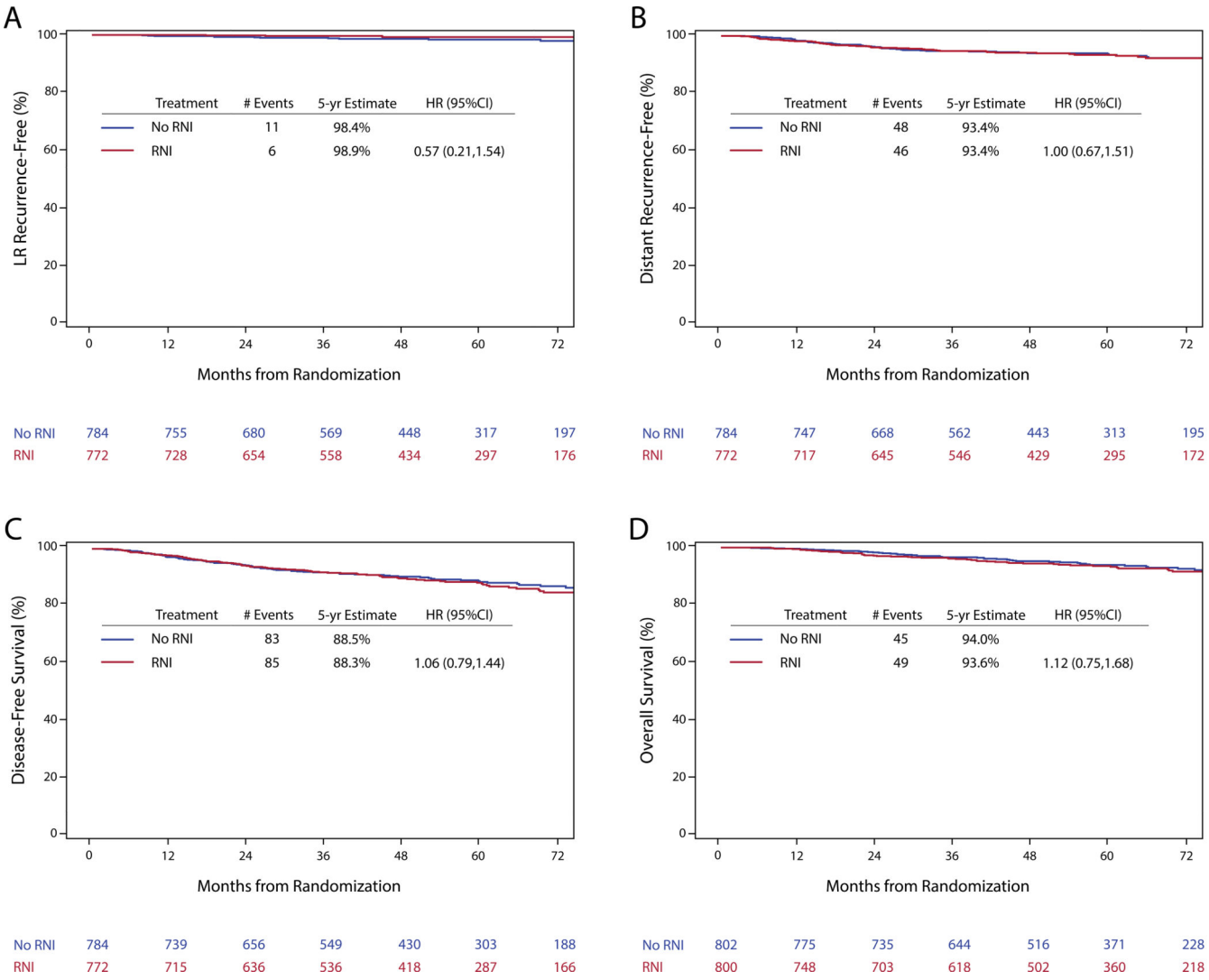

Figure 2: Effects of Regional Nodal Irradiation on Secondary End Points.

Shown are effects 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).

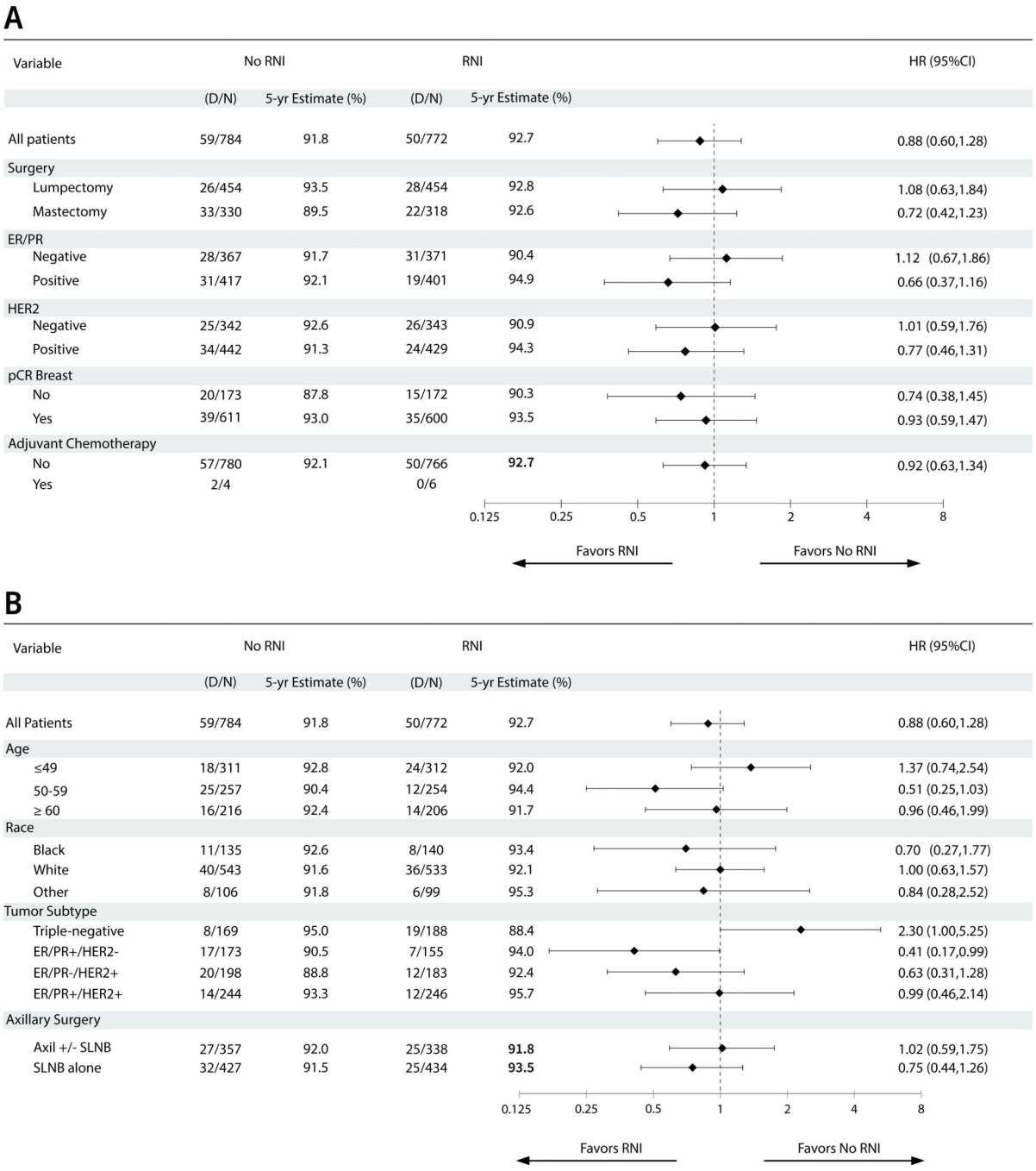

Figure 3: Subgroup Analysis of Invasive Breast Cancer Recurrence-Free Interval.

Shown are results from the main analysis of invasive cancer recurrence-free interval among patients categorized by prespecified subgroups (Panel A) and from an exploratory analysis categorized by 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.

Table 1:

Patient, Tumor, and Treatment Characteristics: NSABP B-51/RTOG 1304

Variable	No regional nodal irradiation (N=821)		regional nodal irradiation (N=820)	
	N	%	N	%
Age				
Median	52		52	
≤39	119	14	120	15
40–49	207	25	215	26
50–59	266	32	274	33
≥60	229	28	211	26
Race				
Asian	64	8	53	6
Black/African American	139	17	147	18
White	569	69	568	69
Other/Unknown	49	6	52	6
Ethnicity				
Hispanic or Latino	114	14	118	14
Not Hispanic or Latino	682	83	675	82
Unknown	25	3	27	3
Type of Surgery				
Lumpectomy	474	58	473	58
Mastectomy	347	42	347	42
Clinical Tumor Size				
T1	171	21	170	21
T2	484	59	499	61
T3	166	20	151	18
Hormone Receptor Status				
Negative	382	47	386	47
Positive	439	53	434	53
HER2 Status				
Negative	356	43	355	43
Positive	465	57	465	57
Tumor Subtype				
Triple negative	175	21	191	23
ER+ and/or PgR+/HER2-	181	22	164	20
ER-/PgR-/HER2+	207	25	195	24
ER+ and/or PgR+/HER2+	258	31	270	33
Adjuvant Chemotherapy				
No	817	99	813	99
Yes	4	<1	7	1

Variable	No regional nodal irradiation (N=821)		regional nodal irradiation (N=820)	
	N	%	N	%
pCR in breast				
No	182	22	176	21
Yes	639	78	644	79
Axillary Staging Surgery				
SLNB	448	55	461	56
Axillary Lymph Node Dissection (± prior SLNB)	373	45	359	44

regional nodal irradiation denotes Regional Nodal Irradiation; SLNB denotes Sentinel Lymph Node Biopsy.

Table 2:

Distribution of the Events for Primary and Secondary End Points: NSABP B-51/RTOG 1304

Event	No regional nodal irradiation	regional nodal irradiation
	no. of patients (%)	
Analyzed for disease-related events	**n = 784**	**n = 772**
Primary endpoint: IBCRFI	59 (7.5)	50 (6.5)
Distant recurrence [*]	36 (4.6)	41 (5.3)
Synchronous LRR with DR [†]	9 (1.1)	2 (0.3)
Isolated LRR	11 (1.4)	4 (0.5)
Death from breast cancer	3 (0.4)	3 (0.4)
Secondary end points		
LRR [††]	11 (1.4)	6 (0.8)
Local recurrences	2 (0.3)	6 (0.8)
Regional recurrences	8 (1.0)	0 (0.0)
Loco-regional recurrences	1 (0.1)	0 (0.0)
DRFI	48 (6.1)	46 (6.0)
Distant recurrence	45 (5.7)	43 (5.6)
Death from breast cancer	3 (0.4)	3 (0.4)
DFS	83 (10.6)	85 (11.0)
Distant recurrence	45 (5.7)	43 (5.6)
LRR	11 (1.4)	6 (0.8) [§]
Second primary cancer	16 (2.0)	19 (2.5)
Death	11 (1.4)	17 (2.2)
Analyzed for survival	**n=802**	**n=800**
Death	45 (5.6)	49 (6.1)

regional nodal irradiation denotes Regional nodal irradiation; LRR denotes Loco-regional recurrence; DR denotes Distant recurrence.

[*] With no evidence of loco-regional recurrence (LRR).

[†] LRR with evidence of DR within 60 days window of LRR.

[††] Local (DCIS [No regional nodal irradiation:0, regional nodal irradiation:2], breast [No regional nodal irradiation:1, regional nodal irradiation:3], chest wall [No regional nodal irradiation:1, regional nodal irradiation:1]), Regional (axilla/infraclavicular), Loco-regional (chest wall/axilla/internal mammary).

[§] Two cases of DCIS.